Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 2, pp. 313-316, 1995

0957-4166/95 $9.50+0.00

0957-4166(95)00001-1

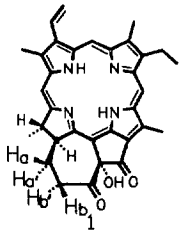
Asymmetric Hydroxylation of Chlorophyll Derivatives: A Facile Entry to Both Diastereomers of Chlorophyllone *a*

Lifu Ma and David Dolphin*

Department of Chemistry, The University of British Columbia,
2036 Main Mall, Vancouver, B.C., Canada V6T 1Z1

Abstract: High stereoselectivity is observed for the asymmetric oxidation of chlorophyll enolates derived from $13^2,17^3$-pheophorbide *a* enol (**3**), pheophorbide *a* methyl ester (**8**) and pheophytin *a* (**9**) with DBU and N-sulfonyl oxaziridines (**4**), (**5**) and (**6**).

Chlorophylls and their derivatives are known to be readily oxidized at the C-13^2 position by triplet O_2 and other oxidants. These oxidation reactions rarely stop at the hydroxylation stage without going further to several degradative products (this process is called allomerization).[1] No efficient synthetic method, especially diastereoselective, has been reported for such transformations.



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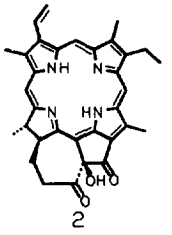

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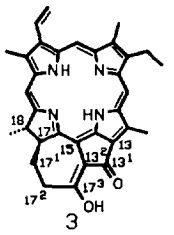

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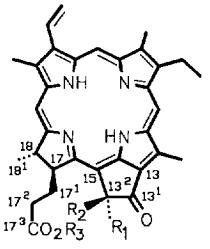
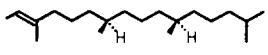
Recently, hydroxychlorins such as 13^2R-hydroxychlorophyllone *a* (**1**) and its epimer 13^2S-hydroxychlorophyllone *a* (**2**) have been isolated, as antioxidants, from the short-necked clam, *Ruditapes philippinarum* and from viscera of the scallop, *Patinopecten yessoensis*.[2] These two compounds seem to be directly bio-oxidized from another natural chlorin, $13^2,17^3$-cyclopheophorbide *a* enol (**3**), which has also been recently isolated from the sponge *Darwinella oxeata*.[3] Discovery of these natural hydroxychlorins attracted our interest and prompted us to explore a direct diastereoselective hydroxylation.

Although there are a few α-keto hydroxylation methods available in the literature, most of them are unsuitable for chlorins or exhibit low stereoselectivity. We chose direct oxidation of enolates with

oxaziridines to achieve this transformation.[4] By modifying Eschenmoser's method,[5] enol **3** was prepared in 85% yield from a Claisen type intramolecular condensation of pyropheophorbide *a* methyl ester (**7**), which was obtained from pheophorbide *a* methyl ester (**8**) by decarboxylation. Although **3** exists in the enol form in polar solvents, it does not react directly with oxaziridines. We found that [1,8]-diazabicyclo[5.4.0] undec-7-ene (DBU) is an excellent base to promote the reaction. Upon addition of DBU (0.4 mL) to a THF solution of **3** (20 mg in 10 mL) at 0°C under N_2, the green solution changed instantly to the reddish-brown enolate (a typical color of the Molish phase-test intermediate).[1] After 10 minutes, 1.2 equiv of (±)-2-(phenylsulfonyl)-3-phenyloxaziridine (**4**)[6] was injected and the reaction was continued for 2 more hours at 0°C. Following a standard workup and flash chromatography on silica a dark green solid was collected (see entry 1 in Table 1). The ^{1}H NMR showed it was a diastereomeric mixture. The most significant changes were that the 17^3-OH peak (13.24 ppm) of **3** disappeared and two new broad OH peaks at 4.56 and 4.14 ppm (exchangeable with CD_3OD) appeared. The absorption spectrum Q band showed a blue shift of 20 nm to 670 nm.



7. R_1=R_2=H, R_3=CH_3
8. R_1=$COOCH_3$, R_2=H, R_3=CH3
9. R_1=$COOCH_3$, R_2=H, R_3=Phytyl
10. R_1=OH, R2=$COOCH_3$, R_3=CH3
11. R_1=$COOCH_3$, R_2=OH, R_3=CH3
12. R_1=OH, R2=$COOCH_3$, R_3=Phytyl
13. R_1=$COOCH_3$, R_2=OH, R_3=Phytyl



