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SYNTHESIS AND ANALGESIC ACTIVITY OF 4,7-DIMETHYL-3,4,4a,5,8,8a-HEXAHYDRO-2*H*-CHROMEN-4,8-DIOLS CONTAINING THIOPHENE SUBSTITUENTS

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*Hexahydro-2*H*-chromenes with thiophene fragments were synthesized via reactions of a* p*-menthane monoterpenoid diol with several thiophenecarboxaldehydes. Most of the synthesized compounds with an additional thiophene fragment displayed analgesic activity* in vivo *tests at a dose of 10 mg/kg. It was found that the activity in either an acetate-writhing test or a hot-plate test depended on the type and location of substituent in the heteroaromatic ring.*

Keywords: monoterpenes, thiophenecarboxaldehyde, clay, heterocyclic compounds, analgesic activity.

The discovery of new analgesic drugs is one of the most important tasks of contemporary pharmacology because those used currently are ineffective, especially for relieving chronic pain, and have many side effects [1–3]. The problem is exacerbated by the sharp drop in the last two decades in the number of new analgesics with regulatory approval [4].

Recently, we found that compounds **1** with the 3,4,4a,5,8,8a-hexahydro-2*H*-chromene skeleton that were synthesized by reacting the monoterpenoid (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-en-1,2-diol (**2**) with aromatic aldehydes **3** in the presence of K10 montmorillonite clay (Scheme 1) exhibited high analgesic activity [5]. Starting **2** could be synthesized in three steps from the very common monoterpenoid (–)-verbenone (**4**) using available reagents [6].

Heteroaromatic fragments instead of an aromatic ring with methoxy and/or hydroxy substituents can also produce analogs of **1** with high analgesic activity. The goals of the present work were to synthesize type **1** compounds containing a thiophene substituent and to study their analgesic activity.

The study began by reacting diol **2** with thiophene-2-carbaldehyde (**5a**) using K10 montmorillonite clay as a catalyst, which was used successfully earlier to perform similar transformations [7–10]. The reaction was carried out without a solvent. The reagents were evenly applied to the clay using CH_2Cl_2, which was then evaporated. The reaction mixture was stored for the required time at room temperature.

The reaction of **2** and **5a** occurred in 45 min, giving target product **6a** in 42% yield (Scheme 1), in contrast with previously studied reactions of **2** with aromatic aldehydes in the presence of K10 clay, complete conversion of which required up to 24 h [11]. The reaction time increased sharply (>20 h) and a complicated mixture of unidentified compounds formed if the reaction was performed without removing the solvent. Like for **1**, **6a** was formed as a mixture of diastereomers at the C atom bonded to the methyl and hydroxyl. The (*S*)–(*R*) isomeric ratio in this instance was 3.3:1.

Introducing a Br atom or methyl substituent into the aldehyde increased the reaction time to 2–2.5 h and gave product yields of 47–55% (Scheme 1). Dehydration product **7** was isolated in 26% yield together with target **6f** (38% yield) from the reaction mixture if 5-nitrothiophene-2-carbaldehyde (**5f**) was used (Scheme 1).

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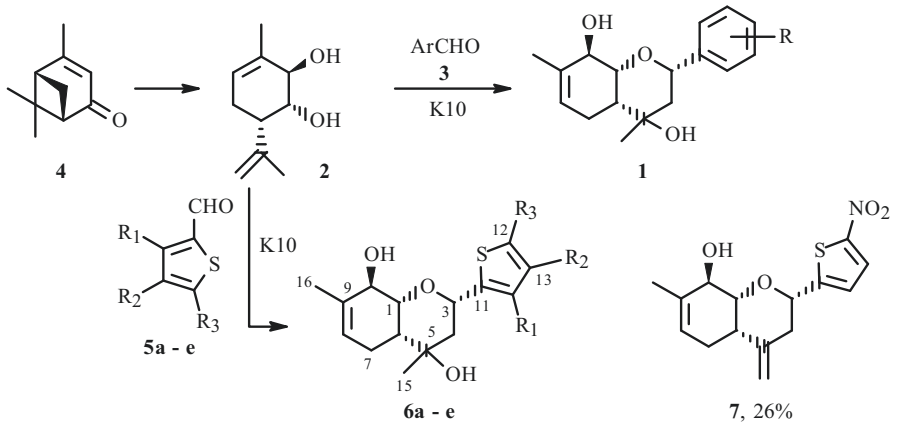
TABLE 1. Analgesic Activity of **6a**–**g**, **8**, **9**, **11**, and Sodium Diclofenac at a Dose of 10 mg/kg

Agent [(*S*)–(*R*) isomeric ratio]	Acetic writhing, number		Hot plate, s	
	control	agent (MPE, %)[a]	control	agent (protection, %)[b]
6a (3.1:1)	11.1 ± 0.6	10.3 ± 0.5	14.4 ± 1.7	15.6 ± 0.9
6b (1:1)	9.6 ± 0.9	9.0 ± 1.5	9.8 ± 0.8	13.4 ± 2.2 (37)*
6c (1.8:1)	9.6 ± 0.9	7.1 ± 1.2	9.8 ± 0.8	14.6 ± 1.4 (49)**
6d (1.4:1)	10.9 ± 0.5	7.6 ± 0.8 (30)**	18.4 ± 2.1	13.0 ± 1.8
6e (1.2:1)	10.9 ± 0.5	9.1 ± 0.6	18.4 ± 2.1	9.5 ± 1.5 (–48)**
6f (1.9:1)	10.0 ± 0.9	5.1 ± 1.1 (49)**	20.4 ± 3.2	20.5 ± 3.5
6g (2.0:1)	8.6 ± 0.6	5.4 ± 1.5	14.4 ± 2.5	15.3 ± 2.1
8	8.1 ± 1.1	9.7 ± 0.9	9.0 ± 1.3	7.3 ± 0.5
9	8.1 ± 1.1	8.3 ± 1.4	9.0 ± 1.3	10.6 ± 2.4
11 (1.4:1)	8.4 ± 1.5	7.3 ± 1.1	14.0 ± 1.2	11.8 ± 1.7
Sodium diclofenac	10.1 ± 1.9	5.0 ± 1.1 (50)***	9.6 ± 1.6	15.6 ± 2.4 (62)**

[a]MPE (maximum possible effect) (%) = 100% × ($K_{control} - K_{test}$)/$K_{control}$; [b]protection (%) = 100% × ($K_{test} - K_{control}$)/$K_{control}$; *P < 0.05; **P < 0.001 compared with the control group.



