90. Synthesis of Vitamin B_{12} Derivatives with a Peripheral Metal Binding Site

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The synthesis and structural characterization of the vitamin B_{12} derivatives **9** and **10** equipped with a peripheral EDTA (ethylenediaminetetraacetic acid) binding site is described. It is based on the condensation of an activated ester of cobester-*c*-acid with ethane-1,2-diamine or 2-aminoethanol followed by acylation of the resulting amines with the monoanhydride **8** of EDTA. The title compounds **9** and **10** can be used as modifiers for metal oxide semiconductor electrodes and are potential precursors for the synthesis of bimetallic, supramolecular catalysts.

Introduction. – Vitamin B_{12} and related macrocyclic cobalt complexes exhibit a unique set of reactivities that can be summarized by *Eqns. 1–3*. The sequence of reactions *1* → *2* → *3* reveals an important application of vitamin B_{12}, that is the catalysis of the reductive generation of C-centered radicals from alkyl halides under mild reductive conditions (possibly in the presence of visible light). The radical R$^{\bullet}$ can undergo synthetically useful inter- or intramolecular follow-up reactions, such as C,C-bond formation or rearrangements [1–3].

$$Co^{II} + e^- \rightarrow Co^{I} \quad E^{\circ}_{(1)} \tag{1}$$

$$Co^{I} + RX \rightarrow Co^{III}\text{-}R + X^- \tag{2}$$

$$Co^{III}\text{-}R + h\nu \text{ (or } e^-\text{, or } \Delta) \rightarrow Co^{II} + R^{\bullet} \text{ (or } R^-) \tag{3}$$

The vitamin-B_{12}-mediated catalysis is usually carried out in a photo-electrochemical cell with the catalyst dissolved homogeneously in the reaction mixture. However, the electro- and photochemical steps as well as the workup of the reaction mixture would be more efficient if the reaction could be performed on an illuminated transparent electrode with a vitamin-B_{12}-functionalyzed surface. Moreover, the same modified electrodes of smaller size could be used as alkyl-halide sensor, since the reactions of *Eqns. 1* and *2* can be triggered by an external electro- or photochemical stimulus [4].

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The radicals produced according to *Eqn. 3* are 'free radicals', as it is the case with all other methods of C-radical production known today. The radicals tend to diffuse away from the generator site several tens or even hundreds of Ångstrom (depending on the rate of the followup reaction and on their diffusion coefficient). Thus, all chiral information from the corrine macrocycle is lost, when the C,C-bond formation or the radical rearrangement takes place. The preferential addition of an achiral radical to one of the enantiotopic sides of a C=C bond, or the enantioselective addition of a prochiral radical (with the center of prochirality at the radical-bearing C-atom) to a C=C bond with two homotopic sides would require an optically active catalyst that is in tight contact with at least one of the reaction partners in the moment of C,C-bond formation. This problem has been tackled so far mainly by derivatization of one of the reagents with a stoichiometric amount of an optically active auxiliary that is cleaved off afterwards. Another possibility consists in the transient complexation of the olefinic radical acceptor with a chiral *Lewis* acid. This principle was borrowed from the field of enantioselective cycloaddition and proved to be valuable for the introduction of some enantioselectivity in free radical C,C-bond forming reactions [5–7]. Catalytic conditions (*i.e.* substoichiometric amounts of the optically active *Lewis* acid) may be feasible if the rate of radical attack is increased upon complexation and if the complexation constant is decreased upon addition of the radical. Another approach towards enantioselective radical reactions evolves from studies in the field of supramolecular, nonenzymatic catalysis of radical rearrangements induced by vitamin B_{12} derivatives. Thus, *Keese* and coworkers have presented evidence that a radical can be kept close to the environment of a vitamin B_{12} derivative for a prolonged period of time, if the cobalt complex and the radical are provided with functional groups that allow for association by hydrophobic interactions and H-bonding [8] [9].

We present here the synthesis of the two cobyrinic acid derivatives **9** and **10** which are equipped with a peripheral EDTA (ethylenediaminetetraacetic acid) chelating unit. One application of these compounds consists in the coordination of a solution metal ion (M^+) by the pentadentate EDTA moiety, preferentially an electroactive transition metal with at least one labile coordination site, *e.g.* Ru^{II}. The Ru moiety is supposed to bind olefins or amines at the sixth coordination site depending on its oxidation state II or III, respectively. As in the case presented by *Keese* and coworkers, such a molecular device combines a radical generator site and a substrate coordination site; however, the affinity of the binding site would be electrochemically adjustable (*Fig., a*). A hypothetical reaction sequence would include *i*) binding of the radical precursor to Co upon polarization of the electrode in the range of $E^0_{(1)}$ (*Eqns. 1* and *2*), *ii*) binding of the reaction partner to Ru upon polarization of the electrode on the $Ru^{III}/^{II}$ redox couple, *iii*) radical generation according to *Eqn. 3*, and *iv*) expulsion of the product by a reverse electrochemical stimulus on the $Ru^{III}/^{II}$ redox couple. This type of supramolecular catalysis is under current investigation.

Compounds **9** and **10** have also been used for the modification of transparent metal oxide semiconductor electrodes, such as nanocrystalline thin film TiO_2 (*Fig. b*). The three free COOH groups are able to chelate up to three TiO_2 centers resulting in a stable anchoring of the corrine on the nanoparticle surface. Preliminary results of this application have been reported [10] [11].

