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Chemo-enzymatic synthesis of both enantiomers of rugulactone

Gowrisankar Reddipalli, Mallam Venkataiah, Nitin W. Fadnavis *

Biotransformation Laboratary, Indian Institute of Chemical Technology, Uppal Road, Habsiguda, Hyderabad 500 007, India

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ABSTRACT

The synthesis of both the (*R*)- and (*S*)-enantiomers of the natural product rugulactone has been achieved. *Candida rugosa* lipase hydrolyzes the butyrate ester of the protected 3-hydroxy homoallylic alcohol with very high enantioselectivity ($E = 244$) and provides the key intermediates with high enantiomeric purity (ee 98–99%) and excellent yields.

1. Introduction

The synthesis of biologically active natural products is of great interest because of their medicinal use. Recently, rugulactone **1** isolated from the plant *Cryptocarya rugulosa*[1] extract has been reported to exhibit the inhibition of constitutive nuclear factor NF-κB activity in human lymphoma cell lines. This observation has led to the possibility of its application in cancer chemotherapy and as an antiviral agent[1–3], and already two approaches to its stereoselective synthesis have been reported.[2,3] In the first approach by Venkateswarlu et al.,[3] the key intermediate homoallylic alcohol (*R*)-6-(benzyloxy)-1-hexen-4-ol has been synthesized via asymmetric allylation using (*R*)-BINOL and $Ti(O^iPr)_4$ while the second approach of Yadav et al.[2] employs the Jacobsen's hydrolytic kinetic resolution of an epoxide which is then converted to homoallylic alcohol. The intermediate is also useful in the synthesis of polycavernoside A,[4] obolactone,[5] spongistatin 1[6], and others. The approaches involving asymmetric synthesis provide a single enantiomer, for example, (*R*)-enantiomer, in the reaction sequence. In order to obtain the (*S*)-enantiomer, the reaction needs to be repeated with the chiral catalyst of the opposite configuration. It is generally argued that the synthesis of a single enantiomer with the possibility of >90% yield is preferred over a kinetic resolution with a maximum yield of 50%. However, it is well known that the biological activity of the two enantiomers can differ widely and it is important to synthesize and study the biological activity of both the enantiomers. In such a situation, the resolution of a racemic mixture to obtain both the enantiomers with high enantiomeric purity and yields nearing 45% (90% of theoretical) is preferable since some of the steps preceding the resolution need not be repeated. Herein we report the resolution of the racemic homoallylic alcohol **4** via lipase-catalyzed enantioselective hydrolysis of the corresponding butyrate ester **5**. Both (*R*)-**5** and (*S*)-**4** are obtained in excellent yield and enantiomeric purity. The intermediates so obtained are converted to the (*R*)- and (*S*)-enantiomers of rugulactone **1** (Scheme 1).

2. Results and discussion

Enantiomerically pure rugulactone was prepared in the following manner. The monosilyl ether of 1,3-propanediol **2** was prepared by selective protection with *tert*-butyldimethylsilyl chloride to obtain compound **3** in 85% yield. The primary alcohol was oxidized by Swern oxidation to the corresponding aldehyde and allylated by Barbier's procedure to obtain the racemic homoallylic alcohol **4** (92% over two steps). This was esterified with butyric acid to obtain racemic **5**. The enantioselective hydrolysis of **5** was carried out with seven different lipases to screen and identify the most useful biocatalyst (Table 1). Typically, the lipase (50 mg) was dissolved in Tris–HCl buffer (50 mM, pH 7.5, 10 mL) and the racemic ester (100 mg) was added as an ethanolic solution with vigorous stirring. The contents were stirred in vials on a magnetic stirrer for 24 h and then extracted with *n*-hexane. The hexane extracts were analyzed by chiral HPLC to determine the enantiomeric purity of the unreacted ester. The homoallylic alcohol, which was obtained as the product of the enzymatic hydrolysis, was separated by column chromatography and converted to its butyrate derivative again to determine its enantiomeric purity. It was observed that the lipases from *Rhizopus arrhizus*, *Rhizopus niveus*, and wheat germ showed very little selectivity. The lipases from porcine pancreas, *Pseudomonas cepacia*, and *Candida antarctica* displayed a reasonable enantioselectivity toward the (*R*)-enantiomer ($E = 14–25$), but were not enough to be of preparative interest. The best enantioselectivity was displayed by a lipase from *Candida rugosa* ($E = 244$) and enzymatic hydrolysis provided the (*S*)-alcohol with ee 98% at approximately 45% conversion. When the reaction was allowed to proceed for a longer period, the reaction virtually stopped at 50–52% conversion and provided the unreacted ester with ee >99%.

