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Stereoselective first total synthesis of (*R*)-rugulactone

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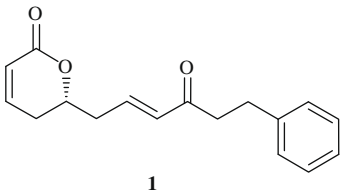
ABSTRACT

A simple and highly efficient stereoselective synthetic route has been developed for the synthesis of (*R*)-rugulactone, a 6-arylalkyl-5,6-dihydro-2*H*-pyran-2-one, from readily available substrates such as 1,3-propanediol and 3-phenyl-1-propanal employing Keck's asymmetric allylation and cross metathesis as key steps.

1. Introduction

6-Arylalkyl-5,6-dihydro-2*H*-pyran-2-ones are important structural features of the genus of *Cryptocarya* of Lauraceae family, lacking a substituent at C-4.[1] Due to the Michael acceptor properties of the α,β-unsaturated α-pyrones toward amino acid residues of receptors, these α-pyrone molecules possess interesting biological activities such as antitumor, anti-inflammatory, antibacterial, antiviral, and antifungal activities.[2] The arylalkyl-substituted α,β-unsaturated δ-lactones are ubiquitous metabolites of the evergreen trees of *Cryptocarya* genus which are well known for their legendary medicinal properties.[2] Recently, a 6-arylalkyl-5, 6-dihydro-2*H*-pyran-2-one, (*R*)-rugulactone **1** was isolated from the dichloromethane extract of *Cryptocarya rugulosa* by Cardellina et al.[3] The structure was established via NMR and HRMS studies and the absolute configuration was determined by a CD spectrum. Biological assays of (*R*)-rugulactone found it to inhibit the nuclear factor-κB (NF-κB) activation pathway that is active in many types of cancers, exhibiting up to fivefold induction of IκB at 25 μm/mL.[3] In a continuation of our interest in the synthesis of biologically active natural products,[4] we planned to synthesize compound **1**. To the best of our knowledge, the synthesis of **1** has not been reported in the literature and hence we herein report an efficient stereoselective first total synthesis of (*R*)-rugulactone **1**.



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Our synthetic approach to (*R*)-rugulactone is outlined in Scheme 1, which involves a Grubb's cross metathesis reaction between compounds **2** and **3**. The key fragment **2** was prepared via Still–Gennari modification of the Horner–Emmons reaction from **8**, which could be readily prepared via Keck's asymmetric allylation route from the easily available 1,3-propanediol **6**. The vinyl ketone **3** in turn was prepared from 3-phenyl-1-propanal **4**.

2. Results and discussion

As outlined in Scheme 1, the 1,3-propanediol **6** was selectively protected with benzyl bromide[5] to mono benzyl ether **7**. The primary alcohol in **7** was oxidized using iodoxybenzoic acid (IBX) in DMSO to afford the corresponding aldehyde, which was subjected to the catalytic asymmetric allyl stannation developed by Keck et al.[6] to furnish the homoallylic alcohol **8** in 80% yield with an excellent enantioselectivity of 97.5% ee (determined by chiral HPLC).[7] The spectroscopic and analytical data[8] were in good agreement with the literature values. The absolute stereochemistry of the newly generated stereogenic center in compound **8** bearing the hydroxyl group was determined by preparing the MPTA esters by a modified Mosher's method,[9] and were found to have an (*R*)-configuration (Fig. 1). The negative chemical shift difference to the left side of the MTPA plane and the positive chemical shift differences to the right side of the MTPA plane indicated that the hydroxyl stereochemistry had an (*R*)-configuration (Fig. 1).

The secondary hydroxyl group in **8** was protected as its TPS ether using TPSCl and imidazole in dry DCM to yield **9**. Next, the benzyl group in compound **9** was removed using lithium naphthalenide (LN)[10] to yield primary alcohol **10** in 81%. The primary alcohol in compound **10** was oxidized using IBX in DMSO to yield the aldehyde which was subjected to Still–Gennari modification of the Horner–Emmons olefination reaction[11] to afford unsaturated ester **11** with a *Z*/*E* ratio of 95:05 in 80% yield. Compound **11** upon treatment with 3% HCl in MeOH afforded 6-allyl-5,6-dihydro-α-pyrone **2** in 78% yield (Scheme 2).

