Tetrahedron Vol. 40, No. 14, pp. 2711 to 2720, 1984
Printed in the U.S.A.

0040-4020/84 $3.00 + .00

SYNTHESIS OF (±)-ASCOCHLORIN, (±)-ASCOFURANONE AND LL-Z 1272α†

KENJI MORI* and TAKAFUMI FUJIOKA‡
Department of Agricultural Chemistry, The University of Tokyo, Yayoi l-l-l, Bunkyo-ku, Tokyo 113, Japan

(Received in Japan 30 August 1983)

Abstract—Three antibiotics with a common structural feature as prenylated phenols were synthesized: (+)-ascochlorin (5-chloro-2,4-dihydroxy-6-methyl-3-[(2*E*′,4*E*′)-5′-(1″,2″,6″-trimethyl-3″-oxocyclohexyl)-3′-methyl-2′,4′-pentadienyl]benzaldehyde), (±)-ascofuranone (5-chloro-2,4-dihydroxy-6-methyl-3-[(2′*E*,6′*E*)-7′-(3″,3″-dimethyl-4″-oxo-2″-oxacyclopentyl)-3′,7′-dimethyl-2′,6′-heptadienyl]benzaldehyde) and LL-Z1272α (5-chloro-2,4-dihydroxy-6-methyl-3-[(2′*E*,6′*E*)-3′,7′,11′-trimethyl-2′,6′,10′-dodecatrienyl]benzaldehyde).

Many prenylated phenols are known as microbial metabolites. Among them, LL-Z1272a 1,' ascofuranone **2**[2–4] and ascochlorin **3**[5,6] are of special interest because of their unique properties as antibiotics. The peculiar structural feature of these me tabolites is the combination of a fully substituted benzene ring with a sesquiterpenoidal side-chain. The challenges posed by the structures 2 and 3 are therefore (i) the construction of the hexa-substituted benzene ring; (ii) the construction of the sesquiterpene moiety; and (iii) the coupling of the two building blocks. The early phase of our work was focused on the construction of the fully substituted benzene ring under mild conditions and culminated in the synthesis of colletochlorin B **4**.[7] We now report the full details of the synthesis of LL-Z1272a 1, (±)-ascofuranone **2**,[8] (±)-ascochlorin **3**[9] and some related compounds such as (±)-**5** (Fig. 1).

Synthesis of LL-Z 1272a and colletochlorin B

LL-Z1272a 1 is a metabolite from an unidentified *Fusarium* species isolated by Ellestad *et al.*' It is a growth-inhibitor of the protozoan, *Tetrahymena pyriformis*. To confirm the applicability of our synthetic method for prenylated phenols,' we carried out the preparation of LL-Z1272α 1 as shown in Fig. 2. Alkylation of 1,5-dimethoxy-3-methyl-1,4-cyclohexadiene 7 with famesyl bromide 6 yielded 8 in 67% yield employing t-BuLi as the base. This was treated with N-chlorosuccinimide (NCS) to give crude 9 in 61% yield. Dehydrochlorination of 9 with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave 10 in 73% yield. For the introduction of the CHO group, 10 was treated with EtMgBr in Et_2O followed by $HC(OEt)_3$.[10] This procedure was superior to the Duff reaction previously employed by us for the same purpose.' Finally treatment of the crude product with dil HCl effected the hydrolysis of $-CH(OEt)_2$ to –CHO yielding LL-Z1272α 1, m.p. 6869" (lit.' m.p. 72.5–73.0°), whose spectral data were identical with those reported by Ellestad *et al.*'

Recently Chen and Joullié reported a'synthesis of colletochlorin D 13 by the direct alkylation of 5-chloro-orsellinaldehyde 12 with isoprenyl bromide lla in the presence of KOH aq in a yield of 25%.[11] [We previously reported the m.p. of 12 to be 130–132°.[7] Further purification of our crude 12 by chromatography and recrystallization yielded pure 12 with m.p. 170–172° (from $CHCl_3$–n-hexane) (lit[11] m.p. 168–170°).] Application of this method to the synthesis of colletochlorin B 4 was attempted so as to define the scope and limitation of their short-cut procedure. Colletochlorin B 4, m.p. 90–96° (lit[7] m.p.

†Synthetic microbial chemistry-IV. This work was presented by K.M. as a part of his lecture at the 10th Conference on Isoprenoids. Trebon. Czechoslovakia (October 1983). Part III, K. Mori, *Tetrahedron* **39**, 3107 (1983).

‡Research Fellow on leave from Otsuka Pharmaceutical Co. Ltd., Tokushima Research Institute (1981-83).

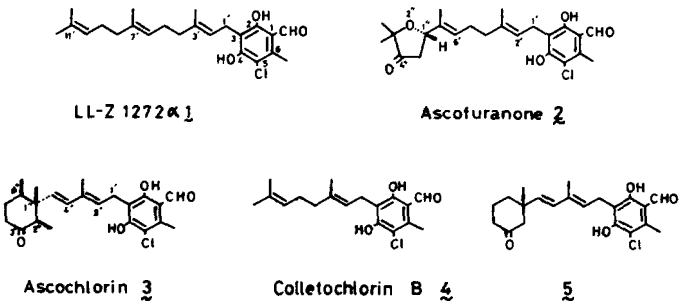

Fig. 1. Structures of the target molecules.

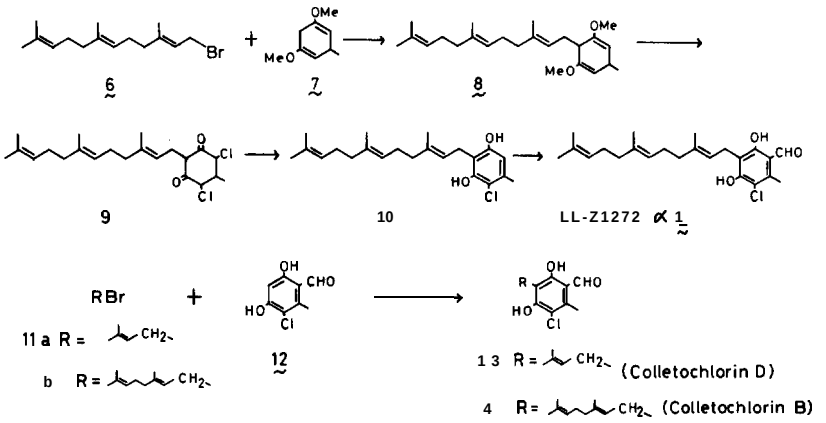

Fig. 2. Synthesis of **LL-Z1272α** and colletochlorin B.

90–91°), was obtained in 16.5% yield by alkylating **12** with geranyl bromide **IIb.** However, the alkylation of 12 with famesyl bromide 6 could not give any useful result. We therefore decided to employ our own procedure of prenylating the cyclohexadiene 7 for the synthesis of more complicated compounds such as ascofuranone 2 and ascochlorin 3.

Synthesis of (±)-*ascofuranone*

(-)-Ascofuranone 2 is a hypolipidemic antibiotic isolated from the mycelium of ***Ascochyta viciae*** by **Ando** et ***al.***[2–4] Its structure including the (S)-absolute configuration was established by an X-ray crystallographic analysis of **4-O-ethylascofuranone.**[4]† Recently its antitumor protective effect on L-1210 leukemia was discovered when it was administered once seven days before tumor **challenge.**[12] The **furanone** structure 2 coupled with its unique bioactivity makes ascofuranone an attractive target for synthetic **chemists.** Indeed an attempted synthesis of 2 had been reported by **Joullié** et ***al.***[13]

Our successful synthesis of (+)-2 started from geraniol 14 to build up the sesquiterpene part of the molecule (Fig. 3). The aldehyde 15 was prepared from 14 as previously described by **us.**[14] A cross-aldol reaction between 15 and **3-hydroxy-3-methyl-2-**butanone gave **(±)-16** in 73% yield in the presence of $LiN(SiMe_3)_2$ as the base (see Ref. 15). However, when $LiNPr_2^i$ was employed as the base, the major product was i and the yield of the desired 16 was only 15%. Cyclization of 16 to the furanone **(±)-17a** was initially attempted with $MsCl/C_5H_5N$ or $p\text{-}TsCl/C_5H_5N$ as the dehydrating agents, but the yield of **(±)-17a** was at best **25%,** the simple dehydration product i having been the major product. We therefore tried to protect the CO group in 16 prior to the cyclization to prevent the /?-elimination of the **allylic** OH group. To our pleasure, instead of the acetalization of the CO group, the desired cyclization to (+)-17a was effected in 53% yield by the treatment of 16 with **p-TsOH** in $CH(OMe)_3$ containing a small amount of **MeOH.** Removal of the THP protective group in **(±)-17a** gave **(±)-17b,** whose homogeneity as the desired **(2*E*,6*E*)-isomer** was confirmed by its ^{13}**C-NMR** and

†**In** our preliminary **communication,**[8] we erroneously stated that the absolute configuration of **ascofuranone** was unknown. This is untrue. We thank Dr. Y. Nawata, **Chugai** Pharmaceutical Co. Ltd., for drawing our attention to their X-ray **studies.**[4]

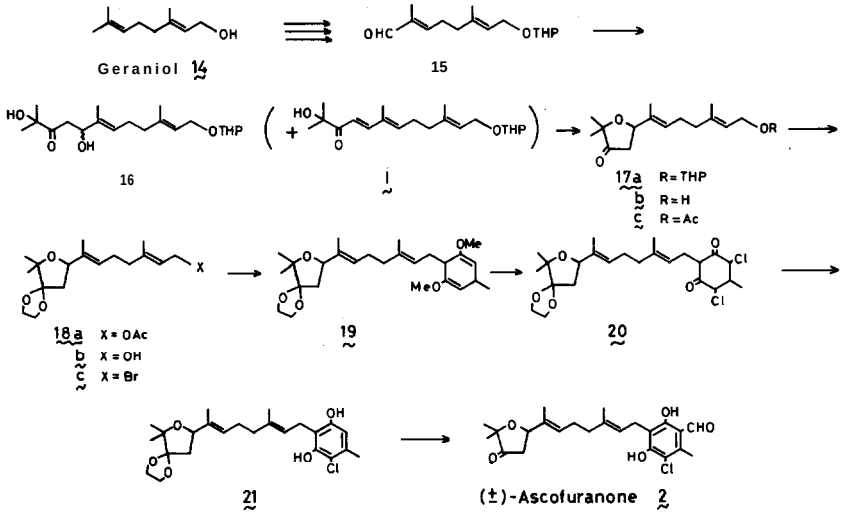

Fig. 3. Synthesis of **(±)-ascofuranone.**

HPLC analyses. This means that no isomerization of the (6*E*)-double bond took place either in the course of the aldol reaction or at the stage of the furanone formation. Conversion of (±)-17b to the bromide (±)-18c, the required alkylating reagent, was straight-forward. Acetylation of (±)-17b to (±)-17c was followed by Noyori's acetalization.[16] Thus the CO group in (±)-17c was protected as an ethylene acetal to give (±)-18a in 80% yield by treatment with $Me_3SiO(CH_2)_2OSiMe_3$ and Me_3SiOTf in CH_2Cl_2. Alkaline hydrolysis of (±)-18a gave (±)-18b. This was converted to the desired bromide (±)-18c upon successive treatments with n-BuLi, p-TsCl and LiBr.[17]

The later stages leading to (f)-ascofuranone 2 followed the route employed for the synthesis of LL-Z1272a 1. Alkylation of 7 with (±)-18c was effected with t-BuLi as the base to give (+)-19 in 33% yield. Treatment of (+)-19 with NCS yielded (±)-20 in 63% yield. Aromatization of (+)-20 with DBU gave (±)-21 (50% yield). Finally formylation of (±)-21 with EtMgBr and $CH(OEt)_3$ followed by acid hydrolysis of the product gave (+)-ascofuranone 2, m.p. 87–91°, in 21% yield. Its IR and 400 MHz 'H-NMR spectra were identical with those of (-)-ascofuranone kindly provided by Prof. G. Tamura.

