Synthesis P. Das et al. Paper

Synthesis of D-Fagomine and Its Seven- and Eight-Membered Higher-Ring Analogues, and the Formal Synthesis of (+)-Australine from L-Xylose-Derived Chiron

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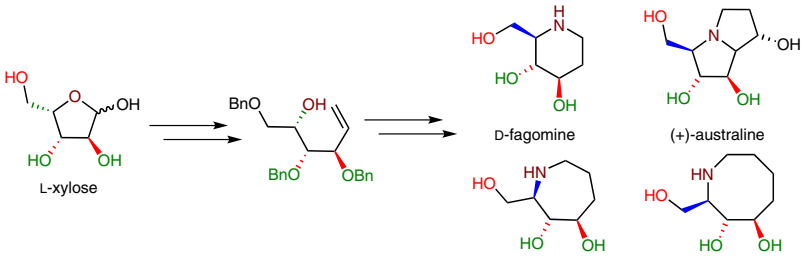

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Abstract The synthesis of D-fagomine and its seven- and eight-membered higher-ring analogues from commercially available L-xylose is reported. The syntheses involve elaboration of a common alkenol precursor obtained from L-xylose-derived hemiacetal. The key steps in the syntheses are intramolecular reductive amination and ring-closing metathesis for the synthesis of D-fagomine and seven-/eight-membered iminosugar, respectively. We have also extended our synthetic strategy for the formal synthesis of (+)-australine using zinc-mediated fragmentation reaction and ring-closing metathesis as key steps.

Key words D-fagomine, aminocyclitols, metathesis, (+)-australine, reductive amination

Natural and synthetic polyhydroxylated pyrrolidines, piperidines, piperazines, indolizines, etc., and higher homologues, commonly known as iminosugars, can be viewed as carbohydrate analogues in which the endocyclic oxygen atom has been replaced with nitrogen.[1] Iminocyclitols and their derivatives are potent glycosidase inhibitors. Their potency arises from the similarity of these compounds to the oxocarbenium ion like transition state of the enzymatic reactions for most glycosidases. Glycosidases and glycosyltransferases are involved in numerous biological processes such as metabolism, lysosomal catabolism, and glycoprotein processing, which, in turn, regulate many significant biological activities such as viral infection, cell–cell recognition and inflammation.[2] Potent and selective glycosidase inhibition activities of iminocyclitols have made them attractive drug candidates for a number of diseases such as viral infections, AIDS, lysosomal storage disorders, cancer and diabetes,[3] thus making glycosidase inhibitors the subject of intense interest for nearly half a century.[4] Naturally occurring polyhydroxylated 1,2-dideoxy azasugars represent an important class of glycosidase inhibitors.[5]

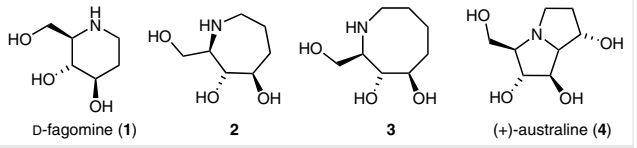
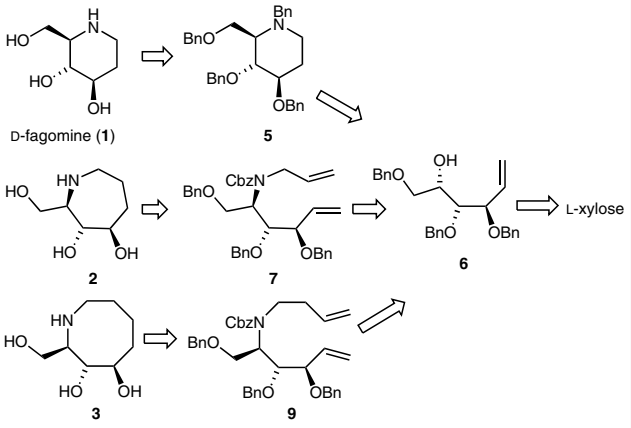


Figure 1 Examples of some natural and synthetic iminosugars

D-Fagomine (**1**; Figure 1), a polyhydroxylated piperidine,[6] was first isolated in 1974 from the seeds of Japanese buckwheat *Fagopyrum esculentum* Moench,[7] and later from the seeds of *Castanospermum australe* (Leguminosae).[8] In 1997, D-fagomine and 6-deoxyfagomine were also isolated from the roots of *Lycium chinense* (Solanaceae).[9] Although D-fagomine is well known for its potent inhibitory activity against mammalian intestinal glucosidases and galactosidase,[10] it has also been shown to exhibit strong antihyperglycemic effect on streptozocin-induced diabetic mice, thereby enhancing glucose-induced insulin secretion.[11] Since its first isolation, several synthetic approaches have been reported for the synthesis of D-fagomine and its isomers.[12] Over the last 30 years, many synthetic efforts have been focused on the design and synthesis of five- and six-membered iminocyclitols, but their higher analogues, i.e., substituted azepanes and azocanes, have received very little attention. Azepane iminosugars were first synthesized by Paulsen in 1967.[13] Later, Wong and co-workers in 1996 first reported the promising glycosidase inhibitory activity of polyhydroxy azepanes against a broad range of glycosidases.[14] In 2004, Martin et al. first reported the synthesis and biological evaluation of eight-membered iminoalditol.[15] It has been found that eight-membered iminosugars and their N-substituted analogues showed weak to moderate glycosidase activity, thus creating a need for further structural modifications.[16,17] We report herein the total syntheses of (–)-fagomine and higher ring analogues from

commercially available L-xylose. We also extended our synthetic strategy to the formal synthesis of bicyclic polyhydroxylated natural product (+)-australine[18] from a common chiron intermediate.

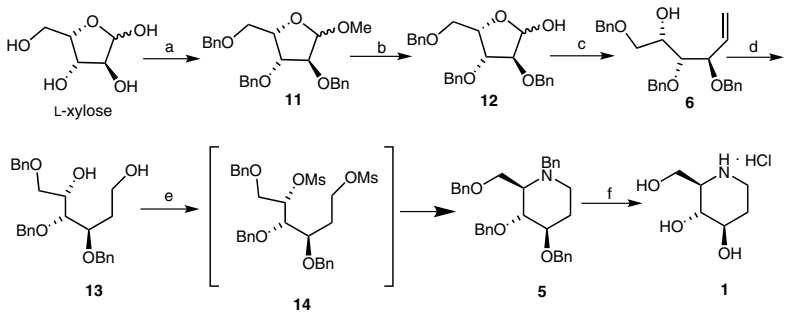
Our retrosynthetic analysis, shown in Scheme 1, illustrates that the target molecule D-fagomine **1** could be obtained from **5**, which, in turn, could be accessible from olefin **6**, which could ultimately be prepared from L-xylose. The retrosynthetic analysis for the target azepane natural product **2** and eight-membered iminosugar **3** showed that these compounds could be obtained from diene **7** and N-Cbz protected diene **9**, respectively. Both the latter two compounds could be synthesized from the same olefin **6** through Mitsunobu inversion reaction.



