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Titanocene(III) chloride mediated radical induced addition-elimination route to the synthesis of racemic and optically active trisubstituted tetrahydrofurans: Formal synthesis of magnofargesin and 7′-epimagnofargesin

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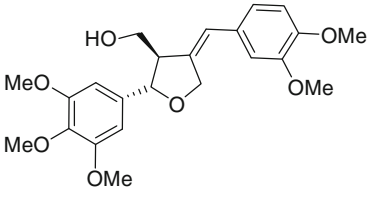
Abstract. Titanocene(III) Chloride mediated radical induced synthesis of 4-benzylidene substituted tetrahydrofuran, a typical lignan skeleton, has been accomplished in good yield through addition-elimination route in racemic as well as in optically active forms. The method has been applied to the synthesis of furano lignans, magnofargesin (**1**) and 7′-epimagnofargesin (**2**) in optically active forms.

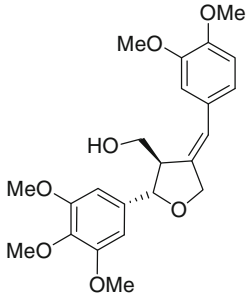
Keywords. Titanocene(III) chloride; radical; tetrahydrofurans; synthesis; furano lignans.

1. Introduction

Radical induced addition-elimination process has been used as a tool for the synthesis of bioactive natural products due to mild and simple reaction conditions along with a vast substrate tolerance. The early report[1] by Kharasch *et al*., has further been developed[2] by Heiba and Dessau describing an unexpected cascade radical cyclization initiated by intermolecular addition of carbon-centered trichloromethyl radical to alkynes. Interestingly, Baldwin *et al*., synthesized[3] the cyclopentanoid isonitrile, the core skeleton of antibiotic metabolites of fungi in the genus *trichoderma*, *via* a novel radical addition-elimination method. Harris and Weiler[4] prepared stereospecific exocyclic alkene by a consecutive radical cyclization-elimination process in 1987. In the same year, Pattenden and his group developed[5] a cobalt-mediated addition-elimination protocol for the synthesis of carbon-carbon double bond. Baichi and Bosch[6] used the identical protocol for the synthesis of bicyclic β-lactams. Naito *et al*., successfully applied the addition-elimination process for asymmetric synthesis of (-)-α-Kainic acid[7a] and a concise formal synthesis of (–)-martinellic acid.[7b] Some strained functionalized alkylidene-cyclobutanes[8a] and fused spirocyclic imines[8b] were also prepared using this technique. Banwell used this technique as a key step for the synthesis of aromatic erythrina alkaloids[9a] and chemoenzymatic approach towards the total synthesis of (+)-Brunsvigine.[9b] Such a useful technique in the field of radical chemistry has neither been cultivated nor used extensively[10] by using titanocene(III) species as a radical initiator specially for the synthesis of natural products.[11a,b] Herein, we depict a novel methodology for the synthesis of benzylidene substituted tetrahydrofurans using Cp_2TiCl induced radical based addition-elimination strategy that has been implemented to the total synthesis of two furano lignans, magnofargesin (**1**) and its isomer 7′-epimagnofargesin (**2**).[11c] The radical initiator titanocene(III) chloride (Cp_2TiCl) was prepared from commercially available Cp_2TiCl_2 and Zn dust in THF under argon atmosphere.[12]



Magnofargesin (**1**)



7'-Epimagnofargesin (**2**)

*For correspondence

2. Experimental

^{1}H NMR were recorded in $CDCl_3$ on 300, 400 and 500 MHz and ^{13}C NMR were recorded on 75, 100 and 125 MHz spectrometer respectively using TMS as an internal standard. IR spectra were recorded on a Shimadzu FTIR-8300 instrument. High-resolution mass spectra (HRMS) were obtained using a Qtof Micro YA263 instrument. Ethyl acetate was dried over anhydrous calcium chloride. Petroleum ether of boiling range 60-80°C and diethyl ether were dried over sodium. Silica gel of 60-120 mesh was used for column chromatography. THF used for radical cyclisation was super dried by distilling twice with sodium. DCM solvent was used after freshly distilling over P_2O_5. All the reactions were carried out either in argon or nitrogen atmosphere with oven-dried glass apparatus. Most of the compounds described are already reported in the literature and are characterized by NMR, IR and MASS spectral studies and have been compared with authentic samples.

Allylic alcohols **4a-g**[13] and the epoxides **5a-g**[14c,15–17] were prepared following the standard literature procedures.

2.1 *Preparation of the epoxy ether **6a***

To a stirred suspension of NaH (53 mg, 50% dispersion, 1.1 mmol) in dry THF (1 mL) was added dropwise a solution of epoxy alcohol **5a** (75 mg, 0.50 mmol) in dry THF (5 mL) at 0°C under nitrogen. After the liberation of hydrogen gas ceased (approx. 25 min), a solution of dibromo compound **12** (166 mg, 0.60 mmol) in dry THF (7.5 mL) was added dropwise at 0°C over 10 min. The reaction mixture was stirred at RT for 3h and then carefully quenched with ice water. After removal of most of the solvent under reduced pressure, the resulting residue was extracted with diethyl ether (4 × 25 mL). The combined ether extract was successively washed with water (2 × 10 mL) and brine (1 × 10 mL) and finally dried (Na_2SO_4). Solvent was removed under reduced pressure and the crude mass obtained was purified by column chromatography over silica gel to furnish *2-(-2-bromo-3-phenylallyloxy)(phenyl)methyl)oxirane* (**6a**, 146 mg, 85%) as a viscous liquid and as an inseparable mixture of two isomers in approx. 3:1 ratio. IR (Neat): 3058, 2854, 1598, 1490, 1257, 1068, 756, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66 (dd, J = 2.4, 4.8 Hz, 0.75H), 2.75-2.83 (m, 1.25H), 3.23-3.24 (m, 0.25H), 3.27-3.30 (m, 0.75H), 4.21-4.52 (complex multiplets, 2.75H), 4.64 (d, J = 4.4 Hz, 0.25H), 7.29-7.43 (m, 10H (aromatic hydrogens) + 1H (olefinic hydrogen); ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.3, 45.2, 54.2, 55.0, 55.2, 57.1, 79.4, 81.9, 84.8, 84.9, 86.5, 86.7, 122.6, 122.7, 127.2, 127.4, 127.7, 128.2, 128.3, 128.5, 128.6, 128.8, 129.1, 131.8, 137.4; HRMS: calcd. for $C_{18}H_{17}BrO_2$ $[M+Na]^+$ 367.0304; found: 367.0300.

Compounds **6b-6g** were prepared following the similar procedure used for the preparation of **6a**.

2.2 *2-(-2-Bromo-3-phenylallyloxy)(4-chlorophenyl) methyl)oxirane (**6b**)*

Viscous liquid as an inseparable mixture of two isomers in approx. 1.5:1 ratio. Yield 88%. IR (Neat): 3055, 1596, 1488, 1257, 1078, 1014, 756, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62-2.65 (m, 0.60H), 2.72-2.78 (m, 1H), 2.81-2.84 (m, 0.40H), 3.18-3.26 (m, 1H), 4.20-4.52 (complex multiplets, 2.60H), 4.60 (d, J = 6 Hz, 0.40H), 7.28-7.44 (m, 9H (aromatic hydrogens) + 1H (olefinic hydrogen); ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.28, 45.3, 54.0, 54.8, 57.2, 57.3, 78.9, 81.0, 84.5, 84.6, 86.8, 87.0, 122.5, 122.6, 128.4, 128.6, 128.8, 128.9, 129.0, 129.1, 131.8, 131.9, 134.5, 135.9; HRMS: calcd. for $C_{18}H_{16}BrClO_2$ $[M+Na]^+$ 400.9914; found, 400.9912.

2.3 *2-(-2-Bromo-3-phenylallyloxy)(p-tolyl)methyl) oxirane (**6c**)*

Viscous liquid as an inseparable mixture of two isomers in approx. 2:1 ratio. Yield 84%. IR (Neat): 2921, 1514, 1490, 1263, 1076, 756, 692 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (2s merged, 3H), 2.63-2.65 (m, 0.67H), 2.74-2.82 (m, 1.33H), 3.21-3.23 (m, 0.33H), 3.26-3.29 (m, 0.67H), 4.14-4.48 (complex multiplets, 2.67H), 4.61 (d, J = 4.5Hz, 0.33H), 7.10-7.63 (m, 9H (aromatic hydrogens) + 1H (olefinic hydrogen); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 44.4, 44.5, 45.1, 74.4, 74.6, 79.7, 82.5, 121.9, 127.2, 127.4, 127.6, 127.8, 128.2, 128.3, 128.4, 128.5, 128.6, 129.1, 129.2, 129.3, 129.4, 129.5, 131.9, 134.6, 135.2, 138.5; HRMS: calcd. for $C_{19}H_{19}BrO_2$ $[M + Na]^+$ 381.0466; found, 381.0465.

