Synthesis, 2009, 11, 1886-1896

Application of phenolate ion-mediated intramolecular epoxide ring opening in the enantioselective synthesis of functionalized 2,3-dihydrobenzofuran and 1-benzopyran derivatives [#]

Subal Kumar Dinda, Sajal Kumar Das, and Gautam Panda [*]

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow-226001, UP, India

Fax: +91-522-2223405, 2223938.

E-mail: gautam.panda@gmail.com

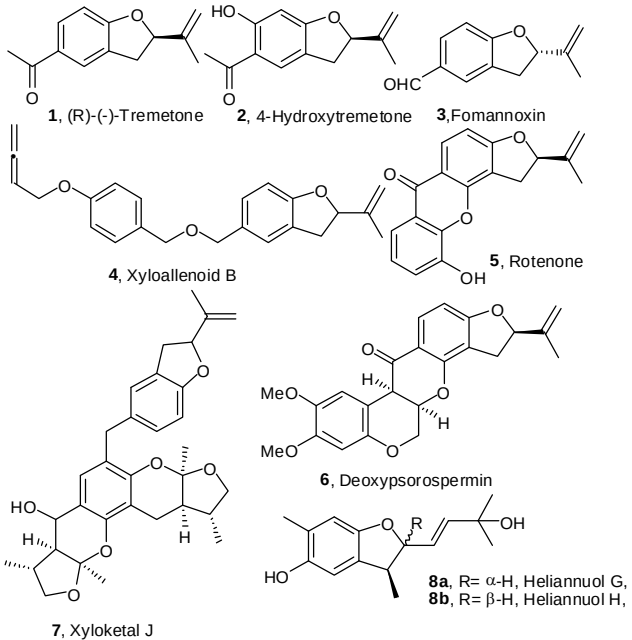
Abstract: The enantioselective synthesis of 2-isopropenyl-2,3-dihydrobenzofurans, 4-(2,3-dihydrobenzofuran-2-yl)-2-methylbut-3-en-2-ols, 2-hydroxymethylchromans, and 4-chroman-2-yl-2-methyl-but-3-en-2-ols has been achieved using Sharpless asymmetric epoxidation-derived enantiomerically enriched epoxy alcohols as chiral building blocks. A phenolate ion-mediated intramolecular epoxide ring opening reaction was the key step for every cyclization reaction.

Key words: 2-isopropenyl-2,3-dihydrobenzofuran, 2-hydroxymethyl chromans, Epoxidation, Epoxides, Polycycles, Ring opening.

2,3-Dihydrobenzofuran and 1-benzopyran derivatives are common in numerous natural products and unnatural molecules.[1,2] The wide ranging biological properties of these heterocycles have attracted the considerable attention of organic and medicinal chemists.[3,4] The 2-isopropenyl-2,3-dihydrobenzofuran framework is an integral part of numerous bioactive natural products[5] such as tremetone **1**, 4-hydroxytremetone **2**, fomannoxin **3**, and xyloallenolide B **4** (Figure 1)**.** In addition to these structurally simple molecules, more complex compounds such as rotenone **5**, 3',4'-deoxypsorospermin **6**, and xyloketal J **7** also contain the same structural unit.

Figure 1. Representative examples of natural products containing the 2-substituted 2,3-dihydrobenzofuran moiety.

The history of the synthesis of this class of compounds dates back to 1963 when the first asymmetric synthesis of **1** was achieved from the corresponding chiral 2,3-dihydrobenzofuran-2-carboxylic acid, both enantiomers of which were obtained by a chiral resolution procedure.[5a] Recently, Yamaguchi and co-workers achieved kinetic resolution of the enantiomers of several racemic 2-isopropenyl-2,3-dihydrobenzofurans utilizing Sharpless asymmetric dihydrox-



ylation.[6] However, the above two methods of synthesizing chiral 2-isopropenyl-2,3-dihydrobenzofurans suffered from various drawbacks such as very low yield of the resolution step and low enantiomeric excess (ee) of the desired isomer. Very recently, Koning and co-workers achieved an efficient enantioselective synthesis of the 2-isopropenyl-2,3-dihydrobenzofuran skeleton of tremetone and hydroxytremetone from (*E*)-4-(2-hydroxyphenyl)-2-methyl-2-butenyl methyl carbonate and (*E*)-4-(2,6- dihydroxyphenyl)-2-methyl-2-butenyl methyl carbonate, respectively.[7] The key step was a catalytic palladium-mediated reaction in the presence of the chiral Trost ligand.

Among various 2-substituted 1-benzopyran derivatives, enantiomerically pure 2-hydroxymethyl chromans are important intermediates for the synthesis of numerous medicinally important 2-substituted chroman derivatives (Figure 2).[8-13]It is worth mentioning that biological activities of 2-substituted chromans are dependent on the absolute configuration of the stereogenic centre as illustrated in the development of repinotan **11** and sarizotan **12** as single enantiomer.

Figure 2. Medicinally important 2-substituted chroman derivatives.

A literature survey shows that enantiomerically pure 2-hydroxymethyl chromans can be synthesized from optically pure chroman-2-carboxylic acids,[14] which, in turn can be obtained *via* chemical[15] as well as enzymatic[16] resolution of the racemate for which facile syntheses[17] have been reported. However, we could find only two reported enantioselective routes to **9**. The first one involved the synthesis of 2-hydroxymethyl chromans from enantiomerically enriched 2-vinylchroman (*ee* up to 53%), which was synthesized from palladium-catalyzed cyclization of hydroxy allylic carbonate in the presence of various chiral ligands.[18] The second one described in an US patent involved Sharpless asymmetric dihydroxylation reaction of 4-aryl-1-butene derivatives furnishing 2-hydroxymethyl chromans of very low ee.[19]

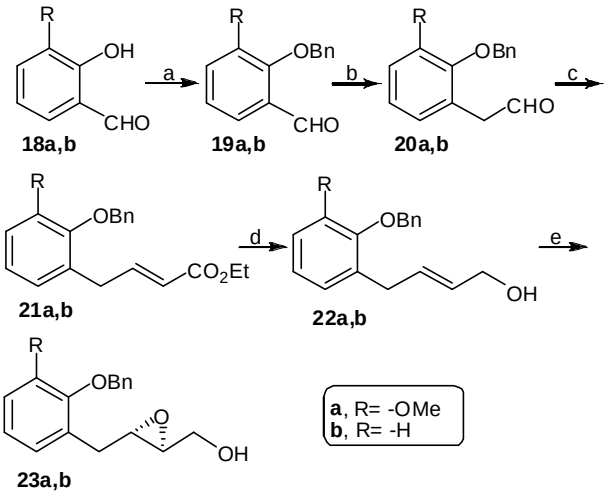
Taking into account of all these facts and our interest in the asymmetric synthesis of heterocycles,[20] we herein describe our results that illustrate efficient enantioselective synthetic routes to 2-isopropenyl-2,3-dihydrobenzofurans, 4-(2,3-dihydrobenzofuran-2-yl)-2-methylbut-3-en-2-ols, 2-hydroxymethyl chromans, and 4-chroman-2-yl-2-methylbut-3-en-2-ols through phenolate ion-mediated intramolecular ring opening of Sharpless asymmetric epoxidation-derived enantiomerically enriched epoxy alcohols.

Our envisioned retrosynthetic analysis for a general enantioselective synthetic strategy to 2-isopropenyl-2,3-dihydrobenzofuran **13** is depicted in Scheme 1. The double bond of the target molecule **13** was anticipated to be fashioned by a Wittig reaction of 2-acetyl-2,3-dihydrobenzofuran obtained from the oxidation of alcohol **14.** Compound **14** was expected to be accessible from dihydroxy compound **15.** Epoxide **16** was thought to be the key intermediate to provide diol **15** *via* a phenolate ion-mediated intramolecular 5-*exo-tet* epoxide ring opening reaction.[20c]

Scheme 1. Retrosynthetic analysis of 2-isopropenyl-2,3-dihydrobenzofurans.

Our model synthesis to obtain enantiopure 2-isopropenyl-2,3-dihydrobenzofurans commenced with the benzylation of commercially available 2-hydroxy-3-methoxybenzaldehyde **18a** and 2-hydroxybenzaldehyde **18b** with (bromomethyl)benzene and anhydrous K_2CO_3 in dry acetone under reflux condition furnishing 2-benzyloxybenzaldehydes **19a,b** in good yields (Scheme 2). Next, Wittig olefination of **19a,b** with methoxymethyl-triphenylphosphonium chloride and LHMDS in dry THF at 0^{o}C followed by hydrolysis of the resulting olefines with 1.5 (N) HCl in THF under reflux condition furnished corresponding one-carbon homologated aldehydes **20a,b**. Another Wittig olefination of aldehydes **20a,b** with [(ethoxycarbonyl)methylene]-triphenylphosphorane in dry CH_2Cl_2 at room temparature

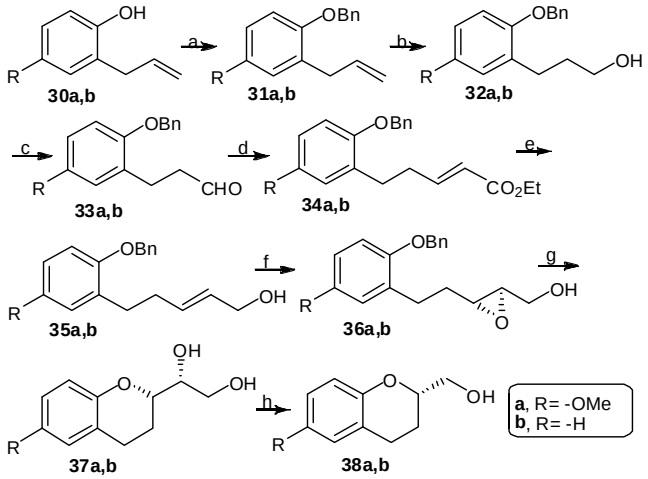
furnished the corresponding *trans*-unsaturated esters **21a,b** exclusively. Next, DIBAL-H reduction of **21a,b** in dry toluene at 0 °C gave *trans*-allylic alcohols **22a,b,** which were used for the subsequent Sharpless asymmetric epoxidation reaction.[21] Thus, **22a,b** were treated with titanium tetraisopropoxide and *tert*-butyl hydroperoxide in the presence of L-(+)-DIPT under asymmetric epoxidation conditions to get chiral epoxides **23a,b** in high yields (Scheme 2). The enantiomeric excess (ee) values of **23a,b** were determined to be 96% and 97%, respectively.[22]

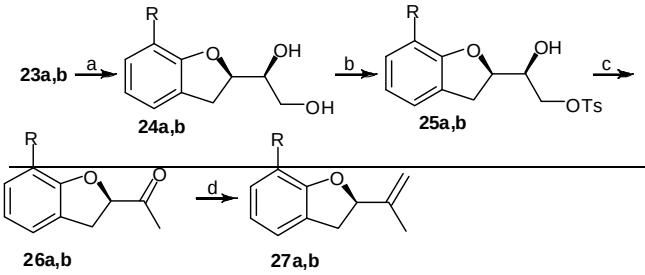


Scheme 2. Reagents and conditions: (a) BnBr, anhyd. K_2CO_3, dry acetone, reflux, 4 h, 1**9a** (85%), 1**9b** (85%). (b) (i) $CH_3OCH_2Ph_3P^+Cl^-$, LHDMS, dry THF, 0 °C-rt, 3 h. (ii) 1.5 (N) HCl, THF, reflux, 3 h, **20a** (70%), **20b** (71%); based on two steps. (c) $Ph_3P{=}CHCO_2Et$, dry CH_2Cl_2, rt, overnight, **21a** (81%), **21b** (75%). (d) DIBAL-H, dry toluene, 0 °C-rt, 2 h, **22a** (95%), **22b** (94%). (e) L-(+)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −25 °C, 18 h, **23a** (85%), **23b** (88%).

