Design and Synthesis of Compartmental Ligands and their Complexes for the Production of Catalytic Antibodies

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This work is dedicated to the memory of my respected Ph.D. advisor Prof. *Luigi M. Venanci*

The synthesis and coordination properties of mixed N,O-compartmental ligands is described. Macrocyclic ligands **8** and **15** were designed to mimic transition-state analogs for the production of catalytic antibodies for C–H activation reactions. Reaction of **8** with vanadyl cations yields the dinuclear complex **9**, which was characterized by X-ray crystallography. Amputated ligands **17** and **18** react with various transition-metal cations to yield complexes designed to act as coenzymes for the catalytic antibodies. The Ni complex of **17** (**19**) was also structurally characterized by X-ray crystallography.

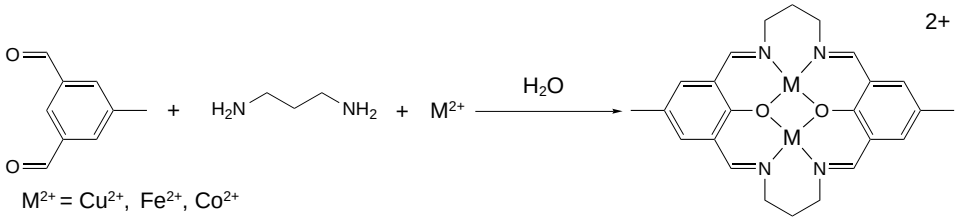
Introduction. – Ever since the first reports on catalytic antibodies by *Schulz* [1] and *Lerner* [2] and their co-workers, the field has considerably expanded, producing hundreds of novel catalytic antibodies for a broad variety of organic transformations [1–8]. Catalytic antibodies have now been induced with haptens that are designed to use a number of different strategies for effecting catalysis: distortion, charge stabilization, and proximity have all been used to advantage. To date, most of the effort has focused primarily on organic transition-state analogs, with perhaps an 'exotic' element (Si, S, P) present to mimic a transition-state geometry for carbon. Catalytic antibodies that incorporate transition-metal ions have received much less attention, although a few reports exist on porphyrin-containing catalytic antibodies [9–16].

Despite the broad interest in carboxylate-bridged bimetallic activation of small molecules [17][18], we are not aware of any attempt to elicit an immune response with a bimetallic hapten. This contribution reports the design, synthesis and characterization of dinuclear transition-state analogs for the production of catalytic antibodies as well as coenzymes for subsequent incorporation into the resulting host proteins.

Results and Discussion. – *Hapten- and Coenzyme Design.* The lack of precise knowledge concerning the transition-state geometry of transition-metal-catalyzed reactions renders the rational design of a transition-state analog (hapten) difficult. To circumvent this problem, we rely on our knowledge of metalloenzyme mimics, which are known to promote or catalyze certain reactions even in the absence of proteins.

Over the years, the *Robson* compartmental ligand and its derivatives have proven versatile for the activation of small molecules as well as for the modelling of the active site of various metalloenzymes [19–21]. The template condensation of the ligand itself suggests that such systems are capable of hydroxylating aromatic substrates (*Scheme 1*). Furthermore, we speculated that the presence of two Ph moieties in a hapten may be strongly immunogenic, potentially forming a precise 'imprint' for later

Scheme 1. *Template Synthesis of a* Robson*-Type Compartmental Ligand* via *Hydroxylation of the Aromatic Moieties*



recognition of the coenzyme and for delivering an aromatic substrate to be functionalized (*e.g.*, hydroxylated) during catalysis.

In addition to their thermodynamic stability and inertness, indispensible criteria for immunization purposes, *Robson*-type complexes were shown to possess catalytic- or stoichiometric activity in various biologically relevant transformations, mimmicking catalase [22–27], catecholase [28–31], as well as oxygenase [28][32]. We thus set out to synthesize an inert *Robson*-type complex as a transition-state analog for the hydroxylation of benzene derivatives. Concerning the coenzymes to be incorporated into the host proteins, catalytically active metals should be incorporated in a *structurally-related but amputated ligand*, thus allowing substrate (*i.e.*, benzene) activation and functionalization.

Several features were considered in designing the transition-state analog as well as the coenzyme: *i*) the appropriate skeleton, and *ii*) the metals and the co-ligands which complete the coordination sphere.

i) In order to elicit an immune response, a hapten should be conjugated to a carrier protein, typically, keyhole lympet hemocyanin (KLH). For this purpose, either a free carboxylic acid or an amine was remotely anchored to the *Robson* ligand. Furthermore, to prevent hydrolysis of the imine functionalities of the *Robson* ligand, these were reduced to the corresponding secondary amines. For the coenzymes, one of the phenol moieties of the hapten was amputated, thus yielding an equatorial pentadentate donor ligand. In conjunction with the protein raised against a full ligand, it was speculated that a hydrophobic pocket would favor the approach of an incoming substrate (*i.e.*, an aromatic moiety to be hydroxylated).

It has long been recognized that subtle differences in the coordination environment of iron enzymes play a determining role in the fate of coordinated O_2. While an oxygen-rich environment (such as found in methane monooxygenase) is better suited for O_2 activation, a nitrogen-rich ligand sphere favors reversible O_2 coordination (such as in hemerythrin) [17][18]. Thus, both N_4O- and N_2O_3-donor-set ligands were synthesized for the coenzymes.

ii) To allow for O_2 coordination and subsequent activation, a divanadyl moiety, was chosen as the transition-state analog. On the one hand, the vanadyl unit is one of the most stable diatomic moieties; on the other hand, it was speculated that the presence of terminal oxide ligands in the hapten would elicit the presence of H-donors in the active site of the antibody, which could help activate the coordinated O_2 for subsequent reactions with the organic substrate to be hydroxylated. Due to the pronounced *trans*-

effect of the oxo-donors, vanadyl complexes often display a $5+1$ geometry, the sixth ligand located *trans* to the oxo being weakly bound. It was speculated that these sites may be occupied by a bridging carboxylate provided by the protein upon immunization (*i.e.*, 'bait and switch' catalysis) [1]. The coenzyme should contain *catalytically active* metals coordinated to an amputated ligand. The remaining coordination sites should be occupied by labile ligands, to allow docking on a bridging carboxylate elicited by the divanadyl hapten. A summary of the design criteria for the hapten and coenzymes is shown in *Fig. 1*.

