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# SYNTHESIS OF OPTICALLY ACTIVE FORMS OF FARANAL, THE TRAIL PHEROMONE OF PHARAOH'S ANT†

KENJI MORI* and HIRAKI UEDA‡
Department of Agricultural Chemistry, The University of Tokyo, Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

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**Abstract**—Both (3*S*,4*R*)-(+)- and (3*R*,4*S*)-(−)-enantiomers of faranal [(6*E*,10*Z*)-3,4,7,11-tetramethyl-6,10-tridecadienal] were synthesized. The former was comparable in bioactivity with that of the natural trail pheromone isolated from *Monomorium pharaonis*.

In 1977 Ritter *et al.* isolated 70 μg of a pure substance, which has a very high trail-following activity, from $10^5$ worker ants of *Monomorium pharaonis* (Pharaoh's ant).[1] This was named faranal and its structure was shown to be (3*R*,4*S*,6*E*,10*Z*)-3,4,7,11-tetramethyl-6,10-tridecadienal or its antipode.[1,2] A recent bioorganic synthesis coupled with the bioassay of the products enabled Kobayashi *et al.* to assign (3*S*,4*R*)-stereochemistry to faranal as shown in **1** on the basis of the known stereospecificity of farnesyl pyrophosphate synthetase.[3] Herein we report in detail a synthesis of both enantiomers of faranal with known absolute configuration depending entirely on organochemical methods.[4]

The structure of faranal **1** was so similar to Juvenile Hormone II[5] that we adopted the strategy previously used in our juvenile hormone synthesis.[6] Our plan was therefore to connect the two key intermediates **2b** and **3** followed by one-carbon elongation to complete the synthesis (Scheme 1).

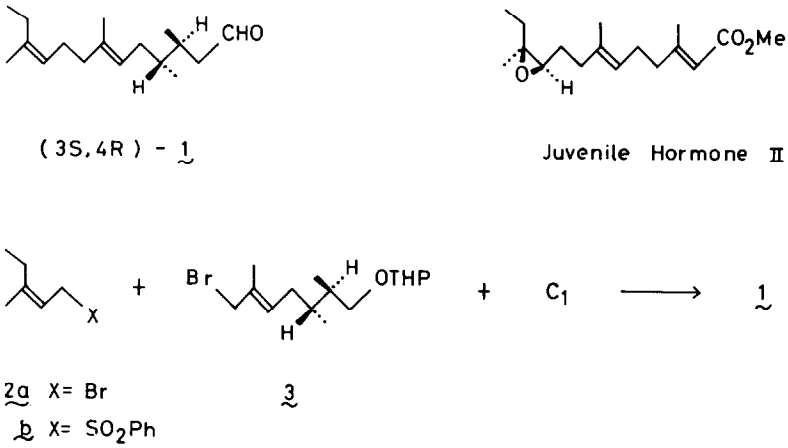
The plenylsulfone **2b** was readily obtainable in crystalline form from the known (*Z*)-alkenyl bromide **2a** by treatment with $NaSO_2Ph$ in DMF.[7] The bromide **2a** in turn was synthesized from acetylene and methyl vinyl ketone in four steps according to our method.[8]

The synthesis of the chiral bromide **3** was more complicated. Retrosynthetic analysis indicated that a racemic lactone **9** might be an ideal starting material if it could be resolved successfully (Scheme 2). An obvious precursor of **9** was *cis*-3,4-dimethyl-cyclopentanone **8**. We synthesized a sufficient amount of this ketone **8** in the following manner. Diethyl 4-cyclohexene-1,2-dicarboxylate **4** was prepared starting from butadiene and maleic anhydride.[9,10] This was converted to the required ketone **8** by essentially the same procedure as reported by Haber and Klug[11] with some modifications (Experimental). Reduction of the tosylate **5b** with LAH was successfully carried out by using N-methylmorpholine as a solvent to give **6** in 73% yield.[12] Instead of ozonolysis in the original procedure,[11] permanganate oxidation[13] was employed for the cleavage of the double bond in **6**. The overall yield of the ketone **8** from the diester **4** was 26% *via* **5a**, **5b**, **6** and **7**. Subsequent Baeyer–Villiger oxidation of the ketone **8** with MCPBA in $CHCl_3$ smoothly yielded the desired (±)-lactone **9** in 90% yield.

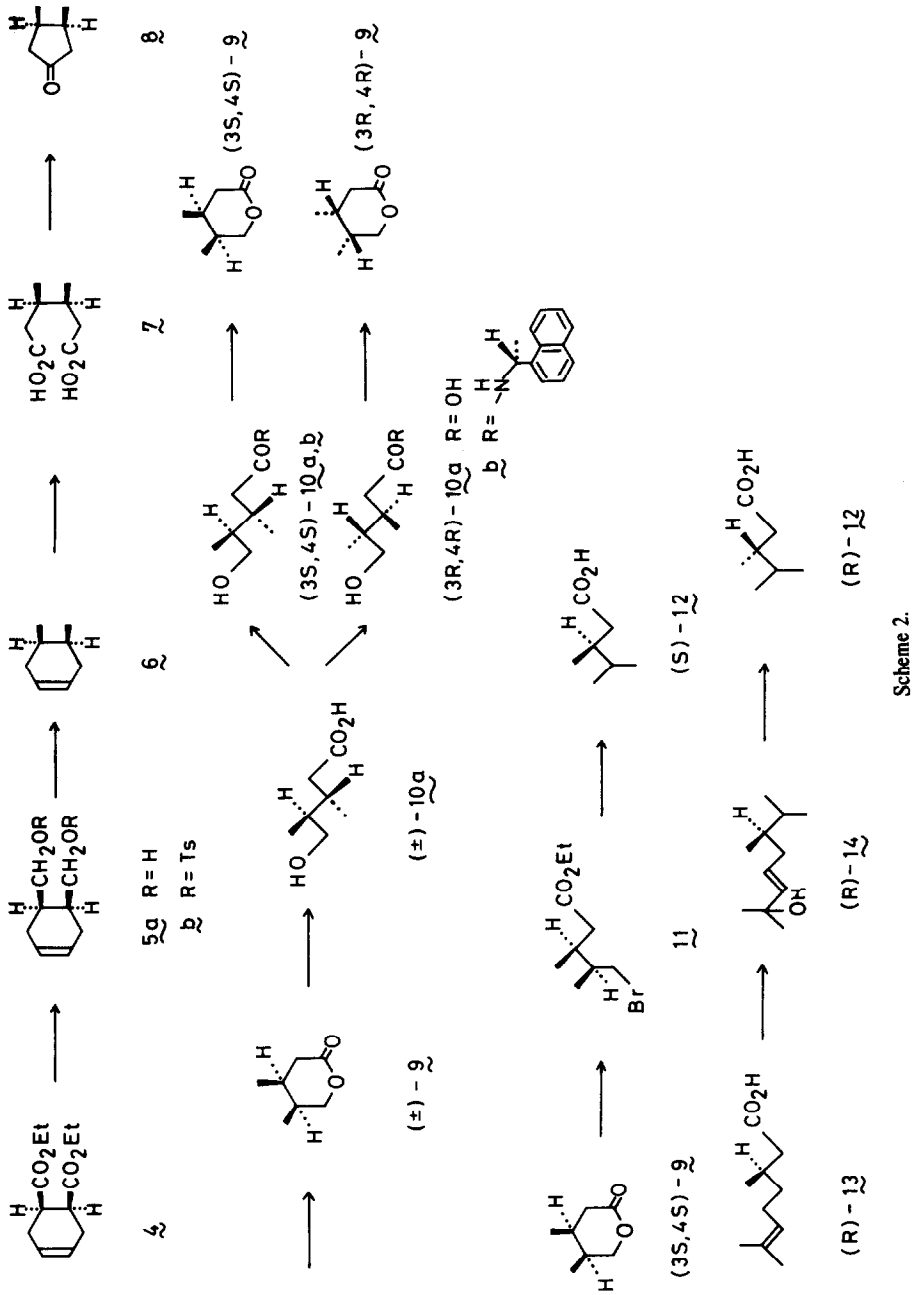
Optical resolution of the (±)-lactone **9** was achieved by first converting it to a (±)-hydroxy acid **10a** by alkaline hydrolysis followed by neutralization to pH 5. Then (*R*)-(+)-α-phenethylamine was added to **10a**. The resulting solid was recrystallized four times to give the

†Pheromone Synthesis—51. This work was presented by K.M. at the XVIth International Congress of Entomology in Kyoto, Japan, on August 8, 1980, Part 50, K. Mori and S. Kuwahara, *Tetrahedron* **38**, 521 (1982).