2.4 *2-(-2-Bromo-3-phenylallyloxy)(4-methoxyphenyl) methyl)oxirane (**6d**)*

Viscous liquid as an inseparable mixture of two isomers in approx. 1:1 ratio. Yield 85%. IR (Neat): 2997, 1610, 1512, 1249, 1074, 757, 692 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.63 (dd, J = 2.5, 5.0 Hz, 0.50H), 2.74-2.76 (m, 1H), 2.82 (dd, J = 4.0, 5.0 Hz 0.50H), 3.22-3.24 (m, 0.50H), 3.26-3.28 (m, 0.50H), 3.81 (s, 3H), 4.18-4.48 (complex multiplets, 2.50H), 4.60 (d, J = 4.0 Hz, 0.50H), 6.92 (d, J = 8.0 Hz, 2H), 7.29-7.34 (m, 6H), 7.41-7.43 (m, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 44.3, 45.2, 54.1, 55.0, 55.3, 56.7, 56.8, 78.9, 81.4, 84.9, 85.0, 86.4, 86.6, 113.7, 114.0, 114.1, 122.6, 122.7, 128.3, 128.4, 128.5, 128.7, 129.1, 129.2, 129.3, 131.8, 159.9; HRMS: calcd. for $C_{19}H_{19}BrO_3$ $[M+Na]^+$ 397.0415; found: 397.0417.

2.5 *2-(-2-Bromo-3-phenylallyloxy)(naphthalen-6-yl) methyl)oxirane (**6e**)*

Viscous liquid as an inseparable mixture of two isomers in approx. 2:1 ratio. Yield 89%. IR (Neat): 3056, 1598, 1488, 1078, 910, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.72-2.73 (m, 0.66H), 2.74-2.80 (m, 0.67H), 2.84-2.88 (m, 0.67H), 3.34-3.36 (m, 0.33H), 3.39-3.41 (m, 0.67H), 4.27-4.61 (complex multiplets, 2.67H), 4.84 (d, J = 4.0 Hz, 0.33H), 7.31-7.33 (m, 3H), 7.43-7.48 (m, 2H), 7.52-7.62 (m, 3H), 7.82-7.87 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 44.4, 45.3, 54.2, 55.0, 57.1, 57.2, 79.7, 82.0, 84.9, 122.6, 124.9, 125.1, 126.3, 126.4, 126.8, 127.3, 127.8, 128.1, 128.3, 128.5, 128.6, 131.8, 133.3, 134.8; HRMS: calcd. for $C_{22}H_{19}BrO_2$ $[M+Na]^+$ 417.0461; found: 417.0464.

2.6 *2-(-2-Bromo-3-phenylallyloxy)(oxiran-2-yl) methyl)-3a,7a-dihydrobenzo[d][1,3]dioxole (**6f**)*

Viscous liquid as an inseparable mixture of two isomers in approx. 2:1 ratio. Yield 85%. IR (Neat): 2995, 1614, 1519, 1249, 1080, 768, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.54-2.56 (m, 0.67H), 2.64-2.74 (m, 1.33H), 3.10-3.16 (m, 1H), 4.09-4.47 (complex multiplets, 2H), 5.10-5.12 (m, 0.67H), 5.25-5.29 (m, 0.33H), 5.88 (2s merged, 2H), 6.70-6.79 (m, 2H), 6.83-6.84 (m, 1H), 7.16-7.35 (m, 6H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 44.4, 45.3, 54.2, 55.1, 56.8, 75.4, 79.2, 81.5, 84.8, 84.9, 86.6, 86.7, 107.9, 108.0, 108.3, 108.4, 115.1, 115.4, 121.1, 121.6, 122.6, 122.7, 126.4, 127.8, 128.2, 128.3, 128.4, 128.5, 128.6, 129.1, 129.2, 131.1, 131.3, 131.8, 131.9, 140.4, 142.7, 147.9, 148.1; HRMS: calcd. for $C_{19}H_{17}BrO_4$ $[M+Na]^+$ 411.0208; found: 411.0206.

2.7 *2-(1-(-2-bromo-3-phenylallyloxy)pentyl)oxirane (**6g**)*

Viscous liquid as an inseparable mixture of two isomers in approx. 4:1 ratio. Yield 84%. IR (Neat): 2929, 1507, 1490, 1255, 1083, 756, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.80 (t, J = 7.0 Hz , 3H), 1.17-1.62 (m, 6H), 2.45 (dd, J = 3.0, 4.5 Hz, 0.80H), 2.70 (t, J = 4.5 Hz, 0.80H), 2.74 (d, J = 3.5 Hz, 0.40H), 2.84-2.87 (m, 0.20H), 2.92-2.94 (m, 0.80H), 3.12-3.16 (m, 0.80H), 3.36-3.40 (m, 0.20H), 4.37 (d, J = 4.0 Hz, 0.20H), 4.48 (AB_q, J = 15.5 Hz, 0.80H), 7.18-7.23 (m, 4H), 7.33-7.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.7, 24.9, 25.2, 31.9, 32.0, 32.3, 32.8, 43.3, 45.7, 53.3, 54.8, 58.1, 58.2, 80.2, 85.6, 85.8, 122.9, 128.3, 128.4, 128.5, 131.8; HRMS: calcd. for $C_{16}H_{21}BrO_2$ $[M+Na]^+$ 347.0623; found: 347.0627.

2.8 *Typical Cp_2TiCl mediated addition-elimination procedure for the synthesis of benzylidene substituted furan derivative **7a***

A solution of titanocene dichloride (564 mg, 2.28 mmol) in dry THF (10 mL, strictly deoxygenated) was stirred with activated zinc dust (360 mg, 5.5 mmol) for 1h under argon (activated zinc dust was prepared by washing 20g of commercially available zinc dust with 60 mL of 4M HCl and thorough washing with water and finally with dry acetone and then dried in vacuum). The resulting green solution was then added dropwise to a stirred solution of the epoxy ether **6a** (345 mg, 1.0 mmol) in dry THF (20 mL) at RT under argon during 1h. The reaction mixture was stirred for 6 hours and was quenched with a saturated solution of sodium dihydrogen phosphate (5 mL). Most of the solvent was removed under reduced pressure and the residue was extracted with diethyl ether (4 × 30 mL). The combined ether layer was washed with saturated $NaHCO_3$ (2 × 25 mL) and finally dried over Na_2SO_4. After removal of the solvent under reduced pressure the crude residue obtained was purified by column chromatography over silica gel to afford the substituted furan compound *(2S,3R)-4-benzylidene-tetrahydro-2-phenylfuran-3-yl)methanol* (E:Z =1:2) (**7a**, 192 mg, 72%) as a mixture of two isomers in 1:2 ratio. IR (Neat): 3330, 1598, 1488, 1078, 910, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.00-3.01 (m, 0.33H), 3.45-3.49 (m, 0.67H), 3.76-3.79 (m, 1H), 3.81-3.85 (m, 0.50H) 3.93-3.97 (m, 0.50H), 4.61-4.95 (complex multiplets, 2.33H), 5.22 (d, J = 3.6 Hz, 0.67H), 6.45 (q, J = 2.0 Hz, 0.33H), 6.49 (d,J = 2.0 Hz, 0.67H), 7.16-7.45 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 52.1, 55.9, 61.9, 63.1, 70.3, 73.2, 82.3, 84.6, 122.1, 126.1, 126.3, 127.1, 127.2, 127.7, 127.9, 128.1, 128.2, 128.6, 128.7, 136.6, 136.9, 140.6, 141.4, 141.6; HRMS: calcd. for $C_{18}H_{18}O_2$ $[M+Na]^+$ 289.1204; found: 289.1205.

Compounds **7b-7g** were prepared following the similar procedure used for the preparation of **7a**.

