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Total Synthesis of S (+)-Curcuphenol, S (+)-Curcuquinone and S (+)-Curcuhydroquinone

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A synthesis of (-)-curcuphenol, (-)-curcuquinone and (-)-curcuhydroquinone from *o*-valerolactone is described. The key steps include an Evans asymmetric methylation of 5-(benzyloxy)pentanoic acid (**5**), an oxidative aromatization of enone (**11**) and a regioselective oxidation of the phenol to *o*-quinone derivative with *bis*(trifluoro acetate)iodobenzene.

Keywords: Evans asymmetric methylation, Robinson annulation, [1,3]-Oxidative rearrangement.

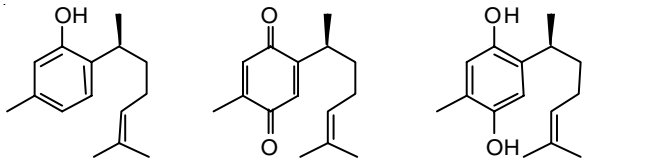
INTRODUCTION

Naturally occurring (-)-curcuphenol, (-)-curcuquinone and (-)-curcuhydroquinone are similar type of phenolic sesquiterpenes of the bisabolane family [1] (Fig. 1), isolated from the Caribbean gorgonian *Pseudopterogorgia rigid* [2] and exhibit potent antibacterial activity towards *Staphylococcus aureus* and the marine pathogen *Vibro anguillarum* [2a]. These popular synthetic targets [3] used for the synthesis of heliannuols [4]. The noteworthy of its monocarbocyclic skeleton structure has resulted in considerable attention from the synthetic community [3-6].

To date, only few syntheses of (-)-curcuphenol, (-)-curcuquinone and (-)-curcuhydroquinone have been reported. Despite these different approaches, none has revealed accessibility of oxidative aromatization. Thus, our group has focused on the asymmetric synthetic route of common key intermediate.

EXPERIMENTAL

All the chemicals employed in this study were procured from Sigma Aldrich. In present study, all the synthetic reactions were monitored by TLC. All the synthesized compounds were confirmed by different spectroscopic methods. The IR spectra were recorded using KBr pellets on a Perkin Elmer IR spectrophotometer. ^{1}HNMR spectra were recorded on Brucker 300 MHz Avance NMR spectrophotometer using $CdCl_3$ as solvent and TMS as internal standard (chemical shifts in δ ppm). The Mass spectra were recorded on Agilent 6300 series ion trap.



(-)-Curcuphenol (-)-Curcuquinone (-)-Curcuhydroquinone

Fig. 1. Examples of some aromatic bisabolene sesquiterpene

Synthesis

5-(Benzyloxy)pentanoic acid (5): To a stirred solution of δ-valerolactone (**4**) (21 g, 210 mmol,) in toluene (200 mL), KOH (47 g, 840 mmol) and benzyl chloride (72 g, 420 mmol,) were added and the mixture was stirred at 120 °C overnight, then cooled to room temperature and treated with 0.5 N HCl (300 mL) solution to adjust pH to 2. The resulting mixture was extracted with diethylether (4 × 200 mL) and the organic phase was washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*, purification on column chromatography using silica gel (60-100 mesh), with 30 % AcOEt in hexane to afforded 21.1 g of desired product **5** in 49 % yield as a colourless oil; IR (neat, cm^{-1}): 3447, 2929, 1708, 1211, 743, 698; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.2 (m, 1H), 7.25 (m, 5H), 4.46(s, 2H), 3.45 (t, J = 6.0 Hz, 2H), 2.36 (t, J = 6.8 Hz, 2H), 1.78-1.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$); HRMS (ESI): Calculated for $C_{12}H_{16}O_3Na$ (M^++Na) 231.0997, found 231.1005.

(S)-4-Benzyl-3-[5-(benzyloxy)pentanoyl]oxazolidin-2-one (6): To the stirred solution of carboxylic acid **5** (13.5 g,

27 mmol) in dry THF, triethylamine (16.6 mL, 157.7 mmol) and pivallyl chloride (8.6 mL, 70 mmol) were added at -20 °C and stirred for 1 h. Then LiCl (4.0 g, 94.2 mmol) was added and after 10 min and (S or R)-oxazolidinone (11g, 62.8 mmol) was also added and continued for another 1 h at -20 °C. The mixture was warmed to 0 °C over a period of 2 h. The reaction was quenched with NH_4Cl solution and with EtOAc (3 × 100 mL). The organic phase washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. purification on column chromatography using silica gel (60-100 mesh), with 10 % AcOEt in hexane to afforded auxiliary product 20 g with 85 % yield; IR (neat, cm^{-1}): 2926, 1779, 1699, 1209, 1100, 750, 700; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.15 (m, 10H), 4.57 (m, 1H), 4.48 (s, 2H), 4.09 (d, *J* = 5.0 Hz, 2H), 3.50 (t, *J* = 6.0 Hz, 2H), 3.28 (dd, *J* = 12.8, 3.0 Hz, 1H), 3.03-2.84 (m, 2H), 2.66 (m, 1H), 1.84-1.64 (m, 4H). HRMS (ESI): Calculated *m/z* for $C_{22}H_{25}O_4NNa$ (M^++Na) 390.1681, found 390.1696.

4-Benzyl-3-[5-(benzyloxy)-2-methylpentanoyl]oxazolidin-2-one (7): To the stirred solution of auxiliary compound (20 g, 54 mmol) in dry THF was added 1 M solution of NaHMDS (5.8 mL, 58 mmol) at -78 °C and stirred for 1h. Then CH_3I (16.8 mL, 270 mmol) was added and the stirring was continued for 0.5 h and the mixture was allowed to warm ambient temperature. Upon completion of reaction, the resulting mixture was quenched with NH_4Cl solution and extracted with Et_2O (3 × 150 mL). The organic phase washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. purification on column chromatography using silica gel (60-100 mesh), with 10 % AcOEt in hexane to afforded (4*S*)-4-benzyl-3-[(2*S*)-5-(benzyloxy)-2-methylpentanoyl]-1,3-oxazolan-2-one (11.4 g) with 55 %yield as pale yellow oily liquid; $[\alpha]_D^{34.1}$: + 8.5 (*c* = 0.55, $CHCl_3$). IR (neat, cm^{-1}): 2928, 1778, 1696, 1452, 1203, 1101, 1019, 739, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36-7.16 (m, 10H), 4.57 (m, 1H), 4.45 (s, 2H), 4.14-3.97 (m, 2H), 3.72 (m, 1H), 3.51-3.41 (m, 2H), 3.26 (dd, *J* = 12.8, 3.0 Hz, 1H), 2.69 (dd, *J* = 13.5, 9.8 Hz, 1H), 1.83 (m, 1H), 1.69-1.59 (m, 2H), 1.53 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 3H); HRMS (ESI): *m/z* 420 (M^++ K)

