

Synthesis of Both Enantiomers of Flavanone and 2-Methylchromanone

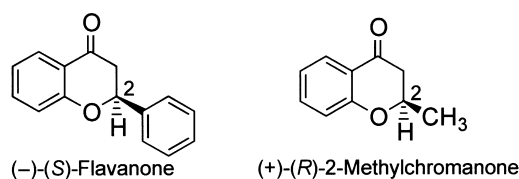
by Yoshihiro Noda* and Morio Watanabe

Department of Materials Chemistry and Engineering, College of Engineering, Nihon University,
Tamura-machi, Koriyama, Fukushima, 963-8642 Japan
(e-mail: noda@chem.ce.nihon-u.ac.jp)

Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

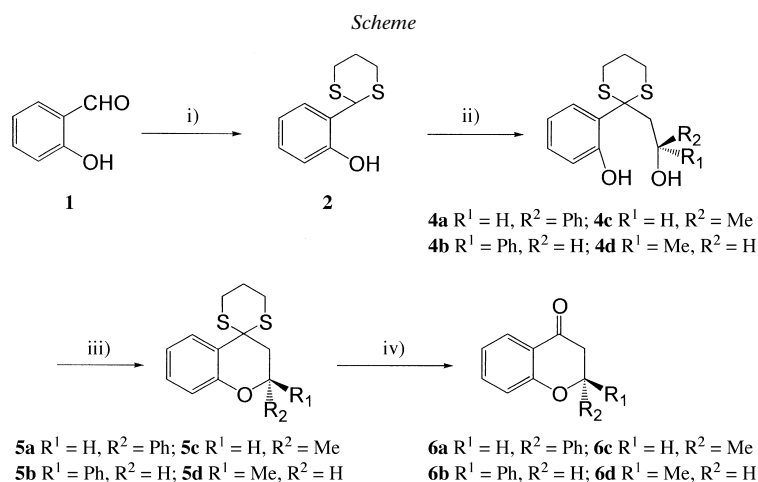
An efficient enantiospecific synthesis of the (*R*)- and (*S*)-enantiomers of flavanone and 2-methylchromanone is described. The key steps are a C,C-bond formation by ring opening of a chiral epoxide with a dithiane anion, followed by a *Mitsunobu* cyclization. The products obtained have high enantiomeric purity.

Flavanones (=2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-ones) constitute an important class of the wide group of flavanoids, and 2-methylchromanones (=2,3-dihydro-2-methyl-4*H*-1-benzopyran-4-ones) are also found in several biologically active natural products. A stereogenic center is present in their structures. Notwithstanding that they are crucial substituents in a number of naturally occurring and pharmacologically important compounds, there has been no simple and general method described to obtain optically active flavanones and 2-methylchromanones.



Syntheses of optically active flavanones and 2-methylchromanones have been reported by four groups: *a*) *Saengchantara* and *Wallace* reported the synthesis of 2-methylchromanone by the diastereoselective conjugate addition of lithium dimethylcuprate to (*S*)-3-(*p*-tolylsulfinyl)chromanone [1]. Recently, they have prepared the natural products (*S*)-2,6-dimethylchromanone and LL-D253α [2]. *b*) *Solladie et al.* has applied the *Wallace* method, *i.e.*, conjugate addition of PhMgBr to (*S*)-5,7-dimethoxy-8-methyl-3-(*p*-tolylsulfinyl) chromenone in the presence of dilithium tetrachlorocuprate as an efficient catalyst, to synthesize (+)-(R)-5-hydroxy-6-(hydroxymethyl)-7-methoxy-8-methylflavanone [3]. *c*) *Rama Rao et al.* reported the synthesis of both enantiomers of 5,7-dimethoxy-2-methylchromanone and (*R*)-7-methoxy-2-methylchromanone by inter- and intramolecular *Houben-Hoesch* reaction [4]. *d*) Recently, *Hodgetts* reported the synthesis of the biologically active natural product (–)-pinostrobin (= (*R*)-5-hydroxy-7-methoxyflavanone) [5].

