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Simple Stereoselective Synthesis of Unsaturated Lactone Intermediates and Their Conversion into Natural Dihydropyranones and Their Enantiomers[#]

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Abstract: The stereoselective synthesis of the unsaturated lactone intermediates, (*S*) - and (*R*)-2-(6-oxo-3, 6-dihydro-2*H*-pyran-2-yl) acetaldehydes has been accomplished from propane 1,3 diol employing Maruoka asymmetric allylation and ring closing metathesis reaction. The intermediates were converted into two natural dihydropyranones, 6 (*R*)-4-oxopent-2-enyl 5,6-dihydro-2*H*-pyran-2-one and (*R*)- rugulactone and their enantiomers through Wittig olefination.

Keywords: Lactone intermediates, Wittig olefination, maruoka asymmetric allylation, 6 -(*R*)-4-oxopent-2-enyl 5,6-dihydro-2*H*-pyran-2-one, (*R*)- rugulactone, enantiomer.

INTRODUCTION

The compounds containing 5,6-dihydro-2*H*-pyran-2-one unit have been isolated from plants and marine organisms [1]. These compounds are known to possess a broad range of biological activities including cytotoxic, antibacterial and antifungal properties [2]. They act as excellent Michael acceptors for nucleophilic amino acid residues of the natural receptor [3]. Due to interesting structural pattern and important biological activities these compounds are attractive target to the total synthesis [4].

As a part of our ongoing program [5] on the synthesis of naturally occurring bioactive compounds we realized to discover a simple synthesis of an intermediate **1** [(*S*)-2-(6-oxo-3,6-dihydro-2*H*-pyran-2-yl)acetaldehyde] which can be converted into different natural dihydropyranone derivatives such as dodoneine [6] (**2**), 6 (*R*)-[4-oxopent-2-enyl] 5,6-dihydro-2*H*-pyran-2-one [7] (**3**), (*R*)- rugulactone [8] (**4**), (-)-tarconanthus lactone [9] (**5**), and (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one [10] (**6**) and others (Fig. **1**). The enantiomer **1a** of the intermediate **1** can generate the enantiomers of these natural products. Here we report a simple synthesis of the intermediates **1** and **1a** and their conversion into naturally occurring dihydropyranones **3** and **4** and their enantiomeric analogs. Compound **3** was isolated [7] from *Piper reticulactum* while compound **4** from *Cryptocarya rugulosa* [8]. The latter inhibits constituents NF-κB activity in human lymphoma cell lines [11].

RESULTS AND DISCUSSION

Our retrosynthetic study (Scheme **1**) depicts that the compounds **1** and **1a** can be prepared from olefinic esters **7** and **7a** respectively which can be produced from propane 1,3 diol (**9**) via the allylic alcohols **8** (for **1**) and **8a** (for **1a**).

The synthesis of **1** was initiated with propane 1,3-diol (**9**) which was converted into monobenzyl ether **10** by using benzyl bromide and KOH [12] (Scheme **2**). The primary hydroxy group of **10** was oxidized with pyridinium chlorochromate (PCC) to the corresponding aldehyde which was converted [13] to the homoallyl alcohol **8** with a high enantioselectivity (*ee* 97%) through Maruoka allylation [14] using allyl (tributyl) tin and titanium complex (*S, S*-**1**). Compound **8** was esterified with acryloyl chloride in the presence of triethyl amine and catalytic amount of DMAP to give the acryloyl ester **7**. The ring closing metathesis [15] (RCM) of **7** was successfully accomplished by using Grubbs 1st generation catalyst to produce the unsaturated lactone **11**. The debenzylation of **11** was achieved [16] by treatment with titanium tetrachloride ($TiCl_4$) to furnish the alcohol **12**. This alcohol **12** was then oxidized with iodobenzoic acid (IBX) to form the corresponding aldehyde **1** which was directly used for further conversion into natural dihydropyranones.

The C-6 enantiomer **1a** of the intermediate **1** was also synthesized from the compound **10** prepared from propane 1,3-diol (**9**) (Scheme **2**). Oxidation of the compound **10** to the corresponding aldehyde was achieved using pyridinium chlorochromate (PCC) and the aldehyde was then converted [13] to the homoallyl alcohol **8a** with high enantioselectivity (*ee* 97%) through Maruoka allylation [14] using allyl (tributyl) tin and titanium complex (*R, R*-**1**). The subsequent conversion of this homoallylic alcohol **8a** into the intermediate **1a** was completed by following the same sequence of reaction as carried out above for conversion of the enantiomeric homoallylic alcohol **8** into the intermediate **1** (i.e., acrylation with acryloyl chloride to form **10a**, and ring closing metathesis [15] to produce **11a** followed by debenzylation [16] to give alcohol **12a** and finally oxidation to generate **1a**).

