Research Paper www.ijcps.com

International Journal of
Chemical and Pharmaceutical Sciences
2013, June., Vol. 4 (2)

ISSN: 0976-9390
IJCPS

Stereoselective Total Synthesis of 6*R*-[5*R*,6*S*-(diacetyloxy)-1*S*,2*R*-(dihydroxy)-3*E*-heptenyl]-5,6-dihydro-2*H*-pyran-2-one and (1*R*,2*R*,5*R*,6*S*,*E*)-1-((*R*)-6-oxo-3,6-dihydro-2H-pyran-2-yl)hept-3-ene-1,2,5,6-tetrayl tetraacetate

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ABSTRACT

An efficient stereoselective total synthesis of α-pyrone: 6*R*-[5*R*,6*S*-(diacetyloxy)-1*S*,2*R*-(dihydroxy)-3*E* heptenyl]-5,6-dihydro-2*H*-pyran-2-one and ((1*R*,2*R*,5*R*,6*S*,*E*)-1-((*R*)-6-oxo-3,6-dihydro-2H-pyran-2-yl)hept-3-ene-1,2,5,6-tetrayl tetraacetate have been described starting from commercially available D-(−)-diethyl tartarate and (*S*) -ethyl lactate. Key reactions involved in the synthesis are Horner-Wadsworth-Emmons olefination with subsequent allylation and ring-closing metathesis (RCM).

Keywords: α- Pyrones, HWE olefination, Allylation, RCM.

1. INTRODUCTION

α-Pyrone containing natural products continues to attract significant attention both from chemists and biologists towards their synthesis and their significant biological activities [1-8]. The wide range of biological properties include anti microbial [9-10], anti inflammatory [11] and anti fungal activities as well as cytotoxicity against human tumor cells. Few examples of this class of molecules include (+)-synargentolide A (2), [12] hyptolide (3), [13] anamarine (4), [14] spicigerolide (5), [15] synrotolide (6), [16] that are isolated from *Syncolostemon* and *Hyptis* species (Fig. 1). In continuation of the investigation towards isolation and structural elucidation of bioactive constituents from medicinal plants of Lamiaceae, Pereda-Miranda *et al* have isolated a novel 6-substituted α-pyrone namely 6*R*-[5*R*,6*S*-(diacetyloxy)-1*S*,2*R*-(dihydroxy)-3*E*-heptenyl]-5,6-dihydro-2*H*-pyran-2-one(1)[17] and (1*R*,2*R*,5*R*,6*S*,*E*)-1-((*R*)-6-oxo-3,6-di-hydro-2H-pyran-2-yl)hept-3-ene-1,2,5,6 tetrayl tetraacetate (1a) from the leaves extract of *Hyptis oblongifolia* that was found to display moderate activity in the brine shrimp larvicidal assay.

The retro synthetic analysis is outlined in the scheme 1. It was envisioned that the target molecule 1a could be achieved from lactone 7 through acylation and acetonide deprotection. The compound 7 can be obtained from ring closing metathesis of the acryloyl ester derived from 8. Compound 8 is accessible from 9 via selective deprotection of 1° TBS-ether, oxidation and allylation. Compound 9 could be constructed by sequence of reactions from enone 10, which in turn could be obtained from D-(-)- diethyl tartarate and (*S*) -ethyl lactate.

