# Preparation of Tripeptide-Bridged Dicatechol Ligands and Their Macrocyclic Molybdenum(VI) Complexes: Fixation of the RGD Sequence and the WKY Sequence of Urotensin II in a Cyclic Conformation

**Markus Albrecht,*[a] Patrick Stortz,[a] Jan Runsink,[a] and Patrick Weis[b]**

**Abstract:** Dicatechol ligands were prepared with caprylic acid (**6**-$H_4$) or the naturally occurring RGD (**23**-$H_4$) or WKY sequences (**32**-$H_4$) as spacers. **6**-$H_4$ was prepared by solution-phase amide coupling chemistry, while **16**, the precursor of **23**-$H_4$, was obtained by solution-phase and solid-phase preparation. In the latter case, a polystyrene resin with a hydrazine benzoate linker was used as the solid support. The last coupling step was performed simultaneously with cleavage of the peptide from the resin. The protecting groups of **16** were all removed in one step to yield the free ligand **23**-$H_4$. The WKY-bridged derivative **32**-$H_4$ was obtained by a similar solid-phase synthesis followed by deprotection. The reaction of all three ligands with dioxomolybdenum(VI) bis(acetylacetonate) afforded 19-membered metallamacrocycles in which the short peptides are conformationally fixed in a turn-type structure. Hereby, the side-chain functionalities of the peptides do not interfere in the metal complexation.

**Keywords:** macrocycles · molybdenum · peptides · solid-phase synthesis

## Introduction

The α helix, β sheet, and various turns are common structural motifs that are found in proteins. Hereby, the secondary structures of different protein domains are enforced, either by intra- or interstrand noncovalent interactions, like hydrogen bonding, electrostatic attraction or repulsion, and hydrophobic/hydrophilic interactions, or by the formation of covalent disulfide bridges. The spatial arrangement of the side-chain functionalities of the amino acids is crucial for biological activity. Very often this activity depends on the action of only a short peptide sequence, which is conformationally fixed by attachment to the protein. Short linear peptides (up to 15 residues) do not usually adopt a well-defined structure.[1] However, in small cyclopeptides a turn structure is fixed, which often is responsible for the observed activity.[2]

Metal coordination is a strong noncovalent interaction that can also induce a secondary peptide structure. This is found in nature[3] as well as in artificial systems.[4] For example, the zinc finger protein adopts a random-coil structure when no metal is present.[5] However, in the presence of zinc(II), the metal coordinates to two cysteine and two histidine residues and induces a β-sheet domain as well as an α-helix domain. The latter is able to bind to DNA and, for example, plays a crucial role in transcription factors.[6]

Following nature's example, we had the idea to attach metal-binding sites to both termini of short linear tri- or tetrapeptides.[7] Upon coordination of the ligand units to appropriate metals a metallamacrocycle should be formed in which the peptide conformation is fixed in a turn- or loop-type structure (Scheme 1).[8] For the metal-binding site we chose catechol units, which are known to show extraordinarily strong binding to metal ions,[9] and for the metal-complex

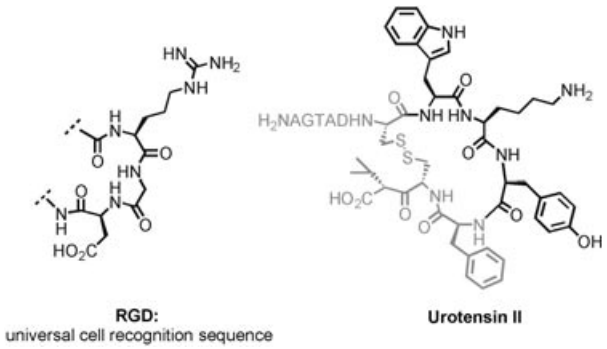


Figure 1. The arginine–glycine–aspartic acid (RGD) sequence and the structure of urotensin II containing the tryptophan–lysine–tyrosine (WKY) sequence.

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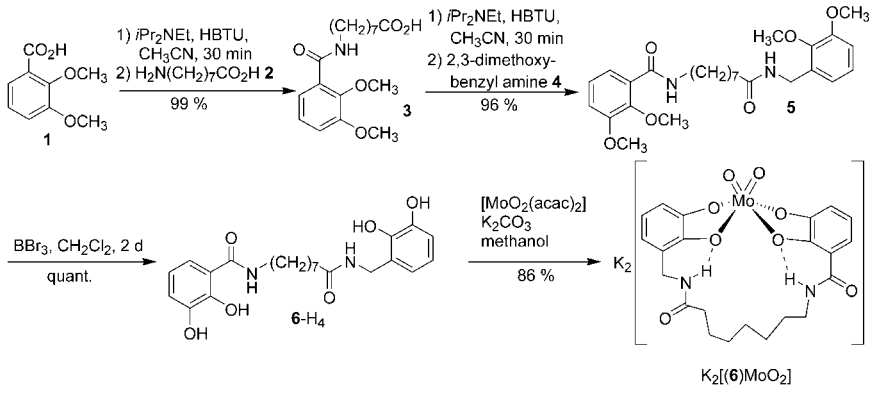
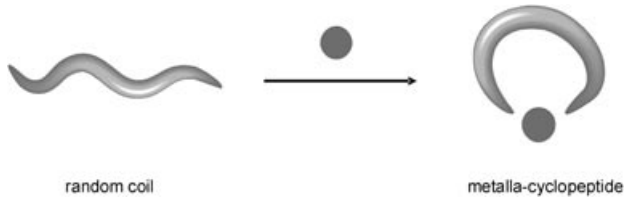
fragment the *cis*-$Mo^{VI}O_2$ moiety, which is able to bind two catechols, was chosen.[10] Following this concept, we have already described metallacyclopeptides[11] that possess the WAGV or WAG sequence of the naturally occurring segetalins A and B.[12] Other metallacyclopeptides were presented by Imperiali,[13] Fairlie and Kelso,[14] and Constable,[15] with their respective co-workers.




Scheme 2. Solution-phase synthesis of **6**-$H_4$ and $K_2$[(**6**)$MoO_2$]. HBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, acac = acetylacetone.

The segetalins do not possess high functionalization in their amino acid side chains. For this reason, they were our first targets. In the present study we have investigated whether it is possible to obtain metallacyclopeptides with a high degree of functionality without the functional groups interfering in the metal coordination.

As nature's model for our studies we chose the universal cell recognition sequence arginine–glycine–aspartic acid (RGD), which was shown to possess a high affinity for cell surfaces by binding to the integrins (Figure 1). A cyclic conformation even favors a strong interaction.[16]




Scheme 1. Schematic representation of the formation of conformationally fixed metallacyclopeptides from random-coil peptides.

Just recently urotensin II was thoroughly studied due to its vasoconstrictor activity.[17] The tryptophan–lysine–tyrosine (WKY) sequence of the cyclopeptide part was shown to be the active part of this molecule (Figure 1).[18]

The high degree of functionality of the arginine and aspartic acid residues made the RGD sequence an appropriate target for our studies, while basic lysine and phenolic tyrosine are present in the WKY sequence. However, prior to coordination studies, appropriate RGD- or WKY-bridged dicatechols had to be prepared.

## Results and Discussion

**Investigation of the simple model system 6-$H_4$ and [(6)$MoO_2$]$^{2-}$**: Initially we synthesized the simple ligand **6**-$H_4$ (Scheme 2). The spacer, 8-aminocaprylic acid (**2**), possesses the same number of backbone atoms as is found in a tripeptide. However, **2** shows a higher degree of flexibility. For the preparation of **6**-$H_4$, we started with 2,3-dimethoxybenzoic acid (**1**), which was activated by reaction with HBTU in the presence of ethyldiisopropylamine (Hünig's base). Addition of 8-aminocaprylic acid (**2**) resulted in the formation of compound **3**. Again the carboxylic acid had to be activated before 2,3-dimethoxybenzylamine (**4**) was attached to the C-terminus and derivative **5** was obtained.[19,20] The methyl ethers were cleaved by addition of $BBr_3$, to yield the unprotected ligand **6**-$H_4$.[21]

Reaction of ligand **6**-$H_4$ with [$MoO_2$(acac)$_2$] and potassium carbonate in methanol resulted in the formation of the macrocyclic molybdenum(VI)dioxo complex $K_2$[(**6**)$MoO_2$].[22] IR spectroscopy of the complex showed the typical frequencies of a *cis*-dioxomolybdenum unit at $\tilde{\nu}$ = 896 and 863 $cm^{-1}$.[23] For the free ligand **6**-$H_4$, separated signals were observed by $^1$H NMR spectroscopy in [$D_4$]-methanol for the aromatic protons at $\delta$ = 7.24, 7.00, 6.81, 6.75, 6.72, and 6.65 ppm. Upon complex formation the signals converged and appeared at $\delta$ = 7.20, 6.70, and 6.46 ppm (4H). The resonance of the benzylic methylene group acted as an NMR spectroscopy probe. In the free ligand **6**-$H_4$ it appeared as a singlet at $\delta$ = 4.52 ppm and upon complex formation it split into two signals at $\delta$ = 4.44 and 4.31 ppm, due to the presence of the chiral biscatecholate molybdenum(VI)dioxo moiety.

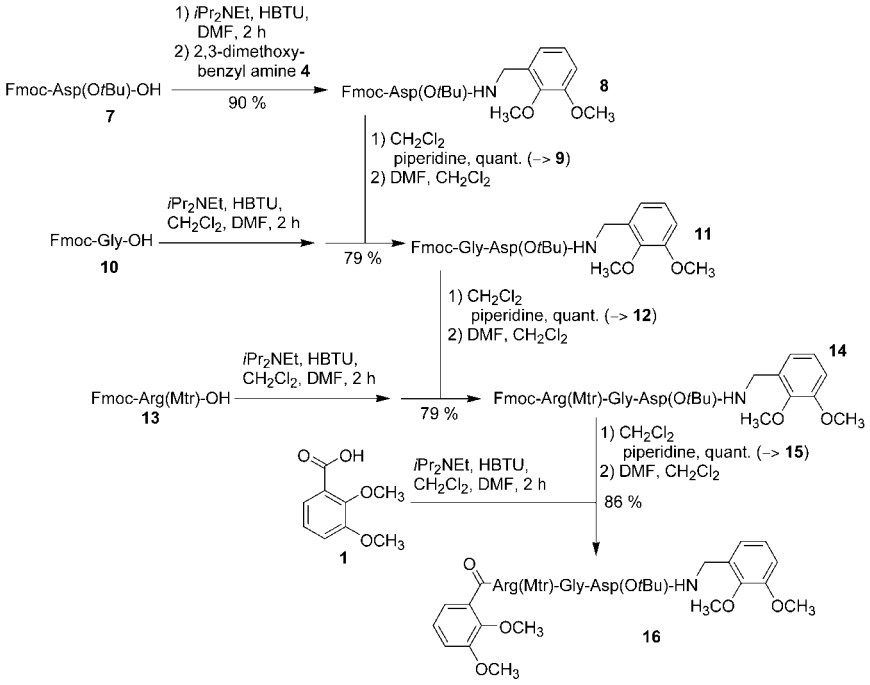
Negative ESI-MS showed that the mononuclear 19-membered metallamacrocycle $K_2$[(**6**)$MoO_2$] was formed. Corresponding peaks were observed at *m*/*z* 543 {H[(**6**)$MoO_2$]}$^-$ and 581 {K[(**6**)$MoO_2$]}$^-$.