Although the overall yield of (f)-ascofuranone was 0.82% from 15 in 11 steps, the first synthesis of this interesting antibiotic was thus completed, making it possible to synthesize various analogs of ascofuranone.

Synthesis of (±)-ascochlorin

(−)-Ascochlorin 3 is an antiviral antibiotic isolated from the mycelium of *Ascochyta viciae* by Tamura et *al.*[5] Its structure including absolute stereochemistry was determined by an X-ray analysis as depicted in 3.[6] Later biosynthetic studies on 3 by Tanabe *et al.* definitely proved its dual biosynthetic origin as a prenylated phenol.[18] Mainly because of its structural novelty coupled with potentially useful bioactivity and partly because it was discovered in our Department, we initiated our synthetic work on ascochlorin. In this case, the structure of the sesquiterpene part of the molecule is rather complicated and hence is more difficult to synthesize than that of ascofuranone.

As shown in Fig. 4, we chose (±)-3,4-dimethyl-2-cyclohexenone 22[19] and 3-methyl-2-penten-4-yn-1-ol 23a[20] as our starting materials. Hydrostannation of 23b with $(n\text{-}Bu)_3SnH$ was followed by metal exchange with n-BuLi to give a lithiated diene.[21] A mixed cuprate derived from the lithiodiene and n-PrC≡CCu in ether-$(Me_2N)_3P$[21,22] was reacted with (±)-22 to give (±)-24 in 81% yield after quenching with aq NH_4Cl. Conjugate addition of this mixed cuprate to 2,3,4-trimethyl-2-cyclohexenone failed to give (±)-27a. Both (*E*)- and (*Z*)-23b gave the same (+)-24 as a mixture of geometrical isomers at C-2 with (2*E*)/(2*Z*) ratio = 2: 1. The (*E*,*Z*)-mixture of 23b was therefore employed as the starting material. Unfortunately, the trapping experiments with Me1 of an enolate anion generated by the conjugate addition of the cuprate reagent to (±)-22 gave poor results of low reproducibility in securing (±)-27a directly. So as to achieve the regioselective introduction of a Me group at C-2', the sterically less crowded C-4' position was blocked by the formylation of (+)-24 with HCO_2Et–NaH to give (±)-25. This was converted to a dianion by treatment with 2 eq of $LiNPr^i_2$, whose alkylation with 1.1 eq of Me1 yielded (±)-26. Hydrolysis of (±)-26 with 2% NaOH aq gave (±)-27a in 55% yield from (+)-24. Treatment of (±)-27a with AcOH–THF aq gave (±)-27b, whose acetylation afforded (±)-27c in 86.5% yield from (±)-27a. The ethylene acetal (+)-%a was obtained in 86% yield from (±)-27c by treatment with $MeOCH(O_2C_2H_4)$ and p-TsOH. This was hydrolyzed with K_2CO_3 to give (±)-28b in 96% yield. Separation of the desired (2*E*)-isomer of (±)-28b from the (2*Z*)-isomer was carried out by medium pressure LC. In their 'H-NMR spectra, (±)-(2*E*)-28b showed a 3H-signal due to –C=C(CH_3)– at δ 1.71, while (±)-(2*Z*)-28b showed it at 6 1.80. The (2*E*)-alcohol 28b was

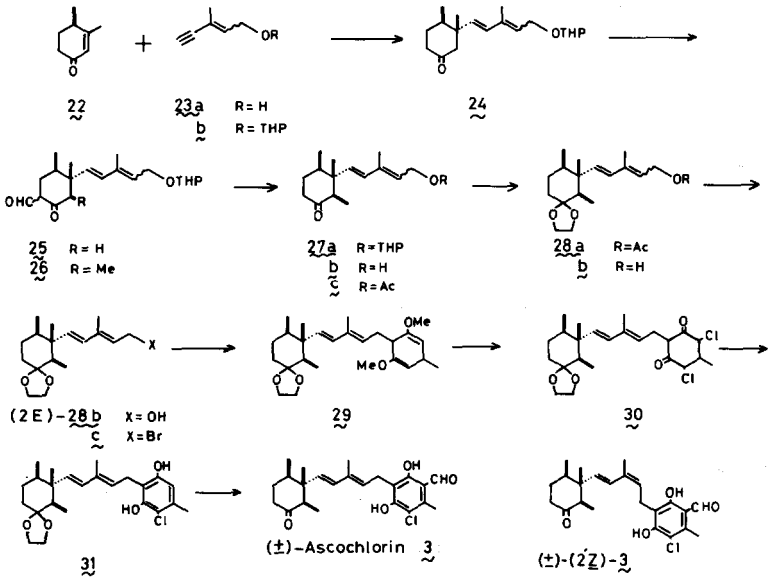

Fig. 4. Synthesis of (±)-ascochlorin.

converted to the corresponding bromide (±)-(2*E*)-**28c** in the conventional manner." This concluded the synthesis of the sesquiterpene moiety of the target molecule. There was no trouble in establishing the required stereochemistry around the cyclohexane ring with three equatorial substituents at C-l', C-2' and C-6'.

To complete the synthesis, we followed our general and reliable route. Alkylation of 7 with (±)-(2*E*)-**28c** yielded (±)-**29** in 40% yield. Treatment of (±)-**29** with 2.2 eq of NCS in DMF aq in the presence of $CaCO_3$ gave (±)-**30** in 43% yield. Aromatization of (±)-**30** to (±)-**31** was achieved in 43% yield by heating (f)-30 with DBU in THF. Finally the CHO group was introduced to (±)-**31** by treatment with EtMgBr in Et_2O followed by $HC(OEt)_3$.[10] The crude product was treated with 35% $HClO_4$–Et_2O to give (±)-ascochlorin 3, m.p. 142-146". The IR and 400 MHz 'H-NMR data of our product were identical to those of (−)-ascochlorin 3 kindly provided by Prof. G. Tamura. In entirely the same manner, (±)-(2*Z*)-**28b** yielded the (2'*Z*)-isomer 3, m.p. 180–184°, of (±)-ascochlorin. It should be added that (+)-3 and its (2'*Z*)-isomer could not be separated by prep TLC. Although the overall yield of our synthesis is rather unsatisfactory (0.64% from 22 in 13 steps), this completed the first synthesis of (±)-ascochlorin 3.

To prove the generality of our approach, an analog (+)-bisnorascochlorin 5 was also synthesized. The route shown in Fig. 5 is exactly similar to the route developed for the syntheses of (±)-ascochlorin itself except that the ethoxyethyl (EE) protective group was employed in protecting the OH group in the enyne alcohol **23a**. Starting from 3-methyl-2-cyclohexenone 32 and *via* the intermediates (±)-**33**, (±)-**34**, (±)-**35**, (±)-**36** and (±)-**37**, (±)-bisnorascochlorin 5, m.p. ~ 100" and its (2'*Z*)-isomer, m.p. 147–152°, were obtained as the racemates. In this case these two geometrical isomers were separable by prep TLC.

In conclusion, the fist total syntheses of both (±)-ascofuranone 2 and (±)-ascochlorin 3 were accomplished. The syntheses were flexible enough to enable the preparation of their analogs which might possess useful bioactivity as antibiotics. The synthesis of the optically active forms of these two antibiotics is now in progress in our laboratory.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra refer to films for oils and Nujol mulls for solids and were measured on a Jasco IRA 102 spectrometer. NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer, unless otherwise stated. The numbering systems shown in Fig. 1 were used in naming the compounds described below.

6-Farnesyl-1,5-dimethoxy-3-methyl-1,4-cyclohexadiene **8.** To a stirred and cooled soln of t-BuLi (2.6 M in n-hexane. 4.2 ml, 10.9 mmole) in THF (50 ml) was added **7** (1.5 g, 9.7 mmole) at −78" under Ar. The stirring was continued for 1 hr at −78". HMPA (2 ml) was added to the mixture at -78". The stirring was continued for 10 min at -78". To the stirred and cooled mixture was added 6 (4.0 g) gradually. At the end of the addition the red color of the anion of 7 faded. The mixture was left to stand for a while with gradual raise of the reaction temp to room temp. It was then poured into brine and extracted with ether. The ether soln was washed with brine, dried (K_2CO_3) and concentrated *in vacuo* to give *5.7 g* of a crude oil. This was chromatographed over SiO_2 (Mallinckrodt CC-7, 80 g). Elution with n-hexane-EtOAc (100: 1–100: 3) gave 2.33 g (66.8% from 7) of 8, ν_{max} 1610 cm^{-1}. This was employed in the next step without further purification.

4,6-Dichloro-2-farnesyl-5-methyl-1,3-cyclohexanedione **9.** $CaCO_3$ (184 mg, 1.84 mmole) was added to a soln of 8 (1.2 g, 3.35 mmole) in DMF (17 ml) and H_2O (1.5 ml). Ar was bubbled into the mixture for 10 min to remove any dissolved O_2. NCS (983 mg, 7.36 mmole) was added to the stirred mixture at O-5". After the addition, the mixture was stirred overnight at room temp. then poured into water. The aq mixturewas stirred for 30 min, acidified with N-HCl to pH 4–5, and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 1.55 g of a semi-solid. This was chromatographed over SiO_2 (Mallinckrodt CC-7, 45 g). Elution with n-hexane-EtOAc (100: l-2: 1) gave 810 mg (60.6%) of 9, ν_{max} 3225 (m), 1610 (s) cm-'. This was employed in the next step without further purification.

