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Asymmetric synthesis of Pachastrissamine (Jaspine B) and its diastereomers *via* η^3-allylpalladium intermediates

Mikko Passiniemi and Ari M. P. Koskinen*

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A short route for the synthesis of Pachastrissamine (Jaspine B), an anhydrosphingosine derivative, and all three of its diastereomers is presented. The route consists of only 9 steps from the commercially available Garner's aldehyde. The furan framework is formed *via* an η^3-allylpalladium intermediate.

Introduction

Polysubstituted tetrahydrofurans are common structural motifs found in natural products and biologically active molecules such as annonaceous acetogenins,[1] lignans,[2] polyether ionophores[3] and macrodiolides.[4] Due to their biological activities including antitumour, antihelmic, antimalarial, antimicrobial and antiprotozoal activity as well as challenging structures, development of methods for synthesizing differently substituted tetrahydrofurans stereoselectively have become important. There are many approaches described in the literature for the formation of tetrahydrofuran ring systems.[5] They include oxidative cyclisation,[6] radical cyclisation,[7] cycloisomerisation,[8] Prins/Prins-Pinacol type cyclisation,[9] Palladium mediated Tsuji–Trost allylation reaction[10] among others (Fig. 1).

The marine environment has frequently afforded a variety of biologically active compounds with strong anticancer and cytotoxic properties. Pachastrissamine (Jaspine B) **1** (Fig. 2), the first naturally occurring anhydrosphingosine derivative, was isolated in 2001 by Higa and co-workers[11] from an Okinawan marine sponge *Pachastrissa sp.* (family calthropellidae). Later in 2003 Debitus and co-workers[12] isolated the same compound from a Vanuatuan marine sponge genus *Jaspis*. It was found to possess marked cytotoxicity at a level of IC_{50} 0.01 μg mL^{-1} against P388, A549, HT29 and Mel 28 cell lines. Due to the biological

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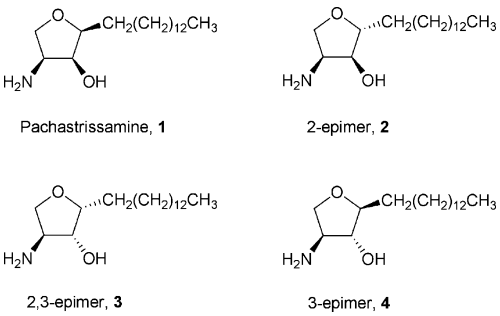


Fig. 2 Structure of Pachastrissamine and its diastereomers.

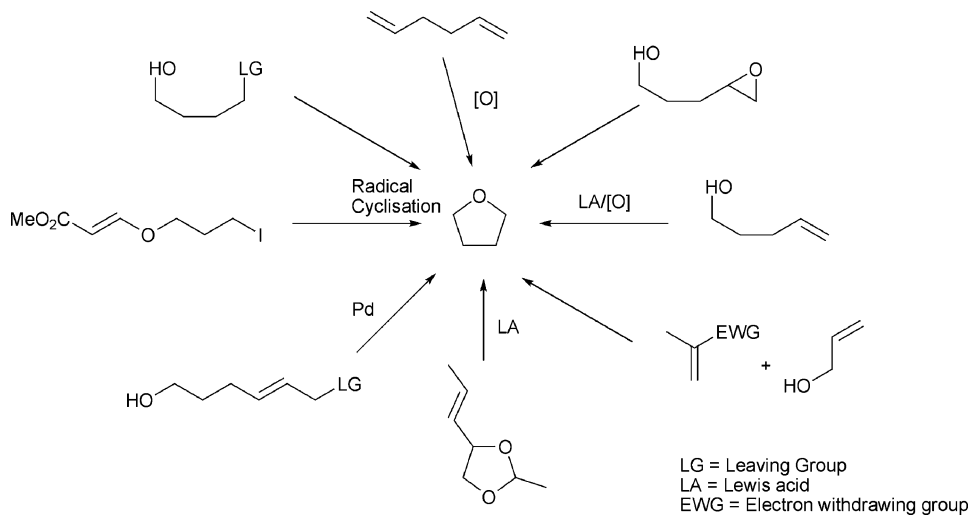
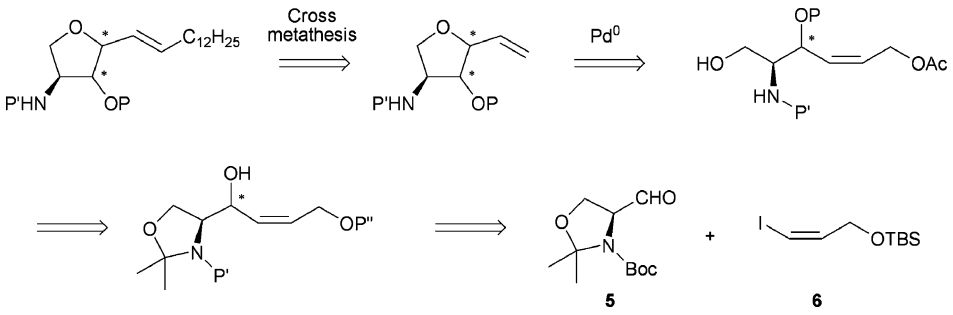
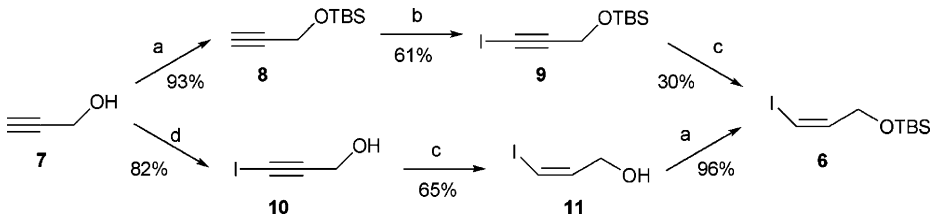


Fig. 1 Some examples for the preparation of tetrahydrofuran/dihydrofuran ring systems.



Scheme 1 Retrosynthetic analysis.



Scheme 2 a) TBSCl, imidazole, DMF, 0 °C → rt; b) I_2, *n*-BuLi, THF, –78 °C; c) $KO_2CN{=}NCO_2K$, AcOH, MeOH; d) I_2, KOH, MeOH–H_2O.

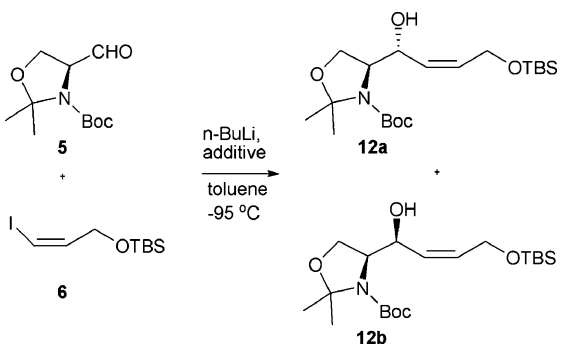
activity and challenging chemical structure, a great deal of effort has been devoted to the synthesis of Pachastrissamine[13] including our own.[14] Lesser, but lately increasing, attention has been paid to the synthesis of other diastereomers of Pachastrissamine. Delgado and co-workers[13q] and Ohno and co-workers[13x] have both synthesized four diastereomers of Pachastrissamine (**1**, C_2 epimer **2**, C_2&C_3 epimer **3** and C_3 epimer **4**) and other groups only the epimer **2**.[13c,k,n,s] Herein, we report a short synthesis of all four diastereomers of Pachastrissamine from Garner's aldehyde.

Results and discussion

Our synthetic plan is depicted in Scheme 1. Retrosynthetically the carbon skeleton of **1** can be considered to arise from a cross metathesis reaction of a vinyltetrahydrofuran and a terminal alkene. We anticipated that the (2,3,4)-substituted tetrahydrofuran framework, the key intermediate of our route, could be achieved *via* an η^3-allylpalladium intermediate. Depending on the selectivity of the cyclization step both isomers at C_2 should be achievable. After simple functional group manipulations the synthon for the tetrahydrofuran framework can be envisaged to arise from an allylic oxazoline, which itself can be derived from a stereoselective coupling of Garner's aldehyde **5** with a suitably protected vinyliodide **6**.

The synthesis commenced with the preparation of *Z*-iodide **6** (Scheme 2). We first attempted a route first published by Luithle and Pietruszka.[15] Propargyl alcohol **7** was protected as a silyl ether with TBSCl (93%).[16] The TBS ether **8** was then subjected to iodination with elemental iodine at –78 °C (61%).[17] The triple bond of **9** was reduced with diimide (HN=NH)[18] to give the *Z*-double bond in a modest yield (30%) with the overall yield being just 17% (over three steps). The poor yield of the reduction reaction is partly explained by overreduction of the triple bond to single bond. By simply changing the order of reactions the overall yield improved to 51%. Iodination of propargyl alcohol **7** provided iodide **10**[19] in good yield (82%). The yield is lowered due to the high volatility of the iodide **10** (despite it being crystalline). This iodide can be distilled under vacuum (10–15 mmHg). *N.B. Iodide* **10** *is explosive at high temperatures!* Diimide reduction of **10** proceeded smoothly to provide the *Z*-alkene **11**[20] in a fairly good yield (65%). TBS protection proceeded with ease providing the *Z*-iodide **6**[21] in almost quantitative yield (96%). This three step procedure can be performed with a single purification process, distillation of the final *Z*-iodide **6**.