Our investigations with the simple ligand **6** showed that the chain length of 8-aminocaprylic acid, which corresponds to that of a tripeptide, is appropriate to form a macrocycle by coordination of the two terminal catechol units to a molybdenum(VI)dioxo moiety.[8]

**The RGD-bridged dicatechol ligand 23-$H_4$ and its molybdenum(VI)dioxo complex $K_2$[(23)$MoO_2$]**: The precursor for the RGD-bridged dicatechol ligand, **16**, was prepared by two different approaches. The possibilities were to follow a 9-fluorenylmethoxycarbonyl (Fmoc) protection/deprotection strategy in solution or to prepare the compound by solid-phase synthesis.[20]

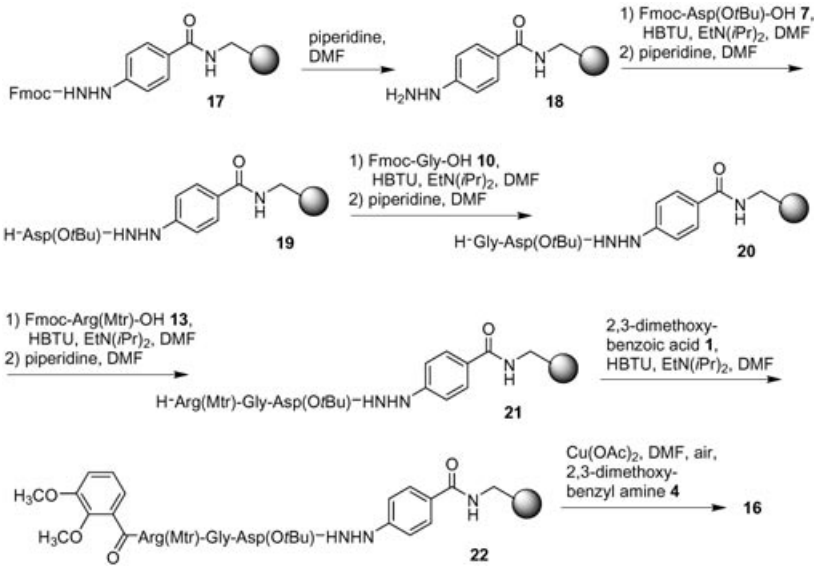
***Solution-phase synthesis of 16*:** In the solution-phase synthesis of **16** we started with the N-terminus- and side-chain-protected aspartic acid derivative **7** and applied a repeating sequence of amide coupling and Fmoc cleavage (Scheme 3).[20]

Fmoc-Asp(O*t*Bu)-OH (**7**) was activated with HBTU and Hünig's base in DMF and the benzyl amine **4** was added to obtain amide **8** in 90% yield after work up. The Fmoc group of **8** was quantitatively removed by treatment with piperidine to yield the corresponding amine **9**. Fmoc-Gly-OH (**10**) was first activated (Hünig's base, HBTU) and then amine **9** was added to produce **11** in 79%. This was also deprotected with piperidine to yield the free amine **12** (quantitative yield). The same sequence was used to prepare amide **14** (79%) from amine **12** and activated Fmoc-Arg(Mtr)-OH (**13**). Fmoc removal with piperidine afforded amine **15** (quantitative yield). Finally, 2,3-dimethoxybenzoic acid (**1**) was activated with HBTU and Hünig's base and amine **15** was added. The protected RGD-bridged ligand precursor **16** was obtained in 86% yield. Thus, by starting from **7**, the ligand precursor **16** was prepared in seven steps in 48% overall yield.




Scheme 3. Solution-phase synthesis of precursor **16**. Mtr = 4-methoxy-2,3,6-trimethylbenzoylsulfonyl.

***Synthesis of 16 on solid support*:** In a second approach, **16** was prepared by solid-phase synthesis on a polystyrene resin bearing the 4-Fmoc-hydrazinobenzoyl linker, **17** (Scheme 4).[24,25]




Scheme 4. Solid-phase synthesis of precursor **16**.

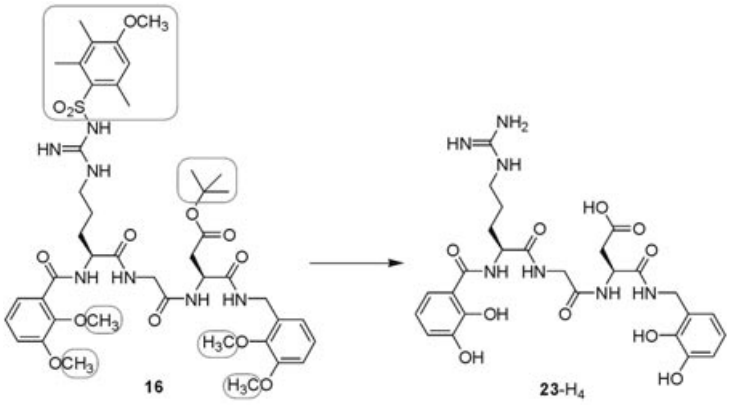
First, the Fmoc protecting group of **17** was removed by treatment with piperidine to yield the free hydrazine **18**. Next, the amino acids were successively attached by treatment with Fmoc-protected acids **7**, **10**, and **13** that had been activated with HBTU and Hünig's base. Prior to amide coupling the Fmoc groups were cleaved. Thus, successively, the derivatives **19**, **20**, and **21** were obtained. The N-terminal ligand unit was introduced by addition of activated 2,3-dimethoxybenzoic acid (**1**). Attachment of the C-terminal ligand moiety was performed with concomitant cleavage of the peptide from the solid support. Thus, the hydrazyl amide of **22** was oxidized by copper(II) acetate and air and the labilized C terminus was attacked by 2,3-dimethoxybenzylamine (**4**) as a nucleophile. The protected ligand **16** was purified by column chromatography and was finally obtained in 64% overall yield.

With the higher overall yield and the more simple reaction procedures, the solid-phase synthesis of **16** was clearly superior to the synthesis in solution.

***Deprotection of 16 to obtain the RGD-bridged ligand 23-$H_4$*:** The ligand precursor **16** possessed an Mtr group at the arginine residue, a *tert*-butyl group at the aspartic acid resi-

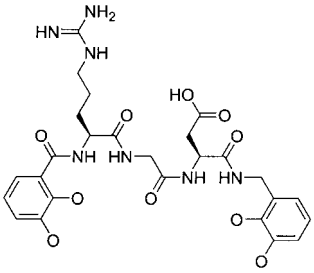
due, and four methyl groups protecting the catechol moieties. Our intention was to remove all of those groups in only one step (Scheme 5). Usually, the Mtr group is removed by treatment with protic acid, which attacks at the sulfonate unit.[26] The methyl ethers on the catechol groups, on the other hand, are removed by cleavage with Lewis acids.[21] Our idea was to perform the deprotection with only Lewis acids. Hereby, the catechol methyl ethers as well as the *tert*-butyl group should be removed. The Mtr group would not be attacked at the sulfonate unit but the Lewis acid would cleave the methyl ether and, thus, should labilize and remove the protecting group.



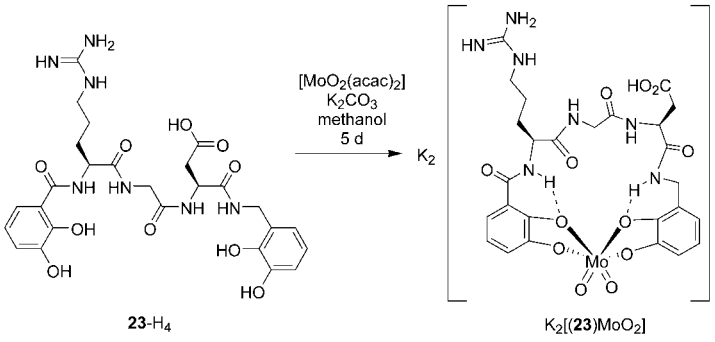

Scheme 5. One-step deprotection of precursor **16** to form ligand **23**-$H_4$.

The protected compound **16** was treated with $BBr_3$ in dichloromethane and the Mtr moiety, as well as the *tert*-butyl group, was removed smoothly. However, the methyl ethers were not completely cleaved under the mild conditions. Reaction with 1 M $BBr_3$ led to the isolation of a compound in which the Mtr unit, *tert*-butyl group, and only three of the methyl ethers were cleaved. The last methyl group remained on the molecule. Upon applying harsher conditions, **16** was cleaved at the peptide chain. Therefore, other cleavage conditions were tested. Reaction of **16** with $AlBr_3$ or $AlCl_3$ also did not lead to the desired ligand **23**-$H_4$. The deprotected RGD-bridged dicatechol **23**-$H_4$ was finally obtained in a yield of 45% by removal of all protecting groups by treatment with $AlCl_3$ and ethanethiol[27] in dichloromethane, followed by purification by HPLC.

Table 1. $^1$H NMR spectroscopy data in [$D_4$]-methanol for the ligand **23**-$H_4$ and the complex $K_2$[(**23**)$MoO_2$].



| | H-aryl | H-benzyl | Arg | | Gly | Asp | |
|---|---|---|---|---|---|---|---|
| | | | $\alpha$-H | $CH_2$ | | $\alpha$-H | $CH_2$ |
| **23**-$H_4$ | 7.35, 6.95, 6.75, 6.69, 6.66, 6.61 | 4.35 | 4.80 | 2.01, 1.84, 1.70 | 3.90 | 4.60 | 2.88, 2.77 |
| $K_2$[(**23**)$MoO_2$] | 7.21, 6.72, 6.46, 6.39 (2H), 6.30 | 4.79, 4.34 | 4.90 | 2.96, 2.88, 1.87, 1.24, 1.15, 0.92 | 3.90, 3.78 | 4.61 | 3.18, 2.48 |




Scheme 6. Complexation of ligand **23**-$H_4$ to form $K_2$[(**23**)$MoO_2$].