Here, we describe a novel route to the optically active flavanone and 2-methylchromanone starting from salicylaldehyde (**1**) which was converted to dithiane derivative **2** by BF_3 -catalyzed reaction with propane-1,3-dithiol in 95% yield [6] (*Scheme*). Treatment of **2** with 2 equiv. of BuLi in THF and a commercially available optically active epoxide, e.g., (+)-(*R*)- and (–)-(*S*)-styrene oxide (**3a** and **3b**, resp.) and (+)-(*R*)- and (–)-(*S*)-propylene oxide (**3c** and **3d**, resp.) gave the corresponding diols **4a** (52% yield), **4b** (52%), **4c** (72%), and **4d** (86%). Mitsunobu cyclization [7][8] of diols **4a**–**4d** by treating with Ph_3P and diethyl azodicarboxylate (DEAD) in dry THF gave **5a** (68% yield), **5b** (72%), **5c** (85%), and **5d** (91%), respectively. In this cyclization, the absolute configuration was converted completely by an $\text{S}_{\text{N}}2$ -type nucleophilic displacement. Each cyclized compound, **5a**–**5d**, was hydrolyzed in aqueous MeCN with HgCl_2 in the presence of CaCO_3 [6] to afford the flavanones **6a** (70% yield) and **6b** (73%), and 2-methylchromanones **6c** (62% yield) and **6d** (66%), respectively.



i) Propane-1,3-dithiol, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CHCl_3 , r.t. ii) 2 equiv. BuLi, epoxides ((+)-(*R*)-styrene oxide (**3a**), (–)-(*S*)-styrene oxide (**3b**), (+)-(*R*)-propylene oxide (**3c**), (–)-(*S*)-propylene oxide (**3d**)) THF, -18° . iii) PPh_3 , diethyl azodicarboxylate (DEAD), THF, r.t. iv) HgCl_2 , CaCO_3 , MeCN/ H_2O , r.t.

Our samples of (+)-(*R*)-**6a** (m.p. 77° (hexane/ CH_2Cl_2), $[\alpha]_{\text{D}}^{22} = +62.8$ ($c = 0.5$, CHCl_3)), (–)-(*S*)-**6b** (m.p. 77 – 78° (hexane/ CH_2Cl_2), $[\alpha]_{\text{D}}^{22} = -63.6$ ($c = 0.5$, CHCl_3))¹, and 2-methylchromanones (–)-(*S*)-**6c** (m.p. 43 – 44° (hexane/ CH_2Cl_2), $[\alpha]_{\text{D}}^{21} = -46.7^\circ$ ($c = 1.4$, CHCl_3)), (+)-(*R*)-**6d** (m.p. 43 – 44° (hexane/ CH_2Cl_2), $[\alpha]_{\text{D}}^{19} = +47.9$ ($c = 0.8$, CHCl_3))², were shown to be of high enantiomeric purity (flavanone (+)-(*R*)-**6a**: 95% ee, (–)-(*S*)-**6b**: 97% ee, 2-methylchromanone (–)-(*S*)-**6c**: 97% ee,

¹) Reported data for (+)-(*R*)- and (–)-(*S*)-flavanone [9]: m.p. 77° , $[\alpha]_{\text{D}} = +67.2$ ($c = 0.35$, CHCl_3), and m.p. 76 – 77° , $[\alpha]_{\text{D}} = -64.4$ ($c = 0.35$, CHCl_3), resp.; [10]: m.p. 76° (petroleum ether), $[\alpha]_{\text{D}}^{25} = +52$ ($c = 0.75$, CHCl_3), and m.p. 77 – 78° (petroleum ether), $[\alpha]_{\text{D}}^{25} = -53.5$ ($c = 2.27$, CHCl_3), resp.; [11]: m.p. 72 – 74° , $[\alpha]_{\text{D}} = +12.4^\circ$ (benzene), and m.p. 75 – 76° , $[\alpha]_{\text{D}} = -9.35^\circ$ (benzene), resp.

²) Reported data for (–)-(*S*)-2-methylchromanone m.p. 39 – 40° , $[\alpha]_{\text{D}}^{22} = -50$ – -4° ($c = 2$, CHCl_3), reference [1], (+)-(*R*)-[$\alpha]_{\text{D}} = +51^\circ$ ($c = 1$, CHCl_3), reference [5].

