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原 著

Expected Physiological Activity Derivatives: Preparation of the New Designed *cis* -6-Hexyl-5-methoxy-3,4-ditiglyloxychroman and *trans* -4-Isopropylamino-6-methoxycarbonyl-3-tiglyloxychroman Compounds

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期待される生理活性誘導体：新規にデザインされたシス-6-ヘキシル-5-メトキシ-3,4-ジチグリルオキシクロマンおよびトランス-4-イソプロピルアミノ-6-メトキシカルボニル-3-チグリルオキシクロマン化合物の製法

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Summary

Khellactones and chromans have been reported to possess the various biological activities, for instance, antiviral and immunostimulating agents, platelet activating factor (PAF) antagonist, and anti-HIV agents, *etc*.

Here, the new designed two chemical chroman compounds with naturally similar molecular skeleton, that is , (±)-*cis* - 6-hexyl-5-methoxy-2,2-dimethyl-3,4-ditiglyloxychroman (**10**) from starting material dihydroxybenzaldehyde (**12**), and (±)-*trans* -4-isopropylamino-6-methoxycarbonyl-2,2-dimethyl-3-tiglyloxychroman (**11**) from starting material methyl 4-hydroxybenzoate (**20**) by chemical transformations were prepared.

These were namely investigating to find the leading chroman compound (derivatives) that might be pointed to have more potent the physiological activity considering to structure activity relationship, especially, PAF antagonistic effect, *etc*.

Key Words
chroman compound, preparation, tiglyloxy group, natural compound, expected physiological activity (PAF antagonistic effect)

Summary（和文）

ケールラクトン類やクロマン類は、様々な生理活性作用を持っていることが報告されて来た。例えば、抗ウイルス薬、免疫活性化薬、血小板活性化因子（パフ）に対する拮抗作用、抗ヒト免疫不全ウイルス薬などがある。

ここに、天然化合物と同様の分子骨格構造を有する新規にデザインした２つの化学的なクロマン化合物、すなわち出発物質ジヒドロキシベンズアルデヒド（**12**）から（±）-シス-6-ヘキシル-5-メトキシ-2,2-ジメチル-3,4-ジチグリルオキシクロマン化合物（**10**）、および出発物質メチル 4-ヒドロキシベンゾエート（**20**）から（±）-トランス-4-イソプロピルアミノ-6-メトキシカルボニル-2,2-ジメチル-3-チグリルオキシクロマン化合物（**11**）が、化学的な変換により調製された。

これらは、構造活性相関を考慮し、より効果的な生理活性作用へと指向されるかもしれない先導的クロマン化合物発見のための探索研究を行ったものである。特に、パフに対する拮抗作用を指向するものである。

Key words（和文）
クロマン化合物、製法、チグリルオキシ基、天然化合物、期待される生理活性（パフ拮抗作用）

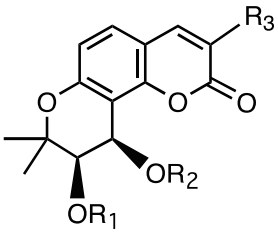
Ⅰ. Introduction

Various biological activities of natural and chemical khellactones, namely, hypotensive effects,[1] piscicidal effects,[1] vasodilation,[1,2] calcium antagonistic action,[3] inhibition of platelet aggregation,[4] antispasmodic properties,[1,5] antiviral and immunostimulating agents,[6] and anti-HIV (human immunodeficiency virus) agents,[7] have been reported.

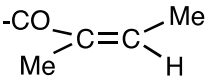
It was formerly found that the natural (constituent of *Peucedanum japonicum* Thunb.) and synthetic prenyl coumarins had calcium and histamine antagonistic activities and cerebral blood flow increasing effects.[8]

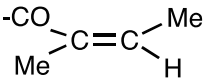
Also, the natural khellactone (**1**), and praeruptorin A (**2**) and B (**3**) isolated from *Peucedanum praeruptorum*,[9] had been investigated to have the specific antagonistic effect on platelet activating factor (PAF)[10] among several platelet aggregating agents as shown in Chart 1.[11]

The natural compounds with chroman molecular skeleton, Leptin D (**4**), E (**5**) and F (**6**) *etc.* are known to be isolated from plants as shown in Chart 2.[12,13]



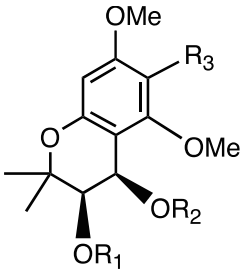
1 : $R_1 = R_2 = R_3 = H$

2 : $R_1 =$  , $R_2 = COMe$, $R_3 = H$

3 : $R_1 = R_2 =$  , $R_3 = H$

Natural compound:
Khellactone (**1**)
Praeruptorin A (**2**) and B (**3**)

