Insecticidal Activity of Lignan Analogs Chromano-Sesquilignans with a Dihydroprecocene Skeleton+

Gotanda, Hiroshi
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

Yamauchi, Satoshi
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

Takeya, Ryuko
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

Taniguchi, Eiji
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

https://doi.org/10.5109/24028

出版情報：九州大学大学院農学研究院紀要. 37 (3/4), pp.349-358, 1993-03. Kyushu University
バージョン：
権利関係：

J. Fac. Agr., Kyushu Univ., 37 (3•4), 349-358 (1993)

Insecticidal Activity of Lignan Analogs Chromano-Sesquilignans with a Dihydroprecocene Skeleton+

Hiroshi Gotanda, Satoshi Yamauchi, Ryuko Takeya and Eiji Taniguchi*

Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University 46-02, Fukuoka 812, Japan

(Received ***December*** *21, 1992)*

Two stereoisomers of a chromano-lignan were synthesized as the analogs of an insecticidal 1,4-benzodioxano-sesquilignan by employing the well-known anti-juvenile hormone, precocene I, as a building block for the synthesis. Both isomers, (±)-(1*S**,2*R**, 5*R**,6*S**)-2-(2,6-dimethoxyphenoxy)-6-(2,2-dimethyl-7-methoxy-3,4-dihydro-2*H*-chromen-6-yl)-1-hydroxy-3,7-dioxabicyclo[3.3.0]octane and its 6*R** isomer, showed neither insect growth-regulatory property nor insecticidal activity.

INTRODUCTION

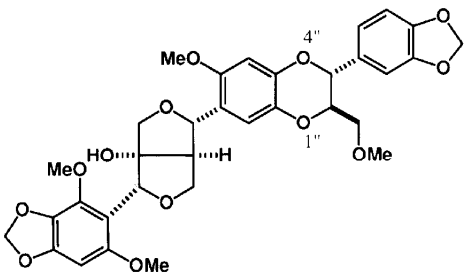
Haedoxan A, a unique sesquilignan belonging to the class of neolignan of 1,4-benzodioxane type (Fig. 1), was isolated as the insecticidal constituent of *Phryma leptostachya* L. (Taniguchi *et al.*, 1989). By a sustaining investigation on the correlation between structure and activity of the lignan, it has been made evident that the 6-methoxy-2-methoxymethyl-3-(3,4-methylenedioxyphenyl)-1,4-benzodioxan-7-yl moiety is indispensable for the potent activity of haedoxan (Yamauchi *et al.*, 1992; Yamauchi and Taniguchi, 1992a,b).

In a scope of the structure-activity relationship of the bioactive lignan, it was proposed to estimate the activity of two chromano-analogs such as **CA1** and CA2 (Fig. 1) replacing the 1"-or 4"-oxygen atom of the haedoxan molecule by a methylene group. On purpose to establish a synthetic route for these analogs, the synthesis of (±)-(1*S**, 2*R**,5*R**,6*S**)-2-(2,6-dimethoxyphenoxy)-6-(2,2-dimethyl-7-methoxy-3,4-dihydro-2*H*-chromen-6-yl)-1-hydroxy-3,7-dioxabicyclo[3.3.0] octane **(15a)** has been carried out as a preliminary to the application of the method developed for the synthesis of haedoxans and their analogs (Ishibashi and Taniguchi, 1989; Yamauchi *et al.*, 1990). In the synthesis, a stereoisomer **(15b)** with 6*R**-(2,2-dimethyl-7-methoxy-3,4-dihydro-2*H*-chromen-6-yl) group was also obtained as a by-product. Bioactivity of these chromano-analogs was assessed on the housefly and silkworm.

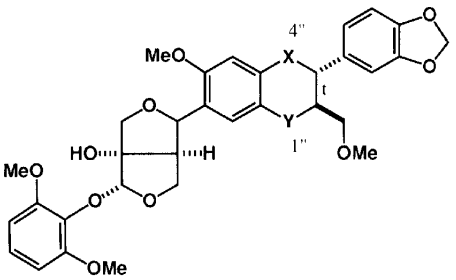
MATERIALS AND METHODS

All melting points (mp) and boiling points (bp) were uncorrected. The ^{1}H-NMR

+ Synthesis and Insecticidal Activity of Lignan Analogs. Part 9.
* To whom correspondence should be addressed.



Haedoxan A



CA1: X=CH_2, Y=O
CA2: X=0, Y=CH_2

Fig. 1. Structures of haedoxan A and chromano-lignans.

spectra were determined with JEOL FX100 spectrometer in deuterochloroform with tetramethylsilane (δ_H 0.0) as an internal standard. Gravity chromatography and medium-pressure column chromatography were performed with Wakogel C-300. Preparative TLC was conducted with $60F_{254}$ pre-coated silica gel sheets in thickness of 0.5mm supplied by E. Merck.

2.2-Dimethyl-7-methoxychroman (1). Precocene I (2,2-dimethyl-7-methoxychromene, Aldrich Chemical, 0.88g, 4.63mmol) and a palladium catalyst (Nacalai Tesque, 260mg, a 5% Pd on carbon) in ethyl acetate (12ml) was vigorously stirred for 1.5hr at room temperature under a hydrogen atmosphere (1 atm). The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography (9:1 hexane-ethyl acetate) to give a colorless oil (0.73g, 82%). ***Anal.*** Found: C, 75.21; H, 8.47. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%. 100 MHz NMR δ_H($CDCl_3$): 1.24 (6H, s), 1.68 (2H, t, J=6), 2.62 (2H, t, J=6), 3.66(3H, s), 6.14-6.46 (2H, m), 6.70-6.98 (1H, m).

