Flexible and enantioselective access to jaspine B and biologically active chain-modified analogues thereof†

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Whereas the all-*cis* tetrahydrofuran framework of the cytotoxic anhydrophytosphingosine jaspine B is considered as a relevant pharmacophore, little is known about the influence of the aliphatic chain of this amphiphilic molecule on its activity. We developed a synthetic strategy allowing flexible introduction of various lipophilic fragments in the jaspine's skeleton. The route was validated with two distinct approaches to jaspine B. Five chain-modified analogues were also prepared. Biological evaluation of these derivatives demonstrated a good correlation between their cytotoxicity and their capacity to inhibit conversion of ceramide into sphingomyelin in melanoma cells. A series of potent and selective inhibitors of sphingomyelin production was thus identified. Furthermore, the good overall potency of an ω-aminated analogue allowed us to dissociate of the pharmacological action of jaspine B from its amphiphilic nature.

Introduction

In 2003, Debitus *et al.*[1] disclosed the isolation from the marine sponge *Jaspis* sp. of two related natural products: jaspine B (**1**), which proved identical to the pachastrissamine reported one year before[2] and jaspine A, an oxazolidine derivative of jaspine B (Fig. 1).

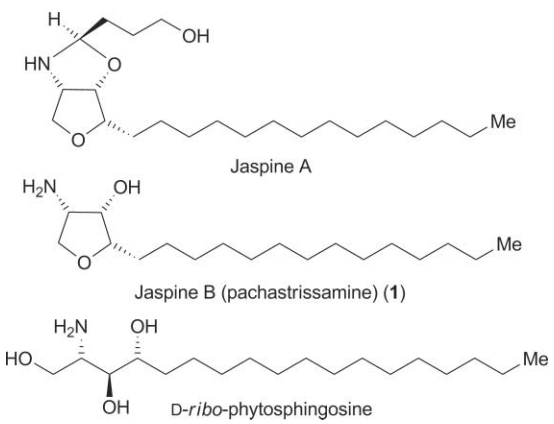

Fig. 1 Natural anhydrophytosphingosines and related sphingoid base.

The jaspines' tetrahydrofuran framework derives from the D-*ribo*-phytosphingosine by a formal cyclodehydration. It shares a stereochemical pattern identical to that of the natural sphingoid base at the C-2/C-3 aminoalcohol fragment and with opposite configuration at C-4 (sphingosine numbering). The natural jaspine B was reported to be strongly cytotoxic (IC_{50} 0.24 μM against A549 cells).[1] We found that jaspine B displays a strong dose- and time-dependent cytotoxicity towards melanoma cells (murine B16 and human SK- Mel28) with an IC_{50} of 0.5 μM.[3] On the other hand, the phytosphingosine was revealed to be approximately 100 times less toxic under the same conditions,[3] pointing out the tetrahydrofuran fragment of jaspines as a relevant pharmacophore. Yet, little is known regarding structure–activity relationship in this series. Delgado and colleagues[4] have reported three diastereoisomeric jaspine B analogues as being 10–20 times less cytotoxic towards A549 cells than the parent all-*cis* tetrahydrofuran. Other observations have been recorded on a distinct cancer cell line (MCF7) by Rao and colleagues.[5] These data indicate a strong impact of the tetrahydrofuran framework stereochemistry on cytotoxicity. The influence of the lipophilic portion of the molecule, on the other hand, was less studied. Jaspine B bears a C14 aliphatic chain that is likely to contribute to its overall biological profile (solubility, interaction with membranes, binding to the target protein). We recently described and evaluated a truncated jaspine B derivative possessing a C8 linear chain.[6] This compound retained a biological activity comparable to that of the parent natural product, thus indicating some room for structural variations in this region of the molecule. Along these lines, we wish to report here our results toward the preparation and biological evaluation of further chain modified jaspine B analogues.

Results and discussion

Chemistry

1. Synthetic approach. Owing to its relatively simple structure and its potent activity, jaspine B has stimulated an important body of synthetic chemistry.[7–11] More than 15 total syntheses of

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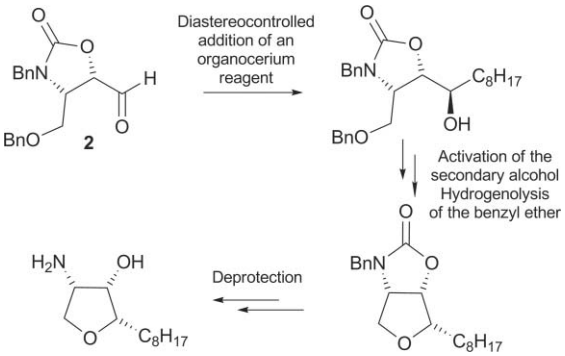
† Electronic supplementary information (ESI) available: Copies of the ^{1}H NMR spectrum for natural jaspine B (**1**) and of the ^{1}H and ^{13}C NMR spectra for all tested compounds (synthetic **1**, **33**, **38**, **40**, **43** and **52**). CCDC reference numbers 769812 and 769813. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c004218h

the natural product and/or stereoisomers have been disclosed since its isolation. Additionally, several hemi-synthetic approaches starting from D-*ribo*-phytosphingosine have been developed. Other synthetic studies led to truncated analogues. In 2007, we reported the first route towards japines' skeleton solely relying on the use of asymmetric synthesis.[6]

Our work was based on the use of the chiral non-racemic aldehyde **2** embedding the four carbon atoms of the polar head of japines (Scheme 1). Diastereoselective *anti*-selective addition of the aliphatic chain relied on the use of an organocerium reagent. In turn, construction of the tetrahydrofuran with the required all-*cis* stereochemical arrangement occurred upon activation of the secondary alcohol and spontaneous intramolecular S_N2 displacement during the hydrogenolytic debenzylation of the primary hydroxyl group. Subsequent deprotection then required Birch reduction to cleave the *N*-benzyl group, strongly reluctant to standard hydrogenolysis conditions.

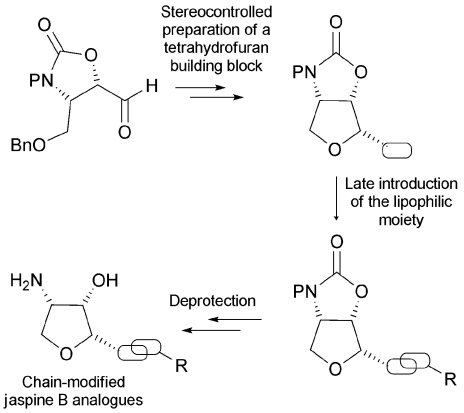


Scheme 1 Our previous synthetic route towards jaspine B skeleton.

We decided to modify our approach, seeking for more flexibility regarding the nature of the lipophilic moiety of the targeted structures. The natural compound jaspine B possesses a marked amphiphilic structure that may greatly influence its interaction with biological membranes (permeation, diffusion, disruption). Subtle alterations of the aliphatic portion of the sphingosine backbone (length, flexibility) of ceramide derivatives were shown to impact their related physico-chemical properties (lateral packing) and hence their overall biological activities.[12] In addition, as pointed out for other single chain sphingolipids,[13] jaspine B may also exert, to some extant, surfactant activity.

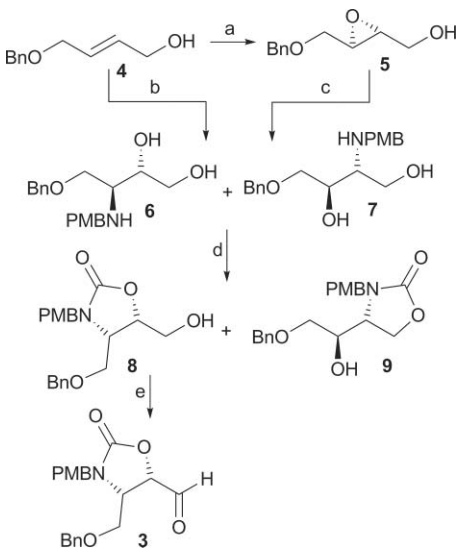
We thus chose to postpone the introduction of this lipophilic fragment to a late stage of the synthetic sequence. The use of a pivotal tetrahydrofuran building block potentially allowing smooth introduction of large variety of lipophilic residues was envisioned (Scheme 2). The appropriate choice of the reactive appendage and the branching methodology was crucial. Two options were considered: a Sonogashira-type coupling onto an acetylenic fragment and an olefin cross-metathesis involving an ethylenic moiety.

2. Second generation aldehyde. In order to warrant smooth deprotection of the nitrogen atom as well as orthogonality with the *O*-benzyl group, we shifted from benzyl to *para*-methoxybenzyl protecting group. Not only it appeared advantageous to avoid the cleavage under Birch conditions, the prospect of preserving an unsaturation in the lipophilic chain was also attractive.



Scheme 2 Our general synthetic approach.

The targeted aldehyde **3** was easily accessed from the *trans*-allylic alcohol **4** or *trans*-epoxyalcohol **5** according to our previous synthetic route (Scheme 3).[6] Practical one pot preparation of aminodiol **6** was realised from the allylic alcohol **4** thanks to an asymmetric *anti*-aminohydroxylation process. After completion of a Sharpless asymmetric epoxidation reaction, reduction of the excess of oxidant with resin-supported Ph_3P followed by addition at room temperature of an excess of Lewis acid and *para*-methoxybenzylamine led to the smooth *in situ* opening of the oxirane. The overall transformation delivered a 65 : 35 mixture (according to ^{1}H NMR analysis) of **6** and its regioisomer **7** in 95% yield. Alternatively, treatment of *trans*-epoxyalcohol **5** in refluxing CH_2Cl_2 with an excess of amine and Ti(O*i*-Pr)$_4$ afforded a 80 : 20 mixture (according to HPLC analysis) of regioisomers **6** and **7** isolated in 83% yield.



Scheme 3 Preparation of the key aldehyde **3**. *Reagents and conditions*: (a) Ref. 6 (b) (i) Ti(O*i*-Pr)$_4$, (–)-DET, *t*-BuOOH, 4 Å MS, CH_2Cl_2, –23 °C; (ii) resin-supported PPh_3, CH_2Cl_2, –23 °C to rt; (iii) Ti(O*i*-Pr)$_4$, $PMBNH_2$, CH_2Cl_2, rt, 95%, **6**/**7** 65 : 35. (c) Ti(O*i*-Pr)$_4$, $PMBNH_2$, CH_2Cl_2, reflux, 83%, **6**/**7** 80 : 20. (d) (i) MeOCOCl, K_2CO_3, THF, rt; (ii) 10% KOH in MeOH, rt, 66% in **8** and 18% in **9**. (e) DMP, CH_2Cl_2, rt, 89%.

The use of Zr(O*i*-Pr)$_4$ in place of the Ti(IV) alkoxide did not affect the course of this reaction.[14] HPLC purification allowed

analysis and separation of the two aminodiols **6** and **7** for complete characterisation. However, it was found to be more practical to carry on the reaction sequence with this mixture. Indeed, the corresponding oxazolidinones **8** and **9** obtained upon treatment with methylchloroformate and subsequent saponification proved easily separable. At this stage, X-ray crystallography analysis of the minor component allowed it unambiguous structural assignment as the oxazolidinone **9** involving the primary alcohol (Fig. 2). Pleasingly, this data confirmed the characterisation initially based on NMR studies in the *N*-benzyl series. Oxidation of the primary hydroxyl group in **8** proceeded uneventfully. Aldehyde **3** was thus prepared in 4 steps and 47% overall yield from allylic alcohol **4**.

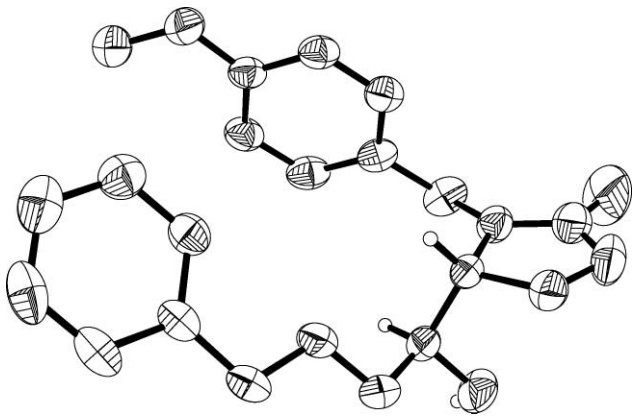
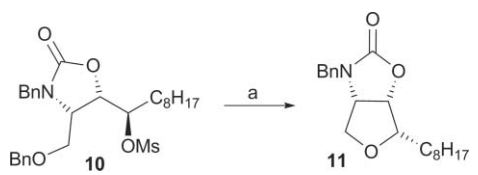


Fig. 2 Molecular view of the oxazolidinone **9** in the solid state (thermal ellipsoids at 50% probability); hydrogen are omitted for clarity excepted on asymmetric carbons and hydroxyl group oxygen.[15]

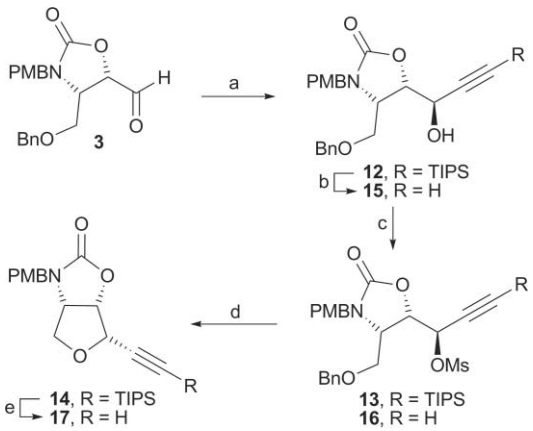
3. Acetylenic and vinylic building blocks. Access to tetrahydrofuran building blocks bearing an unsaturated appendage required new cyclisation conditions. Indeed, in our previous work, the formation of the tetrahydrofuran was triggered by the hydrogenolysis of the *O*-benzyl group. An alternative cyclisation procedure came from a serendipitous finding in the course of preliminary experiments aiming at the intermolecular displacement of the activated secondary alcohol by an amine. Indeed, when mesylate **10** was treated with 1.5 eq. of $BnNH_2$ and 3.0 eq. of Et_3N in DMSO at 80 °C for 20 h the formation of the expected nucleophilic substitution product was not observed. We isolated instead the known all-*cis* tetrahydrofuran **11** in 74% yield and as a single diastereoisomer (Scheme 4).



Scheme 4 Serendipitous finding of the cyclisation procedure. *Reagents and conditions*: (a) $BnNH_2$, Et_3N, DMSO, 80 °C, 74%.

The product was easily identified thanks to a recognisable ^1H NMR signal pattern due to the heterocyclic protons. This finding indicated that the S_N2-type intramolecular cyclisation was highly favoured over an intermolecular displacement of the mesylate. The rigid *cis*-oxazolidinone scaffold likely induced this behaviour, pre-organising the substrate in a reactive conformation. We took advantage of this practical cyclisation procedure in the rest of our study.

Preparation of the acetylenic building block started with the addition of the TIPS-acetylene-derived organocerium reagent onto aldehyde **3** (Scheme 5). Secondary alcohol **12** was obtained as a single diastereoisomer in 65% yield. After mesylation of the secondary alcohol, treatment of **13** under the previously mentioned cyclisation conditions (1.5 eq. of $BnNH_2$, 3.0 eq. of Et_3N, DMSO, 80 °C, 4 h) delivered the expected cyclisation product **14** in 85% yield. At this stage, we assessed the influence of both amines on the reaction course. We observed that the presence of either 1.5 eq. of $BnNH_2$ or 3.0 eq. of Et_3N, under otherwise similar conditions (DMSO, 80 °C, 4 h), was able to promote this transformation with a comparable efficiency (80% isolated yield). We also ran the reaction in the absence of any amine and found that the reaction, despite of being rather sluggish (DMSO, 80 °C, 16 h), was still proceeding very cleanly (80% isolated yield).

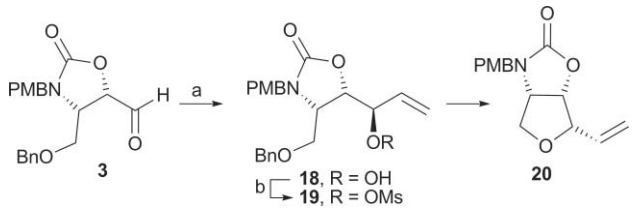


Scheme 5 Preparation of the acetylenic building blocks **14** and **17**. *Reagents and conditions*: (a) TIPSCCLi/$CeCl_3$, THF, −78 °C, 65% yield, 100% d.e. (b) TBAF, THF, −10 °C, 80%. (c) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 84% in **13** from **12**, 98% in **16** from **15**. (d) $BnNH_2$, Et_3N, DMSO, 80 °C, 85% in **14** from **13**, 71% in **17** from **16**. (e) TBAF, THF, −10 °C, 96%.

We speculated that the presence of the sterically demanding TIPS group might be detrimental to the cyclisation process. Deprotection of the acetylenic terminal position was thus achieved with TBAF to give **15**. After mesylation of the hydroxyl group, the cyclisation procedure (1.5 eq. of $BnNH_2$, 3.0 eq. of Et_3N, DMSO, 80 °C, 4 h) was applied to intermediate **16**. Quite surprisingly the latter displayed a reactivity comparable (71% in **17**) to that of its silylated counterpart **13**. Cleavage of the TIPS group was also easily achieved after the cyclisation delivering **17** in high yield.

The vinylic building block was secured using a similar reaction sequence. *Anti*-selective addition of the organocerium reagent prepared from vinyl magnesium bromide led to the formation of secondary alcohol **18** in 51% yield (Scheme 6). Upon activation, this intermediate proved highly reactive. In particular, spontaneous cyclisation of the mesylate **19** was observed during purification over silica gel. This led to the one-pot formation of tetrahydrofuran **20** in 87% yield from **18**.

Importantly, the exact structure of **20** was confirmed by X-ray diffraction analysis of a single crystal (Fig. 3). These data gave insight into the cyclisation process, indicating a neat



Scheme 6 Preparation of the vinylic building block **20**. *Reagents and conditions*: (a) $C_2H_5MgBr/CeCl_3$, THF, −78 °C, 51% yield, 100% d.e.. (b) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 87% in **20** from **18**.

