A Stereoselective Aldol Approach for the Total Syntheses of Two 6-Alkylated 2*H*-Pyran-2-ones

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A simple and highly efficient stereoselective total synthesis of the 6-alkylated pyranones (6*R*)-6-[(1*E*,4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one (**1**) and (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (**2**) was developed using *Crimmins*' aldol reaction, SmI_2 reduction, *Grubbs-II*-catalyzed olefin cross-metathesis, and *Still*'s modified *Horner–Wadsworth–Emmons* reaction.

Introduction. – The α-pyrone (=2*H*-pyran-2-one) ring system occurs in a number of natural products and is also featured in many intermediates that are required for the synthesis of biologically important compounds [1]. 5,6-Dihydro-α-pyrone-containing natural products with a substituted arylalkyl side chain at C(6) have attracted much attention over the last decade due to the *Michael*-acceptor nature of the α,β-unsaturated α-pyrones for the amino acid residues of receptors [2]. In particular, α,β-unsaturated α-pyrones have been shown to exhibit a wide range of biological activities including inhibition of HIV protease, and antileukemic, anticancer, antifeedent, antifungal, antibacterial, and antitumor activities [3]. Most of these compounds carry a (poly)hydroxylated chain at C(6) of the α-pyrone moiety, *e.g.*, (6*R*)-6-[(1*E*,4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one (**1**), (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (**2**) and, (+)-strictifolione (**3**) (*Fig.*). Compounds **1** and **2** were isolated from *Ravensara crassifolia* by *Hostetmann* and co-workers [4a], and a structurally similar compound **3** was isolated by *Aimi* and co-workers [4b] from the stem bark of *Cryptocarya strictifolia*. The structures and absolute configurations were established through NMR spectroscopic studies. Compounds **1** and **2** exhibited antifungal activities against the phytopathogenic fungus *Cladosporium cucumarinum*. Therefore, the syntheses of both compounds **1** [5] and **2** [6] have recently become attractive targets to organic chemist. Recently, we reported the synthesis of compound **2** [6a] and evaluated its biological properties. Our continuing interest towards the total synthesis of lactone-containing natural products [7] and important biological properties of **1** and **2** (*Fig.*) prompted us to undertake the

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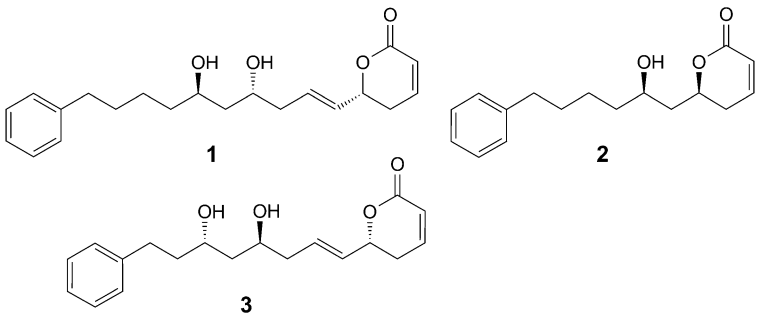


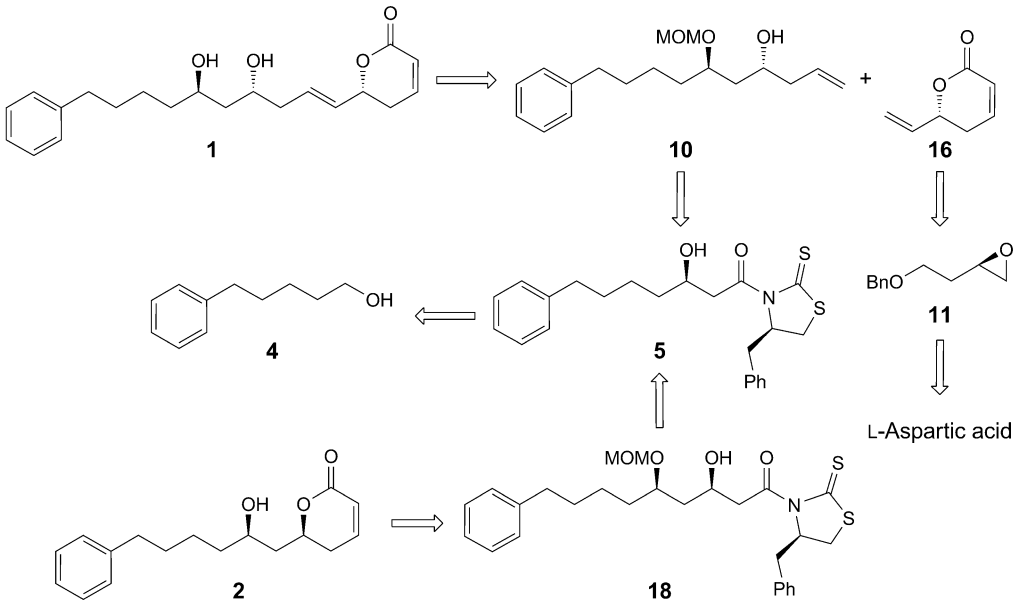
Figure. *Structures of (6*R*)-6-[(1*E*,4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one* (**1**), *(6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one* (**2**), *and (+)-strictifolione* (**3**)

synthesis of these compounds starting from a common, commercially available starting material.

