Enantioselective Synthesis of the Natural Product (*S*)-Rugulactone

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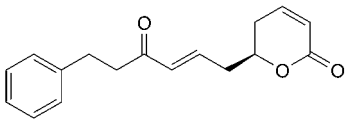
A simple and efficient enantioselective synthesis of (6*S*)-5,6-dihydro-6-[(2*E*)-4-oxo-6-phenylhex-2-en-1-yl]-2*H*-pyran-2-one (=(*S*)-rugulactone) has been accomplished. The synthesis started from commercially available propane-1,3-diol and ethyl 3-phenylpropanoate and involve the *Horner–Wadsworth–Emmons* (*HWE*) and *Still*'s modified *HWE* olefinations, and *Sharpless* asymmetric epoxidation.

Introduction. – Natural products possessing pyranone moieties exhibit a variety of pharmacological properties, which include antifungal, antitumor, antibacterial, anti-diabetic, anti-inflammatory, antiviral, anti-*Alzheimer*, antioxidant, antigrowth effects. The broad range of biological activities reported for this class of compounds has been ascribed to their inherent tendency to act as *Michael* acceptors. In accord with their biological importance, the syntheses of naturally occurring pyranones have been the subject of intense research [1]. The (arylalkyl)-substituted α,β-unsaturated δ-lactones are omnipresent metabolites of the evergreen trees of genus *Cryptocarya*, which are well-known for their potential medicinal properties [2]. Rugulactone (**1**), a 6-(arylalkyl)-5,6-dihydro-2*H*-pyran-2-one, is a natural product, isolated for the first time in 2009 from the plant *Cryptocarya rugulosa* by *Cardellina* and co-workers [13]. Rugulactone (**1**) was found to inhibit the nuclear factor-κB (NF-κB) activation pathway and is active against many types of cancer, exhibiting up to fivefold induction of IκB at 25 μg/ml concentration in human lymphoma cell lines [3]. The biological activity of **1** has attracted many researchers and led to its synthesis in different ways [4][5]. The majority of the previous synthetic pathways involved the use of costly reagents and resulted in low yields. Our synthetic route involves the use of commercially available reagents, is highly enantioselective, and leads to the product in high yield.

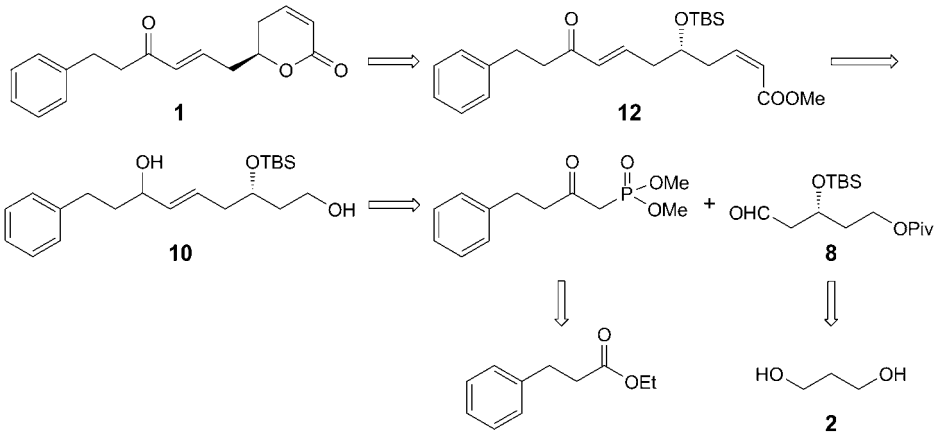


(*S*)-Rugulactone (**1**)

Results and Discussion. – As part of our research program on asymmetric synthesis of biologically active natural and synthetic compounds [6], herein we report a simple

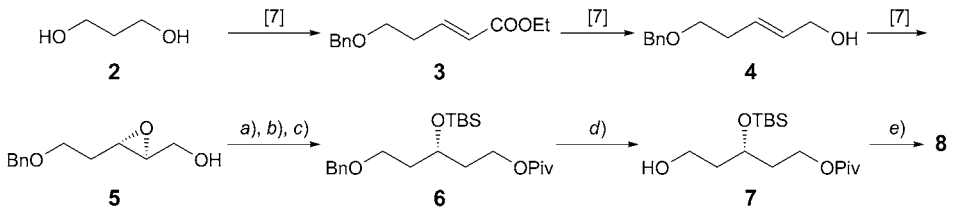
and efficient enantioselective synthesis of (*S*)-rugulactone (**1**). Our synthetic strategy started from commercially available propane-1,3-diol (**2**) and ethyl 3-phenylpropanoate (*Scheme 1*).

