DISSERTATION

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Synthesis and Chromatography of [RuCp]$^+$-labelled Diaryl Ether Peptoids as Precursors of the Bastadins from the Marine Sponge *Ianthella basta*

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Prof. Dr. Manfred Wießler

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List of Abbreviations

ACE:	Angiotensin I converting enzyme
Bn:	Benzyl
Bz:	Benzoyl
BnBr:	Benzyl bromide
Boc_2O:	Di-*tert*-butyl-dicarbonate
Cp*:	Pentamethyl-cyclopentadienyl
Cp:	Cyclopentadienyl
DCC:	*N*, *N*-Dicyclohexylcarbodiimide
DHPR:	Dihydropyridine receptors
DMF:	Dimethylformamide
DMSO:	Dimethylsulfoxide
DOPA:	3, 4-Dihydroxy-phenylalanine
DOTA:	1, 4, 7, 10-tetra-(carboxymethyl)-1, 4, 7, 10-tetraazacyclododecane
DTPA:	Diethylenetriaminepentaacetate
EDCI:	*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
Et_3N:	Triethylamine
FABMS:	Fast Atom Bombardment Mass Spectrometry
HMBC:	Heteronuclear Multiple Bond Correlation
HOBT:	Hydroxy-benzotriazol
HPLC:	High Performance Liquid Chromatography
HRFABMS:	High Resolution FABMS
HRP:	Horseradish Peroxidase
IC_{50}:	Inhibitory Concentration 50 %
Im:	Imidazol
i. p.:	Intraperitoneal
iPr_2NEt:	Di-*iso*-propyl-ethylamine
IR:	Infrared
KO*t*Bu:	Potassium *tert*-butylate
MCA:	Mycothiol *S*-conjugate amidase
MTO:	Methylthioxorheniu
Na, K-ATPase:	Sodium, potassium ATP-dependent pump

NCI:	National Cancer Institute
NMR:	Nuclear Magnetic Resonance
PCWP:	Peroxotungstophosphate
Phe:	Phenylalanine
resp.:	respectively
Ry_1R:	Ryanodine Receptor type 1
S_NAr:	Nucleophilic aromatic substitution
SOP:	Soybean Peroxidase
SR:	Sarcoplasmatic Reticulum
THF:	Tetrahydrofurane
TLC:	Thin layer chromatography
TMP:	*Iso*-octane
TS-1 and TS-2:	Titanium silicate molecular sieves type 1 and type 2
TTN:	Thallium Trinitrate
UV:	Ultra-violet
s:	strong (IR)
m:	medium (IR)
w:	weak (IR)
s:	singlet (NMR)
d:	doublet (NMR)
t:	triplet (NMR)
m:	multiplet (NMR)
br:	broad (NMR)
dd:	double doublet (NMR)

I Theory

1 Introduction and objectives

Natural products are secondary metabolites that are not directly involved in primary metabolic processes. They play important biological roles in the interactions between organisms.

The relationship between biological activity and toxicity of natural products isolated from marine organisms long been a question of study due to phenomena like the red tides and human seafood poisonings. For example, saxitoxin and tetrodotoxin, which are important tools used to investigate cell biochemistry, are responsible for severe seafood poisoning[1].

While chemical investigations of terrestrial plants and insects started in the beginning of the 19 th century, the first reports of marine natural products chemistry did not appear until early in the 20 th century, with the isolation of sterols from marine sponges by Henze[2] and Doree[3] followed by the isolation and characterisation of the ancient Egyptian dye tyrian purple from molluscs[4]. In 1943, Bergmann isolated gorgosterol from a gorgonian[5], but only in 1969, when Weinheimer and Spraggins discovered prostaglandins in the octocoral *Plexaura homomalla*[6], did the pharmaceutical industry become interested in the discovery of new natural products from marine origin.

The retarded development of marine compared to "terrestrial" natural product chemistry was mainly due to the difficulties involved in the collection of marine organisms. Only with the development of the SCUBA diving technology in the 1960's were scientists finally able to explore the seas to look for new compounds with interesting biological and pharmacological activities. Over the past 30 years, marine natural products have been isolated from many types of marine organisms, including algae, invertebrates, and micro-organisms [7]. Since many of the organisms are unique to the marine environment, many novel secondary metabolites have been discovered.

Among the bioactive compounds isolated from marine organisms, those currently under intense investigation as potential anticancer agents include ecteinascidin 743 (**1**), halichondrin B (**2**), dehydrodidemnin B (aplidine) (**3**), bryostatin 1 (**4**), and dolastatin 10 (**5**) (Figure 1). Presently, the most promising anticancer agent is ecteinascidin 743 (**1**), a tetrahydroisoquinoline alkaloid isolated from the marine tunicate *Ecteinascidia turbinata*[8] which is in phase II clinical trials. A total of 381 patients have been already treated with **1** in phase I and all toxicities observed were manageable[9]. The phase II studies of ecteinascidin 743 (**1**) are very promising [9d]. Ecteinascidin 743 has recently become available by total synthesis and fro aquaculture[10, 11].

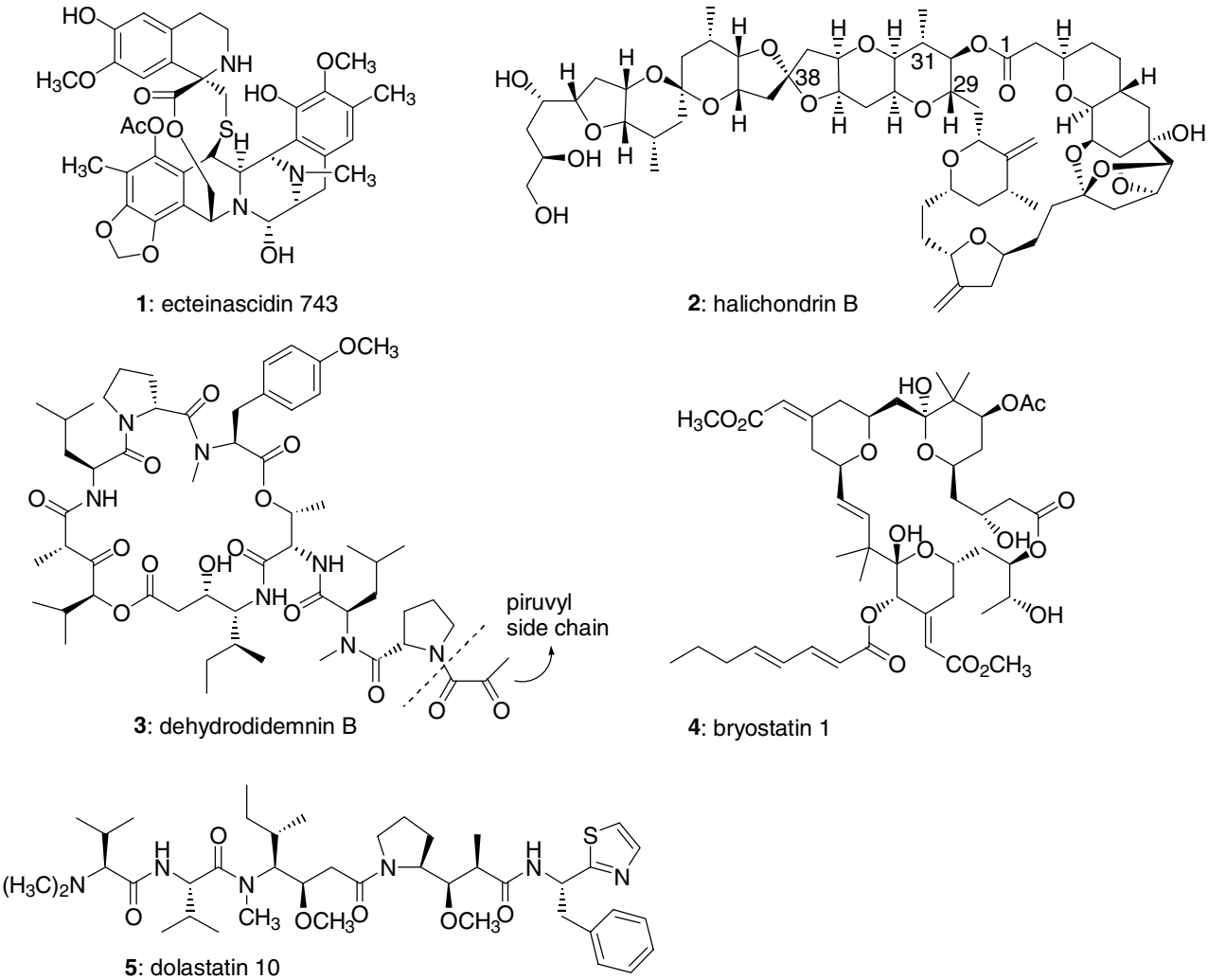


Figure 1: Bioactive marine derived compounds under intense investigation as anticancer agents.

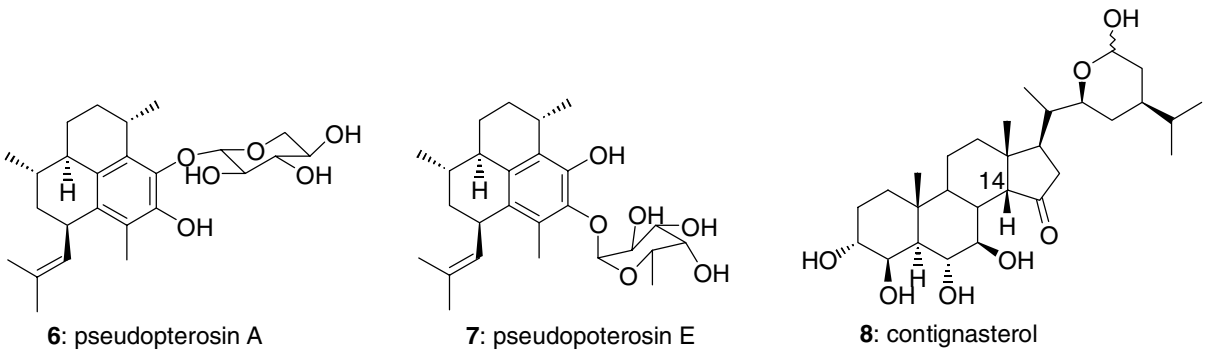
Halichondrin B (**2**), a polyether macrolide originally isolated from the marine sponge *Halichondria okada* [12], is a potent anticancer agent in preclinical development at the NCI (National Cancer Institute) and is expected to start phase I trials soon. The limited supply of **2** from marine sources was circumvented by its total synthesis [13], allowing for the preparation and subsequent evaluation of more than 180 macrocyclic analogues. It was concluded that the biological activity of halichondrin B is related to its macrocyclic lactone ring[14, 15].

Didemnin B , a cyclic depsipeptide isolated from the tunicate *Tridemnum solidum*[16], was the first marine metabolite to enter phase I and II clinical trials, but was later found to be cardiotoxic during phase II studies[17]. Dehydrodidemnin B (aplidine) (**3**) is a close structural analogue of didemnin B, differing in the presence of a pyruvyl instead of a lactyl side chain (highlighted in Figure 1) [18]. **3** lacks cardiotoxicity and has reached phase I clinical trials as a potent anticancer agent made by the company Pharmamar[17d].

Bryostatin 1 (**4**) is a marine-derived macrolactone isolated from the bryozoan *Bugula neritina*[19] which possesses antineoplastic activity. Dolastatin 10 (**5**) is a novel pentapeptide anticancer agent originally isolated from the marine mollusc *Dolabella auricularia*[20]. Both **4** and **5** are currently in phase II clinical trials. Bryostatin 1 (**4**) has been administrated to patients with relapsed multiple myeloma [21], soft tissue sarcoma[22], and head and neck cancer [22] while dolastatin 10 (**5**) was used to treat patients with advanced melanoma[23]. Unfortunately, preliminary studies revealed no objective response to these administrated drugs.

Anti-inflammatory agents such as the tricyclic diterpene glycosides pseudopterosins A (**6**) and E (**7**)[24] (Figure 2) have been isolated from the sea fan *Pseudopterogorgia elisabethae*[24]. **6** and **7** have shown potent anti-inflammatory activity[25] and are in preclinical trials. The partially purified extract of this sea fan, containing a mixture of pseudopterosins, is used in the Estée Lauder cosmetic product Resiliance.

Contignasterol (**8**, figure 2) is a highly oxygenated steroid with the unnatural 14 β configuration from the marine sponge *Petrosia contignata*[26]. **8** is in phase II clinical trials conducted by the company Inflazyme as an anti-asthma agent. It is also in preclinical development to treat respiratory disease and psoriasis because of its topical anti-inflammatory effect in tracheobronchial airways[27].



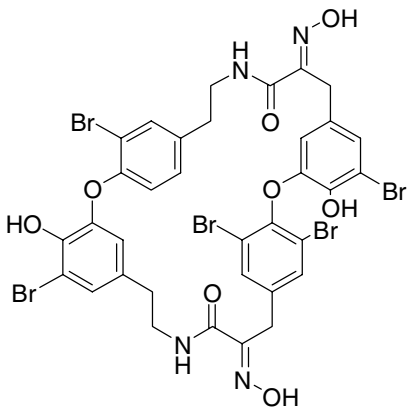
6: pseudopterosin A **7**: pseudopoterosin E **8**: contignasterol

Figure 2: Structures of the anti-inflammatory agents pseudopterosins A (**6**) and E (**7**) and of the anti-asthma agent contignasterol (**8**).

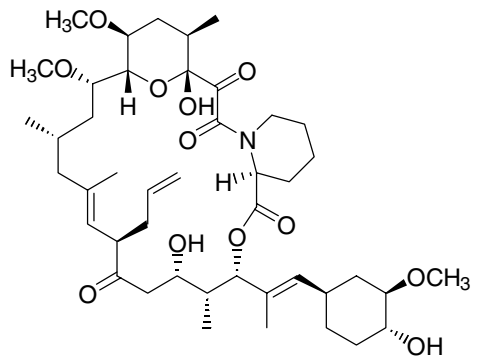
Many other marine derived secondary metabolites possess interesting biological activities. Their limited availability from natural sources, however, limits further investigation about their activities making them attractive targets for studies toward their total synthesis. Beyond the investigation of selected marine natural products exhibiting important biological activities, basic research must take the opportunity to identify and explore the underlying principles of its biological function. Diaryl ether linkages constitute an important structural element of peptoid secondary metabolites[28]. Among them, the antibiotic vancomycin is used clinically as the "last resort" in the case of resistance to β-lactam antibiotics.

The bastadins are a family of highly modified bromotyrosine tetrapeptides isolated from the marine sponge *Ianthella basta*[29]. Most of them are macrocyclic and exhibit antibacterial[29c, 29f], cytotoxic [29f] or anti-inflammatory activities[30]. Among these tetrapeptides, bastadin 5 (**9**, figure 3) is of special interest due to its capacity to inhibit Ca^{+2} uptake into the sarcoplasmatic reticulum, being antagonised by the important immunosuppressant natural product FK506 (**10**, figure 3)[30].

The total synthesis of bastadin 5 (**9**) is essential for availability of the required quantities needed for further tests. Three total syntheses of selected bastadins (bastadins 1-3, 6 and 12) have been reported[31] but produce in low yields because of the employed methods of diaryl ether coupling.



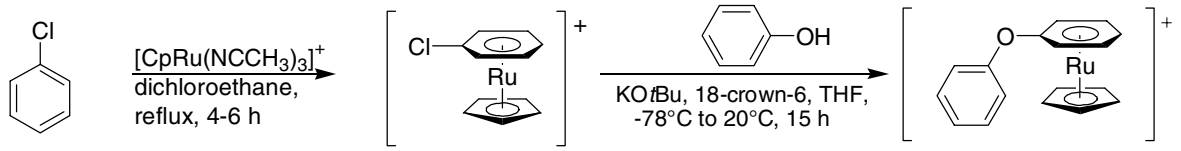
9: bastadin 5



10: FK506

Figure 3: Structure of bastadin 5 (**9**) and FK506 (**10**).

The usage of nucleophilic attack by phenolates to [RuCp] $^{+}$-complexed chloroarenes offers unique advantages (Scheme 1) [32, 33]. Ruthenium sandwich complexes are readily formed, even from electron-poor arenes and give stable [RuCp] $^{+}$-complexed diaryl ether products under mild reaction conditions in high yields. Furthermore, $[RuCp]^{+}$-complexes can be used for the labelling of unprotected amino acids and peptides with aromatic side chains. The availability of various rutheniu radioisotopes makes them attractive for application in diagnostic nuclear medicine [34]. One of the central obstacles in ruthenium arene chemistry is the difficult purification of these $[RuCp]^{+}$-complexes, which has limited their use in organic and bioorganic chemistry.



Scheme 1: Formation of $[RuCp]^{+}$-complexed diaryl ethers.

Facing the need to supply bastadin 5 in sufficient quantities for further biological activity investigation and the perspective of developing ruthenium-labelled peptoids, the following questions were addressed in this thesis:

- Ruthenium mediated synthesis of diaryl ethers;
- Purification and separation of charged ruthenium sandwich complexes;
- Extension of the application of ruthenium arene chemistry in organic synthesis;
- Use of ruthenium arene chemistry in the synthesis of the bastadin skeleton.

2 Bromotyrosines from marine sponges

Although seawater contains a much higher concentration of chloride (559 mM) than bromide (0.86 mM) or iodide (0.45 µM), brominated secondary metabolites predominate in marine organisms. Bromide is more easily and readily oxidised than chloride[1] and the resulting bromonium ions undergo electrophilic addition to alkenes and aromatic systems[35]. Haloperoxidases are the enzymes which are able to oxidise chloride, bromide and iodide in the marine environment. Consequently, various marine organisms effectively used the available bromonium ions in the biosynthesis of defensive and other necessary constituents [36]. Out of nearly 3200 known natural organohalogen compounds, more than 1600 contain bromine. Illustrative are the bromotyrosine-derived secondary metabolites of marine sponges and certain tunicates[7].

Marine sponges (phylum Porifera) are a rich source of secondary metabolites with novel structures and interesting biological activities[7]. Over the past 30 years, an ever increasing number of bromotyrosine-derived secondary metabolites have been isolated from marine sponges, mainly from the order Verongida.

2.1 Structures, biogenetic relationship and function

Marine sponges belonging to the order Verongida (Table 1) show a peculiar biochemistry characterised by the production of sterols with an apysane skeleton and of bromo compounds biogenetically related to tyrosine. These bromotyrosine-derived metabolites are considered distinct chemotaxonomic markers for Verongid sponges and range from simple monomeric metabolites, such as aeroplysinin-1 (**18**), to more complex structures such as the bastadins (see chapter 2.2)[29].

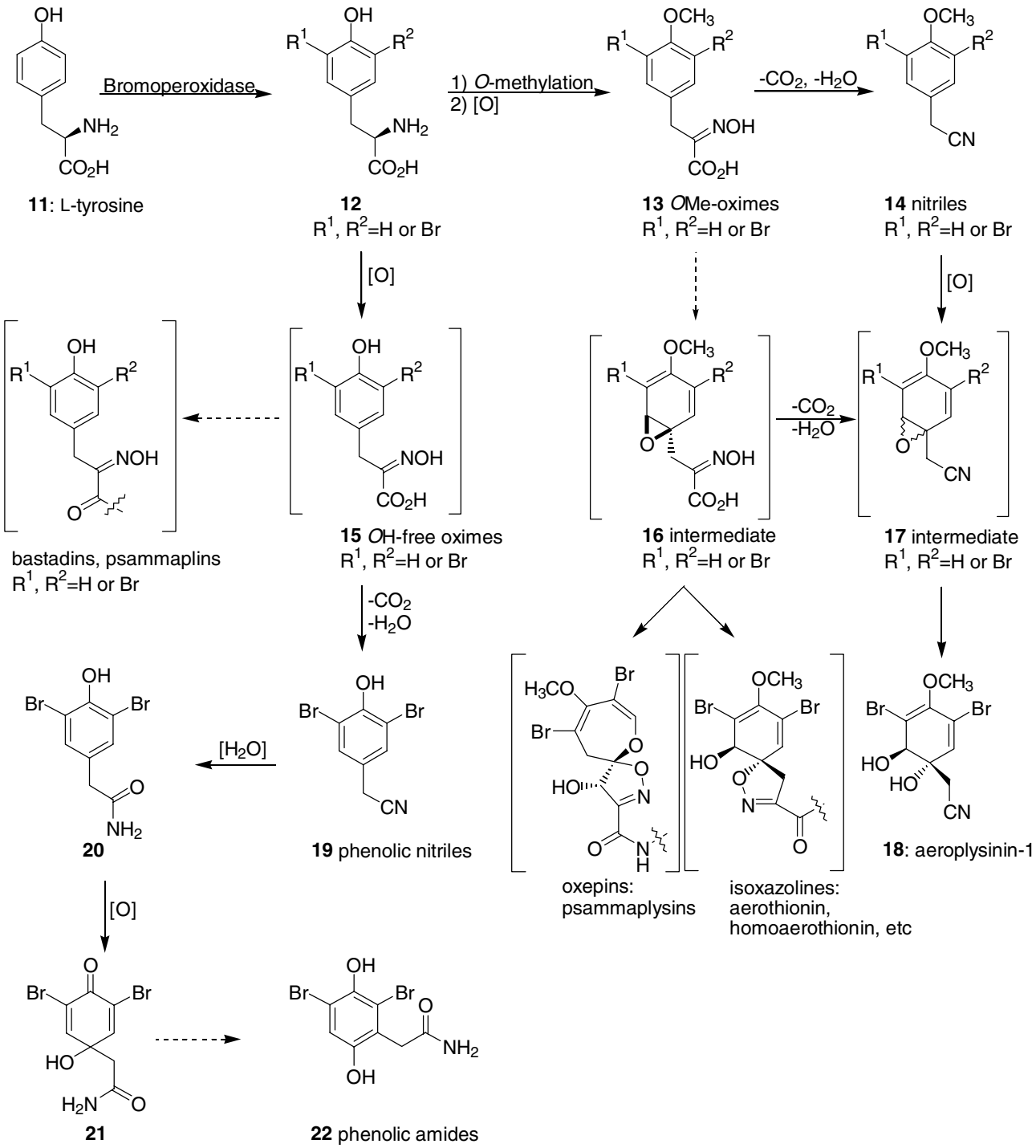
[1] Oxidation potentials: Cl^--Cl_2 = 1.36 E°/V; Br^--Br_2 = 1.07 E°/V.

Table 1: Systematic distribution of sponges of the order Verongida (phylum Porifera, class Demospongiae, subclass Ceractinomorpha)[37].

Order	**Family**	**Genera**
Verongida	Aplysinidae	*Aplysina*
		Verongula
	Aplysinellidae	*Aplysinella*
		Psammaplysilla
		Porphyria
		Pseudoceratina
		Suberea
	Ianthellidae	*Anomoianthella*
		Bajalus
		Ianthella

Biosynthetic studies of sponges are very difficult to conduct. Sponges have very slo growth rates and possess a plethora of symbiotic microorganisms [38]. Therefore, very few studies have been performed which elucidated the biosynthetic mechanisms involved in the production of secondary metabolites. The first experiment was performed by Rinehart and Tymiak [39a], in which they administered ^{14}C-, ^{15}N-radiolabelled precursors to sponges in solution with sea water[39a]. In 1995, Rinehart and Carney conducted feeding experiments with *Aplysina fistularis* using U-^{14}C-labelled bromine and *O*-methylated tyrosine derivatives as well as methoxybenzyl [^{14}C]cyanide[39c]. The results of both biosynthetic studies showed that the metabolic pathway employed by Verongid sponges (Scheme 2) involves a bromination of the tyrosine (**11**) aromatic ring as the first step. It was suggested [39c] that the brominated tyrosines (**12**) can follow two different pathways (Scheme 2): I) oxidation of the amine to an oxime (**15**) or II) *O*-methylation of the tyrosine followed by oxidation of the amine to an oxime (**13**). The first pathway gives phenolic nitriles (**19**) and amides (**22**) or bastadins and psammaplins. The second pathway can follow two different biosynthetic routes: A) dehydration and decarboxylation to give the *O*-methylated nitriles (**14**), which can be oxidised to arene oxides (**17**) followed by nucleophilic opening of the epoxide leading to aeroplysinin-1 (**18**); B) direct epoxide formation (**16**) which leads to isoxazoline rings giving metabolites like aerothionin, or homoaerothionin or to oxepins giving the psammaplysins. The *O*-methylated tyrosine

epoxide intermediate (**16**) could also be dehydrated and decarboxylated (**17**) followed by nucleophilic opening of the epoxide also leading to aeroplysinin-1 (**18**)[39].



Scheme 2: Biotransformation of brominated secondary metabolites of Verongid marine sponges. Compounds in dashes were not isolated and therefore, their biosynthetic pathways are proposed.

A large number of brominated tyrosines containing a novel spirocyclic isoxazoline ring has been found in several Verongid sponges. The first examples are aerothionin (**23**) and homoaerothionin (**24**) (Figure 4). Aerothionin (**23**) was isolated from several species of *Aplysina*[40], as well as fro *Psammaplysilla purpurea*[40c] and *Pseudoceratina durissima*[40d], and possesses antibacterial activity. Homoaerothionin (**24**) was also isolated from *Aplysina*[40a, b, e] spp. and *Pseudoceratina durissima*[40d]. Both compounds affect the behaviour and survival of several invertebrates in an attempt to prevent colonisation of the sponge. Additionally, it was demonstrated that mechanical injury to the sponge stimulates the release of these compounds at concentrations 10-100x higher [41] than that normally measured near an intact organism. Another interesting chemical defence mechanism observed in this order is the enzymatic conversion of biologically inactive storage compounds into active defence metabolites following disruption of the sponge's cells. The spirocyclic isoxazolines aerophobin-2 (**25**)[7, 42] from *Aplysina* spp. and isofistularin-3 (**26**)[43] from *Aplysina*[43a-d] and *Pseudoceratina*[43e] spp. (Figure 4), undergo enzymatic biotransformation into active metabolites, aeroplysinin-1 (**18**) and dienone (**27**) (Figure 4), when the sponge is injured[41]. These two metabolites have been found in all Verongid families[43b,e, 44] and exhibit cytotoxic and antimicrobial activities.

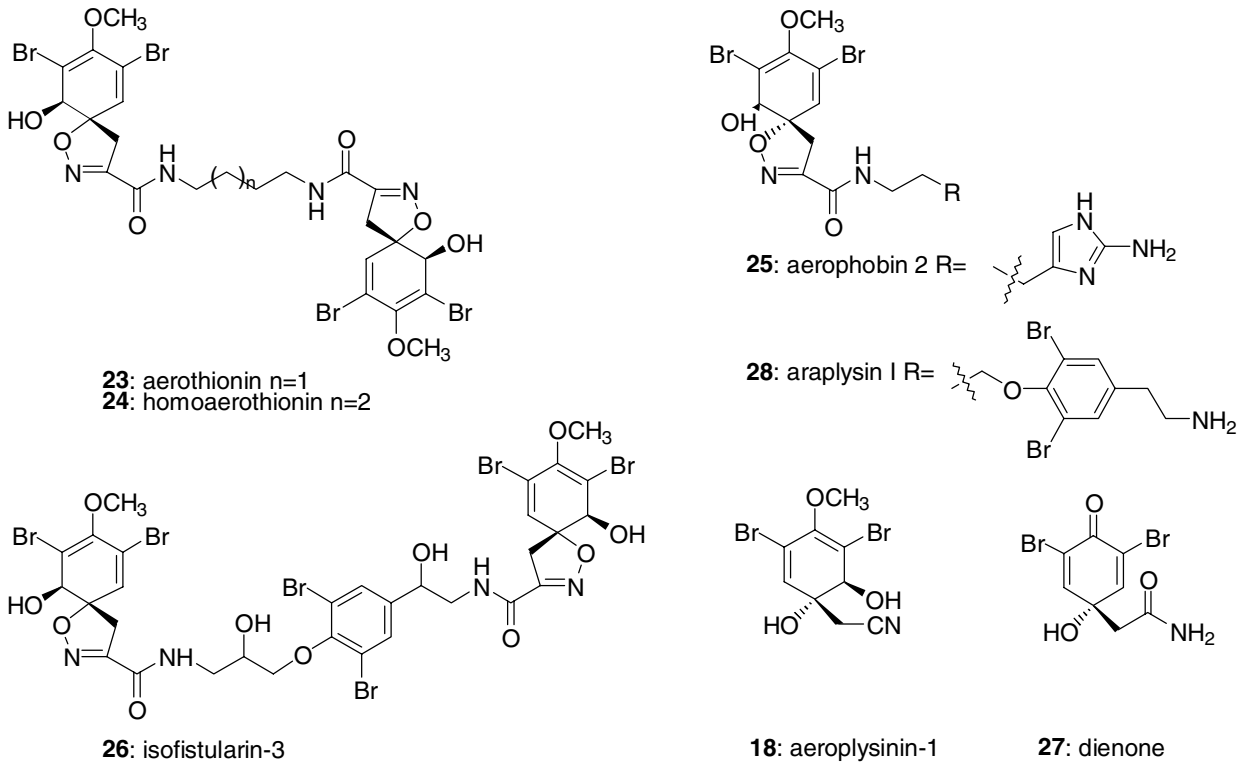
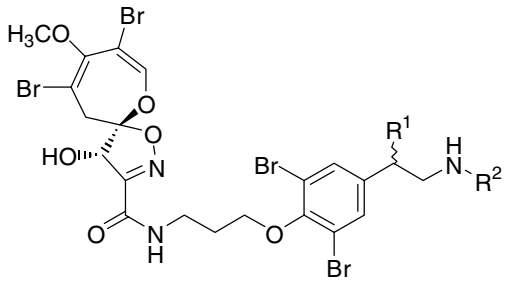


Figure 4: Bromotyrosine-derived metabolites of Verongid marine sponges.

The bromotyrosine-derived metabolites, aside from their ecological functions, have other interesting biological properties. For example, araplysin I (**28**) from *Psammaplysilla arabica* (Figure 4) possesses antimicrobial as well as Na^+ and K^+-ATPase inhibition activities[45].

Among the spirocyclic oxazolines, the psammaplysins A-F (**29**-**34**)[46] and the ceratinamides A and B (**35** and **32**, *resp.*) (Figure 5) are a small family of unique metabolites which contain an oxepin moiety, possibly formed from epoxidation followed by electrocyclic opening of the oxirane ring. The psammaplysins are found in *Psammaplysilla purpurea*[46a,b], *Pseudoceratina purpurea* [46e] and *Aplysinella* sp.[46c,d] while the ceratinamides are found in *Pseudoceratina purpurea*[46e]. The psammaplysins A (**29**) and E (**33**) and the ceratinamides A (**35**) and B (**32**) possess anti-fouling properties[46e]. Psammaplysin A (**29**) shows antibacterial activity[46a] and psammaplysins C (**31**) and E (**33**) are cytotoxic[46d].

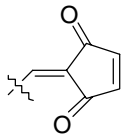


29: psammaplysin A R^1=R^2=H

30: psammaplysin B R^1=OH, R^2=H

31: psammaplysin C R^1=OH, R^2=CH_3

32: psammaplysin D or ceratinamide B R^1=H, R^2=$CO(CH_2)_{11}CH(CH_3)_2$

33: psammaplysin E R^1=H, R^2= 

34: psammaplysin F R^1=H, R^2=CH_3

35: ceratinamide A R^1=H, R^2=CHO

Figure 5: Psammaplysins A-E (**29**-**34**, *resp.*) and ceratinamides A and B (**35** and **32**, *resp.*) are spirocyclic oxazolines bearing an oxepin moiety.

Some bromotyrosine metabolites have been isolated from non-Verongid species such as **36** from the marine sponge *Oceanapia* sp.[47]. This compound (**36**) which contains an unprecedented imidazolyl-quinoline substructure inhibits a novel mycobacterial enzyme, MCA (mycothiol *S*-conjugate amidase)[47].

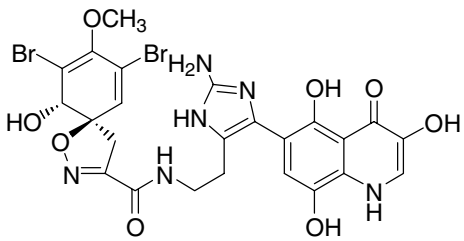


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Figure 6: **36**, a bromotyrosine-derived metabolite from the non-Verongid species *Oceanapia* sp.

Examples of Verongid tyrosine oximes are verongamine (**37**)[44h, 48] and purealidin C (**38**)[49] (Figure 7). Verongamine (**37**) is a histamine-H_3 antagonist and inhibits settling of barnacle larvae[44h, 48]. Purealidin C (**38**) has antifungal, antibacterial and antineoplastic properties[49].

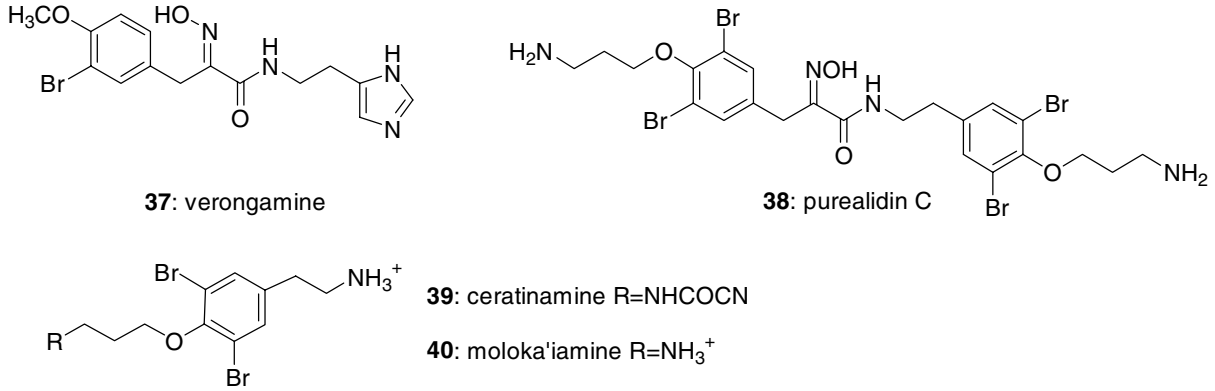
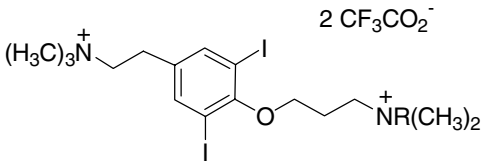


Figure 7: Bioactive bromotyrosine-derived metabolites.

The simple bromotyrosine metabolites ceratinamine (**39**)[7, 46e, 50] and moloka'iamine (**40**)[7, 46e, 50] (Figure 7), common components in Verongid sponges, are known to be cytotoxic, antiviral and antifouling agents.

Turbotoxins A (**41**) and B (**42**) (Figure 8) are novel diiodotyramine-derived metabolites from the gastropod *Turbo marmorata*[51] (Figure 8). Investigations about the structure-toxicity of **41** and **42** revealed that both are acutely toxic when administered to mice i. p., and that the iodine and the quaternary ammonium groups are important in causing the observed toxicity. These two metabolites are structurally similar to ceratinamine (**39**)[7, 46e, 52], moloka'iamine(**40**) [7, 46e, 50] and other related dibromotyrosine-derived metabolites[7, 53].

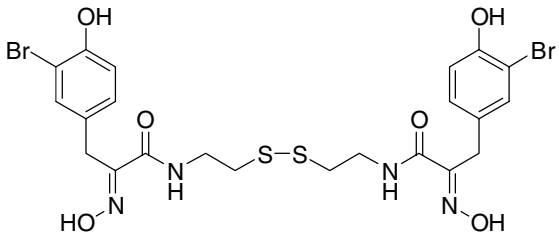


41: turbotoxin A R=CH_3

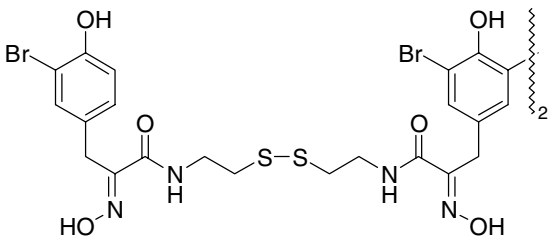
42: turbotoxin B R=H

Figure 8: Turbotoxins A (**41**) and B (**42**), diiodotyrosine-derived metabolites which are structurally related to dibromotyrosine derivatives found in Verongid sponges.

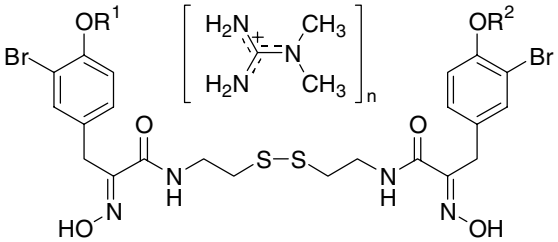
The psammaplins and other related compounds comprise a small group of metabolites possibly biosynthesised via the linear connection of bromotyrosines and modified cysteines. They were found in *Psammaplysilla* sp.[54a], *P. purpurea*[54b] and in *Aplysinella rhax*[54c]. Psammaplin A (**43**)[54a], the first metabolite of this series, is a symmetrical tetrapeptide composed of two units each of bromotyrosines and cysteines (Figure 9). Bisaprasin (**44**)[54a] is a biphenylic dimer of psammaplin A. Other psammaplins (**45-49**) are linear di- and tripeptides containing thiocyanate (**47**) or sulphonamide (**48**) on a modified cysteine chain (Figure 9)[54]. Psammaplin A (**43**), bisaprasin (**44**) and psammaplins A_1 (**45**) and A_2 (**46**) exhibit moderate cytotoxicity and inhibitory activities against farnesyl protein transferase and leucine aminopeptidase[54c]. Psammaplin D (**49**) showed antimicrobial activity against gram-positive and gram-negative bacteria, as well as activity against tyrosine kinase[54b].



43: psammaplin A

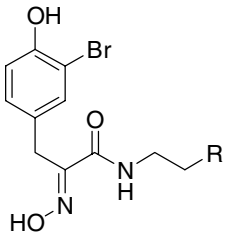


44: bisaprasin



45: psammaplin A_1 R^1=H, R^2=SO_3^-; n=1

46: psammaplin A_2 R^1=R^2=SO_3^-; n=2



47: psammaplin B R=SCN

48: psammaplin C R=SO_2NH_2

49: psammaplin D R=

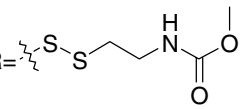
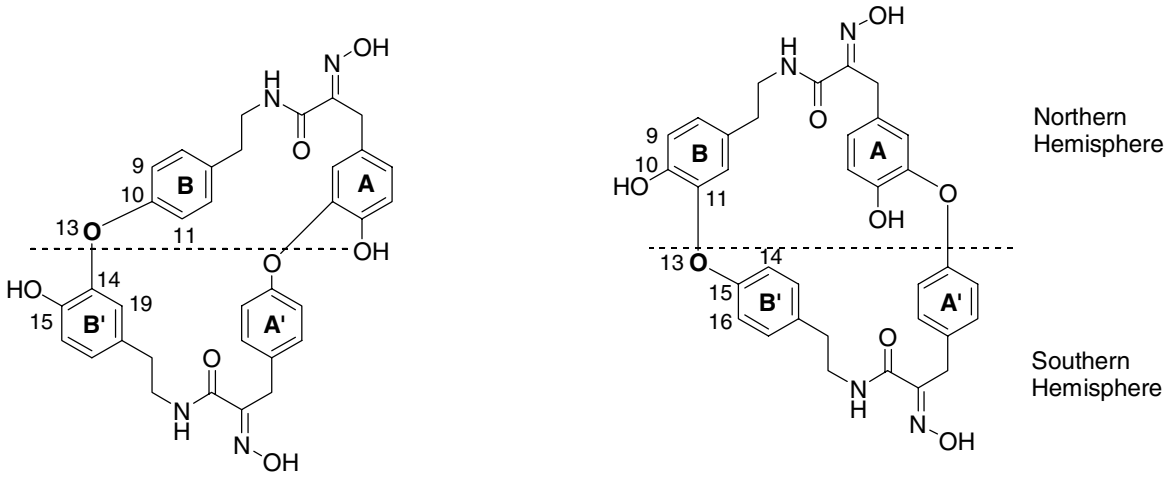


Figure 9: Bromotyrosine-cysteine-derived metabolites of Verongid sponges.

2.2 Biological activity of the bastadins, unique macrocyclic diaryl ethers from *Ianthella basta*, *Ianthella* sp. and *Psammaplysilla purpurea*.

The bastadins constitute a family of highly modified tetrapeptides, which have been isolated from the Verongid marine sponges *Ianthella* sp.[29g, h], *I. basta* [29a-e, i-n] and *Psammaplysilla purpurea*[29f]. They are composed of two tyrosine and two tyramine units. With four exceptions (bastadins 1 (**52**)[29a, b], 2 (**53**)[29a, b], 3 (**54**)[29b] and 10-*O*-sulfatobastadin-3 (**71**)[29n]), they are all macrocyclic. The bastadin macrocycle can be divided into two hemibastadin units which are the northern and the southern hemispheres (Figure 10). Almost all bastadins possess the bastarane (**50**) skeleton (Figure 10), and only four of them (bastadin 13 (**63**)[29e], bastadin 19 (**69**)[30], bastadin 20 (**70**)[29n] and 34-*O*-sulfatobastadin 13 (**73**)[29h], figure 11) possess isobastarane (**51**) geometry (Figure 10). Both skeletons have different oxidative modi of cyclisation. In bastarane geometry the oxygen comes from the B-tyramine unit (Figure 10) while in isobastarane geometry the oxygen is derived from the B'-tyramine unit (Figure 10).

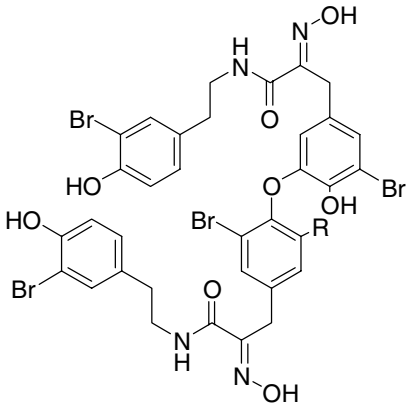


50 bastarane geometry

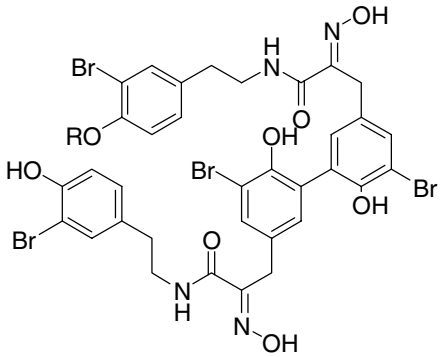
51 isobastarane geometry

Figure 10: Bastarane and isobastarane geometries.

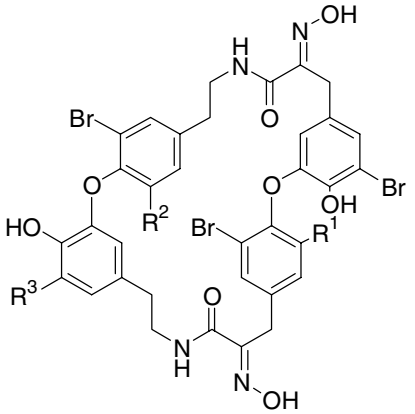
Bastadins 1 (**52**) and 2 (**53**) were isolated first[29a], directly followed by the isolation of bastadins 3 (**54**) 4 (**55**), 5 (**9**), 6 (**56**) and 7 (**57**) (Figure 11)[29b]. These 7 bastadins were shown to have antimicrobial activity against gram-positive bacteria [29b]. Bastadins 8-11 (**58**-**61**, respectively) have been reported by Podersino and Schmitz[29c] together with other known bastadins. Bastadins 4 (**55**), 8 (**58**) and 9 (**59**) showed cytotoxic activity against P-388 leukaemia cells and inhibited inflammation in a mouse ear assay[29c].



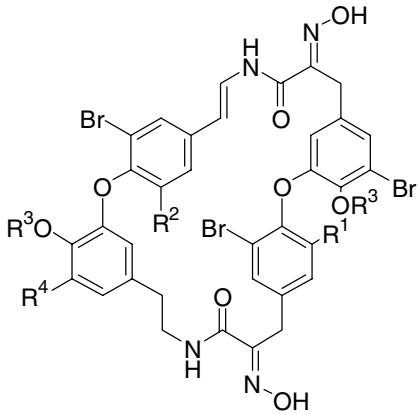
52: bastadin 1 R=H
53: bastadin 2 R=Br



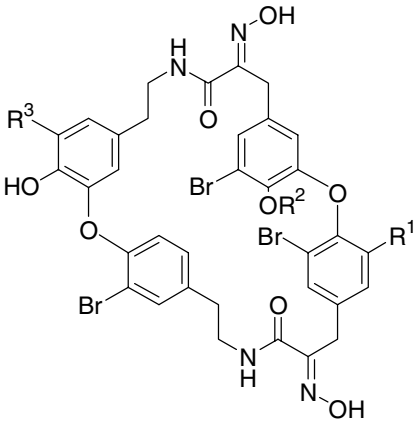
54: bastadin 3 R=H
71: 10-*O*-sulfatobastadin 3 R=SO_3Na



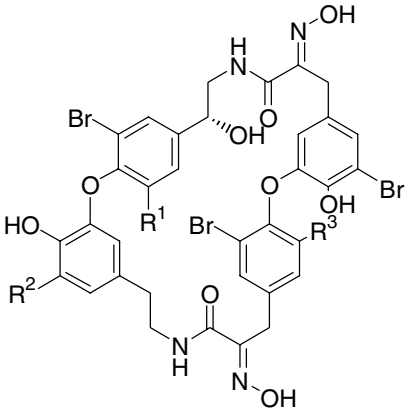
9: bastadin 5 R^1=R^3=Br, R^2=H
56: bastadin 6 R^1=R^2=R^3=Br
59: bastadin 9 R^1=Br, R^2=R^3=H
65: bastadin 15 R^1=H, R^2=R^3=Br
66: bastadin 16 R^1=R^2=Br, R^3=H
68: bastadin 18 R^1=R^2=H, R^3=Br



55: bastadin 4 R^1=R^4=Br, R^2=R^3=H
57: bastadin 7 R^1=R^2=R^3=H, R^4=Br
72: 15,34-*O*-disulfatobastadin 7 R^1=R^2=H, R^3=SO_3Na, R^4=Br
61: bastadin 11 R^1=Br, R^2=R^3=R^4=H
64: bastadin 14 R^1=R^3=H, R^2=R^4=Br



63: bastadin 13 R^1=Br, R^2=R^3=H
73: 34-*O*-sulfatobastadin 13 R^1=Br, R^2=SO_3Na, R^3=H
69: bastadin 19 R^1=R^3=Br, R^2=H
70: bastadin 20 R^1=R^2=H, R^3=Br



58: bastadin 8 R^1=H, R^2=R^3=Br
60: bastadin 10 R^1=R^3=H, R^2=Br
62: bastadin 12 R^1=R^2=Br, R^3=H
67: bastadin 17 R^1=R^2=H, R^3=Br

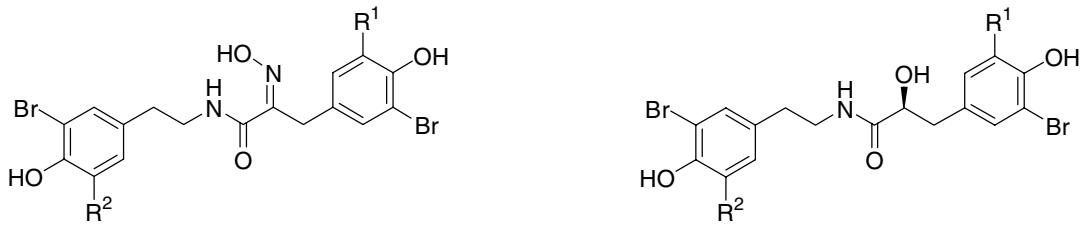
Figure 11: Structures of all isolated bastadins from the marine sponges *Ianthella* sp., *I. basta* and *Psammaplysilla purpurea*.