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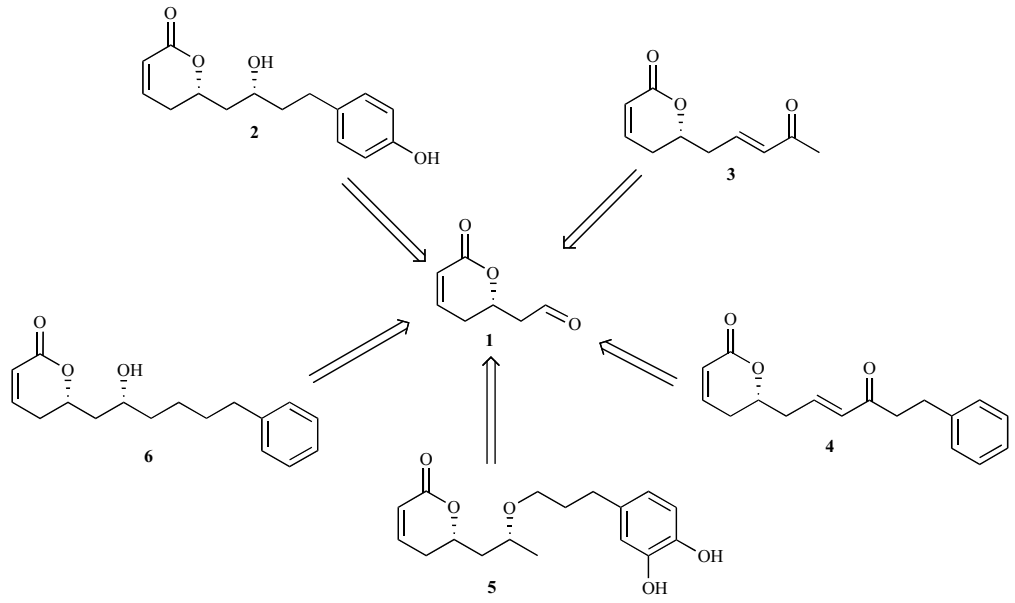
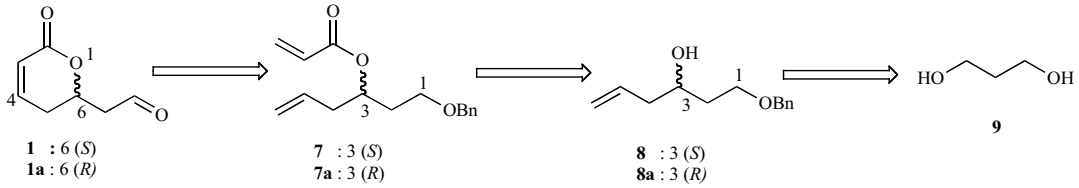


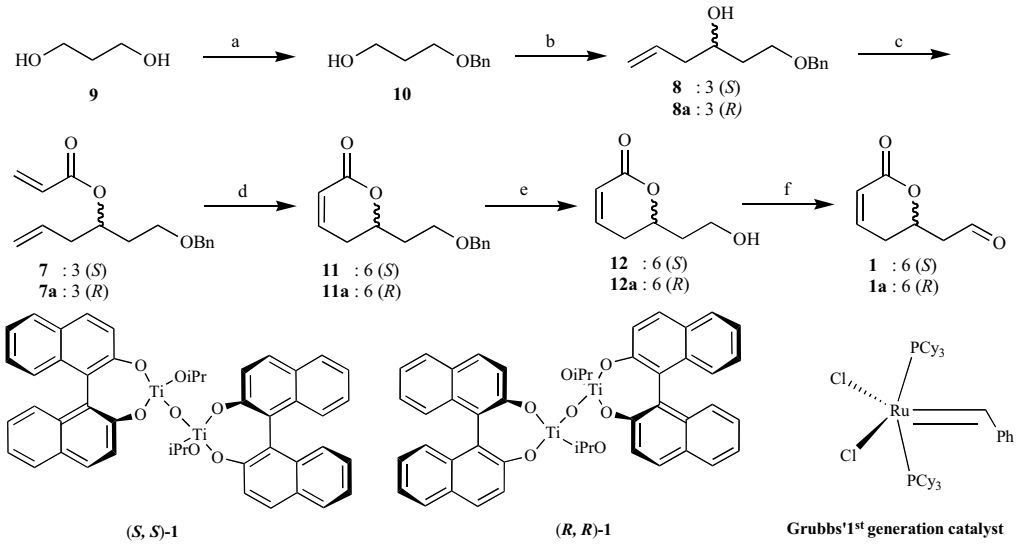
Fig. (1). Structures of naturally occurring dihydropyranones.



