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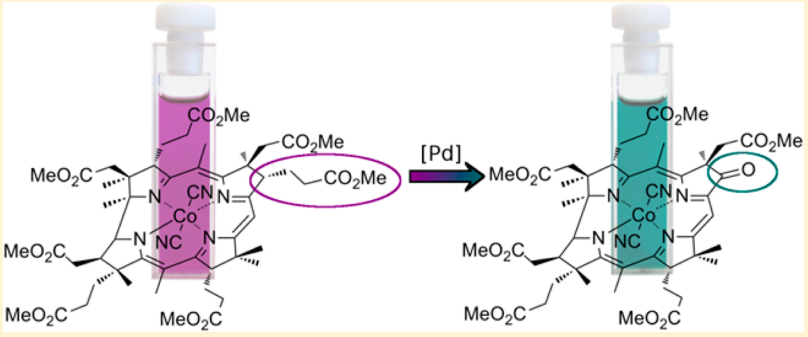
Cobryketone Derived from Vitamin B_{12} *via* Palladium-Catalyzed Cleavage of the sp^3–sp^3 Carbon–Carbon Bond

Sylwester Kurcoń, Keith ó Proinsias, and Dorota Gryko*

Institute of Organic Chemistry PAS, Kasprzaka 44/52, 01-224 Warsaw, Poland

Supporting Information



ABSTRACT: Heptamethyl cobyrinate was transformed into hexamethyl 8-*nor*-cobyrinate. The crucial step involved the synthesis of new, vitamin B_{12} derived cobryketone *via* palladium-catalyzed cleavage of the sp^3–sp^3 carbon–carbon bond with the liberation of the ketone. The replacement of sp^3 carbon atom with sp^2 (C=O) at the 8-position produces a bathochromic shift of all absorption bands and makes α and β bands equal as a consequence of the expansion of the existing conjugated system of double bonds.

INTRODUCTION

The total synthesis of vitamin B_{12} reported by Eschenmoser/Woodward is one of the most spectacular and most complex in the history of organic chemistry (Figure 1).[1] As a consequence, its derivatives have been exclusively obtained *via* modifications of the natural compound.[2] They have been studied as cyanide detoxifying agents,[3] sensors for the optical detection of cyanide ion,[4] oral delivery vehicles for therapeutic agents,[5,6] artificial and model enzymes, and catalysts for various organic reactions.[2b] These applications require efficient methods for the synthesis of such compounds. The most valuable are, of course, selective modifications relying on the transformation of the peripheral functional groups or reactions at the cobalt center.[2] For example, alkylation of the cobalt atom with alkyl/acyl halides, epoxides, *O*-sulfonates *etc.*[7] Treatment of vitamin B_{12} with a carbonyl group equivalent (CDI, 1,1′-carbonyldiimidazole or CDT, 1,1′-carbonyl-di(1,2,4-triazole)) followed by addition of nucleophiles gives carbamates/carbonates at 5′-hydroxyl group on the ribose moiety.[6b−d] This methodology was used for coupling of therapeutic agents to vitamin B_{12} due to its specific uptake pathway.[5] Complete methanolysis of peripheral amides furnished hydrophobic heptamethyl cobyrinate,[8] but for further functionalization *c*-monoacid hexamethyl cobyrinate obtained from the reductive ring opening of *c*-lactone is the most useful.[9] Recently, we have shown that *c*-lactone allows selective modifications not only at the *c*- but also at the *d*-position.[10] It is also possible to modify the structure at the *d*-position without interfering with position *c* using $(CN)_2Cby(OMe)_7$-10NH_2 as a starting material.[11] It was found that these compounds activate guanylyl cyclase (sGC) better than cobinamide, suggesting that modifications to vitamin B_{12} may provide an attractive approach toward more effective regulators.[10] As a part of our ongoing project we

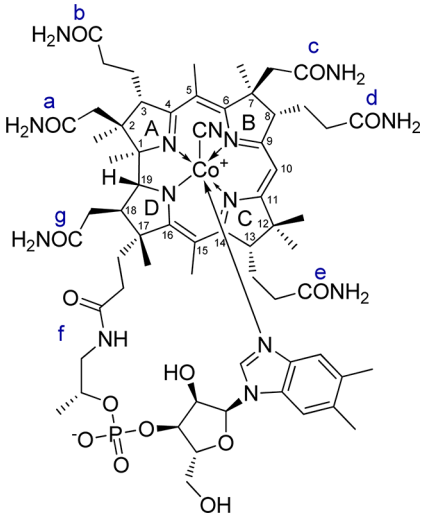


Figure 1. Conjugated system of double bonds in vitamin B_{12}.

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wanted to determine structural features of cobyrinic acid derivatives crucial for enzyme binding; for example, removal of one or two side chains may give rise to the precise orientation of the bound molecule.

There are few reports describing alterations to the corrin core. One of the rare examples is the green corrinoid reported by Brown et al.[12] Treatment of vitamin B_{12} derivative possessing a urethane moiety at the 8-position with KOH furnishes the modified corrinoid with up to 40% yield. The B pyrrole ring aromatizes by the loss of the $-CH_2NH_2$ substituent from position 7 and loss of hydrogen from position 8. Recently, Kräutler et al. have shown that partial degradation of cobalamin in the presence of sodium bicarbonate leads to a blue corrinoid in 6% yield.[13] Similarly, pyrolysis of heptamethyl cobyrinate furnishes deep-green pyrocobester with perturbed chromophore in 34% yield.[14] Dicyano-18,19-didehydrocobyrinic acid hexamethylester *c*-amide obtained by Koppenhagen also exhibits substantial bathochromic shifts of the absorption bands.[15] On the other hand, cleavage of the corrin macrocycle leads to yellow corrinoids, which commonly arise in cobalamin chemistry.[16] For example, oxidation of heptamethyl cobyrinate with oxygen in the presence of ascorbic acid gives a disrupted corrinoid in 30% yield.[16a,b] It possesses hydroxyl groups at positions 5 and 6 with the latter being involved in lactone formation. The breakage of the conjugation between C5 and C6 was reported by Sheldrick, who isolated a yellow lactam with the amine group attached to C6 position.[16a,h]

RESULTS AND DISCUSSION

We envisaged that the system of conjugated double bonds in the corrin ring could be expanded *via* selective cleavage of one or more of the peripheral propionate or acetate side chains under oxidative conditions. Our first attempted oxidation of $(CN)_2Cby(III)(OMe)_7$ **1a** with $KMnO_4$ gave a complex mixture of products with no detectable color change (Scheme 1; Table 1, entry 1).