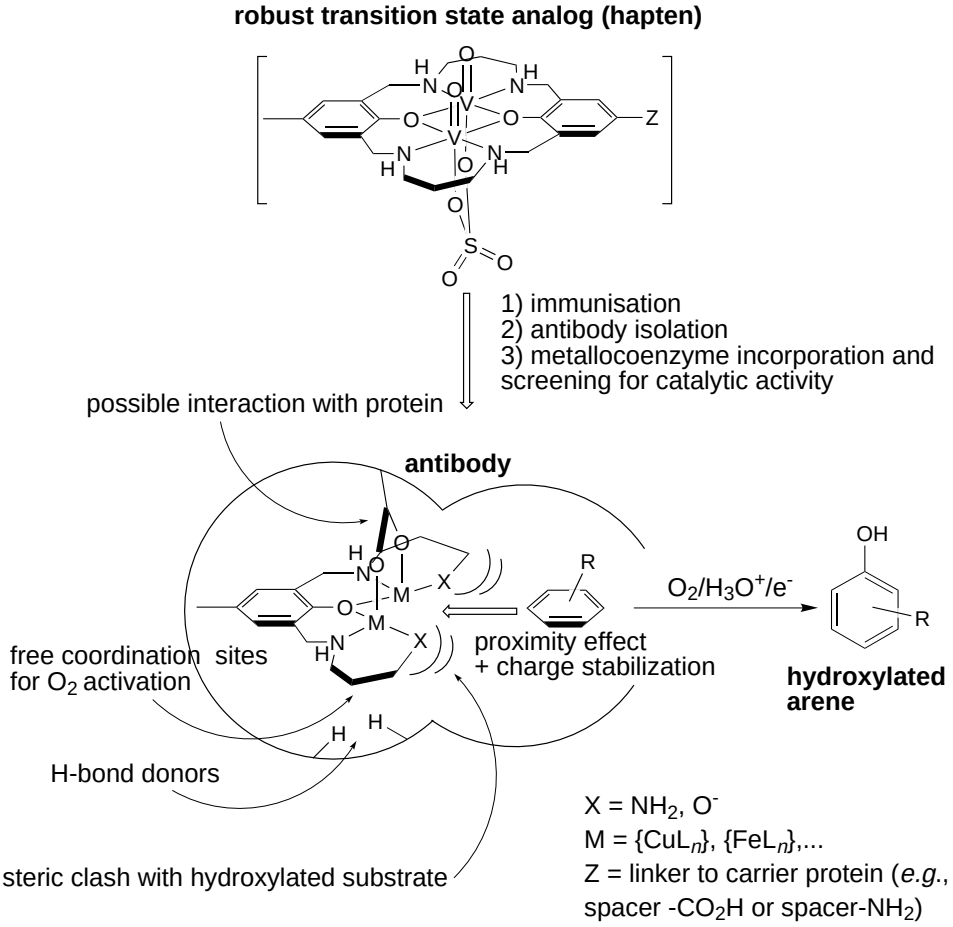
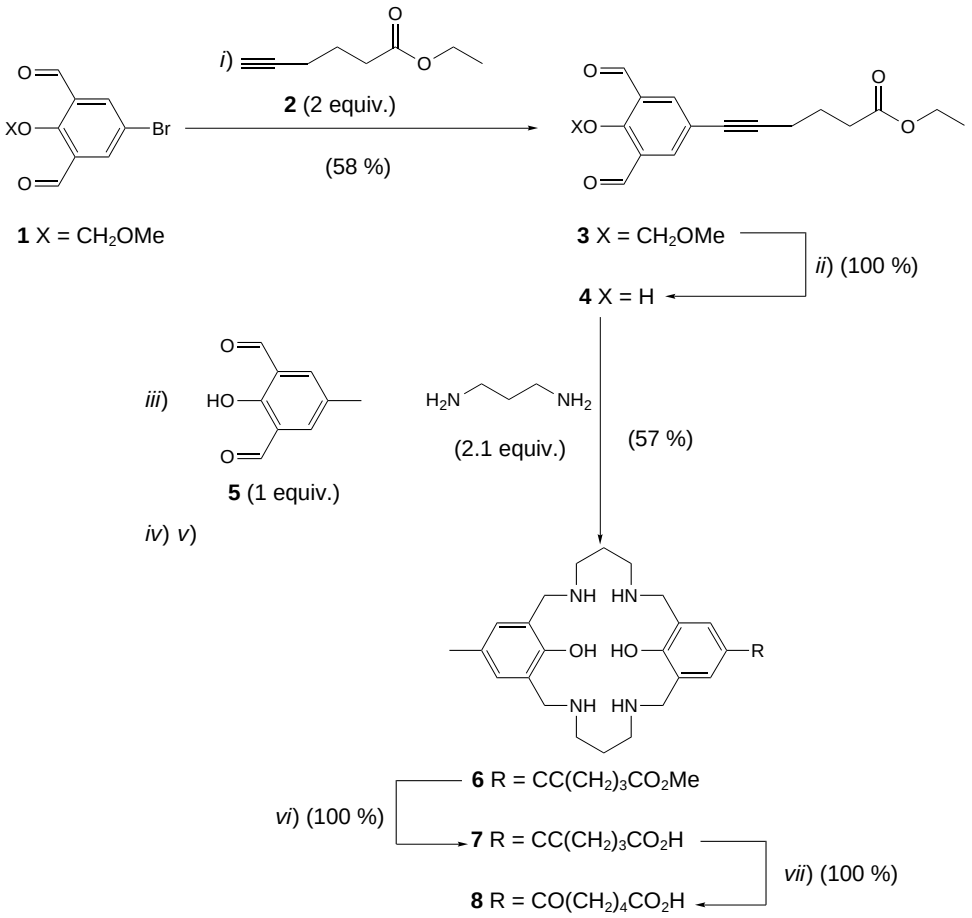


Fig. 1. *Design of a dinuclear transition-state analog and coenzymes based on compartmental ligands for the production of catalytic antibodies*

Hapten Synthesis and Characterization. Since a hapten must be conjugated to a carrier protein, a reactive functionality (carboxylic acid or amine) was covalently linked *via* a spacer to one of the aromatic moieties of the compartmental ligand, yielding an asymmetric N_4O_2 hexadentate ligand. The synthetic route is outlined in *Schemes 2* and *3*.

Scheme 2. *Synthesis of Ligand* **8**



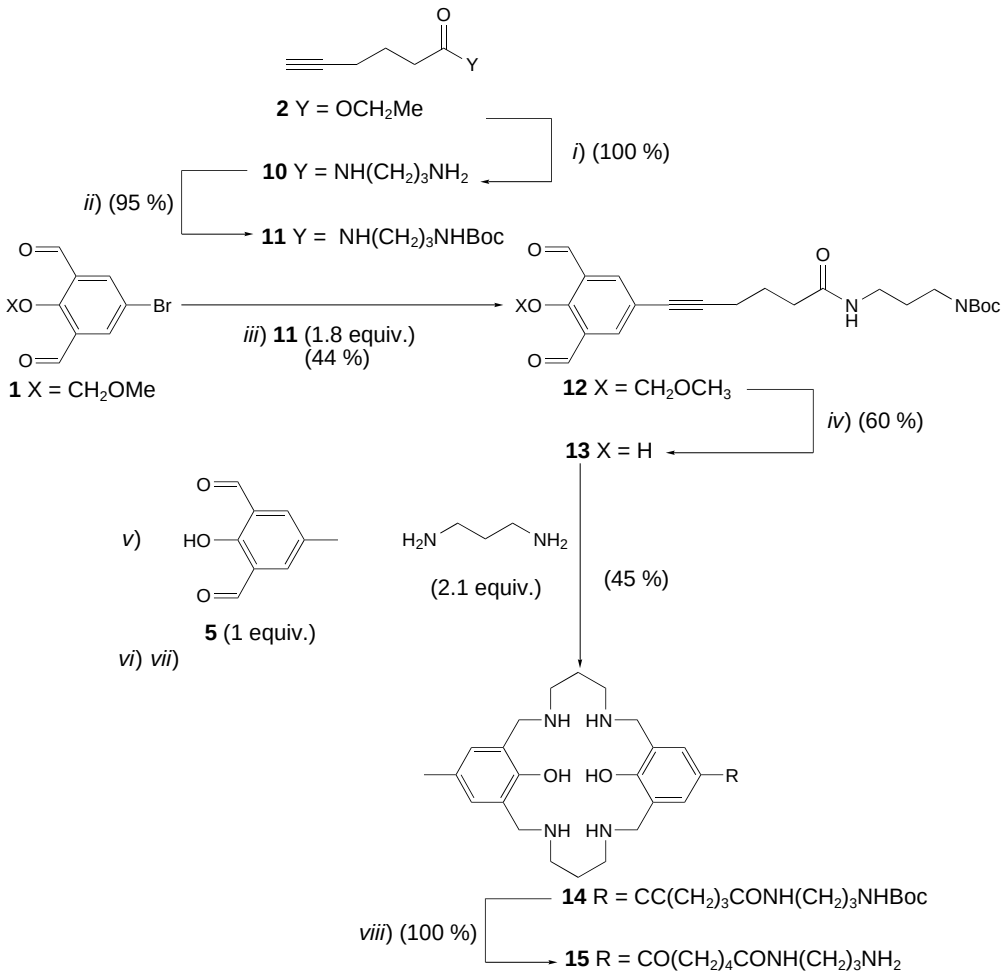
i) $Pd(PPh_3)_4$ (0.04 equiv.), CuI (0.05 equiv.), THF, piperidine, reflux. *ii*) NaI (1 equiv.), cat. HCl, acetone, 50°. *iii*) $Pb(AcO)_2 \cdot 3H_2O$ (1 equiv.), $Pb(NO_3)_2$ (1 equiv.), MeOH, DMF, reflux. *iv*) $NaBH_4$, MeOH, r.t. *v*) MeOH, H_2SO_4 (8M), r.t. *vi*) LiOH (20 equiv.), MeOH, H_2O, r.t. *vii*) MeOH, TFA (10%), r.t.