2,2-Dimethyl-6-formyl-7-methoxychroman ***(2).*** Chroman 1 (0.73g, 3.80mmol) and phosphorous oxychloride (5.70mmol) in dimethyl formamide (2.6ml) was heated at 60°C for lhr. After the reaction mixture had been treated with 10% aqueous sodium carbonate (50ml), it was extracted with ethyl acetate. The extract was dried and concentrated, and the residue was purified by column chromatography to give 2 (0.80g, 96%) as colorless crystals, mp 74-76°C ($isoPr_2O$). ***Anal.*** Found: C, 71.02; H, 7.34. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%. 100 MHz NMR δ_H($CDCl_3$): 1.38 (6H, s), 1.82 (2H, t, J=6), 2.76 (2H, t, J=6), 3.88 (3H, s), 6.18 (1H, s), 7.62 (1H, s), 10.28 (1H, s).

4-Ethenyl-2-[(trimethylsilyl)oxy]-4,5-dihydrofuran ***(3)*** was prepared from 3-vinylbutanolide according to the method described in the literature (Ainsworth *et al.*, 1972) to obtain a colorless oil, bp 84-87°C/33mmHg. ***Anal.*** Found: C, 59.04; H, 8.94. Calcd. for $C_9H_{16}O_2Si$: C, 58.65; H, 8.75%. 100 MHz NMR δ_H($CDCl_3$): 0.28 (9H, s), 3.44-3.68 (1H, m), 3.98 (1H, dd, J=8,6), 4.43 (1H, dd, J=8,8), 4.87-5.38 (2H, m), 5.47 (1H, broad d, J=6), 5.63-6.02 (1H, m).

(±)-(3S,4R*,1'R*/S*)-3-[1'-Hydroxy-1'-(2,2-dimethyl-7-methoxy-3,4-dihydro-2H-chromen-6-yl)methyl]-4-vinyldihydro-2(3H)-furanones* ***(5).*** A mixture of trityl chloride (Nacalai Tesque, 45mg, 0.16mmol) and tin (II) chloride (Aldrich Chemi-

cal, 30.3mg, 0.16mmol) in dry dichloromethane (2ml) was stirred for 30min at room temperature and cooled to -75°C. To the cooled and stirred mixture a solution of 2 (0.71g, 3.23mmol) and 3 (0.89g, 4.84mmol) in dichloromethane (6ml) was added. After the mixture had been stirred for 6hr at the same temperature, it was treated with 5% aqueous sodium bicarbonate and extracted with ethyl acetate. The extract was passed through a silica gel column (3:1 hexane-ethyl acetate) to obtain trimethylsilyl ether 4 (1.04g, 80%). The silyl ether was readily reacted with tetra-*n*-butylammonium fluoride (Janssen Chemica, 3.1ml, a 1 M solution in tetrahydrofuran, 3.1mmol) in dry tetrahydrofuran (9ml) at 0°C for 2hr. The reaction mixture was treated with 5% aqueous ammonium chloride (2ml) and extracted with ethyl acetate. The extract was purified by chromatography (3:1 hexane-ethyl acetate) to obtain 5 (0.56g, 66%) as a colorless oil. ***Anal.*** Found: C, 68.97; H, 7.49. Calcd. for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28%. 100 MHz NMR $\delta_H(CDCl_3)$: 1.26 (6H, s), 1.70 (2H, t, J=6), 2.62-3.30 (2H, m), 2.64 (2H, t, J=6), 3.66 (3H, S), 3.81 (1H, dd, J=10,8), 4.00 (1H, d, J=4), 4.28 (1H, dd, J=lO, 8), 4.50-4.82 (2H, m), 4.98-5.30 (1H, m), 5.34-5.50 (1H, m), 6.22 (1H, s), 7.03 (0.4H, s), 7.08 (0.6H, s).

The following compounds were obtained by the same reactions as those described in the literatures (Ishibashi and Taniguchi, 1986; Yamauchi and Taniguchi, 1992 etc.), the data being briefly described here.

(±)-(3S,4R*,1'R*/S*)-3-{1'-[(tert-Butyldimethylsilyl)oxy]-1'-(2,2-dimethyl-7-methoxy-3,4-dihydro-2H-chromen-6-yl)methyl}-4-vinyldihydro-2(3H)-furanones* (6). Silylation [**5** 1.66mmol (0.55g), *tert*-butyldimethylsilyl triflate 2.48mmol, 2,6-lutidine 3.35mmol in dichloromethane 4ml at room temperature for 4hr]. A colorless oil (0.55g, 74%). ***Anal.*** Found: C, 67.01; H, 8.54. Calcd. for $C_{25}H_{38}O_5Si$: C, 67.23; H, 8.58%. 100 MHz NMR $\delta_H(CDCl_3)$: -0.13 (1.2H, s), -0.08 (1.8H, s), 0.08 (1.2H, s), 0.09 (1.8H, s), 0.94 (9H, s), 1.30 (2.4H, s), 1.34 (3.6H, s), 1.78 (2H, t, J=6), 2.54-3.42 (2H, m), 2.68 (2H, t, J=6), 3.72 (1.2H, s), 3.75 (1.8H, s), 3.92 (1H, dd, J=10, 8), 4.40 (1H, dd, J=10, 8), 4.58-4.78 (1H, m), 4.98-5.46 (2H, m), 5.46-5.78, (1H, m), 6.06 (1H, s), 7.10 (0.6H, s), 7.26 (0.4H, s).

