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A New Lignan Having A Chromene Moiety: Synthesis of Haedoxan Analogue with Precocene I Skeleton

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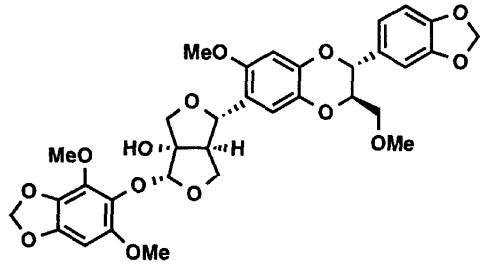
A new lignoid replacing the 6-methoxy-2-methoxymethyl-(3,4-methylenedioxyphenyl)-1,4-benzodioxan-7-yl group of an insecticidal lignan, haedoxan, to an anti-juvenile hormone, 2,2-dimethyl-7-methoxychromene (precocene I), was synthesized from 3-benzyloxy-2,2-dimethyl-7-methoxychroman-6-carbaldehyde through 16 steps in a 0.92% overall yield. This analogue showed no insect growth-regulatory activity at a level of 200pg dose in a bioassay using the 4th instar larvae of the silkworm.

INTRODUCTION

Haedoxan A, (+)-(1*S*, 2*R*, 5*R*, 6*S*, 2"*R*, 3"*R*)-1-hydroxy-2-(2',6'-dimethoxy-3',4'-methylenedioxyphenoxy)-6-[2",3"-dihydro-6"-methoxy-2"-methoxymethyl-3"-(3,4-methylenedioxyphenyl)-1",4"-benzodioxine-7"-yl]-3,7-dioxabicyclo[3.3.0]octane, was isolated as the main constituent of the insecticidal neolignans of *Phryma leptostachya* L. (haedokusou) (Taniguchi *et al.*, 1989). The 1,4-benzodioxan framework in this unique sesquilignan was essential for its insecticidal activity (Yamauchi and Taniguchi, 1991, 1992a, b, c, d). In a challenge to explore new biological activities, a haedoxan analogue (21) possessing antiJH hormone (precocene I isolated from *Ageratum Xoustonianum)* (Bowers and Ohta, 1976) structure resembling to 1,4-benzodioxan framework of haedoxan was synthesized (Fig. 1), and assayed on the 4th instar larvae of the silkworm.



(+)-Haedoxan A 21

Fig. 1. The structures of(+)-Haedoxan A and analogue (21).

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MATERIALS AND METHODS

All melting points (mp.) and boiling point (bp.) are uncorrected. ^{1}H-NMR spectra were measured with a JEOL-EX 400 spectrometer, and chemical shifts are reported as values in parts per million relative to tetramethylsilane (δ_H 0.0) as an internal standard. Data are reported as the chemical shifts (integrated intensity, multiplicity and coupling constant). Gravity column chromatography was carried out with Merck silica-gel 60 (230-400 mesh ASTM). Preparative TLC was performed on precoated $60F_{254}$ silica-gel plates supplied by E. Merck.

2,2-Dimethyl-7-methoxychromene (precocene I) (1). Precocene I was prepared from 3-methoxyphenol (11.0 ml, 0.10 mol) and 3,3-dimethylacrylic acid (11.0 g, 0.11 mol) according to the method described in the literature (Ohta and Bowers, 1977). A colourless oil (11.8 g, 62%). bp. 125-128 °C/4 mmHg (lit. bp. 97-100 °C/2 mmHg). NMR δ_H ($CDCl_3$) : 1.42 (6H, S), 3.77 (3H, S), 5.47 (1H, d, J=9.77 Hz), 6.27 (1H, d, J=9.77 Hz), 6.37 (1H, d, J=2.44 Hz), 6.88 (1H, d, J=2.44, 8.30 Hz), 7.74 (1H, d, J=8.30 Hz). *Anal.* Found: C, 75.67; H, 7.51. Calcd. for $C_{12}H_{14}O_2$: C, 75.75; H, 7.42%.

2,2-Dimethyl-7-methoxychroman-3,4-diol (2). A mixture of precocene I (10.0 g, 52.6 mmol), *N*-methylmorpholine N-oxide (NMO; 6.80 g, 57.9 mmol) and OsO_4 (2 ml of a 2% aqueous solution) in acetone (140 ml), *tert*-BuOH (70 ml) and H_2O (70 ml) was stirred at room temperature for 72hr under N_2 atmosphere in the dark. After quenching (aqueous soln. of $NaHSO_3$), the reaction mixture was filtered through a celite pad, and the filtrate was evaporated. The residue was extracted with EtOAc. The extract was dried over Na_2SO_4, filtered, and the solvent was evaporated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc=2 : 1) to obtain 2 (7.0 g, 58%) as white crystals. mp. 102-103 °C. NMR δ_H ($CDCl_3$): 1.30 (3H, S), 2.01 (1H, d, J=8.30 Hz), 2.47 (1H, d, J=9.28 Hz), 3.70 (1H, dd, J=4.40, 8.30 Hz), 3.77 (3H, S), 4.77 (1H, dd, J=4.40, 9.28 Hz), 6.37 (1H, d, J=2.44 Hz), 6.58 (1H, dd, J= 2.44, 7.81 Hz), 7.41 (1H, d, J=7.81 Hz). *Anal.* Found: C, 64.21; H, 7.12. Calcd. for $C_{12}H_{16}O_4$: C, 64.26; H, 7.20%.

2,2-Dimethyl-7-methoxychroman-3-one (3). To a stirred solution of 2 (7.0 g, 30.7 mmol) in THF (200 ml) was added *conc.* HCl (10 ml) and refluxed for lhr. The solution was neutralized with *sat.* $NaHCO_3$ solution and extracted by EtOAc. The extract was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica-gel chromatography (eluent; hexane : EtOAc=4 : 1) to obtain **3** (6.23 g, *quant.) as a* colourless syrup. NMR δ_H ($CDCl_3$): 1.41 (6H, S), 3.53 (2H, S), 3.79 (3H, S), 6.53-6.61 (2H, m), 6.98 (1H, d, J=8.30 Hz).

