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Synthesis of a linear α-hydroxymethyl-pentapyrrole derivative and its cyclization to uroporphyrinogens

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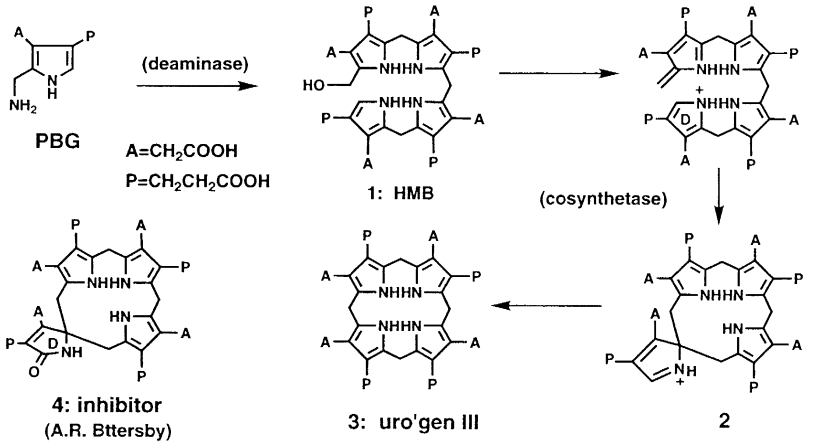
Abstract

A linear pentapyrrole bearing α-hydroxymeythyl group in the terminal was synthesized by the stepwise coupling of α-free pyrrole with azafulvenium ion **6**. When it was treated with a catalytic amount of *p*-toluensulfonic acid under anaerobic condition, followed by aerial oxidation of the products, a statistical mixture of uroporphyrin I–IV octamethyl esters was obtained. It is proposed that this transformation proceeds through a spiro-pyrrolenine as a key intermediate. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: coupling reaction; linear pentapyrrole derivatives; rearrangement; spiro-pyrrolenine intermediate.

Hydroxymethylbilane (**1**; HMB), constructed by assembling four molecules of porphobilinogen (PBG) with loss of four molecules of ammonia in the presence of deaminase, acts as the substrate for a second enzyme (cosynthetase) which cyclizes the bilane with concomitant intramolecular rearrangement of the terminal ring-D to generate uroporphyrinogen III (**3**; uro'gen III).[1,2] The spiro-pyrrolenine **2** is a most favorite intermediate, since the corresponding ring-D lactam **4** has been shown to function as an inhibitor of cosynthetase.[3–6]



