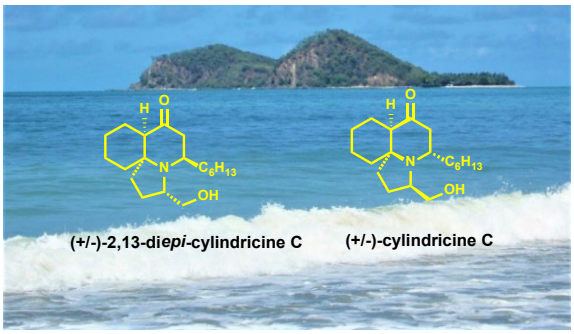
Synthesis of the Marine Alkaloid Cylindricine C and Serendipitous Synthesis of its 2,13-Di-*epi* Stereoisomer

Arnaud Pastor[a], Rohen Prinsloo[a], Kristen N. Burford[a], Andrew R. Macdonald[a], Masood Parvez[a], Chris Gendy[a] and Thomas G. Back[a]*

[a]Department of Chemistry, University of Calgary, 2500 University Drive N.W., Calgary, Alberta, Canada, T2N 1N4

E-mail: tgback@ucalgary.ca

Graphic Abstract



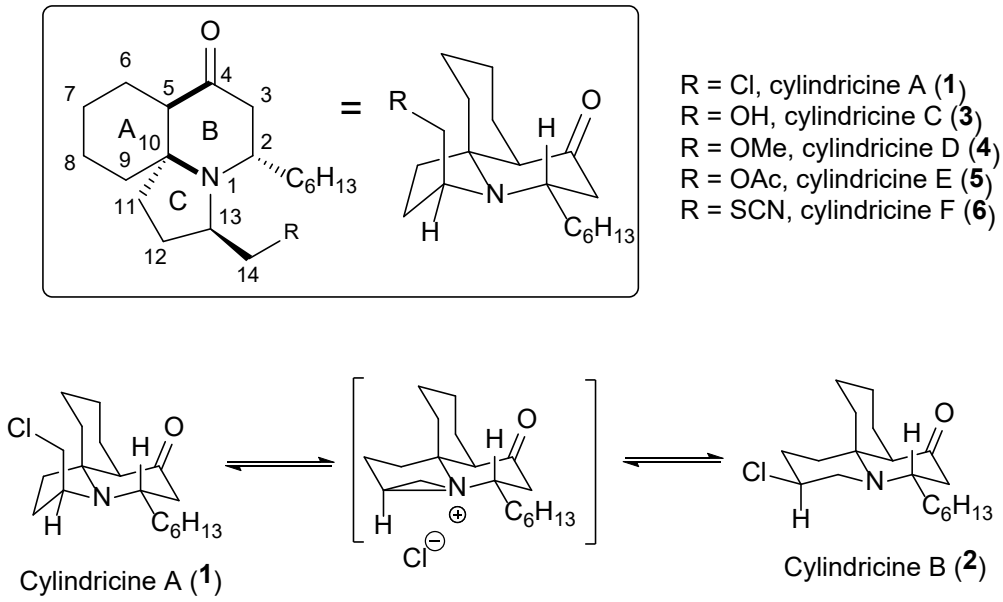
Abstract

A new approach to the marine alkaloid cylindricine C afforded its previously unreported (±)-2,13-di-*epi* stereoisiomer as the major product along with a minor amount of the racemic parent alkaloid. Key steps included a stereoselective dianion alkylation of a monoester of 1,2-cyclohexanedicarboxylic acid and an annulation based on the tandem conjugate addition of a primary amine to an acetylenic sulfone, followed by intramolecular acylation of the resulting sulfone-stabilized carbanion. The *cis*-azadecalin moiety thus formed, comprising the cyclohexane A-ring and enaminone B-ring of the products, was further elaborated by the selenenyl chloride-induced cyclofunctionalization of a pendant butenyl substituent with the enaminone moiety, followed by a seleno-Pummerer reaction. Desulfonylation and enaminone reduction afforded the final products. Molecular modeling and x-ray crystallography provided further insight into these processes.

Introduction

The cylindricine family of marine alkaloids comprises several structurally related compounds that were first isolated by Blackman et al.[1] from the ascidian (sea squirt) *Clavelina cylindrica* off the eastern coast of Tasmania. These compounds include cylindricines A (**1**) and B (**2**[1a] which are interconvertible via the corresponding aziridinium species (Scheme 1). Further investigations led to the discovery of cylindricines C (**3**), D (**4**), E (**5**) and F (**6**), differing only in the nature of the C-14 substituent, while sharing an *n*-hexyl substituent at C-2 and a *cis*-1-azadecalin moiety that comprises the A/B ring system.[1b] Cylindicines G (**7**),[1b] H (**8**), I (**9**) and J (**10**)[1c] contain an *n*-butyl group at C-2 instead of the *n*-hexyl substituent. Unlike the five-membered C-rings in **1** and **3**-**9**, all three rings in **2** and **10** are six-membered. The enone moiety in cylindricine K (**11**) is unique to this class[1c] (Scheme 1 and Chart 1).

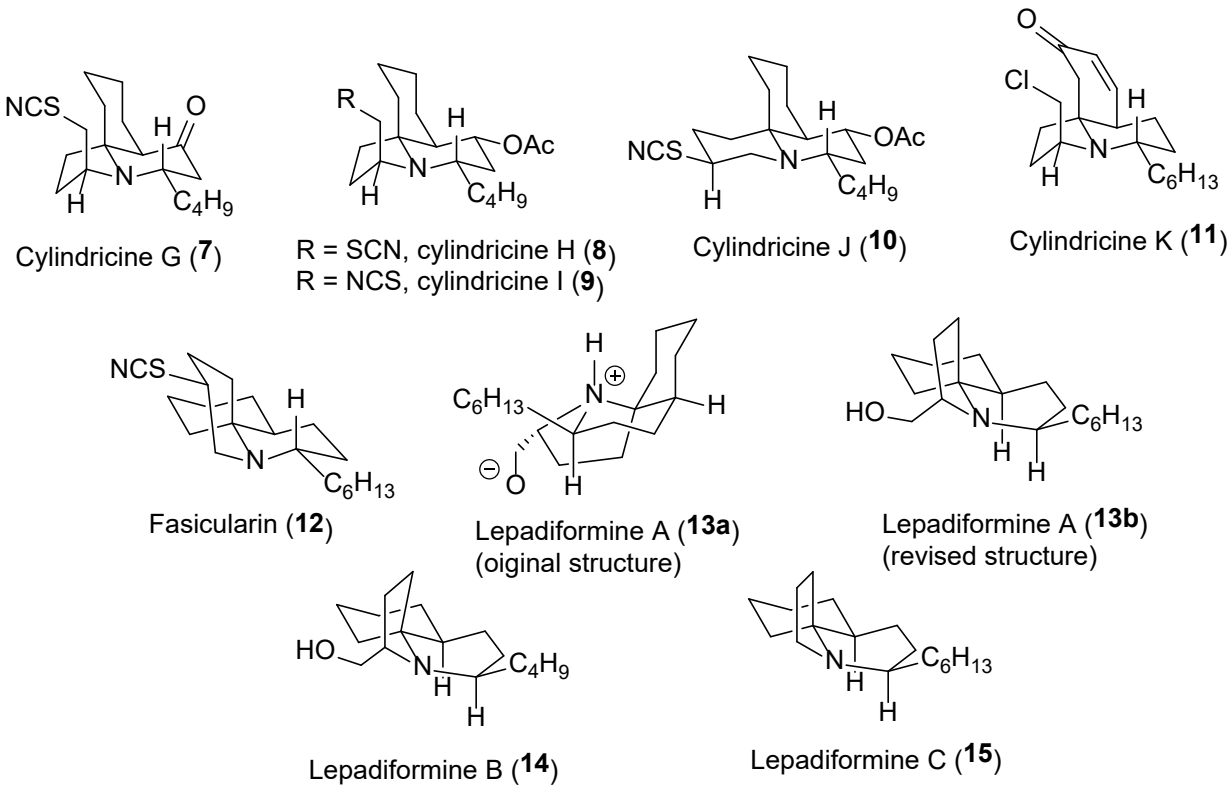
Scheme 1



Other researchers subsequently identified several other related marine alkaloids, including fasicularin (**12**)[2] and the lepadiformine A (**13b**),[3] both of which contain a *trans*-1-azadecalin

moiety. The zwitterionic structure **13a**[3a] first proposed for lepadiformine A was questioned by Weinreb et al.[4] and later corrected to **13b** by his group, and by Kibayashi et al.[5] through synthesis. The latter structure avoids an axial *n*-hexyl group by adopting a B-ring boat conformation (Chart 1).

Chart 1.