Since it is well-known that C−C bond cleavage can occur *via* transition-metal-catalyzed reactions, we considered them as an option.[17] The first example of ruthenium-catalyzed deallylation

Scheme 1. Cobryketone 2 Synthesis

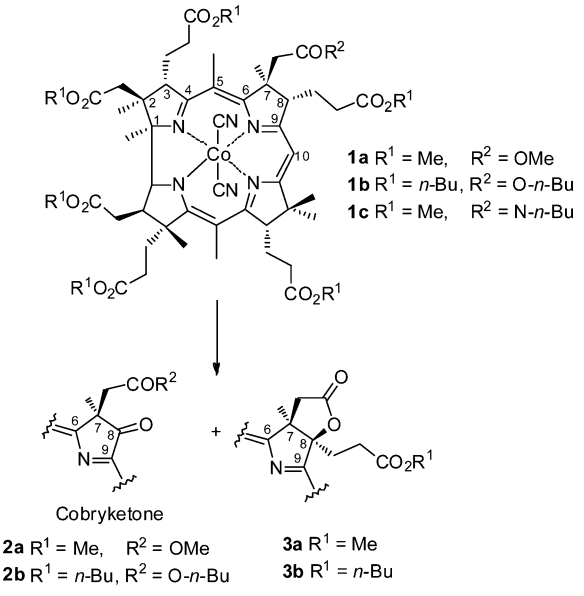

Table 1. Oxidation of Heptamethyl Cobyrinate 1a[a]

entry	reagent	time [h]	temp [°C]	result
1[b]	$KMnO_4$	5	40	c. m.[c]
2	$Pd(OAc)_2$	24	50	traces of **2a**
3	$RuCl_2PPh_3$	24	50	n. d.[d]

[a]Reaction conditions: $(CN)_2Cby(III)(OMe)_7$ **1a** (4.6 μmol), reagent (20% mol), DMF conc 0.07 M. [b]25 equiv of reagent, pyridine instead of DMF used, conc 0.02 M. [c]Complicated mixture. [d]Not detected.

of tertiary homoallyl alcohols *via* selective cleavage of C−C bond leading to a ketone was reported by Kondo and Mitsudo et al.[18] It was also found that aryl−aryl coupling can be achieved *via* C−C bond cleavage.[19] For example, α,α-disubstituted arylmethanols react with aryl halides in the presence of palladium acetate with the liberation of ketones to give biaryls.[19] Hence, heptamethyl cobyrinate **1a** was treated with either Pd or Ru complexes in DMF. Interestingly, in our case the reaction in the presence of Pd changed color and furnished traces of a blue-green product, while ruthenium-catalyzed reaction gave no conversion. The structure of blue-green compound **2a** was elucidated on the basis of MS, UV−vis, elemental analysis, and $^{13}C/^{1}H$ NMR techniques and assigned as cobryketone **2a**.

Subsequently, the synthesis of unique vitamin B_{12} derivative **2a** was optimized. Continuing from the synthesis using $Pd(OAc)_2$, the possibility that cobryketone **2a** formation proceeded in the absence of an oxidant was very unlikely. Indeed a reaction conducted under rigorously dry and deoxygenated conditions led to the recovery of starting material **1a** (Table 2, entry 1).

Table 2. Screening of Reaction Conditions[a]

entry	oxidant	phosphine	additive	time [h]	yield of **2a** [%]
1[b]				24	n. d.[d]
2			H_2O	4.5	n. d.[d]
3	O_2			3	14
4[c]	**O_2**	**PPh_3**	**H_2O**	**4.5**	**32**
5	O_2	PPh_3		3	24
6	O_2	PPh_3	H_2O	4.5	26
7	O_2	DavePhos	H_2O	4.5	22
8	O_2	*t*-Bu_3P	H_2O	4.5	19
9	O_2	Cy_3P	H_2O	4.5	trace
10	O_2	PPh_3	H_2O, KOAc	4.5	21
11	O_2	PPh_3	H_2O, CsOAc	4.5	10

[a]Reaction conditions: $(CN)_2Cby(III)(OMe)_7$ **1a** (14 μmol), $Pd(OAc)_2$ (20% mol), phosphine (40% mol), additive 2 equiv each, DMF saturated O_2, conc 0.07 M, 80 °C. [b]Degassed solvent, deoxygenated condition. [c]1 equiv of additive. [d]Not determined.

This suggested oxidation as a key step in the reaction pathway with O_2 or water acting as the source of oxygen. When oxygen was passed through the reaction mixture the yield increased to 14% (entry 3). There are only few examples for arylation of alcohols *via* β-carbon elimination. Miura et al. found that certain α,α-disubstituted arylmethanols react with aryl bromides to give biaryls *via* cleavage of the sp^2-sp^3 C−C bond in the presence of $Pd(OAc)_2$ and PPh_3.[20] The role of phosphines in coupling reactions is to stabilize the Pd(0) state and tune the reactivity of palladium;[21] therefore when PPh_3 was incorporated into the studied reaction the yield further increased to 32% (entry 4). Additionally, in palladium-catalyzed

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reactions ligands play a crucial role in determining rates of various steps by controlling the detailed coordination environment at palladium.[21] Thus, various phosphines were examined, but yields decreased in all cases (entries 7–9). Subsequently, the effects of different solvents were investigated focusing on those that absorb oxygen well (Table 3).

Table 3. Solvent Screening[a]

entry	solvent	time [h]	yield of **2a** [%]
1	DMSO	3	29
2	DMAc[b]	72	21
3	MeCN	72	traces
4	DCE[c]	72	n. d.[d]
5	toluene	72	n. d.[d]
6	NMP	60	23
7	THF	24	n. d.[d]

[a]Reaction condition: $(CN)_2$Cby(III)$(OMe)_7$ **1a** (14 μmol), $Pd(OAc)_2$ 20% mol, PPh_3 40% mol, H_2O 1 equiv, solvent saturated O_2, conc 0.07 M, 80 °C. [b]Dimethylacetamide. [c]1,2-Dichloroethane. [d]Not detected.

However, only the reaction in DMSO was comparable with the reaction rate in DMF (entry 1), even though the solubility of oxygen in DMSO has half the capacity of DMF.[22] Further optimizations regarding the choice of catalyst and oxidants did not give any significant improvement (see Supporting Information).