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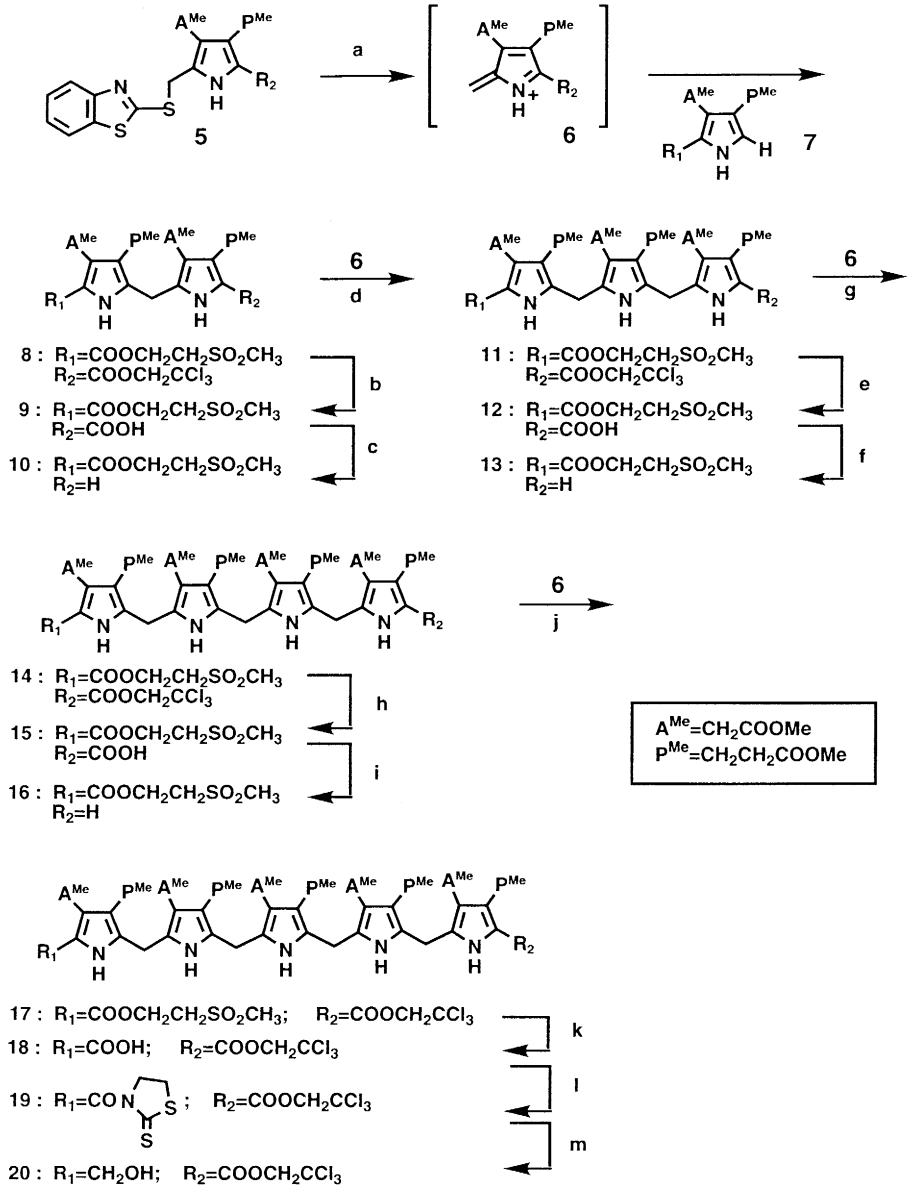
Based on biosynthetic mechanism of uroporhyrinogen III, we undertook the synthesis of linear pentapyrrole derivative bearing terminal azafulvenium chromophore **21**, which would be a model for the natural intermediate in rearrangement. The synthetic strategy of precursor **17** was based on our previous work of pyrromethane synthesis under neutral conditions: treatment of 2-mercaptobenzothiazolylmethyl-pyrrole **5** in dry benzene with silver (I) trifrate generates the azafulvenium ion **6**,[7] which condenses with α-free pyrrole **7** to give pyrromethane **8** in excellent yield. Pyrromethane **8** was converted to α-free tripyrrole **10** by deprotection of trichloroethyl ester **8** and decarboxylation of **9**. Coupling of **10**



Scheme 1. *Reagents and conditions*: (a) AgOTf–Na_2HPO_4/benzene, 10 min, 97.3%; (b) Zn/80% AcOH–THF, 3 h, 97.3%; (c) AcOH/135°C, Ar, 10 min, 83.3% (90.5%); (d) in CH_3CN, 1 h, 71.9% (97.2%); (e) Zn/80% AcOH–THF, 3 h, 84.8% (98.0%); (f) AcOH/135°C, Ar, 2 min, 52.0% (95.0%); (g) in CH_3CN, 1 h, 53.3% (91.4%); (h) Zn/80% AcOH–THF, 3 h, 76.5% (90.9%); (i) AcOH/135°C, Ar, 1 min, 21.5% (82.0%); (j) in CH_3CN, 1 h, 52.9% (63.6%); (k) 0.1 N KOH–MeOH/CH_2Cl_2-MeOH (1:1), 15 min, 63.4% (70.3%); (l) 2-mercaptothiazole/DCC–DMAP/CH_2Cl_2, 4 h, 65.5% (85.6%); (m) $NaBH_4$/CH_2Cl_2-MeOH (2:1), 10 min, SiO_2 short column/CH_2Cl_2-MeOH (100:3)

