Tetrahedron. Vol 32, pp 1867 to 1871. Pergamon Press 1976 Printed in Great Britain

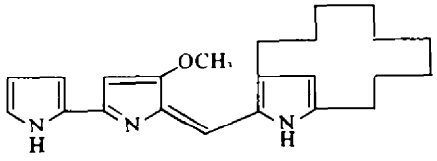
THE SYNTHESIS OF METACYCLOPRODIGIONSIN

H. H. WASSERMAN,* D. D. KEITH and J. NADELSON
Department of Chemistry, Yale University, New Haven, CT 06520, U.S.A.

(*Received in the UK 30 December 1975; Accepted for publication 19 January 1976*)

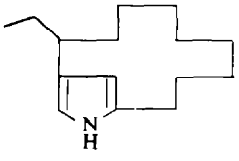
Abstract—Metacycloprodigiosin **1**, a tripyrrole pigment isolated from *Streptomyces longisporus ruber*, has been synthesized by condensation of the meta-fused pyrrole **2**, prepared from cyclododecanone, with the known methoxybipyrrole aldehyde precursor **3**.

In an accompanying paper[1] we have reported the isolation and structure determination of metacycloprodigiosin **1**, a tripyrrole pigment isolated from *Streptomyces longisporus ruber*. In an earlier preliminary communication, we described the synthesis of the racemic form of this pigment, which served to confirm the structural assignment.[2] In this paper, we provide full details on the synthesis of this novel prodigiosin analogue.

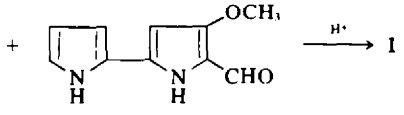


1

During the work on the structure determination of **1**,[1] a partial synthesis was accomplished by the acid-catalyzed condensation of the meta-fused pyrrole, 9-ethyl[9](2,4)pyrrolophane **2**, a degradation product arising from soda-lime pyrrolysis of the pigment, with the known[3,4] and previously synthesized[4] methoxybipyrrole aldehyde **3**. To complete the synthesis of **1**, it was thus necessary to prepare the metafused pyrrole **2** by an unambiguous route.

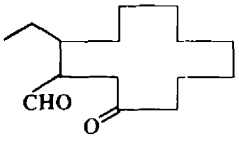


2



3

Earlier studies in these laboratories[5] have shown that [9](2,4)pyrrolophanes, such as **2**, could be made via the classical Paal-Knorr condensation of ammonia with a 1,4-dicarbonyl compound. Consequently, our immediate goal was the synthesis of 4-ethyl-3-formylcyclododecanone **4**. The sequence of steps employed in the preparation of **4** and then **2** is outlined in Scheme 1. An interesting feature of this synthesis involves the application of the Wharton reaction[14] for the transposition of the chromophore in an α,β-unsaturated ketone (e.g. **10**→**13**).



4

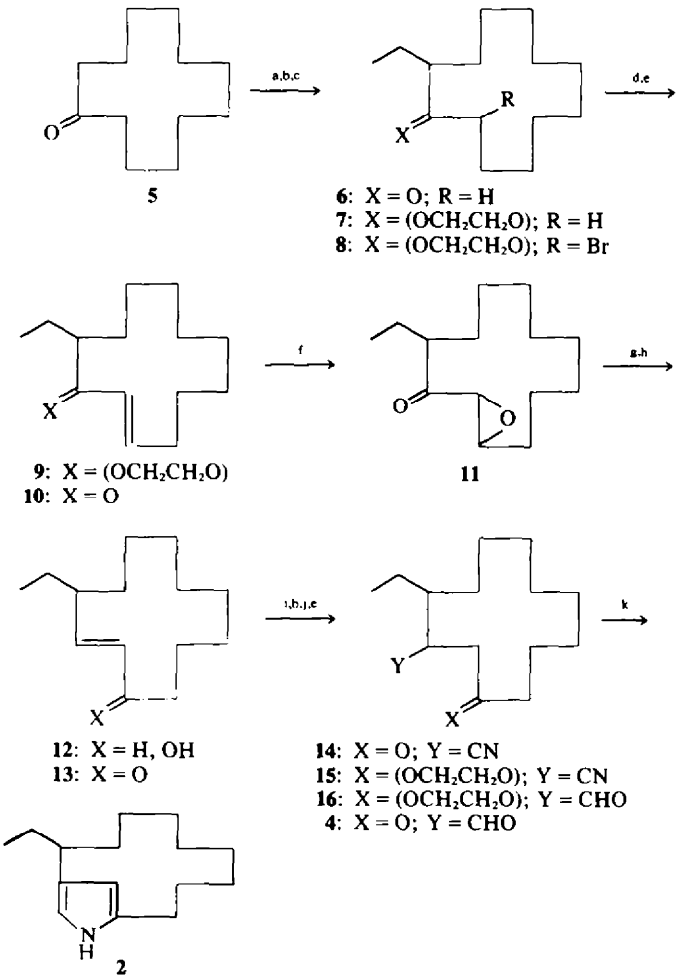
The reaction of cyclododecanone **5** with sodamide in glyme followed by treatment of the resultant enolate anion with ethyl bromide yielded a mixture consisting of 2-ethylcyclododecanone **6**, diethylcyclododecanone and starting material. Distillation of the reaction mixture through an annular teflon spinning band column gave pure **6** in 45% yield. Treatment of **6** with ethylene glycol/*p*-toluenesulfonic acid in benzene at reflux temperature produced a 50:50 mixture of the starting ketone and the ethylene ketal **7**. Fractionation of the product using an annular teflon spinning band column afforded the pure ketal. By recycling the starting material, the ethylene ketal **7** was obtained in an overall yield of 70%. The hindrance to ketalization by α-alkyl groups is a well-documented phenomena.[6] Thus, the problem associated with the ketalization of **6** is not exceptional.

