# Synthesis of Protoporphyrin XIII and Protoporphyrin III

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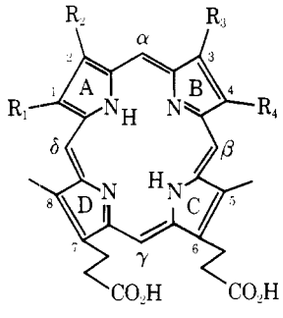
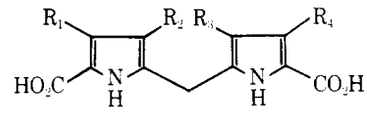
The synthesis of protoporphyrin XIII dimethyl ester [1,4-vinyl-2,3,5,8-tetramethyl-6,7-bis(β-methoxycarbonylethyl)porphine] and of protoporphyrin III dimethyl ester [1,4,5,8-tetramethyl-2,3-vinyl-6,7-bis(β-methoxycarbonylmethyl)porphine] was achieved. For the synthesis of protoporphyrin XIII the precursor ethyl 2,3-dimethyl-4-(β-ethoxycarbonylmethyl)-5-pyrrocarboxylate was obtained by the catalytic hydrogenation of the corresponding 3-formylpyrrole. The dimethylpyrrole was converted into its dimeric dipyrrylmethane through its acetate, and the former was reduced to the corresponding bis(β-hydroxethyl)dipyrrylmethane. Saponification with dilute potassium hydroxide afforded the 5,5′-dicarboxydipyrrylmethane, which was condensed with the 5,5′-diformyldipyrrylmethane **7** to give the 1,4-bis(β-hydroxyethyl)porphyrin. The latter was transformed into protoporphyrin XIII dimethyl ester through the β-chloroethyl intermediate. Protoporphyrin III was obtained either by a similar sequence, or from the benzyl 3,3′-bis(β-chloroethyl)-4,4′-dimethyl-5,5-dipyrrylmethanedicarboxylate.

Protoporphyrin IX (**1**) is the only natural divinylporphyrin involved in a major metabolism. Its iron chelate (heme)—the prosthetic group of hemoglobin—is an important metabolic factor for the in vivo induction of the synthesis of globin and other proteins,[1] and its regulatory properties in hemoglobin biosynthesis are firmly established.[2] It has no other natural analogues, since the specificity of the enzymes involved in the biosynthesis of protoporphyrin IX from coproporphyrinogen III preclude the formation of isomeric protoporphyrins from other coproporphyrinogen isomers.[3] We have found, however, that when coproporphyrinogen IV (**2**) was incubated with duck blood hemolysates, it was transformed in good yields into a protoporphyrin isomeric with protoporphyrin IX.[4] Similar results were obtained by Jackson and co-workers using chicken hemolysates,[5] and by Battersby and co-workers using been liver mitochondria.[6] Both reached the conclusion that the isomeric protoporphyrin was protoporphyrin XIII (**3**) (Fischer's notation[7]). The synthesis of **3** will be described in this paper. The synthetic product was also found by us to be identical with the product of the enzymatic reaction (see below). Since the enzyme spares the vicinal 6,7-β-carboxyethyl chains and only decarboxylates the propionic acid residues of rings A and B, the formal oxidative decarboxylation of coproporphyrinogen II (**4**) will afford protoporphyrin III )**5**).[8] Although protoporphyrin III was never isolated before as a natural product, its synthesis can make it available for further studies on hemoglobin biosynthesis. Protoporphyrin I—the formal decarboxylation product of coproporphyrinogen I—was recently prepared by synthesis.[9] Protoporphyrin IX (**1**) was also prepared by total synthesis.[10]

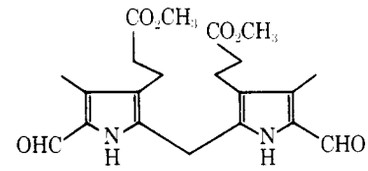


**1**, $R_1 = R_3 = CH_3$; $R_2 = R_4 = CH{=}CH_2$
**2**, $R_1 = R_4 = CH_2CH_2CO_2H$; $R_2 = R_3 = CH_3$ (hexahydro derivative)
**3**, $R_1 = R_4 = CH{=}CH_2$; $R_2 = R_3 = CH_3$ (dimethyl ester)
**4**, $R_1 = R_4 = CH_3$; $R_2 = R_3 = CH_2CH_2CO_2H$ (hexahydro derivative)
**5**, $R_1 = R_4 = CH_3$; $R_2 = R_3 = CH{=}CH_2$ (dimethyl ester)
**16**, $R_1 = R_4 = CH_2CH_2OH$; $R_2 = R_3 = CH_3$ (dimethyl ester)
**17**, $R_1 = R_4 = CH_2CH_2Cl$; $R_2 = R_3 = CH_3$ (dimethyl ester)
**18**, $R_1 = R_4 = CH_3$; $R_2 = R_3 = CHOHCH_3$
**23**, $R_1 = R_4 = CH_3$; $R_2 = R_3 = CH_2CH_2Cl$ (dimethyl ester)
**29**, $R_1 = R_4 = CH_3$; $R_2 = R_3 = CH_2CH_2OH$ (dimethyl ester)