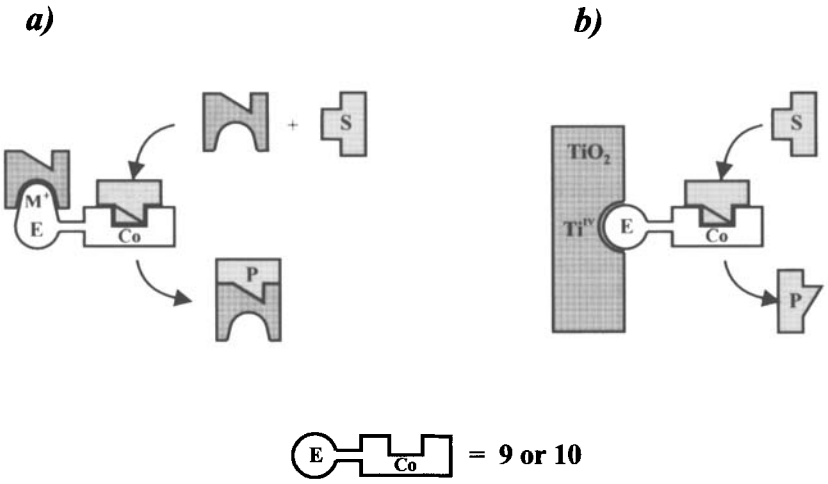


Figure. *Possible applications of the vitamin B_{12} derivatives* **9** *and* **10** *carrying a peripheral metal coordination site:* a) *as a precursor for bimetallic reduction catalysts with radical generation site* (Co) *and an electroactive metal ion that coordinates a quencher of C-radicals* (M^+); b) *for surface modification of transparent metal oxide semiconductor electrodes,* e.g., *nanocrystalline TiO_2 films and the preparation photo-electrocatalytic electrodes* [10] [11]. S = substrate, P = product, E = EDTA subunit; Co = vitamin B_{12} subunit.

Results and Discussion. – As the cobyrinates mimic well the photo- and electrochemistry of vitamin B_{12} (except for axial coordination chemistry), and as they are generally easier to handle and derivatize than the parent compound, we used cobester-*c*-acid (= cob(III)yrinic acid *a, b, d, e, f, g*-hexamethyl ester) as a vitamin B_{12} subunit. The carboxylic *c*-side chain was covalently linked to EDTA using 2-aminoethanol or ethane-1,2-diamine as linker. The (*tert*-butoxy)carbonyl(Boc)-protected linker **1** and **2** were obtained by standard protecting group chemistry in excellent yield.

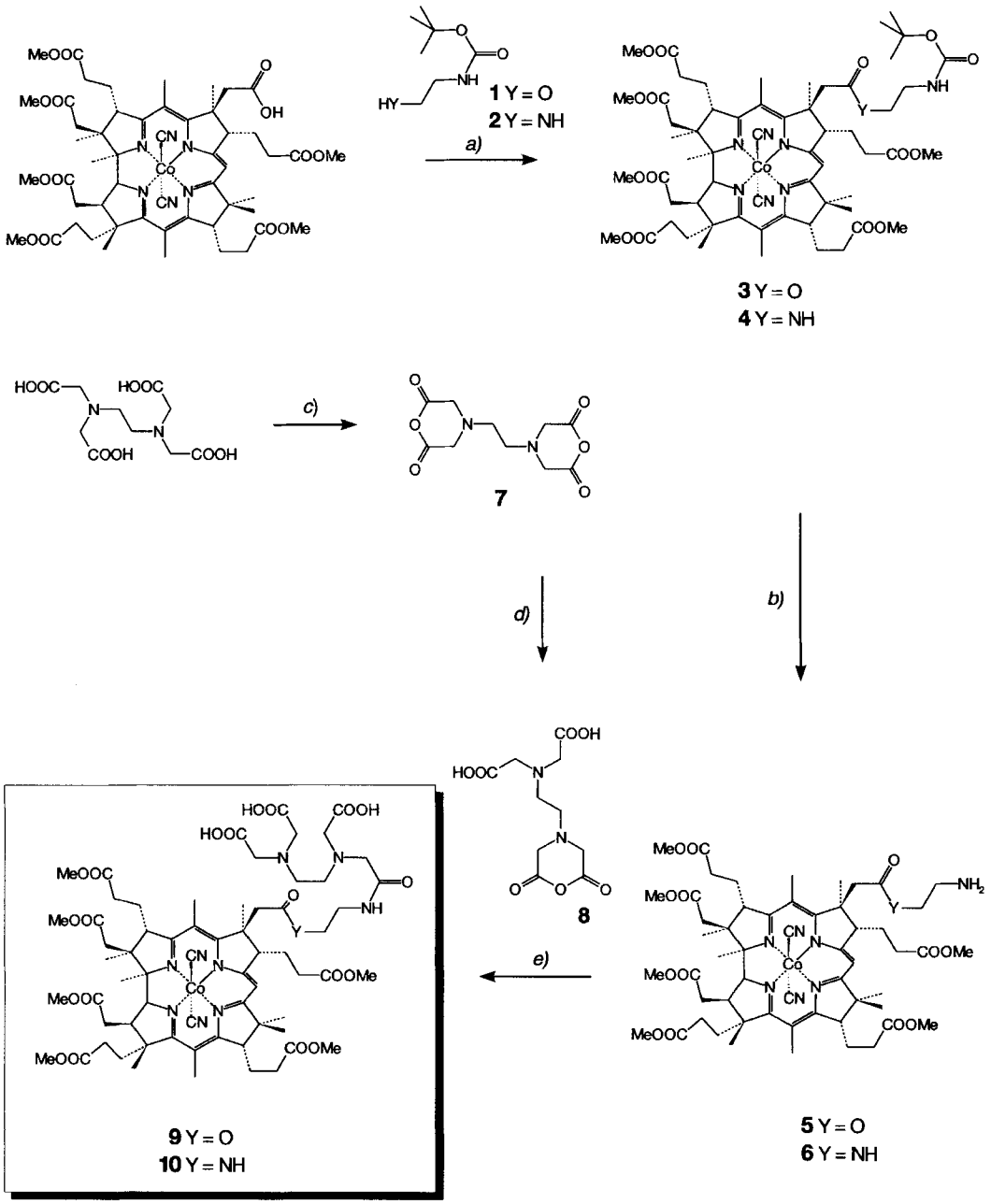
The synthesis of cobester-*c*-acid was performed according to [12]. Cobester-*c*-acid was activated with 'trichloro-*tert*-butyl chloroformate' (= 2,2,2-trichloro-1,1-dimethylethyl carbonochloridate) and reacted with a large excess of the mono-protected alcohol **1** or amine **2**. Notably, the Boc protecting groups did not only prevent di-acylation of the diamine and the aminoethanol, but also rendered **3** and **4** suitable for column chromatography on silica gel. The purified cobyrinic acid derivatives **3** and **4** were obtained in 33 and 30% yield, respectively, and were deprotected quantitatively in THF/CF_3COOH. After cyanidation, the corresponding cobyrinates were obtained as the free amines **5** and **6**.