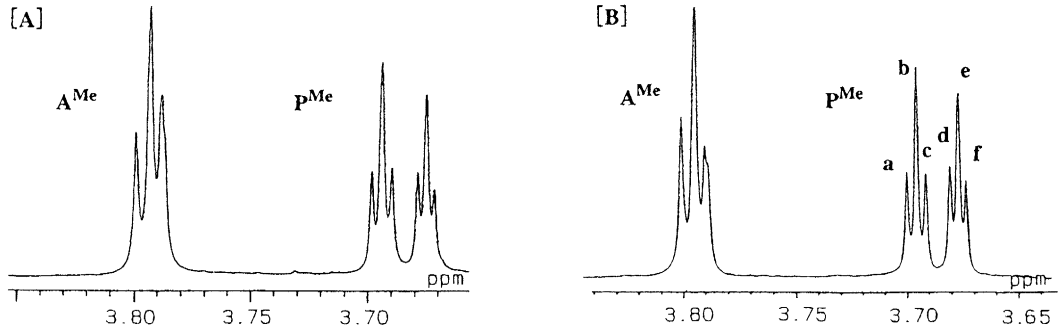
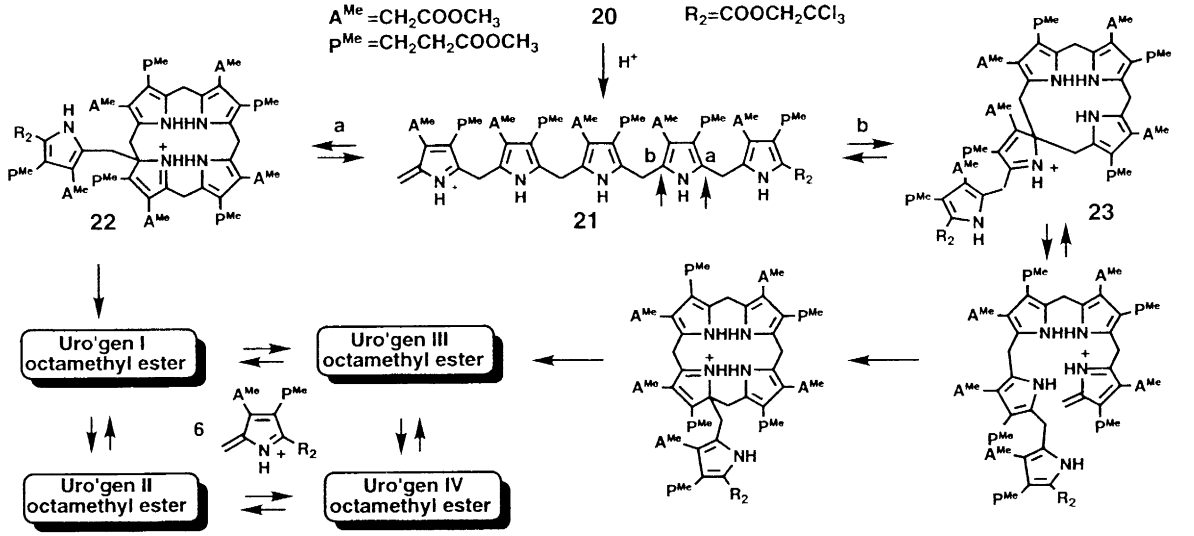


Fig. 1. The Me ester regions of acetic acid ($\mathbf{A^{Me}}$) and propionic acid ($\mathbf{P^{Me}}$) side chain of the 400 MHz NMR spectra ($CDCl_3$), involved in the isomers of uroporphyrin octamethyl ester, are described. [**A**] is the spectrum of a mixture of uroporphyrin octamethyl esters obtained from **20** and [**B**] is the spectrum of a statistical mixture of uroporphyrin octamethyl esters of type I, II, III and IV (1:1:4:2): marked **a**=III (1.5H); **b**=I (1.5H)+IV (1.5H); **c**=III (1.5H); **d**=IV (1.5H); **e**=III (3H); **f**=II (1.5H)

