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

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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, (\pm)-(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 (\pm)-(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 ¹H-NMR

+ Synthesis and Insecticidal Activity of Lignan Analogs. Part 9.

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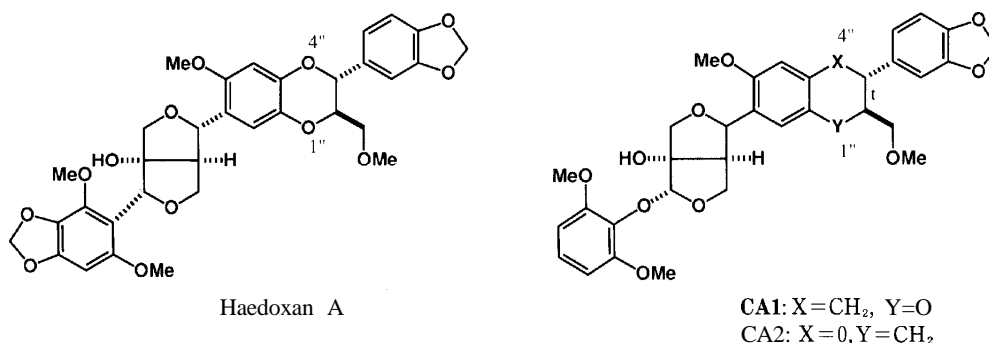


Fig. 1. Structures of haedoxan A and chromano-lignans.

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 60F₂₅₄ 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 C₁₂H₁₆O₂: C, 74.97; H, 8.39%. 100 MHz NMR δ_{H} (CDCl₃): 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 1hr. 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 (isoPr₂O). **Anal.** Found: C, 71.02; H, 7.34. Calcd. for C₁₃H₁₆O₃: C, 70.89; H, 7.32%. 100 MHz NMR δ_{H} (CDCl₃): 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 C₉H₁₆O₂Si: C, 58.65; H, 8.75%. 100 MHz NMR δ_{H} (CDCl₃): 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 Chemicals, 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 $\text{C}_{19}\text{H}_{24}\text{O}_5$: C, 68.65; H, 7.28%. 100 MHz NMR $\delta_{\text{H}}(\text{CDCl}_3)$: 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, $J=10,8$), 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.

(\pm)-(3*S**,4*R**,1'*R**/*S**)-3-{1'-[(*tert*-Butyldimethylsilyl)oxy]-1'-(2,2-dimethyl-7-methoxy-3,4-dihydro-2*H*-chromen-6-yl)methyl}-4-vinyldihydro-2(3*H*)-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 $\text{C}_{25}\text{H}_{38}\text{O}_5\text{Si}$: C, 67.23; H, 8.58%. 100 MHz NMR $\delta_{\text{H}}(\text{CDCl}_3)$: -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).

(\pm)-(2*R**,3*R**,1'*R**/*S**)-2-{1'-[(*tert*-Butyldimethylsilyl)oxy]-1'-(2,2-dimethyl-7-methoxy-3,4-dihydro-2*H*-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 $\text{C}_{25}\text{H}_{42}\text{O}_5\text{Si}$: C, 66.63; H, 9.39%. 100 MHz NMR $\delta_{\text{H}}(\text{CDCl}_3)$: -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).

(\pm)-(2*R**/*S**,3*R**,4*R**,1'*R**/*S**)-4-{1'-[(*tert*-Butyldimethylsilyl)oxy]-1'-(2,2-dimethyl-7-methoxy-3,4-dihydro-2*H*-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 $\text{C}_{24}\text{H}_{40}\text{O}_6\text{Si}$: C, 63.68; H, 8.91%. 100 MHz NMR $\delta_{\text{H}}(\text{CDCl}_3)$: -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 C₂₄H₃₈O₆Si: C, 63.97; H, 8.50%. 100 MHz NMR δ_{H} (CDCl₃): -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 C₂₄H₃₆O₅Si: C, 66.63; H, 9.39%. 100 MHz NMR δ_{H} (CDCl₃): -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-methylmorpholine 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 C₂₄H₃₈O₇: C, 61.77; H, 8.21%. 100 MHz NMR δ_{H} (CDCl₃): -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 1hr]. A colorless oil (61.7mg 63%). *Anal.* Found: C, 61.79; H, 7.09. Calcd. for C₁₈H₂₄O₇Si: C, 61.35; H, 6.87%. 100 MHz NMR δ_{H} (CDCl₃): 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 60F₂₅₄ 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 C₁₈H₂₂O₆: C, 64.66; H, 6.63%.