Bromination of ketal **7** was accomplished with pyridinium hydrobromide perbromide[7] in dry tetrahydrofuran at reflux temperature.[8,9] These conditions gave an almost quantitative yield of the crystalline 2-bromo-12-ethylcyclododecanone ethylene ketal **8**. The location of the bromine at the least substituted position was confirmed by the NMR spectrum of **8** which exhibits a two multiplet, 5-proton absorption in the region τ 5.6–5.9, associated with the groups $-OCH_2CH_2O-$ and $-CHBr-$.

Dehydrobromination of **8** was effected by heating it at 110° for 72 h in 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[10] furnishing a 90.5% yield of the α,β-unsaturated ethylene ketal **9**. Hydrolysis of the ketal **9** with aqueous acid in acetone gave a 95% yield of the α,β-unsaturated ketone **10**.

The preparation of the ketone **10** was an important goal in our projected synthesis of the keto aldehyde **4**. By suitable functional group modification, we hoped to transpose the α,β-unsaturated system in **10** to the new α,β-unsaturated ketone **13**. Addition of an appropriate one-carbon fragment to **13** would then permit the formation of the 1,4-dicarbonyl system in **4**. The key ketone transposition (**10**→**13**) was accomplished in the manner outlined below.

Treatment of ketone **10** with hydrogen peroxide and



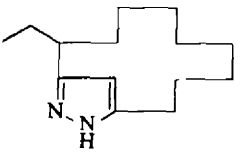
Scheme 1.

[a]$NaNH_2$, EtBr. [b]Ethylene glycol, *p*-TsOH, reflux temp. in benzene. [c]Pyridinium hydrobromide perbromide, THF. [d]DBN, 110°. [e]H_2O, acetone, *p*-TsOH. [f]H_2O_2, NaOH. [g]$NH_2NH_2 \cdot H_2O$, HOAc, EtOH. [h]$Na_2Cr_2O_7$, H_2SO_4, H_2O, Et_2O. [i]KCN, NH_4Cl, H_2O, DMF, 103°. [j]Diisobutylaluminum hydride, Et_2O. [k]$(NH_4)_2CO_3$, H_2O, DMF, 115°.

sodium hydroxide in methanol at 10° gave the α,β-epoxyketone **11** (96%).[11] Gas chromatographic analysis indicated that the product was a mixture of two diastereomers. A sharp doublet (τ 6.7, 1 H) in the NMR spectrum of the mixture of isomers could be correlated with the α-proton of the α,β-epoxy ketone moiety. The magnitude of the coupling constant ($J_{\alpha,\beta}$ = 2 Hz) indicated that each of the diastereomers was *trans*-substituted on the epoxy ring.[12,13] This evidence required that the two epoxide isomers differ only in the stereochemistry of the ethyl group.

The mixture of α,β-epoxy ketones **11** upon treatment with 85% aqueous hydrazine hydrate and a catalytic amount of acetic acid in ethanol at 25° for 12 h[14] gave the allylic alcohol **12** (33%). In addition to the desired alcohol **12**, a second compound was isolated from this reaction (44%). Absorptions in the NMR [τ −2.5 (broad, 1 H), 4.1 (s, 1 H), 7.4 (m, 3 H)] and the IR [3240–3150 (NH), 3075 (=CH), 1580 cm^{-1}] indicated that this second compound was the meta-fused pyrazole **17**.[15]

Oxidation of the allylic alcohol **12** with sodium dichromate/sulfuric acid[16] produced 4-ethyl-2-cyclododecanone **13** in 91% yield. This step thus completed the transposition of the α,β-unsaturated ketone chromophore in **10**. The unsaturated ketone **13** was



17

then transformed into the 1,4-aldehydo ketone **4** using the following method developed earlier in our studies on the synthesis of model [9](2,4)pyrrolophanes.[5]

Conjugate addition of cyanide to **13** was accomplished by heating the ketone with potassium cyanide and ammonium chloride in 1:10 water/N,N-dimethylformamide at 105° for 18 h[17] giving a 42% yield of the cyano ketone **14**. Ketalization with ethylene glycol and *p*-toluenesulfonic acid in benzene at reflux temperature afforded **15** (97%). Reduction of the nitrile function in **15** with diisobutylaluminum hydride[18] gave the ketal aldehyde **16** (80%) which was hydrolyzed with aqueous acid to yield the keto aldehyde **4** (97%).

