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Enantioselective total synthesis of both the stereoisomers of dihydrokawain-5-ol

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Abstract—The enantioselective synthesis of both the stereoisomers of dihydrokawain-5-ol is described. The key features of the synthetic strategy include (a) Sharpless asymmetric dihydroxylation, (b) Wittig olefination, and (c) formation of β-keto ester to access the highly enantiomerically pure kavalactones.

1. Introduction

Kavalactones are isolated from the kava plant *Piper methystcum* (Piperaceae), which is found mostly in the South Pacific islands[1] including Fiji and Hawaii. Traditionally, the roots and rhizomes of the plant are ground down and made into a liquid beverage for consumption during formal social or religious engagements.[2] The extract of this plant contains at least six pharmacologically active compounds referred to as kavapyrones,[3] which mediate the local anesthetic sedating, anticonvulsive, muscle relaxant and sleep stimulating effects of the plant.[4] The potential use of this kava extract is being considered in the treatment of fear and anxiety-related disorders.[5] In clinical trials, kava has been found to be superior to placebo and effectively relieved anxiety as well as tension.[6] However, the FDA and CDC have issued warnings about the severe cause of liver injury probably associated with the use of kava containing dietary supplements. This has prompted the investigation[7] of all the major compounds in a systematic manner that are present in kava. Therefore, the synthesis of various kava-based compounds particularly in enantiopure form is of much importance (Fig. 1).

As part of our studies directed towards the synthesis of these kavalactones,[8a] and other biologically active molecules,[8b–d] we herein report the synthesis of the functionalized moieties of these molecules in suitably protected forms, employing the Sharpless asymmetric dihydroxylation as the source of chirality starting from commercially available hydrocinnamaldehyde, in a short and efficient manner. However, the syntheses of dihydrokawain-5-ol have previously been reported in the literature,[7] although most of them have their limitations.

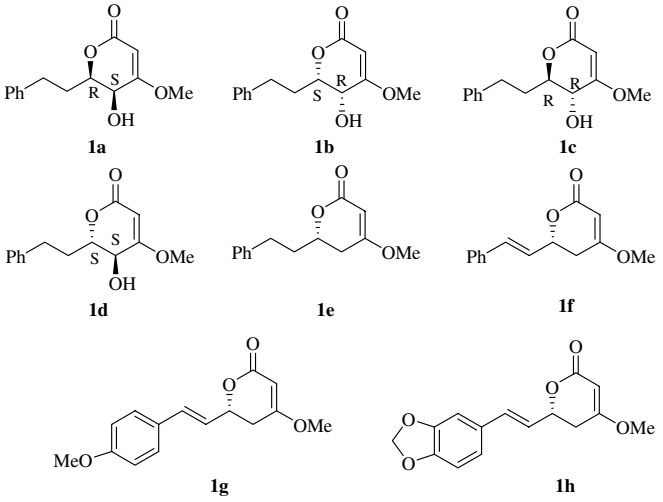

Figure 1. Kavalactones.

2. Results and discussion

Our initial retrosynthetic plan is outlined in Scheme 1. Strategic disconnection of the target dihydrokawain-5-ols **1a** and **1b** at the C_2–C_3 double bond and a choice of the

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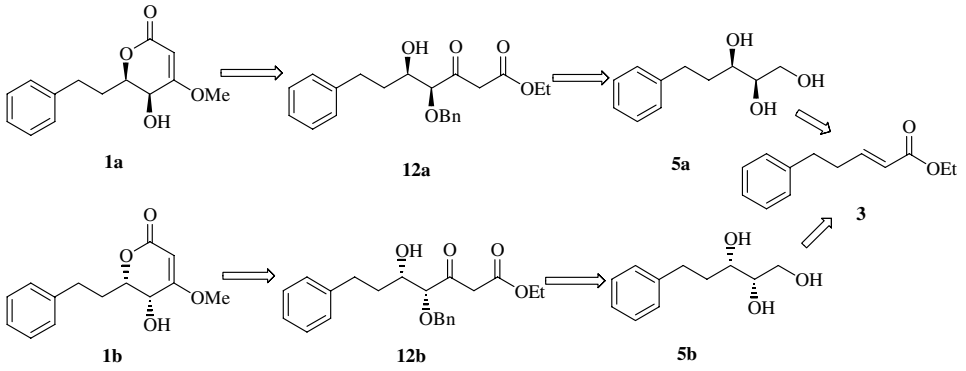


