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Stereoselective Total Synthesis of Polyrhacitides A and B

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Two aliphatic polyketide natural products, polyrhacitides A and B, have been synthesized in a concise and highly stereoselective manner. The synthesis involved an auxiliary-based acetate aldol reaction to generate the initial stereogenic center and an iterative Wittig reaction, intramolecular oxa-Michael addition, and chelation-controlled reduction reaction as the key steps to generate additional stereocenters. One-pot acid-mediated global deprotection and cyclization reactions shape the final bicyclic lactone core.

Introduction

In 2008, two aliphatic polyketide natural products bearing a bicyclic lactone motif, polyrhacitide A (**1**) and polyrhacitide B (**2**), were isolated by Jiang et al.[1] from Chinese medicinal ant species, *Polyrhacis Lamellidens* Smith (Figure 1). These ants are widely distributed in mainland China and have been used clinically as folk medicine for treating rheumatoid arthritis and hepatitis.[2] It has also been found that ethanolic extracts of *P. lamllidens* exhibit analgesic and anti-inflammatory effects, which supports the traditional use of the medicinal ants in the treatment of various diseases associated with inflammation.[3] These compounds have *syn*-centered polyhydroxy groups with a bicyclolactone unit that is unusual in ants. This unit was also recently found to be present as a constituent in the molecules obtained from the tree extracts of Cryptocarya species,[4] although related compounds occur in plants of various other families.[5] The structures of polyrhacitides A and B were identified by exhaustive NMR studies and their absolute configurations were assigned by using the acetonide and Mosher's ester methods.[1] However, despite the use of ants in traditional medicine, the biological activities of polyrhacitides have not been extensively studied, presumably due to the limited supply from natural sources.

The distinctive biological activities, fascinating architectures, and scarce availability of polyrhacitides have stimulated many groups to direct synthetic efforts towards their total synthesis. Recently, Menz and Kirsch[6] reported the first total synthesis of polyrhacitides A and B by using the catalytic asymmetric Overman esterification to install all the stereogenic centers through a five-step iterative sequence. Polyrhacitide A alone was reported by Ghosh and Nageswara Rao[8] from malic acid. Our efforts towards the total synthesis of polyketide molecules[9] have led to the development of two distinct routes for polyrhacitide A.[7] We herein report a concise stereoselective route to the total synthesis of polyrhacitides A and B by a successful implementation of strategies developed for the synthesis of an all-*syn*-1,3-polyol functionality.

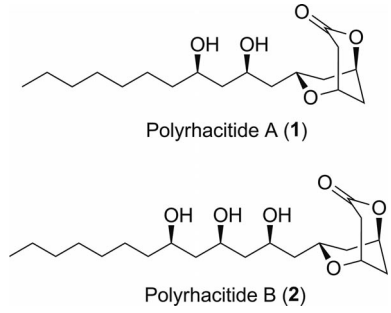

Figure 1. Structures of polyrhacitides A (**1**) and B (**2**).

Polyrhacitide B is a higher homologue of polyrhacitide A. These two compounds consist of a long-chain aliphatic consecutive *syn*-1,3-polyol functionality with a bicyclic lactone core. As the 1,3-polyol functionality is the main feature in many natural products that exhibit distinct biological activity,[10] a large number of methods have been developed to construct this functionality from chiral as well as achiral building blocks.[11] The construction of the bicyclic lactone moiety is a challenging task, however, it has been simplified by the intramolecular oxa-Michael addition reaction of an ω-hydroxy α,β-unsaturated δ-lactone.[9a,12] Recently, our group has developed a novel, alternative iodolactonization strategy for the synthesis of the bicyclic lactone core.[7b]

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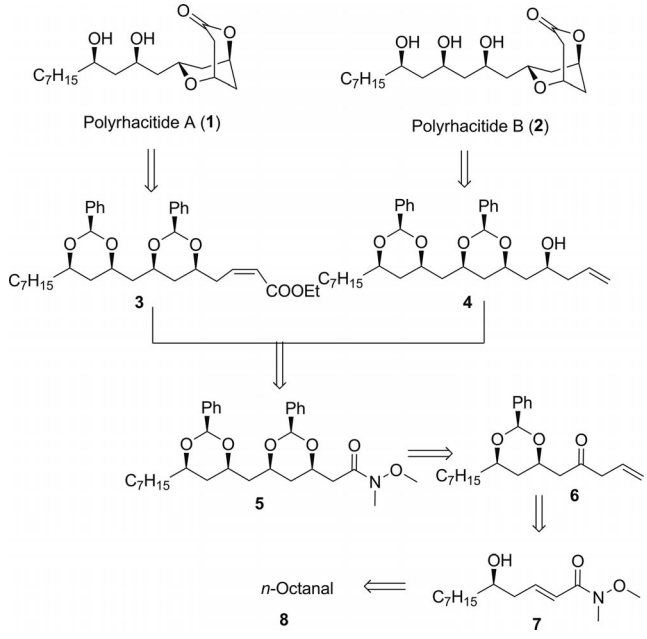
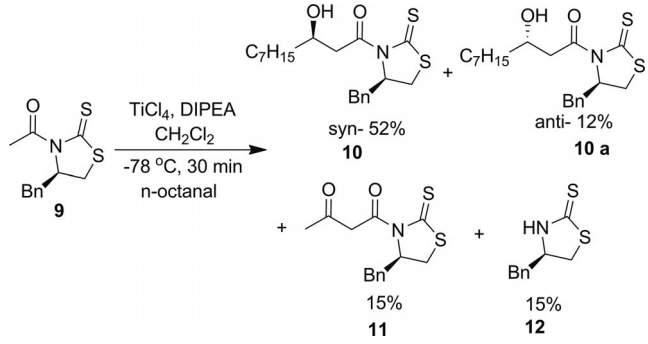
Results and Discussion

The retrosynthetic analysis in Scheme 1 shows that the target compounds **1** and **2** should be obtained from the same key intermediate **5**. Selective reduction of amide **5** and two-carbon homologation by Wittig reaction gives *Z* olefin **3**, which can undergo acid-mediated one-pot deprotection, lactonization, and oxa-Michael addition to give **1**. On the other hand, allylation of amide **5** and chelation-controlled *syn* reduction of the resulting ketone gives intermediate **4**. Further acylation with acryloyl chloride, ring-closing metathesis followed by dibenzylidene acetal deprotection and oxa-Michael reaction gives compound **2**. The key precursor **5** could be achieved from **6** by a sequential *syn*-selective reduction, oxidative degradation of the olefin, Wittig reaction, and Evans' mixed acetal oxa-Michael addition as the key steps. The ketone **6** in turn can be obtained from **7** by Evans' mixed acetal protocol and allylation reactions. Compound **7** was initially prepared from commercially available *n*-octanal (**8**) by auxiliary-based asymmetric aldol reaction, cleavage of the auxiliary followed by a Wittig reaction.

