Total Synthesis of Rhoiptelol B

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Abstract: A simple and efficient total synthesis of rhoiptelol B, isolated from the the leaves and fruits of *Rhoiptelea chiliantha*, is achieved using Sharpless asymmetric epoxidation, 1,3-*anti*-chiral allylation, olefin cross-metathesis, Sharpless asymmetric dihydroxylation, and ferric chloride catalyzed intramolecular S_N2 cyclization as the key steps.

Key words: rhoiptelol B, Sharpless asymmetric epoxidation, allylation, cross-metathesis, diarylheptanoids

The tetrahydropyran (THP) motif is frequently found in biologically active natural products, and hence there has been long-standing interest in the stereoselective synthesis of this ring system. Diarylheptanoids are a family of biologically active natural products isolated from Asian herbs;[1] structurally they exist in either linear or cyclic form. The diarylheptanoid, rhoiptelol B, the structure of which contains a tetrahydropyran ring, was isolated from the fruits of *Rhoiptelea chiliantha* in 1996, along with two other diarylheptanoids, rhoiptelols A and C (Figure 1).[2] In 2007, rhoiptelol B was isolated from the bark of *Alnus hirsuta* (Betulaceae) and was found to exhibit inhibitory activity against lipopolysaccharide (LPS) induced nuclear factor-*k*B (NF-*k*B) activation, nitric oxide (NO) and tumor necrosis factor-α (TNF-α) production, and hypoxia-inducible factor (HIF-1) inhibition in AGS cells.[3] As a result, several approaches including Diels–Alder reaction,[4] Prins cyclization,[5] oxa-Michael reaction,[6] reductive etherification,[7] Maitland–Japp reaction (Knoevenagel/Michael addition cascades),[8] olefin metathesis[9] and palladium-mediated cyclization[10] have been developed for the synthesis of tetrahydropyran scaffolds. To date, there has been only one report on the synthesis of rhoiptelol B.[11]

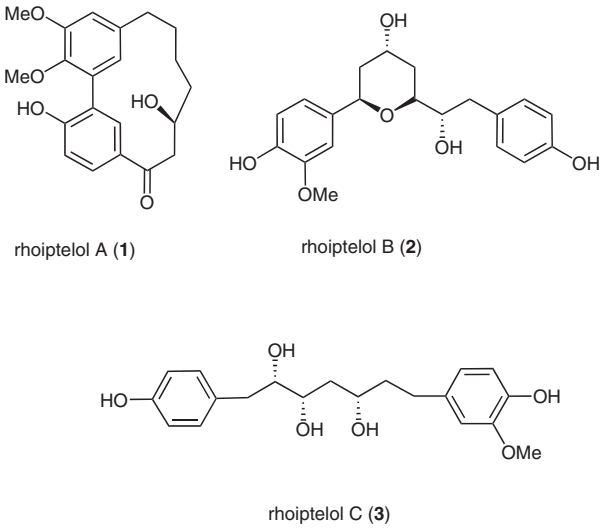
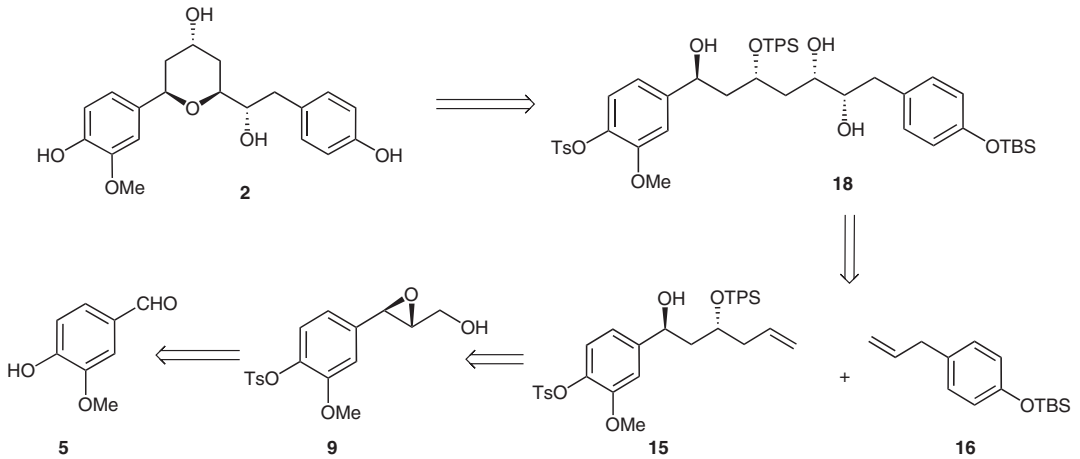


Figure 1 Structures of rhoiptelols A, B and C

In continuation of our interest in the total synthesis of biologically active natural products, we herein report a simple and straightforward approach for the preparation of the diarylheptanoid, rhoiptelol B, via Sharpless asymmet-