The fragment 5-phenyl-pent-1-en-3-ol **3** was prepared from phenyl-1-propanal **4**. Compound **4** was reacted with vinyl magnesium bromide to yield allyl alcohol **5**,[12] which on oxidation with

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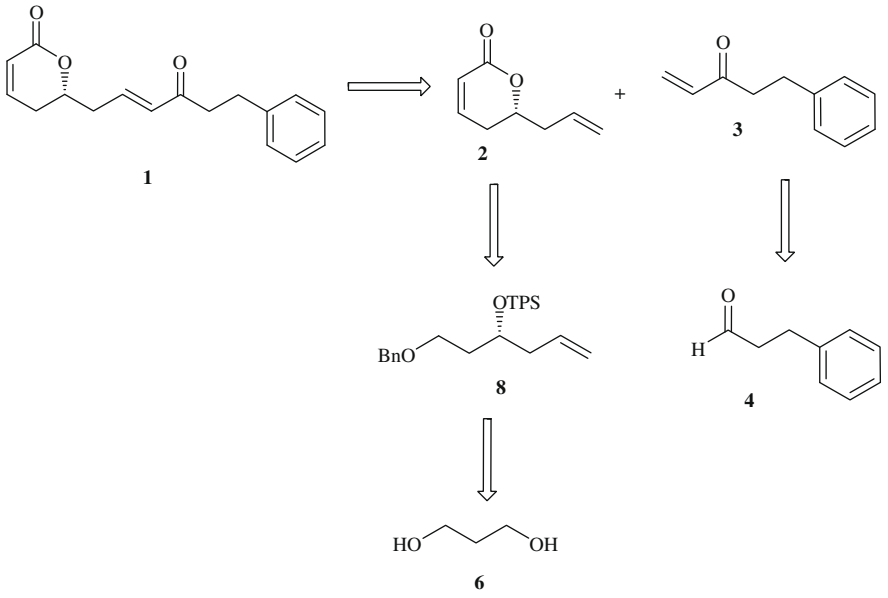


Scheme 1.

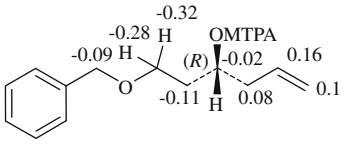


Figure 1. Determination of the absolute configuration and $\Delta\delta$ values for the (*S*)- and (*R*)-MTPA ester derivatives of **8** ($\Delta\delta = \delta_S - \delta_R$).

IBX in DMSO afforded vinyl ketone **3** in good yield.[13] Finally, compounds **2** and **3** in a 1:3 ratio were subjected to cross metathesis using second generation Grubb's catalyst (5 mol %)[14] in dichloromethane under reflux conditions to yield desired (*R*)-rugulactone **1** in 74% yield (Scheme 3). The ^{1}H and ^{13}C NMR spectra of synthetic compound **1** are in good agreement with those of the natural (*R*)-rugulactone and as a result we are able to report for the first time the specific rotation of **1** as $[\alpha]_D^{25} = -61.9$ (*c* 0.5, $CHCl_3$).

3. Conclusion

In conclusion, the asymmetric synthesis of (*R*)-rugulactone has been achieved from commercially available inexpensive 1,3-propane diol **6** and 3-phenyl-1-propanal **4** by the successful utilization of the Keck's asymmetric allylation and Grubb's cross metathesis reaction.