Scheme 1. Retrosynthetic analysis of dihydrokawain-5-ols **1a** and **1b**.

selective 1,3-protection of triol **5a** provides the appropriate precursor **12a** for the synthesis of proposed dihydrokawain-5-ol **1a**. Compound **12a** could be derived from triol **5a**. The *syn*-diol [(5*R*,6*S*) and (5*S*,6*R*)] stereochemistries can be introduced by Sharpless asymmetric dihydroxylation of an allylic alcohol **4**, that could be obtained by the reduction of α,β-unsaturated ester **3** with DIBAL–H. This ester **3** could inturn be derived from Wittig homologation of **2**.

Accordingly, we commenced the synthesis of target molecule **1a** from the commercially available hydrocinnamaldehyde as the starting material. This aldehyde, upon Wittig olefination with the stabilized ylide (ethoxycarbonyl methylene)triphenylphosphorane in benzene under reflux conditions exclusively furnished the *E*-isomer in the form of α,β-unsaturated ester **3**. Ester **3** was reduced by DIBAL–H to *E*-allylic alcohol **4** in quantitative yield. Compound **4** upon Sharpless asymmetric dihydroxylation[9] using AD-mix-β at 0 °C furnished triol **5a** in 90% yield with 95% ee. Selective 1,3-protection of triol **5a** gave a six-membered acetal as *p*-methoxybenzylidene acetal **6a** [*p*-methoxybenzaldehyde dimethylacetal, CSA, CH_2Cl_2] in 85% yield, along with 1,2-protection of the five-membered *p*-methoxybenzaldehyde acetal **7a** in 10% yield. These two acetals **6a** and **7a** were separated by column chromatography.

The hydroxyl group of **6a** was protected as benzyl ether **8a** (BnBr, NaH, THF) and subsequently, this upon regioselective reduction by DIBAL–H gave unmasked primary alcohol **9a** using the literature procedure.[10] Compound **9a** upon oxidation using Dess–Martin periodinate[11] in CH_2Cl_2 gave aldehyde **10a** in good yield. Aldehyde **10a**, without further purification, was treated with ethyl diazoacetate in the presence of a catalytic amount of anhydrous tin(II)chloride[12] in CH_2Cl_2 to afford β-keto ester **11a**. Intermediate **11a** upon PMB deprotection[13] using $ZrCl_4$ in acetonitrile at 0 °C gave **12a**. Lactonization and methylation of **12a** gave the benzylated ether of dihydrokawain-5-ol **13a**, which upon debenzylation using titanium chloride in CH_2Cl_2, provided the required dihydrokawain-5-ol **1a** as depicted in Scheme 2. Similarly, the other stereoisomer dihydrokawain-5-ol **1b** was also obtained from **4** using AD-mix-α and by following a similar sequence of reactions, as illustrated in Scheme 3.

3. Conclusion

In conclusion, we have accomplished a short and efficient linear total synthesis of both the stereoisomers of dihydrokawain-5-ol with high enantioselectivities, in which the stereocentres were established by Sharpless asymmetric dihydroxylation from commercially available starting materials. The synthesis of related compounds of this family is currently underway in our laboratory.