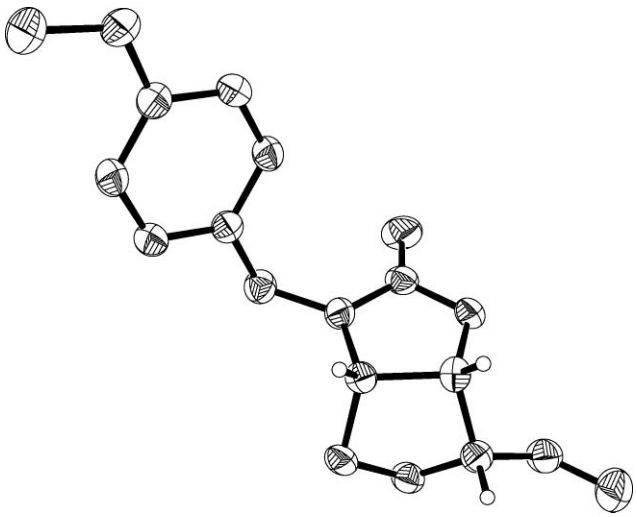
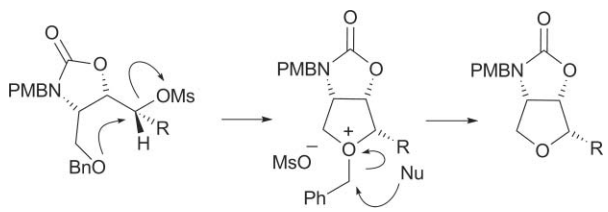


Fig. 3 Molecular view of the oxazolidinone **20** in the solid state (thermal ellipsoids at 50% probability); hydrogen atoms are omitted for clarity excepted on asymmetric carbons.[16]

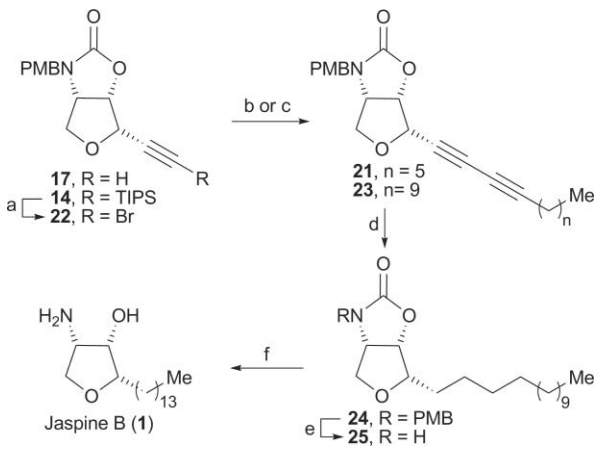
intramolecular S_N2 process with inversion of configuration at the activated allylic position.

Gathering these experimental data, one can suggest a mechanism for the cyclisation step (Scheme 7). The process would be initiated by the intramolecular attack of a lone pair of the *O*-benzyl group oxygen atom onto the activated secondary position. The thus formed oxonium intermediate would in turn suffer an intermolecular nucleophilic attack at the benzylic position leading to the cleavage of the C–O bond. The exact nature of the nucleophilic species remained undetermined. Although the reaction was accelerated by the presence of amines, traces of water might also account for this debenzylation. The higher reactivity of the allylic mesylate compared to its propargylic counterpart may be correlated to the stronger electron-withdrawing effect of the vinylic appendage.



Scheme 7 Proposed mechanism for the cyclisation process.

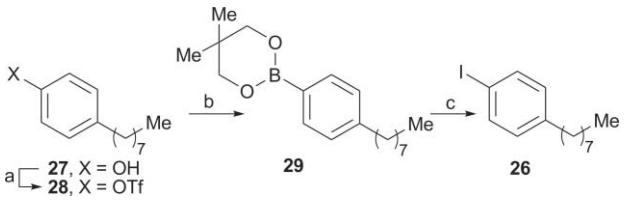
4. First synthesis of jaspine B and preparation of aromatic ring-containing chain-modified analogues. With an access to the acetylenic building block **17**, we studied the branching of an aliphatic chain. One option was the simple alkylation of the corresponding lithium acetylide. Ramana and co-workers[17] reported a similar transformation in the course of their synthesis of jaspine B. However, in our case, treatment of alkyne **17** with *n*-BuLi in THF/HMPA at low temperature led to complete decomposition and subsequent alkylation met with failure. We thus turned our attention to a palladium-catalysed Sonogashira-type reaction with the prospect of preparing a diyne intermediate by means of an sp–sp coupling. Gently reacting the alkyne **17** at room temperature with 1-bromooctyne[18] in the presence of $PdCl_2(PPh_3)_2$, CuI and *i*-$PrEt_2N$ afforded the expected coupling product **21** in 24% yield (Scheme 8). Reasoning that the instability of the acetylide derived from **17** might be responsible for this moderate efficiency, we decided to introduce this building block as the halide reagent of the Sonogashira coupling. The bromide **22** was secured applying the one-pot desilylation/bromination procedure reported by Kim and co-workers.[19] Treatment of the TIPS-protected acetylene **14** with NBS and AgF delivered **22** in high yield as a stable solid. When the latter was subjected to the identical coupling conditions, diyne **21** was isolated in 48% yield. We thus decided to apply this transformation to the synthesis of jaspine B. Coupling of bromide **22** with 1-dodecyne proceeded with comparable efficiency. Nearly quantitative hydrogenation of the thus formed diyne **23** led to the protected jaspine B **24**. The overall efficiency of these two transformations was slightly increased avoiding purification of the intermediate diyne (35% overall yield in **24** from bromide **22**). Finally, a two-step deprotection sequence including oxidative cleavage of the PMB group to give **25** and saponification of the carbamate delivered jaspine B (**1**). Our synthetic material displayed spectral and physico-chemical data in agreement with that of a sample of the natural compound.



Scheme 8 The route to jaspine B from acetylenic building blocks **14** and **17**. *Reagents and conditions*: (a) NBS, AgF, MeCN, 93%. (b) 1-Bromooct-1-yne, $Pd(PPh_3)_2Cl_2$, CuI, *i*-Pr_2NH, THF, 24% in **21** from **17**. (c) Oct-1-yne or tetradec-1-yne, $Pd(PPh_3)_2Cl_2$, CuI, *i*-Pr_2NH, THF, 48% in **21** or 32% in **23** from **22** respectively. (d) $Pd(OH)_2$, H_2, AcOEt–MeOH, 94%. (e) CAN, MeCN–H_2O, 63%. (f) KOH, EtOH–H_2O, 85 °C, 70%.

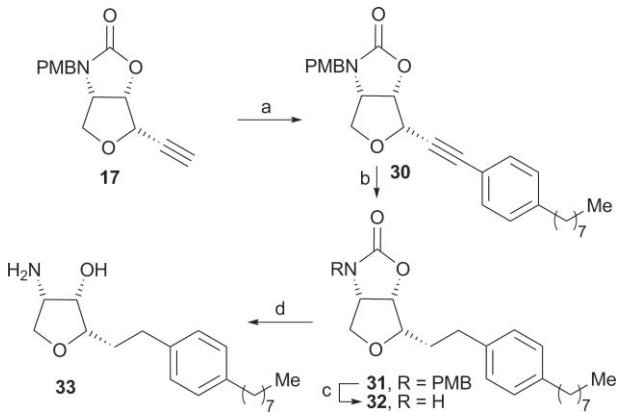
We then exploited this synthetic route for the preparation of chain-modified analogues of jaspine B. We focused on the introduction of a phenyl moiety in the aliphatic portion of the molecule. This type of structural rigification already proved

beneficial for activity in the development of the immunosuppressive agent FTY 720, a sphingosine-1-phosphate receptor agonist.[20] Branching of the aromatic nucleus was smoothly accomplished by means of a Sonogashira coupling with alkyne **17**. 1-Iodo-4-octylbenzene (**26**) was considered as a representative aromatic halide. The latter was prepared from the corresponding phenol **27** in 48% overall yield using the following three-step procedure: (1) formation of the triflate **28**; (2) Pd-catalysed borylation using bis(neopentylglycato)diboron[21] yielding to **29** and (3) treatment with *in situ* generated iodine[22] (Scheme 9).



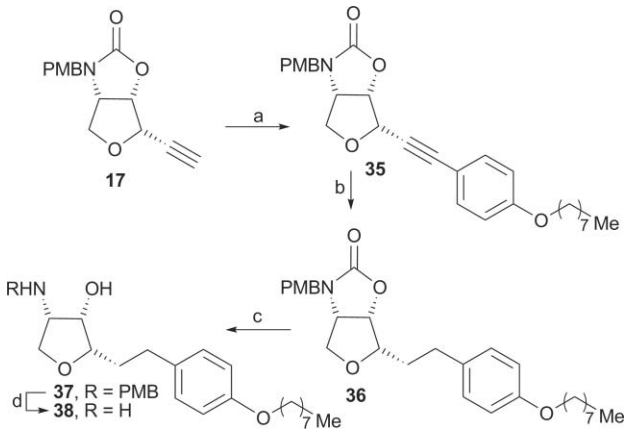
Scheme 9 Preparation of the iodide **26**. *Reagents and conditions*: (a) pyridine, $(CF_3SO_2)O$, CH_2Cl_2, –10 °C, 99%. (b) $PdCl_2$(dppf), KOAc, bis(neopentylglycato)diboron, DMSO, 80 °C, 50%. (c) Chloramine-T, NaI (0.1% solution in aq. NaOH), THF–H_2O, 98%.

Reaction of the iodide **26** with alkyne **17** smoothly delivered the expected coupling product **30** in 77% yield (Scheme 10). After saturation of the triple bond under hydrogenation conditions, treatment with CAN giving **32** and saponification of the oxazolidinone efficiently led to the jaspine B analogue **33**.



Scheme 10 Preparation of the jaspine B analogue **33**. *Reagents and conditions*: (a) iodide **26**, $Pd(PPh_3)_2Cl_2$, CuI, *i*-Pr_2NH, THF, 77%. (b) $Pd(OH)_2$, H_2, AcOEt–MeOH, 99%. (c) CAN, MeCN–H_2O, 90%. (d) KOH, EtOH–H_2O, 85 °C, 99%.

The flexibility of this route was illustrated in preparing another aromatic derivative. We selected 1-(octyloxy)-4-iodobenzene (**34**) as the halide partner of the Sonogashira coupling due to its ready access by etherification of 4-iodophenol (1.5 eq. *n*-OctI, 2.5 eq. Cs_2CO_3, CH_3CN, 85 °C, 99% yield). The Pd-catalysed coupling proceeded as before and the catalytic hydrogenation of **35** delivered the saturated intermediate **36** in high yield (Scheme 11). However in the course of the CAN-promoted deprotection of the PMB group, the benzylic methylene was readily oxidised to yield the corresponding ketone (as notably indicated by a peak at δ 195.4 ppm in ^{13}C NMR and an absorption at $\nu_{C=O}$ 1712 cm^{-1} in IR). The presence of the electron-donating *para*-octyloxy substituent is

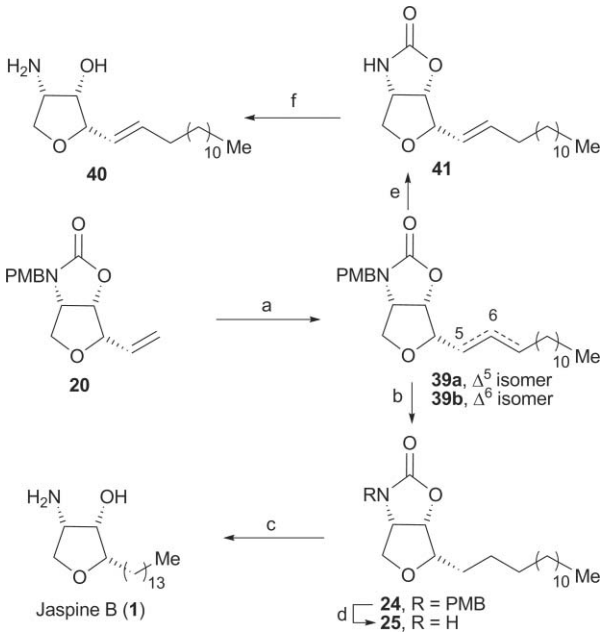


Scheme 11 Preparation of the jaspine B analogue **38**. *Reagents and conditions*: (a) iodide **34**, $Pd(PPh_3)_2Cl_2$, CuI, *i*-Pr_2NH, THF, 69%. (b) $Pd(OH)_2$, H_2, AcOEt–MeOH, 97%. (c) KOH, EtOH–H_2O, 85 °C, 68%. (d) $Pd(OH)_2$, H_2 (10 bar), CH_2Cl_2–MeOH, 96%.

likely to be responsible for this reactivity. We thus first hydrolyzed the carbamate and accomplished the hydrogenolysis of the PMB group in **37** under 10 bar of H_2 in CH_2Cl_2–MeOH to obtain the targeted analogue **38** in 65% overall yield from **36**.

5. Second synthesis of jaspine B and preparation of unsaturated and ω-functionalised chain-modified jaspine B analogues. In the last part of this work, we studied the use of the vinylic building block **20** as a precursor of the jaspine B and chain-modified analogues. Our plan was to rely on olefin cross metathesis reaction to introduce the lipophilic portion of the molecule.[23] There again, we first targeted jaspine B in order to validate the synthetic route. Treatment of olefin **20** with 1-tetradecene in the presence of the Grubbs' II catalyst in refluxing CH_2Cl_2 led to a 70 : 30 mixture (as estimated by ^1H NMR) of isomeric olefins in 72% isolated yield. Careful NMR analysis (COSY, HSQC and HMBC 2D experiments) confirmed that the main reaction product was the expected Δ^5-*E*-unsaturated derivative **39a** (Scheme 12). On the other hand, NMR homo- and heteronuclear correlation experiments revealed that the minor component of the olefin mixture was another *E*-isomer resulting from the isomerisation of the unsaturation. Moreover, the presence of an apparent triplet at 2.47 ppm due to a methylene both adjacent to the olefin and the tetrahydrofuran ring was a clear indication of the formation of the Δ^6-isomer **39b**. Isomerisation is a well-known side reaction of the olefin metathesis.[24] However, double bond relocation giving the Δ^6-isomer was quite unexpected. Precedents have shown that the shift toward a trisubstituted enol ethers can be sterically impeded.[25] Catalytic hydrogenation of the mixture of olefins **39a**,**b** led to the saturated intermediate **24** in almost quantitative yield. The final two-step deprotection sequence proceeded uneventfully to deliver synthetic jaspine B (**1**). Analytical data of this sample revealed essentially identical to that of obtained with the jaspine B prepared *via* the previous route.

So as to demonstrate the flexibility of our synthetic approach, we also prepared the Δ^5-unsaturated jaspine B analogue **40** (Scheme 12). Noteworthy, the presence and the precise location of the unsaturation of the sphingosine backbone of ceramide are known to influence its biological functions.[26] The mixture of olefins **39a**,**b** was thus subjected to *N*-deprotection with CAN. The



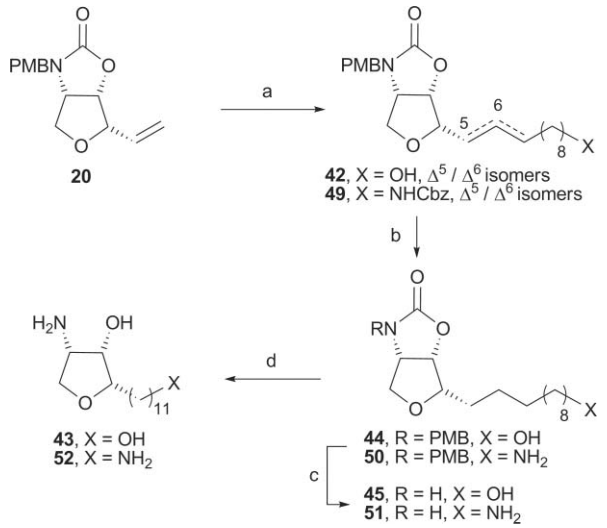
Scheme 12 The route to jaspine B (**1**) and its Δ^5-unsaturated analogue **40** from vinylic building block **20**. *Reagents and conditions*: (a) Grubbs' II, CH_2Cl_2, reflux, 72%, Δ^5-**39a**/Δ^6-**39b** 70 : 30. (b) $Pd(OH)_2$, H_2, AcOEt–MeOH, 94%. (c) CAN, MeCN–H_2O, 63%. (d) KOH, EtOH–H_2O, 85 °C, 70%. (e) CAN, MeCN–H_2O, 37%. (f) KOH, EtOH–H_2O, 85 °C, 64%.

transformation delivered Δ^5-unsaturated intermediate **41** as a sole product in 37% yield (56% yield based on the starting Δ^5-**39a**), possibly as a result of the decomposition of the minor Δ^6-isomer **39b** under these oxidative conditions. The final saponification of the oxazolidinone ring afforded the targeted Δ^5-unsaturated jaspine B analogue **40** in 64% yield.

We wished to take advantage of the present synthetic approach to ω-functionalised with a polar residue the jaspine B skeleton in order to annihilate its amphiphilic nature. Indeed it has been shown that amphiphilic aminoalcohols (*N*-alkyl iminosugars) interacting with sphingolipid metabolism were able to exert cytotoxicity through local membrane disruption and cell fragmentation, and this at concentrations below their critical micelle concentration (CMC).[27] We confirmed experimentally by the hanging drop technique the marked surfactant behaviour (CMC 500 μM)[3] of jaspine B chlorohydrate, this amine being likely protonated at physiological pH.

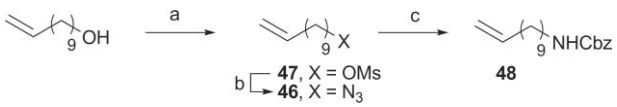
Toward this aim, introduction of a terminal hydroxyl group was first considered. Olefin cross metathesis with undec-10-en-1-ol under the previously used conditions produced a 66 : 34 mixture of olefins **42** (as indicated by reverse phase LC/MS analysis) in 77% yield. The composition of this mixture was assigned to the Δ^5- and Δ^6-isomers **42** on the basis of the previous example (Scheme 13). Worth of note, its ^{1}H NMR spectra displayed a methylene signal as an apparent triplet at 2.42 ppm for the minor Δ^6 component. The expected ω-hydroxylated jaspine B analogue **43** was secured from this mixture in 64% overall yield by means of a three-step sequence including saturation of the double bonds yielding **44** and deprotection of the aminoalcohol moiety (Scheme 13).