The replacement of methyl ester group with *n*-butyl at the *c*-position did not suppress *c*-lactone formation (Table 4, entry

Table 4. Cobryketones[a]

entry	R^1	R^2	time [h]	yield of ketone [%]	yield of *c*-lactone [%]
1	Me	OMe	4.5	32	40
2	*n*-Bu	O-*n*-Bu	24	21	13
3	*n*-Bu	O-*n*-Bu	48	14	17
4	Me	N-*n*-Bu	48	n. d.[b]/c. m.[c]	n. d.[b]/c. m.[c]

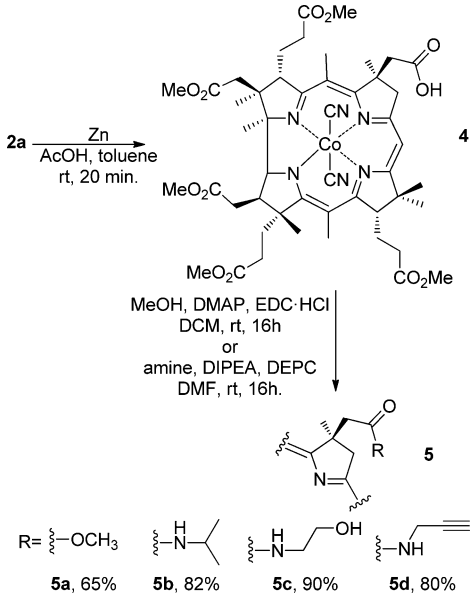
[a]Reaction condition: cobyrinate (14 μmol), $Pd(OAc)_2$ (20% mol), PPh_3 (40% mol), H_2O (1 equiv), DMF saturated O_2, conc 0.07 M, 80 °C. [b]Not detected. [c]Complicated mixture.

2). The reaction of hepta-*n*-butyl cobyrinate, though much slower, gave a mixture of cobryketone **2b** and *c*-lactone **3b** with yields remaining at the same level. To suppress lactone formation process, *c*-monoamide **1c** was used as a starting material. Unfortunately, the reaction resulted in a complicated mixture of products with no evidence of the desired compound found.

Examples of vitamin B_{12} lacking one or more of the peripheral side chains especially at β positions are scarce. To the best of our knowledge the only synthetically useful example came from Kräutler's laboratory.[23] Reduction of pyrocobester with Zn in acetic acid gave hexamethyl cobyrinate lacking the *c*-side chain. In our case, by removing the ketone moiety present at the C8 position using a similar reduction method *c*-acid **4** devoid of the *d*-side chain was isolated in a high yield of 81%. Direct esterification of compound **4** gave hexamethyl 8-*nor*-cobyrinate **5a** in 65% yield (Scheme 2). Also the reaction of acid **4** with various amines proceeded smoothly furnishing desired *c*-amides **5b–d** in excellent yields.

Structure Elucidation. The ESI-MS of cobryketone **2a** displayed no molecular ion peaks; instead $[M - CN]^+$

Scheme 2. Synthesis of *c*-Acid 4 from Cobryketone 2a



$C_{49}H_{65}CoN_5O_{13}$ (m/z = 990.39) and $[M + Na]^+$ $C_{49}H_{65}CoN_5O_{13}$ (m/z = 1039.38) were observed, which is common for hydrophobic cobalamines. The MS analysis clearly showed a decrease in the molecular mass from $[M - CN]^+$ m/z = 1062.44 for compound **1a** to $[M - CN]^+$ m/z = 990.39 for cobryketone **2a** suggesting the loss of C_4H_8O (72.05), which related to the cleavage of one of the methyl propionate moiety and the addition of the oxygen atom. The absorption spectrum of cobryketone **2a** varies from most of known corrinoids except Inhoffen's blue vitamin B_{12} derivative,[14] suggesting the expansion of conjuation of the double bond system on the corrin ring (Figure 2).

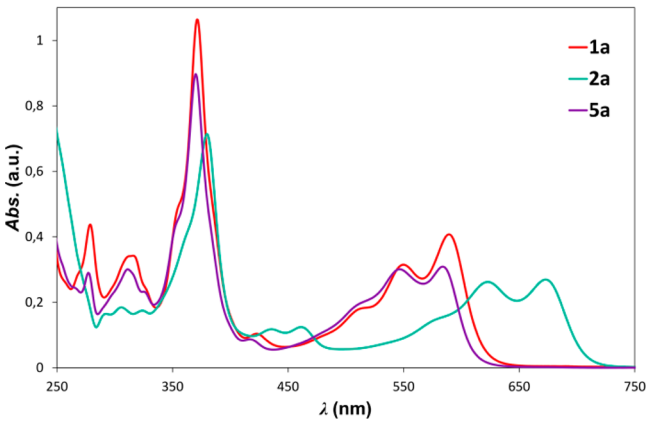


Figure 2. Overlapped UV–vis spectra of heptamethyl cobyrinate **1a**, cobryketone **2a**, and hexamethyl cobyrinate **5a** (35 μM solution) in DCM.

The comparison of absorption spectra showed that the replacement of the propionate side chain with C=O caused a stepwise bathochromic shift of all bands as a consequence of the expansion of the existing conjugated system (Table 5).

However, this was expected as a very pronounced color change could be seen in the isolated compound. The biggest differences were for β and α bands with Δ of ~80 nm, while the γ band was only slightly affected (entries 1, 2). The intensity of

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Table 5. Comparison of the Effect of Core Modification on Absorption Spectra[a]

		λ [nm]			
entry	compound	ε	γ	β	α
1	**1a**	315	371	549	589
2	**2a**	324	380	623	673
3	**5a**	311	370	547	584

[a]Spectra recorded in DCM.

all bands decreased and the ratio of intensity of the β band relatively to the α band increased from 0.77 to 1.00 suggesting a change in the vibronic structure of the corrinoid. On the other hand the removal of the *d*-propionate side chain had little effect on the absorption spectra (entry 3).

The complete assignment of signals in ^{1}H and ^{13}C NMR spectra was based on two-dimensional NMR techniques (COSY, HSQC, and HMBC, Figure 3).

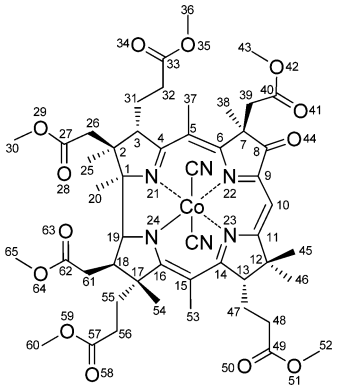

Figure 3. Numbering scheme for cobryketone **2a**.

Surprisingly, the perturbation to the B corrin ring has a substantial effect in almost all proton resonances and direct comparison with heptamethyl cobyrinate **1a** was impossible (see Figure 4).

The assignment started from the B-ring where the ketone group was located as the remaining part of the compound was unmodified. One of the main features of this spectrum was the presence of the *meso*-proton resonance at 6.41 ppm, indicating that no modification had occurred at this position, and the lack of signals corresponding to C8 H. The second important aspect was the presence of only six singlets corresponding to six $-CO_2CH_3$ groups, whereas for heptamethyl cobyrinate **1a** seven resonances are present, confirming the loss of one methylester group (see Figure 4).