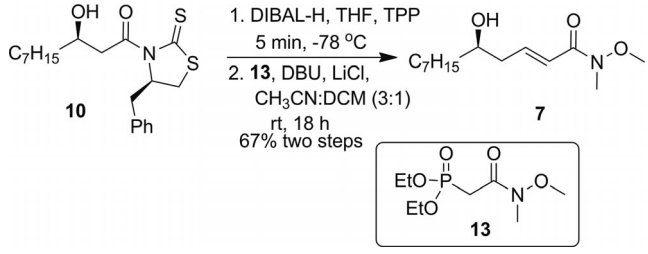


Scheme 1. Retrosynthetic analysis of polyrhacitides A and B.

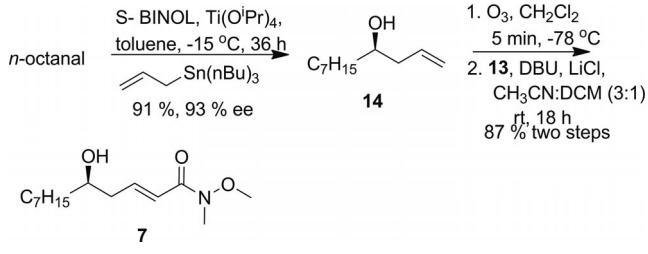
As pointed out in our preceding paper,[7a] we decided to synthesize both **1** and **2** by using efficient synthetic strategies in an iterative manner to increase the overall yields. Our initial task was to synthesize unsaturated amide **7** in optically pure form. This was realized by the generation of the initial chirality by the auxiliary-based asymmetric acetate aldol reaction with (*S*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone (**9**) and *n*-octanal (**8**) in the presence of titanium(IV) chloride and diisopropylethylamine (DIPEA; Scheme 2).[13] Although the reaction proceeded well, the resulting diastereomer **10** was formed in low yield (52%). Careful analysis of the reaction products revealed the formation of the unexpected compound[14] **11** in significant yield, which may be attributed to the self-acylation of the titanium enolate of *N*-acetylthiazolidinethione. The selective reduction of **10** with DIBAL-H followed by Wittig–Horner reaction[15] with *N*-methoxy-*N*-methyl-2-(diethoxyphosphoryl)acetamide (**13**) afforded the δ-hydroxy-α,β-unsaturated amide **7** exclusively as the *E* isomer in an overall yield of 35% in three steps (Scheme 3). To improve the overall yield of **7** an alternative approach was devised in which allylation of the aldehyde provides one aldol equivalent. Thus, we proceeded with asymmetric Keck allylation of *n*-octanal[16] to provide homoallylic alcohol **14** in 91% yield and 93% *ee* (Scheme 4). Exposure of **14** to ozone in dichloromethane at –78 °C followed by Horner–Wittig reaction[15] with **13** gave **7** with an higher overall yield of 79% in three steps.



Scheme 2. Auxiliary-based acetate aldol reaction.



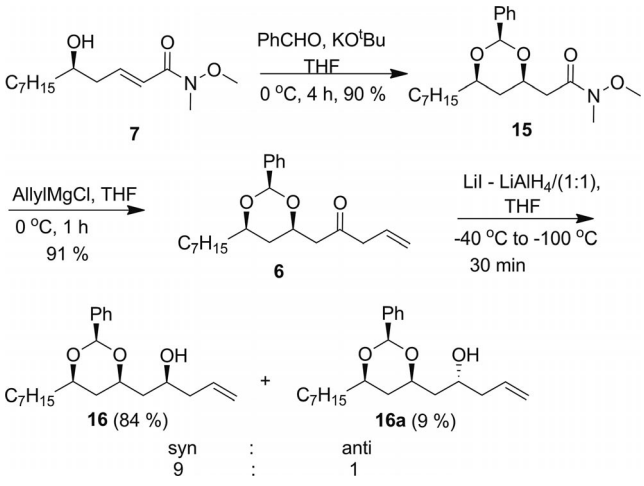
Scheme 3. Synthesis of δ-hydroxy-α,β-unsaturated amide **7**.



Scheme 4. Synthesis of δ-hydroxy-α,β-unsaturated amide **7**.

The amide **7** is an advanced intermediate that possesses the required chirality and can provide three contiguous hydroxy groups by implementing the appropriate strategy. Treatment of **7** with benzaldehyde in the presence of a catalytic amount of potassium *tert*-butoxide at 0 °C afforded **15** in 90% yield[17] along with recovery of the starting material (Scheme 5). Addition of freshly prepared allylmagnesium chloride to amide **15** at room temperature yielded ketone **6**

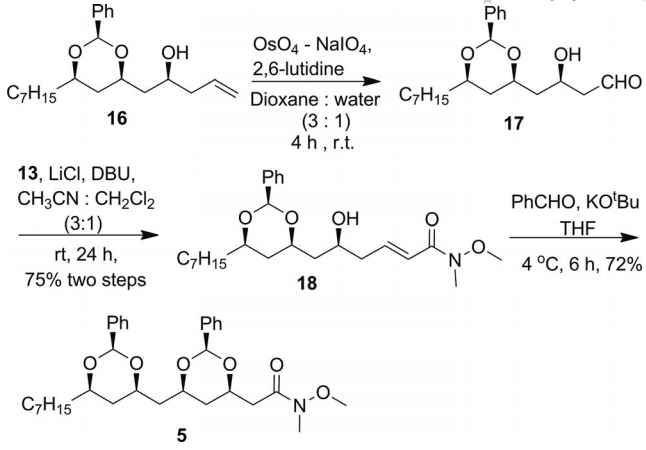
in good yield.[7a] However, the yield of **6** was further improved to 91% by the careful addition of both allyl chloride and amide in THF to a stirred solution of magnesium in THF. The ketone functionality of **6** was selectively reduced under the chelation-controlled conditions of Mori et al.[18] to give the *syn*-polyol **16** in 84% yield along with the easily separable *anti* isomer **16a**.



Scheme 5. Synthesis of the homoallylic alcohol **16**.

