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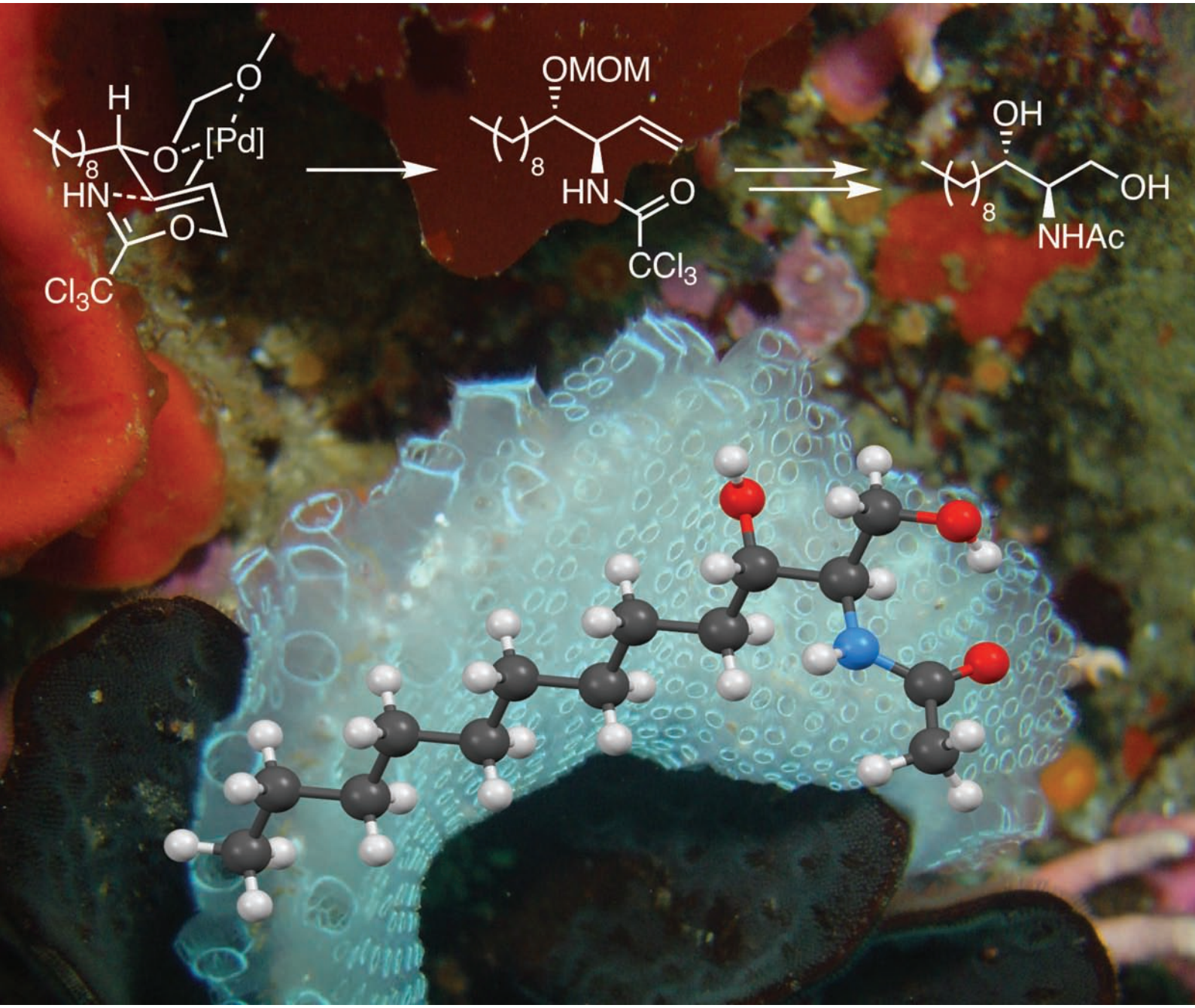

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PAPER

Total synthesis of clavaminol A, C and H†

Ahmed M. Zaed and Andrew Sutherland*

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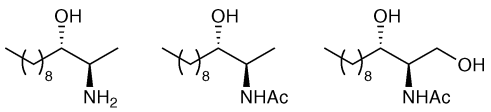
The first total synthesis of clavaminol A and C, (2*R*,3*S*)-2-amino-3-alkanols from the Mediterranean ascidian *Clavelina phlegraea* has been achieved in 29% overall yield. The key step involved a palladium(II)-catalysed directed Overman rearrangement to create the C–N bond and install the *erythro* configuration while a one-pot, tributyltin hydride-mediated reduction allowed simultaneous formation of the methyl side-chain and *N*-acetyl group. Similarly, the first total synthesis of clavaminol H was completed in 48% overall yield using an approach that also provided the cytotoxic des-acetyl analogue.

Introduction

Clavaminols are a new class of 2-amino-3-alkanols recently isolated from the Mediterranean ascidian *Clavelina phlegraea*.[1,2] As well as the usual spectroscopic techniques used for their characterisation, comparison of the CD spectra of benzoyl derivatives with stereoisomers of known standards[3] allowed determination of the absolute configuration of these compounds. Interestingly, the 2-amino-3-alkanols isolated from *Clavelina phlegraea* were found to have (2*R*,3*S*)-configuration, the opposite absolute configuration to that of the well-known sphingolipids[4] or other 2-amino-3-alkanols such as (2*S*,3*R*)-2-aminododecan-3-ol,[3] an antifungal agent isolated from *Clavelina oblonga* and (2*S*,3*R*)-2-aminotetradecan-3-ol, an inhibitor of cell proliferation isolated from *Spisula* polynima.[5]

Despite having (2*R*,3*S*)-configuration, biological testing of the clavaminols showed these natural products to be cytotoxic.[1] In particular, (–)-clavaminol A (**1**) was found to be the most active, inducing cell death in three different cell lines (A549, lung carcinoma; T47D, breast carcinoma and AGS, gastric carcinoma) by activation of the apoptotic machinery.[6] (+)-Clavaminol H (**3**) showed no significant activity, although its des-acetyl form was active against AGS gastric carcinoma.[2] These results suggested that a free amino group at C-2 and a free hydroxyl group at C-3 was necessary for cytotoxic activity, while a C-1 hydroxyl group made the compounds less active but more selective.

Due to the unusual stereochemical configuration of these natural products and the potential interest in their cytotoxic activity, we were interested in developing an efficient route for their synthesis. We now report a new general, stereoselective approach for the preparation of *erythro* amino alkanols that has led to the first total synthesis of (–)-clavaminol A (**1**), (+)-clavaminol C (**2**) and (+)-clavaminol H (**3**) (Fig. 1). The key step in this approach involved using a palladium(II)-catalysed directed Overman rearrangement to install the crucial C–N bond. As well as the synthesis of the (2*R*,3*S*)-stereoisomers, we also report the synthesis of the (2*S*,3*R*)-enantiomers, allowing confirmation of the original absolute stereochemical assignment of these natural products.[7]



(–)-**1** (+)-**2** (+)-**3**

Fig. 1 Structures of (–)-clavaminol A (**1**), (+)-clavaminol C (**2**) and (+)-clavaminol H (**3**).

