Tetrahedron Letters, Vol.32, No.34, pp 4231-4234, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

TOTAL SYNTHESIS OF CORALLISTIN A

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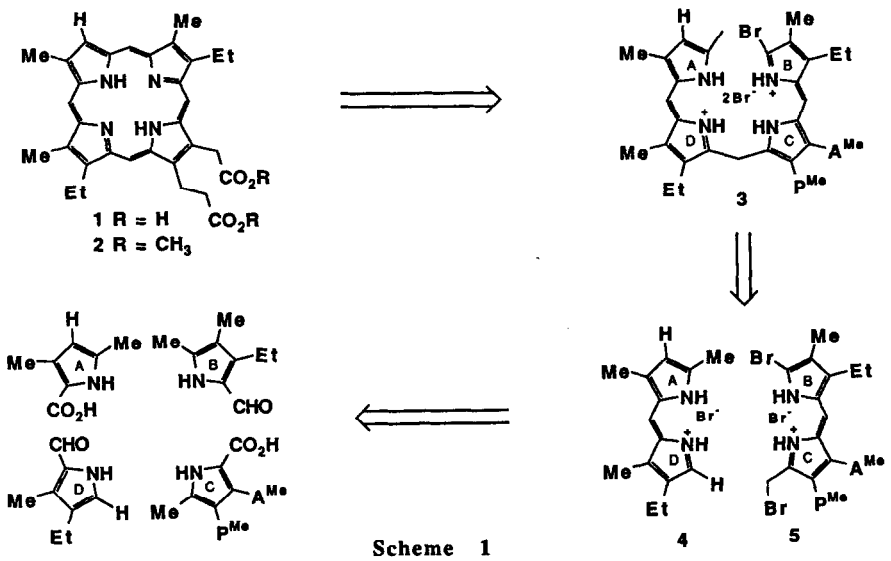
ABSTRACT: Corallistin A, a free porphyrin isolated from a demosponge of the Coral Sea has been synthesized as its dimethyl ester by application of Johnson's a,c-biladiene route, thus providing a definite proof of the structure that has been proposed for the natural pigment.

The presence of free porphyrins in invertebrates is well established. A survey of the phyla of these invertebrates reveals the occurrence of porphyrins such as uroporphyrin I, coproporphyrin I, coproporphyrin III and protoporphyrin IX.[1] Another class of porphyrin-like pigment isolated from living organisms is the chlorin macrocycle, exemplified by bonellin from the worm *Bonellia viridis*,[2] 13[2], 17[3]-cyclopheophorbide enol from the marine demosponge *Darwinella oxeata* [3] and tunichlorin from the ascidian *Trididemnum solidum*.[4] Recently, Pietra and co-workers have reported the isolation (as the dimethyl ester) of a novel tetrapyrrolic pigment, Corallistin A, displaying strong visible absorption at 400 nm with less intense bands from 498 to 618 nm from the sponge *Corallistes* sp. found in the Coral Sea.[5] On the basis of its absorption spectrum, nmr spectra (^1H and ^{13}C) and low resolution mass spectrum, the Italian group proposed structure **2** for the pigment, which is a novel porphyrin containing 1H, 3Me, 2Et, $1CH_2CO_2CH_3$ and $1CH_2CH_2CO_2CH_3$ groups as the peripheral substituents. We have now confirmed the proposed structure of Corallistin A by total synthesis of **2**.



