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SYNTHESIS OF BOTH THE ENANTIOMERS OF SCLEROSPORIN AND SCLEROSPORAL, SPOROGENIC SUBSTANCE OF *SCLEROTINIA FRUCTICOLA*+

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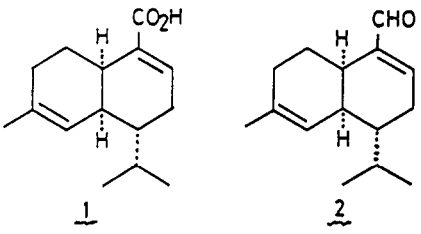
Abstract: Both the enantiomers of sclerosporin 1 and sclerosporal 2 were synthesized from (-)-carvone. (4R,9R,10S)-(+)-Sclerosporin and (4R,9R,10S)-(-)-sclerosporal were identified as the natural enantiomers by a comparison of their CD-spectra. An intramolecular Diels-Alder route was proved to be an efficient method of preparing sufficient amounts of (+)-1 for the biological study.

Sclerosporin 1, the main sporogenic substance isolated together with sclerosporal 2 by Katayama and Marumo from *Sclerotinia fructicola*, was remarkable in that it induced the formation of asexual arthrospores in the fungal mycelium even at extremely low concentration (1 ng / ml).[1] The structures first proposed were *trans*-guaiane sesquiterpenes[2], but these were shown to be questionable by the synthesis of the proposed structures.[3] Later, Katayama and Marumo revised their structures to *cis*-cadalane systems; these were confirmed by the synthesis of their racemates.[4]



1 2

Fig 1

In our preliminary communication, we reported the synthesis of both the enantiomers of 1 and 2, and the determination of the absolute configuration of natural sclerosporin as (4R,9R,10S)-(+)-1.[5] Here, we describ in detail the improved synthesis of natural (+)-1 to afford the substantial amount required for biological studies.

Synthesis of unnatural enantiomers, (4S,9S,10R)-1 and 2

Our synthetic plan was based on the Diels-Alder reaction of dienophile C with a chiral diene B, the reaction being expected to give endo adducts D and / or E. As shown in Fig II, it was assumed that the desired adduct D might be predominant if the substituent Y was large enough. Structure D would then be convertible to (-)-1 by an intramolecular aldol condensation via an intermediate similar to A. The major problem, the preparation of the chiral diene B, was solved by employing readily available (-)-carvone 3 as a chiral starting material and converting it to intermediate 5, a useful bifunctional precursor to both enantiomers of B.

Selective hydrogenation of the unconjugated double bond of 3 over a platinum catalyst below 20 °C gave carvotanacetone (97% pure) along with a tetrahydro derivative. Carvotanacetone was converted to an acetal ester 4a through several steps: ozonolysis and subsequent reductive workup

+ Synthetic Microbial Chemistry Part XII. Part XI, K. Mori and T. Otsuka, Tetrahedron, in press.
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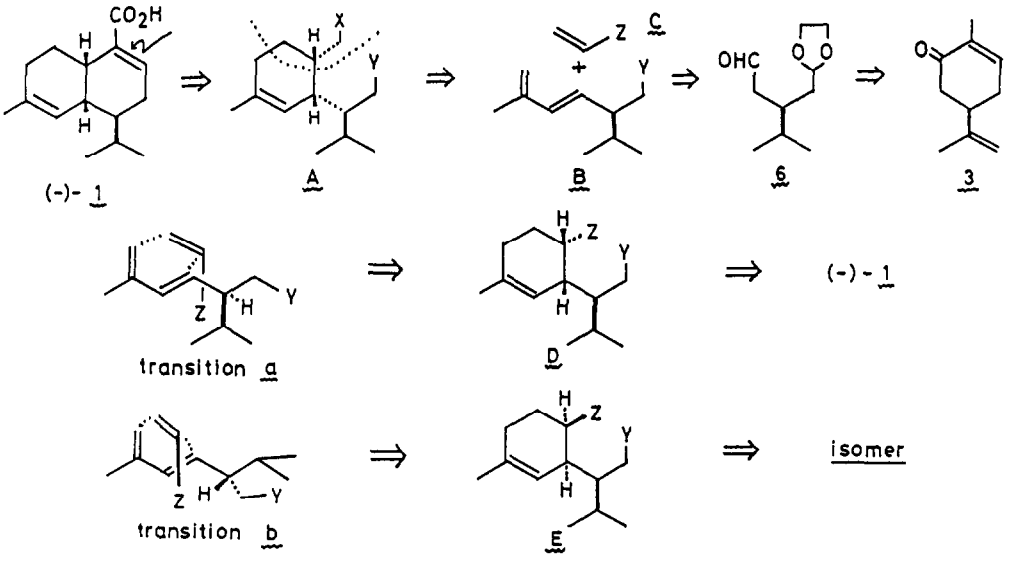


Fig II

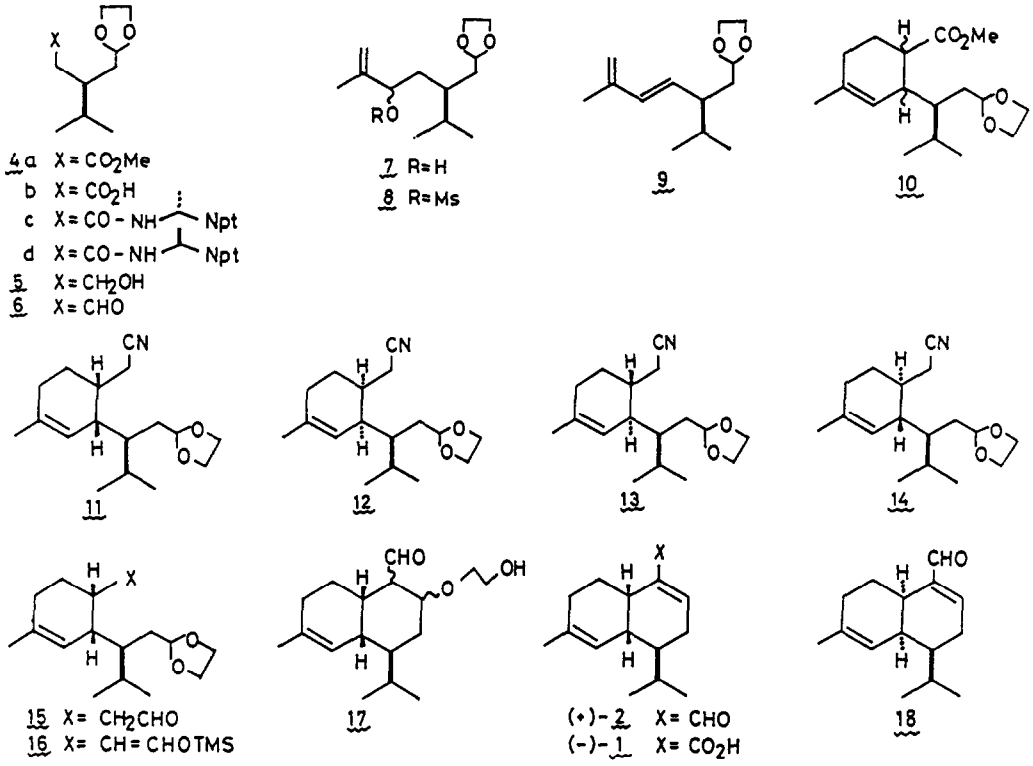


Fig III

with Me_2S, oxidative cleavage with $NaIO_4$, treatment with excess ethylene glycol in the presence of p-TsOH and finally transesterification with 1% MeONa in MeOH, in 82% overall yield from 3. In order to determine its optical purity, 4a was hydrolyzed and the resulting acid 4b was converted to both (R)-(+)- and (S)-(-)-α-(1-naphthyl)ethylamides, 4c and 4d. Analysis of these derivatives by HPLC showed the optical purity of 4a to be 95.0% e.e.[6] This was consistent with the value (95.8%) estimated by comparing the optical rotation of our starting material 3 with the reported value.[7]

Reduction of 4a with $LiAlH_4$ gave an alcohol 5, which was oxidized with PCC-NaOAc[8] to give an aldehyde 6 (73%). The aldehyde underwent a Grignard reaction with 2-propenylmagnesium bromide to afford an allyl alcohol 7. Dehydration via an unstable mesylate 8 to obtain the diene 9 was a troublesome step. Our attempts to increase the yield are summarized in Table I. Using inorganic bases or alkylammonium salts gave little or no product. In the case of DBU being used as a base,

the reaction proceeded very fast, but the yield of 9 did not exceed 10%; the main product was a water-soluble ammonium salt formed by an S_N2' type substitution with DBU. This result prompted us to use more hindered bases, sym-collidine and $EtN(i\text{-}Pr)_2$ under various conditions. The most effective set of condition (55% yield) involved using $EtN(i\text{-}Pr)_2$ as a base in HMPA at 140 °C for 10 min.

