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An efficient aldol-based approach for the synthesis of dihydrokawain-5-ol

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ABSTRACT

An efficient and simple aldol-based convergent approach toward the total synthesis of (+)- and (−)-dihydrokawain-5-ol is described. The key features of this synthetic strategy include Evans' aldol reaction and an ethyl acetate addition reaction for the formation of the six-membered ring.

1. Introduction

The δ-lactone ring system is found in a number of natural products and is also featured in many intermediates that are required for the synthesis of biologically important compounds.[1] These δ-lactones have been shown to exhibit a wide range of biological activities such as antibiotic, anticancer, anti-inflammatory, antimicrobial and insecticidal.[2] The δ-lactone, (+)-dihydrokawain-5-ol **1b** (6-alkyl-5-hydroxy-5,6-dihydropyran-2-one) has been isolated from the methanol extracts of the kava plant (*Piper mythisticum*), a Polynesian shrub of the pepper family, which is mostly found in the South Pacific islands including Fiji and Hawaii.[3] Traditionally, the roots and rhizomes of this plant are ground and made into a liquid beverage for consumption during formal, social, or religious engagements.[4]

The extracts of this plant contain at least six pharmacologically active compounds referred to as kavapyrones,[5] which mediate the local anesthetic, sedating, anticonvulsive, muscle relaxant, and sleep stimulating effects.[6] The potential use of this kava extracts is being considered in the treatment of fear and anxiety-related disorders.[7] Kava has been found to be superior to placebos and effectively relieves anxiety as well as tension.[8] However, the FDA and CDC have issued warnings about the severe cases of liver injury probably associated with the use of kava-containing dietary supplements. This has prompted the investigation of all the major compounds in a systematic manner that are present in kava. Therefore, the synthesis of various kava-based compounds particularly in their enantiopure form is of importance (Fig. 1).

The absolute (5*R*,6*S*)-configuration in (+)-dihydrokawain-5-ol **1b** has been assigned by its synthesis through SeO_2 allylic oxidation of (+)-dihydrokawain **1e**, derived from kawain **1f**.[9] Some approaches have been developed in the literature for the synthesis of (+)-dihydrokawain-5-ol **1b** by employing different protocols. Friesen et al.[10a] synthesized dihydrokawain-5-ol **1b** in a racemic form while later the synthesis of (+)-dihydrokawain-5-ol was accomplished by Arai et al.[10b] utilizing chiral sulfoxides, whereas Singh et al.[10c] have obtained its (+)-form and the other stereoisomers from α-D-glucose. Recently, we have reported the synthesis of both the (+)- and (−)-dihydrokawain-5-ol from dihydrocinnamaldehyde utilizing Sharpless asymmetric dihydroxylation process.[10d]

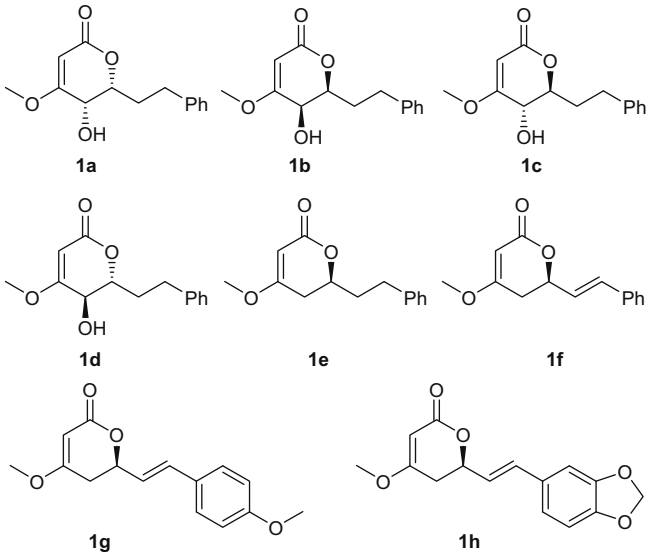

Figure 1. Kavalactones.