(+)-(R)-**6d**: 99% ee) by HPLC analysis under optimized conditions for racemic standard on a chiral stationary phase (*Sumichiral OA-7000*).

In conclusion, we have developed a general and efficient synthesis of optically active flavanone and 2-methylchromanone of high enantiomeric purity from readily available starting materials. The method presented may be generally applicable to the synthesis of natural products.

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Experimental Part

General. M.p.: Yanako MP-500D melting-point apparatus; uncorrected. Prep. TLC: Kieselgel GF254. Column chromatography (CC): silica gel (Merck, Kieselgel 60, 70–230 mesh). Specific rotations: JASCO DIP-360 polarimeter, CHCl₃ as solvent; concentration in g/100 ml. IR Spectra: Perkin-Elmer Paragon 1000 FT-IR spectrometer, in CHCl₃ soln. ¹H- and ¹³C-NMR spectra: Hitachi R3000 (300- (¹H) or 75-MHz (¹³C)) instrument; all spectra were recorded with TMS as internal standard in CDCl₃ as solvent. MS: at 70 eV with a JEOL GC mate instrument. Solvent systems used are shown in parentheses. Anh. MgSO₄ was employed to dry extracts.

2-(1,3-Dithian-2-yl)phenol (2). Salicylaldehyde (=2-hydroxybenzaldehyde, **1**; 4.88 g, 40 mmol), propane-1,3-dithiol (4.83 g, 45 mmol), and BF₃·Et₂O (2.00 g, 14 mmol) were stirred in CHCl₃ (100 ml) at 25° for 10 h; 10% NaHCO₃ (50 ml) was added, and the mixture was extracted with CH₂Cl₂ (3 × 50 ml). The combined org. phase washed with sat. NaCl soln. (100 ml), dried (MgSO₄), and filtered. Evaporation gave a yellow solid, which was recrystallized (hexane/CH₂Cl₂) to give **2** (8.05 g, 95%). M.p. 138–139° (hexane/CH₂Cl₂), IR (CHCl₃): 3590, 3425, 3007, 1578, 1487, 1277, 1227, 1170. ¹H-NMR (300 MHz): 1.9–2.2 (*m*, 2 H, dithiane); 3.0 (*m*, 4 H, dithiane); 5.42 (*s*, H–C(4)); 6.04 (*br. s.*, OH); 6.8–7.4 (*m*, 4 arom. H). ¹³C-NMR (75 MHz): 24.8; 31.6; 47.2; 117.2; 120.7; 123.6; 129.0; 130.0; 154.3. EI-MS: 124 (15), 123 (20), 122 (100), 147 (32), 139 (25), 138 (100), 137 (93), 105 (19). HR-MS: 212.03356 (C₁₀H₁₂OS₂; calc. 212.03295).

C,C-Bond Formation by Ring Opening of a Chiral Epoxide with 2. General Procedure. Addition of 3.55 ml (5.7 mmol) of a 1.6M BuLi soln. in hexane to 482 mg (2.27 mmol) of **2** in 20 ml of anh. THF at –18° and stirring for 3 h. To a soln. of dithiane anion were added 546 mg (4.55 mmol) of styrene oxide in 5 ml of anh. THF and, after stirring for 3 h, sat. NH₄Cl soln. was added, and the mixture was extracted with Et₂O (3 × 50 ml). The org. layer was dried and evaporated, and the residue purified by CC and prep. TLC to give the alcohol.