2.9 *(2S,3R)-4-Benzylidene-2-(4-chlorophenyl) tetrahydrofuran-3-yl)methanol (E:Z=1:1) (**7b**)*

IR (Neat): 3363, 2871, 1596, 1490, 1213, 1062, 825, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.87 (d, J =

5.5 Hz, 0.50H), 3.33 (s, 0.50H), 3.64-3.76 (m, 1.50H), 3.86-3.89 (m, 0.50H), 4.56 (q, J = 7.5 Hz, 1H), 4.68-4.86 (complex multiplets, 1.50H), 5.12 (d, J = 3.5 Hz, 0.50H), 6.37 (d,J = 1.5 Hz, 0.50H), 6.42 (d, J = 1.0 Hz, 0.50H), 7.07-7.31 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 52.1, 56.0, 61.8, 63.0, 70.3, 73.1, 81.6, 83.9, 116.3, 122.4, 122.5, 127.2, 127.4, 127.5, 127.7, 128.0, 128.2, 128.7, 128.8, 133.4, 133.6, 136.4, 136.8, 140.0, 140.8, 141.0; HRMS: calcd. for $C_{18}H_{17}ClO_2$ $[M+Na]^+$ 323.0815; found: 323.0815.

2.10 *(2S,3R)-4-Benzylidene-tetrahydro-2-p-tolylfuran-3-yl)methanol (E:Z=1:1) (**7c**)*

IR (Neat): 3360, 2921, 1598, 1512, 1269, 1176, 813, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.33 and 2.34 (2 s, 3H), 2.99 (d, J = 6.0 Hz, 0.50H), 3.45 (d, J = 3.5 Hz, 0.50H), 3.76 (d, J = 6.0 Hz, 0.5H), 3.82 (dd, J = 5.0, 11.0 Hz, 0.50H), 3.91-3.97 (m, 1H), 4.64 (ABq, J = 13.0 Hz, 1H), 4.74-4.93 (complex multiplets, 1.50H), 5.17 (d, J = 3.5 Hz, 0.50H), 6.45 (brs, 0.5H), 6.49 (brs, 0.50H), 7.05-7.47 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2, 52.0, 55.8, 56.1, 56.3, 61.8, 63.0, 70.2, 73.1, 82.2, 84.5, 109.1, 110.5, 122.0, 126.1, 126.4, 127.1, 127.2, 128.1, 128.2, 128.7, 129.3, 129.6, 136.6, 137.0, 137.4, 137.7, 138.2, 139.0, 140.8, 141.8; HRMS: calcd. for $C_{19}H_{20}O_2$ $[M+Na]^+$ 303.1361; found: 303.1362.

2.11 *(2S,3R)-4-Benzylidene-tetrahydro-2-(4-methoxyphenyl)(furan3-yl)methanol (E:Z=1:2) (**7d**)*

IR (Neat): 3417, 2934, 1612, 1513, 1248, 1175, 1033, 756, 695 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.96-3.00 (m, 0.33H), 3.42-3.45 (m, 0.67 H), 3.74 (d, J = 6.0 Hz, 1H), 3.79-3.82 (m, 3.67H), 3.92-3.95 (m, 0.33H), 4.60 (ABq, J = 13.5 Hz, 1H), 4.75-4.89 (complex multiplets, 1.33H), 5.14 (d, J = 4.0 Hz, 0.67H), 6.45(d, J = 2.5 Hz, 0.33H), 6.49 (d, J = 2.5 Hz, 0.67H), 6.86-6.89 (m, 2H), 7.16-7.38 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.9, 55.4, 55.6, 61.8, 63.0, 70.2, 72.9, 82.1, 84.3, 114.0, 114.1, 121.9, 122.0, 127.1, 127.2, 127.5, 127.8, 128.1. 128.2, 128.7, 133.2, 134.1, 136.6, 137.0, 140.9, 141.9, 159.3, 159.5; HRMS: calcd. for $C_{19}H_{20}O_3$ $[M+Na]^+$ 319.1305; found: 319.1310.

2.12 *(2S,3R)-4-Benzylidene-tetrahydro-2-(naphthalene-2-yl)furan-3-yl)methanol (E:Z=1:2) (**7e**)*

IR (Neat): 3421, 2939, 1598, 1508, 1062, 819, 752, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.09-3.11 (m, 0.33H), 3.54-3.58 (m, 0.67H), 3.81-3.89 (m, 1.50H), 3.98-4.02 (m, 0.50H), 4.67-4.79 (m, 1.33H), 4.82-5.03 (m, 0.67H), 5.12 (d, J = 6.4 Hz, 0.33H), 5.39 (d, J = 3.6 Hz, 0.67H), 6.47(d, J = 2.4 Hz, 0.33H), 6.52 (d, J = 1.6 Hz, 0.67H), 7.17-7.52 (m, 8H), 7.80-7.86 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.1, 55.9, 61.9, 63.1, 70.4, 73.3, 82.4, 84.7, 122.2, 122.3, 124.2, 124.8, 125.3, 126.0, 126.1, 126.2, 126.3, 127.1, 127.3, 127.7, 127.8, 128.1, 128.3, 128.5, 128.6, 128.7, 133.0, 133.4, 136.5, 137.0, 138.8, 139.5, 140.5, 141.5; HRMS: calcd. for $C_{22}H_{20}O_2$ $[M+Na]^+$ 339.1356; found: 339.1361.

2.13 *(2S,3R)-2-(Benzo[d][1,3]dioxol-6-yl) (4-benzylidene-tetrahydrofuran-3-yl)methanol (E:Z=1:2) (**7f**)*

IR (Neat): 3411, 2885, 1488, 1444, 1247, 1037, 933, 756, 694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.86-2.87 (m, 0.33H), 3.32-3.33 (m, 0.67H), 3.63-3.68 (m, 1H), 3.71-3.74 (m, 0.50H), 3.83-3.87 (m, 0.50H), 4.54 (ABq, J = 13.0 Hz, 1H), 4.64-4.83 (complex multiplets, 1.33H), 5.03 (d, J = 3.5 Hz, 0.67H), 5.85 and 5.86 (two singlets, 2H), 6.36 (brs, 0.33H), 6.41 (brs, 0.67H), 6.67-6.82 (m, 3H), 7.08-7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.1, 55.7, 61.7, 62.9, 70.2, 73.1, 82.2, 84.5, 101.1, 106.7, 106.8, 108.2, 119.6, 120.0, 122.1,122.2, 127.1, 127.3, 128.1, 128.2, 128.7, 136.1, 136.5, 136.9, 140.5, 141.5, 147.1, 147.4, 148.0; HRMS: calcd. for $C_{19}H_{18}O_4$ $[M+Na]^+$ 333.1103; found: 333.1106.

2.14 *(2R,3R)-4-Benzylidene-2-butyl-tetrahydrofuran-3-yl)methanol (E:Z=1:2) (**7g**)*

IR (Neat): 3414, 2930, 1723, 1449, 1038, 913, 754, 695 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87-0.89 (m, 3H), 1.22-1.62 (m, 6H), 2.67-2.68 (m, 0.33H), 3.11 (m, 0.67H), 3.61-3.82 (complex multiplets, 2H), 3.92 (q, J = 5.5 Hz, 0.33H), 4.16-4.17 (m, 0.67H), 4.43-4.45 (m, 1.33H), 4.64 (ABq, J = 14.5 Hz, 0.67H), 6.44 (s, 1H), 7.13-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 20.6, 22.7, 25.7, 31.9, 34.4, 34.6, 49.5, 53.3, 62.3, 64.0, 69.0, 71.8, 80.8, 83.3, 122.3, 126.9, 127.1, 128.0, 128.1, 128.6, 128.7, 136.8, 137.1, 141.2, 142.4; HRMS: calcd. for $C_{16}H_{22}O_2$ $[M+Na]^+$ 269.1517; found: 269.1520.

2.15 *Preparation of 1-((Z)-3-(1-(4-methoxyphenyl) allyloxy)-2-bromoprop-1-enyl)benzene (**18**)*

The compound **18** (316 mg, 88%) was prepared from compound **17** (164 mg, 1.0 mmol) following the similar procedure used for the preparation of compounds **6a**. IR (neat): 2993, 1610, 1512, 1247, 1068, 750, 692

cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.81 (d, J = 3.0 Hz, 3H), 4.27-4.39 (m, 2H), 5.05 (d, J = 6.5 Hz, 1H), 5.23-5.33 (m, 2H), 5.96-6.03 (m, 1H), 6.90 (d, J = 9.0 Hz, 2H), 7.30-7.36 (m, 6H), 7.43-7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4, 56.1, 73.9, 81.0, 81.6, 85.5, 86.2, 114.0, 116.7, 116.9, 122.6, 122.9, 128.2, 128.5, 128.7, 129.1, 131.9, 132.3, 132.5, 135.3, 138.4, 138.6, 159.5; HRMS: calcd. for $C_{19}H_{19}BrO_2$ $[M+Na]^+$ 381.0466; found: 381.0465.