2,2-Dimethyl-7-methoxychroman-3-ol (4). To a stirred suspension of $LiAlH_4$ (0.76 g, 22.4 mmol) in dry THF (100 ml) was added a solution of 3 (6.0 g, 29.1 mmol) in dry THF (100 ml) at room temperature and stirred for 2hr. The reaction mixture was quenched by the addition of *sat.* $MgSO_4$ soln. and anhydrous K_2CO_3, and stirred for 2hr. The mixture was filtered through a celite pad, and the filtrate was concentrated. The crude product was purified by silica-gel chromatography (eluent; hexane : EtOAc=4 : 1) to obtain 4 (4.88 g, 81%) as colourless crystals. mp. 65-66 °C. NMR δ_H ($CDCl_3$) : 1.32 (3H, S), 1.36 (3H, S), 1.72 (1H, d, J=7.81 Hz), 2.71 (1H, dd, J=5.37, 16.6 Hz), 3.01 (1H, dd, J=4.89, 16.6 Hz), 3.76 (3H, S), 3.77 (1H, m), 6.40 (1H, d, J=2.44 Hz), 6.48 (1H, dd, J=2.44, 8.30 Hz), 6.92 (1H, d, J=8.30 Hz). *Anal.* Found: C, 69.22; H, 7.73. Calcd. for $C_{12}H_{16}O_3$: C, 69.19;

H. 7.75%.

3-Benzyloxy-2,2-dimethyl-7-methoxychroman (5). To a stirred and ice-cooled suspension of NaH (0.92 g, a 60% dispersion in mineral oil, 23.0 mmol) in dry THF (100 ml) was added a solution of 4 (4.73 g, 22.74 mmol) in dry THF (50 ml) under N_2 atmosphere. The mixture was allowed to reach room temperature and stirred for 30 min. To the mixture was added benzyl bromide (4.1 ml, 34.5 mmol) and $^nBu_4NI$ (0.2 g), and stirred at room temperature for 20hr before quenching by a addition of H_2O (30 ml). The reaction mixture was extracted by EtOAc. The extract was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc=20 : 1) to obtain 5 (5.94 g, 88%) as a colourless oil. NMR $\delta_H(CDCl_3)$: 1.27 (3H, S), 1.39 (3H, S), 2.57 (1H, dd, *J*=8.30, 15.62 Hz), 2.96 (1H, dd, *J*=5.37, 15.62 Hz), 3.54 (1H, dd, *J*=5.37, 8.30 Hz), 3.74 (3H, S), 4.55 (1H, d, *J*=12.21 Hz), 4.72 (1H, d, *J*=12.21 Hz), 6.37 (1H, d, *J*=2.41 Hz), 6.45 (1H, m), 6.93 (1H, d, *J*=8.30 Hz), 7.29 (1H, m), 7.34 (2H, S), 7.35 (2H, S). *Anal.* Found: C, 76.47; H, 7.43. Calcd. for $C_{19}H_{22}O_3$: C, 76.47; H, 7.44%.

3-Benzyloxy-2,2-dimethyl-7-methoxychroman-6-carbaldehyde (6). To a cooled (0 "C) solution of 5 (1.42 g, 4.76 mmol) in dry DMF (10 ml) was added $POCl_3$ (0.82 ml, 9.52 mmol) as drops. The mixture was stirred at room temperature for 30 mm., then stirred at 80 ˚C for 3hr. After cooling to room temperature, the solution was quenched by NaOAc solution (4 g in 18 ml H_2O). The mixture was extracted by Et_2O. The extract was washed with *sat.* $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc= 8 : 1) to obtain 6 (1.37 g, 88%) as a colourless oil. NMR $\delta_H(CDCl_3)$: 1.33 (3H, S), 1.38 (3H, S), 2.78 (1H, dd, *J*=7.32, 16.11 Hz), 2.96 (1H, dd, *J*= *4.89,* 16.11 Hz), 3.54 (1H, dd, *J*=4.88, 7.32 Hz), 3.85 (3H, S), 4.53 (1H, d, *J*=12.21 Hz), 4.71 (1H, d, *J*=12.21 Hz), 6.38 (1H, S), 7.28-7.36 (5H, **m) ,** 7.58 (1H, **S),** 10.26 (1H, S). *Anal.* Found: C, 73.49; H, 6.88. Calcd. for $C_{20}H_{22}O_4$: C, 73.59; H. 6.8%.

3-[(3-Benzyloxy-2,2-dimethyl-7-methoxychroman-6-yl)hydroxymethyl]-4-vinyldihydro-2(3*H*)-furanones (7). To a stirred and cooled (-70 "C) solution of potasssium bis-(trimethylsilyl)amide (35.6 ml, a 0.5M sol. in toluene, 17.8 mmol) in dry THF (25 ml) under N_2 atmosphere. After stirring the mixture at -75 ˚C for 30 mm., a solution of 6 (3.24 *g, 9.94* mmol) in dry THF (100 ml) was added as drops. The mixture was stirred at -75 ˚C for 8hr, and *sat.* metanolic NH_4Cl solution (5 ml) and *sat.* NH_4Cl solution (150 ml) were added sequentially. The mixture was allowed to reach room temperature and extracted by EtOAc. The extract was washed by brine, dried over Na_2SO_4, filtered and concentrated. Silica-gel chromatography of the residue gave an yellow oily product, and crystallization of the product from diisopropyl ether afforded *erythro*-**7** (3.03 g, 70%) as white crystals. mp. 102-104˚C. NMR $\delta_H(CDCl_3)$: 1.28 (1.5H, S), 1.37 (3H, S), 2.60 (0.5H, d, *J*=5.37 Hz), 2.67 (0.5H, d, *J*=5.37 Hz), 2.70-2.77 (1H, m), 2.95 (1H, dt, *J*=5.37, 16.0 Hz), 3.04 (1H, m), 3.25 (1H, dd, *J*=8.79, 17.58 Hz), 3.52 (1H, dd, *J*=4.88, 7.81 Hz), 3.74 (3H, S), 3.87 (1H, dd, *J*=8.79, 17.58 Hz), 4.34 (1H, dt, *J*=1.96, *8.79* Hz), 4.54 (1H, d, *J*=12.21 Hz), 4.67-4.79 (3H, m), 5.25-5.38 (1H, m), 5.52 (1H, m), 6.31 (1H, S), 7.12 (1H, S), 7.28-7.35 (5H, m). *Anal.* Found: C, 71.12; H, 6.89. Calcd. for $C_{26}H_{30}O_6$: C, 71.2; H. 6.9%.

