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Synthesis and Phytotoxic Activities of (8*S*, 9*S*, 11*R*)-(−)-Monocerin and (9*S*, 11*R*)-(+)-Fusarentin 4, 5-dimethyl ether

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Abstract : For the examination of the role of monocerin(**1**) on the biological activity, (8*S*, 9*S*, 11*R*)-(−)-monocerin(**20**) and (9*S*, 11*R*)-(+)-fusarentin 4, 5-dimethyl ether(**19**) were synthesized by a condensation of the benzylic anion of ethyl 2, 3, 4-trimethoxy-6-methylbenzoate(**16**) with modifyed (*R*)-ethyl 3-hydroxyhexanoate (**9**). In a key step, bioreduction with active dried baker's yeast in organic solvent system was employed to get a chiral aldehyde **12**. Their phytotoxic activities were tested on rice seedlings and lettuce seeds (Received June 27 1994, accepted October 6, 1994).

Introduction

Monocerin(**1**), which was first isolated from *Helminthosporium monoceras*, has antifungal, insecticidal and phytotoxic activity.[1,2,3,5] Subsequently, during studies on the entomogenous fungus *Fusarium larvarum*, Grove and Pople[3] isolated monocerin(**1**) and a number of closely related fusarentin ethers (**5-7**). Three minor metabolites, related to monocerin, were also isolated; hydroxy monocerin(**2**), monocerolide(**3**), monocerone(**4**) (Fig. 1). Mori et al. in 1989 and Simpson group in 1992 synthesized monocerin(**1**).[4] The phytotoxic properties of monocerin(**1**) were reported by Robeson and Strobel during studies on the fungus *Exserohilum turcicum*.[5]

However, previous works of monocerin(**1**) on biological activity[2,3,5] did not show the effect of the structure-activity relationship. A study of the structure-activity relationship is therefore important and interesting. Here, in order to elucidate the structure-activity relationship of monocerin(**1**), the author synthesized a synthesis of (8*S*, 9*S*, 11*R*)-(−)-monocerin(**20**) and (9*S*, 11*R*)-(+)-fusarentin 4, 5-dimethyl ether(**19**), employing a condensation of the benzylic anion derived from benzoate **16** with modifyed (*R*)-ethyl 3-hydroxyhexanoate (**9**). Their biological activities were tested on rice seedlings and lettuce seeds. To get a chiral aldehyde (*R*)-3-tetrahydropyranyloxyhexanal(**9**) from ethyl 3-oxohexanoate(**8**), bioreduction with baker's yeast in organic solvent system was employed[6].

Materials and Methods

^{1}H and ^{13}C-NMR spectra were recorded on JEOL JNM-GX-270 spectrometers with $CDCl_3$ as solvent, unless otherwise stated, using tetramethylsilane as the internal standard. NMR chemical shifts are given in δ values as ppm downfield of tetramethylsilane. IR spectra were measured on a JASCO IR-810 infra-red spectrometer. Opitical rotations were measured using a Perkin Elmer 241 MC polarimeter. Mass spectra were recorded on a JEOL HX-105 mass spectrometer. All organic solvents were distilled prior to use and purification of all compounds was carried out by distillation. Reactions involving chemicals or intermediates sensitive to air and/or moisture were performed under a nitrogen

Key words : Monocerin, fusarentin 4, 5-dimethyl ether, phytotoxic activity, structure activity relationship.
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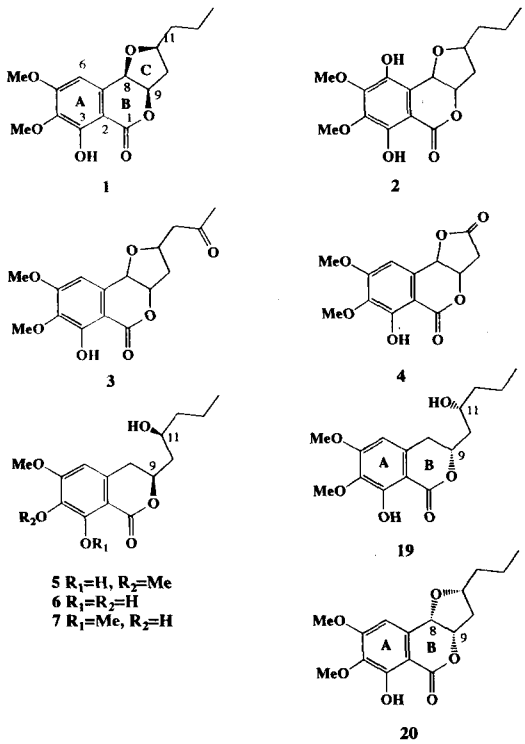