* Corresponding author. Fax: +91 40 27160512.
E-mail addresses: fadnavis@iict.res.in, fadnavisnw@yahoo.com (N.W. Fadnavis).

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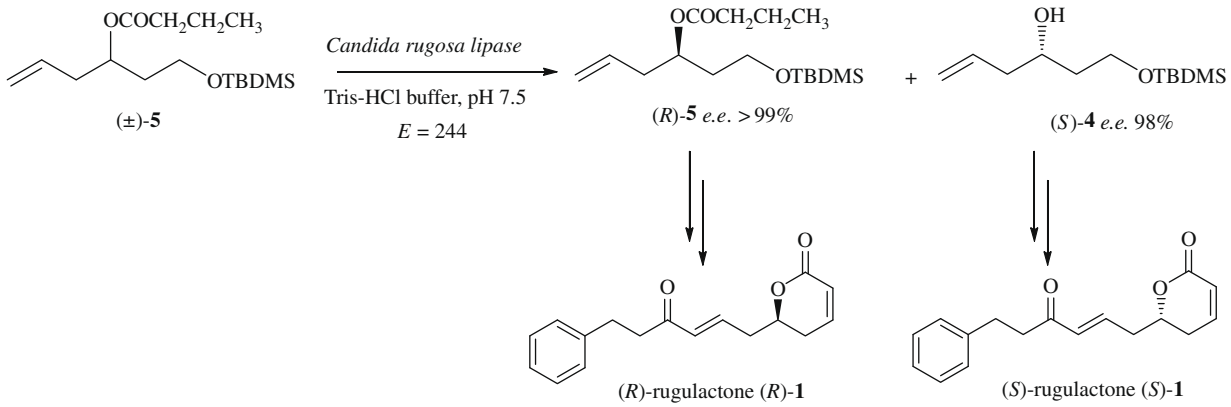


Scheme 1.

Table 1
Hydrolysis of (±)-**5** with various lipases[a]

Enzyme	ee (%)	Selectivity	Conversion *c* (%)	Enantioselectivity *E*
Lipase from *Candida rugosa*	85	(*S*)	45	244
Lipase from *Candida antarctica*	50	(*R*)	37	14
Lipase from *Pseudomonas cepacia*	30	(*R*)	24	16
Lipase from porcine pancreas	30	(*R*)	25	25
Lipase from wheat germ	15	(*R*)	33	2
Lipase from *Rhizopus arrhizus*	14	(*R*)	51	1.5
Lipase from *Rhizopus niveus*	12	(*R*)	26	2.2

[a] Reaction conditions: [Substrate] = 100 mg in 10 mL Tris–HCl buffer, 0.05 M, pH 7.5; lipase 50 mg. Reaction period 24 h. Product configuration was assigned on the basis of the specific rotation and comparison with the literature.

The two products were easily separated by column chromatography. The (*R*)-butyrate ester was hydrolyzed with K_2CO_3 in methanol to obtain alcohol (*R*)-**4** without racemization, which was treated with PTSA in methanol to obtain the diol (*R*)-**6**.

The diol (*R*)-**6** was selectively oxidized with TEMPO and BAIB to give the aldehyde (*R*)-**7**, which was used without purification for olefination to obtain the unsaturated ester (*R*)-**8** via the Still–Gennari modification of the Horner–Emmons olefination reaction[7] (*Z*/*E* ratio of 95:5). The isomers were separated by column chromatography to obtain the pure *Z*-isomer (71% over two steps). Upon treatment with PTSA in benzene, the ester cyclized to the lactone (*R*)-**9** (95%). The cross-metathesis[8] reaction of the lactone with 5-phenyl-pent-1-en-3-one[9] in the presence of a Grubbs's second-generation catalyst gave enantiomerically pure (*R*)-rugulactone **1a** (Scheme 2) (75%). (*S*)-Rugalactone **1b** was also synthesized in a similar manner starting with the (*S*)-homoallylic alcohol.