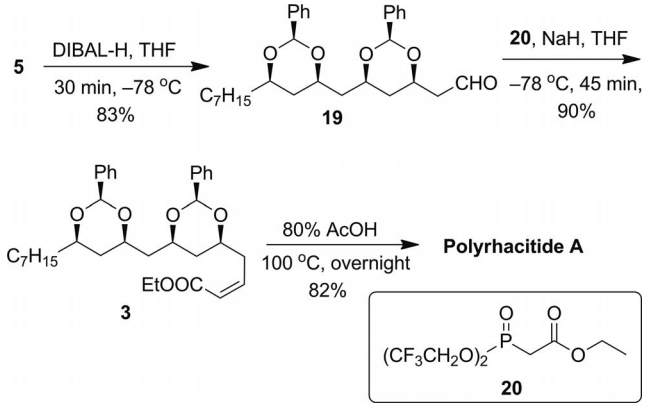
Towards the key precursor **5**, one more iterative procedure, that is, a three-step sequential olefinic oxidation, Wittig reaction, and tethered oxa-Michael addition, was required. Thus, **16** was subjected to ozonolysis followed by a Wittig reaction with **13** to provide **18** in 62% yield. The poor yield observed here might be due to the side reactions of the benzylidene moiety during ozonolysis. To improve the yield, the one-step dihydroxylation/oxidation protocol of Jin and co-workers[19] was followed to obtain the aldehyde, which was treated immediately with **13** in the presence of DBU and LiCl at room temperature for 24 h to give the α,β-unsaturated amide **18** in 75% yield over two steps (Scheme 6). Evans' acetal-forming reaction of compound **18** installed the fourth stereocenter to give the product **5**. It was observed that the equilibrium towards the formation of the acetal was a minimum at 0 °C, but prolonged stirring at a slightly elevated temperature produced **5** in 72% yield.

With the key precursor bis-benzylidene amide **5** in hand, we proceeded with the total synthesis of polyrhacitide A (**1**). Thus, compound **5** was treated with DIBAL-H to give the corresponding aldehyde **19**, which was then subjected to the Horner–Wittig reaction[20] with ethyl 2-[bis(2,2,2-trifluoroethyloxy)phosphoryl]acetate (**20**) to give the *Z* olefinic precursor **3** with an all-*syn* dibenzylidene-protected tetrol and an α,β-unsaturated ester. Exposure of this key precursor **3** to 80% AcOH at 100 °C for 18 h gave rise to the desired bicyclic product polyrhacitide A (**1**) in 82% yield (Scheme 7). The reaction conditions were well optimized leading to an increase in the previous overall yield of polyrhacitide A from 8.4 to 21.5%. The structural integrity of the synthetic polyrhacitide A (**1**) was confirmed by comparison of its spectral (^{1}H and ^{13}C NMR) data and specific



Scheme 6. Synthesis of key intermediate bis-benzylidene amide **5**.

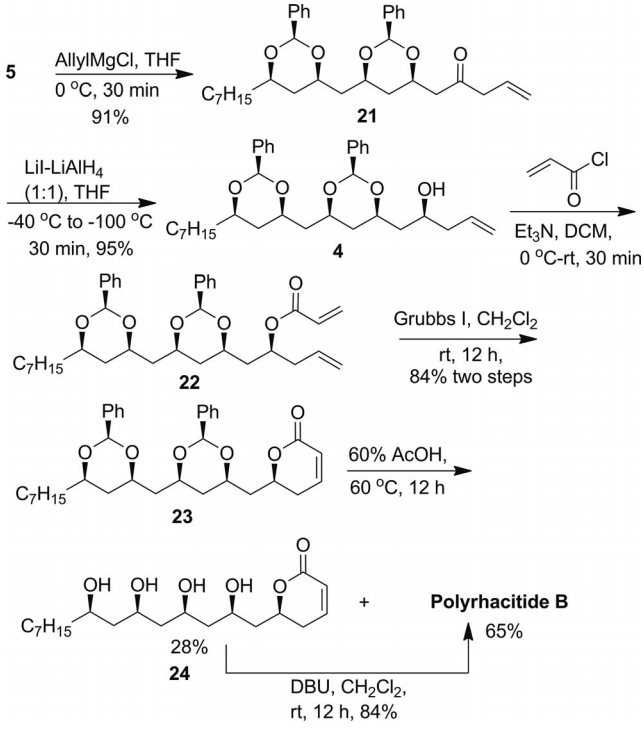
rotation with reported data for the natural product {synthetic: $[\alpha]_D^{30}$ = +7.8 (*c* = 0.4, MeOH); ref.:[1] $[\alpha]_D^{25}$ = +8.3 (*c* = 0.6, MeOH)}.



Scheme 7. Synthesis of polyrhacitide A (**1**).

The conversion of intermediate **5** into (+)-polyrhacitide B (**2**) is outlined in Scheme 8. One more iterative sequence of allylation and *syn* reduction offered the desired intermediate **4**. For this, intermediate **5** was treated with allylmagnesium chloride to give the ketone **21**. *syn* reduction of the ketone functionality provided inseparable diastereomers of homoallylic alcohol **4**, which were even inseparable after further steps. After many trials we obtained a single diastereomer[21] of **4** in 95% yield by using a large excess of LiAlH$_4$/LiI (30 equiv. each) under high dilution conditions. Acylation of the free hydroxy group with acryloyl chloride and triethylamine in dichloromethane gave compound **22**, which upon exposure to Grubbs' 1st generation catalyst provided unsaturated lactone **23** in 84% yield[22] over two steps. Finally, polyrhacitide B (**2**) was achieved by a one-pot sequential deprotection, lactonization, and cyclization reaction using 60% acetic acid at 60 °C, affording[23] **2** as a white solid in 65% yield along with the simple deprotected lactone **24** in 28% yield. Also, the fully deprotected lactone **24** was treated with DBU in dichloromethane for 12 h to afford the targeted polyrhacitide B in 84% yield.[6] The structural integrity of the synthetic polyrhacitide B (**2**) was

confirmed by comparison of its spectral (^{1}H and ^{13}C NMR) data and specific rotation with literature data for the natural product {synthetic: $[\alpha]_D^{30}$ = +6.3, (*c* = 0.8, MeOH); ref.[1]: $[\alpha]_D^{25}$ = +7.2 (*c* = 0.6, MeOH)}.



Scheme 8. Synthesis of polyrhacitide B (**2**).

Conclusions

We have demonstrated herein a highly stereoselective synthesis of polyrhacitides A (**1**) and B (**2**). The strategies used for the construction of the skipped polyol functionality are highly selective. For each, the iterative synthetic procedure involves a five-step sequence of olefinic oxidation, a modified Wittig–Horner reaction, Evans' mixed acetal oxa-Michael reaction, allylation, and chelation-controlled *syn* reduction reactions. To the best of our knowledge, this is the shortest strategy adopted so far for the synthesis of polyrhacitides A and B and involves 12- and 14-step sequences, respectively. Compared with our previous report, the present reaction conditions are also well optimized to enhance the overall yields of polyrhacitide A (21.5%) and polyrhacitide B (22.5%).

Experimental Section

General: Air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under argon in oven- or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, toluene, and diethyl ether from Na and benzophenone, CH_2Cl_2 and DMSO from CaH_2. Commercial reagents were used without purification. Column chromatography was carried out by using Spectrochem silica gel (60–120 mesh). Specific optical rotations $[\alpha]_D$ are given in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded in $CHCl_3$ or neat (as mentioned) and are reported in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in Hz. The following abbreviations have been used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad.

