Tetrahedron Letters,Vol.25,No.41,pp 4685-4688,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF THE ENANTIOMERS OF SCLEROSPORIN AND SCLEROSPORAL TO DETERMINE THE ABSOLUTE CONFIGURATION OF THE NATURAL PRODUCTS

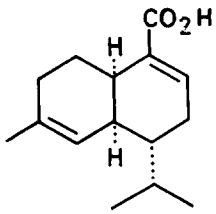
Takeshi Kitahara,* Tatsuji Matsuoka, Masato Katayama,+ Shingo Marumo+ and Kenji Mori

Department of Agricultural Chemistry, The University of Tokyo, Tokyo 113, Japan
+Department of Agricultural Chemistry, Nagoya University, Nagoya 464, Japan

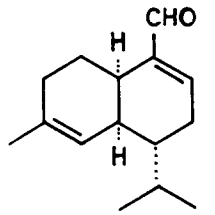
Summary: Both the enantiomers of sclerosporin 1 and sclerosporal 2 were synthesized from (-)-carvone. (4R, 9R, 10R)-(+)-Sclerosporin and (4$\bar{R}$, 9R, 10R)-(-)-sclerosporal were identified as natural enantiomers by bio-assay and by the CD-spectral comparison.

Sclerosporin 1, the main sporogenic substance isolated together with sclerosporal 2 by Katayama and Marumo from Sclerotinia fructicola, induced remarkably the formation of asexual arthrospore in the fungal mycelium.[1] Their structures were proposed as cis-cadalane sesquiterpenes, 1 and 2, which were confirmed by the synthesis of racemates.[2] The absolute configuration, however, remained unknown.

Here, we wish to describe a synthesis of both the enantiomers of 1 and 2 from optically pure (-)-carvone 3 and determination of the absolute configuration as (4R, 9R, 10R)-1 for natural sclerosporin.

