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Synthesis of 7-substituted chlorophyll-*a* derivatives as chlorophyll-*b* analogs with specific visible absorption bands

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ABSTRACT

Methyl 3-substituted 13^1-deoxo-pyropheophorbides-*a* possessing the 7-methyl group were transformed into the corresponding 13^1-deoxo-pyropheophorbides-*b* bearing the 7-formyl group via the regioselective mono-dehydration of *cis*-7,8-diols to 7-hydroxymethyl-chlorins under mild acidic conditions. The exclusive production of the 7^1-hydroxy-chlorins without detection of the 8^1-hydroxy-chlorins in the reaction mixture did not depend on the 3-substituents. The regioselectivity was regulated by the 13-functional groups, and the ratio of the 8^1-OH over 7^1-OH products enhanced with an increase of the group electronegativity. Methyl mesopyropheophorbide-*b* (7-formyl-13^1-oxo-chlorin) was efficiently obtained by modifying methyl mesopyropheophorbide-*a*, one of the chlorophyll-*a* derivatives, through the protection of the 13^1-oxo moiety and the aforementioned mono-dehydration. The effects of the 7-substituents on the visible absorption spectra in a solution were comparable to those of naturally occurring, photosynthetically active chlorophylls-*a*/*b* and bacteriochlorophylls-*c*/*e* bearing the 7-methyl/formyl groups.

1. Introduction

Chlorophyll-*a* (Chl-*a*) is a major photosynthetically active pigment of oxygenic phototrophs, whereas Chl-*b* is an accessory pigment in some photosynthetic organisms. Chls-*a* and *b* are differentiated by the 7-substituents (see R^7 in the left drawing of Fig. 1) and possess methyl and formyl groups at the 7-position, respectively.[1] Chl-*b* is biosynthesized by the oxidation of the 7-methyl group of Chl-*a* or the oxidation of the 7-Me of chlorophyllide-*a* (Chlide-*a*) followed by the esterification at the 17-propionate residue.[2] The oxidation of the 7-methyl to formyl group is performed by Chl(ide)-*a* oxygenase (CAO).[3,4] The CAO enzyme catalyzes the following sequential oxidations: 7-Me → 7-CH_2OH → 7-CHO (see Fig. 2, upper). The transformation affects the visible absorption bands of the pigments and the Soret/Qy bands at the blue/red regions are shifted to longer/shorter wavelengths.[4–6] Therefore, Chl-*b* is able to absorb efficiently the visible light which Chl-*a* absorbs less and the excited energy is transferred from Chl-*b* to Chl-*a* in natural light-harvesting antenna systems.[7]

Bacteriochlorophyll-*c* (BChl-*c*) is the major antenna pigment in most species of photosynthetic green bacteria and BChl-*e* is dominantly found in brown-colored species of green sulfur bacteria. These molecules are solely different at the 7-substituent, similarly as in Chls-*a*/*b*: BChls-*c*/*e* bear the 7-Me/CHO moieties, respectively (Fig. 1, middle).[1] BChl-*e* is biosynthetically produced by the oxidation of the 7-methyl group of bacteriochlorophyllide-*c* (BChlide-*c*) to the 7-formyl group of BChlide-*e* via the 7-hydroxymethyl group (Fig. 2) and the successive esterification of BChlide-*e* with a farnesyl group to BChl-*e*. The oxidation in anoxygenic green bacteria is recently found to be catalyzed by BChlide-*c* oxygenase (BciD).[8] The structural modification induces bathochromic and hypsochromic shifts of the Soret and Qy maxima, respectively, as aforementioned in Chls-*a*/*b*.[5,9] The brown-colored species possessing BChl-*e* in the main light-harvesting antenna system can effectively utilize green light for their photosynthesis which is less absorbed by other phototrophs including green bacteria with BChl-*c*[9,10] and survive in the deep regions of sea and lake.[11]

The 7-methyl groups of Chl(ide)-*a* and BChlide-*c* are regioselectively oxidized by the CAO and BciD enzymes in vivo and in vitro to smoothly give Chl(ide)-*b* and BChlide-*e*, respectively, bearing the 7-formyl group. In contrast, the selective oxidation of a 7-methyl-chlorin to the corresponding 7-formyl analog is hard to