3. Conclusion

The lipase-catalyzed resolution provides an efficient route to the synthesis of both the enantiomers of a biologically active natural products as shown by the synthesis of (*R*)- and (*S*)-rugulactone.

4. Experimental

4.1. General

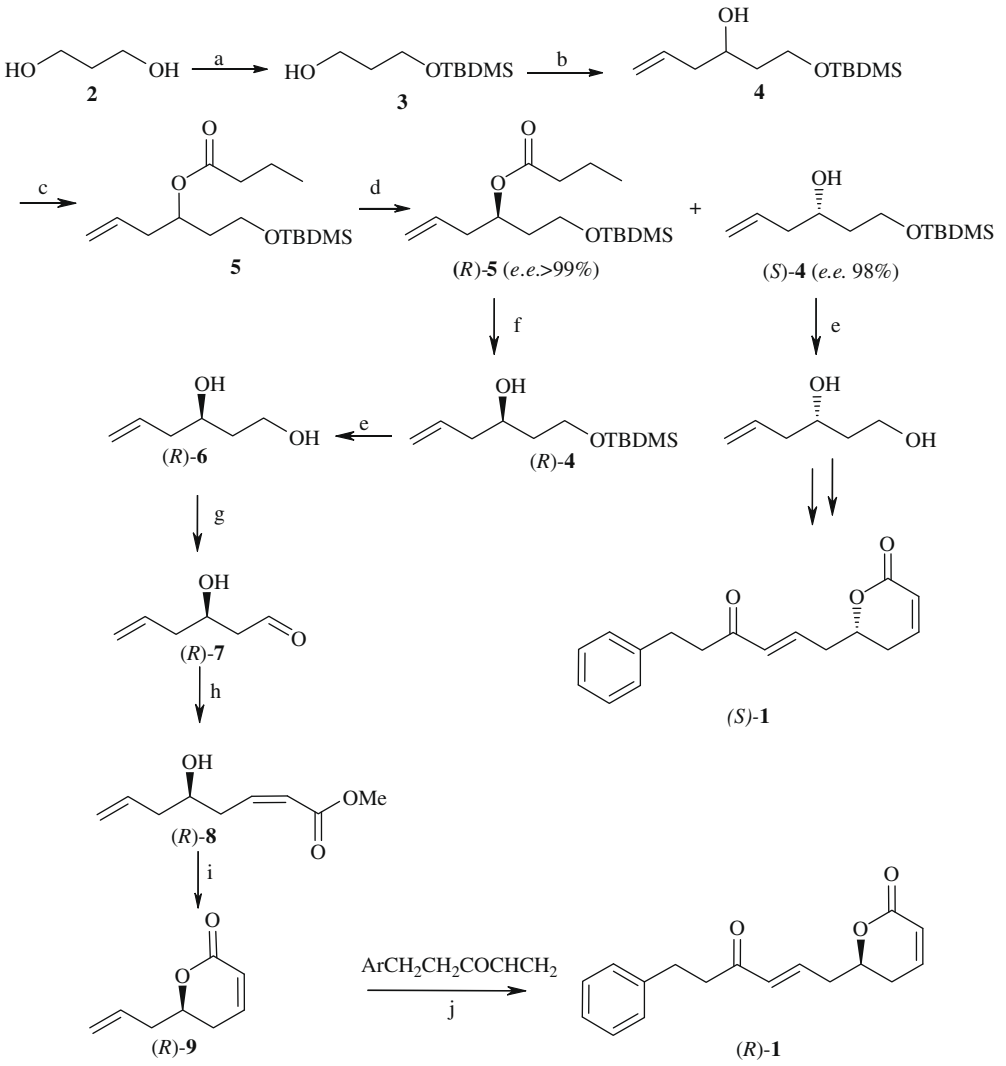
All the reagents were purchased from Sigma–Aldrich. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Avance-300 MHz spectrometer. Optical rotations were measured with a Horiba-SEPA-300 digital polarimeter. Mass spectra were recorded on a Q STAR mass spectrometer (Applied Biosystems, USA). HPLC analyses were carried out on a Hewlett Packard HP1090 unit with diode array detector and HP Chem Station software. Chiral HPLC columns were obtained from Daicel, Japan.