With **23a,b** in our hand, attention was then turned to their elaboration into the corresponding 2-isopropenyl-2,3-dihydrobenzofuran derivatives. Thus debenzylation of **23a,b** by means of 10% Pd-C catalyzed hydrogenolysis followed by treatment of the resulting phenolic derivatives with 10% NaOH solution saturated with NaCl furnished the corresponding dihydroxy compound **24a,b** *via* 5-*exo*-*tet* intramolecular epoxide ring opening. Next, selective tosylation of the primary hydroxyl group of **24a,b** gave monotosyloxy products **25a,b**.[23] $LiAlH_4$ mediated reductive removal of the tosyloxy functionality of **25a,b** followed by PDC oxidation of the resulting alcohols yielded 2-acetyl-2,3-dihydrobenzofuran derivatives **26a,b**. Finally, Wittig olefination of **26a,b** with methyl-triphenylphosphonium iodide and potassium *tert*-butanolate in dry THF gave 2-isopropenyl-2,3-dihydrobenzofuran derivatives **27a,b** (Scheme 3). The enantiomeric excess (ee) values of 27**a** and 27**b** were determined to be 94% and 96%, respectively.[24]

Scheme 3. Reagents and conditions: (a) (i) 10% Pd-C, ethyl acetate, H_2, 2 h. (ii) 10% NaOH solution saturated with NaCl, 0°C, 3 h, **24a** (80%), **24b** (78%); based on two steps. (b) TsCl, anhyd. Et_3N, dry CH_2Cl_2, 0 °C,overnight, **25a** (75 %), **25b** (77%). (c) (i) $LiAlH_4$, dry THF, 0 °C-rt, 3 h. (ii) PDC, dry CH_2Cl_2, 0 °C-rt, 24 h, **26a** (68%), **26b** (66%); based on the last two steps. (e) $CH_3Ph_3P^+I^-$, *t*-BuOK, dry THF, 0 °C-rt, 12 h, **27a** (78%), **27b** (75%).





After the enantioselective synthesis of 2-isopropenyl-2,3-dihydrobenzofurans, our next attention was to synthesize 4-(2,3-dihydrobenzofuran-2-yl)-2-methylbut-3-en-2-ols. This type of structural motif is the core structure of the revised structure of helliannuol G **8a** and helliannuol H **8b** (Figure 1).[25] Towards that objective, diols **24a,b** were cleaved with $NaIO_4$ in MeOH-H_2O furnishing the corresponding 2-formyl 2,3-dihydrobenzofurans which on treatment with [(ethoxycarbonyl)methylene]-triphenylphosphorane in dry CH_2Cl_2 at room temparature furnished the corresponding *trans*-unasaturated esters **28a,b** (Scheme 4). Next, treatment of the esters **28a,b** with an excess of methylmagnesium iodide furnished the tertiary alcohols **29a,b** in very high yields**.**

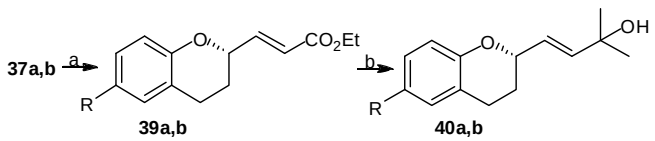
Scheme 4. Reagents and conditions: (a) (i) $NaIO_4$, MeOH-H_2O, 0 °C, 2 h. (ii) $Ph_3P{=}CHCO_2Et$, dry CH_2Cl_2, rt, overnight, **28a** (85%), **28b** (87%); based on two steps. (c) MeMgI, dry ether, 0 °C-reflux, 4 h, **29a** (94%), **29b** (93%); based on two steps.

Next, we became interested to synthesize enantiomerically pure 2-hydroxymethyl chromans applying a similar strategy. Towards that objective, known 5-methoxy-2-allylphenol[26] **30a** and commercially available 2-allylphenol **30b** were treated with (bromomethyl)benzene and anhydrous K_2CO_3 in dry acetone under reflux condition to get the corresponding benzylated products **31a,b** in excellent yields (Scheme 5). Next, hydroboration of **31a,b** with 9-BBN followed by oxidation with $NaOH/H_2O_2$ furnished the primary alcohols **32a,b** in high yields. PCC oxidation of **32a,b** followed by Wittig olefination of the resulting aldehydes **33a,b** furnished the corresponding *trans*-unasaturated esters **34a,b**. DIBAL-H reduction of **34a,b** gave *trans*-allyl alcohols **35a,b** . Next, **35a,b** were treated with titanium tetraisopropoxide and *tert*-butyl hydroperoxide in the presence of D-(-)-DIPT under asymmetric epoxidation conditions to get chiral epoxides **36a,b** in good yields. The enantiomeric excess (ee) values of **36a,b** were determined to be 98% and 97%, respectively.[22] Epoxides **36a,b** were then converted into diols **37a,b** as solid crystalline compounds by essentially following the same route as that described for the synthesis of **24a,b** from **23a,b**.[27] $NaIO_4$ mediated cleavage reaction of **37a,b** furnished the corresponding 2-formyl benzopyrans which were then reduced to their respective 2-hydroxymethyl chromans **38a,b**. The enantiomeric excess (ee) values of **38a,b** were determined to be >99%.[28]

Scheme 5. Reagents and conditions: (a) BnBr, anhyd. K_2CO_3, dry acetone, reflux, 4 h, **31a** (95%), **31b** (96%). (b) (i) 9-BBN, dry THF, rt, 4 h. (ii) 30% H_2O_2, NaOH, reflux, 2 h, **32a** (94%), **32b** (96%). (c) PCC, dry CH_2Cl_2, 0 °C–rt, 5 h, **33a** (76%), **33b** (72%). (d) $Ph_3P{=}CHCO_2Et$, dry CH_2Cl_2, rt, overnight, **34a** (80%), **34b** (77%). (e) DIBAL-H, dry toluene, 0 °C–rt, 4 h, **35a** (96%), **35b** (95%) (f) D(-)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −25 °C, 18 h, **36a** (88%), **36b** (90%). (g) (i) 10% Pd-C, ethyl acetate, H_2, 2 h. (ii) 10% NaOH solution saturated with NaCl, 0 °C, 3 h, **37a** (83%), **37b** (84%); based on two steps. (h) (i) $NaIO_4$, MeOH-H_2O, 0 °C, 2 h. (ii) $NaBH_4$, MeOH, 0 °C to rt, 0.5 h, **38a** (87%), **38b** (89%), based on two steps.

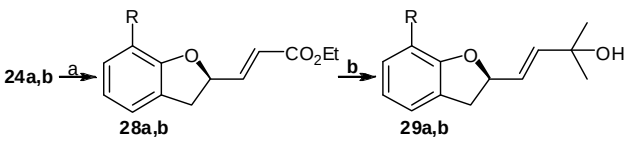
Next, we were interested to utilize diols **37a,b** for the synthesis of 1-benzopyran analogues of 2-(2,3-dihydrobenzofuran-2-yl)-2-methylbut-3-en-2-ols. Towards that direction, **37a,b** were converted into **40a,b** using the same reaction sequence as that described for the synthesis of **29a,b** from **24a,b** (Scheme 6)**.**

Scheme 6. Reagents and conditions: (a) (i) $NaIO_4$, MeOH-H_2O, 0 °C, 2 h. (ii) $Ph_3P{=}CHCO_2Et$, dry CH_2Cl_2, rt, overnight, **39a** (88%), **39b** (90%),



based on two steps. (c) MeMgI, dry ether, 0 °C-reflux, 4 h, **40a** (93%), **40b** (95%).

In conclusion, an efficient asymmetric synthesis of 2-isopropenyl-2,3-dihydrobenzofurans, 4-(2,3-dihydrobenzofuran-2-yl)-2-methylbut-3-en-2-ols, 2-hydroxymethyl chromans, and 4-chroman-2-yl-2-methyl-but-3-en-2-ols has been developed. Key steps include Sharpless asymmetric epoxidation reaction on suitable allyl alcohols



and construction of the 2,3-dihydrobenzofuran and 1-benzopyran nuclei by phenolate ion-mediated intramolecular

epoxide ring opening reactions. Further applications of these and related intermediates for the construction of biologically important molecules will be disclosed in due course.

All dry reactions were carried out under nitrogen in oven-dried glassware using standard gas-light syringes, cannulas, and septa. All reagents and solvents were dried prior to use according to the standard methods. Commercial reagents were used without further purification unless otherwise stated. Reactions were monitored on silica gel TLC plates (coated with TLC grade silica gel, obtained from Merck). Detecting agents used (for TLC) were iodine vapors and/or spraying with an aqueous solution of vanillin in 10% sulfuric acid followed by heating at 150 °C. Column chromatography was performed over silica gel (100-200 mesh) procured from Qualigens (India) using freshly distilled solvents. Mass spectra were recorded using electron spray ionization (ESI-MS) or Fast atom bombardment spectra (FAB-MS) on a JEOL SX 102 spectrometer using argon/xenon as the FAB gas. Elemental analyses were done on Varian EL-III C H N analyzer. Melting points were determined on COMPLAB melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR RXI spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Brucker DPX-200 (operating at 200 MHz for ^{1}H and 50 MHz for ^{13}C) or DPX-300 (operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometer using $CDCl_3$ or $CDCl_3$ plus CCl_4. Tetramethylsilane (0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. All spectra were recorded at 25°C. Coupling constants (*J* values) are given in Hertz (Hz). Chemical shifts were expressed in parts per million. Optical rotations were measured at the sodium D-line at ambient temperature, with a Perkin Elmer 141 polarimeter.