Chart 1



4 : $R_1 = H$, $R_2 = H$, $R_3 = COMe$

5 : $R_1 = H$, $R_2 = CH_2CH_3$, $R_3 = COMe$

6 : $R_1 = H$, $R_2 = CH_2CH_2CH_2CH_3$, $R_3 = COMe$

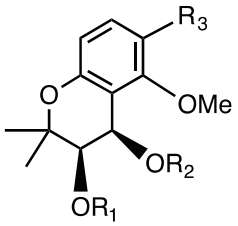
Natural compound: (Chroman Skeleton Type)
Leptin D (**4**), E (**5**) and F (**6**)

Chart 2

The chroman compound (derivatives) with naturally similar molecular skeleton have exhibited the various biological activities, for instance, antiviral and immunostimulating agents,[6] PAF antagonistic effect,[11] and anti-HIV agents,[7] *etc.*

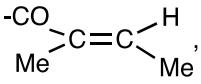
Previously, chroman compound derivatives (**7**), (**8**) and (**9**) having a alkyl group at the 6-position, a methoxy group at the 5-position, and acyl groups (relatively larger substituent, tiglyloxy groups) at the 3- and 4-positions were reported to possess a specific PAF antagonistic effect as well as khellactones as shown in Chart 3.[11]

On the other hand, similar 2,2-dimethylchroman analogs having larger substituents (bulky camphanoyloxy groups) at the 3- and 4-positions were known to have anti-HIV activity in several literatures of other researcher.[7]



7 : $R_1 = R_2 = H$, $R_3 = CH_2CH_2CH_3$, COOMe, etc.

8 : $R_1 = R_2 = COMe$, $R_3 = CH_2CH_2CH_3$, COOMe, etc.

9 : $R_1 = R_2 =$ 

, $R_3 = CH_2CH_2CH_3$, COOMe, etc.

Chemical compound:
Synthetic known chroman derivatives with similar molecular structures, compounds (**7**), (**8**) and (**9**)

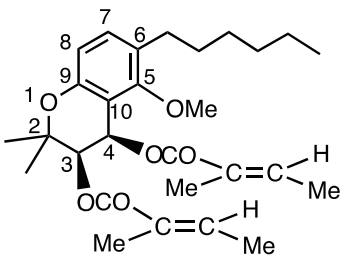
Chart 3

At this time, it planned to prepare for chroman compound which might be pointed to have more potent biological activity, especially, expected PAF antagonistic activity *etc.* , considering to structure activity relationship of the previously synthesized compounds.[7,11)]

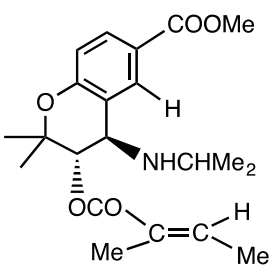
This paper report the preparation of the new designed chroman compound (**10**), (±)-*cis* -6-hexyl-5-methoxy-2,2-dimethyl-3,4-ditiglyloxychroman, and chroman compound (**11**), (±)-*trans* -4-isopropylamino-6-methoxycarbonyl-2,2-dimethyl-3-tiglyloxychroman as shown in Chart 4.

Ⅱ. Results and Discussion

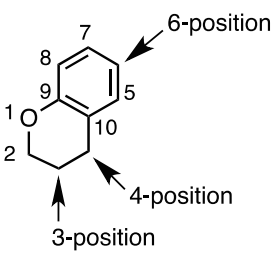
In this paper, it was designed that two chroman derivatives, compounds (**10**) and (**11**), having a moderate molecular length at 6-position and moderate larger substituent at the 3- and 4-positions might be suitable for structure modification to show potent PAF antagonist activity.



10



11



Chroman skeleton

Designed chemical chroman compounds (**10**) and (**11**)

Chart 4

Firstly, the new compound (**10**) having a hexyl group at 6-position, a methoxy group at 5-position, and two tiglyloxy groups at 3- and 4-positions (the same substituent pair of *cis* type) of chroman skeleton was planned as shown in Chart 4.

Etherification of dihydroxybenzaldehyde (**12**) with 3-chloro-3-methyl-1-butyne in the presence of K_2CO_3 in DMF, followed by cyclization reaction afforded the 6-formyl-5-hydroxy-2,2-dimethyl-2*H* -chromen (**13**) in 14.0% yield as shown in Chart 5.

Methylation of **13** with methyl iodide in the presence of K_2CO_3 in DMF gave the 6-formyl-5-methoxy-2,2-dimethyl-2*H* -chromen (**14**) in 91.9% yield. Oxidation of **14** with OsO_4 and *N* -methylmorpholine *N* -oxide (NMO) in acetone provided the (±)-*cis* -6-formyl-5-methoxy-2,2-dimethylchroman-3,4-diol (**15**) in 99.6% yield.