The synthesis of (±) - 9 - ethyl[9](2,4)pyrrolophane **2** was completed by the reachion of the keto aldehyde **4** with ammonium carbonate in 1:6 water/N,N-dimethylformamide solution at 115° for 3 h. The meta-fused pyrrole, obtained in 58% yield, has NMR, MS, and

solution IR identical with the spectra of the pyrrole obtained by soda-lime pyrolysis[1] of the natural pigment **1**.

Condensation of pyrrole **2** with the known[3,4] bipyrrole aldehyde **3** in ethanolic HCl solution at 25° for 4 h afforded, after chromatography on basic alumina, a 90% yield of a brilliant red pigment, the spectroscopic properties of which (UV, visible, solution IR, NMR and MS), are identical with those of natural metacycloprodigiosin. The structure of metacycloprodigiosin **1** is thus confirmed by synthesis.

EXPERIMENTAL

M.ps and b.ps are uncorrected. IR spectra were recorded on either a Perkin–Elmer, Model 421 Recording Infrared Spectrometer or a Perkin–Elmer, Model 237 Grating Spectrophotometer. NMR spectra were taken on a Varian Model A60-A Spectrometer. Chemical shifts are reported in τ units using TMS as internal standard. Mass spectra were recorded on a A-EI, Model MS-9 instrument. UV and visible spectra were recorded on a Cary, Model 11-S, or on a Bausch and Lomb, Model 550, recording spectrophotometer. GLC analyses and sample collections were obtained with a Varian Aerograph, Model A90-P3 instrument. A 5′ × 1/4″ 20% Silicon Gum Rubber (SE-30) on 60/80 mesh Chromosorb W column was used for analytical purposes, and a 8′ × 3/8″ 20% Silicon Gum Rubber (SE-30) on 60/80 mesh Chromosorb W column was used for preparative purposes unless otherwise noted. The helium flow rate was 200 ml/min unless otherwise specified.

2-Ethylcyclododecanone **6**

Sodamide (107 g, 2.75 mol) and glyme (1000 ml) were placed in a 3 neck, round-bottomed flask equipped with a nitrogen inlet tube, a thermometer, a mechanical stirrer, an addition funnel, and a reflux condenser. A solution consisting of 501 g (2.75 mol) of cyclododecanone **5** in glyme (1500 ml) was added rapidly with stirring. The mixture was then heated at 90° for 5 h during which time a thick precipitate formed making stirring difficult. The reaction mixture was cooled to 50°, and ethyl bromide (350 g, 3.2 mol) in glyme (1000 ml) was added over a period of 1 h. The subsequent reaction was exothermic and the temperature rose from 50 to 70°. After addition was complete, the reaction mixture was heated at 90° for 8 h, allowed to cool, divided into 3 parts, and each part subjected to the following work-up: one third of the reaction mixture was poured into water (1500 ml), and the resultant aqueous mixture was extracted with 4 portions of ether (250 ml). The combined ether extracts were washed with 0.1 N HCl (200 ml), 5 portions of water (250 ml), and NaCl soln (250 ml). The ether solutions from each of the work-up procedures were combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield 550 g of an oil. Analysis by GLC indicated the oil consisted of approximately 70% 2-ethylcyclododecanone **6**, 15% cyclododecanone, and 15% diethylcyclododecanone. Distillation of the oil employing an annular teflon spinning band column afforded 256 g (45%) of pure 2-ethylcyclododecanone **6**: b.p. 80–81° (0.1 mm); 2,4-DNP, m.p. 168–170° [lit[19] 151.2°]; IR (neat) 2940, 2860, 1706, 1470, 1445 cm^{-1}; NMR (CCl_4) τ 7.65 (m, 3 H), 8.1–8.9 (m peaking at 8.75, 20 H), 9.18 (t, 3 H, J = 7 Hz). (Found: C, 80.09; H, 12.40. Calc. for $C_{14}H_{26}O$: C, 79.94; H, 12.46%).