The synthesis of **3** and **5** was carried out by condensation of a 5,5′-dicarboxydipyrrylmethane **6** containing the substituents of rings A and B with the known[10] diformyldipyrrylmethane **7.** The vinyl side chains in **3** and **5** were derived

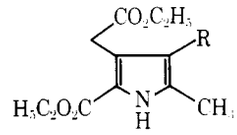


**6**

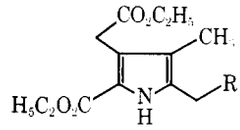


**7**

from a preformed β-chloroethyl residue.[10] The synthesis of protoporphyrin XIII (**3**) hence required a preparative synthesis of the 2,3-dimethylpyrrole **8.** We have recently prepared **8** by the reductive methylation of **9** with paraformaldehyde and hydriodic acid.[11] A new and very convenient method for the synthesis of **8** was found by the catalytic reduction of the readily available aldehyde **10** with hydrogen over 10% palladium on charcoal. The aldehyde **10** was in turn prepared by the Vilsmaier–Haak formylation of the easily available β-free pyrrole **9.** The 2,3-dimethylpyrrole **8** was transformed into its 2-acetoxymethyl derivative **11** by a prior treatment with sulfuryl chloride, followed by the reaction of the resulting 2-chloromethylpyrrole **12** with sodium acetate in acetic acid.

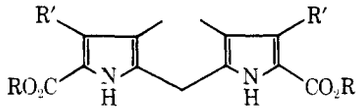


**8**, R = $CH_3$
**9**, R = H
**10**, R = CHO



**11**, R = $OCOCH_3$
**12**, R = Cl

The direct oxidation of **10** with lead tetraacetate gave poor yields of **11**. Dimerization of **11** afforded the dipyrrylmethane **13** in 80% yield. Treatment of **13** with diborane resulted in the

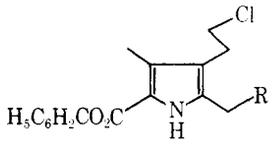


**13**, R = $C_2H_5$; R′ = $CH_2CO_2C_2H_5$
**14**, R = $C_2H_5$; R′ = $CH_2CH_2OH$
**15**, R = H; R′ = $CH_2CH_2OH$

reduction of the side-chain esters and the dipyrrylmethane **14** was thus obtained. Saponification of **14** produced the 5,5′-dicarboxydipyrrylmethane **15** which was condensed without further purification with the aldehyde **7** in the presence of *p*-toluensulfonic acid.[10,12]

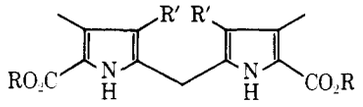
The porphyrin **16** was thus obtained in 26% yield; and by treatment with mesyl chloride in pyridine it was transformed into the β-chloroethylporphyrin **17**. Vinylation of **17** with potassium *tert*-butoxide afforded protoporphyrin XIII (**3**) which was isolated as its dimethyl ester. It was found to be identical in its spectral properties and melting point with the dimethyl ester of the protoporphyrin isolated by the enzymatic decarboxylation of coproporphyrinogen IV.[4,13]

Protoporphyrin III (**5**) dimethyl ester was prepared by Fischer[8] by dehydration of 1,4,5,8-tetramethyl-2,3-di(α-hydroxyethyl)-6,7-di(β-carboxyethyl)porphine (hematoporphyrin III) (**18**). The latter was in turn obtained by reduction of the corresponding 2,3-diacetylporphyrin prepared by acetylation of deuteroporphyrin III. When planning the total synthesis of **5**, we first made use of the known[14] 2-acetoxymethylpyrrole **19**. By dimerization of **19** in ethanol–hydrochloric acid the β-chloroethyldipyrrylmethane **20** was obtained in 33% yield. The yields were low owing to the ethanolysis of the acetoxymethyl residue of **19**, which resulted in the simultaneous formation of the ethyl ether **21**. The dimerization attempts of **21** were unsuccessful.