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

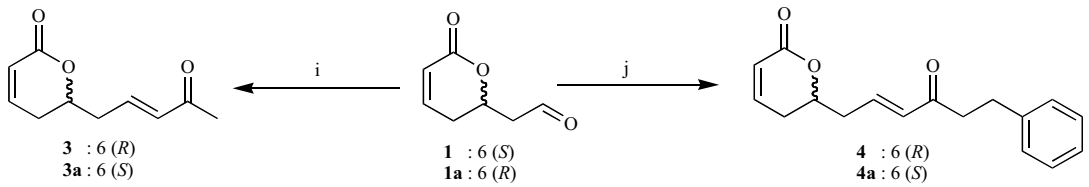
The intermediates **1** and **1a** were then separately subjected to Wittig olefination [17] with 1-triphenylphosphoranylidene -2-propanone (commercially available) to afford the natural dihydropyranones, 6- (*R*)-[4-oxopent-2-enyl] 5, 6-dihydro-2*H*-pyran-2-one (**3**) and its enantiomer (**3a**) respectively in good yields. This is the second report [18a] of the total synthesis of **3** (Scheme **3**). For preparation of the other natural product dihydropyranone derivative, rugulactone **4** and its enantiomer **4a** the 1-triphenylphosphoranylidene -4-phenylbutan-2-one (**17**) was synthesized from bromomethylbenzene (**13**) (Scheme **4**).

The latter was treated with acetyl acetone (**14**) using

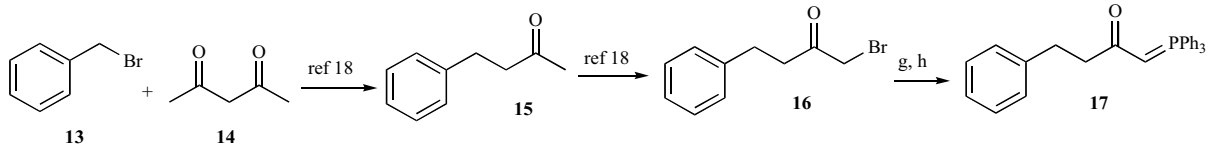


Scheme 2. Synthesis of **1** and **1a**.

Reagents, conditions and yields: a) BnBr, KOH r.t., 1 h, 80%, b) i. PCC, Celite, CH_2Cl_2, r.t., 1 h, 95 %, ii. [(*S,S*)-**1**, 10 mol %, for **8**], [(*R,R*)-**1**, 10 mol %, for **8a**], Bu_3SnCH_2-CH=CH_2, CH_2Cl_2, -15 °C to 0 °C, 15 h, 82 %, c) acryloyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C to r.t., 30 min 96%, d) Grubbs' 1st generation catalyst, CH_2Cl_2, 50 °C, 24 h, 85% e) $TiCl_4$, CH_2Cl_2, 0 °C to r.t., 1 h, 89%, f) IBX, DMSO, r.t., 5 h.



Scheme 3. Synthesis of **3**, **3a**, **4** and **4a**.
Reagents, conditions and yields: i) $CH_3COCH=PPh_3$, C_6H_6, reflux, 10 h, 80 %, j) $PhCH_2CH_2COCH=PPh_3$, C_6H_6, reflux, 14 h, 72 %.



Scheme 4. Synthesis of **17**.
Reagents, conditions and yields: g) PPh_3, benzene, reflux, 85% 24 h; h) 1 % NaOH, CH_2Cl_2, r.t., 1 h, 78%.

methanolic K_2CO_3 to afford the keto compound **15** which on bromination with bromine in MeOH produced bromo compound **16** [19]. The bromo compound **16** was subsequently treated with triphenylphosphine (PPh_3) to yield the required 1-triphenylphosphoranylidene -4-phenylbutan-2-one (**17**) [20]. The intermediate **1** and **1a** were then separately treated with the phosphorane **17** to yield rugulactone (**4**) (Scheme **3**) and its enantiomer (**4a**) respectively. The synthesis of rugulactone was reported earlier [13-18] but the present method constitutes an easy access to this molecule.