(±)-(2R,3R*,1'R*/S*)-2-{1'-[(tert-Butyldimethylsilyl)oxy]-1'-(2,2-dimethyl-7-methoxy-3,4-dihydro-2H-chromen-6-yl)methyl}-3-vinyl-1,4-butanediols* ***(7).*** Reduction [**6** 1.21mmol (0.54g), lithium aluminium hydride 1.58mmol in ethyl ether-tetrahydrofuran (2:1) 18ml at -10°C for 1.5hr]. A colorless oil (0.32g, 58%). ***Anal.*** Found: C, 66.99; H, 9.56. Calcd. for $C_{25}H_{42}O_5Si$: C, 66.63; H, 9.39%. 100 MHz NMR $\delta_H(CDCl_3)$: -0.30 (3H, s), 0.00 (3H, s), 0.86 (9H, s), 1.34 (6H, s), 1.60 (1H, broad s), 1.68-1.98 (1H, m), 1.78 (2H, t, J=6), 2.70 (2H, t, J=6), 2.72-3.04 (1H, m), 3.24-4.02 (5H, m), 3.81 (3H, s), 5.02-5.40 (3H, m), 5.76-6.20 (1H, m), 6.34 (1H, s), 7.12 (1H, broad s).

(±)-(2R/S*,3R*,4R*,1'R*/S*)-* ***4*** *-{1'-[(tert-Butyldimethylsilyl)oxy]-1'-(2,2-dimethyl-7-methoxy-3,4-dihydro-2H-chromen-6-yl)methyl}-2-hydroxy-3-hydroxymethyltetrahydrofurans* ***(8).*** Oxidation [**7** 0.69mmol (0.31g), a catalytic amount of osmium tetroxide, N-methylmorpholine N-oxide 0.77mmol, *tert*-butyl alcohol 5ml, water 5ml, acetone 10ml at room temperature for 20 hr under nitrogen in the dark]. Oxidation [sodium metaperiodate 0.84mmol in ethyl acetate 50ml at room temperature for 40hr]. A viscous oil (0.28g, 90%). ***Anal.*** Found: C, 63.96; H, 8.99. Calcd. for $C_{24}H_{40}O_6Si$: C, 63.68; H, 8.91%. 100 MHz NMR $\delta_H(CDCl_3)$: -0.36 (3H, s), -0.06 (3H, s), 0.86 (9H, s), 1.34 (6H, s), 1.72 (1H, broad s), 1.78 (2H, t, J=6), 2.30-2.54 (1H, m), 2.70 (2H,

t, J=6), 2.86-3.30 (2H, m), 3.42-4.45 (4H, m), 3.68-3.82 (3H, s x 2), 5.14 (1H, d, J=6), 5.48 (1H, d, J=2), 6.28-6.30 (1H, s x 2), 7.10 (1H, broad s).

(±)-(*3R*,4R*,1'R*/S*)-4-{1'-[(tert-Butyldimethylsilyl)oxy]-1'-(2,2-dimethyl-7-methoxy-3,4-dihydro-2H-chromen-6-yl) methyl}-3-hydroxymethyldihydro-2(3H)-furanones (9).* Oxidation [**8**, 0.60mmol (0.27g), silver carbonate 0.62mmol on Celite in refluxing benzene 12ml for 10min]. A colorless oil (0.21g, 78%). *Anal.* Found: C, 63.65; H, 8.42. Calcd. for $C_{24}H_{38}O_6Si$: C, 63.97; H, 8.50%. 100 MHz NMR δ_H($CDCl_3$): -0.30 (3H, s), 0.08 (3H, s), 0.90 (9H, s), 1.34 (6H, s), 1.80 (2H, t, J=6), 2.70 (2H, t, J=6), 2.74-2.98 (2H, m), 3.02-3.30 (1H, m), 3.78 (3H, s), 3.90-4.26 (4H, m), 5.21 (1H, d, J=6), 6.32 (1H, s), 7.06 (1H, broad s).

(±)-(*4R*,1'R*/S*)-4-{1'-[(tert-Butyldimethylsilyl)oxy]-1'-(2,2-dimethyl-7-methoxy-3,4-dihydro-2H-chromen-6-yl)methyl}-3-methylenedihydro-2(3H)-furanones* (10). Mesylation [**9** 0.44mmol, (0.20g), mesyl chloride 0.67mmol, triethylamine 0.88mmol in dry benzene 10ml at room temperature for 2hr.] Desulfonation [1,8-diazabicyclo [5.4.0] undec-7-ene 0.669mmol, 30min, room temperature]. The reactions were carried out as a one-pot reaction. A colorless oil (0.17g, 89%). *Anal.* Found: C, 66.89; H, 9.44. Calcd. for $C_{24}H_{36}O_5Si$: C, 66.63; H, 9.39%. 100 MHz NMR δ_H ($CDCl_3$): -0.22 (3H, s), 0.02 (3H, s), 0.88 (9H, s), 1.36 (6H, s), 1.80 (2H, t, J=6), 2.68 (2H, t, J=6), 3.12-3.36 (1H, m), 3.76 (3H, s), 4.12-4.36 (2H, m), 5.09 (1H, d, J=6), 5.24 (1H, broad s), 6.26 (1H, broad s), 6.32 (1H, s), 7.02 (1H, broad s).