2-Benzyloxy-3-methoxybenzaldehyde (19a). To a solution of commercially available 2-hydroxy-3- methoxybenzaldehyde **18a** (6.00 g, 39.43 mmol) in dry acetone (100 mL) was added anhydrous K_2CO_3 (8.17 g, 59.14 mmol) and (bromomethyl)benzene (5.63 mL, 47.31 mmol) and the resulting mixture was then refluxed for 4 h. The mixture was then filtered through celite and the filter cake was washed with acetone (100 mL). The filtrate was concentrated and the resulting residue was redissolved in ethyl acetate (100 mL), washed with water (2x100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (6% ethyl acetate in *n*-hexane) afforded **15a** (8.12 g, 85%) as a colorless solid. M.p. 59-60^{o}C.

IR (KBr): 2929, 2363, 1687, 1586, 1479, 1371, 1257, 1070, 755 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 10.22 (s, 1H), 7.40-7.32 (m, 6H), 7.16-7.12 (m, 2H), 5.17 (s, 2H), 3.93 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 190.5, 153.3, 151.3, 136.6, 130.6, 129.0, 128.9, 128.8, 124.5, 119.3, 118.3, 76.6, 56.3.

MS (ESI): *m/z* 242 $[M]^+$, 91 $[C_6H_5CH_2]^+$.

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.43; H, 5.95.

The above physical and spectroscopic data were as consistent with as literature data.[29] Using the above procedure compound **19b** was prepared from **18b** in 85% yield and its physical and spectroscopic data were in full agreement with our previously reported data of the same compound.[20c]

2-[2-(benzyloxy)-3-methoxyphenyl]acetaldehyde (20a). To a stirring suspension of methoxymethyltriphenylphosphonium chloride (16.97 g, 49.52 mmol) in dry THF (60 mL) was added a solution of LiHMDS (1 M in THF, 50 mL, 50 mmol) dropwise under nitrogen atmosphere at 0 ^{o}C. The resulting red solution was stirred at this temperature for 45 min, at which point compound **19a** (6.00 g, 24.76 mmol) in THF (30 mL) was added dropwise over 15 min. The reaction mixture was allowed to stirr at room temperature for 2 h, at which point saturated aq. NH_4Cl (50 mL) was added. The resulting mixture was extracted with diethyl ether (3×50 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to give a yellow oil. The resulting oil was loaded on a small pad of silica gel and eluted with diethyl ether to remove the baseline impurities. The crude product thus obtained was used for the next step without further purification.

A solution of the above crude product in THF (60 mL) and 1.5 *N* HCl (25 mL) was refluxed for 3 h. The reaction mixture was then diluted with water (50 mL) and extracted with ether (2×100 mL). The combined organic layer was washed with aqueous $NaHCO_3$ solution and brine, and dried over $MgSO_4$. Evaporation of the solvent and purification of the residue over a silica gel column using 6% ethyl acetate in *n*-hexane as eluent furnished aldehyde **20a** as a colorless oil (4.76 g, 70%).

IR (Neat): 3019, 2360, 1722, 1588, 1476, 1270, 1215, 1082, 759 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 9.51 (t, 1H, J = 2.0), 7.40-7.27 (m, 5H), 7.06-6.98 (m, 1H), 6.87 (dd, 1H, J_1 = 1.6, J_2 = 8.2), 6.69 (dd, 1H, J_1 = 1.4, J_2 = 8.2), 5.00 (s, 2H), 3.85 (s, 3H), 3.52 (d, 2H, J = 2.0).

^{13}C NMR (50 MHz, $CDCl_3$): δ 199.4, 152.7, 145.9, 137.2, 128.2, 128.1, 127.8, 126.6, 124.1, 122.6, 111.8, 74.3, 55.5, 45.0.

MS (ESI): *m/z* 256 $[M]^+$.

Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.85; H, 6.42.

Using the above procedure compound **20b** was also prepared from compound **19b** in 71% yield and its physical and spectroscopic data were in full agreement with our previously reported data of the same compound.[20c]

(*E*)-ethyl 4-[2-(benzyloxy)-3-methoxyphenyl]but-2-enoate (21a). To a solution of **20a** (4.00 g, 15.6 mmol) in dry CH_2Cl_2 (40 mL) was added [(ethoxycarbonyl)methylene]-triphenylphosphorane (7.06 g, 20.28 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (4% ethyl acetate in *n*-hexane) to afford **21a** (4.10 g, 81%) as a colorless oil.

IR (KBr): 3019, 2361, 1709, 1475, 1271, 1216, 1082, 756, 669 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 7.43-7.27 (m, 5H), 7.04-6.95 (m, 2H), 6.83 (dd, 1H, J_1 = 1.2, J_2 = 8.1), 6.71 (dd, 1H, J_1 = 1.2, J_2 = 7.6), 5.70 (td, 1H, J_1 = 1.5, J_2 = 15.6), 4.99 (s, 2H), 4.13 (q, 2H, J = 7.1), 3.91 (s, 3H), 3.43 (dd, 2H, J_1 = 1.4, J_2 = 6.6), 1.23 (t, 2H, J = 7.1).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 152.8, 147.2, 145.7, 137.6, 131.8, 128.3, 128.0, 127.8, 124.0, 122.0, 111.0, 74.6, 60.0, 55.6, 32.5, 14.1.

MS (FAB): *m/z* 327 $[M+1]^+$, 281 $[M\text{-}OEt]^+$.

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.67; H, 6.92.

Using the above procedure compound **21b** was also prepared from **20b** in 75% yield and its physical and spectroscopic data were in full agreement with our previously reported data of the same compund.[20c]

***(E)*-4-[2-(benzyloxy)-3-methoxyphenyl]but-2-en-1-ol (22a).** To an ice-cooled stirred solution of **21a** (3.50 g, 10.72 mmol) in dry toluene (30 mL) was added DIBAL-H (1 M in toluene, 27 mL, 27 mmol)) dropwise under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h, cooled to 0 °C, carefully quenched with methanol (5 mL) and a saturated aq. sodium potassium tartarate solution (25 mL). The resulting mixture was vigorously stirred for 45 min. at rt and then extracted with ethyl acetate (2x50 mL), washed with water (50 mL) and brine (100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (20% ethyl acetate in *n*-hexane) afforded **22a** (2.90 g, 95%) as a colorless gum.

IR (KBr): 3421, 3017, 2361, 1638, 1474, 1272, 1216, 1081, 759 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): 7.42-7.28 (m, 5H), 7.01-6.93 (m, 1H), 6.81-6.68 (m, 2H), 5.74-5.65 (m, 1H), 5.59-5.50 (m, 1H), 4.97 (s, 2H), 3.99 (d, 2H, J = 5.6), 3.86 (s, 3H), 3.29 (d, 2H, J = 6.3).

^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 152.9, 145.9, 138.1, 134.2, 131.2, 130.2, 128.5, 128.3, 128.0, 127.8, 123.9, 121.2, 110.8, 74.6, 63.5, 55.8, 32.8.

MS (ESI): *m/z* 302 $[M+NH_4]^+$, 267 $[M\text{-}OH]^+$.

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.15; H, 7.21.

(*E*)-4-[2-(benzyloxy)phenyl]but-2-en-1-ol (22b). Using 3.50 g (11.8 mmol) of **21b**, the title compound was prepared in the same manner as that described for **22a**. Purification of the crude product by silica gel column chromatography (18% ethyl acetate in *n*-hexane) afforded **22b** (2.82 g, 94%) as a colorless gum.

IR (Neat): 3385, 3032, 2921, 2863, 1597, 1493, 1452, 1240, 1010, 974, 750, 697 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ 7.44-7.33 (m, 5H), 7.17-7.13 (m, 2H), 6.94-6.87 (m, 2H), 5.84-5.80 (m, 1H), 5.72-5.67 (m, 1H) ,5.07 (s, 2H), 4.07 (d, 2H, J = 5.6), 3.43 (d, 2H, J = 6.6).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 137.2, 131.1, 129.94, 129.91, 128.8, 128.4, 127.7, 127.4, 127.1, 120.8, 111.7, 69.8, 63.6, 33.0.

MS (ESI): *m/z* 237 $[M\text{-}OH]^+$, 272 $[M+NH_4]^+$.

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.21; H, 7.26.

[(2*S*,3*S*)-3-(2-(benzyloxy)-3-methoxybenzyl]oxiran-2-yl)methanol (23a). To a cooled (−25 °C) suspension of activated and powdered 4 Å MS (2.00 g) in dry CH_2Cl_2 (30 mL) were added L-(+)-DIPT (1.80 mL, 10.55 mmol) and $Ti(O^iPr)_4$ (2.87 mL, 9.67 mmol). The resulting mixture was then stirred for 20 min at the same temperature and then TBHP (5.6 M in n-decane, 4.7 mL, 26.37 mmol) was added dropwise. After 20 min, a solution of **22a** (2.50 g, 8.79 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise over 15 min. The resulting mixture was kept at -25 °C freeze for 18 h. The reaction mixture was allowed to warm to 0 °C and poured into a freshly prepared and cooled (0 °C) solution of ferrous sulfate and tartaric acid (2.50 g and 1.00 g, respectively) in deionised water (20 mL). The two-phase mixture was stirred for 30 min, aqueous phase separated and extracted with CH_2Cl_2. The combined organic phases were treated with a pre-cooled (0 °C) solution of 30% NaOH (20 mL) in saturated brine. The two-phase mixture was then stirred for 1 h at room temperature and the aqueous layer separated. It was extracted with CH_2Cl_2 (2x30 mL), washed with brine (30 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated under re-

duced pressure. Purification of the crude product by silica gel column chromatography (30% ethyl acetate in n-hexane) afforded **23a** (2.24 g, 85%) as a colorless oil. $[\alpha]^{25}_{D}$: -12.37 (*c* 2.6, $CHCl_3$).