Blackman and coworkers reported that the mixture of cylindricine A and B displayed cytotoxicity in a brine shrimp assay.[1] Furthermore, fasicularin showed activity against a DNA repair-deficient strain of yeast and cytotoxicity against Vero cells with an IC_{50} of 14 μg/mL[2] More recently, the ability of fasicularin to alkylate and damage DNA was reported by Gates et al.[6] This activity was attributed to the formation of an electrophilic aziridinium ion, as in the interconversion

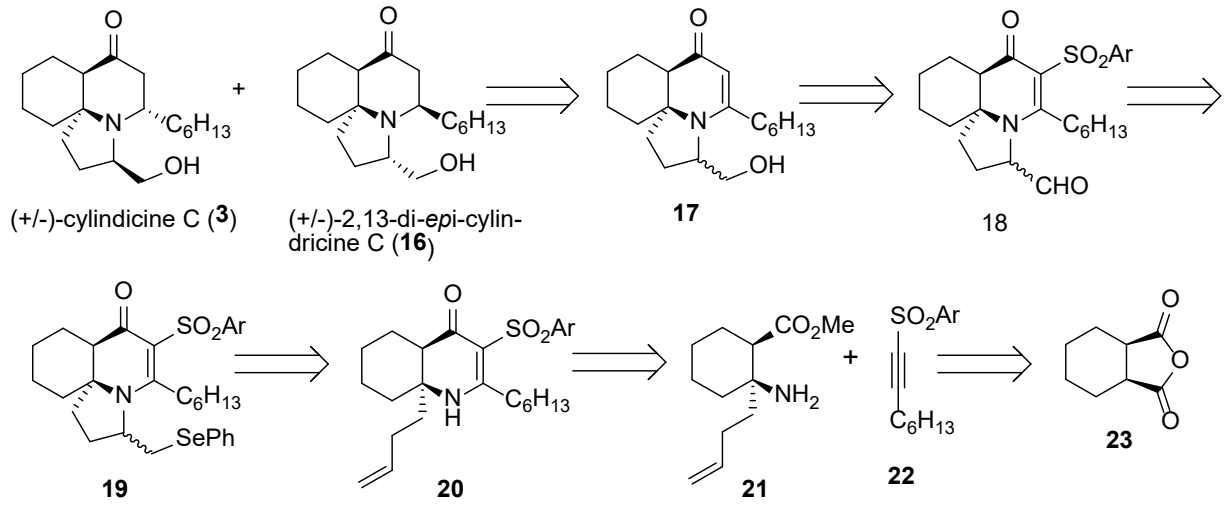
of cylindricines A and B shown in Scheme 1. Lepadiformine A showed moderate *in vitro* cytotoxicity against nasopharynx carcinoma (KB) and non-small-cell lung carcinoma (NSCLC-N6), as reported by Biard and coworkers.[3a] They also discovered that it possesses antiarrhythmic properties and induces induction of bradycardia, hypotension and prolongation of ECG parameters.[3b] Finally, compound **13b**, as well as derivatives **14** and **15**, block the cardiomyocyte K_{ir} channel, thus influencing membrane potential and the diameter of vascular smooth muscles.[7] These findings suggest potential therapeutic applications in the treatment of cancer and cardiac disease.

The unusual tricyclic structure of cylindricine C (**3**), as well as the hindered tertiary amine moiety and the four stereocenters, particularly the quaternary center at C-10, create a challenging target for synthetic efforts. Not surprisingly, a number of racemic[8] and enantioselective syntheses of **3** have been reported,[9,10] along with those of its 2-*epi*,[8c,9f,9g,9i,10b,10c,10d,] 5-*epi*[11] and 13-*epi*[8d] derivatives. Reviews of earlier syntheses of cylindricine, fasicularin, lepadiformine and their congeners were published independently by Weinreb, Renaud and Chiba.[12] We now report the synthesis of **3** and of its previously unknown 2,13-di-*epi* stereoisomer **16** as minor and major products, respectively.

Results and Discussion

A retrosynthetic analysis is provided in Scheme 2, showing key steps that include the conjugate addition of amine **21** to acetylenic sulfone **22**, followed by an intramolecular acylation to create the A/B ring system in enaminone **20**. The electrophilic selenium-mediated cyclization, employed in tandem with a rarely reported seleno-Pummerer reaction, for construction of the C-ring of **18** via selenide **19** is also noteworthy.

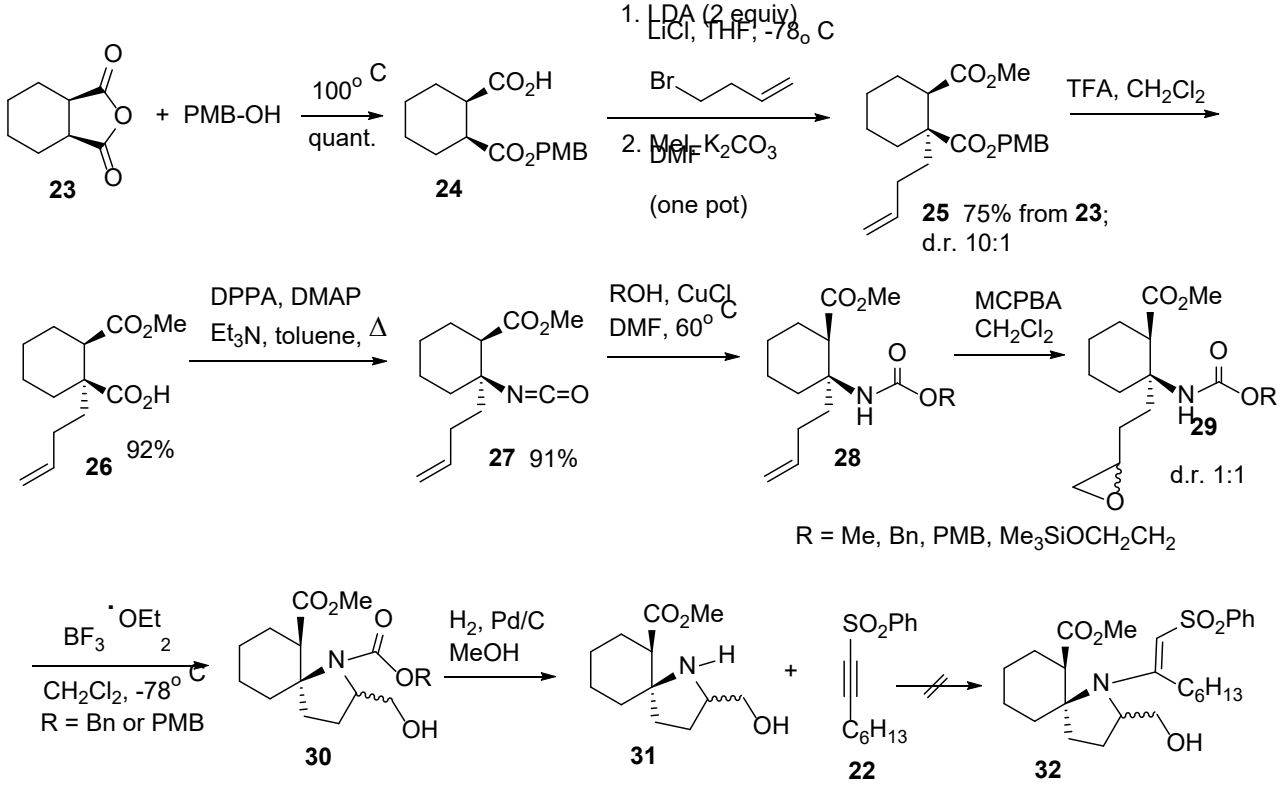
Scheme 2



The synthesis began with cyclic anhydride **23**, which reacted quantitatively with an equimolar amount *p*-methoxybenzyl alcohol (PMB-OH) in the absence of solvent to afford half-ester **24**. The dianion of **24**, generated by treatment with two equiv of LDA, was quenched with 4-bromo-1-butene, followed by methyl ester formation to provide the unsymmetrical *cis*-diester **25** in 75% yield, in a 10:1 ratio with the corresponding *trans*-diester. Selective hydrolysis of the PMB ester with trifluoroacetic acid (TFA) proceeded smoothly and the resulting carboxylic acid **26** was converted to the corresponding isocyanate **27** by means of a Curtius rearrangement using diphenylphosphoryl azide (DPPA),[13] with complete retention of configuration. We next attempted to close the C-ring by conversion of **27** to various carbamate derivatives, including PMB, Bn, Me and 2-(trimethylsilyloxy)ethyl derivatives, followed by epoxidation of the alkene moiety, cyclization and deprotection. This approach afforded poor overall yields (<30%) of the spiro compound **31** from **27** via **28**-**30**, with essentially complete lack of stereoselectivity in the epoxidation step. Furthermore, attempted conjugate addition of **31** to the acetylenic sulfone **22** failed to deliver adduct **32**, presumably due to the steric hindrance around the nucleophilic nitrogen

atom (Scheme 3). The sulfone **22** was easily prepared from the corresponding lithium acetylide and diphenyl disulfide, followed by oxidation to the sulfone.[14]

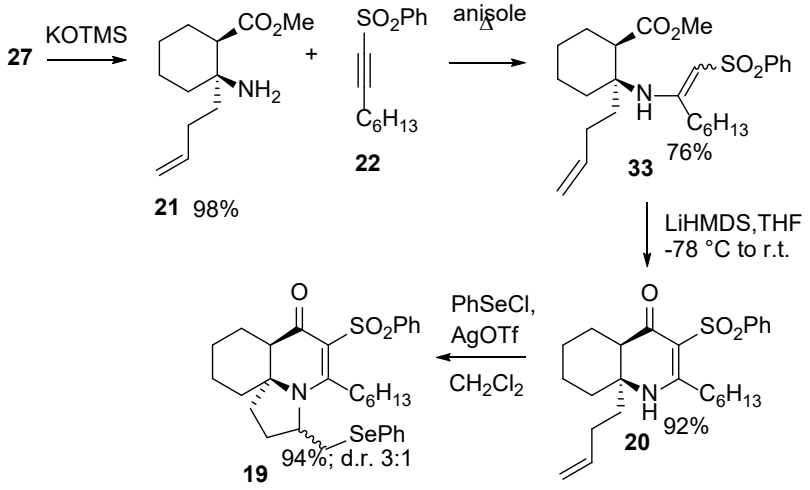
Scheme 3



The failure to obtain **32** in this manner prompted a revised approach, based on the formation of the B-ring prior to that of the C-ring. The hydrolysis and decarboxylation of the hindered isocyanate **27** proved surprisingly difficult, but was successfully achieved with potassium trimethylsilanolate (KOTMS). Conjugate addition of the resulting primary amine **21** to acetylenic sulfone **22** proceeded slowly and in poor yield in refluxing toluene or 1,4-dioxane, but afforded a 76% yield of **33** in refluxing anisole. Deprotonation of the enamine moiety with LiHMDS followed by an efficient cyclization via intramolecular acylation provided 92% of the enaminone **20**.[15] The cyclization of the remaining C-ring was achieved with benzeneselenenyl triflate, formed in situ

from the corresponding selenenyl chloride and silver triflate. NMR analysis indicated that selenide **19** was obtained in high yield, but in a poor diatereomeric ratio (d.r.) of 3:1[16] that was carried forward without separation (Scheme 4). Desulfonylation of **20** prior to the cyclization of the C-ring could be accomplished with sodium in liquid ammonia, but was accompanied by over-reduction of both the enaminone C=C bond, as well as of the ketone moiety.

