STUDIES ON HINDERED PHENOLS AND ANALOGUES. 4. FORMATION OF 3,9-DIOXABICYCLO[4.3.1]DECANES AND ITS APPLICATION FOR ANTIDIABETIC AGENTS

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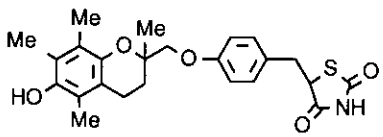
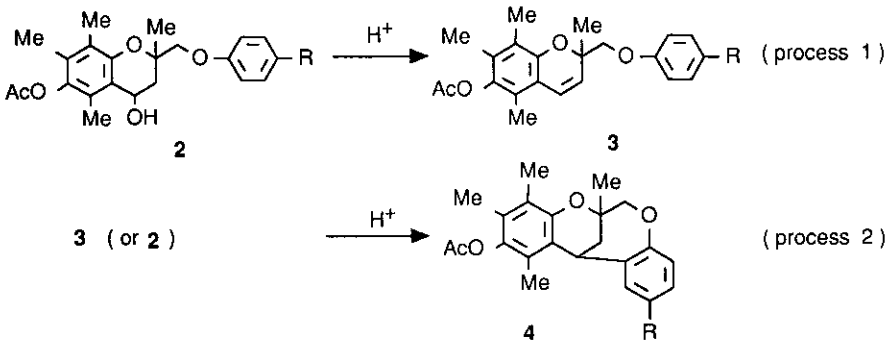
Abstract---6-Acetoxy-2,5,7,8-tetramethyl-2-phenoxymethylchroman-4-ol(**2**) gave a couple of dehydration products, the corresponding chromene (**3**), and a bicyclo compound (**4**). The product ratios **3**/**4** changed with the reaction conditions and the substituent of the phenoxymethyl group. The bicyclo compound (**4**) was confirmed to be given *via* the chromene (**3**). Using the bicyclo ring system, a new thiazolidine-2,4-dione (**16**) was prepared. This compound (**16**) showed hypoglycemic activity.

In previous synthetic work on a ^{14}C-labelled compound[1] of (±)-5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, **CS-045** (**1**),[2] which is a new oral antidiabetic agent effective



1 (CS-045)

in insulin resistant animals, we found that 6-acetoxy-2,5,7,8-tetramethyl-2-phenoxymethylchroman-4-ol (**2a**, R=H) gave a dehydration product, 2*H*-chromene (**3a**, R=H), together with another dehydration product (**4a**, R=H) having a 3,9-dioxabicyclo[4.3.1]decane ring system (Scheme 1).[1] There has been only one report on this ring system.[3] In the present paper, we wish to report a configurational effect of the hydroxyl group at the 4 position and a substituent effect of the phenoxymethyl group at the 2 position of the chroman-4-ol (**2**) in the dehydration step. In addition, we will discuss whether the formation of the ring system occurs stepwisely



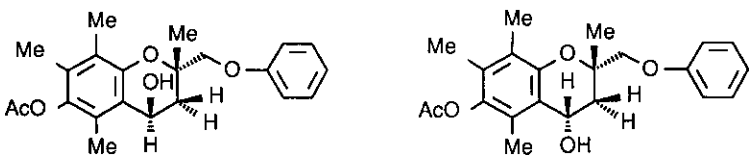
Scheme 1

with process 1 followed by process 2, or concertedly with an elimination of the hydroxyl group followed by a C-C bond formation due to π electron transfer from the phenoxymethyl group. We also describe the preparation of a new thiazolidine compound (**16**) having the above ring system, analogous to CS-045 (**1**), and the hypoglycemic activity of **16**.