Scheme 1



Desymmetrization of propane-1,3-diol (**2**) was achieved by the known method to afford the mono benzylated compound, 3-(benzyloxy)propan-1-ol in 75% yield [7] (*Scheme 2*). The OH group was subjected to oxidation under *Swern* [8] conditions at low temperature to afford 3-(benzyloxy)propanal, and thus obtained crude aldehyde was further subjected to *Wittig* [9] reaction to yield ethyl (2*E*)-5-(benzyloxy)pent-2-enoate (**3**) in very good yield. The olefin **3** was reduced with diisobutylaluminum hydride (DIBAL-H) [10] in CH_2Cl_2 at low temperature to give (2*E*)-5-(benzyloxy)pent-2-en-1-ol (**4**) in excellent yield. Thus obtained alcohol **4** was subjected to a well-known *Sharpless* asymmetric epoxidation [11] using (+)-diethyl tartrate, $Ti(O^iPr)_4$, and ^{t}BuOOH in the presence of molecular sieves in CH_2Cl_2 at $-20°$ to furnish {(2*S*,3*S*)-3-[2-(benzyloxy)ethyl]oxiran-2-yl}methanol (**5**) in excellent yield and with excellent enantioselectivity ($[\alpha]_D^{29} = -29.2$, $c = 1$, $CHCl_3$). Epoxy alcohol **5** was reacted with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) for regioselective ring

Scheme 2



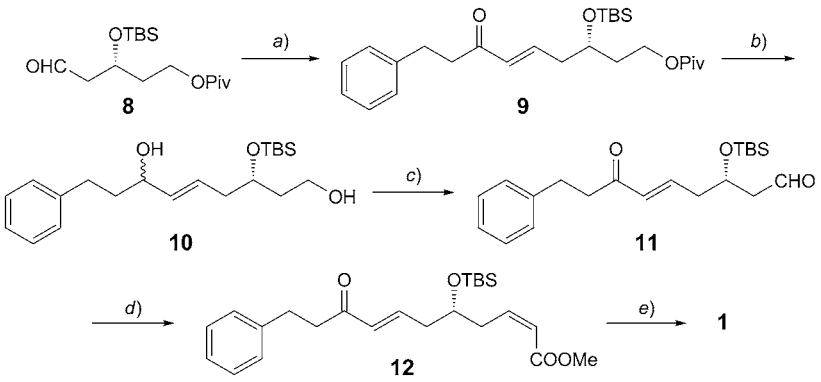
a) [12]; *b*) Me_3CCOCl, pyridine, CH_2Cl_2, 0° – r.t., 81%; *c*) ^{t}BuMe$_2$SiCl (TBSCl), 1*H*-imidazole, 4-(dimethylamino)pyridine, CH_2Cl_2, 0° – r.t., 6 h, 95%; *d*) 10% Pd/C, H_2, MeOH, r.t., 8 h, 92%; *e*) $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, $-78°$, 3 h.

opening [12]. This reaction was very clean and completed within 4 h to afford (3*R*)-5-(benzyloxy)pentane-1,3-diol exclusively in very good yield. The latter was reacted with pivaloyl chloride in the presence of pyridine in CH_2Cl_2 to selectively protect the primary alcohol [13].

The secondary alcohol group was protected by treatment with ^{t}BuMe$_2$SiCl in the presence of 1*H*-imidazole and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 to give (3*S*)-5-(benzyloxy)-3-{[(*tert*-butyl)(dimethyl)silyl]oxy}-pentyl 2,2-dimethylpropanoate (**6**) [14] in 95% yield ($[\alpha]_D^{29} = -27.0$, $c = 1$, $CHCl_3$). The fully protected compound **6** was subjected to debenzylation under H_2 using Pd/C in MeOH to afford (3*S*)-3-{[(*tert*-butyl)(dimethyl)silyl]oxy}-5-hydroxypentyl 2,2-dimethylpropanoate (**7**; $[\alpha]_D^{29} = -17.0$, $c = 1$, $CHCl_3$).

Compound **7** was oxidized under *Swern* conditions to give (3*R*)-3-{[(*tert*-butyl)(dimethyl)silyl]oxy}-5-oxopentyl 2,2-dimethylpropanoate (**8**) in very good yield. The latter was subjected to *Horner–Wadsworth–Emmons* reaction to afford (3*S*,5*E*)-3-{[(*tert*-butyl)(dimethyl)silyl]oxy}-7-oxo-9-phenylnon-5-en-1-yl 2,2-dimethylpropanoate (**9**) in 80% yield [15] ($[\alpha]_D^{29} = -29.5$, $c = 1$, $CHCl_3$) (*Scheme 3*). The (*E*)-configuration was evidenced by the coupling constant ($J = 16.0$ Hz) of the olefinic H-atoms. The optimized conditions were evaluated as 1:1 ratio of aldehyde and phosphonate[1]) in the presence of $Ba(OH)_2$ in THF/H_2O at room temperature. Compound **9** was subjected to reduction with (DIBAL-H) in CH_2Cl_2 at low temperature to yield (3*S*,5*E*)-3-{[(*tert*-butyl)(dimethyl)silyl]oxy}-9-phenylnon-5-ene-1,7-diol (**10**).

