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Highly Regioselective Oxirane Ring-Opening of a Versatile Epoxypyrrolidine Precursor of New Imino-Sugar-Based Sphingolipid Mimics

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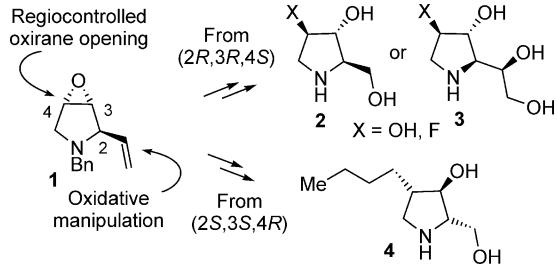
An in-depth study of the oxirane ring-opening reaction of a pivotal epoxypyrrolidine is reported. The introduction of various carbon- and heteroatom-centered nucleophiles at C4 has been achieved with high regiocontrol. The structures of the major products were assigned on the basis on an X-ray crystallographic study of six examples. A mechanistic study carried out at the B3LYP/6-31G** level of theory suggested that the steric control of the vinyl substituent was responsible for the regioselectivity. Finally, this approach was used to design and prepare imino-sugar-based sphingolipid mimics. A highly cytotoxic *C*-octylpyrrolidine is described. This compound was shown to interfere with the metabolism of sphingolipids in murine melanoma cells, notably in inhibiting the production of glucosylceramide.

Introduction

Imino sugars form a wide family of naturally occurring alkaloids originally recognized as sugar mimics with potent glycosidase inhibitory properties.[1] Affecting intestinal sugar digestion, the maturation of glycoproteins, and the lysosomal catabolism of glycoconjugates, imino sugars are promised great therapeutic development.[2] Applications as antiviral agents and more recently in anticancer therapy have been pursued.[3] Two imino-sugar-based drugs have been commercialized: The *N*-alkyl-1-deoxynojirimycine derivatives Miglitol and Miglustat for the treatment of diabetes and Gaucher's disease, respectively.[4] The recent phase II clinical trial of the use of *N*-butyldexonojirimycine in the treatment of cystic fibrosis (mucoviscidosis) further illustrates the pharmacological potential of imino sugars.[5] The synthetic chemistry of imino sugars is also an active field of research.[6] The last decade has notably witnessed the emergence of new *C*-alkyl six-membered-ring derivatives with high glucosylceramide β-glucosidase inhibitory activity and promising applications as pharmacological chaperons for the treatment of Gaucher's disease.[7]

In the course of the development of our synthetic approach towards imino sugars we gained access to both enantiomers of the versatile epoxypyrrolidine intermediate **1** (Scheme 1).[8] Earlier studies aimed at the stereoselective preparation of five-membered imino sugars and original deoxyfluoro analogues thereof (**2** and **3**) revealed the inherent propensity of this oxirane to undergo highly regioselective ring-opening reactions during either acidic hydrolysis or substitution by a fluoride anion (Scheme 1). We thus decided to evaluate the scope of this regiocontrolled oxirane ring-opening reaction and to apply it to the preparation of biologically important *C*-alkyl imino sugars **4**.[9] Herein we present a full account of this study.



Scheme 1. Oxirane ring-opening of epoxypyrrolidine intermediate **1** in the synthesis of imino sugars.

Results and Discussion

Preparation of the Pivotal Epoxypyrrolidine

As reported previously, chiral nonracemic building block **1** has been obtained in a straightforward four-step sequence

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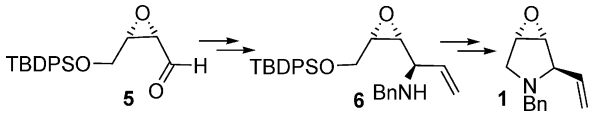
from the readily available epoxy aldehyde **5** (Scheme 2).[8c] The highly stereoselective formation of the *anti*-epoxyamine **6** relies on the addition of vinylmagnesium chloride to the corresponding epoxyimine in accord with the Felkin–Anh rule. In turn, the pyrrolidine framework was prepared by an Appel cyclization after desilylation to the primary alcohol. The epoxypyrrolidine **1** was thus obtained in 53% overall yield from the enantioenriched aldehyde **5**.



Scheme 2. Preparation of epoxypyrrolidine intermediate **1**.

Former Examples of the Oxirane Ring-Opening Reaction with the Epoxypyrrolidine Intermediate

We have already taken advantage of the epoxypyrrolidine building block **1** in the synthesis of five-membered-ring imino sugars and the deoxyfluoro analogues thereof.[8c] To do so, we performed an acidic hydrolysis or a reaction with the HF·pyridine complex in THF, respectively, and observed in both cases clean and efficient C4 oxirane ring-opening. The stereochemistry of the major ring-opened product **2** (X = OH) was at the time assigned by chemical correlation with 1,4-dideoxy-1,4-imino-D-arabinitol. Since then we have unambiguously confirmed the (3*R*,4*R*) configuration by X-ray diffraction analysis of a single crystal of the major 1,2-diol **2** (X = OH) resulting from the acidic hydrolysis of the (2*R*,3*R*,4*S*)-epoxypyrrolidine (Figure 1).