2.16 *Preparation of the bromo ether **24***

To a stirred suspension of NaH (53 mg, 50% dispersion, 1.1 mmol) in dry THF (1 mL) was added dropwise a solution of alcohol **22a** (124 mg, 0.50 mmol) in dry THF (5 mL) at 0°C under nitrogen. After the evolution of hydrogen ceased (approx. 25 min), a solution of dibromo compound **12** (166 mg, 0.60 mmol) in dry THF (7.5 mL) was added dropwise at 0°C over 10 min. The reaction mixture was stirred at RT for 3h and then carefully quenched with ice water. After removal of most of the solvent under reduced pressure, the resulting residue was extracted with diethyl ether (4 × 25 mL). The combined ether extract was successively washed with water (2 × 10 mL) and brine (1 × 10 mL) and finally dried (Na_2SO_4). Solvent was removed under reduced pressure and the crude mass obtained was purified by column chromatography over silica gel (30% ethyl acetate-petroleum ether) to furnish **24** (209 mg, 83%) as a viscous liquid. $[\alpha]_D^{25} = -156.24$ (c = 5.0, $CHCl_3$); IR (Neat): 2990, 1522, 1250, 1069, 750, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.24-1.70 (m, 10H), 3.58 (dd, J = 7.0, 9.0 Hz, 1H), 3.68 (dd, J = 6.5, 8.5 Hz, 1H), 3.87-3.88 (m, 6H), 4.16 (d, J = 16 Hz, 1H), 4.36-4.45 (m, 2H), 4.55 (d, J = 8.0 Hz, 1H), 6.83-6.91 (m, 3H), 7.25-7.30 (m, 4H), 7.39-7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.9, 24.1, 25.2, 35.2, 35.3, 36.4, 55.8, 56.0, 56.6, 65.6, 65.9, 78.6, 78.7, 82.0, 85.3, 86.4, 110.6, 110.7, 110.8, 111.1, 120.5, 120.7, 122.9, 128.1, 128.2, 128.3, 128.4, 128.8, 129.1, 129.8, 130.0, 131.7, 131.8, 149.3, 149.4; HRMS: calcd. for $C_{26}H_{31}BrO_5$ $[M+Na]^+$ 525.1253; found: 525.1255.

2.17 *Preparation of compound **25***

Compound **24** (503 mg, 1.0 mmol) was stirred with 80% aqueous acetic acid (2 mL) for 6 h at 40°C (monitored by TLC). After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 30 mL) and the combined organic layer was washed with brine (5 mL) then dried over Na_2SO_4. Solvent was removed under reduced pressure and the residue obtained was purified by column chromatography over silica gel (40% ethyl acetate- petroleum ether) to furnish **25** (385 mg, 91%) as a viscous liquid. $[\alpha]_D^{25} = -133.84$ (c = 9.2, $CHCl_3$); IR (neat): 3350, 1522, 1250, 1069, 750, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.37 (dd, J = 4.8, 11.6 Hz, 1H), 3.55 (dd, J = 3.2, 11.6 Hz, 1H), 3.81-3.91 (m, 7H), 4.13 (d, J = 16 Hz, 1H), 4.36 (d, J = 16 Hz, 1H), 4.57 (d, J = 8.0 Hz, 1H), 6.83-6.92 (m, 3H), 7.29-7.30 (m, 4H), 7.40-7.42 (m, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.0, 56.7, 62.6, 75.5, 81.6, 84.8, 86.7, 110.3, 111.2, 120.6, 122.5, 128.4, 128.6, 129.5, 131.8, 149.4; HRMS: calcd. for $C_{20}H_{23}BrO_5$ $[M+Na]^+$ 445.0627; found: 445.0627.

2.18 *Preparation of compound **26***

A solution of compound **25** (423 mg, 1.0 mmol) in DCM (20 mL) was treated with pyridine (0.64 mL, 8.0 mmol) and TsCl (248 mg, 1.3 mmol) was added to it at 0°C and then stirred for overnight at RT. The mixture was poured into ice water, the organic layer was separated and the aqueous portion was extracted with DCM (3 × 50 mL). The combined organic layers were washed successively with 2M HCl solution (10 mL), water (10 mL) and brine (10 mL) and finally dried over Na_2SO_4.The solvent was removed under reduced pressure followed by column chromatography over silica gel (25% ethyl acetate-petroleum ether) to afford the monotosylated derivative **26** (514 mg, 89%) as a viscous oil. $[\alpha]_D^{25} = -86.49$ (c = 3.4, $CHCl_3$); IR (Neat): 3344, 2937, 1595, 1356, 1240, 1069, 754, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.32 (s, 3H), 3.72-3.87 (m, 8H), 3.94 (dd, J = 3.0, 10.5 Hz, 1H), 4.03-4.08 (m, 1H), 4.28 (d, J = 15.5 Hz, 1H), 4.50 (d, J = 7.0 Hz, 1H), 6.75-6.81 (m, 3H), 7.19-7.25 (m, 6H), 7.33-7.35 (m, 2H), 7.66 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.7, 55.9, 56.0, 56.9, 70.0, 73.3, 80.4, 84.5, 86.9, 110.3, 111.3, 120.4, 122.4, 128.0, 128.4, 128.7, 129.9, 131.7, 131.8, 132.8, 144.9, 149.5; HRMS: calcd. for $C_{27}H_{29}BrO_7S$ $[M+Na]^+$ 599.0715; found: 599.0715.

2.19 *Preparation of compound **27***

To a stirred suspension of sodium hydride (53 mg, 50% dispersion, 4.0 mmol) in dry THF (10 mL) at 0°C was added dropwise a solution of mono tosylate derivative **26** (865 mg, 1.50 mmol) in dry THF (10 mL) under N_2 for 30 min. The reaction mixture was stirred for 1 h at 0°C at RT for 3 h. It was then carefully quenched with ice-water. After removal of most of THF under reduced pressure, the resulting residue was extracted with diethyl ether (3 × 50 mL). The combined ether

extract was washed with water (10 mL) and brine (10 mL) and finally dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a viscous liquid which was purified by column chromatography over silica gel (25% ethyl acetate-petroleum ether) to furnish **27** (510 mg, 84%) as a viscous liquid. $[\alpha]_D^{25} = -125.34$ (c = 2.6, $CHCl_3$); IR (Neat): 2967, 1545, 1389, 1276, 1023, 759, 688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.66 (dd, J = 3.0, 5.0 Hz, 1H), 2.74-2.84 (m, 1H), 3.23-3.29 (m, 1H), 3.86-3.92 (m, 6H), 4.28-4.32 (m, 2H), 4.44-4.50 (m, 1H), 6.86-6.98 (m, 3H), 7.28-7.36 (m, 4H), 7.41-7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.4, 54.2, 55.1, 56.0, 56.1, 56.9, 81.5, 85.0, 86.5, 110.2, 111.2, 120.1, 120.5, 122.7, 128.2, 128.3, 128.4, 128.5, 129.1, 129.9, 131.9, 149.4; HRMS: calcd. for $C_{20}H_{21}BrO_4$ $[M+Na]^+$ 427.0521; found: 427.0520.

2.20 *Preparation of compound **28***

The compound **28** (246 mg, 73%) was prepared from compound **27** (400 mg, 0.98 mmol) by radical cyclization reaction following the similar procedure used for the preparation of compound **7a**. The isolated compound was found to be an inseparable mixture of two isomers in a ratio of 1:1. IR (neat): 3440, 2958, 1560, 1299, 1276, 1033, 750, 678 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.00-3.01 (m, 0.50H), 3.45-3.46 (m, 0.50H), 3.77-3.95 (complex multiplex including several singlets, 8H), 4.64 (q, J = 13 Hz, 1H), 4.75-5.08 (complex multiplets, 1.50H), 5.13 (d, J = 4.0 Hz, 0.50H), 6.47 (brs, 0.50H), 6.53 (d, J = 1.5 Hz, 0.50H), 6.84-6.90 (m, 1H), 6.93-6.97 (m, 2H), 7.18-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.9, 55.6, 56.0, 56.1, 61.7, 62.8, 70.36, 73.0, 82.3, 84.5, 109.5, 111.2, 118.6, 118.9, 122.0, 122.1, 127.1, 127.3, 128.1, 128.2, 128.7, 133.2, 134.1, 136.6, 137.0, 140.9, 141.9, 159.3, 159.5; HRMS: calcd. for $C_{20}H_{22}O_4$ $[M+Na]^+$ 349.1416; found: 349.1417.