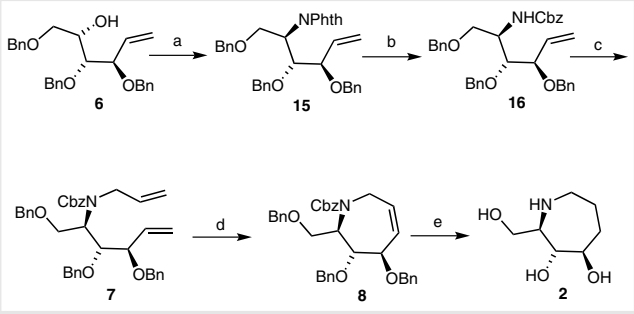
Scheme 1 Retrosynthetic analysis

The synthesis of fagomine **1** began with commercially available L-xylose (Scheme 2). Selective anomeric methylation of L-xylose with acetyl chloride in methanol followed by benzylation of the crude methylated product furnished methyl furanoside **11**.[19] In the next step, **11** was converted into its hemiacetal **12** by heating with trifluoroacetic acid (TFA) in acetonitrile and water solvent mixture at 80 °C.[20] Wittig olefination of **12** was optimized by varying the number of equivalents of methyltriphenylphosphonium bromide and *n*-BuLi (2 M in THF) at different temperatures. It was found that performing the reaction with six equivalents of methyltriphenylphosphonium bromide and three equivalents of *n*-BuLi at –20 °C resulted the formation of the desired olefin **6** in 72% yield. The preparation of **6** has previously been described starting from arabinose, but with more steps.[21] Hydroboration–oxidation reaction of alkene **6** with BH_3SMe_2 in THF at 0 °C proceeded smoothly to give the diol **13** in 72% yield.[22] The resulting diol was then esterified with MsCl in the presence of Et_3N and a catalytic amount of DMAP in CH_2Cl_2. The crude dimesylate, owing to its instability, was immediately subjected to cyclization with benzylamine at 80 °C to furnish piperidine **5** in 66% yield over two steps. Finally, debenzylation of **5** was performed with Pd/C under a hydrogen atmosphere to give the HCl salt of D-fagomine **1** in 90% yield.[23] Its analytical data are in complete agreement with those of previous reports.[24]

The synthesis of seven-membered iminoalditol **2** was also initiated from L-xylose-derived olefin **6**. Phthalimido compound **15** was synthesized from **6** under Mitsunobu conditions. Thus, alcohol **6** was treated with phthalimide (1.5 equiv), PPh_3 (1.5 equiv) and diisopropyl azodicarboxylate (DIAD; 1.5 equiv) in THF at –20 °C to room temperature to obtain the desired inverted phthalimido compound **15** in 68% yield.[25] The latter compound was then converted into its corresponding amine by treatment with 40% aqueous $MeNH_2$ at 60 °C for 3 h.[26] The crude primary amine was subjected to Cbz protection by reaction with triethylamine and benzyl chloroformate at 0 °C in CH_2Cl_2 to give protected amine **16** in 65% overall yield. Allylation of **16** with allyl bromide and NaH in THF at 0 °C furnished the diene **7** in 88% yield. With the diene assembly **7** in hand, the stage was set for the crucial ring-closing metathesis reaction. To accomplish this, diene **7** was treated with 5 mol% Grubbs II catalyst in dichloromethane under argon atmosphere to give the protected azepane **8** in 92% yield. Finally, hydrogenation of **8** was achieved in the presence of Pd/C to give azepane **2** in 90% yield (Scheme 3).[27]

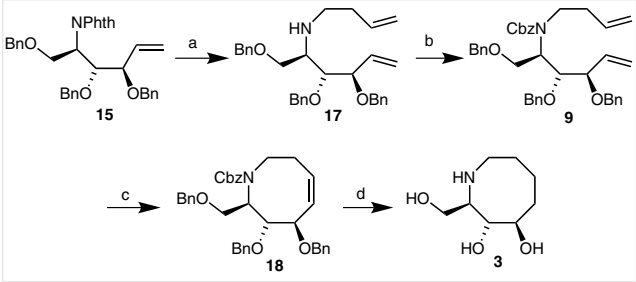


Scheme 2 Synthesis of D-fagomine **1**. *Reagents and conditions*: (a) i. MeOH, AcCl, 0 °C to r.t., 2 h; ii. NaH, BnBr, DMF, 0 °C to r.t., 12 h (b) MeCN–H_2O–TFA (5:4:2), 80 °C, 4 h, 75%; (c) Ph_3PCH_3Br, *n*-BuLi, THF, –20 °C, 3 h, 72%; (d) BH_3·Me_2S, THF, H_2O_2-NaOH, 0 °C to r.t., 6 h, 72%; (e) i. MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 2 h; ii. $BnNH_2$, 80 °C, 3 h, 66% for two steps; (f) H_2, Pd/C, MeOH–1N HCl, 48 h, 90%.



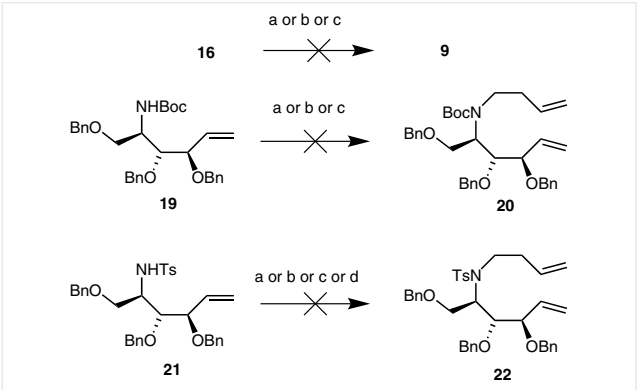
Scheme 3 Synthesis of azepane **2**. *Reagents and conditions*: (a) PPh_3, DIAD, phthalimide, THF, –20 °C to r.t., 4 h, 68%; (b) i. 40% $MeNH_2$, 60 °C, 3 h; ii. CbzCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, 65%, for two steps; (c) allyl bromide, NaH, THF, 0 °C, 3 h, 88%; (d) Grubbs II (5 mol%), CH_2Cl_2 (0.01 M), reflux, 6 h, 92%; (e) H_2, Pd/C, MeOH–1 N HCl, 48 h, 90%.

Synthesis of eight-membered iminosugar **3** started from phthalimido compound **15** (Scheme 4). The phthalimido functionality was hydrolyzed with $MeNH_2$ to afford an amine, which was used for the next step without further purification. The next step of the synthetic sequence involved N-alkylation of the crude amine to obtain the corresponding diene **17**. Thus, the crude amine intermediate was subject to N-alkylation with 4-bromobut-1-ene (1.2 equiv) in the presence of base K_2CO_3 and DMF as solvent. The required N-alkylated diene **17** was obtain in 48% overall yield in two steps.



Scheme 4 Synthesis of azocane **3**. *Reagents and conditions*: (a) i. 40% aq $MeNH_2$, 60 °C, 3 h; ii. 4-bromobut-1-ene, K_2CO_3, DMF, 18 h, 48% overall two steps; (b) CbzCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, 85%; (c) Grubbs II (5 mol%), CH_2Cl_2 (0.01 M), reflux, 10 h, 89%; (d) H_2, Pd/C, MeOH–1 N HCl, 72 h, 90%.

In the next step compound **17** was protected as N-Cbz by using benzyl chloroformate and triethylamine in CH_2Cl_2 to obtain N-Cbz protected diene **9**. The poor yield of **17** could be due to the formation of dialkylated product because the mono-alkylated product was more reactive than the free primary amine. Therefore, to avoid the dialkylation issue, we tried to synthesize **9** through a different approach. We first protected the free amine with a Cbz group prior to the alkylation step to obtain mono-protected amine **16** and then attempted the alkylation step by using 4-bromobut-1-ene as alkylating agent in the presence of different bases. Unfortunately alkylation did not take place with **16** to give amine **9**, which may be attributed to the lower basicity of amidic N-H (Scheme 5). The same result was obtained with Boc- and Ts-protected amines **19** and **21**.