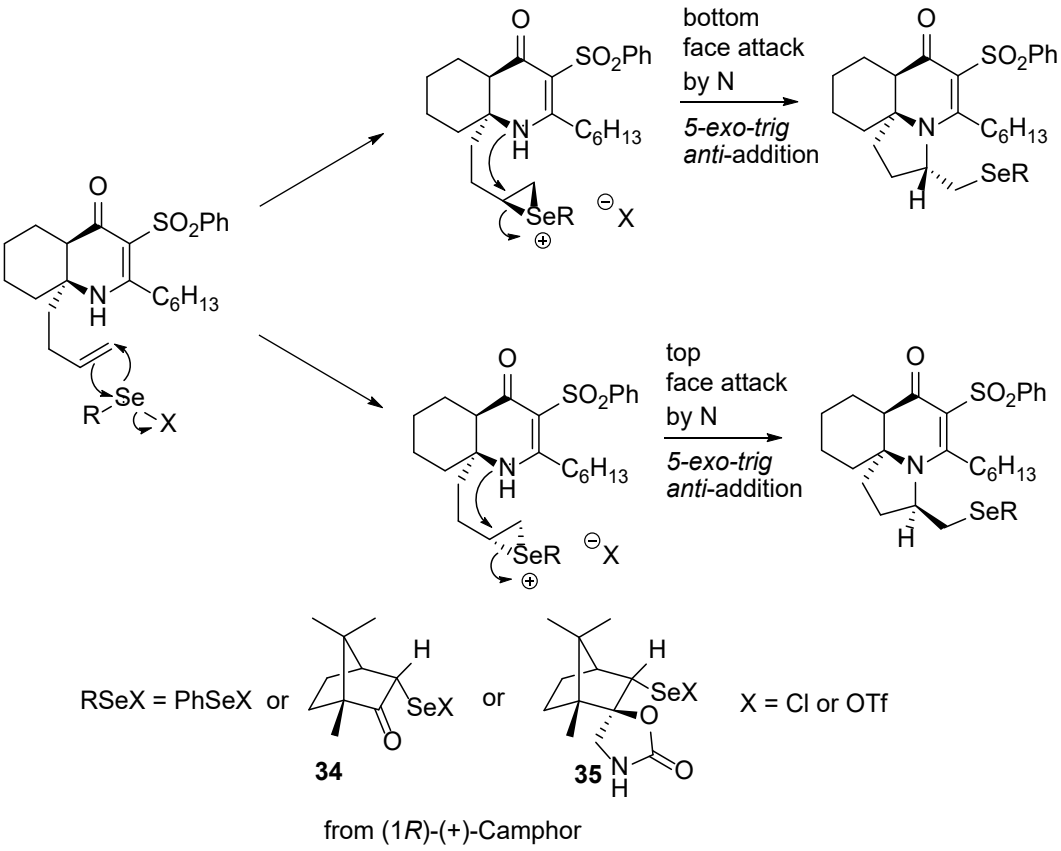
Scheme 4



Addition reactions and cyclizations of alkenes with selenenyl chlorides or similar selenium electrophiles, are known to proceed via the corresponding seleniranium ions,[17] followed by S_N2-like reaction with an external or internal nucleophile, accompanied by inversion of configuration.[18,] Typically, 5-*exo-trig* cyclizations are favoured over 6-*endo-trig*.[19] In the case of cyclizations with nitrogen nucleophiles, amides or carbamates[20] have been employed, while dialkylamines generated selenenamides that serve as selenenylating agents of enolizable carbonyl compounds.[21] To our knowledge, the annulation of a cyclic enaminone with a tethered alkene by means of a selenenyl chloride or triflate has not yet been reported. The stereochemical outcome of such processes is determined by facial selectivity during the addition of the selenenic electrophile

to the alkene (Scheme 5). In the present case, the poor diastereoselectivity is attributed to the excessive distance between the alkene and existing stereocenters, and the extensive free rotation in the unsaturated substituent that results in poor substrate control. In order to improve the stereoselectivity, chiral selenenyl chlorides were prepared, with the expectation that the 3:1 ratio would be increased by an electrophile of one configuration via double differentiation and decreased or reversed with the opposite configuration. We therefore investigated both enantiomers of the camphor-based selenenyl chlorides/triflates **34** and **35** (Scheme 5; only the 1*R*-enantiomers are shown).[22] Unfortunately, no cyclization was observed at low or room temperature, while higher temperatures afforded complex mixtures of products. The reaction of **20** in Scheme 4 with MCPBA, or under Prévost or Woodward-Prévost conditions, as well as Jacobsen asymmetric epoxidation and Sharpless asymmetric dihydroxylation failed to afford acceptable yields or to change the d.r. significantly. Reduction of the enaminone C=C bond of **19** at this stage with a variety of borohydride reagents, including DIBAL, Zn/HOAc, Mg/MeOH, high pressure catalytic hydrogenation, or Stryker's reagent[23] either failed to proceed or afforded complex mixtures. This step was therefore postponed until a later stage.

Scheme 5



Oxidation and Pummerer rearrangement[24] of selenide **19** provided aldehyde **18** via the selenoxide **36** and selenoacetal **37**, while selective aldehyde reduction of **18** with sodium borohydride afforded a 3:1 mixture of alcohol **38a** and **38b** in excellent overall yield (Scheme 6). Crystallization and x-ray diffraction of the major product **38a** (Figure 1A) indicated that the A- and B-rings were *cis*-fused as in cylindricine C and that the product had the 13-*epi* configuration. The minor isomer **38b** was similarly subjected to X-ray diffraction, which confirmed that it also had the *cis*-azadecalin structure, but with the same relative configuration at C-13 as cylindricine C (Figure 1B).[25] It is noteworthy that the enolizable stereocenter at C-5 remained unchanged during the preceding transformations. Finally, silylation of the mixture of **38a**/**38b** provided the epimers **39a** and **39b**, which were more easily separated by chromatography.

Scheme 6

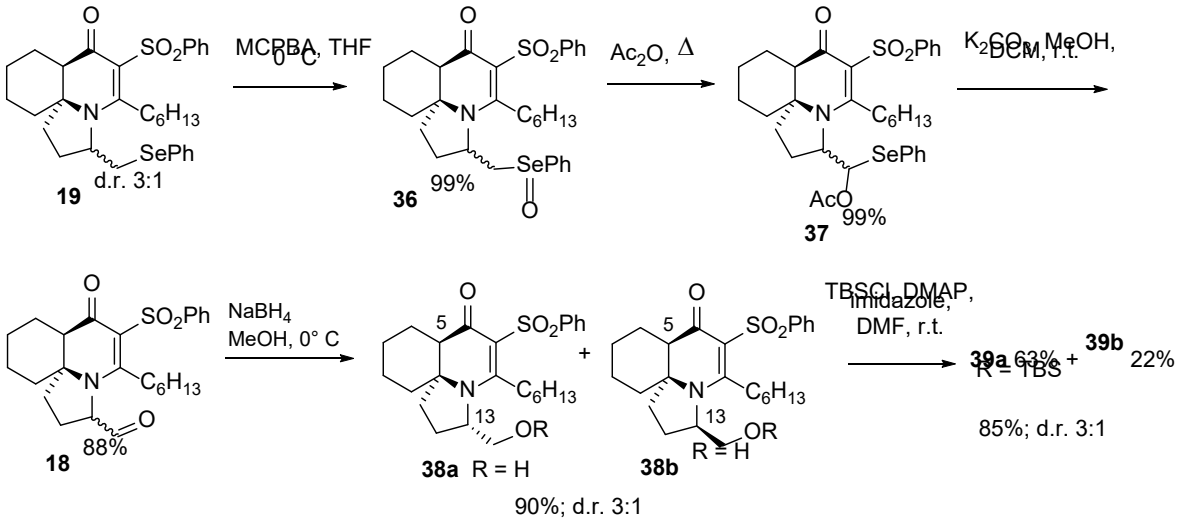
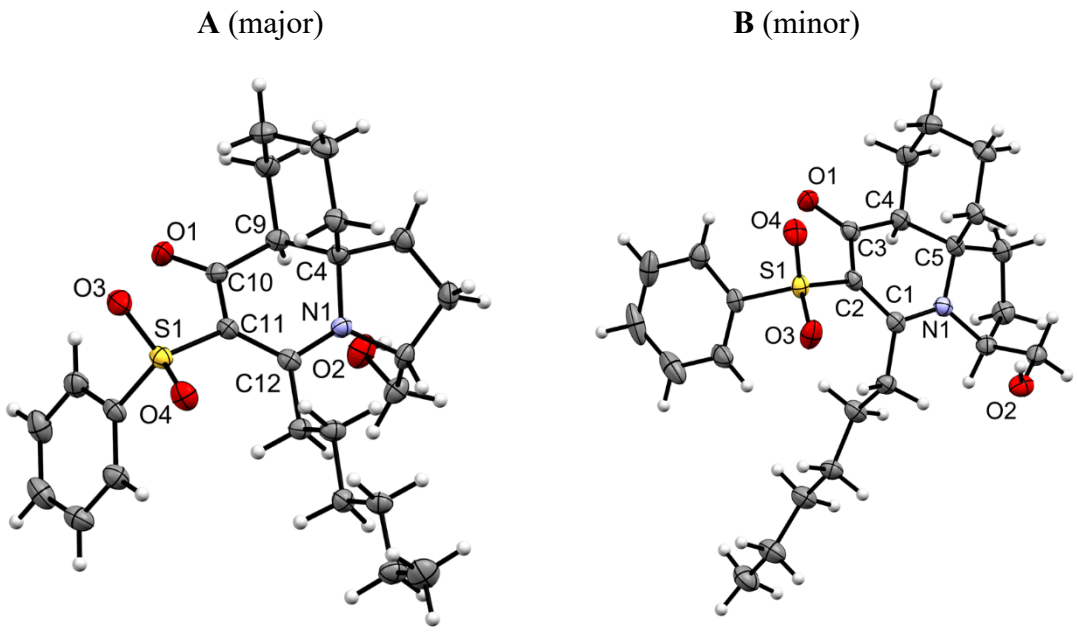