2.21 *Preparation of (Z)-2-bromo-3-(4-methoxyphenyl) prop-2-en-1-ol (35az) and (Z)-2-bromo-3-(3,4-dimethoxyphenyl)prop-2-en-1-ol (**35bz**)*

Dibromo compounds **35az** and **35bz** were prepared following the standard literature procedure.[18c,d]

*Spectral data of **35bz**:* IR (neat): 3492, 2933, 1515, 1465, 1271, 1143, 1024, 873 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.86 (s, 6H), 4.39 (s, 2H), 6.84 (d, J = 8.5 Hz, 1H), 6.99 (s, 1H), 7.15 (dd, J = 1.0, 7.5 Hz, 1H), 7.30-7.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.9, 69.6, 110.7, 110.8, 122.5, 123.4, 127.5, 127.6, 148.4, 149.0; HRMS: calcd, for $C_{11}H_{13}BrO_3$ $[M+Na]^+$ 294.9946; found: 294.9946.

2.22 *Preparation of 1-((Z)-2,3-dibromoprop-1-enyl)-4-methoxybenzene (**36a**)*

A solution of PBr_3 (0.12 mL, 1.3 mmol) in diethyl ether (10 mL) was added dropwise to the compound **35az** (243 mg, 1.0 mmol) at 0°C and the solution was stirred for 1h. After completion of the reaction (monitored by TLC) the solution was then neutralized by aqueous saturated $NaHCO_3$ solution and extracted with dihloromethane (3 × 10 mL). The combined organic extract was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afforded the dibromo compound **36a** (70%) which was directly used in the next step without any further purification.

2.23 *Preparation of 4-((Z)-2,3-dibromoprop-1-enyl)-1,2-dimethoxybenzene (**36b**)*

The compound **36b** (72%) was prepared from **35bz** following the same protocol which was used for the preparation of compound **36a** and was directly used in the next step without any further purification.

2.24 *Preparation of 2-(((Z)-2-bromo-3-(4-methoxyphenyl)allyloxy)(phenyl)methyl)oxirane (**37a**)*

The compound **37a** (292 mg, 78%) was prepared from **5a** (150 mg, 1.0 mmol) and **36a** (366 mg, 1.2 mmol) following the similar procedure used for the preparation of compounds **6a-g**. IR (neat): 3001, 1606, 1510, 1249, 1178, 910, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.89 (dd, J = 3.0, 5.0 Hz, 0.50H), 2.98-3.03 (m, 1H), 3.06 (dd, J = 3.5, 6.0 Hz, 0.50H), 3.46-3.47 (m, 0.40H), 3.51-3.53 (m, 0.60H), 4.03-4.06 (m, 3H), 4.41-4.73 (m, 2.70H), 4.87 (d, J = 4.5 Hz, 0.30H), 7.06-7.08 (m, 1H), 7.13-7.17 (m, 1H), 7.57-7.67 (m, 7H), 7.84-7.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 44.3, 44.4, 45.1, 45.3, 54.2, 55.1, 55.2, 55.3, 57.2, 74.9, 79.4, 81.8, 82.3, 83.4, 113.6, 114.0, 119.7, 127.2, 127.3, 127.4, 127.6, 127.7, 128.6, 128.7, 128.8, 129.0, 129.8, 130.6. 133.3, 133.4, 137.5, 137.7, 159.6, 159.9; HRMS: calcd. for $C_{19}H_{19}BrO_3$ $[M+Na]^+$ 397.0415; found: 397.0417.

2.25 *Preparation of (4-(4-methoxybenzylidene)-tetrahydro-2-phenylfuran-3-yl) (**38a**)*

The compound **38a** (107 mg, 68%) was prepared from **37a** (200 mg, 0.53 mmol) as a mixture of two isomers in

1:1.5 ratio following the similar procedure used for the preparation of compounds **7a-g**. IR (neat): 3477, 2956, 1606, 1510, 1251, 1178, 1031, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.97-2.98 (m, 0.40H), 3.44 (m, 0.60H), 3.75-3.82 (m, 4H), 3.93 (dd, $J = 6.0$, 11.0 Hz, 1H), 4.59-4.67 (m, 1H), 4.73-4.94 (complex multiplets, 1.40H), 5.20 (d, $J = 3.5$ Hz, 0.60H), 6.38 (d, $J = 2.0$ Hz, 0.40H), 6.43 (d, $J = 1.0$ Hz, 0.60H), 6.84 (d, $J = 8.5$ Hz, 2H), 6.91 (d, $J = 11.5$ Hz, 1H), 7.10 (d, $J = 9$ Hz, 1H), 7.24-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.0, 55.3, 55.4, 55.9, 61.9, 63.1, 70.3, 73.2, 82.3, 84.6, 114.1, 114.2, 121.5, 121.7, 126.1, 126.3, 127.6, 127.9, 128.6, 129.2, 129.3, 129.5, 129.8, 138.4, 139.0, 141.5, 142.2, 158.7; HRMS: calcd. for $C_{19}H_{20}O_3$ $[M+Na]^+$ 319.1310; found: 319.1312.

2.26 *Preparation of (R)-(3,4,5-trimethoxyphenyl) ((R)-oxiran-2-yl)methanol (**41a**)*

Activated powdered 4-Å molecular sieves (150 mg, 25 wt %) in dry CH_2Cl_2 (5 mL) were placed in a flame-dried two-necked round-bottom flask under an argon atmosphere. It was cooled to –20°C and a solution of (-)-DET (104 mg, 0.505 mmol) in dry CH_2Cl_2 (2 mL) [previously stirred with 4-Å molecular sieves (50 mg) for 20 min] and a solution of Ti(*i*-PrO)$_4$ (0.1 mL, 0.337 mmol) in dry CH_2Cl_2 (2 mL) [previously stirred with 4-Å molecular sieves (50 mg) for 20 min] were cannulated sequentially into the reaction flask with stirring. After 20 min, 5.5 M *t*-BuOOH in decane (0.61 mL) was added to the mixture and it was stirred at –20°C for another 0.5 h. Then, a solution of allylic alcohol **40** (760 mg, 3.37 mmol) in dry CH_2Cl_2 (4 mL) [previously stirred with 4-Å molecular sieves (75 mg) for 20 min] was cannulated into the mixture and the stirring was continued for further 4 h. Finally, an aqueous solution of 30% tartaric acid (3.4 mL) was added, the mixture was stirred for 0.5 h, and the temperature was allowed to warm to 0°C. Most of the CH_2Cl_2 was removed under reduced pressure and the residue was stirred at 0°C for 0.5 h with 30% aq NaOH (3.5 mL) saturated with NaCl. The resulting mixture was filtered through celite using Et_2O and the filtrate was placed in a separatory funnel and the organic layer was separated. The aqueous layer was extracted with Et_2O (1 × 30 mL) and the combined ethereal extracts were washed with brine (30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue obtained was purified by column chromatography over silica gel (30% ethyl acetate–light petroleum) to give pure chiral epoxide **41a** (347 mg, 43%). as a colorless viscous liquid. $[\alpha]_D^{25} = -22.8$ (c = 1, $CHCl_3$); IR (Neat): 3447, 3016, 1541, 1458, 1217, 1130, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.79 (t, $J = 4.8$ Hz, 1H), 2.95 (dd, $J = 2.8$, 4.8 Hz, 1H), 3.22 (d, $J = 3.2$ Hz, 1H), 3.84 (s, 3H), 3.87 (s, 6H), 4.83 (d, $J = 2.8$ Hz, 1H), 6.62 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 43.9, 55.2, 56.3, 61.0, 71.1, 103.4, 135.3, 153.6; HRMS: calcd. for $C_{12}H_{16}O_5$ $(M+Na^+)$ 263.0895; found: 263.0892.

