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Asymmetric synthesis of (6*R*)-4-hydroxy-6-substituted-δ-lactones

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ABSTRACT

A novel approach for the asymmetric synthesis of (6*R*)-4-hydroxy-6-substituted-δ-lactones has been achieved using asymmetric reduction of a prochiral ketone in the presence of (*S*)-(−)-diphenyl-prolinol/borane as a key step. The enantiomeric purity of the products was determined by chiral GC.

1. Introduction

Lactones bearing 4-hydroxy-5,6-dihydropyran-2-one ring are ubiquitous in natural products and various biological activities are associated with them, such as sex pheromone, highly potent anti-inflammatory, hypocholesterolemic,[1] anti-HIV, anti-bacterial, anti-fungal, anti-tumor anticonvulsant, muscle-relaxing, sedative and analgesic activities. The statin class of drugs contain (4*R*,6*R*)-4-hydroxy-6-substituted-δ-lactone moiety **1** or the corresponding open chain structure **2** (Fig. 1), which reduce cholesterol levels in blood by inhibiting the rate limiting step of cholesterol biosynthesis in humans by binding to the enzyme HMG Co-A reductase. Simvastatin (Zocor) **1**, atorvastatin (Lipitor) **2**, pitavastatin (Livalo), rosuvastatin (Crestor), and fluvastatin (Lescol) are some examples of statins and several combinations of statins are available.[2–8]

1,7-Diarylheptanoids display pharmacological activities such as antioxidant, anticancer, inhibitory activity on nitric oxide production, anti-inflammatory and anti-leishmanial activities. (−)-Diospongins A **3** and B **4** are cyclic 1,7-diaryl-heptanoids, which have been isolated from the rhizomes of *Dioscorea spongiosa*, *via* a bioassay guided fractionation. Diospongins A **3** and B **4** possess a 2,6-*cis*- and 2,6-*trans*-substituted tetrahydro-2*H*-pyran-4-ol ring, respectively.[9,10] The C1-C8-unit of antitumor (+)-discodermolide **5** contains the 4-hydroxy-δ-lactone with (4*S*,6*R*)-configuration.

Several syntheses of these molecules have been reported.[11–14] The prominent key steps among these are the asymmetric dihydroxylation or epoxidation of 5,6-dihydropyranone; the selective reduction of the epoxide; lipase catalysed *trans*-esterification or asymmetric hydrolysis; D-2-deoxyribose-5-phosphate aldolase enzyme catalyzed sequential condensation of three aldehydes,[9] stereocontrolled cyclization of 1,3-diols; asymmetric catalytic reduction of 3,5-diketo-esters, asymmetric addition of diketene to aldehydes; asymmetric addition of carbon monoxide to epoxides etc.[12a,b]

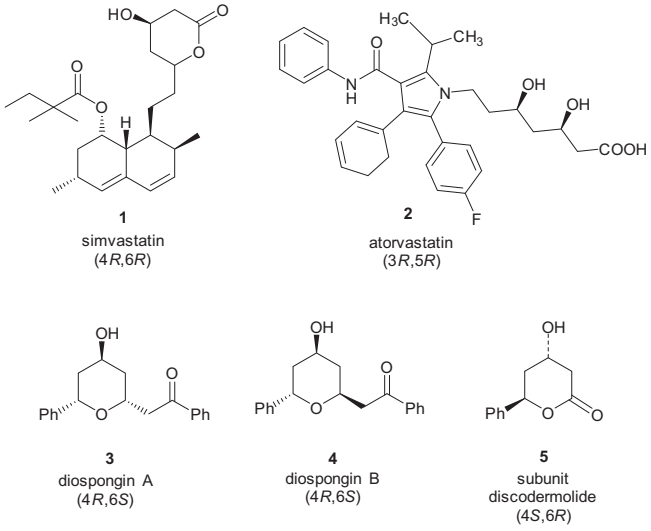

Figure 1. Bioactive 4-hydroxy-δ-lactones and analogues.

