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Tetrahedron
Tetrahedron 62 (2006) 3739–3751

Synthesis and structure of 8-hydroxy-6-methoxy-3,7-dimethylisochromane and its analogues

Tsuneo Suzuki,[a,*] Kiyoshi Tanemura,[a] Takaaki Horaguchi[b] and Kimiyoshi Kaneko[c]

[a]*School of Dentistry at Niigata, The Nippon Dental University, Hamaura-cho 1-8, Niigata 951-8580, Japan*
[b]*Department of Chemistry, Faculty of Science, Niigata University, Ikarashi, Niigata 950-2181, Japan*
[c]*Faculty of Pharmaceutical Science, Niigata University of Pharmacy and Applied Life Science, 5-13-2 Kamishin'ei-cho, Niigata 950-2081, Japan*

Received 27 September 2005; accepted 10 January 2006

Available online 28 February 2006

Abstract—The title compound **1** was obtained by the reaction of alcohol **18** and triethyl orthoformate catalyzed by aluminum chloride followed by catalytic hydrogenation in good yield. Similarly, compounds **1** and **3** were obtained by intramolecular cyclization of MOM ether **19** with titanium(IV) chloride in moderate yields and isochromanes **1**, **3**, **26** and **27** by intramolecular cyclization of ether **20** with titanium(IV) chloride in high yields. The structures of compounds **1**–**3** were elucidated by analysis of spectroscopic data and chemical reactions. The mechanisms on the formation of **1** and **3** are discussed.

1. Introduction

Isochromane **1** is a toxic metabolite of *Penicillium steckii* Zalecki[1] and *Penicillium corylophilum* Dierckx.[2] Compound **1** was highly toxic to 1-day-old chickens (lethal dose 50%: 800 mg/kg)[1] and inhibited growth of etiolated coleoptiles of wheat by 100 and 43% at 10^{-3} and 10^{-4} M, respectively.[2] Hemiacetal **2** was produced by a marine-derived strain of *P. steckii* together with compound **1** and tanzawaic acids E and F.[3] Compound **1** and its regioisomer **3** were synthesized from dimethoxy isochromane **4** as shown in Scheme 1 and the phytotoxic activity of compounds **1** and **3** and their ethers and esters had been investigated in detail (Fig. 1).[4]

Numerous methods have been developed to synthesize isochromanes by using the C–O bond[5]—or the C–C bond[6]—forming cyclization. Practical reactions are shown in Scheme 1. Compound **4**, which was a precursor of isochromanes **1** and **3**, was afforded by heating of **5** with chloromethyl methyl ether and sodium hydride in tetrahydrofuran. Dimethyl ether **4** may be formed via methoxymethyl (MOM) ether of **5** under thermal conditions.[4] Chloroisochromane **7** was obtained by the reaction of **6** with chloromethyl methyl ether in the presence of Lewis acid.[7] Methoxyethoxymethyl (MEM) ethers **8a–d** were converted to isochromanes **9a–d** by intramolecular cyclization catalyzed by titanium(IV) chloride.[8] Compound **10** was obtained by catalytic hydrogenation of compound **11**, which was afforded by formylation of **12** with triethyl orthoformate.[9]

Synthesis and properties of 1-hydroxyisochromanes have been reported by several groups. These compounds were prepared by saponification of 5-formylmellein,[10] reduction of isocoumarins with hydrides,[11] reaction of benzocyclobutenols and aromatic aldehydes in the presence of lithium 2,2,6,6-tetramethylpiperidide,[12] photo-induced hetero Diels–Alder reaction of 2-methylbenzaldehydes,[13] oxidation of 2-hydroxyethyl-5-isopropylbenzyl alcohol[14] or 2-hydroxymethyl-1-(2′-hydroxyphenyl)naphthalene (**13**)[15] with non-activated manganese dioxide or pyridinium chlorochromate (PCC). In the case of compound **13**, a complex mixture of aldehyde **14**, hemiacetal **15** and bisacetal **16** was obtained by oxidation of **13** with PCC as illustrated in Scheme 2 and an equilibrium between compounds **14** and **15** was found.[15] Thus, it is suggested that compound **2** is synthetically equivalent to aldehyde **17**, which would be formed by formylation of the corresponding alcohol **18** (Fig. 2).

In this paper, we wish to describe the synthesis of the title compound **1** by the formylation of alcohol **18** followed by catalytic hydrogenation and by the intramolecular cyclization of MOM ethers **19** and **20** and discuss the reaction

Keywords: Heterocycles; Mycotoxin; Isochromane; Formylation; Catalytic reduction; Intramolecular cyclization.
* Corresponding author. Tel.: +81 25 267 1500; fax: +81 25 267 1134; e-mail: suzukit@ngt.ndu.ac.jp

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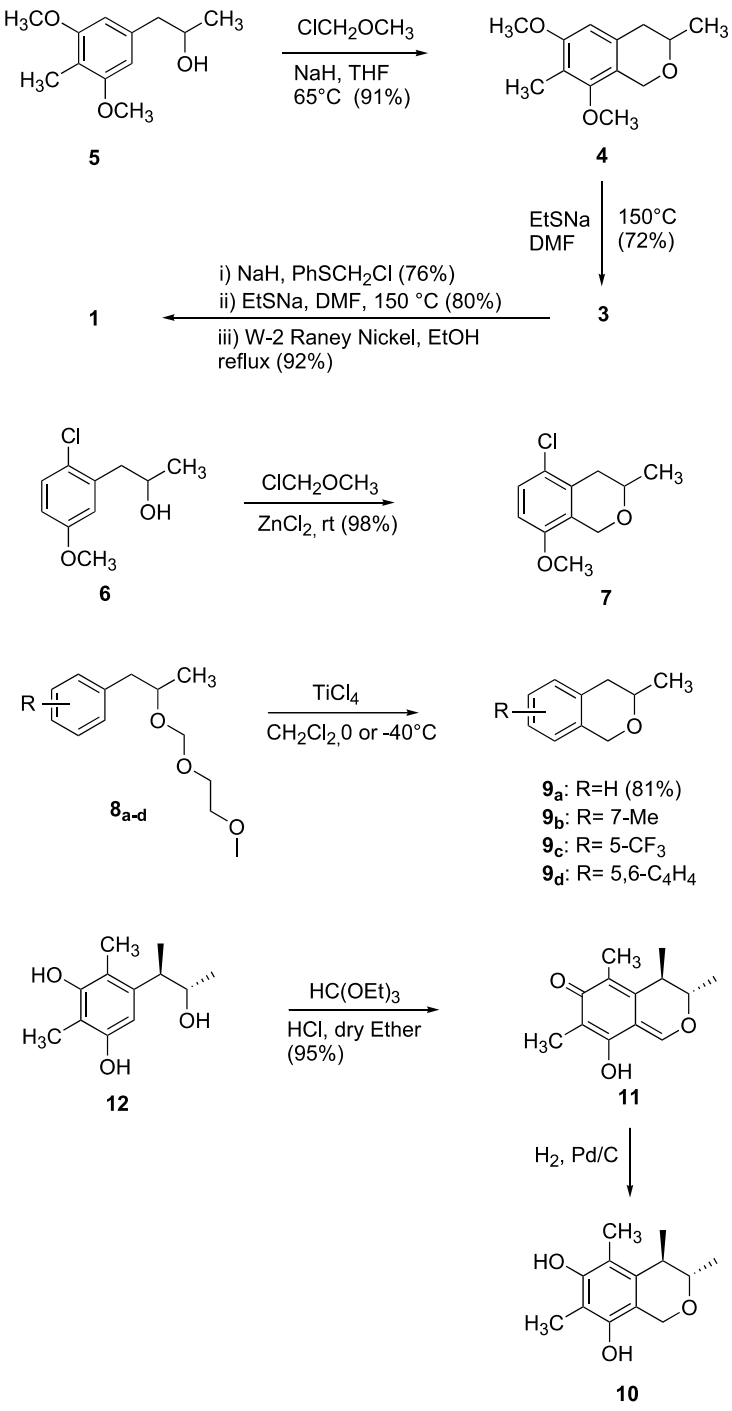
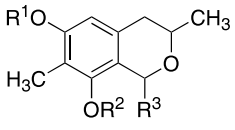
doi:10.1016/j.tet.2006.01.079



Scheme 1. Synthesis of isochromanes.