2.27 *Preparation of (R)-2-((R)-((Z)-2-bromo-3-(3,4-dimethoxyphenyl)allyloxy)(3,4,5-trimethoxyphenyl) methyl)oxirane (**42a**)*

Compound **42a** (386 mg, 78%) was prepared from **41a** (240 mg, 1.0 mmol) and **36b** (403 mg, 1.2 mmol) using the similar procedure used for the preparation of compound **6a**. $[\alpha]_D^{25} = -59.2$ (c = 2.81, $CHCl_3$); IR (Neat): 3018, 1593, 1463, 1215, 1130, 756, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.83 (dd, $J = 2.8$, 12.4 Hz, 2H), 3.19 (m, 1H), 3.81-3.92 (m, 15H), 4.24-4.45 (m, 3H), 6.59-6.63 (m, 2H), 6.76-6.80 (m, 2H), 6.85-6.92 (m, 1H), 7.17 (t, $J = 3.2$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 45.3, 45.9, 54.1, 54.3, 54.4, 55.1, 55.8, 55.9, 56.1, 57.1, 60.4, 60.8, 69.6, 73.6, 75.1, 80.1, 80.4, 80.5, 83.2, 86.7, 104.1, 104.2, 104.4, 110.7, 110.9, 111.5, 111.7, 111.7, 112.0, 114.4, 114.6, 121.2, 121.3, 122.4, 122.6, 122.7, 125.1, 126.7, 126.8, 127.4, 127.5, 128.2, 129.5, 133.0, 133.1, 133.3, 137.0, 137.2, 137.9, 148.5, 148.6, 148.8, 149.0, 149.1, 149.7, 153.3, 153.4, 153.5; HRMS: calcd for $C_{23}H_{27}BrO_7$ $[M+Na]^+$ 517.0838; found: 517.0840.

2.28 *Synthesis of a mixture of magnofargesin (**1**) and 7′-epimagnofargesin (**2**)*

A solution of titanocene dichloride (564 mg, 2.28 mmol) in dry and deoxygenated THF (10 mL) was stirred with activated zinc dust (360 mg, 5.5 mmol) for 1h under argon (activated zinc dust was prepared by washing 20g of commercially available zinc dust with 60mL of 4 M HCl and thorough washing with water and finally with dry acetone and then dried in vacuum). The resulting green solution was then added dropwise to a stirred solution of the epoxy ether **42a** (495 mg, 1 mmol) in dry THF (20 mL) at room temperature under argon during 1h. The reaction mixture was stirred for 6 h and was quenched with a saturated solution of sodium dihydrogen phosphate (5 mL). Most of the solvent was removed under reduced pressure and the residue was extracted with diethyl ether (4 × 30 mL). The combined ether layer was washed with saturated $NaHCO_3$ (2 × 25 mL) and finally dried over Na_2SO_4. After removal of the solvent under reduced pressure the crude residue obtained was purified by column chromatography

over silica gel (30% ethyl acetate-petroleum ether) to afford magnofargesin (**1**) and 7′-epimagnofargesin (**2**) as a mixture of two isomers in 1: 1 ratio (324 mg, 78%). IR (neat): 3442, 3020, 1595, 1494, 1217, 1128, 767, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.98 (m, 0.50H, C8-*H* for **1**), 3.41 (m, 0.50H, C8-*H* for **2**), 3.79-3.89 (m, 16H, 5 × OC*H*$_3$ and C9-*H*), 3.97 (dd, J = 5.6, 11.2 Hz, 1H, C9-*H*), 4.63 (dd, J = 1.6, 14.0 Hz, 1H, C9′-*H* for **2**), 4.73-4.77 (m, 0.50H, C9′-*H* for **1**), 4.85 (d, J = 6.4 Hz, 0.50H, C7-*H* for **1**), 4.93 (dd, J = 1.6, 14.0 Hz, 0.50H, C9′-*H* for **1**), 5.07 (d, J = 3.6 Hz, 0.50H, C7-*H* for **2**), 6.39 (d, J = 2.0 Hz, 0.50H, C7′-*H* for **1**), 6.47 (d, J = 1.6 Hz, 0.50H, C7′-*H* for **2**), 6.61 (s, 1H, C2-*H* and C6-*H* for **2**), 6.63 (s, 1H, C2-*H* and C6-*H* for **1**), 6.70-6.74 (m, 1H, Ar*H*), 6.81-6.93 (m, 2H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.0, 55.7, 56.0, 56.3, 60.9, 61.8, 62.8, 70.3, 73.1, 82.4, 84.6, 103.1, 103.2, 111.3, 111.6, 120.6, 120.8, 121.8, 122.1, 129.4, 130.0, 136.9, 137.8, 138.8, 139.4, 148.3, 148.4, 149.0, 153.4, 153.5; HRMS: calcd. for $C_{23}H_{28}O_7$ $[M+Na]^+$ 439.1733; found: 439.1735.

The two isomers could not be separated by usual chromatographic methods. But, the spectral and analytical data of the mixture of two isomers were in agreement with the reported values.[12,19]

3. Results and Discussion

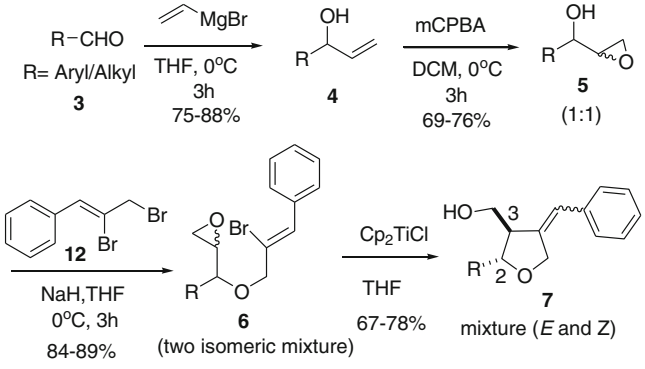
Thus, the bromo epoxide **6** was prepared as an inseparable mixture of two isomers in different ratio from the corresponding aldehyde **3** following standard chemical transformations as shown in scheme 1. The bromo epoxide **6** on treatment with Cp_2TiCl in THF under argon afforded the tetrahydrofuran **7** *via* radical induced cyclization-elimination pathway as an inseparable mixture of *cis-trans* isomers in different ratio. In some cases, the ratio was found to be 1:1 depending on the substrate. In all cases, radical cyclization of the bromo epoxide afforded only the 2,3-*trans* products as revealed from our earlier studies.[11]

The dibromo compound **12** was prepared from cinnamaldehyde **8** following standard chemical transformations (scheme 2). Thus, a solution of cinnamaldehyde **8** in DCM was stirred for 15 min with Br_2 at 0′C followed by the addition of Et_3N and stirred for 15 min to yield a 1:10 mixture of E/Z isomers **9** as an yellow oil. After keeping for 3 days at room temperature the mixture of isomers in **9** completely converted to *Z*-α-bromocinnamaldehyde **10** in the form of a bright yellow solid. Reduction of the aldehyde **10** with sodium borohydride in the presence of $CeCl_3.7H_2O$ furnished the alcohol **11** which was finally brominated using PBr_3 to yield the dibromo compound **12**.[13]

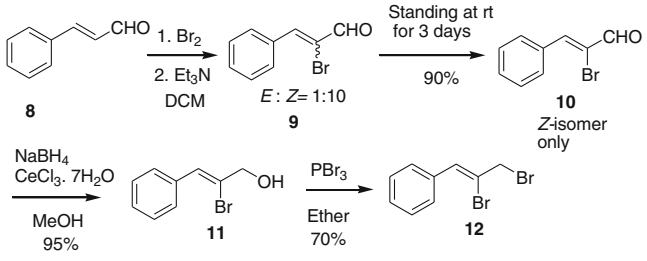
Thus, a series of bromoepoxides were prepared and subjected to radical cyclization using titanocene(III) chloride and the results are summarized in table 1. The methodology worked well for aromatic (Entry 1-6, table 1) as well as aliphatic substrate (Entry 7, table 1) with comparable yield.

Two possible pathways may be predicted for the formation of the cyclized product **7** as shown in scheme 3. Path A involves the radical **13** that undergoes cyclization to furnish the intermediate **14**. Then, the expulsion of the bromine radical from **14** yielded the intermediate **15** which on acidic work up provided the desired product **7** as an inseparable mixture of two isomers (E/Z). In path B, a diradical species **16** may be formed which undergoes radical coupling to form the intermediate **15** and finally to the product **7**. But, formation of aryl/vinyl radical in path B may be discarded as observed[20] by Campaña and Cuerva in a control experiment of intramolecular conjugate addition using aryl iodide and Cp_2TiCl.

In support of path A, a separate experiment was carried out where the bromo compound **18** was treated with Cp_2TiCl in THF under identical reaction conditions (scheme 4). It was observed that only the unreacted starting bromide **18** was isolated without a trace of the cyclized product **19** ensuring the inability of Cp_2TiCl to form a vinyl radical from vinyl bromide.