2-[(S)-2-(2-Hydroxy-2-phenylethyl)-1,3-dithian-2-yl]phenol (4a). From 492 mg (2.27 mmol) of **2** and 546 mg (4.55 mmol) of (+)-(R)-styrene oxide (**3a**), 392 mg (52%) of **4a** was obtained. Colorless liquid. [α]_D²⁵ = –4.0 (*c* = 0.8, CHCl₃). IR (CHCl₃): 3474, 3195, 3008, 2911, 1605, 1573, 1477, 1457, 1423, 1282, 1226, 1193, 1047, 908. ¹H-NMR (300 MHz): 2.0 (*m*, 2 H, dithiane); 2.34–2.6 (*m*, CH₂); 3.0 (*m*, 4 H, dithiane); 4.84 (*d*, *J* = 8.7, CHOH); 6.98 (*m*, 2 arom. H); 7.22 (*m*, 6 arom. H); 7.93 (*m*, 1 arom. H); 8.63 (*s*, OH). ¹³C-NMR (75 MHz): 24.2; 27.7; 28.0; 51.5; 57.0; 70.7; 119.3; 120.6; 123.3; 125.5; 127.3; 128.3; 130.2; 131.5; 143.7; 155.9. EI-MS: 332 (27), 224 (75), 225 (83), 211 (22), 152 (61), 151 (48), 137 (21), 119 (100), 107 (28), 105 (35), 91 (37), 79 (30), 78 (27). HR-MS: 332.08984 (C₁₈H₂₀O₂S₂; calc. 332.09046).

2-[(R)-2-(2-Hydroxy-2-phenylethyl)-1,3-dithian-2-yl]phenol (4b). From 469 mg (2.21 mmol) of **2** and 530 mg (4.42 mmol) (–)-(S)-styrene oxide (**3b**), 382 mg (52%) of **4b** was obtained. Colorless liquid. [α]_D²⁵ = +3.7 (*c* = 0.8, CHCl₃).

2-[(R)-2-(2-Hydroxypropyl)-1,3-dithian-2-yl]phenol (4c). From 759 mg (3.58 mmol) of **2** and 415 mg (7.2 mmol) (+)-(R)-propylene oxide (**3c**), 696 mg (72%) of **4c** was obtained. Colorless liquid. [α]_D²⁵ = +6.3 (*c* = 1.3, CHCl₃). IR (CHCl₃): 3197, 3008, 2911, 1605, 1573, 1477, 1456, 1423, 1281, 1225, 1152, 1047. ¹H-NMR (300 MHz): 1.09 (*d*, *J* = 6, Me); 1.95–2.05 (*m*, 2 H, dithiane); 2.06–2.17 (*m*, CH₂); 2.85 (*m*, 4 H, dithiane); 4.0 (*br.*, CHOH); 6.95 (*m*, 2 arom. H); 7.27 (*t*, *J* = 7.5, 1 arom. H); 7.90 (*d*, *J* = 7.5, 1 arom. H); 8.61 (*s*, OH). ¹³C-NMR (75 MHz): 24.3; 24.7; 28.0; 28.4; 51.2; 57.3; 65.0; 120.0; 121.0; 123.8; 130.6; 131.8; 156.4. MS: 270 (96), 211 (28), 195 (35), 178 (28), 163 (100), 152 (45), 151 (46), 145 (22), 137 (30), 91 (58). HR-MS: 270.07477 (C₁₃H₁₈O₂S₂; calc. 270.07481).

2-[(S)-2-(2-Hydroxypropyl)-1,3-dithian-2-yl]phenol (4d). From 759 mg (3.58 mmol) of **2** and 415 mg (7.2 mmol) (–)-(S)-propylene oxide (**3d**), 831 mg (86%) of **4d** was obtained. Colorless liquid. [α]_D²⁵ = –6.6 (*c* = 1.2, CHCl₃).

Mitsunobu Cyclization. General Procedure. To a soln. of 957 mg (3.65 mmol) Ph_3P in 10 ml of anh. THF was added at r.t. 1.6 g (1.66 mmol) of diethyl azodicarboxylate (DEAD), and, after stirring 1 h, the mixture was added to 303 mg (0.91 mmol) of **4a**. After 2 h, the reaction was monitored by TLC, then the mixture was diluted with H_2O (30 ml) and extracted with Et_2O (3×50 ml). The combined Et_2O extracts were dried and evaporated. Purification (TLC) and recrystallization (hexane/ CH_2Cl_2) afforded the cyclized compound **5a**.