Bastadin 12 (**62**) (= bastadin 9 of Miao et al.[29d]) and bastadin 13 (**63**) (= bastadin 12 of Butler et al.[29e]) have been renamed by Carney et al. (Figure 11) [29f]. Bastadin 13 (**63**) was the first bastadin isolated with an alternative oxidative cyclisation modus, the isobastarane geometry. This metabolite showed activity against the gram-positive bacteriu *Bacillus subtilis* (Figure 11)[29h]. Bastadin 14 (**64**), isolated from *Psammaplysilla purpurea*[29f], and bastadin 15 (**65**) from *Ianthella* sp.[29g] were the first bastadins isolated from sponges other than *I. basta* (Figure 11). Bastadin 14 (**64**) exhibited modest cytotoxicity and inhibited the enzymes topoisomerase-II and dehydrofolate reductase[29f]. 34-*O*-Sulfatobastadin 13 (**73**), isolated fro *Ianthella* sp., was the first sulphated compound of the bastadin series (Figure 11) [29h]. This bastadin did not show the same antibacterial activity as its *O*H-free analogue, bastadin 13 (**63**). The free phenolic group may be required for this activity[29h].

Bastadins 16 (**66**)[29i, k], 17 (**67**)[29i, m] and 18 (**68**)[29j] (Figure 11) were isolated fro *Ianthella basta* , but no biological tests have been reported about these three compounds.

Bastadins 19 (**69**)[30, 29n], 20 (**70**)[29n], 10-*O*-sulfatobastadin 3 (**71**)[29n] and 15, 34-*O*-dissulfatobastadin 7 (**72**)[29n] have also been isolated fro *Ianthella basta* (Figure 11). The later was the first reported bastadin disulphate ester.

The isolation of the hemibastadins 1 (**77**), 2 (**78**) and 3 (**79**), and the hemibastadinols 1 (**80**), 2 (**81**) and 3 (**82**) from *Ianthella basta* was also reported[55] (Figure 12). These compounds provide some information about the biosynthetic routes of the bastadins, since they represent the northern or southern hemispheres of the bastadin macrocycle. Except for bastadin 6 (**56**), compounds **77-82** inhibited growth of *Neisseria gonorrhoeae*.[55] With the exception of the hemibastadinols 1-3, all other tested metabolites inhibited the growth of gram-positive *Enterococcus faecalis* and *Staphylococcus aureus*. None of those compounds were active against *Escherichia coli* or the fungi *Candida albicans* and *Cryptococcus neoformans*.



74: hemibastadin 1 R^1=R^2=H
75: hemibastadin 2 R^1=Br, R^2=H
76: hemibastadin 3 R^1=H, R^2=Br

77: hemibastadinol 1 R^1=R^2=H
78: hemibastadinol 2 R^1=Br, R^2=H
79: hemibastadinol 3 R^1=H, R^2=Br

Figure 12: Hemibastadins and hemibastadinols fro *Ianthella basta*.

The bastadins are efficient and novel modulators of the ryanodine receptor type 1 (Ry_1R) Ca^{2+} channels[30]. Dihydropyridine receptors (DHPR) are voltage sensitive channels which allow the influx of Ca^{2+} into the sarcoplasm. This influx mediates the efflux of Ca^{2+} from the sarcoplasmatic reticulum (SR) through calcium-sensitive channels, the ryanodine receptors (Figure 13). This activation represents the major physiological Ca^{2+}-release pathway from the sarcoplasmatic reticulum (SR) during excitation-contraction coupling in skeletal muscle (Figure 13)[30, 56]. The 12 kDa protein FKBP12 forms a heterocomplex with Ry_1R (FKBP12-Ry_1R), which stabilises the closed conformation of the Ca^{2+} release channel. Nanomolar concentrations of immunosuppressant drugs, including FK506 and its analogues, promote dissociation of FKBP12[30, 56, 57]. The dissociated FKBP12 forms a complex with FK506 which inhibits the activity of calcineurin (a Ca^{2+}/calmodulin-stimulated protein phosphatase, which plays a key role in T-cell activation)[58]. This inhibition is necessary for the immunossupressive effect of FK506.

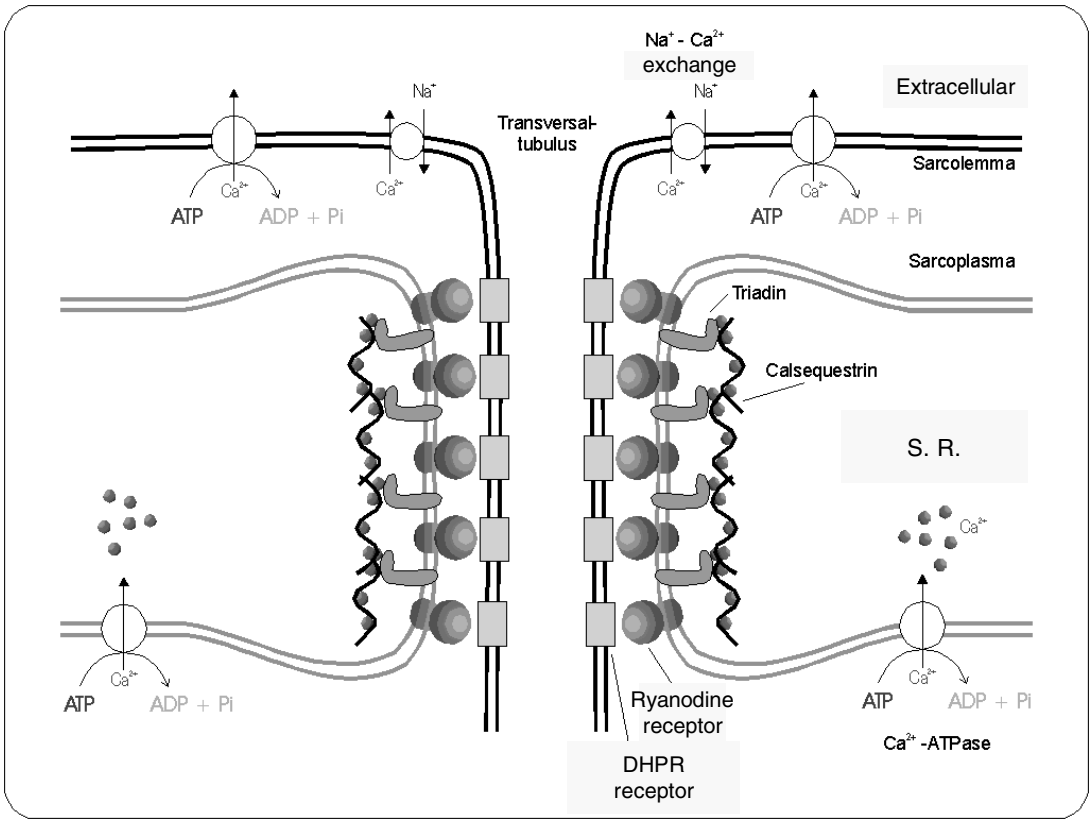


Figure 13: Components of the electromechanical coupling (excitation-contraction-coupling) in the skeletal muscle[59].

SR membranes possess different leak and channel states (opened or closed) of the FKBP12-Ry_1R complex. The channel-to-leak ratio depends on the kind of interaction between this complex and proteins.

Some experiments have been performed with bastadins in order to find out and understand the influence of those metabolites on SR Ca^{2+} transport[30, 56].

Bastadin 5 (**9**) alone significantly decreases the steady-state loading capacity of SR vesicules to 50 %, whereas in combination with ryanodine or ruthenium red, bastadin 5 (**9**) increases the capacity of the SR vesicules by 2-3-fold[56, 57]. Interestingly, FK506 alone enhances the Ca^{2+} loading capacity of SR vesicules by only 23 %, but with ryanodine, this activity is increased by 2 fold [56]. Bastadin 19 (**69**), the regioisomer of bastadin 5 (**9**), lacks this activity, but effectively diminishes the action of bastadin 5 (**9**)[30, 56].

In the presence of physiological concentrations of K^+ and Na^+, bastadins 5 (**9**), 7 (**57**) and 10 (**60**) interact with the FKBP12-Ry_1R channel complex enhancing the channel leak ratio[56, 57]. This leads to an increase in high affinity sites for ryanodine and enhances Ca^{2+}-induced Ca^{2+} release rates. With this result, it was proposed that the bastadins, through their modulatory action on the FKBP12-Ry_1R complex, convert ryanodine-insensitive leak states into ryanodine-sensitive channels.

The influence on the SR Ca^{2+} transport of bastadin 5 (**9**) and of a mixture of bastadins 5 (**9**), 7 (**57**), 10 (**60**), 18 (**68**) and 20 (**70**) was evaluated. Both are able to activate high-affinity binding of [^{3}H]ryanodine to SR membranes, but the activity of the mixture is 5 fold lower than that of the bastadin 5 [56]. Unlike bastadin 5 (**9**), the mixture releases Ca^{2+} from actively loaded vesicles, even when the extravesicular Ca^{2+} concentration is below 1 μM[30]. Further investigation showed that this property is attributed to bastadin 10 (**60**)[57], which also relieves inhibition caused by physiological Mg^{2+}. Both actions reported for bastadin 10 (**60**) are rapidly reversible[57].

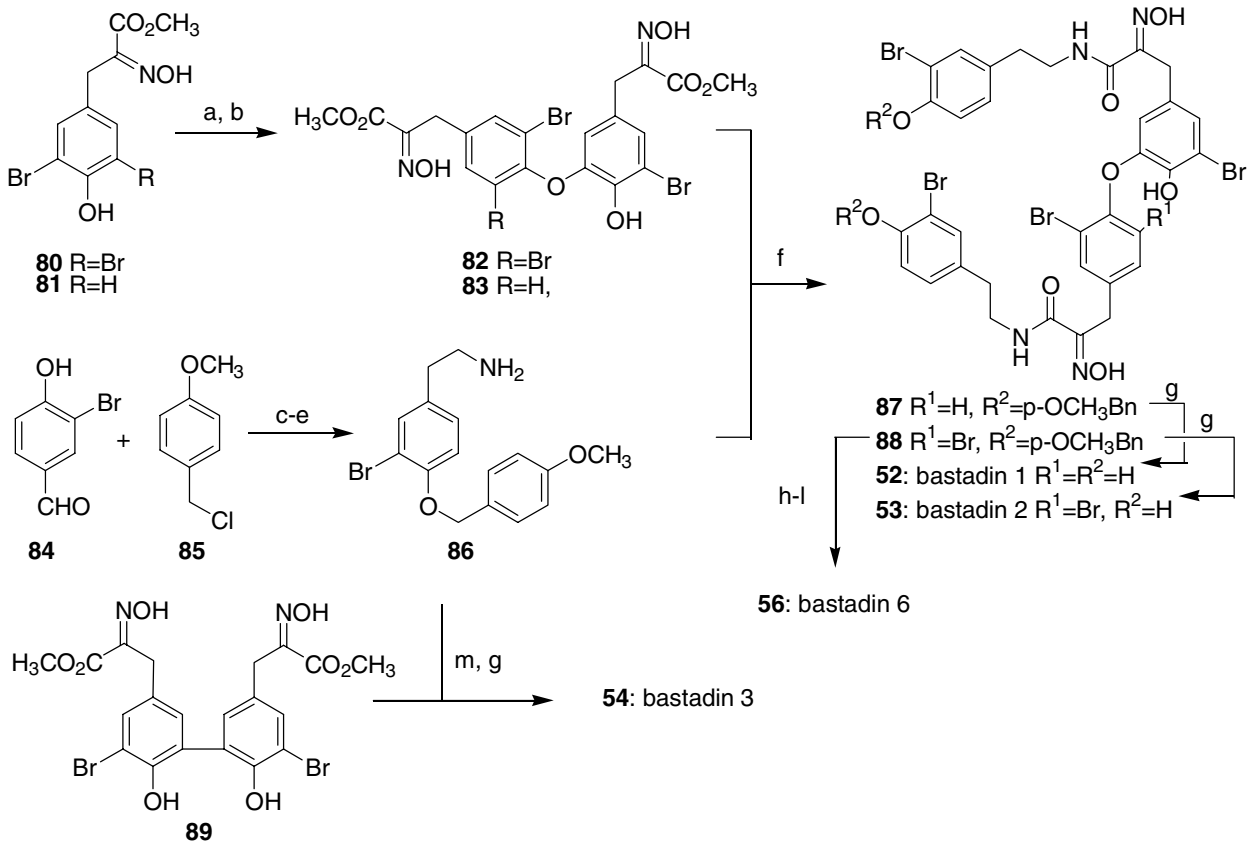
The actions of the bastadins are all antagonised by FK506 in a dose-dependent manner[57]. Bastadin 5 (**9**) alone, unlike FK506, does not dissociate the FKBP12-Ry_1R channel complex [30]. Although, in the presence of FK506, bastadin 5 (**9**) enhances the ability of FK506 to dissociate FKBP12 from SR membranes.

Since the regulatory actions of the bastadins are all eliminated by FK506, it has been suggested that the pharmacological actions of the bastadins are mediated by a novel modulation site which requires integrity of the FKBP12-Ry_1R channel complex[57].

2.3 Bastadin synthesis

The bastadins constitute a new class of biologically active secondary metabolites. Their modulatory action on the FKBP12-Ry_1R channel complex is unique. Therefore, they are attractive candidates for the investigation of the functional significance of immunophilin/ryanodine-sensitive Ca^{2+} channel interactions in skeletal muscle.

Three total syntheses of the bastadins have been reported [31]. Yamamura et al. reported the total syntheses of bastadins 1 (**52**), 2 (**53**), 3 (**54**)[31b] and 6 (**56**)[31a]. They used thallium trinitrate oxidation to construct the diaryl ether moieties and to achieve the macrocyclisation to bastadin 6 (**56**) (Scheme 3).

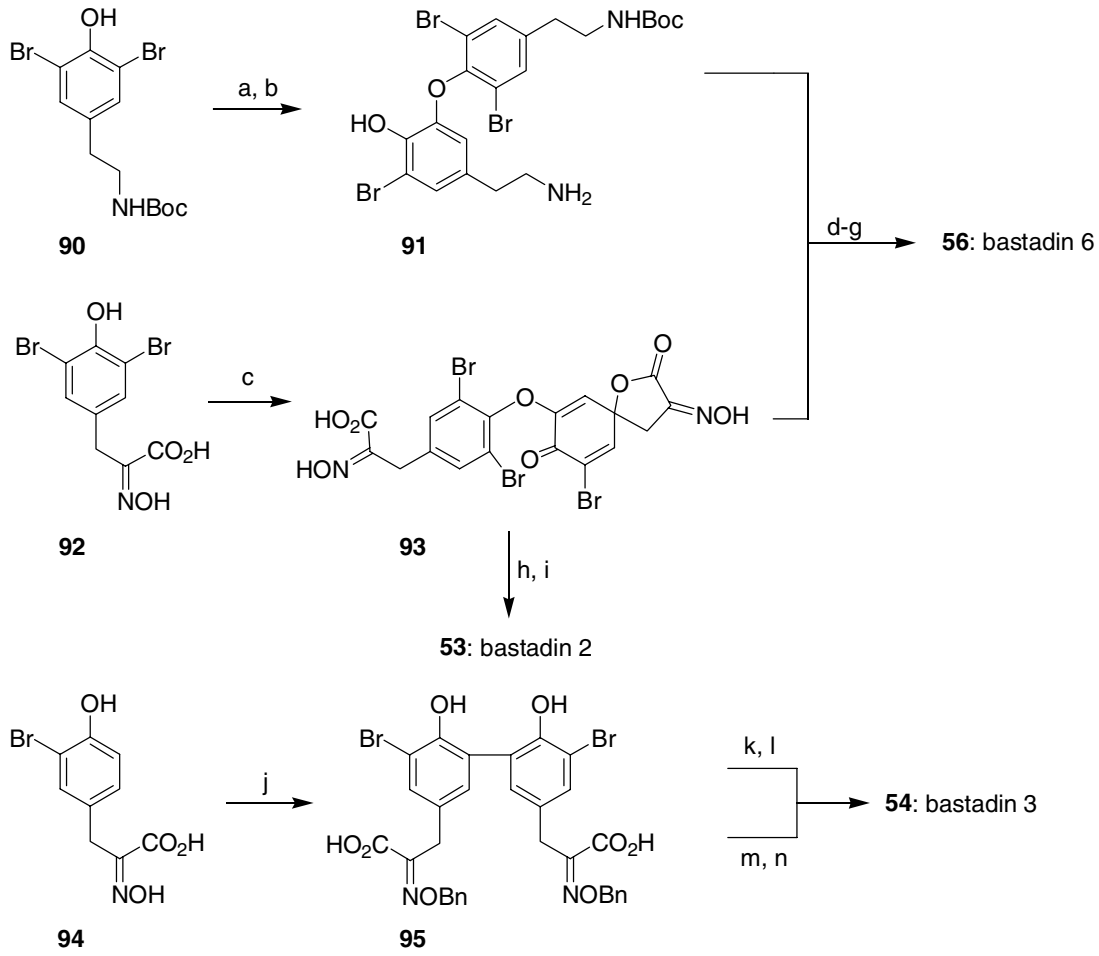


Scheme 3: Total synthesis of bastadins 1, 2, 3 and 6 by Yamamura et al. [31a,b]: a) $Tl(NO_3)_3$, CH_3OH, -35 °C, 20 h; b) Zn powder, THF, 0 °C, 35 min; c) K_2CO_3, DMF, r.t., 14 h, then CH_3NO_2, THF, K_2CO_3, r.t., 18 h; d) Ac_2O-pyridine, then $NaBH_4$, diglyme, 0 °C, 1 h; e) Zn powder, dioxane, AcOH, 0-5 °C, 40 min; f) 60 °C, 36-41 h; g) TFA, CH_2Cl_2, r.t., 20 min; h) BnCl, K_2CO_3, r.t., 2 days, then TFA, CH_2Cl_2, r.t.; i) Br_2, $CHCl_3$, r.t.; j) $Tl(NO_3)_3$, CH_3OH, 4 °C, 3.5 h[2]; k) Zn powder, AcOH, THF, r.t.; l) H_2/Pd, AcOH, dioxane; m) 60 °C, 4 days.

[2] This step gave two macrocyclic dienones in 13 % and 10 % yields, respectively. The former was reduced affording bastadin 6.

This synthetic route, however, gave very low yields[3], mainly because of the low diaryl ether regioselectivity achieved with the thallium trinitrate method[4].

Sih et al. reported an alternative route for the synthesis of bastadins 2, 3 and 6 [31c]. The required diaryl ethers were produced by enzymatic phenolic coupling using horseradish (HRP) and soybean (SOP) peroxidase (Scheme 4).



Scheme 4: Total synthesis of bastadins 2, 3 and 6 by Sih *et* al.[31c]: a) SPO, H_2O_2, pH 5, r.t., 46 %; b) $CrCl_2$, r.t., 98 %; c) SPO, H_2O_2, pH 4, r.t., 47 %; d) DCC, HOBt, r.t., 72 %, e) $NaHSO_3$, NaOH, r.t., 99 %, f) TFA, 95 %; g) DCC, HOBt, 0 °C-r.t., 64 %; h) $NaHSO_3$, NaOH, r.t., 98 %; i) 3-bromotyramine, DCC, HOBt, 0 °C-r.t., 68 %; j) HRP, H_2O_2, pH 4, r.t., 30 %; k) 3-bromotyramine, HOBt, EDCI, 0 °C, 57 %; l) BBr_3, 80 %; m) Pd/C, EtOH, 74 %; n) 3-bromotyramine, HOBt, EDCI, 0 °C, 73 %.

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[3] Up the diaryl ether conversion step, the bastadins 1, 2, 3 and 6 were obtained in an overall yields of 0.6 %, 9 %, 0.7 % and 1.1 %, respectively.

[4] The thallium trinitrate oxidation gave 3 coupling by-products in 5-10 % yield each[31a,b].

The overall yields of the bastadins[5] were higher than the reported by Yamamura et al.[31a, b], but the enzymatic diaryl ether formation is neither regioselective nor gives complete conversion. All the steps involving the diaryl ether coupling afforded at least 2 by-products in 5-10 % yields as well as starting material[31c].

Two other research groups reported alternative routes for the synthesis of the bastadins. Couladouros and Moutsos presented the synthesis of the bastadin 12 skeleton (**96**, figure 14) using the iodonium salt method for the diaryl ether coupling[31d, e]. The authors mentioned that the use of the triazene method developed by Nicolaou et al.[60] would not be appropriate because of the difficulties involved in the removal of the triazenes in the final reaction steps. With this methodology the authors achieved the stereosselective construction of the bastadin 12 skeleton (**96**) in 4 % overall yield, where the diaryl ether products were obtained in 68-78 % yield. Despite of these higher yields, it is important to note that the phenolic oxidation step using the iodonium salt methodology does not allow for the presence of sensitive groups in the molecule, since this reaction requires high temperatures[31d, e].

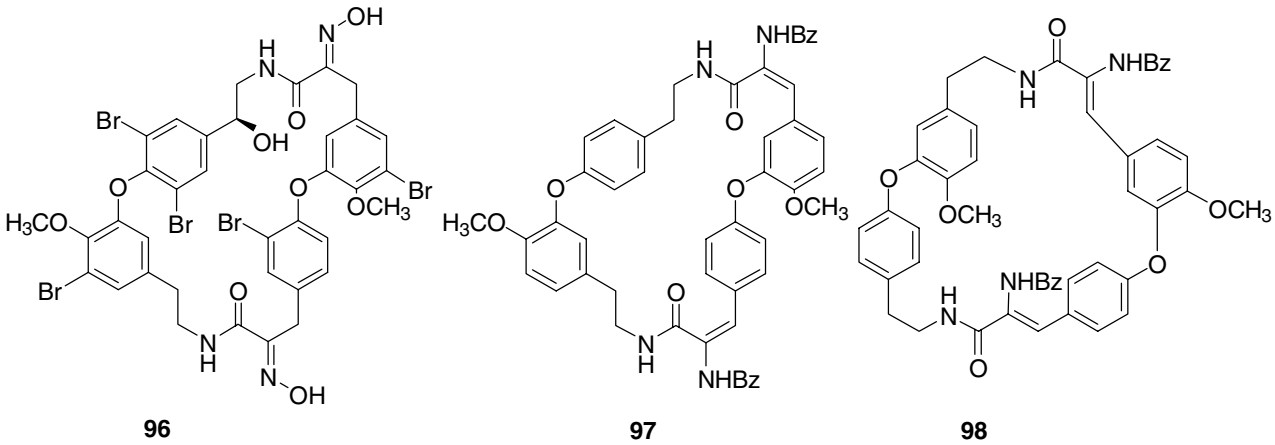

Figure 14: Bastadin 12 skeleton (**96**) and tyrosine cyclic peptides **97** and **98** by Couladouros and Moutsos[31d, e] and by Molinski et. al[31f], respectively.

Molinski et. al synthesised the tyrosine cyclic peptides **97** and **98** as a 1:1 mixture[31f]. The diaryl ethers were obtained via Ullmann coupling of commercially available

[5] Up to the diaryl ether coupling reaction step, the bastadins 2, 3 and 6 were obtained in 30 %, 13-16 % and 19 % yield, respectively.

benzaldehyde derivatives. The synthetic route did not show any macrocyclisation regioselectivity and the products were obtained in very low yields[6].

The efforts towards the synthesis of the bastadins has not yet satisfied the necessities required for a successful synthetic methodology. A synthetic route which is highly selective, gives products in higher yields, enables the presence of sensitive groups, and is flexible must be still found.

3 Ruthenium mediated synthesis of diaryl ethers

3.1 Inert sandwich complexes of aromatic amino acids and peptides

Compared to other research fields in chemistry, bioorganometallic chemistry has only recently emerged. Known difficulties in the handling of organometallic complexes including air-instability and toxicity, are the main reasons for the relatively late development of this particular field. Only when chemists and biologists started to focus their attention on the potential properties organometallic compounds, (*e. g.* specific binding of biologically interesting molecules such as amino acids and peptides) did interest in the development of this field start. Needless to say, this was supported by the discovery of metal stable complexes.

Studies of platinum compounds initiated a new era in cancer therapy. Other group VIII transition metals were also investigated, specifically those that induced filamentous growth in *Escherichia coli*, including some ruthenium complexes[34]. Presently several metal compounds are in clinical use[34, 61]. The platinum complexes cisplatin and carboplatin play a very important role in the treatment of cancer. The Pt(IV) complex *cis*, *trans*, *cis*-$[PtCl_2(OAc)_2(NH_3)(C_6H_{11}NH_2)]$ is in phase II clinical trials as an orally active anti-cancer agent against a wide range of cancer types and Pt-resistant cells[61]. The gold complexes myocrisin and auranofin are anthiarthritic drugs while some silver complexes are used as antimicrobial agents and in the

[6] The regioisomers were obtained in 30 % yield (referred only to the last step) as a 1:1 mixture from amide coupling reaction between the two diaryl ethers moieties: tyramine-tyramine and tyrosine-tyrosine.

therapy of burn wounds[61]. The iron complex, $Na_2[Fe(NO)(CN)_3]$ is a vasodilator and a good example for a drug which carries the reactive ligand to the target site [61]. In the diagnostic field, X-ray imaging is being replaced by NMR imaging as new imaging agents are developed and in clinical use including the stable, non-toxic DTPA [7] and DOTA[7] gadolinium complexes[61]. Complexes of the radioisotopes ^{111}In and especially ^{99m}Tc are used for imaging myocardial and cerebral perfusion and monitoring kidney function[61, 62].

Some complexes of Ru^{III} have been synthesised and their biological activities have been evaluated[34, 61, 63]. The interest in ruthenium complexes started with the concept "activation by reduction". Ruthenium complexes may be selectively toxic for tumour cells. The reduction potential of $Ru^{III,II}$ (~0.25 E°/V)[8] is biologically accessible when compared to other metals such as $Fe^{III,II}$ (0.77 E°/V)[8] [63]. The high metabolism of tumour cells requires rapid oxygen and glucose consumption, and therefore these cells have low pH and low O_2 concentrations. These conditions favour the reduction of Ru^{III} to Ru^{II} which is the active, toxic form. Examples of those complexes are *trans*-$[Ru(Im\ _2Cl_4]ImH]$ (Im=imidazol), which entered clinical trials[61, 63] and *cis*-$[Cl_2(NH_3)_4Ru]Cl_2$[63]. Both complexes preferentially bind at the N-7 of guanine and inhibit DNA replication, mutagenic activity and induction of the SOS repair modus. The first demonstrated activity against non-small cell lung, breast and renal cancers as well as clonogenic cells from freshly explanted human tumours[63].

Ruthenium sulfoxide complexes, in particular, NAMI (Na-*trans*-Cl_4(DMSO)(Im)Ru), have antimetastatic properties. NAMI is active against various tumours and dramatically reduces lung metastases with minimal toxic side-effects[34, 63].

Transition metals are also very interesting markers. They are selective and their IR and UV spectra have intensive characteristic absorptions in ranges which are not common for bioorganic molecules. Their signals are easily differentiated fro bioorganic molecules and the complexed substrates can be detected even in picomolar concentrations[64, 65].

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[7] DTPA: diethylenetriaminepentaacetate; DOTA: 1, 4, 7, 10-tetra (carboxy-methyl)-1, 4, 7, 10-tetraaza-cyclododecane)

[8] The reduction potential is referred to an acidic environment. The values can differ depending on the ligands.

Ruthenium red, $[(NH_3)_5Ru^{III}ORu^{IV}(NH_3)_4ORu^{III}(NH_3)_5]^{6+}$, is known as a cytological stain. Other biological properties have been attributed to ruthenium red like immunosupressant and anti-tumour activity. Ruthenium red can selectively bind to carboxylic or sulphate groups of acidic polysaccharides. Since tumour cells have a protective mucopolysaccharide cell wall, ruthenium red concentrates in these sites inhibiting tumour growth. Furthermore, this characteristic makes ruthenium red useful for specific tumour scanning agents [34, 63]. Ruthenium polypyridyl complexes (Rubipy and related ions) have been evaluated as visualising agents due to their fluorescent properties. Their photo-stability in solution and molecular weight enables studies of low molecular weight antigens [63].

The potential of rutheniu π-arene complexes studied in this thesis is still under evaluation[66]. Moriarty et al.[33a] reported the facile introduction of $[RuCp(NCCH_3)_3]PF_6$ in amino acids.[33a] Sheldrick et al. extended this methodology to the selective labelling of peptides [67]. Grotjahn et al. showed the specific π-arene binding of the $[RuCp]^+$-complexes to amino acids and peptides, even in the presence of S- and N-donors, and the stability of these complexes in reactions occurring in water[68]. These results, taken with the characteristics of the ruthenium radioisotopes [^{97}Ru ($\tau_{1/2}$=2.9 days), ^{103}Ru ($\tau_{1/2}$=39.4 days) and ^{106}Ru($\tau_{1/2}$=368 days)][9] undoubtedly make these complexes attractive biomarkers.

Although still very limited (probably due to their difficult purification), some applications of these complexes have been reported. Radiolabelled ruthenocenylalanine has been investigated as a pancreatic imaging agent [69], and $[RuCp^*]^+$-labelled estradiol has been used in the analysis and recognition of the active sites on hormone receptors[70].

The employment of $[RuCp]^+$-complexes has been more widely investigated in nucleophilic aromatic substitution for the synthesis of important biologically active compounds (see chapter 3.2).

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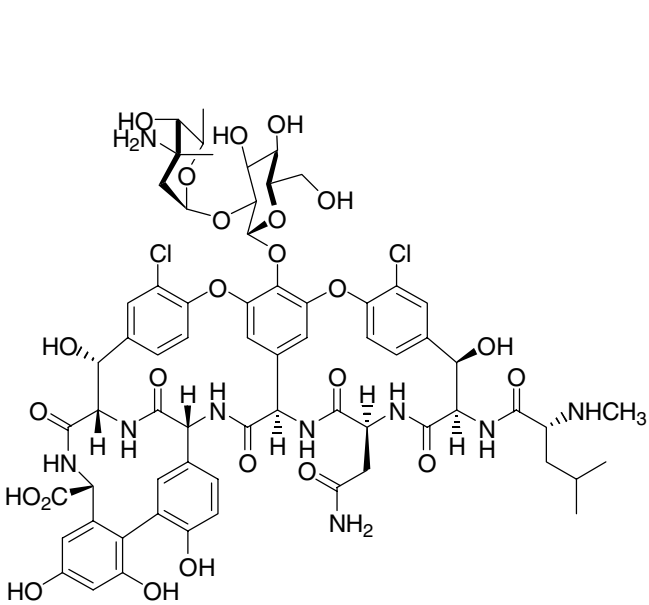
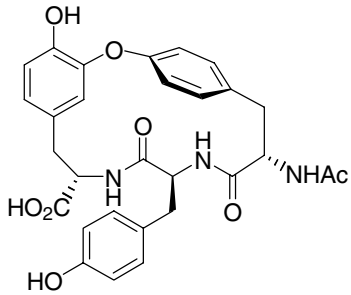
[9] Emission energy: ^{99}Ru = EC (orbital electron capture); ^{103}Ru = β^-; ^{106}Ru = β^-.

3.2 Application of [RuCp]$^+$-complexes in the synthesis of natural products

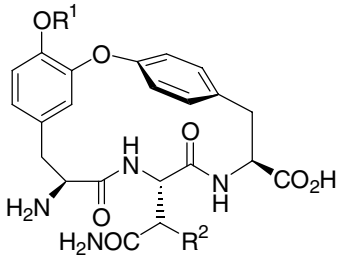
Diaryl ethers are structural components of many naturally occurring biologically active peptide-derived compounds, such as vancomycin (**99**), K-13 (**100**) and OF4949 I-IV (**101-104**) (Figure 15). Vancomycin (**99**) is a natural glycopeptide antibiotic isolated from the bacteria *Nocardia orientalis*. It is clinically used in the treatment of methicillin-resistant *Staphylococcus aureus* infections or in patients allergic to β-lactam antibiotics[71]. K-13 (**100**) and OF4949 I-IV (**101-104**) are isodityrosine-derived cyclic tripeptides. K-13 was isolated from the bacteria *Micromonospora halophytica* ssp. *exilisia* and is a natural potent, noncompetitive angiotensin I converting enzyme (ACE) inhibitor[72]. OF4949 I-IV were isolated fro the fungus *Penicillium rugulosum*, are potent inhibitors of aminopeptidase B and possess anti-tumour and immunopotentiating activities[73].



99: vancomycin



100: K-13



101: OF4949 I R^1=CH_3,R^2=OH
102: OF4949 II R^1=H, R^2=OH
103: OF4949 III R^1=CH_3, R^2=H
104: OF4949 IV R^1=R^2=H

Figure 15: Biologically important natural products bearing diaryl ether moieties: Vancomycin (**99**), K-13 (**100**) and OF4949 I-IV (**101-104**).

Construction of the diaryl ethers moieties from compounds possessing sensitive amino acid functionalities in their side chains is an important step in the synthesis of

this class of natural products. Despite the existence of many methods described for oxidative couplings, the synthesis of cyclic diaryl ether peptides is still limited.

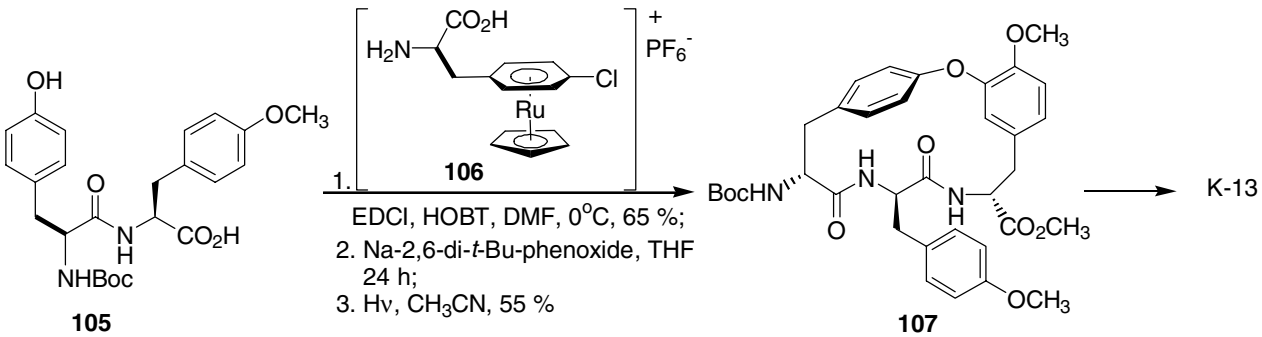
The most common procedure for the preparation of diaryl ethers is the classical Ullmann coupling. The disadvantages of this method, including the modified Ullmann couplings by Boger et al.[74a] and by Smith et al.[74b], are the harsh conditions required which are incompatible with the sensitive amino acid functionalities. Some research groups developed and continue developing new methods for the synthesis of diaryl ethers at lower temperatures. The thallium trinitrate (TTN) method, introduced by Yamamura et al.[75] and modified by Evans et al.[76], gives diaryl ether products at lo temperatures, but the thallium salt used is highly toxic and the reaction is not regioselective giving the desired product in low yields. Zhu reported the reaction of *o*-fluoro nitroarenes with phenolates at room temperature and its application to the synthesis of 14-, 16-, and 17-membered macrocycles found in natural products[77]. Nicolaou et al. employed a similar methodology with *o*-dihalogenated aromatic triazenes for the total synthesis of vancomycin [78]. The disadvantage of these methods is that both require the presence of an electron withdrawing group, (nitro and triazene for Zhu's and Nicolaou's procedures, respectively) whose removal needs at least two reaction steps. Evans et al.[79] and Chan et al.[80] reported the use of aryl boronic acids with cooper diacetate for the diaryl ether coupling. This reaction occurs at room temperature with high yields and is applicable to phenolates and aryl boronic acids with a wide variety of substituents.

The nucleophilic attack of phenolates at π–arene metal complexes of manganese, iron, and ruthenium is a very interesting and an efficient alternative for the synthesis of diaryl ethers[28, 81]. Iron and manganese π–arene complexes give diaryl ether products in high yields under mild reaction conditions [82]. However the reaction conditions necessary for the attachment of the $[FeCp]^+$- ($AlCl_3$, Al, high temperature)[83] and of the $Mn(CO)_3^+$-complexes[84], is too harsh for the amino acid functionalities[85]. Therefore, some groups promote the manganese or iron diaryl ether coupling before the amino acids are built up [82b, c]. The removal of the metal occurs very easily, especially of the manganese complex [33c, 82a].

The simple removal of the metal complex is an advantage, but not always desired, like in the field of peptoid metal labelling (see chapter 3.1). $[RuCp]^+$- complexed

chloroarenes are easily formed under reaction conditions compatible with the amino acid functionalities. Moriarty et al. [33a], Sheldrick et al.[67] and Grotjahn et al. [68] reported the specific π-arene binding of the $[RuCp]^+$-complexes to amino acids and peptides in the presence of S- and N-donors as well as the stability of these complexes in water[68]. The high yields obtained from the nucleophilic attack of phenolates at $[RuCp]^+$-complexed chloroarenes under very mild reaction conditions, first reported by Nesmeyanov et al. [32a] and Segal[32b], was later used for the synthesis of natural products[33, 85b, 86], including formal[86a, e] and total[86g] synthesis of K-13[86a, g] and OF4949 III [86e, g] (Scheme 5), and the synthesis of ring systems of ristocetin A[33d, 86c, h, i, l] and of teicoplanin[86d, k].

The purification of the charged $[RuCp]^+$-complexes is very difficult and, therefore, these complexes are only used in the last reaction step (Scheme 5). After conversion to the metal-labelled diaryl ether, the crude product is directly subjected to photochemical demetallation followed by purification of the non-complexed product.



Scheme 5: Total synthesis of K-13[86g]. After ruthenium mediated macrocyclisation, the product is directly subjected to photochemical demetalation.

Compared to other methodologies, the use of ruthenium arene chemistry for the synthesis of natural products exhibiting diaryl ether moieties comprise som advantages, such as high yields obtained under mild reaction conditions, as well as their ease of handling due to their stability. The $[RuCp]^+$-complexed intermediates, obtained during the synthesis of a natural product, could be used as labelled amino acids and peptides. However, these advantages have yet to be exploited. The limited use of the $[RuCp]^+$-arene complexes is probably a consequence of the lack of efficient protocols for their purification.

4 Building blocks of the bastarane skeleton

Almost all bastadins are macrocyclic and consist of two tyrosine and two tyramine units linked via diaryl ether and peptide bonds (Figure 16). Presently, three synthetic routes towards the bastadins have been reported [31] employing I) low yielding phenol oxidation[31a-c]; II) iodonium salt method[31d,e] and III) Ullmann coupling [31f]. Among the isolated bastadins, bastadin 5 (**9**) is of especial importance because of its biological and pharmacological activities. Bastadin 5 (**9**) inhibits the Ca^{2+} uptake into the sarcoplasmatic reticulum, which is antagonised by the immunosuppressant natural product FK506[30, 87].

The application of ruthenium arene chemistry promotes diaryl ether coupling in moderate to high yields under mild reaction conditions and even enables the presence of sensitive groups.

These advantages, together with our interest in metal-labelled peptoids, were the reasons to select ruthenium arene chemistry for skeleton synthesis of the pharmacologically interesting bastadin 5 (**9**).

4.1 Retrosynthetic analysis of the 'ABB'A'-bastarane macrocycle

A detailed retrosynthetic analysis of the bastarane macrocycle is presented in figure 16.

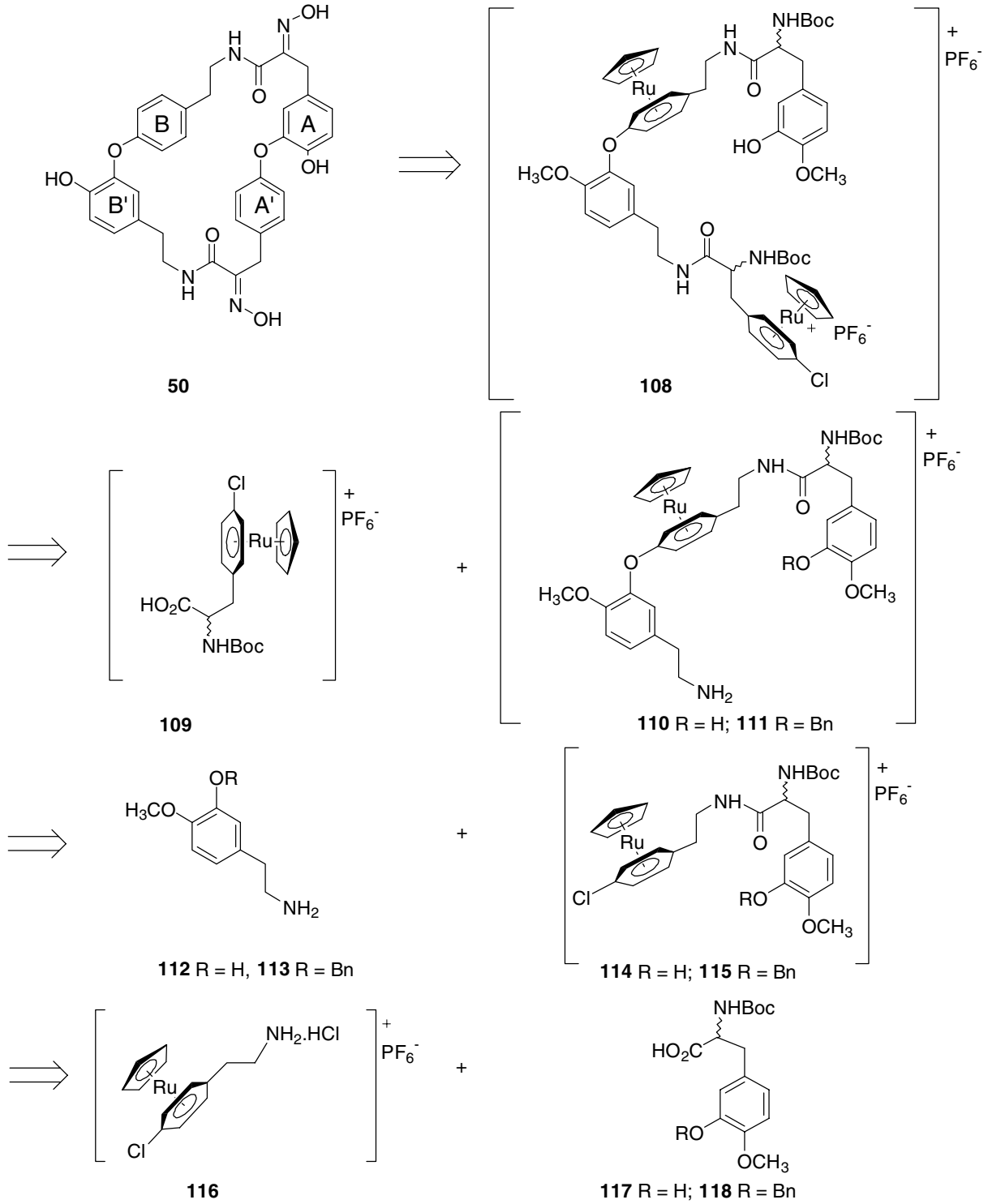


Figure 16: Retrosynthetic analysis of the bastarane skeleton. The two tyrosine and tyramine units of the macrocycle have been labelled (AA') and (BB') respectively in order to facilitate this interpretation.

The AA'BB' units represent the four tyrosine/tyramine building blocks of the bastarane skeleton (Figure 16). Considering the required protection of sensitive functional groups present in those ABA'B'-units during the macrocycle synthesis, the retrosynthesis presented in figure 16 saves some protection-deprotection steps compared to other retrosynthetic possibilities.

The first step is the amide coupling reaction between the $[RuCp]^{+}$-complexed 2-(4-chlorophenyl)ethylamine (**116**) B and the DOPA derivative (A) **118**, where the amino group and the free phenols of the amino acid have been protected. The next step is the ruthenium-promoted diaryl ether coupling between AB (**115**) and the dopamine derivative (B') **112**. To assure that the desired phenol group couples with the $[RuCp]^{+}$-complexed chlorobenzene derivative, the protection of all other present phenols in **118** was promoted. For the additional *O*Bn protection one more reaction step was necessary.

Another group that could compete in this reaction is the free carboxylic acid, which is never present in this retrosynthetic pathway. Here, all carboxylic acid moieties have reacted with the respective amines before the diaryl ether coupling takes place. Analysing the possibility of first promoting the amide coupling between the B'A'-units, with a previously phenol-protected B'-unit (**113**), the next step would involve the introduction of the DOPA derivative (A) **117**. This strategy would require extra protection of the free carboxylic acid of the DOPA derivative **117** requiring two extra steps (protection and deprotection) and consequently lower overall yields.

The approach, starting with the diaryl ether coupling between the BB'-units would require two different amine protections. This strategy would involve the same number of protection steps as the one that started with the construction of the AB-unit. Investigations comparing amine protection versus phenol protection showed that the latter was the most convenient. The benzyl protecting group remains intact under the reaction conditions involved in this strategy and can be easily removed under mild reductive conditions in high to quantitative yields. The conditions required for the removal of the benzyl protecting group does not affect the other functional groups present in the target molecule.

The introduction of the fourth tyrosine unit again should be an amide coupling between the free amine of ABB'-unit **111** and the $[RuCp]^+$-complexed cholorophenylalanine derivative (A') **109**. The macrocycle is finally achieved by intramolecular ruthenium (II) promoted diarylether coupling, after deprotection of the benzylated phenol. Demetalation and oxidation of the amines should afford the bastarane skeleton **50**.

4.2 Synthesis of all four tyrosine/tyramine bastarane subunits

Following the chosen retrosynthetic route (Figure 16), the synthesis of the intermediates **109**, **112** , **116-118** could be envisaged (Figure 17).

