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A GENERAL SYNTHETIC METHOD FOR PRENYLATED PHENOLS OF MICROBIAL ORIGIN

SYNTHESIS OF COLLETOCHLORINS A AND B†

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Abstract—Prenylated phenols with a fully substituted benzene ring, such as colletochlorins A and B, were synthesized by first prenylating 1,5 - dimethoxy - 3 - methyl - 1,4 - cyclohexadiene and then effecting the aromatization of the prenylated product.

Recent discoveries of antiviral antibiotics such as ascochlorin[1,2] and ascofuranone[3] evoked our interest in devising a general synthetic method for these prenylated phenols of microbial origin. Herein we report our initial efforts toward the synthesis of ascochlorin, which resulted in the synthesis of two simpler natural prenylated phenols, colletochlorin B **1**[4] and colletochlorin A **2**[5] (Fig. 1).

The existing method for prenylation of phenols is illustrated by Canonica's synthesis of methyl mycophenolate C[6]. Alkylation of **A** with **B** gave **C** in 36% yield when Ag_2O was used as a base (Fig. 2). We tested the

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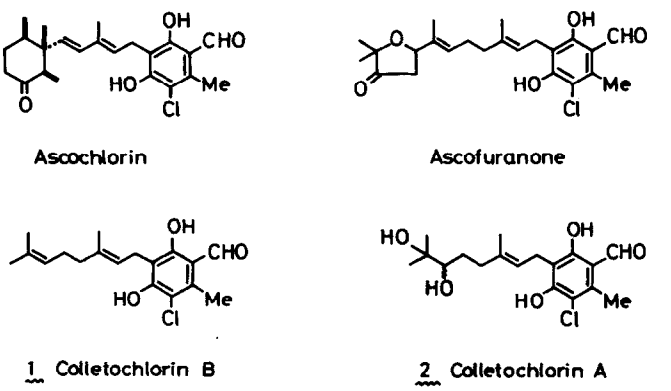

Fig. 1.

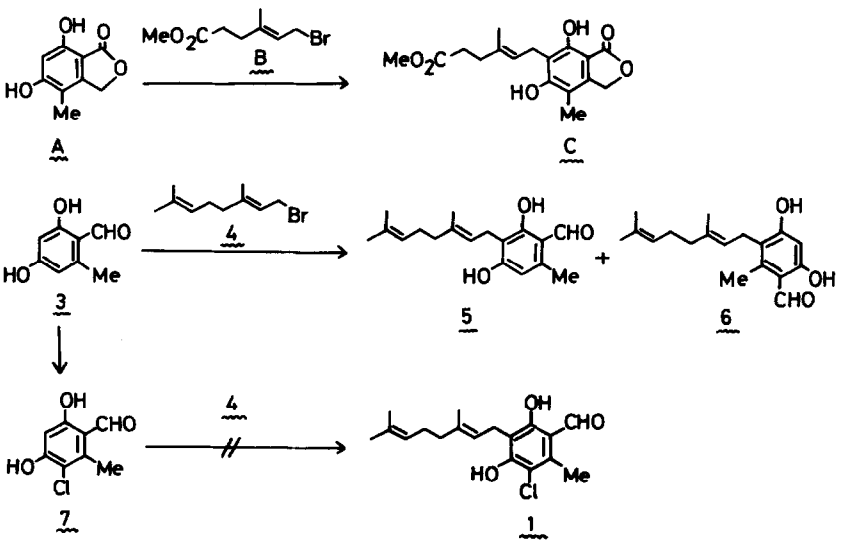

Fig. 2.

applicability of this method in our case. Thus orcylaldehyde **3** was alkylated with geranyl bromide **4** using Ag_2O as a base. Even in the presence of a crown ether, the yield of the desired product **5** was disappointingly low (7.6%) and an undesired isomer **6** was also obtained in 4.6% yield. With farnesyl bromide as an alkylating agent, no prenylated product was obtained. Alkylation of 5-chloroorcylaldehyde **7** with geranyl bromide **4** was not successful either, due to the deactivating effect of the Cl atom. At this point we decided to develop a new method which proved to be more fruitful.

C-Alkylation of phenols generally accompanies formation of undesired regioisomer(s) and O-alkylation product(s). To circumvent these difficulties, use of 1,5 - dimethoxy - 3 - methyl - 1,4 - cyclohexadiene **9a** as the equivalent synthon of orcinol was envisaged (see Ref. 7). After alkylating **9a**, however, the alkylated diene should be aromatized and functionalized to give the desired fully substituted benzene ring system in **1** and **2**. Only very mild reactions should be employed for this purpose so as not to damage the vulnerable side chains of **1** and **2**. We first solved this aromatization problem (Fig. 3). The diene **9a** was prepared from orcinol **8a** by methylation to orcinol dimethyl ether **8b**[8] followed by Birch reduction (Li/liq NH_3-THF-t-BuOH) in 69% overall yield. Treatment of **9a** with 2 eq of N-chlorosuccinimide (NCS) in the presence of a small amount of $CaCO_3$ in DME-H_2O afforded a dichlorodiketone **10a** in 50% yield. This was heated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF to give 4-chloroorcinol **11a**, m.p. 138–139°, in 25% yield. The spectral data of **11a** was identical with those reported for colletochlorin G by Kosuge.[9] Direct comparison of the synthetic product with an authentic sample of **11a** prepared by the known methods[10,11] confirmed its structure.

