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The First Stereoselective Total Synthesis of Putaminoxin E and Its Epimer and Evaluation of Their Biological Properties[‡]

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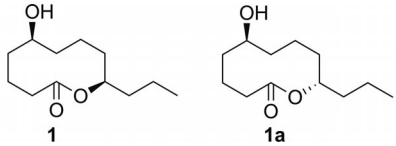
Putaminoxin E, a natural nonanolide, and its C-9 epimer were synthesized for the first time starting from pentane-1,5-diol and butyraldehyde. The synthetic sequences involve Maruoka asymmetric allylation, Sharpless kinetic resolution, and ring-closing metathesis as the key steps. The cytotoxic and antimicrobial activities of these compounds were evaluated.

Introduction

Ten-membered lactonic compounds (nonanolides) are commonly found as naturally occurring secondary metabolites. Putaminoxins are the recent example of these compounds.[1] Various putaminoxins have been isolated in small amounts from culture filtrates of *Phoma putaminoxum*.[1] This fungus is a causal agent of leaf necrosis of *Erigeron annuus*, a weed widely found in fields and pastures. Some of the putaminoxins are known to possess interesting phytotoxic activity.

In continuation of our work[2] on the stereoselective construction of natural products we were interested in the total synthesis of putaminoxin E. The structure of the compound was established as 5-*epi*-6,7-dihydroputaminoxin (**1**) having the stereochemistry of 5*S* and 9*R*.[1c,3] The synthesis of this compound has not yet been reported. Herein we report the first total synthesis of **1** and its C-9 epimer, **1a**, and the evaluation of their biological properties.



[‡] Synthetic Studies on Natural Products, 53; Part 52: D. B. Shinde, B. S. Kanth, M. Srilatha, B. Das, *Synthesis* **2011**, in press.

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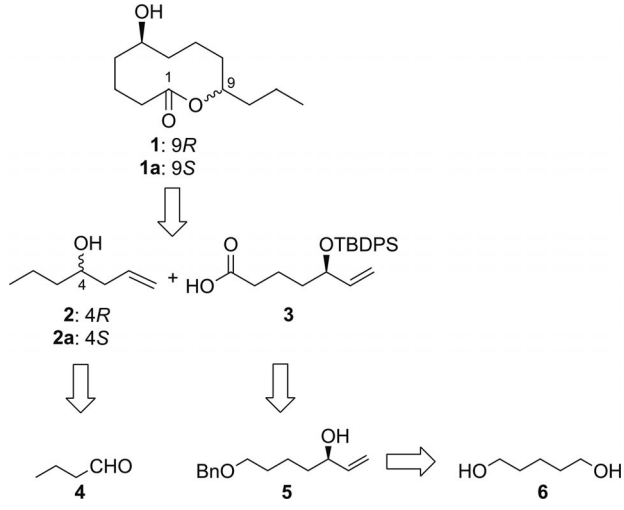
Results and Discussion

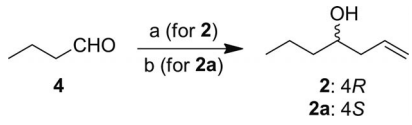
Retrosynthetic analysis (Scheme 1) revealed that **1** can be obtained from two fragments: olefinic alcohol **2** and olefinic acid **3**. Fragment **2** can be prepared from butyraldehyde **4**, whereas fragment **3** can be prepared from benzylic ether **5** generated from pentane-1,5-diol (**6**). Similarly, epimer **1a** can be obtained (Scheme 1) by the coupling of fragment **2a** with the same olefinic acid **3**. Fragment **2a** can also be prepared from butyraldehyde (**4**).



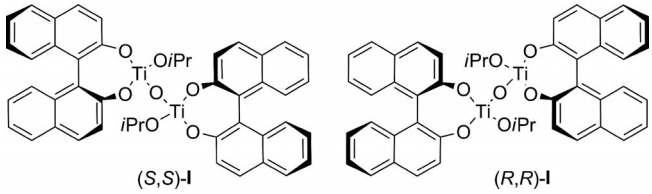
Scheme 1. Retrosynthetic route to putaminoxin E and its epimer.