Scheme 1 Retrosynthetic analysis of rhoiptelol B

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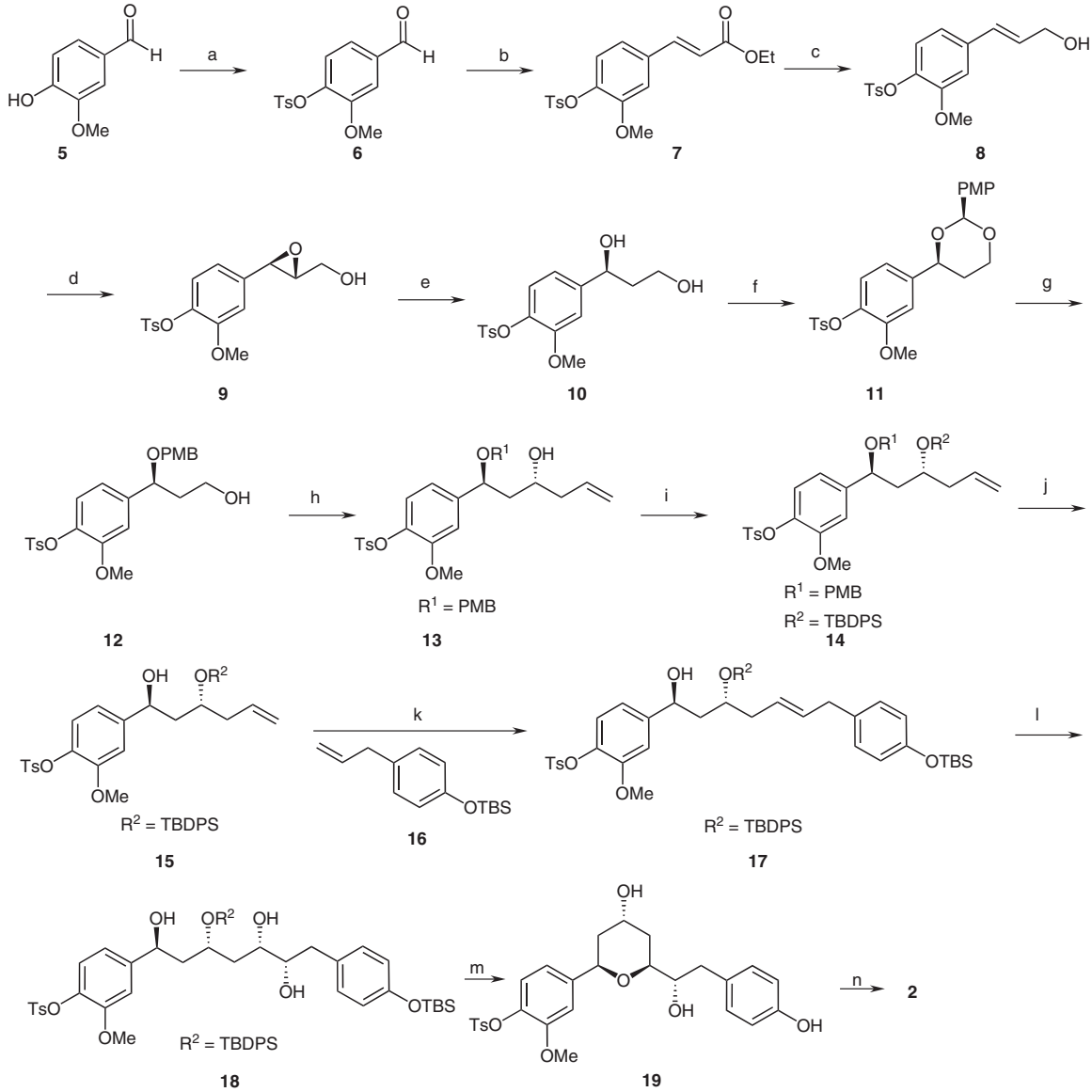
ric epoxidation, cross-metathesis, Sharpless asymmetric dihydroxylation and ferric chloride catalyzed intramolecular cyclization as the key steps.

In our retrosynthetic analysis (Scheme 1), we envisaged that the target molecule, rhoiptelol B (**2**), could be accessed from key intermediate **18**, itself prepared by olefin cross-metathesis between alkenes **15** and **16** followed by a Sharpless asymmetric dihydroxylation. Compound **15** could be obtained through ring-opening of epoxy alcohol **9** [obtained from vanillin (**5**) via Wittig olefination and reduction] followed by stereoselective allylation.

The synthesis of target molecule **2** began from commercially available vanillin (**5**), tosylation of which followed by Wittig olefination with the stable ylide, (ethoxycarbonylmethylene)triphenylphosphorane in benzene at reflux temperature gave the α,β-unsaturated ester **7**, exclusively as the *E*-isomer (Scheme 2). Reduction of ester **7** with diisobutylaluminum hydride afforded the corresponding *E*-allylic alcohol **8** in excellent yield. Sharpless asymmetric epoxidation of allyl alcohol **8** using (–)-diisopropyl tartrate gave the epoxy alcohol **9**.[12] Reductive ring-opening of epoxide **9** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®) in 1,2-dimethoxyethane gave the expected 1,3-diol **10** in 70% yield. Protection of the 1,3-diol moiety with *p*-anisaldehyde dimethylacetal in the presence of 10-camphorsulfonic acid gave the *p*-methoxybenzylidene acetal **11**. Regioselective ring-opening of **11** with diisobutylaluminum hydride at –78 °C to 0 °C proceeded at the sterically less-hindered side resulting in for-



