DOI: 10.1002/ejoc.200901041

Total Synthesis of a Diarylheptanoid, Rhoiptelol B

Chada Raji Reddy,*[a] Nagavaram Narsimha Rao,[a] and Boinapally Srikanth[a]

Keywords: Rhoiptelol B / Total synthesis / Natural products / Reductive etherification / Aldol reactions

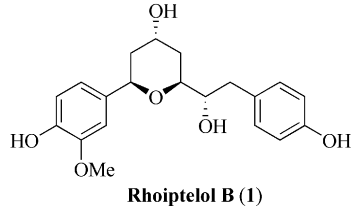
A stereoselective total synthesis of rhoiptelol B has been accomplished for the first time. The four asymmetric centers were efficiently generated through Keck allylation, Jacobson epoxidation Aldol reaction and reductive etherification as the key steps.

Introduction

Diarylheptanoids constitute an important class of natural products due to their interesting biological and pharmacological properties (antiinflammatory, antioxidant, anticancer, inhibition of nitric oxide production, DPPH-radical scavenging activity, etc.).[1] The structure of diarylheptanoids is either cyclic or linear. Predominantly, diarylheptanoids containing a tetrahydropyran (THP) ring such as centrolobines,[2] calyxins,[3] diospongins[4] and others[5] have found substantial interest to medicinal as well as synthetic organic chemists.

Rhoiptelol B (**1**, Figure 1), a diarylheptanoid containing a tetrahydropyran ring, was first isolated in 1996 from the fruits of *Rhoiptelea chiliantha* along with other two diarylheptanoids.[6] Later, in 2007 it was also isolated from the bark of *Alnus hirsuta* (which has been traditionally employed as a herbal medicine for the treatment of inflammatory diseases in Asia) and investigated for their inhibitory activity against LPS-induced NF-*k*B activation, NO and TNF-α production and HIF-1 in AGS cells.[7,8] Till date there is no report on synthesis of rhoiptelol B. The interesting structural feature of this molecule is presence of a chiral hydroxy group on adjacent carbon to tetrahydropyran ring, which is not present in any other diarylheptanoids containing a THP-ring. The above observations combined with our interest on diarylheptanoids[2u] have driven us for the synthesis of rhoiptelol B (**1**).

A variety of approaches have been devised for the synthesis of THP-ring containing diarylheptanoids, which involves the tetrahydropyran ring formation as the key step. This was achieved using a different sequence of reactions such as Prins cyclization,[2a–2f,3a,4e,4f,5] reductive etherification,[2g–2m,4b,4g] oxa-Michael reaction,[2m,4a,4c,4h,4i] Diels–Alder reaction,[2n,3b] palladium mediated cyclization,[2o,4d] $FeCl_3$-mediated cyclization,[2p] radical cyclization,[2q] Maitland–Japp reaction,[2r,2s] olefin metathesis,[2t] etc. However, Keck allylation, Aldol reaction followed by reductive etherification sequence has not been utilized for the synthesis of THP-ring diarylheptanoids. Herein, we presented the first total synthesis of rhoiptelol B.



Rhoiptelol B (1)

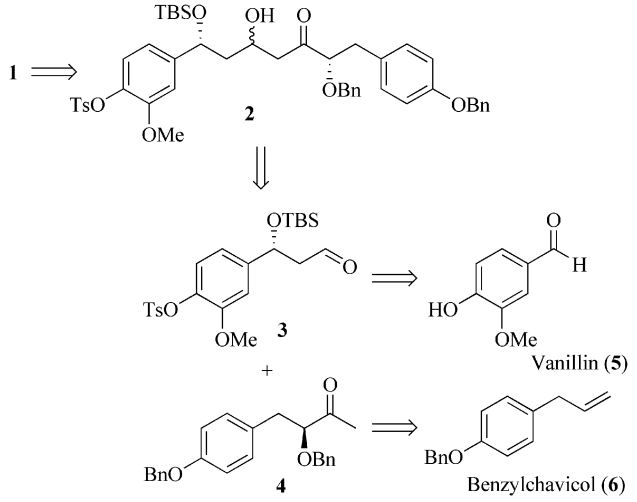
Figure 1. Structure of rhoiptelol B.

Results and Discussion

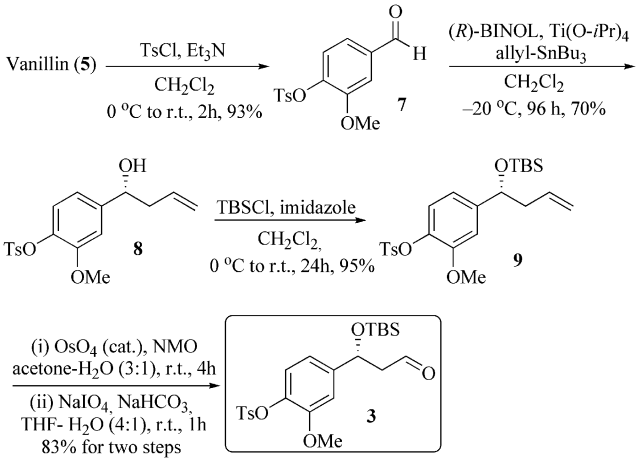
The strategy we have used for the rhoiptelol B (Scheme 1) involves the tetrahydropyran ring formation using reductive etherification of an oxidative derivative of aldol product **2**, which can be obtained via lithium-mediated aldol reaction of aldehyde **3** and α-benzyloxy ketone **4**. Access to these two intermediate fragments **3** was envisioned starting from vanillin (**5**) using Keck allylation and fragment **4** from benzylchavicol (**6**) using Jacobson epoxidation and Wacker oxidation as the key steps.

The synthesis of the aldehyde **3** was started through the tosylation of vanillin (**5**) followed by Keck allylation under (*R*)-BINOL-Ti(O*i*Pr)$_4$ conditions[9] to yield the homoallylic alcohol **8** in 70% yield.[10] The free hydroxy group of **8** was protected as *tert*-butyldimethyl silyl ether **9** (95%), which was subjected to dihydroxylation (OsO_4, NMO) followed by sodium periodate oxidation to provide the aldehyde **3** in 83% yield over two steps (Scheme 2).

[a] Organic Division-I (NPL), Indian Institute of Chemical Technology,
Hyderabad 500607, India
Fax: +91-040-27160512
E-mail: rajireddy@iict.res.in

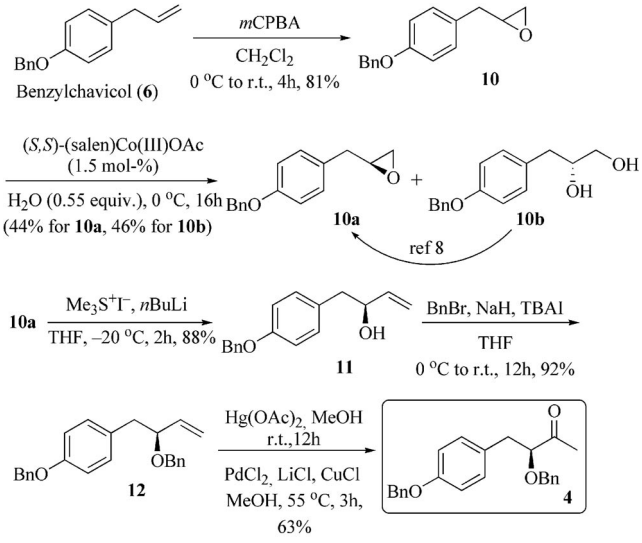


Scheme 1. Retrosynthetic analysis of rhoiptelol B (**1**).