The coupling step was performed by means of Pd-catalyzed reaction between alkyne **2** and the MOM-protected bromophenol **1**. Deprotection of the coupled product **3** was possible only by addition of stoichiometric amounts of NaI under acidic conditions to afford phenol **4**. Template condensation with dialdehyde **5**, 1,3-diaminopropane, and Pb salts yielded a bright yellow precipitate that could not be solubilized [33]. Therefore, the suspension was reduced by $NaBH_4$ and subsequently acidified with H_2SO_4 to afford a mixture of the three free ligands, including the asymmetric compartmental ligand **6**. Reversed-phase HPLC (RP-HPLC) with H_2O/MeCN (TFA 0.1%) gradient elution allowed separation of all three compartmental ligands resulting from aldehyde cross-condensation.

The ^{1}H-NMR analysis of the isolated ligand revealed that the ethyl ester functionality had been *trans*-esterified to the corresponding methyl ester **6**. Furthermore, the alkyne functionality had been partially hydrated to afford a ketone. Therefore, **6** was saponified to **7**, which was fully hydrated to afford the ligand **8** in 33% overall isolated yield.

The synthesis of the ligand **15**, which contains a primary amine for conjugation purposes, was by a similar route (*Scheme 3*). Ester **2** reacted in neat 1,3-diaminopropane to afford **10**, which was Boc-protected to afford **11**. Coupling with **1** yielded, after deprotection, the dialdehyde **13**. Template cross-condensation with dialdehyde **5**, imine reduction, ligand separation, triple-bond hydration and Boc-deprotection provided the ligand **15** in 12% overall yield.

Scheme 3. *Synthesis of Ligand* **15**



i) Neat 1,3-diaminopropane, 60°. *ii*) $(Boc)_2O$ (1.5 equiv.), dioxane, sat. $NaHCO_3$, 0°. *iii*) $Pd(PPh_3)_4$ (0.04 equiv.), CuI (0.05 equiv.), THF, piperidine, reflux. *iv*) NaI (1 equiv.), cat. HCl, acetone, 50°. *v*) $Pb(AcO)_2 \cdot 3H_2O$ (1 equiv.), $Pb(NO_3)_2$ (1 equiv.), MeOH, DMF, reflux. *vi*) $NaBH_4$, MeOH, r.t. *vii*) MeOH, H_2SO_4 (8M), r.t. *viii*) TFA (10%), 60°.

Addition of two equivalents of $[VO(SO_4)] \cdot 3H_2O$ in MeOH in the presence of Et_3N to either hexadentate ligands **8** or **15** afforded the desired divanadyl haptens **9** and **16** quantitatively. To test the stability of these complexes under immunization conditions, **9** was incubated in the presence of an excess of bovine serum albumin (BSA) at 37° and pH 7. HPLC Analysis of the mixture after one week revealed that complex **9** is totally inert under these conditions.

Depending on which acid was used in electron-spray-ionization mass-spectral analysis, different molecular weights were obtained. For example, when formic acid was used, the molecular peak appeared at $m/z = 703.30$ (corresponding to $\mathbf{9} + HCOO^-$): upon addition of TFA, the molecular peak occurred at $m/z = 771.5$ ($\mathbf{9} + TFA$), suggesting a weakly coordinated carboxylic acid, in line with our design concept.

Recrystallization of **9** in MeOH afforded violet crystals suitable for X-ray-diffraction studies. The refined structure of **9** is depicted in *Fig. 2*. Most importantly, both vanadyl groups occupy eclipsed axial positions with a weakly bound bridging carboxylate in the *trans*-position. Although solution studies (*i.e.*, MS data) suggest that

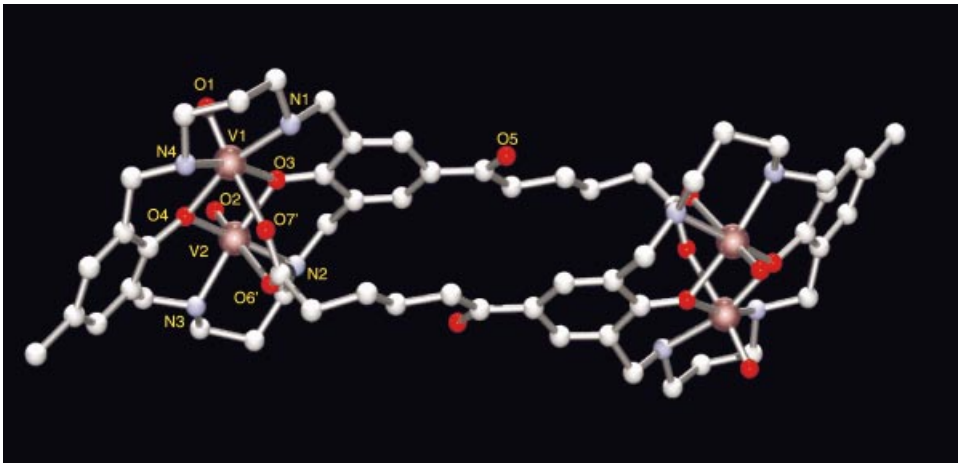


Fig. 2. *Molecular structure* **9**. H-Atoms and TFA counter ions have been omitted for clarity.

various carboxylates can occupy the bridging sites *trans* to both vanadyls, the solid-state structure reveals that the bridging carboxylate is provided intramolecularly. The structure data closely resemble those of a related sulfate-bridged compound recently reported by *Nag* and co-workers (*Table 1*) [34].

Coenzyme Synthesis and Characterization. As outlined above, the coenzyme should contain a pentadentate ligand structurally related to the hexadentate ligand **8** used for immunization. To tune the coenzyme reactivity, ligands having both N_4O or N_2O_3 donor sets were synthesized according the route outlined in *Scheme 4*[1]). *Schiff*-base condensation between dialdehyde **5** and two equivalents of either 1,3-diaminopropane

[1]) After initiation of this project, *Brooker* and co-workers reported their synthesis of ligand **17** using an acetamide- rather than a Boc-protecting group [35]. Interestingly, they succeeded in condensing this ligand with a 1-thio-2,6-dialdehyde to afford an asymmetric compartmental ligand. We had initially planned to use a similar approach to the synthesis of ligands **8** and **15**, but all of our attempts were unsuccessful.

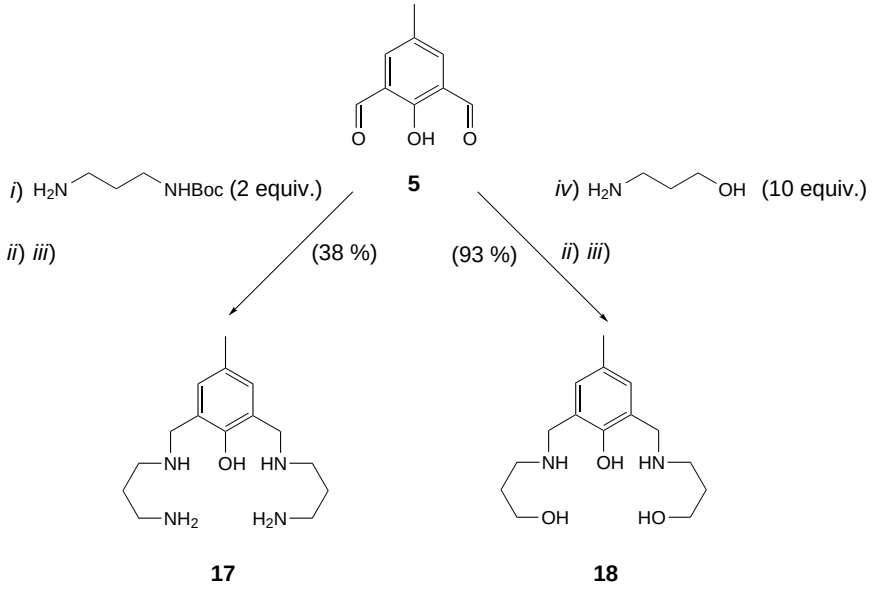
Table 1. *Selected Bond Lengths* [Å] *and Angles* [°] *for* **9**. Comparison with $[(VO)_2(\mu\text{-}SO_4)L(R^1)_2]$ [34]

	9	$[(VO)_2(\mu\text{-}SO_4)L(R^1)_2]$
V(1)–O(1)	1.600(5)	1.590(6)
V(1)–O(4)	2.027(6)	2.029(6)
V(1)–O(3)	2.067(6)	2.020(6)
V(1)–O(7′)	2.134(6)	2.173(6)
V(1)–V(2)	3.0511(15)	3.077(7)
V(2)–O(2)	1.579(5)	1.573(6)
V(2)–O(3)	2.047(6)	2.016(6)
V(2)–O(4)	2.050(6)	2.005(6)
V(2)–O(6′)	2.126(6)	2.180(6)
V(1)–N(1)	2.152(7)	2.091(7)
V(1)–N(4)	2.113(8)	2.093(8)
V(2)–N(2)	2.138(8)	2.103(8)
V(2)–N(3)	2.093(8)	2.132(7)
V(2)–O(3)–V(1)	95.7(3)	99.0(3)
V(1)–O(4)–V(2)	96.9(3)	99.7(3)
V(displ.)[a])	0.27[a])	0.264[a])

[a]) V(1) displacement towards the vanadyl O-atom from the plane N(1)N(4)O(3)O(4).

or 3-aminopropan-1-ol affords, after imine reduction, ligands **17** (after acidic Boc-deprotection) and **18** in 38% and 93% yield, respectively. Both ligands were obtained as TFA salts after RP-HLPC purification.