Finally, we targeted an analogue of jaspine B bearing a protonable terminal primary amine. 11-Azidoundec-1-ene (**46**) was



Scheme 13 Preparation of ω-functionalised jaspine B analogues **43** and **52**. *Reagents and conditions*: (a) undec-10-en-1-ol or olefin **48**, Grubbs' II, CH_2Cl_2, reflux, 77% in **42** (Δ^5/Δ^6 66 : 34) or 65% in **49** (Δ^5/Δ^6 70 : 30) respectively. (b) $Pd(OH)_2$, H_2, AcOEt–MeOH, 86% in **44** and 92% in **50**. (c) CAN, MeCN–H_2O, 73% in **45** and 41% in **51**. (d) KOH, EtOH–H_2O, 85 °C, 85% in **43** and 78% in **52**.

first considered as the olefin cross metathesis partner. The latter was obtained from undec-10-en-1-ol *via* mesylate **47** following standard procedures (Scheme 14). However, olefin **46** proved reluctant to cross metathesis under standard procedure (1.0 eq. of **20**, 5.0 eq. of **46**, 0.15 eq. of Grubbs' II catalyst, CH_2Cl_2, reflux, 24 h). Examples of olefins metathesis reaction impeded by an azido group have been reported.[28] Interestingly, no dimerisation of the vinylic building block **20** could be evidenced neither. We thus shifted to the NHCbz derivative **48**, readily prepared treating the corresponding azide with Me_3P in the presence of benzyl chloroformate, according to Vilarrasa's protocol (Scheme 14).[29]



Scheme 14 Preparation of the olefin **48**. *Reagents and conditions*: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 98%. (b) NaN_3, DMSO, 50 °C, 92%. (c) Me_3P, CbzCl, THF, 54%.

When an excess of olefin **48** was reacted as before with the tetrahydrofuran intermediate **20**, 65% of a mixture of olefins **49** was isolated (Δ^5/Δ^6-isomers *ca.* 70 : 30 by ^{1}H NMR). Catalytic hydrogenation both cleanly saturated the double bonds and hydrogenolysed the benzyloxycarbonyl group yielding **50**. The deprotection sequence delivered the ω-aminated jaspine B analogue **52** in 32% overall yield from **50**.

Biology

The ability of chain-modified jaspine B analogues to inhibit tumour cell growth was evaluated in B16 melanoma cells by MTT assay and the natural product was used as a positive control. As shown in Fig. 4, the synthetic jaspine B (**1**) exhibited a dose-dependent cytotoxicity comparable to the lethal effects of the natural compound (IC_{50} 0.5 μM). The ω-aminated analogue

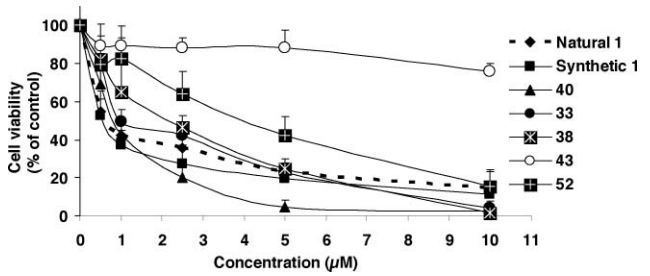


Fig. 4 Comparative cytotoxic dose-dependent effects of natural and synthetic jaspine B as well as chain-modified analogues **33**, **38**, **40**, **43** and **52** on B16 melanoma cells viability. Cells were incubated for 24 h with the indicated concentrations of each compound in the absence of FCS in the medium. Then, cell viability was assessed by MTT. Data are expressed as percentage of the values measured in the absence of the molecules and are the mean ± S.E.M. of at least three independent experiments performed in triplicate.

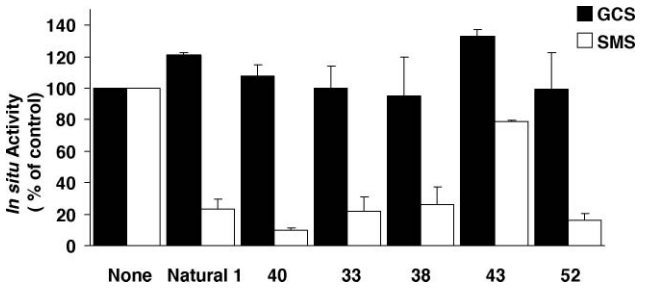


Fig. 5 Effect of natural jaspine B and chain-modified analogues **33**, **38**, **40**, **43** and **52** on SMS and GCS activities in B16 melanoma cells. Cells were incubated for 6 h in the absence or presence of each compound at 5 μM and further incubated up to 2 h with C6-NBD-ceramide at 5 μM. Cells were collected and the specific activities of GCS and SMS were determined by quantifying the fluorescence of NBD-C6-SM and NBD-C6-GlcCer. Results are expressed as the percentage of the activities measured in the absence of compounds. Data are means ± S.E.M. of at least three independent experiments.

52 retained a substantial cytotoxicity (IC_{50} 4 μM). On the other hand, its hydroxylated counterpart **43** proved not cytotoxic at the concentrations used. Further analysis revealed that treatment with increased doses of **43** had a small effect on the survival of B16 melanoma cells (71% of survival at 80 μM). Both aromatic analogues **33** and **38** displayed cytotoxicity comparable to that of the natural anhydrophytosphingosine with IC_{50} values of 1 μM and 2.2 μM respectively. Finally, compound **40**, containing the C_5–C_6 unsaturation, was the most active among all the chain-modified derivatives tested. Its effect on B16 melanoma cells (IC_{50} 0.75 μM) was equivalent to the cytotoxicity displayed by the natural compound.

In addition, we also investigated the effects of chain-modified jaspine B analogues on sphingomyelin synthase (SMS) activity, an enzyme that restores homeostasis between sphingomyelin and ceramide pools.[30] Indeed, there is a growing body of evidence highlighting the role played by SMS as a putative regulator of cancer cell growth and resistance to chemotherapy.[31] Moreover, few selective SMS inhibitors have been identified to date.[32–34] We recently observed that jaspine B was able to kill melanoma cells by increasing the intracellular levels of pro-apoptotic ceramide through the inhibition of its conversion into sphingomyelin (SM). The *in situ* SMS activity was measured by incubating intact living cancer cells with a fluorescent analogue of ceramide that is converted into fluorescent SM. Under these experimental conditions, short-chain fluorescent ceramide is also converted into fluorescent glucosylceramide (GlcCer), allowing quantification of the activity of another important ceramide-metabolizing enzyme, named glucosylceramide synthase (GCS). As illustrated in Fig. 5, the natural jaspine B (**1**) itself inhibited 78% of the production of SMS at 5 μM. The analogue **52** bearing a terminal amino group on the aliphatic chain also revealed a good inhibitor of the conversion of ceramide into SM (84% of inhibition). In sharp contrast, the ω-hydroxylated analogue **43** was only weakly potent. The aromatic derivatives **33** and **38** displayed 78% and 74% of inhibition respectively, an activity comparable to that observed for jaspine B. Finally, the Δ^5-unsaturated jaspine B derivative **40** elicited the strongest decrease in SMS activity reaching 90% inhibition at 5 μM. The GCS activity was not significantly modified upon treatment with all the different analogues.

The overall biological activity observed for the ω-aminated derivative **52**, a non-amphiphilic analogue, is in agreement with the notion that jaspine B essentially exerts its effect on cell viability through a pharmacological effect. On the other hand, the observed drop in potency for the hydroxylated compound **43** reinforced the relationship between jaspine B-induced SMS inhibition and cell death. Rapid *in cellulo* functionalisation of the terminal hydroxyl group (*i.e.* acylation, as reported for ω-hydroxylated ceramide in keratinocytes)[35] might be responsible for such a lack of activity. Interestingly, most of the compounds tested revealed good inhibitors of the conversion of ceramide into SM, and not into GlcCer, indicating a good selectivity regarding this cellular manifold. Moreover, the inhibitory potency of the unsaturated jaspine B **40** analogue proved higher than that of the parent natural compound at 5 μM.

Conclusions

By means of an original cyclisation procedure, two enantioenriched building blocks **17** and **20** embedding the protected tetrahydrofuran core of the jaspine B were prepared from the pivotal aldehyde **3** in two to four steps and 44% overall yield. From the acetylenic intermediate **14**, the use of a Sonogashira coupling allowed us to accomplish a first synthesis of jaspine B. Two phenyl ring-containing chain-modified analogues were also accessed in 44–68% overall yield following a similar four-step sequence from **17**. Application of an olefin cross metathesis reaction to the building block **20** led to jaspine B in four steps and 11% overall yield. This route also allowed us to prepare the Δ^5-*E* analogue of the natural compound. Furthermore, two ω-functionalized derivatives were synthesised in four steps and 19–41% overall yield from **20**.

These five new chain-modified jaspine B analogues were evaluated regarding their capacity to inhibit growth of murine melanoma B16 cells. All the compounds displayed cytotoxicity in the same order of magnitude as the natural and synthetic jaspine B, with the exception of the ω-hydroxylated derivative that only displayed a marginal activity. The unsaturated analogue **40** revealed the most cytotoxic member of the series with an IC_{50} of 0.75 μM. We also assessed the inhibitory effect of these jaspine

B analogues on the conversion of ceramide into sphingomyelin in intact living B16 cells. A good correlation between the inhibition of sphingomyelin production and the cytotoxicity was observed. The most efficient compound was again the unsaturated analogue **40** that displayed a 90% inhibition at 5 μM, without altering the glucosylceramide production. We thus described here a series of potent and selective sphingomyelin synthase inhibitors. Furthermore, the good overall potency of the ω-aminated analogue allowed us to dissociate the pharmacological action of jaspine B from its amphiphilic character. The tolerance for such a terminal substitution also opens prospects for eventual immobilization of jaspine B on solid support or tagging with a fluorescent probe. Further works along these lines are in progress in our laboratory and will be reported in due course.

Experimental

General details

The following solvents and reagents were dried prior to use: CH_2Cl_2, MeOH, DMF (from calcium hydride), 1,2-dimethoxyethane, Et_2O, petroleum ether, THF, toluene (freshly distilled from sodium/benzophenone), Et_3N (from calcium hydride, stored over potassium hydroxide pellets). Analytical thin layer chromatography (TLC) was performed using Merck silica gel $60F_{254}$ precoated plates. Chromatograms were observed under UV light and/or were visualised by heating plates that were dipped in 10% phosphomolybdic acid in ethanol or Dragendorff reagent. Column chromatographies were carried out with SDS 35–70 μm flash silica gel. LC-MS analyses and preparative HPLC purifications were done using a Waters Autopurif apparatus. Analytical HPLC analyses were run with an Alliance 2695 pump and a PDA 2996 UV detector. NMR spectroscopic data were obtained with Bruker Advance 300. Chemical shifts are quoted in parts per million (ppm) relative to residual solvent peak. *J* values are given in Hz. For matter of homogeneity, sphingolipid numbering is used for NMR assignment throughout the experimental section. Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR 1725X spectrometer. Mass spectrometry (MS) data were obtained on a ThermoQuest TSQ 7000 spectrometer. High-resolution mass spectra (HRMS) were performed on a ThermoFinnigan MAT 95 XL spectrometer. Optical rotations were measured on a Perkin-Elmer model 241 spectrometer. For crystallographic analysis, the selected crystals were mounted on a glass fibber using perfluoropolyether oil and cooled rapidly in a stream of cold N2. The data were collected on a Bruker-AXS APEX II diffractometer equipped with the Bruker Kryo-Flex cooler device and using a graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods (SHELXS-97[36] or SIR92[37]) and all non-hydrogen atoms were refined anisotropically using the least-squares method on F^2.[38] Natural jaspine B was purified from crude extracts of the sponge *Jaspis* sp. kindly provided by Dr C. Debitus (UMR 152 IRD, Toulouse, France). DMEM, trypsin–EDTA and fetal calf serum (FCS) were from Invitrogen (Cergy-Pontoise, France). 3-(4,5-Dimethylthiazol-2-yl)-,5-diphenyltetrazolium bromide (MTT) was supplied from Euromedex (Mundolsheim, France). C_6-NBD-ceramide was purchased from Interchim (Montluçon, France). Murine B16 melanoma cell line was purchased from American Type Culture Collection (LGC, Molsheim, France).

General procedures

Organocerium addition onto aldehyde 3. A suspension of anhydrous $CeCl_3$ (5.0 eq.) in anhydrous THF (0.5 M) under nitrogen atmosphere was stirred overnight at room temperature. The suspension of $CeCl_3$ was cooled to −78 °C and the organolithium or organomagnesium solution was added dropwise. The reaction mixture was stirred at −78 °C for 1 h. Aldehyde **3** (1.0 eq.) in solution in anhydrous THF (0.5 M) was then added and the mixture stirred at −78 °C for 6 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl and the mixture was directly filtered over Celite eluted by AcOEt. The aqueous layer was extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuum.

Mesylation of the secondary alcohols. To solution of alcohol (1.0 eq.) in anhydrous CH_2Cl_2 (0.6 M) at 0 °C under nitrogen atmosphere was added Et_3N (1.5 eq.). After 15 min of stirring at the same temperature mesyl chloride (1.5 eq.) was added and the solution was stirred at 0 °C for 30 min then at room temperature for 1 h. The reaction was quenched by addition of water and the mixture was extracted three times with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuum.

Cyclisation of the mesylates. To a solution of mesylate (1.0 eq.) in anhydrous DMSO (0.1 M) at room temperature and under nitrogen atmosphere was added Et_3N (3.0 eq.) and $BnNH_2$ (1.5 eq.). The solution was heated at 80 °C with stirring for 4 h. The mixture was then diluted with CH_2Cl_2 and the reaction quenched by addition of water. The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated in vacuum.

Hydrogenation of the double and triple bonds. A solution of unsaturated compound (1.0 eq.) in AcOEt–MeOH 1/1 (0.1 M) containing $Pd(OH)_2$ (20 wt%) was stirred under H_2 at atmosphere pressure (balloon) overnight. The reaction mixture was then filtered over Celite. The precipitate was rinsed with CH_2Cl_2 and the filtrate was concentrated in vacuum.

Saponification. KOH (10 eq.) was added to a solution of oxazolidinone (1.0 eq.) in EtOH–H_2O (8 : 2) (0.05 M). The mixture was heated at 85 °C for 7–10h (TLC monitoring) before being cooled to room temperature and diluted with AcOEt and brine. The mixture was extracted three times with AcOEt and the combined extracts were concentrated in vacuum.

Oxidative cleavage of the *p*-methoxybenzyl group. To a solution of *N*-PMB intermediate (1.0 eq.) in CH_3CN–H_2O (9 : 1) (0.05 M) was added CAN (6.0 eq.). The mixture was stirred at room temperature for 2 h, then diluted with water and extracted three times with AcOEt. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and with brine, dried over $MgSO_4$ and concentrated in vacuum.

***C*-desilylation.** To a solution of trialkylsilyl intermediate (1.0 eq.) in THF (0.1 M) at −10 °C was added TBAF (1.2 eq. as a 1 M solution in THF). The mixture was stirred at −10 °C for 1 h before being diluted with AcOEt and water. The mixture was

extracted three times with AcOEt and the combined extracts were concentrated in vacuum.

Sonogashira coupling. To a solution of alkyne (1.0 eq.) and halide (1.2 eq.) in degassed THF (0.1 M) under argon in the dark was added $Pd(PPh_3)_2Cl_2$ (0.02 eq.), CuI (0.02 eq.) and diisopropylamine (2.5 eq.). The reaction mixture was stirred for 4 h at room temperature and quenched with saturated NH_4Cl solution. The mixture was extracted at three times with AcOEt and the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuum.

Olefin cross metathesis. To a solution of vinyl derivative (1.0 eq.) and alkene (5.0 eq.) in degassed CH_2Cl_2 (0.1 M) and under argon was added Grubbs' II catalyst (0.15 eq.). The reaction mixture was heated at reflux with stirring under N_2 for 20 h. The solution was cooled to room temperature and concentrated in vacuum.

(2*S*,3*S*)-4-(benzyloxy)-3-(4-methoxybenzylamino)butane-1,2-diol 6 and (2*S*,3*S*)-4-(benzyloxy)-2-(4-methoxybenzyl-amino)-butane-1,3-diol 7. Procedure A (from allylic alcohol **4**): to a solution of Ti(O*i*-Pr)$_4$ (100 µL, 0.35 mmol) in anhydrous CH_2Cl_2 (1.0 mL) containing 4 Å molecular sieves (100 mg) at −23 °C and under nitrogen atmosphere was added (−)-diethyl tartrate (90 µL, 0.52 mmol). The mixture was stirred for 10 min and a solution of allylic alcohol **4** (314 mg, 1.76 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was added. After 30 min of stirring, *t*-butyl hydroperoxide (640 µL of a 5.5 M solution in decane, 3.52 mmol) was added. The mixture was then stirred at −23 °C for 72 h after which anhydrous CH_2Cl_2 (16 mL) was added followed by Ph_3P supported on resin (1.7 g at 1–1.5 mmol g^{-1}, 1.70–2.55 mmol). The stirring continued for 5 h at room temperature. Anhydrous *p*-methoxybenzylamine (500 µL, 2.1 mmol) was then added followed by Ti(O*i*-Pr)$_4$ (1.50 mL, 5.17 mmol) and the mixture allowed to stir at room temperature for 72 h. The resin was filtered off and to the filtrate was added a 10% aqueous NaOH solution saturated in NaCl (1.7 mL). After 5 h of vigorous stirring at room temperature, the mixture was filtered over Celite®, the cake was rinsed with CH_2Cl_2 and the solution concentrated in vacuum. The crude material was purified by column chromatography on SiO_2 eluting with AcOEt–MeOH–NH_4OH (97 : 2 : 1) to give a 65 : 35 mixture (according to ^{1}H NMR analysis) of **6** and **7** (390 mg, 95%) as a colourless oil.

Procedure B (from epoxyalcohol **5**): to a solution of epoxyalcohol **5** (1.9 g, 10.2 mmol) in anhydrous CH_2Cl_2 (40 mL) at room temperature and under nitrogen atmosphere was added Ti(O*i*-Pr)$_4$ (10.6 mL, 35.7 mmol). The mixture was stirred for 1 h and anhydrous *p*-methoxybenzylamine (3.30 mL, 25.5 mmol) was added. The mixture was then stirred at 45 °C for 24 h. The reaction was quenched by addition of a 10% aqueous NaOH solution saturated in NaCl (50 mL). After 5 h of vigorous stirring at room temperature, the mixture was filtered over Celite® and extracted three times with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated in vacuum. The crude material was purified by column chromatography on SiO_2 eluting with AcOEt–MeOH–NH_4OH (98.8 : 1 : 0.2 to 97.8 : 2 : 0.2) to give mixture of **6** and **7** (2.3 g, 83%) as a colourless oil. Analytical HPLC (Sunfire C18, 5 µ, 4.6 × 150 mm, 1 mL min^{-1}, MeOH/0,1% aqueous TFA, R_t minor 4.20 min, R_t Major 4.58 min) of this mixture indicated a 80 : 20 ratio. Analytical samples of compounds **6** and **7** were isolated by semi-preparative HPLC (Sunfire C18, 5 µ, 19 × 150 mm, 15 mL min^{-1}, λ 273 nm) eluting with PE–*i*-PrOH–Et_2NH (69.8 : 30 : 0.2).