Herein we report an efficient synthesis of (4*S*,6*R*)-4-hydroxy-6-phenyl-δ-lactone **6a** and (4*R*,6*R*)-4-hydroxy-6-(phenyl-ethyl)-δ-lactone **6b** using an inexpensive asymmetric reduction[15] catalyzed by (*S*)-(−)-1,1-diphenyl-pyrrolidin-2-yl-methanol / borane (oxazaborolidine) as the key step.

2. Result and discussion

The retrosynthetic analysis for the desired lactones is shown in Fig. 2.

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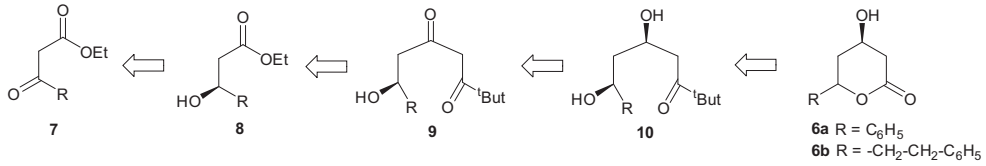
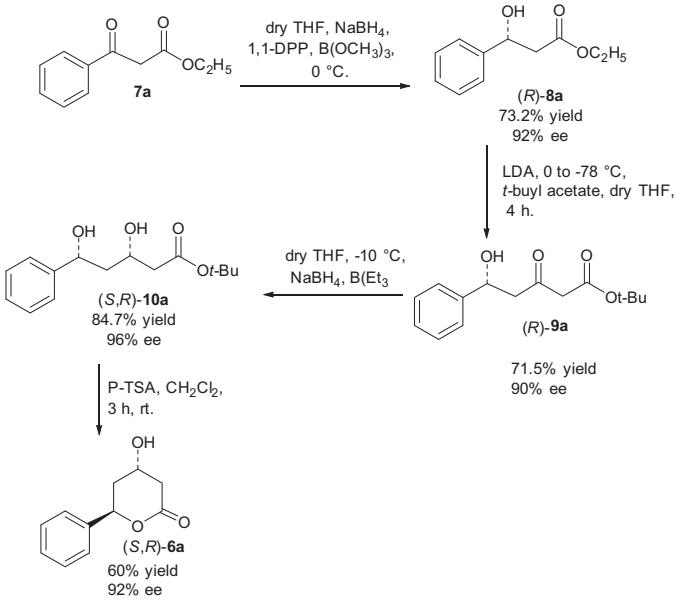


Figure 2. Retrosynthetic analysis of lactones **6a** and **6b**.

The ethyl (*R*)-3-hydroxy-phenyl-propionate **8a** (R = $-C_6H_5$) was obtained by the asymmetric reduction of β-keto-ester **7a** in the presence of (*S*)-(−)-α,α-diphenyl-prolinol, trimethylborate and sodium borohydride (Scheme 1). The reaction was carried out under dry conditions and in an N_2 atmosphere at 0 °C for 4 h. The (*R*)-stereochemistry of the newly formed 3-hydroxy-group was assigned based on the positive specific rotation, and the ^{1}H and ^{13}C NMR values of compound **8a**, which were in agreement with the literature values.[16] Subsequent condensation of ethyl (*R*)-3-hydroxy-3-phenyl-propanoate **8a** with *t*-butyl acetate in the presence of LDA at −78 °C in dry THF afforded *t*-butyl (*R*)-5-hydroxy-3-oxo-5-phenyl-pentanoate **9a**. Product **9a** was confirmed by ^{1}H NMR absorption at δ 0.92 (s, 9H), which corresponded to the *t*-butyl group and at δ 5.14 for proton under –OH. ^{13}C NMR of **9a** showed two peaks at δ 199.8 and 172.6 for the ketone and ester, respectively. The IR spectrum of **9a** showed bands at 1728, 1714, 3392 cm^{-1} for the ester, ketone and hydroxyl groups, respectively. The stereospecific reduction[15c] of **9a** was effected by using $NaBH_4$ and triethylborane at −30 °C to give *t*-butyl (3*S*,5*R*)-3,5-dihydroxy-5-phenyl-pentanoate **10a**. The IR spectrum of **10a** had bands at 3414 and 1735 cm^{-1} due to the hydroxyl and ester groups, respectively. Diol **10a** was cyclized in the presence of *p*-toluenesulfonic acid in dry CH_2Cl_2 to yield the lactone (4*S*,6*R*)-tetrahydro-4-hydroxy-6-phenyl-pyran-2-one **6a**. The specific rotation, and the ^{1}H NMR and ^{13}C NMR data of lactone **6a** were in agreement with the previously reported values.[12b]



Scheme 1. Synthesis of (4*R*,6*R*)-tetrahydro-4-hydroxy-6-phenylpyran-2-one.