2. Results and discussion

As part of our continuing studies directed toward the synthesis of lactones and other biologically active molecules,[11] we herein report a new synthetic route to (+)- and (−)-dihydrokawain-5-ol employing the well-known and widely used Evans' asymmetric aldol

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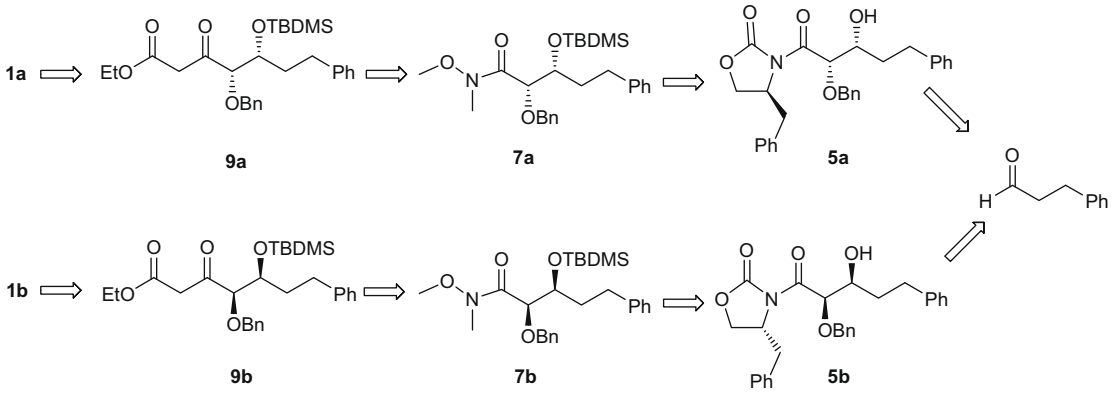
reaction[12] as the key step in their preparation. By using this methodology, two *syn*-hydroxyl groups are introduced at the C_5 and C_6 positions in their skeleton. Our initial retrosynthetic plan is outlined in Scheme 1. Retrosynthetically, (−)-dihydrokawain-5-ol can be obtained from intermediate **9a**, which can be formed by the condensation of the aldehyde of Weinreb amide **7a** with ethyl acetate. Moreover, this Weinreb amide can be produced by the transamidation of aldol product **5a**. This aldol product can be prepared from the commercially available dihydrocinnamaldehyde.

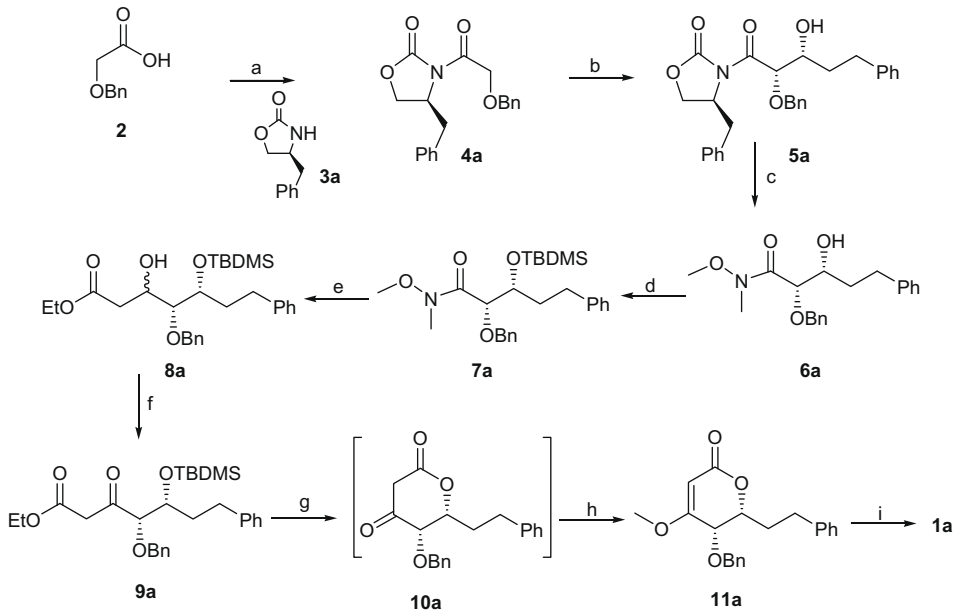
The synthesis of **1a** starts by the coupling of the 2-(benzyloxy)acetic acid derivative with oxazolidinone **3a** by employing Ho's protocol[13] to afford (4*S*)-4-benzyl-3-[2-(benzyloxy)acetyl]-1,3-oxazolan-2-one **4a** in 90% yield. Aldol reaction of hydrocinnamaldehyde with **4a** using dibutylboron triflate and triethylamine in CH_2Cl_2 at −78 °C for 4 h gives the *syn*-aldol product[14] **5a** in good yield (81%) as a single diastereomer. The chiral auxiliary in **5a** is removed by transamidation to afford Weinreb amide **6a** in 84% yield. The hydroxyl group of **6a** is protected as the TBDMS ether using TBDMS triflate and triethylamine at −78 °C for 4 h to provide **7a** in 83% yield. At this stage the condensation of **7a** with ethyl acetate using different bases in a variety of solvents was attempted, however, the desired product **9a** was not obtained. Therefore the Weinreb amide was initially treated with DIBAL-H to afford the aldehyde, which without further purification underwent EtOAc addition at −78 °C (EtOAc/LiHMDS/THF/−78 °C) to give the diastereomeric alcohol **8a** in 68% yield. Compound **8a** upon oxidation with Dess–Martin periodinate in CH_2Cl_2 forms the β-keto ester **9a** in good yield.