‡Research Fellow on leave from Otsuka Pharmaceutical Co., Ltd (1979–1981).




Scheme 1.



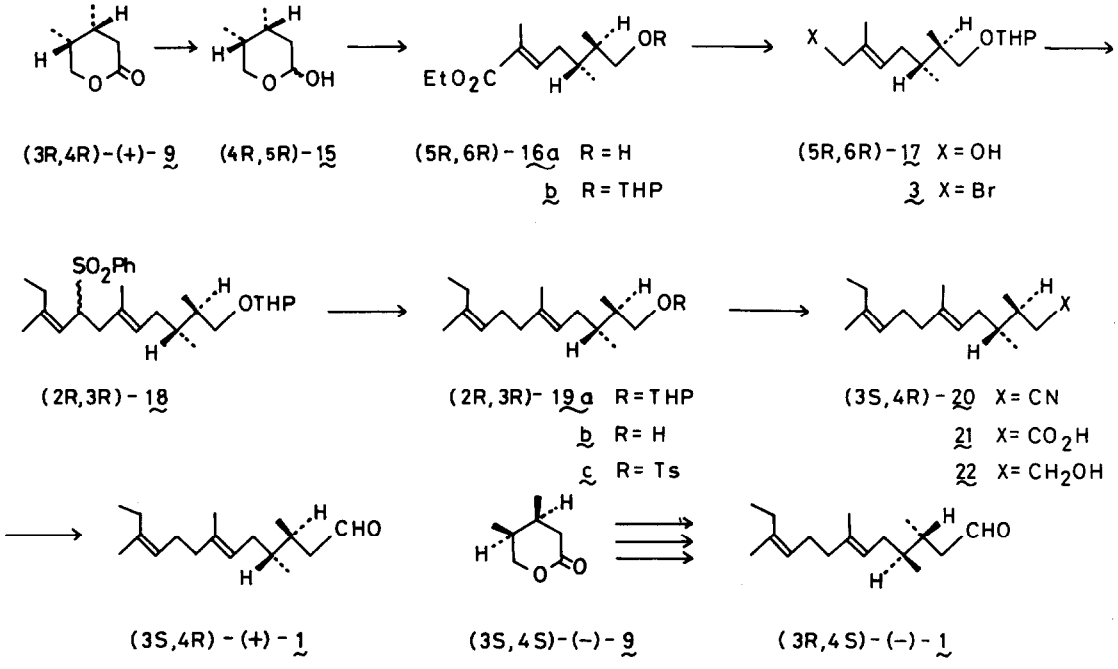
Scheme 2.

purified (+)-salt, m.p. 135.5–136.6°, $[\alpha]_D^{22}$ + 5.02° (MeOH), in 12.2% yield. Acidification of the salt yielded (−)-lactone **9**, $[\alpha]_D^{22}$ − 47.2° (MeOH). Similarly resolution of (±)-**10a** with (*S*)-(−)-α-phenethylamine afforded the (−)-salt in 9.1% yield, m.p. 133–134°, $[\alpha]_D^{22}$ − 4.96° (MeOH). This gave (+)-lactone **9**, $[\alpha]_D^{22}$ + 46.3° (MeOH), upon acidification. The absolute configuration of the resolved lactone was determined by a chemical correlation with a known compound. Thus partially resolved (−)-lactone **9**, $[\alpha]_D^{23}$ − 34.1° (MeOH), was treated with HBr–EtOH to give a bromo ester **11**. Hydrogenolysis ($H_2$/Pd–C, $CaCO_3$, MeOH) of **11** was followed by alkaline hydrolysis to give (−)-3,4-dimethylpentanoic acid **12**. An authentic sample of (*R*)-**12** was synthesized from (*R*)-(+)-citronellic acid **13** *via* an alcohol (*R*)-**14**, and found to be dextrorotatory.† The positive optical rotation of (*R*)-**12** allowed the assignment of (*S*)-configuration to (−)-**12**. The (−)-lactone was therefore (3*S*,4*S*)-**9**, while the (+)-lactone was (3*R*,4*R*)-**9**. In order to determine the optical purity of the resolved lactones **9**, they were heated with (*R*)-(+)-α-naphthylethylamine to give amide derivatives (3*S*,4*S*)-**10b** and (3*R*,4*R*)-**10b**. By analyzing their diastereomeric ratio by hplc, the optical purity of the lactones was shown to be 90% in the case of (3*R*,4*R*)-(+)-**9** and 92% in the case of (3*S*,4*S*)-(−)-**9**.

With optically active lactones **9** in hand, we proceeded to the next stage (Scheme 3). In the remaining steps to faranal, no reaction was involved which might affect the two chiral centers in **9**. The optical purity of the resolved lactone was therefore thought to be retained in the final product, faranal. All of the subsequent reactions were first carried out with the racemate to establish the reaction condition and then with the enantiomers. Reduction of (3*R*,4*R*)-(+)-lactone **9** with DIBALH gave a lactol **15** (86% yield). This was submitted to the Horner condensation with triethyl α-phosphonopropionate in the presence of NaOEt in DMF to give an ester **16a** (54% yield) contaminated with 15% of its (*Z*)-isomer as revealed by glc analysis. After protecting the OH group as a THP ether, the ester **16b** was reduced with LAH–$AlCl_3$ in THF–ether[14] to give an allylic alcohol (5*R*,6*R*)-**17** in 78% yield. This was converted to the desired bromide (5*R*,6*R*)-**3** in 52% yield by treatment with *n*-BuLi–TsCl–LiBr in ether–HMPA.[15] Alkylation of a carbanion derived from **2b** (*n*-Buli/THF-HMPA) with (5*R*,6*R*)-**3** yielded (2*R*,3*R*)-**18** in 92% yield.[7] This was reduced with Li/$EtNH_2$ to give (2*R*,3*R*)-**19a** (61% yield), whose THP-protecting group was removed (TsOH/MeOH) to afford (2*R*,3*R*)-alcohol **19b** in 87% yield. For the purpose of one-carbon elongation **19b** was tosylated to **19c** (98% yield). The tosylate **19c** was then treated with NaCN/DMSO to give a nitrile (3*S*,4*R*)-**20** in 98% yield. This was hydrolyzed with NaOH to a carboxylic acid **21** (97% yield). Reduction of the acid **21** with LAH gave an alcohol **22** in 93% yield. Oxidation of **22** with pyridinium chlorochromate (PCC)[16] concluded the synthesis yielding crude faranal **1** (72% yield). So as to remove impurities such as (6*Z*)-isomer of **1**, the crude product was purified by preparative glc to give (3*S*,4*R*)-faranal **1**, $[\alpha]_D^{23}$ + 16.2° (*n*-hexane). Similarly (3*S*,4*S*)-**9** yielded (3*R*,4*S*)-faranal **1**, $[\alpha]_D^{23}$ − 16.5° (*n*-hexane).

The synthesized faranal enantiomers were thought to be ~90% optically pure reflecting the optical purity of the starting lactone enantiomers **9**. The chemical purity of the both enantiomers of faranal was ~90% as shown by glc analysis using a capillary column. Faranal was observed as a major peak (~90%) at $R_t$ 8.90 min, while an

†Details of this conversion will be reported separately in connection with the synthesis of brassinolide, a plant-growth promoting steroid.




Scheme 3.

unidentified impurity appeared at $R_t$ 9.15 min (~10%)† The 300 MHz NMR spectra of our farnal enantiomers were kindly taken at TNO, Delft, by the courtesy of Dr. F. J. Ritter. They were identical with that of natural farnal except for some very smaller signals due to the impurities. The bioassay of our synthetic enantiomers of **1** was also carried out by Dr. F. J. Ritter *et al.* (3*S*,4*R*)-(+)-Faranal was far more active than the (−)-isomer and comparable in activity with that of the natural pheromone. When artificial trails of faranal enantiomers were directly compared in a competitive test at equal concentration (about 0.05 and about 0.5 ng/cm), the trail of (+)-faranal was clearly preferred. When the enantiomers were tested separately, the trail of (+)-faranal was very well followed by the workers of the Pharaoh's ant over a concentration range of 0.005 to 0.5 ng/cm. A trail of (−)-faranal, when tested in the absence of (+)-isomer, was followed very well at 0.5 ng/cm only. The activity of (−)-faranal may be due to the contaminating (~5%) (+)-isomer.

In conclusion the present work established the absolute configuration of the natural faranal to be (3*S*,4*R*) by organic synthetic means combined with the bioassay data.

## EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra refer to films unless otherwise specified and were determined on a Jasco IRA-1 or a Jasco A-102 spectrometer. NMR spectra were recorded at 60 MHz as $CCl_4$ soln with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated. Optical rotations were measured on a Jasco DIP-4 polarimeter.

(Z)-3-*Methyl*-1-*phenylsulfonyl*-2-*pentene* **2b**

A soln of **2a** (10.0 g) in dry DMF (10 ml) was added dropwise to a stirred soln of $NaSO_2Ph$ (11.0 g) in dry DMF (40 ml). The mixture was stirred for 6 hr at room temp. Then it was poured into ice-water and extracted with ether. The ether soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from $CH_2Cl_2$-pet. ether to give 12.29 g (89%) of **2b**, m.p. 39°, $\nu_{max}$ 3050 (w), 2960 (m), 2920 (m), 2860 (m), 1660 (w), 1580 (w), 1445 (s), 1410 (m), 1380 (m), 1355 (w), 1320 (s), 1305 (s), 1240 (m), 1210 (m), 1150 (s), 1130 (s), 1110 (m), 1085 (s), 1040 (w), 1020 (m), 1000 (m), 965 (w), 885 (m), 840 (m), 775 (m), 740 (m), 690 (m) $cm^{-1}$; $\delta$ 0.75 (3H, t, J = 7 Hz), 1.73 (3H, s), 1.79 (2H, q, J = 7 Hz), 3.80 (2H, d, J = 8 Hz), 5.17 (1H, t, J = 8 Hz), 7.40–8.05 (5H, m).

cis-1,2-*Ditoxyloxymethyl*-4-*cyclohexene* **5b**

*p*-TsCl (410 g) was added portionwise to a stirred and cooled soln of **5a** (150 g) in dry $C_5H_5N$ (1500 ml) at −5~5°. The mixture was stirred for 2 days in a cold room at 3°. Then it was poured into crashed ice and acidified with HCl soln. The solid was collected on a filter, washed thoroughly with water and air-dried. Then it was recrystallized from MeOH to give 333 g (80%) of **5b** as colorless prisms, m.p. 93–94° (lit.[11] m.p. 93.5–94.5°); $\nu_{max}$ (nujol) 1600 (m), 1355 (s), 1190 (s), 1170 (s), 960 (s), 830 (s), 810 (s), 760 (s), 665 (s) $cm^{-1}$; $\delta$ 1.41–2.51 (6H, m), 2.41 (6H, s), 3.85 (4H, d, J = 6 Hz), 5.43 (2H, br. s), 7.26 (4H, d, J = 8 Hz), 7.68 (4H, d, J = 8 Hz).

cis-4,5-*Dimethyl*-1-*cyclohexene* **6**

Solid **5b** (630 g) was added portionwise to a stirred and warmed suspension of LAH (125 g) in N-methylmorpholine (2700 ml) at 60–75°. After the addition the mixture was stirred at 70° for 2.5 hr. Then the temp was raised to 100° and the heating was discontinued. After cooling, water (820 ml) was added cautiously to the mixture and the product was steam-distilled. The distillate was collected. The upper hydrocarbon layer was separated, washed with dil HCl and water, dried ($MgSO_4$) and distilled to give 118.7 g (73%) of **6**, b.p. 121–123°, $n_D^{23}$ 1.4480; $\nu_{max}$ 3020 (m), 2950 (s), 2880 (s), 2820 (m), 1650 (w), 1450 (m), 1435 (m), 1380 (m), 1020 (m), 990 (m), 865 (m) $cm^{-1}$; $\delta$ 0.85 (6H, d, J = 7 Hz), 1.39–2.49 (6H, m), 5.46 (2H, br. s).

(3R*, 4S*)-3,4-*Dimethylhexanedioic acid* **7**

$KMnO_4$ (200 g) was added portionwise to a stirred mixture of **6** (50.3 g) and $NaHCO_3$ (40 g) in acetone (3000 ml). The mixture was stirred overnight and filtered. The filter cake was stirred with 3% $Na_2CO_3$ aq (3000 ml) and filtered. The alkaline filtrate was concentrated and acidified with conc HCl. The soln was concentrated *in vacuo* and extracted with ether. The ether soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from EtOAc–*n*-hexane to give 47.0 g (59%) of **7** as colorless prisms, m.p. 132.5–133° (lit.[11] m.p. 134–135°), $\nu_{max}$ (nujol) ~3700–~2000 (m), 1700 (s), 1415 (m), 1320 (m), 1290 (m), 1175 (m), 950 (br.m) $cm^{-1}$. (Found: C, 54.74; H, 7.96. Calc. for $C_8H_{14}O_4$: C, 55.16; H, 8.10%).

(3R*, 4S*)-3,4-*Dimethylcyclopentanone* **8**

A mixture of **7** (53.2 g) and $Ba(OH)_2 \cdot 8H_2O$ (3.0 g) was heated at 300° and the distillate was collected. The distillate was mixed with $K_2CO_3$ to salt out the ketone and extracted with ether. The ether soln was washed with sat NaCl aq, dried ($MgSO_4$) and concentrated. The residue was distilled to give 25.5 g (75%) of **8**, b.p. 160–164°, $n_D^{23}$ 1.4370; $\nu_{max}$ 2950 (m), 2860 (m), 1740 (s), 1460 (w), 1410 (w), 1385 (w), 1250 (w), 1160 (m), 1095 (w) $cm^{-1}$; $\delta$ 0.97 (6H, d, J = 6 Hz), 1.56–2.76 (6H, m); MS; *m/z* 112 ($M^+$).

(3R*, 4R*)-(±)-3,4-*Dimethyl*-5-*pentanolide* (±)-**9**

MCPBA (80% purity, 75 g) was added portionwise to a stirred soln of **8** (35 g) in $CHCl_3$ (800 ml) and the mixture was stirred for 22 hr at room temp. Then it was filtered to remove MCBA. The filtrate was washed with $NaHSO_3$ aq, water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 36 g (90%) of (±)-**9**, b.p. 73–76°/0.55 mm, $n_D^{23}$ 1.4654; $\nu_{max}$ 2950 (m), 2900 (m), 1740 (s), 1480 (w), 1455 (w), 1405 (m), 1380 (m), 1350 (m), 1290 (w), 1260 (m), 1240 (m), 1200 (m), 1175 (m), 1100 (m), 1045 (m), 1015 (w), 995 (m), 950 (w), 900 (w), 880 (w), 820 (w), 800 (w) $cm^{-1}$; $\delta$ 0.94 (3H, d, J = 7 Hz), 0.95 (3H, d, J = 6 Hz), 1.80–2.45 (4H, m), 3.95–4.25 (2H, m). (Found: C, 64.95; H, 9.57. Calc. for $C_7H_{12}O_2$: C, 65.59; H, 9.44%).

(3S, 4S)-(−)-3,4-*Dimethyl*-5-*pentanolide* (−)-**9**

A mixture of (±)-**9** (84 g) and 4 N NaOH aq (200 ml) was stirred and heated under reflux for 1.5 hr. After cooling, the soln was neutralized with 6 N HCl (80 ml) to pH 5. Then it was extracted with ether. (*R*)-(+)-α-Phenethylamine (80 g) was added to the ether soln and the resulting mixture was concentrated. The resulting solid was recrystallized four times from acetone to give 10.7 g (12.2%) of colorless needles, m.p. 135.5–136.5°, $[\alpha]_D^{22}$ +5.02° (c = 2.25, MeOH); $\nu_{max}$ (nujol) 3350 (m), ~2650 (br.m), 2520 (m), 2200 (w), 1620 (m), 1550 (s), 1520 (s), 1450 (m), 1400 (s), 1035 (m), 765 (m), 755 (w), 700 (m) $cm^{-1}$. (Found: C, 67.56; H, 8.92; N, 5.30. Calc. for $C_{15}H_{25}O_3N$: C, 67.38; H, 9.43; N, 5.30%). This salt (10.7 g) was mixed with 4 N HCl (30 ml) and the mixture was stirred for 30 min at room temp. Then it was extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 4.57 g (91% recovery) of (−)-**9**, b.p. 75°/0.5 mm, $n_D^{23}$ 1.4629; $[\alpha]_D^{22}$ −47.2° (*c* = 1.23, MeOH). The IR and NMR spectra were identical with those of (±)-**9**.