4.1.1. 3-(*tert*-Butyldimethylsilanyloxy)-propan-1-ol 3

Sodium hydride (60% dispersion in mineral oil, 1.61 g, 40.3 mmol) was suspended in dry DME (30 mL). 1,3-Propanediol **2** (2.04 g, 26.8 mmol) dissolved in dry DME (8 mL) was added and the reaction mixture was cooled in an ice bath. *tert*-Butyldimethylsilyl chloride (4.05 g, 26.8 mmol) was added slowly at 0 °C, after which cooling was removed and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl solution (5 mL) under cooling. The solvent was evaporated under reduced pressure. The residue was extracted with EtOAc (2 × 30 mL) and dried with anhydrous Na_2SO_4. After evaporation of ethyl acetate, the residue was chromatographed over silica gel (60–120 mesh, EtOAc/hexane, 2:8) yielding **3** (4.34 g, 85%) as a colorless oil. IR(neat) ν_{max} = 758, 1089, 1215, 1470, 3019 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.90 (s, 9H), 1.77 (qn, *J* = 5.82 Hz, 2H), 3.80 (t, *J* = 5.82 Hz, 2H), 3.82 (t, *J* = 5.82 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.4, 18.3, 25.9, 34.2, 62.36, 62.9. ESI-MS: *m*/*z* = 191 (M+1).

4.1.2. 1-(*tert*-Butyldimethylsilyloxy)hex-5-en-3-ol 4

At first, DMSO (3.21 g, 41.1 mmol) was added dropwise to a solution of oxalyl chloride (2.6 g, 20.5 mmol) in dry CH_2Cl_2 (20 mL) at −78 °C. The reaction mixture was stirred for 25 min, then the mono-protected alcohol **3** (2.6 g, 13.7 mmol) was added and the contents were stirred for 1 h. The reaction was quenched with triethylamine (8.3 g, 82.2 mmol) at −78 °C. The solvent was then evaporated under reduced pressure, after which the residue was extracted with CH_2Cl_2 (2 × 30 mL), and dried over anhydrous Na_2SO_4. After the evaporation of DCM, the crude aldehyde obtained was used as such without purification (2.51 g, 96%).



Scheme 2. Reagents and conditions: (a) NaH, TBDMSCl, DME, rt overnight; (b) (i) $(COCl)_2$, DMSO, DCM, −78 °C 1 h; (ii) Zn, allyl bromide, NH_4Cl in THF 3 h; (c) DCC, DMAP, butyric acid in DCM, 2 h; (d) Tris–HCl buffer, 0.05 M, pH 7.5; *Candida rugosa* lipase, 48 h; (e) PTSA, MeOH, 1 h; (f) K_2CO_3, MeOH, 4 h; (g) BAIB, TEMPO, DCM, 4 h; (h) Methyl *P,P*-bis(2,2,2-trifluoroethyl)phosphonoacetate, NaH, THF, −78 °C; (i) PTSA, benzene reflux, 1 h; (j) $ArCH_2CH_2COCHCH_2$, Grubbs's second-generation catalyst, DCM, 50 °C, 5 h.

To a stirred solution of crude aldehyde in THF, zinc dust (1.74 g, 26.7 mmol) and allyl bromide (2.40 g, 20 mmol) were added at room temperature. After stirring for 5 min in an ice bath, saturated NH_4Cl solution (4 mL) was added dropwise with cooling and then the reaction mixture was stirred at 0–5 °C for 3 h. The reaction was then quenched with an excess amount of saturated NH_4Cl solution (5 mL) and filtered through a pad of Celite. The filtrate was evaporated under reduced pressure, after which the residue was extracted with ethyl acetate, and dried over Na_2SO_4. After evaporation of the ethyl acetate, the residue was chromatographed over silica gel (60–120 mesh, EtOAc/hexane, 1:9) yielding **4** (2.90 g, 92% overall yield) as a colorless oil.

