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Stereoselective Total Synthesis of (–)-Batzellasides A, B, and C

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Total synthesis of (–)-L-batzellasides A, B, and C has been achieved in 13 steps from known lactone **2** in 12.6, 13.2, and 13.8 % overall yields, respectively. The key steps in this synthesis were the stereoselective introduction of an allyl group at the C1 position by acyliminium chemistry and Brown's asymmetric allylation of the corresponding aldehydes to construct a stereocenter on the side chain.

Introduction

Batzellasides A, B, and C were isolated from a Madagascan sponge *Batzella* sp., which was collected off the west coast of Madagascar by Crews in 2005,[1] and showed antibacterial activities against *Staphylococcus epidermidis* with minimum inhibitory concentrations (MICs) of less than 6.3 μg/mL (Figure 1). In addition, these compounds were the first example of an iminosugar from a marine organism, which is an important structural framework for the inhibition of glycosidases.[2] For these reasons, batzellasides are an attractive synthetic target. The first total synthesis of natural (+)-D-batzellaside B was reported by Yoda's group in 2011,[3a] and the absolute configuration of natural (+)-D-batzellaside B was determined to be 1*S*,3*S*,4*S*,5*R*,8*S*. However, the synthesis required 22 steps starting from a known tribenzyl ether derived from L-arabinose, and only resulted in a 3.9% overall yield, although a new formal synthetic route has been reported.[3b] Herein, we report on the efficient and stereoselective total synthesis of (–)-L-batzellasides A, B, and C, which are the enantiomers of these natural products, starting from commercially available tri-*O*-benzyl-D-glucal (**1**).[4]

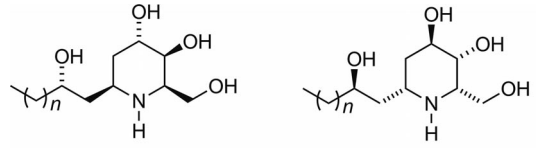

Figure 1. Structure of natural D-batzallasides A, B, and C and L-enantiomers.

Results and Discussion

The synthesis began with pyridinium chlorochromate (PCC) oxidation of tri-*O*-benzyl-D-glucal (**1**), following the method of Squarcia et al.,[5] which resulted in a 55% yield of lactone **2**. The direct conversion of **2** into methyl ester **3** under Fischer's esterification conditions has been reported,[5] however we obtained a very low yield of **3** under the same reaction conditions. As an alternative route to **3**, we performed hydrolysis of **2** with LiOH, followed by esterification with diazomethane at 0 °C, which resulted in a 94% yield of **3** in two steps. Azide **4** was synthesized in one step from **3** by a Mitsunobu reaction with HN_3 and diethyl azodicarboxylate (DEAD), resulting in an 82% yield. A previous synthesis of azide **4** required a two-step conversion, involving mesylation and substitution with NaN_3.[4] Catalytic hydrogenation of **4** over Pd/C gave rise to lactam **5** in an 98% yield (Scheme 1).

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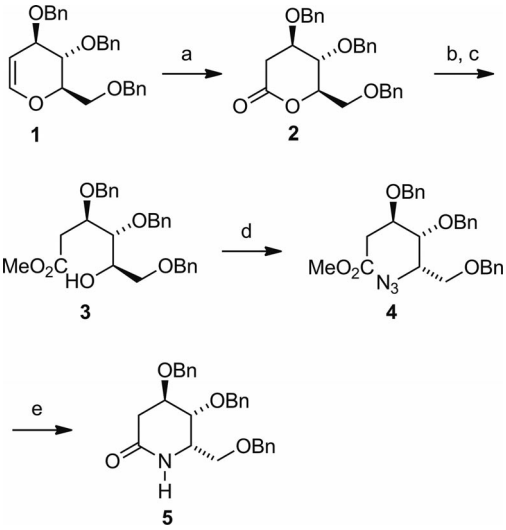
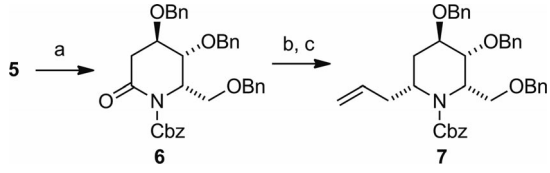


Scheme 1. Synthesis of **5**. *Reagents and conditions:* (a) PCC, CH_2Cl_2, reflux (55%); (b) LiOH, MeOH/H_2O (3:1), reflux; (c) CH_2N_2, EtOAc, 0 °C (94%, 2 steps); (d) HN_3, Ph_3P, DEAD, THF, 0 °C to room temp. (82%); (e) H_2, 10% Pd/C, EtOAc (98%).

Lactam **5** was converted into carboxybenzyl (Cbz)-imide **6**, which was subjected to allylation of the corresponding acyliminium ion. Treatment of **6** with diisobutylaluminium hydride (DIBAL) at –78 °C followed by allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$ gave an allylated product in a ratio of 10:1 (estimated from ^1H NMR spectroscopic data), and major product **7** was isolated in 50% yield (Scheme 2). The stereochemistry of **7** was determined to be as shown in Figure 2 based upon correlation between protons H^a and H^b from a NOESY experiment.



Scheme 2. Synthesis of **7**. *Reagents and conditions:* (a) Lithium bis(trimethylsilyl)amide, CbzCl, THF, –78 °C to 0 °C (83%); (b) DIBAL, CH_2Cl_2, –78 °C; (c) allyltrimethylsilane, $BF_3{\cdot}Et_2O$, CH_2Cl_2, –78 °C (50%, 2 steps).

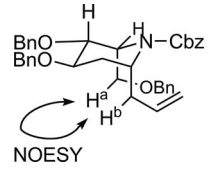


Figure 2. Stereochemistry of **7**.

The stereoselectivity of the above allylation reaction was explained by $A^{(1,3)}$ strain[6] and stereoelectronic effects[7] as shown in Figure 3.

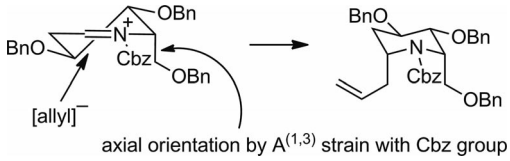
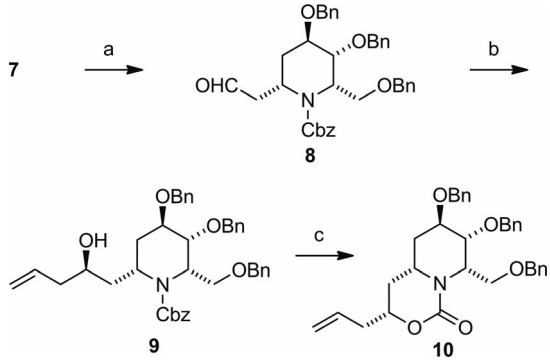


Figure 3. Stereoselectivity of allylation of iminium salt.

Once key and common intermediate **7** was obtained, we next focused our attention on the construction of the stereocenter on the side chain. For this purpose, we adopted Brown's asymmetric allylation reaction[8] of aldehyde **8**, which was easily derived from **7**. The Lemieux–Johnson oxidation of **7** afforded **8**, which was treated with (+)-*B*-allyldiisopinocampheylborane [(+)-$(Ipc)_2B$(allyl)] solution to provide adduct **9** as a single diastereomer in 70% yield. The stereochemistry of the newly formed stereocenter on **9** was determined by a NOESY experiment of cyclic carbamate **10** derived from **9** (Scheme 3). From the observed NOE between H^a and H^b in **10**, the stereochemistry at C8 was determined to be *R*, unambiguously (Figure 4).



