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

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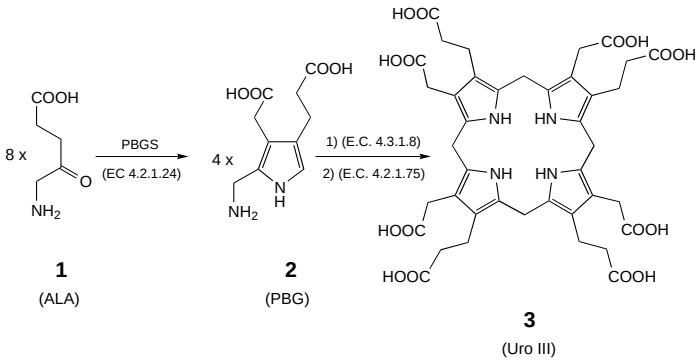
Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

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.

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]

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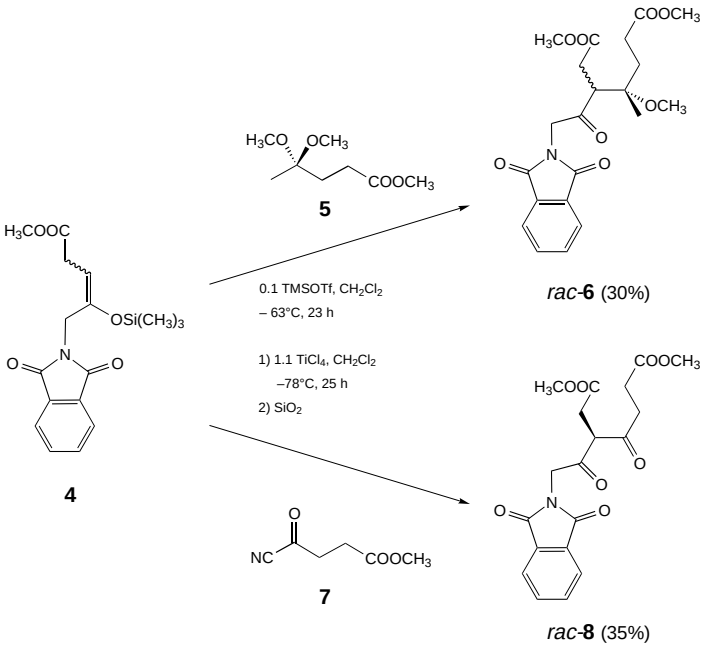
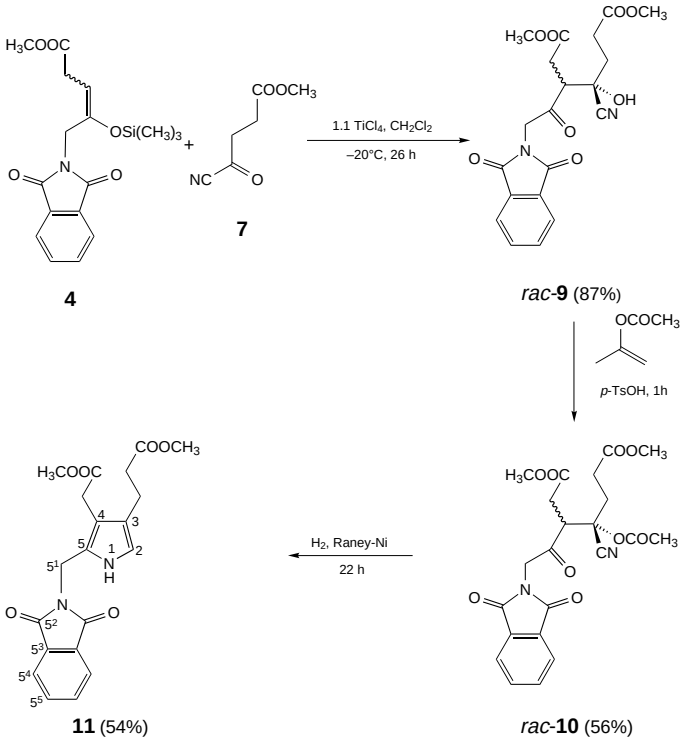
The starting point for our synthesis was the preparation of alkyl-substituted pyrroles using the two-step procedure consisting of a Mukaiyama aldol reaction followed by the reduction of the azido function to give the amino group.[6] The silyl enol ether **4**, obtained from 5-phthalimidomethyllevulinate 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).



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

Under optimized conditions at $-20^{\circ}C$ 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**.

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 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.

Keywords: aldol reactions · biomimetic synthesis · bioorganic chemistry · porphobilinogen · porphyrinoids

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[13] NMR data of the protected porphobilinogen **11**: ^1H 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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