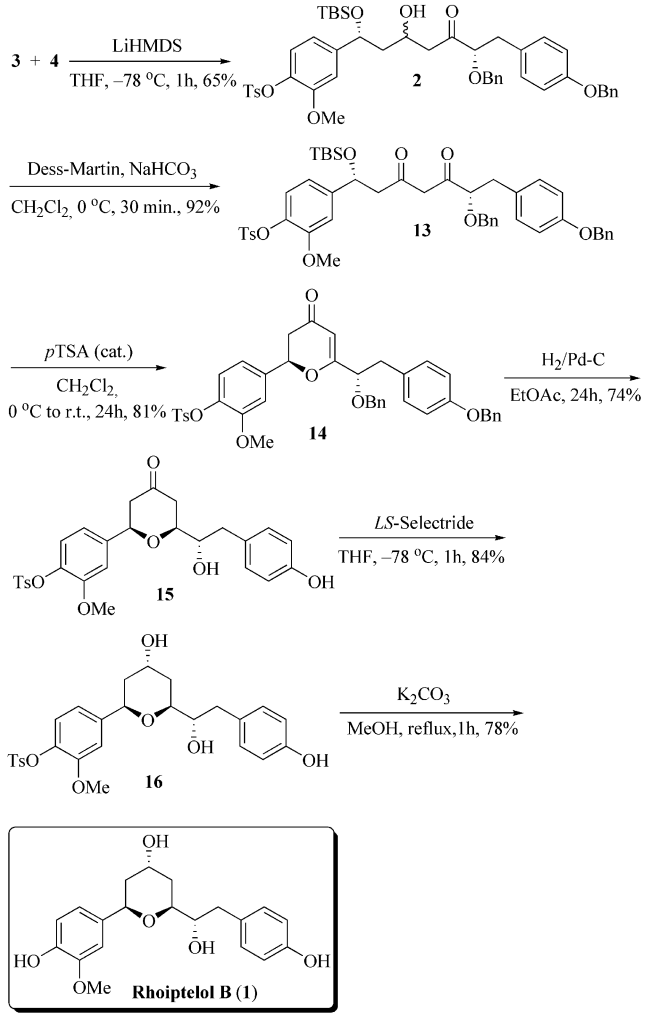
Scheme 2. Synthesis of aldehyde fragment (**3**).

Next, the synthesis of benzyloxy ketone fragment **4** (Scheme 3) was begun with the known benzylchavicol (**6**), which can be obtained in two steps using reported protocol.[11] Thus, epoxidation of benzylchavicol (**6**) using *m*CPBA furnished the epoxide **10** in 81% yield. Resolution of racemic epoxide **10** to chiral epoxide **10a** has been accomplished using Jacobsen resolution method.[12] This resolution reaction provided the chiral epoxide **10a** along with the diol **10b** in 44% and 46% yields, respectively. However, the diol **10b** was also converted into the required epoxide **10a** using a well-known sequence.[13] The enantiomeric excess of this epoxide **10a** was confirmed at a later stage intermediate (**11**) by chiral HPLC.[14] As anticipated, the treatment of epoxide **10a** with trimethylsulfonium iodide in presence of *n*-BuLi as a base in THF at –20 °C revealed the allyl alcohol **11** in 88% yield.[15] The benzyl protection of allylic alcohol **11** using benzyl bromide/NaH gave **12** (92% yield), which was then subjected to modified Wacker oxidation[16,17] to obtain the desired ketone fragment **4** in 63% yield.[18]



Scheme 3. Synthesis of ketone fragment (**4**).

Having both aldehyde **3** and ketone **4** fragments in hand, our next task was to do the lithium-mediated aldol reaction followed by the conversion of aldol product to tetra-



Scheme 4. Synthesis of rhoiptelol B from **3** and **4**.

hydropyran ring. Thus, the treatment of ketone **4** with lithium bis(trimethylsilyl)amide at –78 °C followed by the addition of aldehyde **3** at the same temperature gave the coupled product **2** in 65% yield as mixture of diastereomers.[19] This inseparable mixture of diastereomers was oxidized using Dess–Martin periodinane to the corresponding β-diketone **13** in 92% yield, which was entirely existed as the enol ketone (confirmed by ^{1}H NMR).[20] Then, the reaction of **13** with *p*TsA in CH_2Cl_2 was promoted the silyl ether cleavage followed by cyclization and dehydration reactions to yield dihydropyranone **14** in 81% yield.[21] Subsequently, the selective reduction of olefin and debenzylation of **14** was accomplished in one-pot under hydrogenation reaction conditions to afford tetrahydropyranone **15** (74% yield) as a single isomer.[22] *LS*-Selectride reduction of the tetrahydropyranone **15** provided the desired alcohol **16** in 84% yield with a 10:1 diastereoselectivity.[23] The compound **16** was extensively characterized by nOe studies.[24] Finally, detosylation of **16** with K_2CO_3 in MeOH under refluxing conditions afforded the rhoiptelol B (**1**), (Scheme 4). The spectroscopic data (^{1}H NMR, ^{13}C NMR and mass) of synthetic rhoiptelol was identical and the optical rotation {$[\alpha]_D^{28}$ = +77.2 (*c* = 0.2, MeOH)} was comparable with the reported data for natural product.[6,7]

Conclusions

In conclusion, we have accomplished the first total synthesis of rhoiptelol B in 15 steps in a convergent fashion. The key steps used were Keck allylation, Jacobson resolution, lithium-mediated aldol reaction and reductive etherification for the generation of required chiral centers. Further elaboration of this sequence of reactions to construct the other tetrahydropyran ring containing biologically active compounds is underway in our laboratory.

Experimental Section

General: ^{1}H NMR and ^{13}C NMR spectra were recorded either in $CDCl_3$ or in [D_4]MeOH solvent on 300 MHz, 500 MHz or 75 MHz spectrometer at ambient temperature. Chemical shifts δ is given in ppm, coupling constant *J* are in Hz. The chemical shifts are reported in ppm on scale downfield from TMS as internal standard and signal patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; td, triplet of doublet; t, triplet; m, multiplet;br. s, broad singlet. FTIR spectra were recorded as thin films on KBr or neat. Optical rotations were measured on digital polarimeter using a 1 mL cell with a 1 dm path length. For low (MS) and High (HRMS) resolution, *m*/*z* ratios are reported as values in atomic mass units. HPLC was done using Eurocel 01, chiral IA columns and 2-propanol and hexane as eluents. All the reagents and solvents were reagent grade and used without further purification unless specified otherwise. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. Tetrahydrofuran (THF) when used as solvent for the reactions was freshly distilled from sodium benzophenone ketyl. Column chromatography was carried out using silica gel (60–120 mesh & 100–200 mesh) packed in glass columns. All the reactions were performed under an atmosphere of nitrogen in flame- or oven-dried glassware with magnetic stirring.

