Tetrahedron Vol. 42, No. 10, pp. 2635 to 2642, 1986
Printed in Great Britain.

0040-4020/86 $3.00 + .00
Pergamon Journals Ltd.

A CONVENIENT SYNTHESIS OF (+) ASCOCHLORIN

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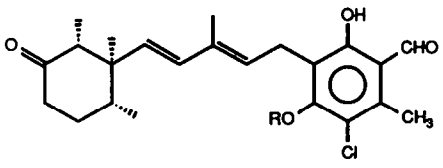
(*Received in USA* 13 *January* 1986)

Abstract: A convergent total synthesis of (+) ascochlorin is described.

Ascochlorin (1) is an antibiotic and hypolipidemic agent which also exhibits other types of biological activity.[1-3] For instance, ascochlorin inhibits the growth of the protozoan Tetrahymena pyriformis,[4] and has been reported to be active against herpes simplex and Newcastle disease viruses, as well as against some tumors.[2,5,6] Derivatives of 1, also exhibit interesting biological action (Scheme I). While the 4-O-methylated derivative of 1 (2) increases copper excretion, the 4-O-acylated derivative (3) has hypotensive action. More recently, the 4-O-carboxymethyl derivative (4) has been reported to potentiate insulin action in streptozotocin diabetic mice.[7] When administered orally to genetically obese diabetic mice, this compound improved polydipsia, polyuria, and urinary glucose excretion without affecting body weight and diet intake.[5,8] These results represent the first example of a natural product potentiating insulin action by enhancing sensitivity in insulin sensitive tissues.

SCHEME I



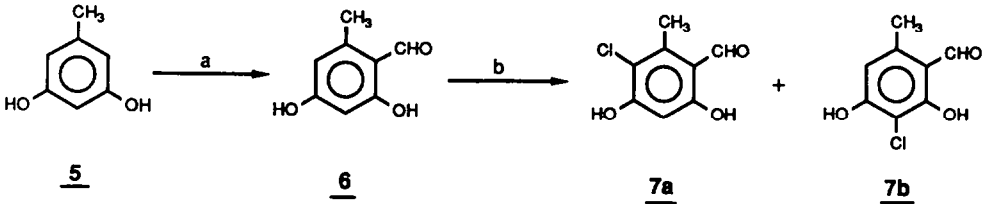
1, R=H
2, R=CH_3
3, R=$COCH_3$
4, R=CH_2CO_2H

The diverse and potent biological properties of 1 and its derivatives make them attractive synthetic targets and further structural modifications of these compounds also appear appropriate. Although the synthesis of 1 has been reported,[9,10] we believe we have devised a simpler route, more suitable for analog studies.

We first envisioned a convergent approach utilizing three main sections of the molecule: (1) the pentasubstituted aromatic ring; (2) the trimethyl substituted prenylated cyclohexanone; and (3) the intervening terpenoid chain. Synthesis of the aromatic portion (Scheme II) began with a modified Gatterman formylation of orcinol (5), using zinc cyanide and hydrogen chloride gas, followed by aqueous hydrolysis to afford the corresponding aromatic aldehyde (6) in 85% yield.[11] Treatment of 6 with sulfuryl chloride in diethyl ether yielded two regioisomers (7a and 7b) which were separated by column chromatography (silica, ethyl acetate:hexane, 15:85).

The synthesis of the cyclohexanone moiety is shown in Scheme III and began with the Birch reduction of 2,6-dimethylanisole (8) using lithium metal in liquid ammonia, followed by acid catalyzed hydrolysis in THF, to give 2,6-dimethyl-2-cyclohexenone[12-15] (10) in 71% yield. Alternatively, compound 10 could be prepared from 2,6-dimethylcyclohexanone (9) in 71% yield by

