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Synthesis of Methyl Bacteriopheophorbide-*d* with 8-Propyl Group

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Abstract: Methyl bacteriopheophorbide-*d* possessing propyl and methyl groups at the 8- and 12-positions, respectively, was prepared by modification of chlorophyll-*a* with 8-ethyl and 12-methyl groups. © 1997 Elsevier Science Ltd.

Bacteriochlorophyll(=BChl)-*d* is one of the major pigments in the main light-harvesting antennae (=chlorosomes) of photosynthetic green bacteria.[1] BChl-*d* is composed of several formulae which have alkyl groups at the 8- and 12-positions as shown in Figure 1.[2] One metal-free bacteriopheophorbide(=BPhe)-*d* derivative (R^8=Et, R^{12}=Me, farnesyl→methyl ester in Figure 1 and also see compound **2** in Scheme 1) has been synthesized from chlorophyll(=Chl)-*a* with 8-ethyl and 12-methyl groups (vide infra).[3] Other BChls-*d* have been isolated from natural chlorosomes[2] but have not yet been prepared by synthetic procedures, to our knowledge.[4] Here we report on the synthesis of methyl BPhe-*d* (**10**) with a *propyl* group at the 8-position by modification of easily available Chl-*a* with 8-*ethyl* group.

Methyl pyropheophorbide-*a* (**1**) was prepared from *Spirulina* Chl-*a*.[5] The vinyl group at the 3-position of **1** was hydrated to give methyl 8-Et-12-Me-BPhe-*d* **2** ($3^1R/3^1S$ = 1/1 mixture) in a yield of 83% by slight modification of the procedures reported by Smith and collaborates[3] (see Scheme 1). The 1-hydroxyethyl group at the 3-position of **2** was oxidized to give 3-acetylchlorin **3** (86%).[6] OsO_4–pyridine oxidation[7] of **3** site-

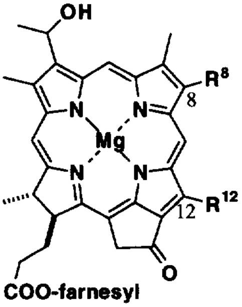
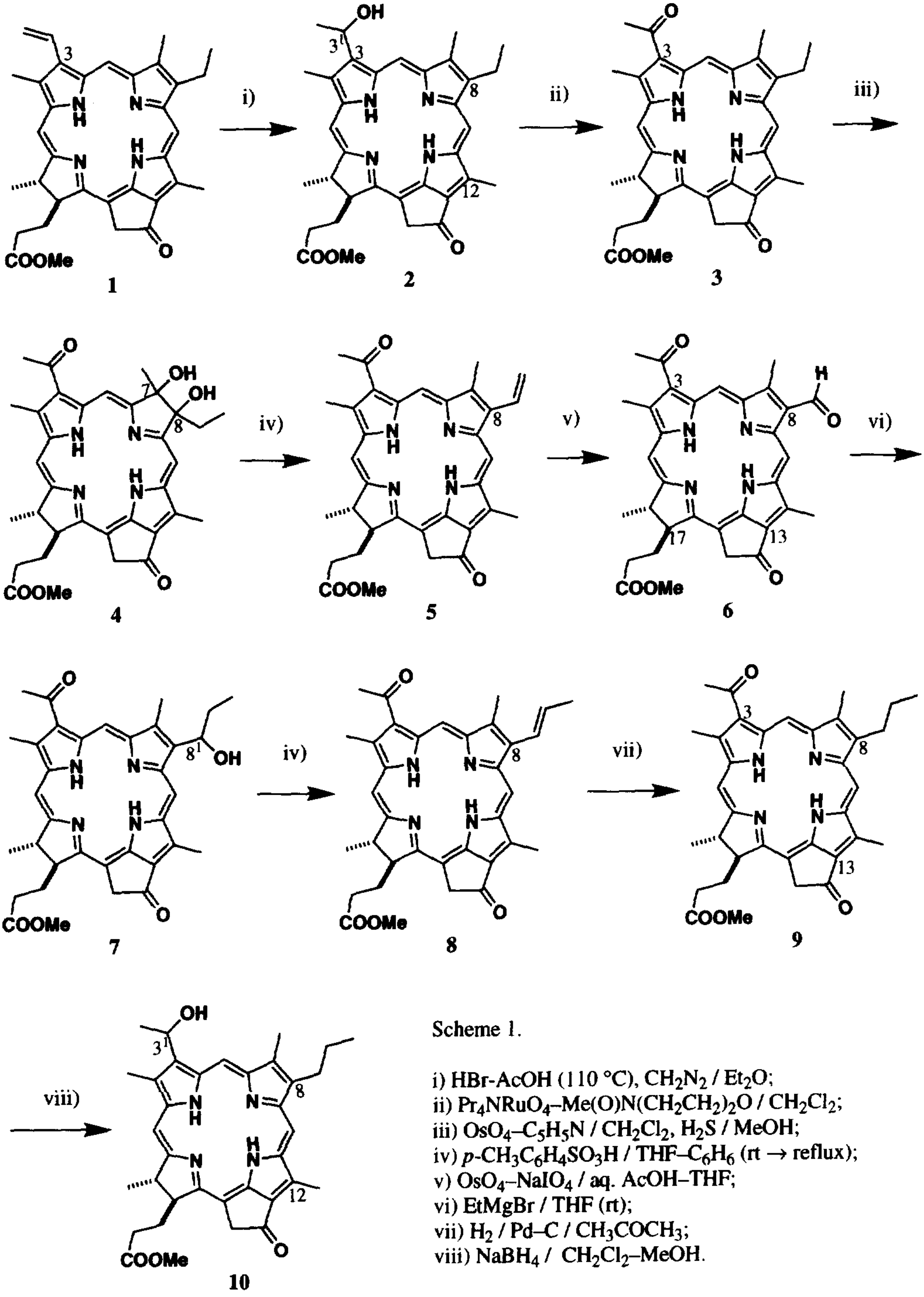