Nucleophilic addition to Garner's aldehyde has been very thoroughly studied.[22] Pioneering research was done separately by Herold[22a] and Garner.[22b] The stereochemical outcome can be controlled either through the use of additives or chelating agents. HMPA is known to solvate lithium cations very well. This coordination enhances the nucleophilicity of the lithiated species, which favours the attack of the nucleophile from the least hindered side *via* a Felkin–Ahn transition state (leading to *anti*-diastereomer). Bidentate metal cations (*e.g.* Mg, Zn) tend to chelate to the carbonyl groups and affect the stereochemical outcome. Under chelation control *syn*-diastereomers are produced as major products. Iodide **6** was then coupled with Garner's aldehyde **5** (Scheme 3). *anti*/*syn*-Selectivities are reported in Table 1. High *anti*-selectivity (upto 17 : 1 *anti*/*syn*) was best achieved with DMPU or HMPA as an additive. Without additives the selectivity



Scheme 3 Coupling reaction.

Table 1 Diastereoselectivity of the addition of (*Z*)-iodoalkene **6** to Garner's aldehyde **5**

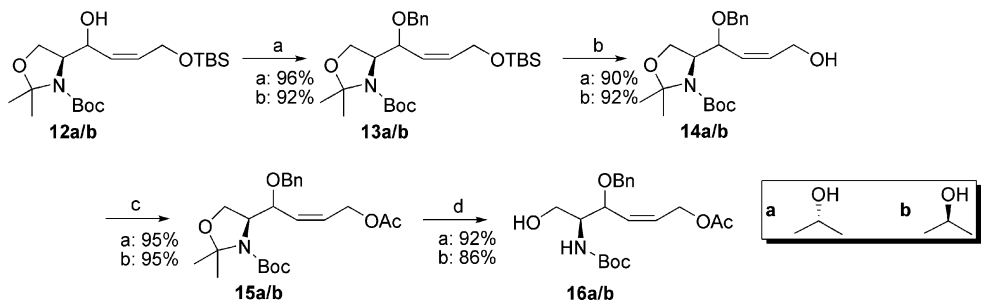
Entry	Additive	Solvent	*anti* : *syn*[a]	Conversion
1	HMPT	Toluene	12 : 1	55%
2	DMPU	Toluene	16.9 : 1	57%
3	no additive	Toluene	4 : 1	63%
4	$SnCl_4$	Toluene	1 : 1.8	41%
5	$ZnCl_2$	Toluene/Et_2O	1 : 5.7	72%
6	$BF_3{\cdot}Et_2O$	Toluene	1 : 6	70%

[a] *anti*/*syn* selectivity was checked by chiral HPLC (column: Supelco Cyclodextrin γ)

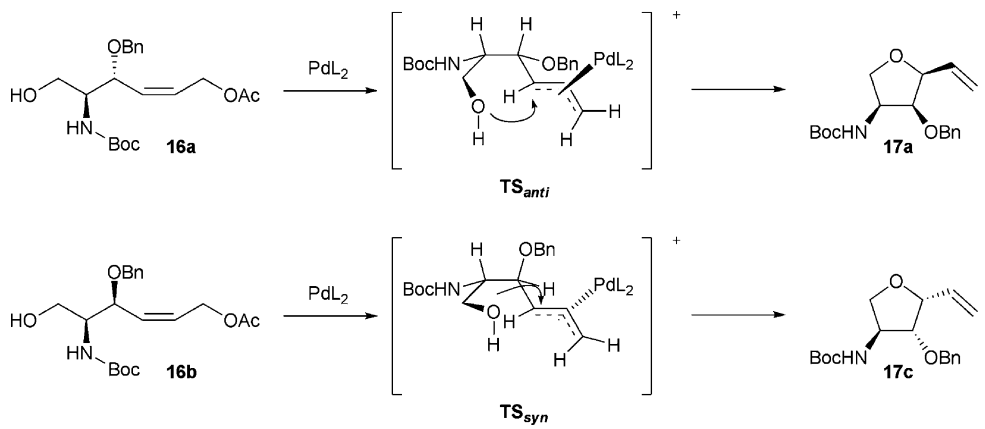
was 4 : 1 (*anti*/*syn*), which manifests the enantioface controlling effect of the *N*-Boc protected dimethyloxazolidine ring unit. For *syn*-selective coupling we turned to chelating metals/Lewis acids. Best results were obtained with $ZnCl_2$ dissolved in Et_2O or $BF_3{\cdot}Et_2O$ (1 : 6 *anti*/*syn*). Yields of these coupling reactions varied between 40–70% depending on the reaction conditions.

Alcohols **12a** and **12b** were protected as benzyl ethers with BnBr, TBAI and NaH in refluxing THF in a good yield (for **13a** 96% and for **13b** 92%). Removal of the TBS protecting groups from **13a/b** with TBAF proceeded quickly and smoothly providing alcohols **14a** (90%) or **14b** (92%) in excellent yields (Scheme 4). The reaction was instantly over with both diastereomers **13a/b** as soon as 100 mol% of TBAF had been added. Free alcohols **14a/b** were esterified with Ac_2O, DMAP/Et_3N in CH_2Cl_2. Again, this reaction proved to be fast and efficient Full conversion was reached with both diastereomers **14a/b** within 5 min after the addition of the anhydride (isolated yield with both **15a** and **15b** 95%). Cleavage of the *N*,*O*-acetal was best achieved with $FeCl_3$ adsorbed on silica gel in $CHCl_3$.[23] 80% AcOH at 50 °C can also be used, but on larger scales this reagent esterifies the newly formed free alcohol to some extent.

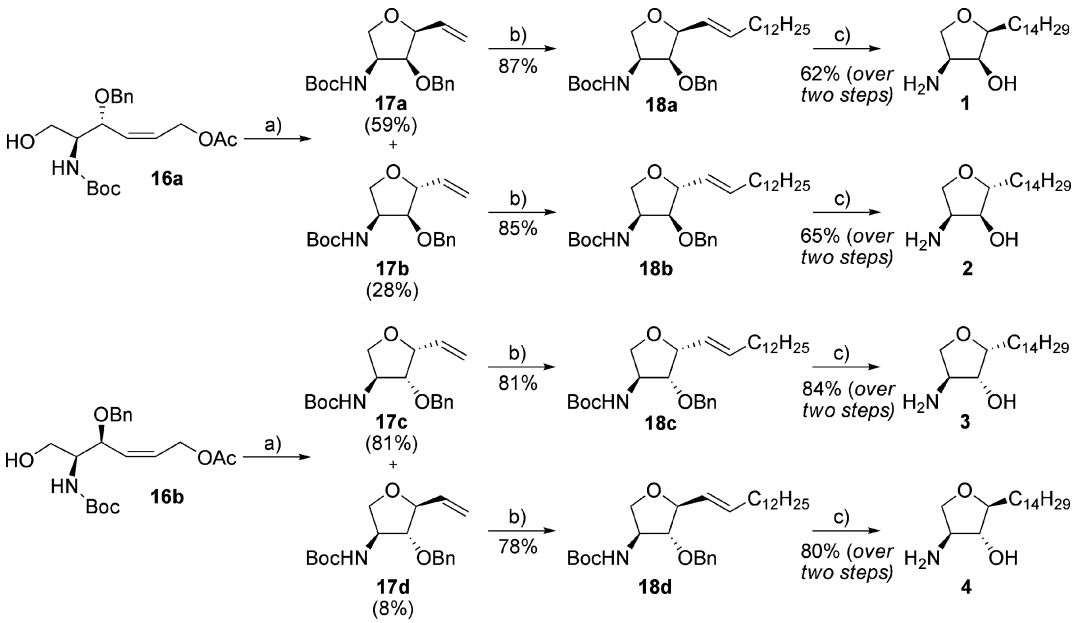
The key reaction, cyclization into a furan ring, we had envisioned to proceed *via* an allylpalladium intermediate.[10,24] It is known that with chiral allylic acetates (or esters in general) in the formation of the allylpalladium complex, the initial attack of Pd^0 occurs from the least hindered side (*anti*-attack) thus inverting the stereochemistry of the complex. Soft carbon nucleophiles and heteroatoms (such as N and O) attack in a S_N2 type manner inverting the stereochemistry of the allylpalladium complex. The overall outcome of the reaction is retention of stereochemistry. We anticipated that the stereogenic center at C_4 (the allylic benzyl ether would provide enough internal asymmetric induction for the cyclization. With **16b**, the Pd catalyst would coordinate to the allylic system from the least hindered side forcing the nucleophile to replace Pd from the backside (**TS**$_{anti}$ in Scheme 5). With the *anti*-isomer **16a** the cyclization reaction proceeded smoothly with catalytic $Pd(PPh_3)_4/PPh_3$ in THF at 55 °C. It became immediately evident that the selectivity of the cyclisation was modest. Crude ^1H NMR showed that a ~2 : 1 mixture of **17a** and **17b** had formed favoring the all *syn* (3*S*,4*S*,5*S*) configuration. With the *syn*-isomer **16b** the selectivity rose substantially to over 9 : 1 (**17c** : **17d**) favoring the (3*S*,4*R*,5*R*) configuration (overall yield 88%). The lower selectivity of **16a** can possibly be explained by π-σ-π-isomerization of the Pd intermediate. This kind of isomerization could be feasible due to the lower energy difference between the Pd intermediates, *i.e.* the intermediates equilibrate more rapidly than cyclize. Hence the lower selectivity from the cyclization. Both



Scheme 4 a) BnBr, TBAI, NaH, THF, reflux; b) TBAF, THF, rt; c) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt; d) $FeCl_3$-SiO_2, $CHCl_3$, rt.



Scheme 5 Proposed transition states leading to diastereomers **17a** and **17c**.