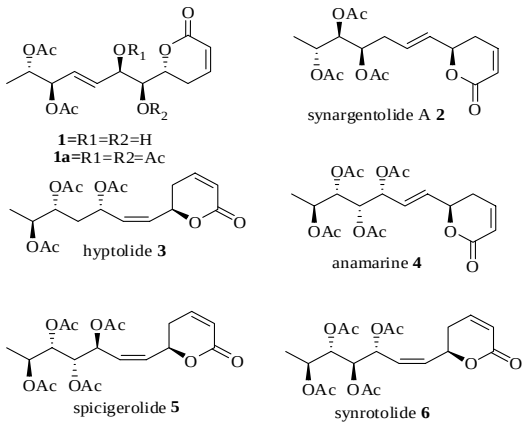
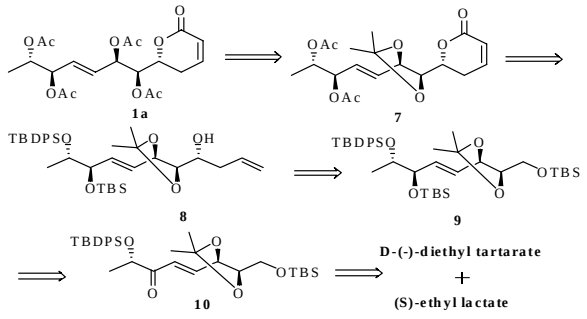
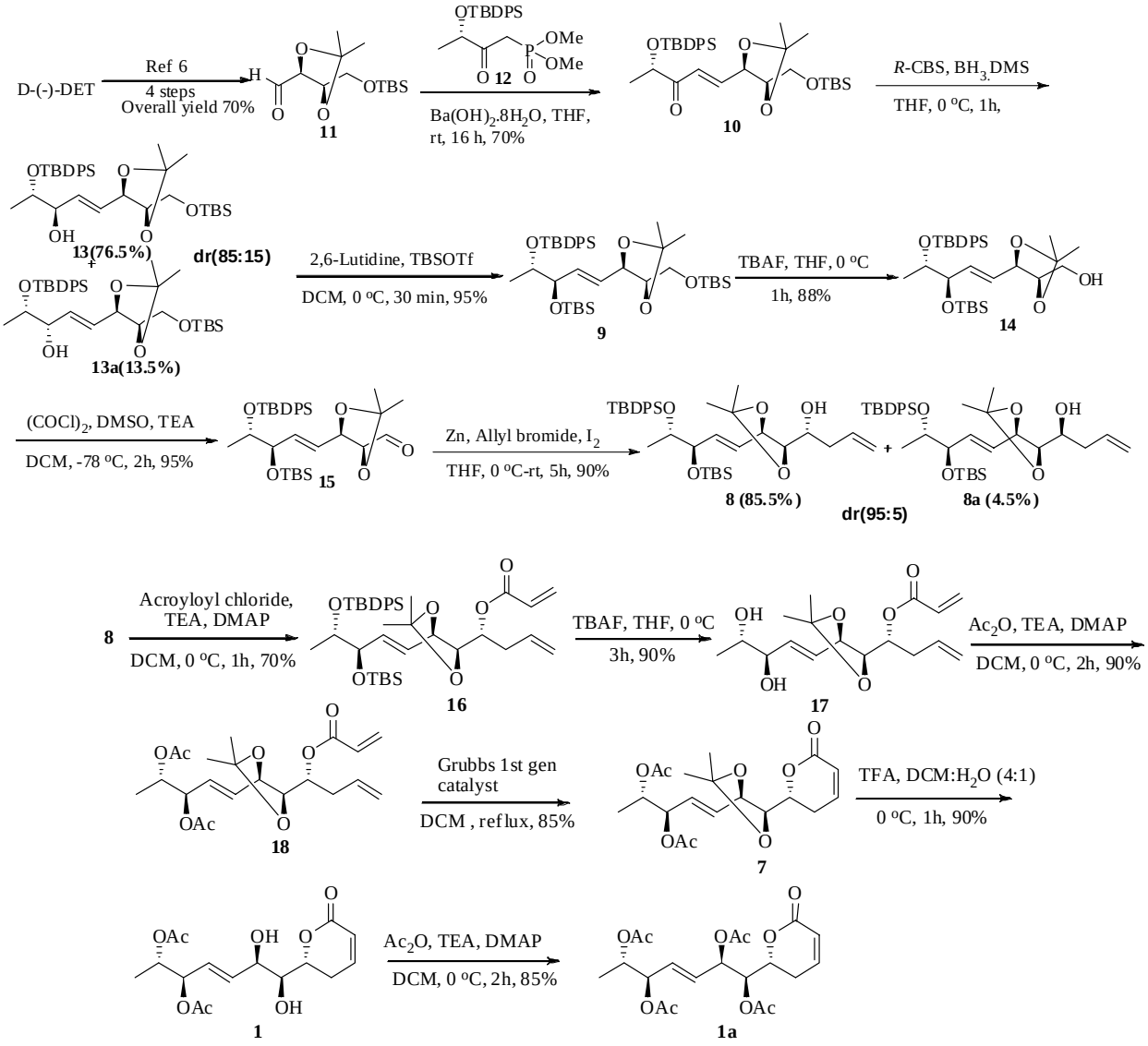


Figure - 1: α, β-unsaturated δ-lactone natural products.



