A New and Efficient Synthesis of Substituted 2-Hydroxymethyl-2-methyl-2*H*-chromenes

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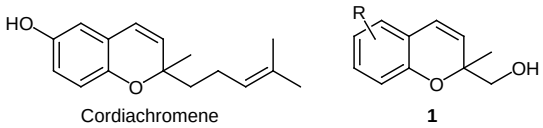
Abstract: A new and efficient three step procedure for the synthesis of functionalized 2*H*-chromenes **1** is described, starting from commercially available salicylaldehydes **2** and 2-methylpropenylmagnesium chloride **3**, which involves catalytic acid-mediated intramolecular cyclization of phenolic epoxide **5** as the key step.

Key words: 2*H*-chromenes, chromenemethanols, 2,2-disubstituted 2*H*-chromenes, 2-hydroxymethyl-2-methyl-2*H*-chromenes, 2*H*-1-benzopyran

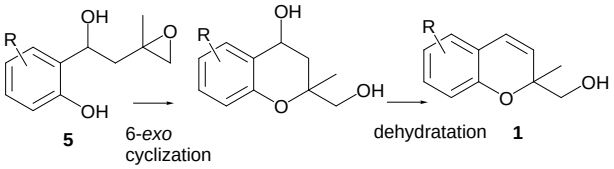
Synthesis of Substituted 2-Hydroxymethyl-2-methyl-2*H*-chromenes

2*H*-Chromenes are key heterocyclic units in many natural and biologically polyoxygenated active compounds.[1] Moreover, they are widely employed as useful intermediates in the synthesis of medicinal agents such as cordiachromene,[2] potassium channel activating drugs[3] and a range of tannins.[4] A common building block for the synthesis of such structures is 2-hydroxymethyl-2-methylchromene **1** (Scheme 1).



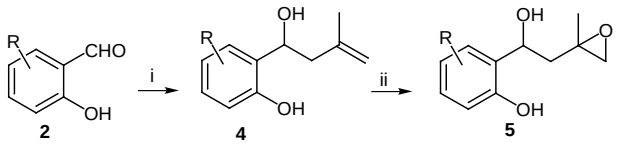
Scheme 1

Although several methods have been reported in literature[5] for the construction of such various 2,2-dialkylchromene skeletons, only few direct preparations of 2-functionalized chromenes have been described.[2,6] We herein report a new and facile route to diverse 2-hydroxymethyl-2-methylchromenes **1**, starting from commercially available salicylaldehydes **2**, which involves the cyclization of **5**, a nucleophilic epoxide opening reaction as the key step. The synthetic strategy requires the preparation of epoxides **5**, whose aryl ether-forming reaction provides chromenemethanols **1** via a (6-*exo*) mode of cyclization, followed by an intramolecular dehydratation reaction (Scheme 2).



Scheme 2

Preparation of epoxide **5** is outlined in Scheme 3. The treatment of salicylaldehydes **2** with an excess of 2-methylpropenylmagnesium chloride **3** in THF afforded the corresponding homoallylic alcohols **4** in good to excellent yields (Table 1). For the preparation of key epoxides **5**, homoallylic alcohols **4** were subjected to standard epoxidation with *m*-CPBA in CH_2Cl_2. The reaction was carried out at 0 °C for 4 hours. Purified by column chromatography on silica, the corresponding epoxides **5a**–**d** were obtained in a 70–75% yield. It will be noteworthy that in the case of compounds **4e,f**, *m*-CPBA epoxidation leads to epoxides **5e,f** in only 20–30% yields. These low yields are due to the instability of compounds **5e,f** on silica. To improve these yields, phenolic groups of compounds **2e,f** were protected by the TBS group,[7] then allylmetallation and epoxidation reactions were successful (Table 1, entries 7 and 8). Subsequent O-silyldeprotection of **5g,h** with TBAF[7] gave corresponding phenolic epoxides **5e,f** in quantitative yields. These epoxides were, then, immediately used in the next step without further purification.



Scheme 3 *Reagents and conditions* i) $CH_2=C(CH_3)CH_2MgCl$ (**3**), THF, –20°C. ii) *m*-CPBA, CH_2Cl_2, 0 °C.

In the last step (Scheme 4), the crucial cyclization of epoxides **5a**–**e** with $AlCl_3$ (2 equiv) in THF at 0 °C did not give the expected chromanemethanols **1a**–**e** but instead bicyclic compounds **7a**–**e**. The naphthalene derivative **5f** leads, under these conditions, to the expected chromene **1f**. Alternatively, by using catalytic amounts of camphor sulfonic acid (20 mol%) in CH_2Cl_2 at room temperature, epoxides **5a-e** were also converted into **7a**–**e.** Heating **7a**–**e** in benzene at reflux for 16 hours in the presence of 4

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1437-2096,E;2002,0,02,0322,0324,ftx,en;G31201ST.pdf.