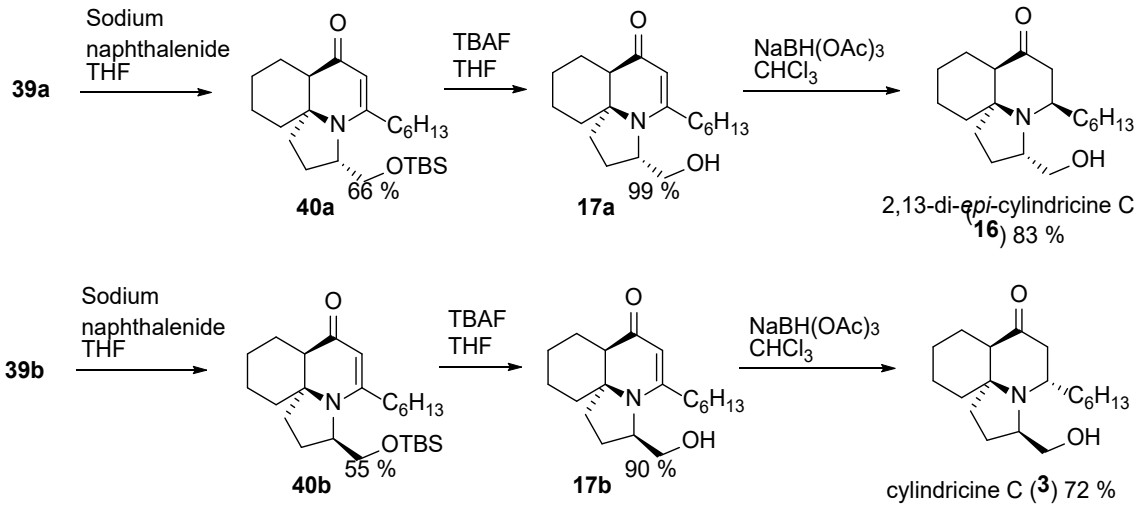
Figure 1. (A) X-ray structure of **38a**; (B) X-ray structure of **38b**



Footnotes to Figure 1. The products were racemic and the indicated absolute configurations of **38a** and **38b** are arbitrary. Thermal ellipsoids are drawn at the 50% probability level. For larger structures and more detailed descriptions, see the Supporting Information.

The remaining steps in the synthesis of cylindricine C and its stereoisomer from **39b** and **39a**, respectively, are provided in Scheme 7. Desulfonylation was achieved with sodium naphthalenide in THF,[26] followed by desilylation with TBAF. The final step generated the remaining stereocenter at C-2 by reduction of the enaminone double bonds of **17a** and **17b** with sodium triacetoxyborohydride. Thus, the overall yields for cylindricine C and its 2,13-di-*epi* isomer were 2.4% and 11%, respectively.

Scheme 7



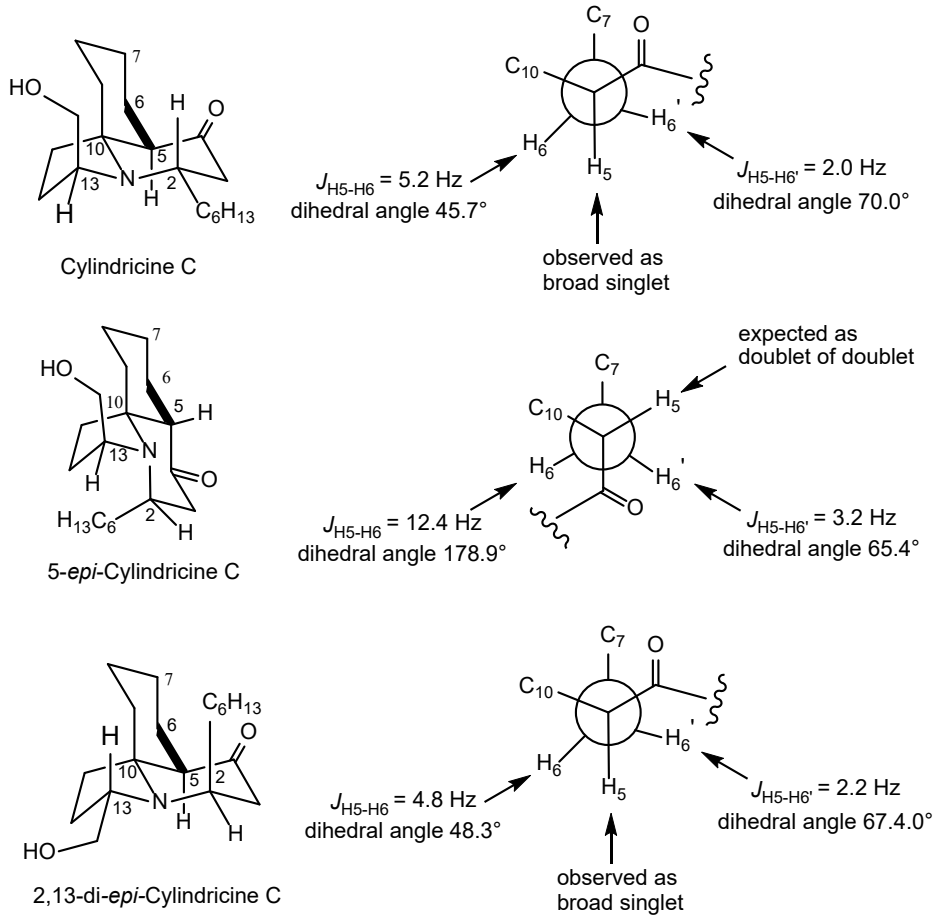
The minor product obtained from **17b** produced NMR spectra in close agreement with those previously reported for cylindricine C (**3**). The major product was determined to be the 2,13-di-*epi* isomer **16** as follows. Several attempts failed to provide suitable crystals for x-ray diffraction, both from **16** itself and from its derivatives, including hydrochloride and picrate salts, as well as nitro- and bromobenzoate and ferrocenyl carboxylate esters.[27] However, a combination of molecular modelling and NMR spectroscopy confirmed this assignment. First, it was established that product **16** was indeed a stereoisomer of cylindricine C, as the HRMS was consistent with the formula $C_{19}H_{33}NO_2$ and the ^{13}C NMR spectrum revealed the expected 19

signals (see the Supporting Information). The four stereocenters in cylindricine C result in eight possible diastereomers. Since the synthesis was racemic, structures are arbitrarily shown with the 10(*R*) configuration and the configurations at other stereocenters are relative to C-10. Furthermore, The 2- and 13-*epi* diastereomers have been reported in the literature (*vide supra*) and both displayed NMR spectra significantly different from the present compound. These structures can therefore be ruled out for the major diastereomer **16** obtained in the present work. Thus, the 5-*epi*, 2,5-, 2,13- and 5,13-di-*epi*-cylindricines remained possible candidates, along with 2,5,13-tri-*epi*-cylindricine C. It will be recalled that x-ray crystal structures of key intermediates **38a,b** indicated that the A and B rings were in the *cis*-1-azadecalin form. However, since H-5 is adjacent to the C-4 carbonyl group it is, in principle, enolizable. The possibility that epimerization at C-5 might have taken place during subsequent transformations could not be excluded a priori, but both Hsung et al.[11] and Renaud et al.[8d] reported that the *cis*-1-azadecalin configuration is more stable than the *trans* during epimerization experiments with similar intermediates. No epimerization at C-5 was observed when **16** was treated with various bases.

Molecular modeling of **3**, **16** and 5-*epi*-cylindricine C was performed with the DFT B3LYP platform and minimization of various starting conformations was first performed with the 6-31G basis set, with further optimization of the lowest energy structures with the 6-311G(d) basis set. As expected, the A and B rings of cylindricine C (**3**) were found to exist in the chair conformation as part of a *cis*-1-azadecalin substructure, containing an equatorial hexyl substituent at C-2. The H-5 proton assumes a gauche orientation with both of the two H-6 protons, resulting in relatively small coupling constants. Geometry optimizations indicated that the H-5/H-6 and H-5/H-6' dihedral angles were 45.7 and 70.0 degrees, corresponding to coupling constants J = 5.2 and 2.0 Hz, respectively.[28] In contrast, isomers containing the 5-*epi* configuration contain a *trans*-1-

azadecalin structure where one of the H-5/H-6 interactions is *trans*-diaxial, with a much larger coupling constant. Modeling of 5-*epi*-cylindricine C indicated H5/H6 and H5/H6'dihedral angles of 178.9 and 65.4 degrees, corresponding to J = 12.4 and 3.2 Hz (Figure 2). Similar *trans*-diaxial couplings of 12.3 Hz, 12.2 Hz and 12.4 Hz were calculated for the as yet unreported 2,5-di-*epi*, 5,13-di-*epi* and 2,5,13-tri-*epi* diastereomers, respectively. In contrast, the present stereoisomer **16** shows a broad singlet at 2.4 ppm for H-5, indicating much smaller coupling constants than expected for the 5-*epi* derivatives. Thus, structures containing the 5-mono-*epi* configuration and *trans*-1-azadecalin moieties can be ruled out for **16**.