Table I. Reaction Conditions and Yields of the Diene 9.

Run	Base	Solvent	Reaction Time	Temperature (°C)	Yield of 9 (%)
1	Triton B	DMF	4 h	60	0
2	$LiCl\text{-}Li_2CO_3$	HMPA	24 h	100	trace
3	DBU	Toluene	15 min	reflux	10
4	s-Collidine	s-Collidine	60 min	110--130	12
5	s-Collidine	HMPA	50 min	100	30
6	$i\text{-}Pr_2NEt$	HMPA	45 min	100--110	33
7	$i\text{-}Pr_2NEt$	HMPA	10 min	140	55

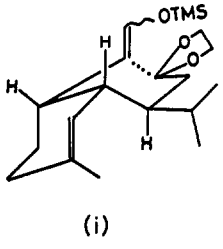
The Diels-Alder reaction of 9 with methyl acrylate at 120 °C for 8.5 h afforded a mixture of adducts 10 (65%). In GLC analysis, 10 exhibited three peaks (I; Rt 33.43 min, II; Rt 35.83 min, III; Rt 39.86 min). The two peaks, I and II, were identified as *trans*-isomers and broad peak III was due to a mixture of *cis*-isomers.+ This implied that *all four possible isomers were produced during the Diels-Alder reaction without any stereoselectivity.* It would be very surprising if exo-addition was more predominant than endo-addition, and therefore, it is more likely that the initially formed *cis*-isomers epimerized to *trans*-isomers during the reaction. This explanation was supported by the fact that the ratio of *cis*- and *trans*-isomers varied from 54/46--37/63 by the lot even under similar reaction conditions. Several trials to minimize the epimerization were unsuccessful and in order to avoid further epimerization, separation of the desired *cis*-isomer was executed at later stage.

Reduction of 10 with $LiAlH_4$ followed by tosylation and then treatment with KCN in DMSO gave a mixture of nitriles 11 -- 14 in 72% yield which was separated by medium pressure chromatography and fractional recrystallization. The *cis*- and *trans*-isomers were identified by comparing GLC data of a mixture of 11 -- 14 with that of 10, because both mixtures showed almost the same pattern with the same intensities. Both *cis*-isomers, 11 and 12, were obtained as crystalline products, although the identification of each isomer was postponed to the cyclization step. The *trans*-isomers were isolated in the pure state. Determination of their structures, however, was not further examined. The nitrile 11 was reduced with DIBAL and the resulting aldehyde 15 subjected to an intramolecular directed aldol condensation[9] through a silyl enol ether 16[10] to give (+)-sclerosporal 2 (32% from 11). The stereochemistry of 2 was rigorously assigned on the basis of its 400 MHz ^{1}H-NMR spectrum. In the case of 12, however, the same treatment as above afforded 18 in extremely poor yield (< 1%).++

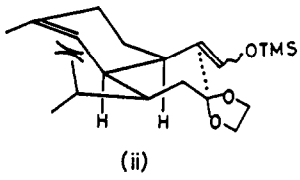
Finally, oxidation of (+)-2 with $NaClO_2$[11] gave a crystalline (4S,9S,10R)-(-)-sclerosporin (-)-1 (90%), whose spectral data were identical with those of an authentic sample. The synthetic (-)-1 showed a positive Cotton effect in its CD spectrum, opposite to that of the natural sclerosporin. Thus, the absolute configuration of natural sclerosporin was determined to be (4R,9R,10S).

+ After the treatment of the mixture 10 with MeONa-MeOH, most of peak III disappeared and peaks I and II were equally enhanced.

++ In case of the desired isomer (i) a bulky isopropyl group is located at the convex site in the transition state. In the other *cis*-isomer (ii), however, the isopropyl group has to be present at sterically hindered concave site during cyclization and thus, intermolecular condensation (polymerization) was prefered to intramolecular reaction. In practice, it was unnecessary to separate the isomers; treating the mixture in the same manner as described above afforded mostly pure (+)-2.



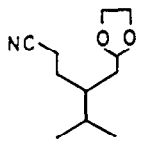
(i)



(ii)

Synthesis of natural (4R,9R,10S)-(+)-1

Since it became obvious that intermolecular Diels-Alder reaction did not give the desired adduct selectively, we decided to use the intramolecular Diels-Alder process reported by Taber.[12] The key intermediate was the diene nitrile 20 which should be convertible to Taber's intermediate 22 in optically active form. Again the alcohol 5 was employed for the preparation of 20.



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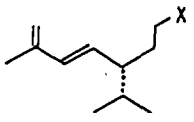
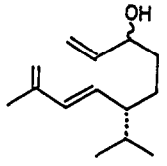


20 X = CN
21 X = CHO



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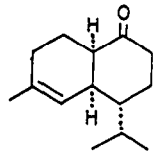

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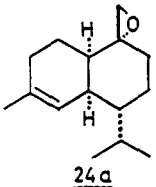
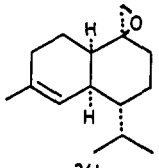
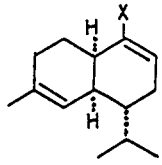


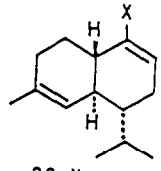
24a



24b



25 X = CH_2OH
(-)-2 X = CHO
(+)-1 X = CO_2H
27 X = CO_2Me



26 X = CH_2OH
28 X = CO_2H
29 X = CO_2Me

Fig IV

Tosylation of 5 and subsequent treatment with NaCN in DMSO gave the nitrile 19 (93.5%). Acid hydrolysis of the nitrile gave an aldehyde which without purification was submitted to the same process (*vide supra*) to give the diene nitrile (53% from 19). DIBAL reduction afforded a dienal 21, which on treatment with vinylmagnesium bromide gave an allyl alcohol 22 (74.5%). Chromic acid oxidation of 22 afforded mainly a *cis*-octalone 23 (84.5% pure in GLC) as a result of spontaneous cyclization. Chromatographic purification gave 23 (91.9% pure; containing ca. 8% of other stereoisomer) in 69.7% yield.

Transformation of 23 to (-)-2 and (+)-1 was executed in the following manner.+ Addition of dimethylsulfoxonium methylide[13] to 23 gave (1R)-epoxide 24a as the major product in 88.5% yield [24a : 24b = 88 : 12]. On the other hand using dimethylsulfonium methylide in the same manner, the (1S)-epoxide 24b became the major product as was expected [24a : 24b = 29 : 71].[13++] Rearrangement of the epoxide 24a to an allylic alcohol 25 was examined using several reagents and solvents under various conditions.[14] The results are summarized in Table II.

Aluminum isopropoxide was shown to be the best of choice as reagent. Unfortunately, epimerization at the C-9 position during the rearrangement reaction caused to form substantial amount of other isomers (mainly a *trans* isomer 26) and the ratio of the desired 25 to 26 and other products was significantly changed by the reaction condition. For example, it took more than three hours to complete the reaction by refluxing in xylene and the ratio of 25 to 26 and other products was about 3 : 1 : 1 (GLC purity of 25 was 47%). On the other hand, the reaction proceeded extremely fast in diethylaniline and at 200 °C the rearrangement was complete in only a minute in nearly quantitative yield. The ratio of products, however, was no better than when xylene was used. After several trials at different temperature, we found that the optimum temperature and reaction time were 160 °C and 10 min respectively. Under this set of conditions with 0.95 equivalent of aluminum isopropoxide in diethylaniline, the ratio of the products was ca 4.1 : 1 : 0.8 (GLC purity of 25 was 70%) and the combined yield was 94.5%.

Crude allyl alcohol 25 containing other isomers was oxidized with chromic acid to give (-)-

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+ In the preliminary communication, we reported a different route to synthesize (+)-1 from 23. The overall yield of (+)-1 from 23, however, was very poor (3.2%). In this paper, only the improved procedure (overall yield; 20.2%) is described.

++ When the epoxide derived via dimethylsulfonium methylide route was used for the rearrangement reaction, the yield of the allyl alcohol 25 was much worse than using the other epoxide, containing 24a predominantly. (1R)-Epoxide 24a was presumably the better substrate for the rearrangement reaction than (1S)-epoxide 24b.

