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PARTIAL SYNTHESIS OF CHLOROPHYLL-A FROM RHODOCHLORIN

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Abstract —A synthesis of chlorophyll-a from a relay degradation product, rhodochlorin dimethyl ester, is described. Key steps involve formation of methyl pheophorbide-a by thallium(III) promoted photocyclization of the corresponding chlorin-6-β-keto-ester, and magnesium(II) insertion using Eschenmoser's BHT method.

Twenty years ago, Woodward *et al.* described their remarkable approach[1] to the synthesis of chlorin-e_6 trimethyl ester and chlorophyll-a. This achievement contributed in no small way to the total body of inspired work for which the 1965 Nobel Prize for "*meritorious contributions in the art of organic synthesis*" was awarded.[2]

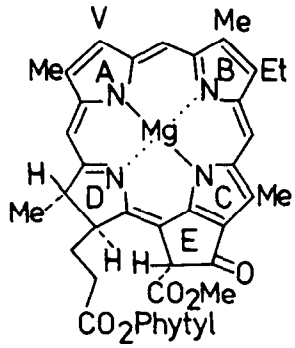
A key structural feature in the chlorophyll-a (**1**) molecule is the 5-membered carbocyclic ring ("E") which is formed biosynthetically from the 6-propionic side chain in protoporphyrin-IX (**2**). During the course of a study to investigate the possibility that a porphyrin-6-β-keto-ester magnesium(II) complex is a metabolic intermediate between **2** and **1**, we have achieved efficient syntheses of porphyrin-6-β-keto-esters[3] and have successfully cyclized these to pheoporphyrins using a novel thallium(III) promoted photo-reaction.[4] In the present paper we describe an application of this fundamental chemistry to the chlorin series, thereby establishing an efficient route from rhodochlorin dimethyl ester (**3**) to methyl pheophorbide-a (**4**). Furthermore, we also describe a method for transformation of methyl pheophorbide-a (**4**) into chlorophyll-a(**1**). Woodward's chlorophyll-a synthesis depended upon "well trodden paths"[1] for conversion of chlorin-e_6 ester (**5**) into chlorophyll-a, but though both the phytyl ester formation and magnesiation reactions are feasible,[5] no experimental details were available for the magnesiation of pheophytin. In our hands, magnesium insertion using Grignard reagents decomposed with alcohols leads to products which have suffered transesterification;[6] no doubt the Grignard reagent decomposed with phytol would have been effective in the synthesis of chlorophyll-a from pheophytin, but the recent introduction of Eschenmoser's "butylated hydroxy-toluene" method[7] has elegantly solved any real problems which might have existed.

For elaboration of the carbocyclic ring in the chlorin series we chose the chlorophyll-a degradation product, rhodochlorin dimethyl ester (**3**). This compound is readily available from natural pheophytin-a,[8] and is related to 2-vinylrhodoporphyrin-XV dimethyl ester (**6**) which lacks only the *trans*-hydrogens present in ring D of **3**. Since we have already achieved a total synthesis of 2-vinylrhodoporphyrin-XV dimethyl ester (**6**)[9] it was hoped that we might eventually achieve our own synthesis of chlorophyll-a if we could transform 2-vinylrhodoporphyrin-XV dimethyl ester into rhodochlorin dimethyl ester. So far, this "simple" addition of two hydrogens has eluded us, but this has not deterred us from completing the synthesis by transforming rhodochlorin into chlorophyll-a.

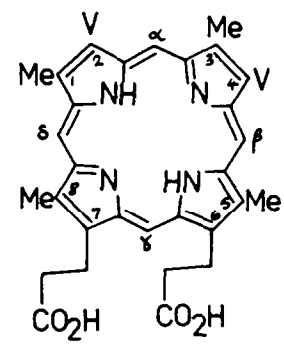
Treatment of rhodochlorin dimethyl ester (**3**) with methanolic potassium hydroxide effected hydrolysis of both esters, and gave rhodochlorin (**7**) which was partially esterified at the propionic side chain using 5% sulfuric acid in methanol, to give **8**. With N,N'-carbonyldi-imidazole, (**8**) gave the imidazolide (**9**) in 82% yield. This was treated with the magnesium salt (**10**) of methyl hydrogen malonate[10] and gave a 73% yield of the chlorin-β-keto-ester (**11**). Cyclization of the β-keto-ester to give methyl pheophorbide-a (**4**) was achieved in 46% yield by photolysis of the keto-ester after addition of about 2 mol equiv of thallium(III) trifluoroacetate[4] and the product, obtained as a thallium(III) chelate, was demetalated using sulfur dioxide and hydrochloric acid.[11] NMR spectroscopy showed that the cyclization had occurred to give the expected mixture of methyl pheophorbide-a and methyl pheophorbide-a' (the 10-epimer).[12]