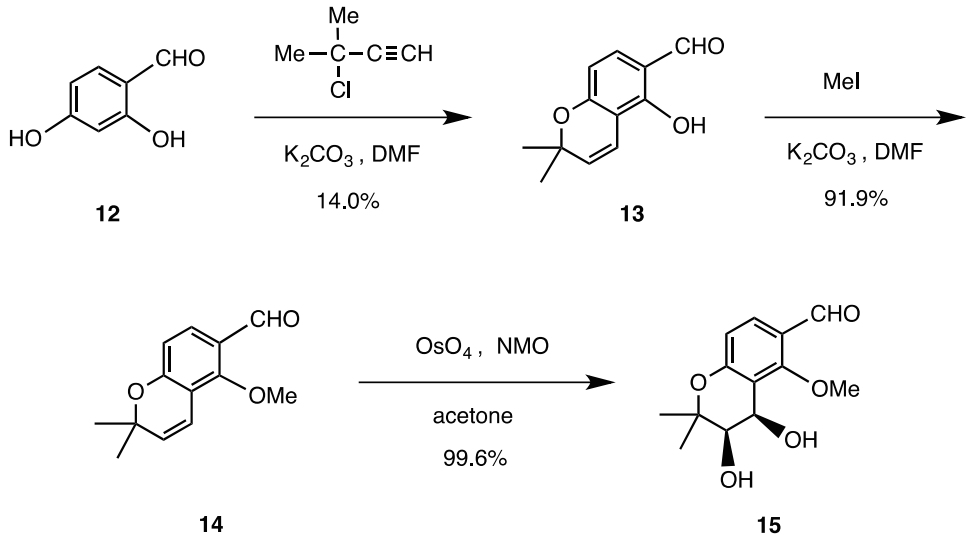


Chart 5

Protection of diol **15** with acetone in the presence of *p* -TsOH yielded (±)-*cis* -6-formyl-3,4-isopropylidenedioxy-5-methoxy-2,2-dimethylchroman (**16**) in 75.0% yield as shown in Chart 6. Wittig reaction of **16** with pentyltriphenylphosphonium iodide in THF gave (±)-*cis* -6-(1-*Z* -hexenyl)-3,4-isopropylidenedioxy-5-methoxy-2,2-dimethylchroman (**17**) in 91.2% yield.

Hydrogenation of **17** in the presence of 5% palladium carbon in MeOH provided (±)-*cis* -6-hexyl-3,4-isopropylidenedioxy-5-methoxy-2,2-dimethylchroman (**18**) in 92.0% yield. Deprotection of **18** with 1M HCl in MeOH afforded (±)-*cis* -6-hexyl-5-methoxy-2,2-dimethylchroman-3,4-diol (**19**) in 36.5% yield.

Acylation of **19** with tiglic anhydride in the presence of DMAP in pyridine yielded the new desired chroman compound (**10**), (±)-*cis* -6-hexyl-5-methoxy-2,2-dimethyl-3,4-ditiglyloxychroman, in 6.7% yield.