Scheme 2 *Reagents and conditions*: (a) TsCl, K_2CO_3, acetone, reflux, 24 h, 95%; (b) Ph_3PCHCO_2Et, benzene, 6 h, reflux, 95%; (c) DIBAL-H, –78 °C, 2 h, 93%; (d) anhyd 5.4 M TBHP in CH_2Cl_2, 4 Å MS, cat. Ti(O*i*-Pr)$_4$ (10 mol%), cat. (–)-DIPT (12 mol%), CH_2Cl_2, –20 °C, 3.5 h, 96%; (e) Red-Al®, DME, 0 °C to r.t., 12 h, 70%, (f) *p*-anisaldehyde dimethylacetal, CSA, CH_2Cl_2, r.t., 3 h, 92%; (g) DIBAL-H, CH_2Cl_2, –78 °C to 0 °C, 18 h, 88%; (h) (i) oxalyl chloride, DMSO, CH_2Cl_2, –78 °C, Et_3N, 6.5 h; (ii) allyltributylstannane, $MgBr_2{\cdot}OEt_2$, CH_2Cl_2, –10 °C, 3 h (80% over two steps); (i) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to r.t. 2.5 h, 98%; (j) DDQ, CH_2Cl_2–H_2O (9:1), 15 min, 80%; (k) **4**, CH_2Cl_2, r.t., 6 h, 65%; (l) AD-mix-α, *t*-BuOH–H_2O (1:1), $MeSONH_2$, 24 h, 0 °C, 90%; (m) $FeCl_3$, CH_2Cl_2, r.t., 30 min, 75%; (n) K_2CO_3, MeOH, reflux, 2 h, 75%.

mation of primary alcohol **12** in 88% yield. Next, Swern oxidation of **12** followed by chelation-controlled allylation[13] with allyltributylstannane in the presence of magnesium bromide diethyl etherate ($MgBr_2 \cdot OEt_2$) gave a separable mixture of diastereomers in which the *anti* isomer **13** was obtained predominantly (*anti*/*syn* = 9:1). Protection of allyl alcohol **13** as the *tert*-butyldiphenylsilyl ether followed by cleavage of the *p*-methoxybenzyl group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gave the alcohol **15** in 81% yield over the two steps. Cross-metathesis of alkenes **15** and **16**[14] using Grubbs' 2nd generation catalyst **4** (5 mol%; Figure 2) in dichloromethane at reflux temperature for four hours resulted in the formation of compound **17**[12b,15] as a mixture of *E*- and *Z*-isomers in the ratio 6:1. Sharpless asymmetric dihydroxylation of alkene **17** using AD-mix-α at 0 °C in *tert*-butyl alcohol–water (1:1) afforded the diol[16] **18** in 90% yield. Treatment of compound **18** with ferric chloride resulted in formation of the tetrahydropyran ring along with concomitant deprotection of the *tert*-butyldimethylsilyl and *tert*-butyldiphenylsilyl groups to give the cyclized product **19**[17] in 75% yield. Finally, cleavage of the tosyl group with potassium carbonate in methanol gave the target molecule, rhoiptelol B (**2**).

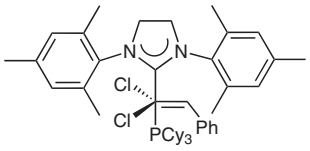


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Figure 2

In conclusion, we have developed a simple and concise route for the total synthesis of rhoiptelol B (**2**) involving Sharpless asymmetric epoxidation, chiral allylation, olefin cross-metathesis, Sharpless asymmetric dihydroxylation and ferric chloride induced intramolecular S_N2 cyclization to form the tetrahydropyran ring, as key steps. This synthetic sequence should enable the efficient preparation of other diarylheptanoids.

Reactions were conducted in anhydrous solvents under N_2 unless otherwise stated. Air-sensitive reagents were transferred using a syringe or cannula. Column chromatography was performed on silica gel (60–120 mesh, Acme Chemical Co., India). All reactions were monitored by TLC (Merck 60 F-254 silica gel coated plates, and made visual under UV light). IR spectra were obtained using a Perkin-Elmer model 683 spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_3OD using Varian VXR Unity 400 MHz (Innova) or Bruker UXNMR FT-300 MHz (Avance) spectrometers. Chemical shifts (δ) are reported relative to TMS (δ = 0.0 ppm) as the internal standard. MS (ESI) and HRMS (ESI) were recorded at 70 eV using an LC-MSD (Agilent Technologies) spectrometer. Optical rotations were measured with a JASCO DIP-370 Polarimeter at 20 °C.

4-Formyl-2-methoxyphenyl 4-Methylbenzenesulfonate (6)

To a soln of vanillin (**5**) (5.0 g, 32.8 mmol) in anhyd acetone (50 mL) was added anhyd K_2CO_3 (9.1 g, 65.7 mmol). The mixture was allowed to stir at r.t. for 10 min and then TsCl (7.52 g, 39.4 mmol) was added. The mixture was heated at reflux temperature for 24 h and then cooled to r.t., filtered and concentrated in vacuo. Hexane was added to the crude residue which was heated and then allowed to cool to r.t. The resulting solid was filtered under vacuum and washed with cold hexane to afford **6** as an off-white solid.

Yield: 9.57 g (95%); mp 125–128 °C.

IR (KBr): 2922, 2854, 1699, 1598, 1412, 1159, 1115, 1031, 856 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.93 (s, 1 H), 7.74 (d, *J* = 8.3 Hz, 2 H), 7.46–7.28 (m, 5 H), 3.63 (s, 3 H), 2.46 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.9, 152.5, 145.5, 142.9, 135.6, 132.7, 129.5, 128.5, 124.5, 124.3, 110.9, 55.6, 21.5.

ESI-MS: *m*/*z* = 329 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{14}O_5NaS$: 329.0459; found: 329.0456.