The phytyl ester was introduced using a modification of a method developed by Willstätter and Stoll.[13] Synthetic methyl pheophorbide-a (**4**) was hydrolyzed to the free acid (**12**) by treatment with cold conc hydrochloric acid, and upon treatment with purified commercial phytol and phosgene, gave pheophytin-a (**13**) in an overall yield of 80%.

Magnesiation of pheophytin-a was accomplished using iodomagnesium(II) 2,6-di-t-butyl-4-methyl-phenoxide,[7] which avoids all problems such as transesterification and degradation of the carbocyclic ring which could be brought about by treatment of pheophytin-a with strong nucleophiles. In a trial reaction, natural methyl pheophorbide-a was treated with a freshly prepared solution of Eschenmoser's reagent[7] in dry methylene chloride/ether under an atmosphere of dry argon for 10 min at ambient temperature. This resulted in complete magnesiation (spectrophotometry) and methyl chlorophyllide-a (**14**)

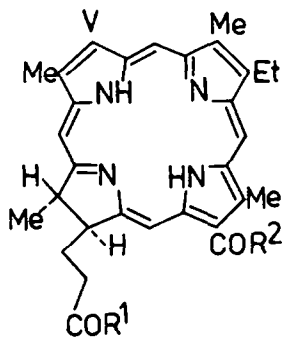


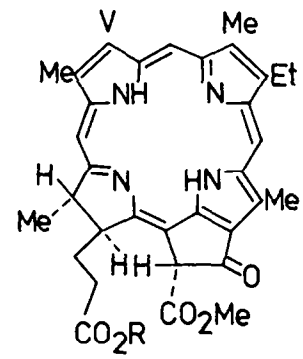
(1)



(2)

V = CH=CH$_2$

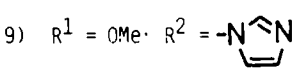




(3) $R^1 = R^2 = OMe$

(7) $R^1 = R^2 = OH$

(8) $R^1 = OMe$; $R^2 = OH$

(9) $R^1 = OMe$; $R^2 =$ 

(4) R = Me

(12) R = H

(13) R = Phytyl

was obtained in 87% yield after purification. A similar reaction with synthetic pheophytin-a (**13**) gave synthetic chlorophyll-a (**1**) in 54% yield.

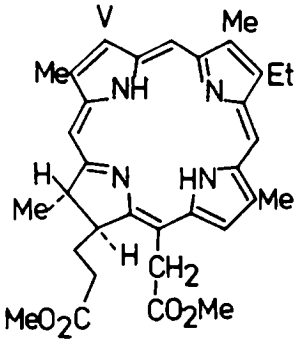
Attempts to reduce 2-vinylrhodoporphyrin dimethyl ester (**6**) to give rhodochlorin dimethyl ester (**3**) have so far been unsuccessful. Completion of a synthesis of chlorophyll-a would also require resolution and attachment of a sample of chiral phytol.

EXPERIMENTAL

M.ps were measured on a hot-stage apparatus, and are uncorrected. Neutral alumina (Fluka) was used for column chromatography, and reactions were monitored using glass microscope slides coated with Merck GF 254 silica gel. Electronic absorption spectra were measured on Unicam SP800 and SP8000 spectrophotometers with samples dissolved in CH_2Cl_2, and NMR spectra were recorded at 100 or 220 MHz using Varian XL100 or Perkin–Elmer R34 spectrometers; samples were dissolved in $CDCl_3$ with TMS as an internal standard. Mass spectra were determined using AEI MS 12 or MS 902 instruments (direct insertion probe, 70 eV, 50 μA, source temperature approx. 200°).