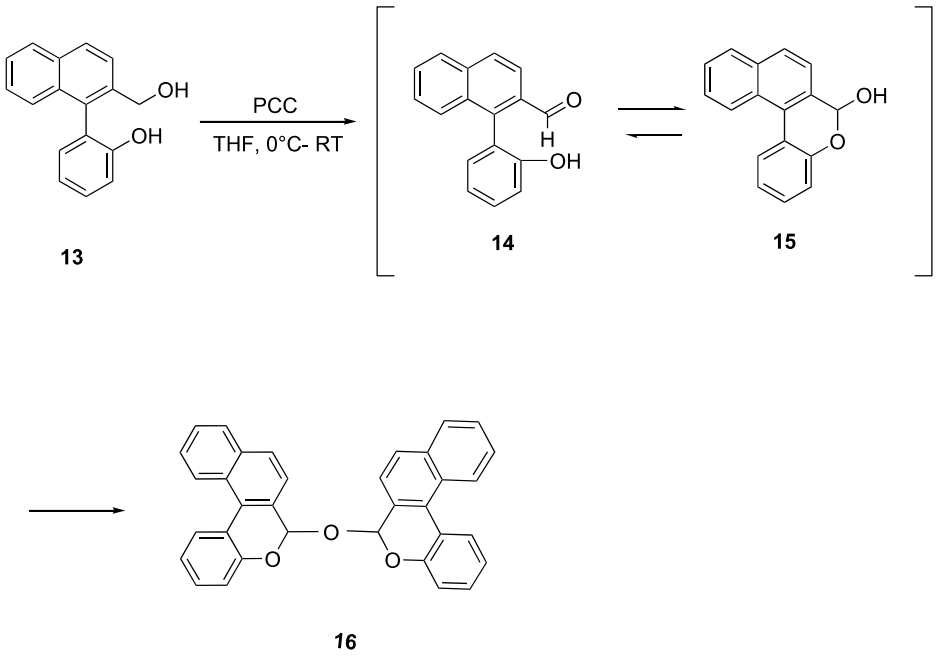
1: R^1=CH_3; R^2=R^3=H
2: R^1=CH_3; R^2=H; R^3=OH
3: R^1=R^3=H; R^2=CH_3
4: R^1=R^2=CH_3; R^3=H

Figure 1.

mechanisms. The structures of compounds **1**–**3** were determined by analysis of spectral data and chemical reactions, though compounds **1**–**3** have been reported till now.

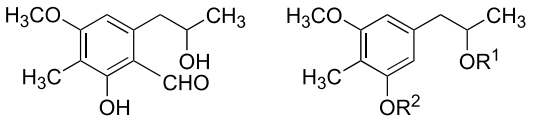
2. Results and discussion

Initially, the synthesis of isochromane **1** was examined as shown in Scheme 3. Ketone **21**[16] was reduced with lithium aluminum hydride in ether at 0 °C to give alcohol **18** in 99.0% yield. Compound **18** was subjected to formylation with triethyl orthoformate catalyzed by anhydrous aluminum chloride in dry toluene at −53 to −30 °C to give aldehyde **17** and bisacetal **22** in 48.9 and 42.6% yields, respectively (Scheme 3). The structure of aldehyde **17** was confirmed by ^{1}H NMR measurement. The ^{1}H NMR spectrum showed the two proton signals of C_1–CHO and C_2–OH at δ 10.21



13 14 15 16

Scheme 2. Syntheses of aldehyde **14**, hemiacetal **15** and bisacetal **16**.



17

18: R^1=R^2=H
19: R^1=MOM, R^2=H
20: R^1=R^2=MOM

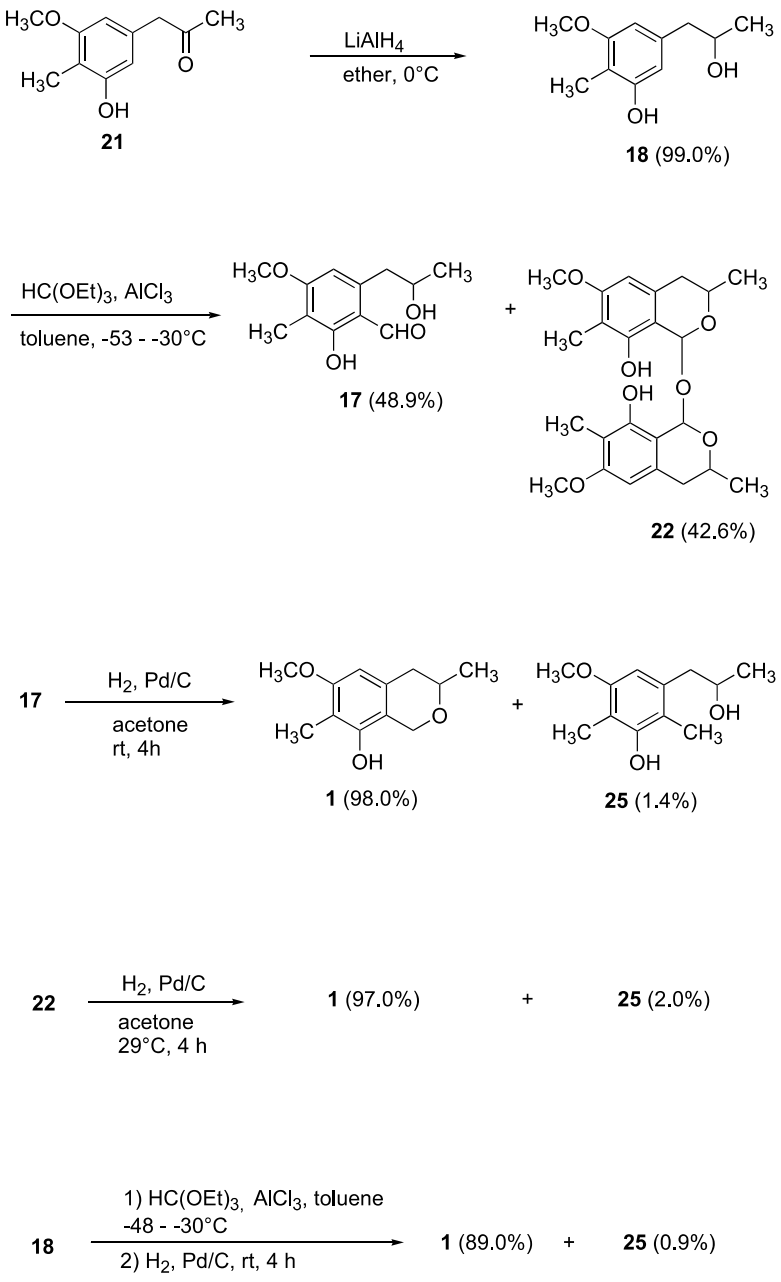
Figure 2.

and 12.65, respectively. The signal for C_2–OH was shifted to downfield because of intramolecular hydrogen bonding with C_1–CHO. The structure of bisacetal **22** was determined by the measurements of ^{1}H NMR, Mass and IR spectra and by the results of elemental analysis. The ^{1}H NMR spectrum showed the methine proton signal of C_1–H at 6.10 ppm. The mass spectrum did not show the molecular ion of **22** (M^+430) but contained two ions at *m*/*z* 223 and 207, which corresponded to the molecular formulas $C_{12}H_{15}O_4$ and $C_{12}H_{15}O_3$, respectively. Furthermore, the absorption band of formyl group was not found in the infrared absorption spectra. Bisacetal **22** was also obtained by heating of aldehyde **17** at 180 °C for 0.5 h.

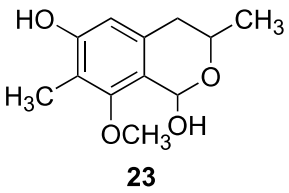
Hemiacetal **2** was not obtained by the formylation of **18** with triethyl orthoformate in the presence of aluminum chloride as described above. Compound **2** would be converted into aldehyde **17** or bisacetal **22** during the treatment of a reaction mixture with the usual way. For this reasons, detection of **2** by the spectroscopic method was carried out. By the ^{1}H NMR measurements of the residue, which was provided by a careful work-up of a reaction mixture, compound **2** was detected together with **17** in a ratio of 81:19, respectively. Hemiacetal **2** was changed partly to aldehyde **17** when a solution of **2** and **17** in acetone-d_6 was left at room temperature for several hours. The methine proton signal of C_1–H was located at 5.64 ppm and the C_1, C_6 and C_8 carbon signals appeared at 96.27, 159.05 and 153.67 ppm for **2** in acetone-d_6, respectively. Those NMR data were not identical with the corresponding signals of an authentic sample obtained from *P. steckii* reported in the literature[3] (C_1–H at 5.51 ppm; C_1, C_6 and C_8 at 95.4, 155.1 and 155.2 ppm, respectively, in methanol-d_4). This compound must be assigned to compound **23** (Fig. 3) because the ^{13}C NMR peaks of C_6 and C_8 carbon atoms were similar to that of **3** and the differences of chemical shifts of C_8 and C_6 carbon atoms was 0.1 ppm as described below. As shown in Scheme 4, aldehyde **17** might be produced by hydrolysis of diethyl acetal **24**, which was obtained exclusively from **18** via intermediate **A** by *ortho*-formylation.[17] Compound **2** is formed by intramolecular hemiacetalization of **17** and dimerized to bisacetal **22**.[15]

To synthesize isochromane **1**, compounds **17** and **22** were hydrogenated as shown in Scheme 3. In the case of **17**, compounds **1** and dimethyl alcohol **25** were obtained in 98.0 and 1.4% yields, respectively, by treatment of **17** with hydrogen in the presence of 10% palladium on charcoal in acetone at room temperature for 4 h. When compound **22** was treated with hydrogen in the presence of 10% palladium on charcoal in acetone at room temperature for 4 h, compounds **1** and **25** were obtained in 97.0 and 2.0% yields, respectively. Additionally, a crude mixture of **2**, **17** and **22** in a ratio of 70:15:15, which was obtained from the reaction of **18** with triethyl orthoformate catalyzed by $AlCl_3$, was stirred in acetone with 10% palladium on charcoal under hydrogen atmosphere at room temperature for 4 h, compounds **1** and **25** were obtained in 89.0 and $<$1.0% yields, respectively. Thus, compound **1** was obtained from **18** in good yield in two steps without purification of the reaction products **2**, **17** and **22**.