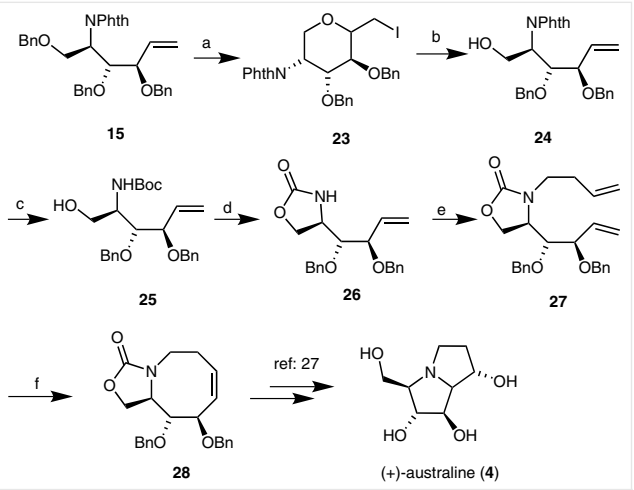
Scheme 5 *Reagents and conditions*: (a) 4-bromobut-1-ene, K_2CO_3, DMF, 0 °C to r.t.; (b) 4-bromobut-1-ene, Et_3N, CH_2Cl_2, 0 °C to r.t.; (c) 4-bromobut-1-ene, NaH, THF, TBAI, 60 °C; (d) PPh_3, DIAD, phthalimide, 1-butenol, THF.

Free amines are unsuitable substrates for ring-closing metathesis; hence, we protected the amines with Cbz protecting groups. Ring-closing metathesis of suitably N-protected diene **9** by using 5 mol% Grubbs II catalyst proceeded smoothly in CH_2Cl_2 heated to reflux, to obtain azacyclooctene **18** (Scheme 4).[28] Hydrogenation of the latter by using Pd/C under hydrogen atmosphere furnished eight-membered iminosugar **3** in 90% yield.

We were also interested to show the utility of the chiral amide intermediate **15** in the total synthesis of polyhydroxylated pyrrolizidine alkaloids. To achieve our goal, we identified (+)-australine **4**, the formal synthesis of which was envisaged from **15**. Australine was isolated from *Castanospermum austral* and was found to be an inhibitor of fungal amyloglucosidase and some glycoprotein-processing enzymes and also displayed antiviral activity, including anti-HIV activity.[29]

Our synthetic strategy started from phthalimido intermediate **15** (Scheme 6). Its iodocyclization with I_2 in CH_2Cl_2 gave primary iodo compound **23**. Zinc-mediated fragmentation reaction (ring opening) of the latter in EtOH heated to reflux furnished olefin **24** in good yield. Subsequent hydrolysis by heating with methylamine at 60 °C followed by Boc-protection of the crude primary amine in CH_2Cl_2 using excess triethylamine as base afforded *N*-Boc-protected compound **25**. We envisioned that the use of an excess of triethylamine may lead to one-pot conversion of **25** into oxazolidinone **26** through simple nucleophilic attack of the alcohol to the carbonyl carbon of the carbamate; unfortunately, no trace of oxazolidinone **26** was detected. To form the oxazolidinone ring, we treated compound **25** with sodium hydride in THF at 0 °C and, gratifyingly, obtained the desired oxazolidinone **26** in 89% yield within three hours. N-Alkylation of **26** was performed with sodium hydride

and 4-bromobut-1-ene in THF to afford diene **27**, the RCM of which in CH_2Cl_2 heated to reflux using 5 mol% Grubbs II catalyst afforded cyclooctene **28** in 86% yield (Scheme 6). The spectral data and optical rotation for **28** are in complete agreement with those reported earlier. The title natural product **4** could be obtained from **28** in three steps by adopting the reaction sequences reported by White et al.[30]



Scheme 6 *Reagents and conditions*: (a) I_2, CH_2Cl_2, 0 °C to r.t., 3 h, 84%; (b) Zn, EtOH, 80 °C, 82%; (c) i. 40% aq $MeNH_2$, 60 °C, 3 h; ii. Boc_2O, Et_3N, CH_2Cl_2, for two steps 66%; d. NaH, THF, 89%; (e) 4-bromobut-1-ene, NaH, THF, cat. TBAI, 0 °C to r.t., 78%; f. Grubbs II (5 mol%), CH_2Cl_2 (0.01 M), reflux, 10 h, 86%.

We have demonstrated a new concise total synthesis of D-fagomine **1**, azepane **2**, and eight-membered iminosugar **3** from L-xylose-derived common chiron **6**. Mitsunobu amination and ring-closing metathesis were the key steps for the synthesis of D-fagomine and azepines, respectively. The synthetic strategy discussed herein can easily be applied to the preparation of a broad range of biologically active polyhydroxylated compounds or other natural product analogues containing a nitrogen atom in the ring. The formal synthesis of (+)-australine was also exemplified from the same chiron **6**. The iodocyclization reaction of **15** and zinc-mediated fragmentation are the key steps here. The azacyclooctene precursor **28** was generated by ring-closing metathesis. Unsaturated iminocycloheptene **8** and iminocyclooctene **18** will undoubtedly find applications as useful chiral building blocks in the synthesis of a variety of biologically relevant molecules, including natural products.

Organic solvents were dried by using standard methods. Analytical TLC was performed using 2.5 × 5 cm plates coated with a 0.25 mm thickness of silica gel (60F-254), visualization was achieved with $CeSO_4$ and subsequent charring over a hot plate. Silica gel (60–120 mesh, 100–200 mesh, and 230–400 mesh) was used in column chromatography. All the products were characterized by ^1H, ^{13}C NMR and IR spectroscopic analysis and by ESI-HRMS analysis. NMR spectra were recorded with a Bruker Avance 300 MHz spectrometer at 300 MHz (^1H) and 75 MHz (^{13}C), or 400 MHz spectrometer at 400 MHz (^1H) and 100 MHz (^{13}C). Experiments were recorded in $CDCl_3$ and D_2O at 25 °C. Chemical shifts are given on the δ scale and are referenced to the TMS at δ = 0.00 ppm for ^1H and δ = 0.00 ppm for ^{13}C nuclei. For ^{13}C NMR spectra, reference $CDCl_3$ appeared at δ = 77.40 ppm. IR spectra were recorded with Perkin–Elmer 881 and FTIR-8210 PC Shimadzu spectrophotometers. Optical rotations were determined with an Autopol III polarimeter and Digipol 781M6U, NOVA polarimeter using a 1 dm cell at 17–32 °C in $CHCl_3$/MeOH/H_2O as solvents; concentrations are in g/100 mL. Mass spectra were recorded with a JEOL JMS-600H high-resolution spectrometer using EI mode at 70 eV. ESI-HRMS were recorded with a JEOL-AccuTOF, JMS- T100LC spectrometer.

(2*S*,3*R*,4*R*)-1,3,4-Tris(benzyloxy)hex-5-en-2-ol (6)

Methyltriphenyl phosphonium bromide (5.09 g, 14.27 mmol) was taken in anhydrous THF (40 mL) and the mixture was cooled to –20 °C. *n*-BuLi (2 M in cyclohexane, 3.57 mL, 7.13 mmol) was added to the mixture dropwise under N_2 atmosphere and the resulting mixture was stirred for 1 h at the same temperature. Hemiacetal **12** (1 g, 2.38 mmol) in THF (20 mL) was added dropwise to the reaction mixture, which was then gradually warmed to 0 °C, stirred for 1 h and for a further 3 h at r.t. Upon completion of the reaction it was quenched with sat. aq NH_4Cl, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed twice with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give a residue. Column chromatographic purification (EtOAc/hexane, 1:7 v/v) of the residue gave compound **6**.