Fig. 1. Monocerin and its analogs.

atomsphere. Melting points were determined on micro-melting point apparatus Yanagimoto No. 1593. All melting and boiling points are uncorrected. Preparative TLC was carried out on Merck Kieselgel $60PF_{254}$ of 0.25 mm thickness.

Modifications to ethyl (*R*)-3-hydroxyhexanoate(**9**)

Ethyl 3-oxohexanoate(**8**) was prepared by deprotection from the acylation of Meldrum's acid.[6]

Ethyl (*R*)-3-hydroxyhexanoate(**9**): Baker's yeast(2 g) was suspened with in 60 m*l* of hexane in the presence of 2% v/v of water. Ethyl 3-oxohexanoate (**8**, 1 mmol, 0.158 g) was added to the suspension and the mixture was shaken(ca. 250 rpm) for 24 hr. at 28℃. The usual work-up provided a colorless oil. This was identical with a sample prepared earlier[6] in IR and ^{1}H-NMR.

Ethyl (*R*)-3-tetrahydropyranyloxyhexanoate(**10**): A mixture of **9**(1.7 mmol, 0.272 g) and 3,4-dihydro-2*H*-pyran(8.5 mmol, 0.720 g) were stirred for overnight in CH_2Cl_2(10 m*l*) containing a few drops of trifluoroacetic acid. The reaction mixture was poured into water. The aqueous solution was extracted with diethyl ether and the solvent removed *in vacuo* yielding **10**(98%, 0.415 g) as a colorless oil. IR ν_{max}(film)cm^{-1}: 3411(OH). ^{1}H-NMR($CDCl_3$) δ: 0.91-0.93(# H, 2xt, J=7.2 Hz), 1.34-1.75(12H, m), 2.59(1H, br. s) 3.56-3.66(1H, m), 3.64(2H, t, J=6.5 Hz), 3.82-3.88(1H, m), 4.09(1H, m), 4.50-4.52(1H, 2xt, J=3.4 Hz).

(*R*)-3-Tetrahydropyranyloxyhexanal(**12**): To a solution of hexanol **11**(1 mmol, 0.201 g) in CH_2Cl_2(20 m*l*) was added freshly pyridinium dichromate(1.12 mmol, 0.422 g) and the reaction mixture left for overnight. The resulting dark solution was filtered over silica gel and the solvent was evaporated. Purification by chromatography (AcOEt: herxane=3 : 1) yielded aldehyde **12**(62%, 0.124 g) as a colorless oil. IR ν_{max}(film)cm^{-1}: 1723(C=O). ^{1}H-NMR($CDCl_3$) δ: 0.93, 0.96(3H, 2xt, J=7.3 Hz), 1.23-1.86(10H, m), 2.53(2H, m), 3.48(1H, m), 3.84(1H, m), 4.16(1H, m), 9.80, 9.81(1H, 2xt, J=2.3 Hz). MS m/z 200(M^+, 2%), 101(18%), 84(44%), 73(21%), 69(20%), 57(33%), 55 (100%).