Table II. Reaction Conditions of Rearrangement and the Ratio of Products.

Run	Substrate	Reagent	amount (molar eq.)	Solvent	Temp	Time	GLC ratio 25	26	(%) Other isomers
1	24a	$Al(Oi\text{-}Pr)_3$	(3.0)	toluene	reflux	7 h	53	4	43
2	24a	$Al(Oi\text{-}Pr)_3$	(1.08)	xylene	reflux	4 h	60	19	21
3	24b	$Al(Oi\text{-}Pr)_3$	(1.08)	xylene	reflux	4 h	10	31	59
4	24a	$Al(Ot\text{-}Bu)_3$	(1.0)	xylene	reflux	3 h	0	0	100
5	24a	DEATMP	(5.0)	benzene	0 °C	overnight	20	23	57
6	24a	$Al(Oi\text{-}Pr)_3$	(0.95)	DEA	200 °C	1 min	53	10	37
7	24a	$Al(Oi\text{-}Pr)_3$	(0.95)	DEA	170 °C	10 min	68	16	16
8	24a	$Al(Oi\text{-}Pr)_3$	(0.95)	DEA	160 °C	10 min	70	17	13

(cf). DEATMP; Diethylaluminum 2,2,6,6-tetramethylpiperidide.

DEA; N,N-Diethylaniline.

sclerosporal (-)-2 (85% pure) in 51% yield. Oxidation of (-)-2 with $NaClO_2$ gave a crystalline (4R,9R,10S)-(+)- sclerosporin (24% from 24) as a pure product, which was identical with natural product in all respects including its CD spectrum. Overall yield of (+)-1 in this synthesis was 5.1% over 18 steps from (-)-carvone.

In conclusion, synthesis of both the enantiomers of sclerosporin was accomplished and the absolute configuration of natural sclerosporin was determined as (4R,9R,10S). The efficient synthesis of a substantial amount of (4R,9R,10S)-(+)-1 was carried out via intramolecular Diels-Alder route. A detailed biological study of the synthetic (+)-1 is now under investigation.

EXPERIMENTAL

All b.ps and m.ps are uncorrected. IR spectra were recorded on a Jasco A-102 spectrophotometer. NMR were determined on Hitachi R-24A (60 MHz) and Jeol GX-1 (400 MHz) spectrometers for ^1H and a Jeol JNM-FX 100 (25.4 NHz) spectrometer for ^{13}C; chemical shifts are given in δ with Me_4Si as the internal standard. Low resolution mass spectra were taken on a Hitachi RMU-6L mass spectrometer. High resolution mass spectrum was obtained with a Jeol DX-300 mass spectrometer. GLC analyses were carried out on a Hitachi 163 with FID detector. Optical rotations were measured on a Jasco DIP-140 polarimeter. Unless otherwise noted, Merck Kieselgel-60 (70--230 mesh) was used for column chromatography.

Methyl (3R)-5,5-ethylenedioxy-3-(1-methylethyl)-pentanoate (4a)

Starting material, (-)-carvone, kindly provided from Shiono Koryo Co. Ltd. was redistilled before use. 3; bp 109--110 °C / 3.8 mmHg, $[\alpha]_D^{23}$ -59.85° (neat); d^{23} = 0.962. (Lit.[7] $[\alpha]_D$ -62.46°). Optical purity 95.8%. To a mechanically stirred mixture of (-)-carvone 3 (200 g, 1.33 mol) and PtO_2 (500 mg) in 95% EtOH (580 ml) was introduced H_2 gas below 20 °C until 31.5 l of hydrogen (105% of theoretical amount) was absorbed. The mixture was filtered through celite bed and the filtrate was concentrated in vacuo to give crude carvotanacetone (205 g), purity; 97% (GLC). A pure sample was obtained by distillation: bp 114--116 °C / 6.4 mmHg; n_D^{23}=1.4731; $[\alpha]_D^{23}$ -54.2° (neat); d^{23} = 0.924.

Ozone was bubbled into a solution of crude carvotanacetone (51 g) in MeOH (500 ml) at -50-- -60 °C. Being checked the complete conversion to a ozonide by TLC, N_2 gas was introduced to remove excess ozone over 15 min. To this was added a mixture of Me_2S (45 ml), water (50 ml) and MeOH (150 ml) and the mixture was stirred overnight at ambient temperature. The reaction mixture was neutralized with a 28% solution of MeONa in MeOH to pH 6--7 and concentrated in vacuo to a half volume. To the residue was added slowly a solution of $NaIO_4$ (72 g, 0.34 mol) in water (500 ml) and the mixture was stirred vigorously for 2 h at room temperature. The white precipitate was filtered and washed with EtOAc repeatedly. The filtrate was extracted with EtOAc (x 3) and the extract was washed with water (x 2) and brine, dried over $MgSO_4$ and concentrated to give a crude aldehydo acid. To this was added ethylene glycol (50 ml), p-TsOH (500 mg) and benzene (500 ml) and the mixture was heated under reflux for 6 h with an azeotropic removal of water. The reaction mixture was washed with aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and concentrated. The residue was dissolved in MeOH (1 l) and to this was added a 28% solution of MeONa in MeOH (20 ml) slowly. The mixture was stirred overnight at room temperature. The reaction mixture was neutralized with AcOH to pH 7.5 and MeOH was evaporated off in vacuo. The residue was dissolved in ether (700 ml) and the ether layer was washed with water (x 2) and brine, dried over $MgSO_4$ and concentrated. The residue was distilled to give an acetal ester 4a (58.3 g, 82.1%): bp 105--110 °C / 3 mmHg; n_D^{23}=1.4439; $[\alpha]_D^{23}$ -0.58° (c = 2.12, $CHCl_3$). νmax (film), 2970 (s), 2890 (s), 1740 (s), 1465 (m), 1435 (m), 1415 (m), 1390 (m), 1370 (m), 1335 (m), 1304 (m), 1260 (m), 1162 (s), 1045 (m), 1008 (m), 960 (m), 945 (m), 885 (m), 845 (w), 822 (sh), 775 (w) cm^{-1}; δ(60 MHz, CCl_4), 0.86 (6H, d, J = 6 Hz), 1.6--2.4 (6H, m), 3.63 (3H, s), 3.7--4.0 (4H, m), 4.88 (1H, t, J = 5 Hz). (Found: C, 61.20; H, 9.23. Calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32%).

Determination of the optical purity of 4a

A solution of 4a (2 g, 9.26 mmol) and KOH (770 mg, 13.7 mmol) in 95% EtOH (10 ml) was refluxed for 1 h. After cooling, the mixture was diluted with water (20 ml) and extracted with ether (2 x

10 ml). The aqueous layer was acidified with 1N-HCl (ca. 9 ml) to pH 4--5, saturated with NaCl and extracted with ether (25 ml x 3). The ether layer was dried over Na_2SO_4, and passed through a short column of SiO_2 and concentrated to give a crude acid 4b (1.0 g), which was used for the next step after azeotropic removal of water by heating twice with toluene.

To a cooled solution of 4b (100 mg) in dry CH_2Cl_2 (0.6 ml) was added DCC (110 mg) and the mixture was stirred at 0 °C for 15 min. (R)-(+)-1-(1-naphthyl)ethylamine *l*-tartrate (560 mg) was treated with 20% aqueous NaOH (5 ml) and the separated base was extracted with ether (5 ml). The extract was washed with brine, dried briefly with $CaCl_2$ and concentrated. The residue dissolved in dry CH_2Cl_2 (0.4 ml) was added at once to the suspension of DCC and 4b (*vide supra*) and the mixture was stirred at ambient temperature. The white precipitate was filtered off through celite bed. The filtrate was poured into ice-water and extracted with CH_2Cl_2. The extract was washed with 1N-HCl, aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated to give an amide 4c (145 mg, 82.5% from 4b). In the same manner, 4d was obtained from 4a and (S)-(-)-1-(1-naphthyl)-ethylamine.

Hplc analytical conditions are: Column, Nucleosil® 50-5, 25 cm x 4.6 mmφ; Eluent, n-hexane-THF (3 : 1), Flow rate 0.77 ml / min; Detector, UV, 254 nm. 4c: Rt 16.78 min [2.45%, (S)-acid + (R)-amine], Rt 20.09 min [97.55%, (R)-acid + (R)-amine]. 4d: Rt 16.78 min [97.48%, (R)-acid + (S)-amine], Rt 20.09 min [2.52%, (S)-acid + (S)-amine]. Optical purity of 4a = 95.10 + 94.96 / 2 = 95.03 = 95.0% e.e.