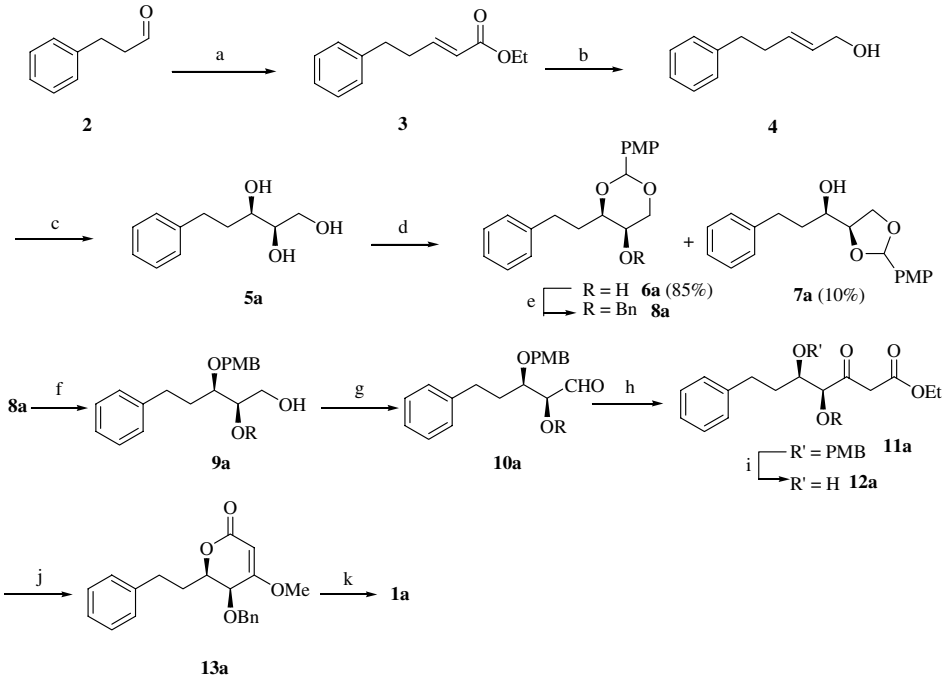
4. Experimental

4.1. General

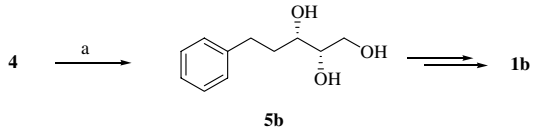
All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on a Horiba 360 digital polarimeter. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200, Brucker Avance 300. Chemical shifts are reported in ppm with respect to the internal TMS. Coupling constants (*J*) are quoted in Hertz. Mass spectra were recorded on VG micromass-7070H (70 eV). THF was freshly distilled from $LiAlH_4$. DIBAL–H was purchased from Merck while all the remaining chemicals were purchased from Aldrich and used as received.

4.2. 5-Phenylpent-2-enoicacidethylester 3

To a stirred solution of aldehyde **2** (1.0 g, 7.46 mmol) in benzene, Wittig ylide Ph_3PCHCO_2Et (2.6 g, 7.46 mmol) was added for 6 h under reflux conditions. After completion of the reaction, benzene was evaporated and the resulting crude was purified by column chromatography to give α,β-unsaturated ester **3** as a liquid (1.44 g, 95%). IR (KBr) ν_{max}: 1719, 1653, 1267 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, 3H, $J = 6.8$ Hz), 2.46–2.58 (m, 2H), 2.77 (t, 2H, $J = 7.5$ Hz), 4.16 (q, 2H, $J_1 = 7.5$ Hz, $J_2 = 14.3$ Hz), 5.81 (d, 1H, $J = 15.1$ Hz), 6.90–7.03 (m, 1H), 7.09–7.30 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 33.8, 34.3, 60.1, 121.8, 126.0, 128.3, 128.4, 140.7, 147.9, 166.5 ppm; LCMS (*m*/*z*): 227 $(M+Na)^+$; HRMS $(M+H)^+$: Calcd for $C_{13}H_{17}O_2$: 205.1228. Found: 205.1233.



Scheme 2. Reagents and conditions: (a) Ph_3PCHCO_2Et, benzene, 6 h, reflux, 95%; (b) DIBAL–H, −78 °C, 2 h, 93%; (c) AD-mix-β, *t*-BuOH–H_2O, $MeSONH_2$, 20 h, 0 °C, 90%; (d) $PMB(OMe)_2$, CH_2Cl_2, CSA, 0 °C to rt, 1 h, 85%; (e) BnBr, NaH, THF, 0 °C to rt, 4 h, 88%; (f) DIBAL–H, CH_2Cl_2, 0 °C, 1 h, 88%; (g) Dess–Martin periodinate, CH_2Cl_2, 0 °C to rt, 1 h; (h) N_2CHCO_2Et, anhydrous $SnCl_2$, CH_2Cl_2, 0 °C to rt, 80% for two steps; (i) $ZrCl_4$, CH_3CN, 0 °C to rt, 2 h, 85%; (j) K_2CO_3, MeOH, 0 °C to rt, 2 h, then acetone, Me_2SO_4, 10 h, 75%; (k) $TiCl_4$, CH_2Cl_2, 0 °C to rt, 15 min, 90%.



Scheme 3. Reagents and conditions: (a) AD-mix-α, *t*-BuOH–H_2O, $MeSONH_2$, 20 h, 0 °C, 90%.