2-Ethylcyclododecanone ethylene ketal **7**

A mixture consisting of 102 g (0.485 mol) of 2-ethylcyclododecanone **6**, ethylene glycol (298 g, 4.8 mol), *p*-toluene-sulfonic acid monohydrate (9.1 g, 0.048 mol) and benzene (200 ml) was placed in a 3 neck, round-bottomed flask equipped with a mechanical stirrer, a Dean Stark water separator, and a reflux condenser. The mixture was heated at reflux temperature for 50 h during which time 15 ml of an immiscible liquid was collected. The reaction mixture was allowed to cool, poured into 0.25 N $NaHCO_3$ soln (2000 ml), and the layers were separated. The aqueous layer was extracted with 4 portions of ether (200 ml). The organic layer and the ethereal extracts were combined and washed with 4 portions of water (200 ml) and one portion of sat NaCl soln (200 ml). The organic solution was dried ($MgSO_4$) and the solvent removed *in vacuo* to yield 115 g of an oil which was distilled using an annular teflon spinning band column. The first fraction collected consisted of 52 g (51%) of 2-ethylcyclododecanone **6**, b.p. 75° (0.05 mm). The compound was identified by comparison of its IR and NMR with those of an authentic sample. The second fraction collected consisted of 45 g (37%) of 2-ethylcyclododecanone ethylene ketal **7**: b.p. 114° (0.5 mm); IR (neat) 2945, 2875, 1465, 1440, 1180, 1165, 1150, 1100, 1085, 1075 cm^{-1}; NMR (CCl_4) τ 6.20 (s, 4 H), 8.61 (broad s, 23 H), 9.1 m, 3 H). (Found: C, 75.67; H, 11.90. Calc. for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89%). By recycling the starting material **6**, an overall yield of 70% was obtained for **7**.

2-Bromo-12-ethylcyclododecanone ethylene ketal **8**

The procedure described is a modification of that used by Eaton.[9] Pyridinium hydrobromide perbromide[7] (49 g, 0.153 mol) was added with stirring to a solution consisting of 40 g (0.157 mol) of 2-ethylcyclododecanone ethylene ketal **7** in dry tetrahydrofuran (960ml). The orange color of the perbromide disappeared rapidly, and a white precipitate formed. The reaction mixture was heated at reflux temperature for 1 h, allowed to cool, and poured into water (2000 ml). The aqueous mixture was extracted with 4 portions of ether (250 ml), and the combined extracts were washed with 1 N $NaHCO_3$ soln (250 ml), 4 portions of water (250 ml), and one portion of sat NaCl soln (250 ml). The ethereal solution was then dried ($MgSO_4$), and the ether was removed *in vacuo* yielding 60 g of crude crystalline 2-bromo-12-ethylcyclododecanone ethylene ketal **8**. A portion was purified by recrystallization from methanol: m.p. 59.5–60°; IR (CCl_4) 2935, 2860, 1470, 1450, 1207, 1185, 1117, 1092, 1085, 1035 cm^{-1}; NMR (CCl_4) τ 5.6 (m, 3 H), 5.95 (m, 2 H), 7.9–8.9 (m, peaking at 8.6, 21 H), 9.0 (m, 3 H). (Found: C, 57.95; H, 8.71; Br, 24.10. Calc. for $C_{16}H_{29}BrO_2$: C, 57.71; H, 8.71; Br, 23.99%).

12-Ethyl-2-cyclododecenone ethylene ketal **9**

A flask equipped with a reflux condenser and a nitrogen inlet tube was charged with 96.6 g (0.29 mol) of 2 - bromo - 12 - ethylcyclododecanone ethylene ketal **8** and 1,5-diazabicyclo-[4.3.0]non - 5 - ene (174 g, 1.4 mol, Aldrich Chemical Co.). The mixture was heated at 110° for 48 h, allowed to cool, and poured into water (2000 m). The aqueous mixture was extracted with 5 portions of ether (250 ml), and the combined extracts were washed with 5 portions of water (250 ml) and one portion of sat NaCl soln (250 ml). The solution was dried and the ether removed *in vacuo* yielding 66 g (90.3%) of crude 12-ethylcyclododecenone ethylene ketal **9**. A sample was purified by distillation (short-path apparatus), b.p. 85° (0.03 mm), followed by preparative GLC (190°): IR (CCl_4) 2950, 2900, 1667, 1465, 1445, 1207, 1183, 1104, 1030, 992, 953 cm^{-1}; NMR (CCl_4) τ 4.53 (m, 1 H), 4.8 (d, 1 H, J = 16 Hz), 6.37 (s, 4 H), 7.85 (m, 2 H), 8.2–8.9 (m peaking at 8.7, 17 H), 9.1 (m, 3 H). (Found: C, 76.41; H, 10.94. Calc. for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18%).

