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Synthesis of cylindricine C and a formal synthesis of cylindricine A

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ABSTRACT

This paper reports the synthesis of the alkaloid natural product (±)-cylindricine C, in addition to a formal synthesis of (±)-cylindricine A. The key step in our sequence is the (*ipso*) regioselective addition of an alkyl Grignard reagent to a C-2 substituted pyridinium salt to generate the dihydropyridone core of the alkaloid targets. After cyclisation to form the A and C rings of the cyclindricines the net outcome is a short (13 steps) synthesis of this natural product.

1. Introduction

In 1993, Blackman et al. reported the isolation of two novel alkaloids from the ascidian *Clavelina cylindricia*, collected off the coast of Tasmania.[1] Cylindricine A, the more abundant alkaloid, was identified as having a pyrrolo[2,1-*j*]quinoline ring system, while cylindricine B (with which cylindricine A is in equilibrium via an aziridinium ion intermediate) has a pyrido[2,1-*j*]quinoline ring system (Fig. 1). Further samples were collected in the following years, yielding alkaloids with the same skeleton as cylindricine A but with differing functionality on the C ring side-chain, and were named cylindricines C–G.[2] Further modification of the natural product skeleton has also been reported with the isolation of additional members of this family, subsequently named cylindricines H–K.[3]

To date the only biological activity reported for these molecules has been in a bioassay containing brine shrimp larvae (*Artemia salina*), where they have been shown to induce 93% mortality in 24 h. Nevertheless, the tricyclic system of the cylindricines comprising a spirocyclic amine makes them interesting synthetic targets, with cylindricines A and C being synthesised several times.[4–16] In terms of retrosynthetic disconnections of the natural products, we were interested in a unique approach that started with the six-membered B ring intact from the beginning (**6**, Scheme 1), and left construction of the five-membered C ring until the latter stages of the synthesis. This approach is significantly different to those reported in the literature, which usually rely upon late-stage construction of the six-membered B ring.

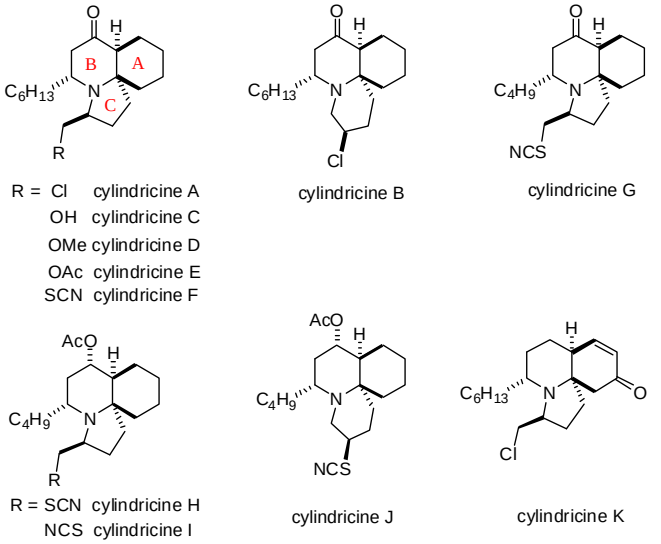

Figure 1. The cylindricines.

In addition to examining a new disconnection to these targets, our approach would also allow us to apply the recently developed regioselective addition of Grignard reagents to electron-deficient and substituted pyridinium salts in natural product synthesis.[17] In this case, the addition reaction would figure early in the route (see **6**→**5**, Scheme 1), allowing us to construct a dihydropyridone, which could then be elaborated as shown with the retrosynthesis for cyclindricine C in Scheme 1.

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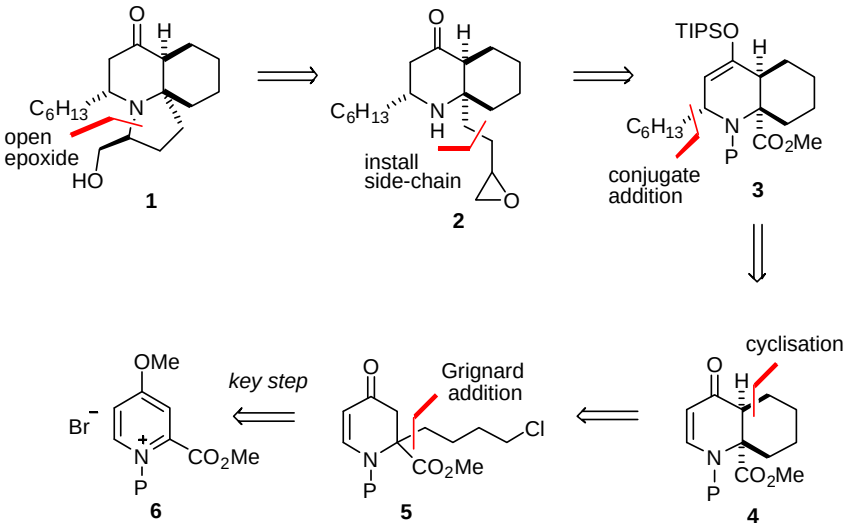
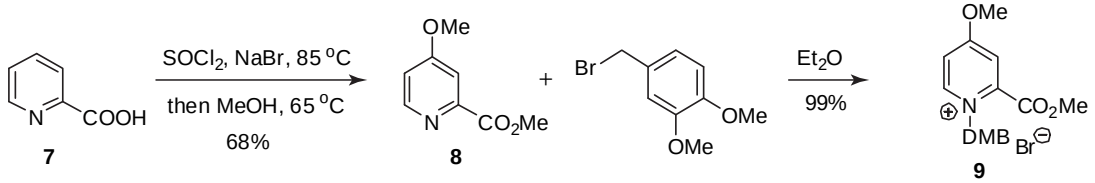


Scheme 1. Retrosynthesis.

2. Results and discussion

2.1. Investigation of Grignard addition reactions to *N*-DMB protected pyridinium salts

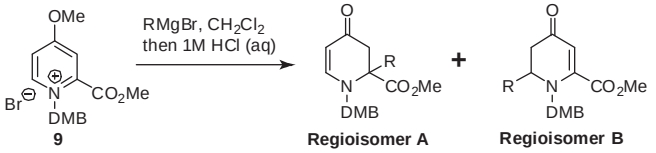
Our synthesis began with the preparation of pyridine **8** from commercially available picolinic acid **7** in a one-pot procedure employing conditions reported by Sundberg.[18] *N*-DMB-pyridinium salt **9** was then prepared by reaction of pyridine **8** with 4-(bromomethyl)-1,2-dimethoxybenzene (Scheme 2).



Scheme 2. Preparation of DMB salt **9**.

While we have previously reported the addition of Grignard reagents to ester substituted *N*-methyl and *N*-allyl pyridinium salts,[17] we wished to extend this methodology to encompass the *N*-DMB protected pyridinium salts required for application in the synthesis of the dihydropyridone core of the cylindricines. Table 1 shows the yields from the addition of alkyl, alkenyl, aryl and alkynyl Grignard reagents to pyridinium salt **9** to give either the C-2 or C-6 addition products, with harder nucleophiles (alkyl) adding at position 2 and softer nucleophiles (alkenyl, aryl and alkynyl) adding at position 6. In contrast to our previous work using *N*-allyl pyridinium salts, it was not necessary to use organozinc reagents to selectively add phenyl, vinyl, or 1-propynyl groups to C-6, showing that this addition reaction is highly dependent upon the nature of the protecting group on nitrogen. The structures of the products from this scheme had NMR data that was consistent with that reported in the literature. Moreover, we were able to confirm the structures of compounds **10** and **12** by X-ray crystallography (data not shown).

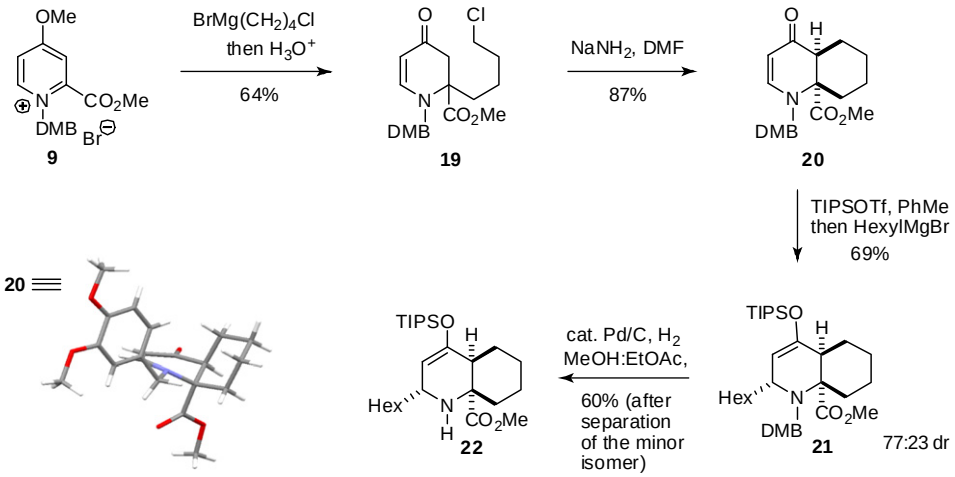
Table 1



RMgBr	Compound	Regioisomer	Yield (%)
Ph	**10**	B	77
Me	**11**	A	66
Et	**12**	A	72
Vinyl	**13**	B	87
Homoallyl	**14**	A	83
4-Methoxyphenyl	**15**	B	89
Isopropenyl	**16**	B	93
Benzyl	**17**	A	69
1-Propynyl	**18**	B	72