Yield: 0.714 g (1.71 mmol, 72%); colorless oil; R_f = 0.4 (EtOAc/hexane, 1:4); $[\alpha]_D^{28}$ +3.4 (*c* 0.53, $CHCl_3$).

IR (neat): 3435, 3028, 2870, 1751 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.20 (m, 15 H), 5.83–5.74 (m, 1 H), 5.31–5.25 (m, 2 H), 4.78 (d, *J* = 11.2 Hz, 1 H), 4.56–4.46 (m, 2 H), 4.39–4.28 (m, 3 H), 4.02 (dd, *J* = 6.8, 7.5 Hz, 1 H), 3.84 (br s, 1 H), 3.54–3.52 (m,1 H), 3.39–3.31 (m, 2 H), 2.41 (br s,1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 138.6, 138.4, 135.6, 128.7, 128.7, 128.6, 128.6, 128.2, 128.1, 128.1, 128.0, 119.7, 82.5, 80.6, 75.4, 73.6, 71.5, 71.0, 70.3.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{30}O_4$: 419.2222; found: 419.2217.

(3*R*,4*R*,5*R*)-3,4,6-Tris(benzyloxy)hexane-1,5-diol (13)

BH_3·Me_2S (10 M in THF, 0.25 mL, 2.54 mmol) was added dropwise to a solution of **6** (531 mg, 1.27 mmol) in anhydrous THF (10 mL) at 0 °C and the solution was allowed to warm to r.t. and stirred for 3 h. Upon complete consumption of starting material, 3 N aqueous NaOH (3 mL, 9 mmol) was added carefully at 0 °C followed by 30% aq H_2O_2 (0.5 mL) and the mixture was stirred at r.t. for 3 h. The organic layer was extracted with EtOAc (4 × 10 mL), washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/hexane, 2:3 v/v) over 100–200 mesh silica gel to afford alcohol **13**.

Yield: 430 mg (0.99 mmol, 78%); colorless oil; R_f = 0.4 (EtOAc/hexane, 2:1); $[\alpha]_D^{28}$ +29.4 (*c* 4.30, $CHCl_3$).

IR (neat): 3401, 3020, 2925, 1731, 1654 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.17 (m, 15 H), 4.67–4.55 (m, 2 H), 4.50–4.35 (m, 4 H), 3.87 (br s, 1 H), 3.80–3.76 (m, 1 H), 3.64–3.61 (m, 3 H), 3.39 (ddd, *J* = 6.2, 9.5, 15.5 Hz, 2 H), 2.57 (br s, 1 H), 2.18 (br s, 1 H), 1.88–1.81 (m, 1 H), 1.76–1.69 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 138.3, 138.2, 128.8, 128.7, 128.7, 128.5, 128.3, 128.2, 128.1, 128.1, 128.0, 79.3, 78.2, 74.8, 73.6, 73.4, 71.7, 69.6, 60.4, 33.6.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{33}O_5$: 437.2328; found: 437.2424.

(2*S*,3*R*,4*R*)-1-Benzyl-3,4-bis(benzyloxy)-2-[(benzyloxy)methyl]piperidine (5)

To a solution of diol **13** (380 mg, 0.87 mmol) dissolved in CH_2Cl_2 (8 mL) was added Et_3N (0.3 mL, 2.18 mmol), methanesulfonyl chloride (0.17 mL, 2.18 mmol), and a catalytic amount of DMAP at 0 °C. The reaction mixture was then stirred at r.t. for 2 h. Upon completion of the reaction (monitored by TLC) it was quenched with H_2O (10 mL) and the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude dimesylate product was carried on to the next step without further purification.

The dimesylate was dissolved in benzylamine (2 mL) and the reaction mixture was heated at 80 °C for 3 h, then diluted with Et_2O and washed with 1 N HCl, H_2O, and brine. The combined organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography (EtOAc/hexane, 1:12 v/v) to give **5**.

Yield: 290 mg (0.57 mmol, 66%); colorless oil; R_f = 0.62 (EtOAc/hexane, 1:4); $[\alpha]_D^{28}$ +128.6 (*c* 0.20, $CHCl_3$).

IR (neat): 2924, 2853, 1453, 1092 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.14 (m, 20 H), 4.87 (d, *J* = 10.9 Hz, 1 H), 4.60–4.41 (m, 5 H), 4.03 (d, *J* = 13.7 Hz, 1 H), 3.77–3.70 (m, 2 H), 3.58–3.51 (m, 1 H), 3.41–3.35 (m, 1 H), 3.26 (d, *J* = 13.7 Hz, 1 H), 2.75–2.71 (m, 1 H), 2.32 (d, *J* = 9.1 Hz, 1 H), 1.97–1.86 (m, 2 H), 1.59–1.44 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.3, 139.2, 138.6, 129.5, 128.7, 128.5, 128.4, 128.4, 128.0, 127.9, 127.9, 127.8, 127.2, 82.4, 79.5, 75.3, 73.6, 71.6, 67.6, 65.6, 57.6, 49.7, 29.1.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{38}NO_3$: 508.2852; found: 508.2847.

(2*R*,3*R*,4*R*)-2-(Hydroxymethyl)piperidine-3,4-diol (1)

A catalytic amount of 10% Pd/C (20 mg) was added to a solution of **5** (90 mg, 0.177 mmol) in a mixture of MeOH and 1 N HCl (4:1 v/v, 5 mL). A vacuum was applied briefly, then the reaction mixture was stirred under a positive pressure of H_2 in a balloon. Upon completion of the reaction (monitored by TLC, 48 h), the catalyst was removed by filtration, washed with MeOH twice and the combined washings was filtered and concentrated to give the HCl salt of fagomine **1**.

Yield: 17 mg (0.12 mmol, 68%); colorless semisolid; $[\alpha]_D^{26}$ +7.9 (*c* 0.24, CH_3OH) {Lit.[22] $[\alpha]_D^{29}$ +8.4 (*c* 0.27, CH_3OH)}.

IR (neat): 3685, 3409, 3022, 2410 cm^{-1}.

^{1}H NMR (400 MHz, D_2O): δ = 3.97–3.95 (m, 2 H), 3.77 (m, 1 H), 3.61–3.48 (m, 2 H), 3.19–3.12 (m, 1 H), 2.28–2.25 (m, 1 H), 1.80–1.77 (m, 1 H).

^{13}C NMR (100 MHz, D_2O): δ = 70.6, 69.7, 60.2, 57.9, 42.0, 28.7.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_6H_{14}NO_3$: 148.1802; found: 148.0969.

2-[(2*R*,3*R*,4*R*)-1,3,4-Tris(benzyloxy)hex-5-en-2-yl]isoindoline-1,3-dione (15)

A solution of phthalimide (684 mg, 4.66 mmol), triphenyl phosphine (1.22 g, 4.66 mmol), and alcohol **6** (1.3 g, 3.11 mmol) in anhydrous THF (30 mL) was cooled to –20 °C under argon atmosphere. A solution of DIAD (0.916 mL, 4.66 mmol) in anhydrous THF (10 mL) was added dropwise to the solution and the reaction mixture was stirred at the same temperature for 2 h and then overnight at r.t. The reaction mixture was evaporated under reduced pressure and purified by column chromatography (EtOAc/hexane, 1:12 v/v) to give **15**.