Results and discussion

Our strategy for the synthesis of the clavaminols involved using a directed Overman rearrangement of a suitably derived allylic alcohol. As such, allylic alcohol **9** was prepared in seven steps as outlined in Scheme 1. Protection of (*R*)-glycidol (**4**) as the *tert*-butyldimethylsilyl ether was followed by a regioselective ring opening reaction with octylmagnesium bromide in the presence of a copper(I) salt that gave alcohol **5** in 94% yield. Protection of the secondary hydroxyl as the MOM-ether followed by removal of the silyl ether under standard conditions gave primary alcohol **7** in quantitative yield. A one-pot Swern oxidation/Horner–Wadsworth–Emmons reaction[8] of alcohol **7** gave exclusively *E*-α,β-unsaturated ester **8**.[9] Reduction of the ester moiety with DIBAL-H completed the synthesis of allylic alcohol **9** in 85% overall yield.

Allylic alcohol **9** was then subjected to an Overman rearrangement (Scheme 2).[10] Initially, allylic trichloroacetimidate **10** was prepared using a catalytic amount of DBU and trichloroacetonitrile.[11] Diastereoselective MOM-ether directed Overman rearrangement[12] of **10** using bis(acetonitrile)palladium(II) chloride (10 mol%) in the presence of *p*-benzoquinone[13] gave the *erythro* and *threo*-allylic trichloroacetamides in a 13 : 1 ratio, respectively. Column chromatography allowed the

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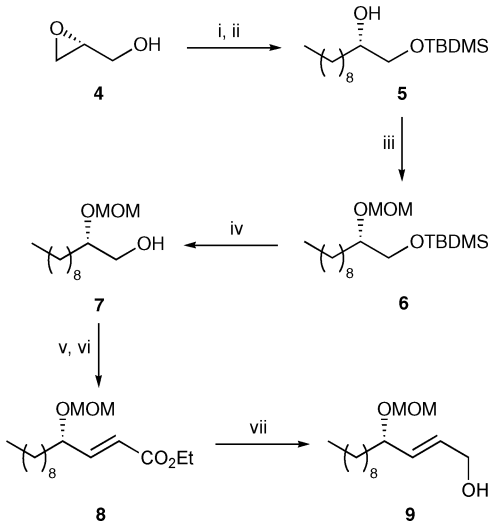
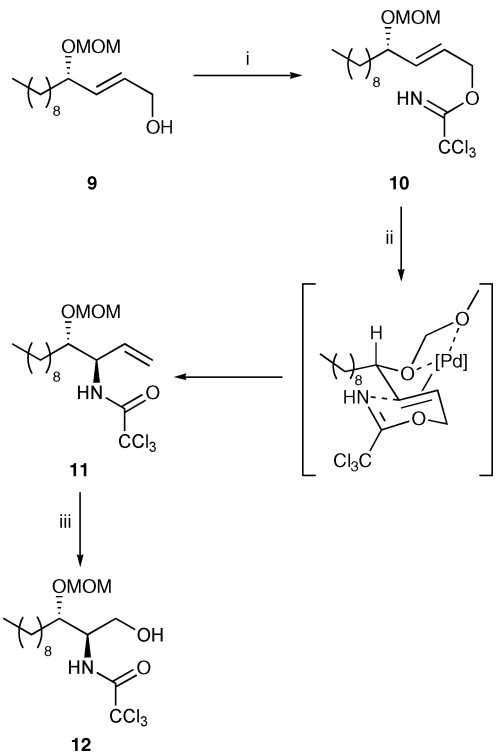
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/c1ob06060k



Scheme 1 *Reagents and conditions*: i. TBDMSCl, imidazole, THF, rt, 100%; ii. $Me(CH_2)_7MgBr$, $CuBr{\cdot}SMe_2$, THF, −78 °C, 94%; iii. MOMBr, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, Δ, 100%; iv. TBAF, THF, 0 °C, 100%; v. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; vi. $(EtO)_2P(O)CH_2CO_2Et$, DBU, LiCl, MeCN, rt, 95% over two steps; vii. DIBAL-H, Et_2O, −78 °C, 95%.



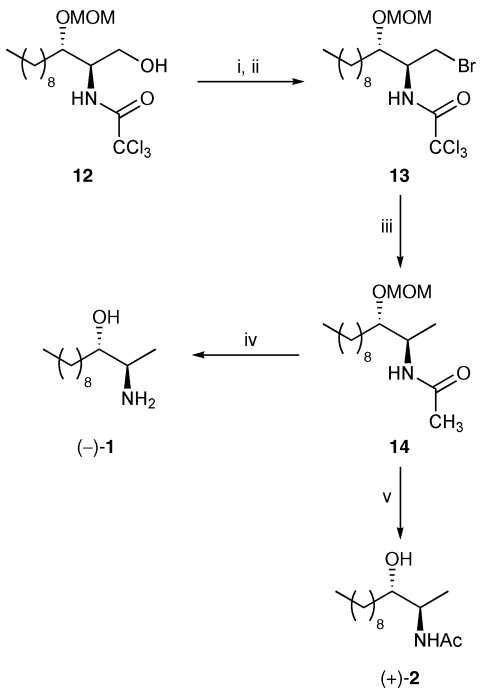
Scheme 2 *Reagents and conditions*: i. Cl_3CCN, DBU, CH_2Cl_2, rt; ii. $PdCl_2(MeCN)_2$, *p*-benzoquinone, toluene, 45 °C, 70% from **9**; iii. O_3, MeOH, CH_2Cl_2, −78 °C, then $NaBH_4$, 0 °C, 88%.

straightforward isolation of the major *erythro*-diastereomer **11** in 70% overall yield from allylic alcohol **9**. To form the methyl or methylene hydroxyl side chains required for the clavaminols, allylic trichloroacetamide **11** was subjected to ozonolysis under reductive conditions.[14]

This gave the corresponding alcohol **12** in 88% yield. It should be noted that although sodium borohydride is known to reduce trichloroacetamides,[15] at 0 °C only clean reduction of the ozonide to give alcohol **12** was observed.

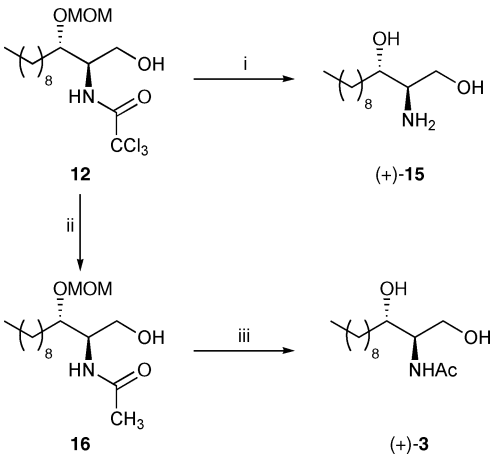
To access the methyl side chain required for (−)-clavaminol A (**1**) and (+)-clavaminol C (**2**), a two stage process involving conversion of alcohol **12** to the corresponding bromide followed by a tin-mediated reduction was proposed. An advantage of using this mild and selective method for reduction of the C–Br bond meant that the *N*-acetyl group required from clavaminol C could also be formed by simultaneous *in situ* reduction of the trichloroacetamide group.

Bromide **13** was prepared in two steps in good yield from alcohol **12** by conversion to the mesylate followed by reaction with sodium bromide (Scheme 3). The one-pot cleavage of the C–Br bond and reduction of the *N*-trichloroacetyl to the *N*-acetyl group under neutral conditions with *n*-tributyltin hydride in the presence of AIBN led to the formation of **14** in 85% yield.[16] The synthesis of (−)-clavaminol A (**1**) was completed by treatment of **14** with 6 M hydrochloric acid at 60 °C. This gave (−)-clavaminol A (**1**) in 29% overall yield after 14 steps. Selective removal of the MOM-protecting group of **14** using 2 M hydrochloric acid at room temperature gave (+)-clavaminol C (**2**) in the same overall yield after 14 steps.