4-Formyl-2-methoxyphenyl-4-methylbenzenesulfonate (7): To a stirred solution of vanillin **5** (5 g, 32.8 mmol) in dichloromethane (65 mL) at 0 °C was added triethylamine (3.31 g, 32.8 mmol) followed by *p*-toluenesulfonyl chloride (6.26 g, 32.8 mmol). Then, the reaction temperature was raised to 25 °C and stirred for 2 h. The reaction was diluted with 1 N HCl (30 mL) and the layers were separated. The organic layer was further washed with 1 N HCl (2 × 20 mL) followed by saturated aqueous $NaHCO_3$ (20 mL) and with brine (20 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (15% ethyl acetate in hexanes) to give **7** (9.3 g, 93%) as a color less solid; m.p. 126–128 °C. IR (KBr): $\tilde{\nu}_{max}$ = 2922, 2851, 1699, 1596, 1422, 1149, 1115, 1029, 857, 713 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.91 (s, 1 H, CHO), 7.75 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.46–7.28 (m, 5 H, Ar-H), 3.63 (s, 3 H, OCH_3), 2.4 (s, 3 H, Ar-CH_3) ppm. ^{13}C NMR (75 MHz): δ = 190.7, 152.4, 145.4, 142.8, 135.6, 132.6, 129.4, 128.4, 124.3, 124.1, 110.9, 55.6, 21.5 ppm. HRMS (ESI): (*m*/*z*) calcd. for $C_{15}H_{14}O_5NaS$, 329.0459 [M + Na]$^+$; found 329.0456.

(*R*)-4-(1-Hydroxybut-3-enyl)-2-methoxyphenyl-4-methylbenzenesulfonate (8): To the stirred solution of oven-dried 4-Å molecular sieves (10 g) in CH_2Cl_2 (40 mL) under N_2 atmosphere, was added (*S*)-BINOL (0.93 g, 3.2 mmol) a 1.0 M solution of Ti(O*i*Pr)$_4$ (0.4 g, 1.63 mmol) in CH_2Cl_2 and a freshly prepared 1.0 M solution of TFA (13 mg, 0.11 mmol) in CH_2Cl_2. The reaction mixture was heated at reflux for a period of 3 h, and then allowed to cool to room temperature. Aldehyde **7** (5 g, 16.3 mmol) in CH_2Cl_2 (20 mL), was added to the reaction mixture. After the mixture stirred for 0.5 h at room temperature, cooled to –78 °C, allyltributyltin (6.5 mL, 21.2 mmol) was slowly added. The reaction mixture as stirred for an additional 10 min at –78 °C, then kept in a –20 °C freezer. After 4 d, the reaction mixture was filtered through a pad of celite in to a 500 mL flask that contained a stirring saturated aqueous $NaHCO_3$ solution (50 mL) and the resulting mixture was stirred for 1 h, then the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The crude residue was purified by column chromatography (12% ethyl acetate in hexanes) to give **8** (4.0 g, 70%) as a colorless oil: $[\alpha]_D^{25}$ = +17 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3541, 2931, 1600, 1502, 1369, 1273, 1175, 1034, 847, 753, 661 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.27 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.06 (d, *J* = 8.3 Hz, 1 H, Ar-H), 6.86 (d, *J* = 1.5 Hz, 1 H, Ar-H), 6.80 (dd, *J* = 8.3, 2.2 Hz, 1 H, Ar-H), 5.84–5.68 (m, 1 H, CH=CH_2), 5.18–5.09 (m, 2 H,CH_2=CH), 4.68–4.61 (m, 1 H, CHOH), 3.57 (s, 3 H, OCH_3), 2.52–2.33 (m, 2 H, CH_2-CH=CH_2), 2.45 (s, 3 H, Ar-CH_3) ppm. ^{13}C NMR (75 MHz): δ = 151.6, 145.0, 144.3, 137.3, 134.1, 133.1, 129.3, 128.5, 123.6, 118.5, 117.8, 110.1, 72.6, 55.5, 43.8, 21.6 ppm. HRMS (ESI): (*m*/*z*) calcd. for $C_{18}H_{24}NO_5S$, 366.1375 [M + NH_4]$^+$; found 366.1377.

(*R*)-4-[1-(*tert*-Butylmethylsilyloxy)but-3-enyl]-2-methoxyphenyl-4-methylbenzenesulfonate (9): To a stirred solution of alcohol **8** (4.0 g, 11.4 mmol), in CH_2Cl_2 (40 mL) was added imidazole (1.17 g, 17.2 mmol) and DMAP (140 mg, 1.14 mmol) fallowed by *tert*-butyldimethylsilyl chloride (2.0 g, 13.2 mmol) at 0 °C. Then the reaction temperature was raised to room temperature and stirred for 24 h. After the addition of saturated aqueous $NaHCO_3$ (20 mL), the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4,

filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (5% ethyl acetate in hexanes) to give **9** (5.0 g, 95%) as a colorless oil. $[\alpha]_D^{28}$ = +23.8 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2931, 2856, 1600, 1502, 1373, 1176, 1089, 840, 778, 660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.24 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.08 (d, *J* = 8.3 Hz, 1 H, Ar-H), 6.79 (d, *J* = 1.5 Hz, 1 H, Ar-H), 6.73 (dd, *J* = 8.3, 2.2 Hz, 1 H, Ar-H), 5.78–5.62 (m, 1 H, CH=CH_2), 5.03–4.93 (m, 2 H, CH_2=CH), 4.62–4.56 (m, 1 H, CHOSi), 3.52 (s, 3 H, OCH_3), 2.44 (s, 3 H, Ar-CH_3), 2.42–2.24 (m, 2 H, CH_2-CH=CH_2), 0.86 [s, 9 H, $(CH_3)_3Si$], 0.02 (s, 3 H, CH_3Si), –0.15 (s, 3 H, CH_3Si) ppm. ^{13}C NMR (75 MHz): δ = 151.6, 145.6, 145.0, 137.2, 134.9, 133.2, 129.3, 128.9, 123.6, 118.0, 117.4, 110.2, 74.6, 55.5, 45.5, 25.9, 21.8, 18.3, –4.5, –4.7 ppm. HRMS (ESI): (*m*/*z*) calcd. for $C_{24}H_{38}NO_5SSi$, 480.2234 $[M + NH_4]^+$; found 480.2241.