CONCLUSION

In conclusion, we have developed a simple stereoselective synthesis of two isomeric *α, β*-unsaturated *δ*-lactone intermediates and converted them into two naturally occurring dihydropyranones, 6- (*R*)-[4-oxopent-2-enyl] 5,6-dihydro-2*H*-pyran-2-one and (*R*)- rugulactone and their enantiomers. The present synthetic method can also be utilized for the preparation of several other related bioactive natural dihydropyranones.

EXPERIMENTAL

General Procedures

The spectra were recorded with the following instruments; IR: Perkin Elmer RX1 FT-IR spectrophotometers. NMR: Varian Gemini 200 MHz, Bruker 300 MHz (^{1}H) and 50 MHz (^{13}C) spectrometer; ESI-MS; VG-Autospec micromass. Optical rotations were recorded on Jasco Dip 360 digital polarimeter. The column chromatography was performed using silica gel (BDH 100-200 Mesh) and TLC with silica gel GF_{254} precoated plates.

3-(benzyloxy)propan-1-ol (10)

Propane 1,3-diol (**9**) (4.00 g, 52.63 mmol) and KOH pellets (3.03 g, 52.63 mmol) were stirred for 5 min. Benzyl bromide (4.50 g, 26.32 mmol) was added in one portion and the resulting mixture was stirred at room temperature for 1 h. After completion of the reaction as indicated by TLC, cold water (10 mL) was added in the reaction mixture and mixture was extracted with ethyl acetate (3 × 100 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by using column chromatography (ethyl acetate / hexane, 3: 7) to afford pure 3-(benzyloxy)propan-1-ol (**10**) (7.07 g, 80%) as a colorless liquid. IR: 3410, 1493, 1465, 1363, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.38-7.22 (5H, m), 4.48 (2H, s), 3.69 (2H, t, *J* = 7.0 Hz), 3.58 (2H, t, *J* = 7.0 Hz), 2.96 (1H, brs), 1.89-1.78 (2H, m); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.0, 128.0, 127.2, 72.8, 67.9, 59.9, 32.1; EIMS: m/z 167 $[M+H]^{+\cdot}$.

(*S*)-1-(benzyloxy)hex-5-en-3-ol (8)

A solution of compound **10** (3.00 g, 18.07 mmol) in DCM (40 mL) was added slowly to a suspension of celite (6.00 g) in DCM (30 mL) at room temperature. To this suspension pyridinium chlorochromate (PCC) (5.76 g, 26.76 mmol) was added at 0 °C and the reaction was kept at room temperature where the reaction was stirred for 1 h. Celite pad filtration followed by concentration of the filtrate provided a residue that was purified by column chromatography (1:9). The purified aldehyde (2.82 g, 95%) was directly subjected to allylation.

$Ti(O^iPr)_4$ (0.65 g, 2.29 mmol) was added to a solution of $TiCl_4$ (0.14 g, 0.76 mmol) in DCM (15 mL) at 0 °C under N_2 environment and the mixture was warmed to room temperature and stirred for 1.5 h. Silver (I) oxide (0.35 g, 1.52 mmol) was then added and the reaction was stirred for 6 h prohibiting direct light. Later DCM (40 mL) followed by (*S*)-BINOL (0.86 g, 3.05 mmol) were added to reaction mixture at room temperature and the reaction was allowed to stir for 2.5 h to give the chiral bis-Ti(IV) oxide (*S*, *S*)-**1**. The resulting complex was cooled to -15 °C to which aldehyde (2.50 g, 15.24 mmol) followed by allyltributyltin (6.58 g, 19.81 mmol) were added. The reaction was allowed to warm to 0 °C and was further stirred for 15 h. The reaction was quenched by adding saturated aqueous $NaHCO_3$ (50 mL) and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layer were separated and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (ethyl acetate / hexane, 1: 9) to afford pure (*S*)-1-(benzyloxy) hex-5-en-3-ol (**8**) (2.57 g, 82 %, *ee* 97%) as a colorless liquid. The optical rotation of the compound was

$[\alpha]_D^{32}$ = - 2.6 (c = 1.0, $CHCl_3$); IR: 3444, 1640, 1492, 1451, 1363, 1207 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.38-7.22 (5H, m), 5.79 (1H, m), 5.11-5.02 (2H, m), 4.50 (2H, s), 3.82 (1H, m), 3.73-3.54 (2H, m), 2.71 (1H, brs), 2.21 (2H, t, *J* = 7.0 Hz), 1.77-1.66 (2H, m); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.1, 135.0, 128.4, 127.9, 127.8, 118.0, 73.5, 70.5, 69.0, 42.2, 36.0; ESIMS: m/z 229 $[M+Na]^{+.}$.