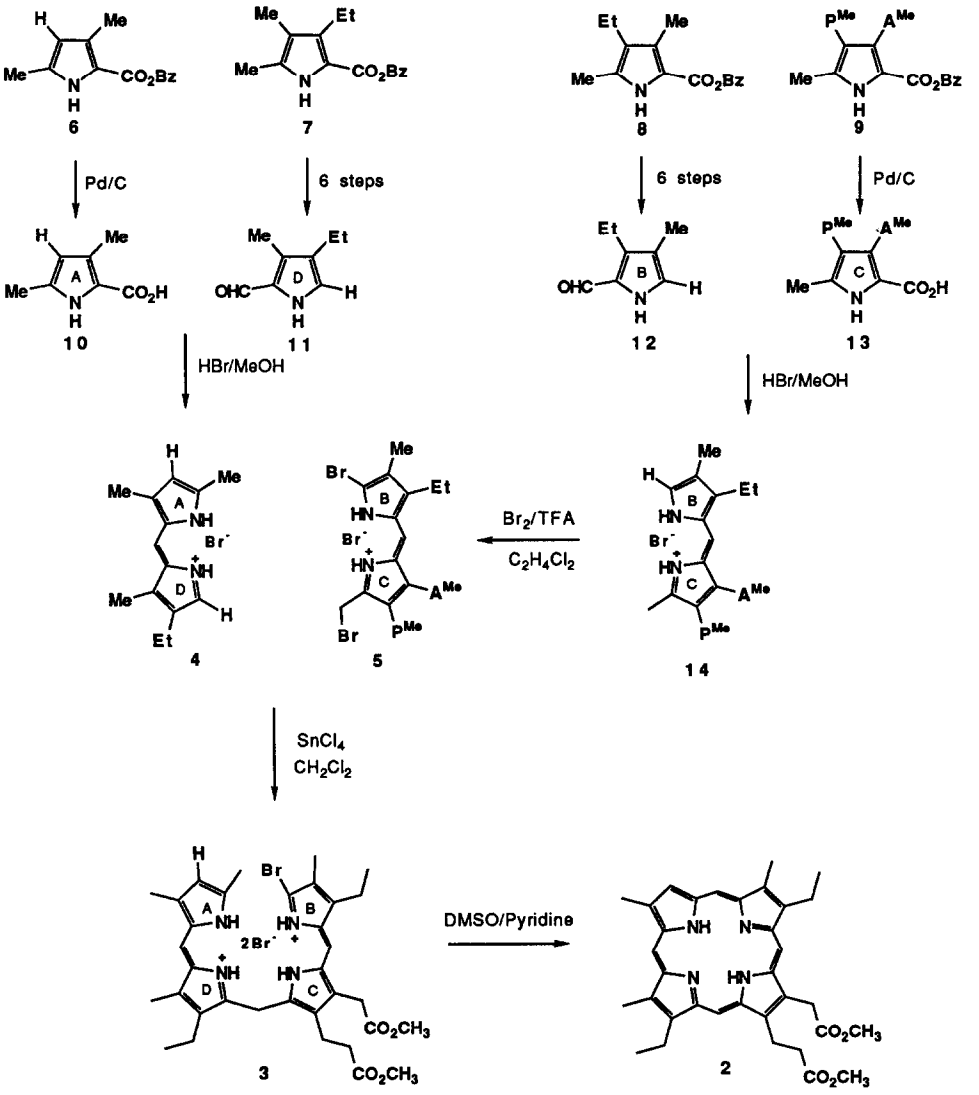
Scheme 1

In our synthetic planning, we opted for a method that would allow us to carry the unsubstituted peripheral (or β) position in ring A without protection. Of the few methods which have been used for the synthesis of totally unsymmetrical porphyrins,[6-9] Johnson's regioselective synthetic route was chosen for the present work. A retrosynthetic analysis of the target molecule suggested that the linear tetrapyrrole, 1-bromo-19-methylbiladiene-ac **3** would be a good substrate for the cyclization step leading to the porphyrin. Further disconnection as shown in Scheme 1, indicated the necessity for preparing two dipyrromethenes A-D (west side) and B-C (east side), viz the 5'-unsubstituted-5-methyldipyrromethene **4** and the 5-bromo-5'-bromomethyldipyrromethene **5** respectively. In turn, the two halves could be prepared from the four pyrrole building units **10**, **11**, **12** and **13** which can be obtained by well established procedures from pyrrolic precursors.

Pyrrole **10**, destined to carry the β-unsubstituted position of ring A was prepared from pyrrole **6** (Scheme 2).[10] Hydrogenolysis of the benzyl ester of **6** over palladium-charcoal gave the corresponding carboxypyrrole **10** in 98 % yield. Ring A was linked with ring D (2-formyl-4-ethyl-3-methylpyrrole **11**) to give the dipyrromethene salt **4**. The synthesis of **11** followed the well established route described by Dolphin and co-workers from pyrrole **7** via six steps with an overall yield of 60-65%.[11] Coupling of carboxypyrrole **10** with the 5-unsubstituted-2-formylpyrrole **11** in the presence of 48% aqueous hydrobromic acid, with in situ decarboxylation, gave the 5'-unsubstituted-5-methyldipyrromethene **4** in 85% yield.[12]

Pyrrole **12** required for ring B, is an isomer of pyrrole **11** and was synthesized from its precursor pyrrole **8**[13] according to the above procedure. Pyrrole **13**, which is destined to carry the acetate and propionate substituents of ring C was prepared from precursor pyrrole **9**. The synthesis of the latter (PA series) is well established because of its usefulness in the synthesis of uroporphyrins.[14] Hydrogenolysis of the benzyl ester of **9** gave the corresponding carboxypyrrole **13** in 95% yield. Condensation of 2-formyl-3-ethyl-4-methylpyrrole **12** with the carboxypyrrole **13** gave the dipyrromethene **14** in 78% yield.[12] The 5'-unsubstituted-5-methyldipyrromethene **14** was then converted with bromine in a 20% TFA-1,2-dichloroethane mixture into the crucial 5-bromo-5'-bromomethyldipyrromethene **5** in 82% yield.[12] It is interesting to note that the bromination reaction was slow (3 weeks!) for this particular dipyrromethene using the modified procedure introduced by Paine and co-workers.[15] However, we have found that this reaction time can be halved by doubling the number of equivalents of bromine used.