(R)-2,3-Dihydro-2-phenylspiro[4H-1]benzopyran-4,2'-[1,3]dithiane] (**5a**). From 303 mg (0.91 mmol) of **4a**, 195 mg (68%) of **5a** was obtained. M.p. 147–148° (hexane/ CH_2Cl_2). $[\alpha]_D^{25} = -63.5$ ($c = 0.6$, CHCl_3). IR (CHCl_3): 3010, 1606, 1578, 1480, 1453, 1220, 1041, 916. $^1\text{H-NMR}$ (300 MHz): 1.98–2.2 (m , 2 H, dithiane); 2.5–2.6 (m , $\text{CH}_2(3)$); 2.6–2.8 (m , 2 H, dithiane); 3.05–3.15 (m , 2 H, dithiane); 5.32 (d , $J = 10.2$, $\text{H-C}(2)$); 6.8–7.8 (m , 9 arom. H). $^{13}\text{C-NMR}$ (75 MHz): 24.7; 27.8; 27.9; 43.8; 48.5; 75.5; 117.3; 121.0; 123.6; 126.4; 128.2; 128.6; 129.6; 129.7; 140.3; 154.7. EI-MS: 332 (27), 224 (75), 225 (83), 211 (22), 152 (61), 151 (48), 137 (21), 119 (100), 107 (28), 105 (35), 91 (37), 79 (30), 78 (27). HR-MS: 332.09046 ($\text{C}_{18}\text{H}_{20}\text{O}_2\text{S}_2$; calc. 332.09046).

(S)-2,3-Dihydro-2-phenylspiro[4H-1]benzopyran-4,2'-[1,3]dithiane] (**5b**). From 214 mg (0.64 mmol) of **4b**, 148 mg (73%) of **5b** was obtained. M.p. 147–148° (hexane/ CH_2Cl_2). $[\alpha]_D^{25} = +61.1$ ($c = 0.6$, CHCl_3).

(S)-2,3-Dihydro-2-methylspiro[4H-1]benzopyran-4,2'-[1,3]dithiane] (**5c**). From 620 mg (2.3 mmol) of **4c**, 492 mg (85%) of **5c** was obtained. M.p. 118–119° (hexane/ CH_2Cl_2). $[\alpha]_D^{25} = -167.5$ ($c = 1.4$, CHCl_3). IR (CHCl_3): 3008, 2979, 2908, 1579, 1480, 1455, 1279, 1230, 1125, 1069. $^1\text{H-NMR}$ (300 MHz): 1.46 (d , $J = 6.6$, Me); 1.95 (m , $\text{CH}_2(3)$); 2.6–2.8 (m , 2 H, dithiane); 2.8–3.0 (m , 2 H, dithiane); 4.42 (m , $\text{H-C}(2)$); 6.80 (d , $J = 8.1$, 1 arom. H); 6.92 (t , $J = 7.5$, 1 arom. H); 7.19 (t , $J = 7.5$, 1 arom. H); 7.82 (d , $J = 8.1$, 1 arom. H). $^{13}\text{C-NMR}$ (75 MHz): 20.7; 24.7; 27.8; 27.9; 42.9; 48.2; 69.6; 117.0; 120.6; 123.6; 129.6; 129.7; 154.8. EI-MS: 253 (17), 252 (85), 237 (43), 179 (24), 178 (100), 177 (45), 163 (58), 145 (66), 131 (15). HR-MS: 252.06412 ($\text{C}_{13}\text{H}_{16}\text{OS}_2$; calc. 252.06425).

(R)-2,3-Dihydro-2-methylspiro[4H-1]benzopyran-4,2'-[1,3]dithiane] (**5d**). From 720 mg (2.67 mmol) of **4d**, 611 mg (91%) of **5d** was obtained. M.p. 116–117° (hexane/ CH_2Cl_2). $[\alpha]_D^{25} = +171.7$ ($c = 0.1$, CHCl_3).

Hydrolysis of Dithianes. General Procedure. A suspension of 314 mg (1.16 mmol) of HgCl_2 , 116 mg (1.16 mmol) of CaCO_3 , and 146 mg (0.46 mmol) of **5a** in 10 ml of $\text{MeCN}/\text{H}_2\text{O}$ 4 : 1 were stirred at r.t. After 3 h, the mixture was filtered off and extracted with CH_2Cl_2 (3×30 ml). The combined org. layer was dried and evaporated. Purification (prep. TLC) and recrystallization (hexane/ CH_2Cl_2) afforded flavanone (and 2-methylchromanone).