Synthesis of ethyl 2,3,4-trimethoxy-6-methylbenzoate(**16**)

Ethyl 3-formyl-2-hydroxy-4-methylbenzoate(**14**): This was prepared from orcinnol(**13**) in five steps applying D. Taub's method[7] and Gattermann reaction.[8] ^{1}H-NMR($CDCl_3$) δ: 1.42(3H, t, J=7.2 z), 2.76(3 H, t, J=7.2 Hz), 2.76(3H, s), 3.90(3H, s), 4.43(2H, q, J=7.2 Hz), 6.38(1H, s), 10.45(1H, s), 11.98(1H, s).

Ethyl 2,3-dihydroxy-4-methoxy-6-methylbenzoate (**15**): A solution of **14**(4.2 mmol, 1.0 g) in a mixture of dioxane(5 m*l*) and 4N-NaOH(1.5 m*l*) solution was stirred vigorously at 0~5℃. 30% Hydrogen peroxide(1.8 m*l*) solution was added to the reaction mixture, and after stirring for 4 hr at room temperature, the reaction mixture was quenched with cooled 1N-HCl and extracted with Et_2O. The solvent was evaporated and then the product was purified by recrystallization. Colorless prisms **15**(90%, 0.86 g) m.p. 89~91℃ (benzen-hexane). ^{1}H-NMR($CDCl_3$)

δ: 1.36(3H, t, J=7.2 Hz), 2.22(3H, s), 3.87(3H, s), 4.37(2H, q, J=7.2 Hz), 6.27(1H, s), 11.75(1H, s).

Ehtyl 2,3,4-trimethoxy-6-methylbenzoate(**16**): To a stirred solution of **15**(1.74 g, 7.7 mmol) and anhydrous K_2CO_3(7.5 g) in dry acetone(50 m*l*) was added dimethyl sulphate(2.45 g, 19.3 mmol). The reaction mixture was stirred under reflux for 18 hr. The mixture was filtered and the solvent removed *in vacuo* yielding a yellow oil. Purification by silica gel chromatography yielded **16**(81%, 1.62 g) as a clear oil. ^{1}H-NMR($CDCl_3$) δ: 1.38(3H, t, J=7.1 Hz), 2.28(3H, s), 3.84(3H, s), 3.86(3H, s), 3.90(3H, s), 4.34 (q, 2H, J=7.1 Hz), 6.49(1H, s). MS m/z: 254(M^+, 87%), 208(M^+-EtOH, 33%).

Condensation reaction for(8*S*, 9*S*, 11*R*)-(−)-monocerin(**20**) and (9*S*, 11*R*)-(+)-fusarentin 4,5-dimethyl ether(**19**)

To a stirred solution of LDA(containing a slight of HMPA) in 20 m*l* of dry THF, was added 0.78 mmol of ethyl 2,3,4-trimethoxy-6-methylbenzoate **16**(0.2 g) at −78℃. After stirring for 15 min, 0.78 g (3.9 mmol) of aldehyde **12** was rapidly added reaction mixture at −84℃. After further stirring for 30 min at −84℃, the mixture was poured into aqeous 5% ammonium chloride and extracted with Et_2O. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The product was treated with trifluoroacetic acid(2 m*l*) in MeOH and stirred for overnight. The volatile materials were removed under reduced pressure and the residue was purified by silica gel chromatography to give a maxture of diastereoisomers(62%, 157 mg). ^{1}H-NMR($CDCl_3$) δ: 0.92(3H, t, J=7.1 Hz), 1.36-1.52(4H, m), 1.62-2.07(3H, m), 2 .84 (1H, m), 3.86(3H, s), 3.91(3H, s), 3.89-4.12(1H, m), 4.71(1H, m), 6.50(1H, s). To separate the diastereoisomer of mixture was used to a 0.25 mm TLC plate with 30% AcOEt-hexane.