12-Ethyl-2-cyclododecenone **10**

A solution consisting of 65 g (0.258 mol) of 12 - ethyl - 2 - cyclododecenone ethylene ketal **9**, *p*-toluenesulfonic acid monohydrate (4.9 g, 0.0258 mol), water (100 ml) and acetone (390 ml) was stirred for 20 h at room temperature. Analysis of GLC indicated that almost all of the starting material had reacted. The reaction mixture was poured into water (2000 ml) and the aqueous mixture was extracted with 3 portions of ether (250 ml). The ether extracts were washed with 2 portions of water (250 ml), one portion of sat NaCl soln (200 ml), and dried ($MgSO_4$). Removal of the solvent *in vacuo* yielded 51 g (95%) of crude 12-ethyl-2-cyclododecanone **10**. A portion of the crude ketone was purified by distillation (6″ Vigreux column), b.p. 98–101° (0.2 mm), followed by preparative GLC (190°): semicarbazone, m.p. 157–159°; λ_{max}^{EtOH} 230 nm (ϵ 10,200); IR (CCl_4) 2950, 2880, 1692, 1666, 1625, 1460, 1440, 990 cm^{-1}; NMR (CCl_4) τ 3.31 (hex, 1 H, J = 7 Hz, 16 Hz), 3.72 (d, 1 H, J = 16 Hz), 7.7 (m, 3 H), 8.2–8.9 (m, peaking at 8.75, 16 H), 9.17 (t, 3 H, J = 8 Hz). (Found: C, 80.67; H, 11.53. Calc. for $C_{14}H_{24}O$: C, 80.71; H, 11.61%).

12-Ethyl-2,3-epoxycyclododecanone **11**

The procedure described is a modification of that used by Wasson and House.[11] A solution consisting of 26.2 g (0.126 mol) of 12 - ethyl - 2 - cyclododecenone **10** and 30% hydrogen peroxide (43.5 g, 0.38 mol) in methanol (390 ml) was placed in a 3 neck, round-bottomed flask equipped with an internal thermometer and mechanical stirrer. The solution was cooled to 10° in an ice bath, and 6 N NaOH (10.5 ml) was added dropwise with stirring at a rate slow enough to keep the temperature at 10°. After addition was complete, the reaction mixture was allowed to warm to room temperature, and was stirred for an additional 3 h. The reaction mixture was then poured into water (1000 ml), and the aqueous mixture was extracted with 3 portions of ether (200 ml). The combined extracts were washed with 0.05 N HCl (200 ml), 0.05 N $NaHCO_3$ (200 ml), 3 portions of water (200 ml), and NaCl soln (200 ml). The solution was dried ($MgSO_4$) and the solvents removed *in vacuo* to yield 27 g (96%) of crude 12 - ethyl - 2,3 - epoxycyclododecanone **11**. Analysis by GLC (200°) indicated that two isomers were present. Crystallization from methanol afforded one of the isomers, m.p. 67.5–69°: IR (CCl_4) 2950, 2890, 1717, 1460, 1440, 1420 cm^{-1}; NMR (CCl_4) τ 6.73 (d, 1 H, J = 2 Hz), 7.2 (m, 2 H), 7.5–8.9 (m peaking at 8.6, 18 H), 9.1 (t, 3 H, J = 7 Hz). (Found: C, 75.27, 75.21, H, 10.77, 10.85. Calc. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78%). The IR and NMR spectra of the crude mixture of isomers were essentially identical to those of the pure isomer.

4-Ethyl-2-cyclododecenol **12** *and* *1-Ethyl*[9](2,4)*pyrazolophane* **17**

The procedure described is a modification of that used by Wharton.[14] A solution consisting of 40.5 g (0.18 mol) of 12 - ethyl - 2,3 - epoxycyclododecenone **11**, 85% hydrazine hydrate (37 g), and acetic acid (2.15 g, 0.035 mol) in ethanol (330 ml) was stirred for 15 h. The effervescence of a gas (nitrogen) was observed. The reaction mixture was then poured into water (2000 ml) and the resultant aqueous mixture extracted with 5 portions of ether (250 ml). The combined ethereal extracts were washed with 250 ml portions of water until the washings were neutral. They were then washed with 250 ml of sat NaCl soln, dried ($MgSO_4$), and the ether removed *in vacuo* yielding 37 g of an oil which was distilled (6" Vigreux column). The fraction collected between 97 and 115° (0.1 mm) (12.5 g, 33%) was 4-ethyl-2-cyclododecenol **12**. A sample was purified by preparative GLC (190°): IR (CCl_4) 3636, 3490, 2950, 2875, 1695, 1460, 980 cm^{-1}; NMR (CCl_4) τ 4.73 (m, 2 H), 6.08 (m, 1 H), 8.23 (s, 1 H), 7.5–8.9 (m peaking at 8.7, 19 H), 9.15 (t, 3 H, J = 6 Hz). (Found: C, 80.32, 80.19; H, 12.21, 12.09. Calc. for $C_{14}H_{26}O$: C, 79.94; H, 12.46%).