The reaction pathways for the formation of compound **1** and **25** by hydrogenation of **2**, **17** and **22** with palladium on charcoal are illustrated in Scheme 5. Hemiacetal **2**, which was formed by intramolecular hemiacetalization of **17** or by



Scheme 3. Synthesis of isochromane **1** and dimethyl alcohol **25**.

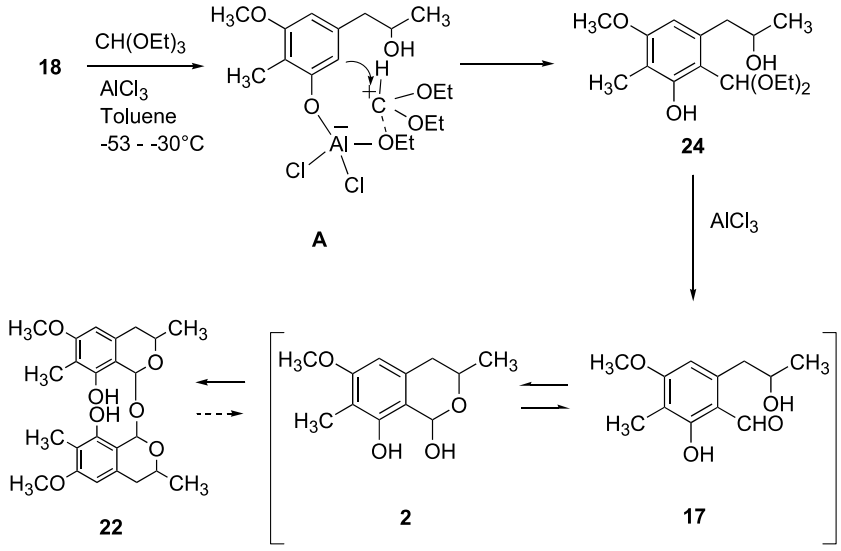


23

Figure 3.

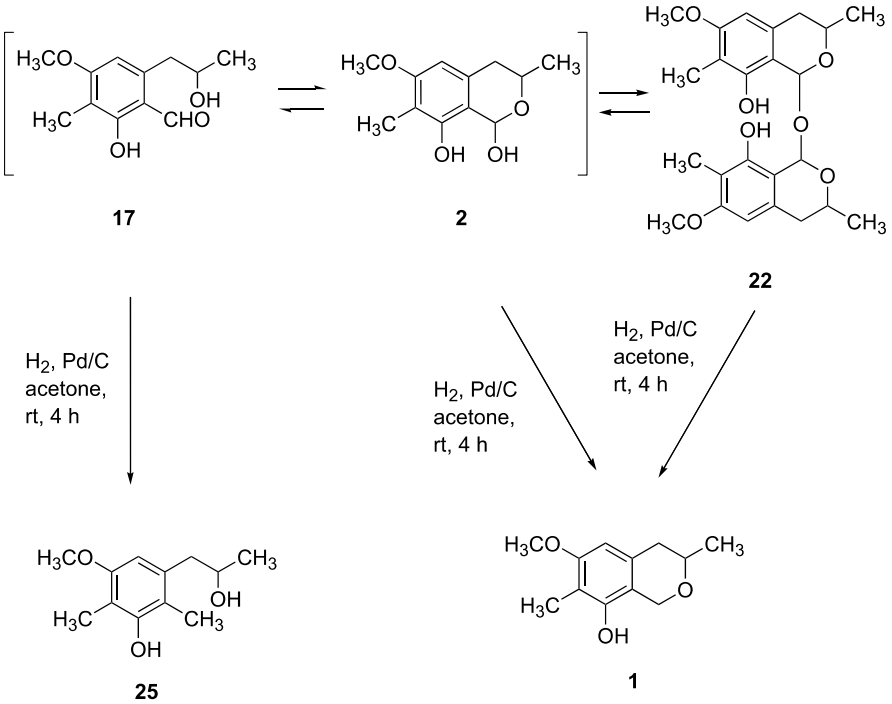
hydrolysis of **22**, is a common intermediate for the production of **1** since isochromane **1** was produced predominantly by catalytic reduction of crude **2**, **17** and **22**, respectively. In the case of **22**, compound **1** would be afforded by catalytic reduction of **22**. On the other hand, dimethyl alcohol **25** must be formed by catalytic reduction of **17**.[18] The structure of **1** was described below.

Next, intramolecular cyclization[8a] of MOM ether **19** was examined to synthesize compound **1** and its regioisomer **3** and to elucidate the structures of **1** and **3**, respectively, since the ^{1}H and ^{13}C NMR spectra of **1**, which was obtained above, did not agree with those of an authentic sample reported in the literature.[1,4] Compounds **19** was obtained by methoxymethylation of **18** with chloromethyl methyl ether and *N*-ethyldiisopropylamine in 39.3% yields together with ether **20** (55.9%) as shown in Scheme 6. When MOM ether **19** was treated with 0.7 equiv of titanium(IV) chloride at −49 °C for 15 min, a mixture of compounds **1** and **3** was obtained in 66.1% yield (the ratio of **1** and **3** was 79:21) (Scheme 6). The ^{1}H and ^{13}C NMR data and selected HMBC correlations for compounds **1** and **3** are summarized in Tables 1 and 2, respectively. The assignment of ^{1}H and ^{13}C NMR spectra of **1** and **3** was

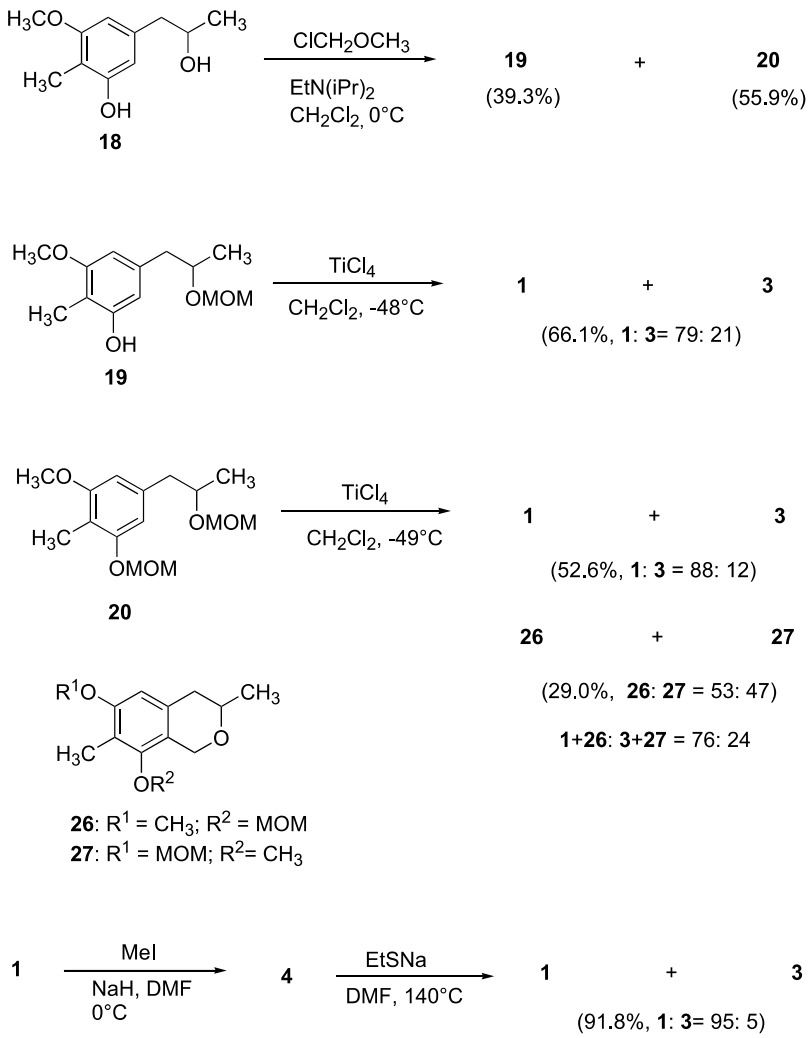


Scheme 4. Reaction pathways for the formation of **2**, **17** and **22** by the formylation of **18**.

