Synthesis of 2,6-Epithio-3-benzazocine Derivatives

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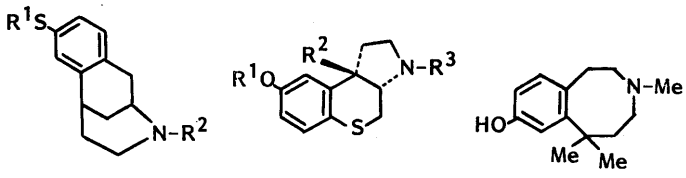
2,6-Epithio-3-benzazocines (9-thiabenzomorphans) in which the carbon atom at the 11-position is replaced by a sulfur atom, were synthesized by treatment of 1-(2-ethoxycarbonylaminoethyl)isothiochroman sulfoxides (16) with acetic anhydride or by heating 3-acetoxyisothiochromans (17) in Dowtherm A.

The hetero-acetal moiety of this novel heterocycle (15) was stable to lithium aluminum hydride and boron tribromide. Reduction of 15 with lithium aluminum hydride gave the *N*-methyl derivative (19) and demethylation of the 8-methoxy derivative (19b) with boron tribromide gave the 8-hydroxy derivative (20).

Keywords 2,6-epithio-3-benzazocine; 9-thiabenzomorphan; tetrahydro-1,3-thiazine; hetero-acetal; isothiochroman sulfoxide; Pummerer reaction; thermal cyclization

In connection with the study on sulfur-containing analgesic compounds, we previously reported syntheses and analgesic activities of 8-acylthio-3-benzazocines (**1**) and [1]benzothiopyrano[3,4-*b*]pyrrole derivatives (**2**).[1,2] None of **1** showed a Straub tail reaction, and some of **1** were not antagonized by naloxone. Compounds **2** have moderate analgesic activity. These findings prompted us to investigate the synthesis of analgesic compounds possessing a sulfur atom in the alicyclic moiety. 2,6-Epithio-3-benzazocines (I) in which the carbon atom at the 11-position of 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines is replaced by a sulfur atom would be metabolized through radical cleavage[3] of the C–S bond to give 3-benzazocines (II). As we reported that 8-hydroxy-3,6,6-trimethyl-3-benzazocines (**3**) did not show analgesic activity in man,[4] the 2,6-epithio-3-benzazocines (I) are expected to act as analgesics first and then to be metabolized to non-analgesic and non-narcotic compounds (II). Therefore, it is important to synthesize 2,6-epithio-3-benzazocines (I) which contain a hetero-acetal moiety and to investigate their chemical properties. In this paper, we describe the synthesis of 2,6-epithio-3-benzazocines having 1,1-dimethyl substituents.



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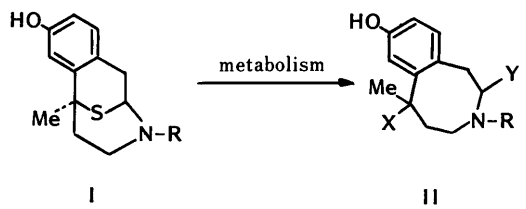


I II

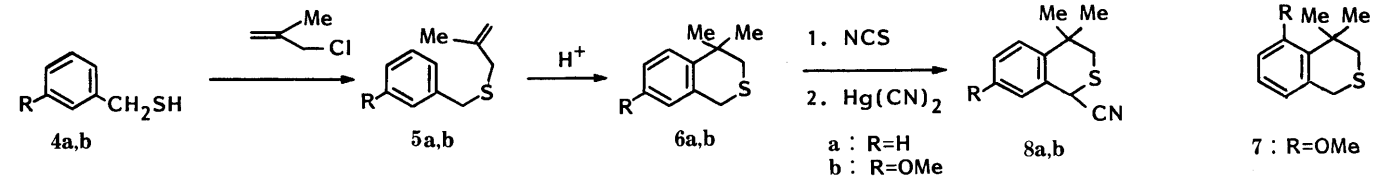
Chart 1

1-Cyano-4,4-dimethylisothiochromans (**8a**, **b**) were synthesized from phenylmethanethiols (**4a**, **b**) through the sequence of reactions shown in Chart 2. Treatment of the thiol **4** with 3-chloro-2-methylpropene afforded the sulfides (**5**), which were cyclized with a mixture of concentrated sulfuric acid and 85% phosphoric acid (1 : 1) to give the cyclic sulfides (**6**). In the case of the methoxy derivative **5b**, the isomeric sulfide (**7**) was not obtained. This regioselectivity was also achieved with polyphosphoric acid, but not with concentrated sulfuric acid, boron trifluoride, aluminum chloride, or *p*-toluenesulfonic acid. The results are summarized in Table I. Though phosphoric acid may play an important role in the regioselective cyclization, the reason for the regioselectivity is not clear so far. The sulfide (**6**) was chlorinated with *N*-chlorosuccinimide (NCS), and then immediately treated with mercury(II) cyanide[5] to give a nitrile (**8**).

TABLE I. Cyclization of **5b**

Reagent	Temp.	Time	Yield (%)	Product ratio **6b**:**7**
Conc.-H_2SO_4	r.t.	5 min	20	1:1
50% H_2SO_4	r.t.	18 h	100	2:1
Conc.-H_2SO_4 +85%H_3PO_4 (1:1)	r.t.	1 h	48	Only **6b**
BF_3–Et_2O (5 eq PhH)	r.t.	3 h	80	2:1
$AlCl_3$ (1 eq PhH)	0 °C	3 h	30	2:1
TsOH (1 eq PhH)	Reflux	16 h	90	2:1
PPA	90 °C	4 h	25	Only **6b**

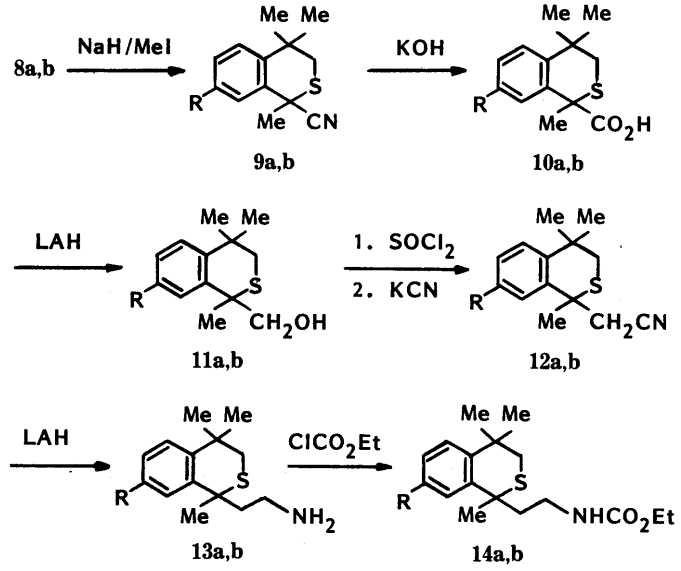
r.t. room temperature.