4.3. 5-Phenylpent-2-en-1-ol 4

To a stirred solution of α,β-unsaturated ester **3** (1.0 g, 5.0 mmol) in dichloromethane at −78 °C, DIBAL–H (5.3 mL, 7.5 mmol, 20% wt in toluene) was added for 2 h. After completion of the reaction, Roche's salt solution was added and stirred for 1 h. The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography to give allylic alcohol **4** as a liquid (0.74 g, 93%). IR (KBr) ν_{max}: 3363, 2926, 2856, 1496, 1453 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.28–2.43 (m, 2H), 2.62–2.76 (m, 2H), 3.90–4.17 (m, 2H), 5.50–5.80 (m, 2H), 7.07–7.31 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.0, 35.6, 63.4, 125.9, 128.4, 128.5, 129.8, 131.9, 141.8 ppm; LCMS (*m*/*z*): 185 $(M+Na)^+$; HRMS $(M+Na)^+$: Calcd for $C_{11}H_{14}ONa$: 185.0942. Found: 185.0946.

4.4. (2*R*,3*R*)-5-Phenylpentane-1,2,3-triol 5a

AD-mix-β (19.0 g, 24.69 mmol) and methane sulfonamide (1.16 g, 12.35 mmol) were dissolved in a solvent mixture of *t*-BuOH–H_2O (10 mL/10 mL). The resulting mixture was stirred at room temperature for 5 min. The mixture was then cooled to 0 °C and a solution of compound **4** (2.0 g, 12.35 mmol) in dichloromethane (10 mL) was added. After stirring the reaction mixture for 20 h at 0 °C, TLC shows that the reaction was complete. A 10% $Na_2S_2O_3$ solution was then added to quench the reaction. The mixture was filtered through a layer of Celite and the filtrate was extracted with EtOAc. The organic layer was combined, dried over Na_2SO_4 and evaporated. The residue was dissolved in THF (3 mL) and TBAF (3 mL, 1 M in THF) was added. The resulting mixture was stirred at room temperature for 4 h after which saturated sodium bicarbonate solution was added. The mixture was extracted with EtOAc and the organic layers were combined, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography to afford the desired compound **5a** as a solid (2.17 g, 90%). The enantiomeric excess (ee) of **5a** is 95 and determined by HPLC (chiral column AS–H; Daicel) employing hexane–2-propanol (90:10) as mobile phase at 0.5 mL/min and monitored by UV (220 nm). Mp: 75–78 °C; $[\alpha]_D^{23.5} = +20.2$ (*c* 1.8, $CHCl_3$); IR (KBr) ν_{max}: 3351, 2941, 2908, 1455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.62–1.90 (m, 2H), 2.44–2.98 (m, 3H), 3.38–3.78 (m, 3H), 7.31–7.60 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.7, 35.2, 64.6, 71.8, 73.9, 125.9, 128.4, 141.7 ppm; LCMS (*m*/*z*): 219 $(M+Na)^+$; HRMS $(M+Na)^+$: Calcd for $C_{11}H_{16}O_3Na$: 219.0997. Found: 219.1008.

4.5. (2*S*,3*S*)-5-Phenylpentane-1,2,3-triol 5b

Ee 92%, $[\alpha]_D^{23.5} = -19.2$ (*c* 1.0, $CHCl_3$).