In ^{13}C spectrum an unusually downfield signal at 200.8 ppm was present, which is characteristic of the resonance of the carbonyl group. Subsequently, in the ^{1}H-detected heteronuclear multiple-bond multiple-quantum coherence (HMBC) experiment the carbonyl peak (200.8 ppm) correlated with four proton signals: 6.41 ppm (C10), 3.10 and 2.75 ppm (both C39; CH_2-*c*-position), and 0.94 ppm (C38; $-CH_3$) supporting the loss of *d*-propionate side chain. Following the trail, C10 H (6.41 ppm) correlated to C8 (200.84 ppm), C11 (178.62 ppm), C9 (152.3 ppm), and C12 (47.6 ppm). C39 (CH_2-*c*-postion) correlated to C40 (C═O, 168.8 ppm), which in turn correlated to C43 ($-CH_3$, 53.3 ppm) on the methylester. This therefore proves the state of the B-ring. A detailed correlation

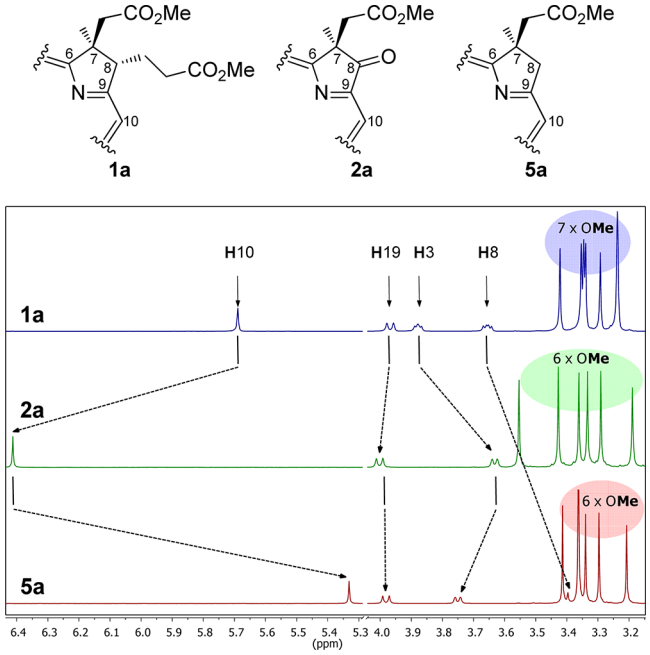

Figure 4. Comparison of ^{1}H NMR spectra of compounds **1a**, **2a**, and **5a**.

table for cobryketone **2** can be found in the Supporting Information.

The full assignment of heptamethyl cobyrinate **1a** was undertaken by Battersby et al., and we compared it to the spectra of hexamethyl cobyrinate **5a** (see Figure 4).[24] The loss of the *d*-side chain caused substantial changes to the ^{1}H NMR spectra of ester **5a**. As expected only six well resolved signals corresponding to methyl esters were present. Moreover, the resonances of C10 H and C8 H were upfield shifted. In the HMBC experiment the signal at 5.33 ppm (C10 H) cross-peaked with four carbon signals corresponding to C12 (46.5 ppm), C11 (176.4 ppm), C9 (168.5 ppm) and C8 (49.6 ppm). Subsequently, in the ^{1}H-detected heteronuclear single-bond multiple-quantum coherence (HSQC) experiment the signal relating to C8 (49.6 ppm) correlated with two doublets at 3.38 and 2.56 ppm. These two signals were coupled to each other with geminal coupling constant confirming the 8-position as CH_2. Furthermore, the correct assignment was supported by the presence of crosspeaks of C10 H (5.33 ppm), C39 H (2.46 and 2.40 ppm), and C38 H (1.14 ppm) with C8 at 49.6 ppm. For a correlation table see Supporting Information.

Mechanistic Considerations. The main byproduct formed in the studied reaction is *c*-lactone **3a**, which proved not to transform into cobryketone **2a**; hence the unwanted byproduct is generated competitively to desired ketone **2a**. Thus, we assume that the first step requires oxidation at the C8 position to alcohol **A** (Scheme 3). Such unusual hydroxylation at this position in cobyrinic acid derivatives has been already observed in the synthesis of cobinamides *via* the aminolysis of esters.[25]

Miura et al. have found that alcoholic substrates can undergo aryl−aryl coupling *via* C−C bond cleavage and that alcoholic oxygen can act as an effective coordinating group.[20] Although such types of reactions are most common in strained four-membered ring systems,[26] they can also proceed with the liberation of ketones for acyclic alcohols. For example, the reaction of 2-naphtyl-2-propanol with bromobenzene in the

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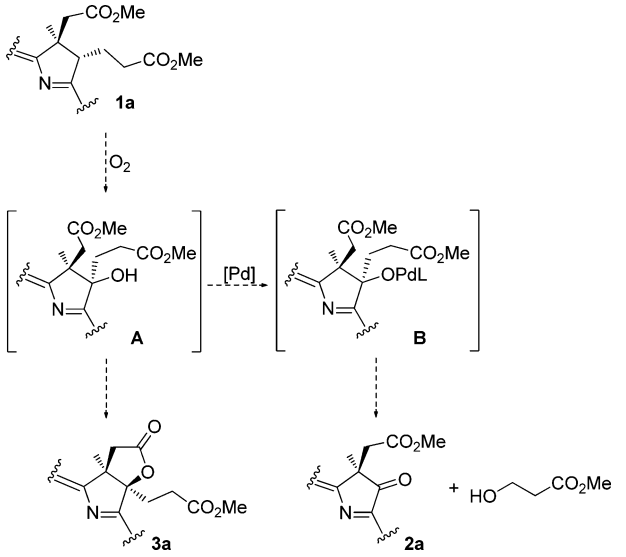
Scheme 3. Mechanistic Hypothesis



presence of $Pd(OAc)_2/PPh_3/Cs_2CO_3$ furnishes 2-phenylnaphtalene in 94% yield with the liberation of acetone.[19]