5a, 6a: $R_1 = R_2 = R_3 = H$; **5b, 6b:** $R_1 = R_3 = H$, $R_2 = Br$; **5c, 6c:** $R_1 = R_2 = H$, $R_3 = Br$
5d, 6d: $R_1 = Me$, $R_2 = R_3 = H$; **5e, 6e:** $R_1 = R_2 = H$, $R_3 = Me$; **5f, 6f:** $R_1 = R_2 = H$, $R_3 = NO_2$

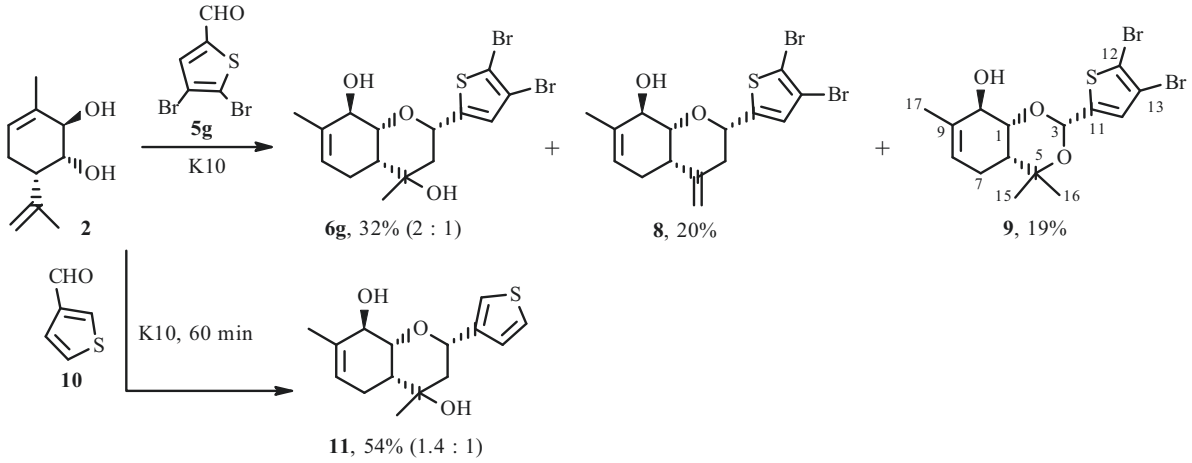
Scheme 1

The reaction of diol **2** with 4,5-dibromothiophene-2-carbaldehyde (**5g**) required a whole day for complete conversion of starting aldehyde **5g** with a 50% excess of **2**. Besides chromenes **6g** and **8**, compound **9** with the 1,3-benzodioxine skeleton was obtained in 19% yield (Scheme 2). Compounds with this skeleton were observed from the reaction of aldehydes with *cis*-verbenol epoxide [12] but not with **2**. The exception was the reaction of **2** with 3-hydroxy-4-methoxybenzaldehyde, which also produced a compound with the 1,3-benzodioxine skeleton but in very low (3%) yield [13].

The reaction of diol **2** with 3-thiophenecarboxaldehyde (**10**) in the presence of K10 clay formed heterocyclic product **11** in 54% yield (Scheme 2).

In all instances, diastereomers at the 4-position [(*S*)–(*R*) isomeric ratio given in parentheses after the yield in Scheme 2] were formed in comparable amounts.

The isomerism of (*S*)- and (*R*)-**6a**–**g** and **11** was due to different configurations of the methyl and hydroxyl groups on the same C atom. The ratio of (*S*)- and (*R*)-diastereomers was determined from PMR spectra from the ratio of H-3 peak areas. The vicinal spin–spin coupling constants (SSCC) between H-3 and H-4 and also between H-6 and H-7 were consistent with axial H-3 and H-6 in **6a**–**g** and **11**. Conversely, the vicinal SSCC between H-1 and H-10 indicated that they were equatorial. The CH_3-15 resonances in (*S*)-**6f**, (*S*)-**6g**, and (*S*)-**11** appeared as doublets with W-SSCC $^4J_{15,4a} \sim 0.6$–0.7 Hz, which indicated that the methyl was axial. The same constant was also observed for (*S*)-**6b**–(*S*)-**6e** with artificial line narrowing. This confirmed that the methyls were axial. As expected, all (*R*)-compounds **6a**–**g** and **11** had axial OH groups that caused paramagnetic shifts of the H-1 ($\delta \sim 0.4$ ppm) and H-3 ($\delta \sim 0.3$ ppm) resonances through 1,3-diaxial coupling. Resonances in ^{13}C NMR spectra were assigned using 2D ^{13}C–^1H spectra for direct SSCC ($^1J_{C,H} = 160$ Hz).



Scheme 2

Analgesic activity of the synthesized heterocyclic compounds was studied at a dose of 10 mg/kg using standard experimental acetic-writhing [14] and hot-plate [15] mouse pain models. The reference drug was sodium diclofenac injected at the same dose.

Table 1 presents data for **6a** and **11** with unsubstituted heteroaromatic rings that did not exhibit any analgesic activity. Introducing a Br atom into the molecule (**6b** and **6c**) produced significant analgesic activity in the hot-plate test although **6b** and **6c** were inactive in the acetic-writhing test. This was somewhat unexpected because analogous compounds containing a substituted phenyl fragment instead of a heteroaromatic one usually demonstrated analgesic activity in the acetic-writhing test and much more rarely in the hot-plate test [5].

Replacing the heteroaromatic 5-Br by a methyl on going from **6c** to **6e** reversed the nature of the observed effect, i.e., **6e** decreased significantly the residence time of the animals on the hot plate, thereby causing hyperalgesia instead of the analgesic effect found for **6c**. Moving the methyl from the 5- to the 3-position (**6d**) produced an analgesic effect in the acetic-writhing test. Hyperalgesia in the hot-plate test appeared only as a trend. Statistically significant differences were not found.

Debrominated **6g**, **8**, and **9** did not exhibit significant analgesic activity in both tests.

Compound **6f** with a nitro group was the most effective drug in the acetic-writhing test and was about as effective as the reference drug sodium diclofenac. However, it was inactive in the hot-plate test.

Thus, compounds with the hexahydro-2*H*-chromene skeleton were synthesized via the reaction of monoterpenoid **2** with heteroaromatic aldehydes contain S atoms. Compounds **6a** and **11** with unsubstituted heteroaromatic substituents did not show any analgesic activity. Compounds **6b** and **6c** with one Br atom on the heteroaromatic ring were active at a dose of 10 mg/kg in the hot-late test but were inactive in the acetic-writhing test. Also, **6f** with a nitro group demonstrated an analgesic effect in the acetic-writhing test although it was inactive in the hot-plate test. Replacing the 5-Br on the thiophene ring in **6c** by a methyl on going to **6e** produced hyperalgesia instead of an analgesic effect.