4.6. (5*R*,6*R*)-2-(4-Methoxyphenyl)-6-phenethyl-[1,3]dioxan-5-ol 6a

To a stirred solution of **5a** (1.5 g, 7.65 mmol) in dichloromethane (15 mL), *p*-methoxybenzylidene dimethylacetal (2 mL, 11.5 mmol) and CSA (10 mg) were sequentially added. The mixture was stirred at 23 °C for 1 h and after completion of the reaction, was quenched with Et_3N (two drops). The mixture was concentrated and the residue purified by column chromatography to afford the desired compound **6a** (2.0 g, 85%) along with **7a** (0.24 g, 10%) as a liquid. $[\alpha]_D^{23.5} = +75.9$ (*c* 2.0, $CHCl_3$); IR (KBr) ν_{max}: 3439, 2931, 1613, 1517, 1248 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.77–1.93 (m, 1H), 2.06–2.23 (m, 1H), 2.52 (d, 1H, $J = 12.1$ Hz), 2.61–2.82 (m, 2H), 3.36 (d, 1H, $J = 11.3$ Hz), 3.82 (s, 3H), 3.94 (d, 1H, $J = 11.3$ Hz); 4.15 (d, 1H, $J = 11.3$ Hz), 5.42 (s, 1H), 6.85 (d, 2H, $J = 8.3$ Hz), 7.09–7.42 (m, 7H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.8, 32.5, 55.2, 65.5, 72.6, 78.6, 101.2, 113.5 (2C), 125.8, 127.1 (2C), 128.3, 128.4 (2C), 130.4, 141.4, 159.9 ppm; LCMS (*m*/*z*): 315 $(M+H)^+$, 337 $(M+Na)^+$; HRMS $(M+Na)^+$: Calcd for $C_{19}H_{22}O_4Na$: 337.1415. Found: 337.1418.

4.7. (5*S*,6*S*)-2-(4-Methoxyphenyl)-6-phenethyl-[1,3]dioxan-5-ol 6b

$[\alpha]_D^{23.5} = -71.9$ (*c* 1.0, $CHCl_3$).

4.8. (5*R*,6*R*)-5-Benzyloxy-2-(4-methoxyphenyl)-6-phenethyl-[1,3]dioxane 8a

To a stirred solution of the compound **6a** (1.0 g, 3.18 mmol) in dry THF (15 mL), sodium hydride (0.25 g, 4.77 mmol), and benzyl bromide (0.82 g, 4.77 mmol) were added at 0 °C and stirred at room temperature for 4 h. After completion of the reaction, THF was evaporated, crushed ice was added, extracted with dichloromethane (2×50 mL), dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography to afford the desired compound **8a** as a solid (1.03 g, 88%). Mp: 82–85 °C; $[\alpha]_D^{23.5} = +57.75$ (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max}: 2862, 1613, 1515, 1546, 1249 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.70–1.90 (m, 1H), 2.20–2.42 (m, 1H), 2.56–2.77 (m, 2H), 3.13 (s, 1H), 3.80 (s, 3H), 3.68–3.78 (m, 2H), 4.45 (dd, 2H, $J_1 = J_2 = 12.1$ Hz), 4.81 (d, 1H, $J = 12.5$ Hz), 5.45 (s, 1H), 6.84 (d, 2H, $J = 8.0$ Hz), 7.07–7.47 (m, 12H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.9, 32.4, 55.1, 67.8, 70.7, 70.8, 78.2, 101.1, 113.4, 125.7, 127.5, 127.8, 128.2, 128.4, 130.9, 138.1, 141.7, 159.7 ppm; LCMS (*m*/*z*): 405 $(M+H)^+$, 427 $(M+Na)^+$; HRMS: Calcd for $C_{26}H_{28}O_4Na$ $(M+Na)^+$: 427.1885. Found: 427.1896.

4.9. (5*S*,6*S*)-5-Benzyloxy-2-(4-methoxyphenyl)-6-phenethyl-[1,3]dioxane 8b

$[\alpha]_D^{23.5} = -53.7$ (*c* 1.5, $CHCl_3$).

4.10. (2*R*,3*R*)-2-Benzyloxy-3-(4-methoxybenzyloxy)-5-phenylpentan-1-ol 9a

To a stirred solution of compound **8a** (1.0 g, 2.5 mmol) in dichloromethane (15 mL), DIBAL–H (3.6 mL, 5 mmol, 20% wt in toluene) was added dropwise at 0 °C. The mixture was stirred at 0 °C for another 1 h and after completion of the reaction, the excess DIBAL–H was quenched with 10% Roche's salt solution. The mixture was stirred at room temperature for 2 h. The two layers were separated and the aqueous layer was extracted dichloromethane (2×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography to afford the desired compound **9a** as a liquid (0.9 g, 88%). $[\alpha]_D^{23.5} = +25.4$ (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max}: 3446, 2926, 2862, 1610, 1513 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.67–1.82 (m, 1H), 1.88–2.03 (m, 2H), 2.43–2.59 (m, 1H), 2.64–2.79 (m, 1H), 3.44–3.64 (m, 3H), 3.67–3.76 (m, 1H), 3.78 (s, 3H), 4.28–4.50 (q, 2H, $J_1 = 11.3$, $J_2 = 27.1$ Hz), 4.53 (s, 2H), 6.81 (d, 2H, $J = 8.3$ Hz), 7.02–7.40 (m, 12 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.5, 31.9, 55.2, 61.7, 72.2, 72.6, 77.9, 79.4, 113.8, 125.7, 127.7, 127.8, 128.3, 128.4, 128.7, 129.6, 130.3, 138.2, 141.8, 159.3 ppm; LCMS (*m*/*z*): 429 $(M+Na)^+$; HRMS $(M+Na)^+$: Calcd for $C_{26}H_{30}O_4Na$: 429.2041. Found: 429.2048.

