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Transformation of carbonyl to vinylidene groups in the π-conjugated peripheral substituent of chlorophyll derivatives by Tebbe reagent

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ABSTRACT

The 13^1-oxo-moiety of chlorophyll-*a* derivatives including methyl (pyro)pheophorbides-*a*, mesopyropheophorbide-*a*, and bacteriopheophorbide-*d* possessing vinyl, ethyl, and 1-hydroxyethyl groups, respectively, at the 3-position was transformed into the corresponding *exo*-methylene group by treatment of Tebbe reagent. The synthetic procedures were useful for the regioselective conversion of the carbonyl to vinylidene group at the 3-position and naturally occurring chlorophyll-*d* (3-CHO) was successfully modified to chlorophyll-*a* (3-CH=CH_2). Under the methylenation conditions, ester–carbonyl, hydroxy, and allyl groups in the peripheral substituents were tolerant as well as an acid-labile magnesium at the central position of chlorophylls.

Chlorophylls are one family of natural porphyrinoids including hemes and cobalamins.[1] Photosynthetically active chlorophylls are cyclic tetrapyrroles and characterized by a fused and *exo*-five-membered ring, called E-ring, bearing an oxo moiety (see the left drawing of Fig. 1).[2] Recently, (bio)chemical modification of the E-ring has attracted much attention from the viewpoints of chlorophyll metabolism,[3,4] development of novel photoactive pigments,[5–7] and so on. A variety of such semi-synthetic chlorophylls are available in the literature.[8] We have already reported that modification of the 13^1-oxo group of methyl pyropheophorbide-*a* (**1**, see the right drawing of Fig. 1), one of the chlorophyll-*a* derivatives, to the *exo*-methylene group in **2**, caused slight changes of the optical properties including electronic absorption bands: redmost (Qy) maximum = 667 (13-C=O) to 666 nm (13-C=CH_2) in CH_2Cl_2.[5] Therefore, such methylene analogs would be useful for the models of naturally occurring chlorophylls. The reported chemical transformation involved multi-step processes (hydrolysis of the 17-propionate residue, methylation of the 13-carbonyl group to 13-CH(OH)Me, re-esterification of the free carboxylic acid, and acidic dehydration of the resulting 13^1-methyl carbinol **3**) and the total yield was very low (at most 3%).[5,9] Here we report one-step methylenation of the 13^1-oxo moiety using Tebbe reagent, $Cp_2Ti(—Cl—)(—CH_2—)AlMe_2$ (Cp = cyclopentadienyl),[10] for the efficient transformation. Furthermore, the synthetic procedures were applied to the transformation of the 3-carbonyl groups directly conjugated with chlorophyll π-systems to the corresponding vinylidene groups.

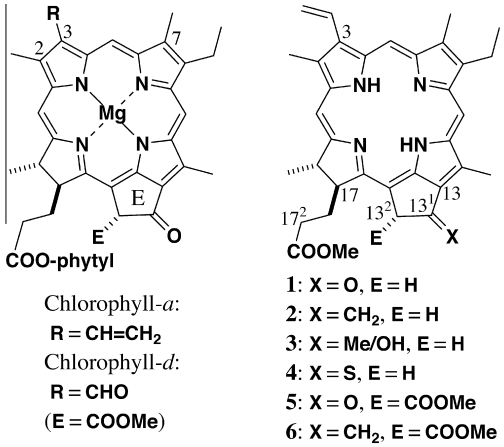

Figure 1. Molecular structures of natural chlorophylls (left) and their synthetic derivatives (right).

First, Wittig reaction of methyl pyropheophorbide-*a* (**1**)[11,12] was applied with methylenetriphenylphosphorane,[13] but the starting ketone was recovered. The 13-keto carbonyl group was inactive with the Wittig reagent, and so was modified to the corresponding thioketo group. Treatment of more reactive methyl 13^1-deoxo-13^1-thioxopyropheophorbide-*a* (**4**)[14] with CH_2=PPh_3 or CH_2N_3

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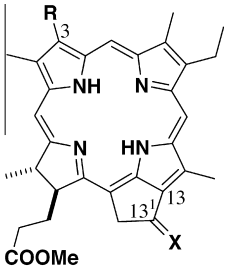

7: R = Et, X = O
8: R = Et, X = CH_2
9: R = CH(OH)Me, X = O
10: R = CH(OH)Me, X = CH_2
11: R = COMe, X = H_2
12: R = CMe=CH_2, X = H_2
13: R = COMe, X = O
14: R = CMe=CH_2, X = O
15: R = CHO, X = O

Figure 2. Molecular structures of semi-synthetic 13^1-oxo- and methylene-chlorins **7**/**9** and **8**/**10** as well as 3^1-oxo- and methylene-chlorins **11**/**13**/**15** and **12**/**14**.

