Enantioselective Synthesis of Cordiachromene

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An enantioselective synthesis of cordiachromene is described. An allylic alcohol moiety is first attached in the *o*-position to the methoxymethoxy substituent in 1-methoxy-4-methoxymethoxybenzene. Then chirality is introduced successively through asymmetric Sharpless epoxidation on the allylic alcohol moiety and regioselective ring-opening. The chiral diol prepared is then cyclized to chromanmethanol with total retention of configuration. Chromenemethanol is obtained after bromination and dehydrobromination. The total synthesis is achieved by reaction between the tosylated chromene chiral moiety and an organomagnesium prenylated compound.

Introduction

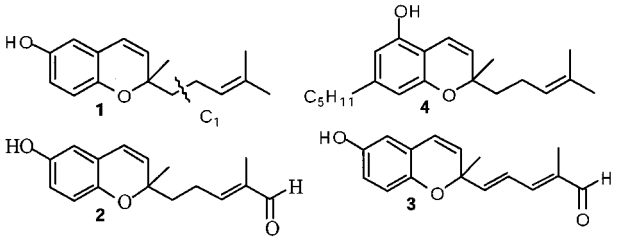
Cordiachromen **1** [6-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)-2*H*-chromene] was first isolated and characterized[1] from the acetone extract of *Cordia alliodora*, an American tree known for its durability in marine use. The parent compounds elaeagin **2** and dehydroelaeagin **3**,[2] extracted from the heartwood of *Cordia elaeagnoides*, show optical activity (**2:** $[\alpha]_D = -3.13$, $c = 1.0$, $CHCl_3$; **3:** $[\alpha]_D = -5.625$, $c = 0.169$, $CHCl_3$). More recently, cordiachromen has been isolated from the Caribbean ascidian *Aplidium antillense*[3] and from the Korean ascidian *Aplidium multiplicatium*.[4] For the latter, optical activity ($[\alpha]_D = +2.8$, $c = 0.025$, $CHCl_3$) was reported.

The anti-inflammatory activity of **1**[5] was tested by the carrageenan-induced rat paw edema assay and compared with the results obtained, under the same conditions, from cannabichromene **4**. It was reported that **1** was twenty times more active than cannabichromene **4.**[6] Moreover, cordiachromen was twice as active as the synthetic, racemic compound. Further tests on each enantiomeric of cordiachromen were required to explain these results, and so both compounds had to be synthesised.

Results and Discussion

Synthetic Strategy

Compound **1** can be synthesised, following disconnection C_1 (Scheme 1), by reaction between a chiral chromene moiety bearing a leaving group X and an activated organometallic prenyl compound. The target molecule has thus become the chiral chromene **18**, which can be constructed as described in the retrosynthetic scheme (Scheme 2).



Scheme 1

The chromene **18** derives from a chroman, which is obtained by cyclization of a diol, itself prepared from an epoxide alcohol by regioselective epoxide opening. A key step in this synthesis is the introduction of chirality by asymmetric Sharpless epoxidation of an allylic alcohol moiety. This allylic alcohol is synthesised from a prenylated chain by hydroxylation of the vinylic methyl moiety. Prenylation is achieved by condensation of prenyl bromide onto an *o*-lithiated *p*-dialkoxybenzene. The two alkyl groups R and R_1 were chosen to enhance the metallation selectivity.

Synthesis of the Target Molecule 18

p-Methoxyphenol was chosen as the starting product. The phenolic hydroxyl was first protected as a methoxymethoxy group. The aromatic ring was selectively metallated on the *o*-position to the methoxymethoxy group with *n*BuLi. Subsequent prenylation was achieved by the addition of prenyl bromide, with copper(I) iodide as the catalyst.[7] Compound **5** was isolated in 85% yield (Scheme 3).

Rapoport et al.[7,8] and Sharpless et al.[9] have intensively studied oxidation in allylic positions. Their results have firmly established that, for *gem*-dimethyl trisubstituted olefins, selenium dioxide oxidation proceeds stereospecifically to give *E* alcohols or *E* aldehydes with greater than 90% specificity. As we expected, compound **5**, stirred with selenium dioxide under the same conditions, gave the *E* allylic alcohol, with a small amount of aldehyde (5 to 10%). However, the addition of sodium borohydride to the reaction

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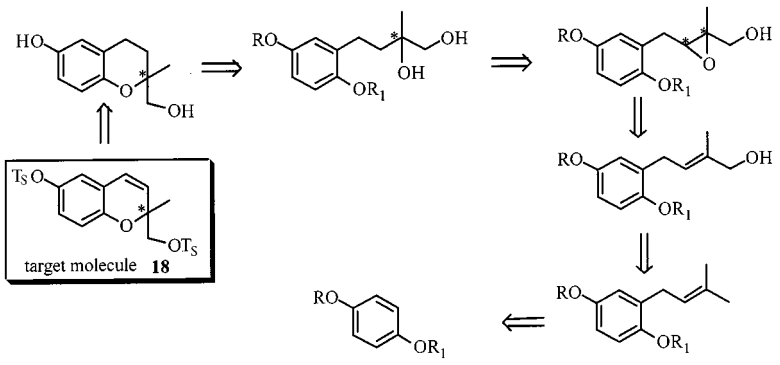
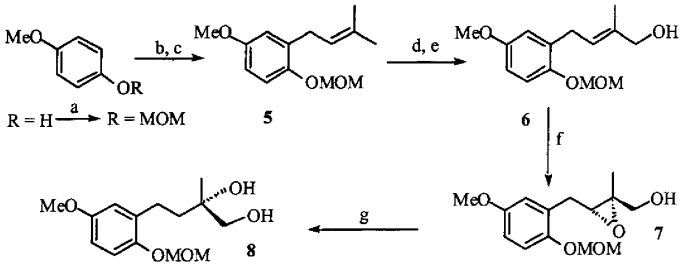


Scheme 2.