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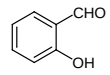
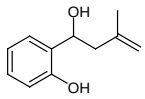
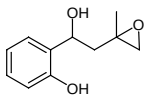
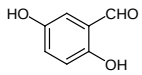
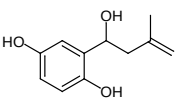
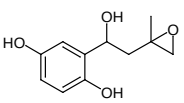
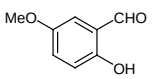
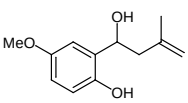
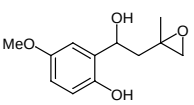
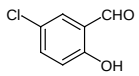
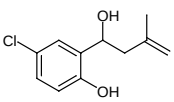
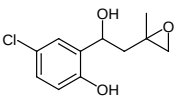
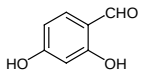
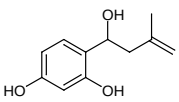
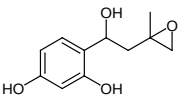
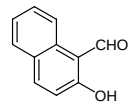
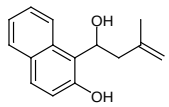
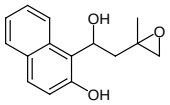
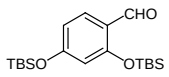
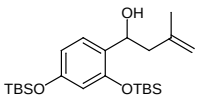
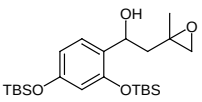
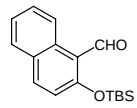
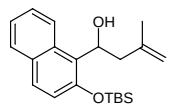
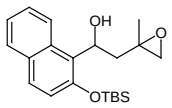
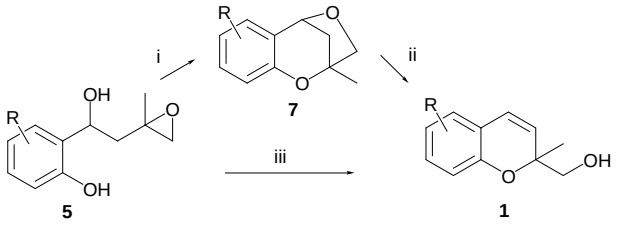
Table 1 Allylation and Epoxidation Reactions

Entry	Aldehyde	Alcohol[a]	Epoxide[a]
1	 **2a**	 **4a** (98)	 **5a** (75)
2	 **2b**	 **4b** (98)	 **5b** (70)
3	 **2c**	 **4c** (97)	 **5c** (74)
4	 **2d**	 **4d** (98)	 **5d** (70)
5	 **2e**	 **4e** (48)	 **5e** (20)
6	 **2f**	 **4f** (75)	 **5f** (30)
7	 **2g**	 **4g** (60)	 **5g** (65)
8	 **2h**	 **4h** (80)	 **5h** (55)

[a] Isolated yield of pure products, all new compounds gave satisfactory analytical data.

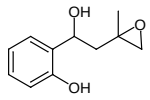
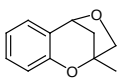
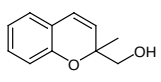
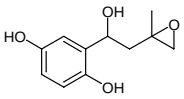
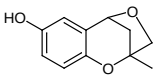
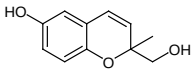
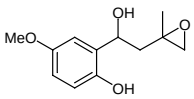
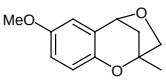
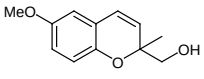
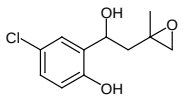
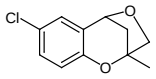
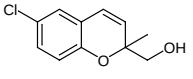
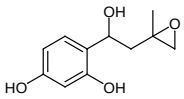
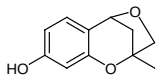
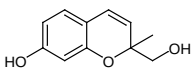
mol% of *p*-TSA afforded the expected chromenes **1a**–**e** in excellent yields (Table 2). On the other hand, treatment of epoxides **5a**–**f** in refluxing benzene with 4 mol% of CSA for 2 hours gave directly chromenemethanols **1a**–**f** in excellent yields (Table 2).

These results can be explained through the formation of a very stable benzylic carbocation. This carbocation can lead, depending on the reaction conditions, to either compounds **1** or **7**. These results are consistent with those of Yoshioka[1a] for analogues of **1** (Scheme 5).



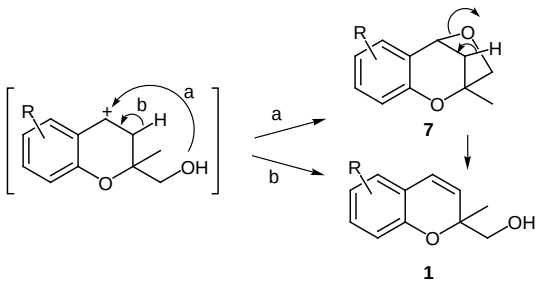
Scheme 4 *Reagents and conditions: Method A* i) $AlCl_3$, THF, 0 °C or CSA (20 mol%), DCM, r.t. ii) *p*-TSA or CSA (4 mol%), benzene, reflux. *Method B* iii) *p*-TSA or CSA (4 mol%), benzene, reflux.