4a,b 5a,b 6a,b a : R=H b : R=OMe 8a,b 7 : R=OMe

Chart 2

The 1-cyanoisothiochromans (**8a**, **b**) were methylated with sodium hydride and methyl iodide to give **9a**, **b**, which were hydrolyzed with potassium hydroxide to give the carboxylic acids (**10a**, **b**).[6] Reduction of **10a**, **b** with lithium aluminum hydride (LAH) gave the alcohols (**11a**, **b**). Alternatively, the alcohol (**11a**) was successfully prepared in 24% overall yield by successive treatment of **6a** with *n*-butyllithium-ethyl formate, sodium hydride-methyl iodide, and LAH.[7] Chlorination of **11a**, **b** with thionyl chloride followed by cyanation with potassium cyanide gave the desired 1-cyanomethyl-1,4,4-trimethylisothiochromans (**12a**, **b**), which were submitted to reduction with LAH and then treated with ethyl chloroformate to afford 1-[2-(ethoxycarbonylamino)ethyl]isothiochromans (**14a**, **b**).



6a $\xrightarrow{1-5}$ 11a 1 : *n*-BuLi 2 : HCO_2Et 3 : NaH 4 : MeI 5 : LAH

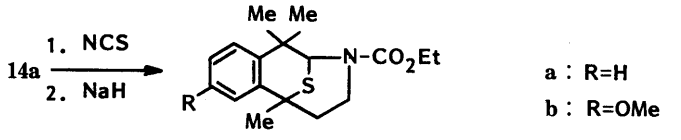


Chart 3

Next, we investigated cyclization of **14a**, **b** to 2,6-epithio-1,2,3,4,5,6-hexahydro-3-benzazocines (**15**). The carbamate (**14a**) was chlorinated with NCS, and then immediately treated with sodium hydride to give the expected cyclized product (**15a**) in 4.6% yield. The infrared (IR) spectrum of **15a** had a carbonyl absorption band at 1700 cm^{-1} and no NH-group band. The mass spectrum (MS) of **15a** showed a strong molecular peak at $m/z = 305$ (M^+). The nuclear magnetic resonance (NMR) spectrum (270 MHz) of **15a** showed five pairs of signals; triplets at 1.27 and 1.32 ppm due to the CH_3 of the ethoxy group, singlets at 1.43 and 1.44 ppm due to the C(1)-β-CH_3, singlets at 1.49 and 1.50 ppm due to the C(1)-α-CH_3, singlets at 5.07 and 5.25 ppm due to the C(2)-H, and quartets at 4.17—4.26 ppm due to the CH_2 of the ethoxy group. This observation was attributed to stereoisomerization of the urethane moiety of **15a** in $CDCl_3$. A similar phenomenon was observed in the NMR spectrum of **22**, synthesized by the reaction of the known compound **21**[8] with ethyl chloroformate (see Experimental).

In order to raise the yield of **15a**, an alternative route using the Pummerer reaction[9] was investigated, as shown in Chart 4. The carbonate (**14a**) was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to the sulfoxide (**16a**) in 86.7% yield. The sulfoxide (**16a**) was refluxed in acetic anhydride for 24 h to give the 2,6-epithio-3-benzazocine (**15a**) in 18.0% yield together with 3-acetoxyisothiochroman (**17a**), and the 3-acetoxy-*N*-acetyl derivative (**18a**) in 34.1% and 45.0% yields, respectively. This reaction was followed by thin layer chromatography (TLC) and it was found that 3-acetoxy compound (**17a**) was produced initially and then changed to **15a** and **18a**. Therefore, the acetoxy derivative (**17a**) was isolated and various cyclization conditions of **17a** to **15a** were investigated. The results are shown in Table II.

Heating **17a** in Dowtherm A at 200—205 °C afforded a higher yield (71.3%) of the cyclized product (**15a**). In spite of the formation of a diastereomeric mixture of the acetate

Table II. Cyclization of **17a**

Conditions	Time (h)	Yield (%) of **15a**
Reflux in xylene	8	—
Reflux in diglyme	16	12.5
200 °C in Dowtherm A	2.5	71.3
Reflux with NaH in THF	2	Only by-product