Ethyl (2E)-3-(3-Methoxy-4-{[(4-methylphenyl)sulfonyl]oxy}phenyl)prop-2-enoate (7)

To a stirred soln of aldehyde **6** (9.4 g, 30.7 mmol) in benzene was added (ethoxycarbonylmethylene)triphenylphosphorane (12.8 g, 36.8 mmol) and the resulting mixture heated for 6 h at reflux temperature. After completion of the reaction, the solvent was evaporated and the crude residue purified by column chromatography (EtOAc–hexane, 1:1) to give α,β-unsaturated ester **7** as a colorless liquid.

Yield: 10.88 g (95%).

IR (neat): 2975, 2931, 1729, 1597, 1505, 1372, 1178, 1117, 851 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.3 Hz, 2 H), 7.59 (d, *J* = 15.8 Hz, 1 H), 7.31 (d, *J* = 8.3 Hz, 2 H), 7.16 (d, *J* = 8.3 Hz, 1 H), 7.05 (dd, *J* = 8.3, 2.2 Hz, 1 H), 6.96 (d, *J* = 2.2 Hz, 1 H), 6.36 (d, *J* = 15.8 Hz, 1 H), 4.24 (q, *J* = 6.7 Hz, 2 H), 3.60 (s, 3 H), 2.45 (s, 3 H), 1.34 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 152.0, 145.1, 143.3, 139.6, 134.3, 133.1, 129.4, 128.6, 124.4, 120.8, 119.2, 111.5, 60.7, 55.6, 21.7, 14.3.

ESI-MS: *m*/*z* = 377 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{21}O_6S$: 377.1058; found: 377.1053.

4-[(1*E*)-3-Hydroxyprop-1-en-1-yl]-2-methoxyphenyl 4-Methylbenzenesulfonate (8)

To a stirred soln of α,β-unsaturated ester **7** (10.6 g, 29.8 mmol) in CH_2Cl_2 at –78 °C, DIBAL-H (29.8 mL, 42.2 mmol, 20% wt in toluene) was added over 2 h. Upon completion of the reaction, a soln of Rochelle's salt (45 mL) was added and the mixture stirred for 1 h. The organic layer was separated and the aq layer extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over anhyd Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography (EtOAc–hexane, 6:4) to give allylic alcohol **8** as a light-yellow viscous oil.

Yield: 8.66 g (93%).

IR (neat): 3395, 2935, 2867, 1596, 1503, 1369, 1297, 1177, 1090, 1030, 855, 712 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.3 Hz, 2 H), 7.27 (d, *J* = 8.1 Hz, 2 H), 7.06 (d, *J* = 8.3 Hz, 1 H), 6.86 (dd, *J* = 8.3, 1.7 Hz, 1 H), 6.80 (d, *J* = 1.7 Hz, 1 H), 6.50 (d, *J* = 15.8 Hz, 1 H), 6.32–6.20 (m, 1 H), 4.33–4.24 (m, 2 H), 3.58 (s, 3 H), 2.46 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.7, 145.0, 137.7, 136.8, 133.1, 129.8, 129.7, 129.3, 128.6, 124.0, 118.8, 110.3, 63.3, 55.4, 21.6.

ESI-MS: m/z = 357 $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{17}H_{18}O_5NaS$: 357.0772; found: 357.0779.

4-[(2*R*,3*R*)-3-(Hydroxymethyl)oxiran-2-yl]-2-methoxyphenyl 4-Methylbenzenesulfonate (9)

To 4 Å MS in anhyd CH_2Cl_2 (50 mL) were added sequentially Ti(O*i*-Pr)$_4$ (0.6 ml, 2.5 mmol) and (–)-DIPT (0.6 mL, 3.7 mmol) at –20 °C. After stirring for 30 min, allylic alcohol **8** (8.5 g, 25.4 mmol) in anhyd CH_2Cl_2 (100 mL) was added and stirring was continued for a further 30 min at –20 °C. *tert*-Butyl hydroperoxide (TBHP) (12.72 mL, 4 M, 50.4 mmol) was added and after stirring for 1 h at –20 °C, the mixture was quenched with H_2O (20 mL) and then stirred at r.t. for 30 min. After cooling to 0 °C, an aq soln of NaOH (30% w/v, 10 mL, sat. with brine) was added and the mixture stirred at 0 °C for 1 h. The organic layer was separated, the solvent removed under reduced pressure and the residue extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (EtOAc–hexane, 6:4) to afford a viscous yellow oil.

Yield: 8.48 g (93%); $[\alpha]_D^{28}$ +18.0 (*c* 1.5, $CHCl_3$).

IR (neat): 3407, 2923, 1599, 1506, 1370, 1175, 1090, 1031, 854, 816, 750, 713, 661 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 7.5 Hz, 2 H), 7.31 (t, *J* = 8.3 Hz, 3 H), 7.08 (d, *J* = 8.3 Hz, 1 H), 6.82 (dd, *J* = 8.3, 2.2 Hz, 1 H), 4.04–3.96 (m, 1 H), 3.87 (d, *J* = 2.2 Hz, 1 H), 3.83–3.73 (m, 1 H), 3.56 (s, 3 H), 3.14–3.10 (m, 1 H), 2.45 (s, 3 H), 1.78 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.9, 145.0, 138.1, 136.9, 133.0, 129.3, 128.4, 123.9, 117.9, 109.3, 62.5, 60.9, 55.5, 54.9, 29.6.

ESI-MS: m/z = 351 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{17}H_{19}O_6S$: 351.0909; found: 351.0902.