4-Chloro-2-farnesylorcinol **10.** DBU (1.5 ml, 10.6 nunole) was added to a soln of 9 (810 mg, 2.03 mmole) in THF (5 ml) under Ar. The soln was stirred and heated under reflux for 4hr. After cooling, the mixture was poured into water, acidified with N-HCl to pH 4-5, and extracted with ether. The ether soln was washed with water and brine, dried

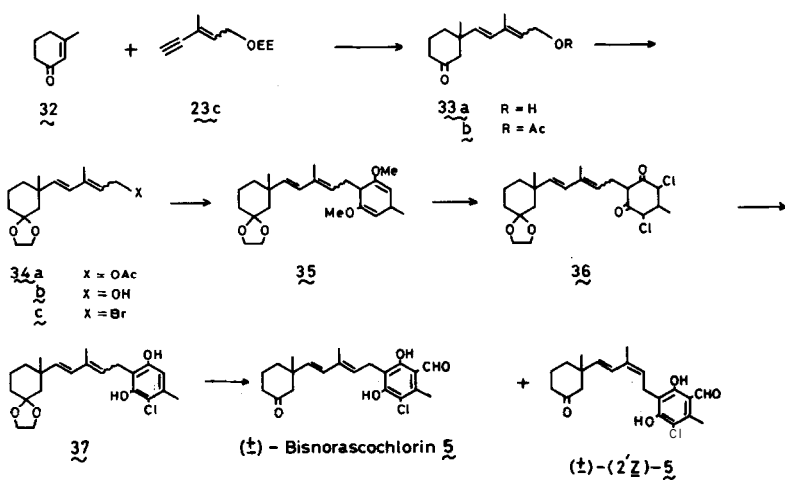

Fig. 5. Synthesis of (±)-bisnorascochlorin.

(MgSO,) and concentrated in *vacuo*. *The* residual semi-solid (681 mg) was chromatographed over SiO_2 (Merck Kieselgel 60, Art 7734, 5 g). Elution with n-hexane–EtOAc (100:1) gave 536mg (72.8%) of **10**, n_D^{21} 1.5221; ν_{max} 3540 (m), 3450 (m), 1620 (m), 1580 (m), 1455 (s), 1410 (s) cm-'; δ (CCl_4) 1.55 (6H, s), 1.63 (3H, s), 1.76 (3H, s), 1.80-2.30 (6H, m), 2.20 (3H, s), 3.35 (2H, d, J = 7 Hz), 4.80–5.30 (3H, br. m), 5.47 (1H, s), 5.68 (1H, s), 6.20 (1H, s); MS: m/z 362 (M^+).

LL-Z1272α (5-chloro-2,4-dihydroxy-6-methyl-3-[(2'E,6'E)-[7',11'-trimethyl--2',6',10'-dodecatrienyl]benzaldehyde) 1. One-third of an ether soln of EtMgBr (7.7 mmole prep from EtBr (0.53 ml) and Mg (187 mg) was added dropwise to a stirred soln of 10 (464 mg, 1.28 mmole) in ether (4 ml) at room temp. After stirring for 30 min, $HC(OEt)_3$ (0.85 ml, 5.12 mmole) was added to the mixture and the reaction temp was gradually raised to remove ether. The residue was heated at 100° for 10 min. After cooling, the mixture was acidified with N-HCl and extracted with ether. The ether soln was washed with water and brine, dried (MgSO,) and concentrated *in vacuo* to give crude 1 (464 mg). This was chromatographed over SiO_2 (Merck Kieselgel 60, Art 7734, 9g). Elution with n-hexane-ether (100:1) gave 259me (51.8%) of 1. This was recrystallized from n-hexane to give 130 mg of 1, m.p. 64–66°. Further recrystallization of this from MeOH aq gave 65 mg of pure 1, m.p. 68-69" (lit.' m.p. 72.5–73.0°); ν_{max} ($CHCl_3$) 3520 (w), 2975 (w), 2910 (m), 2850 (w), 1630 (s), 1460 (w), 1425 (m), 1375 (m), 1330 (w), 1290 (m), 1250 (s), 1110 (m), 960 (w), 905 (w) cm-'; δ ($CDCl_3$) 1.55 (6H, s), 1.64 (3H, s), 1.76 (3H, s), 1.80-2.20 (8H, m), 2.54 (3H, s), 3.36 (2H, d, J = 7 Hz), 4.80–5.40 (3H, br. m), 6.42 (1H, s), 10.12 (1H, s), 12.66 (1H, s); MS: m/z 390 (M^+). The IR and NMR spectral data of our synthetic **1** was identical to those reported by Ellestad *et al.*[1] (Found: C, 70.55; H. 7.96. Calc. for $C_{23}H_{31}O_3Cl$: C, 70.66; H, 7.99%).

Colletochlorin B (5-chloro-2,4-dihydroxy-6-methyl-3-[(E)-*3',7'-dimethyl-2',6'-octadienyl]benzaldehyde) 4. The* crude 12 (m.p. 130–132°)[7] was purified by prep TLC. Further recrystallization of the sample from $CHCl_3$–n-hexane gave the pure 12, m.p. 170-172" (lit." m.p. W-170") ^{13}C-NMR (25 MHz, acetone-d_6) δ 14.74, 102.26, 114.31, 114.43, 152.57, 161.46, 165.04, 194.93. (Found: C, 51.70; H, 3.88. Calc. for $C_8H_7O_3Cl$: C, 51.50; H, 3.78%). This was alkylated with 2 eq of llb in the presence of 2 eq of 10% KOH aq for two days at room temp. The mixture was poured into water and extracted with ether. Further workup and the purification of the product by SiO_2 chromatography and prep TLC gave 4 in 16.5% yield, m.p. 90-96" (lit.' m.p. 90–91°), ν_{max} ($CHCl_3$) 3520 (m), 2970 (m), 2910 (m), 2840 (m), 1630 (s), 1455 (m), 1420 (m), 1375 (m), 1325 (m), 1285 (s), 1250 (s), 1105 (m) cm-'; δ ($CDCl_3$) 1.58 (3H, s), 1.66 (3H, s), 1.80 (3H, s), 2.02 (4H, br), 2.60 (3H, s), 3.42 (2H, d, J = 7 Hz), 4.9-5.5 (2H, m), 6.54 (1H, s), 10.20 (1H, s), 12.72 (1H, s). These spectral data were identical with those of an authentic sample.' The identity was moved by HPLC analvsis under the condition described in Ref. 7.

(±)-2,5,12-*Trihydroxy-2,6,10-trimethyl-6,10-dodecadien-3-one 12-THP ether 16.* A soln of 3-hydroxy-3-methyl-2-butanone (14.2 g, 0.14 mole) in dry THF (150 ml) was added dropwise to a stirred and cooled soln of $LiN(SiMe_3)_2$ (prep from 177 ml of 1.57 M n-BuLi in n-hexane and 58.5 ml of $HN(SiMe_3)_2$; 4 eq) in THF (650 ml) at -20 to -30" under Ar. The stirring was continued for 1 h at -20 to -30". The mixture was then cooled to -78 and a soln of 15 (17.5 g, 0.07 mole) in dry THF (250 ml) was added dropwise over 90min to the mixture. After stirring for 30min at −78°, the reaction was quenched with sat NH_4Cl aq. The mixture was poured into brine and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in *vacuo*. *The* residue was chromatographed over SiO_2 (Mallinckrodt CC-7,300 g). Elution with n-hexane–EtOAc (20: l-l: 1) gave 18.0 g (73.2%) of 16, n_D^{21} 1.4859; ν_{max} 3450 (s), 1710 (s), 1115 (s), 1070 (s), 1050 (s), 1020 (s) cm^{-1}; δ (CCl_4) 1.26 (6H, s), 1.62 (14H, br. s), 1.90–2.35 (6H, mj, 3.10–4.40 (5H, m), 4.55 (1H, sj, 5.00–5.60 (2H, m). This was employed in the next step without further purification.

(±)-(2E,6E)-7-(3',3'-*Dimethyl-4'-oxo-2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadien-1-ol THP ether* 17a *p*-TsOH·H_2O (24 mg, 0.12 mmole) and MeOH (2.0 ml, 0.049 mole) were added to a soln of 16 (17.5 g, 0.049 mole) in $CH(OMe)_3$ (162 ml). The soln was stirred for '8 h at room temp. During that period additional amounts of p-TsOH·H_2O (24 mg x 2) and MeOH (0.5 ml) were added to the mixture. It was then diluted with ether. The ether soln was washed with sat $NaHCO_3$ aq and brine, dried (MgSO,) and concentrated in *vacuo*. *The* residue was chromatographed over SiO_2 (Merck Kieselgel 60, Art 7734, 350 g). Elution with n-hexane-EtOAc (50: l-5: 1) gave 8.8 g (52.9%) of 17a, n_D^{21} 1.4854; ν_{max} 1755 (s), 1110 (s), 1020 (s) cm^{-1}; δ (CCl_4) 1.15 (3H, s), 1.22 (3H, s), 1.64 (12H, br. s), 1.90–2.40 (6H, m), 3.14-4.09 (4H, m), 4.34-4.57 (2H, m), 5.10–5.62 (2H, m). (Found: C, 70.87; H, 9.55. Calc. for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59%.)

(±)-(2E,6E)-7-(3',3'-*Dimethyl-4'-oxo-2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadien-1-ol* 17b. A soln of 17a (8.6 g) in AcOH–THF–H_2O (3 : 1: 1: 1,200 ml) was stirred and heated at 50" for 2 h. It was then poured into H_2O and extracted with ether. The ether soln was washed with sat $NaHCO_3$aq and brine, dried ($MgSO_4$) and concentrated in *vacuo*. *The* residue was chromatographed over SiO_2 (Merck Kieselgel 60, Art 7734, 70g). Elution with n-hexane–EtOAc (10: l-l : 1) gave 6.2 g (96.1%) of 17b, n_D^{21} 1.4606; ν_{max} 3425 (m). 1755 (vs), 1665 (w), 1170 (s), 1110 (s), 995 (s) cm^{-1}; 'H-NMR δ (CCl_4) 1.15 (3H, s), 1.20 (3H, s), 1.61 (6H, s), 1.86-2.43 (6H, m), 2.68 (1H, br), 3.94 (2H, d, J = 7 Hz), 4.42 (1H, t, J = 7 Hz), 5.09-5.70 (2H, m); "C-NMR (25 MHz) δ ($CDCl_3$) 11.20, 16.18, 21.88, 24.13, 25.92, 38.82, 39.93, 58.82, 77.72, 80.62, 124.35, 128.12, 133.27, 137.69, 217.57; MS: m/z 252 (M^+); HPLC (Column, Partsil-5, 25 cm x 4.6 mm; Eluent, n-hexane–THF = 4: 1; 1 ml/min) R_t 13.2 min (single peak).