Scheme 4. *Synthesis of Pentadentate Ligands* **17** *and* **18**



i) MeOH, r.t. *ii*) $NaBH_4$ (10 equiv.), MeOH, r.t. *iii*) MeOH, TFA (10%) r.t. *iv*) benzene, reflux.

Screening of the coordination properties of both ligands **17** and **18** was performed in a 96-well plate with two equivalents of various metal salts (including Ni, Cu, Mn, Co, and Cr) and excess base. The color change and mass-spectral analysis suggested that coordination occurred in most cases. To acertain this, a preparative reaction was carried out between $NiCl_2 \cdot 6H_2O$, Et_3N, and ligand **17** in MeOH. Slow evaporation of the solvent afforded crystals suitable for X-ray analysis. The first crystals diffracted poorly and the resulting data set could not be fully refined, but the structure is instructive (*Fig. 3*,*a*). A second crop of crystals was obtained under very similar recrystallization conditions. These crystals, however, diffracted much better, and the anisotropically refined structure is depicted in *Fig. 3*,*b*. Although similar, these structures differ in one remarkable aspect. In the unrefined structure, which includes Cl^-, the N_4O donor set occupies the equatorial plane of the nearly C_s-symmetric bi-octahedral complex. In the refined structure of **19**, in which Cl^- is absent, the angle between the planes spanned by O(1)N(3)N(4)O(3) and O(1)N(2)N(1)O(4) is 64.15°. This suggests that the ligand is highly flexible, which should be a major advantage that would allow the coenzyme to adapt its geometry to the cavity within the antibody. Furthermore, the bridging TFA anions should readily be displaced by a more nucleophilic carboxylate provided by the protein in the catalytic cavity. Bond-length and -angle data for complex **19** are collected in *Table 2*.

Conclusion. – With the aim to produce catalytic antibodies that incorporate dinuclear coenzymes, we have designed mixed N,O compartmental ligands and studied their coordination properties. Macrocyclic ligands **8** and **15** that include the $H_2N_4O_2$ donor set react with vanadyl cations to yield octahedral complexes **9** and **16**, respectively, to be used as transition-state analogs (haptens) for the production of catalytic antibodies with C–H-bond-activation properties. In designing these tran-

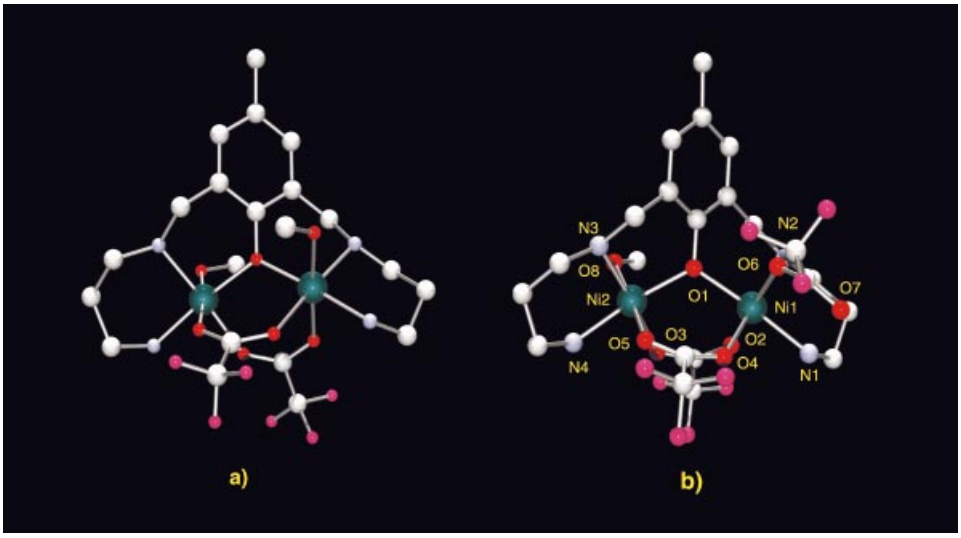


Fig. 3. *Molecular structures of* a) **19**·*$(CF_3COO^-)_2(MeOH)_2Cl^-$ and* b) **19**·*$(CF_3COO^-)_3(MeOH)$*. H-Atoms have been omitted for clarity.

Table 2. *Selected Bond Lengths* [Å] *and Angles* [°] *for* **19** · *(CF$_3$COO$^-$)$_3$(MeOH)*

N(1)–Ni(1)	2.079(3)
N(2)–Ni(1)	2.104(2)
N(3)–Ni(2)	2.090(2)
N(4)–Ni(2)	2.077(2)
Ni(1)–O(1)	2.027(2)
Ni(1)–O(2)	2.073(2)
Ni(1)–Ni(2)	3.520(5)
Ni(1)–O(4)	2.096(2)
Ni(1)–O(6)	2.107(2)
Ni(2)–O(1)	2.0281(19)
Ni(2)–O(5)	2.040(2)
Ni(2)–O(3)	2.097(2)
Ni(2)–O(8)	2.148(2)
Ni(1)–O(1)–Ni(2)	120.49(10)

sition-state analogs, several key features were taken into account including that *i*) the transition-state analog is inert and stable under physiological conditions, *ii*) the transition-state analog possesses two immunogenic aromatic moieties, *iii*) the transition-state analog contains a functional group that can be used to conjugate the hapten to a carrier protein, and *iv*) the transition-state analog possesses two 'free' coordination sites, which may elicit the interaction of a (bridging) carboxylate in the active site of the protein.

For use as coenzymes, compartmental pentadentate ligands **17** and **18** were synthesized. These react smoothly with catalytically active transition metals to yield dinuclear coordination compounds that are structurally related to the transition-state analog **9** but lack a bridging phenol moiety. The Ni complex of **17** (**19**) was characterized by X-ray crystal-structure analysis.

Conjugation of divanadyl complex **9** to a carrier protein and immunizations are underway in our laboratory.

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Experimental Part

General. 5-Bromo-2-hydroxybenzene-1,3-dicarbaldehyde [36] was prepared according to published procedures. All other starting materials were purchased from *Fluka AG* or *Aldrich* and were used without further purification. THF was dried over Na and distilled under N_2. RP-HPLC: *Hewlett-Packard 1100 Series LC* instrument; *C18-Vydac 201TP5* analytical column, with detection at 230 nm and isocratic elution (1.5 ml/min) with an appropriate mixture of mobile phases A (H_2O + 0.1% TFA) and B (MeCN/H_2O 1:1 + 0.1% TFA); HPLC-grade H_2O and MeCN were used. Prep. RP-HPLC: *Waters* prepak cartridge 500 g instrument with a flow rate of 100 ml/min, detection at 230 nm, and in gradient-elution mode (1%/min) with 10–20% less B as compared to the analytical conditions. UV/VIS: λ_{max}/nm (ε/dm^3/mol^{-1}/cm^{-1}); MeOH. IR: KBr disc, $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker AM-300* spectrometer; chemical shifts δ in ppm relative to residual solvent peak, coupling constants J in Hz. Mass spectra: EI = electron ionization; FAB = fast atom bombardment (matrix: nitrobenzylalcohol); ESI = electron-spray ionization (solvent: MeCN/H_2O 1:1 + 0.5% HCOOH, unless stated otherwise); the mass of only the molecular and the most-intense peaks are given. Elemental analyses were carried out at the ETH Zürich.