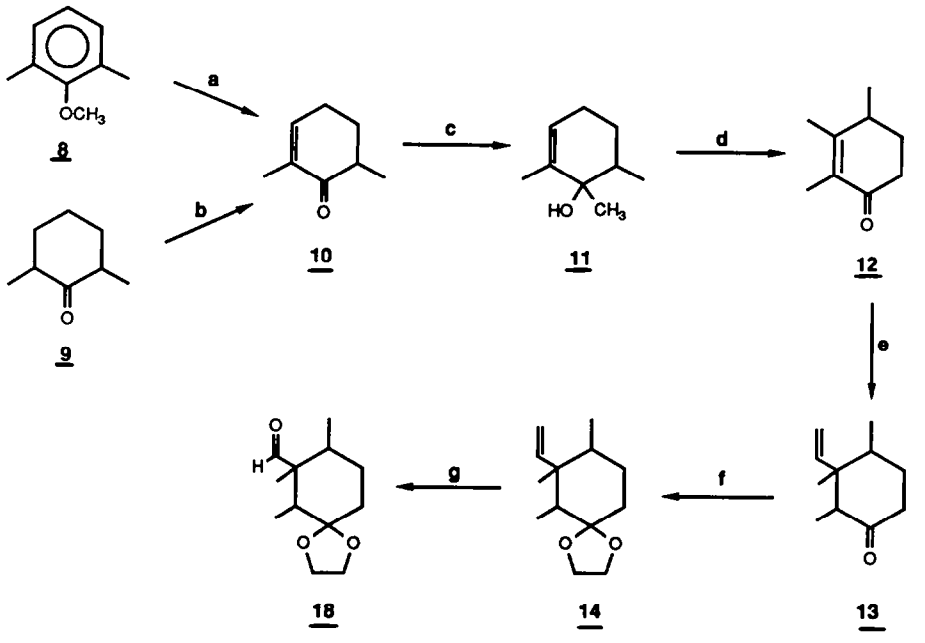
SCHEME II



[a] 1. $Zn(CN)_2$, $HCl_{(g)}$, Et_2O, 25°C; 2. H_2O, 60°C; [b] SO_2Cl_2, Et_2O, 0°C

reaction with sulfuryl chloride followed by dehydrochlorination with lithium chloride in DMF.[16] Reaction of 10 with methyllithium in THF afforded the tertiary allylic alcohol (11) in nearly quantitative yield (~50:50 mixture of diastereomers). The mixture was then oxidized with pyridinium dichromate in methylene chloride to afford (±) 2,3,4-trimethyl-2-cyclohexenone (12)[17-19] in 63% yield, via an allylic rearrangement.[20]

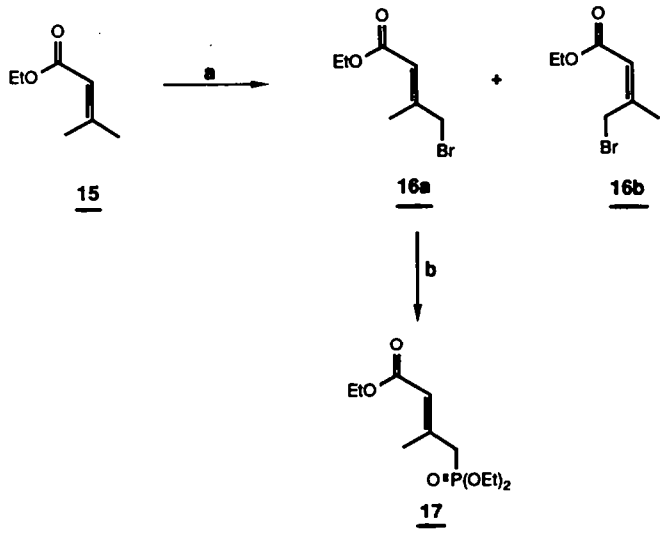
SCHEME III



[a] 1. Li, NH_3, EtOH, THF, -78°C; 2. H_3O^+, THF; [b] 1. SO_2Cl_2; 2. LiCl, DMF, Δ; [c] MeLi, THF, -78°C; [d] PDC, CH_2Cl_2, 25°C; [e] H_2C = $CHMgBr$, $((n\text{-}Bu)_3PCuI)_4$, $BF_3.Et_2O$, THF, -78°C; [f] $HOCH_2CH_2OH$, p-TsOH, C_6H_6, Δ; [g] 1. O_3, MeOH, -78°C; 2. DMS, 25°C.

The key step in the synthesis of the cyclohexanone portion was the 1,4-conjugate addition of a vinyl group. This reaction was accomplished by treating 12 with a divinylcoppermagnesium bromide(tri-n-butylphosphine) complex at -78°C, in the presence of boron trifluoride, to afford 13 in 73% yield. The vinylating reagent was prepared from vinylmagnesium bromide and tetrakisiodo(tri-n-butylphosphine)copper.[21] The steric bulk of the complex caused the 1,4-addition to occur trans to the methyl group at the 4-position, producing only one pair of enantiomers from the racemic starting material. Compound 13 was purified by column chromatography (silica; ethyl acetate:hexane, 1:20). The ketone functionality was protected as its 1,3-dioxolane derivative (14) using ethylene glycol (TsOH,Δ,C_6H_6).