Analysis by IR, NMR and MS indicated that the second fraction, collected between 125 and 135° (0.1 mm), was the metafused pyrazole **17**. the pyrazole was collected as a thick gum. Although attempts to purify it by crystallization from virtually all of the common solvents met with failure, the gum did solidify slowly on standing. Trituration of the resultant solid with pentane at dry ice-acetone temperatures yielded 17.3 g (44%) of the pure pyrazole **17**, m.p. 86–93°: IR (KBr) 3240, 3180, 3150, 3075, 2960, 2900, 1580, 1460, 1350 cm^{-1}; NMR (CCl_4) τ −2.5 (broad, 1 H), 4.1 (s, 1 H), 7.4 (m, 3 H), 8.1–9.5 (m, 19 H), 9.1 (t, 3 H, J = 7 Hz); MS *m/e* (rel intensity) 220 (34), 205 (75), 191 (14), 180 (14), 179 (54), 178 (45), 177 (25) 149 (27), 135 (23), 124 (54), 123 (14), 122 (17), 121 (29), 107 (43), 96 (95). (Found: C, 76.29, H, 10.87, N, 12.67. Calc. for $C_{14}H_{24}N_2$: C, 76.31; H, 10.98; N, 12.71%).

4-Ethyl-2-cyclododecenone **13**

The procedure described is a modification of that used by Brown.[16] A solution consisting of 12.2 g (0.058 mol) of 4 -ethyl - 2 - cyclododecenol **12** in ether (125 ml) was placed in a 3-neck, round-bottomed flask equipped with a mechanical stirrer, an addition funnel, and a reflux condenser. A solution of sodium dichromate (11.7 g, 0.039 mol), and conc. H_2SO_4 (14 ml) in water (110 ml) was added with stirring to the allylic alcohol at a rate sufficient to maintain a gentle reflux. After addition was complete, the reaction mixture was stirred for 3.5 h, poured into 250 ml of water, and subjected to a work-up similar to that used in the isolation of ketone **10**. The yield of crude 4-ethyl-2-cyclododecenone **13** was 11 g (91%). A portion was purified by preparative GLC (200°): λ_{max}^{EtOH} 231 nm (ϵ 11,200); IR (CCl_4) 2995, 2960, 2895, 1694, 1664, 1625, 1470, 1445, 994 cm^{-1}; NMR (CCl_4) τ 3.72 (m, 2 H), 7.60 (m, 2 H), 7.75–8.9 (m peaking at 8.72, 20 H), 9.12 (t, 3 H, j = 6 Hz). (Found: C, 80.79; H, 11.40. Calc. for $C_{14}H_{24}O$: C, 80.70; H, 11.61%).

3-Cyano-4-ethylcyclododecanone **14**

The procedure described is a modification of that used by Nagata.[17] A mixture consisting of 10 g (0.048 mol) of 4 - ethyl - 2 - cyclododecenone **13**, potassium cyanide (6.5 g, 0.1 mol), ammonium chloride (4.0 g, 0.075 mol), N,N-dimethylformamide (60 ml) and water (6 ml) was placed in a round-bottomed flask equipped with a nitrogen inlet tube and a reflux condenser. The mixture was stirred at 103° for 17 h, allowed to cool, poured into 300 ml of water, and the resultant aqueous mixture extracted with 5 portions of ether (100 ml). The combined ether extracts were filtered through infusorial earth to remove tars which had formed during the reaction. The filtrate was washed with 3 portions of water (100 ml), and one portion of sat NaCl soln (100 ml). The ether solution was then decolorized with activated charcoal, dried ($MgSO_4$), and concentrated *in vacuo* leaving a dark oil. Analysis by GLC indicated that the crude product was impure. Distillation (6" Vigreux column) of the impure oil yielded 4.75 g (42%) of 3 - cyano - 4 - ethylcyclododecanone **14**, b.p. 112–116° (0.05 mm). A small sample was further purified by preparative GLC (200°): IR (CCl_4) 2960, 2985, 2244, 1717, 1470, 1445 cm^{-1}; NMR (CCl_4) τ 6.5–8.0 (m, 5 H), 8.0–8.85 (m peaking at 8.70, 17 H), 9.0 (m, 3 H). (Found: C, 76.42; H, 10.60; N, 6.28. Calc. for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95%).

3-Cyano-4-ethylcyclododecanone ethylene ketal **15**

A mixture consisting of 4.3 g (0.019 mol) of 3 - cyano - 4 - ethylcyclododecanone **14**, ethylene glycol (13.2 g, 0.21 mol), *p*-toluenesulfonic acid monohydrate (0.35 g, 0.0186 mol) and benzene (85 ml) was placed in a round-bottomed flask equipped with a Dean–Stark water separator and a reflux condenser. The mixture was heated at reflux temperature for 20 h, cooled, poured in 0.1 N $NaHCO_3$ (500 ml) and the layers separated. The aqueous layer was extracted with two portions of ether (250 ml). The combined organic extracts were washed with 3 portions of water (200 ml) and one portion of sat NaCl soln (250 ml). The solutions were dried ($MgSO_4$) and the solvent removed *in vacuo* leaving 5 g (97%) of crude 3-cyano-4-ethylcyclododecanone ethylene ketal **15**. Crystallization from methanol yielded two distinctly different crystalline forms which were separated with a pair of tweezers, m.p. 96.5–104° and 105–107°. The mixture of crystals was further purified by sublimation: IR (CCl_4) 2950, 2900, 2240, 1470, 1440, 1110, 1060, 950 cm^{-1}; NMR (CCl_4) τ 6.07 (m, 4 H), 7.3 (m, 1 H), 8.2 (m, 2 H), 8.3–8.9 (m peaking at 8.6, 19 H), 9.0 (m, 3 H). (Found: C, 73.23; H, 10.41; N, 5.09. Calc. for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46; N, 5.01%).

