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TOTAL SYNTHESES OF NEW PORPHYRINS ISOLATED FROM THE CORAL SEA DEMOSPONGE *CORALLISTES* SP.

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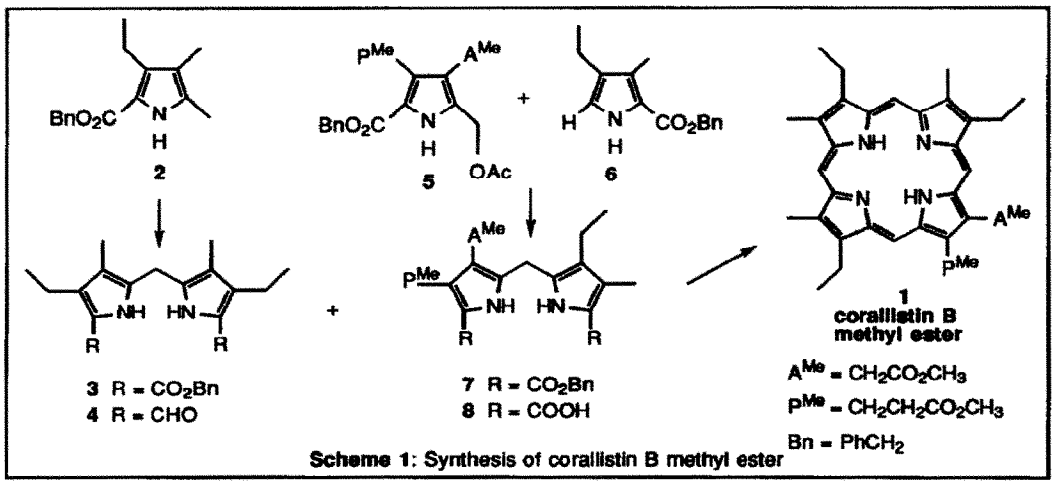
Abstract: Three new metal-free porphyrins, corallistin B, corallistin C and corallistin E isolated from the demosponge *Corallistes* sp. were synthesized as methyl esters in excellent yield by using either the MacDonald or *a,c*-biladiene routes to porphyrins.

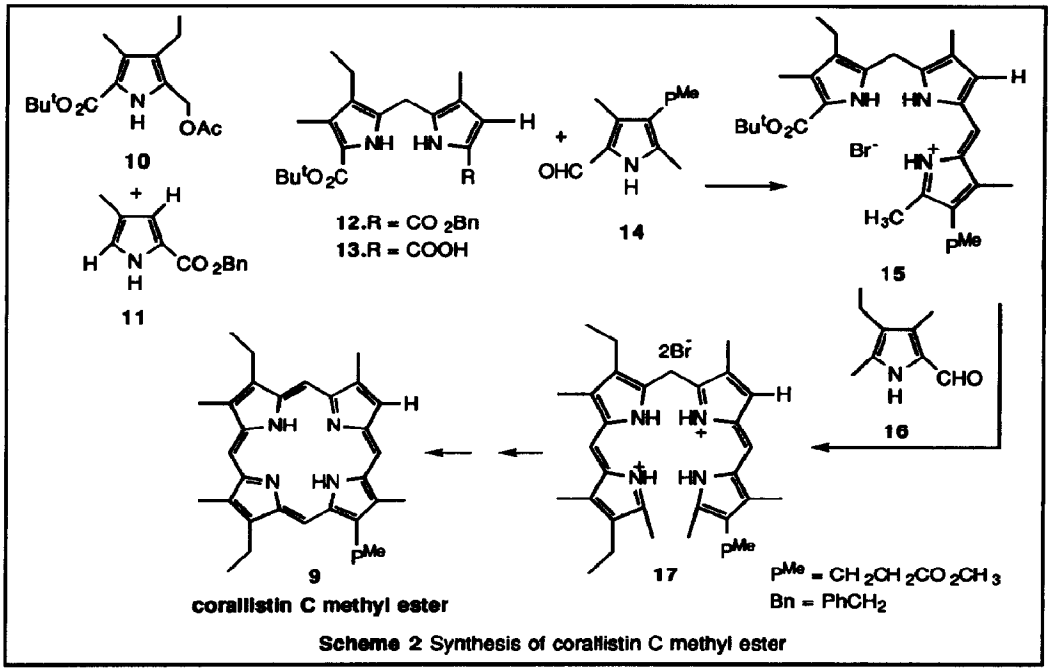
Six free base porphyrins named as corallistin A, B, C, D, E and deuteroporphyrin-IX were recently isolated, as methyl esters after diazomethane treatment of an ethanolic extract of the sponge *Corallistes* sp.[1,2] Surprisingly, these six free base porphyrins accounted for an amazing 60% of material in the total ethanol extract.[2] Among these novel porphyrins, 3-ethyldeuteroporphyrin-IX (IUPAC nomenclature) (called corallistin D) is already known in the literature.[3,4] Additionally, the synthesis of corallistin A has recently been reported by Yon-Hi and Scott.[5] Here we describe the total syntheses of the methyl esters of the remaining new porphyrins in the series, known as corallistin B, C and E. The synthetic strategies chosen for the preparation of these three porphyrins are based on the ease of synthesis of the required monopyrroles.