[(4-Methylhex-5-enyloxy)methyl]benzene (8): To the stirred solution of methylated auxillary compound (10 g, 26 mmol) in MeOH (100 mL) was added $NaBH_4$ (3.0 g, 78 mmol) in portions at 0 °C and stirring was continued under inert atmosphere for 2 h. Then, the reaction mixture was quenched with saturated NH_4Cl solution and removed the solvent under reduced pressure. The residue was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water, brine and dried with Na_2SO_4. Removal of the solvent followed by purification on purification on column chromatography using silica gel (60-100 mesh), with 10 % AcOEt in hexane to afforded pure (S)-5-(benzyloxy)-2-methylpentan-1-ol (4.6 g, 85 %) as colourless liquid; $[\alpha]_D^{25}$: +31.0 (*c* 0.1, $CHCl_3$; IR (neat, cm^{-1}) 3449, 1457, 1009; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36-7.21 (m, 5H), 4.48 (s, 2H), 3.48-3.36 (m, 4H), 1.73-1.42 (s, 5H), 0.91 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 128.3, 127.6, 72.9, 70.6, 67.9, 35.5, 29.5, 27.0, 16.5; HRMS (ESI): Calculated *m/z* for $C_{13}H_{20}O_2Na$ (M^+ + Na) 231.1360, found 231.1362;

To a stirred solution of oxalyl chloride (8.45 mL, 98 mmol) in anhydrous CH_2Cl_2 (250 mL) was added dropwise DMSO (7.5 mL, 107 mmol) in anhydrous CH_2Cl_2 (50 mL) at -78 °C. The mixture was stirred at same temperature for 15 min. To this mixture was added dropwise a solution of primary alcohol (10.5 g, 49 mmol) in anhydrous CH_2Cl_2 (100 mL) and stirring was continued at -78 °C for further 1 h. The reaction was quenched by addition of Et_3N (68 mL, 490 mmol) at –78 °C. The mixture was allowed to warm to ambient temperature and stirring was continued for 40 min. After addition of water, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent followed by rapid chromatography of the resulting residue furnished unstable aldehyde as a colourless liquid and it directly used for next step.

To the solution of methyltriphenyl phosphonium iodide (63 g, 156 mmol) was added 1.6 M *n*-BuLi (48.5 mL, 78 mmol) in anhydrous THF (200 mL) and allowed to stir at room temperature under inert atmosphere for 3 h. Then the stirring was stopped and allowed to settle down the solid. The clear supernatant orange-yellow liquid was transferred into the solution of above crude aldehyde in dry THF (200 mL) at -78 °C. The reaction mixture was stirred -78 °C for another 3 h and then slowly allowed to warm to ambient temperature. Then the reaction was quenched with crushed ice and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Removal of solvent followed by purification on column chromatography using silica gel (60-100 mesh), with 5 % AcOEt in hexane to afforded olefin compound **7** (8.0 g, 90 %) as a pale yellow syrup; IR (neat, cm^{-1}): 2930, 1493, 1104, 735, 696; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.19 (m, 5H), 5.64 (m, 1H), 4.96-4.86 (m, 2H) 4.46 (s, 2H), 3.41 ((t, *J* = 6.6 Hz, 2H), 2.1 (m, 1H), 1.64-1.51 (m, 2H), 1.44-1.30 (m, 3H), 0.99 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.5, 138.7, 128.3, 127.6, 127.5, 125.5, 112.7, 72.8, 70.5, 37.7, 33.0, 27.5, 20.2; HRMS (ESI): *m/z* 227 (M^++ Na).

6-(Benzyloxy)-3-methylhexanal (9): A solid of 9-BBN dimer (10.7g, 44.1 mmol) in dry THF (120 mL) was stirred for 1 h at 0 °C. Then the solution of olefin compound (15 g, 73.5 mmol) taken in dry THF (50 mL) was added to the reaction mixture slowly at 0 °C and stirring was continued for again 1 h. The reaction mixture was warmed to ambient temperature and stirred for overnight. The reaction mixture was cooled to 0 °C and then, 20 % solution of NaOH (22 mL), followed by aqueous 30 % H_2O_2 solution (13 mL) were added and the reaction mixture was stirred again another 12 h at ambient temperature. After completion of the reaction, the aqueous layer was extracted with diethyl ether (3 × 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on column chromatography using silica gel (60-100 mesh), with 5 % AcOEt in hexane to afforded primary alcohol (11.4 g, 70 %) as a colourless liquid; IR (neat, cm^{-1}): 3400, 2930, 1454, 1099, 734, 698; ^1H NMR(300 MHz, $CDCl_3$): δ 7.36-7.24 (m, 5H), 4.47 (s, 2H), 3.46-3.34 (m, 4H), 1.85-1.38 (s, 7H), 0.94 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 128.7, 127.4, 127.3, 72.8, 71.7, 60.8, 39.4, 33.2, 29.1, 27.0, 19.4; HRMS (ESI): *m/z* 222 (M^+).

To a stirred solution of oxalyl chloride (19.4 mL, 226.2 mmol) in anhydrous CH_2Cl_2 (300 mL) was added dropwise

DMSO (17.5 mL, 248 mmol) in anhydrous CH_2Cl_2 (100 mL) at -78 °C. The mixture was stirred at same temperature for 15 min. To this mixture was added dropwise a solution of primary alcohol (25g, 113.1 mmol) in anhydrous CH_2Cl_2 (100 mL) and stirring was continued at -78 °C for further 1 h. The reaction was quenched by addition of Et_3N (78.6 mL, 565.5 mmol) at -78 °C. The mixture was allowed to warm to ambient temperature and stirring was continued for 40 min. After addition of water, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with water, brine and dried (Na_2SO_4). Removal of solvent followed by rapid chromatography of the resulting residue on silica gel with (60-100 mesh, EtOAc-hexane 85:15) furnished unstable aldehyde with quantitative yield as colourless oil.

