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Enantioselective access to a versatile 4-oxazolidinonecarbaldehyde and application to the synthesis of a cytotoxic jaspine B truncated analogue

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Abstract—The preparation of the versatile aldehyde **15** via a concise route based on a formal *anti*-asymmetric aminohydroxylation and its use in a 5-step synthesis of a cytotoxic C_{12} analogue of the natural anhydrophytosphingosine jaspine B is presented.

1. Introduction

Sphingoid bases are long-chain (typically C_{18}) aminopolyols that constitute the backbone of sphingolipids, ubiquitous components of eukaryotic cell membranes.[1] Once N-acylated with a fatty acid they give rise to ceramides, precursors of sphingomyelin and glycosphingolipid through C-1 functionalisation. Most sphingoid bases are of the D-*erythro*-sphingosine type but the less prevalent D-*ribo*-phytosphingosine subclass has attracted great interest (Fig. 1).[2] Notably, the participation of simpler sphingolipids in signal transduction and cell growth regulation has been established. Ceramide is recognised as a second messenger causing various antimitogenic effects, including apoptosis.[3] In contrast, sphingosine-1-phosphate has emerged as a key mitogenic regulator.[4] These observations suggest that the pharmacological manipulation of the sphingolipid metabolism represents a promising approach for the development of novel anticancer therapies.[5]

We recently developed an access to the D-*ribo*-phytosphingosine backbone from a *trans*-2,3-epoxyaldehyde precursor.[6] However, the flexibility of this route is hampered by the sensitivity of the oxirane functionality. Thus, we turned our attention towards a 4-oxazolidinonecarbaldehyde of type **6**, which represents an ideal four carbon electrophilic synthon (Scheme 1). The synthetic usefulness of a similar entity for the synthesis of D-*ribo*-phytosphingosine has

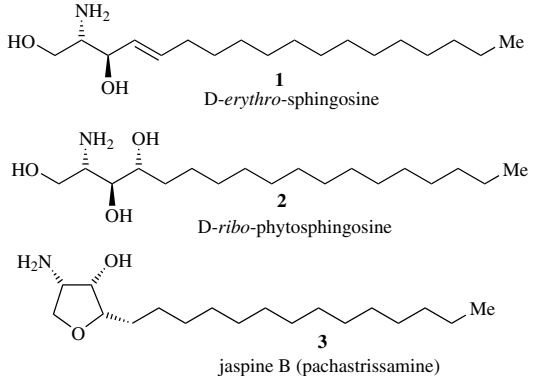
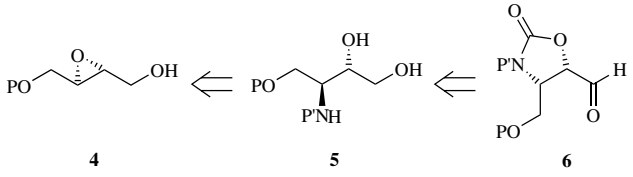


Figure 1. Sphingoid derivatives.



Scheme 1. Retrosynthetic approach to aldehydes of type **6**.

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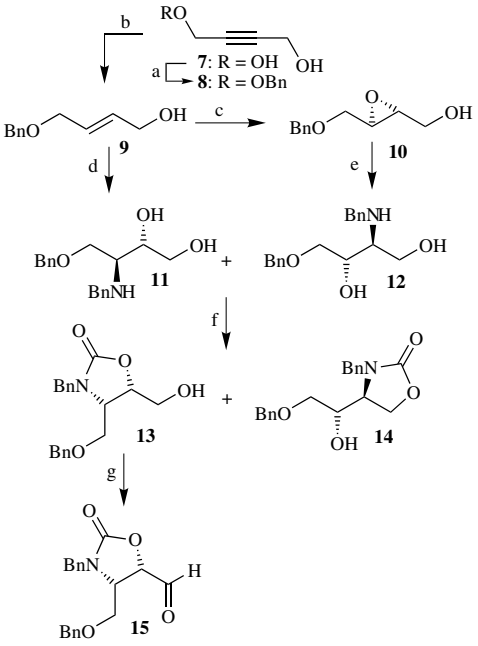
already been demonstrated by Wee[7] who attained such a 4-oxazolidinonecarbaldehyde intermediate via a nine-step chemical route starting from a non-commercial D-mannose-derived phenylsulfide.

2. Results and discussion

Our synthetic plan was centred on the ring opening of a chiral *trans*-2,3-epoxyalcohol **4** by a primary amine (Scheme 1). The resulting aminodiol **5** could in turn be readily transformed into the targeted aldehyde through oxazolidinone ring formation and primary alcohol oxidation.

2.1. Preparation of the 4-oxazolidinonecarbaldehyde intermediate

The starting allylic alcohol **9** was readily obtained by monobenzylation of butyne-1,4-diol followed by LAH reduction (Scheme 2). This was then subjected to Sharpless' asymmetric epoxidation to yield **10**. We then focused on the regio- and stereoselective Ti(O*i*-Pr)$_4$-catalysed ring-opening process developed by Pericàs and Riera.[8] When treated with benzylamine under these conditions, 2,3-epoxyalcohol **10** afforded the expected aminodiols **11** and **12** in 75% yield and in a 70:30 ratio, in favour of C-3 opening. The two regioisomers were separated for full characterisation. These were independently cyclised into the corresponding acetonides (1.2 equiv PTSA, dimethoxypropane, RT, several days) in order to confirm their identity: **11** yielded a 1,3-dioxolane displaying a characteristic ^{13}C NMR signal at δ_C 108.9 ppm for the quaternary ketal carbon. On the other hand, **12** was transformed into the isomeric 1,3-dioxane (δ_C 98.7 ppm for the corresponding quaternary carbon).[9] The use of *p*-methoxybenzylamine as a nucleophile in the epoxide opening gave a comparable result (65% yield of a 60:40 mixture). Notably, the regioselectivity was reversed in favour of the C-2 opening product, using an aluminium-based catalyst (3.5 equiv $AlMe_3$, 2.5 equiv $BnNH_2$, CH_2Cl_2, reflux, 65% yield of a 58:42 mixture). Interestingly, the same result was obtained by gentle heating of **10** in aqueous medium (3 equiv $BnNH_2$, methoxyethanol/water, 65 °C).



Scheme 2. Reagents and conditions: (a) BnBr, KOH, H_2O, rt, 2 days, 70% based on the bromide; (b) $LiAlH_4$, THF, −20 °C to rt, 6 h, 60%; (c) Ti(O*i*-Pr)$_4$, (−)-DET, *t*-BuOOH, 4 Å MS, CH_2Cl_2, −23 °C, 3.5 days, 90%; (d) Ti(O*i*-Pr)$_4$, (−)-DET, *t*-BuO_2H, 4 Å MS, CH_2Cl_2, −23 °C, 3 days, then Me_2S, rt, 3 h, then Ti(O*i*-Pr)$_4$, $BnNH_2$, rt, 1.5 days, 60% of a 70:30 mixture of **11** and **12**; (e) Ti(O*i*-Pr)$_4$, $BnNH_2$, CH_2Cl_2, reflux, 24 h, 75% of a 70:30 mixture of **11** and **12**; (f) (i) K_2CO_3, MeOCOCl, THF, rt, 18 h; (ii) 80% KOH in MeOH, rt, 5 h, 60% overall yield of **13**, 23% overall yield of **14**; (g) DMP, CH_2Cl_2, rt, 3 h, 90%.