(+)-(R)-Flavanone (= (+)-(R)-2,3-Dihydro-2-phenyl-4H-1-benzopyran; **6a**). From 146 mg (0.46 mmol) of **5a**, 73 mg (70%) of **6a** was obtained. M.p. 77° (hexane/ CH_2Cl_2). $[\alpha]_D^{25} = +62.8$ ($c = 0.5$, CHCl_3). HPLC (Sumichiral OA-7000 column, 20 mm phosphate buffer (pH 2.0), $\text{MeCN}/\text{H}_2\text{O}$ 60 : 40): 8.7 min (97.4%), 16.5 min (2.6%), 95% ee. IR (CHCl_3): 3013, 1689, 1606, 1463, 1306, 1228, 1116, 906. $^1\text{H-NMR}$ (300 MHz): 3.0 (dd , ABX , $J = 17, 13, 2$, $\text{CH}_2(3)$); 5.48 (dd , ABX , $J = 13, 3$, $\text{H-C}(2)$); 7.07 (m , 2 arom. H); 7.3–7.6 (m , 6 arom. H); 7.93 (d , $J = 8.1$, 1 arom. H). $^{13}\text{C-NMR}$ (75 MHz): 44.7; 79.6; 118.1; 120.9; 121.6; 127.0; 128.7; 128.8; 136.1; 138.7; 161.5; 191.9.

(-)-(S)-Flavanone (= (-)-(S)-2,3-Dihydro-2-phenyl-4H-1-benzopyran; **6b**). From 129 mg (0.41 mmol) of **5b**, 67 mg (73%) of **6b** was obtained. M.p. 77–78° (hexane/ CH_2Cl_2). $[\alpha]_D^{25} = -63.6$ ($c = 0.5$, CHCl_3). HPLC: 8.8 min (1.4%), 16.6 min (98.6%), 97% ee.

(-)-(S)-2-Methylchromanone (= (-)-(S)-2,3-Dihydro-2-methyl-4H-1-benzopyran; **6c**). From 346 mg (1.37 mmol) of **5c**, 134 mg (62%) of **6c** was obtained. M.p. 43–44° (hexane/ CH_2Cl_2). $[\alpha]_D^{25} = -46.7$ ($c = 1.4$, CHCl_3). HPLC (Sumichiral OA-7000 column, 20 mm phosphate buffer (pH 2.0), $\text{MeCN}/\text{H}_2\text{O}$ 60 : 40): 48.1 min (1.5%), 51.4 min (98.5%), 97% ee. IR (CHCl_3): 3013, 2982, 1693, 1608, 1577, 1473, 1464, 1386, 1349, 1309, 1229, 1153, 1122, 877. $^1\text{H-NMR}$ (300 MHz): 1.52 (d , $J = 5.7$, Me); 2.68 (d , $J = 7.5$, $\text{CH}_2(3)$); 4.59 (dd , $J = 7.5, 5.7$, $\text{H-C}(2)$); 6.9–7.0 (m , 2 arom. H); 7.47 (t , $J = 7.5$, 1 arom. H); 7.87 (d , $J = 7.5$, 1 arom. H). $^{13}\text{C-NMR}$ (75 MHz): 21.0; 44.6; 74.2; 117.8; 120.7; 121.1; 126.9; 135.9; 161.6; 192.3.

(+)-(R)-2-Methylchromanone (= (+)-(R)-2,3-Dihydro-2-methyl-4H-1-benzopyran; **6d**). From 569 mg (2.26 mmol) of **5d**, 241 mg (66%) of **6d** was obtained. M.p. 43–44° (hexane/ CH_2Cl_2). $[\alpha]_D^{25} = +47.9$ ($c = 0.8$, CHCl_3). HPLC: 48.4 min (99.7%), 51.2 min (0.3%), 99% ee.

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