

Jean-Yves Goujon, Alexis Duval and Bernard Kirschleger\*

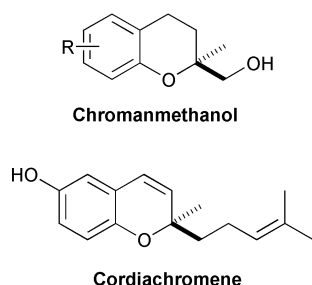
Laboratoire de Synthèse Organique UMR 6513, Faculté des Sciences et des Techniques,  
2, Rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France.  
E-mail: kirschle@chimie.univ-nantes.fr; Fax: 0033-2 5112 5402; Tel: 0033-2 5112 5419

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An enantioselective synthesis of chromanylmethanol is described. An allylic alcohol moiety is, first, introduced on the aromatic ring through a Claisen transposition. Chirality is then introduced through asymmetric Sharpless epoxidation on the allylic alcohol moiety. Cyclization into the benzopyran ring is achieved by an intramolecular coupling between the tertiary alcoholic hydroxy and the hydroquinone moiety with an excellent retention of configuration.

## Introduction

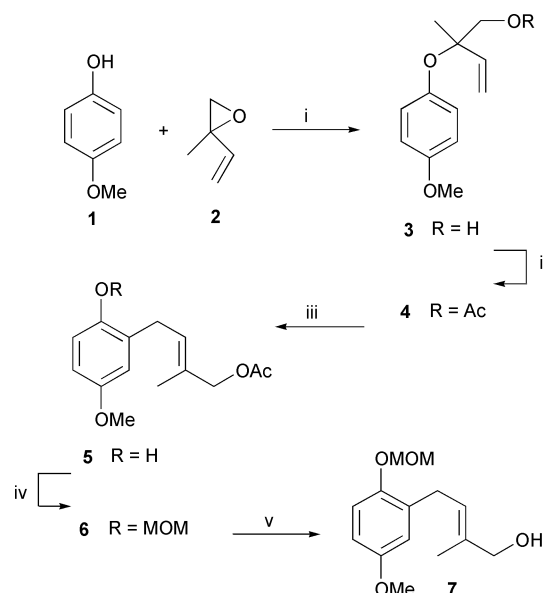
Chroman-2-ylmethanol, as an optically active moiety, is an important synthetic intermediate, which can be used for the synthesis of biologically active compounds such as  $\alpha$ -tocopherol<sup>1</sup> (vitamin E), levcromakalim,<sup>2</sup> cannabichromene<sup>3</sup> or cordiachromene.<sup>4</sup> All syntheses of the chromanylmethanol intermediate of  $\alpha$ -tocopherol are achieved by using optical resolution<sup>5</sup> or asymmetric synthesis.<sup>6</sup> Recently, we have reported a multi-step enantioselective synthesis of cordiachromene<sup>7</sup> using chromanylmethanol **14**, which was formed with an overall yield of 30%. However, further studies were needed for a more efficient access to **14**. In this paper, we describe this useful approach by using a succession of high yielding short and simple reactions.



## Results and discussion

The first part of the synthesis (Scheme 1) was devoted to the coupling of an allylic alcohol moiety in the *o*-position to *p*-dialkoxybenzene using a sequence of short, simple and high yielding reactions. The synthesis started with a regioselective addition<sup>8</sup> of 1-methyl-1-vinyloxirane<sup>9</sup> **2** on the phenolic hydroxy of *p*-methoxyphenol **1** through a  $\pi$ -allylpalladium complex intermediate obtained from vinyloxirane and Pd(O). The crude reaction product **3** was then reacted with acetic anhydride to protect the alcoholic hydroxy as an acetoxy group and this gave **4**. By using anhydrous hydrogen chloride, the latter was transposed<sup>8</sup> (Claisen transposition) into **5**. This sequence was achieved by the protection of the phenolic hydroxy as a methoxymethoxy group (MOM) giving **6**, followed by liberation of the alcoholic hydroxy affording **7**.