An attractive feature of the titanium-catalysed process is the possibility of combining it with Sharpless epoxidation in an overall formal *anti*-asymmetric aminohydroxylation. This one-pot procedure was successfully applied to allylic alcohol **9**. After consumption of the starting olefin, the excess hydroperoxide was reduced with Me_2S. The latter was preferred to the equally efficient, but far more expensive, polymer-bound triphenylphosphine. The addition of an excess amount of Ti(O*i*-Pr)$_4$ and $BnNH_2$ to the reaction medium then smoothly allowed the formation of the desired aminodiols **11** and **12** after 1.5 days at room temperature (60% isolated yield from allylic alcohol **9**) as a 70:30 mixture. Preliminary experiments aimed at the formation of the oxazolidinone moiety showed that the treatment of **11** with trichloromethyl chloroformate (0.5 equiv, CH_2Cl_2/Et_3N 1:1, − 20 °C) exclusively afforded the undesired cyclic carbonate, as indicated, for example, by the infrared data ($\nu_{C=O}$ 1796 cm^{-1}).[10] The formation of the expected cyclic carbamate was, however, accomplished through a convenient two-step procedure: treatment of the aminodiol with methyl chloroformate in excess followed by selective saponification of the carbonate functionalities and spontaneous intramolecular cyclisation. This sequence could be equally applied to major compound **11** or the mixture of regioisomers **11** and **12**. In the latter case,

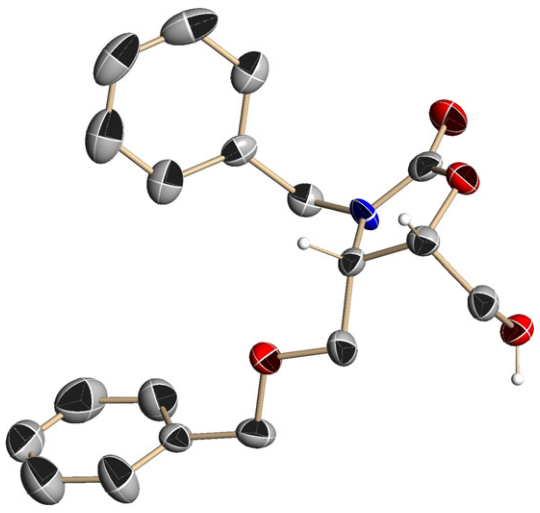


Figure 2. X-ray structure of oxazolidinone **13**.

this led to oxazolidinones **13** and **14** in 83% combined yield. Separation of the regioisomers proved trivial at that stage. X-ray diffraction analysis confirmed the structure of the major product **13** (Fig. 2).[11] The final oxidation procedure had to be carefully chosen to diminish the risk of epimerisation into a *trans*-oxazolidinone ring, as observed, for example, using Swern conditions. The Dess–Martin periodinane proved to be the most suitable, allowing isolation of the expected aldehyde **15** in 90% yield. The latter was thus obtained in a most efficient manner and was fully characterised.

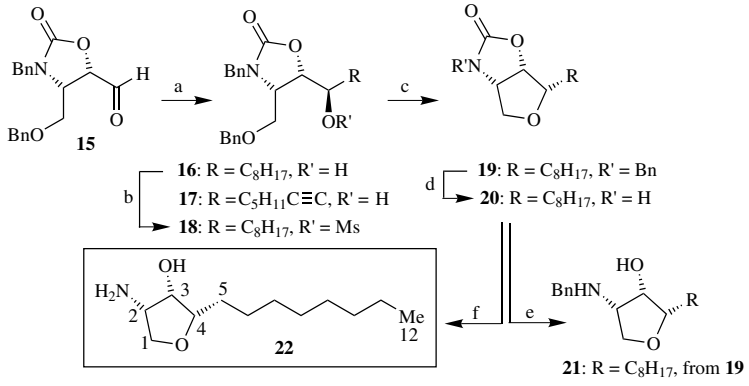
2.2. Synthesis of the truncated jaspine B analogue

Access to **15** constitutes a formal synthesis of natural D-*ribo*-phytosphingosine.[7] In order to further illustrate the synthetic potential of aldehyde **15**, we targeted a biologically relevant analogue of sphingosine, jaspine B (pachastrissamine) (Fig. 1). This anhydrophytosphingosine, isolated from a marine sponge, has been independently described by Higa[14] and Debitus.[15] Either the free base or the hydrochloride displayed a pronounced cytotoxicity towards several cell lines with IC_{50} values in the submicromolar range. Several total syntheses of jaspine B have been reported from a chiral pool derived precursor. Rao[16] and Datta[17] made use of serine while Linhart[18] and Du[19] employed D-xylose. Lately, Falomir and Marco[20] made use of the (*R*)-glycidol as a starting material whereas Chandrasekhar[21] prepared a truncated pachastrissamine from D-xylose. The C-4 epimer of jaspine B is known and no biological activity has been attributed to this D-*ribo* analogue.[22] However, the absence of a proper structure–activity relationship in this series prompted us to develop direct access to the jaspine B skeleton from aldehyde **15**. In particular, the incidence of the aliphatic chain length on cytotoxicity seemed interesting to evaluate. Indeed the high lipophilicity of jaspine B appears disadvantageous for further development.

With regards to the introduction of the lipophilic side chain, we took advantage of the *syn*-selective organocerium nucleophilic addition developed by Wee.[7] Treatment of **15** with the in situ-generated reagent derived from *n*-octyl magnesium bromide resulted in a completely diastereoselective addition (Scheme 3). The same procedure was also carried out using *n*-heptyne lithium, giving adduct **17** as the sole diastereoisomer. The latter represents an interesting precursor for original 5,6-unsaturated phytosphingosine analogues. Elaboration of the all-*cis*-trisubstituted tetrahydrofuran moiety of jaspine B required configuration inversion at C-4. The hydroxyl group was thus activated by conversion to the corresponding mesylate **18**. Pleasingly, we found that the cyclisation occurred spontaneously during the hydrogenolysis of the C-1 benzylic ether, cleanly providing the bicyclic intermediate **19** in 75% yield. Despite the high hydrogen pressure required for the reaction to proceed, the *N*-benzyl carbamate fragment remained unaffected. In fact, this group proved particularly reluctant to cleavage. Pushing the hydrogenation reaction resulted, for example, in saturating the phenyl ring instead of the expected hydrogenolysis reaction. We felt that the highly constrained bicyclic structure of **19** might explain this behaviour. Therefore the carbamate function was hydrolysed and deprotection of the resulting *N*-benzyl amine **21** was attempted.[23] Hydrogenolysis under forcing conditions (10 bars H_2, 10% Pd/C, 12 M HCl, MeOH, 4 days) left the starting material unchanged. A Birch reduction (Na/NH_3, THF, −78 °C, 1 h) resulted in the partial reduction of the aromatic nucleus into a cyclohexadiene ring. We thus reconsidered the reaction sequence and applied a Birch reduction to the oxazolidinone precursor **19**. Gratifyingly the expected debenzylated product **20** was isolated in good yield. The final saponification under standard conditions led smoothly to the targeted truncated jaspine B analogue **22**. Spectral data for the latter were in agreement with that of the natural product.[18] In particular, ^1H NMR of the tetrahydrofuran region allowed confirmation of the all-*cis* configuration.