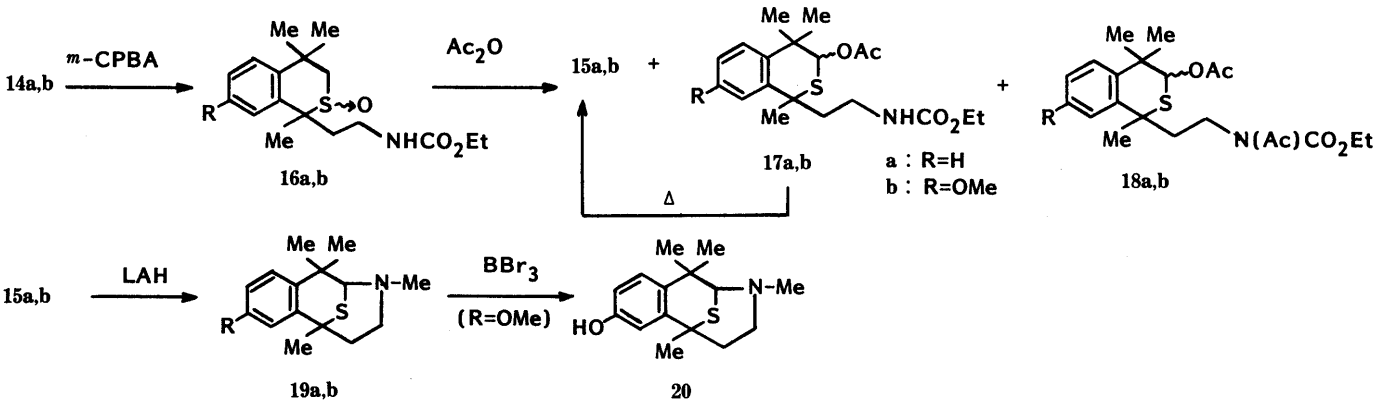


Chart 4

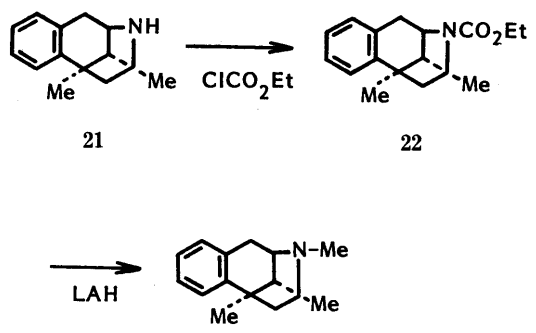


Chart 5

(**17a**) (1 : 1), **15a** was obtained stereoselectively in 71.3% yield, suggesting that this cyclization proceeded via a cation intermediate, but not through an S_N2 mechanism.[10]

When the sulfoxide **16a** was refluxed with acetic anhydride for 1 h to avoid the production of the diacetoxy compound (**18a**), the 3-acetoxy compound (**17a**) was obtained in 86.6% yield. As a result, epithiobenzazocine (**15a**) was obtained from **14a** in 53.5% yield. Similarly, 8-methoxyepithiobenzazocine (**15b**) was obtained in 38.7% yield from **14b**.

The mixtures of stereoisomers of the carbamates (**15a, b, 22**) were reduced with LAH to give the *N*-methyl derivatives (**19a, b, 23**) without the stereoisomer in 93.1%, 44.8%, and 95.2% yields, respectively. The physico-chemical data of **23** were identical with those of an authentic sample.[11] The NMR spectrum (270 MHz) of **19a** showed a broad doublet at 1.04 ppm due to C(5)-equatorial H, three singlets at 1.49, 1.56 and 1.64 ppm due to C(1)-α-CH_3, C(1)-β-CH_3 and C(6)-CH_3, respectively, a double triplet at 2.16 ppm due to C(5)-axial H, a broad doublet at 2.57 ppm due to C(4)-equatorial H, a singlet at 2.68 ppm due to *N*-CH_3, a multiplet at 2.93 ppm due to C(4)-axial H, and a singlet at 3.60 ppm due to C(2)-H. Coupling constants were determined by means of homodecoupling experiments as shown in the experimental section. Finally, **19b** was demethylated with BBr_3[12] to give our target compound, 2,6-epithio-1,2,3,4,5,6-hexahydro-8-hydroxy-1,1,3,6-tetramethyl-3-benzazocine (**20**) in 77.4% yield.

As the 2,6-epithio-3-benzazocine skeleton was found to be stable to LAH reduction and BBr_3 treatment as described above, we are now investigating the synthesis of the 1,1-unsubstituted derivative (2,6-epithio-1,2,3,4,5,6-hexahydro-3-benzazocine derivative).

Experimental

Melting points were measured on a Yanaco PM-2 (a hot stage type) and are uncorrected. IR spectra were determined on a JASCO IR-810 spectrometer. MS were recorded on a JEOL D-300 or a DX-300 spectrometer. ^{1}H-NMR spectra were taken on a Hitachi R-20B, a JEOL PMX-60 or a JEOL JNM-GX270 (270 MHz) instrument in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard unless otherwise stated (a = axial, e = equatorial). Elemental analyses were determined on a Yanaco CHN corder, model MT3. All reactions were carried out under an argon atmosphere. Sodium sulfate was used as a drying agent unless otherwise mentioned.

Benzyl 2-methyl-2-propenyl sulfide (**5a**) and 4,4-dimethylisothiochroman (**6a**) are known compounds,[13] but were synthesized in the same manner as **5b** and **6b**, respectively.

3-Methoxybenzyl 2-Methyl-2-propenyl Sulfide (5b) 3-Chloro-2-methylpropene (0.55 ml, 5.7 mmol) was added dropwise to a mixture of 3-methoxyphenylmethanethiol (**4b**) (0.80 g, 5.2 mmol) and NaOEt (0.2 g of Na in 40 ml of absolute EtOH) during 15 min. The reaction mixture was refluxed for 3 h, then stirred for 36 h at room temperature. After evaporation of the solvent, water was added to the residue and the mixture was extracted with Et_2O. The extract was dried and concentrated. The residue was purified by distillation under reduced pressure to give 0.94 g (86.7%) of **5b** as a colorless oil, bp 183 °C (1 mmHg). *Anal.* Calcd for $C_{12}H_{16}OS$: C, 69.19; H, 7.74. Found: C, 69.03; H, 7.91. IR (film): 1645, 1420 (C=C) cm^{-1}. ^{1}H-NMR δ: 1.85 (3H, t, J=1 Hz, CH_3), 3.05 (2H, s, SCH_2C=), 3.60 (2H, s, $ArCH_2S$), 3.80 (3H, s, OCH_3), 4.90 (2H, m, =CH_2), 6.65—7.50 (4H, m, ArH). MS *m/z*: 208 (M^+).

7-Methoxy-4,4-dimethylisothiochroman (6b) The sulfide **5b** (1.0 g, 4.8 mmol) was added to a mixture of concentrated H_2SO_4 and 85% H_3PO_4 (1 : 1) (20 ml). The reaction mixture was stirred for 1 h at room temperature and then poured into ice-water. After neutralization with dilute NaOH solution, the mixture was extracted with CH_2Cl_2. The extract was dried and evaporated. The residue was chromatographed on a silica gel column (Et_2O : *n*-hexane = 1 : 10) to afford 0.48 g (48.0%) of **6b** as colorless prisms, mp 67—70 °C. *Anal.* Calcd for $C_{12}H_{16}OS$: C, 69.19; H, 7.74. Found: C, 69.04; H, 7.81. ^{1}H-NMR δ: 1.40 (6H, s, C_4-$(CH_3)_2$), 2.70 (2H, s, C_3-H), 3.74 (2H, s, C_1-H_2), 3.75 (3H, s, OCH_3), 6.55—7.30 (3H, m, ArH). MS *m/z*: 208 (M^+).