Scheme 3 *Reagents and conditions*: i. MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 87%; ii. NaBr, DMSO, 60 °C, 75%; iii. *n*-Bu_3SnH, AIBN, toluene, DMA, Δ, 85%; iv. 6 M HCl, 60 °C, 100%; v. 2 M HCl, rt, 100%.

The cytotoxic amine, (+)-des-acetyl-clavaminol H **15** was prepared directly from **12** in quantitative yield by the removal of both protecting groups using 6 M hydrochloric acid (Scheme 4). To access the *N*-acetyl group required for (+)-clavaminol H (**3**), the *N*-trichloroacetyl group was again reduced under neutral conditions with *n*-tributyltin hydride.[16] This gave *N*-acetyl derivative **16** in 91% yield. Selective removal of the MOM-protecting group using 2 M hydrochloric acid completed the total synthesis of (+)-clavaminol H (**3**) in 12 steps and 48% overall yield.



Scheme 4 *Reagents and conditions*: i. 6 M HCl, 60 °C, 100%; ii. *n*-Bu_3SnH, AIBN, toluene, DMA, Δ, 91%; iii. 2 M HCl, rt, 100%.

Spectroscopic data for (−)-clavaminol A (**1**), (+)-clavaminol C (**2**) and (+)-clavaminol H (**3**) matched that reported for the natural products.[1,2] The optical rotation of **1, 2** and **3** were also in close agreement with previously reported data, thus confirming the (2*R*,3*S*)-stereochemical assignment of these natural products.[1,2] In the course of this study, the enantiomers of **1, 2** and **3** were prepared in a similar manner as described above except starting from (*S*)-glycidol.[17] As expected, the optical rotation of the (2*S*,3*R*)-enantiomers of **1, 2** and **3** were of similar value and of opposite sign to that observed for the (2*R*,3*S*)-natural products.

Conclusions

In summary, we have developed the first total synthesis of (−)-clavaminol A (**1**) and (+)-clavaminol C (**2**) in an efficient manner from (*R*)-glycidol. The key steps involved a palladium(II)-catalysed directed Overman rearrangement to install the key C–N bond and create the *erthyro*-configuration as well as a tin-mediated reduction for simultaneous formation of the *N*-acetyl group and the methyl side chain. In similar fashion, the first total synthesis of (+)-clavaminol H (**3**) was completed in 12 steps and 48% overall yield. Comparison of the optical data of these compounds with their enantiomers prepared from (*S*)-glycidol confirmed the (2*R*,3*S*)-absolute configuration of the natural products.[7] Work is currently underway to expand this general approach for the preparation of other biologically active 2-amino-3-alkanols.

Experimental

All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Brine refers to a saturated solution of sodium chloride. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with potassium permanganate. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to tetramethylsilane as the standard. Assignment of ^1H and ^{13}C NMR signals are based on two-dimensional COSY and DEPT experiments, respectively. Infrared spectra were recorded using Golden Gate apparatus on a JASCO FTIR 410 spectrometer and mass spectra were obtained using a JEOL JMS-700 spectrometer. Melting points were determined on a Reichert platform melting point apparatus. Optical rotations were determined as solutions irradiating with the sodium D line ($\lambda = 589$ nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}.

(2*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxypropane[18]

A mixture of (*R*)-(+)-glycidol (**4**) (4.61 g, 60.7 mmol), *tert*-butyldimethylsilyl chloride (9.15 g, 60.7 mmol) and imidazole (4.13 g, 60.7 mmol) were dissolved in tetrahydrofuran (300 mL) and stirred overnight at room temperature. A white precipitate was removed by filtration and washed with diethyl ether (200 mL). The combined filtrate was concentrated and purified by flash column chromatography using (diethyl ether/petroleum ether, 1 : 10), which gave (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxypropane (11.7 g, 100%) as a colourless oil. Spectroscopic data consistent with literature.[18] $[\alpha]_D^{23}$ −6.1 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.09 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.81 (9H, s, $SiC(CH_3)_3$), 2.56 (1H, dd, *J* 5.1, 2.6 Hz, 1-*H*H), 2.70 (1H, dd, *J* 5.1, 4.1 Hz, 1-H*H*), 2.98–3.03 (1H, m, 2-H), 3.60 (1H, dd, *J* 11.9, 4.8 Hz, 3-*H*H), 3.80 (1H, dd, *J* 11.9, 3.1 Hz, 3-H*H*); δ_C (100 MHz, $CDCl_3$) −5.3 (CH_3), −5.2 (CH_3), 18.4 (C), 25.9 (3 × CH_3), 44.5 (CH_2), 52.5 (CH), 63.8 (CH_2); *m*/*z* (CI) 189.1309 (MH^+. $C_9H_{22}O_2Si$ requires 189.1311), 145 (35%), 131 (50), 89 (62), 73 (12).

(2*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxypropane[19]

The reaction was carried out according to the procedure described above using (*S*)-(−)-glycidol (9.93 g, 134.0 mmol). This gave (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxypropane (22.9 g, 91%) as a colourless oil. $[\alpha]_D^{24}$ +2.6 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxypropane.

(2*S*)-1-(*tert*-Butyldimethylsilyloxy)undecan-2-ol (5)

A solution of octylmagnesium bromide (2.0 M in diethyl ether) (26.6 mL, 53.1 mmol) was added dropwise to a solution of copper(I) bromide·dimethyl sulfide (6.01 g, 29.2 mmol) in THF (300 mL) at −78 °C and the white suspension was stirred for 1 h. (2*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxypropane (5.00 g, 26.6 mmol) in tetrahydrofuran (30 mL) was then added and the reaction mixture was warmed to 0 °C and stirred for 3 h. The reaction mixture was quenched by the addition of a saturated solution of ammonium chloride (50 mL) and extracted with ethyl acetate (3 × 100 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/diethyl ether, 30 : 1) gave (2*S*)-1-(*tert*-butyldimethylsilyloxy)undecan-2-ol (**5**) (7.55 g, 94%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3423 (OH), 2927 (CH), 1464, 1254, 1109, 837, 777; $[\alpha]_D^{23}$ −19.4 (*c* 2.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.07 (6H, s, 2 × $SiCH_3$), 0.80–0.84 (12H, m, 11-H_3 and $SiC(CH_3)_3$), 1.22–1.44 (16H, m, 3-H_2, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, and 10-H_2), 2.42 (1H, d, *J* 3.2 Hz, OH), 3.38 (1H, dd, *J* 10.8, 8.4 Hz, 1-*H*H), 3.60–3.65 (2H, m, 1-H*H* and 2-H); δ_C (100 MHz, $CDCl_3$) −5.4 (CH_3), −5.3 (CH_3), 14.1 (CH_3), 18.3 (C),

22.7 (CH_2), 25.6 (CH_2), 25.9 ($3 \times CH_3$), 29.3 (CH_2), 29.6 ($2 \times CH_2$), 29.7 (CH_2), 32.0 (CH_2), 32.8 (CH_2), 67.3 (CH_2), 71.8 (CH); *m/z* (CI) 303.2722 (MH^+. $C_{17}H_{39}O_2Si$ requires 303.2719), 285 (24%), 185 (10), 133 (11), 113 (14), 69 (60).

