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SYNTHESIS OF (±)-ASCOFURANONE, AN ANTIBIOTIC WITH HYPOLIPIDEMIC AND ANTITUMOR PROTECTIVE PROPERTIES

Kenji Mori* and Takafumi Fujioka[1)]

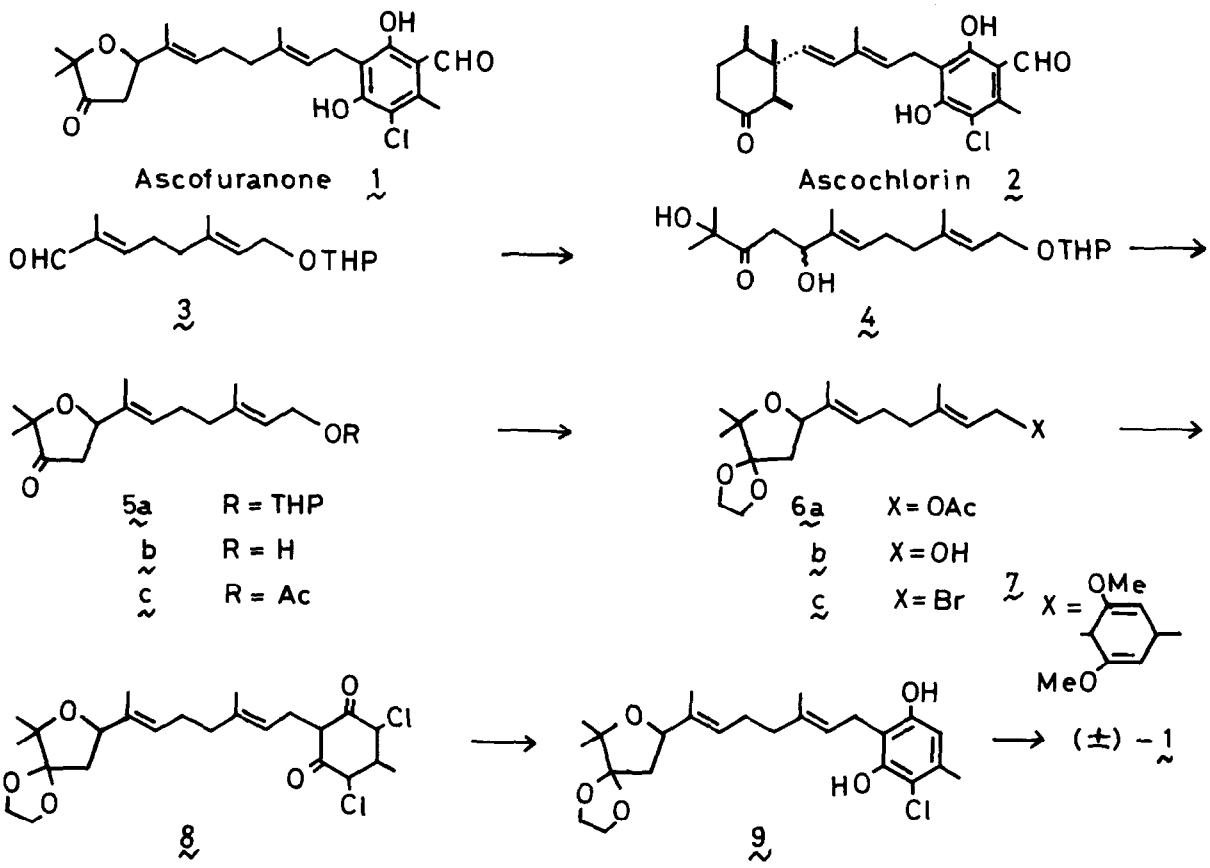
Department of Agricultural Chemistry, The University of Tokyo,
Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

Summary: (±)-Ascofuranone, 5-chloro-2,4-dihydroxy-6-methyl-[(2E,6E)-7-(3,3-dimethyl-4-oxo-2-oxacyclopentyl)3,7-dimethyl-2,6-heptadienyl]benzaldehyde, was synthesized.