Several attempts to obtain the monoanhydride **8** directly from EDTA for the further transformations failed, but the selective monohydrolysis of EDTA dianhydride was successful [13]. Thus, the free amines **5** and **6** were acylated with **8** to give the target cobyrinic acid derivatives **9** and **10** in 35 and 56% yield (after recyanidation).

Experimental Part

General. All reaction vessels were flame-dried under Ar, and the reactions were carried out under Ar using reagents of *puriss.* grade from *Fluka.* THF: distilled over K. CH_2Cl_2: distilled over P_2O_5. DMF: distilled under

Scheme



a) CH_2Cl_2, $ClCOOC(Me)_2CCl_3$, Et_3N, $-30°$ to reflux, 14 h; **3**, 30%, **4**, 33%. *b*) 1) THF, CF_3COOH, 50°, 12 h, quant.; 2) KCN, O_2. *c*) Py, Ac_2O, 70°; 87%. *d*) DMF, H_2O, 75°; 80%. *e*) 1) DMF, 50°; 2) MeOH(0.1%HCN), O_2; **9**, 35%; **10**, 56%.

reduced pressure. Not commercially available starting materials were prepared according to literature procedures and characterized by m.p. and ^{1}H- and ^{13}C-NMR spectra. Column chromatography (CC): commercial-grade solvents, distilled; silica gel (30–60 μm) from *Baker*. TLC: silica gel *Merck-F-254*, precoated sheets, visualization by vanillin/H_2SO_4; reversed-phase: *Macherey-Nagel* plates for nano-TLC, *Nano-Sil C_{18}-50*. UV/VIS: *Hewlett-Packard 8453*; λ_{max} in nm (ε in $1 \cdot mol^{-1} \cdot cm^{-1}$). IR: *Perkin-Elmer-FT-IR-1600*; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR: *Bruker-AC-300* (300 MHz); δ in ppm rel. to the solvent signal ((D$_6$)DMSO δ(H) 2.49, $CDCl_3$ δ(H) 7.24, CD_3OD δ(H) 3.35), *J* in Hz. ^{13}C-NMR: *Bruker-AC-300* (75 MHz); δ in ppm rel. to the solvent signal ((D$_6$)DMSO δ(C) 39.70, $CDCl_3$ δ(C) 77.00, CD_3OD δ(C) 49.30); multiplicities from DEPT spectra. MS-EI: *Varian-MAT-CH-7A*, ionization energy 70 eV; in *m/z* (%). LSI-MS: *Fision Autospec-Q*, acceleration voltage 8 kV, ionization Cs^+ (32 keV); matrix: glycerol, dithiothreitol/dithioerythritol 5:1; in *m/z* (%).

*2-{[(*tert*-Butoxy)carbonyl]amino}ethanol* (**1**). To di(*tert*-butyl) dicarbonate (5 g, 22.9 mmol) in THF (20 ml) at 0°, 2-aminoethanol (1.41 g, 23.1 mmol) in THF (10 ml) was added during 10 min. The mixture was stirred for 12 h at r.t. and evaporated: **1** (3.67 g, 99%). Colorless liquid. TLC (silica gel, hexane/AcOEt 7:3): R_f 0.22. IR (film): 3360*s*, 2978*m*, 2934*m*, 2880*w*, 1692*s*, 1526*s*, 1456*m*, 1392*m*, 1366*s*, 1280*s*, 1252*s*, 1172*s*, 1070*s*. ^{1}H-NMR ($CDCl_3$): 1.44 (*s*, 9 H); 3.20–3.29 (*m*, 2 H); 3.60–3.68 (*m*, 2 H); 4.39 (br. *s*, 1 H); 5.72 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 28.33 (*q*); 42.90 (*t*); 61.53 (*t*); 79.22 (*s*); 156.73 (*s*). EI-MS: 161 (< 1, M^+), 131 (16), 130 (11), 105 (12), 88 (17), 76 (17), 59 (46), 57 (100), 41 (25), 30 (16).