Scheme 3. Synthesis of key intermediate (**10**). *Reagents and conditions:* (a) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O (3:1); (b) (+)-$(Ipc)_2B$(allyl), Et_2O, –78 °C (70% 2 steps); (c) NaH, THF/DMF (3:1) (90%).

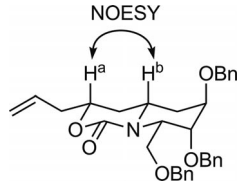


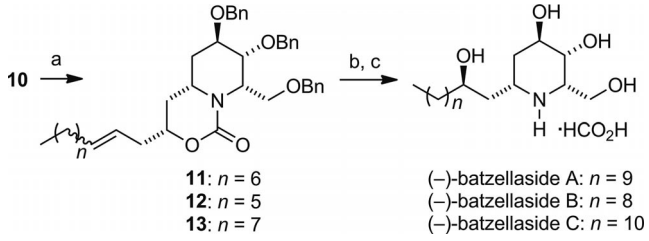
Figure 4. Stereochemistry of **10**.

Installation of a different side chain for batzellasides A, B, and C was achieved by olefin cross metathesis reaction with 1-nonene, 1-octene or 1-decene, which resulted in olefins **11**, **12**, and **13** as a *E*, *Z* mixture in 85, 90, and 91% yields, respectively (Scheme 4). The cross metathesis reaction proceeded smoothly and was catalyzed by Hoveyda–Grubbs' 2nd generation catalyst,[9] rather than Grubbs' catalyst.[10] Finally, hydrogenation of olefins **11**, **12**, and **13** by using Pearlman's catalyst, followed by hydrolysis of the cyclic carbamate with KOH resulted in (–)-L-batzellasides A, B, and C in 75, 67, and 69% yield as formic acid salts,

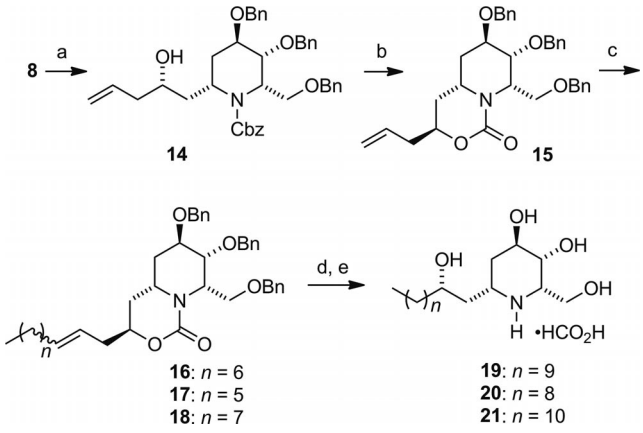
Table 1. NMR spectroscopic data for batzellaside A, B, and C, and C_8 epimers in [D_4]MeOH.

(–)-L-Batzellaside B formic acid salt		(+)-D-Batzellaside B formic acid salt[3a]		(–)-L-Batzellaside A formic acid salt	(–)-L-Batzellaside C formic acid salt	**19**	**20**	**21**
δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_C	δ_C	δ_C	δ_C	δ_C
3.91 br. m	72.1	3.91 ddd (3.0. 3.0. 3.0)	72.0	72.0	72.1	69.7	69.7	69.7
3.83–3.75 m	67.3	3.86–3.75 m	67.3	67.3	67.3	67.2	67.2	67.2
3.59–3.50 m	67.2	3.65–3.49 m	67.2	67.2	67.2	67.1	67.1	67.1
2.01 t (14.9)	60.8	2.01 ddd (14.7. 13.5. 2.4)	60.8	60.9	60.8	61.0	61.0	61
1.84 d (14.3)	58.5	1.83 dt (14.4. 3.0. 3.0)	58.5	58.5	58.5	58.1	58.1	58.1
1.73–1.69 m	53.5	1.76–1.64 m	53.4	53.4	53.4	51.3	51.3	51.3
1.48 br. s	39.5	1.46 br. s	39.4	39.5	39.5	39.2	39.2	39.2
1.32 br. s	39.4	1.30 br. s	39.4	39.4	33.1	38.4	38.4	38.4
0.90 t (6.8)	33.0	0.90 t (6.8)	33.0	33.1	33.0	33.1	33.1	33.1
	32.6		32.5	33.0	32.6	32.0	32.0	32.0
	30.8		30.7	32.6	30.8	30.7	30.80	30.74
	30.7		30.7	30.80	30.7	30.5	30.75	30.70
	30.5		30.6	30.75	30.5	30.4	30.70	30.5
	30.4		30.4	30.70	30.4	26.3	30.4	26.7
	26.3		26.2	30.5	26.3	23.7	26.7	23.7
	23.7		23.7	26.3	23.7	14.4	23.7	14.4
	14.4		14.4	23.7	14.4		14.4	
				14.4				

respectively. The spectroscopic data for synthetic (–)-L-batzellaside B were in good agreement with those reported values as shown in Table 1.[3]



Scheme 4. Synthesis of (–)-batzellasides A, B, and C. *Reagents and conditions:* (a) 2nd generation Hoveyda–Grubbs catalyst (10 mol-%), 1-nonene or 1-octene or 1-decene, CH_2Cl_2, reflux (**11**: 85%, **12**: 90%, **13**: 91%); (b) H_2, $Pd(OH)_2$ (20%), EtOH; (c) KOH (aq.), 2-propanol, reflux, then HCO_2H [(–)-batzellaside A: 75%, (–)-batzellaside B: 67%, (–)-batzellaside C: 69%].



Scheme 5. Synthesis of **19**, **20**, and **21**. *Reagents and conditions:* (a) (–)-$(Ipc)_2B$(allyl), Et_2O, –78 °C (71% 2steps); (b) NaH, THF/DMF (3:1; 87%); (c) 2nd generation Hoveyda–Grubbs catalyst (10 mol-%), 1-nonene, 1-octene or 1-decene, CH_2Cl_2, reflux (**16**: 90%, **17**: 90%, **18**: 88%); (b) H_2, $Pd(OH)_2$ (20%), EtOH; (c) KOH (aq.), 2-propanol, reflux, then CO_2H (**19**: 72%, **20**: 67%, **21**: 55%).

C8 epimers **19**, **20**, and **21** were also synthesized in the same manner as for Schemes 3 and 4 by using (–)-$(Ipc)_2B$(allyl) instead of (+)-$(Ipc)_2B$(allyl) through alcohol **14**, cyclic carbamate **15**, and olefins **16**, **17**, and **18** as shown in Scheme 5.