Scheme -1: Retro synthetic analysis of compounds **1** and 1a



Scheme - 2

The synthesis commenced with the available aldehyde 11 synthesized from commercially available D-(–)-diethyl tartarate, [18-28] which was condensed with the β-ketophosphonate 12 through Horner-Wadsworth-Emmons olefination[29] to get 10. Ketophosphonate 12 in turn was obtained from (*S*)-ethyl lactate in two steps. [30,31] Enone 10 was reduced to allylic alcohol 13 and 13a (85:15) by using *R*-CBS[32,33] and the major product 13 was protected as the corresponding TBS ether 9. Selective deprotection of primary TBS ether with TBAF gave alcohol 14, which was subjected to oxidation under Swern conditions to give the aldehyde 15. Compound 15 upon allylation with allyl bromide in presence of zinc provided the easily separable homoallylic alcohol 8 along with 8a in 95:5(scheme2). [34]

Acryloylation of 8 furnished the ester 16. Cleavage of the disilylether 16 upon treatment with TBAF at 0 °C furnished diol 17, which was further acylated under standard condition to afford 18. The compound 18 on ring-closing metathesis (RCM) reaction with Grubbs' first generation catalyst afforded the lactone 7 in 85% yield as a single isomer. [35-38] Exposure of 7 to TFA/H_2O (4:1) in DCM afforded the target compound 1in 90% yield, which was acylated with using acetic anhydride and TEA and DMAP afforded 1a (scheme 3) The ^1H NMR and ^{13}C NMR spectral data and specific rotation of our synthetic compound were found to be in good agreement with isolated compounds[11] 1 and 1a in the literature.

2. Experimental Section

2.1. General

Air and/or moisture sensitive reactions were carried out in anhydrous solvents under argon atmosphere in an oven or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, toluene and diethyl ether from Na and benzophenone; CH_2Cl_2, DMSO from CaH_2. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120 mesh). Specific optical rotations [α]D are given in 10^{-1} degcm^{2}g^{-1}. Infrared spectra were recorded in $CHCl_3$/neat (as mentioned) and reported in wave number (cm^{-1}). ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, td = triplet of double, q = quartet, m = multiplet, br = broad.

2.2. (*S*, *E*)-1-((4*R*, 5*R*)-5-((*tert*-Butyldimethylsilyloxy) methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(*tert*-butyl diphenylsilyloxy) pent-1-en-3-one(10).

To a slurry of anhydrous $Ba(OH)_2$ (2.06 g, 6.55 mmol) in THF (5 mL) was added phosphonate 12 (2.37 g, 5.47 mmol) and the mixture stirred at rt for 45 min . A solution of aldehyde 11 (1.0 g, 3.64 mmol) in THF (54 mL) and H_2O (0.5 mL) was then added via cannula and the reaction mixture was stirred for a further 16 hr. The reaction mixture was quenched with sat. NH_4Cl (10mL), extracted with ethyl acetate (10mL x 3), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of Column chromatography (EtOAc: hexane 1:9) afforded enone 10 (1.50g, 70%) as a colorless oil .

$[\alpha]_D^{25}$ = -42.3 (*c* 1.3, $CHCl_3$); IR (neat): 2955, 2930, 1700, 1466, 1254, 1108, 836, 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69-7.56 (m, 4H), 7.45-7.30 (m, 6H), 7.02 (dd, 1H, *J* = 15.1 Hz), 6.91 (dd, 1H, *J* = 15.1 Hz), 4.60-4.54 (m, 1H), 4.28 (q, 1H, *J* = 14.3, 6.8 Hz), 3.81-3.70 (m, 3H), 1.44 (s, 3H), 1.40 (s, 3H), 1.22 (d, 3H, *J* = 6.8 Hz), 1.09 (s, 9H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75MHz, $CDCl_3$): δ = 201.7, 143.9, 135.7, 134.7, 129.8, 127.6, 123.3, 109.8, 80.9, 77.8, 70.5, 62.5, 29.7, 26.8, 25.8, 21.1, -5.3, -5.4; HRMS (ESI): calcd. for $C_{33}H_{50}O_5NaSi_2$ [M+Na]$^+$ 605.1512; found 605.1515.

2.3. (3*R*,4*S*,*E*)-1-((4*R*, 5*R*)-5-((*tert*-Butyl dimethylsilyloxy) methyl)-2, 2-dimethyl-1,3-dioxolan-4-yl)-4-(*tert*-butyl diphenylsilyloxy)pent-1-en-3-ol) (13).