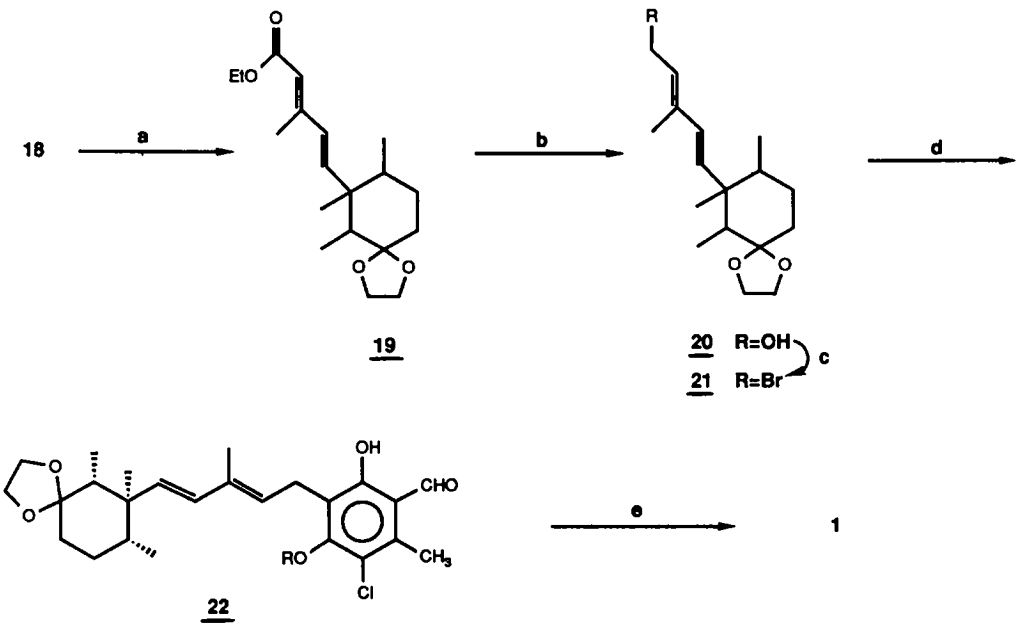
SCHEME IV



[a]NBS, AIBN, CCl_4, reflux; [b]$(EtO)_3P$, 120°C

The third and final segment needed was a Horner-Emmons reagent of sufficient stability to accomplish a trans addition to aldehyde 18 (Scheme V). The reagent was prepared in two steps by first brominating ethyl 3,3-dimethylcrotonate with N-bromosuccinimide (Δ, CCl_4) to afford a 50:50 mixture of E and Z isomers (16a and 16b) (Scheme IV) which were separated by flash column chromatography (silica, ether:petroleum ether, 1:50).[22,23] Conversion of the bromide to the Horner-Emmons phosphonate (17) was accomplished via an Arbuzov reaction[24] with triethyl phosphite. Condensation of this reagent with aldehyde 18, (obtained from the ozonolysis of 14), with lithium diisopropylamide as the base, afforded the 1,5-diene ester 19 stereoselectively as a mixture of two isomers (E,E 19a and E,Z 19b) in a ratio of 6:1 (75% yield). Separation of the isomers was accomplished by fractional recrystallization from pentane. Reduction of the E,E isomer with DIBAL-H in methylene chloride at -78°C gave the alcohol 20 in near quantitative yield (Scheme V). The E,E stereochemistry was assigned from NOE studies. Treatment of 20 with carbon tetrabromide and triphenylphosphine at -78°C gave the corresponding bromide 21. Compound 21 was not purified but treated immediately with the potassium salt of 5-chloroorsellinaldehyde in refluxing toluene to afford 22 in 27.5% yield from alcohol 20. Acidic hydrolysis of the 1,3-dioxolane ring yielded (±) ascochlorin 1. The IR and ^{1}H-Nmr of the synthetic product were identical to those of natural ascochlorin.

SCHEME V



[a]17, LDA, THF, -78°C; [b]DIBAL, CH_2Cl_2, -78°C; [c]CBr_4,PPh_3, -78°C; [d]potassium salt of 5-chloroorsellinaldehyde, toluene, Δ ; [e]HOAc, H_2O, THF.