3,4-Dihydro-6,7,8-trimethoxy-3-(*S*)-(2-(*R*)-hydroxy-n-pentyl)-1*H*-2-benzopyran-1-one(**17**): $[\alpha]_D$+19.3° (c 1.06 in $CHCl_3$). IR ν_{max}(film)cm^{-1}: 3420, 1709. ^{1}H-NMR($CDCl_3$) δ: 0.93(3H, t, J=6.8 Hz), 1.37-1.56(4H, m), 1.67(1H, ddd, J=14.3, 10.1, 3.1 Hz), 1.95(1H, ddd, J=14.3, 9.5, 2.3 Hz), 2.75-2.82(1H, m), 2.86-2.94 (1H, m), 3.86(3H, s), 3.91(3H, s), 3.97(3H, s), 4.09(1 H, m), 4.78(1H, dddd, J=10.1, 7.1, 3.3, 3.0 Hz), 6.51 (1H, s).

3,4-Dihydro-6,7,8-trimethoxy-3-(*R*)-(2-(*R*)-hydroxy-n-pentyl)-1*H*-2-benzo-pyran-1-one(**18**): $[\alpha]_D$ −23.8° (c 0.84 in $CHCl_3$). ^{1}H-NMR($CDCl_3$) ^{1}H-NMR($CDCl_3$) δ: 0.94(3H, t, J=6.8 Hz), 1.37-1.56(4H, m), 1.74(1H, ddd, J=14.3, 5.6, 3.3 Hz), 1.99(1H, ddd, J=14.3, 8.1, 7.2 Hz), 2.83-2.88(1H, m), 2.90-2.98(1H, m), 3.86(3H, s), 3.91(3H, s), 3.97(3H, s), 3.91-3.99(1H, m), 4.58(1H, dddd, J=7.6, 7.2, 5.6, 3.3 Hz), 6.50(1H, s).

(9*S*, 11*R*)-(+)-Fusarentin 4,5-dimethyl ether(**19**): Boron trichloride(0.32 mmol, 0.32 m*l* of 1.0M solution in CH_2Cl_2) was added to a solution of benzopyran-1-one(**17**, 0.3 mmol, 95 mg) in CH_2Cl_2. The mixture stirred at room temperature for 10 min and the solvent removed *in vacuo*. Purification by TLC plate(2:1 hexane: AcOEt) yielded **19**(84 mg, 91%) as a oil. $[\alpha]_D$+21.6°(c 1.86 in CH_3OH). IR ν_{max}(film) cm^{-1}: 3210, 1676. ^{1}H-NMR($CDCl_3$) δ: 0.94(3H, t, J= 6.8 Hz), 1.23-1.49(4H, m), 1.62(1H, br, s) 1.68(1H, dd, J=14.3, 10.2, 3.3 Hz), 1.97(1H, ddd, J=14.3, 9.4, 2.2 Hz), 2.83-2.90(1H, m), 2.90-2.98(1H, m), 3.86(3H, s), 3.91(3H, s), 4.01-4.15(1H, m), 4.86(1H, dddd, J= 10.2, 9.4, 4.6, 3.3 Hz), 6.50(1H, s), 11.08(1H, s). HREIMS m/z: 310.1401 (M^+, $C_{16}H_{22}O_6$ requires 310. 1416).

(8*S*, 9*S*, 11*R*)-(−)-Monocerin(**20**): To a solution of fusarentin 4,5-dimethyl ether(**5**, 0.18 mol, 52 mg) in dried CCl_4(10 m*l*) at 0℃ was added N-bromosuccinimide(0.2 mmol, 36 mg) and the mixture was irradiated(100W). After further stirring for 2 hr at ice-water bath, the mixture was poured into water and extracted CH_2Cl_2. The organic extracts washed with brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by TLC plate(2: 1 hexane: AcOEt) yielded **20**(36 mg, 61%) as a colorless oil. $[\alpha]_D$−38.6°(c 1.06 in CH_3OH). IR ν_{max} (film)cm^{-1}: 3200, 1674, ^{1}H-NMR($CDCl_3$) δ: 0.92(3H, t, J=7.2 Hz), 1.25-1.73(4H, m), 2.16(1H, ddd, J=14.3, 6.0, 2.3 Hz), 2.57(1H, ddd, J=14.3, 7.9, 6.1 Hz), 3.87 (3H, s), 3.93(3H, s), 4.05-4.18(1H, m), 4.56(1H, d, J=3.3 Hz), 5.05(1H, ddd, J=6.2, 3.3, 1.1 Hz), 6.58(1

H, s). ^{13}C-NMR($CDCl_3$) δ: 13.89, 19.02, 37.93, 56.12, 60.65, 74.35, 78.63, 88.20, 101.23, 104.55, 131.10, 137.16, 156.14, 158.58, 167.98. HREIMS m/z: 308.1271 (M^+, $C_{16}H_{22}O_6$ requires 308.1260).