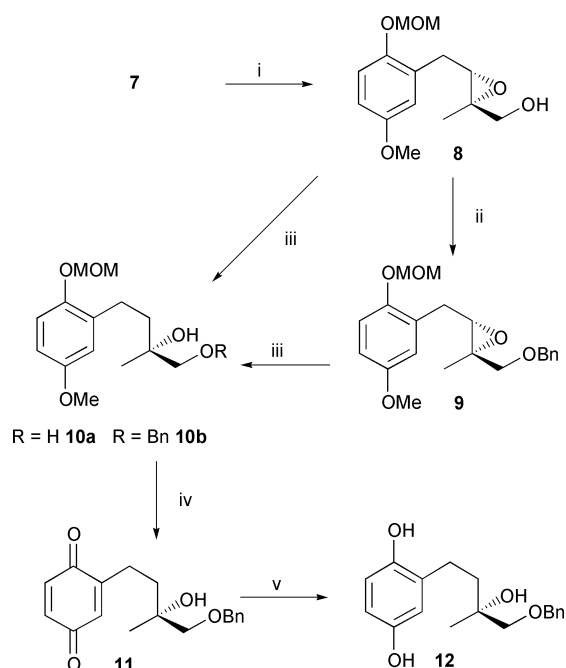
The second part of this synthesis (Scheme 2) was concerned with the introduction of chirality on the allylic double bond through Sharpless asymmetric epoxidation (SAE).<sup>10</sup> Using



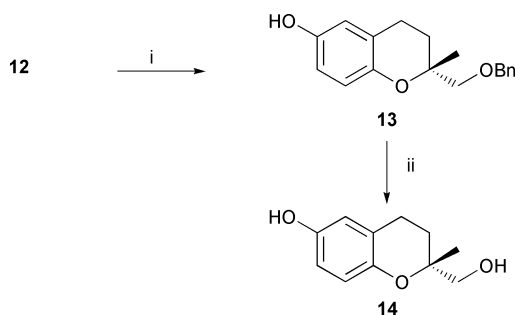
**Scheme 1** Reagents and conditions i) PdP(Ph<sub>3</sub>)<sub>4</sub>, DCM, rt, 4 h, 95%. ii) Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP, AcOEt, rt, 4 h, 98%. iii) HCl(g), DCM, rt, 2 min, 98%. iv) ClCH<sub>2</sub>OCH<sub>3</sub>, *i*Pr<sub>2</sub>NEt, DCM, 40 °C, 12 h, 97%. v) K<sub>2</sub>CO<sub>3</sub>, MeOH, rt, 2 h, 97%.

L-(+)-diethyl tartrate as the chiral reagent, compound **8**, with a (*S,S*)-configuration, was isolated with 85% yield and 93% de (determined by NMR analysis). Before the epoxide ring opening, the alcoholic hydroxy was protected as a benzyl group according to classical methods. The epoxide was then regioselectively opened with lithium aluminium hydride to obtain **10b** in an almost quantitative yield (90% ee). It is noteworthy that starting from **8** the same reaction gave directly diol **10a**.<sup>7</sup>

The third part of this synthesis (Scheme 3) concerned the cyclization into the benzopyran ring. Previous results showed that direct cyclisation was achieved from the 3,5,6-trimethylhydroquinone homologous compound of **12a** by intramolecular coupling between tertiary alcoholic hydroxy and semi-quinonic or quinonic form of the hydroquinone moiety.<sup>6a</sup> An excellent retention of configuration was observed. Before cyclisation, the hydroquinone dialkoxy ether moiety of **10** needed to be deprotected. Starting from **10a**, oxidative cleavage with ceric ammonium nitrate (CAN)<sup>11</sup> failed. However, with **10b**, the same reaction succeeded affording quinone **11** which was, then, reduced with sodium dithionite to give hydroquinone



**Scheme 2** Reagents and conditions i) *t*BuOOH, Ti(OiPr)<sub>4</sub>, L-(+)-DET, DCM, -24 °C, 20 h, 85%. ii) BnBr, NaH, *n*Bu<sub>4</sub>NI, THF, rt, 3h, 88%. iii) LiAlH<sub>4</sub>, diethyl ether, rt, 5 h, 97%. iv) CAN, CH<sub>3</sub>CN, H<sub>2</sub>O, -5 °C, 90 min, 90%. v) Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>, acetone, H<sub>2</sub>O, rt, 30 min, 96%.



**Scheme 3** Reagents and conditions i) *p*-TSA, toluene, 45 °C, 1 h, 94%. ii) H<sub>2</sub>, Pd/C, MeOH, rt, 4 h, 95%.

derivative **12**.<sup>12</sup> In acidic medium (*p*-TSA), **12** was cyclized affording **13** in high yield (94%) which was easily debenzylated to produce chroman-2-ylmethanol **14**. As expected cyclization was achieved with an excellent retention of configuration of the stereogenic carbon (ee = 85%).