Scheme 3



a) *Dimethyl (2-oxo-4-phenylbutyl)phosphonate*, $Ba(OH)_2 \cdot 8\ H_2O$, THF/H_2O, r.t., 78% (2 steps); *b*) diisobutylaluminum hydride (DIBAL-H), CH_2Cl_2, $-78°$, 3 h, 92%; *c*) $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, $-78°$, 3 h; *d*) $(F_3CCH_2O)_2POCH_2CO_2Me$, NaH, THF, $-78°$, 2 h, 86% (2 steps); *e*) TsOH acid, benzene, r.t., 15 h, 91%.

In this reaction, the keto group was reduced to the secondary alcohol, and the pivaloyl group was deprotected to give the primary alcohol. Thus obtained diol **10** was treated under *Swern* condition with oxalyl chloride, Me_2SO at low temperature to

[1]) The phosphonate was prepared by *Claisen* condensation of methyl 3-phenylpropanoate with the Li salt of dimethyl methylphosphonate [16].

afford the oxidized product, (3*S*,5*E*)-3-{[(*tert*-butyl)(dimethyl)silyl]oxy}-7-oxo-9-phenylnon-5-enal (**11**) in very good yield. The latter was subjected to *Still*'s modified *Horner–Wadsworth–Emmons* reaction [17] with methyl [bis(2,2,2-trifluoroethoxy)-phosphoryl]acetate in the presence of NaH in THF at low temperature to furnish a (*Z*)-olefine, *i.e.*, methyl (2*Z*,5*R*,7*E*)-5-{[(*tert*-butyl)(dimethyl)silyl]oxy}-9-oxo-11-phenylundeca-2,7-dienoate (**12**) in very good yield, and the optical rotation of this compound was $[\alpha]_D^{29} = 27$ ($c = 1$, $CHCl_3$). The (*Z*)-configuration of the C(2)=C(3) bond is confirmed by the coupling constant ($J = 12.0$ Hz). Finally, **12** was reacted with TsOH in benzene at room temperature to remove the TBS group, followed by lactonization to afford the desired target molecule (*S*)-rugulactone (**1**; $[\alpha]_D^{29} = +79$, $c = 1$, $CHCl_3$) in excellent yield. In the literature, different optical-rotation values of the natural product rugulactone have been reported, but our value agrees with that reported by *Pietruszka* and co-workers ($[\alpha]_D^{29} = 78.9$ ($c = 0.53$, $CHCl_3$)) [5b]. The structures of all the compounds were established by their ^{1}H- and ^{13}C-NMR, IR and MS data.

Conclusions. – A new stereoselective synthesis of **1** has been accomplished using a *Sharpless* asymmetric epoxidation protocol, *Still*'s modified olefination to afford a (*Z*)-olefinic ester, and *Horner–Wadsworth–Emmons* reaction to afford the (*E*)-olefinic compound. All the reactions were very clean, and the products were obtained in very good yields.

Experimental Part

General. All the reactions were carried out under N_2 in anh. solvents and were monitored by TLC (silica-coated plates *Merck 60 F_{254}*; visualization with α-naphthol charring). Org. solns. were dried (Na_2SO_4), and crude products were purified by column chromatography (CC; silica gel (SiO_2)); *Acmes* 60–120 mesh; AcOEt and hexane). Moisture-sensitive reagents were transferred through syringe. Optical rotations: *JASCO P-1020* instrument. IR Spectra: *Perkin-Elmer FT-IR 240-c* spectrophotometer. ^{1}H-NMR Spectra: *Bruker-300* spectrometer, in $CDCl_3$; TMS as internal standard. MS: *Finnigan MAT 1020* mass spectrometer operating at 70 eV.

3-(Benzyloxy)propan-1-ol [7]. To stirred propane-1,3-diol (5 g, 65.8 mmol) was added powdered KOH (3.3 g, 59.2 mmol) and $PhCH_2Br$ (BnBr; 9 g, 52.6 mmol) in four intervals over a period of 1 h, and stirring was continued for another 1 h at r.t. Then, H_2O (30 ml) was added, and the mixture was extracted with Et_2O (2×20 ml). The combined org. layer was washed with brine, dried (anh. Na_2SO_4), and concentrated. The crude product was purified by CC (SiO_2 (60–120 mesh); AcOEt/hexane 3 : 7). *Pure* 3-(benzyloxy)propan-1-ol was obtained as yellow liquid (8.2 g, 75%).