Compound **23**-$H_4$ was characterized by $^1$H NMR spectroscopy (see Table 1) and by high-resolution FAB-MS, which shows the peak for [**23**-$H_5$]$^+$ at *m*/*z* 604.2367 (calcd: *m*/*z* 604.2392).

***Formation and characterization of $K_2$[(23)$MoO_2$]*:** The metallacyclopeptide $K_2$[(**23**)$MoO_2$] was prepared by treatment of ligand **23**-$H_4$ with $MoO_2$(acac)$_2$ and potassium carbonate in a ratio of 1:1.1:4 (Scheme 6). The reaction was performed in methanol at room temperature and needed about five days to obtain the thermodynamically favored product. Shorter reaction times led to mixtures of oligomeric metal complexes. The final product was purified by filtration over Sephadex LH20.

Negative ESI-MS peaks of the mononuclear metallacyclopeptide were observed at *m*/*z* 807 [{$K_2$[(**23**)$MoO_2$]}−H]$^-$, 769 {K[(**23**)$MoO_2$]}$^-$, 730 {H[(**23**)$MoO_2$]}$^-$, and 383.5 [(**23**)$MoO_2$]$^{2-}$. All peaks showed the expected isotopic pattern.

The $^1$H NMR spectroscopic data for $K_2$[(**23**)$MoO_2$] in [$D_4$]-methanol are shown in Table 1 and the spectrum (including assignment of the signals) is presented in Figure 2. Assignments were done by COSY, TOCSY, and NOE spec-

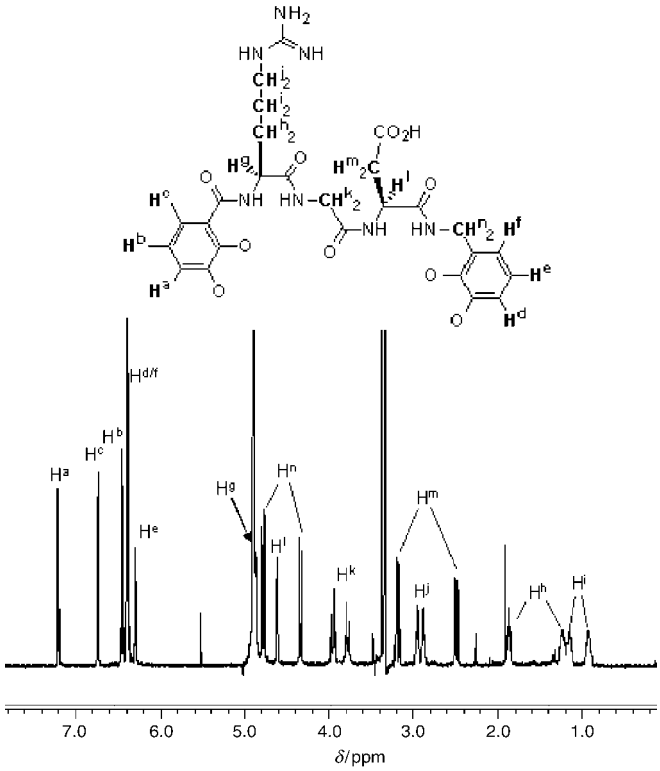
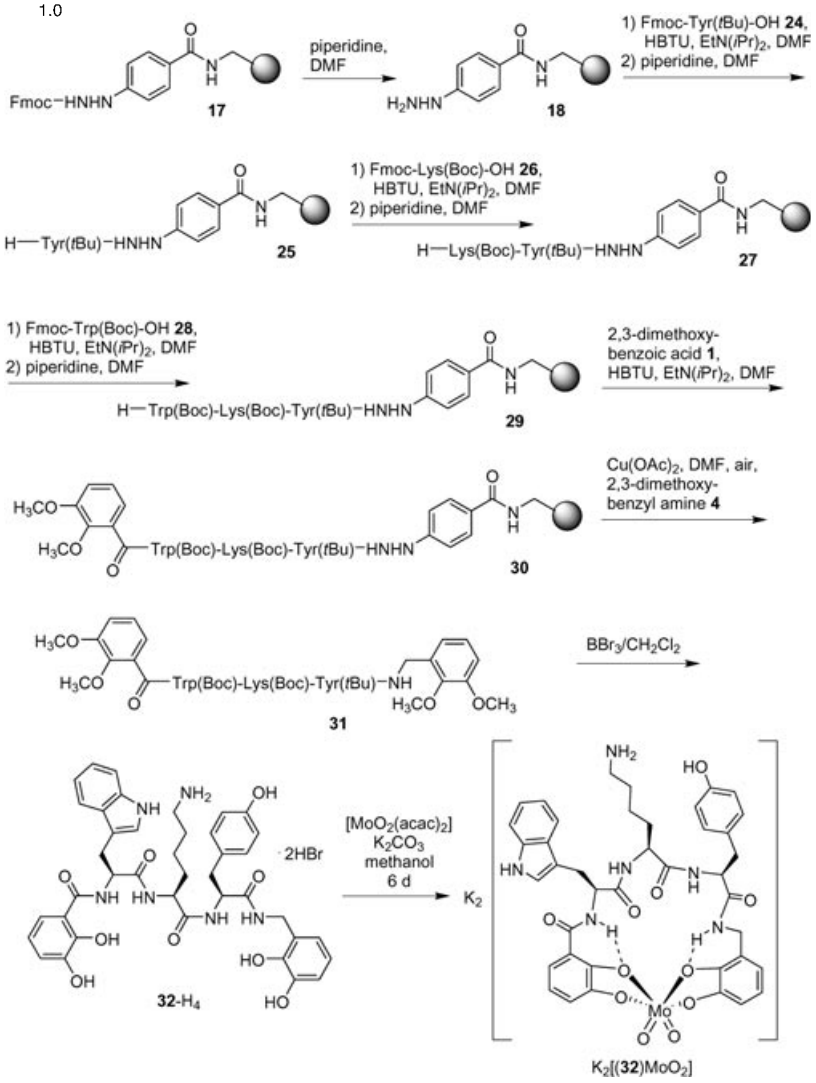



Figure 2. $^1$H NMR spectrum for $K_2$[(**23**)$MoO_2$] in [$D_4$]-methanol including assignment of the signals.

troscopy. $K_2$[(**23**)$MoO_2$] led to a nicely resolved $^1$H NMR spectrum, which showed some significant differences compared to the spectrum of the free ligand **23**-$H_4$. In the free ligand **23**-$H_4$, the resonances of the benzylic and the glycine methylene units appeared as singlets at $\delta = 4.35$ and 3.90 ppm (2H each). It had been expected that the protons of each of the methylene units would result in a separated signal because of diastereotopic behavior. However, due to the high conformational flexibility, the two proton resonances of each of the methylene units appeared at the same ("isochronic") shift. Upon formation of the coordination compound $K_2$[(**23**)$MoO_2$], the conformational flexibility was restricted and each proton resulted in a separate signal, at $\delta = 4.79$ and 4.34 ppm for the benzyl group and at $\delta = 3.90$ and 3.78 ppm for the glycine hydrogen atoms. Furthermore, the methylene units of the arginine residue appeared as three multiplets in the free ligand ($\delta = 2.01$, 1.84, 1.70 ppm; 2H each), whereas six separated resonances were observed at $\delta = 2.96$, 2.88, 1.87, 1.24, 1.15, and 0.92 ppm in $K_2$[(**23**)$MoO_2$].

**WKY-bridged dicatechol ligand 32-$H_4$ and its molybdenum(VI)dioxo complex $K_2$[(32)MoO(acac)]**: The synthesis of the RGD-bridged ligand **23**-$H_4$ in the solution phase or on solid support showed us that the latter is more effective. Therefore, we introduced the WKY sequence, which is a part of the natural product urotensin II, by solid-phase synthesis (Scheme 7).

Again the polystyrene resin with an 4-Fmoc-hydrazinobenzoyl linker, **17**, was used in the synthesis of the protected WKY-bridged ligand precursor **31**.[24,25] Derivative **31** was prepared as described for the solid-phase synthesis of the protected RGD-bridged ligand precursor **16**. First, the Fmoc group of **17** was removed and then the protected Tyr(*t*Bu), Lys(Boc), and Trp(Boc) amino acids were introduced successively in a repetitive activation–coupling–deprotection cycle.[20] Finally 2,3-dimethoxybenzoic acid (**1**) was attached to the N terminus and the peptide was cleaved from the solid support by oxidation (copper(II) acetate, air) and trapping with 2,3-dimethoxybenzylamine (**4**). The ligand precursor **31** was obtained in an overall yield of 67%. The deprotection of **31** by treament with $BBr_3$ smoothly removed the protecting groups and led to ligand **32**-$H_4$ with a WKY tripeptide moiety bridging the two catechol units.[21] The $^1$H NMR spectrum of **32**-$H_4$ in [$D_4$]-methanol is depicted in Figure 3.




Scheme 7. Solid-phase synthesis and complexation of **32**-$H_4$ to form $K_2$[(**32**)$MoO_2$].