confirmed by comparison with the results of NOESY and HMBC experiments, respectively (Figs. 4 and 5). The signal of three protons of methoxy group was located at 3.73 ppm for **1** and at 3.61 ppm for **3**. The ^{13}C NMR showed that the signals of C_6 and C_8 carbon atoms for **1** appeared at 157.68 and 151.60 ppm, respectively. Whereas, the corresponding signals for **3** were 155.91 and 156.73 ppm, respectively. The difference of chemical shift of C_6 and C_8 carbon atoms was 6.08 ppm for **1** and that was 0.82 ppm for **3**. The carbon atom bearing methoxy group was appeared at downfield than that possessing hydroxy group in ^{13}C NMR spectra. The NOESY experiments of **1** showed that three protons of methoxy group attached at C_6 carbon atom had the correlation with aromatic hydrogen attached at C_5 carbon atom (Fig. 4). On the other hand, the correlation between three protons of methoxy group at C_8 carbon atom and two protons at C_1 carbon atom for **3** was observed as shown in Figure 5. It was indicated by HMBC spectra of **1** and **3** that three protons of methoxy group exhibited long-range $^1H/^{13}C$ correlation with C_6 carbon atom for **1**, while the corresponding protons had the same correlation with C_8 carbon atom for **3**. Additionally, the lanthanide induced shifts (LIS) experiments supported the structures of **1** and **3** as shown in Table 3. The large LIS values were observed for C_1–H (2.44 ppm) and C_3–H (2.10 ppm) for **1**. On the other hand, in the case of **3**, C_5–H and C_7–CH_3 had large LIS values of 1.83 and 1.39 ppm, respectively.



Scheme 5. Reaction pathways for the catalytic reduction of compounds **2**, **17** and **22** to isochromane **1** and dimethyl alcohol **25**, respectively.



Scheme 6. Synthesis of MOM ethers **19** and **20** and isochromanes **1**, **3**, **26** and **27**.

Table 1. ^{1}H and ^{13}C NMR data and selected HMBC correlations for isochromane **1** in CD_3CN[a]

C/H	^{13}C	^{1}H	HMBC (H→C)
1	65.10	4.50dt (15.0, 1.5, $H_{a'}$) 4.75d (15.0, $H_{e'}$)	
3	71.19	3.66ddq (10.5, 3.2, 6.3)	C_1–H
4	36.46	2.50dd (16.0, 10.5, $H_{a'}$) 2.60dd (16.0, 3.2, $H_{e'}$)	C_3–CH_3, C_5–H
4a	133.18		C_1–H
5	103.74	6.27s	C_4–H
6[b]	157.68		C_6–OCH_3, C_7–CH_3
7	110.20		C_5–H, C_8–OH
8[c]	151.60		C_1–H, C_7–CH_3
8a	115.67		C_5–H, C_8–OH, C_4–H, C_1–H
C_3–CH_3	21.81	1.24d (6.3)	
C_6–OCH_3[d]	56.18	3.73s	
C_7–CH_3	8.45	1.99s	
C_8–OH		6.02s	

[a] NMR spectra were recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Acetonitrile-d_3 was used as an internal reference instead of TMS (^{1}H NMR: δ 1.93 (CHD_2CN), ^{13}C NMR: δ 1.30).
[b] See Ref. 1. The signal of C_6 carbon atom appeared at 153.69 ppm in $CDCl_3$.
[c] See Ref. 1. The signal of C_8 carbon atom appeared at 152.58 ppm in $CDCl_3$.
[d] See Ref. 1. The signal of three protons of methoxy group appeared at 3.66 ppm in $CDCl_3$.

Table 2. ^{1}H and ^{13}C NMR data and selected HMBC correlations for isochromane **3** in CD_3CN[a]

C/H	^{13}C	^{1}H	HMBC (H→C)
1	65.62	4.57dt (14.9, 1.4, $H_{a'}$) 4.79d (14.9, $H_{e'}$)	
3	72.02	3.66ddq (10.7, 3.2, 6.1)	C_1–H
4	36.71	2.47dd (16.4, 10.7, $H_{a'}$) 2.58dd (16.4, 3.2, $H_{e'}$)	C_3–CH_3, C_5–H
4a	120.82		C_1–H
5	111.93	6.33s	C_4–H, C_6–OH
6[b]	155.91		C_7–CH_3
7	116.68		C_5–H, C_6–OH
8[c]	156.73		C_1–H, C_7–CH_3 C_8–OCH_3
8a	134.26		C_4–H
C_3–CH_3	22.48	1.23d (6.1)	
C_6–OH	56.18	6.68s	
C_7–CH_3	9.47	2.03s	
C_8–OCH_3[d]	61.18	3.61s	

[a] NMR spectra were recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Acetonitrile-d_3 was used as an internal reference instead of TMS (^{1}H NMR: δ 1.93 (CHD_2CN); ^{13}C NMR: δ 1.30).
[b] See Ref. 4a. The signal of C_6 carbon atom appeared at 149.9 ppm in $CDCl_3$.
[c] See Ref. 4a. The signal of C_8 carbon atom appeared at 156.4 ppm in $CDCl_3$.
[d] See Ref. 4a. The signal of three protons of methoxy group appeared at 3.79 ppm in $CDCl_3$. Chloroform was used as an internal reference instead of TMS (^{1}H NMR: δ 7.26).

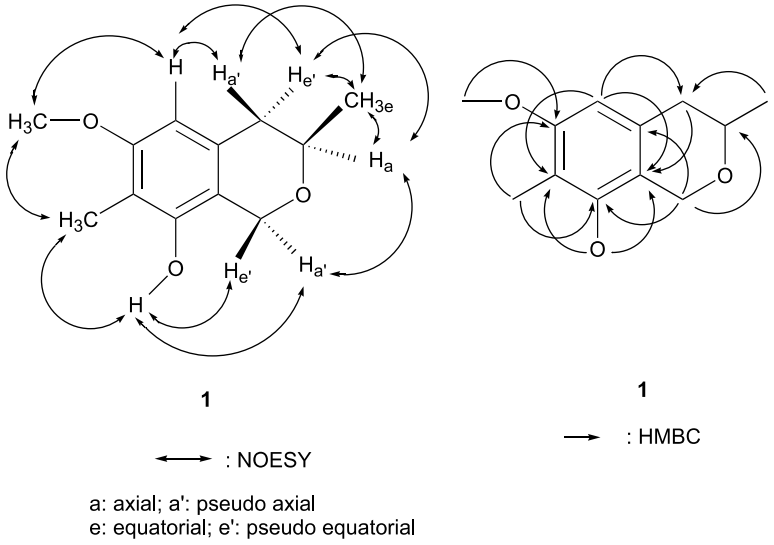


Figure 4. The selective NOESY and HMBC correlations for **1**.