3-[(3-Benzyloxy-2,2-dimethyl-7-methoxychroman-6-yl)*tert*-butyldimethylsilyloxymethyl]-4-vinyldihydro-2(3H)-furanones (8). To a cooled (0°C) and stirred solution of 7

(2.0 g, 4.57 mmol) and 2,6-lutidine (1.6 ml, 13.7 mmol) in dry CH_2Cl_2 (30 ml) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf; 1.57 ml, 6.84 mmol) as drops. The solution was stirred at room temperature for lhr before adding 5% $NaHCO_3$ solution, and extracted by CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc= 3 :1) to obtain 8 (2.14 g, 85%) as colourless crystals. mp. 105-108 "C. NMR δ_H ($CDCl_3$) : -0.08 (1.2H, S), -0.07 (1.8H, S), 0.09 (1.2H, S), 0.10 (1.8H, S), 0.93 (3.6H, S), 0.94 (5.4H, S), 1.25 (1.8H, S), 1.29 (1.2H, S), 1.37 (1.2H, S), 1.39 (1.8H, S), 2.67-2.74 (1H, m), 2.82-2.86 (1H, m), 2.89-2.96 (1H, m), 3.29-3.37 (1H, m), 3.52-3.57 (1H, m), 3.74 (3H, S), 3.85-3.93 (1H, m), 4.35-4.41 (1H, m), 4.53-4.47 (4H, m), 5.22-5.35 (1H, m), 5.56 (1H, m), 6.28 (0.6H, S), 6.29 (0.4H, S), 7.07 (0.6H, S), 7.08 (0.4H, S), 7.29-7.36 (5H, m). *Anal.* Found: C, 69.6; H, 8.09. Calcd. for $C_{32}H_{44}O_6Si$: C, 69.53; H, 8.03%.

2-[(3-Benzyloxy-2,2-dimethyl-7-methoxychroman-6-yl)*tert*-butyldimethylsilyloxymethyl]-3-vinyl-1,4-butanediols (9). To a cooled (-10 "C) and stirred suspension of $LiAlH_4$ (0.17 g, 5.0 mmol) in dry THF (30 ml) was added a solution of 8 (2.12 g, 3.84 mmol) in dry THF (30 ml). The mixture was stirred at -10°C for 2hr before quenching by *sat.* $MgSO_4$ solution and anhydrous K_2CO_3 and stirred for an additional period of lh, and filtered through a celite pad. The filtrate was concentrated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc= 2 : 1) to obtain 9 (1.93 g, 90%) as a colourless syrup. NMR δ_H ($CDCl_3$): -0.31 (1.2H, S), -0.30 (1.8H, S), -0.01 (3H, S), 0.84 (9H, S), 1.27 (1.8H, S), 1.28 (1.2H, S), 1.36 (3H, S), 2.68-2.76 (1H, m), 2.80 (1H, br. S), 2.86 (1H, d, J=4.88 Hz), 2.93 (1H, dt, J=4.88, 16.11 Hz), 3.38 (1H, d, J=9.79 Hz), 3.51-3.55 (1H, m), 3.78 (1.2H, S), 3.79 (1.8H, S), 3.82-3.85 (1H, m), 3.96 (1H, br. S), 4.50-4.56 (1H, m), 4.67-4.73 (1H, m), 5.09-5.14 (2H, m), 5.22 (1H, d, J=8.30 Hz), 5.94-6.03 (1H, m), 6.34 (0.6H, S), 6.35 (0.4H, S), 7.06 (0.6H, S), 7.10 (0.4H, S), 7.27-7.33 (5H, m). *Anal.* Found: C, 69.21; H, 8.56. Calcd. for $C_{31}H_{46}O_7Si$: C, 69.02; H. 8.3%.

4-[3-Benzyloxy-2,2-dimethyl-7-methoxychroman-6-yl)*tert*-butyldimethylsilyloxymethyl]-2-hydroxy-3-hydroxymethyltetrahydrofurans (10). A mixture of 9 (0.47 g, 0.85 mmol), *N*-methylmorpholine *N*-oxid (NMO) (0.12 g, 1.02 mmol), 2% OsO_4 solution (0.5 ml), acetone (6 ml) and H_2O (3 ml) in *tert*-BuOH (3 ml) was stirred at room temperature for 12hr under N_2 atmosphere in the dark. To the reaction mixture was added $NaHSO_3$ solution (0.02 g in 1 ml H_2O). After filtering the mixture through a celite pad, the filtrate was concentrated. The residue was dissolved in EtOAc (10 ml), and $NaIO_4$ (0.20 g, 0.94 mmol) in H_2O (5 ml) was added to the solution, and the mixture was stirred at room temperature for 24hr. The reaction mixture was extracted by EtOAc. The extract was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc=1: 2) to obtain 10 (0.403 g, 85%) as colourless crystals. mp. 61-64 °C. *Anal.* Found: C, 66.63; H, 8.37. Calcd. for $C_{31}H_{46}O_7Si$: C, 66.63; H, 8.3%.

4-[3-Benzyloxy-2,2-dimethyl-7-methoxychroman-6-yl)*tert*-butyldimethylsilyloxymethyl]-3-hydroxymethyldihydro-2(3H)-furanones (11). The mixture of 10 (1.25 g, 2.24 mmol) and Ag_2CO_3-celite (2.24 g containing 2.24 mmol of Ag_2CO_3) in benzene (20 ml) was refluxed for 30 min. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc=3: 1) to obtain 11 (1.21 g, 97%) as colourless crystals. mp. 48-52 "C. NMR δ_H ($CDCl_3$): -0.31

(1.8H, S), -0.29 (1.2H, S), 0.54 (3H, S), 0.87 (9H, S), 1.24 (1.2H, S), 1.26 (1.8H, S), 1.28 (1.2H, S), 1.29 (1.8H, S), 2.67-2.99 (5H, m), 3.10-3.15 (1H, m), 3.51-3.56 (1H, m), 3.75 (3H, S), 3.93-4.16 (5H, m), 4.55 (1H, dd, *J*=9.28, 11.78 Hz), 4.71 (1H, dd, *J*=5.86, 11.78 Hz), 5.18 (1H, m), 6.32 (0.6H, S), 6.33 (0.4H, S), 7.02 (0.6H, S), 7.04 (0.4H, S), 7.33-7.35 (5H, m). *Anal.* Found: C, 66.65; H, 7.97. Calcd. for $C_{31}H_{46}O_7Si$: C, 66.87; H, 7.97%.