2.3. Biological evaluation

The biological activity of **22** was then tested on melanoma cell lines. Melanoma is indeed considered as a radiation- and chemotherapy-refractory neoplasm of increasing incidence. As illustrated in Figure 3, the truncated jaspine B analogue **22** gratifyingly exhibited dose-dependent



Scheme 3. Reagents and conditions: (a) $C_8H_{17}MgBr/CeCl_3$, THF, −78 °C, 5 h, then 0 °C, 1 h, 56% in **16**, or $C_5H_{11}CCLi/CeCl_3$, THF, −78 °C, 6 h, 75% in **17**; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1.5 h, 90%; (c) 10 bar H_2, $Pd(OH)_2$, EtOH, 2 days, 75%; (d) Na/NH_3, THF, −78 °C, 4 h, 83%; (e) LiOH, *p*-dioxane/H_2O, reflux, 2.5 days, 97% br sm at 70% conversion, from **19**; (f) KOH, EtOH/H_2O, 85 °C, 7 h, 95%.

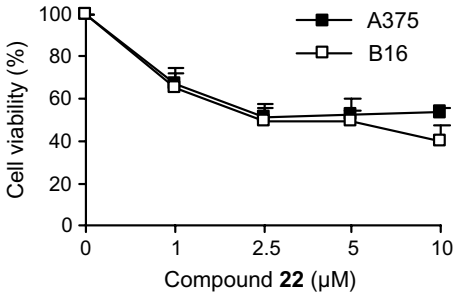


Figure 3. Sensitivity of melanoma cells to compound **22**.

cytotoxicity towards B16 murine and A375 human melanoma cell lines, reaching 50% activity at 2.5 μM.

3. Conclusion

In conclusion, we have developed a practical enantioselective access to 4-oxazolidinonecarbaldehyde **15**, obtained in four steps and in 30% yield from the readily available allylic alcohol **9**. The latter was further transformed into an original C_{12} analogue of jaspine B **22** through a concise five-step sequence. Notably, this truncated anhydrophytosphingosine retains potent cytotoxicity on murine and human melanoma cell lines. The preparation of other various chain-modified jaspine B derivatives potentially active against this typically chemoresistant tumour as well as studies aiming at a better understanding their mode of action are currently in progress.

4. Experimental

4.1. General

Reactions were performed in flame-dried glass, sealed with a rubber septum and stirred with a magnetic stirring bar, under argon or nitrogen if required. Materials were obtained from commercial suppliers and were used without purification, unless otherwise stated. The following solvents were dried prior to use: CH_2Cl_2 (freshly distilled from calcium hydride), Et_2O and THF (distilled from sodium/benzophenone). Thin layer chromatography (TLC) reaction monitoring was carried out with Macherey-Nagel ALUGRAM® SIL G/UV_{254} (0.2 mm) plates visualised with 10% phosphomolybdic acid in ethanol or Dragendorff reagent[24] as dipping solutions. Standard column chromatography was performed with SDS 70–200 μm silica gel. Flash column chromatography was carried out with SDS 35–70 μm silica gel. Medium-pressure liquid chromatography was performed with a Jobin–Yvon apparatus using Merck 15-40 μm silica gel. NMR spectroscopic data were obtained with Bruker AC 250, Avance 300, ARX 400 and Avance 500 instruments operating for ^{1}H NMR spectra at 250, 300, 400 and 500 MHz, respectively, and for ^{13}C NMR spectra at 63, 75, 100 and 125 MHz, respectively. Chemical shifts are quoted in parts per million (ppm) downfield from tetramethylsilane and coupling constants are in Hertz. Infrared (IR) spectra were recorded on a Perkin–Elmer FT-IR 1725X spectrometer. High resolution mass spectra (HRMS) were performed on a ThermoFinnigan MAT 95 XL spectrometer (DCI). Optical rotations were measured on a Perkin–Elmer model 141 polarimeter.

4.1.1. 4-Benzyloxy-2-propyn-1-ol 8. To a solution of KOH (18.8 g, 335.0 mmol) in H_2O (250 mL) was added butyne 1,4-diol **7** (28.9 g, 336.0 mmol) and benzyl bromide (10.0 mL, 84.1 mmol). The mixture was stirred at room temperature for 48 h. Most of the water was then evaporated off and the mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with water and brine, then dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by column chromatography on SiO_2 eluted with PE/ether (70:30 to 60:40) to give **8** (10.4 g, 70% based on the bromide) as a colourless oil. IR (film) ν_{OH} 3392, ν_{CC} 2237 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45–7.15 (m, 5H, Ph), 4.59 (s, 2H, CH_2Ph), 4.31 (s, 2H, H_1), 4.21 (s, 2H, H_4), 2.10 (s, 1H, OH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 137.9 (Cq, Ph), 129.2, 128.9 and 128.7 (CH, Ph), 86.0, 81.7 (C_2 and C_3), 72.4 (*C*H_2Ph), 58.1 (C_1), 51.2 (C_4); MS (DCI/NH_3) *m*/*z* 194 $(M+NH_4)^+$.

4.1.2. 4-Benzyloxy-2-propen-1-ol 9. To a suspension of $LiAlH_4$ (1.95 g, 85.0 mmol) in anhydrous THF (100 mL) at −20 °C and under nitrogen atmosphere was added dropwise a solution of propargylic alcohol **8** (17.6 g, 100.0 mmol) in THF (40 mL). The mixture was stirred at −20 °C for 3 h and at room temperature for 3 h, after which H_2O (4.2 mL) was added, followed by a 10% aqueous NaOH solution (4.2 mL) and water (12.4 mL). The reaction mixture was then filtered over Celite and the cake was rinsed with THF. The resulting solution was concentrated in vacuo and the crude material purified by column chromatography on SiO_2 eluted with PE/AcOEt (70:30 to 60:40) to give allylic alcohol **9** (10.7 g, 60%) as a colour less liquid. IR (film) ν_{OH} 3408 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5H, Ph), 5.89–5.78 (m, 2H, H_2, H_3), 4.53 (s, 2H, OCH_2Ph), 4.20–4.10 (m, 2H, H_1), 4.05 (d, 2H, H_4, $^3J_{H_4-H_3} = 7.0$ Hz), 1.80–1.70 (m, 1H, OH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 138.8 (Cq, Ph), 133.4, 129.1, 128.4, 128.3, 127.8 (CH, Ph, C_2 and C_3), 72.8 (O*C*H_2Ph), 70.8 (C_1), 63.0 (C_4); MS (DCI/NH_3) *m*/*z* 196 $(M+NH_4)^+$.