A previous study demonstrated that (+)-D-batzellasides A, B, and C inhibited the growth of *Staphylococcus epidermidis* with MICs of < 6.3 μg/mL.[1] However, there was no report about glycosidase inhibition. Thus, we first analyzed the inhibitory activities of (–)-L-batzellasides A, B, and C and newly synthesized C8 epimers **19**, **20**, and **21** towards various glycosidases. The IC_{50} values towards specific glycosidases are summarized in Table 2. All of the synthesized compounds showed inhibitory activity against bovine liver β-galactosidase. It is not easy to find the structural requirements against this inhibition but it seems that the deoxy L-xylo configuration of the piperidine ring is important for inhibition. Among them, (–)-L-batzellaside A exhibited the most potent inhibition against this enzyme with IC_{50} values of 6.7 μM. Epimer **21** was also a good inhibitor for β-galactosidase. Epimer **19** had a lower inhibition toward β-galactosidase relative to (–)-L-batzellaside A, and it was the only compound that inhibited β-glucuronidase. Among (–)-L-batzellasides A, B, and C and their epimers **19**, **20**, and **21**, both the length of the side chain and the stereochemistry at the C8 position are important for the inhibitory activities against β-galactosidase and β-glucuronidase. Among them, inhibitors of β-glucuronidase have the potential to become drugs that suppress the side effects of camptotecin derivative CPT-11, an anti-tumor drug used for the treatment of small-cell lung carcinoma and other solid tumors. CPT-11 is changed to an active form SN-38 by the action of carboxyesterase in the liver. SN-38 is fur-

Table 2. Concentration of batzellaside giving 50% inhibition of various glycosidases.

Enzyme	IC_{50} (μM) (–)-Batzellaside A	**19**	(–)-Batzellaside B	**20**	(–)-Batzellaside C	**21**
α-Glucosidase (from yeast)	n.i.[a]	n.i.	897	n.i.	n.i.	n.i.
β-Glucosidase (from bovine liver)	43	50	83	n.i.	n.i.	43
α-Galactosidase (from coffee beans)	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
β-Galactosidase (from bovine liver)	6.7	18	26	45	35	7.5
α-Mannosidase (from Jack beans)	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
β-Mannosidase (from snail)	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
α-L-Fucosidase (from bovine kidney)	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
α-L-Rhamnosidase (from *Penicillium decumbens*)	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
β-Glucronidase (from *E. coli*)	n.i.	85	n.i.	n.i.	n.i.	n.i.
Trehalase (from porcine kidney)	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
Amyloglucosidase (from *Aspergillus niger*)	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.

[a] n.i.: no inhibition (less than 50% inhibition at 1000 mM).

ther changed to inactive SN-38 glucuronate conjugate, which is excreted into bile.[11] By the action of β-glucuronidase from intestinal bacteria, deconjugation of SN-38 glucuronide gives rise to SN-38, which causes the severe diarrhea in patients treated with CPT-11. Therefore, the inhibitory activity of compound **19** against β-glucuronidase is noteworthy.

Conclusions

We have achieved the efficient and stereoselective total synthesis of (–)-L-batzellasides A, B, and C, and the enantiomers of these natural products, in 13 steps beginning with known lactone **2**. The total synthesis of (–)-L-batzellasides A, B, and C resulted in 12.6, 13.2, and 13.8% overall yields, respectively, whereas C8 epimers **19**, **20**, and **21** resulted in 13.0, 12.1, and 9.7% overall yields, respectively. (–)-L-Batzellasides A and epimer **21** showed potent inhibition against bovine liver β-galactosidase, with IC_{50} values of 6.7 and 7.5 μM, respectively. Epimer **19** was a moderate inhibitor for β-glucuronidase. The flexible and synthetic route developed here is currently being used to synthesize additional congeners possessing shorter side chains, and studies of the inhibitory activities of these congeners towards various glycosidases are in progress.

Experimental Section

General Information: Flash chromatography was performed with Kanto Kagaku silica gel 60N (63-210 mm). NMR spectra were recorded with a JEOL a-GX 400 or ECP-NMR 600 spectrometer in the solvent indicated. Chemical shifts (δ) are reported downfield from tetramethylsilane and referenced with $CHCl_3$ (δ = 7.26 ppm) as an internal standard. Peak multiplicities are designated by the following abbreviations: s singlet, d doublet, t triplet, q quartet, m multiplet, br. broad. High-resolution mass spectroscopic data was obtained with a JEOL MStation JMS-700. All commercial reagents were used as received unless otherwise noted.

(4*R*,5*S*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)tetrahydropyran-2-one (2): PCC (43.6 g, 0.20 mol) and silica gel (60 g) were added to a solution of **1** (42.1 g, 0.10 mol) in CH_2Cl_2 (100 mL). The resulting suspension was heated to reflux for 12 h. After cooling, the reaction mixture was filtered through a Celite pad. The Celite pad was washed several times with AcOEt, and the filtrates were combined and concentrated resulting in a black oil, which was purified by chromatography on silica gel (160 g, *n*-hexane/acetone, 10:1) to give **2** (23.9 g, 55.5 mmol, 55%) as a pale yellow solid. The spectroscopic data were identical with those of reported values.[4]

Methyl (3*R*,4*R*,5*R*)-3,4,6-Tris(benzyloxy)-5-hydroxyhexanoate (3): The procedure in ref.[4] was modified as described. Aqueous LiOH (1 N, 1.4 mL) was added to a solution of **2** (0.62 g, 1.44 mmol) in MeOH (4.2 mL). The reaction mixture was heated to reflux for 2 h. After cooling, the reaction mixture was acidified with 10% HCl to pH 4 and then the aqueous mixture was extracted with AcOEt (3 × 10 mL). The organic layers were combined, washed with brine, and dried with anhydrous $MgSO_4$. After removal of the solvent, the residue was dissolved in Et_2O (5 mL) and treated with ethereal CH_2N_2, prepared from *N*-nitroso-*N*-methylurea (371 mg, 3.6 mmol) and a solution of KOH (0.57 g, 10.2 mmol) in a mixture of H_2O (2 mL) and Et_2O (3 mL), at 0 °C for 30 min. The reaction mixture was concentrated resulting in a pale yellow oil, which was purified by chromatography on silica gel (30 g, AcOEt/*n*-hexane, 1:4) to give **3** (0.63 g, 1.35 mmol, 94%) as a pale yellow oil. The spectroscopic data were identical with those of reported values.[4]

Methyl (3*R*,4*R*,5*S*)-5-Azido-3,4,6-tris(benzyloxy)hexanoate (4): The procedure in ref.[4] was modified as shown below. Ph_3P (6.51 g, 24.8 mmol) was added to a solution of **3** (8.87 g, 19.1 mmol) in tetrahydrofuran (THF; 25 mL). A solution of HN_3 (0.8 N, 38.2 mmol) in benzene (48 mL), prepared from NaN_3 (3.26 g, 50.2 mmol) and concentrated H_2SO_4 (1.26 mL, 23.7 mmol) in a mixture of H_2O (36 mL) and benzene (60 mL) at 0 °C, was added to the stirred mixture. Diethyl azodicarboxylate (≈ 2.2 mol/L, 11.2 mL, 24.9 mmol) at 0 °C was added slowly to the stirred mixture. The reaction mixture was stirred for 12 h at room temperature. The solvent was removed to give a pale yellow oil, which was purified by chromatography on silica gel (80 g, AcOEt/*n*-hexane, 1:10) to give **4** (7.67 g, 15.7 mmol, 82%) as a colorless oil. The spectroscopic data were identical with those for the reported values.[4]

(4*R*,5*R*,6*S*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)piperidin-2-one (5): Pd/C (10%, 491 mg) was added to a solution of **4** (6.15 g, 12.6 mmol) in AcOEt (13 mL), and the resulting suspension was hydrogenated at 1 atm under a hydrogen atmosphere for 48 h. The catalyst was filtered off through a Celite pad and the filtrate was evaporated to give **5** (5.34 g, 12.4 mmol, 98%) as a colorless oil. This compound was used directly in the next step without further purification. The spectroscopic data were identical with those for the reported values.[4]