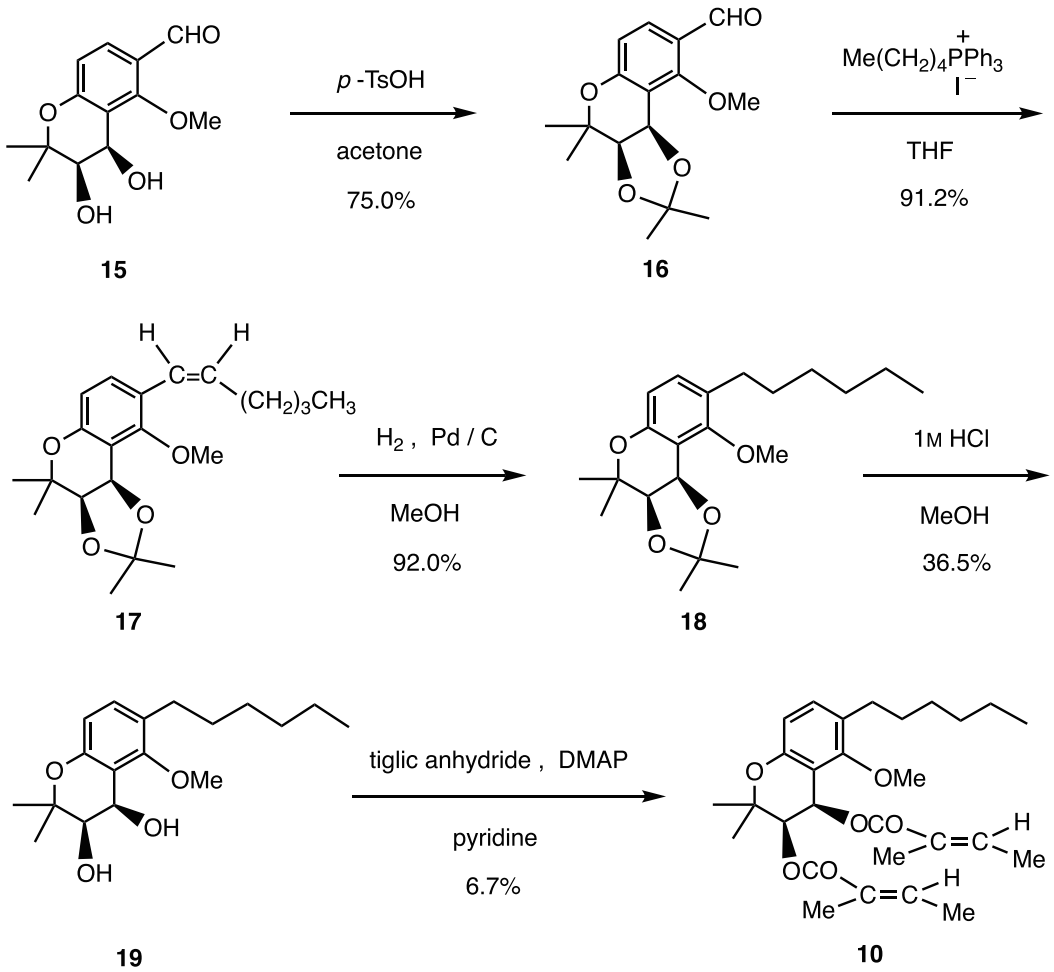


Chart 6

Next, the new compound (**11**) having a methoxycarbonyl group at 6-position, a tiglyloxy group at 3-position and an isopropylamino group at 4-position (the different substituent pair of *trans* type at 3- and 4-positions) of chroman skeleton was planned as shown in Chart 4.

Compound (**11**) was prepared as shown in Chart 7.[14,15] The reaction of 6-methoxycarbonyl-2,2-dimethyl-2*H* -chromen (**22**)[15a] with *N* -bromosuccinimide (NBS) in H_2O-DMSO afforded the (±)-*trans* -3-bromo-6-methoxycarbonyl-2,2-dimethylchroman-4-ol (**23**)[15a], and then dehydrohalogenation with NaOH in H_2O-dioxane provided the (±)-3,4-epoxy-6-methoxycarbonyl-2,2-dimethylchroman (**24**)[15a], followed by the amination reaction with isopropylamine in ethanol gave the (±)-*trans* -4-isopropylamino-6-methoxycarbonyl-2,2-dimethylchroman-3-ol (**25**).