1-Cyano-4,4-dimethylisothiochroman (8a) NCS (13.4 g, 100 mmol) was added portionwise to a stirred solution of **6a** (15.0 g, 84.1 mmol) in CH_2Cl_2 (80 ml) at 0—5 °C. After being stirred for 30 min, the reaction mixture was filtered and the filtrate was concentrated. The residue was heated with $Hg(CN)_2$ (22.4 g, 88.7 mmol) at 90 °C for 30 min. The reaction mixture was extracted with *n*-hexane–benzene (1 : 1). The extract was washed with brine, dried and concentrated. The residue was chromatographed on a silica gel column (Et_2O : *n*-hexane = 1 : 5) to give 10.0 g (58.5%) of **8a** as colorless prisms, mp 92—94 °C. *Anal.* Calcd for $C_{12}H_{13}NS$: C, 70.89; H, 6.45; N, 6.89. Found: C, 70.95; H, 6.51; N, 6.88. IR (KBr): 2210 (CN) cm^{-1}. ^{1}H-NMR δ: 1.42 (3H, s, C_4-CH_3), 1.47 (3H, s, C_4-CH_3), 2.66 (1H, dd, J=13.5, 4.0 Hz, C_3-H), 3.35 (1H, d, J=4.0 Hz, C_3-H), 4.63 (1H, d, J=4.0 Hz, C_1-H), 7.10—7.50 (4H, m, ArH). MS *m/z*: 203 (M^+), 130 (base).

1-Cyano-7-methoxy-4,4-dimethylisothiochroman (8b) In a similar manner to that used for the synthesis of **8a**, **6b** (0.5 g, 2.4 mmol) afforded 0.25 g (45.2%) of **8b** as colorless prisms, mp 112 °C. *Anal.* Calcd for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00. Found: C, 66.80; H, 6.48; N, 6.01. IR (KBr): 2240 (CN) cm^{-1}. ^{1}H-NMR δ: 1.40 (3H, s, C_4-CH_3), 1.45 (3H, s, C_4-CH_3), 2.65 (1H, dd, J=15, 1 Hz, C_3-H), 3.35 (1H, d, J=15 Hz, C_3-H), 3.77 (3H, s, OCH_3), 4.55 (1H, d, J=1 Hz, C_1-H), 6.50—7.40 (3H, m, ArH). MS *m/z*: 233 (M^+).

1-Cyano-1,4,4-trimethylisothiochroman (9a) NaH (60%; 3.00 g, 125 mmol) was added portionwise to a solution of **8a** (7.95 g, 39.1 mmol) in dimethylformamide (DMF) (40 ml) at 0 °C. The mixture was stirred for 3 h at 20 °C, then methyl iodide (10.2 ml, 164 mmol) was added portionwise at 0 °C and the whole was stirred for 12 h at 20 °C. The mixture was poured into ice-water and extracted with Et_2O. The extract was dried and concentrated, and the residue was chromatographed on a silica gel column (Et_2O : *n*-hexane = 1 : 50) to give 5.18 g (60.9%) of **9a** as colorless prisms, mp 79—80 °C. *Anal.* Calcd for $C_{13}H_{15}NS$: 71.84; H, 6.96; N, 6.44. Found: C, 71.62; H, 7.08; N, 6.41. IR (KBr): 2220 (CN) cm^{-1}. ^{1}H-NMR δ: 1.45 (6H, s, C_4-$(CH_3)_2$), 2.13 (3H, s, C_1-CH_3), 2.99 (2H, ABq, J=14.3 Hz, $\Delta\nu$=35.5 Hz, CH_2), 7.00—7.55 (4H, m, ArH). MS *m/z*: 217 (M^+).

1-Cyano-7-methoxy-1,4,4-trimethylisothiochroman (9b) In a similar manner to that described for the synthesis of **9a**, **8b** (0.5 g, 2.1 mmol) afforded 0.53 g (100%) of **9b** as colorless prisms, mp 120—121 °C. *Anal.* Calcd for $C_{14}H_{17}NOS$: C, 67.98; H, 6.93; N, 5.66. Found: C, 67.92; H, 6.93; N, 5.62. IR (KBr): 2220 (CN) cm^{-1}. ^{1}H-NMR δ: 1.42 (6H, s, C_4-$(CH_3)_2$), 2.00 (3H, s, C_1-CH_3), 2.95 (2H, ABq, J=15 Hz, $\Delta\nu$=36 Hz, CH_2), 3.77 (3H, s, OCH_3), 6.50—7.40 (3H, m, ArH). MS *m/z*: 247 (M^+).

1,4,4-Trimethylisothiochroman-1-carboxylic Acid (10a) A mixture of **9a** (4.70 g, 2.16 mmol) and KOH (3.80 g, 67.7 mmol) in ethyleneglycol (100 ml) and water (20 ml) was stirred for 48 h at 125 °C. The reaction mixture was poured into water, and acidified with dilute HCl. The resulting precipitate was filtered, the filtrate was dried and the product was recrystallized from AcOEt–*n*-hexane to give 4.28 g (84.3%) of **10a** as colorless prisms, mp 179—180.5 °C. *Anal.* Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82. Found: C, 66.12; H, 6.98. IR (KBr): 1690 (C=O) cm^{-1}. ^{1}H-NMR δ: 1.45 (3H, s, C_4-CH_3), 1.49 (3H, s, C_4-CH_3), 1.82 (3H, s, C_1-CH_3), 2.93 (2H, ABq, J=14.3 Hz, $\Delta\nu$=30.9 Hz, CH_2), 7.00—7.55 (4H, m, ArH). MS *m/z*: 236 (M^+).

7-Methoxy-1,4,4-trimethylisothiochroman-1-carboxylic Acid (10b) In a

similar manner to that used for the synthesis of **10a**, **9b** (0.5 g, 2 mmol) afforded 0.54 g (100%) of **10b**, mp 141—142 °C. *Anal.* Calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81. Found: C, 63.33; H, 6.88. IR (KBr): 1690 (C=O) cm^{-1}. ^{1}H-NMR δ: 1.40 (3H, s, C_4-CH_3), 1.42 (3H, s, C_4-CH_3), 1.75 (3H, s, C_1-CH_3), 2.85 (2H, ABq, J=14 Hz, $\Delta\nu$=65 Hz, CH_2), 3.70 (3H, s, OCH_3), 6.60—7.40 (3H, m, ArH), 11.75 (1H, s, COOH). MS *m/z*: 266 (M^+).