Similarly, the ethyl (*R*)-3-hydroxy-5-phenylpentanoate **8b** (R = $-C_6H_5$) was obtained by the asymmetric reduction of 3-keto-ester **7b** in the presence of (*S*)-(−)-1,1-diphenyl-prolinol, triethylborane and sodium borohydride (Scheme 2). The (*R*)-stereochemistry of the newly formed 3-hydroxy-group was assigned based on positive specific rotation, and the ^{1}H and ^{13}C NMR values of compound **8b**, which were in agreement with the literature values.[17] Subsequent condensation of ethyl ester (*R*)-**8b** with *t*-butyl acetate in the presence of LDA at −78 °C in dry THF afforded *t*-butyl (*R*)-5-hydroxy-3-oxo-5-phenylheptanoate **9b**. Product **9b** was supported by ^{1}H NMR peak at δ 1.48 (s, 9H) corresponding to the *t*-butyl group. ^{13}C NMR of **9b** showed two peaks at δ 192.2 and 173.2 for ketone and ester respectively. IR spectrum of **9b** showed bands at 1730, 1714, 3428 cm^{-1} for ester, ketone and hydroxyl group respectively. The stereospecific reduction of **9b** was carried out by using $NaBH_4$ and triethylborane at −30 °C to give *t*-butyl (3*R*,5*R*)-3,5-dihydroxy-7-phenylheptanoate **10b**.

Diol **10b** was cyclised in the presence of *p*-toluene-sulfonic acid in dry CH_2Cl_2 to yield the product (4*R*,6*R*)-tetrahydro-4-hydroxy-6-phenethylpyran-2-one **6b**. The specific rotation, and ^{1}H NMR and ^{13}C NMR data of lactone **6b** were in agreement with the previously reported values.[14]

3. Conclusion

In conclusion, a facile asymmetric synthesis of (6*R*)-4-hydroxy-6-substituted-δ-lactones has been achieved using an asymmetric reduction in the presence of (*S*)-(−)-1,1-diphenyl-prolinol/trimethylborate (oxazaborolidine)/sodium borohydride as the key step. The resulting (*R*)-(+)-β-hydroxy esters **8a** and **8b** were condensed with the enolate of *t*-butyl acetate at low temperature to yield the corresponding β-keto-δ-hydroxy esters, which were further subjected to stereoselective reduction to yield β,δ-dihydroxy esters. Further acid catalysed cyclization gave the title molecules in good yield and with good enantiomeric excess. The enantiomeric purity of the products was checked by chiral GC.