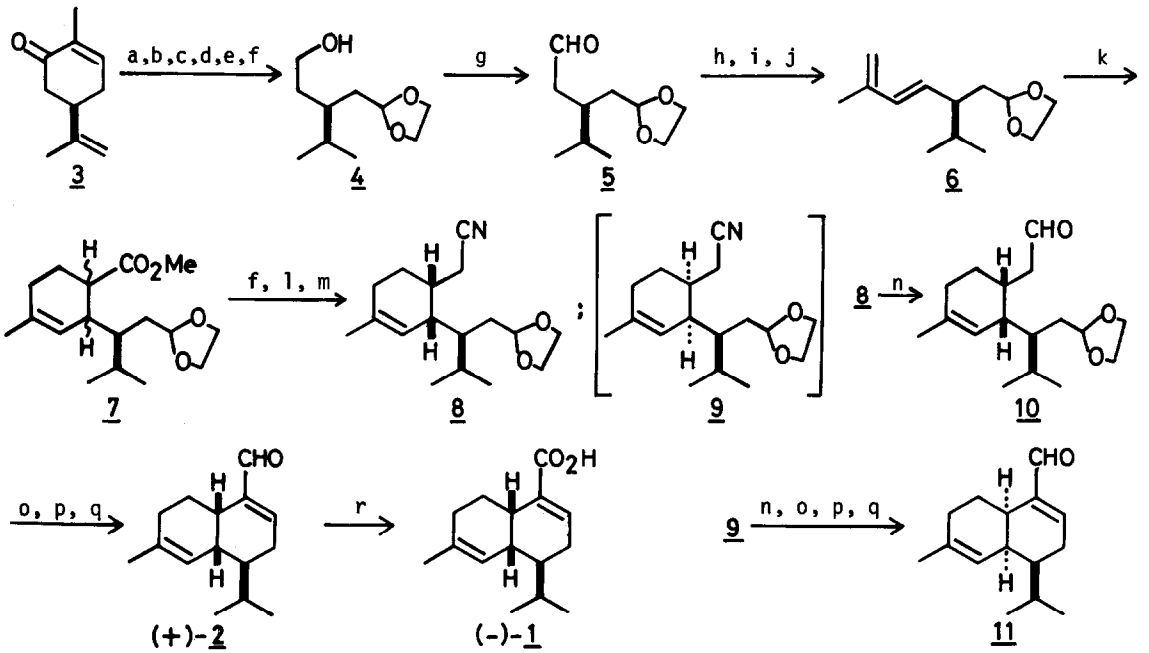


1

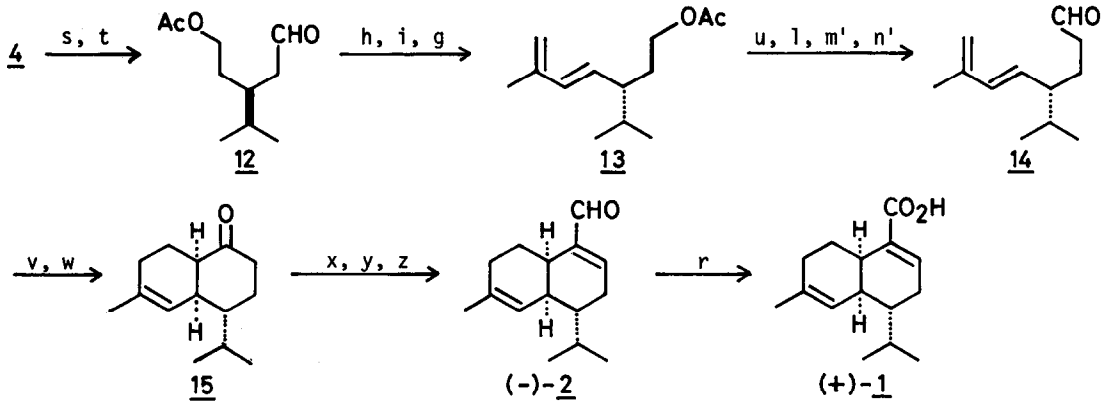


2

Inter- and Intramolecular Diels-Alder reactions were employed for our synthesis and in order to obtain both the enantiomers, a bifunctional starting material 4 was prepared from (-)-carvone 3 through several steps without isolation of intermediates as illustrated in the scheme (77% overall). PCC-NaOAc[3] oxidation gave an aldehyde 5 (76%) which was treated with methallylmagnesium bromide and the resulting allyl alcohol was converted to a diene 6 in two steps, mesylation and then elimination with i-Pr_2NEt in HMPA at 140 °C for 10 min (55%).[4] Diels-Alder reaction with methyl acrylate provided a mixture of the adducts 7 (65%).[5] One carbon homologation in the conventional manner afforded a mixture of nitriles (72%). Each isomer could be separated by MPLC with a Lobar column at this stage and among them, cis-isomers 8 and 9 were isolated as a crystalline product.[6] DIBAL reduction of 8, followed by



a H_2, PtO_2; b O_3, -78° Me_2S/MeOH; c $NaIO_4$; d HO⟋OH, p-TsOH, C_6H_6; e 2.5% MeONa/MeOH; f $LiAlH_4/Et_2O$; g PCC-NaOAc/CH_2Cl_2; h ⟩MgBr/THF, 0°--20°/20 min; i MsCl, Et_3N/CH_2Cl_2, -10°/5 min; j i-Pr_2NEt/HMPA, 140°/10 min; K ⟋CO_2Me, 120°/8.5 h; l p-TsCl/C_5H_5N, 0°; m KCN/DMSO, 60°/24 h; n DIBAL-H/THF, 45°/40 min; o TMSCl, Et_3N, $ZnCl_2/C_6H_6$, 60°/20 h; p $TiCl_4$-Ti(Oi-Pr)$_4/CH_2Cl_2$, -70°/50 min; q molecular sieves 5A, p-TsOH(cat)/xylene, 140°/75 min; r Jones



s Ac_2O-C_5H_5N; t 35% $HClO_4$-Et_2O (1:1), 0°/5 min; u KOH/MeOH; v ⟋MgBr/THF; w $H_2Cr_2O_7$-Et_2O; x LiCH(OMe)SPh; y $SOCl_2$; z $NaIO_4$; m' NaCN/DMF, rt/24 h; n' DIBAL-H/THF rt/90 min

intramolecular directed aldol condensation of the resulting aldehyde 10 under Mukaiyama's procedure[7] gave (+)-2[8] (32% from 8), whose stereochemistry was unambiguously assigned from J values (H_9 - H_{10} = 4.9Hz, H_4 - H_{10} = 10.7Hz) in its ^{1}H-NMR spectrum. In the case of 9, however, the same treatment as above afforded 11 in extremely poor yield (1%).[9] Jones oxidation of (+)-2 gave a crystalline (4S, 9S, 10S)-(-)-sclerosporin.[10]

In order to synthesize the antipodes from 3, the alcohol 4 was converted to the Taber's intermediate 14[11] for the intramolecular Diels-Alder reaction. Thus, acetylation and subsequent acetal cleavage yielded an aldehyde 12, which was treated in the same manner as described for the preparation of 6 to give a diene 13 (30% from 4). After the hydrolysis of acetate, one carbon elongation was executed via the similar procedure as before to give a dienal 14 (68%). Grignard reaction with vinylmagnesium bromide was followed by oxidation with chromic acid to give a cis-octalone 15 with spontaneous cyclization (33%),[12] which was transformed to (-)-sclerosporal 2 and (+)-sclerosporin 1[10] by the reported procedure.[2b]

Spectral data of synthetic (+)-1 and (-)-1 were identical with those of an authentic sample. As shown in Table, (+)-1 showed strong sporogenic activity at 5 μg / ml, while (-)-isomer showed only weak activity in preliminary result. (-)-1 showed a positive Cotton effect in its CD spectrum which was opposite to that of the natural sclerosporin.

