The Stereoselective Total Synthesis of (6*S*)-5,6-Dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one *via Prins* Cyclization

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The stereoselective total synthesis of an antiproliferative and antifungal α-pyrone natural product (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one is described. The key steps involved are the *Prins* cyclization, *Mitsunobu* reaction, and ring-closing metathesis reaction.

Introduction. – Antiproliferative and antifungal α-pyrone natural product (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (**1**) was isolated by *Hostettmann* and co-workers in 2001 from *Ravensara crassifolia* [1]. The α-pyrone moiety is one of the most commonly encountered structural motif among the various natural-product skeletons. Many of these natural products exhibit varied pharmacological properties such as antimicrobial, antifungal, and cytotoxicity against human tumor cells [2]. Some of these compounds such as fostriecin [3] and goniothalamin [3] are known to display anticancer properties, and (−)-pyronetin [4] is known to exhibit immunosuppressive activity. Passifloricin-A [5] and strictifolione [6] are found to exhibit antifungal activity. (6*S*)-5,6-Dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (**1**) is also one such natural product which is known to exhibit antifungal activity against phytopathogenic fungus *Cladosporium cucumarinum* (*Fig.*) [1]. In a recent investigation, this compound was found to display antiproliferative activity against three human cancer cell lines: leukemia (THP-1 and U-937) and melanoma (A-375) [7].

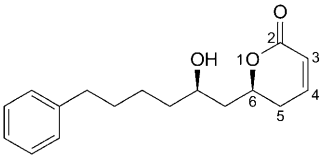

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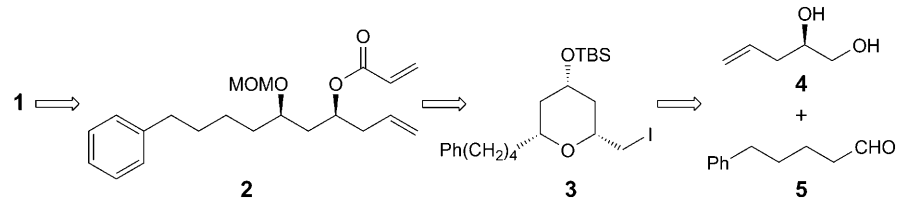
Figure. *Structure of (6*S*)-5,6-Dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one* (**1**)

The *Prins* cyclization is a powerful synthetic tool for the construction of tetrahydropyran scaffolds and has been utilized in the synthesis of several natural products [8]. Our group has made a significant effort to explore the utility of *Prins* cyclization in the synthesis of various polyketide intermediates and applied it to the total synthesis of some natural products [9]. The structural uniqueness of compound **1**,

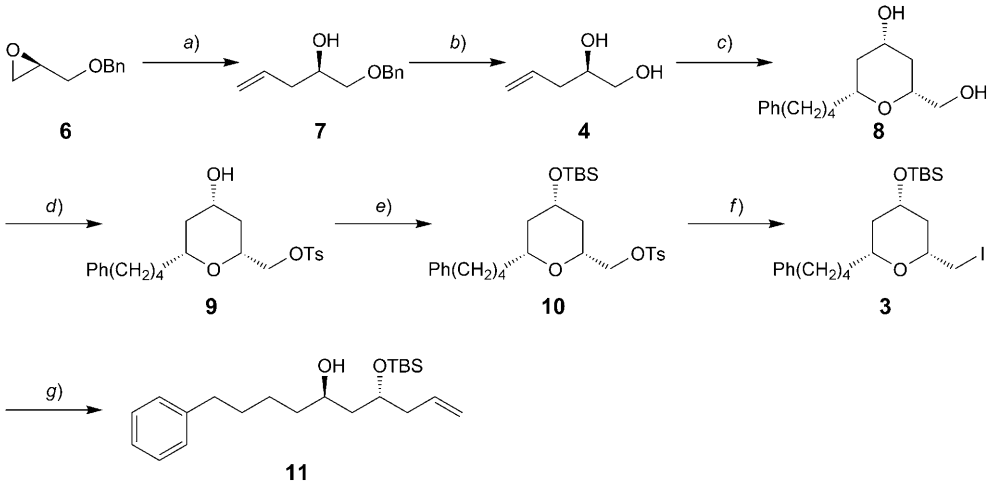
coupled with interesting biological activity and our interest on the 6-substituted α,β-unsaturated-δ-lactones [10], prompted us to explore the total synthesis *via* the *Prins* cyclization. In our retrosynthetic analysis, we envisaged that the target molecule **1** could be achieved from the diene ester **2** by a ring-closing metathesis approach. The ester **2** can be easily prepared from 2,4,6-trisubstituted tetrahydropyran **3**, which could in turn be obtained *via* the *Prins* cyclization of homoallylic alcohol **4** with aldehyde **5** (*Scheme 1*).