Major compound 6. $[\alpha]_D^{20}$ +27.1 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3366 and 2861; δ_H (300 MHz, $CDCl_3$) 7.39-7.27 (5H, m, OCH_2Ph), 7.20 (2H, d, ^3J 8.6, NCH_2Ph), 6.85 (2H, d, ^3J 8.6, NCH_2Ph), 4.50 (2H, ABq, $\Delta\delta$ 15.8, $^2J_{gem}$ 11.9, OCH_2Ph), 3.84-3.72 (6H, m, NCH_2Ph, OCH_3, 2-H), 3.68-3.62 (4H, m, 2 × 1-H and 2 × 4-H), 3.15 (1H, bs, OH) and 2.87 (1H, dt, ^3J 5.8 and 4.7, 3-H); δ_C (75 MHz, $CDCl_3$) 158.6, 137.6, 131.6 (Cq, Ph), 129.3, 128.3, 127.7, 127.6, 113.7 (CH, Ph), 73.2 (OCH_2Ph), 70.0 (C-2), 68.0 (C-4), 65.1 (C-1), 59.6 (C-3), 55.1 (OCH_3) and 50.9 (NCH_2Ph); *m*/*z* (HRMS, CI) 332.1866 (M + H$^+$, $C_{19}H_{26}NO_4$ requires 332.1862).

Minor compound 7. $[\alpha]_D^{20}$ +4.6 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3298 and 2930; δ_H (300 MHz, $CDCl_3$+D_2O) 7.40-7.28 (5H, m, OCH_2Ph), 7.22 (2H, d, ^3J 8.6, NCH_2Ph), 6.84 (2H, d, ^3J 8.6, NCH_2Ph), 4.53 (2H, s, OCH_2Ph), 3.92 (1H, dt, ^3J 6.1 and 5.0, 2-H), 3.94 (3H, s, OCH_3), 3.78-3.70 (2H, m, NCH_2Ph), 3.71-3.64 (2H, m, 2 × 1-H) and 3.55 (2H, AB of an ABX, $\Delta\delta$ 20.6, $^2J_{gem}$ 9.7, ^3J 6.4 and 4.9, 2 × 4-H), 2.74 (1H, dt, ^3J 4.7 and 4.6, 3-H); δ_C (75 MHz, $CDCl_3$+D_2O) 158.8, 137.5, 131.7 (Cq, Ph), 129.4, 128.5, 127.9, 127.8, 113.8 (CH, Ph), 73.6 (OCH_2Ph), 71.5 (C-4), 70.2 (C-3), 60.1 (C-1), 59.1 (C-2), 55.2 (OCH_3) and 50.6 (NCH_2Ph); *m*/*z* (HRMS, CI) 332.1868 (M + H$^+$, $C_{19}H_{26}NO_4$ requires 332.1862).

(4*S*,5*S*)-4-(benzyloxymethyl)-5-(hydroxymethyl)-3-(4-methoxy-benzyl)oxazolidin-2-one 8 and (*S*)-4-((*S*)-2-(benzyloxy)-1-hydroxyethyl)-3-(4-methoxybenzyl)oxazolidin-2-one 9. To a solution of a mixture of isomers **6** and **7** (1.1 g, 3.4 mmol) in anhydrous THF (30 mL) at room temperature and under nitrogen atmosphere was added anhydrous K_2CO_3 (3.8 g, 27.7 mmol) and methyl chloroformate (1.30 mL, 17.4 mmol). The mixture was stirred at room temperature for 18 h after which it was filtered over Celite®, the cake was rinsed with THF and the filtrate concentrated in vacuum. The crude material was then taken up in a 10% solution of KOH in methanol (30 mL) and the mixture stirred at room temperature for 5 h. The solution was acidified by addition of a 1 M aqueous solution of HCl, the methanol was evaporated off and the mixture was extracted three times with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The crude material was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–Et_2O (40 : 60 to 50 : 50) to give **8** (810 mg, 66%) as a colourless oil and **9** (221 mg, 18%) as a white solid.

Major compound 8. $[\alpha]_D^{20}$ +27.6 (*c* 0.6, $CHCl_3$); ν_{max}(film)/cm^{-1} 3419 and 1740; δ_H (300 MHz, $CDCl_3$) 7.36-7.16 (5H, m, OCH_2Ph), 7.05 (2H, d, ^3J 8.6, NCH_2Ph), 6.75 (2H, d, ^3J 8.6, NCH_2Ph), 4.61 (1H, d, ^2J 15.0, NCH_2Ph), 4.46 (1H, dt, ^3J 8.3 and 5.4, 2-H), 4.39 (2H, ABq, $\Delta\delta$ 15.0, $^2J_{gem}$ 11.8, OCH_2Ph), 3.92 (1H, d, $^2J_{gem}$ 15.0, NCH_2Ph), 3.85-3.76 (2H, m, 1-H), 3.75-3.68 (4H, m, OCH_3, 3-H), 3.55 (2H, AB of an ABX, $\Delta\delta$ 15.8, $^2J_{gem}$ 10.3, ^3J 6.0 and 4.5, 2 × 4-H) and 2.61 (1H, bs, OH); δ_C (75 MHz, $CDCl_3$) 159.2 (Cq, Ph), 157.7 (C=O), 136.6 (Cq, Ph), 129.3, 128.5, 128.2, 127.9 (CH, Ph), 127.8 (Cq, Ph), 114.0 (CH, Ph), 76.1 (C-2), 73.6 (OCH_2Ph), 65.5 (C-4), 60.3 (C-1), 55.6 (C-3), 55.2 (OCH_3) and 45.9 (NCH_2Ph);

m/z (HRMS, CI) 380.1471 (M + Na^+, $C_{20}H_{23}NO_5Na$ requires 380.1474).

Minor compound 9. $[\alpha]_D^{20}$ +10.9 (*c* 1.7, $CHCl_3$); ν_{max}(film)/cm^{-1} 3433 and 1729; δ_H (300 MHz, $CDCl_3$) 7.36-7.18 (7H, m, 5×H of OCH_2Ph and 2×H of NCH_2Ph), 6.88 (2H, d, ^3J 8.6, NCH_2Ph), 4.73 (1H, d, $^2J_{gem}$ 15.0, NCH_2Ph), 4.43 (2H, s, OCH_2Ph), 4.40 (1H, dd, $^2J_{gem}$ 8.7, ^3J 6.2, 1-H), 4.16 (1H, apparent t, $^2J_{gem}$ and ^3J 8.9, 1′-H), 4.12-4.02 (2H, m, NCH_2Ph, 3-H), 3.82-3.72 (4H, m, 2-H, OCH_3) and 3.42 (2H, AB of an ABX, $\Delta\delta$ 17.1, $^2J_{gem}$ 10.2, ^3J 5.7 and 5.1, 2 × 4-H); δ_C (75 MHz, $CDCl_3$) 161.2 (Cq, Ph), 160.9 (C=O), 139.3 (Cq, Ph), 130.5, 129.4 (CH, Ph), 129.0 (Cq, Ph), 128.8, 128.7, 115.2 (CH, Ph), 74.4 (OCH_2Ph), 72.0 (C-4), 67.0 (C-3), 64.0 (C-1), 57.8 (C-2), 55.7 (OCH_3) and 46.1 (NCH_2Ph); *m/z* (HRMS, CI) 380.1485 (M + Na^+, $C_{20}H_{23}NO_5Na$ requires 380.1474). Crystallographic data for **9**: $C_{20}H_{23}NO_5$, M = 357.39, monoclinic, space group $P2_1$, a = 7.4011(2) Å, b = 21.6780(6) Å, c = 11.5033(4) Å, β = 92.832(2)°, V = 1843.35(10) $Å^3$, Z = 4, crystal size 0.60 × 0.50 × 0.20 mm^3, 31473 reflections collected (10457 independent, R*int* = 0.0276), 477 parameters, $R1$ [$I > 2\sigma(I)$] = 0.0439, $wR2$ [all data] = 0.1130, largest diff. peak and hole: 0.263 and –0.182 $eÅ^{-3}$.

(4*S*,5*S*)-4-(benzyloxymethyl)-3-(4-methoxybenzyl)-2-oxooxazolidine-5-carbaldehyde 3. To a solution of alcohol **8** (280 mg, 0.7 mmol) in anhydrous CH_2Cl_2 (4 mL) at room temperature and under nitrogen atmosphere was added Dess–Martin periodinane (437 mg, 1.0 mmol). The mixture was stirred for 4 h after which it was diluted with ethyl acetate and $Na_2S_2O_3$ (1.1 mg, 7.2 mmol) in a saturated aqueous $NaHCO_3$ (20 mL) solution was added. The mixture was extracted three times with AcOEt and the combined extracts were washed with brine and dried over $MgSO_4$. Most of the solvent was then gently evaporated off in vacuum and the resulting concentrated solution was directly filtered over Florisil® eluting with AcOEt. The filtrate was concentrated in vacuum and the crude material was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–AcOEt (90 : 10 to 80 : 20) to give aldehyde **3** (249 mg, 89%). $[\alpha]_D^{20}$ +9.5 (*c* 0.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 1751; δ_H (300 MHz, $CDCl_3$) 9.68 (1H, d, ^3J 1.5, *CH*O), 7.40-7.20 (5H, m, OCH_2Ph), 7.10 (2H, d, ^3J 8.6, NCH_2Ph), 6.82 (2H, d, ^3J 8.6, NCH_2Ph), 4.69 (1H, d, $^2J_{gem}$ 15.0, NCH_2Ph), 4.62 (1H, dd, ^3J 9.9 and 1.4, 2-H), 4.29 (2H, ABq, $\Delta\delta$ 57.6, $^2J_{gem}$ 11.8, OCH_2Ph), 3.98-3.88 (2H, m, 3-H containing at 3.90 a d, $^2J_{gem}$ 15.0, NCH_2Ph), 3.77 (3H, s, OCH_3) and 3.37 (2H, AB of an ABX, $\Delta\delta$ 84.1, $^2J_{gem}$ 10.9, ^3J 1.9, 2 × 4-H); δ_C (75 MHz, $CDCl_3$) 198.5 (*C*HO, ald.), 159.4 (Cq, Ph), 156.9 (N*C*OO), 136.6 (Cq, Ph), 129.3, 128.5, 128.1, 127.8, (CH, Ph), 127.1 (Cq, Ph), 114.2 (CH, Ph), 76.4 (C-2), 72.8 (OCH_2Ph), 62.5 (C-4), 57.8 (C-3), 55.2 (OCH_3) and 45.6 (NCH_2Ph); *m/z* (HRMS, ESI) 356.1495 (M + H^+, $C_{20}H_{22}NO_5$ requires 356.1498).

(4*S*,5*S*)-4-(benzyloxymethyl)-5-((*R*)-1-hydroxy-3-(triisopropylsilyl)prop-2-ynyl)-3-(4-methoxybenzyl)oxazolidin-2-one 12. Prepared from aldehyde **3** (395 mg, 1.11 mmol) according to the general procedure for organocerium addition. A freshly prepared solution of lithium acetylide generated by addition of *n*-BuLi (5.0 eq. of a 1.6 M commercial solution in hexanes) to TIPS-acetylene (5.0 eq.) in anhydrous THF (0.5 M) at 0 °C was used. The crude material was purified by column chromatography on SiO_2 eluting with PE–AcOEt (80 : 20 to 60 : 40) to give **12** (378 mg, 65%) as a colourless oil. $[\alpha]_D^{20}$ +25.2 (*c* 1.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 3392 and 1736; δ_H (300 MHz, $CDCl_3$) 7.43-7.28 (5H, m, OCH_2Ph), 7.07 (2H, d, ^3J 8.6, NCH_2Ph), 6.81 (2H, d, ^3J 8.6, NCH_2Ph), 4.77 (1H, d, $^2J_{gem}$ 15.0, NCH_2Ph), 4.77 (1H, d, ^3J 4.7, H_4), 4.57 (1H, dd, ^3J 8.0 and 4.7, H_3), 4.54 (2H, ABq, $\Delta\delta$ 50.6, $^2J_{gem}$ 11.6, OCH_2Ph), 4.00-3.75 (7H, m, 2 × 1-H, 2-H containing at 3.91 a d, $^2J_{gem}$ 15.0, NCH_2Ph and at 3.80 a s, OCH_3) and 1.11-1.09 (21H, m, 3×Si*CH*$(CH_3)_2$, 3×CH($CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 159.3 (Cq, Ph), 157.5 (N*C*OO), 136.4 (Cq, Ph), 129.5, 128.7, 128.5, 128.3 (CH, Ph), 127.7 (Cq, Ph), 114.1 (CH, Ph), 103.9 (C-5), 88.9 (C-6), 77.4 (C-3), 73.7 (OCH_2Ph), 64.9 (C-1), 61.8 (C-4), 55.6 (C-2), 55.3 (OCH_3), 45.8 (NCH_2Ph), 18.6 (3×Si*CH*$(CH_3)_2$) and 10.9 (3×SiCH(*C*$H_3)_2$); *m/z* (HRMS, CI) 538.2993 (M + H^+, $C_{31}H_{44}NO_5Si$ requires 538.2989).

(4*S*,5*S*)-4-(benzyloxymethyl)-5-((*R*)-1-hydroxyprop-2-ynyl)-3-(4-methoxybenzyl)oxazolidin-2-one 15. Prepared from the triisopropylsilyl derivative **12** (40.0 mg, 0.07 mmol) according to the general procedure for *C*-desilylation. The crude material was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–AcOEt (90 : 10 to 85 : 15) to give **15** (23.0 mg, 80%) as white solid. $[\alpha]_D^{20}$ + 30.5 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3430 and 1733; δ_H (300 MHz, $CDCl_3$) 7.44-7.28 (5H, m, OCH_2Ph), 7.07 (2H, d, ^3J 8.6, NCH_2Ph), 6.81 (2H, d, ^3J 8.6, NCH_2Ph), 4.76-4.66 (2H, m, 4-H containing at 4.70 a d, $^2J_{gem}$ 15.0, NCH_2Ph), 4.51 (1H, dd, ^3J 8.0 and 5.7, 3-H), 4.50 (2H, ABq, $\Delta\delta$ 46.3, $^2J_{gem}$ 11.8, OCH_2Ph), 3.90 (1H, d, $^2J_{gem}$ 15.0, NCH_2Ph), 3.86-3.74 (6H, m, OCH_3, 2 × 1-H, 2-H, OH), 3.72-3.64 (1H, m, 1′-H) and 2.50 (1H, d, ^4J 2.5, 6-H); δ_C (75 MHz, $CDCl_3$) 159.2 (Cq, Ph), 157.3 (N*C*OO), 136.1 (Cq, Ph), 129.3, 128.6, 128.4, 128.3 (CH, Ph), 127.5 (Cq, Ph), 114.1 (CH, Ph), 80.7 (C-5), 77.0 (C-3), 75.0 (C-6), 73.5 (OCH_2Ph), 64.3 (C-1), 60.9 (C-4), 55.6 (C-2), 55.2 (OCH_3) and 45.7 (NCH_2Ph); *m/z* (HRMS, ESI) 382.1636 (M + H^+, $C_{22}H_{24}NO_5$ requires 382.1654).

(*R*)-1-((4*S*,5*S*)-4-(benzyloxymethyl)-3-(4-methoxybenzyl)-2-oxooxazolidin-5-yl)prop-2-ynyl methanesulfonate 16. Prepared from alcohol **15** (21.3 mg, 0.05 mmol) according to the general procedure for mesylation. The crude material was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–AcOEt (95 : 5 to 90 : 10) to give the mesylate **16** (25.3 mg, 98%) as colorless oil. $[\alpha]_D^{20}$ +28.9 (*c* 1.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 3435 and 1757; δ_H (300 MHz, $CDCl_3$) 7.44-7.28 (5H, m, OCH_2Ph), 7.06 (2H, d, ^3J 8.6, NCH_2Ph), 6.81 (2H, d, ^3J 8.6, NCH_2Ph), 5.69 (1H, dd, ^3J 6.4, ^4J 2.2, 4-H), 4.72-4.62 (2H, m, 3-H containing at 4.69 a d, $^2J_{gem}$ 15.0, NCH_2Ph), 4.49 (2H, ABq, $\Delta\delta$ 64.3, $^2J_{gem}$ 11.8, OCH_2Ph), 3.89 (1H, d, $^2J_{gem}$ 15, NCH_2Ph), 3.84-3.74 (4H, m, OCH_3, 2-H), 3.73-3.62 (m, 2 × 1-H), 3.15 (3H, s, O_3SCH_3) and 2.80 (1H, d, ^4J 2.2, 6-H); δ_C (75 MHz, $CDCl_3$) 159.3 (Cq, Ph), 156.6 (N*C*OO), 136.8 (Cq, Ph), 129.4, 128.5, 128.1, 128.0 (CH, Ph), 127.3 (Cq, Ph), 114.1 (CH, Ph), 79.4 (C-5), 75.8 (C-6), 74.6 (C-3), 73.2 (OCH_2Ph), 68.5 (C-4), 64.4 (C-1), 55.4 (C-2), 55.2 (OCH_3), 45.8 (NCH_2Ph) and 39.5 (O_3SCH_3); *m/z* (HRMS, CI) 460.1439 (M + H^+, $C_{23}H_{26}NO_7S$ requires 460.1430).