4-[(S)-5-(Benzyloxy)pentan-2-yl]cyclohex-2-enone (10): To a stirred solution of primary aldehyde product in CH_3CN (400 mL), methyl vinyl ketone (13.9 mL, 169 mmol) and tri methyl silyl diethyl amine ($TMSEt_2N$) (2.1 mL, 11.3 mmol) were added under inert atmosphere at ambient temperature. The reaction mixture was refluxed for 48 h and then the reaction mixture was cooled to ambient temperature. The reaction mixture was concentrated under reduced pressure. The resulted residue was diluted with EtOAc and was also added H_2O. The mixture was extracted with EtOAc (3 × 120 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel (60-100 mesh) 10 % EtOAc-hexane as eluent to give Michael addition product (22.9 g, 70 %) as pale yellow oil; $[\alpha]_D^{36.1}$: -12.2 (c = 0.5, $CHCl_3$): IR (neat, cm^{-1}): 1790, 1677, 2925, 1454, 1101, 743, 699; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.57 (m, 1H), 7.31-7.22 (m, 5H), 4.46 (s, 2H), 3.46-3.40 (m, 2H), 2.55-2.29 (m, 2H), 2.09 (s, 3H), 1.82 (m, 1H), 1.61-1.45 (m, 2H), 1.00-0.87 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.2, 205.6, 135.7, 128.1, 127.1, 127.0, 73.1, 70.5, 55.9, 42.1, 34.2, 32.5, 31.3, 29.8, 27.4, 17.8; HRMS (ESI): Calculated *m/z* for $C_{18}H_{26}O_3Na$ (M^++Na) 313.1779, found 313.1785;

To a stirred solution of Michael addition compound (15 g, 51.7 mmol) in THF (100 mL) were added Bu_4NOH (4 mL), diethyl ether (300 mL) and also 5 % KOH (aq) solution (150 mL), respectively. The resulting reaction mixture was stirred under inert atmosphere at ambient temperature for 10 min. After that the reaction mixture was refluxed with vigorous stirring for 8 h and then the reaction mixture was cooled to ambient temperature. The reaction mixture was concentrated under reduced pressure. The residue with aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel (60-100 mesh) 5 % EtOAc-hexane as eluent to give α,β-unsaturated enone **9** (11.3 g, 80 % yield) as colourless liquid; $[\alpha]_D^{34.1}$: - 2.2 (c =0.55, $CHCl_3$): IR (neat, cm^{-1}): 2933, 1715, 1453, 1100, 739, 698; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.20 (m, 5H), 6.79 (t, J = 12.6 Hz, 1H), 5.98 (d, J = 10.2 Hz, 1H), 4.46 (s, 2H), 3.43 (t, J = 5.8 Hz, 2H), 2.54-2.22 (m, 3H), 1.94 (m, 1H), 1.59-1.43 (m, 3H), 1.36-1.21 (m, 2H), 0.96-0.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.9, 155.1, 138.3, 129.5, 128.2, 127.5, 127.4, 72.8, 70.2, 41.5, 40.9, 37.4, 36.3, 27.6, 25.7, 23.8; HRMS (ESI): Calculated *m/z* for $C_{18}H_{24}O_2Na$ (M^++Na) 295.1673, found 295.1687;

6-[(S)-5-Hydroxypentan-2-yl]-3-methylcyclohex-2-enone (11): To the stirred solution of activated Mg turnings (2.7 g, 111 mmol) in dry Et_2O (150 mL) was added CH_3I (6.95 mL, 111 mmol) dropwise at 0 °C under inert atmosphere and stirring was continued for another 2 h. To this generated CH_3MgI was added α,β-unsaturated compound (10 g, 37 mmol) very slowly drop wise at 0 °C under inert atmosphere. The reaction mixture was warmed to ambient temperature and stirring was continued for 12 h. The reaction was quenched with saturated NH_4Cl solution drop wise at 0 °C. The mixture was extracted with EtOAc (3 × 100 mL) and filtered. The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel (60-100 mesh) 15 % EtOAc-hexane as eluent to give the diastereomeric mixture of Grignard product (7.7 g, 72 %) as colourless oil; $[\alpha]_D^{35.2}$: 6.0 (c =0.5, $CHCl_3$): IR (neat, cm^{-1}): 3409, 2931, 1646, 1454, 1108, 738, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.18 (m, 5H), 5.62-5.44 (m, 2H), 4.46 (s, 2H), 3.41 (t, J = 6.8 Hz, 2H), 2.09 (m, 1H), 1.84 (m, 1H), 1.74-1.29 (m, 6H), 1.27-1.15 (m, 5H), 0.88-0.81 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 134.6, 131.7, 130.5, 128.2, 127.5, 72.7, 70.5, 69.6, 39.9, 38.0, 36.4, 30.3, 28.3, 24.0, 22.2; HRMS (ESI): Calculated *m/z* for $C_{19}H_{28}O_2Na$ (M^+ + Na) 311.1987, found 311.1978.

To a well stirred solution of Grignard compound (4 g, 13.9 mmol) in dry CH_2Cl_2 (100 mL) was added pyridinium chlorochromate (PCC) (9.0 g, 41.7 mmol) under inert atmosphere at 0 °C. The reaction mixture was warmed to ambient temperature and stirring was continued for 3 h. When the reaction was complete, the reaction mixture was extracted with Et_2O (5 × 100 mL). The resultant solids were removed by filtration using celite pad and then washed with Et_2O (2 × 100 mL). The combined organic filtrate and washings were washed with 5 % NaOH, diluted HCl and saturated $NaHCO_3$ aqueous solutions respectively. Then the organic extract was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on silica gel (60-100 mesh) 15 % EtOAc-hexane as eluent to give product **11** (2.9 g, 70 %) with [1:1] diastereomeric mixture as colourless oil, $[\alpha]_D^{34.5}$: - 17.8 (c = 0.5, $CHCl_3$): IR (neat, cm^{-1}): 2932, 1664, 1451, 1101, 742, 697 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.34-7.20 (m, 5H), 5.85 (s, 1H), 4.47 (s, 2H), 3.47-3.41 (t, 2H), 2.34-2.24 (m, 3H), 2.17-2.06 (m, 1H), 1.94 (s, 3H), 1.85-1.70 (m, 1H), 1.70-1.47 (m, 2H), 1.39-1.21 (m, 3H), 0.93 (d, J = 6.8 Hz, 1H), 0.79 (d, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.8, 161.1, 160.9, 138.5, 128.2, 127.5, 126.9, 126.8, 72.8, 70.6, 51.1, 49.7, 30.9, 30.7, 30.3, 29.5, 27.6, 23.3, 22.2, 17.3, 15.5; HRMS (ESI): Calculated *m/z* for $C_{19}H_{26}O_2Na$ (M^++Na) 309.1830, found 309.1822.

(S)-1-[5-(Benzyloxy)pentan-2-yl]-2-methoxy-4-methylbenzene (16): To a stirred solution of enone **11** (300 mg, 1.1 mmol) was added molecular iodine (838 mg, 3.3 mmol) in anhydrous MeOH (10 mL) at ambient temperature under inert atmosphere. The reaction mixture was heated under reflux for 14 h. When the reaction was completed, the reaction mixture was cooled to ambient temperature and solvent was removed

under reduced pressure. The residue was extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were quenched with sodium thiosulfate and then washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on column chromatography using silica gel silica gel (60-100 mesh) 10 % EtOAc-hexane as eluent to give aromatic product compound (219 mg, 60 %) as pale yellow syrupy liquid; IR (neat, cm^{-1}): 2932, 1459, 1100, 810, 764; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.21 (m, 5H), 6.97 (d, *J* = 8.08 Hz, 1H), 6.66 (d, 1H), 6.58 (s, 1H), 4.42 (s, 2H), 3.77 (s, 3H), 3.39 (t, *J* = 6.6 Hz, 2H), 3.13 (m, 1H), 2.31 (s, 3H), 1.70-1.45 (m, 4H), 1.16 (d, *J* = 7.3 Hz, 3H); HRMS (ESI): *m/z* 299 (M^++ H).

