# Enantioselective Synthesis of (−)-(*R*)-Cordiachromene and (−)-(*R*)-Dictyochromenol Utilizing Intramolecular $S_N$Ar Reaction

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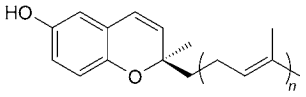
Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

A simple and efficient enantioselective synthesis of chromene, (−)-(*R*)-cordiachromene (**1**), and (−)-(*R*)-dictyochromenol (**2**) has been accomplished. This convergent synthesis utilizes intramolecular $S_N$Ar reaction for the formation of chroman ring, and *Seebach*'s method of '*self-reproduction of chirality*' should establish the (*R*)-configuration of the C(2) side chain as key steps.

**Introduction.** – Chromenes (benzopyrans) are most ubiquitous heterocyclic building blocks in both natural products and synthetic compounds with important biological activities.




Cordiachromene (**1**) *n* = 1
Dictyochromenol (**2**) *n* = 2

Cordiachromene (=2-methyl-2-(4-methylpent-3-en-1-yl)-2*H*-chromen-6-ol; **1**) was first isolated from the American tree *Cordia alliodora* in 1977 by *Manners and Jurd* [1] and later from *Aplidium constellatum* [2], *Aplidium antillens* [3], and *Aplidium multiplicantium* [4]. This chromene **1** displays antibacterial activity against *Staphylococcus aureus* [3] and anti-inflammatry activity [5].

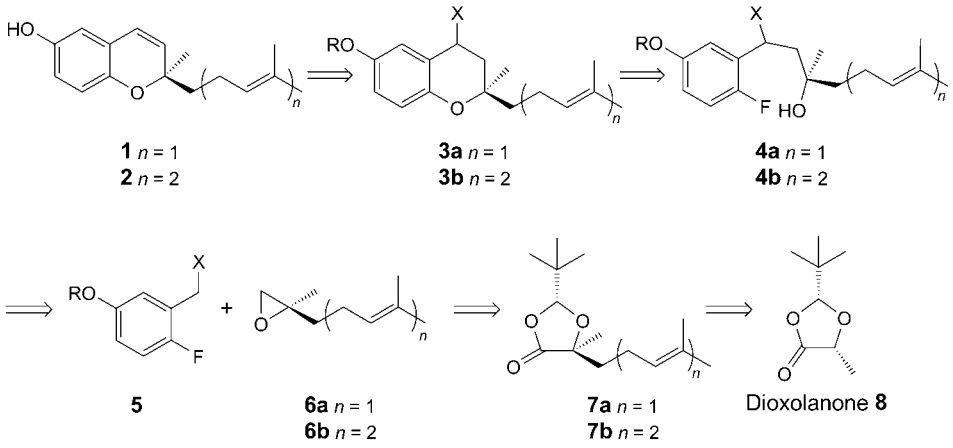
The short synthesis of racemic **1** using a *Claisen* rearrangement of propargyl ether has been reported [6]. The asymmetric total synthesis of **1** has been achieved by utilizing the *Sharpless* enantioselective epoxidation [7] and lipase-catalyzed kinetic resolution of racemic acetates [8]. Recently, *Takenaka et al.* [9] have reported the synthesis of **1** by an enantioselective 6-*endo*-trig *Wacker*-type cyclization of hydroquinone and geraniol in two steps.

Dictyochromenol (=2-[(3*E*)-4,8-dimethylnona-3,7-dien-1-yl]-2-methyl-2*H*-chromen-6-ol; **2**) was first isolated from brown alga *Dictyopteris undulata* in 1984 by *Dave et al.* [10] and later from *Piper tricuspe* [11]. This chromene **2** shows antifeedant [10], antimalarial [11], and antioxidant [11] activities.

The asymmetric total synthesis of **2** has been achieved by utilizing lipase catalyzed kinetic resolution of racemic acetates [9], and synthesis of both enantiomers by *Sharpless* enantioselective epoxidation in 2002 by *Aoki et al.* [12].

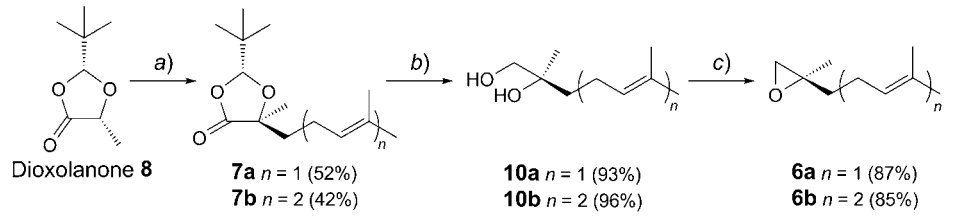
In this article, we report a new approach to the enantioselective total synthesis of (−)-(*R*)-**1** and (−)-(*R*)-**2**. Our strategy for the synthesis of (−)-(*R*)-**1** and (−)-(*R*)-**2**, outlined in *Scheme 1*, relies on the two key reactions. We envisioned that chromene ring system could be effectively prepared using the enantioselective intramolecular $S_NAr$ (aromatic nucleophilic substitution) reaction methodology [13], developed in our labolatory [14]. The *Seebach*'s method [15] of '*self-reproduction of chirality*' should then establish the (*R*)-configuration at C(2) of chromene.