(*R*)-1-(benzyloxy)hex-5-en-3-ol (8a)

A solution of compound **10** (3.00 g, 18.07 mmol) in DCM (40 mL) was added slowly to a suspension of celite (6.00 g) in DCM (30 mL) at room temperature. To this suspension pyridinium chlorochromate (PCC) (5.76 g, 26.76 mmol) was added at 0 °C and the reaction was kept at room temperature where the reaction was stirred for 1 h. Celite pad filtration followed by concentration of the filtrate provided a residue that was purified by column chromatography (1:9). The purified aldehyde (2.82 g, 95%) was directly subjected to allylation.

$Ti(O^iPr)_4$ (0.65 g, 2.29 mmol) was added to a solution of $TiCl_4$ (0.14 g, 0.76 mmol) in DCM (15 mL) at 0 °C under N_2 environment and the mixture was warmed to room temperature and stirred for 1.5 h. Silver (I) oxide (0.35 g, 1.52 mmol) was then added and the reaction was stirred for 6 h prohibiting direct light. Later DCM (40 mL) followed by (*R*)-BINOL (0.86 g, 3.05 mmol) were added to reaction mixture at room temperature and the reaction was allowed to stir for 2.5 h to give the chiral bis-Ti(IV) oxide (*R*, *R*)-**1**. The resulting complex was cooled to -15 °C to which aldehyde (2.50 g, 15.24 mmol) followed by allyltributyltin (6.58 g, 19.81 mmol) were added. The reaction was allowed to warm to 0 °C and was further stirred for 15 h. The reaction was quenched by adding saturated aqueous $NaHCO_3$ (50 mL) and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were separated and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (ethyl acetate / hexane, 1: 9) to afford pure (*R*)-1-(benzyloxy) hex-5-en-3-ol (**8a**) (2.57 g, 82 %, *ee* 97%) as a colorless liquid. The optical rotation of the compound was $[\alpha]_D^{32}$ = + 2.4 (c = 1.0, $CHCl_3$). The spectral data (proton NMR, carbon NMR and MS) of **8a** were found to be identical as those of **8**.

(*S*)-1-(benzyloxy)hex-5-en-3-yl acrylate (7)

Et_3N (1.96 g, 19.42 mmol) and DMAP (0.12 g, 0.97 mmol) were added slowly to a solution of compound **8** (2.00 g, 9.71 mmol) in DCM (20 mL) at 0 °C and the mixture was stirred for 10 min. Acryloyl chloride (1.05 g, 11.65 mmol) was added and the reaction was brought to room temperature and stirred for 3 h. After the completion of reaction, water (20 mL) was added and the mixture was extracted with DCM (3 × 30 mL). The organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the gummy mixture was purified by using column chromatography (ethyl acetate/hexane, 1:9) which afforded pure (*S*)-1-(benzyloxy) hex-5-en-3-yl acrylate (**7**) (2.42 g, 96%) as a yellow liquid. The optical rotation of compound was $[\alpha]_D^{32}$ = - 22.6 (c = 0.7, $CHCl_3$); IR: 1713, 1640, 1492, 1451, 1363, 1207 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.32-7.19 (5H, m), 6.38 (1H, d, *J* = 16.0 Hz), 6.03 (1H, m), 5.80-5.71 (2H, m), 5.15 (1H, m), 5.04 (1H, m), 4.42 (2H, s), 4.10 (1H, m), 3.51-3.42 (2H, m), 2.41-2.31 (2H, m), 1.92-1.80 (2H, m); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 185.0, 157.9, 152.8, 150.0, 148.1, 147.8, 146.8, 137.3, 92.2, 90.0, 85.9, 58.1, 53.0; ESIMS: m/z 261 $[M+H]^{+.}$.

