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SYNTHESIS OF THE NATURAL ENANTIOMERS OF ASCOCHLORIN, ASCOFURANONE AND ASCOFURANOL†

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Abstract---Three fungal metabolites with a common structural feature as prenylated phenols were synthesized in their naturally occurring and optically active forms: ascochlorin [(2'E,4'E,1"R,2"E,6"R)-(-)-5-chloro-2,4-dihydroxy-6-methyl-3-[5'-(1",2",6"-trimethyl-3"-oxocyclohexyl)-3'-methyl-2',4'-pentadienyl]benzaldehyde], ascofuranone [(2'E,6'E,1"S)-(-)-5-chloro-2,4-dihydroxy-6-methyl-3-[7'-(3",3"-dimethyl-4"-oxo-2"-oxacyclopentyl)-3',7'-dimethyl-2',6'-heptadienyl]benzaldehyde] and ascofuranol [(2'E,6'E,1"S,4"S)-(-)-5-chloro-2,4-dihydroxy-6-methyl-3-[7'-(3",3"-dimethyl-4"-hydroxy-2"-oxacyclopentyl)-3',7'-dimethyl-2',6'-heptadienyl]benzaldehyde]. (+)-Ascofuranone and (+)-ascofuranol were also synthesized. By the present synthesis the absolute configuration of the natural (-)-ascofuranol was established as (1"S,4"S).

Three interesting metabolites were isolated from the mycelia of Ascochyta viciae Libert as shown in Fig. 1. (-)-Ascochlorin **1** was isolated by Tamura et al. in 1968 as an antiviral antibiotic.[1] The structure **1** including (1"R,2"R,6"R)-absolute stereochemistry was assigned by Nawata et al. by an X-ray analysis of its 4-O-p-bromobenzenesulfonyl derivative.[2] Its dual biosynthetic origin as a prenylated phenol was proved later by Tanabe's biosynthetic studies.[3] Subsequently (-)-ascofuranone **2** was isolated by Sasaki et al. in 1972 as a hypolipidemic antibiotic.[4,5] As in the case of ascochlorin, the structure of (-)-ascofuranone **2** including its (1"S)-absolute configuration was established by an X-ray analysis of its 4-O-ethyl derivative by Ando et al.[6] Tamura's group later discovered its antitumor protective effect on L-1210 leukemia when it was administered once seven days before tumor challenge.[7] Together with ascofuranone **2**, a compound named (-)-ascofuranol **3a** was isolated and chemically correlated to ascofuranone **2** by its Collins oxidation.[5] However, its absolute configuration at C-4" remained unknown. Besides in Japan, Ellestad et al. in the U. S. A.[8] and Aldridge et al. in the U. K.[9] also isolated fungal metabolites related to ascochlorin.

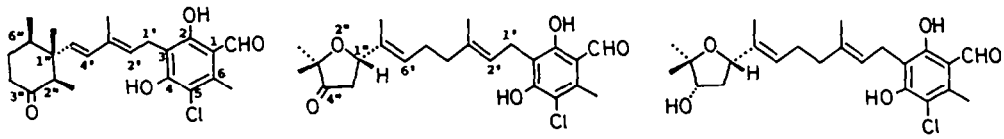


Fig. 1. Structures of the target molecules

† Synthetic Microbial Chemistry---X. This paper is cordially dedicated to Prof. Gakuzo Tamura on the occasion of his retirement from Department of Agricultural Chemistry, the University of Tokyo, on March 31, 1985. The experimental part of this work was taken from the M. Sc. thesis of S. T. (March, 1985). Part IX, K. Mori and A. K. Gupta, Tetrahedron, in the press.

The compounds **1~3a** are attractive targets for synthetic chemists with unique structures as the combination of a fully substituted benzene ring with a sesquiterpenoidal side-chain. In continuation of our studies on the synthesis of fungal metabolites with a hexa-substituted benzene ring,[10] we recently reported the full details of the synthesis of (±)-ascochlorin **1** and (±)-ascofuranone **2**.[11~13] Later Chen and Joullié also announced their synthesis of (±)-ascofuranone **2** in a preliminary communication.[14] Herein we describe the synthesis of (-)-ascochlorin **1**, (-)- and (+)-ascofuranone **2** and (-)- and (+)-ascofuranol **3a**. The present work unambiguously established the absolute configuration at C-4" of (-)-ascofuranol **3a** as (S).

Synthesis of (-)-ascochlorin. The peculiar stereochemical feature of the cyclohexane moiety of ascochlorin **1** is the equatorial nature of the alkadienyl side-chain and the two out of three Me groups. This means that ascochlorin **1** possesses a stable cyclohexane conformation which is not so difficult to generate. The success of a chiral synthesis of (-)-ascochlorin **1** is therefore heavily dependent on the selection of a suitable chiral starting material of high optical purity. As shown in Fig. 2, we chose (R)-(+)-pulegone **4** as our starting material which was available in optically pure state (100 % e.e.).[15] This, through several steps, would give (R)-3,4-dimethyl-2-cyclohexen-1-one **8**, whose racemate was the starting material in our previous synthesis of (±)-ascochlorin **1**. One of the key-steps in our synthesis of (±)-**1** was the conjugate addition to (±)-**8** of a mixed alkenylcuprate derived from **9**. This reaction yielded stable (±)-**10** with two eq substituents at C-3" and C-4". In the present chiral synthesis we expected to obtain the optically active **10** without significant racemization at C-3". Then it would be possible to synthesize (-)-ascochlorin **1** of high e.e. by the route employed for the synthesis of (±)-**1**. Our chiral synthesis was executed as detailed below.

(R)-(+)-Pulegone **4** was treated with dil HCl to give (R)-(+)-3-methylcyclohexanone **5**. Further conversion of (R)-**5** to (R)-(+)-4-methyl-2-cyclohexen-1-one **6** was carried out by the method of Barieux and Gore.[16] Our (R)-**6** was obtained in 9.1 % overall yield from (R)-**4** and showed the specific rotation of $[\alpha]_D^{20}$+123°(EtOH) or +117°($CHCl_3$) [lit.[16] $[\alpha]_D^{20}$+112°(EtOH); lit.[17] $[\alpha]_D^{22}$ +105° ($CHCl_3$)]. The higher $[\alpha]_D$ value of our material suggested its higher optical purity than those described by others,[16,17] although it did not necessarily ensure the 100 % e.e. of our (R)-**6**. The next task was the conversion of (R)-**6** to (R)-**8**. Since both (R)-**6** and (R)-**8** can racemize under non-neutral condition due to the acid- or base-catalyzed epimerization at C-4, we had to employ a mild method based on organoselenium chemistry.[18] An enolate anion generated by the addition of Me_2CuLi to (R)-**6** was trapped with PhSeBr and Ph_2Se_2 to give **7**. Oxidation of **7** with O_3 in CH_2Cl_2 at -78°was followed by thermal elimination of PhSeOH to give (R)-**8** in 59% yield from (R)-**6**. When the elimination of PhSeOH was carried out by H_2O_2 oxidation of **7**, the yield of (R)-**8** from (R)-**6** dropped to ca. 26 %. We repeated the synthesis of (R)-**8** for several times and every batch of (R)-**8** consistently showed the $[\alpha]_D$ value of +111°($CHCl_3$). We therefore assumed that the conversion of (R)-**6** to (R)-**8** took place without significant racemization. After the completion of our work, another synthesis of (R)-**8** from (R)-**6** by a different method (60 % overall yield) was reported by Danishefsky *et al.*[19]

With the key chiral intermediate (R)-**8** in hand, we proceeded to the next step of the conjugate addition to (R)-**8** of a mixed cuprate derived from **9**. Hydrostannation of **9** with $(n\text{-}Bu)_3SnH$ in the presence of AIBN was followed by metal exchange with n-BuLi to give a lithiodiene. A mixed cuprate derived from the lithiodiene and n-PrC≡CCu[20,21] in the presence of $(Me_2N)_3P$[22] was reacted with (R)-**8** to give **10** in 66 % yield. After workup a small amount of unreacted (R)-**8**, $[\alpha]_D^{20}$+98° ($CHCl_3$), was recovered. Since the specific rotation of the starting (R)-**8** was +111°($CHCl_3$), the recovered material still retained 88 % of the rotatory power of the starting material. This implies that the racemization caused in the course of the conjugate addition was less than 12 %, because further racemization at C-3' of the product **10** was impossible after its formation . The optical purity of **10** was therefore considered to be satisfactory for further synthetic operations.

The later steps from **10** to (-)-**1** followed the route already described for the synthesis of (±)-**1**.[13] After blocking the sterically less crowded C-4' CH_2 group with a CHO group to give **11**,

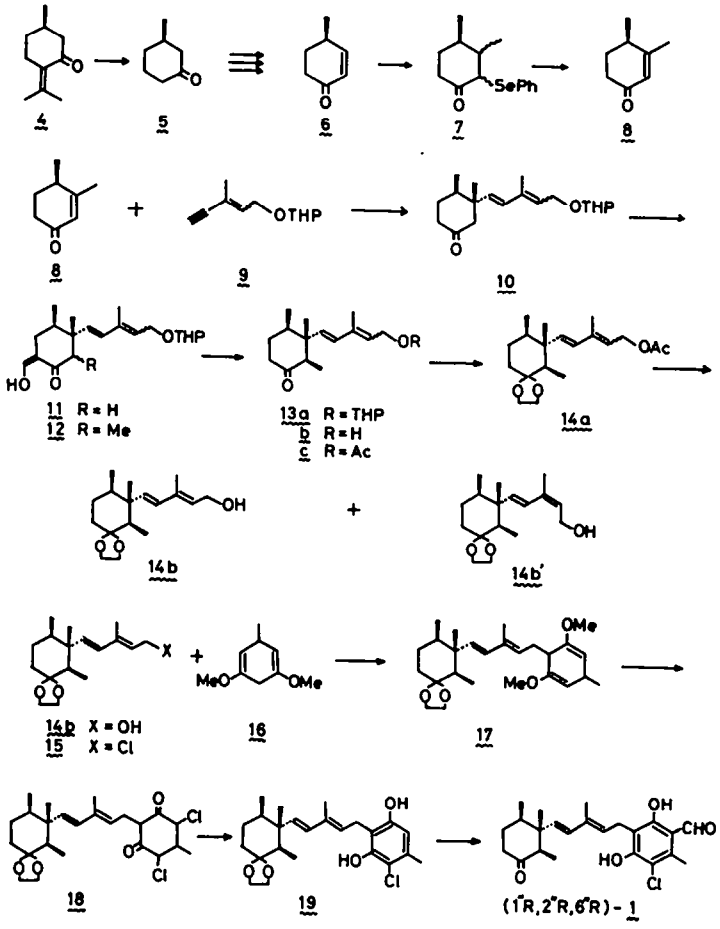


Fig. 2. Synthesis of (-)-ascochlorin.

the dianion of **11** was methylated to afford **12**. Hydrolysis of **12** with 2 % NaOH gave **13a** as the single isolable isomer with an eq Me Group at C-2'. This completed the introduction of the all of the three chiral centers of (-)-**1**. Treatment of **13a** with aq AcOH-THF gave **13b**, whose acetylation yielded an acetate **13c**. The acetate **13c** was treated with $MeOCH(OCH_2)_2$[23] and p-TsOH to furnish **14a**. This was hydrolyzed with K_2CO_3 to give a mixture of **14b** and **14b'**. It should be added that all of the intermediates **10**~**14a** were also obtained as a mixture of two geometrical isomers at C-2. As was in the case of the racemate, the desired (2E)-isomer **14b** was separated from the undesired (2Z)-isomer **14b'** by medium pressure LC to give pure **14b** as an oil, $[\alpha]_D^{22}$-1.4°($CHCl_3$), and pure **14b'**, m.p. 75.5~77°, $[\alpha]_D^{22}$-9.7°($CHCl_3$), in the ratio of 2:1. The (2E)-isomer **14b** was converted to the corresponding chloride **15** by the method of Stork et al.[24]