In our case the initially formed alcohol can undergo either lactonization to *c*-lactone **3a** or C−C bond cleavage leading to cobryketone **2a**. These may imply C−C bond cleavage proceeding *via* coordination of the alcoholic oxygen to $Pd(OAc)_2$ followed by selective elimination (Scheme 3). In such type of reactions coordination of the phenolic oxygen to phenylpalladium(II) species is the key step.[19,20] If an analogous mechanism operates in our reaction, cobryketone formed must be accompanied by some kind of methyl propionate derivative. GC−MS of the crude reaction mixture revealed the presence of a compound with m/z = 103. Its fragmentation pattern is in agreement with the database spectra recorded for methyl 3-hydroxypropanoate (see Supporting Information).[27] Consequently, it was added as an internal standard supporting its formation during the reaction of heptamethyl cobyrinate with palladium acetate. For hepta-*n*-butyl cobyrinate **1b** GC−MS analysis showed the presence of 3-butoxypropanoic acid instead of *n*-butyl 3-hydroxypropanoate. However, addition of an internal standard revealed that isomerization of the *n*-butyl 3-hydroxypropanoate to 3-butoxypropanoic acid occurred during the GC−MS experiment. To the best of our knowledge the palladium catalyzed C−C bond cleavage providing ketones has only been observed during aryl−aryl coupling.[19,20] However, in our case, the addition of bromobenzene and Cs_2CO_3 as a base to the reaction mixture did not result in the arylation of the corrin macrocycle. The role of water in the reaction is still unknown. Experiments with isotope labeled H_2O^{17} showed no incorporation of O^{17} into neither *c*-lactone nor cobryketone. The GC−MS of crude reaction also showed no differences in the fragmentation pattern of methyl 3-hydroxypropanoate.

Other possible mechanisms that can be considered involve oxidation of the C8 position to afford hydroperoxide. Upon cleavage of the C−C bond ketone and alcohol are formed.[28] Such cumene rearranged type reaction involves radicals as intermediates. To figure out whether the radical intermediate was involved in the reaction, the inhibition experiment with the addition of TEMPO as a trap for the radical[29] was performed. Desired cobryketone **2a** was obtained in the same yield as the initial experiment, ruling out any radical type mechanism (see Supporting Information).

CONCLUSIONS

In conclusion, blue-green cobryketone **2a** was synthesized from heptamethyl cobyrinate **1a** *via* a rare palladium-catalyzed carbon−carbon bond cleavage. We assume that in the first step introduction of the hydroxyl group at the C8 position occurred followed by C−C bond cleavage proceeding *via* coordination of the alcoholic oxygen to $Pd(OAc)_2$. Subsequent selective elimination furnishes desired ketone. The comparison of absorption spectra of cobryketone **2a** with corrinoid **1a** showed that the replacement of the propionate side chain with C═O caused a stepwise bathochromic shift of all bands to longer wavelengths as a result of the expansion of the vitamin's conjugate system of double bonds.

The reduction of cobryketone **2a** with Zn led to hexamethyl cobyrinate **5a** in excellent yield. This new derivative represent a rare example of vitamin B_{12} related corrinoids that lack one or more peripheral side chain.

EXPERIMENTAL SECTION

General information. Analytical grade solvents were used as received. ^1H and ^{13}C NMR spectra were recorded at room temperature with TMS as an internal standard or calibrated on the solvent residual peak (C_6D_6, 7.15 ppm; toluene-d_8, 2.08 ppm). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), td (triplet of doublets), qdd (quartet of double of doublets), and m (multiplet). Coupling constants, *J*, are reported in hertz. Dry column vacuum chromatography (DCVC)[30] was performed using silica gel GF_{254} (10−40 μm). Thin layer chromatography (TLC) was performed using silica gel GF_{254}, 0.20 mm thickness. Low and high resolution mass spectra were recorded using electrospray ionization (ESI) method and time of flight (TOF) detector. UV−vis absorption spectra were recorded in DCM unless otherwise noted. Melting points are uncorrected. $(CN)_2Cby(III)(OMe)_7$ **1a**,[31] $(CN)_2Cby(III)(O\text{-}n\text{-}Bu)_7$ **1b**,[8a] and monoamide **1c**[10b] were synthesized according to the literature procedures.

$(CN)_2Cby(III)(8\text{-}CO)(OMe)_6$ (2a). Dry DMF was saturated with oxygen by passing it through for 1 h at room temperature. Palladium(II) acetate (0.6 mg, 2.8 μmol), triphenylphosphine (1.4 mg, 5.5 μmol), and heptamethyl cobyrinate **1a** (15 mg, 14 μmol) were weighed into a screw cap Schlenk tube. A H_2O in DMF (0.2 mL; 0.07 M) solution was prepared and added to the reaction mixture. A balloon of oxygen was attached, and the mixture was stirred at 80 °C in darkness for 4.5 h. The mixture was then diluted with DCM (20 mL) and washed with NaCN aq (20 mL). The product was extracted using DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified using DCVC, 1−3% MeOH in toluene. Recrystallization from hexane/toluene gave cobryketone **2a** as a blue-green solid (4.5 mg, 32%): mp 140−142 °C. R_f 0.41 (15% MeOH in toluene); ^1H NMR (500 MHz, C_6D_6, 303 K) δ 6.41 (s, 1H), 4.00 (d, J = 10.4 Hz, 1H), 3.63 (d, J = 8.1 Hz, 1H), 3.55 (s, 3H), 3.43 (s, 3H), 3.36 (s, 3H), 3.33 (s, 3H), 3.29 (s, 3H), 3.19 (s, 3H), 3.10 (d, J = 16.2 Hz, 1H), 2.92−2.83 (m, 2H), 2.82 (t, J = 6.0 Hz, 1H), 2.75 (d, J = 16.2 Hz, 1H), 2.76−2.68 (m, 1H), 2.60−2.50 (m, 2H), 2.49−2.34 (m, 3H), 2.33−2.12 (m, 4H), 2.21 (s, 3H), 2.11−1.95 (m, 2H), 2.03 (s, 3H), 1.91−1.68 (m, 3H), 1.45 (s, 3H), 1.15 (s, 3H), 0.94 (s, 3H), 0.92 (s, 6H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6, 303 K) δ 200.8, 178.6, 176.2, 174.0, 173.6, 172.7, 172.2, 171.9, 171.7, 168.8, 163.7, 157.2, 152.3, 105.9, 105.6, 87.6, 83.4, 76.0, 58.7, 57.6, 54.2, 53.3, 51.7, 51.5, 51.3, 51.2, 51.0, 50.4, 47.6, 46.7, 42.2, 41.1, 39.8, 34.3, 33.4, 31.7, 30.7, 30.0, 29.9, 25.9, 24.9, 23.0, 21.5, 19.3, 18.6, 16.6, 16.0, 14.9 ppm; HRMS ESI (m/z) calcd for $C_{49}H_{65}CoN_5O_{13}$ $[M - CN]^+$ 990.3905, found 990.3914; UV−vis (CH_2Cl_2) λ (ε, M^{-1} cm^{-1}) 305 (5.63×10^3), 324 (5.30×10^3), 380 (2.13×10^4), 436 (3.53×10^3), 461 (3.63×10^3), 623 (7.94×10^3),

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673 (7.93×10^3). Anal. Calcd for $C_{50}H_{65}CoN_6O_{13}$: C 59.05, H 6.44, N 8.26. Found: C 58.89, H 6.55, N 8.04.