(3R, 4R)-(+)-3,4-*Dimethyl*-5-*pentanolide* (+)-**9**

The lactone **9** (52 g), enriched in (+)-**9**, was recovered from the above described resolution experiment. This was mixed with 4 N HaOHaq (125 ml) and the mixture was stirred and heated under reflux for 1.5 hr. Subsequent resolution procedure with (S)-(−)-α-

†This impurity may be (10*E*)-isomer of faranal. However, we could not rigorously identify it due to the scarcity of the material. The impurity might have resulted from the contaminating (10*E*)-isomer of the impure sulfone **2b**, although carefully purified sulfone **2b** did not seem to contain the (10*E*)-isomer upon reexamination.[c.f.4]

phenethylamine (50 g) as described above yielded 8.0 g (9.1%) of pure (−)-salt, m.p. 133–134°, $[\alpha]_D^{22}$ −4.96° ($c$ = 2.34, MeOH). The IR spectrum was superimposable on that of the (+)-salt. (Found: C, 67.61; H, 9.41; N, 5.21. Calc. for $C_{15}H_{25}O_3N$: C, 67.38; H, 9.43; N, 5.24%). This salt was converted to 3.45 g (91% recovery) of (+)-**9**, b.p. 76°/0.6 mm, $n_D^{23}$ 1.4633; $[\alpha]_D^{22}$ +46.3° ($c$ = 1.85, MeOH). The IR and NMR spectra were identical with those of (−)-**9**.

*Determination of the optical purity of* (+)-**9** *and* (−)-**9**

A mixture of (+)-, (−)- or (±)-**9** (100 mg) and (*R*)-(+)-α-naphthylethylamine (98% optical purity, 3 ml) was stirred and heated at 100° for 1.5 hr. After cooling, the mixture was diluted with $CHCl_3$. The $CHCl_3$ soln was washed with 10% HCl aq and water, dried ($MgSO_4$) and concentrated *in vacuo*. The residual **10b** was analyzed by hplc using Shimadzu LC-2F apparatus. hplc (Column; Zorbax SIL, 25 cm × 6.2 mm; Eluent, EtOAc–MeOH 20:1 v/v); Flow rate, 1.0 ml/min): $R_t$ 19.2 min (amide derived from (+)-**9**), 21.5 min (amide derived from (−)-**9**). The hplc analysis showed the optical purity of (+)-**9** to be 90.0% and that of (−)-**9** to be 92.4%.

*Ethyl* (3S, 4S)-5-*bromo*-3,4-*dimethylpentanoate* **11**

Dry HBr was bubbled for 40 min into a stirred and ice-cooled soln of the partially resolved lactone (−)-**9** (1.37 g $[\alpha]_D^{23}$ −34.1° ($c$ = 1.49, MeOH)) in dry EtOH (15 ml). The soln was left to stand overnight at room temp, then poured into ice-water and 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 1.79 g (70%) of **11**, b.p. 87–90°/1.0 mm, $n_D^{24}$ 1.4586; $\nu_{max}$ 2975 (m), 1730 (s), 1450 (m), 1370 (m), 1270 (m), 1175 (s), 1095 (m), 1030 (m) $cm^{-1}$; δ 0.44–1.25 (6H, m), 1.22 (3H, t, J = 7 Hz), 1.44–2.54 (4H, m), 3.00–3.55 (2H, m), 4.07 (2H, q, J = 7 Hz).

(S)-(−)-3,4-*Dimethylpentanoic acid* **12**

5% Pd-C (0.50 g) and $CaCO_3$ (0.40 g) were added to a soln of **11** (1.79 g) in MeOH (20 ml). The mixture was shaken under $H_2$ for 20 hr and then filtered. NaOH (4 g) and water (10 ml) were added to the filtrate and the basic mixture was stirred and heated under reflux for 2 hr. MeOH was removed *in vacuo*. The residue was acidified with conc HCl and extracted with ether. The ether soln was shaken with sat $NaHCO_3$ aq. The aq layer was acidified with HCl and extracted with ether. The ether soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated. The residue was distilled to give 0.18 g (18%) of **12**, b.p. 92°/4 mm (bath temp), $n_D^{24}$ 1.4219; $[\alpha]_D^{24}$ −7.64° ($c$ = 2.5, $CHCl_3$); $\nu_{max}$ 3400 (br.m), 2960 (s), 2660 (br.m), 1710 (s), 1460 (m), 1410 (m), 1290 (m), 1210 (m), 1110 (m), 930 (m) $cm^{-1}$; δ 0.7–1.1 (9H, m), 1.5–2.7 (4H, m), 11.42 (1H, s); glc (Column, 3% SE-30, 90 cm × 2 mm at 80–180° (+10°/min); Carrier gas, $N_2$, 0.6 kg/cm²): Rt 3.7 min (single peak). (Found: C, 64.31, H, 10.64. Calc. for $C_7H_{14}O_2$: C, 64.58; H, 10.84%). As neutral fraction 0.63 g (65%) of (−)-**9** was recovered. (*R*)-**12** with $[\alpha]_D^{23.5}$ +13.7° ($c$ = 1.5, $CHCl_3$) was prepared from 100% optically pure (*R*)-(+)-citronellic acid **13**.

(4*R**, 5*R**)-4,5-*Dimethyl*-2-*tetrahydropyranol* **15**

(a) *Racemate.* DIBALH (25% in *n*-hexane, 42 ml) was added dropwise during 15 min to a stirred soln of (±)-**9** (3.13 g) in dry THF (40 ml) at −70 ~ −55° under Ar. After the addition the mixture was stirred for 3 hr at −65°. Then the reaction was quenched by the addition of sat $NH_4Cl$ aq (15 ml). The cooling-bath was removed and the mixture was diluted with ether (200 ml). $MgSO_4$ was added to the mixture. Then it was filtered through Celite. Removal of the solvent yielded 2.93 g (92%) of (±)-**15**, $\nu_{max}$ 3360 (s), 2940 (s), 2870 (s), 1460 (m), 1370 (m), 1270 (m), 1180 (m), 1110 (s), 1085 (m), 1045 (m) 1030 (m), 1015 (m), 990 (s), 860 (m), 840 (m) $cm^{-1}$. This was employed for the next step without further purification.

(b) (4R, 5R)-*Isomer.* In the same manner 3.22 g of (+)-**9** gave 2.82 g (86%) of (4*R*, 5*R*)-**15**.

(c) (4S, 5S)-*Isomer.* In the same manner 4.00 g of (−)-**9** yielded 3.46 g (85%) of (4*S*, 5*S*)-**15**.

*Ethyl* (5R*, 6R*, 2E)-7-*hydroxy*-2,5,6-*trimethyl*-2-*heptenoate* **16a**

(a) *Racemate.* Triethyl α-phosphonopropionate (10.85 g) was added to a stirred suspension of NaOEt (3.10 g) in dry DMF (15 ml) under Ar. The mixture was stirred for 1 hr at room temp. A soln of (±)-**15** (2.50 g) in dry DMF (3 ml) was added dropwise to the stirred and ice-cooled soln of the sodio-phosphonate. The mixture was stirred overnight at room temp. Then it was diluted with ice-water and extracted with ether. The ether soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over $SiO_2$ to give 2.80 g (68%) of (±)-**16a**, $\nu_{max}$ 3400 (m), 2960 (s), 2860 (m), 1710 (s), 1640 (m), 1460 (m), 1370 (m), 1280 (s), 1220 (m), 1140 (m), 1100 (s), 1030 (s), 740 (w) $cm^{-1}$; δ 0.90 (6H, d, J = 7 Hz), 1.29 (3H, t, J = 7 Hz), 1.81 (3H, s), 3.3–3.7 (2H, m), 4.17 (2H, q, J = 7 Hz), 6.79 (1H, t, J = 7 Hz); glc (Column, 3% SE-30, 1.5 m × 2 mm at 120–240° (+8°/min); Carrier gas, $N_2$, 1.3 kg/cm²): Rt 5.3 min [15%, (*Z*)-isomer], 6.5 min [85%, (±)-**16a**]; MS: *m/z* 214 ($M^+$).

(b) (5R, 6R, 2E)-*Isomer.* In the same manner 3.72 g of (4*R*, 5*R*)-**15** yielded 2.44 g (53%) of (5*R*, 6*R*, 2*E*)-**16a**.

(c) (5S, 6S, 2E)-*Isomer.* In the same manner 4.55 g of (4*S*, 5*S*)-**15** gave 2.48 g (50%) of (5*S*, 6*S*, 2*E*)-**16a**.