;

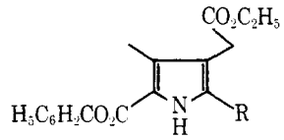
**19**, R = $OCOCH_3$
**21**, R = $OC_2H_5$



**20**, R = $CH_2C_6H_5$; R′ = $CH_2CH_2Cl$
**22**, R = H; R′ = $CH_2CH_2Cl$
**26**, R = $CH_2C_6H_5$; R′ = $CH_2CO_2C_2H_5$
**27**, R = $CH_2C_6H_5$; R′ = $CH_2CH_2OH$
**28**, R = H; R′ = $CH_2CH_2OH$

Hydrogenolysis of the benzyl ester group of **20** afforded the acid **22**, which was not purified but condensed directly with the usual technique with the diformyldipyrrylmethane **7** to give the bis(β-chloroethylporphyrin) **23** in 30% yield.

Due to the low yields obtained in the preparation of **20**, a second approach to **23** was developed analogous to the sequence used for the obtention of **17**. The readily available pyrrole **24** was transformed into its 2-acetoxymethylpyrrole **25** by treatment with lead tetraacetate. The dimerization of **25** afforded the dipyrrylmethane **26** in 59% yield. By reduction of **26** with diborane the bis(β-hydroxyethyl)dipyrrylmethane **27** was obtained in 90% yield. Hydrogenolysis of the benzyl esters of **27** and condensation of the crude diacid **28** with the diformyldipyrrylmethane **7** afforded the β-hydroxyethyl-



**24**, R = $CH_3$
**25**, R = $CH_2OCOCH_3$

porphyrin **29** in 32% yield. The latter was transformed into **23** by treatment with mesyl chloride. Vinylation of **23** with potassium *tert*-butoxide followed by esterification with methanol–sulfuric acid gave protoporphyrin III dimethyl ester (**5**) in 55% yield.

Although the dimethyl esters of both protoporphyrin XIII and protoporphyrin III markedly differ in their melting point and solubility properties, they could not be separated by TLC on silica gel, or by TLC on cellulose of the corresponding acids.

## Experimental Section[15]

**Ethyl 2-Methyl-4-(ethoxycarbonylmethyl)-3-formyl-5-pyrrolecarboxylate (10).** Phosphorus oxychloride (43.2 mL, 0.48 mol) was added dropwise to 52 mL of dimethylformamide at 5 °C, and the mixture was kept during 15 min at 20 °C. A solution of 12 g (0.05 mol) of pyrrole **9**[16] in 100 mL of dimethylformamide was then slowly added to the former solution while the mixture was kept at 5 °C with continuous stirring under moisture exclusion conditions. The resulting solution was heated at 75 °C for 1 h and cooled, and a concentrated sodium hydroxide solution was added to adjust the mixture to pH 8. After a further heating at 75 °C during 15 min, the mixture was poured over 3 L of ice water and filtered, and the aldehyde **10** was recrystallized from methanol–water: 10.8 g (80%); mp 155–157 °C (lit.[17] mp 151–152 °C); NMR ($CDCl_3$) 1.35 (m, 6, $CH_2CH_3$), 2.5 (s, 3, $CH_3$), 4.3 (m, 6, $CH_2CO$, $CH_2CH_3$), 10.0 ppm (s, 1 CHO).

Anal. Calcd for $C_{13}H_{17}O_5N$: C, 58.4; H, 6.4; N, 5.2. Found: C, 58.4; H, 6.3; N, 5.1.

**Ethyl 2,3-Dimethyl-4-(ethoxycarbonylmethyl)-5-pyrrolecarboxylate (8).** The aldehyde **10** (3 g) was dissolved in 150 mL of ethanol and was reduced with hydrogen at 50 psi during 15 h over 3 g of 10% palladium on charcoal. The catalyst was filtered, the solution was evaporated to dryness, and the residue was crystallized from methanol–water: 2.35 g (85%); mp 113–114 °C (lit.[11] mp 113–114 °C); NMR ($CDCl_3$) 1.25 (m, 6, $CH_3CH_2$), 1.94 (s, 3, $C_3CH_3$), 2.2 (s, 3, $C_2CH_3$), 3.8 (s, 2, $CH_2$), 4.2 (m, 4, $cH_2CH_3$), 9.1 ppm (b, 1, NH).

**Ethyl 2-Chloromethyl-3-methyl-4-ethoxycarbonylmethyl-5-pyrrolecarboxylate (12).** To a solution of 1.5 g (6 mmol) of **8** in 50 mL of dry carbon tetrachloride was added 0.48 mL (6 mmol) of distilled sulfuryl chloride. The mixture was stirred and heated at 50 °C for 4 h, after which it was evaporated to dryness. The residue was crystallized from methylene chloride–hexane: 1.7 g (100%); mp 93–95 °C; NMR ($CDCl_3$) 1.3 (m, 6, $CH_2CH_3$), 2.0 (s, 3, $CH_3$), 3.8 (s, 2, $CH_2CO$), 4.14, 4.34 (m, 4, $CH_2CH_3$), 4.6 ppm (s, 2, $CH_2Cl$).