Benzyl (4*R*,5*R*,6*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-6-oxopiperidine-1-carboxylate (6): A solution of lithium bis(trimethylsilyl)amide (10.4 mL, 16.6 mmol, 1.6 mol/L, in THF) at –78 °C was added to a stirred solution of **5** (5.55 g, 12.9 mmol) in THF (26 mL). The resulting mixture was stirred at –78 °C for 0.5 h. Benzyl chloroformate (2.75 mL, 19.3 mmol) was added dropwise to the mixture, and the reaction mixture was stirred at –78 °C for 1 h. The reaction was quenched with saturated $NaHCO_3$ (aq.) and then the aqueous mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, washed with brine, dried with anhydrous $MgSO_4$, and evaporated to give a pale yellow oil, which was purified by chromatography on silica gel (80 g, AcOEt/*n*-hexane, 1:10) to give **6** (6.1 g, 10.8 mmol, 83%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.17 (m, 20 H), 4.76–4.58 (m, 6 H), 4.74–4.39 (m, 3 H), 4.25 (ddd, *J* = 9.0, 7.6, 7.6 Hz, 1 H), 3.92 (dd, *J* = 9.9, 1.2 Hz, 1 H), 3.85 (dd, *J* = 9.0, 5.4 Hz, 1 H), 3.64 (dd, *J* = 9.9, 3.6 Hz, 1 H), 3.01 (dd, *J* = 17.1, 7.6 Hz, 1 H), 2.52 (dd, *J* = 17.1, 7.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 153.5, 138.0, 137.5, 137.3, 135.0, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.4, 127.3, 127.1, 78.4, 74.4, 73.2, 72.9, 72.2, 68.5, 65.9, 54.8, 40.5 ppm. IR (neat): $\tilde{\nu}$ = 1774, 1721 cm^{-1}. MS (ESI): *m*/*z* = 565 [M$^+$]. HRMS (ESI): calcd. for $C_{35}H_{35}NO_6$ 565.2464; found 565.2454. $[\alpha]_D^{24}$ = +11.8 (*c* = 0.98, $CHCl_3$).

Benzyl (2*S*,3*R*,4*R*,6*R*)-6-Allyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)piperidine-1-carboxylate (7): A solution of DIBAL (1 M, 11.2 mL, 1.16 mmol, in *n*-hexane) at –78 °C was added to a solution of **6** (5.07 g, 8.98 mmol) in CH_2Cl_2 (20 mL), and the reaction mixture was stirred at the same temperature for 0.5 h. The reaction was quenched with MeOH (6 mL) and Rochella salt (30%, aq.) and then the aqueous mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, washed with brine, dried with anhydrous $MgSO_4$ and evaporated to give a pale yellow oil, which was purified by chromatography on silica gel (80 g, AcOEt/*n*-hexane, 1:15) to give **7** (2.66 g, 4.49 mmol, 50%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.22 (m, 20 H), 5.70 (br., 1 H), 5.20–5.09 (m, 2 H), 5.02–4.86 (m, 2 H), 4.78–4.44 (m, 7 H), 4.32 (dd, *J* = 6.4, 6.4 Hz, 1 H), 3.95–3.87 (m, 1 H), 3.82 (dd, *J* = 10.2, 5.7 Hz, 1 H), 3.65 (br., 1 H), 3.66 (dd, *J* = 10.2, 5.1 Hz, 1 H), 2.46–2.41 (m, 1 H), 2.26–2.15 (m, 1 H), 2.04 (ddd, *J* = 12.0, 6.6, 6.4 Hz, 1 H), 1.57 (ddd, *J* = 12.0, 6.6, 6.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8, 138.6, 138.2, 138.1, 136.5, 135.6, 128.3, 128.2, 128.1, 127.77, 127.67, 127.59, 127.53, 127.45, 127.41, 127.38, 127.25, 117.1, 100.5, 80.6, 73.0, 72.94, 72.86, 72.5, 69.5, 67.4, 53.2, 50.8, 39.1 ppm. IR (neat): $\tilde{\nu}$ = 1679 cm^{-1}. MS (ESI): *m*/*z* = 591 [M$^+$]. HRMS (ESI): calcd. for $C_{38}H_{41}NO_5$ 591.2985; found 591.2980. $[\alpha]_D^{23}$ = –8.2 (*c* = 1.10, $CHCl_3$).

Benzyl (2*S*,3*R*,4*R*,6*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-6-[(2*R*)-2-hydroxypent-4-enyl]piperidine-1-carboxylate (9): A 1,4-dioxane/H_2O mixture (3:1, 40 mL) in a solution of **7** (1.92 g, 3.24 mmol) was added to 2,6-lutidine (0.75 mL, 6.48 mmol) and OsO_4 (4.0 mL, 0.648 mmol, 4% in H_2O) at 0 °C. $NaIO_4$ (2.77 g, 13.0 mmol) was added to the resulting mixture. The reaction mixture was stirred at room temperature for 2 h. After the reaction was complete, HCl (10%, aq., 20 mL) was added, and the aqueous mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, washed with brine, dried with anhydrous $MgSO_4$ and evaporated to give aldehyde **8** as a colorless oil, which was used directly in the next step.

(+)-$(Ipc)_2$B(allyl) solution (1.0 M, 2.7 mL, 2.67 mmol, in *n*-pentane) was added to a solution of aldehyde **8** in Et_2O (5 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 2 h. After the reaction was complete, MeOH (2.0 mL) and 2-aminoethanol (4.0 mL) were added. The resulting mixture was stirred at room temperature for 17 h. The reaction solvent was removed to give a pale yellow oil, which was purified by chromatography on silica gel (60 g, AcOEt/*n*-hexane, 1:15) to give **9** (1.44 g, 2.27 mmol, 70%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 20 H), 5.74 (1 H, br.), 5.10–5.00 (m, 5 H), 4.76–4.57 (m, 6 H), 4.45 (dd, *J* = 6.3, 6.3 Hz, 1 H), 3.90–3.86 (m, 2 H), 3.64–3.58 (m, 2 H), 2.18–2.12 (m, 3 H), 1.94 (ddd, *J* = 13.1, 6.5, 6.3 Hz, 1 H), 1.67 (ddd, *J* = 13.1, 6.5, 6.3 Hz, 1 H), 1.66–1.65 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 138.5, 138.1, 137.9, 136.3, 134.6, 128.3, 128.24, 128.21, 128.0, 127.6, 127.53, 127.46, 117.5, 80.6, 77.4, 76.6, 73.2, 73.07, 72.97, 72.6, 69.0, 68.7, 67.6, 53.3, 48.7, 42.3, 33.9 ppm. IR (neat): $\tilde{\nu}$ = 3447, 1692 cm^{-1}. MS (ESI): *m*/*z* = 635 [M$^+$]. HRMS (ESI): calcd. for $C_{40}H_{45}NO_6$ 635.3247; found 635.3261. $[\alpha]_D^{22}$ = –15.3 (*c* = 1.60, $CHCl_3$).