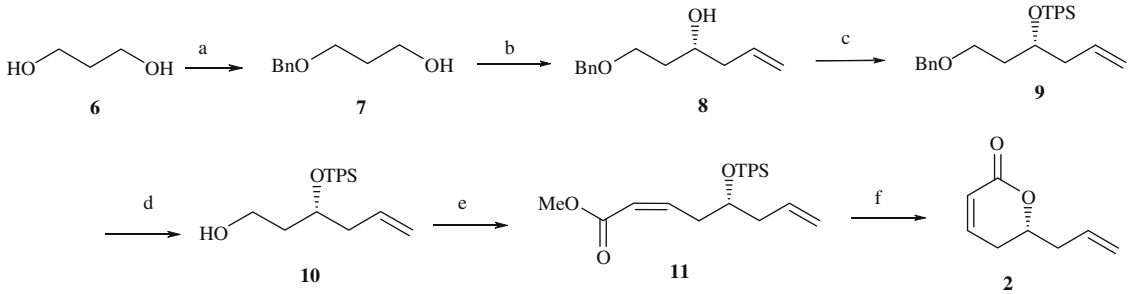
4. Experimental

4.1. General

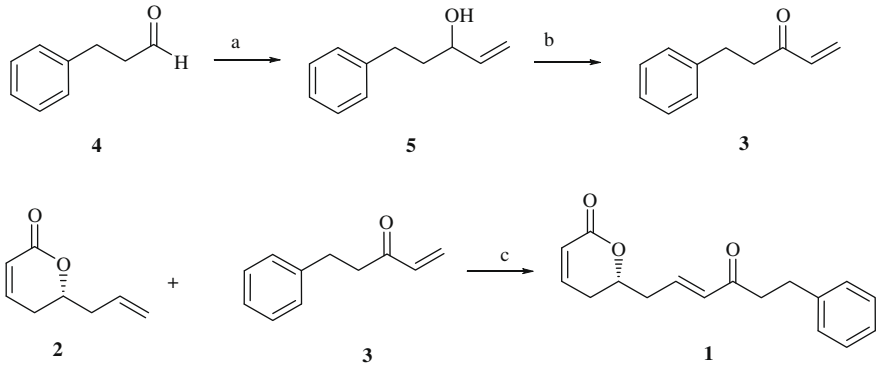
The reactions were carried out under N_2 in anhydrous solvents such as CH_2Cl_2, THF, and EtOAc. All reactions were monitored by TLC (silica-coated plates and visualized under UV light). Yields refer to material after chromatography and which is spectroscopically (^{1}H, ^{13}C NMR) homogeneous. Air-sensitive reagents were transferred by a syringe or a double-ended needle. Evaporation of solvents was performed at reduced pressure on a Buchi rotary evaporator. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200 and Brucker Avance 300 spectrometers. Chemical shifts (δ) are reported relative to TMS ($\delta = 0.0$) as an internal standard. Mass spectra were obtained on MS-EI, MS-ESI, and HRMS mass spectrometers. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. IR (FT-IR) spectra were recorded either on KBr pellets or neat as thin film. Optical rotations were recorded on JASCO DIP–360 digital polarimeter at 25 °C.

4.1.1. 3-(Benzyloxy)propane-1-ol 7[5]

To a solution of 1,3-propanediol **6** (2 g, 26.31 mmol) in dry THF (50 mL) was added sodium hydride (605 mg, 26.30 mmol) at 0 °C,



Scheme 2. Reagents and conditions: (a) BnBr, NaH, TBAI, THF. 0 °C to rt, 2 h, 85%; (b) (i) IBX, dry DMSO; dry CH_2Cl_2, 5 h, 88%, (ii) (*R*)-BINOL, 4 Å MS, $Ti(O^iPr)_4$, allyltributylstannane, CH_2Cl_2, −78 °C to −20 °C, 80%; (c) TBDPSCl, imidazole, dry CH_2Cl_2, 4 h, 95%; (d) Li in naphthalene, −20 °C, 3 h, 81%; (e) (i) IBX, dry DMSO, dry CH_2Cl_2, 5 h, 85%, (ii) $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, dry THF, −78 °C, 2 h, 76%; and (f) 3% HCl in MeOH 30 min, 78%.



Scheme 3. Reagents and conditions: (a) vinyl magnesium bromide, dry THF, 0 °C to rt, 1 h, 86%; (b) IBX, dry DMSO, dry CH_2Cl_2, 3 h, 90%; and (c) Grubb's 2nd generation catalyst (5 mol %), dry CH_2Cl_2, 40 °C, 12 h, 74%.