100 MHz NMR δ_{H} (CDCl₃): 1.34 (6H, s, 2'-(CH₃)₂), 1.78 (2H, t, J=6, 3'-H), 2.72 (2H, t, J=6', 4-H), 3.13 (0.5H, m, 5 α -H), 3.49 (0.5H, m, 5 α -H), 3.63-4.76 (5H, m, 1-OH, 4-CH₂, 8-H), 3.76 (3H, s, OCH₃), 5.10 (0.5H, d, J=6, 6 β -H), 5.34 (0.5H, d, J=6, 6 α -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).

(\pm)-(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 C₁₈H₂₄O₆: C, 64.27; H, 7.19%. 100 MHz NMR δ_{H} (CDCl₃): 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 \times 2), 3.60-4.40 (5H, m), 4.83 (1H, d, J=6), 5.12 (1H, broad s), 6.32-6.36 (1H, s \times 2), 7.18-7.26 (1H, s \times 2).

(\pm)-(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 [60F₂₅₄ 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 C₂₆H₃₂O₈: C, 66.09; H, 6.83%. 100 MHz NMR δ_{H} (CDCl₃): 1.34 (6H, s, 2''-(CH₃)₂), 1.78 (2H, t, J=6, 3''-H₂), 2.54-2.82 (1H, m, 5 β -H), 2.74 (2H, t, J=6, 4''-H₂), 3.71 (1H, d, J=10, 8 α -H), 3.76 (3H, s, 7''-OCH₃), 3.88 (6H, s, 2'-OCH₃, 6'-OCH₃), 4.10 (1H, dd, J=9, 2, 4 α , -H), 4.28 (1H, broad s, 1-OH), 4.33 (1H, d, J=10, 8 α -H), 4.60 (1H, dd, J=9, 7, 4 β -H), 4.90 (1H, d, J=6, 6 α -H), 5.38 (1H, s, 2 α -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 (11mg, 28%). *Rf* 0.51. **Anal.** Found: C, 66.25; H, 6.88. Calcd. for C₂₆H₃₂O₈: C, 66.09; H, 6.83%. 100 MHz NMR δ_{H} (CDCl₃): 1.33 (3H, s, 2''-CH₃), 1.34 (3H, s, 2''-CH₃), 1.78 (2H, t, J=6, 3''-H₂), 2.70 (2H, t, J=6, 4''-H₂), 3.13 (1H, m, 5 β -H), 3.50-4.30 (4H, m), 3.76 (3H, s, 7''-OCH₃), 3.88 (6H, s, 2'-OCH₃, 6'-OCH₃), 4.42 (1H, s, 1-OH), 5.36 (1H, s, 2 α -H), 5.38 (1H, d, J=4, 6 β -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 (\pm)-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 (\pm)-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 (\pm)-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 (\pm)-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- γ -butyrolactone 9, α -methylene- γ -butyrolactone 10, α -hydroxy- α -hydroxymethyl- γ -butyrolactone 11, triol 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 1*S**,5*R**,6*S** and 1*S**,5*R**,6*R** 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 5 α -proton of the 6*S**(6 α) and 6*R**(6 β) isomers, respectively.