(Barton–Kellogg reaction)[15] gave no desired *exo*-methylene product. Then, Tebbe methylenation was examined. Methyl pyropheophorbide-*a* (**1**) was dissolved in dry THF under an argon atmosphere and cooled down to −20 °C in the presence of pyridine, to which was added commercially available Tebbe reagent (10 equiv, 0.5 M in toluene); the μ-methylene reagent was reacted with pyridine to form CH_2=$TiCp_2$ as a transient active species.[10] After being stirred for 10 min in the dark, the reaction was quenched with an aqueous sodium hydrogen carbonate. The reaction mixture was extracted with dichloromethane, dried over sodium sulfate, filtered, and chromatographed with silica gel (0–2% Et_2O–CH_2Cl_2) to successfully give methyl 13^1-deoxo-13^1-methylenepheophorbide-*a* (**2**)[5,16] in a 35% yield. The yield of one-step methylenation was 10-fold larger than that of the multi-step transformation reported earlier.[5] Reactive Tebbe reagent was useful for methylenation of the less reactive 13-keto carbonyl group. Under the present reaction conditions, the ester carbonyl group in the 17-propionate residue was not modified due to its much lower reactivity. The reactions for a longer time (>10 min) and/or at a higher temperature (>−20 °C) substantially decreased the isolated yield.

Methyl pheophorbide-*a* (**5**)[12] has a similar 13-carbonyl group to methyl pyropheophorbide-*a* (**1**), but the former carbonyl group is more sterically crowded than the latter due to the neighboring 13^2-methoxycarbonyl group. In spite of the steric disturbance, Tebbe reaction of methyl pheophorbide-*a* (**5**) afforded the 13^1-methylene product **6**.[16] It is noted that the undesired product methylenated at the 13^2-methoxycarbonyl group was not observed from the reaction mixture. Additionally, the 3-ethyl analog of methyl pyropheophorbide-*a* (**7**, methyl mesopyropheophorbide-*a*, see Fig. 2) and its 3^1-hydroxy derivative **9** (methyl bacteriopheophorbide-*d*)[11,12] were modified by the same Tebbe reaction to their 13^1-methylene-chlorins **8** and **10**,[16] respectively, in comparable yields to **1** → **2** (3-vinyl analog). Such substituents at the diagonally opposite 3-position did not disturb the Tebbe methylenation at the 13^1-oxo moiety.

Based on the aforementioned methylenation of keto–carbonyl groups at the 13-position, the 3-acetyl group was reacted with Tebbe reagent. 3-Acetyl-13^1-deoxochlorin **11**[6] was similarly treated with Tebbe reagent to give desired 3^1-methylene product **12**[16] in a 26% yield. Moreover, methyl 3-acetyl-3-devinylpyropheophorbide-*a* (**13**)[11,12] was methylenated with Tebbe reagent to afford methyl 3^1-methylpyropheophorbide-*a* (**14**)[16] as a major isolated product (15%). In the reaction mixture, the further 13^1-methylenated derivative of **14** was observed, but no singly 13^1-methylenated product of **13** was visible. The regioselectivity is ascribable to the fact that the 3-C=O is more reactive to nucleophiles than the 13-C=O.[17]

Since aldehydes are attacked by nucleophiles more rapidly than ketones, methyl pyropheophorbide-*d* (**15**)[12] bearing the 3-formyl group was reacted with Tebbe reagent to afford the corresponding 3-vinylchlorin **1**, methyl pyropheophorbide-*a* (61% isolated yield). Under the same reaction conditions, chlorophyll-*d* (3-CHO, see the left drawing of Fig. 1) isolated from culturing cells of a cyanobacterium *Acaryochloris marina*[12,18] was treated with Tebbe reagent and chlorophyll-*a* (3-CH=CH_2) was successfully detected by HPLC. Both the central magnesium and the phytyl ester in the propionate residue remained in the reaction. This is the reverse reaction of biosynthesis from chlorophyll(ide)-*a* to chlorophyll(ide)-*d*.[19]

