Synthesis of Thiochromans by Means of a [4⁺ + 2] Polar Cycloaddition of *m*-Tolylthiomethyl Chloride with Substituted Alkenes: A Simple Synthesis of (±)-Cuparene and Related Sesquiterpenoids

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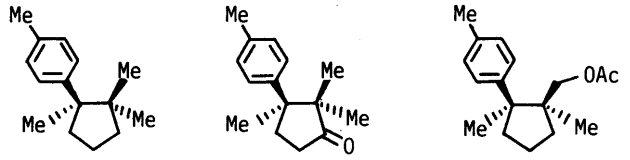
(±)-Cuparene, (±)-α-cuparenone, and (±)-tochuinyl acetate were synthesized from *m*-tolylthiomethyl chloride by using a Lewis acid-mediated [4⁺ + 2] polar cycloaddition with substituted cyclopentenes as a key step.

Keywords polar cycloaddition; thiochroman; *m*-tolylthiomethyl chloride; cuparene; α-cuparenone; tochuinyl acetate; Pummerer rearrangement; desulfurization

Cuparene (**1**),[1] α-cuparenone (**2**),[2] and tochuinyl acetate (**3**),[3] members of a class of aromatic sesquiterpenoids, contain vicinal quaternary carbon centers in a cyclopentane ring. Because of this structural feature, these compounds have been chosen as target molecules by synthetic chemists and a variety of synthetic methods for the construction of such ring systems have been developed.[4,5]

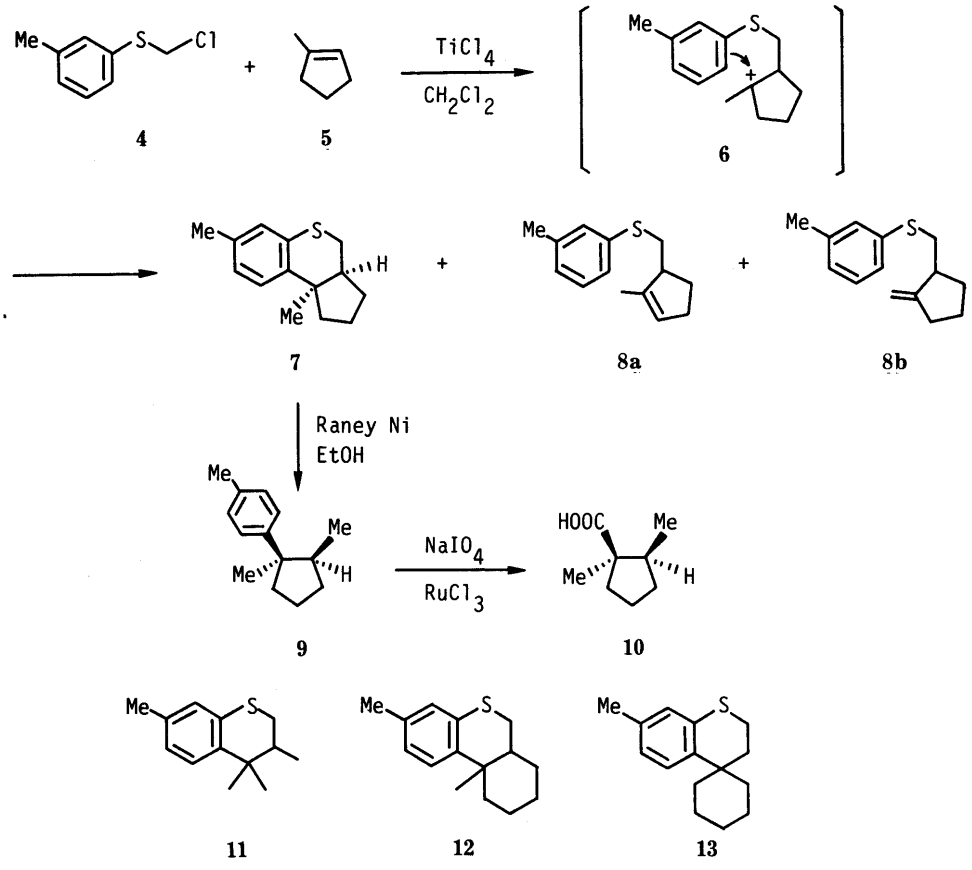
Our approach to these sesquiterpenoids involves a Lewis acid-mediated [4⁺ + 2] polar cycloaddition[6] of *m*-tolylthiomethyl chloride (**4**) with tri- or tetra-substituted cyclopentenes as a key step. This step is followed by desulfurization of the resulting thiochromans directly or after introduction of an appropriate functional group. In this paper we present the full account of this approach.[7]



