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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 (R⁸=Et, R¹²=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 chlorosomes² 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 collaborates³ (see Scheme 1). The 1-hydroxyethyl group at the 3-position of 2 was oxidized to give 3-acetylchlorin 3 (86%).⁶ OsO₄-pyridine oxidation⁷ of 3 site-



Figure 1.

Bacterichlorophylls-d (=BChls-d) (R⁸=E t, Pr, *iso*-Bu, *neo*-Pn; R¹²=Me, E t)

















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- $CH_3C_6H_4SO_3H / THF-C_6H_6$ ($rt \rightarrow reflux$); v) OsO_4 -NaIO₄ / aq. AcOH-THF; vi) EtMgBr / THF (rt); vii) H_2 / Pd - C / CH_3COCH_3 ; viii) NaBH₄ / 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 OsO₄-NaIO₄^{5,9} produced 8formylchlorin **6** (97%). Grignard reaction¹⁰ 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 8¹position of **7** is a chiral center and the ¹H-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 8propylchlorin **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 nonstereoselectively to give a mixture of $3^1R/3^1S = 1/1$ (from the ¹H-NMR spectral analysis²). 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 (R⁸=Pr, R¹²=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., ²H, ¹³C, ¹⁴C)¹⁰ should induce the synthesis of BChls-d with labeled 8-alkyl group. Synthesis of metal complexes of diastereomeric pure 10 (3¹*R*- and 3¹*S*-epimers) including Mg and Zn chlorins as models for BChls-d and the study on their self-aggregation¹² are in progress.

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