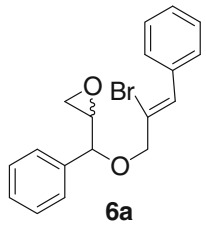
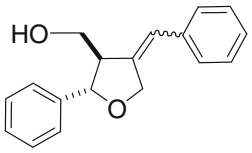
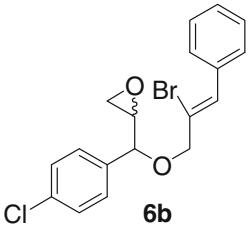
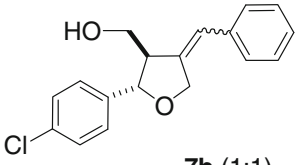
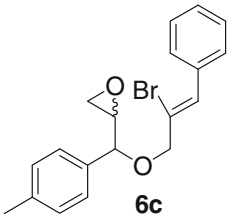
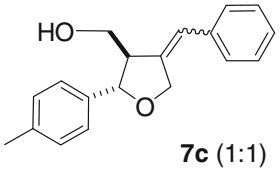
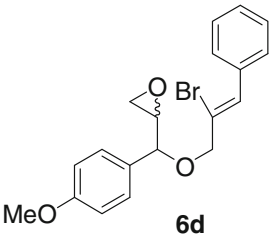
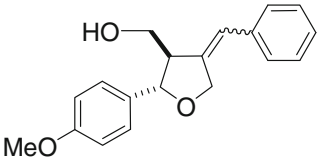
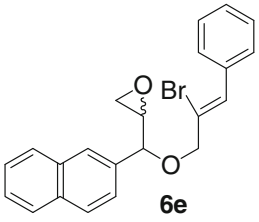
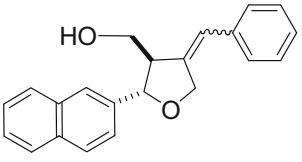
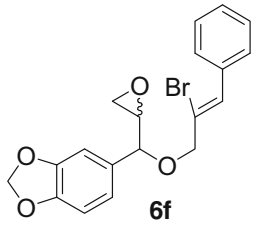
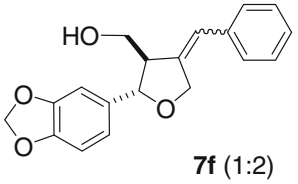
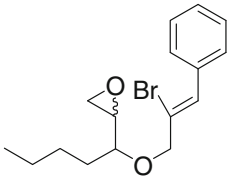
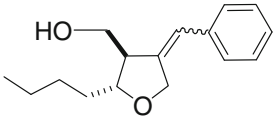


Scheme 1. Radical induced synthesis of tetrahydrofurans.

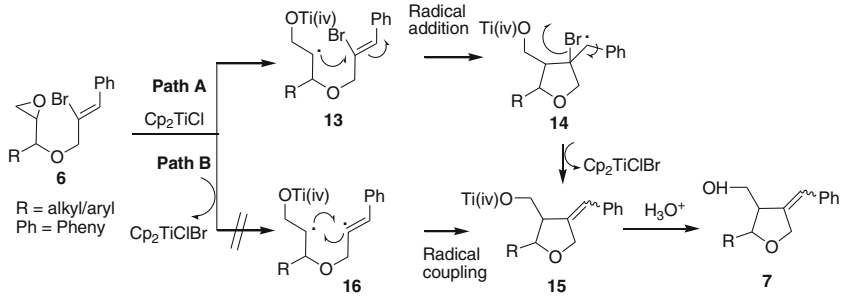


Scheme 2. Synthesis of dibromo compound.

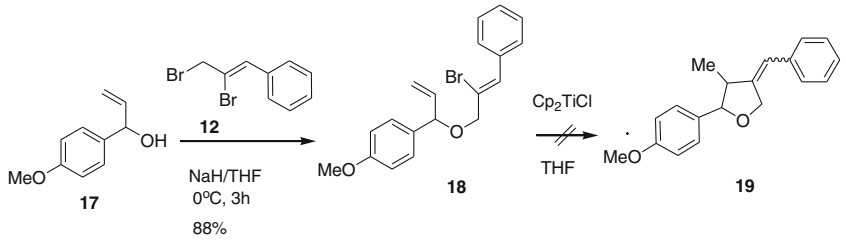
Table 1. Synthesis of various benzylidene substituted furan moieties.

Sl. No.	Substrate	Product (E:Z)	Yield (%)[a]
1	 **6a**	 **7a** (1:2)	72
2	 **6b**	 **7b** (1:1)	70
3	 **6c**	 **7c** (1:1)	67
4	 **6d**	 **7d** (1:2)	68
5	 **6e**	 **7e** (1:2)	78
6	 **6f**	 **7f** (1:2)	76
7	 **6g**	 **7g** (1:2)	67

[a]Yield refers to pure isolated product.

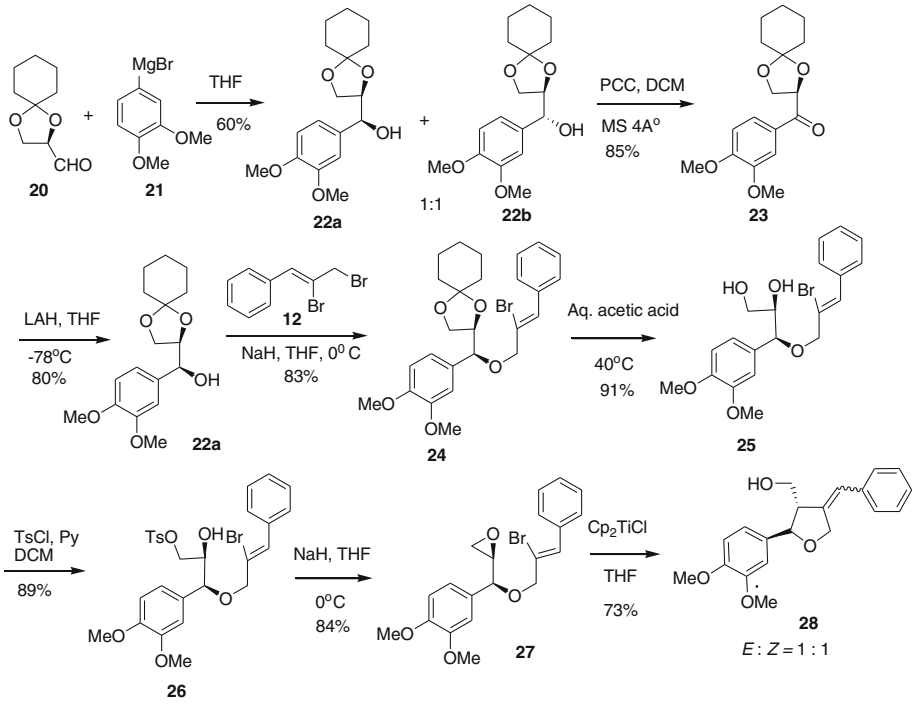


Scheme 3. Probable Mechanism for radical cyclization.



Scheme 4. Experimental support in favour of path A.

For asymmetric synthesis of tetrahydrofurans, easily accessible *R*-2,3-*O*-cyclohexylidine glyceraldehyde **20** was used as a source of chiral pool. Freshly prepared 3,4-dimethoxyphenyl magnesium bromide **21** was added to the aldehyde **20** to obtain an inseparable mixture of two isomeric alcohols **22a** and **22b** in a ratio of 1:1 (scheme 5). The crude mixture of **22** was subjected to PCC oxidation to produce the ketone **23** in good yield. The ketone **23** was reduced by $LiAlH_4$ in THF at -78°C to afford the known alcohol **22a** as the sole product.[21c] The high selectivity of the nucleophilic addition of hydride to carbonyl moiety in **23** may be explained with the analogy as reported earlier.[21] The alcohol **22a** was then alkylated with dibromo compound **12** in the presence of NaH in THF under argon to furnish **24**. The aryl ether **24** on treatment with 80%



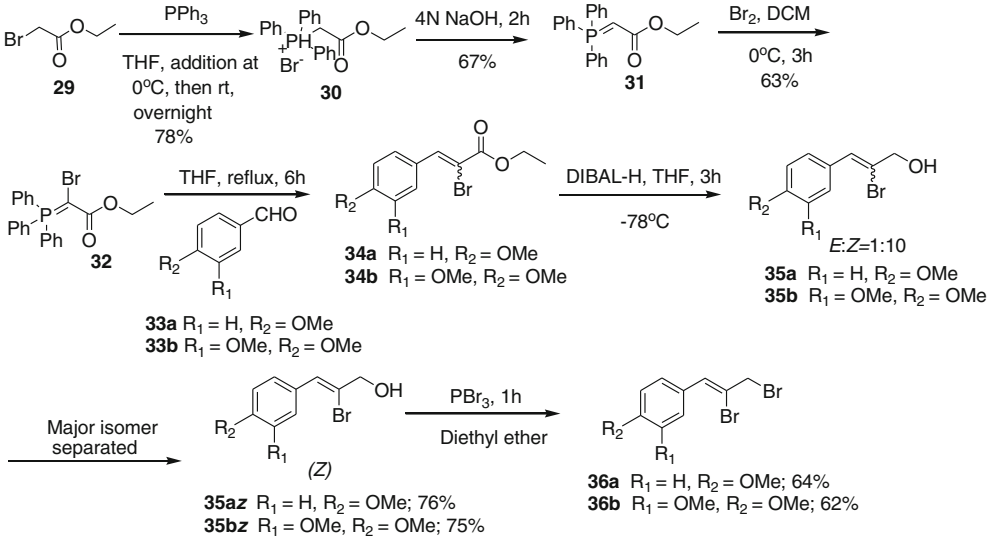
Scheme 5. Asymmetric synthesis of tetrahydrofurans.

aqueous acetic acid at 40°C afforded the diol **25**. The diol **25** was selectively *mono*-tosylated using tosyl chloride with excess of pyridine in DCM to furnish the *mono*-tosylated alcohol **26** which on treatment with NaH in THF produced the chiral epoxide **27** in 84% yield. The chiral radical precursor **27** on treatment with Cp_2TiCl in THF under argon produced the cyclized product **28** as an inseparable mixture of two isomers in equal ratio (E:Z = 1:1).