(±)-(2E,6E)-7-(3',3'-*Dimethyl-4'-oxo-2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadienyl acetate* 17c. Ac_2O (0.15 ml) was added to a soln of 17b (271 mg) in C_5H_5N (1.4 ml) and the mixture was stirred overnight at room temp. It was then poured into dil HCl and extracted with ether. The ether soln was washed with water and brine, dried (MgSO,) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, Art 7734, 5 g). Elution with n-hexane–EtOAc (100: 8) gave 285 mg (90.0%) of 17c, n_D^{21} 1.4760; ν_{max} 1755 (s), 1740 (s), 1665 (w), 1230 (s), 1170 (m), 1110 (m), 1020 (m), 995 (m) cm-': δ (CCl_4) 1.14 (3H, Sj, 1.20 (3H, s), 1.62 (3H, s), 1.69 (3H, s), 1.95 (3H, s), 1.86-2.45 (6H, m), 4.42 (1H, t, J = 7 Hz), 4.46 (2H, d, J = 7 Hz), 5.10–5.69 (2H, m); MS: *m/z* 294 (M^+). (Found: C, 69.43; H, 8.86. Calc. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90%.)

(±)-(2E,6E)-7-(3',3'-*Dimethyl-4',4'-ethylenedioxy-2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadienyl acetate* 18a. A soln of 17c (1.65 g, 5.6 mmole) and $Me_3SiO(CH_2)_2OSiMe_3$ (1.58 g, 7.6 mmole) in CH_2Cl_2 (2 ml) was added dropwise to a stirred and ice-cooled soln of Me_3SiOTf in CH_2Cl_2 (4 mole%, 2.2 ml) under Ar. After stirring for 7 h at 0–5°, the reaction was quenched by the addition of C_5H_5N (22 μl). The mixture was poured into sat NaHCO, aq and extracted with ether. The ether soln was washed with brine, dried (K_2CO_3) and concentrated in *vacuo*. The residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 60 g). Elution with n-hexane-EtOAc (100:2–100:30) gave 1.52 g (80.4%) of 18a, n_D^{21} 1.4832; ν_{max} 1740 (s), 1670 (w), 1230 (s), 1145 (s), 1025 (s) cm-'; 6 (CCl_4) 1.12 (6H, s), 1.55 (3H, s), 1.70 (3H, s), 1.97 (3H, s), 1.90–2.35 (6H, m). 3.86 (4H, s), 4.22 (1H, t, J = 7 Hz), 4.49 (2H, d, J = 7 Hz), 5.10-5.55 (2H, m); MS: m/z 338 (M^+). (Found: C, 67.50; H, 8.98. Calc. for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94%.)

(±)-(2E,6E)-7-(3',3'-*Dimethyl-4',4'-ethylenedioxy-*

2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadien-1-ol **18b**. A soln of K_2CO_3 (1.41 g) in MeOH (0.7 ml) and H_2O (3.5 ml) was added dropwise to a stirred soln of **18a** (691 mg) in MeOH (2.3 ml). The stirring was continued overnight at room temp. The mixture was then poured into water and extracted with ether. The ether soln was washed with brine, dried (K_2CO_3) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 15 g). Elution with n-hexane–ether (10:1) gave 563mg (93.1%) of **18b**, n_D^{21} 1.4937; ν_{max} 3425 (m), 1670 (w), 1150 (s), 1030 (s) cm^{-1}; δ (Ccl$_4$) 1.11 (6H, s), 1.53 (3H, s), 1.62 (3H, s), 1.80–2.21 (6H, m), 3.85 (4H, s), 3.70–4.40 (3H, m), 5.10–5.60 (2H, m); MS: m/z 296 (M^+). (Found: C, 68.46: H, 9.46. Calc. for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52%.)

(±)-(2E,6E)-7-(3',3'-Dimethyl-4',4'-ethylenedioxy-2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadienyl bromide **18c**. A soln of n-BuLi (1.50 M in n-hexane, 1.25 ml, 1.88 mmole) was added dropwise to a stirred and ice-cooled soln of **18b** (557 mg, 1.88 mmole) in dry ether (1.9 ml) and HMPA (0.66 ml). A soln of pTsCl(376 mg, 1.97 mmole) in dry ether (1.9 ml) was then added dropwise to the stirred and ice-cooled mixture. After stirring for 5 min, LiBr (330 mg, 3.8 mmole) was added to the mixture. The stirring was continued overnight at room temp. The mixture was diluted with ether and poured into sat $NaHCO_3$ aq. The ether soln was separated, washed with water and brine, dried (K_2CO_3) and concentrated *in uacuo* to give 600mg (quantitative) of crude **18c**. ν_{max} 1655 (w), 1145 (s), 1030 (s) cm^{-1}; δ (Cdl$_4$) 1.10 (6H, s), 1.53 (3H, s), 1.70 (3H, s), 1.89–2.31 (6H, m), 3.82 (4H, s), 3.80–4.40 (3H, m), 5.20-5.70 (2H, m). This was employed in the next step withour further purification.

(±)-3-[(2'E,6'E)-7'-(3",3"-Dimethyl-4",4"-ethylenedioxy-2"-oxacyclopentyl)-3',7'-dimethyl-2',6'-heptadienyl]-2,4-dimethoxy-6-methyl-1,4-cyclohexadiene **19**. A soln of 7 (3 19 mg, 2.07 mmole) in THF (1.5 ml) was added dropwise to a stirred and cooled soln of t-BuLi (2.6 M in n-hexane, 0.9 ml, 2.3 mmole) in THF (8 ml) at –78" under Ar. The stirring was continued for 45 min at –78". Then HMPA (0.42 ml) was added to the mixture and the stirring was continued for 10 min at -78". To this stirred and cooled mixture was added a soln of **18c** (600 mg, *ca.* 1.88 mmole) in THF (2 ml). The mixture was further stirred for 30min at -78". The temp was then raised to –20° and the reaction was quenched by the addition of sat NH_4Cl aq. The mixture was poured into brine and extracted with ether. The ether soln was washed with brine, dried (K_2CO_3) and concentrated in *oacuo. The* residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 25g). Elution with n-hexane–EtOAc (100:1–100:4) gave 270mg (33.2% from **18b**) of **19**, n_D^{21} 1.5040; ν_{max} 1690 (s), 1655 (m), 1225 (s), 1200 (s), 1145 (s), 1050 (s), 1025 (s), 810 (m) cm-'; MS: *m/z* 432 (M^+). This was employed in the next step without further purification.

(±)-3-[(2'E,6'E)-7'-(3",3"-Dimethyl-4",4"-ethylenedioxy-2"-oxacyclopentyl)-3',7'-dimethyl-2',6'-heptadienyl]-1,5-dichloro-6-methyl-2,4-cyclohexanedione *20*. $CaCO_3$ (33 mg, 0.33 mmole) was added to a soln of 19 (256 mg, 0.59 mmole) in DMF (3 ml) and H_2O (0.27 ml). Ar was bubbled into this mixture for 10 min to remove 0, comnletely. NCS (174 ma. 1.3 mmole) was gradually add&i to the stirred and ice-c&led mixture under Ar. The stirring was continued overnight at room temp. The mixture was then poured into water, acidified to pH 4–5 by adding N-HCl and extracted with ether. The ether soln was washed with water and brine, dried (MgSO,) and concentrated *in uacuo. The* residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 9 g). Elution with n-hexane-EtOAc (50: l-2: 1) gave 177 mg (63.2%) of crude **20**, ν_{max} 3200 (m), 1725 (s), 1620 (s), 1140 (s) cm^{-1}. This was employed in the next step without further purification.

(±)-4-*Chloro*-2-[(2'E,6'E)-7'-(3",3"-*dimethyl*-4",4"-*ethylenedioxy*-2"-*oxacyclopentyl*)-3',7'-*dimethyl*-2'6'-*heptadienyl*]*orcinol* **21**. DBU (0.28 ml) was added to a soln of **20** (177 mg) in THF (0.9 ml) and the mixture was stirred and heated under reflux for 4 h under Ar. After cooling, the mixture was poured into water, acidified with N-HCl to pH 4-5 and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in *vacuo. The* residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 5g). Elution with n-hexane–EtOAc (50: 1) gave 80 mg (50.0%) of 21, ν_{max} 3550 (m), 3380 (m), 3320 (m), 1655 (w), 1610 (m), 1585 (m), 1140 (s), 1060 (m), 1025 (m) cm^{-1}; 6 (CCl_4) 1.19 (6H, s), 1.51 (3H, s), 1.68 (3H, s), 1.75–2.40 (6H, m), 2.20 (3H, s), 3.23 (2H, d, J = 7 Hz), 3.85 (4H, s), 4.29 (1H, t, J = 7 Hz), 4.91-5.51 (2H, m), 5.65 (1H, br. s), 6.16 (1H, s), 6.36 (1H, br); MS: m/z 436.2002. Calc. for $C_{24}H_{33}O_5Cl$: 436.2016.