IR (Neat): 3020, 2360, 1730, 1474, 1216, 760, 670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.32 (m, 5H), 7.04-6.99 (m, 1H), 6.87-6.82 (m, 2H), 5.10-4.9 (m, 2H), 3.90 (s, 3H), 3.77 (d,1H, J = 12.5), 3.50 (d, 1H, J = 11.4), 3.07- 3.03 (m, 1H), 2.92-2.76 (m, 3H), 2.17 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 152.7, 146.0, 137.8, 131.2, 128.3, 127.9, 124.0, 122.4, 111.2, 74.6, 61.6, 58.5, 55.7, 55.5, 32.2.

MS (ESI): *m/z* 301 $[M+1]^+$, 318 $[M+NH_4]^+$.

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.17; H, 6.68.

[(2*S*,3*S*)-3-(2-(benzyloxy)benzyl)oxiran-2-yl]methanol (23b). Using 2.50 g (9.83 mmol) of **22b**, the title compound was prepared in the same manner as that described for **23a**. Purification of the crude product by silica gel column chromatography (30% ethyl acetate in *n*-hexane) afforded **23b** (2.34 g, 88%) as a colorless oil. $[\alpha]^{25}_{D}$: -1.7 (*c* 2.2, $CHCl_3$).

IR (Neat): 3434, 3019, 2926, 1495, 1216, 1020, 760, 669 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43-7.30 (m, 5H), 7.24-7.17 (m, 2H), 6.94-6.87 (m, 2H), 5.05 (s, 2H), 3.85-3.74 (m, 1H), 3.59-3.48 (m, 1H), 3.22-3.17 (m, 1H), 2.99-2.89 (m, 3 H), 2.15 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 137.1, 130.7, 128.67, 128.62, 128.1, 128.0, 127.4, 127.3, 125.7, 120.9, 111.7, 70.0, 61.6, 58.7, 55.2, 32.6.

MS (ESI): *m/z* 271 $[M+1]^+$, 288 $[M+NH_4]^+$.

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.47; H, 6.88.

(*R*)-1-[(*S*)-7-methoxy-2,3-dihydrobenzofuran-2-yl]ethane-1,2-diol (24a). To a stirred solution of **23a** (2.00 g, 6.65 mmol) in ethyl acetate (30 mL) was added 10% Pd-C (250 mg). After stirring for 2 h at room temperature under pressure of a hydrogen balloon, the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to get the corresponding debenzylated product as a colorless solid which was used for the next step without further purification.

To an ice-cooled stirred solution of the above debenzylated product in CH_2Cl_2 (20 mL), was added a pre-cooled (0 °C) solution of 30% NaOH (20 mL) in saturated brine. The two-phase mixture was then stirred for 3 h at room temperature and the aqueous layer separated. It was extracted with CH_2Cl_2 (2x30 mL), washed with brine (30 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (35% ethyl acetate in *n*-hexane) afforded **24a** (1.12 g, 80%) as a colorless crystalline solid. M.p.: 102-103 0^oC. $[\alpha]^{25}_{D}$: -7.4 (*c* 1.07, MeOH).

IR (KBr): 3408, 3020, 2360, 1710,1215, 761, 670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84-6.80 (m, 2H), 6.75-6.70 (m, 1H), 4.84-4.76 (m, 1H), 4.04-3.99 (m, 1H), 3.84 (s, 3H), 3.79-3.68 (m, 2H), 3.33-3.12 (m, 2H), 3.00 (s, 1H), 2.63 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 147.2, 144.2, 127.8, 121.3, 117.2, 110.8, 83.6, 72.7, 63.1, 55.8, 31.2.

MS (ESI): *m/z* 211 $[M+1]^+$, 228 $[M+NH_4]^+$.

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.95; H, 6.55.

***(R)*-1-[(*S*)-2,3-dihydrobenzofuran-2-yl]ethane-1,2-diol (24b).** Using 2.00 g (7.39 mmol) of **23b**, the title compound was prepared in the same manner as that described for **24a**. Purification of the crude product by silica gel column chromatography (35% ethyl acetate in *n*-hexane) afforded **24b** (1.04 g, 78%) as a colorless crystalline solid. M.p.: 55-56 0^oC. $[\alpha]^{25}_{D}$ -6.68 (*c* 0.49, MeOH).

IR (KBr): 3430, 3021, 2924, 1216, 1020, 760, 669 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26-7.07 (m, 2H), 6.89-6.75 (m, 2H), 4.83-4.72 (m, 1H), 3.99-3.92 (m, 1H), 3.88-3.79 (m, 2H), 3.25 (d, 2H, J = 8.6), 2.38 (s, br, 1H), 2.04 (s, br, 1H).

^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 159.1, 128.0, 126.4, 125.1, 120.8, 109.3, 82.7, 73.0, 63.3, 31.3.

MS (ESI): *m/z* 181 $[M+1]^+$, 198 $[M+NH_4]^+$.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.79; H, 6.51.

***(R)*-2-hydroxy-2-[(*S*)-7-methoxy-2,3-dihydrobenzofuran-2-yl]ethyl 4-methylbenzenesulfonate (25a).** To a solution of diol **24a** (1.00 g, 4.75 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C was added dry triethyl amine (1.16 mL, 8.31 mmol) followed by tosyl chloride (0.91 g, 4.75 mmol) and kept in the refrigerator for overnight. The reaction mixture was diluted with H_2O, and extracted with CH_2Cl_2 (2x30 mL). The combined organic layers were washed with water (25 mL), brine (25 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pres-

sure and purification of the crude product by silica gel column chromatography (20% ethyl acetate in *n*-hexane) afforded **25a** (1.30 g, 75%) as a colorless solid. M.p.: 108-110 ^{o}C. $[\alpha]^{25}_{D}$: -1.9 (*c* 2.58, MeOH).

IR (KBr): 3493, 2363, 1593, 1490, 1192, 1088, 809 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, 2H, *J* = 8.4), 7.34 (d, 2H, *J* = 8.1), 6.84-6.70 (m, 3H), 4.86-4.69 (m, 1H), 4.30-3.95 (m, 3H), 3.81 (s, 3H), 3.30-3.14 (m, 2H), 2.71-2.65 (m, 1H), 2.44 (s, 3H).

MS (ESI): *m/z* 382 $[M+NH_4]^+$, 387 $[M+Na]^+$.

Anal. Calcd for $C_{18}H_{20}O_6S$: C, 59.33; H, 5.53. Found: C, 59.42; H, 5.71.

(*R*)-2-[(*S*)-2,3-dihydrobenzofuran-2-yl]-2-hydroxyethyl 4-methylbenzenesulfonate (25b). Using 1.00 g (5.55 mmol) of **24b**, the title compound was prepared in the same manner as that described for **25a**. Purification of the crude product by silica gel column chromatography (20% ethyl acetate in *n*-hexane) afforded **25b** (1.43 g, 77%) as a colorless semi-solid. $[\alpha]^{25}_{D}$: -7.66 (*c* 0.95, EtOH).

IR (KBr): 3429, 2921, 1635, 1474, 1357, 1175, 757 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.81 (d, 2H, *J* = 8.3), 7.35 (d, 2H, *J* = 8.1), 7.17-7.05 (m, 2H), 6.88-6.80 (m, 1H), 6.70 (d, 2H, *J* = 7.9), 4.70-4.62 (m, 1H), 4.33-4.26 (m, 1H), 4.19-4.11 (m, 1H), 3.97-3.95 (m, 1H), 3.22 (d, 2H, *J* = 8.2), 2.45 (s, 3H).

MS (ESI): *m/z* 352 $[M+NH_4]^+$, 357 $[M+Na]^+$.

Anal. Calcd for $C_{17}H_{18}O_5S$: C, 61.06; H, 5.43. Found: C, 61.23; H, 5.28.

(*R*)-1-(7-methoxy-2,3-dihydrobenzofuran-2-yl)ethanone (26a). To an ice-cooled suspension of $LiAlH_4$ (0.26 g, 6.85 mmol) in dry THF (10 mL) was added a solution of **25a** (1.00 g, 2.74 mmol) in dry THF (15 mL) dropwise and the resulting mixture was stirred for 3h at rt. It was quenched by dropwise addition of ethyl acetate (5 mL) at 0°C and water (20 mL). The mixture was extracted with ethyl acetate (2x30 mL), washed with brine (25 mL), The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure to obtain a colorless gum which was used for the next step without further purification.

To an ice-cooled stirring solution of the above crude product in dry CH_2Cl_2 (30 mL), was added PDC (2.78 g, 7.38 mmol). The mixture was then stirred for 24 h at room temperature. After evaporating dichloromethane the reaction mixture was diluted with diethyl ether (50 mL) and filtered through a small pad of silica gel. Concentration of the filtrate and purification of the residue by silica gel column chromatography (10% ethyl acetate in *n*-hexane) afforded **26a** (0.37 g, 68%) as a colorless semi-solid. $[\alpha]^{25}_{D}$: +4.7 (*c* 1.0, $CHCl_3$).

IR (KBr): 3021, 2360, 1719, 1493, 1289, 1215, 1086, 760, 670 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.91-6.75 (m, 3H), 5.13-5.04 (m, 1H), 3.90 (s, 3H), 3.57-3.26 (m, 2H), 2.33 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 208.5, 147.1, 144.5, 126.3, 121.9, 116.9, 111.5, 86.1, 56.0, 33.1, 26.0.

MS (ESI): *m/z* 210 $[M+NH_4]^+$.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.85; H, 6.37.

(*S*)-1-(2,3-dihydrobenzofuran-2-yl)ethanone (26b). Using 1.00 g (2.99 mmol) of **25b**, the title compound was prepared in the same manner as that described for **26a**. Purification of the crude product by silica gel column chromatography (10% ethyl acetate in *n*-hexane) afforded **26b** (0.35 g, 66%) as a light yellow gum. $[\alpha]^{25}_{D}$: +3.7 (*c* 3.2, $CHCl_3$).

IR (KBr): 3021, 2927, 2361, 1729, 1217, 1045, 761, 670 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20-7.12 (m, 2H), 6.93-6.86 (m, 2H), 5.08-4.99 (m, 1H), 3.48-3.31 (m, 2H), 2.29 (s, 3H).

MS (ESI): *m/z* 180 $[M+NH_4]^+$.