EXPERIMENTAL

We used commercially available reagents (Sigma-Aldrich, Acros) of at least 98% purity. (1*R*,2*R*,6*S*)-3-Methyl-6-(prop-1-en-2-yl)cyclohex-3-en-1,2-diol (**2**) {$[\alpha]_D^{31}$ –49.1° (*c* 2.6, $CHCl_3$)} was synthesized from (–)-verbenone (**4**) (Sigma-Aldrich) by the published method [6]. The catalyst was K10 clay (Fluka) that was calcined at 105°C for 3 h immediately before use. CH_2Cl_2 was passed over calcined Al_2O_3.

The reaction mixture was separated by column chromatography (CC) over silica gel (Macherey-Nagel, 60–200 μ) with elution by EtOAc (0–100%) in hexane. Fractions were analyzed by GC on an Agilent 7820A instrument with an HP-5 quartz column (copolymer of 5% diphenyl- and 95% dimethoxysiloxane, 30 m × 0.25 mm, 0.25 μm), flame-ionization detector, and He carrier gas (flow rate 2 mL/min, flow division 99:1). GC-MS spectra were recorded on a Hewlett–Packard 5890/II GC with an HP MSD 5971 quadrupole mass spectrometer as the detector, an HP-5ms quartz column (30000 × 0.25 mm), and He carrier gas.

PMR and ^{13}C NMR spectra were recorded using resonances of $CD(H)Cl_3$ (δ_H 7.24, δ_C 76.90 ppm) or $CD_3OD(H)$ (δ_H 3.34, δ_C 49.00 ppm) as internal standards on a Bruker DRX-500 spectrometer (^1H 500.13 MHz, ^{13}C 125.76 MHz). Structures of products were established by analyzing PMR and ^{13}C NMR spectra using ^1H–^1H double resonance, 2D homonuclear ^1H–^1H correlations (^1H–^1H COSY), and 2D heteronuclear ^{13}C–^1H correlations for direct spin–spin coupling constants (C–H COSY, $^1J_{C,H}$ = 160 Hz). Multiplicities of resonances in ^{13}C NMR spectra were determined from spectra recorded in J-modulation mode (JMOD); the elemental composition, from mass spectra recorded on a Thermo Scientific DFS spectrometer in full-scan mode over the range 0–500 *m/z* with electron-impact ionization at 70 eV and direct sample introduction. Specific rotation was measured on a PolAAr 3005 polarimeter from $CHCl_3$ solutions.

Reaction of (1*R*,2*R*,6*S*)-3-Methyl-6-(prop-1-en-2-yl)cyclohex-3-en-1,2-diol (2) with Aldehydes 5a–g and 11. General Method. A suspension of K10 clay in CH_2Cl_2 (5 mL) was treated with a solution of the appropriate aldehyde in CH_2Cl_2 (3 mL) and then a solution of **2** in CH_2Cl_2 (3 mL). The solvent was distilled off. The reaction mixture was stored at room temperature for the required time and worked up with EtOAc (10 mL). The catalyst was filtered off. The solvent was distilled off. The solid was separated by CC over silica gel.

(2*S*,4*S*(*R*),4a*R*,8*R*,8a*R*)-4,7-Dimethyl-2-(thiophen-2-yl)-3,4,4a,5,8,8a-hexahydro-2*H*-chromen-4,8-diol (6a). The reaction of **2** (0.300 g, 1.79 mmol) with **5a** (0.200 g, 1.79 mmol) in the presence of K10 clay (1.00 g) for 45 min produced an isomeric mixture of (*S*)- and (*R*)-**6a** [(*S*)–(*R*) ratio 3.1:1] (0.197 g, 40%) and (*S*)-**6a** (0.012 g, 2%). The overall yield of **6a** was 42% [(*S*)–(*R*) ratio 3.3:1].

(*S*)-6a. ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.52 (3H, s, CH_3-15), 1.80 (3H, br.s, CH_3-16), 1.79–1.84 (1H, m, H_a-6), 1.84 (1H, dd, ^2J = 13.3, $J_{4e,3a}$ = 2.6, H_e-4), 2.09 (1H, dd, ^2J = 13.3, $J_{4a,3a}$ = 11.8, H_a-4), 2.14–2.20 (2H, m, H-7), 3.84 (1H, br.t, $J_{1e,6a(10e)}$ = 2.2, H_e-1), 3.93 (1H, br.s, H_e-10), 4.68 (1H, dd, $J_{3a,4a}$ = 11.8, $J_{3a,4e}$ = 2.6, H_a-3), 5.61–5.65 (1H, m, H-8), 6.93 (1H, dd, $J_{13,12}$ = 5.0, $J_{13,14}$ = 3.5, H-13), 6.97 (1H, br.d, $J_{14,13}$ = 3.5, H-14), 7.22 (1H, dd, $J_{12,13}$ = 5.0, $J_{12,14}$ = 1.0, H-12). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 77.89 (d, C-1), 73.30 (d, C-3), 42.73 (t, C-4), 70.92 (s, C-5), 38.49 (d, C-6), 22.55 (t, C-7), 124.69 (d, C-8), 131.26 (s, C-9), 70.52 (d, C-10), 144.75 (s, C-11), 124.79 (d, C-12), 126.35 (d, C-13), 123.87 (d, C-14), 27.10 (q, C-15), 20.63 (q, C-16). $[\alpha]_D^{27}$ –62° (*c* 3, MeOH). Found *m/z* 280.1132 $[M]^+$, $C_{15}H_{20}O_3S$. Calcd $[M]^+$ 280.1128.

(*R*)-6a. ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.26 (3H, s, CH_3-15), 1.68 (1H, br.t, $J_{6,7}$ = 8.5, H_a-6), 1.77 (1H, ddd, ^2J = 13.9, $J_{4e,3a}$ = 2.8, $J_{4e,6a}$ = 1.2, H_e-4), 1.80 (3H, m, all J ≤ 2.5, CH_3-16), 1.93 (1H, dd, ^2J = 13.9, $J_{4a,3a}$ = 11.7, H_a-4), 1.97–2.03 (2H, m, H-7), 3.93 (1H, br.s, H_e-10), 4.26 (1H, dd, $J_{1e,10e}$ = 2.2, $J_{1e,6a}$ = 2.1, H_e-1), 5.04 (1H, dd, $J_{3a,4a}$ = 11.7, $J_{3a,4e}$ = 2.8, H_a-3), 5.54–5.58 (1H, m, H-8), 6.92 (1H, dd, $J_{13,12}$ = 5.0, $J_{13,14}$ = 3.5, H-13), 6.95 (1H, ddd, $J_{14,13}$ = 3.5, $J_{14,12}$ = 1.2, $J_{14,3a}$ = 0.8, H-14), 7.19 (1H, dd, $J_{12,13}$ = 5.0, $J_{12,14}$ = 1.2, H-12). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 75.47 (d, C-1), 71.73 (d, C-3), 41.82 (t, C-4), 70.73 (s, C-5), 38.20 (d, C-6), 24.45 (t, C-7), 124.03 (d, C-8), 131.74 (s, C-9), 70.41 (d, C-10), 145.51 (s, C-11), 124.47 (d, C-12), 126.32 (d, C-13), 123.67 (d, C-14), 28.35 (q, C-15), 20.73 (q, C-16). Found *m/z* 280.1132 $[M]^+$, $C_{15}H_{20}O_3S$. Calcd $[M]^+$ 280.1128.