4.1.3. 1-(*tert*-Butyldimethylsilyloxy)hex-5-en-3-yl butyrate 5

To a stirred solution of **4** (2.60 g, 11.34 mmol), DCC (2.56 g, 12.42 mmol) and DMAP (catalytic amount, 15 mg) in 20 mL CH_2Cl_2 was added butyric acid (5.36 g, 60.74 mmol) at 0 °C. Cooling was stopped and the contents were stirred at room temperature for 2 h. The solution was filtered and the solvent was removed under reduced pressure. The residue was chromatographed over silica gel (60–120 mesh, hexane) yielding **5** (3.26 g, 96%) as a colorless oil.

4.1.4. (*R*)-1-(*tert*-Butyldimethylsilyloxy)hex-5-en-3-yl butyrate (*R*)-5 and (*S*)-1-(*tert*-butyldimethylsilyloxy)hex-5-en-3-ol (*S*)-4

4.1.4.1. Enzymatic hydrolysis. Racemic substrate **5** (1.44 g, 4.80 mmol) was dispersed into a mixture of Tris–HCl buffer (20 mL, 5 mM, pH 7.5 containing 5 mM $CaCl_2$) with sonication. The lipase enzyme from *C. rugosa* (0.6 g) was added as a solution in Tris–HCl buffer (5 mL) and the contents were stirred at room temperature on a magnetic stirrer while maintaining the pH of the reaction mixture at 7.5 with 0.2 M NaOH. The reaction was followed by monitoring the amount of NaOH consumed. After 45% conversion (consumption of 10.8 mL NaOH, 36 h), the reaction mixture was extracted with hexane and dried with anhydrous Na_2SO_4. After the evaporation of hexane, the residue was chromatographed over silica gel (60–120 mesh, EtOAc/hexane, 1:19) yielding (*S*)-**4** (0.65 g, 45%) as a colorless oil.

The enantiomeric purity of the butyrate ester was determined directly by chiral HPLC analysis. Since the alcohol was difficult to analyze, it was again converted to the butyrate derivative and analyzed for its enantiomeric purity. Thus the analysis of the recovered products on chiral stationary phase provided the values for the enantiomeric excesses of substrate (ee_s) and product (ee_p). The enantioselectivity *E* was calculated according to Sih et al.[10] Product

configurations were assigned on the basis of their specific rotation and comparison with the literature value.

4.1.4.2. HPLC analysis with chiral stationary phase. The enantiomeric purity was determined by HPLC analysis on a Chiralcel AD-H column (250 × 5 mm), Daicel Chemical Industries, Japan. Mobile phase 1% 2-propanol in hexane containing. Flow rate 0.5 mL/min. Detection wavelength 220 nm. Retention times (*R*)-**5**: 6.6 min; (*S*)-**5**: 7.5 min.

(*S*)-**4**: $[\alpha]_D^{25} = -6.9$ (*c* 1, $CHCl_3$), ee 98%; lit.[11] = −4.8 (*c* 1, $CHCl_3$), ee 66%. IR(neat) ν_{max} = 777, 836, 914, 1001, 1255, 1471, 1643, 2363, 2860, 2932, 3077, 3419 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.90 (s, 9H), 1.59–1.68 (m, 2H), 2.17–2.27 (m, 2H), 3.02 (s, 1H), 3.74–3.92 (m, 3H), 5.03–5.12 (m, 2H), 5.73–5.89 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.6, 18.1, 25.8, 37.7, 41.9, 62.5, 71.2, 117.2, 134.9. ESI-MS: *m/z* = 253 (M+Na).