Hydrogenation fo Monocerin(1)

Monocerin(**1**, 28 mg, 0.9 mmol)[13] in 10 m*l* of methanol with 5%-palladium(12 mg) was hydrogenated over 3 days. The solution was filtered and concentrated. The residue was purified by TLC plate to yield 5 as a oil: $[\alpha]_D$ −26.4(c 0.10 in methanol). This compound was exactly the same as those reported in the litherature.[2-4]

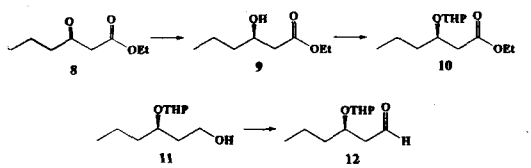
Growth inhibitory against lettuce(Lactuca sativa L. var Green Lake). Seven lettuce seeds were germinated in a sample tube with a culture medium(1.5 g of $Ca(NO_3)_2 \cdot 4h_2O$, 0.25 g of KCl, 0.25 g of $MgSO_4 \cdot 7H_2O$, 0.05 g of KH_2PO_4 in 1000 m*l* of water) containing 0.7% of agar. After growing for 5days at 28℃ (2000 lux), the number of germinated seeds and the length of roots were measured.

Rice seedlings: Rice seedling(*Oryza sativa L. var.* Sasanishiki), which were germinated in water for 2days at 28℃, were grown in a sample solution containing 0.7% agar with previously described medium. After growing for 5days at 28℃ in the light (2000 lux), the length of the second leaf sheath was measured.

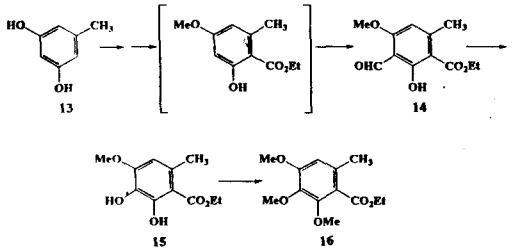
Results and Discussions

For the synthesis of (8*S*, 9*S*, 11*R*)-(−)-monocerin (**20**) and (9*S*, 11*R*)-(+)-fusarentin 4,5-dimethyl ether(**19**), the aldehyde **12** as required chiral compound was easily prepared from ethyl (*R*)-3-hydroxyhexanoate(**9**). Baker's yeast reductions of β-keto esters is well known to give β-hydroxy esters in optical purities. The β-keto ester **8** was converted by an bioreduction with baker's yeast in organic solvent to a high enantiomeric alcohol **9**, about over 95%. Enantiomeric alcohol **9** was characterized by comparing their spectral data in the preceding paper.[6] It is of interest to note that the use of active dried baker's yeast with organic solvent was of greater advantage than that of free baker's yeast with water system in terms of the separation of the product from the catalyst and of the optical purity. Lithium aluminium hydride reduction of a monoTHP ether **10**, which was prepared from alcohol **9** in the usual manner, yielded the monoprotected diol **11**. Oxidation of **11** with PDC[9] gave the chiral aldehyde **12** in 62% yield(51% overall yield from ethyl 3-oxohexanoate **8**, Scheme 1). Dakin's oxidation[10] and then methylation of compound **14**, which was prepared from orcinol **13** in five steps, gave the corresponding ethyl benzoate **15** in a good yield(Scheme 2).