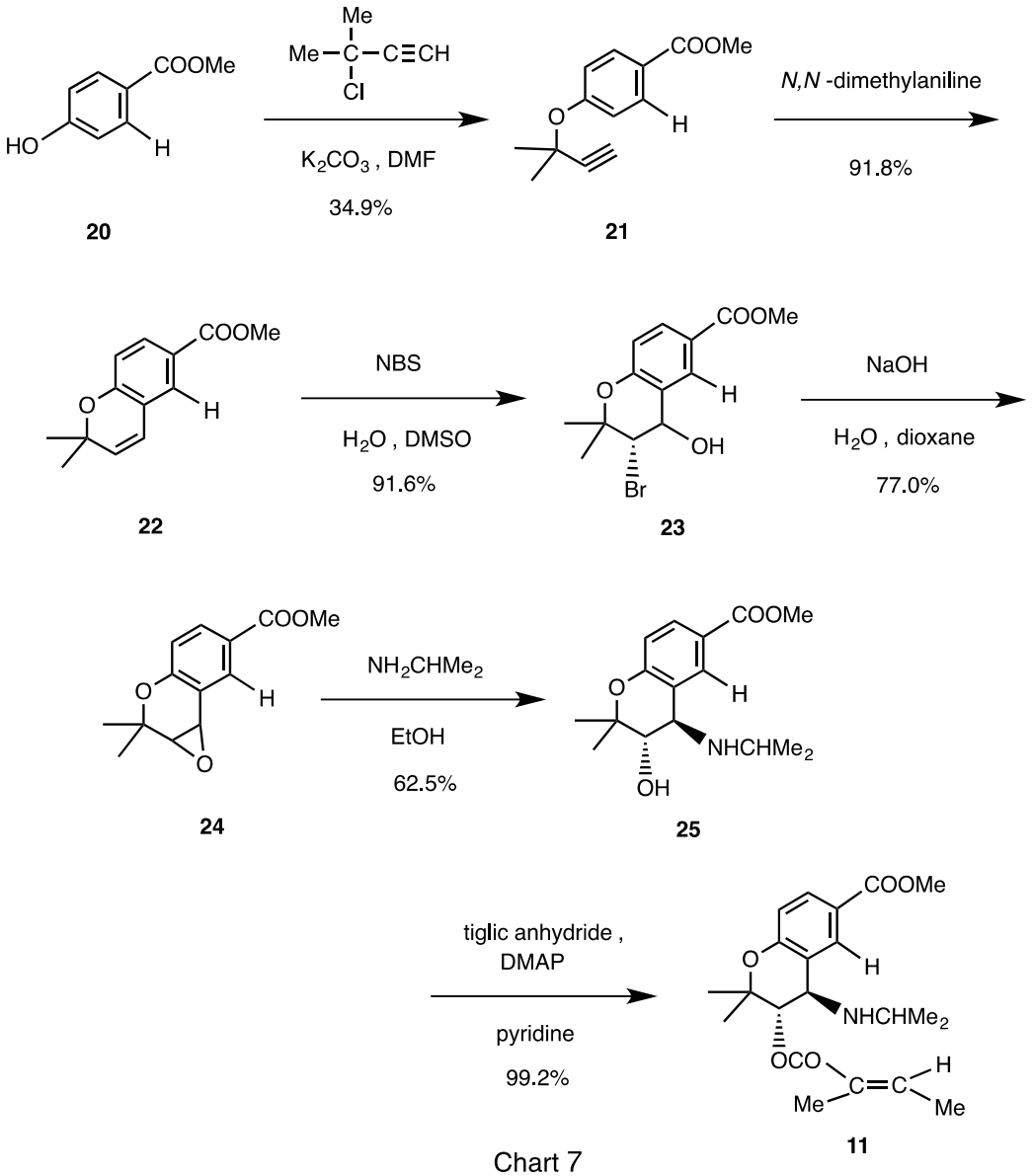


Chart 7

Acylation of **25** with tiglic anhydride in the presence of DMAP in pyridine provided the another new desired chroman compound (**11**), (±)-*trans* -4-isopropylamino-6-methoxycarbonyl-2,2-dimethyl-3-tiglyloxychroman, in 99.2% yield.

Ⅲ. Conclusion

In this study, the chroman compound, (±)-*cis* -6-hexyl-5-methoxy-2,2-dimethyl-3,4-ditiglyloxychroman (**10**) was designed and prepared from commercially available starting material dihydroxybenzaldehyde (**12**), *via* eight steps chemical transformations. And (±)-*trans* -4-isopropylamino-6-methoxycarbonyl-2,2-dimethyl-3-tiglyloxychroman (**11**) was also designed and prepared from starting material methyl 4-hydroxybenzoate (**20**), *via* six steps chemical transformations.

These compounds (**10**) and (**11**) were prepared for the first time and characterized by NMR, IR, high resolution mass spectrometry, and elemental analysis. The physiological activity, especially, PAF antagonistic activity *etc*., might be expected from the compounds (**10**) and (**11**).

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and were uncorrected. IR spectra were recorded with a JASCO FT/IR-200 or JASCO FT/IR-8000 spectrometer, and ^{1}H-NMR and ^{13}C-NMR, 2D NMR spectra with a JEOL EX-90 or JEOL JNM-α500 spectrometer, with tetramethylsilane as an internal standard. MS were recorded with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed with a Yanaco CHN-corder MT-3.

Ordinary-phase silica gel column chromatography (Silica gel 60 [Merck]) was used for column chromatography, and thin layer chromatography (TLC) was carried out on precoated Silica gel 60 F_{254} (0.2 mm; Merck, Darmstadt, Germany). NH-silica gel (basic 100 Å type silica gel, NH-DM 1020, Fuji Silysia Chemical, Ltd.) was used for column chromatography and NH-TLC. Ordinary-phase medium pressure liquid chromatography (MPLC) [packed SiO_2 column, 21×310 mm, C.I.G. I.D.-15, Kusano Kagakukikai Co., Japan] was used for column chromatography.

TLC spots were detected by UV radiation (254 nm). Organic solutions were dried over anhydrous $MgSO_4$.

6-Formyl-5-hydroxy-2,2-dimethyl-2*H*-chromen (13):

K_2CO_3 (14.0 g, 101.3 mmol) was added to a solution of 2,4-dihydroxybenzaldehyde (**12**) (2.0 g, 14.5 mmol) and 3-chloro-3-methyl-1-butyne (11.7 g, 114.1 mmol) in DMF (100 ml) and the mixture was stirred at 120℃ for 16 h, then poured into water. The mixture was acidified with 10% HCl, and extracted with ethyl acetate. The organic layer was washed with saturated NaCl solution, then dried and evaporated. The residue was subjected to silica gel column chromatography. The eluate with 5% ethyl acetate in hexane gave 414.1 mg (14.0%) of **13** as colorless needles (ether-hexane), mp 59-61℃ .

IR (nujol) cm^{-1} : 3300, 1640, 1615, 1570. ^{1}H-NMR ($CDCl_3$) δ : 1.46 (6H, s, -Me), 5.61 (1H, d, J = 10.1 Hz, olefinic H), 6.43 (1H, d, J = 8.6 Hz, aromatic H), 6.70 (1H, d, J = 10.1 Hz, olefinic H), 7.29 (1H, d, J = 8.6 Hz, aromatic H), 9.66 (1H, s, -CHO), 11.60 (1H, s, -OH). CI-MS m/z : 205 (M^++1).

6-Formyl-5-methoxy-2,2-dimethyl-2*H*-chromen (14):

K_2CO_3 (3.37 g, 24.4 mmol) was added to a solution of **13** (487 mg, 2.39 mmol) and MeI (3.51 g, 24.4 mmol) in DMF (16.4 ml) and the mixture was stirred at room temperature for 2 days, then poured into water. The mixture was acidified with 10% HCl, and extracted with ethyl acetate. The organic layer was washed with saturated NaCl solution, then dried and evaporated. The residue was subjected to silica gel column

chromatography. The eluate with 5% ethyl acetate in hexane gave 477.8 mg (91.9%) of **14** as a yellow oil.

