An Expedient Stereoselective Synthesis of the Antifungal Agent (6*S*)-6-[(2*R*)-2-Hydroxy-6-phenylhexyl]-5,6-dihydro-2*H*-pyran-2-one

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Received 20 June 2011; revised 22 July 2011

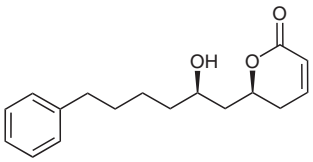
This work is dedicated to Dr J. S. Yadav on the occasion of his 60th birthday

Abstract: An efficient and straightforward stereoselective synthesis of (6*S*)-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-5,6-dihydro-2*H*-pyran-2-one is described. The chiral centers were generated by Sharpless asymmetric epoxidation followed by regioselective epoxide ring opening with Red-Al to afford 1,3-diols, exclusively. All the reactions were very clean and the products were obtained in very good yields.

Keywords: Wittig reactions, epoxidations, diols, pyrans

Natural products containing pyrone moieties exhibit a variety of pharmacological properties, including antifungal, antitumor, antibacterial, and antigrowth effects. The broad range of biological activities reported for this class of compounds has been ascribed to their inherent tendency to act as good Michael acceptors. Because of their biological importance, the synthesis of naturally occurring pyrones has been the subject of intense research.[1] The natural product (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (**1**) was isolated from the evergreen tree *Ravensara crassifolia* and has been reported to act as an antifungal agent against the phytopathogenic fungus *Cladosporium cucumerinum*.[2]

An earlier synthesis of **1** involved Keck allylation, ring-closing metathesis, olefin cross-metathesis, vinyl-Grignard reaction, asymmetric allylation, Prins cyclization, and regioselective ring opening of an epoxide under Grignard conditions.[3] As part of our research program on the synthesis of biologically active molecules,[4] we report an enantioselective synthesis of **1** based on the Sharpless asymmetric epoxidation protocol.

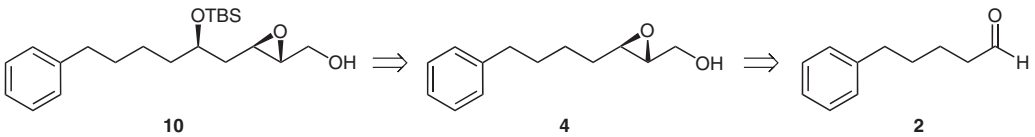


1

Figure 1 (6*S*)-5,6-Dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (**1**)

A retrosynthetic analysis (Scheme 1) suggested that the key steps would be the Sharpless asymmetric epoxidation of an allylic alcohol derived from aldehyde **2** and regioselective ring opening of epoxide **4** with Red-Al [sodium dihydrobis(2-methoxyethoxy)aluminate].