4.1.3. Aminodiols 11 and 12. To a solution of Ti(O*i*-Pr)$_4$ (1.67 mL, 5.64 mmol) in anhydrous CH_2Cl_2 (10 mL) containing 4 Å molecular sieves (1.2 g) at −23 °C and under nitrogen atmosphere was added (−)-diethyl tartrate (1.4 mL, 8.15 mmol). The mixture was stirred for 10 min and a solution of allylic alcohol **9** (4.0 g, 22.5 mmol) in anhydrous CH_2Cl_2 (35 mL) was added. After 30 min of stirring, *t*-butyl hydroperoxide (8.2 mL of a 5.5 M solution in decane, 45.0 mmol) was added. The mixture was then stirred at −23 °C for 72 h, after which anhydrous dimethyl sulfide (2.4 mL, 33.7 mmol) was added and the stirring continued for 3 h at −23 °C. Anhydrous benzylamine (7.4 mL, 67.4 mmol) was added followed by Ti(O*i*-Pr)$_4$ (10.0 mL, 33.7 mmol) and the mixture then allowed to stir at room temperature for 36 h. The reaction was quenched by the addition of a 10% aqueous NaOH solution saturated in

NaCl (22 mL) and stirring at room temperature for 5 h. The mixture was filtered over Celite, the cake rinsed with CH_2Cl_2 and the solution concentrated in vacuo. The crude material was purified by column chromatography on SiO_2 eluted with PE/*i*-PrOH/Et_3N (79.85:20:0.15 to 69.85:30:0.15) to give a 70:30 mixture of **11** and **12** (4.1 g, 60%). Compounds **11** and **12** were separated by MPLC column chromatography on SiO_2 eluted with PE/*i*-PrOH/Et_3N (79.85:20:0.15 to 69.85:30:0.15). A 90% ee was assigned to compounds **11** and **12** on the basis of that of the epoxide intermediate measured by chiral HPLC (CHIRALCEL OD, hexane/*i*-PrOH, 85:15, 1 mL/min).

4.1.3.1. (2*S*,3*S*)-3-Benzylamino-4-(benzyloxy)propan-1,2-diol 11. White solid; mp: 74 °C; $[\alpha]_D^{20} = +28.0$ (*c* 1.4, $CHCl_3$); IR (film) $\nu_{OH,NH}$ 3405 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3 + D_2O$) δ 7.40–7.28 (m, 10H, Ph), 4.53 (ABq, 2H, OCH_2Ph, $^2J_{gem} = 11.9$ Hz, $\Delta\delta = 17.0$ Hz), 3.79 (pseudoq, 1H, $J_{H_2-H_1} = J_{H_2-H_3} = 5.5$ Hz, H_2), 3.80 (ABq, 2H, NCH_2Ph, $^2J_{gem} = 13.0$ Hz, $\Delta\delta = 23.5$ Hz), 3.68–3.62 (m, 4H, $2 \times H_1$ and $2 \times H_4$), 2.89 (dt, 1H, H_3, $^3J_{H_3-H_2} = 5.9$ Hz, $^3J_{H_3-H_4} = 4.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3 + D_2O$) δ 139.9 (Cq, NCH_2Ph), 137.9 (Cq, OCH_2Ph), 128.9, 128.5, 128.2, 128.0, 127.5 (CH, Ph), 73.6 (O*C*H_2Ph), 70.7 (C_2), 68.3 (C_1 or C_4), 65.3 (C_4 or C_1), 59.9 (C_3), 51.8 (N*C*H_2Ph); MS (DCI/NH_3) *m*/*z* 302 $(M+H)^+$; HRMS (CI) *m*/*z* calcd for $C_{18}H_{24}NO_3$: 302.1756; found, 302.1755. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.25; H, 7.64; N, 4.54.

4.1.3.2. (2*S*,3*S*)-2-Benzylamino-4-(benzyloxy)propan-1,3-diol 12. Colourless oil; $[\alpha]_D^{20} = +6.7$ (*c* 1.3, $CHCl_3$); IR (film) $\nu_{OH,NH}$ 3401 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3 + D_2O$) δ 7.40–7.28 (m, 10H, Ph), 4.55 (s, 2H, OCH_2Ph), 3.95 (dt, 1H, $^3J_{H_3-H_4} = {}^3J_{H_3-H_2} = 4.9$ Hz, $^3J_{H_3-H_{4'}} = 6.4$ Hz, H_3), 3.81 (ABq, 2H, NCH_2Ph, $^2J_{gem} = 13.0$ Hz, $\Delta\delta = 21.9$ Hz) 3.69 (d, 2H, $2 \times H_1$ $^3J_{H_1-H_2} = 4.6$ Hz), 3.58 (AB of an ABX, 2H, $2 \times H_4$, $^2J_{gem} = 9.7$ Hz, $^3J_{H_{4'}-H_3} = 6.4$ Hz, $^3J_{H_4-H_3} = 4.9$ Hz, $\Delta\delta = 22.3$ Hz), 2.74 (dt, 1H, H_2, $^3J_{H_2-H_3} = 4.9$ Hz, $^3J_{H_2-H_1} = 4.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3 + D_2O$) δ 140.1 (Cq, NCH_2Ph), 137.9 (Cq, OCH_2Ph), 128.8, 128.7, 128.5, 128.2, 128.1, 127.4 (CH, Ph), 73.8 (O*C*H_2Ph), 72.1 (C_4), 70.6 (C_3), 60.4 (C_1), 59.5 (C_2), 51.5 (N*C*H_2Ph); MS (DCI/NH_3) *m*/*z* 302 $(M+H)^+$; HRMS (CI) *m*/*z* calcd for $C_{18}H_{24}NO_3$: 302.1756; found, 302.1758.

4.1.4. Oxazolidinones 13 and 14. To a solution of a mixture of regioisomers **11** and **12** (1.37 g, 4.55 mmol) in anhydrous THF (34 mL) at room temperature and under a nitrogen atmosphere was added anhydrous K_2CO_3 (5.1 g, 37.0 mmol) and methyl chloroformate (1.8 mL, 23.2 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 vacuo. The crude material was then taken up in a 10% solution of KOH in methanol (31 mL) and the mixture stirred at room temperature for 5 h. The solution was acidified by the addition of a 1.2 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 Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography on SiO_2 eluted with CH_2Cl_2/AcOEt (80:20) to give **13** (893 mg, 60%) and **14** (342 mg, 23%).

4.1.4.1. (4*S*,5*S*)-3-Benzyl-4-(benzyloxymethyl)-5-(hydroxymethyl)-2-oxazolidinone 13. White solid; mp: 64–65 °C; $[\alpha]_D^{20} = +27.5$ (*c* 1.3, $CHCl_3$); IR (film) ν_{OH} 3435, $\nu_{C=O}$ 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.21 (m, 10H, Ph), 4.58 (dt,1H, H_2, $^3J_{H_2-H_1} = 5.4$ Hz, $^3J_{H_2-H_3} = 8.3$ Hz), 4.47 (ABq, 2H, OCH_2Ph, $^2J_{gem} = 11.8$ Hz, $\Delta\delta = 16,6$ Hz), 4.42 (ABq, 2H, $^2J_{gem} = 15.2$ Hz, $\Delta\delta = 269$ Hz, NCH_2Ph), 3.89 (AB of an ABX, 2H, $2 \times H_1$, $^2J_{gem} = 12.5$ Hz, $^3J_{H_1-H_2} = {}^3J_{H_{1'}-H_2} = 5.4$ Hz), 3.84–3.81 (m, 1H, H_3), 3.60 (AB of an ABX, 2H, $2 \times H_4$, $^2J_{gem} = 10.3$ Hz, $^3J_{H_4-H_3} = 6.0$ Hz, $^3J_{H_{4'}-H_3} = 4.0$ Hz, $\Delta\delta = 21.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0 (C=O) 136.8 (Cq, OCH_2Ph), 136.2 (Cq, NCH_2Ph), 129.0, 128.9, 128.5, 128.3, 128.2, 128.1 (CH, Ph), 76.4 (C_2), 73.9 (O*C*H_2Ph), 65.7 (C_4), 60.0 (C_1), 56.0 (C_3), 46.8 (N*C*H_2Ph); MS (DCI/NH_3) *m*/*z* 328 $(M+H)^+$; HRMS (CI) *m*/*z* calcd for $C_{19}H_{22}NO_4$: 328.1549; found, 328.1551. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28; Found: C, 69.69; H, 6.49; H, 4.08.