and the reaction mixture was stirred at room temperature for 30 min and again cooled to 0 °C. To this cooled solution were added slowly benzyl bromide (4 g, 23.68 mmol) and tetra-*N*-butylammonium iodide (cat.) and the reaction mixture was stirred for 2 h at room temperature. After completion of the reaction as indicated by TLC, the reaction was quenched with cold water, and the reaction mixture was extracted into EtOAc (3 × 30 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to yield crude compound **7** as an oil which was purified on silica gel column chromatography using EtOAc–hexane (2:8) as eluent to furnish the pure monobenzyl-protected alcohol **7** (3.71 g, 85%) as a colorless oil. IR (neat): *ν* 3624, 3413, 3017, 2941, 2867, 2401, 1952, 1702, 1496, 1455, 1363, 1216, 1099, 957, 932, 850, and 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.33–7.27 (m, 5H), 4.50 (br s, 2H), 3.61 (t, *J* = 5.7 Hz, 2H), 3.50 (t, *J* = 6.6 Hz, 2H), 2.41 (br s 1H), 1.73–1.62 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 137.9. 128.0, 127.3, 127.2, 72.5, 69.9, 61.7, 26.0. EIMS: *m/z* 166 $[M]^+$.

4.1.2. (*R*)-6-(Benzyloxy)-1-hexen-4-ol 8[8]

To a stirred solution of IBX (7.59 g, 27.07 mmol) in dry DMSO (10 mL), a solution of **7** (3.0 g, 18 mmol) in dry DCM (50 mL) was added at room temperature and stirred for 5 h at room temperature. After completion of the reaction as indicated by TLC, the mixture was filtered, diluted with water (25 mL), and extracted into DCM (2 × 50 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and evaporated to give crude aldehyde, which was purified on silica gel column using EtOAc–hexane (1:9) to give pure aldehyde (2.6 g, 88%) as a colorless liquid. Separately, a mixture of (*R*)-BINOL (0.443 g, 1.58 mmol) and $Ti(O^iPr)_4$ (0.50 g, 1.585 mmol) in CH_2Cl_2 (60 mL) in the presence of 4 Å molecular sieves (MS) (4 g) was stirred at reflux. After 1 h, the reaction mixture was cooled to room temperature and to it was added the previously prepared aldehyde (2.6 g, 15.85 mmol) in dry DCM and the resulting mixture was stirred for 10 min. The reaction mixture was then cooled to −78 °C and allyl tributylstannane (6.29 g, 19.02 mmol) was added to the reaction mixture and the stirring was continued at −20 °C for 36 h. After completion of the reaction as noticed by TLC, the reaction was quenched with saturated $NaHCO_3$ solution (10 mL) and the reaction mixture was stirred for an additional 30 min and extracted into CH_2Cl_2 (40 mL). The organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give crude residue, which was purified over silica gel column chromatography using EtOAc–hexane (2:8) to afford homoallylic alcohol **8** (2.61 g, 80%) as a clear liquid with ee >97%. $[\alpha]_D^{25} = +2.2$ (*c* 1, $CHCl_3$). IR (neat): *ν* 3444, 3069, 3030, 2921, 2862, 1640, 1492, 1451, 1363, 1207, 1096, 1025, 914 and 739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.37–7.26 (m, 5H), 5.91–5.76 (m, 1H), 5.15–5.07 (m, 2H), 4.52 (br s, 2H), 3.93–3.83 (m, 1H), 3.68 (AB, J_{AB} = 5.2 Hz, 2H), 2.63 (br s, 1H), 2.25 (dt, *J* = 7.1 Hz, 1.4 Hz, 2H). 1.82–1.72 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 137.9, 134.8, 128.4, 127.7, 127.6, 117.5, 73.3, 70.3, 68.9, 41.9, and 35.8. EIMS: *m/z* 206 $[M]^+$.