Alkylation of the lithiated **16**[cf.25] with **15** yielded **17** in 54 % yield. Use of the chloride **15** was superior to that of the corresponding bromide, which was too unstable to be handled. Treatment of **17** with N-chlorosuccinimide (NCS) gave a dichlorodiketone **18**. Aromatization of **18** to **19** was effected by heating **18** with DBU in THF. For the introduction of the CHO group, **19** was treated with EtMgBr in ether followed by $HC(OEt)_3$ according to Casnati.[26] Finally acid treatment of the crude product effected the hydrolysis of $-CH(OEt)_2$ to -CHO yielding (1"R,2"R,6"R)-(-)-ascochlorin **1** (11 mg), m.p. 171~172°, $[\alpha]_D^{23}$-31.5°(MeOH) [an authentic sample of **1**, m.p. 171~172°, $[\alpha]_D^{23}$ -30.7° (MeOH)]. The identity of our synthetic (-)-ascochlorin with the natural product was proved

by the mixed m.p. determination (m.m.p. 170.5~171.5 °) and the comparisons of IR (KBr disc) and 400 MHz ^{1}H-NMR spectra. The overall yield of (-)-ascochlorin **1** was 0.035 % in 22 steps from (R)-(+)-pulegone **4** or 0.32 % in 16 steps from (R)-(+)-4-methyl-2-cyclohexen-1-one **6**.

Synthesis of (-)-ascofuranol and (-)-ascofuranone. In contrast to the synthesis of (-)-ascochlorin **1**, there was no readily available chiral starting material for the synthesis of (-)-ascofuranone **2**. We therefore decided to attempt the optical resolution of an appropriate intermediate. As shown in Fig. 3, an obvious candidate for optical resolution was a ketone like **20a**. In the early phase of this work, we tried the separation of a diastereomeric mixture of **22** prepared by utilizing SAMP [(S)-1-amino-2-(methoxymethyl)pyrrolidine][27] as a chiral derivatizing agent. Although the diastereoisomers were separable neither by TLC nor by medium pressure LC, the separation was successful by means of reversed phase HPLC. However, the conversion of the purified diastereoisomer of **22** to optically active ascofuranone was unsuccessful after all. We then prepared an acetal of (±)-**20a** employing (2R,3R)-(-)-2,3-butanediol as a chiral derivatizing agent. The diastereomeric acetals were separable by medium pressure LC. Further transformation of the more polar diastereoisomer (+)-**23**, $[\alpha]_D^{22}$+1.63°($CHCl_3$), to ascofuranone **2** by our method used for the synthesis of (±)-**2** gave (R)-(+)-ascofuranone **2**, proving the absolute configuration of the more polar (+)-**23** to be (R) as depicted. The specific rotation of (+)-**2**, however, was rather small, $[\alpha]_D^{22}$ +15.9° (MeOH), while an authentic (-)-**2** showed $[\alpha]_D^{19}$value of -37°(MeOH). This implied

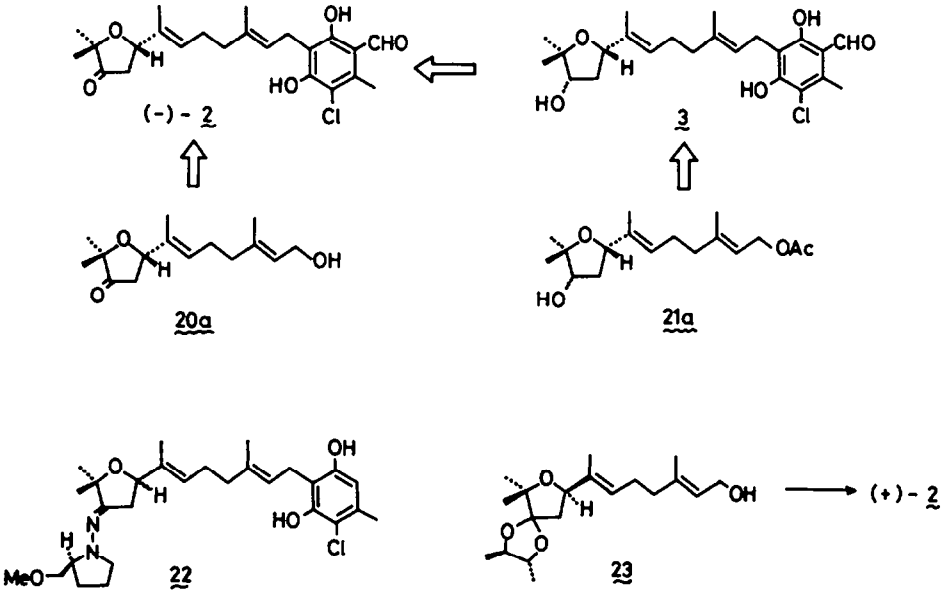


Fig. 3 Earlier studies on the synthesis of (-)-ascofuranone

that partial racemization at the chiral center took place in the course of the conversion of (+)-**23** to (+)-**2**. The chiral center of **2** is located at an allylic position, which is also a position β to the CO group. Therefore ascofuranone **2** could racemize under a drastic condition.

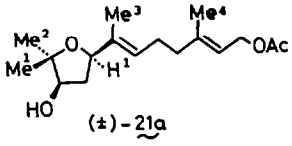
The above described negative results as provided by Mr. T. Fujioka in early 1983 made us to change our strategy. We envisaged that an alcohol like (±)-**21a** should be chosen as the candidate for optical resolution. There were dual advantages for this choice: (i) Reduction of the CO group at C-4' to CHOH would eliminate the possibility of racemization at C-1' *via* a retro-Michael reaction, and (ii) Even if slight racemization might take place at C-1'(an allylic position) after resolving (±)-**21a**, it would generate a diastereoisomer sharing the same configuration at C-4' with

that of the non-racemized **21a**. The unwanted diastereoisomer would be removed by chromatography or recrystallization.

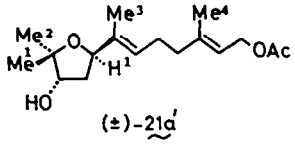
The synthesis of the enantiomers of ascofuranone **2** started from geraniol **24** by the route shown in Fig. 4. The aldehyde **25** was prepared in 41 % yield from geraniol **24** as reported by us.[28] A cross-aldol reaction between **25** and a dianion derived from 3-hydroxy-3-methyl-2-butanone gave (±)-**26** in 51 % yield by employing $LiN(SiMe_3)_2$ as the base. Cyclization of (±)-**26** to the furanone (±)-**20b** was achieved in 49 % yield by treating (±)-**26** with p-TsOH in 2-methoxy-1,3-dioxolane [$MeOCH(OCH_2)_2$] containing a small amount of MeOH. Reduction of (±)-**20b** with $NaBH_4$ in MeOH yielded a mixture of two alcohols (±)-**21a** and (±)-**21a'**. When the reduction was carried out at room temp, the product consisted of a less polar alcohol and a more polar one in a ratio of 9:1. The reduction was more selective at -70°, and the ratio of the two diastereoisomers was 16:1. The assignment of the relative stereochemistry to these two products was made possible by the NMR measurement in the presence of a shift reagent $Eu(fod)_3$. As can be seen from Table 1, the 1H signal due to H^1 of the major product suffered less extensive down-field shift than that of the minor product upon addition of $Eu(fod)_3$, while the 3H signal due to Me^3 suffered more extensive down-field shift in the case of the major product than in the case of the minor product. The major product therefore must be (±)-**21a** with (1'S*,4'S*)-relative stereochemistry, while the minor one should be (±)-**21a'**. The minor isomer (±)-**21a'** could be oxidized to (±)-**20b**, which could be reduced again to give an additional amount of (±)-**21a**.

With a sufficient amount of (±)-**21a** in hand, we moved on the problem of the optical resolution. Pirkle's method of resolution via naphthylethylcarbamate[29] seemed to be particularly appropriate for our purpose, because the carbamate could be removed selectively with $HSiCl_3$ under a mild condition[30] keeping the AcO group of **21a** intact. This was of importance in defferentiating the two oxygen functions of **21a**. Treatment of (±)-**21a** with the isocyanate (R)-**27** at 80°for 14 h yielded a diastereomeric mixture of (1'S,4'S)-**21b** and (1'R,4'R)-**21b**. These two were separable by

Table 1. 60 MHz ^{1}H-NMR data of (±)-**21a** and (±)-**21a'** in the presence of $Eu(fod)_3$-d_{27}*



(±)-21a



(±)-21a'

Amounts of the added $Eu(fod)_3$-d_{27}	δ-Values of the protons specified below of (±)-**21a** (the major product)					(±)-**21a'** (the minor product)				
	H^1	Me^1	Me^2	Me^3	Me^4	H^1	Me^1	Me^2	Me^3	Me^4
0 mg	4.11	1.11	1.11	1.53	1.66	4.37	1.14	1.14	1.52	1.69
10	4.41	----	----	----	----	4.75	----	----	----	----
20	4.70	2.26	1.59	2.00	1.91	5.20	1.58	1.98	1.76	1.88
30	5.05	2.87	1.84	2.24	2.03	5.79	1.83	2.49	1.93	2.02
Δδ(δ30 mg- δ0 mg)	0.94	1.76	0.73	0.71	0.37	1.42	0.69	1.35	0.41	0.33

*To a soln of 38 mg of (±)-**21a** or (±)-**21a'** in 0.30 ml of CCl_4, $Eu(fod)_3$-d_{27} was added. $Eu(fod)_3$=tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium.