Scheme 6 a) cat. $Pd(PPh_3)_4$, PPh_3, THF, 55 °C; b) cat. Grubbs' 2nd gen., 1-tetradecene, CH_2Cl_2, 45 °C; c) (i) cat. Pd/C, H_2 (1 atm), MeOH, rt; (ii) HCl (g), MeOH, 0 °C → rt.

cyclizations proceeded with high overall yields (varying between 87–95% for **17a/17b** and 89–95% for **17c/17d**, respectively). The relative stereochemistry of all four diastereomers were elucidated based on ^1H, ^{13}C & 2D NMR studies and later confirmed by the physical data of free amines **1**, **2**, **3** and **4**.

With means of synthesizing all four diastereomers **17a–d** (Scheme 6), we then investigated the cross-metathesis reaction.[25] Highest conversions (78–87%) were obtained with Grubbs' 2nd generation catalyst[26] and a 10-fold excess of 1-tetradecene in CH_2Cl_2 at 45 °C (closed vessel). The catalyst loading had to be at least 10 mol%, otherwise the metathesis reaction did not proceed as efficiently and we could detect and isolate unreacted starting materials. The final hydrogenation and global deprotection was performed in two steps. First the double bond and benzyl ether were hydrogenated over Pd/C at an atmospheric pressure of H_2 gas. Next the *t*-butyl carbamate was cleaved off with HCl in MeOH at 0 °C and after basic work up Pachastrissamine **1** and its three diastereomers **2**, **3** and **4** were isolated as free bases.

Conclusion

In summary, we have shown that the coupling reaction of Garner's aldehyde **5** with the vinyl lithium compound derived from the *Z*-alkene **6** can be controlled to give either the *anti* or *syn* diastereomer in high diastereoselectivity. The open-chain allyl acetates **16a** and **16b** cyclise through an η^3-allylpalladium intermediate with moderate to good stereoselectivities to tetrahydrofurans. The method presented gives easy access to Pachastrissamine **1** and all three of its diastereomers **2**, **3**, **4** in 9 steps starting from commercially available Garner's aldehyde **5**.

Our nine step procedure provides Pachastrissamine **1** in a total yield of 13%. In comparison **1** has been synthesized from Garner's aldehyde in ten (overall yield 22%, TFA salt),[13a] eleven (overall yield 11%),[13t] seven (overall yield 26%)[13v] and five (38%)[13x] steps. Overall yields for **2**, **3** and **4** were 6%, 23% and 2% respectively. Garner's aldehyde has been also used by others for the synthesis of *epi*-pachastrissamines: overall yields have been 10%[13a] and 43%[13x] for **2**, 17% for **3** and 20% for **4**.[13x]

Experimental

General Experimental

All reactions were carried out under argon atmosphere in flame-dried glassware unless otherwise noted. Non-aqueous reagents were transferred under argon *via* syringe or cannula and dried prior to use. Et_3N, benzene and toluene were distilled from metallic Na. THF was distilled from Na/benzophenone, CH_2Cl_2 from CaH_2 and DMF from molecular sieves (4 Å)/ninhydrin. Other solvents and reagents were used as obtained from supplier. Analytical TLC was performed using Merck silica gel F_{254} (230–400 mesh). Column chromatography was performed using Merck silica gel 60 (230–400 mesh) and p.a. grade solvents. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 (^1H 399.98 MHz; ^{13}C 100.59 MHz) spectrometer. The chemical shifts are reported in ppm relative to $CHCl_3$ (δ 7.26 ppm for ^1H and 77.0 ppm for ^{13}C) or $CHCl_2CHCl_2$ (δ 5.96 ppm for ^1H and 73.7 ppm for ^{13}C). Melting points were determined in open capillaries using Stuart SMP3 melting point apparatus. Optical rotations were obtained with Perkin–Elmer 343 polarimeter. High resolution mass spectrometric data were measured using MicroMass LCT Premier spectrometer.

3-Iodoprop-2-yn-1-ol 10

Propargyl alcohol **7** (5.71 g, 102 mmol, 100 mol%) was dissolved in MeOH (100 mL) and cooled to 0 °C. KOH (14.36 g, 256 mmol, 251 mol%) dissolved in H_2O (20 mL) was added in one portion to the solution. After 10 min, iodine (28.46 g, 112 mmol, 110 mol%) was added to the solution. The mixture was stirred at 0 °C for

5 min before it was allowed to warm to room temperature. MeOH was removed under reduced pressure and the crude product was partitioned between H_2O (100 mL) and Et_2O (100 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with sat. Na_2SO_3, dried (Na_2SO_4) and concentrated *in vacuo*. The iodide **10** was collected as white crystals (15.25 g, 82%), mp 47–49 °C. *N.B. The iodide **10** can be purified by vacuum distillation* (*bp 80–90 °C*, *15 mmHg*), *but **10** is also explosive at high temperatures!* δ_H (400 MHz, $CDCl_3$) 1.85 (1H, t, *J* 6.1 Hz), 4.42 (2H, d, *J* 6.0 Hz); δ_C (100 MHz, $CDCl_3$) 2.6, 52.6, 92.5; EI-MS *m/z* 182 M^+, 165, 152, 139, 127, 55.

Preparation of potassium (*E*)-diazene-1,2-dicarboxylate[27]

KOH (59.8 g, 1.07 mol, 250 mol%) was dissolved in distilled H_2O (110 mL). The solution was stirred vigorously and cooled to 0 °C. Azodicarbonamide (49.7 g, 0.43 mol, 100 mol%) was added in small portions to the solution (3–5 g each). After the addition of azodicarbonamide the mixture was stirred for 30 min before the azodicarbocylate salt was collected as a bright yellow precipitate by filtration (79.2 g, 95%). The filtrate was washed with cold H_2O until washings were neutral, then with MeOH and finally with Et_2O.

(*Z*)-3-Iodoprop-2-en-1-ol 11

Iodide **10** (30.0 g, 0.165 mol, 100 mol%) was dissolved in MeOH (400 mL) and the dipotassium diazocarboxylate (68.7 g, 0.354 mmol, 215 mol%) was added to the reaction flask. Glacial acetic acid (40.5 mL, 0.707 mmol, 430 mol%) in MeOH (100 mL) was slowly added to the solution. The rate of addition was controlled so that the solvent didn't start to boil. Gas evolution was immediate when the addition of AcOH was started and the evolved gas was released through a three-way tap. After the addition of acetic acid the contents of the flask were allowed to react for 1.5 h. MeOH was evaporated *in vacuo* and the residue was partitioned between H_2O (200 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was stirred in n-butylamine (50 mL) for 16 h. The solution was partitioned between distilled H_2O (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic layers were washed with 1 M HCl solution (200 mL). Drying of the solvents (Na_2SO_4) was followed by concentration. The crude (*Z*)-iodide **11** was purified by filtering through a short pad (~5 cm) of silica. The iodide was collected as a pale yellow oil (19.6 g, 65%); δ_H (400 MHz, $CDCl_3$) 1.91 (1H, br s), 4.24 (2H, dd, *J* 1.5, 5.7 Hz), 6.36 (1H, td, *J* 1.6, 7.6 Hz), 6.49 (1H, td, *J* = 5.8, 7.7 Hz); δ_C (100 MHz, $CDCl_3$) 65.7, 82.6, 140.0; EI-MS *m/z* 184 M^+, 183, 167, 153, 127, 55.

(*Z*)-*tert*-Butyl(3-iodoallyloxy)dimethylsilane 6

(*Z*)-iodide **11** (13.30 g, 0.105 mol, 100 mol%) was dissolved in dry DMF (50 mL). Imidazole (15.80 g, 0.232 mol, 220 mol%) was added and allowed to dissolve before TBSCl (16.60 g, 0.105 mol, 100 mol%) was added. The reaction was complete in 30 min and pentane (100 mL) was added. Phases were separated and the DMF layer was extracted with pentane (2 × 50 mL). The combined organic extracts were washed with H_2O (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by Kugelrohr distillation to afford the fully protected (*Z*)-iodide **6** as a colorless oil (30.15 g, 96%); b. 65 °C (0.15 mmHg); δ_H (400 MHz, $CDCl_3$) 0.11 (6H, s), 0.93 (9H, s), 4.26 (2H, dd, *J* 1.8, 5.3 Hz), 6.25 (1H, td, *J* 1.8, 7.7 Hz), 6.43 (1H, td, *J* 5.3, 7.7 Hz); δ_C (100 MHz, $CDCl_3$) −5.2, 18.2, 25.8, 66.8, 80.0, 141.3; EI-MS *m/z* 299 (M + 1)$^+$, 143, 131, 115, 73.

