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# Enantioselective Synthesis of Hematoporphyrin Stereoisomers

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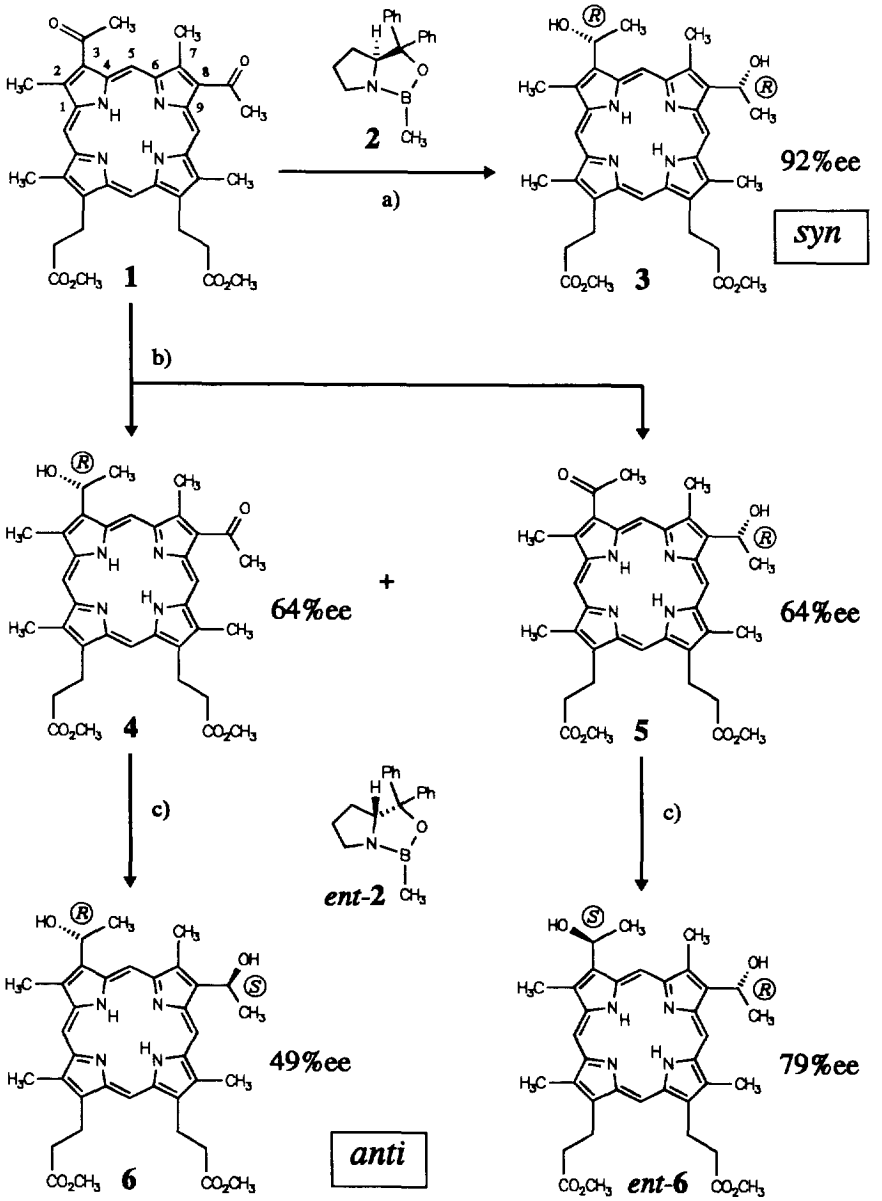
**Abstract:** The reduction of 3,8-diacetyl porphyrin **1** with borane-methyl sulfide complex, BMS, as stoichiometric reductant and methyloxazaborolidine **2** and *ent*-**2** as catalysts allows the enantioselective preparation of hematoporphyrin IX dimethyl ester stereoisomers.

Hematoporphyrin was first obtained by THUDICHUM in 1867 by acid hydrolysis of the red blood pigment heme[1]. Since the hydrolysis is non-stereoselective, loss of the central iron ion and hydration of the vinyl groups led to four hematoporphyrin stereoisomers - two pairs of *syn/anti* diastereomeric enantiomers *rac*-**3** and *rac*-**6**. Hematoporphyrin and hematoporphyrin derivatives like Photofrin II® are of interest as sensitizers for photodynamic tumor therapy (PDT)[2]. Porphyrin c, the prosthetic group of ubiquitously distributed cytochrome c[3], is identical with one of the *anti* hematoporphyrin stereoisomers[4]. The selective synthesis and the determination of the configuration of all hematoporphyrin stereoisomers should allow the elucidation of the absolute configuration of porphyrin c by comparison with synthetic material.