CONFIGURATIONAL EFFECT ON THE DEHYDRATION

1.STRUCTURAL DETERMINATION OF DIASTEREOISOMER OF CHROMAN-4-OL (2)

Chroman-4-ol (**2a**), prepared by $NaBH_4$ reduction of the corresponding 4-oxo compound, is constituted with two diastereoisomers, more polar (**2a-1**) and less polar (**2a-2**). Before the investigation of the configurational effect on the dehydration reaction, we determined the configuration of **2a-1** and **2a-2** by examining nuclear Overhauser effects on the methyl proton at the 2 position, the methylene proton at the 3 position, and the methine proton at the 4 position of the chroman ring in the nmr spectroscopy. On the more polar chroman-4-ol (**2a-1**), an enhancement of the methylene proton signal in a higher field was observed by irradiating the methyl proton signal, and an enhancement of another methylene proton signal in a lower field



2a-1 2a-2

Scheme 2

was observed by irradiating the methine proton signal. On the less polar chroman-4-ol (**2a-2**), a similar enhancement of the methylene proton signal in a higher field was observed by irradiating the methyl proton signal, but a larger enhancement of the methylene proton signal in a higher field was observed by irradiating the methine proton signal. In Scheme 2 is drawn a relative configuration. These observations show that **2a-1** has a *cis* configuration on the methyl and the hydroxyl groups.

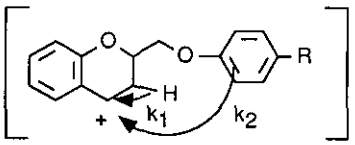
2.COMPARISON OF TWO DIASTEREOISOMERS IN THE DEHYDRATION REACTION

We have speculated that an elimination of the hydroxyl group in **2a-1** is faster than that in **2a-2** according to the participation of the lone-pair electrons of the oxygen atom in the phenoxyl group and/or π electrons of the benzene ring (Scheme 2). Thus, the rates of the elimination reactions of the chroman-4-ols (**2a-1**) and (**2a-2**) were compared by measuring the relative intensity of the methine proton signal of **2a**. However, there was no remarkable difference between the rates. Accordingly, the contribution of the participation may be small. Under milder reaction conditions in this experiment, we observed the formation of the 2*H*-chromene (**3**) as a sole product, as is described in detail later.

SUBSTITUENT EFFECT ON THE DEHYDRATION

1.FORMATION OF THE CHROMENE (**3a**, R=H) AND THE BICYCLO COMPOUND (**4a**, R=H)

Refluxing the benzene solution of chroman-4-ol (**2a-1**, R=H) for 3 h gave the chromene (**3a**, R=H) and the bicyclo compound (**4a**, R=H) in 22 and 70 % yields, respectively, in the presence of 20 mol % of $TsOH \cdot H_2O$, while under milder reaction conditions, such as on heating the same solution for 1 h in the presence of 4 mol % of the catalyst, **2a** gave **3a** selectively. The chromene (**3a**) was further heated in the benzene solution under refluxing for 3 h in the presence of 20 mol % of the catalyst, to give the bicyclo compound (**4a**) in an excellent yield. These results support that the formation of the ring system occurs stepwisely with process 1 followed by process 2 (Scheme 1), and suggest that the rate constant k_1 of the double bond formation is larger than k_2 of the ring formation (Scheme 3). The value of k_2 should be affected with the electron donating activity controlled by the substituent R of the benzene ring.

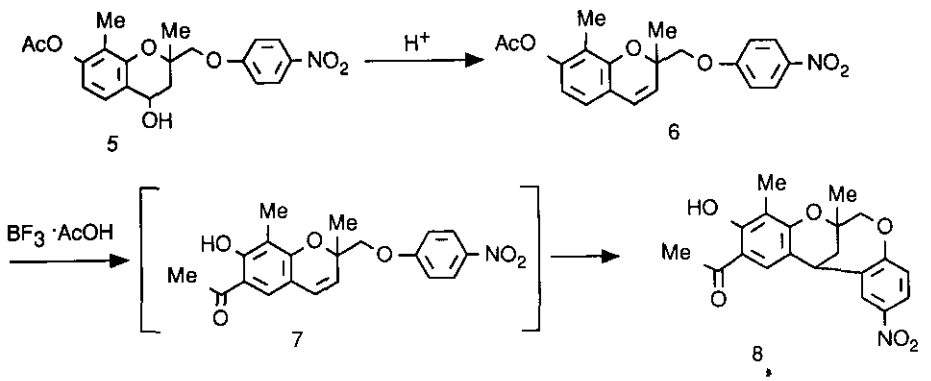


Scheme 3

2.FORMATION OF THE CHROMENE (**3b**, R=NO_2)