Figure 2. Calculated H-5/H-6 coupling constants (*J*) and (H-5)-(C-5)-(C6)-(H6) dihedral angles in cylindicine C, 5-*epi*-cylindricine C and 2,13-di-*epi*-cylindricine C.



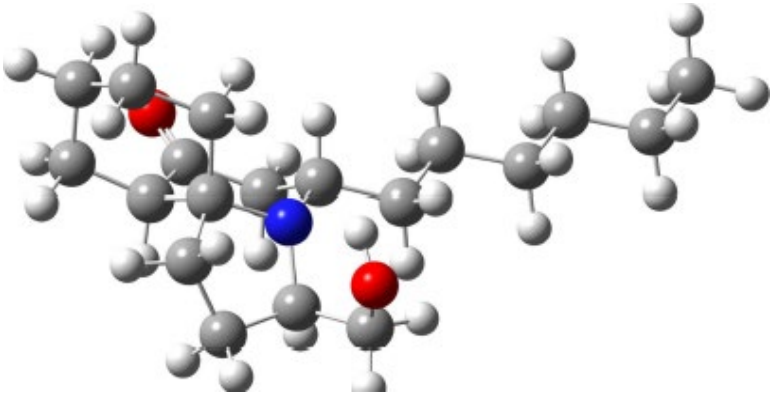
By the process of elimination, these arguments point to the 2,13-di-*epi*-cylindricine C structure for the unknown major product. Furthermore, geometry optimization again indicated chair conformations for both the A- and B-rings of **16**, but the hexyl group occupies an axial position, leading to an energy that is 3.07 kcal mol^{-1} higher than that of cylindricine C. The H-5/H-6 and H-5/H-6' dihedral angles were computed to be 48.3 and 67.4 degrees, leading to J = 4.8 and 2.2 Hz, consistent with the broad singlet at 2.4 ppm assigned to H-5 in this product. This signal did not undergo D_2O exchange, ruling out its assignment to the hydroxyl group.

Moreover, a NOESY spectrum revealed the expected interactions of H-3 with H-2 and H-5, as well as of H-14 with H-2 and H-13. In particular, this indicates a 1,3-diaxial interaction between the methine H-5 proton and one of the methylene H-3 protons, as expected for the *cis*-azadecalin structure. Since other signals are in close proximity to that of H-5, these results are tentative, but consistent with the major product as the 2,13-di-*epi*-cylindricine C diastereomer.

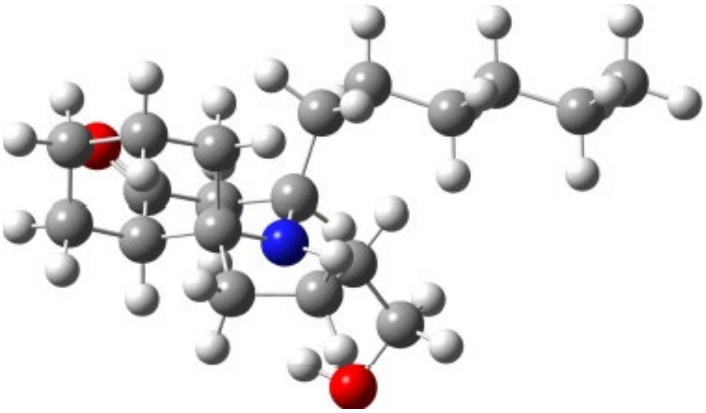
The computations also indicated that both cylindricine C and the 2,13-di-*epi* isomer possess intramolecular hydrogen bonds, with OH---N interatomic distances of 2.23 Å and 2.25 Å, respectively. It is also evident that the final reduction of the C-2/C-3 double bond with sodium triacetoxyborohydride, which generated the C-2 stereocenter, occurred from the face of the B-ring *syn* to the hydroxymethylene substituent. This results in a *trans* orientation of the *n*-hexyl and hydroxymethylene substituents in both cylindricine C and its 2,13-di-*epi* isomer. This observation is in accord with that of Hsung et al.,[10b] who noted a similar directing effect of the hydroxyl group during borohydride reduction of **17b**. Optimized structures of **3** and **16** are provided in Figure 3 and NMR data and computational details are shown in the Supporting Information.

Figure 3. Geometry-optimized conformations of cylindricine C (**3**) and its 2,13-di-*epi* isomer **16**.

Cylindricine C



2,13-Di-*epi*-cylindricine C



Conclusions

The present work provides access to cylindricine C as a minor product and reports the previously unknown 2,13-di-*epi* stereoisomer **16** as the major product. The two stereoisomers were obtained in overall yields of 2.4% and 11%, respectively, in 15 steps. This synthesis exemplifies the utility of acetylenic sulfones in cyclizations of amino esters by conjugate addition and intramolecular acylation, where the disposable sulfonyl group can be removed subsequently by reduction. This approach also employed a highly efficient, but poorly stereoselective, selenium-

based electrophilic cyclization of the C-ring in tandem with a rarely reported seleno-Pummerer rearrangement that introduced the eventual hydroxymethylene group.

Experimental

General experimental

The ^{1}H, ^{13}C and ^{77}Se NMR spectra were recorded at 400 MHz, 101 MHz and 76 MHz, respectively. All ^{13}C NMR spectra were proton-decoupled. Diphenyl diselenide (463.0 ppm relative to dimethyl selenide) was employed as an external standard for ^{77}Se NMR spectra.[29] Heating of reaction mixtures was performed using an oil bath with an immersion heater and thermostat. Chromatograhy was conducted on flash-grade silica-gel. Computational and x-ray diffraction details are provided in the Supporting Information. Camphor diselenides **34** and **35** were obtained as described previously.[22]

1-(4-Methoxybenzyl)-2-methyl 1-(but-3-enyl)cyclohexane-1,2-dicarboxylate (25).

1,2-Cyclohexanedicarboxylic anhydride (**23**) (10.00 g, 64.86 mmol) and *p*-methoxybenzyl alcohol (8.04 mL, 9.00 g, 65.2 mmol) were stirred at 100 °C for 3 h. The resulting half ester **24** was placed under vacuum overnight to remove any volatile material and was obtained as a viscous oil of sufficient purity for use directly in the following procedure.

A solution of LDA was prepared by adding *n*-butyllithium (72 mL, 2.5 M, 180 mmol, to a solution of diisopropylamine (27.2 mL, 19.6 g, 193 mmol) in dry THF (200 mL) at -78 °C under an argon atmosphere. The mixture was warmed to 0 °C, stirred for 30 min and cooled again to -78 °C. LiCl (2.28 g, 53.8 mmol,) was added to a solution of the above half ester **24** dissolved in dry THF (50 mL), and the reaction mixture was added to the LDA solution and stirred for 1 h while warming

to room temperature Then, 4-bromo-1-butene (7.24 mL, 9.63 g, 71.3 mmol,) was added dropwise and the reaction mixture was stirred for 4 days at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and ethyl acetate was added. The layers were separated, and the organic fraction was washed with saturated aqueous NH_4Cl. The combined aqueous fractions were extracted with ethyl acetate and the combined organic fractions were washed with brine, dried, filtered, and evaporated under reduced pressure to give a yellow oil.

The resulting product was dissolved in dry DMF (120 mL) containing K_2CO_3 (14.4 g, 104 mmol,) and iodomethane (6.58 mL, 15.0 g, 106 mmol,) and the reaction mixture was stirred overnight at room temperature. The solution was poured into water and ethyl acetate was added. The layers were separated and the organic fraction was washed with water and the combined aqueous fractions were extracted with ethyl acetate. The combined organic fractions were washed with brine, dried, filtered and concentrated in vacuo to give a yellow oil. The crude product was flash chromatographed on silica gel (1:4 ethyl acetate/hexanes) to yield diester **25** (17.7 g, 75%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 5.78-5.68 (m, 1H), 5.02 (d, J = 1.9 Hz 2H), 4.98-4.92 (m, 2H), 3.82 (s, 3H), 3.57 (s, 3H), 2.82 (t, J = 4.9 Hz, 1H), 2.20-1.20 (m, 12H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$), δ 176.2, 174.6, 159.6, 138.2, 130.1, 128.4, 114.9, 113.9, 66.0, 55.4, 51.6, 46.9, 46.8, 34.9, 28.3, 28.1, 24.9, 22.5, 21.3. HRMS (EI-TOF) *m/z*: [M^+] Calc'd for $C_{21}H_{28}O_5$ 360.1937; found: 360.1930.

1-(But-3-enyl)-2-(methoxycarbonyl)cyclohexanecarboxylic acid (26).

To a solution of diester **25** (17.30 g, 48.0 mmol) in dichloromethane (450 mL) was added dropwise trifluoroacetic acid (36.8 mL, 54.8 g, 48.0 mmol) and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with aqueous NaOH and stirred for 30 min at room temperature. The organic layer was extracted with aqueous NaOH and the combined aqueous

fractions were washed with dichloromethane. The aqueous layer was acidified with conc. HCl to *p*H = 1 while stirring and then was extracted with dichloromethane. The combined organic extracts were dried, filtered, and evaporated under reduced pressure to yield carboxylic acid **26** (10.61 g, 92%) as a white solid: mp 83-84 °C (from hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.30 (broad s, 1H), 5.77 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 5.02 (crude d, 1H), 4.94 (crude d, 1H), 3.66 (s, 3H), 2.78 (t, *J* = 5.1 Hz, 1H), 2.23-1.36 (m, 12H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$), δ (ppm): 182.4, 174.9, 138.0, 115.1, 51.9, 47.2, 46.9, 34.9, 28.3, 25.1, 22.7, 21.3. HRMS (ESI-TOF), *m/z*: [M + Na]$^{+}$ Calc'd for $C_{13}H_{20}NaO_4$ 263.1254; found: 263.1254.