5-Bromo-2-(methoxymethoxy)benzene-1,3-dicarbaldehyde (**1**). To a soln. of 5-bromo-2-hydroxybenzene-1,3-dicarbaldehyde (22 g, 96 mmol) in DMF (250 ml), solid K_2CO_3 (53 g, 384 mmol) was added. The mixture was cooled to 0° and methylchloromethylether (10 g, 124 mmol) was added dropwise. The resulting mixture was stirred for 15 h at r.t. Addition of H_2O (300 ml) resulted in a precipitate, which was collected by filtration, washed (H_2O), and dried under vacuum. The crude product was purified by chromatography on silica gel (AcOEt/hexane 1:3) to give **1** as a white powder (17.3 g, 66%). ^{1}H-NMR ($CDCl_3$): 3.62 (*s*, Me); 5.21 (*s*, CH_2); 8.20 (*s*, 2 arom. H); 10.30 (*s*, 2 HCO). ^{13}C-NMR ($CDCl_3$): 59.04 (Me); 103.68 (CH_2); 138.02 (arom. C); 188.17 (HCO); 119.44, 132.60, 161.48 (3 arom. C). EI-MS: 272 (^{80}Br-**1**), 274 (^{82}Br-**1**) (M^+).

Ethyl Hex-5-ynoate (**2**). A mixture of hex-5-ynoic acid (4.87 g, 43.5 mmol) and conc. H_2SO_4 (0.5 ml) was refluxed in abs. EtOH (60 ml) for 15 h. Once cooled, a sat. soln. of $NaHCO_3$ was added, and the ester was extracted with CH_2Cl_2, washed (sat. NaCl soln.), dried ($MgSO_4$), and the solvent was evaporated. Distillation at 67° (13 mbar) gave the desired ester **2** as a colorless oil (4.70 g, 77%). ^{1}H-NMR ($CDCl_3$): 1.25 (*t*, *J* = 7.17, Me); 1.84 (*tt*, *J* = 7.35, 6.99, CH_2); 1.96 (*t*, *J* = 2.57, HC); 2.25 (*dt*, CCH_2); 2.43 (*t*, CH_2CO$_2$Et); 4.12 (*q*, CO$_2$CH_2Me). ^{13}C-NMR ($CDCl_3$): 14.87 (Me); 18.51, 24.32, 33.61 (3 CH_2); 61.00 (*C*H$_2$Me); 69.70 (HC); 83.95 (C); 173.69 (CO). EI-MS: 140 (M^+).

Ethyl 6-[3,5-Diformyl-4-(methoxymethoxy)phenyl]hex-5-ynoate (**3**). A round bottomed *Schlenk* flask was charged with **1** (2.0 g, 7.32 mmol), dry piperidine (50 ml), and THF (50 ml). The resulting soln. was flushed with Ar, and alkyne **2** (2.05 g, 14.6 mmol) was added. The catalyst, consisting of $Pd(PPh_3)_4$ (0.31 g, 0.29 mmol) and CuI (0.07 g, 0.37 mmol) was added as a solid. The resulting mixture was refluxed for 40 h. After cooling at r.t., the red soln. was poured into a 3-fold volume of ice/HCl (3:1) and immediately extracted with CH_2Cl_2. The org. layer was dried (Na_2SO_4) and the solvent evaporated. The crude product was purified by flash chromatography (FC; AcOEt/hexane 1:3) to give **3** as an orange solid (1.40 g, 58%). ^{1}H-NMR ($CDCl_3$): 1.28 (*t*, *J* = 7.17, Me); 1.94 (*tt*, *J* = 7.35, 6.99, $CH_2CH_2CH_2$); 2.50 (2*t*, CH_2CH$_2$CH_2); 3.60 (*s*, MeO); 4.16 (*q*, CO$_2$CH_2Me); 5.21 (*s*, OCH$_2$O); 8.09 (*s*, 2 arom. H); 10.31 (*s*, 2 HCO). ^{13}C-NMR ($CDCl_3$): 14.91 (Me); 59.03 (MeO); 19.46, 24.35, 33.76 (3 CH_2); 61.11 (CO$_2$*C*H$_2$Me); 103.67 (OCH$_2$O); 138.52 (arom. C); 189.04 (HCO); 79.37, 92.21 (C=C); 122.21, 131.07, 173.63 (3 arom. C). EI-MS: 332 (M^+).

Ethyl 6-(3,5-Diformyl-4-hydroxyphenyl)hex-5-ynoate (**4**). MOM-Protected arene **3** (1.30 g, 3.91 mmol) and NaI (0.59 g, 3.91 mmol) were dissolved in acetone (15 ml). After addition of HCl (1 drop, 1M) the mixture was heated at 50° overnight. After cooling at r.t., the mixture was acidified with HCl (1M), extracted with AcOEt, washed (H_2O), dried (Na_2SO_4), and evaporated to give phenol **4** as an orange solid (1.13 g, quant.). ^{1}H-NMR ($CDCl_3$): 1.25 (*t*, *J* = 7.17, Me); 1.94 (*tt*, *J* = 7.35, $CH_2CH_2CH_2$); 2.49 (*t*, CH_2CH$_2$CH_2); 4.16 (*q*, CO$_2$CH_2Me); 7.97 (*s*, 2 arom. H); 10.20 (*s*, 2 HCO); 11.66 (*s*, OH). ^{13}C-NMR ($CDCl_3$): 14.88 (Me); 19.45, 24.36, 33.81 (3 CH_2); 61.25 (CO$_2$*C*H$_2$Me); 138.55 (arom. C); 189.32 (HCO); 79.65, 92.80 (C≡C); 117.20, 131.03, 166.42 (3 arom. C). EI-MS: 288 (M^+). Anal. calc. for $C_{16}H_{16}O_5$ + MeCO$_2$CH$_2$Me: C 63.82, H 6.43; found: C 63.91, H 6.14.

Methyl 6-(25,26-Dihydroxy-23-methyl-3,7,15,19-tetraazatricyclo[19.3.1.1^{9,13}]hexacosa-1(24),9,11,13(26),21(25),22-hexaen-11-yl)hex-5-ynoate (**6**). Equimolar amounts of **5** (0.23 g, 1.39 mmol) and **4** (0.40 g, 1.39 mmol) were dissolved in MeOH (30 ml). A hot DMF soln. (10 ml) containing $Pb(OAc)_2 \cdot 3H_2O$ (0.53 g, 1.39 mmol) and $Pb(NO_3)_2$ (0.46 g, 1.39 mmol) was added with stirring, followed by 1,3-diaminopropane (0.23 ml, 2.77 mmol). The resulting mixture was refluxed for 15 h. After evaporation of the solvent, the yellow solid was washed (MeOH) and dried under vacuum. IR Analysis of the crude product revealed the presence of a C=N stretching band (1635) and the absence of the CHO stretching frequency (1685). This insoluble mixture of the three Pb complexes was suspended in MeOH (100 ml) without purification to be reduced by portionwise addition of $NaBH_4$ (0.53 g, 13.9 mmol). Stirring was continued overnight and the soln. was filtered to remove undissolved material. The light yellow filtrate was reduced in volume to 10 ml and diluted with H_2O (100 ml). The soln. was then acidified with cold H_2SO_4 (8M). The precipitated $PbSO_4$ was removed by filtration and washed with cold H_2O. The pH of the filtrate was adjusted with aq. NH_3 (25%) to 10. The aq. soln. was extracted with $CHCl_3$, dried (Na_2SO_4), and, finally, evaporated to dryness to give a mixture of the three ligands (0.35 g) (*i.e.*: $H_2L(R^1)_2$/$H_2LR^1R^2$ (**6**)/$H_2L(R^2)_2$, where R^1 = Me, R^2 = CC(CH$_2$)$_3$CO$_2$Me, and with a statistical ratio of 0.25:0.50:0.25). The asymmetric ligand **6** was isolated as a white solid (0.21 g, 57% yield) by prep. RP-HPLC (60% B). ^{1}H-NMR (CD_3OD): 1.73 (*tt*, *J* = 7.35, $CH_2CH_2CH_2$); 2.00 (*tt*, NCH_2CH_2); 2.14 (*s*, Ph*Me*); 2.32, 2.37 (2*t*, 2 CH_2); 2.97 (*t*, 4 NCH_2); 3.55 (*s*, Me); 4.12 (*s*, 2 PhCH_2); 4.13 (*s*, 2 PhCH_2); 7.09 (*s*, 2 arom. H); 7.32 (*s*, 2 arom. H). ^{13}C-NMR (CD_3OD): 20.23 (PhCH_3); 19.25, 24.70, 25.06, 33.52, 44.84, 44.91, 46.99, 47.37 (8 CH_2); 52.05, 135.26, 137.81 (3 CH); 80.54, 89.80, 118.87, 121.60, 121.80, 132.98, 153.69, 155.86, 175.38 (9 C). ESI-MS: 523.25 ([M + 1]$^+$).