Treatment of compound **9a** with PTSA in methanol[15] resulted in the deprotection of the TBDMS ether as well as the formation of a cyclized lactone **10a**, which was not isolated. Upon treatment with Me_2SO_4 and K_2CO_3 in acetone the desired precursor **11a** was obtained in good yield. After the lactone formation benzyl-protected alcohol was then deprotected. Compound **11a** was then treated with $TiCl_4$ in CH_2Cl_2[16,10d] at 0 °C to afford the required target compound (−)-dihydrokawain-5-ol **1a**. The spectroscopic and analytical data were comparable to the previously reported data in the literature.[10c,d]

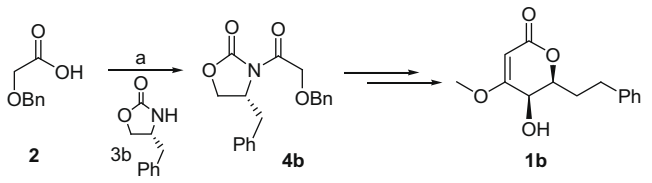
Similarly the synthesis of (+)-dihydrokawain-5-ol **1b**, was carried out by employing (4*R*)-4-benzyl-3-[2-(benzyloxy)acetyl]-1,3-oxazolan-2-one as the starting material, followed by the same set of reactions as in Scheme 2, as depicted in Scheme 3. The spectro-



Scheme 1. Retrosynthetic analysis of **1a** and **1b**.



Scheme 2. Reagents and conditions: (a) pivolyl chloride, Et_3N, THF, **3a**, LiCl, Et_3N, 90%; (b) Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C, 4 h, 81%; (c) *N*-methoxy-*N*-methylamine hydrochloride, Me_3Al, THF, 0 °C to rt, 1 h, 84%; (d) TBDMS triflate, Et_3N, −78 °C–rt, 4 h, 83%; (e) (i) DIBAL-H, CH_2Cl_2, −78 °C, 2 h; (ii) EtOAc, LiHMDS, THF, −78 °C, 1 h, 68%; (f) Dess–Martin periodinate, CH_2Cl_2, 0 °C to rt, 1 h; (g) PTSA, methanol, 8 h, 0 °C to rt, (h) Me_2SO_4, K_2CO_3, acetone, 10 h; (i) $TiCl_4$, CH_2Cl_2, 0 °C–rt, 15 min, 89%.



Scheme 3. Reagents and conditions: (a) pivolyl chloride, Et_3N, THF, **3b**, LiCl, Et_3N.

scopic and analytical data were comparable to the previously reported data in the literature.[10b–d]

3. Conclusion

In conclusion, we have developed an efficient and convenient approach for the synthesis of (+)- and (−)-dihydrokawain-5-ol. In this protocol, stereocenters are established by an Evans' asymmetric aldol reaction that has been chosen as the key step for the synthesis of these molecules by using simple commercially available starting materials. The syntheses of related compounds of this family are currently underway in this laboratory.