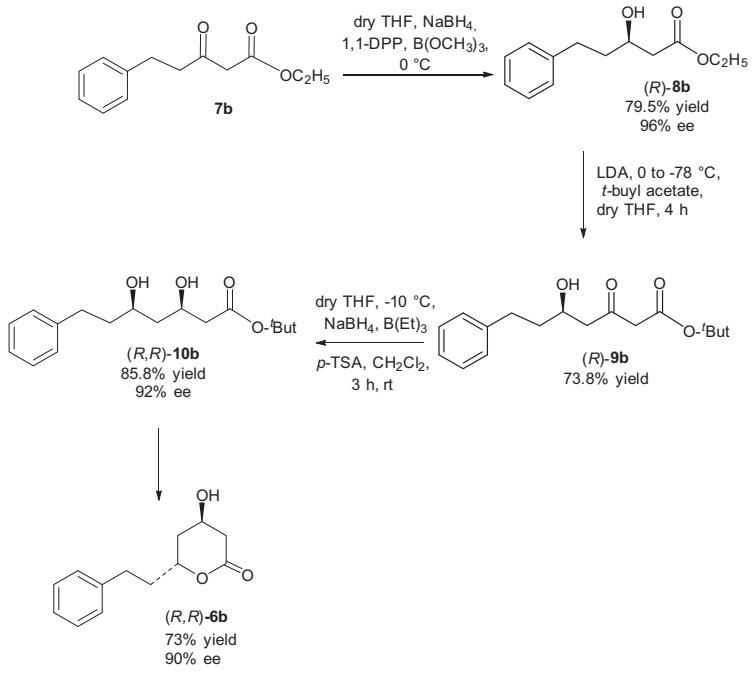
4. Experimental

4.1. General

Analytical TLC was performed on silica gel 60 F254 plates and visualized using anisaldehyde sulfuric acid reagent. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature on spectrometers at 500 MHz and 125 MHz, respectively. Chemical shifts are reported in parts per million relative to residual solvent $CDCl_3$ (^{1}H, 7.27 ppm; ^{13}C, 77.00 ppm). Multiplicities are reported as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, m = multiplet, q = quartet, bs = broad singlet. Electrospray ionization and a TOF mass analyzer were used for HRMS measurements. GC-MS analysis was carried on instrument, where GC-6890 with coupled mass spectrometer MS-5973N with quadrupole mass detector, using phenyl-methyl-siloxane (5%) column. The enantiomeric excess (*ee%*) of products was obtained by GC analysis using chiral Beta-Dex column (30 m × 0.25 μm × 0.25 mm.

4.2. Synthesis of ethyl 3-oxo-3-phenylpropanoate 7a

A mixture of acetophenone (10 g, 0.083 mol), diethyl carbonate (29.49 g, 0.249 mol) and dry toluene (30 mL) was stirred for 5 min.



Scheme 2. Synthesis of (4*R*,6*R*)-tetrahydro-4-hydroxy-6-phenethylpyran-2-one.

Next, NaH (3.1 g, 0.129 mol) (55%) was added in small portions to the resulting solution at ambient temperature. After the addition, exotherm was observed. The reaction was carried out at rt for 30 min. The reaction mixture was then poured into ice water (100 mL) containing a small amount of acetic acid (1 mL). The resulting mixture was extracted with EtOAc (50 × 2 mL). The extract was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed in *vacuum* and the residue was subjected to column chromatography to yield **7a**, Yield: 11.90 g (74.4%), colorless liquid; IR ν_{max}: 3063, 2983, 1742, 1683, 1598, 1449, 1360, 1265, 1198 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz): δ 7.95–7.10 (m, 5H), 3.96 (q, 2H), 2.40 (s, 2H), 1.10 (t, J = 7 Hz, 3H); GCMS (*m*/*z*): 192 (M^+), 192, 146, 122, 105, 91, 77, 51; HRMS (*m*/*z*) calcd for $C_{11}H_{12}O_3$; 192.2140.; found: 192.2132.

4.3. Synthesis of ethyl (*R*)-3-hydroxy-3-phenylpropionoate 8a

To a stirred solution of $NaBH_4$ (2.03 g, 0.052 M) in dry THF (20 mL), cooled at 0 °C under an N_2 atmosphere was added catalyst (*S*)-(−)-1,1-diphenyl-prolinol (0.554 g, 2.2 mM). The mixture was stirred for 5 min. To this solution was added trimethylborate (0.245 mL, 2.17 mmol) followed by the dropwise addition of 3-oxo-3-phenylpropanoate **7a** (10 g, 0.052 M), while maintaining the temperature at 0 °C and the stirring was continued for 4 h. The reaction was quenched with 2 N HCl solution, after which THF was removed in *vacuum*. To the residue, EtOAc was added. Aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in *vacuum* and the residue was subjected to column chromatography on silica gel to yield hydroxyl compound **8a**, Yield: 7.40 g (73.20%), colorless liquid; $[\alpha]_D^{20}$ = +28.6 (*c* 0.50, $CHCl_3$); (lit[16] $[\alpha]_D^{20}$ = +34.7 (*c* 1.4, $CHCl_3$); Chiral GC analysis: t_R(minor) = 15.67 min, t_R(major) = 15.90 min; IR ν_{max}: 3392, 3029, 2927, 1729, 1493, 1452, 1371, 1297 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40–7.26 (m, 5H), 5.13 (dd, J = 3.65, 8.95 Hz, 1H), 4.18 (q, J = 7.5 Hz, 2H), 3.34 (s, 1H), 2.75 (dd, J = 9.0, 16.35 Hz, 1H), 2.70 (dd, J = 3.85, 16.35, 1H), 1.27 (t, J = 7.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 142.7, 128.7, 127.9, 127.7, 127.1, 125.8, 70.5, 61.0, 43.5, 14.3; GCMS (*m*/*z*): 194 (M^+), 194, 165, 147, 120, 107, 91, 79, 60, 43; HRMS (*m*/*z*) calcd for $C_{11}H_{14}O_3$; 194.2298; found: 194.2292.