Rhodochlorin dimethyl ester (**3**)

Methyl pheophorbide-a (540 mg)[8] in freshly distilled pyridine (3 ml) was added to a 25% soln of KOH in dry MeOH (70 ml) and cooled to 0° in an ice-bath. The soln was saturated for 15 min with a stream of O_2 and the intense green soln was kept at 0° with stirring for 30 min. N_2 was then passed through the soln for 25 min, after which it was heated under reflux for another 10 min. The mixture was cooled rapidly, diluted with water (270 ml) and the green alkaline soln was acidified with 18% HCl aq in the presence of CH_2Cl_2 (400 ml) until pH 3. The organic phase was separated and the aqueous layer was further extracted with CH_2Cl_2 (3 × 100 ml) before evaporation of all the organic fractions to dryness (some residual water was azeotroped with toluene). The residue was dissolved in MeOH (50 ml) and treated with excess ethereal diazomethane for 15 min before evaporation to dryness. The residual black solid was chromatographed on alumina (Brockmann Grade III, elution with CH_2Cl_2) and the appropriate eluates were evaporated to dryness. Crystallization from CH_2Cl_2/MeOH gave the required diester as shiny blue crystals (340 mg; 69%), m.p. 206–208° (lit.[14] 207°). NMR, δ ppm, 9.80, 9.72, 9.58, 8.74 (each 1 H, s, 4 meso H); 8.12–7.97, 6.37–3.12 (1 H, m and 2 H, m, CH=CH$_2$); 4.50 (1 H, m, 8-H); 4.40–4.30 (1 H, m, 7-H); 4.36, 3.80, 3.64, 3.46, 3.28 (each 3 H, s, 5 × Me); 3.84–3.67, 1.72 (2 H, m, 3 H, t, CH_2CH_3); 2.82–2.30 (4 H, m, $CH_2CH_2CO_2Me$); 1.90 (3 H, d,



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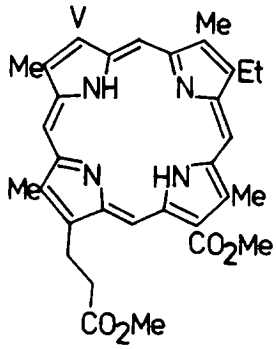

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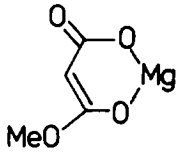

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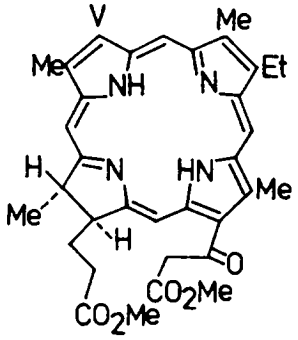
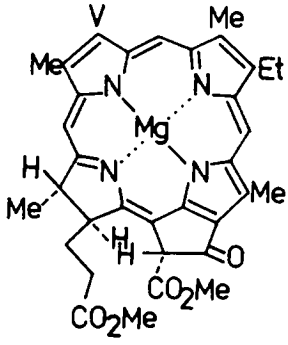


(11)



(14)

8-Me). MS, *m/e* (%), 566 (100), 551 (26), 535 (7), 503 (7), 479 (76), 449 (10), 420 (7), 405 (12). λ_{max} 399 (ε 86, 300), 496 (6700), 526 (2500), 558 (1200) and 664 nm (28,000).

6-Imidazoylrhodochlorin methyl ester (**8**)