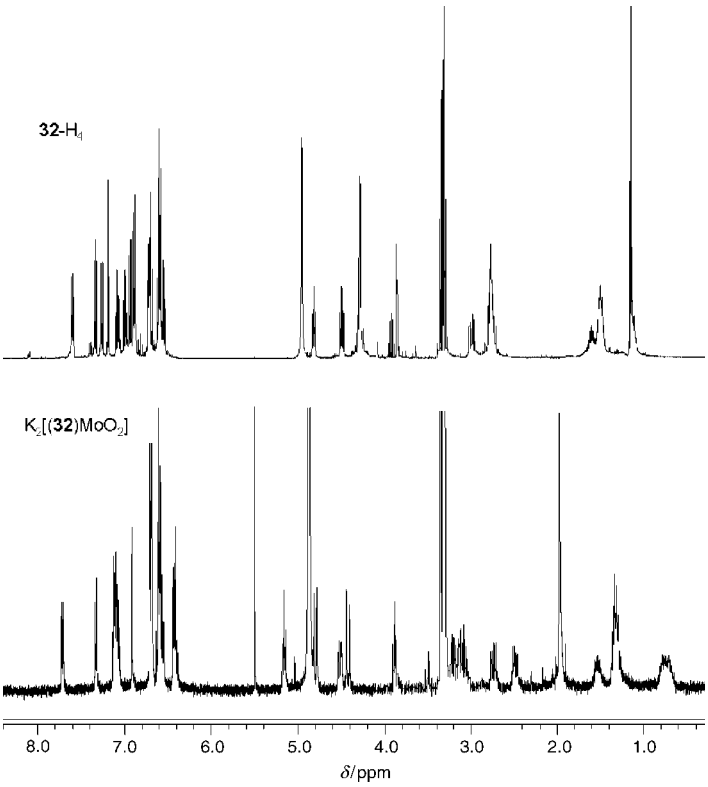



Figure 3. $^1$H NMR spectra for **32**-$H_4$ and $K_2[(\mathbf{32})MoO_2]$ in [$D_4$]-methanol. The spectrum for the conformationally constrained metallamacrocycle $K_2[(\mathbf{32})MoO_2]$ is more resolved than that for the free ligand **32**-$H_4$.

Reaction of ligand **32**-$H_4$ with $[MoO_2(acac)_2]$ and potassium carbonate in methanol for six days led to the macrocyclic complex $K_2[(\mathbf{32})MoO_2]$. Negative ESI-MS showed characteristic signals of the coordination compound at $m/z$ 916 $\{K[(\mathbf{32})MoO_2]\}^-$ and 879 $\{H[(\mathbf{32})MoO_2]\}^-$. In addition, a dominating peak is observed at $m/z$ 1000, which was tentatively assigned as $\{K(HBr)[(\mathbf{32})MoO_2]\}^-$. The characteristic bands of the $MoO_2$ unit were observed by IR spectroscopy at $\tilde{\nu}=896$ and 865 $cm^{-1}$.[23]

$^1$H NMR spectroscopy in [$D_4$]-methanol (Figure 3) again led to more resolved spectra in case of the conformationally constrained metallamacrocycle $K_2[(\mathbf{32})MoO_2]$ than for the free ligand **32**-$H_4$. For example, the benzylic protons of the 2,3-dihydroxybenzylamide appeared for **32**-$H_4$ as one signal at $\delta=4.27$ ppm. For the complex $K_2[(\mathbf{32})MoO_2]$ the two diastereotopic protons of this unit were observed as nicely separated doublets at $\delta=4.81$ and 4.42 ppm with a coupling constant of $J=13.8$ Hz. Signals at $\delta=5.50$ and 1.97 ppm corresponded to acetylacetone, which was observed by elemental analysis as well and may be bound by hydrogen-bonding interactions. The nicely resolved $^1$H NMR spectra of $K_2[(\mathbf{32})MoO_2]$ indicated that the conformation of the peptide was constrained in the macrocycle and that only a low degree of flexibility was left.

Attempts to crystallize the metallocyclopeptides to obtain X-ray crystal structure analyses were unfortunately not successful.

CD spectra of **23**-$H_4$, $K_2[(\mathbf{23})MoO_2]$, **32**-$H_4$, and $K_2[(\mathbf{32})MoO_2]$ were taken in methanol. For the free ligands **23**-$H_4$ and **32**-$H_4$ no significant CD signals can be observed, a result indicating a nonspecific "random-coil" structure. The metal complexes $K_2[(\mathbf{23})MoO_2]$ and $K_2[(\mathbf{32})MoO_2]$ show very similar CD spectra with a very strong negative band at about 230 nm and a strong negative band at 350 nm; these bands are both due to transitions at the metal complex moieties. This indicates that both complexes possess dicatechol molybdenumdioxo units with the same configuration.

## Conclusion

In this paper we have presented the synthesis of three dicatechol ligands which form metallamacrocycles with molybdenum(VI)dioxo moieties. One of the ligands is a simple model system without any side chains or functionalities, while the other two contain tripeptide sequences which were adopted from natural products (RGD sequence of, for example, echistatin or WKY sequence of urotensin II) with an interesting biological activity. Our preferred synthetic entry to prepare such tripeptide-bridged ligands is to use a polystyrene resin with an Fmoc-hydrazidobenzoate linker, because the cleavage of the residue from the solid support proceeds simultaneously with the last coupling step.[24,25] Multiple deprotection of the ligand precursors can be performed in one step.

Coordination studies with the ligands and dioxomolybdenum(VI) bis(acetylacetonate) shows that, in all cases, the 19-membered macrocycle is formed. The functionalized side chains of the amino acid residues (Tyr, Asp, Arg, Lys, Trp) are tolerated and do not interfere with metal binding. The $^1$H NMR spectra of the obtained compounds show nicely resolved resonances, a result indicating a high conformational fixation of the peptide.

Herein, we have presented a method to use metal coordination as a tool for the conformational fixation of short cyclic peptide structures. However, before such derivatives can be applied to binding studies with biological systems, more knowledge of their properties and structures has to be gained and some adjustments of the ligands and/or the metal ions will surely have to be done.

## Experimental Section

NMR spectra were recorded on Bruker DRX 500 or WM 400, Varian Inova 400, or Unity 500 spectrometers. FT-IR spectra were recorded by diffuse reflection (KBr) on a Bruker IFS spectrometer. Mass spectra (EI, 70 eV; FAB with 3-nitrobenzoic acid (3-NBA) as the matrix) were taken on Finnigan MAT 90, 95, or 212 mass spectrometers. UV/Vis spectra were obtained with a Perkin–Elmer Lambda2 spectrometer. Elemental analyses were obtained with a Heraeus CHN-O-Rapid analyzer. Melting points were measured on Büchi B-540 apparatus and are uncorrected.

**Compound 3**: Hünig's base (118 μL, 0.69 mmol) and HBTU (286 mg, 0.75 mmol) were added to a solution of 2,3-dimethoxybenzoic acid (**1**; 114 mg, 0.63 mmol) in acetonitrile (10 mL). Before addition of 8-aminocaprylic acid (**2**; 100 mg, 0.628 mmol), the mixture was stirred for 30 minutes. After stirring overnight, the solvent was distilled off under vacuum and the crude product was dissolved in ethyl acetate and washed with

sat. aqueous $NH_4Cl$, water, and brine. Compound **3** was obtained as a yellow wax (200.5 mg, 0.62 mmol, 99%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 11.3 (brs, 1H, COOH), 8.04 (brs, 1H, NH), 7.54 (dd, $J$ = 7.9, 1.7 Hz, 1H), 7.02 (t, $J$ = 7.9 Hz, 1H), 6.94 (dd, $J$ = 7.9, 1.7 Hz, 1H), 3.79 (s, 6H, OMe), 3.35 (q, $J$ = 6.9 Hz, 2H), 2.25 (t, $J$ = 7.4 Hz, 2H), 1.52 (m, 4H), 1.26 (m, 6H) ppm; $^{13}$C NMR ($CDCl_3$, 75.4 MHz): $\delta$ = 178.5 (C), 165.7 (C), 152.6 (C), 147.4 (C), 140.0 (C), 124.5 (CH), 122.6 (CH), 115.5 (CH), 61.3 ($CH_3$), 56.1 ($CH_3$), 39.8 ($CH_2$), 34.1 ($CH_2$), 29.3 ($CH_2$), 29.0 ($CH_2$), 28.9 ($CH_2$), 26.8 ($CH_2$), 24.7 ($CH_2$) ppm; MS (DIP): $m/z$: 323.09 $[M]^+$, 324.12 $[M+H]^+$; IR (KBr): $\tilde{\nu}$ = 2935, 1721, 1626, 1577, 1542, 1477, 1386, 1311, 1266, 1234, 1086, 997, 845, 753 cm$^{-1}$.

**Protected ligand 5**: Derivative **3** (1.02 g, 3.14 mmol), Hünig's base (590 µL, 3.45 mmol) and HBTU (1.43 g, 3.77 mmol) were dissolved in acetonitrile (70 mL) and stirred for 30 min. Then, 2,3-dimethoxybenzyl amine (**4**; 465 µL, 3.14 mmol) was added to the activated acid and the reaction mixture was stirred overnight. The solvent was removed under vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with sat. aqueous $NH_4Cl$, sat. aqueous $NaHCO_3$, water, and brine. The by-products were removed by silica gel chromatography with $CH_2Cl_2$ as the eluent and the product was obtained by eluting with $CH_2Cl_2$/methanol 4:1. Compound **5** was obtained as a yellow wax (1.43 g, 3.01 mmol, 96%). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.91 (t, $J$ = 5.4 Hz, 1H, NH), 7.50 (dd, $J$ = 7.9, 1.7 Hz, 1H), 6.99 (t, $J$ = 8.2 Hz, 1H), 6.91 (dd, $J$ = 8.2, 1.6 Hz, 1H), 6.86 (t, $J$ = 7.9 Hz, 1H), 6.75 (m, 2H), 6.70 (dd, $J$ = 8.2, 1.6 Hz, 1H), 4.33 (d, $J$ = 5.8 Hz, 2H), 3.77 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.30 (m, 2H), 2.09 (t, $J$ = 7.56 Hz, 2H), 1.50 (m, 4H), 1.22 (m, 6H) ppm; $^{13}$C NMR ($CDCl_3$, 100.6 MHz): $\delta$ = 173.0 (C), 165.0 (C), 164.8 (C), 152.5 (C), 152.4 (C), 147.2 (C), 132.2 (C), 26.8 (C), 124.2 (CH), 124.0 (CH), 122.4 (CH), 121.0 (CH), 115.3 (CH), 11.9 (CH), 61.2 ($CH_3$), 60.6 ($CH_3$), 56.0 ($CH_3$), 55.8 ($CH_3$), 39.6 ($CH_2$), 39.1 ($CH_2$), 36.5 ($CH_2$), 29.5 ($CH_2$), 29.2 ($CH_2$), 29.0 ($CH_2$), 26.9 ($CH_2$), 25.7 ($CH_2$) ppm; LC-MS (ESI): $m/z$: 472.3 $[M]^+$, 495.5 $[M+Na]^+$; IR (KBr, drift): $\tilde{\nu}$ = 3000, 2934, 1647, 1578, 1537, 1477, 1431, 1308, 1269, 1223, 1083, 1002, 846, 754 cm$^{-1}$; elemental analysis calcd (%) for $C_{26}H_{36}N_2O_6 \cdot 1.5\,H_2O$: C 62.51, H 7.87, N 5.61; found: C 62.58, H 7.65, N 5.64.