2.2. Formation of the 6,6 ring system of the cylindricines

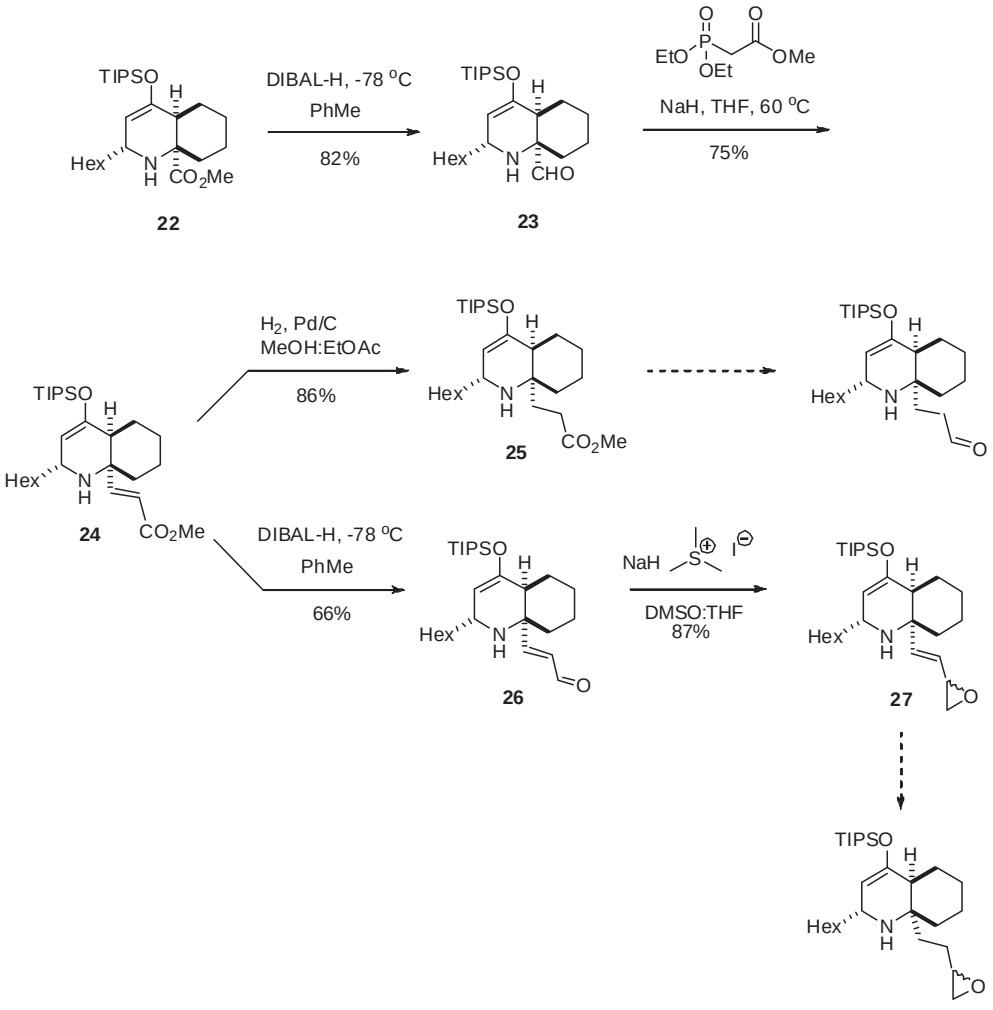
Our proposed synthesis relied upon the C-2 addition of 4-chlorobutyl magnesium bromide to **9**. Pleasingly, this reaction occurred in a regioselective (*ipso*) manner at C-2 and generated the desired quaternary centre (an in situ acid quench hydrolysed the enol ether to generate pyridone **19** in good yield, Scheme 3).[19,20] Subsequent ring closure using an unhindered base afforded the core bicyclic ring system **20** in excellent yield, and the exclusive formation of the *cis*-fused ring system under kinetically controlled conditions was verified by X-ray crystallography (Scheme 3, X-ray data is included in Supplementary data). Activation of the dihydropyridone carbonyl of **20** with a silyl triflate was followed by regio- and stereoselective addition of hexyl magnesium bromide to produce compound **21** in a 77:23 ratio with the desired product, originating from nucleophilic attack from the convex face of **20**, as the major one.[21,22] The relative stereochemistry of these compounds was assessed by reduction of the ester group to a CH_2OH unit, and subsequent NOE experiments on both diastereomers. At this point it was found to be expedient to remove the DMB protecting group by hydrogenolysis



Scheme 3. Formation of the bicyclic core.

so that the minor diastereoisomer could be separated from the mixture to furnish compound **22**.

We then proceeded to reduce the ester group at C-2 to an aldehyde to facilitate installation of the side-chain, Scheme 4. Reduction of **22** with DIBAL-H occurred smoothly and furnished aldehyde **23** in 82% yield. It is noteworthy that selective partial reduction of DMB protected amine **21** to the corresponding aldehyde was not an efficient process. Subsequent olefination of **23** using a Horner–Wadsworth–Emmons phosphonate gave alkene **24** in good yield,[23,24] which was hydrogenated using Pd/C to give **25**. DIBAL-H reduction of the ester and olefination would then allow a formal synthesis of cylindricine A to be completed. However



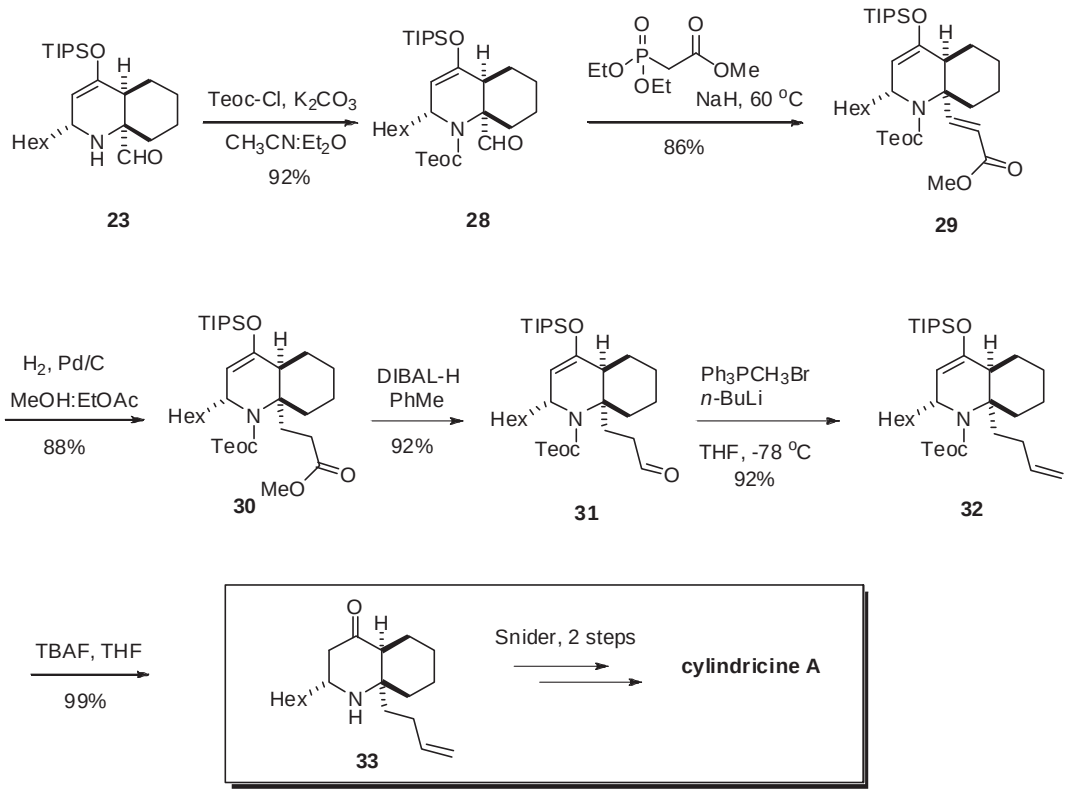
Scheme 4. Attempted side-chain homologation.

despite repeated attempts, the partial reduction of ester **25** led only to products of reductive amination, whereby the unprotected nitrogen had cyclised onto carbonyl intermediates formed during the reduction. These adducts were themselves also prone to reduction and the process could not be stopped, controlled or reversed. Our attention was then turned to synthesising cyclindricine A from ester **24** by manipulating the ester group before reduction of the *E*-alkene (which would prevent any intramolecular reaction of the nitrogen atom). Reduction of **24** using DIBAL-H to the aldehyde (**26**) and subsequent reaction with the Corey–Chaykovsky reagent[25] afforded epoxide **27**. Unfortunately all attempts at selective hydrogenation of the alkene failed with hydrogenolysis of the epoxide being observed in each case. Therefore, we concluded that the end-game with nitrogen unprotected was not viable and thus we sought to remedy this problem.