To a stirred solution of Al powder (0.45 g, 16.5 mol) was added molecular iodine (2.62 g, 11.5 mol) in anhydrous CH_2Cl_2 (20 mL) at ambient temperature under inert atmosphere. The reaction mixture was heated under reflux for 1 h. To the resulted AlI_3 solution was cooled to -10 °C. To this cooled AlI_3 solution was added benzyl protected anisole compound (0.1 g, 0.337 mol) slowly and stirring was continued for 0.5 h at -10 °C. The reaction mixture was quenched with saturated NH_4Cl and sodium thiosulphate. Later the mixture was warmed to ambient temperature and solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were quenched with sodium thiosulfate and then washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on column chromatography using silica gel silica gel (60-100 mesh) 40 % EtOAc-hexane as eluent to give product **16** (42 mg, 60 %) as pale yellow syrup; $[\alpha]_D^{27}$: +4.5 (c = 1.7, MeOH): IR (neat, cm^{-1}): 3384, 2931, 1611, 1100, 1043, 764, 810; ^1H NMR (300 MHz, $CDCl_3$): δ 6.99 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 7.6 Hz,1H), 6.60 (s, 1H), 3.80 (s, 3H), 3.57 (t, *J* = 6.8 Hz, 2H), 3.20-3.07 (m,1H), 2.31 (s, 3H), 1.65-1.41 (m,4H), 1.18 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 136.3, 132.4, 128.7, 128.3, 121.1, 63.1, 55.4, 33.1, 31.2, 30.8, 21.2, 20.8; HRMS (ESI): Calculated *m/z* for $C_{13}H_{20}O_2Na$ (M^+ + Na) 231.1360, found 231.1365.

Curcuphenol: To a stirred solution of iodoxybenzoic acid (0.084 g, 0.3 mmol) in DMSO (0.5 mL) was added the compound **16** (0.042 g, 0.2 mmol), which was dissolved in dichloromethane (4 mL). The resulting reaction mixture was stirred at room temperature for a period of 4 h and the completion of the reaction was confirmed by TLC. After addition of water (10 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent followed by rapid chromatography of the resulting residue on silica gel (60-100 mesh) 15 % EtOAc-hexane as eluent to give product furnished unstable aldehyde.

To a solution of *i*PrPPh$_3$I (0.192 g, 0.446 mmol, 2.3 equiv) in THF (3 mL) was added *n*-BuLi (0.28 mL, 0.42 mmol, 1.5 M in THF, 2.2 equiv) dropwise at -10 °C. The mixture wasstirred for 15 min before being cooled to -78 °C. A solution of aldehyde (0.04 g, 0.194 mmol, 1 equiv) in THF (1 mL) was added dropwise. After stirring for 1 h, the reaction mixture was quenched with aqueous saturated NH_4Cl and then extracted with Et_2O. The organic layer was washed with brine, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent: 95 % hexanes 5 % ethyl acetate) to afford methylated curcuphenol $[\alpha]_D^{23.1}$ –3.9 (*c*. 0.26, $CHCl_3$) (Lit) $[\alpha]_D^{25}$ –5.8 (*c*. 1.0, $CHCl_3$): IR (neat, cm^{-1}): 2917, 1612, 1506,1452, 1258; ^1H NMR (300 MHz, $CDCl_3$): δ 7.06 (d, *J* = 7.7 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 6.69 (s, 1H), 5.13 (1H), 3.82 (s, 3H), 3.15(m, 1H), 2.35 (s, 3H), 2.03-1.85 (m, 2H), 1.71-1.62 (m, 1H), 1.69 (br. s, 3H), 1.58-1.49 (m, 1H) 1.56 (br. s, 3H), 1.19(d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 136., 132.8, 131.1, 126.5, 124.9, 121.1, 111.5, 55.3, 37.2, 31.4, 26.3, 25.7, 21.4, 21.1, 17.6. EI-MS: *m/z* 261 (M^++Na).

2-[5-(Benzyloxy)pentan-2-yl]-5-methylphenol (12): To a well stirred solution of α,β-unsaturated enone **11** (1g, 3.6 mmol) in dioxane (20 mL) was added $VOSO_4$ (0.060g, 0.4 mmol) and tetrabutylammonium bromide (1.9 g, 7.4 mmol) under inert atmosphere at ambient temperature and then trifluoro acetate (0.6 mL, 7.2 mmol) was added drop wise at 0 °C. The reaction mixture was refluxed at 110 °C with vigorous stirring over a period of 20 h. The reaction mixture was concentrated under reduced pressure. Then distilled H_2O was added to reaction mixture and then the resultant aqueous solution of mixture was extracted with Et_2O (5 × 20 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on column chromatography using silica gel (60-100 mesh) 15 % EtOAc-hexane as eluent to give pure phenolic product (0.204 g, 20 % yield) as colourless oil; IR (neat, cm^{-1}); ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.28 (m, 5H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 1H), 6.55 (s, 1H), 5.74 (bs, 1H), 4.53-4.50 (m, 2H), 3.53-3.43 (m, 2H), 3.07 (m, 1H), 2.25 (s, 3H), 1.70-1.47 (m, 4H), 1.12 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.3, 135.1, 133.8, 128.7, 127.9, 127.8, 126.8, 126.1, 121.4, 116.2, 73.2, 70.8, 35.4, 34.2, 31.2. 27.1, 21.3; ESI-MS: *m/z* 307 (M^++ Na); HRMS(ESI): Calculated *m/z* for $C_{19}H_{24}O_2Na$ (M^+ +Na) 307.1673, found 307.1684

2-[5-(Benzyloxy)pentan-2-yl]-5-methylcyclohexa-2,5-diene-1,4-dione (13): To a solution of the compound **12** (0.2 g, 0.7 mmol) in methanol was added dropwise a solution of BTI (0.635 g, 1.477 mmol) in methanol at 0 °C and the resulting mixture was stirred at 0 °C until TLC showed disappearance of the compound **13** (2 h). Removal of the solvent followed by purification on column chromatography using silica gel (60-100 mesh) 60 % EtOAc-hexane as eluent to give pure pure quinone compound 0.167 g, 80 %; $[\alpha]_D^{33.8}$+ 7.7 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.33-7.21(m, 6H), 6.7(d, *J* = 2.0 Hz, 1H), 6.47 (s, 1H), 4.44 (s, 2H), 3.43-3.37 (m, 2H), 2.94-2.86 (m, 1H), 2.03 (d, *J* = 2.0 Hz, 3H), 1.63-1.54 (m, 2H), 1.54-1.47(m, 2H), 1.12 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.2, 181.8, 154.0, 138.4, 134.0, 131.2, 128.7, 128.0, 118.2, 73.2, 70.1, 32.4, 31.2, 27.8, 19.8, 15.3; ESI-MS: *m/z* 321 (M^++ Na); HRMS(ESI): Calculated *m/z* for $C_{19}H_{22}O_3Na$ (M^+ +Na) 321.1466, found 321.1451.