4.1.4.2. (4*S*)-3-Benzyl-4-[(1*S*)-2-benzyloxy-1-(hydroxymethyl)]-2-oxazolidinone 14. Colourless oil; $[\alpha]_D^{20} = +4.0$ (*c* 1.2, $CHCl_3$); IR (film) ν_{OH} 3420, $\nu_{C=O}$ 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.25 (m, 10H, Ph), 4.51 (ABq, 2H, NCH_2Ph, $^2J_{gem} = 15.3$ Hz, $\Delta\delta = 198$ Hz), 4.49 (s, 2H, OCH_2Ph), 4.30 (AB of an ABX, 2H, $2 \times H_1$, $^2J_{gem} = 8.9$ Hz, $^3J_{H_1-H_2} = 8.9$ Hz, $^3J_{H_{1'}-H_2} = 6.5$ Hz, $\Delta\delta = 82.4$ Hz), 4.04–4.01 (m, 1H, H_3), 3.77 (ddd, 1H, H_2, $J_{H_2-H_1} = 9.0$ Hz, $J_{H_2-H_{1'}} = 6.5$ Hz, $J_{H_2-H_3} = 2.3$ Hz), 3.45 (AB of an ABX, 2H, $2 \times H_4$, $^2J_{gem} = 9.9$ Hz, $^3J_{H_4-H_3} = 5.7$ Hz, $^3J_{H_{4'}-H_3} = 4.8$ Hz, $\Delta\delta = 15.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (C=O) 137.5 (Cq, OCH_2Ph), 136.3 (Cq, NCH_2Ph), 129.2, 128.8, 128.3, 128.2, 128.0 (CH, Ph), 73.9 (O*C*H_2Ph), 70.5 (C_4), 67.4 (C_3), 62.9 (C_1), 57.1 (C_2), 46.7 (N*C*H_2Ph); SM (DCI/NH_3) *m*/*z* 345 $(M+NH_4)^+$; HRMS (CI) *m*/*z* calcd for $C_{19}H_{22}NO_4$: 328.1549; found, 328.1549.

4.1.5. (4*S*,5*S*)-3-Benzyl-4-(benzyloxymethyl)-5-(formyl)-2-oxazolidinone 15. To a solution of alcohol **13** (210 mg, 0.64 mmol) in anhydrous CH_2Cl_2 (4 mL) at room temperature and under a nitrogen atmosphere was added Dess–Martin periodinane (351 mg, 0.83 mmol). The mixture was stirred for 3 h after which it was diluted with diethyl ether and $Na_2S_2O_3$ (950 mg, 6.0 mmol) in a saturated aqueous $NaHCO_3$ (12 mL) solution was added. The mixture was extracted three times with diethyl ether and the combined extracts were washed with brine and dried over Na_2SO_4. Most of the solvent was then gently evaporated off in vacuo and the resulting concentrated solution was directly filtered over Florisil eluted with diethyl ether. Gentle evaporation of the solvent in vacuo gave aldehyde **15** (188 mg, 90%). A sample was further purified by column chromatography on SiO_2 eluted with CH_2Cl_2/AcOEt (80:20) for complete characterisation. $[\alpha]_D^{20} = +11.0$ (*c* 2.2, $CHCl_3$); IR (neat) $\nu_{C=O}$ 1744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 9.72 (d, 1H, $H_{ald.}$, $^3J_{H_{ald.}-H_2} = 1.5$ Hz), 7.42–7.18

(m, 10H, Ph), 4.68 (dd, 1H, H_2, $^3J_{H_2-H_3} = 10.0$ Hz, $^3J_{H_2-H_{ald.}} = 1.5$ Hz), 4.32 (ABq, 2H, OCH_2Ph, $^2J_{gem} = 11.8$ Hz, $\Delta\delta = 74.8$ Hz), 4.40 (ABq, 2H, NCH_2Ph, $^2J_{gem} = 15.3$ Hz, $\Delta\delta = 314.0$ Hz), 3.96 (dt, 1H, H_3, $^3J_{H_3-H_2} = 10.0$ Hz, $^3J_{H_3-H_4} = 2.0$ Hz), 3.40 (AB of an ABX, 2H, $2 \times H_4$, $^2J_{gem} = 11.0$ Hz, $^3J_{H_4-H_3} = 2.0$ Hz, $\Delta\delta =$ 108.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 198.7 (C=O, ald.), 157.2 (C=O, carbamate), 136.8 (Cq, OCH_2*Ph*), 135.5 (Cq, NCH_2*Ph*), 129.1, 128.8, 128.4, 128.3, 128.2, 128.1 (CH, Ph), 76.7 (C_2), 73.1 (O*C*H_2Ph), 62.8 (C_4), 58.2 (C_3), 46.4 (N*C*H_2Ph); SM (DCI, NH_3) *m/z* 343 (MNH_4^+); HRMS (ESI) *m/z* calcd for $C_{19}H_{20}NO_4$: 326.1392; found, 326.1393.

4.1.6. (4*S*,5*S*)-3-Benzyl-4-(benzyloxymethyl)-5-[(1*R*)-1-(hydroxyoctyl)]-2-oxazolidinone 16. A suspension of anhydrous $CeCl_3$ (1.5 g, 6.0 mmol) in anhydrous THF (23 mL) under a nitrogen atmosphere was stirred overnight at room temperature. The mixture was then cooled to −78 °C. *n*-Octyl magnesium bromide (3.0 mL of a 2 M commercial solution in diethyl ether, 6.0 mmol) was then added dropwise and the solution was stirred at −78 °C for 1 h. Aldehyde **15** (465 mg, 1.43 mmol) in solution in anhydrous THF (2 mL) was added and the mixture stirred at −78 °C for 5 h and then at 0 °C for 1 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (42 mL) and then stirred at 0 °C for 30 min. The mixture was diluted by the addition of THF, vigorously stirred at room temperature and decanted. The organic layer was separated and the extraction repeated with AcOEt (3×50 mL). The combined extracts were washed with brine, died over Na_2SO_4 and concentrated to dryness. The crude material was purified by column chromatography on SiO_2 eluted with PE/Et_2O (60:40 to 50:50) to give **16** (350 mg, 56%) as a colourless oil. $[\alpha]_D^{20} = +26.4$ (*c* 1.65, $CHCl_3$); IR (film) ν_{OH} 3410, $\nu_{C=O}$ 1735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.27 (m, 8H, Ph), 7.25–7.20 (m, 2H, Ph), 4.40 (ABq, 2H, NCH_2Ph, $^2J_{gem} =$ 15.4 Hz, $\Delta\delta = 302.0$ Hz), 4.52 (ABq, 2H, OCH_2Ph, $^2J_{gem} = 11.6$ Hz, $\Delta\delta = 26.0$ Hz), 4.20 (dd, 1H, H_3, $^3J = 9.4$ Hz and 7.0 Hz), 3.81–3.76 (m, 2H, H_2, H_4), 3.58 (AB of an ABX, 2H, $2 \times H_1$, $^2J_{gem} = 10.0$ Hz, $^3J_{H_1,H_2} =$ 8.4 Hz, $^3J_{H_{1'},H_2} = 3.0$ Hz $\Delta\delta = 36.4$ Hz), 1.82–1.75 (m, 1H, H_5), 1.60–1.22 (m, 13H, $H_{5'}$, H_6–H_{11}), 0.91 (t, 3H, $^3J = 6.8$ Hz, Me), ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7 (C=O), 136.3, 136.2 (Cq, NCH_2*Ph*, OCH_2*Ph*), 129.1, 129.0, 128.8, 128.5, 128.3, 128.1 (CH, Ph), 79.5 (C_3), 74.1 (O*C*H_2Ph), 68.2 (C_4), 64.7 (C_1), 56.3 (C_2), 46.7 (N*C*H_2Ph), 33.7, 32.1, 29.8, 29.7, 29.5, 25.0, 22.9 (C_5–C_{11}), 14.3 (CH_3); MS (APCI) *m/z* 440 $(M+H)^+$; HRMS (CI) *m/z* calcd for $C_{27}H_{38}NO_4$: 440.2801; found, 440.2804.