4.11. (2*S*,3*S*)-2-Benzyloxy-3-(4-methoxybenzyloxy)-5-phenylpentan-1-ol 9b

$[\alpha]_D^{23.5} = -24.6$ (*c* 1.0, $CHCl_3$).

4.12. (4*S*,5*R*)-4-Benzyloxy-5-(4-methoxybenzyloxy)-3-oxo-7-phenylheptanoicacidethylester 11a

To a stirred solution of compound **9a** in CH_2Cl_2, Dess–Martin periodinate (2.12 g, 5 mmol) was added at 0 °C for 1 h. After completion of the reaction, the reaction mixture was quenched with saturated sodium thiosulfate solution (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The reaction mixture was extracted with dichloromethane (2×50 mL), dried over anhydrous Na_2SO_4 and concentrated at 30 °C. The residue of aldehyde **10a** was used directly in the next step without further purification.

To a stirred solution of aldehyde **10a** (1.0 g, 2.5 mmol) in dichloromethane (15 mL), ethyl diazoacetate (0.4 mL, 3.75 mmol) and anhydrous $SnCl_2$ (0.05 g, 0.25 mmol) were added sequentially at 0 °C for 1 h. After completion of the reaction, the reaction mixture was washed with aqueous sodium bicarbonate, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography to afford the desired compound **11a** as a liquid (0.96 g, 80%). $[\alpha]_D^{23.5} = -21.0$ (*c* 1.2, $CHCl_3$); IR (KBr) ν_{max}: 1748, 1725 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.27 (t, 3H, $J = 7.3$ Hz), 1.68–2.09 (m, 2H), 2.31–2.70 (m, 2H), 3.50–3.70 (m, 2H), 3.81 (s, 3H), 3.98–4.78 (m, 8H), 6.82 (d, 2H, $J = 8.8$ Hz), 7.00–7.43 (m, 12H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 31.4, 31.6, 46.8, 55.1, 61.1, 72.0, 73.3, 78.8, 84.5, 90.8, 113.6, 127.7, 128.1, 128.2, 128.3, 128.4, 129.7, 136.8, 141.2, 159.2, 167.3, 204.8 ppm; LCMS (*m*/*z*): 513 $(M+Na)^+$; HRMS $(M+Na)^+$: Calcd for $C_{30}H_{34}O_6Na$: 513.2253. Found: 513.2232.

4.13. (4*R*,5*S*)-4-Benzyloxy-5-(4-methoxybenzyloxy)-3-oxo-7-phenylheptanoicacidethylester 11b

$[\alpha]_D^{23.5} = +23.4$ (*c* 1.2, $CHCl_3$).

4.14. (4*S*,5*R*)-4-Benzyloxy-5-hydroxy-3-oxo-7-phenyl-heptanoicacidethylester 12a

To a stirred solution of compound **11a** (1.0 g, 2.0 mmol) in dry acetonitrile (15 mL), $ZrCl_4$ (0.1 g, 0.412 mmol) was added and the mixture stirred at room temperature for 2 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL), washed with brine (1×10 mL), water (1×10 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography to afford the desired compound **12a** as a liquid (0.64 g, 85%). $[\alpha]_D^{23.5} = -40.6$ (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max}: 1748, 1725, 1611, 1512 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.09–1.49 (m, 3H), 1.62–1.94 (m, 2H), 2.90–2.92 (m, 2H), 3.33–3.90 (m, 4H), 4.00–4.82 (m, 4H), 6.93–7.53 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 31.6, 34.9, 46.0, 61.3, 71.4, 73.6, 90.9, 125.8, 128.1, 128.2, 128.3, 128.4, 128.5, 136.5, 141.2, 167.2, 205.3 ppm; LCMS (*m*/*z*): 393 $(M+Na)^+$; HRMS $(M+Na)^+$: Calcd for $C_{22}H_{26}O_5Na$: 393.1677. Found: 393.1673.