Yield: 1.15 g (2.11 mmol, 68%); colorless semisolid; R_f = 0.62 (EtOAc/hexane, 1:4); $[\alpha]_D^{28}$ +144.9 (*c* 0.3660, $CHCl_3$).

IR (neat): 3432, 2924, 2852, 1453 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.62 (m, 2 H), 7.56–7.54 (m, 2 H), 7.22–7.00 (m, 15 H), 5.90–5.81 (m, 1 H), 5.25–5.17 (m, 2 H), 4.76–4.62 (m, 2 H), 4.50–4.28 (m, 5 H), 4.14–4.11 (m, 1 H), 4.00 (t, *J* = 10.2 Hz, 1 H), 3.84–3.82 (m, 1 H), 3.78–3.74 (m,1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 138.5, 138.1, 138.0, 135.0, 133.9, 132.4, 128.7, 128.5, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.6, 123.4, 119.9, 80.6, 77.9, 74.7, 72.9, 71.0, 67.7, 51.2.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{34}NO_5$: 548.2437; found: 548.2449.

Benzyl [(2*R*,3*R*,4*R*)-1,3,4-Tris(benzyloxy)hex-5-en-2-yl]carbamate (16)

A solution of **15** (520 mg, 0.95 mmol) in aq $MeNH_2$ (10 mL, 40%), was stirred in an open flask for 1.5 h at 50 °C, then concentrated under reduced pressure, dissolved in H_2O (10 mL) and the mixture was extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4, and evaporated under reduced pressure.

To a solution of crude amine in CH_2Cl_2 (15 mL), Et_3N (0.95 mmol, 0.132 mL) was added at 0 °C and, after 5 min, benzyl chloroformate (0.11 mL, 0.95 mmol) was added dropwise at the same temperature and the mixture was stirred for 2 h at r.t. Upon completion of the reaction, the mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layer was dried over Na_2SO_4, evaporated under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane, 1:8 v/v) to give **16**.

Yield: 340 mg (0.62 mmol, 65% for 2 steps); colorless oil; R_f = 0.48 (EtOAc/hexane, 1:4); $[\alpha]_D^{28}$ –16.3 (*c* 0.16, $CHCl_3$).

IR (neat): 3446, 2925, 2853, 1693, 1455 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.15 (m, 20 H), 5.90–5.81 (m, 1 H), 5.52 (d, *J* = 6.3 Hz, 1 H), 5.22–5.13 (m, 2 H), 4.98 (br s, 2 H), 4.53–4.46 (m, 3 H), 4.34–4.27 (m, 2 H), 4.18–4.15 (m, 2 H), 3.90–3.88 (m, 1 H), 3.60–3.49 (m, 2 H), 3.34–3.30 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 138.5, 138.3, 138.2, 137.1, 135.6, 128.8, 128.7, 128.7, 128.6, 128.4, 128.3, 128.1, 128.0, 119.5, 81.3, 80.0, 73.9, 73.4, 70.8, 69.2, 66.8, 51.4.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{38}NO_5$: 552.2750; found: 552.2720.

Benzyl Allyl[(2*R*,3*R*,4*R*)-1,3,4-Tris(benzyloxy)hex-5-en-2-yl]carbamate (7)

A solution of amine **16** (310 mg, 0.562 mmol) in THF (5 mL) was treated sequentially with NaH (34 mg, 0.843 mmol) and allyl bromide (0.073 mL, 0.843 mmol) at 0 °C. Upon completion of the reaction, H_2O (30 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine, dried over

anhydrous Na_2SO_4, evaporated under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane, 1:9 v/v) to give **7**.

Yield: 0.312 g (0.495 mmol, 88%); yellowish oil; R_f = 0.52 (EtOAc/hexane, 1:4); $[\alpha]_D^{28}$ +51.1 (*c* 0.66, $CHCl_3$).

IR (neat): 3402, 3019, 2866, 1633 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.18 (m, 20 H), 5.84–5.71 (m, 2 H), 5.23–4.8 (m, 6 H), 4.71–4.64 (m, 1 H), 4.48–4.20 (m, 6 H), 3.84–3.62 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 138.7, 136.3, 135.9, 128.8, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 119.5, 115.9, 82.4, 82.1, 81.7, 75.1, 73.2, 70.9, 68.4, 67.6, 67.3.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{38}H_{42}NO_5$: 592.3063; found: 592.3068.

(2*R*,3*R*,4*R*)-Benzyl 3,4-Bis(benzyloxy)-2-[(benzyloxy)methyl]-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate (8)

To a 50 mL two-necked, oven-dried, round-bottom flask fitted with a reflux condenser and septum was added Grubbs II catalyst (12 mg, 0.014 mmol) under argon atmosphere. Anhydrous CH_2Cl_2 (5 mL) was then added and the solution was stirred. Compound **7** (171 mg, 0.289 mmol) in CH_2Cl_2 (20 mL) was added to the stirring reaction mixture, which was then heated at reflux for 6 h. The temperature of the reaction mixture was brought slowly to r.t. and the organic solvent was evaporated under reduced pressure to give a black residue, which was purified by column chromatography (EtOAc/hexane, 1:8, v/v) to give **8**.

Yield: 149 mg (0.266 mmol, 92%); colorless liquid; R_f = 0.5 (EtOAc/hexane, 1:4); $[\alpha]_D^{28}$ –23.8 (*c* 0.860, $CHCl_3$).

IR (neat): 3435, 3066, 3014, 1641 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.11 (m, 20 H), 5.63–5.62 (m, 2 H), 5.05–5.04 (m, 2 H), 4.87–4.81 (m, 1 H), 4.71–4.55 (m, 2 H), 4.50–4.15 (m, 6 H), 3.79–3.63 (m, 3 H), 3.54–3.43 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (rotamers) = 156.6, 156.4, 128.8, 128.7, 128.5, 128.3, 128.2, 128.0, 128.0, 127.9, 80.8, 80.5, 80.3, 75.2, 75.0, 74.1, 73.8, 73.3, 73.2, 69.7, 67.9, 67.7, 58.4, 58.0, 43.3.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{38}NO_5$: 564.2750; found: 564.2743.

(2*R*,3*R*,4*R*)-2-(Hydroxymethyl)azepane-3,4-diol (2)

A catalytic amount of 10% Pd/C (20 mg) was added to a solution of **8** (80 mg, 0.142 mmol) in a mixture of MeOH and 1 N HCl (4:1 v/v, 5 mL). A vacuum was applied briefly, then the reaction mixture was stirred under a positive pressure of H_2 in a balloon. Upon completion of the reaction (monitored by TLC, 48 h), the catalyst was removed by filtration, washed with MeOH twice, and the combined filtrate was concentrated to afford the crude compound, which was purified by column chromatography (Et_2O–MeOH–NH_2OH, 10:40:2 v/v/v) to give **2**.

Yield: 18 mg (0.1 mmol, 79%); colorless oil; $[\alpha]_D^{28}$ +6.2 (*c* 1.0, CH_3OH).

IR (neat): 3478, 3066, 2985, 1693 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 4.00–3.71 (m, 4 H), 3.37–3.25 (m, 3 H), 2.08–1.76 (m, 4 H).