Scheme 1: Synthesis of corallistin B methyl ester

For the preparation of corallistin B dimethyl ester **1**, pyrrole **2**[6] was converted into

dipyrromethane **3** by following a literature method.[7] Hydrogenation of **3**, and subsequent reaction with trifluoroacetic acid/triethyl orthoformate[8] gave the 1,9-diformyldipyrromethane **4** in 70% yield. Dipyrromethane dicarboxylic acid **8**, the other half of the desired porphyrin, was obtained by hydrogenolysis of the respective dibenzyl ester analogue **7**, which in turn was obtained by reacting the acetoxymethylpyrrole **5**[9] with 2-unsubstituted pyrrole **6**.[10] Condensation of **4** with **8** under standard MacDonald reaction conditions[11] afforded corallistin B dimethyl ester **1** in 35% yield (Scheme 1).

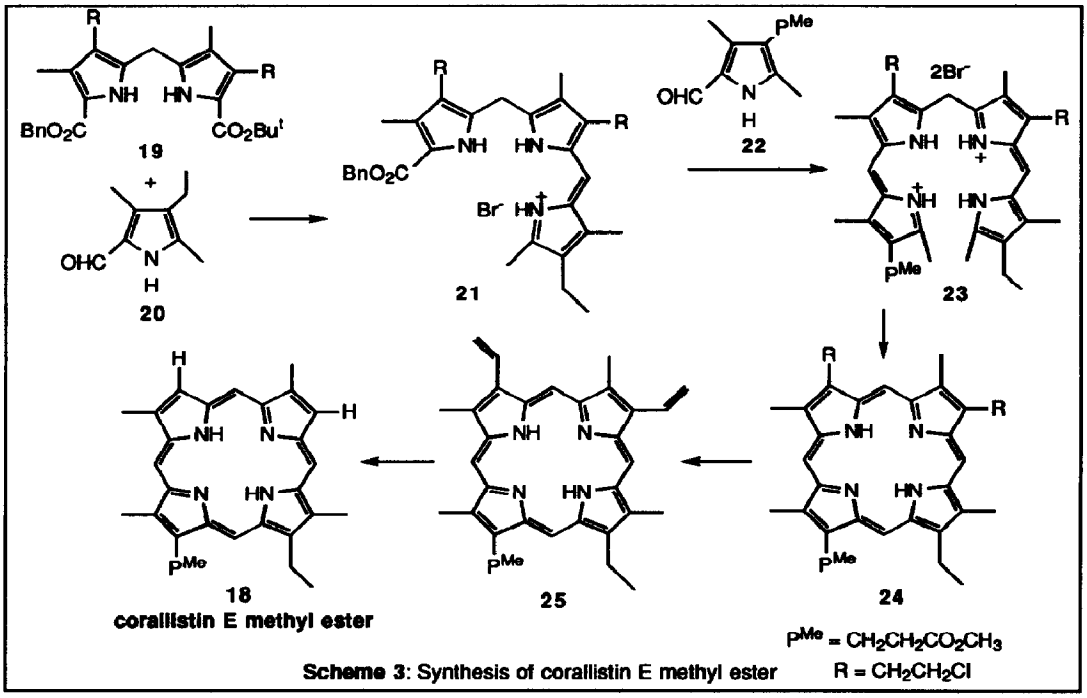


Scheme 2 Synthesis of corallistin C methyl ester

The *a,c*-biladiene approach[12] was used for the preparation of corallistin C methyl ester **9**, as shown in Scheme 2. Briefly, condensation of acetoxymethylpyrrole **10**[13] with 2-unsubstituted pyrrole **11**[13] (using Montmorillonite K-10 clay as a catalyst[14]) produced dipyrromethane **12** in >95% yield. This was then hydrogenated to afford **13** before being reacted with formylpyrrole **14**[15] in presence of p-toluene sulfonic acid; the tripyrrene **15** was isolated in 72% yield as the hydrobromide salt. Further reaction of tripyrrene **15** with another formylpyrrole **16**[16] gave *a,c*-biladiene dihydrobromide **17** as red powder in 70% yield. Oxidative macrocyclization[12,17] with $Cu(OAc)_2$/DMF (at 140°C) gave the desired porphyrin, corallistin C methyl ester **9**, in 32% yield from **17**.