(*R*)-1-((4*S*,5*S*)-4-(benzyloxymethyl)-3-(4-methoxybenzyl)-2-oxooxazolidin-5-yl)-3-(triisopropylsilyl)prop-2-ynyl methanesulfonate 13. Prepared from alcohol **12** (372 mg, 0.71 mmol) according to the general procedure for mesylation. The crude material was purified by column chromatography on SiO_2 eluted with PE–AcOEt (80 : 20) to give mesylate **13** (399 mg, 84%) as colourless

oil. $[\alpha]_D^{20}$ +11.9 (*c* 0.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 1763; δ_H (300 MHz, $CDCl_3$) 7.44-7.28 (5H, m, OCH_2Ph), 7.07 (2H, d, ^3J 8.6, NCH_2Ph), 6.80 (2H, d, ^3J 8.6, NCH_2Ph), 5.66 (1H, d, ^3J 5.5, 4-H), 4.71 (1H, d, $^2J_{gem}$ 15.0, NCH_2Ph), 4.64 (1H, dd, ^3J 8.4 and 5.5, 3-H), 4.50 (2H, ABq, $\Delta\delta$ 66.2, $^2J_{gem}$ 11.9, OCH_2Ph), 3.90-3.68 (7H, m, NCH_2Ph, OCH_3, 2 × 1-H, 2-H), 3.15 (3H, s, O_3SCH_3) and 1.07 (21H, br s, 3×SiC*H*$(CH_3)_2$, 3×CH$(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 159.2 (Cq, Ph), 156.7 (N*C*OO), 136.9 (Cq, Ph), 129.4, 128.4, 127.9 (CH, Ph), 127.2 (Cq, Ph), 114.0 (CH, Ph), 98.1 (C-5 or C-6), 94.5 (C-6 or C-5), 75.0 (C-3), 73.3 (OCH_2Ph), 69.5 (C-4), 65.0 (C-1), 55.2 (C-2), 55.1 (OCH_3), 45.8 (NCH_2Ph), 39.5 (O_3SCH_3), 18.3 (3×Si*C*H$(CH_3)_2$) and 10.9 (3×SiCH$(CH_3)_2$); *m*/*z* (HRMS, ESI) 616.2735 (M + H^+, $C_{32}H_{46}NO_7SiS$ requires 616.2764).

(3a*S*,6*S*,6a*S*)-3-(4-methoxybenzyl)-6-((triisopropylsilyl)-ethynyl)tetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 14

Prepared from mesylate **13** (399 mg, 0.65 mmol) according to the general procedure for cyclisation. The crude material was purified by column chromatography on SiO_2 eluting with PE–AcOEt (70 : 30) to give **14** (238.3 mg, 85%) as a white solid. $[\alpha]_D^{20}$ + 85.7 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 1750; δ_H (300 MHz, $CDCl_3$) 7.18 (2H, d, ^3J 8.6, NCH_2Ph), 6.86 (2H, d, ^3J 8.6, NCH_2Ph), 4.82 (1H, dd, ^3J 7.8 and 4.5, 3-H), 4.68 (1H, d, $^2J_{gem}$ 15.0, NCH_2Ph), 4.41 (1H, d, ^3J 4.5, 4-H), 4.14-4.02 (2H, m, 2-H containing at 4.09 a d, $^2J_{gem}$ 15.0, NCH_2Ph), 3.94 (1H, d, $^2J_{gem}$ 10.5, 1-H), 3.79 (3H, s, OCH_3), 3.43 (1H, dd, $^2J_{gem}$ 10.5, ^3J 4.3, 1′-H) and 0.97 (21H, br s, 3×SiC*H*$(CH_3)_2$, 3×SiCH$(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) δ 159.4 (Cq, Ph), 157.0 (N*C*OO), 129.6 (CH, Ph), 127.1 (Cq, Ph), 114.2 (CH, Ph), 98.0 (C-5 or C-6), 91.5 (C-6 or C-5), 76.9 (C-3), 73.6 (C-4), 69.7 (C-1), 59.1 (C-2), 55.2 (OCH_3), 46.3 (NCH_2Ph), 18.5 (3×Si*C*H$(CH_3)_2$) and 11.0 (3×SiCH$(CH_3)_2$); *m*/*z* (HRMS, ESI) 430.2415 (M + H^+, $C_{24}H_{36}NO_4Si$ requires 430.2414).

(3a*S*,6*S*,6a*S*)-6-ethynyl-3-(4-methoxybenzyl)tetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 17. Prepared from mesylate **16** (23.0 mg, 0.05 mmol) according to the general procedure of cyclization or from the triisopropylsilyl intermediate **14** (40.7 mg, 0.09 mmol) according to the general procedure for *C*-desilylation. The crude material was purified by column chromatography on SiO_2 eluted with CH_2Cl_2–AcOEt (95 : 5) to give **17** (9.7 mg, 71% or 24.8 mg, 96% respectively) as a white solid. $[\alpha]_D^{20}$ +106.9 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 1740; δ_H (300 MHz, $CDCl_3$) 7.19 (2H, d, ^3J 8.6, NCH_2Ph), 6.87 (2H, d, ^3J 8.6, NCH_2Ph), 4.86 (1H, dd, ^3J 7.7 and 4.3, 3-H), 4.67 (1H, d, $^2J_{gem}$ 15.0, NCH_2Ph), 4.34 (1H, dd, ^3J 4.2, ^4J 2.2, 4-H), 4.18-4.08 (2H, m, 2-H containing at 4.10 a d, $^2J_{gem}$ 15.0, NCH_2Ph), 3.95 (1H, d, $^2J_{gem}$ 10.6, 1-H), 3.79 (3H, s, OCH_3), 3.41 (1H, dd, $^2J_{gem}$ 10.6, ^3J 4.2, 1′-H) and 2.64 (1H, d, ^4J 2.2, 6-H); δ_C (75 MHz, $CDCl_3$) δ 159.5 (Cq, Ph), 156.8 (N*C*OO), 129.5 (CH, Ph), 127.0 (Cq, Ph), 114.3 (CH, Ph), 77.6 (C-5), 76.9 (C-3), 75.2 (C-6), 73.0 (C-4), 69.7 (C-1), 59.4 (C-2), 55.2 (OCH_3) and 46.3 (NCH_2Ph); *m*/*z* (HRMS, CI) 296.0919 (M + Na^+, $C_{15}H_{15}NO_4Na$ requires 296.0899).

(4*S*,5*S*)-4-(benzyloxymethyl)-5-((*R*)-1-hydroxyallyl)-3-(4-methoxybenzyl)oxazolidin-2-one 18. Prepared from aldehyde **3** (406 mg, 1.14 mmol) according to the general procedure for organocerium addition. A commercial vinyl magnesium bromide solution 1.0 M in THF was used. The crude material was purified by column chromatography on SiO_2 eluting with PE–CH_2Cl_2–AcOEt (20 : 64 : 16) to give **18** (200 mg, 50.7%) as colourless oil. $[\alpha]_D^{20}$ + 39.7 (*c* 0.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 3408 and 1729; δ_H (300 MHz, $CDCl_3$) 7.44-7.26 (5H, m, OCH_2Ph), 7.10 (2H, d, ^3J 8.6, NCH_2Ph), 6.82 (2H, d, ^3J 8.6, NCH_2Ph), 5.96 (1H, ddd, ^3J 17.2, 10.6 and 5.1 Hz, 5-H), 5.40 (1H, apparent dt, ^3J 17.2, $^2J_{gem} \approx {}^4J$ 1.4, 6-H), 5.25 (1H, apparent dt, ^3J 10.6, $^2J_{gem} \approx {}^4J$ 1.4, 6′-H), 4.69 (1H, d, $^2J_{gem}$ 15.0, NCH_2Ph), 4.50 (2H, ABq, $\Delta\delta$ 19.1, $^2J_{gem}$ 11.9, OCH_2Ph), 4.43-4.34 (1H, m, 4-H), 4.22 (1H, dd, ^3J 8.8 and 7.2, 3-H), 3.94 (1H, d, $^2J_{gem}$ 15.0, NCH_2Ph), 3.79 (3H, s, OCH_3), 3.77-3.70 (1H, m, 2-H), 3.68-3.58 (2H, m, 2 × 1-H) and 3.31 (1H, bs, OH); δ_C (75 MHz, $CDCl_3$) 159.3 (Cq, Ph), 157.3 (N*C*OO), 136.3 (Cq, Ph), 136.0 (C-5), 129.3, 128.6, 128.3, 128.0 (CH, Ph), 127.9 (Cq, Ph), 117.1 (C-6), 114.1 (CH, Ph), 78.5 (C-3), 73.7 (OCH_2Ph), 69.2 (C-4), 64.7 (C-1), 55.9 (C-2), 55.2 (OCH_3) and 45.8 (NCH_2Ph); *m*/*z* (HRMS, CI) 384.1819 (M + H^+, $C_{22}H_{26}NO_5$ requires 384.1811).

(3a*S*,6*S*,6a*S*)-3-(4-methoxybenzyl)-6-vinyltetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 20. Prepared from secondary alcohol **18** (240 mg, 0.62 mmol) according to the general procedure for mesylation. The crude material was purified by column chromatography on SiO_2 eluted with PE–AcOEt (70 : 30) to give the bicyclic product **20** (150 mg, 87%) as a white solid upon spontaneous cyclisation. $[\alpha]_D^{20}$ +103.8 (*c* 1.4, $CHCl_3$); ν_{max}(film)/cm^{-1} 1737; δ_H (300 MHz, $CDCl_3$) 7.17 (2H, d, ^3J 8.7, NCH_2Ph), 6.84 (2H, d, ^3J 8.7, NCH_2Ph), 5.95 (1H, ddd, ^3J 17.3, 10.5 and 7.3, 5-H), 5.40 (1H, apparent dt, ^3J 17.3, $^2J_{gem} \approx {}^4J$ 1.3, 6-H), 5.34 (1H, apparent dt, ^3J 10.5, $^2J_{gem} \approx {}^4J$ 1.3, 6′-H), 4.79 (1H, dd, ^3J 7.3 and 3.9, 4-H), 4.64 (1H, d, $^2J_{gem}$ 15.0, NCH_2Ph), 4.10 (1H, dd, ^3J 7.5 and 3.9, 3-H), 4.09 (1H, d, $^2J_{gem}$ 15.0, NCH_2Ph), 3.99 (1H, dd, ^3J 7.5 and 4.0, 2-H), 3.95 (1H, d, $^2J_{gem}$ 10.7, 1-H), 3.76 (3H, s, OCH_3) and 3.35 (1H, dd, $^2J_{gem}$ 10.7, ^3J 4.0, 1′-H); δ_C (75 MHz, $CDCl_3$) 159.3 (Cq, Ph), 157.1 (N*C*OO), 130.5 (C-5), 129.3 (CH, Ph), 127.1 (Cq, Ph), 120.2 (C-6), 114.1 (CH, Ph), 83.9 (C-4), 78.3 (C-3), 69.3 (C-1), 55.9 (C-2), 55.1 (OCH_3) and 46.0 (NCH_2Ph); *m*/*z* (HRMS, CI) 276.1229 (M + H^+, $C_{15}H_{18}NO_4$ requires 276.1236). Crystallographic data for **20**: $C_{15}H_{17}NO_4$, $M = 275.30$, monoclinic, space group $P2_1$, $a = 4.5326(2)$ Å, $b = 25.9051(12)$ Å, $c = 6.2404(3)$ Å, $\beta = 110.523(3)°$, $V = 686.23(5)$ Å^3, $Z = 2$, crystal size 0.24 × 0.16 × 0.06 mm^3, 7458 reflections collected (1727 independent, R*int* = 0.0548), 182 parameters, $R1$ [$I > 2\sigma(I)$] = 0.0475, $wR2$ [all data] = 0.1144, largest diff. peak and hole: 0.185 and –0.206 eÅ^{-3}.

(3a*S*,6*S*,6a*S*)-6-(bromoethynyl)-3-(4-methoxybenzyl)tetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 22. To a solution of triisopropylsilyl intermediate **14** (50.0 mg, 0.11 mmol) in CH_3CN (2 mL) was added NBS (25.0 mg, 0.14 mmol) and AgF (19.0 mg, 0.15 mmol) in the dark. The mixture was stirred for 2 h at room temperature then filtered through a pad of Celite®. The filtrate was diluted with AcOEt, washed with water, dried over $MgSO_4$ and concentrated in vacuum. The resulting residue was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–AcOEt (90 : 10) to give the bromide **22** (38.1 mg, 93%) as a white solid. $[\alpha]_D^{20}$ +127.1 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 1738; δ_H (300 MHz, $CDCl_3$) 7.19 (2H, d, ^3J 8.6, NCH_2Ph), 6.87 (2H, d, ^3J 8.6, NCH_2Ph), 4.85 (1H, dd, ^3J 7.8 and 4.3, 3-H), 4.65 (1H, d, ^2J 15.0, NCH_2Ph), 4.35 (1H, d, ^3J 4.3, 4-H), 4.15 (1H, d, $^2J_{gem}$ 15.0, NCH_2Ph), 4.10 (1H, dd, ^3J 7.8 and 4.2, 2-H), 3.92 (1H, d, $^2J_{gem}$ 10.7, 1-H), 3.80 (3H, s, OCH_3) and 3.39 (1H, dd, $^2J_{gem}$ 10.7, ^3J 4.2, 1′-H); δ_C (75 MHz, $CDCl_3$) δ 159.3 (Cq, Ph), 157.2 (N*C*OO), 129.3 (CH,

Ph), 126.7 (Cq, Ph), 114.2 (CH, Ph), 77.2 (C-3), 73.7 (C-4), 71.6 (C-5), 69.4 (C-1), 59.5 (C-2), 55.1 (O*C*H$_3$), 50.1 (C-6) and 46.2 (N*C*H$_2$Ph); *m/z* (HRMS, CI) 352.0176 (M + H$^+$, $C_{15}H_{15}NO_4Br$ requires 352.0184, most abundant isotope).

(3a*S*,6*S*,6a*S*)-6-(deca-1,3-diynyl)-3-(4-methoxybenzyl)tetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 21. Prepared from alkyne **17** (42.0 mg, 0.15 mmol) and 1-bromooct-1-yne or bromide **22** (32.0 mg, 0.10 mmol) and n-octyne according to the general procedure for Sonogashira coupling. The crude material was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–AcOEt (95 : 5) to give the diyne **21** (14.0 mg, 24% or 17.0 mg, 48% respectively) as a white solid. $[\alpha]_D^{20}$ +181.6 (*c* 1.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 1739; δ_H (300 MHz, $CDCl_3$) 7.19 (2H, d, ^3J 8.7, NCH$_2$*Ph*), 6.87 (2H, d, ^3J 8.7, NCH$_2$*Ph*), 4.84 (1H, dd, ^3J 7.7 and 4.3, 3-H), 4.65 (1H, d, $^2J_{gem}$ 15.0, NC*H*$_2$Ph), 4.37 (1H, d, ^3J 4.3, 4-H), 4.14 (1H, d, $^2J_{gem}$ 15.0, NC*H*$_2$Ph), 4.09 (1H, dd, ^3J 7.8 and 4.2, 2-H), 3.92 (1H, d, $^2J_{gem}$ 10.7, 1-H), 3.79 (3H, s, OC*H*$_3$), 3.38 (1H, dd, $^2J_{gem}$ 10.7, ^3J 4.2, 1′-H), 2.27 (2H, d, ^3J 6.9, 9-H), 1.58-1.46 (2H, m, 2 × 10-H), 1.45-1.20 (6H, m, 3×C*H*$_2$, 11-H to 13-H) and 0.88 (3H, t, ^3J 6.8, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 159.5 (Cq, Ph), 156.9 (N*C*OO), 129.5 (CH, Ph), 127.0 (Cq, Ph), 114.3 (CH, Ph), 82.8 (C-5 or C-6), 77.2 (C-3), 74.1 (C-6 or C-5), 73.7 (C-4), 69.7 (C-1), 66.4 (C-7 or C-8), 64.3 (C-7 or C-8), 59.4 (C-2), 55.2 (O*C*H$_3$), 46.4 (N*C*H$_2$Ph), 31.2, 28.4, 27.9, 22.4, 19.2 (C-9 to C-13) and 14.0 (*C*H$_3$); *m/z* (HRMS, CI) 382.2014 (M + H$^+$, $C_{23}H_{28}NO_4$ requires 382.2018).

(3a*S*,6*S*,6a*S*)-6-(tetradeca-1,3-diynyl)-3-(4-methoxybenzyl)-tetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 23. Prepared from bromide **22** (40.0 mg, 0.11 mmol) and tetradecyne according to the general procedure for Sonogashira coupling. The crude material was purified by column chromatography on SiO_2 eluting with PE–CH_2Cl_2–AcOEt (50 : 40 : 10) to give diyne **23** (16.1 mg, 32%) as a white solid. $[\alpha]_D^{20}$ +151.1 (*c* 0.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 1739; δ_H (300 MHz, $CDCl_3$) 7.19 (2H, d, ^3J 8.7, NCH$_2$*Ph*), 6.87 (2H, d, ^3J 8.7, NCH$_2$*Ph*), 4.84 (1H, dd, ^3J 7.7 and 4.3, 3-H), 4.65 (1H, d, $^2J_{gem}$ 15.0, NC*H*$_2$Ph), 4.37 (1H, d, ^3J 3.9, 4-H), 4.15 (1H, d, $^2J_{gem}$ 15.1, NC*H*$_2$Ph), 4.09 (1H, ddd, ^3J 7.8, 4.3 and 1.0, 2-H), 3.92 (1H, d, $^2J_{gem}$ 10.7, 1-H), 3.80 (3H, s, OC*H*$_3$), 3.38 (1H, dd, $^2J_{gem}$ 10.7, ^3J 4.3, 1′-H), 2.27 (2H, d, ^3J 6.9, 9-H), 1.58-1.46 (2H, m, 2 × 10-H), 1.45-1.20 (14H, m, 6×CH$_2$, 11-H to 17-H) and 0.98-0.84 (3H, m, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 159.6 (Cq, Ph), 157.0 (N*C*OO), 129.6 (CH, Ph), 127.1 (Cq, Ph), 114.4 (CH, Ph), 82.9 (C-5 or C-6), 77.3 (C-3), 74.2 (C-6 or C-5), 73.8 (C-4), 69.8 (C-1), 66.5 (C-7 or C-8), 64.4 (C-7 or C-8), 59.5 (C-2), 55.3 (O*C*H$_3$), 46.5 (N*C*H$_2$Ph), 31.9, 29.6, 29.5, 29.3, 29.1, 28.9, 28.0, 22.7, 19.3 (C-9 to C-17) and 14.1 (*C*H$_3$); *m/z* (HRMS, CI) 438.2649 (M + H$^+$, $C_{27}H_{36}NO_4$ requires 438.2644).