In conclusion, Tebbe reagent is useful for the methylenation of carbonyl groups at the peripheral position of naturally occurring chlorophyll as well as semi-synthetic chlorophyll derivatives. The reactivity of carbonyl groups decreased in the order of 3-CHO > 3-COMe > 13-CO ≫ 13^2-CO and 17^2-CO. Alcohol and ester functional groups as well as acidic labile central magnesium are tolerant of the present methylenation. Such regioselective transformation of C=O to C=CH_2 is promising for the methylenation of other natural chlorophylls than chlorophyll-*d* (3-CHO): 2-CHO in chlorophyll-*f*, 3-COMe in (zinc) bacteriochlorophylls-*a*(′)/*b* and bacteriopheophytins-*a*/*b*, and 7-CHO in (divinyl)chlorophyll-*b* and bacteriochlorophylls-*e*/*f*.[20]

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References and notes

1. Senge, M. O.; MacGowan, S. A.; O'Brien, J. M. *Chem. Commun.* **2015**, *51*, 17031–17063.
2. Tamiaki, H.; Shibata, R.; Mizoguchi, T. *Photochem. Photobiol.* **2007**, *83*, 152–162.
3. Kashiyama, Y.; Tamiaki, H. *Chem. Lett.* **2014**, *43*, 148–156; Harada, J.; Teramura, M.; Mizoguchi, T.; Tsukatani, Y.; Yamamoto, K.; Tamiaki, H. *Mol. Microbiol.* **2015**, *98*, 1184–1198.
4. Ogasawara, S.; Tamiaki, H. *Bioorg. Med. Chem.* **2015**, *23*, 6612–6621.
5. Tamiaki, H.; Koizumi, S.; Tsuji, K.; Kinoshita, Y.; Miyatake, T. *Tetrahedron Lett.* **2014**, *55*, 1093–1096.
6. Tamiaki, H.; Tanaka, T. *Tetrahedron* **2015**, *71*, 1915–1923.
7. Tamiaki, H.; Kuno, M.; Kunieda, M. *Tetrahedron Lett.* **2014**, *55*, 2825–2828; Tamiaki, H.; Kuno, M.; Ohata, M. *Photochem. Photobiol.* **2014**, *90*, 1277–1286; Stranius, K. S.; Iashin, V.; Nikkonen, T.; Muuronen, M.; Helaja, J.; Tkachenko, N. *J. Phys. Chem. A* **2014**, *118*, 1420–1429; Wang, K.-K.; Li, J.; Kim, B.-J.; Lee, J.-H.; Shin, H.-W.; Ko, S.-H.; Lee, W.-Y.; Lee, C.-H.; Jung, S. H.; Kim, Y.-R. *Int. J. Photoenergy* **2014**, 793723.
8. Recent reports (during the past two years) of modification of substituents on the E-ring without ring-opening and expanding; see Refs. 5–7 and the following: Ogasawara, S.; Tamiaki, H. *Tetrahedron Lett.* **2014**, *55*, 3618–3621; Ogasawara, S.; Tamiaki, H. *Tetrahedron: Asymmetry* **2015**, *26*, 46–52; Takahashi, N.; Hirota, K.; Saga, Y. *J. Porphyrins Phthalocyanines* **2015**, *19*, 631–637; Loughlin, P. C.; Willows, R. D.; Chen, M. *J. Porphyrins Phthalocyanines* **2015**, *19*, 1007–1013; Belykh, D. V.; Ashikhmina, E. V. *Macroheterocycles* **2014**, *7*, 88–90; Stolypko, A. L.; Belykh, D. V.; Startseva, O. M. *Macroheterocycles* **2015**, *8*, 47–49; Yang, X.; Tan, G.; Qu, F.; Jin, Y.; Wang, J. *Chin. J. Org. Chem.* **2014**, *34*, 1206–1211; Yang, X.; Yin, J.; Jin, Y.; Qi, C.; Wang, J. *Chin. J. Org. Chem.* **2014**, *34*, 2279–2287; Yang, X.; Zhang, S.; Zhang, P.; Zhang, Q.; Wang, Z.; Jin, Y.; Qi, C.; Wang, J. *Chin. J. Org. Chem.* **2015**, *35*, 181–190; Li, J.; Cheng, J.; Zhang, P.; Wu, J.; Jin, Y.; Wang, J. *Chin. J. Org. Chem.* **2015**, *35*, 1294–1301; Gao, N.; Zhang, S.; Wang, Z.; Wang, J. *Chin. J. Org. Chem.* **2015**, *35*, 1715–1725; Zhang, Z.; Jiang, Q.; Zhang, Q.; Wu, J.; Wang, J. *Chin. J. Org. Chem.* **2015**, *35*, 1929–1938; Li, J.; Liu, Y.; Xu, X.-S.; Li, Y.-L.; Zhang, S.-G.; Yoon, I.; Shim, Y. K.; Wang, J.-J.; Yin, J.-G. *Org. Biomol. Chem.* **2015**, *13*, 1992–1995.
9. Tamiaki, H.; Monobe, R.; Koizumi, S.; Miyatake, T.; Kinoshita, Y. *Tetrahedron: Asymmetry* **2013**, *24*, 967–972.
10. Pine, S. H. *Org. React.* **2004**, *43*, 1–91.
11. Tamiaki, H.; Ariki, N.; Sugiyama, H.; Taira, Y.; Kinoshita, Y.; Miyatake, T. *Tetrahedron* **2013**, *69*, 8412–8421.
12. Tamiaki, H.; Machida, S.; Mizutani, K. *J. Org. Chem.* **2012**, *77*, 4751–4758.
13. Michalski, T. J.; Hunt, J. E.; Hindman, J. C.; Katz, J. J. *Tetrahedron Lett.* **1985**, *26*, 4875–4878; Fischer, R.; Engel, N.; Henseler, A.; Gossauer, A. *Helv. Chim. Acta* **1994**, *77*, 1046–1050; Wang, L.; Wang, Z.; Yang, Z.; Jin, Y.; Wang, J. *Chin. J. Org. Chem.* **2012**, *32*, 2154–2161.
14. Pandey, R. K.; Shiau, F.-Y.; Sumlin, A. B.; Dougherty, T. J.; Smith, K. M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 491–496.
15. Tamiaki, H.; Xu, M.; Kinoshita, Y. *J. Photochem. Photobiol., A* **2013**, *252*, 60–68.