(3*R*,4a*R*,6*R*,7*R*,8*S*)-3-Allyl-6,7-bis(benzyloxy)-8-[(benzyloxy)methyl]hexahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (10): THF/dimethylformamide (DMF; 3:1, 4 mL) in a solution of **9** (0.20 g, 0.314 mmol) was added to NaH (17.6 mg, 0.441 mmol, 60% suspension in mineral oil). The stirred reaction mixture was heated to reflux for 20 h. After cooling, H_2O (10 mL) was added, and then the aqueous mixture was extracted with AcOEt (3 × 10 mL). The organic layers were combined, washed with brine, dried with $MgSO_4$, and evaporated to give a brown oil, which was purified by chromatography on silica gel (5 g, *n*-hexane/AcOEt, 10:1) to give **10** (0.149 g, 0.283 mmol, 90%) as a pale brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 15 H), 5.79 (ddt, *J* = 16.9, 10.3, 6.7 Hz, 1 H), 5.14 (d, *J* = 16.9 Hz, 1 H), 5.13 (d, *J* = 10.3 Hz, 1 H), 4.73–4.44 (m, 6 H), 4.29–4.28 (m, 1 H), 4.23 (dtd, *J* = 11.1, 6.7, 2.8 Hz, 1 H), 3.97 (dd, *J* = 10.3, 4.3 Hz, 1 H), 3.96–3.93 (m, 1 H), 3.73 (dd, *J* = 10.3, 2.6 Hz, 1 H), 3.68 (dddd, *J* = 11.1, 10.5, 2.8, 2.2 Hz, 1 H), 2.49 (dt, *J* = 14.2, 6.7 Hz, 1 H), 2.32 (dt, *J* = 14.2, 6.7 Hz, 1 H), 2.18 (dd, *J* = 14.0, 5.5 Hz, 1 H), 1.93 (dt, *J* = 13.5, 2.8 Hz, 1 H), 1.76 (dd, *J* = 14.0, 2.2 Hz, 1 H), 1.42 (dt, *J* = 13.5, 11.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.9, 138.3, 138.2, 137.9, 132.2, 128.3, 128.2, 127.6, 127.58, 127.53, 127.4, 127.3, 118.6, 78.1, 77.4, 75.8, 75.5, 73.3, 72.3, 71.5, 66.8, 54.0, 48.0, 39.5, 35.3, 34.3, 29.8 ppm. IR (neat): $\tilde{\nu}$ = 1682 cm^{-1}. MS (ESI): *m*/*z* = 527 [M$^+$]. HRMS (ESI): calcd. for $C_{33}H_{37}NO_5$ 527.2672; found 527.2661. $[\alpha]_D^{23}$ = –20.5 (*c* = 0.46, $CHCl_3$).

(3*R*,4a*R*,6*R*,7*R*,8*S*)-6,7-Bis(benzyloxy)-8-(benzyloxymethyl)-3-(dec-2-en-1-yl)hexahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (11): 1-Nonene (0.099 mL, 0.569 mmol) was added to a solution of **10** (30 mg, 56.9 μmol) in CH_2Cl_2 (2 mL) at room temperature. Second-generation Hoveyda–Grubbs catalyst (3.7 mg, 5.69 μmol) was added to the stirred mixture. The stirred reaction mixture was heated to reflux for 24 h. After cooling, the reaction solvent was removed in vacuo to give a black oil, which was purified by chromatography on silica gel (5 g, AcOEt/*n*-hexane, 1:10) to give **11** (30.2 mg, 48.3 μmol, 85%) as a pale brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.17 (m, 15 H), 5.44 (dt, *J* = 16.5, 5.3 Hz, 1 H), 5.31 (ddd, *J* = 16.5, 10.5, 5.1 Hz, 1 H), 4.64–4.40 (m, 6 H), 4.21 (br., 1 H), 4.10 (dtd, *J* = 11.1, 6.7, 2.8 Hz, 1 H), 3.89 (dd, *J* = 7.5, 3.0 Hz, 1 H), 3.85–3.84 (m, 1 H), 3.73 (dd, *J* = 7.5, 1.8 Hz, 1 H), 3.62–3.56 (m, 1 H), 2.38–2.33 (m, 1 H), 2.20–2.12 (m, 1 H), 1.93–1.82 (m, 2 H), 1.69 (d, *J* = 10.8 Hz, 1 H), 1.36–1.19 (m, 14 H), 0.82–0.79 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.1, 138.4, 138.3, 138.0, 135.0, 134.9, 133.8, 131.7, 128.3, 128.2, 127.7, 127.62, 127.57, 127.5, 127.3, 127.2, 78.1, 76.1, 75.8, 73.3, 72.2, 71.4, 66.8, 54.0, 47.9, 38.4, 35.6, 35.3, 34.3, 31.8, 31.6, 29.5, 29.3, 29.1, 22.6, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 1691 cm^{-1}. MS (ESI): *m*/*z* = 625 [M$^+$]. HRMS (ESI): calcd. for $C_{40}H_{51}NO_5$ 625.3767; found 625.3778.

(3*R*,4a*R*,6*R*,7*R*,8*S*)-6,7-Bis(benzyloxy)-8-(benzyloxymethyl)-3-(non-2-en-1-yl)hexahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (12): 1-Octene (0.146 mL, 0.93 mmol) was added to a solution of **10** (49 mg, 93.0 μmol) in CH_2Cl_2 (4 mL) at room temperature. Second-generation Hoveyda–Grubbs catalyst (5.0 mg, 9.3 μmol) was added to the stirred mixture. The stirred reaction mixture was heated to reflux for 15 h. After cooling, the reaction solvent was removed in vacuo to give a black oil, which was purified by chromatography on silica gel (10 g, *n*-hexane/acetone, 20:1) to give **12** (51 mg, 83.7 μmol, 90%) as a pale brown oil. ^{1}H NMR (500 MHz $CDCl_3$): δ = 7.33–7.27 (m, 15 H), 5.34 (dt, J = 14.3, 7.2 Hz, 1 H), 5.50–5.31 (m, 1 H), 4.75–4.41 (m, 6 H), 4.28 (1 H, br.), 4.22–4.15 (m, 1 H), 3.96 (dd, J = 10.1, 4.4 Hz, 1 H), 3.94–3.87 (m, 2 H), 3.80 (dd, J = 10.1, 2.6 Hz, 1 H), 3.72–3.65 (m, 1 H), 2.53–2.11 (m, 2 H), 2.04–1.55 (m, 6 H), 1.37–1.26 (m, 8 H), 0.88 (t, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.2, 138.5, 138.4, 138.0, 135.0, 134.97, 134.8, 133.8, 128.4, 128.36, 128.26, 127.7, 127.67, 127.66, 127.61, 127.5, 127.4, 78.1, 76.1, 75.9, 73.3, 72.3, 71.4, 66.8, 54.0, 47.9, 38.4, 35.3, 35.2, 34.3, 32.6, 31.7, 29.3, 28.8, 22.7, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 1690 cm^{-1}. MS (ESI): m/z = 611 [M$^+$]. HRMS (ESI): calcd. for $C_{39}H_{49}NO_5$ 611.3611; found 611.3616.