4. Experimental

4.1. General experimental

Reagents and chemicals were purchased from Aldrich. All solvents and reagents were purified by standard techniques. THF was freshly distilled from $LiAlH_4$. Crude products were purified by column chromatography on 60–120 silica gel. 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. Mass spectra were recorded on VG micromass-7070H (70 Ev).

4.2. (4*S*)-4-Benzyl-3-[(2*S*,3*R*)-2-(benzyloxy)-3-hydroxy-5-phenylpentanoyl]-1,3-oxazolan-2-one 5a

To a stirred solution of chiral auxiliary **4a** (5 g, 15.38 mmol) in dry CH_2Cl_2 (50 mL) at −78 °C was added triethylamine (2.56 mL, 18.46 mmol) followed by the dropwise addition of dibutylboron triflate (16.92 mL, 16.92 mmol, 1 M solution in CH_2Cl_2) and stirred for 1 h at the same temperature. The solution was warmed to 0 °C for 45 min and recooled to −78 °C. Dihydrocinnamaldehyde (2.22 mL, 16.92 mmol) solution in CH_2Cl_2 (5 mL) was added dropwise via a cannula. The reaction mixture was allowed to stir at −78 °C for 2 h. The reaction was quenched with MeOH (25 mL) followed by pH 7 buffer (12 mL). After 1 h, 30% aqueous H_2O_2 (5 mL) was added dropwise and stirred at 0 °C for 1 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 30:70) to afford the compound **5a** (5.71 g, 81%) as a solid. Mp: 97–99 °C. $[\alpha]_D^{25} = +70.5$ (*c* 1.5, $CHCl_3$); IR (neat): γ_{max}: 3507, 2928, 1788, 1685, 1453, 1211, 757, 701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.11 (m, 15H), 5.1 (d, *J* = 2.9 Hz, 1H), 4.64–4.57 (m, 1H), 4.54 (q, *J* = 11.7 Hz, 2H), 4.27–4.09 (m, 2H), 3.85 (br s, 1H), 3.27 (dd, *J* = 2.9, 13.2 Hz, 1H), 2.87–2.49 (m, 3H), 2.23 (br s, 1H), 1.93 (q, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 153.3, 141.6, 136.9, 134.9, 129.2, 128.8, 128.4, 128.3, 128.2, 128.1, 127.3, 125.68, 79.2, 72.8, 72.1, 66.9, 55.4, 37.5, 35.6, 31.74; ESI–MS: *m/z* = 460.6 $(M+H)^+$.

4.3. (2*S*,3*R*)-2-(Benzyloxy)-3-hydroxy-*N*-methoxy-*N*-methyl-5-phenylpentanamide 6a

To a stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride (4.6 g, 47.93 mmol) in dry THF (100 mL) at 0 °C was added trimethylaluminum (17.97 mL, 35.94 mmol, 2 M in toluene) dropwise. Then the mixture was allowed to stir at room temperature for 30 min and recooled to 0 °C. Compound **5a** (5.5 g, 11.98 mmol) in dry THF (10 mL) was added dropwise and then stirred at room temperature for 2 h. After completion of the reaction, the reaction was slowly quenched with dil HCl. Next, THF was evaporated and extracted with EtOAc (2 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 40: 60) to afford the compound **6a** (3.45 g, 84%) as a colorless liquid. $[\alpha]_D^{25} = -13.5$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3430, 2931, 1660, 1454, 750, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.36–7.08 (m, 10H), 4.53 (dd, *J* = 11.7 Hz, 2H), 4.17 (d, *J* = 4.4 Hz, 1H), 3.81 (m, 1H), 3.46, (s, 3H), 3.17 (s, 3H), 2.85–2.52 (m, 2H), 2.01–1.6 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 141.6, 137.1, 128.3, 128.2, 128.1, 127.96, 125.7, 77.4, 71.9, 71.3, 61.1, 34.7, 32.3, 31.7; ESI–MS: *m/z* = 344.6 $(M+H)^+$.