(*R*)-4-[1-(*tert*-Butylmethylsilyloxy)-3-oxopropyl]-2-methoxyphenyl-4-methylbenzenesulfonate (3): To a solution of silyl ether **9** (3.5 g, 7.5 mmol) in 40 mL mixture of acetone/water (3:1) was added OsO_4 (0.48 mL, 4% aqueous solution, 0.075 mmol) and NMO (1.06 g, 9.0 mmol) at 25 °C and stirred at for 5 h. The solvent was evaporated and the residue was extracted with ethyl acetate (30 mL). The organic layers were washed with brine (20 mL), dried with Na_2SO_4 and concentrated in vacuo. To a solution of above crude diol in 50 mL mixture of THF/H_2O (4:1) was added $NaIO_4$ (3.2 g, 15.0 mmol) and the reaction mixture was stirred at 25 °C for 1 h. The solid was removed by filtration and the filtrate was extracted with ethyl acetate (30 mL). The organic layers were washed with brine (20 mL), dried with Na_2SO_4 and concentrated in vacuo. The crude aldehyde was purified by flash chromatography (15% ethyl acetate in hexanes) to give aldehyde **3** (2.9 g, 83%) as a colorless oil. $[\alpha]_D^{30}$ = +27.3 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$= 2931, 2856, 1726, 1600, 1502, 1371, 1176, 1093, 843, 779, 661 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.76 (t, *J* = 2.2 Hz, 1 H, CHO) 7.72 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.28 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.12 (d, *J* = 8.3 Hz, 1 H, Ar-H), 6.86 (d, *J* = 1.5 Hz, 1 H, Ar-H), 6.82 (dd, *J* = 8.3, 2.2 Hz, 1 H, Ar-H), 5.17 (dd, *J* = 8.1, 3.9 Hz, 1 H, CHOSi), 3.53 (s, 3 H, OCH_3), 2.87–2.76 (m, 1 H, CH_2-CHO), 2.65–2.56 (m, 1 H, CH_2-CHO), 2.44 (s, 3 H, Ar-CH_3), 0.86 [s, 9 H, $(CH_3)_3Si$], 0.04 (s, 3 H, CH_3Si), –0.14 (s, 3 H, CH_3Si) ppm. ^{13}C NMR (75 MHz): δ = 200.6, 151.7, 144.9, 144.1, 137.4, 133.0, 129.2, 128.6, 123.9, 117.5, 109.7, 70.0, 55.4, 53.8, 25.6, 21.6, 18.0 –4.7, –5.1 ppm. HRMS (ESI): (*m*/*z*) calcd. for $C_{23}H_{36}NO_6SSi$, 482.2027 $[M + NH_4]^+$; found 482.2036.

2-[4-(Benzyloxy)benzyl]oxirane (10): To a solution of benzyl chavicol **6** (10.0 g, 44.6 mmol) in CH_2Cl_2 (50 mL) was added *m*-chloroperbenzoic acid (14.0 g, 80.0 mmol) at 0 °C in small portions. The reaction mixture was stirred for an additional 5 min at 0 °C, then warmed up to room temperature and stirring was continued for another 3 h at this temperature. Saturated aqueous $NaHSO_3$ (100 mL) was added to the reaction mixture at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL) and the organic phase was dried with Na_2SO_4. Concentration of the organic phase under vacuum gave crude epoxide, which was purified by flash chromatography (5% ethyl acetate in hexanes) to obtain epoxide **10** (8.6 g, 81%) as a white solid; m.p. 50–52 °C. IR (KBr): $\tilde{\nu}_{max}$ = 2920, 2853, 1616, 1510, 1239, 1019, 835, 739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.27 (m, 5 H, Ar-H), 7.16 (d, *J* = 8.5 Hz, 2 H, Ar-H), 6.92 (d, *J* = 8.5 Hz, 2 H, Ar-H), 5.00 (s, 2 H, Ar-CH_2-O), 3.15–3.07 (m, 1 H, CH-O), 2.90–2.70 (m, 3 H, Ar-CH, CH_2-O), 2.51 (dd, *J* = 4.9, 2.6 Hz, 1 H, Ar-CH) ppm. ^{13}C NMR (75 MHz): δ = 157.5, 136.9, 129.9, 129.3, 128.4, 127.8, 127.3, 114.7, 69.9, 52.5, 46.7, 37.7 ppm. HRMS (ESI): (*m*/*z*) calcd. for $C_{16}H_{16}O_2Na$, 263.1047 $[M + Na]^+$; found 263.1058.

(*S*)-2-[4-(Benzyloxy)benzyl]oxirane (10a): Glacial acetic acid (0.0043 mL, 0.748 mmol with respect to catalyst) was added to a reddish orange solution of (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-cobalt(II) (226 mg, 0.375 mmol) in toluene (5 mL) at room temperature and the resulting solution was stirred for 1 h at room temperature in a flask open to the air. The reaction solution was then evaporated in vacuo, affording a brown solid. Racemic epoxide **10** (6.0 g, 25.0 mmol) in dry THF (6 mL) was added to this solid, and the resulting brown-black solution was stirred for 10 min at 0 °C before distilled water (0.247 mL, 13.75 mmol) was added. The resulting solution was vigorously stirred at 0 °C for an additional 5 min before it was warmed to room temperature and stirred for a further 18 h. solvent was removed under vacuum. Purified by column chromatography (5% ethyl acetate in hexanes) gives enantio-enriched epoxide **10a** (2.64 g, 44%) along with diol **10b** (2.9 g, 46%). See spectroscopic data for **10a** epoxide above. $[\alpha]_D^{30}$ = +0.9 (*c* = 1.0, $CHCl_3$). Diol (**10b**): m.p. 70–72 °C. $[\alpha]_D^{26}$ = +9.3 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3454, 2905, 1639, 1512, 1247, 1014, 810, 771, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.28 (m, 5 H, Ar-H), 7.13 (d, *J* = 8.5 Hz, 2 H, Ar-H), 6.93 (d, *J* = 8.5 Hz, 2 H, Ar-H), 5.05 (s, 2 H, Ar-CH_2-O), 3.95–3.84 (m, 1 H, CH-OH), 3.73–3.63 (m, 1 H, CH_2-OH), 3.56–3.45 (m, 1 H, CH_2-OH), 2.79–2.62 (m, 2 H, Ar-CH_2), 2.15 (br. s, 1 H, OH), 2.07 (br. s, 1 H, OH) ppm. ^{13}C NMR (75 MHz): δ = 157.3, 136.9, 130.2, 130.0, 128.4, 127.8, 127.3, 114.8, 73.1, 69.9, 65.7, 38.6 ppm. HRMS (ESI): (*m*/*z*) calcd. for $C_{16}H_{18}O_3Na$, 281.1153 $[M + Na]^+$; found 281.1141.

(*S*)-1-[4-(Benzyloxy)phenyl]but-3-en-2-ol (11): A solution of trimethylsulfonium iodide (6.8 g, 33.3 mmol) in THF (65 mL) was cooled to –20 °C, *n*BuLi (2.5 M solution in hexane, 12.6 mL, 31.2 mmol) was added drop wise and the resulting solution was stirred for 1 h at –20 °C. A solution of the epoxide **10a** (2.0 g, 8.3 mmol) in THF (10 mL) was added and a cloudy suspension was formed. The stirring was continued for another 1 h at –20 °C. The reaction mixture was cooled to 0 °C and quenched with water (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification of crude compound by flash chromatography (8% ethyl acetate in hexanes) gave alcohol **11** (1.86 g, 88%) as a pale yellow oil. $[\alpha]_D^{26}$ = +3.3 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3413, 2922, 1610, 1510, 1239, 1018, 738, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.27 (m, 5 H, Ar-H), 7.14 (d, *J* = 8.5 Hz, 2 H, Ar-H), 6.92 (d, *J* = 8.5 Hz, 2 H, Ar-H), 5.98–5.85 (m, 1 H, CH=CH_2), 5.23 (td, *J* = 17.0, 1.3 Hz, 1 H, CH_2=CH), 5.12 (td, *J* = 10.3, 1.3 Hz, 1 H, CH_2=CH), 5.00 (s, 2 H, Ar-CH_2-O), 4.29 (q, *J* = 6.6 Hz, 1 H, CH-OH), 2.87–2.66 (m, 2 H, Ar-CH_2) ppm. ^{13}C NMR (75 MHz): δ = 157.5, 140.1, 137.0, 130.4, 130.3, 130.2, 129.8, 129.5, 127.8, 127.4, 115.0, 114.8, 73.6, 69.9, 42.8 ppm. HRMS (ESI): (*m*/*z*) calcd. for $C_{17}H_{22}NO_2$, 272.1645 $[M + NH_4]^+$; found 272.1647.