1 M solution of (*R*)-CBS in toluene (0.34 mL, 0.34 mmol) and 1M solution of $BH_3.S(CH_3)_2$inTHF (1.71 mL, 1.71 mmol) was stirred at 0 °C for 30 min. A solution of ketone 10 (1.00 g, 1.71 mmol) in THF (10mL) was added to reaction mixture at -78 °C for 1 h. The reaction mixture was quenched with sat. NH_4Cl and extracted with EtOAc (3 x 5mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was purified by column chromatography (EtOAc: hexane 2:8) afforded enal 13 (0.764g, 76.5%) as a colorless oil.

$[\alpha]_D^{25}$ = -48.9 (*c* 1.4, $CHCl_3$); IR (neat): 3472, 2930, 2858, 1465, 1099,774 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71-7.62 (m, 4H), 7.44-7.32 (m, 6H), 5.65 (dd, 1H, *J* = 15.6, 7.9 Hz), 5.21 (dd, 1H, *J* = 15.6, 6.8 Hz), 4.11 (t, 1H, *J* = 7.1 Hz), 3.96 (t, 1H, *J* = 7.1 Hz), 3.79-3.64 (m, 2H), 3.36 (ddd, 1H, *J* = 7.3, 3.5 Hz), 3.26 (ddd, 1H, *J* = 11.1, 3.7 Hz), 2.38 (br s, 1H), 1.40 (s, 6H), 1.07 (s, 9H), 0.99 (d, 3H, *J* = 6.2 Hz), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ = 135.7, 135.7, 133.8, 133.1, 132.8, 129.7, 129.6, 127.6, 127.4, 108.8, 81.4, 77.7, 76.0, 72.7, 61.9, 26.9, 26.8, 25.8, 19.2, 19.2, 18.2, -5.3, -5.4; HRMS (ESI): calcd. for $C_{33}H_{52}O_5NaSi_2$ [M + Na]$^+$ 607.3245; found 607.3254.

2.4. (5*R*,6*S*)-5-((*E*)-2-((4*R*,5*R*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)vinyl)-2,2,3,3,6,9,9-heptamethyl-8,8-diphenyl-4,7-dioxa-3,8-disiladecane (9).

To a stirred solution of alcohol 13 (1.0 g, 1.71 mmol) in DCM (10 mL) was added 2,6-lutidine (0.40 mL, 3.42 mmol) and TBSOTf (0.61 mL, 2.56 mmol) at 0 °C. After 30 min quench with $NaHCO_3$ aq. Solution (5 mL) and extracted with DCM (3 x 5 mL). The combined organic layer was washed with brine (10 mL) and concentrated under reduced pressure. The residue was purified on column chromatography (EtOAc: hexane 5:95) afforded TBS ether 9 (1.13 g, 95%) as a colorless oil.

$[\alpha]_D^{25}$ = -18.5 (*c* 1.0, $CHCl_3$); IR (neat): 2956, 2932, 2859, 1469, 1253, 837, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72-7.62 (m, 4H), 7.43-7.32 (m, 6H), 5.59 (dd, 1H, *J* = 15.8, 6.8 Hz), 5.27 (dd, 1H, *J* = 15.8, 6.0 Hz), 4.34 (t, 1H, *J* = 7.5 Hz), 4.12 (d, 1H, *J* = 7.5 Hz), 3.80-3.69 (m, 2H), 3.63 (dd, 1H, *J* = 7.5, 3.7 Hz), 3.46 (dd, 1H, *J* = 11.3, 3.7 Hz), 1.36 (s, 3H), 1.31 (s, 3H), 1.05 (s, 9H), 0.92 (d, 3H, *J* = 6.0 Hz), 0.89 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ = 136.0, 135.9, 135.8, 129.4, 128.5, 127.4, 127.3, 108.9, 81.3, 78.9, 77.9, 72.6, 62.3, 27.0, 26.9, 25.9, 19.3, 18.3, 18.2, -4.5, -4.6, -5.3, -5.4; HRMS (ESI): calcd. for $C_{39}H_{66}O_5NaSi_3$ [M + Na]$^+$ 721.4110; found 721.4109;

2.5. ((4*R*,5*R*)-5-((3*R*,4*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-

butyldiphenylsilyloxy)pent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (14)

To stirred solution of silylether 9 (3.0 g, 4.29 mmol) in THF (30 mL), was added TBAF (5.1 mL, 5.15 mmol) at 0 °C. The mixture was stirred for 3 h for rt and quenched with water (10 mL). The resulting mixture was diluted with EtOAc (3 x 8 mL). The organic phase was successively washed with water (15 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography using (EtOAc:hexane 2:8) afforded alcohol 14 (2.22 g, 88%) as a colorless oil.