## Conclusion

Chroman-2-ylmethanol **14** was synthesised in 12 steps with an overall yield of 48%. The method we have presented advantageously complemented the synthesis previously reported, with efficient reactions and short work-up.

## Experimental

Every starting material was obtained from commercial suppliers and used without further purification. Each solvent (diethyl ether, THF, DMF, toluene) was dried by distillation from sodium–benzophenone before use. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 200 and 50 MHz on a Bruker AC 200 with CDCl<sub>3</sub> as solvent and TMS as internal standard; chemical shifts ( $\delta$ ) were expressed in ppm and coupling constants (*J*) in Hertz. Mass spectra (EI) were recorded on a Hewlett Packard 5989A (70 eV). Optical rotations were measured on a 341 Perkin Elmer polarimeter and are given in 10<sup>-1</sup> deg cm<sup>2</sup> g<sup>-1</sup>. Enantiomeric excesses were determined by HPLC analysis using a column packed with Chiracel OD–H 150 × 4.6.

Elemental analyses were carried out by the CNRS Analysis Laboratory, Vernaison, France.

### 1-(1-Hydroxy-2-methylbut-3-en-2-yloxy)-4-methoxybenzene (3)

To a deoxygenated solution of *p*-methoxyphenol **1** (8.54 g, 68.9 mmol) and vinyloxirane **2** (8.68 g, 103.3 mmol) in DCM (40 mL) was added PdP(Ph<sub>3</sub>)<sub>4</sub> (1.2 g, 1 mmol). The mixture was stirred at rt for 4 h. Then, the mixture was filtered on a Celite pad to remove the catalyst and the solvent was evaporated *in vacuo*. A colourless oily residue remained (14.22 g, 95%) and it was used without further purification.  $\delta_{\text{H}}$  6.93–6.72 (m, 4H, 4CH<sub>ar</sub>), 6.07 (dd, 1H, *J* 11.3, *J* 17.5, CH=), 5.27 (dd, 1H, *J* 11.3, *J* 1, CH=), 5.18 (dd, 1H, *J* 17.5, *J* 1, CH=), 3.74 (s, 3H, OCH<sub>3</sub>), 3.67 (dt, 1H, *J* 6.6, *J* 10.1, CH<sub>2</sub>O), 3.56 (dt, 1H, *J* 6.6, *J* 10.1, CH<sub>2</sub>O), 2.34 (t, 1H, *J* 6.6, OH), 1.32 (s, 3H, CH<sub>3</sub>).  $\delta_{\text{C}}$  155.6, 148.3, 139.7, 123.8, 116.5, 113.9, 79.9, 69.3, 55.4, 20.4. MS, *m/z* (relative intensity) 208 (15%, M<sup>+</sup>), 124 (71), 85 (100), 15 (8).

### 1-(1-Acetyloxy-2-methylbut-3-en-2-yloxy)-4-methoxybenzene (4)

To a solution of **3** (0.208 g, 1 mmol) and dimethylaminopyridine (catalytic amount) in ethyl acetate (30 mL) was added a solution of acetic anhydride (0.306 g, 3 mmol) and triethylamine (0.303 g, 3 mmol). The mixture was stirred at rt for 4 h, then brine (30 mL) was added. The organic layer was separated and dried over MgSO<sub>4</sub>. The solvent was evaporated *in vacuo*. A yellow oily residue remained (0.250 g, 98%) and it was used without further purification.  $\delta_{\text{H}}$  6.94–6.73 (m, 4H, 4CH<sub>ar</sub>), 6.05 (dd, 1H, *J* 10.8, *J* 17.8, CH=), 5.27 (dd, 1H, *J* 10.8, *J* 1, CH=), 5.26 (dd, 1H, *J* 17.8, *J* 1, CH=), 4.16 (s, 2H, CH<sub>2</sub>O), 3.76 (s, 3H, OCH<sub>3</sub>), 2.12 (s, 3H, CH<sub>3</sub>), 1.35 (s, 3H, CH<sub>3</sub>).  $\delta_{\text{C}}$  170.8, 155.6, 148.3, 139.7, 123.8, 116.5, 113.8, 79.8, 68.9, 55.4, 20.9, 20.4. MS, *m/z* (relative intensity) 250 (6%, M<sup>+</sup>), 177 (10), 127 (100), 124 (65), 85 (16), 43 (70).