The present synthesis (Scheme 2) started with commercially available butyraldehyde (**4**), which was subjected to enantioselective Maruoka allylation[4] with titanium complex (*S*,*S*)-**I** and allyltributyltin to form homoallylic alcohol

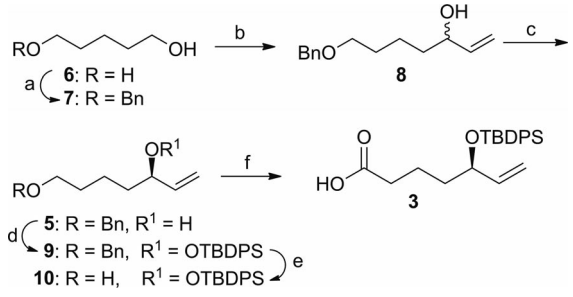
2 with 97%*ee* (determined by chiral HPLC: Chiralcel OB-H; *i*PrOH/hexane, 1:99). When aldehyde **4** was treated with (*R*,*R*)-**I** and allyltributyltin, homoallylic alcohol **2a** was obtained with equal enantioselectivity.



Scheme 2. Reagents and conditions: (a) allyltributyltin, (*S*,*S*)-**I**, dry DCM, –15 to 0 °C, 72 h, 89%; (b) allyltributyltin, (*R*,*R*)-**I**, dry DCM, –15 to 0 °C, 72 h, 89%.

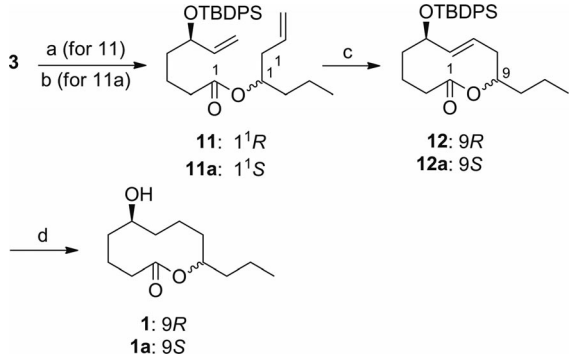


Olefinic acid fragment **3** was synthesized (Scheme 3) by converting pentane-1,5-diol (**6**) into benzylic ether **7** by treatment with benzyl bromide and NaH. Compound **7** underwent Swern oxidation, and the corresponding aldehyde was treated with vinylmagnesium bromide to afford racemic alcohol **8**. The Sharpless kinetic resolution[5] of **8** by using (+)-DET, Ti(O*i*Pr)$_4$, and TBHP produced desired chiral alcohol **5** with 97%*ee* (determined by chiral HPLC), which was separated from the epoxy product by column chromatography. The hydroxy group of **5** was protected as the TBDPS ether to form compound **9** upon treatment with TBDPSCl and imidazole, and subsequently, its benzylic ether moiety was deprotected with DDQ to produce alcohol **10**. Compound **10** was then oxidized with PDC in DMF to generate required olefinic acid **3**.



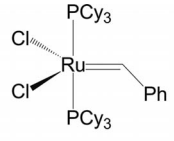
Scheme 3. Reagents and conditions: (a) NaH, BnBr, dry THF, 0 °C to r.t., 2 h, 78%. (b) 1. Oxalyl chloride, DMSO, Et_3N, –78 °C, 3 h; 2. vinylMgBr, 0 °C to r.t., 2 h, 79%. (c) (+)-DET, Ti(O*i*Pr)$_4$, –20 °C, TBHP, 45%. (d) TBDPSCl, imidazole, dry DCM, 0 °C to r.t., 2 h, 90%. (e) DDQ, DCM/H_2O (19:1) reflux, 2 h, 86%. (f) PDC, DMF, r.t., 2 h, 78%.

The coupling of **3** with alcohol **2** was carried out with DCC and DMAP to afford ester **11** (Scheme 4). Compound **11** underwent ring-closing metathesis[6] by employing Grubbs first generation catalyst under high-dilution condition to furnish cyclic compound **12** (*E*:*Z* = 9:1). The Grubbs first generation catalyst was used here, as the second generation catalyst is more expensive and improved the yield of product **12** (derived from **11**) only to a small extent (59% yield, *E*/*Z* = 9:1).[6c,6d] When the silyl group of **11** was deprotected and the corresponding product was subjected to ring-closing metathesis by using Grubbs first generation catalyst the yield was also found to be lower (35%) and the conversion took longer (48 h). Finally, treatment of **12** with H_2 in the presence of Pd/C followed by TBDPS deprotection with TBAF produced target molecule **1**, whose spectral properties were found to be identical to those of natural putaminoxin E.[1c] The optical rotation of the compound was not reported earlier.



Scheme 4. Reagents and conditions: (a) DCC, **2**, DMAP, DCM, 0 °C to r.t., 3 h, 72%. (b) DCC, **2a**, DMAP, DCM, 0 °C to r.t., 3 h, 72%. (c) 1. **12**, Grubbs first generation catalyst (5 mol-%), DCM, reflux, 28 h, 56%, (*E*/*Z* = 9:1); 2. **12a**, Grubbs first generation catalyst (5 mol-%), DCM, reflux, 22 h, 59%, (*E*/*Z* = 9:1). (d) 1. H_2/Pd-C, EtOAc, r.t., 1 h; 2. TBAF, THF, 1 h, overall yield 61%.