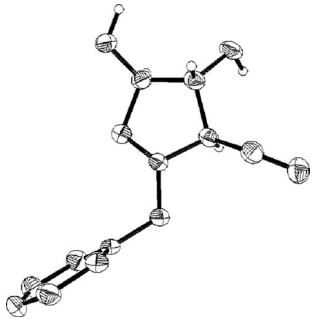


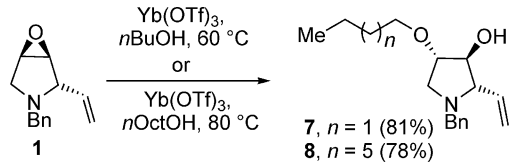
Figure 1. Molecular view of the *trans*-diol **2** (X = OH) in the solid state (thermal ellipsoids at the 50% probability level). Hydrogen atoms have been omitted for clarity.

Noteworthy in these earlier examples was the degree of regio- and stereocontrol (typically ≥90:10) in spite of the relatively high reaction temperatures (60–100 °C) and the moderate size of the incoming nucleophile. These attractive features prompted us to explore this transformation further. We first extended the scope of the nucleophile.

Generalization to Diverse Nucleophilic Reagents

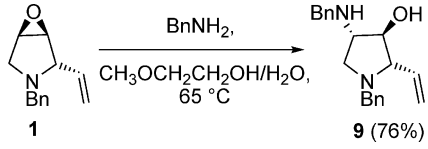
Heteroatom-Centered Nucleophiles

In view of the facile acidic hydrolysis of our oxirane, we attempted the ring-opening reaction with alcohols. The few synthetically useful examples of this reaction reported in the literature with nonactivated disubstituted epoxides were essentially based on activation with $Et_2O{\cdot}BF_3$, which proved inefficient in our case. With a stoichiometric amount of the more gentle and user-friendly $Yb(OTf)_3$, the reaction readily occurred upon heating epoxypyrrolidine **1** at 60 °C in *n*-butanol (Scheme 3). The expected ether **7** resulting from C4 attack was isolated as a single isomer in 81% yield. A similar result was obtained with *n*-octanol as the nucleophile. Surprisingly, no reaction at all was observed in methanol at reflux.



Scheme 3. Oxirane ring-opening with aliphatic alcohols.

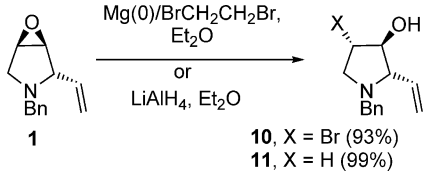
We then focused our attention on the introduction of a nitrogen atom. Surprisingly, epoxypyrrolidine **1** proved totally unaffected by the presence of the azide anion under Sharpless' conditions (2 equiv. NaN_3, 5 equiv. NH_4Cl, acetone/water, 70 °C, 5 h).[10] We thus turned our attention to benzylamine, a common ammonia equivalent. First attempts using a classic Lewis acid activation [3 equiv. $Ti(OiPr)_4$, 2 equiv. $BnNH_2$, CH_2Cl_2, reflux, 45 h] left the starting material unchanged.[11] Interestingly, a clean and selective C4 ring-opening reaction was observed when a 1.25 M solution of our epoxypyrrolidine in an aqueous solvent mixture was simply heated in the presence of an excess of benzylamine, delivering the *trans*-amino alcohol **9** with good yield and selectivity (Scheme 4).[12] No other isomer was detected in the crude reaction mixture by ^1H NMR analysis. The structure of this ring-opened product was furthermore determined unambiguously by X-ray diffraction analysis of a single crystal, which allowed the assignment of the *all-trans* relative configuration of the stereochemical triad in **9** (see the Supporting Information).



Scheme 4. Oxirane ring-opening with a primary amine.

Ring-opening with the halide anion proved to be much more spontaneous and the resulting halohydrins were in fact isolated as byproducts under several reaction conditions. For example, exploratory experiments aimed at the alcoholysis of the oxirane with *n*-butanol by catalysis with $FeCl_3/SiO_2$ (20 mol-%, 10 h, 40 °C) surprisingly delivered the corresponding chlorohydrin (not shown).[13] Similarly, when epoxide **1** was treated with MeMgI/CuI in a preliminary attempt to open the oxirane with a methyl group, the iodohydrin resulting from the incorporation of iodine at C4 was obtained in high yield (not shown). We attributed this

result to the reaction with MgI_2 resulting from the Schlenk equilibrium. As expected, the C4 ring-opening reaction with $MgBr_2$, preformed in situ from Mg^0 and dibromoethane, cleanly delivered a single isomer of the desired bromohydrin **10** (Scheme 5).



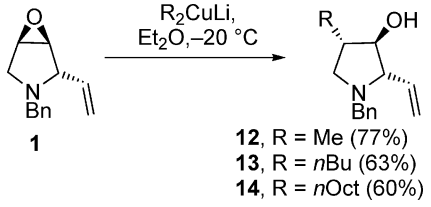
Scheme 5. Oxirane ring-opening with a hydride or halide nucleophile.