With this success in hand we then attempted the introduction of a formyl group. For this purpose a model compound **11b** with an alkyl side-chain was synthesized. Alkylation of **9a** with n-octyl bromide proceeded smoothly in 88% yield by employing t-BuLi in THF-HMPA. This was converted to **11b** by the same sequence of reaction as described for **11a** in 29% yield. After some experimentation, a formyl group was successfully introduced into **11b** giving **12**, m.p. 70–72°, in 75% yield by the Duff reaction [12–14] employing hexamethylenetetramine (urotropine) in AcOH. The overall yield of **12** from **9a** was 19%. The Duff reaction is mild enough to allow its application for our purpose.

By employing geranyl bromide **4** instead of n-octyl bromide in the alkylation step, colletochlorin B **1**[4] was synthesized in the following manner. Colletochlorins A **2** and B **1** are fungal metabolites isolated from culture filtrate of *Colletotrichum nicotianae* by Kosuge *et al.*[4,5,9] They are structurally similar to ascochlorin and nice targets to test the generality of our synthetic method. Due to the presence of two isolated double bonds in the carbon chain which caused side-reactions, the yield was only moderate in each step and **11c** was obtained in 12% overall yield from **9a**. Introduction of a formyl group by the Duff reaction went smoothly to give crude **1** in 52% yield (218 mg). Upon hplc analyses, however, **11c** and **1** were found to be impure and contained about 1/3 of unknown impurities. Therefore crude **1** was purified by preparative tlc to give 11 mg of pure **1**, m.p. 90–91°, together with 20 mg of a by-product, m.p. 100–101°. Our synthetic colletochlorin B showed an NMR spectrum superimposable to that of the natural product. By examining its NMR and MS data the by-product was shown to be **14**. The compound contaminated in **11c** was therefore **13**. At present we have no explanation for this abnormal reduction of the terminal double bond.

Finally (±) - colletochlorin A **2** was synthesized by employing the acetonide of 6,7 - dihydroxy - 6,7 - dihydrogeranyl bromide **19** as the alkylating agent (Fig. 4). This bromide **19** was prepared from geranyl acetate **15** in 54% overall yield as follows. Hydroxylation of geranyl acetate with OsO_4 and N-methylmorpholine-N-oxide[15] yielded a diol **16**. This was converted to an acetonide **17**. Hydrolysis of the acetate **17** with K_2CO_3 yielded an alcohol **18**. This was treated with PBr_3 to give the bromide **19**. Alkylation of **9a** with **19** afforded **20** as an oil. Chlorination-dehydrochlorination of **20** yielded a phenol **22**, m.p. 91–92°, in 12.7% overall yield from **9a**. Formylation of **22** was followed by the removal of the acetonide protecting group to give (±) - colletochlorin A **2**, m.p. 120–122°, whose NMR spectrum was identical with that of the natural product.

In conclusion the present method for the synthesis of prenylated phenols was proved to be quite a general one owing to its mildness, enabling us to achieve the first

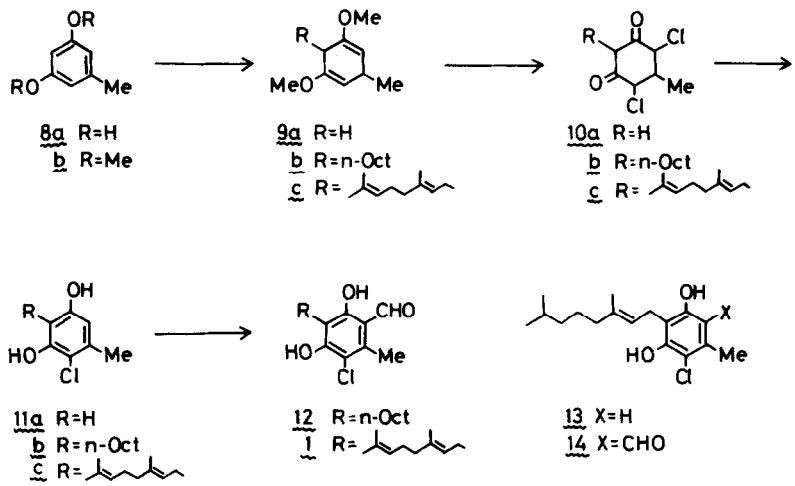

Fig. 3.

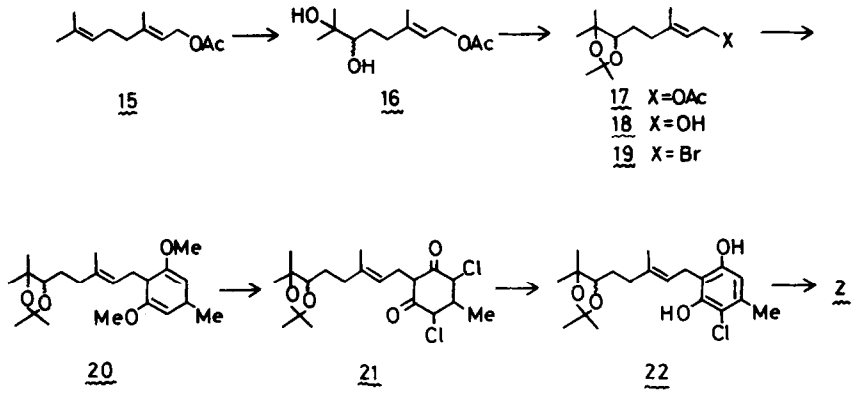

Fig. 4.

synthesis of colletochlorins A and B. Synthesis of ascochlorin and ascofuranone is now under way 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 determined on a Jasco IRA-1 or A 102 spectrometer. NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer. Mass spectra were recorded on a Hitachi RMU-6L spectrometer at 70 eV. Glc analyses were performed on a Yanaco GCG-550F gas chromatograph.