Similarly, epimer **1a** of putaminoxin E was synthesized by coupling **3** with alcohol **2a** followed by ring-closing metathesis of resulting ester **11a** by using Grubbs first generation catalyst to produce cyclic ester **12a** (*E*/*Z* = 9:1), which was subsequently treated with H_2 in the presence of Pd/C followed by TBDPS deprotection with TBAF (Scheme 4).



Grubbs first generation catalyst

Putaminoxin E (**1**) and C-9 epimer **1a** were examined for in vitro cytotoxicity against five cancerous cell lines: A-549 (human alveolar adenocarcinoma), MDA-MB-231 (human breast adenocarcinoma), MCF-7 (human breast adenocarcinoma) HeLa (human cervical cancer), and Neuro-2a (mouse neuroblastoma). Doxorubicin was used as the positive control. The MTT assay (according to the method of Mosmann[7]) was utilized to evaluate the activity. The IC_{50}

value for each cell line was determined after four individual observations (Table 1). The results showed that both **1** and **1a** exhibited significant cytotoxic activity against all of the five cell lines. However, the former showed higher activity against the MDA-MB-231 cell line, whereas the latter showed higher activity against A-549, Neuro-2a, and HeLa cell lines.

Table 1. Cytotoxic activity of **1** and **1a**.

Cell line	IC_{50} [μM]		
	Putaminoxin E (**1**)	Epimer **1a**	Doxorubicin (control)
A-549	11.27	8.29	1
Neuro-2a	20.36	10.65	1.2
HeLa	37.36	6.97	<1
MDA-MB-231	6.79	9.01	<1
MCF-7	24.4	24.4	1

The antimicrobial activity of putaminoxin E (**1**) and epimer **1a** was also tested against several bacterial organisms: *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 121), *Staphylococcus aureus* MLS16 (MTCC 2940), *Micrococus luteus* (MTCC 2470), *Klebsiella planticola* (MTCC 530), *Escherichia coli* (MTCC 739), and *Pseudomonas arruginosa* (MTCC 2453) Neomycin was used as the positive control and microtiter broth dilution method was applied to determine the activity.[8] The minimum inhibitory concentration (MIC) value with each pathogen was evaluated after four individual observations (Table 2).

Table 2. Antimicrobial activity of **1** and **1a**.

Test pathogen	IC_{50} [μM]		
	Putaminoxin E (**1**)	Epimer **1a**	Neomycin (control)
S. aureus (MTCC 96)	4.68	–	18.75
B. subtilis (MTCC 121)	–	–	18.75
S. aureus MLS 16 (MTCC 2940)	9.37	–	18.75
M. luteus (MTCC 2470)	–	–	18.75
K. planticola (MTCC 530)	–	–	18.75
E. coli (MTCC 739)	9.37	–	18.75
P. arruginosa (MTCC 2453)	–	4.68	18.75

Putaminoxin E (**1**) showed impressive activity against *P. arruginosa*, whereas epimer **1a** showed activity against *S. aureus* and *E. coli*. Thus, it is assumed that the stereochemistry of **1** and **1a** at C-9 has an important role on both the cytotoxicity and microbial activity of these compounds.

Conclusions

In conclusion, we have developed the first total synthesis of the natural nonanolide putaminoxin E and its C-9 epimer starting from pentane-1,5-diol and butyrolactone involving some simple steps. The cytotoxic and antimicrobial properties of both of these compounds have also been reported.

Experimental Section

General: All commercially available reagents were used directly without further purification unless otherwise stated. The solvents used were all of AR grade and were distilled under a positive pressure of dry nitrogen wherever necessary. The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) performed on Merck Silica Gel 60 F_{254} plates. Column chromatography was carried out by using silica gel 60–120 mesh (Qingdao Marine Chemical, China). IR spectra were recorded with a Perkin–Elmer RX1 FTIR spectrophotometer. Mass spectra were recorded with a VG-Autospec micromass. NMR spectra were recorded with a Gemini 200 MHz spectrometer with tetramethylsilane as the internal standard by using $CDCl_3$. Yields are reported for purified compounds and are not optimized. Optical rotations were measured with a JASCO DIP 300 digital polarimeter at 25 °C.