(3S)-5,5-Ethylenedioxy-3-(1-methylethyl)-1-pentanol (5)

To a stirred suspension of $LiAlH_4$ (13.4 g, 0.353 mol) in dry ether (1.0 l) was added dropwise a solution of 4a (100 g, 0.463 mol) in dry ether (100 ml) at 5--10 °C. After the addition was complete, the mixture was stirred for 1 h and quenched by adding water (13.4 ml), 15% NaOH (13.4 ml) and water (40.2 ml). The precipitate was filtered through celite bed and washed thoroughly with THF and the combined filtrate was dried over $MgSO_4$. Evaporation of the solvent and distillation gave 5 (86 g, 98.8%): bp 108--111 °C / 2.3 mmHg; n_D^{23} = 1.4556; $[\alpha]_D^{23}$ +11.5° (c = 2.12, $CHCl_3$). νmax (film) 3430 (m), 2955 (s), 2880 (s), 1462 (m), 1432 (m), 1405 (m), 1382 (m), 1365 (m), 1305 (w), 1250 (sh), 1210 (m), 1135 (s), 1118 (sh), 1095 (m), 1040 (s), 1025 (sh), 985 (sh), 940 (m), 920 (sh), 875 (w), 830 (w) cm^{-1}, δ(60 MHz, CCl_4), 0.85 (6H, d, J = 7 Hz), 1.1--2.1 (6H, m), 2.8--3.4 (1H, broad), 3.49 (2H, t, J = 6 Hz), 3.6--4.0 (4H, m), 4.76 (1H, t, J = 5 Hz). (Found: C, 63.80; H, 10.64. Calcd. for $C_{10}H_{20}O_3$: C, 63.70; H, 10.69%).

(3S)-5,5-Ethylenedioxy-3-(1-methylethyl)pentanal (6)

To a stirred suspension of 5 (52 g, 0.276 mol) and NaOAc (9.2 g, 0.112 mol) in CH_2Cl_2 (900 ml, dried over molecular sieves 4A) was added at once PCC (119.2 g, 0.553 mol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with ether (900 ml) and passed through florisil column (500 g) and the filtrate was concentrated. The residue was dissolved in ether, filtered through florisil bed and concentrated. Distillation of the residue gave 6 (37.0 g, 71.9%): bp 75--80 °C / 1.5 mmHg; n_D^{21} =1.4504; $[\alpha]_D^{21}$ -6.48° (c = 1.37, $CHCl_3$). νmax (film), 2960 (s), 2890 (s), 2730 (m), 1725 (s), 1410 (m), 1390 (m), 1370 (m), 1135 (br s), 1095 (m), 1035 (br s), 970 (m), 942 (m), 882 (w), 833 (w) cm^{-1}. δ(60 MHz, CCl_4), 0.85 (6H, d, J = 7 Hz), 1.1--2.45 (6H, m), 3.6--4.0 (4H, m), 4.78 (1H, t, J = 5 Hz), 9.73 (1H, t, J = 2 Hz).

(5S,3E)-7,7-Ethylenedioxy-2-methyl-5-(1-methylethyl)-1,3-heptadiene (9)

To a stirred suspension of Mg (9.64 g, 0.397 g atom) and catalytic amount of I_2 in dry THF (65 ml) was added a solution of 2-bromopropene (48 g, 0.397 mol) in dry THF (300 ml) with ice-cooling and the mixture was stirred for 1 h at room temperature. To this was added dropwise a solution of 6 (37 g, 0.199 mol) in dry THF (200 ml) below 20 °C. The mixture was stirred at ambient temperature and quenched with aqueous NH_4Cl. The precipitate was filtered off and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated to give a crude 7 as a yellowish oil (45.4 g): νmax (film), 3460 (br s), 1660 (w), 1138 (s), 1040 (s), 945 (m), 900 (m) cm^{-1}. This was employed for the next step without further purification. To a solution of 7 (7.0 g, 30.7 mmol) and dry Et_3N (8.54 ml, 61.3 mmol) in dry CH_2Cl_2 (70 ml) was added through syringe MsCl (2.8 ml, 36.2 mmol) at -10 °C and the mixture was stirred for 5 min at -10 °C. The reaction mixture was diluted with ether (300 ml), washed with aqueous $NaHCO_3$ (x 3), water (x 2) and brine, dried over $MgSO_4$ and K_2CO_3 and concentrated in vacuo below 30 °C. The residual crude 8 was dissolved in i-Pr_2NEt (10.7 ml, 61.4 mmol) and dry HMPA (21 ml) and the solution was quickly heated to 140 °C for 10 min (bath temperature --180 °C). The reaction mixture was poured into cold water and extracted with pentane. The extract was washed with cold 1N-HCl, water, aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2 (140 g). Elution with n-hexane-EtOAc (99 / 1) gave 9 (3.5 g, 54.3%): bp 100 °C / 3.0 mmHg (bath temperature); $n_D^{21.2}$= 1.4760; $[\alpha]_D^{21.2}$ -29.6° (c = 1.47, $CHCl_3$); νmax (film), 3130 (w), 3000 (s), 2915 (s), 1652 (w), 1619 (m), 1470 (sh), 1460 (m), 1440 (m), 1415 (m), 1390 (m), 1375 (m), 1318 (w), 1200 (w), 1135 (s), 1070 (sh), 1030 (br m), 970 (s), 945 (sh), 910 (m), 892 (m), 822 (m) cm^{-1}; δ(60 MHz, CCl_4), 0.82 (3H, d, J = 6 Hz), 0.86 (3H, d, J = 6 Hz), 1.67 (3H, br s), 1.1--2.25 (4H, m), 3.55--3.9 (4H, m), 4.61 (1H, t, J = 5 Hz), 4.77 (2H, s), 5.35 (1H, dd, J = 8 and 16 Hz), 5.98 (1H, d, J = 16 Hz). m/z, 210 (M^+), 167, 141, 73 (100%). (Found: C, 73.80; H, 10.58. Calcd. for $C_{13}H_{24}O_3$: C, 74.24; H, 10.54%).

Methyl 2-[(1S)-3,3-ethylenedioxy-1-(1-methylethyl)]-4-methyl-3-cyclohexenecarboxylate (10)

A mixture of 9 (1.28 g, 6.10 mmol) and freshly distilled methyl acrylate (5.49 ml, 6.10 mmol) with 1% BHT was heated in sealed tube at 120 °C (bath temperature) for 8.5 h. The cooled reaction mixture was washed with aqueous $NaHCO_3$ and water, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2 (50 g). Elution with n-hexane-EtOAc (99 / 1 and 97 / 3) gave recovered 9 (trace) and 10 (1.17 g, 64.9%). 10: νmax (film), 3055 (sh), 2990 (s), 2915 (s), 1745 (s), 1470 (sh), 1458 (sh), 1440 (m), 1385 (sh), 1375 (m), 1308 (m), 1260 (m), 1235 (m), 1195 (m), 1160 (s), 1130 (sh), 1035 (m), 968 (m), 945 (m), 895 (w), 860 (w), 820 (w) cm^{-1}. m/z, 296 (M^+), 253. GLC: (10% PEG 20M 4 mmφ x 2.0 m) N_2 1.1 kg / cm^2, column temperature 190 °C, Peak I; Rt 33.43 min

(24.5%), Peak II; Rt 35.83 min (29.4%), Peak III; Rt 39.86 min (37.9%).

2-[(1S)-3,3-ethylenedioxy-1-(1-methylethyl)]-4-methyl-3-cyclohexeneacetonitriles (11--14)

To a stirred suspension of $LiAlH_4$ (4.5 g, 118 mmol) in dry ether (250 ml) was added dropwise a solution of crude 10 (17.5 g) obtained from 9 (15.6 g, 74.3 mmol) in dry ether at 0--10 °C and the mixture was stirred for 1 h at room temperature. Usual workup and evaporation of solvent gave a crude mixture of alcohols (15 g), νmax (film) 3470 cm^{-1}.