4-[3-Benzyloxy-2,2-dimethyl-7-methoxychroman-6-yl)*tert*-butyldimethylsilyloxymethyl]-3-methylenedihydro-2(3*H*)-furanones (12). To an ice-cooled solution of **11** (1.20 g, 2.16 mmol) and Et_3N (0.60 ml, 4.32 mmol) in benzene (15 ml) was added methanesulfonyl chloride (0.25 ml, 3.24 mmol) as drops, and the mixture was stirred at room temperature for 2hr. To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.48 ml, 3.24 mmol), and the mixture was stirred at room temperature for lhr. The reaction mixture was diluted with EtOAc, washed with 5% citric acid solution, 5% $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc=4 : 1) to obtain 12 (0.91 g, 78%) as a colourless syrup. NMR δ_H ($CDCl_3$): -0.23 (3H, S), 0.02 (1.2H, S), 0.03 (1.8H, S), 0.85 (3.6H, S), 0.86 (5.4H, S), 1.29 (1.2H, S), 1.30 (1.8H, S), 1.37 (1.8H, S), 1.38 (1.2H, S), 2.66-2.74 (1H, m), 2.86-3.00 (1H, m), 3.23 (1H, m), 3.54 (1H, m), 3.75 (3H, S), 4.17-4.29 (2H, m), 4.54 (1H, m), 4.71 (1H, m), 5.07 (1H, m), 5.14 (0.6H, S), 5.23 (0.4H, S), 6.22 (1H, d, *J*=5.38 Hz), 6.33 (1H, S), 6.96 (0.6H, S), 6.99 (0.4H, S), 7.27-7.35 (5H, m). *Anal.* Found: C, 68.84; H, 7.89. Calcd. for $C_{31}H_{42}O_6Si$: C, 69.11; H, 7.86%.

4-[3-Benzyloxy-2,2-dimethyl-7-methoxychroman-6-yl)*tert*-butyldimethylsilyloxymethyl]-3-hydroxy-3-hydroxymethyldihydro-2(3*H*)-furanones (13). A mixture of 12 (0.90 g, 1.67 mmol), 2% OsO_4 solution (0.5 ml), NMO (0.22 g, 1.88 mmol), acetone (12 ml), *tert*-BuOH (6 ml) and H_2O (6 ml) was stirred at room temperature for 12hr under N_2 atmosphere. To the mixture was added $NaHSO_3$ solution (0.13 g, in 1 ml H_2O). After filtering through a celite pad, the filtrate was concentrated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc=2 : 1) to obtain 13 (0.80 g, 83%) as a colourless syrup. NMR δ_H ($CDCl_3$): 1.29 (3H, S), 1.37 (3H, S), 2.71 (1H, dd, *J*=7.32, 16.11 Hz), 2.92 (2H, dd, *J*=4.88, 16.11 Hz), 3.06 (1H, dd, *J*=5.86, 13.18 Hz), 3.12-3.21 (1H, m), 3.36 (1H, S), 3.50-3.54 (1H, m), 3.79 (3H, S), 3.81-4.11 (5H, m), 4.55 (1H, d, *J*=12.21 Hz), 4.71 (1H, d, *J*=12.21 Hz), 5.04-5.09 (1H, m), 6.37 (1H, S), 6.90 (6H, S), 6.98 (0.4H, S), 7.28-7.37 (5H, m). *Anal.* Found: C, 65.45; H, 7.68. Calcd. for $C_{31}H_{44}O_8Si$: C, 65.0; H, 7.75%.

4-[3-Benzyloxy-2,2-dimethyl-7-methoxychroman-6-yl)hydroxymethyl]-3-hydroxy-3-hydroxymethyldihydro-2(3*H*)-furanones (14). To a cooled (0°C) solution of 13 (0.79 g, 1.38 mmol) in dry THF (10 ml) was slowly added tetrabutylammonium fluoride (TBAF; 1.66 ml, a 1.0M solution in THF, 1.66 mmol), and stirred at 0°C for 1.5hr. The reaction mixture was diluted with EtOAc, washed with 10% NH_4Cl solution, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc=1 : 2) to obtain 14 (0.44 g, 70%) as colourless crystals. mp. 146-149°C. NMR δ_H ($CDCl_3$): 1.29 (3H, S), 1.37 (3H, S), 2.72 (1H, dd, *J*=7.32, 16.11 Hz), 2.93 (2H, dd, *J*=4.88, 16.11 Hz), 3.05 (1H, dd, *J*=5.86, 13.18 Hz), 3.12-3.21 (1H, m), 3.36 (1H, S), 3.50-3.54 (1H, m), 3.79 (3H, S), 3.88 (1H, dt, *J*=2.93, 9.28 Hz), 3.96 (1H, m), 4.03 (1H, dd, *J*=5.86, 11.72 Hz), 4.09 (1H, dd, *J*=5.37, 11.72 Hz), 4.55 (1H, d, *J*=12.21 Hz), 4.71 (1H, d, *J*=12.21 Hz), 5.06 (1H, m), 6.37 (1H, S), 6.97 (1H, S), 7.28-7.35 (5H, m). *Anal.*

Found: C, 65.21; H, 6.65. Calcd. for $C_{25}H_{30}O_8$: C, 65.47; H, 6.60%.