(*R*)-Hept-1-en-4-ol (2): To a stirred solution of $TiCl_4$ (0.018 g, 0.10 mmol) in DCM (5 mL) was added dried $Ti(OiPr)_4$ (0.05 g, 0.20 mmol) at 0 °C under an atmosphere of nitrogen. The solution was warmed to room temperature. After 1 h, silver(I) oxide (0.048 g, 0.20 mmol) was added at room temperature, and the whole mixture was stirred for 5 h under exclusion of direct light. The mixture was diluted with DCM (10 mL) and treated with (*S*)-binaphthol (0.118 g, 0.41 mmol) at room temperature over 2 h to furnish chiral (*S,S*)-**I**. In situ generated (*S,S*)-**I** was cooled to –15 °C and treated sequentially with butyraldehyde (0.150 g, 2.08 mmol) in DCM (50 mL) and allyltributyltin (1.032 g, 3.12 mmol) at –15 °C. The whole mixture was warmed to 0 °C and stirred for 16 h. The reaction mixture was quenched with saturated $NaHCO_3$ (10 mL) and extracted with diethyl ether (100 mL). The organic extracts were dried with Na_2SO_4. Evaporation of the solvents and purification of the residue by column chromatography (ethyl acetate/hexane, 3:7) afforded pure **2** (0.210 g, 89%) as a yellowish liquid.[9] $[\alpha]_D^{25}$ = –17.4 (*c* = 1.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3377, 1623, 1462, 1341, 1275 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.79 (m 1 H), 5.13–5.02 (m, 2 H), 3.58 (m, 1 H), 2.30–2.04 (m, 2 H), 1.48–1.31 (m, 4 H), 0.91 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 134.8, 117.6, 70.1, 41.5, 38.3, 18.2, 13.8 ppm. MS (EI): *m*/*z* = 115 $[M + H]^+$.

(*S*)-Hept-1-en-4-ol (2a): To a stirred solution of $TiCl_4$ (0.018 g, 0.10 mmol) in DCM (5 mL) was added dried $Ti(OiPr)_4$ (0.05 g, 0.20 mmol) at 0 °C under an atmosphere of nitrogen. The solution was warmed to room temperature. After 1 h, silver(I) oxide (0.048 g, 0.20 mmol) was added at room temperature, and the whole mixture was stirred for 5 h under exclusion of direct light. The mixture was diluted with DCM (10 mL) and treated with (*R*)-binaphthol (0.118 g, 0.41 mmol) at room temperature over 2 h to furnish chiral (*R,R*)-**I**. In situ generated (*R,R*)-**I** catalyst was cooled to –15 °C and treated sequentially with butyraldehyde (0.15 g, 2.08 mmol) in DCM (50 mL) and allyltributyltin (1.032 g, 3.12 mmol) at –15 °C. The whole mixture was warmed to 0 °C and stirred for 16 h. The reaction mixture was quenched with saturated $NaHCO_3$ (10 mL) and extracted with diethyl ether (100 mL). The organic extracts were dried with Na_2SO_4. Evaporation of the solvents and purification of the residue by column chromatography (ethyl acetate/hexane, 3:7) afforded pure **2a** (210 mg, 89%) as a yellowish liquid. $[\alpha]_D^{25}$ = +19.4 (*c* = 1.1, $CHCl_3$). The characterization data (^1H NMR, ^{13}C NMR, and MS) of **2a** were found to be the same as those of **2**.

5-(Benzyloxy)pentan-1-ol (7): To a stirred solution of NaH in dry THF (0.276 g, 11.53 mmol) was slowly added alcohol **6** (1 g, 9.61 mmol) in anhydrous THF (15 mL) at 0 °C. After stirring for 10 min, benzyl bromide (1.14 mL, 9.61 mmol) was added dropwise.

The reaction mixture was stirred at room temperature for 4 h and then quenched with cold water (20 mL). The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic phase was dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 7:3) to afford pure **7** (1.45 g, 78%) as a light yellow oil.[10] IR (neat): $\tilde{\nu}$ = 3388, 1454, 1363, 1207 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.32–7.18 (m, 5 H), 4.45 (s, 2 H), 3.54 (t, J = 7.0 Hz, 2 H), 3.42 (t, J = 7.0 Hz, 2 H), 2.61 (br. s, 1 H), 1.68–1.34 (m, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.5, 128.2, 127.2, 127.1, 72.9, 70.0, 62.9, 32.2, 29.1, 22.2 ppm. MS (ESI): m/z = 195 $[M + H]^+$.

