Tetrahedron 70 (2014) 1629–1634

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 3^2-nitro-chlorophyll-*a* derivatives and their electronic absorption/emission data

Hitoshi Tamiaki *, Masaki Ohata, Yusuke Kinoshita, Shinnosuke Machida

Graduate School of Life Sciences, Ritsumeikan University, Kusatsu, Shiga 525-8577, Japan

ARTICLE INFO

Article history:
Received 20 December 2013
Received in revised form 11 January 2014
Accepted 13 January 2014
Available online 17 January 2014

Keywords:
Henry reaction
Nitro-olefin
Pyropheophorbide
Substitution effect
Visible absorption
Fluorescence emission

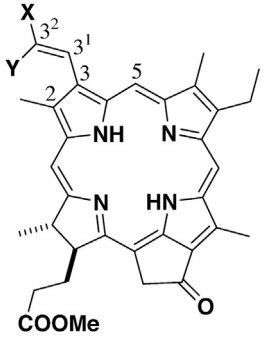
ABSTRACT

The formyl group at the 3-position of methyl pyropheophorbide-*d*, one of chlorophyll-*a* derivatives, was efficiently transformed to the 3^2-*cis*-unsubstituted/methyl- or 3^2-*cis*-phenyl-3^2-*trans*-nitro-vinyl groups by Henry (nitro-aldol) or nitro-Mannich (aza-Henry) reactions with nitromethane/ethane or nitrophenylmethane, respectively. The introduction of a nitro group at the terminal of the 3-ethenyl moieties directly connected with the chlorin π-system red-shifted and broadened their Qy electronic absorption and fluorescence emission bands in a solution. The fluorescence intensities were largely suppressed by the substitution with the nitro group.

1. Introduction

Photosynthetically active chlorophylls (Chls) are cyclic tetrapyrroles bearing various substituents at their peripheral positions.[1,2] Several functional groups are available at the 3-position, where a vinyl group is often observed. Indeed, Chls-*a*, *b*, *c*, *f*, and bacteriochlorophyll(BChl)-*g* possess the 3-vinyl group in their molecules. The 3-vinyl group is directly bound with a tetrapyrrole π-system, which affects their photophysical properties including electronic absorption and emission data. Co-planarization of the tetrapyrroles with 3-vinyl moiety elongates the π-conjugation in a molecule to decrease the singlet excited energy levels and shift the redmost (Qy) absorption and main emission bands to longer wavelengths. In photosynthetic apparatuses, the above (B)Chl pigments are fixed inside proteins and the conformation of the 3-vinyl group is restricted. X-ray crystallographic analyses of the proteins containing Chls-*a*/*b* showed that some of the 3-vinyl groups were not fully π-conjugated with tetrapyrrole systems and the C3–C3^1 bond (see Fig. 1) was rotated to give distorted and perpendicular conformers.[3] Such a partial and complete disconnection of the two π-systems led to blue-shifts of the above absorption/emission maxima. The same situation was observed for the 3-acetyl group in photosynthetic proteins.[4]

In a solution, the 3-vinyl group of Chls and their derivatives can take an energetically stable conformer where the vinyl moiety is co-planar with their tetrapyrrole π-systems, due to free rotation around the C3–C3^1 bond. Chemical modification of the 3-vinyl group can affect the Qy bands. Introduction of any functional groups at the 3^2-*trans*-position (X in Fig. 1) shifted the Qy bands bathochromically.[2,5] Substitution with π-conjugated moieties, vinyl (X=CH=CH_2) and phenyl groups (X=Ph) at the above position of methyl pyropheophorbide-*a* (**1d**) red-shifted the Qy maxima in dichloromethane from 667 to 674 and 673 nm, respectively. Moreover, electron-withdrawing groups in X of Fig. 1 induced larger red-shifts of the Qy peaks: 667 (X=H) <684 (X=COOMe) <689 (X=CN) <691 nm (X=CHO) in dichloromethane.