(*R*)-1-[(*R*)-4-Benzyl-2-thioxothiazolidin-3-yl]-3-hydroxydecan-1-one (10): $TiCl_4$ (1.9 mL, 17.5 mmol) and *i*Pr_2NEt (3.2 mL, 17.5 mmol) were successively added to a stirred solution of (*R*)-**9** (3.50 g, 15.98 mmol) in CH_2Cl_2 (70 mL) at –78 °C under nitrogen and then the mixture was stirred for 1 h. A solution of *n*-octanal (3.07 g, 24 mmol) in CH_2Cl_2 (30 mL) was added through a cannula at –78 °C. The mixture was stirred for 30 min and then the reaction was quenched with saturated aqueous NH_4Cl. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with H_2O and saturated brine, dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification by column chromatography (silica gel BW-100, hexane/EtOAc, 20:1 to 10:1) gave the aldol adduct **10** (3.14 g, 52%) as a yellow oil. $[\alpha]_D^{30}$ = –169 (*c* = 1.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3155, 2925, 2854, 1695, 1603, 1490, 1262, 1162, 1039, 1007, 745, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.98, 13.40 Hz, 3 H), 1.21–1.39 (m, 10 H), 1.40–1.61 (m, 2 H), 2.68–2.82 (br. s, 1 H), 2.90 (d, *J* = 11.5 Hz, 1 H), 3.0–3.18 (m, 2 H), 3.19–3.26 (dd, *J* = 3.96, 13.21 Hz, 1 H), 3.40 (qd, *J* = 0.75, 7.17, 11.52, 18.69 Hz, 1 H), 3.64 (dd, *J* = 2.45, 17.75 Hz, 1 H), 4.10–4.19 (m, 1 H), 5.36–5.44 (m, 1 H), 7.24–7.38 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.5, 29.2, 29.5, 31.8, 32.0, 36.4, 36.8, 45.9, 67.8, 68.3, 127.2, 128.9, 129.4, 136.4, 173.3, 201.3 ppm. MS (ESI): *m*/*z* = 380 [M + H]$^+$. HRMS: calcd. for $C_{20}H_{29}NO_2NaS_2$ 402.1537; found 402.1538.

(*R*,*E*)-5-Hydroxy-*N*-methoxy-*N*-methyldodec-2-enamide (7): DIBAL-H (11.4 mL, 1.58 mmol, 20% solution in toluene) was added to the stirred solution of aldol adduct **10** (3.0 g, 7.90 mmol) in dry THF (100 mL) under nitrogen at –78 °C. The reaction was monitored by TLC and quenched with sat. aqueous potassium sodium tartrate solution (30 mL). After addition of EtOAc (100 mL), stirring was continued for 2 h (until a clear solution formed). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. The free auxiliary **12** (1.1 g, 76%) was recovered by recrystallization in hexane and the yellow-colored mother liquor was concentrated in vacuo to afford the aldehyde as a yellow oil. The crude product was directly used in further step without any purification.

LiCl (0.52 g, 11.8 mmol) and DBU (1.76 mL, 11.8 mmol) were added to a stirred solution of **13** (2.67 g, 11.8 mmol) in dry CH_3CN (30 mL) and the mixture was stirred for 30 min at room temp. The crude aldehyde (7.9 mmol) in dry CH_2Cl_2 (10 mL) was added to this solution and the reaction mixture was stirred for 18 h at room temp. The reaction mass was quenched by the addition of sat. aqueous NH_4Cl (20 mL) and further CH_2Cl_2 (50 mL) was added and the organic layer was separated. The aqueous layer was extracted again with CH_2Cl_2 (2 × 50 mL) and the combined organic extracts were washed with brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. Purification by column chromatography (silica gel, hexane/EtOAc, 6:4) gave unsaturated amide **7** (1.36 g, 67%) as a yellow liquid. $[\alpha]_D^{30}$ = +1.3 (*c* = 1.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3419, 2923, 2852, 1629, 1452, 1456, 1378 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H), 1.23–1.35 (m, 10 H), 1.44–1.52 (m, 2 H), 2.31–2.46 (m, 1 H), 2.47–2.60 (m, 1 H), 3.19 (s, 1 H), 3.24 (s, 3 H), 3.70 (s, 3 H), 4.06–4.17 (m, 1 H), 6.48 (d, *J* = 15.4 Hz, 1 H), 6.93–7.04 (m, 1 H) ppm. ^{13}C NMR (75 MHz,

$CDCl_3$): δ = 14.0, 22.5, 25.5, 29.1, 29.4, 31.7, 36.9, 40.5, 61.6, 67.7, 70.4, 121.0, 144.0, 166.6 ppm. MS (ESI): m/z = 258 $[M + H]^+$.

(*R*)-Undec-1-en-4-ol (14): Ti(*i*PrO)$_4$ (140 mg, 0.46 mmol) was added to a stirred solution of (*S*)-BINOL (280 mg, 0.98 mmol) and 4 MS (560 mg) in anhydrous toluene (80 mL). The reaction mixture was stirred for 2.5 h at room temp. and then cooled to –15 °C. Allyltributyltin (19.5 g, 59 mmol) and *n*-octanol (5.0 g, 39.2 mmol) were added. After 36 h at –15 °C, a 2:1 mixture of CsF/CsOH (10.0 g) and silica gel (20.0 g) were added. The reaction mixture was stirred for 2 h. The solvent was evaporated and the crude product was purified by column chromatography (silica gel, hexane/EtOAc, 95:5) to give **14** (6.04 g, 91%) as a clear liquid. $[\alpha]_D^{30}$ = +6.3 (c = 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.7 Hz, 3 H), 1.22–1.36 (m, 10 H), 1.40–1.51 (m, 3 H), 1.73 (d, J = 6.2 Hz, 1 H), 2.07–2.20 (m, 1 H), 2.30 (dt, J = 5.2, 13.7 Hz, 1 H), 3.64 (m, 1 H), 5.10 (s, 1 H), 5.15 (d, J = 2.8 Hz, 1 H), 5.75–5.91 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 25.6, 29.2, 29.6, 31.8, 36.8, 41.9, 70.6, 117.9, 134.9 ppm.

