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Stereoselective synthesis of (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one

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Abstract—A stereoselective synthesis of (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one is reported. The strategy utilizes an olefin cross-metathesis, *syn*-benzylidene acetal formation and a preferential (*Z*)-Wittig olefination reaction and lactonization as the key steps.
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1. Introduction

The α-pyrone moiety is one of the most commonly encountered structural motifs among natural product skeletons, many of which exhibit varied pharmacological properties.[1a] The α-pyrone (6-substituted 5,6-dihydro-2*H*-pyran-2-one or α,β-unsaturated-δ-lactone) containing natural products are most often connected through a polyoxygenated chain to a lactone moiety.[1b] The various biological activities shown by these compounds include antimicrobial, antifungal, and cytotoxicity against human tumor cells.[2] (6*S*)-5,6-Dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one,[3] is one such natural product, which was isolated from *Ravensara crassifolia*, the synthesis of which was reported earlier.[4] As a part of our interest in the synthesis of the lactone skeleton containing bioactive natural products,[5] we herein report the stereoselective synthesis of **1** through an olefin cross-metathesis reaction to obtain an homoallylic alcohol, which was treated with benzaldehyde in presence of potassium *tert*-butoxide to obtain the acetal and then its subsequent elaboration to the target compound.

The retrosynthetic analysis envisions that **1** could be obtained from **2** by functional group transformations and lactonization, while **2** could in turn be visualized from **3** by reduction and (*Z*)-selective Wittig olefination. Compound **3** was obtained by the treatment of homoallyl alcohol with benzaldehyde to garner the requisite 1,3-*syn*-polyol system. Compound **4** in turn could be derived from **5** by olefin cross-metathesis.

2. Results and discussion

The synthesis of **1** (Scheme 1) began from commercially available 5-phenylpentan-1-ol **6**. The known homoallyl alcohol **5**[5a] olefin cross-metathesis with ethyl acrylate and second generation Grubbs' catalyst[6] in dichloromethane at 40 °C led to unsaturated ester **4** (87%) as the *E*-isomer exclusively. Independently, **4** was also realized through the dihydroxylation/oxidative cleavage, followed by the Wittig reaction in 65% yield over three steps (*E*:*Z*, 95:5 ratio). Later, homoallylic alcohol **4** was treated with benzaldehyde in presence of potassium *tert*-butoxide in THF at 0 °C and pH 7 phosphate buffer to afford benzylidene acetal **3** (57%).[7] The ester function was reduced with DIBAL–H in dry THF at −78 °C to afford the aldehyde, which was then chain-elongated via a Wittig reaction to give the corresponding α,β-unsaturated ester **2** {$(F_3CCH_2O)_2POCH_2COOMe$, KHMDS, 18-crown-6, THF, −78 °C, 76% over two steps} predominantly as the *Z*-isomer,[8] as characterized by ^1H and ^{13}C NMR spectroscopy. For example the coupling constant ($J = 11.3$ Hz) of the olefinic protons confirmed the (*Z*)-geometry of the olefin.

Finally acid catalyzed (80% aq AcOH) deprotection of the benzylidene acetal followed by concomitant lactone

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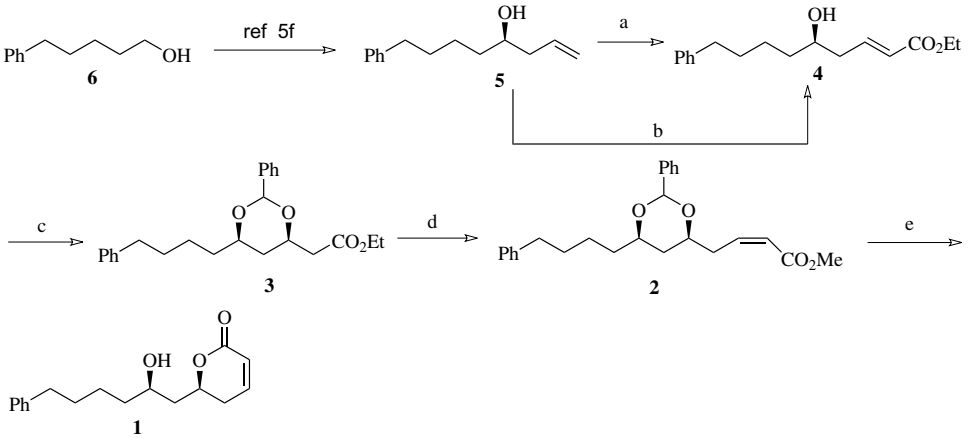