4-[(1*S*)-1,3-Dihydroxypropyl]-2-methoxyphenyl 4-Methylbenzenesulfonate (10)

To a stirred soln of **9** (8.0 g, 22.8 mmol) in anhyd DME (80 mL) under an N_2 atm was added Red-Al® (46.9 mL, 68.5 mmol, 70% w/w soln in toluene) at 0 °C. The mixture was stirred at r.t. for 12 h, quenched with sat. aq NH_4Cl soln (50 mL) and then extracted with EtOAc (150 mL). The organic extract was washed with brine (50 mL), dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (EtOAc–hexane, 8:2) to afford **10** as a viscous yellow oil.

Yield: 7.2 g (90%); $[\alpha]_D^{28}$ –22.4 (*c* 1.3, $CHCl_3$).

IR (neat): 3380, 2940, 1503, 1367, 1275, 1174, 1089, 857, 816 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.3 Hz, 2 H), 7.28 (d, *J* = 8.3 Hz, 2 H), 7.04 (d, *J* = 8.3 Hz, 1 H), 6.88 (d, *J* = 2.2 Hz, 1 H), 6.78 (dd, *J* = 8.3, 2.2 Hz, 1 H), 4.87–4.81 (m, 1 H), 3.83–3.76 (m, 2 H), 3.57 (s, 3 H), 2.45 (s, 3 H), 1.91–1.81 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.7, 145.1, 144.8, 137.2, 133.0, 129.4, 128.5, 123.6, 117.5, 109.9, 73.3, 61.0, 55.5, 40.4, 21.6.

ESI-MS: m/z = 375 $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{17}H_{20}O_6NaS$: 375.0878; found: 375.0895.

2-Methoxy-{4-[(2*S*,4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]phenyl} 4-Methylbenzenesulfonate (11)

To a stirred soln of **10** (3.0 g, 8.5 mmol) and CSA (213 mg, 0.85 mmol) in anhyd CH_2Cl_2 (50 mL) was added *p*-anisaldehyde dimethylacetal (1.55 g, 8.5 mmol) at 0 °C and the resulting mixture stirred at r.t. for 3 h. The mixture was neutralized with solid $NaHCO_3$ (2 g) and the solvent evaporated. The residue was purified by column chromatography (EtOAc–hexane, 4:6) to give product **11** as a viscous oil.

Yield: 3.67 g (92%); $[\alpha]_D^{28}$ –3.3 (*c* 1.0, $CHCl_3$).

IR (neat): 2962, 2843, 1606, 1510, 1369, 1248, 1176, 1116, 1092, 1031, 829, 753 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.3 Hz, 2 H), 7.40 (d, *J* = 8.3 Hz, 2 H), 7.28 (d, *J* = 8.3 Hz, 2 H), 7.04 (d, *J* = 8.3 Hz, 1 H), 6.90 (d, *J* = 1.5 Hz, 1 H), 6.88–6.81 (m, 3 H), 5.59 (s, 1 H), 4.82 (dd, *J* = 11.3, 2.2 Hz, 1 H), 4.32 (dd, *J* = 11.3, 3.7 Hz, 1 H), 4.13–4.01 (m, 1 H), 3.80 (s, 3 H), 3.59 (s, 3 H), 2.45 (s, 3 H), 2.07–1.98 (m, 1 H), 1.74 (dd, *J* = 11.3, 1.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.0, 151.8, 144.9, 141.8, 137.7, 133.3, 130.9, 129.3, 128.6, 127.4, 123.7, 117.8, 113.6, 110.3, 78.5, 67.1, 61.5, 55.6, 55.3, 40.5, 21.6.

ESI-MS: m/z = 493 $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{25}H_{26}O_7NaS$: 493.1296; found: 493.1303.

4-{(1*S*)-3-Hydroxy-1-[(4-methoxybenzyl)oxy]propyl}-2-methoxyphenyl 4-Methylbenzenesulfonate (12)

To a stirred soln of **11** (3.5 g, 7.4 mmol) in anhyd CH_2Cl_2 (100 mL), DIBAL-H (8.6 mL, 14.8 mmol, 20% soln in toluene) was added dropwise at –78 °C. The mixture was allowed to stir at r.t. for 18 h then quenched with a soln of Rochelle's salt (15 mL) and stirred for 2 h. The organic layer was separated and the aq layer extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried over anhyd Na_2SO_4 and evaporated under vacuum. The crude product was purified by column chromatography (EtOAc–hexane, 7:3) to give **12** as a yellowish viscous oil.

Yield: 3.0 g (88%); $[\alpha]_D^{28}$ –80.5 (*c* 1.0, $CHCl_3$).

IR (KBr): 3420, 2930, 1603, 1506, 1368, 1248, 1175, 1088, 1032, 855, 819 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 8.3 Hz, 2 H), 7.15 (d, *J* = 8.3 Hz, 2 H), 7.12 (d, *J* = 8.3 Hz, 1 H), 6.86–6.80 (m, 4 H), 4.49 (dd, *J* = 8.3, 3.1 Hz, 1 H), 4.40 (d, *J* = 11.4 Hz, 1 H), 4.18 (d, *J* = 11.4 Hz, 1 H), 3.80 (s, 3 H), 3.76–3.64 (m, 2 H), 3.60 (s, 3 H), 3.38 (t, *J* = 7.2 Hz, 1 H), 2.47 (s, 3 H), 2.00–1.72 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 152.0, 144.9, 142.1, 137.6, 133.2, 129.6, 129.4, 129.2, 128.5, 123.8, 118.6, 113.8, 110.3, 79.7, 70.3, 60.6, 55.5, 55.2, 40.4, 21.6.