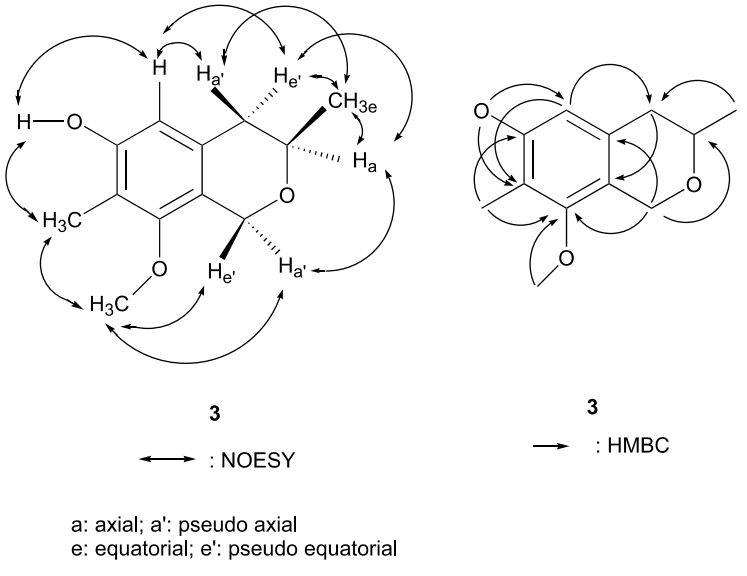
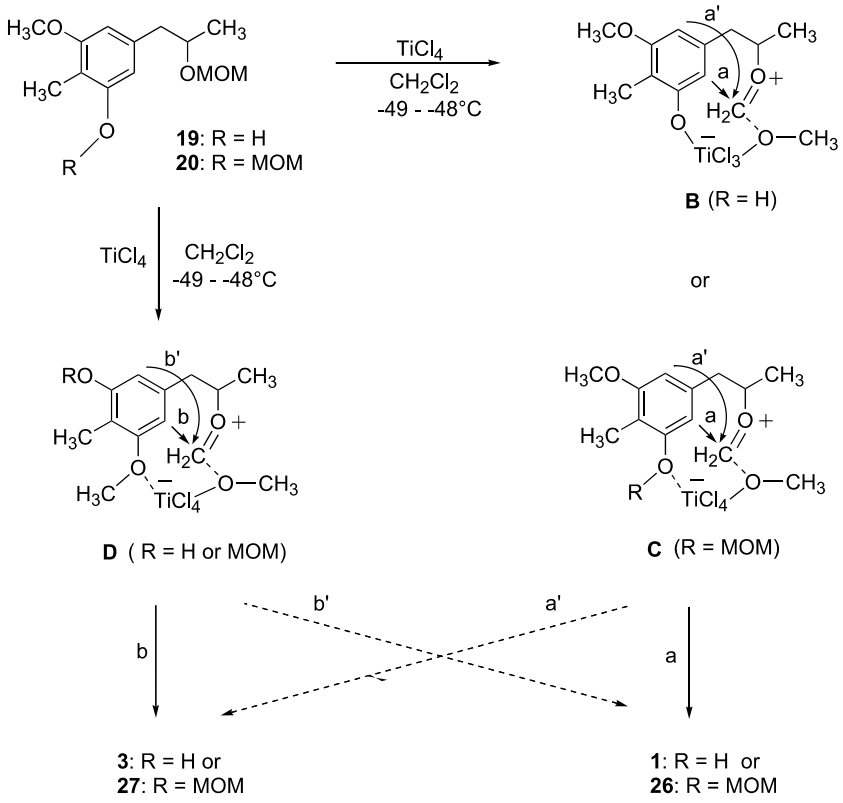


Figure 5. The selective NOESY and HMBC correlations for **3**.

Table 3. Eu(dpm)$_3$ induced shifts (ppm) of isochromanes **1** and **3**[a]

Compound	Proton (shift value/ppm)
1	C_1–H (2.44), C_3–H (2.10), C_3–CH_3 (1.16), C_4–H (1.09), C_5–H (0.31), C_6–OCH_3 (0.27), C_7–CH_3 (0.57), C_8–OH (−[b])
3	C_1–H (0.89), C_3–H (−[c]), C_3–CH_3 (0.78), C_4–H (0.40), C_5–H (1.83), C_6–OH (−[b]), C_7–CH_3 (1.39), C_8–OCH_3 (1.17)

[a] Shift studies were carried out by stepwise addition of known amounts of Eu(dpm)$_3$ to ca. 0.37–0.27 M solutions of substrates in $CDCl_3$. The LIS data were obtained by graphic extrapolation of the observed shifts to a 1:1 shift reagent–substrate ratio.
[b] Signals of hydroxyl group were disappeared by the addition of Eu(dpm)$_3$.
[c] A signal of C_3–H was not measured as it was week and multiple by addition of Eu(dpm)$_3$.



Scheme 7. Plausible mechanisms for the formation of isochromanes **1** and **3** or their MOM ethers **26** and **27**.

Those results indicate that the europium(III) atom is coordinated to the oxygen of C_8 hydroxy group for **1** and to the oxygen of C_6 hydroxy group for **3**, respectively, though the LIS values of phenolic protons were not obtained.

Compounds **1** and **3** were tried to synthesize by an alternate route (Scheme 6). Dimethoxyisochromane **4**, which was obtained by methylation of compound **1** with MeI was treated with sodium ethyl sulfide in *N*,*N*-dimethyformamide (DMF) at 140 °C for 3 h to give a mixture of compounds **1** and **3** (**1**:**3**=95:5) in 91.8% yield.[4,19] Compounds **1** and **3** were identified by comparison of their spectra to those of authentic samples obtained above. The sterically more-hindered C_8 methoxy group was selectively demethylated though the reason is not clear.[†]

Although the structure of compound **1** was elucidated by the substituent effects of hydroxy group to the ^{13}C chemical shifts of **1**,[1] above results indicated that the isochromane, which was obtained from the metabolite of *P. steckii*[1,3] and *P. corylophilum*[2] is compound **3** and the 1-hydroxyisochromane, which was separated from the culture of *P. steckii*[3] is compound **23**. Similarly, isochromanes **1** and **3**, which are shown in Scheme 1 must be corrected to compound **3** and **1**, respectively.

Finally, intramolecular cyclization of ether **20** was carried out by using equimolecular amount of titanium(IV) chloride as catalyst in dry dichloromethane (Scheme 6).[8a] Mixtures of compounds **26** and **27** (29.0%; **26**:**27**=53:47) and **1** and **3** (52.6%; **1**:**3**=88:12) were obtained. Compound **1** or **3** must be obtained by deprotection of MOM ether **26** or **27** with $TiCl_4$. The structures of **26** and **27** were identified by the comparison of their spectra to those of authentic samples obtained by the reaction of **1** and **3** with chloromethyl methyl ether and *N*-ethyldiisopropylamine in dichloromethane, respectively. Plausible mechanisms for the production of **1**, **3**, **26** and **27** are illustrated in Scheme 7. In the case of **19** (R=H), the oxocarbenium intermediate **B** (R=H) must be produced by the interaction of titanium(IV) chloride with the two oxygens of MOM group and C_8 hydroxyl group. On the other hand, the oxocarbenium

[†] Cutler et al.[4] showed that demethylation of compound **4** with sodium ethyl sulfide gave compound **3** because nucleophilic substitution occurred at the less sterically hindered C_6 methoxyl carbon atom (Scheme 1).

intermediate **D** (R=H) must be formed by the interaction of $TiCl_4$ with the two oxygens of MOM group and C_6 methoxy group.[20] By the intramolecular nucleophilic attack of aromatic ring to the carbon atom of intermediates **B** and **D**, compounds **1** and **3** would be afforded, respectively. In the case of **20** (R=MOM), the oxocarbenium intermediates **C** and **D** (R=MOM) were formed by the interactions between $TiCl_4$ with two oxygen atoms of two MOM groups and MOM group and C_6 methoxy group, respectively. MOM ethers **26** and **27** were produced by the intramolecular nucleophilic attack of aromatic ring to the carbon atom of intermediates **C** and **D**, respectively. Compound **1** or **26** would be produced predominantly via path a, whereas compound **3** or **27** would be produced via path b as the yield of **1** or **1** and **26** was larger than that of **3** or **3** and **27** for the reaction of **19** or **20** with $TiCl_4$.[21]

Thus, isochromane **1** was synthesized from the reaction of alcohol **18** with triethyl orthoformate in the presence of $AlCl_3$ followed by catalytic reduction of compounds **2**, **17** and **22** with or without purification in good yields, respectively. On the other hand, mixtures of **1** and **3** or of **1**, **3**, **26** and **27** were obtained from cyclization of MOM ether **19** or ether **20** by treatment with $TiCl_4$, respectively. The structures of **1**–**3** were determined by chemical reaction, ^1H and ^{13}C NMR spectra and NOESY, HMBC, and LIS experiments. The isochromane and the 1-hydroxyisochromanes, which were obtained from the culture of *P. steckii*[1,3]or *P. corylophilum*[2] were 6-hydroxyisochromane **3** and its 1-hydroxy compound **23**, respectively. The structure of demethylated compound obtained by the reaction of **4** with sodium ethyl sulfide in DMF was assigned to compound **1** by comparison with an authentic sample.