Herein, we report the stereoselective synthesis of (6*R*)-6-[(1*E*,4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one (**1**) by applying *Crimmins*' aldol reaction, SmI_2 reduction of an alkoxy ketone, *Grubbs-II*-catalyzed olefin cross-metathesis from commercially available 5-phenylpentan-1-ol (**4**) and L-aspartic acid. The synthesis of (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (**2**) was accomplished by *Crimmin*'s aldol reaction and *Still*'s modified *Horner–Wadsworth–Emmons* olefination reaction as key steps starting from commercially available 5-phenylpentan-1-ol (**4**). The retrosynthetic analyses of compounds **1** and **2** are depicted in *Scheme 1*.

Results and Discussion. – The synthesis of **1** and **2** started from 5-phenylpentan-1-ol (**4**), which was subjected to oxidation using 2-iodoxybenzoic acid (IBX) in DMSO to give the corresponding aldehyde in 94% yield. The latter was reacted with (*R*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone [8] in the presence of EtN^iPr_2 and $TiCl_4$ according to the *Crimmins*' protocol to give the easily separable diastereoisomers of the β-hydroxy amide with the required *syn*-product **5** and *anti*-product **5a** in 82% yield (*syn*/*anti* 8.4:1.6 [9]; *Scheme 2*). The diastereoselectivity of the *Crimmins*' aldol reaction was determined by HPLC (column, *DISCOVERY C8* 250 × 4.6 mm, 5 μm; MeCN/H_2O 60:40; flow rate, 1.0 ml/min, $\lambda = 210$ nm: t_R 17.01 min (minor; 16%), 17.98 min (major; 84%). The OH group in compound **5** was then protected as MOM (methoxymethyl) ether **6**, and subsequent reaction with DIBAL-H afforded aldehyde **7** [6e] (*Scheme 2*), which was subjected to the Zn-mediated allylation in aqueous medium to afford diastereoisomers of secondary alcohol **8** (1:1), which, on further oxidation with *Dess–Martin* periodinane (DMP), furnished the ketone **9**. The stereoselective reduction of the oxo group in **9** with SmI_2 [10a] (*Scheme 2*) in THF and MeOH as proton source for 12 h afforded the required *anti*-1,3-diastereoisomer **10** as the major product (*Yadav et al.* prepared this intermediate *via* a different approach using a *Prins* cyclization [6f]). The 1,3-*anti*-relationship of the two OH groups in **9** was established by analysis of the ^{13}C-NMR spectrum of the corresponding acetonide [10b].

Scheme 1. *Retrosynthetic Analysis*

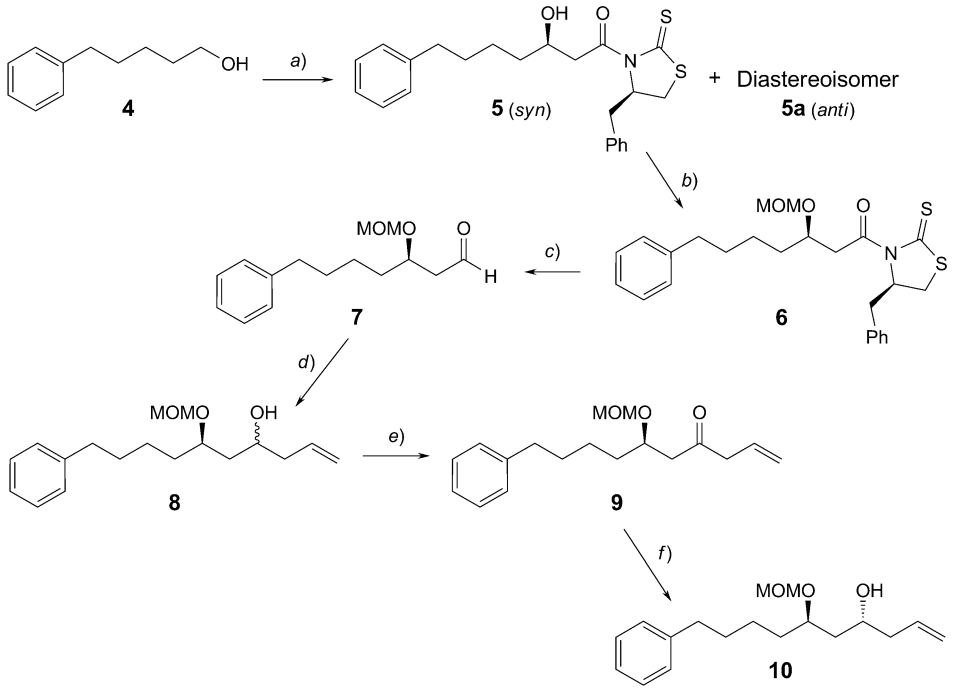


The lactone **16** is a key intermediate in the syntheses of various compounds and has been prepared by several groups [11]; thus, there is still a need for a simple and efficient procedure for its synthesis. We have prepared **16** according to a known procedure [11e] from the chiral synthon **11**, which was obtained from L-aspartic acid [12] (*Scheme 3*). Opening of epoxide **11** with Me_3SI and BuLi in dry THF provided the secondary allyl alcohol **12** in 77% yield (*Scheme 3*), which was protected as its methoxymethyl (MOM) ether **13**. Deprotection of the Bn group in compound **13** was achieved with lithium naphthalenide [13] to yield the primary alcohol **14** in 81% yield. The OH group of **14** was oxidized using 2-iodoxybenzoic acid (IBX) in DMSO to give the corresponding aldehyde in 85% yield, which was subjected to *Still*'s modified *Horner–Wadsworth–Emmons* olefination reaction [14] to afford the unsaturated ester **15** in 76% yield. Compound **15** was treated with TsOH in benzene to afford 5,6-dihydro-6-vinyl-α-pyrone **16** in 80% yield (*Scheme 3*).