Scheme 1. *Retrosynthetic Analysis for the Preparation of* **1** *and* **2**




**Results and Discussion.** – To establish the configuration at C(2) of the chromene, the *Seebach*'s method of 'self-reproduction of chirality' using (2*R*,5*R*)-2-(*tert*-butyl)-5-methyl-1,3-dioxolan-4-one (**8**; *Scheme 2*) was employed. Compound **8** was obtained from the condensation of pivalaldehyde and (*S*)-lactic acid in pentane in high yield. The dioxolanone **8** was treated with lithium diisopropylamide (LDA) in THF and alkylated with homoprenyl iodides **9a** or **9b**, which had been synthesized according to [16]. The substituted dioxolanones **7a** or **7b** were reduced to the diols **10a** and **10b**, respectively, with $LiAlH_4$ in absolute $Et_2O$. The ring closure to the epoxides **6a** and **6b** was carried out applying a phase transfer-catalyzed one-pot procedure [17]: a soln. of

*Scheme 2*

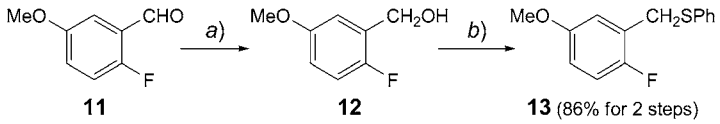



*a*) LDA, THF, 5-iodo-2-methylpent-2-ene or (*E*)-9-iodo-2,6-dimethylnonane-2,6-diene (**9a** or **9b**, resp.), −78° to r.t. *b*) $LiAlH_4$, $Et_2O$, −78° to r.t. *c*) TEBA, TsCl, $CH_2Cl_2$/50% NaOH aq.

the diols **10a** and **10b**, respectively, in $CH_2Cl_2$ was vigolously stirred for 15 min with TsCl, benzyl(triethyl)ammonium chloride (TEBA), and 50% NaOH aqueous solution (*Scheme 2*).

The sulfide **13** was prepared from 2-fluoro-5-methoxybenzaldehyde (**11**). The aldehyde **11** was reduced with $NaBH_4$ in MeOH to give the alcohol **12**. Compound **12** was then treated with PhSSPh and $Bu_3P$ in pyridine to give **13** in 86% yield for two steps (*Scheme 3*).

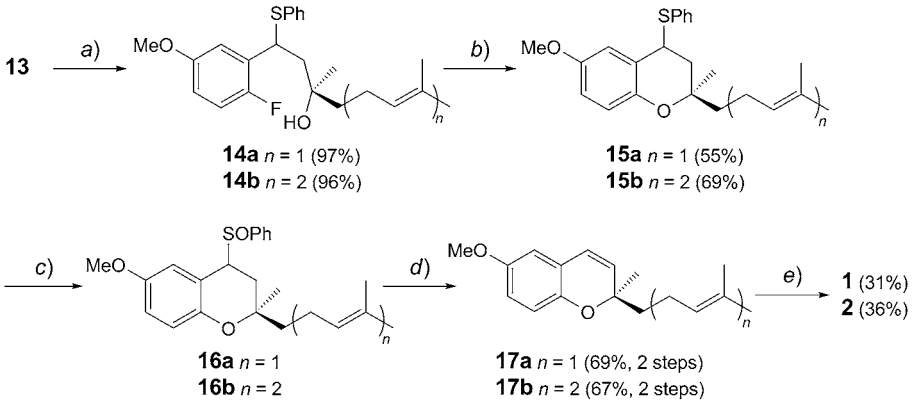
*Scheme 3*




*a*) $NaBH_4$, MeOH, 0°. *b*) PhSSPh, $Bu_3P$, pyridine.

The lithium salt, prepared from **13** with BuLi, was treated with epoxides **6a** and **6b** in THF (−78°) to give the *tertiary* alcohols **14a** and **14b**, respectively (*Scheme 4*). Cyclization reaction was carried out with $^t$BuOK in THF to furnish **15a** and **15b** (55 and 69%, resp.). The chroman system was formed through an intramolecular aromatic nucleophilic substitution reaction ($S_NAr$). In this cyclization, the absolute configuration of C(2) was retained. In this type of nucleophilic attacks, F is used to be the best leaving group.

*Scheme 4*




*a*) BuLi, THF, **6a** or **6b**, −78°. *b*) $^t$BuOK, THF, reflux. *c*) *m*CPBA, $CH_2Cl_2$, 0°. *d*) $CaCO_3$, toluene, reflux. *e*) EtSNa, DMF, reflux.

Oxidation of sulfides **15a** and **15b** with *m*-chloroperbenzoic acid (*m*CPBA) in $CH_2Cl_2$ yielded sulfoxides **16a** and **16b**, respectively. Without purification, **16a** and **16b** with a $\beta$-H-atom readily underwent *syn*-elimination on pyrolysis to form chromenes **17a** and **17b**, respectively. Finally, conversion of the methyl ether to alcohol in the methoxy-cordiachromene **17a** and methoxy-dictyochromenol **17b** with NaSEt in DMF furnished the (−)-(*R*)-cordiachromene (**1**) and (−)-(*R*)-dictyochromenol (**2**). All the

intermediate compounds, including (−)-(*R*)-**1**, and (−)-(*R*)-**2**, were fully characterized by $^1$H- and $^{13}$C-NMR, IR, and MS data. Comparison of our physical and spectroscopic data with those published in [7], [12] confirmed our successful synthesis of (−)-(*R*)-cordiachromene (**1**; $[\alpha]_D^{22} = -110.7$ ($c = 0.65$, $CHCl_3$), [7]: antipode: $[\alpha]_D^{20} = +101.6$ ($c = 0.83$, $CHCl_3$)), and (−)-(*R*)-dictyochromenol (**2**; $[\alpha]_D^{21} = -86.5$ ($c = 0.38$, $CHCl_3$), [12]: $[\alpha]_D^{20} = -82.4$ ($c = 0.83$, $CHCl_3$)).