3. Experimental

3.1. General

Melting points were determined with a Shimadzu MM-2 micro melting point determination apparatus and are uncorrected. IR spectra were recorded on a Hitachi I-3000 spectrophotometer. ^1H NMR spectra were measured with a Hitachi R-24B (60 MHz), a Hitachi R-1200 (60 MHz), a Varian Unity 500plus (500 MHz), or a JEOL ECA 500 (500 MHz) NMR spectrometer. ^{13}C NMR spectra were measured with a Varian Unity 500plus (125 MHz), or a JEOL ECA 500 (125 MHz) NMR spectrometer. Tetramethylsilane was used as internal standard unless otherwise stated. Mass spectra were recorded on a JEOL JMS-AX505WA mass spectrometer using electron-impact mode (70 eV). Shibata glass tube oven model GTO-350RS was employed for heating of aldehyde **17**. Thin-layer chromatography was performed on pre-coated Kieselgel 60 F_{254} plates (Merck) and spots were visualized under UV light. Unless otherwise stated silica gel (Wakogel C-200, Wako) was employed for the column chromatography as the packing materials and anhydrous sodium sulfate as the drying agent. DMF, ethanol and toluene were dried according to the reported procedures.[16] Dichloromethane was refluxed with calcium hydride, distilled and stored over molecular sieves 4 Å under an argon atmosphere. Ether refers to diethyl ether. Tris (2,2,6,6-tetramethyl-3,5-heptanedionato)europium(III) (>95%) was purchased from Tokyo Kasei Kogyo and was used without further purification. Ketone **21** was prepared according to the reported procedure.[16]

3.1.1. 1-(3-Hydroxy-5-methoxy-4-methylphenyl)-2-propanol (18). To a stirred suspension of lithium aluminum hydride (280 mg, 7.38 mmol) in dry ether (66.5 mL) was added a solution of ketone **21** (779 mg, 4.01 mmol) in ether (17.0 mL) dropwise at 0 °C for 32 min. After being stirred for 30 min at 0 °C, the reaction was quenched by addition of 3 M HCl solution (60 mL). Products were extracted with 100 mL of ether twice and the combined organic layer was washed with water and dried over anhydrous magnesium sulfate. By evaporation of solvents in vacuo, the residue (891 mg) was obtained. The residue was chromatographed on silica gel (30 g, Kieselgel 60, Merck). By elution with hexane–acetone (6/1) compound **18** (780 mg, 99.0%) was obtained as colorless crystals, mp 84–85 °C (ether–hexane); IR (KBr): ν_{max} 3404 (OH), 3160 (OH), 2972, 2932, 2832, 1622, 1598, 1518, 1458, 1418, 1232, 1114, 812 cm^{-1}; ^1H NMR (CD_3COCD_3, 500 MHz): δ 1.12 (3H, d, J=6.5 Hz, –CH(OH)C*H*$_3$), 2.01 (3H, s, C_4–CH_3), 2.52 (1H, dd, J=13.5, 6.5 Hz, –C*H*$_2$CH(OH)–), 2.66 (1H, dd, J=13.5, 6.7 Hz, –C*H*$_2$CH(OH)–), 3.60 (1H, d, J=5.0 Hz, –CH(O*H*)–), 3.80 (3H, s, C_5–OCH_3), 3.94 (1H, m, –C*H*(OH)–), 6.35 (1H, s, C_2–H or C_6–H), 6.38 (1H, s, C_2–H or C_6–H), 8.04 (1H, s, C_3–OH); ^{13}C NMR (CD_3COCD_3, 125 MHz): δ 8.32, 23.34, 46.89, 55.75, 69.07, 104.12, 109.89, 110.32, 138.65, 156.41, 159.38. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.31; H, 8.22.

3.1.2. 2-Hydroxy-6-(2-hydroxypropyl)-4-methoxy-3-methylbenzaldehyde (17) and 1,1′-oxydi(8-hydroxy-6-methoxy-3,7-dimethylisochromane) (22). To a stirred suspension of anhydrous aluminum chloride (302 mg, 2.15 mmol) and dry toluene (2.6 mL) at −53 °C was added dropwise a solution of alcohol **18** (249 mg, 1.27 mmol) and triethyl orthoformate (4.2 mL, 25.34 mmol) in dry toluene (2.6 mL) over a period of 20 min. The reaction mixture was allowed to warm to −30 °C over a period of 30 min and then stirred for another 35 min at the same temperature. After addition of 6 M HCl solution (7 mL), cooling bath was removed and the resulting mixture was stirred at room temperature for 5 min and then water (10 mL) was added and stirring was continued at room temperature for an another 10 min. The reaction mixture was extracted with ether (100 mL) three times and combined organic layer was washed with brine and dried with anhydrous magnesium sulfate. Solvents were removed by a rotary evaporator at 60 °C to gave 280.1 mg of pale yellow crystals. The crystals were treated with a small portion of ether and insoluble materials were removed by filtration. By fractional recrystallization of insoluble materials from benzene, bisacetal **22** (116 mg, 42.6%) was obtained as colorless short needles and aldehyde **17** (24.4 mg, 8.6%) as colorless crystals, respectively. The residue obtained by concentration of filtrate and the liquor of fractional recrystallization was chromatographed on silica gel (30 g). By elution with benzene–ether (volume ratio was varied from 10/1 to 4/1) followed by recrystallization from benzene, aldehyde **17** (114.5 mg, 40.3%) was afforded.

Compound **17** was transformed to bisacetal **22** by heating at 180 °C for 30 min in a glass tube oven. The IR spectrum of heated compound was same to that of bisacetal **22** obtained above.

Compound **17**: colorless crystals, mp 125–127 °C (benzene); IR (KBr): ν_{max} 3260 (OH), 2980, 2956, 2924, 2904, 2856, 1630, 1574, 1494, 1416, 1404, 1364, 1304, 1256, 1142, 1006, 932, 910, 822, 794, 724, 566 cm^{-1}; ^1H NMR (CD_3COCD_3, 500 MHz): δ 1.22 (3H, d, J=5.5 Hz, $CHCH_3$), 1.99 (3H, s, C_3–CH_3), 3.00 (1H, dd, J=14.0, 5.0 Hz, Ar-CH_2–), 3.09 (1H, dd, J=14.0, 7.5 Hz, Ar-CH_2–), 3.87 (1H, d, J=4.5 Hz, –CH(O*H*)–, disappeared by D_2O), 3.93 (3H, s, C_4–OCH_3), 3.99 (1H, m, –C*H*(OH)–), 6.56 (1H, s, C_5–H), 10.21 (1H, s, CHO), 12.65 (1H, s, C_2–OH, disappeared by D_2O); ^{13}C NMR (CD_3COCD_3, 125 MHz): δ 7.28, 23.81, 41.78, 56.30, 69.40, 106.49, 111.24, 114.64, 145.23, 163.26, 164.67, 195.92; MS: *m/z* (%) 224 (M^+, 49), 206 (61), 191 (58), 180 (98), 179 (100). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found C, 64.41; H, 7.20.

Compound **22**: colorless short needles from benzene, mp 258–260 °C; IR (KBr): ν_{max} 3436 (OH), 3012, 2972, 2928, 2848, 1612, 1590, 1456, 1422, 1330, 1298, 1136, 1106, 980, 920, 876, 844, 830, 804 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz): δ 1.33 (6H, d, J=6.5 Hz, C_3–CH_3×2), 2.25–2.29 (2H, m, C_4–$H_{a'}$×2), 2.43–2.48 (2H, m, C_4–$H_{e'}$×2), 2.77 (6H, s, C_7–CH_3×2), 3.39 (6H, s, C_6–OCH_3×2), 4.62–4.69 (2H, m, C_3–H×2), 6.10 (2H, s, C_1–H×2), 6.16 (2H, s, C_5–H×2). MS: *m/z* (%) 223 (46), 207 (21), 206 (100), 191 (53), 179 (37), 163 (32), 91 (31). Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 67.00; H, 6.83.

3.1.3. Detection of 1,8-dihydroxy-6-methoxy-3,7-dimethylisochromane (2). Alcohol **18** (124 mg, 0.63 mmol) was formylated with triethyl orthoformate (2.1 mL, 12.67 mmol) in the presence of 95% aluminum chloride (156 mg, 1.11 mmol) and the reaction mixture was worked up in a manner similar to that described above. The extracts were concentrated by a rotary evaporator at 60 °C until a small amount of liquor was remained and then volatile materials were removed at room temperature in vacuo to give the residue (152.4 mg) as oily crystals. The residue was dissolved in acetone-d_6 (1.2 mL) and insoluble compound **22** (6.9 mg, 5.0%) was removed by filtration. A ^1H NMR analysis of the filtrate showed that a ratio of **2** and **17** was 81:19, respectively. After the acetone-d_6 solution in a ^1H NMR tube was allowed to stand at room temperature for 7.67 h, the ratio of **2** and **17** was 67:33, respectively. Hemiacetal **2** was changed partly to **17** in acetone-d_6 by standing at room temperature.

Compound **2**: ^1H NMR (CD_3COCD_3, 500 MHz): δ 1.28 (3H, d, J=6.0 Hz, $CHCH_3$), 2.02 (3H, s, C_7–CH_3), 2.49 (1H, dd, J=16.0, 11.0 Hz, Ar-CH_2–), 2.60 (1H, dd, J=16.0, 3.0 Hz, Ar-CH_2–), 3.77 (3H, s, C_6–OCH_3), 4.08 (1H, ddq, J=11.0, 6.0, 3.0 Hz, C_3–H), 5.64 (1H, s, C_1–H), 6.29 (1H, s, C_5–H), 6.94 (1H, s, C_1–OH); ^{13}C NMR (CD_3COCD_3, 125 MHz): δ 8.31 (C_7–CH_3), 20.97 (C_3–CH_3), 36.64 (C_4), 55.80 (CH_3O), 64.46 (C_3), 96.27 (C_1), 102.48 (C_5), 111.54 (C_7), 114.39 (C_{4a} or C_{8a}), 134.22 (C_{4a} or C_{8a}), 153.67 (C_8), 159.05 (C_6).