(*S*)-4-[(*Z*)-(*R*)-4-(*tert*-Butyldimethylsilanyloxy)-1-hydroxybut-2-enyl]-2′,2′-dimethyloxazolidine-3′-carboxylic acid *tert*-butyl ester 12a

The (*Z*)-iodide **6** (2.490 g, 8.34 mmol, 200 mol%) was dissolved in dry toluene (36 mL). The flask was cooled to −78 °C and *n*-BuLi (2.00 M in hexanes, 4.2 mL, 8.4 mmol, 201 mol%) was added dropwise. This mixture was stirred for 45 min before DMPU (1.02 mL, 8.5 mmol, 203 mol%) was added. Another 45 min later serinal **5** (957 mg, 4.18 mmol, 100 mol%) dissolved in toluene (6 mL) was added at −95 °C. The mixture was allowed to react for 2 h before it was quenched with saturated NH_4Cl solution (20 mL). The aqueous layer was diluted with distilled H_2O (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Purification of the crude with column chromatography (20% EtOAc/hexanes) provided a mixture of alcohols **12a/12b** as a colourless oil (922.0 mg, 55%, *anti/syn* ratio 16.9 : 1); $[\alpha]_D$ −36.7 (*c* 1.02, $CHCl_3$); IR (neat) 3410, 2978, 2932, 2870, 2850, 1698 cm^{-1}; δ_H (400 MHz, $CDCl_2CDCl_2$, 90 °C) 0.10 (6H, s), 0.93 (9H, s), 1.51 (12H, s), 1.58 (3H, s), 3.05 (1H, bs), 3.92–4.02 (3H, m), 4.28 (1H, ddd, *J* 1.5, 5.7, 13.5 Hz), 4.37 (1H, ddd, *J* 1.5, 6.2, 13.5 Hz), 4.59 (1H, m), 5.48 (1H, tdd, *J* 1.7, 8.0, 11.4 Hz), 5.70 (1H, tdd, *J* 0.9, 5.8, 11.5 Hz); δ_C (100 MHz, $CDCl_2CDCl_2$, 90 °C) −5.41, −5.37, 17.9, 24.0, 25.7, 26.3, 28.2, 59.5, 61.8, 64.2, 68.5, 80.4, 94.2, 129.1, 132.9, 152.9; HRMS (M + Na)$^+$ calcd for $C_{20}H_{39}NO_5NaSi$ 424.2495, found 424.2516.

(*S*)-4-[(*Z*)-(*S*)-4-(*tert*-Butyldimethylsilanyloxy)-1-hydroxybut-2-enyl]-2′,2′-dimethyloxazolidine-3′-carboxylic acid *tert*-butyl ester 12b

The (*Z*)-iodide **6** (2.42 g, 8.11 mmol, 201 mol%) was dissolved in dry toluene (38 mL). The flask was cooled to −78 °C and *n*-BuLi (2.28 M in hexanes, 3.6 mL, 8.21 mmol, 203 mol%) was added dropwise. After an hour the flask was cooled to −95 °C and $BF_3{\cdot}Et_2O$ (820 μL, 6.47 mmol, 160 mol%) was added. The reaction mixture was stirred for another 30 min before the serinal **5** (926.6 mg, 4.04 mmol, 100 mol%) dissolved in toluene (6 mL) was added. The mixture was stirred at −95 °C for 2.5 h before the reaction was quenched with saturated NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL) and combined organic phases dried (Na_2SO_4) and concentrated. Purification by column chromatography (15% EtOAc : hexanes) afforded 1.26 g (3.12 mmol, 77%) of **12b** (*syn/anti* ratio 6.2 : 1); $[\alpha]_D$ −28.1 (*c* 1.00, $CHCl_3$); IR (neat) 3436, 2956, 2932, 2885, 2858, 1695 cm^{-1}; δ_H (400 MHz, $CDCl_2CDCl_2$, 90 °C) 0.09 (6H, s), 0.92 (9H, s), 1.51 (12H, s), 1.57 (3H, s), 3.36 (1H, bs), 4.00–3.85 (3H, m), 4.23 (1H, ddd, *J* 1.6, 5.7, 13.5 Hz), 4.34 (1H. ddd, *J* 1.7, 6.5, 13.6 Hz), 4.60 (1H, app. t, *J* = 8.0 Hz), 5.47 (1H, m), 5.73 (1H, m); δ_C (100 MHz, $CDCl_2CDCl_2$, 90 °C) −5.42, −5.38, 17.9, 23.9, 25.7, 26.4, 28.2,

59.3, 61.7, 64.8, 69.3, 80.2, 94.0, 129.4, 133.7, 153.6; HRMS (M + Na)$^+$ calcd for $C_{20}H_{39}NO_5NaSi$ 424.2495, found 424.2511.

(*S*)-*tert*-Butyl 4-((*R*,*Z*)-1-(benzyloxy)-4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate 13a

anti-Alcohol **12a** (1.205 g, 3.00 mmol, 100 mol%) was dissolved in dry THF (20 mL) and cooled to 0 °C. NaH (60% dispersion in oil, 170 mg, 4.25 mmol, 142 mol%) was added and the mixture was stirred for 15 min before TBAI (111 mg, 0.30 mmol, 10 mol%) followed by BnBr (476 µL, 4.00 mmol, 133 mol%) were added. The mixture was heated to reflux for 16 h. When the reaction was complete, the mixture was cooled to 0 °C and quenched with saturated NH_4Cl solution (10 mL). The mixture was diluted with H_2O (5 mL) and EtOAc (10 mL) and phases were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Purification by column chromatography (20% EtOAc : hexanes) afforded the benzyl ether **13a** as an oil (1.415 g, 96%); $[\alpha]_D$ –27.4 (*c* 1.50, CH_2Cl_2); IR (neat) 3070, 2940, 2872, 1700, 1605, 1586 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 50 °C) 0.08 (6H, s), 0.93 (9H, s), 1.47 (9H, s), 1.50 (3H, s), 1.56 (3H, s), 3.91 (2H, m), 4.13 (1H, app. d, *J* 6.3 Hz), 4.19 (1H, dd, *J* 4.6, 13.1 Hz), 4.33 (1H, dd, *J* 6.9, 13.1 Hz), 4.39 (1H, d, *J* 12.1 Hz), 4.39–4.45 (1H, m), 4.60 (1H, d, *J* 12.2 Hz), 5.43 (1H, app. t, *J* 10.8 Hz), 5.80 (1H, app. td, *J* 5.8, 11.7 Hz), 7.24–7.40 (5H, m); δ_C (100 MHz, $CDCl_3$, 50 °C) –5.4, 17.9, 24.3, 25.7, 26.5, 28.2, 59.3, 60.2, 64.3, 70.5, 74.3, 79.6, 94.0, 127.2, 127.4, 128.0, 128.1, 128.3, 134.6, 138.4, 152.0; HRMS calcd. for $C_{27}H_{45}NO_5SiNa$ [M$^+$+Na] 514.2965, found 514.2951.

(*S*)-*tert*-Butyl 4-((*S*,*Z*)-1-(benzyloxy)-4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate 13b

syn-Alcohol **12b** (1.260 g, 3.14 mmol, 100 mol%) was dissolved in dry THF (20 mL) and cooled to 0 °C. NaH (60% dispersion in oil, 173.3 mg, 4.33 mmol, 138 mol%) was added and the mixture was stirred for 15 min before TBAI (116 mg, 0.314 mmol, 10 mol%) followed by BnBr (480 µL, 4.03 mmol, 128 mol%) were added. The mixture was heated to reflux for 20 h. When the reaction was complete, the mixture was cooled to 0 °C and quenched with saturated NH_4Cl solution (15 mL). The mixture was diluted with H_2O (5 mL) and EtOAc (10 mL) and phases were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Purification by column chromatography (20% EtOAc : hexanes) afforded the benzyl ether **13b** as an oil (1.420 g, 92%); $[\alpha]_D$ +8.7 (*c* 1.40, CH_2Cl_2); IR (neat) 3065, 2928, 2872, 1699, 1603, 1586 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 60 °C) 0.0671 (3H, s), 0.0716 (3H, s), 0.92 (9H, s), 1.45 (9H, s), 1.47 (3H, s), 1.52 (3H, s), 3.92 (1H, dd, *J* 6.5, 9.6 Hz), 4.08 (1H, ddd, *J* 1.8, 4.5, 13.5 Hz), 4.05–4.20 (1H, m), 4.18 (1H, dd, *J* 1.4, 9.5 Hz), 4.32 (1H, m), 4.42 (1H, d, *J* 12.0 Hz), 4.62 (1H, d, *J* 11.9 Hz), 4.60–4.75 (1H, m), 5.50 (1H, app. tdd, *J* 1.6, 9.9, 11.4 Hz), 5.89 (1H, app. ddd, *J* 4.2, 7.3, 11.4 Hz), 7.25–7.38 (5H, m); δ_C (100 MHz, $CDCl_3$, 60 °C) δ –5.14, –5.12, 18.2, 24.3, 25.9, 26.3, 28.5, 59.4, 60.1, 63.6, 70.8, 72.9, 79.9, 94.4, 126.8, 127.5, 127.7, 128.3, 136.6, 138.8, 152.2; HRMS calcd. for $C_{27}H_{45}NO_5SiNa$ [M$^+$+Na] 514.2965, found 514.2972.

(*S*)-*tert*-Butyl 4-((*R*,*Z*)-1-(benzyloxy)-4-hydroxybut-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate 14a

Benzyl ether **13a** (1.40 g, 2.85 mmol, 100 mol%) was dissolved in THF (20 mL). To this solution was added TBAF (1 M in THF, 3.0 mol, 3.0 mmol, 105 mol%). The reaction was complete in 15 min and the solvent was evaporated *in vacuo*. The crude alcohol was purified by column chromatography (30% EtOAc : hexanes) to afford the *anti*-acohol **14a** as a viscous oil (966 mg, 90%); $[\alpha]_D$ –40.3 (*c* 1.88, CH_2Cl_2); IR (neat) 3449, 3089, 3064, 2979, 2935, 2874, 1698, 1608, 1587 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 50 °C) 1.46 (9H, s), 1.49 (3H, s), 1.57 (3H, s), 2.15 (1H, br s), 3.88–3.98 (2H, m), 4.12 (1H, ddd, *J* 1.3, 6.1, 13.0 Hz), 4.15 (1H, m), 4.20 (1H, ddd, *J* 1.0, 7.3, 13.1 Hz), 4.39 (1H, d, *J* 11.9 Hz), 4.52 (1H, m), 4.31 (1H, d, *J* 11.9 Hz), 5.52 (1H, app. dd, *J* 9.8, 10.8 Hz), 5.87 (1H, dddd, *J* 1.0, 6.2, 7.1, 11.3 Hz), 7.23–7.35 (5H, m); δ_C (100 MHz, $CDCl_3$, 50 °C) 24.6, 26.7, 28.4, 58.6, 60.8, 64.3, 70.9, 74.0, 80.3, 94.3, 127.6, 127.8, 128.3, 130.8, 133.5, 138.3, 152.7; HRMS calcd. for $C_{21}H_{31}NO_5Na$ [M$^+$+Na] 400.2100, found 400.2097.