We investigated the substituent effect of the *p*-nitro group and confirmed that the chroman-4-ol (**2b**, R=NO_2) gave only the chromene (**3b**, R=NO_2) under the same reaction conditions as described above. These observations are consistent with those of Omokawa et al.[3]

In connection with another work in our laboratories,[4] we tried to prepare another chromene derivative (**7**) by applying our findings. We could obtain the chromene (**6**) under similar reaction conditions to those described above. But we could not obtain the target compound (**7**) during the reaction conditions of Fries

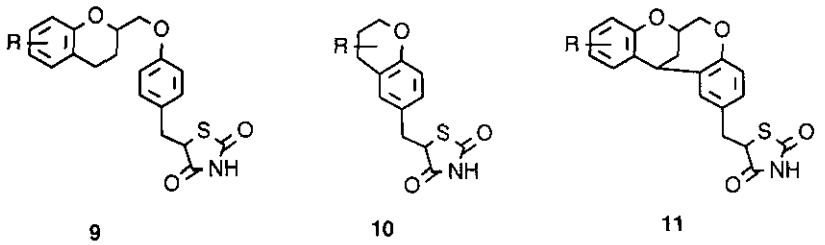


Scheme 4

rearrangement. Instead of **7**, we obtained the bicyclo compound (**8**), although **7** has a *p*-nitro group in the phenoxymethyl group (Scheme 4). These results show that the ring formation proceeds depending on the kind of acidic catalyst used.

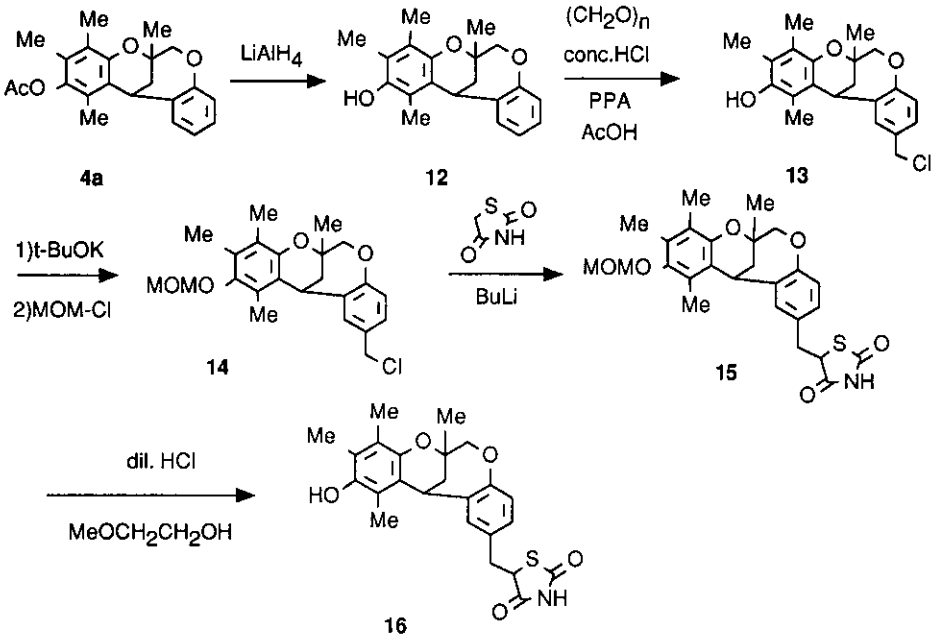
APPLICATION OF THE BICYCLO RING SYSTEM FOR ANTIDIABETIC AGENTS

There have been many reports, including patent works, on the antidiabetic agents with a substructure of the thiazolidine-2,4-dione.[1,5,6] Some examples have a chroman ring as an additional structural part as shown in