$[\alpha]_D^{25}$ = -10.0 (*c* 0.9, $CHCl_3$); IR (neat): 2955, 2931, 2858, 1252, 1108, 835, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.71-7.61 (m, 4H), 7.43-7.32 (m, 6H), 5.57 (dd, 1H, *J* = 15.6, 8.3 Hz), 5.23 (dd, 1H, *J* = 15.6, 7.3 Hz), 4.29 (t, 1H, *J* = 7.9 Hz), 4.10 (d, 1H, *J* = 7.3 Hz), 3.83-3.73 (m, 2H), 3.54 (dd, 1H, *J* = 11.8, 3.9 Hz), 3.35 (m, 1H), 1.37 (s, 3H), 1.31 (s, 3H), 1.10-1.02 (m, 12H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.0, 135.9, 134.0, 129.4, 127.4, 127.3, 109.1, 81.2, 78.8, 77.3, 73.6, 60.8, 27.0, 26.9, 26.8, 25.8, 19.3, 18.5, 18.1, -4.5, -4.6; HRMS (ESI): calcd. for $C_{33}H_{52}O_5NaSi_2$ $[M + Na]^+$ 607.3247; found 607.3241.

2.6. (*R*)-1-((4*R*,5*R*)-5-((3*R*,4*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldiphenylsilyloxy)pent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (8)

To pre–cooled (-78 °C) DMSO (1.78 mL, 34.2 mmol) in DCM (15 mL) and oxalyl chloride (1.49 mL, 17.1 mmol) was added at same temperature. A solution of the alcohol 14 (5.0 g, 8.56 mmol) in DCM (30 mL) was introduced via syringe into the flask and stirred 1 h at -78 °C. Triethyl amine (7.20 mL, 51.3 mmol) was added to reaction mixture and stir 15 min at same temperature. The reaction mixture quench with water and extracted with DCM (3 x 10 mL), combined organic layers were washed with brine (8 mL) and dried over Na_2SO_4. Evaporation of solvent gave the crude residue, which was purified by column chromatography using ((EtOAc:hexane 1:9) afforded aldehyde 15 (4.732 g, 95%) as a colorless oil.

To a solution of aldehyde 15 (4.732 g, 8.1mmol), zinc (1.59 g, 24.3 mmol) and catalytic amount of iodine (50 mg) were added in anhydrous THF (70 mL). The mixture was stirred for 30 min at 0 °C, and then allyl bromide (1.41 mL, 16.2 mmol) was added drop wise for a period of 15 min. After 5 h of stirring at room temperature the reaction mixture was quenched with saturated NH_4Cl solution, filtered through a small pad of celite and the residue was washed with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure, which gave the diastereomeric mixture of allylalcohols (95:5) ratio. The crude diastereomeric mixture was purified by silica gel column chromatography using hexane/ethyl acetate (9:1) as eluent to afford allylic alcohol 8 (4.48 g, 85.5%).

$[\alpha]_D^{25}$ = -48.3 (*c* 0.6, $CHCl_3$); IR (neat): 3472, 2926, 2855, 1463, 1105, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.71-7.62 (m, 4H), 7.43-7.31 (m, 6H), 5.86-5.72 (m, 1H), 5.60 (dd, 1H, *J* = 15.3, 6.4 Hz), 5.29 (dd, 1H, *J* = 15.3, 5.6 Hz), 5.17-5.07 (m, 2H), 4.28 (t, 1H, *J* = 6.4 Hz), 4.10-4.00 (m, 2H), 3.87-3.80 (m, 1H), 3.72-3.61(m, 1H), 3.35 (dd, 1H, *J* = 12.0, 4.0 Hz), 2.29-2.12 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H), 1.06 (s, 9H), 0.94 (d, 3H, *J* = 6.4 Hz), 0.89 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75MHz, $CDCl_3$): δ = 136.0, 136.0, 135.9, 134.7, 134.3, 134.3, 129.4, 127.4, 118.0, 108.8, 82.9, 79.0, 77.2, 73.7, 70.4, 37.2, 27.0, 26.9, 25.8, 19.4, 18.2, -4.5, -4.6; HRMS (ESI): calcd. for $C_{36}H_{56}O_5NaSi_2$ $[M + Na]^+$ 647.3558; found 647.3566.