(±)-(*3S*,4R*, 1'R*/S*)-4-{1'-[(tert-Butyldimethylsilyl)oxy]-1'-(2,2-dimethyl-7-methoxy-3,4-dihydro-2H-chromen-6-yl)-1-hydroxymethyl}-3-hydroxy-3-hydroxymethyldihydro-2(3H)-furanones* (11). Oxidation [**10** 0.37mmol (0.16g), a catalytic amount of osmium tetroxide, N-metylmorpholine N-oxide 0.41mmol, water 5ml, *tert*-butyl alcohol 5ml, acetone 10ml for 14hr at room temperature under nitrogen in the dark]. A colorless oil (0.17g, 81%). *Anal.* Found: C, 62.20; H, 8.34. Calcd. for $C_{24}H_{38}O_7$: C, 61.77; H, 8.21%. 100 MHz NMR δ_H($CDCl_3$): -0.32 (3H, s), 0.06 (3H, s), 0.90 (9H, s), 1.34 (6H, s), 1.66 (1H, s), 1.80 (2H, t, J=6), 2.70 (2H, t, J=6), 2.94-3.26 (1H, m), 3.10 (1H, s), 3.78 (3H, s), 3.82-4.22 (4H, m), 5.29 (1H, d, J=6), 6.32 (1H, s), 7.06 (1H, s).

(±)-(*3S*,4R*,1'R*/S*)-4-[1'-Hydroxy-1'-(2,2-dimethyl-7-methoxy-3,4-dihydro-2H-chromen-6-yl)methyl]-3-hydroxy-3-hydroxymethyldihydro-2(3H)-furanones (12).* Desilylation [**11** 0.279mmol (0.13g)), tetra-n-butylammonium fluoride 0.335mmol in dry tetrahydrofuran 5ml at 0°C for lhr]. A colorless oil (61.7mg 63%). *Anal.* Found: C, 61.79; H, 7.09. Calcd. for $C_{18}H_{24}O_7Si$: C, 61.35; H, 6.87%. 100 MHz NMR δ_H($CDCl_3$): 1.34 (6H, s), 1.78 (2H, t, J=6), 2.68 (2H, t, J=6), 3.02-3.38 (1H, m), 3.38-3.66 (2H, broad), 3.78 (3H, s), 3.82-4.18 (5H, m), 5.11 (1H, dd, *J*=8, 4), *6.36* (1H, s), 7.02(1H, s).

(±)-(*1S*,5R*,6R*/S*)-6-[2,2-Dimethyl-7-methoxy-3,4-dihydro-2H-chromen-6-yl)-1-hydroxy-3,7-dioxabicyclo [3.3.0] octan-2-ones (13).* To a stirred and ice-cooled solution of 12 (57.5mg, 0.163mmol) in dry dichloromethane (5ml) containing molecular sieves 4A was added a catalytic amount of 10-camphorsulfonic acid. After the stirring had been continued for 1.5hr at 0°C, the reaction mixture was treated with a few drops of triethylamine and concentrated. The residue was purified by preparative TLC (Silica gel $60F_{254}$ pre-coated plate of 0.5mm thickness/hexane-AcOEt 1:1) to give colorless crystals (43.6mg, 80%), mp 151-153°C. ***Anal.*** Found: C, 64.89; H, 6.72. Calcd. for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63%.

100 MHz NMR δ_H($CDCl_3$): 1.34 (6H, s, 2'-(CH_3)$_2$), 1.78 (2H, t, J=6, 3'-*H*), 2.72 (2H, t, J=6', 4-H), 3.13 (0.5H, m, 5α-*H*), 3.49 (0.5H, m, 5α-*H*), 3.63-4.76 (5H, m, l-OH, 4-CH_2, 8-H,), 3.76 (3H, s, OCH_3), 5.10 (0.5H, d, *J* =6, 6β-*H*), 5.34 (0.5H, d, *J* =6, 6α-*H*), 6.32 (0.5H, s, 8'-*H*), 6.36 (0.5H, s, 8'-*H*), 7.12 (0.5H, s, 5'-H), 7.18 (0.5H, s, 5'-H).

(±)-(*1S*,2R*/S*,5R*,6R*/S*)-1,2-Dihydroxy-6-(2,2-dimethyl-7-methoxy-3,4-dihydro-2H-chromen-6-yl)-3,7-dioxabicyclo*[*3.3.0*] ***octanes (14).*** Reduction [**13** 0.112mmol (37.4mg), diisobutylaluminium hydride 0.425mmol in toluene 10ml for 1.5hr at -70°C under nitrogen] . A colorless resinous material (30.1mg, 80%). ***Anal.*** Found: C, 64.57; H, 7.20. Calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19%. 100 MHz NMR δ_H ($CDCl_3$): 1.34 (6H, s), 1.76 (2H, t, J=6), 2.56 (0.5H, m), 2.72 (2H, t, J=6), 3.24 (0.5H, m), 3.32 (1H, broad s), 3.74-3.78 (3H, s×2) 3.60-4.40 (5H, m), 4.83 (1H, d, J=6), 5.12 (1H, broad s), 6.32-6.36 (1H, s×2), ***7.18-7.26*** (1H, s × ***2).***

(±)-(*1S*,2R*,5R*,6R*/S**)-*2-(2,6-Dimethoxyphenoxy)-* ***6*** *-(2,2-dimethyl-* ***7*** *-methoxy-3,4-dihydro* ***-2H*** *-chromen-6-yl)-* ***1-*** *hydroxy-3,7-dioxabicyclo*[*3.3.0*] ***octanes*** **(15a** and **15b).** Acetalization[**14** 0.081mmol (27.3mg), 2,6-dimethoxyphenol 2.01mmol, a catalytic amount of pyridinium P-toluenesulfonate in benzene 2ml, reflux for 1.5hr under nitrogen with azeotropic removal of the water]. Preparative TLC[$60F_{254}$ pre-coated silica gel plate of thickness in 0.5mm/5% ethyl alcohol in a mixture of hexane and ethyl acetate (2:1)].