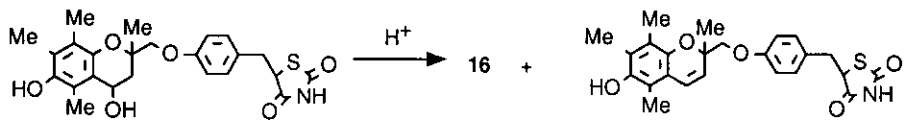
Scheme 5

structure of compounds (**9** and **10**). However no attempt was made to use the bicyclo ring system analogous to the chroman ring as a following thiazolidine compound (**11**). For preparing the target compound, application of the process of the ring formation is suitable. Thus, the target compound (**16**) was prepared according to the reported process[1] as shown in Scheme 6. Benzyl chloride derivative (**14**) was prepared as follows: compound (**4a**) was deacetylated by LAH reduction to give **12**. Chloromethylation of **12**, followed by protection using an MOM group yielded **14**. Alkylation of the 5 position of thiazolidine-2,4-dione with the benzyl chloride (**14**) followed by hydrolysis yielded the target compound (**16**). This compound (**16**) was also prepared by the dehydration of chroman-4-ol (**17**)[7] *together with chromene* (**18**) *in the presence* of an acidic catalyst (Scheme 7).



4a 12 13 14 15 16

Scheme 6



17 18

Scheme 7

HYPOGLYCEMIC ACTIVITY

Compound (**16**) and CS-045 (**1**) showed 39.0 and 33.0 % decreases in a serum glucose level, respectively, at a dose of 50 mg/kg body weight 3 h after administration by a method similar to that reported.[2]

EXPERIMENTAL SECTION

Mass spectra were recorded on a JEOL-JMS-01SG or JEOL-JMS-D300 mass spectrometer. The abbreviation "thia" means 2,4-thiazolidin-5-yl group ($C_3H_2NO_2S$). Nmr spectra were recorded on a 90 MHz Varian EM-390 or 270 MHz JEOL GX-270 spectrometer with tetramethylsilane as an internal standard. The abbreviation "nd" means that precise identification of the signal was not possible because of overlap by other signals or absorption of solvent. All nmr spectra were consistent with the structures assigned. Melting points were determined using a Yanaco micro melting point apparatus and are uncorrected.

PREPARATION OF CHROMAN-4-OLS (**2a-1** and **2a-2**)

To a solution of 14.11 g (38.3 mmol) of 6-acetoxy-2,5,7,8-tetramethyl-2-phenoxymethylchroman-4-one in 150 ml of MeOH was added, portionwise, 1.45 g (38.3 mmol) of sodium borohydride at -7 to -5 °C. The reaction mixture was stirred for 1 h in an ice bath. The solution was acidified with 3N HCl, concentrated under reduced pressure, and extracted with ethyl acetate. The extract was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [eluent; hexane : ethyl acetate = 3:1] to give 7.54 g (54%) of the more polar chroman-4-ol (**2a-1**), melting at 135.5-137 °C (cyclohexane-benzene), and 4.63 g (33%) of the less polar chroman-4-ol (**2a-2**), melting at 121-123 °C (cyclohexane). Ms (m/z): 370 (M^+), 352 (M^+-H_2O), 328 (M^+-CH_3CO +H), 263 (M^+-$CH_2OC_6H_5$). Nmr ($CDCl_3$) δ; **2a-1** : 1.53 (3H, s), 1.72 (1H, br d, J=4 Hz), 2.04 (3H, s), 2.08 (3H, s), 2.19 (3H, s), 2.20 (1H, dd, J=15 and 3 Hz), 2.32 (1H, dd, J=15 and 5 Hz), 2.34 (3H, s), 3.95 (1H, d, J=9 Hz), 4.02 (1H, d, J=9 Hz), 4.95-5.0 (1H, m), 6.9-7.0 (3H, m), 7.25-7.35 (2H, m). *Anal.* Calcd for $C_{22}H_{26}O_4$: C, 71.33; H, 7.07. Found: C, 71.72; H, 7.27. **2a-2** : 1.53 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 2.08 (1H, dd, J=15 and 5 Hz), 2.18 (3H, s), 2.34 (3H, s), 2.45 (1H, dd, J=15 and 2 Hz), 4.01 (1H, d, J=10 Hz), 4.21 (1H, d, J=10 Hz), 4.85-4.95 (1H, m), 6.8-9.65 (3H, m), 7.2-7.25 (2H, m). *Anal.* Calcd for $C_{22}H_{26}O_4$: C, 71.33; H, 7.07. Found: C, 71.39; H, 7.27.