3 - *Geranylorcylaldehyde* **5** *and* 5 - *geranylorcylaldehyde* **6**. A soln of dicyclohexyl - 18 - crown - 6 (3.35 g) in dry dioxan (30 ml) was added to a stirred mixture of **3** (1.0 g) and Ag_2O (2.3 g) in dry dioxan (30 ml). The mixture was stirred for 30 min at room temp under Ar. Then geranyl bromide (2.3 g) was added dropwise to the stirred mixture. The stirring was continued for 2 days at 80°. The resulting dark brown mixture was filtered through Celite. The filtrate was concentrated *in vacuo* to give 7.0 g of an oil. This was chromatographed over SiO_2 (Merck Kieselgel 60, 70 g) to give 600 mg of a mixture of **5** and **6**. This was further purified by chromatography (Merck Kieselgel 60, 60 g) to give two pure compounds. From the earlier eluted fractions 143 mg (7.6%) of **5** was obtained as prisms from C_6H_6-pet. ether, m.p. 109–110°, ν_{max} 3250 (br.m), 1620 (s), 1590(s), 1420 (m), 1310 (w), 1290 (w), 1240 (s), 1220 (s), 1190 (m), 1170 (s), 1130 (m), 910 (w), 860 (w)cm^{-1}; δ (100 MHz, $CDCl_3$) 1.54 (3H,s), 1.62 (3H,s), 1.73 (3H,s), 1.99 (4H, br.m), 2.44 (3H,s), 3.24 (2H,d,J = 6.5 Hz), 4.96 (2H,br.m), 6.14 (1H,s). 10.02 (1H,s), 12.27 (1H,s). (Found: C, 74.61; H, 8.66. Calc for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39%). From the later eluted fractions 87 mg (4.6%) of **6** was obtained as prisms from MeOH–water, m.p. 105–107°, ν_{max} 3100 (br,m), 1600 (s), 1320 (w), 1300 (m), 1280 (m), 1260 (s), 1220 (w), 1175 (w), 1100 (w), 1000 (w), 880 (w), 830 (m), 750 (m) cm^{-1}; δ ($CDCl_3$) 1.60 (3H,s), 1.68 (3H,s), 1.80 (3H,s), 2.08 (4H, br.m), 2.48 (3H,s), 3.36 (2H,d,J = 6.4 Hz), 5.05–5.30 (2H,br), 6.16 (1H,s), 10.00 (1H,s), 12.66 (1H,s). Both **5** and **6** were converted to the corresponding diacetates in the conventional manner. In their NMR spectra, the diacetate derived from **5** showed a signal due to H-Ar at $\delta = 6.61$, while that from **6** showed at $\delta = 6.79$. This was in accord with the assigned structure.

5 - *Chloroorcylaldehyde* **7**. SO_2Cl_2 (0.36 ml) was added dropwise to a stirred soln of **3** (1.0 g) in dry ether (5 ml) under Ar. The mixture was stirred and heated under reflux for 10 min. After cooling, the mixture was diluted with ether. The ether soln was washed three times with 10% $NaHCO_3$ aq. The $NaHCO_3$ aq was acidified with 3N HCl and extracted with ether. The ether soln was washed with NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residual solid was recrystallized from MeOH–H_2O to give 250 mg (18%) of 3,5 - dichloroorcylaldehyde as needles, m.p. 137–138°, ν_{max} 3100 (br,m), 1610 (s) cm^{-1}; δ (CCl_4 + DMSO – d_6) 2.56 (3H,s), 10.11 (1H,s), 12.91 (1H,s). The original ether soln was washed three times with 10% KOH aq. The combined KOH aq was acidified with 3N HCl and extracted with ether. The ether soln was washed with NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residual solid was recrystallized from ligroin to give 878 mg (71%) of **7** as needles, m.p. 130–132°, ν_{max} 1600 (s) cm^{-1}; δ (CCl_4 + acetone d_6) 2.62 (3H,s), 6.33 (1H,s), 9.60 (1H,br.s), 10.11 (1H,s), 12.36 (1H,s); ^{13}C-NMR (acetone-d_6) 14.68, 102.20, 111.51, 114.26, 142.45, 161.41, 164.86, 194.76; MS: *m/z* 186, 188 (2.8 : 1) (M^+). (Found: C, 52.18; H, 3.77. Calc. for $C_8H_7O_3Cl$: C, 51.49; H, 3.78%).

1,5 - *Dimethoxy* - 3 - *methyl* - 1,4 - *cyclohexadiene* **9a**. Li (1.5 g) was added portionwise during 30 min to a stirred soln of **8b** (3.5 g) in dry THF (23 ml), t-BuOH (23 ml) and liq NH_3 (160 ml). Then the mixture was stirred at −30 ~ −40° for 6 hr. EtOH was added to destroy the excess Li. NH_3 was allowed to evaporate. The residue was diluted with water and concentrated *in vacuo* to remove THF, t-BuOH and EtOH. The residue was extracted with ether. The ether soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 2.6 g (73%) of **9a**, b.p. 75–76°/9 mm, n_D^{20} 1.4780; ν_{max} 3070 (w), 3010 (m), 2980 (s), 2930 (m), 2880 (m), 2830 (m), 1695 (s), 1665 (m), 1240 (s), 1210 (s), 1150 (vs), 1030 (m), 900 (m), 815 (m) cm^{-1}; δ (CCl_4) 1.03 (3H,d,J = 6 Hz), 2.63 (2H,s),2.80–3.17 (1H,br), 3.40 (6H,s), 4.36 (2H,d,J = 7 Hz); glc (Column, 15% FFAP, 1.5 m × 2 mm at 80–200° (+8°/min); Carrier gas, N_2, 1.5 kg/cm^2): R_t 5.2 min (98%), impurities at 2.0, 3.0, 8.7 min. (Found: C, 70.43; H, 9.26. Calc. for $C_9H_{14}O_2$: C, 70.10; H, 9.15%).