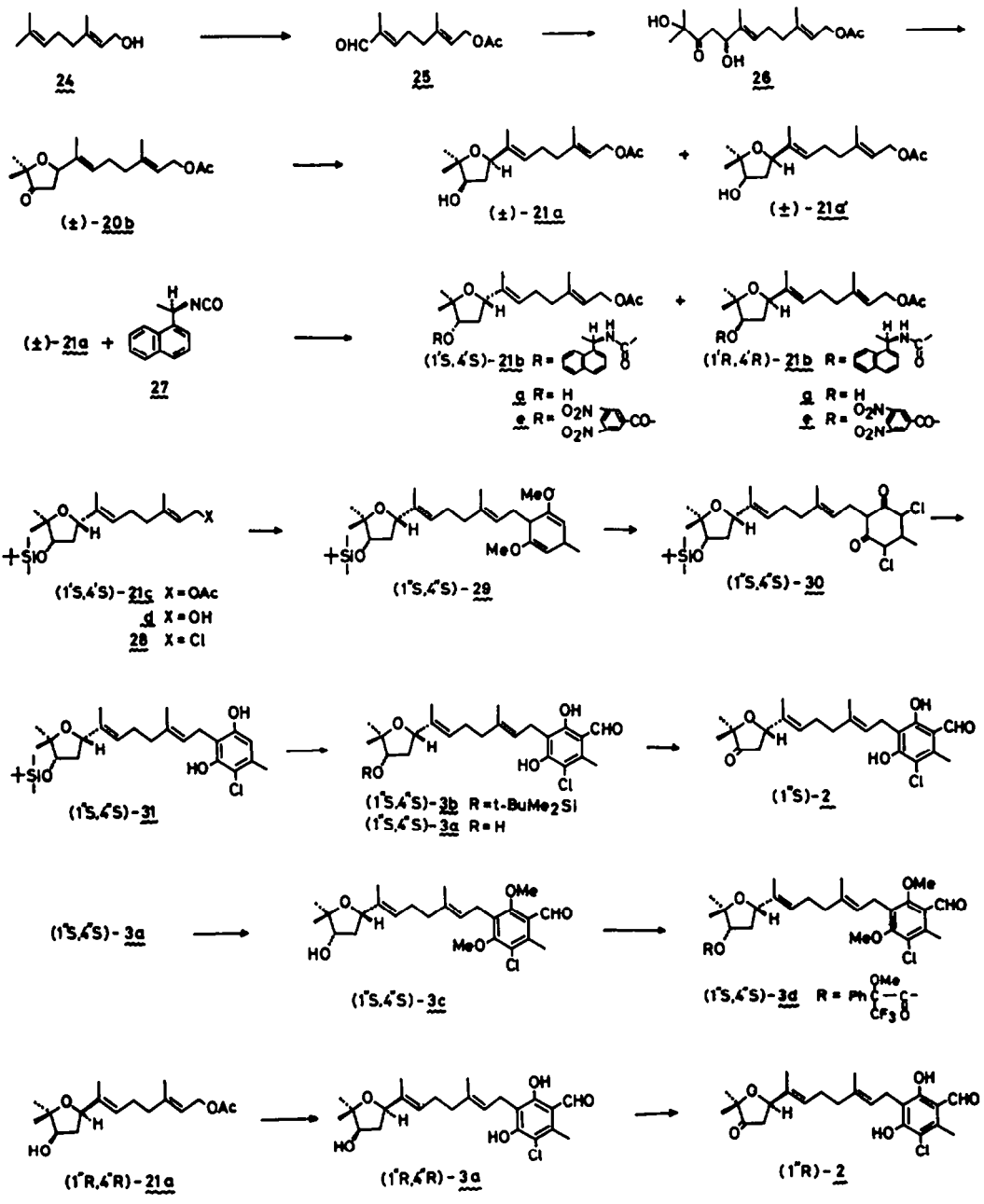


Fig.4. Synthesis of the enantiomers of ascofuranol and ascofuranone.

medium pressure LC over SiO_2. Upon treatment with $HSiCl_3$ the less polar carbamate **21b** yielded (+)-**21a**, $[\alpha]_D^{21}$+15.4°($CHCl_3$), and the more polar diastereoisomer gave (-)-**21a**, $[\alpha]_D^{21}$-15.6° ($CHCl_3$). The efficiency of this resolution was 58.3 % in the case of (+)-**21a** and 54.6 % in the case of (-)-**21a**, respectively, basing on the amount of the enantiomers contained in the starting (±)-**21a**. The absolute configuration of (+)-**21a** was shown to be (1'S,4'S) by its later conversion to (S)-(-)-ascofuranone **2**.

The remaining task is the conversion of the enantiomers of **21a** to the enantiomers of ascofuranone **2** and ascofuranol **3a** by a route similar to that used in our previous synthesis of (±)-**2**. After protecting the OH group of (1'S,4'S)-(+)-**21a** with t-$BuMe_2SiCl$, the resulting (1'S,4'S)-(+)-**21c** was treated with K_2CO_3 to give (+)-**21d**. The corresponding chloride (1'S,4'S)-**28** was prepared by the Stork procedure[24] and used for the alkylation step to give (1"S,4"S)-(+)-**29**. Treatment of (+)-**29** with NCS yielded **30**, whose aromatization with DBU furnished (1"S,4"S)-(+)-**31**. To this was introduced a CHO group to give (1"S,4"S)-**3b**, whose desilylation with aq HF-MeCN[31] gave (1"S,4"S)-(-)-ascofuranol **3a**, m.p. 91~92°, $[\alpha]_D^{21}$-3.1°(MeOH). In the same manner, (1'R,4'R)-(-)-**21a** yielded (1"R,4"R)-(+)-ascofuranol **3a**, m.p. 91~92°, $[\alpha]_D^{21}$+3.2°(MeOH). The 500 MHz ^{1}H-NMR spectrum of our synthetic (-)-ascofuranol **3a** was completely identical with that of an authentic sample of (-)-**3a**. The reported physical data [m.p. 75°, $[\alpha]_D^{21}$-7°(MeOH)][5] of the natural (-)-**3a**, however, were not in good accord with ours. Because of the limited availability (<1 mg) of the authentic sample of (-)-**3a**, we thought it desirable to rigorously prove the high optical purity of our synthetic (-)-**3a**. For that purpose a small amount of our (-)-**3a** was treated with MeI and K_2CO_3 to give a dimethyl derivative (1"S,4"S)-**3c**. This was acylated with (R)- or (S)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA)[32] to give (1"S,4"S)-**3d**. The HPLC analysis of **3d** proved its high diastereomeric purity (>99 %), which implied the high optical purity (>99 %) of the original (-)-**3a**.

The concluding step for the completion of our ascofuranone synthesis was the oxidation of **3a** to **2**. In the course of their structural studies on (-)-ascofuranol **3a**, Sasaki et al. oxidized (-)-**3a** with $CrO_3 \cdot C_5H_5N$ in CH_2Cl_2 to give (-)-ascofuranone **2** in 20 % yield.[4] We tried other methods, too. The Swern oxidation with DMSO-$(COCl)_2$[33] of (-)-**3a** gave no useful result. PDC (pyridinium dichromate) oxidation[34] was also fruitless. Finally PCC (pyridinium chlorochromate) oxidation[35] of (-)-**3a** gave (-)-ascofuranone **2**, m.p. 83~84°, $[\alpha]_D^{19}$-37°(MeOH), in 22 % yield. Similarly (+)-ascofuranol **3a** was oxidized with PCC to give (+)-ascofuranone **2**, m.p. 80~81°, $[\alpha]_D^{19}$ +43° (MeOH), in 32 % yield. An authentic sample of (-)-ascofuranone **2** as recrystallized by ourselves showed the following properties: m.p. 80~81°, $[\alpha]_D^{19}$-37°(MeOH) [lit.[5] m.p. 84~85°, $[\alpha]_D^{21}$ -50°(MeOH)]. Our synthetic (-)-ascofuranone **2** was shown to be identical with the authentic sample by the mixed m.p. determination (m.m.p. 82~84°) and the comparisons of IR (KBr disc) and 400 MHz ^{1}H-NMR spectra. The overall yield of (-)-ascofuranone **2** was 0.073 % from geraniol **24** in 17 steps or 0.71 % from (±)-**20b** in 12 steps.

In conclusion, the optically active forms of ascochlorin, ascofuranone and ascofuranol were synthesized for the first time. The method described herein should be useful in preparing various analogs of these fungal metabolites of medicinal interest.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra refer to films for oils and KBr discs for solids and were measured on a Jasco IRA-102 spectrometer. ^{1}H-NMR spectra were recorded on a Hitachi R-24A (60 MHz) or a Jeol JNM FX-400 (400 MHz) or a Bruker AM-500 (500 MHz) spectrometers with TMS as an internal standard. ^{13}C-NMR spectra were recorded on a Jeol FX-100 (25 MHz) spectrometer. MS were recorded on a Jeol DX-300 (70 eV) spectrometer. Optical rotations were measured on a Jasco DIP-140 polarimeter. For chromatographic separation, Merck Kieselgel 60 (Art 7734) was used unless otherwise specified.

(R)-(+)-3,4-Dimethyl-2-cyclohexen-1-one **8**. A soln of Me_2CuLi in dry ether was prepared by the dropwise addition of 1.59 M MeLi in ether (88 ml, 140 mmol) over 40 min to a stirred and cooled suspension of CuI (13.3 g, 70 mmol) in ether (260 ml) at -40° under Ar. The soln was stirred for 10 min at -40°. Then a soln of **6** (5.10 g, 46 mmol) in ether (31 ml) was added in one portion to the stirred and cooled soln. After stirring for 10 min, a soln of Ph_2Se_2 (21.7 g, 69 mmol) and Br_2 (1.9 ml, 37 mmol) in dry THF (64 ml) was added with stirring and cooling at -40°. The temp was allowed to rise to room temp and the reaction was quenched by the addition of sat NH_4Cl aq (250 ml) and n-pentane-ether (1:1, 500 ml). The mixture was filtered and the org layer was separated. The aq layer was extracted with n-pentane-ether (1:1, 200 ml x 2). The combined org soln was washed with water (150 ml) and brine (150 ml), dried ($MgSO_4$) and concentrated in vacuo to give an oil (24.5 g). This was chromatographed over SiO_2 (100 g). Elution with EtOAc-n-hexane (0:1~1:4) gave 11.2 g (86.5 %) of **7**, νmax 1710 (s), 1585 (w), 735 (s), 690 (s) cm^{-1}. O_3 was bubbled into a soln of **7** (11.2 g, 40 mmol) in CH_2Cl_2 (60 ml) with cooling at -70°. When the soln turned blue (excess O_3), an additional bubbling of O_3 was continued for 10 min. Then N_2 was bubbled to remove excess O_3 at -70°. Et_2NH (4.79 ml, 46 mmol) was added to the reaction mixture at -70°. In a separate vessel, CCl_4 (300 ml) was heated under reflux. To this were added Et_2NH (2.40 ml, 23 mmol) followed by the ozonized reaction mixture. The mixture was added in one portion while its temp was still -70°. The heating was stopped and the mixture was allowed to cool to room temp. The organic soln was washed with 10 % HCl (50 ml), sat $NaHCO_3$ aq (50 ml) and brine, dried ($MgSO_4$) and concentrated in vacuo to give 23 g of a crude oil. This was chromatographed over SiO_2 (120 g). Elution with ether-n-pentane (1:9~3:7) gave 3.37 g (58.7 % from **6**) of **8**, b.p. 102.5~104°/23 Torr; n_D^{21} 1.4895; $[\alpha]_D^{21}$ +111° (c=1.06, $CHCl_3$); νmax 3340 (w), 3045 (w), 1670 (br.s), 1625 (s), 860 (m) cm^{-1}; δ (60 MHz, CCl_4) 1.19 (3H, d, J=6 Hz), 1.93 (3H, s), 1.60~2.60 (5H, m), 5.69 (1H, br.s); GLC (Column, 10 % PEG 20M, 2 m x 3 mm at 50~200° with gradient increase of 10°/min; Carrier gas, N_2, 1.1 kg/cm^2) Rt 14.0 min (>99 %). (Found: C, 77.10; H, 9.68. Calc for $C_7H_{12}O$: C, 77.37; H, 9.75 %).