3-(Benzyloxy)propanal [7]. To a stirred soln. of $(COCl)_2$ (7.65 g, 60 mmol) in dry CH_2Cl_2 (30 ml) was added Me_2SO (9.4 g, 120 mmol) under N_2 at $-78°$, and, after 45 min stirring, a soln. of 3-(benzyloxy)propan-1-ol (5 g, 30 mmol) in CH_2Cl_2 (20 ml) was added. Stirring was continued for 2 h, then Et_3N (18 g, 180 mmol) was added, and stirring was continued for further 1 h at the same temp. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to 0° and stirred for 30 min, and then H_2O (30 ml) was added, followed by CH_2Cl_2 (30 ml). The mixture was stirred for 10 min at r.t. The org. layer was separated, washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The obtained crude product was used for the *Wittig* reaction without purification.

*Ethyl (2*E*)-5-(Benzyloxy)pent-2-enoate* (**3**) [7]. To a stirred soln. of 3-(benzyloxy)propanal (5 g, 30.5 mmol) in benzene (30 ml) was added (ethoxycarbonyl)(triphenylphosphonio)methanide (12.7 g, 36.6 mmol) at r.t., and stirring was continued for 3 h. After completion of the reaction (TLC), the mixture was extracted with AcOEt (2×25 ml). The combined org. layer was washed with brine, dried

(Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by CC (SiO_2 (60–120 mesh); AcOEt/hexane 1:9) to yield pure **3** (6.15 g, 86%). Yellow liquid.

*(2*E*)-5-(Benzyloxy)pent-2-en-1-ol* (**4**) [7]. To a stirred soln. of **3** (5 g, 21.4 mmol) in CH_2Cl_2 (30 ml) under N_2 at $-78°$ was added DIBAL-H (6 g, 42.7 mmol) slowly over a period of 15 min, and stirring was continued for 3 h under similar conditions. After completion of the reaction (TLC), aq. sat. soln. of potassium sodium tartrate at $-78°$, and stirring was continued for 1 h at r.t. Then, the mixture was extracted with CH_2Cl_2 (2×25 ml). The combined org. layer was washed with brine, dried (Na_2SO_4), and concentrated. The crude **4** was purified by CC (SiO_2 (60–120 mesh); AcOEt/hexane 2:8) to afford 3.7 g (90%) of yellow liquid.

*{(2*S*,3*S*)-3-[2-(Benzyloxy)ethyl]oxiran-2-yl}methanol* (**5**). See [7].

*(3*R*)-5-(Benzyloxy)pentane-1,3-diol.* See [12].

*(3*S*)-5-(Benzyloxy)-3-hydroxypentyl 2,2-Dimethylpropanoate.* To a stirred soln. of (3*R*)-5-(benzyloxy)pentane-1,3-diol (3.5 g, 16.7 mmol) in CH_2Cl_2 (30 ml) was added pyridine (1.6 g, 20 mmol) at 0°, and after 15 min stirring was added pivaloyl chloride (2.2 g, 18.3 mmol) under the same condition. After 10 min stirring, cooling was removed, and stirring was continued at r.t. for 3 h. After completion of the reaction (TLC), the mixture was extracted with CH_2Cl_2 (2×25 ml). The combined org. layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by CC (SiO_2 (60–120 mesh); AcOEt/hexane 3:7). Pure (3*S*)-5-(benzyloxy)-3-hydroxypentyl 2,2-dimethylpropanoate (3.97 g, 81%) was obtained as colorless liquid. $[\alpha]_D^{29} = +10.5$ ($c = 1$, $CHCl_3$). IR (neat): 3457, 3031, 2965, 2931, 2869, 1726, 1479, 1457, 1399, 1364, 1287, 1163, 1099, 1034, 742, 698. ^{1}H-NMR ($CDCl_3$): 1.19 (*s*, 9 H); 1.69–1.79 (*m*, 4 H); 3.59–3.64 (*m*, 1 H); 3.67–3.72 (*m*, 1 H); 3.82–3.88 (*m*, 1 H); 4.10–4.16 (*m*, 1 H); 4.25–4.31 (*m*, 1 H); 4.51 (*s*, 2 H); 7.23–7.33 (*m*, 5 H). EI-MS: 295 (100, $[M+1]^+$), 277 (45), 242 (10), 207 (15), 187 (25), 176 (20), 145 (20), 129 (15).