4,6 - *Dichloro* - 5 - *methyl* - 1,3 - *cyclohexanedione* **10a**. NCS (2.5 g) was gradually added to a stirred and ice-cooled mixture of **9a** (1.5 g), $CaCO_3$ (0.23 g), dimethoxyethane (DME, 10 ml) and water (10 ml) under Ar. The stirring was continued for 3 hr at room temp. The mixture was acidified to pH2 with N HCl and extracted with ether. The ether soln was washed with water and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give 3.4 g of a crude oil. This was chromatographed over SiO_2 (Merck Kieselgel 60, 50 g) to give 0.94 g (50%) of **10a**, ν_{max} 3350 (br.s), 1730 (m), 1595 (s), 1200 (s), 1150 (s) cm^{-1}. This was used for the next step without further purification.

4 - *Chloroorcinol* **11a**. DBU (622 mg) was added dropwise to a stirred soln of crude **10a** (208 mg) in dry THF (10 ml) under Ar. The soln was stirred and heated under reflux for 3 hr. After cooling, it was acidified with N HCl to pH2 and extracted with ether. The ether soln was washed with water and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 4 g) to give 34 mg (25%) of **11a** as prisms, m.p. 138–139° (lit.[10] 138–138.5°, lit.[11] 137–138°), ν_{max} 3300 (s), 1615 (m), 1600 (s), 1335 (m), 1270 (s), 1160 (s), 990 (m) cm^{-1}; δ ($CDCl_3$ + DMSO – d_6) 2.22 (3H,s), 6.2–6.5 (2H,br.m), 7.0–8.0 (2H,br); MS: *m/z* 158, 160 (3 : 1) (M^+) (Found: C, 52.99; H, 4.44. Calc. for $C_7H_7O_2Cl$: C, 53.00; H, 4.45%).

2,4 - *Dimethoxy* - 6 - *methyl* - 3 - *octyl* - 1,4 - *cyclohexadiene* **9b**. To a soln of t-BuLi (1.6N in pentane, 21.6 ml) in dry THF (10 ml) was gradually added **9a** (5.0 g) with stirring and cooling at −65° under Ar. After stirring for 1 hr at −65°, HMPA (6.6 g) was added. After 10 min stirring the soln turned deep red. n-$C_8H_{17}Br$ (6.3 g) was slowly added and the mixture was stirred for 10 min.

Then the cooling bath was removed and the inner temp was raised to −20°. The reaction was quenched by the addition of NH_4Cl aq. The mixture was diluted with water and extracted with ether. The ether soln was washed with water and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 7.6 g (88%) of **9b**, b.p. 105–112°/0.20 mm, n_D^{23} 1.4726; ν_{max} 3030 (w), 2980 (m), 2900 (s), 2830 (s), 1680 (s), 1650 (s), 1600 (w), 1540 (w), 1460 (s), 1445 (s), 1435 (w), 1390 (m), 1225 (s), 1200 (vs), 1145 (vs), 1120 (m), 900 (m), 805 (m) cm^{-1}; δ (CCl_4) 0.90 (3H, deformed t, J = 7 Hz), 1.05 (3H,d,J = 7 Hz), 1.1–1.8 (14H,m,1.23, 1.60), 2.68–2.98 (2H,m), 3.48 (6H,s), 4.4–4.6 (2H,m). (Found: C, 76.56; H, 11.32. Calc. for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35%).

4,6 - *Dichloro* - 5 - *methyl* - 2 - *octyl* - 1,3 - *cyclohexanedione* **10b**. NCS (9.1 g) was added portionwise during 1 hr to a stirred and ice-cooled mixture of **9b** (7.6 g), $CaCO_3$ (0.9 g), DME (40 ml) and water (40 ml) under Ar. The stirring was continued overnight at room temp. The mixture was acidified with N HCl to pH2, poured into water and extracted with ether. The ether soln was washed with water and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give an oil (8 g). This was chromatographed over SiO_2 (Merck Kieselgel 60, 150 g) to give 3.5 g (40%) of **10b**. This crystallized after storage in a refrigerator. Recrystallization from n-hexane gave plates, m.p. 84–85°, ν_{max} ~ 3300 (br.s), 2700 (br.m), 2250 (br.w), 1600 (s), 1250 (m), 1125 (m) cm^{-1}; MS: *m/z* 306, 308 (1.6 : 1) (M^+). (Found: C, 58.49; H, 7.78. Calc. for $C_{15}H_{24}O_2Cl_2$: C, 58.65; H, 7.81%).