4.1.3. [1-(2-Benzyloxy-ethyl)-but-3-enyloxy]-*tert*-butyl-diphenyl-silane 9

To a stirred cooled (0 °C) solution of compound **8** (2.5 g, 12.13 mmol) and imidazole (2.06 g, 30.25 mmol) in dry dichloromethane (30 mL) was added *tert*-butyldiphenylsilylchloride (4.0 g, 14.55 mmol) dropwise. Stirring was then continued for 4 h. After completion of reaction, the reaction mixture was diluted with water (20 mL) and extracted into dichloromethane (3 × 30 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhyd Na_2SO_4, and concentrated under vacuum to furnish the crude residue, which was purified by column chromatography on silica gel eluting with AcOEt–hexane (1:19) to afford the pure compound **9** (5.11 g, 95% yield): $[\alpha]_D^{25} = -6.3$ (*c* 1, $CHCl_3$). IR (neat): *ν* 2961, 1645, 1621, 1489, 1461, 1349, 1353, 1217, 1097, 1024, 918 and 749. ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.71–7.65 (m, 5H), 7.43–7.18 (m, 10H), 5.79–5.64 (m, 1H), 4.93 (m, 2H), 4.33 (br s, 2H), 3.96 (m, 1H), 3.48 (AB, J_{AB} = 4.3 Hz, 2H), 2.25 (m, 2H), 1.82–1.77 (m, 2H), 1.05 (s, 9H) .^{13}C NMR (75 Hz, $CDCl_3$): 135.9, 134.5, 134.4, 129.5, 128.2, 127.5, 127.4, 127.4, 127.3, 117.0, 72.7, 70.3, 66.9, 41.5, 36.0, 27.0, 19.3. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{29}H_{36}O_2NaSi$: 467.2382, found: 467.2385.

4.1.4. 3-(*tert*-Butyl-diphenyl-silanyloxy)-hex-5-en-1-ol 10

To solution of naphthalene (14.41 g, 112.60 mmol) in dry THF (20 mL) was added lithium metal (810 mg, 135.13 mmol). After 30 min, a dark green color developed which turned darker after 1.25 h. This solution was cooled to −25 °C and to this, a solution of compound **9** (5 g, 11.26 mmol) in dry THF (3 mL) was added by a cannula. The resulting mixture was stirred at −25 °C for 3 h. After completion of the reaction as noticed by TLC, the reaction was quenched with saturated aqueous ammonium chloride (15 mL) and water (15 mL). The resulting solution was extracted into ether (3 × 30 mL), washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to yield crude compound **10** which was purified over silica gel column chromatography using EtOAc–hexane (1:9) to afford primary alcohol **10** (3.22 g, 81%). $[\alpha]_D^{25} = -23$ (*c* 1, $CHCl_3$): IR (neat): *ν* 3424, 2961, 1646, 1620, 1354, 1216, 1047, 1024, 919 and 747 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.76–7.65 (m, 4H), 7.46–7.34 (m, 6H), 5.66–5.55 (m, 1H), 4.87 (m, 2H), 4.04–3.94 (m, 1H), 3.69–3.61 (m, 2H),

2.35–2.23 (m, 1H), 2.23–2.11 (m, 1H), 1.95–1.75 (m, 1H), 1.70–1.60 (m, 1H), 1.06 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 135.8, 129.8, 127.6, 127.5, 117.3, 71.6, 59.7, 41.0, 37.5, 27.0,19.2. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{22}H_{30}O_2NaSi$: 377.1912, found: 377.1921.

4.1.5. 5-(*tert*-Butyl-diphenyl-silanyloxy)-octa-2,7-dienoic acid methyl ester 11

To stirred solution of IBX (3.70 g, 13.22 mmol) in dry DMSO (10 mL) was added a solution of **10** (3.12 g, 8.81 mmol) in DCM (50 mL) at room temperature and stirred for 5 h at room temperature. After completion of the reaction, the mixture was filtered, diluted with water (25 mL), and extracted into dichloromethane (2 × 50 mL). The combined organic layer was washed with brine (20 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure to give the crude aldehyde, which was purified on column chromatography using EtOAc–hexane (1:9) to give pure aldehyde **10** (2.2 g, 9.56 mmol, 92%) as a colorless liquid. The aldehyde was used directly for the next reaction. To a cooled (0 °C) suspension of NaH (358 mg, 14.94 mmol) in dry THF (10 mL) under a N_2 atmosphere was added bis-(2,2,2-trifluoromethyl)(methoxy carbonyl methyl) phosphonate (2.37 g, 7.45 mmol) in dry THF (10 mL) and was allowed to stir for 30 min. The reaction temperature was brought to −78 °C, then a solution of aldehyde **10** (2.63 g, 7.47 mmol) in dry THF (10 mL) was added dropwise over a period of 10 min. The resulting mixture was stirred for 2 h at −78 °C. After completion of the reaction, the reaction was quenched with saturated NH_4Cl and the reaction mixture was extracted into diethyl ether (3 × 20 mL). The combined organic phase was dried over anhyd Na_2SO_4 and the solvent was evaporated under reduced pressure to obtain the crude product, which was purified over silica gel column chromatography using EtOAc–hexane (1:19) to afford (*Z*)-acrylate **11** (2.31 g, 76% yield) as a yellow oil. $[\alpha]_D^{25} = +13.6$ (*c* 1, $CHCl_3$). IR (neat): *ν* 3121, 2930, 2856, 1725, 1642, 1435, 1388, 1251, 1045, 918, 796, 742, 618 and 621 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77–7.64 (m, 4H), 7.48–7.33 (m, 6H), 6.33 (dd, *J* = 11.7 Hz, 7.5 Hz, 1H), 5.79 (dt, *J* = 11.7 Hz, 1.6 Hz, 1H), 5.76–5.62 (m, 1H), 4.96 (m, 2H), 3.98–3.85 (m, 1H), 3.66 (s, 3H), 2.96–2.84 (m, 1H), 2.82–2.71 (m, 1H), 2.19 (m, 2H), 1.08 (br s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 146.2, 135.7, 133.8, 134.0, 129.5, 127.4, 120.5, 117.2, 96.0, 72.0, 41.3, 35.3, 26.9, 19.2. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{22}H_{30}O_2NaSi$: 431.2018, found: 431.2020.