(±)-6-ACETOXY-2,5,7,8-TETRAMETHYL-2-PHENOXYMETHYL-2*H*-CHROMENE (**3a**) FROM CHROMAN-4-OL (**2a-1**)

A mixture of 500 mg (1.35 mmol) of **2a-1**, 10 mg (0.053 mmol) of TsOH·H_2O, and 7 ml of benzene was heated at 60°C for 1 h. The reaction mixture was washed with aq. $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give 470 mg (99%) of **3a** as an oily substance. Ms (m/z): 352 (M^+), 245 (M^+-$CH_2OC_6H_5$), 203 (M^+-$CH_2OC_6H_5$ -CH_3CO +H). Nmr ($CDCl_3$) δ: 1.57 (3H, s), 2.02 (3H, s), 2.08 (6H, s), 2.31 (3H, s), 4.01 (2H, s), 5.76 (1H, d, J=10 Hz), 6.63 (1H, d, J=10 Hz), 6.8-7.1 (3H, m), 7.15-7.4 (2H, m).

PREPARATION OF COMPOUND (**3a**) AND BICYCLO COMPOUND (**4a**) FROM **2a-1**

A mixture of 200 mg (0.54 mmol) of **2a-1**, 20 mg (0.105 mmol) of TsOH·H_2O, and 3 ml of benzene was heated under reflux for 3 h. The solution was diluted with benzene, washed with aq. $NaHCO_3$ and brine, and dried over Na_2SO_4. The crude product was purified by silica gel column chromatography [eluent; hexane : ethyl acetate = 9:1], to give 42 mg (22%) of **3a** and 133 mg (70%) of **4a** as a colorless powder, melting at 183-185°C. **4a**; ms (m/z): 352 (M^+), 310 (M^+-CH_3CO +H). Nmr ($CDCl_3$) δ: 1.30 (3H, s), 1.8-2.5 (2H, nd),

1.88 (3H, s), 2.00 (3H, s), 2.19 (3H, s), 2.23 (3H, s), 3.57 (1H, d, J=13 Hz), 3.99 (1H, dd, J=6 and 2 Hz), 4.30 (1H, dd, J=13 and 2 Hz), 6.8-7.45 (4H, m). *Anal.* Calcd for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.75; H, 6.87.

PREPARATION OF BICYCLO COMPOUND (**4a**) FROM **3a**

A mixture of 500 mg (1.42 mmol) of **3a**, 50 mg (0.263 mmol) of $TsOH \cdot H_2O$, and 7 ml of benzene was heated under reflux for 3 h. The solution was diluted with benzene, washed with brine, and dried over Na_2SO_4. The crude product was purified by silica gel column chromatography [eluent; hexane : ethyl acetate = 9:1] to yield 460 mg (92%) of **4a**.

(±)-6-ACETOXY-2,5,7,8-TETRAMETHYL-2-(4-NITROPHENOXYMETHYL)-2*H*-CHROMENE (**3b**)

A mixture of 101 mg (0.243 mmol) of 6-acetoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman-4-ol (**2b**), 10 mg (0.053 mmol) of $TsOH \cdot H_2O$, and 2 ml of benzene was heated under reflux for 3 h. The reaction mixture was diluted with benzene, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting crude product was purified by silica gel column chromatography [eluent; hexane : ethyl acetate = 3:1] to give 91 mg (94%) of **3b** as a pale yellow powder, melting at 197-199.5°C. Ms (m/z): 397 (M^+), 354 (M^+-CH_3CO), 245 (M^+-$CH_2OC_6H_4NO_2$). Nmr ($CDCl_3$)δ : 1.57 (3H, s), 2.00 (3H, s), 2.03 (3H, s), 2.07 (3H, s), 2.33 (3H, s), 4.05 and 4.11 (2H, AB type, J=10 Hz), 5.70 (1H, d, J=10 Hz), 6.66 (1H, d, J=10 Hz), 6.94 (2H, d, J=9 Hz), 8.17 (2H, d, J=9 Hz). *Anal.* Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.66; H, 5.80; N, 3.53.