**Conclusions.** – We have developed an efficient enantioselective protocol for the synthesis of (−)-(*R*)-cordiachromene (**1**) and (−)-(*R*)-dictyochromenol (**2**) by employing intramolecular $S_N$Ar reaction and *Seebach*'s method of 'self-reproduction of chirality' as the key reaction steps.

## Experimental Part

*General.* Anh. $MgSO_4$ was employed to dry extracts. Prep. TLC: *Kieselgel GF 254*. Column chromatography (CC): silica gel ($SiO_2$, *Kieselgel 60*, 70–230 mesh; *Merck*). Specific rotations: *JASCO DIP-360* polarimeter, $CHCl_3$ as solvent; concentration in g/100 ml. IR Spectra: *Perkin-Elmer Paragon 1000* FT-IR spectrometer, in $CHCl_3$ soln. $^1$H- and $^{13}$C-NMR spectra: *Hitachi R3000* (300 ($^1$H) or 75 MHz ($^{13}$C)) instrument; all spectra were recorded with TMS as internal standard and $CDCl_3$ as solvent. MS: at 70 eV with a *JEOL GC mate* instrument.

*(2*R,5S*)-2-(*tert*-Butyl)-5-methyl-5-(4-methylpent-3-en-1-yl)-1,3-dioxolan-4-one* (**7a**). BuLi (5.6 ml, 9.45 mmol; 1.6M in hexane) was added to a stirred cold (−78°) soln. of 1.3 g (10 mmol) of $^i$Pr$_2$NH in 20 ml of dry THF. After 1 h, 995 mg (6.3 mmol) of dioxolanone **8**, dissolved in 4 ml of THF, was added dropwise. After stirring for 30 min, 1.6 g (7.6 mmol) of homoprenyl iodide *5-iodo-2-methylpent-2-ene* (**9a**) in 3 ml of THF was added, and the mixture was allowed to warm to r.t. during 20 h. Sat. $NH_4Cl$ soln. (30 ml) was added, and the mixture was extracted with $Et_2O$ (3 × 30 ml). The combined org. phase washed with $H_2O$ and brine, dried, and filtered. Evaporation and purification by CC ($Et_2O$/hexane 1:10) afforded 787 mg (52%) of **7a**. Colorless liquid. $[\alpha]_D^{26} = +38.3$ ($c = 0.65$, $CHCl_3$); [15b]: $[\alpha]_D^{20} = +30.2$ ($c = 2.40$, $CHCl_3$). $^1$H-NMR (300 MHz): 0.96 (*s*, $^t$Bu); 1.44 (*s*, Me); 1.61 (*s*, Me); 1.68 (*s*, Me); 1.72–1.79 (*m*, $CH_2$); 2.0–2.2 (*m*, $CH_2$); 5.18 (*s*, CH). $^{13}$C-NMR (75 MHz): 17.7; 22.3; 22.7; 23.3; 25.6; 34.6; 36.3; 79.8; 108.5; 122.7; 132.7; 175.7.

*(2*R,5S*)-2-(*tert*-Butyl)-5-[(3*E*)-4,8-dimethylnona-3,7-dien-1-yl]-5-methyl-1,3-dioxolan-4-one* (**7b**). From 1.5 g of **8** (9.5 mmol) and 3.17 g of *(*E*)-9-iodo-2,6-dimethylnonane-2,6-diene* (**9b**, 11.4 mmol), 1.23 g (42%) of **7b** was obtained. Colorless liquid. $[\alpha]_D^{24} = +33.3$ ($c = 0.49$, $CHCl_3$). $^1$H-NMR (300 MHz): 0.96 (*s*, $^t$Bu); 1.43 (*s*, Me); 1.60 (br. *s*, Me); 1.63 (br. *s*, Me); 1.69 (br. *s*, Me); 2.0 (br. *t*, $J = 7.2$, $CH_2$); 2.0–2.2 (*m*, $CH_2$); 2.6–2.7 (*m*, 2 $CH_2$); 5.10 (br., 2 CH); 5.18 (*s*, CH). $^{13}$C-NMR (75 MHz): 15.7; 17.7; 21.6; 22.7; 23.4; 25.7; 27.0; 34.6; 35.6; 39.3; 79.9; 108.4; 123.0; 124.0; 131.3; 133.4; 133.8; 175.8.