$(CN)_2$Cby(III)(8-CO)(O-*n*-Bu)$_6$ (2b). Following the procedure described for the synthesis of ketone **2a**, compound **2b** was obtained from hepta-*n*-butyl cobyrinate (**1b**) (77 mg, 5.5 μmol), palladium(II) acetate (5.5 mg, 11 μmol), and triphenylphosphine (5.8 mg, 22 μmol). The reaction was stirred with a continuous stream of O_2 passing through the solution for 24 h. The crude product was purified using DCVC, 0.5−3% *i*-PrOH in DCM. Ketone **2b** was obtained as a blue-green solid (14.5 mg, 21%): mp 114−117 °C. R_f 0.41 (15% *i*-PrOH in hexane); ^{1}H NMR (500 MHz, C_6D_6, 303 K) δ 6.40 (s, 1H), 4.22 (m, 2H), 4.14−3.93 (m, 10H), 3.93−3.86 (m, 3H), 3.10 (d, J = 15.9 Hz, 1H), 3.02−2.93 (m, 2H), 2.89−2.80 (m, 2H), 2.76 (d, J = 15.9 Hz, 1H), 2.71−2.44 (m, 5H), 2.41−2.25 (m, 3H), 2.31 (s, 3H), 2.24−1.97 (m, 5H), 2.13 (s, 3H), 1.96−1.88 (m, 1H), 1.82−1.72 (m, 1H), 1.52 (s, 3H), 1.50−1.31 (m, 16H), 1.30 (s, 3H), 1.28−1.12 (m, 15H), 0.91 (s, 3H), 0.85−0.72 (m, 18H) ppm; ^{13}C NMR (125 MHz, C_6D_6, 303 K) δ 200.8, 178.5, 176.3, 174.1, 173.3, 172.4, 172.0, 171.7, 171.4, 168.3, 163.8, 157.3, 152.5, 105.8, 105.7, 87.6, 83.5, 76.1, 66.0, 65.1, 64.8, 64.7, 64.6, 64.2, 58.8, 57.7, 54.2, 50.4, 47.5, 46.7, 42.5, 41.3, 39.8, 34.5, 33.6, 32.0, 31.03, 30.95, 30.92, 30.89, 30.74, 30.72, 30.69, 30.3, 30.2, 30.1, 25.9, 25.0, 23.0, 21.4, 19.5, 19.42, 19.37, 19.34, 19.1, 18.7, 16.7, 15.8, 14.9, 13.9, 13.79, 13.78, 13.73, 13.70 ppm; HRMS ESI (m/z) calcd for $C_{67}H_{101}CoN_5O_{13}$ $[M - CN]^+$ 1242.6728, found 1242.6771; UV−vis (CH_2Cl_2) λ (ε, M^{-1} cm^{-1}) 305 (6.82×10^3), 380 (2.57×10^4), 434 (4.30×10^3), 460 (4.21×10^3), 623 (9.91×10^3), 673 (1.01×10^4). Anal. Calcd for $C_{68}H_{101}CoN_6O_{13} + H_2O$: C 63.43, H 8.06, N 6.53. Found: C 63.27, H 8.01, N 6.30.

$(CN)_2$Cby(III)(*c*-lactone)(O-*n*-Bu)$_6$ (3b). Following the procedure described for the synthesis of ketone **2a** compound **3b** was obtained from hepta-*n*-butyl cobyrinate **1b** (77 mg, 5.5 μmol), palladium(II) acetate (5.5 mg, 11 μmol), and triphenylphosphine (5.8 mg, 22 μmol). The reaction was stirred with a continuous stream of O_2 passing through the solution for 24 h. The crude product was purified using DCVC, 0.5−5% *i*-PrOH in DCM. Lactone **3b** was obtained as a purple solid (9 mg, 13%): mp 98−102 °C. R_f 0.32 (15% *i*-PrOH in hexane); ^{1}H NMR (500 MHz, C_6D_6, 303 K) δ 5.87 (s, 1H), 4.15−3.86 (m, 14H), 3.02 (d, J = 15.0 Hz, 1H), 2.94 (m, 1H), 2.83−2.63 (m, 4H), 2.62−2.34 (m, 8H), 2.32−2.23 (m, 3H), 2.25 (s, 3H), 2.20−1.93 (m, 5H), 1.96 (s, 3H), 1.87 (m, 1H), 1.78 (m, 1H), 1.52−1.06 (m, 30H), 0.98 (s, 3H), 0.96 (s, 3H), 0.92 (s, 3H), 0.84−0.75 (m, 15H), 0.73 (t, J = 7.3 Hz, 3H), 0.68 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, C_6D_6, 303 K) δ 178.7, 176.1, 175.4, 173.3, 172.4, 172.2, 171.93, 171.89, 171.7, 171.4, 166.0, 163.6, 160.6, 104.2, 103.8, 93.7, 89.1, 83.1, 75.5, 65.1, 64.9, 64.64, 64.59, 64.57, 64.1, 58.6, 57.2, 54.1, 50.7, 47.5, 46.2, 42.2, 41.9, 39.8, 33.9, 33.3, 32.0, 31.04, 30.99, 30.91, 30.85, 30.73, 30.71, 30.4, 30.2, 29.2, 26.0, 25.0, 22.3, 19.43, 19.37, 19.36, 19.33, 19.33, 19.29, 18.9, 18.2, 17.04, 17.02, 15.7, 13.82, 13.80, 13.78, 13.74, 13.65 ppm; HRMS ESI (m/z) calcd for $C_{70}H_{105}CoN_5O_{14}$ $[M - CN]^+$ 1298.6990, found 1298.7003; UV−vis (CH_2Cl_2) λ (ε, M^{-1} cm^{-1}) 279 (1.06×10^3), 319 (9.50×10^3), 370 (2.65×10^4), 422 (2.80×10^3), 577 (9.03×10^3), 595 (1.03×10^4). Anal. Calcd for $C_{71}H_{105}CoN_6O_{14} + H_2O$: C 63.47, H 8.03, N 6.25. Found: C 63.63, H 7.95, N 6.16.