EXPERIMENTAL

General: ^{1}H-Nmr spectra were obtained in designated solvents on a Bruker WM (250 MHz) or an IBM WP 200 SY (200 MHz) Fourier transform spectrometer. Chemical shifts are in parts per million (δ) relative to tetramethylsilane. Coupling constants (*J* values) are in Hertz (Hz). Multiplicities are designated as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). All samples were run in deuteriochloroform unless otherwise indicated. ^{13}C and NOE studies were carried out on an IBM WP 200 SY (200 MHz) Fourier transform spectrometer. High resolution mass spectra were obtained on a V.G. MICROMASS 7070H spectrometer interfaced with a Kratos DS-50-S data system. Infrared spectra (IR) were obtained on an IBM IR/97 Fourier transform spectrometer, as a thin film (neat) on sodium chloride plates, or as potassium bromide disks (KBr pellets).

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Elemental microanalyses were performed at Mic Anal Organic Microanalysis, P.O. Box 41838, Tucson, AZ 85717. Analytical thin layer chromatography (TLC) was performed on precoated silica gel plates (250μm) with a fluorescent indicator supplied by E. Merck (silica gel 60). Visualization was effected with ultraviolet light (UV)-254nm, 7% W/V ethanolic 12-phosphomolybdic acid (PMA), or 0.4% W/V 2,4-dinitrophenylhydrazine in 2N HCl (DNP). Preparative thin layer chromatography (PTLC) was performed on precoated silica gel plates (1000 μm) with a fluorescent indicator, supplied by Analtech, Inc. Flash column chromatography was performed on Merck silica gel 60 (230-400 mesh). All solvents used were reagent grade. Anhydrous diethyl ether, tetrahydrofuran (THF), and benzene were distilled from sodium and benzophenone; methanol was distilled from magnesium turnings and a small amount of iodine; methylene chloride was distilled from phosphorus pentoxide (P_2O_5) or calcium hydride; toluene, and N,N-dimethyl formamide (DMF) were distilled from calcium hydride.

Vapor phase chromatographic analyses were obtained on a Perkin-Elmer 3920 gas chromatograph interfaced with a Hewlett-Packard 3390A integrator (Alltech 3% SE-30 on Gas Chrom Q,

100/120m, 6'x2mm glass column). The gas chromatograph was equipped with a linear temperature programmer. All analyses were run from 80°C to 280°C, the temperature increasing at 16°C/min.

3-Chloro-4,6-dihydroxy-2-methylbenzaldehyde (7). Orcinol (5) was formylated under Gatterman conditions with zinc cyanide in dry ether and anhydrous hydrogen chloride to afford 6 in yields varying from 70-72%, mp 180-183°C (lit.[11] mp 178-180°C). Sulfuryl chloride (1.08 g, 8 mmol) was dissolved in dry ether (25 ml) and added dropwise to a stirred solution of 6 (1.11 g, 7.3 mmol) in dry ether (125 ml) at 0°C. The reaction was stirred at 0°C for 1.5 h, and then at room temperature for 8 h. The reaction was followed by TLC (hexane:EtOAc, 6:1). After the disappearance of the starting material, the solution was washed with $NaHCO_3$, saturated sodium chloride solution and water. It was dried ($MgSO_4$) and concentrated in vacuo. Separation of 7a and 7b was accomplished by flash column chromatography using 15% EtOAc in hexane as the eluant. Pure 7a (1.14 g, 76.5% yield) was obtained as a white solid, mp 169-172°C, lit[11] mp 168-170°C. IR (KBr) 3076 (OH), 1630 (C=O); ^{1}H-Nmr (C_3D_6O) 2.67 (s, 3H), 6.41 (s, 1H), 10.00 (br s, 1H) 10.22 (s, 1H), 12.55 (s, 1H).

2,6-Dimethylcyclohex-2-ene-1-one (10). 2,6-Dimethylanisole (8) (50 g, 0.37 mol) dissolved in dry THF (140 ml) and absolute ethanol (140 ml) was added dropwise to dry liquid NH_3 (1000 ml) at -78°C. Clean lithium wire (5.65 g, 0.814 gat) was added in small portions (1 g) under mechanical stirring. After the addition was completed, water (500 ml) was added and the solution was extracted with pentane (4x100 ml). The organic layer was washed with saturated sodium chloride solution, dried over $MgSO_4$ and concentrated to a residue (41.9 g) which was immediately hydrolysed by dissolving it in THF (250 ml) and 1N HCl (40 ml). The mixture was stirred for 16 h, neutralized with $NaHCO_3$ solution, and extracted with ether (4x100 ml). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was distilled to afford pure 10 (27.1 g, 59% yield); bp 91°C/22mm, n_D^{20} 1.4750, IR (neat) 2928 (CH), 1680 (C=O), 1645 (C=C) cm^{-1}; lit[13] IR (neat) 1670 cm^{-1}; ^{1}H-Nmr 1.17 (d, J=7, 3H), 1.74 (m, 1H), 1.77 (s, 3H), 2.06 (m, 1H), 2.34 (m, 3H), 6.66 (t, J=2, 1H).