*Ethyl* (5*R**, 6*R**, 2*E*)-7-*tetrahydropyranyloxy*-2,5,6-*trimethyl*-2-*heptenoate* **16b**

(a) *Racemate.* Dihydropyran (1.86 g) and *p*-TsOH (trace amount) were added to a soln of (±)-**16a** (3.80 g) in dry ether (60 ml). The mixture was stirred overnight. The ether soln was washed with dil $Na_2CO_3$ aq, water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give 5.30 g (quantitative) of (±)-**16b**, $\nu_{max}$ 2940 (s), 2860 (m), 1710 (s), 1645 (w), 1290 (m), 1140 (s), 1120 (s), 1030 (s), 970 (m), 910 (m), 870 (m) $cm^{-1}$; δ 0.92 (6H, d, J = 7 Hz), 1.28 (3H, t, J = 7 Hz), 1.80 (3H, s), 4.14 (2H, q, J = 7 Hz), 4.50 (1H, br.s), 6.71 (1H, t, J = 7 Hz). This was employed for the next step without further purification.

(b) (5R, 6R, 2E)-*Isomer.* In the same manner 2.44 g of (5*R*, 6*R*, 2*E*)-**16a** gave 3.38 g (99%) of (5*R*, 6*R*, 2*E*)-**16b**.

(c) (5S, 6S, 2E)-*Isomer.* In the same manner 2.60 g of (5*S*, 6*S*, 2*E*)-**16a** yielded 3.47 g (96%) of (5*S*, 6*S*, 2*E*)-**16b**.

(5R*, 6R*, 2E)-7-*Tetrahydropyranyloxy*-2,5,6-*trimethyl*-2-*heptenol* **17**

(a) *Racemate.* A soln of $AlCl_3$ (0.89 g) in dry ether (70 ml) was added dropwise to a stirred and ice-cooled suspension of LAH (0.70 g) in dry THF (20 ml). After stirring for 30 min at 0–5°, a soln of (±)-**16b** (5.30 g) in dry ether (20 ml) was added to the stirred and ice-cooled soln. The stirring was continued for 2 hr at 0–5°. Then ether (150 ml) and water (6 ml) were carefully added to destroy excess $AlH_3$. The mixture was filtered through Celite. The filtrate was washed with sat NaCl aq, dried ($K_2CO_3$) and concentrated *in vacuo*. The residue was chromatographed over neutral $Al_2O_3$ (Woelm, Grade II, 100 g) to give 3.94 g (92%) of (±)-**17**, $n_D^{23}$ 1.4750, $\nu_{max}$ 3360 (m), 2920 (s), 2860 (s), 1450 (m), 1380 (m), 1300 (m), 1140 (s), 1120 (s), 1080 (s), 1060 (s), 1025 (s), 970 (m), 900 (m), 865 (m), 810 (m) $cm^{-1}$; δ 0.87 (6H, d, J = 7 Hz, br.), 1.20–2.30 (13H, m; 1.59 (s)), 2.60 (1H, br.s), 2.87–4.10 (6H, br.m), 4.55 (1H, br.s), 5.32 (1H, t, J = 7 Hz). (Found: C, 70.01; H, 11.03. Calc. for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01%).

(b) (5R, 6R, 2E)-*Isomer.* In the same manner 3.19 g of (5*R*, 6*R*, 2*E*)-**16b** yielded 2.14 g (78%) of (5*R*, 6*R*, 2*E*)-**17**.

(c) (5S, 6S, 2E)-*Isomer.* In the same manner 3.47 g of (5*S*, 6*S*, 2*E*)-**16b** gave 1.86 g (62%) of (5*S*, 6*S*, 6*E*)-**17**.

(5R*, 6R*, 2E)-7-*Tetrahydropyranyloxy*-2,5,6-*trimethyl*-2-*heptenyl bromide* **3**.

(a) *Racemate.* *n*-BuLi (1.6 N in *n*-hexane, 9.35 ml) was added to a stirred and ice-cooled soln of (±)-**17** (3.83 g) in dry ether-HMPA (1:1, 40 ml). Then *p*-TsCl (2.96 g) was added portionwise with stirring and ice-cooling. After the addition of LiBr (3.50 g), the cooling bath was removed and the stirring was continued overnight at room temp. Then the mixture was poured into water and extracted with ether. The ether soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography to give 2.30 g (48%) of (±)-**3**, $\nu_{max}$ 2920 (s), 2850 (s), 1455 (m), 1430 (m), 1380 (m), 1270 (m),

phenethylamine (50 g) as described above yielded 8.0 g (9.1%) of pure (−)-salt, m.p. 133–134°, $[\alpha]_D^{22}$ −4.96° (*c* = 2.34, MeOH). The IR spectrum was superimposable on that of the (+)-salt. (Found: C, 67.61; H, 9.41; N, 5.21. Calc. for $C_{15}H_{25}O_3N$: C, 67.38; H, 9.43; N, 5.24%). This salt was converted to 3.45 g (91% recovery) of (+)-**9**, b.p. 76°/0.6 mm, $n_D^{23}$ 1.4633; $[\alpha]_D^{22}$ +46.3° (*c* = 1.85, MeOH). The IR and NMR spectra were identical with those of (−)-**9**.

*Determination of the optical purity of* (+)-**9** *and* (−)-**9**

A mixture of (+)-, (−)- or (±)-**9** (100 mg) and (*R*)-(+)-α-naphthylethylamine (98% optical purity, 3 ml) was stirred and heated at 100° for 1.5 hr. After cooling, the mixture was diluted with $CHCl_3$. The $CHCl_3$ soln was washed with 10% HCl aq and water, dried ($MgSO_4$) and concentrated *in vacuo*. The residual **10b** was analyzed by hplc using Shimadzu LC-2F apparatus. hplc (Column; Zorbax SIL, 25 cm × 6.2 mm; Eluent, EtOAc–MeOH 20:1 v/v); Flow rate, 1.0 ml/min): $R_t$ 19.2 min (amide derived from (+)-**9**), 21.5 min (amide derived from (−)-**9**). The hplc analysis showed the optical purity of (+)-**9** to be 90.0% and that of (−)-**9** to be 92.4%.

*Ethyl* (3S, 4S)-*5-bromo-3,4-dimethylpentanoate* **11**

Dry HBr was bubbled for 40 min into a stirred and ice-cooled soln of the partially resolved lactone (−)-**9** (1.37 g $[\alpha]_D^{23}$ −34.1° (*c* = 1.49, MeOH)) in dry EtOH (15 ml). The soln was left to stand overnight at room temp, then poured into ice-water and 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 1.79 g (70%) of **11**, b.p. 87–90°/1.0 mm, $n_D^{24}$ 1.4586; $\nu_{max}$ 2975 (m), 1730 (s), 1450 (m), 1370 (m), 1270 (m), 1175 (s), 1095 (m), 1030 (m) $cm^{-1}$; δ 0.44–1.25 (6H, m), 1.22 (3H, t, J = 7 Hz), 1.44–2.54 (4H, m), 3.00–3.55 (2H, m), 4.07 (2H, q, J = 7 Hz).

(S)-(−)-3,4-*Dimethylpentanoic acid* **12**

5% Pd-C (0.50 g) and $CaCO_3$ (0.40 g) were added to a soln of **11** (1.79 g) in MeOH (20 ml). The mixture was shaken under $H_2$ for 20 hr and then filtered. NaOH (4 g) and water (10 ml) were added to the filtrate and the basic mixture was stirred and heated under reflux for 2 hr. MeOH was removed *in vacuo*. The residue was acidified with conc HCl and extracted with ether. The ether soln was shaken with sat $NaHCO_3$ aq. The aq layer was acidified with HCl and extracted with ether. The ether soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated. The residue was distilled to give 0.18 g (18%) of **12**, b.p. 92°/4 mm (bath temp), $n_D^{24}$ 1.4219; $[\alpha]_D^{24}$ −7.64° (*c* = 2.5, $CHCl_3$); $\nu_{max}$ 3400 (br.m), 2960 (s), 2660 (br.m), 1710 (s), 1460 (m), 1410 (m), 1290 (m), 1210 (m), 1110 (m), 930 (m) $cm^{-1}$; δ 0.7–1.1 (9H, m), 1.5–2.7 (4H, m), 11.42 (1H, s); glc (Column, 3% SE-30, 90 cm × 2 mm at 80–180° (+10°/min); Carrier gas, $N_2$, 0.6 kg/cm²): Rt 3.7 min (single peak). (Found: C, 64.31, H, 10.64. Calc. for $C_7H_{14}O_2$: C, 64.58; H, 10.84%). As neutral fraction 0.63 g (65%) of (−)-**9** was recovered. (*R*)-**12** with $[\alpha]_D^{23.5}$ +13.7° (*c* = 1.5, $CHCl_3$) was prepared from 100% optically pure (*R*)-(+)-citronellic acid **13**.