Table 2 Cyclization Reactions

Entry	Epoxide	Bicyclic Compound[a]	Chromene[b]
1	 **5a**	 **7a** (97%)	 **1a** (85%)
2	 **5b**	 **7b** (88%)	 **1b** (78%)
3	 **5c**	 **7c** (89%)	 **1c** (78%)
4	 **5d**	 **7d** (82%)	 **1d** (65%)
5	 **5e**	 **7e** (74%)	 **1e** (65%)
6	**5f**	-	**1f** (80%)

[a] Isolated yield of pure products, all new compounds gave satisfactory analytical data.
[b] Yield obtained with *Method B.*

In summary, a simple and general three step procedure for the preparation of 2-functionalized chromenes is now available. This approach constitutes an attractive alternative strategy for the formation of variously substituted chromene systems. Further synthetic application of this methodology is currently in progress and will be reported in due course.



Scheme 5

Allylmetallation of Aldehydes

To a solution of metallylmagnesium chloride **3** (0.6 M, 6.3 mmol) in THF was added dropwise aldehyde **2** (2.1 mmol) in THF (10 mL) at –20 °C. At the end of the addition, the mixture was stirred for 1 h at r.t. and quenched with an aq soln of NH_4Cl. The aq layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography on silica gel (hexane–EtOAc mixtures).

Epoxidation of Homoallylic Alcohols

To a solution of homoallylic alcohol **4** (2.4 mmol) in CH_2Cl_2 (15 mL) was added at 0 °C a solution of *m*-CPBA (1.2 g, 4.8 mmol) in CH_2Cl_2 (20 mL) and the mixture was stirred at this temperature for 4 h. After filtration, the solution was concentrated and then the crude product was diluted with EtOAc (30 mL) and washed with aq $NaHCO_3$ (20 %, 3 × 20 mL) and brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc mixtures).

Cyclisation of Epoxides

Method A: A solution of epoxide **5** (2.57mmol) in THF (5 mL) at 0 °C was treated with $AlCl_3$ (5.15 mmol). After 1 h, an aq soln of NH_4Cl (10 mL) was added, the aq layer was extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc mixtures) to give the bicyclic compound **7**.

A solution of **7** (2 mmol) in benzene (20 mL) with $TsOH·H_2O$ (75 mg, 0.4mmol) was refluxed for 16 h. After cooling, the solution was washed with aq $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography on silica gel (hexane–EtOAc mixtures) to give chromenemethanol **1**.

Method B: A solution of epoxide **5** (2.57 mmol) and CSA (23.9 mg, 4 mol%) in benzene (10 mL) was refluxed for 2 h. After cooling, the solution was washed with aqueous $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography on silica gel (hexane–EtOAc mixtures) to give chromenemethanol **1**.

Typical Data for New Compounds 7

7a: ^{1}H NMR (200 MHz, DMSO), δ 1.54 (s, 3 H, CH_3), 2.06 (d, 1 H, *J* = 12 Hz, CH), 2.16 (dd, 1 H, *J* = 4.6Hz, *J* = 12Hz, CH), 3.74 (d, 1 H, *J* = 9.8 Hz, CHO), 4.15 (d, 1 H, *J* = 9.8 Hz, CHO), 4.91 (d, 1 H, *J* = 4.6 Hz, CHO), 6.72–7.19 (m, 4 H, H_{ar}). ^{13}C NMR (50.3 MHz, DMSO), δ 20.8, 38.2, 76.1, 79.0, 83.4, 115.7, 119.9, 125.6, 127.7, 130.7, 153.9. *m/z* (EI): 176 (77), 159 (24), 147 (62) 131 (100), 91 (27). IR (liquid film): 2975, 2941, 2876, 1482 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86; O, 18.16. Found: C, 74.75; H, 6.89; mp = 28 °C.

Typical Data for New compounds 1

1a: ^{1}H NMR (200 MHz, $CDCl_3$), δ 1.36 (s, 3 H, CH_3), 2.03 (br s, 1 H, OH), 3.59 (d, 1 H, *J* = 11.6 Hz, CH-O), 3.68 (d, 1 H, *J* = 11.6 Hz, CH-O), 5.56 (d, 1 H, *J* = 9.9 Hz, CH=), 6.45 (d, 1 H, *J* = 9.9Hz, CH=), 6.76-7.15 (m, 4 H, H_{ar}). ^{13}C NMR (50.3 MHz, $CDCl_3$), δ 22.6, 68.7, 79.2, 116.1, 120.8, 121.1, 124.7, 126.6, 126.7, 129.3, 153.9. *m/z* (EI): 176 (3), 145 (100), 115 (13), 91 (5). IR (liquid film): 3396, 2972, 2927, 1486, 1240, 1053, 773 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86; O, 18.16. Found : C, 74.82; H, 6.91.

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