(±)-*Ascofuranone* (5-*chloro*-2,4-*dihydroxy*-6-*methyl*-[(2'E,6'E)-7'-(3",3"-*dimethyl*-4"-*oxo*-2"-*oxacyclopentyl*)-3',7'-*dimethyl*-2',6'-*heptadienyl*]*benzaldehyde* **2**. A soln of 21 (79 mg, 0.18 mmole) in ether (1 ml) was added drop wise to a soln of EtMgBr (0.36 mmole) in ether at room temp. The stirring was continued for 30 min at room temp. Subsequently $HC(OEt)_3$ (0.12 ml. 0.72 mmole) was added to the mixture. Ether was distilled off from the mixture and the residue was heated at 100" for 10 min. After cooling, the residue was acidified with N-HCl and extracted with ether. The residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 3.5 g). Elution with n-hexane-ether (20: 1) gave a crude product (73 mg) with the intact ethylene acetal group. This was. dissolved in AcOH–H_2O (12:1. 2 ml) and the soln was stirred and heated under reflux for 30 min. After cooling, the mixture was diluted with water and extracted with ether. The ether soln was washed with water, $NaHCO_3$ aq and brine, dried ($MgSO_4$), and concentrated in *oacuo. The* residue was purified by prep TLC (Merck, developed with n-hexane–EtOAc = 2: 1) to give 38 mg of an oil. This was dissolved in ether, filtered to remove insoluble impurities and concentrated *in oacuo.* Crystallization of the residue (33 mg) from n-hexane-ether gave 24 mg (3 1.5%) of crystalline 2. Recrystallization from acetone-n-hexane gave 16 mg (21.0%) of 2 as colorless fibrous needles m.p. 87-91"; ν_{max} ($CHCl_3$) 3520 (m), 2970 (m), 2925 (m), 1755 (s), 1630 (vs), 1460 (m), 1420 (m), 1375 (m), 1325 (m), 1285 (s), 1250 (vs), 1220 (sh. m), 1165 (m), 1110 (m), 990 (m), 900 (w) cm^{-1}; δ (400 MHz, $CDCl_3$) 1.22 (3H, s), 1.28 (3H, s), 1.63 (3H, s), 1.79 (3H, s), 2.00–2.09 (2H, m), 2.10–2.21 (2H, m), 2.35 (1H, dd, J= 10, 18 Hz), 2.42 (1H, dd, J= 7, 18 Hz), 2.60 (3H, s), 3.39 (2H, d, J = 7 Hz), 4.52 (1H, dd, J = 7, 10 Hz), 5.21 (1H, t, J = 7 Hz), 5.51 (1H, t, J = 7 Hz), 6.46 (1H, s), 10.14 (1H, s), 12.70 (1H, s); MS: *m/z* 420 (M^+). The spectral data (IR and NMR) were identical to those of an authentic (–)-**2**. (Found: C, 65.66, H, 6.94. Calc. for $C_{23}H_{29}O_5Cl$: C, 65.63; H, 6.94%.)

(E)-3-*Methyl*-2-*penten*-4-*yn*-1-*ol THP ether* **23b**. A catalytic amount of p-TsOH·H_2O was added to a soln of (*E*)-**23a** (5.2 g)[20] and dihydropyran (6.9 ml) in ether (100 ml) with stirring and ice-cooling. The mixture was stirred overnight at room temp, washed with 5% K_2CO_3 aq and brine, dried (K_2CO_3) and concentrated *in uacuo. The* residue was distilled to give 8.47 g (86.9%) of (*E*)-**23b**, b.p. 104–107°/10 mm; n_D^{20} 1.4820; ν_{max} 3290 (m), 2090 (w), 1640 (w). 1120 (s), 1025 (s) cm^{-1}; δ (CCl_4) 1.61 (6H, br. s), 1.82 (3H, s), 3.21–4.21 (4H, m). 4.56 (1H, br. s), 5.98 (1H, t, J = 7 Hz). This was employed in the next step without further purification. In the same manner (*Z*)-**23b** and (*EZ*)-**23b** were also prepared.

(±)-(2EZ,4E)-5-(1',6'-*Dimethyl*-3'-*oxocyclohexyl*)-3-*methyl*-2,4-*pentadien*-1-*ol THP ether* **24**. A catalytic amount of AIBN and (n-Bu)$_3$SnH (4.4 ml, 16.5 mmole) were added to **23b** (2.0 g, 11 mmole) under Ar, and the mixture was heated at 100° for 30min. The excess (n-Bu)$_3$SnH was distilled off *in oacuo* at 100". The residue was dissolved in THF (20 ml) and cooled to –78". A soln of n-BuLi (1.50 M in n-hexane, 8.8 ml, 13.2 mmole) was added over 20 min to the mixture and the stirring was continued for 40min at -78". To this was added a soln of n-PrC≡CCu (1.2 g,

9.2 mmole) in ether (15 ml) and $(Me_2N)_3P$ (3.4 ml, 18.4 mmole) over 15 min with stirring and cooling at -78". The stirring was continued for 2 h at– 78". A soln of (±)-**22** (0.8 g, 6.4 mmole)[19] in ether (10 ml) was added dropwise to the stirred and cooled dark green-colored soln of the mixed cuprate at – 78" and the stirring was continued for 1.5 h at -78". The reaction was quenched by the addition of sat NH_4Cl aq and the mixture was extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, Art 7734, 70 g). Elution with n-hexane–EtOAc (SO: l-10: 1) gave 1.17 g (59.7%, or 81.3% on the basis of consumed 22. Some 22 was recovered after chromatography), n_D^{22} 1.5095: ν_{max} 1715 (s), 1640 (w), 1200 (m), 1135 (m), 1120 (m), 1075 (m), 1025 (s), 970 (m), 890 (m) cm^{-1}; δ (CCl_4) 0.92 (3H, d, J = 6 Hz), 0.92 (3H, s), 1.16–2.00 (12H, m), 2.00-2.53 (4H, m), 3.08–4.35 (4H, m), 4.53 (1H, br. s), 5.20–5.76 (2H, m), 5.76–6.60 (1H, m). (Found: C, 74.23; H, 10.09. Calc. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.86%.)

(±)-(2EZ,4E)-5-(1′,2′,6′-*Trimethyl*-3′-*oxocyclohexyl*)-3-*methyl*-2,4-*pentadien*-1-*01 THP ether* 27a. (i) 50% NaH in mineral oil (0.45 g, 9.4 mmole) was washed with n-pcntane and NaH was suspended in dry C_6H_6 (8 ml). To this suspension was added a soln of **24** (1.74 g, 5.7 mmole) and HCO_2Et (0.7 ml, 8.7 mmole) in dry C_6H_6 (8ml) in one portion with stirring and ice-cooling. The mixture was stirred for 2 h at 10°. The excess NaH was destroyed by the addition of water and the mixture was acidified with N-HCI to pH 4. It was then extracted with ether. The ether soln was washed with dil $NaHCO_3$, water and brine, dried (MgSO,) and concentrated in *uacuo* to give 1.7 g of crude **25**, ν_{max} 1640 (s), 1590 (s) cm-'. This was employed in the next step without further purification.

(ii) A soln of $LiNPr_2^i$ (13.2 mmole) was prepared by the addition of n-BuLi (1.50 M in n-hexane, 8.5 ml) to a soln of $(i\text{-}Pr)_2NH$ (1.7 ml) in THF (12 ml). To this was added a bln of 25 (1.7 g) in THF (6 ml) gradually at –20° with stirring. After stirring for 20 min at –20°, MeI (0.4 ml, 6.4 mmole) and HMPA (2.2 ml) were added to the mixture. The stirring was continued for 1.5 h at– 20". The reaction was quenched by the addition of sat NH_4Cl aq. The mixture was acidified with N-HCI to pH 5 and extracted with ether. The ether soln was washed with water and brine, dried (MgSO,) and concentrated in *uacuo* to give 1.75 g of crude 26, ν_{max} 1640 (s), 1590 (s) cm^{-1}; δ (CCl_4) 0.7-1.2 (9H, m). This was employed in the next step without further purification.

(iii) **26** (1.75 g) was dissolved in 2% NaOH aq (23 ml) and the soln was stirred and heated under reflux for 4 h. It was then diluted with water, acidified with N-HCl to pH 5 and extracted with ether. The ether soln was washed with water and brine, dried (MgSO,) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, Art 7734, 60 g). Elution with n-hexane–EtOAC (25: 1) gave l.Og (54.9% from 24) of **27a**, n_D^{22} 1.5154; ν_{max} 1715 (s), 1615 (w), 11 15 (s), 1075 (m), 1025 (s), 975 (m) cm-'; δ (CCl_4) 0.72 (3H, s), 0.78 (3H, d, J = 6 Hz), 0.82 (3H, d, J = 6 Hz), 0.9–2.5 (15H, m, signals at δ 1.78 and 1.83), 3.12–4.32 (4H, m), 4.53 (1H, s), 5.19–6.48 (3H, m). (Found: C, 74.43; H, 10.14. Calc. for $C_{20}H_{32}O_2$: C. 74.96: H. 10.07%

(±)-(2EZ,4E)-5-(1′,2′,6′-*Trimethyl*-3′-*oxocyclohexyl*)-3-*methyl*-2,4-*pentadien*-1-*ol* **27b**. A soln of **27a** (1.1 g) in AcOH–THF–H_2O (2:2:1, 30ml) was stirred and heated at 40–50° for 3 h. It was then poured into water and extracted with ether. The ether soln was washed with dil $NaHCO_3$ aq, water and brine, dried (MgSO,) and concentrated in *uacuo*. *The* residue was chromatographed over SiO_2 (Merck Kieselgel 60, Art 7734, 10 g). Elution with n-hexane–EtOAc (20: l-l : 1) gave 0.8 g (98.6%) of **27b**, n_D^{23} 1.5261; ν_{max} 3410 (m), 1710 (s), 1015 (s), 970 (s) cm-'; 6 0.71 (3H, s), 0.74 (3H, d, J = 6 Hz), 0.76 (3H, d, J = 6 Hz), 0.92-1.11 (2H, m), 1.60–1.95 (4H, m), 2.11-2.51 (3H, m), 2.65 (1H, br. s), 4.11 (2H, d, J = 7 Hz), 5.1 l-5.69 (2H, m), 5.69–6.40 (1H, m); MS: m/z 236 (M^+). (Found: C, 74.84; H, 10.01. Calc. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24%.) This was employed in the next step without further purification in spite of the rather unsatisfactory elemental analytical data.

(±)-(2EZ,4E)-5-(1′,2′,6′-*Trimethyl*-3′-*oxocyclohexyl*)-3-*methyl*-2,4-*pentadienyl acetate* **27c**. Ac_2O (3 ml) was added to a soln of **27b** (6.1 g, 25.8 mmole) in dry C_5H_5N (50 ml). The mixture was stirred overnight at room temp, poured into iced-dil HCl and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in *vacuo*. *The* residue was chromatographed over SiO_2 (Merck Kieselgel 60, Art 7734, 150 g). Elution with n-hexane–EtOAc (10: l-3: 1) gave 6.3 g (87.7%) of **27c**, n_D^{22} 1.5116; ν_{max} 1740 (s), 1710 (s), 1645 (w), 1235 (s), 1020 (m), 970 (m) cm-'; δ (CCl_4) 0.72 (3H, s), 0.82 (6H, d, J = 6 Hz), 1.81 (3H, s), 1.98 (3H, s), 1.4–2.1 (3H, m), 2.1-2.5 (3H, m), 4.58 (2H, d, J = 7 Hz), 5.20–5.70 (2H, m), 5.7-6.5 (1H, m). (Found: C, 72.79; H, 9.37. Calc. for $C_{17}H_{26}O_3$: C, 73.35; H, 9.37%.)

