Pergamon

Tetrahedron Letters, Vol. 37, No. 31, pp. 5431-5434, 1996
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0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01143-4

A CONVENIENT SYNTHETIC APPROACH TO 8-VINYL-CHLOROPHYLL DERIVATIVES

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Abstract: Partial syntheses of two 8-vinyl-derivatives (**3** and **6**) of chlorin-e_6 trimethyl ester **5** are reported; in certain organisms, 8-de-ethyl-8-vinylchlorophyll-a **3** has been proposed to be a biosynthetic precursor of the plant chlorophylls and of the bacteriochlorophylls.
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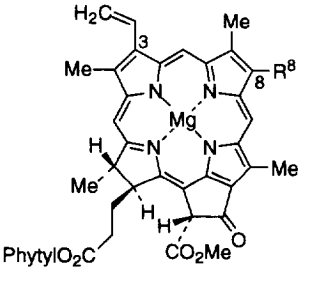
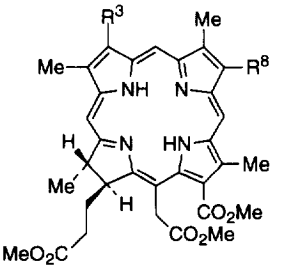
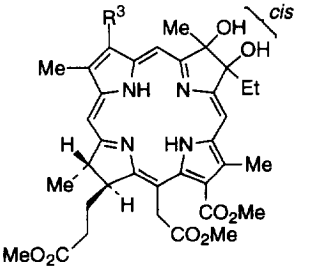
Divinyl derivatives (e.g. **1**) of the green plant pigment chlorophyll-a **2**, bearing a vinyl instead of an ethyl group at position-8, have recently been found to be intermediates during chloroplast biogenesis in plants and bacteria.[1,2] Based on Woodward's synthesis[3] of **2** a key intermediate in any synthetic approach to 8-vinyl-derivatives of the plant chlorophylls would be the 8-de-ethyl-3,8-divinyl-chlorin-e_6 trimethyl ester **3**; indeed, this compound was first found as a serendipitous by-product from a dehydration reaction of the chlorin-e_6 diol **4**, obtained by photo-oxygenation of a chlorin-e_6 phlorin.[4] We now report efficient synthetic approaches, from chlorin-e_6 trimethyl ester **5**, to 8-de-ethyl-8-vinylchlorin-e_6 trimethyl ester **3** and 8-de-ethyl-8-vinylmesochlorin-e_6 trimethyl ester **6**.