N-*[(*tert*-Butoxy)carbonyl]ethane-1,2-diamine* (**2**). Di(*tert* butyl)dicarbonate (5 g, 22.9 mmol) in CH_2Cl_2 (50 ml) was added during 2 h to a stirred soln. of ethane-1,2-diamine (4.31 g, 68.7 mmol) in CH_2Cl_2 (50 ml). The mixture was stirred for 18 h. The resulting white precipitate was filtered off and washed with CH_2Cl_2, the combined filtrate evaporated, and the crude product purified by CC (AcOEt/EtOH 1:1): **2** (3.41 g, 91%). Yellow oil. TLC (silica gel, AcOEt/EtOH 1:1): R_f 0.46. IR (film): 3342*m*, 2976*m*, 2932*m*, 1764*w*, 1696*s*, 1522*s*, 1458*m*, 1392*m*, 1366*s*, 1274*s*, 1252*s*, 1172*s*. ^{1}H-NMR ($CDCl_3$): 1.23 (*s*, 2 H); 1.31 (*s*, 9 H); 2.65 (*t*, *J* = 5.9, 2 H); 3.03 (*dd*, *J* = 5.7, 5.9, 2 H); 5.38 (br. *t*, 1 H). ^{13}C-NMR ($CDCl_3$): 28.29 (*q*); 41.74 (*t*); 43.30 (*t*); 78.82 (*s*); 156.23 (*s*). EI-MS: 161 (12, $[M + H]^+$), 160 (10), 118 (47), 105 (36), 104 (47), 103 (43), 89 (10), 88 (39), 87 (84), 86 (45), 85 (18), 84 (31), 77 (15), 76 (68), 75 (81), 74 (44), 70 (27), 62 (38), 60 (10), 59 (53), 58 (47), 57 (100), 56 (45), 55 (29), 49 (19), 46 (10), 45 (27), 44 (73), 43 (95), 42 (38), 41 (64), 40 (14), 39 (28), 31 (40), 30 (91), 29 (50), 28 (29), 27 (22), 18 (40).

Coα,Coβ-*Dicyanocob(III)yrinic Acid* c-{2{[(tert-*Butoxy)carbonyl]amino}ethyl*} a,b,d,e,f,g-*Hexamethyl Ester* (**3**). At –30°, '2,2,2-trichloro-*tert* butyl chloroformate' (152 mg, 0.64 mmol) and Et_3N (291 mg, 2.88 mmol) in CH_2Cl_2 (2 ml) were added to cobester-*c*-acid (505 mg, 0.47 mmol) in CH_2Cl_2 (30 ml). The mixture was warmed to r.t. within 2 h, and a soln. of **1** (1.9 g, 11.78 mmol) in CH_2Cl_2 (8 ml) was added dropwise. The mixture was refluxed for 14 h. Evaporation, CC (hexane/AcOEt 2:1 to remove the superfluous **1**, CH_2Cl_2/MeOH (0.1% HCN) 20:1 to eluate crude **3**) and an additional CC (hexane/CH_2Cl_2 i-PrOH/MeOH (0.1% HCN) 8:2:1:1) gave (190 mg, 33%). Dark violet solid. TLC (silica gel, CH_2Cl_2/MeOH (0.1% HCN) 10:1): R_f 0.47. IR ($CHCl_3$): 3020*s*, 2980*w*, 2954*w*, 2360*w*, 2342*w*, 1732*s*, 1582*m*, 1502*m*, 1438*m*, 1402*w*, 1368*m*, 1220*s*, 1156*m*, 1106*w*, 1008*w*. ^{1}H-NMR ($CDCl_3$): 1.22, 1.28, 1.37, 1.38 (4*s*, 12 H); 1.42 (*s*, 9 H); 1.51, 1.59 (2*s*, 6 H); 1.60–2.78 (*m*, 16 H), superimposed at 2.18, 2.25 (2*s*, 6 H); 2.84 (*m*, H–C(18)); 3.06 (*m*, H–C(13)); 3.30–3.50 (*m*, CH_2CH_2NH, H–C(8)); 3.62, 3.67, 3.69, 3.70, 3.71, 3.76 (6*s*, 18 H; hidden below; 2 H, H–C(3), H–C(19)); 4.04–4.30 (*m*, CH_2CH_2NH); 5.35 (*m*, CH_2CH_2NH); 5.56 (*s*, H–C(10)). ^{13}C-NMR ($CDCl_3$): 15.25 (*q*); 15.84 (*q*); 16.89 (*q*); 18.36 (*q*); 19.13 (*q*); 19.68 (*q*); 22.02 (*q*); 24.87 (*t*); 25.61 (*t*); 26.12 (*t*); 28.35 (*q*, Me_3C); 29.68 (*t*); 30.59 (*t*); 30.87 (*t*); 31.08 (*q*); 31.71 (*t*); 32.47 (*t*); 33.64 (*t*); 39.19 (*d*, C(18)); 39.47 (*t*); 41.08 (*t*); 42.53 (*t*); 45.60 (*s*); 46.91 (*s*); 48.71 (*s*); 51.57 (*q*); 51.66 (*q*); 51.82 (*q*); 52.37 (*q*); 53.51 (*d*); 54.33 (*d*); 56.54 (*d*); 58.30 (*s*, C(17)); 63.84 (*t*, CH_2CH_2NH); 74.72 (*d*, C(19)); 79.17 (*s*, Me_3C); 82.53 (*d*, C(1)); 91.16 (*d*, C(10)); 102.26 (*s*); 103.78 (*s*); 130.44 (*s*); 130.83 (*s*); 155.84 (*s*); 163.26 (*s*); 170.35 (*s*); 171.22 (*s*); 171.73 (*s*); 171.84 (*s*); 172.67 (*s*); 172.84 (*s*); 173.67 (*s*); 173.82 (*s*); 175.24 (*s*); 175.62 (*s*); 176.12 (*s*). LSI-MS: 1166 (100, $[M^+ - 2\ CN]^+$), 1110 (26), 1051 (30), 1037 (47), 1025 (32), 876 (22).