4-Ethyl-3-formylcyclododecanone ethylene ketal **16**

The procedure described is a modification of that used by Zakharkin.[18] A solution consisting of 5 g (0.018 mol) of 3 - cyano - 4 - ethylcyclododecanone ethylene ketal **15** in ether (50 ml) was placed in a 3 neck, round-bottomed flask equipped with a nitrogen inlet tube, a magnetic stirrer, an addition funnel, and a reflux condenser. Diisobutylaluminum hydride (DIBAL) (4.0 g, 0.028 mol) was placed in the addition funnel under nitrogen. Ether (35 ml) was added to the DIBAL and the mixture was swirled to attain solution. The ethereal solution of DIBAL was then added dropwise with stirring to the cyanide. After addition was complete, the reaction mixture was stirred for an additional 2 h. The aluminum salts were decomposed by the dropwise addition of 10% sulfuric acid solution. The layers were separated and the aqueous layer was extracted with 2 portions of ether (75 ml). The combined organic layers were washed with 0.5 N $NaHCO_3$ (100 ml), 3 portions of water (100 ml) and one portion of sat NaCl soln (100 ml). The ether solution was dried ($MgSO_4$), and the solvent was removed *in vacuo* yielding 4.05 g (80% of the crude ketal aldehyde **16**. A portion of the crude material was purified by preparative GLC (225°); IR (CCl_4) 2960, 2900, 2820, 2712, 1723, 1465, 1440, 1105, 1070 cm^{-1}; NMR (CCl_4) τ 0.40 (m,

1 H), 6.20 (m, 4 H), 7.5 (m, 1 H), 7.9–8.9 (m peaking at 8.60, 21 H), 9.1 (m, 3 H). (Found: C, 72.12; H, 10.60. Calc. for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71%).

4-Ethyl-3-formylcyclodecanone **4**

A solution consisting of 3.7 g (0.013 mol) of 4 - ethyl - 3 - formylcyclododecanone ethylene ketal **16** and *p*-toluenesulfonic acid monohydrate (0.25 g, 0.0013 mol) in acetone-water (40:20) was stirred at 50° for 18 h. The reaction mixture was then cooled and subjected to a work-up similar to that used in the isolation of ketone **10**. The yield of crude 4-ethyl-3-formylcyclododecanone **4** was 3 g (97%). A small portion was purified by preparative GLC (225°): IR (CCl_4) 2925, 2850, 2820, 2722, 1724, 1710, 1470, 1450 cm $^{-1}$; NMR (CCl_4) τ 0.23 (m, 1 H), 6.9 (m, 1 H), 7.35 (m, 2 H), 7.68 (m, 2 H), 7.9–8.8 (m peaking at 8.7, 17 H), 9.0 (m, 3 H). (Found: C, 75.68; H, 10.71. Calc. for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99%).

(±)-9-Ethyl[9](2, 4)*pyrrolophane* **2**

A mixture consisting of 3.5 g (0.0145 mol) of 3 - formyl - 4 - ethylcyclododecanone **4**, ammonium carbonate (12 g, 0.23 mol), N,N-dimethylformamide (60 ml), and water (10 ml) was placed in 3-neck, round-bottomed flask equipped with a nitrogen inlet tube, a mechanical stirrer and a reflux condenser. The mixture was heated with stirring at 115° for 1 h. At this time an additional 10 g of ammonium carbonate was added, and the mixture was heated for a further 2 h. While the mixture was being heated, much foaming occurred, and ammonium carbonate formed on the walls of the condenser. It was therefore necessary to push the solid back into the reaction mixture with a glass rod to prevent the condenser from becoming plugged. The reaction mixture was allowed to cool, poured into 500 ml of water, and the resultant aqueous mixture extracted with 5 portions of ether (90 ml). The combined ethereal extracts were washed with 4 portions of water (100 ml) followed by one portion of sat NaCl soln (100 ml). The ethereal extracts were then dried ($MgSO_4$) and the ether removed *in vacuo* leaving a dark brown oil which was distilled (short-path apparatus) to yield 1.8 g (58%) of (±) - 9 - ethyl[9](2, 4)-pyrrolophane **2**, b.p. 109–111° (0.2 mm). A sample was purified by preparative GLC (190°) followed by sublimation, m.p. 59–61°. The purified sample has NMR, MS and solution IR identical with those of the pyrrole obtained by pyrrolysis of metacycloprodigiosin **1**.[1] (Found: C, 82.16, 81.95; H, 11.35, 11.25; N, 6.46, 6.28. Calc. for $C_{15}H_{25}N$: C, 82.13; H, 11.49; N, 6.38%).