Finally, compounds **10** and **16** (in a 1:3 ratio) were subjected to olefin cross-metathesis using *Grubbs-II* catalyst (5 mol-%) [15] in CH_2Cl_2 under reflux conditions to yield the desired compound **17** in 74% yield (*Scheme 4*). The MOM protecting group in **17** was removed by treatment with $CeCl_3 \cdot 7\ H_2O$, MeCN/MeOH 1:1 to afford **1** in 78% yield (*Scheme 4*). The optical rotation, ^{1}H- and ^{13}C-NMR data of the synthetic compound **1** are in good agreement with those of the natural product [4].

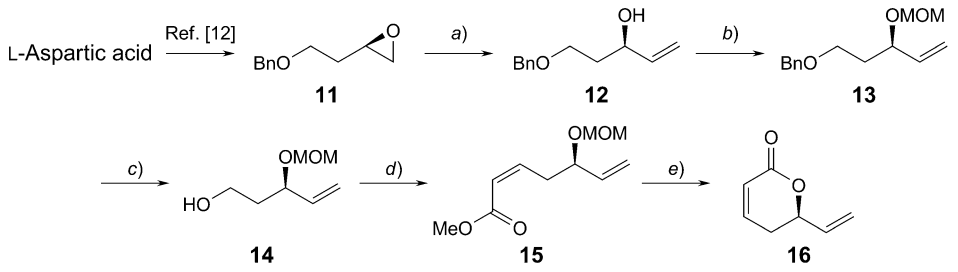
After having accomplished the synthesis of **1**, we prepared compound **2**, by reacting aldehyde **7** with (*R*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone in the presence of $TiCl_4$ using *Crimmins*' protocol to give the easily separable diastereoisomers of β-hydroxy amide, *i.e.*, the required *syn*-product **18** and the *anti*-product **18a** in 79% yield (*syn*/*anti* 7.8:2.8; *Scheme 5*). The OH group of **18** was protected as MOM ether **19**,

Scheme 2



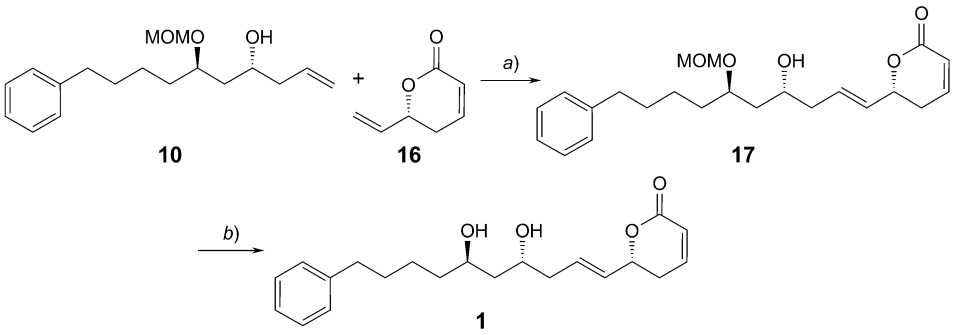
a) 1. IBX (*2*-Iodoxybenzoic acid), dry DMSO, dry CH_2Cl_2, 0° to r.t., 2 h; 94%; 2. 1-[(4*R*)-4-benzyl-2-thioxo-1,3-thiazolidin-3-yl]ethanone, $TiCl_4$, EtN^iPr_2, dry CH_2Cl_2, −78°, 30 min, 82%. *b*) Methoxymethyl chloride (MOMCl), EtN^iPr_2, dry CH_2Cl_2, 0° to r.t., 4 h; 87%. *c*) Diisobutylaluminium hydride (DIBAL-H), dry CH_2Cl_2, −78°, 3 h; 90%. *d*) Zn, allyl bromide (C_3H_5Br), NH_4Cl, 0° to r.t., 4 h; 92%. *e*) *Dess–Martin* periodinane (DMP), $NaHCO_3$, dry CH_2Cl_2, 0° to r.t., 3 h; 90%. *f*) SmI_2, MeOH/THF, r.t., 12 h, 76%.

Scheme 3



a) Me_3SI (trimethylsulfonium iodide), BuLi, dry THF, −10° to r.t., 12 h; 77%. *b*) MOMCl, EtN^iPr_2, dry CH_2Cl_2, 0° to r.t., 3 h; 85%, *c*) Li in naphthalene, −20°, 3 h; 81%. *d*) 1. IBX, dry DMSO, dry CH_2Cl_2, 0° to r.t., 3 h; 85%; 2. $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, dry THF, −78°, 4 h; 76%. *e*) TsOH, dry benzene, reflux, 12 h; 80%.