1,4,4-Trimethylisothiochroman-1-ylmethanol (11a) Method A: A mixture of **10a** (3.95 g, 16.7 mmol) and LAH (1.4 g, 36.9 mmol) in Et_2O (150 ml) was refluxed for 3 h. After the reaction mixture was treated with water, concentrated HCl was added and then extracted with Et_2O. The extract was dried and concentrated to give 3.50 g (94.2%) of **11a** as a colorless oil.

Method B: A 1 N solution of *n*-BuLi in Et_2O (30.0 ml, 30.0 mmol) was added dropwise to a stirred solution of **6a** (5.35 g, 30.0 mmol) in tetrahydrofuran (THF) (100 ml) at −40—−30 °C. The mixture was stirred for 3 h, then ethyl formate (3.20 ml, 39.6 mmol) was added dropwise at −65 °C and stirring was continued for 2 h. The temperature was raised to 0 °C, and the reaction mixture was poured into ice-water, acidified with dilute H_2SO_4, and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried and concentrated. The residue was taken up in THF (800 ml). NaH (60%; 1.00 g, 25.0 mmol) was added to the THF solution at 0—5 °C and the mixture was stirred for 30 min. MeI (1.70 ml, 27.3 mmol) was added to the reaction mixture at 0—5 °C and stirring was continued for 8 h at room temperature. LAH (1.00 g, 26.4 mmol) was added to the reaction mixture at 0—5 °C and stirring was continued for 12 h at room temperature. The reaction mixture was treated with water and concentrated HCl, and extracted with Et_2O. The Et_2O extract was separated, dried, and evaporated. The residue was chromatographed on a silica gel column (Et_2O : *n*-hexane = 1 : 20—1 : 6) to give 1.60 g (24.0%) of **11a**. IR (film): 3400 (OH) cm^{-1}. ^{1}H-NMR δ: 1.40 (3H, s, C_4-CH_3), 1.46 (3H, s, C_4-CH_3), 1.60 (3H, s, C_1-CH_3), 2.60 (1H, br s, OH), 2.65 (2H, ABq, J=13.7 Hz, $\Delta\nu$=21.2 Hz, C_3-H_2), 3.63 (2H, ABq, J=12 Hz, $\Delta\nu$=11.8 Hz, CH_2OH), 7.00—7.50 (4H, m, ArH). MS *m/z*: 222 (M^+). High-resolution MS *m/z*: 222.1077. Found: 222.1061.

7-Methoxy-1,4,4-trimethylisothiochroman-1-ylmethanol (11b) In a similar manner to that described for the synthesis of **11a** (method A), **10b** (0.53 g, 1.97 mmol) afforded 0.37 g (76.0%) of **11b** as colorless prisms, mp 48—49 °C. *Anal.* Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99. Found: C, 66.43; H, 7.98. IR (KBr): 3440 (OH) cm^{-1}. ^{1}H-NMR δ: 1.35 (3H, s, C_4-CH_3), 1.40 (3H, s, C_4-CH_3), 1.57 (3H, s, C_1-CH_3), 2.45 (1H, br s, OH), 2.60 (2H, ABq, J=13.5 Hz, $\Delta\nu$=36.6 Hz, C_3-H_2), 3.58 (2H, ABq, J=12 Hz, $\Delta\nu$=11.8 Hz, CH_2OH), 3.75 (3H, s, OCH_3), 6.60—7.40 (3H, m, ArH). MS *m/z*: 252 (M^+).

1,4,4-Trimethylisothiochroman-1-ylacetonitrile (12a) Thionyl chloride (2.00 ml, 27.5 mmol) was added to a stirred solution of **11a** (385 mg, 1.37 mmol) in CH_2Cl_2 (60 ml) at 0—5 °C. After being stirred for 1 h, the reaction mixture was filtered and the filtrate was concentrated. KCN (110 mg, 1.69 mmol), water (10 ml) and ethanol (50 ml) were added to the residue. After being refluxed for 3 h, the reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The extract was dried and concentrated. The residue was chromatographed on a silica gel column (Et_2O : *n*-hexane = 1 : 20—1 : 4) to give 2.64 g (64.1%) of **12a** as colorless prisms, mp 122.5—124 °C. *Anal.* Calcd for $C_{14}H_{17}NS$: C, 72.68; H, 7.41; N, 6.05. Found: C, 72.88; H, 7.55; N, 6.01. IR (KBr): 2250 (CN) cm^{-1}. ^{1}H-NMR δ: 1.45 (6H, s, C_4-$(CH_3)_2$), 1.80 (3H, s, C_1-CH_3), 2.78 (2H, ABq, J=14.3 Hz, $\Delta\nu$=24.7 Hz, C_3-H_2), 2.99 (2H, ABq, J=11.5 Hz, $\Delta\nu$=4.9 Hz, CH_2CN), 7.05—7.55 (4H, m, ArH). MS *m/z*: 231 (M^+).

7-Methoxy-1,4,4-trimethylisothiochroman-1-ylacetonitrile (12b) In a similar manner to that used for the synthesis of **12a**, **11b** (0.5 g, 1.98 mmol) afforded 0.52 g (100%) of **12b** as colorless prisms, mp 112—114 °C. *Anal* Calcd for $C_{15}H_{19}NOS$: C, 68.93; H, 7.33; N, 5.36. Found: C, 69.02; H, 7.42; N, 5.35. IR (KBr): 2250 (CN) cm^{-1}. ^{1}H-NMR δ: 1.40 (6H, s, C_4-$(CH_3)_2$), 1.77 (3H, s, C_1-CH_3), 2.74 (2H, ABq, J=14.7 Hz, $\Delta\nu$=25 Hz, C_3-H_2), 2.96 (2H, ABq, J=11 Hz, $\Delta\nu$=6.5 Hz, CH_2CN), 3.77 (3H, s, OCH_3), 6.70—7.40 (3H, m, ArH). MS *m/z*: 261 (M^+).