4.1.6. 6-Allyl-5, 6-dihydro-pyran-2-one 2

Ester **11** (2.2 g, 5.39 mmol) was taken in 3% HCl in methanol solution (10 mL) and stirred for 30 min. After completion of the reaction as indicated by TLC, the reaction was quenched with saturated $NaHCO_3$ and the reaction mixture was extracted into ethyl acetate (3 × 25 mL). The combined organic extract was washed with brine solution, dried over anhyd Na_2SO_4, and evaporated under reduced pressure to give crude lactone **2**, which was purified over silica gel column chromatography using EtOAc–hexane (2:8) to afford pure compound **2** as a clear liquid (580 mg 78%). $[\alpha]_D^{25} = -115.8$ (*c* 1, $CHCl_3$). IR (neat): *ν* 3077, 2922, 2854, 1720, 1644, 1430, 1387, 1249, 1042 and 921 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92–6.85 (m, 1H), 6.03 (d, *J* = 9.8 Hz, 1H), 5.90–5.77 (m, 1H), 5.22–5.14 (m, 2H), 4.56–4.44 (m, 1H), 2.60–2.45 (m, 2H), 2.39–2.33 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 144.9, 133.9, 121.3, 118.7, 76.3, 39.0, 28.6. HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_8H_{10}O_2Na$: 161.0573, found: 161.0568.

4.1.7. 5-Phenyl-pent-1-en-3-ol 5[12]

To a cooled (0 °C) stirred solution of vinylmagnesium bromide (1 M, 11.2 mL, 11.18 mmol) in THF was added dropwise 3-phenyl-1-propanal **4** (1.0 g, 7.462 mmol) in THF (20 mL) and the reaction temperature was brought to room temperature and stirring was continued for 1 h. After completion of the reaction as indicated by TLC the reaction was quenched with saturated ammonium chloride solution, and the reaction mixture was extracted into diethyl ether (3 × 50 mL). The combined organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure to afford crude vinyl alcohol, which was purified over silica gel column chromatography using EtOAc–hexane (1:9) to afford pure compound **3** as a clear liquid (1.038 mg, 86%). IR (neat): *ν* 3349, 1604, 1498, 1455, 1428, 1403, 750 and 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.14 (m, 5H), 5.96–5.82 (m, 1H), 5.28–5.10 (m, 2H), 4.13–4.07 (m, 1H), 2.7 (t, *J* = 7.2 Hz, 2H), 1.88–1.80 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1, 140.9, 128.4, 125.8, 114.8, 72.6, 38.6, 31.7. EIMS: *m/z* = 162 $[M]^+$.