Reduction

A highly efficient and C4 selective reduction was achieved by simple treatment of epoxypyrrolidine **1** with an excess of $LiAlH_4$ in Et_2O, which yielded secondary alcohol **11** (Scheme 5).

Carbon-Centered Nucleophile

We first explored oxirane ring-opening with alkyl halide derived organometallic reagents avoiding the use of simple Grignard reagents due to the competitive formation of halohydrins (see above). The use of Gilman cuprates of the general structure R_2CuLi gave good results, contradicting previous reports.[14] For example, a methyl group was introduced at C4 in a yield of 77%. Reaction with nBu$_2$CuLi and nOct$_2$CuLi gave the expected alkylation products **13** and **14** in 63 and 60% isolated yields, respectively. In each case, ^{1}H NMR analysis of the crude mixture failed to detect any other isomer (Scheme 6).



Scheme 6. Oxirane ring-opening with Gilman cuprates.

Gratifyingly, a single crystal of 4-octylpyrrolidine **14** proved suitable for X-ray diffraction analysis, which confirmed the structure of the major ring-opened product (Figure 2). Based on literature precedents, we also attempted the addition of a high-order cuprate.[15] However, when the epoxypyrrolidine **1** was treated with nBu$_2$Cu(CN)Li$_2$ the expected alkylation product **13** was isolated in only 39% yield, still as a single isomer.

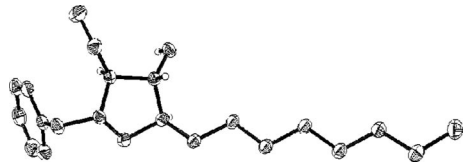
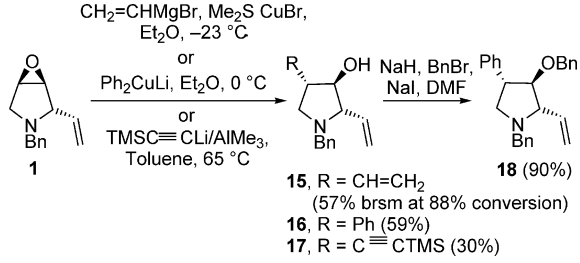


Figure 2. Molecular view of 4-octylpyrrolidine **14** in the solid state (thermal ellipsoids at the 50% probability level). Hydrogen atoms have been omitted for clarity.

We then studied reactions with sp^2-hybridized carbon-centered nucleophiles and the vinyl entity was first selected. A slow conversion was observed upon prolonged treatment of epoxypyrrolidine **1** at –23 °C with an excess of vinylmagnesium bromide in the presence of Me_2S·CuBr.[16] The expected C4 ring-opened product **15** was obtained in 57% isolated yield, again as the sole reaction product (Scheme 7). Conversely, a large excess of Ph_2CuLi at 0 °C was required for the preparation of 4-phenylpyrrolidine **16** in 59% yield.



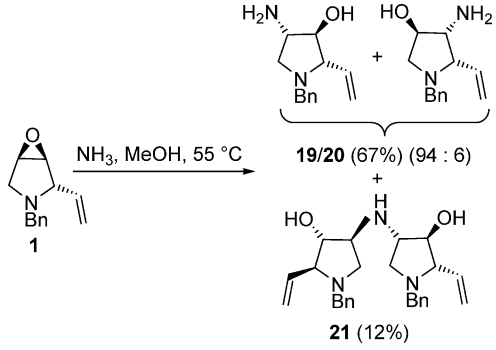
Scheme 7. Oxirane ring-opening with sp^2 and sp carbon-centered organometallic reagents.

The structures of the ring-opened products **15** and **16** were again confirmed by X-ray crystallographic analysis of a sample of the free alcohol of the 4-vinyl derivative or the corresponding *O*-benzyl derivative **18** of the 4-phenyl analogue, respectively (see the Supporting Information). Introduction of an sp-hybridized carbon-centered nucleophile was explored with a TMS-acetylene-derived organoalane reagent under Vasella's conditions.[17] The reaction was rather sluggish and prolonging the reaction time to obtain a significant conversion led to some decomposition, the expected ring-opened product **17** being isolated in 30% yield (Scheme 7).

Mechanistic Study

The high level of regio- and stereoselectivity observed in the course of the oxirane ring-opening process thus seemed to only weakly depend on the reaction conditions and the nature of the nucleophilic reactant. Such a general and pronounced trend, consonant with the scarce literature precedents, prompted us to seek a possible rationale.[18] On qualitative grounds, the major pathway logically corresponds to an S_N2 attack of the epoxide site distal from the neighboring vinyl moiety, located on the same face of the pyrrolidine framework as the incoming nucleophile. However, the level of control appeared to be relatively high in

relation to the moderate steric bulk of the ethylenic appendage. A theoretical study was conducted to gain mechanistic insights into the observed selectivity. Owing to its simplicity, the uncatalyzed ring-opening reaction of the oxirane with ammonia was selected as a suitable model reaction. Thus, a 0.75 M solution of epoxypyrrolidine **1** in a saturated solution of NH_3 in MeOH was heated in a sealed reaction vessel for 1 week at 55 °C. Purification by flash chromatography then allowed two separate fractions to be isolated that contained ring-opened products (79% global yield, based on starting material recovering at 88% of conversion) along with unreacted starting epoxide (12% recovery) (Scheme 8).