(3a*S*,6*S*,6a*S*)-3-(4-methoxybenzyl)-6-tetradecyltetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 24. Prepared from diyne **23** (16.0 mg, 0.037 mmol) or from the mixture of olefins **39a**,**b** (48.0 mg, 0.11 mmol) according to the general procedure for hydrogenation. The crude material was purified by column chromatography on SiO_2 eluting with PE–CH_2Cl_2–AcOEt (50 : 40 : 10) to give the protected jaspine B **24** (16.5 mg, quant. or 45.0 mg, 94% respectively) as a white solid. $[\alpha]_D^{20}$ +57.3 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 1746; δ_H (300 MHz, $CDCl_3$) 7.19 (2H, d, ^3J 8.7, NCH$_2$*Ph*), 6.87 (2H, d, ^3J 8.7, NCH$_2$*Ph*), 4.75 (1H, dd, ^3J 7.6 and 3.8, 3-H), 4.71 (1H, d, $^2J_{gem}$ 14.9, NC*H*$_2$Ph), 4.08 (1H, d, $^2J_{gem}$ 14.9, NC*H*$_2$Ph), 4.07 (1H, dd, ^3J 7.6 and 4.0, 2-H), 3.94 (1H, d, $^2J_{gem}$ 10.6, 1-H), 3.80 (3H, s, OC*H*$_3$), 3.48 (1H, td, ^3J 6.8 and 3.8, 4-H), 3.30 (1H, dd, $^2J_{gem}$ 10.6, ^3J 4.0, 1′-H), 1.84-1.68 (2H, m, 5-H), 1.50-1.16 (24H, m, 12×C*H*$_2$) and 0.88 (3H, t, ^3J 6.7, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) δ 159.5 (Cq, Ph), 157.6 (N*C*OO), 129.6 (CH, Ph), 127.4 (Cq, Ph), 114.3 (CH, Ph), 83.5 (C-4), 77.8 (C-3), 69.3 (C-1), 59.9 (C-2), 55.3 (O*C*H$_3$), 46.2 (N*C*H$_2$Ph), 31.9, 29.6, 29.5, 29.4, 28.0, 26.0, 22.7 (13×*C*H$_2$, C-5 to C-17) and 14.1 (*C*H$_3$); *m/z* (HRMS, CI) 446.3266 (M + H$^+$, $C_{27}H_{44}NO_4$ requires 446.3270).

(3a*S*,6*S*,6a*S*)-6-tetradecyltetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 25. Prepared from *N*-PMB derivative **24** (59.0 mg, 0.13 mmol) according to the general procedure for the oxidative deprotection. The crude material was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–AcOEt (60 : 40) to give **25** (27.1 mg, 63%) a white solid. $[\alpha]_D^{20}$ +66.5 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 1758; δ_H (300 MHz, $CDCl_3$) 6.46 (1H, bs, N*H*), 4.93 (1H, dd, ^3J 7.4 and 3.6, 3-H), 4.37 (1H, dd, ^3J 7.4 and 3.8, 2-H), 3.94 (1H, d, $^2J_{gem}$ 10.4, 1-H), 3.58-3.44 (2H, m, 4-H containing at 3.52 a d, $^2J_{gem}$ 10.4, 1′-H), 1.86-1.66 (2H, m, 5-H), 1.54-1.16 (24H, m, 12×C*H*$_2$) and 0.87 (3H, t, ^3J 6.7, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 159.5 (N*C*OO), 83.2 (C-4), 80.9 (C-3), 73.3 (C-1), 57.1 (C-2), 31.9, 29.7, 29.6 (×3), 29.5, 29.4, 29.3, 28.1, 26.0, 22.7 (13×*C*H$_2$, C-5 to C-17) and 14.1 (*C*H$_3$); *m/z* (HRMS, CI) 326.2714 (M + H$^+$, $C_{19}H_{36}NO_3$ requires 326.2695).

(2*S*,3*S*,4*S*)-4-amino-2-tetradecyltetrahydro-furan-3-ol (jaspine B) 1. Prepared from oxazolidinone **25** (20.0 mg, 0.06 mmol) according to the general procedure for saponification. The crude material was purified by column chromatography on SiO_2 eluting with AcOEt–MeOH–NH_4OH (84.2 : 15 : 0.8) to give jaspine B (**1**) (12.8 mg, 70%) as a white solid. $[\alpha]_D^{20}$ +20.9 (*c* 1.1, $CHCl_3$) ($[\alpha]_D^{20}$ +24.3 (*c* 0.85, $CHCl_3$) for natural jaspine B); ν_{max}(film)/cm^{-1} 3340; δ_H (300 MHz, $CDCl_3$) 3.92 (1H, dd, ^2J 8.3, ^3J 7.5, 1-H), 3.86 (1H, dd, ^3J 4.5 and 3.7, 3-H), 3.73 (1H, ddd, ^3J 10.0, 7.0 and 3.4, 4-H), 3.69-3.58 (1H, m, 2-H), 3.51 (1H, dd, ^2J 8.3, ^3J 6.8, 1′-H), 2.00 (3H, br s, NH_2, OH) 1.76-1.54 (2H, m, 2 × 5-H), 1.50-1.20 (24H, m, 12×C*H*$_2$) and 0.87 (3H, t, ^3J 6.7, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 83.2 (C-4), 72.3 (C-1), 71.7 (C-3), 54.3 (C-2), 31.9 (C-5), 29.8, 29.7 (×2), 29.6, 29.5, 29.4, 29.3, 26.3, 22.7 (12×*C*H$_2$, C-6 to C-17) and 14.1 (*C*H$_3$); *m/z* (DCI, NH_3) 300 (M+H$^+$, 100%).

4-octylphenyl trifluoromethanesulfonate (28). To a solution of 4-octylphenol (412 mg, 2.0 mmol) in anhydrous CH_2Cl_2 (5 mL) at −10 °C and under nitrogen atmosphere was added pyridine (323 µL, 4.0 mmol). The mixture was stirred for 5 min and trifluoromethanesulfonic anhydride (405 µL, 2.40 mmol) was added dropwise. The mixture was stirred for 15 min after which it was extracted three times with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The solvent was evaporated off in vacuum and the crude material was purified by column chromatography on SiO_2 eluting with PE–Et_2O (95 : 5) to give the triflate **28** (670 mg, 99%) as pale yellow liquid. δ_H (300 MHz, $CDCl_3$) 7.28-7.12 (4H, m, Ph), 2.62 (2H, t, ^3J 7.7, PhC*H*$_2$), 1.68-1.54 (2H, m, PhCH$_2$C*H*$_2$), 1.40-1.18 (10H, m, 5×C*H*$_2$) and 0.88 (3H, t, ^3J 6.7, C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 147.7, 143.5 (Cq, Ph), 129.9, 120.9 (CH, Ph), 118.8 (q, $^1J_{C-F}$ 321, *C*F$_3$), 35.3, 31.8, 31.3, 29.4, 29.2, 22.6 (7×CH$_2$) and 14.0 (*C*H$_3$); *m/z* (EI) 338 (M$^{+\cdot}$, 100%), 239 (M -.C_7H_{15}, 50%)

5,5-dimethyl-2-(4-octylphenyl)-1,3,2-dioxaborinane 29. To a solution of aryl triflate **28** (338 mg, 1.0 mmol) in anhydrous DMSO (6 mL) in a 2-necked round-bottomed flask under nitrogen atmosphere was added $PdCl_2$(dppf) (24.0 mg, 0.03 mmol), KOAc (283 mg, 3.0 mmol) and bis(neopentyl glycato)diboron. The mixture was heated at 80 °C with stirring for 4 h after witch it was extracted three times with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The crude material was purified by column chromatography on SiO_2 eluting with PE–Et_2O (95 : 5) to give **29** (152 mg, 50%) as a solid. δ_H (300 MHz, $CDCl_3$) 7.77 (2H, d, ^3J 7.8, Ph), 7.22 (2H, d, ^3J 7.8, Ph), 3.79 (4H, s, 2×OCH_2), 2.65 (2H, t, ^3J 7.7, PhCH_2), 1.74-1.58 (2H, m, PhCH$_2$CH_2), 1.42-1.24 (10H, m, 5×CH_2), 1.05 (6H, s, 2×CCH_3) and 0.92 (3H, t, ^3J 6.7, CH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) δ 145.6 (Cq, Ph), 133.8 (*C*H, Ph), 127.7 (*C*H, B-Cq, Ph), 72.2 (2×O*C*H$_2$), 36.1 (Ph*C*H$_2$), 31.9 (*C*CH$_3$), 31.8, 31.3, 29.4, 29.3, 29.2, 22.6 (6×*C*H$_2$), 21.9 (2×C*C*H$_3$) and 14.0 (*C*H$_3$); *m*/*z* (EI) 302 ($M^{+\cdot}$, 39%), 203 (M^+ -.C_7H_{15}, 100%).

1-iodo-4-octylbenzene 26. To a solution of aryl arylboronate **29** (122 mg, 0.40 mmol) in THF–H_2O 1 : 1 (2 mL) was added chloramine-T (229 mg, 1.01 mmol). The mixture was stirred for 5 min at room temperature after witch was added of a solution of NaI (300 mg, 2.0 mmol) in 1 mL of 0.1% aqueous NaOH. The reaction was stirred for 30 min in the dark after witch is was extracted three times with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The crude material was purified by column chromatography on SiO_2 eluting with PE–Et_2O (95 : 5) to give iodide **26** (125 mg, 98%) as a pale yellow oil. δ_H (300 MHz, $CDCl_3$) 7.58 (2H, d, ^3J 8.3, Ph), 6.93 (2H, d, ^3J 8.3, Ph), 2.54 (2H, t, ^3J 7.7, PhCH_2), 1.66-1.52 (2H, m, PhCH$_2$CH_2), 1.38-1.18 (10H, m, 5×CH_2) and 0.88 (3H, t, ^3J 6.7, CH_3); δ_C (75 MHz, $CDCl_3$) 142.5 (Cq, Ph), 137.2, 130.5 (*C*H, Ph), 90.5 (Cq, Ph), 35.4 (Ph*C*H$_2$), 31.8, 31.3, 29.4, 29.2, 29.1, 22.6 (6×*C*H$_2$) and 14.1 (*C*H$_3$); *m*/*z* (DCI/CH_4) 317 (M+H$^+$, 100%), 345 (M+$C_2H_5^+$, 28%).

(3a*S*,6*S*,6a*S*)-3-(4-methoxybenzyl)-6-((4-octylphenyl)ethynyl)-tetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 30. Prepared from alkyne **17** (50.0 mg, 0.18 mmol) and iodide **26** according to the general procedure for Sonogashira coupling. The crude material was purified by column chromatography on SiO_2 eluting with PE–CH_2Cl_2–AcOEt (50 : 40 : 10) to give **30** (65.0 mg, 77%) as a white solid. $[\alpha]_D^{20}$ +136.8 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 1737; δ_H (300 MHz, $CDCl_3$) 7.40 (2H, d, ^3J 8.2, Ph), 7.20 (2H, d, ^3J 8.6, NCH$_2$*Ph*), 7.11 (2H, d, ^3J 8.2, Ph), 6.87 (2H, d, ^3J 8.6, NCH$_2$*Ph*), 4.90 (1H, dd, ^3J 7.8 and 4.3, 3-H), 4.66 (1H, d, $^2J_{gem}$ 15.0, NCH_2Ph), 4.56 (1H, d, ^3J 4.3, 4-H), 4.17 (1H, d, $^2J_{gem}$ 15.0, NCH_2Ph), 4.13 (1H, dd, ^3J 7.5 and 3.8, 2-H), 3.97 (1H, d, $^2J_{gem}$ 10.6, 1-H), 3.79 (3H, s, OCH_3), 3.45 (1H, dd, $^2J_{gem}$ 10.6, ^3J 4.3, 1′-H), 2.58 (2H, t, ^3J 7.7, PhCH_2), 1.64-1.50 (2H, m, PhCH$_2$CH_2), 1.38-1.18 (10H, m, 5×CH_2) and 0.87 (3H, t, ^3J 6.6, CH_3); δ_C (75 MHz, $CDCl_3$) 159.4 (Cq, Ph), 157.1 (N*C*OO), 144.1 (Cq, Ph), 131.9, 129.5, 128.3 (CH, Ph), 127.1, 118.9 (Cq, Ph), 114.3 (CH, Ph), 89.3 (C-5), 79.7 (C-6), 77.2 (C-3), 73.9 (C-4), 69.6 (C-1), 59.5 (C-2), 55.2 (O*C*H$_3$), 46.4 (N*C*H$_2$Ph), 35.8, 31.8, 31.1, 29.4, 29.2, 22.6 (7×*C*H$_2$) and 14.0 (*C*H$_3$); *m*/*z* (HRMS, CI) 462.2639 (M + H$^+$, $C_{29}H_{36}NO_4$ requires 462.2644).

(3a*S*,6*S*,6a*S*)-3-(4-methoxybenzyl)-6-(4-octylphenethyl)tetra-hydrofuro[3,4-*d*]oxazol-2(3H)-one 31. Prepared from alkyne **30** (50.0 mg, 0.11 mmol) according to the general procedure for hydrogenation. The crude material was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–AcOEt (90 : 10) to give **31** (50.1 mg, 99%) as a white solid. $[\alpha]_D^{20}$ +63.8 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 1736; δ_H (300 MHz, $CDCl_3$) 7.20 (2H, d, ^3J 8.7, NCH$_2$*Ph*), 7.14-7.04 (4H, m, Ph), 6.88 (2H, d, ^3J 8.7, NCH$_2$*Ph*), 4.74 (1H, dd, ^3J 7.5 and 3.9, 3-H), 4.71 (1H, d, $^2J_{gem}$ 15.2, NCH_2Ph), 4.09 (1H, d, $^2J_{gem}$ 15.2, NCH_2Ph), 4.06 (1H, dd, ^3J 7.6 and 3.9, 2-H), 3.95 (1H, d, $^2J_{gem}$ 10.6, 1-H), 3.80 (3H, s, OCH_3), 3.45 (1H, ddd, ^3J 7.3, 6.3 and 3.9, 4-H), 3.29 (1H, dd, $^2J_{gem}$ 10.6, ^3J 4.1, 1′-H), 2.83-2.65 (2H, m, 2 × 5-H), 2.56 (2H, t, ^3J 7.7, PhCH_2), 2.22-1.97 (2H, m, 2 × 6-H), 1.65-1.52 (2H, m, PhCH$_2$CH_2), 1.40-1.20 (10H, m, 5×CH_2) and 0.87 (3H, t, ^3J 6.7, CH_3); δ_C (75 MHz, $CDCl_3$) δ 159.4 (Cq, Ph), 157.5 (N*C*OO), 140.6, 138.2 (Cq, Ph), 129.5, 128.4, 128.2 (CH, Ph), 127.3 (Cq, Ph), 114.3 (CH, Ph), 82.2 (C-4), 77.6 (C-3), 69.3 (C-1), 59.9 (C-2), 55.3 (O*C*H$_3$), 46.2 (N*C*H$_2$Ph), 35.5, 31.8, 31.5, 29.4, 29.3, 29.2, 22.6 (9×*C*H$_2$) and 14.1 (*C*H$_3$); *m*/*z* (HRMS, CI) 466.2960 (M + H$^+$, $C_{29}H_{40}NO_4$ requires 466.2957).

(3a*S*,6*S*,6a*S*)-6-(4-octylphenethyl)tetra-hydrofuro[3,4-*d*]oxazol-2(3H)-one 32. Prepared from *N*-PMB intermediate **31** (45.0 mg, 0.09 mmol) according to the general procedure for oxidative deprotection. The crude material was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–AcOEt (60 : 40) to give **32** (30.2 mg, 90%) as a white solid. $[\alpha]_D^{20}$ +78.3 (*c* 0.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 3322 and 1747; δ_H (300 MHz, $CDCl_3$) 7.16-7.04 (4H, m, Ph), 6.38 (1H, br s, NH), 4.92 (1H, dd, ^3J 7.5 and 3.7, 3-H), 4.35 (1H, dd, ^3J 7.5 and 4.0, 2-H), 3.96 (1H, d, $^2J_{gem}$ 10.5, 1-H), 3.55-3.44 (2H, m, 1′-H, 4-H), 2.85-2.65 (2H, m, 2 × 5-H), 2.56 (2H, t, ^3J 7.7, PhCH_2), 2.22-1.96 (2H, m, 2 × 6-H), 1.64-1.50 (2H, m, PhCH$_2$CH_2), 1.40-1.18 (10H, m, 5×CH_2) and 0.88 (3H, t, ^3J 6.7, CH_3); δ_C (75 MHz, $CDCl_3$) 159.4 (N*C*OO), 140.7, 138.2 (Cq, Ph), 128.4, 128.2 (CH, Ph), 82.0 (C-4), 80.9 (C-3), 73.3 (C-1), 57.2 (C-2), 35.5, 31.8, 31.5, 29.6, 29.4, 29.3, 29.2, 22.6 (9×*C*H$_2$) and 14.1 (*C*H$_3$); *m*/*z* (HRMS, CI) 346.2368 (M + H$^+$, $C_{21}H_{32}NO_3$ requires 346.2382).

(2*S*,3*S*,4*S*)-4-amino-2-(4-octylphenethyl)tetrahydrofuran-3-ol 33. Prepared from oxazolidinone **32** (22.5 mg, 0.06 mmol) according to the general procedure for saponification. The crude material was purified by column chromatography on SiO_2 eluting with AcOEt–MeOH–NH_4OH (89.2 : 10 : 0.8) to give **33** (20.7 mg, 99%) as a white solid. $[\alpha]_D^{20}$ +16.5 (*c* 0.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 3356; δ_H (300 MHz, $CDCl_3$) 7.14-7.02 (4H, m, Ph), 3.98-3.76 (3H, m, 1-H, 3-H, 4-H), 3.55-3.40 (2H, m, 1′-H, 2-H), 2.74-2.58 (2H, m, 2 × 5-H), 2.55 (2H, t, ^3J 7.6, PhCH_2), 2.00-1.80 (2H, m, 2 × 6-H), 1.68-1.50 (2H, m, PhCH$_2$CH_2), 1.40-1.20 (10H, m, 5×CH_2) and 0.89 (3H, t, ^3J 6.6, CH_3); δ_C (75 MHz, $CDCl_3$) 141.5, 140.6 (Cq, Ph), 129.4, 129.3 (CH, Ph), 83.5 (C-4), 73.4 (C-3), 72.3 (C-1), 56.1 (C-2), 36.6, 33.1, 32.9, 32.8, 32.7, 30.6, 30.5, 30.4, 23.8 (9×*C*H$_2$) and 14.5 (*C*H$_3$); *m*/*z* (HRMS, CI) 320.2584 (M + H$^+$, $C_{20}H_{34}NO_2$ requires 320.2590).