^{13}C NMR (100 MHz, D_2O): δ = 73.6, 71.9, 60.2, 59.5, 45.9, 28.3, 18.9.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_7H_{16}NO_3$: 162.1130; found: 162.1126.

(2*R*,3*R*,4*R*)-1,3,4-Tris(benzyloxy)-*N*-(but-3-en-1-yl)hex-5-en-2-amine (17)

Compound **15** (520 mg, 0.95 mmol) was dissolved in aq $MeNH_2$ (15 mL, 40%), and the resulting mixture was stirred in an open flask for 1.5 h at 50 °C. The reaction mixture was then concentrated under reduced pressure, and the residue was dissolved in H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude material was used for the next step without purification.

To a solution of crude amine in DMF (10 mL), K_2CO_3 (190 mg, 1.38 mmol) was added at 0 °C and, after 5 min, 4-bromobut-1-ene (95%; 0.122 mL, 1.15 mmol) was added dropwise at the same temperature and the mixture was stirred for 12 h at r.t. Upon completion of the reaction, H_2O was added and the mixture and was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over Na_2SO_4, evaporated under reduced pressure and the residue was purified by column chromatography (EtOAc/hexane, 1:7 v/v) to give **17**.

Yield: 215 mg (0.46 mmol, 48% for 2 steps); colorless oil; R_f = 0.5 (EtOAc/hexane, 1:3); $[\alpha]_D^{28}$ –1.5 (*c* 0.90, $CHCl_3$).

IR (neat): 3317, 2925, 1640 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.16 (m, 15 H), 5.85–5.76 (m, 1 H), 5.69–5.59 (m, 1 H), 5.22–5.18 (m, 2 H), 4.96–4.87 (m, 2 H), 4.67–4.27 (m, 7 H), 4.07 (dd, *J* = 4.8, 7.5 Hz, 1 H), 3.58–3.48 (m, 1 H), 2.87–2.83 (m, 1 H), 2.57–2.51 (m, 1 H), 2.43–2.37 (m, 1 H), 2.02 (dd, *J* = 6.9, 13.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.3, 139.0, 138.9, 137.1, 136.5, 129.0, 128.7, 128.6, 128.6, 128.4, 128.4, 128.1, 128.0, 127.9, 127.8, 127.8, 127.4, 118.6, 116.3, 81.9, 81.6, 75.2, 73.5, 71.0, 69.1, 65.8, 58.6, 47.3, 35.1.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{38}NO_3$: 472.2852; found: 472.2818.

Benzyl But-3-en-1-yl[(2*S*,3*R*,4*R*)-1,3,4-tris(benzyloxy)hex-5-en-2-yl]carbamate (9)

To a solution of amine **17** (298 mg, 0.63 mmol) in CH_2Cl_2 (5 mL), sat. aq sodium bicarbonate (5 mL) was added at 0 °C and, after 5 min, benzyl chloroformate (0.11 mL, 0.95 mmol) was added dropwise at the same temperature and the mixture was stirred for 2 h at r.t. Upon completion of the reaction, the mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layer was dried over Na_2SO_4, evaporated under reduced pressure, and purified by column chromatography (EtOAc/hexane, 1:19 v/v) to give **9**.

Yield: 324 mg (0.635 mmol, 84%); colorless oil; R_f = 0.5 (EtOAc/hexane, 1:9); $[\alpha]_D^{28}$ +10.0 (*c* 3.25, $CHCl_3$).

IR (neat): 3400, 3019, 2926, 1641 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.12 (m, 20 H), 5.89–5.47 (m, 2 H), 5.22–4.59 (m, 7 H), 4.48–4.17 (m, 6 H), 3.87–3.54 (m, 4 H), 3.28–2.99 (m, 2 H), 2.34–2.20 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3, 138.7, 138.6, 137.3, 136.9, 136.1, 136.0, 135.9, 128.8, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 119.4, 116.3, 82.5, 82.0, 81.6, 75.2, 73.2, 70.9, 68.6, 67.5, 67.1, 34.1.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{39}H_{44}NO_5$: 606.3219; found: 606.3213.

(2*R*,3*R*,4*R*,*Z*)-Benzyl 3,4-Bis(benzyloxy)-2-[(benzyloxy)methyl]-3,4,7,8-tetrahydroazocine-1(2*H*)-carboxylate (18)

To a 100 mL two-necked, oven-dried, round-bottom flask fitted with a reflux condenser and septum was added Grubbs II catalyst (19 mg, 0.024 mmol) under argon atmosphere. Anhydrous CH_2Cl_2 (5 mL) was then added and the solution was stirred. Compound **9** (271 mg, 0.446 mmol) in CH_2Cl_2 (40 mL) was added to the stirring reaction mixture, which was then heated at reflux for 6 h. The temperature of the reaction mixture was brought slowly to r.t. and the organic solvent was evaporated under reduced pressure to give a black residue, which was purified by column chromatography (EtOAc/hexane, 1:20 v/v) to give **18**.

Yield: 149 mg (0.229 mmol, 92%); colorless liquid; R_f = 0.5 (EtOAc/hexane, 1:9); $[\alpha]_D^{28}$ +86.0 (*c* 0.20, $CHCl_3$).

IR (neat): 3401, 3019, 2925, 1644 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.14 (m, 20 H), 5.76–5.47 (m, 2 H), 4.90–3.96 (m, 10 H), 3.84–3.65 (m, 3 H), 3.21–2.79 (m, 2 H), 2.33–1.96 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 155.5, 139.0, 138.9, 138.7, 138.4, 137.3, 136.8, 132.7, 132.2, 129.8, 128.7, 128.7, 128.6, 128.6, 128.6, 128.5, 128.4, 128.3, 128.3, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 80.9, 79.9, 78.6, 74.9, 73.3, 73.2, 71.8, 71.7, 70.1, 69.3, 67.5, 66.7, 63.2, 61.7, 48.8, 27.4, 27.3.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{37}H_{40}NO_5$: 578.2906; found: 578.2903.

(2*R*,3*R*,4*R*)-2-(Hydroxymethyl)azocane-3,4-diol (3)

To a solution of **18** (160 mg, 0.277 mmol), in MeOH (5 mL) and concd HCl (0.5 mL), was added Pd/C (15 mg) and the resulting mixture was stirred under positive pressure of hydrogen for 3 days. Upon completion of reaction, the catalyst was removed by filtration and washed twice with methanol. The solution was concentrated in vacuo and purified by flash column chromatography (Et_2O–MeOH–NH_2OH, 30:20:1 v/v/v) to give **3**.

Yield: 42 mg (0.244 mmol, 90%); colorless semisolid; $[\alpha]_D^{28}$ –6.7 (*c* 0.75, H_2O).

IR (neat): 3385, 3264, 3014, 2951 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 4.08–3.91 (m, 4 H), 3.41–3.27 (m, 3 H), 2.03–1.75 (m, 6 H).

^{13}C NMR (100 MHz, D_2O): δ = 72.6, 68.4, 59.3, 59.0, 46.4, 28.3, 23.3, 18.4.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_8H_{18}NO_3$: 176.1287; found: 176.1273.

***tert*-Butyl [(2*R*,3*R*,4*R*)-1,3,4-Tris(benzyloxy)hex-5-en-2-yl]carbamate (19)**

To a stirred solution of crude amine obtained from hydrolysis of **15** (120 mg, 0.288 mmol) in CH_2Cl_2 (5 mL), Et_3N (0.06 mL, 0.43 mmol) and a catalytic amount DMAP were added at 0 °C. After 5 min, $(Boc)_2O$ (0.1 mL, 0.43 mmol) was added to the reaction mixture and stirring was continued for 2 h. H_2O was added and the resulting mixture was extracted with CH_2Cl_2 and the organic layer was concentrated under reduced pressure to give a residue, which was purified by column chromatography (EtOAc/hexane, 1:9 v/v) to give **19**.