1a: X = NO_2, Y = H
1b: X = NO_2, Y = Me
1c: X = NO_2, Y = Ph
1d: X = Y = H

Fig. 1. Molecular structures of methyl (3^2-nitro-)pyropheophorbides-*a* **1a**–**d**.

* Corresponding author. Fax: +81 77 561 2659; e-mail address: tamiaki@fc.ritsumei.ac.jp (H. Tamiaki).

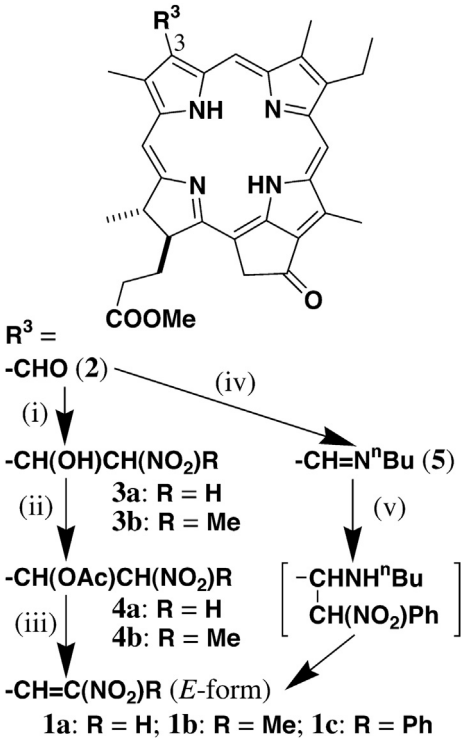
0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.01.020

Here we report the synthesis of Chl-*a* derivative **1a** possessing a nitro group at the *trans*-position of the 3-vinyl group (Fig. 1), since a nitro group is more electron-withdrawing than the above functional groups: electronegativity=2.17 (H), 2.83 (COOMe), 2.86 (CHO), 3.20 (CN), and 3.42 (NO_2).[6] The electronic absorption and emission data of **1a** in a diluted solution were compared with those of the corresponding 3^2-unsubstituted form **1d**. Additionally, the substitution effect at the 3^2-*cis*-position of **1a** as in **1b** and **1c** is also discussed.

2. Results and discussion

2.1. Synthesis of methyl 3^2-nitro-pyropheophorbides-*a* 1a–c

Henry reaction (nitro-aldol condensation) of the 3-formyl group of methyl pyropheophorbide-*d* (**2**) with nitromethane was examined (Scheme 1). The nitro-aldol condensation in nitromethane as the solvent proceeded following the addition of triethylamine at room temperature in the dark under nitrogen. After the reaction mixture was stirred for 1 h, starting aldehyde **2** disappeared and a new spot was visible on silica gel thin layer chromatography (TLC) with 10% diethyl ether and dichloromethane as an eluent: R_f-values of the former (red) and latter (black) were 0.5 and 0.4, respectively. The visible spectra also supported the consumption of **2** and concomitant production of a new chlorin compound: the Qy absorption maximum of the reaction mixture=695→666 nm in dichloromethane. After evaporation under a reduced pressure, the residue was subjected to silica gel flash column chromatography (FCC). First, **2** was eluted, then the product was given. Based on the findings that **2** was invisible in the completed reaction mixture and re-FCC of the pure product partially afforded **2** (ca. 10%), the product was rather unstable in silica gel and decomposed to **2** by retro-nitro-aldol condensation. Simple purification of the reaction mixture with recrystallization from dichloromethane and hexane gave desired nitro-aldol product **3a**, methyl 3^2-nitro-bacteriopheophorbide-*d* (3^1-hydroxy-3^2-nitro-mesopyropheophorbide-*a*), in 93% yield (Scheme 1): *m*/*z*=611 (M^+). The reaction was so clean that no other products were isolated.



Scheme 1. Synthesis of methyl 3^2-nitro-pyropheophorbides-*a* **1a**–**c** from methyl pyropheophorbide-*d* (**2**): (i) RCH_2NO_2, Et_3N, rt; (ii) Ac_2O, DMAP/CH_2Cl_2, rt; (iii) Et_3N, rt; (iv) $^nBuNH_2$, $Et_3N/CHCl_3$, reflux; (v) $PhCH_2NO_2$, AcOH, rt.