Scheme 1. *Retrosynthetic Analysis of Compound* (**1**)



Results and Discussion. – The synthesis of the natural product **1** started with chiral homoallyl alcohol **4** (*Scheme 2*). The precursor **4** was prepared in two steps by Cu^I-mediated regioselective opening [11] of (–)-(*R*)-2-[(benzyloxy)methyl]oxirane (**6**) with vinyl magnesium bromide, followed by subsequent reductive cleavage of benzyloxy alcohol **7** with Li in liquid NH_3. The *Prins* cyclization of **4** with 5-phenylpentanal (**5**) in the presence of TFA (10 equiv.), followed by hydrolysis of the resulting trifluoroacetate, gave the trisubstituted pyran **8** in 50% yield [12]. The

Scheme 2



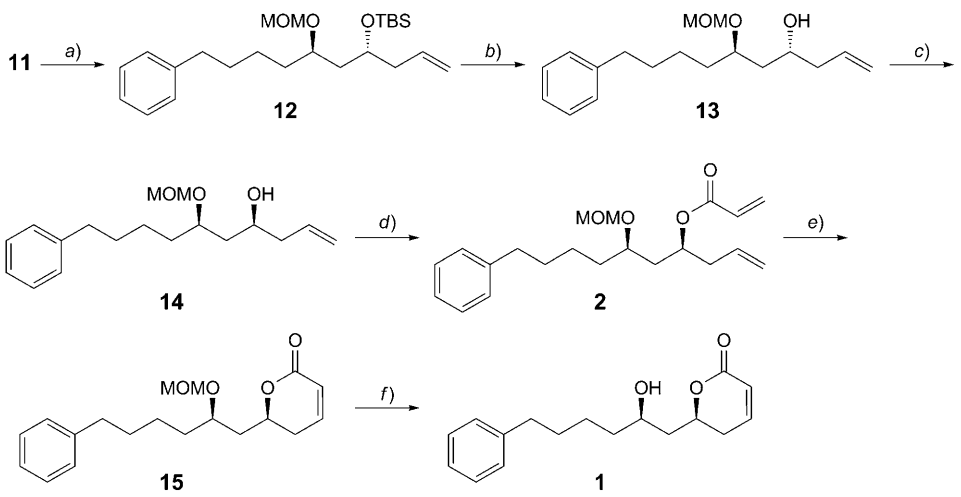
a) CH_2=CHMgBr, CuCN, –78° to –40°, 4 h; 92%. *b*) Li, liquid NH_3, THF, 20 min; 75%. *c*) 5-Phenylpentanal (**5**), CF_3COOH (TFA), CH_2Cl_2, then K_2CO_3, MeOH, r.t., 3 h; 50%. *d*) Et_3N, TsCl, CH_2Cl_2, 0° to r.t., 3 h; 96%. *e*) (*t*-Bu)Me_2SiCl (TBSCl), 4-(dimethylamino)pyridine (DMAP), 1*H*-imidazole, CH_2Cl_2, 0° to r.t., 3 h; 95%. *f*) NaI, acetone, reflux, 24 h; 95%. *g*) Zn, EtOH, reflux, 1 h; 98%.

stereochemistry of step *c* leading to **8** was assumed to be in accordance with previous results [9]. However, it was later established after elaborating compound **8** to the target molecule **1**, which in all respects was identical with that described in literature [1].