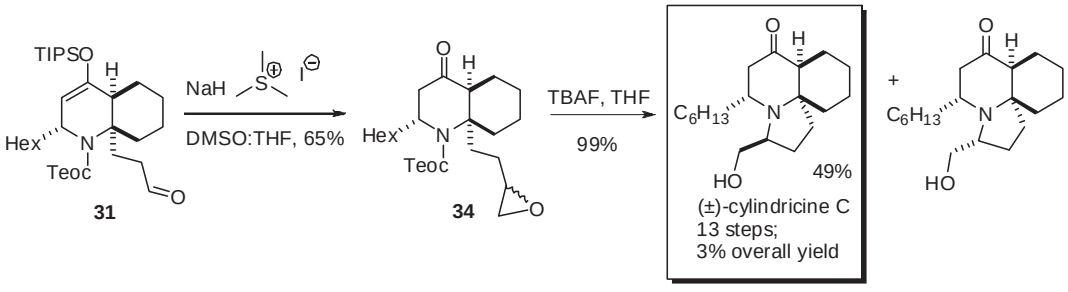
2.3. Alternative protecting group strategy

Following our unsuccessful attempts at proceeding with the unprotected amine, we proposed that N-protection would enable completion of the syntheses. The Teoc protecting group has already been utilised in a previous synthesis of cylindricine A and so we added a Teoc group to form **28**, knowing that it could be readily deprotected at a later stage with a fluoride source.[5] Subsequent olefination, hydrogenation and partial reduction with DIBAL-H afforded aldehyde **31** in good yield. Our initial aim was to complete a formal synthesis of cylindricine A by conversion of **31** to terminal alkene **32**, followed by TBAF induced deprotection of both the Teoc and TIPS groups. This two-step procedure gave compound **33**, which displayed spectroscopic data (^{1}H, ^{13}C NMR) identical to that reported in the literature.[4,5] The formation of **33** therefore constituted a formal synthesis of cylindricine A since it has been converted to the natural product in two steps by both Snider[4] and then Heathcock (Scheme 5).[5]

Next, we sought to complete the synthesis of cylindricine C by epoxidation of aldehyde **31**, Scheme 6. This was again accomplished by reaction with the Corey–Chaykovsky reagent,[25] which furnished epoxide **34** (as a 1:1 mix of diastereoisomers). Note that while these particular conditions led to deprotection of the TIPS enol ether, they did not remove the Teoc group from the nitrogen.



Scheme 5. Formal synthesis of cylindricine A.



Scheme 6. Synthesis of cylindricine C.

Thus, in order to complete the synthesis, we reacted compound **34** with TBAF to effect removal of the Teoc group and encourage in situ opening of the epoxide at the proximal position. This protocol did indeed furnish the natural product cyclidricine C, together with an easily separable diastereoisomer, the mixture originating from opening of the two epoxide stereoisomers. As expected, the synthetic cylindricine C exhibited spectroscopic data that was a very good match with that reported in the literature.[2,6,8,9] Supplementary data contains a full comparison of the data exhibited by both compound **33** and cylindricine C with that reported in the literature.

3. Conclusions

In summary, we have described an efficient synthesis of cylindricine C and a formal synthesis of cylindricine A from a common intermediate and the synthetic utility of the regioselective nucleophilic attack of Grignard reagents onto substituted pyridinium salts has been highlighted. The dihydropyridones formed using this methodology are furnished with considerable functionality that can be readily manipulated to allow the synthesis of natural products. In addition to a formal total synthesis of cyclindricine A, we have also completed the synthesis of cylindricine C, in 13 steps and 3% overall yield. Future work will concentrate on the formation of enantiopure adducts from the Grignard addition reaction.

4. Experimental

4.1. General

Solvents and reagents: Tetrahydrofuran, dichloromethane, methanol and toluene were dried prior to use by an alumina column. Triethylamine and diisopropylamine were dried by stirring over and distilling from calcium hydride and were stored over potassium hydroxide. Other solvents were used as supplied without purification. Light petroleum refers to the fraction of petroleum ether, which boils in the range 30–40 °C. Reagents obtained from Acros, Aldrich, Avocado, Fluka and Lancaster fine chemicals suppliers were used as supplied. Chromatography: column fractions and reactions were monitored by thin-layer chromatography (TLC). TLC was performed on Merck Kieselgel 60 F_{254} 0.25 mm pre-coated aluminium backed silica plates. Compounds were visualised with UV light and/or by staining with basic potassium permanganate solution. Column chromatography was carried out according to the method described by Still et al. using Merck Kieselgel 60 (40–63 μm), using head pressure by means of head bellows. NMR Spectroscopy: ^{1}H NMR spectra were recorded using a Bruker AVANCE AV400 (400 MHz), a Bruker DRX500 (500 MHz) or a Bruker AV11 500 (500 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) relative to residual solvent peaks. Signal splittings are recorded as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) and apparent (app). Coupling constants (J) are given to the nearest 0.1 Hz. ^{13}C NMR spectra were recorded on Bruker AVANCE AV400 (100 MHz), a Bruker DRX500 (125 MHz) or a Bruker AV11 500 (125 MHz) spectrometer and referenced in the same way. Assignments of both ^{1}H and ^{13}C NMR were aided by COSY (correlated spectroscopy), HMQC (heteronuclear multiple-quantum correlation) and HMBC (heteronuclear multiple-bond correlation). IR spectroscopy: Infra-red spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Compounds were analysed as thin films on NaCl plates or pressed into a KBr disk. Absorption maxima are quoted in wavenumbers (cm^{-1}). Mass Spectrometry: mass spectra (m/z) were recorded on a Fisons Platform II and accurate mass (HRMS) on a Bruker MicroTof (resolution=10,000 FWHM) under the conditions of electrospray ionisation (ESI). The lock-mass used for calibration was tetraoctylammonium bromide in positive ion and sodium dodecyl sulfate in negative ion mode. m/z values are reported in Daltons, followed by the percentage abundance in parentheses. Melting Points: melting points were determined using a Leica Galen III heated-stage microscope and are uncorrected. General: all reactions were carried out under an atmosphere of argon and performed using standard vacuum line techniques and flame-dried glassware.

4.2. Experimental procedures

*4.2.1. Methyl 4-methoxypicolinate (**8**)[18].* Picolinic acid (10.00 g, 81.00 mmol) and sodium bromide (1.00 g, 8.10 mmol) were dissolved in thionyl chloride (70 mL) and the mixture was heated at reflux for 16 h. The reaction mixture was concentrated in vacuo and cooled to 0 °C. Methanol (35 mL) was added cautiously and the reaction mixture was heated at reflux for 36 h. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 (100 mL) followed by addition of Na_2CO_3 (12.80 g, 120 mmol) and the mixture stirred for 3 h. Water (100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (5×50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (SiO_2, Et_2O) and re-crystallised (hexane) to furnish the product (9.20 g, 68%) as colourless needles. ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 8.50–8.46 (1H, m), 7.63–7.59 (1H, m), 6.94–6.90 (1H, m), 3.94 (3H, s), 3.85 (3H, s); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 166.5, 165.7, 150.9, 149.5, 113.0, 111.1, 55.5, 52.9.

*4.2.2. 1-(3,4-Dimethoxybenzyl)-4-methoxy-2-(methoxycarbonyl) pyridinium bromide salt (**9**).* Pyridine ester **8** (0.50 g, 3.00 mmol) was added to a stirred solution of 3,4-dimethoxybenzyl bromide (0.69 g, 3.00 mmol) in Et_2O (5 mL) and stirred for 48 h under an atmosphere of argon at room temperature. The solvent was removed in vacuo, and the residue washed with dry THF (2×10 mL). The resulting solid was dried under high vacuum to furnish the pyridinium salt (1.19 g, 99%) as a colourless powder. Mp 101–102 °C; IR ν_{max} (film)/cm^{-1} 3417, 1743, 1517, 1263, 1143, 1020; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 10.20 (1H, d, J 7.2), 7.89 (1H, dd, J 7.2 and 3.2), 7.68 (1H, d, J 3.2), 7.17 (1H, d, J 2.0), 6.93 (1H, dd, J 8.3 and 2.0), 6.80 (1H, d, J 8.3), 6.16 (2H, s, NCH_2), 4.22 (3H, s), 4.02 (3H, s), 3.90 (3H, s), 3.85 (3H, s); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 171.4, 160.2, 152.0, 149.6, 143.2, 125.6, 121.8, 117.7, 114.1, 112.3, 111.2, 60.8, 59.01, 56.5, 55.9, 54.8; MS m/z (ESI) 318 (M^+ 100%), HRMS (ESI) for $C_{17}H_{20}NO_5$ requires 318.1341 found (M^+) 318.1336.

*4.2.3. General procedure for the addition of Grignard reagents to pyridinium salt **9**.* Grignard reagent (2 equiv) was added dropwise over 5 min to a solution of pyridinium salt **9** (1 equiv) in CH_2Cl_2 (10 mL) at −78 °C. The reaction mixture was allowed to stir for 4 h 30 min at the same temperature before adding 1 M HCl (5 mL). The mixture was warmed slowly to room temperature and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography.

*4.2.4. Methyl-1-(3,4-dimethoxybenzyl)-4-oxo-6-phenyl-1,4,5,6-tetrahydropyridine-2-carboxylate (**10**).* Yield 0.73 g, 77%, pale yellow oil; IR ν_{max} (film)/cm^{-1} 3468, 1641, 1262; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 7.39–7.24 (5H, m), 6.84–6.82 (1H, m), 6.73–6.72 (2H, m), 5.43 (1H, s), 4.75 (1H, d, J 15.4), 4.61 (1H, t, J 6.4), 4.02 (1H, d, J 15.7), 3.91 (3H, s), 3.89 (3H, s), 3.84 (3H, s), 2.88 (1H, dd, J 16.6 and 7.0), 2.68 (1H, dd, J 16.4 and 6.1); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 199.8, 164.9, 159.0, 149.2 148.9, 137.7, 129.1, 128.5, 128.3, 126.7, 120.2, 111.1, 110.8, 101.6, 60.2, 55.9, 54.1, 53.2, 42.9; MS m/z (ESI) 404.2 ($M+Na^+$,

65% and M+H$^+$ 382.2, 25%), HRMS (ESI) for $C_{22}H_{23}NNaO_5$ requires 404.1468, found (M+Na$^+$) 404.1464.