(±)-7-ACETOXY-2,8-DIMETHYL-2-(4-NITROPHENOXYMETHYL)-2*H*-CHROMENE (**6**)

A mixture of 4.1 g (10.59 mmol) of 7-acetoxy-2,8-dimethyl-2-(4-nitrophenoxymethyl)chroman-4-ol (**5**), 0.22 g (1.16 mmol) of $TsOH \cdot H_2O$, and 50 ml of benzene was heated under reflux 1 h. The reaction mixture was poured into water and extracted with benzene. The crude oil was purified by silica gel column chromatography [eluent; benzene : ethyl acetate = 10:1] to give 2.66 g (68%) of **6** as an oily substance. Ms (m/z): 369 (M^+), 326 (M^+-CH_3CO), 217 (M^+-$CH_2OC_6H_4NO_2$), 175 (M^+-CH_3CO -$CH_2OC_6H_4NO_2$ +H). Nmr ($CDCl_3$)δ : 1.58 (3H, s), 1.91 (3H, s), 2.27 (3H, s), 4.10 (2H, s), 5.03 (1H, d, J=10 Hz), 6.48 (1H, d, J=10 Hz), 6.58 (1H, d, J=7 Hz), 6.86 (1H, d, J=7 Hz), 6.93 (2H, d, J=9 Hz), 8.18 (2H, d, J=9 Hz).

PREPARATION OF BICYCLO COMPOUND (**8**)

A mixture of 1 g (2.71 mmol) of **6** and 5 ml of ca. 40 % boron trifluoride acetic acid complex was heated at 100 °C for 3 h and at 120 °C for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. After the solvent was removed under

reduced pressure, the resulting crude oil was purified by silica gel column chromatography [eluent; benzene : ethyl acetate = 20:1] to yield 450 mg (45%) of **8** as a foamy solid, melting at 255-256°C. Ms (m/z): 369 (M^+), 354 (M^+-CH_3). Nmr (DMSO-d_6)δ : 1.38 (3H, s), 2.03 (3H, s), 2.2-2.4 (2H, nd), 2.43 (3H, s), 3.85 (1H, d, J=13 Hz), 4.2-4.5 (2H, m), 7.10 (1H, d, J=9 Hz), 7.54 (1H, s), 8.08 (1H, dd, J=9 and 3 Hz), 8.55 (1H, d, J=2 Hz), 12.87 (1H, s).

PREPARATION OF COMPOUND (12)

To a suspension of 1.1 g (29.0 mmol) of lithium aluminum hydride in 50 ml of THF was added, dropwise, a solution of 10 g (28.4 mmol) of **4a** in 80 ml of THF at 5-10 °C. The reaction mixture was stirred for 1 h at the same temperature. After ethyl acetate was added, dropwise, to decompose excess reagent, the mixture was acidified with 3N HCl. The mixture was concentrated under reduced pressure and extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a pale orange oil. The oil was triturated with isopropyl ether and filtrated with hexane, to yield 8.24 g (94%) of **12** as a colorless powder, melting at 133-137 °C (hexane-Et_2O). Ms (m/z): 310 (M^+), 295 (M^+-CH_3), 203 (M^+-$CH_2OC_6H_4$ -H). Nmr ($CDCl_3$)δ : 1.30 (3H, s), 1.8-2.4 (2H, nd), 2.00 (3H, s), 2.13 (3H, s), 2.14 (3H, s), 2.20 (3H, s), 3.58 (1H, d, J=13 Hz), 3.9-4.15 [1H, nd, changed to 4.02 (1H, dd, J=6 and 2 Hz) by adding D_2O], 4.00 (1H, s, disappeared by adding D_2O), 4.29 (1H, dd, J=13 and 2 Hz), 6.8-7.45 (4H, m). *Anal.* Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.47; H, 7.20.