1: R^8 = CH=CH$_2$
2: R^8 = Et

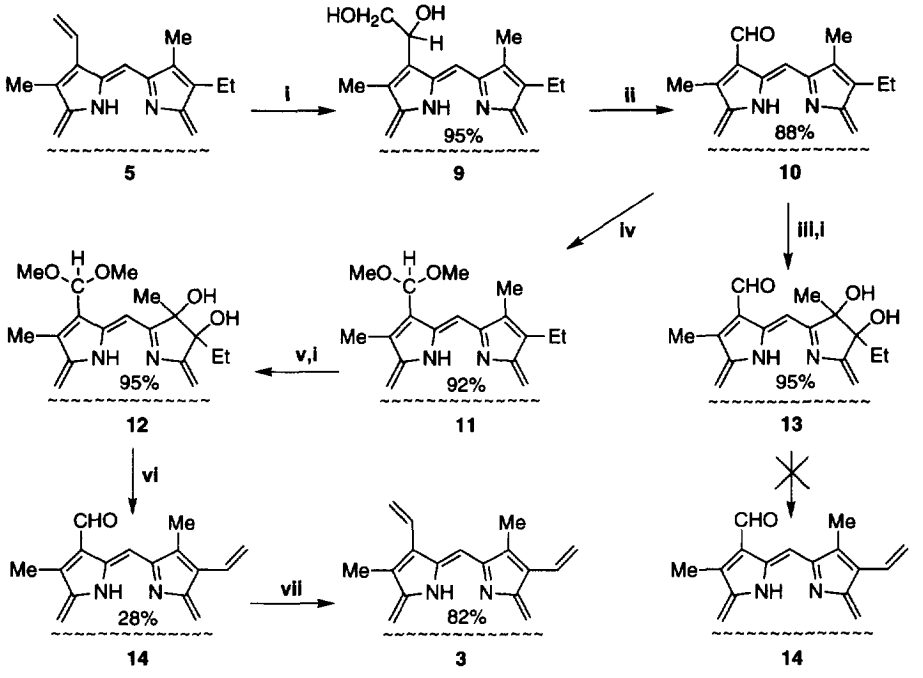


3: R^3 = R^8 = CH=CH$_2$
5: R^3 = CH=CH$_2$, R^8 = Et
6: R^3 = Et, R^8 = CH=CH$_2$
7: R^3 = R^8 = Et



4: R^3 = CH=CH$_2$
8: R^3 = Et

Chlorin-e_6-trimethyl ester **5** is readily available[5] from chlorophyll-a found in *Spirulina pacifica* alga.[6] Catalytic hydrogenation of the 3-vinyl group in **5** gave mesochlorin-e_6 trimethyl ester **7**, and following reaction with OsO_4 to afford the 7,8-diol **8**,[7,8] dehydration[9] in hot toluene containing pyridinium p-toluenesulfonate (PPTs) gave the 3-ethyl-8-vinylchlorin-e_6 trimethyl ester **6**, a constitutional isomer of **5**, in 60% yield (40% overall).



Scheme 1: Synthetic route to 8-de-ethyl-8-vinylchlorin-e_6 trimethyl ester **3**

Reaction Conditions: **i**: 1. OsO_4/py, THF, 0°C, 30 min. 2. $NaHSO_3$, MeOH/H_2O, rt, 30 min. **ii**: $NaIO_4/SiO_2$, THF/H_2O, rt, 20 min. **iii**: 1. OsO_4/py, THF, rt, 10 d. **iv**: $HC(OMe)_3$/p-TsOH, MeOH, reflux, 30 min. **v**: 1. OsO_4/py, THF, rt, 6 d. **vi**: 25 Torr, 90°C, 5 d. **vii**: $Ph_3P^+MeBr^-/NaN(SiMe_3)_2$, THF, reflux, 90 min, then **14**, 50°C, 30 s.

Synthesis of the 3,8-divinylchlorin-e_6 **3** was more difficult because the 3-vinyl group of chlorin-e_6 trimethyl ester **5** is the most reactive double bond in the molecule. In order to carry the vinyl through the reaction sequence, it must be protected before the OsO_4 reagent can regioselectively[8] attack the C7-C8 double bond in **5**. Though we have used the (2-chloroethyl) substituent for reversible vinyl group protection in a number of our syntheses,[10] in the present series the best method for vinyl-protection involved preparation of diol **9** by treatment of **5** with OsO_4/pyridine, followed by glycol cleavage using sodium periodate on silica, to give the 3-formyl-chlorin-e_6 **10** (Scheme 1). This compound was then converted into its dimethylacetal **11** by treatment with trimethyl orthoformate in methanol (and p-toluenesulfonic acid as catalyst). The 7,8-diol **12** was then obtained[8] in excellent yield by use of OsO_4/pyridine. The electron-withdrawing effect of the formyl group in 3-formyl-diol **13**, obtained by osmium-oxidation of **10**, appeared to favor pinacol rearrangement, so the dehydration of acetal-diol **12** was accomplished in moderate yield by heating under vacuum. Under these conditions the 8-vinyl group was formed with concomitant cleavage of the acetal to give the 3-formyl-8-vinylchlorin-e_6 **14**; a Wittig reaction between **14** and methylene triphenylphosphorane[11] easily afforded **3**.[12,13]

Figure 1A shows the vinyl region in the proton NMR spectra (300 MHz) of chlorin-e_6 trimethyl ester; beneath this can be seen the vinyl proton spectra of the 3-ethyl-8-vinylchlorin e_6 isomer **6** (Fig. 1B) and the divinyl compound **3** (Fig. 1C). Figure 1C, to a first order approximation, appears as a composite of the two monovinyl isomers.