The chemoselective tosylation of primary alcohol **8** with 1.1 equiv. of TsCl in the presence of Et_3N in CH_2Cl_2 gave the corresponding tosyl derivative **9** in 96% yield [13]. TBS Protection of the secondary alcohol **9** with TBSCl, DMAP, and 1*H*-imidazole afforded the TBS ether **10** in 95% yield. Treatment of **10** with NaI in refluxing acetone gave the corresponding iodo compound **3** in 95% yield, which, on exposure to activated Zn in refluxing EtOH, furnished key intermediate **11**.

Secondary alcohol **11** was protected as its methoxymethyl (MOM) ether **12** using MOM-Cl and $EtN(i\text{-}Pr)_2$ in CH_2Cl_2 (*Scheme 3*). Deprotection of TBS ether **12** with Bu_4NF in THF gave the alcohol **13** in 90% yield, which was subjected to standard *Mitsunobu* reaction conditions [14] using diethyl azodicarboxylate (DEAD), PPh_3, and 4-nitrobenzoic acid, followed by hydrolysis of the resulting ester with K_2CO_3 in MeOH, to give the homoallylic alcohol **14** with inversion of configuration. Homoallyl alcohol **14** was then subjected to esterification with acryloyl chloride to obtain the diene ester **2**. The obtained ester **2** was used for the ring-closing metathesis (RCM) with *Grubbs*' first-generation catalyst (5 mol-%) to provide the desired lactone **15** [15]. Finally, deprotection of MOM ether **15** was achieved with 6N HCl/THF/H_2O 1:2:1 to afford the target natural product **1**. The spectral and physical data of all the compounds were in good agreement with literature values [1].

Scheme 3



a) Methoxymethyl chloride (MOM-Cl), DIPEA, CH_2Cl_2, 4 h, 0°; 93%. *b*) Bu_4NF, THF, 0° to r.t., 2 h; 90%. *c*) 4-Nitrobenzoic acid, diethyl azodicarboxylate (DEAD), PPh_3 then K_2CO_3, MeOH, r.t., 0.5 h; 86%. *d*) Acryloyl chloride, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, 0° to r.t.; 83%. *e*) *Grubbs*' I generation catalyst [$(PCy_3)_2Cl_2Ru{=}CHPh$] (5 mol-%), dry CH_2Cl_2, 55°, 12 h; 90%. *f*) 6N HCl/THF/H_2O 1:2:1, r.t., 24 h; 92%.

In conclusion, we have established the versatility of the *Prins* cyclization and a subsequent reductive cleavage in natural-product synthesis by achieving the stereo-

selective synthesis of the antiproliferative and antifungal natural product (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (**1**). To the best of our knowledge, this is the first report on the total synthesis of **1** by means of the *Prins* cyclization.

Experimental Part

General. Solvents were dried over standard drying agents and freshly distilled prior to use. The reagents were purchased from the *Aldrich* and *Acros*, and were used without further purification unless otherwise stated. All moisture-sensitive reactions were carried out under N_2. Org. solns. were dried over anh. Na_2SO_4 and concentrated *in vacuo* below 40°. Column chromatography (CC): silica gel (SiO_2; 60–120 mesh, *Acme*). Optical rotations: *Horiba* high-sensitive polarimeter *SEPA-300* at 25°. IR Spectra: *Perkin-Elmer IR-683* spectrophotometer with NaCl optics. ^{1}H- (300 MHz) and ^{13}C-NMR (75 MHz) spectra: *Bruker Avance 300* instrument with TMS as internal standard in $CDCl_3$; *J* values in Hz. MS: *Agilent Technologies 1100 Series* (Agilent Chemistation Software).