7-(Benzyloxy)hept-1-en-3-ol (8): To a stirred solution of oxalyl chloride (0.92 mL, 15.10 mmol) in dry DCM (30 mL) was added DMSO (0.69 mL, 22.65 mmol) at –78 °C, and the mixture was stirred at the same temperature for 0.5 h. A solution. of 5-phenylpentan-1-ol (**7**; 1.45 g, 7.55 mmol) in DCM (20 mL) was added at –78 °C, and the mixture was stirred for 1.5 h at the same temperature. Et_3N (5.25 mL, 37.75 mmol) was added at 0 °C, and the mixture was stirred for an additional 30 min. The mixture was diluted with H_2O (30 mL) and extracted with DCM (2 × 50 mL). The combined organic layer was washed with brine (20 mL), dried (Na_2SO_4), and concentrated to give the corresponding aldehyde (1.21 g, 85%) as a colorless liquid. Because of extensive oxidation of the aldehyde to the corresponding acid it was used immediately in the next step. Under a N_2 atmosphere, a solution of vinylmagnesium bromide (1 M in THF, 7.6 mL) was added to a solution of 5-phenylpentanal (1.21 g, 6.3 mmol) in dry THF (20 mL) at 0 °C, and the mixture was allowed to reach room temperature. After stirring the mixture for 2 h, the reaction was quenched by the addition of sat. aq. NH_4Cl (20 mL). The mixture was extracted with EtOAc (2 × 50 mL) and dried (Na_2SO_4). Evaporation of the solvents resulted in the crude alcohol, which was purified by column chromatography (ethyl acetate/hexane, 5:5) to afford pure **8** (1.10 g, 79%) as a viscous liquid. The characterization data (^1H NMR, ^{13}C NMR, and MS) of **8** were found to be the same as those of **5**.

(*R*)-7-(Benzyloxy)hept-1-en-3-ol (5): To a suspension of powered molecular sieves (4 Å, 50 mg) in dry DCM (15 mL) was sequentially added $Ti(OiPr)_4$ (0.71 mL, 2.5 mmol) and (+)-DET (0.5 mL, 3 mmol) at –20 °C. After stirring for 30 min, allyl alcohol **8** (1.10 g, 5 mmol) in dry DCM (15 mL) was added, and stirring was continued for another 30 min at the same temperature. Then, TBHP (4 M in toluene, 0.68 mL, 2.75 mmol) was added, and after stirring for another 5 h at the same temperature, the reaction mixture was quenched by the addition of water (15 mL). It was allowed to remain at room temperature with stirring for 30 min. After re-cooling to 0 °C, an aqueous solution of NaOH (30% w/v, 7 mL saturated with brine) was added, and the mixture was stirred at 0 °C for 1 h. The solvent was removed under reduced pressure, and the residue was extracted with diethyl ether (3 × 20 mL). The combined organic extract was washed with brine (2 × 10 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 5:5) to afford pure compound **5** (0.495 g, 45%) as a viscous yellow liquid. $[\alpha]_D^{25}$ = +14.2 (c = 0.6, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3375, 1456, 1353, 1251 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.37–7.20 (m, 5 H), 5.80 (m, 1 H), 5.20 (dd, J = 14.0, 2.0 Hz, 1 H), 5.05 (dd, J = 8.0, 2.0 Hz, 1 H), 4.49 (s, 2 H), 4.05 (m, 1 H), 3.42 (d, J = 7.0 Hz, 2 H), 1.66–1.41 (m, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.1, 138.3, 128.2, 127.9, 127.8, 104.8, 73.0, 72.9, 70.0, 36.4, 29.5, 22.1 ppm. MS (ESI): m/z = 221 $[M + H]^+$. HRMS (ESI): calcd. for $C_{14}H_{21}O_2$ $[M + H]^+$ 221.1531; found 221.1536.

(*R*)-[7-(Benzyloxy)hept-1-en-3-yloxy](*tert*-butyl)diphenylsilane (9): To a stirred solution of alcohol **5** (0.495 g, 2.25 mmol) and imidazole (0.306 g, 4.5 mmol) in dry DCM (20 mL) was added TBDPSCl (0.69 mL, 2.7 mmol) portionwise at 0 °C. The mixture was stirred at room temperature for 2 h and then quenched with H_2O. The DCM layer was separated, and the aqueous layer was extracted with additional DCM (2 × 20 mL). The combined organic layer was washed with H_2O (20 mL) and brine (20 mL) and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by column chromatography (ethyl acetate/hexane, 2:8) to afford pure **9** (0.927 g, 90%) as a yellowish oil. IR (neat): $\tilde{\nu}$ = 1456, 1363, 1251 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.78–7.61 (m, 5 H), 7.43–7.22 (m, 10 H), 5.78 (m, 1 H), 5.01–4.90 (m, 2 H), 4.46 (s, 2 H), 4.13 (m, 1 H), 3.33 (t, J = 7.0 Hz, 2 H), 1.54–1.22 (m, 6 H), 1.09 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.9, 138.8, 136.0, 135.9, 134.9, 134.5, 129.9, 129.8, 128.5, 128.1, 128.0, 127.9, 127.8, 114.6, 74.5, 72.8, 70.2, 37.2, 29.8, 27.1, 26.5, 21.1 ppm. MS (ESI): m/z = 476 $[M + NH_4]^+$. HRMS (ESI): calcd. for $C_{30}H_{39}O_2Si$ $[M + H]^+$ 459.2721; found 459.2714.