Scheme 3. a: $ClCH_2OCH_3$, iPr_2NEt, CH_2Cl_2, 40 °C; b: BuLi, ether, 25 °C; c: CuI, THF, −78 °C; d: SeO_2, aq. ethanol, reflux, 30 min.; e: $NaBH_4$, ethanol, 0 °C, 1 h; f: *t*BuOOH, $Ti(OiPr)_4$, D-(−)-DET, CH_2Cl_2, −25 °C, 24 h; g: $LiAlH_4$, ether, 25 °C, 5 h

mixture easily reduced the aldehyde, and compound **6** was finally obtained in 80% yield (Scheme 3).

The next reaction was the key step in this synthesis, with the introduction of chirality by the well known asymmetric Sharpless epoxidation of the allylic double bond.[10] With D-(−)-diethyl tartrate as the chiral reagent, compound **7**, with an (*R,R*)-epoxy alcohol, was isolated in 88% yield. The epoxide was then opened regioselectively with lithium aluminium hydride, which gave the isolated diol **8** in 95% yield.

The formation of the benzopyran ring required good chirality control. Previous results[11] (from vitamin E synthesis) suggested that, for the benzopyran, the cyclization should be achieved with excellent retention of configuration from the parent hydroquinone or quinone diol. With compound **8** as the starting material (Scheme 4), one attempt to synthesise the corresponding quinone by direct oxidative demethylation with ceric ammonium nitrate (CAN) failed. However, if **8** was first converted into ketal **9**, oxidative demethylation then occurred to give the quinone ketal **10** (90%) along with the corresponding quinone diol **11** (10%). The overall yield was 90%. Then, the mixture of compounds **10** and **11** was simply stirred in acidic methanol to give the cyclic ketal **12** in 70% yield. The synthesis of chromanmethanol **13** was achieved by the reduction of compound **12** with sodium bis(methoxyethoxy)aluminum hydride (Red-Al). The yield was 81%.

The next effort was directed towards the synthesis of chromenemethanol. However, before introducing the double bond into the pyran ring, it was necessary to protect the alcoholic hydroxy group. The *p*-toluenesulfonyl group was chosen as a good leaving group, with both hydroxy groups protected in this reaction. Compound **15** was obtained in 81% yield.

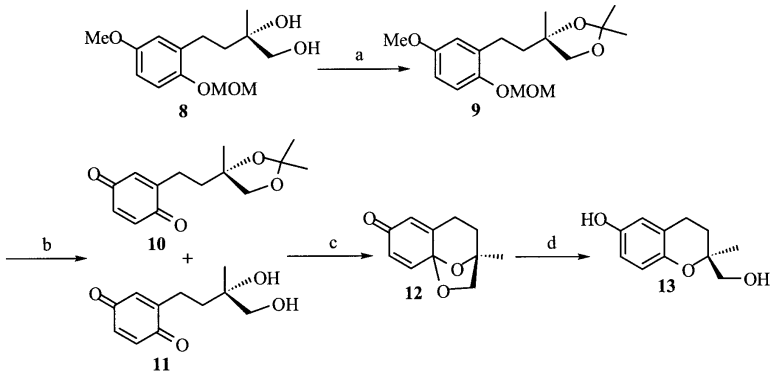
The direct dehydrogenation of chroman **14** with dichlorodicyanobenzoquinone[12] failed. The introduction of bromide at the benzylic position, using *N*-bromosuccinimide, gave bromochroman 1**5** (Scheme 5). A subsequent dehydrobromination with pyridine gave chromene **18**. However, this suffered from a lack of selectivity in the monobromination, which was often accompanied by undesired formation of the *gem*-dibromide derivative **16** (5%). Alternatively, to circumvent this lack of selectivity, chroman **14** was reacted with excess *N*-bromosuccinimide to give a nearly quantitative yield of crude 4,4-dibromochroman **16**, which was directly dehydrobrominated in refluxing pyridine to yield 4-bromochromene **17**. Then, reduction with tributyltin hydride gave the chromene **18** (Scheme 5). The total yield of these two pathways was equal (65−68%) but the path through compound **17** was easier experimentally.

The Synthesis of Cordiachromen (1)

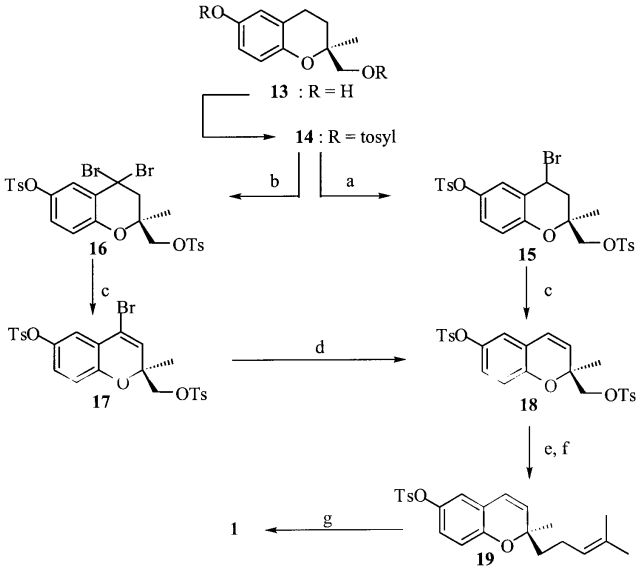
At this stage, the prenyl chain was attached by cross coupling of tosylate **18** with a prenylmagnesium cuprate[13] (Scheme 5). Tosylated cordiachromene **20** was isolated in 75% yield. Then the phenolic hydroxyl was deprotected, to give (*R*)-cordiachromene **1** in 80% yield.