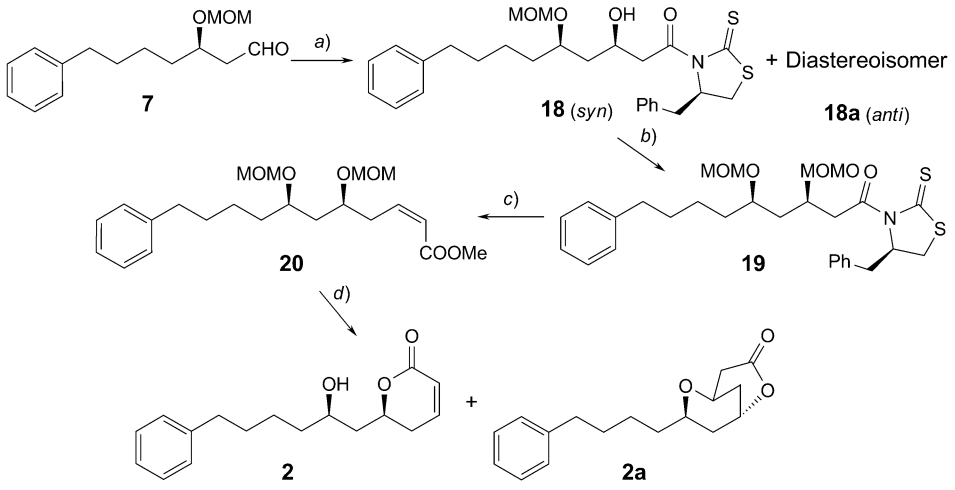
Scheme 4



a) *Grubbs-II*-catalyst (5 mol-%), dry CH_2Cl_2, 40°, 12 h; 74%. *b*) $CeCl_3 \cdot 7\ H_2O$, MeCN/MeOH 1:1, reflux, 6 h; 85%.

which was reduced with DIBAL-H to yield the corresponding aldehyde, which was further subjected to *Still*'s modified *Horner–Wadsworth–Emmons* olefination reaction [14] to afford the unsaturated ester **20** in a (*Z*)/(*E*) ratio of 95:5 and 74% yield. Lactonization of compound **20** was carried out by treatment with 3% HCl in THF to afford a separable mixture of the natural product **2** and compound **2a** (7:3) in 78% yield. The formation of a significant amount of the bicyclic lactone **2a** was presumably due to the involvement of the OH group of **2** (*Scheme 5*) in the *Michael* addition

Scheme 5



a) 1-[(4*R*)-4-Benzyl-2-thioxo-1,3-thiazolidin-3-yl]ethanone, $TiCl_4$, EtN^iPr_2, dry CH_2Cl_2, −78°, 30 min; 79%. *b*) MOMCl, EtN^iPr_2, dry CH_2Cl_2, 0° to r.t., 5 h; 83%. *c*) 1. DIBAL-H, dry CH_2Cl_2, −78°, 3 h; 82%; 2. $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, dry THF, −78°, 4 h; 74%. *d*) 3M HCl/THF 1:1, 0° to r.t., 3 h; 78%.

reaction. The optical rotation, and ^{1}H- and ^{13}C-NMR data of the synthetic compound **2** are in good agreement with those of the natural product [4].

Conclusions. – In conclusion, total syntheses of (6*R*)-6-[(1*E*,4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one (**1**) and (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (**2**) have been achieved by successful application of *Crimmins*' aldol reaction, SmI_2 reduction of alkoxy ketone, and *Grubbs-II*-catalyzed olefin cross-metathesis as key steps starting from commercially available 5-phenylpentan-1-ol (**4**) and L-aspartic acid.

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Experimental Part

General. Solvents were dried over standard drying agents and freshly distilled prior to use. The reagents were purchased from *Aldrich* and *Acros*, and were used without further purification unless otherwise stated. All moisture-sensitive reactions were carried out under N_2. Org. soln. were dried over anh. Na_2SO_4 and concentrated *in vacuo* below 40°. Column chromatographic (CC) separations: silica gel (*Acme*'s, 60–120 mesh and 100–200 mesh; SiO_2). Optical rotations: *Horiba* highly sensitive polarimeter *SEPA-300* at 25°. IR Spectra: *PerkinElmer IR-683* spectrophotometer with NaCl optics. ^{1}H- and ^{13}C-NMR (300 and 75 MHz, resp.) 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).