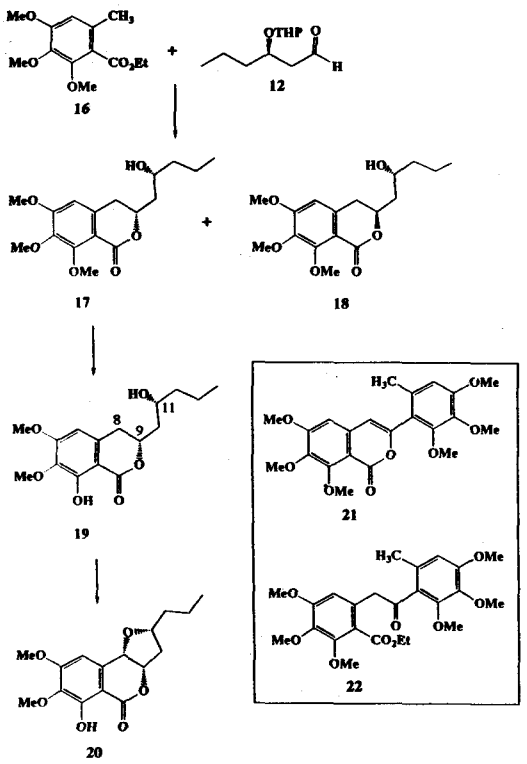
Staunton and co-worker reported generation of the anion of ethyl o-toluate to get mellein methyl ester.[4,11] This reaction seemed a possible synthetic route to the (8*S*, 9*S*, 11*R*)-(−)-Monocerin(**20**) and (9*S*, 11*R*)-(+)-fusarentin 4,5-dimethyl ether(**19**). The reaction of ethyl 2,3,4-trimethoxy-6-methylbenzoate(**16**) with aldehyde **12** in the presence of LDA at −78℃ gave no evidence of anion formation, only starting material was recovered. Treatment of **16** in the presence of n-BuLi at −78℃ gave a mixture of many products, the major product were



Scheme 1. Preparation of (*R*)-3-tetrahydropyranyloxyhexanal *via* ethyl (*R*)-3-hydroxyhexanoate, using bioreduction in organic solvent.



Scheme 2. Preparation of ethyl 2,3,4-trimethoxy-6-methylbenzoate.



Scheme 3. Synthetic pathway of (8*S*, 9*S*, 11*R*)-(−)-monocerin and (9*S*, 11*R*)-(+)-fusarentin 4,5-dimethyl ether.

identified products(**21** and **22**) of self-condensation from their ^{1}H-NMR. Condensation of **16** with **12** was achieved by LDA containing catalytic amount of HMPA at −78 to −84℃. Without separation, the reaction mixture was deprotected to afford diastereomeric mixture of dihydro-isocoumarine **17** and **18** in 62% yield(Scheme 3). These diastereoisomers were separated by TLC in a 3:1 ratio. The stereochemistry was assigned by comparison of the chemical shifts of the protons attached to C-9 and C-11 with that of the structurally related fusaretin 4,5-dimethyl ether(**5**), of known configuration.[3] Deprotection of **17** with BCl_3 gave **19**, confirming the 9(*S*), 11(*R*) stereochemistry, in 91% yield. The opticial rotation of synthetic compound **19**, $[\alpha]_D$+21.6°, compares with that of the natural product **5** $[\alpha]_D$ −29°, confirming the 9(*R*), 11(*S*).[3] By a comparison of the ^{1}H-NMR spectra, **17** was clearly distinguishable from **18**. In the spectrum of the 9(*S*), 11(*R*) isomer, the proton of C-9 and C-11 appeared as a multiplet at 4.78 and 4.07 ppm, respectively. And, the proton of C-9 and C-11 of 9(*R*), 11(*R*) isomer, appeared at 3.91-3.99 and 4.58 ppm for each. The final cyclization under bromination conditions yielded **20** in 61% yield, $[\alpha]_D$ −38.6° (Natural Monocerin[3] $[\alpha]_D$+50.5). This cyclization demonstrated that activation of the benzylic position led to spontaneous ring closure.