Coα,Coβ-*Dicyanocob(III)yrinic Acid* a,b,d,e,f,g-*Hexamethyl Ester* c-{2-{[(tert-*Butoxy)carbonyl]amino}-ethyl}amide* (**4**). As described for **3** at –10° with '2,2,2-trichloro-*tert* butyl chloroformate' (359 mg, 1.50 mmol), Et_3N (730 mg, 7.21 mmol), CH_2Cl_2 (5 ml), cobester-*c*-acid (1.264 g, 1.17 mmol), CH_2Cl_2 (50 ml), and **2** (3.25 g, 20.29 mmol) in CH_2Cl_2 (2 ml; 18 h reflux). Evaporation, CC (CH_2Cl_2/MeOH (0.1% HCN) 28:1), and an additional CC (CH_2Cl_2/MeOH (0.1% HCN) 33:1), **4** gave (423 mg, 30%). Dark violet solid. TLC (silica gel, CH_2Cl_2/MeOH (0.1% HCN) 24:1): R_f 0.34. IR (film): 3340*m*, 2954*m*, 2120*w*, 1732*s*, 1652*m*, 1580*m*, 1504*s*, 1436*m*, 1366*m*, 1150*m*, 1014*w*, 910*w*, 784*w*. UV/VIS ($CHCl_3$): 240 ($2.0 \cdot 10^4$), 279 ($1.3 \cdot 10^4$), 316 ($1.0 \cdot 10^4$), 371 ($3.1 \cdot 10^4$), 589 ($1.2 \cdot 10^4$). ^{1}H-NMR ($CDCl_3$): 1.17, 1.22 (2*s*, 6 H); 1.33 (*s*, 9 H; hidden below: *s*, 3 H); 1.34 (*s*, 3 H); 1.47 (*s*, 3 H); 1.5–2.7 (*m*, 22 H), superimposed at 1.74 (*s*, 3 H); 2.04 (*s*, 3 H); 2.20 (*s*, 3 H); 2.78 (*m*, H–C(18)); 2.85–3.07 (*m*, $NHCH_2CH_2NH$); 3.11 (*m*, H–C(8)); 3.59, 3.64, 3.65, 3.658, 3.662, 3.73 (6*s*, 18 H;

hidden below: 2 H, H–C(3), H–C(19)); 5.47 (br. *t*, 1 N*H*); 5.51 (*s*, H–C(10)); 7.10 (br. *t*, 1 N*H*). ^{13}C-NMR ($CDCl_3$): 15.10 (*q*); 15.22 (*q*); 16.80 (*q*); 18.11 (*q*); 19.10 (*q*); 19.59 (*q*); 21.85 (*q*); 24.71 (*t*); 25.57 (*t*); 28.25 (*q*, *Me*$_3$C); 29.46 (*t*); 30.61 (*t*); 30.72 (*t*); 31.40 (*q*); 31.52 (*t*); 32.17 (*t*); 33.47 (*t*); 39.05 (*d*, C(18)); 40.13, 40.30 (2*t*, NH*C*H$_2$*C*H$_2$NH); 41.68 (*t*); 46.01 (*s*, C(2)); 46.79 (*s*, C(12)); 47.16 (*t*); 51.40 (*q*); 51.46 (*q*); 51.48 (*q*); 51.69 (*q*); 51.71 (*q*); 51.90 (*q*); 52.28 (*q*); 53.37 (*d*, C(13)); 56.39 (*d*, C(8)); 58.32 (*s*, C(17)); 58.71 (*d*, C(3)); 74.44 (*d*, C(19)); 78.54 (*s*, Me$_3$C); 82.55 (*s*, C(1)); 91.30 (*d*, C(10)); 102.22 (*s*, C(15)); 106.58 (*s*, C(5)); 155.76 (*s*, *C*OO(*t*-Bu); 160.98 (*s*, C(14)); 163.43 (*s*, C(6)); 170.01 (*s*); 171.19 (*s*); 171.22 (*s*); 171.45 (*s*); 172.32 (*s*); 172.67 (*s*); 173.41 (*s*); 173.63 (*s*); 175.39 (*s*); 175.76 (*s*); 175.89 (*s*). LSI-MS: 1164 (100, [*M* – 2 CN]$^+$), 1109 (15), 962 (20).