Scheme 8. Oxirane ring-opening with ammonia.

The major isolated fraction (67% yield) was composed of a 94:6 mixture of two isomers of the expected amino alcohol, as determined by LC–MS analysis ($[MH]^+$ at m/z = 219). The structure of the major component was established after HPLC purification as the expected C4 ring-opened product **19**, in particular, by X-ray diffraction analysis (Figure 3). The minor element of the mixture was identified as the *trans*-amino alcohol **20**, produced from the less favorable C3 attack. The experimentally observed ratio between the major C4 and the minor C3 attack during the course of this oxirane ring-opening reaction with ammonia in methanol was established to be ≥94:6.

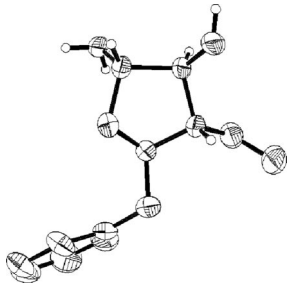


Figure 3. Molecular view of 4-aminopyrrolidine **19** in the solid state (thermal ellipsoids at the 50% probability level). Hydrogen atoms have been omitted for clarity.

Quite unexpectedly, the minor isolated compound (12% yield), in spite of presenting ^1H and ^{13}C NMR analyses in complete agreement with the structure of a C4 ring-opened product, displayed a molecular mass peak $[MH]^+$ at m/z = 420 (in DCI/NH_3, FAB and ESI). Because the odd-numbered molecular mass of 419 indicates the presence of an odd number of nitrogen atoms, we assigned to this compound the structure of the triamine **21** (Scheme 8). Such a dimeric structure may indeed arise, under prolonged heating, from the opening of the oxirane of the starting epoxypyrrolidine by the nitrogen atom of the expected ring-opened product **19**. This side-product is therefore thought to result indirectly from the weak nucleophilicity of ammonia.

On theoretical grounds, various conformations of the starting epoxypyrrolidine **1** may be envisaged depending on (i) the boat or chair conformation of the morpholine ring encompassing the fused oxirane and envelope-shaped pyrrolidine rings, (ii) the rotation of the benzyl group about the N–CH_2 bond, (iii) the rotation of the phenyl ring about the C–Ph bond, and (iv) the rotation of the vinyl group about the CH–CH bond. Starting from various conformations of epoxypyrrolidine moieties extracted from the Cambridge Data Base or obtained by preliminary molecular mechanics calculations of the epoxypyrrolidine **1**, several quasi-idegenerate conformers were isolated on the gas-phase singlet-spin-state potential energy surface. Beyond minor differences (of low energetic cost) in the orientation of the benzyl *N*-substituent, it can be noticed that the minimum-energy conformation selected in this way is boat-shaped (Figure 4a), but remains 0.6 kcal/mol higher in energy, that is, almost isoenergetic, than the chair conformation obtained by starting from the X-ray crystal structure of product **19** (Figure 4b).

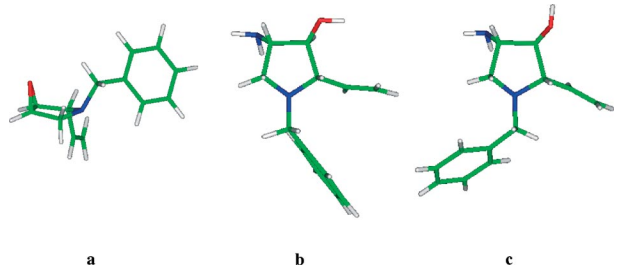


Figure 4. (a) Conformer of the starting epoxypyrrolidine **1** used in this work, with a boat-shaped morpholine ring. (b) Calculated structure of the *trans*-amino alcohol **19** resulting from nucleophilic attack of C4 by NH_3 (B3LYP/6-31G**). (c) Experimental X-ray crystal structure of the major *trans*-amino alcohol product **19**.

The experimental and calculated structures of the product are in remarkable agreement therefore validating the B3LYP/6-31G** level of theory used here (Figure 4b and Table 1). In a preliminary approach, the propensity of the isolated epoxide to be attacked at the C3 or C4 atoms was analyzed under the assumption of an initial charge-controlled process.