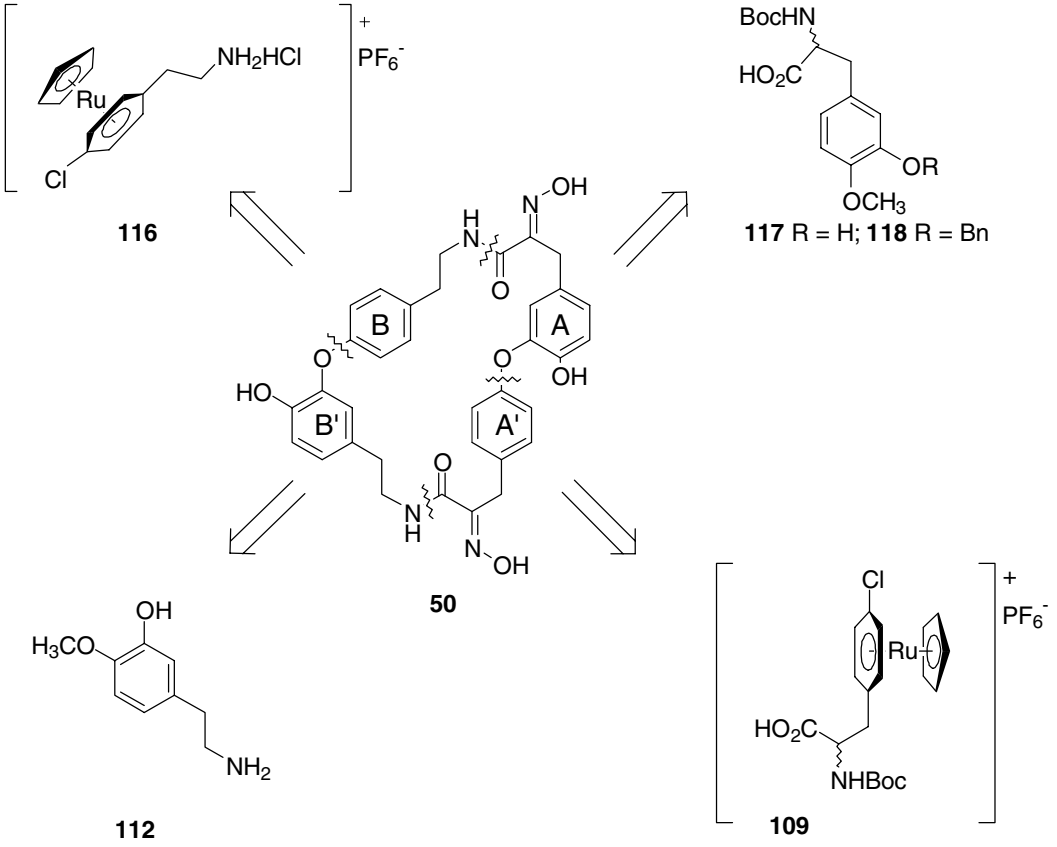
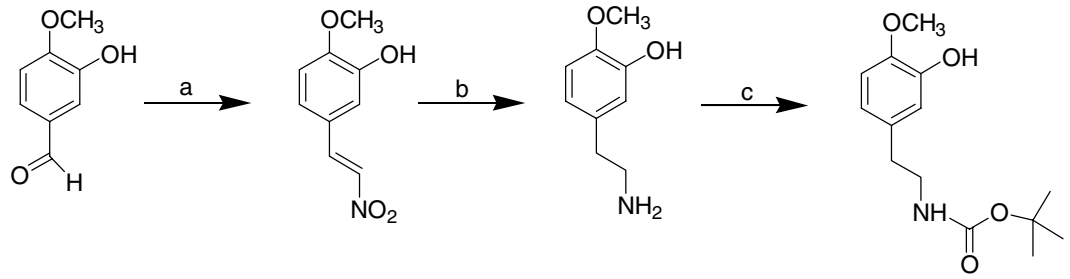


Figure 17: Bastarane macrocycle split into its four tyrosine/tyramine units.

4.2.1. Synthesis of the B' unit: *N*-Boc- (119) and 2-(3-hydroxy-4-methoxyphenyl)ethylamine (112)[88]

2-(3-hydroxy-4-methoxyphenyl)ethylamine (**112**) was synthesised with an overall yield of 60 %. The synthesis started from the aldol condensation between commercially available isovaniline (**120**) and nitromethane under basic conditions, followed by $LiAlH_4$ reduction of the obtained β-nitrostyrene **121**. The already selectively protected dopamine[88] **112** was then converted into its *tert*-butoxycarbonyl (Boc) derivative **119** under standard conditions (Scheme 6). Amine protection with Boc_2O was chosen because this group should remain intact under all reaction conditions and its removal should occur quantitatively by treatment with 4N HCl in CH_3OH at room temperature.



Scheme 6: Synthesis of B': a) $CH_3NH_2{\cdot}HCl$, Na_2CO_3, CH_3OH, CH_3NO_2, dark, r.t., 50 h, 88 %; b) $LiAlH_4$, Et_2O, Soxhlet extraction, 18 h, 68 %; c) Et_3N, CH_2Cl_2-CH_3OH (1:1), Boc_2O, r.t., 3 h, 93 %.

Following the retrosynthesis shown in figure 16, the dopamine derivative (**112**) should couple in the third reaction step with the carboxylic acid moiety of the $[RuCp]^+$-complex **109**, forming the tetrapeptide ABB'A'. This free amine derivative **112** has two nucleophilic sites, the free phenol and the amine moiety, which can compete in the second reaction step for the nucleophilic aromatic substitution (S_NAr).

The behaviour of this ambidental nucleophile will be discussed in detail in chapter 5.2 when diaryl ether couplings involving both the free **112** and the protected **119** dopamine derivatives are reported.

4.2.2. Synthesis of the A unit: *N*-Boc-D,L-(3-hydroxy-4-methoxy)-phenylalanine (117)[89], its methyl ester (128) and *N*-Boc-D,L-(3-benzyloxy-4-methoxy)-phenylalanine (118)

The synthesis of the bastarane macrocycle does not require the asymmetric preparation of the DOPA derivative, since all stereocenters present in the building blocks will be oxidised to oximes in later steps.

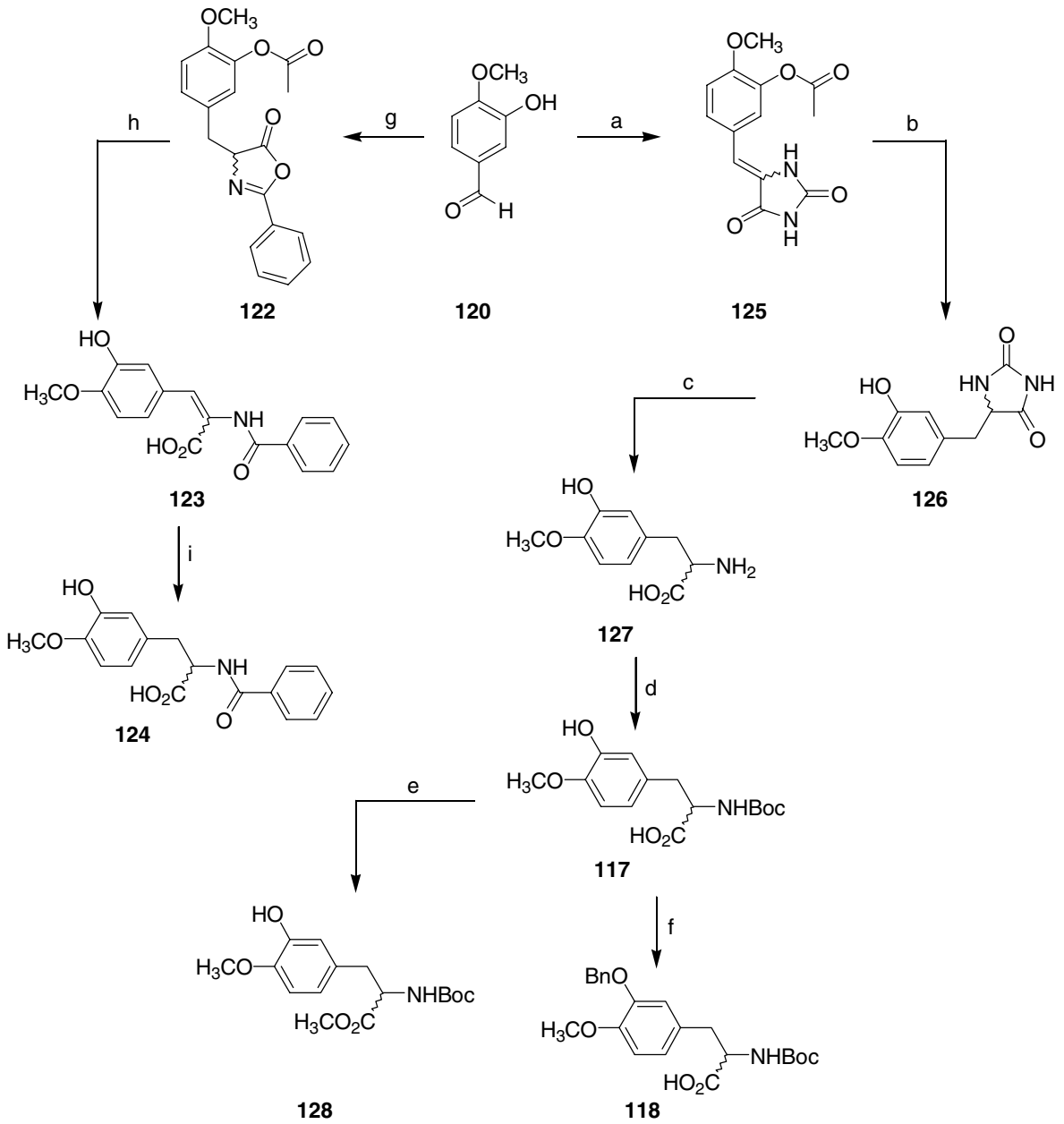
Starting from isovaniline (**120**), the racemic DOPA derivative **117** can be prepared in two ways[89] by aldol condensation with either commercially available hippuric acid or hydantoin. Comparing both pathways, the use of hippuric acid afforded product **124** with an overall yield of 14 % whereas hydantoin led to the *N*-Boc protected product **117** with an overall yield of 31 %, although this procedure requ ires one additional step (Scheme 7).

After an aldol condensation of **120** with hydantoin, the product **125** was treated with NaHg under basic conditions to give the reduction product **126**. Hydrolysis with $Ba(OH)_2 \cdot 8\ H_2O$ under reflux and Boc_2O protection utilising Jung and Lazarova's procedure[90] afforded the desired *N*-Boc protected amino acid **117**.

The conversion of **117** to its methyl ester analogue **128** was achieved according to Hassner and Alexanian[91]. The intention for the preparation of this compound was its use in a model reaction involving ruthenium mediated S_NAr.

On the basis of the synthetic route (Figure 16) outlined above, the free phenol of the racemic (3-hydroxy-4-methoxy)phenylalanine moiety **117** present in the dipeptoid AB (**114**) could compete as a potential nucleophile with the phenol from 2-(3-hydroxy-4-methoxyphenyl)ethylamine (**112**) in the diaryl ether coupling step. To verify this proposition, the synthesis of both AB dipeptoids with **115** and without **114** further phenol protection was necessary and, therefore, the preparation of the precursor **118**. Selective benzylation of the phenol of **117** (Scheme 7) was acchived utilising benzylchloride following Grewe and Fischer's procedure[92]. The reaction conditions allowed the selective protection of the phenol without conjunctive formation of its benzylester analogue. This protecting group was chosen because of its stability under the reaction conditions used in this work and the simple cleavage under mild

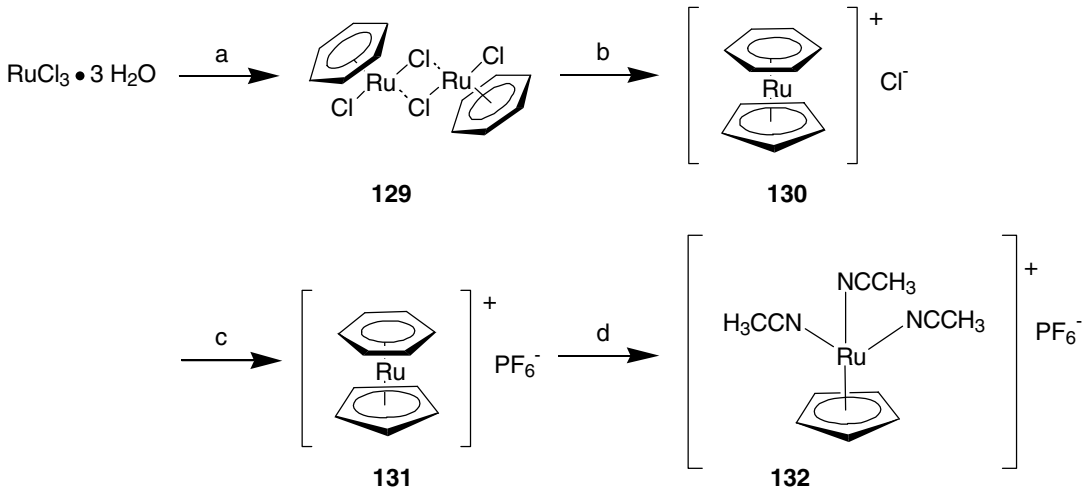
conditions using Pd-C, 1,4-cyclohexadiene. These conditions neither involve concomitant removal of the methyl protecting groups of the other phenols nor affect the sensitive functions of the target molecule. Moreover, the benzyl group resembles the side chains of polystyrene polymers as putative supports for solid phase syntheses of ruthenium-labelled peptoids.



Scheme 7: Synthesis of the A Unit: a) hydantoin, NaOAc, Ac_2O, reflux, 30 min, 84 %; b) H_2O, NaOH (10 %), NaHg, r.t., 90 %; c) $Ba(OH)_2$ 8 H_2O, H_2O, reflux, 63 %, d) Et_3N, Boc_2O, CH_3OH-H_2O (1:1), 0 °C (30 min), r.t., 48 h, 66 %; e) EDCI, CH_2Cl_2, CH_3OH, 4-pyrrolidine-pyridine, r.t., 96 h, 77 %; f) CH_3OH, NaOH, BnCl, reflux, 15 h, 65 %; g) hippuric acid, NaOAc, Ac_2O, reflux, 30 min, 38 %; h) aq. NaOH (2 %), reflux, 58 %; i) H_2O, NaHg, r.t., 63%.

4.2.3. Synthesis of tris-(acetonitrile)(η^5-cyclopentadienyl)ruthenium hexa-fluorophosphate (132)[93]

[RuCpBz]Cl (**129**) was prepared from $RuCl_3 \cdot 3\ H_2O$ via the method described by Zelonka and Baird[93a, b]. After anion exchange using NH_4PF_6[93c], the complex **131** was subjected to irradiation (8 hours) in acetonitrile with a mercury medium pressure lamp to give $[RuCp(NCCH_3)_3]^+PF_6^-$ (**132**)[93c] (Scheme 8). This complex is the starting material of all $[RuCp]^+$-complexed benzene derivatives synthesised in this thesis. The acetonitrile ligands are very labile and, therefore, can easily be exchanged by the corresponding η^6-arene ligand.

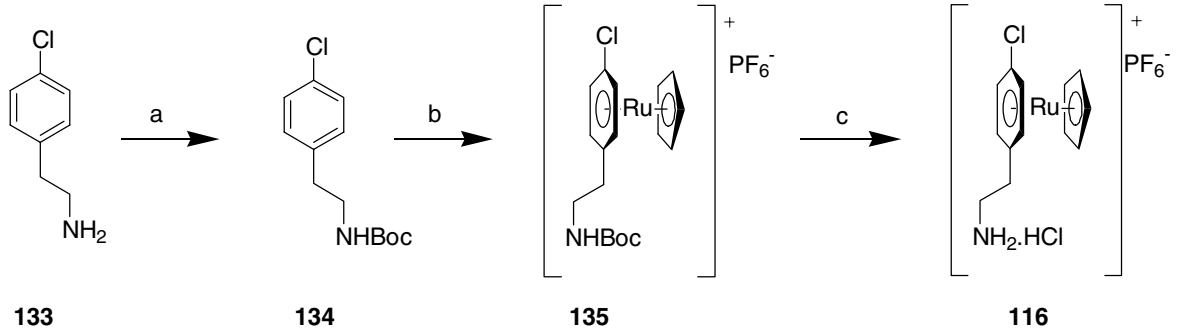


Scheme 8: Synthesis of $[RuCp(NCCH_3)_3]PF_6$ (**132**) a) 1,3-cyclohexadiene, EtOH:H_2O (9:1), reflux, 3 h, 95 %; b) TlCp, CH_3CN, r.t. 1 h, 70 %; c) NH_4PF_6, H_2O, r.t., 1 h, 68 %; d) Hg-medium pressure lamp (150 W), CH_3CN, r.t., 8 h, quant.

4.2.4. Synthesis of the $[RuCp]^+$-complexes: A' (109)[85b] and B (116)[94] units

After treatment of commercially available 2-(4-chlorophenyl)ethylamine (**133**) with $[RuCp(NCCH_3)_3]PF_6$ (**132**) under reflux[93c] a mixture of unidentified products was obtained. It is likely that the free amine competes with the benzene for the complexation with ruthenium (II). To prevent this undesired reaction, 2-(4-chlorophenyl)ethylamine (**133**) was Boc-protected under standard conditions (Scheme 9).

Complexations of arenes possessing a free amine functionality have already been reported[67a, 68a, 86g, 86j]. Rich and Janetka showed that the ruthenium complex of an amino acid bearing a free amino group can be formed selectively at the aromatic ring[86g]. Matassa et al. repeated this procedure and arrived at the same result[86j].

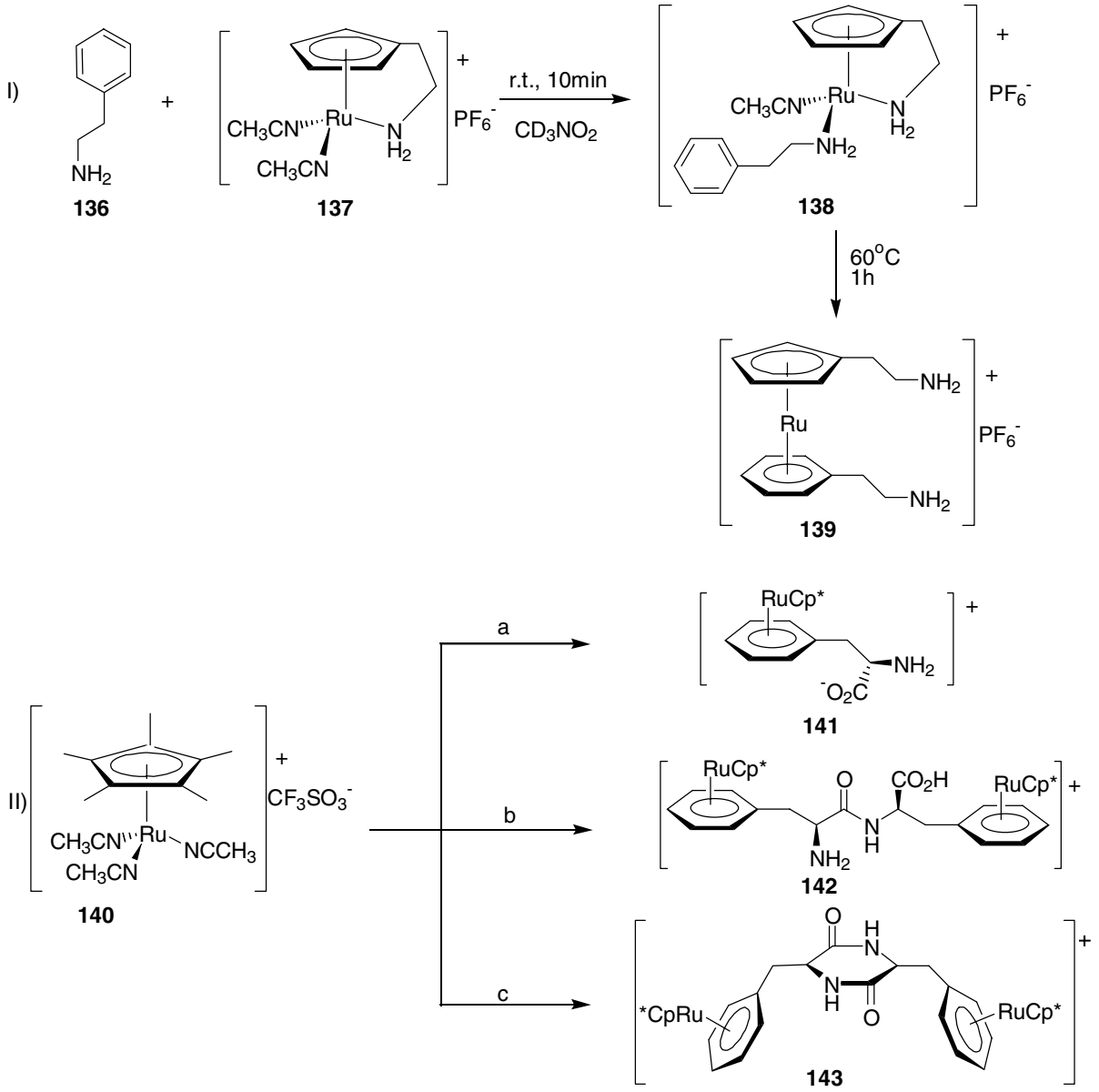


Scheme 9: Synthesis of the B unit (**116**): a) Boc_2O, CH_2Cl_2, r.t., 4 h, 98 %; b) $[RuCp(NCCH_3)_3]PF_6$ complex, 1,2-dichloroethane, reflux, 4 h, 65 %; c) 4N HCl in CH_3OH, r.t., 3 h, quant.

Grotjahn et al. reported in a series of experiments using free amine and sulphur compounds that η^1-*N* or η^1-*S* coordination is kinetically favoured but that arene coordination is thermodynamically preferred (Scheme 10-I) [68a]. Sheldrick et al. investigated the synthesis of peptides labelled with (η^5-Cp*)Ru(II) (Scheme 10-II)[67a]. The authors quantitatively obtained η^1-*N*, *O*-coordinated complex at low temperatures and, at reflux, the corresponding η^6-peptide complex. However, they observed that the reaction mixture always contained about 10 % of the η^1-*N*, *O*-coordinated complex[67a]. The reaction of the dipeptoids **142** and **143** could be performed at room temperature (Scheme 10-II), whereas stronger conditions were required for η^6-L-HPheOH **141** formation (12 hours, reflux). This reflects the fact that the competitive formation of a η^1-*N*, *O*-coordinated five-membered chelate ring as for L-phenylalanine will be less favourable for HPhe-PheOH and impossible for cyclo(-Phe-Phe-)[67a].

Despite of all this available information about free amines during rutheniu complexation, in this work it was found that it is more convenient and more effective to prepare the $[RuCp]^+$-complexed 2-(4-chlorophenyl)ethylamine via its *N*-Boc analogue (**145**).

D,L-4-Chlorophenylalanine (**144**) was converted to its Boc analogue (**145**)[90]. Its methylester derivative **146**[85b] was prepared for a model reaction[91].

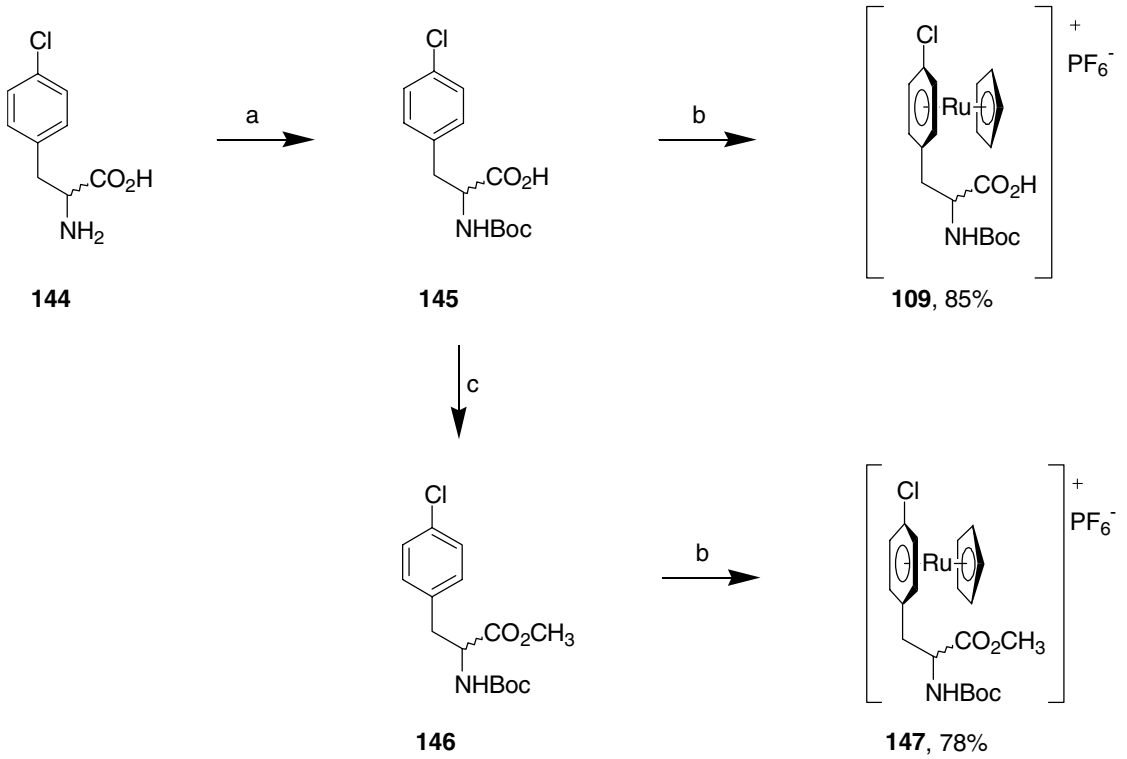


Scheme 10-I) η^1-N coordination is kinetically favoured, but the arene coordination is thermodynamically preferred[68a]; 10-II) a) Phenylalanine, CH_3OH, 12 h, reflux; b) HPhe-PheOH, CH_3OH, r.t; b) cyclo(-Phe-Phe-); CH_3OH; r.t.

Complexation of the *N*-Boc protected DL-4-chlorophenylalanine (**145**), its methylester analogue **146** (Scheme 11) and 2-(4-chlorophenyl)ethylamine (**134**) (Scheme 9) were performed according to Gill and Mann[93c]. Products were isolated from the reaction mixture by precipitation upon addition of diethyl ether and were analysed without further purification. The success of those reactions could be confirmed by analysis of their ^{1}H and ^{13}C NMR spectra, where all aromatic protons and carbons were shifted

to higher fields compared to the non-complexed analogues. The ^{1}H NMR spectra showed upfield shifts ($\Delta\delta$) of 0.5 to 0.9 ppm and the ^{13}C $\Delta\delta$ of 30-45 ppm.

Removal of the Boc protecting group from $[RuCp]^{+}$-complex (**135**) with 4N HCl in CH_3OH quantitatively gave {1-(2-amino)ethyl-4-chloro-η^6-benzene}(η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**116**) (Scheme 9).



Scheme 11: Synthesis of A' unit: a) Boc_2O, Et_3N, CH_3OH-H_2O (1:1), 0 °C (30 min), r.t. 42 h, 64 %; b) $[RuCp(NCCH_3)_3]^{+}PF_6^{-}$ complex, 1,2-dichloroethane, reflux, 4 h; c) EDCI, CH_2Cl_2, CH_3OH, 4-pyrrolidine-pyridine, r.t., 96 h, 85 %.

The ruthenium (II) complexation of the chloroarenes **134**, **145** and **146** gave moderate to high yields, but their purification was a challenge.

Chromatography of charged ruthenium sandwich complexes has rarely been described[95]. Even simple reaction controls by thin layer chromatography (TLC) are not reported. The usual work-up of $[RuCp]^{+}$-complexes combines filtration on alumina, followed by precipitation upon addition of Et_2O. Of course, mixtures of different sandwich complexes can not be separated by this procedure. Instead, separation and purification problems are circumvented by photochemical demetalation immediately following the diaryl ether coupling. As a consequence, the

analytical and preparative separation of the charged sandwich complexes *from each other* is of fundamental importance for the success of [RuCp] $^{+}$-complexes in both organic synthesis and bioinorganic chemistry[68b].

On silica gel and on cellulose the ruthenium complexes **109**, **116**, **135** and **147** did not move even after using many eluents with different polarities. On several common stationary phases (DIOL, alumina, LH-20, RP-8 and RP-18) the complexes migrated from the origin, but with identical R_f values. In this preliminary analysis, the only phase which showed promising results for the purification and separation of these charged complexes was aminopropyl-functionalised silica. The next challenge was the elaboration of an efficient methodology for the preparative separation of those complexes.

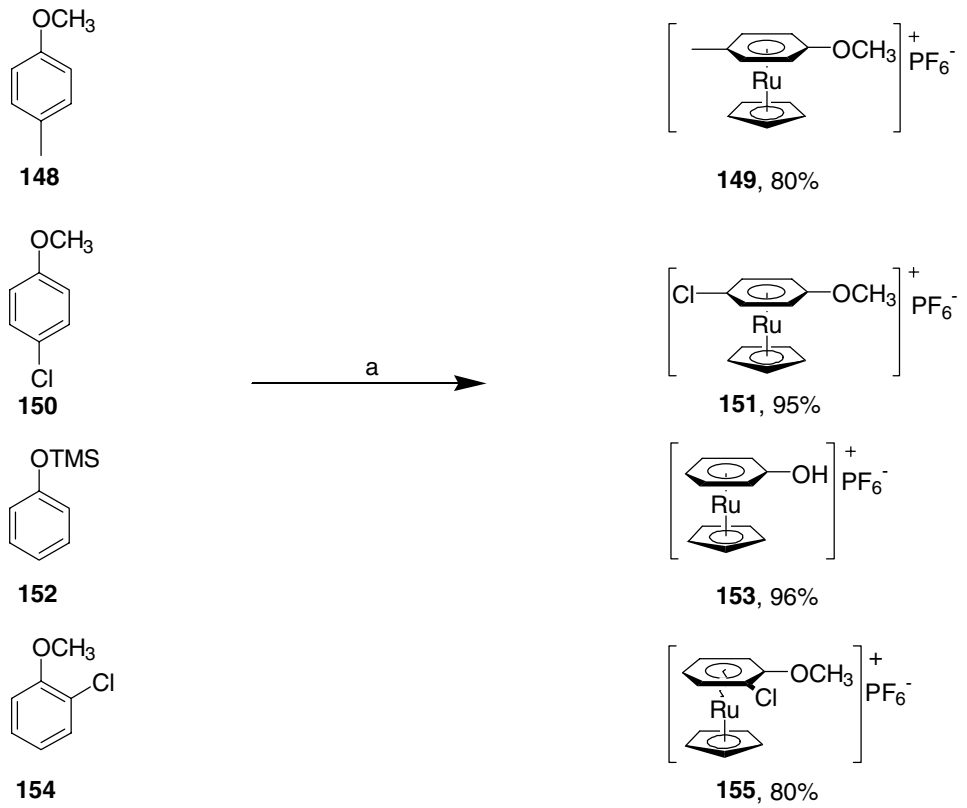
4.3 Chromatography of charged [RuCp]$^{+}$-sandwich complexes on aminopropyl silica

Despite more than 20 papers on the application of [(η^5-Cp)Ru(η^6-arene)]$^{+}$-complexes to the synthesis of peptide-like diaryl ethers[33, 86], no general protocol yet exists for the purification of charged ruthenium sandwich complexes by chromatography. Their limited use in organic synthesis may be the result of their difficult purification and, if desired, demetalation.

Model compounds have been prepared in order to investigate this problem and find a reproducible method for the separation and purification of those sandwich complexes (Scheme 12).

4.3.1. Synthesis of model complexes for the chromatographic study

The model compounds **149**, **151**[96], **153**[97a] and **155** were obtained by treatment of their respective commercially available arene derivatives **148**, **150**, **152** and **154** with [RuCp($NCCH_3$)$_3$]PF_6 in dichloroethane under reflux[93c] (Scheme 12).



Scheme 12: Synthesis of model ruthenium sandwich complexes. a) $[RuCp(NCCH_3)_3]PF_6$, 1,2-dichloroethane, reflux, 4 h.

The phenol complex **153**[97a] was obtained fro *O*-trimethylsilylphenol and did not form a zwitterion[97b], as concluded from FAB^+, FAB^-MS and elemental analyses.

The $[RuCp]^+$-complexed diaryl ethers **156** and **157** (Figure 18) represent the western and eastern halves of the bastarane skeleton (**50**). Figure 19 (chapter 4.3.2) completes the series of sandwich complexes, sorted by increasing polarity, which has been synthesised and subjected to a detailed chromatographic study [94].

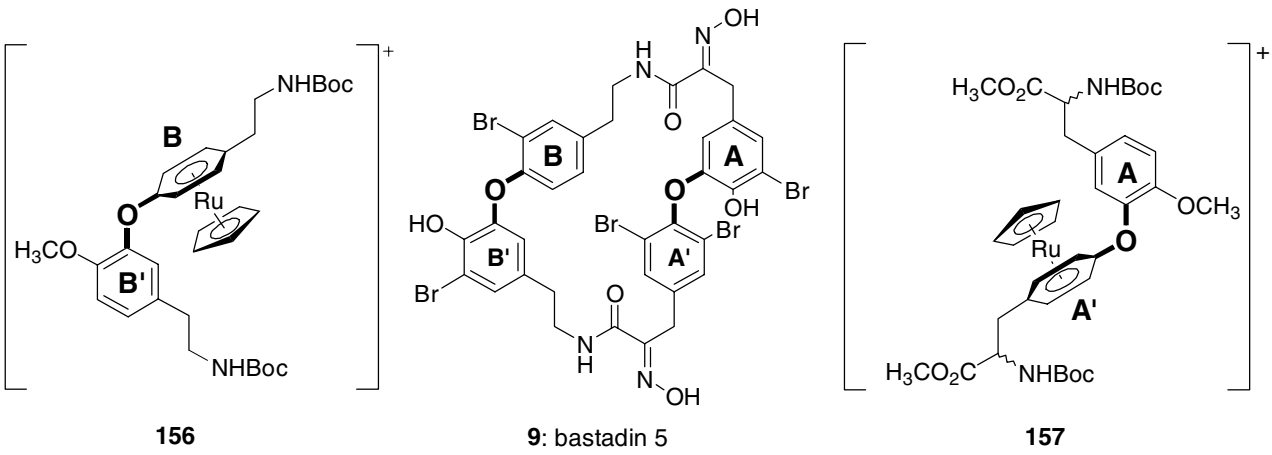
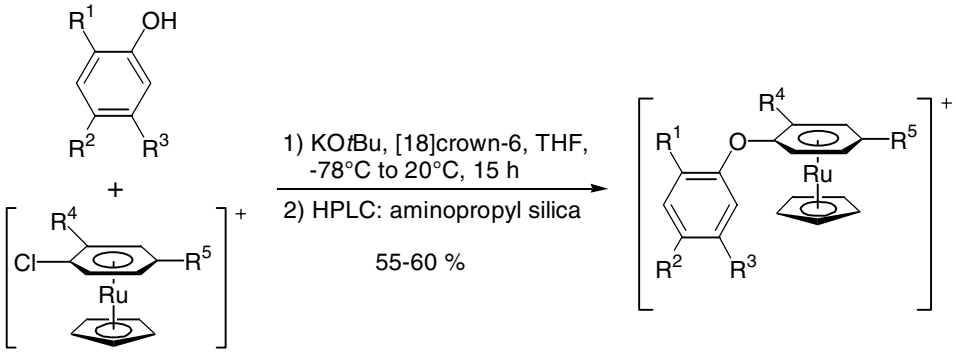


Figure 18: Bastadin 5 (**9**) from the marine sponge *Ianthella basta* and the ruthenium-complexes **156** and **157** (anion hexafluorophosphate) representing the western and eastern partial structures.

The synthesis of the $[RuCp]^+$-complexed diaryl ethers **156-160** (Figures 18 and 19, chapter 4.3.2) is outlined in scheme 13. The appropriate phenolate generated using KO*t*Bu/[18]crown-6 in THF, was added to the $[RuCp]^+$-complexed chloroarenes **135**, **147**, **151** and **155** (Scheme 13 and Figure 19)[94].

The commonly used bases for this coupling reaction, Na-2,6-di- *tert*-butylphenol and NaH[86], did not give complete diaryl ether formation (TLC analysis). KO *t*Bu in the presence of [18]crown-6 proved to be much more efficient.



Scheme 13: Outline of the synthesis of the $[RuCp]^+$-complexed diaryl ethers **156-160** via S_NAr reaction (Figure 19), followed by chromatographic purification on aminopropyl silica.

4.3.2. Separation of the ruthenium sandwich complexes by HPLC

The idea to investigate aminopropyl-functionalised silica as a stationary phase for a true chromatography of the inert, positively charged ruthenium sandwich complexes resulted from the consideration that ionic interactions should be minimal on basic stationary phases that cannot be deprotonated. It was expected that the free amino groups would not attack the $[RuCp]^+$-complexes, because the free amine **116** was observed to be stable (Scheme 9, chapter 4.2.4).

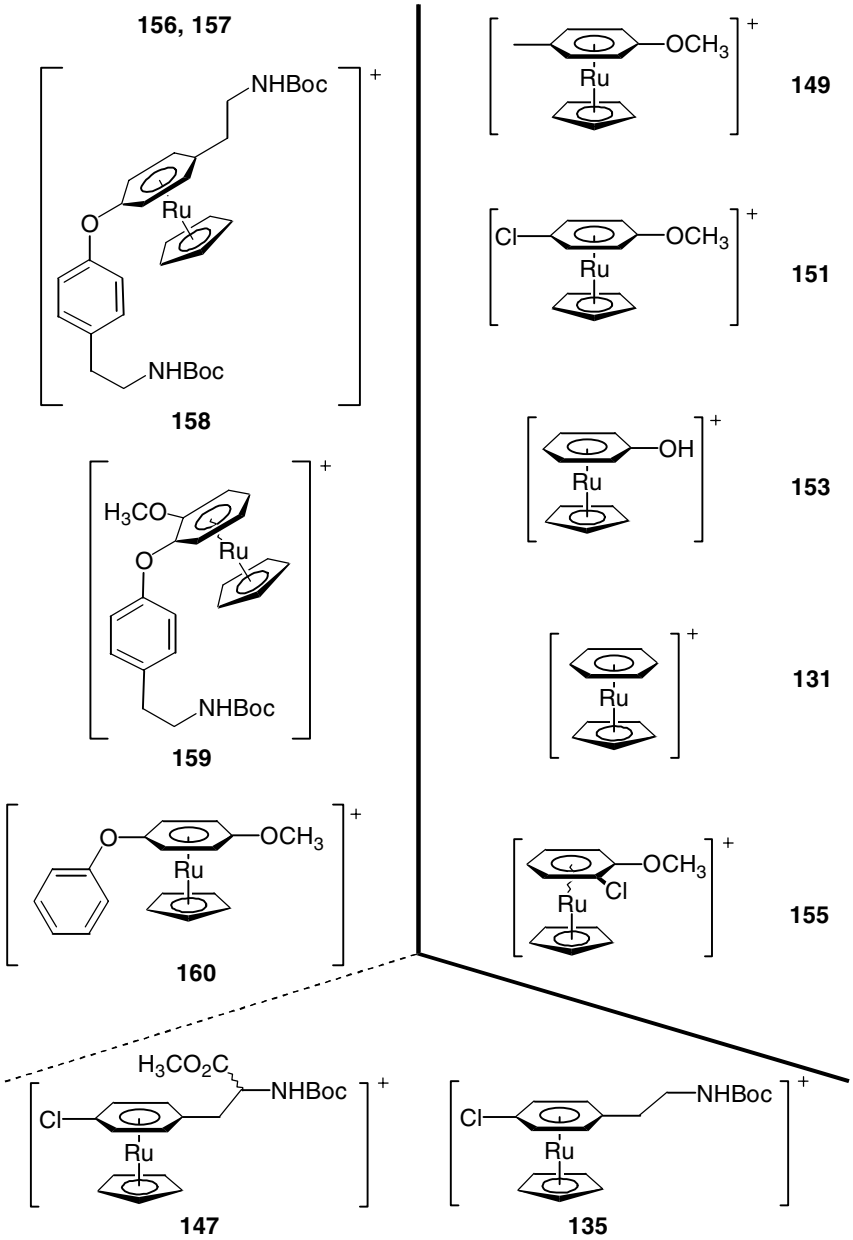


Figure 19: Ruthenium sandwich complexes **131**, **135**, **147**, **149**, **151**, **153**, **155-160** (anion hexafluorophosphate), grouped by increasing HPLC retention volumes on aminopropylsilica as stationary phase. The bold and dotted lines indicate separation using *i*PrOH-CH_3CN (4:1) and (8:1) as mobile phases, respectively.

Figure 20 gives retention volumes of the diaryl ethers **156**, **158**, **159**, **160**, and chloroarenes **135**, **151**, **155**, as well as of **131**, **149** and **153** obtained by preparative HPLC. Compound **157** has been omitted because it was obtained as a mixture of diastereomers showing a double-peaked band (**157** contains a stereogenic center and a stereogenic plane). In all cases the products were separable from the respective starting materials. The mobile phase *i*PrOH-CH_3CN (4:1) allowed the separation (resolution > 1.5) of the less polar (**135**, **147**, **156**, **158-160**) from the more polar compounds (**131**, **149**, **151**, **153** and **155**), as indicated by the bold line in figure 19. The less polar mobile phase *i*PrOH-CH_3CN (8:1) differentiated between the diarylethers (**156**, **158-160**) and the chloroarenes **135** and **147** (dotted lines in Figure 19). Using pure *i*PrOH as eluent the diarylethers **156** and **158** were separated fro **159** and **160**.

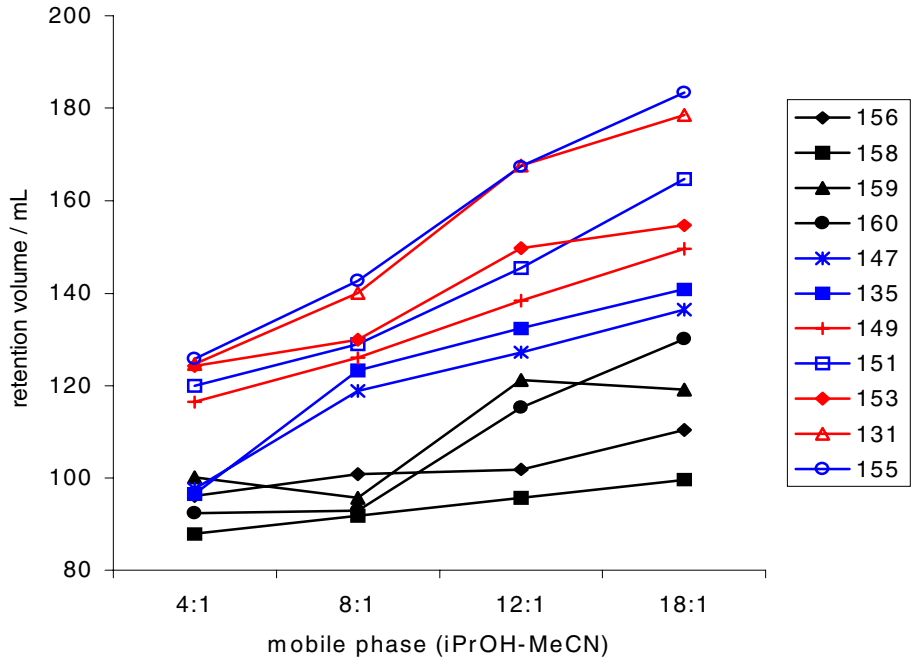


Figure 20: Preparative HPLC separation of the $[RuCp]^+$-complexed diaryl ethers (black lines) from the corresponding chloroarenes (blue lines). Retention volumes (HPLC) are given for different *i*PrOH-CH_3CN mixtures as mobile phases (stationary phase aminopropyl silica, column length 25 cm, particle size 25-40 µm, flow rate 15 $mL \cdot min^{-1}$).

Even compounds **135**, **155** and **158** were separated completely by preparative HPLC in one injection employing *i*PrOH-CH_3CN (12:1) as the mobile phase (Figure 21).

Aminopropyl silica appears to act in the normal-phase mode [98] when using *i*PrOH-CH_3CN mixtures as mobile phases.

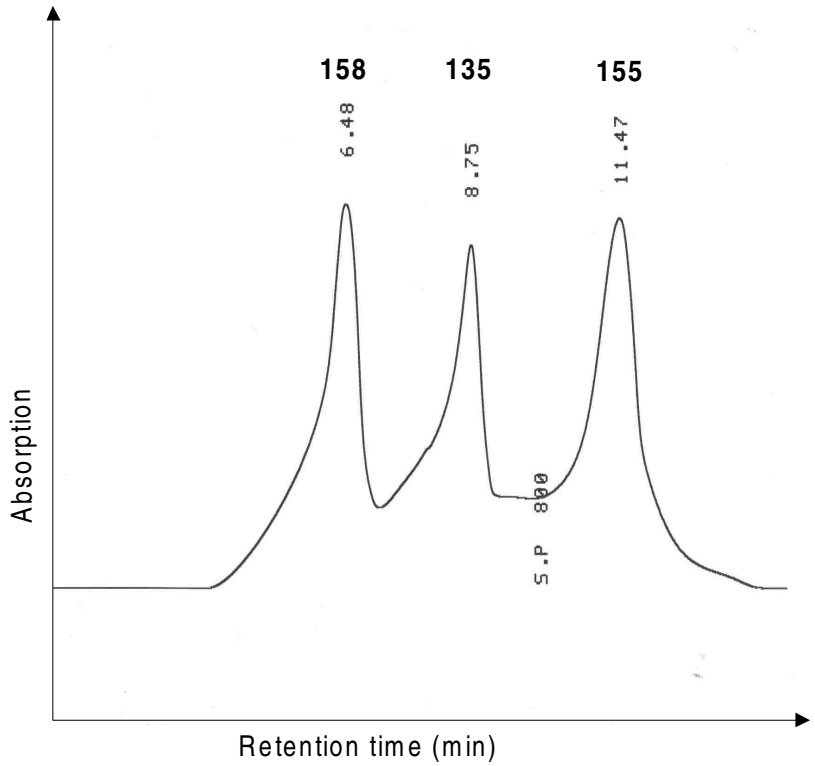


Figure 21: Chromatogram of a mixture of **135**, **155** and **158** employing *i*PrOH-CH_3CN (12:1) as mobile phase (UV-detection at 254 nm, flow rate 15 mL min^{-1}, colum diameter 25 mm, length 250 mm, 10 mg of each compound).

The new separation protocol also solves earlier reported problems concerning the removal of [18]crown-6[86f]. Despite the fact that [18]crown-6 and KO *t*Bu gives complete ruthenium complexed diarylation products, its use was not yet been extended because of the impossible separation of the ruthenium complexed products from [18]crown-6[86f]. It is known that the employment of [18]crown-6 and KO *t*Bu as a base accelerates diaryl ether formation[99]. This could be confirmed in the synthesis of **156-160**. On aminopropyl-functionalised silica, [18]crown-6 elutes later than the diarylethers **156-160** when toluene-CH_3CN (3:1) or *i*PrOH-CH_3CN (18:1) are used as mobile phases [94]. Furthermore, the frequently observed impurity[10] [RuCp(benzene)]PF_6 (**131**, resulting from incomplete formation of the original tris-

[10] The $[RuCp]^+$-introducing complex $[CpRu(NCCH_3)_3]PF_6$ is obtained from [CpRu(benzene)]PF_6 and always somewhat contaminated with starting material. See reference [94].

acetonitrile complex, red triangles in figure 20), is effectively removed on the diaryl ether level using aminopropyl silica.

The HPLC results are directly reflected by the behaviour of the sandwich complexes on aminopropyl silica TLC plates. The kinetic stability of the complexes can be estimated by the fact that the characteristic, reddish staining of the rutheniu complexes on the TLC treated with 1,10-phenanthroline in ethanol only occurs after intense heating.

Pure crystals of the diaryl ether complex **160** obtained after this chromatographic study, followed by recrystallisation fro *i*PrOH-EtOH, have been submitted to X-ray crystallographic analysis (Figure 22).