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

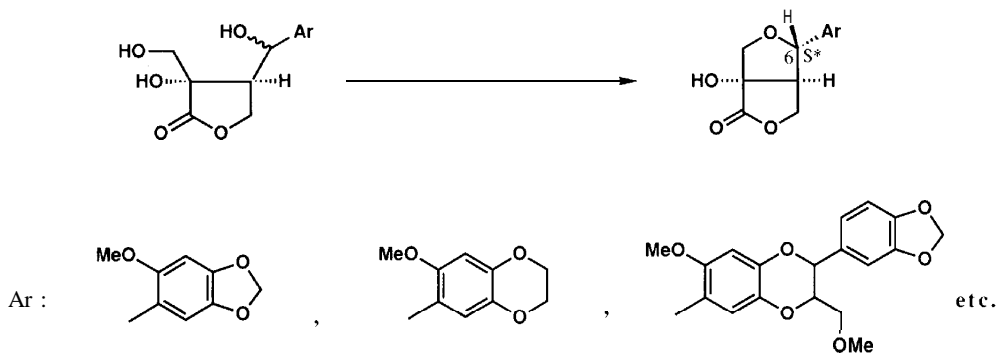
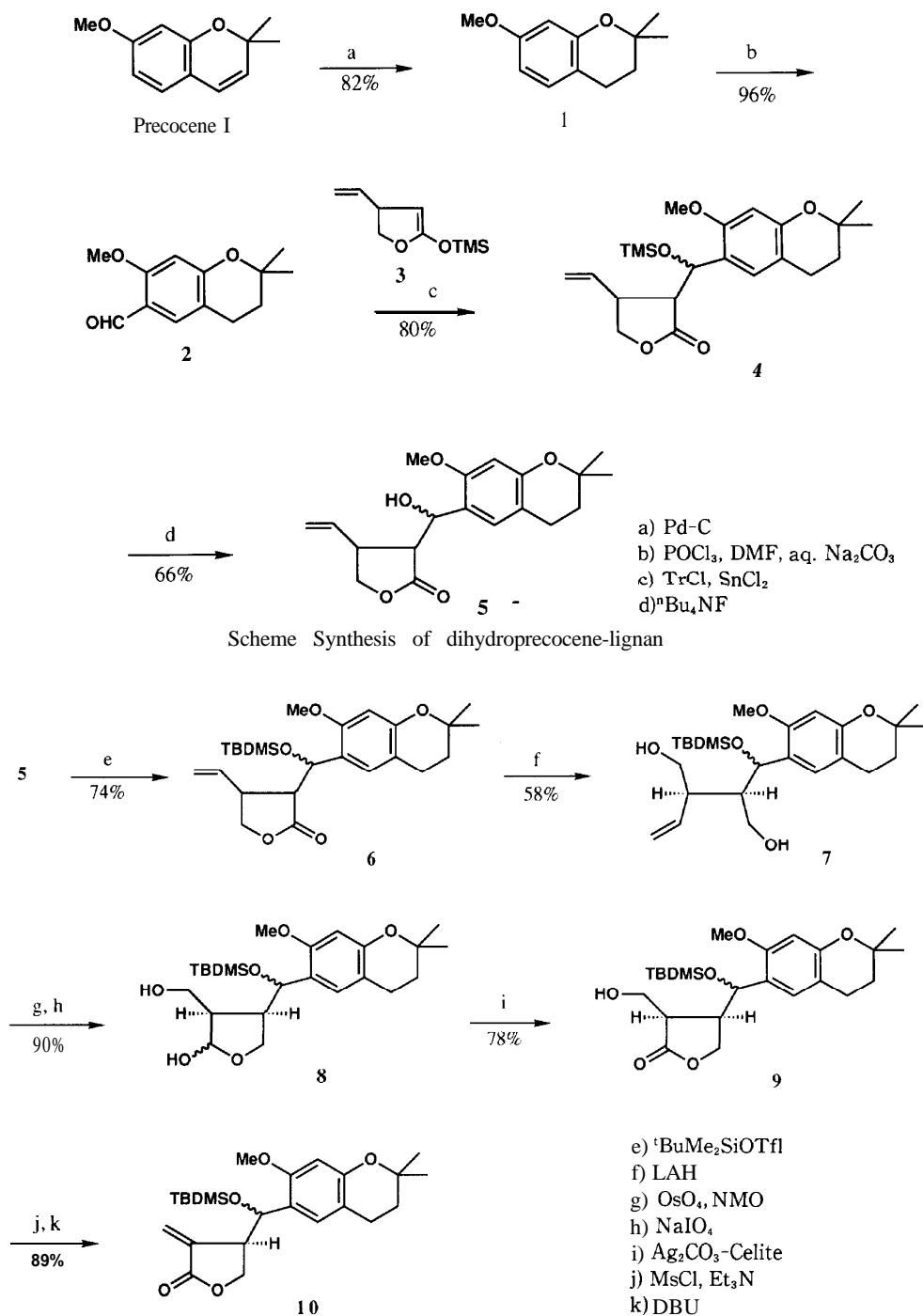
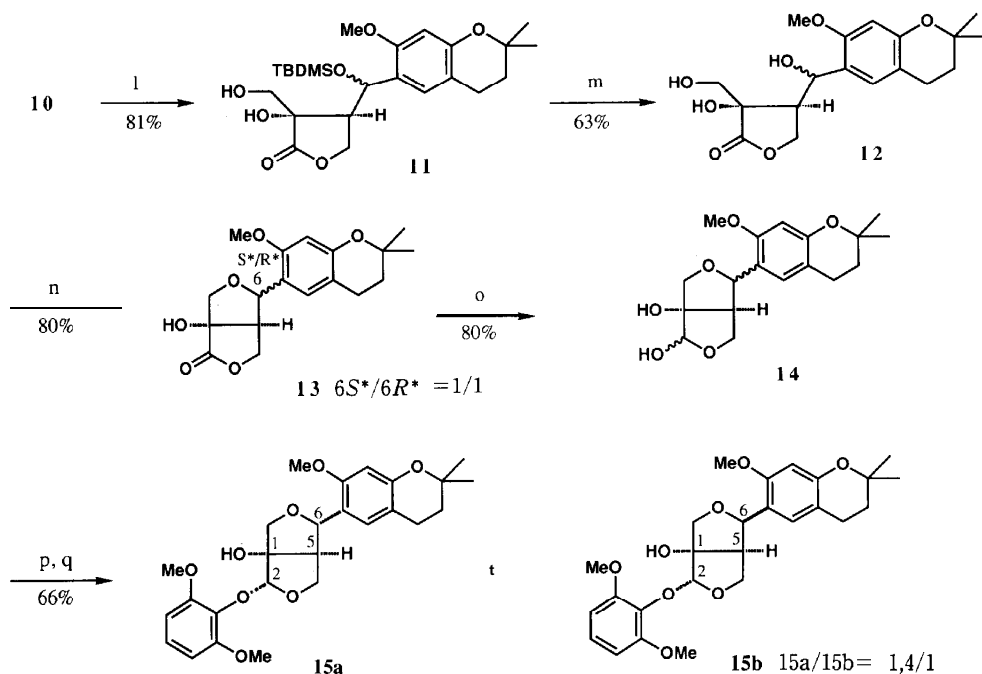


Fig. 2. Stereoselective cyclization of the triols having a polyalkoxyphenyl group,





1) OsO₄, NMO m) ⁿBu₄F n) CSA, MS(4A) o) DIBAL-H p) 2,6-dimethoxyphenol, cat. PPTS q) chromatographic separation

Scheme (continued)

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

The 6 α / β - 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 2 α -acetal as the equimolecular mixture of (\pm)-(1S*, 2R*, 5R*, 6S*)-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 (\pm)-(1S*, 2R*, 5R*, 6R*)-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 5 α -H (Taniguchi *et al.*, 1989; Pelter *et al.*, 1976); the protons of the 6S*(α) and 6R*(β) 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 μ g, and also ineffective on the growth of the 4th instar larvae of the silkworm, *Bombyx mori* (C. 146 x N. 137), at 200 μ g per larva, the housefly and silkworm being

treated with each compound in a 1 μ l 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.

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