6 α-(3-Benzyloxy-2,2-dimethyl-7-methoxychroman-6-yl)-1α-hydroxy-2-oxo-3,7-dioxabicyclo[3.3.0]octanes (15). To an ice-cooled solution of 14 (0.43 g, 0.94 mmol) in dry CH_2Cl_2 (20 ml) was added a catalytic amount of 10-camphorsurfonic acid, and the mixture was stirred at 0 ℃ for 1.5hr before quenching with a few drops of Et_3N. The solvent was evaporated. The residue was purified by silica-gel chromatography (eluent; hexane: EtOAc=2: 1) to obtain 15 (0.353 g, 86%) as colourless crystals. mp. 62-65 ℃. NMR $\delta_H(CDCl_3)$: 1.26 (1.2H, S), 1.29 (1.8H, S), 1.38 (3H, S), 2.74 (1H, dd, J=7.81,16.11 Hz), 2.96 (1H, S), 2.93-2.99 (1H, m), 3.12 (1H, m), 3.53 (1H, m), 3.76 (3H, S), 4.12-4.22 (2H, m), 4.37-4.42 (1H, m), 4.47-4.67 (2H, m), 4.72 (1H, d, J=11.72 Hz), 5.08 (1H, d, J=4.89 Hz), 6.36 (1H, S), 7.15 (1H, S), 7.27-7.35 (5H, m). *Anal.* Found: C, 67.68; H, 6.50. Calcd. for $C_{25}H_{28}O_7$: C, 68.15; H. 6.41%.

6 α-(3-Benzyloxy-2,2-dimethyl-7-methoxychroman-6-yl)-1α-*tert*-butyldimethylsilyloxy-2-oxo-3,7-dioxabicyclo[3.3.0]octanes (16). To a cooled (0 "C) solution of 15 (0.34 g, 0.77 mmol) and 2,6-lutidine (0.27 ml, 2.32 mmol) in dry CH_2Cl_2 (10 ml) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) (0.27 ml, 1.18 mmol) by a syringe. The solution was stirred at room temperature for 24hr. After 24hr, the same amount of 2,6-lutidine and TBDMSOTf were added to the mixture, and stirred at room temperature for 24hr before quenching by an addition of 5% $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted by CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc=4 : 1) to obtain 16 (0.37 g, 86%) as a colourless syrup. NMR $\delta_H(CDCl_3)$: 0.02 (1.8H, S), 0.03 (1.2H, S), 0.17 (1.8H, S), 0.18 (1.2H, S), 0.78 (3.6H, S), 0.79 (5.4H, S), 1.28 (1.2H, S), 1.29 (1.2H, S), 1.38 (1.2H, S), 1.39 (1.8H, S), 2.73 (1H, dt, J=7.81, 16.6 Hz), 2.93 (1H, dd, J=5.37, 16.11 Hz), 3.01 (1H, m), 3.52 (1H, m), 3.75 (3H, S), 4.10-4.16 (1H, m), 4.23 (1H, dd, J=3.41, 9.76 Hz), 4.34 (1H, dd, J=1.95, 4.88 Hz), 4.53-4.61 (2H, m), 4.72 (1H, d, J=11.72 Hz), 5.07 (1H, d, J=4.40 Hz), 6.35 (0.6H, S), 6.36 (0.4H, S), 7.11 (1H, S). *Anal.* Found: C, 66.85; H, 7.70. Calcd. for $C_{31}H_{42}O_7Si$: C, 67.12; H. 7.64%.

1α-*tert*-Butyldimethylsilyloxy-6α-(2,2-dimethyl-3-hydroxy-7-methoxychroman-6-yl)-2-oxo-3,7-dioxabicyclo[3.3.0]octanes (17). A mixture of 16 (0.344 g, 0.62 mmol) and 20% $Pd(OH)_2$-C (0.25 g) in EtOAc (50 ml) was vigorously stirred for 10min under H_2 atmosphere. The suspension was filtered, and the filtrate was concentrated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc=2 : 1) to obtain 17 (0.254 g, 88%) as colourless crystals. mp. 103-106 ℃. NMR $\delta_H(CDCl_3)$: 0.02 (1.2H, S), 0.03 (1.8H, S), 0.17 (3H, S), 0.77 (3.6H, S), 0.79 (5.4H, S), 1.31 (3H, S), 1.36 (3H, S), 1.67 (1H, d, J=7.81 Hz), 2.67-2.75 (1H, m), 2.97-3.04 (2H, m), 3.77 (3H, S), 3.78-3.80 (1H, m), 4.14 (0.6H, d, J=9.77 Hz), 4.24 (0.4H, d, J=9.77 Hz), 4.34 (1H, m), 4.59 (1H, m), 5.08 (1H, m), 6.38 (1H, S), 7.13 (0.4H, S), 7.14 (0.6H, S). *Anal.* Found: C, 62.0; H, 7.84. Calcd. for $C_{24}H_{36}O_7Si$: C, 62.04; H. 7.82%.

1α-*tert*-Butyldimethylsilyloxy-6α-(2,2-dimethyl-7-methoxychromen-6-yl)-2-oxo-3,7-dioxabicyclo[3.3.0]octane (18). To an ice-cooled solution of 17 (53.4 mg, 0.115 mmol) and 4-dimethylaminopyridine (0.10 g, 0.82 mmol) in dry CH_2Cl_2 (4 ml) was added methanesulfonyl chloride (53.4 μl, 0.69 mmol) by a micro syringe, and stirred at room temperature for 48hr. To the reaction mixture was added H_2O, acidified by 5% citric acid

solution and extracted by CH_2Cl_2. The extract was washed with *sat.* NaHCO,, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative TLC (1.0 mm thickness, eluent; hexane : EtOAc=2 : 1) to obtain a mesylate (61.0 mg, 98%) as a colourless oil. To a solution of mesylate (37.5 mg, 0.069 mmol) in toluene (3 ml) was added DBU (0.10 ml, 0.67 mmol), and refluxed for 12h. The solution was diluted by benzene, washed with 5% citric acid solution, *sat.* NaHCO,,, brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by preparative TLC (0.25 mm thickness, eluent; hexane: EtOAc=2 : 1) to obtain 18 (22.2 mg, 72%) as colourless crystals. mp. 106-109°C. NMR δ_H ($CDCl_3$): 0.04 (3H, S), 0.17 (3H, S), 0.80 (9H, S), 1.42 (3H, S), 1.43 (3H, S), 3.00 (1H, m), 3.79 (3H, S), 4.13 (1H, d, *J*=10.26 Hz), 4.34 (1H, dd, *J*=4.88, 9.77 Hz), 4.59 (1H, dd, *J*=7.81, 9.77 Hz), 5.07 (1H, d, *J*=4.39 Hz), 5.48 (1H,d, *J*=9.77 Hz), 6.28 (1H, d, *J*=9.77 Hz), 6.37 (1H, S), 7.07 (1H, S). *Anal.* Found: C, 64.67; H, 7.61. Calcd. for $C_{24}H_{34}O_6Si$: C, 64.54; H. 7.68%.