Phytyl

Table 1. Asymmetric Hydroxylation of **3**, **7**, **8** with oxaziridines **4**, **5**, **6** in THF

entry	oxaziridine	substrate	Reaction temperature and time (h)	product	13^2R:13^2S[a]	% isolated yield
1	(±)-**4**	**3**	0°C (2)	**1,2**	38:62	75
2	(±)-**4**	**3**	–25°C (12)	**1,2**	11:89	98
3	(–)-**5**	**3**	0°C (2)	**1,2**	5:95	93
4	(–)-**5**	**3**	–25°C (12)	**1,2**	5:95	94
5	(+)-**6**	**3**	0°C (2)	**1,2**	43:57	77
6	(+)-**6**	**3**	–25°C (2)	**1,2**	68:32	88
7	(±)-**4**	**8**	0°C (2)	**10,11**	69:31	85
8	(–)-**5**	**8**	0°C (2)	**10,11**	94:6	88
9	(–)-**5**	**8**	–25°C (12)	**10,11**	95:5	92
10	(+)-**6**	**8**	0°C (2)	**10,11**	57:43	49
11	(+)-**6**	**8**	–25°C (12)	**10,11**	42:58	82
12	(±)-**4**	**9**	–25°C (12)	**12,13**	80:20[b]	55
13	(–)-**5**	**9**	–25°C (12)	**12,13**	100:0[b]	91
14	(+)-**6**	**9**	–25°C (12)	**12,13**	66:34[b]	87

a: The % d.e.'s determined by reversed-phase HPLC. b: The % d.e. 's determined by ^{1}H NMR.

A FABMS analysis showed a molecular mass increase of 17 units to 533 (M+1) and reversed-phase HPLC analysis confirmed a 62:38 mixture of diastereomers (close to the intensity ratio in the ^{1}H NMR). The two diastereomers were separated by preparative HPLC. The more mobile band was Chlorophyllone *a* (**1**)

and the less mobile band was **2**. The newly introduced 13^2-OH group caused downfield shifts in the ^{1}H-NMR of nearby protons (H-17, $H_a{}^1$-17^1, $H_b{}^1$-17^2, in **1**; H_a-17^1, H_b-17^2 and H-18 in **2**) compared to those in the starting material **3** (Table 2). The synthetic chlorins **1** and **2** exhibit the same spectral[7] data as their natural counterparts.[2]

To achieve direct diastereoselective hydroxylation, two enantiopure oxidants have been used. Reaction of **3** with (–)-(1R)-(10-camphorsulfonyl)oxaziridine (**5**) (98%, Aldrich) using the above procedure gave a 93% yield of **1** (90% d.e.) (entry 3). Higher selectivity was obtained at lower temperature where reaction of **3** with (±)-**4** and (–)-**5** respectively at -25°C for 12 hours, gave a 98% yield (78% d.e.) and 94% of **1** (90% d.e.). Reaction with (+)-**6** (98%, Aldrich), an enantiomer of **5**, gave slightly lower yields and diastereomeric selectivity (entry 5 and 6). These observations can be rationalized as resulting from the bulk of the 17-propionic group which hinders the approach of **6** from the *re* face of the chlorin enolate.

In a similar fashion, treatment of pheophorbide *a* methyl ester (**8**) and pheophytin *a* (**9**)[8] with the oxaziridines gave excellent yields and diastereoselectivity. As described above, the 17-propionic group affects the stereoselectivity. With an increased size of the 17-propionic ester chain from **8** to **9**, the d.e.% of their products after reaction with (±)-**4** and (–)-**5** increased (entry 9 and 13), in the latter case, a 100% d.e. was observed with *re* face recognition of the nucleophilic oxaziridine **5** in contrast to a 90% d.e. in the reaction with the smaller ester where only a 32% d.e. was observed in the reaction of **9** with (+)-**6** (entry 14) along with reversed stereoselectivity such that **12** and **13** were produced in a ratio of 66:34 (entry 14). The bulky phytyl ester (methyl ester) and 13^2-methoxycarbonyl moieties are on opposite sides of the molecular plane in **13** (**11**) while they are on the same side in **12** (**10**). The 13^2S configuration (which gave lower d.e. and yields) is thermodynamically more stable than the 13^2R configuration, showing that these products are kinetically-controlled. No epimeric conversion between them has been observed at room temperature, but epimerization takes place in refluxing pyridine. Diastereomerically pure **10** and **11** were prepared by HPLC separation of the products from entries 9 and 11. In these cases the downfield shifts in the ^{1}H-NMR were less pronounced due to the greater distance between the 17-alkyl protons and the OH group (Table 2).

Table 2: Selected ^{1}H-NMR Spectral Data ($CDCl_3$, 400MHz)

Proton	Compound							
	1[a]	**2**[b]	**3**[a]	**8**[a]	**10**[b]	**11**[a]	**12**[a]	**13**[c]
H-18	4.31(dq)	4.75(dq)	2.93(dq)	4.47(q)	4.49(dq)	4.49(dq)	4.47(dq)	4.55(dq)
H-17	4.90(dt)	3.82(ddd)	2.58(dt)	4.20(q)	4.69(dt)	4.15(dt)	4.68(dt)	4.15(dt)
H_a-17^1	2.23(ddt)	3.71(dddd)	1.71(dt)[d]	2.62(dt)	2.13(dddd)	2.92(dddd)	2.09(dddd)	2.91(dddd)
$H_a{}^1$-17^1	2.88(dddd)	2.65(dddd)	1.71(dt)[d]	2.31(dt)	2.46(dddd)	2.28(dddd)	2.42(dddd)	2.25(dddd)
H_b-17^2	2.78(ddd)	3.83(ddd)	2.45(t)[d]	2.50(t)	2.09(ddd)	2.55(ddd)	1.99(ddd)	2.53(ddd)
$H_b{}^1$-17^2	4.33(ddd)	2.95(ddd)	2.45(t)[d]	2.24(t)	2.29(ddd)	2.26(ddd)	2.24(ddd)	2.25(ddd)
13^2-OH/H	4.56(br s)	4.14(br s)		6.27(s)	5.32(s)	5.43(s)	5.32(s)	5.49(s)
17^3-OH			13.24(s)					