(*R*)-**5**: $[\alpha]_D^{25} = -10.2$ (*c* 1, $CHCl_3$), ee >99%. IR(neat) ν_{max} = 758, 836, 920, 1095, 1216, 1255, 1727, 2358, 2959, 3020 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.88 (s, 9H), 0.95 (t, *J* = 7.55 Hz, 3H), 1.64 (qt, *J* = 7.55 Hz, 2H), 1.69–1.79 (m, 2H), 2.23 (t, *J* = 7.55 Hz, 2H), 2.33 (qt, *J* = 7.55 Hz, 2H), 3.56–3.65 (m, 2H), 4.97–5.10 (m, 3H), 5.65–5.80 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.5, 13.7, 18.3, 18.5, 25.9, 36.5, 36.6, 38.8, 59.4, 70.3, 117.6, 133.6, 173.1. ESI-MS: *m/z* = 323 (M+Na).

4.1.5. (*R*)-1-(*tert*-Butyldimethylsilyloxy)hex-5-en-3-ol (*R*)-4

The recovered butyrate ester (0.75 g, ee 80%) from enzymatic hydrolysis was re-suspended in Tris–HCl buffer containing the enzyme as described above and the reaction mixture was stirred for 24 h. The enantiomeric purity of the ester was monitored by chiral HPLC analysis. The ee of the product reached >99% in 24 h. The reaction was then stopped and the product (*R*)-**5** was recovered as described in Section 4.1.4 (0.63 g, 44%).

Compound (*R*)-**5** (670 mg, 2.23 mmol) was stirred with a solution of K_2CO_3 (616 mg, 4.47 mmol) in methanol (10 mL) for 4 h at room temperature and the solvent was then evaporated under reduced pressure. The residue was extracted with ethyl acetate (3 × 15 mL); the ethyl acetate layer was dried over anhydrous Na_2SO_4 and evaporated to obtain (*R*)-**4** (504 mg, 98%) as a colorless oil. $[\alpha]_D^{25} = +7.8$ (*c* 1, $CHCl_3$).

4.1.6. (*R*)-Hex-5-ene-1,3-diol (*R*)-6

Compound (*R*)-**4** (441 mg, 1.91 mmol) was stirred with a solution of PTSA (13 mg, 0.05 mmol) in methanol (10 mL) for 1 h at room temperature. Methanol was removed by evaporation under reduced pressure, after which sodium carbonate solution (1 mL, 10%) was added and the product was extracted with ethyl acetate (3 × 15 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and evaporated, yielding (*R*)-**6** (241 mg, 96%) as a colorless oil. $[\alpha]_D^{25} = +9.1$ (*c* 1, $CHCl_3$). IR(neat) ν_{max} = 917, 997, 1054, 1432, 1643, 2935, 3079, 3352 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.57–1.77 (m, 2H), 2.18–2.32 (m, 2H), 2.95 (br, 2H), 3.71–3.93 (m, 3H), 5.05–5.16 (m, 2H), 5.71–5.87 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.8, 42.1, 61.0, 70.5, 118.0, 134.5. ESI-MS: *m/z* = 139 (M+Na).

4.1.7. (*R,Z*)-Methyl 5-hydroxyocta-2,7-dienoate (*R*)-8

To a stirred solution of (*R*)-**6** (162 mg, 1.3 mmol) in dry CH_2Cl_2 (5 mL), BAIB (675 mg, 2.09 mmol) and TEMPO (13 mg, catalytic amount) were added at room temperature and stirred for 4 h. The reaction was then quenched with saturated $Na_2S_2O_3$ solution (2 mL), extracted with CH_2Cl_2 (2 × 8 mL), dried over anhydrous Na_2SO_4,, and concentrated under reduced pressure to obtain crude aldehyde (*R*)-**7** (151 mg, 93%).