1-(2-Aminoethyl)-1,4,4-trimethylisothiochroman (13a) LAH (0.57 g, 15 mmol) was added portionwise to a stirred solution of **12a** (1.33 g, 5.75 mmol) in Et_2O (60 ml) at 0 °C during 5 min. After being refluxed for 3.5 h, the reaction mixture was treated with 5% NaOH and filtered. The filtrate was concentrated to give 1.23 g (91.0%) of **13a** as a yellowish oil. IR (film): 3370, 3290 (NH_2) cm^{-1}. ^{1}H-NMR δ: 1.30 (2H, s, NH_2), 1.42 (6H, s, C_4-$(CH_3)_2$), 1.66 (3H, s, C_1-CH_3), 1.80—3.00 (4H, m, CH_2CH_2N), 2.73 (2H, s, C_3-H_2), 7.00—7.50 (4H, m, ArH). MS *m/z*: 235 (M^+).

The oxalate of **13a** was recrystallized from acetone to give colorless prisms, mp 157—159 °C. *Anal.* Calcd for $C_{16}H_{23}NO_4S \cdot 0.5\ H_2O$: C, 57.46; H, 7.23; N, 4.19. Found: C, 57.58; H, 7.16; N, 4.08.

1-(2-Aminoethyl)-7-methoxy-1,4,4-trimethylisothiochroman (13b) In a similar manner to that described for the synthesis of **13a**, **12b** (0.1 g, 0.4 mmol) afforded 93 mg (87.6%) of **13b** as a yellowish oil. IR (film): 3360, 3290 (NH_2) cm^{-1}. ^{1}H-NMR δ: 1.39 (6H, s, C_4-$(CH_3)_2$), 1.64 (3H, s, C_1-CH_3), 1.80—3.00 (4H, m, CH_2CH_2N), 1.97 (2H, br s, NH_2), 2.70 (2H, s, C_3-H_2), 3.77 (3H, s, OCH_3), 6.60—7.50 (3H, m, ArH). MS *m/z*: 265 (M^+).

The oxalate of **13b**, colorless prisms, mp 166—168 °C. *Anal.* Calcd for $C_{15}H_{25}NO_5S \cdot 0.5\ H_2O$: C, 56.02; H, 7.19; N, 3.84. Found: C, 55.76; H, 7.03; N, 3.56.

1-[2-(Ethoxycarbonylamino)ethyl]-1,4,4-trimethylisothiochroman (14a) A mixture of **13a** (3.18 g, 13.5 mmol), ethyl chloroformate (1.5 ml, 15.8 mmol) and $NaHCO_3$ (1.3 g, 15.5 mmol) in dry benzene (120 ml) was refluxed for 6 h, washed with dilute HCl, dried, and concentrated to give 3.89 g (93.7%) of **14a** as colorless prisms, mp 58.5—61 °C. *Anal.* Calcd for $C_{17}H_{25}NO_2S$: C, 66.39; H, 8.19; N, 4.59. Found: C, 66.13; H, 8.34; N, 4.48. IR (KBr): 3340 (NH), 1715, 1690 (C=O) cm^{-1}. ^{1}H-NMR δ: 1.20 (3H, t, J=7 Hz, $CO_2CH_2CH_3$), 1.40 (6H, s, C_4-$(CH_3)_2$), 1.65 (3H, s, C_1-CH_3), 1.75-2.70 (2H, m, CH_2CH_2N), 2.72 (2H, s, C_3-H_2), 3.00—3.50 (2H, m, CH_2CH_2N), 4.08 (2H, q, J=7 Hz, $CO_2CH_2CH_3$), 4.75—5.25 (1H, br, NH), 7.00—7.50 (4H, m, ArH). MS *m/z*: 307 (M^+).

1-[2-(Ethoxycarbonylamino)ethyl]-7-methoxy-1,4,4-trimethylisothiochroman (14b) In a similar manner to that used for the synthesis of **14a**, **13b** (0.1 g, 0.37 mmol) afforded **14b** (80 mg, 61.0%) as a colorless oil. An analytical sample was purified by preparative thin layer chromatography on silica gel. *Anal.* Calcd for $C_{18}H_{27}NO_3S$: C, 64.06; H, 8.06; N, 4.15. Found: C, 63.87; H, 8.18; N, 3.89. IR (film): 3320 (NH), 1710 (C=O) cm^{-1}. ^{1}H-NMR δ: 1.14 (3H, t, J=7 Hz, $CO_2CH_2CH_3$), 1.31 (6H, s, C_4-$(CH_3)_2$), 1.58 (3H, s, C_1-CH_3), 1.50—2.50 (2H, m, CH_2CH_2N), 2.62 (2H, s, C_3-H_2), 2.90—3.50 (2H, m, CH_2CH_2N), 3.70 (3H, s, OCH_3), 4.01 (2H, q, J=7 Hz, $CO_2CH_2CH_3$), 4.75 (1H, br, NH), 6.55—7.40 (3H, m, ArH). MS *m/z*: 337 (M^+).

1-[2-(Ethoxycarbonylamino)ethyl]-1,4,4-trimethylisothiochroman 2-Oxide (16a) *m*-CPBA (0.64 g, 3.71 mmol) was added portionwise to a solution of **14a** (1.14 g, 3.71 mmol) in CH_2Cl_2 (50 ml) at 0 °C during 15 min. After being stirred for 15 min, the reaction mixture was washed with 5% $NaHCO_3$, dried, and concentrated. The residue was chromatographed on a silica gel column (Et_2O : acetone = 5 : 1) to give 1.10 g (91.7%) of **16a** as a colorless oil. IR (film): 3280 (NH), 1705 (C=O), 1030 (SO) cm^{-1}. ^{1}H-NMR δ: 1.20 and 1.24 (3H, each t, J=7 Hz, $CO_2CH_2CH_3$), 1.52 (6H, br s, C_4-$(CH_3)_2$), 1.54 and 1.83 (3H, each s, C_1-CH_3), 1.75—3.60 (6H, m, CH_2CH_2N and C_3-H_2), 4.11 and 4.17 (2H, q, J=7 Hz, $CO_2CH_2CH_3$), 4.80—5.25 (1H, br, NH), 7.05—7.65 (4H, m, ArH). MS *m/z*: 323 (M^+). High-resolution MS *m/z*: 323.1585. Found: 323.1556.