4.1.7. (4*S*,5*S*)-3-Benzyl-4-(benzyloxymethyl)-5-[(1*R*)-1-hydroxy-2-(heptynyl)]-2-oxazolidinone 17. A suspension of anhydrous $CeCl_3$ (562 mg, 2.28 mmol) in anhydrous THF (9 mL) under a nitrogen atmosphere was stirred overnight at room temperature. Meanwhile a solution of *n*-heptyne lithium was prepared by the addition of *n*-BuLi (1.5 mL of a 1.6 M commercial solution in hexanes) to *n*-heptyne (300 μL, 2.28 mmol) in anhydrous THF (10 mL) at 0 °C. The suspension of $CeCl_3$ was then cooled to −78 °C, the *n*-heptyne lithium solution added dropwise and the reaction mixture stirred at −78 °C for 1 h. Aldehyde **15** (184 mg, 0.57 mmol) in solution in anhydrous THF (1 mL) was added and the mixture stirred at −78 °C for 6 h. The reaction was then quenched by the addition of a saturated aqueous solution of NH_4Cl (15 mL) and stirring at 0 °C for 30 min. The mixture was diluted by the addition of THF, vigorously stirred at room temperature and decanted. The organic layer was separated and the extraction repeated with AcOEt (3×30 mL). The combined extracts were washed with brine, died over Na_2SO_4 and concentrated to dryness. The crude material was purified by column chromatography on SiO_2 eluted with PE/AcOEt (70:30 to 60:40) to give **17** (180 mg, 75%) as a colourless oil. $[\alpha]_D^{20} = +22.0$ (*c* 1.32, $CHCl_3$); IR (film) ν_{OH} 3400, ν_{CC} 2228, $\nu_{C=O}$ 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.30 (m, 8H, Ph), 7.21–7.18 (m, 2H, Ph), 4.74–4.68 (m, 1H, H_4), 4.52 (dd, 1H, H_3, $^3J = 8.0$ Hz and 5.6 Hz), 4.50 (ABq, 2H, OCH_2Ph, $^2J_{gem} = 11.6$ Hz, $\Delta\delta = 52.0$ Hz), 4.41 (ABq, 2H, NCH_2Ph, $^2J_{gem} = 16.4$ Hz, $\Delta\delta = 303.0$ Hz), 3.87–3.82 (m, 2H, H_1, H_2), 3.74 (dd, 1H, H1′, $^2J_{gem} = 11.2$ Hz, $^3J_{H_{1'}-H_2} = 6.2$ Hz), 2.20 (dt, 2H, H_7, $^3J_{H_7-H_8} = 7.0$ Hz, $^5J_{H_7-H_4} = 2.0$ Hz), 1.55–1.45 (m, 2H, H_8), 1.40–1.27 (m, 4H, H_9, H_{10}), 0.91 (t, 3H, Me, $^3J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4 (C=O), 136.6, 136.1 (Cq, NCH_2*Ph*, OCH_2*Ph*), 129.0, 128.9, 128.6, 128.5, 128.2, 128.1 (CH, Ph), 88.3 (C_5 or C_6), 77.8 (C_3), 77.1 (C_6 or C_5), 73.8 (O*C*H_2Ph), 65.2 (C_1), 61.4 (C_4), 56.1 (C_2), 46.7 (N*C*H_2Ph), 31.3 (C_9), 28.3 (C_8), 22.4 (C_{10}), 18.9 (C_7), 14.2 (CH_3) MS (DCI/NH_3) *m/z* 439 $(M+NH_4)^+$; HRMS (CI) *m/z* calcd for $C_{26}H_{32}NO_4$: 422.2331; found, 422.2332.

4.1.8. (4*S*,5*S*)-3-Benzyl-4-(benzyloxymethyl)-5-[(1*R*)-1-(methanesulfonyloxyoctyl)]-2-oxazolidinone 18. To a solution of alcohol **16** (168 mg, 0.38 mmol) in anhydrous CH_2Cl_2 (6 mL) at 0 °C under a nitrogen atmosphere was added mesyl chloride (40 μL, 0.52 mmol). After 5 min Et_3N (80 μL, 0.57 mmol) was added and the solution stirred for 25 min at 0 °C and 1 h at room temperature. Water (10 mL) was then added and the reaction mixture extracted three times with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography on SiO_2 eluted with PE/CH_2Cl_2/AcOEt (70:24:6 to 60:32:8) to give **18** (178 mg, 90%) as a colourless oil. $[\alpha]_D^{20} = +26.0$ (*c* 1.0, $CHCl_3$); IR (film) $\nu_{C=O}$ 1752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.26 (m, 8H, Ph), 7.20–7.14 (m, 2H, Ph), 5.14 (pseudoq, 1H, H_4, $^3J_{H_4-H_3} = {}^3J_{H_4-H_5} = 6.8$ Hz), 4.60–4.52 (m, 1H, H_3), 4.50 (ABq, 2H, OCH_2Ph, $^2J_{gem} = 14.1$ Hz, $\Delta\delta = 59.5$ Hz), 4.35 (ABq, 2H, NCH_2Ph, $^2J_{gem} = 18.3$ Hz, $\Delta\delta = 261.0$ Hz), 3.73–3.68 (m, 2H, H_1, H_2), 3.60 (dd, 1H, $H_{1'}$, $^2J_{gem} =$ 13.9 Hz, $^3J_{H_{1'}-H_2} = 4.9$ Hz), 2.99 (s, 3H, OSO_2CH_3), 1.95–1.80 (m, 2H, H_5), 1.55–1.20 (m, 12H, H_6–H_{11}), 0.88 (t, 3H, Me, $^3J = 7.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3 (C=O), 137.2, 135.8 (Cq, Ph), 128.8, 128.7, 128.6, 128.2, 128.1, 128.0 (CH, Ph), 79.2 (C_3), 75.3 (C_4), 73.2 (O*C*H_2Ph), 64.5 (C_1), 56.3 (C_2), 46.3 (N*C*H_2Ph), 39.2 (OSO_2CH_3), 31.8, 30.9, 29.6, 29.4, 29.2, 23.9, 22.6 (C_5–C_{11}), 14.1 (Me); MS (DCI/NH_3) *m/z* 535 $(M+NH_4)^+$; HRMS (ESI) *m/z* calcd for $C_{28}H_{39}NO_6SNa$: 540.2396; found, 540.2394.