To a stirred solution of methyl *P,P*-bis(2,2,2-trifluoroethyl)phosphonoacetate (508 mg, 1.58 mmol) in dry THF (8 mL) at 0 °C was added sodium hydride (80 mg, 2 mmol, 60% dispersion in mineral oil) and the resulting ylide solution was stirred for 45 min at 0 °C and then cooled to −78 °C . The crude aldehyde (*R*)-**7**, dissolved in dry THF (3 mL) was added dropwise with stirring at −78 °C and then stirring was continued for 3 h. The reaction was quenched with saturated NH_4Cl (2 mL) solution at 0 °C. The solvent was evaporated under reduced pressure, after which the residue was extracted with EtOAc (2 × 10 mL) and dried with anhydrous Na_2SO_4. After evaporation of ethyl acetate, the residue was chromatographed (silica gel, 60–120 mesh, EtOAc/hexane, 2:98) to obtain (*R*)-**8** (169 mg, 71% overall yield) as a colorless oil. $[\alpha]_D^{25} = +4.5$ (*c* 1, $CHCl_3$). IR(neat) ν_{max} = 817, 920, 1046, 1173, 1439, 1645, 1723, 2952, 3456 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.19–2.39 (m, 2H), 2.74–2.89 (m, 2H), 3.71 (s, 3H), 3.81 (br s, 1H), 4.40–4.56 (m, 1H), 5.05–5.19 (m, 2H), 5.72–5.86 (m, 1H), 5.90 (d, *J* = 11.33 Hz, 1H), 6.38 (dt, *J* = 3.77, 8.30 Hz, 1H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.8, 41.8, 51.2, 70.1, 118.3, 121.4, 134.4, 146.2. ESI-MS: *m/z* = 193 (M+Na).

4.1.8. (*R*)-6-Allyl-5,6-dihydro-2*H*-pyran-2-one (*R*)-9

Compound (*R*)-**8** (123 mg, 0.72 mmol) was stirred with a solution of PTSA (7.5 mg, 0.03 mmol) in benzene (3 mL) and refluxed for 1 h. Benzene was removed by evaporation under reduced pressure, after which sodium carbonate solution (0.5 mL, 10%) was added, and the product was extracted with ethyl acetate (3 × 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed over silica gel (60–120 mesh, EtOAc/hexane, 6:4) yielding (*R*)-**9** (95 mg, 95%) as a colorless oil. $[\alpha]_D^{25} = -114.1$ (*c* 1, $CHCl_3$). IR(neat) ν_{max} = 815, 920, 1045, 1248, 1389, 1728, 2920 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.29–2.39 (m, 2H), 2.40–2.62 (m, 2H), 4.40–4.53 (m, 1H), 5.05–5.21 (m, 2H), 5.74–5.92 (m, 1H), 5.96–6.05 (dt, *J* = 1.70, 6.42 Hz, 1H), 6.79–6.88 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.5, 38.9, 77.0, 118.7, 121.1, 132.1, 145.0, 164.2. ESI-MS: *m/z* = 139 (M+1).

4.1.9. (*R,E*)-6-(4-Oxo-6-phenylhex-2-enyl)-5,6-dihydro-2*H*-pyran-2-one (*R*)-rugulactone (*R*)-1

To a stirred solution of (*R*)-**9** (42 mg, 0.3 mmol) and 5-phenylpent-1-en-3-one (145 mg, 0.91 mmol) in dry 1.5 mL CH_2Cl_2 was added Grubbs' second-generation catalyst (2.6 mg, 10 mol %), and the reaction mixture was stirred at 50 °C for 5 h. After completion of the reaction, the solvent was removed under reduced pressure and the residue was chromatographed over silica gel (60–120 mesh, EtOAc/hexane, 4:5) to yield **1a** (62 mg, 75%) as a colorless oil. $[\alpha]_D^{25} = -46.9$ (*c* 1, $CHCl_3$), lit.[2] $[\alpha]_D^{25} = -46.5$ (*c* 1, $CHCl_3$). IR(neat) ν_{max} = 761, 816, 962, 1046, 1191, 1247, 1385, 1671, 1727, 2556, 2879, 3027, 3452 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.29–2.36 (m, 2H), 2.59–2.69 (m, 2H), 2.85–2.98 (m, 4H), 4.49–4.60 (m, 1H), 6.04 (dt, *J* = 1.51, 6.04 Hz, 1H), 6.20 (dt, *J* = 1.51, 14.35 Hz, 1H), 6.75–6.84 (m, 1H), 6.85–6.92 (m, 1H), 7.15–7.23 (m, 3H), 7.25–7.31 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.8, 29.62, 29.85, 37.44, 41.63, 76.0, 121.3, 126.0, 128.3, 128.4, 133.4, 140.0, 140.9, 144.7, 163.7, 199.0. ESI-MS: *m/z* = 293 (M+Na).

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