(2EZ,4E,1'R,6'R)-(-)-5-(1',6'-Dimethyl-3'-oxocyclohexyl)-3-methyl-2,4-pentadien-1-ol THP ether **10** A catalytic amount of AIBN and $(n\text{-}Bu)_3SnH$ (10.5 ml, 40 mmol) were added to **9** (7.5 g, 41 mmol) under Ar, and the mixture was heated at 100° for 30 min. The excess $(n\text{-}Bu)_3SnH$ was removed by heating in vacuo for 10 min at 100°. The residue was dissolved in THF (54 ml) and cooled to -70°. A soln of n-BuLi in n-hexane (1.68 M, 24 ml, 40 mmol) was added over 12 min to the stirred and cooled mixture and the stirring was continued for 40 min at -70°. To this was added over 10 min a soln of n-PrC≡CCu (6.2 g, 47 mmol) in ether (60 ml) and $(Me_2N)_3P$ (17.1 ml, 93 mmol) with stirring and cooling at -70°. The stirring was continued for 2 h at -70°. A soln of **8** (2.78 g, 22 mmol) in ether (30 ml) was added over 8 min to the stirred and cooled mixture at -70°. The stirring was continued for 2.5 h at -75°. The reaction was quenched by the addition of sat NH_4Cl aq. The org soln was separated and the aq layer was extracted with ether. The combined organic soln was washed with water and brine, dried (K_2CO_3 and $MgSO_4$) and concentrated in vacuo to give 43.6 g of an oil. This was purified by chromatography over SiO_2 (300 g). Elution with EtOAc-n-hexane (0:1~1:9) gave 4.53 g (66.0 %) of **10**, n_D^{20} 1.5119; $[\alpha]_D^{20}$ -24.1°(c=1.01, $CHCl_3$); ν max 1715 (s), 1650 (w), 1020 (s) cm^{-1}; δ(60 MHz, CCl_4) 0.91 (3H, d, J=6 Hz), 0.92 (3H, s), 1.10~2.05 (12H, m, $-CH_3$ singlet at 1.74 (E), 1.82 (Z)), 2.05~2.50 (4H, m), 3.15~4.25 (4H, m), 4.54 (1H, br.s), 5.20~5.80 (2H, m), 5.95 (0.62H, d, J=16 Hz (E)), 6.32 (0.38H, d, J=16 Hz (Z)). (Found: C, 74.19; H, 9.52. Calc for $C_{19}H_{30}O_3$: C, 74.47; H, 9.86 %).

(2EZ,4E,1'R,2'R,6'R)-(-)-5-(1',2',6'-Trimethyl-3'-oxocyclohexyl-3-methyl-2,4-pentadien-1-ol THP ether **13a**. (i) 50 % NaH in mineral oil (1.16 g, 24.2 mmol) was suspended in C_6H_6 (20 ml) under Ar. To this was added a soln of **10** (4.50 g, 14.7 mmol) and HCO_2Et (1.82 ml, 22.5 mmol) in C_6H_6 (20 ml) over 3 min with stirring and cooling at 7~8°. The mixture was stirred for 3 h at 10° and the reaction was quenched by the addition of cold water (30 ml). The aq layer was acidified to pH 4 by the addition of N-HCl (ca. 23 ml) and extracted with ether. The ether soln was washed with water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo to give 5.30 g of crude **11**, νmax 1640 (s), 1590 (s) cm^{-1}. This was employed in the next step without further purification. (ii) A soln of $LiN(i\text{-}Pr)_2$ (32.3 mmol) was prepared by the addition of n-BuLi (1.55 M in n-hexane, 20.8 ml) to a soln of $(i\text{-}Pr)_2NH$ (4.52 ml) in THF (30 ml) under Ar. To this was added a soln of the crude **11** (5.30 g) in THF (17 ml) over 15 min with stirring and cooling below -15°. After stirring for 20 min at -20°, a soln of MeI (1.38 ml, 22.2 mmol) in HMPA (4.5 ml) was added over 5 min. The stirring was continued for 1 h at -20°. The reaction was quenched by the addition of sat NH_4Cl aq (30 ml). The mixture was acidified with N-HCl (ca. 53 ml) to pH 4 and the org layer was separated. The aq layer was extracted with ether. The combined org soln was washed with water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo to give 5.75 g of crude **12**, νmax 1640 (s), 1595 (s) cm^{-1}. This was employed in the next step without further purification. (iii) A soln of the crude **12** (5.75 g) in 2 % NaOH aq (120 ml) was stirred and heated under reflux for 1 h. It was acidified with N-HCl (60 ml) under ice-cooling to pH 4 and extracted with ether. The ether soln was washed with water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (4.97 g) was chromatographed over SiO_2 (120 g). Elution with EtOAc-n-hexane (5:95) gave 2.00 g (43 %) of **13a** with recovery of 0.66 g of **10**. The yield of **13a** from **10** was 50 % based on the consumed **10**. The physical data of **13a** were: n_D^{20} 1.5130; $[\alpha]_D^{20}$ -35.9°(c=0.92, $CHCl_3$); ν max 1715 (s), 1020 (s) cm^{-1}; δ (60 MHz, CCl_4) 0.73 (3H, s), 0.79 (3H, d, J=6 Hz), 0.82 (3H, d, J=6 Hz), 0.95~2.10 (12H, m, $-CH_3$ signals at 1.78 and 1.85), 2.10~2.52 (3H, m), 3.14~4.26 (4H, m), 4.56 (1H, br.s), 5.16~5.73 (2H, m), 5.90 and 6.28 (total 1H, each d, J=16 Hz). MS: m/z 320.2414 (M^+, Calc for $C_{20}H_{32}O_3$=320.2351).

(2EZ,4E,1'R,2'R,6'R)-(-)-5-(1',2',6'-Trimethyl-3'-oxocyclohexyl)-3-methyl-2,4-pentadien-1-ol **13b**. A soln of **13a** (3.20 g, 10.0 mmol) in AcOH-THF-water (2:2:1, 100 ml) was stirred and heated at 40° for 1 day. It was then diluted with cold water (200 ml) and extracted with ether. The ether soln was washed with water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (50 g). Elution with ether-n-hexane (1:4~1:1) gave 1.50 g (64 %) of **13b**, n_D^{21} 1.5255; $[\alpha]_D^{21}$ -52.0°(c=1.01, $CHCl_3$); νmax 3420 (br.s), 1715 (s), 1640 (w), 1010 (br.s) cm^{-1}; δ (60 MHz, CCl_4) 0.71 (3H, s), 0.77 (3H, d, J=6 Hz), 0.79 (3H, d, J=6 Hz), 0.93~1.12 (2H, m), 1.50~1.97 (4H, m), 2.10~2.51 (4H, m), 4.13 (2H, d, J=6 Hz), 5.11~5.86 (2H, m), 5.88 and 6.21 (total 1H, each d, J=16 Hz). MS: m/z 236.1835 (M^+, Calc for $C_{15}H_{24}O_2$: 236.1776).

(2EZ,4E,1'R,2'R,6'R)-(-)-5-(1',2',6'-Trimethyl-3'-oxocyclohexyl)-3-methyl-2,4-pentadienyl acetate **13c**. A mixture of **13b** (1.40 g, 5.92 mmol) and Ac_2O (0.70 ml) in C_5H_5N (12 ml) was stirred for 30 h at room temp. Then it was acidified with ice-cooling by the addition of 2 N-HCl (ca. 90 ml) to pH 2, and extracted with ether. The ether soln was washed with water,

sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (15 g). Elution with EtOAc-n-hexane (3:97~1:9) gave 1.49 g (90 %) of **13c**, n_D^{21}1.5119; $[\alpha]_D^{21}$-43.6°(c=0.99, $CHCl_3$); ν max 1740 (s), 1715 (s), 1650 (w), 1235 (s) cm^{-1}; δ(60 MHz, CCl_4) 0.73 (3H, s), 0.82 (6H, d, J=6 Hz), 1.82 (3H, s), 1.98 (3H, s), 1.66~2.10 (3H, m), 2.10~2.60 (3H, m), 4.56 (2H, d, J=7 Hz), 5.20~5.90 (2H, m), 5.88 and 6.27 (total 1H, each d, J=16 Hz). (Found: C, 73.77; H, 9.80. Calc for $C_{17}H_{26}O_3$: C, 73.55; H, 9.37 %).

(2E,4E,1'R,2'R,6'R)-(-)-5-(3',3'-Ethylenedioxy-1',2',6'-trimethylcyclohexyl)-3-methyl-2,4-pentadienyl acetate **14a**. A soln of p-TsOH in C_6H_6 (3.5 %, 2 ml) and MeOH (0.1 ml) were added to a soln of **13c** (1.46 g, 5.23 mmol) in 2-methoxy-1,3-dioxolane (7 ml). The mixture was stirred for 4 days at room temp. During that period, MeOH (0.1 ml x 3) and p-TsOH in C_6H_6 (2 ml x 3) were added to the soln. It was then mixed with sat $NaHCO_3$ aq (50 ml) and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$ and K_2CO_3), and concentrated in vacuo. The residue was chromatographed over SiO_2 (14 g). Elution with EtOAc-n-hexane (3:97) gave 1.69 g (quantitative) of **14a**, n_D^{20}1.5074; $[\alpha]_D^{22}$-4.4°(c=1.03, $CHCl_3$); νmax 1740 (s), 1235 (s), 1070 (s) cm^{-1}; δ(60 MHz, CCl_4) 0.50~1.05 (9H, m, signals at 0.64, 0.75, 0.86, 0.90), 1.80 (3H, s), 1.96 (3H, s), 1.20~2.10 (6H, m), 3.63~4.06 (4H, m), 4.57 (2H, d, J=7 Hz), 5.10~5.69 (2H, m), 5.87 and 6.21 (total 1H, each d, J= 16 Hz). (Found: C, 71.04; H, 9.30. Calc for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38 %).

(2E,4E,1'R,2'R,6'R)-(-)-5-(3',3'-Ethylenedioxy-1',2',6'-trimethylcyclohexyl)-3-methyl-2,4-pentadien-1-ol **14b** and its (2Z,4E,1'R,2'R,6'R)-(-)-isomer **14b'**. To a stirred soln of K_2CO_3 (3.6 g, 26 mmol) in MeOH (6.6 ml) and water (9.0 ml) was added **14a** (1.60 g, 4.96 mmol). The mixture was stirred overnight at room temp and then heated at 40°for 4 h. It was diluted with sat $NaHCO_3$ aq (50 ml) and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$ and K_2CO_3) and concentrated in vacuo. The residue was chromatographed over SiO_2 (12 g). Elution with ether-n-hexane (1:9~1:1) gave 1.19 g (86 %) of a mixture of **14b** and **14b'**. The mixture (1.10 g) was chromatographed over a Merck Lobar column (LiChroprep®Si60, 40~63 μm, Grösse C). Elution with ether-n-hexane (3:7) effected the separation of the two isomers. The more polar isomer (0.65 g, 59 %) was shown to be the (2E)-isomer **14b**, n_D^{22}1.5225; $[\alpha]_D^{22}$-1.4 °(c=0.98, $CHCl_3$); νmax 3425 (br.s), 1645 (w), 1625 (w), 1100 (m), 1070 (s), 1015 (m), 1000 (m), 970 (m) cm^{-1}; δ(60 MHz, CCl_4) 0.69 (3H, d, J=6 Hz), 0.80 (3H, d, J=6 Hz), 0.85 (3H, s), 1.72 (3H, s), 1.15~1.95 (6H, m), 2.40 (1H, s), 3.47~3.95 (4H, m), 4.10 (2H, d, J= 7 Hz), 5.27 (1H, d, J=16 Hz), 5.55 (1H, t, J=7 Hz), 5.87 (1H, d, J=16 Hz). MS: m/z 280.2037 (M^+, Calc for $C_{17}H_{28}O_3$: 280.2037). The less polar isomer (0.32 g, 29 %) was shown to be the (2Z)-isomer **14b'**, m.p. 69~74°. An analytical sample of **14b'** was recrystallized from n-hexane, m.p. 75.5~77°(rhombs); $[\alpha]_D^{22}$-9.7°(c=1.12, $CHCl_3$); ν max (nujol) 3520 (s), 1640 (m), 1060 (s), 1010 (s) cm^{-1}; δ(60 MHz, CCl_4) 0.69 (3H, d, J=6 Hz), 0.80 (3H, d, J=6 Hz), 0.87 (3H, s), 1.79 (3H, s), 1.15~1.95 (7H, m), 3.47~3.95 (4H, m), 4.09 (2H, d, J=7 Hz), 5.31 (1H, d, J=16 Hz), 5.32 (1H, t, J=7 Hz), 6.12 (1H, d, J=16 Hz). (Found: C, 72.63; H, 10.06. Calc for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06 %).