1-[2-(Ethoxycarbonylamino)ethyl]-7-methoxy-1,4,4-trimethylisothiochroman 2-Oxide (16b) In a similar manner to that used for the synthesis of **16a**, **14b** (0.2 g, 0.6 mmol) afforded 0.13 g (63.3%) of **16b** as a colorless prisms, mp 131—133 °C. *Anal* Calcd for $C_{18}H_{27}NO_4S$: C, 61.16; H, 7.70; N, 3.96. Found: C, 61.10; H, 7.89; N, 3.98. IR (film): 3280 (NH), 1700 (C=O), 1030 (SO) cm^{-1}. ^{1}H-NMR δ: 1.20 and 1.22 (3H, each t, J=7 Hz, $CO_2CH_2CH_3$), 1.45 (6H, br s, C_4-$(CH_3)_2$), 1.51 (3H, s, C_1-CH_3), 1.80—3.50 (6H, m, CH_2CH_2N and C_3-H_2), 3.81 and 3.83 (3H, each s, OCH_3), 4.09 and 4.12 (2H, each q, J=7 Hz, $CO_2CH_2CH_3$), 5.00—5.40 (1H, br, NH), 6.70—7.40 (3H, m, ArH). MS *m/z*: 353 (M^+), 221 (base).

2,6-Epithio-3-ethoxycarbonyl-1,2,3,4,5,6-hexahydro-1,1,6-trimethyl-3-benzazocine (15a) Method A: A mixture of **14a** (0.35 g, 1.14 mmol) and NCS (0.15 g, 1.12 mmol) in CCl_4 (8 ml) and CH_2Cl_2 (2 ml) was stirred for 1 h at 20 °C, then filtered and the filtrate was concentrated. NaH (60%; 46.0 mg, 1.15 mmol) was added to a solution of the residue in THF (10 ml) at 0 °C. After being refluxed for 8 h, the reaction mixture was poured into ice-water and extracted with Et_2O. The extract was dried and concentrated. The residue was purified on TLC (Et_2O : *n*-hexane = 1 : 2) to give 16 mg (4.6%) of **15a** as colorless prisms, mp 83.5—85.5 °C. *Anal.* Calcd for $C_{17}H_{23}NO_2S$: C, 66.85; H, 7.59; N, 4.59. Found: C, 66.69; H, 7.57; N, 4.54. IR (KBr): 1700 (C=O) cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.27 and 1.32 (3H, each t, J=7 Hz, $CO_2CH_2CH_3$), 1.43, 1.44 (3H, each s, C_1-β-CH_3), 1.49, 1.50 (3H, each s, C_1-α-CH_3), 1.53—1.61 (1H, m, C_5-H_e), 2.02—2.15 (1H, m, C_5-H_a), 2.67—2.87 (1H, m, C_4-H_a), 4.08—4.30 (1H, m, C_4-H_e), 4.17—4.26 (2H, each q, J=7 Hz, $CO_2CH_2CH_3$), 5.07, 5.25 (1H, each s, C_2-H), 7.13—7.27 (3H, m, $C_{8,9,10}$-H), 7.35 (1H, br d, J=8 Hz, C_7-H). MS *m/z*: 305 (M^+).

Method B: A mixture of **16a** (2.70 g, 8.35 mmol) and acetic anhydride (180 ml) was refluxed for 24 h, and concentrated. The residue was purified by silica gel column chromatography (Et_2O : *n*-hexane = 1 : 10) to give 459 mg (18.0%) of **15a**, 1.04 g (34.1%) of **17a**, and 1.53 g (45.0%) of **18a**.

17a: IR (film): 3330 (NH), 1740, 1690 (C=O) cm^{-1}. ^{1}H-NMR δ: 1.21 (3H, t, J=7.0 Hz, $CO_2CH_2C\underline{H}_3$), 1.45 (3H, s, C_4-CH_3), 1.48 (3H, s, C_4-CH_3), 1.67 and 1.80 (3H, each s, C_1-CH_3), 2.02 (3H, s, $COCH_3$), 1.80—3.70 (4H, m, C_1-CH_2CH_2N), 4.08 (2H, q, J=7.0 Hz, $CO_2C\underline{H}_2CH_3$), 4.75—5.25 (1H, br, NH), 5.90 and 5.95 (1H, each s, C_3-H), 7.10—7.60 (4H, m, ArH). MS m/z: 365 (M^+).

18a: IR (film): 1730, 1695 (C=O) cm^{-1}. ^{1}H-NMR δ: 1.35 and 1.37 (3H, each t, J=7.0 Hz, $CO_2CH_2C\underline{H}_3$), 1.45 (3H, s, C_4-CH_3), 1.48 (3H, s, C_4-CH_3), 1.69 and 1.81 (3H, each s, C_1-CH_3), 2.03 (3H, s, $COCH_3$), 2.46 (3H, s, $NCOCH_3$), 1.80—2.90 (2H, m, C_1-$C\underline{H}_2CH_2N$), 3.05—4.05 (2H, m, C_1-$CH_2C\underline{H}_2N$), 4.26 and 4.29 (2H, each q, J=7.0 Hz, $CO_2C\underline{H}_2CH_3$), 5.91 and 5.95 (1H, each s, C_3-H), 7.05—7.55 (4H, m, ArH). MS m/z: 407 (M^+).

Method C: A mixture of **17a** (180 mg, 4.92 mmol) and Dowtherm A (12 ml) was heated at 200—205 °C for 2.5 h and chromatographed on a silica gel column (Et_2O : *n*-hexane = 1 : 2) to give 107 mg (71.3%) of **15a**.

2,6-Epithio-3-ethoxycarbonyl-1,2,3,4,5,6-hexahydro-8-methoxy-1,1,6-trimethyl-3-benzazocine (15b) Compound **16b** (0.10 g, 0.28 mmol) was refluxed in acetic anhydride (50 ml) for 1 h and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel to give 98 mg (88.3%) of **17b** as a pale yellow oil. In a similar manner to method C described for **15a**, **17b** (90 mg, 0.234 mmol) afforded 54 mg (69.2%) of **15b** as a colorless oil. *Anal.* Calcd for $C_{18}H_{25}NO_3S$: C, 64.45; H, 7.51; N, 4.18. Found: C, 64.16; H, 7.69; N, 3.93. IR (film): 1710, 1690 (C=O) cm^{-1}. ^{1}H-NMR δ: 1.21 and 1.31 (3H, each t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.40 (3H, s, C_1-CH_3), 1.46 (3H, s, C_1-CH_3), 1.67 (3H, s, C_6-CH_3), 1.80—3.30 (3H, m, C_4-H and C_5-H_2), 3.78 (3H, s, OCH_3), 3.90—4.50 (1H, m, C_4-H), 4.19 and 4.23 (2H, each q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 5.06 and 5.24 (1H, each s, C_2-H), 6.70—7.40 (3H, m, ArH). MS m/z: 335 (M^+).