6S(α)*-isomer 15a. A colorless resinous material (14.5mg, 38%). *Rf 0.55*. ***Anal.*** Found: C, 66.28; H, 6.91. Calcd. for $C_{26}H_{32}O_8$: C, 66.09; H, 6.83%. 100 MHz NMR δ_H($CDCl_3$): 1.34 (6H, s, 2"-(CH_3)$_2$), 1.78 (2H, t, J=6, 3"-H_2), 2.54-2.82 (1H, m, 5β-*H*), ***2.74*** (2H, t, J=6, 4"-H_2), 3.71 (1H, d, J=10, 8α-*H*), 3.76 (3H, s, 7"-OCH_3), 3.88 (6H, s 2'-OCH_3, 6'-OCH_3) 4.10 (1H, dd, J=9, 2, 4α, -*H*), *4.28* (1H, broad s, l-OH), 4.33 (1H, d, J=10, 8α-*H*), 4.60 (1H, dd, J=9, 7, 4β-*H*), 4.90 (1H, d, J=6, 6α-*H*), 5.38 (1H, s, 2α-*H*), *6.34* (1H, s, *8"-H*), *6.61* (1H, d, J=9, 3'/5'-*H*), 6.62 (1H, d, *J* =7, 3'/5'-*H*), *7.07* (1H, m, 4'-*H*), *7.33* (1H, s, *5"-H*).

6R(β)*-isomer **15b.** A colorless resinous material (llmg, 28%). Rf 0.51. ***Anal.*** Found: C, 66.25; H, 6.88. Calcd. for $C_{26}H_{32}O_8$: C, 66.09; H, 6.83%. 100 MHz NMR δ_H($CDCl_3$): 1.33 (3H, s, 2"-CH_3), 1.34 (3H, s, 2"-CH_3), 1.78 (2H, t, J=6, 3"-H_2), 2.70 (2H, t, J=6, 4"-H_2), 3.13 (1H, m, 5β-*H*), ***3.50-4.30*** (4H, m), ***3.76*** (3H, ***s*** 7"-OCH_3), *3.88* (6H, *s*, 2'-OCH_3, 6'-OCH_3), *4.42* (1H, s, l-OH), *5.36* (1H, s, 2α-*H*), 5.38 (1H, d, J=4, 6β-*H*), 6.32 (1H,s, 8"-H), 6.59 (1H, d, *J* =10, 3'/5'-*H*), 6.60 (1H, d, *J* =8, 3'/5'-*H*), ***7.04*** (1H, m, ***4'***-*H*), 7.20 (1H, s, 5"-H).

RESULTS AND DISCUSSION

The synthesis of the chromano-lignans is shown in Scheme. Precocene I, 7-methoxy-2,2-dimethylchromene, was readily converted to 7-methoxy-2,2-dimethyl-6-formylchroman 2 by sequential hydrogenation and the Vilsmeier formylation in a 79 % overall yield. The chromancarbaldehyde scarcely reacted with the lithium enolate of (±)-3-vinylbutanolide (Kondo and Mori, 1974) in dry tetrahydrofuran; this result was dissimilar to those of the aldol condensation for an alkoxybenzaldehyde and 1,4-benzodioxanecarbaldehydes using in the earlier syntheses of phrymarolin (Ishibashi and Taniguchi, 1986, 1989) and haedoxans (Yamauchi ***et al.,*** 1992; Yamauchi and Taniguchi, 1992a, b). A cross aldol reaction using a cerium enolate (Imamoto ***et al.,***

1983) of the butanolide was also not progressive. Finally, in the application of a modified aldol reaction using Lewis acid (Mukaiyama et al., 1987), a trimethylsilyl enol ether 3 preparative from (±)-3-vinylbutanolide by the reported method (Ainsworth et al., 1972) was reacted with chromancarbaldehyde 2 in the presence of trityl chloride and tin (II) chloride to produce trimethylsilylated (±)-3,4-*trans*-aldol **4** as a mixture of the *erythro* and *threo* adducts in an 80% yield. In the present analog synthesis, every reaction for the intermediates 4-12 was successively carried out by employing a mixture of *erythro* and *threo* isomers, since each isomer of the products of those reactions was unable to be isolated in pure form by chromatographic separation. Thus, the mixture of trimethylsilyl ethers 4 was desilylated by treating with tetra-*n*-butylammonium fluoride in tetrahydrofuran (Corey *et al.*, 1981) to afford (±)-3,4-*trans*-aldols 5 in a 53% overall yield from 2, the NMR data of 5 suggesting the ratio of the *erythro*/*threo* isomers to be 3/2. A *tert*-butyldimethylsilylation (Corey and Venkateswarlu, 1972; Stewart and Miller, 1980) of the aldols was followed by sequential reduction, oxidation (3 steps), mesylation, elimination, glycolization, desilylation, and acid-catalyzing intramolecular cyclization accompaying dehydration (Ishibashi and Taniguchi, 1986, 1989; Yamauchi *et al.*, 1992) to give rise diol 7, lactol 8, α-hydroxymethyl-y-butyrolactone 9, α-methylene-γ-butyrolactone 10, α-hydroxy-α-hydroxymethyl-y-butyrolactone 11, trio1 12, and the key intermediary 1-hydroxy-6-(2,2-dimethyl-7-methoxy-3,4-dihydro-2*H*-chromen-6-yl)-3,7-dioxabicyclo[3.3.0]octan-2-one (**13**), respectively. The key intermediate 13 was obtained as a mixture of equimolecular amounts of $1S^*,5R^*,6S^*$ and $1S^*,5R^*,6R^*$ isomers in a 12% overall yield for ten steps from aldols 5. In a NMR spectrum of 13, the multiplets at 3.13ppm (0.5H) and 3.49ppm (0.5H) were assigned to each 5α-proton of the $6S^*(6\alpha)$ and $6R^*(6\beta)$ isomers, respectively.