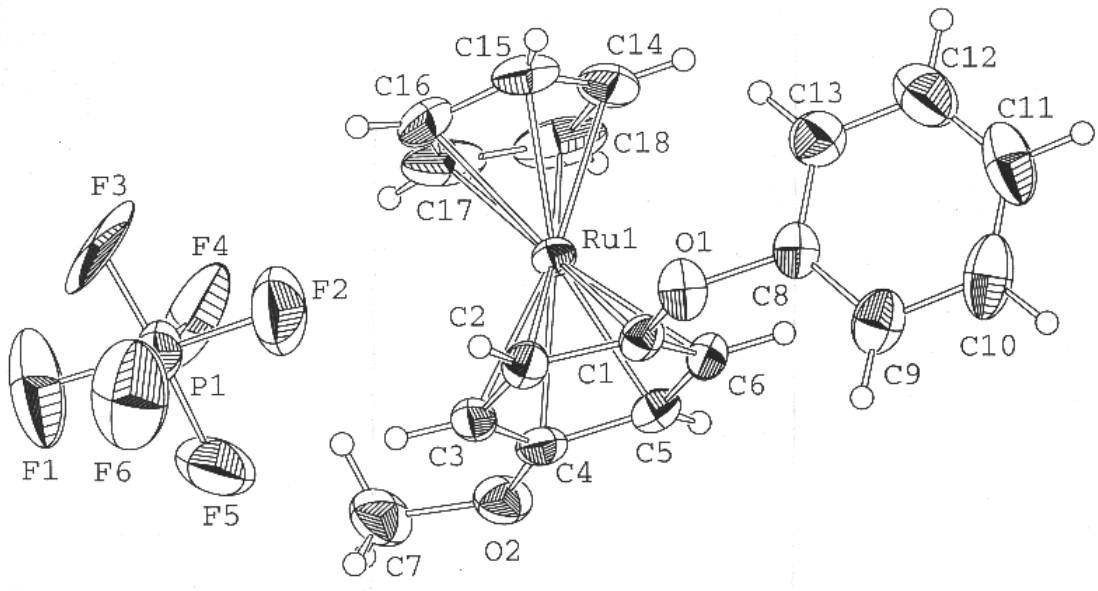


Figure 22: Structure of the $[RuCp]^+$-complex **160** in the crystal.

5 The ABB'A' System

The synthesis of all building blocks required for all later steps has been discussed in chapter 4.2. Chromatography, as one of the central obstacles in ruthenium mediated diaryl ether synthesis, has made substantial progress (chapter 4.3). Throughout the text, compounds composed of amino acid-analogue building blocks are considered as di-, tri-, or tetrapeptoids. Although the term "oligopeptoid" was originally proposed for oligomers of *N*-substituted glycines,[100] the true meaning of the ending "-oid" stemming from the Old Greek ειδος ("eidos" = picture) justifies the extension to all compounds representing peptide-like structures. Similar use is made in the literature, *e. g.*, of the terms "benzoid" or "metaloid".

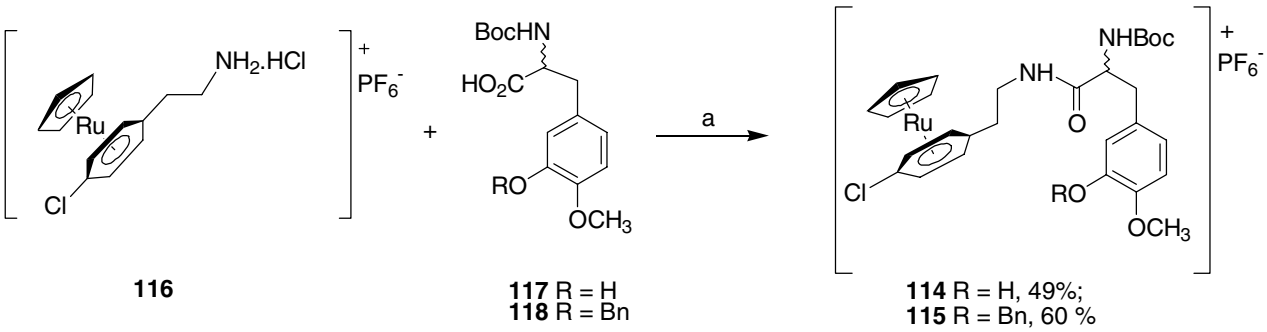
5.1 Synthesis of an *O*-benzylated AB system

Reaction of the free amine $[RuCp]^+$-complex **116** to the DOPA derivative **117** was promoted using *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI) and hydroxybenzotriazol (HOBt) as coupling reagents to give the dipeptoid complex **114** in 49 % yield. The *O*-benzylated DOPA analogue **118** was reacted with the same complexed amine to give the dipeptoid **115** in 60 % yield (Scheme 14).

The use of carbodiimide derivatives is of crucial importance for amide formation. This class of reagents reacts with the carboxyl group of the acid, thus activating it towards nucleophilic substitution.[101]

After work-up, the $[RuCp]^+$-dipeptoid complex **114** was purified by preparative HPLC on aminopropyl silica (*i*PrOH:H_2O (9:1), flow rate 15 mL·min^{-1}, 17 mg per injection, Figure 23). The use of aminopropyl silica for the purification of the simple $[RuCp]^+$-phenol complex **153** is described in chapter 4.3, but the application of this methodology for the purification of a more functionalised $[RuCp]^+$-phenol complex has not yet been explored. The result obtained from the preparative HPLC purification of the $[RuCp]^+$-complexed dipeptoid **114** was one more advance in the use of this stationary phase. No interaction between the free phenol and the basic

stationary phase was observed. This behaviour allows further investigation in the application of aminopropyl silica in complexes possessing acid functionalities.



Scheme 14: Synthesis of the AB system. The dipeptoids AB **115** and **114** were prepared using *O*-benzylated and *O*-free phenol, respectively. a) HOBt, EDCI, *i*Pr$_2$NEt, 0 °C (4 h), r.t., 30-40 h.

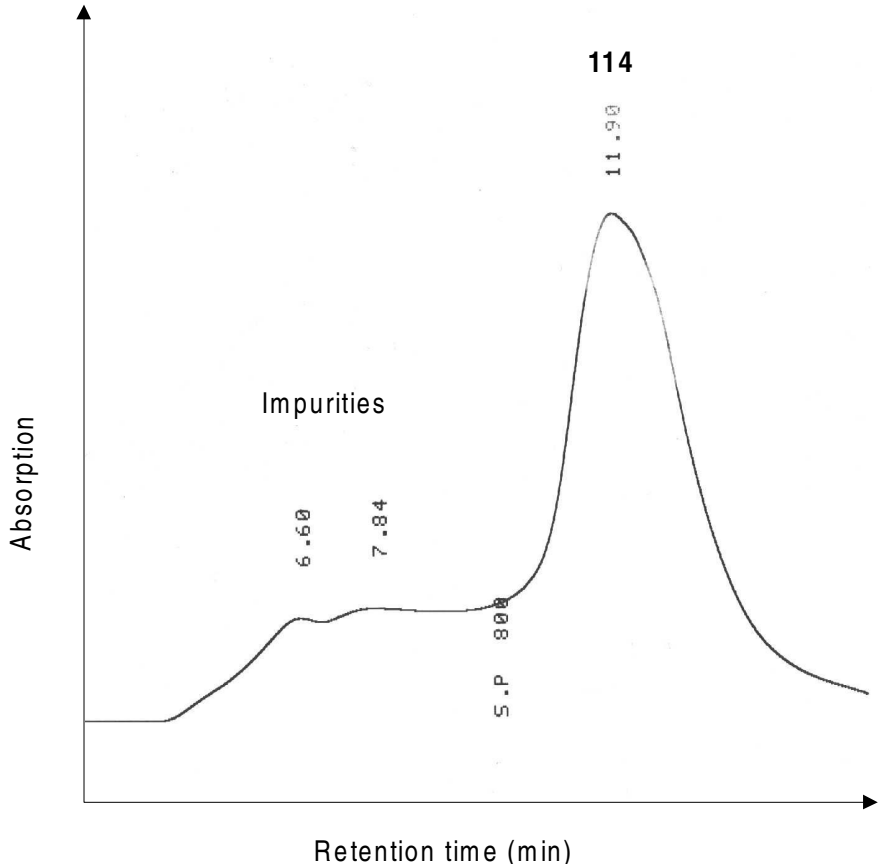


Figure 23: HPLC chromatogram of the purification of the crude dipeptoid **114** employing *i*PrOH-H$_2$O (9:1) as mobile phase (UV-detection at 254 nm, flow rate 15 mL·min^{-1}, column diameter 25 mm, length 250 mm, 17 mg per injection).

The *O*-benzylated dipeptoid analogue **115** was purified by column chromatography on aminopropyl silica (*i*PrOH-CH$_3$CN (4:1)) followed by preparative HPLC (*i*PrOH-CH$_3$CN (4:1), Figure 24). Recrystallisation from H$_2$O (at 80 °C, where *i*PrOH was

slowly added until complete solubilisation) gave the pure ruthenium complex as a colourless powder.

Dipeptoid **114** was prepared in order to investigate its nucleophilic behaviour in the ruthenium mediated S_NAr. Its metal-free analogue **161** was also synthesised with the purpose of comparing both NMR spectra.

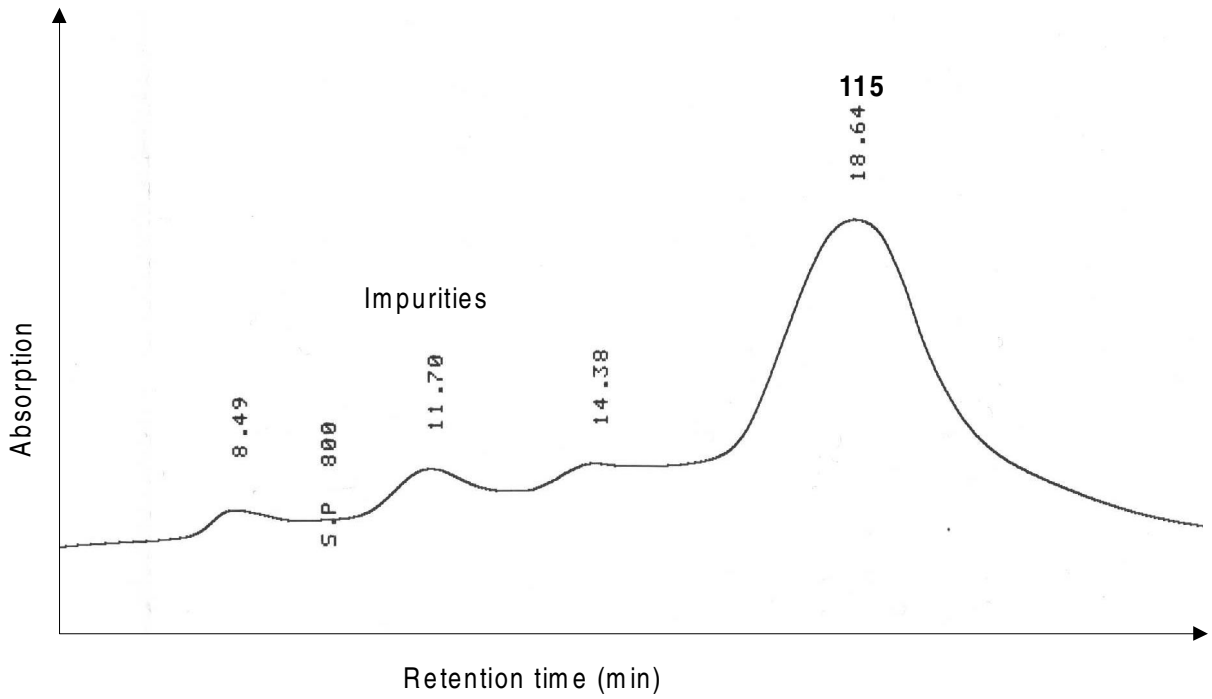
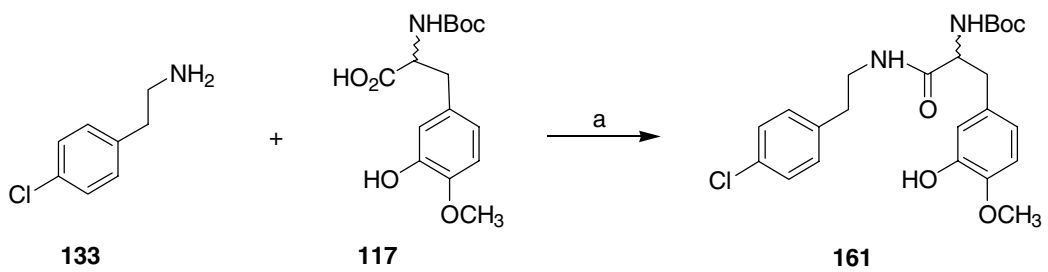


Figure 24: HPLC chromatogram of the crude *O*-benzylated dipeptoid **115** employing *i*PrOH-CH_3CN (4:1) as mobile phase (UV detection at 254 nm, flow rate 12 mL min^{-1}, column diameter 25 mm, length 250 mm, 10 mg per injection).

The metal-free dipeptoid **161** has been prepared using HOBt and EDCI as coupling reagents for amide linkages (Scheme 15). Purification by recrystallisation from TMP was sufficient to give pure colourless crystals in 79 % yield.



Scheme 15: Preparation of the non-complexed dipeptoid **161**. a) HOBt, EDCI, *i*Pr_2NEt, 0 °C (4 h), r.t., 26 h, 79 %.

Comparison of both ^{1}H and ^{13}C NMR spectra of dipeptoids **114** and **161** are shown in figure 25. The NMR spectra of the complexed dipeptoid **114** demonstrates that ruthenium generates an electronic field on the chloroarene aromatic ring, shielding both protons and carbons. The protons show a high field shift of 0.3-1.2 ppm while the carbon atoms a high field shift up to 40 ppm.

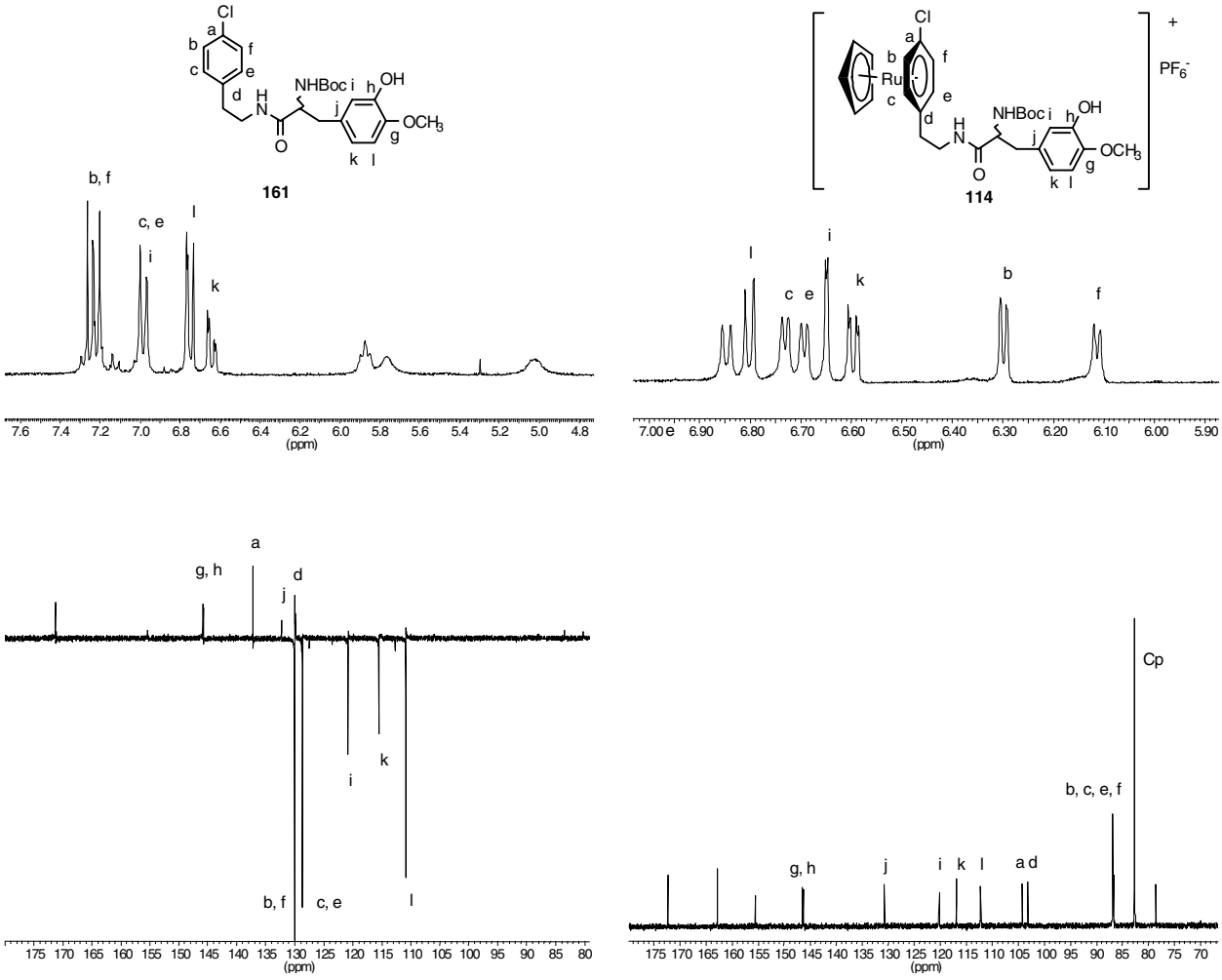
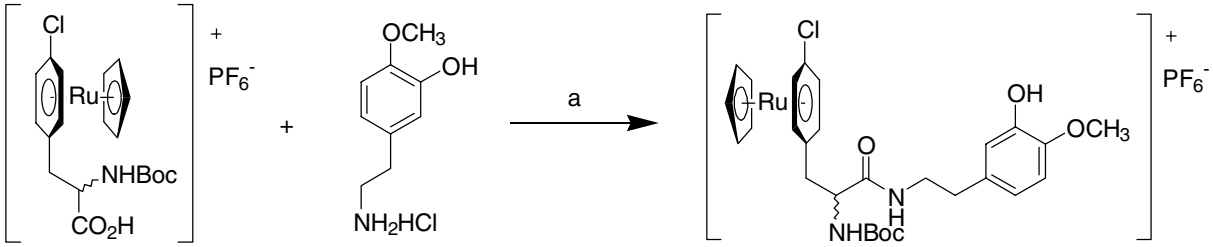


Figure 25: NMR spectra of the metal-free and -complexed dipeptoids **161** (^{1}H NMR, 250 MHz, $CDCl_3$; ^{13}C NMR, 60.9 MHz, $CDCl_3$) and **114** (^{1}H NMR, 500 MHz, $[D_6]DMSO$; ^{13}C NMR, 125 MHz, $[D_6]DMSO$), respectively.

5.2 Synthesis of the A'B' unit

The dipeptoid corresponding to the bastarane A'B' partial structure (Figure 16, chapter 4.2) was obtained in 59 % yield from the $[RuCp]^{+}$-complex **109** and dopamine derivative **112** using the same reaction conditions previously described for

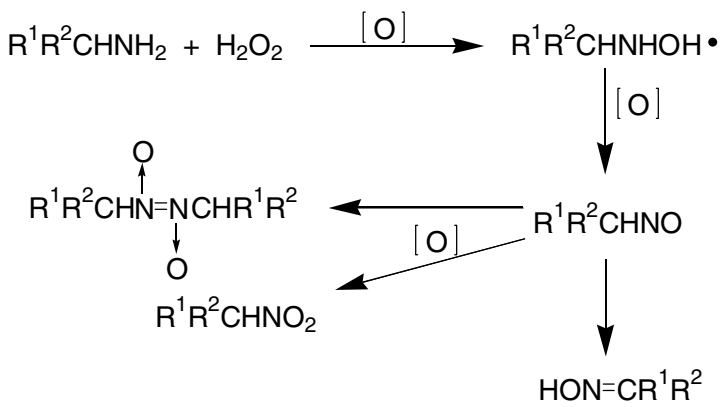
the preparation of all AB-dipeptoids (Scheme 16). This complex was not intended to be used in the synthesis of the bastarane skeleton, since its use would require an additional protection step (Figure 16, chapter 4.1). Nevertheless, the behaviour of **162** in comparison to the AB dipeptoid **114** in diaryl ether formation conditions was investigated.



Scheme 16: Preparation of the A'B' unit **162**. a) HOBt, EDCI, *i*Pr$_2$NEt, THF:CH$_3$OH (1:1), 0 °C (4 h), r.t., 26 h, 59 %.

5.3 Alternative approach towards the AB unit using α-thioxo acids

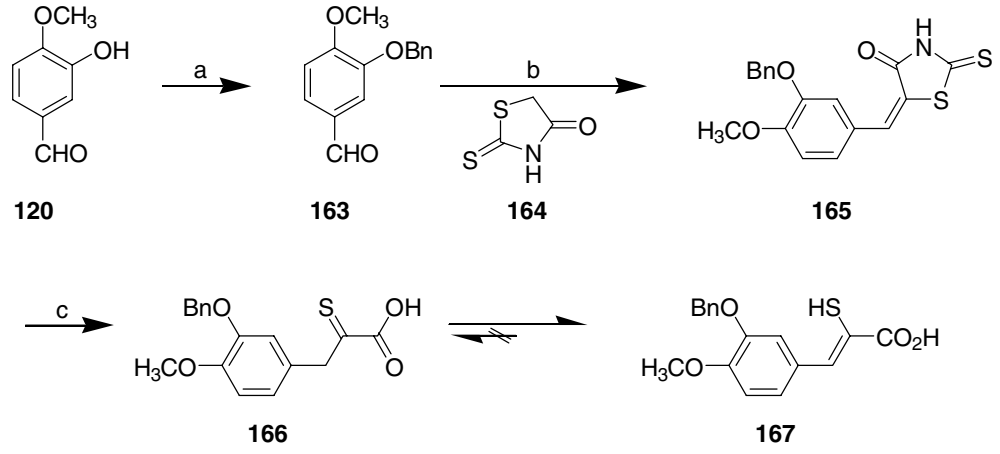
Oxidation of primary amines into their respective oximes can lead to the formation of nitro and dinitroso compounds as by-products (Scheme 17). The use of reagents like the sodium salts of tungstic, molybdic or vanadic acid [102], peroxotungstophosphate (PCWP [103], sodium perborate [104], titanium silicate molecular sieves (TS-1 and TS-2)[105] and methyltrioxorhenium (MTO)[106] have been investigated as possible solutions to this problem. The most promising procedure described involves using MTO[106] in the presence of hydrogen peroxide. This catalyst allows the oxidation of primary amines to the respective oximes in 70 to 90 % yields under mild reaction conditions.



Scheme 17: General reaction pathways in the oxidation of primary aliphatic amines with α-hydrogen atoms in presence of a mono-oxygen atom donor.

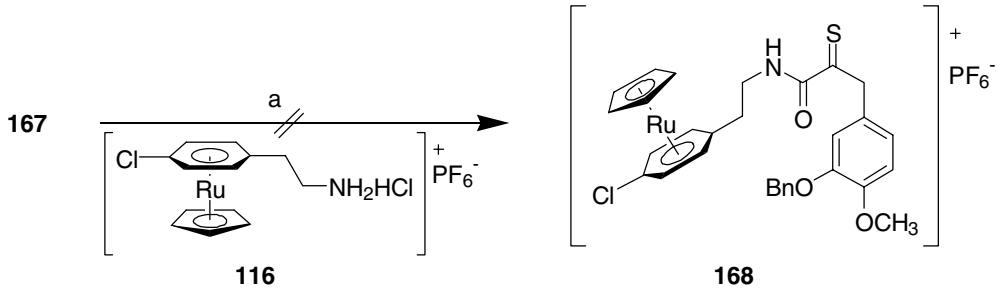
α-Thioxo acids can be converted to the corresponding oximes with no by-products in moderate to high yields using hydroxylamine, base and heat at 70 °C [107]. In a synthesis of the bastarane macrocycle, the tyrosine units are to be replaced by the appropriate thioketo acids. After ruthenium demetalation the keto functionalities would be transformed into oximes.

The synthesis started with the benzylation of **120** from commercially available isovaniline using standard conditions followed by aldol condensation with rhodanine (**164**). Hydrolysis of the benzylidenerhodanine **165** under reflux did not afford the respective β-phenylthiopyruvic acid **166** tautomer, but 2-mercaptopropenoic acid **167** in 41 % overall yield (Scheme 18) as concluded from the ^{1}H and ^{13}C NMR spectra. The reaction conditions used for the preparation of this class of compounds afford the *Z*-diastereomer[108].



Scheme 18: Synthesis of the *Z*-2-mercaptopropenoic acid **167**. a) BnBr, K_2CO_3, acetone, reflux, 20 h, 74 %; b) AcOH, NaOAc, reflux, 3 h, 92 %; c) i. NaOH (8 %), reflux, ii. HCl 3N, 0 °C, 30 min, 60 %.

Unfortunately, amide formation using the 2-mercaptopropenoic acid **167** and the $[RuCp]^{+}$-complexed 2-(4-chlorophenyl)ethylamine (**116**) did not provide the product expected for the continuation of this alternative approach (Scheme 19).



Scheme 19: Reaction of the 2-mercaptopropenoic acid **167** with the $[RuCp]^+$-complex **116** did not afford the desired $[RuCp]^+$-complexed amide **168**. a) HOBt, EDCI, *i*Pr_2NEt, THF:CH_3OH (1:1), 0 °C (4 h), r.t., 72 h, no reaction.

This reaction was repeated several times using either EDCI or DCC (dicyclohexylcarbodiimide) as amide coupling agents in large excess, but after stirring for many days under reflux no amide coupling reaction could be observed; however, the degradation of the *Z*-2-mercaptopropenoic acid **167** was detected.

5.4 Nucleophilic reactivity of phenolic hydroxy and aliphatic amino groups

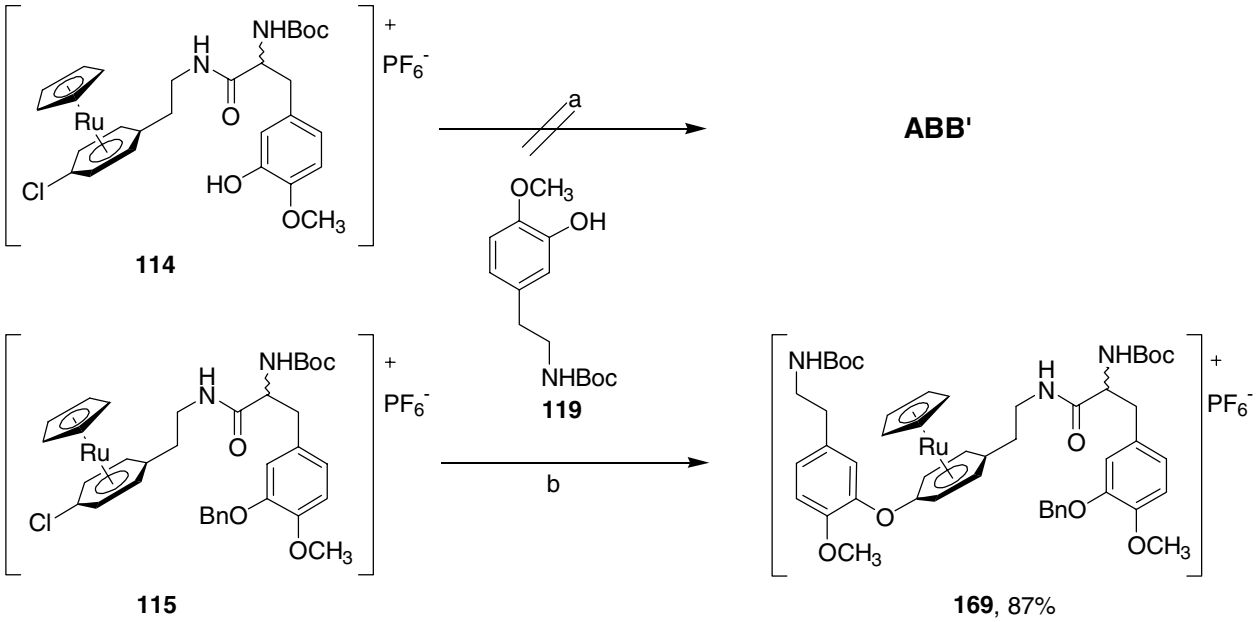
5.4.1. Synthesis of the $[RuCp]^+$complexed tripeptoid ABB' (169)

With the synthesis of $[RuCp]^+$-complexed AB units **114** and **115** completed, accompanied by a developed purification methodology it was possible to continue synthesis of the bastarane skeleton.

The reaction of both the *O*Bn-protected and unprotected, complexed amides **115** *resp*. **114** with *N*-Boc-4-*O*-methyldopamine (**119**) were tested using KO*t*Bu/[18]crown-6 as a base (Scheme 20). The unprotected amide **114** did not yield any ABB' product, despite the use of excess of external nucleophile. The NMR spectra of the isolated reaction mixture could not be analysed because of many overlapping chemical shifts. Separation of the products was also impossible. TLC analysis on aminopropyl silica of the products also failed, as they did not move fro the origin after employing several different mobile phase systems. These observations indicate that the competition by intermolecular condensation is overwhelming in this reaction. Intramolecular cyclisation products could not be observed.

In contrast, nucleophilic aromatic substitution proceeded smoothly in the case of the *O*Bn-protected amide **115**. Reaction with the Boc-protected dopamine **119** provided the $[RuCp]^+$-complexed diaryl ether amide ABB' (**169**) in 87 % yield after purification by column chromatography on aminopropyl silica (*i*PrOH-CH_3CN (4:1)) and by preparative HPLC (aminopropyl silica, *i*PrOH:CH_3CN (4:1), Figure 26). The formation of the diaryl ether linkage can be concluded from the downfield effect in the ^{13}C NMR spectrum from 105.62 ppm (η-C_{ar}Cl, dipeptoid **115**) to 132.57 ppm (**169**, η-C_{ar}OPh).

Purification of this more complex system bearing one diaryl ether and one amide function was a new advance in the application of aminopropyl silica.



Scheme 20: Formation of the tripeptoid ABB' **169** using both ruthenium-complexed dipeptoids **114** and **115**. The non-protected amide-complex did not give the desired ABB' product. a) KO *t*Bu, [18]crown-6, THF:CH_3CN (1:1), -78 °C (1 h), r.t. 16 h, no product; b) KO*t*Bu, [18]crown-6, THF, -78 °C (1 h), r.t., 16 h, 87 %.

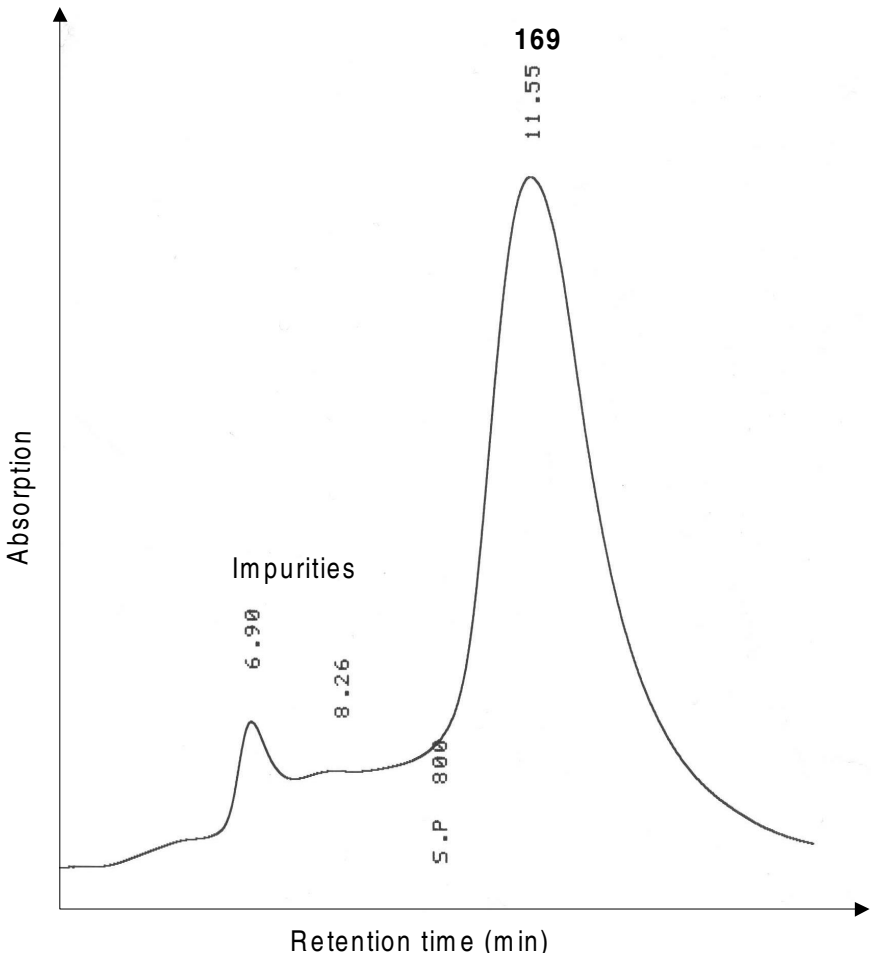
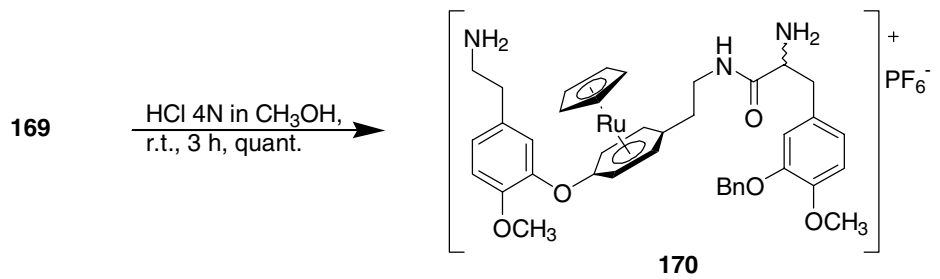


Figure 26: HPLC chromatogram of the purification of the crude tripeptoid **169** employing *i*PrOH-CH_3CN (4:1) as mobile phase (UV-detection at 254 nm, flow rate 15 mL·min^{-1}, column diameter 25 mm, length 250 mm, 10 mg per injection).

The next step concerned the introduction of the fourth unit, A', into the tripeptoid ABB' **169,** by amide formation.

Upon treatment of the ABB' tripeptoid **169** with 4N HCl, both Boc groups were cleaved off and the $[RuCp]^+$-complexed tripeptoid **170** possessing both a free amine and a free amino acid moiety was obtained (Scheme 21). For the first time, a $[RuCp]^+$-complex possessing these free functions was prepared.



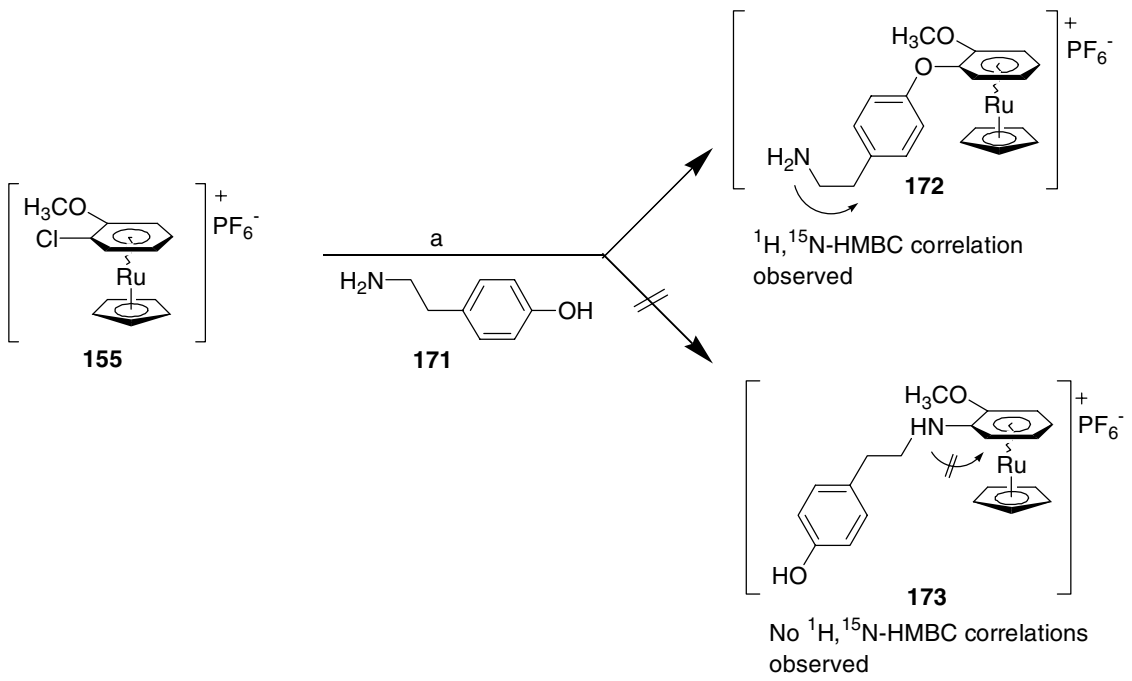
Scheme 21: Cleavage of the Boc-protecting groups off the complexed tripeptoid **170**.

5.4.2. Ambident nucleophiles in the ruthenium mediated S_NAr reaction

Ruthenium mediated S_NAr reaction of various nucleophiles is well characterised[33e, 109]. Substitution products were obtained even using malonate[33e, 85a]. However, those studies did not reveal how compounds possessing different nucleophiles would behave upon reaction with a chloroarene complex.
Since the $[RuCp]^+$-complexed tripeptoid **170** could not be used in the continuance of this strategy, the next question was whether an ambidental nucleophile, i.e. possessing a free amine and a free phenol, would exclusively promote the formation of the diaryl ether product. A model reaction utilising the commercially available unprotected tyramine (**171**) with $[RuCp]^+$-complexed *o*-chloroanisol (**155**)[94] was performed. The $[RuCp]^+$-complexed diaryl ether **172** was formed in 81 % yield without concomitant formation of any by-product (Scheme 22). The product was purified by column chromatography on aminopropyl silica with CH_3CN to remove [18]crown-6 and with *i*PrOH:H_2O (6:1), followed by recrystallisation fro *i*PrOH.

The ^{13}C NMR signals of the aromatic part of the diaryl ethers **159** and **172** are presented in figure 27. The comparison of the ^{13}C NMR chemical shifts of the aromatic carbons of the *N*-free diaryl ether to those of its *N*-Boc analogue shows that the chemical shift of δ 125.67 ppm is indicative of the successful diaryl ether bond formation.

The $^1H,^{15}N$-HMBC spectrum of **172** did not show any correlation between the nitrogen and the aromatic hydrogen atoms. This positive result encouraged the continuation of the chosen strategy.



Scheme 22: Model reaction involving a molecule containing a free amine and a free phenol as nucleophiles. a) KO *t*Bu, [18]crown-6, THF:CH_3CN (1:1), -78 °C (1 h), r.t. 16 h, 81 %.

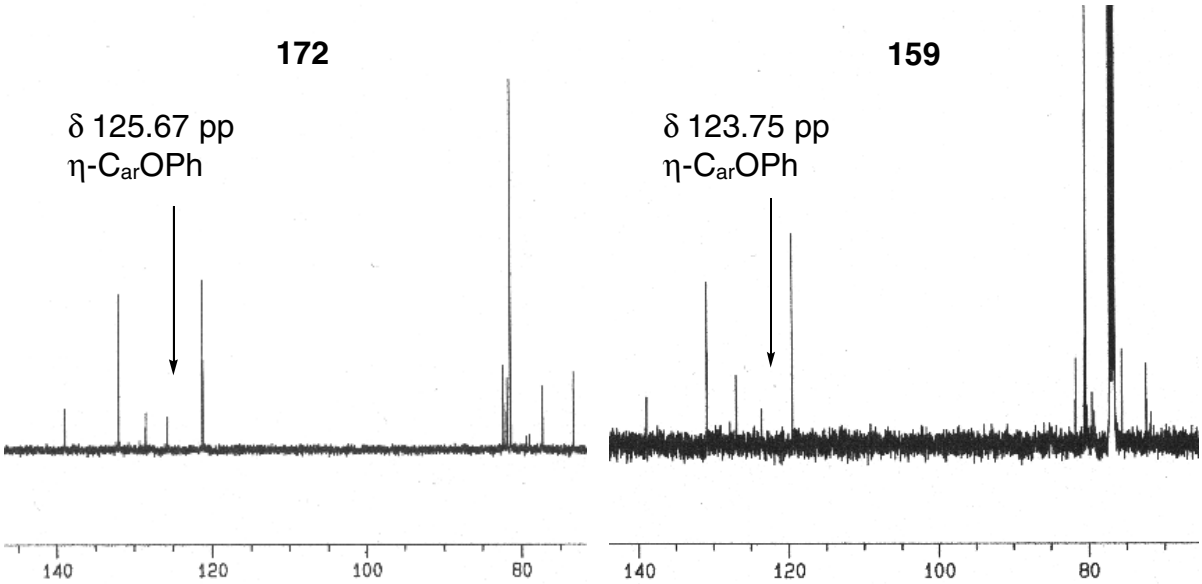


Figure 27: ^{13}C NMR spectra of the diaryl ether complexes **172** (^{13}C NMR, 125 MHz, CD_3OD) and **159** (^{13}C NMR, 125 MHz, $CDCl_3$). The signal at δ 125.67 reveals the formation of a diaryl ether linkage.

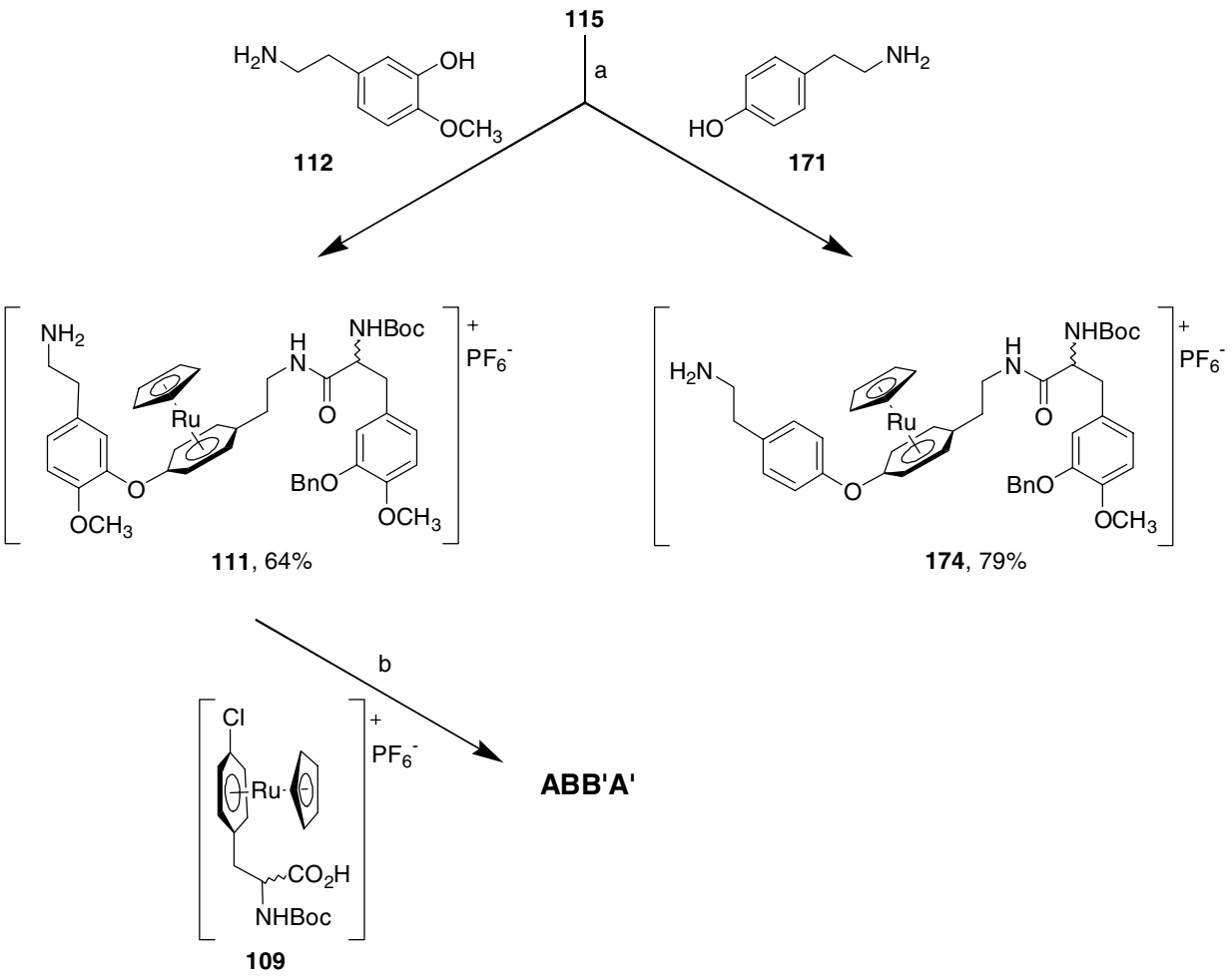
5.5 Formation of an open-chain ABB'A' system

As envisaged from the model reaction discussed above, the diaryl ether amide **111** could be prepared in 64 % yield from the dipeptoid **115** and *N*-free dopamine **112** (Scheme 23). The same procedure was employed using the dipeptoid **115** and the commercially available *N*-free tyramine (**171**). The respective tripeptoid **174** was obtained in 79 % yield (Scheme 23). The diaryl ether substitution product again could be confirmed by comparison of the ^{13}C NMR spectra of **111** (δ 134.31 ppm, η-$C_{ar}OPh$) with the spectra of its Boc-analogue **169** (δ 132.57 ppm, η-$C_{ar}OPh$). The ^{13}C NMR spectra of **174** also revealed diaryl ether formation due to the chemical shift of δ 131.28 ppm.

Compound **115** is the first $[RuCp]^+$-complexed amide which was subjected to a ruthenium mediated diaryl ether coupling with an ambidental nucleophile. The selective diaryl ether formation with either 1,2-substituted (**155**) or 1,4-substituted (**115**) chloroarene complexes and *m*- (**112**) or *p*-phenolates (**171**) indicates that this selective behaviour does not depend on the substitution pattern of both ($[RuCp]^+$-complexed chloroarene and phenolate) aromatic systems.

The preparation of the $[RuCp]^+$-complexed tripeptoids **111**, **169** and **174** was a further advance in ruthenium arene chemistry. For the first time $[RuCp]^+$-complexes were carried through more than one reaction step, and further, the resulting tripeptoid complexes could be isolated, purified and completely characterised.

These results are also of great interest to bioorganic chemistry studies when rutheniu π arene complexes are used in labelling of amino acids and peptides.



Scheme 23: a) KO *t*Bu, [18]crown-6, THF:CH_3CN (1:1), -78 °C (1 h), r.t. 16 h; b) HOBt, EDCI, *i*Pr_2NEt, THF:CH_3OH (1:1), 0 °C (4 h), r.t., 26 h, 38 %.

An ambitious experiment was the introduction of the fourth unit, the [RuCp] $^+$-chorophenylalanine complex **109**, into the tripeptoid **111**. The amide coupling was indeed achieved by treating the chlorophenylalanine complex (**109**) with EDCI and HOBt (Scheme 23, Figure 28). Analysis of the FABMS (Figure 28) and HRFABMS spectra of the product revealed the formation of the open-chain ABB'A' system of the bastarane skeleton. The low yield obtained (38 %) can be attributed to the difficult work-up and purification of the twice [RuCp] $^+$-complexed tetrapeptide **175**. The purification of this system represents a new challenge to the application of aminopropyl-functionalised silica.