Conclusion

Using *p*-methoxyphenyl as the starting material, (*R*)-cordiachromen has been synthesised in 13 steps, with an overall yield of 12%. The enantiomeric excess of **1** was determined by chiral HPLC to be 92%. The *S* configuration at the chiral carbon has been presumed, assuming firstly that Sharpless epoxidation on allylic alcohol **6** with D-di-



Scheme 4. a: $(CH_3)_2C(OCH_3)_2$, TsOH, 25 °C, 30 min.; b: CAN, CH_3CN/H_2O, 0 °C, 2 h; c: MeOH, HCl 1 N, 25 °C, 24 h; d: Red-Al, 0 °C, 90 min.



Scheme 5. a: NBS (1 equiv.), K_2CO_3, $C_6H_5CO_3H$, CCl_4, reflux; b: NBS (2 equiv.), K_2CO_3, $C_6H_5CO_3H$, CCl_4, reflux; c: pyridine, reflux; d: Bu_3SnH, AIBN, C_6H_6, reflux; e: $BrCH_2CH{=}C(CH_3)_2$, Mg, THF, −20 °C; f: Li_2CuCl_4, −70 °C; g: KOH, H_2O/EtOH, reflux

ethyl tartrate gives the *R,R* epoxide and, secondly, that the cyclisation of the mixture of compounds **11** and **12** proceeds with a total retention of configuration. However, these results still require confirmation by X-ray crystal structure analysis, and work is in progress to crystallize the oily cordiachromen.

Experimental Section

General: Each starting material was obtained from commercial suppliers and used without further purification. All solvents (ether, THF, DMF, toluene) were dried by distillation on sodium-benzophenone before use. Prenyl bromide was prepared using a known method.[7] ^1H and ^{13}C NMR spectra were recorded at 90 and 22.5 MHz, respectively, on a Jeol FX 90 Q spectrometer, with $CDCl_3$ as solvent and TMS as internal standard; chemical shifts (δ) are expressed in ppm and coupling constants (^nJ) in Hz. Mass spectra were recorded on a Hewlett Packard 5989A (70 eV) and IR spectra on a Perkin−Elmer 420 (cm^{-1}). Optical rotations were measured on a 341 Perkin−Elmer polarimeter. The enantiomeric excess of **1** was determined by HPLC analysis using a column packed with Chiracel OD-H.

1-Methoxy-4-methoxymethoxybenzene: To a stirred solution of *p*-methoxyphenol (5 g, 40.3 mmol) and diisopropylethylamine (10.4 g, 80.5 mmol) in CH_2Cl_2 (100 mL) was slowly added methoxymethyl chloride (6 mL, 80.5 mmol) at room temp. After stirring at 40 °C for 12 h, sat. aq. NH_4Cl was added. The organic layer was extracted with ether, washed with water and brine, dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 8:2) to give a colourless oil (6.56 g, 39 mmol, 97%).
^1H NMR: δ = 7.02−6.6 (m, 4 H, C_6H_4), 5.10 (s, 2 H, OCH_2O), 3.45 (s, 3 H, OCH_3) − ^{13}C NMR: δ = 154.4 ($C_{Ar}OMOM$), 149.1 ($C_{Ar}OMe$), 115.7, 111.2 (4 $CH{=}_{Ar}$), 95.3 (OCH_2O), 55.6 (OCH_3), 55.1 (OCH_3).

4-Methoxy-1-methoxymethoxy-2-(3-methylbut-2-en-1-yl)benzene (5): To a solution of 1-methoxy-4-methoxymethoxybenzene (3.36 g, 20 mmol) in anhydrous THF (100 mL), under a nitrogen atmosphere at 0 °C, was added a solution of *n*BuLi (14.7 mL, 1.5 M, 22 mmol) in hexane and Et_2O (30 mL). The mixture was stirred at room temp. for 6 h; then it was cooled to −78 °C. THF (50 mL) and CuI (0.57 g, 3 mol-%) were added; then, slowly, prenyl bromide (3 g, 20 mmol). Once the addition was complete, water was added and the solution was filtered. The organic layer was extracted with ether, washed successively with aq. NH_3, water, aq. HCl, water and brine, dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 8:2) to give a yellow oil (4.01 g 17 mmol, 85%).
^1H NMR: δ = 7.02−6.60 (m, 3 H, C_6H_3), 5.30 (t, J = 7.3 Hz, 1 H, CH=), 5.10 (s, 2 H, OCH_2O), 3.74 (s, 3 H, OCH_3), 3.45 (s, 3 H, OCH_3), 3.31 (d, J = 7.3 Hz, 2 H, CH_2), 1.74 (s, 6 H, $2CH_3$). − ^{13}C NMR: δ = 154.5 ($C_{Ar}OCH_2$), 149.1 ($C_{Ar}OCH_3$), 133.1 (C_q=), 132.9 ($C_{Ar}CH_2$), 123.1 (CH=), 119.1, 115.7, 111.1 (3 $CH{=}_{Ar}$), 95.2 (OCH_2O), 55.8, 55.2 (2 OCH_3), 29.3 (CH_2), 25.4, 17.3 (2 CH_3).