Sporogenic Activity of Synthetic (+)- and (-)-Sclerosporin on *Sclerotinia fructicola*

dose (μg)/ agar medium (1 ml)	conditions	numbers of arthrospores
0	dark	1460
0	light	67
(+)-1 0.005	light	78
0.05	"	122
0.5	"	368
5	"	1044
(-)-1 0.05	light	67
0.5	"	112
5	"	166

In conclusion, (4R, 9R, 10R)-(+)-sclerosporin and (4R, 9R, 10R)-(-)-sclerosporal were identified as the natural product. Interestingly, the absolute configuration of this cadalane sesquiterpene 1 from microbial world is opposite to those isolated from plant kingdom.

Further studies on the improved synthesis and bio-assay of 1 are in progress and will be reported in a full account.

Acknowledgment: We thank Shiono Koryo Co. Ltd. for the generous gift of (-)-carvone and Japan Spectroscopic Co. Ltd. for the CD measurement.

References and Notes

1. M. Katayama and S. Marumo, Agric. Biol. Chem., 42, 1505 (1978).
2. a). M. Katayama and S. Marumo, Tetrahedron Lett., 1773 (1979).
   b). M. Katayama and S. Marumo, ibid., 24, 1703 (1983).
3. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 2647 (1975).

4. Using DBU as a base, water-soluble substitution product (immonium salt) was mainly obtained and the yield of the diene did not exceed 10%.
5. According to the endo-rule, the reaction should give only the cis-isomers (possibly two). In fact, however, formation of trans-isomers other than cis-isomers (ca. 1 : 1) was observed by GLC analysis. Although the reason why exo-adducts were obtained so much extent was not clear, a possible explanation is that epimerization of endo adducts occurred during the Diels-Alder reaction. Base-catalyzed epimerization of a mixture 7 produced mostly trans-isomers. Details on the identification of these isomers will be discussed in a full account.
6. Recrystallized from pentane: 8; mp 52--3 °C, 9; mp 19 °C, trans-isomers; bp 130 °C / 0.05 mmHg (bath temperature).
7. a). T. Mukaiyama and A. Ishida, Chem. Lett., 1201 (1975).
   b). T. Mukaiyama, Angew. Chem. Internat. Ed. Engl., 16, 817 (1977).
8. (+)-2: bp 110 °C / 1.1 mmHg (bath temperature). $[\alpha]_D^{19}$ +35.3° (c = 0.69, $CHCl_3$). IR (film); 3055, 2715, 1688, 1645 cm^{-1}. ^{1}H-NMR (400 MHz), δ($CDCl_3$); 0.85 (3H, d, J = 7Hz), 0.94 (3H, d, J = 7Hz), 1.30--1.40 (1H, m), 1.54--1.62 (1H, m, H_4), 1.69 (3H, d, J = 0.4Hz), 1.83--1.92 (2H, m), 1.97 (1H, d-t, J_{4-10} = 10.7Hz, J_{9-10} = 4.9Hz, H_{10}), 2.00--2.16 (3H, m), 2.29 (1H, d-t, J = 20.0 and 4.9Hz), 2.61 (1H, d-m, J = 12.0Hz, H_9), 5.51 (1H, m), 6.80 (1H, d-d, J = 2.9 and 5.1Hz), 9.40 (1H, s).
   (-)-2: $[\alpha]_D^{20}$ -33.3° (c = 0.62, $CHCl_3$) (without distillation).
9. Among two cis-isomers, bulky isopropyl group is located at concave site in the epimeric aldehyde 11. Because of this severe steric hindrance in the transition state, cyclization of the silyl enol ether derived from 9 was extremely disfavored.
10. (-)-1: mp 159--160 °C. $[\alpha]_D^{20}$ -11.4° (c = 0.09, MeOH). IR ($CHCl_3$ solution); 3450--2300, 1688, 1645 cm^{-1}. ^{1}H-NMR (400 MHz), δ($CDCl_3$); 0.84 (3H, d, J = 7Hz), 0.92 (3H, d, J = 7Hz), 1.34--1.46 (1H, m), 1.49--1.58 (1H, m), 1.70 (3H, s), 1.85--2.12 (6H, m), 2.16 (1H, d-t, J = 20 and 5.1Hz), 2.59 (1H, d-m, J = 12.0Hz), 5.51 (1H, m), 7.15 (1H, d-d, J = 3 and 5Hz), 11.3 (1H, broad). CD(MeOH): $[\theta]_{214\ nm}$ +55960.
    (+)-1: mp 159--160 °C, $[\alpha]_D^{20}$ +11.1° (c = 0.035, MeOH)
11. D. F. Taber and B. P. Gunn, J. Am. Chem. Soc., 101, 3992 (1979).
12. cis-Octalone 15 was the major isomer (84.5%) accompanied with other isomers (15.5%) in GLC.

(Received in Japan 25 June 1984)