2-[(2*R*,4*R*,6*R*)-6-Heptyl-2-phenyl-1,3-dioxan-4-yl]-*N*-methoxy-*N*-methylacetamide (15): KO*t*Bu (108 mg, 0.97 mmol) was added to a stirred solution of amide **7** (2.5 g, 9.69 mmol) in dry THF (50 mL) at 0 °C. After 5 min, freshly distilled benzaldehyde (1.23 g, 11.6 mmol) was added and stirring was continued for 30 min. KO*t*Bu and benzaldehyde were added twice at 30 min intervals whilst stirring at 0 °C. The reaction was quenched after 4 h with phosphate buffer (pH 7, 50 mL), the organic layer was separated, and the aqueous layer was extracted with EtOAc (3× 50 mL). The combined organic layers were washed with brine and dried with anhydrous sodium sulfate. Evaporation of the solvent in vacuo followed by purification by column chromatography (silica gel, hexane/EtOAc, 9:1) gave benzylidene amide **15** [2.61 g, 74% (90%[17])] as a pale-yellow oil. $[\alpha]_D^{30}$ = +22 (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2927, 2854, 2073, 1646, 1455, 1113, 1019, 771, 699 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.7 Hz, 3 H), 1.22–1.55 (m, 12 H), 1.60–1.70 (m, 1 H), 1.77 (dt, J = 2.0, 12.8 Hz, 1 H), 2.48 (dd, J = 6.2, 15.6 Hz, 1 H), 2.92 (dd, J = 6.7, 14.9 Hz, 1 H), 3.16 (s, 3 H), 3.65 (s, 3 H), 3.77–3.87 (m, 1 H), 4.27–4.38 (m, 1 H), 5.51, (s, 1 H), 4.25–7.34 (m, 3 H), 7.41–7.47 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 22.7, 25.1, 29.3, 29.7, 31.9, 36.0, 37.0, 38.2, 61.2, 65.0, 73.4, 76.6, 100.6, 126.1, 127.9, 128.4, 138.8, 171.2 ppm. MS (ESI): m/z = 364 $[M + H]^+$, 386 $[M + Na]^+$. HRMS: calcd. for $C_{21}H_{33}NO_4Na$ 386.2307; found 386.2324.

1-[(2*R*,4*R*,6*R*)-6-Heptyl-2-phenyl-1,3-dioxan-4-yl]pent-4-en-2-one (6): 1,2-Dibromoethane (0.05 mL) was added to a stirred solution of Mg (0.5 g, 20.8 mmol) in dry THF (20 mL) in a 100 mL two-necked round-bottomed flask fitted with a reflux condenser and rubber septum at room temp. After 10 min, a solution of amide **15** (2.5 g, 6.88 mmol) and allyl chloride (1.4 mL, 17.2 mmol) in dry THF (25 mL) were carefully added over a period of 1 h. The reaction mixture was stirred at room temp. for 1 h and the reaction was monitored by TLC and quenched with sat. aqueous NH_4Cl (10 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2× 50 mL). The combined organic layers were washed with brine and dried with anhydrous sodium sulfate followed by evaporation of the solvent in vacuo. Purification by column chromatography (silica gel, hexane/EtOAc, 95:5) gave ketone **6** (2.15 g, 91%) as a clear liquid. $[\alpha]_D^{30}$ = –3.6 (c = 0.9, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2927, 2855, 1714, 1669, 1633, 1452, 1344, 1112, 841, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.9 Hz, 3 H), 1.23–1.37 (m, 10 H), 1.41–1.55 (m, 2 H), 1.64 (t, J = 2.4, 2.2 Hz, 1 H), 1.68 (t, J = 2.2 Hz, 1 H), 2.51 (dd, J = 5.6, 5.8 Hz, 1 H), 2.84 (dd, J = 6.7, 6.7 Hz, 1 H), 3.19 (dd, J = 0.9, 6.9 Hz, 2 H), 3.74–3.84 (m, 1 H), 4.22–4.32 (m, 1 H), 5.07–5.2 (m, 2 H), 5.48 (s, 1 H), 5.82–5.96 (m, 1 H), 7.28–7.36 (m, 3 H), 4.41–7.46 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 22.7, 25.1, 29.3, 29.6, 31.9, 35.9, 36.8, 48.1, 48.8, 72.9, 76.6, 100.5, 119.0, 126.0, 128.0, 128.4, 130.2, 138.6, 205.5 ppm. MS (ESI): m/z = 345 $[M + H]^+$, 367 $[M + Na]^+$. HRMS: calcd. for $C_{22}H_{32}O_3Na$ 367.2249; found 367.2241.

(*S*)-1-[(2*R*,4*S*,6*R*)-6-Heptyl-2-phenyl-1,3-dioxan-4-yl]pent-4-en-2-ol (16): LiI (3.8 g, 28.9 mmol) was added to a stirred solution of alkoxy ketone **6** (1.0 g, 2.8 mmol) in dry ether (40 mL) at –40 °C. The stirring was continued for 10 min. The reaction mixture was then cooled to –100 °C and, after 5 min, $LiAlH_4$ (1.1 g, 28.9 mmol) was added and the mixture was stirred at –100 °C for 30 min. The reaction mixture was then quenched with 10% aqueous potassium sodium tartrate solution, and the mixture was stirred until a clear solution formed. The organic layer was separated and the aqueous layer was extracted with EtOAc (2× 20 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate and concentrated under vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 9:1) to yield homoallylic alcohol **16** (0.84 g, 84%) as a clear liquid. $[\alpha]_D^{30}$ = –3.9 (c = 1.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3460, 2925, 2854, 2361, 1641, 1459, 1114, 1019, 768 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.9 Hz, 3 H), 1.21–1.39 (br. s, 10 H), 1.41–1.57 (m, 3 H), 1.58–1.83 (m, 3 H), 2.25 (t, J = 6.6 Hz, 2 H), 3.18 (s, 1 H), 3.77–3.87 (m, 1 H), 3.92–4.01 (m, 1 H), 4.00–4.15 (m, 1 H), 5.08 (s, 1 H), 5.13 (d, J = 7.1 Hz, 1 H), 5.55 (s, 1 H), 5.77–5.92 (m, 1 H), 7.29–7.38 (m, 3 H), 7.43–7.49 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 24.9, 29.1, 29.2, 31.8, 35.8, 37.0, 41.9, 41.9, 70.4, 76.9, 77.3, 100.6, 117.5, 125.9, 128.2, 128.7, 134.7, 138.3 ppm. MS (ESI): m/z = 369 $[M + Na]^+$. HRMS: calcd. for $C_{22}H_{34}O_3Na$ 369.2303; found 369.2318.

(*S*,*E*)-6-[(2*R*,4*S*,6*R*)-6-Heptyl-2-phenyl-1,3-dioxan-4-yl]-5-hydroxy-*N*-methoxy-*N*-methylhex-2-enamide (18): 2,6-Lutidine (0.56 mL, 5.76 mmol), OsO_4 (0.72 mL, 0.05 M in toluene), and $NaIO_4$ (1.2 g, 5.76 mmol) were sequentially added to a stirred solution of **16** (0.50 g, 1.44 mmol) in dioxane and water (3:1, 10 mL) at room temperature and the mixture was stirred for 4 h. After completion of the reaction (monitored by TLC), 1,4 dioxane was removed under vacuum and the residue was diluted with CH_2Cl_2 (10 mL). The organic layer was washed with 1 N HCl (2× 5 mL) to remove excess 2,6-lutidine and then by brine (2× 5 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by short-column flash chromatography over silica gel (hexane/ethyl acetate, 10:1) afforded aldehyde **17** as pale-yellow oil.