**Ligand 6-H$_4$**: $BBr_3$ (0.65 mL, 6.81 mmol) was added to a solution of **5** (128.7 mg, 0.27 mmol) in dichloromethane (17 mL). The mixture was stirred for two days at room temperature and then was hydrolyzed with methanol (10 mL). If the ether cleavage reaction was not complete, the residue was once again suspended in $CH_2Cl_2$, mixed with $BBr_3$ (0.65 mL, 6.81 mmol), and stirred overnight. After quenching with methanol, the solvents were removed under vacuum. The residue was dissolved in methanol and then the solvent was distilled off to remove all $BBr_3$. Ligand **6**-$H_4$ was obtained as a yellow wax (113 mg, quantitative); $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ = 7.24 (dd, $J$ = 8.0, 1.4 Hz, 1H), 7.00 (dd, $J$ = 8.0, 1.4 Hz, 1H), 6.81 (dd, $J$ = 7.7, 1.7 Hz, 1H), 6.75 (t, $J$ = 8.0 Hz, 1H), 6.72 (dd, $J$ = 7.7, 1.7 Hz, 1H), 6.65 (t, $J$ = 7.8 Hz, 1H), 4.52 (s, 2H), 3.42 (t, $J$ = 7.1 Hz, 2H), 2.57 (m, 2H), 1.64 (m, 3H), 1.36 (m, 7H) ppm; MS (DIP): $m/z$: 416.4 $[M]^+$, 417.5 $[M+H]^+$; IR (KBr): $\tilde{\nu}$ = 3461, 2934, 2859, 1636, 1593, 1547, 1331, 1259, 742 cm$^{-1}$.

**Complex K$_2$[(6)MoO$_2$]**: Ligand **6**-$H_4$ (56.6 mg, 0.14 mmol) was dissolved in methanol (10 mL) and $K_2CO_3$ (75 mg, 0.54 mmol) and $[MoO_2(acac)_2]$ (53 mg, 0.163 mmol) were added. The reaction mixture was stirred overnight, then the solvent was distilled off and the residue was filtrated over Sephadex LH20 with methanol. The coordination compound $K_2[(\mathbf{6})MoO_2]$ was obtained as a yellow wax (63 mg, 0.12 mmol, 86%). $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ = 7.20 (brs, 1H), 6.70 (m, 1H), 6.46 (m, 4H), 4.44 (m, 1H), 4.31 (m, 1H), 3.15 (m, 2H), 2.20 (m, 1H), 1.95 (m, 1H), 1.63 (m, 1H), 1.50 (m, 1H), 1.20 (m, 8H) ppm; negative ESI-MS: $m/z$: 543 $\{H[(\mathbf{6})MoO_2]\}^-$, 581 $\{K[(\mathbf{6})MoO_2]\}^-$; IR (KBr): $\tilde{\nu}$ = 3461, 2934, 2859, 1636, 1593, 1547, 1331, 1259, 896, 863, 742 cm$^{-1}$; elemental analysis calcd (%) for $C_{22}H_{24}N_2O_8MoK \cdot 4\,H_2O$: C 38.26, H 4.67, N 4.06; found: C 38.50, H 4.44, N 3.60.

**Preparation of RGD-bridged compounds**

***Solution-phase synthesis***

**Compound 8**: Hünig's base (0.92 mL, 5.35 mmol) and a solution of HBTU (2.21 g, 5.83 mmol) in DMF (20 mL) was added to a solution of Fmoc-Asp(O*t*Bu)-OH (**7**; 2.00 g, 4.86 mmol) in dichloromethane (100 mL). After two hours 2,3-dimethoxybenzylamine (**4**; 0.72 mL, 4.86 mmol) was added and the mixture was stirred overnight. The mixture was diluted with dichloromethane and then washed with sat. aqueous $NH_4Cl$ solution, sat. aqueous $NaHCO_3$ solution, water, and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product was recrystallized from dichloromethane and hexane. Compound **8** was obtained as a white solid (2.46 g, 4.39 mmol, 90%). M.p. 125°C (decomp); $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 7.75 (m, 2H, Fmoc), 7.67–7.54 (m, 2H, Fmoc), 7.38 (m, 2H, Fmoc), 7.31–7.26 (m, 2H, Fmoc), 6.96 (t, $J$ = 7.9 Hz, 1H, aryl), 6.88 (brs, 1H, NH), 6.83 (m, 2H, aryl), 5.98 (d, $J$ = 8.1 Hz, 1H, NH), 4.53 (brs, 1H, $\alpha$-H), 4.46 (m, 2H, $CH_2$ Fmoc), 4.44–4.35 (m, 2H, $CH_2$ benzyl), 4.19 (t, $J$ = 7.0 Hz, 1H, CH Fmoc), 3.83 (s, 3H, OMe), 3.82 (s, 3H, OMe), 2.69 (dd, $J$ = 16.9, 6.4 Hz, 1H, $CH_2$ Asp), 2.91–2.81 (m, 1H, $CH_2$ Asp), 1.41 (s, 9H, *t*Bu) ppm; $^{13}$C NMR ($CDCl_3$, 125.7 MHz): $\delta$ = 171.1 (C), 170.1 (C), 152.6 (C), 147.1 (C), 143.8 (2 C), 143.7 (C), 141.3 (2 C), 131.4 (C), 127.7 (2 CH), 127.1 (2 CH), 125.0 (2 CH), 124.1 (CH), 121.0 (CH), 120.0 (2 CH), 111.9 (CH), 81.8 (C), 67.2 ($CH_2$), 60.7 ($CH_3$), 55.7 ($CH_3$), 51.2 (CH), 47.1 (CH), 38.9 ($CH_2$), 37.5 ($CH_2$), 28.0 (3$CH_3$) ppm; FAB-MS (3-NBA/DMSO): $m/z$: 561.3 $[M+H]^+$, 583.3 $[M+Na]^+$; elemental analysis calcd (%) for $C_{32}H_{36}N_2O_7 \cdot H_2O$: C 66.42, H 6.62, N 4.84; found: C 66.53, H 6.49, N 4.77; IR (KBr, drift): $\tilde{\nu}$ = 3295, 2977, 2936, 1728, 1482, 1274, 1155 cm$^{-1}$; UV ($CHCl_3$): $\lambda_{max}$ = 227, 267, 289, 301 nm.

**Amine 9**: Piperidine (0.36 mL, 3.67 mmol) was added to a solution of **8** (1.71 g, 3.06 mmol) in dichloromethane (45 mL) and the mixture was stirred overnight. The solvents were distilled off and the residue was washed with hexane overnight. Compound **9** was obtained as a bright yellow solid (237 mg, 0.67 mmol, quantitative). $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 7.77 (s, 1H, NH), 6.99 (t, $J$ = 7.9 Hz, 1H, aryl), 6.88–6.83 (m, 2H, aryl), 4.46 (m, 2H, $CH_2$ benzyl), 3.86 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.14 (m, 1H, $\alpha$-H), 2.89 (dd, $J$ = 16.8, 4.4 Hz, 1H, $CH_2$ Asp), 2.61 (dd, $J$ = 16.8, 7.8 Hz, 1H, $CH_2$ Asp), 1.42 (s, 9H, *t*Bu) ppm; $^{13}$C NMR ($CDCl_3$, 125.7 MHz): $\delta$ = 172.1 (C), 171.1 (C), 152.6 (C), 147.2 (C), 131.8 (C), 124.1 (CH), 121.2 (CH), 111.9 (CH), 81.4 (C), 60.7 ($CH_3$), 55.7 ($CH_3$), 51.8 (CH), 39.8 ($CH_2$), 38.6 ($CH_2$), 28.0 (3$CH_3$); FAB-MS (DMSO/3-NBA): $m/z$: 339.3 $[M+H]^+$, 361.3 $[M+Na]^+$; IR (KBr, drift): $\tilde{\nu}$ = 2948, 1725, 1668, 1482, 1274, 1154 cm$^{-1}$; UV ($CHCl_3$): $\lambda_{max}$ = 228, 249, 258, 247 nm.

**Compound 11**: Fmoc-Gly-OH (**10**; 295 mg, 0.99 mmol) was dissolved in a mixture of $CH_2Cl_2$ (10 mL) and DMF (2.4 mL). Then, Hünig's base (0.19 mL, 1.09 mmol) und a solution of HBTU (452 mg, 1.19 mmol) in DMF (2.6 mL) were added and the mixture was stirred together for two hours. Meanwhile **9** (352 mg, 1.04 mmol) was suspended in DMF (7 mL) and $CH_2Cl_2$ (2 mL) was added, followed by the activated amino acid mixture. The reaction mixture was stirred for three days, filtered, and then diluted with $CH_2Cl_2$. The organic layer was washed with sat. aqueous $NH_4Cl$ solution, sat. aqueous $NaHCO_3$ solution, water, and brine. It was dried over $MgSO_4$ and the solvent was distilled off under vacuum. The crude product was purified by chromatography over silica gel with ethyl acetate/hexane 2:1. Compound **11** was obtained as a white solid (481 mg, 0.78 mmol, 79%). $R_f$ = 0.29 (ethyl acetate/hexane 2:1); m.p. 115°C (decomp); $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 7.76 (d, $J$ = 7.5 Hz, 2H, Fmoc), 7.56 (d, $J$ = 7.3 Hz, 2H, Fmoc), 7.40 (t, $J$ = 7.4 Hz, 2H, Fmoc), 7.35–7.30 (brs, 1H, NH), 7.30 (m, 2H, Fmoc), 7.08 (brs, 1H, NH), 6.90 (t, $J$ = 8.0 Hz, 1H, aryl), 6.80 (m, 1H, aryl), 6.75 (d, $J$ = 8.0 Hz, 1H, aryl), 5.50 (brs, 1H, NH), 4.79 (d, $J$ = 2.7 Hz, 1H, $\alpha$-H), 4.44 (t, $J$ = 6.1 Hz, 2H, $CH_2$ benzyl), 4.33 (d, $J$ = 7.1 Hz, 2H, $CH_2$ Fmoc), 4.18 (t, $J$ = 6.9 Hz, 1H, CH Fmoc), 3.87 (d, $J$ = 5.0 Hz, 2H, $CH_2$ Gly), 3.82 (s, 6H, OMe), 2.95 (dd, $J$ = 16.9, 3.4 Hz, 1H, $CH_2$ Asp), 2.56 (dd, $J$ = 16.9, 6.5 Hz, 1H, $CH_2$ Asp), 1.39 (s, 9H, *t*Bu) ppm; $^{13}$C NMR ($CDCl_3$, 125.7 MHz): $\delta$ = 171.3 (C), 169.8 (C), 168.7 (C), 156.8 (C), 152.5 (C), 147.0 (C), 143.7 (C), 141.3 (C), 131.5 (C), 127.7 (2CH), 127.1 (2CH), 125.1 (2CH), 124.1 (CH), 120.8 (CH), 120.0 (2CH), 111.8 (CH), 81.9 (C), 67.4 ($CH_2$), 60.6 ($CH_3$), 55.7 ($CH_3$), 49.3 (CH), 47,0 (CH), 44.7 ($CH_2$), 38.8 ($CH_2$), 36.8 ($CH_2$), 27.9 (3$CH_3$) ppm, two C signals are not visible; FAB-MS (3-NBA/DMSO): $m/z$: 617.1 $[M]^+$, 618.1 $[M+H]^+$, 640.2 $[M+Na]^+$; elemental analysis calcd (%) for $C_{34}H_{39}N_3O_8$: C 66.11, H 6.36, N 6.80; found: C 65.78, H 6.39, N 6.69; IR (KBr): $\tilde{\nu}$ = 3304, 2978, 2937, 1727, 1660, 1533, 1273 cm$^{-1}$; UV ($CHCl_3$): $\lambda_{max}$ = 227, 267, 289, 301 nm.

