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SYNTHESIS OF (±)-SOLANAPYRONE A

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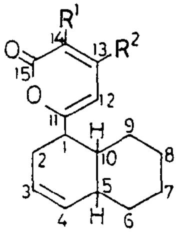
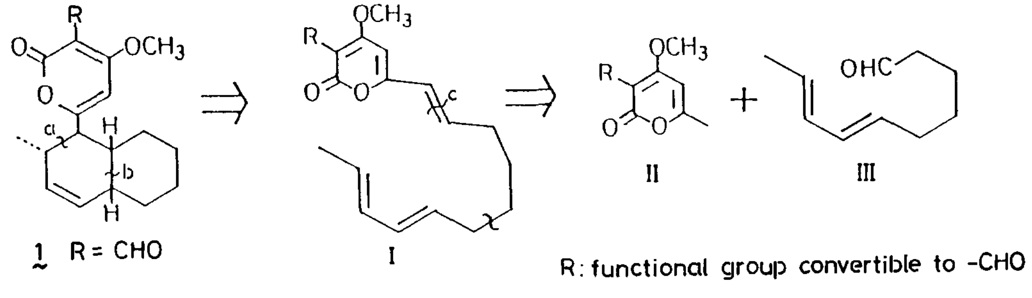
Abstract: The first synthesis of solanapyrone A (1), a phytotoxin from Alternaria solani, has been completed through the intramolecular Diels-Alder reaction.

Solanapyrone A (1) is a principal phytotoxin recently isolated along with other metabolites, solanapyrones B (2), C (3)[1] and zinnolide[2], from the culture broth of Alternaria solani, a causal fungus of early blight disease of potato and tomato. 1 induced a necrotic lesion on the leaf of potato, and showed MIC value of 25 - 50 ppm to Pyricularia oryzae. Since this toxin has been obtained as an oil, the structure and stereochemistry have been elucidated on the basis of spectroscopic data and chemical reactions[1,3]. In order to confirm the structure including stereochemistry and to develop an effective synthetic method of the phytotoxin, synthesis of 1 has been undertaken. Retrosynthesis (Scheme I) envisaged the intramolecular Diels-Alder reaction of the triene I, a key intermediate, which is further divided into a pyrone moiety II and a diene moiety III.