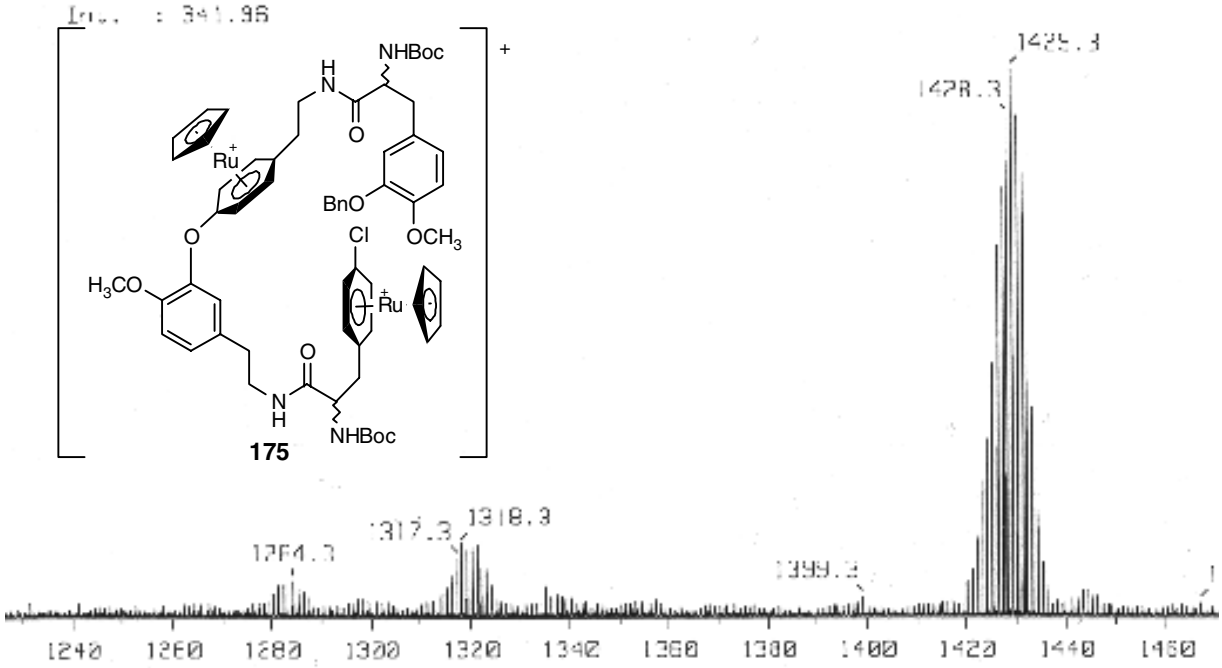


Figure 28: FABMS spectra of the open-chain ABB'A' system. The isotope pattern of the $[M^+]$ ion (m/z 1420 to 1436) indicates the formation of this tetrapeptoid bis-ruthenium complex **175**.

The feasibility to form the tetrapeptoid bis-ruthenium complex **175** shows that the demetalation is not required after diaryl ether coupling and that the reaction between two $[RuCp]^+$-complexes is possible. These results extend the use of the rutheniu arene chemistry to natural products which have more than one diaryl ether moiety in different aromatic rings (*e. g.* bastadins).

The purification of this bis-ruthenium complex (**175**) has not yet been completed. However, due to the positive results in separation and purification on aminopropyl silica stationary phase, it is likely that compound **175** can also be purified via this technique.

6 Summary

The bastadins (**9**: bastadin 5) have been isolated as natural products from the marine sponge *Ianthella basta* since 1981 [29]. Characteristically, the two tyrosine and two tyramine units of these tetrapeptoid macrocycles are linked via two diaryl ether bridges and two amide bonds. The diaryl ether moiety is present in clinically important peptoids, such as the antibiotic vancomycin, and may serve as a key structural motif for medicinal application of peptide-like molecules.

The synthesis of ruthenium-labelled peptoids explored in this thesis makes use of the nucleophilic attack of phenolates on $[RuCp]^+$-complexed chloroarenes to form diaryl ethers in the preparation of metal-labelled bastadin model compounds. The full purification and characterisation of $[RuCp]^+$-labelled peptoids has not, until now, been systematically studied. Earlier work described the cleavage of metal to produce metal-free products[85, 86]. Despite the attractive properties of ruthenium radioisotopes (long half-lives, stability and non-toxic) for diagnostic medicine, applications of the air and water-stable $[RuCp]^+$-labelled amino acids and more advanced peptides are still very limited.

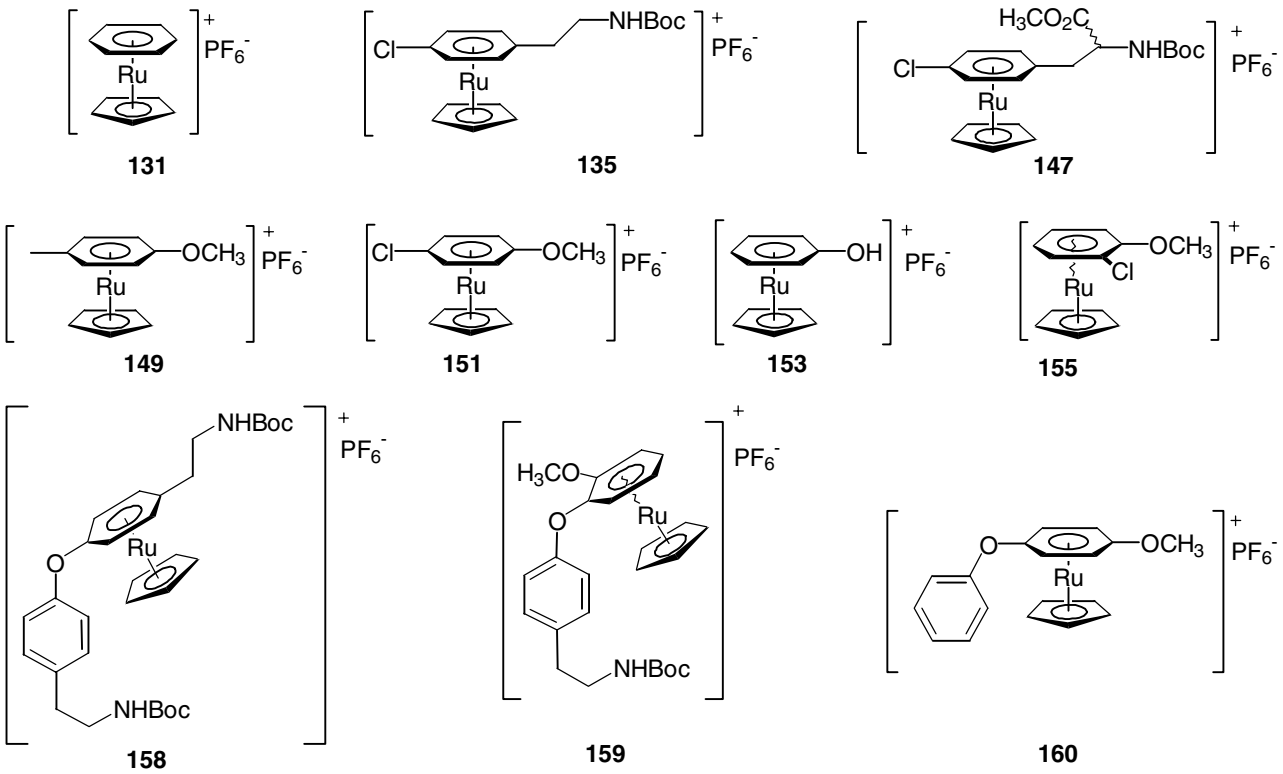


Figure 29: $[RuCp]^+$-complexes for the chromatography study using aminopropyl-functionalised silica as stationary phase.

A protocol has been developed to ease the purification problems with [RuCp] $^{+}$-complexes. The first analyses were performed with the simple model compounds **131**, **135**, **147**, **149**, **151**, **153**, **155**, with three model diaryl ether complexes **158-160** (Figure 29) and finally with the two [RuCp]$^{+}$-complexed diaryl ethers which represent the western **156** and eastern **157** halves of the bastarane skeleton (Figure 30).

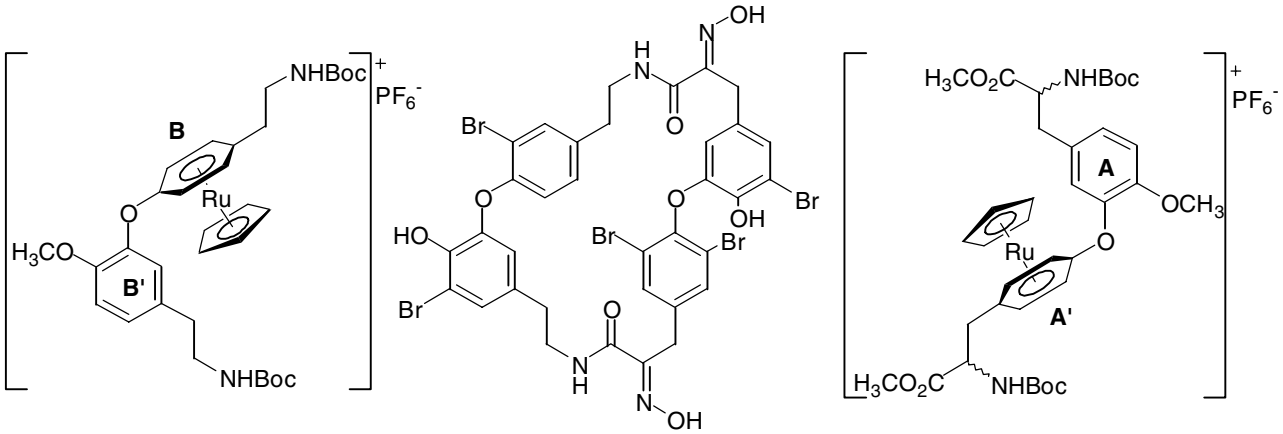
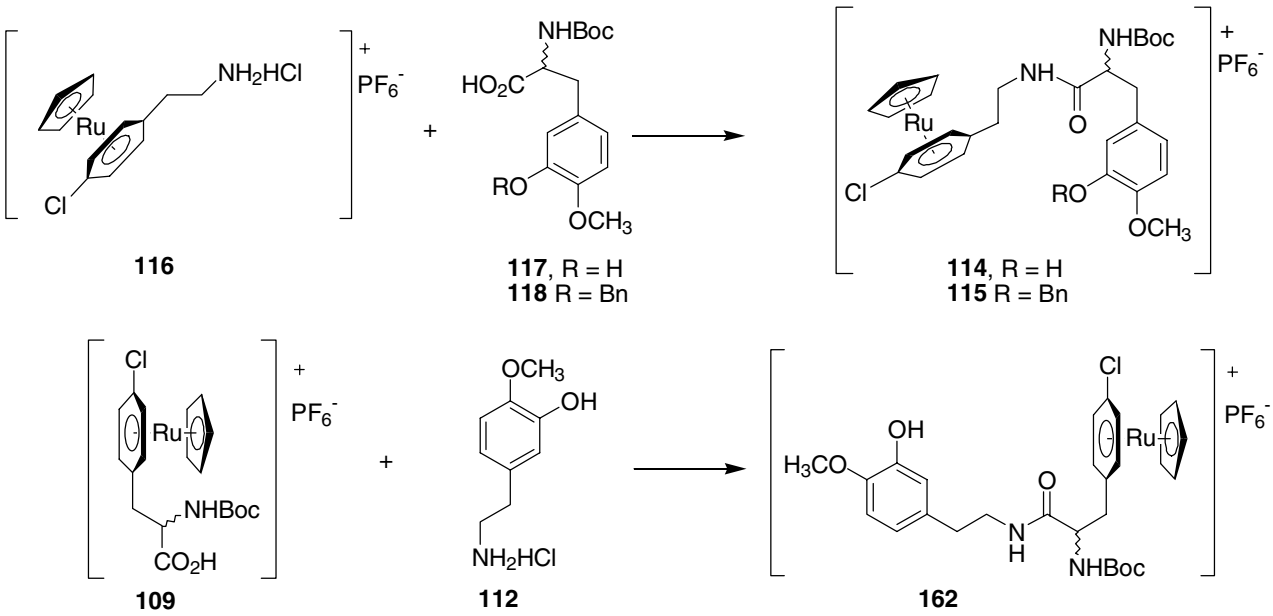


Figure 30: Western (**156**) and eastern (**157**) halves of the bastarane skeleton.

For the first time, aminopropyl functionalised silica was employed as stationary phase for the purification and separation of [RuCp] $^{+}$-complexes *from each other*, using gradients of *i*PrOH-CH_3CN as mobile phase. The purification of the [RuCp] $^{+}$-complexes also solved other problems which existed in the ruthenium mediated S_NAr: reaction monitoring by TLCs (selectively staining ruthenium-complexes by heating with 1,10-phenanthroline) and removal of 18-crown-6 used for the diaryl ether formation[86f]. These results enabled continuation of the strategy for synthesis of the bastarane skeleton.

The preparation of the northern (**114** and **115**) and southern (**162**) hemispheres of the bastarane skeleton (Scheme 24) was an additional step towards the synthesis of the bastarane skeleton. The purification of the *O*H-free dipeptide **114** (northern hemisphere) on aminopropyl silica was successful. This result showed that the aminopropyl silica is also appropriate for more complex structures bearing an acidic moiety.



Scheme 24: Synthesis of the northern (**114** and **115**) and southern (**162**) halves of the bastarane skeleton.

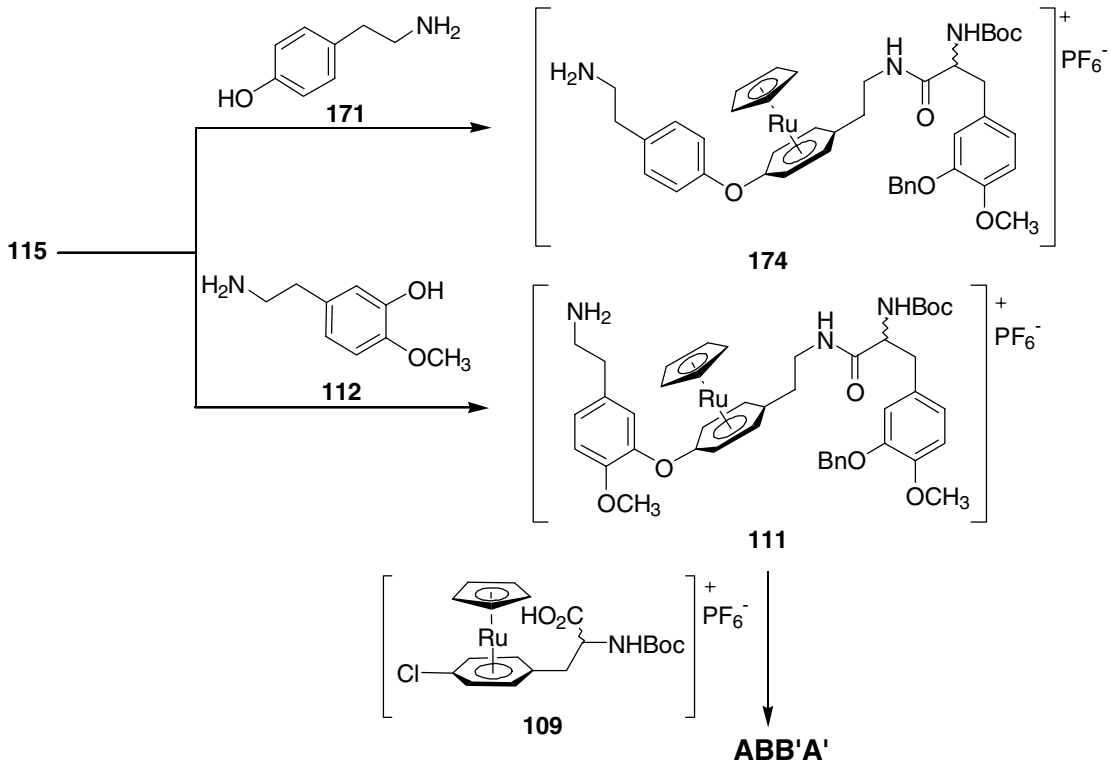
The introduction of the third unit was only possible when the *O*Bn-protected dipeptoide **115** was used. The unprotected dipeptoide **114** gave a probable mixture of intermolecular condensation products which could neither be separated nor characterised.

The behaviour of ambident nucleophiles simultaneously possessing free amine and free phenol functionalities has also been investigated in the ruthenium mediated synthesis of diaryl ethers. The results clearly revealed the preference for the phenol but not for the amine as a nucleophile.

This information encouraged the continuation of the strategy with the synthesis of the tripeptoides **111** and **174** (Scheme 25). The $[RuCp]^+$-complexed tripeptoides (**111** and **174**) could also be purified on aminopropyl silica and were thoroughly characterised.

The tripeptoides **111** and **174** are the first $[RuCp]^+$-complexes possessing one amide linked by ruthenium mediated S_NAr to a free amine. Furthermore, the preparation of these two complexes extended the use of the ruthenium arene chemistry to an additional reaction step. Normally, the ruthenium complexes are submitted to photo-demetallation directly after the diaryl ether coupling reaction step and the $[RuCp]^+$-complex formed is not isolated from the reaction mixture.

The synthesis of the open-chain bis-[RuCp]$^+$-complexed ABB'A' system was also achieved (Scheme 25) as indicated by high resolution mass spectra. The purification of this product, as well as its macrocyclisation, are challenges that still remain unsolved.



Scheme 25: Synthesis of the [RuCp]$^+$-complexed tripeptides **111** and **174** of the open-chain bis-[RuCp]$^+$-complexed ABB'A' system.

This thesis brought important progress to ruthenium arene chemistry, mainly through: I) employment of a base which promotes complete diaryl ether formation; II) monitoring of the reactions with TLC; III) use of the [RuCp]$^+$-complexes in more than one reaction step, thus extending the use of this methodology to include more complex natural products' syntheses and IV) preparation of [RuCp]$^+$-complexes as metal-labelled peptoids. The results of this thesis may now enable us and other research groups to further explore and promote ruthenium arene chemistry.

II Experimental Section

1 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 rutheniu sandwich complexes) and 0.25 mm E. Merck alumina plates Si $F_{254}S$]. TLCs were analysed under UV light (λ = 254 nm), followed by heating after treatment with 1,10-phenanthroline (dipping solution in EtOH) for ruthenium sandwich complexes and with ninhydrine for amines and amino acids. A Hereaus TQ 150 mercury mediu pressure lamp, 150 W, was used for the irradiation of the ruthenium complexes. 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.

HPLC

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). CH_3CN, H_2O and *i*PrOH were HPLC-grade. The detector used 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, each injection contained 10 mg of sample.

Melting Point

Melting points were determined with a Reichert melting point microscope and are uncorrected.

UV/VIS

The UV/VIS-spectra were recorded using a Hewlett-Packard UV-Spectrophotometer HP 8452 Diode Array System.

IR Spectra

All infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer.

NMR Spectra

NMR spectra were recorded on Bruker WM 250, AM 360, and AM 500 and on Varian INOVA-400 spectrometers. The NMR shifts were calibrated using TMS as internal reference and assigned on the basis of HSQC and HMBC experiments. The multiplicities are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad.

Mass Spectra

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.

Elemental Analyses

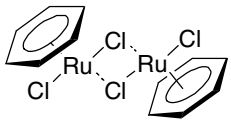
Elemental analyses were performed at the automatic microanalysator Foss-Heraeus Vario EL.

X-Ray Analysis

X-ray structural analysis of **160** was performed at a Nonius MACH 3 4-Circle-diffractometer (graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å)).

2 Synthesis of the tris(acetonitrile)(η^5-cyclopentadienyl) ruthenium hexafluorophosphate (132)

2.1 Bis-{(η^6-Benzene)-dichloro-ruthenium} (129)[93a]



1,3-Cyclohexadiene (6.8 mL; 72 mmol) is added to a pre-heated solution (50 °C) of $RuCl_3 \bullet 3\ H_2O$ (1.880 g; 7.2 mmol) in 110 mL 90 % aqueous EtOH. The solution is heated at 90 °C for 3 hours. The resulting red precipitate is collected, washed with cold EtOH and dried in vacuum.

Yield: 1.774 g (95 %)

Melting Point.: up 245 °C starts decomposition without melting

^{1}H NMR (250 MHz, [D_6]DMSO) δ = 5.97 (s, 12H, η-CH_{ar}).

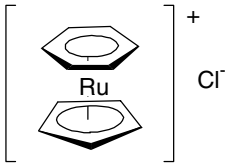
^{13}C NMR (90.6 MHz, [D_6]DMSO) δ = 87.60 (η-C_{ar}H).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3448 (m), 3037 (m), 1432 (s), 1149 (w), 976 (w), 844 (s), 617 (w).

MS (FAB$^+$, NBA): m/z (%) 500/501/502 (93/90/100) [M$^+$].

Elemental Analysis: $C_{12}H_{12}Cl_4Ru_2$ (500.178)
Calculated: C: 28.82 H: 2.42
Found: C: 29.21 H: 2.68

2.2 (η^6-Benzene)(η^5-cyclopentadienyl)rutheniumchloride (130)[93b]



Thallium cyclopentadienide (1.736 g; 12.9 mmol) is added to a solution of bis-{(η^6-benzene)dichloro-ruthenium} (**129**) (3.33 g; 6.449 mmol) in 1166 mL CH_3CN to give, after 1 hour a precipitate of thallium chloride. The precipitate is filtered and the solvent is removed under vacuum. Residue is recrystallised from CH_3CN-Et_2O to give a pale brown powder.

Yield: 2.525 g (70 %)

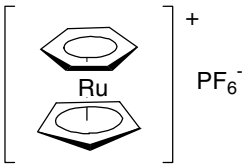
Melting Point.: up 160 °C starts decomposition without melting

^{1}H NMR (360 MHz, $CDCl_3$) δ = 6.37 (s, 6H, η-C*H*$_{ar}$), 5.54 (s, 5H,.Cp).

^{13}C NMR (90.6 MHz, $CDCl_3$) δ = 86.38 (η-*C*$_{ar}$H), 80.81 (Cp).

MS (FAB$^+$, NBA): m/z (%) 244/245/247 (60/100/61) [M$^+$].

2.3 (η^6-Benzene)(η^5-cyclopentadienyl)ruthenium hexafluorophosphate (131)[93c]



(η^6-Benzene)(η^5-cyclopentadienyl)rutheniumchloride (**130**) (1155 mg; 4.13 mmol) is dissolved in H_2O and filtered. To the filtrate is added ammoniu hexafluorophosphate (685 mg; 4.2 mmol) and immediately (η^6-benzene)(η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**131**) precipitates. After 1 hour, under stirring, the product is collected as a pale brown powder. The impurities are

removed by dissolving the product in acetone and eluting it through a neutral alumina column (acetone). The product is recrystallised fro *i*PrOH yielding light yellow needles.

Yield: 1137 mg (68 %)

TLC (NH_2-Si, CH_3CN): R_f = 0.81

HPLC retention volumes: 104 mL (CH_3CN), 105 mL (*i*PrOH-CH_3CN – (1:1)), 110 mL (*i*PrOH-CH_3CN – (2:1)), 125 mL (*i*PrOH-CH_3CN – (4:1)), 140 mL (*i*PrOH-CH_3CN – (8:1)), 168 mL (*i*PrOH-CH_3CN – (12:1)), 179 mL (*i*PrOH-CH_3CN – (18:1)).

Melting Point: up 280 °C starts decomposition

^{1}H NMR (360 MHz, [D_6]acetone) δ = 6.34 (s, 6H, η-CH_{ar}), 5.54 (s, 5H, Cp).

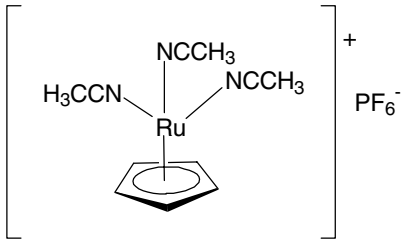
^{13}C NMR (90.6 MHz, CD_3OD) δ = 87.18 (η-C_{ar}H), 81.46 (Cp).

UV/Vis (CH_3OH): λ_{max} (ε) = 264 (630), 222 nm (1900 $mol^{-1}dm^3cm^{-1}$); (CH_2Cl_2): λ_{max} (ε) = 316 (240), 230 nm (2100 $mol^{-1}dm^3cm^{-1}$).

MS (FAB$^+$, NBA): m/z (%) 244/245/247 (55/100/56) [M^+].

Elemental Analysis: $C_{11}H_{11}F_6PRu$ (389.2421)
Calculated: C: 33.94 H: 2.85
Found: C: 33.77 H: 2.99

2.4 tris-(Acetonitrile)(η^5-cyclopentadienyl)ruthenium hexafluorophosphate (132)[93c]



(η^6-Benzene)(η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**131**) (600 mg, 1.5 mmol) is dissolved in dry CH_3CN (100 mL) and is transferred to a quartz waterjacket of an inversion medium pressure mercury UV-lamp. The jacket is stoppered and the solution is degassed by bubbling with argon for 30 min. The stirred solution is irradiated with the output of a 150 W mercury medium pressure lamp for 8 hours under argon at room temperature. After irradiation, the solution is kept under refrigeration for the next step.

Yield: 651 mg (quant., yellow needles)

^{1}H NMR (250 MHz, CD_3CN) δ = 4.28 (s, 5H, Cp), 2.84 (s, 9H, C*H*$_3$CN).

^{13}C NMR (90.6 MHz, CD_3CN) δ = 91.20 (η-N*C*CH_3), 69.67 (Cp), 67.41 (NC*C*D_3).

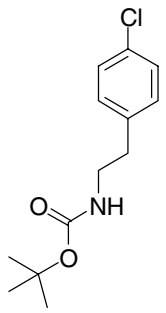
Obs.: The instability of the product did not allow further structure analysis.

3 General procedure for the preparation of the ruthenium sandwich complexes:

At 70 °C, $[RuCp(NCCH_3)_3]PF_6$ (**132**)[93] (concentrated from a CH_3CN solution immediately prior to use) is added to a solution of the respective chlorobenzene derivative (1 eq.) in 1,2-dichloroethane (20 mL) and the reaction mixture is refluxed for 4 hours.

3.1 [1-{2-(*tert*-Butoxycarbonylamino)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (135)[94]

3.1.1. [2-(4-Chloro-phenyl)ethyl]-carbamic acid *tert*-butyl ester (134)



Boc_2O (3.838 g, 17.6 mmol) is added to a solution containing 2-(4-chloro-phenyl)ethylamine (**133**) (2.22 mL, 16 mmol) in CH_2Cl_2. After stirring for 4 hours at room temperature the solvent is removed and the product is recrystallised fro *n*heptane affording colourless needles.

Yield: 4.008 g (98 %)

TLC (Si, TMP-EtOAc (8:2)): R_f = 0.58

Melting Point : 66-68 °C

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.5 Hz, 2H, CH_{ar}), 7.11 (d, J = 8.4 Hz, 2H, CH_{ar}), 4.57 (brs, 1H, CH_2NH), 3.33 (t, J = 6.8 Hz, 2H, CH_2NH), 2.76 (t, J = 7.0 Hz, 2H, CH_2CH_2NH), 1.43 (s, 9H, OC(CH_3)$_3$).

^{13}C NMR (62.9 MHz; $CDCl_3$): δ = 155.78 (C=O), 137.46 (C_{ar}Cl), 132.18 ($C_{ar}CH_2$), 130.09 (C_{ar}H), 128.61 (C_{ar}H), 79.28 (OC(CH_3)$_3$), 41.64 (CH$_2$NH), 35.59 (CH$_2$CH$_2$NH), 28.33 (OC(CH$_3$)$_3$).

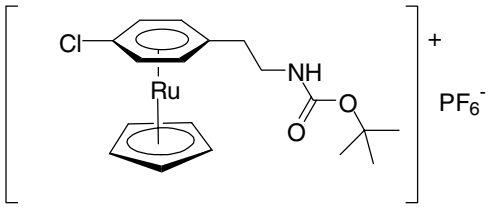
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3315 (s), 3039 (m), 2981 (s), 2931 (m), 1899 (w), 1694 (s), 1538 (m), 1489 (s), 1446 (m), 1408 (m), 1365 (s), 1283 (s), 1248 (s), 1166 (s), 1086 (s), 1052 (s), 1016 (s), 973 (s), 812 (s), 664 (s), 643 (s).

UV/Vis (CH_3OH): λ_{max} (ε) = 276 (840), 268 (890), 222 (7950), 204 n (6100 $mol^{-1}dm^3cm^{-1}$).

MS (EI, 70 eV): m/z (%) 255 (4) [M^+], 199 (76) [$M-C_4H_8^+$], 138 (74) [$M-C_5H_{11}NO_2^+$], 57 (100).

Elemental Analysis: $C_{13}H_{18}ClNO_2$ (255.74)
Calculated: C: 61.05 H: 7.09 N: 5.48
Found: C: 60.80 H: 6.84 N: 5.26

3.1.2. [1-{2-(*tert*-Butoxycarbonylamino)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (135)[94]



Prepared from [2-(4-chloro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (**134**) (1100 mg, 2.4 mmol). After solvent concentration, the residue is dissolved in CH_3CN and is pre-purified by column filtration (alumina, CH_3CN). The product is purified by column chromatography on aminopropyl silica (*i*PrOH) and is finally recrystallised from *i*PrOH giving colourless needles.

Yield: 910 mg (65 %)

TLC (NH_2-Si, *i*PrOH): R_f = 0.46

HPLC retention volumes: 103 mL (CH_3CN), 95 mL (*i*PrOH-CH_3CN (1:1)), 95 mL (*i*PrOH-CH_3CN (2:1)), 97 mL (*i*PrOH-CH_3CN (4:1)), 123 mL (*i*PrOH-CH_3CN (8:1)), 132 mL (*i*PrOH-CH_3CN (12:1)), 141 mL (*i*PrOH-CH_3CN (18:1)), 230 mL (*i*PrOH).

Melting Point : 127 °C (decomposes)

^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.47 (d, *J* = 6.1 Hz, 2H, η-C*H*$_{ar}$), 6.31 (d, *J* = 6.3 Hz, 2H, η-C*H*$_{ar}$), 5.47 (s, 5H, Cp), 5.20 (brt, 1H, CH_2N*H*), 3.37 (dt, *J* = 6.7 Hz, 2H, C*H*$_2$NH), 2.73 (t, *J* = 6.7 Hz, 2H, C*H*$_2$CH$_2$NH), 1.39 (s, 9H, OC(C*H*$_3$)$_3$).

^{13}C NMR (90.6 MHz; $CDCl_3$): δ = 156.10 (*C*=O), 104.83 (η-*C*$_{ar}$Cl), 103.86 (η-*C*$_{ar}$CH$_2$), 86.85 (η-*C*$_{ar}$H), 86.66 (η-*C*$_{ar}$H), 82.74 (Cp), 79.60 (O*C*(CH$_3$)$_3$), 40.80 (*C*H$_2$NH), 33.90 (*C*H$_2$CH$_2$NH), 28.32 (OC(*C*H$_3$)$_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3369 (s), 3125 (m), 3096 (w), 2987 (m), 2937 (m), 1684 (s), 1524 (s), 1453 (s), 1369 (m), 1281 (s), 1251 (m), 1176 (s), 1094 (m), 839 (s).

UV/Vis (CH_3CN): λ_{max} (ε) = 224 (11000), 200 nm (46000 mol^{-1}dm^{3}cm^{-1}).

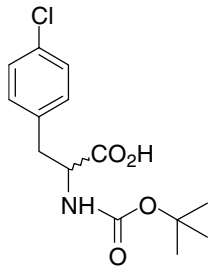
MS (FAB$^+$, NBA): m/z (%) 421/422/424 (61/100/78) [M$^+$].

HRMS (FAB): calcd. for $C_{18}H_{23}{}^{35}ClO_2N\,{}^{102}Ru$ [M$^+$]: 422.0463, found 422.0449.

Elemental Analysis: $C_{18}H_{23}ClF_6NO_2PRu$ (566.87)
Calculated: C: 38.14 H: 4.09 N: 2.47
Found: C: 37.86 H: 4.30 N: 2.27

3.2 [1-{2-(*tert*-Butoxycarbonylamino)-2-(carboxy)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (109)[85b]

3.2.1. 2-*tert*-Butoxycarbonylamino-3-(4-chloro-phenyl)-propionic acid (145)



Et_3N (3.2 ml, 22.8 mmol) is added to a solution of D,L-4-chloro-phenylalanine (**144**) (3.034 g, 15.2 mmol) in CH_3OH-H_2O (1:1) (55 mL). The reaction is cooled to 0 °C and

Boc_2O (3.635 g, 17.2 mmol) is added. After 30 min the cold bath is removed and the mixture is allowed to stir for further 42 hours at room temperature. The mixture is concentrated and the residue is dissolved in H_2O-EtOAc (1:1). The organic layer is ignored and the aqueous phase is brought to pH 1 with HCl 1N and is back extracted with EtOAc. The organic extracts are washed with brine and dried over Na_2SO_4. The solvent is removed and the product is recrystallised from petroleum ether yielding colourless needles.

Yield: 2.921 g (64 %)

TLC (Si, EtOAc-TMP (7:3)): R_f = 0.64

Melting Point : 149-150 °C

^{1}H NMR (250 MHz, CD_3OD): δ = 7.26 (d, J = 8.5 Hz, 2H, CH_{ar}), 7.20 (d, J = 8.5 Hz, 2H, CH_{ar}), 4.33 (dd, J = 5.4, 8.9 Hz, 1H, CH_2CH(CO)NH), 3.15 (dd, J = 5.1, 14.0 Hz, 1H, CHHCH(CO)NH), 2.88 (dd, J = 9.3, 14.1 Hz, 1H, CHHCH(CO)NH), 1.37 (s, 9H, OC(CH_3)$_3$).

^{13}C NMR (62.9 MHz; CD_3OD): δ = 175.11 (C=O), 157.74 (C=O), 137.56 (C_{ar}Cl), 133.63 ($C_{ar}CH_2$), 132.00 (C_{ar}H), 129.43 (C_{ar}H), 80.60 (O C(CH_3)$_3$), 56.12 ($CH_2$$C$H(CO)NH), 38.14 ($C$$H_2$CH(CO)NH), 28.68 (OC($C$$H_3$)$_3$).

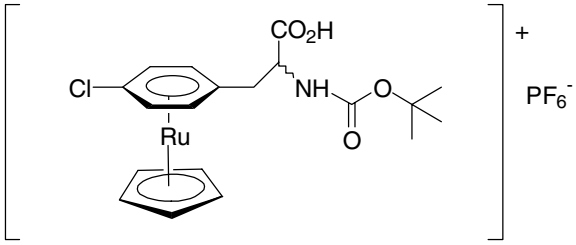
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3372 (m), 2986 (m), 1708 (s), 1691 (s), 1527 (s), 1491 (w), 1450 (w), 1424 (w), 1367 (w), 1320 (m), 1307 (m), 1269 (m), 1239 (m), 1170 (s), 1056 (m), 1033 (w), 936 (w), 810 (w), 777 (w), 735 (w), 641 (w), 567 (w).

UV/Vis (CH_3OH): λ_{max} (ε) = 276 (1500), 222 (11800), 204 nm (11400 mol^{-1}dm^{3}cm^{-1}).

EI (EI, 70 eV): m/z (%): 299 (1) [M$^+$], 243 (11) [M$^+$-C_4H_4], 182 (67) [M$^+$-$C_5H_{11}NO_2$], 125 (26) [M$^+$-$C_7H_{12}NO_4$], 57 (100).

Elemental Analysis: $C_{14}H_{18}ClNO_4$ (299.75)
Calculated: C: 56.10 H: 6.05 N: 4.67
Found: C: 55.68 H: 6.10 N: 4.54

3.2.2. [1-{2-(*tert*-Butoxycarbonylamino)-2-(carboxy)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (109)[85b]



Prepared from 2-*tert*-butoxycarbonylamino-3-(4-chloro-phenyl)-propionic acid (**145**) (596 mg, 1.985 mmol). After solvent concentration, the residue is dissolved in 2 mL CH_3OH-CH_2Cl_2 (1:1) and 50 mL Et_2O is added to promote product precipitation. The pale brown powder is collected and is purified by column chromatography on aminopropyl silica (*i*PrOH-H_2O (6:1) to (4:1)) giving a pale brown powder.

Yield: 880 mg (85 %)

TLC (NH_2-Si, *i*PrOH-H_2O (6:1)): R_f = 0.53.

^{1}H NMR (250 MHz, CD_3OD): δ = 6.69 (dd, *J* = 2.8, 7.5 Hz, 2H, η-C*H*$_{ar}$), 6.39 (d, *J* = 6.0 Hz, 1H, η-C*H*$_{ar}$), 6.30 (d, *J* = 6.6 Hz, 1H, η-C*H*$_{ar}$), 5.52 (s, 5H, Cp), 4.35 (bq, 1H, CH_2C*H*(CO)NH), 3.07 (dd, *J* = 6.9, 13.8 Hz, 1H, C*H*HCH(CO)NH), 2.75 (dd, *J* = 8.3, 13.8 Hz, 1H, C*H*HCH(CO)NH), 1.40 (s, 9H, OC(C*H*$_3$)$_3$).

^{13}C NMR (90.6 MHz; CD_3OD): δ = 173.55 (*C*=O), 157.78 (*C*=O), 106.41 (η-*C*$_{ar}$Cl), 103.29 (η-*C*$_{ar}$$CH_2$), 88.52 (η-*C*$_{ar}$H), 88.36 (η-*C*$_{ar}$H), 88.33 (η-*C*$_{ar}$H), 88.22 (η-*C*$_{ar}$H), 83.98 (Cp), 81.11 (O *C*(CH_3)$_3$), 55.60 (CH_2*C*H(CO)NH), 37.28 (*C*H_2CH(CO)NH), 28.67 (OC(*C*H_3)$_3$).

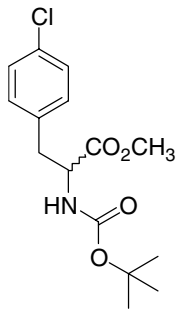
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3415 (s), 3065 (m), 2963 (m), 2924 (m), 1701 (s), 1617 (s) 1454 (m), 1384 (m), 1366 (m), 1249 (w), 1166 (m), 1087 (m), 1053 (m), 1024 (w), 854 (w).

UV/Vis (CH_3OH): λ_{max} (ε) = 266 (5500), 206 nm (30700 mol^{-1}dm^{3}cm^{-1}).

MS (FAB$^+$, NBA): m/z (%) 465/466/468 (61/100/77) [M$^+$].

3.3 [1-{2-*N*-(*tert*-Butoxycarbonylamino)-2-(methoxycarbonyl)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (147)[85b]

3.3.1. 2-*tert*-Butoxycarbonylamino-3-(4-chloro-phenyl)-propionic acid methyl ester (146)



2-*tert*-Butoxycarbonylamino-3-(4-chloro-phenyl)-propionic acid (**145**) (581 mg, 1.94 mmol) is dissolved in dry CH_2Cl_2 and DCC (440 mg, 2.13 mmol), CH_3OH (0.86 mL, 2.13 mmol) and 4-pyrrolidine-pyridine (29 mg, 0.194 mmol) are added. The reaction is allowed to stir at room temperature for 24 hours and then the DCC-urea formed is filtered. The organic layer is washed well with saturated aqueous solution of $NaHCO_3$ and with H_2O and is finally dried over Na_2SO_4. The solvent is removed and the product is purified by flash chromatography on silica gel (TMP-EtOAc (7:3)) affording colourless needles.

Yield: 427 mg (85 %)

TLC (Si, TMP-EtOAc (7:3)): R_f = 0.70

Meting Point : 78 °C

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.4 Hz, 2H, CH_{ar}), 7.06 (d, J = 8.3 Hz, 2H, CH_{ar}), 5.90 (d, J = 9.4 Hz, 1H, NH), 4.57 (q, J = 7.0 Hz, 1H, CH_2CH(CO)NH), 3.71 (s, 3H, CO_2CH_3), 3.09 (dd, J = 5.8, 13.8 Hz, 1H, CHHCH(CO)NH), 3.00 (dd, J = 5.9, 14.0 Hz, 1H, CHHCH(CO)NH), 1.53 (s, 9H, OC(CH_3)$_3$).

^{13}C NMR (90.6 MHz; $CDCl_3$): δ = 172.09 (*C*=O), 155.02 (*C*=O), 134.58 ($C_{ar}Cl$), 132.98 ($C_{ar}CH_2$), 130.66 ($C_{ar}H$), 128.69 ($C_{ar}H$), 80.09 (O $C(CH_3)_3$), 54.30 ($CH_2CH(CO)NH$), 52.31 (CO_2CH_3), 37.79 ($CH_2CH(CO)NH$), 28.28 ($OC(CH_3)_3$).

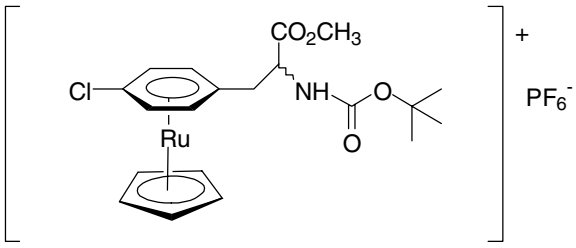
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3356 (s), 2994 (m), 2952 (m), 1735 (s), 1679 (s), 1524 (s), 1494 (m), 1437 (m), 1407 (w), 1370 (m), 1351 (s), 1297 (s), 1274 (s), 1230 (s), 1167 (s), 1091 (m), 1056 (m), 1014 (s), 971 (m), 935 (w), 860 (w), 834 (w), 809 (m), 735 (w), 613 (m), 519 (m), 415 (m).

UV/Vis (CH_3OH): λ_{max} (ε) = 276 (3350), 222 (24500), 204 nm (17000 $mol^{-1}dm^3cm^{-1}$).

MS (EI, 70 eV): m/z (%) 313 (1) [M^+], 257 (41) [M^+-C_4H_8], 240 (32) [M^+-C_4H_9O], 212 (10) [M^+-$C_5H_9O_2$], 196 (45) [M^+-$C_5H_9O_2$-NH_2].

Elemental Analysis: $C_{15}H_{20}ClNO_4$ (313.78)
Calculated: C: 57.42 H: 6.42 N: 4.46
Found: C: 57.68 H: 6.42 N: 4.21

3.3.2. [1-{2-(*tert*-Butoxycarbonylamino)-2-(methoxycarbonyl)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (147)[85b]



Prepared from 2-*tert*-butoxycarbonylamino-3-(4-chloro-phenyl)-propionic acid methyl ester (**146**) (502 mg, 1.60 mmol). After solvent concentration, the residue is dissolved in CH_3CN and is pre-purified by column filtration on alumina (CH_3CN). The product is purified by column chromatography on aminopropyl silica (*i*PrOH) and is recrystallised fro *i*PrOH giving a colourless powder.

Yield: 780 mg (78 %)

TLC (NH_2-Si, *i*PrOH): R_f = 0.43

HPLC retention volumes: 102 mL (CH_3CN), 98 mL (*i*PrOH-CH_3CN – (1:1)), 98 mL (*i*PrOH -CH_3CN – (2:1)), 98 mL (*i*PrOH -CH_3CN – (4:1)), 119 mL (*i*PrOH -CH_3CN – (8:1)), 127 mL (*i*PrOH -CH_3CN – (12:1)), 136 mL (*i*PrOH -CH_3CN – (18:1)), 236 mL (*i*PrOH).

Meting Point : 70-71 °C (decomposes)

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.57 (t, *J* = 6.3 Hz, 2H, η-C*H*$_{ar}$), 6.31 (t, *J* = 6.3 Hz, 2H, η-C*H*$_{ar}$), 5.50 (s, 5H, Cp), 5.43 (d, *J* = 4.3 Hz, 1H, CH_2N*H*), 4.47 (m, 1H, CH_2C*H*(CO)NH), 3.09 (dd, *J* = 6.5, 14.7 Hz, 1H, C*H*HCH(CO)NH), 2.83 (dd, *J* = 7.8, 14.5 Hz, 1H, C*H*HCH(CO)NH), 1.38 (s, 9H, OC(C*H*$_3$)$_3$).

^{13}C NMR (62.9 MHz; $CDCl_3$): δ = 170.80 (*C*=O), 155.35 (*C*=O), 105.11 (η-*C*$_{ar}$Cl), 101.37 (η-*C*$_{ar}$$CH_2$), 87.22 (η-*C*$_{ar}$H), 87.03 (η-*C*$_{ar}$H), 86.93 (η-*C*$_{ar}$H), 83.05 (Cp), 80.53 (O*C*(CH_3)$_3$), 54.31 (CH_2*C*H(CO)NH), 52.96 (CO_2*C*H_3), 36.73 (*C*H_2CH(CO)NH), 28.17 (OC(*C*H_3)$_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3425 (w), 3121 (w), 2980 (w), 1746 (s), 1711 (s), 1506 (m), 1461 (m), 1417 (w), 1367 (m), 1289 (w), 1256 (w), 1167 (m), 1094 (w), 1056 (w), 1011 (w), 833 (s), 556 (s).

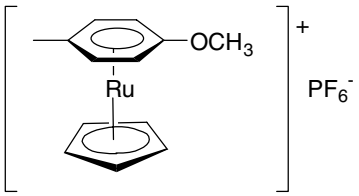
UV/Vis (CH_3OH): λ_{max} (ε) = 206 (25700), 2046 nm (26200 mol^{-1}dm^{3}cm^{-1}).

MS (FAB$^+$, NBA): m/z (%) 479/480/482 (62/100/79) [M$^+$].

HRMS (FAB): calcd. for $C_{20}H_{25}{}^{35}ClO_4N^{102}Ru$ [M$^+$]: 480.0520, found 480.0522.

Elemental Analysis: $C_{18}H_{23}ClF_6NO_2PRu$ (566.87)
Calculated: C: 38.44 H: 4.03 N: 2.24
Found: C: 38.22 H: 4.27 N: 2.12

3.4 (η^5-Cyclopentadienyl)(1-methoxy-4-methyl-η^6-benzene)ruthenium hexafluorophosphate (145)[94]



Prepared from 4-methylanisol (**148**) (69.0 mg, 0.07 mL, 0.565 mmol). The solvent is concentrated and the product is dissolved in CH_3CN followed by pre-purification on a neutral alumina column (CH_3CN). The solvent is evaporated and the product is finally purified by column chromatography on aminopropyl silica (*i*PrOH) followed by recrystallisation from *i*PrOH to yield a colourless powder.

Yield: 197 mg (80 %)

TLC (NH_2-Si, *i*PrOH): R_f = 0.26

HPLC retention volumes: 108 mL (CH_3CN), 104 mL (*i*PrOH-CH_3CN (1:1)), 107 mL (*i*PrOH-CH_3CN (2:1)), 116 mL (*i*PrOH-CH_3CN (4:1)), 126 mL (*i*PrOH-CH_3CN (8:1)), 138 mL (*i*PrOH-CH_3CN (12:1)), 150 mL (*i*PrOH-CH_3CN (18:1)).

Melting Point: 147-148 °C (decomposes)

^{1}H NMR (360 MHz, [D_6]acetone): δ = 6.34 (d, J = 6.7 Hz, 2H, η-CH_{ar}), 6.26 (d, J = 6.7 Hz, 2H, η-CH_{ar}), 5.48 (s, 5H, Cp), 3.84 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3).

^{13}C NMR (90.6 MHz; [D_6]acetone): δ = 134.73 (η-C_{ar}OCH$_3$), 100.46 (η-C_{ar}CH$_3$), 86.27 (η-C_{ar}H), 81.13 (Cp), 74.67 (η-C_{ar}H), 57.71 (OCH$_3$), 19.69 (η-C$_{ar}$$CH_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 118 (m), 1549 (s), 1491 (s), 1446 (s), 1264 (s), 1011 (s), 840 (s).

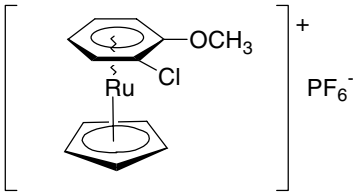
UV/Vis (CH_3CN): λ_{max} (ε) = 280 (10800), 226 (15600), 200 nm (61600 mol^{-1}dm^{3}cm^{-1}).