**Amine 12**: Piperidine (0.37 mL, 3.76 mmol) was added to a solution of **11** (1.94 g, 3.14 mmol) in $CH_2Cl_2$ (30 mL). The mixture was stirred overnight, then the solvent was removed under reduced pressure and the resi-

due was dried under vacuum. The obtained solid was washed overnight with hexane and then dried under vacuum. Compound **12** was obtained as a bright yellow solid (1.09 g, 2.76 mmol, 88%). $^1$H NMR (DMSO, 500 MHz): $\delta$ = 8.26 (brs, 1H, NH), 8.00 (brs, 1H, NH), 6.89 (t, $J$ = 7.9 Hz, 1H, aryl), 6.77–6.73 (m, 2H, aryl), 4.67 (d, $J$ = 4.4 Hz, 1H, $\alpha$-H), 4.22 (d, $J$ = 5.9 Hz, 2H, $CH_2$ benzyl), 3.75 (s, 3H, OMe), 3.71 (s, 3H, OMe), 2.61 (d, $J$ = 6.2 Hz, 2H, $CH_2$ Asp), 1.33 (s, 9H, *t*Bu) ppm, the $CH_2$ Gly signal is covered by the $H_2O$ signal at 3.4 ppm; $^{13}$C NMR ($CDCl_3$, 125.7 MHz): $\delta$ = 171.8 (C), 170.6 (C), 169.9 (C), 152.4 (C), 146.5 (C), 132.4 (C), 123.9 (CH), 120.3 (CH), 111.5 (CH), 80.8 (C), 60.4 ($CH_3$), 55.8 ($CH_3$), 49.4 (CH), 44.4 ($CH_2$), 37.7 ($CH_2$), 28.04 (3 $CH_3$), 22.6 ($CH_2$) ppm; FAB-MS (3-NBA/DMSO): *m*/*z*: 396.3 $[M+H]^+$, 418.3 $[M+Na]^+$, 396.3 $[M-t\text{Bu}+2H]^+$; IR(KBr): $\tilde{\nu}$ = 3305, 2940, 2937, 1727, 1660, 1481, 1273, 1156, 727 cm$^{-1}$; UV ($CH_2Cl_2$): $\lambda_{max}$ = 217, 272 nm.

**Compound 14**: Fmoc-Arg(Mtr)-OH (**13**; 1.68 g, 2.76 mmol) was dissolved in $CH_2Cl_2$ (30 mL) and then Hünig's base (0.52 mL, 3.04 mmol) and a solution of HBTU (1.26 g, 3.31 mmol) in DMF (8.5 mL) were added. After 8 min, a suspension of **12** (1.09 g, 2.76 mmol) in a mixture of DMF (4 mL) and $CH_2Cl_2$ (16 mL) was added. The mixture was stirred overnight and then washed with sat. aqueous $NH_4Cl$, sat. aqueous $NaHCO_3$, water, and brine. After drying over $MgSO_4$, the solvent was distilled off and the residue was purified by chromatography over silica gel with ethyl acetate/hexane 2:1. Product **14** was obtained as a white solid (2.16 g, 2.19 mmol, 79%) by eluting with ethyl acetate/methanol 2:1. $R_f$ = 0.65 (ethyl acetate/methanol 2:1); m.p. 120 °C (decomp); $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 7.93 (brs, 1H, NH), 7.72 (d, $J$ = 7.5 Hz, 2H, Fmoc), 7.56 (m, 2H, Fmoc), 7.42 (brs, 1H, NH), 7.35 (t, $J$ = 7.3 Hz, 2H, Fmoc), 7.23 (m, 2H, Fmoc), 6.84 (t, $J$ = 8.0 Hz, 1H, aryl), 6.73 (m, 1H aryl), 6.69 (d, $J$ = 8.0 Hz, 1H, aryl), 6.45 (s, 1H, aryl Mtr), 6.37 (brs, 1H, NH), 6.05 (brs, 1H, NH), 4.77 (m, 1H, $\alpha$-H Asp), 4.40–4.24 (m, 5H, $CH_2$ benzyl, $CH_2$ Fmoc, $\alpha$-H Arg), 4.13 (t, $J$ = 6.7 Hz, 1H, CH Fmoc), 3.88 (m, 2H, $CH_2$ Gly), 3.75 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.72 (s, 3H, OMe Mtr), 3.32–3.24 (m, 1H, $CH_2$ Asp), 3.14–3.04 (m, 1H, $CH_2$ Asp), 2.63 (s, 3H, $CH_3$ Mtr), 2.58 (s, 3H, $CH_3$ Mtr), 2.06 (s, 3H, $CH_3$ Mtr), 1.84–1.75 (m, 1H, $CH_2$ Arg), 1.62–1.44 (m, 5H, $CH_2$ Arg), 1.32 (s, 9H, *t*Bu) ppm; $^{13}$C NMR ($CDCl_3$, 125.7 MHz): $\delta$ = 173.5 (C), 170.8 (C), 170.5 (C), 169.6 (C), 156.6 (C), 152.4 (C), 146.6 (C), 143.8 (C), 143.7 (C), 141.2 (2C), 131.6 (C), 127.7 (2CH), 127.1 (2CH), 125.1 (2CH), 124.0 (CH), 120.6 (CH), 120.0 (2CH), 111.8 (CH), 111.6 (CH), 81.7 (C), 67.0 ($CH_2$), 60.5 ($CH_3$), 55.6 ($CH_3$), 55.4 ($CH_3$), 54.1 (CH), 49.7 (CH), 47.1 (CH), 43.3 ($CH_2$), 38.4 ($CH_2$), 37.0 ($CH_2$), 29.5 ($CH_2$), 27.9 (3$CH_3$), 24.2 ($CH_3$), 18.4 ($CH_3$), 11.9 ($CH_3$) ppm, the missing C and $CH_2$ signals could not be observed; FAB-MS (3-NBA/DMSO): *m*/*z*: 930.5 $[M-t\text{Bu}+H]^+$, 952.4 $[M-t\text{Bu}+H+Na]^+$, 985.5 $[M]^+$, 986.5 $[M+H]^+$, 1008.5 $[M+Na]^+$; elemental analysis calcd (%) for $C_{50}H_{63}N_7O_{12}S\cdot 3H_2O$: C 57.73, H 6.69, N 9.43; found: C 57.88, H 6.31, N 9.54; IR (KBr): $\tilde{\nu}$ = 3338, 2939, 1666, 1548, 1260, 1121 cm$^{-1}$; UV ($CHCl_3$): $\lambda_{max}$ = 227, 255, 289, 301 nm.

**Amine 15**: Compound **14** (1.90 g, 1.97 mmol) was dissolved in $CH_2Cl_2$ (20 mL) and piperidine (0.23 mL, 2.36 mmol) was added. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was dried under vacuum. The solid was washed with hexane overnight and dried once again under vacuum. Compound **15** was obtained as a bright yellow solid (1.78 g, 2.33 mmol, quantitative). $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 8.28 (brs, 1H, NH), 7.54 (brs, 1H, NH), 6.91 (t, $J$ = 7.6 Hz, 1H, aryl), 6.76 (brs, 2H, aryl), 6.66 (brs, 1H, NH), 6.48 (brs, 1H, Mtr), 4.76 (brs, 1H, $\alpha$-H), 4.36 (brs, 2H, $CH_2$ benzyl), 3.96 (brs, 2H, $CH_2$ Gly), 3.79 (s, 6H, OMe), 3.79 (s, 3H, OMe), 3.46 (brs, 1H, $CH_2$ Asp), 3.15 (brs, 1H, $CH_2$ Asp), 2.63 (s, 3H, $CH_3$ Mtr), 2.57 (s, 3H, $CH_3$ Mtr), 2.08 (s, 3H, $CH_3$ Mtr), 1.59–1.40 (m, 6H, $CH_2$ Arg), 1.36 (s, 9H, *t*Bu) ppm, the second $\alpha$-H cannot be assigned; $^{13}$C NMR ($CDCl_3$, 125.7 MHz): $\delta$ = 176.4 (C), 171.0 (C), 170.5 (C), 169.7 (C), 158.4 (C), 156.7 (C), 152.4 (C), 146.6 (C), 138.4 (C), 136.4 (C), 133.4 (C), 131.7 (C), 128.7 (CH), 124.8 (C), 124.1 (CH), 120.5 (CH), 111.7 (CH), 81.7 (C), 60.6 ($CH_3$), 55.7 ($CH_3$), 55.4 ($CH_3$), 54.1 (CH), 49.6 (CH), 44.7 ($CH_2$), 43.3 ($CH_2$), 38.4 ($CH_2$), 36.9 ($CH_2$), 27.9 (3$CH_3$), 24.2 ($CH_3$), 22.6 ($CH_2$), 22.4 ($CH_2$), 18.4 ($CH_3$), 11.9 ($CH_3$) ppm; FAB-MS (3-NBA/DMSO): *m*/*z*: 764.3 $[M+H]^+$, 786.3 $[M+Na]^+$; IR (KBr): $\tilde{\nu}$ = 3324, 2938, 1669, 1551, 1270, 1112 cm$^{-1}$; UV ($CH_2Cl_2$): $\lambda_{max}$ = 219, 247, 256, 305 nm.