Methyl 2(but-3-enyl)-2-isocyanatocyclohexanecarboxylate (**27**).

Triethylamine (6.22 mL, 4.52 g, 44.6 mmol), 4-(dimethylamino)pyridine (5.45 g, 44.6 mmol,) and diphenyl phosphoryl azide (9.62 mL, 44.7 mmol) were added to a stirred solution of acid **26** (9.75 g, 40.6 mmol) in toluene (150 mL) and the mixture was refluxed overnight. After cooling to room temperature, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with diethyl ether. The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure to give a yellow oil that was purified by flash chromatography (5:95 ethyl acetate/hexane) to yield isocyanate **27** (8.76 g, 91%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$), δ 5.75 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.01 (crude d, 1H), 4.94 (crude d, 1H), 3.68 (s, 3H), 2.38 (dd, *J* = 11.7, 3.9 Hz, 1H), 2.21-2.03 (m, 2H), 1.90-1.68 (m, 5H), 1.65-1.58 (m, 3H), 1.32-1.17 (m, 2H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$), δ 173.3, 137.6, 122.3, 115.2, 60.8, 51.7, 51.5, 41.2, 36.5, 27.9, 25.8, 24.5, 21.5. HRMS (ESI-TOF) *m/z*: [M+Na]$^{+}$ Calc'd for $C_{13}H_{19}NNaO_3$ 260.1257; found 260.1258.

(Octyn-1-ylsulfonyl)benzene (22).

The acetylenic sulfone **22** was prepared as by the method of of Trost et al.,[14] from 1-octyne (8.8 mL, 60 mmol) and diphenyl disulfide (13.8 g, 63.2 mmol) via the corresponding sulfide as a clear, colourless oil in 87% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-7.99 (m, 2H), 7.68-7.64 (m, 1H), 7.59-7.54 (m, 2H), 2.35 (t, *J* = 7.1 Hz, 2H), 1.54 (p, *J* = 7.1 Hz, 2H), 1.36-1.21 (m, 6H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 142.2, 134.0, 129.4, 127.3, 98.1, 78.3, 31.1, 28.5, 27.0, 22.4, 19.0, 14.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calc'd for $C_{14}H_{19}O_2S$ 251.1100; found 251.1094.

Methyl 2-amino-2-(but-3-enyl)cyclohexanecarboxylate (21).

To a solution of isocyanate **27** (7.78 g, 32.8 mmol) in dry THF (1.35 L) was added potassium trimethylsilanolate (9.25 g, 72.1 mmol) and the mixture was stirred at 0 °C for 2 h. The mixture was warmed to room temperature, water and ethyl acetate were added, and the layers were separated. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with brine, dried, filtered and evaporated under reduced pressure to yield amino ester **21** (6.78 g, 98 %) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.00 (dd, *J* = 17.1, 1.7 Hz, 1H), 4.91 (dd, *J* = 10.1, 2.1, 1H), 3.64 (s, 3H), 2.36 (dd, *J* = 11.7, 3.7 Hz, 1H), 2.09 (dd, J = 11.7, 3.7 Hz, 1H), 1.85-1.49 (m, 8H), 1.45-1.38 (m, 3H), 1.30-1.19 (m, 2H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 175.6, 139.1, 114.4, 52.1, 51.4, 51.2, 42.5, 36.3, 27.8, 25.5, 25.0, 21.2. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calc'd for $C_{12}H_{21}NNaO_2$ 234.1465; found 234.1467.

Methyl 2-(but-3-enyl)-2-(1-(phenylsulfonyl)oct-1-en-2-ylamino)cyclohexanecarboxylate (33).

Amino ester **21** (7.55 g, 35.7 mmol) and acetylenic sulfone **22** (14.76 g, 58.95 mmol)[30] were refluxed in anisole (360 mL) overnight. The reaction mixture was concentrated in vacuo and the crude product was purified by column chromatography (1:4 ethyl acetate/hexane) to yield enamine **33** (12.52 g, 76 %; mixture of *E/Z* isomers) as an orange oil. The mixture was used directly in the following step.

8a-(But-3-enyl)-2-hexyl-3-(phenylsulfonyl)-4a,5,6,7,8,8a-hexahydroquinolin-4(1H)-one (20).

Lithium bis(trimethylsilyl)amide (37.4 mL, 1 M in THF) 37.4 mmol) was added to a solution of **33** (11.5 g, 24.9 mmol) in dry THF (200 mL) and the reaction mixture was warmed to room temperature and stirred overnight. Saturated aqueous NH_4Cl was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were washed with brine, dried, filtered, and evaporated under reduced pressure to give an orange oil. The residue was purified by flash chromatography (1:2 ethyl acetate/hexane, then 100 % ethyl acetate) to yield enaminone **20** (9.84 g, 92%) as a yellow solid with mp 108 – 110 °C (from ethyl acetate); ^{1}H NMR 400 MHz, $CDCl_3$) δ 7.93-7.92 (m, 2H), 7.47-7.40 (m, 3H), 5.94 (s, 1H), 5.71-561 (m, 1H), 4.98-4.91 m, 2H), 3.15 (ddd, *J* = 12.8, 9.8, 5.9 Hz, 1H), 2.84 (ddd, *J* = 12.8, 9.8, 6.1 Hz, 1H), 2.10-1.20 (m, 21 H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 190.3, 168.2, 144.4, 137.6, 131.9, 128.2, 126.9, 115.2, 106.0, 56.6, 51.1, 36.4, 34.1, 32.5, 31.5, 30.2, 29.4, 27.4, 26.1, 23.3, 22.6, 21.5, 14.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calc'd for $C_{25}H_{36}NO_3S$ 430.2410; found 430.2407.

6-(Benzenesulfonyl)-5-hexyl-3-(phenylselanylmethyl)-1,2,3,7a,8,9,10,11-octahydropyrrolo-[2,1-j]quinolin-7-one (19).

Benzeneselenenyl chloride (5.44 g., 28.4 mmol,) was dissolved in dry dichloromethane (100 mL) in a flask wrapped in aluminum foil containing silver triflate (7.30 g, 28.4 mmol,) The reaction mixture was stirred for 30 min at room temperature. A solution of enaminone **33** (10.0 g, 23.3 mmol) in dry dichloromethane (130 mL) was added and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with water (200 mL) and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with brine, dried, filtered and evaporated under reduced pressure to give a brown residue. The crude product was purified by flash chromatography (1:99 ethyl acetate/dichloromethane) to give selenide **19** (12.8 g, 94 %) as a yellow solid containing a ca. 3:1 mixture of diastereomers. HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calc'd for $C_{31}H_{40}NO_3S^{80}Se$: 586.1889; found 586.1880.

Major Diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.61 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.44 – 7.40 (m, 3H), 7.34 – 7.31 (m, 3H), 4.09 – 4.01 (m, 1H), 3.31 (t, *J* = 9.7 Hz, 1H), 3.03 (d, *J* = 12.6 Hz, 1H), 2.71 (t, *J* = 12.1 Hz, 1H), 2.38 – 2.16 (m, 4H), 2.08 (td, *J* = 12.4, 6.3 Hz, 1H), 1.98 – 1.70 (m, 4H), 1.57 (d, *J* = 13.0 Hz, 2H), 1.38 – 1.05 (m, 10H), 1.00 – 0.92 (m, 1H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.80 – 0.63 (m, 1H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$), δ (ppm): 188.8, 166.1, 144.6, 135.1, 131.8, 129.7, 128.7, 128.2, 127.4, 112.3, 66.8, 60.6, 52.4, 33.14, 33.06, 31.6, 31.5, 29.8, 29.5, 26.32, 26.28, 23.5, 23.4, 22.7, 20.8, 14.2; ^{77}Se{1H} NMR (76 MHz, $CDCl_3$) δ 299.18.

Minor Diastereomer: The following signals were sufficiently distinct to attribute to the minor diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (td, *J* = 12.9, 4.7 Hz, 1H), 3.13 (d, *J* = 12.7 Hz, 1H), 2.90 (t, *J* = 12.4 Hz, 1H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 186.4,

166.9, 144.6, 134.9, 131.7, 128.1, 127.4, 127.3, 109.2, 67.0, 62.3, 47.5, 34.1, 32.6, 31.4, 31.2, 30.5, 29.3, 28.3, 23.0, 22.6, 20.9, 14.2; ^{77}Se{1H} NMR (76 MHz, $CDCl_3$) δ 301.02.

6-(Benzenesulfonyl)-5-hexyl-3-(phenylseleninylmethyl)-1,2,3,7a,8,9,10,11-octahydro-pyrrolo[2,1-j]quinolin-7-one (36).

To a solution of selenide **19** (12.6 g, 21.6 mmol) in dry dichloromethane (50 mL) at 0 °C was added purified MCPBA[31] (3.72 g, 21.6 mmol) and the mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with a saturated solution of $NaHCO_3$ and the layers were separated. The organic fraction was washed with saturated $NaHCO_3$ and the combined organic extracts were washed with brine, dried, filtered, and evaporated under reduced pressure to yield selenoxide **36** (12.8 g, 99%) as an oil, containing an inseparable mixture of four diastereomers: ^{77}Se{1H} NMR (76 MHz, $CDCl_3$) δ 859.1, 857.5, 847.7, 845.7. HRMS (ESI-TOF), *m/z*: $[M+H]^+$ Calc'd for $C_{31}H_{40}NO_4S^{80}Se$ 602.1838; found 602.1851.