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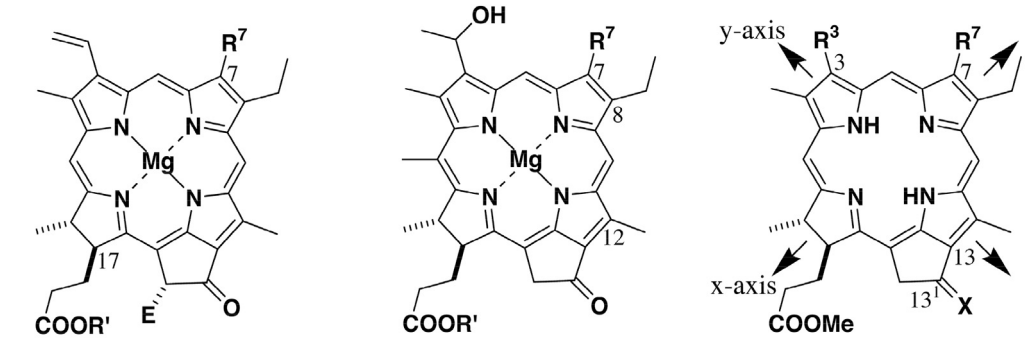

Chl-*a*: **R^7 = Me, R' = phytyl**
Chlide-*a*: **R^7 = Me, R' = H**
Chl-*b*: **R^7 = CHO, R' = phytyl**
Chlide-*b*: **R^7 = CHO, R' = H**

BChl-*c*: **R^7 = Me, R' = farnesyl**
BChlide-*c*: **R^7 = Me, R' = H**
BChl-*e*: **R^7 = CHO, R' = farnesyl**
BChlide-*e*: **R^7 = CHO, R' = H**

4a–e: **R^7 = Me, X = H$_2$**
2a–e: **R^7 = CH$_2$OH, X = H$_2$**
3a–e: **R^7 = CHO, X = H$_2$**
4g: **R^7 = Me, X = O**
3g: **R^7 = CHO, X = O**

Fig. 1. Molecular structures of natural occurring Chl(ide)-*a*/*b* (left; E = COOMe) and BChl(ide)-*c*/*e* (middle; one of their homologs with the 8-ethyl and 12-methyl groups) as well as synthetic Chl-*a* derivatives, methyl pyropheophorbides (right; **a**: R^3 = CHO, **b**: R^3 = COMe, **c**: R^3 = CH$_2$OH, **d**: R^3 = CH(OH)Me, **e**/**g**: R^3 = Et).

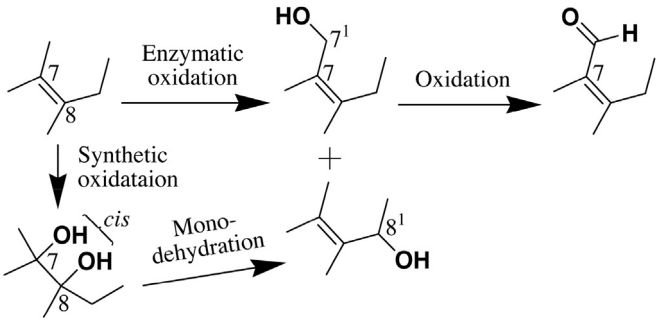

Fig. 2. Oxidation steps of the 7-methyl group of (B)Chl(ide)s and their derivatives to the 7-formyl group via the 7-hydroxymethyl group.