a: Concentration: 1.5mg/0.6mL, b: 1.0mg/0.6mL, c: 2.0mg/0.6mL 38% d.e.[9], d: overlapping signals

It should be noted that reaction of oxaziridines with chlorin enolates formed by ionic bases, such as $(TMS)_2NNa$, LDA and KOH/ROH, did not yield the desired hydroxychlorins, but further oxidative (degradative) products were produced. Additional hydroxylation methods have also been tested to better

understand the different reactivities. For example, reaction of the enolate of **8** formed by DBU, with MCPBA at room temperature for 10 hours, gave less than 5% hydroxylation product. Bubbling molecular oxygen into the enolate of **8** in the presence of DBU and triethyl phosphite at room temperature for 5 hours gave no reaction and the starting material was recovered. Furthermore, reaction of the enolate of **8**, formed by ionic bases, with MCPBA (30 mins at room temperature) or O_2 (5 min at 0°C) led to exocyclic ring cleavage.

To our knowledge, this is the first report showing the use of DBU as a base for α-ketohydroxylation, and the first successful diastereoselective oxidation of chlorophyll derivatives. The mild conditions, high yields and d.e.% make it an efficient method to introduce an hydroxy group into β-dicarbonyl chlorins.[10] These hydroxychlorins will serve as models for an understanding of chlorophyll allomerization mechanisms.

13^2S-Hydroxypheophytin a (**13**), recently isolated from *Silkworm excreta*, is reported to possess a high quantum efficiency (50%) for the photosensitized production of singlet oxygen[11] suggesting that the compounds reported here have a potential as drugs for photodynamic therapy.

ACKNOWLEDGEMENT

This work was supported by the Natural Sciences and Engineering Research Council of Canada.

REFERENCES:

1. H. Fischer and H. Orth, in: *"Die Chimie des Pyrrols"*, Akademische Verlag, Leipzig, 1940, Vol.II, Part 2.
2. (a). K. Sakata, K. Yamamoto, N. Watanabe, *ACS Symp. Ser.* ,1994, **547**, 164.
   (b). N. Watanabe, K. Yamamoto, H. Ihshikawa and A. Yagi, *J. Nat. Prod.* 1993, **56**, 305.
3. P. Karuso, P.R. Bergquist, J.S. Buckleton, R.C. Cambie, G.R. Clak and C.E.F. Rickard, *Tetrahedron Lett.* 1986, **27**, 2177.
4. F.A. Davis and B. Chen, *Chem. Rev.* 1992, **92**, 919.
5. H. Falk, G. Hoornaert, H.P. Isenring and A. Eschenmoser, *Helv. Chim. Acta* 1975, **58**, 2347.
6. F.A. Davis and O.D. Stringer, *J. Org. Chem.* 1982, **47**, 1774.
7. All new compounds were characterized spectroscopically. None melted below 300°C except 12 (mp 199-200°C). UV-vis spectra $\lambda_{max(nm)}^{CHCl3}(\varepsilon \times 10^{-3})$; **1**, 416 (111), 506 (12.5), 536 (10.2), 612 (9.2), 670 (50.9). **2** 416 (113), 508 (12.9), 538 (11.1), 616 (10), 674 (48.3). **3** 364 (67.2), 430 (66), 456 (47.2), 592 (5.2), 630 (4.8), 690 (33.4). **10** 416 (136.6), 506 (15.5), 538 (11.6), 560 (4.2), 612 (11.5), 670 (62.1). **11** 414 (141.2), 506 (9.8), 536 (15.8), 612 (11.3), 670 (63.5). **12** 416 (101), 506 (11.8), 536 (9.5), 612 (9), 670 (45.6).
8. **8** and **9** exist in an epimeric equilibrium at $C13^2$. 13^2R *vs.* 13^2S is ~ 83:17 in $CDCl_3$ at room temperature.
9. HPLC separation of **13** from its epimeric mixture was less successful. Its spectrum was derived from a 38% d.e. mixture knowing the ^{1}H-NMR spectrum of its pure epimer **12**.
10. This method can run on a large scale. 500mg of **8** and **9** have been reacted with (–)-**5** and (+)-**6**. Similar yields and d.e.% were observed.
11. R. Dai, R. Shoemaker, D. Farrens, M.J. Han, C.S. Kim and P. Song, *J. Nat. Prod.* 1992, **55**, 1241.

(*Received in USA* 6 *October* 1994)