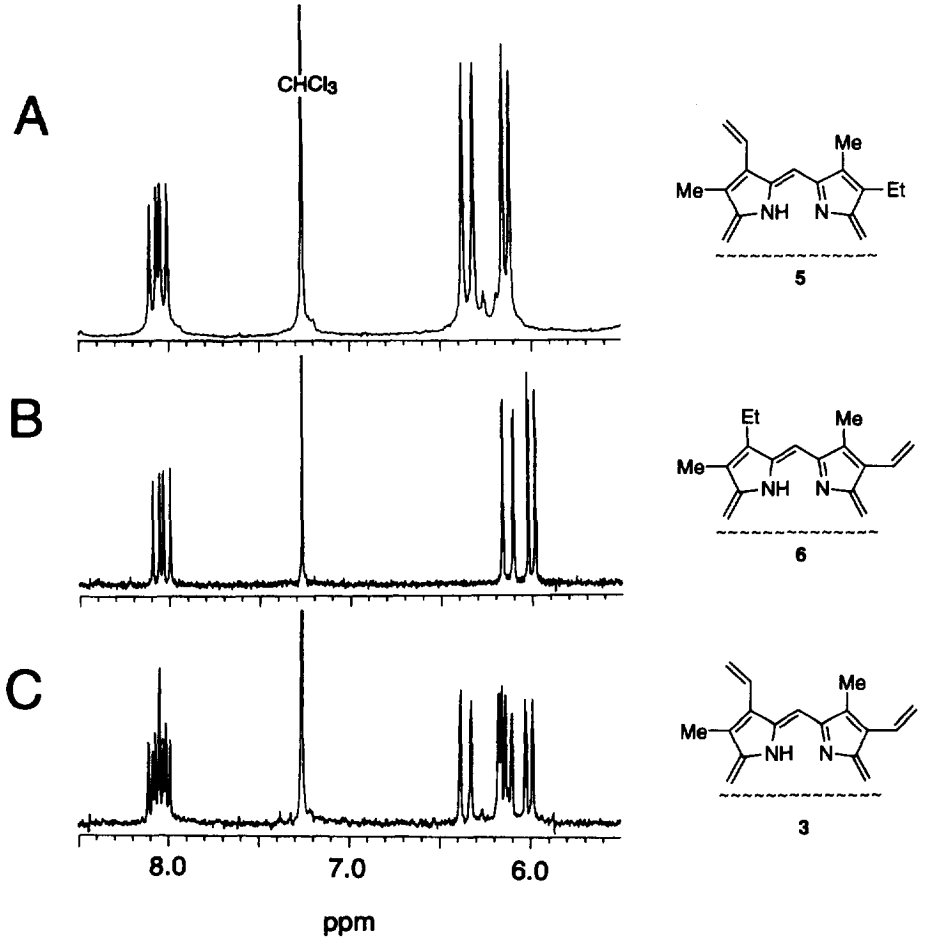


Figure 1: ^{1}H-NMR Spectra (300 MHz, vinyl region only) in $CDCl_3$ of: (A) chlorin-e_6 trimethyl ester **5**; (B) 8-de-ethyl-8-vinylmesochlorin-e_6 trimethyl ester **6**; (C) 8-de-ethyl-8-vinylchlorin-e_6 trimethyl ester **3**.

Transformation of **3** and **6** into the corresponding pheophorbides and chlorophylls[14] is in progress, and will be reported in a full paper.

Acknowledgments: We thank the National Science Foundation (CHE-93-05577) for support of this research. Mass spectrometric analyses were performed by the UCSF Mass Spectrometry Facility (A. L. Burlingame, Director) supported by the Biomedical Research Technology Program of the National Center for Research Resources, NIH NCRR BRTP 01614.

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13. Typical physical data: Compound **3**: mp 201-203°C, λ_{max} (CH_2Cl_2), 410 nm (ε 149,000), 506 (11,000), 608 (4000), 662 (40,000). Compound **6**; mp 204-206°C, λ_{max} (CH_2Cl_2), 404 nm (ε 163,000), 502 (12,000), 596 (5000), 650 (39,000). Compound **11**: mp 158-160°C, λ_{max} (CH_2Cl_2), 399 nm (ε 146,000), 498 (13,000), 524 (5000), 548 (3000), 604 (5000), 658 (45,000). Compound **14**: mp 237-239°C, λ_{max} (CH_2Cl_2), 422 nm (ε 112,000), 516 (11,000), 552 (7000), 632 (5000), 688 (51,000).
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(*Received in USA* 30 *April* 1996; *accepted* 4 *June* 1996)