6-(Benzenesulfonyl)-5-hexyl-7-oxo-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-3-yl-phenylselanyl-methyl acetate (37).

Selenoxide **36** (12.8 g, 21.3 mmol) was dissolved in acetic anhydride (400 mL) and heated at 70 ^{o}C overnight. The reaction mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography (1:1 ethyl acetate/hexane) to afford the acetoxy selenide **37** (13.6 g, 99%) as an oil containing a mixture of four diastereomers. A small amount of the major isomer was cleanly isolated by a second chromatography; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.63 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.47 – 7.40 (m, 4H), 7.36 (t, *J* = 7.8 Hz, 2H), 6.01 (d, *J* = 10.2 Hz, 1H), 4.12 (dd, *J* = 10.4, 7.0, 1H), 3.39 (ddd, *J* = 13.2, 11.2, 4.3 Hz, 1H), 2.37 – 1.80 (m, 8H), 1.75 (s, 3H), 1.74 – 1.55 (m, 1H), 1.35 – 1.11 (m, 12H), 1.08 – 0.68 (m, 1H), 0.91

(t, J = 7.1 Hz, 3H); ^{13}C{1H} NMR (101) MHz, $CDCl_3$) δ 189.8, 169.0, 167.9, 144.8, 137.2, 132.0, 129.8, 129.7, 128.3, 127.4, 124.5, 113.9, 73.9, 66.8, 61.7, 52.5, 33.5, 32.0, 31.7, 30.5, 29.6, 29.0, 27.0, 26.0, 23.9, 23.7, 22.8, 20.9, 20.6, 14.2; ^{77}Se{1H} NMR (76 MHz, $CDCl_3$) δ 452.17. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calc'd for $C_{33}H_{42}NO_5S^{80}Se$: 644.1943; found: 644.1965.

6-(Benzenesulfonyl)-5-hexyl-7-oxo-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-3-carbaldehyde (18).

Potassium carbonate (27.8 g, 0.201 mol) was added to a solution of acetoxy selenide **37** (13.6 g, 21.2 mmol) in methanol (200 mL) and the suspension was stirred for 3 h at room temperature. The reaction was quenched with water and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried, filtered, and evaporated under reduced pressure to give a brown residue. The crude product was purified by flash chromatography (2:1 EtOAc/Hex.) to yield aldehyde **18** (8.28 g, 88%) as a colourless oil containing an inseparable mixture of diastereomers in the ratio of 2.3:1. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calc'd for $C_{25}H_{33}NNaO_4S$ 466.2023; found 466.2038.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.02 – 7.93 (m, 2H), 7.50 – 7.40 (m, 3H), 4.81 – 4.75 (m, 1H), 3.45 (t, J = 10.0 Hz, 1H), 2.41 – 1.10 (m, 22H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 196.4, 188.6, 166.7, 144.6, 131.9, 128.3, 127.2, 111.7, 68.1, 66.7, 50.4, 33.2, 32.4, 31.4, 29.7, 29.0, 26.2, 23.6, 23.1, 22.9, 22.7, 20.8, 14.1.

Minor diastereomer: The following signals were sufficiently distinct to attribute to the minor diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, J = 1.1 Hz, 1H), 8.02 – 7.93 (m, 2H), 7.50 – 7.40 (m, 3H), 4.66 (dd, J = 9.3, 3.4 Hz, 1H), 3.84 – 3.74 (m, 1H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 196.6, 186.9, 167.5, 144.8, 131.9, 128.2, 127.3, 110.2, 68.8, 67.8, 48.8, 34.7, 32.3, 31.4, 29.9, 29.5, 28.7, 24.7, 23.0, 22.6, 21.0, 14.1.

6-(Benzenesulfonyl)-5-hexyl-3-(hydroxymethyl)-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-7-one (38).

Sodium borohydride (378 mg, 10.0 mmol) was added to a solution of aldehyde **18** (4.44 g, 10.0 mmol) in methanol (15 mL) at 0 °C and the mixture was stirred for 3 h. The reaction was quenched with water (20 mL) and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried, filtered, and evaporated under reduced pressure to give a colourless oil. The crude product was purified by flash chromatography (3:1 ethyl acetate/hexane) to yield alcohol **38`** (4.02 g, 90%) as a colourless oil containing a mixture of two diastereomers. Flash chromatography failed to separate the mixture completely, but collection of leading and trailing fractions afforded small amounts of the pure products, followed by crystallization by slow evaporation from dichloromethane. The products were then subjected to x-ray diffraction (see Figure 1 and the Supporting Information for additional x-ray crystallographic data).

*Major isomer **38a***: mp 160-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.46 - 7.43 (m, 3H), 4.32 – 4.18 (m, 1H), 3.78 (dd, *J* = 11.1, 5.3 Hz, 1H) 3.71 (dd, J = 11.2, 6.2 Hz, 1H), 3.43 – 3.35 (m, 1H), 2.76 (crude t, 1H), 2.35 (s, 1H), 2.26 (dd, J = 11.8, 5.4 Hz, 1H), 2.22 – 1.77 (m, 5H), 1.69 – 1.03 (m, 14H), 0.90 (t, *J* = 7.1 Hz, 3H), 0.50 (m, 1H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 189.9, 167.9, 144.8, 131.8, 128.2, 127.5, 111.9, 66.9, 65.4, 61.6, 51.2, 33.4, 32.0, 31.6, 29.9, 29.4, 26.8, 25.4, 23.6, 23.5, 22.8, 20.9, 14.2. HRMS (ESI-TOF) *m/z* calc'd for $C_{25}H_{36}NO_4S$: 446.2360 $[M+H]^+$; found: 446.2380.

*Minor isomer **38b**:* m.p. 129-130 °C (from dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-8.02 (m, 2H), 7.50 – 7.40 (m, 3H), 4.21 (dd, J = 10.8, 7.9 Hz, 1H), 4.01-3.94 (m, 1H), 3.79 (dd, *J* = 10.8, 5.8 Hz, 1H), 3.70 (dd, *J* = 16.8, 6.3 Hz, 1H), 2.56 – 2.46 (m, 1H), 2.41 – 2.29 (m, 2H), 2.25 (s, 1H), 2.19 – 1.95 (m, 5H), 1.73 –1.13 (m, 15H), 0.88 (t, J = 6.9 Hz, 3H), 0.84 – 0.71 (m, 1H);

$^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 186.7, 168.1, 145.0, 131.8, 128.3, 127.4, 109.4, 66.9, 63.6, 63.2, 47.7, 34.5, 31.9, 31.8, 31.6, 30.4, 29.7, 26.9, 23.6, 23.0, 22.7, 21.1, 14.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calc'd for $C_{25}H_{36}NO_4S$ 446.2360; found 446.2362.

6-(Benzenesulfonyl)-3-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-5-hexyl-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-7-one (39a,b)

tert-Butyldimethylsilyl chloride (977 mg, 6.48 mmol), DMAP (792 mg, 6.48 mmol) and imidazole (411 mg, 6.04 mmol) were added to a solution of alcohols **38a,b** (2.22 g, 4.98 mmol) in dry DMF (50 mL) and the reaction mixture was stirred overnight. The reaction was quenched with brine and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were dried, filtered and evaporated under reduced pressure to give a yellow oil. The crude product was purified by flash chromatography (3:7 ethyl acetate/hexane) to yield the easily separated silyl ethers **39a** (1.75 g, 63%) and **39b** (0.62 g, 22 %) as colourless oils.

*Major diastereomer **39a***: ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.48 – 7.38 (m, 3H), 4.20 – 4.11 (m, 1H), 3.59 (dd, *J* = 10.2, 4.7 Hz, 1H), 3.52 (dd, *J* = 10.2, 7.1 Hz, 1H), 3.49-3.37 (m, 1H), 2.63 (td, *J* = 12.6, 3.3 Hz, 1H), 2.29 (dd, *J* = 12.5, 4.3 Hz, 1H), 2.17 (s, 1H), 2.10 – 1.93 (m, 4H), 1.82 – 1.68 (m, 1H), 1.62 – 1.11 (m, 13H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.85 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 189.0, 167.2, 144.9, 131.7, 128.1, 127.4, 112.1, 66.7, 65.7, 61.6, 52.0, 33.5, 31.7, 31.5, 29.8, 29.7, 26.4, 25.9, 25.2, 23.6, 23.4, 22.7, 20.9, 18.3, 14.1, -5.1, - 5.4. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calc'd for $C_{31}H_{50}NO_4SSi$ 560.3224; found 560.3226.

*Minor diastereomer **39b***; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H), 7.52 – 7.35 (m, 3H), 4.17 (dd, *J* = Hz, 1H), 3.98 (td, *J* = 13.2, 4.9 Hz, 1H), 3.71 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.64 (dd, *J* = 10.3, 7.5 Hz, 1H), 2.51 (td, *J* = 13.3, 4.9 Hz, 1H), 2.35 (d, *J* = 13.3 Hz, 1H), 2.24 (s, 1H), 2.17 –

1.95 (m, 5H), 1.77 – 1.14 (m, 14H), 0.92 (s, 9H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.80 – 0.68 (m, 1H), 0.10 (s, 3H), 0.09 (s, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 186.6, 167.9, 145.1, 131.6, 128.1, 127.4, 109.5, 66.9, 64.2, 63.5, 47.6, 34.6, 31.94, 31.90, 31.5, 30.3, 29.7, 26.8, 25.9, 23.5, 23.0, 22.7, 21.0, 18.3, 14.1, -5.25, -5.27. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calc'd for $C_{31}H_{50}NO_4SSi$ 560.3224; found 560.3212.