6-(25,26-Dihydroxy-23-methyl-3,7,15,19-tetraazatricyclo[19.3.1.1^{9,13}]hexacosa-1(24),9,11,13(26),21(25),22-hexaen-11-yl)-hex-5-ynoic Acid (**7**). Saponification of **6** (70 mg, 0.13 mmol) was performed in MeOH (1 ml)

with LiOH (60 mg, 2.68 mmol) dissolved in H_2O (0.5 ml). After stirring 1 h at r.t., the suspension was filtered, and the filtrate was treated with TFA (10%) and evaporated to dryness to give **7** as a pink solid (66 mg, quantitative yield). ^{1}H-NMR (CD_3OD): 1.66 (*tt*, *J* = 7.35, $CH_2CH_2CH_2$); 1.95 (*tt*, 2 NCH_2CH_2); 2.07 (*s*, Ph*Me*); 2.28 (2*t*, 2 CH_2); 2.90 (*t*, 4 NCH_2); 4.06 (*s*, 2 $PhCH_2$); 4.08 (*s*, 2 $PhCH_2$); 7.03 (*s*, 2 arom. H); 7.26 (*s*, 2 arom. H). ^{13}C-NMR (CD_3OD): 20.18 (Me); 19.28, 24.62, 25.00, 33.73, 44.76, 44.82, 47.00, 47.37 (8 CH_2); 135.24, 137.82 (2 CH); 80.52, 89.68, 118.78, 121.49, 121.71, 132.83, 153.64, 155.79 (8 C); 177.44 (COOH). ESI-MS: 509.51 ($[M+1]^+$).

6-(25,26-Dihydroxy-23-methyl-3,7,15,19-tetraazatricyclo[19.3.1.1^{9,13}]hexacosa-1(24),9,11,13(26),21(25),22-hexaen-11-yl)-6-oxohexanoic Acid (**8**). Acidic hydration of **7** (66 mg, 0.13 mmol) in a MeOH soln. (10% TFA) for 2 d at r.t. produced **8** as a white solid (68 mg, quant.). ^{1}H-NMR (CD_3OD): 1.49 (*m*, $COCH_2(CH_2)_2CH_2CO$); 1.94 (*quint.*, *J* = 7.18, 2 $NCH_2CH_2CH_2N$); 2.02 (*s*, Ph*Me*); 2.14 (*t*, *J* = 6.92, $CO(CH_2)_3CH_2CO$); 2.76 (*t*, *J* = 6.80, $COCH_2(CH_2)_3CO$); 2.88 (*t*, *J* = 6.52, 2 $NCH_2(CH_2)_2N$); 2.90 (*t*, *J* = 6.50, 2 $N(CH_2)_2CH_2N$); 4.04 (*s*, 2 $PhCH_2$); 4.11 (*s*, 2 $PhCH_2$); 6.99 (*s*, 2 arom. H); 7.83 (*s*, 2 arom. H). ^{13}C-NMR (CD_3OD): 19.22 (Me); 23.74, 24.03, 24.66, 33.91, 37.42, 43.71, 43.80, 46.54, 47.36 (9 CH_2); 133.88, 134.14 (2 CH); 112.79, 115.70, 118.61, 119.86, 120.55, 121.52 (6 C); 177.44 (COOH); 199.20 (CO). ESI-MS: 527.52 ($[M+1]^+$).

*[(VO)$_2$(N$_4$O$_2$-**8**)]$^{2+}$* (**9**). Compound **8** (100 mg, 0.19 mmol) was dissolved in MeOH (5 ml), Et_3N (130 µl, 0.95 mmol) was added, a soln. of $VOSO_4 \cdot 3H_2O$ (83 mg, 0.40 mmol) in MeOH (4 ml) was added dropwise, and the resulting mixture was refluxed overnight. After filtration, the soln. was evaporated to dryness to yield a pale green solid **9**, which was washed with cold MeOH. Recrystallization from MeOH produced crystals suitable for X-ray crystallography (86 mg, 60% yield). UV/VIS: 280 (8800); 520 (70); 661 (80). IR: 3223*w* ($\tilde{\nu}$(NH)), 1600*m* (δ(NH)), 1168*s*, 1113*s* ($\tilde{\nu}$(S−O)); 958*s* ($\tilde{\nu}$(V=O)). ESI-MS: 703.30 ($[M+HCOO^-]^+$). Anal. calc. for $C_{29}H_{40}N_4O_7V_2 \cdot 2\ CF_3COO^- \cdot CF_3COOH \cdot 8.5\ H_2O$: C 36.50, H 5.08, N 4.86; found: C 36.20, H 4.60, N 5.29.

N-*(3-Aminopropyl)hex-5-ynamide* (**10**). Compound **2** (2 g, 14.3 mmol) was heated for 48 h at 60° in neat 1,3-diaminopropane (50 ml). After evaporation of the excess 1,3-diaminopropane, the residue was dried overnight under high vacuum. Amide **10** was obtained as a yellow oil (2.40 g, quant.). ^{1}H-NMR ($CDCl_3$): 1.56 (*tt*, *J* = 6.61, $HNCH_2CH_2$); 1.76 (*tt*, *J* = 7.35, 6.98, CCH_2CH_2); 1.92 (*t*, *J* = 2.57, HC); 2.10 (br. *s*, NH_2); 2.16 (*dt*, CCH_2); 2.23 (*t*, CH_2CO); 2.70 (*t*, *J* = 6.25, CH_2NH_2); 3.25 (*dt*, $HNCH_2$); 6.90 (br. *t*, NH). ^{13}C-NMR ($CDCl_3$): 18.39, 24.81, 32.68, 35.58, 38.05, 40.28 (6 CH_2); 69.61 (HC); 84.08 (C); 172.90 (CO). EI-MS: 169 ($[M+1]^+$).

tert-*Butyl [3-(Hex-5-ynoylamino)propyl]carbamate* (**11**). A sat. soln. of $NaHCO_3$ (50 ml) was added to a soln. of **10** (2.40 g, 14 mmol) in dioxane (50 ml). The mixture was cooled to 0° and $(Boc)_2O$ (4.67 g, 21 mmol) in dioxane (20 ml) was slowly added. The resulting soln. was stirred overnight at r.t. Extraction with AcOEt, followed by washing (H_2O) and drying ($MgSO_4$), afforded **11** as a yellow oil (3.65 g, 95% yield). ^{1}H-NMR ($CDCl_3$): 1.39 (*s*, 3 Me); 1.57 (*quint.*, *J* = 6.25, $HNCH_2CH_2$); 1.82 (*quint.*, *J* = 7.35, CCH_2CH_2); 1.94 (*t*, *J* = 2.70, HC); 2.21 (*dt*, *J* = 2.70, 6.90, CCH_2); 2.29 (*t*, *J* = 7.35, CH_2CO); 3.11 (*q*, *J* = 6.25, CH_2NHBoc); 3.25 (*dt*, *J* = 6.25, $HNCH_2$); 5.11 (br. *s*, NHBoc); 6.46 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 28.98 (Me); 18.47, 24.84, 30.80, 35.71, 36.47, 37.65 (6 CH_2); 69.72 (HC); 79.80 (C (Boc)); 85.76 (C); 147.32 (CO_2 (Boc)); 173.23 (CO). EI-MS: 269 ($[M+1]^+$).