*(3*R*)-1-[(4*R*)-4-Benzyl-2-thioxo-1,3-thiazolidin-3-yl]-3-hydroxy-7-phenylheptan-1-one* (**5**). To a cooled (0°) stirred soln. of IBX (5.56 g, 19.87 mmol) in dry DMSO (15 ml) was added a soln. of **4** (2.2 g, 13.25 mmol) in dry CH_2Cl_2 (25 ml) at 0°, and the mixture was stirred for 2 h at r.t. After completion of the reaction, the mixture was filtered, diluted with H_2O (15 ml), and extracted into CH_2Cl_2 (2 × 30 ml). The combined org. extract was washed with brine, dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude residue was purified by CC (AcOEt/hexane 1:9) to give pure aldehyde (2.04 g, 94%) as a colorless liquid. The aldehyde was directly used for the next reaction. To a cooled (0°) soln. of the chiral 1-[(4*R*)-4-benzyl-2-thioxo-1,3-thiazolidin-3-yl]ethanone [8] (3.06 g, 12.19 mmol) in dry CH_2Cl_2 (25 ml) was added dropwise $TiCl_4$ (1.60 ml, 14.63 mmol), and the soln. was stirred for 5 min turning to a yellow color, followed by the addition of EtN^iPr_2 (3.05 ml, 17.56 mmol) [9]. The suspension now turned to dark red (enolate) and was stirred for 20 min at 0° and then cooled to −78°. The above aldehyde (2.0 g, 12.19 mmol) in dry CH_2Cl_2 (15 ml) was added dropwise, and the mixture was stirred for 15 min at −78°. After completion, the reaction was quenched with sat. NH_4Cl (15 ml) soln., and the mixture was extracted with CH_2Cl_2 (3 × 40 ml). The combined org. extract was washed with brine, dried (anh. Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 3:7): pure **5** (4.12 g, 82%). Yellow liquid. $[\alpha]_D^{25} = -281$ ($c = 1.65$, $CHCl_3$), determined by chiral HPLC (*DISCOVERY C8* 250 × 4.6 mm, 5 μm; MeCN/H_2O 60:40; flow rate, 1.0 ml/min, λ = 210 nm): t_R 17.01 min (minor; 16%), 17.98 min (major; 84%). IR (neat): 3448, 3025, 2927, 2855, 1698, 1452, 1366, 1263, 1165, 1102, 1036, 916, 746, 701. ^{1}H-NMR: 7.36–7.08 (*m*, 10 H); 5.41–5.32 (*m*, 1 H); 4.14–4.04 (*m*, 1 H); 3.63 (*dd*, *J* = 2.2, 17.3, 1 H); 3.39 (*dd*, *J* = 7.5, 11.3, 1 H); 3.22 (*dd*, *J* = 3.0, 12.8, 1 H); 3.10–2.98 (*m*, 2 H); 2.89 (*d*, *J* = 12.0, 1 H); 2.63 (*t*, *J* = 7.5, 2 H); 1.73–1.23 (*m*, 6 H). ^{13}C-NMR: 201.3; 173.1; 142.4; 136.3; 129.3; 128.8; 128.3; 128.2; 127.2; 125.6; 68.2; 67.6; 45.8; 36.7; 36.1; 35.9; 31.8; 31.3; 25.1. ESI-MS: 436 ($[M + Na]^+$).

*(3*R*)-1-[(4*R*)-4-Benzyl-2-thioxo-1,3-thiazolidin-3-yl]-3-(methoxymethoxy)-7-phenylheptan-1-one* (**6**). To a cooled (0°) soln. of **5** (3.2 g, 7.74 mmol) in dry CH_2Cl_2 (10 ml), EtN^iPr_2 (2.69 ml, 15.49 mmol) and then dropwise MOMCl (0.87 ml, 11.62 mmol) were added, and the mixture was stirred for 4 h. After completion of the reaction, the mixture was extracted with CH_2Cl_2, washed with brine, dried (anh. Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 2:8): pure **6** (3.08 g,

87%). Colorless liquid. $[\alpha]_D^{25} = -232.72$ ($c = 0.55$, $CHCl_3$). IR (neat): 3425, 3025, 2927, 2854, 1688, 1601, 1493, 1451, 1342, 1261, 1163, 1042, 745, 700. ^{1}H-NMR: 7.37–7.24 (*m*, 8 H); 7.20–7.16 (*m*, 2 H); 5.36–5.27 (*m*, 1 H); 4.70 (*d*, *J* = 6.7, 1 H); 4.64 (*d*, *J* = 6.7, 1 H); 3.57 (*dd*, *J* = 7.9, 17.3, 1 H); 3.42–3.29 (*m*, 5 H); 3.23 (*dd*, *J* = 3.7, 12.4, 2 H); 3.09–2.98 (*m*, 1 H); 2.88 (*d*, *J* = 11.5, 1 H); 2.63 (*t*, *J* = 7.5, 2 H); 1.72–1.58 (*m*, 4 H); 1.49–1.37 (*m*, 2 H). ^{13}C-NMR: 201.2; 171.9; 142.5; 136.5; 129.4; 128.9; 128.4; 128.2; 127.2; 125.6; 96.6; 74.9; 68.6; 55.6; 44.2; 36.6; 35.8; 35.0; 32.1; 31.4; 24.8. ESI-MS: 480 ($[M + Na]^+$).

*(3*R*)-3-(Methoxymethoxy)-7-phenylheptanal* (**7**) [6e]. To a cooled (−78°) soln. of **6** (0.7 g, 1.53 mmol) in dry CH_2Cl_2 (10 ml) was added 1M DIBAL-H in toluene (1.83 ml, 1.83 mmol), and the mixture was stirred for 10 min at −78°. After completion, the reaction was quenched with sat. sodium potassium tartarate (10 ml), and the mixture was stirred for 0.5 h and then extracted with CH_2Cl_2 (3 × 15 ml). The combined org. extract was washed with brine, dried (anh. Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 2:8): **7** (0.344 g, 90%). Colorless liquid. IR (neat): 3432, 3061, 3026, 2934, 2858, 2728, 1724, 1602, 1494, 1454, 1373, 1210, 1147, 1102, 1035, 917, 747. ^{1}H-NMR: 9.79 (*t*, *J* = 2.2, 1 H); 7.32–7.14 (*m*, 5 H); 4.65 (*s*, 2 H); 4.12–4.02 (*m*, 1 H); 3.33 (*s*, 3 H); 2.70–2.48 (*m*, 4 H); 1.74–1.52 (*m*, 4 H); 1.47–1.34 (*m*, 2 H). ^{13}C-NMR: 201.3; 142.2; 128.3; 128.2; 125.7; 95.8; 73.0; 55.5; 48.7; 35.7; 34.7; 31.2; 24.7. ESI-MS: 273 ($[M + Na]^+$).