4.4. Synthesis of *t*-butyl (*R*)-5-hydroxy-3-oxo-5-phenylpentanoate 9a

A mixture of diisopropyl amine (4.97 g, 22.4 mmol) and dry THF (40 mL), cooled to 0 °C under an N_2 atmosphere was added *n*-BuLi (48 mL, 73.4 mmol) over 10 min, after which stirring was continued for 20 min. After 20 min, the solution was cooled to −78 °C and *t*-butyl acetate (6.38 g, 47.0 mmol) was added over 5 min. After 20 min, the resulting solution at −78 °C was transferred via syringe over 5 min to a solution of the reactant (2.3 g, 11.0 mmol) and THF at 0 °C. The reaction flask was placed in a water bath and stirred for 1.5 h at room temperature. The reaction was quenched with saturated NH_4Cl solution (1.0 mL). THF was removed in *vacuum* and the residue was extracted in EtOAc. The aqueous layer was washed by EtOAc. The solvent was removed in *vacuum* and the residue was subjected to column chromatography on silica gel to yield **9a** 2.26 g (71.50%), colourless liquid; $[\alpha]_D^{20}$ = +36.95 (*c* 0.4385, $CHCl_3$); lit[12d] $[\alpha]_D^{20}$ = +32.3 (*c* 0.1, $CHCl_3$); Chiral GC analysis: t_R(major) = 24.13 min; IR ν_{max}: 3392, 3030, 2930, 1728, 1714, 1493, 1453, 1369, 1154, 1078, 1029, 899, 767 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.42–7.26 (m, 5H), 5.14 (dd, J = 3.75, 8.85 Hz, 2H), 4.13 (d, J = 6.70 Hz, 1H), 3.40 (s, 1H), 2.78 (dd, J = 5.45, 16.25 Hz, 1H), 2.71 (dd, J = 3.80, 16.25 Hz, 1H), 0.92 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8, 172.6, 142.7, 133.2, 128.7, 128.5, 128.3, 127.8, 70.4, 64.8, 45.5, 43.4, 30.7, 19.2, 13.8; GCMS (*m*/*z*): 264 (M^+), 265, 241, 207, 161, 130, 115, 88, 69, 43; HRMS (*m*/*z*) calcd for $C_{15}H_{20}O_4$; 264.3206; found: 264.3202.

4.5. Synthesis of *t*-butyl (3S,5*R*)-3,5-dihydroxy-5-phenylpentanoate 10a

To a stirred solution of compound **9a** (0.8 g, 3.03 mmol) in dry THF (15 mL), cooled at −10 °C under an N_2 atmosphere was added triethylborane (0.278 mL, 2.7 mmol). The reaction was stirred for