3-Hydroxy-2,3,4-trimethylcyclohexene (11). Compound 10 (10 g, 0.08 mol) was dissolved in dry THF (75 ml) and added dropwise into a stirred solution of methyllithium (0.10 mol) at -78°C. The reaction was first allowed to reach ambient temperature followed by dilution with a saturated NH_4Cl solution. The layers were separated and the aqueous phase extracted with ether (2x50 ml). The combined organic layers were washed ($NaHCO_3$, saturated sodium chloride solution) and dried ($MgSO_4$). Concentration of the residue afforded 11.3 g of crude 11. This material was purified by column chromatography, using hexane:EtOAc (8:1) as the eluting solvent, to afford 11 as a mixture (50:50) of diastereomers (9.27 g, 82.7% yield); bp 140°C/10 mm, n_D^{20} 1.4886; IR (neat) 3320 (OH); 1640 (C=C) cm^{-1}; ^{1}H-Nmr 0.99 (d, 3H), 1.03 (d, 3H), 1.15 (s, 6H), 1.42 (m, 6H), 1.59 (m, 3H), 1.77 (d, J=2, 6H), 1.97 (m, 3H), 2.15 (m, 3H), 3.17 (s, 2H, D_2O exchangeable), 5.38 (br s, 1H), 5.42 (br s, 1H); HRMS, m/e calcd. for $C_9H_{16}O$, 140.1197, found 140.1167.

2,3,4-Trimethylcyclohex-2-ene-1-one (12). Compound 11 (31.7 g, 0.23 mol) was dissolved in dry CH_2Cl_2 (200 ml). Pyridinium dichromate (102 g, 0.27 mol) was added to this solution and the mixture stirred at ambient temperature for 8 h. The solution was diluted with ether (200 ml) and the resulting black precipitate removed by filtration. The yellow solution was dried ($MgSO_4$) and concentrated to a brown oil. Column chromatography (hexane:EtOAc, 20:1) afforded 12 (26.3 g, 82.7% yield); n_D^{20} 1.4859; IR (neat) 1668 (C=O), 1632 (C=C) cm^{-1}; lit[19] IR 1675, 1645 cm^{-1}. ^{1}H-Nmr 1.20 (d, J=5, 3H), 1.70 (m, 1H), 1.76 (s, 3H), 1.92 (s, 3H), 2.11 (m, 1H), 2.42 (m, 3H); HRMS, m/e calcd for $C_9H_{14}O$, 138.1041, found 138.1039.

2,3,4-Trimethyl-3-vinylcyclohexanone (13). Tetrakisiodo(tri-n-butylphosphine)copper (22.8 g, 0.058 mol) was placed in a 500 ml, three-necked round-bottomed flask fitted with rubber septums, nitrogen inlet and a mechanical stirrer. The solid was dissolved in dry THF (100 ml) and the solution cooled to -78°C. Vinylmagnesium bromide (0.116 mol, 0.88 M solution in THF) was added dropwise via a syringe. The solution turned dark brown after addition of the first equivalent of Grignard reagent, then changed to a light yellow solution while a grey precipitate formed during addition of the second equivalent. Freshly distilled $BF_3.Et_2O$ (65 ml) was added via a syringe. A solution of 12 (4 g, 0.028 mol) in THF (25 ml) was added via a syringe pump (slow = 0.4 ml/min). The reaction was stirred for 3 h at -78°C and then quenched with a saturated NH_4Cl solution (100 ml). The layers were separated and the aqueous layer washed with ether (3x30 ml). The combined organic layers were washed with saturated sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (hexane:EtOAc, 15:1) to afford 13 (3.53 g, 73.5% yield), as a mixture of stereoisomers; IR (neat) 1716, 1701 (C=O), 1684, 1653 (C=C) cm^{-1}; ^{1}H-Nmr 0.70 (s, 3H), 0.84 (d, J=3, 3H), 0.88 (d, J=4, 3H), 0.97 (m, 1H), 1.93 (m, 2H), 2.41 (m, 3H), 4.93 (d, J=12, 1H), 5.12 (d, J=5, 1H), 5.62 (dd, J=12, 5, 1H); HRMS, m/e calcd. for $C_{11}H_{18}O$, 166.1357, found 166.1340.