(*S*)-1-(Benzyloxy)-4-[2-(benzyloxy)but-3-enyl]benzene (12): NaH (139.8 mg, 5.82 mmol) was washed with hexane (3 × 2 mL), suspended in THF (15 mL) and cooled to 0 °C. Alcohol **11** (740 mg, 2.91 mmol) in THF (10 mL) was added drop wise into the reaction and the solution stirred for 10 min at 0 °C. Benzyl bromide (0.52 mL, 4.36 mmol) was added slowly, followed by TBAI (107.5 mg, 0.29 mmol). The reaction was warmed to room temperature and stirred for 12 h. Saturated NH_4Cl was added to quench the reaction at 0 °C and the reaction mixture was warmed

to room temperature. The layers were separated and the aqueous layer was further extracted with ethyl acetate (15 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (5% ethyl acetate in hexanes) gave benzyl ether **12** (922 mg, 92%) as a pale yellow oil. $-[\alpha]_D^{30} = -20.5$ (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2921, 2854, 1610, 1509, 1238, 1068, 736, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.16 (m, 10 H, Ar-H), 7.12 (d, J = 8.5 Hz, 2 H, Ar-H), 6.89 (d, J = 8.5 Hz, 2 H, Ar-H), 5.85–5.69 (m, 1 H, CH=CH_2), 5.25–5.09 (m, 2 H, CH_2=CH), 5.00 (s, 2 H, Ar-CH_2-O), 4.58 (d, J = 12.0 Hz, 1 H, Ar-CH-O), 4.32 (d, J = 12.0 Hz, 1 H, Ar-CH-O) 3.91 (q, J = 6.6 Hz, 1 H, CH-OBn), 2.91 (dd, J = 13.7, 7.3 Hz, 1 H, Ar-CH), 2.75 (dd, J = 13.7, 5.8 Hz, 1 H, Ar-CH) ppm. ^{13}C NMR (75 MHz): δ = 157.3, 138.5, 138.2, 137.1, 130.7, 130.5, 128.5, 128.3, 128.1, 127.8, 127.7, 127.5, 127.4, 127.2, 117.3, 114.4, 81.5, 70.1, 69.9, 41.3 ppm. HRMS (ESI): (m/z) calcd. for $C_{24}H_{28}NO_2$, 362.2115 $[M + NH_4]^+$; found 362.2122.

(*S*)-3-(Benzyloxy)-4-[4-(benzyloxy)phenyl]butan-2-one (4): To a solution of alkene **12** (850 mg, 2.47 mmol) in MeOH (17 mL) added mercuric acetate (944.9 mg, 2.96 mmol) was stirred at room temperature for overnight. Then the reaction mixture was transferred to a solution of LiCl (205 mg, 4.94 mmol), $PdCl_2$ (438 mg, 2.47 mmol) and $CuCl_2$ (996.6 mg, 7.41 mmol) in MeOH (8 mL) and was further stirred at 55 °C for 3 h. Saturated $NaHCO_3$ (20 mL) was added, and the product was extracted with diethyl ether (3 × 25 mL). The organic extracts were dried with Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (8% ethyl acetate in hexanes) to furnish methyl ketone **4** (560 mg, 63%) as a colorless oil. $[\alpha]_D^{31} = -34.9$ (c = 0.66, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2922, 2854, 1714, 1612, 1509, 1237, 1104, 1021, 742, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.21 (m, 8 H, Ar-H), 7.17–7.12 (m, 2 H, Ar-H), 7.09 (d, J = 8.5 Hz, 2 H, Ar-H), 6.84 (d, J = 8.5 Hz, 2 H, Ar-H), 5.03 (s, 2 H, Ar-CH_2-O), 4.48 (d, J = 11.7 Hz, 1 H, Ar-CH-O), 4.36 (d, J = 11.7 Hz, 1 H, Ar-CH-O), 3.87 (dd, J = 7.5, 4.7 Hz, 1 H, CH-OBn), 2.95–2.78 (m, 2 H, Ar-CH_2), 2.07 (s, 3 H, CH_3-CO) ppm. ^{13}C NMR (75 MHz): δ = 210.8, 157.6, 137.3, 137.0, 130.4, 129.2, 128.5, 128.3, 127.8, 127.7, 127.6, 127.4, 114.7, 85.9, 72.5, 69.9, 37.5, 26.0 ppm. HRMS (ESI): (m/z) calcd. for $C_{24}H_{28}NO_3$, 378.2064 $[M + NH_4]^+$; found 378.2076.

4-{(1*R*,6*S*)-6-(Benzyloxy)-7-[4-(benzyloxy)phenyl]-1-(*tert*-butyldimethylsilyloxy)-3,5-dioxoheptyl}-2-methoxyphenyl 4-Methylbenzenesulfonate (13): To a stirred solution of ketone **4** (360 mg, 1.0 mmol) in THF (3 mL) at –78 °C was added drop wise a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 1.5 mL, 1.5 mmol). After stirring at –78 °C for 45 min, aldehyde **3** (696 mg, 1.5 mmol) in THF (3 mL) was added. The resulting solution was stirred at –78 °C for another 45 min and was then quenched with saturated NH_4Cl (3 mL), two layers were separated. The aqueous layer was extracted with ethyl acetate (10 mL) and the combined organic extracts were washed with brine (3 mL), dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (15% ethyl acetate in hexanes) to give aldol adduct **2** as a mixture of diastereomers.

To a stirred solution of diastereomeric mixture of aldol adduct **2** (450 mg, 0.54 mmol) in dry CH_2Cl_2 (5.4 mL) was added $NaHCO_3$ (91.7 mg, 1.09 mmol) and Dess–Martin periodinane (347 mg, 0.81 mmol) in one portion. The mixture was stirred for 1 h at room temperature and quenched with saturated aqueous $Na_2S_2O_3$ (5 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine (3 mL), dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (15% ethyl acetate in hexanes) to give β-diketone **13** (412 mg, 92%) as a viscous liquid. $[\alpha]_D^{25} = -5.5$ (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2929, 2856, 1727, 1603, 1507, 1373, 1247, 1175, 1091, 835, 748, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, J = 8.3 Hz, 2 H, Ar-H), 7.47–7.05 (m, 15 H, Ar-H), 6.93–6.80 (m, 4 H, Ar-H), 5.86 (s, 1 H, CH=COH), 5.13–5.01 (m, 1 H, CH_2OSi), 5.06 (s, 2 H, Ar-CH_2-O), 4.60–4.46 (m, 1 H, Ar-CH-O), 4.32–4.21 (m, 1 H, Ar-CH-O), 3.98–3.90 (m, 1 H, CH-OBn), 3.52 (s, 3 H, OCH_3), 3.01–2.78 (m, 2 H, CH_2-CO), 2.66–2.47 (m, 2 H, Ar-CH_2), 2.43 (s, 3 H, Ar-CH_3), 0.82 [s, 9 H, $(CH_3)_3Si$], –0.02 (s, 3 H, CH_3Si), –0.17 (s, 3 H, CH_3Si) ppm. ^{13}C NMR (75 MHz): δ = 195.3, 190.6, 157.5, 151.6, 144.8, 144.6, 137.3, 137.0, 133.0, 130.4, 129.7, 129.6, 129.1, 128.6, 128.5, 128.2, 127.8, 127.6, 127.5, 127.4, 117.5, 114.6, 109.7, 98.5, 82.4, 72.2, 71.8, 69.9, 55.4, 49.9, 39.3, 25.6, 21.6, 18.0, –4.8, –5.3 ppm. HRMS (ESI): (m/z) calcd. for $C_{47}H_{54}NaO_9SSi$, 845.3150 $[M + Na]^+$; found 845.3162.