*(3*S*)-5-(Benzyloxy)-3-{[(*tert*-butyl)(dimethyl)silyl]oxy}pentyl 2,2-Dimethylpropanoate* (**6**). To a stirred soln. of (3*S*)-5-(benzyloxy)-3-hydroxypentyl 2,2-dimethylpropanoate (3.7 g, 12.6 mmol) in CH_2Cl_2 (30 ml) was added 1*H*-imidazole (3.42 g, 50.3 mmol), followed by ^{t}BuMe$_2$SiCl (TBS-Cl; 2.83 g, 18.9 mmol) and 4-(dimethylamino)pyridine (DMAP; 50 mg) at 0°. The resulting mixture was stirred at r.t. for 8 h. After completion of the reaction (TLC), the mixture was extracted with CH_2Cl_2 (2×30 ml). The combined org. layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude **6** was purified by CC (SiO_2 (60–120 mesh); AcOEt/hexane 2:8) to afford pure **6** (4.88g, 95%). Colorless liquid. $[\alpha]_D^{29} = -27.0$ ($c = 1$, $CHCl_3$). IR (neat): 3167, 2957, 2929, 2857, 1729, 1462, 1399, 1364, 1284, 1254, 1159, 1102, 1055, 837, 773, 698. ^{1}H-NMR ($CDCl_3$): 0.10 (*s*, 6 H); 0.88 (*s*, 9 H); 1.18 (*s*, 9 H); 1.71–1.81 (*m*, 4 H); 3.45–3.53 (*m*, 2 H); 3.95–4.20 (*m*, 3 H); 4.45 (*s*, 2 H); 7.22–7.32 (*m*, 5 H). ^{13}C-NMR ($CDCl_3$): 178.4; 138.4; 120.2; 127.5; 127.4; 72.9; 66.6; 66.4; 61.1; 37.2; 36.1; 27.1; 25.8; 18.0; −4.67; −4.62. EI-MS: 426 (100, $[M+18]^+$), 409 (50, $[M+1]^+$), 370 (15), 358 (10), 277 (15), 267 (15), 193 (40), 167 (20).

*(3*S*)-3-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-5-hydroxypentyl 2,2-Dimethylpropanoate* (**7**). To a stirred soln. of **6** (4.5 g, 11 mmol) in MeOH (30 ml) was added 10% Pd/C (100 mg), and the resulting mixture was stirred under H_2 for 10 h at r.t. After the completion of the reaction (TLC), the mixture filtered through *Celite*. The filtrate was concentrated, and the crude compound **7** was purified by CC (SiO_2 (60–120 mesh); AcOEt/hexane 2:8) to furnish pure **7** (3.2 g, 92%). Colorless liquid. $[\alpha]_D^{29} = -17.0$ ($c = 1$, $CHCl_3$). IR (neat): 3447, 2957, 2933, 2860, 1728, 1472, 1392, 1367, 1287, 1255, 1161, 1107, 1058, 838, 776, 721. ^{1}H-NMR ($CDCl_3$): 0.10 (*s*, 6 H); 0.90 (*s*, 9 H); 1.19 (*s*, 9 H); 1.56–1.72 (*m*, 1 H); 1.74–1.94 (*m*, 3 H); 3.60–3.88 (*m*, 2 H); 3.96–4.20 (*m*, 3 H). ^{13}C-NMR ($CDCl_3$): 178.4; 68.1; 61.0; 59.6; 38.6 38.3; 35.6; 27.1; 25.7; 17.8; −4.7. EI-MS: 341 (50, $[M+Na]^+$), 242 (20), 221 (20), 198 (25), 187 (100), 169 (10), 157 (15).

*(3*R*)-3-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-5-oxopentyl 2,2-Dimethylpropanoate* (**8**). The procedure described for 3-(benzyloxy)propanal from 3-(benzyloxy)propan-1-ol was applied on **7** (3 g, 9.42 mmol). The crude product was used for further reaction without any purification.

*(3*S*,5*E*)-3-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-7-oxo-9-phenylnon-5-en-1-yl 2,2-Dimethylpropanoate* (**9**). To a stirred soln. of dimethyl (2-oxo-4-phenylbutyl)phosphonate (4.13 g, 16.13 mmol) in THF (30 ml) was added $Ba(OH)_2 \cdot 8\ H_2O$ (5.39 g, 17 mmol), and stirring was continued for 30 min. Then, a soln. of **8** (3 g, 9.49 mmol) in THF/H_2O 40:1 (10 ml) was added, and stirring was continued for 30 min at r.t. After completion of the reaction (TLC), sat. NH_4Cl soln. was added, and the mixture was extracted