*4.2.5. Methyl-1-(3,4-dimethoxybenzyl)-2-methyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate (**11**).* Yield 0.53 g, 66%, pale yellow oil; IR ν_{max} (film)/cm^{-1} 3443, 2084, 1641, 1262; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 7.01 (1H, d, *J* 7.8), 6.89–6.81 (3H, m), 5.03 (1H, d, *J* 7.8), 4.48 (1H, d, *J* 15.2), 4.38 (1H, d, *J* 15.2), 3.90 (6H, s), 3.76 (3H, s), 2.95 (1H, d, *J* 16.4), 2.64 (1H, d, *J* 16.4), 1.55 (3H, s); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 190.0, 173.3, 154.3, 149.4, 148.8, 129.3, 120.2, 111.3, 110.6, 99.8, 65.9, 56.0, 54.7, 53.0, 47.0, 22.5; MS *m*/*z* (ESI) 342.1 (M+Na$^+$, 65%), HRMS (ESI) for $C_{17}H_{21}NaNO_5$ requires 342.1312, found (M+Na$^+$) 342.1308.

*4.2.6. Methyl-1-(3,4-dimethoxybenzyl)-2-ethyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate (**12**).* Yield 0.60 g, 72%, pale yellow oil; IR ν_{max} (film)/cm^{-1} 3468, 2084, 1641, 1262; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 6.98 (1H, d, *J* 7.8), 6.87 (2H, s), 6.81 (1H, s), 5.00 (1H, d, *J* 7.8), 4.53 (1H, d, *J* 14.9), 4.39 (1H, d, *J* 14.9), 3.89 (6H, s), 3.74 (3H, s), 2.89 (1H, d, *J* 16.4), 2.72 (1H, d, *J* 16.4), 2.01 (2H, d, *J* 14.3 and 7.2), 1.00 (3H, t, *J* 7.5); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 190.6, 173.2, 154.4, 149.4, 148.8, 129.0, 120.5, 111.3, 111.0, 99.8, 69.3, 55.9, 53.7, 52.8, 43.0, 27.8, 8.4; MS *m*/*z* (ESI) 356.2 (M+Na$^+$, 60%), HRMS (ESI) for $C_{18}H_{23}NNaO_5$ requires 356.1468, found (M+Na$^+$) 356.1466.

*4.2.7. Methyl-1-(3,4-dimethoxybenzyl)-4-oxo-6-vinyl-1,4,5,6-tetrahydropyridine-2-carboxylate (**13**).* Yield 0.72 g, 87%, pale yellow oil; IR ν_{max} (film)/cm^{-1} 3444, 2063, 1731, 1644, 1516, 1259, 1138, 1065, 1026; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 6.87 (1H, s), 6.84 (2H, s), 5.84 (1H, ddd, *J* 17.2, 10.4 and 6.8), 5.34 (1H, s), 5.28 (1H, d, *J* 17.2), 5.22 (1H, d, *J* 10.4), 4.71 (1H, d, *J* 15.4), 4.16 (1H, d, *J* 15.4), 4.07–4.00 (1H, m), 3.89 (6H, s), 3.86 (3H, s), 2.72 (1H, dd, *J* 16.6 and 6.7), 2.37 (1H, dd, *J* 16.4 and 3.8); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 191.1, 164.8, 152.4, 149.3, 148.9, 132.2, 129.2, 120.2, 118.4, 111.1, 110.7, 101.0, 59.2, 55.9, 53.8, 53.1, 40.4; MS *m*/*z* (ESI) 354.1 (M+Na$^+$, 55% and M+H$^+$ 332.2, 25%), HRMS (ESI) for $C_{18}H_{21}NaNO_5$ requires 354.1312, found (M+Na$^+$) 354.1309.

*4.2.8. Methyl-2-(but-3-enyl)-1-(3,4-dimethoxybenzyl)-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate (**14**).* Yield 0.90 g, 83%, colourless oil; IR ν_{max} (film)/cm^{-1} 3447, 3059, 2954, 2837, 1734, 1644, 1516, 1027, 857, 734; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 6.97 (1H, dd, *J* 7.8 and 1.4), 6.87 (2H, s), 6.80 (1H, s), 5.76–5.67 (1H, m), 5.01–4.97 (3H, m), 4.50 (1H, d, *J* 14.9), 4.38 (1H, d, *J* 14.9), 3.80 (6H, s), 3.73 (3H, s), 2.91 (1H, d, *J* 16.3), 2.72 (1H, dd, *J* 16.3 and 1.3), 2.18–1.96 (4H, m); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 190.2, 172.9, 154.1, 149.4, 148.9, 136.4, 128.9, 120.6, 115.8, 111.4, 111.0, 68.8, 56.0, 53.8, 52.9, 43.5, 33.8, 28.0; MS *m*/*z* (ESI) 382 (M+Na$^+$, 40%), HRMS (ESI) for $C_{20}H_{25}NNaO_5$ requires 382.1625, found (M+Na$^+$) 382.1625.

*4.2.9. Methyl-1-(3,4-dimethoxybenzyl)-6-(4-methoxyphenyl)-4-oxo-1,4,5,6-tetrahydropyridine-2-carboxylate (**15**).* Yield 0.92 g, 89%, pale yellow oil; IR ν_{max} (film)/cm^{-1} 3442, 2062, 1732, 1643, 1463, 1253, 1138, 1026; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 7.17 (2H, m, *J* 8.8), 6.88 (2H, m, *J* 8.8), 6.83–6.81 (1H, m), 6.72–6.71 (2H, m), 5.39 (1H, s), 4.70 (1H, d, *J* 15.4), 4.54 (1H, t, *J* 6.6), 4.01 (1H, d, *J* 15.4), 3.89 (6H, s), 3.84 (3H, s), 3.81 (3H, s), 2.82 (1H, dd, *J* 16.6 and 6.7), 2.64 (1H, dd, *J* 16.4 and 6.6); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 191.1, 165, 159.5, 154.0, 149.2, 148.8, 129.7, 128.7, 128.1, 120.2, 114.4, 111.1, 110.7, 101.5, 59.8, 55.9, 53.8, 53.3, 53.2, 43.2; MS *m*/*z* (ESI) 434.2 (M+Na$^+$, 85%), HRMS (ESI) for $C_{23}H_{25}NNaO_6$ requires 434.1574, found (M+Na$^+$) 434.1577.

*4.2.10. Methyl-1-(3,4-dimethoxybenzyl)-4-oxo-6-(prop-1-en-2-yl)-1,4,5,6-tetrahydropyridine-2-carboxylate (**16**).* Yield 0.80 g, 93%, pale yellow oil; IR ν_{max} (film)/cm^{-1} 3444, 2063, 1731, 1644, 1516, 1259, 1138, 1026; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 6.86–6.80 (3H, m), 5.30 (1H, s), 5.00 (1H, s), 4.93 (1H, s), 4.73 (1H, d, *J* 15.4), 4.07 (1H, d, *J* 15.4), 3.98 (1H, dd, *J* 7.5 and 4.4), 3.89 (3H, s), 3.88 (3H, s), 3.86 (3H, s), 2.69 (1H, dd, *J* 16.7 and 7.6), 2.51 (1H, dd, *J* 16.6 and 4.2), 1.75 (3H, s); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 191.1, 164.9, 153.3, 149.3, 148.8, 139.5, 129.1, 120.1, 114.3, 111.1, 110.7, 100.7, 61.7, 55.9, 53.9, 53.1, 39.2, 19.0; MS *m*/*z* (ESI) 368.2 (M+Na$^+$, 55%), HRMS (ESI) for $C_{19}H_{23}NNaO_5$ requires 368.1468, found (M+Na$^+$) 368.1466.

*4.2.11. Methyl-2-benzyl-1-(3,4-dimethoxybenzyl)-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate (**17**).* Yield 0.68 g, 69%, pale yellow oil; IR ν_{max} (film)/cm^{-1} 3449, 2083, 1642, 1516, 1260, 1026; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 7.31–7.26 (3H, m), 7.13 (2H, dd, *J* 7.2 and 1.9), 6.96 (1H, d, *J* 7.8), 6.89–6.84 (2H, m), 6.78 (1H, s), 5.03 (1H, d, *J* 7.8), 4.64 (1H, d, *J* 15.4), 4.62 (1H, d, *J* 15.4), 3.89 (3H, s), 3.88 (3H, s,), 3.65 (3H, s), 3.48 (1H, d, *J* 13.4), 3.10 (1H, d, *J* 13.4), 2.86 (1H, d, *J* 16.4), 2.64 (1H, d, *J* 16.2); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 190.2, 172.2, 153.7, 149.4, 148.8, 134.1, 130.5, 129.4, 128.5, 127.5, 120.1, 111.3, 110.6, 99.9, 69.5, 55.9, 54.7, 52.7, 43.9, 40.0; MS *m*/*z* (ESI) 418.2 (M+Na$^+$, 65%), HRMS (ESI) for $C_{23}H_{25}NNaO_5$ requires 418.1625, found (M+Na$^+$) 418.1619.