Compound **3** (400 mg) in freshly distilled THF (20 ml) was treated with a 10% soln of KOH in dry MeOH (20 ml) and stirred at room temp for about 20 hr. Glacial AcOH (3 ml) was added dropwise until the soln was slightly acidic and the resulting black ppt was washed with water and dried *in vacuo*. The rhodochlorin (386 mg) was suspended in a 5% soln of conc HSO_4 in MeOH (150 ml) overnight with stirring before being poured into a stirred mixture of $CHCl_3$ (200 ml) and a 5% aqueous soln of 0.880 ammonia (300 ml). The organic phase was washed with water (2 × 200 ml), dried over Na_2SO_4, and evaporated. The residue was crystallized from THF/hexane to give black crystals (378 mg) which were dissolved in freshly distilled THF (100 ml) containing N,N'-carbonyldi-imidazole (410 mg) and then heated under reflux for 30 min. The soln was evaporated to about 50 ml and then applied to an alumina column (Brockmann Grade V; elution with CH_2Cl_2). The appropriate eluates were evaporated and the residue was crystallized from CH_2Cl_2/hexane to give **8** as blue-black needles (368 mg; 82%), m.p. 208–209°. (Found: C, 71.91; H, 6.35; N, 14.09. $C_{36}H_{38}N_6O_3$ requires: C, 71.74; H, 6.36; N, 13.95%). NMR, δ ppm, 9.63, 9.59, 9.57, 9.53 (each 1 H, s, 4 meso H); 8.20, 7.73, 7.22 (each 1 H, s, m, m, 3 imidazole H); 8.16–7.92, 6.32–5.97 (1 H, m, 2 H, m, $CH{=}CH_2$); 4.55–4.18 (2 H, m, 7- and 8-H); 3.70–3.60, 1.65 (2 H, m, 3 H, t, CH_2CH_3); 3.54, 3.49, 3.36, 3.19 (each 3 H, s, 4 × Me); 2.70–2.45 (4 H, m, $CH_2CH_2CO_2Me$), 1.80 (3 H, d, 8-Me). MS, *m/e* (%), 602 (100), 587 (5), 566 (9), 535 (47), 503 (9), 515 (14), 449 (20). λ_{max} 399 (ε 102,500), 496 (8800), 525 (3200), 554 (1500), 607 (4100) and 662 nm (37,800).

6-(Methoxycarbonylacetyl)-rhodochlorin methyl ester (**11**)

A soln of i-PrMgBr was prepared by refluxing under dry N_2 a mixture of Mg turnings (300 mg) and i-PrBr (1 g) in freshly distilled THF (30 ml). When the metal had dissolved the soln was cooled to 0° and redistilled methyl hydrogen malonate (750 mg) in dry THF (6 ml) was added. The mixture was warmed to 65° and stirred for 10 min before introduction of a soln of **8** (100 mg) in dry CH_2Cl_2 (30 ml). Stirring was maintained for 2.5 hr while heating under reflux, and glacial AcOH (3 ml) was added. Heating and stirring were continued for a further 15 min after which the mixture was diluted with $CHCl_3$ (300 ml), washed with 0.1 M HCl (300 ml) and water (2 × 300 ml), and then dried over $NaSO_2$ and evaporated to dryness. The residue was chromatographed on alumina (Brockmann Grade V; elution with 5% acetone in CH_2Cl_2) and after evaporation of the appropriate eluates the product was recrystallized from CH_2Cl_2/hexane to give the required chlorin-β-keto-ester as dark blue needles (74 mg; 73%), m.p. 149–151°. (Found: C, 70.92; H, 6.59; N, 9.27. $C_{36}H_{40}N_4O_5$

requires: C, 71.03; H, 6.62; N, 9.21%). NMR, δ ppm, 13.16 (1 H, s, enol-OH); 9.70 (2 H, m) 9.62 (1 H, s) 9.52 (2 H, m), 9.28 (1 H, s), 8.80 (1 H, s), 8.66 (1 H, s) (8 × meso H, i.e. 4 for keto and 4 for enol forms); 8.06–7.86, 6.21–5.94 (2 H, m, 5 H, m, 2 × CH=CH_2 and CH=C(OH) in enol); 4.80–4.20 (4 H, m, 2 × 7 H and 2 × 8 H); 4.60, 3.96, 3.86, 3.66, 3.58, 3.44, 3.38, 3.27, 3.22, 3.20 (each 3 H, s, 10 × Me); 3.72–3.64, 1.78, 1.76 (4 H, m, 3 H, t, 3 H, t, 2 × CH_2CH_3); 2.94–2.26 (10 H, m, 2 × $CH_2CH_2CO_2$Me and $COCH_2CO_2$Me); 1.88, 1.82 (each 3 H, d, 2 × 8-Me). MS, *m/e* (%), 608 (42), 591 (11), 530 (66), 488 (100), 473 (22), 443 (25), 401 (78). λ_{max} 399 (ε 164,400), 496 (12,800), 527 (3700), 558 (1200), 611 (4900), and 666 nm (59,600).