Scheme 1. Reagents and conditions: (a) Ethyl acrylate, Grubbs'-**II**, CH_2Cl_2, 40 °C, 12 h, 85%; (b) (i) OsO_4, NMO, THF:H_2O, rt, 8 h; (ii) $NaIO_4$, $NaHCO_3$, CH_2Cl_2, rt, 6 h; (iii) $Ph_3P{=}CHCOOEt$, benzene, reflux, 1 h (65% over three steps); (c) Benzaldehyde, *t*-BuOK, THF, pH 7 buffer; 1 h, 57%; (d) (i) DIBAL–H, CH_2Cl_2, −78 °C, 30 min; (ii) $(F_3CCH_2O)_2POCH_2CO_2Me$, KHMDS, 18-crown-6, −78 °C, 1 h (76% over two steps); (e) (i) 80% aq AcOH, 60 °C, 3 h; (ii) PTSA, benzene, 4 h, 61%.

cyclization with *p*-toluene sulfonic acid in benzene yielded target compound **1** (61%). Mp 33–35 °C; $[\alpha]_D^{25} = -65.5$ (c 0.81, $CHCl_3$); {lit.[3] mp 37 °C; $[\alpha]_D^{25} = -66.0$ (c 2.0, $CHCl_3$)}. The physical and spectroscopic data of **1** were identical to the reported values of the natural product.

3. Conclusion

In conclusion, the stereoselective synthesis of **1** has been accomplished by a versatile strategy wherein an olefin cross-metathesis reaction, and a benzylidene acetal reaction were effectively utilized for installing the 1,3-*syn*-polyol system, followed by the preferential (*Z*)-Wittig olefination and lactonization led to the target compound.

4. Experimental

4.1. General methods

Solvents were dried over standard drying agents and freshly distilled prior to use. Chemicals were purchased and used without further purification. All column chromatographic separations were performed using silica gel (Acme's, 60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo. ^1H NMR (200 MHz, 300 MHz, and 400 MHz) and ^{13}C NMR (50 MHz, 75 MHz and 100 MHz) spectra were measured with a Varian Gemini FT-200 MHz spectrometer, Bruker Avance 300 MHz and Unity 400 MHz with tetramethylsilane as internal standard for solutions in deuteriochloroform. *J* values are given in Hz. IR spectra were recorded on a Perkin–Elmer IR-683 spectrophotometer with NaCl optics. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25 °C. Mass spectra were recorded on CEC-21-11013 or Fannigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system or LC/MSD Trap SL (Agilent Technologies).

4.1.1. Ethyl (*E*,5*R*)-5-hydroxy-9-phenyl-2-nonenoate 4. A solution of **5** (0.20 g, 0.98 mmol), ethyl acrylate (0.1 mL, 0.98 mmol) and second generation Grubbs' catalyst (0.04 g, 0.05 mmol) in anhydrous CH_2Cl_2 (15 mL) was stirred at reflux temperature for 12 h. After completion of the reaction, the solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel, EtOAc–hexane, 1:4) to afford **4** (0.204 g, 85%) as a colorless syrup. $[\alpha]_D^{25} = -13.1$ (c 0.93, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.25–7.10, (m, 5H), 6.95–6.86 (m, 1H), 5.84 (d, 1H, J 17.3 Hz), 4.18 (t, 2H, J 7.5 Hz), 2.41–2.08 (m, 2H), 1.71–1.58 (m, 3H), 1.55–1.35 (m, 3H), 1.29 (t, 3H, J 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.1, 146.2, 139.5, 129.7, 128.2, 128.1, 126.2, 72.9, 40.9, 36.7, 35.7, 35.5, 31.5, 24.9, 14.4; IR (thin film): 3380, 1721, 1639, 1254 cm^{-1}; LCMS; 299 $[M+Na]^+$. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.28; H, 9.84.