IR (neat) cm^{-1} : 1690, 1600, 1580, 1470. ^{1}H-NMR ($CDCl_3$) δ : 1.47 (6H, s, -Me), 3.90 (3H, s, -Me), 5.69 (1H, d, J = 10.0 Hz, olefinic H), 6.58 (1H, d, J = 10.0 Hz, olefinic H), 6.68 (1H, d, J = 8.6 Hz, aromatic H), 7.66 (1H, d, J = 8.6 Hz, aromatic H). High-resolution EI-MS m/z : Calcd for $C_{13}H_{14}O_3$ (M^+): 218.0943. Found: 218.0965.

(±)-*cis*-6-Formyl-5-methoxy-2,2-dimethylchroman-3,4-diol (15):

OsO_4 (4.2 mg, 0.02 mmol) in *t*-BuOH (0.7 ml) was added to a solution of **14** (218.0 mg, 1.0 mmol) and *N*-methylmorpholine *N*-oxide (NMO) (190.0 mg, 1.62 mmol) in acetone (2.8 ml) in H_2O (5 ml) and the mixture was stirred at the room temperature for 19.5 h. $Na_2S_2O_3$ (63.5 mg, 0.40 mmol) and Talc (hydrous magnesium silicate) (759.6 mg, 2.00 mmol) in H_2O (7 ml) was added to the reaction mixture and the mixture was stirred at the room temperature for 1 h. The reaction mixture was filtered by Celite. The filtrate was acidified with 1M H_2SO_4 to pH 2, and extracted with ethyl acetate. The organic layer was washed with saturated NaCl solution, then dried and evaporated. The residue was subjected to silica gel column chromatography. The eluate with 33% ethyl acetate in hexane gave 251 mg (99.6%) of **15** as colorless needles (ether-hexane), mp 134-138℃.

IR (KBr) cm^{-1} : 3380, 1670, 1600, 1580. ^{1}H-NMR ($CDCl_3$) δ : 1.31 (3H, s, -Me), 1.45 (3H, s, -Me), 3.02 (1H, d, J = 3.3 Hz, -OH), 3.79 (1H, d, J = 4.6 Hz, methine H), 3.95 (1H, d, J = 4.2 Hz, -OH), 4.00 (3H, s, -Me), 5.04 (1H, d, J = 4.6 Hz, methine H), 6.70 (1H, d, J = 8.8 Hz, aromatic H), 7.69 (1H, d, J = 8.8 Hz, aromatic H), 10.09 (1H, s, -CHO). High-resolusion EI-MS m/z : Calcd for $C_{13}H_{16}O_5$ (M^+): 252.0996. Found: 252.0981.

(±)-*cis*-6-Formyl-3,4-isopropylidenedioxy-5-methoxy-2,2-dimethylchroman (16):

p-Toluenesulfonic acid (10.2 mg, 0.06 mmol) was added to a solution of **15** (147.9 mg, 0.59 mmol) in acetone (9 ml) and the mixture was refluxed for 5 min, then poured into water. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, and NaCl solution, then dried and evaporated. The residue was subjected to silica gel column chromatography. The eluate with 15% ethyl acetate in hexane gave 128.5 mg (75.0%) of **16** as a colorless oil.

IR (neat) cm^{-1} : 1680, 1600, 1580. ^{1}H-NMR ($CDCl_3$) δ : 1.24 (3H, s, -Me), 1.34 (3H, s, -Me), 1.45 (3H, s, -Me), 1.53 (3H, s, -Me), 4.05 (3H, s, -Me), 4.19 (1H, d, J = 6.4 Hz, methine H), 5.35 (1H, d, J = 6.4 Hz, methine H), 6.71 (1H, d, J = 8.8 Hz, aromatic H), 7.75 (1H, d, J = 8.8 Hz, aromatic H), 10.21 (1H, s, -CHO). High-resolution EI-MS m/z : Calcd for $C_{16}H_{20}O_5$ (M^+): 292.1310. Found: 292.1365.

Pentyltriphenylphosphonium Iodide:

PPh_3 (9.93 g, 37.9 mmol) was added to a solution of 1-iodopentane (5.0 g, 25.2 mmol) in acetonitrile (150 ml) and the mixture was stirred at 90℃ for 24 h, then was stirred at the room temperature for 18 h. The reaction mixture was filtered off, washed with THF, and dried *in vacuo*. These gave 11.49 g (98.8%) of pentyltriphenylphosphonium iodide as a white solid. (This compound was used as reagent without purification) ^{1}H-NMR

($CDCl_3$) δ : 0.82 (3H, t, J = 6.9 Hz, -Me), 1.10-1.90 (6H, m, methylene H), 3.45-3.90 (2H, m, methylene H), 7.54-8.01 (15H, m, aromatic H).