Figure 1.

Bacterichlorophylls-*d* (=BChls-*d*)
(**R^8=Et, Pr, *iso*-Bu, *neo*-Pn; R^{12}=Me, Et**)



Scheme 1.

i) HBr-AcOH (110 °C), CH_2N_2 / Et_2O;
ii) Pr_4NRuO_4–$Me(O)N(CH_2CH_2)_2O$ / CH_2Cl_2;
iii) OsO_4–C_5H_5N / CH_2Cl_2, H_2S / MeOH;
iv) p-$CH_3C_6H_4SO_3H$ / THF–C_6H_6 (rt → reflux);
v) OsO_4–$NaIO_4$ / aq. AcOH–THF;
vi) EtMgBr / THF (rt);
vii) H_2 / Pd–C / CH_3COCH_3;
viii) $NaBH_4$ / CH_2Cl_2–MeOH.

selectively gave 7,8-*cis*-diol **4** (3:4 mixture, the stereo-configurations at 7-and 8-positions were not determined) in a yield of 82%. Double dehydration of the mixture of bacteriochlorin **4** exclusively afforded 8-vinylchlorin **5**[8] (49%) as an isolable product. Oxidative cleavage of the 8-vinyl group of **5** by OsO_4–$NaIO_4$[5,9] produced 8-formylchlorin **6** (97%). Grignard reaction[10] of the 8-formyl group of **6** with EtMgBr gave the carbinol **7** in 60% yield based on the consumed **6**. The Grignard reagent site-selectively attacked more reactive 8-formyl group in spite of the presence of 3,13-keto carbonyl groups and ester group on the 17-propionate. The 8^1-position of **7** is a chiral center and the ^{1}H-NMR spectra showed that **7** was a diastereomeric 1:1 mixture. The Grignard reagent attacked the 8-formyl group non-stereoselectively. Dehydration of the 1-hydroxypropyl group of **7** gave *trans*-isomer **8** and successive hydrogenation of the produced 1-propenyl group gave 8-propylchlorin **9** (73%). The acetyl group at the 3-position of **9** was selectively reduced to form methyl 8-Pr-12-Me-BPhe-*d* **10**[11] in a yield of 85%. The 3-acetyl group is more reactive than the 13-keto-carbonyl group mainly because the latter is tightly conjugated with the chlorin π-chromophore.[6] The reduction occurred non-stereoselectively to give a mixture of $3^1R/3^1S$ =1/1 (from the ^{1}H-NMR spectral analysis[2]). The overall 9-step yield from **1** to **10** was 10%.

Transformation of methyl ester of **10** to farnesyl and magnesium insertion would lead to BChl-*d* (R^8=Pr, R^{12}=Me). The present synthetic approach should be adapted for preparation of BChl-*d* with 8-*iso*-butyl and 12-methyl groups using *iso*-PrMgBr instead of EtMgBr and other Grignard reagents should also give novel BChl-*d* analogues with several 8-substituents. Use of isotopically labeled alkyl halides for preparation of Grignard reagents (e.g., ^{2}H, ^{13}C, ^{14}C)[10] should induce the synthesis of BChls-*d* with labeled 8-alkyl group. Synthesis of metal complexes of diastereomeric pure **10** (3^1R- and 3^1S-epimers) including Mg and Zn chlorins as models for BChls-*d* and the study on their self-aggregation[12] are in progress.

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