*(6*R*)-6-(Methoxymethoxy)-10-phenyldec-1-en-4-ol* (**8**). To a cooled (0°) stirred soln. of **7** (0.3 g, 1.2 mmol), Zn dust (0.23 g, 3.6 mmol), and allyl bromide (C_3H_5Br) (0.16 ml, 2.4 mmol) in THF (15 ml), a sat. NH_4Cl soln. (0.4 ml) was added dropwise. The mixture was stirred for 4 h at r.t., until the aldehyde was totally consumed (TLC). The mixture was filtered, and the precipitate was thoroughly washed with AcOEt. The aq. layer was separated and treated with 5% HCl to dissolve the suspended turbid material. The clear soln. was extracted with AcOEt. The combined org. extract was washed with 10% $NaHCO_3$, dried (anh. Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 2:8): pure **8** (0.32 g, 92%). Colorless liquid. IR (neat): 3454, 3026, 2935, 2858, 1640, 1602, 1494, 1448, 1211, 1148, 1035, 915, 746, 700. ^{1}H-NMR: 7.31–7.14 (*m*, 5 H); 5.92–5.76 (*m*, 1 H); 5.16–5.06 (*m*, 2 H); 4.72–4.60 (*m*, 2 H); 3.97–3.75 (*m*, 2 H); 3.38 (*s*, 3 H); 2.65–2.58 (*t*, *J* = 7.5, 2 H); 2.27–2.19 (*t*, *J* = 7.5, 2 H); 1.69–1.29 (*m*, 8 H). ESI-MS: 315 ($[M + Na]^+$).

*(6*R*)-6-(Methoxymethoxy)-10-phenyldec-1-en-4-one* (**9**). To a cooled (0°) soln. of **8** (0.2 g, 0.68 mmol) in dry CH_2Cl_2 (10 ml) was added *Dess–Martin* periodinane (DMP; 0.58 g, 1.36 mmol), and the mixture was stirred for 3 h at r.t. After completion, the reaction was quenched with sat. $Na_2S_2O_3$ soln., and the mixture was washed with sat. $NaHCO_3$, extracted with CH_2Cl_2 (2 × 5 ml), and washed with brine, dried (anh. Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 2:8): pure **9** (0.18 g, 90%). Colorless liquid. IR (neat): 3024, 2934, 2858, 1714, 1639, 1453, 1370, 1147, 1098, 1037, 918, 745, 700. ^{1}H-NMR: 7.31–7.31 (*m*, 5 H); 5.99–5.84 (*m*, 1 H); 5.21–5.09 (*m*, 2 H); 4.62 (*q*, *J* = 6.7, 2 H); 4.08–3.99 (*m*, 1 H); 3.31 (*s*, 3 H); 3.20 (*dt*, *J* = 1.5, 6.7, 2 H); 2.74 (*q*, *J* = 6.7, 1 H); 2.61 (*t*, *J* = 7.5, 2 H); 2.52 (*d*, *J* = 4.5, 1 H); 1.69–1.49 (*m*, 6 H). ^{13}C-NMR: 207.0; 142.3; 130.2; 128.3; 128.2; 125.6; 118.9; 95.9; 74.3; 55.5; 48.5; 47.4; 35.7; 34.5; 31.3; 24.7. ESI-MS: 313 ($[M + Na]^+$).

*(4*R*,6*R*)-6-(Methoxymethoxy)-10-phenyldec-1-en-4-ol* (**10**) [6f]. To a stirred soln. of **9** (0.15 g, 0.51 mmol) in THF (1 ml) at r.t. was added MeOH (0.6 ml, 15.3 mmol), followed by drtopwise addition of 0.1M SmI_2 in dry THF (17.83 ml, 1.78 mmol). The resulting mixture was stirred for 12 h before the septum was removed and stirring was continued until the color of the soln. changed. The reaction was then quenched with sat. $Na_2S_2O_3$ soln. (5 ml), the mixture was extracted with AcOEt (3 × 5 ml), and the combined org. extract was washed with H_2O (2 × 5 ml), dried (anh. Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 2:8): pure **10** (0.11 g, 76%).

*(6*R*)-5,6-Dihydro-6-[(1*E*,4*R*,6*R*)-4-hydroxy-6-(methoxymethoxy)-10-phenyldec-1-en-1-yl]-2*H*-pyran-2-one* (**17**). A soln. of **10** (0.03 g, 0.1 mmol) and **16** (0.038 g, 0.3 mmol) in dry CH_2Cl_2 (25 ml) in a 1:3 ratio was first bubbled with N_2 flow, then *Grubbs-II* catalyst (0.017 g, 0.02 mmol) was added at once, and the resulting mixture was heated under N_2 at 40° for 12 h. After completion of the reaction, the solvent was removed, and the residue was purified by CC (AcOEt/hexane 3:7): pure **17** (0.029 g, 74%). Colorless liquid. $[\alpha]_D^{25} = -4.37$ ($c = 0.8$, $CHCl_3$). IR (neat): 3455, 3024, 2926, 2855, 1718, 1456, 1382, 1248, 1147, 1033, 969, 816, 746. ^{1}H-NMR: 7.31–7.14 (*m*, 5 H); 6.92–6.84 (*m*, 1 H); 6.05 (*d*, *J* = 9.8, 1 H); 5.95–5.83 (*m*, 1 H); 5.68 (*dd*, *J* = 6.7, 15.8, 1 H); 4.90 (*q*, *J* = 7.5, 1 H); 4.64 (*s*, 2 H); 3.99–3.89 (*m*, 1 H); 3.85–3.74 (*m*, 1 H); 3.39 (*s*, 3 H); 2.62 (*t*, *J* = 7.5, 2 H); 2.47–2.39 (*m*, 2 H); 2.29–2.20 (*m*, 2 H); 1.71–1.48 (*m*,