It is noticeable that in the epoxide, atoms C3 and C4 are initially locally equivalent. The C3–O and C4–O bonds are indeed almost identical in length, whatever the surrounding medium: 1.438 Å in the gas-phase structure, 1.443(4) Å with one interacting MeOH molecule, and 1.451(3) Å in a combined implicit and explicit solvent medium. Because the atomic charges of both atoms were also calculated as being identical (Mulliken: +0.1 e^- and AIM: +0.4 e^-), the regiose-

Table 1. Selected geometrical data for the experimental and calculated structures of the major product **19**.[a]

	Bond lengths [Å]						Envelope
	C4–N	C3–O	C3–C4		C–N	N–Bn	bending angle [°]
Exp.	1.472	1.413	1.547	1.493	1.461	1.469	39.1
Calcd.	1.467	1.418	1.549	1.499	1.469	1.462	44.1

[a] Calculated at the B3LYP/6-31G** level of theory.

lectivity of the ring-opening could mainly be dictated by differential steric effects. The reaction pathway of the S_N2 process was therefore further investigated.

The reaction pathway was assumed to proceed in two steps. The opening of the epoxide, yielding a zwitterionic betaine-like intermediate, is taken as the determining step and the subsequent proton transfer is assumed to occur without or with almost no barrier. The distance of C4 (or C3–N) to the N atom of the approaching NH_3 moiety was selected as the intrinsic reaction coordinate. The reaction profiles corresponding to the nucleophilic attack of C3 and C4 are displayed in Figure 5. The calculations were performed by combining one explicit MeOH molecule interacting with the oxirane or the alcoholate and a polarizable continuum of dielectric constant ε = 32.63 (implicit methanol solvent). In the absence of ammonia, the methanol interacts with the oxirane through hydrogen bonding (MeOH···oxirane = 1.895 Å). Such hybrid solvation approaches have been claimed to better account for the solvation of ions by producing more reliable solvation energies.[19]

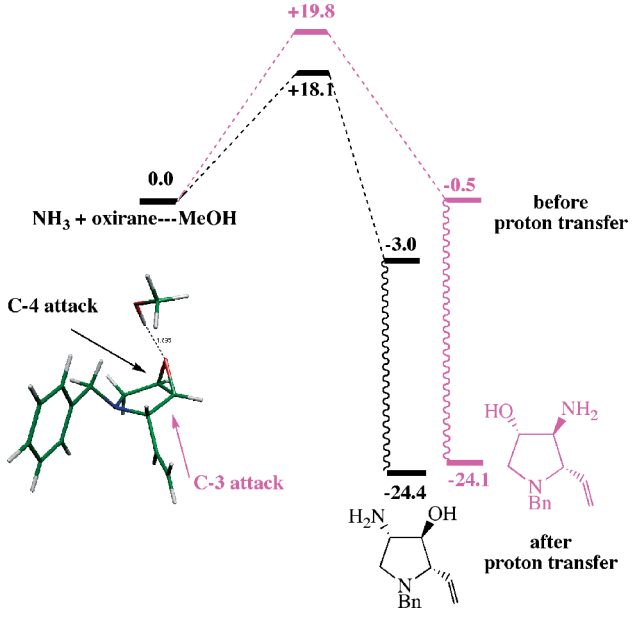


Figure 5. Energy profiles of the nucleophilic attack of NH_3 at C4 (black) and at C3 (magenta) of the epoxypyrrolidine **1** interacting with one molecule of methanol in a continuum medium (PCM ε = 32.63). Calculated at the B3LYP/6-31G** level of theory.

The nucleophilic attack of C4 by NH_3 was found to be both thermodynamically and kinetically favored. The major betaine-like intermediate is indeed more stable by 2.5 kcal/mol. The proton transfer is quasi-irreversible, but we notice however that the final *trans*-amino alcohols resulting from the subsequent proton transfer are quasi-isoenergetic.

The activation energy of the oxirane ring-opening is rather high (18.1 kcal/mol), but compatible with the heating conditions used experimentally. The nucleophilic attack on C4 is kinetically favored by 1.7 kcal/mol over C3 attack. This value corresponds to a calculated 93:7 ratio of C4 versus C3 attack at 328 K, which is in very good agreement with the observed ratio of 96:4.

The transition states arising from C3 (NImag = 408i cm^{-1}) and C4 attack (NImag = 446i cm^{-1}) are shown in Figure 6. According to the Hammond postulate, the more exothermic the reaction, the earlier the transition state:[20] The C4–N distance (2.117 Å) is indeed slightly longer than the C3–N distance (2.100 Å) and the N–C4–O valence angle is wider (151.8°) than the N–C3–O valence angle (146.5°). Both transition states are rather similar in their global structure and intermediate between the reactant and the betaine product, with a conformation of the five-membered heterocycle different from the starting epoxypyrrolidine **1**. The proximity of the transition states to the product is likely to preclude the use of reactivity indices such as frontier orbitals or Fukui indices of the isolated reactant. Anyhow, the steric control of the vinyl substituent appears to be the determining factor.