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.22; H, 6.31.

(*R*)-7-methoxy-2-(prop-1-en-2-yl)-2,3-dihydrobenzofuran (27a). To a suspension of methyltriphenylphosphonium iodide (1.88 g, 4.65 mmol) in dry THF (15 mL) under a nitrogen atmosphere at 0 °C was added *t*-BuOK (0.52 g, 4.65 mmol). The reaction mixture was stirred for 15 min at 0 °C and was then warmed to rt while stirring was continued for 45 min. The solution was then recooled to 0 °C, and a solution of ketone **22a** (0.30 g, 1.55 mmol) in dry THF (10 mL) was added dropwise. The reaction mixture was then warmed to rt and stirred for an additional 12 h. The reaction was quenched with saturated aq. NH_4Cl solution (10 mL) and extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (4% ethyl acetate in *n*-hexane) to give alkene **27a** (0.23 g, 78%) as a colorless oil. $[\alpha]^{25}_{D}$: +12.9 (c 0.79, EtOH).

IR (Neat): 3020, 2928, 2361, 1490, 1287, 1216, 1087, 761, 669 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83-6.72 (m, 3H), 5.29-5.19 (m, 1H), 5.10 (s, 1H), 4.91 (s, 1H), 3.87 (s, 3H), 3.37-3.29 (m, 1H), 3.12-3.03 (m, 1H), 1.78 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 148.1, 144.3, 143.6, 127.8, 120.8, 117.0, 112.4, 111.3, 86.5, 56.0, 35.1, 17.1.

MS (ESI): *m/z* 190 $[M]^+$, 208 $[M+NH_4]^+$.

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.83; H, 7.31.

(*R*)-2-(prop-1-en-2-yl)-2,3-dihydrobenzofuran (27b). Using 0.30 g (1.85 mmol) of **26b**, the title compound was prepared in the same manner as that described for **27a**. Purification of the crude product by silica gel column chromatography (4% ethyl acetate in *n*-hexane) afforded **27b** (0.22 g, 75%) as a colorless oil.[26] $[\alpha]^{25}_D$: +10.6 (*c* 1.0, EtOH), (literature[30] $[\alpha]^{25}_D$: +10.9, EtOH).

IR (KBr): 3020, 2927, 2360, 1216, 1045, 761, 670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16-7.08 (m, 2H), 6.85-6.78 (m, 2H), 5.16 (1H, t, J = 8.9), 5.09 (1H, s), 4.91 (1H, s), 3.37-3.29 (m, 2H), 3.08-3.00 (m, 2H), 1.77 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 144.0, 128.0, 126.5, 124.7, 120.3, 111.9, 109.2, 85.6, 34.7, 17.2.

MS (ESI): *m/z* 160 $[M]^+$, 178 $[M+NH_4]^+$.

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.22; H, 6.31.

The above physical and spectroscopic data were as consistent with as literature data.[7]

(*R*,*E*)-ethyl 3-(7-methoxy-2,3-dihydrobenzofuran-2-yl)acrylate (28a). To a stirred solution of diol **24a** (100 mg, 0.47 mmol) in methanol (5 mL) at 0°C was added a solution of $NaIO_4$ (152 mg, 0.71 mmol) in water (2 mL). After stirring the reaction mixture at 0°C for 2 h, methanol was evaporated in vacuo at low temperature. The aqueous solution was extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the crude aldehyde as a colorless gum which was used for the next step without further purification.

To a solution of the above crude aldehyde in dry CH_2Cl_2 (5mL) was added [(ethoxycarbonyl)methylene]-triphenylphosphorane (235 mg, 0.67 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (4% ethyl acetate in *n*-hexane) to afford **28a** (99 mg, 85%) as a colorless gum. $[\alpha]^{25}_D$: +18.08 (*c* 0.62, MeOH).

IR (Neat): 3020, 2935, 2361, 1715, 1492, 1273, 1216, 1087, 759 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.94 (dd, 1H, J_1 = 5.2, J_2 = 15.6), 6.75-6.66 (m, 3H), 6.06 (dd, 1H, J_1 = 1.4, J_2 = 15.6), 5.36-5.28 (m, 1H), 4.12 (q, J = 7.1), 3.81 (s, 3H), 3.44-3.36 (m, 1H), 3.03-2.95 (m, 1H), 1.22 (t, J = 7.1).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 147.3, 145.3, 144.5, 126.5, 121.5, 121.4, 117.0, 111.7, 81.0, 60.3, 55.8, 35.9, 14.1.

MS (ESI): *m/z* 266 $[M+NH_4]^+$.

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.85; H, 6.63.

(*R*,*E*)-ethyl 3-(2,3-dihydrobenzofuran-2-yl)acrylate (28b). Using 100 mg (0.55 mmol) of **24b**, the title compound was prepared in the same manner as that described for **28a**. Purification of the crude product by silica gel column chromatography (4% ethyl acetate in *n*-hexane) afforded **28b** (104 mg, 87%) as a colorless gum. $[\alpha]^{25}_D$: +18.08 (*c* 1.46, MeOH).

IR (Neat): 3021, 2929, 2361, 1726, 1475, 1216, 1087, 761 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15-7.10 (m, 2H), 7.01 (dd, 1H, J_1 = 5.0, J_2 = 15.6), 6.88-6.80 (m, 2H), 6.12 (dd, 1H, J_1 = 0.8, J_2 = 15.6), 5.38-5.31 (m, 1H), 4.20 (q, J = 7.1), 3.51-3.43 (m, 1H), 3.08-3.00 (m, 1H), 1.31 (t, J = 7.1).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 159.1, 145.7, 128.3, 125.2, 124.8, 121.4, 120.8, 109.6, 80.4, 60.4, 35.6, 14.2.

MS (ESI): *m/z* 236 $[M+NH_4]^+$.

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.68; H, 6.37.

(*R*,*E*)-4-(7-methoxy-2,3-dihydrobenzofuran-2-yl)-2-methylbut-3-en-2-ol (29a). To a freshly prepared, magnetically stirred, ice-cold suspension of methylmagnesium iodide [prepared from iodomethane (0.28 mL, 3.5 mmol) and magnesium (0.085 g, 3.5 mmol) in 10 mL of dry diethyl ether] was added a solution of ester **15a** (75 mg, 0.30 mmol) in dry THF (5 mL). The reaction mixture was refluxed for 4 h, cooled, and quenched with aqueous NH_4Cl solution (10 mL). The mixture was extracted with ethyl acetate (2x25 mL), washed with water (25 mL) and brine (25 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (12% ethyl acetate in *n*-hexane) afforded **29a** (0.07 mg, 94%) as a colorless gum. $[\alpha]^{25}_D$: -2.08 (*c* 0.75, MeOH).

IR (Neat): 3021, 2361, 1593, 1216, 763 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 6.77-6.66 (m, 3H), 5.93-5.75 (m, 2H), 5.21-5.13 (m, 1H), 3.79 (s, 3H), 3.33-3.25 (m, 1H), 2.99-2.9 (m, 1H), 1.26 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 147.6, 144.4, 141.2, 127.8, 125.8, 121.0, 117.0, 111.0, 83.9, 70.5, 55.8, 36.6, 29.6. MS (ESI): *m/z* 217 $[M\text{-}OH]^+$, 233 $[M\text{-}1]^+$.

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found C, 71.90; H, 7.67.

***(R,E)*-4-(2,3-dihydrobenzofuran-2-yl)-2-methylbut-3-en-2-ol (29b).** Using 75 mg (0.34 mmol) of **28b**, the title compound was prepared in the same manner as that described for **29a**. Purification of the crude product by silica gel column chromatography (12% ethyl acetate in *n*-hexane) afforded **28b** (65 mg, 93%) as a light yellow gum. $[\alpha]^{25}_D$: -7.72 (*c* 0.6, MeOH).

IR (Neat): 3430, 3019, 2361, 1729, 1478, 1219, 761 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ 7.15-7.08 (m, 2H), 6.86-6.76 (m, 2H), 6.01-5.83 (m, 2H), 5.23-5.15 (m, 1H), 3.41-3.33 (m, 1H), 3.04-2.96 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 159.3, 140.9, 128.1, 126.4, 126.2, 124.8, 120.5, 109.4, 82.9, 70.5, 36.3, 29.8.

MS (ESI): *m/z* 287 $[M\text{-}OH]^+$, 203 $[M\text{-}1]^+$.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.63; H, 7.99.

3-Allyl-4-benzyloxyanisole (31a). To a solution of **30a** (4.00 g, 24.36 mmol) in dry acetone (50 mL) was added anhydrous K_2CO_3 (5.0 g, 36.17 mmol) and (bromomethyl)benzene (2.9 mL, 24.36 mmol) and refluxed for 4 h. The mixture was then filtered through celite and the filter cake was well washed with acetone (100 mL). The filtrate was concentrated and the resulting residue was redissolved in ethyl acetate (100 mL), washed with water (2x50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated under vacuo. Purification of the crude product by silica gel column chromatography (2% ethyl acetate in *n*-hexane) afforded **31a** (5.88 g, 95%) as a colorless oil.

IR (Neat): 2924, 2362, 1639, 1495, 1558, 1216, 1043, 731, 693 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ 7.40-7.29 (m, 5H), 6.84-6.66 (m, 3H), 6.01-5.92 (m, 1H), 5.09 (m, 2H), 5.00 (s, 2H), 3.73 (s, 3H), 3.42 (d, 2H, J = 6.5).

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.2, 151.0, 138,0, 137.2, 130.8, 128.9, 128.1, 127.6, 116.5, 116.2, 113.5, 111.7, 78.1, 71.2, 56.0, 35.0.

MS (ESI): *m/z* 254 $[M]^+$, 91 $[C_6H_5CH_2]^+$.

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.35; H, 7.32.

Using the above procedure compound **31b** was prepared from **30b** in 96% yield and its physical and spectroscopic data were in full agreement with our previously reported data of the same compound.[20c]

3-[2-(benzyloxy)-5-methoxyphenyl]propan-1-ol (32a). To a stirred solution of **31a** (4.00 g, 15.72 mmol) in anhydrous THF (30 mL) was added a 0.5 M THF solution of 9-BBN (47 mL) dropwise under a nitrogen atmosphere at 0 °C and the mixture was stirred at room temperature for 4 h. H_2O (5 mL) was added followed by 3 N NaOH solution (40 mL) and 30% aqueous hydrogen peroxide solution (30 mL). The reaction mixture was stirred for 2 h at 60 °C. The mixture was extracted with ethyl acetate (2x50 mL), washed with water (150 mL) and brine (150 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

Purification of the crude product by silica gel column chromatography (8% ethyl acetate in *n*-hexane) afforded alcohol **32a** (4.02 g, 94%) as a colorless gum. R_f: 0.32 (20% ethyl acetate in n-hexane).