6 H); 1.44–1.18 (*m*, 2 H). ^{13}C-NMR: 164.0; 144.6; 142.3; 131.3; 129.3; 128.3; 128.2; 125.6; 121.5; 96.3; 77.9; 75.9; 67.0; 55.8; 40.7; 40.1; 35.8; 34.6; 31.4; 29.6; 25.0. ESI-MS: 406 ($[M+NH_4]^+$).

*(6*R*)-6-[(1*E*,4*R*,6*R*)-4,6-Dihydroxy-10-phenyldec-1-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one* (**1**) [5]. To a stirred soln. of **17** (0.02 g, 0.05 mmol) in a mixture of MeOH (3 ml) and MeCN (3 ml) was added $CeCl_3 \cdot 7\ H_2O$ (0.019 g, 0. 05 mmol) under N_2, then the mixture was stirred at reflux for 6 h. After completion, the reaction was quenched with solid $NaHCO_3$, the mixture was filtered, and the filtrate was concentrated, diluted with H_2O and extracted in to AcOEt (3×5 ml). The combined org. extract was washed with brine, dried (anh. Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 4:6): **1** (0.015 g, 85%). White solid. M.p. 62–64°.

*(3*R*,5*R*)-1-[(4*R*)-4-Benzyl-2-thioxo-1,3-thiazolidin-3-yl]-3-hydroxy-5-(methoxymethoxy)-9-phenylnonan-1-one* (**18**). To a cooled (0°) soln. of the chiral 1-[(4*R*)-4-benzyl-2-thioxo-1,3-thiazolidin-3-yl]ethanone [8] (0.5 g, 2.0 mmol) in dry CH_2Cl_2 (15 ml) was added dropwise $TiCl_4$ (0.263 ml, 2.4 mmol), and the soln. was stirred for 5 min, the color turning to a yellow, followed by the addition of EtN^iPr_2 (0.41 ml, 2.4 mmol). The suspension now turned to dark red (enolate) and was stirred for 20 min at 0°. To this entirely dark red enolate, **7** (0.5 g, 2.0 mmol) in dry CH_2Cl_2 (10 ml) was added dropwise, and the mixture was stirred for 15 min at −78°. After completion, the reaction was quenched with sat. NH_4Cl (5 ml) soln., and the mixture was extracted with CH_2Cl_2 (2×20 ml). The combined org. extract was washed with brine, dried (anh. Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 3:7): pure **18** (0.79 g, 79%). Yellow liquid. $[\alpha]_D^{25} = -128.1$ ($c = 2.2$, $CHCl_3$). IR (neat): 3445, 3032, 2931, 1690, 1496, 1455, 1343, 1282, 1271, 1169, 1032, 755, 740. ^{1}H-NMR: 7.39–7.24 (*m*, 8 H); 7.21–7.14 (*m*, 2 H); 5.43–5.34 (*m*, 1 H); 4.67 (*q*, $J = 6.7$, 2 H); 4.41–4.30 (*m*, 1 H); 3.87–3.77 (*m*, 1 H); 3.53 (*dd*, $J = 3.0, 17.5$, 1 H); 3.44–3.39 (*m*, 1 H); 3.38 (*s*, 3 H); 3.34–3.19 (*m*, 2 H); 3.05 (*dd*, $J = 10.5, 13.4$, 1 H); 2.89 (*d*, $J = 11.5$, 1 H); 2.63 (*t*, $J = 3.3$, 2 H); 1.88–1.75 (*m*, 1 H); 1.72–1.50 (*m*, 5 H); 1.46–1.34 (*m*, 2 H). ^{13}C-NMR: 201.2; 172.5; 142.4; 136.4; 129.4; 128.8; 128.3; 128.2; 127.2; 125.6; 95.2; 76.4; 68.4; 66.5; 55.7; 46.1; 40.6; 36.7; 35.8; 34.1; 32.0; 31.5; 24.5. ESI-MS: 524 ($[M+Na]^+$).