(±)-Metacycloprodigiosin **1**

A solution consisting of 0.126 g (0.575 mmol) of (±) - 9 - ethyl[9](2, 4)pyrrolophane **2** in ethanol (10 ml) was added to a warm ethanolic solution of bipyrrole aldehyde **3**[3,4] (51.7 mg, 0.27 mmol). Upon addition of 0.5 ml of conc HCl, the solution turned a deep red. The solution was allowed to stand at room temperature for 12 h and at −5° for an additional 12 h. The reaction mixture was diluted with 150 ml of water and the resultant aqueous mixture extracted with 3 portions of methylene chloride (50 ml). The combined extracts were washed with 0.1 N NaOH (100 ml), dried (Na_2SO_4), and the solvent removed *in vacuo*. The remaining residue was taken up in petroleum ether and applied to a column of basic alumina (5 g of Fisher, Brockman Activity 1). The column was developed with 150 ml portions of petroleum ether, petroleum ether-chloroform, increasing the percentage of chloroform by 3% increments. A yellow band was eluted with 3% chloroform, but was present in such small quantity that it was discarded. (±)-Metacycloprodigiosin **1** was eluted with 12% chloroform. A blue pigment was eluted with 5% methanol in chloroform but was present in such small quantity that it was discarded.

The fractions containing the (±)-metacycloprodigiosin were washed with 0.25 N HCl (100 ml), dried (Na_2SO_4), and the solvents removed *in vacuo* to yield a dark red residue. The residue was crystallized from carbon tetrachloride to yield pure (±)-metacycloprodigiosin hydrochloride (105 mg, 90%), m.p. 232–235°. The synthetic pigment has UV, visible solution IR, NMR and MS identical with those of the natural pigment.[1]

REFERENCES

[1] H. H. Wasserman, D. D. Keith and G. C. Rodgers, *Tetrahedron* **32**, 1855 (1976).

[2] H. H. Wasserman, D. D. Keith and J. Nadelson, *J. Am. Chem. Soc.* **91**, 1264 (1969).

[3] H. H. Wasserman, J. E. McKeon, L. A. Smith and P. Forgione, *J. Am. Chem. Soc.* **82**, 506 (1960).

[4] H. Rapoport and K. Holden, *J. Am. Chem. Soc.* **84**, 635 (1962).

[5] H. H. Wasserman, E. Gosselink, D. D. Keith, J. Nadelson and R. J. Sykes, *Tetrahedron* **32**, 1863 (1976).

[6] M. Sulzbacher, E. Bergmann and E. R. Briser, *J. Am. Chem. Soc.* **70**, 2827 (1948).

[7] C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.* **70**, 417 (1948).

[8] A. Marquet, H. Kagan, M. Dvolaitzky, L. Mamlok, C. Weidmann and J. Jacques, *Compt. Rend.* **248**, 984 (1959).

[9] P. E. Eaton, *J. Am. Chem. Soc.* **94**, 2344 (1962).

[10] H. Oediger, H. Kabbe, F. Muller and K. Eiter, *Chem. Ber.* **99**, 2012 (1966), and references contained therein.

[11] R. L. Wasson and H. O. House, *Org. Syn.* **37**, 58 (1957).

[12] C. Reilly and J. Swalen, *J. Chem. Phys.* **32**, 1378 (1960); C. Reilly and J. Swalen, *Ibid.* **34**, 980 (1961).

[13] W. Brügel, *Nuclear Magnetic Resonance Spectra.* Academic Press, New York (1967).

[14] P. S. Wharton and D. H. Bohlen, *J. Org. Chem.* **26**, 3615 (1961); P. S. Wharton, *Ibid.* **26**, 4781 (1961).

[15] W. E. Parham and J. F. Dooley, *J. Am. Chem. Soc.* **89**, 985 (1967); W. E. Parham and J. F. Dooley, *J. Org. Chem.* **33**, 1476 (1968).

[16] H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.* **83**, 2952 (1961).

[17] W. Nagata, S. Hirai, H. Itazaki and K. Takeda, *J. Org. Chem.* **26**, 2413 (1961).

[18] L. I. Zakharkin and I. M. Khorlina, *Dokl. Akad. Nauk SSSR* **116**, 422 (1957); *cf. Chem. Abstr.* **52**, 8040f (1958).

[19] L. I. Zakharkin and V. V. Korneva, *Izv. Akad. Nauk SSSR, Ser. Khim.* 2102 (1964).