Anal. Calcd for $C_{13}H_{18}O_4NCl$: C, 54.2; H, 6.3; N, 4.9. Found: C, 54.3; H, 6.2; N, 4.8.

**Diethyl 3,3′-Dimethyl-4,4′-(ethoxycarbonylmethyl)-5,5′-dipyrrylmethanedicarboxylate (13).** The 2-chloromethylpyrrole **12** (1.7 g) was dissolved in 60 mL of glacial acetic acid containing 1% of anhydrous sodium acetate. After keeping the mixture for 1 h at 20 °C, it was evaporated to dryness and the dry solid residue of **11** was dissolved in 120 mL of absolute ethanol containing 6 mL of concentrated hydrochloric acid. The solution was heated at 100 °C during 4 h, after which it was cooled and poured into 500 mL of ice water. The aqueous mixture was extracted with chloroform (3 × 100 mL), and the pooled extracts were washed with a 5% bicarbonate solution (50 mL), then with water (100 mL), dried ($Na_2SO_4$), and evaporated to dryness. The residue was crystallized from methanol–water: 1.16 g (80%); mp 105–107 °C; NMR ($CDCl_3$) 1.27 (m, 12, $CH_2CH_3$), 1.97 (s, 6, $CH_3$), 3.78 (s, 4, $CH_2CO$), 3.89 (s, 2, $-CH_2-$), 4.22 ppm (m, 8, $CH_2CH_3$).

Anal. Calcd for $C_{25}H_{34}O_8N_2$: C, 61.2; H, 3.9; N, 5.7. Found: C, 61.1; H, 6.8; N, 5.9.

**Benzyl 2-Acetoxymethyl-3-ethoxycarbonylmethyl-4-methyl-5-pyrrolecarboxylate (25).** Lead tetraacetate (1.95 g) was added in small portions during 30 min to a stirred solution of 1.5 g of **24**[18] in 15 mL of glacial acetic acid. The solution was kept at 20 °C with constant stirring during a further 2 h. It was then poured into 500 mL of ice water, and the precipitate was filtered and crystallized from

ethanol–water: 1.24 g (70%); mp 112–114 °C; NMR ($CDCl_3$) 1.2 (t, $J$ = 6 Hz, 3, $CH_2CH_3$), 2.0 (s, 3, $CH_3$), 2.3 (s, 3, $CH_2CO$), 3.5 (s, 2, $CH_2COO$), 4.1 (q, $J$ = 6 Hz, 2, $CH_2CH_3$), 5.1 (s, 2, $CH_2OCO$), 5.3 (s, 2, $CH_2C_6H_5$), 7.4 ppm (b, 5, $C_6H_5$).

Anal. Calcd for $C_{20}H_{23}O_6N$: C, 64.3; H, 6.2; N, 3.7. Found: C, 64.2; H, 6.1; N, 3.6.

**Dibenzyl 3,3′-(Ethoxycarbonylmethyl)-4,4′-dimethyl-5,5′-dipyrrylmethanedicarboxylate (26).** The acetate **25** (1.19 g) was dissolved in 22 mL of absolute ethanol containing 1.1 mL of concentrated hydrochloric acid, and the mixture was heated under reflux during 6 h. The solution was cooled, and the precipitate was filtered and crystallized from ethanol: 575 mg (60%); mp 158–160 °C; NMR ($CDCl_3$) 1.25 (t, $J$ = 6 Hz, 6 $CH_2CH_3$), 2.35 (s, 6, $CH_3$), 3.5 (s, 4, $CH_2CO$), 3.9 (s, 2, $-CH_2-$), 4.1 (q, $J$ = 6 Hz, 4, $CH_2CH_3$), 5.3 (s, 4, $CH_2C_6H_5$), 7.4 ppm (s, 10, $C_6H_5$).

Anal. Calcd for $C_{35}H_{38}O_8N_2$: C, 68.4; H, 6.2; N, 4.6. Found: C, 68.3; H, 6.2; N, 4.5.