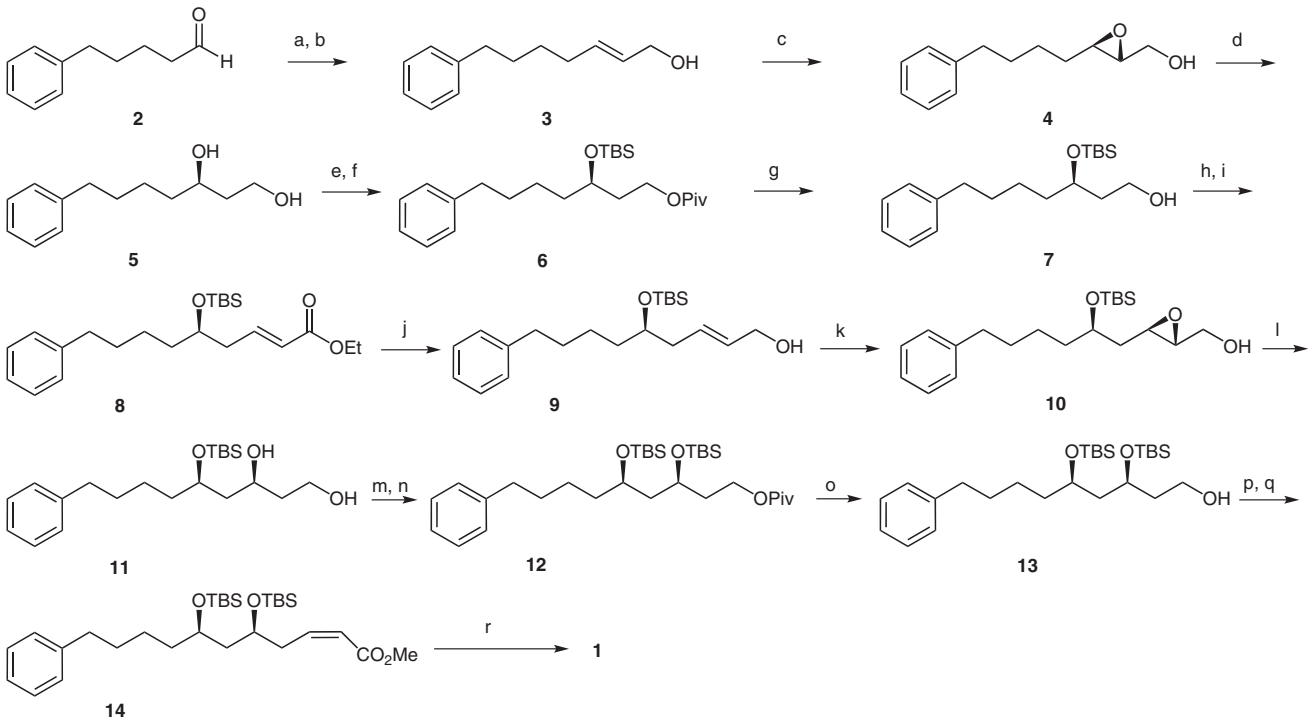
Our synthetic strategy began with a Wittig two-carbon extension of 5-phenylpentanal (**2**) in benzene[5] to give ethyl (2*E*)-7-phenylhept-2-enoate in 90% yield. The product was subjected to mixed hydride reduction with lithium aluminum hydride and aluminum trichloride in anhydrous tetrahydrofuran at 0 °C to give (2*E*)-7-phenylhept-2-en-1-ol (**3**) in 75% yield.[6] Allylic alcohol **3** was subjected to Sharpless asymmetric epoxidation with titanium tetraisopropoxide and diethyl (–)-tartrate at –20 °C in the presence of powdered molecular sieves to give the chiral epoxy alcohol **4** in 90% yield and excellent enantioselectivity.[7] The epoxide ring in **4** was regioselectively cleaved by treatment with Red-Al at 0 °C.[8] This reaction was very clean and was completed within three hours to give the 1,3-diol **5** exclusively. Treatment of diol **5** with pivaloyl chloride in the presence of pyridine in dichloromethane resulted in selective protection of the primary alcohol group.[9] Derivatization of the secondary alcohol with *tert*-butyl(dimethyl)silyl chloride in the presence of imidazole in dichloromethane gave the pivalate **6**[10] in 95% yield. The pivaloyl group in **6** was selectively removed by treatment with diisobutylaluminum dihydride (DIBAL-H) at –78 °C.[11] The resulting primary alcohol **7** was subjected to Swern oxidation[12] with oxalyl chloride and dimethyl sulfoxide, and the resulting aldehyde was, without purification, subjected to a Wittig reaction to give the chain-extended ester **8** in 90% yield. Ester **8** was reduced with



10 **4** **2**

Scheme 1

SYNTHESIS 2011, No. 20, pp 3271–3276
Advanced online publication: 08.09.2011
DOI: 10.1055/s-0030-1260214; Art ID: Z61911SS



Scheme 2 *Reagents and conditions*: (a) $Ph_3P{=}CHCO_2Et$, benzene, 2 h, 90%; (b) LAH, $AlCl_3$, anhyd THF, 0 °C to r.t., 3 h, 75%; (c) Ti(O*i*-Pr)$_4$, (–)-DET, –20 °C, CH_2Cl_2, 12 h, 90%; (d) Red-Al, anhyd THF, 0 °C, 3 h, 90%; (e) PivCl, pyridine, CH_2Cl_2, r.t., 3 h, 95%; (f) TBSCl, imidazole, CH_2Cl_2, r.t., 1 h, 95%; (g) DIBAL-H, THF, –78 °C, 30 min, 90%; (h) Swern oxidation, –78 °C, 2 h. 90%; (i) $Ph_3P{=}CHCO_2Et$, benzene, 2 h, 90%; (j) LAH, $AlCl_3$, anhyd THF, 0 °C to r.t. °C, 75%; (k) Ti(O*i*-Pr)$_4$, (–)-DET, –20 °C, CH_2Cl_2, 12 h, 90%; (l) Red-Al, anhyd THF, 0 °C, 3 h, 90%; (m) PivCl, pyridine, CH_2Cl_2, r.t., 3 h, 95%; (n) TBSCl, imidazole, CH_2Cl_2, r.t., 1 h, 95%; (o) DIBAL-H, THF, –78 °C, 30 min, 90%; (p) Swern oxidation, –78 °C, 2 h. 90%; (q) $(F_3CCH_2O)_2P(O)CH_2CO_2Me$, NaH, anhyd THF, 75%; (r) TsOH, MeOH, r.t., 30 min, 90%.

lithium aluminum hydride and aluminum trichloride in anhydrous tetrahydrofuran at 0 °C to room temperature to give the allylic alcohol **9** in 75% yield.