(2*S*,4*S*(*R*),4a*R*,8*R*,8a*R*)-2-(4-Bromothiophen-2-yl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromen-4,8-diol (6b). The reaction of **2** (0.300 g, 1.79 mmol) with **5b** (0.340 g, 1.79 mmol) in the presence of K10 clay (1.30 g) for 150 min produced **6b** [(*S*)–(*R*) ratio 1:1] (0.324 g, 51%).

(*S*)-6b. ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.48 (3H, s, CH_3-15), 1.76 (1H, ddd, ^2J = 13.0, $J_{4e,3a}$ = 2.8, $J_{4e,6a}$ = 1.1, H_e-4), 1.79 (3H, br.s, CH_3-16), 1.78–1.83 (1H, m, H_a-6), 1.99 (1H, dd, ^2J = 13.0, $J_{4a,3a}$ = 12.0, H_a-4), 2.05–2.20 (2H, m, H-7), 3.79 (1H, dd, $J_{1e,10e}$ = 2.3, $J_{1e,6a}$ = 2.0, H_e-1), 3.88 (1H, br.s, H_e-10), 4.60 (1H, ddd, $J_{3a,4a}$ = 12.0, $J_{3a,4e}$ = 2.8, $J_{3a,14}$ = 0.7, H_a-3), 5.59–5.62 (1H, m, H-8), 6.86 (1H, dd, $J_{14,12}$ = 1.5, $J_{14,3a}$ = 0.7, H-14), 7.09 (1H, d, $J_{12,14}$ = 1.5, H-12). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 77.89 (d, C-1), 72.81 (d, C-3), 42.29 (t, C-4), 70.77 (s, C-5), 38.30 (d, C-6), 22.49 (t, C-7), 124.55 (d, C-8), 131.17 (s, C-9), 70.33 (d, C-10), 146.05 (s, C-11), 121.86 (d, C-12), 108.92 (s, C-13), 126.37 (d, C-14), 26.96 (q, C-15), 20.61 (q, C-16). Found *m/z* 358.0233 $[M]^+$, $C_{15}H_{19}O_3SBr$. Calcd $[M]^+$ 358.0233.

(*R*)-6b. ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.24 (3H, s, CH_3-15), 1.68 (1H, ddm, $J_{6a,7a}$ = 10.8, $J_{6a,7e}$ = 6.6, H_a-6), 1.73 (1H, ddd, ^2J = 14.1, $J_{4e,3a}$ = 2.9, $J_{4e,6a}$ = 1.3, H_e-4), 1.79 (3H, br.s, CH_3-16), 1.83 (1H, dd, ^2J = 14.1, $J_{4a,3a}$ = 11.5, H_a-4), 1.88–2.01 (2H, m, H-7), 3.90 (1H, br.s, H_e-10), 4.23 (1H, dd, $J_{1e,10e}$ = 2.3, $J_{1e,6a}$ = 2.0, H_e-1), 4.95 (1H, ddd, $J_{3a,4a}$ = 11.5, $J_{3a,4e}$ = 2.9, $J_{3a,14}$ = 0.7, H_a-3), 5.53–5.56 (1H, m, H-8), 6.84 (1H, dd, $J_{14,12}$ = 1.5, $J_{14,3a}$ = 0.7, H-14), 7.08 (1H, d, $J_{12,14}$ = 1.5, H-12). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 75.44 (d, C-1), 71.31 (d, C-3), 41.34 (t, C-4), 70.64 (s, C-5), 37.99 (d, C-6), 24.34 (t, C-7), 123.93 (d, C-8), 131.64 (s, C-9), 70.31 (d, C-10), 146.82 (s, C-11), 121.60 (d, C-12), 108.88 (s, C-13), 126.11 (d, C-14), 28.22 (q, C-15), 20.71 (q, C-16). Found *m/z* 358.0233 $[M]^+$, $C_{15}H_{19}O_3SBr$. Calcd $[M]^+$ 358.0233.

(2*S*,4*S*(*R*),4a*R*,8*R*,8a*R*)-2-(5-Bromothiophen-2-yl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromen-4,8-diol (6c). The reaction of **2** (0.300 g, 1.79 mmol) with **5c** (0.340 g, 1.79 mmol) in the presence of K10 clay (1.30 g) for 150 min

produced an isomeric mixture of (*S*)- and (*R*)-**6c** [(*S*)–(*R*) ratio 1.8:1] (0.300 g, 41%) and (*R*)-**6c** (0.038 g, 6%). The overall yield of **6c** was 47% [(*S*)–(*R*) ratio 1.3:1].

(*S*)-6c. ^{1}H NMR spectrum ($CDCl_3$ + CD_3OD, δ, ppm, J/Hz): 1.47 (3H, s, CH_3-15), 1.76 (1H, ddd, J = 13.1, 2.8, 1.2, H_e-4), 1.79 (3H, m, all J ≤ 2.5, CH_3-16), 1.80–1.85 (1H, m, H_a-6), 2.01 (1H, dd, J = 13.1, 12.0, H_a-4), 2.05–2.20 (2H, m, H-7), 3.79 (1H, dd, J = 2.4, 2.1, H_e-1), 3.82 (1H, br.s, H_e-10), 4.62 (1H, ddd, J = 12.0, 2.8, 0.8, H_a-3), 5.60–5.63 (1H, m, H-8), 6.73 (1H, dd, J = 3.8, 0.8, H-14), 6.88 (1H, d, J = 3.8, H-13). ^{13}C NMR spectrum ($CDCl_3$ + CD_3OD, δ, ppm): 78.75 (d, C-1), 73.76 (d, C-3), 42.19 (t, C-4), 70.62 (s, C-5), 38.72 (d, C-6), 23.00 (t, C-7), 124.75 (d, C-8), 131.52 (s, C-9), 70.36 (d, C-10), 147.33 (s, C-11), 111.95 (s, C-12), 129.54 (d, C-13), 124.47 (d, C-14), 26.79 (q, C-15), 20.83 (q, C-16). Found *m/z* 358.0232 $[M]^+$, $C_{15}H_{19}O_3SBr$. Calcd $[M]^+$ 358.0233.