### 2-(4-Acetyloxy-3-methylbut-2-en-1-yl)-4-methoxyphenol (5)

Through a solution of **4** (2.10 g, 15 mmol) in DCM (40 mL), anhydrous HCl was bubbled for 2 min. The solvent was evaporated *in vacuo*. A yellow oily residue remained (2.09 g, 98%) which was used without further purification.  $\delta_{\text{H}}$  6.77–6.59 (m, 3H, 3CH<sub>ar</sub>), 5.64 (t, 1H, *J* 7.4, CH=), 4.50 (s, 2H, CH<sub>2</sub>O), 3.74 (s, 3H, OCH<sub>3</sub>), 3.38 (d, 2H, *J* 7.4, CH<sub>2</sub>), 2.08 (s, 3H, CH<sub>3</sub>), 1.78 (s, 3H, CH<sub>3</sub>).  $\delta_{\text{C}}$  171.5, 153.5, 148.0, 131.5, 127.8, 127.0, 116, 112, 70.1, 55.7, 28.7, 20.9, 14.0. MS, *m/z* (relative intensity) 250 (4%, M<sup>+</sup>), 190 (34), 175 (100), 91 (12), 77 (15), 43 (64).

### (E)-2-(4-Acetyloxy-3-methylbut-2-en-1-yl)-4-methoxy-1-methoxymethoxybenzene (6)

To a stirred solution of **5** (1.43 g, 5.7 mmol) and diisopropylethylamine (2.21 g, 1.7 mmol) in DCM (25 mL) was slowly added methoxymethyl chloride (1.38 g, 1.7 mmol) at 0 °C. After stirring at 40 °C for 12 h, sat. aq. NH<sub>4</sub>Cl (30 mL) was added. The organic layer was extracted with diethyl ether (2 × 30 mL), washed with water (20 mL) and brine (20 mL), dried over MgSO<sub>4</sub> and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, hexane–EtOAc, 8 : 2) to give a colourless oil (1.62 g, 97%).  $\delta_{\text{H}}$  7.02–6.64 (m, 3H, 3CH<sub>ar</sub>), 5.62 (t, 1H, *J* 7.4, CH=), 5.12 (s, 2H, OCH<sub>2</sub>O), 4.49 (s, 2H, CH<sub>2</sub>O), 3.76 (s, 3H, OCH<sub>3</sub>), 3.47 (s, 3H, OCH<sub>3</sub>), 3.38 (d, 2H, *J* 7.4, CH<sub>2</sub>), 2.06 (s, 3H, CH<sub>3</sub>), 1.77 (s, 3H, CH<sub>3</sub>).  $\delta_{\text{C}}$  170.8, 154.4, 149.0, 130.9, 128.3, 127.2, 115.7, 111.3, 95.2, 70.0, 55.8, 55.5, 28.5, 20.9, 13.9. MS, *m/z* (relative intensity) 294 (10%, M<sup>+</sup>), 190 (53), 175 (100), 45 (50), 43 (25).

### (E)-2-(4-Hydroxy-3-methylbut-2-en-1-yl)-4-methoxy-1-methoxymethoxybenzene (7)

**6** (1.3 g, 4.4 mmol) was added to a solution of methanol (20 mL) and sat. aq. K<sub>2</sub>CO<sub>3</sub> (2 mL). The mixture was stirred at

rt for 2 h. Then water (20 mL) and diethyl ether (20 mL) were added. The two layers were separated, the aqueous layer was extracted with diethyl ether (20 mL). The combined organic layer was dried over MgSO<sub>4</sub>. The solvent was evaporated *in vacuo*. A colourless oily residue remained (1.09 g, 97%) and it was used without further purification. Spectroscopic data were in accordance with ref. 7.

**(2S,3S)-(–)-2-(2,3-Epoxy-4-hydroxy-3-methylbutyl)-4-methoxy-1-methoxymethoxybenzene (8)**

See ref. 7.

