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STEREOSELECTIVE SYNTHESIS AND STEREOCHEMISTRY OF ALTILOXIN A

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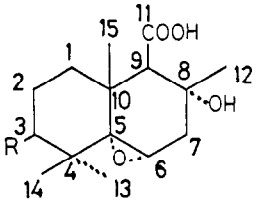
Abstract: Stereoselective synthesis of (±)-altiloxin A not only confirmed the relative configuration but also opened the route providing the phytotoxin. Absolute configuration of (-)-altiloxin A was clarified by correlation with (-)-11-acetoxydriman-8-ol.

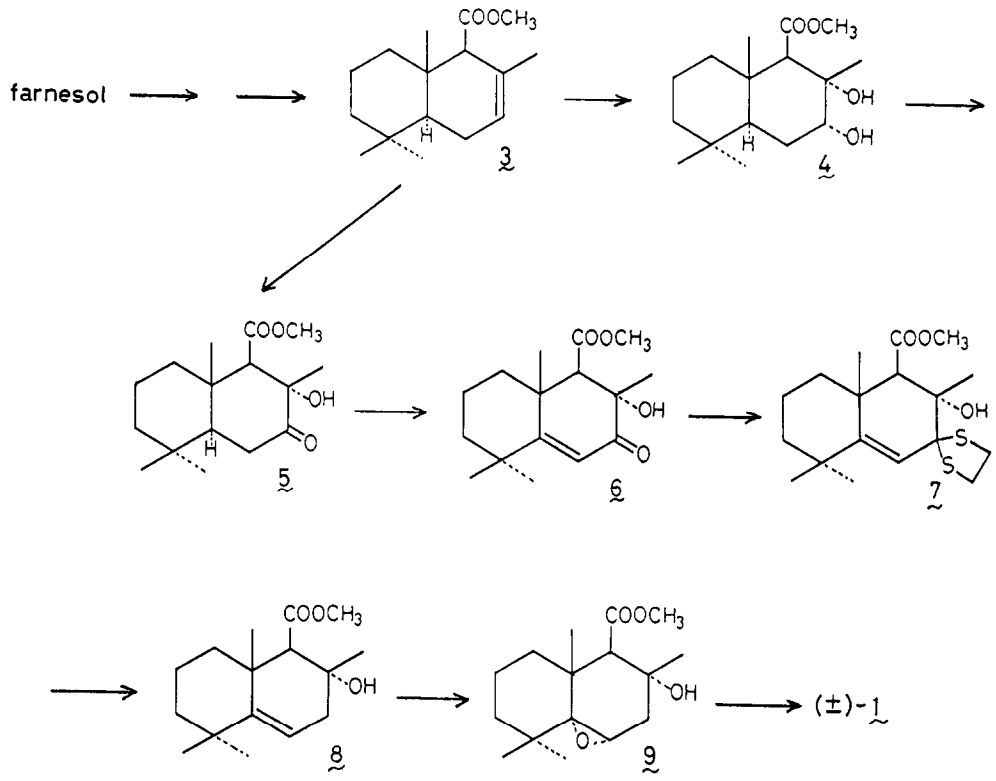
Altiloxins A (1) and B (2)[1] are phytotoxic metabolites isolated, along with dihydrogradiolic acid[2], from the culture filtrate of Phoma asparagi Sacc, causal fungus of stem blight disease on asparagus. Structures of these phytotoxins were elucidated from spectroscopic data and chemical reactions, especially the stereochemistry of the oxirane ring in 2 was deduced from only NOE experiments in the ^{1}H NMR spectrum.[1] In order to confirm the stereochemistry of altiloxins and also to develop an efficient route supplying these phytotoxins, stereoselective synthesis and correlation of altiloxin A (1) have been carried out as follows.