(2'E,4'E,1"R,2"R,6"R)-3-[5'-(3",3"-Ethylenedioxy-1",2",6"-trimethylcyclohexyl)-3'-methyl-2',4'-pentadienyl]-2,4-dimethoxy-6-methyl-1,4-cyclohexadiene **17**. (i) A soln of n-BuLi in n-hexane (1.54 M, 1.1 ml, 1.69 mmol) was added dropwise to a stirred and ice-cooled soln of **14b** (470 mg, 1.68 mmol) in ether (1.5 ml) under Ar. HMPA (0.80 ml) was added to the mixture. Then a soln of p-TsCl (384 mg, 2.02 mmol) in ether (1.0 ml) was added dropwise to the stirred mixture at 0°. After stirring for 30 min at 0°, a soln of LiCl (213 mg, 5.03 mmol) in HMPA (2.0 ml) was added dropwise and the stirring was continued for 30 min. The reaction was quenched by the addition of sat $NaHCO_3$ aq (10 ml). The workup was carried out in a cold room (4°) to prevent the decomposition of **15**. The mixture was extracted with ether (80 ml). The ether soln was washed thoroughly with ice-water (x 4) and brine, dried ($MgSO_4$) and concentrated in vacuo at 0°to give 0.58 g of crude **15**. This material was so unstable that it was used immediately in the next step. (ii) A soln of **16** (500 mg, 3.24 mmol) in THF (1 ml) was added dropwise to a stirred and cooled soln of t-BuLi in a n-hexane (1.8 M, 1.5 ml, 2.70 mmol) in THF (2.5 ml) at -70°under Ar. After stirring for 20 min at -70°, HMPA (1.2 ml) was added to the mixture. The stirring was continued for 20 min at -70°. A soln of the crude **15** (0.58 g) in THF (1.5 ml) was added dropwise to the stirred mixture at -70°. After stirring for 30 min at -70°, the temp was allowed to rise to -15°over 15 min. The reaction was quenched at -15°by the addition of sat NH_4Cl aq (5 ml). The mixture was diluted with brine (10 ml) and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$ and K_2CO_3), and concentrated in vacuo. The residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 20 g). Elution with EtOAc-n-hexane (1:99~1.5:98.5) gave 378 mg (54.0 % from **14b**) of **17**, ν max 1690 (s), 1655 (m), 1600 (w), 1205 (s), 1175 (s), 1145 (s), 1070 (s) cm^{-1}; δ(60 MHz, CCl_4) 0.45~1.10 (12H, m), 1.60 (3H, s), 1.15~1.90 (6H, m), 2.32~3.08 (4H, m), 3.48 (6H, s), 3.65~4.10 (4H, m), 4.48 (2H, m), 4.85~5.38 (2H, m), 5.80 (1H, d, J=16 Hz). This material was employed in the next step without further purification.

(2'E,4'E,1"R,2"R,6"R)-3-[5'-(3",3"-Ethylenedioxy-1",2",6"-trimethylcyclohexyl)-3'-methyl-2',4'-pentadienyl]-1,5-dichloro-6-methyl-2,4-cyclohexanedione **18**. To a soln of **17** (370 mg, 0.89 mmol) in DMF (4.3 ml) and water (0.40 ml), $CaCO_3$ (32.8 mg, 0.33 mmol) was added under Ar. The vessel was slightly evacuated to remove O_2 dissolved in the solvents. NCS (261 mg, 1.95 mmol, 2.2 eq) was added to the stirred and cooled mixture at 0°. The temp was allowed to rise to room temp and the stirring was continued for 12 h. Water (20 ml) was added to the mixture and the stirring was further continued for 30 min. The mixture was acidified with N-HCl to pH 5 and extracted with ether (40 ml x 4). The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Mallinckrodt CC-7, 12 g). Elution with EtOAc-n-hexane (1:9~3:7) gave 179 mg (44.1 %) of **18**, νmax 3350 (br.m), 1720 (m), 1620 (br.m), 1375 (s), 1065 (s) cm^{-1}. This was employed in the next step without further purification.

(2'E,4'E,1"R,2"R,6"R)-4-Chloro-2-[5'-(3",3"-ethylenedioxy-1",2",6"-trimethylcyclohexyl)-3'-methyl-2',4'-pentadienyl]orcinol **19**. DBU (210 μl, 1.40 mmol) was added to a soln of **18** (125 mg, 0.27 mmol) in THF (0.80 ml). The mixture was stirred and heated under reflux for 2.5 h under Ar. It was diluted with water (4 ml), acidified with N-HCl to pH 5 and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by prep TLC (Merck Kieselgel 60F, Art 5717; Developed with EtOAc-n-hexane=5:4; Elution with ether) to give 72 mg (62.6 %) of **19**. νmax 3540 (w), 3350 (br.m), 1610 (m), 1585 (m), 1065 (s) cm^{-1}; δ(60 MHz, CCl_4) 0.40~1.08 (9H, m), 1.10~1.92 (6H, m), 1.83 (3H, s), 2.20 (3H, s), 3.38 (2H, d, J=7 Hz), 3.60~4.05 (4H, m), 4.90~6.40 (6H, m).

(2'E,4'E,1"R,2"R,6"R)-(-)-5-Chloro-2,4-dihydroxy-6-methyl-3-[5'-(1",2",6"-trimethyl-3"-oxocyclohexyl)-3'-methyl-2',4'-pentadienyl]benzaldehyde [(-)-ascochlorin] **1**. A soln of **19** (50 mg, 0.12 mmol) in ether (0.50 ml) was added gradually to a soln of EtMgBr (0.30 mmol) in ether (0.50 ml) with stirring under Ar at room temp. After the addition, the stirring was continued for 30 min. Then $HC(OEt)_3$ (100 μl, 6.0 mmol) was added and ether was distilled off from the mixture by raising the bath temp to 100°. The mixture was heated at 100° for 10 min. After cooling, the reaction was quenched by the addition of 0.5 N-HCl (4 ml). The mixture was extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by prep TLC (Merck Kieselgel 60F, Art 5717; Developed with EtOAc-n-hexane=5:2; Elution with ether) to give the acetal of **1** (56 mg). This was dissolved in ether (1 ml). To this was added 35 % $HClO_4$ aq (0.4 ml) with stirring and cooling at 0°. After stirring for 10 min, the mixture was neutralized by the addition of 10 % K_2CO_3 aq (2 ml) and water (5 ml). It was then extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (0.50 g). Elution with EtOAc-n-hexane (17:83) gave 21 mg (43.7 %) of (-)-**1**. One recrystallization from acetone-n-hexane gave 11 mg (22.9 %) of (-)-**1**, m.p. 167~169°. Further recrystallization from acetone-n-hexane gave (-)-**1** as pale yellow needles, m.p. 171~172°, m.m.p. 170.5~171.5° (authentic sample m.p. 171~172°); $[\alpha]_D^{23}$ -31.5° (c=0.16, MeOH); νmax (KBr disc) 3410 (br.m), 2990 (m), 2950 (m), 2890 (m), 1710 (s), 1635 (vs), 1465 (m), 1455 (m), 1425 (s), 1395 (m), 1380 (m), 1330 (m), 1290 (s), 1250 (vs), 1170 (m), 1110 (m), 1080 (w), 1015 (w), 975 (m), 910 (w), 790 (m), 715 (w) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.69 (3H, s), 0.81 (3H, d, J=6.6 Hz), 0.83 (3H, d, J=6.6 Hz), 1.60 (1H, m), 1.92 (3H, s), 1.94 (2H, m), 2.39 (3H, m), 2.60 (3H, s), 3.54 (2H, d, J=7.3 Hz), 5.38 (1H, d, J=16.0 Hz), 5.52 (1H, t, J=7.3 Hz), 5.90 (1H, d, J=16.0 Hz), 6.40 (1H, s), 10.14 (1H, s), 12.71 (1H, s); ^{13}C-NMR (25 MHz, $CDCl_3$) 9.0, 10.4, 12.7, 14.5, 16.4, 22.3, 31.2, 40.9, 41.6, 48.5, 53.7, 113.2, 113.7, 113.9, 127.6, 133.2, 134.2, 135.7, 137.8, 156.2, 162.3, 193.3, 212.7. These spectral data were identical with those of an authentic sample. (Found: C, 68.23; H, 7.06. Calc for $C_{23}H_{39}O_4Cl$: C, 68.22; H, 7.22 %).

(±)-(6E,10E)-12-Acetoxy-2,5-dihydroxy-2,6,10-trimethyl-6,10-dodecadien-3-one **26**. A soln of 3-hydroxy-3-methyl-2-butanone (19.4 g, 0.19 mol) in THF (160 ml) was added dropwise to a stirred and cooled soln of $LiN(SiMe_3)_2$ (prepd from 250 ml of 1.52 M n-BuLi in n-hexane and 80 ml of $HN(SiMe_3)_2$; 0.38 mol) at -40~-30° under Ar. After the addition, the stirring was continued for 2 h at -30°. The mixture was then cooled to -60° and a soln of **25** (20 g, 0.095 mol) in THF (200 ml) was added dropwise over 30 min with stirring at -60°. After stirring for 15 min at -60°, the reaction was quenched by the addition of sat NH_4Cl aq (50 ml). The cooled reaction mixture was poured into a mixture of conc HCl (60 ml), sat brine (400 ml) and water (200 ml). The organic layer was separated and the aq layer was extracted with ether. The combined org soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (400 g). Elution with EtOAc-n-hexane (3:7) gave 14.5 g (50.7 %) of **26**, n_D^{22} 1.4828; νmax 3450 (s), 1740 (s), 1710 (s), 1230 (s), 1020 (s) cm^{-1}; δ (60 MHz, CCl_4) 1.28 (6H, s), 1.61 (3H, s), 1.70 (3H, s), 2.01 (3H, s), 2.00~2.30 (4H, m), 2.49 (1H, dd, J=4, 16 Hz), 2.91 (1H, dd, J=9, 16 Hz), 3.47 (1H, br.s, OH), 4.03 (1H, br.s, OH), 4.32 (1H, br.s), 4.52 (2H, d, J=7 Hz), 5.10~5.60, (2H, m). (Found: C, 65.38; H, 8.77. Calc for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03 %).