*(2*R*)-2,6-Dimethylhept-5-ene-1,2-diol* (**10a**). Compound **7a** 1.5 g (6.25 mmol) in 10 ml of dry THF was added dropwise to a mixture of $LiAlH_4$ (430 mg, 11.3 mmol) and 20 ml of THF under Ar at −78°. The mixture was allowed to warm to r.t. during 20 h. at 0°, and 1 ml $H_2O$ was added. The precipitate was filtered. The org. layer was dried and evaporated. The residue purified by CC ($Et_2O$/hexane 8:1) to give 918 mg (93%) of **10a**. Colorless liquid. $[\alpha]_D^{21} = -1.49$ ($c = 1.05$, $CHCl_3$); [15b]: $[\alpha]_D^{20} = +1.7$ ($c = 2.76$, $CHCl_3$). $^1$H-NMR (300 MHz): 1.17 (*s*, Me); 1.47–1.57 (*m*, $CH_2$); 1.62 (br. *s*, Me); 1.68 (*s*, Me); 2.04 (br. *q*, $J = 7$, $CH_2$); 2.85 (br., 2 OH); 3.39 (*d*, $J = 11$, CH); 3.46 (*d*, $J = 11$, CH); 5.11 (br. *t*, $J = 7$, CH). $^{13}$C-NMR (75 MHz): 17.6; 22.4; 23.0; 25.7; 38.4; 69.6; 73.1; 124.1; 131.8.

*(2*R,5E*)-2,6,10-Trimethylundeca-5,9-diene-1,2-diol* (**10b**). From 1.5 g (4.87 mmol) of **7b**, 1.06 g (96%) of **10b** was obtained. Colorless liquid. $[\alpha]_D^{23} = -0.41$ ($c = 0.70$, $CHCl_3$). $^1$H-NMR (300 MHz): 1.16 (*s*, Me); 1.48 (*s*, Me); 1.62 (br. *s*, Me); 1.68 (*s*, Me); 1.9–2.0 (*m*, 2 $CH_2$); 2.0–2.07 (*m*, 2 $CH_2$); 2.97 (br., 2 OH); 3.38 (*d*, $J = 11$, CH); 3.45 (*d*, $J = 11$, CH); 5.12 (br., 2 CH). $^{13}$C-NMR (75 MHz): 15.8; 17.7; 22.3; 23.0; 25.7; 26.9; 38.3; 39.6; 69.6; 73.0; 123.2; 124.1; 131.2; 134.8.

(2*R*)-*2-Methyl-2-(4-methylpent-3-en-1-yl)oxirane* (**6a**). The mixture of 900 mg (5.7 mmol) of **10a**, 50 mg (0.2 mmol) of benzyl(triethyl)ammonium chloride in $CH_2Cl_2$ (30 ml) and 5 ml of 50% NaOH soln. was vigorously stirred at r.t. for 15 min. At 0°, a soln. of 1.2 g (6.3 mmol) of TsCl in 1 ml of $CH_2Cl_2$ was added. The mixture was allowed to warm up to r.t. for 2 h. The two layers were separated, and the org. layer was washed with $H_2O$. The org. layer dried and evaporated. The residue was distilled (80–90° bath temp./15 Torr) and afforded 694 mg of **6a** (87%). Colorless liquid. $[\alpha]_D^{25} = -11.3$ ($c = 0.52$, $CHCl_3$); [15b]: $[\alpha]_D^{20} = -7.6$ ($c = 2.33$, $CHCl_3$). IR ($CHCl_3$): 3671, 2969, 2858, 1672, 1451, 1390, 1234. $^1$H-NMR (300 MHz): 1.33 (*s*, Me); 1.5–1.6 (*m*, $CH_2$); 1.62 (*s*, Me); 1.69 (*s*, Me); 2.08 (*q*, $J = 7.5$, $CH_2$); 2.58 (*d*, $J =$ 5.1, CH); 2.63 (*d*, $J = 5.1$, CH); 5.10 (br. *t*, $J = 5.7$ CH). $^{13}$C-NMR (75 MHz): 17.6; 20.9; 23.8; 25.7; 36.8; 53.9; 56.9; 123.5; 131.9.

*(2*R*)-2-[(3*E*)-4,8-Dimethylnona-3,7-dien-1-yl]-2-methyloxirane* (**6b**). From 1.0 g (4.2 mmol) of **10b**, 782 mg (85%) of **6b** was obtained. Colorless liquid. $[\alpha]_D^{25} = -6.7$ ($c = 0.41$, $CHCl_3$). IR ($CHCl_3$): 3670, 3041, 2969, 2928, 1668, 1449, 1380, 1234. $^1$H-NMR (300 MHz): 1.31 (*s*, Me); 1.48–1.56 (*m*, $CH_2$); 1.59 (*s*, Me); 1.60 (*s*, Me); 1.67 (*s*, Me); 1.95–2.18 (*m*, 3 $CH_2$); 2.54 (*d*, $J = 4.5$, CH); 2.65 (*d*, $J = 4.5$, CH); 5.09 (br. *q*, $J = 6.6$, 2 CH). $^{13}$C-NMR (75 MHz): 15.8; 17.5; 20.8; 23.6; 25.5; 26.4; 36.6; 39.5; 53.7; 56.6; 123.3; 124.0; 131.0; 135.2.

*1-Fluoro-4-methoxy-2-[(phenylsulfanyl)methyl]benzene* (**13**). *2-Fluoro-5-methoxybenzaldehyde* (**11**; 1.0 g, 6.49 mmol) in 10 ml of MeOH was added to a mixture of 296 mg (7.79 mmol) of $NaBH_4$ and 5 ml of MeOH. The mixture was stirred at r.t. for 10 min. $H_2O$ (10 ml) was added, and the mixture was extracted with $Et_2O$ (3 × 30 ml). The combined org. phase washed with sat. NaCl soln. (30 ml), dried and filtered. Evaporation gave **12** (986 mg).