Ascofuranone is a hypolipidemic antibiotic isolated from the mycelium of Ascochyta viciae LIBERT by Ando and his co-workers.[2,3)] Its structure was confirmed by an X-ray analysis as depicted in 1,[4)] although its absolute configuration still remains unknown. Recently its antitumor protective effect on L-1210 leukemia was discovered when it was administered once seven days before tumor challenge.[5)] After the completion of our synthetic work on ascochlorin 2,[6)] we turned our attention to ascofuranone 1. Herein we report the first synthesis of (±)-1.[7)]

An aldehyde 3 was prepared from geraniol as previously described by us.[8)] A cross-aldol reaction between 3 and 3-hydroxy-3-methyl-2-butanone [LiN(TMS)$_2$/THF, -78°] gave 4 (73.2% yield).[cf.9)] This was treated with p-TsOH in CH(OMe)$_3$ containing a small amount of MeOH to give a furanone 5a (52.9%). Removal of the THP protective group [AcOH-THF-H_2O (3 : 1 : 1), 50°] of 5a gave 5b (96.1%),[10)] which was acetylated (Ac_2O/C_5H_5N, room temp) to 5c (90.0%). Its CO group was protected as an ethylene acetal to give 6a (80.4%) by Noyori's method [TMSOTf/TMSO$(CH_2)_2$OTMS/CH_2Cl_2,0°].[11)] Hydrolysis of 6a (K_2CO_3/MeOH-H_2O) gave 6b (93.1%). This yielded a bromide 6c by the successive treatment with (i) n-BuLi/Et_2O-HMPA (ii) p-TsCl/Et_2O and (iii) LiBr.

The later stages of the present synthesis followed the route previously employed by us in the synthesis of ascochlorin 2 and the related microbial metabolites.[6,12)] Alkylation of 1,5-dimethoxy-3-methyl-1,4-cyclohexadiene with 6c (t-BuLi/THF-HMPA, -78°) gave 7 (33.2% from 6b). Treatment of 7 with N-chlorosuccinimide yielded 8 (63/2%). Aromatization of 8 was effected with DBU in THF (reflux, 4 hr) to give 9 (50.0%). Formylation of 9 [(i) EtMgBr/Et_2O, (ii) CH(OEt)$_3$ (iii) heating at 100°] was followed by acid hydrolysis [AcOH-H_2O (2 : 1), reflux, 30 min] to give (±)-ascofuranone 1 (21.0%) as fine needles, mp 87~91° (Found: C, 65.66; H, 6.94. Calc. for $C_{23}H_{29}O_5Cl$: C, 65.63; H, 6.94%). Its IR and NMR spectra were identical to those reported for the natural ascofuranone.[3)]



REFERENCES AND FOOTNOTES

1) Research Fellow on leave from Otsuka Pharmaceutical Co., Ltd (1981-1983).
2) H. Sasaki, T. Okutomi, T. Hosokawa, Y. Nawata and K. Ando, Tetrahedron Letters, 2541 (1972).
3) H. Sasaki, T. Hosokawa, M. Sawada and K. Ando, J. Antibiotics, 26, 676 (1973).
4) K. Ando, H. Sasaki, T. Hosokawa, Y. Nawata and Y. Iitaka, Tetrahedron Letters, 887 (1975).
5) J. Magae, T. Hosokawa, K. Ando, K. Nagai and G. Tamura, J. Antibiotics, 35, 1547 (1982).
6) K. Mori and T. Fujioka, Tetrahedron Letters, in press.
7) For the synthetic efforts in this area, see: (a) A.E. Guthrie, J.E. Semple and M.M. Joullié, J. Org. Chem., 47, 2369 (1982). (b) K. -M. Chen and M.M. Joullié, Tetrahedron Letters, 23, 4567 (1982).
8) K. Mori, M. Ohki and M. Matsui, Tetrahedron, 30, 715 (1974).
9) P.J. Jerris, P.M. Wovkulich and A.B. Smith, III, Tetrahedron Letters, 4517 (1979).
10) The homogeneity of 5b as the desired (2E,6E)-isomer was proved both by ^{13}C-NMR and by HPLC analyses.
11) T. Tsunoda, M. Suzuki and R. Noyori, Tetrahedron Letters, 1359 (1980).
12) K. Mori and K. Sato, Tetrahedron, 38, 1221 (1982).
13) ^{1}H-NMR spectral data of (±)-1 : δ(400MHz, $CDCl_3$) 1.22 (3H, s), 1.28 (3H,s) 1.63(3H,s), 1.79(3H,s), 2.00∿2.09(2H,m), 2.10∿2.21(2H,m), 2.35(1H,dd,J_1=18, J_2=10Hz), 2.42(1H,dd,J_1=18, J_2=7Hz), 2.60(3H,s), 3.39(2H,d,J=7Hz),4.52(1H,dd, J_1=10,J_2=7Hz),5.21(1H,t,J=7Hz),5.51(1H,t,J=7Hz),6.46(1H,s),10.14(1H,s), 12.70(1H,s).

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