ESI-MS: m/z = 495 $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{25}H_{28}O_7NaS$: 495.1453; found: 495.1476.

4-{(1*S*,3*R*)-3-Hydroxy-1-[(4-methoxybenzyl)oxy]hex-5-enyl}-2-methoxyphenyl 4-Methylbenzenesulfonate (13)

To a soln of oxalyl chloride (0.95 g, 7.7 mmol) in anhyd CH_2Cl_2 (10 mL) at –78 °C was added dropwise anhyd DMSO (0.72 g, 9.48 mmol). After 30 min, alcohol **12** (2.9 g, 5.9 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving a copious white precipitate. After stirring for 2 h at –78 °C, Et_3N (3.2 mL, 23.7 mmol) was added slowly and the mixture stirred for 30 min and then allowed to warm to r.t. The mixture was diluted with H_2O (20 mL) and CH_2Cl_2 (50 mL), the organic layer separated and washed with H_2O (20 mL) followed by brine (20 mL), and then dried over anhyd Na_2SO_4. The solvent was evaporated to give the crude aldehyde which was used in the next reaction without purification.

The crude aldehyde (2.7 g, 5.5 mmol) in anhyd CH_2Cl_2 (25 mL) was treated with $MgBr_2 \cdot Et_2O$ (2.65 g, 16.5 mmol) and allyltributylstannane (2.55 mL, 8.2 mmol) at 0 °C, and stirred for 3 h. The mixture

was quenched with 2 M HCl (30 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried over anhyd Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (EtOAc–hexane, 7:3) to give alkene **13** as a colorless liquid.

Yield: 2.55 g (83%); $[\alpha]_D^{28}$ –29.0 (*c* 1.2, $CHCl_3$).

IR (neat): 3450, 3070, 2930, 1604, 1508, 1370, 1249, 1175, 1090, 1032, 856, 820, 752, 716, 662, 554 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.7 Hz, 2 H), 7.29 (d, *J* = 8.5 Hz, 2 H), 7.18–7.07 (m, 3 H), 6.85–6.78 (m, 4 H), 5.82–5.71 (m, 1 H), 5.10–5.02 (m, 2 H), 4.57 (dd, *J* = 9.3, 2.3 Hz, 1 H), 4.41–4.36 (m, 1 H), 4.19 (d, *J* = 11.7 Hz, 1 H), 3.89 (m, 1 H), 3.79 (s, 3 H), 3.60 (s, 3 H), 2.46 (s, 3 H), 2.23–2.11 (m, 2 H), 1.85–1.78 (m, 1 H), 1.67–1.59 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 152.0, 144.9, 142.5, 137.6, 134.6, 133.3, 129.8, 129.5, 129.3, 128.5, 123.9, 118.5, 117.8, 113.8, 110.3, 77.5, 70.5, 67.3, 55.5, 55.2, 44.6, 41.8, 21.6.

ESI-MS: *m*/*z* = 535 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{32}O_7NaS$: 535.1766; found: 535.1776.

4-{(1*S*,3*R*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-1-[(4-methoxybenzyl)oxy]hex-5-enyl}-2-methoxyphenyl 4-Methylbenzenesulfonate (14)

To a stirred soln of alcohol **13** (2.5 g, 4.8 mmol) in CH_2Cl_2 (25 mL) was added imidazole (0.99 g, 14.6 mmol) at 0 °C and the mixture stirred for 30 min. TBDPSCl (1.4 mL, 5.3 mmol) was added and stirring was continued for a further 2 h at r.t. After completion of the reaction, the mixture was diluted with CH_2Cl_2 (20 mL), the organic layer washed with brine (25 mL), dried over anhyd Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography (EtOAc–hexane, 3:7) to afford silyl ether **14** as a colorless liquid.

Yield: 3.57 g (98%); $[\alpha]_D^{28}$ +72.0 (*c* 0.25, $CHCl_3$).

IR (neat): 2934, 2858, 1604, 1507, 1373, 1248, 1178, 1104, 1036, 820, 706 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.3 Hz, 2 H), 7.72–7.57 (m, 4 H), 7.43–7.22 (m, 8 H), 7.05–6.89 (m, 3 H), 6.77–6.61 (m, 4 H), 5.74–5.55 (m, 1 H), 4.98–4.79 (m, 2 H), 4.34 (dd, *J* = 9.8, 3.0 Hz, 2 H), 4.15–3.94 (m, 2 H), 3.77 (s, 3 H), 3.52 (s, 3 H), 2.45 (s, 3 H), 2.23–2.12 (m, 2 H), 1.97–1.79 (m, 1 H), 1.73–1.60 (m, 1 H), 1.06 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 151.9, 144.8, 142.3, 137.6, 135.5, 135.2, 134.3, 133.2, 129.7, 129.5, 129.4, 129.2, 128.5, 127.6, 123.6, 118.1, 117.5, 113.7, 110.2, 77.5, 70.7, 67.3, 55.5, 55.2, 44.9, 42.8, 26.8, 21.6, 19.1.

ESI-MS: *m*/*z* = 773 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{44}H_{50}O_7NaSSi$: 773.2944; found: 773.2954.

4-{(1*S*,3*R*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-1-hydroxyhex-5-enyl}-2-methoxyphenyl 4-Methylbenzenesulfonate (15)

To a soln of **14** (3.4 g, 4.5 mmol) in CH_2Cl_2–H_2O (9:1) (40 mL) was added DDQ (1.13 g, 4.9 mmol, 1.1 equiv) at 0 °C. After 15 min, the mixture was quenched with aq sat. $NaHCO_3$ soln (7.5 mL). The mixture was diluted with H_2O (45 mL) and CH_2Cl_2 (40 mL), and the aq layer extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phase was washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified on silica gel (EtOAc–hexane, 4:6) to give **15** as a colorless oil.