The allylic alcohol was subjected to a second Sharpless asymmetric epoxidation to give the epoxy alcohol **10** in 90% yield and excellent selectivity. The product **10** was reduced with Red-Al in anhydrous tetrahydrofuran to give the corresponding 1,3-diol **11** in 90% yield. The 1,3-diol was selectively esterified with pivaloyl chloride in the presence of pyridine to protect the primary hydroxy group, and then silylated with *tert*-butyl(dimethyl)silyl chloride in the presence of imidazole to protect the secondary alcohol; both reactions occurred in very good yields. The pivaloyl group was selectively removed from the protected diol **12** by treatment with DIBAL-H in tetrahydrofuran at –78 °C to give the silylated derivative **13** in 90% yield. The primary alcohol group in **13** was subjected to oxidation under Swern conditions using oxalyl chloride to give the corresponding aldehyde, which was treated with methyl-2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetate to give the *Z*-olefin **14** in a very good yield. Finally, the olefin **14** was treated with 4-toluenesulfonic acid in methanol at room temperature to remove the silyl protecting group and cyclize the compound to give the target molecule (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (**1**) in a very good yield. All the products were characterized by means of ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy and optical rotation measurements, and by comparison with literature reports.

In conclusion, we successfully performed a stereoselective synthesis of **1** by using the Sharpless asymmetric epoxidation protocol as a source of chirality. All the reactions were clean, and the products were all obtained in very good yields.

IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker 300 MHz, spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

Ethyl (2*E*)-7-Phenylhept-2-enoate

Wittig ylide $Ph_3P{=}CHCO_2Et$ (12.5 g, 3.7 mmol) was added to a stirred soln of 5-phenylpentanal (**2**; 5 g, 3.08 mmol) in benzene (50 mL). The mixture was then refluxed for 2 h until the reaction was complete (TLC). The solvent was then removed under reduced pressure, and the residue was extracted with EtOAc (2 × 50 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane (1:9)] to give a colorless liquid; yield: 6.4 g (90%).

IR (neat): 3026, 2982, 2932, 2858, 1719, 1653, 1495, 1454, 1368, 1309, 1268, 1148, 1096, 1042, 980, 851, 747, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 6.5 Hz, 3 H), 1.48–1.58 (m, 2 H), 1.62–1.73 (m, 2 H), 2.50 (q, *J* = 7.5 Hz, 2 H), 2.62 (t, *J* = 7.5 Hz, 2 H), 4.18 (q, *J* = 6.5 Hz, 2 H), 5.80 (d, *J* = 15.9 Hz, 1 H), 6.85–6.95 (m, 1 H), 7.10–7.30 (m, 5 H).

MS (EI, 70 eV): *m/z* = 255 [M + Na], 233 [M$^+$], 196, 177, 155, 150, 121.

(2*E*)-7-Phenylhept-2-en-1-ol (3)

A suspension of $AlCl_3$ (3.27 g, 2.45 mmol) in anhyd THF (30 mL) was added to a stirred mixture of LAH (2.05 g, 5.4 mmol) in anhyd THF (20 mL) at 0 °C, and the mixture was stirred for 15 min. A soln of ethyl (2*E*)-7-phenylhept-2-enoate (5.7 g, 2.45 mmol) in anhyd THF (50 mL) was then slowly added and the resulting mixture was stirred for 3 h at 0 °C to r.t. until the reaction was complete (TLC). The reaction was quenched by adding crushed ice. EtOAc (100 mL) was added and the mixture was stirred well then filtered. The filtrate was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane (2:8)] to give a colorless liquid; yield: 3.5 g (75%).

IR (neat): 3361, 3026, 2929, 2856, 1669, 1603, 1495, 1454, 1088, 970, 745, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38–1.48 (m, 2 H), 1.58–1.66 (m, 2 H), 2.08 (q, *J* = 7.5 Hz, 2 H), 2.60 (t, *J* = 7.5 Hz, 2 H), 4.05 (t, *J* = 7.5 Hz, 2 H), 5.52–5.72 (m, 2 H), 7.05–7.30 (m, 5 H).

MS (EI, 70 eV): *m/z* = 208 [M + 18], 190 [M$^+$], 173, 161, 145, 131, 118, 105, 91.