1 R = H
2 R = Cl

Methyl bicyclofarnesoate (3) which was derived easily from (2E, 6E)-farnesol according to the known procedure[3,4] was chosen as a starting material for this synthesis. Dihydroxylation of 3 with OsO_4 in pyridine yielded a diol 4, mp 157~162°C, in 67% yield.[5] The stereochemistry of the diol 4 was deduced by the fact that the signal at δ 3.64 due to the proton (7-Heq) α to sec. hydroxyl group was appeared as a broad singlet in the ^{1}H NMR spectrum, and was confirmed by NOE experiments of the ketol 5 derived from 4 as follows. The diol 4 was then oxidized with pyridinium dichromate to a ketol 5, mp 126~127°C, in 38% yield. On the other hand, oxidation of 3 with $KMnO_4$ in the presence of $NaHCO_3$ in acetone afforded directly the ketol 5 in 47% yield. The stereochemistry of 5 was confirmed by difference NOE experiment in the ^{1}H NMR spectrum. Thus, irradiation of 12-CH_3 increased the intensities of the signals

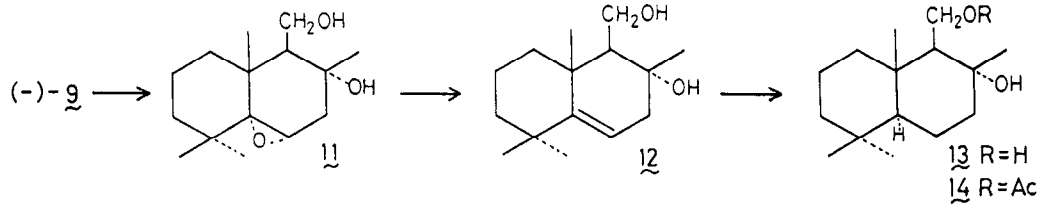
due to 15-CH_3 and 6-Hax, and irradiation of 15-CH_3 increased the intensities due to 12-CH_3, 14-CH_3, 1-Heq and 6-Hax.[6] These observations surely support the relative configuration of



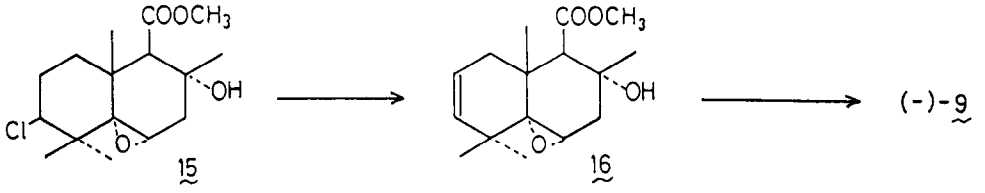
the ketol as depicted in 5, and the stereoselective oxidation would be explained by the attack of permanganate from less hindered α side of the molecule. Treatment of the ketol 5 with phenylselenenyl chloride in ethyl acetate[7] yielded a selenylated product, which was easily converted with hydrogen peroxide to an α,β-unsaturated ketone 6, mp 115~116°C, in 65% yield. The α,β-unsaturated ketone 6 was treated with ethanedithiol and BF_3 etherate to give a thioacetal 7, mp 118.5~119.5°C, in quantitative yield. Although reductive removal of the thioacetal in 7 with Raney-Ni (W-2) yielded an olefinic compound 8 in low yield (30%), reduction with n-Bu_3SnH in the presence of azobisisobutyronitrile[8] afforded 8 in 80% yield. Epoxidation of the olefin 8 with m-CPBA in CH_2Cl_2 at -18°~20°C gave (±)-altiloxin A methyl ester 9, mp 90~91°C (lit.[1] (-)-9, mp 120 121°C) in 56% yield, and a small amount of isomeric methyl ester 10,[9] mp 104~108°C, in 10% yield.[10] Spectroscopic data (^1H NMR, MS) of the former are completely identical with those of natural (-)-altiloxin A methyl ester (9). Stereoselective epoxidation of 8 would be rationalized by the steric hindrance due to three methyl groups of 12-CH_3, 14-CH_3 and 15-CH_3, and neighboring participation due to 8-OH. Hydrolysis of the ester (9) was carried out by heating at 165°C with DBU in o-xylene[11] to give

(±)-altiloxin A (1), mp 136.5~138°C (lit.[1] (-)-1, mp 136~137°C), whose spectroscopic data are identical with those of natural (-)-altiloxin A (1). The present synthesis surely proves the relative configuration of altiloxin A (1).