To a soln. of 986 mg (6.3 mmol) of *2-fluoro-5-methoxybenzenemethanol* (**12**) in 5 ml of pyridine were added 1.9 g (7.58 mmol) of $Bu_3P$ and 1.65 g (7.85 mmol) of PhSSPh in 5 ml of pyridine, and the mixture was stirred 20 min at r.t. The mixture was diluted with $H_2O$ (30 ml). The combined $Et_2O$ extracts were dried and evaporated. Purification by CC ($Et_2O$/hexane 1:20) afforded **13** (1.3 g, 86%; two steps). Colorless liquid. IR ($CHCl_3$): 3062, 3007, 2938, 1584, 1501, 1282, 1037. $^1$H-NMR (300 MHz): 3.66 (*s*, MeO); 4.07 (*s*, $CH_2$); 6.67–6.73 (*m*, H–C(4), H–C(6)); 6.91 (*t*, $J = 8.7$, H–C(3)); 7.18–7.26 (*m*, 3 arom. H); 7.31–7.34 (*m*, 2 arom. H). $^{13}$C-NMR (75 MHz): 32.3; 32.3; 55.6; 114.0; 115.1; 115.6; 115.9; 125.2; 125.4; 126.7; 128.8; 130.5; 135.5; 153.4; 155.3; 156.6. EI-MS: 250 (10), 249 (28), 248 (56), 140 (30), 139 (100), 109 (42), 96 (28), 83 (17). HR-MS: 248.0671 ($M^+$, $C_{14}H_{13}FOS^+$; calc. 248.0671).

*(3*R*)-1-(2-Fluoro-5-methoxyphenyl)-3,7-dimethyl-1-(phenylsulfanyl)oct-6-en-3-ol* (**14a**). To a stirred soln. of **13** (400 mg, 1.61 mmol) in dry THF (8 ml) was added BuLi (2.4 mmol; 1.6M in hexane; 1.5 ml) at −78° under Ar. The mixture was stirred for 2 h, and a soln. of **6a** (248 mg, 1.77 mmol) in dry THF (2 ml) was added dropwise with stirring. The mixture allowed to warm to r.t. for 20 h. The reaction was quenched with sat. $NH_4Cl$ soln. (20 ml), and the mixture was extracted with $Et_2O$ (3 × 30 ml), dried, and evaporated. The crude product was purified by CC ($Et_2O$/hexane 1:2) to afford **14a** (606 mg, 97%). Colorless liquid. IR ($CHCl_3$): 3595, 3504, 3060, 3006, 2968, 1584, 1499, 1198, 1037. $^1$H-NMR (300 MHz): 1.16 (*s*, Me); 1.45–1.55 (*m*, $CH_2$); 1.58 (*s*, Me); 1.67 (*s*, Me); 1.88–2.0 (*m*, $CH_2$); 2.15 (*d*, $J = 6.6$, $CH_2$); 3.72 (*s*, MeO); 4.73 (*dd*, $J = 9$, 6.6, CH); 5.04 (br., CH); 6.62–6.72 (*m*, H–C(4)); 6.82–6.89 (*m*, H–C(3), H–C(6)); 7.2–7.3 (*m*, 5 arom. H). $^{13}$C-NMR (75 MHz): 17.6; 17.7; 22.5; 22.7; 25.7; 26.6; 27.2; 41.6; 41.7; 42.8; 46.3; 46.4; 55.7; 113.6; 113.7; 115.6; 116.0; 124.0; 124.1; 127.5; 128.7; 131.8; 132.6; 132.6; 133.9; 133.9; 152.6; 155.6; 155.6. EI-MS: 388 (9), 370 (10), 278 (12), 260 (30), 247 (20), 152 (58), 109 (100) 69 (84). HR-MS: 388.1878 ($M^+$, $C_{23}H_{29}FO_2S^+$; calc. 388.1872).

*(3*R*,6*E*)-1-(2-Fluoro-5-methoxyphenyl)-3,7,11-trimethyl-1-(phenylsulfanyl)dodeca-6,10-dien-3-ol* (**14b**). From 400 mg (1.61 mmol) of **13** and 366 mg (1.76 mmol) of **6b**, 705 mg (96%) of **14b** was obtained. Colorless liquid. IR ($CHCl_3$): 3590, 3492, 3061, 3007, 2970, 1584, 1498, 1199, 1036. $^1$H-NMR (300 MHz): 1.16 (*s*, Me); 1.45–1.55 (*m*, $CH_2$); 1.58 (*s*, 2 Me); 1.68 (*s*, Me); 1.85–2.18 (*m*, 3 $CH_2$); 2.15 (*d*, $J = 6.6$, $CH_2$); 3.72 (*s*, MeO); 4.73 (*dd*, $J = 9$, 6.6, CH); 5.07 (br., 2 CH); 6.64–6.67 (*m*, H–C(4)); 6.82–6.88 (*m*, H–C(3), H–C(6)); 7.2–7.3 (*m*, 5 arom. H). $^{13}$C-NMR (75 MHz): 16.0; 16.1; 17.7; 22.4; 22.6; 25.7; 26.6; 27.2; 39.6; 41.6; 41.7; 41.7; 42.8; 46.3; 46.4; 55.7; 72.7; 72.9; 113.5; 113.6; 113.7; 115.6; 116.0; 123.9; 124.0; 124.1; 127.5; 128.7; 130.7; 131.8; 132.5; 132.6; 133.9; 133.9; 136.3; 155.6; 155.6. EI-MS: 456 (5), 438 (15), 328 (28), 247 (60), 177 (40), 152 (35), 149 (40), 109 (38) 69 (100). HR-MS: 456.2500 ($M^+$, $C_{28}H_{37}FO_2S^+$; calc. 456.2498).