To a solution of the alcohols (15 g) in dry pyridine (80 ml) was added *p*-TsCl (17 g, 89.2 mmol) at 0--5°C and the mixture was stirred overnight at 0--5 °C. The reaction mixture was poured into water and extracted with ether. The extract was washed with aqueous $CuSO_4$ repeatedly, aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and concentrated. A mixture of the resulting crude tosylates (18.5 g) and KCN (4.3 g, 66.1 mmol) in DMSO (180 ml) was stirred for 24 h at 60--70 °C. The reaction mixture was poured into cold water and extracted with ether. The extract was washed with water, aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2 (200 g). Elution with n-hexane-EtOAc (95 / 5) gave a mixture of nitriles (11--14, 9.5 g, 46.2% from 9). Separation of the mixture was executed by MPLC with Lobar column größe C (Merck) employing n-hexane-EtOAc (97 / 3--95 / 5) as solvent system. Repetition of MPLC (18 times) and recrystallization from pentane gave a nearly complete separation of these isomers. 11; 1.43 g, 12; 1.41 g, 13; 2.90 g, 14; 2.60 g and a 1 : 1 mixthre of 11 and 12; 0.90 g. 11 (1.88 g, 9.1% from 9), mp 52--53 °C, $[\alpha]_D^{24}$ +14.8° (c = 1.01, $CHCl_3$). νmax (nujol), 3050 (sh), 2240 (w), 1655 (w), 1400 (m), 1385 (m), 1365 (m), 1345 (w), 1300 (w), 1225 (w), 1205 (w), 1130 (s), 1095 (m), 1080 (sh), 1065 (m), 1035 (m), 1020 (sh), 990 (m), 965 (w), 942 (m), 925 (m), 910 (w), 830 (m), 818 (w) cm^{-1}. δ(60 MHz, $CDCl_3$), 0.76 (3H, d, J = 7 Hz), 0.91 (3H, d, J = 7 Hz), 1.64 (3H, s), 1.1--2.8 (12H, m), 3.7--4.0 (4H, m), 4.83 (1H, d-d, J = 7 and 4 Hz), 5.3 (1H, br). ^{13}C-NMR δ(25.4 MHz, $CDCl_3$), 134.7, 121.0, 120.2, 104.8, 64.8, 41.0, 39.2, 32.2, 31.3, 28.2, 26.5, 26.3, 23.7, 21.8, 16.6, 15.3. (Found: C, 73.21; H, 9.63; N, 4.99. Calcd. for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05%). 12 (1.86 g, 9.0% from 9), mp 19 °C, bp 160 °C / 1mmHg (bath temperature), $n_D^{20.4}$ 1.4948, $[\alpha]_D^{20.4}$ +4.5° (c = 0.92, $CHCl_3$). νmax (film) 2970 (s), 2940 (s), 2890 (s), 1662 (w), 1460 (m), 1450 (sh), 1442 (m), 1405 (m), 1382 (m), 1365 (m), 1255 (m), 1208 (m), 1135 (s), 1035 (s), 1015 (sh), 990 (sh), 962 (m), 940 (m), 920 (sh), 833 (m) cm^{-1}. δ(60 MHz, $CDCl_3$), 0.85 (3H, d, J = 6 Hz), 0.87 (3H, d, J = 6 Hz), 1.61 (3H, br s), 1.1--2.5 (12H, m), 3.7--4.0 (4H, m), 4.81 (1H, d-d, J = 7 and 5 Hz), 5.18 (1H, br). ^{13}C-NMR δ(25.4 MHz, $CDCl_3$), 134.2, 121.5, 120.0, 104.8, 64.8, 64.7, 39.6, 38.6, 34.0, 33.2, 29.8, 26.2, 26.1, 23.7, 19.1, 18.7, 15.8. (Found: C, 73.92; H, 9.88; N, 5.08. Calcd. for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05%).

Trans isomer 13 or 14 (2.90 g, 14.1% from 9), bp 130 °C / 0.05 mmHg (bath temperature) n_D^{20} = 1.4909, $[\alpha]_D^{20}$ +17.2° (c = 1.20, $CHCl_3$). νmax (film), 2960 (s), 2935 (s), 2880 (s), 2245 (w), 1665 (w), 1460 (sh), 1450 (sh), 1430 (m), 1405 (m), 1382 (m), 1365 (sh), 1318 (w), 1255 (w), 1205 (w), 1130 (s), 1085 (m), 1035 (m), 975 (m), 940 (m), 915 (m), 845 (w), 830 (w), 800 (w) cm^{-1}. δ(60 MHz, $CDCl_3$), 0.90 (3H, d, J = 6 Hz), 0.94 (3H, d, J = 6 Hz), 1.62 (3H, br s), 1.0--2.5 (12H, m), 3.67--3.99 (4H, m), 4.78 (1H, t, J = 5 Hz), 5.13 (1H, br). ^{13}C-NMR δ(25.4 MHz, $CDCl_3$), 135.8, 121.0, 119.0, 104.7, 64.8, 64.6, 40.9, 33.7, 33.6, 31.2, 29.2, 28.0, 23.7, 21.8, 21.3, 20.5. (Found: C, 73.50, H, 9.71; N, 4.96. Calcd. for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05%).

Trans isomer 13 or 14 (2.60 g, 12.6% from 9), νmax (film), 2960 (s), 2930 (s), 2875 (s), 2245 (w), 1660 (w), 1460 (sh), 1445 (sh), 1435 (m), 1420 (sh), 1382 (m), 1365 (m), 1310 (w), 1255 (w), 1210 (w), 1135 (s), 1100 (sh), 1035 (s) 975 (m), 942 (m), 910 (m), 840 (sh), 825 (w), 800 (w), 730 (s) cm^{-1}. δ(60 MHz, $CDCl_3$), 0.78 (3H, d, J = 6 Hz), 0.88 (3H, d, J = 6 Hz), 1.62 (3H, br s), 1.1--2.5 (12H, m), 3.65--4.0 (4H, m), 4.81 (1H, t, J = 5 Hz), 5.31 (1H, br s). ^{13}C-NMR δ(25.4 MHz, $CDCl_3$), 133.7, 121.4, 119.2, 104.5, 64.8, 64.6, 42.8, 41.5, 32.2, 32.0, 27.8, 27.4, 25.5, 23,7, 22.7, 21.5, 17.6.

(+)-Sclerosporal [(+)-2]

To a solution of 11 (700 mg, 2.53 mmol) in dry THF (7 ml) was added dropwise a 25% solution of DIBAL in hexane (2.16 ml, 3.80 mmol) at 0 °C under argon atmosphere. The mixture was heated to 45 °C with stirring for 40 min. Being cooled with ice-water, the reaction mixture was quenched carefully with water (7 ml) and to this was added 1N tartaric acid (28 ml). The mixture was stirred for 2 h at 10--12 °C and dissolved in ether. The ether solution was washed with water, aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated to give 15 (683 mg); νmax (film), 2715 (m), 1724 (s), 1661 (w), 1135 (s), 1037 (s) cm^{-1}. This was employed for the next step without further purification.

A mixture of anhydrous $ZnCl_2$ (35 mg, 0.257 mmol) and dry Et_3N(1.25 ml, 8.97 mmol) was stirred for 1 h. To the resulting white suspension was added a solution of 15 (683 mg) in dry benzene (1.4 ml) and then Me_3SiCl (1.03 ml, 8.12 mmol). The mixture was stirred overnight at 50--60 °C. Pentane was added to the reaction mixture and the resulting suspension was filtered through celite bed. The filtrated was washed with sat.$NaHCO_3$ (x 3), dried over K_2CO_3 and concentrated to give a silylenol ether 16 as a E / Z mixture containing small amount of 15, (875 mg); νmax (film), 2725 (w), 1725 (w), 1656 (s), 1250 (s), 1140 (s), 1100 (s), 1058 (s), 1040 (s), 940 (s), 840 (s), 750 (m) cm^{-1}. To a solution of $Ti(Oi\text{-}Pr)_4$ (1.18 ml, 4.29 mmol) in dry CH_2Cl_2 (17.5 ml) was added a 11.6% (W / V) solution of $TiCl_4$ in dry CH_2Cl_2 (7.2 ml, 4.40 mmol) at -78 °C under argon atmosphere. The mixture was stirred for 10 min at -78 °C and warmed to -20 °C. This solution was added to a solution of the crude 16 (875 mg) in dry CH_2Cl_2 (70 ml) over 3 min at -78 °C under argon atmosphere and the mixture was stirred for 50 min at -78 °C. The reaction mixture was quenched with aqueous NH_4Cl and diluted with ether. The organic layer was washed with aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and concentrated to give a crude 17 (700 mg); νmax (film), 3440 (m), 2725 (m), 1725 (s), 1250 (s), 1110 (s), 1050 (s), 890 (s), 870 (s), 838 (s) cm^{-1}. This was employed for the next step without further purification.