2-(4-Hydroxy-3-methylbut-2-en-1-yl)-4-methoxy-1-methoxymethoxybenzene (6): Compound **6** (3.5 g, 14.8 mmol) and SeO_2 (2.75 g, 24.8 mmol) were stirred in EtOH (100 mL) at reflux for 30 min. Solid selenium compounds were removed by filtration. Then $NaBH_4$ (0.56 g, 14.8 mmol) was added at 0 °C and the mixture was stirred for 1 h. Aq. HCl was added and the organic layer was extracted with ether, dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 5:5) to give an orange/yellow oil (2.98 g, 11.8 mmol, 80%).

^{1}H NMR: δ = 7.01−6.60 (m, 3 H, C_6H_3), 5.55 (t, *J* = 7.3 Hz, 1 H, CH=), 5.09 (s, 2 H, OCH_2O), 3.98 (s, 2 H, CH_2OH), 3.72 (s, 3 H, OCH_3), 3.45 (s, 3 H, OCH_3), 3.35 (d, *J* = 7.3 Hz, 2 H, CH_2), 1.75 (s, 3 H, CH_3). − ^{13}C NMR: δ = 154.7 ($C_{Ar}OCH_2$), 149.3 ($C_{Ar}OCH_3$), 136.0 ($C_{Ar}CH_2$), 131.8 (C_q=), 123.6 (CH_2), 115.9, 115.8, 111.3 (3 $CH=_{Ar}$), 95.4 (OCH_2O), 68.3 (CH_2OH), 55.9, 55.5 (2 OCH_3), 28.5 (CH_2), 13.7 (CH_3). − MS: *m*/*z* (%) = 252 (4) [M^+], 190 (53), 175 (100), 159 (11), 137 (16), 91 (9), 77 (8), 45 (73). − IR (KBr): ν̃ = 3409, 2954−2855, 1608, 1600−1450, 1380−1280, 1044, 1015.

(*2R*,*3R*)-(+)-2-(2,3-Epoxy-4-hydroxy-3-methylbut-1-yl)-4-methoxy-1-methoxymethoxybenzene (7): Under a nitrogen atmosphere, Ti(O*i*Pr)$_4$ (3.15 g, 11.1 mmol) and D-(−)diethyl tartrate (2.74 g, 13.3 mmol) were mixed and stirred in CH_2Cl_2 (80 mL) with some molecular sieves at −24 °C for 20 min. Then **6** (2.8 g, 11.1 mmol) and *tert*-butylhydroperoxide (7.4 mL of 3 M toluene solution, 22.2 mmol) were added. The mixture was stirred mechanically at −24 °C for 24 h. Then, 10% aq. tartaric acid was added and stirring was continued for 2 h. The organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 5:5) to give a pale yellow oil (2.62 g, 88%).
^{1}H NMR: δ = 7.08−6.63 (m, 3 H, C_6H_3), 5.12 (s, 2 H, OCH_2O), 3.74 (s, 3 H, OCH_3), 3.62 (s, 2 H, CH_2OH), 3.45 (s, 3 H, OCH_3), 3.28 (m, 1 H, CHO), 2.93−2.87 (m, 2 H, CH_2), 2.38 (s, 1 H, OH), 1.40 (s, 3 H, CH_3). − ^{13}C NMR: δ = 154.6 ($C_{Ar}OCH_2$), 149.4 ($C_{Ar}OCH_3$), 128.3 (C_{qAr}), 116.2, 115.6, 112.3 (3 $CH=_{Ar}$), 95.3 (OCH_2O), 65.9 (CH_2OH), 61.6 (C_qO), 59.9 (CHO), 55.9, 55.5 (2 OCH_3), 29.3 (CH_2), 14.3 (CH_3). − MS: *m*/*z* (%) = 268 (12) [M^+], 250 (4), 218 (4), 206 (5), 205 (9), 189 (9), 175 (14), 161 (11), 149 (36), 121 (12), 91 (10), 87 (32), 45 (100). − IR (KBr): ν̃ = 3452, 2936−2834, 1610−1460, 1380−1280, 1044, 1012−1010. − $C_{14}H_{20}O_5$ (268.13): calcd. C 62.67, H 7.51; found C 62.31, H 7.38. − [α] = +10.5° (*c* = 2.66, acetone).