*(1*R*)-1,5-Anhydro-2,4-dideoxy-1-(4-phenylbutyl)-*L-threo-*hexitol* (**8**). Trifluoroacetic acid (TFA; 23.4 ml, 306 mmol) was added to a soln. of homoallylic alcohol **4** (1.04 g, 10.18 mmol) and 5-phenylpentanal (5 g, 30.6 mmol) in dry CH_2Cl_2 (30 ml) under N_2. The progress of the reaction was followed by TLC. Upon completion, the reaction was quenched with aq. $NaHCO_3$ soln., and the pH was adjusted to >7 by addition of Et_3N. The aq. phase was extracted with CH_2Cl_2 (3 × 20 ml), and the combined org. layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude trifluoroacetate was then dissolved in MeOH (20 ml) and treated with K_2CO_3 (770 mg, 7.2 mmol) overnight. After complete conversion, MeOH was removed under reduced pressure, and then the reaction was quenched with H_2O (20 ml), and the mixture was extracted with CH_2Cl_2 (3 × 25 ml). The combined org. layers were dried ($MgSO_4$) and concentrated *in vacuo*. The product was then purified by flash CC to afford **8** (310 mg, 50% yield over two steps). White solid. $[\alpha]_D^{20} = -1.1$ ($c = 1.4$, $CHCl_3$). IR (KBr): 3310, 3083, 3025, 2929, 2855, 1941, 1702, 1605, 1472, 1369, 1260, 1159, 1077, 1018, 934, 828, 694, 635. ^{1}H-NMR: 7.29–7.05 (*m*, 5 H); 3.85–3.65 (*m*, 1 H); 3.61–3.21 (*m*, 4 H); 2.60 (*t*, *J* = 7.5, 2 H); 2.09–1.72 (*m*, 4 H); 1.71–1.31 (*m*, 5 H); 1.29–1.00 (*m*, 2 H). ^{13}C-NMR: 142.4; 128.3; 128.2; 125.6; 75.8; 75.5; 67.8; 65.8; 40.9; 36.7; 35.8; 35.7; 31.3; 25.0. LC/MS: 287 ($[M+Na]^+$).

*(1*R*)-1,5-Anhydro-2,4-dideoxy-6-*O*-[(4-methylphenyl)sulfonyl]-1-(4-phenylbutyl)-*L-threo-*hexitol* (**9**). To a soln. of **8** (300 mg, 1.16 mmol) in dry CH_2Cl_2 (10.0 ml), Et_3N (0.32 ml, 2.32 mmol) was added at 0°. Then, TsCl (265 mg, 1.39 mmol) was added over 2 h. The resulting mixture was allowed to stir at r.t. for 3 h. Then, the mixture was treated with 1M aq. HCl (4 ml) and extracted with CH_2Cl_2 (3 × 5 ml). The org. layer was washed with sat. $NaHCO_3$ (5 ml) and H_2O (5 ml). The combined org. phases were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (FC) of the crude product afforded **9**. $[\alpha]_D^{20} = +13.2$ ($c = 0.55$, $CHCl_3$). ^{1}H-NMR: 7.76 (*d*, *J* = 8.0, 2 H); 7.34–7.07 (*m*, 7 H); 4.01–3.90 (*m*, 1 H); 3.80–3.63 (*m*, 1 H); 3.58–3.42 (*m*, 1 H); 3.30–3.13 (*m*, 1 H); 2.63–2.53 (*m*, 2 H); 2.45 (*s*, 3 H); 1.96–1.69 (*m*, 3 H); 1.67–1.48 (*m*, 2 H); 1.47–1.20 (*m*, 4 H); 1.19–0.86 (*m*, 2 H). ^{13}C-NMR: 144.7; 142.4; 132.8; 129.7; 128.3; 128.2; 127.8; 125.5; 75.6; 72.7; 71.9; 67.5; 40.6; 36.8; 35.7; 35.5; 31.3; 25.0; 21.5. LC/MS: 441 ($[M+Na]^+$).