$(CN)_2$-8-*nor*-Cby(III)(*c*-acid)(OMe)$_5$ (4). Compound **2** (61 mg, 60 μmol) was dissolved in toluene (4 mL) and AcOH (0.8 mL). The mixture was degassed by sonicating and bubbling argon for 2 min. It was then vigorously stirred, and freshly activated zinc dust (930 mg, 14.2 mmol) was added. The reaction was left at room temperature in darkness for 30 min. It was then passed through Celite and washed with DCM until the Celite remained colorless. The filtrate was then neutralized with $NaHCO_3$ aq and washed with NaCN aq, and organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified using DCVC, 2−25% MeOH in toluene. Recrystallization from hexane/DCM gave acid **4** as a red solid (48 mg, 81%) and was used without further purification: R_f 0.46 (25% MeOH in toluene); HRMS ESI (m/z) calcd for $C_{48}H_{65}CoN_5O_{12}$ $[M - CN]^+$ 962.3962, found 962.3951.

The broadening of peaks in the ^{1}H NMR spectrum made it impossible to decipher, and consequently high resolution ^{13}C spectra could not be obtained. This was caused by the presence of the acid group.

$(CN)_2$-8-*nor*-Cby(III)(OMe)$_6$ (5a). *c*-Acid **4** (29 mg, 29 μmol), EDC·HCl (14 mg, 88 μmol), and DMAP (11 mg, 88 μmol) were dissolved in dry DCM (3 mL) and cooled in an ice bath. The mixture was then treated with methanol (0.5 mL, 12 mmol) under an argon atmosphere in darkness and allowed to stir at room temperature for 16 h, after which the reaction mixture was diluted with DCM (25 mL) and washed with NaCN aq (25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified using DCVC, 0.5−4% MeOH in toluene. Recrystallization from hexane/toluene gave compound **5a** as a purple solid (19.0 mg, 65%): mp 178−182 °C. R_f 0.37 (5% MeOH in toluene); ^{1}H NMR (500 MHz, C_6D_6, 303 K) δ 5.33 (s, 1H), 3.98 (d, J = 10.5 Hz, 1H), 3.75 (d, J = 7.7 Hz, 1H), 3.41 (s, 3H), 3.38 (d, J = 17.7 Hz, 1H), 3.364 (s, 3H), 3.362 (s, 3H), 3.34 (s, 3H), 3.30 (s, 3H), 3.21 (s, 3H), 2.94 (d, J = 15.3 Hz, 1H), 2.85 (td, J = 10.1 and 3.1 Hz, 1H), 2.78 (t, J = 5.6 Hz, 1H), 2.77−2.68 (m 2H), 2.56 (d, J = 17.7 Hz, 1H), 2.53−2.30 (m, 8H), 2.24 (d, J = 15.3 Hz, 1H), 2.20 (s, 3H), 2.22−2.09 (m, 2H), 2.02 (s, 3H), 2.08−1.97 (m, 1H), 1.96−1.74 (m, 3H), 1.49 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H), 0.95 (s, 3H) ppm; ^{13}C NMR (125 MHz, C_6D_6, 303 K) δ 176.4, 175.4, 174.7, 173.8, 172.9, 172.3, 172.1, 171.7, 170.5, 168.5, 164.7, 163.9, 103.7, 102.3, 89.9, 82.9, 75.4, 58.4, 57.4, 53.8, 51.7, 51.5, 51.4, 51.3, 51.2, 51.0, 49.6, 46.7, 46.3, 44.8, 42.2, 41.4, 39.8, 34.2, 33.3, 31.9, 30.9, 30.7, 30.0, 26.0, 24.9, 24.7, 22.5, 19.6, 18.4, 16.8, 15.5, 15.4 ppm; HRMS ESI (m/z) calcd for $C_{50}H_{67}CoN_6O_{12}$ $[M]^+$ 1002.4149, found 1002.4133; UV−vis (CH_2Cl_2) λ (ε, M^{-1} cm^{-1}) 277 (8.21×10^3), 311 (8.52×10^3), 370 (2.54×10^4), 417 (2.46×10^3), 546 (8.52×10^3), 584 (8.75×10^3). Anal. Calcd for $C_{50}H_{67}CoN_6O_{12} + H_2O$: C 58.82, H 6.81, N 8.23. Found: C 58.97, H 6.84, N 8.02.

$(CN)_2$-8-*nor*-Cby(III)(*c*-2-propylamide)(OMe)$_5$ (5b). Compound **4** (30 mg, 30 μmol), isopropylamine (11 μL, 135 μmol), and DIPEA (12 μL, 70 μmol) were dissolved in dry DMF (2 mL) under an argon atmosphere in darkness. DEPC (22 μL, 145 μmol) was then added, and the mixture stirred at room temperature for 16 h, after which it was diluted with DCM (25 mL) and washed with NaCN aq (25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified using DCVC, 0.5−2.5% MeOH in DCM. Recrystallization from hexane/toluene gave compound **5b** as a purple solid (26 mg, 82%): mp 149−151 °C. R_f 0.35 (15% MeOH in toluene); ^{1}H NMR (500 MHz, toluene-d_8, 303 K) δ 7.04−6.93 (m, 1H), 5.31 (s, 1H), 4.15 (dq, J = 13.5 and 6.7 Hz, 1H), 3.84 (m, 1H), 3.74 (d, J = 10.6 Hz, 1H), 3.43 (s, 3H), 3.40 (s, 3H), 3.38 (s, 3H), 3.34 (s, 3H), 3.31 (s, 3H), 2.83−2.76 (m, 2H), 2.73 (d, J = 15.4 Hz, 1H), 2.70−2.18 (m, 13H), 2.16 (s, 6H), 2.14−2.06 (m, 1H), 2.02−1.90 (m, 3H), 1.81−1.64 (m, 2H), 1.60 (s, 3H), 1.45 (s, 3H), 1.15 (s, 3H), 1.05 (d, J = 2.2 Hz, 3H), 1.04 (d, J = 2.2 Hz, 3H), 1.03 (s, 3H), 0.94 (s, 3H), 0.89 (s, 3H) ppm; ^{13}C NMR (125 MHz, toluene-d_8, 303 K) δ 176.0, 175.5, 175.3, 173.8, 172.8, 172.3, 171.8, 171.6, 168.6, 163.8, 163.6, 106.1, 102.1, 90.4, 83.1, 75.1, 58.5, 57.4, 53.8, 52.4, 51.7, 51.4, 51.3, 51.2, 51.0, 48.0, 46.5, 46.1, 46.0, 41.6, 41.5, 39.8, 33.8, 32.9, 31.9, 31.5, 30.6, 29.8, 25.8, 24.9, 23.2, 22.7, 22.6, 22.4, 19.5, 18.0, 16.9, 16.1, 15.6 ppm; HRMS ESI (m/z) calcd for $C_{52}H_{72}CoN_7O_{11}Na$ $[M + Na]^+$ 1052.4520, found 1052.4518; UV−vis (CH_2Cl_2) λ (ε, M^{-1} cm^{-1}) 278 (1.06×10^4), 312 (9.13×10^3), 371 (2.60×10^4), 422 (2.48×10^3), 547 (8.26×10^3), 587 (1.01×10^4). Anal. Calcd for $C_{52}H_{72}CoN_7O_{11} + 2H_2O$: C 58.58, H 7.19, N 9.20. Found: C 58.75, H 7.22, N 9.17.