To a well stirred solution of *p*-quinone (0.167 g, 0.56 mmol) in MeOH (18 mL) and H_2O (0.5 mL) was added $Na_2S_2O_4$ (0.048 g, 0.28 mmol) solid in portions and stirring was continued for 0.5 h to reduce unstable *o*-quinone to their catachol forms. When the reaction was complete, the reaction mixture was concentrated under reduced pressure. The residue was extracted with Et_2O (3 × 10 mL) and filtered. The combined

organic layers were washed with water, brine and dried with Na_2SO_4. Removal of the solvent followed by purification on column chromatography using silica gel (60-100 mesh) 15 % EtOAc-hexane as eluent to afford desired pure catachol product 12 (0.138 g) with 82 % yield as colourless syrup oil; $[\alpha]_D^{32.2}$: - + 2.7 (*c* = 0.47, $CHCl_3$): IR (neat, cm^{-1}) 3420, 2922, 1461, 1084, 738, 563; ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.30-7.24 (m, 5H), 6.52-6.48 (d, 2H), (br, 1H), 4.52 (s, 2H), 4.32 (br, 1H), 3.54-3.36 (m, 2H), 3.11-2.98 (m, 1H), 1.92-1.82 (m, 1H), 1.65-1.47 (m, 3H), 1.19 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; HRMS (ESI): Calculated *m/z* for $C_{19}H_{25}O_3$ (M^++ H) 301.0000, found 301.0000.

4-(2,5-Dimethoxy-4-methylphenyl)pentan-1-ol (14): To the stirred solution of catachol derivative (200 mg, 0.67 mmol) in DMSO (5 mL) was added pulverized KOH (150 mg, 2.68 mmol) in portions. Then MeI (0.2 mL, 3.35 mmol) was added slowly dropwise at 0 °C and stirring was continued for 12 h. Removal of solvent followed by purification on column chromatography solvent followed by purification on column chromatography using silica gel (60-100 mesh) 2 % EtOAc-hexane as eluent to afford desired pure colourless liquid; IR (neat, cm^{-1}) 2923, 1630, 1455, 1050, 738, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.24 (m, 5H), 6.57(d, 2H), 4.43 (s, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 3.39 (td, *J* = 6.0, 1.5 Hz, 2H), 3.18-3.05 (m, 1H), 2.15 (s, 3H), 1.69-1.46 (m, 4H), 1.18 (d, *J* = 6.8 Hz, 3H); HRMS (ESI): Calculated *m/z* for $C_{21}H_{28}O_3Na$ (M^+ + Na) 351.1936, found 351.1950.

To a stirred solution of Al powder (500 mg, 18.5 mmol) was added molecular iodine (3.3 g, 12.9 mmol) in anhydrous CH_2Cl_2 (40 mL) at ambient temperature under inert atmosphere. The reaction mixture was heated under reflux for 1 h. To the resulted AlI_3 solution was cooled to -10 °C. To this cooled AlI_3 solution was added benzyl protected compound (120 mg, 0.37 mmol) dropwise and stirring was continued for 0.5 h at -10 °C. The reaction mixture was quenched with saturated NH_4Cl. Later the mixture was warmed to ambient temperature and solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sodium thiosulfate followed by washed with water, brine and dried with Na_2SO_4. Removal of the solvent followed by column chromatography using silica gel (60-100 mesh) 30 % EtOAc-hexane as eluent to afford desired pure furnished required benzyl deprotected alcohol product (53 mg, 60 %) as pale yellow liquid. IR (neat, cm^{-1}): 3363, 2937, 1505, 1464, 1398, 1209, 1046; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (d, *J* = 6.8 Hz, 3H), 1.44 (s, 1H, OH, D_2O exchangeable), 1.44-1.65 (m, 2H), 2.20 (s, 3H), 3.17 (sext., *J* = 6.8 Hz, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 6.67 (d, 2H); EI-MS: *m/z* 261 (M^++Na).

1,4-Dimethoxy-2-methyl-5-(6-methylhept-5-en-2-yl)benzene (15): To a stirred solution of iodoxybenzoic acid (0.070 g, 0.251 mmol) in DMSO (0.5 mL) was added the compound **14** (0.04 g, 0.167 mmol), which was dissolved in DCM (4 mL). The resulting reaction mixture was stirred at room temperature for a period of 4 h and the completion of the reaction was confirmed by TLC. After addition of water (10 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent followed by rapid chromatography of the resulting residue on silica gel with to furnished unstable aldehyde.

To a solution of *i*PrPPh$_3$I (0.174 g, 0.389 mmol) in THF (3 mL) was added *n*-BuLi (0.24 mL, 0.372 mmol, 1.5 M in THF) dropwise at -10 °C. The mixture was stirred for 15 min before being cooled to -78 °C. A solution of aldehyde (0.04 g, 0.169 mmol) in THF (1 mL) was added dropwise. After stirring for 1 h, the reaction mixture was quenched with aqueous saturated NH_4Cl and then extracted with Et_2O. The organic layer was washed with brine, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by solvent followed by purification on column chromatography using silica gel (60-100 mesh) 5 % EtOAc-hexane as eluent to afford desired pure curcuhydroquinone dimethyl ether as a clear, colourless oil (0.065 g, 65 %); syrup; IR (neat, cm^{-1}): 2961, 1464, 1398, 1206, 1048, 825, 798; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67(d, 2H), 5.13 (br. t, *J* = 7.2 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.15 (m, 1H), 2.22 (s, 3H), 2.01-1.85 (m, 2H), 1.68 (s, 3H), 1.67-1.56 (m, 2H), 1.55 (s, 3 H), 1.20 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.8, 150.8, 134.0, 131.1, 124.8, 124.2, 114.3, 109.8, 56.4, 56.1, 37.3, 31.8, 26.3, 25.7, 21.3, 17.6, 16.1); EI-MS: *m/z* 261 (M^++ Na).