Methyl pheophorbide-a (**4**)

The foregoing **11** (100 mg) in dry CH_2Cl_2 (100 ml) was treated with a soln of freshly prepared thallium(III) trifluoroacetate[15] (240 mg; 2.05 mol equiv) in dry THF (25 ml). Using a quartz-iodine lamp, the soln was photolyzed for 2 hr before SO_2 was bubbled through the soln for 1 min and conc HCl (0.5 ml) was added. The mixture was then washed with water (100 ml), sat $NaHCO_3$ aq (100 ml), water again (2 × 100 ml) and then dried over $NaSO_4$. The soln was evaporated to dryness and the residue was chromatographed on alumina (Brockmann Grade III, elution with 2% acetone in CH_2Cl_2). The appropriate eluates were collected, evaporated to dryness, and the residue was crystallized from CH_2Cl_2/MeOH to give methyl pheophorbide-a as black shiny plates (58 mg; 59%), m.p. 220–225° (lit.[16] 229°, lit.[8] 224–226°). Mixed mp with authentic methyl pheophorbide-a, 220–225°. (Found: C, 71.11; H, 6.38; N, 9.10. $C_{36}H_{38}N_4O_5$ requires: C, 71.26; H, 6.31; N, 9.24%). NMR, δ ppm, 9.49, 9.35, 8.57 (each 1 H, s, 3 meso H, each peak having a small resonance to higher field for the a' compound); 8.05–7.91, 6.34–6.16 (1 H, m, 2 H, m, CH=CH_2); 6.28, 4.51, 4.25 (1 H, s, 1 H, m, 1 H, m, 10-H, 8-H and 7-H); 3.91, 3.71, 3.61, 3.41, 3.22 (each 3 H, s, 5 × Me); 3.75–3.60, 1.69 (2 H, m, 3 H, t, CH_2CH_3); 2.40–2.20 (4 H, m, $CH_2CH_2CO_2$Me); 1.83 (3 H, d, 8-Me). MS, *m/e* (%), 606 (100), 574 (34), 548 (96), 487 (8), 459 (26). λ_{max} 411 (ε 116,500), 506 (9300), 535 (8400), 558 (3700), 606 (7500), 666 nm (39,600).

Pheophytin-a (**13**). Methyl pheophorbide-a (100 mg) in cold conc HCl (20 ml) was stirred for 30 min before addition of ether (100 ml) and dilution with water until no more color remained in the aqueous layer. The etheral soln was washed with water (5 × 100 ml), dried over Na_2SO_4, and then evaporated to give pheophorbide-a (80 mg) which was dissolved in freshly distilled pyridine (3 ml). Distilled phytol (125 mg) was added and the soln was cooled to 0° before bubbling in a gentle stream of dry phosgene gas for about 10 min with stirring, until the soln became a solid greenish-white mass. The mixture was left in a closed vessel for 3 hr with cooling in ice, and was then cooled to −10° in an ice/salt bath. To this now completely solid mass was added, with care, a 0.5% HCl aq soln, until the violent reaction subsided. The temp was kept at 0° throughout, and as excess HCl was added the phytyl ester precipitated as greasy lumps which were filtered, washed thoroughly with water, and dried in a desiccator. The crude pheophytin-a was dissolved in CH_2Cl_2 (40 ml), washed with a 1% HCl aq soln (3 × 40 ml), and then dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on alumina (Brockmann Grade V, elution with CH_2Cl_2), the appropriate eluates being collected, evaporated to dryness, and the residue being crystallized from CH_2Cl_2/hexane to give pheophytin-a (116 mg; 80%), m.p. 178–181° (lit.[17] 178–180°). A mixed mp with authentic pheophytin had mp 175–180°. (Found: C, 76.14; H, 8.64; N, 6.67. $C_{55}H_{74}N_4O_5$ requires: C, 75.86; H, 8.51; 6.44%). NMR, δ ppm, 9.45, 9.31, 8.56 (each 1 H, s, 3 meso-H); 8.10–7.80, 6.24–6.10 (1 H, m, 2 H, m, CH=CH_2); 6.30 (2 H, m, 19 CH of phytyl and 10-H); 5.25–5.10 (1 H, m, 8-H); 4.55–4.40 (2 H, m, 2-OCH_2 of phytyl); 4.30–4.18 (1 H, m, 7-H); 3.88, 3.67, 3.37, 3.16 (each 3 H, s, 4 × Me); 3.74–3.54, 1.66 (2 H, m, 3 H, t, CH_2CH_3); 2.60–2.10 (4 H, m, $CH_2CH_2CO_2$Phy); 1.80 (3 H, d, 8-Me); 1.57 (3 H, s, 18-Me of phytyl); 1.40–0.90 (18 H, m, phytyl CH_2's). MS, *m/e* (%), 870 (11), 856 (9), 855 (7), 854 (10), 575 (10), 278 (100). λ_{max} 410 (ε 121,000), 471 (5800), 504 (12,300), 533 (8800), 555 (3900), 603 (7300), and 659 nm (48,300).