(*3S*)-(+)-2-(3,4-Dihydroxy-3-methylbut-1-yl)-4-methoxy-1-methoxymethoxybenzene (8): Epoxide **7** (2.5 g, 9.32 mmol) was slowly added to a solution of $LiAlH_4$ (0.71 g, 18.6 mmol) in ether (50 mL) at room temp. The mixture was stirred for 5 h. Water (25 mL) was added. The organic layer was extracted with ether, dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 7:3) to give a colourless oil (2.4 g, 95%).
^{1}H NMR: δ = 7.03−6.63 (m, 3 H, C_6H_3), 5.12(s, 2 H, OCH_2O), 3.74 (s, 3 H, OCH_3), 3.52 (s, 2 H, CH_2OH), 3.48 (s, 3 H, OCH_3), 2.77−2.58 (m, 2 H, CH_2), 1.85 −1.67 (m, 2 H, CH_2), 2.38 (s, 2 H, 2 OH), 1.23 (s, 3 H, CH_3). − ^{13}C NMR: δ = 154.8 ($C_{Ar}OCH_2$), 149.5 ($C_{Ar}OCH_3$), 133.4 (C_{qAr}), 116.0, 111.6 (3 $CH=_{Ar}$), 95.7(OCH_2O), 73.1 (CH_2OH), 69.8 (C_qOH), 56.1, 55.6 (2 OCH_3), 39.2 (CH_2), 25.0 (CH_2), 23.2 (CH_3). − MS: *m*/*z* (%) = 270 (18) [M^+], 238 (30), 190 (31), 175 (45), 137 (34), 77 (11), 45 (100). − IR (KBr): ν̃ = 3413, 2938−2840, 1600−1460, 1380−1280, 1150, 1042, 1020. − [α] = +2.7° (*c* = 1.84, acetone).

(*3S*)-(+)-2-[2-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)ethyl]-4-methoxy-1-methoxymethoxybenzene (9): Diol **8** (2.35 g, 8.7 mmol) and dimethoxypropane (15 mL) were stirred with *p*-toluenesulfonic acid (0.15 g, 0.87 mmol) for 30 min. A sat. aq. $NaHCO_3$ solution was added. The organic layer was extracted with ether, washed with brine, dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 7:3) to give a pale yellow oil (2.56 g, 95%).
^{1}H NMR: δ = 7.02−6.56 (m, 3 H, C_6H_3), 5.09 (s, 2 H, OCH_2O), 3.91−3.65 (m, 2 H, CH_2O), 3.71 (s, 3 H, OCH_3), 3.45 (s, 3 H, OCH_3), 3.28 (m, 1 H, CHO), 2.80−2.56 (m, 2 H, CH_2C_q), 2.00−1.71 (m, 2 H, CH_2C_{qAr}), 1.40 [s, 6 H, $C(CH_3)_2$], 1.34 (s, 3 H, CH_3). − ^{13}C NMR: δ = 154.6 ($C_{Ar}OCH_2$), 149.4 ($C_{Ar}OCH_3$), 132.9 (C_{qAr}), 115.9, 115.6, 111.4 (3 $CH=_{Ar}$), 109.1 ($C_q(CH_3)_2$), 95.3 (OCH_2O), 81.1 (C_qO), 74.1 (CH_2O), 55.9, 55.5 (2 OCH_3), 40.5 (CH_2), 27.2 ($(CH_3)_2Cq$), 24.9 (CH_3), 23.2 (CH_2). − MS: *m*/*z* (%) = 310 (9) [M^+], 266 (8), 252 (25), 203 (10), 191 (48), 190 (44), 177 (24), 175 (46), 164 (10), 161 (10), 150 (27), 149 (9), 137 (20), 115 (13), 72 (14), 57 (13), 45 (100). − IR (KBr): ν̃ = 2983−2835, 1610−1460, 1378−1270, 1042, 1012−1010. − [α] = +3.2° (*c* = 1.72, acetone).

(*3S*)-(+)-2-[2-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)ethyl]-1,4-quinone (10) and (*2S*)-(+)-2-(3,4-dihydroxy-3-methylbut-1-yl)-1,4-quinone (11): To a water/acetonitrile (1:1) solution (50 mL) of ceric ammonium nitrate (9.1 g, 16.6 mmol) was added at −5 °C a solution of ketal **9** (2.45 g, 7.9 mmol) in CH_3CN (20 mL). The mixture was stirred at −5 °C for 2 h. The organic phase was extracted with CH_2Cl_2, dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 6:4) to give quinone ketal **10** (1.67 g, 90%) and quinonediol **11** (0.165 g, 10%) as yellows oils.
10: ^{1}H NMR: δ = 6.75−6.60 (m, 3 H, C_6H_3), 3.86 (d, ***XX*** H, *J* = 8.5 Hz, CH_2O), 3.74 (d, ***XX*** H, *J* = 8.5 Hz, CH_2O), 2.64−2.44 (m, 2 H, CH_2C_q), 1.83−1.62 (m, 2 H, CH_2C_{qAr}), 1.39 [s, 6 H, $(CH_3)_2C_q$], 1.34 (s, 3 H, CH_3). − ^{13}C NMR: δ = 187.4, 187.1 (2 C=O), 149.4 (C_{qAr}), 136.6, 136.2, 132.3 (3 $CH=_{Ar}$), 109.3 ($C_q(CH_3)_2$), 80.3 (C_qO), 73.9 (CH_2O), 38.0 (CH_2), 26.9, 26.8 [2 CH_3, $(CH_3)_2C_q$], 24.6 (CH_3), 24.2 (CH_2). − MS: *m*/*z* (%) = 250 (1) [M^+], 235 (42), 175 (52), 193 (3), 147 (13), 123 (18), 115 (26), 72 (32), 164 (10), 161 (10), 150 (27), 149 (9), 137 (20), 59 (26), 43 (100), 39 (11), 18 (37). − [α] = +2.8 (*c* = 1.4, acetone)
11: ^{1}H NMR: δ = 6.73−6.3 (m, 3 H, C_6H_3), 3.61 (s, 2 H, CH_2OH), 2.83−2.64 (m, 2 H, CH_2), 1.89 −1.68 (m, 2 H, CH_2), 2.38 (s, 2 H, 2 OH), 1.23 (s, 3 H, CH_3). − ^{13}C NMR: δ = 187.3, 187.0 (2 C=O), 149.3 (C_{qAr}), 136.5, 136.1, 132.2 (3 $CH=_{Ar}$), 73.2 (CH_2OH), 69.8 (C_qOH), 39.1, 25.1 (2 CH_2), 23.4 (CH_3). − [α] = + 2.1° (*c* = 1.7, acetone).