1 **2** **3**

Chart 1

Reaction of *m*-Tolylthiomethyl Chloride with Tri-substituted Alkenes: Synthesis of (±)-α-Cuparenone A solution of equimolar amounts of **4** and 1-methylcyclopentene (**5**) in methylene chloride was treated with titanium tetrachloride ($TiCl_4$) at −20 °C to give an inseparable mixture consisting of three products, the thiochroman **7** and the 'ene' products **8a** and **8b** in a ratio of 53 : 37 : 10 [determined by high performance liquid chromatography (HPLC)] (57% total yield). It was noted that the reaction conditions had a pronounced effect on the proportions of **7** and **8**. Thus, when the reaction was carried out at 0 °C for 1 h, the



4 **5** **6** **7** **8a** **8b** **9** **10** **11** **12** **13**

Chart 2

amount of **7** in the products (68% total yield) slightly increased [the ratio of **7**:**8a**:**8b** was 62:35:3]. Raising the reaction temperature to room temperature (1 h) gave only the thiochroman **7** in 62% yield as a single stereoisomer. Use of ethylaluminum dichloride ($EtAlCl_2$) instead of $TiCl_4$ gave essentially the same result.

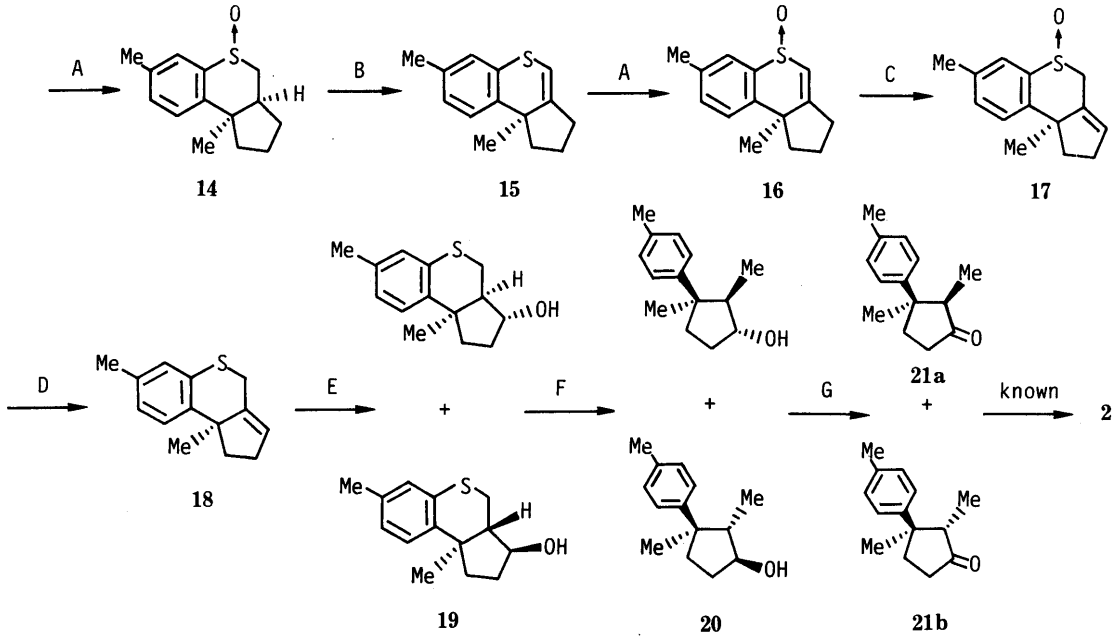
The structure and stereochemistry of the thiochroman **7** were established by a combination of spectral and chemical evidence. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum revealed two methyl singlets at δ 1.26 and 2.21 and a multiplet (3H) in the aromatic region between δ 6.7 and 7.4. Desulfurization of **7** with Raney nickel followed by oxidation of the resulting cyclopentane **9** with $RuCl_3$–$NaIO_4$[8] gave the known carboxylic acid **10**.[9] The structures of the 'ene' products **8a** and **8b** were deduced from the ^{1}H-NMR spectrum of the mixture of **7** and **8a**, **b**, which showed two multiplets due to the vinyl protons centered at δ 4.93 [$=CH_2$ for **8b**] and 5.43 [$=CH-$ for **8a**]. Furthermore, when a benzene solution of the crude reaction mixture containing **7** and **8a**, **b** was refluxed in the presence of *p*-toluenesulfonic acid (the reaction was followed by HPLC), the 'ene' products **8a**, **b** gradually decreased in amount and, after 1 h, were completely converted into the thiochroman **7** in a quantitative yield.

A plausible mechanism for the formation of **7** and **8a**, **b** would involve the initial formation of a carbenium ion intermediate **6**, which undergoes either a Friedel–Crafts type cyclization leading to the [$4^+ + 2$] cycloadduct **7** or a regioselective deprotonation assisted by the sulfur atom[10] to give the 'ene' products **8a** and **8b**. The fact that only the thiochroman **7** was obtained when the reaction was carried out at higher temperature, seems to suggest that the 'ene' products **8a**, **b** are readily reprotonated to revert to the carbenium ion intermediate **6**, which undergoes an irreversible cylization to **7**.