Chlorophyll-a (**1**)

(a) 0.87 *M Ethyl magnesium iodide*. Washed dry Mg turnings (250 mg) in a 50 ml 2-necked flask containing dry ether (7 ml) and a crystal of I_2 was flushed with dry N_2 and a soln of freshly distilled EtI (1.6 g) in dry ether (7 ml) was added slowly until the reaction was initiated, and then steadily to keep the mixture at reflux temp. When all of the EtI was added the mixture was heated under reflux for 30 min.

(b) 0.2 *M Iodomagnesium(II) 2,6-t-butyl-4-methylphenoxide*.[7] 2,6-t-Butyl-4-methylphenol (2.34 g) in dry CH_2Cl_2 (40 ml) in a 3-necked flask protected from light (Al foil) was treated, through a rubber septum, with freshly prepared 0.87 M EtMgI (12 ml) carefully over a period of about 15 sec. The clear and colorless soln was stirred for 10 min and then used immediately.

(c) *Magnesium insertion*. A soln of pheophytin-a (73 mg) in dry CH_2Cl_2/ether (86:14, 5 ml) was added to 10 ml of the soln prepared in (b), and the mixture was stirred at room temp under an atmosphere of argon for 10 min. The mixture was poured into pH 4.5 phosphate buffer M/15 aqueous soln of NaH_2PO_4 (200 ml) and ether (200 ml); the ether layer was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in the minimum volume of CH_2Cl_2 and chromatographed on alumina (Brockmann Grade V, elution with CH_2Cl_2). The first greyish-blue band collected was unreacted pheophytin-a, but the second, slower-running, bright-green band was chlorophyll-a. Evaporation of the eluates gave a dark green shiny solid (35 mg; 54%) which proved very difficult to crystallize from CH_2Cl_2/hexane, only 2.5 mg of dark green microcrystals being isolated, m.p. 118–120° (lit.[18] 117–120°). A mixed m.p. with authentic chlorophyll-a had m.p. 117–120°. NMR, δ ppm, 9.56, 9.33, 8.35 (each 1 H, s, 3 meso-H); 8.10–7.80 (1 H, m, CH=CH_2); 6.32–5.89 (4 H, m, 19-CH of phytyl, 10-H, and CH=CH_2), 3.10–3.50 (1 H, m, 8-H); 4.65–4.60 (2 H, m, 20-CH_2 of phytyl); 4.40–4.30 (1 H, m, 7-H); 3.66, 3.47, 3.27, 3.15 (each 3 H, s, 4 × Me); 3.80–3.50, 1.59 (2 H, m, 3 H, t, CH_2CH_3); 2.41–2.15 (4 H, m, $CH_2CH_2CO_2$Phy); 1.70 (3 H, d, 8-Me); 1.56 (3 H, s, 18-Me of phytyl); 1.40–0.90 (18 H, m, CH_2's of phytyl). λ_{max} 406 (ε 120,500), 426 (86,200), 497 (4600), 526 (4400), 569 (6300), 608 (14,800) and 656 nm (88,000).

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