*4.2.12. Methyl-1-(3,4-dimethoxybenzyl)-4-oxo-6-(prop-1-ynyl)-1,4,5,6-tetrahydropyridine-2-carboxylate (**18**).* Yield 0.62 g, 72%, yellow oil; IR ν_{max} (film)/cm^{-1} 3447, 2955, 2837, 2250, 1558; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 6.93–6.83 (3H, m), 5.47 (1H, s), 4.74 (1H, d, *J* 14.9), 4.29 (1H, d, *J* 15.2), 4.23 (1H, m), 3.89 (3H, s), 3.88 (3H, s), 3.86 (3H, s), 2.62 (1H, dd, *J* 16.2 and 6.1), 2.48 (1H, dd, *J* 16.0 and 4.4), 1.82 (3H, d, *J* 2.3); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 191.2, 164.6, 152.1, 149.3, 148.9, 128.7, 120.6, 111.1, 111.0, 102.5, 82.2, 74.2, 55.9, 53.8, 53.0, 48.9, 41.7, 3.6; MS *m*/*z* (ESI) 366.2 (M+Na$^+$, 80%), HRMS (ESI) for $C_{19}H_{21}NNaO_5$ requires 366.1312, found (M+Na$^+$) 366.1315.

*4.2.13. Methyl-2-(4-chlorobutyl)-1-(3,4-dimethoxybenzyl)-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate (**19**).* Freshly prepared 4-chlorobutyl magnesium bromide in THF was added dropwise over 5 min to a solution of pyridinium salt **9** (0.25 g, 0.63 mmol) in CH_2Cl_2 (1.5 mL) cooled at −30 °C. The reaction mixture was stirred for 4 h 30 min at the same temperature before the addition of 1 M HCl (5 mL). The reaction mixture was warmed to room temperature and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried (Na_2CO_3), filtered and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, Et_2O followed by Et_2O:CH_2Cl_2 7:3) to furnish the product (0.16 g, 64%), as a colourless oil; IR ν_{max} (film)/cm^{-1} 2954, 1735, 1645, 1587, 1516, 1462, 1262, 1140, 1025; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 6.96 (1H, d, *J* 7.8), 6.86 (2H, s), 6.81 (1H, s), 4.88 (1H, d, *J* 7.8), 4.47 (1H, d, *J* 14.7) 4.37 (1H, d, *J* 14.7), 3.88 (6H, s), 3.73 (3H, s), 3.49 (2H, m), 2.88 (1H, d, *J* 16.4), 2.72 (1H, d, *J* 16.4), 1.98–1.93 (2H, m), 1.80–1.65 (2H, m), 1.60–1.49 (2H, m); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 190.2, 172.9, 154.1, 149.4, 148.9, 128.7, 120.0, 111.3, 111.1, 99.9, 68.9, 55.9, 53.9, 52.9, 44.3, 43.5, 33.8, 32.3, 21.3; MS *m*/*z* (ESI) 396.00 (M+H$^+$ 100%), HRMS (ESI) for $C_{20}H_{27}Cl^{35}NO_5$ requires 396.1572, found (M+H$^+$) 396.1572 (Using 10 g of **9** we obtained **19** in a yield of 62%.).

*4.2.14. (4aS,8aR)-Methyl-1-(3,4-dimethoxybenzyl)-4-oxo-1,4,4a,5,6,7,8,8a-octahydroquinoline-8a-carboxylate (**20**).* Dihydropyridone **19** (8.20 g, 20.76 mmol) was dissolved in DMF (40 mL) and cooled to −40 °C before addition of $NaNH_2$ (2.03 mL, 60% suspension in PhMe, 31.14 mmol). The reaction mixture was then allowed to warm slowly to 0 °C over 20 min before quenching with saturated NH_4Cl solution in H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were washed with H_2O (5×50 mL), dried ($MgSO_4$) and the crude product purified by flash column chromatography (SiO_2, Et_2O/

EtOAc 1:1) to furnish the product (6.50 g, 87% yield) as a colourless oil; mp 141–143 °C; IR ν_{max} (KBr)/cm^{-1} 2949, 1732, 1644, 1587, 1513, 1238; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 6.93 (1H, d, *J* 7.8) 6.88 (2H, m), 6.84 (1H, d, *J* 1.4), 4.90 (1H, dd, *J* 7.8 and 1.3), 4.49 (1H, d, *J* 14.2), 4.40 (1H, d, *J* 14.2), 3.88 (3H, s), 3.87 (3H, s), 3.70 (3H, s), 2.70 (1H, dd, *J* 3.6 and 1.0), 2.29 (1H, m), 1.86–1.66 (4H, m), 1.53–1.33 (3H, m); ^{13}C NMR δ_C (100 MHz; $CDCl_3$)194.5, 173.9, 153.5, 149.3, 148.8, 128.5, 121.3, 111.6, 111.4, 99.2, 68.9, 55.9, 52.8, 52.5, 50.3, 30.8, 26.4, 24.3, 21.7; MS *m*/*z* (ESI) 360.3 (M+H$^+$, 100%), HRMS (ESI) for $C_{20}H_{25}NNaO_5$ requires 382.1627, found (M+Na$^+$) 382.1625.

*4.2.15. (2R,4aS,8aR)-Methyl-1-(3,4-dimethoxybenzyl)-2-hexyl-4-(triisopropylsilyloxy)-1,2,4a,5,6,7,8,8a-octahydroquinoline-8a-carboxylate and (2S,4aS,8aR)-methyl-1-(3,4-dimethoxybenzyl)-2-hexyl-4-(triisopropylsilyloxy)-1,2,4a,5,6,7,8,8a-octahydroquinoline-8a-carboxylate (**21**).* Triisopropylsilyl trifluoromethanesulfonate (4.10 mL, 15.32 mmol) was added to a solution of **20** (2.80 g, 7.66 mmol) in PhMe (40 mL) under an atmosphere of argon and stirred for 45 min. The mixture was cooled to 0 °C before the dropwise addition of *n*-hexyl magnesium bromide (5.80 mL, 2 M in Et_2O, 11.49 mmol). The reaction mixture was stirred for 4 h 30 min before the addition of NH_4Cl (20 mL, saturated aqueous solution). The aqueous layer was extracted with Et_2O (3×30 mL) and the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (SiO_2, gradient of neat petrol to petrol/Et_2O 9:1) to furnish the mixture of products (3.18 g, 69% yield) as an oil; IR ν_{max} (film)/cm^{-1} 3442, 2062, 1732, 1643, 1463, 1253, 1138, 1026; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 7.10 (1H, m), 7.02 (1H, m, ArH), 6.93–6.90 (1H, m), 6.88–6.86 (1H, m), 6.81–6.80 (1H, m), 6.79–6.77 (1H, m), 4.66 (1H, d, *J* 2.8), 4.58 (1H, d, *J* 2.8), 4.34 (1H, d, *J* 15.4), 3.96 (1H, d, *J* 15.1), 3.87 (12H, s), 3.74 (1H, d, *J* 17.9), 3.70–3.68 (1H, m), 3.64 (3H, s), 3.60 (3H, s), 3.51–3.40 (2H, m), 3.14 (1H, d, *J* 7.6), 2.45–2.41 (1H, m), 2.18–1.92 (2H, m), 1.78–1.72 (4H, m), 1.62–1.56 (4H, m), 1.51–1.42 (6H, m), 1.35–1.65 (62H), 0.95–0.82 (6H, m); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 177.8, 151.5, 141.3, 132.3, 129.4, 128.5, 125.8, 118.5, 110.7, 102.1, 68.2, 65.0, 55.9, 55.7, 52.9, 51.3, 47.6, 43.5, 42.1, 37.4, 37.1, 34.4, 34.1, 31.9, 31.8, 29.6, 29.5, 28.4, 26.4, 25.9, 24.3, 22.8, 22.5, 22.4, 18.7, 17.7, 14.1, 12.8, 12.7, 12.3 (for clarity we have normalised the ratio of the two diastereomers as 1:1); MS *m*/*z* (ESI) 602.4 (M+H$^+$, 100%), HRMS (ESI) for $C_{35}H_{60}NO_5Si$ requires 602.4235, found (M+H$^+$) 602.4234.

*4.2.16. (2R,4aS,8aR)-Methyl-2-hexyl-4-(triisopropylsilyloxy)-1,2,4a,5,6,7,8,8a-octahydroquinoline-8a-carboxylate and (2S,4aS,8aR)-methyl-2-hexyl-4-(triisopropylsilyloxy)-1,2,4a,5,6,7,8,8a-octahydroquinoline-8a-carboxylate (**22**).* Palladium on carbon (0.24 g, 10% loading) was added to a solution of **21** (1.60 g, 2.6 mmol) in EtOAc/MeOH (1:5, 30 mL) under an atmosphere of hydrogen. The reaction mixture was stirred for 2 h before filtration through Celite. The mixture was concentrated and the crude residue was purified via flash column chromatography (SiO_2, 95:5 petrol/Et_2O) to furnish the deprotected compound **22** (720 mg, 60%) and its minor diastereomer (210 mg, 18%) in a ratio of 3.4:1 with an overall yield of 78%. Both compounds were isolated as colourless oils.

Major: IR ν_{max} (film)/cm^{-1} 3441, 2930, 2865, 1731, 1667, 1463, 1205; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 4.64 (1H, s), 3.67 (3H, s), 3.44 (1H, m), 2.71 (1H, br s), 2.02–1.98 (1H, m), 1.84–1.72 (1H, m), 1.71–1.38 (5H, m), 1.37–1.25 (11H, m), 1.18–1–15 (4H, m), 1.07–1.04 (17H, m), 0.86–0.83 (3H, m); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 176.1, 150.7, 103.3, 61.2, 51.9, 50.5, 40.7, 37.4, 31.7, 30.4, 29.3, 25.9, 25.4, 22.8, 22.5, 22.3, 18.0, 14.1, 12.8; MS *m*/*z* (ESI) 452.30 (M+H$^+$, 95%), HRMS (ESI) for $C_{26}H_{50}NO_3Si$ requires 452.3554, found (M+H$^+$) 452.3552.