A similar reaction of **4** with 2-methylbut-2-ene and 1-methylcyclohexene at room temperature in the presence of $TiCl_4$ gave the corresponding thiochroman derivatives **11** and **12** in 60 and 34% yields, respectively. Interestingly, even methylenecyclohexane gave the thiochroman **13** in 48% yield.

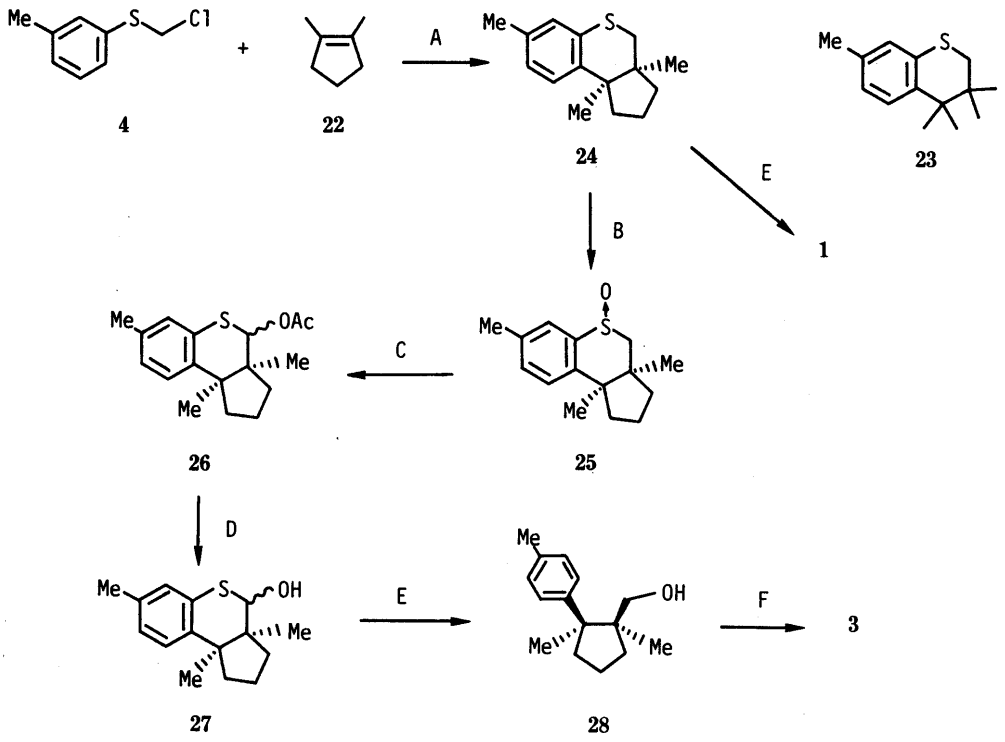
The thiochroman **7** was next transformed into (±)-α-cuparenone (**2**). Thus, oxidation of **7** with *m*-chloroperbenzoic acid (MCPBA) in methylene chloride followed by treatment of the resulting sulfoxide **14** with trifluoroacetic anhydride in methylene chloride gave the vinyl sulfide **15** in 50% overall yield. The vinyl sulfide **15** was reoxidized with MCPBA to give a diastereomeric mixture of the sulfoxide **16**. After chromatographic separation, the major sulfoxide of **16** was treated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C and then quenched with an ammonium chloride solution to afford the allyl sulfoxide **17** in 94% yield. Interestingly, the minor sulfoxide of **16** was recovered unchanged under the reaction conditions used. The reason for this is not clear at the present time. Reduction of the sulfoxide **17** with titanium trichloride ($TiCl_3$)[11] gave the allyl sulfide **18** in 80% yield. Hydroboration-oxidation of **18** gave an inseparable mixture of two diastereomeric alcohols **19** in 56% yield (the ratio was 3:2), which resulted from nonselective attack of borane from both α- and β-sides. Desulfurization of the mixture of the alcohols **19** with Raney nickel followed by oxidation of the resulting alcohols **20** with Collins' reagent gave a 3:2 mixture of two isomeric ketones **21a** and **21b** in 90% yield. The spectral data of the ketones **21** are in good agreement with the literature values.[12] The ketones have already been converted into (±)-α-cuparenone by Eilbracht and coworkers.[5k]

Reaction of *m*-Tolylthiomethyl Chloride with Tetra-substituted Alkenes: Synthesis of (±)-Cuparene and (±)-Tochuinyl Acetate *m*-Tolylthiomethyl chloride (**4**) was found to react with tetra-substituted alkenes to give the corresponding thiochroman derivatives. In this case, use of