4.1.2. Ethyl (*E*,5*R*)-5-hydroxy-9-phenyl-2-nonenoate 4. To a solution of **5** (0.2 g, 0.98 mmol) in acetone–water (4:1) was added 5% OsO_4 solution in toluene (0.05 mL, 0.01 mmol), after 15 min, an aqueous 50% NMO solution (0.45 mL, 1.9 mmol) was added and the mixture was stirred for 12 h. To the solution were added Na_2SO_3 and Na_2SO_4. Then the mixture was filtered through Celite pad, and the filtrate was evaporated and extracted with ethylacetate (2×15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a residue, which was used directly for next reaction.

To a solution of the above obtained triol in CH_2Cl_2 was added $NaIO_4$ (0.42 g, 1.9 mmol) and saturated $NaHCO_3$ solution (0.1 mL) and stirred for 6 h. Then the mixture was added Na_2SO_4 (0.1 g) and concentrated in vacuo to afford the crude aldehyde, which was used without purification in the next reaction.

To a solution of the aldehyde in benzene (2.0 mL) was added $Ph_3P{=}CH{-}COOEt$ (0.41 g, 1.1 mmol) and stirred at reflux for 1 h. After completion of the reaction, the solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel, EtOAc–hexane, 1:99) to afford **4** (0.156 g, 65% over three steps) as a colorless syrup as an *E*/*Z* mixture in a 95:5 ratio.

4.1.3. Ethyl 2-[(4*R*,6*R*)-2-phenyl-6-(4-phenylbutyl)-1,3-dioxan-4yl]acetate 3. To a solution of alcohol **4** (0.5 g, 1.81 mmol) in THF (30 mL) at 0 °C was added distilled benzaldehyde (0.22 mL, 1.99 mmol), followed by *t*-BuOK (0.02 g, 0.19 mmol). The yellow solution was stirred for 15 min at 0 °C. The addition of benzaldehyde/*t*-BuOK was repeated twice and allowed to warm to room temperature after which the reaction was quenched with of pH 7 phosphate buffer (15 mL). The layers were separated, and the aqueous layer was extracted with ether (3×15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo and purified by column chromatography (silica gel, EtOAc–hexane, 1:48) to obtain **3** (0.39 g, 57%) as a colorless syrup. $[\alpha]_D^{25} = -3.6$ (c 0.76, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.37 (m, 2H), 7.34–7.20 (m, 5H), 7.15–7.11 (m, 3H), 5.50 (s, 1H), 4.30–4.20 (m, 1H), 4.13 (q, 2H, J 14.3, 6.7 Hz), 3.86–3.77 (m, 1H), 2.68 (dd, 1H, J 15.8, 6.9 Hz), 2.61 (t, 2H, J 7.5 Hz), 2.47 (dd, 1H, J 15.8, 6.0 Hz), 1.70–1.34 (m, 8H), 1.26 (t, 3H, J 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 142.7, 138.7, 128.4, 128.3, 128.1, 128.0, 125.9, 125.5, 100.4, 76.4, 73.1, 60.4, 40.1, 36.4, 35.7, 35.6, 31.3, 24.6, 14.1; IR (neat): 2857, 1735, 1268 cm^{-1}; LCMS; 405 $[M+Na]^+$. Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.35; H, 7.90.