16. Specific spectral data of methylenated chlorins; **2**: ^{1}H NMR ($CDCl_3$) δ = 6.27 (1H, s, 13^1=CH *cis* to C13^1—C13), 5.84 (1H, s, 13^1=CH *trans* to C13^1—C13) and HRMS (APCI) m/z = 547.3068 (MH^+); **6**: δ = 6.32, 6.03 (each 1H, s, *cis*-, *trans*-13^1=CH) and m/z = 605.3110 (MH^+); **8**: δ = 6.24, 5.81 (each 1H, s, *cis*-, *trans*-13^1=CH) and m/z = 549.3224 (MH^+); **10**: δ = 6.30, 5.84 (each 1H, s, *cis*-, *trans*-13^1=CH) and m/z = 565.3173 (MH^+); **12**: δ = 6.09 (1H, s, 3^1=CH *cis* to C3^1—C3), 5.64 (1H, s, 3^1=CH *trans* to C3^1—C3) and m/z = 549.3225 (MH^+); **14**: δ = 6.31, 5.89 (each 1H, s, *cis*-, *trans*-3^1=CH) and m/z = 563.3016 (MH^+).
17. Tamiaki, H.; Miyatake, T.; Tanikaga, R. *Tetrahedron Lett.* **1997**, *38*, 267–270.
18. Fukusumi, T.; Matsuda, K.; Mizoguchi, T.; Miyatake, T.; Ito, S.; Ikeda, T.; Tamiaki, H.; Oba, T. *FEBS Lett.* **2012**, *586*, 2338–2341.
19. Loughlin, P. C.; Willows, R. D.; Chen, M. *Sci. Rep.* **2014**, *4*, 6069.
20. Tamiaki, H.; Teramura, M.; Tsukatani, Y. Bull. Chem. Soc. Jpn. **2016**, *89*, in press. http://dx.doi.org/10.1246/bcsj.20150307.