*(1*R*)-1,5-Anhydro-3-*O*-[(*tert*-butyl)(dimethyl)silyl]-2,4-dideoxy-6-*O*-[(4-methylphenyl)sulfonyl]-1-(4-phenylbutyl)-*L-threo-*hexitol* (**10**). To a soln. of **9** (300 mg, 0.71 mmol) in dry CH_2Cl_2 (5 ml) and 1*H*-imidazole (98 mg, 1.43 mmol) at 0° under N_2 was added (*t*-Bu)Me_2SiCl (TBSCl; 215 mg, 1.43 mmol), and the resulting mixture was allowed to stir for 3 h at r.t. Then, the mixture was diluted with H_2O (3 ml) and extracted with CH_2Cl_2 (2 × 5 ml). The combined org. layers were washed with brine (1 × 5 ml), dried (Na_2SO_4), and concentrated under vacuum to afford the crude product. CC of the crude product gave **10**. Colorless liquid. $[\alpha]_D^{20} = +2.3$ ($c = 1.15$, $CHCl_3$). ^{1}H-NMR: 7.97–7.94 (*d*, *J* = 8.3, 2 H); 7.50–7.36 (*m*, 5 H); 7.33–7.26 (*m*, 2 H); 4.15–4.08 (*m*, 2 H); 3.91–3.80 (*m*, 1 H); 3.72–3.62 (*m*, 1 H); 3.41–3.31 (*m*, 1 H); 2.76 (*t*, *J* = 7.5, 2 H); 2.62 (*s*, 3 H); 1.95–1.83 (*m*, 2 H); 1.82–1.70 (*m*, 2 H); 1.69–1.39 (*m*, 4 H); 1.37–1.22 (*m*, 2 H); 1.03 (*s*, 9 H); 0.20 (*s*, 6 H). ^{13}C-NMR: 144.6; 142.5; 129.7; 128.3; 128.2; 127.9; 125.5; 75.6; 72.7; 72.1; 68.1; 41.2; 37.4; 35.8; 35.6; 31.4; 25.7; 25.0; 21.6; 17.9; −4.5. LC/MS: 555 ($[M+Na]^+$).

*(*tert*-Butyl){[(2*R*,4*S*,6*R*)-2-(iodomethyl)-6-(4-phenylbutyl)tetrahydro-2*H*-pyran-4-yl]oxy}dimethylsilane* (**3**). NaI (493 mg, 3.28 mmol) was added to a soln. of **10** (350 mg, 0.657 mmol) in 10 ml of acetone and heated to reflux for 24 h. Acetone was removed under reduced pressure, the residue was diluted with H_2O and AcOEt, and the org. layer was separated, dried (Na_2SO_4), and concentrated *in vacuo*. The resulting crude product was purified by CC to afford **3**. Colorless liquid. $[\alpha]_D^{20} = -11.4$ ($c = 1.1$, $CHCl_3$). IR (KBr): 3449, 3025, 2930, 2855, 1636, 1495, 1461, 1254, 1130, 1073, 838, 774, 746, 697. ^{1}H-NMR: 7.45–7.23 (*m*, 5 H); 3.95–3.82 (*m*, 1 H); 3.51–3.36 (*m*, 1 H); 3.35–3.24 (*m*, 2 H); 2.80–2.73 (*m*, 2 H); 2.21–2.11 (*m*, 2 H); 1.89–1.48 (*m*, 6 H); 1.46–1.23 (*m*, 2 H); 1.03 (*s*, 9 H); 0.20 (*s*, 6 H). ^{13}C-NMR: 142.7; 128.3; 128.3; 125.5; 75.8; 75.2; 68.4; 41.3; 41.2; 35.9; 35.7; 31.4; 25.8; 25.3; 18.0; 9.0; −4.5. LC/MS: 489 ($[M+H]^+$).