IR (Neat): 3431, 2929, 2361, 1497, 1214, 1042, 756, 698 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ 7.44-7.34 (m, 5H), 7.85 (d, 1H, J = 8.7), 6.76-6.66 (m, 2H), 5.02 (s, 2H), 3.75 (s, 3H), 3.57 (t, 2H, J = 6.3), 2.74 (t, 2H, J = 7.2), 1.88-1.70 (m, 2H), 1.77 (s, br, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.3, 151.3, 137.7, 132.3, 129.0, 128.3, 127.7, 116.8, 113.5, 111.6, 71.5, 62.1, 56.0, 33.4, 26.7.

MS (ESI): *m/z* 272 $[M]^+$, 255 $[M\text{-}OH]^+$, 91 $[C_6H_5CH_2]^+$.

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, C, 74.88; H, 7.58.

Using the above procedure compound **32b** was prepared from **31b** in 96% yield and its physical and spectroscopic data were in full agreement with our previously reported data of the same compound.[20c]

3-[2-(benzyloxy)-5-methoxyphenyl]propanal (33a). To a stirred solution of **32a** (3.00 g, 11.01 mmol) in dry CH_2Cl_2 (50 mL) was added 4 Å molecular sieve (3.85 g) and PCC (3.20 g, 14.84 mmol) at 0 °C and the mixture was stirred at room temperature for 5 h. After evaporating CH_2Cl_2 the reaction mixture was diluted with ether (50 mL)

and filtered through a small pad of silica gel. Concentration of the filtrate and purification of the residue by silica gel column chromatography (4% ethyl acetate in *n*-hexane) afforded **36a** (2.26 g, 76%) as a colorless gum.

^{1}H NMR (200 MHz, $CDCl_3$): δ 9.69 (t, 1H, *J* = 1.5), 7.36-7.29 (m, 5H), 6.81-6.64 (m, 3H), 4.96 (s, 2H), 3.68 (s, 3H), 2.93 (t, 2H, *J* = 7.3), 2.70-2.63 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 202.5, 154.2, 151.1, 137.8, 130.8, 129.0, 128.3, 127.6, 117.4, 113.3, 112.3, 71.0, 56.0, 44.3, 24.0.

MS (FAB): *m/z* 270 $[M]^{+\cdot}$.

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.63; H, 6.88.

Using the above procedure compound **33b** was prepared from **32b** in 72% yield and its physical and spectroscopic data were in full agreement with our previously reported data of the same compound.[20c]

(*E*)-ethyl 5-[2-(benzyloxy)-5-methoxyphenyl]pent-2-enoate (34a). To a solution of **33a** (2.00 g, 7.39 mmol) in dry CH_2Cl_2 (30 mL) was added [(ethoxycarbonyl]methylene)triphenylphosphorane (3.21 g, 9.21 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (4% ethyl acetate in *n*-hexane) to afford **34a** (2.01 g, 80%) as a colorless gum.

IR (KBr): 2926, 2359, 1708, 1649, 1496, 1211, 1035, 736 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.37-7.22 (m, 5H), 7.04-6.94 (m, 1H), 6.77-6.60 (m, 3H), 5.79 (d, 1H, *J* = 15.6), 4.93 (s, 2H), 4.14-4.07 (m, 2H), 3.65 (s, 3H), 2.77-2.72 (m, 2H), 2.48-2.41 (m, 2H), 1.20 (t, 3H, *J* = 7.1).

^{13}C NMR (75 MHz, $CDCl_3$): *δ* 166.1, 153.4, 150.3, 148.1, 137.2, 130.5, 128.1, 127.3, 126.7, 121.2, 115.9, 112.4, 110.9, 70.1, 59.6, 55.0, 32.1, 28.8, 13.9.

MS (FAB): *m/z* 340 $[M]^+$.

Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.21; H, 7.03.

Using the above procedure compound **34b** was prepared from **33b** in 77% yield and its physical and spectroscopic data were in full agreement with our previously reported data of the same compound.[20c]

(*E*)-5[2-(benzyloxy)-5-methoxyphenyl]pent-2-en-1-ol (35a). Starting from 2.00 g (5.87 mmol) of **34a**, the title compound was prepared in the same manner as that described for **22a**. Purification of the crude product by silica gel column chromatography (20% ethyl acetate in n-hexane) afforded **35a** (1.68 g, 96%) as a colorless semi-solid.

IR (Neat): 3417, 2930, 2361, 1499, 1217, 1043, 754 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): *δ δ* 7.42-7.27 (m, 5H), 6.81 (d, 1H, *J* = 8.8), 6.73 (d, 1H, *J* = 3.0), 6.66 (dd, 1H, J_1 = 3.1, J_2 = 8.7), 5.78-5.55 (m, 2H), 5.01 (s, 2H), 4.04 (d, 2H, *J* = 5.5), 3.74 (s, 3H), 2.75-2.70 (m, 2H), 2.35 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): *δ* 153.6, 150.8, 137.6, 132.6, 131.8, 129.3, 128.4, 127.6, 127.0, 116.3, 112.8, 110.9, 70.6, 63.6, 55.5, 32.4, 30.2.

MS (ESI): *m/z* 316.1 $[M+NH_4]^+$.

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.35; H, 7.68.

(*E*)-5-[2-(benzyloxy)phenyl]pent-2-en-1-ol (35b). Starting from 2.00 g (6.44 mmol) of **34b**, the title compound was prepared in the same manner as that described for **22a**. Purification of the crude product by silica gel column chromatography (20% ethyl acetate in *n*-hexane) afforded **35b** (1.64 g, 95%) as a colorless gum.

IR (Neat): 3417, 2930, 2361, 1499, 1217, 1043, 754, 697 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): *δ* 7.42-7.35 (m, 5H), 7.29-7.13 (m, 2H), 6.91(d, 2H, *J* = 6.0), 5.75-5.58 (m, 2H), 5.08 (s, 2H), 4.05 (d, 2H, *J* = 5.0), 2.77 (t, 2H, *J* =7.2), 2.43-2.42 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): *δ* 157.0, 137.9, 133.3, 130.9, 129.7, 128.9, 128.2, 127.5, 127.4, 121.1, 112.0, 70.2, 64.1, 32.8, 30.6.

MS (ESI): *m/z* 268 $[M]^+$.

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.59; H, 7.45.

{(2*R*,3*R*)-3-[2-(benzyloxy)-5-methoxyphenethyl]oxiran-2-yl}methanol (36a). Starting from 1.50 g (5.02 mmol) of **35a**, the title compound was prepared in the same manner as that described for **23a**. Purification of the crude product by silica gel column chromatography (30% ethyl acetate in *n*-hexane) afforded **36a** (1.39 g, 88%) as a colorless gum. $[\alpha]^{25}_D$: +15.2 (*c* 1.9, $CHCl_3$).

IR (Neat): 3425, 2926, 1621, 1500, 1219, 1042, 745, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.28 (m, 5H), 6.83 (d, 1H, J = 8.8), 6.75 (d, 1H, J = 3.0), 6.68 (dd, 1H, J_1= 3.1, J_2 = 8.8), 5.01 (s, 2H), 3.79-3.78 (m, 1H), 3.75 (s, 3H), 3.55-3.48 (m, 1H), 2.98-2.94 (m, 1H), 2.87-2.70 (m, 3H), 1.99-1.72 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 153.0, 148.4, 139.7, 126.2, 121.9, 117.2, 113.8, 113.2, 75.3, 70.3, 55.3, 29.6, 29.5, 27.8, 24.5.

MS (ESI): *m/z* 315 $[M+1]^+$, 332 $[M+NH_4]^+$.

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.71; H, 7.11.

{(2*R*,3*R*)-3-[2-(benzyloxy)phenethyl]oxiran-2-yl}methanol (36b). Starting from 1.50 g (5.59 mmol) of **35b**, the title compound was prepared in the same manner as that described for **23a**. Purification of the crude product by silica gel column chromatography (30% ethyl acetate in *n*-hexane) afforded **36b** (1.43 g, 90%) as a colorless gum. $[\alpha]^{25}_D$: +24.7 (*c* 1.54, $CHCl_3$).

IR (Neat): 3434, 2927, 1598, 1495, 1240, 1023, 752 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.29 (m, 5H), 7.20-7.15 (m, 2H), 6.92-6.87 (m, 2H), 5.07 (s, 2H), 3.79-3.75 (m, 1H), 3.55-3.47 (m, 1H), 2.98-2.74 (m, 4H), 2.00-1.78 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.5, 137.2, 130.0, 129.8, 128.5, 127.8, 127.4, 127.1, 120.8, 111.7, 69.9, 61.7, 58.6, 55.7, 31.7, 26.9.

MS (ESI): *m/z* 285 $[M+1]^+$, 302 $[M+NH_4]^+$.

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.19; H, 7.16.

(*R*)-1-[(*S*)-6-methoxychroman-2-yl]ethane-1,2-diol (37a). Starting from 1.25 g (3.97 mmol) of **36a**, the title compound was prepared in the same manner as that described for **24a**. Purification of the crude product by silica gel column chromatography (40% ethyl acetate in *n*-hexane) afforded **37a** (0.74 g, 83%) as a colorless solid. M.p.: 87-88 ^oC. $[\alpha]^{25}_D$: +16.56 (*c* 0.56, MeOH).

IR (KBr): 3397, 2924, 2360, 1496, 1219, 1041, 761 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.72 (d, 1H, J = 8.8), 6.65 (dd, 1H, J_1= 2.7, J_2 = 8.8), 6.59 (d, 1H, J = 2.5), 4.01-3.96 (m, 1H), 3.88-3.84 (m, 3H), 3.74 (s, 3H), 2.90-2.71 (m, 3H), 2.34-2.29 (m, 1H), 2.14-2.07 (m, 1H), 1.91-1.77 (m, 2H).

MS (ESI): *m/z* 285 $[M+1]^+$, 302 $[M+NH_4]^+$.

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.19; H, 7.32.