4.4. (2*S*,3*R*)-2-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*-methyl-5-phenylpentanamide 7a

To a stirred solution of Weinreb amide **6a** (3.2 g, 9.32 mmol) in dry CH_2Cl_2 (40 mL) at −78 °C were added TBSOTf (2.35 mL, 10.26 mmol) and triethylamine (1.55 mL, 11.19 mmol) and allowed to stir at room temperature for 4 h. After completion of the reaction, the reaction was quenched by satd NH_4Cl solution (20 mL) and the reaction mixture was extracted with $CHCl_3$ (2 × 75 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 5:95) to afford **7a** (3.53 g, 83%) as a colorless liquid. $[\alpha]_D^{25} = -4.4$ (*c* 1.4, $CHCl_3$); IR (neat): γ_{max}: 2930, 1670, 1458, 1113, 835, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.06 (m, 10H), 4.55 (dd, *J* = 11.9 Hz, 2H), 4.24 (d, *J* = 6.4 Hz, 1H), 4.1–4.03 (m, 1H), 3.5 (s, 3H), 3.15 (s, 3H), 2.71–2.49 (m, 2H), 1.85–1.74 (m, 1H), 1.7–1.58 (m, 1H), 0.908 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.5, 142.4, 137.6, 128.2, 128.06, 127.64, 127.61, 125.6, 79.3, 72.9, 72.9, 60.9, 35.3, 32.2, 31.5, 25.5, 18.1, −4.1, −4.7; ESI–MS: *m/z* = 458.6 $(M+H)^+$.

4.5. Ethyl(4*R*,5*R*)-4-(benzyloxy)-5-[1-(*tert*-butyl)-1,1-dimethyl silyl]oxy-3-hydroxy-7-phenylheptanoate 8a

To a stirred solution of compound **7a** (3.3 g, 7.22 mmol) in dry CH_2Cl_2 (50 mL) at −78 °C was added DIBAl-H (3.97 mL, 7.94 mmol, 2 M in toluene) and stirred for 1 h at the same temperature. After completion of the reaction, the reaction was quenched with sodium potassium tartarate solution, and the reaction mixture was stirred for 30 min at room temperature and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuo to afford the crude aldehyde, which was used for the next step without purification. To a stirred solution of ethyl acetate (2.13 mL, 21.85 mmol) in THF at −78 °C was added LiHMDS (18.21 mL, 18.21 mmol, 1 M in THF) dropwise and stirred for 45 min. To this reaction mixture the aldehyde (2.9 g, 7.28 mmol) obtained above was taken in THF (8 mL) and added slowly with stirring for 2 h at −78 °C. After completion of the reaction, the reaction was quenched with aqueous ammonium chloride solution. Next THF was evaporated and extracted with $CHCl_3$ (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo.

The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 10:90) to afford compound **8a** (2.38 g, 68%) as a colorless liquid. $[\alpha]_D^{25} = +33.4$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3507, 2931, 1733, 1095, 837, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.18 (m, 10H), 4.72–4.57 (m, 2H), 4.11 (q, *J* = 7.5, 14.3 Hz, 2H), 4.28–4.2 (m, 1H), 3.89 (m, 1H), 3.31 (t, 1H), 2.78–2.43 (m, 5H), 2.08–1.97 (m, 1H), 1.88–1.75 (m, 1H), 1.24 (t, *J* = 7.5, 14.3 Hz, 3H), 0.91 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 142.1, 137.9, 128.42, 128.35, 128.32, 127.93, 125.7, 82.5, 73.8, 71.6, 67.3, 60.5, 39.7, 34.2, 32.1, 25.8, 18.1, 14.1, −4.1, −4.6; ESI–MS: *m/z* = 487 $(M+H)^+$.