Yield: 2.36 g (83%); $[\alpha]_D^{28}$ +154.2 (*c* 0.15, $CHCl_3$).

IR (neat): 3478, 2933, 2858, 1599, 1502, 1371, 1176, 1109, 1035, 852, 752, 706 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.77–7.64 (m, 6 H), 7.47–7.33 (m, 6 H), 7.30–7.22 (m, 2 H), 7.04–6.97 (m, 1 H), 6.79 (d, *J* = 1.7 Hz, 1 H), 6.65 (dd, *J* = 8.1, 1.7 Hz, 1 H), 5.66–5.44 (m, 1 H), 5.00–4.76 (m, 3 H), 4.12–3.96 (m, 1 H), 3.55 (s, 3 H), 2.76 (br s, 1 H), 2.45 (s, 3 H), 2.42–2.33 (m, 1 H), 2.30–2.19 (m, 1 H), 1.84–1.66 (m, 2 H), 1.10 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.8, 144.8, 142.4, 137.6, 135.5, 135.2, 133.3, 129.7, 129.6, 129.3, 128.7, 127.8, 123.8, 118.2, 117.7, 110.3, 70.9, 68.8, 55.3, 44.5, 42.6, 26.6, 21.5, 19.1.

ESI-MS: *m*/*z* = 653 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{36}H_{42}O_6NaSSi$: 653.2369; found: 653.2375.

4-{(1*S*,3*R*,5*E*)-7-(4-[(*tert*-Butyldimethylsilyl)oxy]phenyl)-3-[(*tert*-butyldiphenylsilyl)oxy]-1-hydroxyhept-5-enyl}-2-methoxyphenyl 4-Methylbenzenesulfonate (17)

Grubbs's second generation catalyst **4** (0.14 g, 5 mol%) was placed in a two-necked flask equipped with an N_2 inlet, a magnetic stir bar and a rubber septum. A soln of **15** (2.2 g, 3.4 mmol) and **16** (1.73 g, 6.9 mmol) in CH_2Cl_2 (20 mL) was introduced at 40 °C, and the resulting soln stirred for 6 h (TLC monitoring). Following complete consumption of **15**, the reaction mixture was exposed to air and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc–hexane, 3:7) to give olefin **17** as a colorless liquid.

Yield: 1.91 g (65%); $[\alpha]_D^{25}$ +1.8 (*c* 0.85, $CHCl_3$).

IR (neat): 3480, 3022, 2931, 2893, 2857, 1602, 1505, 1372, 1258, 1174, 1109, 913, 844, 751, 705, 662, 553 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.76–7.75 (m, 6 H), 7.45 (m, 8 H), 7.01 (d, *J* = 8.3 Hz, 1 H), 6.89–6.77 (m, 3 H), 6.68–6.55 (m, 3 H), 5.51–5.39 (m, 1 H), 5.26–5.15 (m, 1 H), 4.90–4.80 (m, 1 H), 4.06–3.98 (m, 1 H), 3.53 (s, 3 H), 3.15 (d, *J* = 6.0 Hz, 2 H), 2.45 (s, 3 H), 2.42–2.33 (m, 1 H), 2.28–2.19 (m, 1 H), 1.84–1.66 (m, 2 H), 1.09 (s, 9 H), 0.97 (s, 9 H), 0.16 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.6, 145.1, 144.8, 135.8, 133.4, 133.2, 132.6, 131.2, 129.9, 129.3, 129.2, 128.5, 127.7, 127.6, 126.3, 124.7, 123.6, 119.8, 117.4, 109.7, 71.9, 70.1, 55.4, 43.9, 39.3, 38.1, 26.9, 25.6, 21.6, 19.2, 18.2, –4.5.

ESI-MS: *m*/*z* = 873 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{49}H_{62}O_7NaSSi_2$: 873.3652; found: 873.3668.

4-{(1*S*,3*S*,5*S*,6*S*)-7-(4-[(*tert*-Butyldimethylsilyl)oxy]phenyl)-3-[(*tert*-butyldiphenylsilyl)oxy]-1,5,6-trihydroxyheptyl}-2-methoxyphenyl 4-Methylbenzenesulfonate (18)

To a 250 mL round-bottom flask were added *t*-BuOH (25 mL), H_2O (25 mL), AD-mix-α (2.95 g, 1.4 g/mmol) and methanesulfonamide (0.39 g, 4.2 mmol). The mixture was stirred at r.t. for about 5 min and then cooled to 0 °C. To this soln was added alkene **17** (1.8 g, 2.1 mmol) and the mixture stirred for 24 h at 0 °C. The soln was quenched with solid Na_2S (10 g) at r.t. and diluted with EtOAc (50 mL). The aq layer was extracted with EtOAc (3 × 30 mL) and the combined organic layer washed with brine (30 mL) and dried over anhyd Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography (EtOAc–hexane, 3:7) to give the title compound **18** as a viscous liquid.

Yield: 1.64 g, (89%).