2.7. (*R*)-1-((4*R*,5*R*)-5-((3*R*,4*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldiphenylsilyloxy)pent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-enyl acrylate (16)

To a solution of the alcohol 8 (2.5 g, 4.0 mmol), in DCM (25 mL) at 0 °C were added triethyl amine (0.79 mL, 6.00 mmol) and followed by freshly distilled acryloyl chloride (0.47 mL, 6.0 mmol) and the mixture was stirred at 0 °C for 5 min. To the reaction mixture at 0 °C was added catalytic amount of DMAP and stirred for 1 hour at room temperature. The reaction mixture was quenched with water and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatography of the crude product using hexane: EtOAc (95:5) as an eluent afford the acryloylated compound 16 (1.90 g, 70%) as a colorless liquid.

$[\alpha]_D^{25}$ = -6.8 (*c* 3.0, $CHCl_3$); IR (neat): 2957, 2930, 2858, 1730, 1255, 1187, 1109, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.73-7.64 (m, 4H), 7.45-7.32 (m, 6H), 6.36 (t, 1H, *J* = 18.4 Hz) , 6.04 (ddd, 1H, *J* = 17.3, 10.1 Hz), 5.86-5.69 (m, 2H), 5.56 (dd, 1H, *J* = 15.4, 6.7 Hz), 5.26 (dd, 1H, *J* = 15.4, 5.6 Hz), 5.11-5.03 (m, 2H), 4.22 (t, 1H, *J* = 5.6 Hz), 4.10-4.06 (m, 1H), 3.79-3.72 (m, 2H), 3.52 (d, 1H, *J* = 6.0 Hz), 2.40-2.25 (m, 2H), 1.38 (s, 3H), 1.32 (s, 3H), 1.07 (s, 9H), 0.93 (d, 3H, *J* = 6.7 Hz), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75MHz, $CDCl_3$): δ =

165.2, 136.0, 135.9, 133.9, 132.4, 131.1, 129.4, 128.1, 127.3, 118.1, 109.3, 81.0, 78.6, 73.5, 72.5, 68.1, 35.5, 27.0, 26.8, 26.0, 19.4, 18.2, 18.1, -4.5, -4.6; HRMS (ESI): calcd. for $C_{39}H_{58}O_6NaSi_2$ [M + Na]$^+$ 701.3664; found 701.3672.

2.8. (*R*)-1-((4*R*,5*R*)-5-((3*R*,4*S*,*E*)-3,4-Dihydroxypent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-enyl acrylate (17)

To stirred solution of silylether 16 (0.85 g, 1.25 mmol) in THF (10 mL), was added TBAF (3.75 mL, 3.75mmol) at 0 ^{o}C. The mixture was stirred for 2 h for rt and quenched with water (5 mL). The resulting mixture was diluted with EtOAc (3 x 5 mL). The organic phase was successively washed with water (2 x 2mL) and brine (2mL) dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography using (EtOAc: hexane 2:8) afforded diol 17 (0.367 g, 91%) as a colorless oil.

$[\alpha]_D^{25}$ = +11.2 (*c* 0.8, $CHCl_3$); IR (neat): 3434, 2926, 1725, 1406, 1189, 1061, 727 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.44 (d, 1H, *J* = 17.3 Hz), 6.18-6.07 (m, 1H), 5.85 (dd, 1H, *J* = 15.4, 5.2 Hz), 5.80-5.69 (m, 2H), 5.20-5.05 (m, 3H), 4.39 (t, 1H, *J* = 7.5 Hz), 4.18 (t, 1H, *J* = 7.1 Hz), 4.13-4.06 (m, 1H), 3.88-3.80 (m, 2H), 2.53-2.38 (m, 2H), 1.42 (s, 3H), 1.40 (s, 3H), 1.14 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (75MHz, $CDCl_3$): δ = 165.4, 132.8, 131.5, 130.5, 129.2, 128.1, 118.3, 109.6, 80.8, 78.8, 75.4, 72.4, 69.9, 35.3, 26.9, 26.8, 17.7,; HRMS (ESI): calcd. for $C_{17}H_{26}O_6Na$ [M + Na]$^+$ 349.1621; found 349.1623.