MS (FAB$^+$, NBA): m/z (%) 288/289/291 (61/100/60) [M$^+$].

HRMS (FAB): calcd. for $C_{13}H_{15}O\ ^{102}Ru\ [M^+]$: 289.0170, found 289.0159.

Elemental Analysis: $C_{13}H_{15}F_6OPRu$ (433.30)
Calculated: C: 36.04 H: 3.49
Found: C: 35.64 H: 3.50

3.5 (1-Chloro-2-methoxy-η^6-benzene)(η^5-cyclopentadienyl)ruthenium hexafluorophosphate (155)[94]



Prepared from 2-chloroanisol (**154**) (116 mg, 0.10 mL, 0.825 mmol). The solvent is concentrated and the product is dissolved in CH_3CN and is pre-purified on a neutral alumina column (CH_3CN). The solvent is evaporated and the product is finally purified by column chromatography on aminopropyl silica (*i*PrOH-CH_3CN (12:1)) followed by recrystallisation fro *i*PrOH affording colourless needles.

Yield: 300 mg (80 %)

TLC (NH_2-Si, *i*PrOH): R_f = 0.24

HPLC retention volumes: 109 mL (CH_3CN), 100 mL (*i*PrOH-CH_3CN (1:1)), 114 mL (*i*PrOH-CH_3CN (2:1)), 126 mL (*i*PrOH-CH_3CN (4:1)), 143 mL (*i*PrOH-CH_3CN (8:1)), 167 mL (*i*PrOH-CH_3CN (12:1)), 183 mL (*i*PrOH-CH_3CN (18:1)).

Melting Point : 147-149 °C (decomposes)

^{1}H NMR (360 MHz, [D_6]acetone): δ = 6.78 (d, J = 5.7 Hz, 1H, η-CH_{ar}), 6.69 (d, J = 6.0 Hz, 1H, η-CH_{ar}), 6.25 (t, J = 5.5 Hz, 1H, η-CH_{ar}), 6.21 (t, J = 5.4 Hz, 1H, η-CH_{ar}), 5.58 (s, 5H, Cp), 4.06 (s, 3H, OCH_3).

^{13}C NMR (90.6 MHz; [D$_6$]acetone): δ = 132.30 (η-C_{ar}OCH$_3$), 96.45 (η-C_{ar}Cl), 86.81 (η-C_{ar}H), 84.52 (η-C_{ar}H), 83.90 (η-C_{ar}H), 81.50 (Cp), 72.71 (η-C_{ar}H), 58.13 (OCH$_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3109 (m), 1521 (s), 1465 (s), 1435 (s), 1276 (s), 1011 (s), 841 (s), 823 (s), 557 (s).

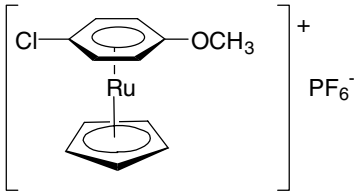
UV/Vis (CH$_3$CN): λ_{max} (ε) = 232 (4000), 204 nm (26500 mol^{-1}dm^{3}cm^{-1}).

MS (FAB$^+$, NBA): m/z (%) 308/309/311 (61/100/78) [M$^+$].

HRMS (FAB): calcd. for C$_{12}$H$_{12}$^{35}ClO ^{101}Ru [M$^+$]: 308.9620, found = 308.9642.

Elemental Analysis: C$_{12}$H$_{12}$ClF$_6$OPRu (454)
Calculated: C: 31.77 H: 2.67
Found: C: 31.85 H: 2.81

3.6 (1-Chloro-4-methoxy-η^6-benzene)(η^5-cyclopentadienyl)ruthenium hexafluorophosphate (151)[96]



Prepared from 4-chloroanisol (**150**) (46 mg, 0.04 mL, 0.326 mmol). The solvent is concentrated and the product is dissolved in CH$_3$CN followed by pre-purification on a neutral alumina column (CH$_3$CN). The solvent is evaporated and the product is purified by column chromatography on aminopropyl silica (*i*PrOH-CH$_3$CN (8:1)) and is finally recrystallised fro *i*PrOH giving colourless needles.

Yield: 140 mg (95 %)

TLC (NH$_2$-Si, *i*PrOH): R_f = 0.24

HPLC retention volumes: 110 mL (CH_3CN), 107 mL (*i*PrOH-CH_3CN – (1:1)), 110 mL (*i*PrOH-CH_3CN – (2:1)), 120 mL (*i*PrOH-CH_3CN – (4:1)), 129 mL (*i*PrOH-CH_3CN – (8:1)), 146 mL (*i*PrOH-CH_3CN – (12:1)), 165 mL (*i*PrOH-CH_3CN – (18:1)).

Melting Point : 166-167 °C (decomposes)

^{1}H NMR (250 MHz, CD_3OD): δ = 6.60 (d, J = 6.5 Hz, 2H, η-CH_{ar}), 6.39 (d, J = 6.4 Hz, 2H, η-CH_{ar}), 5.52 (s, 5H, Cp), 3.79 (s, 3H, OCH_3).

^{13}C NMR (62.9 MHz; CD_3OD): δ = 135.35 (η-C_{ar}OCH$_3$), 103.34 (η-C_{ar}Cl), 86.84 (η-C_{ar}H), 82.91 (Cp), 74.98 (η-C_{ar}H), 58.01 (OCH$_3$).

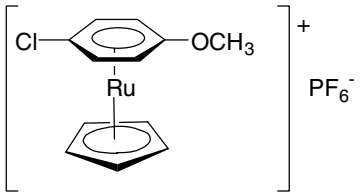
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3126 (s), 2941 (m), 1889 (w), 1528 (s), 1464 (s), 1441 (s), 1418 (s), 1256 (s), 1096 (s), 1005 (s), 905 (s), 848 (s), 640 (s).

UV/Vis (CH_3OH): λ_{max} (ε) = 206 (20200), 204 nm (19800 mol^{-1}dm^{3}cm^{-1}).

MS (FAB$^+$, NBA): m/z (%) 308/309/311 (61/100/78) [M$^+$].

HRMS (FAB): calcd. for $C_{12}H_{12}{}^{35}ClO^{102}Ru$ [M$^+$]: 308.9620, found = 308.9641.

3.7 (η^5-Cyclopentadienyl)(hydroxy-η^6-benzene)ruthenium hexafluorophosphate (153)[97]



Prepared from phenoxy-trimethylsilane (**152**) (133 mg, 0.15 mL, 0.8 mmol). The solvent is concentrated and the product is dissolved in CH_3CN and is pre-purified on a neutral alumina column (CH_3CN). The solvent is concentrated to 2 mL and after Et_2O addition the precipitate is collected. Recrystallisation fro *i*PrOH affords a colourless powder.

Yield: 310 mg (96 %)

TLC (NH_2-Si, *i*PrOH): R_f = 0.16

Melting Point : at 170 °C starts decomposition without melting

HPLC retention volumes: 109 mL (CH_3CN), 107 mL (*i*PrOH-CH_3CN – (1:1)), 112 mL (*i*PrOH-CH_3CN – (2:1)), 124 mL (*i*PrOH-CH_3CN – (4:1)), 130 mL (*i*PrOH-CH_3CN – (8:1)), 150 mL (*i*PrOH-CH_3CN – (12:1)), 155 mL (*i*PrOH-CH_3CN – (18:1)).

^{1}H NMR (360 MHz, CD_3OD): δ = 6.10 (d, *J* = 6.0 Hz, 2H, η-CH_{ar}), 6.07 (t, *J* = 5.6 Hz, 2H, η-CH_{ar}), 5.87 (t, *J* = 5.2 Hz, 1H, η-CH_{ar}), 5.34 (s, 5H, Cp).

^{13}C NMR (90.6 MHz; CD_3OD): δ = 85.49 (η-C_{ar}H), 83.11 (η-C_{ar}H), 80.81 (Cp), 76.39 (η-C_{ar}H).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3420 (m), 3007 (w), 1623 (w), 1479 (m), 1467 (m), 1409 (w), 1363 (w), 1267 (w), 1176 (m), 1102 (m), 944 (m), 841 (s), 559 (s).

UV/Vis (CH_3OH): λ_{max} (ε) = 234 (2200), 210 nm (5800 $mol^{-1}dm^3cm^{-1}$).

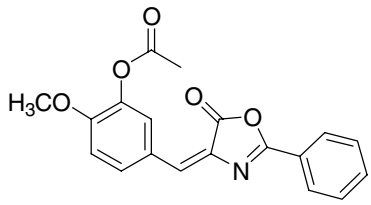
MS (FAB$^+$, NBA): m/z (%) 260/261/263 (64/100/59) [M^+].

HRMS (FAB): calcd. for $C_{11}H_{11}O^{102}Ru$ [M^+]: 260.9856, found = 260.9889.

4 Synthesis of Tyrosine Sub-Units

4.1 3-(3-Benzyloxy-4-methoxy-phenyl)-2-*tert*-butoxycarbonylamino-propionic acid (118)

4.1.1. Acetic acid 2-methoxy-5-(5-oxo-2-phenyl-oxazol-4-ylidenemethyl)-phenyl ester (122)[89]



Isovaniline (**120**) (4.50 g, 29.58 mmol), hippuric acid (5.50 g, 30.73 mmol), sodiu acetate (2.50 mg, 30.49 mmol) and acetic anhydride (9 mL) are allowed to stir under reflux for 30 min. The mixture is cooled to room temperature and EtOH (9 mL) is added. The yellow crystals obtained are filtered and recrystallised from EtOH.

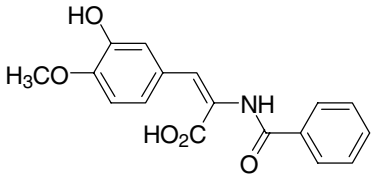
Yield: 4.056 g (38 %)

Melting Point: 137-139 °C

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 6.8 Hz, 2H, o-C*H*$_{ar}$), 8.08 (d, *J* = 2.1 Hz, 1H, C*H*$_{ar}$), 7.95 (dd, *J* = 2.1, 8.7 Hz, 1H, C*H*$_{ar}$), 7.58 (d, *J* = 7.1 Hz, 1H, *p*-C*H*$_{ar}$), 7.52 (t, *J* = 6.9 Hz, 2H, *m*-C*H*$_{ar}$), 7.16 (s, 1H, C*H*=(CO_2)N), 7.03 (d, *J* = 8.6 Hz, 1H, C*H*$_{ar}$), 3.91 (s, 3H, OC*H*$_3$), 2.37 (s, 3H, OC*H*$_3$).

^{13}C NMR (90.6 MHz; $CDCl_3$): δ = 168.81 (*C*=O), 167.73 (*C*=O), 162.96 (*C*(O)=N), 153.78 ($C_{ar}OCH_3$), 140.04 (C_{ar}OAc), 133.19 (*C*H=C), 132.42 (*p*-C_{ar}H), 131.93 (C_{ar}C=(O)N), 130.81 (C_{ar}H), 128.93 (*o*-C_{ar}H), 128.29 (*m*-C_{ar}H), 126.81 (C_{ar}CH=C), 126.42 (C_{ar}H), 125.72 (C_{ar}CH=*C*), 112.25 (C_{ar}H), 56.08 (O*C*H$_3$), 20.70 (C=O*C*H$_3$).

4.1.2. 2-Benzoylamino-3-(3-hydroxy-4-methoxy-phenyl)-acrylic acid (123)[89]



Acetic acid 2-methoxy-5-(5-oxo-2-phenyl-oxazol-4-ylidenemethyl)-phenyl ester (**122**) (4.00 g, 11.11 mmol) is dissolved in 400 mL aqueous NaOH 2 % and is stirred under reflux. The azalactone hydrolyses and dissolves. When everything is dissolved, the impurities are filtered and the solution is acidified to pH 4-5 with concentrated HCl. The solution rests for 24 hours on the refrigerator to allow complete precipitation. The precipitate is filtered and is recrystallised from H_2O to afford light yellow crystals.

Yield: 2.30 mg (58 %)

TLC (Si, CH_3OH-$CHCl_3$ ((1:10)): R_f = 0.24

Melting Point : 129-130 °C

^{1}H NMR (360 MHz, [D_6]DMSO): δ = 9.79 (s, 1H, CO_2H), 9.14 (s, 1H, N*H*Bz), 8.00 (d, *J* = 7.1 Hz, 2H, *o*-CH_{ar}), 7.60 (d, *J* = 7.1 Hz, 1H, *p*-CH_{ar}), 7.54 (t, *J* = 7.0 Hz, 2H, *m*-CH_{ar}), 7.33 (s, 1H, CH_{ar}), 7.20 (s, 1H, C*H*=(CO_2H)NH), 7.11 (d, *J* = 8.4 Hz, 1H, CH_{ar}), 6.93 (d, *J* = 8.4 Hz, 1H, CH_{ar}), 3.77 (s, 3H, OCH_3).

^{13}C NMR (90.6 MHz; [D_6]DMSO): δ = 166.64 (*C*=O), 166.01 (*C*=O), 149.07 ($C_{ar}OCH_3$), 149.07 (C_{ar}OH), 133.79 (C_{ar}CONH), 133.70 (*C*H=C), 131.67 (*p*-C_{ar}H), 128.41 (*o*-C_{ar}H), 128.10 (*m*-C_{ar}H), 126.52 (C_{ar}CH=C), 124.94 (C $_{ar}$CH=*C*), 122.67 (C_{ar}H), 116.58 (C_{ar}H), 111.80 (C_{ar}H), 55.57 (O*C*H_3).

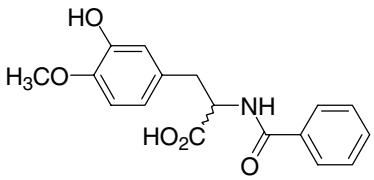
IR (KBr): $\tilde{\nu}$ (cm^{-1}) $\tilde{\nu}$ 3290 (m), 1709 (m), 1683 (s), 1634 (s), 1579 (m), 1516 (s), 1489 (m), 1435 (m), 1265 (m), 1126 (m), 1018 (w), 723 (m), 613 (m).

UV/Vis (CH_3OH): λ_{max} (ε) = 318 (9260), 292 (7450), 220 (20600), 208 n (18200 $mol^{-1}dm^3cm^{-1}$).

MS (EI, 70 eV): m/z (%) 313 (96) [M^+], 295 (21) [M^+–H_2O], 265 (12) [M^+–CO_2], 194 (10) [M^+–C_7H_5NO], 163 (22), 137 (17) [M^+–$C_9H_6NO_3$], 105 (100) [M^+–$C_{10}H_{10}NO_4$].

Elemental Analysis: $C_{17}H_{15}NO_5$ (313)
Calculated: C: 65.17 H: 4.83 N = 4.47
Found: C: 65.19 H: 5.07 N = 4.11

4.1.3. 2-Benzoylamino-3-(3-hydroxy-4-methoxy-phenyl)-propionic acid (124)[89]



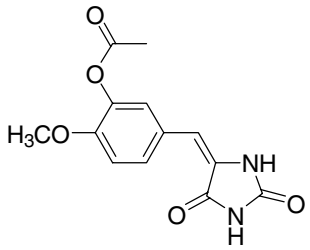
2-Benzoylamino-3-(3-hydroxy-4-methoxy-phenyl)-acrylic acid (**123**) (2.30 g, 6.5 mmol) is dissolved in 23 mL H_2O and 15 g of NaHg divided in 4 portion is added to the solution at each 15 min under vigorous stirring. After addition, the mixture is allowed to stir at room temperature until complete decolouration. The mercury is separated and the solution is brought to pH 4-5 with concentrated HCl. The product starts to precipitate and, after staying overnight in refrigerator, the product is filtered and recrystallised from H_2O giving pale yellow crystals.

Yield: 1.285 g (63 %)

^{1}H NMR (250 MHz, CD_3OD): δ = 7.77 (d, J = 6.4 Hz, 2H, *o*-CH_{ar}), 7.49 (d, J = 6.7 Hz, 1H, *p*-CH_{ar}), 7.42 (t, J = 6.8 Hz, 2H, *m*-CH_{ar}), 6.83 (d, J = 7.9 Hz, 1H, CH_{ar}), 6.78 (d, J = 1.5 Hz, 1H, CH_{ar}), 6.71 (dd, J = 1.8, 8.3 Hz, 1H, CH_{ar}), 4.66 (dd, J = 5.2, 8.3 Hz, 1H, CH_2C*H*(CO)NH), 3.78 (s, 3H, OC H_3), 3.21 (dd, J = 5.3, 13.2 Hz, C*H*HCH(CO)NH), 2.99 (dd, J = 8.3, 13.6 Hz, C*H*HCH(CO)NH).

^{13}C NMR (90.6 MHz; CD_3OD): δ = 174.99 (*C*=O), 170.17 (*C*=O), 147.98 ($C_{ar}OCH_3$), 147.48 (C_{ar}OH), 135.42 (C_{ar}CONH), 132.75 (*p*-C_{ar}H), 131.46 ($C_{ar}CH_2$), 129.51 (*o*-C_{ar}H), 128.59 (*m*-C_{ar}H), 121.50 (C_{ar}H), 117.29 (C_{ar}H), 112.75 (C_{ar}H), 56.41 (O*C*H_3), 55.83 (CH_2*C*H(CO)NH), 37.64 (*C*H_2CH(CO)NH).

4.1.4. Acetic acid 5-(2,5-dioxo-benzylidene-imidazolidin-4-ylidene-methyl)-2-methoxy-phenyl ester (125)[89]



Isovaniline (**120**) (4.20 g, 27.6 mmol), hydantoin (2.80 g, 28 mmol), sodium acetate (2.60 g, 31.7 mmol) and acetic anhydride (10 mL) are stirred under reflux for 30 min. After that period, the mixture is cooled and H_2O is added. The precipitate is filtered and washed with hot H_2O followed by recrystallisation from EtOAc which affords yellow needles.

Yield: 6.422 g (84 %)

TLC (Si, EtOAc-*n*BuOH-AcOH-H_2O (1:1:1:1)): R_f = 0.80

Melting Point : 197-199 °C

^{1}H NMR (250 MHz, [D_6]DMSO): δ = 11.12 (brs, 1H, N*H*), 7.54 (dd, *J* = 2.2, 8.6 Hz, 1H, CH_{ar}), 7.50 (d, *J* = 2.1 Hz, 1H, CH_{ar}), 7.17 (d, *J* = 8.5 Hz, 1H, CH_{ar}), 6.54 (s, 1H, C*H*=C), 3.82 (s, 3H, OCH_3), 2.28 (s, 3H, C=OCH_3).

^{13}C NMR (90.6 MHz; [D_6]DMSO): δ = 168.27 (*C*=O), 168.01 (*C*=O), 161.83 (*C*=O), 151.58 ($C_{ar}OCH_3$), 151.43 (C_{ar}OAc), 139.37 (C_{ar}CH=*C*), 129.25 (*C*H=C), 125.22 (C_{ar}CH=C), 123.54 (C_{ar}H), 112.88 (C_{ar}H), 109.71 (C_{ar}H), 55.91 (O CH_3), 26.16 (C=OCH_3).

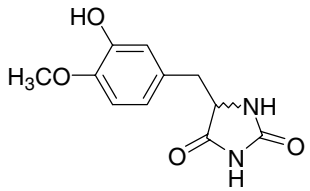
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3440 (m), 3226 (m), 1795 (m), 1743 (s), 1705 (s), 1656 (s), 1608 (m), 1524 (m), 1455 (m), 1377 (s), 1279 (s), 1203 (s), 1127 (s), 1015 (m), 803 (w), 763 (m).

UV/Vis (CH_3OH): λ_{max} (ε) = 334 (3500), 212 (3900 $mol^{-1}dm^3cm^{-1}$).

MS (EI, 70 eV): m/z (%) 276 (22) [M^+], 234 (100) [M^+–C_2H_2O], 219 (10) [M^+–CHN_2O], 163 (10), 148 (19).

Elemental Analysis: $C_{13}H_{12}N_2O_5$ (276)
Calculated: C: 56.52 H: 4.38 N: 10.14
Found: C: 56.24 H: 4.67 N: 9.80

4.1.5. 5-(3-Hydroxy-4-methoxy-benzyl)-imidazoline-2,4-dione (126)[89]



Acetic acid 5-(2,5-dioxo-benzylidene-imidazolidin-4-ylidene-methyl)-2-methoxy-phenyl ester (**125**) (6.20 g, 22.46 mmol) is dissolved in 190 mL H_2O and aqueous NaOH (10 %) is added until everything dissolves. The mixture is treated with three portions of 20 g of NaHg each, which are added every 15 min under stirring. When the mixture becomes colourless, the mercury is separated and the solution is neutralised with concentrated HCl. The product starts to precipitate and after staying overnight in refrigerator, it is filtered and recrystallised from H_2O yielding colourless needles.

Yield: 4.755 g (90 %)

TLC (Si, CH_3OH-CH_3Cl (1:10)): R_f = 0.21

Melting Point : 165-166 °C

^{1}H NMR (360 MHz, [D_6]DMSO): δ = 10.41 (brs, 1H, N*H*), 8.85 (brs, 1H, N*H*), 7.86 (s, 1H, O*H*), 6.80 (d, *J* = 8.0 Hz, 1H, CH_{ar}), 6.63 (s, 1H, CH_{ar}), 6.57 (d, *J* = 8.0 Hz, 1H, CH_{ar}), 4.25 (brt, 1H, CH_2CH(CO)NH), 3.73 (s, 3H, OCH_3), 2.80 (d, *J* = 4.3 Hz, 2H, CH_2CH(CO)NH).

^{13}C NMR (90.6 MHz; [D$_6$]DMSO): δ = 175.47 (*C*=O), 157.35 (*C*=O), 146.61 ($C_{ar}OCH_3$), 146.02 ($C_{ar}OH$), 128.05 ($C_{ar}CH_2CH$), 120.62 ($C_{ar}H$), 117.30 ($C_{ar}H$), 111.93 ($C_{ar}H$), 58.72 ($CH_2CH(CO)NH$) 55.66 (OCH_3), 35.81 ($CH_2CH(CO)NH$).

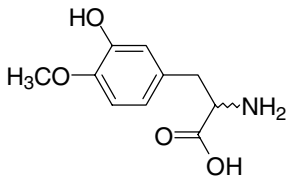
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3413 (s), 3248 (s), 3175 (s), 3068 (s), 1772 (s), 1720 (s), 1591 (m), 1512 (s), 1439 (s), 1415 (s), 1364 (m), 1276 (s), 1247 (s), 1200 (s), 1131 (s), 1019 (s), 948 (w), 888 (w), 791 (m), 762 (m), 673 (m), 642 (m).

UV/Vis (CH_3OH): λ_{max} (ε) = 230 (1800), 204 (31600 mol^{-1}dm^{3}cm^{-1}).

MS (EI, 70 eV): m/z (%) 236 (38) [M$^+$], 137 (100) [M$^+$–$C_3H_4N_2O_2$], 122 (23) [M$^+$–$C_4H_7N_2O_2$].

Elemental Analysis: $C_{11}H_{12}N_2O_4$ (236)
Calculated: C: 55.93 H: 5.12 N: 11.86
Found: C: 55.50 H: 5.25 N: 11.94

4.1.6. 2-Amino-3-(3-hydroxy-4-methoxy-phenyl)-propionic acid (127)[89]



5-(3-Hydroxy-4-methoxy-benzyl)-imidazoline-2,4-dione (**126**) (4.00 g, 17.2 mmol) is dissolved in a solution of barium hydroxide octahydrate (85 g, 270 mmol) in 170 mL H_2O. The mixture is heated to reflux until complete ammonium liberation. Then the mixture is diluted with hot H_2O and the barium is precipitated with concentrated H_2SO_4. The filtrate is concentrated to 100 mL and the impurities are removed by extraction with Et_2O. The solvent is removed affording brown-yellow needles.

Yield: 2.30 g (63 %)

TLC (Si, EtOAc-AcOH-*n*BuOH-H_2O (1:1:1:1)): R_f = 0.15

Melting Point : 225 °C starts decomposition

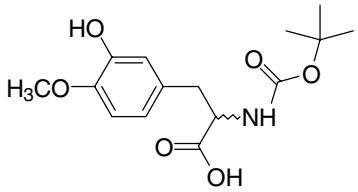
^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 6.81 (d, *J* = 8.2 Hz, 1H, C*H*$_{ar}$), 6.71 (d, *J* = 1.8 Hz, 1H, C*H*$_{ar}$), 6.62 (dd, *J* = 1.9, 7.8 Hz, 1H, C*H*$_{ar}$), 4.25 (brm, 1H, CH$_2$C*H*(CO)NH), 3.72 (s, 3H, OC*H*$_3$), 3.01 (dd, *J* = 4.2, 14.6 Hz, 1H, C*H*HCH(CO)NH), 2.70 (dd, *J* = 8.0, 14.1 Hz, 1H, C*H*$_2$CH(CO)NH).

^{13}C NMR (90.6 MHz; [D$_6$]DMSO): δ = 169.50 (*C*=O), 146.40 (*C*$_{ar}$OCH$_3$), 146.34 (*C*$_{ar}$OH), 129.95 (*C*$_{ar}$CH$_2$CH), 119.72 (*C*$_{ar}$H), 116.59 (*C*$_{ar}$H), 112.22 (*C*$_{ar}$H), 58.68 (CH$_2$*C*H(CO)NH), 55.59 (O*C*H$_3$), 36.22 (*C*H$_2$CH(CO)NH).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3473 (s), 1772 (m), 1675 (s), 1456 (s), 1410 (s), 1213 (m), 1069 (w), 1019 (w), 902 (w), 866 (m), 849 (m), 781 (w), 686 (m), 651 (m), 598 (s).

UV/Vis (CH$_3$OH): λ_{max} (ε) = 208 nm (6600 mol^{-1}dm^{3}cm^{-1}).

4.1.7. 2-*tert*-Butoxycarbonylamino-3-(3-hydroxy-4-methoxy-phenyl)-propionic acid (117)



2-Amino-3-(3-hydroxy-4-methoxy-phenyl)-propionic acid (**127**) (4.50 g, 21.80 mmol) is dissolved in 80 mL CH$_3$OH-H$_2$O (1:1) and Et$_3$N (4.6 mL, 32.70 mmol) is added. The mixture is brought to 0 °C followed by addition of Boc$_2$O (5.07 g, 23.30 mmol). The reaction mixture remains at this temperature for further 30 min and then is brought to room temperature, where is allowed to stir for further 48 hours. The solvent is concentrated and H$_2$O-EtOAc (1:1) is added. The aqueous layer is brought to pH 1 with 1N HCl and is extracted with EtOAc. The organic layer is washed with brine and dried over Na$_2$SO$_4$. The solvent is removed and a light pink-orange powder is obtained.

Yield: 4.45 g (66 %)

Melting Point: 110 °C

TLC (Si, EtOAc-TMP (7:3)): R_f = 0.47

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.78 (d, *J* = 8.3 Hz, 1H, C*H*$_{ar}$), 6.76 (d, *J* = 2.2 Hz, 1H, C*H*$_{ar}$), 6.67 (dd, *J* = 2.2, 8.2 Hz, 1H, C*H*$_{ar}$), 4.98 (brd, 1H, N*H*), 4.54 (m, 1H, CH_2C*H*(CO)NH), 3.85 (s, 3H, OC *H*$_3$), 3.05 (m, 1H, C*H*$_2$CH(CO)NH), 1.42 (s, 9H, OC(C*H*$_3$)$_3$).

^{13}C NMR (90.6 MHz; $CDCl_3$): δ = 176.08 (*C*=O), 155.48 (*C*=O), 145.85 (*C*$_{ar}$OCH$_3$), 145.53 (*C*$_{ar}$OH), 128.86 (*C*$_{ar}$CH$_2$CH), 120.95 (*C*$_{ar}$H), 115.63 (*C*$_{ar}$H), 110.94 (*C*$_{ar}$H), 80.27 (O *C*(CH$_3$)$_3$), 55.90 (O *C*H$_3$), 54.28 (CH$_2$*C*H(CO)NH), 37.04 (*C*H$_2$CH(CO)NH), 28.24 (OC(*C*H$_3$)$_3$).

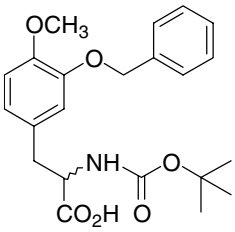
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3391 (m), 2978 (m), 2934 (m), 1729 (s), 1703 (s), 1687 (s), 1593 (m), 1520 (s), 1443 (m), 1368 (m), 1278 (s), 1248 (s), 1160 (s), 1132 (s), 1027 (m), 974 (w), 852 (w), 800 (m), 762 (m), 618 (w).

UV/Vis (CH_3OH): λ_{max} (ε) = 282 (7800), 224 (13300), 204 nm (47000 mol^{-1}dm^{3}cm^{-1}).

MS (EI, 70 eV): m/z (%) 311 (10) [M$^+$], 255 (26) [M$^+$–C$_4$H$_8$], 238 (12) [M$^+$–C$_4$H$_9$O], 194 (32), 137 (100) [M$^+$–C$_7$H$_{12}$NO$_4$].

HRMS (EI): calcd. for $C_{22}H_{27}NO_6$ [M$^+$]: 311.1369, found 311.1369.

4.1.8. 3-(3-Benzyloxy-4-methoxy-phenyl)-2-*tert*-butoxycarbonylamino-propionic acid (118)



2-*tert*-Butoxycarbonylamino-3-(3-hydroxy-4-methoxy-phenyl)-propionic acid (**117**) (3.23 g, 10 mmol) is dissolved in 30 mL CH_3OH and to this solution is given NaOH (0.88 g, 22 mmol). The mixture is brought to reflux followed by the addition of benzylchloride (2.785 g, 2.53 mL, 22 mmol). When the reaction mixture becomes neutral (after 2.5 hours) further NaOH (0.44 g, 11 mmol) in 0.44 mL H_2O is added. The mixture is allowed to stir for further 12 hours under reflux, and after this period the solvent is removed. The mixture is dissolved in H_2O and the impurities are removed by extraction with $CHCl_3$. The product precipitates after acidification of the aqueous layer with H_2SO_4 5N under vigorous stirring. The precipitate is then collected and recrystallised from toluene to give a colourless powder.

Yield: 2.60 g (65 %)

TLC (Si, EtOAc-TMP (7:3)): $R_f = 0.18$

Melting Point: 149-150 °C

^{1}H NMR (400 MHz, CD_3OD): δ = 7.45 (d, J = 7.2 Hz, 2H; *o*-CH_{ar}, Bn), 7.35 (t, J = 7.2 Hz, 2H; *m*-CH_{ar}, Bn), 7.30 (d, J = 7.3 Hz, 1H; *p*-CH_{ar}, Bn), 6.94 (d, J = 1.8 Hz, 1H; CH_{ar}), 6.85 (d, J = 8.1 Hz, 1H; CH_{ar}), 6.78 (d, J = 8.1 Hz, 1H; CH_{ar}), 5.07 (s, 2H; OCH_2Ph), 4.20 (dd, J = 5.0, 7.0 Hz, 1H; (CH_2C*H*(NH)CO), 3.79 (s, 3H; OCH_3), 3.07 (dd, J = 4.8, 13.6 Hz, 1H; CH *H*CH(CO)NH), 2.83 (dd, J = 7.2, 13.6 Hz, 1H, CH*H*CH(CONH)), 1.37 (s, 9H, OC(CH_3)$_3$).

^{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, Bn), 128.89 (*o*, *p*-C_{ar}H, Bn), 123.78 (C_{ar}H), 117.20 (C_{ar}H), 113.55 (C_{ar}H), 79.99

(O*C*$(CH_3)_3$), 72.35 (O *C*H_2Ph), 58.25 (CH_2*C*H(NH)CO), 56.72 (O*C*H_3), 39.34 (*C*H_2CH(NH)CO), 28.84 (OC(*C*H_3)$_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3534 (m), 3384 (s), 2961 (m), 2928 (m), 2586 (w), 1729 (s), 1684 (s), 1669 (s), 1630 (m), 1606 (m), 1592 (m), 1520 (s), 1444 (m), 1365 (m), 1277 (s), 1242 (s), 1167 (s), 1140 (s), 1044 (w), 1024 (m), 849 (w), 808 (w), 730 (m), 700 (w).

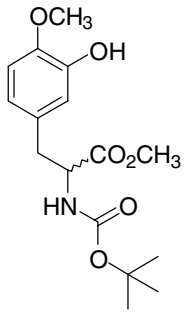
UV/Vis (CH_3OH): λ_{max} (ε) = 280 (4900), 204 (13900), 202 nm (13600 $mol^{-1}dm^3cm^{-1}$).

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^+-$C_5H_{10}NO_2$], 227 (68) [M^+-$C_7H_{12}O_4$], 137 (48) [M^+-($C_7H_{12}O_4$ + Bn)], 91 (100).

HRMS (EI): calcd. for $C_{22}H_{27}NO_6$ [M^+]: 401.1838, found 401.1838.

Elemental Analysis: $C_{22}H_{27}NO_6$ (401.45)
Calculated: C: 65.79 H: 6.78 N: 3.49
Found: C: 65.31 H: 7.15 N: 3.04.

4.2 2-*tert*-Butoxycarbonylamino-3-(3-hydroxy-4-methoxy-phenyl)-propionic acid methyl ester (128)



2-*tert*-Butoxycarbonylamino-3-(3-hydroxy-4-methoxy-phenyl)-propionic acid (**117**) (1000 mg, 4.656 mmol) is dissolved in dry CH_2Cl_2. To the reaction mixture are added EDCI (1003 mg, 5.12 mmol), CH_3OH (2.07 ml, 5.12 mmol) and 4-pyrrolidine-pyridine (69 mg, 0.4656 mmol). The reaction is allowed to stir at room temperature under argon for 96 hours. After this period the EDCI-urea formed is filtered and the organic layer is washed with saturated aqueous $NaHCO_3$ solution, with H_2O and is finally

dried over Na_2SO_4. The solvent is removed and the product is purified by flash chromatography on silica gel (TMP-EtOAc (7:3)) yielding a colourless powder.

Yield: 1166 mg (77 %)

TLC (Si, TMP-EtOAc (7:3)): R_f = 0.30

Melting Point: 137-138 °C

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 8.2 Hz, 1H; C*H*$_{ar}$), 6.68 (d, *J* = 2.0 Hz, 1H; C*H*$_{ar}$), 6.59 (dd, *J* = 2.2, 8.2 Hz, 1H; C*H*$_{ar}$), 5.61 (s, C_{ar}O*H*), 4.97 (d, *J* = 7.8 Hz, 1H; N*H*), 4.53 (brq, *J* = 7.0 Hz, 1H; (CH_2C*H*(NH)CO), 3.86 (s, 3H; C=OC*H*$_3$), 3.73 (s, 3H; OC*H*$_3$), 2.99 (d, *J* = 5.1 Hz, 1H; C*H*$_2$CH(CO)NH), 1.42 (s, 9H, OC(C*H*$_3$)$_3$).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 172.45 (*C*=O), 155.20 (*C*=O), 145.79 ($C_{ar}OCH_3$), 145.66 ($C_{ar}OCH_2Ph$), 129.11 ($C_{ar}CH_2CH(NH)CO$), 120.75 ($C_{ar}H$), 115.62 ($C_{ar}H$), 110.82 ($C_{ar}H$), 79.91 (O *C*(CH_3)$_3$), 55.94 (O*C*H$_3$), 55.52 (CH_2*C*H(NH)CO), 52.19 (CO_2*C*H$_3$), 37.63 (*C*H$_2$CH(NH)CO), 28.31 (OC(*C*H$_3$)$_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3508 (s), 3357 (s), 2972 (m), 1747 (s), 1706 (s), 1595 (m), 1516 (s), 1447 (m), 1367 (m), 1280 (s), 1220 (s), 1170 (s), 1062 (m), 1025 (s), 960 (m), 893 (w), 826 (m), 761 (m), 527 (m).

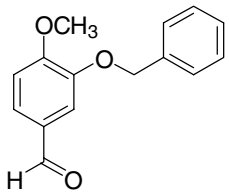
UV/Vis (CH_3OH): λ_{max} (ε) = 282 (12700), 226 (21100), 204 nm (80900 $mol^{-1}dm^3cm^{-1}$).

MS (EI, 70 eV): m/z (%): 325 (5) [M^+], 269 (13) [M^+-C_4H_8], 208 (38), 137 (100) [M^+-$C_8H_{14}NO_4$].

HRMS (EI): calcd. for $C_{16}H_{23}NO_6$ [M^+]: 325.1525, found 325.1525.

4.3 3-(3-Benzyloxy, 4-methoxy)-2-thiopropionic acid (167)

4.3.1. 3-Benzyloxy, 4-methoxy-benzaldehyde (163)[92]



To a stirred suspension of isovaniline (**120**) (7.608 g, 50 mmol) and K_2CO_3 (21.0 g, 150 mmol) in 143 mL dry acetone is added benzylbromide (12.75 ml, 105 mmol) in one portion. The mixture is refluxed for 20 hours and after this period it is brought to room temperature. The mixture is filtered followed by solvent removal in vacuum. The product is purified by flash chromatography on silica gel (TMP-EtOAc (8:2)) and is finally recrystallised from TMP to yield colourless needles.

Yield: 9.00 g (74 %)

TLC (Si, TMP-EtOAc (7:3)): $R_f = 0.29$

Melting Point: 62-64 °C

^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.81 (s, 1H, C*H*O), 7.47-7.44 (m, 5H; *o*-, *m*-, *p*-CH_{ar}, Bn), 7.39 (d, *J* = 2.0 Hz, 1H; CH_{ar}), 7.34 (dd, *J* = 2.0, 8.4 Hz, 1H; CH_{ar}), 6.98 (d, *J* = 8.7 Hz, 1H; CH_{ar}), 5.18 (s, 2H; PhOCH_2Ph), 3.95 (s, 3H; OCH_3).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 190.71 (*C*HO), 154.98 ($C_{ar}OCH_3$), 148.63 ($C_{ar}OCH_2Ph$), 136.23 ($C_{ar}CH_2OPh$), 129.91 ($C_{ar}CHO$), 128.55 (*m*-C_{ar}H, Bn), 128.03 (*p*-C_{ar}H, Bn), 127.40 (*o*-C_{ar}H, Bn), 126.78 (C_{ar}H), 111.33 (C_{ar}H), 110.72 (C_{ar}H), 70.77 (PhO*C*H_2Ph), 56.08 (O*C*H_3).

UV/Vis ($CHCl_3$): λ_{max} (ε) = 308 (8740), 278 (11100), 240 nm (7300 $mol^{-1}dm^3cm^{-1}$).

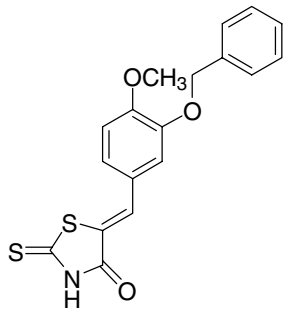
MS (EI, 70 eV): m/z (%): 242 (10) $[M]^+$, 91 (100) $[M-C_8H_7O_3]^+$.

Elemental Analysis: $C_{15}H_{14}O_3$ (242.27)

Calculated: C: 74.36 H: 5.82

Found: C: 74.19 H: 5.96

4.3.2. 5-(3-Benzyloxy-4-methoxy-benzylidene)-2-thioxo-thiazolidin-4-one (165)[107]



3-Benzyloxy, 4-methoxy benzaldehyde (**163**) (5.00 g, 20.66 mmol) and rhodanine (**164**) (2.752 g, 20.66 mmol) are dissolved in glacial acetic acid (15.7 mL) and are refluxed for 3 hours with fused NaOAc (5.462 g, 66.61 mmol). To the mixture is added H_2O and the product is filtered. The orange powder is recrystallised fro AcOH yielding orange crystals.

Yield: 6.90 g (92 %)

TLC (Si, TMP-EtOAc (7:3)): $R_f = 0.25$

Melting Point: 223-225 °C

^{1}H NMR (360 MHz, [D$_6$]DMSO): $\delta = 7.56$ (s, 1H, PhC*H*=C(CO)S), 7.48 (d, $J = 6.9$ Hz, 2H; *o*-CH_{ar}, Bn), 7.41 (t, $J = 7.0$ Hz, 2H; *m*-CH_{ar}, Bn), 7.36 (d, $J = 7.1$ Hz, 1H, *p*-CH_{ar}, Bn), 7.21 (s, 1H, CH_{ar}), 7.20 (d, $J = 7.8$ Hz, 1H; CH_{ar}), 7.15 (d, $J = 8.5$ Hz, 1H; CH_{ar}), 5.19 (s, 2H; PhOCH_2Ph), 3.89 (s, 3H, OCH_3).

^{13}C NMR (90.6 MHz, [D$_6$]DMSO): δ = 195.49 (*C*=S), 169.39 (*C*=O), 151.59 (C_{ar}OCH$_3$), 147.96 (C_{ar}OCH$_2$Ph), 136.63 (C_{ar}CH$_2$OPh), 132.12 (Ph *C*H=C(CO)S), 128.48 (*m*-C_{ar}H, Bn), 128.01 (*p*-C_{ar}H, Bn), 127.85 (*o*-C_{ar}H, Bn), 125.53 (C_{ar}CH=C),

125.08(C_{ar}H), 122.46 (PhCH=*C*(CO)S), 115.03 (C_{ar}H), 112.48 (C_{ar}H), 69.96 (PhO*C*H_2Ph), 55.82 (O*C*H_3).

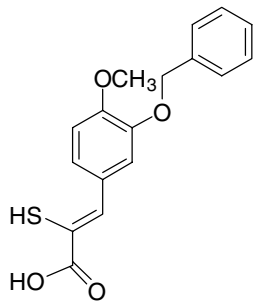
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3143 (w), 3040 (w), 2933 (w), 2838 (w), 1688 (s), 1587 (s), 1511 (s), 1433 (s), 1386 (m), 1347 (m), 1304 (s), 1258 (s), 1213 (s), 1168 (m), 1136 (s), 1073 (w), 1005 (m), 858 (w), 809 (w), 751 (w), 698 (w), 670 (w), 607 (w).

UV/Vis ($CHCl_3$): λ_{max} (ε) = 410 (11800), 292 (3700), 266 (3500), 228 (8000), 218 (8040), 210 (8300), 204 nm (8200 $mol^{-1}dm^3cm^{-1}$).

MS (EI, 70 eV): m/z (%): 357 (12) [M^+], 266 (1) [M^+-C_7H_7], 179 (2), 91 (100) [M^+-$C_8H_7O_3$].

Elemental Analysis: $C_{18}H_{15}NO_3S_2$ (357.45)
Calculated: C: 60.48 H: 4.23 N: 3.92
Found: C: 60.21 H: 4.38 N: 3.80

4.3.3. 3-(3-Benzyloxy, 4-methoxy-phenyl)-2-mercapto-acrylic acid (167)[107]



5-(3-Benzyloxy-4-methoxy-benzylidene)-2-thioxo-thiazolidin-4-one (**165**) (8.00 g, 31.13 mmol) is cleaved with NaOH (8 %, 78.4 mL) under reflux. The mixture is stirred well until a clear solution is obtained. The mixture is filtered, cooled to 0 °C and then is acidified with HCl 3N under vigorous stirring. After stirring for 30 min, the acid is collected and washed well with H_2O. EtOH is added (only necessary amount to dissolve the product) and double H_2O amount is added under vigorous stirring. After 1 hour the product is filtered and dried well yielding a light yellow powder.

Yield: 5.86 g (60 %)

TLC: decomposes on silica gel

Melting Point: 145-146 °C

^{1}H NMR (360 MHz, $CDCl_3$): δ = 10.21 (brs, 1H, CO_2H), 7.79 (s, 1H, PhC*H*=C(CO)SH), 7.46 (d, *J* = 7.1 Hz, 2H; *o*-CH_{ar}, Bn), 7.36 (t, *J* = 6.7 Hz, 2H; *m*-CH_{ar}, Bn), 7.32 (d, *J* = 1.7 Hz, 1H, CH_{ar}), 7.30 (d, *J* = 7.3 Hz, 1H, *p*-CH_{ar}, Bn), 7.24 (dd, *J* = 1.8, 8.7 Hz, 1H; CH_{ar}), 6.91 (d, *J* = 8.7 Hz, 1H; CH_{ar}), 5.19 (s, 2H; PhOCH_2Ph), 4.58 (s, 1H, S*H*), 3.90 (s, 3H, OCH_3).

^{13}C NMR (90.6 MHz, [D_6]DMSO): δ = 170.67 (*C*=O), 150.70 ($C_{ar}OCH_3$), 147.75 ($C_{ar}OCH_2Ph$), 137.58 (Ph*C*H=C(CO)SH), 136.57 ($C_{ar}CH_2OPh$), 128.53 (*m*-C_{ar}H, Bn), 127.92 (*p*-C_{ar}H, Bn), 127.43 (C_{ar}CH=C), 127.34 (*o*-C_{ar}H, Bn), 125.15 (C_{ar}H), 119.05 (PhCH=*C*(CO)SH), 115.31 (C_{ar}H), 111.33 (C_{ar}H), 70.95 (PhO*C*H_2Ph), 55.89 (O*C*H_3).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 2933 (m), 2814 (m), 2623 (w), 2560 (m), 2500 (w), 1671 (s), 1589 (s), 1514 (s), 1420 (s), 1390 (m), 1322 (s), 1254 (s), 1136 (s), 1048 (w), 1007 (s), 904 (m), 848 (w), 809 (m), 751 (m), 699 (m), 622 (w).

UV/Vis ($CHCl_3$): λ_{max} (ε) = 336 (14300), 206 nm (118600 $mol^{-1}dm^3cm^{-1}$).

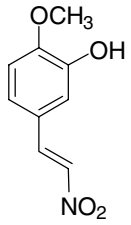
MS (EI, 70 eV): m/z (%): 316 (28) [M^+], 270 (8) [M^+-CH_2O_2], 225 (7) [M^+-C_7H_7], 193 (5), 91 (100) [M^+-$C_8H_7O_3$].

Elemental Analysis: $C_{17}H_{16}O_4S$ (316.37)
Calculated: C: 64.54 H: 5.10
Found: C: 64.37 H: 5.04

5 Synthesis of Tyramine-Subunits

5.1 [2-(3-Hydroxy-4-methoxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (119)

5.1.1. 2-Methoxy-5-(2-nitro-vinyl)-phenol (121)[88]



A mixture of methylamine hydrochloride (0.146 g, 2.17 mmol), Na_2CO_3 (0.209 g, 1.97 mmol) and CH_3OH (1.6 mL, 3.94 mmol) are stirred well, filtered and added to a solution of isovaniline (**120**) (3.00 g, 19.7 mmol) and nitromethane (1.352 g, 1.2 mL, 22.17 mmol) in 8.5 mL CH_3OH. The solution is allowed to rest for 50 hours in the dark. After this period the mixture is filtered and washed with cold CH_3OH. The product is recrystallised from CH_3OH yielding a strong yellow powder.

Yield: 3.386 g (88 %)

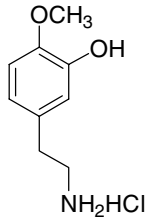
Melting Point: 160 °C

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 13.6 Hz, 1H; CH=C*H*NO_2), 7.47 (d, *J* = 13.6 Hz, 1H; C*H*=$CHNO_2$), 7.09 (dd, *J* = 1.9, 7.4 Hz, 1H; CH_{ar}), 7.08 (d, *J* = 2.0 Hz, 1H; CH_{ar}), 6.88 (d, *J* = 7.6 Hz, 1H, CH_{ar}), 5.85 (brs, 1H, O*H*), 3.95 (s, 3H; OCH_3).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 150.18 ($C_{ar}OCH_3$), 146.35 ($C_{ar}OH$), 139.71 (CH=*C*HNO_2), 135.60 (*C*H=$CHNO_2$), 123.75 ($C_{ar}CH=CHNO_2$), 123.56 ($C_{ar}H$), 113.74 ($C_{ar}H$), 110.94 ($C_{ar}H$), 56.18 (O*C*H_3).