4.1.8. 5-Phenyl-pent-1-en-3-one 3[13]

To stirred solution of IBX (2.074 g, 7.4 mmol) in dry DMSO was added a solution of **5** (800 mg, 4.92 mmol) in dichloromethane (20 mL) at room temperature and stirred for 3 h at room temperature. After completion of the reaction, the mixture was filtered, diluted with water (10 mL), and extracted into DCM (2 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over anhyd Na_2SO_4, and evaporated to give crude vinyl ketone **3**, which was purified over silica gel column chromatography using EtOAc–hexane (1:19) to afford pure vinyl ketone **3** (710 mg, 90%) as a colorless liquid. IR (neat): *ν* 3061, 3027, 2925, 2856, 1709, 1605, 1495, 1450, 1403, 750 and 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.11 (m, 5H), 6.41–6.40 (m, 2H), 5.90–5.75 (m, 1H), 3.00–2.80 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.9, 141.0, 139.0136.4, 128.4, 128.3, 126.1, 41.1 and 28.7. EIMS: *m/z* 160 $[M]^+$.

4.1.9. 6-(4-Oxo-6-phenyl-hex-2-enyl)-5,6-dihydro-pyran-2-one 1

A solution of compound **2** (200 mg, 1.449 mmol) and compound **3** (695 mg, 4.347 mmol) in DCM (100 mL) in 1:3 ratio was first bubbled with a nitrogen flow, then Grubbs type II catalyst (61.5 mg, 0.0725 mmol) was added at once and the resulting mixture was heated under nitrogen at 40 °C for 12 h. After completion of the reaction, the solvent was removed under reduced pressure and the residue was purified over silica gel column chromatography using AcOEt–hexane (2:8) to afford lactone **1** (289 mg, 74%) as a yellow oil. $[\alpha]_D^{25} = -61.9$ (*c* 0.5, $CHCl_3$); IR (neat): *ν* 3077, 2922, 2854, 1720, 1644, 1430, 1387, 1249, 1158, 1042, 996, 921, 814 and 757 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.15 (m, 5H), 6.98–6.84 (m, 1H), 6.80 (dt, *J* = 16.0 Hz, 7.1 Hz, 1H), 6.20 (d, *J* = 16.0 Hz, 1 H), 6.04 (d, *J* = 9.8 Hz, 1H), 4.54 (m, 1H), 3.02–2.83 (m, 4H), 2.73–2.58 (m, 2H), 2.40–2.31 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.0, 163.3, 144.5, 141.0, 140.0, 133.5, 128.5, 128.3, 126.1, 121.4, 76.1, 41.7, 37.5, 29.9, 28.9. HRMS (ESI): *m/z* $[M+NH_4]^+$ calcd for $C_{17}H_{22}NO_3$: 288.1594; found: 288.1593.

4.1.10. 7-Mosher's ester derivative of 8[8,9]

N,*N*^{1}-Dicyclohexylcarbodiimide (DCC) (45 mg, 0.21 mmol), a catalytic amount of 4-dimethylaminopyridine (DMAP), and CH_2Cl_2 (2 mL) taken under a nitrogen atmosphere were allowed to cool at 0 °C for 10 min after which a solution of homoallylic alcohol **8** (30 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) was added. This was allowed to stir for an additional 10 min, followed by the dropwise addition of (*S*)-α-methoxy-α-trifluoromethyl phenylacetic acid (34 mg, 0.15 mmol) in CH_2Cl_2 (2 mL). This reaction mixture was then stirred at 0 °C for 1 h and then at room temperature for 12 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated sodium bicarbonate solution (50 mL), dried over anhydrous Na_2SO_4, and evaporated to give crude (*S*)-Mosher's ester of **8**, which was purified over silica gel column chromatography using EtOAc–hexane (1:19) to afford a colorless oil (*S*)-Mosher's ester of **8**. (41 mg, 67%) $[\alpha]_D^{25} = -47.1$ (*c* 1, $CHCl_3$); IR (neat): 2856, 1744, 1643, 1493, 1451, 1363, 1259, 1166, 1104, 1018, 992, 915, 735,

695. ^{1}H NMR (300 MHz, $CDCl_3$): 7.58–7.46 (m, 2H), 7.40–7.24 (m, 8H), 5.84–5.69 (m, 1H), 5.38–5.28 (m, 1H), 5.14–5.04 (m, 2H), 4.35 (s, 2H), 3.52 (s, 3H), 3.31 (dd, J = 5.3 Hz, 2.7 Hz, 1H), 3.17 (dd, J = 5.3 Hz, 2.9 Hz, 1 Hz), 2.49–2.41 (m, 2H), 1.82–1.95 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.6, 132.9, 129.4, 129.2, 128.5, 128.2, 128.1, 127.4, 126.8, 118.1, 84.4, 73.4, 72.9, 65.6, 56.5, 55.4, 49.8, 38.6, 33.5. ESIMS: m/z = 442 $[M+Na]^+$. Similarly, the (*R*)-Mosher's ester of **8** was also prepared adopting the above procedure.