[(2*R*,3*R*)-3-(4-Phenylbutyl)oxiran-2-yl]methanol (4)

Ti(O*i*-Pr)$_4$ (0.9 mL, 0.3 mmol) and (–)-DET (0.68 mL, 0.39 mmol) were added to constantly stirred mixture of 4-Å MS (4 g) in anhyd CH_2Cl_2 (30 mL) at –20 °C. After 20 min, a soln of enol **3** (3 g, 1.5 mmol) in CH_2Cl_2 (20 mL) at –20 °C was added and the mixture was stirred for 30 min. *t*-BuOOH (2.2 mL, 2.25 mmol) and the resulting mixture was stirred at –20 °C for 12 h until the reaction was complete (TLC). The reaction was then quenched with H_2O [13.5 mL, 20 times the weight of Ti(O*i*-Pr)$_4$ used in the reaction] at 0 °C and the mixture was stirred for 10 min. 30% aq NaOH (3 mL) was added and stirring was continued for 45 min at r.t. The mixture was then extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane (2:8)] to give a colorless liquid; yield: 2.9 g (90%); $[\alpha]_D^{27}$ +16.6 (*c* 1.5, $CHCl_3$).

IR (neat): 3423, 3025, 2924, 2854, 1603, 1458, 1029, 898, 746, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44–1.62 (m, 4 H), 1.65–1.71 (m, 2 H), 2.62 (t, *J* = 7.0 Hz, 2 H), 2.85–2.95 (m, 2 H), 3.56–3.61 (m, 1 H), 3.86 (dd, *J* = 3.5, 9.0 Hz, 1 H), 7.11–7.25 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.3, 128.3, 128.2, 125.6, 61.5, 58.5, 55.8, 35.7, 31.3, 31.0, 25.5.

MS (EI, 70 eV): *m/z* = 229 [M + Na], 206 [M$^+$], 185, 171, 149, 133, 105, 102, 91.

(3*R*)-7-Phenylheptane-1,3-diol (5)

A 65% soln of Red-Al in toluene (5.25 mL, 1.7 mmol) was slowly added to a stirred soln of epoxide **4** (2.9 g, 1.4 mmol) in anhyd THF (30 mL) at 0 °C, and the mixture was stirred for 3 h at 0 °C until the reaction was complete (TLC). The reaction was quenched by adding sat. aq sodium potassium tartrate. The mixture was stirred for 30 min then extracted with EtOAc (2 × 25 mL). The combined organic layers was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane (3:7)] to give a colorless liquid; yield: 2.63 g (90%); $[\alpha]_D^{27}$ +13.5 (*c* 1.5, $CHCl_3$).

IR (neat): 3369, 3085, 3062, 3026, 2926, 2855, 1944, 1603, 1495, 1453, 1331, 1150, 1058, 868, 801, 746, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.72 (m, 8 H), 2.61 (t, *J* = 7.0 Hz, 2 H), 2.95 (br s, 1 H), 3.70–3.89 (m 3 H), 7.10–7.25 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.4, 128.3, 128.2, 125.6, 71.9, 61.5, 38.1, 37.5, 35.8, 31.4, 25.1.

MS (EI, 70 eV): *m/z* = 231 [M + Na], 186, 173, 131, 123, 117, 105.

(3*R*)-3-Hydroxy-7-phenylheptyl Pivalate

Pyridine (1.25 mL, 1.5 mmol) and PivCl (1.82 mL, 0.68 mmol) were successively added to a stirred mixture of diol **5** (2.63 g, 1.26 mmol) and CH_2Cl_2 (30 mL) at 0 °C, and the resulting mixture was stirred at 0 °C to r.t. for 3 h until the reaction was complete (TLC). The mixture was then neutralized by adding 1 M HCl and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane (2:8)] to give a colorless liquid; yield: 3.5 g (95%).

IR (neat): 3443, 3064, 3027, 2932, 2858, 1730, 1639, 1463, 1365, 1285, 1254, 1157, 1101, 1066, 1011, 939, 837, 805, 775 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 9 H), 1.27–1.81 (m, 8 H), 2.60 (t, *J* = 7.0 Hz, 2 H), 3.58 (br s, 1 H), 4.04–4.12 (m, 1 H), 4.28–4.37 (m, 1 H), 7.09–7.11 (m, 3 H), 7.19–7.24 (m, 2 H).

MS (EI, 70 eV): *m/z* = 315 [M + Na], 293 [M$^+$], 275, 173, 131, 117, 103.

(3*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-phenylheptyl Pivalate (6)

Imidazole (3.25 g, 4.7 mmol) and TBSCl (2.15 g, 1.43 mmol) were added to a stirred soln of (3*R*)-3-hydroxy-7-phenylheptyl pivalate (3.5 g, 1.19 mmol) in anhyd CH_2Cl_2 (40 mL) at 0 °C, and the mixture was stirred for 5 min at 0 °C. A catalytic amount of DMAP was then added and stirring was continued further for 1 h at r.t. until the reaction was complete (TLC). Crushed ice was added, and the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The crude product was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane (1:9)] to give a colorless liquid; yield: 4.62 g (95%); $[\alpha]_D^{27}$ +9.2 (*c* 1.5, $CHCl_3$).