(*R*)-1-[(*S*)-chroman-2-yl]ethane-1,2-diol (37b). Starting from 1.25 g (4.39 mmol) of **36b**, the title compound was prepared in the same manner as that described for **24a**. Purification of the crude product by silica gel column chromatography (40% ethyl acetate in *n*-hexane) afforded **37b** (0.71 g, 84%) as a colorless solid. M.p.: 63-64 ^oC. $[\alpha]^{25}_D$: +26.28 (*c* 0.76, MeOH).

IR (KBr): 3385, 3020, 2361, 1586, 1216, 761 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12-7.05 (m, 2H), 6.89-6.79 (m, 2H), 4.08-4.03 (m, 1H), 3.92-3.84 (m, 3H), 2.88-2.81 (m, 3H), 2.55 (s, br, 2H), 2.18-2.12 (m, 1H), 1.92-1.85 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 152.9, 128.3, 126.0, 120.8, 119.2, 115.3, 75.1, 72.0, 62.1, 23.0, 22.0.

MS (ESI): *m/z* 285 $[M+1]^+$, 302 $[M+NH_4]^+$.

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.16; H, 7.29.

(*S*)-(6-methoxychroman-2-yl)methanol (38a). To a stirred solution of diol **37a** (250 mg, 1.11 mmol) in methanol (8 mL) at 0°C was added a solution of $NaIO_4$ (380 mg, 1.77 mmol) in water (4 mL). After stirring the reaction mixture at 0°C for 2 h, methanol was evaporated in vacuo at low temperature. The aqueous solution was extracted with CH_2Cl_2 (2x10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude aldehyde as a colorless gum which was used for the next step without further purification.

To an ice-cooled solution of the above crude aldehyde in methanol (6 mL) was added $NaBH_4$ (50 mg, 1.31 mmol) and the reaction mixture was stirred for 30 min at rt. Methanol was removed under reduced pressure and the residue was dissolved in ethyl acetate (15 mL) and water (15 mL). The organic layer was separated and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (20% ethyl acetate in *n*-hexane) afforded **38a** (18 mg, 87%) as a colorless gum. $[\alpha]_D^{20}$: +104.8 (*c* 1.5, $CHCl_3$).

IR (Neat): 3397, 2924, 2360, 1496, 1219, 1041, 761 cm^{-1}.

^{1}H NMR($CDCl_3$, 300 MHz) δ 6.76 (d, 1H, J = 8.8), 6.65 (dd, 1H, J_1= 2.9, J_2 = 8.8), 6.60 (d, 1H, J = 2.8), 4.10–4.02 (m, 1H), 3.87-3.66 (m, 5H), 2.94-2.70 (m, 2H), 2.10 (br, s, 1H), 1.97–1.76 (m, 2H).

^{13}C NMR (75 MHz): δ 153.4, 148.4, 122.4, 117.2, 114.0, 113.3, 76.2, 65.6, 55.7, 24.7, 23.7.

MS (ESI): *m/z* 194 $[M]^+$.

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.11; H, 7.35.

(*S*)-chroman-2-ylmethanol (38b). Starting from 250 mg (1.28 mmol) of **37b**, the title compound was prepared in the same manner as that described for **38a**. Purification of the crude product by silica gel column chromatography (20% ethyl acetate in *n*-hexane) afforded **38b** (188 mg, 89%) as a colorless gum. $[\alpha]_D^{20}$: +110.6 (*c* 1.55, MeOH), (literature[31] $[\alpha]^{25}_D$: +113.4, *c* 1.1, MeOH).

IR (Neat): 3422, 2933, 1651, 1430, 1054, 706 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.14–7.07 (m, 2H), 6.90–6.84 (m, 2H), 4.18–4.11 (m, 1H), 3.89-3.76 (m, 2H), 2.92-2.81 (m, 2H), 2.02 (br, s, 1H), 1.98–1.86 (m, 2H).

^{13}C NMR (75 MHz): δ 153.2, 128.3, 126.0, 120.6, 119.2, 115.4, 75.1, 64.3, 23.2, 22.4.

MS (ESI): *m/z* 164 $[M]^+$.

Anal. calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.27; H, 7.48.

The above spectral data agreed with literature data.[31]

(*S,E*)-ethyl 3-(6-methoxychroman-2-yl)acrylate (39a). Starting from 0.10 g (0.44 mmol) of **37a**, the title compound was prepared in the same manner as that described for **28a**. Purification of the crude product by silica gel column chromatography (4% ethyl acetate in *n*-hexane) afforded **39a** (0.10 g, 88%) as a colorless gum. $[\alpha]^{25}_D$: +5.4 (*c* 1.21, MeOH).

IR (Neat): 3020, 2400, 1708, 1496, 1426, 1216, 761, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98 (dd, 1H, J_1= 4.1, J_2 = 15.7), 6.78 (d, 1H, J = 8.9), 6.67 (dd, 1H, J_1= 2.8, J_2 = 8.9), 6.56 (d, 1H, J = 2.7), 6.14 (dd, 1H, J_1= 1.7, J_2 = 15.7), 4.69-4.64 (m, 1H), 4.21 (q, 2H, J = 7.1), 3.74 (s, 3H), 2.91-2.69 (m, 2H), 2.16-2.07 (m, 1H), 1.91-1.78 (m, 1H), 1.31 (q, 3H, J = 7.1).

^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 166.0, 153.5, 147.9, 146.1, 121.7, 121.4, 117.3, 113.8, 113.5, 73.7, 60.3, 55.4, 27.0, 24.3, 14.2.

MS (ESI): *m/z* 280 $[M+NH_4]^+$.

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.83; H, 6.88.

(*S,E*)-ethyl 3-(chroman-2-yl)acrylate (39b). Starting from 0.10 g (0.51 mmol) of **41b**, the title compound was prepared in the same manner as that described for **28a**. Purification of the crude product by silica gel column chromatography (4% ethyl acetate in *n*-hexane) afforded **39b** (0.11 g, 90%) as a colorless gum. $[\alpha]^{25}_D$: -17.8 (*c* 1.46, MeOH).

IR (Neat): 3020, 2361, 1713, 1480, 1217, 763, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12-6.96 (m, 3H), 6.86-6.82 (m, 2H), 6.15 (dd, 1H, J_1= 1.8, J_2 = 15.7), 4.75-4.69 (m, 1H), 4.20 (q, 2H, J = 7.2), 2.90-2.70 (m, 2H), 2.17-2.08 (m, 1H), 1.90-1.78 (m, 1H), 1.29 (q, 3H, J = 7.1).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 153.8, 146.0, 129.4, 127.4, 121.4, 120.5, 116.7, 73.8, 60.4, 26.9, 23.9, 14.1.

MS (ESI): *m/z* 250 $[M+NH_4]^+$.

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.53; H, 6.85.

(*S,E*)-4-(6-methoxychroman-2-yl)-2-methylbut-3-en-2-ol (40a). Starting from 75 mg (0.28 mmol) of **39a**, the title compound was prepared in the same manner as that described for **29a**. Purification of the crude product by silica gel column chromatography (18% ethyl acetate in *n*-hexane) afforded **40a** (66 mg, 93%) as a colorless gum. $[\alpha]^{25}_D$: +13.91 (*c* 1.75, MeOH).

IR (Neat): 3413, 3019, 2361, 1713, 1496, 1216, 758, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.75 (d, 1H, J = 8.9), 6.64 (dd, 1H, J_1= 2.8, J_2 = 8.9), 6.55 (d, 1H, J = 2.8), 5.94 (dd, 1H, J_1= 0.9, J_2 = 15.7), 5.77 (dd, 1H, J_1= 5.8, J_2 = 15.7), 4.46-4.41 (m, 1H), 3.72 (s, 3H), 2.88-2.64 (m, 2H), 2.29 (s, br, 1H), 2.04-1.95 (m, 1H), 1.85-1.72 (m, 1H), 1.34 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 153.0, 148.4, 139.7, 126.2, 121.9, 117.2, 113.8, 113.2, 75.3, 70.3, 55.3, 29.6, 29.5, 27.8, 24.5.

MS (ESI): *m/z* 231 $[M-OH]^+$, 247 $[M-1]^+$.

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.43; H, 8.18.

(*S,E*)-4-(chroman-2-yl)-2-methylbut-3-en-2-ol (40b). Starting from 75 mg (0.32 mmol) of **39b**, the title compound was prepared in the same manner as that described for **29a**. Purification of the crude product by silica gel column chromatography (18% ethyl acetate in n-hexane) afforded **40b** (67 mg, 95%) as a colorless gum. $[\alpha]^{25}_{D}$: +7.5 (*c* 0.4, $CHCl_3$).

IR (Neat): 3410, 3019, 2361, 1713, 1586, 1216, 760 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 7.10-7.01 (m, 2H), 6.84-6.82 (m, 2H), 5.97 (d, 1H, J = 15.8), 5.81 (dd, 1H, J_1= 5.8, J_2 = 15.7), 4.55-4.49 (m, 1H), 2.91-2.70 (m, 2H), 2.08-1.99 (m, 1H), 1.89-1.76 (m, 1H), 1.67 (s, br, 1H), 1.34 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.4, 139.9, 129.4, 127.2, 126.2, 121.7, 120.1, 116.7, 75.6, 70.55, 29.3, 29.6, 27.9, 24.3.

MS (ESI): *m/z* 201 $[M\text{-}OH]^+$, 217 $[M\text{-}1]^+$.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.19; H, 8.47.

Acknowledgment

This research project was supported by Department of Science and Technology (SR/S1/OC-23/2005) and Indian Council of Medical Research (ICMR) New Delhi, India. S. K. Dinda and S. K. Das thank the CSIR, New Delhi for providing fellowships.

References

[#] CDRI communication number 7184.

(1) For selected recent examples of 2,3-dihydrobenzofuran containing natural and unnatural molecules, see: (a) Chu, G.-H.; Gu, M. H.; Cassel, J. A.; Belanger, S.; Graczyk, T. M.; DeHaven, R. N.; Conway-James, N.; Koblish, M.; Little, P. J.; DeHaven-Hudkins, D. L.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5114. (b) Shi, G. Q.; Dropinski, J. F.; Zhang, Y.; Santini, C.; Sahoo, S. P.; Berger, J. P.; MacNaul, K. L.; Zhou, G.; Agrawal, A.; Alvaro, R.; Cai, T.-q.; Hernandez, M.; Wright, S. D.; Moller, D. E.; Heck, J. V.; Meinke, P. T. *J. Med. Chem.* **2005**, *48*, 5589. (c) Yang, X.-W.; Zhao, P.-J.; Ma, Y.-L.; Xiao, H.-T.; Zuo, Y.-Q.; He, H.-P.; Li, L.; Hao, X.-J. *J. Nat. Prod.* **2007**, *70*, 521. (d) Xu, F.; Zhang, Y.; Wang, J.; Pang, J.; Huang, C.; Wu, X.; She, Z.; Vrijmoed, L. L. P.; Jones, E. B. G.; Lin, Y. *J. Nat. Prod.* **2008**, *71*, 1251.