(*R*)-5-(*tert*-Butyldiphenylsilyloxy)hept-6-en-1-ol (10): To a stirred solution of **9** (0.927 g, 2.02 mmol) in DCM/water (19:1, 5 mL) was added DDQ (0.918 g, 4.04 mmol), and the mixture was stirred at reflux for 4 h. Saturated aq. $NaHCO_3$ (5 mL) was added to the reaction mixture, which was extracted with DCM (3 × 10 mL). The combined organic layer was washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by column chromatography (ethyl acetate/hexane, 7:3) to afford pure **10** (0.639 g, 86%) as colorless syrup. IR (neat): $\tilde{\nu}$ = 3363, 1426, 1397, 1259 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.71–7.60 (m, 4 H), 7.45–7.30 (m, 6 H), 5.80 (m, 1 H), 5.05–4.94 (m, 2 H), 4.13 (m, 1 H), 3.49 (t, J = 7.0 Hz, 2 H), 1.51–1.20 (m, 6 H), 1.09 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.9, 136.1, 136.0, 134.6, 134.3, 129.8, 129.7, 127.6, 127.5, 114.5, 74.8, 62.9, 37.2, 32.9, 27.4, 19.9, 19.5 ppm. MS (ESI): m/z = 391 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{23}H_{32}O_2SiNa$ $[M + Na]^+$ 391.2064; found 391.2035.

(*R*)-5-(*tert*-Butyldiphenylsilyloxy)hept-6-enoic Acid (3): To a stirred solution of **10** (0.639 g, 1.7 mmol) in DMF (5 mL) was added PDC (1.01 g, 3.4 mmol) at room temperature. After 10 h, the mixture was quenched with cold water (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with $KHSO_4$ (15 mL, 1 mol/L), water (10 mL), and brine (10 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 9:1) to afford pure **3** (0.515 g, 78%) as a viscous light yellow liquid. $[\alpha]_D^{25}$ = +9.5 (c = 0.4, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3446, 1709, 1426, 1261 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.68–7.60 (m, 4 H), 7.42–7.28 (m, 6 H), 5.75 (m, 1 H), 5.06–4.95 (m, 2 H), 4.12 (m, 1 H), 2.19 (t, J = 7.0 Hz, 2 H), 1.62–1.41 (m, 4 H), 1.09 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.3, 140.5, 136.1, 134.2, 134.1, 129.9, 128.0, 127.9, 115.0, 74.1, 36.9, 34.1, 27.0, 19.8, 19.7 ppm. MS (ESI): m/z = 405 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{23}H_{30}O_3SiNa$ $[M + Na]^+$ 405.1861; found 405.1868.

(*R*)-[(*R*)-Hept-1-en-4-yl]">5-(*tert*-Butyldiphenylsilyloxy)hept-6-enoate (11): To a stirred solution of acid **3** (0.25 g, 0.65 mmol) and DMAP (0.039 g, 0.32 mmol) in anhydrous DCM (15 mL) was added alcohol **2** (0.148 g, 1.3 mmol) in DCM (4 mL) at room temperature. The reaction mixture was cooled to 0 °C and DCC (0.401 g, 1.95 mmol) in DCM (3 mL) added. The mixture was stirred for 10 min at 0 °C and then brought to room temperature and stirred for 8 h. The white precipitate formed was filtered off and washed with 2 N HCl, 5% $NaHCO_3$, and finally water. Esterification product **11** was purified by column chromatography (ethyl acetate/hexane, 1:9) to afford pure **11** (0.22 g, 72%) as a colorless

