ing MCM-41 for the more polar epoxide is higher than that of the relatively hydrophobic aluminum-free MCM-41 framework. This observation is supported by thermogravimetric analysis, which indicated that both the water content and the dehydration temperature for the aluminum-free MCM-41 (1%, 49°C) are much lower than that of the the aluminum-containing MCM-41 (5%, 60°C). The higher polarity of the aluminum-containing MCM-41 materials is likely to induce leaching.[8] In contrast, the degree of apolarity of an aluminum-free MCM-41 molecular sieve is ideal for both strong adsorption of the catalyst, leading to a heterogeneous system, and diffusion of the organics through the MCM-41 channel. In contrast to physically enclosed systems, this will lead to a *self-assembled heterogeneous catalyst* that is prone to neither leaching nor deactivation.[9]

Conventional silica gel (Silica Grace SG360, total pore volume ca. $0.9-1.0\ cm^3\,g^{-1}$, surface area roughly $600\ m^2\,g^{-1}$) also adsorbs complex **1**. During catalyst testing, however, this material undergoes a significant degree of leaching (see Table 1). From this finding we conclude that a silica with channel-type pores such as an aluminum-free MCM-41 molecular sieve is essential for an irreversible adsorption of the silsesquioxane complex.

Experimental Section

The different MCM-41 samples were prepared following the procedure used by Beck et al.[10] and adapted by Busio et al.[4] In a typical adsorption experiment 50 mL of a 10^{-3} M solution of **1**[2b] in hexane (p.a., Acros) was added slowly to a suspension of 2 g of dried MCM-41 in hexane (50 mL), and the suspension was stirred for 24 h. The impregnated MCM-41 was subsequently filtered off, washed with hexane (3×20 mL), and dried in air at 80°C for 24 h.

In a typical silylation experiment 0.5 g of a dried and degassed impregnated MCM-41 sample was refluxed in a solution of 70 mL of hexane with 2.5 g of dichlorodiphenylsilane (96%, Acros) under an inert atmosphere for 72 h. The obtained material was filtered off, washed with hexane (3×20 mL) and acetone (p.a., Acros, 3×20 mL), and dried in air at 80°C for 24 h.

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A Biomimetic Synthesis of a Porphobilinogen Precursor Using a Mukaiyama Aldol Reaction**

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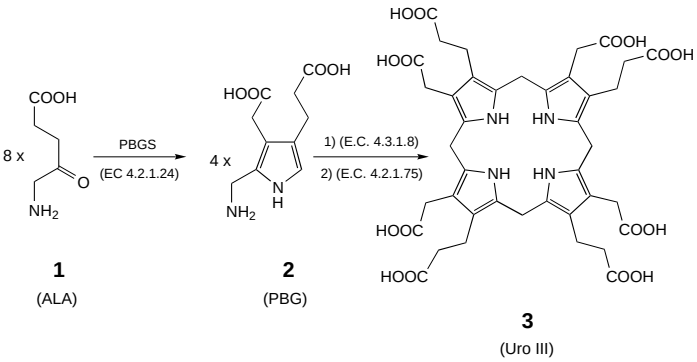
Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

The tetrapyrrolic "pigments of life" fulfill many different functions and therefore have a special position among natural pigments.[1] The structures of the intermediates (δ-aminolevulinic acid (ALA, **1**) and porphobilinogen (PBG, **2**)) leading to uroporphyrinogen (Uro) III (**3**), the precursor of all tetrapyrroles, were determined in the early 1950s (Scheme 1).[2] Even early on, the second and third steps of this elegant and convergent biosynthesis could be mimicked chemically.[3]



Scheme 1. Biosynthesis of uroporphyrinogen III (**3**). PBGS = porphobilinogen synthetase.

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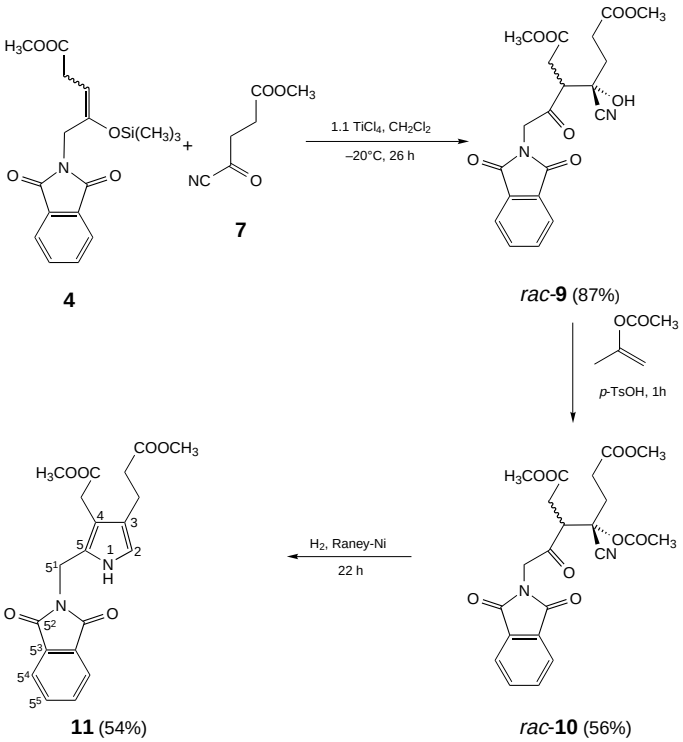
In this context the question arose whether the biosynthesis of porphobilinogen (**2**), which formally corresponds to a Knorr synthesis, could be imitated in the test tube.[4] Despite efforts in different laboratories the process could not be imitated satisfactorily so far. We are examining whether one can imitate the mechanism for the biosynthesis of **2** proposed by Shemin and Nandi[5] and use it for the synthesis of pyrroles.[6] We report here on the synthesis of an N-protected derivative of PBG, which relies on the Mukaiyama aldol reaction.[7] Since the structure determination of **2** 40 years ago, six different synthetic strategies have been developed.[2a, 8] Despite the simplicity of the structure, the synthesis of this natural product in large quantities has remained difficult. In recent years several groups have developed novel approaches to porphobilinogen (**2**).[9]