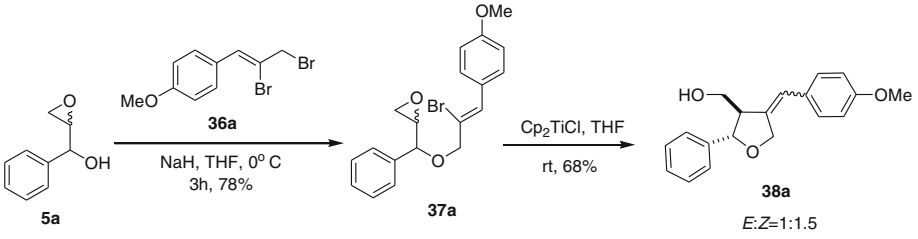
To study the scope of the method an attempt to prepare substituted dibromo compound **36a,b** following the procedure as stated in scheme 2 was unsuccessful as it produced only a mixture of unidentified products. Finally, the aromatic substituted dibromo compounds **36a** and **36b** were prepared following the procedure as depicted in scheme 6.

Thus, phosphonium ylide **31**[18a,b] prepared from bromophoshphonium salt **30** which was selectively brominated following standard literature method[18c] to form bromo carbethoxymethylenetriphenylphosphorane **32**. The bromide **32** was refluxed separately with aldehyde **33a** and **33b** to furnish the isomeric unsaturated bromoesters **34a** and **34b** respectively (E/Z = 1:10). Without further purification, the mixture of esters in **34a** and **34b** was separately treated with DIBAL-H in THF at -78°C to produce the corresponding isomeric mixture of bromo alcohols **35a** and **35b** in 1:10 ratio (E/Z). The major Z-isomer in **35az** (76%) and **35bz** (75%) was separated by column chromatography over silica gel.[18d] Alcohols **35az** and **35bz** were brominated separately with PBr_3 to produce the corresponding methoxy substituted dibromo compounds **36a** (64%) and **36b** (62%). Alkylation of **5a** with the dibromo compound **36a** furnished the epoxy ether **37a**. The epoxy ether **37a** was then treated with Cp_2TiCl in THF under argon to furnish the furan moiety **38a** in 68% yield (scheme 7). The result showed no significant change in the diastereomeric ratio (E/Z =1:1.5) which implied that the electronic effect of the methoxy group in the aromatic moiety failed to incorporate much selectivity.

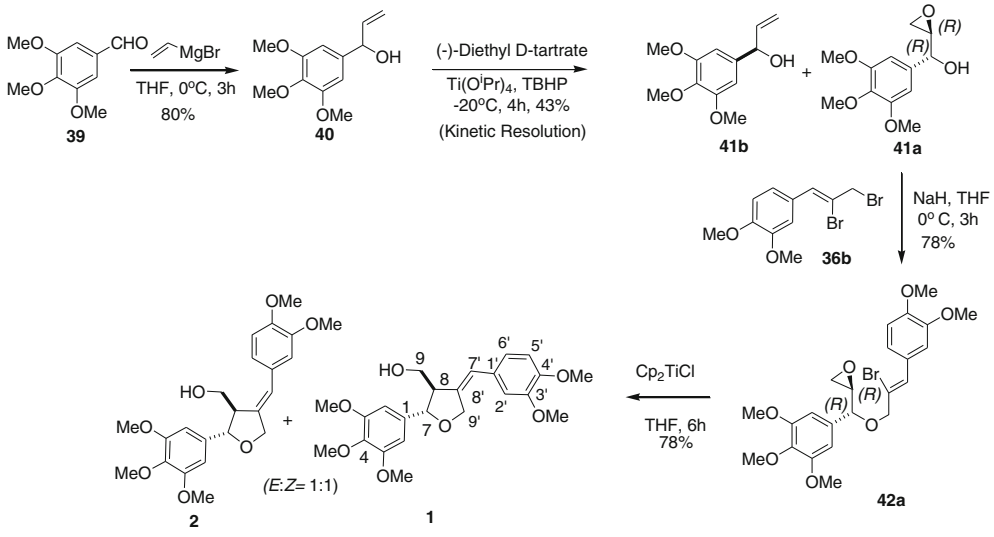
We then turned our attention to the synthesis of furano lignans using the similar protocol. Lignans have attracted much interest over last few decades on account of their widespread occurrence in nature[22] and broad range of biological activities.[19,23–27] Magnofargesin, an antagonist of platelet-activity factor (PAF)[28] is a class of lignan and has been a long standing interest for synthetic chemists. Although plentiful synthetic



Scheme 6. Synthesis of aromatic substituted dibromides.



Scheme 7. Synthesis of tetrahydrofurans.



Scheme 8. Formal synthesis of magnofargesin and 7′-epimagnofargesin.

strategies leading to benzyledene substituted tetrahydrofurans have been reported in the literature, the major drawbacks are tedious reaction procedures, low yield and tedious separation technique.[29] In continuation of our study on Cp_2TiCl mediated radical induced synthesis of natural product, we demonstrated the formal synthesis of magnofargesin (**1**) and its stereoisomer *epi*-magnofargesin (**2**)[11] in optically active forms using addition-elimination methodology. Thus, 3,4,5-trimethoxybenzaldehyde **39** was treated with vinyl magnesium bromide to furnish the allyl alcohol **40** which on Sharpless kinetic resolution,[14] using (-)-diethyl tartrate, titanium(IV) isopropoxide [$Ti(^iPrO)_4$], *tert*-butyl hydroperoxide and 4-Å molecular sieves in DCM at -20°C afforded the chiral epoxy alcohol **41a** in 43% isolated yield (95% ee, determined from the corresponding Mosher ester)[14c] (scheme 8). The other enantiomer of the allylic alcohol **41b** was isolated as such.

The pure epoxy alcohol **41a** was then alkylated using the dibromo compound **36b** in the presence of NaH in THF to furnish the chiral epoxy ether **42a** in good yield. Finally, the chiral radical precursor **42a** when treated with Cp_2TiCl in THF under argon afforded a mixture of **1** and **2** in a ratio of 1:1. The ratio of the two isomers was determined from the ^1H NMR spectrum of the crude cyclized product and compared with the values reported in the literature.[11,29] Since, the total synthesis of **1** and **2** has been reported by Wardrop[29] by separating two isomers using special technique, we accomplished the formal synthesis of two naturally occurring furano lignans, magnofargesin (**1**) and 7′-epimagnofargesin (**2**) in optically active forms through Cp_2TiCl mediated radical induced addition-elimination pathway.

4. Conclusions

In conclusion, we have successfully developed a simple and efficient Cp_2TiCl mediated radical induced synthetic protocol for the synthesis of benzylidene substituted tetrahydrofurans following the addition-elimination strategy. The technique has been applied to the total synthesis of a mixture of naturally occurring furano lignans, magnofargesin and its epimer 7′-epimagnofargesin, through addition-elimination process. Since, magnofargesin and its epimer 7′-epimagnofargesin have already been separated earlier from the mixture by Wardrop using special technique, we acomplished the formal synthesis of two naturally occurring furano lignans, magnofargesin (**1**) and 7′-epimagnofargesin (**2**) in optically active forms.

Supplementary Information (SI)

Copies of NMR spectra of unknown compounds are available in Supplementary Information at www.ias.ac.in/chemsci.

Acknowledgements

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