4 - *Chloro* - 2 - *octylorcinol* **11b**. DBU (6.9 g) was added dropwise to a stirred soln of **10b** (3.5 g) in dry THF (30 ml) at room temp under Ar. The mixture was stirred and heated under reflux for 8 hr. After cooling, the mixture was acidified with N HCl to pH2 and extracted with ether. The ether soln was washed with water and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give an oil (4 g). This was chromatographed over SiO_2 (Merck Kieselgel 60, 100 g) to give 2.5 g (72%) of **11b**, as needles, m.p. < 30°, ν_{max} (film) 3550 (m), 3450 (sh), 2960 (s), 2930(s), 2850 (s), 1620 (m), 1585 (m), 1410 (s), 1110 (s) cm^{-1}; δ ($CDCl_3$) 0.89 (3H, deformed t, J = 7 Hz), 1.28 (12H,br), 2.26 (3H,s), 2.40–2.75 (2H,br), 5.59 (1H,s,-OH), 6.24 (1H,s); λ_{max} (MeOH) 275 nm (ϵ = 16,000); MS: *m/z* 270, 272 (3 : 1) (M^+). (Found: C, 66.49; H, 8.68. Calc. for $C_{15}H_{23}O_2Cl$: C, 66.52; H, 8.56%).

5 - *Chloro* - 3 - *octylorcylaldehyde* **12**. A mixture of **11b** (200 mg), hexamethylenetetramine (140 mg) and AcOH (10 ml) was stirred and heated at 110–120° for 3 hr under Ar. Then water (100 ml) was added and the mixture was stirred and heated under reflux for 3 hr. After cooling, it was poured into water and extracted with ether. The ether soln was washed with water and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give an oil (272 mg). This was chromatographed over SiO_2 (Mallinckrodt CC-7, 6 g) to give 165 mg (75%) of **12**. Recrystallization from MeOH–H_2O gave needles, m.p. 70–72°, ν_{max} 3200 (m), 1600 (s), 1415 (m), 1275 (m), 1235 (s), 1175 (sh), 1125 (s), 1095 (m), 1015 (m), 915 (w), 855 (w), 800 (w), 750 (w), 710 (w) cm^{-1}; δ (100 MHz, $CDCl_3$) 0.85 (3H, deformed t, br), 0.97–1.70 (12H, br.s, 1.25), 2.58 (3H,s), 2.50–2.75 (2H,m), 10.10 (1H,s), 12.59 (1H,s,-OH); λ_{max} (MeOH) 293 nm (ϵ = 10,300), 346 nm (ϵ = 5,100); MS: *m/z* 298, 300 (3 : 1) (M^+). (Found: C, 64.58; H, 7.76. Calc. for $C_{16}H_{23}O_3Cl$: C, 64.30; H, 7.76%).

6 - *Geranyl* - 1,5 - *dimethoxy* - 3 - *methyl* - 1,4 - *cyclohexadiene* **9c**. In the same manner as described for the preparation of **9b**, **4** (4.5 g), **9a** (3.0 g) and 1.24N-t-BuLi (17.2 ml) yielded 3.1 g (55%) of **9c**, b.p. 118–122°/0.40 mm, n_D^{23} 1.4967; ν_{max} 3050 (w), 2950 (m), 2920 (m), 2860 (m), 1690 (m), 1655 (m), 1605 (m), 1225 (m), 1200 (s), 1145 (vs), 1050 (m), 905 (w), 805 (m) cm^{-1}; MS: *m/z* 290 (M^+). (Found: C, 78.26; H, 10.72. Calc. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41%).

4,6 - *Dichloro* - 2 - *geranyl* - 5 - *methyl* - 1,3 - *cyclohexanedione* **10c**. In the same manner as described for the preparation of **10b**, **9c** (3.45 g) and NCS (3.0 g) yielded 1.24 g (50%) of **10c**, ν_{max} 3220 (br.s), 1660 (w), 1615 (s), 1305 (m), 1255 (m), 1220 (m), 1170 (w), 1150 (w), 735 (w), 710 (w) cm^{-1}; MS: *m/z* 331, 333 (1.4 : 1) (M^+).

4 - *Chloro* - 2 - *geranylorcinol* **11c**. In the same manner as described for the preparation of **11b**, **10c** (1.24 g) and DBU (2.71 g) gave 383 mg (35%) of crude **11c** as a brown oil, ν_{max} 3540 (s), 3450 (s), 2950 (s), 2920 (s), 2850 (m), 1615 (m), 1580 (m), 1490 (m), 1450 (s), 1410 (s), 1345 (m), 1250 (m), 1150 (s), 1055 (s) cm^{-1}. hplc (Column, Whatman Partisil-5, 25 cm × 4.6 mm; Eluent, n-hexane–EtOAc 5 : 1, 1 ml/min; Detection at 280 nm): Rt 30.5 min (60%, **11c**), impurities at 27.5 min (22%, probably **13**), 34.7 min (7%), 37.7 min (11%). This was used directly for the next step.