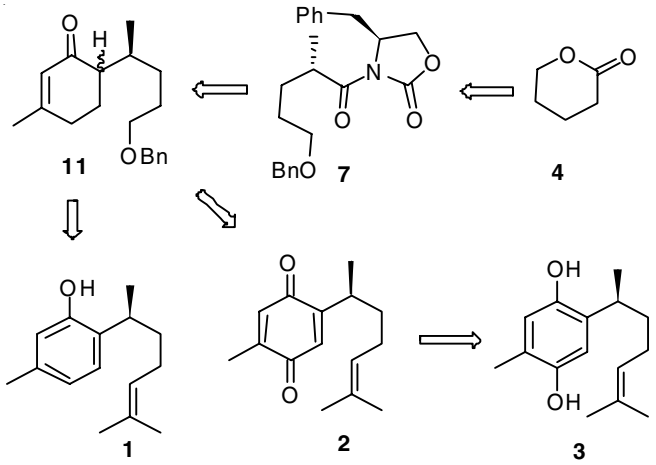
Curcuquinone: Solution of CAN (0.324 g, 0.591 mmol) in H_2O (2 mL) was added dropwise to a solution of Curcuhydroquinone dimethyl ether (**15**) (0.050 g, 0.19 mmol) in MeCN (4 mL) and one drop of petroleum ether at room temperature. The reaction was stirred for 0.5 h before being extracted into CH_3Cl (2 × 10 mL), concentrated *in vacuo* and followed by purification on column chromatography using silica gel (60-100 mesh) 5 % EtOAc-hexane as eluent to afford desired pure curcuquinone as a bright yellow oil (0.0185 g, 42 %). All characterization data matched that reported in the literature; IR (neat, cm^{-1}): 2961, 1464, 1398, 1206, 1048, 825, 798; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.69 (s, 1H), 6.68 (s, 1H), 5.13 (br. t, *J* = 7.2 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.15 (m, 1H), 2.22 (s, 3H), 2.01-1.85 (m, 2H), 1.68 (s, 3H), 1.67-1.56 (m, 2H), 1.55 (s, 3 H), 1.20 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.8, 150.8, 134.0, 131.1 (C-6), 124.8, 124.2, 114.3, 109.8, 56.4, 56.1, 37.3, 31.8, 26.3, 25.7, 21.3, 17.6, 16.1, EI-MS: *m/z* 255 (M^++Na).

Curcuhydroquinone: To a well stirred solution of curcuquinone (**2**) (0.03 g, 0.129mmol) in MeOH (6 mL) and H_2O (0.1 mL) was added $Na_2S_2O_4$ (0.044 g, 0.258 mmol) solid in portions and stirring was continued for 0.5 h. When the reaction was completed, the reaction mixture was concentrated under reduced pressure. The residue was extracted with Et_2O (3 × 10 mL) and filtered. The combined organic layers were washed with water, brine and dried with Na_2SO_4. Removal of the solvent followed by purification on column chromatography using silica gel (60-100 mesh) 10 % EtOAc-hexane as eluent to afford desired pure to afford desired pure product **1** 0.024 g with 80 % yield as colourless syrup, $[\alpha]_D^{20}$ + 47.0 (*c* 1.0, CH_3Cl) Lit. (*S*)-enantiomer $[\alpha]_D^{20}$ + 47.1 (*c* 1.0, CH_3Cl); ^{1}H NMR ($CDCl_3$, 300 MHz) 6.59 (s, 1H), 6.57 (q, 1H), 5.13 (m, 1H, 5-H), 4.32 (br. s, 1H, OH), 4.28 (br. s, 1H, OH), 2.94 (m, 1H), 2.18 (s, 3H,), 2.00-1.89 (m, 2H, 4-H_2), 1.69 (q, 3H), 1.67-1.54 (m, 2H), 1.55 (d, 3H), 1.21 (d, 3H) ^{13}C NMR ($CDCl_3$, 75 MHz) 147.8, 146.6, 132.2, 131.7, 124.5, 121.7, 117.9, 113.4,

37.4, 31.4, 26.0, 25.7,21.1, 15.4, 12.7. EI-MS: *m/z* 257 (M^+ + Na).

RESULTS AND DISCUSSION

In retro synthetic analysis, outlined in **Scheme-I**, we envisaged that the target molecules prepared from *o*-valerolactone **4** takes the advantage of Evans asymmetric methylation of 5-(benzyloxy)pentanoic acid **5** to correctly install the chiral methyl centre at C-2 position, an oxidative aromatization using iodine in methanol. Then a regioselective oxidation of the phenol derivative to derive *o*-quinone would easily provide the final target molecules.

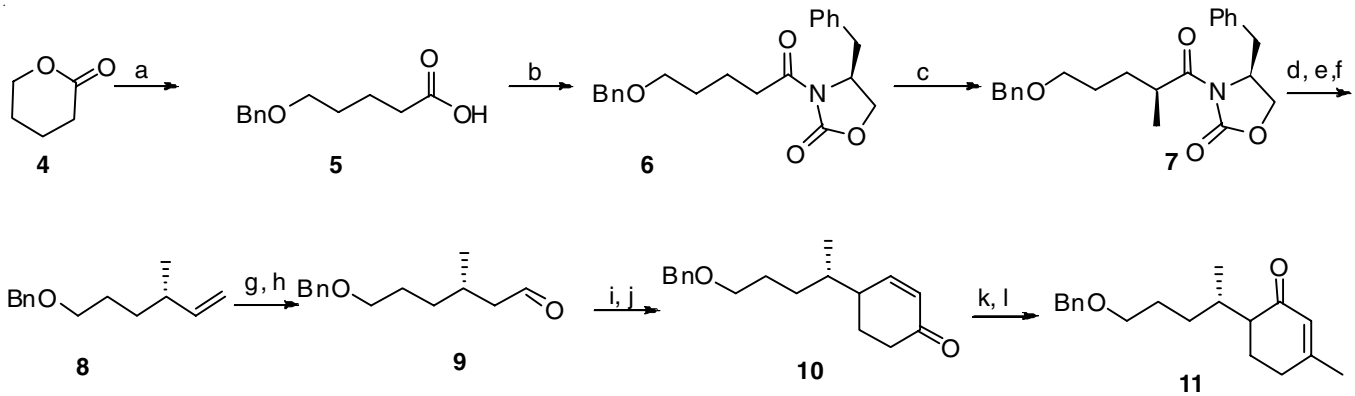


Scheme-I: Retro synthetic analysis of target molecules (-)-curcuphenol (**1**), (-)-curcuquinone (**2**) and (-)-curcuhydroquinone (**3**)