For the sake of elucidation of its absolute configuration, correlation of (-)-altiloxin A methyl ester (9) with (-)-11-acetoxydriman-8-ol[12] was next attempted. Thus, reduction of the methyl ester 9 derived from natural altiloxin A with $LiAlH_4$ in THF furnished a diol 11, FD-MS m/z 254 (M^+), in 74% yield. Deoxygenation of the epoxide in the diol 11 was accomplished by treating with $TiCl_3/LiAlH_4$ in THF[13] to yield and olefinic diol 12, EI-MS m/z 238 (M^+). Hydrogenation of 12 over PtO_2 in ethanol afforded a single product, driman-8,11-diol 13[14] which in turn was treated with Ac_2O-pyridine to give (-)-11-acetoxydriman-8-ol 14, $[\alpha]_D^{20}$



-8.2°(c 0.39, $CHCl_3$);[12,15] molecular formula $C_{17}H_{30}O_3$ from the high resolution MS m/z 222.1993 (M^+-CH_3COOH, calcd, 222.1983). Since authentic sample from natural origin has the same optical rotation, $[\alpha]_D^{20}$-9°(c 0.53, $CHCl_3$), the acetate should be depicted as 14. Further correlation of altiloxin B (2) with altiloxin A (1) was undertaken as follows. Treatment of the methyl ester (15) of altiloxin B with 1,5-diazabicyclo [5. 4. 0] undec-5-ene in o-xylene at 165°C for 23 hr gave a reaction mixture, which was methylated with diazomethane to yield



a dehydrochlorinated product 16, mp 93.5~94.5°C, molecular formula $C_{16}H_{24}O_4$ from the high resolution MS m/z 280.1663 (M^+, calcd, 280.1673).[16] Hydrogenation of 16 over Pd-C (10%) in methanol afforded a product, mp 119.5~120.5°C, $[\alpha]_D^{20}$-23°(c 0.2, $CHCl_3$), which was identical with methyl ester (9)[1] of altiloxin A (1), mp 120~121°C, $[\alpha]_D^{20}$-24.73°(c 1.65, $CHCl_3$), in all respects. From above results, we concluded that the absolute configurations of altiloxins A and B are 1 and 2 respectively.

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References and Notes

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4. P. A. Stadler, A. Eschenmoser, H. Schinz, G. Stork, Helv. Chim. Acta, 40, 2191 (1957).
5. All new compounds had satisfactory spectroscopic data (IR, NMR) and acceptable high resolution mass spectroscopic data.
6. Though irradiation of 15-CH_3 in 5 also increased slightly the intensity of the signal due to 9-H, the proton would be located in antiplanar axial position to 15-CH_3, since alkaline treatment of 5 gave no epimerized ester.
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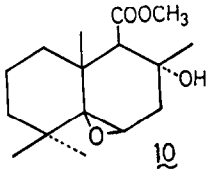
9. Spectroscopic data of 10: high resolution MS: m/z 282.1843. calcd. for $C_{16}H_{26}O_4$ 282.1831; IR ν_{max}^{KBr} cm^{-1}: 3420, 1720, 1425, 1315; ^1H NMR (100 MHz): $\delta_{TMS}^{CDCl_3}$ 0.86(3H, s, 13-CH_3), 0.97 (3H, s, 14-CH_3), 1.24 (3H, s, 15-CH_3), 1.57 (3H, s, 12-CH_3), 2.30 (1H, dd, J=2.5, 1.47 Hz, 7β-H), 2.46 (1H, s, 9-H), 3.33 (1H, dd, J=2.2, 2.5 Hz, 6-H), 3.66 (3H, s, 16-CH_3). Rather upper field shift (δ 0.97) of 14-CH_3 in 10 would be due to shielding effect of the β oxirane ring.



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10. In the case of epoxidation with perbenzoic acid below -22°C, only single product (±)-9 was obtained in 63% yield.
11. Usual hydrolysis using acidic or basic media containing water was all failed.
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14. The structure of 13 was confirmed by comparison of the spectral data of the natural compound in the literature[12] with those of 13, and then by direct comparison with (±)-driman-8,11-diol, Cf. M. Nishizawa, H. Takenaka, H. Nishide, Y. Hayashi, Tetrahedron Lett., 24, 2581 (1983).
15. Because of low optical rotation ($[\alpha]_D^{20}$+1.6°) of natural driman-8,11-diol (13),[12] (-)-11-acetoxydriman-8-ol (14) was used for the comparison.
16. The same amount (16.5%) of unreacted starting material 15 was recovered.

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