5 - *Chloro* - 3 - *geranylorcylaldehyde* (*colletochlorin B*) **1** *and* 5 - *chloro* - 3 - (6′,7′ - *dihydrogeranyl*)*orcylaldehyde* **14**. In the same manner as described for the preparation of **12**, crude **11c** (380 mg) and hexamethylenetetramine (270 mg) yielded 218 mg (52%) of crystals. Hplc analysis revealed this to be a two-component mixture. This was purified by preparative tlc (Merck Kieselgel 60 F_{254}, n-hexane–EtOAc, 10 : 1) to give 11 mg (2.6%) of pure **1**. Recrystallization from C_6H_6–n-hexane yielded needles, m.p. 90–91°, ν_{max} 3350 (br.m), 1625 (s), 1535 (w), 1430 (m), 1335 (w), 1285 (m), 1240 (s), 1220 (sh), 1165 (m), 1120 (m), 1065 (w), 1025 (w), 965 (w), 910 (m), 880 (w), 840 (w), 800 (m), 760 (w), 720 (w) cm^{-1}; δ (60 MHz, $CDCl_3$) 1.58 (3H,s), 1.65 (3H,s), 1.79 (3H,s), 2.01 (2H,br), 2.60 (3H,s), 3.40 (2H,d,J = 7 Hz), 4.90–5.32 (2H,m), 6.42 (1H,br.-OH), 10.14 (1H,s), 12.70 (1H,s,-OH); δ (400 MHz, $CDCl_3$) 1.57 (3H,s), 1.64 (3H,s), 1.79 (3H,s), 1.9–2.0 (2H,m), 2.05 (2H,t,J = 6.9 Hz), 2.60 (3H,s), 3.40 (2H,d,J = 7.1 Hz), 5.05 (1H,t,J = 6.3 Hz), 5.22 (1H,t,J = 7.1 Hz), 6.42 (1H,s), 10.14 (1H,s), 12.69 (1H,s); ^{13}C-NMR (25 MHz, $CDCl_3$) 14.39, 16.15, 17.61, 22.00, 25.62, 26.61, 39.78, 113.26, 113.61, 114.43, 120.46, 124.20, 131.40, 136.90, 137.60, 156.44, 162.17; 193.17, MS: *m/z* 322, 324 (2.6 : 1) (M^+); hplc (Column, Partisil-5, 25 cm × 4.6 mm; Eluent, n-hexane–THF-MeOH, 1000 : 500 : 2, 1 ml/min; Detection at 295 nm) R_t 34.5 min (98%, **1**), an impurity at 31.8 min (probably **14**). (Found: C, 66.61; H, 7.35. Calc. for $C_{18}H_{25}O_3Cl$: C, 66.96; H, 7.18%). The ^1H-NMR data of **1** were identical with those of the natural product. Preparative tlc of the crude product also afforded **14** (20 mg) as the slightly less polar fraction. This was recrystallized from MeOH–H_2O to give needles, m.p. 100–101°, ν_{max} 3350 (br.m), 1625 (s), 1535 (w), 1430 (m), 1335 (w), 1285 (m), 1240 (s), 1220 (sh), 1165 (m), 1120 (m), 1065 (w), 1020 (w), 965 (w), 910 (m), 880 (w), 835 (w), 795 (m), 790 (m), 710 (w) cm^{-1}; δ ($CDCl_3$) 0.83 (6H,d,J = 6 Hz), 1.10–1.35 (4H, m), 1.55 (1H,m), 1.76 (3H,s), 1.90–2.10 (2H,br), 2.55 (3H,s), 3.34 (2H,d,J = 7 Hz), 5.0–5.3 (1H,m), 6.33 (1H,s,-OH), 10.15 (1H,s), 12.66 (1H,s,-OH); MS: *m/z* 324, 326 (2.8 : 1) (M^+); hplc (Column, Partisil-5, 25 cm × 4.6 mm; Eluent, n-hexane–THF-MeOH, 1000 : 500 : 2, 2 ml/min; Detection at 295 nm): R_t 15.2 min (90%, **14**), impurity at 16.5 min (10%, **1**). (Found: C, 66.34; H, 7.72. Calc. for $C_{18}H_{25}O_3Cl$: C, 66.54; H, 7.76%).

6,7 - *Dihydroxy* - 6,7 - *dihydrogeranyl acetate* **16**. OsO_4 (127 mg) in t-BuOH (6.4 ml) was added to a stirred soln of **15** (30.0 g) and N-methylmorpholine-N-oxide (30.0 g) in acetone (30 ml) and water (70 ml) under Ar. The mixture was stirred for 12 hr at 50°. Then OsO_4 was reduced by stirring with $NaHSO_3$ (12 g) and Celite (2 g). The mixture was filtered and the filtrate was extracted six times with EtOAc–ether (1 : 1). The extract was dried ($MgSO_4$) and concentrated *in vacuo* to give 34.3 g of crude **16**. This was directly used for the next step. An analytical sample was prepared by chromatographic purification over Mallinckrodt CC-7 followed by distillation, b.p. 139–141°/0.25 mm, n_D^{21} 1.4691; ν_{max} 3450 (br.m), 2960 (m), 2930 (m), 2860 (m), 1740 (s), 1720 (sh), 1665 (w), 1445 (m), 1365 (m), 1235 (s), 1155 (w), 1140 (w), 1110 (w), 1070 (m), 1040 (m), 1020 (m), 950 (m) cm^{-1}; δ (CCl_4) 1.08 (3H,s), 1.11 (3H,s), 1.2–1.7 (2H,m), 1.70 (3H,s), 1.95 (3H,s), 2.0–2.3 (2H,m), 2.80 (2H,s,-OH), 3.25 (1H,dd,J_1 = 4, J_2 = 7 Hz), 4.42 (2H,d,J = 7 Hz), 5.25 (1H,t,J = 7 Hz). (Found: C, 62.78; H, 9.86. Calc. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63%).

(E) - 6,7 - O - *Isopropylidene* - 3,7 - *dimethyl* - 2 - *octene* - 1,6,7 - *triol* - 1 - *acetate* **17**. *p*-TsOH was added to crude **16** (34.3 g) to adjust its pH to 3. Then dry C_6H_6 (60 ml), 2,2-dimethoxypropane (23.1 g) and a small amount of $MgSO_4$ was added to it. The mixture was stirred overnight at room temp and filtered. The filtrate was poured into water and extracted with ether. The ether soln was washed with water, $NaHCO_3$ aq, water and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 28.5 g (69% from **15**) of **17**, b.p. 122–130°/0.25 mm, n_D^{21} 1.4448; ν_{max} 2980 (s), 2940 (s), 2860 (m), 1745 (s), 1670 (w), 1455 (m), 1380 (s), 1370 (s), 1270 (m), 1230 (s), 1200 (s),

1115 (s), 1060 (m), 1020 (s), 1000 (s), 955 (m), 935 (w), 910 (m), 855 (m), 820 (w) cm^{-1}; δ (CCl_4) 1.00 (3H,s) 1.15 (3H,s) 1.2–1.6 (2H,m), 1.24 (3H,s), 1.33 (3H,s), 1.70 (3H,s), 1.90 (3H,s), 2.0–2.3 (2H,m), 3.37 (1H,dd,J_1 = 5, J_2 = 8 Hz), 4.27 (2H,d,J = 7 Hz), 5.13 (1H,t,J = 7 Hz). (Found: C, 66.87; H, 10.02. Calc. for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69%).