**(2S,3S)-(–)-2-(4-Benzyloxy-2,3-epoxy-3-methylbutyl)-4-methoxy-1-methoxymethoxybenzene (9)**

To a solution of **8** (0.459 mg, 1.71 mmol) in THF (50 mL) was slowly added NaH (0.072 g, 1.8 mmol) at 0 °C. Then, *n*Bu<sub>4</sub>NI (catalytic amount) and benzyl bromide (0.224 mL, 1.8 mmol) were added. The mixture was stirred at rt for 3 h. Water (50 mL) was added. The organic layer was extracted with diethyl ether (2 × 30 mL). The combined organic layer was dried over MgSO<sub>4</sub> and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, hexane–EtOAc, 7 : 3) to give a colourless oil (0.54 g, 88%). δ<sub>H</sub> 7.41–7.23 (m, 5H, 5CH<sub>ar</sub>), 7.07–6.68 (m, 3H, 3CH<sub>ar</sub>), 5.12 (s, 2H, OCH<sub>2</sub>O), 4.55 (d, 1H, *J* 12, OCH<sub>2</sub>Ar), 4.48 (d, 2H, *J* 12, OCH<sub>2</sub>Ar), 3.74 (s, 3H, OCH<sub>3</sub>), 3.52 (d, 1H, *J* 10, CH<sub>2</sub>OBn), 3.45 (s, 3H, OCH<sub>3</sub>), 3.44 (d, 1H, *J* 10, CH<sub>2</sub>OBn), 3.15 (t, 1H, *J* 6.2, CHO), 2.91 (d, 2H, *J* 6.2, CH<sub>2</sub>), 1.46 (s, 3H, CH<sub>3</sub>). δ<sub>C</sub> 154.5, 149.3, 138.1, 128.3, 128.1, 127.8, 127.6, 116.0, 112.3, 95.3, 74.7, 73.0, 60.4, 60.1, 55.9, 55.6, 29.3, 14.7. MS, *m/z* (relative intensity) 358 (22%, M<sup>+</sup>), 205 (42), 91 (100), 45 (96), 43 (12). [α]<sub>D</sub><sup>22</sup> –0.2 (*c* 1 in CHCl<sub>3</sub>).

**(3R)-(–)-2-(3,4-Dihydroxy-3-methylbutyl)-4-methoxy-1-methoxymethoxybenzene (10a)**

See ref. 7

**(3R)-(–)-2-(4-Benzyloxy-3-hydroxy-3-methylbutyl)-4-methoxy-1-methoxymethoxybenzene (10b)**

Epoxide **9** (0.42 g, 0.74 mmol) was slowly added to a LiAlH<sub>4</sub> solution (0.059 g 1.48 mmol) in diethyl ether (10 ml) at rt. The mixture was stirred for 5 h. Water (25 ml) was added. The organic layer was extracted with diethyl ether, dried over MgSO<sub>4</sub> and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, hexane–EtOAc, 7 : 3) to give a colourless oil (0.41 g, 97%). δ<sub>H</sub> 7.41–7.23 (m, 5H, 5CH<sub>ar</sub>), 7.00–6.62 (m, 3H, 3CH<sub>ar</sub>), 5.09 (s, 2H, OCH<sub>2</sub>O), 4.56 (s, 2H, OCH<sub>2</sub>Ar), 3.74 (s, 3H, OCH<sub>3</sub>), 3.45 (s, 3H, OCH<sub>3</sub>), 3.41 (d, 1H, *J* 8.8, CHOBn), 3.32 (d, 1H, *J* 8.8, CHOBn), 2.72–2.63 (m, 2H, CH<sub>2</sub>), 1.86–1.74 (m, 2H, CH<sub>2</sub>), 1.66 (s, 3H, CH<sub>3</sub>). δ<sub>C</sub> 154.5, 149.3, 138.2, 133.2, 128.4, 127.6, 115.8, 111.4, 95.4, 77.4, 73.5, 72.2, 56.0, 55.6, 39.5, 24.9, 23.7. MS, *m/z* (relative intensity) 360 (11%, M<sup>+</sup>), 328 (59), 298 (23), 137 (43), 91 (100), 65 (11), 45 (58). [α]<sub>D</sub><sup>22</sup> –4.0 (*c* 1 in CHCl<sub>3</sub>). ee = 90%.

**(3R)-(–)-2-(4-Benzyloxy-3-hydroxy-3-methylbutyl)-2-quinone (11)**

To a water–acetonitrile (1 : 1) solution (10 ml) of ceric ammonium nitrate (1.28 g, 2.33 mmol) was added at –5 °C a solution of **10b** (0.161 g, 0.47 mmol) in CH<sub>3</sub>CN (10 ml). The mixture was stirred at –5 °C for 1 h 30 min. Then, DCM (20 mL) was added. The aqueous layer was extracted with DCM. The combined organic layer was dried over MgSO<sub>4</sub> and filtered on a Celite pad to remove the remainder cerium salt. The solvent was evaporated *in vacuo*. The crude product **11** (0.120 g, 90%) was controlled by <sup>1</sup>H NMR and immediately

used in the next reaction. δ<sub>H</sub> 7.41–7.23 (m, 5H, 5CH<sub>ar</sub>), 6.78–6.56 (m, 3H, 3CH<sub>ar</sub>), 4.56 (s, 2H, OCH<sub>2</sub>Ar), 3.37 (d, 1H, *J* 9.0, CHOBn), 3.32 (d, 1H, *J* 9.0, CHOBn), 2.56–2.46 (m, 2H, CH<sub>2</sub>), 1.83–1.56 (m, 2H, CH<sub>2</sub>), 1.23 (s, 3H, CH<sub>3</sub>).