3.1.4. 8-Hydroxy-6-methoxy-3,7-dimethylisochromane (1). *Method A*. A mixture of aldehyde **17** (74 mg, 0.33 mmol), 10% palladium on charcoal (27 mg) and 15.0 mL of acetone was stirred under hydrogen atmosphere at room temperature for 4 h. After removal of insoluble materials by filtration, the filtrate was concentrated under reduced pressure to give the residue (76.1 mg). The residue was chromatographed on silica gel (30 g). By elution with benzene–ether (10/1) isochromane **1** (67.7 mg, 98.0%) was obtained as colorless cubic crystals, mp 153.0–155.3 °C (benzene); R_f: 0.31 (hexane/ether=2:1); IR (KBr): ν_{max} 3324 (OH), 3004, 2972, 2928, 2844, 1622, 1594, 1504, 1470, 1456, 1336, 1274, 1256, 1224, 1204, 1130, 1070, 1052, 918, 856, 820, 756, 608, 566, 488 cm^{-1}; MS: *m/z* (%) 208 (M^+, 100), 207 (54), 166 (33), 165 (100). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.27; H, 7.73.

^1H and ^{13}C NMR data of **1** are summarized at Table 1.

Next, by elution with benzene–ether (5/1) dimethyl alcohol **25** (1.0 mg, 1.4%) was obtained as colorless solid, mp 91.0–93.5 °C; IR (KBr): ν_{max} 3508 (OH), 3420 (OH), 2968, 2928, 2848, 1616, 1588, 1506, 1470, 1418, 1332, 1232, 1128, 1018, 934, 840, 820 cm^{-1}; ^1H NMR (CD_3COCD_3, 60 MHz): δ 1.13 (3H, d, J=6.0 Hz, –CH(OH)CH_3), 2.05 (3H, s, C_2–CH_3 or C_4–CH_3), 2.12 (3H, s, C_2–CH_3 or C_4–CH_3), 2.60–2.77 (2H, m, –CH_2CH(OH)–), 3.44 (1H, d, J=5.4 Hz, –CH(O*H*)–), 3.73 (3H, s, C_5–OCH_3), 3.94 (1H, m, –C*H*(OH)–), 6.38 (1H, s, C_6–H), 6.99 (1H, s, C_3–OH). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found C, 68.61; H, 8.70.

Method B. A mixture of bisacetal **22** (51 mg, 0.12 mmol), 10% palladium on charcoal (18 mg) and acetone (10.0 mL) was stirred under hydrogen atmosphere at room temperature for 4 h. The reaction mixture was worked up in a manner similar to that described above and isochromane **1** (47.6 mg, 97.0%) and dimethyl alcohol **25** (1.0 mg, 2.0%) were prepared, respectively.

Method C. A solution of compound **18** (124 mg, 0.63 mmol) and triethyl orthoformate (2.1 mL, 12.67 mmol) in toluene (1.3 mL) was added dropwise with stirring to a suspension of aluminum chloride (157 mg, 1.12 mmol) in toluene (1.3 mL) at −48 °C under an argon atmosphere. The reaction was carried out similarly as described for the preparation of compounds **17** and **22** and a reaction mixture was worked up in a manner similar to that described for the detection of compound **2** to give the residue (171.6 mg). A ratio of **2** and **17** (82:18) and the yield of **22** (20.5 mg, 15%) in the residue was determined as described for the detection of **2**. A ratio of **2**, **17** and **23**, which was calculated from the above results, was about 70:15:15, respectively. The residue was stirred with 10% Pd on charcoal (60 mg) for 4 h in acetone (26.0 mL) under hydrogen atmosphere without purification. The reaction mixture was worked up in a manner similar to that described for the catalytic hydrogenation of **17** and isochromane **1** (117.5 mg, 89.0%) and dimethyl alcohol **25** (1.2 mg, 0.9%) were obtained, respectively.

3.1.5. 6,8-Dimethoxy-3,7-dimethylisochromane (4). A suspension of isochromane **1** (181 mg, 0.87 mmol), 60% sodium hydride (53 mg, 1.33 mmol) and dry DMF

(12.5 mL) was stirred at 0 °C for 5 min under an argon atmosphere and then methyl iodide (0.54 mL, 8.67 mmol) was added by a syringe. After stirring at the same temperature for 2 h, the reaction mixture was quenched with 3 M HCl solution (30 mL) and extracted with dichloromethane (50 mL) three times. The combined organic layer was washed with brine and dried. The residue obtained by evaporation of solvents in vacuo was chromatographed on silica gel (35 g, Kieselgel 60, Merck). By elution with hexane–ether (15/1) compound **4** (187.6 mg, 97.2%) was obtained as colorless columns, mp 54.5–55.3 °C (hexane) (lit.,[4a] 52.5–54 °C); IR (KBr): ν_{max} 2988, 2968, 2948, 2916, 2844, 1614, 1588, 1490, 1478, 1456, 1364, 1330, 1120, 1086, 1010, 1000, 946, 830, 814 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): δ 1.34 (3H, d, J= 6.0 Hz, C_3–CH_3), 2.11 (3H, s, C_7–CH_3), 2.59–2.70 (2H, m, C_4–H_2), 3.69 (3H, s, C_8–OCH_3), 3.80 (3H, s, C_6–OCH_3), 4.66 and 5.00 (each 1H, d, J=14.8 Hz, C_1–H_2), 6.39 (1H, s, C_5–H). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 70.35; H, 8.26.

3.1.6. Demethylation of 6,8-dimethoxy-3,7-dimethylisochromane (4).[4,19] To a stirred suspension of 60% sodium hydride (83 mg, 2.07 mmol) in dry DMF (2.0 mL) was added dropwise a solution of ethanethiol (154 μL, 2.07 mmol) in dry DMF (1.0 mL) by a syringe under an argon atmosphere and then stirring was continued for an additional 10 min. Dimethy ether **4** (185 mg, 0.83 mmol) in dry DMF (2.1 mL) was added dropwise to the stirred solution by a syringe and heated at 140 °C for 3 h. After cooling, the reaction mixture was acidified with 1 M HCl solution (50 mL) and extracted with ether (50 mL) three times. The combined organic layer was washed with brine, dried and evaporated in vacuo to give the residue (215.8 mg). The residue was chromatographed on silica gel (30 g, Kieselgel 60, Merck). By elution with hexane–acetone (volume ratio was varied from 30/4 to 10/3) a mixture of compounds **1** and **3** (158.8 mg, 91.8%, 95:5) was obtained as colorless solid. The ratio was determined by ^1H NMR spectroscopy. The structure of **1** and **3** was determined by comparison of their spectra to that of authentic samples obtained above.

3.1.7. 1-(3-Hydroxy-5-methoxy-4-methylphenyl)-2-methoxymethoxypropane (19) and 1-(3-methoxy-5-methoxymethoxy-4-methylphenyl)-2-methoxymethoxypropane (20). To a stirred solution of alcohol **18** (180 mg, 0.92 mmol) and *N*-ethyldiisopropylamine (1.42 mL, 8.16 mmol) in dry dichloromethane (1.0 mL) chrolomethyl methyl ether (0.62 mL, 8.16 mmol) was added by a syringe at 0 °C and continued stirring at room temperature for 18 h. The reaction mixture was poured into ice water and extracted with dichloromethane (50 mL) three times. The combined organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue (277.4 mg) obtained by evaporation of solvents in vacuo was chromatographed on silica gel (30 g, Kieselgel 60, Merck). Firstly, by elution with hexane–ether (10/1) followed by hexane–ether (5/1) ether **20** was obtained in 55.9% yield as colorless oil; IR (KBr): ν_{max} 2936, 1612, 1590, 1454, 1428, 1404, 1150, 1126, 1076, 1030, 920, 844, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.19 (3H, d, J=6.0 Hz, –CH(OCH_2OCH_3)CH_3), 2.09 (3H, s, C_4–CH_3), 2.62 (1H, dd, J=13.6, 6.0 Hz, –CH_2CH(OCH_2OCH_3)–), 2.83 (1H, dd, J=13.6, 6.7 Hz, –CH_2CH(OCH_2OCH_3)–), 3.24 (3H, s, –CH(OCH_2OCH_3)–), 3.48 (3H, s, C_3–OCH_2OCH_3), 3.81 (3H, s, C_5–OCH_3), 3.92 (1H, ddq, J=6.7, 6.0, 6.0 Hz, –CH(OCH_2OCH_3)–), 4.54 (1H, d, J=7.0 Hz, –CH(OCH_2 OCH_3)–), 4.64 (1H, d, J=7.0 Hz, –CH(OCH_2CH_3)–), 5.17 (2H, s, C_3–OCH_2OCH_3), 6.42 (1H, s, C_2–H or C_6–H), 6.58 (1H, s, C_2–H or C_6–H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.26, 20.36, 44.01, 55.13, 55.69, 56.01, 74.20, 94.83, 95.00, 105.79, 108.44, 113.48, 137.37, 155.75, 158.20. Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.18; H, 8.55.