(2*R*)-1-(*tert*-Butyldimethylsilyloxy)undecan-2-ol

The reaction was carried out according to the procedure described above using (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxypropane (5.00 g, 26.6 mmol). This gave (2*R*)-1-(*tert*-butyldimethylsilyloxy)undecan-2-ol (8.1 g, 100%) as a colourless oil. $[\alpha]_D^{23}$ +19.0 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*S*)-1-(*tert*-butyldimethylsilyloxy)undecan-2-ol (**5**).

(2*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxymethoxy)undecane (6)

A solution of (2*S*)-1-(*tert*-butyldimethylsilyloxy)undecan-2-ol (**5**) (5.00 g, 16.6 mmol) was dissolved in dichloromethane (300 mL) and cooled to 0 °C. Diisopropylethylamine (8.63 mL, 50.0 mmol) was then added followed by bromomethyl methyl ether (2.76 mL, 33.8 mmol). The solution was stirred for 0.5 h at 0 °C then heated under reflux overnight. The reaction mixture was cooled to room temperature, acidified with 1.0 M hydrochloric acid (15 mL) and extracted with dichloromethane (3 × 100 mL). After removal of the solvent under reduced pressure, the resulting material was purified by flash column chromatography (petroleum ether/diethyl ether, 30 : 1) to give (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)undecane (**6**) as a colourless oil (5.72 g, 100%). (Found: C, 65.92; H, 12.23. $C_{19}H_{42}O_3Si$ requires C, 65.90; H, 12.14%); ν_{max}/cm^{-1} (NaCl) 2927 (CH), 1465, 1254, 1113, 1040, 837, 776; $[\alpha]_D^{23}$ +49.9 (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.01 (6H, s, $Si(CH_3)_2$), 0.83–0.85 (12H, m, 11-H_3 and $SiC(CH_3)_3$), 1.18–1.44 (16H, m, 3-H_2, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, and 10-H_2), 3.32 (3H, s, OCH_3), 3.48–3.60 (3H, m, 1-H_2 and 2-H), 4.59 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.72 (1H, d, *J* 6.8 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) −5.1 ($2 \times CH_3$), 14.1 (CH_3), 18.3 (C), 22.7 (CH_2), 25.4 (CH_2), 25.9 ($3 \times CH_3$), 29.3 (CH_2), 29.6 ($2 \times CH_2$), 29.7 (CH_2), 31.7 (CH_2), 31.9 (CH_2), 55.4 (CH_3), 65.9 (CH_2), 78.2 (CH), 96.3 (CH_2); *m/z* (CI) 347.2983 (MH^+. $C_{19}H_{43}O_3Si$ requires 347.2981), 315 (100%), 285 (24), 259 (8), 221 (6), 133 (7), 97 (18), 81 (52), 69 (68).

(2*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxymethoxy)undecane

The reaction was carried out according to the procedure described above using (2*R*)-1-(*tert*-butyldimethylsilyloxy)undecan-2-ol (5.00 g, 16.53 mmol). This gave (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)undecane (5.70 g, 100%) as a colourless oil. $[\alpha]_D^{23}$ −49.5 (*c* 1.4, $CHCl_3$). All other spectroscopic data as previously reported for (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)undecane (**6**).

(2*S*)-2-(Methoxymethoxy)undecan-1-ol (7)

A solution of tetrabutylammonium fluoride (1.0 M in tetrahydrofuran) (17.3 mL, 17.3 mmol) was added to a solution of (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)undecane (**6**) (5.00 g, 14.5 mmol) in tetrahydrofuran (300 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was then concentrated and the resulting residue was re-suspended in diethyl ether (200 mL). The solution was washed with water (100 mL) and the aqueous layer was then extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), concentrated and purified by flash column chromatography (petroleum ether/diethyl ether, 5 : 2) to give (2*S*)-2-(methoxymethoxy)undecan-1-ol (**7**) as a colourless oil (3.35 g, 100%). ν_{max}/cm^{-1} (NaCl) 3435 (OH), 2925 (CH), 1466, 1106, 1037, 918; $[\alpha]_D^{23}$ +6.7 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.8 Hz, 11-H_3), 1.26–1.52 (16H, m, 3-H_2, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, and 10-H_2), 3.15 (1H, dd, *J* 8.8, 3.2 Hz, OH), 3.43 (3H, s, OCH_3), 3.46–3.62 (3H, m, 1-H_2 and 2-H), 4.70 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.75 (1H, d, *J* 6.9 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 25.5 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 ($2 \times CH_2$), 31.6 (CH_2), 31.8 (CH_2), 55.6 (CH_3), 65.7 (CH_2), 82.5 (CH), 97.0 (CH_2); *m/z* (CI) 233.2119 (MH^+. $C_{13}H_{29}O_3$ requires 233.2117), 215 (10%), 201 (94), 183 (38), 171 (100), 153 (14), 113 (6), 81 (18), 69 (26).

(2*R*)-2-(Methoxymethoxy)undecan-1-ol

The reaction was carried out according to the procedure described above using (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)undecane (3.38 g, 9.75 mmol). This gave (2*R*)-2-methoxymethoxy)undecan-1-ol (2.13 g, 94%) as a colourless oil. $[\alpha]_D^{23}$ −7.1 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*S*)-2-(methoxymethoxy)undecan-1-ol (**7**).

Ethyl (2*E*,4*S*)-4-(methoxymethoxy)tridecan-2-enoate (8)

Dimethyl sulfoxide (4.10 mL, 57.8 mmol) was added to a stirred solution of oxalyl chloride (2.83 mL, 32.4 mmol) in dichloromethane (200 mL) at −78 °C. The reaction mixture was stirred for 0.3 h before (2*S*)-2-(methoxymethoxy)undecan-1-ol (**7**) (5.38 g, 23.1 mmol) in dichloromethane (50 mL) was slowly added. The mixture was stirred for a further 0.3 h before triethylamine (16.1 mL, 115.7 mmol) was added. This reaction mixture was stirred for 0.5 h at −78 °C and then allowed to warm to room temperature and stirred for a further 2 h. Meanwhile, a solution of lithium chloride (1.77 g, 41.8 mmol), triethyl phosphonoacetate (6.88 mL, 34.7 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (4.88 mL, 34.7 mmol) in acetonitrile (200 mL) was prepared and stirred for 1.0 h. The Swern solution was concentrated *in vacuo* and the Horner–Wadsworth–Emmons solution was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched by the addition of a saturated solution of ammonium chloride (50 mL) and concentrated to give an orange residue, which was then extracted with diethyl ether (4 × 100 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to give an orange oil. Purification by flash column chromatography using (diethyl ether/petroleum ether, 1 : 10) yielded ethyl (2*E*,4*S*)-4-(methoxymethoxy)tridecan-2-enoate (**8**) (6.61 g, 95%) as a colourless oil. (Found: C, 67.85; H, 10.86. $C_{17}H_{32}O_4$ requires C, 68.00; H, 10.67%); ν_{max}/cm^{-1} (NaCl) 2927 (CH), 1724 (CO), 1658 (C═C), 1467, 1368, 1268, 1154, 1035, 722; $[\alpha]_D^{23}$ −62.1 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8 Hz, 13-H_3), 1.21–1.62 (19H, m, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2 and OCH_2CH_3), 3.38 (3H, s,

OCH_3), 4.16–4.24 (3H, m, 4-H and OCH_2CH_3), 4.58 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.64 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.97 (1H, dd, *J* 16.0, 1.2 Hz, 2-H), 6.82 (1H, dd, *J* 16.0, 6.4 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 14.3 (CH_3), 22.7 (CH_2), 25.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 31.9 (CH_2), 34.9 (CH_2), 55.7 (CH_3), 60.5 (CH_2), 75.2 (CH), 94.6 (CH_2), 121.8 (CH), 148.0 (CH), 166.4 (C); *m*/*z* (CI) 301.2378 (MH^+. $C_{17}H_{33}O_4$ requires 301.2379), 271 (15%), 239 (100), 173 (6), 145 (5), 69 (17).