tert-*Butyl (3-{-[3,5-Diformyl-4-(methoxymethoxy)phenyl]hex-5-ynoylamino}propyl)carbamate* (**12**). As for compound **3**. Compound **1** (2 g, 7.32 mmol) was reacted with **11** (3.53 g, 13 mmol) in the presence of $Pd(PPh_3)_4$ (0.31 g, 0.30 mmol) and CuI (0.07 g, 0.37 mmol). After workup, the resulting solid was subjected to FC (CH_2Cl_2/MeOH 20 :1) to afford **12** as yellow oil (1.50 g, 44% yield). ^{1}H-NMR ($CDCl_3$): 1.31 (*s*, 3 Me); 1.52 (*quint.*, *J* = 6.25, 5.88, $HNCH_2CH_2$); 1.84 (*quint.*, *J* = 7.35, 6.98, CCH_2CH_2); 2.28 (*t*, CH_2CO); 2.38 (*t*, CCH_2); 3.05 (*q*, CH_2NHBoc); 3.19 (*q*, $HNCH_2$); 3.49 (*s*, MeO); 5.11 (*s*, OCH_2O); 5.29 (*t*, NHBoc); 6.78 (*t*, *J* = 5.15, NHCO); 7.93 (*s*, 2 arom. H); 10.18 (*s*, 2 HCO). ^{13}C-NMR ($CDCl_3$): 28.98 (Me (Boc)); 58.78 (MeO); 19.35, 24.86, 30.62, 35.73, 36.46, 37.61 (6 CH_2); 103.46 (OCH_2O); 138.21 (arom. HC); 188.90 (HCO); 79.07, 92.32 (C=C); 79.60 (C (Boc)); 121.97, 130.84, 161.29 (3 arom. C); 157.11 (CO_2 (Boc)); 173.11 (CO). FAB-MS: 461 ($[M+1]^+$).

tert-*Butyl {3-[6-(3,5-Diformyl-4-hydroxyphenyl)hex-5-ynoylamino]propyl}-carbamate* (**13**). As for **4**, with **12** (0.50 g, 1.08 mmol) and NaI (0.16 g, 1.08 mmol) in acetone (40 ml). Phenol **13** was obtained as an orange oil (0.27 g, 60%). ^{1}H-NMR ($CDCl_3$): 1.38 (*s*, 3 Me); 1.58 (*quint.*, *J* = 6.25, 6.62, $HNCH_2CH_2$); 1.93 (*quint.*, *J* = 7.35, 6.99, CCH_2CH_2); 2.34 (*t*, CH_2CO); 2.43 (*t*, CCH_2); 3.13 (*q*, CH_2NHBoc); 3.26 (*q*, $HNCH_2$); 5.11 (br. *s*, NHBoc); 6.62 (br. *s*, NHCO); 7.93 (*s*, 2 arom. H); 10.15 (*s*, 2 HCO); 11.62 (*s*, OH). ^{13}C-NMR ($CDCl_3$): 28.92 (Me); 19.37, 25.00, 30.69, 35.86, 36.49, 37.65 (6 CH_2); 140.84 (arom. HC); 192.22 (HCO); 78.94, 79.84, 90.69, 116.90, 123.61, 157.28, 171.70, 173.26 (8 C). FAB-MS: 417.

tert-*Butyl {3-[6-(25,26-Dihydroxy-23-methyl-3,7,15,19-tetraazatricyclo[19.3.1.1^{9,13}]hexacosa-1(24),9,11,13(26),21(25),22-hexaen-11-yl)-hex-5-ynoylamino]propyl}carbamate* (**14**). As for **6**, with **12** (0.27 g, 0.65 mmol)

and **5** (0.11 g, 0.65 mmol) in MeOH (12 ml), reacted with a hot DMF soln. (4 ml) of $Pb(OAc)_2 \cdot 3H_2O$ (0.24 g, 0.65 mmol) and $Pb(NO_3)_2$ (0.21 g, 0.65 mmol), and 1,3-diaminopropane (0.12 ml, 1.43 mmol). Ligand **14** was isolated from the mixture (0.35 g) of three ligands (*i.e.:* $H_2L(R^1)_2$/$H_2LR^1R^3$ (**14**)/$H_2L(R^3)_2$, where R^1 = Me and $R^3 = CC(CH_2)_3CONH(CH_2)_3NHBoc$ and with a statistical ratio of 0.25/0.50/0.25) by prep. RP-HPLC (60% B) (0.1 g, 45% yield). ^{1}H-NMR (CD_3OD): 1.31 (*s*, 3 Me); 1.51 (*quint.*, J = 6.62, 6.98, $HNCH_2CH_2CH_2NHBoc$); 2.00 (*quint.*, J = 7.35, 6.98, 2 $HNCH_2CH_2CH_2NH$); 2.00 (*quint.*, J = 7.35, 6.99, CCH_2CH_2); 2.12 (*s*, Me); 2.23 (*t*, CH_2CO); 2.29 (*t*, CCH_2); 2.82 (*t*, CH_2NHBoc); 2.96 (*t*, 2 $HNCH_2CH_2CH_2NH$); 3.08 (*t*, $HNCH_2$); 4.11 (*s*, 2 $PhCH_2$); 4.12 (*s*, 2 $PhCH_2$); 7.08 (*s*, 2 arom. H); 7.31 (*s*, 2 arom. H). ^{13}C-NMR (CD_3OD): 20.32, 28.85 (2 Me); 24.67, 26.82, 29.34, 37.46, 37.56, 38.19, 38.59, 45.22, 45.37, 47.39, 47.72 (11 CH_2); 135.53, 135.74 (2 CH); 79.65, 79.93, 92.07, 114.76, 117.36, 120.92, 121.46, 121.76, 131.70, 133.34, 153.88 (11 C); 157.12, 177.18 (2 CO). ESI-MS: 665.41 ($[M+1]^+$).

N-*(3-Aminopropyl)-6-(25,26-Dihydroxy-23-methyl-3,7,15,19-tetraazatricyclo[19.3.1.1^{9,13}]hexacosa-1(24), 9,11,13(26),21(25),22-hexaen-11-yl)-6-oxohexanamide* (**15**). Alkyne **14** (100 mg, 0.15 mmol) was stirred overnight in aq. TFA (10%, 5 ml) at 60°; quantitative hydration afforded **15** (88 mg). ^{1}H-NMR (CD_3OD): 1.77 (br. *quint.*, $COCH_2(CH_2)_2CH_2CO$); 1.94 (*quint.*, J = 6.95, $HNCH_2CH_2CH_2NH_2$); 2.21 – 2.25 (*m*, 2 $HNCH_2CH_2CH_2NH$); 2.31 (*s*, Me); 2.35 (*t*, J = 6.70, CH_2CO); 3.05 (*tt*, J = 7.46, 2 CH_2NH_2); 3.12 – 3.22 (*m*, 2 $HNCH_2CH_2CH_2NH$, CH_2CO); 4.31 (*s*, 2 $PhCH_2$); 4.43 (*s*, 2 $PhCH_2$); 7.27 (*s*, 2 arom. H); 8.17 (*s*, 2 arom. H). ^{13}C-NMR (CD_3OD): 20.51 (Me); 24.81, 25.00, 26.78, 29.02, 37.04, 37.14, 38.09, 38.49, 45.21, 45.12, 47.36, 47.63 (12 CH_2); 135.52, 135.72 (2 CH); 114.90, 117.73, 120.56, 121.50, 121.87, 131.75, 133.24, 153.97 (8 C); 177.15, 199.85 (2 CO). ESI-MS: 583.21 ($[M+1]^+$).

*[(VO)$_2$(N$_4$O$_2$-**15**)]$^{2+}$* (**16**). The oxidovanadium complex **16** was obtained as for **9**: **15** (50 mg, 0.08 mmol) in MeOH (3 ml) with Et_3N (60 µl, 0.43 mmol) was treated with $VOSO_4 \cdot 3\,H_2O$ (37 mg, 0.17 mmol) in MeOH (3 ml) to yield **16** as a pale green solid (52 mg, 75%). ESI-MS: 811.14 ($[M+1]^+$).