**Dibenzyl 3,3′-(β-Chloroethyl)-4,4′-dimethyl-5,5′-dipyrrylmethanedicarboxylate (20).** The β-chloroethyl acetate **19** (760 mg) was dissolved in a mixture of 50 mL of absolute ethanol and 2.5 mL of concentrated hydrochloric acid, and the solution was heated under reflux during 6 h. Methylene chloride (100 mL) was added to the cooled solution, and the mixture was washed with a 5% sodium bicarbonate solution, then with water, dried ($Na_2SO_4$), and evaporated to dryness. The dipyrrylmethane **20** was isolated by crystallization of the residue from methanol: 200 mg (33%); mp 133–135 °C; NMR ($CDCl_3$) 2.3 (s, 6, $CH_3$), 2.9 (t, $J$ = 6 Hz, 4, $CH_2Cl$), 3.5 (t, $J$ = 6 Hz, 4, $CH_2CH_2Cl$), 3.9 (s, 2, $-CH_2-$), 5.2 (4, s, $CH_2C_6H_5$), 7.3 ppm (s, 10, $C_6H_5$).

Anal. Calcd for $C_{31}H_{32}O_4N_2Cl_2$: C, 65.7; H, 5.7; N, 4.9. Found: C, 65.7; H, 5.7; N, 5.0.

By addition of water to the methanolic crystallization liquors a second product precipitated, 72 mg (10%). It was identified as **21** by its NMR ($CDCl_3$): 1.27 (t, $J$ = 7 Hz, 3, $OCH_2CH_3$), 2.35 (s, 3, $CH_3$), 2.9 (t, $J$ = 6 Hz, 2, $CH_2Cl$), 3.4 (m, 4, $OCH_2CH_3$, $CH_2CH_2Cl$), 4.5 (s, 2, $-CH_2O$), 5.3 (s, 2, $CH_2C_6H_5$), 7.4 (b, 5, $C_6H_5$), 9.1 ppm (b, 1, NH).

**Diethyl 3,3′-Dimethyl-4,4′-bis(β-hydroxyethyl)-5,5′-dipyrrylmethanedicarboxylate (14).** A diborane-carrying nitrogen flux was obtained by addition of 40 mL of boron trifluoride etherate to 12 g of sodium borohydride suspended in 40 mL of diglyme while the mixture was kept under a gentle nitrogen stream. The diborane–nitrogen stream was bubbled through a solution of 1.2 g of dipyrrylmethane **13** in 50 mL of dry tetrahydrofuran. The reduction of the side chain esters was followed by TLC (8% methanol in benzene), until the tetraester ($R_f$ 0.8) as well as the intermediate triester ($R_f$ 0.5) disappeared. The desired diester **14** had $R_f$ 0.3. Methanol was then added to the tetrahydrofuran solution until the effervescence subsided, and the solution was evaporated to dryness. The residue was purified by filtration through a TLC silica gel column (3.5 × 30 cm) packed and eluted with 10% methanol in benzene. The eluates were evaporated to dryness and the residue was crystallized from methanol–water: 450 mg (45%); mp 169–170 °C; NMR ($CDCl_3$) 1.3 (t, $J$ = 7 Hz, 6, $CH_2CH_3$), 1.98, 2.0 (s, s, 8, OH, $CH_3$), 3.0 (t, $J$ = 6 Hz, 4, $CH_2OH$), 3.8 (m, 6, $-CH_2-$, $-CH_2CH_2OH$), 4.25 ppm (q, $J$ = 7 Hz, 4, $CH_2CH_3$).

Anal. Calcd for $C_{21}H_{30}O_6N_2$: C, 62.1; H, 7.4; N, 6.9. Found: C, 62.2; H, 7.5; N, 6.9.

**Dibenzyl 3,3′-(β-Hydroxyethyl)-4,4′-dimethyl-5,5′-dipyrrylmethanedicarboxylate (27).** The reduction of dipyrrylmethane **26** with diborane was carried out following the procedure described for **14**, except for the chromatographic purification, which was unnecessary. From 1 g of **26** was obtained 776 mg (90%) of the dialcohol **27**: mp 134–136 °C; NMR ($CDCl_3$) 1.8 (b, 2, OH), 2.2 (s, 6, $CH_3$), 2.6 (m, 4, $CH_2OH$), 3.65, 3.7 (m, 6, $-CH_2-$, $CH_2CH_2OH$), 5.2 (s, 4, $CH_2C_6H_5$), 7.4 ppm (b, 10, $C_6H_5$).

Anal. Calcd for $C_{31}H_{34}O_6N_2$: C, 70.2; H, 6.1; N, 5.3. Found: C, 70.1; H, 6.1; N, 5.2.