(4*R**, 5*R**)-*4,5-Dimethyl-2-tetrahydropyranol* **15**

(a) *Racemate.* DIBALH (25% in *n*-hexane, 42 ml) was added dropwise during 15 min to a stirred soln of (±)-**9** (3.13 g) in dry THF (40 ml) at −70 ~ −55° under Ar. After the addition the mixture was stirred for 3 hr at −65°. Then the reaction was quenched by the addition of sat $NH_4Cl$ aq (15 ml). The cooling-bath was removed and the mixture was diluted with ether (200 ml). $MgSO_4$ was added to the mixture. Then it was filtered through Celite. Removal of the solvent yielded 2.93 g (92%) of (±)-**15**, $\nu_{max}$ 3360 (s), 2940 (s), 2870 (s), 1460 (m), 1370 (m), 1270 (m), 1180 (m), 1110 (s), 1085 (m), 1045 (m) 1030 (m), 1015 (m), 990 (s), 860 (m), 840 (m) $cm^{-1}$. This was employed for the next step without further purification.

(b) (4R, 5R)-*Isomer.* In the same manner 3.22 g of (+)-**9** gave 2.82 g (86%) of (4*R*, 5*R*)-**15**.

(c) (4S, 5S)-*Isomer.* In the same manner 4.00 g of (−)-**9** yielded 3.46 g (85%) of (4*S*, 5*S*)-**15**.

*Ethyl* (5R*, 6R*, 2E)-*7-hydroxy-2,5,6-trimethyl-2-heptenoate* **16a**

(a) *Racemate.* Triethyl α-phosphonopropionate (10.85 g) was added to a stirred suspension of NaOEt (3.10 g) in dry DMF (15 ml) under Ar. The mixture was stirred for 1 hr at room temp. A soln of (±)-**15** (2.50 g) in dry DMF (3 ml) was added dropwise to the stirred and ice-cooled soln of the sodio-phosphonate. The mixture was stirred overnight at room temp. Then it was diluted with ice-water and extracted with ether. The ether soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over $SiO_2$ to give 2.80 g (68%) of (±)-**16a**, $\nu_{max}$ 3400 (m), 2960 (s), 2860 (m), 1710 (s), 1640 (m), 1460 (m), 1370 (m), 1280 (s), 1220 (m), 1140 (m), 1100 (s), 1030 (s), 740 (w) $cm^{-1}$; δ 0.90 (6H, d, J = 7 Hz), 1.29 (3H, t, J = 7 Hz), 1.81 (3H, s), 3.3–3.7 (2H, m), 4.17 (2H, q, J = 7 Hz), 6.79 (1H, t, J = 7 Hz); glc (Column, 3% SE-30, 1.5 m × 2 mm at 120–240° (+8°/min); Carrier gas, $N_2$, 1.3 kg/cm²): Rt 5.3 min [15%, (*Z*)-isomer], 6.5 min [85%, (±)-**16a**]; MS: *m/z* 214 ($M^+$).

(b) (5R, 6R, 2E)-*Isomer.* In the same manner 3.72 g of (4*R*, 5*R*)-**15** yielded 2.44 g (53%) of (5*R*, 6*R*, 2*E*)-**16a**.

(c) (5S, 6S, 2E)-*Isomer.* In the same manner 4.55 g of (4*S*, 5*S*)-**15** gave 2.48 g (50%) of (5*S*, 6*S*, 2*E*)-**16a**.

*Ethyl* (5*R**, 6*R**, 2*E*)-*7-tetrahydropyranyloxy-2,5,6-trimethyl-2-heptenoate* **16b**

(a) *Racemate.* Dihydropyran (1.86 g) and *p*-TsOH (trace amount) were added to a soln of (±)-**16a** (3.80 g) in dry ether (60 ml). The mixture was stirred overnight. The ether soln was washed with dil $Na_2CO_3$ aq, water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give 5.30 g (quantitative) of (±)-**16b**, $\nu_{max}$ 2940 (s), 2860 (m), 1710 (s), 1645 (w), 1290 (m), 1140 (s), 1120 (s), 1030 (s), 970 (m), 910 (m), 870 (m) $cm^{-1}$; δ 0.92 (6H, d, J = 7 Hz), 1.28 (3H, t, J = 7 Hz), 1.80 (3H, s), 4.14 (2H, q, J = 7 Hz), 4.50 (1H, br.s), 6.71 (1H, t, J = 7 Hz). This was employed for the next step without further purification.

(b) (5R, 6R, 2E)-*Isomer.* In the same manner 2.44 g of (5*R*, 6*R*, 2*E*)-**16a** gave 3.38 g (99%) of (5*R*, 6*R*, 2*E*)-**16b**.

(c) (5S, 6S, 2E)-*Isomer.* In the same manner 2.60 g of (5*S*, 6*S*, 2*E*)-**16a** yielded 3.47 g (96%) of (5*S*, 6*S*, 2*E*)-**16b**.

(5R*, 6R*, 2E)-*7-Tetrahydropyranyloxy-2,5,6-trimethyl-2-heptenol* **17**

(a) *Racemate.* A soln of $AlCl_3$ (0.89 g) in dry ether (70 ml) was added dropwise to a stirred and ice-cooled suspension of LAH (0.70 g) in dry THF (20 ml). After stirring for 30 min at 0–5°, a soln of (±)-**16b** (5.30 g) in dry ether (20 ml) was added to the stirred and ice-cooled soln. The stirring was continued for 2 hr at 0–5°. Then ether (150 ml) and water (6 ml) were carefully added to destroy excess $AlH_3$. The mixture was filtered through Celite. The filtrate was washed with sat NaCl aq, dried ($K_2CO_3$) and concentrated *in vacuo*. The residue was chromatographed over neutral $Al_2O_3$ (Woelm, Grade II, 100 g) to give 3.94 g (92%) of (±)-**17**, $n_D^{23}$ 1.4750, $\nu_{max}$ 3360 (m), 2920 (s), 2860 (s), 1450 (m), 1380 (m), 1300 (m), 1140 (s), 1120 (s), 1080 (s), 1060 (s), 1025 (s), 970 (m), 900 (m), 865 (m), 810 (m) $cm^{-1}$; δ 0.87 (6H, d, J = 7 Hz, br.), 1.20–2.30 (13H, m; 1.59 (s)), 2.60 (1H, br.s), 2.87–4.10 (6H, br.m), 4.55 (1H, br.s), 5.32 (1H, t, J = 7 Hz). (Found: C, 70.01; H, 11.03. Calc. for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01%).

(b) (5R, 6R, 2E)-*Isomer.* In the same manner 3.19 g of (5*R*, 6*R*, 2*E*)-**16b** yielded 2.14 g (78%) of (5*R*, 6*R*, 2*E*)-**17**.

(c) (5S, 6S, 2E)-*Isomer.* In the same manner 3.47 g of (5*S*, 6*S*, 2*E*)-**16b** gave 1.86 g (62%) of (5*S*, 6*S*, 6*E*)-**17**.

(5R*, 6R*, 2E)-*7-Tetrahydropyranyloxy-2,5,6-trimethyl-2-heptenyl bromide* **3**.

(a) *Racemate.* *n*-BuLi (1.6 N in *n*-hexane, 9.35 ml) was added to a stirred and ice-cooled soln of (±)-**17** (3.83 g) in dry ether-HMPA (1:1, 40 ml). Then *p*-TsCl (2.96 g) was added portionwise with stirring and ice-cooling. After the addition of LiBr (3.50 g), the cooling bath was removed and the stirring was continued overnight at room temp. Then the mixture was poured into water and extracted with ether. The ether soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography to give 2.30 g (48%) of (±)-**3**, $\nu_{max}$ 2920 (s), 2850 (s), 1455 (m), 1430 (m), 1380 (m), 1270 (m),

(c) (3R, 4S, 6E, 10Z)-*Isomer.* In the same manner 206 mg of (3*R*, 4*S*, 6*E*, 10*Z*)-**21** gave 156 mg (80%) of (3*R*, 4*S*, 6*E*, 10*Z*)-**22**.