2,6-Bis[[(3-aminopropyl)amino]methyl]-4-methylphenol (**17**). Compound **5** (0.90 g, 5.50 mmol) was dissolved in MeOH (50 ml) and charged with *N*-Boc-1,3-diaminopropane (2 ml, 11.5 mmol) in MeOH (10 ml). The mixture was stirred at r.t. for 2 d. The soln. was diluted with MeOH (50 ml) and the product was reduced with $NaBH_4$ (2.10 g, 55 mmol). The mixture was stirred for 4 h and evaporated to dryness. The product was deprotected by reaction in MeOH (10 ml) and aq. TFA (50 ml, 10%) overnight. The crude product was purified by prep. RP-HPLC (20% B) to afford **17** as the TFA salt (1.54 g, 38%). ^{1}H-NMR (CD_3OD): 1.93 (*quint.*, J = 7.72, 2 $CH_2CH_2CH_2$); 2.09 (*s*, Me); 2.85 (*t*, 2 NH_2CH_2); 2.98 (*t*, 2 CH_2NH); 4.05 (*s*, 2 $PhCH_2$); 7.07 (*s*, 2 arom. H). ^{13}C-NMR (CD_3OD): 20.26 (Me); 25.22, 37.85, 45.59, 47.88 (4 CH_2); 135.04 (CH); 121.73, 132.41, 153.61 (3 arom. C). ESI-MS: 281.25 ($[M+1]^+$). Anal. calc. for $C_{15}H_{28}N_4O \cdot 4\,CF_3COOH$: C 37.51, H 4.38, N 7.61; found: C 37.61, H 4.23, N 7.40.

2,6-Bis{[(3-hydroxypropyl)amino]methyl}-4-methylphenol (**18**). A soln. of **5** (1 g, 6.1 mmol) and 3-aminopropan-1-ol (4.6 ml, 61 mmol) in benzene (60 ml) was refluxed overnight with a *Dean-Stark*-trap system. Evaporation of benzene afforded a yellow oil, which was redissolved in MeOH (60 ml) and reduced with $NaBH_4$ (2.3 g, 61 mmol). Acidification with TFA (10%, 5 ml) followed by evaporation under vacuum afforded the TFA salt of **18** as a yellow oil. The crude product was purified by prep. RP-HPLC (20% B) to afford **18** as a white powder (2.9 g, 93%). ^{1}H-NMR (CD_3OD): 1.78. (*quint.*, 2 $CH_2CH_2CH_2$); 2.16 (*s*, Me), 3.04 (*t*, J = 7.15, 2 $NHCH_2$); 3.55 (*t*, J = 5.70, 2 CH_2OH); 4.10 (*s*, 2 $PhCH_2$); 7.13 (*s*, 2 arom. H). ^{13}C-NMR (CD_3OD): 20.30 (Me); 29.30, 47.19, 47.85, 60.64 (4 CH_2); 134.84 (CH); 121.78, 132.42, 153.60 (3 arom. C). ESI-MS: 283.34 ($[M+1]^+$). Anal. calc. for $C_{15}H_{26}N_2O_3 \cdot 2\,CF_3COOH$: C 44.71, H 5.53, N 5.49; found: C 45.01, H 5.45, N 5.43.

*[Ni$_2$(N$_4$O-**17**)]$^{3+}$* (**19**). To a soln. of **17** · 4 TFA (100 mg, 0.14 mmol) in 2 ml of MeOH was added a soln. of $NiCl_2 \cdot 6H_2O$ (65 mg, 0.28 mmol) in 2 ml of MeOH. After addition of Et_3N (200 µl, 1.4 mmol), the color of the soln. changed from dark green to pale blue. The resulting soln. was allowed to stand at r.t. for 1 week to produce blue crystals suitable for X-ray crystallography (107 mg, 85% yield). UV/VIS: 293 (2110), 243 (3240), 223 (2990), 605 (40). IR: 2943*s*, 2605*s*, 1480*s*, 1671*s*, 1708*s*, 1445*m*. ESI-MS (i-PrOH): 621 ($[Ni_2(N_4O$-**17**$)(CF_3COO)_2]^+$), 567 ($[Ni_2(N_4O$-**17**$))(CF_3COO^-)((CH_3)_2CHO^-)]^+$).

X-Ray Crystallography. Suitable crystals of **9** were grown from MeOH as violet plates. Intensity data were collected at 153 K on a *Stoe Image Plate Diffraction* system [37]: MoK_α-graphite monochromated radiation; image-plate distance 70 mm; ϕ-oscillation scans 0 – 191°; step $\Delta\phi$ = 1.0°; 2θ range 3.27 – 52.1°; $d_{max} - d_{min}$ = 12.45 – 0.81 Å. The structure was solved by direct methods with the program SHELXS-97 [38]. The refinement and all further calculations were carried out with SHELXL-97 [39]. The H-atoms were included in calculated positions and treated as riding atoms according to SHELXL default parameters. The non-H-atoms were refined anisotropically by means of weighted full-matrix least-squares analysis of F^2. The crystal was a twin and diffracted poorly to a maximum of 40° in 2θ and the average $I/\sigma(I)$ was only 1.9. After integration of the image-

plate data, the reflections were treated with the program TWINXLI [40], which indicated that at least 30% of the data were overlapped; these data were eliminated. The least-squares refinement with SHELXL-97 was then carried out with HKLF 5 and BASF (refined value 0.0967) to give a final R^1 value of 0.089 for 2998 observed reflections.

A blue crystal of compound **19** was mounted on a *Stoe Imaging Plate Diffractometer System* (*Stoe & Cie*, 1995) equipped with a one-circle φ goniometer and a graphite-monochromator. Data collection was performed at $-120°$: MoK_α radiation ($\lambda = 0.71073$ Å); 200 exposures (3 min per exposure); image-plate distance 70 mm; $0 < \varphi < 200°$, with the crystal oscillating through 1° in φ; $D_{min} - D_{max}$ 12.45 – 0.81 Å. The structure was solved by direct methods with the program SHELXS-97 [38] and refined by full-matrix least-squares analysis on F^2 with

Table 3. *Crystal Data for* **9** *and* **19**

	9	**19**
Chemical formula	$C_{72}H_{118}F_6N_8O_{28}V_4$ $(C_{58}H_{78}N_8O_{14}V_4(CF_3COO^-)_2 \cdot 10\ MeOH)$	$C_{22}H_{31}F_9N_4Ni_2O_8$
Formula weight	1861.50	767.93
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$C2/c$
8.2731(5)	36.848(3)	
b [Å]	21.3131(16)	9.1058(5)
c [Å]	24.8655(19)	17.5556(13)
α [°]	90	90
β [°]	101.869	90.163(9)(8)
γ [°]	90	90
V [Å^3]	4290.7(5)	5890.5(7)
Z	2	8
μ(MoK_α)/mm^{-1}	0.516	1.387
T [K]	293(2)	153(2)
Reflections measured	20159	22573
Unique reflections	20159	5483
R(int)	0.0000	0.740
R_1, wR_2 ($I > 2\sigma(I)$)	0.0890, 0.1842	0.0386, 0.0931
R_1, wR_2 (all data)	0.3310, 02549	0.0534, 0.0976

SHELXL-97 [41]. The H-atoms were included in calculated positions and treated as riding atoms according to SHELXL-97 default parameters. The figures were drawn with PLATON 99 [42].

Illustrative Examples of Screening for Coordination Properties of **17** *and* **18**. In one well of a 96-well plate, a soln. of $Cu_2(AcO)_2 \cdot H_2O$ (14 mg, 7.13 μmol) in EtOH (200 μl) was added to a soln. (EtOH, 100 μl) of **17** (1 mg, 3.57 μmol) and Et_3N (1.8M in EtOH, 6 μl, 10.7 μmol). The resulting mixture was stirred 1 h at r.t. and subjected to ESI-MS analysis. ESI-MS (MeOH/i-PrOH): 403 ($[M + Cu_2 - H_4]^+$), 405 ($[M + Cu_2 - H_2]^+$).

A similar procedure was used with **18** (1 mg, 3.54 μmol) in EtOH (100 μl), Et_3N (1.8M in EtOH, 10 μl, 17.8 μmol) and $Cu_2(AcO)_2 \cdot H_2O$ (14 mg, 7.09 μmol) in EtOH (200 μl). ESI-MS (MeOH/i-PrOH): 451 ($[M + Cu_2 + EtO - H_3]^+$), 453 ($[M + Cu_2 + EtO - H]^+$).

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