(*6R*,*9S*)-(−)-6,9-Epoxy-9-methyl-7-oxabicyclo[4.4.0]deca-1,4-dien-3-one (12): The above mixture of the two quinones **10** (5.6 mmol) and **11** (0.76 mmol) in methanol (30 mL) was stirred with aq. HCl (1 M) for 24 h. The solution was washed with aq. $NaHCO_3$ and the organic phase was extracted with ether, dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 7:3) to give the tricyclic quinone **12** (0.845 g, 70%) and quinonediol **11** (0.267 g, 20%) as yellow oils.
^{1}H NMR: δ = 6.77−6.61 (m, 3 H, C_6H_3), 4.10−3.62 (s, 2 H, OCH_2C_q), 2.83−2.6 (m, 2 H, CH_2C_q), 2.01−1.67 (m, 2 H, CH_2C_{qAr}), 1.23 (s, 3 H, CH_3). − ^{13}C NMR: δ = 185.6 (C=O), 155.4 ($OC_{qAr}O$), 142.2 (C_{qAr}), 132.0, 121.2 (3 $CH=_{Ar}$), 74.1 (CH_2O), 69.8 (C_qO), 35.8 (CH_2), 26.0 (CH_2), 21.9 (CH_3). − [α] = −37.9° (*c* = 1.8, acetone)

(*2S*)-(+)-6-Hydroxy-2-hydroxymethyl-2-methylchroman (13): Compound **12** (0.79 g, 3.68 mmol.) was stirred with Red-Al [$NaAlH_2(OCH_2CH_2OCH_3)_2$, 7.36 mmol, 2.5 mL of 3 M solution] in THF (15 mL) at 0 °C for 90 min. Then aq. HCl (1 M, 10 mL) was added. The organic phase was extracted with ether, dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 5:5) to give the chroman **13** (0.56 g, 80%) as a colourless oil.
^{1}H NMR: δ = 6.61−6.50 (m, 3 H, C_6H_3), 5.09 (s, 1 H, OH), 3.60 (s, 2 H, CH_2O), 2.84−2.63 (m, 2 H, CH_2C_q), 2.1−1.65 (m, 2 H,

CH_2C_{qAr}), 1.21 (s, 3 H, CH_3). − ^{13}C NMR: δ = 149.8 ($C_{qAr}OH$), 147.8 ($C_{Ar}OC$), 122.5 (C_{qAr}), 119.6, 117.9, 115.6 (3 $CH=_{Ar}$), 76.1 (C_qO), 69.2 (CH_2OH), 27.2 (CH_2), 21.9 (CH_2), 20.6 (CH_3). − MS: *m/z* (%) = 194 (73) [M^+], 163 (100), 161 (42), 136 (46), 124 (91), 123 (61), 107 (31), 94 (11), 45 (20). − IR (KBr): $\tilde{\nu}$ = 3500−3394, 2935−2835, 1600−1460, 1405−1320, 1370−1276, 1219, 1049. − $C_{11}H_{14}O_3$ (194): calcd. C 68.02, H 7.27; found C 67.63, H 7.02. − [α] = +2.78° (*c* = 1.08, acetone).

(2*S*)-(+)-2-Methyl-6-tosyloxy-2-tosyloxymethylchroman (14): *p*-Toluenesulfonyl chloride (0.418 g, 2.19 mmol) was slowly added to a well stirred mixture of compound **13** (0.2 g, 1.04 mmol), triethylamine (0.527 g, 5.2 mmol) and 4-dimethylaminopyridine (2 mg, 0.02 mmol) at 0 °C for 1 h, then at room temp. for 3 h. Water was added. The organic phase was extracted with ether, dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 6:4) to give the tosylated chroman **14** (0.42 g, 81%) as a colourless oil.
^1H NMR: δ = 7.8−7.27 (m, 8 H, 2 C_6H_4tosyl), 6.71−6.53 (m, 3 H, C_6H_3), 3.94 (s, 2 H, CH_2Otosyl), 2.69−2.55 (m, 2 H, CH_2C_q), 2.42 (s, 6 H, 2CH_3tosyl), 1.92−1.65 (m, 2 H, CH_2C_{qAr}), 1.24 (s, 3 H, CH_3). − ^{13}C NMR: δ = 151.4 (C_{qAr}OTs), 145.1 ($C_{qAr}OC$), 144.9, 142.4 (2 C_{qAr}Stosyl), 132.5, 132.4 (2 C_{qAr}Ctosyl), 129.8, 129.6, 128.7, 128.3 (8$CH=_{Ar}$tosyl), 122.8 (C_{qAr}), 121.4, 121.0, 117.6 (3$CH=_{Ar}$), 74.6 (C_qO), 73.1 (CH_2Otosyl), 27.3 (CH_2), 21.7, 21.4 (3CH_3), 21.2 (CH_2). − MS: *m/z* (%) = 502 (16) [M^+], 347 (35), 317 (7), 277 (3), 192 (31), 175 (100), 163 (19), 161 (11), 155 (42), 147 (14), 91 (66), 65 (14), 55 (12). − [α] = +14.2° (*c* = 1.2, acetone).