6 α-(2,2-Dimethyl-7-methoxychromen-6-yl)-1 a-hydroxy-2-oxo-3,7-dioxabicyclo-[3.3.0]octane (19). To a solution of 18 (35.5 mg, 0.079 mmol) in dry THF (3 ml) was added TBAF (0.12 ml, a 1.0M solution in THF, 0.12 mmol) by a micro syringe, and stirred at room temperature for lhr. The reaction mixture was quenched by 10% NH_4Cl solution, and extracted by EtOAc. The extract was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative TLC (0.5 mm thickness, eluent; hexane : EtOAc=l : 2) to obtain 20 (12.0 mg, 63%) as colourless crystals. mp. 149-151 "C. NMR δ_H ($CDCl_3$): 1.43 (6H, S), 2.90 (1H, br. S), 3.03 (1H, m), 3.79 (3H, S), 4.18 (2H, S), 4.39 (1H, dd, *J*=5.37, 9.77 Hz), 4.65 (1H, m), 5.09 (1H, d, *J*=4.39 Hz), 5.48 (1H, d, *J*=9.77 Hz), 6.29 (1H, d, *J*=9.77 Hz), 6.37 (1H, S), 7.11 (1H, S), *Anal.* Found: C, 64.95; H, 6.28. Calcd. for $C_{18}H_{20}O_6$: C, 65.04; H. 6.07%.

1 α,2 α/β-Dihydroxy-6 α-(2,2-dimethyl-7-methoxychromen-6-yl)-3,7-dioxabicyclo-[3.3.0]octanes (20). To a cooled (70°C) solution of 19 (19.1 mg, 0.058 mmol) in dry toluene (4 ml) was added diisobutylaluminium hydride (0.18 ml, a 0.98M solution in hexane, 0.176 mmol) under N_2 atmosphere, and stirred at same temperature for 2hr. The reaction mixture was quenched by 0.5*N* HCl (2 ml), and allowed to reach room temperature. The mixture was extracted by EtOAc. The extract was washed with sat. NaHCO,, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative TLC (0.5 mm thickness, eluent; hexane : EtOAc=l : 1) to obtain 20 (12.0 mg, 63%) as a colourless oil. NMR δ_H ($CDCl_3$): 1.42 (6H, S), 2.52 (1H, dd, *J*=1.95, 6.83 Hz), 3.71 (1H, d, *J*=9.76 Hz), 3.77 (3H, S), 3.80 (1H, br. S), 3.97 (1H, dd, *J*=1.95, 6.83 Hz), 4.26 (1H, d, *J*=9.77 Hz), 4.29 (1H, dd, *J*=6.84, 9.28 Hz), 4.81 (1H, d, *J*=9.77 Hz), 5.19 (1H, S), 5.46 (1H, d, *J*=9.77 Hz), 6.29 (1H, d, *J*=9.77 Hz), 6.35 (1H, S), 7.18 (1H, S). *Anal.* Found: C, 64.85; H, 6.59. Calcd. for $C_{18}H_{22}O_6$: C, 64.66; H. 6.63%.

2 α-(2,6-Dimethoxyphenoxy)-6 α-(2,2-dimethyl-7-methoxychromen-6-yl)-1 α-hydroxy-3,7-dioxabicyclo[3.3.0]octane (21). A solution of 20 (12.0 mg, 0.036 mmol), 2,6-dimethoxyphenol (0.13 g, 0.84 mmol) and a catalytic amount of pyridinium *p*-toluene-sulfonate in benzene (5 ml) was refluxed for lhr with azeotropic removal of the water. The reaction mixture was diluted by EtOAc, washed with 1*N* NaOH, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative TLC (0.25 mm thickness, eluent; hexane : EtOAc=2 : 1) to obtain 21 (3.7 mg, 22%) as a colourless syrup. NMR δ_H ($CDCl_3$): 1.42 (3H, S, 2"-CH_3), 1.43 (3H, S, 2"-CH_3), 2.65 (1H, m, 5 α-*H*),

3.36 (1H, d, J=9.76 Hz, 8 α-*H*), 3.77 (3H, S, 7"-OC*H*$_3$), 3.86 (6H, S, 2',6'-OC*H*$_3$), 4.08 (1H, dd, J=1.95, 9.28 Hz, 4 α-*H*), 4.25 (1H, S, -OH), 4.32 (1H, d, J=9.76 Hz, 8 β-*H*), 4.59 (1H, dd, J=7.32, 9.28 Hz, 4 β-*H*), 5.36 (1H, S, 2 β-*H*), 5.46 (1H, d, J=9.76 Hz, 3"-*H*), 6.31 (1H, d, J=9.76 Hz, 4"-*H*), 6.35 (1H, S, 6"-*H*), 6.60 (2H, d, J=8.30 Hz, 3',5'-*H*), 7.03 (1H, t, J=8.30 Hz, 4'-*H*), 7.26 (1H, S, 5"-*H*), *Anal.* Found: C, 66.51; H, 6.39. Calcd. for $C_{26}H_{30}O_8$: C, *66.37;* H. *6.43%.*

Bioassay: The precocious metamorphosis activity of 21 was assessed on 10 newly molted 4th instar larva of silkworm *(Bombyx mori).* One μl of acetone solutions dissolving 40, 80, 160 and 200 μg each of the compound were topically applied to the head-thorax by a micro applicator, respectively. The control was tested with 1 μl acetone. The activity was evaluated by induction of precocious metamorphosis, spinning a cocoon and subsequent pupation or formation of larval pupal intermediate.