In the next step, the 5-bromo-5'-bromomethyldipyrromethene **5** was condensed with the 5'-unsubstituted-5-methyldipyrromethene **4** in the presence of anhydrous stannic chloride to give the biladiene-ac **3** in a 76% yield.[12] Cyclization of the biladiene-ac in dimethylsulfoxide-pyridine gave the required porphyrin **2** as the sole porphyrin in 32% yield. The mass spectrum of the product exhibited the molecular ion (M^+ = 566) as the base peak and high resolution mass matching indicated the required molecular formula $C_{34}H_{38}N_4O_4$. The ^{1}H-NMR spectrum of **2** ($CDCl_3$, 500 MHz) showed peaks at δ - 3.88 (2H, br s, 2 x NH), 1.88 (6H, t, 2 x CH_2CH_3), 3.34 (2H, t , $CH_2CH_2CO_2CH_3$), 3.63, 3.65, 3.69 (9H, 3 s , 3 x porphyrin-CH_3), 3.72, 3.75 (6H, 2 s, 2 x CO_2CH_3), 4.13 (4H, q, 2 x CH_2CH_3), 4.44 (2H, t, $CH_2CH_2CO_2CH_3$), 5.09 (2H, s, $CH_2CO_2CH_3$), 8.99 (1H, s, β-H), 9.99, 10.10, 10.13, 10.19


Pd/C
6 steps
6 steps
Pd/C
HBr/MeOH
HBr/MeOH
Br2/TFA
C2H4Cl2
SnCl4
CH2Cl2
DMSO/Pyridine
10
11
12
13
4
5
14
3
2

Scheme 2

(4H, 4 s, 4 x meso-**H**). The ^{13}C-NMR spectrum of **2** was identical with that reported for the natural product. The u.v spectrum of **2** was of an etio-type with λ_{max} at 400, 498, 535, 564 and 619 nm. The synthetic compound is therefore identical in all respects with the natural product from the sponge, thus confirming the structure[5] proposed for Corallistin A.

Acknowledgments: We thank the Robert A. Welch Foundation for a Post-doctoral fellowship (to P. Yon-Hin). We also wish to thank Professor Pietra and Dr. D'Ambrosio (Trento, Italy) for providing us with authentic sample of Corallistin A and Professor Dolphin and Dr. Wijesekera (Vancouver, Canada) for the mass spectral data.

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12. Satisfactory analytical data were obtained for all new compounds. Representative data of dipyrromethenes: (**4**) ^{1}H-NMR ($CDCl_3$) δ 1.18 (3H, t, CH_2CH_3), 2.28, 2.37, 2.71 (9H, 3s, CH_3's at 3, 5, 5'), 2.47 (2H, q, CH_2CH_3), 6.21 (1H, s, β-**H**), 7.18 (1H, s, bridge **CH**), 7.62 (1H, d, 5'-**H**), 13.20 (2H, br s, 2 x **NH**); MS m/z 214 (M^+ - HBr); H.R. Calcd for $C_{14}H_{19}N_2Br$ - HBr 214.1470, found 214.1472. (**5**) ^{1}H-NMR ($CDCl_3$) δ 1.22 (3H, t, CH_2CH_3), 2.08 (3H, s,CH_3's at 4'), 2.69, 2.89 (4H, 2t, $CH_2CH_2CO_2CH_3$), 2.77 (2H, q, CH_2CH_3), 3.67, 3.70 (6H, 2s, 2 x CO_2CH_3), 3.76 (2H, s, $CH_2CO_2CH_3$), 4.92 (2H, s, CH_2Br), 7.38 (1H, s, bridge **CH**), 13.40, 13.55 (2H, 2 x br s, 2 x **NH**); MS m/z 518, 516, 514 (M^+ - HBr); H.R. Calcd for $C_{20}H_{25}N_2O_4{}^{81}Br_3$ - $H^{81}Br$ 518.1396, found 518.1402.
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(Received in USA 10 May 1991)