Freshly prepared aldehyde **17** in CH_2Cl_2 was immediately added to a stirred solution of **13** in CH_3CN along with DBU and LiCl. A similar procedure to that described for the synthesis of compound **7** was then followed. Purification of the crude product by short-column flash chromatography over silica gel (hexane/ethyl acetate, 3:2) afforded amide **18** (0.47 g, 75%) as a pale-yellow oil. $[\alpha]_D^{30}$ = –4.2 (c = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3435, 2925, 2854, 1661, 1631, 1456, 1383, 1176, 1025, 663 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.7 Hz, 3 H), 1.20–1.37 (m, 11 H), 1.41–1.54 (m, 2 H), 1.57–1.70 (m, 2 H), 1.71–183 (m, 1 H), 2.34–2.54 (m, 2 H), 3.23 (s, 3 H), 3.69 (s, 3 H), 3.76–3.86 (m, 1 H), 4.04–4.16 (m, 2 H), 5.55 (s, 1 H), 6.49 (d, J = 15.4 Hz, 1 H), 6.90–7.01 (m, 1 H), 7.29–7.38 (m, 3 H), 7.43–7.49 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.9, 29.2, 29.5, 31.7, 35.7, 37.0, 40.5, 42.0, 61.7, 70.2, 76.9, 77.4, 100.6, 121.2, 125.9, 128.2, 128.7, 138.3, 143.4, 166.6 ppm. MS (ESI): m/z = 434 $[M + H]^+$, 456 $[M + Na]^+$. HRMS: calcd. for $C_{25}H_{39}NO_5Na$ 456. 2725; found 456. 2719.

2-[(2*R*,4*R*,6*R*)-6-{[(2*R*,4*R*,6*R*)-6-Heptyl-2-phenyl-1,3-dioxan-4-yl]methyl}-2-phenyl-1,3-dioxan-4-yl]-*N*-methoxy-*N*-methylacetamide (5): Compound **5** was synthesized according to the procedure followed for compound **15** and was obtained in 72% yield as a thick, yellow oil. $[a]_D^{30}$ = +4.2 (*c* = 1.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2924, 2853, 1635, 1452, 1343, 1115, 1025, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H), 1.24–1.35 (m, 10 H), 1.42–1.58 (m, 2 H), 1.6–1.8 (m, 2 H), 1.85–1.92 (m, 1 H), 2.08–2.20 (m, 1 H), 2.53–2.62 (m, 1 H), 2.94–3.03 (m, 1 H), 3.20 (s, 3 H), 3.66 (s, 3 H), 3.75–3.85 (m, 1 H), 4.05–4.18 (m, 2 H), 4.36–4.47 (m, 1 H), 5.52 (s, 1 H), 5.59 (s, 1 H), 7.29–7.41 (m, 6 H), 7.45–7.54 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.0, 29.2, 29.5, 29.7, 31.8, 35.9, 36.8, 36.8, 41.9, 61.4, 65.5, 72.8, 73.0, 73.5, 76.9, 100.5, 100.7, 126.0, 128.1, 128.4, 128.6, 129.0, 129.7, 138.5, 138.9, 171 ppm. MS (ESI): *m*/*z* = 540 $[M + H]^+$, 562 $[M + Na]^+$. HRMS: calcd. for $C_{32}H_{45}NO_6Na$ 562.3144; found 562.3165.

2-[(2*R*,4*R*,6*R*)-6-{[(2*R*,4*R*,6*R*)-6-Heptyl-2-phenyl-1,3-dioxan-4-yl]methyl}-2-phenyl-1,3-dioxan-4-yl]acetaldehyde (19): DIBAL-H (0.32 mL, 0.44 mmol, 20% in toluene) was carefully added to a stirred solution of amide **5** (120 mg, 0.22 mmol) in dry THF (8 mL) at –78 °C under an inert atmosphere. The reaction was monitored by TLC and after 30 min it was quenched with a sat. aqueous potassium sodium tartrate solution. Stirring was continued for 2 h (until a clear solution formed), the organic layer was separated, and the aqueous layer was washed with EtOAc (2× 5 mL). The combined organic layers were washed with water and brine, dried with anhydrous sodium sulfate, and concentrated in vacuo to yield aldehyde **19** (89 mg, 83%) as a clear sticky oil. Compound **19** was used directly in the next step without any purification. $[a]_D^{30}$ = –3.4 (*c* = 1.3, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H), 1.24–1.36 (m, 10 H), 1.44–1.60 (m, 4 H), 1.63–1.83 (m, 2 H), 2.08–2.22 (m, 1 H), 2.63 (dd, *J* = 4.9, 16.8 Hz, 1 H), 2.83 (ddd, *J* = 1.7, 7.1, 15.1 Hz, 1 H), 3.77–3.87 (m, 1 H), 4.01–4.22 (m, 2 H), 4.38–4.48 (m, 1 H), 5.53 (s, 1 H), 5.59 (s, 1 H), 7.31–7.41 (m, 6 H), 7.45–7.55 (m, 4 H), 9.85 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 25.0, 29.2, 29.5, 29.7, 31.8, 35.9, 35.9, 36.4, 36.8, 41.6, 49.3, 71.8, 73.0, 73.1, 76.9, 100.5, 100.7, 126.0, 126.0, 128.1, 128.2, 128.5, 128.8, 138.2, 138.8, 200.3 ppm. MS (ESI): *m*/*z* = 481 $[M + H]^+$. HRMS: calcd. for $C_{30}H_{41}O_5$ 481.2953; found 481.2942.