A mixture of 17 (700 mg), powdered molecular sieves 5A and 13X (small amount) and p-TsOH (Catalytic amount) in dry xylene (40 ml) was heated under reflux for 75 min. After cooling, K_2CO_3 and pentane were added and the resulting suspension was filtered through celite bed. The filtrate

was concentrated. The residue was chromatographed over SiO_2 (80 g). Elution with n-hexane-EtOAc (99.2 / 0.8) gave (+)-2 (174 mg, 31.6% from 11): $n_D^{20.3}$=1.5226; $[\alpha]_D^{20.3}$ +35.3° (c = 0.09, $CHCl_3$). νmax (film), 3055 (w), 3015 (m), 2960 (s), 2938 (s), 2885 (s), 2830 (m), 2715 (m), 1688 (s), 1645 (s), 1468 (m), 1452 (m), 1432 (m), 1422 (m), 1385 (m), 1370 (m), 1342 (m), 1312 (m), 1292 (m), 1279 (m), 1259 (m), 1228 (m), 1190 (m), 1161 (m), 1139 (m), 1122 (m), 1096 (m), 1045 (m), 1021 (m), 1002 (w), 970 (m), 955 (m), 915 (m), 885 (m), 850 (m), 832 (m), 810 (m), 782 (m), 750 (w), 705 (m) cm^{-1}. δ(400 MHz, $CDCl_3$), 0.85 (3H, d, J = 7 Hz), 0.94 (3H, d, J = 7 Hz), 1.30--1.40 (1H, m), 1.54--1.62 (1H, m), 1.69 (3H, d, J = 0.4 Hz), 1.83--1.92 (2H, m), 1.97 (1H, dt, J = 10.7 and 4.9 Hz), 2.00--2.16 (3H, m), 2.29 (1H, dt, J = 20.0 and 4.9 Hz), 2.61 (1H, dm, J = 12.0 Hz), 5.51 (1H, m), 6.80 (1H, dd, J = 2.9 and 5.1 Hz), 9.40 (1H, s). m/z, 218(M^+), 117, 91. (Found: C, 82.48, H, 10.00. Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16%). The ^{1}H-NMR datum was identical with that of authentic sample.

(-)-Sclerosporin (-)-1

To a solution of (+)- 2 (10 mg, 0.046 mmol) and 2-methyl-2-butene (0.08 ml) in t-BuOH (0.4 ml) was added dropwise a solution of $NaHPO_4$ (12.7 mg, 0.11 mmol) and $NaClO_2$ (12.7 mg, 0.14 mmol) in water (0.13 ml) at room temperature and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo at low temperature and the residue was dissolved in ether. The ether solution was washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2 (2 g). Elution with hexane-EtOAc (97 / 3--90 / 10) gave a crystalline product. Recrystallization from pentane-ether afforded pure (-)-1, (9.6 mg, 90%), mp 159--160 °C. $[\alpha]_D^{20}$ -11.10°(c = 0.04,MeOH). νmax ($CHCl_3$solution, 2 mg / 100 μl), 3460--3000 (br, m), 2980 (s), 2945 (m), 2900 (m), 2840 (m), 2700--2200 (br, m), 1685 (s), 1645 (m), 1465 (m), 1450 (m), 1420 (m), 1385 (m), 1369 (m), 1315 (m), 1300 (sh), 1272 (m), 1254 (m), 1220 (sh), 1165 (sh), 1155 (m), 1125 (w), 1110 (w), 1085 (w), 1075 (w), 1036 (w), 1018 (w), 970 (m), 945 (m), 900 (m), 858 (m), 825 (w) cm^{-1}. ^{1}H-NMR δ(400 MHz, $CDCl_3$), 0.84 (3H, d, J = 6.9 Hz), 0.92 (3H, d, J = 6.9 Hz), 1.40 (1H, m), 1.54 (1H, m), 1.70 (3H, br s), 1.85--2.12 (6H, m), 2.16 (1H, d-t, J = 4.9 and 20.0 Hz), 2.59 (1H, d-m, J = 12.0 Hz), 5.51 (1H, m), 7.15 (1H, d-d, J = 3.0 and 5.0 Hz), 11.3 (1H, br s). m/z, 234 (M^+), 191, 173, 147, 145, 135, 123, 105, 91, 69, 57, 41, 29. High MS. Found: 234.1601. Calcd. for $C_{15}H_{22}O_2$: 234.1620. CD. [θ]max (214 nm) +55960 (MeOH).

(4S)-6,6-Ethylenedioxy-4-(1-methylethyl)hexanenitrile (19)

To a solution of 5 (40.3 g, 0.214 mol) and dry pyridine (34 g, 0.43 mol) in dry CH_2Cl_2 (200 ml) was added portionwise TsCl (49 g, 0.257 mol) with ice-cooling and the mixture was stirred overnight at 4 °C. The reaction mixture was diluted with ether (1 l), washed with water, ice-1N HCl (x 2), water, aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated to give crude tosylate: νmax (film), 1595 (m), 1365 (s), 1175 (s), 1135 (m), 1096 (m), 1035 (m), 950 (s) cm^{-1}. This was used for the next step without purification.

A mixture of the tosylate (75 g) and NaCN (12.5 g, 0.255 mol) in dry DMSO (300 ml) was stirred for 3 days at room temperature. The reaction mixture was poured into ice-water and extracted with ether (x 5). The extract was washed with water (x 2), aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The residue was distilled to give 19 (39.4 g, 93.5%): bp 108--110 °C / 0.9 mmHg; $n_D^{22.3}$ = 1.4540; $[\alpha]_D^{22.3}$ +8.8° (c = 2.92, $CHCl_3$). νmax (film); 2970 (s), 2890 (s), 2250 (m), 1460 (m), 1390 (m), 1370 (m), 1130 (s), 1030 (s), 945 (m) cm^{-1}. δ(60 MHz, CCl_4); 0.87 (6H, d, J = 6 Hz), 1.1--2.0 (6H, m), 2.30 (2H, t, J = 6 Hz), 3.6--4.0 (4H, m), 4.79 (1H, t, J = 4 Hz). (Found: C, 66.80; H, 9.68; N, 7.08. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10%.)

(4R,5E)-7-Methyl-4(1-methylethyl)-5,7-octadienenitrile (20)

A solution of 19 (39.0 g, 0.198 mol) in 60 % AcOH (100 ml) was heated to 90 °C for 3 hr with stirring. The reaction mixture was poured carefully into a mixture of K_2CO_3 (70 g), ice-water and ether. The ether layer was separated, the aqueous layer was extracted with ether and the combined ether layer was washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was distilled to give an aldehyde (31 g, containing a few percent of 19): bp 98--100 °C / 1.0 mmHg. νmax (film); 2720 (m), 2240 (m), 1720 (s), 1420 (m), 1387 (m) cm^{-1}. δ(60 MHz, CCl_4); 0.89 (6H, d, J = 7 Hz), 1.2--2.5 (4H, m), 2.33 (4H, t, J = 7 Hz), 9.84 (--1H, t, J = 1 Hz). This was used for the next step.

To a stirred suspension of Mg (7.3 g, 0.3 g atom) and I_2 (catalytic amount) in dry THF (50 ml) was added dropwise a solution of 2-bromopropene (36 g, 0.3 mol) in dry THF (150 ml) below 40 °C under argon and the mixture was stirred for 1 h at room temperature. The resulting solution of Grignard reagent was added slowly to a solution of the aldehyde (31 g) in dry THF (200 ml) at -30 °C under argon. The mixture was stirred for 20 min at 0 °C and quenched with aqueous NH_4Cl. The precipitate was filtered and washed with THF. The combined filtrate was washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was roughly chromatographed over SiO_2 (400 g) to give an allyl alcohol (30.5 g). νmax (film); 3470 (br s), 3090 (m), 2260 (m), 1655 (m), 1170 (w), 1030 (m), 985 (m), 900 (s) cm^{-1}. δ(60 MHz, CCl_4); 0.86 (3H, d, J = 7 Hz), 0.88 (3H, d, J = 7 Hz), 1.1--2.0 (6H, m), 1.70 (3H, s), 2.35 (2H, t, J = 7 Hz), 2.67 (1H, s), 4.00 (1H, m), 4.84 (2H, d, J = 8 Hz). This was used for the next step without further purification.