achieve via one-pot organic synthesis. Such oxidations have succeeded according to the following three steps.[12] Methyl bacteriopheophorbide-*d* (R^3 = CH(OH)Me, R^7 = Me, and X = O in the right drawing of Fig. 1) was dihydroxygenated at the C7=C8 double bond to give the *cis*-7,8-diol as shown in the left of Fig. 2. The selective oxidation occurred at the most reactive C7=C8 in the chlorin chromophore where a porphyrinoid π-circuit was partially broken. The *cis*-diol was mono-dehydrated under acidic conditions to give a regioisomeric mixture of 7^1- and 8^1-hydroxylated chlorins (Fig. 2, middle). The 8^1-hydroxy-chlorin was produced more than the 7^1-hydroxy-chlorin due to the more stable secondary cation at the 8^1-position than the primary cation at the 7^1-position (see Scheme S1). The minor primary alcohol was separated from the major secondary alcohol and oxidized to the corresponding 7-formyl-chlorin, methyl bacteriopheophorbide-*f*. The overall yield was at most 4% because the desired dehydration of the *cis*-diol proceeded less to give a small amount of the 7-hydroxymethyl-chlorin.

It has been preliminarily reported that the regioselectivity was altered by the removal of the 13-carbonyl group and 7-hydroxymethyl-chlorin **2b** was dominantly obtained by the acidic mono-dehydraion of the corresponding *cis*-diol.[13] Here, we report the synthesis of 7-formyl-chlorins **3a**–**e** possessing a variety of the 3-substituents and lacking the 13^1-oxo group by modifying 7-methyl analogs **4a**–**e** through the regioselective production of 7-hydroxymethyl-chlorins **2a**–**e**. The synthetic procedures were applied to the transformation of 7-methyl-13^1-oxo-chlorin **4g** to its 7-formylated chlorin **3g** via the protection of the 13-keto-carbonyl group. In addition, the effects of the oxidation at the 7^1-position on the visible absorption spectra in a solution are discussed.

2. Results and discussion

2.1. Synthesis of *cis*-7,8-diols of methyl 13^1-deoxo-pyropheophorbides

Methyl pyropheophorbide-*a*, one of the Chl-*a* derivatives, in dichloromethane was treated with sodium borohydride in the presence of trifluoroacetic acid (TFA)[14] to give the corresponding 13^1-deoxo-chlorin **4h** (93% yield)[13] as a selectively reduced product [see step (i) of Scheme 1]. The 3-vinyl group of **4h** was oxidatively cleaved under Lemieux-Johnson oxidation conditions [step (ii)][14] to afford 3-formyl-chlorin **4a** (67%).[15] Non-stereoselective hydration [step (iii)] of the 3-vinyl group of **4h** yielded methyl 13^1-deoxo-bacteriopheophorbide-*d* (**4d**, 71%)[16] possessing a 1-hydroxyethyl group at the 3-position as a 3^1-epimeric mixture (3^1*R*:3^1*S* = 1:1). The 3-formyl group of **4a** was selectively reduced by *tert*-butyl-amine borane complex [step (iv)] to the 3-hydroxymethyl group of **4c** (89%) as the 3^1-demethyl form of **4d**.[15] Secondary alcohol **4d** was oxidized with an *N*-oxide by the catalytic action of a ruthenium oxide [step (v)][16] to ketone **4b** (81%).[13]

The C7=C8 double bond of methyl 13^1-deoxo-pyropheophorbide-*d* (**4a**) bearing the 3-formyl group was reacted with osmium tetroxide in the presence of pyridine and the resulting osmate was cleaved by hydrogen sulfide to give *cis*-7,8-diol **1a** (48%) as a 1:1 stereochemical mixture of the (7*R*,8*S*)- and (7*S*,8*R*)-isomers [step (vi)]. Similarly, 3-acetyl-chlorin **4b** was transformed into the corresponding *cis*-diol **1b** (53%) as a diastereomeric mixture (5:4).[13,17] When 3-hydroxymethyl-chlorin **4c** was oxidized under the same conditions as mentioned above, 3-formyl-chlorin **4a** and its further oxidized *cis*-diol **1a** were obtained as the major and minor products, respectively, but desired *cis*-diol **1c** could be hardly detected in the reaction mixture. The present oxidation occurred at the benzylic alcohol (3-CH$_2$OH) more preferably than the C7=C8 moiety. Therefore, aldehyde **1a** was reduced with *t*BuNH$_2$·BH$_3$ as shown in the step (iv) to give **1c** in an isolated yield