(3*R*,4a*R*,6*R*,7*R*,8*S*)-6,7-Bis(benzyloxy)-8-(benzyloxymethyl)-3-(undec-2-en-1-yl)hexahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (13): 1-Decene (0.40 mL, 2.12 mmol) was added to a solution of **10** (112 mg, 0.21 mol) in CH_2Cl_2 (6 mL) at room temperature. Second-generation Hoveyda–Grubbs catalyst (13.0 mg, 21.2 μmol) was added to the stirred mixture. The stirred reaction mixture was heated to reflux for 15 h. After cooling, the reaction solvent was removed in vacuo to give a black oil, which was purified by chromatography on silica gel (10 g, *n*-hexane/acetone, 20:1) to give **13** (123 mg, 0.19 mmol, 91%) as a pale brown oil. ^{1}H NMR (500 MHz $CDCl_3$): δ = 7.34–7.27 (m, 15 H), 5.33 (dt, J = 14.4, 7.2 Hz, 1 H), 5.43–5.33 (m, 1 H), 4.75–4.41 (m, 6 H), 4.29 (br., 1 H), 4.20–4.16 (m, 1 H), 3.98–3.90 (m, 3 H), 3.81 (dd, J = 10.3, 2.9 Hz, 1 H), 3.69–3.65 (m, 1 H), 2.51–2.18 (m, 2 H), 2.05–1.59 (m, 6 H), 1.35–1.26 (m, 12 H), 0.88 (t, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.2, 138.43, 138.37, 138.0, 135.0, 134.96, 133.8, 131.8, 128.4, 128.35, 128.25, 127.7, 127.65, 127.60, 127.5, 127.4, 127.2, 78.1, 76.9, 76.1, 75.8, 73.3, 72.2, 71.4, 66.8, 54.0, 47.9, 38.4, 35.3, 34.2, 32.6, 31.9, 31.8, 29.3, 29.25, 29.1, 22.7, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 1693 cm^{-1}. MS (ESI): m/z = 639 [M$^+$]. HRMS (ESI): calcd. for $C_{41}H_{53}NO_5$ 639.3924; found 639.3927.

(–)-L-Batzellaside A, Formic Acid Salt: $Pd(OH)_2$/C (20%, 3 mg) was added to a solution of **11** (20 mg, 31.9 μmol) in EtOH (3 mL), and the resulting suspension was hydrogenated at 1 atm under a hydrogen atmosphere for 5 d. The catalyst was filtered off through a Celite pad and the filtrate was evaporated to give a hydrogenated product. A solution of KOH (4 M aq., 0.5 mL) was added to a solution of this product in 2-propanol (0.5 mL), and the resulting mixture was heated to reflux for 2 h. After cooling, the solvent was evaporated, and the residue was purified by DOWEX 50W resin (X-8, H^+ form, eluent: 0.7 N aqueous NH_3), subjected to counterion exchange with formic acid/methanol (1% v/v) at room temperature, and concentrated in vacuo to yield (–)-batzellaside A as the formic acid salt (9 mg, 23.9 μmol, 75%). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.91 (br. m, 1 H), 3.83–3.75 (m, 3 H), 3.65–3.51 (m, 2 H), 2.00 (tt, J = 14.4, 2.4 Hz, 1 H), 1.83 (d, J = 14.3 Hz, 1 H), 1.73–1.68 (m, 2 H), 1.47 (br. s,2 H), 1.31 (br. s,16 H), 0.90 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 72.0, 67.3, 67.2, 60.9, 58.5, 53.4, 39.5, 39.4, 33.1, 33.0, 32.6, 30.8, 30.75, 30.70, 30.5, 26.3, 23.7, 14.4 ppm. $[\alpha]_D^{25}$ = –5.9 (c = 0.2, MeOH).

(–)-L-Batzellaside B, Formic Acid Salt: $Pd(OH)_2$/C (20%, 5 mg) was added to a solution of **12** (82 mg, 134 μmol) in EtOH (5 mL), and the resulting suspension was hydrogenated at 1 atm under a hydrogen atmosphere for 7 d. The catalyst was filtered off through a Celite pad and the filtrate was evaporated to give a hydrogenated product. A solution of KOH (4 M aq., 1 mL) was added to a solution of this product in 2-propanol (1 mL), which was heated to reflux for 2 h. After cooling, the solvent was evaporated, and the residue was purified by DOWEX 50W resin (X-8, H^+ form, eluent: 0.7 N aqueous NH_3), subjected to counterion exchange with formic acid/methanol (1% v/v) at room temperature, and concentrated in vacuo to yield (–)-batzellaside B as the formic acid salt (33 mg, 89.8 μmol, 67%). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.91 (br. m, 1 H), 3.83–3.75 (m, 3 H), 3.59–3.50 (m, 2 H), 2.01 (tt, J = 14.9, 2.3 Hz, 1 H), 1.84 (d, J = 14.3 Hz, 1 H), 1.73–1.69 (m, 2 H), 1.48 (br. s,2 H), 1.32 (br. s,16 H), 0.90 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 72.1, 67.3, 67.2, 60.8, 58.5, 53.5, 39.5, 39.4, 33.0, 32.6, 30.8, 30.7, 30.5, 30.4, 26.3, 23.7, 14.4 ppm. $[\alpha]_D^{25}$[3] = –13.5 (c = 0.1, MeOH), for enantiomer, ref.[3a] $[\alpha]_D^{23}$ = +9.3 (c = 0.5, MeOH).

(–)-L-Batzellaside C, Formic Acid Salt: $Pd(OH)_2$/C (20%, 3 mg) was added to a solution of **13** (21 mg, 32.8 μmol) in EtOH (3 mL), and the resulting suspension was hydrogenated at 1 atm under a hydrogen atmosphere for 7 d. The catalyst was filtered off through a Celite pad and the filtrate was evaporated to give a hydrogenated product. A solution of KOH (4 M aq., 0.5 mL) was added to a solution of this product in 2-propanol (0.5 mL), which was heated to reflux for 2 h. After cooling, the solvent was evaporated, and the residue was purified by DOWEX 50W resin (X-8, H^+ form, eluent: 0.7 N aqueous NH_3), subjected to counterion exchange with formic acid/methanol (1% v/v) at room temperature, and concentrated in vacuo to yield (–)-batzellaside C as the formic acid salt (9 mg, 22.6 μmol, 69%). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.91 (br. m, 1 H), 3.83–3.77 (m, 3 H), 3.65–3.50 (m, 2 H), 2.01 (dt, J = 14.9, 2.3 Hz, 1 H), 1.83 (d, J = 14.3 Hz, 1 H), 1.73–1.66 (m, 2 H), 1.47 (br. s,2 H), 1.32 (br. s,18 H), 0.89 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 72.1, 67.3, 67.2, 60.8, 58.5, 53.4, 39.5, 33.1, 33.0, 32.6, 30.8, 30.7, 30.5, 30.4, 26.3, 23.7, 14.4 ppm. $[\alpha]_D^{22}$ = –7.4 (c = 0.1, MeOH).

Benzyl (2*S*,3*R*,4*R*,6*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-6-[(2*S*)-2-hydroxypent-4-enyl]piperidine-1-carboxylate (14): In a 1,4-dioxane/H_2O mixture (3:1, 20 mL), a solution of **7** (0.49 g, 0.84 mmol) was added to 2,6-lutidine (0.19 mL, 1.68 mmol) and OsO_4 (1.0 mL, 0.17 mmol, 4% in H_2O) at 0 °C. To the resulting mixture was added $NaIO_4$ (0.718 g, 3.36 mmol). The reaction mixture was stirred at room temperature for 2 h. After the reaction was complete, HCl (10% aq., 10 mL) was added, and then the aqueous mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, washed with brine, dried with anhydrous $MgSO_4$, and evaporated to give aldehyde **8** as a colorless oil, which was used directly in the next step.