To a solution of the allyl alcohol (30.5 g) and Et_3N (31 g, 0.306 mol) in dry CH_2Cl_2 (300 ml) was added dropwise MsCl (22.7 g, 0.198 mol) at -10 °C and the mixture was stirred for 20 min. The reaction mixture was quenched with water, diluted with ether, washed with water (x 2) and brine, dried over $MgSO_4$ and concentrated in vacuo. Excess Et_3N was removed with vacuum pump to give a crude mesylate (--75 g). A solution of this mesylate and i-Pr_2NEt (30 g, 0.233 mol) in dry HMPA (300 ml) was placed in a 500 ml three necked flask with thermometer and the flask was immersed to an oil bath preheated to 200 °C to maintain the reaction temperature between 140--150 °C for 20 min. The cooled reaction mixture was poured into water and extracted with ether (x 5). The extract was washed with ice-1N HCl, water (x 2), aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2 (400 g). Elution with hexane-EtOAc (98 / 2--92 / 8) gave 20 (18.1 g, 52.5% from 19, 53.6% based on the unrecovered 19) and the recovered 19

(800 mg). 20: bp 93--95 °C / 5 mmHg; n_D^{21} = 1.4744; $[\alpha]_D^{21}$ +56.7° (c = 3.04, $CHCl_3$). νmax (film); 3090 (w), 2970 (s), 2950 (s), 2880 (s), 2240 (m), 1640 (w), 1608 (m), 1450 (m), 1383 (m), 1368 (m), 972 (s), 883 (m) cm^{-1}. δ(60 MHz, CCl_4); 0.86 (3H, d, J = 6 Hz), 0.90 (3H, d, J = 6 Hz), 1.80 (3H, s), 1.0--2.5 (6H, m), 4.86 (2H, s), 5.24 (1H, d-d, J = 9 and 16 Hz), 6.11 (1H, d, J = 16 Hz). (Found: C, 80.91; H, 10.83; N, 7.75. Calcd. for $C_{12}H_{15}N$: C, 81.30; H, 10.80; N, 7.90%).

(4R,5E)-7-Methyl-4-(1-methylethyl)-5,7-octadienal (21)

To a solution of 20 (12 g, 67.8 mmol) in dry hexane (100 ml) was added dropwise a 25% (w/v) solution of DIBAL in hexane (50 ml, 87.9 mmol) at -10-- -5 °C under argon and the mixture was stirred for 90 min at room temperature. Excess DIBAL was decomposed by careful addition of water (50 ml) and then a solution of tartaric acid (20 g) in water (150 ml) was added. The mixture was stirred for 2.5 h at room temperature, diluted with water and extracted with ether (x 3). The extract was washed with water, aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. Crude 21 (13.5 g) was used for the next step without further purification. Analytical sample was obtained by distillation. 21: bp 70--72 °C / 4 mmHg; $n_D^{21.4}$ = 1.4729, $[\alpha]_D^{21.4}$ -14.2° (c = 3.01, $CHCl_3$). νmax (film); 3100 (m), 3025 (m), 2980 (s), 2950 (s), 2895 (s), 2835 (m), 2730 (m), 1732 (s), 1645 (w), 1612 (m), 1453 (m), 1410 (m), 1387 (m), 1368 (m), 973 (s), 885 (s) cm^{-1}. δ(60 MHz, CCl_4); 0.85 (3H, d, J = 6 Hz), 0.89 (3H, d, J = 6 Hz), 1.79 (3H, s), 1.0--2.1 (4H, m), 2.31 (2H, t, J = 6 Hz), 4.81 (2H, s), 5.27 (1H, d-d, J = 9 and 16 Hz), 6.03 (1H, d, J = 16 Hz).

(6R,7E)-9-Methyl-6-(1-methylethyl)-1,7,8-decatrien-3-ol (22)

To a solution of vinylmagnesium bromide in dry THF (140 ml), prepared from Mg (3.2 g, 0.13 g atom) and vinyl bromide (14.4 g, 134.6 mmol), was added dropwise a solution of 21 (13.5 g) in dry THF (100 ml) at 0 °C under argon and the mixture was stirred for 30 min at 0 °C. The reaction mixture was quenched with aqueous NH_4Cl. The precipitate was filtered and washed with THF. The combined organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2 (250 g). Elution with hexane-EtOAc (97 / 3--90 / 10) gave 22 (10.5 g, 74.5% from 20): $n_D^{20.5}$ = 1.4864. νmax (film); 3350 (br, s) 3100 (m), 3025 (m), 2970 (s), 2890 (s), 1640 (m), 1610 (m), 1452 (m), 1383 (m), 1368 (m), 1312 (m), 992 (s), 970 (s), 920 (s), 880 (s) cm^{-1}. δ(60 MHz, CCl_4); 0.80 (3H, d, J = 6 Hz), 0.85 (3H, d, J = 6 Hz), 1.79 (3H, s), 1.0--2.0 (6H, m), 2.25 (1H, s, -OH), 3.90 (1H, m), 4.77 (2H, s), 6.00 (1H, d, J = 16 Hz), 4.7--6.1 (4H, m). (Found: C, 80.89; H, 11.46. Calcd. for $C_{14}H_{24}O$: C, 80.71; H, 11.61%).

(4R,4aS,8aR)-6-Methyl-4-(1-methylethyl)-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-one (23)

To a solution of 22 (10.5 g, 50.5 mmol) in ether (150 ml) was added dropwise a cold aqueous solution of 2N H_2CrO_4 (50 ml , 100 mmol) over 20 min below 0 °C and the mixture was stirred vigorously for 30 min at 0 °C. The reaction mixture was diluted with water and extracted with ether (x 5). The extract was washed with water, aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered through folrisil bed and concentrated. The residue was chromatographed over SiO_2 (250 g). Elution with hexane-EtOAc (99 / 1--97 / 3) gave 23 as a main component of stereoisomeric mixture (7.25 g, 69.7%). GLC purity of 23 was 91.9%. Analytical sample was obtained by careful chromatography followed by distillation. 23: bp 110--115°C/ 0.3 mmHg, $n_D^{21.4}$ = 1.4994; $[\alpha]_D^{21.4}$ -58.0° (c = 2.25, $CHCl_3$). GLC purity 97.0% Rt 8.71 min (5% PEG 20M, 4 mmφ x 1.5 m, N_2 1.0 kg / cm^2, temp 150 °C). νmax (film); 2960 (s), 2940 (s), 2880 (s), 1710 (s), 1446 (m), 1428 (m), 1382 (m), 1365 (m), 1318 (m), 1279 (w), 1250 (m), 1221 (m), 1202 (m), 1145 (m), 1126 (m), 1091 (m), 1062 (m), 1043 (m), 996 (w), 950 (w), 936 (w), 893 (w), 872 (w), 858 (w), 843 (w), 827 (w), 804 (w) cm^{-1}. δ(60 MHz, $CDCl_3$); 0.90 (3H, d, J = 5.5 Hz), 1.00 (3H, d, J = 5.5 Hz). 1.63 (3H, br s), 1.1--2.8 (12H, m), 5.31 (1H, m). m/z; 206 (M^+, 100%), 145, 136, 121. (Found: C, 81.31; H, 10.80. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75%).

(4R,4aS,8aR)-Spiro[6-methyl-4-(1-methylethyl)-1,2,3,4,4a,7,8,8a-octahydronaphthalene-1,2'-oxirane] (24)

To a suspension of NaH (60% in mineral oil dispersion, 1 g, 25 mmol, washed with dry pentane several times) in dry DMSO (20 ml) was added portionwise $Me_3S(O)I$ (6.0 g, 27.3 mmol) and the mixture was stirred for 1 h at room temperature. To this was added dropwise a solution of 23 (3.5 g, 17 mmol) in dry DMSO (10 ml) over 1 h and the mixture was stirred overnight at room temperature. The reaction mixture was poured into ice-water and extracted with ether (x 3). The extract was washed with water (x 2) and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2. Elution with hexane-EtOAc (99 / 1--97 / 3) gave 24 (3.31 g, 88.5%) which was shown to be a mixture of (1R)-epoxide 24a and (1S)-epoxide 24b (24a / 24b = 88 : 12) by GLC. 24a; Rt 13.19 min, 24b; Rt 15.22 min (5% PEG 20M, 4 mmφ x 2.0 m, N_2 1.0 kg / cm^2, temp. 160 °C). $n_D^{21.4}$ = 1.4972, $[\alpha]_D^{21.4}$ +22.7° (c = 2.40, $CHCl_3$). νmax (film); 3050 (m), 3025 (m) 2980 (s), 2950 (s), 2890 (s), 2850 (m), 1670 (w), 1455 (m), 1440 (m), 1390 (m), 1370 (m), 1260 (m), 1183 (w), 1153 (m), 943 (m), 917 (m), 888 (m), 880 (m), 853 (m), 810 (m), 790 (m) cm^{-1}. δ(400 MHz, $CDCl_3$); 0.84 (--3H, d, J = 7.0 Hz), 0.92 (--3H, d, J = 7.0 Hz), 1.65 (3H, br s), 1.1--2.1 (11H, m), 2.20 (1H, m), 2.48 (--0.1 H, d, J = 5.0 Hz, one of epoxide methylene protons in 24b), 2.60 (--0.9H, d, J = 5.0 Hz), 2.62 (--0.9H, d, J = 5.0 Hz), 2.98 (--0.1H, d, J = 5.0 Hz, the other epoxide methylene proton of 24b), 5.55 (1H, m). (Found: C, 81.81; H, 10.99. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98.)