IR (neat): 3063, 3027, 2930, 2856, 1730, 1639, 1463, 1256, 1064, 1035, 836, 803, 744, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.30 (s, 6 H), 1.05 (s, 9 H), 1.38 (s, 9 H), 1.50–1.95 (m, 8 H), 2.80 (t, *J* = 7.5 Hz, 2 H), 3.90–3.99 (m, 1 H), 4.20–4.40 (m, 2 H), 7.28–7.45 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.4, 142.5, 128.3, 128.2, 125.6, 68.9, 61.6, 37.3, 35.9, 35.8, 31.6, 27.2, 25.8, 24.7, 18.1, –4.4, –4.7.

MS (EI, 70 eV): *m/z* = 429 [M + Na], 407 [M$^+$], 275, 173, 131, 103.

(3*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-phenylheptan-1-ol (7)

1 M DIBAL-H (13 mL, 1.1 mmol) was added to a stirred soln of silylated compound **6** (4.5 g, 1.1 mmol) in anhyd THF (50 mL) at –78 °C, and the mixture was stirred for 30 min until the reaction was complete (TLC). The reaction was quenched by adding few drops of MeOH, and the mixture was stirred for 10 min. Sat. aq Rochelle's salt was added and stirring was continued for 4 h. The solvent THF was removed under reduced pressure and the residue was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The crude product was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane (2:8)] to give a colorless liquid; yield: 3.2 g (90%); $[\alpha]_D^{27}$ +7.3 (*c* 1.5, $CHCl_3$).

IR (neat): 3406, 3063, 3027, 2930, 2856, 1605, 1463, 1370, 1256, 1064, 1035, 836, 803, 755, 744, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 0.90 (s, 9 H), 1.28–1.40 (m, 2 H), 1.50–1.82 (m, 6 H), 2.60 (t, *J* = 7.5 Hz, 2 H), 3.60–3.68 (m, 1 H), 3.70–3.80 (m, 1 H), 3.85–3.95 (m, 1 H), 7.10–7.28 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.6, 128.3, 128.2, 125.6, 71.9, 63.8, 40.2, 36.7, 35.9, 31.6, 25.9, 25.1, 18.1, –4.4, –4.5.

MS (EI, 70 eV): *m/z* = 323 [M$^+$], 279, 257, 191, 173, 147, 133, 131, 117, 102.

Ethyl (2*E*,5*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-9-phenylnon-2-enoate (8)

Oxalyl chloride (1.25 mL, 1.5 mmol) was added to a stirred mixture of DMSO (2 mL) and CH_2Cl_2 (10 mL) at –78 °C. A soln of alcohol **7** (3.2 g, 1 mmol) in CH_2Cl_2 (10 mL) was then added, and mixture was stirred at –78 °C for 2 h. Et_3N was added (7 mL, 5 mmol), and the mixture was stirred for 45 min at –78 °C until the reaction was complete (TLC). The mixture was then allowed to warm to 0 °C, sat. aq NH_4Cl was added, and the mixture was stirred well. The mixture was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under vacuum to give the aldehyde (yield: 3 g, 95%), which was used for next reaction without purification.

The aldehyde (3 g, 0.93 mmol) was dissolved in benzene (30 mL) and $Ph_3P{=}CHCO_2Et$ (4.75 g, 1.4 mmol) was added. The resulting mixture was refluxed for 2 h until the reaction was complete (TLC). The solvent was removed under reduced pressure and the residue was extracted with EtOAc (2 × 20 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane (1:9)] to give a colorless liquid; yield: 3.2 g (85%); $[\alpha]_D^{25}$ –13.7 (*c* 1, $CHCl_3$).

IR (neat): 3027, 2933, 2857, 1722, 1656, 1463, 1367, 1318, 1259, 1174, 1096, 1043, 898, 937, 836, 775, 746 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 0.90 (s, 9 H), 1.28 (t, *J* = 7.5 Hz, 3 H), 1.31–1.48 (m, 4 H), 1.56–1.63 (m, 2 H), 2.26–2.33 (m, 2 H), 2.59 (t, *J* = 7.5 Hz, 2 H), 3.71–3.77 (m, 1 H), 4.17 (q, *J* = 7.5 Hz, 2 H), 5.78 (d, *J* = 15.9 Hz, 1 H), 6.82–6.95 (m, 1 H), 7.09–7.25 (m, 5 H).