15 min. To this mixture was added dropwise a solution of $NaBH_4$ (0.238 g, 6.1 mmol) in dry THF (10 mL). The reaction mixture was allowed to stir for 4 h. The reaction was monitored by TLC, then quenched with water, and extracted with EtOAc, washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in *vacuum* and residue was subjected to column chromatography on silica gel to give **10a**, Yield: 0.693 g (84.7%); $[\alpha]_D^{20} = -20.2$ (*c* 0.54, $CHCl_3$); IR ν_{max}: 3414, 2978, 1732, 1404, 1224, 1049, 758, 700 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.15 (m, 5H), 4.97 (dd, *J* = 3.0, 9.0 Hz, 1H), 4.30 (m, 1H), 3.62 (bs, 1H), 2.41 (m, 1H),1.96–1.72 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 144.7, 128.5, 127.6, 125.8, 81.5, 74.4, 68.8, 44.2, 42.7, 28.3; GCMS (*m*/*z*): 266 (M^+), 251, 236, 221, 209, 193, 177, 165, 151, 134, 121, 107, 90, 77, 64, 51, 40; HRMS (*m*/*z*) calcd for $C_{15}H_{22}O_4$; 266.3364; found: 266.3358.

4.6. Synthesis of (4*S*,6*R*)-tetrahydro-4-hydroxy-6-phenylpyran-(2*H*)-2-one 6a

A catalytic amount of *p*-toluenesulfonic acid (0.052 g) was added to a stirred solution of **10a** (0.5 g, 1.87 mmol) in dry CH_2Cl_2 (10 mL) under an N_2 atmosphere and the reaction mixture was stirred at rt for 3 h. After completion of the reaction, the reaction mixture was quenched by the addition of solid $NaHCO_3$ and the solvent was removed under *vacuum*. The crude residue was subjected to column chromatography to give lactone **6a**, Yield: 0.216 g (60.0%); $[\alpha]_D^{20} = +5.6$ (*c* 0.16, $CHCl_3$); lit[8] (4*R*,6*S* isomer, $[\alpha]_D^{20} = -9.4$ (*c* 1.3, $CHCl_3$); Chiral GC analysis: t_R(major) = 34.76 min; IR ν_{max}: 3430, 3015, 2927, 1728, 1495, 1455, 1348, 1257, 1044, 860, 768 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40–7.35 (m, 5H), 5.76 (dd, *J* = 3.0, 11.50 Hz, 1H), 4.45 (q, *J* = 3.9, 1H), 2.86 (dd, 4.9, 17.5, H), 2.74 (ddd, *J* = 1.5, 3.5, 17.5 Hz, H), 2.25–2.05 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 139.4, 128.9, 128.8, 128.5, 125.8, 76.9, 62.6, 38.7, 38.4; GCMS (*m*/*z*): 192 (M^+), 176, 160, 148, 134, 117, 104, 90, 77, 65, 52, 40; HRMS (*m*/*z*) calcd for $C_{11}H_{12}O_3$: 192.2140, found: 192.2132.

4.7. Synthesis of ethyl 3-oxo-5-phenylpentanone 7b

To a solution of diisopropyl amine (3.84 g, 27.0 mmol) in dry THF (20 mL), cooled to −50 °C under an N_2 atmosphere was added *n*-BuLi (20 mL, 30.6 mmol) over 10 min, after which stirring was continued for 20 min, while the reaction mixture was maintained at −50 °C. Next, ethyl acetoacetate (2 g, 15.4 mmol) was added dropwise within period of 15 min, and stirring was continued for 30 min. A solution of benzyl bromide (2.63 g, 15.4 mmol) and dry THF (6 mL) was added dropwise within 20 min and the reaction was maintained at −50 °C for 3 h. After completion of the reaction, it was quenched with saturated NH_4Cl (1 mL). THF was removed in *vacuum*. The residue was extracted in EtOAc and washed with water (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed in *vacuum* and residue was subjected to column chromatography to give compound **7b** 2.31 g (63.0%), liquid; IR ν_{max}: 3028, 2984, 1743, 1714, 1497, 1454, 1368, 1317, 1031, 757 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): δ 7.27 (m, 5H), 4.10 (q, *J* = 7.0 Hz, 3H), 3.40 (s, 2H), 2.90 (m, 4H), 1.22 (t, *J* = 7.0 Hz, 2H); GCMS (*m*/*z*): 220 (M^+), 202, 177, 159, 147, 131, 119, 104, 91, 78, 65, 41; HRMS (*m*/*z*) calcd for $C_{13}H_{16}O_3$; 220.2676; found: 220.2668.