(*R*)-6c. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.24 (3H, s, CH_3-15), 1.68 (1H, dd, J = 10.8, 6.8, H_a-6), 1.72 (1H, ddd, J = 13.9, 2.8, 1.2, H_e-4), 1.78 (3H, m, all J ≤ 2.5, CH_3-16), 1.83 (1H, dd, J = 13.9, 11.6, H_a-4), 1.92 (1H, ddm, J = 17.8, 10.8, H_a-7), 2.00 (1H, dddq, J = 17.8, 6.8, 5.3, 1.4, H_e-7), 3.89 (1H, br.s, H_e-10), 4.22 (1H, dd, J = 2.3, 2.1, H_e-1), 4.93 (1H, ddd, J = 11.6, 2.8, 0.7, H_a-3), 5.53–5.56 (1H, m, H-8), 6.66 (1H, dd, J = 3.8, 0.7, H-14), 6.84 (1H, d, J = 3.8, H-13). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 75.36 (d, C-1), 71.82 (d, C-3), 41.32 (t, C-4), 70.70 (s, C-5), 37.99 (d, C-6), 24.36 (t, C-7), 123.96 (d, C-8), 131.62 (s, C-9), 70.33 (d, C-10), 147.29 (s, C-11), 111.35 (s, C-12), 129.01 (d, C-13), 123.67 (d, C-14), 28.25 (q, C-15), 20.73 (q, C-16). $[\alpha]_D^{27}$ –61° (*c* 7, MeOH). Found *m/z* 358.0232 $[M]^+$, $C_{15}H_{19}O_3SBr$. Calcd $[M]^+$ 358.0233.

(2*S*,4*S*(*R*),4a*R*,8*R*,8a*R*)-4,7-Dimethyl-2-(3-methylthiophen-2-yl)-3,4,4a,5,8,8a-hexahydro-2*H*-chromen-4,8-diol (6d). The reaction of **2** (0.300 g, 1.79 mmol) with **5d** (0.230 g, 1.83 mmol) in the presence of K10 clay (1.00 g) for 120 min produced a reaction mixture that was treated with $CHCl_3$. The resulting precipitate was filtered off to afford (*S*)-**6d** (0.074 g, 14%). The residue was separated by CC over silica gel to afford an isomeric mixture of (*S*)- and (*R*)-**6d** [(*S*)–(*R*) ratio 1.4:1] (0.215 g, 41%). The overall yield of **6d** was 55% [(*S*)–(*R*) ratio 2.2:1].

(*S*)-6d. ^{1}H NMR spectrum ($CDCl_3$ + CD_3OD, δ, ppm, J/Hz): 1.52 (3H, s, CH_3-15), 1.71 (1H, ddd, J = 13.3, 2.7, 1.1, H_e-4), 1.79 (3H, m, all J ≤ 2.5, CH_3-16), 1.87 (1H, br.t, J ≈ 8.5, H_a-6), 2.11 (1H, dd, J = 13.3, 12.1, H_a-4), 2.15–2.20 (2H, m, H-7), 2.24 (3H, s, CH_3-17), 3.82 (1H, br.s, H_e-10), 3.83 (1H, br.t, J ≈ 2.2, H_e-1), 4.76 (1H, dd, J = 12.1, 2.7, H_a-3), 5.61–5.65 (1H, m, H-8), 6.79 (1H, d, J = 5.1, H-13), 7.14 (1H, d, J = 5.1, H-12). ^{13}C NMR spectrum ($CDCl_3$ + CD_3OD, δ, ppm): 79.15 (d, C-1), 72.54 (d, C-3), 42.60 (t, C-4), 70.96 (s, C-5), 39.04 (d, C-6), 23.38 (t, C-7), 124.96 (d, C-8), 131.83 (s, C-9), 70.63 (d, C-10), 138.45 (s, C-11), 123.74 (d, C-12), 130.52 (d, C-13), 134.98 (s, C-14), 26.93 (q, C-15), 20.92 (q, C-16), 13.87 (q, C-17). $[\alpha]_D^{26}$ –112° (*c* 7, MeOH). Found *m/z* 294.1279 $[M]^+$, $C_{16}H_{22}O_3S$. Calcd $[M]^+$ 294.1284.

(*R*)-6d. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.25 (3H, s, CH_3-15), 1.64–1.71 (2H, m, H_e-4, H_a-6), 1.79 (3H, m, all J ≤ 2.5, CH_3-16), 1.92 (1H, dd, J = 14.1, 11.8, H_a-4), 1.99–2.05 (2H, m, H-7), 2.22 (3H, s, CH_3-17), 3.91 (1H, br.s, H_e-10), 4.26 (1H, br.s, H_e-1), 5.07 (1H, dd, J = 11.8, 2.6, H_a-3), 5.55–5.59 (1H, m, H-8), 6.76 (1H, d, J = 5.1, H-13), 7.07 (1H, d, J = 5.1, H-12). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 75.43 (d, C-1), 70.22 (d, C-3), 41.51 (t, C-4), 70.85 (s, C-5), 38.15 (d, C-6), 24.50 (t, C-7), 124.03 (d, C-8), 131.75 (s, C-9), 70.50 (d, C-10), 138.24 (s, C-11), 122.88 (d, C-12), 129.96 (d, C-13), 134.20 (s, C-14), 28.34 (q, C-15), 20.71 (q, C-16), 13.73 (q, C-17). Found *m/z* 294.1279 $[M]^+$, $C_{16}H_{22}O_3S$. Calcd $[M]^+$ 294.1284.

(2*S*,4*S*(*R*),4a*R*,8*R*,8a*R*)-4,7-Dimethyl-2-(5-methylthiophen-2-yl)-3,4,4a,5,8,8a-hexahydro-2*H*-chromen-4,8-diol (6e). The reaction of **2** (0.300 g, 1.79 mmol) with **5e** (0.230 g, 1.83 mmol) in the presence of K10 clay (1.00 g) for 120 min produced a reaction mixture that was treated with $CHCl_3$. The resulting precipitate was filtered off to afford (*S*)-**6e** (0.078 g, 15%). The residue was separated by CC over silica gel to afford an isomeric mixture of (*S*)- and (*R*)-**6e** [(*S*)–(*R*) ratio 1.2:1] (0.206 g, 39%). The overall yield of **6e** was 54% [(*S*)–(*R*) ratio 2.8:1].