(A) MCPBA, CH_2Cl_2, 0 °C→r.t. (B) $(CF_3CO)_2O$, CH_2Cl_2, 0 °C (C) 1) LDA, THF, −78 °C; 2) NH_4Cl soln (D) $TiCl_3$, MeOH-$CHCl_3$ (E) 1) BH_3, THF, r.t.; 2) 30% H_2O_2, 6 N NaOH (F) Raney Ni, EtOH, reflux (G) $CrO_3 \cdot 2py$, CH_2Cl_2

Chart 3



(A) $EtAlCl_2$, CH_2Cl_2, 0 °C→r.t. (B) MCPBA, CH_2Cl_2, 0 °C→r.t. (C) Ac_2O, 100 °C, 3.5 h (D) K_2CO_3, MeOH, H_2O, r.t., 1 h (E) Raney Ni, EtOH, reflux, 8 h (F) Ac_2O, pyridine, overnight

Chart 4

$EtAlCl_2$ instead of $TiCl_4$ as the Lewis acid gave a much better yield. Thus, treatment of **4** with 2,2-dimethylbut-2-ene and 1,2-dimethylcyclopentene (**22**) gave the thiochromans **23** and **24** in 87% (22%) and 60% (36%) yields, respectively (yields in parentheses denote the values obtained by using $TiCl_4$ as the Lewis acid). The thiochroman **24** was obtained as a single stereoisomer. The stereochemistry was determined by its chemical transformation into (±)-tochuinyl acetate (**3**),[3] a sesquiterpenoid recently isolated from skin extracts of the dendronotid nudibranch, *Tochuina tetraquetra*. Thus, oxidation of **24** with MCPBA followed by heating the resulting sulfoxide **25** in acetic anhydride at 100 °C for 3.5 h have the Pummerer rearrangement product **26** in 84% yield. Since an attempt to desulfurize directly the acetate **26** to **3** with Raney nickel resulted in the formation of a mixture of (±)-cuparene (**1**) and the thiochroman **24**, the acetate **26** was hydrolyzed to the alcohol **27** and then treated with Raney nickel to give the expected desulfurized alcohol **28**. The alcohol **28** was then reacetylated with acetic anhydride in pyridine to furnish (±)-tochuinyl acetate **3**, whose ^{1}H-NMR spectral data (300 MHz) were in accord with those reported in the literature.[3]

On the other hand, direct desulfurization of **24** with Raney nickel in refluxing ethanol gave **1** in 77% yield; the infrared (IR) and ^{1}H-NMR spectral data of **1** were identical with those given by Dr. T. Honda, Hoshi University. This is the shortest synthesis of (±)-cuparene so far reported.[4a-w]

Experimental

IR spectra were recorded with a JASCO IRA-1 spectrophotometer. ^{1}H-NMR spectra were determined with a JEOL JNM-PMX 60 (60 MHz) or a Varian XL-300 (300 MHz) spectrometer in $CDCl_3$, unless otherwise stated, and δ values are quoted relative to tetramethylsilane. Exact mass (MS) determinations were obtained on a Hitachi M-80 instrument operating at 20 eV. Chromatographic separation was performed with Silica gel 60 PF_{254} (Merck) under pressure.

Chloromethyl 4-Methylphenyl Sulfide (4) A solution of *m*-thiocresol (10 g, 80.5 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (13.5 g, 88.6 mmol) in acetonitrile (50 ml) was added to bromochloromethane (207 g, 1.6 mol).[13] The resulting solution was stirred at room temperature for 2 h, and poured into water (20 ml). The organic layer was dried over $MgSO_4$, the solvent was evaporated off, and the residue was distilled *in vacuo* to give **4** (7.8 g, 56%), bp 73—74 °C (2 mmHg), lit[14] 125 °C (16 mmHg). ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.32 (3H, s), 4.92 (2H, s), 6.9—7.45 (4H, m).