4.15. (4*R*,5*S*)-4-Benzyloxy-5-hydroxy-3-oxo-7-phenyl-heptanoicacidethylester 12b

$[\alpha]_D^{23.5} = +36.2$ (*c* 1.5, $CHCl_3$).

4.16. (5*S*,6*R*)-5-Benzyloxy-4-methoxy-6-phenethyl-5,6-dihydro-2*H*-pyran-2-one 13a

To a stirred solution of compound **12a** (0.5 g, 1.35 mmol) in methanol (10 mL), K_2CO_3 (0.37 g, 2.7 mmol) was added for 2 h. After completion of the reaction, methanol was evaporated, redissolved in acetone (10 mL), and Me_2SO_4 (0.25 mL, 2.7 mmol) and stirred for 10 h. The residue was purified by column chromatography to afford the desired compound **13a** as a solid (0.35 g, 75%). Mp 85–88 °C; $[\alpha]_D^{23.5} = -120.5$ (*c* 4.5, $CHCl_3$); IR (KBr) ν_{max}: 1704, 1629 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.77–2.06 (m, 1H), 2.24–2.43 (m, 1H), 2.61–2.85 (m, 2H), 3.61–3.68 (m, 1H), 3.71 (s, 3H), 4.17 (m, 1H), 4.61 (dd, 2H, $J_1 = J_2 = 12.1$ Hz), 5.15 (s, 1H), 7.06–7.36 (m, 10H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 30.8, 31.3, 56.0, 71.3, 72.3, 77.9, 92.3, 126.0, 127.8, 128.3, 128.4, 128.4, 137.1, 140.7, 166.0, 171.6 ppm; LCMS (*m*/*z*): 339 $(M+H)^+$, 361 $(M+Na)^+$; HRMS $(M+H)^+$: Calcd for $C_{21}H_{23}O_4$: 339.1596. Found: 339.1605.

4.17. (5*R*,6*S*)-5-Benzyloxy-4-methoxy-6-phenethyl-5,6-dihydro-2*H*-pyran-2-one 13b

$[\alpha]_D^{23.5} = +116.0$ (*c* 3.0, $CHCl_3$).

4.18. (5*S*,6*R*)-5-Hydroxy-4-methoxy-6-phenethyl-5,6-dihydro-2*H*-pyran-2-one 1a

To a stirred solution of **13a** (0.2 g, 0.6 mmol) in dichloromethane (10 mL), $TiCl_4$ (0.08 mL, 0.72 mmol) was added at 0 °C for 15 min. After completion of the reaction, the mixture was taken into dichloromethane, washed with aqueous sodium bicarbonate (10 mL), water (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography to afford the desired compound **1a** as a liquid (0.13 g, 90%) with 94% ee. Enantiomeric excess (ee) was calculated on HPLC using chiral Diacel OD column. $[\alpha]_D^{23.5} = -62.5$ (*c* 2.0, $CHCl_3$); {lit.[7b] $[\alpha]_D^{25} = -66.3$ (*c* 1.02, $CHCl_3$)}; IR (KBr) ν_{max}: 3367, 1683, 1630, 1225 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.85–2.43 (m, 2H), 2.65–2.96 (m, 2H), 3.76 (s, 3H), 3.96 (s, 1H), 4.04–4.26 (m, 1H), 5.10 (s, 1H), 7.08–7.48 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 30.7, 30.8, 56.3, 65.7, 78.3, 91.6, 126, 128.3, 128.3, 140.6, 166.9, 172.7 ppm; LCMS (*m*/*z*): 271 $(M+Na)^+$; HRMS $(M+Na)^+$: Calcd for $C_{14}H_{16}O_4Na$: 271.0946. Found: 271.0947.

4.19. (5*R*,6*S*)-5-Hydroxy-4-methoxy-6-phenethyl-5,6-dihydro-2*H*-pyran-2-one 1b

Mp 88–90 °C [lit.[7b] 90–91 °C]; $[\alpha]_D^{23.5} = +61.0$ (*c* 2.0, $CHCl_3$), {lit.[7b] $[\alpha]_D^{25} = +68.1$ (*c* 1.01, $CHCl_3$)}.

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