**1,4-Bis(β-hydroxyethyl)-2,3,5,8-tetramethyl-6,7-bis(β-methoxycarbonylethyl)porphine (16).** A solution of 410 mg of dipyrrylmethane **14** in 20 mL of ethanol and 20 mL of 4 N potassium hydroxide was kept at 20 °C during 48 h. The ethanol was then evaporated at 30 °C in vacuo, and the solution was adjusted to pH 4 with glacial acetic acid. The precipitated acid **15** was filtered and washed with cold water (180 mg, 0.51 mmol, 52%). The acid was dissolved in a mixture of 150 mL of dry methylene chloride, and 24 mL of methanol containing 222 mg (0.51 mmol) of the diformyldipyrrylmethane **7** added. The resulting solution was divided up into three equal portions, and 150 mg of $p$-toluenesulfonic acid was added to each portion. The mixtures were kept in the dark at 20 °C for 24 h, when 6.2 mL of methanol saturated with zinc acetate dihydrate was added to each portion. After a further period of 72 h at 20 °C in the dark the three batches were pooled and evaporated to dryness at 40 °C, and the residue was dissolved in 90 mL of a 5% sulfuric acid in methanol solution. The mixture was kept during 16 h at 20 °C in the dark; it was then diluted with 200 mL of chloroform, and washed with water (80 mL), then with a 5% sodium carbonate solution (80 mL), again with water (80 mL), dried ($Na_2SO_4$), and evaporated to dryness at 40 °C. The residue was dissolved in 4% methanol in benzene and filtered through a column (3.5 × 30 cm) of TLC silica gel, packed and prewashed with the same solvent. The eluates containing the main porphyrin band (monitored by its fluorescence) were collected and evaporated to dryness, and the residue of porphyrin **16** was crystallized from chloroform–hexane: 85 mg (26%); mp 219–221 °C; NMR ($CDCl_3$–$CD_3OD$, 1:1) 3.36 (m, 4, $CH_2CO_2CH_3$), 3.58, 3.53 (s, s, 12, $CH_3$), 3.66, 3.72 (s, b, 8, $OCH_3$, OH), 4.26 (m, 12, $CH_2CH_2OH$, $CH_2CH_2CO$), 10.06 ppm (s, 4, =CH); MS $m/e$ 626 ($M^+$, 20%), 596 (M $-CH_2OH$, 15%), 566 (596 $-CH_2OH$, 10%).

Anal. Calcd for $C_{36}H_{42}O_6N_4$: C, 69.0; H, 6.7; N, 8.9. Found: C, 68.9; H, 6.7; N, 8.8.

**1,4,5,8-Tetramethyl-2,3-bis(β-hydroxyethyl)-6,7-bis(β-methoxycarbonylethyl)porphine (29).** A solution of 700 mg of the dibenzyldipyrrylmethane **27** in 70 mL of dry tetrahydrofuran containing 20 drops of triethylamine was reduced with hydrogen at 50 psi during 15 h over 600 mg of 10% palladium on charcoal. The catalyst was filtered and washed with aqueous ammonia. The filtrate was evaporated to dryness in vacuo, and the residue was dissolved in the ammonia washings (100 mL). The solution was adjusted to pH 4 with 2 N acetic acid and cooled and the precipitated acid **28** was filtered and dried (420 mg, 90%). It was dissolved in 350 mL of methylene chloride and 280 mL of methanol and 520 mg of the dialdehyde **7** were added to the solution. The mixture was divided up in seven portions and 150 mg of $p$-toluenesulfonic acid was added to each one. The procedure described for the synthesis of **16** was then followed. The TLC silica gel column chromatography was performed by using 10% methanol in chloroform as solvent. Evaporation of the eluates afforded 240 mg (32%) of the β-hydroxyethylporphyrin **29**: mp >360 °C dec; NMR (TFA) 3.1 (m, 4, $CH_2CO$), 3.45, 3.5 (s, 5, 18, $CH_3$, $OCH_3$), 4.3 (m, 12, $CH_2CH_2OH$, $CH_2CH_2CO$), 10.2 ppm (b, 4, =CH); MS $m/e$ 626 ($M^+$, 100%), 595 (M $-CH_2OH$, 80%), 565 (595 $-CH_2OH$, 30%), 553 (M $-CH_2CO_2CH_3$, 30%), 491 (565 $-CH_2CO_2CH_3$, 20%).

Anal. Calcd for $C_{36}H_{42}O_6N_4$: C, 69.0; H, 6.7; N, 8.9. Found: C, 69.1; H, 6.6; N, 8.8.