6,7,8-Trimethyl-7-vinyl-1,4-dioxaspiro[4.5]decane (14). Compound 13 (3.53 g, 0.021 mol) was dissolved in reagent grade benzene (100 ml). Ethylene glycol (3.48 g, 0.056 mol) was added along with a catalytic amount of p-toluenesulfonic acid (0.01 g). The flask was fitted with a

Dean-Stark trap, a reflux condenser and drying tube. The solution was refluxed until no more water formed (8 h). It was then cooled, washed with 0.5 N NaOH (20 ml), saturated NaCl solution and dried ($MgSO_4$). Concentration of the organic layer afforded 14 (4.28 g, 97% yield; 99% pure by GLC analysis); IR (neat) 3084, 2979, 2960, 2931, 2877, 1637, 1456, 1183, 1153, 1074, 906 cm^{-1}; ^{1}H-Nmr 0.76 (dd, J=7, 6, 6H), 0.85 (s, 3H), 1.42 (m, 4H), 1.61 (q, J=6, 2H), 3.90 (m, 4H), 4.88 (d, J=17, 1H), 5.04 (d, J=11, 1H), 5.47 (dd, J=11, 17, 1H); HRMS, m/e calcd. for $C_{13}H_{22}O_2$, 210.1620, found 210.1620.

(Z,E)Ethyl 4-bromo-3-methyl-2-butenoate (16a,b). Ethyl 3,3-dimethylacrylate (15) (20 g, 0.156 mol) was dissolved in dry CCl_4 (250 ml). N-Bromosuccinimide (30 g, 0.17 mol) was added along with a catalytic amount of azobisisobutylnitrile (0.01 g). The solution was refluxed for 3 h, and then cooled. Succinimide was removed by filtration and the filtrate washed with chloroform. The combined organic phases were washed sequentially with saturated Na_2SO_3, saturated NaCl and dried ($MgSO_4$). The dried solution was concentrated to afford a crude product (34.4 g) which was purified[4] by flash column chromatography using ether:petroleum ether (1:50) as eluant. Compound 16a: bp 71°C/1.0 mm Hg; lit[22] bp 65°/3 mm Hg; lit[23] bp 41-45°C/0.03 mm Hg; IR (neat) 1718 (C=O), 1653 (C=C) cm^{-1}; n_D^{25} 1.4941; ^{1}H-Nmr 1.26 (t, J=7.4, 3H), 2.25 (d, J=1.6, 3H), 3.92 (d, J=0.7, 2H), 4.15 (q, J=5.2, 2H), 5.93 (d, J=0.7, 1H). Compound 16b: IR(neat) 1717, 1647 cm^{-1}; ^{1}H-Nmr 1.27 (t, J=7.1, 3H), 2.02 (d,J=1.4, 3H), 4.16 (q,J=7.1, 2H), 4.53 (d,J=1.4, 2H), 5.75 Cd, J=1.4, 1H).

(E,E) Ethyl 4-(diethoxyphosphinyl)-3-methyl-2-butenoate (17). Compound 16a (9.20 g, 0.444 mol) was added to freshly distilled triethyl phosphite (8.12 g, 0.480 mol) in a round-bottomed flask equipped with a reflux condenser. The solution was stirred and heated to 120°C, at which point, a vigorous reaction occured. The temperature was maintained at 120°C for 30 min after which time, the bromoethane formed was removed by evaporation. The reaction was refluxed for 2 h, followed by distillation. The product (17) was collected at 115°C/0.30 mm Hg. The yield of pure product was 10.04 g, 85.6% yield; n_D^{24} 1.4575; IR (neat) 2984, 2935, 2908, 1717 (C=O), 1647 (C=O), 1445, 1393, 1369, 1152, 1248, 1213, 1149, 1097, 1026, 964, 875, 854, 833, 783, 733 cm^{-1}. ^{1}H-Nmr 1.25 (t, 9H), 2.29 (dd, J=1.2, 3.5, 3H), 2.65 (d, J=14, 2H), 4.09 (q, 9H), 6.75 (dd, J=1.2, 5.2, 1H).