Elemental Analysis: $C_9H_9NO_4$ (195.17)
Calculated: C 55.39 H 4.65 N 7.18
Found: C 55.70 H 4.79 N 6.93

5.1.2. 5-(2-Amino-ethyl)-2-methoxy-phenol (112)[88]



2-Methoxy-5-(2-nitro-vinyl)-phenol (**121**) (3.84 g, 17.6 mmol) is added over a period of 18 hours to $LiAlH_4$ (3.406 g, 89.75 mmol) in 465 mL dried Et_2O by the soxhlet extraction technique. The flask is cooled and ice cold H_2SO_4 (210 mL, 1.5N) is added dropwise with vigorous stirring. The H_2O layer is separated and its pH is adjusted to 6 with Li_2CO_3. The solution is heated to boiling and the precipitated $Al(OH)_3$ is removed from the reaction mixture. The filtrate is mixed with picric acid (4.877 g, 17.6 mmol) dissolved in minimum amount hot EtOH. The crystals are filtered and dissolved in 120 mL boiling H_2O. Concentrated HCl (25 mL) is added and the precipitated picric acid is removed. The filtrate is extracted with Et_2O and the aqueous layer is concentrated until crystallisation starts. The product is recrystallised from CH_3OH-EtOAc affording light yellow needles.

Yield: 2.428 g (68 %)

TLC (Si, EtOAc-*n*BuOH-AcOH-H_2O (1:1:1:1)): $R_f = 0.42$

Melting Point: 207 °C

^{1}H NMR (360 MHz, CD_3OD): δ = 6.89 (d, J = 8.1 Hz, 1H; CH_{ar}), 6.74 (d, J = 2.0 Hz, 1H; CH_{ar}), 6.71 (dd, J = 2.0, 8.0 Hz, 1H; CH_{ar}), 3.83 (s, 3H; OCH_3), 3.12 (t, J = 7.7 Hz, 2H; $CH_2CH_2NH_2$), 2.84 (t, J = 8.0 Hz, 2H; $CH_2CH_2NH_2$).

^{13}C NMR (62.9 MHz, CD_3OD): δ = 149.85 ($C_{ar}OCH_3$), 149.22 ($C_{ar}OH$), 130.59 ($C_{ar}CH_2CH_2NH_2$), 120.94 ($C_{ar}H$), 116.71 ($C_{ar}H$), 113.26 ($C_{ar}H$), 56.52 (OCH_3), 42.11 ($CH_2CH_2NH_2$), 33.90 ($CH_2CH_2NH_2$).

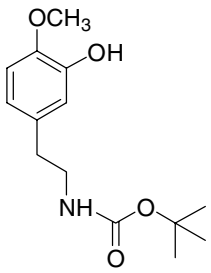
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3332 (s), 3010 (s), 2926 (s), 1991 (w), 1591 (m), 1511 (s), 1463 (m), 1443 (m), 1343 (w), 1281 (s), 1230 (s), 1133 (s), 1024 (s), 946 (m), 876 (m), 806 (s), 761 (m), 621 (m).

UV/Vis (CH_3OH): λ_{max} (ε) = 282 (1100), 226 (3150), 204 nm (21300 $mol^{-1}dm^3cm^{-1}$).

MS (EI, 70 eV): m/z (%): 167 (21) [M^+-HCl], 138 (100) [M^+-CH_3N], 123 (27) [M^+-C_2H_6N].

Elemental Analysis: $C_9H_{14}ClNO_2$ (203.67)
Calculated: C: 53.08 H: 6.93 N: 6.88
Found: C: 52.95 H: 6.93 N: 6.65.

5.1.3. [2-(3-Hydroxy-4-methoxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (119)



Et_3N (1.5 mL, 10.7 mmol) is added to a solution of 5-(2-amino-ethyl)-2-methoxy-phenol (**112**) (1.50 g, 7.36 mmol) in CH_2Cl_2-CH_3OH (1:1) (50 mL). After 15 min Boc_2O (1.71 g, 8.096 mmol) is added and the solution is allowed to stir for further 3 hours. The solvent is removed and the product is purified by flash column chromatography on silica gel (TMP-EtOAc (8:2)). Recrystallisation fro *n*heptane yields colourless needles.

Yield: 1.834 g (93 %)

TLC (Si, TMP-EtOAc (8:2)): R_f = 0.30

Melting Point: 98-99 °C

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.82 (d, *J* = 8.4 Hz, 1H; C*H*$_{ar}$), 6.80 (d, *J* = 1.9 Hz, 1H; C*H*$_{ar}$), 6.71 (dd, *J* = 2.4, 8.0 Hz, 1H; C*H*$_{ar}$), 5.58 (s, 1H, O*H*), 4.57 (brs, 1H, N*H*) 3.86 (s, 3H; OC*H*$_3$), 3.32 (t, *J* = 8.0 Hz, 2H; CH_2C*H*$_2$NH), 2.74 (t, *J* = 7.7 Hz, 2H; C*H*$_2$$CH_2$NH), 1.45 (s, 9H, OC(C*H*$_3$)$_3$).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 159.90 (*C*=O), 145.69 (*C*$_{ar}$$OCH_3$), 145.23 (*C*$_{ar}$OH), 132.31 (*C*$_{ar}$$CH_2CH_2$NH), 120.17 (*C*$_{ar}$H), 114.92 (*C*$_{ar}$H), 110.83 (*C*$_{ar}$H), 79.85 (O*C*($CH_3$)$_3$), 56.01 (O *C*$H_3$), 43.85 ($CH_2$*C*$H_2$NH), 35.55 (*C*$H_2CH_2NH_2$), 28.40 (OC(*C*$H_3$)$_3$).

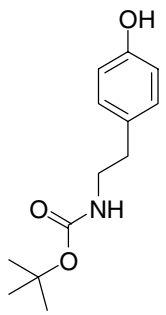
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3514 (m), 3358 (s), 2983 (m), 2940 (m), 2873 (w), 1681 (s), 1591 (w), 1532 (s), 1443 (m), 1367 (m), 1303 (m), 1279 (s), 1248 (s), 1224 (s), 1171 (s), 1131 (s), 1018 (s), 869 (m), 812 (m), 761 (w), 627 (m).

UV/Vis (CH_3OH): λ_{max} (ε) = 282 (4500), 230 (18100), 204 nm (73000 $mol^{-1}dm^3cm^{-1}$).

MS (EI, 70 eV): m/z (%): 267 (14) [M^+], 211 (40) [M^+-C_4H_8], 150 (100) [M^+-$C_5H_{11}NO_2$], 137 (72) [M^+-$C_6H_{12}NO_2$].

Elemental Analysis: $C_{14}H_{21}NO_4$ (267.32)
Calculated: C: 62.90 H: 7.92 N: 5.24
Found: C: 62.96 H: 7.96 N: 4.98.

5.2 [2-(4-Hydroxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (176)



To a solution of Tyramine (**171**) (5.00 g, 36.45 mmol) in CH_3OH-CH_2Cl_2 (1:1) (100 mL) is added Boc_2O (8.706 g, 40.09 mmol). After 2 hours, the solvent is removed and the product is recrystallised from TMP yielding colourless needles.

Yield: 8.50 g (98 %)

TLC (Si, TMP-EtOAc (7:3)): $R_f = 0.36$

Melting Point: 71 °C

^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.24 (brs, 1H, O*H*), 6.99 (d, *J* = 8.4 Hz, 2H; CH_{ar}), 6.79 (d, *J* = 8.5 Hz, 2H; CH_{ar}), 4.68 (brs, 1H, N*H*), 3.32 (q, *J* = 6.2 Hz, 2H; CH_2CH_2NH), 2.69 (t, *J* = 6.8 Hz, 2H; CH_2CH_2NH), 1.44 (s, 9H, $OC(CH_3)_3$).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 156.30 (*C*=O), 154.92 (C_{ar}OH), 130.02 ($C_{ar}CH_2CH_2NH$), 129.71 (C_{ar}H), 115.49 (C_{ar}H), 79.63 (O $C(CH_3)_3$), 42.01 (CH_2CH_2NH), 35.15 ($CH_2CH_2NH_2$), 28.35 ($OC(CH_3)_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3378 (s), 2981 (m), 2940 (m), 2865 (w), 1890 (w), 1686 (s), 1665 (s), 1615 (s), 1596 (s), 1517 (s), 1454 (s), 1394 (m), 1368 (s), 1292 (s), 1262 (s), 1219 (s), 1159 (s), 1106 (m), 1051 (w), 1025 (w), 962 (m), 834 (s), 785 (m), 646 (m), 556 (m), 520 (m).

UV/Vis (CH_3OH): λ_{max} (ε) = 278 (3000), 226 (9450), 224 (9500), 202 nm (9300 $mol^{-1}dm^3cm^{-1}$).

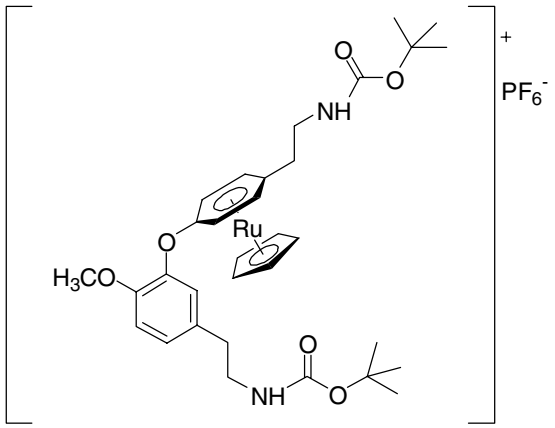
MS (EI, 70 eV): m/z (%): 237 (5) [M^+], 181 (42) [M^+-C_4H_8], 164 (13) [M^+-C_4H_9O], 120 (100) [M^+-$C_5H_{11}NO_2$].

Elemental Analysis: $C_{13}H_{19}NO_3$ (237.29)
Calculated: C: 65.80 H: 8.07 N: 5.90
Found: C: 65.67 H: 8.12 N: 5.76.

6 General procedure for the preparation of the diarylether ruthenium sandwich complexes:

The respective phenol (1.0 eq.) is added to a solution of KO *t*Bu (1.0 eq.) and [18]crown-6 (0.1 eq.) in THF (15 mL). After 30 min the mixture is cooled to 0 °C and is transferred to a pre-cooled (-78 °C) solution of the respective ruthenium aryl complex (1.0 eq.) in THF (20 mL). After 1 hour the reaction is slowly brought to 20 °C. After 16 hour, the reaction mixture is filtered and concentrated.

6.1 [1-{2-(*tert*-Butoxycarbonylamino)ethyl}-4-{(5-(2-(*tert*-butoxycarbonyl-amino)ethyl)-2-methoxy)phenoxy}-η^6-benzene](η^5-cyclopentadienyl) ruthenium hexafluorophosphate (156)[94]



Prepared fro [1-{2-(*tert*-butoxycarbonylamino)}ethyl-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**135**)[94] (100 mg, 0.17 mmol) and from [2-(3-hydroxy-4-methoxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (**119**) (45.0 mg, 0.17 mmol). After column chromatography on aminopropyl silica (toluene-CH_3CN (3:1)), the product is dissolved in *i*PrOH at 60 °C, followed by slo precipitation after addition of trace amounts of Et_2O at room temperature yielding a colourless powder.

Yield: 81 mg (60 %)

TLC (NH_2-Si, *i*PrOH): $R_f = 0.49$

HPLC retention volumes: 109 mL (CH_3CN), 95 mL (*i*PrOH-CH_3CN (1:1)), 95 mL (*i*PrOH-CH_3CN (2:1)), 96 mL (*i*PrOH-CH_3CN (4:1)), 101 mL (*i*PrOH-CH_3CN (8:1)), 102 mL (*i*PrOH-CH_3CN (12:1)), 110 mL (*i*PrOH-CH_3CN (18:1)), 172 mL (*i*PrOH).

Melting Point: 80-81 °C (decomposes)

^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 8.7 Hz, 1H, C*H*$_{ar}$), 7.00 (d, *J* = 8.4 Hz, 1H, C*H*$_{ar}$), 6.88 (s, 1H, η-C*H*$_{ar}$), 6.12 (d, *J* = 6.0 Hz, 2H, η-C*H*$_{ar}$), 6.01 (d, *J* = 5.7 Hz, 2H, η-C*H*$_{ar}$), 5.34 (s, 5H, Cp), 4.95 (m, 1H, CH_2N*H*), 4.36 (t, *J* = 7.1 Hz, 1H, CH_2N*H*), 3.81 (s, 3H, OC*H*$_3$), 3.34 (brd, 4H, C*H*$_2$NH), 2.77 (brt, *J* = 6.7 Hz, 2H, C*H*$_2$$CH_2$NH), 2.67 (brt, 2H, C*H*$_2$$CH_2$NH), 1.40 (s, 18H, OC(C*H*$_3$)$_3$).

^{13}C NMR (90.6 MHz; $CDCl_3$): δ = 156.15 (*C*=O), 155.99 (*C*=O), 149.59 (*C*$_{ar}$$OCH_3$), 140.33 (*C*$_{ar}$O(η-Ph)), 133.12 ($CH_2$*C*$_{ar}$), 132.76 (η-*C*$_{ar}$OPh), 128.46 (*C*$_{ar}$H), 122.37 (*C*$_{ar}$H), 113.41 (*C*$_{ar}$H), 101.18 (η-*C*$_{ar}$$CH_2$), 84.81 (η-*C*$_{ar}$H), 82.74 (Cp), 79.43 (O*C*(CH_3)$_3$), 79.19 (O*C*(CH_3)$_3$), 74.77 (η-*C*$_{ar}$H), 55.98 (O*C*H_3), 41.80 (*C*H_2NH), 41.00 (*C*H_2NH), 35.38 (*C*$H_2$$CH_2$NH), 33.70 (*C*$H_2$$CH_2$NH), 28.37 (OC(*C*$H_3$)$_3$), 28.33 (OC(*C*$H_3$)$_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3440 (m), 3354 (m), 2979 (s), 1700 (s), 1512 (s), 1477 (s), 1367 (s), 1274 (s), 1233 (s), 1171 (s), 1122 (s), 841 (s).

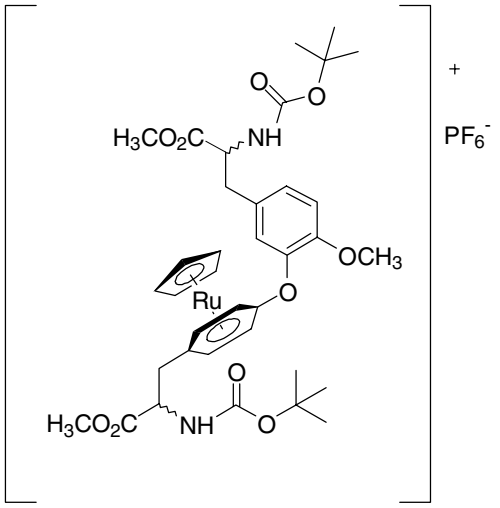
UV/Vis (CH_3CN): λ_{max} (ε) = 282 (30400), 222 (43500), 196 nm (120900 mol^{-1}dm^{3}cm^{-1}).

MS (FAB$^+$, NBA): m/z (%) 652/653/655 (62/100/56) [M$^+$], 596/597/599 (5/7/4) [M$^+$-C_4H_8].

HRMS (FAB): calcd. for $C_{32}H_{43}O_6N_2$ ^{102}Ru [M$^+$]: 653.2174, found = 653.2144.

Elemental Analysis: $C_{32}H_{43}F_6N_2O_6PRu$ (797.74)
Calculated: C: 48.18 H: 5.43 N: 3.51
Found: C: 47.46 H: 5.68 N: 3.20

6.2 [1-{2-(*tert*-Butoxycarbonylamino)-2-(methoxycarbonyl)ethyl}-4-{(5-(2-(*tert*-butoxycarbonylamino)-2-(methoxycarbonyl)ethyl)-2-methoxy)-phenoxy}-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (157)[94]



Prepared from [1-{2-(tert-butoxycarbonylamino)-2-(methoxycarbonyl)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**147**)[85b] (100 mg, 0.16 mmol) and 2- *tert*-butoxycarbonylamino-3-(3-hydroxy-4-methoxy-phenyl)-propionic acid methyl ester (**128**) (52 mg, 0.16 mmol). After column chromatography on aminopropyl silica (toluene-CH_3CN (3:1)), the product is recrystallised fro *i*PrOH yielding colourless needles.

Yield: 87 mg (60 %).

TLC (NH_2-Si, *i*PrOH): $R_f = 0.51$

Melting Point: 98-100 °C (decomposes)

^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.09 (dd, J = 8.4, 2.3 Hz, 1H, CH_{ar}), 7.00 (d, J = 8.4 Hz, 1H, CH_{ar}), 6.83 (d, J = 2.3 Hz, 1H, CH_{ar}), 6.17 (t, J = 8.7 Hz, 1H, η-CH_{ar}), 6.05 (m, 2H, η-CH_{ar}), 5.97 (t, J = 6.7 Hz, 1H, η-CH_{ar}), 5.43 (m, 1H, CHN*H*), 5.35 (s, 5H, Cp), 5.09 (m, 1H, CHN*H*), 4.51 (m, 1H, CH_2C*H*(NH)CO), 4.42 (m, 1H, CH_2C*H*(NH)CO), 3.83 (s, 3H, COOC H_3), 3.81 (s, 3H, COOCH_3), 3.74 (s, 3H, PhOCH_3), 3.12 (brdd, 1H, PhC*H*HCH), 3.00-2.93 (m, 2H, PhC*H*HCH), 2.82 (dd, J = 13.4, 8.7 Hz, 1H, PhCH*H*CH), 1.41 (s, 9H, OC(CH_3)$_3$), 1.40 (s, 9H, OC(CH_3)$_3$).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 172.06 (*C*=O), 170.89 (*C*=O), 155.46 (*C*=O), 155.43 (*C*=O), 150.21 ($C_{ar}OCH_3$), 140.21 ($C_{ar}O(\eta\text{-Ph})$), 132.93 (CH_2C_{ar}), 130.21 ($\eta\text{-}C_{ar}OPh$), 129.23 ($C_{ar}H$), 122.96 ($C_{ar}H$), 113.44 ($C_{ar}H$), 98.95 ($\eta\text{-}C_{ar}CH_2$), 85.72 ($\eta\text{-}C_{ar}H$), 85.58 ($\eta\text{-}C_{ar}H$), 81.13 (Cp), 80.46 ($OC(CH_3)_3$), 80.41 ($OC(CH_3)_3$), 74.86 ($\eta\text{-}C_{ar}H$), 74.76 ($\eta\text{-}C_{ar}H$), 56.04 ($PhOCH_3$), 54.60 ($CH_2CH(NH)CO$), 53.06 (CO_2CH_3), 52.55 (CO_2CH_3), 37.83 ($CH_2CH(NH)CO$), 36.69 ($CH_2CH(NH)CO$), 28.30 ($OC(CH_3)_3$), 28.26 ($OC(CH_3)_3$).

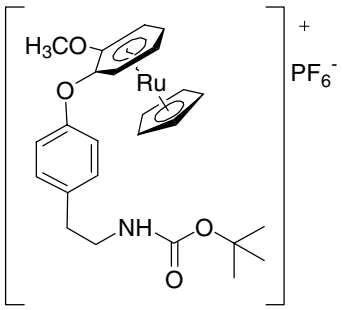
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3420 (w), 2979 (w), 1743 (s), 1717 (s), 1513 (s), 1477 (s), 1368 (m), 1275 (s), 1235 (s), 1166 (s), 1022 (w), 843 (s), 558 (m).

UV/Vis (CH_3CN): λ_{max} (ε) = 278 (11400), 224 (23100), 196 nm (66600 mol^{-1}dm^{3}cm^{-1}).

MS (FAB+, NBA) *m/z* (%) 768/769/771 (61/100/56) [M$^+$].

HRMS (FAB): calcd. for $C_{36}H_{47}O_{10}N_2{}^{102}Ru$ [M$^+$]: 769.2274, found 769.2299.

6.3 [{1-(4-(2-(*tert*-Butoxycarbonylamino)ethyl))phenoxy-2-methoxy}-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (159)[94]



Prepared from (1-chloro-2-methoxy-η^6-benzene)(η^5-cyclopentadienyl)rutheniu hexafluorophosphate (**155**)[94] (110 mg, 0.242 mmol) and from [2-(4-hydroxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (**177**) (57 mg, 0.242 mmol). After column chromatography on aminopropyl silica (toluene-CH_3CN (3:1)), the product is dissolved in *i*PrOH at 60 °C, followed by slow precipitation of a colourless powder after addition of trace amounts of Et_2O at room temperature.

Yield: 86 mg (55 %)

TLC (NH_2-Si, *i*PrOH): R_f = 0.36

HPLC retention volumes: 112 mL (CH_3CN), 93 mL (*i*PrOH-CH_3CN (1:1)), 90 mL (*i*PrOH-CH_3CN (2:1)), 92 mL (*i*PrOH-CH_3CN (4:1)), 93 mL (*i*PrOH-CH_3CN (8:1)), 115 mL (*i*PrOH-CH_3CN (12:1)), 130 mL (*i*PrOH-CH_3CN (18:1)), 273 mL (*i*PrOH).

Melting Point: 70 °C (decomposes)

^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.4 Hz, 2H, C*H*$_{ar}$), 6.99 (d, *J* = 8.7 Hz, 2H, C*H*$_{ar}$), 6.48 (d, *J* = 6.4 Hz, 1H, η-C*H*$_{ar}$), 5.95 (t, *J* = 6.1 Hz, 1H, η-C*H*$_{ar}$), 5.89 (d, *J* = 6.0 Hz, 1H, η-C*H*$_{ar}$), 5.82 (d, *J* = 6.0 Hz, 1H, η-C*H*$_{ar}$), 5.36 (s, 5H, Cp), 4.68 (brm, 1H, CH_2N*H*), 3.95 (s, 3H, OC*H*$_3$), 3.38 (brq, *J* = 6.7 Hz, 2H, C*H*$_2$NH), 2.83 (t, *J* = 7.0 Hz, 2H, C*H*$_2$$CH_2$NH), 1.44 (s, 9H, OC(C*H*$_3$)$_3$).

^{13}C NMR (90.6 MHz; $CDCl_3$): δ = 155.91 (*C*=O), 152.26 ((η-Ph)O*C*$_{ar}$), 137.54 (*C*$_{ar}$$CH_2$), 130.94 (*C*$_{ar}$H), 127.01 (η-*C*$_{ar}$$OCH_3$), 123.75 (η-*C*$_{ar}$OPh), 119.65 (*C*$_{ar}$H), 81.69 (η-*C*$_{ar}$H), 80.70 ((η-*C*$_{ar}$H), 80.61 (Cp), 79.65 (O*C*(CH_3)$_3$), 75.79 ((η-*C*$_{ar}$H), 72.30 ((η-*C*$_{ar}$H), 57.87 (O*C*H_3), 41.75 (*C*H_2NH), 35.71 (*C*$H_2$$CH_2$NH), 28.42 (OC(*C*$H_3$)$_3$).

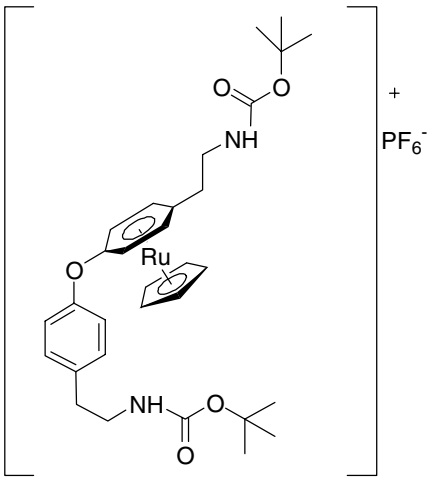
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3438 (m), 2878 (m), 1700 (s), 1528 (s), 1501 (s), 1477 (s), 1277 (s), 1258 (s), 1221 (s), 840 (s).

UV/Vis (CH_3CN): λ_{max} (ε) = 260 (6900), 220 (21600), 196 nm (62200 mol^{-1}dm^{3}cm^{-1}).

MS (FAB$^+$, NBA): m/z (%) 509/510/512 (58/100/54) [M$^+$], 452/453/455 (5/10/5) [M$^+$-C_4H_8], 406/407/409 (3/4/5) [M$^+$-$C_5H_8O_2$].

HRMS (FAB):calcd. for $C_{25}H_{30}O_4N$ ^{102}Ru [M$^+$]: 510.1226, found = 510.1221.

6.4 [1-{2-(*tert*-Butoxycarbonylamino)ethyl}-4-{(4-(2-(*tert*-butoxycarbonylamino)ethyl))phenoxy}-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (158)[94]



Prepared from [1-{2-(*tert*-butoxycarbonylamino)}ethyl-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**135**)[94] (87 mg, 0.15 mmol) and from [2-(4-hydroxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (**177**) (35 mg, 0.15 mmol). After column chromatography on aminopropyl silica (toluene-CH_3CN (3:1)), the product is recrystallised fro *i*PrOH yielding colourless needles.

Yield: 70 mg (60 %)

TLC (NH_2-Si, *i*PrOH): $R_f = 0.70$

Melting Point: 117-118 °C (decomposes)

HPLC retention volumes: 97 mL (CH_3CN), 89 mL (*i*PrOH-CH_3CN (1:1)), 90 mL (*i*PrOH-CH_3CN (2:1)), 88 mL (*i*PrOH-CH_3CN (4:1)), 92 mL (*i*PrOH-CH_3CN (8:1)), 96 mL (*i*PrOH-CH_3CN (12:1)), 100 mL (*i*PrOH-CH_3CN (18:1)), 149 mL (*i*PrOH).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.32 (d, J = 8.5 Hz, 2H, CH_{ar}), 6.95 (d, J = 8.4 Hz, 2H, CH_{ar}), 6.16 (d, J = 6.5 Hz, 2H, η-CH_{ar}), 6.01 (d, J = 6.4 Hz, 2H, η-CH_{ar}), 5.35 (s, 5H, Cp), 5.16 (m, 1H, CH_2NH), 4.79 (m, 1H, CH_2NH), 3.39 (m, 4H, CH_2NH), 2.84 (t, J = 7.0 Hz, 2H, CH_2CH_2NH), 2.70 (t, J = 7.1 Hz, 2H, CH_2CH_2NH), 1.45 (s, 9H, $OC(CH_3)_3$), 1.41 (s, 9H, $OC(CH_3)_3$).

^{13}C NMR (90.6 MHz; $CDCl_3$): δ = 156.13 (*C*=O), 155.79 (*C*=O), 150.68 (C_{ar}O(η-Ph)); 138.32 (CH_2C_{ar}), 132.93 (η-C_{ar}OPh), 131.06 (C_{ar}H), 120.21 (C_{ar}H), 101.60 (η-$C_{ar}CH_2$), 85.12 (η-C_{ar}H), 80.79 (Cp), 79.48 (O*C*(CH_3)$_3$), 79.27 (O*C*(CH_3)$_3$), 75.14 (η-C_{ar}H), 41.60 (CH_2NH), 40.87 (CH_2NH), 35.64 (CH_2CH_2NH), 33.66 (CH_2CH_2NH), 28.29 (OC(CH_3)$_3$), 28.25 (OC(CH_3)$_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3373 (m), 1687 (s), 1366 (s), 1249 (s), 843 (s).

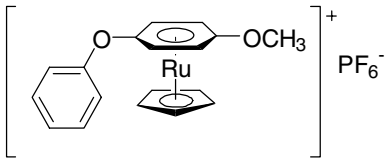
UV/Vis (CH_3CN): λ_{max} (ε) = 266 (8800), 204 (65800), 192 nm (87700 mol^{-1}dm^{3}cm^{-1}).

MS (FAB$^+$, NBA): m/z (%) 622/623/625 (60/100/54) [M$^+$], 566/567/569 (4/7/4) [M$^+$-C_4H_8].

HRMS (FAB): calcd for $C_{31}H_{41}O_5N_2$ ^{102}Ru [M$^+$]: 623.2044, found = 623.2057.

Elemental Analysis: $C_{31}H_{41}F_6N_2O_5PRu$ (797.74)
Calculated: C: 48.50 H: 5.38 N: 3.65
Found: C: 48.22 H: 5.59 N: 3.45

6.5 (η^5-Cyclopentadienyl)(4-methoxy-1-phenoxy-η^6-benzene)ruthenium hexafluorophosphate (160)[94]



Prepared from (1-chloro-4-methoxy-η^6-benzene)(η^5-cyclopentadienyl)rutheniu hexafluorophosphate (**151**)[96] (108 mg, 0.24 mmol) and from phenol (23 mg, 0.24 mmol). After column chromatography on aminopropyl silica (toluene-CH_3CN (3:1)), the product is recrystallised fro *i*PrOH-EtOH yielding a colourless powder.

Yield: 70 mg (57 %)

TLC (NH_2-Si, *i*PrOH): R_f = 0.40

HPLC retention volumes: 107 mL (CH_3CN), 98 mL (*i*PrOH-CH_3CN (1:1)), 100 mL (*i*PrOH-CH_3CN (2:1)), 96 mL (*i*PrOH-CH_3CN (4:1)), 101 mL (*i*PrOH-CH_3CN (8:1)), 121 mL (*i*PrOH-CH_3CN (12:1)), 119 mL (*i*PrOH-CH_3CN (18:1)), 220 mL (*i*PrOH).

Melting Point: 152-153 °C (decomposes).

^{1}H NMR (360 MHz, [D$_6$]acetone): δ = 7.58 (t, J = 8.2 Hz, 2H, CH_{ar}), 7.40 (t, J = 7.5 Hz, 2H, CH_{ar}), 7.27 (d, J = 7.7 Hz, 1H, CH_{ar}), 6.37 (d, J = 6.6 Hz, 2H, η-CH_{ar}), 6.23 (d, J = 6.6 Hz, 2H, η-CH_{ar}), 5.59 (s, 5H, Cp), 3.85 (s, 3H, OCH_3).

^{13}C NMR (90.6 MHz; [D$_6$]acetone): δ = 154.38 (C_{ar}O(η-Ph)), 133.49 (η-C_{ar}OCH$_3$), 131.85 (C_{ar}H), 131.70 (η-C_{ar}OPh), 127.64 (C_{ar}H), 121.73 (C_{ar}H), 81.63 (Cp), 75.26 (η-C_{ar}H), 73.41 (η-C_{ar}H), 58.17 (OCH$_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3447 (w), 3118 (w), 1482 (s), 1238 (s), 1008 (m), 839 (s), 779 (m), 693 (m).

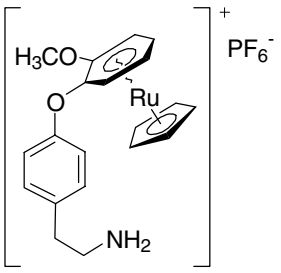
UV/Vis (CH_3CN): λ_{max} (ε) = 264 (5700), 222 (14600), 198 nm (56700 mol^{-1}dm^{3}cm^{-1}).

MS (FAB$^+$, NBA): m/z (%) 366/367/369 (56/100/56) [M$^+$].

HRMS (FAB): calcd for $C_{18}H_{17}O_2{}^{102}Ru$ [M$^+$]: 367.0263, found = 367.0237.

Elemental Analysis: $C_{18}H_{17}F_6O_2PRu$ (511.37)
Calculated: C: 42.28 H: 3.35
Found: C: 42.03 H: 3.48

6.6 [{1-(4-(2-Amino)ethyl)-phenoxy-2-methoxy}-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (172)



Tyramine (**171**) (15.2 mg, 0.111 mmol) is added to a solution of KO*t*Bu (1.0 eq.) and [18]crown-6 (0.1 eq.) in THF-CH_3CN (1:1) (15 mL). After 30 min the mixture is cooled to 0 °C and transferred to a pre-cooled (-78 °C) solution of (1-chloro-2-methoxy-η^6-benzene)(η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**155**)[94] (50 mg, 0.111 mmol) in THF-CH_3CN (1:1) (20 mL). After 1 hour the reaction is slowly brought to 20 °C. After 16 hours, the reaction mixture is filtered and concentrated. To the mixture is added Et_2O and the collected precipitate is purified by column chromatography on aminopropyl silica with CH_3CN (removal of [18]crown-6) and with *i*PrOH-H_2O (6:1), followed by recrystallisation fro *i*PrOH yielding colourless needles.

Yield: 50 mg (81 %)

TLC (NH_2-Si, *i*PrOH-H_2O (6:1)): R_f = 0.33

Melting Point: 148-150 °C (decomposes)

^{1}H NMR (500 MHz, CD_3OD): δ = 7.36 (d, *J* = 8.4 Hz, 2H; C*H*$_{ar}$), 7.11 (t, *J* = 8.5 Hz, C*H*$_{ar}$), 6.51 (d, *J* = 6.1 Hz, η-C*H*$_{ar}$), 6.06 (d, *J* = 6.0 Hz, 1H, η-C*H*$_{ar}$), 5.92 (t, *J* = 5.7 Hz, 1H, η-C*H*$_{ar}$), 5.83 (t, *J* = 5.6 Hz, 1H; η-C*H*$_{ar}$), 5.42 (s, 5H; Cp), 3.94 (3H, s, OC*H*$_3$), 2.93 (t, *J* = 6.9 Hz, 2H, CH_2CH_2NH), 2.81 (t, *J* = 7.1 Hz, 2H, CH_2CH_2NH).

^{13}C NMR (125 MHz, CD_3OD): δ = 153.97 (*C*$_{ar}$O(η-Ph)), 138.92 (CH_2*C*$_{ar}$), 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 (O *C*H_3), 43.86 (CH_2*C*H_2NH), 38.74 (CH_2*C*H_2NH).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3420 (s), 3094 (m), 2926 (m), 2855 (w), 2363 (w), 1554 (s), 1528 (s), 1499 (s), 1476 (m), 1473 (s), 1437 (m), 1414 (m), 1276 (m), 1260 (m), 1220 (s), 1178 (w), 1103 (w), 1007 (w), 844 (s), 668 (w), 558 (w).

UV/Vis (CH_3OH): λ_{max} (ε) = 266 (17300), 224 (43000) 204 nm (90200 $mol^{-1}dm^3cm^{-1}$).

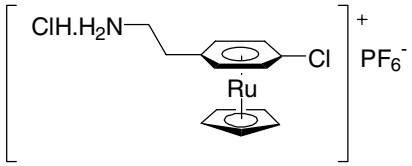
MS (FAB+, NBA): m/z (%): 410/411/412 (92/100/76) [M^+].

HRMS (FAB): calcd for $C_{20}H_{22}NO_2{}^{102}Ru$ [M^+]: 410.0695, found 410.0722.

7 Synthesis of AB-Unit

7.1 [1-{2-(*N*-(2-(*tert*-Butoxycarbonylamino)-1-(3-hydroxy-4-methoxyphenyl)ethyl)carbamoyl)ethyl}-4-chloro-η^6-benzene](\η^5-cyclopentadienyl)ruthenium hexafluorophosphate (114)

7.1.1. {1-(2-Amino)ethyl-4-chloro-η^6-benzene}(η^5-cyclopentadienyl) ruthenium hexafluorophosphate (116)



[1-{2-(*tert*-butoxycarbonylamino)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl) ruthenium hexafluorophosphate (**135**)[94] (2000 mg, 3.4 mmol) is dissolved in 300 mL HCl 4N in CH_3OH and is allowed to stir at room temperature for 3 hours. The solvent is removed well in vacuum and the product is purified by recrystallisation fro *i*PrOH-CH_3OH (3:1) affording colourless needles.

Yield: 1700 mg (quant)

TLC (NH_2-Si, *i*PrOH-H_2O (6:1)): R_f = 0.29

Melting Point: at 175 °C starts decomposition without melting

^{1}H NMR (360 MHz, CD_3OD): δ = 6.75 (d, *J* = 6.0 Hz, 2H; η-C*H*$_{ar}$), 6.49 (d, *J* = 6.1 Hz, 2H; η-C*H*$_{ar}$), 5.59 (s, 5H; Cp), 3.23 (t, *J* = 7.5 Hz, 2H; CH_2CH_2NH), 2.93 (t, *J* = 7.3, Hz, 2H, CH_2CH_2NH).

^{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 ($CH_2CH_2NH_2$).

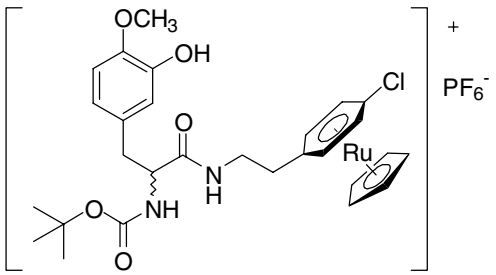
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3424 (m), 3082 (s), 1617 (w), 1525 (s), 1457 (w), 1420 (s), 1375 (w), 1288 (m), 1053 (s), 995 (s), 861 (m), 734 (w), 658 (w), 493 (w).

UV/Vis (CH_3OH): λ_{max} (ε) = 204 nm (33400 mol^{-1}dm^{3}cm^{-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.

7.1.2. [1-{2-(*N*-(2-(*tert*-Butoxycarbonylamino)-1-(3-hydroxy-4-methoxyphenyl)ethyl)carbamoyl)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (114)



2-*tert*-Butoxycarbonylamino-3-(3-hydroxy-4-methoxy-phenyl)-propionic acid (**117**) (95 mg, 0.46 mmol) is dissolved in THF-CH_3OH ((1:1), 10 mL) and HOBt (93 mg, 0.69 mmol) is added. The mixture is cooled to 0 °C followed by addition of EDCI (120 mg, 0.506 mmol). The mixture is stirred for 15 min and then {1-(2-amino)ethyl-4-chloro-η^6-benzene}(η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**116**)

(269 mg, 0.46 mmol) dissolved in CH_3OH (1.2 ml) and in *i*Pr_2Et (0.08 mL, 0.46 mmol) are given. The mixture is stirred at 0 °C for 4 hours and at room temperature for further 30 hours. The solvent is concentrated and the mixture is diluted with 10 mL H_2O and is extracted with CH_2Cl_2. The organic layers are combined and washed with saturated aqueous solution of $NaHCO_3$ and brine and is finally dried over Na_2SO_4. The solution is concentrated to 2 mL and after Et_2O (70 mL) addition, a brown powder precipitates. The product is collected, dried well and purified by preparative HPLC on aminopropyl silica (*i*PrOH-H_2O (9:1), 17 mg each injection, flow rate 15 mL cm^{-1}) giving a light brown powder.

Yield: 171 mg (49 %)

TLC (NH_2-Si, *i*PrOH-H_2O (6:1)): R_f = 0.53

HPLC retention volumes: 179 mL *i*PrOH-H_2O (9:1)).

^{1}H NMR (500 MHz, [D_6]DMSO): δ = 6.84 (d, *J* = 8.2 Hz, 1H, O*H*), 6.80 (d, *J* = 8.2 Hz, 1H CH_{ar}), 6.73 (d, *J* = 5.9 Hz, 1H; η-CH_{ar}), 6.69 (d, *J* = 6.0 Hz, 1H; η-CH_{ar}), 6.65 (d, *J* = 1.9 Hz, 1H, CH_{ar}), 6.59 (dd, *J* = 1.9, 8.1 Hz, 1H, CH_{ar}), 6.30 (d, *J* = 5.9 Hz, 1H, η-C_{ar}H), 6.11 (d, *J* = 5.9 Hz, 1H, η-CH_{ar}), 5.52 (s, 5H; Cp), 4.57 (t, *J* = 5.5 Hz, 1H, CHN*H*CO), 4.09 (bq, *J* = 5.1 Hz, 1H, CH_2N*H*Boc), 3.96 (brq , *J* = 8.7 Hz, 1H, CH_2C*H*(CO)NH), 3.72 (s, 3H, OCH_3), 3.31 (m, 1H, CH_2CH*H*NH), 3.24 (m, 1H, CH_2CH*H*NH), 2.75 (dd, *J* = 5.3, 13.7 Hz, 1H; CH*H*CH(CO)NH), 2.57 (dd, *J* = 9.3, 13.6 Hz, 1H; CH*H*CH(CO)NH), 2.50 (m, 2H, C$H_2$$CH_2$NH), 1.31 (s, 9H, C(C$H_3$)$_3$).

^{13}C NMR (125 MHz, [D_6]DMSO): δ = 172.33 (*C*=O), 155.55 (*C*=O), 146.48 ($C_{ar}$$OCH_3$), 146.23 (C_{ar}OH), 130.69 ($C_{ar}$$CH_2$CH(CO)NH), 120.21 (C_{ar}H), 116.85 (C_{ar}H), 112.23 (C_{ar}H), 104.18 (η-C_{ar}Cl), 103.19 (η-$C_{ar}$$CH_2$), 86.85 (η-$C_{ar}$H), 86.75 (2 x η-$C_{ar}$H), 86.64 (η-$C_{ar}$H), 82.58 (Cp), 78.58 (*C*(CH_3)$_3$), 56.41 (CH_2C*H*(CO)NH), 55.93 (O*C*H_3), 37.21 (CH_2*C*H_2NH), 36.14 (*C*H_2CH(CO)NH), 33.22 (*C*$H_2$$CH_2$NH), 28.39 (C(*C*$H_3$)$_3$).

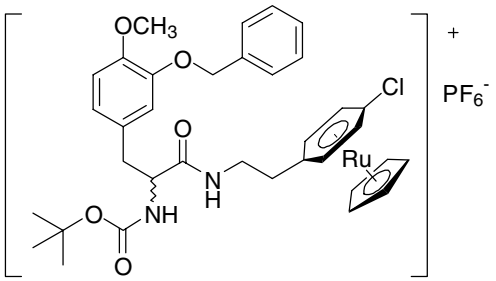
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3418 (w), 3087 (w), 2976 (w), 2935 (w), 1700 (s), 1669 (s), 1591 (w), 1512 (s), 1456 (m), 1368 (m), 1275 (m), 1247 (m), 1164 (s), 1132 (m), 1092 (w), 1024 (w), 842 (s), 732 (w), 558 (s).

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.

7.2 [1-{2-(*N*-(1-(3-Benzyloxy-4-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)ethyl)carbamoyl)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (115)



3-(3-Benzyloxy-4-methoxy-phenyl)-2-*tert*-butoxycarbonylamino-propionic acid (**118**) (239 mg, 0.597 mmol) and HOBt (120 mg, 0.896 mmol) are dissolved in 10 mL THF and are cooled to 0 °C. EDCI (129 mg, 0.657 mmol) is given and, after stirring for 15 min {1-(2-amino)ethyl-4-chloro-η^6-benzene}(η^5-cyclopentadienyl)rutheniu hexafluorophosphate (**116**) (300 mg, 0.597 mmol) with 0.2 mL *i*Pr_2NEt (0.2 mL, 2.2 eq) in CH_3OH are added. The mixture is allowed to stir at 0 °C for 4 hours and at room temperature for further 40 hours. When the reaction finishes, the solvent is removed and the product is purified by column chromatography on aminopropyl silica (*i*PrOH-CH_3CN (4:1)) followed by preparative HPLC on aminopropyl silica (*i*PrOH-CH_3CN (4:1), 10 mg each injection, flow rate 12 mL min^{-1}). Recrystallisation from H_2O (at 80 °C is added dropwise *i*PrOH until everything dissolves) yields colourless crystals.

Yield: 310 mg (60 %)

TLC (NH_2-Si, *i*PrOH): R_f = 0.22

HPLC retention volumes: 224 mL *i*PrOH-CH_3CN (4:1)).

Melting Point: 174 °C (decomposes)

^{1}H NMR (360 MHz, [D_6]acetone): δ = 7.50 (d, *J* = 7.2 Hz, 2H; *o*-C*H*$_{ar}$, Bn), 7.38 (t, *J* = 7.5 Hz, 2H, *m*-C*H*$_{ar}$, Bn), 7.34 (d, *J* = 7.2 Hz, 1H, *p*-C*H*$_{ar}$, Bn), 6.99 (d, *J* = 1.9 Hz, 1H, C*H*$_{ar}$), 6.93 (d, *J* = 8.2 Hz, 1H, C*H*$_{ar}$), 6.81 (dd, *J* = 1.9, 8.1 Hz, 1H, C*H*$_{ar}$), 6.71 (d, *J* = 6.1 Hz, 1H; η-C*H*$_{ar}$), 6.68 (d, *J* = 6.2 Hz, 1H; η-C*H*$_{ar}$), 6.43 (d, *J* = 5.2 Hz, 1H; η-C*H*$_{ar}$), 6.20 (d, *J* = 5.5 Hz, 1H; η-C*H*$_{ar}$), 6.08 (brd, 1H, N*H*), 5.61 (s, 5H; Cp), 5.09 (s, 2H, OC*H*$_2$Ph), 4.21 (brq, *J* = 6.3 Hz, 1H, CH_2C*H*(CO)NH), 3.82 (s, 3H, OC*H*$_3$), 3.50 (brq, *J* = 5.8 Hz, 1H, CH_2C*H*HNH), 3.40 (brq, *J* = 5.7 Hz, 1H, CH_2C*H*HNH), 3.02 (dd, *J* = 6.4, 13.7 Hz, 1H; CH*H*CH(CO)NH), 2.81 (dd, *J* = 8.0, 13.9 Hz, 1H; CH*H*CH(CO)NH), 2.68 (q, *J* = 7.1 Hz, 2H, C*H*$_2$$CH_2$NH), 1.36 (s, 9H, C(C*H*$_3$)$_3$).

^{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_2$Ph), 138.63 (*C*$_{ar}$$CH_2$O), 131.28 (*C*$_{ar}$$CH_2$CH(CO)NHBoc), 129.39 (*m*-*C*$_{ar}$H, Bn), 128.79 (*p*-*C*$_{ar}$H, Bn), 128.71 (*o*-*C*$_{ar}$H, Bn), 123.27 (*C*$_{ar}$H), 116.71 (*C*$_{ar}$H), 113.44 (*C*$_{ar}$H), 105.62 (η-*C*$_{ar}$Cl), 104.56 (η-*C*$_{ar}$$CH_2$), 88.02 (η-*C*$_{ar}$H), 87.96 (2 x η-*C*$_{ar}$H), 87.80 (η-*C*$_{ar}$H), 83.65 (Cp), 79.76 (O *C*(CH_3)$_3$), 71.76 (Ph*C*H_2O), 57.23 (CH_2*C*H(CO)NHBoc), 56.52 (O *C*H_3), 40.60 (CH_2*C*H_2NH), 38.46 (*C*H_2CH(CO)NH), 34.46 (*C*$H_2$$CH_2$$NH_2$), 28.70 (OC(*C*$H_3$)$_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3420 (s), 3290 (m), 3065 (m), 2975 (m), 2929 (m), 1706 (s), 1663 (s), 1512 (s), 1457 (m), 1419 (m), 1364 (m), 1259 (s), 1162 (s), 1139 (m), 1090 (w), 1021 (m), 852 (w), 746 (w), 698 (w), 626 (w).

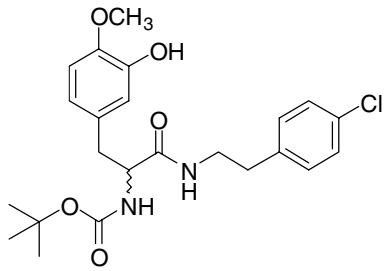
UV/Vis ($CHCl_3$): λ_{max} (ε) = 282 (3800), 242 nm (8000 $mol^{-1}dm^3cm^{-1}$).