4.8. Synthesis of ethyl (*R*)-3-hydroxy-5-phenylpentanoate 8b

To a stirred solution of $NaBH_4$ (0.740 g, 14.2 mmol) in dry THF (15 mL), cooled at 0 °C under an N_2 atmosphere was added (*S*)-(−)-1,1-diphenyl-prolinol (0.290 g, 1.2 mmol). The mixture was stirred for 5 min. To this solution was added trimethylborate (0.2–0.3 mL) followed by the dropwise addition of ethyl 3-oxo-5-phenylpentanone **7b** (1.5 g, 6.8 mmol) while maintaining the temperature at 0 °C and the reaction was kept stirring for 4 h. The reaction was quenched with NH_4Cl solution. THF was removed in *vacuum*. The residue was extracted with EtOAc and the aqueous layer was separated and extracted with EtOAc. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Solvent was removed in *vacuum* and the residue was subjected to column chromatography on silica gel to give hydroxyl compound **8b**, Yield: 1.20 g (79.50%); $[\alpha]_D^{20} = +5.2$ (*c* 0.24, $CHCl_3$); lit[17] $[\alpha]_D^{20} = +1$ (*c* 1, $CHCl_3$); chiral GC analysis: t_R(minor) = 32.53 min, t_R(major) = 33.65 min; IR ν_{max}: 3429, 3027, 2931, 1732, 1603, 1495, 1454, 1373, 1320, 1183 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.24 (m, 5H), 4.17 (q, *J* = 7.5 Hz, 2H), 4.05–3.95 (m, 1H), 3.05 (bs, -OH), 2.50 (dd, *J* = 3.5, 16.5 Hz, 1H), 2.43 (dd, *J* = 8.5, 16.5 Hz, 1H), 2.86–2.79 (m, 1H), 2.73–2.67 (m, 1H), 1.89–1.70 (m, 2H), 1.27 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.0, 141.8, 128.5, 128.5, 125.9, 67.3, 60.7, 41.4, 38.2, 31.8, 28.0, 14.2; GCMS (*m*/*z*): 222 (M^+), 204, 176, 159, 145, 130, 117, 104, 91, 77, 60, 43. HRMS (*m*/*z*) calcd for $C_{13}H_{18}O_3$; 222.2834; 222.2842.

4.9. Synthesis of *t*-butyl (*R*)-5-hydroxy-3-oxo-7-phenylheptanoate 9b

To a mixture of diisopropyl amine (2.26 g, 0.022 mol) and dry THF (20 mL), cooled to 0 °C under an N_2 atmosphere was added *n*-BuLi (14.12 mL, 0.021 M) over 10 min, stirring was continued for 20 min. After 20 min, the solution was cooled to −78 °C and *t*-butyl acetate (2.5 g, 5.4 mmol) was added over 5 min. The stirring was continued for 20 min, and the resulting solution at −78 °C was transferred *via* syringe over 5 min to a solution of compound **8b** (1.2 g, 5.4 mmol) and THF at 0 °C. The reaction flask was placed in a rt water bath and stirred for 1.5 h. The reaction mixture was quenched with saturated NH_4Cl solution. THF was removed in *vacuum* and the residue was extracted in EtOAc. The aqueous layer was washed with EtOAc. The solvent was removed in *vacuum* from the combined extracts and the residue was subjected to column chromatography on silica gel to give **9b**, Yield: 1.15 g (73.80%), liquid; $[\alpha]_D^{20} = -12.8$ (*c* 0.45, $CHCl_3$); lit.[11a] ethyl ester $[\alpha]_D^{20} = -12.5$ (*c* 1, $CHCl_3$); Chiral GC analysis: t_R(minor) = 26.4 min, t_R(major) = 27.5 min; IR ν_{max}: 3428, 2932, 1730, 1714, 1603, 1495, 1454, 1370, 1258, 1154, 1030, 843, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.33–7.18 (m, 5H), 4.16 (t, *J* = 4.45 Hz, 2H), 4.06–3.99 (m, 1H), 2.86–2.67 (m, 2H), 2.50 (dd, J = 3.45, 16.45 Hz, 1H), 2.46 (dd, *J* = 8.7, 16.4 Hz, 1H),3.16 (bs, 1H),1.90–1.70 (m 2H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.2, 173.2, 141.8, 128.9, 128.4, 126.6, 126.4, 67.3, 64.7, 49.4, 38.3, 31.9, 30.7, 28.2, 19.2, 14.1. HRMS (*m*/*z*) calcd for $C_{17}H_{24}O_4$; 292.3742; found: 292.3736.