(–)-$(Ipc)_2$B(allyl) solution (1.0 M, 0.81 mL, 0.81 mmol, in *n*-pentane) was added to a solution of aldehyde **8** in Et_2O (3 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 2 h. After the reaction was complete, MeOH (1.0 mL) and 2-aminoethanol (2.0 mL) were added. The resulting mixture was stirred at room temperature for 17 h. The reaction solvent was removed to give a pale yellow oil, which was purified by chromatography on silica gel (15 g, AcOEt/*n*-hexane, 1:15) to give **14** (0.38 g, 0.60 mmol, 71%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 20 H), 5.78 (br., 1 H), 5.18–5.02 (m, 4 H), 4.86 (br., 1 H), 4.78–4.64 (m, 6 H), 4.44 (dd, J = 5.1, 5.1 Hz, 1 H), 3.92–3.85 (m, 1 H) 3.79–3.69 (m, 1 H), 3.64–3.56 (m, 2 H), 2.24–2.10 (m, 4 H), 1.98 (ddd, J = 13.5, 5.1, 4.2 Hz, 1 H) 1.86–1.73 (m, 2 H), 1.38 (ddd, J

= 13.5, 5.2, 4.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 138.5, 138.1, 138.0, 136.1, 128.4, 128.26, 128.22, 128.0, 127.6, 127.5, 127.4, 127.2, 116.6, 80.3, 77.4, 73.6, 73.4, 72.9, 72.5, 69.1, 66.8, 53.4, 48.1, 42.9, 41.4, 35.0, 32.6, 31.0, 21.5 ppm. IR (neat): $\tilde{\nu}$ = 3448, 1667 cm^{-1}. MS (ESI): *m*/*z* = 635 [M$^+$]. HRMS (ESI): calcd. for $C_{40}H_{45}NO_6$ 635.3247; found 635.3242. $[\alpha]_D^{22}$ = –10.3 (*c* = 1.00, $CHCl_3$).

(3*S*,4a*R*,6*R*,7*R*,8*S*)-3-Allyl-6,7-bis(benzyloxy)-8-(benzyloxymethyl)hexahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (15): NaH (42 mg, 1.0 mmol, 60% suspension in mineral oil) was added to a solution of **14** (0.442 g, 0.70 mmol) in THF/DMF (4:1, 10 mL). The stirred reaction mixture was heated to reflux for 15 h. After cooling, H_2O (10 mL) was added and the aqueous mixture was extracted with AcOEt (3 × 10 mL). The organic layers were combined, washed with brine, dried with $MgSO_4$, and evaporated to give a brown oil, which was purified by chromatography on silica gel (15 g, *n*-hexane/acetone, 10:1) to give **15** (0.320 g, 0.61 mmol, 87%) as a pale brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.21 (m, 15 H), 5.74 (ddt, *J* = 17.3, 10.3, 6.6 Hz, 1 H), 5.08 (d, *J* = 17.1 Hz, 1 H), 5.07 (d, *J* = 10.3 Hz, 1 H), 4.59–4.38 (m, 6 H), 4.34 (m, 1 H), 4.09–3.95 (m, 3 H), 3.86–3.83 (m, 1 H), 3.79–3.77 (m, 1 H), 3.70–3.68 (m, 1 H), 2.48 (dt, *J* = 13.2, 6.6 Hz, 1 H), 2.25 (dt, *J* = 13.2, 6.6 Hz, 1 H), 2.15–2.07 (m, 1 H), 1.88–1.81 (m, 1 H), 1.65–1.56 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.6, 138.5, 138.2, 138.1, 132.6, 128.4, 128.2, 127.7, 127.66, 127.63, 127.55, 127.54, 127.4, 118.6, 75.1, 74.3, 73.0, 72.6, 71.3, 67.4, 56.8, 47.4, 39.1, 34.2, 31.4 ppm. IR (neat): $\tilde{\nu}$ = 1699 cm^{-1}. MS (ESI): *m*/*z* = 527 [M$^+$]. HRMS (ESI): calcd. for $C_{33}H_{37}NO_5$ 527.2672; found 527.2671. $[\alpha]_D^{29}$ = –59.5 (*c* = 1.1, $CHCl_3$).

(3*S*,4a*R*,6*R*,7*R*,8*S*)-6,7-Bis(benzyloxy)-8-(benzyloxymethyl)-3-(dec-2-en-1-yl)hexahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (16): 1-Nonene (0.14 mL, 0.834 mmol) was added to a solution of **15** (44 mg, 83.4 μmol) in CH_2Cl_2 (5 mL) at room temperature. Second-generation Hoveyda–Grubbs catalyst (5.0 mg, 8.34 μmol) was added to the stirred mixture. The stirred reaction mixture was heated to reflux for 24 h. After cooling, the reaction solvent was removed in vacuo to give a black oil, which was purified by chromatography on silica gel (5 g, *n*-hexane/acetone, 20:1) to give **16** (47 mg, 75.1 μmol, 90%) as a pale brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 15 H), 5.55–5.33 (m, 2 H), 4.68–4.44 (m, 6 H), 4.30 (br., 1 H), 4.13–4.02 (m, 3 H), 3.91–3.89 (m, 1 H), 3.84 (dd, *J* = 10.1, 4.9 Hz, 1 H), 3.74–3.72 (m, 1 H), 2.53–2.11 (m, 2 H), 2.09–1.51 (m, 6 H), 1.31–1.26 (m, 10 H), 0.88 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.8, 138.6, 138.5, 138.2, 134.9, 134.6, 128.4, 128.3, 128.2, 127.8, 127.7, 127.65, 127.6, 127.4, 127.2, 75.2, 74.5, 73.0, 72.6, 71.4, 69.5, 67.4, 56.6, 53.8, 47.2, 37.9, 34.6, 34.3, 33.2, 32.6, 32.2, 31.7, 31.4, 29.7, 28.8, 22.6, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 1699 cm^{-1}. MS (ESI): *m*/*z* = 625 [M$^+$]. HRMS (ESI): calcd. for $C_{40}H_{51}NO_5$ 625.3767; found 625.3785.

(3*S*,4a*R*,6*R*,7*R*,8*S*)-6,7-Bis(benzyloxy)-8-(benzyloxymethyl)-3-(non-2-en-1-yl)hexahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (17): 1-Octene (0.25 mL, 1.57 mmol) was added to a solution of **15** (83 mg, 157 μmol) in CH_2Cl_2 (8 mL) at room temperature. Second-generation Hoveyda–Grubbs catalyst (10 mg, 17.7 μmol) was added to the stirred mixture. The stirred reaction mixture was heated to reflux for 15 h. After cooling, the reaction solvent was removed in vacuo to give a black oil, which was purified by chromatography on silica gel (10 g, *n*-hexane/acetone, 10:1) to give **17** (86 mg, 141.3 μmol, 90%) as a pale brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 15 H), 5.55–5.33 (m, 2 H), 4.72–4.44 (m, 6 H), 4.29 (br., 1 H), 4.14–4.02 (m, 3 H), 3.93–3.90 (m, 1 H), 3.84 (dd, *J* = 10.1, 4.9 Hz, 1 H), 3.74–3.72 (m, 1 H), 2.53–2.12 (m, 2 H), 2.09–1.56 (m, 6 H), 1.33–1.26 (m, 8 H), 0.88 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.7, 138.5, 138.2, 138.1, 134.8, 128.3, 128.25, 128.2, 127.7, 127.6, 127.55, 127.48, 127.4, 127.3, 75.5, 74.5, 74.3, 73.2, 72.9, 72.4, 71.3, 67.3, 56.6, 56.3, 47.2, 47.0, 37.8, 34.5, 34.2, 32.4, 32.1, 31.6, 31.3, 29.2, 29.0, 28.7, 22.7, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 1699 cm^{-1}. MS (ESI): *m*/*z* = 611 [M$^+$]. HRMS (ESI): calcd. for $C_{39}H_{49}NO_5$ 611.3611; found 611.3590.