(*S*)-6e. ^{1}H NMR spectrum ($CDCl_3$ + CD_3OD, δ, ppm, J/Hz): 1.49 (3H, s, CH_3-15), 1.76 (1H, ddd, J = 13.3, 2.6, 1.1, H_e-4), 1.79 (3H, m, all J ≤ 2.5, CH_3-16), 1.85 (1H, br.t, J ≈ 8.5, H_a-6), 2.09 (1H, dd, J = 13.3, 12.1, H_a-4), 2.13–2.20 (2H, m, H-7), 2.43 (3H, d, J = 1.1, CH_3-17), 3.81 (1H, dd, J = 2.3, 2.1, H_e-1), 3.82 (1H, br.s, H_e-10), 4.64 (1H, dd, J = 12.1, 2.6, H_a-3), 5.60–5.64 (1H, m, H-8), 6.59 (1H, dq, J = 3.4, 1.1, H-13), 6.78 (1H, d, J = 3.4, H-14). ^{13}C NMR spectrum ($CDCl_3$ + CD_3OD, δ, ppm): 79.16 (d, C-1), 74.28 (d, C-3), 42.86 (t, C-4), 71.05 (s, C-5), 39.19 (d, C-6), 23.43 (t, C-7), 125.09 (d, C-8), 131.94 (s, C-9), 70.76 (d, C-10), 143.34 (s, C-11), 140.09 (s, C-12), 125.09 (d, C-13), 124.85 (d, C-14), 27.00 (q, C-15), 20.98 (q, C-16), 15.33 (q, C-17). $[\alpha]_D^{26}$ –115° (*c* 3, MeOH). Found *m/z* 294.1286 $[M]^+$, $C_{16}H_{22}O_3S$. Calcd $[M]^+$ 294.1284.

(*R*)-6e. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.23 (3H, s, CH_3-15), 1.68 (1H, br.t, J ≈ 8.6, H_a-6), 1.71 (1H, ddd, J = 14.0, 2.6, 1.2, H_e-4), 1.77 (3H, m, all J ≤ 2.5, CH_3-16), 1.88 (1H, dd, J = 14.0, 11.7, H_a-4), 1.94–2.00 (2H, m, H-7), 2.40 (3H, d, J = 1.1, CH_3-17), 3.89 (1H, br.s, H_e-10), 4.22 (1H, dd, J = 2.3, 2.0, H_e-1), 4.93 (1H, dd, J = 11.7, 2.6, H_a-3), 5.52–5.56

(1H, m, H-8), 6.54 (1H, dq, J = 3.4, 1.1, H-13), 6.72 (1H, d, J = 3.4, H-14). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 75.35 (d, C-1), 71.78 (d, C-3), 41.47 (t, C-4), 70.76 (s, C-5), 37.97 (d, C-6), 24.38 (t, C-7), 123.99 (d, C-8), 131.64 (s, C-9), 70.39 (d, C-10), 142.98 (s, C-11), 139.07 (s, C-12), 124.29 (d, C-13), 123.73 (d, C-14), 28.21 (q, C-15), 20.72 (q, C-16), 15.13 (q, C-17). Found *m/z* 294.1286 $[M]^+$, $C_{16}H_{22}O_3S$. Calcd $[M]^+$ 294.1284.

(2*S*,4*S*(*R*),4a*R*,8*R*,8a*R*)-4,7-Dimethyl-2-(5-nitrothiophen-2-yl)-3,4,4a,5,8,8a-hexahydro-2*H*-chromen-4,8-diol (6f). The reaction of **2** (0.400 g, 2.38 mmol) with **5f** (0.370 g, 2.36 mmol) in the presence of K10 clay (1.50 g) for 180 min produced starting diol **2** (0.057 g, 86% conversion of **2**), an isomeric mixture of (*S*)- and (*R*)-**6f** [(*S*)–(*R*) ratio 1.9:1] (0.115 g, 17%), (*S*)-**6f** (0.066 g, 10%), (*R*)-**6f** (0.069 g, 11%), and **7** (0.163 g, 26%). The yields were calculated for reacted **2**. The overall yield of **6f** was 38% [(*S*)–(*R*) ratio 1.3:1].

(*S*)-6f. ^{1}H NMR spectrum (CD_3OD, δ, ppm, J/Hz): 1.53 (3H, d, J = 0.6, CH_3-15), 1.84 (3H, m, all J ≤ 2.5, CH_3-16), 1.88 (1H, ddd, J = 13.2, 3.4, 1.1, H_e-4), 1.88–1.93 (1H, m, H_a-6), 1.94 (1H, ddd, J = 13.2, 11.6, 0.6, H_a-4), 2.09 (1H, ddm, J = 17.7, 10.8, H_a-7), 2.19 (1H, dm, J = 17.7, H_e-7), 3.85 (1H, m, all J < 2.5, H_e-10), 3.87 (1H, dd, J =2.3, 2.1, H_e-1), 4.83 (1H, ddd, J = 11.6, 3.4, 0.9, H_a-3), 5.63–5.67 (1H, m, H-8), 7.01 (1H, dd, J = 4.2, 0.9, H-14), 7.87 (1H, d, J = 4.2, H-13). ^{13}C NMR spectrum (CD_3OD, δ, ppm): 79.69 (d, C-1), 74.36 (d, C-3), 43.15 (t, C-4), 71.08 (s, C-5), 39.53 (d, C-6), 23.72 (t, C-7), 125.15 (d, C-8), 132.35 (s, C-9), 71.08 (d, C-10), 156.20 (s, C-11), 151.71 (s, C-12), 129.55 (d, C-13), 123.48 (d, C-14), 26.93 (q, C-15), 21.06 (q, C-16). $[\alpha]_D^{26}$ –66° (*c* 11, MeOH). Found *m/z* 325.0970 $[M]^+$, $C_{15}H_{19}O_5NS$. Calcd $[M]^+$ 325.0979.

(*R*)-6f. ^{1}H NMR spectrum ($CDCl_3$, + CD_3OD, δ, ppm, J/Hz): 1.17 (3H, s, CH_3-15), 1.64 (1H, ddm, J = 10.8, 6.6, H_a-6), 1.68 (1H, dd, J = 14.0, 11.0, H_a-4), 1.73 (1H, ddd, J = 14.0, 3.5, 1.1, H_e-4), 1.75 (3H, br.s, CH_3-16), 1.81 (1H, ddm, J = 17.7, 10.8, H_a-7), 1.95 (1H, dddm, J = 17.7, 6.6, 5.2, H_e-7), 3.81 (1H, br.s, H_e-10), 4.17 (1H, br.t, $J_{1e,10e} \approx J_{1e,6a} \approx 2.2$, H_e-1), 4.95 (1H, ddd, J = 11.0, 3.5, 0.7, H_a-3), 5.48–5.52 (1H, m, H-8), 6.77 (1H, dd, J = 4.2, 0.7, H-14), 7.69 (1H, d, J = 4.2, H-13). ^{13}C NMR spectrum ($CDCl_3$ + CD_3OD, δ, ppm): 75.54 (d, C-1), 71.71 (d, C-3), 41.15 (t, C-4), 69.88 (s, C-5), 37.50 (d, C-6), 24.16 (t, C-7), 123.46 (d, C-8), 131.51 (s, C-9), 69.80 (d, C-10), 155.45 (s, C-11), 150.26 (s, C-12), 128.24 (d, C-13), 121.70 (d, C-14), 27.58 (q, C-15), 20.48 (q, C-16). $[\alpha]_D^{26}$ –1° (*c* 5, MeOH). Found *m/z* 325.0970 $[M]^+$, $C_{15}H_{19}O_5NS$. Calcd $[M]^+$ 325.0979.