(*S*)-*tert*-Butyl 4-((*S*,*Z*)-1-(benzyloxy)-4-hydroxybut-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate 14b

Benzyl ether **13b** (1.340 g, 2.73 mmol, 100 mol%) was dissolved in THF (20 mL). To this solution was added TBAF (1 M in THF, 3.0 mol, 3.0 mmol, 110 mol%). The reaction was complete in 15 min and the solvent was evaporated *in vacuo*. The crude alcohol was purified by column chromatography (30% EtOAc : hexanes) to afford the *syn*-alcohol **14b** as a viscous oil (945 mg, 92%); $[\alpha]_D$ +3.2 (*c* 1.05, CH_2Cl_2); IR (neat) 3437, 3060, 2978, 2935, 2875, 1698, 1601, 1585 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 50 °C) 1.46 (9H, s), 1.47 (3H, s), 1.52 (3H, s), 1.75–1.85 (1H, br s), 3.93 (1H, dd, *J* 6.9, 9.5 Hz), 4.07 (1H, dd, *J* 5.7, 13.3 Hz), 4.06–4.19 (1H, m), 4.17 (1H, dd, *J* 7.2, 12.9 Hz), 4.21 (1H, dd, *J* 1.4, 9.6 Hz), 4.44 (1H, d, *J* 12.0 Hz), 4.61 (1H, d, *J* 12.1 Hz), 4.64–4.72 (1H, m), 5.59 (1H, app. t, *J* 10.6 Hz), 5.93 (1H, app. td, *J* 6.4, 11.6 Hz), 7.25–7.35 (5H, m); δ_C (100 MHz, $CDCl_3$, 50 °C) 24.3, 26.5, 28.4, 58.7, 59.8, 63.5, 70.9, 72.5, 80.4, 94.3, 127.64, 127.68, 128.4, 128.7, 135.0, 138.5, 152.8; HRMS calcd. for $C_{21}H_{31}NO_5Na$ [M$^+$+Na] 400.2100, found 400.2094.

(*S*)-*tert*-Butyl 4-((*R*,*Z*)-4-acetoxy-1-(benzyloxy)but-2-enyl)-2,2-dimethyloxazolidine-3-carboxylate 15a

Alcohol **14a** (802 mg, 2.12 mmol, 100 mol%) was dissolved in CH_2Cl_2 (20 mL) at room temperature. To this solution were added DMAP (51.0 mg, 0.42 mmol, 20 mol%), Et_3N (592 µl, 4.25 mmol, 200 mol%) and finally Ac_2O (324 µL, 3.44 mmol, 162 mol%). The reaction was complete in 10 min. Solvents were evaporated *in vacuo* and the crude acetate was purified by column chromatography (50% EtOAc : hexanes) to afford the the *anti*-acetate **15a** as a colourless oil (850 mg, 95%); $[\alpha]_D$ –52.4 (*c* 1.31, CH_2Cl_2); IR (neat) 3089, 3065, 3030, 2977, 2933, 2873, 1739, 1698, 1607, 1587 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 50 °C) 1.45 (9H, s), 1.50 (3H, s), 1.56 (3H, s), 2.05 (3H, s), 3.91 (1H, dd, *J* 5.8, 9.1 Hz), 3.95 (1H, m), 4.13 (1H, app. dd, *J* 2.0, 9.0 Hz), 4.39 (1H, d, *J* 11.7 Hz), 4.42 (1H, br s), 4.55 (1H, m), 4.60 (1H, d, *J* 11.8 Hz), 4.74 (1H, ddd, *J* 1.0, 7.6, 13.0 Hz), 5.64 (1H, app. t, *J* 10.3 Hz), 5.73–5.85 (1H, br s), 7.26–7.35 (5H, m); δ_C (100 MHz, $CDCl_3$, 50 °C) 20.8, 23.3, 26.1, 28.4, 60.0, 60.3, 64.6, 71.0, 74.3, 80.1, 93.1, 126.8, 127.9, 128.4.,

129.6, 133.0, 138.4, 152.1, 170.5; HRMS calcd. for $C_{23}H_{33}NO_6Na$ [M$^+$+Na] 442.2203, found 442.2206.

(*S*)-*tert*-Butyl 4-((*S*,*Z*)-4-acetoxy-1-(benzyloxy)but-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate 15b

Alcohol **14b** (925 mg, 2.45 mmol, 100 mol%) was dissolved in CH_2Cl_2 (10 mL) at room temperature. To this solution were added DMAP (20.0 mg, 0.164 mmol, 7 mol%), Et_3N (520 µL, 3.68 mmol, 150 mol%) and finally Ac_2O (255 µL, 2.70 mmol, 110 mol%). The reaction was complete in 15 min. Solvents were evaporated *in vacuo* and the crude acetate was purified by column chromatography (50% EtOAc : hexanes) to afford the the *syn*-acetate **15b** as a colourless oil (980 mg, 95%); $[\alpha]_D$ −2.5 (*c* 1.09, CH_2Cl_2); IR (neat) 3065, 3031, 2977, 2930, 2873, 1742, 1699, 1605 cm^{-1} δ_H (400 MHz, $CDCl_3$, 50 °C) 1.44 (9H, s), 1.46 (3H, s), 1.51 (3H, s), 2.04 (3H, s), 3.93 (1H, dd, *J* 6.5, 9.6 Hz), 4.02–4.18 (2H, m), 4.19 (1H, dd, *J* 1.0, 9.6 Hz), 4.39 (1H, d, *J* 11.8 Hz), 4.42–4.47 (1H, br s), 4.61 (1H, d, *J* 11.9 Hz), 4.73 (1H, dd, *J* 7.4, 13.1 Hz), 5.69 (1H, tdd, *J* 1.3, 9.8, 11.3 Hz), 5.87 (1H, m), 7.22–7.38 (5H, m); δ_C (100 MHz, $CDCl_3$, 50 °C) 20.7, 24.1, 25.6, 28.4, 60.0, 60.2, 63.5, 70.9, 72.4, 80.1, 94.5, 127.7, 127.9, 128.4, 130.0, 131.1, 138.5, 152.5, 170.4; HRMS calcd. for $C_{23}H_{33}NO_6Na$ [M$^+$+Na] 442.2203, found 442.2209.

(4*R*,5*S*,*Z*)-4-(Benzyloxy)-5-((*tert*-butoxycarbonyl)amino)-6-hydroxyhex-2-en-1-yl acetate 16a

anti-Acetate **15a** (690 mg, 1.65 mmol, 100 mol%) was dissolved in chloroform (15 mL). To this vigorously stirred solution was added $FeCl_3$-SiO_2 (680 mg). The mixture was stirred for 12 h before solvents were evaporated. The crude alcohol was purified by column chromatography to afford **16a** as a highly viscous oil (574.5 mg, 92%); $[\alpha]_D$ −48.6 (*c* 1.11, CH_2Cl_2); IR (neat) 3423, 3067, 3034, 2976, 2930, 2870, 1741, 1698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s), 2.07 (3H, s), 2.33 (1H, br s), 3.58–3.67 (1H, br s), 3.67 (1H, dd, *J* 3.7, 11.3 Hz), 3.95 (1H, dd, *J* 3.0, 11.2 Hz), 4.34 (1H, d, *J* 11.8 Hz), 4.42 (1H, dd, *J* 5.3, 8.7 Hz), 4.58 (1H, dd, *J* 6.2, 12.3 Hz), 4.61 (1H, d, *J* 11.8 Hz), 4.68 (1H, dd, *J* 7.5, 13.2 Hz), 5.23 (1H, d, *J* 3.8 Hz), 5.67 (1H, app. dd, *J* 9.5, 10.9 Hz), 5.84 (1H, dddd, *J* 0.8, 6.2, 7.2, 11.3 Hz), 7.27–7.38 (5H, m); δ_C (100 MHz, $CDCl_3$) 20.9, 28.3, 54.8, 60.0, 62.3, 71.0, 75.8, 79.5, 127.8, 128.0, 128.5, 129.1, 132.0, 137.5, 155.7, 170.8; HRMS calcd. for $C_{20}H_{29}NO_6Na$ [M$^+$+Na] 402.1893, found 402.1884.