*(5*R*,7*R*)-7-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-1-phenyldec-9-en-5-ol* (**11**). To **3** (300 mg, 0.613 mmol) in EtOH (10 ml), commercial Zn dust (66.3 mg, 9.20 mmol) was added, and the resulting mixture was refluxed for 1 h and then cooled to 25°. Addition of solid NH_4Cl and Et_2O (15 ml), followed by stirring for 5 min, gave a gray suspension which was filtered through *Celite*, and the filtrate was concentrated *in vacuo*. The resulting crude product was purified by FC to give **11**. Colorless liquid. $[\alpha]_D^{20} = -10.6$ ($c = 0.35$, $CHCl_3$). IR (KBr): 3456, 3073, 2931, 2856, 1640, 1462, 1365, 1253, 1072, 1000, 912, 834, 775, 742, 697. ^{1}H-NMR: 7.28–7.07 (*m*, 5 H); 5.78–5.62 (*m*, 1 H); 5.09–4.99 (*m*, 2 H); 4.05–3.96 (*m,* 1 H); 3.93–3.82 (*m,* 1 H); 2.89 (br. *s*, 1 H); 2.60 (*t*, $J = 7.5$, 2 H); 2.36–2.28 (*m*, 2 H); 1.68–1.23 (*m*, 8 H); 0.90 (*s*, 9 H); 0.09 (*s*, 3 H); 0.08 (*s*, 3 H). ^{13}C-NMR: 142.6; 134.6; 128.3; 128.1; 125.8; 117.3; 71.2; 68.0; 41.1; 40.9; 37.7; 35.9; 31.5; 25.7; 25.2; 17.8; −4.5; −4.8. LC/MS: 363 ($[M+H]^+$).

*(4*S*,6*R*)-6-(Methoxymethoxy)-10-phenyldec-1-en-4-ol* (**14**). To a stirred mixture of **13** (200 mg, 0.492 mmol), Ph_3P (387 g, 1.47 mmol), and 4-nitrobenzoic acid (1.3 g, 0.639 mmol) in dry THF (5 ml) at 0° was added diethyl azodicarboxylate (DEAD; 0.18 ml, 1.47 mmol) *via* a syringe. The mixture was then stirred for another 0.5 h at r.t., then diluted with H_2O (5 ml), and extracted with AcOEt (2×15 ml). After removal of the solvent, the crude residue was dissolved in MeOH (5 ml) and treated with K_2CO_3 (66 mg, 0.96 mmol). After stirring the mixture for 4 h at r.t., it was diluted with H_2O (5 ml) and extracted with CH_2Cl_2 (3×5 ml). Removal of solvent under reduced pressure, followed by FC, afforded **14**. Colourless liquid. $[\alpha]_D^{20} = -25.4$ ($c = 1.15$, $CHCl_3$). ^{1}H-NMR: 7.27–7.07 (*m*, 5 H); 5.86–5.74 (*m*, 1 H); 5.11–5.03 (*m*, 2 H); 4.59 (*s*, 2 H); 3.87–3.80 (*m*, 1 H); 3.78–3.72 (*m*, 1 H); 3.34 (*s*, 3 H); 2.61–2.57 (*m*, 2 H); 2.21–2.15 (*m*, 2 H); 1.69–1.45 (*m*, 7 H); 1.42–1.29 (*m*, 2 H). ^{13}C-NMR: 142.1; 134.8; 128.7; 125.8; 117.5; 95.3; 71.1; 67.17; 55.5; 41.9; 40.8; 36.6; 34.1; 31.4; 30.6; 24.3. LC/MS: 292 (M^+).