4.1.4. Methyl (*Z*)-4-[(4*S*,6*R*)-2-phenyl-6-(4-phenylbutyl)-1,3-dioxan-4-yl]-2-butenoate 2. Ester **3** (0.1 g, 0.26 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to −78 °C. To the solution was added a 2 M solution of DIBAL–H in hexane (0.08 mL, 0.17 mmol). After 30 min the reaction was quenched with methanol and potassium sodium tartrate (1 mL, 1:1). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2×2 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give the corresponding aldehyde, which was used directly for further reaction.

To a stirred solution of O,O^I bis-(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (0.1 mL, 0.44 mmol), 18-crown-6 (0.46 g, 1.53 mmol), in dry THF (1 mL) at −78 °C was added potassium (bistrimethylsilyl)amide (0.66 mL, 0.43 mmol, 20% solution in toluene) and stirred for 30 min at −78 °C. To the reaction mixture, the aldehyde (0.1 g, 0.29 mmol) dissolved in dry THF (1 mL) was added and stirred for 30 min at the same temperature. The reaction mixture was quenched with satd NH_4Cl (2 mL) and stirred at room temperature for 10 min. The layers were separated and the aqueous layer extracted with EtOAc (2×3 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo, and the residue purified over silica gel (EtOAc–hexane, 1:99) to afford the unsaturated ester **2** (0.09 g, 76%) as a light yellow syrup. $[\alpha]_D^{25} = -11.65$ (c 0.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.40 (m, 2H), 7.35–7.19 (m, 5H), 7.13–7.10 (m, 3H), 6.50–6.40 (m, 1H), 5.85 (d, 1H, J 11.3 Hz), 5.44 (s, 1H), 3.96–3.86 (m, 1H), 3.82–3.71 (m, 1H), 3.69 (s, 3H), 3.12–3.03 (m, 1H), 2.89–2.78 (m, 1H), 2.61 (t, 2H, J 7.5 Hz), 1.70–1.38 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 146.1, 142.0, 138.7, 133.3, 129.7, 128.7, 128.6, 126.0, 125.5, 121.0, 100.6, 76.0, 74.9, 51.8, 36.7, 35.8, 35.7, 35.2, 31.4, 24.8; IR (neat): 3028, 2856, 1720, 1647, 1254 cm^{-1}; LCMS; 417 $[M+Na]^+$. Anal. Calcd for $C_{25}H_{30}O_4$: C, 76.11; H, 7.66. Found: C, 76.12; H, 7.63.

4.1.5. (6*S*)-5,6-Dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one. Ester **2** (0.2 g, 0.49 mmol) was added to acetic acid (3 mL, 80% aq AcOH) and stirred for 3 h at 60 °C after which the acetic acid was removed under reduced pressure. To this was added benzene (2 mL) and PTSA (0.02 g, cat) and stirred for 4 h. To the reaction mixture was quenched with aq $NaHCO_3$ (1 mL) and the aqueous layer was extracted with EtOAc (2×1 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo and purified by column chromatography (EtOAc–hexane, 1:1) to obtain **1** (0.08 g, 61%) as a pale yellow solid. Mp 33–35 °C; $[\alpha]_D^{25} = -66.5$ (c 0.81, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25–7.08 (m, 5H), 6.89–6.81 (m, 1H), 6.00 (d, 1H, J 9.4 Hz), 4.70–4.65 (m, 1H), 3.92–3.80 (m, 1H), 3.02–2.95 (br s, 1H), 2.61 (t, 2H, J 7.3 Hz), 2.42–2.34 (m, 2H), 2.10–1.60 (m, 4H), 1.60–1.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 145.2, 142.3, 128.3, 128.2, 125.6, 121.1, 76.5, 68.5, 41.7, 37.3, 35.6, 31.2, 29.2, 24.8; IR (neat): 3441, 2930, 2856, 1715, 1254 cm^{-1}; LCMS; 297 $[M+Na]^+$. Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.39; H, 8.02.

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