*(2R)-3,4-Dihydro-6-methoxy-2-methyl-2-(4-methylpent-3-en-1-yl)-4-(phenylsulfanyl)-2*H-*chromene* (**15a**). To a soln. of *t*BuOK (638 mg, 5.7 mmol) in dry THF (20 ml) was added dropwise **14a** (220 mg, 0.57 mmol) in THF (10 ml) at r.t. under Ar. Then, the mixture was refluxed for 15 h. The reaction was quenched with sat. $NH_4Cl$ soln., and the mixture extracted with $Et_2O$ ($3 \times 20$ ml). The org. layer was washed with $H_2O$ and brine, and dried. The solvent was evaporated, and the residue was purified by CC ($Et_2O$/hexane 1:10) to afford 115 mg (55%) **15a** and recovered **14a** (18 mg). Colorless liquid. IR: 3007, 2934, 1614, 1582, 1492, 1465, 1379, 1225, 1039. $^1$H-NMR (300 MHz): 1.19 (*s*, 1.5 H of Me); 1.34 (*s*, 1.5 H of Me); 1.53 (*s*, 1.5 H of Me); 1.62 (*s*, 1.5 H of Me); 1.64 (*s*, 1.5 H of Me); 1.66 (*s*, 1.5 H of Me); 1.5–1.7 (*m*, $CH_2$); 1.9–2.2 (*m*, $CH_2$); 3.74 (*s*, Me); 4.43 (*m*, CH); 5.0 (br. *t*, $J = 6$, 0.5 H of CH); 5.1 (br. *t*, $J = 6$, 0.5 H of CH); 6.73 (*s*, H–C(7), H–C(8)); 7.2–7.4 (*m*, 6 arom. H). $^{13}$C-NMR (75 MHz): 17.5; 17.6; 22.1; 22.3; 22.6; 25.6; 25.7; 26.0; 36.7; 39.1; 39.7; 41.4; 41.7; 55.6; 76.3; 113.1; 115.4; 118.3; 121.7; 123.7; 124.0; 127.1; 127.2; 128.9; 131.6; 131.7; 131.8; 132.1; 134.5; 134.6; 147.6; 147.8; 153.0; 153.1. EI-MS: 368 (28), 259 (94), 203 (95), 177 (100), 137 (45), 109 (33). HR-MS: 368.1804 ($M^+$, $C_{23}H_{28}O_2S^+$; calc. 368.1810).

*(2*R*)-2-[(3*E*)-4,8-Dimethylnona-3,7-dien-1-yl]-3,4-dihydro-6-methoxy-2-methyl-4-(phenylsulfanyl)-2*H-*chromene* (**15b**). From 700 mg (1.54 mmol) of **14b**, 461 mg (69%) of **15b** and recovered **14b** (253 mg) were obtained. Colorless liquid. IR: 3060, 3007, 2970, 2931, 1614, 1582, 1491, 1465, 1379, 1225, 1040. $^1$H-NMR (300 MHz): 1.20 (*s*, 1.5 H of Me); 1.35 (*s*, 1.5 H of Me); 1.57 (*s*, 1.5 H of Me); 1.59 (*s*, 1.5 H of Me); 1.65 (*s*, Me); 1.67 (*s*, 1.5 H of Me); 1.69 (*s*, 1.5 H of Me); 1.5–1.7 (*m*, $CH_2$); 1.9–2.2 (*m*, 3 $CH_2$); 3.75 (*s*, Me); 4.39–4.45 (*m*, CH); 5.0 (br. *t*, $J = 6$, 0.5 H of CH); 5.1 (br. *t*, $J = 6$, 0.5 H of CH); 6.73 (*s*, H–C(7), H–C(8)); 7.2–7.4 (*m*, 6 arom. H). $^{13}$C-NMR (75 MHz): 15.9; 16.0; 17.7; 17.7; 22.0; 22.3; 22.6; 22.6; 25.7; 25.7; 26.1; 26.6; 26.7; 36.7; 39.1; 39.6; 39.6; 41.4; 41.7; 55.7; 76.3; 113.1; 115.4; 115.5; 118.3; 121.7; 123.5; 123.8; 124.1; 124.2; 127.2; 127.3; 129.0; 131.3; 131.3; 131.8; 132.1; 134.4; 134.5; 135.2; 135.4; 147.6; 147.8; 152.9; 153.0. EI-MS: 436 (9), 326 (25), 175 (100), 137 (13), 110 (20). HR-MS: 436.2440 ($M^+$, $C_{28}H_{36}O_2S^+$; calc. 436.2436).