The $6S^*(6\alpha)$ isomer would be thermodynamically more stable than the $6R^*(6\beta)$ isomer and expected to be preferentially formed from trio1 12 by the acid-catalyzing cyclyzation reaction. Really, a trio1 bearing an alkoxyphenyl or a 1,4-benzodioxanyl group in place of the chromanyl group of 12 had selectively produced a 6α isomer (Fig. 2) under a similar reaction condition as that used for the cyclyzation of 12 (Ishibashi and Taniguchi, 1988, 1989; Yamauchi *et al.*, 1992; Yamauchi and Taniguchi, 1992a, b).

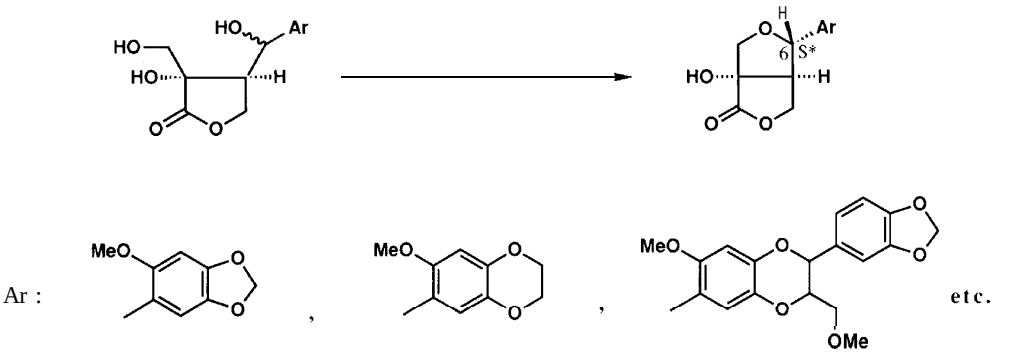
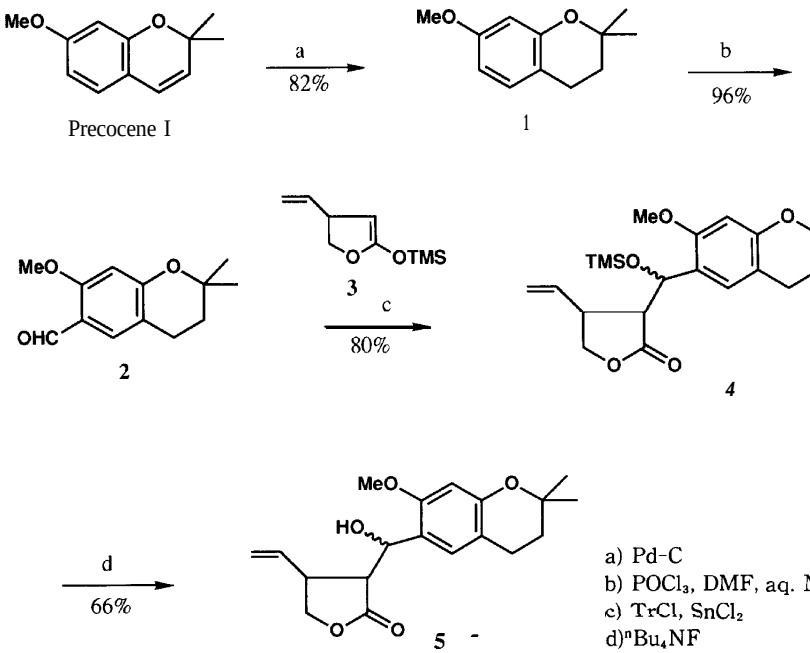
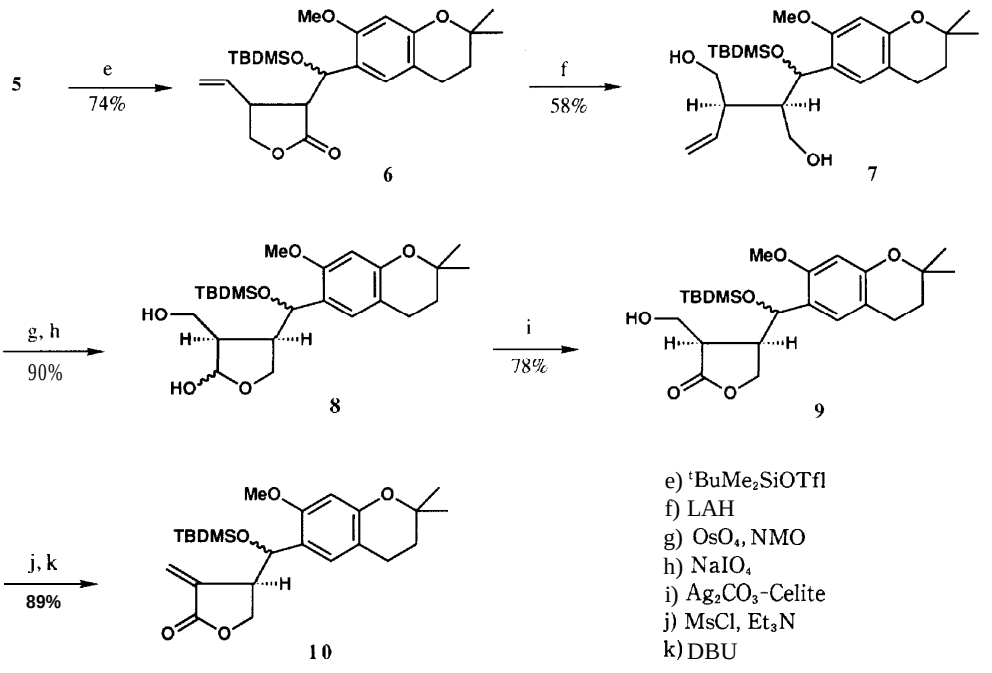