Secondly, MOM ether **19** was obtained by elution with hexane–ether (2/1) in 39.3% yield as colorless prisms, mp 52.5–53.0 °C (hexane–ether); IR (KBr): ν_{max} 3348, 3016, 2968, 2940, 2896, 2844, 1616, 1600, 1520, 1472, 1422, 1322, 1226, 1142, 1112, 1052, 1026, 898, 826, 796, 672, 644, 608 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.18 (3H, d, J=6.0 Hz, –CH(OCH_2OCH_3)CH_3), 2.07 (3H, s, C_4–CH_3), 2.58 (1H, dd, J=13.5, 6.0 Hz, –CH_2CH(OCH_2OCH_3)–), 2.79 (1H, dd, J=13.5, 7.2 Hz, –CH_2CH(OCH_2OCH_3)–), 3.25 (3H, s, –CH(OCH_2OCH_3)–), 3.80 (3H, s, C_5–OCH_3), 3.93 (1H, ddq, J=6.0, 6.0, 7.2 Hz, –CH(OCH_2OCH_3)–), 4.56 (1H, d, J=6.8 Hz, OCH_2O), 4.66 (1H, d, J=6.8 Hz, OCH_2O), 5.34 (1H, s, OH), 6.32 (2H, s, C_2–H and C_6–H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 7.85, 20.29, 43.65, 55.17, 55.71, 74.18, 94.87, 104,28, 109.10, 109.99, 137.40, 154.35, 158.48. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.75; H, 8.44.

3.1.8. The cyclization of MOM ether 19 with $TiCl_4$. A mixture of MOM ether **19** (47 mg, 0.19 mmol) in dry dichloromethane (3.0 mL) was added to a solution of $TiCl_4$ (21 μL, 0.19 mmol) in dichloromethane (3.0 mL) under stirring at −48 °C over a period of 15 min under argon atmosphere and stirred at the same temperature for 15 min. Methanol (0.2 mL) was added to the reaction mixture by a syringe and then 3 M HCl solution (4 mL) was added. After stirring at room temperature, the reaction mixture was extracted with dichloromethane (40 mL) three times. The combined organic layer was washed with brine and dried. The residue (43.8 mg) obtained by evaporation of solvents in vacuo was chromatographed on silica gel (25 g). By elution with hexane–ether (5/1) a mixture of compounds **1** and **3** (26.7 mg, 66.1%, 79:21) was obtained as colorless oil. By repeating chromatography of a mixture of **1** and **3** on silica gel (Kieselgel 60, Merck) eluted with hexane–ether (30/1)[‡] and followed by recrystallization from hexane–ether compound **3** was obtained as colorless crystals, mp 150.5–151.5 °C (hexane–ether); R_f: 0.28 (hexane/ether=2:1); IR (KBr): ν_{max} 3288 (OH), 2980, 2928, 2844, 1616, 1596, 1506, 1460, 1424, 1390, 1366, 1328, 1098, 1048, 1002, 828, 814, 662 cm^{-1}; MS: *m/z* (%) 208 (M^+, 71), 207 (31), 166 (23), 165 (100). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.28; H, 7.84.

The ^1H and ^{13}C NMR data are summarized in Table 2.

[‡] As the difference of R_f values between **1** (R_f: 0.31) and **3** (R_f: 0.28) is small, it is difficult to separate clearly **3** from **1** by column chromatography under the given conditions.

3.1.9. The cyclization of ether 20 with $TiCl_4$. To a stirred solution of $TiCl_4$ (15 μL, 0.14 mmol) in dry dichloromethane (3.0 mL) ether **20** (55 mg, 0.19 mmol) dissolved in dichloromethane (3.0 mL) was added dropwise at −49 °C over a period of 15 min under an argon atmosphere and stirred at the same temperature for 15 min. The reaction mixture was worked up in a manner similar to the reaction of **19** with $TiCl_4$. The residue (42.3 mg) obtained by evaporation of solvents in vacuo was chromatographed on silica gel (25 g). A mixture of compounds **26** and **27** (14.1 mg, 29.0%, 53:47) was obtained by elution with hexane–ether (volume ratio was varied from 20/1 to 10/1). Secondly, a mixture of **1** and **3** (21.1 mg, 52.6%, 88:12) was afforded by elution with hexane–ether (5/1). The structure of **26** and **27** was determined by comparison of their spectra to that of authentic samples obtained by methoxymethylation of **1** and **3**, respectively, as described bellow.

3.1.10. 6-Methoxy-8-methoxymethoxy-3,7-dimethylisochromane (26). To a mixture of compound **1** (71 mg, 0.34 mmol), *N*-ethyldiisopropylamine (217 mg, 1.68 mmol) and dry dichloromethane (1.0 mL) chloromethyl methyl ether (135 mg, 1.68 mmol) was added by a syringe at 0 °C under stirring. After stirring at room temperature for 18 h 45 min, water (10 mL) was added and extracted with dichloromethane (40 mL) three times. The combined organic layer was washed with brine and dried. The residue (89.3 mg) obtained by evaporation of solvents in vacuo was chromatographed on silica gel (25 g). Compound **26** (82.5 mg) was obtained in 96.7% yield by elution with hexane–ether (10/1) followed by hexane–ether (20/1) as colorless oil; R_f: 0.47 (hexane/ether=2:1); IR (neat): ν_{max} 2972, 2936, 2836, 1614, 1590, 1490, 1470, 1362, 1330, 1264, 1160, 1124, 1092, 1050, 982, 930 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.35 (3H, d, J=6.0 Hz, C_3–CH_3), 2.11 (3H, s, C_7–CH_3), 2.65–2.66 (2H, m, C_4–H_2), 3.59 (3H, s, OCH_2OCH_3), 3.75–3.79 (1H, m, C_3–H), 3.80 (3H, s, C_6–OCH_3), 4.73 (1H, d, J=15.0 Hz, C_1–H), 4.92 and 4.94 (each 1H, d, J=6.0 Hz, OCH_2OCH_3), 5.00 (1H, d, J=15.0 Hz, C_1–H), 6.41 (1H, s, C_5–H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 9.39, 21.53, 35.84, 55.56, 57.33, 64.99, 70.53, 99.38, 106.52, 117.10, 120.41, 132.16, 152.87, 157.12. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.35; H, 7.96.

3.1.11. 8-Methoxy-6-methoxymethoxy-3,7-dimethylisochromane (27). To a stirred solution of compound **3** (20 mg, 0.10 mmol) and *N*-ethyldiisopropylamine (62 mg, 0.48 mmol) in dry dichloromethane (0.8 mL) chloromethyl methyl ether (39 mg, 0.48 mmol) was added by a syringe at 0 °C under stirring and continued stirring at room temperature for 19 h. The reaction mixture was worked up in a manner similar to that described above and compound **27** (19.1 mg, 78.9%) was obtained as colorless oil; R_f: 0.51 (hexane/ether=2:1); IR (neat): ν_{max} 2932, 2852, 1614, 1590, 1486, 1450, 1362, 1324, 1262, 1154, 1118, 1086, 1060, 1002, 924, 854, 816 cm^{-1}; ^1H NMR (CD_3COCD_3, 500 MHz): δ 1.25 (3H, d, J=6.0 Hz, C_3–CH_3), 2.10 (3H, s, C_7–CH_3), 2.52 (1H, dd, J=16.0, 11.0 Hz, C_4–H), 2.64 (1H, dd, J=16.0, 3.0 Hz, C_4–H), 3.43 (3H, s, OCH_2OCH_3), 3.67 (3H, s, C_6–OCH_3), 3.69 (1H, m, C_3–H), 4.62 and 4.83 (each 1H, d, J=15.0 Hz, C_1–H_2), 5.17 and 5.19 (each 1H, d, J=6.0 Hz, OCH_2OCH_3), 6.63 (1H, s, C_5–H); ^{13}C NMR (CD_3COCD_3, 125 MHz): δ 8.99, 21.86, 36.47, 56.09, 60.28, 64.89, 71.23, 95.40, 110.87, 118.46, 122.17, 133.48, 155.76, 155.84. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.76; H, 8.11.

Acknowledgements

We thank Professor Mutsuo Okamura (Graduate school of science and technology, Niigata University) for Mass spectral analysis, Mr. Yoshiaki Matsuda (Faculty of science, Niigata University) for ^1H and ^{13}C NMR measurements (500 and 125 MHz) and the Division of Chemical Analysis, the Institute of Physical and Chemical Research (RIKEN) for elemental analyses, respectively.

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