1-iodo-4-(octyloxy)benzene 34. To a solution of 4-iodophenol (500 mg, 2.27 mmol) in CH_3CN (5 mL) was added 1-iodooctane (615 µL, 3.40 mmol) and Cs_2CO_3 (1.84 g, 5.60 mmol). The mixture was heated at reflux 85 °C and stirred for 5 h after which it was

filtered over Celite®. The solvent was evaporated in vacuum and the crude material was purified by column chromatography on SiO_2 eluting with PE–Et_2O (95 : 5) to give **34** (750 mg, 99%) as a pale yellow oil. δ_H (300 MHz, $CDCl_3$) 7.54 (2H, d, ^3J 8.9, Ph), 6.67 (2H, d, ^3J 8.9, Ph), 3.91 (2H, t, ^3J 6.6, PhOCH_2), 1.82-1.70 (2H, m, OCH$_2$CH_2), 1.50-1.20 (10H, m, 5×CH_2) and 0.89 (3H, t, ^3J 6.6, CH_3); δ_C (75 MHz, $CDCl_3$) 159.0 (Cq, Ph), 138.1, 116.9 (CH, Ph), 82.3 (Cq, Ph), 68.1 (PhO*C*H$_2$), 31.8, 29.3, 29.2, 29.1, 25.9, 22.6 (6×*C*H$_2$) and 14.1 (*C*H$_3$); *m*/*z* (HRMS, CI) 333.0698 (M + H$^+$, $C_{14}H_{22}OI$ requires 333.0715).

(3a*S*,6*S*,6a*S*)-3-(4-methoxybenzyl)-6-((4-(octyloxy)phenyl)-ethynyl)tetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 35. Prepared from alkyne **17** (80.0 mg, 0.29 mmol) and 1-iodo-4-(octyloxy)benzene (**34**) according to the general procedure for Sonogashira coupling. The crude material was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–AcOEt (95 : 5) to give **35** (96.0 mg, 69%) as a white solid. $[\alpha]_D^{20}$ +131.3 (*c* 0.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 1737; δ_H (300 MHz, $CDCl_3$) 7.41 (2H, d, ^3J 8.9, CH$_2$O*Ph*), 7.20 (2H, d, ^3J 8.7, NCH$_2$*Ph*), 6.87 (2H, d, ^3J 8.7, NCH$_2$*Ph*), 6.81 (2H, d, ^3J 8.9, CH$_2$O*Ph*), 4.89 (1H, dd, ^3J 7.8 and 4.3, 3-H), 4.65 (1H, d, $^2J_{gem}$ 15.0, NC*H*$_2$Ph), 4.55 (1H, d, ^3J 4.3, 4-H), 4.17 (1H, d, $^2J_{gem}$ 15.0, NC*H*$_2$Ph), 4.13 (1H, dd, ^3J 7.8 and 4.3, 2-H), 4.00-3.90 (3H, m, 1-H, PhOCH_2), 3.79 (3H, s, OCH_3), 3.45 (1H, dd, $^2J_{gem}$ 10.6, ^3J 4.3, 1′-H), 1.84-1.72 (2H, m, OCH$_2$CH_2), 1.50-1.20 (10H, m, 5×CH_2) and 0.81 (3H, t, ^3J 6.8, CH_3); δ_C (75 MHz, $CDCl_3$) 159.6, 159.5 (Cq, Ph), 157.1 (N*C*OO), 133.6, 129.6 (CH, Ph), 127.2 (Cq, Ph), 114.3 (×2, CH, Ph), 113.5 (Cq, Ph), 89.2 (C-5), 78.9 (C-6), 77.2 (C-3), 73.9 (C-4), 69.5 (C-1), 67.9 (PhO*C*H$_2$), 59.5 (C-2), 55.2 (O*C*H$_3$), 46.4 (N*C*H$_2$Ph), 31.7, 29.3, 29.2, 29.1, 25.9, 22.6 (6×*C*H$_2$) and 14.0 (*C*H$_3$); *m*/*z* (HRMS, CI) 478.2613 (M + H$^+$, $C_{29}H_{36}NO_5$ requires 478.2593).

(3a*S*,6*S*,6a*S*)-3-(4-methoxybenzyl)-6-(4-(octyloxy)phenethyl)-tetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 36. Prepared from alkyne **35** (45.0 mg, 0.09 mmol) according to the general procedure for hydrogenation. The crude material was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–AcOEt (95 : 5) to give **36** (43.8 mg, 96.5%) as a white solid. $[\alpha]_D^{20}$ +59.7 (*c* 1.4, $CHCl_3$); ν_{max}(film)/cm^{-1} 1736; δ_H (300 MHz, $CDCl_3$) 7.19 (2H, d, ^3J 8.6, NCH$_2$*Ph*), 7.10 (2H, d, ^3J 8.6, CH$_2$O*Ph*), 6.88 (2H, d, ^3J 8.6, NCH$_2$*Ph*), 6.80 (2H, d, ^3J 8.6, CH$_2$O*Ph*), 4.72 (1H, dd, ^3J 7.7 and 3.8, 3-H), 4.71 (1H, d, $^2J_{gem}$ 15.4, NC*H*$_2$Ph), 4.09 (1H, d, $^2J_{gem}$ 15.1, NC*H*$_2$Ph), 4.06 (1H, dd, ^3J 7.6 and 3.9, 2-H), 3.94 (1H, d, $^2J_{gem}$ 10.6, 1-H), 3.92 (2H, t, ^3J 6.6, PhOCH_2), 3.80 (3H, s, OCH_3), 3.45 (1H, td, ^3J 6.8 and 3.8, 4-H), 3.28 (1H, dd, $^2J_{gem}$ 10.6, ^3J 4.0, 1′-H), 2.80-2.62 (2H, m, 2 × 5-H), 2.18-1.96 (2H, m, 2 × 6-H), 1.84-1.68 (2H, m, PhOCH$_2$CH_2), 1.50-1.20 (10H, m, 5×CH_2) and 0.88 (3H, t, ^3J 6.8, CH_3); δ_C (75 MHz, $CDCl_3$) 159.4 (Cq, Ph), 157.5 (N*C*OO), 132.9 (Cq, Ph), 129.5, 129.2, (CH, Ph), 127.3 (Cq, Ph), 114.4, 114.3 (CH, Ph), 82.2 (C-4), 77.6 (C-3), 69.3 (C-1), 67.9 (PhO*C*H$_2$), 59.9 (C-2), 55.3 (O*C*H$_3$), 46.2 (N*C*H$_2$Ph), 31.8, 31.0, 29.6, 29.3 (×2), 29.2, 26.0, 22.6 (9×*C*H$_2$) and 14.1 (*C*H$_3$); *m*/*z* (HRMS, CI) 482.2899 (M + H$^+$, $C_{29}H_{40}NO_5$ requires 482.2906).

(2*S*,3*S*,4*S*)-4-(4-methoxybenzylamino)-2-(4-(octyloxy)phenethyl)-tetrahydrofuran-3-ol 37. Prepared from oxazolidinone **36** (29.0 mg, 0.06 mmol) according to the general procedure for saponification. The crude material was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–AcOEt (60 : 40) to give **37** (18.7 mg, 68%) as a colourless oil. $[\alpha]_D^{20}$ +12.1 (*c* 0.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 3360; δ_H (300 MHz, $CDCl_3$) 7.22 (2H, d, ^3J 8.6, NCH$_2$*Ph*), 7.11 (2H, d, ^3J 8.6, CH$_2$O*Ph*), 6.87 (2H, d, ^3J 8.6, NCH$_2$*Ph*), 6.81 (2H, d, ^3J 8.6, CH$_2$O*Ph*), 3.96-3.86 (4H, m, 1-H, 3-H, CH_2OPh), 3.80 (3H, s, OCH_3), 3.73 (2H, ABq, $\Delta\delta$ 20.7, $^2J_{gem}$ 12.8, NCH_2Ph), 3.72-3.66 (m, 1H, 1′-H), 3.55 (1H, dd, ^3J 8.4 and 7.3, H$_2$), 3.41 (1H, td, ^3J 7.3 and 5.0, 4-H), 2.78-2.58 (2H, m, 2 × 5-H), 2.38 (2H, br s, OH, NH), 2.40-1.92 (2H, m, 2 × 6-H), 1.82-1.68 (2H, m, CH_2CH$_2$OPh), 1.50-1.20 (10H, m, 5×CH_2) and 0.88 (3H, t, ^3J 6.6, CH_3); δ_C (75 MHz, $CDCl_3$) δ 158.9, 157.3, 133.8, 131.3 (Cq, Ph), 129.3, 129.2, 114.3, 113.9 (CH, Ph), 82.3 (C-4), 70.4 (C-1), 69.6 (C-3), 68.0 (PhO*C*H$_2$), 61.0 (C-2), 55.3 (O*C*H$_3$), 52.1 (N*C*H$_2$Ph), 31.8, 31.4, 31.0, 29.4, 29.3, 29.2, 26.0, 22.6 (8×*C*H$_2$) and 14.1 (*C*H$_3$); *m*/*z* (HRMS, CI) 456.3113 (M+H$^+$, $C_{28}H_{42}NO_4$ requires 456.3114).

(2*S*,3*S*,4*S*)-4-amino-2-(4-(octyloxy)phenethyl)tetrahydrofuran-3-ol 38. A solution of *N*-PMB intermediate **37** (18.7 mg, 0.04 mmol) in CH_2Cl_2–MeOH 1 : 1 (2 mL) containing Pd(OH)$_2$ (20 wt%) was stirred overnight under hydrogen 10 bar atmosphere of H_2. The reaction mixture was then filtered over Celite®, the precipitate was rinsed with CH_2Cl_2 and the filtrate concentrated in vacuum to give **38** (13.2 mg, 96%) as a white solid. $[\alpha]_D^{20}$ +4.1 (*c* 1.3, MeOH); ν_{max}(film)/cm^{-1} 3342; δ_H (300 MHz, $CDCl_3$) 7.10 (2H, d, ^3J 8.6, Ph), 6.80 (2H, d, ^3J 8.6, Ph), 3.98-3.88 (3H, m, PhOCH_2, 3-H), 3.88-3.78 (2H, m, 1-H, 4-H), 3.56-3.40 (2H, m, 1′-H, 2-H), 2.72-2.52 (2H, m, 2 × 5-H), 1.98-1.82 (2H, m, 2 × 6-H), 1.80-1.68 (2H, m, PhOCH$_2$CH_2), 1.54-1.20 (10H, m, 5×CH_2) and 0.91 (3H, t, ^3J 6.8, CH_3); δ_C (75 MHz, $CDCl_3$) 158.8, 135.3 (Cq, Ph), 130.3, 115.5 (CH, Ph), 83.4 (C-4), 73.3 (C-3), 72.2 (C-1), 69.0 (PhO*C*H$_2$), 56.1 (C-2), 33.0, 32.8, 32.3, 30.6, 30.5, 30.4, 27.2, 23.8 (8×*C*H$_2$) and 14.5 (*C*H$_3$); *m*/*z* (HRMS, CI) 336.2529 (M + H$^+$, $C_{20}H_{34}NO_3$ requires 336.2539).

(3a*S*,6*S*,6a*S*)-3-(4-methoxybenzyl)-6-((*E*)-tetradec-1-enyl)-tetrahydrofuro[3,4-*d*]oxazol-2(3*H*)-one 39a and (3a*S*,6*S*,6a*S*)-3-(4-methoxybenzyl)-6-((*E*)-tetradec-2-enyl)tetrahydrofuro[3,4-*d*]oxazol-2(3*H*)-one 39b. Prepared from olefin **20** (142 mg, 0.52 mmol) and 1-tetradecene according to the general procedure for olefins cross metathesis. The crude material was purified by column chromatography on SiO_2 eluting with PE–CH_2Cl_2–AcOEt (70 : 24 : 6 to 60 : 32 : 8) to give **39a** and **39b** (165 mg, 72%) as a 70 : 30 mixture according to ^{1}H NMR analysis. δ_H (300 MHz, $CDCl_3$) for the mixture of major (M) and minor (m) isomers, 7.19 (2H, d, ^3J 8.5, NCH$_2$*Ph*), 6.87 (2H, d, ^3J 8.5, NCH$_2$*Ph*), 5.87 (0.7H, dt, ^3J 15.2 and 6.6, 6M-H), 5.72-5.54 (1H, m, 7m-H, containing at 5.64 a dd, ^3J 15.4 and 7.9, 5M-H), 5.46 (0.3H, dt, ^3J 15.3 and 6.8, 6m-H), 4.80-4.65 (2H, m, 3m-H, containing at 4.75 a dd, ^3J 7.5 and 3.8, 3M-H and at 4.70 a d, $^2J_{gem}$ 15.2, NC*H*$_2$Ph), 4.15-4.02 (2H, m, 2m-H, containing at 4.10 a d, $^2J_{gem}$ 15.2, NC*H*$_2$Ph and at 4.09 a dd, ^3J 7.7 and 3.8, 2M-H), 4.00-3.92 (1.7H, m, 1m-H, containing at 3.96 a d, $^2J_{gem}$ 10.1, 1M-H and at 3.95 a dd, ^3J 7.7 and 2.9, 4M-H), 3.80 (3H, s, OCH_3), 3.50 (0.3H, td, ^3J 7.3 and 3.7, 4m-H), 3.34 (0.7H, dd, $^2J_{gem}$ 10.5, ^3J 4.1, 1′M-H), 3.31 (0.3H, dd, $^2J_{gem}$ 10.3, ^3J 4.0, 1′m-H), 2.47 (0.6H, apparent t, $^2J_{gem} \approx {}^3J$ 6.7, 5m-H), 2.09 (1.4H, apparent q, $^2J_{gem} \approx {}^3J$ 7.0, 7M-H), 1.99 (0.6H, apparent q, $^2J_{gem} \approx {}^3J$ 6.8, 8m-H), 1.50-1.20 (19.4H, m, 8M-H to 17M-H and 9m-H to 17m-H) and 0.98-0.84 (3H, m, CH_3); δ_C (75 MHz, $CDCl_3$) for the mixture of major (M) and minor (m) isomers, 159.5 (Cq, Ph), 157.5 (NCOO), 135.6 (C-6M),

134.4 (C-7m), 129.6 (CH, Ph), 127.4 (Cq, Ph), 124.3 (C-6m), 122.1 (C-5M), 114.4 (CH, Ph), 84.3 (C-4M), 83.3 (C-4m), 78.7 (C-3M), 77.6 (C-3m), 69.5 (C-1m), 69.3 (C-1M), 60.1 (C-2M), 59.8 (C-2m), 55.3 (OCH_3), 46.3 (NCH_2Ph), 32.6 (C-8m), 32.5 (C-7M), 31.4 (C-5m), 32.9, 29.7, 29.6, 29.5, 29.3, 29.2, 28.8, 22.7, 19.3 (C-8M to C-17M and C-9m to C-17m) and 14.1 (CH_3); *m/z* (DCI/NH_3) 444 ($M+H^+$, 28%); 461 ($M+NH_4^+$, 100%).

(3a*S*,6*S*,6a*S*)-6-((*E*)-tetradec-1-enyl)tetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 41. Prepared from a mixture of olefins **39a** and **39b** (90.0 mg, 0.20 mmol) according to the general procedure for oxidative deprotection. The crude material was purified by column chromatography on SiO_2 eluting with PE–CH_2Cl_2–AcOEt (50 : 40 : 10) to give **41** (24.2 mg, 37% or 56% from **39a**) as a white solid. $[\alpha]_D^{20}$ +100.1 (*c* 1.2, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 5.90 (1H, dt, ^3J 15.3 and 6.7, 6-H), 5.63 (1H, dd, ^3J 15.4 and 7.8, 5-H), 4.94 (1H, dd, ^3J 7.4 and 3.7, 3-H), 4.40 (1H, dd, ^3J 7.4 and 4.0, 2-H), 3.97 (1H, d, $^2J_{gem}$ 10.7, 1-H), 3.97 (1H, dd, ^3J 7.5 and 3.3, 4-H), 3.56 (1H, dd, $^2J_{gem}$ 10.5, ^3J 4.0, 1′-H), 2.09 (2H, apparent q, $^2J_{gem} \approx {}^3J$ 6.8, 7-H), 1.60-1.10 (20H, m, 8-H to 17-H) and 1.00-0.85 (3H, m, CH_3); δ_C (75 MHz, $CDCl_3$) 159.4 (N*C*OO), 138.5 (C-6), 122.1 (C-5), 84.1 (C-4), 81.9 (C-3), 73.4 (C-1), 57.4 (C-2), 32.5 (C-7), 31.9, 29.7, 29.6, 29.5, 29.4, 29.2, 28.8, 22.7 (C-8 to C-17) and 14.1 (CH_3); *m/z* (HRMS, CI) 324.2570 ($M+H^+$, $C_{19}H_{34}NO_3$ requires 324.2539).

(2*S*,3*S*,4*S*)-4-amino-2-((*E*)-tetradec-1-enyl)tetrahydrofuran-3-ol 40. Prepared from oxazolidinone **41** (24.0 mg, 0.074 mmol) according to the general procedure for saponification. The crude material was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–EtOH–MeOH–NH_4OH (91 : 5 : 2 : 2) to give **40** (14.0 mg, 64%) as a white solid. $[\alpha]_D^{20}$ +40.0 (*c* 0.9, EtOH); δ_H (300 MHz, $CDCl_3$) 5.81 (1H, dt, ^3J 15.2 and 6.5, 6-H), 5.61 (1H, dd, ^3J 15.4 and 6.8, 5-H), 4.30 (1H, dd, ^3J 6.7 and 3.8, H_4), 3.99 (1H, dd, $^2J_{gem}$ 8.2, ^3J 7.0, 1-H), 3.90 (1H, dd, ^3J 4.7 and 3.9, 3-H), 3.64 (1H, td, ^3J 7.1 and 4.8, 2-H), 3.56 (1H, dd, $^2J_{gem}$ 8.1, ^3J 7.5, 1′-H), 2.08 (2H, q, $^2J_{gem} \approx {}^3J$ 6.9, 7-H), 1.90 (3H, br s, OH, NH_2), 1.43-1.19 (20H, m, 8-H to 17-H) and 0.95-0.80 (3H, m, CH_3); δ_C (75 MHz, $CDCl_3$) 135.9 (C-6), 125.1 (C-5), 83.4 (C-4), 73.0 (C-3), 72.4 (C-1), 54.8 (C-2), 32.5 (C-7), 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 22.7 (C-8 to C-17) and 14.1 (CH_3); *m/z* (HRMS, CI) 298.2761 ($M + H^+$, $C_{18}H_{36}NO_2$ requires 298.2746).

(3a*S*,6*S*,6a*S*)-6-(11-hydroxyundec-1-enyl)-3-(4-methoxybenzyl)-tetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 42. Prepared from olefin **20** (50.0 mg, 0.18 mmol) and according to the general procedure for olefins cross metathesis. The crude material was purified by column chromatography on SiO_2 eluting with PE–CH_2Cl_2–AcOEt (70 : 24 : 6 to 60 : 32 : 8) to give **42** (58.5 mg, 77.2%) as a white solid. LC-MS analysis of this mixture (XBridge C18, 5 µM, 150 × 4.6 mm, 1 mL min^{-1}, 0.1% TFA in CH_3CN/0.1% aqueous TFA, 5 : 95 to 90 : 10 gradient in 10 min, Rt Major 11.07 min, Rt minor 11.74 min) indicated a 66 : 34 ratio of isomers. *m/z* (HRMS, CI) 418.2601 ($M + H^+$, $C_{24}H_{36}NO_5$ requires 418.2593).