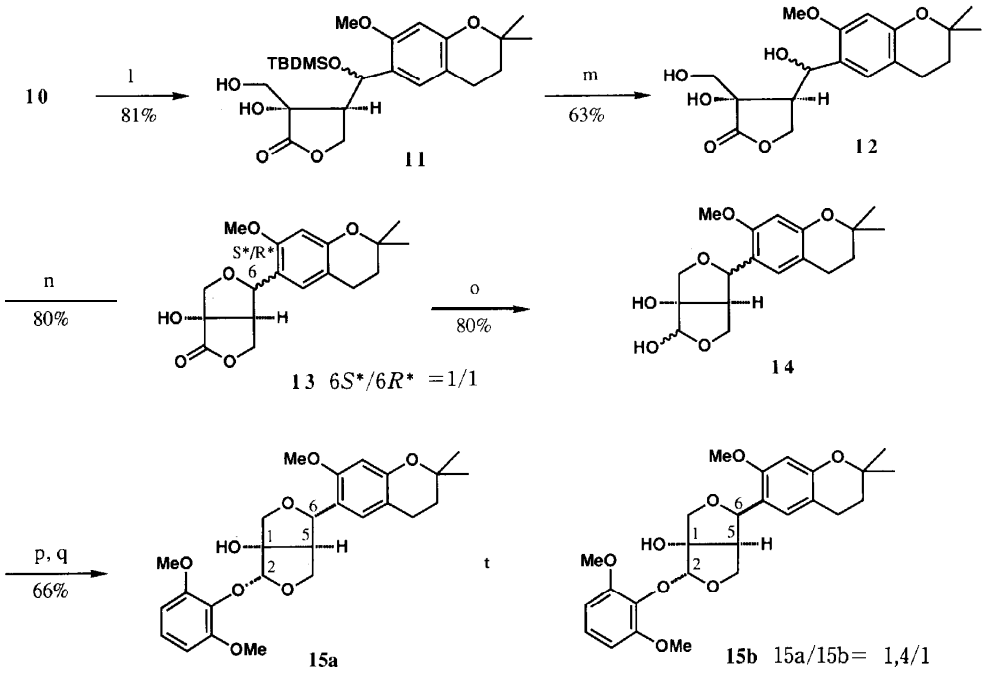
Fig. 2. Stereoselective cyclization of the triols having a polyalkoxyphenyl group,



Scheme Synthesis of dihydroprecocene-lignan



Scheme (continued)



1) OsO_4, NMO m) $^nBu_4F$ n) CSA, MS(4A) o) DIBAL-H p) 2,6-dimthoxyphenol, cat. PPTS q) chromatographic separation

Scheme (continued)

The non-stereoselective cyclization of the trio1 12 remained to be elucidated.

The $6\alpha/\beta$- dihydrochromenyl -3,7- dioxabicyclooctanones 13 were together reduced with diisobutylaluminium hydride, and the resulting lactols 14 were reacted with 2,6-dimethoxyphenol in the presence of pyridinium *p*-toluenesulfonate (Takano et al., 1988) to selectively produce 2α-acetal as the equimolecular mixture of (±)-(1*S**, 2*R**, 5*R**, 6*S**)-2-(2,6-dimethoxyphenoxy)-1-hydroxy-6- [2,2-dimethyl-7-methoxy-3, 4-dihydro-2*H*-chromen-6-yl]-3,7-dioxabicyclo-[3.3.0] octane (15a) and its (±)-(1*S**, 2*R**, 5 *R**, 6*R**)-isomer (15b). These diastereomers were purified by preparative TLC to obtain in 1.73% and 1.27% overall yields from 2, respectively. Their stereochemistry was unequivocally determined on the basis of the chemical shift value of 5α-H (Taniguchi *et al.*, 1989; Pelter ***et al.,*** 1976); the protons of the $6S^*(\alpha)$ and $6R^*(\beta)$ isomers displayed a multiplet at 2.68ppm and 3.13ppm in their NMR spectra, respectively.