(3*S*,4a*R*,6*R*,7*R*,8*S*)-6,7-Bis(benzyloxy)-8-(benzyloxymethyl)-3-(undec-2-en-1-yl)hexahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (18): 1-Decene (0.17 mL, 0.91 mmol) was added to a solution of **15** (48 mg, 0.091 mol) in CH_2Cl_2 (5 mL) at room temperature. Second-generation Hoveyda–Grubbs catalyst (5 mg, 9.1 μmol) was added to the stirred mixture. The stirred reaction mixture was heated to reflux for 15 h. After cooling, the reaction solvent was removed in vacuo to give a black oil, which was purified by chromatography on silica gel (10 g, *n*-hexane/acetone, 20:1) to give **18** (51 mg, 0.08 mmol, 88%) as a pale brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 15 H), 5.52–5.30 (m, 2 H), 4.64–4.47 (m, 6 H), 4.29 (br., 1 H), 4.13–4.02 (m, 3 H), 3.98–3.89 (m, 1 H), 3.84 (dd, *J* = 10.1, 4.9 Hz, 1 H), 3.73–3.71 (m, 1 H), 2.48–2.13 (m, 2 H), 2.04–1.54 (m, 6 H), 1.33–1.26 (m, 12 H), 0.88 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.8, 138.6, 138.3, 135.0, 134.6, 132.7, 131.8, 128.4, 128.35, 128.25, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 75.3, 74.5, 73.2, 73.0, 72.5, 71.4, 70.5, 67.4, 67.1, 56.7, 55.4, 47.2, 45.9, 37.9, 34.6, 34.28, 32.6, 32.2, 31.9, 31.4, 29.7, 29.3, 29.1, 22.7, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 1699 cm^{-1}. MS (ESI): *m*/*z* = 639 [M$^+$]. HRMS (ESI): calcd. for $C_{41}H_{53}NO_5$ 639.3924; found 639.3909.

(2*S*,3*R*,4*R*,6*R*)-6-[(*S*)-2-Hydroxydodecyl]-2-(hydroxymethyl)-piperidine-3,4-diol, Formic Acid Salt (19): $Pd(OH)_2$/C (20%, 5 mg) was added to a solution of **16** (110 mg, 178 μmol) in EtOH (5 mL), and the resulting suspension was hydrogenated at 1 atm under a hydrogen atmosphere for 7 d. The catalyst was filtered off through a Celite pad and the filtrate was evaporated to give a hydrogenated product. A solution of KOH (4 M aq., 1.5 mL) was added to a solution of this product in 2-propanol (1.5 mL), which was heated to reflux for 2 h. After cooling, the solvent was evaporated, and the residue was purified by DOWEX 50W resin (X-8, H^+ form, eluent: 0.7 N aqueous NH_3), subjected to counterion exchange with formic acid/methanol (1% v/v) at room temperature, and concentrated in vacuo to yield **19** (48 mg, 128.2 μmol, 71%). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.93–3.76 (m, 5 H), 3.64 (br., s, 1 H), 3.49 (t, *J* = 6.3 Hz, 1 H), 2.12 (tt, *J* = 13.7, 1.8 Hz, 1 H), 1.98–1.84 (m, 2 H), 1.69–1.66 (m, 1 H), 1.47 (br. s,2 H), 1.31 (br. s,16 H), 0.89 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 69.7, 67.2, 67.1, 61.0, 58.1, 51.3, 39.2, 38.4, 33.1, 32.0, 30.7, 30.5, 30.4, 26.3, 23.7, 14.4 ppm. MS (FAB): *m*/*z* = 378 [M$^+$ + 1]. HRMS (FAB): calcd. for $C_{19}H_{40}NO_6$ 378.2855: found 378.2843. $[\alpha]_D^{28}$ = –16.0 (*c* = 0.1, MeOH).

(2*S*,3*R*,4*R*,6*R*)-2-(Hydroxymethyl)-6-[(*S*)-2-hydroxyundecyl]-piperidine-3,4-diol, Formic Acid Salt (20): $Pd(OH)_2$/C (20%, 5 mg) was added to a solution of **17** (82 mg, 134 μmol) in EtOH (5 mL), and the resulting suspension was hydrogenated at 1 atm under a hydrogen atmosphere for 6 d. The catalyst was filtered off through a Celite pad and the filtrate was evaporated to give a hydrogenated product. A solution of KOH (4 M aq., 1 mL) was added to a solution of this product in 2-propanol (1 mL), which was heated to reflux for 2 h. After cooling, the solvent was evaporated, and the residue was purified by DOWEX 50W resin (X-8, H^+ form, eluent: 0.7 N aqueous NH_3), subjected to counterion exchange with formic acid/methanol (1% v/v) at room temperature, and concentrated in

vacuo to yield **20** (33 mg, 89.8 μmol, 67%). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.92–3.78 (m, 5 H), 3.64 (br. s,1 H), 3.50 (m, 1 H), 2.01 (dt, J = 14.9, 2.3 Hz, 1 H), 1.83 (d, J = 14.3 Hz, 1 H), 1.95–1.82 (m, 2 H), 1.70 (m, 1 H), 1.47 (br. s,2 H), 1.31 (br. s,14 H), 0.90 (t, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 69.7, 67.2, 67.1, 61.0, 58.1, 51.3, 39.2, 38.4, 33.1, 32.0, 30.8, 30.75, 30.70, 30.4, 26.7, 23.7, 14.4 ppm. MS (FAB): m/z = 364 [M^+ + 1]. HRMS (FAB): calcd. for $C_{18}H_{38}NO_6$ 364.2699; found 364.2688. $[a]_D^{23}$ = –7.0 (c 0.1, MeOH), for enantiomer, ref.[3a] $[a]_D^{23}$ = +4.7 (c = 0.2, MeOH).

(2*S*,3*R*,4*R*,6*R*)-2-(Hydroxymethyl)-6-[(*S*)-2-hydroxytridecyl]-piperidine-3,4-diol, Formic Acid Salt (21): $Pd(OH)_2$/C (20%, 3 mg) was added to a solution of **18** (51 mg, 79.7 μmol) in EtOH (3 mL), and the resulting suspension was hydrogenated at 1 atm under a hydrogen atmosphere for 6 d. The catalyst was filtered off through a Celite pad and the filtrate was evaporated to give a hydrogenated product. A solution of KOH (4 M aq., 1 mL) was added to a solution of this product in 2-propanol (1 mL), which was heated to reflux for 2 h. After cooling, the solvent was evaporated, and the residue was purified by DOWEX 50W resin (X-8, H^+ form, eluent: 0.7 N aqueous NH_3), subjected to counterion exchange with formic acid/methanol (1% v/v) at room temperature, and concentrated in vacuo to yield **21** (17 mg, 43.8 μmol, 55%). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.91–3.76 (m, 5 H), 3.63 (br. s,1 H), 3.49 (t, J = 6.6 Hz, 1 H), 2.12 (tt, J = 13.2, 2.3 Hz, 1 H), 1.96–1.82 (m, 2 H), 1.70–1.66 (m, 1 H), 1.47 (m, 2 H), 1.31 (br. s,18 H), 0.89 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 69.7, 67.2, 67.1, 61.0, 58.1, 51.3, 39.2, 38.4, 33.1, 32.0, 30.74, 30.70, 30.5, 26.7, 23.7, 14.4 ppm. MS (FAB): m/z = 392 [M^+ + 1]. HRMS (FAB): calcd. for $C_{20}H_{42}NO_6$ 392.3012; found 392.3023. $[a]_D^{24}$ = –4.4 (c 0.15, MeOH).

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all new compounds as well as NOESY and COSY spectra of **7** and **10**.

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