*(2*R*)-6-Methoxy-2-methyl-2-(4-methylpent-3-en-1-yl)-2*H-*chromene* (**17a**). To a soln. of *m*CPBA (80%; 72 mg, 0.34 mmol) in $CH_2Cl_2$ (5 ml) was added **15a** (116 mg, 0.32 mmol) in $CH_2Cl_2$ at 0° under Ar. The mixture was stirred for 10 min. The reaction was quenched with 5 ml 10% $Na_2S_2O_3$ soln., and the mixture was extracted with $CH_2Cl_2$ ($3 \times 5$ ml). The combined org. soln. was washed with sat. $NaHCO_3$ soln. and brine, and dried. The solvent was evaporated to afford **16a**. Without purification, **16a** in 2 ml of toluene containing 10 mg of $CaCO_3$ was heated for 30 min at 110° under Ar. The mixture was filtered. The solvent was removed *in vacuo*, and the residue was purified by TLC ($Et_2O$/hexane 1:20) to afford **17a** (56 mg, 69%, over two steps). Colorless liquid. $[\alpha]_D^{24} = -112.5$ ($c = 0.58$, $CHCl_3$). IR: 3009, 2970, 2929, 1578, 1491, 1466, 1268, 1228, 1198. $^1$H-NMR (300 MHz): 1.37 (*s*, Me); 1.59 (*s*, Me); 1.65 (*s*, Me); 1.60–1.80 (*m*, $CH_2$); 2.0–2.15 (*m*, $CH_2$); 3.74 (*s*, Me); 5.08–5.12 (*m*, CH); 5.59 (*d*, $J = 9.5$, CH); 6.30 (*d*, $J = 9.5$, CH); 6.53–6.71 (*m*, 3 arom. H). $^{13}$C-NMR (75 MHz): 17.6; 22.7; 25.7; 26.0; 40.9; 55.7; 78.0; 111.4; 114.1; 116.5; 121.7; 122.8; 124.1; 130.7; 131.6; 146.9; 153.5.

*(2*R*)-2-[(3*E*)-4,8-Dimethylnona-3,7-dien-1-yl]-6-methoxy-2-methyl-2*H-*chromene* (**17b**). From 290 mg (0.67 mmol) of **15b**, **17b** (145 mg, 67%) was obtained. Colorless liquid. $[\alpha]_D^{21} = 70.6$ ($c = 0.68$, $CHCl_3$). IR: 3039, 3007, 2969, 2926, 1609, 1578, 1491, 1465, 1267, 1197. $^1$H-NMR (300 MHz): 1.37 (*s*, Me); 1.57 (*s*, Me); 1.58 (*s*, Me); 1.71 (*s*, Me); 1.50–1.76 (*m*, $CH_2$); 1.92–2.14 (*m*, 3 $CH_2$); 3.75 (*s*, Me); 5.07–5.13 (*m*, 2 CH); 5.60 (*d*, $J = 9.8$, CH); 6.31 (*d*, $J = 9.8$, CH); 6.53–6.72 (*m*, 3 arom. H). $^{13}$C-NMR (75 MHz): 16.0; 17.7; 22.6; 25.7; 26.1; 26.7; 40.0; 40.9; 55.7; 78.1; 111.4; 114.1; 116.5; 121.7; 122.8; 123.9; 124.3; 130.8; 131.3; 135.2; 146.9; 153.5.

(–)-(*R*)-*Cordiachromene* (=*(2*R*)-2-Methyl-2-(4-methylpent-3-en-1-yl)-2*H-*chromen-6-ol*; **1**). Ethanethiol (0.05 ml, 0.67 mmol) was added to a suspension of NaH (16 mg, 0.67 mmol) in dry DMF, and the mixture was stirred 15 min at r.t. Then, **17a** (45 mg, 0.17 mmol) was added dropwise. The mixture was stirred for 6 h at 140° under Ar. After cooling, the reaction was quenched by addition of 2N HCl (1 ml). The mixture was extracted with $Et_2O$ ($3 \times 10$ ml). The combined org. phase washed with $H_2O$ and brine, dried and filtered. The solvent was evaporated, and the residue was purified by TLC ($Et_2O$/hexane 1:2) to afford 13 mg (31%) of **1** and recovered **17a** (20 mg). Yellowish liquid. $[\alpha]_D^{22} = -110.7$ ($c = 0.65$, $CHCl_3$); [7] antipode: $[\alpha]_D^{20} = +101.6$ ($c = 0.83$, $CHCl_3$); [4]: $[\alpha]_D^{20} = +2.8$ ($c = 0.025$, $CHCl_3$). IR: 3578, 3384, 3009, 2971, 2927, 1614, 1487, 1456, 1278, 1195. $^1$H-NMR (300 MHz): 1.36 (*s*, Me); 1.57 (*s*, Me); 1.65 (*s*, Me); 1.58–1.75 (*m*, $CH_2$); 2.0–2.15 (*m*, $CH_2$); 4.7 (br., OH); 5.08 (br. *t*, $J = 3$, CH); 5.60 (*d*, $J = 9.8$,

H–C(3)); 6.27 (*d*, *J* = 9.8, H–C(2)); 6.48 (*d*, *J* = 2.9, H–C(5)); 6.56 (*d*, *J* = 8.6, H–C(7)); 6.64 (*d*, *J* = 8.6, H–C(8)). $^{13}$C-NMR (75 MHz): 17.6; 22.7; 25.7; 26.0; 40.9; 78.1; 112.9; 115.4; 116.7; 122.0; 122.6; 124.1; 131.0; 131.7; 147.0; 149.2. EI-MS: 244 (9), 162 (10), 161 (100), 69 (7). HR-MS: 244.1454 ($M^+$, $C_{16}H_{20}O_2^+$; calc. 244.1463).