The compounds 15a and **15b**, which involved in the molecules two structures of both anti-juvenile hormone (Bowers *et al.*, 1976) and insecticidal haedoxan, were totally inactive to the 4-day old housefly, *Musca domestica* (SRS), at a dose level of $10\mu g$, and also ineffective on the growth of the 4th instar larvae of the silkworm, *Bombyx mori* (*C.* 146 x N. 137), at $200\mu g$ per larva, the housefly and silkworm being

treated with each compound in a 1μl of acetone solution at the dorsal thorax and the head-thorax by a micro-applicator, respectively.

The chromano-lignan CA2 with a 7-methoxy-3-methoxymethyl-2-(3,4-methylenedioxyphenyl)-3,4-dihydro-2*H*-chromen-6-yl group has been recently synthesized by applying the method accomplished in this preliminary synthesis, and the compound was proved to be insecticidally active to the housefly (Gotanda *et al., 1993).* Combining the assay results of **15a** and CA2, it is implied that the 2"-(3,4-methylenedioxyphenyl) and 3"-methoxymethyl groups may significantly contribute to the insecticidal activity of chromano-analogs of haedoxan.

ACKNOWLEDGEMENTS

We thank the staffs of the Center of Elemental Analysis, Faculty of Science, Kyushu University for the elemental analyses.

REFERENCES

Ainsworth, C., F. Chen and Y-N. Kuo 1972 Ketene alkytrialkylsilyl acetals: synthesis, pyrolysis and NMR studies. *J. Organomet. Chem., 46:* 59-71

Bowers, W. S., T. Ohta, J. S. Cleere and P. A. Marsella 1976 Discovery of insect anti-juvenile hormones in plants. ***Science,*** 193: 542-547

Corey, E. J. and A. Venkateswarlu 1972 Protection of hydroxyl groups as *tert*-butyldimethylsilyl derivatives. *J. Amer. Chem. Soc., 94:* 6190-6191

Corey, E. J., H. Cho, C. Rucker and D. H. Hua 1981 Studies with trialkylsilytriflates: new syntheses and applications. *Tetrahedron Lett., 22: 3455-3458*

Gotanda, H., S. Yamauchi, F. Ishibashi and E. Taniguchi 1993 Chromano-analogs of insecticidal neolignans of the 1, 4-benzodioxane type. *Biosci. Biotech. Biochem.,* **58**(6): accepted for publication

Imamoto, T., T. Kusumoto and M. Yokoyama 1983 A new aldol reaction *via* cerium enolates. *Tetrahedron Lett., 24: 5233-5236*

Ishibashi, F. and E. Taniguchi 1986 Synthesis and absolute configuration of (+)-phrymarolin I, a lignan. *Chem. Lett.,* 1986: 1771-1774

Ishibashi, F. and E. Taniguchi 1988 Synthesis and absolute configuration of the acetalic lignan (+)-phrymarolin I. *Bull.* Chem. *Soc. Jan.,* 61: 4361-4366

Ishibashi, F. and E. Taniguchi 1989 Syntheses of (+)-haedoxan A, D, E, and their stereoisomers. *Agric. Biol.* Chem., 53: 1565-1573

Kondo, K. and K. Mori 1974 Synthesis of y-lactones by the condensation of 2-alkene-1,4-diols with orthocarboxylic esters. Chem. *Lett.,* 1974: 741-742

Mukaiyama, T., S. Kobayashi, M. Tamura and Y. Sagawa 1987 An efficient and extremely mild catalyst system, combined use of trityl chloride and tin (II) chloride, in the Aldol and Michael reactions. *Chem. Lett.,* 1987: 491-494

Pelter, A., R. S. Ward, E. V. Rao and K. V. Sastry 1976 Revised structures for pluviatilol, methyl pluviatilol and xanthoxylol. *Tetrahedron, 32: 2783-2788*

Stewart, R. F. and L. L. Miller 1980 Oxidation of hydroquinone silyl ethers to quinones. *J. Amer.* Chem. *Soc.,* 102: 4999-5004

Takano, S., T. Ohkawa, S. Tamori, S. Satoh and K. Ogasawara 1988 Enantio-controlled route to the furofuran lignans: the total synthesis of (-)-sesamolin, (-)-sesamin, and (-)-acuminatolide. *J.* Chem. *Soc., Chem. Commun.,* 1988: 189-191

Taniguchi, E., K. Imamura, F. Ishibashi, T. Matsui and A. Nishio 1989 Structure of the novel insecticidal sesquilignan, haedoxan A. *Agric. Biol. Chem., 53:* 631-643

Yamauchi, S., S. Nagata and E. Taniguchi 1992 Effect on insecticidal activity of substituents at the 1,4-benzodioxanyl moiety of haedoxan. *Biosci. Biotech. Biochem., 56: 1193-1197*

Yamauchi, S. and E. Taniguchi 1992a Influence *on* insecticidal activity of the 3-(3,4-methylenedioxyphenyl) group in the 1,4-benzodioxanyl moiety of haedoxans. *Biosci. Biotech. Biochem.*, 56: 1744-1750

Yamauchi, S. and E. Taniguchi 1992b Synthesis and insecticidal activity of sesquilignan analogs with 2-alkyl-6-methoxy-3-(3,4-methylenedioxyphenyl)-1,4-benzodioxanyl group. *Biosci. Biotech. Biochem., 56: 1751-1759*