4-((*R*)-6-{(*S*)-1-(Benzyloxy)-2-[4-(benzyloxy)phenyl]ethyl}-4-oxo-3,4-dihydro-2*H*-pyran-2-yl)-2-methoxyphenyl 4-Methylbenzenesulfonate (14): To a stirred solution of β-diketone **13** (400 mg, 0.48 mmol) in CH_2Cl_2 (2 mL) was added pTsOH (9.2 mg, 0.048 mmol) at room temperature. The reaction was stirred for 24 h and then quenched by the addition of saturated $NaHCO_3$ (2 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (5 mL). The combined organic layers were washed with brine (3 mL), dried with Na_2SO_4 and concentrated in vacuo. The crude compound was purified by flash chromatography (30% ethyl acetate in hexanes) to give cyclized compound **14** (271 mg, 81%) as a pale yellow viscous liquid. $[\alpha]_D^{29} = -39.9$ (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2924, 2865, 1669, 1606, 1508, 1372, 1176, 1091, 848, 748, 661 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.78 (d, J = 8.3 Hz, 2 H, Ar-H), 7.42 (t, J = 7.2 Hz, 2 H, Ar-H), 7.38 (t, J = 7.2 Hz, 2 H, Ar-H), 7.34–7.24 (m, 6 H, Ar-H), 7.21–7.16 (m, 1 H, Ar-H) 7.14 (d, J = 8.3 Hz, 2 H, Ar-H), 7.09 (d, J = 8.3 Hz, 2 H, Ar-H), 6.87 (d, J = 8.3 Hz, 2 H, Ar-H), 6.85–6.77 (m, 2 H, Ar-H), 5.63 (s, 1 H, CH-CO), 5.31 (dd, J = 13.5, 4.1 Hz, 1 H, Ar-CH-O), 5.04 (s, 2 H, Ar-CH_2-O), 4.61–4.53 (m, 1 H, Ar-CH-O), 4.42–4.35 (m, 1 H, Ar-CH-O), 4.05 (t, J = 6.2 Hz, 1 H, CH-OBn), 3.58 (s, 3 H, OCH_3), 3.03–2.92 (m, 2 H, CH_2-CO), 2.78–2.54 (m, 2 H, Ar-CH_2), 2.44 (s, 3 H, Ar-CH_3) ppm. ^{13}C NMR (75 MHz): δ = 191.7, 174.6, 157.6, 152.0, 145.1, 138.4, 137.9, 137.1, 136.8, 133.1, 130.4, 129.4, 128.9, 128.5, 128.4, 128.3, 127.9, 127.7, 127.6, 127.4, 124.2, 118.1, 114.6, 110.4, 104.3, 80.2, 79.8, 72.0, 69.9, 55.6, 42.7, 39.3, 21.6 ppm. HRMS (ESI): (m/z) calcd. for $C_{41}H_{39}O_8S$, 691.2360 $[M + Na]^+$; found 691.2348.

4-{(2*R*,6*S*)-6-[(*S*)-1-Hydroxy-2-(4-hydroxyphenyl)ethyl]-4-oxotetrahydro-2*H*-pyran-2-yl}-2-methoxyphenyl 4-Methylbenzenesulfonate (15): Palladium on carbon (100 mg, 10% wet weight) was added to a solution of compound **14** (200 mg) in EtOAc (2 mL). The reaction mixture was stirred overnight under hydrogen atmosphere. After the completion of reaction, the mixture was filtered through celite and the resulting filtrate was concentrated in vacuo. Column chromatography of the residue on silica gel (50% ethyl acetate in hexanes) gave compound **15** (109 mg, 74%) as an amorphous colorless solid. m.p. 58–60 °C. $[\alpha]_D^{28} = +36.5$ (c = 0.5, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3379, 2924, 2854, 1750, 1602, 1511, 1369, 1174, 1030, 846, 816, 715, 661 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.3 Hz, 2 H, Ar-H), 7.33 (d, J = 8.3 Hz, 2 H, Ar-H), 7.12 (d, J = 8.3 Hz, 1 H, Ar-H), 7.06 (d, J = 8.3 Hz, 2 H, Ar-H), 6.88 (d, J = 8.3 Hz, 2 H, Ar-H), 6.74 (d, J = 8.3 Hz, 2 H, Ar-H), 5.44 (s, 1 H, Ar-OH), 4.58 (dd, J = 11.3, 3.0 Hz, 1 H, Ar-CH-O), 3.84–3.65 (m, 2 H, CH-OH, CH-O-CH), 3.62 (s, 3 H, CH_3O), 2.94–2.33 (m, 6 H, CH_2-CO, CH_2-CO, Ar-CH_2), 2.40 (s, 3 H, Ar-CH_3) ppm. ^{13}C

NMR (75 MHz): δ = 206.1, 154.5, 152.0, 145.1, 140.3, 138.0, 133.2, 130.4, 129.4, 129.1, 128.5, 124.0, 117.6, 115.4, 110.0, 78.1, 78.0, 74.3, 55.6, 49.1, 43.7, 38.6, 29.6, 21.6 ppm. HRMS (ESI): (*m*/*z*) calcd. for $C_{27}H_{32}NO_8S$, 530.1843 $[M + NH_4]^+$; found 530.1848.

4-{(2*R*,4*S*,6*S*)-4-Hydroxy-6-[(*S*)-1-hydroxy-2-(4-hydroxyphenyl)ethyl]tetrahydro-2*H*-pyran-2-yl}-2-methoxyphenyl 4-Methylbenzenesulfonate (16): To a stirred solution of pyranone **15** (50 mg, 0.097 mmol) in THF (1 mL) at –78 °C was added *LS*-selectride (1 M in THF, 0.11 mL, 0.11 mmol). After 1 h at –78 °C, the reaction was quenched with saturated aqueous NH_4Cl (1 mL) and warmed to room temperature. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with brine (1 mL), dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (70% ethyl acetate in hexanes) to obtain compound **16** (42 mg. 84%) as a thick liquid. $[a]_D^{27}$ = +16.3 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3452, 2923, 2852, 1638, 1512, 1461, 1369, 1151, 1090, 865, 771, 719 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.30 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.09–7.01 (m, 3 H, Ar-H), 6.83 (d, *J* = 8.1 Hz, 2 H, Ar-H), 6.69 (d, *J* = 8.3 Hz, 2 H, Ar-H), 4.80 (d, *J* = 11 Hz, 1 H, Ar-CH-O), 4.36 (t, *J* = 3.0 Hz, 1 H, CH-OH), 3.96–3.81 (m, 1 H, CH-O-CH), 3.70 (dd, *J* = 12.0, 5.0 Hz, 1 H, CH-OH), 3.56 (s, 3 H, OCH_3), 2.84 (dd, *J* = 14.0, 5.0 Hz, 1 H, Ar-CH_2), 2.72 (dd, *J* = 14.0, 7.5 Hz, 1 H, Ar-CH_2), 2.44 (s, 3 H, Ar-CH_3), 1.95–1.60 (m, 4 H, CH_2-CH-OH, CH_2-CH-OH) ppm. ^{13}C NMR (75 MHz): δ = 154.4, 151.6, 145.0, 142.8, 137.2, 133.1, 130.3, 129.6, 129.3, 128.4, 123.6, 117.7, 115.3, 110.2, 75.0, 73.6, 73.1, 64.4, 55.5, 40.2, 38.4, 29.6, 21.6 ppm. HRMS (ESI): (*m*/*z*) calcd. for $C_{27}H_{30}O_8NaS$, 537.1559 $[M + Na]^+$; found 537.1577.