Compound 7. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.83 (3H, m, all J ≤ 2.5, CH_3-16), 1.96 (1H, dddq, J = 17.8, 6.7, 5.4, 1.4, H_e-7), 2.23 (1H, ddm, J = 17.8, 10.8, H_a-7), 2.48 (1H, dd, J = 14.0, 3.5, H_e-4), 2.50–2.58 (2H, m, H_a-4, 6), 3.74 (1H, br.dd, $J_{1e,6a} \approx J_{1e,10e} \approx 2.2$, H_e-1), 3.91 (1H, br.s, H_e-10), 4.60 (1H, ddd, J = 11.0, 3.5, 0.8, H_a-3), 4.87 (1H, m, all J ≤ 2.2, H-15), 4.96 (1H, m, all J ≤ 2.2, H-15′), 5.58–5.61 (1H, m, H-8), 6.85 (1H, dd, J = 4.2, 0.8, H-14), 7.76 (1H, d, J = 4.2, H-13). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 80.71 (d, C-1), 75.95 (d, C-3), 37.93 (t, C-4), 144.59 (s, C-5), 36.39 (d, C-6), 25.89 (t, C-7), 124.23 (d, C-8), 131.27 (s, C-9), 69.97 (d, C-10), 154.10 (s, C-11), 150.76 (s, C-12), 128.13 (d, C-13), 121.95 (d, C-14), 111.31 (t, C-15), 20.77 (q, C-16). Found *m/z* 307.1755 $[M]^+$, $C_{15}H_{17}NO_4S$. Calcd $[M]^+$ 307.1748.

(2*S*,4*S*(*R*),4a*R*,8*R*,8a*R*)-2-(4,5-Dibromothiophen-2-yl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromen-4,8-diol (6g). The reaction of **2** (0.190 g, 1.13 mmol) with **5g** (0.200 g, 0.75 mmol) in the presence of K10 clay (0.80 g) for 24 h produced **6g** [(*S*)–(*R*) ratio 2:1] (0.080 g, 32%), **8** (0.048 g, 20%), **9** (0.048 g, 19%), and **2** (0.095 g, 50% conversion of **2**). Recrystallization from $CHCl_3$ of the isomeric mixture of (*S*)- and (*R*)-**6g** produced (*S*)-**6g**. Yields were calculated for reacted diol **2**.

(*S*)-6g. ^{1}H NMR spectrum ($CDCl_3$ + CD_3OD, δ, ppm, J/Hz): 1.47 (3H, d, J = 0.7, CH_3-15), 1.76 (1H, ddd, J = 13.2, 2.8, 1.1, H_e-4), 1.80 (3H, m, all J ≤ 2.5, CH_3-16), 1.84 (1H, ddm, J = 10.6, 6.5, other J < 2.5, H_a-6), 1.96 (1H, dd, J = 13.2, 12.0, H_a-4), 2.06 (1H, dddqd, J = 18.3, 10.6, 2.5, 1.5, H_a-7), 2.15 (1H, dddq, J = 18.3, 6.5, 5.2, 1.5, H_e-7), 3.79 (1H, dd, J = 2.3, 2.1, H_e-1), 3.82 (1H, br.s, H_e-10), 4.61 (1H, ddd, J = 12.0, 2.8, 1.0, H_a-3), 5.59–5.63 (1H, m, H-8), 6.80 (1H, d, J = 1.0, H-14). ^{13}C NMR spectrum ($CDCl_3$ + CD_3OD, δ, ppm): 78.91 (d, C-1), 73.56 (d, C-3), 42.01 (t, C-4), 70.60 (s, C-5), 38.78 (d, C-6), 23.08 (t, C-7), 124.78 (d, C-8), 131.61 (s, C-9), 70.41 (d, C-10), 147.45 (s, C-11), 110.68 and 113.27 (2s, C-12, C-13), 126.69 (d, C-14), 26.79 (q, C-15), 20.89 (q, C-16). $[\alpha]_D^{24}$ –72° (*c* 2, MeOH). Found *m/z* 435.9341 $[M]^+$, $C_{15}H_{18}Br_2O_3S$. Calcd $[M]^+$ 435.9338.

(*R*)-6g. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.25 (3H, s, CH_3-15), 1.66 (1H, ddm, J = 11.2, 6.5, H_a-6), 1.72 (1H, ddd, J = 14.0, 3.0, 1.2, H_e-4), 1.76–1.82 (1H, m, H_a-4), 1.80 (3H, m, all J ≤ 2.5, CH_3-16), 1.85–2.05 (2H, m, H-7), 3.90 (1H, br.s, H_e-10), 4.22 (1H, br.dd, $J_{1e,10e} \approx J_{1e,6a} \approx 2.2$, H_e-1), 4.91 (1H, ddd, J_3 = 11.3, 3.0, 0.8, H_a-3), 5.54–5.57 (1H, m, H-8), 6.72 (1H, d, J = 0.8, H-14). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 75.38 (d, C-1), 71.55 (d, C-3), 41.07 (t, C-4), 70.62 (s, C-5), 38.09 (d, C-6), 24.36 (t, C-7), 123.88 (d, C-8), 131.68 (s, C-9), 70.28 (d, C-10), 147.09 (s, C-11), 111.16 and 112.31 (2s, C-12, C-13), 125.83 (d, C-14), 28.31 (q, C-15), 20.72 (q, C-16). Found *m/z* 435.9341 $[M]^+$, $C_{15}H_{18}Br_2O_3S$. Calcd $[M]^+$ 435.9338.

Compound 8. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.81 (3H, m, all J ≤ 2.5, CH_3-16), 1.95 (1H, dddq, J = 18.1, 6.6, 5.3, 1.5, H_e-7), 2.24 (1H, dddqd, J = 18.1, 10.8, 2.5, 1.6, H_a-7), 2.41 (1H, dd, J = 13.9, 3.0, H_e-4), 2.50–2.58 (2H, m, H_a-4, 6), 3.71 (1H, dd, J = 2.2, 2.2, H_e-1), 3.89 (1H, br.s, H_e-10), 4.50 (1H, ddd, J = 11.5, 3.0, 1.0, H_a-3), 4.84 (1H, dd, J = 2.0, 1.8, H-15), 4.94 (1H, dd, J = 2.0, 1.8, H-15′), 5.58–5.61 (1H, m, H-8), 6.77 (1H, d, J = 1.0, H-14). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 80.59 (d, C-1), 75.92 (d, C-3), 37.65 (t, C-4), 146.51 (s, C-5), 36.52 (d, C-6), 25.98 (t, C-7), 124.41 (d, C-8), 131.29 (s, C-9), 70.12 (d, C-10), 145.12 (s, C-11), 110.38 and 112.85 (2s, C-12, C-13), 126.00 (d, C-14), 110.98 (t, C-15), 20.82 (q, C-16). $[\alpha]_D^{24}$ –16° (*c* 2, $CHCl_3$). Found *m/z* 417.9230 $[M]^+$, $C_{15}H_{16}Br_2O_2S$. Calcd $[M]^+$ 417.9232.