(4*S*,5*S*,*Z*)-4-(Benzyloxy)-5-((*tert*-butoxycarbonyl)amino)-6-hydroxyhex-2-en-1-yl acetate 16b

syn-Acetate **15b** (950 mg, 2.27 mmol, 100 mol%) was dissolved in chloroform (20 mL). To this vigorously stirred solution was added $FeCl_3$-SiO_2 (1.03 g). The mixture was stirred for 12 h before solvents were evaporated. The crude alcohol was purified by column chromatography (30% EtOAc : hexanes) to afford **16b** as a highly viscous oil (740 mg, 86%); $[\alpha]_D$ +11.6 (*c* 1.14, CH_2Cl_2); IR (neat) 3445, 3065, 3031, 2978, 2932, 2871, 1739, 1695 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s), 2.06 (3H, s), 2.60 (1H, br s), 3.66–3.74 (3H, m), 4.34 (1H, d, *J* 11.7 Hz), 4.43 (1H, dd, *J* 1.3, 9.0 Hz), 4.57 (1H, m), 4.59 (1H, d, *J* 11.6 Hz), 4.64 (1H, ddd, *J* 0.9, 7.0, 13.1 Hz), 5.03–5.14 (1H, br s), 5.66 (1H, dd, *J* 9.8, 11.0 Hz), 5.83 (1H, app. td, *J* 6.7, 11.5 Hz), 7.27–7.37 (5H, m); δ_C (100 MHz, $CDCl_3$) 20.9, 28.3, 55.6, 60.1, 63.3, 70.5, 73.7, 79.7, 127.8, 127.9, 128.5, 129.1, 131.4, 137.6, 156.2, 170.7; HRMS calcd. for $C_{20}H_{29}NO_6Na$ [M$^+$+Na] 402.1893, found 402.1898.

Formation of the furan ring

anti-Alcohol **16a** (305 mg, 0.805 mmol, 100 mol%) was dissolved in dry THF (15 mL). To this solution were added PPh_3 (27.2 mg, 0.104 mmol, 12 mol%) and $Pd(PPh_3)_4$ (60.0 mg, 0.0519, 6 mol%). The flask was sealed, placed in an oil bath and heated to 55 °C. After 8 h the reaction was complete and the solution was concentrated. The crude product was purified by column chromatography (20% EtOAc : hexanes) to afford **17a** (152 mg, 59%) and **17b** (73 mg, 28%).

***tert*-Butyl ((3*S*,4*S*,5*S*)-4-(benzyloxy)-5-vinyltetrahydrofuran-3-yl)carbamate 17a.** $[\alpha]_D$ −21.5 (*c* 1.04, CH_2Cl_2); IR (neat) 3342, 3065, 3031, 2977, 2931, 2874, 1713, 1604, 1586 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s), 3.70 (1H, dd, *J* 7.3, 8.6 Hz), 4.02 (1H, dd, *J* 7.2, 8.5 Hz), 4.02–4.08 (1H, m), 4.38 (2H, m), 4.52 (1H, d, *J* 11.7 Hz), 4.65 (1H, d, *J* = 11.7 Hz), 5.03 (1H, d, *J* 7.7 Hz), 5.29 (1H, ddd, *J* 1.1, 1.7, 10.3 Hz), 5.40 (1H, ddd, *J* 1.3, 1.6, 17.2 Hz), 6.03 (1H, ddd *J* 7.0, 10.3, 17.2 Hz), 7.30–7.42 (5H, m); δ_C (100 MHz, $CDCl_3$) 28.3, 52.8, 70.8, 73.6, 79.63, 79.67, 82.3, 118.2, 127.8, 128.0, 128.5, 134.2, 137.6, 155.5; HRMS calcd. for $C_{18}H_{25}NO_4Na$ [M$^+$+Na] 342.1681, found 342.1689.

***tert*-Butyl ((3*S*,4*S*,5*R*)-4-(benzyloxy)-5-vinyltetrahydrofuran-3-yl)carbamate 17b.** $[\alpha]_D$ +12.5 (*c* 1.01, CH_2Cl_2); IR (neat) 3347, 3065, 3032, 2978, 2932, 2875, 1714, 1602, 1585 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s), 3.66 (1H, dd, *J* 7.5, 8.6 Hz), 3.77 (1H, app. dd, *J* 4.5, 5.1 Hz), 4.18 (1H, dd, *J* 7.0, 8.3 Hz), 4.27 (1H, app. td, *J* 6.7, 10.3 Hz), 4.35 (1H, m), 4.56 (1H, d, *J* 11.7 Hz), 4.61 (1H, d, *J* 11.7 Hz), 5.11 (1H, d, *J* 7.0 Hz), 5.18 (1H, app. td, *J* 1.3, 10.5 Hz), 5.33 (1H, app. td, *J* 1.5, 17.1 Hz), 5.79 (1H, ddd, *J* 6.0, 10.5, 17.1 Hz), 7.29–7.40 (5H, m); δ_C (100 MHz, $CDCl_3$) 28.3, 51.3, 71.3, 72.2, 79.7, 81.7, 82.9, 116.8, 127.9, 128.0, 128.5, 136.0, 137.3, 155.6; HRMS calcd. for $C_{18}H_{25}NO_4Na$ [M$^+$+Na] 342.1681, found 342.1684.

Formation of the furan ring

syn-Alcohol **16b** (200 mg, 0.527 mmol, 100 mol%) was dissolved in dry THF (10 mL). To this solution were added PPh_3 (16.6 mg, 0.063 mmol, 12 mol%) and $Pd(PPh_3)_4$ (36.3 mg, 0.031, 6 mol%). The flask was sealed, placed on oil bath and heated to 55 °C. 16 h later the reaction was complete and the solution was concentrated. The crude product was purified by column chromatography (20% EtOAc : hexanes) to afford **17c** (138 mg, 81%) and **17d** (14.5 mg, 8%).

***tert*-Butyl ((3*S*,4*R*,5*R*)-4-(benzyloxy)-5-vinyltetrahydrofuran-3-yl)carbamate 17c.** $[\alpha]_D$ −54.8 (*c* 0.8, CH_2Cl_2); IR 3345, 3065, 3033, 2977, 2929, 2870, 1709,1603, 1585 (neat) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s), 3.61 (1H, dd, *J* 4.3, 11.3 Hz), 3.89 (1H, d, *J* 4.4 Hz), 4.22–4.28 (2H, m), 4.38 (1H, dd, *J* 4.9, 6.0 Hz), 4.62 (1H, d, *J* 11.2 Hz), 4.68 (1H, m), 4.77 (1H, d, *J* 12.1 Hz), 5.27 (1H, ddd, *J* 1.0, 1.3, 10.3 Hz), 5.34 (1H, app. td, *J* 1.1, 17.3 Hz), 6.01 (1H, ddd, *J* 7.0, 10.3, 17.3 Hz), 7.27–7.36 (5H, m); δ_C (100 MHz, $CDCl_3$) 28.4, 56.4, 71.1, 71.5, 79.9, 81.8, 84.6, 117.9, 127.58, 127.64, 128.3, 133.5, 138.0, 155.0; HRMS calcd. for $C_{18}H_{25}NO_4Na$ [M$^+$+Na] 342.1681, found 342.1687.

***tert*-Butyl ((3*S*,4*R*,5*S*)-4-(benzyloxy)-5-vinyltetrahydrofuran-3-yl)carbamate 17d.** $[\alpha]_D$ −33.2 (*c* 0.39, CH_2Cl_2); IR (neat) 3338, 3065, 3031, 2978, 2930, 2872, 1710 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s), 3.68 (1H, d, *J* 3.4 Hz), 3.83 (1H, d, *J* 9.7 Hz), 4.05 (1H, dd, *J* 4.8, 9.7 Hz), 4.21 (1H, m), 4.25 (1H, m), 4.62 (1H, d, *J* 12.0 Hz), 4.71 (1H, m), 4.78 (1H, d, *J* 11.9 Hz), 5.17 (1H, app. td, *J* 1.2, 10.4 Hz), 5.35 (1H, app. td, *J* 1.3, 17.2 Hz), 5.87 (1H, ddd, *J* 5.9, 10.5, 17.2 Hz), 7.28–7.38 (5H, m); δ_C (100 MHz, $CDCl_3$) 28.4, 56.5, 71.7, 72.2, 79.8, 85.0, 88.7, 116.3, 127.8, 127.9, 128.4, 136.3, 137.8, 155.0; HRMS calcd. for $C_{18}H_{25}NO_4Na$ [M^++Na] 342.1681, found 342.1688.

***tert*-Butyl ((3*S*,4*S*,5*S*)-4-(benzyloxy)-5-((*E*)-tetradec-1-en-1-yl)tetrahydrofuran-3-yl)carbamate 18a**

Furan **17a** (43 mg, 0.135 mmol, 100 mol%) was dissolved in dry CH_2Cl_2 (4 mL). To this solution was added 1-tetradecene (350 µL, 1.33 mmol, 10 equiv) and 5 min later Grubbs' catalyst (2nd generation, 14.6 mg, 0.017, 13 mol%). The flask was sealed, placed in an oil bath and stirred at 45 °C for 18 h. When the reaction was complete, the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (100% hexanes → 20% EtOAc : hexanes). Yield of **18a** (57.2 mg, 87%); $[\alpha]_D$ −2.3 (*c* 1.14, CH_2Cl_2); IR (neat) 3350, 3032, 2970, 2925, 2854, 1717 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0 Hz), 1.25 (20H, m), 1.34–1.43 (2H, m), 1.43 (9H, s), 2.07 (2H, m), 3.65 (1H, dd, *J* 7.9, 8.2 Hz), 3.95 (1H, t, *J* 4.7 Hz), 3.99 (1H, dd, *J* 7.7, 8.2 Hz), 4.32 (1H, dd, *J* 4.2, 7.7 Hz), 4.32–4.40 (1H, m), 4.51 (1H, d, *J* 11.7 Hz), 4.66 (1H, d, *J* 11.7 Hz), 5.04 (1H, d, *J* 7.7 Hz), 5.65 (1H, app. tdd, *J* 1.1, 7.7, 15.5 Hz), 5.80 (1H, td, *J* 6.7, 15.4 Hz), 7.28–7.37 (5H, m); δ_C (100 MHz, $CDCl_3$) 14.5, 23.1, 28.8, 29.4, 29.7, 29.8, 29.9, 30.00, 30.04, 30.1, 32.3, 32.8, 53.4, 70.9, 74.1, 80.0, 80.3, 83.0, 125.9, 128.2, 128.3, 128.9, 136.2, 138.1, 156.0; HRMS calcd. for $C_{30}H_{49}NO_4Na$ [M^++Na] 510.3559, found 510.3580.