*(−)-(*R*)-Dictyiochromenol* (= *(2*R*)-2-[(3*E*)-4,8-Dimethylnona-3,7-dien-1-yl]-2-methyl-2*H*-chromen-6-ol*; **2**). From 104 mg (0.32 mmol) of **17b**, 36 mg (36%) of **2** and recovered **17b** (48 mg) were obtained. Yellowish liquid. $[\alpha]_D^{21} = -86.5$ ($c = 0.38$, $CHCl_3$); [12]: $[\alpha]_D^{20} = -82.4$ ($c = 0.83$, $CHCl_3$); [10]: $[\alpha]_D^{20} = +4$; [11]: $[\alpha]_D^{29} = +11$ ($c = 0.182$, $CDCl_3$). IR: 3599, 3386, 3009, 2970, 2926, 1614, 1487, 1455, 1277, 1195. $^1$H-NMR (300 MHz): 1.37 (*s*, Me); 1.57 (*s*, Me); 1.58 (*s*, Me); 1.67 (*s*, Me); 1.50–1.76 (*m*, $CH_2$); 1.90–2.15 (*m*, 3 $CH_2$); 4.71 (*s*, OH); 5.06–5.12 (*m*, CH); 5.60 (*d*, *J* = 9.8, H–C(3)); 6.27 (*d*, *J* = 9.8, H–C(2)); 6.48 (*d*, *J* = 2.9, H–C(5)); 6.56 (*d*, *J* = 8.6, H–C(7)); 6.64 (*d*, *J* = 8.6, H–C(8)). $^{13}$C-NMR (75 MHz): 16.0; 17.7; 22.6; 25.7; 26.0; 26.7; 39.7; 40.8; 78.1; 112.9; 115.4; 116.7; 122.0; 122.6; 123.9; 131.0; 131.4; 135.3; 146.9; 149.2. EI-MS: 312 (12), 162 (10), 161 (100), 69 (9). HR-MS: 312.2087 ($M^+$, $C_{21}H_{28}O_2^+$; calc. 312.2089).

## REFERENCES


[1] G. D. Manners, L. Jurd, *J. Chem. Soc., Perkin Trans. 1* **1977**, 405.
[2] N. M. Targett, W. S. Keeran, *J. Nat. Prod*. **1984**, *47*, 556.
[3] A. F. Benslimane, Y. F. Pouchus, J. L. Boterff, J. F. Verbist, C. Roussakis, F. Monniot, *J. Nat. Prod*. **1988**, *51*, 582.
[4] I. K. Kim, S. K. Park, K. L. Erickson, *Magn. Reson. Chem*. **1993**, *31*, 788.
[5] A. F. Benslimane, Y. F. Pouschus, J. F. Verbist, J.-Y. Petit, D. J. Brion, L. Welin, *J. Clin. Pharmacol.* **1995**, *35*, 298.
[6] P. H. Kahn, J. Cossy, *Tetrahedron Lett*. **1999**, *40*, 8113.
[7] S. Bouzbouz, J.-Y. Goujon, J. Deplanne, B. Kirschleger, *Eur. J. Org. Chem*. **2000**, 3223.
[8] J. Y. Goujon, F. Zammattio, B. Kirschleger, *Tetrahedron: Asymmetry* **2000**, *11*, 2409.
[9] K. Takenaka, Y. Tanigaki, M. I. Patil, C. V. L. Rao, S. Takizawa, T. Suzuki, H. Sasai, *Tetrahedron: Asymmetry* **2010**, *21*, 767.
[10] M.-N. Dave, T. Kusumi, M. Ishituka, T. Iwashita, H. Kakisawa, *Heterocycles* **1984**, *22*, 2301.
[11] A. S. Vega, B. Rojano, S. Blair, C. Segura, B. Figadere, B. Seon, P. Grellier, J. Sáez, *Pharmacol. Online* **2008**, *1*, 1.
[12] K. Aoki, M. Takahashi, M. Hashimoto, T. Okuno, K. Kurata, M. Suzuki, *Biosci., Biotechnol., Biochem*. **2002**, *66*, 1915.
[13] M. B. Smith, J. March, 'March's Advanced Organic Chemistry', 5th edn., John Wiley & Sons, New York, 2001, Chapt. 11.
[14] Y. Noda, *Jpn. Kokai Tokkyo Koho*, JP 2004026724, 2004.
[15] a) R. Naef, D. Seebach, *Liebigs. Ann. Chem*. **1983**, 1930; b) G. Bojack, H. Bornowski, *Tetrahedron* **1991**, *47*, 9179.
[16] Z. Liu, L. Peng, T. Zhang, Y. Li, *Synth. Commun.* **2001**, *31*, 2549; P. Kocienski, S. Wadman, K. Cooper, *J. Org. Chem*. **1989**, *54*, 1215.
[17] W. Szeja, *Synthesis* **1985**, 983.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