General Procedure for the Preparation of the Thiochromans 7, 11—13, 23, and 24 $TiCl_4$ (0.42 g, 2.2 mmol) or $EtAlCl_2$ (1 mol solution in hexane) (2.2 mmol) was added to a solution of the chloride **4** (2 mmol) and the appropriate alkene (2 mmol) in CH_2Cl_2 (5 ml) at 0 °C, and the mixture was stirred at 0 °C for 10 min and then at room temperature for 1 h. The reaction was quenched with water (10 ml) and the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and evaporated. The following compounds were thus obtained. *cis*-1,2,3,3a,4,9b-Hexahydro-7,9b-dimethylcyclopenta[*c*][1]benzothiopyran (**7**) ($TiCl_4$, 62%) from **4** and **5** as an oil. ^{1}H-NMR (60 MHz) δ: 1.26 (3H, s), 1.45—2.1 (7H, m), 2.21 (3H, s), 2.57 (1H, dd, J=6, 12 Hz), 3.00 (1H, dd, J=3, 12 Hz), 6.7—7.4 (3H, m). Exact MS *m/z*: Calcd for $C_{14}H_{18}S$: 218.1127. Found: 218.1126. 3,4-Dihydro-3,4,4,7-tetramethyl-2*H*-1-benzothiopyran (**11**) ($TiCl_4$, 60%) from **4** and 2-methylbut-2-ene as an oil. ^{1}H-NMR (60 MHz) δ: 0.98 (3H, d, J=6 Hz), 1.23 (3H, s), 1.28 (3H, s), 1.7—2.15 (1H, m), 2.22 (3H, s), 2.67 (1H, dd, J=5, 12 Hz), 3.30 (1H, dd, J=4, 12 Hz), 6.6—7.45 (3H, m). Exact MS *m/z*: Calcd for $C_{13}H_{18}S$, 206.1127. Found: 206.1116. 1,2,3,4,4a,10b-Hexahydro-8,10b-dimethylcyclohexa[*c*][1]benzothiopyran (**12**) ($TiCl_4$, 34%) from **4** and 1-methylcyclohexene as an oil. ^{1}H-NMR (60 MHz) δ: 1.14 (3H, s), 1.25—2.0 (9H, m), 2.22 (3H, s), 2.53 (1H, dd, J=2, 12 Hz), 3.54 (1H, dd, J=3, 12 Hz), 6.6—7.35 (3H, m). Exact MS *m/z*: Calcd for $C_{15}H_{20}S$: 232.1285. Found: 232.1302. 3,4-Dihydro-7-methyl-2*H*-1-benzothiopyran-4-spiro-1′-cyclohexane (**13**) ($TiCl_4$, 48%) from **4** and methylenecyclohexane as an oil. ^{1}H-NMR (60 MHz) δ: 0.9—2.0 (10H, m), 2.0—2.2 (2H, m), 2.20 (3H, s), 2.8—3.2 (2H, m), 6.80 (1H, d, J=8 Hz), 6.87 (1H, s), 7.27 (1H, d, J=8 Hz). Exact MS *m/z*: Calcd for $C_{15}H_{20}S$: 232.1285. Found: 232.1260. 3,4-Dihydro-3,3,4,4,7-pentamethyl-2*H*-1-benzothiopyran (**23**) ($EtAlCl_2$, 87%) from **4** and 2,2-dimethylbut-2-ene, mp 80—81 °C. ^{1}H-NMR (60 MHz) δ: 1.01 (6H, s), 1.22 (6H, s), 2.20 (3H, s), 2.79 (2H, s), 6.7—7.4 (3H, m). *Anal.* Calcd for $C_{14}H_{20}S$: C, 76.30; H, 9.15.

Found: C, 76.39; H, 9.42. *cis*-1,2,3,3a,4,9b-Hexahydro-3a,7,9b-trimethylcyclopenta[*c*][1]benzothiopyran (**24**) ($EtAlCl_2$, 60%) from **4** and **22** as an oil. ^{1}H-NMR (300 MHz) δ: 1.14 (3H, s), 1.25 (3H, s), 1.5—1.95 (5H, m), 2.0—2.15 (1H, m), 2.23 (3H, s), 2.58 (1H, d, J=13.1 Hz), 2.88 (1H, d, J=13.1 Hz), 6.84 (1H, br dd, J=2.0, 8.2 Hz), 6.90 (1H, br s), 7.24 (1H, d, J=8.2 Hz). Exact MS *m/z*: Calcd for $C_{15}H_{20}S$: 232.1285. Found: 232.1314.

(1*R,2*S**)-1,2-Dimethyl-1-(*p*-tolyl)cyclopentane (9)** A solution of the thiochroman **7** (0.336 g, 1.54 mmol) in ethanol (5 ml) containing Raney Ni (*ca.* 1.5 g) was heated under reflux for 1 h. The Raney Ni was filtered off, the filtrate was concentrated, and the residue was chromatographed on silica gel (hexane) to give **9** (0.225 g, 78%). ^{1}H-NMR (60 MHz) δ: 0.59 (3H, d, J=7 Hz), 1.28 (3H, s), 1.3—2.45 (7H, m), 2.31 (3H, s), 7.07 (4H, s). Exact MS *m/z*: Calcd for $C_{14}H_{20}$: 188.1564. Found: 188.1589.