***tert*-Butyl ((3*S*,4*S*,5*R*)-4-(benzyloxy)-5-((*E*)-tetradec-1-en-1-yl)tetrahydrofuran-3-yl)carbamate 18b**

Furan **17b** (31.5 mg, 0.099 mmol, 100 mol%) was dissolved in dry CH_2Cl_2 (3 mL). To this solution was added 1-tetradecene (250 µL, 0.982 mmol, 10 equiv) and 10 min later Grubbs' catalyst (2nd generation, 8.9 mg, 0.010, 11 mol%). The flask was sealed, placed in an oil bath and stirred at 45 °C for 16 h. When the reaction was complete, the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (100% hexanes → 20% EtOAc : hexanes). Yield of **18b** (41.0 mg, 85%); $[\alpha]_D$ +10.1 (*c* 1.11, CH_2Cl_2); IR (neat) 3352, 3065, 3032, 2970, 2930, 2854, 1717 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8 Hz), 1.26 (20H, m), 1.31–1.41 (2H, m), 1.45 (9H, s), 2.02 (2H, app. q, *J* 7.0 Hz), 3.61 (1H, dd, *J* 7.7, 8.0 Hz), 3.73 (1H, app. t, *J* 4.9 Hz), 4.16 (1H, dd, *J* 7.0, 8.3 Hz), 4.25 (1H, dd, *J* 6.2, 13.4 Hz), 4.28 (1H, dd, *J* 4.3, 6.7 Hz), 4.55 (1H, d, *J* 11.8 Hz), 4.60 (1H, d, *J* 11.8 Hz), 5.11 (1H, d, *J* 7.5 Hz), 5.38 (1H, app. tdd, *J* 1.4, 7.1, 15.3 Hz), 5.74 (1H, td, *J* 6.8, 15.4 Hz), 7.28–7.38 (5H, m); δ_C (100 MHz, $CDCl_3$) 14.1, 22.7, 28.3, 28.9, 29.2, 29.3, 29.48, 29.58, 29.62, 29.67, 31.9, 32.2, 51.4, 71.2, 72.2, 79.6, 81.9, 83.0, 127.6, 127.7, 127.8, 128.0, 134.6, 137.4, 155.7; HRMS calcd. for $C_{30}H_{49}NO_4Na$ [M^++Na] 510.3559, found 510.3568.

***tert*-Butyl ((3*S*,4*R*,5*R*)-4-(benzyloxy)-5-((*E*)-tetradec-1-en-1-yl)tetrahydrofuran-3-yl)carbamate 18c**

Furan **17c** (41 mg, 0.128 mmol, 100 mol%) was dissolved in dry CH_2Cl_2 (3 mL). To this solution was added 1-tetradecene (335 µL, 1.32 mmol, 10 equiv) and 5 min later Grubbs' catalyst (2nd generation, 16.7 mg, 0.020, 15 mol%). The flask was sealed, placed in an oil bath and stirred at 45 °C for 18 h. When the reaction was complete, the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (100% hexanes → 20% EtOAc : hexanes). Yield of **18c** (50.6 mg, 81%); $[\alpha]_D$ −16.8 (*c* 1.01, CH_2Cl_2); IR (neat) 3341, 3065, 3030, 2978, 2930, 2862, 1712 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.9 Hz), 1.26 (20H, m), 1.35–1.43 (2H, m), 1.46 (9H, s), 2.08 (2H, app. q, *J* 6.9 Hz), 3.56 (1H, dd, *J* 4.5, 11.4 Hz), 3.81 (1H, d, *J* 4.1 Hz), 4.24 (2H, m), 4.31 (1H, dd, *J* 4.2, 6.9 Hz), 4.62 (1H, d, *J* 12.2 Hz), 4.70 (1H, d, *J* 5.6 Hz), 4.76 (1H, d, *J* 12.2 Hz), 5.68 (1H, app. dd, *J* 7.5, 15.5 Hz), 5.76 (1H, td, *J* 6.2, 15.5 Hz), 7.26–7.37 (5H, m); δ_C (100 MHz, $CDCl_3$) 14.1, 22.7, 28.3, 29.0, 29.2, 29.3, 29.51, 29.57, 29.62, 29.66, 31.9, 32.4, 56.5, 71.0, 71.5, 79.8, 81.8, 84.7, 124.8, 127.47, 127.53, 128.2, 135.8, 138.2, 155.0; HRMS calcd. for $C_{30}H_{49}NO_4Na$ [M^++Na] 510.3559, found 510.3555.

***tert*-Butyl ((3*S*,4*R*,5*S*)-4-(benzyloxy)-5-((*E*)-tetradec-1-en-1-yl)tetrahydrofuran-3-yl)carbamate 18d**

Furan **17d** (18.5 mg, 0.058 mmol, 100 mol%) was dissolved in dry CH_2Cl_2 (2 mL). To this solution was added 1-tetradecene (150 µl, 0.59 mmol, 10 equiv) and 5 min later Grubbs' catalyst (2nd generation, 9.3 mg, 0.011, 19 mol%). The flask was sealed, placed in an oil bath and stirred at 45 °C for 16 h. When the reaction was complete, the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (100% hexanes → 20% EtOAc : hexanes). Yield of **18d** (22.0 mg, 78%); $[\alpha]_D$ −14.9 (*c* 1.10, CH_2Cl_2); IR (neat) 3340, 3065, 3030, 2977, 2932, 2860, 1712 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.9 Hz), 1.26 (20H, m), 1.32–1.39 (2H, m), 1.46 (9H, s), 2.03 (2H, app. q, *J* 7.0 Hz), 3.63 (1H, app. d, *J* 3.8 Hz), 3.79 (1H, d, *J* 9.5 Hz), 4.01 (1H, dd, *J* 4.8, 9.7 Hz), 4.18 (2H, m), 4.62 (1H, d, *J* 12.0 Hz),4.76 (1H, d, *J* 12.0 Hz), 4.72–4.76 (1H, m), 5.44 (1H, app. dd, *J* 7.0, 15.4 Hz), 5.77 (1H, tdd, *J* 0.8, 6.9, 15.5 Hz), 7.27–7.39 (5H, m); δ_C (100 MHz, $CDCl_3$) 14.1, 22.7, 28.4, 29.0, 29.2, 29.3, 29.49, 29.58, 29.63, 29.67, 31.9, 32.3, 56.7, 71.6, 72.0, 79.7, 85.1, 88.9, 127.7, 127.82, 127.84, 134.3, 137.9, 155.0; HRMS calcd. for $C_{30}H_{49}NO_4Na$ [M^++Na] 510.3559, found 510.3560.

***tert*-Butyl ((3*S*,4*S*,5*S*)-4-hydroxy-5-tetradecyltetrahydrofuran-3-yl)carbamate**

Compound **18a** (45.0 mg, 0.0923 mmol, 100 mol%) was dissolved in MeOH (3 mL). To this solution was added 10 wt-% Pd/C (9.8 mg, 0.0092 mmol, 10 mol%). The flask was evacuated and the atmosphere was first changed to Ar and finally to H_2 (balloon). The mixture was allowed to react for 8 h before it was filtered through a pad of Celite, followed by evaporation of solvents. This Boc-protected compound was used as such in the following step; $[\alpha]_D$ +1.4 (*c* 1.29, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$, 50 °C) 0.88 (3H, t, *J* 6.9 Hz), 1.22–1.35 (24H, br m), 1.45 (9H, s), 1.57–1.65 (2H, m), 2.6 (1H, br s), 3.57 (1H, t, *J* 8.2 Hz), 3.78 (1H, td, *J* 2.9, 6.8 Hz), 4.02 (1H, t, *J* 8.4 Hz), 4.06 (1H, dd, *J* 3.1, 4.6 Hz), 4.27

(1H, m), 5.11 (1H, br d, *J* 7.7 Hz); δ_C (100 MHz, $CDCl_3$, 50 °C) 14.0, 22.6, 26.1, 28.4, 29.3, 29.56, 29.63, 29.66, 29.72, 31.9, 34.8, 54.5, 70.3, 71.9, 79.9, 82.3, 155.8; HRMS calcd. for $C_{23}H_{45}NO_4Na$ [M + Na] 422.3246, found 422.3250.

(2*S*,3*S*,4*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol (Pachastrissamine) 1

The Boc-protected amine from the previous reaction was dissolved in MeOH (2 mL) and cooled to 0 °C. To this solution was added MeOH saturated with gaseous HCl (1 mL). The mixture was stirred at 0 °C for 15 min, before it was allowed to warm to room temperature. After 2 h solvents were evaporated *in vacuo* and the crude HCl salt was partitioned between 1 M NaOH (5mL) and CH_2Cl_2 (5mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 4 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to afford the free base **1** (17.4 mg, 62% from **18a**); $[\alpha]_D$ +18.4 (*c* 1.00, CH_2Cl_2); IR (neat); 3340, 2919, 2854 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0 Hz), 1.25 (24H, br s), 1.67 (2H, m), 2.14 (3H, br s), 3.51 (1H, dd, *J* 7.3, 8.2 Hz), 3.64 (1H, m), 3.73 (1H, ddd, *J* 3.5, 6.5, 7.0 Hz), 3.87 (1H, dd, *J* 3.6, 4.4 Hz), 3.92 (1H, dd, *J* 7.7, 8.2 Hz); δ_C (100 MHz, $CDCl_3$) 14.1, 22.7, 26.3, 29.3, 29.4, 29.58, 29.60, 29.7, 29.8, 31.9, 54.3, 71.7, 72.3, 83.2; HRMS calcd. for $C_{18}H_{37}NO_2Na$ [M + Na] 322.2722, found 322.2730.