with azafluvenium ion **6** in dry acetonitrile proceeded smoothly at room temperature to give **11** in high yield. Similar deprotection of ester **11** and decarboxylation of **12** followed by coupling reaction of **13** with **6** produced tetrapyrrole **14** as shown in Scheme 1.[8] In the same way, **14** was transformed to the desired linear pentapyrrole **17** through carboxylic acid **15** and α-free pyrrole derivative **16** even in low yield. Finally, conversion of methylsulfonylethyl ester moiety of **17** to hydroxymethyl function was performed by alkaline hydrolysis of **17** to give **18**, which was followed by formation of amide with 2-mercaptothiazoline and selective reduction with sodium borohydride in dichloromethane–methanol (2:1), giving rise to unstable α-hydroxymethylpentapyrrole derivative **20**.[9]

To a solution of **20** (6.2 mg) in dichloromethane (3 ml) was added a cataytic amount of *p*-toluenesulfonic acid (0.1 mg) and the mixture was stirred at room temperature under argon atmosphere for 20 h. A large amount of powdered sodium acetate was added to the mixture which was further stirred for 1 h under oxygen atmosphere for oxidation of the products. The major product (2.2 mg), separated from the mixture on silica gel TLC (CH_2Cl_2:MeOH 100:3), was characterized as a statistical mixture of four isomers of urophorphyrin octamethyl esters (I:II:III:IV=1:1:4:2). ^{1}H NMR spectrum of the product between 3.67–3.85 ppm was absolutely identical with that of an authentic sample as shown in Fig. 1.

We propose that α-hydroxymethyl-pentapyrrole derivative **20** is dehydrated under acidic conditions to



Scheme 2.

generate the pentapyrrole **21** bearing azafulvenium chromophore in the terminal position of the molecule. As illustrated in Scheme 2, compound **21** will then cyclize in two ways, to afford **22** and **23**, the precursor of uro'gen I and uro'gen III octamethyl ester, respectively, during formation of the mixture of uro'gen IIV octamethyl esters as discussed in the previous paper.[10] It is obvious that one of a possible route in the transformation from **20** to uro'gen III octamethyl ester involves azafulvene **21** and spiro-pyrrolenine intermediate **23**. This process is a model for the biosynthetic pathway from HMB **1** to uro'gen III **3**.

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8. Typical procedure for deprotection of ester (**b**), decarboxylation (**c**) and coupling reaction (**d**) are as follows: (**b**) to a solution of **8** (150 mg, 0.19 mmol) in THF-80% AcOH (5:1, 3.6 ml) was added Zn powder (750 mg) and the mixture was stirred vigorously for 3 h at rt. After filtration followed by concentration of the reaction mixture, the resulting residue was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH=100:2) to give **9** (121.5 mg, 97.3%); (**c**) a solution of **9** (325.0 mg, 0.495 mmol) in AcOH (32.5 ml) was heated at 135°C for 10 min under argon in the dark. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (CH_2CCl_2:MeOH=100:1) to give**10** (252.3 mg, 83.3%, corrected yield 90.5%) along with starting material **9** (26.2 mg); (**d**) to a solution of **10** (112 mg, 0.183 mmol) and **5** (211.6 mg, 0.366 mmol) in CH_3CN (5 ml) were added AgOTf (141 mg, 0.549 mmol) and Na_2HPO_4 (233.9 mg, 1.65 mmol) under Ar and the mixture was stirred at rt for 1 h. After dilution with CH_2CCl_2 (50 ml), the mixture was washed with saturated aq. soln of $NaHCO_3$, brine and concentrated. The residue was purified by flash column chromatography on silica gel (CH_2CCl_2:MeOH=200:1) to give **11** (134.6 mg, 71.9%; corrected yield 97.2%) along with **10** (29.12 mg).
9. After passing the reaction mixture through a short silica gel column (H:10 mm, ϕ:10 mm) which was washed with degassed CH_2Cl_2:MeOH (2:1, 5 ml) under Ar, the combined eluates were concentrated under reduced pressure. The residue was used directly for the next reactions.
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