Co*α*,Co*β*-*Dicyanocob(III)yrinic Acid* c-*(2-Aminoethyl)* a,b,d,e,f,g-*Hexamethyl Ester* (**5**). CF_3COOH (5 ml) was added dropwise to a stirred soln. of **3** (220 mg, 0.181 mmol) in THF (5 ml). The mixture was stirred for 12 h at 50°. Evaporation yielded a red solid that was dissolved in CH_2Cl_2 (10 ml) and vigorously stirred with KCN (0.05 g, 0.768 mmol) in phosphate buffer (pH 7; 1M, 100 ml) under air. The org. layer was dried ($MgSO_4$) and evaporated: **5** (197 mg, 97%). Dark violet solid. TLC (silica gel, CH_2Cl_2/MeOH (0.1% HCN) 10:1): R_f 0.33. ^{1}H-NMR ($CDCl_3$): 1.5–2.0 (*m*, 6 H); 2.0–2.75 (*m*, 17 H), superimposed at 1.20, 1.27, 1.51, 1.60, 2.17, 2.24 (6*s*, 18 H); 1.37 (*s*, 6 H); 2.82 (*m*, 1 H); 2.95 (*t*, 1 H); 3.04 (*t*, 1 H); 3.35 (*m*, 1 H); 3.4–3.7 (br. *m*, 4 H), superimposed at 3.63, 3.67, 3.69, 3.70, 3.72, 3.76 (6*s*, 18 H); 4.14 (br. *s*, 2 H); 5.58 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 15.05 (*q*); 15.57 (*q*); 16.71 (*q*); 18.20 (*q*); 19.01 (*q*); 19.49 (*q*); 21.81 (*q*); 24.66 (*t*); 25.42 (*t*); 26.04 (*t*); 29.47 (*t*); 30.43 (*t*); 30.77 (*t*); 30.88 (*q*); 31.49 (*t*); 32.28 (*t*); 33.47 (*t*); 38.99 (*d*, C(18)); 39.66 (*t*); 41.03 (*t*); 42.22 (*t*); 45.43 (*s*); 46.75 (*s*); 48.52 (*s*); 51.40 (*q*); 51.44 (*q*); 51.64 (*q*); 52.17 (*q*); 53.31 (*d*); 54.39 (*d*); 56.37 (*d*); 58.12 (*s*, C(17)); 64.94 (*t*, CH_2*C*H$_2$NH$_2$); 74.51 (*d*, C(19)); 82.35 (*s*, C(1)); 90.95 (*d*, C(10)); 102.04 (*s*); 103.70 (*s*); 162.91 (*s*); 163.13 (*s*); 170.21 (*s*); 171.10 (*s*); 171.56 (*s*); 171.67 (*s*); 172.50 (*s*); 172.70 (*s*); 173.36 (*s*); 173.66 (*s*); 175.08 (*s*); 175.48 (*s*); 176.00 (*s*).

Co*α*,Co*β*-*Dicyanocob(III)yrinic Acid* a,b,e,f,g-*Hexamethyl Ester* c-*(2-Aminoethyl)amide* (**6**). As described for **5**, with CF_3COOH (5 ml), **4** (423 mg, 0.347 mmol), THF (5 ml; 18 h at 55°) CH_2Cl_2 (10 ml), KCN (0.05 g, 0.768 mmol), and phosphate buffer (pH 7; 1M, 100 ml): **6** (387 mg, 100%). Dark violet solid. TLC (silica gel, CH_2Cl_2/MeOH (0.1% HCN) 10:1): R_f 0.22. IR (KBr): 2954*m*, 2124*w*, 1736*s*, 1676*m*, 1580*s*, 1502*s*, 1438*m*, 1402*w*, 1368*m*, 1202*s*, 1174*s*, 1108*m*, 1012*w*, 832*w*, 800*w*, 720*w*. ^{1}H-NMR ($CDCl_3$): 1.1–1.85 (*m*, 4H), superimposed at 1.14, 1.22, 1.33, 1.35, 1.46, 1.60 (6*s*, 18 H); 1.85–2.87 (*m*, 23 H), superimposed at 2.04, 2.20 (2*s*, 6 H); 3.01 (*m*, 2 H); 3.17 (br. *s*, 1 H); 3.40–3.75 (*m*, 4 H), superimposed at 3.59, 3.63, 3.65, 3.66, 3.67, 3.74 (6*s*, 18 H); 5.53 (*s*, H–C(10)); 7.68 (br. *t*, N*H*CH$_2$CH$_2$NH$_2$). ^{13}C-NMR ($CDCl_3$): 15.16 (*q*); 15.20 (*q*); 16.86 (*q*); 18.15 (*q*); 19.20 (*q*); 19.51 (*q*); 21.89 (*q*); 24.76 (*t*); 25.56 (*t*); 25.70 (*t*); 29.52 (*t*); 30.57 (*t*); 30.83 (*t*); 31.09 (*q*); 31.39 (*t*); 32.23 (*t*); 33.50 (*t*); 37.25 (*t*, NHCH$_2$*C*H$_2$NH$_2$); 39.12 (*d*); 39.43 (*t*, NH*C*H$_2$CH$_2$NH$_2$); 41.90 (*t*); 45.44 (*t*); 45.85 (*s*); 46.84 (*s*); 46.88 (*s*); 51.50 (*q*); 51.53 (*q*); 51.65 (*q*); 51.72 (*q*); 51.87 (*q*); 52.27 (*q*); 53.39 (*d*); 56.53 (*d*); 56.87 (*d*); 58.33 (*s*); 74.53 (*d*); 82.56 (*s*); 91.34 (*d*); 102.25 (*s*); 105.38 (*s*); 162.07 (*s*); 163.33 (*s*); 170.81 (*s*); 171.45 (*s*); 171.53 (*s*); 171.66 (*s*); 172.43 (*s*); 172.75 (*s*); 173.44 (*s*); 173.69 (*s*); 175.39 (*s*); 175.87 (*s*); 176.05 (*s*). LSI-MS: 1165 (22, [*M* – 2 CN]$^+$), 963 (7), 277 (10), 185 (100).