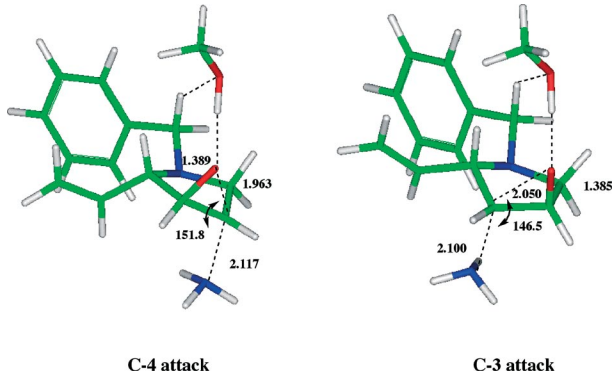


Figure 6. Transition states corresponding to the nucleophilic attack of NH_3 at the C3 and C4 positions. Bond lengths are given in Å and angles in degrees. Calculated at the B3LYP/6-31G** level of theory.

Synthesis of Imino Sugars

Imino-sugar-based inhibitors of the glucosylation/deglucosylation of ceramide have already found applications in therapeutic treatments against Gaucher's disease, a lysosomal storage disorder characterized by inherited deficiencies in glucosylceramide catabolism. Slowing glucosylceramide production corresponds to the so-called "substrate deprivation approach" and has resulted in the commercialization of *N*-butyl-1-deoxynojirimycin (Zavesca®).[21] On the other hand, promising results for enhancing the residual β-glucocerebrosidase activity have been obtained with sub-inhibitory concentrations of *C*-alkyl six-membered-ring imino sugars by the "chemical chaperon approach".[22]

Our interest in the inhibition of glucosylceramide synthase (GCS, EC 2.4.1.80) arises from its emerging role as a key enzymatic target in anticancer chemotherapy.[23] GCS catalyzes the transfer of a glucosyl residue onto the C1 hydroxy of ceramide, a gateway to numerous glucosylceramide-based glycosphingolipids (GSLs). GSLs have been invoked in many cellular processes, including cell–cell communication, cell adhesion, differentiation, proliferation, and oncogenic transformations.[24] Importantly, the overexpression of GCS observed in cancer cells has been related to an ineffective host immune response and to tumor progression and/or metastasis.[25] Moreover, by reducing the accumulation of the pro-apoptotic ceramide, GCS could prevent the response of cancer cell death to some chemotherapeutic agents. Conversely, GCS inhibition may resensitize multidrug resistant (MDR) breast cancer cells to antineoplastic agents, which suggests that elevated GCS activity participates in a new MDR mechanism.[26]

Our approach towards GCS inhibition originates from the notion that a five-membered-ring imino sugar should represent a suitable molecular scaffold on which to base sphingolipid mimicry. In particular, the structure of a (2*S*,3*R*)-3-hydroxy-2-(hydroxymethyl)pyrrolidine bearing a C4 lipophilic residue, such as **23**, may be sufficiently analogous to the D-*erythro*-sphingosine backbone (**22**; Figure 7).

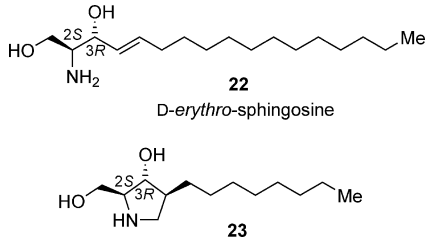


Figure 7. Comparison of the structures of D-*erythro*-sphingosine and the proposed imino-sugar-based sphingolipid mimic.

This proposal was further illustrated by a molecular modeling study (Figure 8). According to the resulting superimposition, the pyrrolidinic framework would hold the 2-hydroxymethyl and the 3-hydroxy groups in a spatial orientation that would allow for possible mimicry of the C1–C3 sphingolipid fragment.[27]

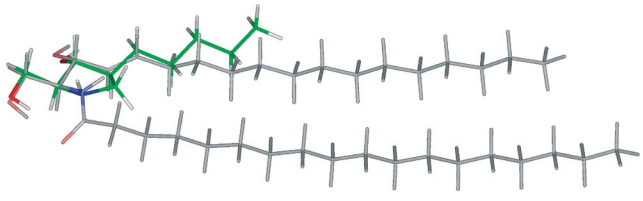
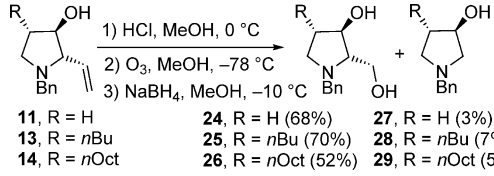


Figure 8. Superimposition of energy-minimized conformers of the proposed sphingosine backbone mimic (green) and of ceramide (grey).

We have already briefly communicated our successful efforts to validate this approach towards novel imino-sugar-derived cytotoxic GCS inhibitors.[9] Herein we present a detailed account of this work.

The key to the entry to the imino sugar series was the introduction of the characteristic hydroxymethyl group from the vinyl appendage of the key intermediates **1** (Scheme 1). In previous work we achieved a standard olefin oxidative cleavage based on the osmium-catalyzed dihydroxylation/periodic acid induced degradation/sodium borohydride reduction sequence. In the search for a simplified procedure that avoids the use of any toxic metal salt, we assessed the usefulness of a reductive ozonolysis reaction.