Yield: 113 mg (0.218 mmol, 76% from crude); yellowish oil; R_f = 0.5 (EtOAc/hexane, 1:4); $[\alpha]_D^{28}$ –12.3 (*c* 5.0, $CHCl_3$).

IR (neat): 3415, 2926, 2870, 1708 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.18 (m, 15 H), 5.87 (ddd, *J* = 8.2, 10.1, 17.8 Hz, 1 H), 5.24–5.15 (m, 3 H), 4.59–4.49 (m, 3 H), 4.33 (dd, *J* = 11.9, 17.8 Hz, 2 H), 4.19 (d, *J* = 11.6 Hz, 1 H), 4.10 (m, 1 H), 3.91 (dd, *J* = 4.4, 7.9 Hz, 1 H), 3.60 (t, *J* = 4.7 Hz, 1 H), 3.52–3.48 (m, 1 H), 3.32 (dd, *J* = 6.4, 9.6 Hz, 1 H), 1.34 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 138.7, 138.5, 138.3, 135.7, 128.7, 128.6, 128.6, 128.5, 128.4, 128.1, 128.0, 119.4, 81.6, 80.4, 79.3, 74.0, 73.3, 70.8, 69.4, 50.7, 28.7.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{40}NO_5$: 518.2906; found: 518.2909.

4-Methyl-*N*-[(2*R*,3*R*,4*R*)-1,3,4-tris(benzyloxy)hex-5-en-2-yl]benzenesulfonamide (21)

To a stirred solution of crude amine, obtained from hydrolysis of **15** (120 mg, 0.288 mmol) in CH_2Cl_2 (5 mL), Et_3N (0.06 mL, 0.43 mmol) and a catalytic amount DMAP were added at 0 °C. After 5 min, *p*-toluenesulfonyl chloride (82 mg, 0.43 mmol) was added and the mixture was stirred for 3 h. H_2O was added to the reaction mixture, which was then extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated under reduced pressure to give a residue, which was purified by column chromatography (EtOAc/hexane, 1:9, v/v) to give **21**.

Yield: 123 mg (0.236 mmol, 75% from crude); colorless oil; R_f = 0.5 (EtOAc/hexane, 1:4); $[\alpha]_D^{28}$ –21.5 (*c* 0.36, $CHCl_3$).

IR (neat): 3436, 2953, 2923, 2111 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.3 Hz, 2 H), 7.33–7.24 (m, 11 H), 7.16–7.13 (m, 6 H), 5.84–5.75 (m, 1 H), 5.57 (d, *J* = 7.1 Hz, 1 H), 5.24–5.17 (m, 2 H), 4.54 (d, *J* = 11.5 Hz, 1 H), 4.42–4.39 (m, 1 H), 4.32–4.27 (m, 3 H), 4.21–4.18 (m, 1 H), 4.01 (dd, *J* = 3.7, 7.9 Hz, 1 H), 3.72–3.67 (m, 1 H), 3.60–3.57 (m, 2 H), 3.22–3.18 (m, 1 H), 2.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.4, 138.4, 138.1, 138.1, 138.0, 135.7, 129.8, 128.7, 128.7, 128.6, 128.2, 128.1, 128.0, 127.6, 119.5, 80.4, 80.2, 74.1, 73.4, 70.9, 69.0, 53.7, 21.8.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{38}NO_5S$: 572.2471; found: 572.2476.

2-[(3*R*,4*R*,5*S*)-4,5-Bis(benzyloxy)-6-(iodomethyl)tetrahydro-2*H*-pyran-3-yl]isoindoline-1,3-dione (23)

To a stirred solution of **15** (1 g, 1.83 mmol) in CH_2Cl_2 (20 mL), I_2 (702 mg, 2.74 mmol) was added at r.t. Upon completion of the reaction (monitored by TLC), the mixture was diluted with CH_2Cl_2 and washed sequentially with aq $Na_2S_2O_3$ and brine. The aqueous layer was washed with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4, evaporated, and purified by column chromatography (EtOAc/hexane, 1:8 v/v) to give **23**.

Yield: 928 mg (1.59 mmol, 84%); pale yellow liquid; R_f = 0.4 (EtOAc/hexane, 1:4); $[\alpha]_D^{28}$ +67.4 (*c* 2.80, $CHCl_3$).

IR (neat): 3405, 3026, 3014, 1641 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.17 (m, 10 H), 6.89–6.83 (m, 4 H), 4.95–4.41 (m, 5 H), 4.24–3.99 (m, 2 H), 3.90–3.72 (m, 3 H), 3.42–3.21 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 168.5, 138.5, 137.7, 137.5, 134.5, 134.4, 134.1, 132.1, 132.0, 129.0, 128.8, 128.6, 128.5, 128.5, 128.3, 128.2, 128.2, 128.1, 128.0, 79.9, 78.8, 78.0, 76.4, 74.9, 73.4, 73.3, 72.8, 72.2, 66.9, 63.9, 49.7, 48.9, 6.1, 3.1.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{27}INO_5$: 584.0934; found: 584.0921.

2-[(2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-1-hydroxyhex-5-en-2-yl]isoindoline-1,3-dione (24)

To a magnetically stirred suspension of Zn dust (836 mg, 12.86 mmol) in anhydrous MeOH (10 mL), a solution of **23** (750 mg, 1.286 mmol) in anhydrous MeOH (10 mL) was added and the resulting solution was heated at reflux for 2 h. The mixture was filtered through a Celite bed and the filtrate was evaporated under reduced pressure. The residue obtained was dissolved in EtOAc (25 mL) and washed with a mixture of brine and water (1:1 v/v, 10 mL each). The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography (EtOAc/hexane, 1:5, v/v) to give alcohol **24**.

Yield: 482 mg (1.055 mmol, 82%); colorless liquid; R_f = 0.4 (EtOAc/hexane, 1:2); $[\alpha]_D^{28}$ +31.8 (*c* 1.25, $CHCl_3$).

IR (neat): 3435, 3066, 3014, 1641 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.58 (m, 2 H), 7.56–7.53 (m, 2 H), 7.30–7.18 (m, 5 H), 7.02–6.94 (m, 5 H), 5.85 (ddd, *J* = 7.5, 10.5, 17.7 Hz, 1 H), 5.27–5.18 (m, 2 H), 4.68 (dd, *J* = 11.1, 17.6 Hz, 2 H), 4.52–4.44 (m, 2 H), 4.25 (d, *J* = 11.3 Hz, 1 H), 4.09–3.93 (m, 3 H), 3.88 (dd, *J* = 3.7, 7.5 Hz, 1 H), 2.75 (d, *J* = 6.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 138.1, 137.9, 134.5, 134.2, 132.2, 128.8, 128.7, 128.4, 128.3, 128.2, 127.6, 123.5, 120.4, 81.1, 76.9, 74.8, 71.3, 63.1, 53.0.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{28}NO_5$: 458.1967; found: 458.1956.

***tert*-Butyl [(2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-1-hydroxyhex-5-en-2-yl]carbamate (25)**

Compound **24** (520 mg, 0.95 mmol) was dissolved in aq $MeNH_2$ (10 mL, 40%), and the resulting mixture was stirred in an open flask for 1.5 h at 60 °C. The reaction mixture was then concentrated under reduced pressure, dissolved in H_2O (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude amine was used for the next step without further purification.