(±)-(2EZ,4E)-5-(3′,3′-*Ethylenedioxy*-1′,2′,6′-*trimethylcyclohexyl*)-3-*methyl*-2,4-*pentadienyl acetate* **28a**. MeOH (0.45 ml) was added to a boln of **27c** (6.3 g, 22.6 mmole) in 2-methoxy-1,3-dioxolane (31 ml). To this was added 9 ml of a soln of anhydrous p-TsOH (100 mg) in dry C&-I, (30 ml). The mixture was stirred for 4 days at room temp. During that period MeOH (0.3 ml x 3) and p-TsOH in C_6H_6 (5 ml x 3) were added to the soln. It was then poured into dil $NaHCO_3$ aq and extracted with ether. The ether soln was washed with water and brine, dried (K_2CO_3) and concentrated in *uacuo*. *The* residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 160 g). Elution with n-hexane-EtOAc (100: 3-50: 3) gave 6.3 g (86.3% of **28a**, n_D^{24} 1.5070; ν_{max} 1740 (s), 1656 (w), 1235 (s), 1070 (s) cm^{-1}; MS: *m/z* 322 (M^+). (Found: C, 70.78; H, 9.43. Calc. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38%.)

(±)-(2EZ,4E)-5-(3′,3′-*Ethylenedioxy*-1′,2′,6′-*trimethylcyclohexyl*)-3-*methyl*-2,4-*pentadien*-1-*ol* **28b**. (i) (2*EZ*,4*E*)-**28b**: A soln of K_2CO_3 (7.7 g) in MeOH (3.5 ml)–H_2O (18 ml) was added to a soln of **28a** (3.0 g) in MeOH (10 ml). The mixture was stirred overnight at room temp. It was then poured into water and extracted with ether. The ether soln was washed with water and brine, dried (K_2CO_3) and concentrated *in vacuo*. *The* residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 30 g). Elution with n-hexane–EtOAc (20:1–2:1) gave 2.5 g (96.2%) of (2*EZ*,4*E*)-**28b**, n_D^{25} 1.5170, ν_{max} 3400 (m), 1640 (w). 1065 (s) cm^{-1}; MS: m/z 280 (M^+).

(ii) *Separation of the two geometrical isomers*. *The* above described mixture (2.5 g) was chromatographed over a Merck Lobar column (Li Chroprep Si 60, 63–125 μm). Elution with n-hexane–ether (2: 1) gave 1.6 g (64%) of (3*E*,4*E*)-**28b**, n_D^{25} 1.5170; ν_{max} 3420 (m), 1640 (w), 1620 (w), 1175 (m), 1150 (m), 1095 (m), 1070 (s), 1010 (m), 995 (m), 965 (m), 900 (m) cm^{-1}; 6 (CCl_4) 0.4–0.9 (9H, m), 1.71 (3H, s), 4.12 (2H, d, J = 7 Hz), 5.0-5.7 (2H, m), 5.95 (1H, d, J = 17 Hz); MS: m/z 280 (M^+), and 0.8 g (32%) of (2*Z*,4*E*)-**28b**, n_D^{25} 1.5137; ν_{max} 3420 (m), 1640 (w). 1175 (m), 1150 (m), 1095 (m), 1065 (s), 1010 (m), 990 (m), 965 (m), 900 (m) cm^{-1}, δ (CCl_4) 0.5–1.0 (9H, m), 1.80 (3H, s), 4.17 (2H, d, J = 7 Hz), 5.10-5.59 (2H, m), 6.26 (1H, d, J= 17 Hz); MS: *m/z* 280 (M^+).

(±)-5-(3′,3′-*Ethylenedioxy*-1′,2′,6′-*trimethylcyclohexyl*)-3-*methyl*-2,4-*pentadienyl bromide* **28c**. (i) (2E,4E)-*Isomer*. A soln of n-BuLi (1.53 M in n-hexane, 2.2 ml, 3.4 mmole) was added dropwise to a stirred and ice-cooled soln of (2*E*,4*E*)-**28b** (0.96 g, 3.4 mmole) in ether (3.4 ml)-HMPA (1.2 ml) under Ar. To this was added dropwise a soln of p-TsCl (666 mg, 3.5 mmole) in ether (3.4 ml). The mixture was stirred for 20 min at 0". Then LiBr (700 mg, 8.1 mmole) was added and the mixture was stirred overnight at room temp. The mixture was poured into dil $NaHCO_3$ aq and extracted with ether. The ether soln was washed with water and brine, dried (MgSO,) and concentrated *in vacuo* to give 1.04 g of crude (2*E*,4*E*)-**28c**, ν_{max} 1640 (w), 1610 (w), 1070 (s) cm-'; δ (CCl_4) 0.5–0.9 (9H, m), 1.82 (3H, s), 3.85 (4H, br.), 5.0–6.5 (3H, m). This was employed

in the next step without further purification. (ii) (2Z,4E)-*Isomer*. In the same manner, (2Z,4E)-**28c**, δ (CCl_4) 0.5–1.0 (9H, m), 1.85 (3H, s), 3.82 (4H, br), 5.0–6.4 (3H, m), was obtained. Its IR spectrum was almost indistinguishable from that of (2E,4E)-**28c**. This was employed in the next step without further purification.

(±) - 3 - [5′ - (3″,3″ - *Ethylenedioxy* - 1″,2″,6″ - *trimethylcyclohexyl*) - 3′ - *methyl* - 2′,4′ - *pentadienyl*] - 2,4 - *dimethoxy* - 6 - *methyl* - 1,4 - *cyclohexadiene* **29**. (i) (2′E,4′E)-*Isomer*. A soln of **7** (0.63 g, 4.1 mmole) in THF (3 ml) was added dropwise to a stirred and cooled soln of t-BuLi (2.6 M in n-hexane, 1.7 ml, 4.4 mmole) in THF (4 ml) at −78° under Ar. After stirring for 30 min at −78°, HMPA (0.93 ml) was added to the mixture. The stirring was further continued for 10 min at −78°. A soln of (2E,4E)-**28c** (1.04 g) in THF (3 ml) was added dropwise to the stirred mixture at −78°. After stirring for 30 min at −78°, the reaction temp was raised to −20°. The reaction was quenched by the addition of sat NH_4Cl aq. The mixture was poured into brine and extracted with ether. The ether soln was dried (K_2CO_3) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 35 g). Elution with n-hexane–EtOAc (100:1) gave 0.56 g (39.5% from **28c**) of (2′E,4′E)-**29**, ν_{max} 1690 (s), 1675 (m), 1595 (m), 1225 (s), 1200 (s), 1175 (s), 1145 (s), 1100 (m), 1085 (s), 970 (s) 905 (s), 810 (s), 785 (s) cm^{-1}; δ (CCl_4) 0.5–1.1 (12H, m), 1.60 (3H, s), 3.48 (6H, s), 3.61–3.90 (4H, m), 4.46 (2H, m), 4.85–6.25 (3H, m); MS: *m/z* 416 (M^+). This was employed in the next step without further purification. (ii) (2′E,4′E)-*Isomer*. In the same manner as above, (2′Z,4′E)-**29**, δ (CCl_4) 0.5–1.1 (12H, m), 1.70 (3H, s), 3.47 (6H, s), 3.65–3.90 (4H, m), 4.50 (2H, m), 4.81–6.45 (3H, m); MS: *m/z* 416 (M^+), was obtained. This was employed in the next step without further purification.

(±) - 3 - [5′ - (3″,3″ - *Ethylenedioxy* - 1″,2″,6″ - *trimethylcyclohexyl*) - 3′ - *methyl* - 2′,4′ - *pentadienyl*] - 1,5 - *dichloro* - 6 - *methyl* - 2,4 - *cyclohexanedione* **30**. (i) (2′E,4′E)-*Isomer*. $CaCO_3$ (54 mg, 0.54 mmole) was added to a soln of (2′E,4′E)-**29** (610 mg, 1.46 mmole) in DMF (7 ml) and H_2O (0.66 ml). Ar gas was bubbled into the mixture to remove O_2. Then NCS (430 mg, 3.22 mmole) was gradually added to the stirred mixture at 0–5°. The mixture was stirred overnight at room temp. It was poured into water, stirred for 30 min, acidified with N–HCl to pH 5 and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 20 g). Elution with n-hexane–EtOAc (10:1–2:1) gave 291 mg (43.4%) of (2′E,4′E)-**30**, ν_{max} 3245 (m), 2650 (w), 1725 (m), 1620 (s), 1370 (s), 1070 (s) cm^{-1}; MS: *m/z* 457, 455 (M^+). This was employed in the next step without further purification. (ii) (2′Z,4′E)-*Isomer*. In the same manner as above,(2′Z,4′E)-**30**, ν_{max} 3250 (m), 2650 (sh. w), 1720 (m), 1620 (s), 1370 (s), 1070 (s) cm^{-1}; MS: *m/z* 457, 455 (M^+), was obtained. This was employed in the next step without further purification.

(±) - 4 - *Chloro* - 2 - [5′ - (3″,3″ - *ethylenedioxy* - 1″,2″,6″-*trimethylcyclohexyl*) - 3′ - *methyl* - 2′,4′ - *pentadienyl*]*orcinol* **31**. (i) (2′E,4′E)-*Isomer*. DBU (0.48 ml, 3.2 mmole) was added to a soln of (2E,4E)-**30** (291 mg) in THF (1.4 ml). The mixture was stirred and heated under reflux for 3 h under Ar. It was then poured into water, acidified with N–HCl to pH 5 and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 9 g). Elution with n-hexane–ether (20:1) gave 114 mg (42.6%) of (2′E,4′E)-**31**, ν_{max} 3550 (w), 3350 (m), 1610 (w), 1590 (w), 1100 (s), 1065 (vs) cm^{-1}; δ 0.45–1.00 (9H, m), 1.84 (3H, s), 2.20 (3H, s), 3.41 (2H, d, J = 7 Hz), 3.60–4.00 (4H, m), 4.90–6.50 (5H, m); MS; *m/z* 420.2068. Calc. for $C_{24}H_{33}O_4Cl$: 420.2067. (ii) (2′Z,4′E)-*Isomer*. In the same manner as above, (2′Z,4′E)-**31**, ν_{max} 3550 (m), 3400 (m), 1615 (w), 1595 (w), 1065 (s) cm^{-1}; δ (CCl_4) 0.45–1.00 (9H, m), 1.72 (3H, s), 2.16 (3H, s), 3.46 (2H, d, J = 7 Hz), 3.60–4.00 (4H, m), 5.00–6.80 (5H, m); MS: *m/z* 420 (M^+), was obtained. This was employed directly in the next step.