7-Formyl-6,7,8-trimethyl-1-4-dioxaspiro[4.5]decane (18). Ozone gas was bubbled through a solution of 14 (1.56 g, 7.42 mmol) in dry MeOH (60 ml) at -78°C for 15 min. The reaction was monitored by TLC (hexane:EtOAc, 5:1). After the disappearance of the starting material, the solution was treated with dry DMS (1 ml), and then warmed to ambient temperature and stirred for 2 h. The solvents were removed under reduced pressure and the resulting residue was purified by column chromatography using hexane:ethyl acetate (20:1) as the eluting solvent, to afford 18 (1.40 g, 89% yield). The instability of compound 18 did not permit us to obtain either an elemental analysis or a high resolution mass spectrum. The aldehyde was used immediately in the next step. IR (neat) 2900, 2830, 1720, 1445, 1370, 1270, 1180, 1150, 1100, 1075, 1019, 1000, 965, 950, 910 and 735 cm^{-1}; ^{1}H-Nmr 0.74 (d, J=7, 6H), 0.96 (s, 3H), 1.06 (q, 1H), 1.52 (m, 3H), 1.80 (m, 2H), 3.90 (m, 4H), 9.27 (s, 1H).

7-[4'-Ethoxycarbonyl-3'-methyl-1',3'-butadienyl]-6,7,8-trimethyl-1,4-dioxaspiro[4.5]decane (19). n-Butyllithium (1.94 ml of 1.6 M solution, 3.11 mmol) was syringed into a stirred solution of diisopropylamine (0.435 ml, 3.11 mmol) in dry THF (10 ml) at -78°C, under nitrogen. The LDA solution was warmed to 0°C for 5 min, then cooled again to -78°C. Phosphonate 17 (821 mg, 3.11 mmol) was syringed into the LDA solution dropwise and the mixture stirred for 15 min. Aldehyde 18 (330 mg, 1.55 mmol) in dry THF (10 ml) was syringed into the solution dropwise. The reaction was warmed to room temperature and stirred for 8 h, under nitrogen. It was then quenched with saturated NH_4Cl, washed with saturated sodium chloride solution, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether:ether, 10:1) to give 19 as a 6:1 mixture of E,E to E,Z isomers. Compound 19 was further purified by recrystallization from pentane (330 mg, 66% yield); mp 73-76°C; IR (KBr) 2932, 2874, 1701, 1632, 1612, 1452, 1402, 1383, 1356, 1325, 1275, 1242, 1159, 1097, 1069, 1026, 995, 982, 920, 905, 866, 818, 766, 743, 675, 532 cm^{-1}; ^{1}H-Nmr 0.72 (dd, J=4, 3H), 0.74 (d, J=5, 3H), 0.93 (s, 3H), 1.31 (t, J=7, 3H), 1.46 (m, 4H), 1.71 (q, J=7, 1H), 1.81 (m, 1H), 2.28 (d, J=1, 3H), 3.91 (m, 4H), 4.16 (q, J=7, 2H), 5.75 (s, 1H), 5.79 (d, J=16, 1H), 6.00 (d, J=16, 1H). HRMS, m/e calcd. for $C_{19}H_{30}O_4$, 322.2144, found 322.2141. Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77, H, 9.38. Found: C, 70.82, H, 9.63.

(E,E) 7-[5'-Hydroxy-4'-methyl-1',3'-pentadienyl]-6,7,8-trimethyl-1,4-dioxaspiro-[4.5]decane (20). A solution of diisobutylaluminum hydride (1M in CH_2Cl_2, 1.6 ml, 1.6 mmol) was added dropwise to a stirred solution of 19 (254 mg, 0.788 mmol) in dry CH_2Cl_2 (3 ml) at -78°C. Following the addition, the solution was stirred at -78°C for 40 min. Ether (40 ml) and water (1 ml) were then added and the resulting solution was allowed to come to ambient temperature. Anhydrous magnesium sulfate (4 g) was added in small portions over a period of 20 min. The drying agent was removed by filtration and the filtrate concentrated to yield 280 mg of crude material which was purified by column chromatography (EtOAc/hexane, 1:15) to afford 205 mg of pure 20 (88.4% yield); IR (neat) 3584, 3433 (OH), 1645 (C=C) cm^{-1}; ^{1}H-Nmr 5.95 (d, J=16, 1H), 5.60 (t, J=7,

1H) 5.36 (d, J=16, 1H), 4.26 (d, J=7, 2H), 3.92 (m, 4H), 2.05 (s, 1H, D_2O exchangeable), 1.78 (s, 3H), 1.7 (q, J=7, 1H), 1.46 (m, 4H), 1.26 (q, J=7, 1H), 0.90 (s, 3H), 0.73 (m, 6H); HRMS, m/e calcd. for $C_{17}H_{28}O_3$, 281.2124; found 281.2105. The E,E stereochemistry was assigned by irradiating the allylic methyl group at 1.78 ppm and observing NOE enhancements at δ 4.26 and δ 5.36 but not at δ 5.95 or δ 5.60.