PREPARATION OF COMPOUND (13)

A mixture of 4.3 g (13.9 mmol) of **12**, 1 g (30.0 mmol) of 90 % paraformaldehyde, 3 ml of 70 % PPA, 10 ml of conc. HCl, and 45 ml of AcOH was heated at 85 °C for 4 h. The reaction mixture was poured into ice water and extracted with ethyl acetate. The extract was successively washed with brine, aq. $NaHCO_3$, and brine, and dried over Na_2SO_3. The solvent was removed under reduced pressure and the resulting residue was purified by silica gel column chromatography [eluent; hexane : ethyl acetate = 6:1] to give 3.46 g (70%) of **13** as a pale yellow foamy solid. Ms (m/z): 358 (M^+), 343 (M^+-CH_3), 323 (M^+-Cl), 310 (M^+-CH_2Cl +H). Nmr ($CDCl_3$)δ : 1.32 (3H, s), 1.9-2.4 (2H, nd), 2.00 (3H, s), 2.13 (3H, s), 2.20 (3H, s), 3.58 (1H, d, J=13 Hz), 3.95-4.2 (1H, nd), 4.03 (2H, s), 6.86 (1H, d, J=8 Hz), 7.13 (1H, dd, J=8 and 2 Hz), 7.42 (1H, d, J=2 Hz).

PREPARATION OF COMPOUND (14)

To a solution of 3.35 g (9.34 mmol) of **13** in 35 ml of THF was added, dropwise and successively, a solution of 1.8 g (16.0 mmol) of potassium t-butoxide in 18 ml of THF and a solution of 2.25 g (28.0 mmol) of MOM-Cl in 11 ml of THF in a dry-ice-EtOH bath. The reaction mixture was stirred for 2 h at room

temperature. The mixture was poured into ice water and extracted with benzene. The extract was washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was purified by silica gel column chromatography [eluent; hexane : ethyl acetate = 6:1] to yield 1.8 g (48 %) of **14** as a colorless foamy solid. Ms (m/z): 402 (M^+), 357 (M^+-CH_2OCH_3), 321 (M^+-CH_2OCH_3 -Cl -H). Nmr ($CDCl_3$)δ : 1.31 (3H, s), 2.05 (3H, s), 2.11 (1H, dd, J=14 and 2 Hz), 2.17 (3H, s), 2.18 (3H, s), 2.27 (1H, ddd, J=14, 6, and 2 Hz), 3.52 (3H, s), 3.60 (1H, d, J=12 Hz), 4.00 (1H, dd, J=6 and 2 Hz), 4.29 (1H, dd, J=12 and 3 Hz), 4.58 (2H, s), 4.73 (2H, s), 6.87 (1H, d, J=8 Hz), 7.12 (1H, dd, J=8 and 2 Hz), 7.39 (1H, d, J=2 Hz).

PREPARATION OF COMPOUND (**15**)

To a solution of 390 mg (3.33 mmol) of thiazolidine-2,4-dione in 6 ml of a 4:1 mixed solvent of THF and HMPA, was added, dropwise, 2.8 ml (7.0 mmol) of 2.5 M BuLi solution in hexane in a dry-ice-EtOH bath. The mixture was stirred for 1 h at the same temperature. To this solution was added a solution of 1.74 g (4.32 mmol) of **14** in 11 ml of the mixed solvent in an ice bath. After the reaction mixture was stirred for 3 h at the same temperature, to this was added conc. HCl, carefully, and then water. The crude product was extracted with benzene and the extract was washed with brine. The extract was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by reversed phase column chromatography [eluent; MeCN : H_2O = 4:1] to give 240 mg (15%) of **15** as a colorless foamy solid. Ms (m/z): 483 (M^+), 438 (M^+-CH_2OCH_3), 367 (M^+-CONHCO-CH_2OCH_3). Nmr ($CDCl_3$)δ : 1.31 (3H, s), 2.0-2.15 (1H, nd), 2.05 (1.5H, s), 2.07 (1.5H, s), 2.16 (1.5H, s), 2.17 (1.5H,), 2.17 (3H, s), 2.27 (1H, ddd, J=14, 6, and 2 Hz), 3.15 (0.5H, dd, J=14 and 9 Hz), 3.17 (0.5H, dd, J=14 and 9 Hz), 3.45 (0.5H, dd, J=14 and 4 Hz), 3.46 (0.5H, dd, J=14 and 4 Hz), 3.54 (3H, s), 3.59 (1H, d, J=12 Hz), 3.98 (1H, br d, J=6 Hz), 4.28 (1H, dd, J=12 and 2 Hz), 4.52 (0.5H, dd, J=9 and 4 Hz), 4.55 (0.5H, dd, J=9 and 4 Hz), 4.74 (1H, s), 4.75 (1H, AB type, J=6 Hz), 6.85 (0.5H, d, J=8 Hz), 6.86 (0.5H, d, J=8 Hz), 6.97 (0.5H, dd, J=8 and 2 Hz), 7.01 (0.5H, dd, J=8 and 2 Hz), 7.22 (1H, d, J=2 Hz), 8.12 (0.5H, br s), 8.31 (0.5H, br s).