Dehydration of β-nitro-alcohol **3a** to the corresponding nitro-olefin was examined in the presence of an acid, *p*-toluenesulfonic acid. While the desired olefin was detected, aldehyde **2** was substantially obtained. The retro-aldol condensation was consistent with the above observation that relatively labile **3a** was transformed to **2** on silica gel. To avoid the undesired reaction, alcohol **3a** was esterified with acetic anhydride in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in dichloromethane at room temperature for 2.5 h and the resulting acetate **4a** was treated with triethylamine for 3 h in the same pot (Scheme 1). After purification of FCC and recrystallization, a nitro-olefin was obtained as an analytically pure sample in 70% yield: *m*/*z*=593 (M^+). It is noteworthy that alcohol **3a** was relatively stable under basic conditions and smoothly esterified to the corresponding acetate **4a**. The 1D ^1H NMR spectrum of the nitro-olefin in deuterated chloroform showed the coupling constant of 14 Hz for the ethylene protons at the $C3^1$=$C3^2$ moiety, indicating that the product was an *E*-isomer as in **1a**. No *Z*-isomer was detected in the ^1H NMR spectrum of the reaction mixture. Stereospecific removal of acetic acid from acetate **4a** occurred in the present reaction. The sole production of *E*-isomeric **1a** was ascribable to the steric factor and also the following electronic factor. Since the 3^2-nitro-vinyl group was coplanar and fully conjugated with the chlorin π-system in **1a**, the *E*-isomer was more energetically stable than the *Z*-isomer.

Using nitroethane instead of nitromethane, aldehyde **2** was transformed to nitro-alcohol **3b** for 4 h in 90% yield (Scheme 1). The yield was comparable to that of **3a**, but the reaction period for consumption of **2** was four times longer than that in **2** to **3a**. The elongation is due to the more steric hindered and less reactive site at the C1 position of nitroethane. The esterification (4.5 h) of **3b** and successive elimination of **4b** (2 days) afforded the corresponding nitro-olefin in 88% yield. The reaction times were longer than those in **3a** to **1a**, which was also explained by the steric factor around the reaction sites. The 2D spectroscopy (NOESY) of the olefinic product clearly showed that no NOE correlation between $C3^1$–H and $C3^2$–CH_3 was observed and $C3^2$–CH_3 was correlated with C2–CH_3 and C5–H. The correlation indicated that the three-substituted olefin took an *E*-configuration. The product was identified as **1b** and the 3^2-*cis*-methylated form of **1a**. The occupation of the *trans*-position with a nitro group was predominant in the above elimination. Molecular modeling (MM+ and PM3)[7] supported that the energy-minimized structure of *E*-**1b** was more stable by about 1 kcal/mol than the corresponding *Z*-isomer.

Similar to the synthesis of β-nitro-alcohols **3a** and **3b**, Henry reaction of **2** with phenylnitromethane was examined but no desired product was isolated. Therefore, nitro-Mannich reaction of **2** with phenylnitromethane was applied.[8] Aldehyde **2** was first transformed to butylimine **5** and successively treated with phenylnitromethane and acetic acid in the same pot (Scheme 1).[9] The reaction mixture was purified by FCC and recrystallization to give a desired nitro-olefin in 56% yield. The total yield for the three steps in one pot without isolation of any intermediates was comparable to those of **2** to **1a**/**b** via **3a**/**b** (65/79%). The NOESY indicated the product to be *E*-isomeric **1c** as the 3^2-*cis*-phenyl-substituted form of **1a**. The proton chemical shift (δ) of C2–CH_3 was situated at 2.83 ppm in **1c** and moved to a higher field than that of **1a** (3.49 ppm). The high-field shift (0.66 ppm) was ascribed to the ring current effect of the neighboring phenyl group at the *cis* position, not the *trans*, which also supported the *E*-configuration. A similar shift has already been reported for *cis*-phenylation at the 3^2-position of **1d**: δ=3.41→2.99 ppm.[5]