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References

1. Cavalheiro, A. J.; Yoshida, M. *Phytochemistry* **2000**, *53*, 811–819.
2. (a) Drewes, S. E.; Schlapelo, B. M.; Horn, M. M.; Scoltt Shaw, R.; Sander, O. *Phytochemistry* **1995**, *38*, 1427–1430; (b) Drewes, S. E.; Horn, M. M.; Shaw, R. S. *Phytochemistry* **1995**, *40*, 321–323; (c) Spencer, G. F.; England, R. E.; Wolf, R. B. *Phytochemistry* **1984**, *23*, 2499–2500; (d) Govindachari, T. R.; Parthasarathy, P. C.; Desai, H. K.; Shanbhag, M. N. *Tetrahedron* **1973**, *29*, 3091–3094; (e) Sam, T. W.; Yeu, C. S.; Jodynis-Liebert, J.; Murias, M.; Bloszyk, E. *Planta Med.* **2000**, *66*, 199–205; (f) Zschocke, S.; Van Staden, J. *J. Ethnopharmacol.* **2000**, *71*, 473–478; (g) Drewes, S. E.; Horn, M. H.; Mavi, S. *Phytochemistry* **1997**, *44*, 437–440; (h) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021–2040.
3. Meragelman, T. L.; Scudiero, D. A.; Davis, R. E.; Staudt, L. M.; McCloud, T. G.; Carde, J. H., II; Shemaker, R. H. *J. Nat. Prod.* **2009**, *7*, 336–339.
4. (a) Selvam, J. J. P.; Rajesh, K.; Suresh, V.; Chanti Babu, D.; Venkateswarlu, Y. *Tetrahedron: Asymmetry* **2009**, *20*, 1115–1119; (b) Narasimhulu, M.; Krishna, A. S.; Rao, J. V.; Venkateswarlu, Y. *Tetrahedron* **2009**, *65*, 2989–2999; (c) Suresh, V.; Selvam, J. J. P.; Rajesh, K.; Venkateswarlu, Y. *Tetrahedron: Asymmetry* **2008**, *19*, 1509–1533.
5. Crimmins, M. T.; Washburn, D. G. *Tetrahedron Lett.* **1998**, *39*, 7487–7490.
6. (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468; (b) Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543–6544; (c) Gogoi, N.; Boruwa, N.; Barua, C. *Eur. J. Org. Chem.* **2006**, 1722–1725; (d) Fatima, A. D.; Kohn, L. K.; Antonio, M. A.; Carvalho, J. E.; Pillia, R. A. *Bioorg. Med. Chem.* **2005**, *13*, 2927–2933.
7. Chiral HPLC conditions: column: eurocel 01(250 × 4.6 mm particle size 5 μm); mobile phase hexane/isopropyl alcohol (90:10); flow rate: 1 mL/min; detection: PDA (ee 97.5%).
8. (a) George, S.; Sudalai, A. *Tetrahedron: Asymmetry* **2007**, *18*, 975–981; (b) Marshall, J. A.; Sabatini, J. J. *Org. Lett.* **2005**, *7*, 4819–4822.
9. (a) Ohtani, I.; Kusumi, J.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096; (b) Yoshido, W. Y.; Bryan, P. J.; Baker, B. J.; McClintock, J. B. *J. Org. Chem.* **1995**, *60*, 780–782.
10. Hsing-JangLiu, Judy Yip. *Tetrahedron Lett.* **1997**, *38*, 2253–2256.
11. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.
12. Sabila, P. S.; Howell, A. R. *Tetrahedron Lett.* **2007**, *48*, 8353–8355.
13. Molander, G. A.; Gerard, L. J. *J. Org. Chem.* **2009**, *74*, 1297–1303.
14. (a) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370; (b) Bouz Bouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* **2004**, *6*, 3465–3467.