(1*R,2*S**)-1,2-Dimethylcyclopentanecarboxylic Acid (10)** According to a procedure developed by Sharpless *et al.*,[8] $RuCl_3$ (5.2 mg, 2.2 mol%) was added to a mixture of compound **9** (0.22 g, 1.2 mmol), sodium metaperiodate (3.56 g, 16.6 mmol), CCl_4 (5 ml), acetonitrile (5 ml), and water (7 ml). The reaction mixture was stirred vigorously at room temperature for 24 h. Work-up gave **10**[9] (0.15 g, 92%) as an oil. ^{1}H-NMR (60 MHz) δ: 1.00 (3H, br d, J=6 Hz), 1.25 (3H, s), 1.4—2.8 (7H, m), 9.68 (1H, br). This carboxylic acid was converted into the crystalline amide *via* the acid chloride ($SOCl_2$ and then ammonia), mp 102.5—103 °C (recrystallized from hexane–AcOEt and then sublimed) (lit.[9] mp 103.5—104.5 °C).

1,2,3,3a,4,9b-Hexahydro-7,9b-dimethylcyclopenta[*c*][1]benzothiopyran-5-oxide (14) MCPBA (80%, 1.08 g, 5.0 mmol) was added to a solution of **7** (1.09 g, 5.0 mmol) in CH_2Cl_2 (30 ml) at 0 °C and the mixture was stirred at room temperature for 1 h. The reaction mixture was washed successively with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (benzene–AcOEt, 2:1) to give the sulfoxide **14** (1.17 g, 99%) as an oil. ^{1}H-NMR (60 MHz) δ: 1.42 (3H, s), 1.55—2.2 (6H, m), 2.37 (3H, s), 2.5—3.3 (3H, m), 7.1—7.7 (3H, m). Exact MS *m/z*: Calcd for $C_{14}H_{18}OS$: 234.1078. Found: 234.1108.

1,2,3,9b-Tetrahydro-7,9b-dimethylcyclopenta[*c*][1]benzothiopyran (15) Trifluoroacetic anhydride (462 mg, 2,2 mmol) was added to a solution of the sulfoxide **14** (510 mg, 2.2 mmol) at 0 °C and the mixture was stirred at room temperature for 30 min. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane) to give the vinyl sulfide **15** (240 mg, 51%). ^{1}H-NMR (60 MHz) δ: 1.12 (3H, s), 1.55—3.0 (6H, m), 2.28 (3H, s), 6.0—6.2 (1H, m), 6.85—7.35 (3H, m). Exact MS *m/z*: Calcd for $C_{14}H_{16}S$: 216.0971. Found: 216.0996.

1,2,3,9b-Tetrahydro-7,9b-dimethylcyclopenta[*c*][1]benzothiopyran-5-oxide (16) Using a procedure similar to that described for the preparation of the sulfoxide **14**, the vinyl sulfide **15** (528 mg, 2.4 mmol) was oxidized with MCPBA (80%, 526 mg, 2.4 mmol). Work-up and chromatography of the crude material on silica gel (AcOEt) gave the less polar sulfoxide (190 mg, 33%) and the polar sulfoxide (380 mg, 67%).

The less polar sulfoxide, an oil. ^{1}H-NMR (60 MHz) δ: 1.12 (3H, s), 1.45—2.9 (6H, m), 2.39 (3H, s), 6.3—6.6 (1H, m), 7.23 (2H, br s), 7.72 (1H, br s). *Anal.* Calcd for $C_{14}H_{16}OS$: C, 72.37; H, 6.94. Found: C, 72.30; H, 7.10.

The polar sulfoxide, an oil. ^{1}H-NMR (60 MHz) δ: 1.64 (3H, s), 2.75—3.0 (6H, m), 2.39 (3H, s), 6.65—6.85 (1H, m), 7.26 (2H, br s), 7.61 (1H, br s). *Anal.* Calcd for $C_{14}H_{16}OS$: C, 72.37; H, 6.94. Found: C, 72.01; H, 7.18.

1,2,4,9b-Tetrahydro-7,9b-dimethylcyclopenta[*c*][1]benzothiopyran-5-oxide (17) A solution of the major sulfoxide of **16** (367 mg, 1.6 mmol) in anhydrous THF (5 ml) was added to a cooled (−78 °C) solution of LDA, prepared from diisopropylamine (176 mg, 1.7 mmol) and butyllithium (15% in hexane) (1.0 ml, 1.6 mmol) in anhydrous THF (5 ml), under a nitrogen atmosphere. The mixture was stirred at −78 °C for 1 h, and then quenched with a saturated aqueous ammonium chloride solution. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel (AcOEt) to give the allyl sulfoxide **17** (345 mg, 94%) as an oil. ^{1}H-NMR (60 MHz) δ: 1.40 (3H, s), 1.7—2.8 (4H, m), 2.37 (3H, s), 3.70 (1H, br d, J=10 Hz), 4.31 (1H, d, J=10 Hz), 5.8—6.0 (1H, m), 7.0—7.5 (2H, m), 7.60 (1H, br s). Exact MS *m/z*: Calcd for $C_{14}H_{16}OS$: 232.0920. Found: 232.0891.

A similar treatment of the minor sulfoxide of **16** resulted in recovery of the unchanged sulfoxide.