Ethylenediaminetetraacetic Acid Dianhydride (= *4,4'-(Ethane-1,2-diyl)bis[morphelin-2,6-dione]*; **7**): Ethylendiaminetetraacetic acid (= [(ethan-1,2-diyl)dinitrilo]tetrakis[acetic acid]) (10 g, 34 mmol) was added to a stirred mixture of Ac_2O (14 g, 137 mmol) and pyridine (12 g, 151 mmol). The suspension was stirred for 24 h at 70°. After cooling to r.t., the white solid was filtered under Ar, washed with Ac_2O and pentane, and dried under reduced pressure: **7** (7.56 g, 87%). White solid. IR (KBr): 2920*m*, 1810*s*, 1765*s*, 1645*s*, 1470*m*, 1425*m*, 1370*m*, 1350*m*, 1325*m*, 1290*m*, 1250*s*, 1130*s*, 1110*s*, 1075*s*, 1000*s*, 960*m*, 930*s*, 880*m*, 820*s*, 785*m*, 610*m*, 560*s*, 500*m*. ^{1}H-NMR ((D$_6$)DMSO): 2.75 (*s*, 4 H); 3.78 (*s*, 8 H). ^{13}C-NMR ((D$_6$)DMSO): 53.03 (*t*); 54.10 (*t*); 167.62 (*s*). EI-MS: 256 (6, M^+), 141 (12), 129 (14), 128 (100), 100 (31), 97 (11), 42 (37).

Ethylenediaminetetraacetic Acid Monoanhydride (= *{[2-(2,6-Dioxomorpholin-4-yl)ethyl]imino}bis[acetic Acid]*; **8**): H_2O (281 µl, 15.6 mmol) was added dropwise to **7** (4 g, 15.6 mmol) in DMF (25 ml) at 75°. The mixture was stirred for 6 h at 75° and for 3 h at r.t. The white precipitation was filtered under Ar, washed with Et_2O, and dried under reduced pressure: **8** (3.42 g, 80%). White solid. IR (KBr): 3440*m*, 3020*m*, 1820*m*, 1770*s*, 1700*s*, 1640*s*, 1400*s*, 1100*s*, 1000*m*, 900*m*, 710*m*, 580*m*, 520*m*. ^{1}H-NMR ((D$_6$)DMSO): 2.67 (*t*, 2 H); 2.86 (*t*, 2 H); 3.51 (*s*, 4 H); 3.80 (*s*, 4 H). ^{13}C-NMR ((D$_6$)DMSO): 52.51 (*t*); 53.77 (*t*); 54.4 (*t*); 56.91 (*t*); 173.91 (*s*); 174.81 (*s*). EI-MS: 256 (8, [*M* – H_2O]$^+$), 216 (9), 187 (15), 184 (16), 172 (52), 171 (88), 146 (44), 143 (48), 142 (10), 141 (13), 129 (25), 128 (100), 127 (26), 102 (18), 101 (13), 100 (27).

Co*α*,Co*β*-*Dicyanocob(III)yrinic Acid* c-{{2-{{2-[*Bis(carboxymethyl)amino]ethyl*}*(carboxymethyl)amino*}-*1-oxoethyl*}*amino*}*ethyl*} a,b,d,e,f,g-*Hexamethyl Ester* (**9**). A soln. of **5** (197 mg, 0.176 mmol) in DMF (2 ml) was added dropwise to a stirred soln. of **8** (50 mg, 0.182 mmol) in DMF (5 ml) at 60°. The mixture was stirred for 12 h at 60°. The solvent was evaporated at 40°, the violet residue dissolved in CH_2Cl_2 (4 ml), H_2O (10 ml) added,