Ethyl (2*E*,4*R*)-4-(methoxymethoxy)tridecan-2-enoate

The reaction was carried out according to the procedure described above using (2*R*)-2-(methoxymethoxy)undecan-1-ol (5.38 g, 23.14 mmol). This gave ethyl (2*E*,4*R*)-4-(methoxymethoxy)tridecan-2-enoate (7.10 g, 100%) as a colourless oil. $[\alpha]_D^{23}$ +63.2 (*c* 1.1, $CHCl_3$). All other spectroscopic data as previously reported for ethyl (2*E*,4*S*)-4-(methoxymethoxy)tridecan-2-enoate (**8**).

(2*E*,4*S*)-4-(Methoxymethoxy)tridecan-2-ene-1-ol (9)

Ethyl (2*E*,4*S*)-4-(methoxymethoxy)tridecan-2-enoate (**8**) (4.70 g, 15.7 mmol) was dissolved in diethyl ether (350 mL) and cooled to −78 °C. DIBAL-H (1.0 M in hexane) (34.5 mL, 34.5 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 3 h, before warming to room temperature. The solution was cooled to 0 °C and quenched by the addition of a saturated solution of ammonium chloride (50 mL) and warmed to room temperature with vigorous stirring over 1 h. The reaction mixture was filtered through a pad of Celite® and washed with diethyl ether (400 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (diethyl ether/petroleum ether, 2 : 5) gave (2*E*,4*S*)-4-(methoxymethoxy)tridecan-2-ene-1-ol (**9**) (3.84 g, 95%) as a colourless oil. (Found: C, 70.15; H, 11.99. $C_{15}H_{30}O_3$ requires C, 69.77; H, 11.63%); ν_{max}/cm^{-1} (NaCl) 3399 (OH), 2925 (CH), 2855, 1466, 1377, 1213, 1152, 1128, 1096, 1036, 973; $[\alpha]_D^{23}$ −87.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.4 Hz, 13-H_3), 1.26–1.62 (17H, m, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2 and OH), 3.37 (3H, s, OCH_3), 4.01 (1H, q, *J* 7.0 Hz, 4-H), 4.16 (2H, td, *J* 5.6, 1.2 Hz, 1-H_2), 4.53 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.70 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.56 (1H, ddt, *J* 15.6, 7.0, 1.2 Hz, 3-H), 5.81 (1H, dt, *J* 15.6, 5.6 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 25.4 (CH_2), 29.3 (CH_2), 29.6 (2 × CH_2), 29.6 (CH_2), 31.9 (CH_2), 35.6 (CH_2), 55.4 (CH_3), 62.9 (CH_2), 76.3 (CH), 93.8 (CH_2), 131.7 (CH), 131.9 (CH); *m*/*z* (CI) 241.2166 ($MH^+ - H_2O$. $C_{15}H_{29}O_2$ requires 241.2168), 197 (100%), 179 (33), 155 (14), 131 (21), 85 (28).

(2*E*,4*R*)-4-(Methoxymethoxy)tridecan-2-ene-1-ol

The reaction was carried out according to the procedure described above using ethyl (2*E*,4*R*)-4-(methoxymethoxy)tridecan-2-enoate (4.80 g, 16.0 mmol). This gave (2*E*,4*R*)-4-(methoxymethoxy)tridecan-2-ene-1-ol (4.00 g, 97%) as a colourless oil. $[\alpha]_D^{23}$ +87.6 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*E*,4*S*)-4-(methoxymethoxy)tridecan-2-ene-1-ol (**9**).

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)tridecan-1-ene (11)

(2*E*,4*S*)-4-(Methoxymethoxy)tridecan-2-ene-1-ol (**9**) (2.55 g, 9.90 mmol) was dissolved in dichloromethane (200 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.34 mL, 2.47 mmol) was then added to the solution followed by trichloroacetonitrile (1.48 mL, 14.8 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was then filtered through a short pad of silica gel and washed with diethyl ether (200 mL). The resulting filtrate was then concentrated to give allylic trichloroacetimidate **10**, which was used without further purification. The resulting allylic trichloroacetimidate **10** was dissolved in toluene (100 mL) and bis(acetonitrile)palladium(II) chloride (0.38 g, 1.48 mmol) and *p*-benzoquinone (2.13 g, 19.8 mmol) were added. The reaction mixture was stirred at 45 °C for 24 h. The reaction mixture was concentrated and purification by flash column chromatography (diethyl ether/petroleum ether, 1 : 20) gave (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)tridecan-1-ene (**11**) as a colourless oil (2.78 g, 70% over 2 steps). ν_{max}/cm^{-1} (NaCl) 3287 (NH), 2855 (CH), 1717 (CO), 1643 (C═C), 1517, 1237, 1036, 822, 758; $[\alpha]_D^{23}$ +66.0 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8 Hz, 13-H_3), 1.24–1.65 (16H, m, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2 and 12-H_2), 3.43 (3H, s, OCH_3), 3.56 (1H, ddd, *J* 8.4, 4.8, 2.0 Hz, 4-H), 4.36–4.41 (1H, m, 3-H), 4.65 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.74 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.30–5.36 (2H, m, 1-H_2), 5.85 (1H, ddd, *J* 17.2, 10.4, 6.8 Hz, 2-H), 8.24 (1H, br d, *J* 7.6 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 29.3 (CH_2), 29.5 (2 × CH_2), 29.5 (CH_2), 31.9 (CH_2), 33.0 (CH_2), 55.9 (CH), 56.7 (CH_3), 83.9 (CH), 93.0 (C), 98.2 (CH_2), 118.9 (CH_2), 131.6 (CH), 161.4 (C); *m*/*z* (CI) 402.1369 (MH^+. $C_{17}H_{31}{}^{35}Cl_3NO_3$ requires 402.1370), 370 (100%), 336 (36), 308 (25), 270 (19), 214 (60), 180 (19), 85 (20), 69 (31).

(3*S*,4*R*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)tridecan-1-ene

The reaction was carried out according to the procedure described above using (2*E*,4*R*)-4-(methoxymethoxy)tridecan-2-ene-1-ol (2.55 g, 9.90 mmol). This gave (3*S*,4*R*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)tridecan-1-ene (2.80 g, 70%) as a colourless oil. $[\alpha]_D^{23}$ −65.8 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)tridecan-1-ene (**11**).