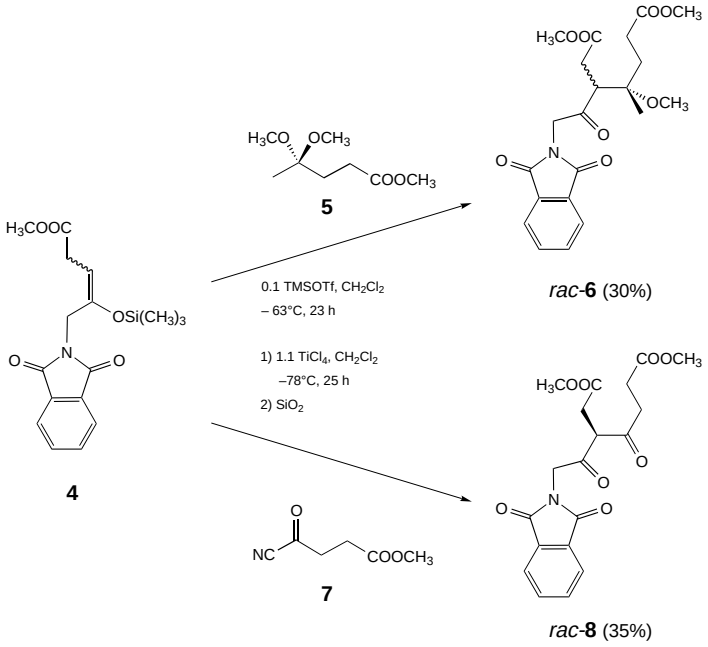
The starting point for our synthesis was the preparation of alkyl-substituted pyrroles using the two-step procedure consisting of a Mukaiyama aldol reaction followed by the reduction of the azido function to give the amino group.[6] The silyl enol ether **4**, obtained from 5-phthalimidomethyllevulinate in 93% yield, was required as starting material for our synthesis.[10] Because **4** is not very nucleophilic, we were unable to couple it under standard conditions with the acetal of 5-azidomethyllevulinate.[6] At temperatures below -40°C $TiCl_4$ was not active enough to catalyze the aldol reaction. At temperatures above -40°C we only could observe decomposition of the starting materials. When we used Lewis acids like TMSOTf[11] or the "super-Lewis acid" $(TMS)B(OTf)_4$ described by Davis[12] we could induce the aldol reaction with the dimethyl acetal of methyllevulinate (**5**). We applied the conditions described by Noyori et al.[11a] with 0.11 equiv TMSOTf as catalyst and were able to isolate 30% of the pure diastereoisomer *rac*-**6** (Scheme 2).

Even with these Lewis acids the crucial C–C bond formation could not be achieved when protected precursors of 5-aminolevulinate were employed. Increasing the reactivity of the carbonyl component seemed the most promising way to solve the problem. When **4** was allowed to react with acylcyanide **7**, the cyanohydrin could be detected in the crude reaction product. However, after aqueous extraction and purification by column chromatography the hydrolysis product *rac*-**8** was obtained in 35% yield (Scheme 2).

Under optimized conditions at -20°C and with $TiCl_4$, which had been freed from HCl by distillation over polyvinylpyridine, the aldol product *rac*-**9** was obtained in 60 to 87% yield (Scheme 3). One diastereoisomer of the aldol



Scheme 3. Synthesis of the protected porphobilinogen **11**.