MS (EI, 70 eV): *m/z* = 391 [M$^+$], 279, 206, 259, 219, 193, 156, 128.

(2*E*,5*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-9-phenylnon-2-en-1-ol (9)

A suspension of $AlCl_3$ (1 g, 0.73 mmol) in THF (15 mL) was added to a stirred mixture of LAH (0.61 g, 1.6 mmol) and anhyd THF (10 mL) at 0 °C, and the mixture was stirred for 15 min at 0 °C. A soln of enoate **8** (3 g, 0.73 mmol) in anhyd THF (30 mL) was then added slowly, and the mixture was stirred at 0 °C to r.t. for 3 h until the reaction was complete (TLC). The reaction was quenched by adding crushed ice, EtOAc (60 mL) was added, and the mixture was stirred well then filtered. The filtrate was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane (2:8)] to give a colorless liquid; yield: 1.92 g (75%); $[\alpha]_D^{26}$ –3.66 (*c* 1.6, $CHCl_3$).

IR (neat): 3346, 3026, 2931, 2856, 1603, 1461, 1365, 1253, 1093, 1033, 934, 834, 774, 744, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 0.90 (s, 9 H), 1.22–1.46 (m, 4 H), 1.52–1.62 (m, 2 H), 2.12–2.18 (m, 2 H), 2.59 (t, *J* = 7.5 Hz, 2 H), 3.60–3.69 (m, 1 H), 4.04 (d, *J* = 6.5 Hz, 2 H), 5.58–5.64 (m, 2 H), 7.08–7.26 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.6, 131.2, 129.5, 128.4, 128.1, 125.6, 71.9, 63.8, 40.2, 36.7, 35.6, 31.6, 25.9, 25.1, 18.1, –4.3, –4.5.

MS (EI, 70 eV): *m/z* = 366 [M + 18], 349 [M$^+$], 279, 263, 217, 191, 151, 145.

[(2*R*,3*R*)-3-((2*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-phenylhexyl)oxiran-2-yl]methanol (10)

Ti(O*i*-Pr)$_4$ (0.25 mL, 0.08 mmol) and (–)-DET (0.13 mL, 0.1 mmol) were added successively to a constantly stirred mixture of powdered 4 Å MS (2 g) in CH_2Cl_2 (20 mL) at –20 °C, and the mixture was stirred for 20 min. A soln of enoate **9** (1.6 g, 0.43 mmol) in CH_2Cl_2 (20 mL) at –20 °C was added followed, after 30 min, by *t*-BuOOH (0.6 mL, 0.65 mmol). The mixture was stirred at –20 °C for 12 h until the reaction was complete (TLC). The reaction was quenched with H_2O (5 mL), and the mixture was stirred for 10 min. 30% aq NaOH (1.5 mL) was added, and the mixture was stirred for 45 min at r.t. then extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane (3:7)] to give a colorless liquid; yield: 1.5 g (90%); $[\alpha]_D^{26}$ –4.32 (*c* 1.5, $CHCl_3$).

IR (neat): 3431, 3062, 3026, 2931, 2857, 1603, 1494, 1464, 1367, 1254, 1070, 941, 835, 775, 745, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 0.90 (s, 9 H), 1.24–1.38 (m, 2 H), 1.44–1.74 (m, 6 H), 2.59 (t, *J* = 7.5 Hz, 2 H), 2.79–2.85 (m, 1 H), 2.97–3.03 (m, 1 H), 3.51–3.59 (m, 1 H), 3.77–3.89 (m, 2 H), 7.07–7.25 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.4, 128.3, 128.2, 125.6, 69.9, 61.9, 59.1, 53.1, 37.6, 36.9, 31.5, 25.5, 24.6, 18.0, –4.5, –4.6.

MS (EI, 70 eV): *m/z* = 229 [M + Na], 365, 206 [M$^+$], 357, 344, 279, 239, 193, 171.

(3*S*,5*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-9-phenylnonane-1,3-diol (11)

A 65% soln of Red-Al in toluene (1.5 mL, 0.49 mmol) was slowly added to a stirred mixture of epoxide **10** (1.5 g, 0.41 mmol) in anhyd THF (20 mL) at 0 °C and the mixture was stirred for 4 h at 0 °C until the reaction was complete (TLC). The reaction was quenched by addition of sat. aq Rochelle's salt, and the mixture was stirred for 30 min then extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane (3:7)] to give a colorless liquid; yield: 1.35 g (90%); $[\alpha]_D^{27}$ –9.45 (*c* 1.5, $CHCl_3$).