E,E-7-[5'-Bromo-4'-methyl-1',3'-pentadienyl]-6,7,8-trimethyl-1,4-dioxaspiro-[4.5]decane (21). A solution of alcohol 20 (0.100 g, 0.357 mmol) in methylene chloride (20 ml) under an argon atmosphere, was cooled to -78°C. At this time, carbon tetrabromide (0.1539 g, 0.464 mmol) was added and followed immediately by triphenylphosphine (0.118 g, 0.4508 mmol). The reaction was stirred at -78°C for 30 min and allowed to warm to ambient temperature. The mixture was then flashed quickly through a short column of silica gel. The crude bromide was used in the next step without further purification, R_f 0.67 ether:petroleum ether (1:1).

Potassium salt of 5-chloroorsellinaldehyde. 5-Chloroorsellinaldehyde (7a) (0.200 g, 1.17 mmol) was dissolved in absolute ethanol (2.5 ml) and treated with a solution of potassium hydroxide in absolute ethanol (1 ml of 1M) added dropwise. The precipitated potassium salt was collected by suction filtration and washed with pentane. The crystals were dried for 2 h at 70°C in a drying pistol, under reduced pressure.

3-Chloro-4,6-dihydroxy-2-methyl-5-[E,E-3-methyl-5-(6,7,8-trimethyl-1,4-dioxaspiro[4.5]decane)-2,4-pentadienyl]benzaldehyde (22). Bromide 21 was added to a round-bottomed flask containing dry toluene (20 ml) and the potassium salt of 5-chloroorsellinaldehyde (0.167 g, 0.743 mmol). The mixture was refluxed for 1½ h, cooled and diluted with 50 ml of ether. The organic layer was washed with 1x3 ml of saturated NH_4Cl, and 1x3 ml of saturated NaCl. It was then dried over Na_2SO_4, and treated with 600 mg of silica gel. The solvent was removed under reduced pressure and the desired compound was adsorbed on the silica gel. The silica gel was placed on a column and the compound purified by flash chromatography using 15% ethyl acetate in hexane as eluant. Compound 22, R_f 0.32 (25% ethyl acetate:hexane). The yield of 22 was 27.5% from alcohol 20 (90.7 mg); IR (($CDCl_3$) 3520, 2990, 2940, 2890, 1730, 1640, 1470, 1420, 1380, 1300, 1290, 1250, 1100, 1070, 970, 910 cm^{-1}; ^{1}H-Nmr 0.71 (d, J=7, 3H), 0.75 (d, J=7, 3H), 0.83 (s, 3H), 1.42 (m, 4H), 1.63 (m, 2H), 1.88 (s, 3H), 2.58 (s, 3H), 3.51 (d, J=7.2, 2H), 3.80 (m, 4H), 5.23 (d, J=16, 1H), 5.46 (t, J=7.2, 1H), 5.87 (d, J=16, 1H), 6.39 (s, 1H), 10.11 (s, 1H), 12.68 (1H, s). HRMS, m/e calcd for $C_{25}H_{33}O_5Cl$, 448.2007, found 448.2006.

Ascochlorin (1). Compound 22 (40 mg) was placed in a round-bottomed flask with tetrahydrofuran (2 ml), glacial acetic acid (0.8 ml), and water (0.5 ml). The solution was heated at 60°C for 5 h, cooled and diluted with 20 ml of ether. The ether layer was washed with 1x3 ml of saturated NaCl solution. At this time 15 ml of toluene was added to azeotrope with the remaining acetic acid. The product was purified by flash column chromatography, using ethyl acetate-hexane, R_f 0.25. The yield of 1 was 94.8% (37 mg).

Acknowledgement

Financial support from Merck, Sharp and Dohme Laboratories for the partial support of this research is greatfully acknowledged.

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+Presented in part at the 188th National Meeting of the American Chemical Society, Philadelphia, August 1984, MEDI 110.

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