(*R*)-1-(benzyloxy) hex-5-en-3-yl acrylate (7a)

Et_3N (1.96 g, 19.42 mmol) and DMAP (0.12 g, 0.97 mmol) were added slowly to a solution of compound **8a** (2.00 g, 9.71 mmol) in DCM (20 mL) at 0 °C and the mixture was stirred for 10 min. Acryloyl chloride (1.05 g, 11.65 mmol) was added and the reaction was brought to room temperature and stirred for 3 h. After the completion of reaction, water (20 mL) was added and the mixture was extracted with DCM (3 × 30 mL). The organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the gummy mixture was purified by using column chromatography (ethyl acetate/hexane, 1:9) which afforded pure (*R*)-1-(benzyloxy) hex-5-en-3-yl acrylate (**7a**) (2.42 g, 96%) as a yellow liquid. The optical rotation of compound was $[\alpha]_D^{32}$ = + 22.1 (c = 0.7, $CHCl_3$). The spectral data (proton NMR, carbon NMR and MS) of **7a** were found to be identical as those of **7**.

(*S*)-6-(2-(benzyloxy)ethyl)-5,6-dihydropyran-2-one (11)

A solution of compound **7** (2.00 g, 7.69 mmol) dissolved in DCM (150 mL) was added slowly to a solution of Grubbs' catalyst (1st generation, 5 mol %) in dry DCM (100 mL) and was stirred at 55 °C for 12 h. After completion of the reaction, the contents were cooled and the solvent was evaporated under reduced pressure. The resulting crude residue was subjected to column chromatography (ethyl acetate/hexane, 2:8) to give pure (*S*)-6-(2-(benzyloxy)ethyl)-5,6-dihydropyran-2-one (**11**) (1.47 g, 85%) as a colorless liquid. The optical rotation of compound was $[\alpha]_D^{32}$ = - 32.6 (c = 1.0, $CHCl_3$); IR: 1715, 1640, 1492, 1451, 1363, 1207 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.38-7.20 (5H, m), 6.83 (1H, m), 5.99 (1H, d, *J* = 9.0 Hz), 4.51 (1H, d, *J* = 12.0 Hz), 4.43 (1H, d, *J* = 12.0 Hz), 3.72-3.55 (2H, m), 2.60-2.27 (2H, m), 2.10-1.83 (2H, m); ^{13}C NMR ($CDCl_3$, 50 MHz): δ163.6, 144.3, 128.2, 127.5, 123.9, 121.8, 74.9, 72.8, 65.3, 35.2, 29.8; ESIMS: m/z 255 $[M+Na]^{+.}$.

(*R*)-6-(2-(benzyloxy)ethyl)-5,6-dihydropyran-2-one (11a)

A solution of compound **7a** (2.00 g, 7.69 mmol) dissolved in DCM (150 mL) was added slowly to a solution of Grubbs' catalyst (1st generation, 5 mol %) in dry DCM (100 mL) and was stirred at 55 °C for 12 h. After the completion of the reaction, the contents were cooled and the solvent was evaporated under reduced pressure. The resulting crude residue was subjected to column chromatography (ethyl acetate/hexane, 2:8) to give pure (*R*)-6-(2-(benzyloxy)ethyl)-5,6-dihydropyran-2-one (**11a**) (1.47 g, 85%) as a colorless liquid. The optical rotation of compound was $[\alpha]_D^{32}$ = + 31.9 (c = 1.0, $CHCl_3$). The spectral data (Proton NMR, Carbon

NMR and MS) of **11a** were found to be identical as those of **11**.

(*S*)-6-(2-hydroxyethyl)-5,6-dihydropyran-2-one (12)

$TiCl_4$ (1.63 mL, 8.62 mmol) was added to a solution of **11** (1.00 g, 4.31 mmol) in dry DCM (20 mL) under a N_2 atmosphere at 0 °C and the content was stirred for 1 h at room temperature. After completion, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL). The mixture was extracted into DCM (3 × 25 mL). The combined organic layer was separated, washed with water (10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. The mixture was concentrated under reduced pressure and the crude product was purified by using to column chromatography (ethyl acetate/hexane, 3:7) which afforded pure (*S*)-6-(2-hydroxyethyl)-5,6-dihydropyran-2-one (**12**) (0.54 g, 89%) as a colorless liquid. The optical rotation of compound was $[\alpha]_D^{32}$ = - 97.2 (c = 1.0, $CHCl_3$); IR: 3444, 1705, 1640, 1492, 1451, 1363, 1207 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.86 (1H, m), 5.98 (1H, d, *J* = 9.0 Hz), 4.65 (1H, m), 3.84 (1H, m), 3.75 (1H, m), 3.37 (1H, m) 2.43-2.31 (2H, m), 2.07-1.82 (2H, m); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 164.2, 144.9, 121.2, 75.0, 57.5, 36.2, 29.7; EIMS: m/z 143 $[M+H]^{+\cdot}$.