Ethyl (*Z*)-4-[(2*S*,4*S*,6*S*)-6-{[(2*R*,4*R*,6*R*)-6-Heptyl-2-phenyl-1,3-dioxan-4-yl]methyl}-2-phenyl-1,3-dioxan-4-yl]but-2-enoate (3): Ethyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (101 mg, 0.32 mmol) in THF (2 mL) was added to a stirred solution of NaH (12.8 mg, 60% w/w in paraffin, 0.32 mmol) at –78 °C. The mixture was stirred for 1 h at –78 °C ad then a solution of aldehyde **19** (120 mg, 0.25 mmol) in THF (1 mL) was added dropwise. The resulting mixture was stirred for 45 min and the reaction was quenched with saturated sodium hydrogencarbonate and warmed to room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine and dried with anhydrous sodium sulfate. Removal of the solvent and separation of the diastereomers by silica gel chromatography yielded **3** (121 mg, 90%) as a thick, light-yellow oil. $[a]_D^{30}$ = –11 (*c* = 1.4, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2923, 2854, 2362, 1723, 1647, 1458, 1179, 1018, 759, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.1, 13.4 Hz, 3 H), 1.24–1.34 (m, 10 H), 1.42–1.81 (m, 7 H), 2.09–2.22 (m, 1 H), 2.86–2.97 (m, 1 H), 3.04–3.16 (m, 1 H), 3.71 (s, 3 H), 3.76–3.86 (m, 1 H), 3.94–4.16 (m, 3 H), 5.52 (s, 1 H), 5.54 (s, 1 H), 5.90 (d, *J* = 11.5 Hz, 1 H), 6.42–6.53 (m, 1 H), 7.31–7.40 (m, 6 H), 7.47–7.53 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.0, 29.2, 29.7, 31.8, 35.1, 35.9, 36.3, 36.9, 41.8, 51.0, 73.0, 73.1, 75.9, 76.9, 100.5, 100.6, 120.8, 126.0, 128.1, 128.1, 128.5, 128.6, 138.6, 138.9, 145.7, 166.7 ppm. MS (ESI): *m*/*z* = 537 $[M + H]^+$, 559 $[M + Na]^+$. HRMS: calcd. for $C_{33}H_{44}O_6Na$ 559.3035; found 559.3063.

Polyrhacitide A (1): A solution of *cis*-enoate **3** (50 mg, 0.046 mmol) in 80% AcOH (4 mL) was heated at 100 °C and stirred overnight. The solvent was then removed under reduced pressure and traces of acetic acid were removed azeotropically with toluene. Purification by column chromatography (silica gel 60–120, $CHCl_3$/MeOH, 98:2) yielded **1** (12.4 mg, 82%) as a white solid; m.p. 68–70 °C. $[a]_D^{30}$ = +7.8 (*c* = 0.4, MeOH). IR (neat): $\tilde{\nu}$ = 3459, 2925, 2854, 1729, 1384, 1220, 1076, 772, 677 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H), 1.24–1.42 (m, 9 H), 1.44–1.76 (m, 8 H), 1.99–2.07 (m, 3 H), 2.77 (dd, *J* = 5.1, 19.2 Hz, 1 H), 2.88 (d, *J* = 19.2 Hz, 1 H), 3.76–3.82 (m, 1 H, 11-H), 4.0–4.07 (m, 2 H, 7-,9-H), 4.38 (br. s, 1 H, 3-H), 4.83–4.86 (m, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 22.8, 25.5, 29.4, 29.7, 29.7, 31.9, 36.5, 37.4, 37.9, 43.1, 43.5, 66.1, 67.0, 72.0, 72.1, 72.6, 168.2 ppm. MS (ESI): *m*/*z* = 329 $[M + H]^+$, 351 $[M + Na]^+$. HRMS: calcd. for $C_{18}H_{32}O_5Na$ 351.2147; found 351.2160.

1-[(2*R*,4*R*,6*R*)-6-{[(2*R*,4*R*,6*R*)-6-Heptyl-2-phenyl-1,3-dioxan-4-yl]methyl}-2-phenyl-1,3-dioxan-4-yl]pent-4-en-2-one (21): Compound **21** was synthesized according to the procedure followed for the synthesis of compound **6**. Compound **21** was obtained in 91% yield. $[a]_D^{30}$ = –5.7 (*c* = 1.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2924, 2853, 1713, 1635, 1455, 1386, 1113, 1019, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.4 Hz, 3 H), 1.22–1.34, (m, 10 H), 1.41–1.56 (m, 3 H), 1.58–1.71 (m, 3 H), 1.72–1.81 (m, 1 H), 1.84–1.94 (m, 1 H), 2.59 (dd, *J* = 6.9, 16.4 Hz, 1 H), 3.24 (d, *J* = 6.9 Hz, 2 H), 3.50–3.64 (m, 1 H), 3.75–3.86 (m, 1 H), 4.01–4.86 (m, 2 H), 4.28–4.42 (m, 1 H), 5.07–5.22 (m, 2 H), 5.52 (s, 1 H), 5.55 (s, 1 H), 5.82–5.97 (m, 1 H), 7.28–7.40 (m, 6 H), 7.42–7.55 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 25.0, 29.2, 29.5, 29.6, 31.8, 35.9, 36.8, 41.7, 48.1, 48.8, 73.0, 73.3, 74.4, 76.9, 100.5, 100.5, 119.1, 126.0, 126.0, 128.1, 128.2, 128.5, 128.6, 130.1, 138.4, 138.8, 206.3 ppm. MS (ESI): *m*/*z* = 521 $[M + H]^+$, 543 $[M + Na]^+$. HRMS: calcd. for $C_{33}H_{44}O_5Na$ 543.3086; found 543.3078.

(*S*)-1-[(2*S*,4*S*,6*S*)-6-{[(2*R*,4*R*,6*R*)-6-Heptyl-2-phenyl-1,3-dioxan-4-yl]methyl}-2-phenyl-1,3-dioxan-4-yl]pent-4-en-2-ol (4): LiI (463 mg, 3.4 mmol) was added to a stirred solution of alkoxy ketone **21** (60 mg, 0.11 mmol) in dry diethyl ether (40 mL) at –40 °C and the mixture was stirred for a further 30 min. Then the mixture was cooled to –100 °C and, after 5 min, $LiAlH_4$ (131 mg, 3.4 mmol) was added in one portion and the mixture was stirred at –100 °C for 45 min. The reaction mixture was quenched with 10% aqueous potassium sodium tartrate solution and stirring was continued until a clear solution formed. The organic layer was separated and the aqueous layer extracted with EtOAc (2× 10 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. Purification by column chromatography (silica gel, hexane–EtOAc 95:5) gave homoallylic alcohol **4** (57 mg, 95%) as a clear liquid. $[a]_D^{30}$ = –4.4 (*c* = 1.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3445, 2923, 2852, 2361, 1633, 1459, 1118, 1029, 768 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.3 Hz, 3 H), 1.24–1.34 (m, 10 H), 1.43–1.56 (m, 3 H), 1.56–1.85 (m, 5 H), 2.10–2.18 (m, 1 H), 2.23–2.30 (m, 2 H), 3.52–3.64 (br. s, 1 H), 3.77–3.83 (m, 1 H), 3.95–4.0 (m, 1 H), 4.01–4.09 (m, 1 H), 4.10–4.16 (m, 2 H), 5.09–5.15 (m, 2 H), 5.51 (s, 0.5 H), 5.58 (s, 0.5 H), 5.80–5.89 (m, 1 H), 7.3–7.39 (m, 6 H), 7.46 (d, *J* = 6.4 Hz, 2 H), 7.50 (d, *J* = 8.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 25.0, 29.2, 29.5, 29.6, 31.8, 35.9, 36.8, 41.7, 41.9, 60.3, 70.2, 73.0, 73.2, 76.9, 77.2, 100.5, 100.6, 117.6, 125.9, 126.0, 128.1, 128.2, 128.5, 128.8, 134.6, 138.2, 138.8 ppm. MS (ESI): *m*/*z* = 545

[M + Na]$^+$. HRMS: calcd. for $C_{33}H_{46}O_5Na$ 545.3237; found 545.3257.