IR (neat): 3378, 3027, 2932, 2857, 1603, 1462, 1368, 1254, 1164, 937, 834, 776, 743, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 0.90 (s, 9 H), 1.24–1.36 (m, 2 H), 1.44–1.66 (m, 8 H), 2.60 (t, *J* = 7.5 Hz, 2 H), 2.90 (br s, 1 H), 3.60 (br s, 1 H), 3.71–3.81 (m, 2 H), 3.87–4.01 (m, 2 H), 7.07–7.26 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.5, 128.3, 128.2, 125.6, 69.9, 61.6, 58.9, 53.0, 37.6, 36.9, 35.9, 31.5, 25.8, 24.7, 18.0, –4.5, –4.6.

MS (EI, 70 eV): *m/z* = 367 [M$^+$], 356, 340, 309, 295, 279, 242, 217, 193, 113.

(3*S*,5*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-hydroxy-9-phenylnonyl Pivalate

Pyridine (0.35 mL, 0.4 mmol) and PivCl (0.5 mL, 0.38 mmol) were added successively to a stirred soln of diol **11** (1.35 g, 0.36 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The mixture was stirred at 0 °C to r.t. for 3 h until the reaction was complete (TLC) and then neutralized with 1 M HCl and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by

column chromatography [silica gel (60–120 mesh), EtOAc–hexane (2:8)] to give a colorless liquid; yield: 1.6 g (95%); $[\alpha]_D^{23.8}$ –7.3 (*c* 1.5, $CHCl_3$).

IR (neat): 3451, 3027, 2933, 2858, 1725, 1636, 1465, 1366, 1286, 1254, 1160, 1068, 937, 834, 775, 743, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.20 (s, 6 H), 0.90 (s, 9 H), 1.20 (s, 9 H), 1.24–1.40 (m, 2 H), 1.46–1.72 (m, 8 H), 2.60 (t, *J* = 7.5 Hz, 2 H), 3.70–3.80 (m, 1 H), 3.85–3.95 (m, 1 H), 4.07–4.30 (m, 2 H), 7.07–7.27 (m, 5 H).

MS (EI, 70 eV): *m/z* = 451[M^+], 433, 338, 319, 301, 263, 199, 157.

(3*S*,5*R*)-3,5-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-9-phenylnonyl Pivalate (12)

Imidazole (0.92 g, 1.3 mmol) and TBSCl (0.6 g, 0.41 mmol) were added to a stirred mixture of (3*S*,5*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-3-hydroxy-9-phenylnonyl pivalate (1.6 g, 0.34 mmol) in anhyd CH_2Cl_2 (20 mL) at 0 °C and the mixture was stirred for 5 min. A catalytic amount of DMAP was added and stirring was continued for a further for 1 h at r.t. until the reaction was complete (TLC). Crushed ice was added and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The crude product was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane (1:9)] to give a colorless liquid; yield: 1.9 g (95%); $[\alpha]_D^{23.8}$ –5.7 (*c* 1.5, $CHCl_3$).

IR (neat): 3027, 2929, 2857, 1731, 1466, 1364, 1284, 1254, 1156, 1103, 1065, 938, 836, 774, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.20 (s, 12 H), 0.85 (s, 9 H), 0.90 (s, 9 H), 1.18 (s, 9 H), 1.22–1.86 (m, 10 H), 2.58 (t, *J* = 7.5 Hz, 2 H), 3.66–3.91 (m, 2 H), 4.04–4.16 (m, 2 H), 7.07–7.27 (m, 5 H).

MS (EI, 70 eV): *m/z* = 565 [M^+], 532, 433, 362, 301, 277, 240, 199, 171, 145.

(3*S*,5*R*)-3,5-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-9-phenylnonan-1-ol (13)

A 1 M soln of DIBAL-H (4.2 mL, 0.36 mmol) was added to a stirred soln of compound **12** (1.9 g, 0.33 mmol) in anhyd THF (20 mL) at –78 °C and the mixture was stirred for 30 min until the reaction was complete (TLC). The reaction was quenched by adding few drops of MeOH and the mixture was stirred for 10 min. Sat. aq Rochelle's salt was added and stirring was continued for 4 h. The THF was removed under reduced pressure and the residue was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The crude product was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane (2:8)] to give a colorless liquid; yield: 1.4 g (90%); $[\alpha]_D^{23.8}$ –12.9 (*c* 1.5, $CHCl_3$).

IR (neat): 3445, 3027, 2932, 2857, 1632, 1465, 1380, 1253, 1060, 939, 835, 774, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.15 (s, 6 H), 0.20 (s, 6 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 1.22–1.90 (m, 10 H), 2.60 (t, *J* = 7.5 Hz, 2 H), 3.62–4.10 (m, 4 H), 7.05–7.25 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.5, 128.3, 128.2, 125.6, 69.9, 69.4, 60.2, 43.8, 37.6, 37.2, 35.9, 31.7, 25.8, 24.6, 17.9, –4.1, –4.4, –4.5, –4.7.