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.

Elemental Analysis: $C_{35}H_{40}ClF_6N_2O_5PRu$ (850.20)
Calculated: C: 49.44 H: 4.74 N 3.29
Found: C: 49.22 H: 4.88 N 3.18

7.3 [1-[2-(4-Chloro-phenyl)-ethylcarbamoyl]-2-(3-hydroxy-4-methoxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (161)



HOBt (283 mg, 2.142 mmol) is added to a solution of 2- *tert*-butoxycarbonylamino-3-(3-hydroxy-4-methoxy-phenyl)-propionic acid (**117**) (464 mg, 1.428 mmol) in THF-CH_3OH ((1:1), 8 mL). The mixture is cooled to 0 °C and EDCI (372 mg, 1.57 mmol) is added. After stirring for 15 min 2-(4-chloro-phenyl)ethylamine (**133**) (0.2 mL, 1.428 mmol) with iPr_2NEt (0.25 mL, 1.428 mmol) are given, and the reaction mixture is allowed to stir for further 4 hours at this temperature and for 26 hours at roo temperature. The solvent is removed and the mixture is dissolved in CH_2Cl_2. The solute is washed successively with $NaHSO_4$ (1N), saturated aqueous solution of $NaHCO_3$ and finally with brine. The organic layer is dried over Na_2SO_4 and after solvent removal, the product is recrystallised from TMP yielding transparent crystals.

Yield: 505 mg (79 %)

TLC (Si, TMP-EtOAc (7:3)): R_f = 0.61

Melting Point: 157-158 °C

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.7 Hz, 2H; C*H*$_{ar}$), 6.98 (d, *J* = 8.3 Hz, 2H, C*H*$_{ar}$), 6.76 (d, *J* = 1.5 Hz, 1H, C*H*$_{ar}$), 6.75 (d, *J* = 8.3 Hz, 1H, C*H*$_{ar}$), 6.64 (dd, *J* =

1.9, 8.3 Hz, 1H, C*H*$_{ar}$), 5.87 (brt, 1H, O*H*), 5.76 (brs, 1H, N*H*), 5.02 (brs, 1H, N*H*), 4.19 (q, *J* = 7.3 Hz, 1H, CH_2C*H*(CO)NH), 3.86 (s, 3H, OC*H*$_3$), 3.42 (dd, *J* = 7.3, 13.7 Hz, 1H, CH_2C*H*HNH), 3.37 (brq, *J* = 7.3, 13.2 Hz, 1H, CH_2C*H*HNH), 2.98 (dd, *J* = 6.9, 14.2 Hz, 1H; CH*H*CH(CO)NH), 2.82 (dd, *J* = 7.8, 13.7 Hz, 1H; CH*H*CH(CO)NH), 2.63 (q, *J* = 6.9 Hz, 2H, C*H*$_2$$CH_2$NH), 1.40 (s, 9H, C(C*H*$_3$)$_3$).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 171.27 (*C*=O), 155.37 (*C*=O), 145.77 (*C*$_{ar}$$OCH_3$), 145.71 (*C*$_{ar}$$OCH_2$Ph), 137.13 (*C*$_{ar}$Cl), 132.31 (*C*$_{ar}$$CH_2$CH(CO)NHBoc), 130.08 (*C*$_{ar}$H), 129.79 (*C*$_{ar}$$CH_2$$CH_2$NHBoc), 128.77 (*C*$_{ar}$H), 120.81 (*C*$_{ar}$H), 115.51 (*C*$_{ar}$H), 110.83 (*C*$_{ar}$H), 80.27 (O *C*$(CH_3)_3$), 56.23 (CH $_2$*C*H(CO)NHBoc), 55.99 (O *C*H_3), 40.58 (CH_2*C*H_2NH), 38.03 (*C*H_2CH(CO)NH), 34.92 (*C*$H_2$$CH_2$$NH_2$), 28.64 (OC(*C*$H_3$)$_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3369 (m), 3239 (m), 3001 (w), 2944 (w), 1687 (s), 1669 (s), 1588 (w), 1545 (s), 1507 (s), 1489 (m), 1442 (m), 1364 (m), 1311 (s), 1279 (s), 1241 (s), 1163 (s), 1092 (w), 1034 (w), 1016 (m), 955 (w), 864 (w), 799 (w), 761 (w), 711 (w), 623 (w).

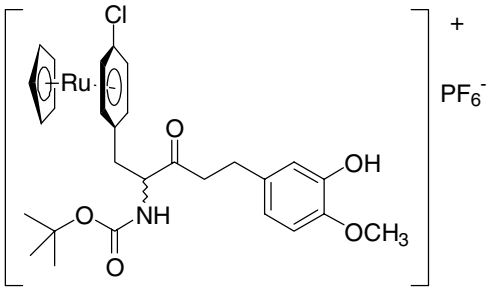
UV/Vis (CH_3OH): λ_{max} (ε) = 282 (10200), 222 (25900), 204 nm (48400 $mol^{-1}dm^3cm^{-1}$).

MS (EI, 70 eV): m/z (%): 448 (4) [M^+], 392 (3) [M^+-C_4H_8], 375 (8) [M^+-C_4H_9O], 331 (78) [M^+-$C_5H_{11}NO_2$], 210 (12) [M^+-$C_5H_{11}NO_2$-$C_7H_6O_2$], 177 (82), 137 (100) [M^+-$C_5H_{11}NO_2$-$C_{10}H_9ClNO$].

Elemental Analysis: $C_{23}H_{29}ClN_2O_5$ (448.94)
Calculated: C: 61.53 H: 6.51 N 6.24
Found: C: 61.26 H: 6.58 N 6.11

8 Synthesis of A'B'-Unit

8.1 [1-{2-(*tert*-Butoxycarbonylamino)-2-(*N*-(2-(3-hydroxy-4-methoxyphenyl)ethyl)carbamoyl)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (162)



To a solution of [1-{2-(tert-butoxycarbonylamino)-2-(carboxy)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**109**)[85b] (432 mg, 0.826 mmol) and HOBt (149 mg, 1.1 mmol) in CH_2Cl_2 (5 mL) and CH_3OH (8 mL) at 0 °C is given EDCI (176 mg, 0.903 mmol). The mixture is stirred for 15 min followed by the addition of a solution of 5-(2-amino-ethyl)-2-methoxy-phenol (**112**)[88] (138 mg, 0.826 mmol) and *i*Pr_2NEt (0.14 mL, 0.826 mmol) dissolved in CH_3OH (3 mL). After stirring for 2 hours at this temperature, the mixture is brought to room temperature where is allowed to stir for further 26 hours. The solvent is removed and the mixture is diluted with H_2O and extracted with CH_2Cl_2. The organic layer is washed with saturated aqueous solution of $NaHCO_3$ and with brine. The organic layer is dried over Na_2SO_4, and after concentration to 3 mL, Et_2O (130 mL) is added and the brown precipitate is filtered and dried well.

Yield: 370 mg (59 %)

TLC (NH_2-Si, *i*PrOH-H_2O (6:1)): R_f = 0.51

^{1}H NMR (500 MHz, [D_6]DMSO): δ = 6.84 (d, J = 6.2 Hz, 1H; η-CH_{ar}), 6.82 (d, J = 8.1 Hz, 1H, CH_{ar}), 6.81 (d, J = 5.8 Hz, 1H, η-CH_{ar}), 6.62 (d, J = 2.0Hz, 1H, CH_{ar}), 6.57 (dd, J = 2.0, 8.2 Hz, 1H, CH_{ar}), 6.34 (d, J = 6.0 Hz, η-CH_{ar}), 6.24 (d, J = 6.1 Hz, 1H; η-CH_{ar}), 5.53 (s, 5H; Cp), 4.56 (m, 1H, N*H*), 4.12 (brm, 1H, CH_2C*H*(CO)NH), 3.72 (s, 3H, OCH_3), 3.13 (brq, J = 5.8 Hz, 1H, CH_2CH_2NH), 2.72 (m, 1H; CH*H*CH(CO)NH), 2.68 (m, 1H; CH*H*CH(CO)NH), 2.55 (m, 2H, C$H_2$$CH_2$NH), 1.29 (s, 9H, C(C$H_3$)$_3$).

^{13}C NMR (125 MHz, [D $_6$]DMSO): δ = 170.22 (*C*=O), 155.32 (*C*=O), 146.46 ($C_{ar}OCH_3$), 146.35 ($C_{ar}OCH_2Ph$), 131.89 ($C_{ar}CH_2CH_2NH$), 119.39 ($C_{ar}H$), 116.16 ($C_{ar}H$), 112.38 ($C_{ar}H$), 104.09 (η-$C_{ar}Cl$), 101.71 (η-$C_{ar}CH_2CH(CO)NH$), 86.85 (η-$C_{ar}H$), 86.57 (η-$C_{ar}H$), 82.51 (Cp), 78.62 (O $C(CH_3)_3$), 55.76 (O CH_3), 53.64 ($CH_2CH(CO)NHBoc$), 40.51 (CH $_2CH_2NH$), 36.20 ($CH_2CH(CO)NH$), 34.45 ($CH_2CH_2NH_2$), 28.11 ($OC(CH_3)_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3372 (s), 3297 (m), 2926 (s), 2850 (s), 1700 (s), 1623 (s), 1589 (s), 1539 (m), 1499 (m), 1465 (m), 1420 (s), 1339 (s), 1238 (s), 1141 (m), 1054 (w), 923 (w), 822 (w), 744 (w), 715 (w).

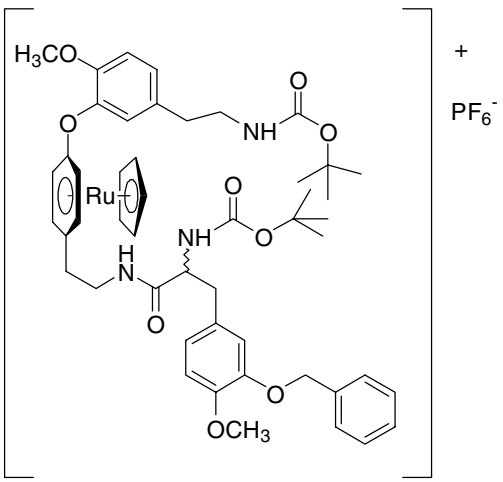
UV/Vis (CH_3OH): λ_{max} (ε) = 332 (6000), 282 (11400), 204 nm (54100 mol^{-1}dm^{3}cm^{-1}); (DMF): 282 (11400), 268 nm (10750 mol^{-1}dm^{3}cm^{-1}); (CH_2Cl_2): 282 (8300), 230 n (15800 mol^{-1}dm^{3}cm^{-1}).

MS (FAB+, NBA): m/z (%): 614/615/617 (70/86/82) [M$^+$].

HRMS (FAB): calcd for $C_{28}H_{34}{}^{35}ClN_2O_5{}^{102}Ru$ [M] $^+$: 615.1205, found 615.1234.

9 Synthesis of ABB'-Unit

9.1 [1-{2-(*N*-(1-(3-Benzyloxy-4-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)ethyl)carbamoyl)ethyl}-4-{(5-(2-(*tert*-butoxycarbonylamino)ethyl)-2-methoxy)phenoxy}-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (169)



[2-(3-Hydroxy-4-methoxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (**119**) (15 mg, 0.053 mmol) is added to a solution of KO *t*Bu (1.0 eq.) and [18]crown-6 (0.1 eq.) in THF-CH_3CN (1:1) (15 mL). After 30 min the mixture is cooled to 0 °C and is transferred to a pre-cooled (-78 °C) solution containing [1-{2-(*N*-(1-(3-Benzyloxy-4-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)ethyl)carbamoyl)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**115**) (50 mg, 0.053 mmol) in THF-CH_3CN (1:1) (20 mL). After 1 hour the reaction is slowly brought to 20 °C. After 16 hours, the reaction mixture is filtered and concentrated. Purification by preparative HPLC on aminopropyl silica (*i*PrOH-CH_3CN (4:1), 10 mg each injection, flow rate 15 mL min^{-1}) followed by recrystallisation from CH_2Cl_2 and Et_2O gives a colourless powder.

Yield: 50 mg (87 %)

TLC (NH_2-Si, *i*PrOH): $R_f = 0.37$

HPLC retention volumes: 176 mL *i*PrOH-CH_3CN (4:1)).

Melting Point: 101-102 °C (decomposes)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.3 Hz, 2H, *o*-C*H*$_{ar}$, Bn), 7.35 (t, *J* = 7.2 Hz, 2H, *m*-C*H*$_{ar}$, Bn), 7.27 (t, *J* = 6.9 Hz, 1H, *p*-C*H*$_{ar}$, Bn), 7.11 (dd, *J* = 1.7, 8.3 Hz, 1H, C*H*$_{ar}$, dopamine), 6.97 (brs, 1H, C*H*$_{ar}$, DOPA), 6.96 (d, *J* = 8.4 Hz, 1H, C*H*$_{ar}$, dopamine), 6.85 (brd, *J* = 8.6 Hz, 1H, C*H*$_{ar}$, DOPA), 6.84 (brs, 1H, C*H*$_{ar}$, dopamine), 6.79 (d, *J* = 8.2 Hz, 1H, C*H*$_{ar}$, DOPA), 6.45 (brs, 1H; η-C*H*$_{ar}$), 6.36 (brs, 1H; η-C*H*$_{ar}$), 5.96 (brt, 5.1 Hz, 2H, η-C*H*$_{ar}$), 5.77 (brd, *J* = 7.8 Hz, 1H, N*H*), 5.33 (s, 5H; Cp), 5.13 (s, 2H, OC*H*$_2$Ph), 4.79 (brt, 1H, N*H*), 4.45 (brq, *J* = 4.9 Hz, 1H, CH_2C*H*(CO)NH), 3.82 (3H, s, OC *H*$_3$), 3.78 (3H, s, OC *H*$_3$), 3.58 (brm, 1H, CH_2C*H*HNH), 3.46 (brm, 1H, CH_2C*H*HNH), 3.32 (brq, *J* = 6.4 Hz, 2H, CH_2C*H*$_2$NH), 3.08 (dd, *J* = ,4.8, 13.6 Hz, 1H, C*H*HCH(CO)NH), 2.94 (m, 1H, C*H*HCH(CO)NH), 2.84 (m, 2H, C*H*$_2$$CH_2$NH); 2.73 (t, *J* = 7.1 Hz, 2H, C*H*$_2$$CH_2$NH); 1.41 (s, 9H, C(C*H*$_3$)$_3$), 1.33 (s, 9H, C(C*H*$_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.78 (*C*=O), 155.94 (*C*=O), 155.45 (*C*=O), 149.63 (*C*$_{ar}$$OCH_3$, dopamine), 148.39 (*C*$_{ar}$$OCH_3$, DOPA), 148.05 (*C*$_{ar}$$OCH_2$Ph), 140.36 (($\eta$-

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, Bn), 128.43 (C_{ar}H, dopamine), 127.93 (*o*-C_{ar}H, Bn), 127.72 (*p*-C_{ar}H, Bn), 122.37 (C_{ar}H, dopamine, 122.37 (C_{ar}H Dopa)), 115.64 (C_{ar}H, DOPA), 113.41 (C_{ar}H, dopamine), 112.02 (C_{ar}H, DOPA), 102.12 (η-$C_{ar}CH_2$), 85.60 (η-C_{ar}H), 85.33 (η-C_{ar}H), 80.75 (Cp), 79.35 (O $C(CH_3)_3$), 79.25 (O$C(CH_3)_3$), 74.68 (η-C_{ar}H), 71.06 (PhCH_2O), 56.43 (CH $_2$CH(CO)NHBoc), 56.11 (OCH_3), 56.07 (O CH_3), 41.80 (CH_2CH_2NH), 39.38 (CH $_2CH_2$NH), 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)$_3$).

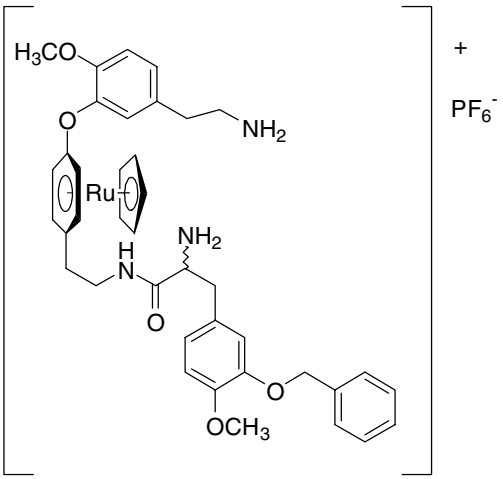
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3407 (m), 3066 (w), 2974 (m), 2931 (m), 1700 (s), 1684 (s), 1663 (s), 1507 (s), 1476 (s), 1442 (w), 1364 (w), 1272 (s), 1232 (s), 1167 (s), 1140 (w), 1121 (w), 1022 (m), 845 (w), 773 (w), 698 (w).

UV/Vis ($CHCl_3$): λ_{max} (ε) = 280 (7800), 242 nm (11200 $mol^{-1}dm^3cm^{-1}$).

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.

9.2 [1-{2-(*N*-(2-Amino-1-(3-benzyloxy-4-methoxyphenyl)ethyl)carbamoyl) ethyl}-4-{(5-(2-amino)ethyl-2-methoxy)phenoxy}-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (170)



[1-{2-(*N*-(1-(3-Benzyloxy-4-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)ethyl) carbamoyl)ethyl}-4-{(5-(2-(*tert*-butoxycarbonylamino)ethyl)-2-methoxy)phenoxy}-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**169**) (40 mg, 0.037 mmol) is treated with HCl 4N in CH_3OH (15 mL) and is allowed to stir at room temperature for 3 hours. The solvent is removed and the product is recrystallised from *i*PrOH.

Yield: 27 mg (quant.)

TLC (NH_2-Si, *i*PrOH:H_2O (6:1)): R_f = 0.32

Melting Point: 174-176 °C (decomposes)

^{1}H NMR (360 MHz, CD_3OD): δ = 7.48 (d, *J* = 7.3 Hz, 2H, *o*-CH_{ar}, Bn), 7.36 (t, *J* = 7.0 Hz, 2H, *m*-CH_{ar}, Bn), 7.33 (t, *J* = 6.8 Hz, 1H, *p*-CH_{ar}, Bn), 7.94 (dd, *J* = 2.3, 8.4 Hz, 1H, CH_{ar}, dopamine), 6.93 (d, *J* = 8.8 Hz, 1H, CH_{ar}, dopamine), 6.85 (d, *J* = 1.8 Hz, 1H, CH_{ar}, dopamine), 6.80 (d, *J* = 8.1 Hz, 1H, CH_{ar}, DOPA), 6.64 (d, *J* = 2.0 Hz, 1H, CH_{ar}, DOPA), 6.57 (dd, *J* = 2.3, 8.1 Hz, 1H, CH_{ar}, DOPA), 5.93 (d, *J* = 6.7 Hz, 2H; η-CH_{ar}), 5.75 (d, *J* = 7.0 Hz, 2H; η-CH_{ar}), 5.27 (s, 5H; Cp), 5.07 (s, 2H, OCH_2Ph), 4.20 (brm, 1H, CH_2C*H*(CO)NH), 3.81 (s, 6H, 2 x OCH_3), 3.63 (brm, 1H, CH_2C*H*HNH), 3.58 (brm, 1H, CH_2C*H*HNH), 3.20 (m, 2H, CH_2CH_2NH), 2.85-2.73 (m, 6H, CH_2CH(CO)NH + C$H_2$$CH_2$NH + C$H_2$$CH_2$NH).

^{13}C NMR (62.9 MHz, CD_3OD): δ = 169.73 (*C*=O), 152.00 ($C_{ar}$$OCH_3$, dopamine), 151.03 ($C_{ar}$$OCH_3$, DOPA), 149.91 ($C_{ar}$$OCH_2$Ph), 142.29 ((η-Ph)OC_{ar}), 138.56 ($C_{ar}$$CH_2$O), 134.13 ($C_{ar}$$CH_2$$CH_2$NH), 131.69 ($\eta$-$C_{ar}$OPh), 129.57 (*m*-$C_{ar}$H, Bn), 129.12 (*p*-$C_{ar}$H, Bn), 128.95 (*o*-$C_{ar}$H, Bn), 128.34 ($C_{ar}$$CH_2$CH(CO)NHBoc), 124.05 (C_{ar}H, dopamine), 123.89 (C_{ar}H, DOPA), 121.96 (C_{ar}H, dopamine), 117.68 (C_{ar}H, DOPA), 115.22 (C_{ar}H, dopamine), 114.10 (C_{ar}H, DOPA), 101.95 (η-$C_{ar}$$CH_2$), 86.25 ($\eta$-$C_{ar}$H), 82.11 (Cp), 76.31 (η-C_{ar}H), 72.59 (Ph*C*H_2O), 56.72 (O *C*H_3), 56.62 (CH_2*C*H(CO)NHBoc), 55.92 (O*C*H_3), 41.91 (CH_2*C*H_2NH), 41.41 (CH_2*C*H_2NH), 38.16 (*C*H_2CH(CO)NH), 34.37 (*C*$H_2$$CH_2$$NH_2$), 33.47 (*C*$H_2$$CH_2$$NH_2$).

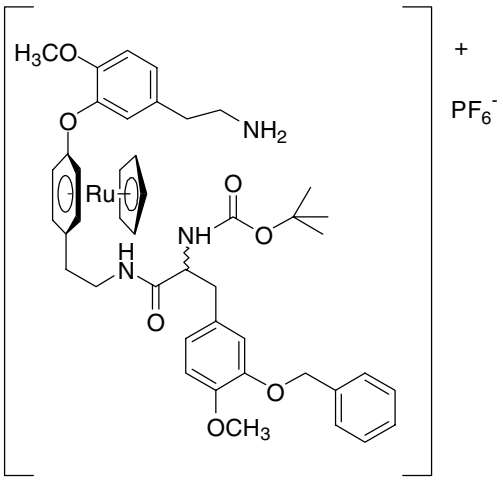
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3411 (s), 3237 (s), 3065 (s), 2933 (s), 1678 (s), 1635 (m), 1617 (m), 1595 (w), 1507 (s), 1473 (s), 1442 (w), 1274 (s), 1230 (s), 1125 (m), 1022 (m), 945 (w), 881 (w), 846 (w), 818 (w), 761 (w), 700 (w).

UV/Vis (CH_3OH): λ_{max} (ε) = 280 (12400), 224 (35100), 204 nm (91200 $mol^{-1}dm^3cm^{-1}$).

MS (FAB+, NBA): m/z (%): 735/736/738 (96/100/83) [M^+], 644/645/646 (47/54/85) [M^+-C_7H_6].

HRMS (FAB): calcd for $C_{39}H_{44}N_3O_5{}^{102}Ru$ [M^+]: 736.2336, found 736.2314.

9.3 [4-{(5-(2-Amino)ethyl-2-methoxy)phenoxy}-1-{2-(*N*-(1-(3-Benzyloxy-4-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)ethyl)carbamoyl)ethyl}-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (111)



KO*t*Bu (13 mg, 0.0954 mmol) and [18]crown-6 (4 mg, 0.1 eq) are dissolved in dry THF-acetone (1:1) (15 mL) and after 15 min 5-(2-amino-ethyl)-2-methoxy-phenol (**112**)[88] (16 mg, 0.0954 mmol) is added. After 30 min the mixture is cooled to 0 °C and is transferred to a pre-cooled (-78 °C) solution of [1-{2-(*N*-(1-(3-Benzyloxy-4-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)ethyl)carbamoyl)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**115**) (90 mg, 0.0954 mmol) in dry THF. The reaction mixture is stirred for 1 hour at this temperature and at room temperature for further 48 hours. The solvent is concentrated to 2 mL and Et_2O is given. The precipitate is filtered on aminopropyl

silica (CH_3CN) in order to remove [18]crown-6 and then is purified by column chromatography on aminopropyl silica (*i*PrOH-H_2O (6:1)) affording a pale yello powder.

Yield: 60 mg (64 %)

TLC (NH_2-Si, *i*PrOH-H_2O (6:1)): R_f = 0.43

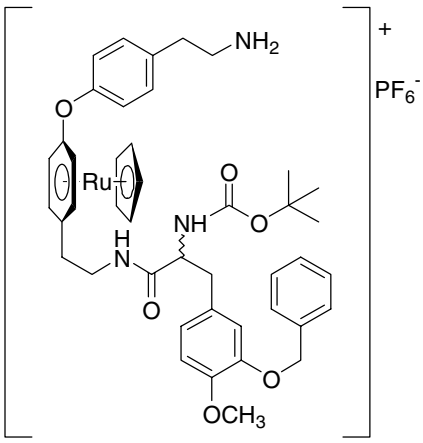
^{1}H NMR (360 MHz, CD_3OD): δ = 7.46 (d, *J* = 6.6 Hz, 2H, *o*-C*H*$_{ar}$, Bn), 7.36 (t, *J* = 7.0 Hz, 2H, *m*-C*H*$_{ar}$, Bn), 7.30 (t, *J* = 7.4 Hz, 1H, *p*-C*H*$_{ar}$, Bn), 7.22 (dd, *J* = 1.5, 8.7 Hz, 1H, C*H*$_{ar}$), 7.15 (d, *J* = 8.7 Hz, 1H, C*H*$_{ar}$), 7.09 (d, *J* = 1.9 Hz, 1H, C*H*$_{ar}$), 7.01 (d, *J* = 2.1 Hz, 1H, C*H*$_{ar}$), 6.93 (d, *J* = 7.8 Hz 1H, C*H*$_{ar}$), 6.84 (dd, *J* = 1.8, 7.8 Hz, 1H, C*H*$_{ar}$), 6.11 (brs, 1H; η-C*H*$_{ar}$), 6.05 (brs, 1H; η-C*H*$_{ar}$), 6.02 (brd, 6.6 Hz, 1H, η-C*H*$_{ar}$), 5.72 (brd, 5.7 Hz, 1H, η-C*H*$_{ar}$), 5.36 (s, 5H; Cp), 5.08 (s, 2H, OC *H*$_2$Ph), 4.15 (m, 1H, CH_2C*H*(CO)NH), 3.81 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC *H*$_3$), 3.52 (brm, 1H, CH_2C*H*HNH(CO)), 3.41 (brm, 1H, CH_2C*H*HNH(CO)), 3.25 (m, 2H, CH_2C*H*$_2$NH), 3.00-2.75 (m, 6H, C*H*$_2$CH(CO)NH, C*H*$_2$$CH_2NH_2$, C*H*$_2$$CH_2$NH(CO)), 1.39 (s, 9H, C(C*H*$_3$)$_3$).

^{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}$$OCH_2$Ph), 141.91 ((η-Ph)O*C*$_{ar}$), 138.68 (*C*$_{ar}$$CH_2$O), 134.87 (*C*$_{ar}$$CH_2CH_2NH_2$), 134.31 (η-*C*$_{ar}$OPh), 131.36 (*C*$_{ar}$$CH_2$CH(CO)NHBoc), 129.59 (*m*-*C*$_{ar}$H, Bn), 129.11 (*o*-C$_{ar}$H, Bn), 128.92 (*p*-C$_{ar}$H, Bn), 123.79 (C$_{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}$$CH_2$), 86.16 (η-*C*$_{ar}$H), 81.65 (Cp), 80.77 (O *C*$(CH_3)_3$), 80.02 (η-*C*$_{ar}$H), 76.09 (η-*C*$_{ar}$H), 75.98 (η-*C*$_{ar}$H), 72.52 (Ph*C*H_2O), 57.93 (CH_2*C*H(CO)NHBoc), 56.72 (O*C*H_3), 56.63 (O*C*H_3), 44.06 (CH_2*C*H_2NH), 41.18 (CH_2*C*H_2NH), 38.83 (*C*H_2CH(CO)NH), 37.71 (*C*$H_2$$CH_2NH_2$), 34.63 (*C*$H_2$$CH_2NH_2$), 28.75 (OC(*C*$H_3$)$_3$).

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.

9.4 [4-{4-(2-Aminoethyl)phenoxy}-1-{2-(*N*-(1-(3-Benzyloxy-4-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)ethyl)carbamoyl)ethyl}-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (174)



KO*t*Bu (6 mg, 0.0424 mmol) and [18]crown-6 (0.1 eq) are dissolved in dry THF-CH_3CN (1:1) (15 mL) and after 15 min tyramine (**171**) (5.8 mg, 0.0424 mmol) is given. After 30 min the mixture is cooled to 0 °C and is transferred to a pre-cooled (-78 °C) solution of [1-{2-(*N*-(1-(3-Benzyloxy-4-methoxyphenyl)-2-(*tert*-butoxy-carbonylamino)ethyl)carbamoyl)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl) ruthenium hexafluorophosphate (**115**) (40 mg, 0.0424 mmol) in dry THF. The reaction mixture is stirred for 1 hour at this temperature and at room temperature for further 16 hours. After solvent removal, the product is purified by column chromatography on aminopropyl silica with *i*PrOH-CH_3CN (6:1) ([18]crown-6 removal) and with *i*PrOH-H_2O (6:1). Recrystallisation fro *i*PrOH gives a light yellow powder.

Yield: 35 mg (79 %)

TLC (NH_2-Si, *i*PrOH-H_2O (6:1) and *i*PrOH-CH_3CN (8:1)): R_f = 0.42 and 0.37, respectively

Melting Point: 104 °C (decomposes)

^{1}H NMR (360 MHz, CD_3OD): δ = 7.45 (d, J = 7.4 Hz, 2H; *o*-CH_{ar}, Bn), 7.36 (d, J = 8.7 Hz, 2H, CH_{ar}, tyramine), 7.36 (t, J = 7.0 Hz, 2H, *m*-CH_{ar}, Bn), 7.31 (d, J = 7.0 Hz, 1H,

p-C*H*$_{ar}$, Bn), 7.10 (d, *J* = 8.7 Hz, 2H, C*H*$_{ar}$, tyramine), 7.02 (d, *J* = 8.6 Hz, 1H, C*H*$_{ar}$, DOPA), 6.93 (d, *J* = 2.1 Hz, 1H, C*H*$_{ar}$, DOPA), 6.83 (dd, *J* = 2.1, 8.2 Hz, 1H, C*H*$_{ar}$, DOPA), 6.72 (d, *J* = 8.6 Hz, 1H, η-C*H*$_{ar}$), 6.07 (dd, *J* = 1.7, 7.4 Hz, 1H; η-C*H*$_{ar}$), 6.04 (dd, *J* = 1.7, 6.2 Hz, 1H; η-C*H*$_{ar}$), 5.79 (d, *J* = 6.2 Hz, 1H, η-C*H*$_{ar}$), 5.38 (s, 5H; Cp), 5.07 (s, 2H, OC*H*$_2$Ph), 4.15 (t, *J* = 7.5 Hz, 1H, CH$_2$C*H*(CO)NH), 3.91 (3H, s, OC*H*$_3$), 3.39 (brdd, *J* = 6.6, 12.8 Hz 1H, CH$_2$C*H*HNH(CO)), 3.25 (dd, *J* = 7.0, 13.6 Hz, 1H, CH$_2$C*H*HNH(CO)), 2.91 (m, 2H, CH$_2$C*H*$_2$NH), 2.87 (m, 1H, C*H*HCH(CO)NH), 2.79 (m, 1H, C*H*HCH(CO)NH), 2.67 (t, *J* = 7.4 Hz, 1H, C*H*$_2$CH$_2$NH), 2.45 (q, *J* = 6.6 Hz, 2H, C*H*$_2$CH$_2$NH), 1.38 (s, 9H, C(C*H*$_3$)$_3$).

^{13}C NMR (90.6 MHz, CD$_3$OD): 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$_2$Ph), 139.73 (*C*$_{ar}$CH$_2$CH$_2$NH$_2$), 138.62 (*C*$_{ar}$CH$_2$O), 134.54 (*C*$_{ar}$CH$_2$CH(CO)NH), 132.21 (C$_{ar}$H, tyramine), 131.28 (η-*C*$_{ar}$OPh), 129.54 (*m*-C$_{ar}$H, Bn), 129.04 (*p*-*C*$_{ar}$H, Bn), 128.88 (*o*-*C*$_{ar}$H, Bn), 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 (O*C*(CH$_3$)$_3$), 76.53 (η-*C*$_{ar}$H), 76.40 (η-*C*$_{ar}$H), 71.20 (Ph*C*H$_2$O), 57.85 (CH$_2$*C*H(CO)NHBoc), 56.66 (O*C*H$_3$), 41.86 (CH$_2$*C*H$_2$NH), 43.73 (CH$_2$*C*H$_2$NH), 41.06 (*C*H$_2$CH(CO)NH), 38.84 (*C*H$_2$CH$_2$NH$_2$), 34.52 (*C*H$_2$CH$_2$NH$_2$), 28.70 (OC(*C*H$_3$)$_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3420 (w), 3336 (m), 3087 (w), 2932 (w), 1684 (s), 1653 (s), 1589 (w), 1559 (m), 1517 (s), 1507 (s), 1476 (s), 1457 (w), 1419 (w), 1368 (w), 1252 (s), 1163 (m), 1137 (m), 1018 (m), 838 (s), 746 (w), 699 (w).

UV/Vis (CH$_3$OH): λ_{max} (ε) = 280 (12400), 230 (24700), 206 (82800) 204 nm (83600 mol^{-1}dm^{3}cm^{-1}).

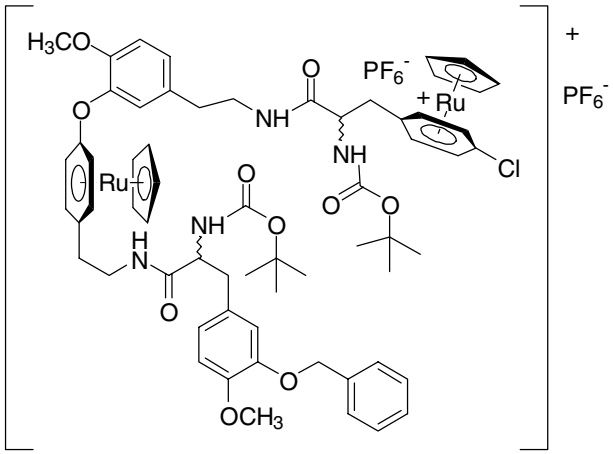
MS (FAB+, NBA): m/z (%): 805/806/808 (63/100/52) [M$^+$].

HRMS (FAB): calcd for C$_{43}$H$_{50}$N$_3$O$_6$^{102}Ru [M$^+$]: 806.2755, found 806.2753.

Elemental Analysis: C$_{43}$H$_{50}$F$_6$N$_3$O$_6$PRu (950.93)
Calculated: C: 54.31 H: 5.30 N 4.42
Found: C: 53.74 H: 5.55 N 3.92

10 Formation of an Open-Chain ABB'A' System (175)

10.1 [1-{2-(*N*-(2-(3-(4-(2-(*N*-(1-(3-Benzyloxy-4-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)ethyl)carbamoyl)ethyl)(η^5-cyclopentadienyl-ruthenio)-η^6-phenoxy-4-methoxyphenyl)ethyl)carbamoyl)-(2-*tert*-butoxycarbonylamino)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium di-(hexafluorophosphate) (175)



[1-{2-[tert-Butoxycarbonylamino)-2-(carboxy)ethyl}-4-chloro-η^6-benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**109**)[85b] (12 mg, 0.02 mmol) and HOBt (4.02 mg, 0.0335 mmol) are dissolved in THF (15 mL) and are cooled to 0 °C. To this mixture is added EDCI (2.84 mg, 0.022 mmol) and after stirring for 15 min [4-{(5-(2-Amino)ethyl-2-methoxy)phenoxy}-1-{2-(*N*-(1-(3-Benzyloxy-4-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)ethyl)carbamoyl)ethyl}-η^6-benzene](η^5-cyclopentadienyl) ruthenium hexafluorophosphate (**111**) (20 mg, 0.02 mmol) with *i*Pr_2NEt (0.003 mL, 1eq) in CH_3OH-THF (1:1) (10 mL) are added. The mixture is allowed to stir at this temperature for 4 hours and at room temperature for further 48 hours. To the reaction is given Et_2O and the precipitate is collected. Purification on aminopropyl silica (*i*PrOH-H_2O (7.5:1)) gives a brown powder.

Yield: 12 mg (38 %)

TLC (NH_2-Si, *i*PrOH-H_2O 7.5:1): R_f = 0.51

MS (FAB+, NBA): m/z (%): 1426/1427/1428/1429/1430/1431 (68/78/91/100/92/81) [M^+].

HRMS (FAB): calcd for $C_{63}H_{73}{}^{37}ClF_6N_4O_{10}P^{100}Ru^{102}Ru$ [M^+]: 1429.2717, found 1429.2708.

11 Enclosure

Table 2: Crystal data and Structure refinement for compound **160**.

Empirical formula: $C_{18}H_{17}F_6O_2PRu$		
Formula Weight: 511.36		
Temperature: 293 (2) K		
Wavelength: 0.71073 Å		
Crystal system: triclinic		
Space group: P1		
Unit cell dimensions:	a: 7.062 (2) Å	α: 74.165 (13)°
	b: 10.3801 (15) Å	β: 75.39 (2)°
	c: 14.371 (2) Å	γ: 76.12 (2)°
Volume: 964.1 (3) $Å^3$		
Z: 2		
Density (calculated): 1.762 g c^{-3}		
Absorption coefficient [μ: (M_o-K_α)]: 0.963 mm^{-1}		
F(000): 508		
Crystal size : 0.57 X 0.33 X 0.10 m		
θ range for data collection: 2.82 to 23.99°		
Index ranges: $0 \leq h \leq 8$, $-11 \leq k \leq 11$, $-15 \leq l \leq 16$		
Reflections collected: 3296		
Independent reflections: 3016 (R_{int}=0.0133)		
Absorption correction: semi-empirical		
Max. and Min. transmission: 0.9991 and 0.8952		
Refinement method: Full-matrix least-squares on F^2		
Data/restraints/parameters: 3016/86/292		
Goodness-of-fit on F^2: 1.124		
Final *R* indices [$I > 2\sigma(I)$]: R_1=0.0330, wR_2=0.0835		
R indices (all data): R_1=0.0397, wR_2=0.0884		
Largest diff. peak and hole: 0.710 and -0.539 $eÅ^{-3}$		

Table 3: Atomic coordinates (x 10^{4}) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for compound **160**. U_{eq} is defined as one third of the trace of orthogonalised U_{ij} tensor.

	X	Y	Z	U_{eq}
Ru1	10240(1)	6121(1)	6955 (1)	42(1)
P1	6567(3)	11142(1)	7198(1)	76(1)
F1	6294(11)	12506(4)	6441(3)	188(3)
F2	6884(9)	9789(4)	7956(4)	163(2)
F3	8165(27)	11620(11)	7510(14)	172(10)
F4	8235(24)	10503(11)	6440(10)	183(10)
F5	5266(28)	10532(11)	6787(14)	154(8)
F6	4824(34)	11721(14)	7936(12)	187(11)
F3A	5908(21)	11910(8)	8046(5)	131(4)
F4A	8691(15)	11314(14)	7155(12)	206(8)
F5A	7270(27)	10452(7)	6304(5)	156(6)
F6A	4435(14)	10991(16)	7277(10)	210(8)
O1	7554(5)	5058(3)	9150(2)	63(1)
O2	7914(6)	6702 (4)	5135(2)	70(1)
C1	7730(6)	5414(4)	8152(3)	48(1)
C2	7239(6)	6806(4)	7746(3)	50(1)
C3	7283(6)	7288(5)	6727(3)	53(1)
C4	7851(6)	6360(5)	6110(3)	53(1)
C5	8496(7)	4983(5)	6507(3)	54(1)
C6	8437(7)	4498(4)	7531(3)	49(1)
C7	7646(10)	8127(7)	4661(5)	90(2)
C8	8189(8)	3703(5)	9606(3)	56(1)
C9	6818(10)	2869(6)	9987(4)	76(2)
C10	7439(14)	1566(7)	10526(5)	100(2)
C11	9360(16)	1174(7)	10663(5)	104(3)
C12	10692(13)	2024(8)	10264(6)	101(2)
C13	10100(10)	3304(6)	9734(5)	81(2)
C14	13254(7)	5247(7)	7170(6)	84(2)
C15	12582(8)	6344(7)	7590(4)	70(2)
C16	12160(9)	7490(6)	6883(6)	83(2)
C17	12599(10)	7125(12)	5992(5)	112(3)
C18	13256(9)	5700(12)	6170(7)	110(3)

Table 4: Interatomic distances for compound **160**.

Atom-atom	Distance (Å)	Atom-atom	Distance (Å)
Ru1-C18	2.147(6)	O1-C1	1.360(5)
Ru1-C16	2.154(5)	O1-C8	1.398(6)
Ru1-C17	2.158(5)	O2-C4	1.341(6)
Ru1-C15	2.164(5)	O2-C7	1.438(7)
Ru1-C14	2.168(5)	C1-C2	1.396(6)
Ru1-C2	2.190(4)	C1-C6	1.400(6)
Ru1-C5	2.200(4)	C2-C3	1.407(7)
Ru1-C3	2.202(4)	C3-C4	1.406(7)
Ru1-C6	2.209(4)	C4-C5	1.396(7)
Ru1-C1	2.245(4)	C5-C6	1.413(6)
Ru1-C4	2.247(4)	C8-C13	1.356(8)
P1-F6A	1.524(7)	C8-C9	1.365(7)
P1-F6	1.528(8)	C9-C10	1.392(9)
P1-F2	1.531(4)	C10-C11	1.367(11)
P1-F5	1.533(8)	C11-C12	1.357(11)
P1-F1	1.537(4)	C12-C13	1.366(9)
P1-F4A	1.537(7)	C14-C15	1.363(8)
P1-F3	1.539(8)	C14-C18	1.385(1)
P1-F4	1.545(8)	C15-C16	1.364(9)
P1-F3A	1.550(6)	C16-C17	1.373(11)
P1-F5A	1.556(6)	C17-C18	1.412(12)

Table 5: Angles (°) of compound **160**.

Atom-atom-atom	Angle (°)	Atom-atom-atom	Angle (°)
C18-Ru1-C16	63.0(3)	C3-Ru1-C6	79.2(2)
C18-Ru1-C17	38.3(3)	C18-Ru1-C1	149.1(4)
C16-Ru1-C17	37.1(3)	C16-Ru1-C1	130.6(2)
C18-Ru1-C15	62.1(2)	C17-Ru1-C1	167.3(3)
C16-Ru1-C15	36.8(2)	C15-Ru1-C1	110.3(2)
C17-Ru1-C15	61.7(2)	C14-Ru1-C1	117.8(2)
C18-Ru1-C14	37.4(3)	C2-Ru1-C1	36.7(2)
C16-Ru1-C14	62.0(3)	C5-Ru1-C1	66.2(2)
C17-Ru1-C14	62.5(3)	C3-Ru1-C1	66.4(2)
C15-Ru1-C14	36.7(2)	C6-Ru1-C1	36.6(2)
C18-Ru1-C2	172.7(3)	C18-Ru1-C4	116.2(2)
C16-Ru1-C2	109.9(2)	C16-Ru1-C4	130.6(2)
C17-Ru1-C2	134.9(3)	C17-Ru1-C4	108.7(2)1
C15-Ru1-C2	113.7(2)	C15-Ru1-C4	167.4(2)
C14-Ru1-C2	142.3(2)	C14-Ru1-C4	148.6(2)
C18-Ru1-C5	107.4(2)	C2-Ru1-C4	66.5(2)
C16-Ru1-C5	161.3(2)	C5-Ru1-C4	36.6(2)
C17-Ru1-C5	125.4(3)	C3-Ru1-C4	36.8(2)
C15-Ru1-C5	155.2(2)	C6-Ru1-C4	66.5(2)
C14-Ru1-C5	121.1(2)	C1-Ru1-C4	77.6(2)
C2-Ru1-C5	78.9(2)	F6A-P1-F2	89.8(4)
C18-Ru1-C3	141.2(3)	F6-P1-F2	90.6(4)
C16-Ru1-C3	109.9(2)	F6-P1-F5	94.0(13)
C17-Ru1-C3	111.7(3)	F2-P1-F5	88.3(4)
C15-Ru1-C3	136.3(2)	F6A-P1-F1	91.5(4)
C14-Ru1-C3	171,9(2)	F6-P1-F1	89.8(4)
C2-Ru1-C3	37.4(2)	F2-P1-F1	178.6(4)
C5-Ru1-C3	66.7(2)	F5-P1-F1	92.9(4)
C18-Ru1-C6	120.6(3)	F6A-P1-F4A	177.8(9)
C16-Ru1-C6	161.1(2)	F2-P1-F4A	89.8(4)
C17-Ru1-C6	155.9(3)	F1-P1-F4A	88.8(4)
C15-Ru1-C6	125.7(2)	F6-P1-F3	95.3(14)
C14-Ru1-C6	108.4(2)	F2-P1-F3	90.0(4)
C2-Ru1-C6	66.7(2)	F5-P1-F3	170.5(11)
C5-Ru1-C6	37.4(2)	F1-P1-F3	88.7(4)

Continuation of table 5:

Atom-atom-atom	Angle (°)	Atom-atom-atom	Angle (°)
F6-P1-F4	176.2(13)	C5-C4-Ru1	69.9(2)
F2-P1-F4	88.6(4)	C3-C4-Ru1	69.9(2)
F5-P1-F4	82.2(10)	C4-C5-C6	120.8(4)
F1-P1-F4	91.1(4)	C6-C5-Ru1	71.7(2)
F6A-P1-F3A	91.5(7)	C1-C6-C5	119.4(4)
F2-P1-F3A	89.7(3)	C1-C6-Ru1	73.1(2)
F1-P1-F3A	89.9(3)	C5-C6-Ru1	70.9(2)
F4A-P1-F3A	86.4(8)	C13-C8-C9	122.6(5)
F6A-P1-F5A	90.2(8)	C13-C8-O1	118.6(5)
F2-P1-F5A	93.5(3)	C9-C8-O1	118.6(5)
F1-P1-F5A	86.8(3)	C8-C9-C10	117.6(7)
F4A-P1-F5A	92.0(9)	C11-C10-C9	119.7(7)
F3A-P1-F5A	176.4(5)	C12-C11-C10	121.2(6)
C1-O1-C8	119.3(3)	C11-C12-C13	119.6(8)
C4-O2-C7	117.8(4)	C8-C13-C12	119.4(7)
O1-C1-C2	115.6(4)	C15-C14-C18	108.0(7)
O1-C1-C6	124.6(4)	C15-C14-Ru1	71.5(3)
C2-C1-C6	119.7(4)	C18-C14-Ru1	70.4(3)
O1-C1-Ru1	130.5(3)	C14-C15-C16	109.5(6)
C2-C1-Ru1	69.5(2)	C14-C15-Ru1	71.8(3)
C6-C1-Ru1	70.3(2)	C16-C15-Ru1	71.2(3)
C1-C2-C3	120.7(4)	C15-C16-C17	108.1(7)
C1-C2-Ru1	73.8(2)	C15-C16-Ru1	72.0(3)
C3-C2-Ru1	71.8(2)	C17-C16-Ru1	71.6(3)
C4-C3-C2	119.6(4)	C16-C17-C18	107.6(6)
C4-C3-Ru1	73.3(3)	C16-C17-Ru1	71.3(3)
C2-C3-Ru1	70.8(2)	C18-C17-Ru1	70.4(4)
O2-C4-C5	115.8(4)	C14-C18-C17	106.8(6)
O2-C4-C3	124.7(4)	C14-C18-Ru1	72.1(3)
C5-C4-C3	119.4(4)	C17-C18-Ru1	71.3(4)
O2-C4-Ru1	130.2(3)		

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