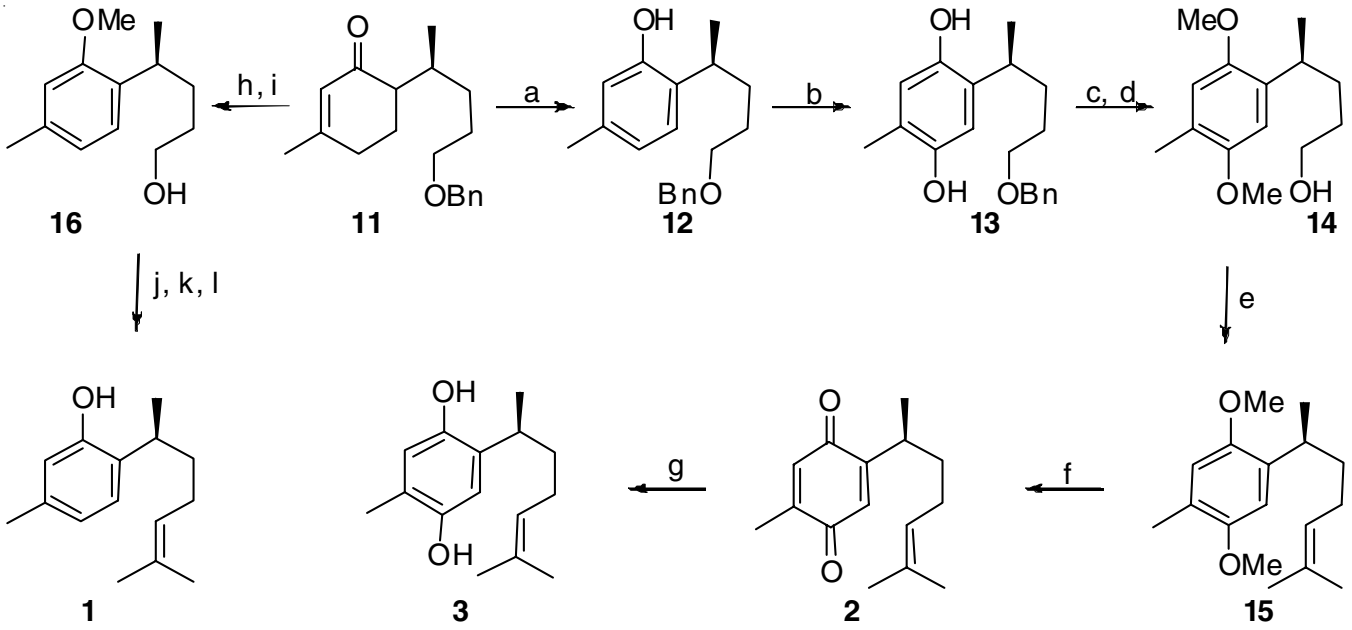
Accordingly, the synthesis of the target molecules started from the commercially available *o*-valerolactone **(Scheme-II)** which was on treatment with BnCl with KOH under refluxed toluene for 16 h provides acid derivative of benzylether [4,6]. Then we synthesized (R or S) oxazolidinone from D-phenylalanine, a chiral auxiliary used to fixed stereo centre of the methyl substituent at benzylic position in 7. For this first the acid derivative **5** was coupled with lithiated chiral auxiliary generated by consecutive addition of triethylamine, pivoloyl chloride and lithium chloride at -20 °C in anhydrous THF to give an imide **6** [7,8] and to this added NaHMDS followed by addition of MeI at -78 °C gave the chiral compound **7** in 76 % yield with high diastereoselectivity (> 99 %). The resultant Evans product was then reduced by $NaBH_4$ in MeOH to furnish the enantiomerically pure alcohol in 70 % yield.

Oxidation of chiral alcohol under Swern conditions gave the aldehyde in quantitative yield, which was immediately subjected to C_1-wittig olefination with triphenylphosphonium iodide using *n*-butyl lithium at 0 °C to afford the olefin **8** in 84 % yield. The olefin derivative **8** was then converted into the corresponding primary alcohol by hydroboration with 9-BBN dimer in dry THF followed by oxidation with H_2O_2 in the presence of sodium hydroxide with 70 % yield [9]. Swern oxidation of the resulting primary alcohol intermediate gave the desired aldehyde **9** in quantitative yield, which was treated with buten-3-one in presence of diethylamine trimethylsilane under refluxing CH_3CN for longer hours gave the Michael adduct in 75 % yield. Then after, the treatment of Michael adduct with a solution of 5 % aqeous KOH with tetrabutylammonium-hydroxide in diethylether/THF under reflux conditions gave the desired Robinson annulated enone **10** in 80 % yield as a diastereomeric mixture. Later on, the racemic enone **10** was treated with CH_3MgI to afford the *tert*-alcohol in 72 % yield. When the resultant *tert*-alcohol treated with pyridinium chlorochromate promotes [1,3]-oxidative rearrangement to produce α,β-unsaturated cyclo-hexenone **11** (**Scheme-II**) in 70 % yield [10]. Here the key intermediate enone **11** was transformed into methyl phenyl ether *via* oxidative aromatization under drastic reflux condition of molecular iodine and methanol mixture with 66 % yield [11], which was subjected to selective debenzylation with AlI_3 at -10 °C under inert atmosphere provides primary alcohol **16** in 60 % yield without disturbing the methyl ether protection [12], which was oxidized into aldehyde using IBX in DMSO/DCM provided 84 % yield and sequential elaboration made with the respective Wittig olefination reagent using *n*-butyl lithium in 65 % yield.

Afterward the resultant curcuphenol methyl ether was treated with AlI_3 at 0 °C under acid mediated demethylation condition accomplished natural bioactive (-)-curcuphenol in 64 % yield [13] (**Scheme-III**). On the other hand, oxidative



Scheme-II: a. BnCl, KOH, PhMe, reflux, 16 h; (b) (i) PivCl, NEt_3, THF, -20 °C, then, LiCl, 84 %; (c) NaHMDS, THF, MeI, HMPA, -78 °C to -30 °C, 2 h, 76 %; (d) $NaBH_4$, MeOH, 0 °C to room temperature, 2 h, 70 %; (e) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then, Et_3N, room temperature, 2 h, quantitative yield; (f) *n*-BuLi, Ph_3PCH_2I, THF, 0 °C to room temperature, 3 h, 84 %; (g) 9-BBN-H, THF, room temperature, 2 h, then 20 % NaOH, 30 % H_2O_2, room temperature, 12 h, 70 %; (h) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then Et_3N, room temperature, 2 h, quantitative yield; (i) MVK, $TMSNEt_2$, CH_3CN, room temperature to reflux, 48 h, 75 %; (j) Bu_4NOH, THF/ether/5 % KOH, reflux, 8 h, 80 %; (k) Mg, CH_3I, ether, 0 °C to room temperature, 72 %; (l) PCC, CH_2Cl_2, 0 °C to room temperature, 2.5 h, 70 %