(±)-*cis* -6-(1-*Z* -Hexenyl)-3,4-isopropylidenedioxy-5-methoxy-2,2-dimethylchroman (17):

BuLi in hexane (1.17 M, 1.34 ml) was added to a solution of pentyltriphenylphosphonium iodide (725 mg, 1.57 mmol) in THF (10.8 ml) and the mixture was stirred at the room temperature for 1 h. Compound **16** (91.9 mg, 0.31 mmol) in THF (12 ml) was added to the reaction mixture, and the mixture was stirred at the room temperature for 30 min. The reaction mixture was poured into water, and extracted with ethyl acetate, then dried and evaporated. The residue was subjected to silica gel column chromatography. The eluate with 5% ethyl acetate in hexane gave 99.3 mg (91.2%) of **17** as a colorless oil.

IR (neat) cm^{-1} : 1600, 1580. ^{1}H-NMR ($CDCl_3$) δ : 0.91 (3H, t, J = 6.2 Hz, -Me), 1.24 (3H, s, -Me), 1.36 (3H, s, -Me), 1.45 (3H, s, -Me), 1.49 (3H, s, -Me), 1.56-1.75 (4H, m, methylene H), 2.27 (2H, t, J = 6.8 Hz, methylene H), 3.81 (3H, s, -Me), 4.14 (1H, d, J = 6.4 Hz, methine H), 5.33 (1H, d, J = 6.4 Hz, methine H), 5.59 (1H, t, J = 7.3 Hz, olefinic H), 5.71 (1H, t, J = 7.3 Hz, olefinic H), 6.58 (1H, t, J = 8.8 Hz, aromatic H), 7.13 (1H, d, J = 8.8 Hz, aromatic H). High-resolution EI-MS m/z : Calcd for $C_{21}H_{30}O_4$ (M^+): 346.2144. Found: 346.2174.

(±)-cis -6-Hexyl-3,4-isopropylidenedioxy-5-methoxy-2,2-dimethylchroman (18):

5% Palladium carbon (25.6 mg) was added to a solution of **17** (302.8 mg, 0.87 mmol) in MeOH (6 ml) and the mixture was hydrogenated at the room temperature for 1 h. The reaction mixture was filtrated, and evaporated. The residue was subjected to silica gel column chromatography. The eluate with ethyl acetate gave 280.2 mg (92.0%) of **18** as a colorless oil.

IR (neat) cm^{-1} : 1600, 1580. ^{1}H-NMR ($CDCl_3$) δ : 0.88 (3H, t, J = 6.8 Hz, -Me), 1.21 (3H, s, -Me), 1.24 (3H, s, -Me), 1.44 (3H, s, -Me), 1.46 (3H, s, -Me), 1.19-1.42 (8H, m, methylene H), 1.52-2.01 (2H, m, methylene H), 3.85 (3H, s, -OMe), 4.13 (1H, d, J = 6.4 Hz, methine H), 5.32 (1H, d, J = 6.4 Hz, methine H), 6.58 (1H, d, J = 8.4 Hz, aromatic H), 7.04 (1H, d, J = 8.4 Hz, aromatic H). High-resolution EI-MS m/z : Calcd for $C_{21}H_{32}O_4$ (M^+): 348.2293. Found: 348.2298.

(±)-cis -6-Hexyl-5-methoxy-2,2-dimethylchroman-3,4-diol (19):

1M HCl (6 ml) was added to a solution of **18** (91.5 mg, 0.26 mmol) in MeOH (6 ml) and the mixture was stirred at the room temperature for 4 h, then poured into water. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, and NaCl solution, then dried and evaporated. The residue was subjected to silica gel column chromatography. The eluate with 25% ethyl acetate in hexane gave 29.6 mg (36.5%) of **19** as a colorless oil.

IR (neat) cm^{-1} : 3480, 1600, 1580. ^{1}H-NMR ($CDCl_3$) δ : 0.88 (3H, t, J = 6.6 Hz, -Me), 1.30 (3H, s, -Me), 1.25-1.42 (6H, m, methylene H), 1.46 (3H, s, -Me), 1.53-1.60 (2H, m,

methylene H), 2.43-2.62 (2H, m, methylene H), 3.09 (1H, d, *J* = 3.7 Hz, -OH), 3.85 (3H, s, -OMe), 3.78 (1H, t, *J* = 4.8 Hz, methine H), 4.32 (1H, s, -OH), 5.05 (1H, d, *J* = 4.8 Hz, methine H), 6.60 (1H, d, *J* = 8.6 Hz, aromatic H), 7.03 (1H, d, *J* = 8.6 Hz, aromatic H). High-resolution EI-MS *m*/*z* : Calcd for $C_{18}H_{28}O_4$ (M^+): 308.1917. Found: 308.1985.

(±)-*cis* -6-Hexyl-5-methoxy-2,2-dimethyl-3,4-ditiglyloxychroman (10):

DMAP (27.3 mg, 0.22 mmol) was added to a solution of **19** (68.9 mg, 0.22 mmol) and tiglic anhydride (326.0 mg, 1.79 mmol) in pyridine (3 ml) and the mixture was stirred at 100℃ for 11 h. Ice water was added to the reaction mixture and the whole was stirred at the room temperature for 3 h, and extracted with ethyl acetate. The organic layer was washed with 10% HCl, saturated $NaHCO_3$ and NaCl solution, then dried and evaporated. The residue was subjected to silica gel column chromatography. The eluate with 10% ethyl acetate in hexane gave 7.1 mg (6.7%) of **10** as a colorless oil.