(2*R*,3*S*)-2-(Trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (12)

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)tridecan-1-ene (**11**) (0.94 g, 2.33 mmol) was dissolved in a mixture of dichloromethane (40 mL) and methanol (20 mL) and cooled to −78 °C. Ozone was bubbled through the reaction mixture until the solution turned slightly blue. After excess ozone was purged with argon gas, sodium borohydride (0.08 g, 2.33 mmol) was added in portions. The solution was stirred for 1.5 h at 0 °C, then acidified with 1 M hydrochloric acid (10 ml). The reaction was quenched by the addition of water (20 mL) and then extracted with diethyl ether (4 × 50 mL). The organic layers were combined,

dried ($MgSO_4$) and concentrated to give an orange oil. Purification by flash column chromatography using (diethyl ether/petroleum ether, 5 : 5) yielded (2*R*,3*S*)-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**12**) (0.84 g, 88% over 2 steps) as a colourless oil. (Found: C, 47.26; H, 7.45; N, 3.32. $C_{16}H_{30}Cl_3NO_4$ requires C, 47.23; H, 7.38; N, 3.44%); ν_{max}/cm^{-1} (NaCl) 3416 (NH), 2926 (CH), 1712 (CO), 1522, 1467, 1214, 1034, 906, 822, 756; $[\alpha]_D^{23}$ +23.3 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 6.8 Hz, 12-H_3), 1.25–1.78 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 2.70 (1H, dd, *J* 9.6, 3.6 Hz, OH), 3.47 (3H, s, OCH_3), 3.74–3.84 (2H, m, 1-*H*H and 3-H), 3.95 (1H, dq, *J* 8.2, 3.6 Hz, 2-H), 4.08 (1H, dt, *J* 12.0, 3.6 Hz, 1-H*H*), 4.65 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.73 (1H, d, *J* 6.8 Hz, OCH*H*O), 8.01 (1H, br d, *J* 8.2 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.5 (2 × CH_2), 31.9 (CH_2), 32.9 (CH_2), 54.7 (CH), 56.1 (CH_3), 61.2 (CH_2), 82.6 (CH), 92.7 (C), 97.9 (CH_2), 162.2 (C); *m*/*z* (CI) 406.1317 (MH^+. $C_{16}H_{31}{}^{35}Cl_3NO_4$ requires 406.1319), 374 (100%), 340 (43), 288 (14), 272 (6), 183 (4), 121 (3), 81 (6).

(2*S*,3*R*)-2-(Trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol

The reaction was carried out according to the procedure described above using (3*S*,4*R*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)tridecan-1-ene (0.50 g, 1.24 mmol). This gave (2*S*,3*R*)-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)-dodecan-1-ol (0.38 g, 76%) as a colourless oil. $[\alpha]_D^{23}$ –23.7 (*c* 1.3, $CHCl_3$). All other spectroscopic data as previously reported for (2*R*,3*S*)-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**12**).

(2*R*,3*S*)-1-Methanesulfonate-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane

A solution of (2*R*,3*S*)-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**12**) (0.38 g, 0.95 mmol) was dissolved in dichloromethane (40 mL). Methanesulfonyl chloride (0.16 mL, 1.47 mmol), triethylamine (0.29 mL, 2.16 mmol) and 4-dimethylaminopyridine (DMAP, catalytic) were added at 0 °C and the solution stirred at room temperature for 24 h. The reaction mixture was then washed with water (20 mL), extracted with dichloromethane (3 × 30 mL). The resulting organic layer was dried ($MgSO_4$) and concentrated to give the crude product, which was purified by flash column chromatography (diethyl ether/petroleum ether, 2 : 3) to give (2*R*,3*S*)-1-methanesulfonate-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (0.39 g, 87%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3346 (NH), 2926 (CH), 1716 (CO), 1524, 1359, 1177, 1034, 823; $[\alpha]_D^{23}$ +25.8 (*c* 1.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.2 Hz, 12-H_3), 1.21–1.72 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 3.06 (3H, s, OSO_2CH_3), 3.45 (3H, s, OCH_3), 3.59–3.65 (1H, m, 3-H), 4.23–4.29 (1H, m, 2-H), 4.34 (1H, dd, *J* 10.4, 7.8 Hz, 1-*H*H), 4.50 (1H, dd, *J* 10.4, 4.4 Hz, 1-H*H*), 4.63 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.74 (1H, d, *J* 6.8 Hz, OCH*H*O), 8.15 (1H, br d, *J* 8.4 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 25.8 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (2 × CH_2), 31.9 (CH_2), 33.0 (CH_2), 37.8 (CH_3), 53.2 (CH), 56.0 (CH_3), 66.4 (CH_2), 82.4 (CH), 92.6 (C), 98.3 (CH_2), 162.2 (C); *m*/*z* (CI) 484.1089 (MH^+. $C_{17}H_{33}{}^{35}Cl_3NO_6S$ requires 484.1094), 452 (83%), 418 (19), 388 (100), 354 (85), 322 (44), 279 (74), 201 (10), 153 (6), 85 (11).

(2*S*,3*R*)-1-Methanesulfonate-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane

The reaction was carried out according to the procedure described above using (2*S*,3*R*)-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (0.23 g, 0.56 mmol). This gave (2*S*,3*R*)-1-methanesulfonate-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (0.23 g, 88%) as a colourless oil. $[\alpha]_D^{23}$ –25.4 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*R*,3*S*)-1-methanesulfonate-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane.

(2*R*,3*S*)-1-Bromo-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (13)

(2*R*,3*S*)-1-Methanesulfonate-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (0.41 g, 0.85 mmol) was dissolved in dimethyl sulfoxide (20 mL), then sodium bromide (0.44 g, 4.26 mmol) was added and the reaction mixture was heated under reflux overnight. The reaction mixture was cooled and concentrated *in vacuo*. The resulting residue was dissolved in diethyl ether (20 mL) and washed with water (2 × 30 mL). The organic layer was dried and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/diethyl ether, 14 : 1) gave (2*R*,3*S*)-1-bromo-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (**13**) (0.30 g, 75%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3337 (NH), 2925 (CH), 1718 (CO), 1523, 1148, 1034, 821; $[\alpha]_D^{23}$ +32.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 6.8 Hz, 12-H_3), 1.16–1.59 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 3.37 (3H, s, OCH_3), 3.50 (1H, dd, *J* 10.8, 7.6 Hz, 1-*H*H), 3.56–3.61 (2H, m, 1-H*H* and 3-H), 4.16–4.23 (1H, m, 2-H), 4.57 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.65 (1H, d, *J* 6.8 Hz, OCH*H*O), 7.62 (1H, br d, *J* 9.2 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 25.4 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.5 (2 × CH_2), 31.4 (CH_2), 31.9 (CH_2), 32.5 (CH_2), 54.6 (CH), 56.1 (CH_3), 81.7 (CH), 92.7 (C), 97.8 (CH_2), 161.8 (C); *m*/*z* (CI) 470.0442 (MH^+. $C_{16}H_{30}{}^{81}Br^{35}Cl_3NO_3$ requires 470.0451), 438 (100%), 436 (63), 408 (16), 354 (9), 201 (4), 171 (3), 95 (2), 69 (8).

(2*S*,3*R*)-1-Bromo-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane

The reaction was carried out according to the procedure described above using (2*S*,3*R*)-1-methanesulfonate-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (0.41 g, 0.85 mmol). This gave (2*S*,3*R*)-1-bromo-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (0.31 g, 75%) as a colourless oil. $[\alpha]_D^{23}$ –34.0 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*R*,3*S*)-1-bromo-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (**13**).