(E) - 6,7 - O - *Isopropylidene* - 3,7 - *dimethyl* - 2 - *octene* - 1,6,7 - *triol* **18**. A soln of K_2CO_3 (35 g) in MeOH (20 ml) and water (100 ml) was added dropwise to a stirred and ice-cooled soln of **17** (14.6 g) in MeOH (60 ml). The stirring was continued for 6 hr at room temp. Then the mixture was poured into water and extracted with ether. The ether extract was washed with NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 11.7 g (95%) of **18**, b.p. 117–122°/0.45 mm, ν_{max} 3400 (br.m), 2940 (s), 2890 (s), 2830 (s), 1655 (w), 1440 (m), 1360 (s), 1270 (m), 1255 (m), 1225 (s), 1195 (s), 1100 (s), 1045 (m), 985 (s), 920 (w), 895 (m), 840 (m) cm^{-1}; δ (CCl_4) 1.01 (3H,s), 1.16 (3H,s), 1.23 (3H,s), 1.30 (3H,s), 1.4–1.6 (2H,m), 1.65 (3H,s), 1.9–2.4 (2H,m), 3.1 (1H,br.s,-OH), 3.50 (1H,dd,J_1 = 5.0, J_2 = 8.0 Hz), 3.95 (2H,d,J = 7 Hz), 5.38 (1H,t,J = 6 Hz). (Found: C, 68.16; H, 10.85. Calc. for $C_{13}H_{24}O_3$: C, 68.44; H, 10.60%).

(E) - 8 - *Bromo* - 2,3 -O - *isopropylidene* - 2,6 - *dimethyl* - 6 - *octene* - 2,3 - *diol* **19**. PBr_3 (0.60 g) was slowly added to a stirred and cooled soln of **18** (1.0 g) in dry ether (10 ml) at −5° under Ar. The mixture was stirred for 20 min, poured onto $NaHCO_3$ aq and extracted with ether. The ether soln was washed with $NaHCO_3$ aq, water and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give 1.1 g (86%) of **19**, ν_{max} 2980 (s), 2940 (m), 2850 (m), 1655 (m), 1450(m), 1380 (s), 1370 (s), 1270 (m), 1260 (m), 1230 (m), 1215 (s), 1200 (s), 1115 (s), 1045 (m), 1000 (s), 930 (w), 910 (w), 850 (m) cm^{-1}; δ (CCl_4) 1.02 (3H,s), 1.15 (3H,s), 1.22 (3H,s), 1.30 (3H,s), 1.4–1.7 (2H,m), 1.73 (3H,s), 2.0–2.3 (2H,m), 3.50 (1H,dd,J_1 = 5, J_2 = 8 Hz), 3.85 (2H,d,J = 8 Hz), 5.45 (1H,t,J = 8 Hz); MS: *m/z* 275, 277 (1 : 1) (M^+). This was used for the next step without further purification.

3 - [(E) - 6',7' - *Dihydroxy* - 3',7' - *dimethyl* - 2' - *octenyl*] - 2,4 - *dimethoxy* - 6 - *methyl* - 1,4 - *cyclohexadiene* - 6',7' - *acetonide* **20**. To a soln of t-BuLi (2.0M in pentane, 6 ml) in dry THF (5 ml) was slowly added **9a** (1.54 g) with stirring and cooling (−60 ~ −70°) under Ar. The stirring was continued at −60 ~ −70° for 30 min. Then **19** (2.6 g) was added dropwise. The cooling bath was removed and the reaction temp was allowed to raise to −20°. The reaction was quenched by the addition of NH_4Cl aq. The mixture was poured into water and extracted with ether. The ether soln was washed with water and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over neutral Al_2O_3 (Woelm Grade III, 160 g) to give 1.50 g (46%) of **20**, n_D^{21} 1.4804, ν_{max} 3050 (w), 2970 (s), 2950 (s), 2850 (s), 1695 (s), 1660 (m), 1465 (m), 1450 (m), 1390 (m), 1375 (s), 1365 (s), 1270 (m), 1260 (m), 1225 (s), 1200 (s), 1150 (s), 1115 (m), 1040 (m), 1000 (m), 905 (m), 850(m), 810(m)cm^{-1}; δ (CCl_4) 0.99 (3H,s), 1.02 (3H,d,J = 6 Hz), 1.13 (3H,s), 1.20 (3H,s), 1.30 (3H,s), 1.4–1.7 (2H,m), 1.54 (3H,s), 1.8–2.1 (2H,m), 2.2–2.5 (2H,m), 2.7–3.0 (2H,m), 3.42 (6H,s), 3.4–3.6 (1H,m), 4.41 (1H,t,J = 3 Hz), 4.90 (1H,t,J = 7.5 Hz); MS: *m/z* 349 (M^+ − 15). (Found: C, 72.29; H, 9.98. Calc. for $C_{22}H_{36}O_4$: C, 72.48; H, 9.96%).