(±) - 5 - *Chloro* - 2,4 - *dihydroxy* - 6 - *methyl* - 3 - [5′ - (1″,2″,6″ - *trimethyl* - 3″ - *oxocyclohexyl*) - 3′ - *methyl* - 2′,4′-*pentadienyl*]*benzaldehyde* **3**. (i) (±)-*Ascochlorin* (2′E,4′E)-**3**. A soln of (2′E,4′E)-**31** (150 mg, 0.24 mmole) in ether (1 ml) was added gradually to a soln of EtMgBr (0.48 mmole) in ether 1 ml with stirring under Ar at room temp. After the addition, the stirring was continued for 20 min. To the mixture was added $HC(OEt)_3$ (0.16 ml, 9.7 mmole). The reaction temp was gradually raised to remove ether. The residue was heated for 10 min at 100°. After cooling, the residue was acidified with N–HCl and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 7 g). Elution with n-hexane–EtOAc (20:1) gave a crude product (72 mg) with the intact ethylene acetal group. This was dissolved in 35% $HClO_4$–ether (2:3, 2 ml) at 0–5°. The mixture was stirred for 10 min, neutralized to pH 7–8 with K_2CO_3 aq and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by prep TLC (Merck Kieselgel G, developed with C_6H_6–MeOH: 4:1) to give 41 mg (42.6%) of crystalline (±)-**3**. This was recrystallized from MeOH to give 13 mg of pure (±)-ascochlorin **3**, as prisms, m.p. 142–146°; ν_{max} (KBr) 3300 (m), 2980 (m), 1705 (s), 1615 (vs), 1450 (m), 1420 (s), 1375 (m), 1285 (s), 1250 (vs), 1170 (m), 1110 (m), 970 (w), 905 (w) 815 (w), 780 (w), 730 (w), 710 (w), 630 (w), 585 (w), 530 (w) cm^{-1}; ν_{max} ($CHCl_3$) 3530 (m), 1705 (s), 1630 (s), 1420 (m), 1375 (m), 1285 (m), 1250 (s) cm^{-1}; δ (400 MHz, $CDCl_3$) 0.70 (3H, s), 0.81 (3H, d, J = 6.59 Hz), 0.83 (3H, d, J = 6.59 Hz), 1.60 (1H, m), 1.92 (3H, s), 1.95 (2H, m), 2.39 (3H, m), 2.60 (3H, s), 3.53 (2H, d, J = 7.33 Hz), 5.39 (1H, d, J = 16.12 Hz), 5.51 (1H, t, J = 7.33 Hz), 5.90 (1H, d, J = 16.12 Hz), 6.39 (1H, s), 10.14 (1H, s), 12.70 (1H, s); MS: *m/z* 404 (M^+); TLC (Merck Kieselgel G developed with C_6H_6–MeOH = 4 : 1) R_f 0.62. Our synthetic (±)-(2′E,4′E)-**3** was identical with the natural (−)-**3** on the basis of IR ($CHCl_3$ and KBr: Coincidence of IR spectrum (KBr) indicated that (±)-**3** is not a racemic compound but a racemic mixture.), NMR, MS and TLC comparisons. (Found: C, 67.90; H, 7.15. Calc. for $C_{23}H_{29}O_4Cl$: C, 68.22; H, 7.22%.) (ii) (2′Z,4′E)-**3**. In the same manner as above, (2′Z,4′E)-**3** was obtained, m.p. 180–184°; ν_{max} (KBr) 3450 (m), 3280 (m), 2980 (m), 1715 (sh. m), 1700 (s), 1635 (s), 1460 (m), 1420 (m), 1380 (m), 1330 (w), 1285 (m), 1250 (s), 1170 (m), 1155 (w), 1115 (m), 965 (m), 915 (m), 825 (m), 800 (m), 790 (m), 605 (m), 590 (m) cm^{-1}; ν_{max} ($CHCl_3$) 3540 (m), 2980 (m), 1705 (s), 1630 (vs), 1425 (m), 1375 (m), 1290 (s), 1255 (vs), 1110 (m) cm^{-1}; δ (400 MHz, $CDCl_3$) 0.82 (3H, s), 0.85 (3H, d, J = 6.59 Hz), 0.88 (3H, d, J = 6.59 Hz), 1.66 (1H, m), 1.81 (3H, s), 1.94 (2H, m), 2.45 (3H, m), 2.59 (3H, s), 3.55 (2H, d, J = 7.33 Hz), 5.49 (1H, t, J = 7.33 Hz), 5.49 (1H, d, J = 16.11 Hz), 6.44 (1H, s), 6.69 (1H, d, J = 16.11 Hz), 10.13 (1H, s), 12.7 (1H, s), MS: *m/z* 404 (M^+); TLC (Merck Kieselgel G, developed with C_6H_6–MeOH = 4:1) R_f 0.62 (same as that of (2′E,4′E)-**3**). (Found: C, 68.37; H, 7.20. Calc. for $C_{23}H_{29}O_4Cl$: C, 68.22; H, 7.22%.)

(EZ)-3-*Methyl*-2-*penten*-4-*yn*-1-*ol EE ether* **23c**. p-TsOH·H_2O (15 mg) was added to a soln of **23a** (15.32 g, 0.159 mole) and ethyl vinyl ether (30.6 ml, 0.32 mole) in dry ether (80 ml) with stirring and ice-cooling. The mixture was stirred for 3 h at 0—5°. It was then washed with 5% K_2CO_3 aq and brine, dried (K_2CO_3) and concenttrated *in vacuo*. The residue was distilled to give 25.46 g (95.0%) of **23c**, b.p. 74–75°/10 mm; n_D^{23} 1.4470; ν_{max} 3300 (m), 2090 (w), 1635 (w), 1130 (s), 1095 (s), 1055 (s), 1030 (s) cm^{-1}; δ (CCl_4) 1.13 (3H, t, J = 7 Hz), 1.20 (3H, d, J = 5 Hz), 1.83 and 1.87 (total 3H, each s), 2.64 and 3.01 (total 1H, each s), 3.12–3.70 (2H, m), 4.07 (2H, d, J = 7 Hz), 4.54 (1H, q, J = 5 Hz), 5.72 (1H, t, J = 6 Hz); GLC (Column, SE 30, 1.5 m × 2 mm at 75°; Carrier gas, N_2, 2 kg/cm^2): R_t 6.33 min (80.7%, (*Z*)-isomer), 7.55 min (12.3%, (*E*)-isomer). This was directly employed in the next step.

(±) - (2EZ,4E) - 5 - (1′ - *Methyl* - 3′ - *oxocyclohexyl*) -

3 - *methyl* - 2,4 - *pentadien* - 1 - *ol* **33a**. This was prepared in the same manner as described for the synthesis of **24** employing the following materials: **23c** (9.4 g, 56 mmole), $(n\text{-Bu})_3SnH$ (19 ml, 71 mmole), AIBN (trace), n-BuLi (1.55 M in n-hexane, 46 ml, 71.6 mmole), n-PrC≡CCu (6.6 g, 51 mmole), $(Me_2N)_3P$ (16 ml, 88mmole) and 32 (5 g, 45 mmole). The crude product (12.5 g) obtained after chromatographic purification over SiO_2 (Merck Kieselgel 60, Art 7734, 300 g) was dissolved in 75% AcOH aq (100 ml). The soln was stirred and heated at 40" for 10 min. It was then diluted with water and extracted with ether. The ether soln was washed with dil $NaHCO_3$ soln, water and brine, dried ($MgSO_4$) and concentrated in *vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 200 g). Elution with n-hexane–EtOAc (10: l-2: 1) gave 7.01 g (60.3% from 32 or 75.4% basing on the amount of the consumed 32) of **33a**, n_D^{18} 1.5210; ν_{max} 3425 (m), 1705 (s), 1220 (m), 1000 (m), 970 (s) cm^{-1}; δ (CCl_4) 1.06 (3H, s), 1.46–2.06 (7H, m), 2.062.46 (4H, m), 3.44 (1H, br. s), 4.11 (2H, d, J = 7 Hz), 5.26-5.74 (2H; m), 5.98 and 6.33 (total 1H, each d, J = 15 Hz); MS: m/z 208 (M^+). This was employed in the next step without further purification.

(±) - (2EZ,4E) - 5 - (1' - *Methyl* - 3' - *oxocyclohexyl*) - 3 - *methyl* - 2,4 - *pentadienyl acetate* 33b. Acetylation of 33a (5.34 g) with Ac_2O (3.7 ml) and C_5H_5N (50 ml) was followed by the usual work-up. The chromatographic purification (Merck Kieselgel 60, Art 7734, 30 g) of the crude product gave 5.9 g (91.9%) of **33b**, n_D^{20} 1.5057; ν_{max} 1740 (s), 1710 (s), 1230 (s) cm^{-1}; δ (CCl_4) 1.07 (3H, s), 1.76 (7H, br. s), 1.96 (3H, s), 2.01-2.41 (4H, m), 4.58 (2H, d, J = 7 Hz), 5.21-5.72 (2H, m), 5.99 and 6.39 (total 1H, each d, J = 15 Hz); MS: m/z 250 (M^+). (Found: C, 71.41; H, 8.80. Calc. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.)

(±) - (2EZ,4E) - 5 - (3',3' - *Ethylenedioxy* - 1' - *methylcyclohexyl*) - 3 - *methyl* - 2,4 - *pentadienyl acetate* **34a**. In the same manner as described for the synthesis of **28a**, 33b (2.59 g, 10.3 mmole), 3-methoxy-1,3-dioxolane (9.9 ml, 103 mmole), MeOH (0.3 ml, 7.5 mmole) and p-TsOH·H_2O (10 mg) yielded 2.7 g (88.6%) of **34a** after chromatographic purification, n_D^{21} 1.5090; ν_{max} 1735 (s), 1645 (w), 1230 (s), 1085 (s), 1020 (s), 960 (s) cm-'; δ (CCl_4) 1.05 and 1.09 (total 3H, each s), 1.48 (8H, br. s), 1.75 (3H, br. s), 1.93 (3H, s). 3.75 (4H, s), 4.52 (2H, d, J = 7 Hz), 5.10–5.91 (2H, m), 5.94 and 6.26 (total 1H, each d, J = 15 Hz; MS: m/z 294 (M+). (Found: C, 69.30; H, 8.85. Calc. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90%.)