with AcOEt (2 × 25 ml). The combined org. layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude **9** was purified by CC (SiO_2 (60–120 mesh); AcOEt/hexane 2:8) to give pure **9** (3.28 g, 78% for 2 steps). Colorless liquid. $[\alpha]_D^{29} = -29.5$ ($c = 1$, $CHCl_3$). IR (neat): 3028, 2928, 2858, 1730, 1675, 1633, 1467, 1367, 1284, 1255, 1157, 1109, 935, 838, 775, 700. ^{1}H-NMR ($CDCl_3$): 0.10 (*s*, 6 H); 0.88 (*s*, 9 H); 1.18 (*s*, 9 H); 1.68–1.76 (*m*, 2 H); 2.28–2.44 (*m*, 2 H); 2.81 (*t*, *J* = 7.5, 2 H); 2.91 (*t*, *J* = 6.0, 2 H); 3.88–3.94 (*m*, 1 H); 4.01–4.07 (*m*, 1 H); 4.11–4.17 (*m*, 1 H); 6.09 (*d*, *J* = 16.0, 1 H); 6.72–6.80 (*m*, 1 H); 7.11–7.26 (*m*, 5 H). ^{13}C-NMR ($CDCl_3$): 199.1; 159.1; 143.1; 141.1 132.5; 128.4; 128.2; 126.0; 67.9; 60.9; 41.6; 40.5; 36.0; 30.0; 27.1; 25.7; 18.0; −4.4; −4.7. EI-MS: 469 (40, $[M + Na]^+$), 458 (100), 446 (15), 348 (10), 315 (20).

*(3*S*,5*E*)-3-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-9-phenylnon-5-ene-1,7-diol* (**10**). To a stirred soln. of **9** (1 g, 2.24 mmol) in dry CH_2Cl_2 (10 ml) was added DIBAL-H (1M in toluene, 0.7 g, 4.93 mmol) at −78° under N_2, and stirring was continued for 30 min. After completion of the reaction (TLC), sat. potassium sodium tartrate soln. at −78°, and then the temp. was raised to r.t., and stirring was continued for 1 h. The mixture was extracted with CH_2Cl_2 (2 × 20 ml), and the combined org. layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude **10** was purified by CC (SiO_2 (60–120 mesh); AcOEt/hexane 3:7) to furnish pure **10** (0.74 g, 92%). Colorless liquid. $[\alpha]_D^{29} = +3.5$ ($c = 1$, $CHCl_3$). IR (neat): 3421, 3028, 2932, 2858, 1632, 1460, 1253, 1062, 974, 836, 775, 741, 698. ^{1}H-NMR ($CDCl_3$): 0.30 (*s*, 6 H); 0.90 (*s*, 9 H); 1.52–1.90 (*m*, 4 H); 2.26 (*t*, *J* = 6.0, 2 H); 2.60–2.80 (*m*, 2 H); 3.62–3.81 (*m*, 2 H); 3.88–3.98 (*m*, 1 H); 4.01–4.12 (*m*, 1 H); 5.48–5.67 (*m*, 2 H); 7.10–7.27 (*m*, 5 H). ^{13}C-NMR ($CDCl_3$): 141.8; 135.6; 128.3; 127.4 127.3; 125.7; 72.0; 70.9; 59.9; 39.6; 38.6; 37.6; 31.7; 25.7; 17.9; −4.4. EI-MS: 365 (100, $[M + 1]^+$), 363 (30), 351 (90), 341 (40), 337 (85), 332 (40), 327 (50), 320 (30), 313 (20), 311 (25).

*(3*S*,5*E*)-3-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-7-oxo-9-phenylnon-5-enal* (**11**). To a stirred soln. of $(COCl)_2$ (0.69 g, 5.5 mmol) in dry CH_2Cl_2 (10 ml) was added Me_2SO (0.86 g, 11 mmol) under N_2 at −78°. After 45 min stirring under the same condition, a soln. of **10** (0.5 g, 1.37 mmol) in dry CH_2Cl_2 (5 ml) was added. The resulting mixture was stirred for 2 h, then Et_3N (1.67 g, 16.5 mmol) was added, and stirring was continued for 1 h at −78°. After completion of the reaction (TLC), the temp. was raised to 0°, and H_2O (10 ml) was added, followed by CH_2Cl_2 (10 ml). The mixture was extracted with CH_2Cl_2 (2 × 10 ml), and the combined org. layer was washed with brine, dried (Na_2SO_4), concentrated under reduced pressure, and the obtained crude product was used for further reaction without purification. Crude compound. ^{1}H-NMR ($CDCl_3$): 0.10 (*s*, 6 H); 0.91 (*s*, 9 H); 2.15–2.35 (*m*, 4 H); 2.90–3.01 (*m*, 4 H); 4.10–4.20 (*m*, 1 H); 6.10 (*d*, *J* = 15.5, 1 H); 6.62–6.80 (*m*, 1 H); 7.05–7.15 (*m*, 5 H); 9.80 (*s*, 1 H).