(±)-5-[6,7-DIHYDRO-2-HYDROXY-1,3,4,6-TETRAMETHYL-6,13-METHANO-13*H*-DIBENZO[e,h][1,4]DIOXONIN-11-YLMETHYL]THIAZOLIDINE-2,4-DIONE (**16**)

A mixture of 197 mg (0.407 mmol) of **15**, 0.5 ml of conc. HCl, and 5 ml of 2-methoxyethanol was heated under reflux for 1 h. The reaction mixture was poured into ice-brine and extracted with ethyl acetate. The crude product was purified by silica gel column chromatography [eluent; hexane : ethyl acetate = 3:1] to yield 158 m (85%) of **16** as a colorless foamy solid, softening at 136-140 °C. Ms (m/z): 439 (M^+), 424 (M^+-CH_3), 368 (M^+-CONHCO), 323 (M^+-thia). Nmr ($CDCl_3$)δ : 1.30 (3H, s), 2.00 (1.5H, s), 2.02 (1.5H, s),

2.08 (1H, ddd, J=14, 3, and 2 Hz), 2.13 (3H, s), 2.19 (3H, s), 2.2-2.35 (1H, m), 3.12 (0.5H, dd, J=14 and 9 Hz), 3.18 (0.5H, dd, J=14 and 9 Hz), 3.47 (1H, dt, J=14 and 4 Hz), 3.58 (0.5H, d, J=13 Hz), 3.59 (0.5H, d, J=13 Hz), 4.00 (1H, br d, J=5 Hz), 4.10 (0.5H, s), 4.12 (0.5H, s), 4.28 (1H, dd, J=13 and 2 Hz), 4.52 (0.5H, dd, J=9 and 4 Hz), 4.55 (0.5H, dd, J=9 and 4 Hz), 6.84 (0.5H, d, J=8 Hz), 6.85 (0.5H, d, J=8 Hz), 6.98 (1H, dt, J=8 and 2 Hz), 7.24 (1H, br s), 8.03 (0.5H, br s), 8.11 (0.5H, br s). *Anal.* Calcd for $C_{24}H_{25}NO_5S$: C, 65.60; H, 5.69; N, 3.19; S, 7.29. Found: C, 64.95; H, 5.72; N, 2.98; S, 6.81.

PREPARATION OF COMPOUNDS (**16**) AND (**18**) FROM CHROMAN-4-OL (**17**)

A mixture of 200 mg (0.438 mmol) of (±)-5-[4-(4,6-dihydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione (**17**), 20 mg (0.105 mmol) of $TsOH \cdot H_2O$, 15 ml of toluene, and 0.4 ml of DMF was heated under reflux for 10 h with a water separator attached. The mixture was poured into water and extracted with benzene. The extract was washed with water and dried over Na_2SO_4. The crude oil was purified by preparative tlc [developing solvent; benzene : ethyl acetate = 7:3] to give 82 mg (43%) of **16** and 37 mg (19%) of (±)-5-[4-(6-hydroxy-2,5,7,8-tetramethyl-2*H*-chromen-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (**18**) as pale brown powders, softening at 173-176°C. **18** ; ms (m/z): 439 (M^+), 323 (M^+-thia), 217 (M^+-$OC_6H_4CH_2$thia), 203 (M^+-$CH_2OC_6H_4CH_2$thia). Nmr (acetone-d_6)δ : 1.50 (3H, s), 2.02 (3H, s), 2.12 (3H, s), 2.18 (3H, s), 3.06 (1H, dd, J=14 and 9 Hz), 3.40 (1H, dd, J=14 and 4 Hz), 3.94 (1H, d, J=19 Hz), 4.05 (1H, d, J=10 Hz), 6.72 (1H, d, J=10 Hz), 6.85 (2H, d, J=9 Hz), 7.19 (2H, d, J=9 Hz).

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