4.6. Ethyl (4*S*,5*R*)-4-(benzyloxy)-5-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-3-oxo-7-phenylheptanoate 9a

To a stirred solution of compound **8a** (2.1 g, 4.33 mmol) in CH_2Cl_2 (40 mL), Dess–Martin periodinate (2.02 g, 4.77 mmol) was added at 0 °C and stirred for 1 h. After completion of the reaction, the reaction was quenched with aqueous sodium thiosulfate solution (20 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The reaction mixture was extracted with CH_2Cl_2 (2 × 50 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 7: 93) to afford **9a** (1.92 g, 92%) as a yellow liquid. $[\alpha]_D^{25} = +6.8$ (*c* 1.1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ = 7.39–7.11 (m, 10H), 4.76 (d, *J* = 11.6 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.36–4.25 (m, 1H), 4.17 (q, *J* = 7.2, 13.8 Hz, 2H), 4.04–3.82 (m, 1H), 3.72–3.51 (m, 2H), 2.58 (m, 2H), 2.13–1.94 (m, 1H), 1.81–1.56 (m, 1H), 1.3 (t, *J* = 7.2, 13.8 Hz, 3H), 0.94 (s, 9H), 0.08 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.6, 167.3, 141.5, 137.1, 128.4, 128.3, 128.2, 128.1, 128.05, 125.85, 86.2, 73.3, 73.0, 61.2, 47.2, 35.1, 31.6, 25.8, 18.0, 14.0, −4.6, −4.7; IR (neat): γ_{max}: 2931, 2858, 1746, 1722, 1254, 837, 776, 699 cm^{-1}. ESI–MS: *m/z* = 485.6 $(M+H)^+$.

4.7. (5*S*,6*R*)-5-(Benzyloxy)-4-methoxy-6-phenethyl-5,6-dihydro-2*H*-2-pyranone 11a

To a stirred solution of **9a** (1.7 g, 3.51 mmol) in dry MeOH (20 mL) at 0 °C was added PTSA (0.06 g, 0.35 mmol) and stirred at room temperature for 8 h. After completion of the starting material, methanol was evaporated. To the above crude compound in acetone at 0 °C was added Me_2SO_4 (0.665 mL, 7.02 mmol) followed by K_2CO_3 (0.96 g, 7.02 mmol). The reaction mixture was stirred for 10 h. After completion of the reaction, solid K_2CO_3 was filtered, and acetone was evaporated and extracted with EtOAc (2 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 40:60) to afford the compound **11a** (0.89 g, 75%) as a solid. Mp 85–88 °C. $[\alpha]_D^{25} = -118.9$ (*c* 1.5, $CHCl_3$); IR (neat): γ_{max}: 1711, 1633, 1221, 1059, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.1 (m, 10H), 5.14 (s, 1H), 4.61 (dd, *J* = 12.1 Hz, 2H), 4.16–4.08 (m, 1H), 3.71 (s, 3H), 3.66–3.65 (m, 1H), 2.84–2.64 (m, 2H), 2.41–2.29 (m, 1H), 1.92–1.8 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 165.9, 140.7, 137.1, 128.41, 128.4, 128.3, 127.7, 126.0, 92.2, 77.8, 72.3, 71.2, 55.9, 31.2, 30.8; ESI–MS: *m/z* = 339 $(M+H)^+$.

4.8. (5*S*,6*R*)-5-Hydroxy-4-methoxy-6-phenethyl-5,6-dihydro-2*H*-2-pyranone 1a

To a stirred solution of **10a** (0.4 g, 1.18 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C was added $TiCl_4$ (0.258 mL, 2.36 mmol) and stirred for 15 min. After completion of the reaction, the reaction was quenched with aqueous sodium bicarbonate solution, and the reaction mixture was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 60:40) to afford compound **1a** (0.26 g, 89%) as a colorless liquid. $[\alpha]_D^{25} = -63.2$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3381, 1685, 1630, 1225, 1051, 749, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.07 (m, 5H), 5.1 (s, 1H), 4.21–4.04 (m, 1H), 3.85 (br s, 1H), 3.75 (s, 3H), 2.89–2.71 (m, 2H), 2.36–2.23 (m, 1H), 2.06–1.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 166.78, 140.69, 128.43, 128.4, 126.06, 91.19, 78.32, 65.90, 56.27, 30.93, 30.78; ESI–MS: *m/z* = 249 $(M+H)^+$.

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