2,6-Epithio-1,1,3,6-tetramethyl-1,2,3,4,5,6-hexahydro-3-benzazocine (19a) A mixture of **15a** (610 mg, 1.99 mmol) and LAH (120 mg, 3.16 mmol) in ether (40 ml) was refluxed for 40 min, treated with dilute NaOH and filtered. The filtrate was evaporated, and the residue was recrystallized with EtOH–H_2O to give 460 mg (93.1%) of **19a** as colorless prisms. mp 64—68 °C. *Anal.* Calcd for $C_{15}H_{21}NS$: C, 72.82; H, 8.56; N, 5.66. Found: C, 73.02; H, 8.72; N, 5.63. ^{1}H-NMR (270 MHz) δ: 1.04 (1H, ddd, J_{5e-5a}=13.5 Hz, J_{5e-4a}=3.5 Hz, J_{5e-4e}=3.5 Hz, C_5-H_e), 1.49 (3H, s, C_1-α-CH_3), 1.56 (3H, s, C_1-β-CH_3), 1.64 (3H, s, C_6-CH_3), 2.16 (1H, ddd, J_{5a-5e}=13.5 Hz, J_{5a-4a}=14 Hz, J_{5a-4e}=4 Hz, C_5-H_a), 2.57 (1H, ddd, J_{4e-4a}=14.5 Hz, J_{4e-5a}=4 Hz, J_{4e-5e}=3.5 Hz, C_4-H_e), 2.68 (3H, s, N-CH_3), 2.93 (1H, ddd, J_{4a-4e}=14.5 Hz, J_{4a-5a}=14 Hz, J_{4a-5e}=3.5 Hz, C_4-H_a), 3.60 (1H, s, C_2-H), 7.08—7.24 (3H, m, $C_{8,9,10}$-H), 7.37 (1H, dd, J_{ortho}=7.5 Hz, J_{meta}=1 Hz, C_7-H). MS m/z: 247 (M^+).

2,6-Epithio-8-methoxy-1,1,3,6-tetramethyl-1,2,3,4,5,6-hexahydro-3-benzazocine (19b) In a similar manner to that used for the synthesis of **19a**, **15b** (70 mg, 0.21 mmol) afforded 26 mg (44.8%) of **19b** as a colorless oil. *Anal.* Calcd for $C_{16}H_{23}NOS$: C, 69.27; H, 8.36; N, 4.88. Found: C, 68.99; H, 8.51; N, 4.88. ^{1}H-NMR δ:0.90—3.30 (4H, m, C_4-H_2 and C_5-H_2), 1.45 (3H, s, C_1-CH_3), 1.53 (3H, s, C_1-CH_3), 1.61 (3H, s, C_6-CH_3), 2.66 (3H, s, N-CH_3), 3.57 (1H, s, C_2-H), 3.77 (3H, s, OCH_3), 6.70—7.45 (3H, m, ArH). MS m/z: 277 (M^+).

2,6-Epithio-8-hydroxy-1,1,3,6-tetramethyl-1,2,3,4,5,6-hexahydro-3-benzazocine (20) A mixture of **19b** (170 mg, 0.61 mmol) and boron tribromide (0.10 ml, 1.10 mmol) in CH_2Cl_2 (30 ml) was stirred at room temperature for 4 h. Water was added to the mixture, and the CH_2Cl_2 layer was separated and dried. After filtration, the filtrate was chromatographed on a silica gel column ($CHCl_3$: MeOH = 10 ; 1) to give 120 mg (77.4%) of **20** as colorless prisms, mp 164 °C. *Anal.* Calcd for $C_{15}H_{21}NOS$: C, 68.40; H, 8.04; N, 5.32. Found: C, 68.13; H, 8.18; N, 5.28. IR (KBr): 3220 (OH) cm^{-1}. ^{1}H-NMR δ: 0.80—3.30 (4H, m, C_4-H_2 and C_5-H_2), 1.43 (3H, s, C_1-CH_3), 1,51 (3H, s, C_1-CH_3), 1.56 (3H, s, C_6-CH_3), 2.66 (3H, s, NCH_3), 3.57 (1H, s, C_2-H), 4.48 (1H, br, OH), 6.60—7.35 (3H, m, ArH). MS m/z: 263 (M^+).

3-Ethoxycarbonyl-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine (22) The mixture of **21**[8] (101 mg, 0.5 mmol), ethyl chloroformate (0.3 ml), and anhydrous K_2CO_3 (1 g) was refluxed in $CHCl_3$ for 72 h, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel (CH_2Cl_2 : *n*-hexane = 1 : 3) to give 116 mg (93.4%) of **22** as a colorless oil. IR (film): 1705 (C=O) cm^{-1}. ^{1}H-NMR (270 MHz) δ: 0.88 (3H, d, J=7 Hz, C_{11}-CH_3), 1.21—1.32 (3H, m, $CO_2CH_2C\underline{H}_3$), 1.38 (3H, s, C_6-CH_3), 1.69 (1H, ddd, J_{5a-5e}=13.5 Hz, J_{5a-4a}=13 Hz, J_{5a-4e}=4 Hz, C_5-H_a), 1.78 (1H, dq, J=7 Hz, J_{11-2}=2 Hz, C_{11}-H), 2.50—2.65 (1H, m, J_{4a-4e}=13.5 Hz, J_{4a-5a}=13 Hz, C_4-H_a), 2.68, 2.72 (1H, each d, $J_{1\beta-1\alpha}$=16 Hz, C_1-β-H), 3.18, 3.20 (each dd, $J_{1\alpha-1\beta}$=16 Hz, $J_{1\alpha-2}$=5.5 Hz, C_1-α-H), 3.80, 3.91 (1H, each dd, J_{4e-4a}=13.5 Hz, J_{4e-5a}=4 Hz, C_4-H_e), 4.13, 4.17 (2H, each q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.31, 4.44 (1H, br s, C_2-H), 7.03—7.20 (3H, m, $C_{8,9,10}$-H), 7.26 (1H, d, J=8 Hz, C_7-H). MS m/z: 248 (M^+).

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