**Protected ligand 16:** 2,3-Dimethoxybenzoic acid (**1**; 358 mg, 1.97 mmol) was dissolved in $CH_2Cl_2$ (30 mL) and mixed with Hünig's base (0.37 mL, 2.16 mmol) and a solution of HBTU (895 mg, 2.36 mmol) in DMF (7.9 mL). After two hours a suspension of **15** (1.78 g, 1.97 mmol) in $CH_2Cl_2$ (12 mL) and DMF (2.5 mL) was added. The reaction mixture was stirred overnight and then washed with sat. aqueous $NH_4Cl$, sat. aqueous $NaHCO_3$, water, and brine. After drying over $MgSO_4$, the solvent was distilled off. The by-products were removed by chromatography over silica gel with ethyl acetate/hexane (2:1 v/v) and the pure product was obtained by eluting with ethyl acetate/methanol (2:1 v/v). Compound **16** was obtained as a white solid (1.56 g, 1.68 mmol, 86%). $R_f$ = 0.72 (ethyl acetate/methanol 2:1). Analytical data: see below.

***Solid-phase syntheses***

**General synthesis of protected tripeptide-bridged ligand precursors on the solid support**: The synthesis of protected tripeptide-bridged ligand precursors was performed on the 4-Fmoc-hydrazinobenzoyl resin **17** (4-Fmoc-hydrazinobenzoyl AM resin, Novabiochem) by using Fmoc-protected amino acids. Initially the resin was swollen in dichloromethane. After washing with DMF, the Fmoc group was cleaved with a 20% solution of piperidine in DMF to yield **18**.[24,25]

For the preparation of the peptide sequences the following protocol was used: The C-terminal-unprotected N-Fmoc amino acid (2 equiv) was activated with Hünig's base (4 equiv) and HBTU (2 equiv) in DMF. After ten minutes, this solution was added to the N-terminal-unprotected resin and the mixture was shaken for one hour. Before attaching the next amino acid, the Fmoc group had to be cleaved by treating the resin with a 20% solution of piperidine in DMF for 15 min.[20] In a final step, 2,3-dimethoxybenzoic acid (**1**) was attached and the resin was washed with DMF, $CH_2Cl_2$, and methanol. After drying under vacuum the peptide was cleaved from the resin with simultaneous formation of the amide with 2,3-dimethoxybenzyl amine (**4**). This was achieved by treatment with copper acetate (1 equiv) in DMF and bubbling air through the mixture for 4 h in the presence of **4**.[24] The resin is filtered off and washed with dichloromethane, then the combined organic layers are washed with aqueous 1 M $KHSO_4$, water, and brine. After drying with $NaSO_4$, the organic solvents are distilled off under vacuum.

**Compound 16**: This was prepared following the general method from resin **17** (305 mg, 0.30 mmol), HBTU (228 mg, 0.60 mmol), Hünig's base (205 µL, 1.20 mmol), Fmoc-Asp(O*t*Bu)-OH (**7**; 247 mg, 0.60 mmol), Fmoc-Gly-OH (**10**; 187 mg, 0.60 mmol), Fmoc-Arg(Mtr)-OH (**13**; 365 mg, 0.60 mmol), 2,3-dimethoxybenzoic acid (**1**; 109 mg, 0.60 mmol), and 2,3-dimethoxybenzylamine (**4**; 1.00 mL, 6.76 mmol). The by-products were removed by chromatography over silica gel with ethyl acetate and the pure product was obtained by eluting with ethyl acetate/methanol 4:1. Compound **16** was obtained as a white solid (179 mg, 0.19 mmol, 64%). M.p. 125 °C (decomp); $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 8.70 (brs, 1H, NH), 8.09 (brs, 1H, NH), 7.67 (brs, 1H, NH), 7.55 (d, $J$ = 7.5 Hz, 1H, aryl), 7.47 (brs, 1H, NH), 7.09 (t, $J$ = 8.0 Hz, 1H, aryl), 7.03 (m, 1H, aryl), 6.40 (brs, 1H, NH), 6.87 (t, $J$ = 8.0 Hz, 1H, aryl), 6.75–7.71 (m, 2H, aryl), 6.47 (s, 1H, Mtr), 4.82–4.72 (m, 2H, $\alpha$-H Asp, $\alpha$-H Arg), 4.35 (m, 2H, $CH_2$ benzyl), 3.97–3.91 (m, 2H, $CH_2$ Gly), 3.89 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.78 (6H, OMe), 3.73 (s, 3H, OMe), 3.38 (m, 1H, $CH_2$ Asp), 3.15 (m, 1H, $CH_2$ Asp), 2.63 (s, 3H, $CH_3$ Mtr), 2.58 (s, 3H, $CH_3$ Mtr), 2.06 (s, 3H, $CH_3$ Mtr), 1.74 (m, 2H, $CH_2$ Arg), 1.58 (m, 4H, $CH_2$ Arg), 1.31 (s, 9H, *t*Bu) ppm; $^{13}$C NMR ($CDCl_3$, 125.7 MHz): $\delta$ = 172.9 (C), 170.8 (C), 170.7 (C), 169.7 (C), 165.6 (C), 162.6 (C), 152.7 (C), 152.4 (C), 148.0 (C), 146.6 (C), 131.6 (C), 124.3 (CH), 124.0 (CH), 122.4 (CH), 120.3 (CH), 115.9 (CH), 111.8 (CH), 81.5 (C), 61.5 ($CH_3$), 60.4 ($CH_3$), 56.1 ($CH_3$), 55.7 ($CH_3$), 55.4 ($CH_3$), 53.4 ($CH_2$), 49.8 (CH), 43.2 ($CH_2$), 38.4 ($CH_2$), 36.9 ($CH_2$), 29.7 ($CH_2$), 27.9 (3 $CH_3$), 24.2 ($CH_3$), 18.4 ($CH_3$), 11.9 ($CH_3$) ppm, the missing signals could not be observed; FAB-MS (DMSO/3-NBA): *m*/*z*: 872.4 $[M-t\text{Bu}+H]^+$, 928.5 $[M+H]^+$, 951.4 $[M+Na]^+$; elemental analysis calcd (%) for $C_{44}H_{61}N_7O_{13}S\cdot 4H_2O$: C 52.84, H 6.95, N 9.80; found: C 52.98, H 6.56, N 9.87; IR (KBr): $\tilde{\nu}$ = 3342, 2936, 1657, 1650, 1548, 1265, 1121 cm$^{-1}$; UV ($CHCl_3$): $\lambda_{max}$ = 227, 245 nm.

**Preparation of the RGD-bridged ligand 23-H$_4$**: $AlCl_3$ (65 mg, 0.49 mmol) was dissolved in ethanethiol (0.5 mL) under ice cooling. Then, a solution of **16** (15 mg, 0.02 mmol) in $CH_2Cl_2$ (1 mL) was added to the $AlCl_3$ solution.[27] The mixture was allowed to warm to room temperature, stirred overnight, and then poured into cold water (7 mL). The solution was acidified with 1 M aqueous HCl. The water layer was separated and was distilled to dryness. The crude product was purified by HPLC (Nucleosil, 250 × 20 mm, 100C18, 7 µm, 5 mL min$^{-1}$) with acetonitrile (containing

0.1% trifluoroacetic acid (TFA)) and water (containing 0.1% TFA). Compound **23**-$H_4$ was obtained as a white solid (4.4 mg, 45%). $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ = 7.35 (dd, $J$ = 7.9, 1.6 Hz, 1H, aryl), 6.95 (dd, $J$ = 7.9, 1.6 Hz, 1H, aryl), 6.75 (t, $J$ = 7.9 Hz, 1H, aryl), 6.69 (dd, $J$ = 7.6, 2.0 Hz, 1H, aryl), 6.66 (dd, $J$ = 7.6, 2.0 Hz, 1H, aryl), 6.61 (t, $J$ = 7.6 Hz, 1H, aryl), 4.80 (dd, $J$ = 7.6, 5.6 Hz, 1H, $\alpha$-H), 4.60 (m, 1H, $\alpha$-H), 4.35 (s, 2H, $CH_2$ benzyl), 3.90 (s, 2H, $CH_2$ Gly), 3.21 (m, 2H, $CH_2$ Arg), 2.88 (dd, $J$ = 16.3, 5.6 Hz, 1H, $CH_2$ Asp), 2.77 (dd, $J$ = 16.3, 7.6 Hz, 1H, $CH_2$ Asp), 2.01 (m, 1H, $CH_2$ Arg), 1.84 (m, 1H, $CH_2$ Arg), 1.70 (m, 2H, $CH_2$ Arg) ppm; $^{13}$C NMR ($CD_3OD$, 125 MHz): $\delta$ = 173.7 (C), 171.9 (C), 171.5 (C), 170.6 (C), 169.8 (C), 157.6 (C), 148.2 (C), 146.2 (C), 143.5 (C), 125.1 (C), 118.9 (CH), 116.4 (C), 114.5 (CH), 53.5 (CH), 50.3 (CH), 42.6 ($CH_2$), 41.0 ($CH_2$), 39.1 ($CH_2$), 35.9 ($CH_2$), 29.0 ($CH_2$), 25.2 ($CH_2$) ppm; high-resolution FAB-MS (3-NBA/DMSO): calcd for $C_{26}H_{34}N_7O_{10}$ $[M+H]^+$: $m/z$: 604.2392; found: 604.2367.