(*R*)-6-(2-hydroxyethyl)-5, 6-dihydropyran-2-one (12a)

$TiCl_4$ (1.63 mL, 8.62 mmol) was added to a solution of **11a** (1.00 g, 4.31 mmol) in dry DCM (20 mL) under a N_2 atmosphere at 0 °C and the content was stirred for 1 h at room temperature. After completion, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL). The mixture was extracted into DCM (3 × 25 mL). The combined organic layer was separated, washed with water (10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. The mixture was concentrated under reduced pressure and the crude product was purified by using column chromatography (ethyl acetate/hexane, 3:7) which afforded pure (*R*)-6-(2-hydroxyethyl)-5,6-dihydropyran-2-one (**12a**) (0.54 g, 89%) as a colorless liquid. The optical rotation of compound was $[\alpha]_D^{32}$ = + 98.0 (c = 1.0, $CHCl_3$). The spectral data (Proton NMR, Carbon NMR and MS) of **12a** were found to be identical as those of **12**.

1-triphenylphosphoranylidene-4-phenyl-butan-2-one (17)

The compound **16** (1.00 g, 4.40 mmol) was dissolved in benzene (20 mL) to which a solution of triphenyl phosphine (1.16 g, 4.40 mmol) in benzene (20 mL) was slowly added dropwise. The reaction content was stirred for 48 h at room temperature where by the oily precipitate became crystalline. This salt was filtered and washed with hexane. A solution of the salt in DCM (35 ml) was treated with 1 % NaOH (35 mL) to yield of 1-triphenylphosphoranylidene -4-phenylbutan-2-one (**17**) (1.40 g, 78%) as a white solid. mp 132-135 ^oC.

(*R*, *E*)-6-(4-oxopent-2-enyl)-5,6-dihydro-pyran-2-one (3)

A solution of compound **12** (0.40 g, 2.82 mmol) in dry DCM (5 mL) was slowly added to IBX (1.20 g, 2.82 mmol) dissolved in dry DMSO (2.5 mL) at room temperature and was stirred for 2 h. After completion ice cold water (2 mL) was added and the mixture was extracted with DCM (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by using column chromatography with mobile phase (ethyl acetate/hexane, 1:9). The purified aldehyde (0.32 g, 80%) was directly subjected to further reaction.

1-triphenylphosphoranylidene -2-propanone (0.34 g, 1.08 mmol) was added to a solution of aldehyde **1** (0.10 g, 0.72 mmol) in benzene (10 mL) and the reaction content was refluxed for 10 h. After cooling, the solvent was evaporated under reduced pressure and the crude product (0.42 g, yellow solid) was purified by using column chromatography (ethyl acetate/hexane 1:8) to give (*R, E*)-6-(4-oxopent-2-enyl)-5,6-dihydropyran-2-one (**3**) (0.10 g, 80%) as a colorless oil. The optical rotation of compound was $[\alpha]_D^{25}$ = - 40.5 (c = 1.2, $CHCl_3$); IR: 1718, 1670, 1635, 1433, 1363, 1247, 1096, 1025 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 6.94-6.71 (2H, m), 6.18 (1H, d, *J* = 16.0 Hz), 6.05 (1H, d, *J* = 9.0 Hz), 4.60 (1H, m), 2.75-2.60 (2H, m), 2.42-2.34 (2H, m), 2.24 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 198.6, 164.2, 144.9, 140.4, 134.8, 121.0, 75.8, 37.5, 29.6, 26.8; ESIMS: m/z 181 $[M+H]^{+\cdot}$.

(*S*, *E*)-6-(4-oxopent-2-enyl)-5,6-dihydro-pyran-2-one (3a)

A solution of compound **12a** (0.40 g, 2.82 mmol) in dry DCM (5 mL) was slowly added to IBX (1.20 g, 2.82 mmol) dissolved in dry DMSO (2.5 mL) at room temperature and was stirred for 2 h. After completion, ice cold water (2 mL) was added to the reaction and the mixture was extracted with DCM (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by using column chromatography (ethyl acetate/hexane, 1:9). The purified aldehyde **1a** (0.32 g, 80%) was directly subjected to further reaction.