3-[[tert-Butyl(dimethyl)silyl]oxymethyl]-5-hexyl-1,2,3,7a,8,9,10,11- octahydropyrrolo[2,1-j]quinolin-7-one (major diastereomer 40a).

A solution of sodium naphthalenide was prepared by adding sodium metal (282 mg, 12.3 g-atom) to a solution of naphthalene (1.57 g, 12.3 mmol) in dry THF (10 mL) and the mixture was stirred for 2 h at room temperature. In another flask, silyl ether **39a** (560 mg, 1.00 mmol) was dissolved in dry THF (10 mL) and cooled to -78 ºC. The sodium naphthalenide solution was added in 0.1 mL increments until TLC showed no remaining starting material (~5 equiv). Ammonium chloride (50 mg) was added and the reaction mixture was warmed to room temperature, poured into water and extracted with ethyl acetate. The combined organic fractions were dried, filtered and concentrated. Flash chromatography on silica gel (3:1 hexanes: ethyl acetate) afforded the desired compound **40a** (277 mg, 66%) as a colourless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.02 (s, 1H), 3.96 – 3.86 (m, 1H), 3.55 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.42 (dd, *J* = 10.0, 7.8 Hz, 1H), 2.48 – 1.95 (m, 8H), 1.79 –1.10 (m, 16H), 0.88 (s superimposed on m, 12H), 0.04 (s, 6H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 194.0, 162.2, 100.1, 67.0, 65.9, 59.8, 51.6, 33.6, 33.4, 31.7, 29.8, 29.0, 28.6, 26.0, 25.9, 25.5, 24.3, 23.1, 22.7, 21.5, 18.4, 14.2, -5.3. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calc'd for $C_{25}H_{46}NO_2Si$ 420.3292; found 420.3288.

3-[[tert-Butyl(dimethyl)silyl]oxymethyl]-5-hexyl-1,2,3,7a,8,9,10,11- octahydropyrrolo[2,1-j]quinolin-7-one (minor diastereomer 40b).

Diastereomer **40b** was prepared as a colourless oil in 55% yield from **39b** by the same procedure as followed for the preparation of **40a** from **39a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (s, 1H), 3.96 – 3.88 (m, 1H), 3.61 (dd, *J* = 10.1, 5.3 Hz, 1H), 3.49 (dd, *J* = 10.0, 8.2 Hz, 1H), 2.51 (d, *J* = 12.5 Hz, 1H), 2.38 (s, 1H), 2.33 – 2.16 (m, 3H), 2.11 – 1.95 (m, 4H), 1.71 – 1.16 (m, 15H), 0.90 (s, 9H), 0.88 (t, J = 4.9 Hz, 3H), 0.07 (s, 6H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 192.4, 162.6, 97.4, 67.0, 64.7, 61.9, 47.8, 34.7, 33.9, 31.7, 31.6, 29.3, 28.5, 27.5, 26.0, 23.8, 23.3, 22.7, 21.7, 18.4, 14.2, -5.2; HRMS (ESI-TOF): calc'd for $C_{25}H_{46}NO_2Si$: 420.3292 $[M+H]^+$; found 420.3280.

5-Hexyl-3-(hydroxymethyl)-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin- 7-one (17a).

Tetrabutylammonium fluoride (2.62 mL, 1.0 M) was added to a solution of **40a** (222 mg, 0.529 mmol) in dry THF (45 mL) at 0 °C and the reaction mixture was stirred for 4 h at room temperature. Saturated aqueous NH_4Cl solution was added and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (3:1 ethyl acetate/hexane) to yield alcohol **17a** (162 mg, 99%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (s, 1H), 4.03 (s, 1H), 3.97 (dd, *J* = 11.7, 5.9 Hz, 1H), 3.59 (d, *J* = 5.3 Hz, 2H), 2.45 – 2.36 (m, 1H), 2.34 (s, 1H), 2.27 (dd, *J* = 12.1, 5.9 Hz), 2.22 – 1.97 (m, 2H), 1.90 – 1.77 (m, 1H), 1.63 (d, *J* = 13.6 Hz, 1H), 1.53 – 1.42 (m, 2H), 1.42 – 1.12 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 194.2, 163.5, 99.7, 67.1, 65.6, 60.0, 51.0, 33.7, 33.6, 31.7, 29.1, 28.5, 26.0, 25.7, 24.2, 23.0, 22.6, 21.5, 14.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calc'd for $C_{19}H_{32}NO_2$ 306.2428; found: 306.2419.

5-Hexyl-3-(hydroxymethyl)-1,2,3,7a,8,9,10,11-octahydropyrrolo[2,1-j]quinolin-7-one (17b).[10c]

The same procedure was employed as for **17a**. Enaminone **40b** (210 mg, 0.500 mmol) afforded **17b** (137 mg, 90 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (s, 1H), 4.04 – 3.97 (m, 1H), 3.68 (dd, *J* = 10.8, 5.4 Hz, 1H), 3.57 (dd, *J* = 10.8, 8.1 Hz, 1H), 2.55 – 2.47 (m, 1H), 2.40 (s, 1H), 2.31 – 2.21 (m, 3H), 2.15 – 1.98 (m, 5H), 1.72 – 1.62 (m, 1H), 1.60 – 1.48 (m, 2H), 1.47 – 1.41 (m, 1H), 1.39 – 1.23 (m, 9H), 1.22 – 1.17 (m, 1H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$), δ 192.5, 162.7, 97.7, 67.0, 64.3, 61.7, 47.9, 34.8, 33.9, 31.74, 31.66, 29.3, 28.5, 27.7, 23.8, 23.3, 22.7, 21.7, 14.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calc'd for $C_{19}H_{32}NO_2$ 306.2428; found 304.2426.

(±)-2,13-Di-epi-cylindricine C (16).

A variation of the procedure reported by Hsung et al.[10b] in the synthesis of cylindricine C was employed. To a solution of alcohol **17a** (121 mg, 0.396 mmol) in chloroform (10 mL) was added $NaBH(OAc)_3$ (424 mg, 2.00 mmol) with a catalytic amount of AcOH (1 drop) and the reaction mixture was refluxed overnight. Saturated aqueous $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with chloroform. The combined organic extracts were washed with brine, dried, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (1:4 ethyl acetate/hexane.) to yield **16** (101 mg, 83%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (dd, *J* = 10.7, 3.4 Hz, 1H), 3.46 (dd, *J* = 10.7, 1.2 Hz, 1H), 3.40 – 3.34 (m, 1H), 3.32-3.17 (m, 1H), 2.60 (dd, *J* = 14.5, 7.6 Hz, 1H), 2.40 (broad s, 1H), 2.36 (dd, *J* = 14.6, 2.4 Hz, 1H), 2.24 – 2.11 (m, 2H), 2.11 – 2.00 (m, 1H), 1.94 – 1.85 (m, 1H), 1.73 - 1.21 (m, 18H), 1.12-1.05 (m, 1H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 211.4, 67.1, 61.1,

57.0, 56.3, 52.7, 44.7, 35.1, 32.4, 32.0, 31.9, 29.4, 28.5, 26.4, 24.3, 23.6, 22.8 21.8, 14.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calc'd for $C_{19}H_{34}NO_2$ 308.2584; found 308.2570.

(±)-Cylindricine C (3).

Cylindricine C was prepared from **17b** (19.7 mg, 0.064 mmol) by the same procedure as in the preparation of **16** from **17a** to afford the product (14.2 mg, 72%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 – 3.50 (m, 2H), 3.43 (d, *J* = 9.3 Hz, 1H), 3.33 – 3.24 (m, 1H), 2.96 (broad s, 1H), 2.35 – 2.17 (m, 5H), 2.12 (dd, *J* = 12.4, 7.7 Hz, 1H), 1.87 – 1.80 (m, 1H), 1.74 – 1.60 (m, 4H), 1.52 – 1.18 (m, 14H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 210.6, 70.9, 66.5, 56.7, 55.5, 50.5, 42.7, 36.6, 36.1, 35.4, 31.9, 29.5, 28.9, 27.3, 24.4, 22.9, 22.7, 22.0, 14.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calc'd for $C_{19}H_{34}NO_2$ 308.2584; found 308.2570.

Associated Content

Data Availability Statement: The data underlying this study are available in the published article, in its Supporting Information, and openly available in the Prism Depository at the University of Calgary (DOI, Accession Number).

Supporting Information: The Supporting Information contains NMR spectra (pp. S2-S21), X-ray crystallographic data for compounds **38a** and **38b** (p. S22 and S24), and Gaussian Z-matrixes, and total energies for compounds **3**, **16** and 5-*epi*-cylindticine C (p. S27). It is available free of charge at https://pubs.acs.org/

Author Information

Corresponding author: Thomas G. Back – Department of Chemistry, University of Calgary, Calgary, Alberta, Canada, T2N 1N4

Orcid: Thomas G. Back 0000-0002-3790-1422

E-mail: tgback@ucalgary.ca

Author: Arnaud Pastor – Department of Chemistry, University of Calgary, Calgary, Alberta, Canada, T2N 1N4.

Author: Rohen Prinsloo - Department of Chemistry, University of Calgary, Calgary, Alberta, Canada, T2N 1N4.

Author: Kristen N. Burford - Department of Chemistry, University of Calgary, Calgary, Alberta, Canada, T2N 1N4.

Author: Andrew R. Macdonald, Department of Chemistry, University of Calgary, Calgary, Alberta, Canada, T2N 1N4.

Author: Masood Parvez, Department of Chemistry, University of Calgary, Calgary, Alberta, Canada, T2N 1N4.

Author: Chris Gendy, Department of Chemistry, University of Calgary, Calgary, Alberta, Canada, T2N 1N4.

Notes

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