RESULTS AND DISCUSSION

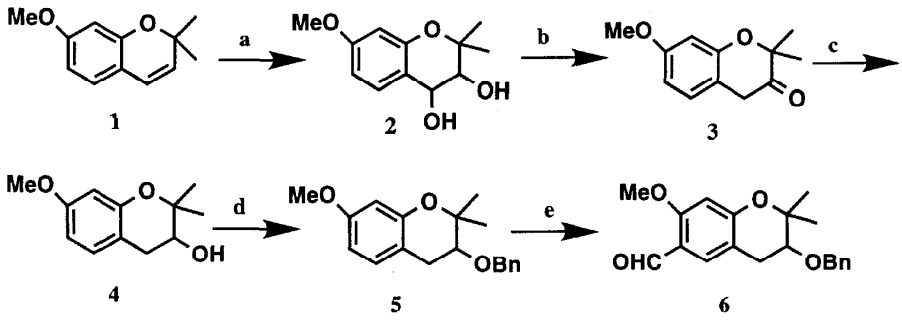
Synthesis

In the synthesis of a haedoxan analogue possessing precocene I (2,2-dimethyl-7-methoxychromene) framework in the molecular structure, protection of the 3,4-olefinic bond of the chromene annoyed us, since the synthetic method of haedoxans involves oxidation reactions using OsO_4 at two steps in their syntheses. (Ishibashi and Taniguchi, 1989). After several preliminary experiments, 3-/4-benzyloxychroman-6-carbaldehydes were selected as the starting material to carry out dehydration reaction at a final step of the synthesis. It was readily found that 4-benzyloxy-2,2-dimethyl-7-methoxychroman was easily dehydrated to give 2,2-dimethyl-7-methoxychromen-6-carbaldehyde in Vilsmeier-formylation reaction. However, successful formylation was achieved by using 3-benzyloxy-2,2-dimethyl-7-methoxychroman (**5**), and 3-benzyloxy-2,2-dimethyl-7-methoxychroman-6-carbaldehyde (6) was obtained in an 88% yield.

A haedoxan analogue 2-(2,6-dimethoxyphenoxy)-6-(2,2-dimethyl-7-methoxychromen-6-yl)-1-hydroxy-3,7-dioxabicyclo[3.3.0]octane (21) was synthesized in the following route.

Precocene I (**1**), which was prepared according to the method in literature (Ohta and Bowers, 1977), was oxidized by OsO_4-*N*-methylmorpholine *N*-oxid (NMO) to obtain a glycol. 2,2-Dimethyl-7-methoxychroman-3,4-diol (2) was converted to 2,2-dimethyl-7-methoxychroman-3-one (3) by treatment with *conc.* HCl solution in tetrahydrofuran (THF). Reduction of 3 with $LiAlH_4$ and benzylation of the product gave 3-benzyloxy-2,2-dimethyl-7-methoxychroman (5). Vilsmeier reaction of 5 furnished 3-benzyloxy-2,2-dimethyl-7-methoxychroman-6-carbaldehyde (6) in an 88% yield. In this manner the chromancarbaldehyde was obtained from precocene I by five steps in a 36% overall yield (Scheme 1).

Similarly to 7-methoxy-2,2-dimethylchroman-6-carbaldehyde (Gotanda *et al.*, 1993), compound 6 scarcely reacted with the lithium enolate of β-vinyl-γ-butyrolactone prepared by using lithium diisopropylamide (LDA) in THF. However, aldol condensation between 6 and potassium enolate of the butyrolactone prepared by using potassium bis-(trimethylsilyl)amide (KHMDS) predominantly gave an *erythro*-aldol (7) in a 70% yield.

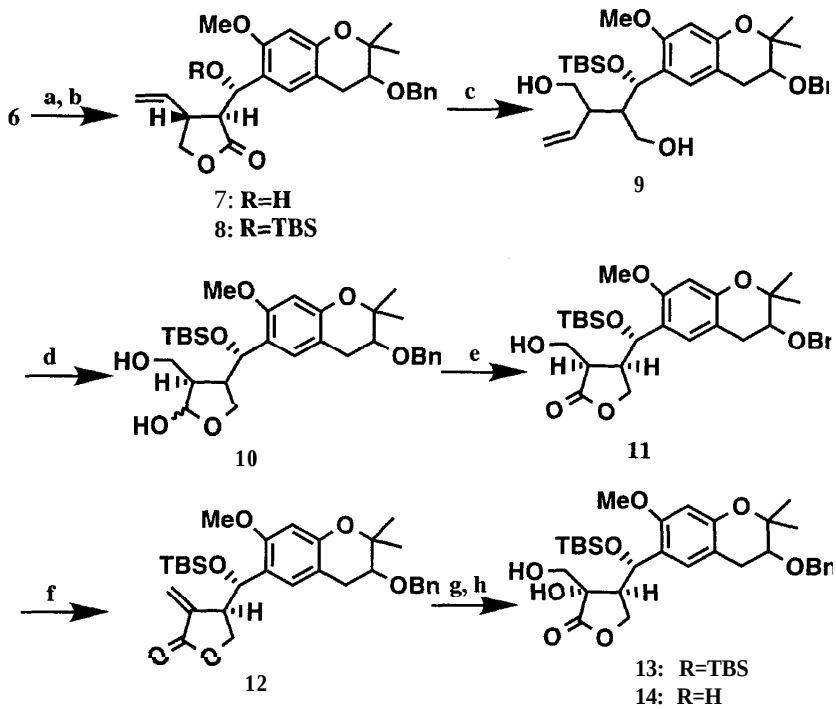


a) cat. OsO_4, NMO/*aq.* acetone, *tert*-BuOH; b) *conc.* HCl/THF
c) $LiAlH_4$/THF; d) NaH, BnBr/THF; e) $POCl_3$/DMF;

Scheme 1. Synthesis of chroman-6-carbaldehyde.