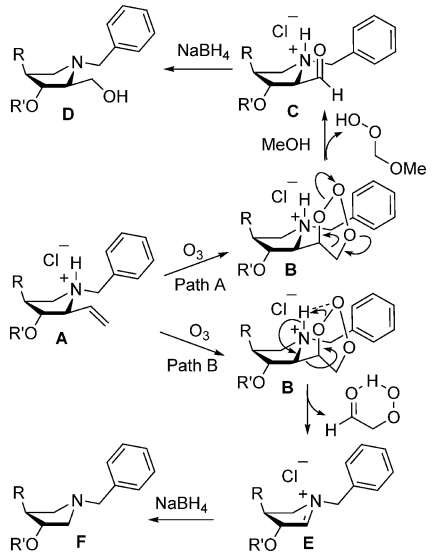
The vinylpyrrolidines were first salified so as to avoid the formation of *N*-oxide derivatives, but no protecting group was introduced onto the secondary alcohol. Thus, a methanolic solution of the 4-butyl derivative **13** hydrochloride was briefly (3–5 min) treated with ozone at –78 °C followed by a large excess of $NaBH_4$ at –10 °C (Scheme 9). The expected primary alcohol **25** was gratifyingly obtained in 70% isolated yield. The same procedure was applied to the preparation of the 4-octyl analogue **26** (52% yield) as well as the C4 unsubstituted derivative **24** (68% yield). Surprisingly, these compounds were obtained along with a small amount (3–7% yield) of an unexpected byproduct, which was identified as the product resulting from the loss of the vinyl appendage (**28**, **29**, and **27**, respectively).



Scheme 9. Ozonolysis of the key vinylpyrrolidine intermediates.

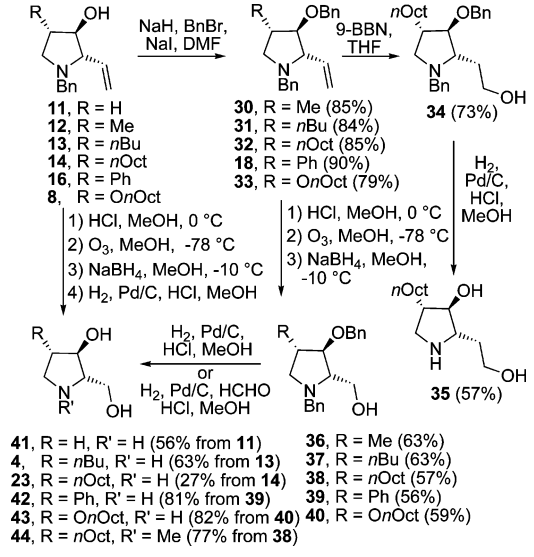
A putative mechanism to account for this side-reaction is proposed in Scheme 10. The mechanism for the ozonolysis in methanol is considered to start with the formation of a transient ozonide by 1,3-dipolar addition of ozone to olefin **A**. In the expected course of the reaction (path A), clockwise decomposition of this ozonide **B** would generate the likely unstable protonated amino aldehyde **C**, which, upon reaction with a hydride source, would deliver the free amino alcohol **D**. On the other hand, the presence of the reactive hydrogen of the ammonium salt might induce the fragmentation of the same ozonide **B** through a six-center mechanism (path B). The resulting imminium chloride **E** would then in turn be reduced to the devinylated pyrrolidine byproduct **F**.

Whereas this route to the imino sugar framework proved to be quite direct, its overall efficiency was lowered by the difficulty in purifying the desired primary alcohol, which required tedious reversed-phase HPLC separation from the devinylated byproduct. For reasons of practical convenience we thus decided to first *O*-benzylate the secondary alcohol of the starting olefins (Scheme 11). This protection did not significantly affect the course of the ozonolysis reaction and



Scheme 10. Putative mechanism for the ozonolysis reaction.

the desired 2-(hydroxymethyl)pyrrolidines were easily separated by routine chromatography. The 4-methyl, 4-butyl, and 4-octyl derivatives **36**, **37**, and **38** were thus secured in a straightforward manner (57–63% yields). To explore the structural requirements for GCS inhibition we also wished to generate some variation in the lipophilic portion of the structure of the inhibitor candidates. Therefore, the 4-phenyl and 4-octyloxy starting vinylpyrrolidines **16** and **8** were *O*-benzylated before being submitted to the aforementioned oxidative olefin cleavage (Scheme 11). Gratifyingly, the ozonolysis step smoothly delivered the corresponding 2-(hydroxymethyl)pyrrolidines **39** and **40** (56 and 59% yields, respectively).



Scheme 11. Preparation of the imino-sugar-based GCS inhibitor candidates.

To evaluate the influence of the hydroxymethyl fragment on the activity against the GCS, a homologue was also targeted. Thus, primary alcohol **34** was prepared by hydroboration of the olefin in the *O*-benzyl derivative **32** with 9-BBN (Scheme 11). The 2-hydroxyethyl derivative **34** was isolated in 73% yield.