(3R*, 4S*, 6E, 10Z)-3, 4, 7, 11-*Tetramethyl*-6, 10-*tridecadienal* (*Faranal*) **1**

(a) *Racemate.* $CrO_3 \cdot C_5H_5N \cdot HCl$ (PCC, 128 mg) was added portionwise to a stirred and ice-cooled soln of (±)-**22** (100 mg) in dry $CH_2Cl_2$ (3 ml). The mixture was stirred for 2 hr at room temp. After dilution with dry ether (20 ml), the mixture was filtered through a short column of florisil. The filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel (Mallinckrodt CC-7) to give (±)-**1** (72 mg, 73%), $n_D^{23}$ 1.4755. This was further purified by preparative glc (20% PEG 20M on chromosorb W, 1 m × 3 mm at 160°; Carrier gas, $N_2$, 40 ml/min). The purified sample showed the following properties: $\nu_{max}$ 2960 (s), 2920 (s), 2860 (s), 2700 (w), 1730 (s), 1450 (m), 1380 (m), 1120 (w), 1080 (w), 1020 (m) $cm^{-1}$; $\delta$ (400 MHz, $C_6D_6$) 0.69 (3H, d, J = 7 Hz), 0.72 (3H, d, J = 7 Hz), 0.94 (3H, t, J = 7.5 Hz), 1.55 (3H, s), 1.69 (3H, s), 5.15 (1H, m), 5.19 (1H, m), 9.39 (1H, q, $J_1$ = 1.5 Hz, $J_2$ = 2.5 Hz); glc (Column, Thermon 1000, 30 m × 0.2 mm at 164–200° (+2°/min); Carrier gas, $N_2$, 1.0 kg/cm²): $R_t$ 8.90 min (~90%), 9.15 min (~10%); MS: *m/z* 250.2327 ($M^+$, $C_{17}H_{30}O$ = 250.41). The NMR spectrum taken at 300 MHz was similar to that at 400 MHz.

(b) (3S, 4R, 6E, 10Z)-*Isomer.* In the same manner 101 mg of (3*S*, 4*R*, 6*E*, 10*Z*)-**22** gave 72.4 mg (72%) of (3*S*, 4*R*, 6*E*, 10*Z*)-**1**, $[\alpha]_D^{23}$ + 16.2° (*c* = 0.50, *n*-hexane).

(c) (3R, 4S, 6E, 10Z)-*Isomer.* In the same manner 131 mg of (3*R*, 4*S*, 6*E*, 10*Z*)-**22** gave 91 mg (70%) of (3*R*, 4*S*, 6*E*, 10*Z*)-**1**, $[\alpha]_D^{23}$ − 16.4° (*c* = 0.22, *n*-hexane).

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# A GENERAL SYNTHETIC METHOD FOR PRENYLATED PHENOLS OF MICROBIAL ORIGIN

## SYNTHESIS OF COLLETOCHLORINS A AND B†

KENJI MORI* and KAZUO SATO
Department of Agricultural Chemistry, The University of Tokyo, Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

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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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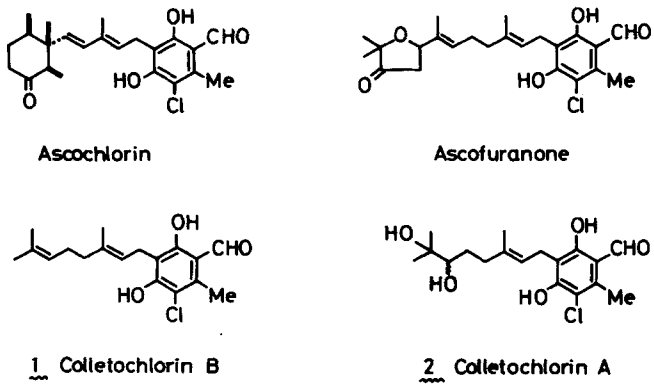


Fig. 1.

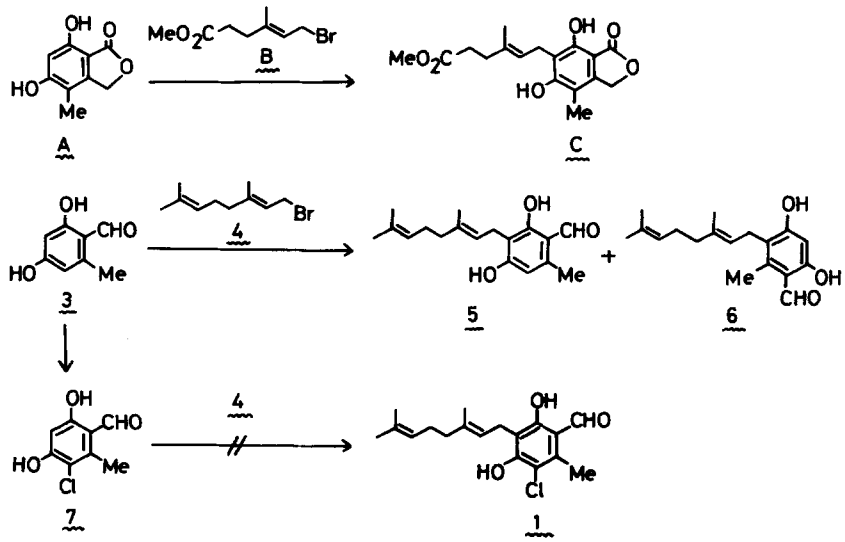


Fig. 2.

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

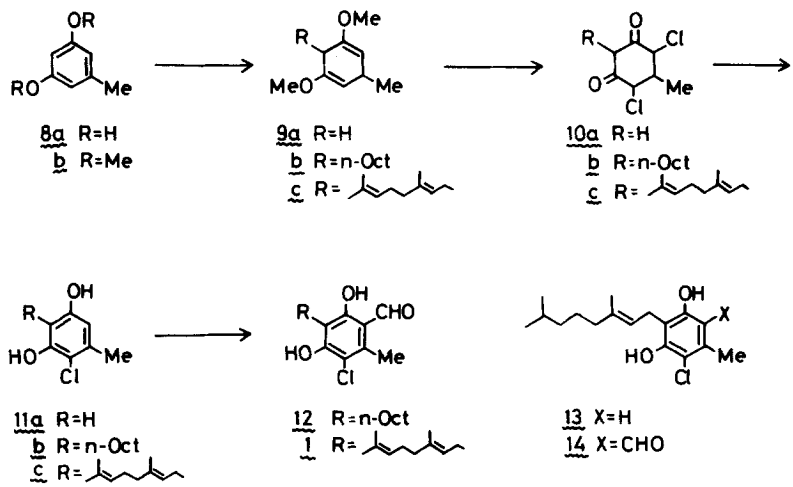


Fig. 3.

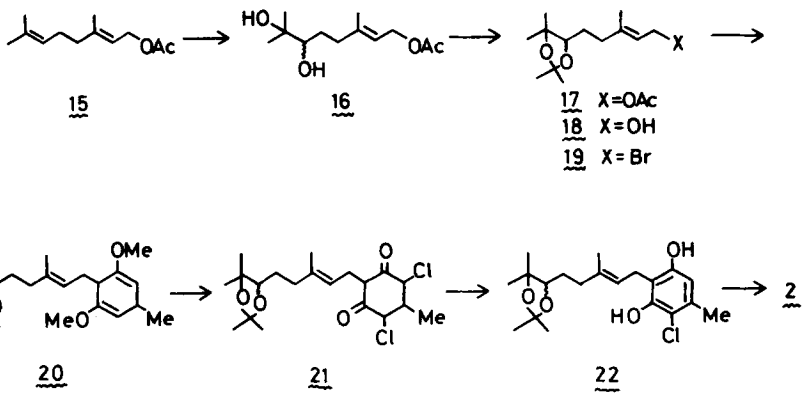


Fig. 4.