4,6 - *Dichloro* - 2 - [(E) - 6',7' - *dihydroxy* - 3',7' - *dimethyl* - 2' - *octenyl*] - 5 - *methyl* - 1,3 - *cyclohexanedione* - 6',7' - *acetonide* **21**. NCS (763 mg) was added to a stirred and ice-cooled mixture of **20** (946 mg) and $CaCO_3$ (95 mg) in DME (10 ml) and water (10 ml) under Ar. The mixture was stirred overnight at room temp, then acidified with N HCl to pH2, poured into water and extracted with ether. The ether soln was washed with water and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 30 g) to give 412 mg (39%) of **21** as amorphous solid, ν_{max} 3200 (br.s), 2990 (s), 2650 (w), 1810 (w), 1740 (w), 1620 (s), 1450 (m), 1370 (s), 1305 (m), 1260 (m), 1210 (s), 1195 (s), 1110 (s), 1020 (m), 1000 (m), 910 (m), 850 (m), 835 (m) cm^{-1}; MS: *m/z* 389, 391, 393 (1 : 0.74 : 0.13) (M^+ − 15). (Found: C, 58.69; H, 7.51. Calc. for $C_{20}H_{30}O_4Cl_2$: C, 59.27; H, 7.46%).

4 - *Chloro* - 2 - [(E) - 6',7' - *dihydroxy* - 3',7' - *dimethyl* - 2' - *octenyl*] *orcinol* - 6',7' - *acetonide* **22**. DBU (250 mg) was added dropwise to a stirred soln of **21** (188 mg) in dry THF (8 ml) at room temp under Ar. The mixture was stirred and heated under reflux for 6 hr. After cooling, the mixture was acidified with N HCl to pH2 and extracted with ether. The ether soln was washed with water and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 6 g) to give 122 mg (71%) of crystalline **22**. This was recrystallized from C_6H_6–n-hexane to give prisms, m.p. 91–92°, ν_{max} 3550 (m), 3320 (s), 1615 (m), 1595 (m), 1510 (w), 1415 (s), 1350 (s), 1280 (w), 1260 (s), 1215 (s), 1205 (m), 1185 (s), 1155 (s), 1120 (s), 1090 (m), 1070 (s), 1025 (w), 1000 (s), 910 (m), 885 (m), 850 (s), 825 (m), 810 (m), 795 (m), 760 (w), 740 (m), 720 (w), 655 (m)cm^{-1}; δ ($CDCl_3$) 1.05 (3H,s), 1.18 (3H,s), 1.24 (3H,s), 1.37 (3H,s), 2.0–2.3 (2H,m), 2.22 (3H,s), 3.33 (2H,d,J = 7 Hz), 3.71 (1H,dd,J_1 = 2, J_2 = 7 Hz), 5.17 (1H,t,J = 6.5 Hz), 5.20 (1H,s,-OH), 6.18 (1H,s); MS: *m/z* 368, 370 (3.2 : 1) (M^+), 353, 355 (3.1 : 1) (M^+ − 15); hplc (Column, Partisil-5, 25 cm × 4.6 mm; Eluent, n-hexane–EtOAc (6:4), 1 ml/min; Detection at 280 nm): Rt 16.1 min (98%), impurity at 20.5 min. (Found: C, 65.42; H, 8.07. Calc. for $C_{20}H_{29}O_4Cl$: C, 65.11; H, 7.92%).

5 - *Chloro* - 3 - [(E) - 6',7' - *dihydroxy* - 3',7' - *dimethyl* - 2' - *octenyl*] *orcylaldehyde*[(±) - *colletochlorin A*] **2**. A mixture of **22** (196 mg) and hexamethylenetetramine (111 mg) in AcOH (10 ml) was stirred and heated at 112° for 3 hr. Then water (100 ml) was added and the mixture was stirred and heated under reflux for 3 hr. After cooling, it was poured into water and extracted with ether. The ether soln was washed with water and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 20 g) to give 57 mg (30%) of crystalline **2**. This was recrystallized from C_6H_6–n-hexane, m.p. 120–122°, ν_{max} 3440 (m), 3140 (m), 1625 (s), 1425 (s), 1360 (m), 1350 (m), 1325 (m), 1290 (s), 1260 (s), 1230 (w), 1210 (w), 1165 (s), 1120 (w), 1095 (w), 1080 (w), 1070 (m), 1055 (m), 1015 (w), 980 (w), 960 (m), 940 (w), 910 (w), 890 (w), 860 (w), 825 (w), 805 (w), 780 (w), 760 (m), 740 (w), 715 (w), 670 (w) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.15 (3H,s), 1.18 (3H,s) 1.4–1.7 (2H,m), 1.81 (3H,s), 2.0–2.3 (2H,m), 2.36 (2H,br.-OH), 2.59 (3H,s), 3.3–3.5 (1H,m), 3.40 (2H,d,J = 7 Hz), 5.29 (1H,t,J = 7 Hz), 6.8 (1H,br.-OH), 10.40 (1H,s), 12.60 (1H,s,OH); MS: *m/z* 338. 1290 (M^+-H_2O). Calc. for $C_{18}H_{23}O_4Cl$: 338. 12906; hplc (Column, Partisil-5, 25 cm × 4.6 mm; Eluent, n-hexane–EtOAc–MeOH (200 : 100 : 3), 4 ml/min): Rt 20.8 min (98%), impurities at 16.1, 17.4, 18.2 min. The NMR spectrum was identical with that of the natural product.

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