*(3*R*,5*R*)-1-[(4*R*)-4-Benzyl-2-thioxo-1,3-thiazolidin-3-yl]-3,5-bis(methoxymethoxy)-9-phenylnonan-1-one* (**19**). To a cooled (0°) soln. of **18** (0.35 g, 0.69 mmol) in dry CH_2Cl_2 (10 ml), EtN^iPr_2 (0.24 ml, 1.39 mmol) and then MOMCl (0.08 ml, 1.0 mmol) was added dropwise, and the mixture was stirred for 5 h. After completion of the reaction, the mixture was extracted with CH_2Cl_2 (2×10 ml), washed with brine, dried (anh. Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 2:8): pure **19** (0.31 g, 83%). Colorless liquid. $[\alpha]_D^{25} = -155.8$ ($c = 0.6$, $CHCl_3$). IR (neat): 3427, 3028, 2924, 1685, 1606, 1493, 1344, 1265, 1166, 1046, 754, 734. ^{1}H-NMR: 7.39–7.12 (*m*, 10 H); 5.37–5.27 (*m*, 1 H); 4.73–4.62 (*m*, 4 H); 4.36–4.25 (*m*, 1 H); 3.72–3.55 (*m*, 2 H); 3.44–3.40 (*m*, 1 H); 3.37 (*s*, 3 H); 3.35 (*s*, 3 H); 3.24 (*dd*, $J = 3.0, 13.5$, 1 H); 3.10–2.98 (*m*, 1 H); 2.89 (*d*, $J = 11.3$, 1 H); 2.63 (*t*, $J = 7.5$, 2 H); 1.78–1.55 (*m*, 5 H); 1.50–1.34 (*m*, 4 H). ^{13}C-NMR: 201.1; 171.7; 142.5; 136.5; 129.4; 128.8; 128.3; 128.2; 127.1; 125.6; 96.7; 95.4; 74.5; 72.5; 68.6; 66.5; 55.7; 44.5; 39.8; 36.5; 35.9; 34.3; 32.1; 31.5; 24.8. ESI-MS: 568 ($[M+Na]^+$).

*Methyl (2*Z*,5*S*,7*R*)-5,7-Bis(methoxymethoxy)-11-phenylundec-2-enoate* (**20**). To a cooled (−78°) soln. of **19** (0.25 g, 0.45 mmol) in dry CH_2Cl_2 (10 ml) was added 1M DIBAL-H in toluene (0.55 ml, 0.55 mmol), and the mixture was stirred at −78° for 10 min. After completion, the reaction was quenched with sat. sodium potassium tartarate (3 ml) soln., and the mixture was srirred for 0.5 h and then extracted with CH_2Cl_2 (3×15 ml). The combined org. extract was washed with brine, dried (anh. Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 2:8): pure aldehyde (0.12 g, 82%). Colorless liquid. The aldehyde was directly used for the next reaction. To a cooled (0°) suspension of NaH (0.017 g, 0.71 mmol) in dry THF (10 ml) under N_2 was added methyl [bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (0.11 ml, 0.53 mmol), and the mixture was stirred for 30 min and then cooled to −78°. The soln. of aldehyde (0.12 g, 0.35 mmol) in dry THF (5 ml) was added dropwise over a period of 5 min. The resulting mixture was stirred for 3 h at −78°. After completion, the reaction was quenched with sat. NH_4Cl soln., and the mixture was extracted with Et_2O (3×5 ml). The combined org. extract washed with brine, dried (Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 2:8): pure **20** (0.1 g, 74%). Colorless liquid. $[\alpha]_D^{25} = +12.7$ ($c = 0.9$, $CHCl_3$). IR (neat): 3433, 2931, 2856, 1722, 1645, 1442, 1406, 1175, 1099, 1036, 917. ^{1}H-NMR: 7.31–7.12 (*m*, 5 H); 6.34 (*dt*, $J =$ 7.1, 11.5, 1 H); 5.92–5.85 (*m*, 1 H); 4.67–4.59 (*m*, 4 H); 3.88–3.78 (*m*, 1 H); 3.70 (*s*, 3 H); 3.69–3.60 (*m*,

1 H); 3.36 (*s*, 3 H); 3.34 (*s*, 3 H); 3.07–2.84 (*m*, 2 H); 2.61 (*t*, *J* = 7.5, 2 H); 1.90–1.77 (*m*, 1 H); 1.70–1.47 (*m*, 5 H); 1.45–1.30 (*m*, 2 H). ^{13}C-NMR: 166.6; 146.0; 142.5; 128.3; 128.2; 125.6; 121.0; 95.4; 95.2; 74.6; 73.8; 55.6; 55.5; 51.0; 39.4; 35.8; 34.3; 33.5; 31.5; 24.7. ESI-MS: 417 ($[M+Na]^+$).

*(6*S*)-5,6-Dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one* (**2**) [6]. To a cooled (0°) soln. of **20** (0.04 g, 0.1 mmol) in THF (2 ml) was added 3M HCl (2 ml), and the mixture was stirred for 3 h. After completion of the reaction, the mixture was diluted with AcOEt, and the reaction was quenched with solid $NaHCO_3$, and the mixture was filtered. The filtrate was washed with brine, dried (anh. Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 1:1): compounds **2** and **2a** (70:30; 78% yield). Compound **2** (0.014 g): pale-yellow solid. M.p. 34–36°.

*(1*R*,7*R*)-7-(4-Phenylbutyl)-2,6-dioxa-bicyclo[3.3.1]nonan-3-one* (**2a**). White solid (0.006 g). M.p. 36–38°. $[\alpha]_D^{25} = -17.1$ ($c = 0.3$, $CHCl_3$). IR (KBr): 2924, 2855, 2102, 1736, 1494, 1078. ^{1}H-NMR: 7.31–7.16 (*m*, 5 H); 4.93–4.88 (*m*, 1 H); 4.38–4.33 (*m*, 1 H); 3.79–3.65 (*m*, 1 H); 2.87–2.78 (*m*, 2 H); 2.58 (*t*, *J* = 7.5, 2 H); 2.05–1.86 (*m*, 3 H); 1.77–1.27 (*m*, 7 H). ^{13}C-NMR: 169.7; 142.4; 128.2 (2); 125.6; 73.0; 65.6; 65.4; 36.8; 36.2; 35.7; 35.4; 31.2; 29.7; 24.6. ESI-MS: 297 ($[M+Na]^+$).

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