(±)-(2E,6E)-7-(3',3'-Dimethyl-4'-oxo-2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadienyl acetate **20b**. p-TsOH·H_2O (100 mg) and MeOH (1.8 ml) were added to a soln of (±)-**26** (14.0 g, 47 mmol) in 2-methoxy-1,3-dioxolane (80 ml). The soln was stirred for 1 h 20 min at room temp. It was then cooled to 0° and the reaction was quenched by the addition of cold water (100 ml) and N-HCl (50 ml). After stirring for 5 min, the mixture was extracted with ether (x 5). The ether soln was washed with water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (180 g). Elution with EtOAc-n-hexane (5:95~1:9) gave 6.46 g (49.1 %) of (±)-**20b**, n_D^{20} 1.4754; νmax 1755 (s), 1735 (s), 1665 (w), 1230 (s) cm^{-1}; δ (60 MHz, CCl_4) 1.17 (3H, s), 1.24 (3H, s), 1.63 (3H, s), 1.72 (3H, s), 1.99 (3H, s), 1.87~2.54 (6H, m), 4.47 (1H, t, J=7 Hz), 4.52 (2H, d, J=7 Hz), 5.16~5.80 (2H, m). This was employed in the next step without further purification.

(2E,6E,1'S*,4'S*)-7-(4'-Hydroxy-3',3'-dimethyl-2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadienyl acetate (±)-**21a** and its (1'S*,4'R*)-isomer (±)-**21a'**. $NaBH_4$ (200 mg, 5.3 mmol) was added to a stirred and cooled soln of (±)-**20b** (2.82 g, 9.6 mmol) in MeOH (30 ml) at -70°. After stirring for 1 h at -70°, the reaction was quenched by the addition of AcOH (0.6 ml). The temp was allowed to rise to room temp and MeOH was removed in vacuo. The residue was dissolved in ether (300 ml). The ether soln was washed with water and sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (45 g). Elution with ether-n-hexane (3:7~1:1) gave 2.47 g of a mixture of **21a** and **21a'**. These two were separated by medium pressure LC on a Merck Lobar column (LiChroprep® Si60, 63~125 μm). Elution with ether-n-hexane (1:1) gave the two isomers in pure state. The less polar isomer (2.27 g, 80 %) was shown to be (1'S*,4'S*)-**21a**, n_D^{21} 1.4830; νmax 3450 (m), 1740 (s), 1665 (w), 1230 (s), 1020 (s) cm^{-1}; δ (60 MHz, CCl_4) 1.11 (6H, s), 1.48~1.80 (1H, m), 1.53 (3H, s), 1.66 (3H, s), 1.90~2.48 (5H, m), 1.92 (3H, s), 2.33 (1H, s, OH), 3.77 (1H, t, J=6 Hz), 4.11 (1H, t, J=7 Hz), 4.43 (2H, d, J=7 Hz), 5.02~5.58 (2H, m). (Found: C, 68.49; H, 9.42. Calc for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52 %). The more polar isomer (0.15 g, 5 %) was shown to be (1'S*,4'R*)-**21a'**, n_D^{21} 1.4833; νmax 3450 (m), 1740 (s), 1665 (w), 1230 (s), 1020 (s) cm^{-1}; δ (60 MHz, CCl_4) 1.14 (6H, s), 1.52 (3H, s), 1.69 (3H, s), 1.62~2.47 (6H, m), 1.98 (3H, s), 2.87 (1H, br.s, OH), 3.80 (1H, t, J=5 Hz), 4.37 (1H, t, J=7 Hz), 4.46 (2H, d, J=7 Hz), 5.10~5.50 (2H, m). (Found: C, 68.68; H, 9.24. Calc for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52 %).

PCC oxidation of (1'S*,4'R*)-**21a'**. A soln of **21a'** (150 mg, 0.53 mmol) in CH_2Cl_2 (1 ml) was added to a suspension of PCC (300 mg, 1.39 mmol) in CH_2Cl_2 (2 ml) at room temp. The mixture was stirred for 3 h at room temp, and filtered through Florisil (1 g). The Florisil column was washed with ether. The combined org soln was concentrated in vacuo. The residue was chromatographed over SiO_2 (2 g). Elution with EtOAc-n-hexane (1:9) gave 140 mg (94.0 %) of (±)-**20b**.

Separation of the carbamate diastereoisomers (1'S,4'S)-**21b** and (1'R,4'R)-**21b**. A mixture of (±)-**21a** (8.10 g, 27.3 mmol) and **27** (7.30 g, 37.0 mmol, 1.36 eq) was stirred and heated at 80° for 14 h. After cooling, the mixture was diluted with C_6H_6 (30 ml) and chromatographed over SiO_2 (600 g). Elution with EtOAc-C_6H_6 (0:1~1:9) gave 11.21 g (83.2 %) of a mixture of (1'S,4'S)-**21b** and (1'R,4'R)-**21b**. These two isomers were separated by medium pressure LC over SiO_2 (Merck Kieselgel 60, Art

9385, 230~400 mesh, 1.0 kg). Elution with EtOAc-C_6H_6 (1:4) gave the two diastereoisomers in pure forms. The less polar isomer (5.14 g) was shown to be (1'S,4'S)-**21b**, n_D^{21} 1.5462; $[\alpha]_D^{21}$ -7.0°(c=1.02, $CHCl_3$); ν max 3350 (m), 1740 (sh), 1715 (s), 1595 (w), 1235 (s) cm^{-1}; δ (60 MHz, $CDCl_3$) 1.18 (3H, s), 1.21 (3H, s), 1.64 (3H, d, J=7 Hz), 1.68 (6H, s), 2.02 (3H, s), 1.85~2.75 (6H, m), 4.30 (1H, t, J=8 Hz), 4.56 (2H, d, J=7 Hz), 4.99 (1H, dd, J=5, 7 Hz), 5.10~5.90 (4H, m), 7.30~8.40 (7H, m); HPLC (Column, Nucleosil®50-5, 25 cm x 4.6 mm; Solvent, n-hexane-THF=20:1; Flow rate, 1.25 ml/min; Detected at 254 nm) Rt 25.3 min (97.3 %). (1'R,4'R)-**21b** was not detectable (~0 %). (Found: C, 72.96; H, 8.03; N, 2.77. Calc for $C_{30}H_{39}O_5N$: C, 72.99; H, 7.96; N, 2.84 %). The more polar isomer (4.97 g) was shown to be (1'R,4'R)-**21b**, n_D^{21} 1.5439; $[\alpha]_D^{21}$ -4.5°(c=1.00, $CHCl_3$); ν max 3350 (w), 1740 (sh), 1715 (s), 1595 (w), 1230 (s) cm^{-1}; δ (60 MHz, $CDCl_3$) 1.20 (6H, br.s), 1.51 (3H, d, J=7 Hz), 1.63 (3H, s), 2.00 (3H, s), 1.80~2.80 (6H, m), 4.28 (1H, t, J=8 Hz), 4.54 (2H, d, J=7 Hz), 4.95 (1H, dd, J=5, 7 Hz), 5.10~5.95 (4H, m), 7.10~8.37 (7H, m); HPLC [under the same condition as used for the analysis of (1'S,4'S)-**21b**] Rt 28.0 min (99.0 %). A small amount of (1'S,4'S)-**21b** (1.0 %) was detected. (Found: C, 72.84; H, 7.78; N, 2.74. Calc for $C_{30}H_{39}O_5N$: C, 72.99; H, 7.96; N, 2.84 %).

(2E,6E,1'S,4'S)-(+)-7-(4'-Hydroxy-3',3'-dimethyl-2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadienyl acetate (+)-**21a**. To a soln of (1'S,4'S)-**21b** (3.91 g, 7.92 mmol) and Et_3N (2.90 ml, 20.9 mmol, 2.6 eq) in C_6H_6 (25 ml) was added a soln of $HSiCl_3$ (2.25 g, 18.7 mmol, 2.4 eq) in C_6H_6 (10 ml) with stirring at room temp under Ar. The stirring was continued for 4 days at room temp. The reaction was quenched by the addition of sat NH_4Cl aq (30 ml), water (50 ml) and ether (50 ml). After stirring for 3 min, the mixture was filtered through a glass filter. The org layer was separated and the aq layer was extracted with ether. The combined org soln was washed with sat NH_4Cl aq, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (150 g). Elution with ether-n-hexane (3:7~1:1) gave 1.79 g (76.3 % or 58.3 % from (±)-**21a**) of (+)-**21a**, n_D^{21} 1.4863; $[\alpha]_D^{21}$ +15.4°(c=1.07, $CHCl_3$). The IR and NMR spectra of (+)-**21a** were identical with those described for (±)-**21a**. (Found: C, 68.99; H, 9.47. Calc for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52 %).

(2E,6E,1'R,4'R)-(-)-7-(4'-Hydroxy-3',3'-dimethyl-2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadienyl acetate (-)-**21a**. In the same manner as described above for (+)-**21a**, (1'R,4'R)-**21b** (3.15 g, 6.38 mmol) was treated with $HSiCl_3$ (1.54 g, 12.8 mmol, 2.0 eq) and Et_3N (2.21 ml, 16.0 mmol, 2.5 eq) in C_6H_6 (30 ml) for 6 days at room temp to give 1.40 g (74.0 % or 54.6 % from (±)-**21a**) of (-)-**21a**, n_D^{21} 1.4878; $[\alpha]_D^{21}$ -15.6°(c=1.07, $CHCl_3$). The IR and NMR spectra of (-)-**21a** were identical with those of (±)-**21a**. (Found: C, 68.62; H, 9.33. Calc for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52 %). The diastereomeric purities of (+)- and (-)-**21a** were estimated by the HPLC analysis of the corresponding 3,5-dinitrobenzoates **21e**: HPLC (Column, Nucreosil®50-5, 25 cm x 4.6 mm; Solvent, n-hexane-THF=10:1; Flow rate, 1.2 ml/min; Detected at 254 nm) Rt 12.1 min for the 3,5-dinitrobenzoate of (1'S*,4'S*)-**21a**, and 16.1 min for that of (1'S*,4'R*)-**21a**. Both (+)- and (-)-**21a** were of 99.42 % diastereomeric purity.

(2E,6E,1'S,4'S)-(+)-7-(4'-t-Butyldimethylsilyloxy-3',3'-dimethyl-2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadienyl acetate (+)-**21c**. t-$BuMe_2SiCl$ (1.71 g, 11.3 mmol) was added to a stirred soln of (+)-**21a** (1.68 g, 5.67 mmol) and imidazole (1.54 g, 22.7 mmol) in DMF (15 ml) under Ar at room temp. The stirring was continued for 6 h at room temp. The mixture was diluted with water (100 ml) and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (50 g). Elution with ether-n-hexane (0:1~1:9) gave 2.33 g (quantitative) of (+)-**21c**, n_D^{21} 1.4641; $[\alpha]_D^{21}$ +14.9°(c=1.04, $CHCl_3$); ν max 1745 (s), 1670 (w), 1235 (s), 1130 (s), 1025 (m), 880 (m), 840 (s), 775 (m) cm^{-1}; δ (60 MHz, CCl_4) 0.04 (6H, s), 0.88 (9H, s), 1.07 (3H, s), 1.12 (3H, s), 1.55 (3H, s), 1.70 (3H, s), 1.75~2.45 (6H, m), 1.97 (3H, s), 3.90 (1H, t, J=7 Hz), 4.14 (1H, dd, J=7, 10 Hz), 4.48 (2H, d, J=7 Hz), 5.09~5.54 (2H, m). (Found: C, 66.97; H, 10.23. Calc for $C_{23}H_{42}O_4Si$: C, 67.27; H, 10.31 %).