1 R^1= CHO, R^2= OCH_3
2 R^1=CH_2OH,R^2= OCH_3
3 R^1= CHO, R^2= $NHCH_2CH_2OH$

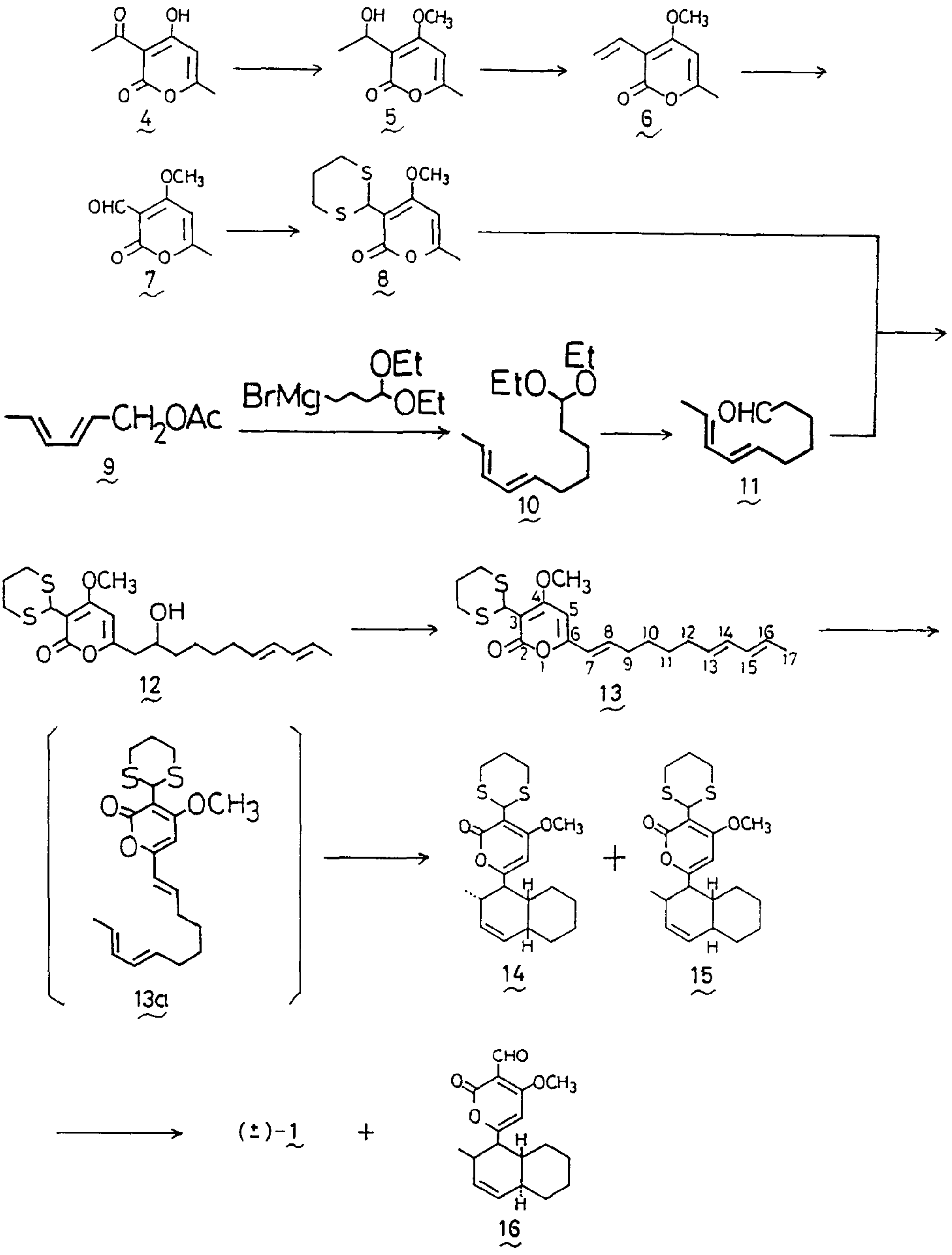


R: functional group convertible to -CHO

Scheme I

The pyrone moiety 8 of solanapyrone A has been prepared from dehydroacetic acid (4) (Scheme II). Thus, methylation ($CHCl_3$, CH_3I, Ag_2O, r.t., 8 hr) and subsequent reduction ($NaBH_4$, $CHCl_3$-CH_3OH, -40°C, 1 hr) of 4 yielded the alcohol 5 in 73 % yield[4]. The alcohol 5 was dehydrated in DMSO (160°C, 14 hr) to give the olefine 6 in 81 % yield. Oxidation (OsO_4-$NaIO_4$, H_2O-ether, r.t., 3 hr) of 6 afforded the aldehyde 7 (82 % yield), which was protected as the dithioacetal 8 in 89 % yield.

On the other hand, the diene moiety 11 was prepared as follows. Condensation (THF, -15°C, 2 hr) of (2E, 4E)-2,4-hexadienyl acetate (9)[5] derived from sorbic acid with the Grignard reagent prepared from 4-bromobutyraldehyde diethyl acetal in the presence of



Scheme II

Li_2CuCl_4 afforded the diene acetal **10** in 62 % yield[6]. Hydrolysis (TsOH, acetone-H_2O) of the acetal **10** yielded the aldehyde **11** in 70 % yield. Aldol condensation (LDA, THF, -60°C) of the aldehyde **11** with the dithioacetal **8** gave the dienol **12** in 53 % yield from **11**[7]. Treatment of the dienol **12** with p-toluenesulfonyl chloride (DMAP, CH_2Cl_2, r.t., 6 hr) led to a triene **13**[8], in which newly formed double bond (Δ^7) has been confirmed to be trans, since the signals with trans ethylenic coupling constants (J=15.4 Hz) appeared at δ 5.96 (1H, dt, J=15.4, 1.5 Hz, 7-H) and at δ 6.78 (1H, dt, J=15.4, 7.3 Hz, 8-H) in the ^1H NMR spectrum. The intramolecular Diels-Alder reaction[9] of **13** in toluene at 180°C for 1 hr in a sealed tube yielded a mixture of the adducts (71 %), which were unable to separate chromatographically. However, the ^1H NMR spectrum disclosed that it consists of two compounds in a ratio of 1 : 2, and the signals ascribable to the minor dithioacetal were identical with those of the dithioacetal **14** derived from natural sample **1**. The other isomer **15** was deduced to have trans ring juncture, which is derived from an endo transition state of (E, E, E)-triene **12**[10]. Removal of the protective group of the adducts with $Tl(ONO_2)_3$ (THF-$CHCl_3$-H_2O, r.t., 20 min.) furnished a mixture of aldehydes which were easily separated to (±)-solanapyrone A (**1**)[11] and its diastereoisomer **16**[12] in a ratio of 2 : 3 (90 %). The spectroscopic data of the former were identical with those of natural specimen. Since the signal of **16**[12] at δ5.56 (1H, ddd, 10.3, 4.3, 2.6 Hz, 3-H) showed rather large allylic coupling constant (J=2.6 Hz) and the signal at δ 5.44 (1H, ddd, 10.3, 1.5, 0~1 Hz, 4-H) showed small one (J=0~1 Hz), its stereostructure was deduced to have a trans ring junction.