Rhoiptelol (1): To a solution of compound **16** (30 mg, 0.058 mmol) in MeOH (2 mL) was added K_2CO_3 (40 mg, 0.29 mmol) and the mixture was heated at reflux for 2 h. The reaction mixture was cooled to 0 °C and acidified with 1 N HCl until pH of the solution reached to 2. The combined aqueous/MeOH solution was extracted with ethyl acetate (2 × 5 mL). The organic extracts were washed with brine (1 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification of crude compound by column chromatography (70% ethyl acetate in hexanes) provided rhoiptelol **1** (16 mg, 78%) as a white amorphous powder; m.p. 68–70 °C. $[a]_D^{28}$ = +77.2 (*c* = 0.2, MeOH) [ref.[6] $[a]_D^{12}$ = +97.0 (*c* = 0.3, MeOH), ref.[7] $[a]_D^{23}$ = +97.0 (*c* = 0.3, MeOH)]. IR (KBr): ῦmax = 3450, 2922, 1638, 1515 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ = 7.04 (br. s, 1 H, Ar-H), 7.03 (d, *J* = 8.1 Hz, 2 H, Ar-H), 6.83 (dd, *J* = 8.1, 1.9 Hz, 1 H, Ar-H), 6.76 (d, *J* = 8.1 Hz, 1 H, Ar-H), 6.68 (d, *J* = 8.1 Hz, 2 H, Ar-H), 4.69 (dd, *J* = 11.1, 3.0 Hz, 1 H, Ar-CH-O), 4.27 (t, *J* = 3.0 Hz, 1 H, CH-OH), 3.87 (s, 3 H, OCH_3), 3.81 (dt, *J* = 12.5, 2.8 Hz, 1 H, CH-O-CH), 3.59 (dt, *J* = 7.0, 3.2 Hz, 1 H, CH-OH), 2.89 (dd, *J* = 13.4, 6.8 Hz, 1 H, Ar-CH_2), 2.69 (dd, *J* = 13.4, 7.3 Hz, 1 H, Ar-CH_2), 1.92 (dd, *J* = 13.5, 3.0 Hz, 1 H, CH_2-CH-OH), 1.83 (dd, *J* = 14.5, 2.6 Hz, 1 H, CH_2-CH-OH), 1.74 (ddd, *J* = 13.9, 11.3, 3.0 Hz, 1 H, CH_2-CH-OH), 1.55 (dd, *J* = 13.4, 2.0 Hz, 1 H, CH_2-CH-OH) ppm. ^{13}C NMR (75 MHz): δ = 156.7, 148.8, 146.8, 136.2, 131.5, 131.4, 131.2, 119.8, 116.0, 115.9, 115.8, 111.1, 76.4, 75.2, 74.3, 65.7, 56.4, 41.3, 39.7, 35.0 ppm. HRMS (ESI): (*m*/*z*) calcd. for $C_{20}H_{24}O_6Na$, 383.1470 $[M + Na]^+$; found 383.1461.

Acknowledgments

N. N. R. and B. S. thank the Council of Scientific and Industrial Research (CSIR), New Delhi for research fellowships.

[1] a) K. Akiyama, H. Aoki, T. Kikuzaki, A. Okuda, N. H. Lajis, N. Nakatani, *J. Nat. Prod.* **2006**, *69*, 1637–1640; b) H. Matsuda, S. Ando, T. Kato, T. Morikawa, M. Yoshikawa, *Bioorg. Med. Chem.* **2006**, *14*, 138–142; c) H.-J. Kim, S.-H. Yeom, M.-K. Kim, J.-G. Shim, I.-N. Paek, M.-W. Lee, *Arch. Pharmacal Res.* **2005**, *28*, 177–179; d) H. Mohamad, N. H. Lajis, F. Abas, A. M. Ali, M. A. Sukari, H. Kikuzaki, N. Nakatani, *J. Nat. Prod.* **2005**, *68*, 285–288; e) P. N. Yadav, Z. Liu, M. M. J. Rafi, *J. Pharmacol. Exp. Ther.* **2003**, *305*, 925–931; f) J. Ishida, M. Kozuka, H. Tokuda, H. Nishino, S. Nagumo, K.-H. Lee, M. Nagai, *Bioorg. Med. Chem.* **2002**, *10*, 3361–3365; g) K.-S. Chun, K.-K. Park, J. Lee, M. Kang, Y.-J. Surh, *Oncol. Res.* **2002**, *13*, 37–45; h) H. Matsuda, T. Morikawa, J. Tao, K. Ueda, M. Yoshikawa, *Chem. Pharm. Bull.* **2002**, *50*, 208–215; i) M. S. Ali, Y. Tezuka, S. Awale, A. H. Banskota, S. Kadota, *J. Nat. Prod.* **2001**, *64*, 289–293; j) M.-W. Lee, J.-H. Kim, D.-W. Jeong, K.-H. Ahn, S.-H. Toh, Y.-J. Surh, *Biol. Pharm. Bull.* **2000**, *23*, 517–518.

[2] a) M. Dziedzic, B. Furman, *Tetrahedron Lett.* **2008**, *49*, 678–681; b) M. Pham, A. Allatabakhsh, T. G. Minehan, *J. Org. Chem.* **2008**, *73*, 741–744; c) C.-H. A. Lee, T.-P. Loh, *Tetrahedron Lett.* **2006**, *47*, 1641–1644; d) K.-P. Chan, T.-P. Loh, *Org. Lett.* **2005**, *7*, 4491–4494; e) G. Sabitha, K. B. Reddy, G. S. K. K. Reddy, N. Fatima, J. S. Yadav, *Synlett* **2005**, 2347–2351; f) S. Marumoto, J. J. Jaber, J. P. Vitale, S. D. Rychnovsky, *Org. Lett.* **2002**, *4*, 3919–3922; g) P. A. Evans, J. Cui, S. J. Gharpure, *Org. Lett.* **2003**, *5*, 3883–3885; h) T. Takeuchi, M. Matsuhashi, T. Nakata, *Tetrahedron Lett.* **2008**, *49*, 6462–6465; i) M. P. Jennings, R. T. Clemens, *Tetrahedron Lett.* **2005**, *46*, 2021–2024; j) L. Boulard, S. BouzBouz, J. Cossy, X. Franck, B. Figadere, *Tetrahedron Lett.* **2004**, *45*, 6603–6605; k) M. C. Carreno, R. Des Mazery, A. Urbano, F. Colobert, G. Solladie, *J. Org. Chem.* **2003**, *68*, 7779–7787; l) F. Colobert, R. Des Mazery, G. Solladie, M. C. Carreno, *Org. Lett.* **2002**, *4*, 1723–1725; m) S. Chandrasekhar, S. J. Prakash, T. Shyamsunder, *Tetrahedron Lett.* **2005**, *46*, 6651–6653; n) T. Washio, R. Yamaguchi, T. Abe, H. Nambu, M. Anada, S. Hashimoto, *Tetrahedron* **2007**, *63*, 12037–12046; o) D. S. Christopher, H. Anyu, S. Nongnuch, *Org. Lett.* **2009**, *11*, 3124–3127; p) K. R. Prasad, P. Anbarasan, *Tetrahedron* **2007**, *63*, 1089–1092; q) E. Lee, H. J. Kim, W. S. Jang, *Bull. Korean Chem. Soc.* **2004**, *25*, 1609–1610; r) P. A. Clarke, W. H. Martin, *Tetrahedron Lett.* **2004**, *45*, 9061–9063; s) P. A. Clarke, W. H. C. Martin, *Tetrahedron* **2005**, *61*, 5433–5438; t) V. Boehrsch, S. Blechert, *Chem. Commun.* **2006**, 1968–1970; u) C. R. Reddy, P. P. Madhavi, S. Chandrasekhar, *Synthesis* **2008**, 2939–2942.