***tert*-Butyl ((3*S*,4*S*,5*R*)-4-hydroxy-5-tetradecyltetrahydrofuran-3-yl)carbamate**

Compound **18b** (40.0 mg, 0.082 mmol, 100 mol%) was dissolved in MeOH (2.5 mL). To this solution was added 10 wt-% Pd/C (8.7 mg, 0.0082 mmol, 10 mol%). The flask was evacuated and the atmosphere was first changed to Ar and finally to H_2 (balloon). The mixture was allowed to react for 12 h before it was filtered through a pad of Celite, followed by evaporation of solvents. This Boc-protected compound was used as such in the following step; $[\alpha]_D$ −21.6 (*c* 1.25, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$, 50 °C) 0.88 (3H, t, *J* 6.9 Hz), 1.22–1.36 (24H, br m), 1.45 (9H, s), 1.50–1.58 (2H, m), 2.43 (1H, br s), 3.50 (1H, m), 3.70 (1H, td, *J* 3.1, 4.4 Hz), 3.91 (1H, t, *J* 4.1 Hz), 4.10 (1H, m), 4.12 (1H, t, *J* 7.0 Hz), 5.02 (1H, br s); δ_C (100 MHz, $CDCl_3$, 50 °C) 14.0, 22.6, 25.8, 28.4, 29.3, 29.53, 29.57, 29.60, 29.63, 29.65, 29.67, 31.9, 33.6, 53.2, 70.5, 75.0, 80.0, 85.3, 156.0;; HRMS calcd. for $C_{23}H_{45}NO_4Na$ [M + Na] 422.3246, found 422.3252.

(2*S*,3*S*,4*R*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol 2

The Boc-protected amine from the previous reaction was dissolved in MeOH (2 mL) and cooled to 0 °C. To this solution was added MeOH saturated with gaseous HCl (1 mL). The mixture was stirred at 0 °C for 15 min, before it was allowed to warm to room temperature. After 2 h solvents were evaporated *in vacuo* and the crude HCl salt was partitioned between 1 M NaOH (5 mL) and CH_2Cl_2 (5mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 4 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to afford the free base **2** (16.0 mg, 65% from **18b**); $[\alpha]_D$ +23.0 (*c* 1.00, CH_2Cl_2); IR (neat) cm−1; 3334, 2914, 2853 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 6.5 Hz), 1.24 (24H, br s), 1.54 (2H, m), 2.22 (3H, br s), 3.39 (1H, app. t, *J* 6.1 Hz), 3.41–3.55 (1H, m), 3.61 (2H, m), 4.11 (1H, app. t, *J* 5.9 Hz); δ_C (100 MHz, $CDCl_3$) 14.0, 22.6, 25.8, 29.3, 29.55, 29.58, 29.63, 29.65, 29.67, 31.9, 33.8, 53.1, 73.5, 75.2, 85.3; HRMS calcd. for $C_{18}H_{37}NO_2Na$ [M + Na] 322.2722, found 322.2728.

***tert*-Butyl ((3*S*,4*R*,5*R*)-4-hydroxy-5-tetradecyltetrahydrofuran-3-yl)carbamate**

Compound **18c** (35.0 mg, 0.0072 mmol, 100 mol%) was dissolved in MeOH (2.5 mL). To this solution was added 10 wt-% Pd/C (7.4 mg, 0.0070 mmol, 10 mol%). The flask was evacuated and the atmosphere was first changed to Ar and finally to H_2 (balloon). The mixture was allowed to react for 16 h before it was filtered through a pad of Celite, followed by evaporation of solvents. This Boc-protected compound was used as such in the following step; $[\alpha]_D$ −13.7 (*c* 1.12, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$, 50 °C) 0.88 (3H, t, *J* 6.9 Hz), 1.24–1.35 (24H, m), 1.45 (9H, s), 1.58–1.67 (2H, m), 2.57 (1H, br s), 3.44 (1H, dd, *J* 3.8, 9.5 Hz), 3.80 (1H, dt, *J* 4.2, 6.6 Hz), 3.99 (1H, dd, *J* 5.7, 8.4 Hz), 4.05 (1H, app. d, *J* 2.2 Hz), 4.22 (1H, dd, *J* 6.3, 9.4 Hz), 4.67 (1H, d, *J* 4.7 Hz); δ_C (100 MHz, $CDCl_3$, 50 °C) 14.0, 22.6, 26.4, 28.4, 29.3, 29.57, 29.59, 29.64, 29.66, 29.67, 29.76, 31.9, 60.2, 70.5, 77.6, 80.2, 81.5, 155.7;; HRMS calcd. for $C_{23}H_{45}NO_4Na$ [M + Na] 422.3246, found 422.3240.

(2*S*,3*R*,4*R*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol 3

The Boc-protected amine from the previous reaction was dissolved in MeOH (2 mL) and cooled to 0 °C. To this solution was added MeOH saturated with gaseous HCl (1 mL). The mixture was stirred at 0 °C for 15 min, before it was allowed to warm to room temperature. After 4 h solvents were evaporated *in vacuo* and the crude HCl salt was partitioned between 1 M NaOH (5mL) and CH_2Cl_2 (5mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 4 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to afford the free base **3** (18.8 mg, 84% from **18c**); $[\alpha]_D$ −2.8 (*c* 0.94, CH_2Cl_2); IR (neat); 3360, 2960, 2853 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.8 Hz), 1.25 (24H, br s), 1.52–1.65 (2H, m), 1.73 (3H, br s), 3.38 (1H, dd, *J* 3.4, 9.2 Hz), 3.45 (1H, app. t, *J* 4.2 Hz), 3.80 (1H, dd, *J* 0.9, 3.2 Hz), 3.88 (1H, ddd, *J* 3.3, 6.2, 7.4 Hz), 4.20 (1H, dd, *J* 5.9, 9.1 Hz); δ_C (100 MHz, $CDCl_3$) 14.1, 22.7, 26.4, 29.3, 29.56, 29.57, 29.60, 29.66, 29.8, 31.9, 60.0, 73.8, 79.7, 80.8; HRMS calcd. for $C_{18}H_{37}NO_2Na$ [M + Na] 322.2722, found 322.2723.

***tert*-Butyl ((3*S*,4*R*,5*S*)-4-hydroxy-5-tetradecyltetrahydrofuran-3-yl)carbamate**

Compound **18d** (24.0 mg, 0.049 mmol, 100 mol%) was dissolved in MeOH (2 mL). To this solution was added 10 wt-% Pd/C (5.4 mg, 0.0051 mmol, 10 mol%). The flask was evacuated and the atmosphere was first changed to Ar and finally to H_2 (balloon). The mixture was allowed to react for 16 h before it was filtered through a pad of Celite, followed by evaporation of solvents. This Boc-protected compound was used as such in the following step; $[\alpha]_D$ −18.4 (*c* 0.90, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$, 50 °C) 0.89 (3H, t, *J* 6.9 Hz), 1.24–1.36 (24H, m), 1.46 (9H, s), 1.55–1.70 (2H, m), 3.35 (1H, br s), 3.60 (1H, m), 3.63 (1H, dd, *J* 4.1, 9.6 Hz), 3.77 (1H, dd, *J* 3.8, 5.9 Hz), 3.91 (1H, m), 4.05 (1H, dd, *J* 6.6, 9.5 Hz), 4.75 (1H, br d, *J* 3.4); δ_C (100 MHz, $CDCl_3$, 50 °C) 14.0, 22.7, 25.9, 28.4, 29.3, 29.55, 29.58, 29.64, 29.66, 29.68, 31.9, 33.7, 60.5,

70.5, 80.3, 82.9, 85.0, 156.5; HRMS calcd. for $C_{23}H_{45}NO_4Na$ [M + Na] 422.3246, found 422.3251.

(2*S*,3*R*,4*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol 4

The Boc-protected amine from the previous reaction was dissolved in MeOH (1 mL) and cooled to 0 °C. To this solution was added MeOH saturated with gaseous HCl (1 mL). The mixture was stirred at 0 °C for 15 min, before it was allowed to warm to room temperature. After 4 h solvents were evaporated *in vacuo* and the crude HCl salt was partitioned between 1 M NaOH (5mL) and CH_2Cl_2 (5mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 4 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to afford the free base **4** (11.8 mg, 80% from **18d**); $[\alpha]_D$ −3.2 (*c* 0.88, CH_2Cl_2); IR (neat); 3359, 2924, 2850 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.7 Hz), 1.25 (24H, br s), 1.55–1.67 (2H, m), 2.13 (3H, br s), 3.33 (1H, dd, *J* 4.9, 6.6 Hz), 3.59 (1H, dd, *J* 4.8, 9.4 Hz), 3.62 (2H, m), 4.00 (1H, dd, *J* 5.9, 9.1 Hz); δ_C (100 MHz, $CDCl_3$) 14.0, 22.7, 26.0, 29.3, 29.57, 29.60, 29.65, 29.67, 31.9, 34.0, 60.5, 73.6, 84.1, 85.2; HRMS calcd. for $C_{18}H_{37}NO_2Na$ [M + Na] 322.2722, found 322.2725.

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