IR (neat): 3392, 2953, 2928, 1595, 1502, 1365, 1174, 1083, 854, 716 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78–7.64 (m, 6 H), 7.49–7.33 (m, 6 H), 7.30–7.23 (m, 2 H), 7.03–6.92 (m, 3 H), 6.75–6.66 (m, 3 H), 6.62–6.49 (m, 1 H), 4.71–4.61 (m, 1 H), 4.30–4.18 (m, 1 H), 3.53 (s, 3 H), 3.57–3.46 (m, 1 H), 3.45–3.33 (m, 1 H), 2.69–2.41 (m, 2 H), 2.45 (s, 3 H), 1.99–1.54 (m, 4 H), 1.07 (s, 9 H), 0.98 (s, 9 H), 0.17 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.4, 145.0, 144.6, 135.7, 133.4, 133.3, 133.2, 131.2, 129.7, 129.3, 129.2, 128.6, 127.5, 124.6, 123.5, 119.6, 117.3, 109.5, 75.2, 71.7, 70.5, 69.0, 55.5, 39.3, 38.5, 38.1, 26.9, 25.6, 21.6, 19.2, 18.2, –4.2.

ESI-MS: *m*/*z* = 907 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{49}H_{64}O_9NaSSi_2$: 907.3707; found: 907.3700.

4-{(2*R*,4*S*,6*S*)-4-Hydroxy-6-[(1*S*)-1-hydroxy-2-(4-hydroxyphenyl)ethyl]tetrahydro-2*H*-2-pyranyl}-2-methoxyphenyl 4-Methylbenzenesulfonate (19)

Compound **18** (1.4 g, 1.5 mmol) in an oven-dried, single neck, 10 mL round-bottom flask was dissolved in anhyd CH_2Cl_2 (10 mL) under an Ar atm. $FeCl_3$ (49 mg, 0.31 mmol) was added at r.t. and the mixture was stirred for 30 min. After the reaction was complete (TLC), it was diluted with Et_2O (20 mL) and washed with sat. aq $NaHCO_3$ soln (3 × 10 mL) and brine (10 mL), and then dried over Na_2SO_4. Removal of the solvent followed by purification on silica gel (EtOAc–hexane, 7:3) gave tetrahydropyran **19** as a viscous liquid.

Yield: 0.60 g (76%).

IR (neat): 3452, 2923, 1638, 1512, 1369, 1151, 1090, 865, 771 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 7.09–7.01 (m, 3 H), 6.83 (d, *J* = 8.1 Hz, 2 H), 6.69 (d, *J* = 8.3 Hz, 2 H), 4.80 (d, *J* = 10.3 Hz, 1 H), 4.35 (m, 1 H), 3.94–3.83 (m, 1 H), 3.70 (dd, *J* = 12.4, 5.2 Hz, 1 H), 3.56 (s, 3 H), 2.88–2.67 (m, 2 H), 2.44 (s, 3 H), 1.95–1.60 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): 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.

ESI-MS: *m*/*z* = 537 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{30}O_8NaS$: 537.1559; found: 537.1577.

Rhoiptelol B (2)

To a soln of compound **19** (0.10 g, 0.17 mmol) in MeOH (5 mL) was added K_2CO_3 (133 mg, 0.95 mmol) and the mixture heated at reflux temperature for 2 h, cooled to 0 °C, acidified with 1 M HCl until pH 2. The combined aq–organic soln was extracted with EtOAc (3 × 5 mL), washed with brine (3 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (EtOAc–hexane, 7:3) gave rhoiptelol B (**2**) as a white, amorphous powder.

Yield: 0.052 g (80%); mp 65–67 °C; $[\alpha]_D^{25}$ +86.2 (*c* 0.3, MeOH).

IR (KBr): 3455, 2923, 1640, 1517, 1457, 1240, 1034, 769 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.05 (br s, 1 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 6.83 (dd, *J* = 8.4, 2.0 Hz, 1 H), 6.75 (d, *J* = 8.4 Hz, 1 H), 6.68 (d, *J* = 8.4 Hz, 2 H), 4.69 (dd, *J* = 10.7, 3.2 Hz, 1 H), 4.27 (t, *J* = 3.2 Hz, 1 H), 3.85 (s, 3 H), 3.80 (dt, *J* = 12.7, 2.9 Hz, 1 H), 3.59 (dt, *J* = 7.4, 3.2 Hz, 1 H), 2.85 (dd, *J* = 13.0, 6.6 Hz, 1 H), 2.68 (dd, *J* = 13.0, 7.4 Hz, 1 H), 1.91 (dd, *J* = 13.3, 3.0 Hz, 1 H), 1.84 (dd, *J* = 14.3, 2.9 Hz, 1 H), 1.73 (ddd, *J* = 13.6, 10.9, 2.8 Hz, 1 H), 1.57 (dd, *J* = 13.6, 2.0 Hz, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 156.5, 148.6, 146.7, 136.0, 131.4, 131.3, 131.1, 119.6, 116.0, 115.9, 115.7, 111.0, 76.5, 75.2, 74.2, 65.5, 56.2, 41.2, 39.7, 35.1.

ESI-MS: *m*/*z* = 383 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{24}O_6Na$: 383.1470; found: 383.1461.

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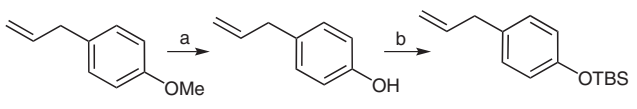
(14) Compound **16** was synthesized from commercially available 4-allyl anisole in two steps (Scheme 3).



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Scheme 3 *Reagents and conditions*: (a) BBr_3, CH_2Cl_2, –78 °C to r.t., 2 h, 70%; (b) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 98%.

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