We recently reported on the preparation of enantiomeric enriched *syn* hematoporphyrin dimethyl ester **3**[4] by enantioselective reduction of 3,8-diacetyl porphyrin **1** with methyloxazaborolidine **2** as homochiral catalyst and borane-methyl sulfide complex, BMS, as stoichiometric reductant[5]. The *R* configuration of the stereogenic centres in **3** could be concluded by transformation of **3** into a dioxoisobacteriochlorin[4] of known configuration. The stereochemical result is in agreement with the transition-state model for this type of reduction suggested by COREY[5e,f]. Best yields and selectivities were achieved with a final porphyrin concentration of about 0.02 M, 0.65 equiv. of catalyst **2**, 1.6 equiv. of BMS, dichloromethane as solvent, -12°C, and a reaction time of 5 hours. The enantiomeric excess of **3** was detected as 88-92% by HPLC determination of the *syn/anti* hematoporphyrin ratio on an achiral phase[4,6] and by HPLC of the corresponding dibenzoates[4,7] on a chiral phase. *Ent*-**3** should be accessible by asymmetric reduction of **1** with *ent*-**2**[5c] as homochiral catalyst.

For the preparation of the enantiomerically enriched *anti* hematoporphyrin stereoisomers **6** and *ent*-**6** the enantioselective reduction of **1**, with **2** as homochiral catalyst, was quenched after 100 minutes by addition of methanol. The mixture was poured into water and worked up by extraction with dichloromethane. Evaporation of the solvent gave a residue which was found to be a mixture of starting porphyrin **1** and enantiomerically enriched hematoporphyrin **3**, as minor components, and the desired enantiomerically enriched acetyl-hydroxyethyl porphyrins **4** and **5**[8] as main products.

The mixture of porphyrins **4** and **5** was separated by column chromatography [Silica gel (ICN), dichloromethane/methanol (50/1)] monitored by analytical HPLC. The 8-acetyl-3-hydroxyethyl isomer **4** was eluted first. The enantiomeric excess of **4** and **5** was about 64%, determined by HPLC analysis of the ratio of the hematoporpyhrin diastereomers, formed as minor products, on an achiral phase[4,6].




**Scheme 1:** a) **2**, $BH_3{\cdot}S(CH_3)_2$, $CH_2Cl_2$, -12°C, 5 h; b) **2**, $BH_3{\cdot}S(CH_3)_2$, $CH_2Cl_2$, -12°C, 100 min; separation of isomers; c) *ent*-**2**, $BH_3{\cdot}S(CH_3)_2$, $CH_2Cl_2$, -8°C, 4 h.

Reduction of the separated, pure acyl-hydroxyethyl porphyrins **4** and **5** with *ent*-**2** as catalyst and BMS as stoichiometric reductand leads to the enantiomeric enriched *anti* hematoporphyrin dimethyl ester **6** and *ent*-**6** respectively[9]. The desired *anti* isomers **6** and *ent*-**6** were separated from *syn* isomers, also formed in low yields, by semipreparative HPLC[10]. The enantiomeric excess of **6** was found to be 49(±2)%, the enantiomeric excess of *ent*-**6** was found as 79(±2)%, by HPLC analysis of the dibenzoates on a chiral phase[11] (Figure 1a,b).