(2E,6E,1'R,4'R)-(-)-7-(4'-t-Butyldimethylsilyloxy-3',3'-dimethyl-2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadienyl acetate (-)-**21c**. In the same manner as described above for (+)-**21c**, (1'R,4'R)-**21a** (1.29 g, 4.35 mmol), t-$BuMe_2SiCl$ (1.31 g, 8.70 mmol) and imidazole (1.19 g, 17.4 mmol) in DMF (15 ml) furnished 1.79 g (98.5 %) of (-)-**21c**, n_D^{21} 1.4630; $[\alpha]_D^{21}$ -14.2° (c=3.01, $CHCl_3$). The IR and NMR spectra of (-)-**21c** were identical with those of (+)-**21c**. (Found: C, 67.37; H, 10.33. Calc for $C_{23}H_{42}O_4Si$: C, 67.27; H, 10.31 %).

(2E,6E,1'S,4'S)-(+)-7-(4'-t-Butyldimethylsilyloxy-3',3'-dimethyl-2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadien-1-ol (+)-**21d**. K_2CO_3 (3.0 g, 21.7 mmol) and (+)-**21c** (1.40 g, 3.41 mmol) were added to MeOH (8 ml) and water (8 ml) and the mixture was stirred for 2 days at room temp. It was then poured into water (80 ml) and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (25 g). Elution with ether-n-hexane (1:4~3:7) gave 1.16 g (92.9 %) of (+)-**21d**, n_D^{21} 1.4745; $[\alpha]_D^{21}$ +25.4°(c=1.06, $CHCl_3$); ν max 3440 (m), 1670 (w), 1130 (s), 1025 (m), 1010 (m), 875 (m), 835 (s), 775 (s) cm^{-1}; δ (60 MHz, CCl_4) 0.04 (6H, s), 0.89 (9H, s), 1.09 (3H, s), 1.14 (3H, s), 1.56 (3H, s), 1.62 (3H, s), 1.85~2.52 (6H, m), 2.95 (1H, br.s, OH), 3.97 (2H, d, J=8 Hz), 3.81~4.31 (2H, m), 5.10~5.60 (2H, m). (Found: C, 68.11; H, 10.86. Calc for $C_{21}H_{40}O_3Si$: C, 68.42; H, 10.94 %).

(2E,6E,1'R,4'R)-(-)-7-(4'-t-Butyldimethylsilyloxy-3',3'-dimethyl-2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadien-1-ol (-)-**21d**. In the same manner as described above for (+)-**21d**, (-)-**21c** (1.64 g, 3.99 mmol) and K_2CO_3 (3.0 g) in MeOH (8 ml) and water (8 ml) yielded 1.38 g (93.8 %) of (-)-**21d**, n_D^{21} 1.4732; $[\alpha]_D^{21}$ -24.5°(c=0.83, $CHCl_3$). The IR and NMR spectra of (-)-**21d** were identical with those of (+)-**21d**. (Found: C, 68.32; H, 10.96. Calc for $C_{21}H_{40}O_3Si$: C, 68.42; H, 10.94 %).

(2E,6E,1'S,4'S)-7-(4'-t-Butyldimethylsilyloxy-3',3'-dimethyl-2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadienyl chloride **28**. To a soln of (+)-**21d** (1.15 g, 3.12 mmol) and Ph_3CH (trace amount) in ether (4 ml) and HMPA (2 ml) was added with stirring and ice-cooling under Ar a soln of n-BuLi in n-hexane (1.5 M, ca. 2.1 ml) until the soln turned red. To this was added over 2 min a soln of p-TsCl (654 mg, 3.43 mmol) in ether (3.0 ml). After stirring for 20 min, LiCl (397 mg, 9.36 mmol) dissolved in HMPA (4 ml) was added and the mixture was stirred for 25 min at 0°. It was then poured into ether (150 ml) and sat $NaHCO_3$ (50 ml). The ether soln was separated, washed with sat $NaHCO_3$ (x 3), dried ($MgSO_4$) and concentrated in

vacuo at 15° to give 1.26 g of crude (1'S,4'S)-**28**. This was used in the next step without further purification.

(2E,6E,1'R,4'R)-7-(4'-t-Butyldimethylsilyloxy-3',3'-dimethyl-2'-oxacyclopentyl)-3,7-dimethyl-2,6-heptadienyl chloride **28**. In the same manner as described above for (1'S,4'S)-**28**, (-)-**21d** (1.30 g, 3.53 mmol), n-BuLi in n-hexane (1.5 M, 2.4 ml, 3.60 mmol), p-TsCl (740 mg, 3.88 mmol) and LiCl (450 mg, 10.6 mmol) yielded 1.51 g of crude (1'R,4'R)-**28**. This was employed in the next step without further purification.

(2'E,6'E,1"S,4"S)-(+)-3-[7'-(4"-t-Butyldimethylsilyloxy-3",3"-dimethyl-2"-oxacyclopentyl)-3',7'-dimethyl-2',6'-heptadienyl]-2,4-dimethoxy-6-methyl-1,4-cyclohexadiene (+)-**29**. A soln of **16** (0.96 g, 6.24 mmol) in THF (2 ml) was added to a stirred and cooled soln of t-BuLi in n-hexane (1.25 M, 4.5 ml, 5.62 mmol) in THF (7.0 ml) under Ar at -70°. The stirring was continued for 30 min at -70°. HMPA (3.0 ml) was then added and the stirring was further continued for 1 h at -70°. To this was added a soln of the crude (1'S,4'S)-**28** (1.26 g) in THF (3 ml) over 3 min. The mixture was stirred for 45 min at -70°. The reaction was quenched by the addition of sat NH_4Cl aq (10 ml) and brine (20 ml). The temp was allowed to rise to room temp and the mixture was extracted with ether. The ether soln was washed with water and brine, dried (K_2CO_3 and $MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Mallinckrodt CC-7; 70 g). Elution with EtOAc-n-hexane (0:1~1:99) gave 1.04 g [66.2 % from (+)-**21d**] of (+)-**29**, n_D^{21}1.4859; $[\alpha]_D^{21}$+21.3°(c=0.98, ether); νmax 1700 (s), 1660 (m), 1600 (w), 1230 (s), 1210 (s), 1155 (vs), 840 (s) cm^{-1}; δ(60 MHz, CCl_4) 0.03 (6H, s), 0.89 (9H, s), 1.02 (3H, d, J=6 Hz), 1.07 (3H, s), 1.12 (3H, s), 1.54 (6H, br.s), 1.68~2.52 (8H, m), 2.62~3.00 (2H, m), 3.49 (6H, s), 3.91 (1H, t, J=7 Hz), 4.14 (1H, dd, J=6, 8 Hz), 4.40~4.60 (2H, m), 4.80~5.51 (2H, m). (Found: C, 71.40; H, 10.07. Calc for $C_{30}H_{52}O_4Si$: C, 71.38; H, 10.38 %).

(2'E,6'E,1"R,4"R)-(-)-3-[7'-(4"-t-Butyldimethylsilyloxy-3",3"-dimethyl-2"-oxacyclopentyl)-3',7'-dimethyl-2',6'-heptadienyl]-2,4-dimethoxy-6-methyl-1,4-cyclohexadiene (-)-**29**. In the same manner as described above for (+)-**29**, (1"R,4"R)-**28** (1.51 g), **16** (925 mg, 6.00 mmol) and t-BuLi (5.25 mmol) yielded 1.25 g [70.2 % from (-)-**21d**] of (-)-**29**, n_D^{21}1.4870; $[\alpha]_D^{21}$ -19.4° (c=0.97, ether). The IR and NMR spectra of (-)-**29** were identical with those of (+)-**29**. (Found: C, 71.09; H, 10.35. Calc for $C_{30}H_{52}O_4Si$: C, 71.38; H, 10.38 %).

(2'E,6'E,1"S,4"S)-3-[7'-(4"-t-Butyldimethylsilyloxy-3",3"-dimethyl-2"-oxacyclopentyl)-3',7'-dimethyl-2',6'-heptadienyl]-1,5-dichloro-6-methyl-2,4-cyclohexanedione **30**. A stirred mixture of (+)-**29** (1.02 g, 2.02 mmol) and $CaCO_3$ (75 mg, 0.75 mmol) in DMF (10.0 ml) and water (0.90 ml) was evacuated to remove dissolved O_2 and then Ar was introduced. To this was added NCS (594 mg, 4.45 mmol, 2.2 eq) in one portion at room temp. The mixture was stirred for 12 h at room temp, diluted with water (80 ml) and further stirred for 40 min. Then the mixture was acidified with N-HCl to pH 4 and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Mallinckrodt CC-7; 40 g). Elution with EtOAc-n-hexane (3:97~1:4) gave 553 mg (50.2 %) of (1"S,4"S)-**30**, νmax ~3150 (br.m), 1670 (m), 1645 (s), 1620 (s), 1370 (s), 1130 (s), 870 (s), 835 (s), 775 (s) cm^{-1}. This was employed in the next step without further purification.

(2'E,6'E,1"R,4"R)-3-[7'-(4"-t-Butyldimethylsilyloxy-3",3"-dimethyl-2"-oxacyclopentyl)-3',7'-dimethyl-2',6'-heptadienyl]-1,5-dichloro-6-methyl-2,4-cyclohexanedione **30**. In the same manner as described above for (1"S,4"S)-**30**, (-)-**29** (1.25 g, 2.48 mmol), $CaCO_3$ (124 mg, 1.24 mmol) and NCS (728 mg, 5.46 mmol) in DMF (12.0 ml) and water (1.10 ml) gave 667 mg (49.3 %) of (1"R,4"R)-**30**. Its IR spectrum was identical with that of (1"S,4"S)-**30**. This was employed in the next step without further purification.

(2'E,6'E,1"S,4"S)-(+)-4-Chloro-2-[7'-(4"-t-butyldimethylsilyloxy-3",3"-dimethyl-2"-oxacyclopentyl)-3',7'-dimethyl-2',6'-heptadienyl]orcinol (+)-**31**. DBU (0.75 ml, 5.0 mmol) was added to a soln of (1"S,4"S)-**30** (550 mg, 1.01 mmol) in THF (3.0 ml) under Ar at room temp. The mixture was stirred and heated under reflux for 6 h. After cooling, the mixture was diluted with water (6 ml) and acidified with N-HCl to pH 3~4. It was then extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (20 g). Elution with EtOAc-n-hexane (3:97~5:95) gave 293 mg (57.0 %) of (+)-**31**, n_D^{21}1.5135; $[\alpha]_D^{21}$+47.0°(c=1.62, $CHCl_3$); νmax 3570 (w), 3320 (m), 1615 (m), 1595 (m), 1460 (s), 1415 (s), 1255 (s), 1130 (s), 870 (s), 835 (s), 775 (s) cm^{-1}; δ(60 MHz, CCl_4) 0.05 (6H, s), 0.90 (9H, s), 1.19 (3H, s), 1.23 (3H, s), 1.56 (3H, s), 1.69 (3H, s), 1.76~2.48 (6H, m), 2.24 (3H, s), 3.27 (2H, d, J=7 Hz), 3.97 (1H, t, J=7 Hz), 4.26 (1H, dd, J=7, 10 Hz), 4.85~5.48 (2H, m), 5.62 (1H, s), 6.20 (1H, s), 6.37 (1H, br.s). (Found: C, 66.02; H, 8.87. Calc for $C_{28}H_{45}O_4ClSi$: C, 66.04; H, 8.91 %).