4.10. Synthesis of *t*-Butyl (3*R*,5*R*)-3,5-dihydroxy-7-phenylheptanoate 10b

To a stirred solution of compound **9b** (0.668 g, 2.28 mmol) in dry THF (15 mL), cooled at −10 °C under an N_2 atmosphere was added triethylborane (0.278 mL, 2.7 mmol). The reaction was stirred for 15 min. To this mixture was added dropwise a solution of $NaBH_4$ (0.180 g, 4.6 mmol) in dry THF (5 mL). The reaction mixture was allowed to stir for 4 h. The reaction was monitored on TLC. It was then quenched with water and extracted with EtOAc, washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in *vacuum* and the residue was subjected to column chromatography on silica gel to give **10b**, Yield: 0.577 g (85.80%), viscous liquid; $[\alpha]_D^{20} = -5.5$ (*c* 0.51, $CHCl_3$); lit.[11a] ethyl ester $[\alpha]_D^{20} = -4.8$ (*c* 1, $CHCl_3$); Chiral GC analysis: t_R(minor) = 29.8 min, t_R(major) = 30.4 min; IR ν_{max}: 3435, 3018, 2981, 1713, 1495, 1454, 1394, 1369, 1216, 1152, 1085, 740; ^1H NMR (500 MHz,

$CDCl_3$): δ 7.30–7.15 (m, 5H), 4.25–4.19 (m, 1H), 3.92–3.86 (m, 1H), 2.84–2.60 (m, 2H), 2.41–2.38 (m, 2H), 1.87–1.53 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 142.2, 128.9, 128.6, 128.5, 128.4, 125.9, 81.6, 71.4, 69.3, 42.7, 39.5, 31.8, 28.1; GCMS (*m*/*z*): 294 (M^+), 281, 257, 234, 204, 189, 177, 159, 147, 131, 117, 104, 91, 78, 65, 45; HRMS (*m*/*z*) calcd for $C_{17}H_{26}O_4$; 294.3900; found: 294.3894.

4.11. Synthesis of (4*R*,6*R*)-tetrahydro-4-hydroxy-6-phenethylpyran-2-one 6b

A catalytic amount of *p*-toluenesulfonic acid (15 mg) was added to a stirred solution of **10b** (0.150 g, 0.51 mmol) in dry CH_2Cl_2 (5 mL) under an N_2 atmosphere and stirring was continued at rt for 3 h. After completion of the reaction, the reaction mixture was quenched by the addition of $NaHCO_3$ (0.092 g). The mixture was filtered, and the solvent was removed in *vacuum*. The crude residue was subjected to column chromatography to give lactone **6b**, Yield: 0.082 g (73.0%); $[\alpha]_D^{20}$ = +37.1 (*c* 0.10, $CHCl_3$); lit[11a] $[\alpha]_D^{20}$ = +47 (*c* 0.3, $CHCl_3$); Chiral GC analysis: t_R(major) = 34.56 min; IR ν_{max}: 3399, 3019, 2927, 1722, 1407, 1215, 1022, 720, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45–7.30 (m, 5H), 4.80–4.55 (m, 1H), 4.20 (m, 1H), 3.10–2.40 (m, 4H), 2.30–1.80 (m, 4H), 1.30 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 140.9, 128.7, 128.7, 128.6, 128.5, 128.4, 76.8, 74.2, 38.4, 37.5, 36.0, 32.0; HRMS (*m*/*z*) calcd for $C_{13}H_{16}O_3$; 220.2676; found: 220.2668.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.12.006.

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