**1,4,5,8-Tetramethyl-2,3-bis(β-chloroethyl)-6,7-bis(β-methoxycarbonylethyl)porphine (23). Procedure A.** Dibenzyl ester **20** (140 mg) dissolved in 100 mL of glacial acetic acid was reduced with hydrogen at 50 psi during 2 h over 140 mg of 10% palladium on charcoal. The catalyst was filtered, the acetic acid was evaporated to dryness in vacuo, and the dry residue (96 mg) was condensed with 90 mg of the dipyrrylmethane aldehyde **7** in one batch following the procedure described for **16**. Final purification of the dimethyl ester **23** was achieved by purification through a TLC silica gel column (2.5 × 30 cm) using 0.5% methanol in chloroform as described above. The porphyrin was crystallized from methylene chloride–hexane: 50 mg (30%); mp 269–271 °C; NMR ($CDCl_3$) 3.25 (m, 4, $CH_2CO_2CH_3$), 3.64 (b, 18, $OCH_3$, $CH_3$), 4.40 (m, $CH_2CH_2Cl$, $CH_2CH_2CO$), 9.9 (b, 1, =CH$\alpha$), 10.05 ppm (b, 3, =CH); MS $m/e$ 663 ($M^+$, 100%), 628 (M $-$ Cl, 40%), 614 (M $-CH_2Cl$, 40%), 590 (M $-CH_2CO_2CH_3$, 30%).

Anal. Calcd for $C_{36}H_{40}O_4N_4Cl_2$: C, 65.2; H, 6.0; N, 8.4. Found: C, 65.1; H, 6.2; N, 8.3.

**Procedure B.** To a solution of β-hydroxyethylporphyrin **29** (240 mg) in 36 mL of pyridine was added 12 mL of mesyl chloride, and the mixture was heated at 75 °C for 35 min under nitrogen. The cooled solution was then diluted with 120 mL of water and extracted with methylene chloride (4 × 50 mL). The extracts were dried ($Na_2SO_4$) and evaporated to dryness in vacuo at 40 °C. The residue was dissolved in a 0.5% methanol in chloroform solution and was filtered through a TLC silica gel column as described above. The bisdichloroethylporphyrin **23** (128 mg, 50%) had mp 269–271 °C and was identical with the porphyrin obtained by procedure A.

**1,4-Bis(β-chloroethyl)-2,3,5,8-tetramethyl-6,7-bis(β-methoxycarbonylethyl)porphine (17).** The bis(β-hydroxyethyl)porphyrin **16** (80 mg) dissolved in 10 mL of pyridine was treated with 3.5 mL of mesyl chloride as described for the preparation of **23**. The bis(β-chloroethyl)porphyrin **17** was isolated after a purification by column chromatography following the procedure described for **17**: 45 mg (50%); mp 201–203 °C (chloroform–hexane); NMR ($CDCl_3$) 3.24 (m, 4, $CH_2CO_2CH_3$), 3.5, 3.6 (s, s, 12, $CH_3$), 3.7 (s, 6, $OCH_3$), 4.3 (m, 12, $CH_2CH_2Cl$, $CH_2CH_2CO$), 9.92, 9.97 (s, s, 3, =CH $\alpha$, $\beta$, $\delta$), 10.12 ppm (b, 1, =CH$\alpha$); MS $m/e$ 663 ($M^+$, 100%), 628 (M $-$ Cl, 80%), 614 (M $-CH_2Cl$, 20%), 590 (M $-CH_2CO_2CH_3$, 20%).

Anal. Calcd for $C_{36}H_{40}O_4N_4Cl_2$: C, 65.2; H, 6.0; N, 8.5. Found: C, 65.0; H, 6.1; N, 8.3.

**1,4,5,8-Tetramethyl-2,3-vinyl-6,7-bis(β-methoxycarbonylethyl)porphine (Protoporphyrin III Dimethyl Ester) (5).** Methanol saturated with zinc acetate (11 mL) was added to a solution of the β-chloroethylporphyrin **23** (64 mg) in 30 mL of dry methylene chloride. The mixture was warmed to 35 °C for a while, and then poured over 100 mL of water. The organic layer was separated, washed with aqueous sodium acetate, then with water, dried ($Na_2SO_4$), and evaporated to dryness. The residue was dissolved in 10 mL of dry tetrahydrofuran, and 30 mL of a 1 M solution of potassium *tert*-butoxide in *tert*-butyl alcohol was added. The mixture was kept in a sealed vessel under vacuum (50 μ) during 96 h at 20 °C. The vessel was then opened, the mixture was poured into water (200 mL), and the solution was adjusted to pH 6 with glacial acetic acid, then extracted with 1% pyridine in methylene chloride (3 × 60 mL). The organic extracts were dried ($Na_2SO_4$) and evaporated to dryness, and the residue was dissolved in 70 mL of 5% sulfuric acid in methanol. After keeping overnight at 20 °C in the dark, chloroform (300 mL) was added and the mixture was washed with aqueous sodium acetate, then with a sodium bicarbonate solution, and finally with water. The organic layer was dried ($Na_2SO_4$), evaporated to dryness, and purified by chromatography through a TLC silica gel column using 0.5% methanol in chloroform as eluent. The eluates were evaporated to dryness and the residue was crystallized from methylene chloride–hexane: 35 mg (60%); mp 262–264 °C (lit.[8] mp 276 °C); visible max spectrum ($CDCl_3$) 404 nm (ε 114 000), 502 (9500), 538 (6400), 574 (4000), 626 (2400); NMR (0.05 M, $CDCl_3$) 3.25 (m, 4, $CH_2CO$), 3.56 (b, 12, $CH_3$), 3.70 (s, 6, $OCH_3$), 4.35 (m, 4, $CH_2CH_2CO$), 6.3 (m, 4, $=CH_2$), 8.15 (m, 2, =CH), 9.93, 10.00 ppm (b, b, 4, meso =CH); MS *m/e* 590 ($M^+$, 100%), 517 ($M - CH_2CO_2CH_3$, 70%).