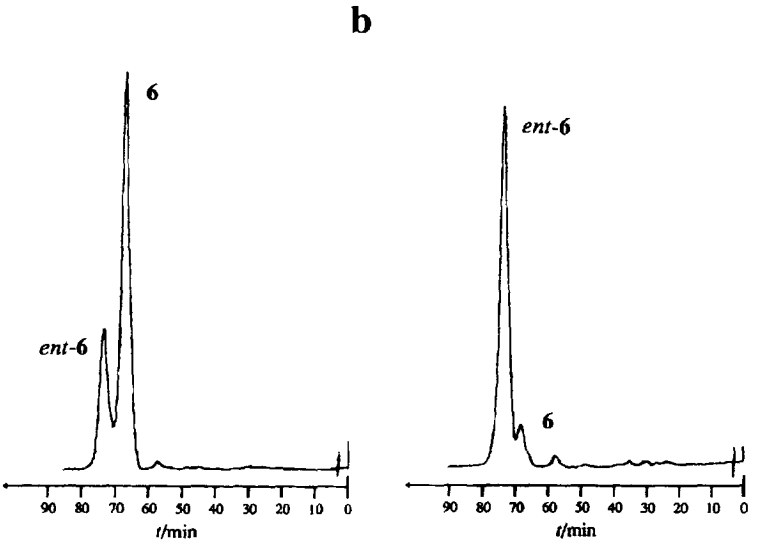



**Figure 1:** HPL-Chromatogram of the dibenzoates of enantiomeric enriched **6** (a) and *ent*-**6** (b) on a homochiral phase [Nucleosil Chiral 2®, *n*-heptane/dioxan (80/20)].

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6) The fractions x of the resulting enantiomers **3** and *ent*-**3**, as well as those of the diastereomers **6** and *ent*-**6**, in the product mixture correspond to the terms of the binomial equation (a) [equations (b)-(d)], where $W_{Si}$ and $W_{Re}$ are the probabilities for attack from the enantiotopic sides of the two keto groups.
(a) $W_{Si}^2 + 2W_{Si}W_{Re} + W_{Re}^2 = 1$ (b) x (**3**) = $W_{Si}^2$
(c) x (**6**) + x (*ent*-**6**) = $2W_{Si}W_{Re}$ (d) x (*ent*-**3**) = $W_{Re}^2$
Analysis by HPLC of the hematoporphyrin ester on an achiral phase gives a diastereomer ratio of (**3** + *ent*-**3**)/(**6** + *ent*-**6**) of 2.53:1, from which an enatiomeric excess **3**/*ent*-**3** of 92% and a *Si*-selectivity ($W_{Si}$) of 83% can be calculated using equations (a)-(d).

7) The mixture of enantiomeric enriched **3** and the diastereomers **6** and *ent*-**6** was converted into the dibenzoate derivatives (benzoic acid anhydride, 4-dimethylaminopyridine, $CH_2Cl_2$, room temperature, 90 min) and chromatographed on Nucleosil Chiral 2® (Macherey-Nagel) with *n*-heptane/dioxane (77/23) (1mL/min) as solvent. $t_R$ (**3**) = 42.3 min, $t_R$ (*ent*-**3**) = 50.8 min, $t_R$ (**6**) = 50.8 min, $t_R$ (*ent*-**6**) = 56.1 min. Although the peaks for *ent*-**3** and for **6** coincide, an enantiomeric excess of 88% and thus a *Si*-selectivity ($W_{Si}$) of 80% could be determined, since the signal for **3** is completely separated.

8) Enantiomerically enriched **4** and **5** were characterized by UV/Vis, IR, and $^1$H NMR spectroscopy, and mass spectrometry. The scaled data agree with the corresponding data in the racemic series (R.K. Pandey, K.M. Smith, T.J. Dougherty, *J. Med. Chem.* **1990**, *33*, 2032).

9) Enantiomerically enriched **6** and *ent*-**6** were characterized by UV/Vis, IR, and $^1$H NMR spectroscopy, and mass spectrometry. Elemental analysis were performed for the diasteromeric mixtures of enantiomeric enriched **6** and *ent*-**6**. **6** [$C_{36}H_{42}N_4O_6$ (626.75)]: calcd. C 68.99, H 6.75, N 8.94; found C 68.82, H 6.79, N 6.88; *ent*-**6** [$C_{36}H_{42}N_4O_6$ (626.75)]: calcd. C 68.99, H 6.75, N 8.94; found C 68.91, H 6.71, N 8.81.

10) Separation of the *syn*/*anti* hematoporphyrin dimethyl ester stereoisomers **3**/*ent*-**3** and **6**/*ent*-**6** was performed by semipreparative HPLC [LiChrosorb RP 18 (Merck) 8x250 mm, methanol/($n$-$C_4H_9)_4NH_2PO_4$ (80/20), 4mL/min].

11) Enantiomeric enriched **6** and *ent*-**6** was converted into the benzoate derivatives and chromatographed on Nucleosil Chiral 2® (Macherey-Nagel) with *n*-heptane/dioxane (80/20) (1mL/min) as solvent. $t_R$ (**6**) = 67.5 min, $t_R$ (*ent*-**6**) = 73.1 min.

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