Minor: IR ν_{max} (film)/cm^{-1} 3444, 2930, 1729, 1665, 1466, 1205; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 4.40 (1H, m), 3.63 (3H, s), 3.52 (1H, br s), 2.44 (1H, dd, *J* 11. 8 and 4.4), 1.97 (1H, dd, *J* 12.6 and 2.5), 1.72–1.47 (8H, m), 1.35–1.24 (10H, m), 1.17–1.04 (21H, m), 0.89–0.86 (3H, m); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 177.7, 153.4, 102.0, 61.7, 51.6, 50.8, 41.8, 38.2, 36.3, 31.9, 29.6, 28.6, 25.5, 25.4, 22.6, 20.8, 18.0, 14.1, 12.7; MS *m*/*z* (ESI) 452.30 (M+H$^+$, 95%), HRMS (ESI) for $C_{26}H_{50}NO_3Si$ requires 452.3554, found (M+H$^+$) 452.3552.

*4.2.17. (2R,4aS,8aR)-2-Hexyl-4-(triisopropylsilyloxy)-1,2,4a,5,6,7,8,8a-octahydroquinoline-8a-carbaldehyde (**23**).* DIBAL-H (12.2 mL, 1 M in hexanes, 12.27 mmol) was added dropwise to a solution of **22** (3.69 g, 8.18 mmol) in PhMe (30 mL) at −78 °C under an atmosphere of argon and stirred for 1 h. MeOH (20 mL) was added to the reaction mixture and stirring continued for 15 min before the addition of H_2O (20 mL) and stirring for a further 15 min. The reaction mixture was warmed to room temperature and the aqueous layer extracted with Et_2O (3×10 mL). The combined organic extracts were washed with NaOH (20 mL, 1 M in H_2O) and brine (20 mL) before being dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the crude product via flash column chromatography (SiO_2, 9:1 petrol/Et_2O) furnished **23** (2.82 g, 82%) as a colourless oil; IR ν_{max} (film)/cm^{-1} 3444, 2930, 1729, 1665, 1466, 1205; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 9.54 (1H, s), 4.69 (1H, dd, *J* 2.3 and 11.0), 3.50–3.45 (1H, m), 2.50 (1H, br s), 1.95–1.78 (2H, m), 1.77 (2H, ddd, *J* 13.0, 9.0 and 4.6), 1.60 (2H, ddd, *J* 13.4, 8.8 and 4.0), 1.50–1.26 (14H, m), 1.20–1.15 (4H, m), 1.10–1.06 (15H, m), 0.90–0.87 (3H, m); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 204.5, 150.7, 103.9, 62.2, 50.6, 38.8, 38.3, 31.8, 29.3, 28.5, 26.1, 25.4, 22.6, 22.5, 22.1, 18.1, 17.7, 14.1, 12.7; MS *m*/*z* (ESI) 422.34 (M+H$^+$, 100%), HRMS (ESI) for $C_{25}H_{48}NO_2Si$ requires 422.3455, found (M+H$^+$) 422.3467.

*4.2.18. (E)-Methyl-3-((2R,4aS,8aS)-2-hexyl-4-(triisopropylsilyloxy)-1,2,4a,5,6,7,8,8a-octahydroquinolin-8a-yl)acrylate (**24**).* To solution of trimethyl phosphonoacetate (0.14 mL, 0.88 mmol) in dry THF (5 mL) at room temperature was added NaH (44.0 mg, 1.07 mmol, 60% suspension in mineral oil), which caused vigorous evolution of gas. The solution was stirred for 20 min before addition of a solution of **23** (0.18 g, 0.43 mmol) in THF (3 mL). The reaction mixture was stirred for 1 h at room temperature before cautiously adding H_2O (3 mL). The mixture was extracted with Et_2O (3×5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), filtered and the solvent removed in vacuo. The residue was purified via flash column chromatography (SiO_2, 8:2 petrol/Et_2O), which furnished the product (0.15 g, 75%) as a colourless oil; IR ν_{max} (film)/cm^{-1} 3444, 2929, 1729, 1666, 1205; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 7.20 (1H, d, *J* 16.2), 6.04 (1H, d, *J* 15.9), 4.75 (1H, s), 3.75 (3H, s), 3.46 (1H, br s), 2.31 (1H, br s), 2.18 (1H, d, *J* 12.6), 2.05–1.97 (1H, m), 1.65–1.60 (2H, m), 1.49–1.16 (17H, m), 1.10–1.07 (18H, m), 0.90–0.87 (3H, m); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 167.5, 154.8, 149.7, 119.2, 104.7, 55.7, 51.6, 49.7, 43.3, 37.6, 31.8, 30.8, 29.4, 25.8, 24.4, 22.9, 22.6, 21.6, 18.1, 14.1, 12.8; MS *m*/*z* (ESI) 478.3 (M+H$^+$, 100%), HRMS (ESI) for $C_{28}H_{52}NO_3Si$ requires 478.3711, found (M+H$^+$) 478.3699.

*4.2.19. Methyl-3-((2R,4aS,8aS)-2-hexyl-4-(triisopropylsilyloxy)-1,2,4a,5,6,7,8,8a-octahydroquinolin-8a-yl)propanoate (**25**).* Palladium on carbon (7.0 mg, 10% loading) was added to a solution of **24** (0.14 g, 0.30 mmol) in MeOH/EtOAc 1:4 under an atmosphere of hydrogen gas. The mixture was stirred for 2 h before filtering through Celite. The solvent was removed in vacuo and the crude product purified by flash column chromatography (SiO_2, 8:2 petrol/Et_2O) to furnish the product (0.12 g, 86%) as a colourless oil; IR ν_{max} (film)/cm^{-1} 3441, 2930, 1729, 1665, 1203, 853; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 4.72 (1H, s), 3.67 (3H, s), 3.35 (1H, br s), 2.41 (2H, m), 2.35–2.31 (1H, d, *J* 13.1), 2.08–2.05 (1H, m), 2.00–1.97 (1H, m), 1.82 (2H, td, *J* 13.0 and 4.3), 1.55 (1H, m), 1.42.1.28 (15H, m),

1.23–1.06 (21H, m), 0.89 (3H, t, *J* 6.8); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 175.2, 150.1, 105.0, 54.4, 51.6, 49.0, 43.6, 33.3, 31.8, 29.5, 29.2, 28.0, 25.7, 23.7, 22.7, 22.6, 21.8, 18.2, 18.1, 14.1, 12.8; MS *m*/*z* (ESI) 480.4 ($M+H^+$, 95%), HRMS (ESI) for $C_{28}H_{54}NO_3Si$ requires 480.3867, found ($M+H^+$) 480.3857.

*4.2.20. (E)-3-((2R,4aS,8aS)-2-Hexyl-4-(triisopropylsilyloxy)-1,2,4a,5,6,7,8,8a-octahydroquinolin-8a-yl)acrylaldehyde (**26**).* To a solution of **24** (0.12 g, 0.24 mmol) in dry PhMe (5 mL) at −78 °C was added DIBAL-H (0.36 mL, 1 M in hexanes, 0.36 mmol) slowly over 10 min. The reaction mixture was stirred at −78 °C for 45 min before addition of MeOH (5 mL) and stirring for 15 min. H_2O (5 mL) was added and the mixture was stirred for a further 15 min before allowing it to warm slowly to room temperature. The reaction mixture was extracted with Et_2O (3×15 mL) and the combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and the solvent removed in vacuo. The crude product was purified via flash column chromatography (SiO_2, 0.5% MeOH in CH_2Cl_2) to furnish **26** (70 mg, 66%), as a yellow oil; IR ν_{max} (film)/cm^{-1} 3441, 2930, 1729, 1665, 1466, 1205, 873; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 9.57 (1H, d, *J* 7.8), 7.00 (1H, d, *J* 16.2), 6.30 (1H dd, *J* 15.9 and 7.8), 4.75 (1H, s), 3.48 (1H, br s), 2.35 (1H, br s), 2.17 (1H, d, *J* 2.2), 2.04 (1H, td, *J* 12.3 and 2.8), 1.65 (2H, m), 1.47–1.35 (11H, m), 1.28–1.05 (23H, m), 0.88 (3H, t, *J* 6.6); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 194.5, 164.2, 149.6, 130.6, 104.6, 56.1, 49.9, 43.2, 37.7, 31.8, 30.9, 29.4, 25.9, 24.7, 22.9, 22.6, 21.7, 18.1, 14.1, 12.8; MS *m*/*z* (ESI) 448.3 ($M+H^+$, 100%), HRMS (ESI) for $C_{27}H_{50}NO_2Si$ requires 448.3533, found ($M+H^+$) 448.3532.