To a stirred solution of crude amine in CH_2Cl_2 (15 mL), Et_3N (0.396 mL, 2.85 mmol) and a catalytic amount DMAP were added at 0 °C. After 5 min, $(Boc)_2O$ (0.22 mL, 0.43 mmol) was added and stirring was continued for 2 h. H_2O was added to the reaction mixture, which was then extracted with CH_2Cl_2 and concentrated under reduced pressure to give a residue, which was purified by column chromatography (EtOAc/hexane, 1:8 v/v) to give **25**.

Yield: 268 mg (0.628 mmol, 66% from crude); colorless liquid; R_f = 0.4 (EtOAc/hexane, 1:3); $[\alpha]_D^{28}$ +19.5 (*c* 3.50, $CHCl_3$).

IR (neat): 3389, 2972, 2928, 1703 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.22 (m, 10 H), 5.86–5.77 (m, 1 H), 5.32–5.21 (m, 3 H), 4.75–4.72 (m, 1 H), 4.56 (dd, *J* = 7.4, 11.6 Hz, 2 H), 4.29 (d, *J* = 11.7 Hz, 1 H), 3.94–3.90 (m, 1 H), 3.75–3.69 (m, 3 H), 3.52 (d, *J* = 8.2 Hz, 1 H), 2.74 (s, 1 H), 1.34 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 138.4, 138.3, 135.0, 128.9, 128.8, 128.5, 128.3, 128.1, 120.3, 82.7, 79.8, 75.2, 70.9, 63.1, 52.6, 28.7.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{34}NO_5$: 428.2437; found: 428.2433.

(*R*)-4-[(1*R*,2*R*)-1,2-Bis(benzyloxy)but-3-en-1-yl]oxazolidin-2-one (26)

To an ice-cooled solution of alcohol **25** (150 mg, 0.35 mmol) in anhydrous THF (5 mL) was added sodium hydride (21 mg, 0.526 mmol), in one portion, under nitrogen atmosphere and the mixture was stirred for 1 h at the same temperature. Upon completion the reaction was quenched by addition of sat. aq NH_4Cl, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5 v/v) to give **26**.

Yield: 110 mg (0.311 mmol, 89%); colorless oil; R_f = 0.4 (EtOAc/hexane, 1:2); $[\alpha]_D^{28}$ +24.6 (*c* 2.30, $CHCl_3$).

IR (neat): 3306, 2915, 1758, 1240 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.14 (m, 10 H), 5.82–5.75 (m, 1 H), 5.69 (s, 1 H), 5.33–5.28 (m, 2 H), 4.58–4.55 (m, 2 H), 4.4 (d, *J* = 11.5 Hz, 1 H), 4.28–4.23 (m, 2 H), 4.18–4.15 (m, 1 H), 3.94–3.92 (m, 1 H), 3.90–3.86 (m, 1 H), 3.46 (dd, *J* = 4.3, 6.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 137.8, 137.6, 134.2, 128.9, 128.8, 128.4, 128.4, 128.3, 119.8, 81.1, 79.4, 74.4, 71.2, 67.7, 53.2.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{24}NO_4$: 354.1705; found: 354.1712.

(*R*)-4-[(1*R*,2*R*)-1,2-Bis(benzyloxy)but-3-en-1-yl]-3-(but-3-en-1-yl)oxazolidin-2-one (27)

A solution of oxazolidinone **26** (90 mg, 0.255 mmol) in THF (4 mL) was treated sequentially with NaH (15 mg, 0.382 mmol) and 4-bromobut-1-ene (0.093 mL, 0.383 mmol) at 0 °C, and the mixture was stirred for 3 h at r.t. Upon completion of the reaction the mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extract was washed with brine, dried (Na_2SO_4), evaporated under reduced pressure, and purified by column chromatography (EtOAc/hexane, 1:3 v/v) to give **27**.

Yield: 72 mg (0.199 mmol, 78%); colorless oil; R_f = 0.5 (EtOAc/hexane, 1:1); $[\alpha]_D^{28}$ +20.8 (*c* 0.60, $CHCl_3$).

IR (neat): 2981, 1748, 1425, 1370 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.17 (m, 10 H), 5.74 (ddd, *J* = 7.2, 10.6, 17.5 Hz, 1 H), 5.66–5.56 (m, 1 H), 5.33–5.26 (m, 2 H), 4.97–4.93 (m, 2 H), 4.65 (d, *J* = 11.7 Hz, 1 H), 4.57 (d, *J* = 5.5, 8.6 Hz, 1 H), 4.49 (d, *J* = 11.7, 1 H), 4.42 (dd, *J* = 5.5, 8.7 Hz, 1 H), 4.27 (d, *J* = 11.9 Hz, 1 H), 4.05 (t, *J* = 8.6 Hz, 1 H), 3.86–3.82 (m, 2 H), 3.63 (dd, *J* = 0.7, 5.1 Hz, 1 H), 3.40–3.32 (m, 1 H), 2.54–2.48 (m, 1 H), 2.17–2.06 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 138.1, 137.9, 135.0, 134.8, 128.9, 128.5, 128.4, 128.3, 128.1, 119.9, 117.7, 80.5, 76.7, 74.2, 71.2, 63.2, 56.0, 40.8, 31.7.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{30}NO_4$: 408.2175; found: 408.2169.

(9*R*,10*R*,10*aR*,*Z*)-9,10-Bis(benzyloxy)-5,6,10,10a-tetrahydro-1*H*-oxazolo[3,4-*a*]azocin-3(9*H*)-one (28)

To a 50 mL two-necked, oven-dried, round-bottom flask fitted with a reflux condenser and septum was added Grubbs II catalyst (6 mg, 0.007 mmol) under argon atmosphere. Anhydrous CH_2Cl_2 (2 mL) was then added to the flask through a syringe and the solution was kept stirring. Compound **27** (53 mg, 0.130 mmol) in CH_2Cl_2 (10 mL) was added through a syringe to the stirring reaction mixture and the solution was heated at reflux for 6 h. The temperature of the reaction

mixture was brought slowly to r.t. and the organic solvent was evaporated under reduced pressure to give a black residue, which was purified by column chromatography (EtOAc/hexane, 1:2 v/v) to give **28**.

Yield: 42 mg (0.112 mmol, 86%); colorless liquid; R_f = 0.5 (EtOAc/hexane, 2:1); $[\alpha]_D^{28}$ +21.4 (*c* 0.30, $CHCl_3$).

IR (neat): 3023, 2920, 2863, 1753, 1460 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.19 (m, 10 H), 5.73–5.63 (m, 2 H), 5.04 (d, *J* = 11.0 Hz, 1 H), 4.64 (d, *J* = 11.8 Hz, 1 H), 4.51–4.41 (m, 2 H), 4.24–4.18 (m, 2 H), 4.08–4.06 (m, 1 H), 3.68 (td, *J* = 5.2, 13.2 Hz, 1 H), 3.44–3.35 (m, 2 H), 3.06–3.02 (m, 1 H), 2.34–2.15 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 138.4, 138.2, 133.3, 128.9, 128.8, 128.7, 128.5, 128.4, 128.1, 128.0, 81.9, 79.0, 76.2, 71.5, 68.8, 59.1, 44.2, 27.3.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{26}NO_4$: 380.1862; found: 380.1826.

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Supporting Information

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