**3R)-(–)-(4-Benzyloxy-3-hydroxy-3-methylbutyl)-2-hydroquinone (12)**

To a solution of **11** (0.12 g, 0.42 mmol) in acetone (40 mL) was added Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> (20 mL, 0.57 M aqueous solution). The mixture was stirred at rt for 30 min. Then DCM (40 mL) was added. The two layers were separated. The aqueous layer was extracted with DCM (2 × 40 mL). The combined organic layer was dried over MgSO<sub>4</sub> and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, hexane–EtOAc, 5 : 5) to give hydroquinone **12** (0.116 g, 96%) as a yellow oil. δ<sub>H</sub> 7.41–7.23 (m, 5H, 5CH<sub>ar</sub>), 6.71–6.53 (m, 3H, 3CH<sub>ar</sub>), 4.56 (s, 2H, OCH<sub>2</sub>Ar), 3.37 (d, 1H, *J* 9.0, CHOBn), 3.31 (d, 1H, *J* 9.0, CHOBn), 2.62 (t, 2H, *J* 7.5, CH<sub>2</sub>Ar), 1.83–1.73 (m, 2H, CH<sub>2</sub>), 1.22 (s, 3H, CH<sub>3</sub>). δ<sub>C</sub> 149.7, 148.3, 137.5, 128.5, 128.4, 127.6, 116.8, 113.9, 77.8, 73.5, 72.1, 41.2, 24.1, 21.2 (Found: C, 71.30; H, 7.11%; C<sub>18</sub>H<sub>22</sub>O<sub>4</sub> requires C, 71.50; H, 7.33%).

**(2R)-(–)-6-Hydroxy-2-benzyloxy-2-methylchromane (13)**

To a solution of **12** (0.069 g, 0.228 mmol) in toluene (15 mL), *p*-TSA (catalytic amount) was added. The mixture was stirred at 45 °C for 1 h. The solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, hexane–EtOAc, 8 : 2) to give **13** (0.063 g, 94%) as a yellow oil. δ<sub>H</sub> 7.41–7.23 (m, 5H, 5CH<sub>ar</sub>), 6.70–6.51 (m, 3H, 3CH<sub>ar</sub>), 4.62 (d, 1H, *J* 12.2, OCHAr), 4.55 (d, 1H, *J* 12.2, OCHAr), 3.50 (d, 1H, *J* 9.6, CHOBn), 3.43 (d, 1H, *J* 9.6, CHOBn), 2.68 (t, 2H, *J* 6.6, CH<sub>2</sub>Ar), 2.00 (dt, 1H, *J* 6.6, *J* 6.6, CHCq), 1.74 (dt, 1H, *J* 6.6, *J* 6.6, CHCq), 1.64 (br s, 1H, OH), 1.22 (s, 3H, CH<sub>3</sub>). δ<sub>C</sub> 148.7, 147.4, 138.3, 128.3, 127.6, 122.0, 117.7, 114.5, 75.7, 75.1, 73.5, 28.5, 22.4, 22.0. MS, *m/z* (relative intensity) 284 (65%, M<sup>+</sup>), 163 (93), 123 (30), 107 (21), 91 (100), 65 (24). [α]<sub>D</sub><sup>22</sup> –8.0 (*c* 1 in CHCl<sub>3</sub>). ee = 85% (Found: C, 76.30; H, 7.01%; C<sub>18</sub>H<sub>20</sub>O<sub>3</sub> requires C, 76.03; H, 7.09%).

**(2R)-(–)-6-Hydroxy-2-hydroxymethyl-2-methylchromane (14)**

To a solution of **13** (0.050 g, 0.17 mmol) in MeOH (10 mL), 10% palladium on carbon (catalytic amount) was added. The mixture was stirred under a hydrogen atmosphere for 4 h. The mixture was filtered and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, hexane–EtOAc, 5 : 5) to give **14** (0.028 g, 95%) as a colourless oil. Spectroscopic data are in accordance with ref. 7. [α]<sub>D</sub><sup>22</sup> –8.1 (*c* 1.15 in acetone). ee = 85%.

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