Scheme-III: (a) $VOSO_4$, Bu_4NBr, O_2, 1,4-dioxane, room temperature to reflux, 48 h; 45 % (b) i) BTI, MeOH, room temperature 3 h, 80 %; ii) $Na_2S_2O_4$, 30 min, room temperature, 84 %; (c) CH_3I, KOH, 0 °C to room temperature,12 h, 60 %; (d) AlI_3, CH_2Cl_2, -10 °C, 30 min, 70 %; (e) (i) IBX, DMSO:CH_2Cl_2 (1:9), room temperature, 4h, 82 %; (ii) $Ph_3P{=}CH(CH_3)_2I$, *n*-BuLi, THF, -78 °C, 3 h, 52 %; (f) CAN, CH_3CN/H_2O, room temperature, 56 %; (g) $Na_2S_2O_4$, THF, H_2O, room temperature, 78 %; (i) I_2, MeOH, room temperature to reflux,12 h, 66 %; (h) AlI_3, CH_2Cl_2, -10 °C, 30 min, 60 %; (j) IBX, DMSO:CH_2Cl_2 (1:9), room temperature, 4 h, 84 %; (k) $Ph_3P{=}CH(CH_3)_2I$, *n*-BuLi, THF, -78 °C, 3 h, 65 %; (l) AlI_3, CH_2Cl_2, 0 °C, 1 h, 64 %

aromatization of a key intermediate **11** using $VOSO_4$, Bu_4NBr and TFA under atmospheric oxygen in refluxing 1,4-dioxane provided the corresponding phenol derivative **12** in 45 % isolated yield [14]. Then oxidation of **12** with *bis*(trifluoroacetate)iodobenzene (BTI) in methanol gave the *p*-quinone in 80 % yield [15], which undergoes reductive aromatization with sodium dithionate delivered compound **13** in 84 % yield. Here after methylation of **13** with MeI in the presence of KOH in DMSO gave the dimethyl ether compound [16] followed by debenzylation using AlI_3 at -10 °C under inert atmosphere gave the primary alcohol **14** in 70 % yield.

Oxidation of the alcohol **15** with IBX in DMSO/DCM gave the aldehyde in 82 % yield, which was then subjected to one carbon Wittig olefination ($Ph_3P{=}CH(CH_3)_2I$) in the presence of *n*-butyllithium gave the dimethoxyaromatic bisabolene **15** in 52 % yield [14]. Finally, oxidative demethylation of dimethoxybisabolene **15** using cericammonium nitrate gave the natural (-)-curcuquinone in 56 % yield [18]. The natural (-)-curcuquinone was subjected to reductive aromatization using sodium dithionate gave the (-)-curcuhydroquinone in 78 % yield [17] (**Scheme-III**).

Conclusion

In conclusion, we have demonstrated the synthesis of phenolic center of aromatic bisabolene skeleton done by two complementary methods involving oxidative aromatization using iodine in methanol and vanadium catalyst induced aromatization. The side chain of bisabolene skeleton **1** and **2** was elaborated using respective Wittig olefination. The natural products (+)-curcuphenol, (-)-curcuhydroquinone and (+)-curcuquinone have been prepared from *o*-valerolactone employing Evan's asymmetric methylation, Robinson annulation, [1,3]-oxidative rearrangement, oxidative aromatization, regioselective oxidation of phenol to *p*-quinone as key steps. Our synthetic sequence is useful for an easy access of aromatic bisabolenes such as heliannuols and glandulone of biological importance.

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REFERENCES

1. (a) Z.-T. Du, S. Zheng, G. Chen and D. Lv, *Molecules*, **16**, 8053 (2011); (b) J. ApSimon, The Total Synthesis of Natural Products, John Wiley & Sons: Hoboken, NJ, USA, p. 135 (1983).
2. (a) F.J. McEnroe and W. Fenical, *Tetrahedron*, **34**, 1661 (1978); (b) F. Bohlmann, C. Zdero, H. Robinson and R.M. King, *Phytochemistry*, **20**, 2245 (1981).
3. (a) J.R. Vyvyan, R.C. Brown and B.P. Woods, *J. Org. Chem.*, **74**, 1374 (2009); (b) N.A. Braun and D. Spitzner, *ARKIVOC*, 273 (2007); (c) S. Serra, *Synlett*, 890 (2000); (d) J.R. Vyvyan, C. Loitz, R.E. Looper, C.S. Mattingly, E.A. Peterson and S.T. Staben, *J. Org. Chem.*, **69**, 2461 (2004); (e) C.X. Zhang, S. Ito, N. Hosoda and M. Asami, *Tetrahedron Lett.*, **49**, 2552 (2008); (f) J.P. Lu, X.G. Xie, B. Chen, X.G. She and X.F. Pan, *Tetrahedron Asymm.*, **16**, 1435 (2005); V.K. Honwad and A.S. Rao, *Tetrahedron*, **21**, 2593 (1965); (h) N.P. Damodaran and S. Dev, *Tetrahedron*, **24**, 4113 (1968).
4. K.-H. Altmann, G. Bold, G. Caravatti, D. Denni, A. Flörsheimer, A. Schmidt, G. Rihs and M. Wartmann, *Helv. Chim. Acta*, **85**, 4086 (2002).
5. P.A. Jacobi and Y. Li, *Org. Lett.*, **5**, 701 (2003).
6. (a) D.A. Evans, *Aldrichim. Acta*, **15**, 23 (1982); (b) J.A. Ager, I. Prakash and D.R. Schaad, *Aldrichim Acta*, **30**, 3 (1997); (c) M.T. Crimmins, B.W. King and E.A. Tabet, *J. Am. Chem. Soc.*, **119**, 7883 (1997); (d) M.T. Crimmins and A.L. Choy, *J. Am. Chem. Soc.*, **121**, 5653 (1999).
7. (a) C. Dubost, I.E. Marko and T. Ryckmans, *Org. Lett.*, **8**, 5137 (2006).; (b) K. Rajesh, V. Suresh, J.J.P. Selvam, D.C. Babu and Y. Venkateswarlu, *Helv. Chim. Acta*, **93**, 147 (2010).

8. (a) E.J. Lenardão, G.V. Botteselle, F. de Azambuja, G. Perin and R.G. Jacob, *Tetrahedron*, **63**, 6671 (2007); (b) H. Hagiwara, T. Okabe, H. Ono, V.P. Kamat, T. Hoshi, T. Suzuki and M. Ando, *J. Chem. Soc., Perkin Trans. I*, 895 (2002); (c) H. Hagiwara, H. Ono and T. Hoshi, *Org. Synth.*, **80**, 195 (2003).
9. J.S. Yadav, E.V. Bhasker and P. Srihari, *Tetrahedron*, **66**, 1997 (2010).
10. A.T. Kreipl, C. Reid and W. Steglich, *Org. Lett.*, **4**, 3287 (2002).
11. J.C. Green and T.R.R. Pettus, *J. Am. Chem. Soc.*, **133**, 1603 (2011).
12. T. Moriuchi, K. Kikushima, T. Kajikawa and T. Hirao, *Tetrahedron Lett.*, **50**, 7385 (2009).
13. A. Wu, Y. Duan, D. Xu, T.M. Penning and R.G. Harvey, *Tetrahedron*, **66**, 2111 (2010).
14. J.Y. LeBrazidec, P.J. Kocienski, J.D. Connolly and K.W. Muir, *J. Chem. Soc., Perkin Trans. I*, 2475 (1998).
15. P. Jacob, P.S. Callery, A.T. Shulgin and N. Castagnoli, *J. Org. Chem.*, **41**, 3627 (1976).
16. (a) A. Kamal, M.S. Malik, A.A. Shaik and S. Azeeza, *Tetrahedron Asymm.*, **18**, 2547 (2007); (b) F.J. McEnroe and W. Fenical, *Tetrahedron*, **34**, 1661 (1978).