The biological activity of synthesized analogs(**19** and **20**) was tested against rice seedlings and lettus seeds. Monocerin(**1**)[12] as a standard was employed for comparision purposes in this test. Fusarentin 4,5-dimethyl ether(**5**) prepared from **1** by a hydrogenation were also tested to compared with the activity of **19** and **20**. Inhibitory effects of monocerin(**1**) on growth of rice seedlings and germination of lettuce seeds were summarized in Tabel 1. In rice seedling, **1** and **5** showed growth inhibitory activity. **1** was more root elongation, as well as causing root necrosis, than that of **5**. However, the activity of **5** on the length of the second leaf sheath was more thana that of **1**. Aslo, **1** and **5** showed strong activity at 100 ppm in the gemination assay of lettuce seeds. (8*S*, 9*S*, 11*R*)-(−)-monocerin (**20**) and (9*S*, 11*R*)-(+)-fusarentin 4,5-dimethyl ether(**19**) showed weak activity in the above two bioassays.

From these results, it was suggested that the ring C system are not essential for apperance of biological activity of monocerin(**1**). As the two opitically active analogs **20** and **19** were less effective than the natural **1** and **5**, the natural configration(8*R*, 9*R*, 11*S*) seems to be an more great role that the unnatural configration(8*S*, 9*S*, 11*R*) for the biological activity.

Strobel et. al., reported the phytotoxic actions of monocerin(**1**) and its analogs on tomato, johnsongrass and cucumber.[5] The present study indicated that the monocerin(**1**) had inhibitory action on growth of rice seedlings and germination of lettuce seed for the first time. The role of monocerin(**1**), in determining the influence of side carbon chain

Table 1. Inhibitory effects of monocerin and its analogs on the growth of rice seedlings and germination of lettuce seeds

Compounds	Concentration (ppm)	Rice seedling growth		Lettuce seeds	
		Length of the second leaf seath (%)	Root (%)	Germination (%)	Root (%)
Control		100	100	100	100
1	250	0	0	0	0
	100	20.1	5.8	0	0
	50	68.9	13.4	100	11.3
	10	94.6	41.0	100	28.4
5	250	0	0	0	0
	100	6.8	18.6	0	0
	50	49.1	28.4	100	41.5
	10	78.1	52.8	100	58.9
10	250	47.1	0	0	0
	100	80.0	81.4	100	67.5
	50	92.0	100	100	92.0
	10	100	100	100	100
20	250	55.8	27.3	0	0
	100	84.6	62.1	91.2	51.0
	50	96.0	82.0	100	89.2
	10	100	100	100	100

and hydroxy of C-11 on the biological activity remains to be determined. Now, examination on the other structure activity relationship of monocerin(**1**) is in progress.

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12. This monocerin was natural product, provided by Prof. T. J. Simpson.

(8*S*, 9*S*, 11*R*)-(−)-Monocerin and (9*S*, 11*R*)-(+)-Fusarentin 4, 5-dimethyl ether의 합성과 생리활성

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초록 : 생리활성물질 monocerin의 구조상관활성을 조사하기 위해서 (8*S*, 9*S*, 11*R*)-(−)-monocerin과 (9*S*, 11*R*)-(+)-fusaretin 4, 5-dimethyl ether를 합성하였는데, 합성은 benzylic anion과 유기용매에서 빵효모를 이용한 생체촉매반응으로 얻어진 (*R*)-aldehyde와의 축합에 의해 완성되었다. 합성되어진 화합물들은 병와 양상치를 대상으로 생리활성을 조사하였다. 특히, 벼의 생리활성검사에서 monocerin은 제2전엽보다 뿌리의 신장을 더 저해하였는데, fusaretin 4, 5-eimethyl ether는 제2전엽의 신장을 더 저해하였다. 생리활성시험의 결과, monocerin의 C 환은 생리활성에 영향을 미치지 않는다는 사실이 예견되었고, 천연물의 입체구조적 배치가 비천연물의 입체구조적 배치보다 더 높은 생물활성을 나타내고 있다는 사실을 알 수 있었다.