*Methyl (2*Z*,5*S*,7*E*)-5-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-9-oxo-11-phenylundeca-2,7-dienoate* (**12**). To a stirred soln. of NaH (0.053 g, 2.22 mmol) in dry THF (5 ml) was added a soln. of methyl [bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (0.35 g, 1.11 mmol) in THF (5 ml) at 0° under N_2, and the mixture was stirred for 30 min. The soln. was cooled to −78°, a soln. of **11** (0.5 g, 1.39 mmol) in dry THF (5 ml) was added, and stirring was continued for 2 h. After completion of the reaction (TLC), sat. NH_4Cl soln. was added at −78°, the temp. was raised to r.t., and stirring was continued for 20 min. The solvent was removed from the mixture under reduced pressure, and the residue was extracted with AcOEt (2 × 20 ml), the combined org. layer was washed with brine, dried (Na_2SO_4), and concentrated. The crude **12** was purified by CC (SiO_2 (60–120 mesh); AcOEt/hexane 2:8) to furnish pure **12** (0.5 g, 86%). Colorless liquid. $[\alpha]_D^{29} = +27$ ($c = 1$, $CHCl_3$). IR (neat): 2925, 2856, 1717, 1639, 1510, 1456, 1366, 1206, 1093, 829, 766, 698. ^{1}H-NMR ($CDCl_3$): 0.10 (*s*, 6 H); 0.88 (*s*, 9 H); 2.34 (*t*, *J* = 7.5, 2 H); 2.71–2.97 (*m*, 6 H); 3.66 (*s*, 3 H); 3.90–3.99 (*m*, 1 H); 5.86 (*d*, *J* = 12.0, 1 H); 6.06 (*d*, *J* = 15.0, 1 H); 6.26–6.36 (*m*, 1 H); 6.73–6.89 (*m*, 1 H); 7.13–7.25 (*m*, 5 H). ^{13}C-NMR ($CDCl_3$): 199.7; 166.3; 145.6; 143.5; 132.4; 128.4; 128.3; 126.1; 125.9; 121.1; 70.5; 56.8; 51.0; 47.3; 41.3; 36.3; 29.6; 25.7; −4.63; −4.68. EI-MS: 439 (100, $[M + Na]^+$), 427 (20), 409 (15), 408 (50), 352 (20), 301 (18), 285 (22), 243 (30), 211 (25).

*(*S*)-Rugulactone* (= *(6*S*)-5,6-Dihydro-6-[(2*E*)-4-oxo-6-phenylhex-2-en-1-yl]-2*H*-pyran-2-one*; **1**). To a stirred soln. of **12** (0.25 g, 0.595 mmol) in benzene (5 ml) was added TsOH (25 mg) under N_2, and the mixture was stirred for 15 h at r.t. After the completion of reaction (TLC), the mixture was extracted with AcOEt (2 × 20 ml), and the combined org. layer was washed with $NaHCO_3$ soln., brine, dried (Na_2SO_4), concentrated under reduced pressure. The crude **1** was purified by CC (SiO_2 (60–120 mesh); AcOEt/hexane 2:8) to give pure **1** (0.15 g, 92%). Colorless liquid. $[\alpha]_D^{29} = +79$ ($c = 1$, $CHCl_3$). IR (neat):

3027, 2923, 2855, 1720, 1632, 1493, 1450, 1381, 1249, 1148, 1039, 976, 811, 751, 700. ^{1}H-NMR ($CDCl_3$): 2.27–2.34 (*m*, 2 H); 2.54–2.68 (*m*, 2 H); 2.83–2.95 (*m*, 4 H); 4.46–4.53 (*m*, 1 H); 6.01 (*d*, *J* = 10.0, 1 H); 6.15 (*d*, *J* = 16.0, 1 H); 6.71–6.78 (*m*, 1 H); 6.80–6.85 (*m*, 1 H); 7.12–7.27 (*m*, 5 H). ^{13}C-NMR ($CDCl_3$): 198.9; 163.6; 144.6; 140.8; 140.2; 133.3; 128.2; 125.9; 121.2; 75.9; 41.6; 37.3; 29.8; 29.5; 28.8. EI-MS: 293 (100, $[M+Na]^+$), 271 (40), 253 (15).