*(1*S*,3*R*)-3-(Methoxymethoxy)-7-phenyl-1-(prop-2-en-1-yl)hept-1-yl Prop-2-enoate* (**2**). To a stirred soln. of **14** (200 mg, 0.69 mmol) in dry CH_2Cl_2 (5 ml) were added acryloyl chloride (0.1 ml, 1.37 mmol) and EtN(i-Pr)$_2$ (0.4 ml, 2.748 mmol) at 0°. The resulting mixture was allowed to stir at r.t. for 3 h. The mixture was then diluted with H_2O (5 ml) and extracted with CH_2Cl_2 (3×5 ml). The combined org. layers were dried (Na_2SO_4), and the solvent was removed under vacuum to give the crude residue, which was purified by SiO_2 CC to afford pure **2**. $[\alpha]_D^{20} = +25.1$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3506, 3432, 1926, 1733, 1450, 1098, 985, 746. ^{1}H-NMR (200 MHz, *Varian gemini FT-200*): 7.21 (*t*, $J = 7.5$, 2 H); 7.11 (*t*, $J = 5.2$, 3 H); 6.36 (*d*, $J = 7.3$, 1 H); 6.12–6.0 (*m*, 1 H); 5.82–5.65 (*m*, 2 H); 5.15–5.01 (*m*, 3 H); 4.63–4.50 (*m*, 2 H); 3.63–3.49 (*m*, 1 H); 3.39–3.28 (*m*, 3 H); 2.59 (*t*, $J = 7.5$, 2 H); 2.45–2.26 (*m*, 2 H); 2.0–1.23 (*m*, 8 H). FAB-MS: 285 ($[M + OCH_2 - OMe]^+$).

*(6*S*)-5,6-dihydro-6-[(2*R*)-2-(methoxymethoxy)-6-phenylhexyl]-2*H*-pyran-2-one* (**15**). To a stirred soln. of bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride (*Grubbs*' catalyst; 22 mg, 5 mol-%) in CH_2Cl_2 (50 ml) at 55° was added a soln. of **14** (190 mg, 0.54 mmol) in CH_2Cl_2 (10 ml). The resulting mixture was heated for 12 h. After completion of the reaction, the contents were cooled, and the solvent was removed under reduced pressure to yield a crude product, which was purified by SiO_2 CC to afford pure **15**. $[\alpha]_D^{20} = -38.6$ ($c = 0.65$, $CHCl_3$). IR (KBr): 2933, 1724, 1386, 1299, 1034, 750. ^{1}H-NMR: 7.22 (*t*, $J = 8.3$, 2 H); 7.11 (*t*, $J = 7.1$, 3 H); 6.87–6.79 (*m*, 1 H); 5.99 (*d*, $J = 9.4$, 1 H); 4.63–4.49 (*m*, 3 H); 3.75–3.66 (*m*, 1 H); 3.30 (*s*, 3 H); 2.60 (*t*, $J = 7.5$, 2 H); 2.41–2.25 (*m*, 2 H); 2.15–2.02 (*m*, 1 H); 1.70 (*m*, 5 H). LC/MS: 318 (M^+).

*(6*S*)-5,6-Dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one* (**1**). Compound **15** (150 mg, 0.414 mmol) was stirred in 4 ml of 6N HCl/THF/H_2O 1:2:1 for 24 h. The reaction was quenched with sat. $NaHCO_3$ (5 ml) and H_2O (5 ml), and the mixture was extracted with AcOEt. The combined org. layers

were washed with brine (1×5 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting crude product was purified by CC to afford **1**. Pale-yellow solid. M.p. 33–35°. $[\alpha]_D^{20} = -64.9$ ($c = 0.65$, $CHCl_3$). IR (KBr): 3457, 2938, 2848, 1695, 1487, 1392, 1254. ^{1}H-NMR: 7.33–7.12 (*m*, 5 H); 6.94–6.84 (*m*, 1 H); 6.02 (*dd*, $J = 1.4$, 9.4, 1 H); 4.82–4.65 (*m*, 1 H); 4.07–3.93 (*m*, 1 H); 2.62 (*t*, $J = 7.2$, 2 H); 2.40–2.30 (*m*, 2 H); 1.97–1.81 (*m*, 1 H); 1.70–1.58 (*m*, 3 H); 1.52–1.38 (*m*, 4 H). ^{13}C-NMR: 164.4; 145.4; 142.3; 128.2; 128.1; 125.5; 121.2; 74.9; 66.8; 42.2; 37.7; 35.8; 31.3; 29.8; 25.1. LC/MS: 275 ($[M+H]^+$).

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