4.1.9. (3a*S*,6*S*,6a*S*)-3-Benzyl-6-octyltetrahydrofuro[3,4-*d*]-[1,3]oxazol-2(3*H*)-one 19. A solution of mesylate **18** (170 mg, 0.33 mmol) in ethanol (3.5 mL) containing $Pd(OH)_2$ (25 mg) was stirred under H_2 atmosphere (10 bars) for 2 days. The reaction mixture was then filtered over Celite, the precipitate was rinsed with CH_2Cl_2 and the filtrate concentrated in vacuo. The crude material was purified by column chromatography on SiO_2 eluted with PE/CH_2Cl_2/AcOEt (70:24:6 to 60:32:8) to give **19** (82 mg, 75%) as a white solid. Mp: 179 °C; $[\alpha]_D^{20} = +69.5$ (*c* 1.0, $CHCl_3$); IR (film) $\nu_{C=O}$ 1751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.30 (m, 3H, Ph), 7.29–7.25 (m, 2H, Ph), 4.78 (dd, 1H, H_3, $^3J_{H_3-H_2} = 8.0$ Hz, $^3J_{H_3-H_4} = 4.0$ Hz), 4.46 (ABq, 2H, NCH_2Ph, $^2J_{gem} = 15.2$ Hz, $\Delta\delta = 130.0$ Hz), 4.09 (dd, 1H, H_2, $^3J_{H_2-H_3} = 7.6$ Hz, $^3J_{H_2-H_{1'}} = 4.0$ Hz), 3.96 (d, 1H, H_1, $^2J_{gem} = 10.4$ Hz), 3.45 (dt, 1H, H_4, $^2J_{H_4-H_5} = 6.8$ Hz, $J_{H_4-H_3} = 4.0$ Hz), 3.31 (dd, 1H, $H_{1'}$, $^2J_{gem} = 10.6$ Hz, $^3J_{H_{1'}-H_2} = 4.2$ Hz), 1.80–1.72 (m, 2H, H_5), 1.48–1.22 (m, 12H, H_6–H_{11}), 0.88 (t, 3H, Me, $^3J = 6.8$ Hz);^{13}C NMR (100 MHz, $CDCl_3$) δ 157 (C=O), 135.6 (Cq, Ph), 129.2, 128.4, 128.3 (CH, Ph), 83.7 (C_4), 78.0 (C_3), 69.5 (C_1), 60.2 (C_2), 47.0 (NCH_2Ph), 32.1, 29.8, 29.7, 29.4, 28.2, 26.2, 22.9 (C_5–C_{11}), 14.3 (Me); MS (DCI/NH_3) *m*/*z* 349 $(M+NH_4)^+$; HRMS (CI) *m*/*z* calcd $C_{20}H_{30}NO_3$: 332.222; found, 332.2229.

4.1.10. (3a*S*,6*S*,6a*S*)-6-Octyltetrahydrofuro[3,4-*d*][1,3]oxazol-2(3*H*)-one 20. A solution of **19** (20 mg, 0.06 mmol) in THF (1 mL) was added to a deep blue solution of Na (100 mg, 4.3 mmol) in liquid NH_3 (ca. 5 mL) at −78 °C under a nitrogen atmosphere and the mixture was stirred at −78 °C for 4 h. The reaction was quenched by the addition of solid NH_4Cl and the ammonia was allowed to evaporate at room temperature. AcOEt was then added and the mixture sonicated before being filtered over Celite. The precipitate was rinsed with AcOEt and the filtrate concentrated in vacuo. The crude material was purified by column chromatography on SiO_2 eluted with CH_2Cl_2/AcOEt (70:30 to 50:50) to give **20** (12 mg, 83%) as a colourless oil. $[\alpha]_D^{20} = +77.7$ (*c* 0.6, $CHCl_3$); IR (film) $\nu_{C=O}$ 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (1s, 1H, NH), 4.88 (dd, 1H, H_3, $^3J_{H_3-H_4} = 3.6$ Hz, $^3J_{H_3-H_2} = 7.5$ Hz), 4.30 (dd, 1H, H_2, $^3J_{H_2-H_1} = 3.9$ Hz, $^3J_{H_2-H_3} = 7.5$ Hz), 3.66 (AB of an ABX, 2H, $2 \times H_1$, $^2J_{gem} = 10.5$ Hz, $^3J_{H_1-H_2} = 3.9$ Hz, $^3J_{H_{1'}-H_2} = 0.0$ Hz $\Delta\delta = 129.0$ Hz), 3.48–3.43 (m, 1H, H_4), 1.75–1.65 (m, 2H, H_5), 1.40–1.15 (m, 12H, H_6–H_{11}), 0.81 (t, 3H, Me, $J = 7.0$ Hz);^{13}C NMR (75 MHz, $CDCl_3$) δ 159 (C=O), 83.2 (C_4), 81.0 (C_3), 73.3 (C_1), 57.2 (C_2), 31.8, 29.6, 29.4, 29.2, 28.1, 26.0, 22.6 (C_5–C_{11}), 14.1 (Me); MS (DCI/NH_3) *m*/*z* 276 $(MNH_4)^+$; HRMS (CI) *m*/*z* calcd $C_{13}H_{24}NO_3$: 242.1756; found, 242.1757.

4.1.11. (2*S*,3*S*,4*S*)-4-Amino-2-(octyl)tetrahydrofuran-3-ol 22. KOH (23 mg, 0.41 mmol) was added to a solution of **20** (10 mg, 0.04 mmol) in EtOH (800 μL) and H_2O (200 μL). The mixture was heated at 85 °C for 7 h before being diluted with AcOEt and brine. The mixture was extracted three times with AcOEt and the combined extracts were concentrated in vacuo. The crude material was purified by column chromatography on SiO_2 eluted with AcOEt/MeOH/NH_4OH (69.2:30:0.8) to give **22** (8.2 mg, 95%) as a white solid. $[\alpha]_D^{20} = +20.0$ (*c* 0.5, $CHCl_3$); IR (neat) $\nu_{OH,NH}$ 3340 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.93 (dd, 1H, H_1, $^2J_{H_1-H_{1'}} = 8.6$ Hz, $^3J_{H_1-H_2} = 7.5$ Hz), 3.86 (dd, 1H, H_3, $^3J_{H_3-H_2} = 5.0$ Hz, $^3J_{H_3-H_4} = 3.6$ Hz), 3.73 (ddd, 1H, H_4, $^3J_{H_4-H_5} = 7.5$ Hz, $^3J_{H_4-H_{5'}} = 6.3$ Hz, $^3J_{H_4-H_3} = 3.4$ Hz), 3.66 (dpseudot, 1H, H_2, $^3J_{H_2-H_1} \approx 7.0$ Hz, $^3J_{H_2-H_3} = 5.2$ Hz), 3.51 (dd, 1H, $H_{1'}$, $^2J_{H_{1'}-H_1} = 8.6$ Hz, $^3J_{H_{1'}-H_2} = 6.8$ Hz), 1.90–1.60 (m, 5H, $2 \times H_5$, NH_2, OH), 1.50–1.20 (m, 12H, $6 \times CH_2$), 0.90 (t, 3H, Me, $^3J = 7.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.2 (C_4), 72.3 (C_1), 71.7 (C_3), 54.3 (C_2), 31.9 (C_5), 29.8, 29.7, 29.5, 29.4, 29.3, 26.3, 22.7 (C_6–C_{11}), 14.1 (C_{12}); SM (DCI, NH_3) *m*/*z* 233 MNH_4^+; HRMS (CI) *m*/*z* calcd $C_{12}H_{26}NO_2$: 216.1964; found, 216.1965.