Present synthesis not only confirmed the structure but also provides the effective synthetic method of solanapyrone A (**1**).

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References and Notes

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4. Satisfactory elemental composition (exact mass spectroscopy) and spectral data were obtained on all new compounds.
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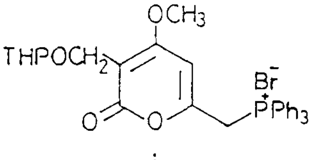
7. All attempts to prepare pyrone derivatives i and ii for the Wittig reaction were failed because of the instability of these compounds.



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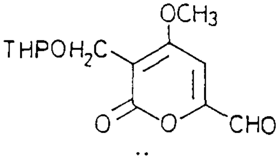

ii

8. Aldol condensation of **8** with a mixture of(E,E)-**11** and(E,Z)-**11** (ca. 1 : 1) prepared from crotyltriphenylphosphorane and 6-acetoxyhexanal followed by dehydration yielded a mixture

of(E,E,E)-**13** and(E,Z,E)-**13** in a ratio of ca. 1 : 1. Photochemical equilibration of the mixture in the presence of diphenylsulfide afforded a mixture of (E, E, E)-**13** and (E, E, Z)-**13** + (E, Z, E)-**13** in a ratio of 5 : 3.
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9. For recent review of the intramolecular Diels-Alder reactions, see W. Oppolzer, Angew, Chem. Int. Ed. Engl. 16, 10 (1977); G. Brieger, J. N. Bennett, Chem. Rev., 80, 63 (1980); A. G. Fallis, Can, J. Chem., 62, 183 (1984); E. Ciganek, Org. React., 32, 1 (1984).

10. cis (**14**) / trans (**15**) ratio in other solvents was studied using the irradiated triene mixture[7] [(E, E, E)-**13**: (E, E, Z)-**13** + (E, Z, E)-**13**, 5 : 3] obtained photochemically (Table 1). In these intramolecular Diels-Alder reactions, no product from (E, E, Z)-**13** and (E, Z, E)-**13** was obtained. Similar kinetic selectivity has also been observed in the synthesis of (+)-diplodiatoxin; A. Ichihara, H. Kawagishi, N. Tokugawa, S. Sakamura, Tetrahedron Lett., 27, 1347 (1986).

Table 1. Intramolecular Diels-Alder reaction of the triene mixture.

solvent	temp (C°)	time (hr)	yield (%)	cis (**14**) : trans (**15**)
chloroform	110	48	50	1 : 2.5
benzene	〃	〃	45	1 : 2
naphthalene	〃	〃	52	1 : 2
H_2O	100	12	60	1 : 7

11. (±)-**1**, HR-MS m/z 302.1496 (M^+), calcd. for $C_{18}H_{22}O_4$ m/z 302.1519; IR ν_{max}^{film} cm^{-1}: 1730, 1690, 1620, 1510; ^1H NMR $\delta_{TMS}^{CDCl_3}$ ppm (200 MHz): 0.95 (3H, d, J=6.8 Hz, 2-CH_3), 1.19 - 1.72 (8H, m, CH_2 x 4), 2.15 (1H, m, 5-H), 2.30 (1H, m, 10-H), 2.47 (1H, dd, J=10.3, 10.3 Hz, 1-H), 2.63 (1H, br q, 2-H), 4.08 (3H, s, OCH_3), 5.44 (1H, ddd, J=9.8, 2.2, 1.9 Hz, 3-H), 5.68 (1H, ddd, J=9.8, 4.9, 2.4 Hz, 4-H), 6.14 (1H, s, 12-H), 10.15 (1H, s, -CHO).

12. **16**, HR-MS m/z 302.1520 (M^+), calcd. for $C_{18}H_{22}O_4$ m/z 302.1519; IR ν_{max}^{film} cm^{-1}: 1700 (br.). 1600, 1500; ^1H NMR $\delta_{TMS}^{CDCl_3}$ ppm (500 MHz); 0.92 (1H, m, CH), 0.99 (3H, d, J=7.3 Hz, 2-CH_3), 1.13 (1H, m, CH), 1.32 (3H, m, CH), 1.67 (2H, m, 10-H), 1.77 (3H, m, 5-H), 2.50 (1H, m, 2-H), 2.74 (1H, dd, J=11.3, 6.0 Jz, 1-H), 4.06 (3H, s, OCH_3), 5.44 (1H, ddd, J=10.3, 1.5, 0∼1 Hz, 4-H), 5.56 (1H, ddd, J=10.3, 4.3, 2.6 Hz, 3-H), 6.11 (1H, s, 12-H), 10.15 (1H, s, -CHO).

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