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°, $\nu_{max}$ 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)$cm^{-1}$; $\delta$ (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°, $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CDCl_3$) 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°, $\nu_{max}$ 3100 (br,m), 1610 (s) $cm^{-1}$; $\delta$ ($CCl_4$ + 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°, $\nu_{max}$ 1600 (s) $cm^{-1}$; $\delta$ ($CCl_4$ + 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; $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CCl_4$) 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**, $\nu_{max}$ 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°), $\nu_{max}$ 3300 (s), 1615 (m), 1600 (s), 1335 (m), 1270 (s), 1160 (s), 990 (m) $cm^{-1}$; $\delta$ ($CDCl_3$ + 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; $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CCl_4$) 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°, $\nu_{max}$ ~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°, $\nu_{max}$ (film) 3550 (m), 3450 (sh), 2960 (s), 2930(s), 2850 (s), 1620 (m), 1585 (m), 1410 (s), 1110 (s) $cm^{-1}$; $\delta$ ($CDCl_3$) 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); $\lambda_{max}$ (MeOH) 275 nm ($\epsilon$ = 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°, $\nu_{max}$ 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) $cm^{-1}$; $\delta$ (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); $\lambda_{max}$ (MeOH) 293 nm ($\epsilon$ = 10,300), 346 nm ($\epsilon$ = 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^{20}$1.4967; $\nu_{max}$ 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**, $\nu_{max}$ 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, $\nu_{max}$ 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°, $\nu_{max}$ 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) $cm^{-1}$; $\delta$ (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); $\delta$ (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 $C_{18}H_{23}O_3Cl$: C, 66.96; H, 7.18%). The $^1$H-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°, $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CDCl_3$) 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; $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CCl_4$) 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; $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CCl_4$) 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, $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CCl_4$) 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**, $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CCl_4$) 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, $\nu_{max}$ 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)$cm^{-1}$; $\delta$ ($CCl_4$) 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, $\nu_{max}$ 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°, $\nu_{max}$ 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)$cm^{-1}$; $\delta$ ($CDCl_3$) 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°, $\nu_{max}$ 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) $cm^{-1}$; $\delta$ (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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# A GENERAL SYNTHETIC METHOD FOR PRENYLATED PHENOLS OF MICROBIAL ORIGIN

## SYNTHESIS OF COLLETOCHLORINS A AND B†

KENJI MORI* and KAZUO SATO
Department of Agricultural Chemistry, The University of Tokyo, Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

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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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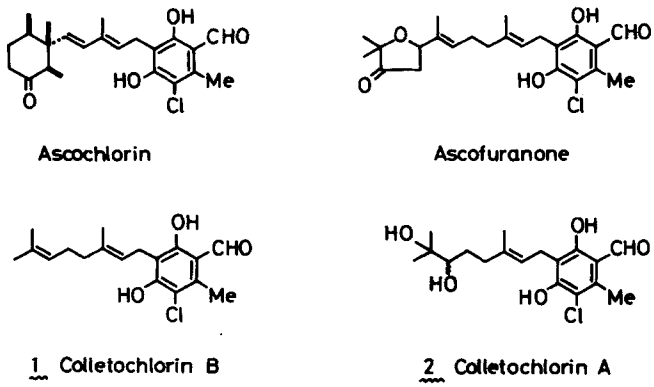


Fig. 1.

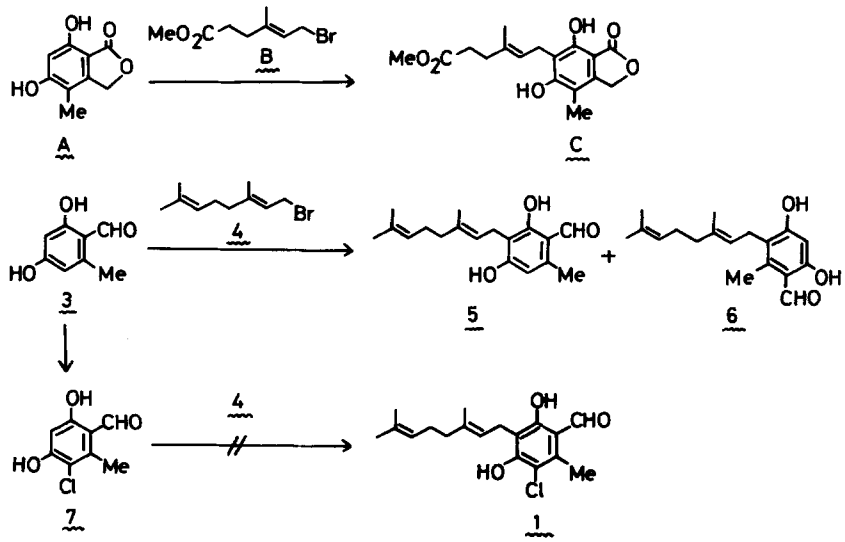


Fig. 2.

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

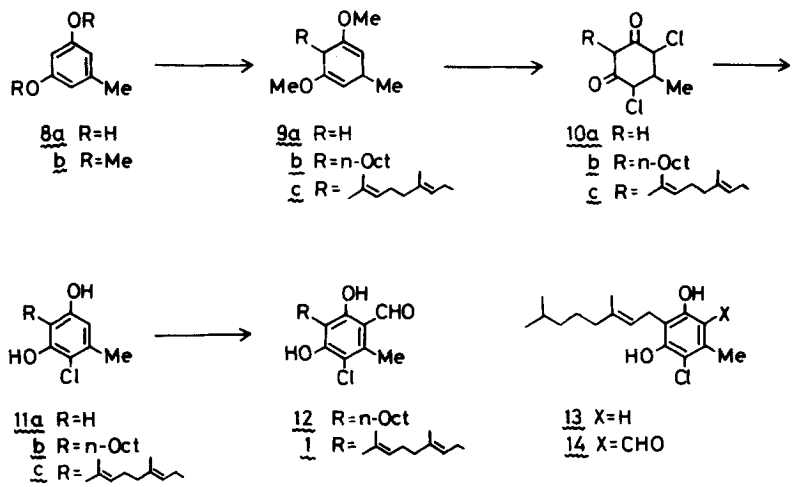


Fig. 3.

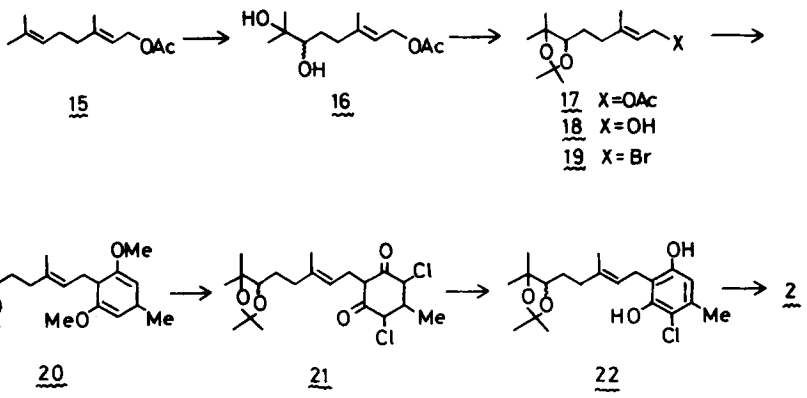


Fig. 4.

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°, $\nu_{max}$ 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)$cm^{-1}$; $\delta$ (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°, $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CDCl_3$) 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°, $\nu_{max}$ 3100 (br,m), 1610 (s) $cm^{-1}$; $\delta$ ($CCl_4$ + 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°, $\nu_{max}$ 1600 (s) $cm^{-1}$; $\delta$ ($CCl_4$ + 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; $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CCl_4$) 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**, $\nu_{max}$ 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°), $\nu_{max}$ 3300 (s), 1615 (m), 1600 (s), 1335 (m), 1270 (s), 1160 (s), 990 (m) $cm^{-1}$; $\delta$ ($CDCl_3$ + 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; $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CCl_4$) 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°, $\nu_{max}$ ~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°, $\nu_{max}$ (film) 3550 (m), 3450 (sh), 2960 (s), 2930(s), 2850 (s), 1620 (m), 1585 (m), 1410 (s), 1110 (s) $cm^{-1}$; $\delta$ ($CDCl_3$) 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); $\lambda_{max}$ (MeOH) 275 nm ($\epsilon$ = 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°, $\nu_{max}$ 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) $cm^{-1}$; $\delta$ (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); $\lambda_{max}$ (MeOH) 293 nm ($\epsilon$ = 10,300), 346 nm ($\epsilon$ = 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^{20}$1.4967; $\nu_{max}$ 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**, $\nu_{max}$ 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, $\nu_{max}$ 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°, $\nu_{max}$ 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) $cm^{-1}$; $\delta$ (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); $\delta$ (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 $C_{18}H_{23}O_3Cl$: C, 66.96; H, 7.18%). The $^1$H-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°, $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CDCl_3$) 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; $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CCl_4$) 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; $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CCl_4$) 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, $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CCl_4$) 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**, $\nu_{max}$ 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) $cm^{-1}$; $\delta$ ($CCl_4$) 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, $\nu_{max}$ 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)$cm^{-1}$; $\delta$ ($CCl_4$) 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, $\nu_{max}$ 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°, $\nu_{max}$ 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)$cm^{-1}$; $\delta$ ($CDCl_3$) 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°, $\nu_{max}$ 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) $cm^{-1}$; $\delta$ (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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