4.1.12. Cell viability experiments. Murine B16 or human A375 melanoma cell lines were seeded in 24-well plates and at 70% confluency, compound **22** was added at the indicated concentrations. After 24 h, cell viability was estimated by assessing the cellular MTT conversion capacity. Data are expressed as a percentage of the values of untreated cells. Shown are the means ± SE ($n = 2$–7).

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References

1. Huwiler, A.; Kolter, T.; Pfeilschifter, J.; Sandhoff, K. *Biochim. Biophys. Acta* **2000**, *1485*, 63–99.
2. For synthetic approaches see: Howell, A. R.; Ndakala, A. J. *Curr. Org. Chem.* **2002**, *6*, 365–391; For α-galactosylceramides as immunostimulatory and antitumour agents see: Hayakawa, Y.; Godfrey, D. I.; Smyth, M. J. *Curr. Med. Chem.* **2004**, *11*, 241–252.
3. Pettus, B. J.; Chalfant, C. E.; Hannun, Y. A. *Biochim. Biophys. Acta* **2002**, *1585*, 114–125.
4. Spiegel, S.; Milstein, S. *Nat. Rev. Mol. Cell Biol.* **2003**, *4*, 397–407.
5. Ogretmen, B.; Hannun, Y. A. *Nat. Rev. Cancer* **2004**, *4*, 604–616; Reynolds, C. P.; Maurer, B. J.; Kolesnick, R. N. *Cancer Lett.* **2004**, *206*, 169–180; Kok, J. W.; Sietsma, H. *Curr. Drug Target* **2004**, *5*, 375–382; Padron, J. M. *Curr. Med. Chem.* **2006**, *13*, 755–770.
6. Ayad, T.; Génisson, Y.; Verdu, A.; Baltas, M.; Gorrichon, L. *Tetrahedron Lett.* **2003**, *44*, 579–582.
7. Wee, A. G. H.; Tang, F. *Tetrahedron Lett.* **1996**, *37*, 6677–6680; Wee, A. G. H.; Tang, F. *Can. J. Chem.* **1998**, *76*, 1070–1081.
8. Canas, M.; Poch, M.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1991**, *32*, 6931–6934; Alcón, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1999**, *10*, 4639–4651; Martin, R.; Alcón, M.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2002**, *67*, 6896–6901.
9. Pihlaja, K.; Kleinpeter, E. *Carbon-13 NMR Chemical Shifts in Structural and Stereochemical Analysis*; VCH: New York, 1994, pp 55–56.
10. Melon, D.; Gravier-Pelletier, C.; Le Merrer, Y.; Depezay, J. C. *Bull. Soc. Fr. Chim.* **1992**, *129*, 585–593.
11. Crystal data for **13**: $C_{19}H_{21}NO_4$, $M = 327.3$, monoclinic, $P2_1$, $a = 4.718(1)$ Å, $b = 31.915(8)$ Å, $c = 11.238(3)$ Å, $\beta =$

92.376(5)°, $V = 1690.5(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.286$ Mg m^{-3}, $F(000) = 696$, $\lambda = 0.71073$ Å, $T = 193(2)$ K, $\mu(Mo_{K\alpha}) = 0.090$ mm^{-1}, crystal dimensions $0.05 \times 0.1 \times 0.7$ mm^3, 8076 reflections (4089 independent, $R_{int} = 0.0684$) were collected at low temperatures using an oil-coated shock-cooled crystal on a Bruker-AXS CCD 1000 diffractometer. The structure was solved by direct method (SHELXS-97)[12] and 435 parameters were refined using the least-squares method on F^2.[13] Largest electron density residue 0.165 e Å^{-3}, R_1 (for $I > 2\sigma(I)$) = 0.0544 and wR_2 (all data) = 0.1049 with $R_1 = \sum|F_o| - |F_c|/\sum|F_o|$ and $wR_2 = w(\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2)^{0.5}$. CCDC 629176 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

12. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467–473.
13. Sheldrick, G. M. SHELXL-*97: Program for Crystal Structure Refinement*; University of Göttingen, 1997.
14. Kuroda, I.; Musman, M.; Ohtani, I. I.; Ichiba, T.; Tanaka, J.; Garcia Gravalos, D.; Higa, T. *J. Nat. Prod.* **2002**, *65*, 1505–1506.
15. Ledroit, V.; Debitus, C.; Lavaud, C.; Massiot, G. *Tetrahedron Lett.* **2003**, *44*, 225–228.
16. Sudhakar, N.; Kumar, A. R.; Prabhakar, A.; Jagadeesh, B.; Rao, B. V. *Tetrahedron Lett.* **2005**, *46*, 325–327.
17. Bhaket, P.; Morris, K.; Stauffer, C. S.; Datta, A. *Org. Lett.* **2005**, *7*, 875–876.
18. Du, Y.; Liu, J.; Linhardt, R. J. *J. Org. Chem.* **2006**, *71*, 1251–1253.
19. Liu, J.; Du, Y.; Dong, X.; Meng, S.; Xiao, J.; Cheng, L. *Carbohydrate Res.* **2006**, *341*, 2653–2657.
20. Ribes, C.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2006**, *62*, 5421–5425.
21. Chandrasekhar, S.; Tiwari, B.; Prakash, S. J. *ARKIVOC* **2006**, *xi*, 155–161.
22. For recent synthetic reports from phytosphingosine see: Jo, S. Y.; Kim, H. C.; Jeon, D. J.; Kim, H. R. *Heterocycles* **2001**, *55*, 1127–1132; van den Berg, R. J. B. H. N.; Boltje, T. J.; Verhagen, C. P.; Litjens, R. E. J. N.; van den Marel, G. A.; Overkleeft, H. S. *J. Org. Chem.* **2006**, *71*, 836–839; Lee, T.; Lee, S.; Kwak, Y. S.; Kim, D.; Kim, S. *Org. Lett.* **2007**, *9*, 429–432.
23. Structure of **21** was assigned on the basis of the following data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.17 (m, 5H, Ph), 3.88–3.82 (m, 2H, H_1, H_3), 3.73 (ABq, 2H, NCH_2Ph, $^2J_{gem} = 13.1$ Hz, $\Delta\delta = 24.0$ Hz), 3.67–3.58 (m, 1H, H_4), 3.52–3.45 (m, 1H, $H_{1'}$), 3.41–3.32 (m, 1H, H_2), 2.55 (1s, 2H, OH, NH), 1.70–1.54 (m, 2H, H_5), 1.38–1.14 (m, 12H, H_6–H_{11}), 0.84–0.76 (m, 3H, Me); SM (DCI, NH_3) *m*/*z* 306 ($M+H^+$).
24. Skidmore, W. D.; Entenman, C. *J. Lipid Res.* **1962**, *3*, 471–475.