Anal. Calcd for $C_{36}H_{38}O_4N_4$; C, 73.2; H, 6.5; N, 9.5. Found: C, 73.1; H, 6.6; N, 9.4.

**1,4-Vinyl-2,3,5,8-tetramethyl-6,7-bis(β-methoxycarbonylethyl)porphine (Porphyrin XIII Dimethyl Ester) (3).** The bis(β-chloroethyl)porphyrin **17** (62 mg) was vinylated with potassium *tert*-butoxide as described in the preparation of **5**. After the purification by chromatography the protoporphyrin dimethyl ester **3** was crystallized from methylene chloride–hexane: 30 mg (55%); mp 208–210 °C (lit.[5] mp 198–200 °C); visible max ($CDCl_3$) 408 nm (ε 117 000), 506 (10 000), 540 (8000), 576 (4400), 630 (3500) (see ref 13 for visible max of the same product obtained by incubation of coproporphyrinogen IV with duck blood erythrocytes); NMR (0.05 M, $CDCl_3$) 3.35, 3.43 (s, s, 12, $CH_3$), 3.62 (s, 6, $OCH_3$), 3.12, 4.22 (t, t, 8, $CH_2CH_2CO$), 6.18, 8.20 (m, m, 6, $CH=CH_2$), 9.58, 9.76, 9.86 (s, s, s, 1, 1, 2, meso =CH). MS *m/e* 590 ($M^+$, 70%), 517 ($M - CH_2CO_2CH_3$, 50%), 416 ($M - 2CH_2CH_2CO_2CH_3$, 80%).

Anal. Calcd for $C_{36}H_{38}O_4N_4$: C, 73.2; H, 6.5; N, 9.5. Found: C, 73.1; H, 6.6; N, 9.3.

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**Registry No.**—**3,** 59969-40-3; **5,** 7034-33-5; **7,** 4792-10-3; **8,** 54278-18-1; **9,** 53700-88-2; **10,** 6122-77-6; **11,** 63089-12-3; **12,** 63089-13-4; **13,** 63089-14-5; **14,** 63089-15-6; **15,** 63122-48-5; **16,** 63089-16-7; **17,** 63089-17-8; **19,** 37945-74-7; **20,** 63089-18-9; **21,** 63089-19-0; **23,** 63089-20-3; **24,** 52091-12-0; **25,** 52091-13-1; **26,** 53727-79-0; **27,** 63089-21-4; **28,** 63089-22-5; **29,** 63089-23-6.

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# Aldol Condensations of Regiospecific Penicillanate and Cephalosporanate Enolates. Hydroxyethylation at C-6 and C-7

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Enolates derived from 6α-bromo- or 6α-iodopenicillanates, 6,6-dibromopenicillanate, and 7α-iodocephalosporanate have been generated in situ by a metal–halogen exchange process at −78 °C using either *n*-butyllithium or methylmagnesium bromide and reacted with acetaldehyde to yield aldols. The condensations consistently provided diastereomeric mixtures of hydroxyethylated products at the α face of the β-lactam nucleus and a *single* diastereomer at the β face. The absolute configuration of one such diastereomer, benzyl 6α-bromo-6β-(1′-hydroxyethyl)penicillanate (**8a**), was determined by x-ray analysis of its *tert*-butyldimethylsilyl derivative **9**. Subsequent reduction of these bromohydrins with zinc–silver couple in methanol or methanolic acetic acid and GLC analysis of the resulting purified products as their trimethylsilyl ether derivatives lead to the absolute structures of benzyl 6-(1′-hydroxyethyl)penicillanates **4a–d**.

Thienamycin (**1**), a highly active β-lactam antibiotic recently discovered in these laboratories,[1] has several features which distinguish it from the more familiar penicillins **2** and cephalosporins **3**. In particular, the hydroxyethyl[2] side chain α to the lactam carbonyl at C-6 is unusual, as generally this substituent is an amide moiety in naturally occurring penicillins and cephalosporins.

We were therefore interested in preparing the hybrid