**Formation of $K_2$[(23)$MoO_2$]**: Ligand **23**-$H_4$ (13.9 mg, 0.02 mmol) was dissolved in methanol (8 mL) and mixed with $K_2CO_3$ (12.4 mg, 0.09 mmol) and $MoO_2(acac)_2$ (8.3 mg, 0.03 mmol). This solution was stirred for five days. The solvent was distilled off under vacuum and the crude product was filtered over Sephadex LH20 with methanol. $K_2$[(**23**)$MoO_2$] was obtained as a red solid (14 mg, 0.02 mmol, quantitative). $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ = 7.21 (dd, $J$ = 8.2, 1.5 Hz, 1H, benzoic acid), 6.72 (dd, $J$ = 7.3, 1.5 Hz, 1H, benzoic acid), 6.46 (m, 1H, benzoic acid), 6.39 (m, 2H, benzyl amine), 6.30 (m, 1H, benzyl amine), 4.90 (covered $\alpha$-H Arg), 4.79 (d, $J$ = 14.0 Hz, 1H, $CH_2$ benzyl), 4.61 (m, 1H, $\alpha$-H Asp), 4.34 (d, $J$ = 14.0 Hz, 1H, $CH_2$ benzyl), 3.90 (d, $J$ = 17.0 Hz, 1H, $CH_2$ Gly), 3.78 (d, $J$ = 17.0 Hz, 1H, $CH_2$ Gly), 3.18 (dd, $J$ = 16.7, 2.4 Hz, 1H, $CH_2$ Asp), 2.96 (m, 1H, $\delta$-$CH_2$ Arg), 2.88 (m, 1H, $\delta$-$CH_2$ Arg), 2.48 (dd, $J$ = 16.7, 5.2 Hz, $CH_2$ Asp), 1.87 (m, 1H, $\beta$-$CH_2$ Arg), 1.24 (m, 1H, $\beta$-$CH_2$ Arg), 1.15 (m, 1H, $\gamma$-$CH_2$ Arg), 0.92 (m, 1H, $\gamma$-$CH_2$ Arg) ppm; ESI-MS: $m/z$: 807 [{$K_2$[(**23**)$MoO_2$]}−H]$^-$, 769 {K[(**23**)$MoO_2$]}$^-$, 730 {H[(**23**)$MoO_2$]}$^-$, 383.5 [(**23**)$MoO_2$]$^{2-}$.

**Preparation of WKY-bridged compounds**: The same solid-phase protocol as was described for the preparation of **16** was used.

**Ligand precursor 31**: This was prepared following the general method from resin **17** (536 mg, 0.53 mmol), HBTU (398 mg, 1.12 mmol), Hünig's base (360 μL, 2.24 mmol), Fmoc-Tyr(*t*Bu)-OH (**24**; 487 mg, 1.12 mmol), Fmoc-Lys(Boc)-OH (**26**; 497 mg, 1.12 mmol), Fmoc-Trp(Boc)-OH (**28**; 558 mg, 1.12 mmol), 2,3-dimethoxybenzoic acid (**1**; 193 mg, 1.12 mmol), and 2,3-dimethoxybenzylamine (**4**; 50 μL, 5.30 mmol). The by-products were removed by chromatography over silica gel with ethyl acetate/hexane 2:1 and the pure product **31** was obtained as a white solid by eluting with ethyl acetate (379.1 mg, 0.36 mmol, 67%). M.p. 130°C (decomp); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 8.62 (d, $J$ = 5.2 Hz, 1H, NH), 8.09 (d, $J$ = 8.6 Hz, 1H, NH), 7.60 (dd, $J$ = 7.8, 1.8 Hz, 1H, aryl), 7.54 (m, 2H), 7.31 (m, 1H, aryl), 7.21 (t, $J$ = 7.2 Hz, 1H, aryl), 7.13 (m, 1H aryl), 7.07 (dd, $J$ = 8.2, 1.6 Hz, 1H, aryl), 7.04–7.00 (m, 3H, aryl), 6.98 (m, 1H, aryl), 6.90 (d, $J$ = 7.4 Hz, 1H, aryl), 6.80 (dd, $J$ = 8.2, 1.4 Hz, 1H, aryl), 6.74 (d, $J$ = 8.52 Hz, 2H, aryl), 6.51 (brs, 1H, NH), 4.86 (brs, 1H, NH Boc-Lys), 4.74 (brs, 2H, $\alpha$-H Trp, $\alpha$-H Tyr), 4.50 (m, 2H, $CH_2$ benzyl), 4.10 (m, 1H, $\alpha$-H Lys), 3.88 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.37 (dd, $J$ = 14.1, 5.4 Hz, 1H, $CH_2$), 3.26 (pseudo-t, $J$ = 6.3, 4.4 Hz, 2H, $CH_2$), 2.92 (dd, $J$ = 13.9, 9.9 Hz, 1H, $CH_2$), 2.81 (brs, 2H, $\varepsilon$-$CH_2$ Lys), 1.67 (s, 9H, *t*Bu), 1.41 (s, 11H, *t*Bu, $\gamma$-$CH_2$ Lys), 1.25 (s, 11H, *t*Bu, $\beta$-$CH_2$ Lys), 1.18 (quin, $J$ = 7.42 Hz, 2H, $\delta$-$CH_2$ Lys) ppm; elemental analysis calcd (%) for $C_{58}H_{76}N_6O_{13}\cdot 1.5\,H_2O$: C 64.85, H 7.22, N 7.82; found: C 64.75, H 7.26, N 7.82; positive FAB-MS (3-NBA/DMSO): $m/z$: 967.0 $[M-\text{Boc}+H]^+$; negative FAB-MS (3-NBA/DMSO): $m/z$: 1065.4 $[M+H]^-$; LC-MS (ESI): $m/z$: 1065.43 $[M+H]^+$, 1087.48 $[M+Na]^+$; IR (KBr): $\tilde{\nu}$ = 3430, 1639, 1509, 1479, 1456, 1384, 1364, 1265, 1164 cm$^{-1}$.

**WKY-bridged ligand 32-$H_4$**: At −18°C, $BBr_3$ (0.23 mL, 2.35 mmol) was added to a solution of **31** (100 mg, 0.09 mmol) in $CH_2Cl_2$ (27 mL). The reaction mixture was stirred for five days and then hydrolyzed by addition of methanol (27 mL, ice-cooled). The solvent was evaporated under vacuum and the residue was dissolved in methanol and evaporated to dryness. This procedure was repeated several times to remove all boron esters. The crude product was recrystallized from isopropanol and hexane. Ligand **32**-$H_4$ was obtained as a grey solid (70.6 mg, 0.09 mmol, quantitative). M.p. 130°C (decomp); $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ = 7.60 (d, $J$ = 8.0 Hz, 1H, aryl), 7.34 (d, $J$ = 8.0 Hz, 1H), 7.26 (dd, $J$ = 8.1, 1.5 Hz, 1H, aryl), 7.19 (s, 1H, indole H), 7.09 (m, 1H), 6.99 (m, 1H), 6.94 (dd, $J$ = 7.8, 1.5 Hz, 1H, aryl), 6.89 (m, 2H, aryl), 6.72 (m, 2H, aryl), 6.59 (m, 3H, aryl), 6.54 (d, $J$ = 14.6 Hz, 1H, aryl), 4.82 (t, $J$ = 6.5 Hz, 1H), 4.50 (t, $J$ = 7.6 Hz, 1H, $\alpha$-H), 4.27 (m, 3H, $\alpha$-H Lys, $CH_2$ benzyl), 3.31 (m, 2H, $CH_2$), 2.99 (m, 1H, $CH_2$), 2.76 (m, 3H, $CH_2$, $\varepsilon$-$CH_2$ Lys), 1.58 (m, 1H, $\beta$-$CH_2$ Lys), 1.49 (m, 3H, $\beta$- and $\gamma$-$CH_2$ Lys), 1.13 (m, 2H, $\delta$-$CH_2$ Lys) ppm; elemental analysis calcd (%) for $C_{40}H_{44}N_6O_9\cdot 2\,H_2O\cdot 2\,HBr$: C 49.60, H 5.41, N 8.68; found: C 49.91, H 5.24, N 8.28; positive FAB-MS (3-NBA/DMSO): $m/z$: 754.4 $[M+H]^+$; negative FAB-MS (3-NBA/DMSO): $m/z$: 752.3 $[M-H]^-$; LC-MS (ESI): $m/z$: 753.19 $[M]^+$; IR (KBr): $\tilde{\nu}$ = 3364, 2943, 1641, 1534, 1252, 746 cm$^{-1}$.

**Formation of $K_2$[(32)$MoO_2$]**: Ligand **32**-$H_4$ (22 mg, 0.03 mmol), $K_2CO_3$ (16 mg, 0.12 mmol), and $[MoO_2(acac)_2]$ (9.6 mg, 0.03 mmol) were dissolved in methanol (11 mL). The mixture was stirred for six days. The solvent was distilled off under vacuum and the crude product was filtered over Sephadex LH20 with methanol. Coordination complex $K_2$[(**32**)$MoO_2$] was obtained as a red solid (15 mg, 0.02 mmol, 67%). $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ = 7.72 (d, $J$ = 7.4 Hz, 1H, aryl), 7.33 (d, $J$ = 7.4 Hz, 1H, aryl), 7.12 (m, 3H, aryl), 6.92 (s, 1H, indole), 6.70 (dd, $J$ = 7.6, 1.6 Hz, 3H, aryl), 6.59 (m, 4H, aryl), 6.42 (m, 2H, aryl), 5.16 (t, $J$ = 6.7 Hz, 1H, $\alpha$-H), 4.81 (d, $J$ = 13.8 Hz, 1H, $CH_2$), 4.51 (dd, $J$ = 11.4, 3.7 Hz, 1H, $\alpha$-H), 4.42 (d, $J$ = 13.8 Hz, 1H, $CH_2$), 3.89 (t, $J$ = 6.3 Hz, 1H, $\alpha$-H), 3.21 (m, 1H), 3.08 (m, 2H), 2.73 (dd, $J$ = 15.1, 6.8 Hz, 1H, $CH_2$), 2.48 (m, 1H, $CH_2$), 1.51 (m, 1H, $CH_2$), 1.32 (m, 4H, $CH_2$), 0.71 (m, 2H) ppm and signals of $CH_3COCH_2COCH_3$ at $\delta$ = 5.50 and 1.97 ppm; elemental analysis calcd (%) for $C_{40}H_{40}K_2N_6O_9MoO_2\cdot(C_5H_8O_2)\cdot 5\,H_2O$: C 47.20, H 5.11, N 7.34; found: C 47.12, H 5.06, N 7.23; ESI-MS: $m/z$: 916 {K[(**32**)$MoO_2$]}$^-$, 879 {H[(**32**)$MoO_2$]}$^-$, 1000 {K(HBr)[(**32**)$MoO_2$]}$^-$; IR (KBr): $\tilde{\nu}$ = 3386, 2929, 1633, 1541, 1449, 1234, 896, 865, 746 cm$^{-1}$.

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