A similar approach was used for the synthesis of corallistin E methyl ester **18**. As shown in Scheme 3, the 3,8-bis(2-chloroethyl)dipyrromethane **19** was obtained by following a literature procedure.[18] The *tert*-butyl ester was cleaved with TFA before reacting with formylpyrrole **20**; the tripyrrene hydrobromide **21** was isolated in 74% yield as a brick red powder. The benzyl ester in tripyrrene **21** was then cleaved[12] upon stirring at room temperature for 6 hours with

TFA/30%HBr/AcOH. The product was reacted with formylpyrrole **22**, and the *a,c*-biladiene dihydrobromide salt **23** was isolated in 71% yield. This was then cyclized[12,17] using $Cu(OAc)_2$/DMF at 140°C for 4 min. After the standard work up, the 3,8-bis(2-chloroethyl)porphyrin **24** was obtained in 35% yield. Dehydrohalogenation of **24** with 3% aqueous KOH/pyridine,[19] and subsequent esterification with $5\%H_2SO_4$/MeOH gave the corresponding 3,8-divinylporphyrin methyl ester **25** in 78% yield. For the final step of the synthesis, porphyrin **25** was converted into its Fe(III) complex,[20] and was then heated in a resorcinol melt at 180°C to accomplish bis-protiodevinylation.[21] Demetallation with HCl/methanol/$FeSO_4$ (the Grinstein method)[22] afforded corallistin E methyl ester **18**, in 60% yield. The structures of new natural porphyrins were confirmed by proton NMR and HRMS/elemental analysis.[23]



Scheme 3: Synthesis of corallistin E methyl ester

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23. Satisfactory analytical data were obtained for all new compounds. Melting points (Bristoline microscopic hot-stage; uncorrected) and ^{1}H NMR data (300 MHz, $CDCl_3$, δ ppm) for corallistin B dimethyl ester **1**, corallistin C methyl ester **9**, and corallistin E methyl ester **19** are as follows:
Corallistin B dimethyl ester **1**: M.p. 216-218°C. ^{1}H NMR: 10.18, 10.11 (each s, 1H, 2 meso H), 10.07 (s, 2H, 2 meso H), 4.45 (t, 2H, $CH_2CH_2CO_2CH_3$), 4.03-4.12 (m, 6H, 3 ring CH_2CH_3), 3.73, 3.70, 3.61, 3.60 and 3.58 (each s, 3H, 2-CO_2CH_3 and 3 ring CH_3), 3.35 (t, 2H, $CH_2CH_2CO_2CH_3$), 1.89 (t, merged, 9H, 3 ring CH_2CH_3), -3.76 (s, 2H, 2NH).
Corallistin C methyl ester **9**: M.p. 192-194°C. ^{1}H NMR: 10.02, 10.07, 10.10 and 10.12 (each s, 1H, 4 meso H), 9.04 (s, 1H ring H), 4.34 (t, 2H, $CH_2CH_2CO_2CH_3$), 4.06 (m, 4 H, 2 ring CH_2CH_3), 3.75, 3.72, 3.70 and 3.68, 3.67 (each s, 3H, CO_2CH_3 and 4 ring CH_3), 3.27 (t, 2H, $CH_2CH_2CO_2CH_3$), 1.87 (t, merged, 6H, 2 ring CH_2CH_3), -3.78 (s, 2H, 2NH).
Corallistin E methyl ester **18**: M.p. 204-206°C. ^{1}H NMR: 10.15, 10.09, 10. 08, 10.03 (each s, 1H, meso H), 9.13 and 9.07 (each s, 1H, 2 ring H), 4.39 (t, 2H, $CH_2CH_2CO_2CH_3$), 4.11 (q, 2H, CH_2CH_3), 3.77, 3.73, 3.67, 3.65, 3.63 (each s, 3H, CO_2CH_3 and 4 ring CH_3), 3.27 (t, 2H, $CH_2CH_2CO_2CH_3$), 2.01 (t, 3H, CH_2CH_3), -3.82 (s, 2H, 2NH).

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