(2) For selected recent examples of 1-benzopyran containing natural and unnatural molecules, see: (a) Wang, Y.; Mo, S.-Y.; Wang, S.-J.; Li, S.; Yang, Y.-C.; Shi, J.-G. *Org. Lett.* **2005**, *7*, 1675. (b) Rukachaisirikul, V.; Tadpetch, K.; Watthanaphanit, A.; Saengsanae, N.; Phongpaichit, S. *J. Nat. Prod.* **2005**, *68*, 1218. (c) Breschi, M. C.; Calderone, V.; Martelli, A.; Minutolo, F.; Rapposelli, S.; Testai, L.; Tonelli, F.; Balsamo, A. *J. Med. Chem.*; **2006**; *49*, 7600. (d) Frederick, R.; Robert, S.; Charlier, C.; Wouters, J.; Masereel, B.; Pochet, L. *J. Med. Chem.*; **2007**, 50, 3645. (e) Richardson, T. I.; Norman, B. H.; Lugar, C. W.; Jones, S. A.; Wang, Y.; Durbin, J. D.; Krishnan, V.; Dodge, J. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3570.

(3) For the enantioselective synthesis of 2,3-dihydrobenzofurans, see: (a) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887. (b) Li, X.; Branum, S.; Russell, R. K.; Jiang, W.; Sui, Z. *Org. Process Res. Dev*. **2005**, *9*, 640. (c) Sun, L.-Q.; Chen, J.; Takaki, K.; Johnson, G.; Iben, L.; Mahle, C. D.; Ryan, E.; Xu, C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1197. (d) Kurosawa, W.; Kobayashi, H.; Kan, T.; Fukuyama, T. *Tetrahedron* **2004**, *60*, 9615. (e) Silveira, G. P. C.; Coelho, F. *Tetrahedron Lett.* **2005**, 46, 6477.

(4) For the recent examples of enantioselective synthesis of 1-benzopyrans, see: (a) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P. *J. Am. Chem. Soc.* **2003**, *125*, 9276. (b) Pitsinos, E. N.; Cruz, A. *Org. Lett.* **2005**, *7*, 2245. (c) Tian, X.; Rychnovsky, S. D. *Org. Lett*. **2007**, *9*, 4955. (d) Pitsinos, E. N.; Moutsos, V. I.; Vageli, O. *Tetrahedron Lett.* **2007**, 48, 1523. (e) Fukamizu, K.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2008**, 130, 10498.

(5) (a) Bowen, D. M.; DeGraw, J. I., Jr.; Shah, V. R.; Bonner, W. A. *J. Med. Chem.* **1963**, *6*, 315. (b) Banskota, A. H.; Tezuka, Y.; Prasain, J. K.; Matsushige, K.; Saiki, I.; Kadota, S. *J. Nat. Prod.* **1998**, *61*, 896. (c) Bittner, M.; Jakupovic, J.; Bohlmann, F.; Silva, M. *Phytochemistry* **1989**, *28*, 2867. (d) Bohlmann, F.; Jakupovic, J.; Schuster, A.; King, R.; Robinson, H. *Phytochemistry* **1982**, *21*, 161. (d) Cespedes, C. L.; Uchoa, A.; Salazar, J. R.; Perich, F.; Pardo, F. *J. Agric. Food Chem.* **2002**, *50*, 2283. (e) Singer, T. P.; Ramsay, R. R. *Biochim. Biophys. Acta*: *Bioenergetics* **1994**, *1187*, 198. (f) Haley, T. J. *J. Environ. Pathol. Toxicol.* **1978**, *1*, 315. (g) Cockerill, G. S.; Levett, P. C.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1103. (h) Habib, A. M.; Ho, D. K.; Masuda, S.; McCloud, T.; Reddy, K. S.; Aboushoer, M.; McKenzie, A.; Byrn, S. R.; Chang, C.-J.; Cassady, J. M. *J. Org. Chem.* **1987**, *52*, 412. (i)

(6) Yamaguchi, S.; Muro, S.; Kobayashi, M.; Miyazawa, M.; Hirai, Y. *J. Org. Chem.* **2003**, *68*, 6274.

(7) Pelly, S. C.; Govender, S.; Fernandes, M. A.; Schmalz, H.-G.; de Koning, C. B. *J. Org. Chem.* **2007**, *72*, 2857.

(8) Heine, H.-G.; Schohe-Loop, R.; Glaser, T.; De Vry, J. M. V.; Dompert, Wo.; Sommermeyer, H. U.S. Patent 5371094, **1994.**.

(9) Jacobsen, E. J.; vanDoornik, F. J.; Ayer, D. E.; Belonga, K. L.; Braughler, J. M.; Hall, E. D.; Houser. D. J.; *J. Med. Chem.* **1992**, *35*, 4464.

(10) (a) Mewshaw, R. E.; Kavanagh, J.; Stack, G.; Marquis, K. L.; Shi, X.; Kagan, M. Z.; Webb, M. B.; Katz, A. H.; Park, A.; Kang, Y. H.; Abou-Gharbia, M.; Scerni, R.; Wasik, T.; Cortes-Burgos, L.; Spangler, T.; Brennan, J. A.; Piesla, M.; Mazandarani, H.; Cockett, M. I.; Ochalski, R.; Coupet, J.; Andree. T. H. *J. Med. Chem.* **1997**, *40,* 4235. (b) Mewshaw, R. E.; Zhao, R.; Shi, X.; Marquis, K.; Brennan, J. A.; Mazandarani, H.; Coupet, J.; Andree, T. H. *Bioorg. Med. Chem. Lett.* **2002**, *12***,** 271.

(11) De Vry, J.; Schohe-Loop, R.; Heine, H.-G.;. Greuel, J. M.; Mauler, F.; Schmidt, B.; Sommermeyer, H.; Glaser. T. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 1082.

(12) Lutsep. H. L. *Curr. Opinion Invest. Drugs*, **2002**, *3*, 924.

(13) McIntyre, J. A.; Castaner, J.; Bayes, M. *Drugs Fut.* **2006**, *31*, 314.

(14) Palucki, M.; Yasuda, N. *Tetrahedron Lett***. 2005**, *46*, 987.

(15) Schaaf, T. K.; Johnson, M. R.; Constantine, J.W.; Bindra, J. S.; Hess, H.-J.; Elger. W. *J. Med. Chem.* **1983**, *26,* 328.

(16) Urban, F. J.; Moore, B. S. *J. Heterocycl. Chem.* **1992**, *29*, 431.
(17) (a) Augstein, J.; Monro, A. M.; Potter, G. W. H.; Scholfield, P. *J. Med. Chem.* **1968**, *11*, 844. (b) Witiak, D. T.; Stratford, E. S.; Nazareth, R.; Wagner, G.; Feller, D. R. *J. Med. Chem.* **1971**, *14*, 758.
(18) Labrosse, J.-R.; Poncet, C.; Lhoste, P.; Sinou, D. *Tetrahedron: Asymmetry* **1999**, *10*, 1069.
(19) Stack, G. P.; Gross, J. L. U.S. Patent 264947, **2004.**
(20) (a) Das, S. K.; Dinda, S. K.; Panda, G. *Euro. J. Org. Chem*. **2009**, 204. (b) Srivastava, A. K.; Panda, G. *Chem. Eur. J.* **2008**, *14*, 4675. (c) Das, S. K.; Panda, G. *Tetrahedron* **2008**, *64*, 4162. (d) Mishra, J. K.; Panda, G. *J. Comb. Chem.* **2007**, *9*, 321. (e) Mishra, J. K.; Garg, P.; Dohare, P.; Kumar, A.; Siddiqi, M. I.; Ray, M.; Panda, G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1326. (f) Mishra, J. K.; Panda, G. *Synthesis* **2005**, 1881.
(21) (a) Katsuki, T.; Sharplesss, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Pfenninger, A. *Synthesis* **1986**, 89. (c) Baker, S. R.; Boot, J. R.; Morgan, S. E.; Osborne, D. T.; Ross, W. J.; Shrubsall, P. R. *Tetrahedron Lett.* **1983**, *24*, 4469.
(22) The enantiomeric excess (ee) values were determined by converting the epoxy alcohols into their Mosher's ester derivatives and analyzing the ^{1}H NMR spectra of the corresponding Mosher esters.
(23) In the tosylation reaction of **24a,b** formation of minor amount of the corresponding ditosylated products was also observed and these undesired products were eliminated by column chromatography.
(24) The enantiomeric excess (ee) values of **27a,b** were determined by chiral HPLC analysis.
(25) Morimoto, S.; Shindo, M.; Yoshida, M.; Shishido, K. *Tetrahedron Lett.* **2006**, *47*, 7353.
(26) Darling, S. D.; Wills, K. D. *J. Org. Chem.* **1967**, *32*, 2794.
(27) Chandrasekhar, S.; Reddy, M. V. *Tetrahedron* **2000**, *56*, 6339.
(28) The enantiomeric excess (ee) values of **38a,b** were determined by chiral HPLC analysis (Chiral Cel OD, petroleum ether/*i*-PrOH (98:2) 1 mL/min, 254 mm.
(29) Lin, C.-F.; Yang, J.-S.; Chang, C.-Y.; Kuo, S.-C.; Lee, M.-R.; Huang, L.-J. *Bioorg. Med. Chem.* **2005**, *13*, 1537.
(30) Kawase, Y.; Yamaguchi, S.; Inoue, O.; Sannomiya, M.; Kawabe, K. *Chem. Lett.* **1980**, 1981.
(31) Urban, F. I.; Moore, B. S. *J. Heterocycl. Chem*. **1992**, *29*, 431.

Application of phenolate ion-mediated intramolecular epoxide ring opening in the enantioselective synthesis of functionalized 2,3-dihydrobenzofuran and 1-benzopyran derivatives

Subal Kumar Dinda, Sajal Kumar Das, and Gautam Panda*