(±)-(2EZ,4E) - 5 - (3',3' - *Ethylenedioxy* - 1' - *methylcyclohexyl*) - 3 - *methyl* - 2,4 - *pentadien* - 1 - *ol* **34b**. In the same manner as described for the synthesis of **28b**, **34a** (11.5 g) was hydrolyzed with K_2CO_3 in MeOH aq to give 10.3 g (98.3%) of **34b** after chromatographic purification, n_D^{21} 1.5190; ν_{max} 3400 (m), 1080 (s) cm^{-1}; δ (CCl_4) 1.08 (3H, s), 1.50 (9H, br. s), 1.72 and 1.80 (total 3H, each s), 3.80 (4H, s), 4.10 (2H, d, J = 7 Hz), 5.13–6.53 (3H, m). This was employed in the next step without further purification.

(±) - (2EZ,4E) - 5 - (3',3' - *Ethylenedioxy* - 1' - *methylcyclohexyl*) - 3 - *methyl* - 2,4 - *pentadienyl bromide* **34c**. In the same manner as described for the synthesis of **28c**, **34b** (2.22 g, 8.3 mmole) gave 2.6 g (quantitative) of crude **34c**, ν_{max} 1640 (w), 1610 (w), 1080 (s) cm^{-1}; δ (CCl_4) l.lOand 1.15 (total 3H. each s), 1.52 (8H. br. s), 1.80 (3H, br. s), 3.78 (4H, s), 3.95 and 4.02 (total 2H, each d, J = 8 Hz), 5.12–6.83 (3H, m). This was employed in the next step without further purification.

(±) - (2'EZ,4'E) - 3 - [5' - (3",3" - *Ethylenedioxy* - 1" - *methylcyclohexyl*) - 3' - *methyl* - 2',4' - *pentadienyl*] - 2,4 - *dimethoxy* - 6 - *methyl* - 1,4 - *cyclohexadiene* **35**. In the same manner as described for the synthesis of 29, **34c** (2.6 g) and 7 (1.4 g) yielded 1.38 g (43.0% from **34b**) of **35** after chromatographic purification, n_D^{22} 1.5216; ν_{max} 1690 (s), 1655 (m), 1225 (s), 1205 (s), 1150 (s), 1085 (s) cm^{-1}; MS: *m/z* 388 (M^+). This was employed directly in the next step.

(±) - (2'EZ,4'E) - 3 - [5' - (3",3" - *Ethylenedioxy* - 1" - *methylcyclohexyl*) - 3' - *methyl* - 2',4' - *pentadienyl*] - 1,5 - *dichloro* - 6 - *methyl* - 2,4 - *cyclohexanedione* **36**. In the same manner as described for the synthesis of 30, **35** (1.28 g, 3.3 mmole) was treated with NCS (970 mg, 7.2 mmole) in the presence of $CaCO_3$ (91 mg, 0.9 mmole) in DMF (13 ml)–H_2O (1.48 ml). Subsequent work-up was followed by chromatographic purification (Mallinckrodt CC-7, 25 g) to give 720 mg (50.9%) of 36, ν_{max} 3200 (m), 2650 (w), 1620 (s). 1080 (s) cm-'; MS: m/z 432, 430, 428 (M^+, 1: 3.2: 4.8; M.W. = 429.384).

(±) - (2'EZ,4'E) - 4 - *Chloro* - 2 - [5' - (3",3" - *ethylenedioxy* - 1" - *methylcyclohexyl*) - 3' - *methyl* - 2',4' - *pentadienyl*]*orcinol* **37**. In the same manner as described for the synthesis of 31, 36 (720 mg, 1.68 mmole) was heated under reflux with DBU (1.3 ml) in THF (3.6 ml). Subsequent work-up was followed by chromatographic purification (Mallinckrodt CC-7,24 g) to give 435 mg (66.5%) of 37, ν_{max} 3350 (m), 1615 (m), 1595 (m), 1460 (s), 1420 (s), 1355 (s), 1170 (s), 1085 (s) cm-'; δ (CCl_4) 1.02 and 1.10 (total 3H, each s), 1.50 (8H, br. s), 1.73 and 1.81 (total 3H, each br. s), 2.17 (3H, s), 3.40 (2H, d, J = 7 Hz), 3.80 (4H, s), 5.02–6.78 (6H, m); MS: m/z 392 (M^+).

(±) - 5 - *Chloro* - 2,4 - *dihydroxy* - 6 - *methyl* - 3 - [5' - (1" - *methyl* - 3" - *oxocyclohexyl*) - 3' - *methyl* - 2',4' - *pentadienyl*]*benzaldehyde* **5**. (i) (±)-*Bisnorascochlorin* (2'E,4'E)-**5**. In the same manner as described for the synthesis of 3, 37 (126 mg, 0.32 mmole) was treated with EtMgBr (0.64 mmole) in ether and $HC(OEt)_3$ (0.1 ml, 0.62 mmole) to give 59 mg (43.7%) of a crude product with the intact ethylene acetal group. This (178 mg) was dissolved in ice-cooled 35% $HClO_4$–ether (1: 1, 4 ml). The mixture was stirred for 5 min at O-5". The conventional work-up gave 150 mg (94.5% from the acetal or 41.3% from 37) of a mixture of (2'*E*,4'*E*)-**5** and (2'*Z*,4'*E*)-**5**. These (83 mg) were separated by prep TLC (Merck Kieselgel G; developed with C_6H_6–MeOH = 4:1) to give (2'*E*,4'*E*)-**5** (31 mg), m.p. ~ 100" (sinter at 65") (from MeOH); ν_{max} ($CHCl_3$ 3650 (w), 3525 (m), 2980 (m), 1705 (s), 1630 (s), 1420 (m), 1285 (s), 1250 (s) cm-'; 6 ($CDCl_3$) 1.01 (3H, s), 1.50-2.00 (4H, m), 1.80 (3H, m), 2.00-2.37 (4H, m), 2.51 (3H, s), 3.39 (2H, d, J = 7 Hz), 5.03–5.60 (2H, m), 5.81 (1H, d, J= 17 Hz), 7.12 (1H, s), 9.97 (1H, s), 12.52 (1H, s); MS: m/z 376.1431. Calc. for $C_{21}H_{25}O_4Cl$: 376.1441. (Found: C, 64.21; H, 7.12. Calc. for $C_{21}H_{25}O_4Cl$·MeOH: C, 64.62; H, 7.15%.) The presence of MeOH in the crystals was proved by the MS showing the presence of M+ due to MeOH. (ii) (2'*Z*,4'*E*)-**5**. From the less polar zone of the prep TLC, (2'*Z*,4'*E*)-**5** (22mg) was obtained, m.p. 147-152" (from MeOH); ν_{max} ($CHCl_3$) 3525 (m). 2960 (m), 1785 (w), 1705 (s), 1630 (vs), 1455 (m), 1420 (m), 1375 (m), 1285 (s), 1250 (vs), 1110 (m), 970 (m) cm^{-1}; δ ($CDCl_3$) 1.11 (3H, s), 1.72 (7H, br. s), 2.10-2.35 (4H, m), 2.52 (3H, s), 3.44 (2H, d, J = 7 Hz), 5.15-5.61 (1H, m), 5.43 (1H, d, J= 17 Hz), 6.72 (1H, d, J= 17 Hz), 7.15 (1H, s), 10.00 (1H, s), 12.55 (1H, s); MS: m/z 376.1438. Calc. for $C_{21}H_{25}O_4Cl$: 376.1441. (Found: C, 66.28; H, 6.66. Calc. for $C_{21}H_{25}O_4Cl$: C, 66.92; H, 6.69%.)

Acknowledgements-We thank Prof. G. Tamura, this Department, for his gift of the authentic samples of ascofuranone and ascochlorin. Financial support by Otsuka Pharmaceutical Co. Ltd. is gratefully acknowledged. This work was partly supported by a Grant-in-Aid for Special Project Research, Japanese Ministry of Education, Science and Culture.

REFERENCES

[1] G. A. Ellestad, R. H. Evans, Jr. and M. P. Kunstmann, *Tetrahedron* **25**, *1323 (1969)*.
[2] H. Sasaki, T. Okutomi, T. Hosokawa, Y. Nawata and K. Ando, *Tetrahedron Letters 2541 (1972)*.
[3] H. Sasaki, T. Hosokawa, M. Sawada and K. Ando, *J. Antibiotics 26, 676 (1973)*.
[4] K. Ando, H. Sasaki, T. Hosokawa, Y. Nawata and Y. Iitaka, *Tetrahedron Letters 887 (1975)*.

[5]G. Tamura, S. Suzuki, A. Takatsuki, K. Ando and K. Arima, *J. Antibiotics 21, 539 (1968).*
[6]Y. Nawata, K. Ando, G. Tamura, K. Arima and Y. Iitaka, Ibid. 22, 511 (1969).
[7]K. Mori and K. Sato, *Tetrahedron 38, 1221 (1982).*
[8]Preliminary communication: K. Mori and T. Fujioka, *Tetrahedron Letters 24, 1547 (1983).*
[9]Preliminary communication: K. Mori and T. Fujioka, *Ibid. 23, 5443 (1982).*
[10]G. Casnati, M. Crisafulli and A. Ricca, *Ibid. 243 (1965).*
"K.-M. Chen and M. M. Joullié, *Ibid. 23, 4567 (1982).*
[12]J Magae, T. Hosokawa, K. Ando, K. Nagai and G. Tamura, *J. Antibiotics 35, 1547 (1982).*
[13]A. E. Guthrie, J. E. Semple and M. M. Joullié, *J.* Org. *Chem.* 47, 2369 (1982).
[14]K Mori, M. Ohki and M. Matsui, *Tetrahedron 30, 715 (1974).*
[15]P. J. Jenis, P. M. Wovkulich and A. B. Smith, III, *Tetrahedron Letters 4517 (1979).*
[16]T. Tsunoda, M. Suzuki and R. 'Noyori, *Ibid.* 1357 (1980).
[17]G. Stork, P. A. Grieco and M. Gregson, *Ibid.* 1393 (1969).
[18]M. Tanabe and K. T. Suzuki, *J. Chem. Soc. Chem. Commun.* 445 (1974).
[19]A. J. Birch, *J. Chem. Soc.* 430 (1944).
[20]K. Mori, M. Ohki, A. Sato and M. Matsui, *Tetrahedron 28, 3739 (1972).*
[21a]E. J. Corey and R. H. Wollenberg, *J. Am. Chem. Soc.* 96, 5581 (1974); [b]E. J. Corey and R. H. Wollenberg, *J. Org. Chem. 40,* 2265 (1975).
[22]S.-M. L. Chen, R. E. Schaub and C. V. Grudzinskas, *Ibid. 43, 3450 (1978).*