Scheme 2. Aldol reaction with silyl enol ether **4**.

product *rac*-**9** could be obtained in 47% yield in analytically pure form after crystallization. Attempts to reduce the cyanohydrin *rac*-**9** directly met with limited success. For the synthesis we protected crude *rac*-**9** by reaction with 2-propenol acetate; the acetylated aldol product *rac*-**10** was obtained in 56% yield. Even the reduction of *rac*-**10** proved to be difficult, but finally we were able to reduce *rac*-**10** smoothly at 65°C under 120 atm H_2 in the presence of Raney nickel. After column chromatography we obtained the protected porphobilinogen **11**[13] in 54% yield and in analytically pure form. Removal of the protecting groups in two steps has been described previously.[14]

We were able to obtain the protected porphobilinogen **11** in a convergent way starting from two easily obtainable starting materials. The central step of the synthesis is the Mukaiyama aldol reaction between the regioselectively formed silyl enol ether **4** as the nucleophile and acylcyanide **7** as the electrophile. Reducing the acetylated cyanohydrin *rac*-**10** yields directly the protected porphobilinogen **11**. This synthesis

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follows the proposal for the biosynthesis made by Nandi and Shemin almost 30 years ago. In contrast to the published syntheses of **11**, the correctly functionalized side chains are introduced with the two starting materials used for the synthesis of the pyrrole ring; subsequent functionalization is therefore not necessary. The bonds formed in this synthetic scheme are the same as those formed in the biosynthesis catalyzed by porphobilinogen synthase. The overall yield starting from 5-phthalimidomethyllevulinate is 25%. The synthesis can be used to obtain selectively labeled porphobilinogen.

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[13] NMR data of the protected porphobilinogen **11**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.56$ (br. s, 1H, NH), 7.83–7.76 (m, 2H, HC5^4, HC5$^{4'}$), 7.73–7.67 (m, 2H, HC5^5, HC5$^{5'}$), 6.49 (d, $J = 2.7$ Hz, 1H, HC2), 4.80 (s, 2H, H_2C5^1), 3.67 (s, 3H, H_3C3^4), 3.65 (s, 3H, H_3C4^3), 3.64 (s, 2H, H_2C4^1), 2.72 (pseudo t, $J \approx 7.6$ Hz, 2H, H_2C3^1), 2.53 (pseudo triplet, $J \approx 7.3$ Hz, 1H, H_2C3^2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.4$ (s, C3^3), 173.1 (s, C4^2), 169.0 (s, C5^2, C5$^{2'}$), 134.7 (d, C5^5, C5$^{5'}$), 132.7 (s, C5^3, C5$^{3'}$), 125.3 (s, C5), 124.0 (s, C5^4, 5$^{4'}$), 122.2 (s, C4), 116.0 (d, C2), 113.7 (s, C3), 52.6 (q, C3^4), 52.1 (q, C4^3), 35.3 (t, C3^2), 33.0 (t, C5^1), 30.3 (t, C4^1), 21.2 (t, C3^1).
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First Isolation and Structural Characterization of a Nickel(III) Complex Containing Aliphatic Thiolate Donors**

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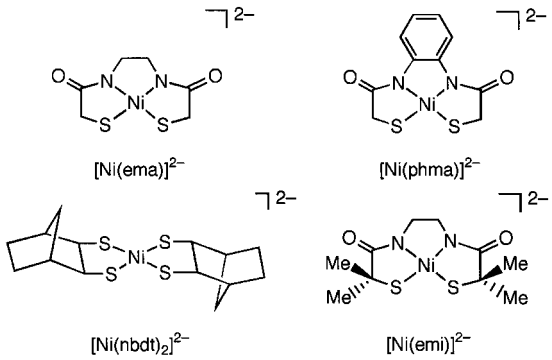
Dedicated to Professor Richard H. Holm on occasion of his 65th birthday

The discovery of a nickel site with a thiolate-rich ligand environment in hydrogenases some 15 years ago stimulated considerable interest in nickel(II) thiolate complexes and their redox behavior.[1] Because of the recent crystal structure determination of the enzyme from the sulfate-reducing bacterium *Desulfovibrio gigas*, the initial description of the nickel site as a mononuclear metal center was revoked, and the heterobimetallic nature firmly established.[2] Efforts towards modeling the structure and reactivity of the active site in nickel-containing hydrogenases are now shifting from the synthesis of mononuclear nickel thiolate complexes towards the synthesis of thiolato-bridged iron–nickel complexes. However, one of the original tasks for inorganic chemists has, to our knowledge, never been accomplished: namely, the preparation *and* isolation of a stable mononuclear nickel(III) complex with aliphatic thiolate donors[3] in the coordination environment. Here we report on the first successful isolation and structural characterization of such a complex.

Previous endeavors to synthesize mononuclear nickel(III) complexes with aliphatic thiolates utilized the nickel(II) complexes depicted in Scheme 1.[4] Although solutions of



Scheme 1. Nickel(II) complexes with aliphatic thiolate ligands which have been used to electrochemically generate nickel(III) complexes in solution.[4]

the relatively stable nickel(III) complexes $[Ni(nbdt)_2]^-$ and $[Ni(emi)]^-$[4] could be electrochemically generated, no solid compounds were isolated. Recently, we showed that stable copper(II) and even copper(III) complexes can be prepared with the quadruply deprotonated ligand *N*,*N*′-1,2-phenylenebis(2-sulfanyl-2-methylpropionamide) (H_4phmi).[5] With respect to its donor-atom set, H_4phmi is related to some of the

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