(*S*)-6-{[(2*R*,4*R*,6*S*)-6-{[(2*R*,4*R*,6*R*)-6-Heptyl-2-phenyl-1,3-dioxan-4-yl]methyl}-2-phenyl-1,3-dioxan-4-yl]methyl}-5,6-dihydropyran-2-one (23): Et_3N (0.04 mL,0.28 mmol) and acryloyl chloride (25 mg, 0.28 mmol) was added to a stirred solution of **4** (100 mg, 0.19 mmol) in dry CH_2Cl_2 (5 mL) under nitrogen at room temp. The mixture was stirred at 0 °C for 30 min and then diluted with water (3 mL) The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine and dried with anhydrous sodium sulfate. The solvent was evaporated and the crude was purified by passing through a small of pad of silica gel column.

The acylated compound was dissolved in dry CH_2Cl_2 (15 mL) under argon and the Grubbs I catalyst (16 mg, 0.019 mmol) was added. The solution was degassed with argon for 5 min, stirred at room temp. for 12 h, the solvents were evaporated, and the product was purified by column chromatography (silica gel 60–120 mesh hexane/EtOAc, 7:3) to give lactone **23** (88 mg, 84% over two steps) as a thick brown liquid. $[\alpha]_D^{30}$ = –11.0 (*c* = 0.16, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2922, 2851, 1634, 1435, 1355, 1217, 1024 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 1.19–1.37 (m, 10 H), 1.44–1.80 (m, 8 H), 1.88–198 (m, 1 H), 2.0–2.08 (m, 1 H), 2.29–2.57 (m, 2 H), 3.78–3.85 (m, 1 H), 4.03–4.24 (m, 3 H), 4.66–4.75 (m, 1 H), 5.53 (s, 1 H), 5.55 (s, 1 H), 6.04 (d, *J* = 9.0 Hz, 1 H), 6.86–6.93 (m, 1 H), 7.30–7.40 (m, 6 H), 7.45–7.54 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 22.7, 25.1, 29.3, 29.6, 29.8, 31.9, 36.0, 36.9, 40.4, 41.8, 72.5, 73.0, 73.2, 74.0, 74.6, 100.5, 100.6, 121.2, 125.9, 126.0, 128.1, 128.2, 128.5. 128.7, 133.0, 138.8, 145.2, 164.2 ppm. MS (ESI): *m*/*z* = 549 [M + H]$^+$, 571 [M + Na]$^+$. HRMS: calcd. for $C_{34}H_{44}O_6Na$ 571.3035; found 571.3062.

Polyrhacitide B (2): Compound **23** (48 mg, 0.087 mmol) was dissolved in 60% aqueous acetic acid and stirred at 60 °C for 12 h. The reaction was monitored by TLC. The solvents were removed under vacuum and traces of acetic acid were removed by azeotropic evaporation with toluene. Column chromatographic purification (silica gel, $CHCl_3$/CH_3OH, 98:2) afforded **2** (21 mg, 65%) as colorless needles along with compound **24** (9 mg, 28%) as a white solid. Data for **2**: M.p. 96–98 °C. $[\alpha]_D^{30}$ = +6.3 (*c* = 0.8, MeOH). IR (neat): $\tilde{\nu}$ = 3445, 2923, 2853, 1716, 1219, 1069, 553 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.4 Hz, 3 H), 1.23–1.36 (m, 10 H), 1.37–1.44 (m, 1 H), 1.44–1.78 (m, 10 H), 1.92–1.99 (m, 1 H), 2.01–2.08 (m, 2 H), 2.82 (dd, *J* = 5.1, 19.3 Hz, 1 H), 2.92 (d, *J* = 19.3 Hz, 1 H), 3.83–3.91 (m, 1 H), 4.01–4.18 (m, 3 H), 4.42 (br. s, 1 H), 4.89 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 22.7, 25.1, 29.3, 29.6, 29.8, 31.9, 36.0, 36.9, 40.4, 41.8, 72.5, 73.0, 73.2, 74.0, 74.6, 100.5, 100.6, 121.2, 125.9, 126.0, 128.1, 128.2, 128.5. 128.7, 133.0, 138.8, 145.2, 164.2 ppm. MS (ESI): *m*/*z* = 395 [M + Na]$^+$. HRMS: calcd. for $C_{20}H_{36}O_6Na$ 395.2409; found 395.2419.

(*S*)-6-[(2*R*,4*R*,6*R*,8*R*)-2,4,6,8-Tetrahydroxypentadecyl]-5,6-dihydropyran-2-one (24): $[\alpha]_D^{30}$ = –29.0 (*c* = 0.44, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3401, 2925, 2854, 1713, 1435, 1219, 1088 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.4 Hz, 3 H), 1.21–1.36 (m, 10 H), 1.41–1.91 (m, 12 H), 1.99–2.09 (m, 1 H), 2.33–2.47 (m, 2 H), 3.85–3.94 (m, 1 H), 4.12–4.22 (m, 3 H), 4.22–4.31 (m, 1 H), 4.66–4.79 (m, 1 H), 6.03 (d, *J* = 9.0 Hz, 1 H), 6.87–6.94 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.2, 29.2, 29.4, 29.5, 31.8, 38.4, 42.1, 43.3, 43.3, 44.0, 69.3, 73.4, 73.5, 73.5, 76.2, 121.2, 145.4, 164.2 ppm. MS (ESI): *m*/*z* = 395 [M + Na]$^+$. HRMS: calcd. for $C_{20}H_{36}O_6Na$ 395.2409; found 395.2395.

Supporting Information (see footnote on the first page of this article): Spectral data of all new compounds.

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not minimize the formation of the unexpected product **11**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3 H), 2.88 (d, J = 11.3 Hz, 1 H), 3.04 (dd, J = 10.5, 10.7 Hz, 1 H), 3.26 (dd, J = 3.2, 3.7 Hz, 1 H), 3.42 (dd, J = 7.5, 7.7 Hz, 1 H), 4.46 (d, J = 2.2 Hz, 2 H), 5.38–5.48 (m, 1 H), 7.21–7.35 (m, 5 H), 13.56 (s, 1 H) ppm. MS (ESI): m/z = 294 $[M + H]^+$, 316 $[M + Na]^+$.

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[23] Similar reaction conditions (80% AcOH at 100 °C) to those used for polyrhacitide A provided poor yields of polyrhacitide B. After optimization, 60% AcOH at 60 °C were found to be the best conditions.

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