(2*R*,3*S*)-2-Acetylamino-3-(methoxymethoxy)dodecane (14)

A mixture of (2*R*,3*S*)-1-bromo-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (**13**) (0.14 g, 0.29 mmol),

tributyltin hydride (1.01 mL, 3.47 mmol), AIBN (0.02 g) in toluene (9 mL) and *N*,*N*-dimethylacetamide (3 mL) were degassed under argon for 0.3 h and then heated under reflux for 24 h. The reaction mixture was cooled, washed with water (20 mL), extracted with diethyl ether (3 × 20 mL) and concentrated *in vacuo.* Purification by flash column chromatography (petroleum ether/diethyl ether, 1 : 8) gave (2*R*,3*S*)-2-acetylamino-3-(methoxymethoxy)dodecane (**14**) (0.07 g, 85%) as a white solid. Mp 35–37 °C; ν_{max}/cm^{-1} (NaCl) 3290 (NH), 2925 (CH), 1648 (CO), 1546, 1374, 1038, 920; $[\alpha]_D^{23}$ +46.1 (*c* 1.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.2 Hz, 12-H_3), 1.11 (3H, d, *J* 6.8 Hz, 1-H_3), 1.28–1.62 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 1.98 (3H, s, $COCH_3$), 3.43–3.48 (4H, m, OCH_3 and 3-H), 3.98–4.06 (1H, m, 2-H), 4.64 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.74 (1H, d, *J* 6.8 Hz, OCH*H*O), 6.65 (1H, br d, *J* 7.6 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 14.1 (CH_3), 22.7 (CH_2), 23.6 (CH_3), 25.9 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.9 (CH_2), 32.7 (CH_2), 47.2 (CH), 55.7 (CH_3), 84.4 (CH), 98.1 (CH_2), 169.1 (C); *m*/*z* (CI) 288.2543 (MH^+. $C_{16}H_{34}NO_3$ requires 288.2539), 256 (29%), 226 (9), 184 (3), 131 (4), 86 (5).

(2*S*,3*R*)-2-Acetylamino-3-(methoxymethoxy)dodecane

The reaction was carried out according to the procedure described above using (2*S*,3*R*)-1-bromo-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (0.05 g, 0.10 mmol). This gave (2*S*,3*R*)-2-acetylamino-3-(methoxymethoxy)dodecane (0.03 g, 100%) as a white solid. $[\alpha]_D^{23}$ –45.7 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*R*,3*S*)-2-acetylamino-3-(methoxymethoxy)dodecane (**14**).

(2*R*,3*S*)-2-Amindododecan-3-ol (clavaminol A) (1)[1]

(2*R*,3*S*)-2-Acetylamino-3-(methoxymethoxy)dodecane (**14**) (0.02 g, 0.06 mmol) was dissolved in 6 M hydrochloric acid (10 mL) and heated to 60 °C for 24 h. The reaction mixture was then cooled before being washed with diethyl ether (3 × 10 mL). The aqueous layer was concentrated to give (2*R*,3*S*)-2-aminododecan-3-ol (**1**) (0.014 g, 100%) as a white solid. Mp 107–109 °C; ν_{max}/cm^{-1} (NaCl) 3389 (NH), 2928 (CH), 1610, 1500, 1025, 721; $[\alpha]_D^{23}$ –4.5 (*c* 1.5, MeOH), lit.[1] $[\alpha]_D^{25}$ –4.25 (*c* 0.0094, MeOH); δ_H (400 MHz, CD_3OD) 0.93 (3H, t, *J* 7.2 Hz, 12-H_3), 1.24 (3H, d, *J* 6.8 Hz, 1-H_3), 1.31–1.59 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 3.30 (1H, qd, *J* 6.8, 3.2 Hz, 2-H), 3.70–3.75 (1H, m, 3-H); δ_C (100 MHz, CD_3OD) 12.1 (CH_3), 14.5 (CH_3), 23.8 (CH_2), 27.0 (CH_2), 30.5 (CH_2), 30.7 (CH_2), 30.7 (2 × CH_2), 33.1 (CH_2), 34.0 (CH_2), 52.6 (CH), 71.7 (CH); *m*/*z* (CI) 202.2175 (MH^+. $C_{12}H_{28}NO$ requires 202.2171), 184 (15%), 156 (10), 97 (4), 85 (6), 71 (7).

(2*S*,3*R*)-2-Aminododecan-3-ol

The reaction was carried out according to the procedure described above using (2*S*,3*R*)-2-acetylamino-3-(methoxymethoxy)dodecane (0.015 g, 0.05 mmol). This gave (2*S*,3*R*)-2-aminododecan-3-ol (0.011 g, 100%) as a white solid. $[\alpha]_D^{23}$ +5.4 (*c* 1.0, MeOH). All other spectroscopic data as reported above for (2*R*,3*S*)-2-aminododecan-3-ol (**1**).

(2*R*,3*S*)-2-Acetylaminododecan-3-ol (clavaminol C) (2)[1]

(2*R*,3*S*)-2-Acetylamino-3-(methoxymethoxy)dodecane (**14**) (0.02 g, 0.07 mmol) was dissolved in 2 M hydrochloric acid (10 mL) and stirred at room temperature for 24 h. The reaction mixture was washed with diethyl ether (3 × 10 mL) and the organic layers were concentrated *in vacuo*. Purification by flash column chromatography (diethyl ether/methanol, 15 : 1) yielded (2*R*,3*S*)-2-acetylaminododecan-3-ol (**2**) (0.02 g, 100%) as a white solid. Mp 103–105 °C; ν_{max}/cm^{-1} (NaCl) 3283 (NH), 2918 (CH), 1645 (CO), 1558, 1467, 1126, 747; $[\alpha]_D^{23}$ +11.1 (*c* 2.1, MeOH), lit.[1] $[\alpha]_D^{25}$ +11.4 (*c* 0.0022, MeOH); δ_H (400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.2 Hz, 12-H_3), 1.03 (3H, d, *J* 6.8 Hz, 1-H_3), 1.17–1.43 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 1.92 (3H, s, $COCH_3$), 2.12 (1H, d, *J* 6.0 Hz, OH), 3.54–3.61 (1H, m, 3-H), 3.90–3.98 (1H, m, 2-H), 5.71 (1H, br d, *J* 7.2 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 14.2 (CH_3), 22.7 (CH_2), 23.5 (CH_3), 26.0 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.9 (CH_2), 33.6 (CH_2), 49.5 (CH), 74.3 (CH), 170.0 (C); *m*/*z* (CI) 244.2275 (MH^+. $C_{14}H_{30}NO_2$ requires 244.2277), 226 (5%), 151 (5), 113 (5), 85 (39), 69 (58).

(2*S*,3*R*)-2-Acetylaminododecan-3-ol

The reaction was carried out according to the procedure described above using (2*S*,3*R*)-2-acetylamino-3-(methoxymethoxy)dodecane (0.027 g, 0.24 mmol). This gave (2*S*,3*R*)-2-acetylaminododecan-3-ol (0.018 g, 81%) as a white solid. $[\alpha]_D^{23}$ –13.3 (*c* 1.0, MeOH). All other spectroscopic data as previously reported for (2*R*,3*S*)-2-acetylaminododecan-3-ol (**2**).