syrup. $[\alpha]_D^{25}$ = +13.3 (*c* = 0.3, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1736, 1634, 1450, 1260 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.69–7.59 (m, 4 H), 7.41–7.28 (m, 6 H), 5.80–5.60 (m, 2 H), 5.08–4.82 (m, 5 H), 4.11 (m, 1 H), 2.24 (t, *J* = 7.0 Hz, 2 H), 2.10 (t, *J* = 7.0 Hz, 2 H), 1.60–1.41 (m, 6 H), 1.31 (m, 2 H), 1.06 (m, 9 H), 0.89 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.2, 141.0, 136.8, 134.8, 134.7, 134.2, 129.9, 128.0, 127.9, 117.9, 115.1, 74.3, 72.2, 39.0, 37.1, 36.0, 27.1, 20.5, 19.3, 18.4, 13.9 ppm. MS (ESI): *m*/*z* = 479 $[M + H]^+$. HRMS (ESI): calcd. for $C_{30}H_{42}O_3SiNa$ $[M + Na]^+$ 501.2800; found 501.2804.

(*R*)-[(*S*)-Hept-1-en-4-yl] 5-(*tert*-Butyldiphenylsilyloxy)hept-6-enoate (11a): To a stirred solution of acid **3** (0.25 g, 0.65 mmol) and DMAP (0.039 g, 0.32 mmol) in anhydrous DCM (15 mL) was added alcohol **2a** (0.148 g, 1.3 mmol) in DCM (4 mL) at room temperature. The reaction mixture was cooled to 0 °C and DCC (0.401 g, 1.95 mmol) in DCM (3 mL) added. The mixture was stirred for 10 min at 0 °C and then brought to room temperature and stirred for 8 h. The white precipitate formed was filtered off and washed with 2 N HCl, 5% $NaHCO_3$, and finally water. Esterification product **11a** was purified by column chromatography (ethyl acetate/hexane, 1:9) to afford pure **11a** (0.22 g, 72%) as a colorless syrup. $[\alpha]_D^{25}$ = +5.6 (*c* = 0.3, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1736, 1634, 1450, 1260 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.68–7.60 (m, 4 H), 7.41–7.29 (m, 6 H), 5.79–5.62 (m, 2 H), 5.04–4.83 (m, 5 H), 4.12 (m, 1 H), 2.29–2.21 (m, 2 H), 2.11 (t, *J* = 7.0 Hz, 2 H), 1.56–1.21 (m, 8 H), 1.07 (m, 9 H), 0.99 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.5, 140.8, 136.1, 136.0, 134.1, 134.0, 133.9, 130.0, 129.9, 127.8, 127.7, 117.9, 114.6, 74.1, 72.3, 39.1, 36.9, 36.1, 34.3, 27.1, 20.2, 19.8, 18.8, 14.0 ppm. MS (ESI): *m*/*z* = 479 $[M + H]^+$. HRMS (ESI): calcd. for $C_{30}H_{42}O_3SiNa$ $[M + Na]^+$ 501.2800; found 501.2804.

(6*R*,10*R*,*E*)-6-(*tert*-Butyldiphenylsilyloxy)-10-propyl-3,4,5,6,9,10-Hexahydro-2*H*-oxecin-2-one (12): To a stirred solution of bis(tricyclohexylphosphanyl)dichlororuthenium(IV) (Grubbs first generation catalyst; 0.008 g, 5 mol-%) in DCM (40 mL) at 55 °C was added **11** (0.22 g, 0.46 mmol) dissolved in DCM (10 mL). The resulting mixture was stirred for 28 h, by which time all of the starting material had been consumed (TLC). The solvent was removed under reduced pressure to yield the crude product, which was purified by column chromatography (ethyl acetate/hexane, 2:8) to afford pure (*E*)-**12** (0.115 g, 56%) as a yellow oil. $[\alpha]_D^{25}$ = –12.6 (*c* = 0.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1736, 1634, 1450, 1260 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.70–7.59 (m, 4 H), 7.41–7.28 (m, 6 H), 5.74 (m, 1 H), 4.97 (m, 1 H), 4.81 (m, 1 H), 4.12 (m, 1 H), 2.31–2.16 (m, 2 H), 2.10 (t, *J* = 7.0 Hz, 2 H), 1.61–1.23 (m, 8 H), 1.08 (m, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.0, 140.9, 136.1, 136.0, 134.3, 134.2, 130.0, 129.9, 127.9, 127.8, 115.2, 74.2, 73.1, 37.9, 37.2, 36.2, 34.8, 27.1, 20.2, 19.8, 18.9, 14.1 ppm. MS (ESI): *m*/*z* = 473 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{28}H_{38}O_3SiNa$ $[M + Na]^+$ 473.2487; found 473.2571.