2.9. (2*S*,3*R*,*E*)-5-((4*R*,5*R*)-5-((*R*)-1-(acryloyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-ene-2,3-diyl diacetate (18)

Anhydrous Et_3N (0.34 mL, 2.45 mmol), Ac_2O (0.12 mL, 1.37 mmol), DMAP (10mg) were added to a solution of alcohol 17 (0.20g, 0.61 mmol) in anhydrous DCM (10 mL) under a nitrogen atmosphere at room temperature. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, the mixture was purified by silica gel column chromatography using petroleum ether: EtOAc (9:1) as eluent to furnish 18 (0.226 g, 90 %) as a colorless oil.

$[\alpha]_D^{25}$ = -5.3 (*c* 1.7, $CHCl_3$); IR (neat): 3781, 2919, 1733, 1370, 1222, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.42 (t, 1H, *J* = 17.6 Hz), 6.12 (ddd, 1H, *J* = 17.3, 10.5 Hz), 5.89-5.84 (dd, 1H, *J* = 10.5, 6.0 Hz), 5.78-5.72 (m, 3H), 5.43-5.38 (m, 1H),5.18-4.98 (m, 4H), 4.37 (dd, 1H, *J* = 7.1, 4.9 Hz), 3.81 (t, 1H, *J* = 7.1 Hz), 2.54-2.43 (m, 2H), 2.07 (s, 3H), 2.02 (s, 3H), 1.40 (s, 3H), 1.39 (s,3H), 1.18 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (75MHz, $CDCl_3$): δ = 170.3, 169.8, 165.2, 132.7, 132.2, 131.5, 128.0, 127.7, 118.3, 109.7, 80.7, 78.6, 74.0, 72.6, 70.5, 35.6, 26.9, 26.8, 21.1, 21.0, 14.7; HRMS (ESI): calcd. for $C_{21}H_{30}O_8Na$ [M + Na]$^+$ 433.1832; found 433.1830.

2.10. (2*S*,3*R*,*E*)-5-((4*R*,5*R*)-2,2-Dimethyl-5-((*R*)-6-oxo-3,6-dihydro-2H-pyran-2-yl)-1,3-dioxolan-4-yl)pent-4-ene-2,3-diyl diacetate (7)

The compound 18 (50 mg, 0.12 mmol) was dissolved in anhydrous DCM (50 mL) at room temperature. The reaction mixture was degassed under an argon atmosphere during 20 min. Then to this solution was added Grubbs' Ist generation catalyst (10 mg, 10 mol %). Again the reaction mixture was degassed under an argon atmosphere during 10 min. The resultant mixture was refluxed under an argon atmosphere for 5 h. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The resulting crude residue was purified by silica gel column chromatography using hexane: EtOAc (6:4) as an eluent to give lactone 7 (0.039 g, 85%) as a colorless liquid.

$[\alpha]_D^{25}$ = +43.3 (*c* 1.7, $CHCl_3$); IR (neat): 2926, 1735, 1453, 1373, 1230, 1065, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.91(dt, 1H, *J* = 9.6, 3.6 Hz), 6.03 (dd, 1H, *J* = 9.9 Hz), 5.88-5.85 (m, 2H), 5.42-5.38 (m, 1H), 5.06 (dq, 1H, *J* = 7.1, 4.9 Hz), 4.51-4.41 (m, 2H), 3.88 (t, 1H, *J* = 7.1 Hz), 2.56-2.50 (m, 2H), 2.08 (s, 3H), 2.04 (s, 3H), 1.43 (s, 3H), 1.42 (s,3H), 1.21 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (75MHz, $CDCl_3$): δ = 170.3, 169.8, 162.6, 144.5, 132.3, 127.3, 121.3, 110.3, 80.8, 79.0, 77.9, 74.4, 70.6, 26.9, 26.9, 26.2, 21.1, 21.0, 15.0; HRMS (ESI): calcd. for $C_{19}H_{26}O_8Na$ [M + Na]$^+$ 405.1519; found 405.1518;

2.11. 6*R*-[5*R*,6*S*-(Diacetyloxy)-1*S*,2*R*-(dihydroxy)-3*E*-heptenyl]-5,6-dihydro-2*H*-pyran-2-one (1)

To a stirred solution of 7 (0.02 g, 0.052 mmol) in DCM (3 mL) was added a mixture of water (0.02 mL) and TFA (0.1 mL) at 0 ^{o}C and allowed to room temperature for 15 min. The reaction mixture was quenched with sat.$NaHCO_3$ (1 mL), extracted with DCM (3 x 2 mL), washed with brine , dried over Na_2SO_4 , and evaporated under reduced pressure. The resulting crude residue was purified by silica gel column chromatography using EtOAc/hexane (7:3) as an eluent to give 1 (0.016 g, 90%) colorless oil.