(3a*S*,6*S*,6a*S*)-6-(11-hydroxyundecyl)-3-(4-methoxybenzyl)-tetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 44. Prepared from a mixture of olefins **42** (60.0 mg, 0.14 mmol) according to the general procedure for hydrogenation. The crude material was purified by column chromatography on SiO_2 eluted with CH_2Cl_2–AcOEt (60 : 40) to give **44** (52.0 mg, 86%) as a white solid. $[\alpha]_D^{20}$ +58.0 (*c* 1.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 3350 and 1737; δ_H (300 MHz, $CDCl_3$) 7.19 (2H, d, ^3J 8.7, NCH_2Ph), 6.87 (2H, d, ^3J 8.7, NCH_2Ph), 4.75 (1H, dd, ^3J 7.7 and 3.8, 3-H), 4.70 (1H, d, $^2J_{gem}$ 15.1, NCH_2Ph), 4.07 (1H, d, $^2J_{gem}$ 15.1, NCH_2Ph), 4.06 (1H, dd, ^3J 7.7 and 4.0, 2-H), 3.93 (1H, d, $^2J_{gem}$ 10.6, 1-H), 3.79 (3H, s, OCH_3), 3.63 (2H, t, ^3J 6.6, 2 × 15-H), 3.48 (1H, td, ^3J 6.8 and 3.8, 4-H), 3.30 (1H, dd, $^2J_{gem}$ 10.6, ^3J 4.0, 1′-H), 1.84-1.70 (2H, m, 5-H), 1.62-1.51 (2H, m, 14-H) and 1.46-1.18 (16H, m, 8×CH_2); δ_C (75 MHz, $CDCl_3$) 159.4 (Cq, Ph), 157.5 (N*C*OO), 129.5 (CH, Ph), 127.3 (Cq, Ph), 114.3 (CH, Ph), 83.4 (C-4), 77.7 (C_3), 69.2 (C-1), 63.0 (C-15), 59.8 (C-2), 55.3 (OCH_3), 46.1 (NCH_2Ph), 32.8, 29.5 (×2), 29.4 (×2), 29.3 (×2), 28.0, 26.0 and 25.7 (10×CH_2, C-5 to C-14); *m/z* (HRMS, CI) 420.2777 ($M + H^+$, $C_{24}H_{38}NO_5$ requires 420.2750).

(3a*S*,6*S*,6a*S*)-6-(11-hydroxyundecyl) tetrahydrofuro[3,4-*d*]-oxazol-2(3H)-one 45. Prepared from the *N*-PMB intermediate **44** (29.0 mg, 0.07 mmol) according to the general procedure for oxidative deprotection. The crude material was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–MeOH (95 : 5) to give **45** (15.2 mg, 73%) as a white solid. $[\alpha]_D^{20}$ +66.0 (*c* 1.1, MeOH); ν_{max}(film)/cm^{-1} 3400 and 1719; δ_H (300 MHz, $CDCl_3$) 5.00 (1H, dd, ^3J 7.5 and 3.6, 3-H), 4.38 (1H, dd, ^3J 7.5 and 3.9, 2-H), 3.84 (1H, d, $^2J_{gem}$ 10.3, 1-H), 3.62-3.48 (4H, m, 4-H, 1′-H, 2 × 15-H), 1.76-1.64 (2H, m, 5-H) and 1.58-1.24 (m, 18H, 9×CH_2); δ_C (75 MHz, $CDCl_3$) 161.7 (N*C*OO), 84.3 (C-4), 82.5 (C-3), 74.3 (C-1), 63.0 (C-15), 58.8 (C-2), 33.7, 30.8 (×2), 30.7 (×2), 30.6 (×2), 29.3, 27.1 and 27.0 (10×CH_2, C-5 to C-14); *m/z* (HRMS, CI) 300.2177 ($M + H^+$, $C_{16}H_{30}NO_4$ requires 300.2175).

(2*S*,3*S*,4*S*)-4-amino-2-(11-hydroxyundecyl)tetrahydrofuran-3-ol 43. Prepared from oxazolidinone **45** (14.2 mg, 0.047 mmol) according to the general procedure for saponification. The crude material was purified by column chromatography on SiO_2 eluting with AcOEt–MeOH–NH_4OH (79.2 : 20 : 0.8) to give **43** (11.0 mg, 85%) as a white solid. $[\alpha]_D^{20}$ +17.6 (*c* 0.8, MeOH); ν_{max}(film)/cm^{-1} 3430; δ_H (300 MHz, $CDCl_3$) 3.90 (1H, apparent t, $^3J \approx {}^2J_{gem}$ 7.3, 1-H), 3.88-3.76 (2H, m, 3-H, 4-H), 3.53 (2H, t, ^3J 6.6, 2 × 15-H), 3.62-3.48 (2H, m, 1′-H, 2-H), 1.72-1.46 (m, 4H, 2 × 5-H, 2 × 14-H) and 1.44-1.24 (m, 16H, 8×CH_2); δ_C (75 MHz, $CDCl_3$) 84.4 (C-4), 73.3 (C-3), 72.1 (C-1), 63.0 (C-15), 56.1 (C-2), 33.7, 30.9, 30.8, 30.7 (×3), 30.6, 27.2, 27.0 (10×CH_2, C-5 to C-14); *m/z* (HRMS, CI) 274.2387 ($M + H^+$, $C_{15}H_{32}NO_3$ requires 274.2382).

Undec-10-enyl methanesulfonate 47. Prepared from undec-10-en-1-ol (608 mg, 3.57 mmol) according to the general procedure of mesylation. The crude material was purified by column chromatography on SiO_2 eluting with PE–AcOEt (70 : 30) to give **47** (870.0 mg, 98%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 5.80 (1H, ddt, ^3J 16.9, 10.2 and 6.7, 10-H), 5.04-4.88 (2H, m, 2 × 11-H), 4.21 (2H, t, ^3J 6.6, 1-H), 2.99 (3H, bs, OSO_2CH_3), 2.08-1.98 (2H, m, 2 × 9-H), 1.80-1.68 (2H, m, 2 × 2-H) and 1.46-1.22 (12H, m, 6×CH_2); δ_C (75 MHz, $CDCl_3$) 139.1 (C-10), 114.1 (C-11), 70.1 (C-1), 37.3 (OSO_2CH_3), 33.7 (C-9), 29.3, 29.2, 29.1, 29.0, 28.9, 28.8 and 25.3 (7×CH_2, C-2 to C-8); *m/z* (DCI/CH_4) 153 (M^+-•OSO_2CH_3, 22%), 111 (M^+-•$(CH_2)_3OSO_2CH_3$, 100%).

11-azidoundec-1-ene 46. To a solution of mesylate **47** (735 mg, 2.96 mmol) in distilled DMSO (5 mL) under nitrogen atmosphere was added NaN_3 (962 mg, 14.81 mmol). The mixture was heated and stirred for 2 h at 50 °C after which it was diluted with water. The mixture was extracted three times with diethyl ether and the

combined extracts were washed with brine and dried over $MgSO_4$. The solvent was evaporated in vacuum and the crude material was purified by column chromatography on SiO_2 eluting with PE–Et_2O (98 : 2) to give **46** (531.0 mg, 92%) as colourless oil. δ_H (300 MHz, $CDCl_3$) 5.81 (1H, ddt, ^3J 16.9, 10.2 and 6.7 Hz, 2-H), 5.06-4.98 (m, 2H, 2 × 1-H), 3.25 (2H, t, ^3J 6.9, 11-H), 2.10-1.98 (2H, m, 2 × 3-H), 1.66-1.52 (m, 2H, 2 × 10-H) and 1.44-1.22 (m, 12H, 6×CH_2); δ_C (75 MHz, $CDCl_3$) 139.1 (C-2), 114.1 (C-1), 51.4 (C-11), 33.8 (C-3), 29.4, 29.3, 29.1, 29.0, 28.9, 28.8 and 26.7 (7×CH_2, C-4 to C-10); (DCI/CH_4) m/z 196 (M+H$^+$, 26%), 168 (M$^+$-•C_2H_3, 100%), 166 (70%).

Benzyl undec-10-enylcarbamate 48. To a solution of 11-azidoundec-1-ene **46** (63.0 mg, 0.32 mmol) in anhydrous THF (1 mL) under nitrogen atmosphere at room temperature was added Me_3P (0.35 mL of a 1.0 M solution in THF, 0.35 mmol). The mixture was stirred until complete formation of the phosphazene (*ca.*2 h) (TLC monitoring). Benzyl chloroformate (60.6 mg, 0.35 mmol) was then added and the reaction was allowed to proceed for 30 min after which it was quenched with water. The mixture was extracted three times with CH_2Cl_2 and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was evaporated in vacuum and the crude material was purified by column chromatography on SiO_2 eluting with PE–AcOEt (80 : 20) to give carbamate **48** (53.1 mg, 54%) as colourless oil. δ_H (300 MHz, $CDCl_3$) 7.42-7.28 (m, 5H, Ph), 5.81 (1H, ddt, ^3J 16.9, 10.1 and 6.7, 10.H), 5.09 (2H, bs, OCH_2Ph), 5.05-4.88 (2H, m, 2 × 11-H), 4.7 (1H, bs, NH), 3.26-3.10 (2H, m, 1-H), 2.12-1.98 (2H, m, 2 × 9-H), 1.54-1.44 (2H, m, 2 × 2-H) and 1.40-1.20 (m, 12H, 6×CH_2); δ_C (75 MHz, $CDCl_3$) 156.4 (N*C*OO), 139.1 (C-10), 136.6 (Cq, Ph), 128.4, 128.1, 128.0 (CH, Ph), 114.1 (C-11), 66.5 (O*C*H$_2$Ph), 41.1 (C-1), 33.7 (C-9), 29.9, 29.4, 29.3, 29.2, 29.0, 28.8 and 26.7 (7×CH_2, C-2 to C-8); m/z (DCI/NH_3) m/z 304 (M+H$^+$, 31%), 321 (M+NH_4^+, 100%).

Benzyl 11-((3a*S*,6*S*,6a*S*)-3-(4-methoxybenzyl)-2-oxohexahydrofuro[3,4-*d*]oxazol-6-yl)undec-10-enylcarbamate 49. Prepared from olefin **20** (58.0 mg, 0.21 mmol) and olefin **48** according to the general procedure for olefins cross metathesis. The crude material was purified by column chromatography on SiO_2 eluting with PE–CH_2Cl_2–AcOEt (20 : 64 : 16) then CH_2Cl_2–AcOEt (80 : 20) to give **49** (75.0 mg, 65%) as a white solid. A 70 : 30 ratio of isomers was estimated by ^{1}H NMR analysis of the mixture of major (M) and minor (m) compounds (signals at 3.30 (0.3H, m, 4m-H) and at 3.16 (1H, m, 1-H)). m/z (HRMS, CI) 551.3123 (M + H$^+$, $C_{32}H_{43}N_2O_6$ requires 551.3121).

(3a*S*,6*S*,6a*S*)-6-(11-aminoundecyl)-3-(4-methoxybenzyl)tetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 50. Prepared from a mixture of olefins **49** (65.0 mg, 0.12 mmol) according to the general procedure for hydrogenation. The crude material was purified by column chromatography on SiO_2 eluting with AcOEt–MeOH–NH_4OH (89.2 : 10 : 0.8) to give **50** (45.0 mg, 92%) as a white solid. $[\alpha]_D^{20}$ +55.3 (*c* 0.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 3426 and 1738; δ_H (300 MHz, $CDCl_3$) 7.19 (2H, d, ^3J 8.7, NCH$_2$*Ph*), 6.87 (2H, d, ^3J 8.7, NCH$_2$*Ph*), 4.75 (1H, dd, ^3J 7.8 and 3.8, 3-H), 4.71 (1H, d, $^2J_{gem}$ 15.1, NCH_2Ph), 4.07 (1H, d, $^2J_{gem}$ 15.1, NCH_2Ph), 4.05 (1H, dd, ^3J 7.8 and 4.0, 2-H), 3.93 (d, 1H, $^2J_{gem}$ 10.6, 1-H), 3.75 (3H, s, OCH_3), 3.48 (1H, td, ^3J 6.8 and 3.8, 4-H), 3.30 (1H, dd, $^2J_{gem}$ 10.6, ^3J 4.0, 1′-H), 2.67 (2H, t, ^3J 6.9, 2 × 15-H), 1.82-1.70 (2H, m, 5-H), 1.68-1.50 (4H, m, 2 × 14-H, NH_2) and 1.48-1.16 (16H, m, 8×CH_2); δ_C (75 MHz, $CDCl_3$) 159.4 (Cq, Ph), 157.5 (N*C*OO), 129.5 (CH, Ph), 127.3 (Cq, Ph), 114.3 (CH, Ph), 83.5 (C-4), 77.7 (C-3), 69.3 (C-1), 59.9 (C-2), 55.3 (O*C*H$_3$), 46.2 (N*C*H$_2$Ph), 42.2 (C-15), 33.7, 29.6, 29.5, 29.4, 28.0, 26.8 and 26.0 (10×CH_2, C-5 to C-14); m/z (HRMS, CI) 419.2915 (M + H$^+$, $C_{24}H_{39}N_2O_4$ requires 419.2910).

(3a*S*,6*S*,6a*S*)-6-(11-aminoundecyl)tetrahydrofuro[3,4-*d*]oxazol-2(3H)-one 51. Prepared from the *N*-PMB intermediate **50** (42.0 mg, 0.10 mmol) according to the general procedure of oxidative deprotection. The crude material was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–MeOH–NH_4OH (89.2 : 10 : 0.8) to give **51** (12.2 mg, 40.8%) a white solid. $[\alpha]_D^{20}$ +57.7 (*c* 1.2, MeOH); ν_{max}(film)/cm^{-1} 3408 and 1758; δ_H (300 MHz, $CDCl_3$) 4.98 (1H, dd, ^3J 7.5 and 3.6, 3-H), 4.36 (1H, dd, ^3J 7.5 and 4.0, 2-H), 3.82 (1H, d, $^2J_{gem}$ 10.3, 1-H), 3.58-3.47 (m, 2H, 1′-H, 4-H), 2.64 (t, 2H, 2 × 15-H), 1.74-1.62 (m, 2H, 5-H) and 1.54-1.22 (m, 18H, 9×CH_2); δ_C (75 MHz, $CDCl_3$) 161.8 (N*C*OO), 84.3 (C-4), 82.5 (C-3), 74.3 (C-1), 58.8 (C-2), 42.4 (C-15), 33.1, 30.8 (×3), 30.7, 30.6 (×2), 29.4, 28.0 and 27.1 (10×CH_2, C-5 to C-14); m/z (HRMS, CI) 299.2355 (M + H$^+$, $C_{16}H_{31}N_2O_3$ requires 299.2335).

(2*S*,3*S*,4*S*)-4-amino-2-(11-aminoundecyl) tetrahydrofuran-3-ol 52. Prepared from oxazolidinone **51** (12.0 mg, 0.04 mmol) according to the general procedure for saponification. The crude material was purified by column chromatography on SiO_2 eluting with CH_2Cl_2–MeOH–NH_4OH (84.2 : 15 : 0.8) to give **52** (8.50 mg, 78%) as a white solid. $[\alpha]_D^{20}$ +20.0 (*c* 0.5, MeOH); ν_{max}(film)/cm^{-1} 3402; δ_H (300 MHz, $CDCl_3$) 3.90 (1H, apparent t, $^2J_{gem} \approx {}^3J$ 7.3, 1-H), 3.86-3.78 (2H, m, 3-H, 4-H), 3.54-3.44 (1H, ddd, ^3J 9.4, 7.5 and 4.2, 2-H), 3.41 (1H, dd, $^2J_{gem}$ 9.2, ^3J 7.2, 1′-H), 2.64 (2H, t, ^3J 7.2, 2 × 15-H), 1.72-1.54 (2H, m, 2 × 5-H), 1.52-1.42 (2H, m, 2 × 14-H) and 1.40-1.24 (16H, m, 8×CH_2); δ_C (75 MHz, $CDCl_3$) 84.4 (C-4), 73.4 (C-3), 72.3 (C-1), 56.1 (C-2), 42.5 (C-15), 33.5, 31.0, 30.8, 30.7, 30.6, 28.0 and 27.2 (10×CH_2, C-5 to C-14); m/z (HRMS, CI) 273.2551 (M + H$^+$, $C_{15}H_{33}N_2O_2$ requires 273.2542).

Biological evaluations. Murine B16 melanoma cells were grown in a humidified 5% CO_2 atmosphere at 37 °C in DMEM medium containing Glutamax (2 mM), and heat-inactivated FCS (10%). Compounds were added to the cells as ethanolic solution. Control cells were treated with the same concentration of solvent (which did not exceed 0.5%).

Cell viability. After treatment with natural, synthetic jaspine B or chain-modified analogues, cell viability of murine B16 melanoma cells was evaluated by using the MTT assay based on the cleavage of the tetrazolium salt MTT to formazan crystals by metabolically active cells as described earlier.[39] The formazan crystals formed were solubilised by adding dimethylsulfoxide for 1 h at 37 °C and quantified spectrophotometrically using an ELISA reader (the absorbance was measured at λ = 560 nm). Data are presented as means ± S.E.M.

Determination of *in situ* sphingomyelin synthase and glucosylceramide synthase activities. Murine B16 melanoma cells were incubated with natural jaspine B or its chain-modified analogues in the absence of FCS for 6 h at 5 μM. Then, 5 μM C_6-NBD-ceramide was added to the medium as an ethanolic solution. After incubation for 2 h at 37 °C, cellular lipids were extracted with

chloroform–methanol (2 : 1, v/v) as described.[40] After centrifugation (1000 × *g*, 10 min), the lower phases were concentrated under nitrogen and resolved by TLC developed in chloroform–methanol–30% ammonia–water (70 : 30 : 3 : 2, by vol.). C_6-NBD-ceramide (C_6-NBD-Cer), C_6-NBD-glucosylceramide (C_6-NBD-GlcCer) and C_6-NBD-sphingomyelin (C_6-NBD-SM) were eluted from the silica and quantified spectrofluorometrically (λ_{ex} = 470 nm and λ_{em} = 530 nm). Data are presented as means ± S.E.M.

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