IR (neat) cm^{-1} : 1720, 1650, 1610, 1580. ^{1}H-NMR ($CDCl_3$) δ : 0.88 (3H, t, *J* = 6.9 Hz, -Me), 1.25-1.34 (6H, m, methylene H), 1.38 (3H, s, -Me), 1.47 (3H, s, -Me), 1.56 (6H, s, -Me), 1.76-1.81 (2H, m, methylene H), 1.78 (3H, d, *J* = 7.0 Hz, -Me), 1.79 (3H, d, *J* = 7.0 Hz, -Me), 2.48-2.58 (2H, m, methylene H), 3.66 (3H, s, -OMe), 5.30 (1H, d, *J* = 4.9 Hz, methine H), 6.50 (1H, d, *J* = 4.9 Hz, methine H), 6.62 (1H, d, *J* = 8.6 Hz, aromatic H), 6.80 (2H, q, *J* = 7.2 Hz, olefinic H), 7.10 (1H, d, *J* = 8.6 Hz, aromatic H). High-resolution EI-MS *m*/*z* : Calcd for $C_{28}H_{40}O_6$ (M^+): 472.2700. Found: 472.2822.

(±)-*trans* -4-Isopropylamino-6-methoxycarbonyl-2,2-dimethylchroman-3-ol (25):

Isopropylamine (71.4 mg, 1.21 mmol) was added to a solution of (±)-3,4-epoxy-6-methoxycarbonyl-2,2-dimethylchroman (**24**)[15a] (239 mg, 1.02 mmol) in ethanol (7 ml) and the mixture was refluxed for 30 h. The reaction mixture was evaporated. The residue was subjected to silica gel column chromatography. The eluate with 30% ethyl acetate in hexane gave 187 mg (62.5%) of **25** as colorless needles (ether-hexane), mp 96-100℃ .

IR (KBr) cm^{-1} : 3322, 1710, 1570, 1490. ^{1}H-NMR ($CDCl_3$) δ : 1.14 (3H, d, *J* = 6.2 Hz, -Me), 1.22 (3H, d, *J* = 6.2 Hz, -Me), 1.25 (3H, s, -Me), 1.50 (3H, s, -Me), 3.19-3.50 (1H, m, methine H), 3.30 (1H, d, *J* = 9.9 Hz, methine H), 3.60 (1H, d, *J* = 9.9 Hz, methine H), 3.86 (3H, s, -Me), 6.77 (1H, d, *J* = 8.6 Hz, aromatic H), 7.82 (1H, d, *J* = 8.6 Hz, aromatic H), 8.01 (1H, s, aromatic H). High-resolution EI-MS *m*/*z* : Calcd for $C_{16}H_{23}NO_4$ (M^+): 293.1627. Found: 293.1654.

(±)-*trans* -4-Isopropylamino-6-methoxycarbonyl-2,2-dimethyl-3-tiglyloxychroman (11):

DMAP (116 mg, 0.95 mmol) was added to a solution of **25** (279 mg, 0.95 mmol) and tiglic anhydride (1.73 g, 9.5 mmol) in pyridine (6 ml), and the mixture was stirred at 100°C for 19 h, then poured into water. The mixture was extracted with ethyl acetate. The organic layer was washed with 10% HCl, saturated $NaHCO_3$ and NaCl solution, then dried and evaporated. The residue was subjected to silica gel column chromatography. The eluate with 20% ethyl acetate in hexane gave 354 mg (99.2%) of

11 as colorless prisms (ethyl acetate-hexane), mp 91-95℃ .

IR (KBr) cm^{-1} : 2970, 1715, 1650, 1580. ^{1}H-NMR ($CDCl_3$) δ : 1.05 (3H, d, J = 6.2 Hz, -Me), 1.18 (3H, d, J = 6.2 Hz, -Me), 1.34 (3H, s, -Me), 1.43 (3H, s, -Me), 1.81 (3H, d, J = 8.4 Hz, -Me), 1.84 (3H, s, -Me), 3.01-3.30 (1H, m, methine H), 3.82 (1H, d, J = 6.8 Hz, methine H), 3.88 (3H, s, -Me), 5.13 (1H, d, J = 6.8 Hz, methine H), 6.83 (1H, d, J = 8.6 Hz, aromatic H), 6.78-6.92 (1H, m, olefinic H), 7.84 (1H, dd, J = 8.6, 1.7 Hz, aromatic H), 8.15 (1H, d, J = 1.7 Hz, aromatic H). High-resolution EI-MS m/z : Calcd for $C_{21}H_{29}NO_5$ (M^+): 375.2044. Found: 375.2044. *Anal.* Calcd for $C_{21}H_{29}NO_5$: C, 67.18 ; H, 7.79 ; N, 3.73. Found: C, 67.18 ; H, 7.79 ; N, 3.37.

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Conflict of Interest

The author declares no conflict of interest.

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