(2'E,6'E,1"R,4"R)-(-)-4-Chloro-2-[7'-(4"-t-butyldimethylsilyloxy-3",3"-dimethyl-2"-oxacyclopentyl)-3',7'-dimethyl-2',6'-heptadienyl]orcinol (-)-**31**. In the same manner as described above for (+)-**31**, (1"R,4"R)-**30** (665 mg, 1.22 mmol) and DBU (0.90 ml, 6.03 mmol) gave (-)-**31** (420 mg, 67.7 %), n_D^{21}1.5145; $[\alpha]_D^{21}$-47.1°(c=2.00, $CHCl_3$). The IR and NMR spectra of (-)-**31** were identical with those of (+)-**31**. (Found: C, 65.59; H, 8.77. Calc for $C_{28}H_{45}O_4ClSi$: C, 66.04; H, 8.91 %). This was employed in the next step without further purification.

(2'E,6'E,1"S,4"S)-5-Chloro-2,4-dihydroxy-6-methyl-3-[7'-(4"-t-butyldimethylsilyloxy-3",3"-dimethyl-2"-oxacyclopentyl)-3',7'-dimethyl-2',6'-heptadienyl]benzaldehyde **3b**. To a stirred soln of EtMgBr in ether (1.7 M, 1.1 ml, 1.9 mmol) under Ar was added gradually a soln of (+)-**31** (280 mg, 0.55 mmol) in ether (1.5 ml) at room temp. After the addition, the soln was stirred for 1 h 10 min at room temp. To the soln was added $HC(OEt)_3$ (0.41 ml, 2.5 mmol). The mixture was then heated with stirring to remove ether over 10 min until the temp reached 100°. The mixture was kept at 100°for 10 min, then cooled, acidified with 0.5 N-HCl to pH 4 and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (40 g). Elution with EtOAc-n-hexane (5:95) yielded 165 mg (55.9 %) of (1"S,4"S)-**3b**, ν max 3550 (w), 3300 (m), 1635 (s), 1285 (m), 1250 (s), 1130 (s), 875 (s), 840 (s), 775

(s) cm^{-1}. This was employed in the next step without further purification.

(2'E,6'E,1"R,4"R)-5-Chloro-2,4-dihydroxy-6-methyl-3-[7'-(4"-t-butyldimethylsilyloxy-3",3"-dimethyl-2"-oxacyclopentyl)-3',7'-dimethyl-2',6'-heptadienyl]benzaldehyde **3b**. In the same manner as described above for (1"S,4"S)-**3b**, (-)-**31** (360 mg, 0.71 mmol), EtMgBr (2.5 mmol) and $HC(OEt)_3$ (0.58 ml, 3.55 mmol) gave 177 mg(46.6 %) of (1"R,4"R)-**3b**, whose IR spectrum was identical with that of (1"S,4"S)-**3b**. This was employed in the next step without further purification.

(2'E,6'E,1"S,4"S)-(-)-5-Chloro-2,4-dihydroxy-6-methyl-3-[7'-(3",3"-dimethyl-4"-hydroxy-2"-oxacyclopentyl)-3',7'-dimethyl-2',6'-heptadienyl]benzaldehyde [(-)-ascofuranol] (-)-**3a**. To a soln of (1"S,4"S)-**3b** (165 mg, 0.31 mmol) in MeCN (2.0 ml) was added 46 % HF aq (0.10 ml). The mixture was stirred for 1 h at room temp. It was then poured into sat $NaHCO_3$ aq (5 ml) and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (10 g). Elution with EtOAc-n-hexane (0:1~1:4) gave 116 mg of crude (-)-**3a**. This solidified upon storage in a deep-freezer (-40°). Recrystallization of the solid from acetone-n-hexane gave 91 mg (71.0 %) of (-)-**3a**. Further recrystallization from acetone-n-hexane yielded an analytical sample of (-)-**3a**, m.p. 91~92°(pale yellow needles); $[\alpha]_D^{21}$ -3.1°± 0.2 °(c=0.37, MeOH); νmax (KBr disc) 3360 (m), 3000 (w), 2920 (w), 1615 (s), 1460 (m), 1420 (m), 1370 (w), 1335 (w), 1280 (m), 1250 (s), 1240 (s), 1210 (m), 1160 (m), 1115 (m), 1100 (m), 1010 (w), 910 (w), 845 (w), 785 (w), 765 (w), 715 (w) cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.20 (3H, s), 1.27 (3H, s), 1.58 (3H, s), 1.75 (3H, s), 1.76 (1H, ddd, J=4.0, 6.2, 13.8 Hz), 2.01~2.21 (4H, m), 2.39 (1H, ddd, J=6.2, 8.1, 13.8 Hz), 2.59 (3H, s), 3.36 (1H, dd, J=6.3, 14.8 Hz), 3.38 (1H, dd, J=6.3, 14.8 Hz), 3.92 (1H, dd, J=4.0, 8.1 Hz), 4.29 (1H, t, J=6.2 Hz), 5.15 (1H, deformed t, J=6.3 Hz), 5.49 (1H, deformed t, J=6.3 Hz), 7.02 (1H, br.s), 10.13 (1H, s), 12.68 (1H, s) (No signal due to OH at C-4" could be observed clearly); ^{13}C-NMR (25 MHz, $CDCl_3$) δ 12.4, 14.5, 16.1, 22.0, 22.5, 25.7, 26.1, 39.1, 39.2, 78.5, 79.9, 83.0, 113.5, 113.6, 114.4, 121.6, 124.8, 136.2, 136.3, 137.8, 156.9, 162.1, 193.2. (Found: C, 65.43; H, 7.46. Calc for $C_{23}H_{31}O_5Cl$: C, 65.31; H, 7.39 %). The 500 MHz ^{1}H-NMR spectrum of (-)-**3a** coincided with that of an authentic sample.

(+)-Ascofuranol (2'E,6'E,1"R,4"R)-(+)-**3a**. In the same manner as described for (-)-**3a**, (1"R,4"R)-**3b** (165 mg, 0.31 mmol) yielded 87 mg (70.0 %) of (+)-**3a** as crystals. Further recrystallization of (+)-**3a** from acetone-n-hexane gave an analytical sample of (+)-**3a**, m.p. 91~92°(pale yellow needles), $[\alpha]_D^{21}$+3.2 °± 0.2°(c=0.54, MeOH). The IR and NMR spectra of (+)-**3a** were identical with those of (-)-**3a**. (Found: C, 65.52; H, 7.46. Calc for $C_{23}H_{31}O_5Cl$: C, 65.31; H, 7.39 %).

Determination of the optical purity of (-)-ascofuranol **3a** by the HPLC analysis of (1"S,4"S)-2,4-O-dimethylascofuranol-4"-MTPA ester **3d**. To the stirred soln of (-)-**3a** (8 mg, 19 μmol) in acetone (0.3 ml) were added K_2CO_3 (230 mg, 1.7 mmol) and MeI (25 μl, 0.40 mmol). The mixture was stirred and heated under reflux for 20 min. After cooling, the mixture was diluted with ether, filtered through Celite and concentrated in vacuo. The residue was purified by prep TLC (Merck Kieselgel 60F, Art 5717; Developed two times with EtOAc-n-hexane=2:1) to give 7 mg (82 %) of (1"S,4"S)-**3c**, νmax 3460 (m), 1695 (s), 1380 (m), 1305 (m), 1225 (m), 1095 (s), 1080 (sh) cm^{-1}. Both (R)- and (S)-MTPA ester **3d** of **3c** (7 mg) were prepared in the usual manner[32] and analyzed by HPLC (Column, Nucleosil® 50-5, 25 cm x 4.6 mm; Solvent, n-hexane-THF=20:1; Flow rate, 1.25 ml/min; Detected at 254 nm) Rt 30.5 min [(1"S,4"S)-(R)-MTPA ester]; 33.7 min [(1"S,4"S)-(S)-MTPA ester]. Optical purity of (-)-**3a** was >99 % e.e.

(2'E,6'E,1"S)-(-)-5-Chloro-2,4-dihydroxy-6-methyl-3-[7'-(3",3"-dimethyl-4"-oxo-2"-oxacyclopentyl)-3',7'-dimethyl-2',6'-heptadienyl]benzaldehyde [(-)-ascofuranone] **2**. A soln of (-)-**3a** (60 mg, 0.14 mmol) in CH_2Cl_2 (1.0 ml) was added dropwise to a stirred suspension of PCC (91.7 mg, 0.43 mmol, 3 eq) in CH_2Cl_2 (1.0 ml). The mixture was stirred for 3 h at room temp. During that period, an additional amount of PCC (30 mg, 0.14 mmol) was added to the mixture. The mixture was then filtered through Florisil (0.5 g) and the Florisil column was washed with ether (10 ml). The combined filtrate and washings were concentrated in vacuo. The residue was chromatographed over SiO_2 (2 g). Elution with EtOAc-n-hexane (5:95~1:4) gave 17.5 mg of crude **2** as an oil. This was dissolved in n-hexane (3 ml) and set aside to deposit 13.3 mg (22.2 %) of crystalline (-)-**2**. Recrystallization of it from n-hexane gave an analytical sample of (-)-**2**, m.p. 83~84°(colorless fine needles); m.m.p. 82~84°(authentic sample: m.p. 79.5~80.5°); $[\alpha]_D^{19}$-37.0 °± 1.0°(c=0.13, MeOH); νmax (KBr disc) 3370 (m), 3000 (m), 2950 (m), 1745 (s), 1635 (s), 1465 (m), 1425 (m), 1375 (m), 1360 (w), 1350 (w), 1330 (w), 1305 (m), 1285 (s), 1250 (vs), 1200 (w), 1170 (m), 1115 (s), 1060 (w), 1010 (m), 905 (w), 825 (m), 810 (m), 710 (w) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, s), 1.28 (3H, s), 1.63 (3H, s), 1.79 (3H, s), 2.01~2.10 (2H, m), 2.11~2.20 (2H, m), 2.36 (1H, dd, J=10.0, 18.3 Hz), 2.41 (1H, dd, J=6.5, 18.3 Hz), 2.61 (3H, s), 3.39 (2H, d, J=7.0 Hz), 4.52 (1H, dd, J=6.5, 10.0 Hz), 5.21 (1H, deformed t, J=7.0 Hz), 5.51 (1H, deformed t, J=7.0 Hz), 6.45 (1H, s), 10.14 (1H, s), 12.69 (1H, s); ^{13}C-NMR (25 MHz, $CDCl_3$) δ 11.3, 14.6, 16.2, 22.1 (x 2), 24.3, 26.1, 39.1, 40.1, 77.9, 80.8, 113.3, 113.7, 114.4, 121.4, 128.6, 133.1, 136.1, 137.8, 156.4, 162.2, 193.4, 218.0. (Found: C, 65.51; H, 6.82. Calc for $C_{23}H_{29}O_5Cl$: C, 65.63; H, 6.94 %).

(+)-Ascofuranone **2**. In the same manner as described above for (-)-**2**, (+)-**3a** (40 mg, 0.095 mmol) and PCC (82 mg, 0.38 mmol) gave 12.8 mg (32.2 %) of crystalline (+)-**2**. Recrystallization from n-hexane gave an analytical sample of (+)-**2**, m.p. 80~81° (colorless fine needles); $[\alpha]_D^{19}$+42.8° ± 1.1°(c=0.14, MeOH). The IR and NMR spectra of (+)-**2** were identical with those of (-)-**2**. (Found: C, 65.59; H, 6.84. Calc for $C_{23}H_{29}O_5Cl$: C, 65.63; H, 6.94 %).

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