Compound 9. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.23 (3H, s, CH_3-16), 1.47 (3H, s, CH_3-15), 1.50 (1H, ddd, J = 10.8, 6.1, 1.9, H_a-6), 1.79 (3H, m, all J < 2.6, CH_3-17), 2.04 (1H, dddq, J = 17.9, 6.1, 5.3, 1.5, H_e-7), 2.34 (1H, dddqd, J = 17.9, 10.8, $J_{7a,8} = J_{7a,17}$ = 2.5, 1.6, H_a-7), 3.86 (1H, br.s, H_e-10), 4.30 (1H, dd, J = 2.3, 1.9, H_e-1), 5.61–5.64 (1H, m, H-8), 5.90 (1H, d, J = 0.7, H-3), 6.90 (1H, d, J = 1.0, H-14). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 74.98 (d, C-1), 91.65 (d, C-3), 75.50 (s, C-5), 33.88 (d, C-6), 22.79 (t, C-7), 125.29 (d, C-8), 130.58 (s, C-9), 70.24 (d, C-10), 143.37 (s, C-11), 111.64 and 112.80 (2s, C-12, C-13), 127.57 (d, C-14), 22.58 (q, C-15), 26.96 (q, C-16), 20.46 (q, C-17). $[\alpha]_D^{24}$ –36° (*c* 4, $CHCl_3$). Found *m/z* 435.9330 $[M]^+$, $C_{15}H_{18}Br_2O_3S$. Calcd $[M]^+$ 435.9338.

(2*S*,4*S*(*R*),4a*R*,8*R*,8a*R*)-4,7-Dimethyl-2-(thiophen-3-yl)-3,4,4a,5,8,8a-hexahydro-2*H*-chromen-4,8-diol (11). The reaction of **2** (0.300 g, 1.79 mmol) with **10** (0.200 g, 1.79 mmol) in the presence of K10 clay (1.00 g) for 60 min produced starting diol **2** (0.070 g, 77% conversion of **2**) and **11** (0.205 g, 54% calculated for reacted diol **2**) [(*S*)–(*R*) ratio 1.4:1].

(*S*)-11. ^{1}H NMR spectrum ($CDCl_3$ + CD_3OD, δ, ppm, J/Hz): 1.51 (3H, d, J = 0.7, CH_3-15), 1.72 (1H, ddd, J = 13.3, 2.6, 1.2, H_e-4), 1.80 (3H, m, all J ≤ 2.5, CH_3-16), 1.87 (1H, br.t, J = 8.9, H_a-6), 2.02 (1H, dd, J = 13.3, 12.1, H_a-4), 2.14–2.19 (2H, m, H-7), 3.82 (1H, dd, J = 2.4, 2.1, H_e-1), 3.84 (1H, br.s, H_e-10), 4.59 (1H, dd, J = 12.1, 2.6, H_a-3), 5.62–5.65 (1H, m, H-8), 7.07 (1H, dd, J = 5.0, 1.3, H-14), 7.24 (1H, ddd, J = 3.0, 1.3, 0.7, H-12), 7.30 (1H, dd, J = 5.0, 3.0, H-13). ^{13}C NMR spectrum ($CDCl_3$ + CD_3OD, δ, ppm): 79.03 (d, C-1), 74.64 (d, C-3), 42.32 (t, C-4), 71.11 (s, C-5), 39.21 (d, C-6), 23.50 (t, C-7), 125.12 (d, C-8), 131.98 (s, C-9), 70.80 (d, C-10), 143.96 (s, C-11), 121.78 (d, C-12), 126.28 (d, C-13), 126.66 (d, C-14), 27.00 (q, C-15), 21.02 (q, C-16). Found *m/z* 280.1130 $[M]^+$, $C_{15}H_{20}O_3S$. Calcd $[M]^+$ 280.1128.

(*R*)-11. ^{1}H NMR spectrum ($CDCl_3$ + CD_3OD, δ, ppm, J/Hz): 1.15 (3H, s, CH_3-15), 1.58–1.67 (2H, m, H_e-4, H_a-6), 1.72 (3H, m, all J ≤ 2.5, CH_3-16), 1.73 (1H, dd, J = 14.0, 11.8, H_a-4), 1.87–1.94 (2H, m, H-7), 3.81 (1H, br.s, H_e-10), 4.13 (1H, dd, J = 2.4, 2.1, H_e-1), 4.80 (1H, dd, J = 11.8, 2.6, H_a-3), 5.48–5.51 (1H, m, H-8), 6.97 (1H, dd, J = 5.0, 1.3, H-14), 7.10 (1H, ddd, J = 3.0, 1.3, 0.7, H-12), 7.17 (1H, dd, J = 5.0, 3.0, H-13). ^{13}C NMR spectrum ($CDCl_3$ + CD_3OD, δ, ppm): 75.27 (d, C-1), 72.11 (d, C-3), 40.79 (t, C-4), 70.15 (s, C-5), 37.68 (d, C-6), 24.31 (t, C-7), 123.66 (d, C-8), 131.63 (s, C-9), 70.02 (d, C-10), 143.50 (s, C-11), 120.58 (d, C-12), 125.38 (d, C-13), 125.74 (d, C-14), 27.74 (q, C-15), 20.50 (q, C-16). Found *m/z* 280.1130 $[M]^+$, $C_{15}H_{20}O_3S$. Calcd $[M]^+$ 280.1128.

Analgesic Activity. All experiments were conducted using laboratory male mice (22–25 g). Test groups consisted of eight animals each. Tested agents were injected intragastrically at a dose of 10 mg/kg as aqueous Tween suspensions one hour before inducing the model. Control animals were injected with the corresponding solvent.

The acetic-writhing test was induced by i.p. injection of AcOH (0.75%, 0.1 mL/10 g of body mass). The degree of the pain reaction was assessed 5 min after AcOH injection from the number of convulsions of each animal in 3 min.

The hot-plate test placed animals on a metallic surface heated to 54 ± 0.5°C that was surrounded by a transparent cylinder. The latent time of the pain reaction (licking hind paws or rearing) in seconds was recorded for each animal.

The studied agents of general formulas **6** and **11** were injected without separating diastereomers. Table 1 presents the results. Statistical processing used the Statistica 8.0 software.

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