MS (EI, 70 eV): *m/z* = 481 [M^+], 451, 433, 403, 362, 349, 305, 279, 242, 217, 199.

Methyl (2*Z*,5*S*,7*R*)-5,7-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-11-phenylundec-2-enoate (14)

Oxalyl chloride (0.3 mL, 0.3 mmol) was added to a stirred mixture of DMSO (0.25 mL, 0.31 mmol) and CH_2Cl_2 (5 mL) at –78 °C, and the mixture was stirred for 20 min. A soln of alcohol **13** (1 g, 0.2 mmol) in CH_2Cl_2 (5 mL) was added and stirring was again continued for 2 h at –78 °C. Et_3N (1.4 mL, 1.04 mmol) was added and the mixture was stirred at –78 °C for 45 min. The mixture was then allowed to warm to 0 °C in an ice bath and the reaction was quenched with sat. aq NH_4Cl. The mixture was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The crude aldehyde that was obtained [yield; 0.95 g (95%)] was used in the next step without purification.

Methyl-2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (0.8 g, 0.26 mmol) was added to a stirred mixture of NaH (0.15 g, 0.6 mmol) and THF (10 mL) at 0 °C, and the resulting mixture was stirred for 30 min. The mixture was then cooled to –78 °C and a soln of the aldehyde in anhyd THF (5 mL) was added. The mixture was stirred for 1 h at –78 °C until the reaction was complete (TLC). The reaction was then quenched with sat. aq NH_4Cl, and the mixture was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The crude product was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane (1:9)] to give a colorless liquid; yield: 0.94 g (85%); $[\alpha]_D^{27}$ –51.12 (*c* 0.5, $CHCl_3$).

IR (neat): 2927, 2856, 1726, 1645, 1462, 1366, 1256, 1175, 1093, 1039, 834, 775, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.15 (s, 6 H), 0.20 (s, 6 H), 0.82 (s, 9 H), 0.90 (s, 9 H), 1.22–1.45 (m, 8 H), 2.58 (t, *J* = 7.5 Hz, 2 H), 2.65–2.76 (m, 1 H), 2.95–3.05 (m, 1 H), 3.70 (s, 3 H), 3.75–3.85 (m, 1 H), 3.95–4.01 (m, 1 H), 5.85 (d, *J* = 11.0 Hz, 1 H), 6.30–6.40 (m, 1 H), 7.10–7.30 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 146.6, 142.6, 128.3, 128.2, 125.6, 120.6, 69.3, 68.5, 50.9, 44.5, 37.2, 36.0, 35.9, 31.7, 29.6, 25.9, 25.8, 24.7, 18.0, –4.3, –4.4, –4.5, –4.6.

MS (EI, 70 eV): *m/z* = 557 [M + Na], 535 [M^+], 417, 403, 330, 288, 271, 196, 102.

(6*S*)-6-[(2*R*)-2-Hydroxy-6-phenylhexyl]-5,6-dihydro-2*H*-pyran-2-one (1)

A catalytic amount of TsOH was added to a stirred soln of compound **14** (0.9 g) in MeOH at r.t., and the mixture was stirred for 30 min until the reaction was complete (TLC). The reaction was quenched with sat. aq $NaHCO_3$ and the mixture was stirred for 30 min. The mixture was then filtered and the filter was washed with MeOH. The soln was concentrated under reduced pressure to give a crude product that was purified by column chromatography [silica gel (60–120 mesh), EtOAc–hexane (3:7)] to give a pale yellow low-melting solid; yield: 0.45 g (90%); mp 33–35 °C; $[\alpha]_D^{20}$ –62.33 (*c* 0.65, $CHCl_3$).

IR (neat): 3457, 2938, 2848, 1695, 1487, 1392, 1254, 835, 775, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.50 (m, 3 H), 1.55–1.70 (m, 3 H), 1.80–1.95 (m, 1 H), 2.30–2.40 (m, 3 H), 2.62 (t, *J* = 7.0 Hz, 3 H), 3.90–4.10 (m, 1 H), 4.65–4.85 (m, 1 H), 6.02 (dd, *J* = 1.5 & 9.5 Hz, 1 H), 6.85–6.95 (m, 1 H), 7.10–7.30 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.4, 145.4, 142.3, 128.2, 128.1, 125.5, 121.1, 74.9, 66.7, 42.2, 37.7, 35.7, 31.2, 29.8, 25.0.

MS (EI, 70 eV): *m/z* = 297 [M + Na], 275 [M^+].

Acknowledgment

R.S.G. is grateful to CSIR-New Delhi for the provision of a fellowship.

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