CH_2Cl_2 evaporated, and the aq. layer twice washed with Et_2O. HCl (2N) was added dropwise until pH 3 was reached. The mixture was extracted with CH_2Cl_2 (3 × 10 ml), the combined org. layer dried ($MgSO_4$). MeOH (0.1% HCN; 1 ml) added, and the mixture vigorously stirred under air and evaporated: **9** (85.3 mg, 35%). Dark violet solid. TLC (reversed-phase, MeCN/AcOH 17:3): R_f 0.70; estimated purity > 95%. UV/VIS ($CHCl_3$): 276 ($1.1 \cdot 10^4$), 324 ($9.5 \cdot 10^5$), 361 ($2.1 \cdot 10^4$), 541 ($8 \cdot 10^5$). ^{1}H-NMR (CD_3OD): 0.75–1.9 (*m*, 28 H); 1.9–3.15 (*m*, 27 H); 3.21 (*q*, 6 H); 3.23–3.45 (*m*, 2 H); 3.45–3.77 (*m*, 20 H); 3.77–4.25 (*m*, 2 H); 5.65 (*s*, 1 H); 6.32 (*s*, 1 H). ^{13}C-NMR (CD_3OD): 18.20; 18.37; 18.51; 19.80; 19.87; 19.97; 20.79; 22.23; 25.18; 28.23; 28.45; 29.21; 29.32; 33.11; 34.23; 34.38; 34.67; 36.79; 37.02; 43.14; 45.69; 49.53; 49.65; 49.79; 54.50; 54.59; 54.74; 54.82; 55.26; 57.20; 60.41; 62.24; 63.77; 66.49; 78.57; 86.48; 86.55; 86.62; 95.06; 106.45; 108.99; 166.78; 167.13; 167.23; 174.22; 174.78; 174.96; 175.67; 175.89; 175.96; 176.19; 176.34; 176.66; 176.83; 176.91; 177.44; 177.48; 177.54; 177.65; 177.80; 179.99; 180.22; 180.31; 180.47. LSI-MS: 1360 (9, [*M* − 3 H + Na − 2 CN]), 1134 (9), 1108 (14), 1094 (13), 1023 (69), 963 (100), 876 (66), 802 (33), 716 (24).

Coα,Coβ-*Dicyanocob(III)yrinic Acid* a,b,d,e,f,g-*Hexamethyl Ester* c-{{*2*-{-{{*2*-[*Bis(carboxymethyl)amino*]-*ethyl*}(*carboxymethyl)amino*}-*1-oxoethyl*}*amino*}*ethyl*}*amide* (**10**). As described for **9**, with **6** (278 mg, 0.248 mmol), DMF (5 ml) **8** (116 mg, 0.423 mmol), DMF (5 ml; at 50°, then 6 h at 50°). Workup with CH_2Cl_2 (10 ml) and H_2O (50 ml), then Et_2O, HCl (2N), CH_2Cl_2 (3 × 10) and MeOH (0.1% HCN; 2 ml): **10** (193 mg, 56%). Dark violet solid. TLC (reversed-phase, MeCN/AcOH 17:3): R_f 0.63; estimated purity > 95%. IR (KBr): 3434*m*, 2954*m*, 2134*w*, 1732*s*, 1644*s*, 1580*s*, 1544*m*, 1502*s*, 1438*s*, 1368*s*, 1302*m*, 1200*s*, 1174*s*, 1108*m*, 1004*m*. UV/VIS ($CHCl_3$): 277 ($1.1 \cdot 10^4$), 327 ($9.6 \cdot 10^5$), 361 ($2.2 \cdot 10^4$), 541 ($8.1 \cdot 10^5$). ^{1}H-NMR (CD_3OD): 1.1–1.85 (*m*, 6 H), superimposed at 1.12, 1.20, 1.23, 1.36, 1.44, 1.55 (6*s*, 18 H); 1.85–2.8 (*m*, 24 H), superimposed at 2.05, 2.28 (2*s*, 6 H); 2.8–3.32 (*m*, 10 H); 3.32–4.0 (*m*, 4 H), superimposed at 3.36, 3.38 (2*s*, 6 H); 3.47 (*s*, 6 H); 3.49 (*s*, 3 H); 3.66 (*s*, 3 H); 5.37 (*s*, 1 H); 6.33 (br. *s*, 1 H). ^{13}C-NMR (CD_3OD): 16.30 (*q*); 16.97 (*q*); 18.02 (*q*); 19.71 (*q*); 20.67 (*q*); 21.42 (*q*); 24.91 (*q*); 26.28 (*t*); 27.21 (*t*); 28.35 (*t*); 29.84 (*q*); 31.14 (*t*); 32.01 (*t*); 32.50 (*t*); 34.13 (*t*); 34.88 (*t*); 39.75 (*t*); 40.44 (*t*); 41.33 (*d*); 42.83 (*t*); 47.50 (*s*); 47.59 (*t*); 50.04 (*s*); 50.54 (*t*); 51.09 (*t*); 52.41 (*q*); 52.47 (*q*); 52.62 (*q*); 52.75 (*q*); 52.79 (*q*); 53.18 (*q*); 53.55 (*s*); 55.76 (*d*); 56.36 (*t*); 58.30 (*d*); 59.17 (*d*); 60.28 (*d*); 77.05 (*s*); 84.79 (*s*); 95.36 (*d*); 105.89 (*s*); 108.49 (*s*); 164.94 (*s*); 165.91 (*s*); 168.59 (*s*); 170.26 (*s*); 173.00 (*s*); 173.27 (*s*); 173.75 (*s*); 174.24 (*s*); 174.65 (*s*); 174.83 (*s*); 175.20 (*s*); 175.42 (*s*); 178.55 (*s*); 179.31 (*s*); 179.54 (*s*). LSI-MS: 1338 (100, [*M* − 2 CN]$^+$), 1280 (40), 1234 (18), 1190 (20), 1164 (78), 1106 (45), 1064 (40).

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