According to the procedures developed in haedoxan synthesis (Ishibashi and Taniguchi, 1989), compound 7 was converted to a 6-(3-benzyloxy-2,2-dimethyl-7-methoxychroman-6-yl)-1-hydroxy-2-oxo-3,7-dioxabicyclo[3.3.0]octane (15) through 8 steps in a 25% overall yield. Debenzylation by catalytic hydrogenation of 15 was not successful in the use of a 10% Pd-C reagent, but the hydrogenation smoothly proceeded on a 20% $Pd(OH)_2$-C (Pearlman, 1967). The resulting hydroxyl group at 3'position was completly resistant to treatment with p-toluenesulfonic acid at room temperature. Treatments with *p*-toluenesulfonyl chloride/pyridine or pyridine-4-dimethylaminopyridine (DMAP)/CH_2Cl_2 were also inactive and gave a mixture of l-, 3'-tosylate and 1,3'-ditosylate in poor yields. Finally, 1-hydroxyl group of compound 15 was protected by silylation with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf), and the 1-silylate was successfully debenzylated with the Pearlman catalyst. Mesylation of 3'-position was achieved with a large excess of methanesulfonyl chloride/DMAP in CH_2Cl_2. The sulfonyl group of methanesulfonate was eliminated by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBIJ) in refluxing toluene to furnish 1 α-*tert*-butyldimethylsilyloxy-6 α-(2,2-dimethyl-7-methoxychromen-6-yl)-2-oxo-3,7-dioxabicyclo[3.3.0]octane (18) in an acceptable yield. Thus, precocene framework in a haedoxan structure was constructed from 6 through 13 steps in a 9.2% overall yield. The *tert*-butyldimethylsilyl function was deprotected by tetrabutylammonium fluoride (TBAF) in THF, the resulting 6 α-(2,2-dimethyl-7-methoxychromen-6-yl)-1 a-hydroxy-2-oxo-3,7-dioxabicyclo[3.3.0]octane (19) was converted to 1 α,2 α/β -dihydroxy-6 α-(2,2-dimethyl-7-methoxychromen-6-yl)-3,7-dioxabicyclo-[3.3.0]octanes (20) by diisobutyl aluminumhydride (DIBAL) reduction. The lactol was reacted with 2,6-dimethoxyphenol in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (Takano et al., 1988) in dry benzene under reflux to furnish the target compound 2 α-(2,6-dimethoxyphenoxy)-6 α-(2,2-dimethyl-7-methoxychromen-6-yl)-1 α-hydroxy-3,7-dioxabicyclo[3.3.0]octane (21). The stereochemistry was assigned from the chemical shift values by comparison with those of the stereoisomers of phrymarolins and

haedoxans. Thus, an insecticidal sesquilignan analogue possessing anti-juvenile hormone structure was synthesized from 3-benzyloxy-2,2-dimethyl-7-methoxychroman-6-carbaldehyde and β -vinyl- γ-butyrolactone through 16 steps in a 0.92% overall yield (Scheme 2, 3).

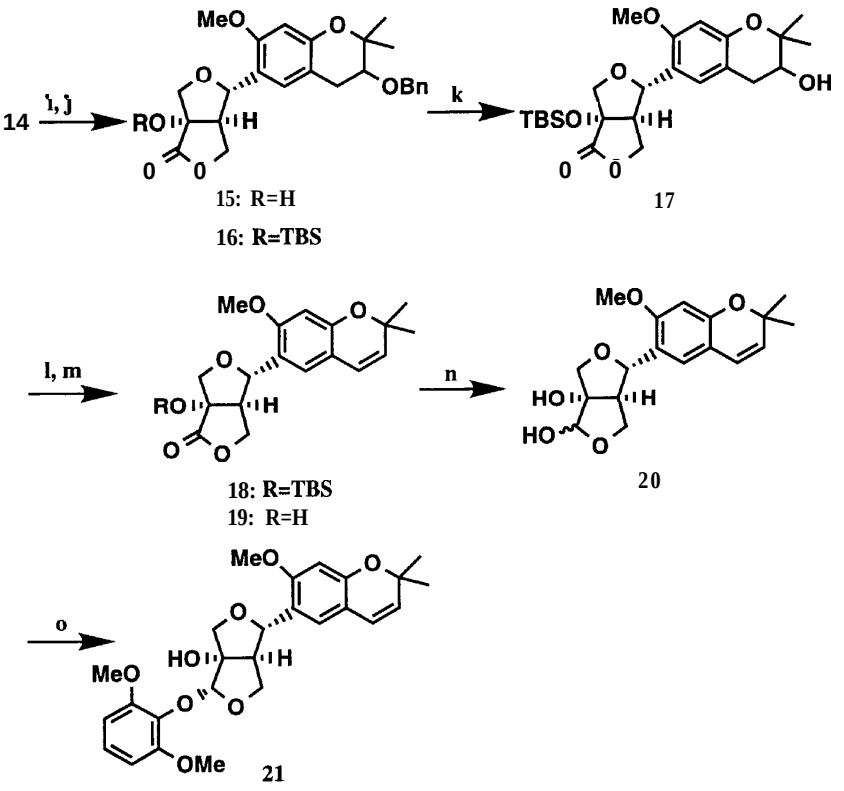


a) β-vinyl-γ-butyrolactone, KHMDS/THF; b) TBDMOTf, 2,6-lutidine/CH_2Cl_2;
c) $LiAlH_4$/THF; d) (i) cat. OsO_4, NMO/*aq*. acetone, *tert*-BuOH, (ii) $NaIO_4/H_2O$
e) Ag_2CO_3-celite/benzene; f) (i) MsCl, Et_3N/benzene, (ii) DBU/benzene;
g) cat. OsO_4, NMO/*aq*. acetone, *tert*-BuOH; h) TBAF/THF

Scheme 2. Synthesis of the chromeno-lignan analogue.

Bioassay

The hybrid compound of insecticidal lignan/antijuvenile hormonal chromene was assessed to the 4th instar larvae of the silkworm (*Bombyx mori*), and this compound was inactive at a dose level of 200 μg per larva.



i) CSA/CH_2Cl_2; j) TBDMSOTf, 2,6-lutidine/CH_2Cl_2; k) H_2, 20%Pd(OH)$_2$/EtOAc; l) (i) MsCl, DMAP/CH_2Cl_2; (ii) DBU/toluene; m) TBAF/THF; n) DIBAL/toluene o) 2,6-dimethoxyphenol, *cat.* PPTS/benzene;

Scheme 3. Synthesis of the chromeno-lignan analogue (cont.).

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