1,2,4,9b-Tetrahydro-7,9b-dimethylcyclopenta[*c*][1]benzothiopyran (18) $TiCl_3$ (15% (w/v) aqueous solution, 1 ml) was added to a solution of the allyl sulfoxide **17** (222 mg, 0.96 mmol) in methanol (3 ml) and chloroform (1.5 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h, then poured into water and extracted with chloroform. The organic layer was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane) to give the allyl sulfide **18** (166 mg, 80%) as an oil. ^{1}H-NMR (60 MHz) δ: 1.32 (3H, s), 1.7—2.7 (4H, m), 2.21 (3H, s), 3.40 (1H, d, J=12 Hz), 3.81 (1H, dd, J=2, 12 Hz), 5.4—5.6 (1H, m), 6.65—7.2 (3H, m). Exact MS *m/z*: Calcd for $C_{14}H_{16}S$: 216.0971. Found: 216.0971.

1,2,3,3a,4,9b-Hexahydro-3-hydroxy-7,9b-dimethylcyclopenta[*c*][1]-benzothiopyran (19) A solution of borane in THF (0.2 ml of 1.0 M solution) was added to a solution of **18** (44 mg, 0.2 mmol) in anhydrous THF (3 ml), and the reaction mixture was stirred at room temperature for 1 h. Water (2 ml) was cautiously added, followed by 30% H_2O_2 (0.1 ml) and 6 N NaOH (1 ml). The reaction mixture was heated to 50—60 °C for 1 h, then cooled, saturated with potassium carbonate, and extracted with ether. The extract was dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel (benzene–AcOEt, 4:1) to give **19** (27 mg, 56%) as an oily mixture of two isomeric alcohols in a ratio of 3:2 (determined by HPLC). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620, 3370, 1610. ^{1}H-NMR (60 MHz) δ: 1.01 (3H × 2/5, s), 1.25 (1H, br), 1.35 (3H × 3/5, s), 1.45—2.35 (5H, m), 2.22 (3H, s), 2.75—3.4 (2H, m), 3.8—4.6 (1H, m), 6.6—7.1 (3H, m). Exact MS *m/z*: Calcd for $C_{14}H_{18}OS$: 234.1077. Found: 234.1090.

2,3-Dimethyl-3-(*p*-tolyl)cyclopentanol (20) Using a procedure similar to that described for the preparation of **9**, the alcohol **19** (26 mg, 11 mmol) was desulfurized with Raney Ni (*ca.* 1 g). Work-up and purification by chromatography on silica gel (benzene–AcOEt, 2:1) gave the alcohol **20**[12] (18 mg, 82%) as a mixture of two diastereomers in a ratio of 3:2 as estimated by NMR spectroscopy. ^{1}H-NMR (60 MHz) (CCl_4) δ: 0.61 (3H × 2/5, d, J=7 Hz), 0.93 (3H × 3/5, d, J=7 Hz), 1.14 (3H × 3/5, s), 1.30 (1H, s), 1.42 (3H × 2/5, s), 1.55—2.6 (5H, m), 2.28 (3H, s), 3.5—4.05 (1H, m), 6.8—7.3 (4H × 3/5, m), 6.97 (4H × 2/5, s).

2,3-Dimethyl-3-(*p*-tolyl)cyclopentanone (21) A solution of the alcohol **20** (26 mg, 0.13 mmol) in CH_2Cl_2 (2 ml) was added to a solution of Collins' reagent [prepared from CrO_3 (49 mg) and pyridine (4 ml) in CH_2Cl_2 (2 ml)]. After stirring at room temperature for 30 min, the reaction mixture was poured into a saturated $NaHCO_3$ solution. The organic layer was separated, washed successively with cold 1 N HCl, a saturated $NaHCO_3$ solution, and brine, then dried (Na_2SO_4). The solvent was evaporated off to give the ketone **21**[12] (23 mg, 90%) as an oily mixture of **21a** and **21b** in a ratio of 3:2. ^{1}H-NMR (60 MHz) (CCl_4) δ: 0.77 (3H × 2/5, d, J=7 Hz), 0.96 (3H × 3/5, d, J=7 Hz), 1.16 (3H × 3/5, s), 1.38 (3H × 2/5, s), 1.7—2.75 (5H, m), 2.31 (3H, s), 6.7—7.4 (4H × 2/5, m), 7.00 (4H × 3/5, s).