(2*R*,3*S*)-2-Aminododecan-1,3-diol (15)

(2*R*,3*S*)-2-(Trichloromethylcarbonylamino)-3-(methoxymethoxy)-dodecan-1-ol (**12**) (0.04 g, 0.10 mmol) was dissolved in 6 M hydrochloric acid (10 mL) and heated to 60 °C for 24 h. The reaction mixture was then cooled before being washed with diethyl ether (3 × 10 mL). The water layer was concentrated to give (2*R*,3*S*)-2-aminododecan-1,3-diol (0.02 g, 100%) (**15**) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3348 (NH/OH), 2924 (CH), 1600, 1467, 1051; $[\alpha]_D^{23}$ +6.6 (*c* 0.6, MeOH); δ_H (400 MHz, CD_3OD) 0.92 (3H, t, *J* 6.8 Hz, 12-H_3), 1.25–1.58 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 3.33–3.35 (1H, m, 2-H), 3.73 (1H, dd, *J* 11.6, 8.8 Hz, 1-*H*H), 3.79–3.85 (1H, m, 3-H), 3.87 (1H, dd, *J* 11.6, 3.6 Hz, 1-H*H*); δ_C (100 MHz, CD_3OD) 14.5 (CH_3), 23.8 (CH_2), 27.1 (CH_2), 30.5 (CH_2), 30.6 (CH_2), 30.7 (2 × CH_2), 33.1 (CH_2), 34.2 (CH_2), 58.5 (CH), 58.9 (CH_2), 70.3 (CH); *m*/*z* (CI) 218.2113 (MH^+. $C_{12}H_{28}NO_2$ requires 218.2120), 200 (4%), 186 (3), 171 (4), 81 (5), 69 (6).

(2*S*,3*R*)-2-Aminododecan-1,3-diol[7b]

The reaction was carried out according to the procedure described above using (2*S*,3*R*)-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (0.10 g, 0.24 mmol). This gave (2*S*,3*R*)-2-aminododecan-1,3-diol (0.05 g, 100%) as a colourless oil. $[\alpha]_D^{23}$ –6.3 (*c* 1.0, MeOH), lit.[7b] $[\alpha]_D^{20}$ –6.0 (*c* 0.1, MeOH). All other spectroscopic data as previously reported for (2*R*,3*S*)-2-aminododecan-1,3-diol (**15**).

(2*R*,3*S*)-2-Acetylamino-3-(methoxymethoxy)dodecan-1-ol (16)

A mixture of (2*R*,3*S*)-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**12**) (0.30 g, 0.73 mmol), tributyltin hydride (2.50 mL, 8.85 mmol), AIBN (0.02 g) in toluene (9 mL) and *N*,*N*-dimethylacetamide (3 mL) were degassed under argon for 0.3 h and then heated under reflux for 24 h. The reaction mixture was cooled, washed with water (20 mL), extracted with diethyl ether (3 × 20 mL) and the organic layers were concentrated *in vacuo.* Flash column chromatography using (diethyl ether/methanol, 15 : 1) yielded (2*R*,3*S*)-2-acetylamino-3-(methoxymethoxy)dodecan-1-ol (**16**) (0.20 g, 91%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3297 (NH/OH), 2925 (CH), 1656 (CO), 1551, 1376, 1035; $[\alpha]_D^{23}$ +34.6 (*c* 2.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.75 (3H, t, *J* 6.8 Hz, 12-H_3), 1.10–1.52 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 1.89 (3H, s, $COCH_3$), 3.18 (1H, dd, *J* 8.6, 3.2 Hz, OH), 3.29 (3H, s, OCH_3), 3.48 (1H, ddd, *J* 8.4, 4.8, 3.2 Hz, 3-H), 3.55 (1H, ddd, *J* 11.2, 8.6, 3.2 Hz, 1-*H*H), 3.71–3.77 (1H, m, 1-H*H*), 3.80–3.86 (1H, m, 2-H), 4.47 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.54 (1H, d, *J* 6.8 Hz, OCH*H*O), 6.60 (1H, br d, *J* 8.0 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 23.4 (CH_3), 25.8 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (2 × CH_2), 31.9 (CH_2), 32.7 (CH_2), 53.3 (CH), 56.0 (CH_3), 62.4 (CH_2), 82.7 (CH), 98.0 (CH_2), 170.6 (C); *m*/*z* (CI) 304.2483 (MH^+. $C_{16}H_{34}NO_4$ requires 304.2488), 272 (58%), 242 (8), 200 (3), 147 (4), 102 (4), 85 (4).

(2*S*,3*R*)-2-Acetylamino-3-(methoxymethoxy)dodecan-1-ol

The reaction was carried out according to the procedure described above using (2*S*,3*R*)-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (0.10 g, 0.24 mmol). This gave (2*S*,3*R*)-2-acetylamino-3-(methoxymethoxy)dodecan-1ol as a colourless oil (0.07 g, 84%). $[\alpha]_D^{23}$ −32.8 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*R*,3*S*)-2-acetylamino-3-(methoxymethoxy)dodecan-1-ol (**16**).

(2*R*,3*S*)-2-Acetylaminododecan-1,3-diol (clavaminol H) (3)[2]

(2*R*,3*S*)-2-Acetylamino-3-(methoxymethoxy)dodecan-1-ol (**16**) (0.02 g, 0.08 mmol) was dissolved in 2 M hydrochloric acid (10 mL) and stirred at room temperature for 24 h. The reaction mixture was washed with diethyl ether (3 × 10 mL) and the organic layers were concentrated *in vacuo*. Flash column chromatography using (diethyl ether/methanol, 15 : 1) yielded (2*R*,3*S*)-2-acetylaminododecan-1,3-diol (**3**) (0.02 g, 100%) as a white solid. Mp 107–109 °C; ν_{max}/cm^{-1} (NaCl) 3289 (NH/OH), 2917 (CH), 1650 (CO), 1551, 1371, 1091; $[\alpha]_D^{23}$ +3.3 (*c* 1.4, MeOH), lit.[2] $[\alpha]_D^{25}$ +3.19 (*c* 0.0013, MeOH); δ_H (400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 6.8 Hz, 12-H_3), 1.14–1.53 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 1.99 (3H, s, $COCH_3$), 2.44 (1H, d, *J* 6.8 Hz, 3-OH), 2.53 (1H, dd, *J* 6.8, 3.6 Hz, 1-OH), 3.66–3.80 (3H, m, 1-*H*H, 2-H and 3-H), 3.96 (1H, dt, *J* 11.2, 3.6 Hz, 1-H*H*), 6.35 (1H, br d, *J* 7.2 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 23.5 (CH_3), 26.0 (CH_2), 29.3 (2 × CH_2), 29.6 (2 × CH_2), 31.9 (CH_2), 34.6 (CH_2), 53.6 (CH), 62.5 (CH_2), 74.4 (CH), 170.4 (C); *m*/*z* (CI) 260 (MH^+, 100%), 242 (29), 228 (6), 186 (4), 102 (3), 85 (18).

(2*S*,3*R*)-2-Acetylaminododecan-1,3-diol

The reaction was carried out according to the procedure described above using (2*S*,3*R*)-2-acetylamino-3-(methoxymethoxy)dodecan-1-ol (0.03 g, 0.08 mmol). This gave (2*S*,3*R*)-2-acetylaminododecan-1,3-diol (0.03 g, 100%) as a white solid. $[\alpha]_D^{23}$ –4.1 (*c* 1.0, MeOH). All other spectroscopic data as previously reported for (2*R*,3*S*)-2-acetylaminododecan-1,3-diol (**3**).

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