[3] a) X. Tian, J. J. Jaber, S. D. Rychnovsky, *J. Org. Chem.* **2006**, *71*, 3176–3183; b) W. Takuya, N. Hisanori, A. Masahiro, H. Shunichi, *Tetrahedron: Asymmetry* **2007**, *18*, 2606–2612.

[4] a) G. Sabitha, P. Padmaja, J. S. Yadav, *Helv. Chim. Acta* **2008**, *91*, 2235–2239; b) H. Wang, B. J. Shuhler, M. Xian, *Synlett* **2008**, *17*, 2651–2654; c) R. W. Bates, P. Song, *Tetrahedron* **2007**, *63*, 4497–4499; d) N. Kawai, S. Mahadeo, J. Uenishi, *Tetrahedron* **2007**, *63*, 9049–9056; e) J. S. Yadav, B. Padmavani, B. V. S. Reddy, C. Venugopal, A. B. Rao, *Synlett* **2007**, 2045–2048; f) M. A. Hiebel, B. Pelotier, O. Piva, *Tetrahedron* **2007**, *63*, 7874–7878; g) K. B. Sawant, M. P. Jennings, *J. Org. Chem.* **2006**, *71*, 7911–7914; h) C. Bressy, F. Allais, J. Cossy, *Synlett* **2006**, *20*, 3455–3456; i) S. Chandrasekhar, T. Shyamsunder, J. S. Prakash, A. Prabhakar, B. Jagadeesh, *Tetrahedron Lett.* **2006**, *47*, 47–49.

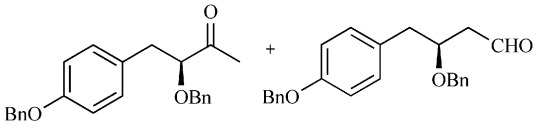
[5] L. W. Christine, D. P. Gregory, T. S. Peter, *Tetrahedron Lett.* **2009**, *50*, 3686–3689.

[6] Z.-H. Jiang, T. Tanaka, H. Hirata, R. Fukuoka, I. Kouno, *Phytochemistry* **1996**, *43*, 1049–1054.

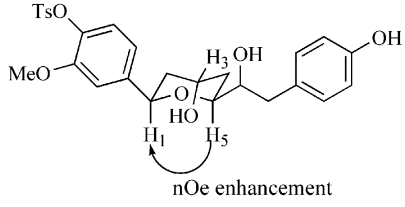
[7] W. Y. Jin, X. F. Cai, M. Na, J. J. Lee, K. Bae, *Arch. Pharmacal Res.* **2007**, *30*, 412–418.

[8] W. Y. Jin, X. F. Cai, M. Na, J. J. Lee, K. Bae, *Biol. Pharm. Bull.* **2007**, *30*, 810–813.

[9] a) G. E. Keck, K. H. Tarbet, L. S. Geraci, *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468; b) G. E. Keck, D. Krishnamurthy, *Org. Synth.* **1998**, *75*, 12–18.
[10] Enantiomeric excess (*ee*) of homoallylic alcohol **8** was determined by chiral HPLC [Eurocel01, 250×4.6 mm, 5 micron, *i*PrOH/hexanes (15:85), flow rate 1.0 mL/min, retention time 9.51 (7.52%), 10.87 (92.47%)].
[11] D. G. Vassao, D. R. Gang, T. Koeduka, B. Jackson, E. Pichersky, L. B. Davin, N. Lewis, *Org. Biomol. Chem.* **2006**, *4*, 2733–2744.
[12] M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, *277*, 936–938.
[13] L. A. Paquette, J. Chang, Z. Liu, *J. Org. Chem.* **2004**, *69*, 6441–6448.
[14] Enantiomeric excess (*ee*) of allylic alcohol **11** was, determined by chiral HPLC [chiral IA, 250x4.6 mm, 5 μ, 5% *i*PrOH in hexanes (0.1% diethylamine), flow rate 1.0 mL/min, retention time 12.70 (5.01%), 13.62 (94.99%)].
[15] L. Alcaraz, J. J. Harnett, C. Mioskowski, J. P. Martel, T. Le Gall, D.-S. Shin, J. R. Falck, *Tetrahedron Lett.* **1994**, *35*, 5449–5452.
[16] The standard wacker oxidation reaction conditions ($PdCl_2$, $CuCl_2$, O_2, and DMF) gave the inseparable mixture of ketone and aldehyde as shown below. Therefore the modified procedure was adopted (ref.[17]).



[17] a) G. T. Rodeheaver, D. F. Hunt, *J. Chem. Soc., Chem. Commun.* **1971**, 818–819; b) K. C. Nicolaou, J. Y. Xu, S. Kim, J. Pfefferkorn, T. Ohshima, D. Vourloumis, S. Hosokawa, *J. Am. Chem. Soc.* **1998**, *120*, 8661–8673.
[18] Enantiomeric excess (*ee*) of compound **4** was determined by chiral HPLC [chiral IA, 250×4.6 mm, 5 μ, 5% *i*PrOH in hexanes, flow rate 1.0 mL/min, retention time 8.53 (4.07%), 9.17 (95.93%)].
[19] Compound **13** completely existed in enol form and the enolization may occur from either of the ketone.
[20] a) J. S. Crossman, M. V. Perkins, *J. Org. Chem.* **2006**, *71*, 117–124; b) W. R. Roush, T. D. Bannister, M. D. Wendt, J. A. Jablonowski, K. A. Scheidt, *J. Org. Chem.* **2002**, *67*, 4275–4283.
[21] H. Wang, B. J. Shuhler, M. Xian, *J. Org. Chem.* **2007**, *72*, 4280–4283.
[22] There is no over reduction (ring opening at benzylic position) observed during the conversion of **14** to **15**, this may be due to the presence of tosyl group.
[23] a) W. Peter, T. R. Jonathan, *Chem. Commun.* **2002**, 2066–2067; b) S. D. Rychnovsky, J. K. David, *J. Am. Chem. Soc.* **2001**, *123*, 8420–8421.
[24] The nOe effect between H-1 and H-5 confirmed the *cis* relation and absence of effect between H-1/H-5 and H-3 confirmed the *trans* relation in structure **16**.



Received: September 10, 2009
Published Online: November 27, 2009