(2*S*)-(+)-4-Bromo-2-methyl-6-tosyloxy-2-tosyloxymethylchroman 15: A mixture of compound **15** (174 mg, 0.35 mmol), *N*-bromosuccinimide (64 mg, 0.36 mmol), potassium carbonate (69 mg, 0.5 mmol) and benzoyl peroxide (4 mg, 0.025 mmol) in CCl_4 (20 mL) was stirred at reflux for 9 h. Then *N*-succinimide was filtered off and the solvent evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 8:2) to give the bromochroman **15** (161 mg, 80%) as a pale yellow oil.
^1H NMR: δ = 7.78 −7.24 (m, 8 H, 2C_6H_4tosyl), 6.85−6.53 (m, 3 H, C_6H_3), 5.20−5.00 (m, 1 H, CHBr), 4.1−3.8 (m, 2 H, CH_2OTs), 2.69−2.55 (m, 2 H, CH_2C_q), 2.42 (s, 6 H, 2CH_3tosyl), 1.24 (s, 3 H, CH_3). − ^{13}C NMR: δ = 151.4 (C_{qAr}Otosyl), 145.1 (C_qOC), 144.9, 142.4(2 C_qStosyl), 132.5, 132.4 (C_qCtosyl), 129.8, 129.6, 128.7.128.3 (8 $CH=_{Ar}$tosyl), 122.8 ($CH=_{Ar}$), 121.8 (C_{qAr}), 121.0, 117.6 (2 $CH=_{Ar}$), 74.6 (C_qO), 73.1 (CH_2Otosyl), 71.6 (CHBr), 27.3 (CH_2), 21.7, 21.4 (3 CH_3), 21.2 (CH_2). − MS: *m/z* (%) = 581 (1) [M^+], 500 (1), 393 (6), 317 (7), 316 (18), 315 (100), 175 (6), 161 (8), 161 (8), 160 (17), 155 (10), 91 (48), 65 (15). − [α] = +31.2° (*c* = 2, acetone)

(2*R*)-(+)-4-Bromo-2-methyl-6-tosyloxy-2-tosyloxymethyl-2*H*-chromene (17): A mixture of compound **14** (74 mg, 0.15 mmol), *N*-bromosuccinimide (54 mg, 0.30 mmol), potassium carbonate (56 mg, 0.42 mmol) and benzoyl peroxide (3.4 mg, 0.021 mmol) in CCl_4 (15 mL) was stirred at reflux for 9 h. Then *N*-succinimide was filtered off and the solvent evaporated. The crude product **16**, dissolved in pyridine (5 mL), was stirred at reflux for 1 h. Aq. HCl (1 M) was added. The organic phase was extracted with ether, washed with brine, dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 8:2) to give the bromochromene **17** (77 mg, 90%) as a colourless oil.
^1H NMR: δ = 7.84−7.29 (m, 8 H, 2 C_6H_4tosyl), 6.98−6.87 (m, 3 H, C_6H_3), 5.90 (s, 1 H, CH=), 3.98 (s, 2 H, CH_2Otosyl), 2.41 (s, 6 H, 2 CH_3tosyl), 1.25 (s, 3 H, CH_3). − ^{13}C NMR: δ = 151.4 (C_{qAr}Otosyl), 145.0, 144.9 (2 C_qStosyl), 142.2 (C_{qAr}Otosyl), 132.4, 132.3 (2 C_{qAr}Ctosyl), 129.8, 129.6, 128.7, 128.3 (8 $CH=_{Ar}$tosyl), 127.1 (CH=), 123.1 ($CH=_{Ar}$), 121.6 (C_{qAr}), 121.3 ($CH=_{Ar}$), 119.1 (C_qBr), 117.6 ($CH=_{Ar}$), 78.5 (C_qO), 73.1 (CH_2Otosyl), 21.7, 21.3 (3CH_3). − MS: *m/z* (%) = 579 (1) [M^+], 499 (8), 394 (23), 160 (30), 155 (12), 91 (36), 65 (11). − [α] = +16.2° (*c* = 1, acetone)