4-Acetoxy-1,2,3,3a,4,9b-hexahydro-3a,7,9b-trimethylcyclopenta[*c*][1]-benzothiopyran (26) MCPBA (80%, 0.30 g, 1.4 mmol) was added to a solution of the thiochroman **24** (0.32 g, 1.4 mmol) in CH_2Cl_2 (20 ml) at 0 °C and the mixture was stirred at room temperature for 1 h. The reaction mixture was washed with a saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (benzene–AcOEt, 1:1) to give the sulfoxide **25** (0.30 g, 88%). The sulfoxide (0.30 g, 1.22 mmol) was dissolved in acetic anhydride (1.25 ml) and the mixture was heated at 100 °C for 3.5 h. The excess of acetic anhydride was evaporated off and the residue was chromatographed on silica gel (hexane–AcOEt) to give **26** (0.29 g, 84%) as a 3:1 mixture of two diastereomers. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1750, 1615. ^{1}H-NMR (60 MHz) δ: 1.1—2.8 (6H, m), 1.18 (3H, s), 1.31 (3H × 1/4, s), 1.40 (3H × 3/4, s), 2.02 (3H, s), 2.23 (3H, s), 5.84 (1H × 1/4, s), 5.92 (1H × 3/4, s), 6.7—7.5 (3H, m). Exact MS *m/z*: Calcd for $C_{17}H_{22}O_2S$: 290.1338. Found: 290.1311.

1,2,3,3a,4,9b-Hexahydro-4-hydroxy-3a,7,9b-trimethylcyclopenta[*c*][1]-benzothiopyran (27) Potassium carbonate (0.15 g, 1.1 mmol) was added to a solution of the acetate **26** (0.21 g, 0.73 mmol) in methanol (10 ml) and water (1 ml), and the mixture was stirred at room temperature for 1 h. Methanol was evaporated off, and water (10 ml) was added. After extraction with CH_2Cl_2, the extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 10:1) to give **27** (0.18 g, quant.) as a 5:2 mixture of two diastereomers. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3420, 1610. ^{1}H-NMR (60 MHz) δ: 1.15 (3H × 2/7, s), 1.20 (3H × 5/7, s), 1.24 (3H × 2/7, s). 1.37 (3H × 5/7, s), 1.45—2.2 (6H, m), 2.22 (3H, s), 2.3—2.7 (1H, m), 4.65—5.0 (1H, m), 6.7—7.4 (3H, m). Exact MS *m/z*: Calcd for $C_{15}H_{20}O_2S$: 248.1234. Found: 248.1250.

(1*S,2*R**)-1,2-Dimethyl-2-(*p*-tolyl)cyclopentanemethanol (28)** By using a procedure similar to that described for the preparation of **9**, compound **27** (61 mg, 0.25 mmol) was desulfurized with Raney Ni (*ca.* 500 mg) in ethanol (2 ml). Work-up gave **28**[3] (53 mg, quant.) as an oil. ^{1}H-NMR (60 MHz) δ: 0.87 (1H, br), 1.13 (3H, s), 1.30 (3H, s), 1.4—2.1 (6H, m), 2.30 (3H, s), 3.03 (2H, br s), 7.03 (2H, d, J=8 Hz), 7.23 (2H, d, J=8 Hz).

(1*S,2*R**)-1-Acetyloxymethyl-1,2-dimethyl-2-(*p*-tolyl)cyclopentane**

[(±)-Tochuinyl Acetate] (3) A solution of **28** (54 mg, 0.25 mmol) and acetic anhydride (25.5 mg, 0.25 mmol) in pyridine (2 ml) was stirred at room temperature for 24 h. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–AcOEt, 10:1) to give **3** (64 mg, quant.), whose IR and ^{1}H-NMR (300 MHz) spectra were identical with those reported for (−)-tochuinyl acetate.[3] IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 2960, 2880, 1730, 1520, 1480, 1470, 1380, 1240, 1040. ^{1}H-NMR (300 MHz) δ: 1.13 (3H, s), 1.42—1.61 (1H, m), 1.7—1.9 (4H, m), 1.93 (3H, s), 2.30 (3H, s), 2.43—2.55 (1H, m), 3.36 (1H, d, J=11 Hz), 3.59 (1H, d, J=11 Hz), 7.08 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz). Exact MS *m/z*: Calcd for $C_{17}H_{24}O_2$: 260.1774. Found: 260.1763.

(±)-Cuparene (1) Using a procedure similar to that described for the preparation of **9**, compound **24** (63 mg, 0.27 mmol) was desulfurized with Raney Ni (*ca.*1 g) in ethanol (2 ml). Work-up and purification by chromatography on silica gel (hexane) gave **1** (42 mg, 77%). ^{1}H-NMR (60 MHz) δ: 0.56 (3H, s), 1.05 (3H, s), 1.25 (3H, s), 1.35—2.05 (6H, m), 2.30 (3H, s), 7.02 (2H, d, J=9 Hz), 7.22 (2H, d, J=9 Hz). Exact MS *m/z*: Calcd for $C_{15}H_{22}$: 202.1720. Found: 202.1724.

Acknowledgement The authors thank Dr. T. Honda (Hoshi University) for providing the spectral data of (±)-cuparene.

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