(6*R*,10*S*,*E*)-6-(*tert*-Butyldiphenylsilyloxy)-10-propyl-3,4,5,6-9,10-hexahydro-2*H*-oxecin-2-one (12a): To a stirred solution of bis(tricyclohexylphosphanyl)dichlororuthenium(IV) (Grubbs first generation catalyst; 0.008 g, 5 mol-%) in DCM (40 mL) at 55 °C was added **11a** (0.22 g, 0.46 mmol) dissolved in DCM (10 mL). The resulting mixture was stirred for 22 h, by which time all of the starting material had been consumed (TLC). The solvent was removed under reduced pressure to yield the crude product, which was purified by column chromatography (ethyl acetate/hexane, 2:8) to afford pure (*E*)-**12a** (0.124 g, 59%) as a yellow oil. $[\alpha]_D^{25}$ = +20.1 (*c* = 0.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1736, 1634, 1450, 1260 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.69–7.60 (m, 4 H), 7.41–7.30 (m, 6 H), 5.75 (m, 1 H), 5.00 (m, 1 H), 4.90 (m, 1 H), 4.20 (m, 1 H), 2.36–2.21 (m, 2 H), 2.24–2.12 (m, 2 H), 1.72–1.38 (m, 8 H), 1.05 (m, 9 H), 0.79 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.0, 140.9, 136.1, 136.0, 134.6, 134.5, 130.0, 129.9, 127.8, 127.7, 115.0, 75.2, 74.0, 37.9, 37.1, 35.0, 34.4, 27.2, 20.9, 19.9, 19.0, 14.2 ppm. MS (ESI): *m*/*z* = 473 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{28}H_{38}O_3SiNa$ $[M + Na]^+$ 473.2571; found 473.2487.

(6*S*,10*R*)-6-Hydroxy-10-propyloxecan-2-one (1): Palladium on charcoal (10%, 0.03 g) was added to a solution of **12** (0.115 g, 0.25 mmol) in EtOAc (6 mL), and the mixture was hydrogenated for 1 h. The solution was filtered through Celite and washed well with EtOAc. The filtrate was concentrated under reduced pressure. This residue was dissolved in THF and then treated with TBAF in THF (1 M in THF, 0.5 mL, 0.5 mmol) at 0 °C. The mixture was stirred for 1 h and then quenched with water (20 mL). The mixture was extracted with ethyl acetate (50 mL). The organic extracts were washed with brine (30 mL) and dried with anhydrous Na_2SO_4, and the solvent was then evaporated under reduced pressure to yield the crude product, which was purified by column chromatography (ethyl acetate/hexane, 4:6) to afford pure **1** (0.033 g, 61%) as a colorless liquid. $[\alpha]_D^{25}$ = +14.8 (*c* = 0.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3455, 1730, 1449, 1262 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.91 (m, 1 H), 4.08 (m, 1 H), 2.40–2.31 (m, 2 H), 2.08–1.43 (m, 14 H), 1.08 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.0, 76.0, 69.9, 35.5, 35.2, 32.0, 29.9, 29.7, 21.0, 20.9, 18.8, 14.1 ppm. MS (ESI): *m*/*z* = 237 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{12}H_{22}O_3Na$ $[M + Na]^+$ 237.1461; found 237.1458.

(6*S*,10*S*)-6-Hydroxy-10-propyloxecan-2-one (1a): Palladium on charcoal (10%, 0.03 g) was added to a solution of **12a** (0.124 g, 0.28 mmol) in EtOAc (6 mL), and the mixture was hydrogenated for 1 h. The solution was filtered through Celite and washed well with EtOAc. The filtrate was concentrated under reduced pressure. This residue was dissolved in THF and then treated with TBAF in THF (1 M in THF, 0.5 mL, 0.5 mmol) at 0 °C. The mixture was stirred for 1 h and then quenched with water (20 mL). The mixture was extracted with ethyl acetate (50 mL). The organic extracts were washed with brine (30 mL) and dried with anhydrous Na_2SO_4, and the solvent was then evaporated under reduced pressure to yield the crude product, which was purified by column chromatography (ethyl acetate/hexane, 4:6) to afford pure **1a** (0.036 g, 61%) as a colorless liquid. $[\alpha]_D^{25}$ = +8.1 (*c* = 0.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3455, 1730, 1449, 1262 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.92 (m, 1 H), 4.06 (m, 1 H), 2.39–2.28 (m, 2 H), 2.11–1.38 (m, 14 H), 0.98 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.0, 76.1, 69.9, 35.4, 35.2, 32.1, 29.8, 29.7, 21.1, 20.7, 18.9, 14.1 ppm. MS (ESI): *m*/*z* = 237 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{12}H_{22}O_3Na$ $[M + Na]^+$ 237.1461; found 237.1468.

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