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REFERENCES

[1] S. D. Rychnovsky, *Chem. Rev.* **1995**, *95*, 2021; M. Mondon, J. P. Gesson, *Curr. Org. Synth*. **2006**, *3*, 41.
[2] J. A. Marco, M. Carda, J. Murga, E. Falomir, *Tetrahedron* **2007**, *63*, 2929; P. Kasaplar, O. Yılmazer, A. Çağir, *Bioorg. Med. Chem*. **2009**, *17*, 311.
[3] T. L. Meragelman, D. A. Scudiero, R. E. Davis, L. M. Staudt, T. G. McCloud, J. H. Cardellina II, R. H. Shoemaker, *J. Nat. Prod*. **2009**, *72*, 336.
[4] D. K. Mohapatra, P. P. Das, D. S. Reddy, J. S. Yadav, *Tetrahedron Lett*. **2009**, *50*, 5941; D. K. Reddy, V. Shekhar, T. S. Reddy, S. P. Reddy, Y. Venkateswarlu, *Tetrahedron: Asymmetry* **2009**, *20*, 2315; G. Reddipalli, M. Venkataiah, N. W. Fadnavis, *Tetrahedron: Asymmetry* **2010**, *21*, 320; F. Cros, B. Pelotier, O. Piva, *Eur. J. Org. Chem*. **2010**, 5063; D. K. Reddy, V. Shekhar, P. Prabhakar, B. C. Babu, B. Siddhardha, U. S. N. Murthy, Y. Venkateswarlu, *Eur. J. Med. Chem*. **2010**, *45*, 4657.
[5] a) F. Allais, M. Aouhansou, A. Majira, P. H. Ducrot, *Synthesis* **2010**, 2787; b) D. Böse, E. Fernández, J. Pietruszka, *J. Org. Chem*. **2011**, *76*, 3463; c) A. Goswami, P. P. Saikia, B. Saikia, D. Chaturvedi, N. C. Barua, *Tetrahedron Lett*. **2011**, *52*, 5133; d) B. Das, Y. Srinivas, C. Sudhakar, P. R. Reddy, *Helv. Chim. Acta*. **2011**, *94*, 1290; e) S. F. Kirsch, P. Klahn, H. Menz, *Synthesis* **2011**, 3592; f) M. B. Nodwell, H. Menz, S. F. Kirsch, S. A. Sieber, *ChemBioChem* **2012**, *13*, 1439.
[6] A. V. Narsaiah, J. K. Kumar, *Synthesis* **2010**, 1989; A. V. Narsaiah, P. Narsimha, G. Navitha, *Int. J. Appl. Biol. Pharm. Tech*. **2010**, *1*, 736; A. V. Narsaiah, J. K. Kumar, *Int. J. Ind. Chem*. **2011**, *3*, 154; A. V. Narsaiah, B. Nagaiah, *Synthesis* **2010**, 2705; A. V. Narsaiah, J. K. Kumar, *Synth. Commun*. **2011**, *41*, 1603; A. V. Narsaiah, R. S. Ghogare, *Synthesis* **2011**, 3271; A. V. Narsaiah, P. Narsimha, *Med. Chem. Res*. **2012**, *21*, 538; A. V. Narsaiah, B. Nagaiah, B. K. Devi, *J. Heterocycl. Chem*. **2012**, *49*, 829; S. B. Wadavrao, R. S. Ghogare, A. V. Narsaiah, *Tetrhedron Lett*. **2012**, *53*, 3955.
[7] J. J. Kiddle, D. L. C. Green, C. M. Thompson, *Tetrahedron* **1995**, *51*, 2851; A. M. Heapy, Margaret A. Brimble, *Tetrahedron* **2010**, *66*, 5424.
[8] K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651; A. J. Mancuso, D. Swern, *Synthesis* **1981**, 165.
[9] G. Wittig, U. Schöllkopf, *Chem. Ber*. **1954**, *87*, 1318; R. W. Hoffmann, *Angew. Chem., Int. Ed*. **2001**, *40*, 1411.
[10] S. Kim, K. H. Ahn, *J. Org. Chem*. **1984**, *49*, 1717.
[11] Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko, K. B. Sharpless, *J. Am. Chem. Soc*. **1987**, *109*, 5765.
[12] J. M. Finan, Y. Kishi, *Tetrahedron Lett*. **1982**, *23*, 2719; X. Zhu, B. Yu, Y. Hui, R. Higuchi, T. Kusano, T. Miyamoto, *Tetrahedron Lett*. **2000**, *41*, 717.
[13] M. J. Robins, S. D. Hawrelak, T. Kanai, J. M. Siefer, R. Mengel, *J. Org. Chem*. **1979**, *44*, 1317.
[14] E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc*. **1972**, *94*, 6190; K. K. Ogilvie, D. J. Iwacha, *Tetrahedron Lett*. **1973**, *14*, 317.
[15] I. Paterson, K.-S. Yeung, J. B. Smaill, *Synlett* **1993**, 774; T. K. Chakraborty, M. Sreekanth, K. K. Pulukuri, *Tetrahedron Lett*. **2011**, *52*, 59.
[16] M. A. Evans, J. P. Morken, *Org. Lett*. **2005**, *7*, 3371.
[17] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405.

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