$(CN)_2$-8-*nor*-Cby(III)(*c*-2-hydroxyethylamide)(OMe)$_5$ (5c). Following the procedure of compound **5b**, compound **5c** was synthesized using ethanoloamine (8 μL, 135 μmol) instead of isopropylamine. The crude product was purified using DCVC, 1−5% EtOH in DCM. Recrystallization from hexane/toluene gave compound **5c** as a purple solid (28 mg, 90%): mp 138−142 °C. R_f 0.45 (20% MeOH in toluene); ^{1}H NMR (500 MHz, toluene-d_8, 303 K) δ 7.05−7.00 (m, 1H), 5.30 (s, 1H), 4.00 (t, J = 6.5 Hz, 1H), 3.91 (m, 1H), 3.69 (d, J = 10.6 Hz, 1H), 3.53 (m, 2H), 3.43 (s, 3H), 3.41−3.37 (m, 2H), 3.40 (s, 3H), 3.39 (s, 3H), 3.38 (s, 3H), 3.35 (s, 3H), 2.83−2.76 (m, 3H), 2.67 (m, 1H), 2.58 (m, 1H), 2.48 (d, J = 15.9 Hz, 1H), 2.45−2.32 (m, 5H), 2.31−2.20 (m, 2H), 2.20−2.11 (m, 3H), 2.17 (s, 3H), 2.15 (s, 3H),

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2.03−1.86 (m, 4H), 1.76 (m, 1H), 1.67 (m, 1H), 1.51 (s, 3H), 1.45 (s, 3H), 1.16 (s, 3H), 1.04 (s, 3H), 0.96 (s, 3H), 0.85 (s, 3H) ppm; ^{13}C NMR (125 MHz, toluene-d_8, 303 K) δ 176.2, 175.8, 175.7, 173.7, 172.7, 172.2, 171.9, 171.6, 169.6, 168.4, 163.7, 162.7, 106.9, 102.3, 90.3, 83.0, 75.1, 61.9, 58.5, 57.0, 53.8, 52.4, 51.7, 51.3, 51.2, 51.0, 48.0, 46.7, 46.5, 46.4, 43.8, 41.7, 39.7, 33.9, 32.8, 31.7, 31.5, 30.5, 29.8, 25.7, 24.9, 23.6, 22.4, 19.5, 17.9, 17.0, 15.7, 15.6 ppm; HRMS ESI (m/z) calcd for $C_{51}H_{70}CoN_7O_{12}Na$ $[M + Na]^+$ 1054.4312, found 1054.4303; UV−vis (CH_2Cl_2) λ (ε, M^{-1} cm^{-1}) = 278 (1.09×10^4), 311 (9.18×10^3), 370 (2.71×10^4), 420 (2.49×10^3), 547 (8.68×10^3), 586 (9.52×10^3). Anal. Calcd for $C_{51}H_{70}CoN_7O_{12} + 2H_2O$: C 57.35, H 6.98, N 9.18. Found: C 57.38, H 6.77, N 9.17.

$(CN)_2$-8-*nor*-Cby(III)(*c*-propargylamide)$(OMe)_5$ (5d). Following the procedure of compound **5b**, compound **5d** was synthesized using acid **4** (10 mg, 10 μmol), propargylamine (2.9 μL, 45 μmol) instead of isopropylamine, DIPEA (4 μL, 23 μmol), DEPC (7.3 μL, 48 μmol), and dry DMF (0.7 mL). The crude product was purified using DCVC, 0.5−2.5% MeOH in DCM. Recrystallization from hexane/toluene gave compound **5d** as a purple solid (8.3 mg, 80%): mp 145−147 °C. R_f 0.40 (15% MeOH in toluene); ^{1}H NMR (500 MHz, toluene-d_8, 303 K) δ 7.39 (t, J = 5.4 Hz, 1H), 5.30 (s, 1H), 3.95 (qdd, J = 17.3 and 5.4 and 2.4 Hz, 2H), 3.74 (t, J = 9.4 Hz, 2H), 3.43 (s, 3H), 3.40 (s, 3H), 3.39 (s, 3H), 3.34 (s, 3H), 3.34 (s, 3H), 2.84−2.77 (m, 2H), 2.73−2.53 (m, 4H), 2.53−2.32 (m, 7H), 2.32−2.14 (m, 4H), 2.18 (s, 3H), 2.11 (s, 3H), 2.02−1.93 (m, 2H), 1.93−1.84 (m, 2H), 1.81−1.66 (m, 2H), 1.52 (s, 3H), 1.44 (s, 3H), 1.16 (s, 3H), 1.04 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H) ppm; ^{13}C NMR (125 MHz, toluene-d_8, 303 K) δ 178.7, 178.1, 177.9, 176.2, 175.2, 174.8, 174.5, 174.1, 171.7, 170.9, 166.3, 165.8, 108.6, 104.7, 92.8, 85.5, 83.5, 77.6, 73.1, 61.1, 59.9, 56.3, 54.2, 54.1, 53.9, 53.8, 53.7, 53.5, 50.0, 49.1, 48.8, 47.8, 44.3, 42.2, 36.3, 35.5, 34.4, 33.8, 33.1, 32.3, 31.3, 28.3, 27.3, 26.1, 24.9, 22.0, 20.6, 19.4, 18.4, 18.1 ppm; HRMS ESI (m/z) calcd for $C_{52}H_{68}CoN_7O_{11}Na$ $[M + Na]^+$ 1048.4207, found 1048.4200; UV−vis (CH_2Cl_2) λ (ε, M^{-1} cm^{-1}) 278 (8.84×10^3), 312 (7.42×10^3), 371 (2.18×10^4), 421 (2.07×10^3), 547 (6.86×10^3), 587 (8.41×10^3). Anal. Calcd for $C_{52}H_{68}CoN_7O_{11} + H_2O$: C 59.82, H 6.76, N 9.39. Found: C 59.80, H 6.73, N 9.17.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

All experimental details and complete analytical data for new products including ^{1}H/^{1}H COSY, ^{13}C/^{1}H HSQC and ^{13}C/^{1}H HMBC NMR spectra and correlation tables for compounds **2a** and **5a**, GC−MS results. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dorota.gryko@icho.edu.pl

Notes

The authors declare no competing financial interest.

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