*4.2.21. (2R,4aS,8aS)-2-Hexyl-8a-((E)-2-(oxiran-2-yl)vinyl)-4-(triisopropylsilyloxy)-1,2,4a,5,6,7,8,8a-octahydroquinoline (**27**).* To a suspension of trimethylsulfonium iodide (73.0 mg, 0.36 mmol) in dry THF (5 mL) at room temperature was added NaH (29.0 mg, 60% suspension in oil, 0.72 mmol) and the reaction mixture was stirred for 15 min before the addition of a solution of **26** (80.0 mg, 0.18 mmol) in THF (3 mL). The reaction mixture was warmed to 60 °C in an oil bath and stirred for 2 h before cooling to 0 °C and H_2O (5 mL) was carefully added. The mixture was extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine and concentrated in vacuo. Flash column chromatography (SiO_2, CH_2Cl_2/MeOH 99:1) afforded the product (72 mg, 87%) as a colourless oil, 1:1 mixture of diastereomers. This compound contained an impurity, which caused the region δ 1.47–1.07 to integrate for an extra 9H in the ^{1}H NMR spectrum; IR ν_{max} (film)/cm^{-1} 3442, 2895, 1724, 1466, 1205; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 6.16 (1H, dd, *J* 15.9 and 12.9), 5.37 (1H, ddd, *J* 16.0, 8.2 and 2.9), 4.76–4.74 (1H, m), 3.44 (1H, m), 3.40–3.36 (1H, m), 2.98 (1H, td, *J* 4.6 and 1.6), 2.69 (1H, td, *J* 3.0 and 1.8), 2.32 (1H, br s), 2.23–2.21 (1H, m), 2.01–1.94 (1H, m), 1.68 (3H, m), 1.47–1.15 (24H, m), 1.10–1.07 (20H, m), 0.90 (3H, m); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 149.9, 149.8, 143.0, 126.7, 126.5, 104.7, 104.6, 55.5, 52.8, 52.8, 49.5, 49.4, 48.9, 48.8, 43.7, 43.4, 37.5, 31.8, 30.6, 30.1, 29.7, 29.4, 25.8, 24.1, 23.1, 22.6, 21.5, 21.4, 18.2, 18.1, 14.1, 12.8; MS *m*/*z* (ESI) 462.4 ($M+H^+$, 100%), HRMS (ESI) for $C_{28}H_{52}NO_2Si$ requires 462.3762, found ($M+H^+$) 462.3776.

*4.2.22. (2R,4aS,8aR)-2-(Trimethylsilyl)-ethyl-8a-formyl-2-hexyl-4-(triisopropylsilyloxy)-4a,5,6,7,8,8a-hexahydroquinoline-1(2H)-carboxylate (**28**).* To a solution of **23** (2.90 g, 6.89 mmol) in CH_3CN/Et_2O 4:1 (20 mL) at room temperature was added K_2CO_3 (3.70 g, 27.56 mmol), followed by Teoc-Cl (2.48 g, 13.28 mmol). The slurry was stirred at room temperature for 48 h, then the solution was transferred to a separating funnel containing CH_2Cl_2 (20 mL) and saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated in vacuo. The crude was purified via flash column chromatography (SiO_2, 5:95 Et_2O/petrol) to furnish the product (3.58 g, 92%) as a colourless oil; IR ν_{max} (film)/cm^{-1} 2950, 1678, 1250, 838; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 9.62 (1H, br s), 4.98 (1H, dd, *J* 6.14 and 2.2), 4.21–4.13 (3H, m), 2.80 (1H, br s), 2.44 (1H, d, *J* 13.8), 2.13 (1H, d, *J* 14.0), 1.86–1.83 (1H, m), 1.76 (1H, br s), 1.53–1.39 (6H, m), 1.28–1.21 (9H, m), 1.17–1.09 (20H, m), 1.03–0.93 (2H, m), 0.90–0.87 (3H, m), 0.03 (9H, s); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 199.6, 157.1, 151.0, 101.1, 66.0, 64.2, 52.6, 38.0, 31.8, 29.1, 25.9, 25.9, 23.0, 22.6, 22.2, 21.3, 18.1, 18.0, 17.8, 14.1, 12.8, −1.6; MS *m*/*z* (ESI) 566.4 ($M+H^+$, 100%), HRMS (ESI) for $C_{31}H_{59}NNaO_4Si_2$ requires 588.3862, found ($M+Na^+$) 588.3862.

*4.2.23. (2R,4aS,8aS)-2-(Trimethylsilyl)-ethyl-2-hexyl-8a-((E)-3-methoxy-3-oxoprop-1-enyl)-4-(triisopropylsilyloxy)-4a,5,6,7,8,8a-hexahydroquinoline-1(2H)-carboxylate (**29**).* Trimethyl phophonoacetate (0.36 mL, 1.59 mmol) was dissolved in dry THF (15 mL) and NaH (70.0 mg, 1.75 mmol, 60% suspension in oil) was added. The reaction mixture was stirred for 20 min at room temperature. A solution of **28** (0.45 g, 0.80 mmol) in dry THF (5 mL) was then added and the reaction flask placed in a preheated oil bath at 60 °C. The reaction mixture was allowed to stir for 2 h before addition of H_2O (5 mL) to quench. The mixture was extracted with Et_2O (3×20 mL). The combined organic extracts were then washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The crude was purified via flash column chromatography (SiO_2, Et_2O/petrol 5:95) to furnish the product (0.43 g, 86%) as a colourless oil; IR ν_{max} (film)/cm^{-1} 3440, 2947, 1648, 1250, 837; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 7.44 (1H, d, *J* 16.2), 5.90 (1H, d, *J* 16.7), 4.97 (1H, d, *J* 6.1), 4.32 (1H, ddd, *J* 10.2, 6.4 and 3.4), 4.11–4.06 (2H, m), 3.74 (3H, s), 2.57 (1H, br s), 2.25 (1H, d, *J* 12.9), 1.93–1.91 (2H, m), 1.80–1.76 (2H, m), 1.64 (1H, s), 1.58–1.37 (7H, m), 1.32–1.17 (12H, m), 1.11–1.05 (15H, m), 0.99–0.94 (2H, m), 0.90–0.88 (3H, m), 0.02 (9H, s); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 167.5, 155.5, 155.1, 150.8, 118.3, 101.0, 63.2, 61.1, 53.5, 51.5, 45.2, 38.1, 31.8, 29.1, 26.9, 24.2, 22.6, 18.1, 18.0, 17.8, 17.7, 14.1, 12.7, 12.3, −1.6; MS *m*/*z* (ESI) 644.4 ($M+Na^+$, 100%), HRMS (ESI) for $C_{34}H_{63}NNaO_5Si_2$ requires 644.4143, found ($M+Na^+$) 644.4129.

*4.2.24. (2R,4aS,8aS)-2-(Trimethylsilyl)-ethyl-2-hexyl-8a-(3-methoxy-3-oxopropyl)-4-(triisopropylsilyloxy)-4a,5,6,7,8,8a-hexahydroquinoline-1(2H)-carboxylate (**30**).* Palladium on carbon (10.0 mg, 10% loading) was added to a solution of **29** (0.20 g, 0.32 mmol) in EtOAc/MeOH (1:5, 5 mL) under an atmosphere of hydrogen. The reaction mixture was stirred for 1 h before filtration through a pad of Celite. The mixture was concentrated and the crude residue was purified via flash column chromatography (SiO_2, 95:5 petrol/Et_2O) to furnish the product (172 mg, 88%) as a colourless oil; IR ν_{max} (film)/cm^{-1} 3441, 1644, 1249; ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 4.76 (1H, d), 4.41–4.37 (1H, m), 4.15–4.10 (2H, m), 3.66 (3H, s), 2.66 (1H, br s), 2.50–2.24 (4H, m), 2.05 (2H, br s), 1.80–1.77 (2H, m), 1.65–1.52 (4H, m), 1.38–1.15 (13H, m), 1.12–1.08 (18H, m), 1.03–0.98 (2H, m), 0.90–0.87 (3H, m), 0.04 (9H, s); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 174.6, 156.1, 150.9, 98.5, 62.9, 60.5, 53.5, 51.5, 45.2, 37.9, 34.2, 31.7, 29.1, 27.0, 24.2, 22.5, 18.1, 18.0, 17.8, 14.1 12.8, −1.5; MS *m*/*z* (ESI) ($M+H^+$, 624.05), HRMS (ESI) for $C_{34}H_{65}NNaO_5Si_2$ requires 646.4293, found ($M+Na^+$) 646.4306.

*4.2.25. (2R,4aS,8aS)-2-(Trimethylsilyl)-ethyl-2-hexyl-8a-(3-oxopropyl)-4-(triisopropylsilyloxy)-4a,5,6,7,8,8a-hexahydroquinoline-1(2H)-carboxylate (**31**).* A solution of **30** (0.50 g, 0.80 mmol) in PhMe (15 mL) was cooled to −78 °C before the slow addition of DIBAL-H (0.96 mL, 1 M in hexanes, 0.61 mmol). The solution was stirred at −78 °C for 1 h before the addition of MeOH (5 mL) and further stirring for 15 min. H_2O (5 mL) was added and the reaction mixture was stirred for a further 15 min. The reaction mixture was allowed to warm slowly to room temperature before extracting with EtOAc (3×15 mL). The combined organic extracts were washed with brine,

dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified via flash column chromatography (SiO_2, 95:5 petrol/Et_2O), to furnish the product (0.44 g, 92%) as a colourless oil; IR ν_{max} (film)/cm^{-1} 3453, 2953, 2094, 1644, 1250; ^1H NMR δ_H (400 MHz; $CDCl_3$) 9.80 (1H, t, *J* 1.5), 4.76 (1H, d, *J* 4.55), 4.39 (1H, m), 4.13 (2H, m), 2.61 (2H, m), 2.38 (3H, m), 2.05 (2H, br s), 1.76 (2H, br s), 1.63–1.57 (6H, m), 1.35–1.16 (13H, m), 1.11–1.08 (16H, m), 1.03–0.99 (2H, m), 0.89 (3H, t, *J* 7.0), 0.05 (9H, s); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 202.6, 156.1, 150.9, 99.4, 63.0, 63.0, 53.5, 41.3, 39.2, 38.2, 34.2, 31.8, 29.1, 27.0, 22.5, 22.5, 18.1, 17.8, 12.7, −1.5; MS *m*/*z* (ESI) 594.5 ($M+H^+$, 50%), HRMS (ESI) for $C_{33}H_{63}NNaO_4Si_2$ requires 616.4208, found ($M+Na^+$) 616.4208.