$[\alpha]_D^{25}$ =+25.3 (*c* 0.7, $CHCl_3$); IR (neat): 3461, 3030, 3013, 2928, 1738, 1435, 1230, 1049, 859 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.95 (ddd, 1H, *J* = 9.4, 5.3, 3.0 Hz), 6.01 (d, 1H, *J* = 9.7 Hz), 5.87 (dd, 1H, *J* = 15.8, 5.3 Hz), 5.79 (dd, 1H, *J* =

15.8, 6.7 Hz), 5.31 (dd, 1H, *J* = 6.4, 3.7 Hz) , 5.05 (qd, 1H, *J* = 6.4, 3.7 Hz), 4.54-4.49 (m, 1H), 4.48-4.46 (m, 1H), 3.70 (dd, 1H, *J* = 6.7, 2.5 Hz), 2.60-2.48 (m, 2H), 2.93 (bs, 1H), 2.81 (bs, 1H), 2.07 (s, 3H), 2.04 (s, 3H), 1.19 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (75MHz, $CDCl_3$): δ = 170.5, 170.3, 163.7, 145.8, 134.2, 126.7, 121.0, 76.9, 75.0, 74.3, 70.5, 69.6, 25.6, 21.1, 21.0, 15.1; HRMS (ESI): calcd. for $C_{16}H_{22}O_8Na$ $[M + Na]^+$ 365.1206; found 365.1211;

2.12. ((1*R*,2*R*,5*R*,6*S*,*E*)-1-((*R*)-6-oxo-3,6-dihydro-2H-pyran-2-yl)hept-3-ene-1,2,5,6-tetrayl tetraacetate (1a)

Anhydrous Et_3N (0.004 mL, 0.028 mmol), Ac_2O (0.002 mL, 0.028 mmol), DMAP (2mg) were added to a solution of alcohol 1 (0.008g, 0.023 mmol) in anhydrous DCM (3 mL) under a nitrogen atmosphere at room temperature. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, the mixture was purified by silica gel column chromatography using petroleum ether: EtOAc (1:1) as eluent to furnish 1a (0.008 g, 85 %) as a white solid .

$[\alpha]_D^{25}$ =+11.3 (*c* 0.3, $CHCl_3$); mp 105-107 ^oC; IR (neat): 3035, 3013, 2928, 1738, 1435, 1230, 859 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.87 (ddd, 1H, *J* = 9.9, 5.9, 2.9 Hz), 6.03 (dt, 1H, *J* = 9.9, 1.6 Hz), 5.77 (dd, 1H, *J* = 15.7, 6.5 Hz), 5.68 (dd, 1H, *J* = 15.6, 5.6 Hz), 5.62 (dd, 1H, *J* = 5.4, 4.4 Hz) ,5.35-5.23(m, 2H), 5.03 (qd, 1H, *J* = 6.4, 4.1 Hz), 4.54(dt, 1H, *J* = 6.5, 4.2 Hz), 2.55-2.44 (m, 1H), 2.39-2.31(m, 1H), 2.11 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.15 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (75MHz, $CDCl_3$): δ = 170.2, 169.7, 169.4, 169.2, 162.4, 144.2, 128.9, 128.8, 121.3, 74.5, 74.3, 72.6, 70.4, 70.0, 25.2, 21.0, 20.9, 20.8, 20.5, 15.4; HRMS (ESI): calcd. for $C_{20}H_{26}O_{10}Na$ $[M + Na]^+$ 449.1424; found 449.1421.

3. CONCLUSION

In conclusion, we have demonstrated an efficient stereo selective total synthesis of α-pyrone, 6*R*-[5*R*,6*S*-(diacetyloxy)-1*S*,2*R*-(dihydroxy)-3*E* heptenyl]-5,6-dihydro-2*H*-pyran-2-one and ((1*R*,2*R*,5*R*,6*S*,*E*)-1-((*R*)-6-oxo-3,6-dihydro-2H-pyran-2-yl)hept-3-ene-1,2,5,6-tetrayl tetraacetate with 11.0%, 9.6% overall yield in 15 and 16 steps respectively. Application of this strategy for synthesis of other analogues is currently under progress.

Acknowledgements

G.M.R and B.T thank CSIR, New Delhi, India for the award of fellowships

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