Reaction of 23 with dimethylsulfonium methylide

To a suspension of NaH (60% mineral oil dispersion, 54 mg, 135 mmol; mineral oil was removed by washing with dry pentane) in dry DMSO (1 ml) and dry THF (2 ml) was added slowly a solution of $Me_3S^+I^-$ (314 mg, 1.54 mmol) in dry DMSO (2 ml) at 0 °C and the mixture was stirred for an additional 1 min. To this was added a solution of 23 (75 mg, 0.36 mmol) in dry THF (1 ml) at 0 °C and the mixture was stirred for 90 min at room temperature. The reaction mixture was quenched with cold water and extracted with ether. The extract was washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2 (15 g). Elution with hexane-EtOAc (99 / 1 --97 / 3) gave the epoxide (63 mg, 78.7%): $n_D^{18.7}$ = 1.4991; $[\alpha]_D^{21.2}$ -22.8° (c = 1.95, $CHCl_3$).

GLC (5% PEG 20M, 4 mmφ x 1.5 m, N_2 1.0 kg / cm^2, temp. 150 °C); 23; Rt 7.46 min (3.9%), 24a; Rt 8.49 min (27.8%), 24b; Rt 9.86 min (68.3%). 24a / 24b = 29 / 71. νmax (film); 3070 (m), 2970 (s), 2900 (s), 1672 (w), 1494 (w), 1438 (s), 1392 (m), 1373 (m), 1340 (m), 1250 (w), 1220 (w), 1188 (w), 1160 (w), 1095 (w), 1072 (w), 1040 (w), 995 (w), 947 (m), 917 (m), 878 (m), 855 (w), 833 (m), 822 (m), 743 (w), 723 (m) cm^{-1}. δ(400 MHz, $CDCl_3$); 0.81 (3H, d, J = 7.0 Hz), 0.94 (3H, d, J = 7.0 Hz), 1.66 (3H, br s), 1.1--2.1 (11H, m), 2.22 (1H, m), 2.48 (1H, d, J = 5.0 Hz), 2,98 (1H, d, J = 5.0 Hz), 5.55 (1H, m). It showed several signals with ca. 30% intensities due to the presence of 24a: chemical shifts are given above.

(4R,4aS,8aR)-6-methyl-4-(1-methylethyl)-3,4,4a,7,8,8a-hexahydronaphthalene-1-methanol (25)

A solution of 24 (2.0 g, 9.09 mmol) obtained via $Me_3S(O)I$ route and $Al(Oi\text{-}Pr)_3$ in dry diethylaniline (20 ml) was heated to 160 °C (bath temperature) for 10 min with stirring. The reaction mixture was cooled rapidly with ice-water, poured into ice-1N HCl and extracted with ether (x 3). The extract was washed with 1N HCl, aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2 (70 g). Elution with hexane-EtOAc (97 / 3--90 / 10) gave a mixture of allyl alcohols 25, 26 and others (1.89 g, 94.5%). GLC: 25, Rt 13.34 min (70.0% of a mixture); 26, Rt 15.55 min. (17.0% of a mixture). (5% PEG 20 M, 4 mmφ x 2.0 m, N_2 1.4 kg / cm^2, temp. 220 °C). νmax (film); 3360 (br s), 2990 (s), 2960 (s), 2900(s), 1675 (w), 1470 (m), 1455 (m), 1440 (m), 1390 (m), 1373(m), 1185 (m), 1157 (m), 1126 (m), 1100 (m), 1050 (m), 1013 (m), 972 (m), 887 (m), 853 (m), 832 (m), 817 (m) cm^{-1}. δ(60 MHz, $CDCl_3$); 0.84 (3H, d, J = 6 Hz), 0.90 (3H, d, J = 6 Hz), 1.68 (3H, s), 1.0--2.5 (11H, m), 4.08 (2H, m), 5.2--5.85 (2H, m). This was used for the next step without further purification.

(-)-Sclerosporal; (4R,4aS,8aR)-6-methyl-4-(1-methylethyl)-3,4,4a,7,8,8a-hexahydronaphthalene-1-carboxaldehyde[(-)-2]

To a solution of 25 (GLC purity 70%, 1.89 g, 8.59 mmol) in ether (15 ml) was added dropwise aqueous 2N H_2CrO_4 (8.6 ml, 17.2 mmol) over 15 min with ice-cooling and the mixture was stirred vigorously for 10 min at 0 °C. The reaction mixture was diluted with water and extracted with ether (x 4). The extract was washed with water, aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered through florisil bed and concentrated to give an oil (1.32 g). The crude product was chromatographed over SiO_2 (70 g). Elution with hexane-EtOAc (99 / 1) gave (-)-2 (85% pure, 786 mg, 51%): GLC; Rt 10.89 min (5% PEG 20M, 4 mmφ x 2.0 m, N_2 1.0 kg / cm^2, temp. 220°C). IR and NMR were identical with those of (+)-2. This was used for the next step without further purification.

(4R,9R,10S)-(+)-Sclerosporin; (4R,4aS,8aR)-6-Methyl-4-(1-methylethyl)-3,4,4a,7,8,8a-hexahydronaphthalene-1-carboxylic acid [(+)-1]

(-)-2 (85% pure, 786 mg, 3.61 mmol) was oxidized in the same manner as (+)-2. Crude products were chromatographed over SiO_2 (35 g) four times (hexane / EtOAc = 97/3--90 / 10). First fraction was recrystallized from n-pentane-ether to give pure (+)- 1 (490 mg, 23.0% from 24): mp 158--160 °C; $[\alpha]_D^{22}$ +10.6° (c = 0.31, MeOH). IR and NMR were identical with those of (-)-1. CD; [θ]max (214 nm) -59300 (MeOH). (Found: C, 76.88; H, 9.19. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%.)

Treatment of (+)-1 with CH_2N_2 gave the methyl ester 27, whose GLC showed single peak. Thus, (+)-1 was proved to be 100% pure material. 27: GLC; Rt 12.12 min (5% PEG 20 M, 4 mmφ x 2.0 m, N_2 1.0 kg / cm^2, temp. 220 °C).

Second fraction was also crystalline product. Recrystallization from n-pentane-ether gave pure *trans*-isomer (+)-28 (110 mg, 5.4% from 24): mp 160--162 °C; $[\alpha]_D^{22}$ +203.4° (c = 0.64, MeOH). νmax ($CHCl_3$ solution, 2 mg / 100 μl), 3500-2200(br, m), 2980 (s), 2960 (m), 2900 (m), 2850 (m), 1690 (s), 1645 (m), 1460 (m), 1428 (m), 1395 (sh), 1376 (sh), 1302 (sh), 1280 (m), 1260 (m), 1210 (br, m), 1175 (br, m), 1145 (sh), 1108 (w), 1092 (w), 1047 (w), 1017 (w), 990 (w), 953 (w), 893 (w), 840 (w), 800--720 (m) cm^{-1}. ^{1}H-NMR δ(400 MHz, $CDCl_3$), 0.80 (3H, d, J = 7 Hz), 0.93 (3H, d, J = 7 Hz), 1.26 (1H, m), 1.43 (1H, m), 1.68 (3H, s), 1.85--2.30 (7H, m), 2.52 (1H, d-d, J = 7 and 12.5 Hz), 5.60 (1H, br), 6,99 (1H, t, J = 3 Hz). CD; [θ]max (196 nm) +36200 (MeOH).

Its methyl ester 29 showed single peak in GLC: Rt 14.13 min (5% PEG 20M, 4 mmφ x 2.0 m, N_2 1.0 kg / cm^2, temp 220°C).

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