(2*R*)-(+)-2-Methyl-6-tosyloxy-2-tosyloxymethyl-2*H*-chromene (18): From compound **15**: Compound **15** (146 mg, 0.251 mmol) was dissolved in pyridine and stirred at reflux for 1 h. Aq. HCl (1 M) was added and the organic phase was extracted with ether, washed with brine, dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 7:3) to give the chromene **18** (100 mg, 85%) as a yellow oil.
From compound **17**: Compound **17** (53 mg, 0.091 mmol) was dissolved in benzene (5 mL). Bu_3SnH (30.5 mg, 0.105 mL) and AIBN (4 mg, catalytic) were added and the mixture was stirred at reflux for 2 h. The solvent was evaporated and the crude product was directly purified by column chromatography (silica gel, hexane/EtOAc, 7:3) to give the chromene **18** (33 mg, 72%) as a yellow oil.
^1H NMR: δ = 7.82−7.28 (m, 8 H, 2 C_6H_4tosyl), 6.75−6.68 (m, 3 H, C_6H_3), 6.35 (d, *J* = 9.9 Hz, 1 H, CH=), 5.52 (d, *J* = 9.9 Hz, 1 H, CH=), 3.96 (s, 2 H, CH_2Otosyl), 2.41 (s, 6 H, 2CH_3tosyl), 1.23 (s, 3 H, CH_3). − ^{13}C NMR: δ = 151.3 (C_{qAr}Otosyl), 145.0 ($C_{qAr}OC$), 144.9, 142.3 (2 $C_q$tosyl), 132.4, 132.3 (C_{qAr}tosyl), 130.7 (CH=), 129.8, 129.6, 128.7, 128.3 (8 CH=tosyl), 122.9 ($CH=_{Ar}$), 122.6 (CH=), 121.6 (C_{qAr}), 121.3 ($CH=_{Ar}$), 117.6 ($CH=_{Ar}$), 78.2 (C_qO), 73.1 (CH_2Otosyl), 21.7, 21.4 (3CH_3). − MS: *m/z* (%) = 500 (1) [M^+], 344 (6), 343 (6), 316 (21), 315 (100), 173 (6), 160 (11), 155 (3), 91 (14), 65 (4). − $C_{25}H_{24}O_7S_2$ (500.59): calcd. C 59.98, H 4.83; found C 59.17, H 4.45. − [α] = +10.6° (*c* = 0.9, acetone).

(2*R*)-(+)-2-Methyl-2-(4-methylpent-3-en-1-yl)-6-tosyloxy-2*H*-chromen (19): Prenylmagnesium bromide was prepared from Mg (10 mg, 0.38 mmol) and prenyl bromide (54 mg, 0.36 mmol) in THF at −20 °C. The solution was cooled to −70 °C and Li_2CuCl_4 (0.5 mL, 1 M solution in THF) was added. After 30 min, compound **18** (90 mg, 0.18 mmol) in THF (4 mL) was slowly added. The mixture was then slowly allowed to warm to at room temp. for 5 h. Sat. aq. NH_4Cl was added and the organic phase was extracted with ether, washed with brine, dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 7:3) to give the tosylated cordiachromen **19** (53 mg, 75%) as a yellow oil.
^1H NMR: δ = 7.70−7.20 (m, 4 H, C_6H_4tosyl), 6.60−6.45 (m, 3 H, C_6H_3), 6.10 (d, *J* = 9.9 Hz, 1 H, CH=), 5.50 (d,; *J* = 9.9 Hz, 1 H, CH=), 5.00 (t, *J* = 7.1 Hz, 1 H, CH=), 2.40 (s, 3 H, CH_3tosyl), 2.10−1.90 (m, 2 H, CH_2), 1.70−1.50 (m, 2 H, CH_2), 1.60 (s, 3 H, CH_3), 1.55 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3). − ^{13}C NMR: δ = 151.3 (C_{qAr}Otosyl), 145.2 ($C_{qAr}OC$), 143.0 (C_qStosyl), 132.4 ($C_{qAr}CH_3$), 131.8 (C_q), 130.8 (CH=), 129.7, 128.5(4 $CH=_{Ar}$tosyl), 123.8 (CH=), 122.4 (CH=), 122.0 ($CH=_{Ar}$), 121.7 (C_{qAr}), 120.0 ($CH=_{Ar}$), 116.5 ($CH=_{Ar}$), 79.0 (C_qO), 41.2 (CH_2), 26.5 (CH_2), 25.6 (CH_3), 21.7 (CH_3), 22.6 (CH_2), 17.6 (CH_3). − MS: *m/z* (%) = 398 (11) [M^+], 383 (15), 316 (21), 315 (100), 243 (5), 69 (40). − [α] = +46.1° (*c* = 0.78, acetone)

(2*R*)-(+)-6-Hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)-2*H*-chromen (1): A KOH solution [3.5 mL, prepared from KOH (0.5 g), water (8.5 mL) and ethanol (8.5 mL)] was slowly added to compound **19** (48 mg, 0.122 mmol). The mixture was stirred at reflux for 3 h and then neutralised with CH_3COOH and concentrated. The organic phase was extracted with ether, washed with aq. $NaHCO_3$, water and brine, dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography

(silica gel, hexane/EtOAc, 8:2) to give the cordiachromen **1** (26 mg, 87%) as a yellow oil.

^{1}H NMR: δ = 6.68−6.47 (m, 3 H, C_6H_3), 6.28 (d, J = 9.9 Hz, 1 H, CH=), 5.59 (d, J = 9.9 Hz, 1 H, CH=), 5.10 (t, J = 7.1 Hz, 1 H, CH=), 2.18−1.97 (m, 4 H, 2 CH_2), 1.68 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3). − ^{13}C NMR: δ = 149.1 ($C_{Ar}OH$), 146.7 ($C_{Ar}OC$), 131.5 (C_q), 130.8 (CH=), 124.0 (CH=), 122.5 (CH=), 121.8 (C_{qAr}), 116.5, 115.6, 112.8 (3 CH=$_{Ar}$), 78.0 (C_qO), 40.7 (CH_2), 25.8 (CH_2), 25.5 (CH_3), 22.5 (CH_2), 17.5 (CH_3). − MS: *m/z* (%) = 244 (41) [M^+], 229 (10), 161 (100), 69 (35). − $C_{16}H_{20}O_2$ (244.33): calcd. C 78.65, H 8.25; found C 78.23, H 7.98. − [α] = +101.6° (c = 0.83, acetone).

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