1-triphenylphosphoranylidene -2-propanone (0.34 g, 1.08 mmol) was added to a solution of aldehyde **1a** (0.10 g, 0.72 mmol) in benzene (10 mL) and the reaction content was refluxed for 10 h. After cooling, the solvent was evaporated under reduced pressure and the crude product (0.42 g, yellow solid) was purified by using column chromatography (ethyl acetate/hexane 1:8) to give (*S*, *E*)-6-(4-oxopent-2-enyl)-5,6-dihydropyran-2-one (**3a**) (0.10 g, 80%) as a colorless oil. The optical rotation of compound was $[\alpha]_D^{25}$ = + 41.1 (c = 1.2, $CHCl_3$). The spectral data (Proton NMR, Carbon NMR and MS) of **3a** were found to be identical as those of **3**.

(*R*, *E*)-6-(4-oxo-6-phenylhex-2-enyl)-5,6-dihydropyran-2-one [(*R*)-Rugulactone] (4)

Compound **12** (0.40 g, 2.82 mmol) dissolved in dry DCM (5 mL) was slowly added to a solution of IBX (1.20 g, 2.82 mmol) in dry DMSO (2.5 mL) at room temperature and was stirred for 2 h. After completion, ice cold water (2 mL) was added to the reaction and the mixture extracted into DCM (3 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was subjected to column chromatography (ethyl acetate/hexane, 1:9). The purified aldehyde **1** (0.32 g, 80%) was directly subjected to further reaction.

1-triphenylphosphoranylidene -4-phenylbutan-2-one (**17**) (0.41 g, 1.28 mmol) was added to a solution of aldehyde **1** (0.10 g, 0.72 mmol) in benzene (10 mL) and the reaction content was refluxed for 14 h. After cooling, the solvent was evaporated under reduced pressure and the crude product (1.42 g, yellow solid) was purified using column chromatography (ethyl acetate/hexane 1:8) to give (*R*, *E*)-6-(4-oxo-6-phenylhex-2-enyl)-5,6-dihydropyran-2-one (rugulactone) (**4**) (0.14 g, 72%) as a colorless oil. The optical rotation of the compound was $[\alpha]_D^{25}$ = - 34.2 (c = 1.0, $CHCl_3$); IR: 1722, 1676, 1639, 1437, 1362, 1247 cm^1; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.30-7.22 (2H, m),7.20-7.14 (3H, m), 6.85 (1H, m), 6.79 (1H, m), 6.19 (1H, d, *J* = 16.0 Hz), 6.04 (1H, d, *J* = 9.0 Hz), 4.55 (1H, m), 2.98-2.85 (4H, m), 2.71-2.57 (2H, m), 2.38-2.29 (2H, m); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 199.2, 165.2, 141.0, 140.8, 132.5, 130.6, 128.0, 127.8, 125.7, 119.2, 71.3, 40.8, 34.6, 35.8, 30.0; ESIMS: m/z 271 $[M+H]^+$.

(*S*, *E*)-6-(4-oxo-6-phenylhex-2-enyl)-5,6-dihydropyran-2-one [(*S*)-Rugulactone] (4a)

Compound **12a** (0.40 g, 2.82 mmol) dissolved in dry DCM (5 mL) was slowly added to a solution of IBX (1.20 g, 2.82 mmol) in dry DMSO (2.5 mL) at room temperature and was stirred for 2 h. After completion, ice cold water (2 mL) was added to the reaction and the mixture extracted into DCM (3 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was subjected to column chromatography (ethyl acetate/hexane, 1:9). The purified aldehyde **1a** (0.32 g, 80%) was directly subjected to further reaction.

1-triphenylphosphoranylidene -4-phenylbutan-2-one (**17**) (0.41 g, 1.28 mmol) was added to a solution of aldehyde **1a** (0.10 g, 0.72 mmol) in benzene (10 mL) and the reaction content was refluxed for 14 h. After cooling, the solvent was evaporated under reduced pressure, and the crude product (1.42 g, yellow solid) was purified using column chromatography (ethyl acetate/hexane 1:8) to give (*S*, *E*)-6-(4-oxo-6-phenylhex-2-enyl)-5,6-dihydropyran-2-one (rugulactone) (**4a**) (0.14 g, 72%) as a colorless oil. The optical rotation of the compound was $[\alpha]_D^{25}$ = + 35.4 (c = 1.0, $CHCl_3$). The spectral data (Proton NMR, Carbon NMR and MS) of **4a** were found to be identical as those of **4**.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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