*4.2.26. (2R,4aS,8aS)-2-(Trimethylsilyl)-ethyl-8a-(but-3-enyl)-2-hexyl-4-(triisopropylsilyloxy)-4a,5,6,7,8,8a-hexahydroquinoline-1(2H)-carboxylate (**32**).* Methyltriphenylphosphonium bromide salt (0.27 g, 0.76 mmol) was dried at 60 °C for 30 min under high vacuum before the addition of dry THF (5 mL) and cooled to 0 °C. To the suspension was added *n*-BuLi (0.39 mL, 1.6 M in hexanes, 0.63 mmol) and the mixture was stirred for 30 min, which gave a bright orange colour. The solution was then cooled to −78 °C before the slow addition of a cooled solution of **31** (0.15 g, 0.25 mmol) in dry THF (2 mL). After 1 h H_2O (3 mL) was added and the mixture was allowed to warm to room temperature. The aqueous layer was separated and extracted with Et_2O (3×5 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the crude mixture purified via flash column chromatography (SiO_2, Et_2O/petrol 5:95) to furnish the product (136 mg, 92%) as a colourless oil; IR ν_{max} (film)/cm^{-1} 3439, 2945, 1640, 1249; ^1H NMR δ_H (400 MHz; $CDCl_3$) 5.81 (1H, ddt, *J* 16.9, 10.4 and 6.4), 4.99 (1H, d, *J* 17.3), 4.92 (1H, d, *J* 10.1), 4.75 (1H, d, *J* 4.4), 4.39 (1H, dt, *J* 10.4 and 3.5), 4.15–4.11 (2H, m), 2.77 (1H, br s), 2.15–2.14 (1H, m), 2.06–1.97 (3H, m), 1.67–1.66 (1H, m), 1.58–1.51 (8H, m), 1.42–1.16 (12H, m), 1.10–1.07 (18H, m), 1.03–0.99 (2H, m), 0.89 (3H, t, *J* 6.9), −0.05 (9H, s); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 156.1, 151.0, 139.1, 113.9, 98.4, 62.7, 60.8, 53.6, 45.6, 37.9, 37.1, 36.8, 34.4, 31.8, 29.1, 28.1, 27.1, 24.5, 22.7, 22.6, 18.1, 17.8, 14.1, 12.7, −1.5; MS *m*/*z* (ESI) 592.5 ($M+H^+$, 85%, $M+Na^+$, 614.4 100%), HRMS (ESI) for $C_{34}H_{66}NO_3Si_2$ requires 591.4576, found ($M+H^+$) 592.4573.

*4.2.27. (2R,4aS,8aS)-8a-(But-3-enyl)-2-hexyloctahydroquinolin-4(1H)-one (**33**).* A solution of **32** (0.07 g, 0.12 mmol) in THF (2 mL) was cooled to 0 °C before adding TBAF (0.35 mL, 1 M in THF, 0.35 mmol). The solution was stirred at room temperature for 50 min, then H_2O (2 mL) was added and the mixture was transferred to a separating funnel containing 6 M aqueous NaOH (3 mL) and Et_2O (3 mL). The mixture was shaken and the layers were separated. The aqueous layer was extracted with Et_2O (3×5 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo to yield an oil. Flash column chromatography (SiO_2, EtOAc/CH_2Cl_2 5:95) afforded the product (35 mg, 99%) as a colourless oil; ^1H NMR δ_H (400 MHz; $CDCl_3$) 5.88 (1H, ddt, *J* 17.0, 10.3 and 6.5), 5.07 (1H, dd, *J* 17.0 and 1.5), 4.99 (1H, dd, *J* 10.0 and 1.8), 3.13 (1H, ddd, *J* 11.8, 6.0 and 2.8), 2.38 (1H, dd, *J* 13.5 and 2.8), 2.26 (1H, m), 2.24–2.08 (2H, m), 1.97 (1H, t, *J* 12.4), 1.82 (1H, ddd, *J* 14.2, 11.5 and 5.4), 1.70 (1H, ddd, *J* 14.0, 11.5 and 5.3), 1.59 (2H, td, *J* 13.0 and 3.6), 1.51–1.36 (6H, m), 1.34–1.26 (10H, m), 0.88 (3H, t, *J* 6.9); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 210.9, 138.9, 114.7, 58.2, 53.7, 49.9, 48.8, 37.7, 37.6, 31.6, 29.3, 27.2, 25.6, 22.6, 22.5, 21.4, 14.1; MS *m*/*z* (ESI) 292.26 ($M+H^+$, 100%), HRMS (ESI) for $C_{19}H_{34}NO$ requires 292.2635, found ($M+H^+$) 292.2641.

*4.2.28. (2R,4aS,8aS)-2-(Trimethylsilyl)-ethyl-2-hexyl-8a-(2-(oxiran-2-yl)ethyl)-4-(triisopropylsilyloxy)-4a,5,6,7,8,8a-hexahydroquinoline-1(2H)-carboxylate (**34**).* To a mixture of trimethylsulfonium iodide (0.15 g, 0.75 mmol) and NaH (27.0 mg, 60% suspension in oil, 0.68 mmol) at −5 °C was added THF/DMSO 1:1 (10 mL) and stirred until evolution of hydrogen gas was finished. A solution of the **31** (0.20 g, 0.34 mmol) in THF/DMSO 1:1 (10 mL) was then added slowly. The reaction mixture was stirred for 45 min before the addition of H_2O (10 mL). The reaction mixture was extracted with EtOAc (3×10 mL). The combined organic extracts were washed with H_2O (5×20 mL), brine (20 mL) and dried ($MgSO_4$). The mixture was filtered and concentrated in vacuo. Flash column chromatrography (SiO_2, petrol/Et_2O 9:1) gave the product as a mixture of diastereomers in a ratio of 1:1 (100 mg, 65%) as colourless oil' IR ν_{max} (film)/cm^{-1} 3442, 2094, 1643; ^1H NMR δ_H (400 MHz; $CDCl_3$) 4.33 (1H, br s), 4.19–4.14 (2H, m), 2.97–2.92 (1H, m), 2.78 (2H, dt, *J* 12.1 and 4.3), 2.69–2.64 (2H, m), 2.64–2.55 (1H, m), 2.48 (1H, dt, *J* 5.0 and 2.5), 2.42 (1H, d, *J* 13.2), 2.13 (1H, m), 1.94 (1H, m), 1.66 (1H, m), 1.60–1.43 (7H, m), 1.37–1.25 (12H, m), 1.06–1.00 (2H, m), 0.88 (3H, t, *J* 6.8), 0.06 (9H, s); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 209.3, 156.1, 63.4, 61.4, 61.2, 52.4, 52.1, 51.1, 48.6, 47.4, 41.4, 37.5, 37.4, 35.7, 31.7, 29.8, 29.6, 29.3, 28.9, 27.9, 27.9, 27.0, 26.9, 22.5, 22.3, 22.1, 22.1, 21.9, 21.2, 14.0, −1.5; MS *m*/*z* (ESI) 474.3 ($M+Na^+$, 100%), HRMS (ESI) for $C_{25}H_{45}NNaO_4Si$ requires 474.3016, found ($M+Na^+$) 474.3019.

4.2.29. (±)-Cylindricine C. To a solution of **34** (0.06 g, 0.13 mmol) in dry THF (5 mL) at 0 °C was added TBAF (0.16 mL, 1 M in THF, 0.16 mmol) and the reaction mixture was stirred for 50 min at this temperature before addition of water. The reaction mixture was transferred into a separating funnel containing 6 M NaOH aqueous solution (5 mL) and Et_2O (5 mL). The mixture was shaken and layers separated. The aqueous layer was extracted with Et_2O (3×10 mL) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified via flash column chromatography (SiO_2, gradient of neat petrol to 8.5:1.5 petrol/Et_2O) to furnish (±)-cylindricine C (20 mg, 49%) and *epi*-(±)-cylindricine C (20 mg, 49%) as colourless oils.

(±)-Cylindricine C: ^1H NMR δ_H (400 MHz; $CDCl_3$) 3.54 (2H, m), 3.43 (1H, d *J* 9.8), 3.29 (1H, m), 2.89 (1H, br s), 2.33 (2H, m), 2.24 (2H, dd, *J* 13.2, 2.5), 2.12 (1H, dd, *J* 12.1, 8.0), 1.84 (1H, dd, *J* 12.6, 9.1), 1.71–1.61 (5H, m), 1.49 (1H, m), 1.42–1.26 (13H, m); ^{13}C NMR δ_C (100 MHz; $CDCl_3$) 210.5, 70.7, 66.4, 56.5, 55.3, 50.3, 42.5, 36.4, 35.9, 35.2, 31.7, 29.3, 28.7, 27.1, 24.3, 22.7, 21.9, 14.0.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.05.044.

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