The final hydrogenolysis step proceeded efficiently by using 10–12 bars of hydrogen and a catalytic amount of HCl, which delivered the targeted secondary amines in good yields, either directly from the 3-hydroxy derivatives (in the case of the 4-unsubstituted, 4-butyl, and 4-octyl compounds **41**, **4**, and **23**) or from the 3-benzyloxy intermediate (for the 4-phenyl and the 4-octyloxy compounds **42** and **43**; Scheme 11). The known imino sugar **41** was thus prepared in this way. To assess the influence of the substitution on the nitrogen atom of the pyrrolidine framework, an *N*-methyl derivative was prepared by a practical one-pot hydrogenolysis/reductive amination sequence (Scheme 11). Catalytic hydrogenation of the *N*-benzyl precursor **38** in the presence of aqueous formaldehyde delivered the expected *N*-methylpyrrolidine **44** in 77% yield.

Biological Evaluations

The five-membered-ring imino sugars were tested on a mouse melanoma B16 cell line. Melanoma is considered as a radiation-, immunotherapy-, and chemotherapy-refractory neoplasm. Moreover, melanoma cells show dysfunction in the apoptotic program, providing exciting new targets for rationally designed anti-melanoma therapeutic strategies.

The first set of experiments aimed at evaluating the in situ GCS activity by incubating intact living cells with a fluorescent analogue of ceramide (Table 2). The new structures **35**, **42**, **43**, and **44** were thus compared with the 4-octyl derivative **23**, which exhibited 50% inhibition at 10 μM, which is five times greater than that of *N*-butyl-1-deoxynojirimycin (50% at 50 μM, data not shown) under the same conditions.

Table 2. Inhibition of glucosylceramide synthase (GCS).[a]

Conc. [μM]	% Inhibition[b]				
	23	**35**	**42**	**43**	**44**
5	29	n.i.	n.d.	n.i.	n.i.
10	47	n.i.	n.d.	20	n.i.
25	76	n.i.	n.i.	39	n.i.

[a] See the Supporting Information for experimental details. [b] n.i.: no inhibition; n.d.: not determined.

As Table 2 shows, of the four analogues of **23** evaluated, only the octyl ether **43** exerted an inhibitory effect, although somewhat lower than its *C*-alkyl counterpart. The absence of activity of the 4-phenyl derivative **42** and the homologue **35** further illustrates the importance of the two structural elements, the C4 aliphatic chain and the hydroxymethyl appendage. The fact that the more basic *N*-methyl derivative **44** was also inactive could be attributed to either steric or coulombic factors.

We next investigated the cytotoxic effect of five-membered-ring imino sugars **23**, **35**, and **42**–**44** on melanoma cells. As Table 3 indicates, compounds **23** and **43** exhibited

a dose-dependent cytotoxic action after 24 h incubation. Derivative **23** displayed a strong cytotoxicity with an IC_{50} of less than 5 μM. These cell viability data parallel those of GCS inhibition and it is worth noting that a slight modification in the structure of **23**, such as in **35**, **43**, or **44**, alter both its GCS inhibitory and cytotoxic effects.

Table 3. Cytotoxic effects of imino-sugar-based sphingolipid compounds on melanoma cells.[a]

	% Viability[b,c]				
Conc. [μM]	**23**	**35**	**42**	**43**	**44**
1	97 ± 7	101 ± 3	n.d.	112 ± 11	116 ± 17
2	60 ± 8	98 ± 6	n.d.	91 ± 7	118 ± 17
5	38 ± 6	97 ± 1	n.d.	30 ± 7	122 ± 16
10	27 ± 5	104 ± 10	n.d.	29 ± 8	115 ± 17
25	26 ± 9	91 ± 12	n.d.	25 ± 9	117 ± 12
50	14 ± 0	61 ± 1	113 ± 10	18 ± 1	119 ± 17

[a] See the Supporting Information for experimental details. [b] Data are expressed as a percentage of the values of untreated cells and are presented as mean ±S.E.M. [c] n.d.: indicates not determined.

We then focused on the 4-octyl compound **23** to further characterize its effect on melanoma cells. In this regard, we explored whether **23** could affect tumor cell progression. As illustrated in Figure 9 (left-hand graph), caspase-3-like activity, as measured by the cleavage of the fluorogenic tetrapeptide substrate Ac-DEVD-AMC, increased in murine B16 melanoma cells within 6 h post-treatment. Increased pro-apoptotic sphingolipid ceramide content was also observed, which suggests that derivative **23** is able to trigger ceramide-mediated apoptotic cell death in melanoma cells (Figure 9, middle graph).

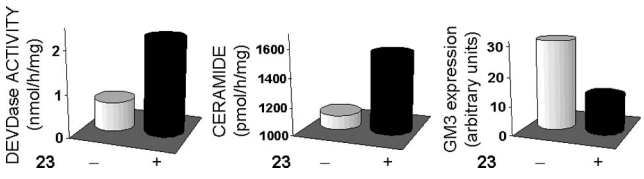


Figure 9. Effect of imino sugar **23** on caspase-3-like activity, ceramide cell content, and GM3 expression. B16 mouse melanoma cells were incubated for 6 h in the absence (−) or presence (+) of 10 μM (left and middle) or 50 μM (right) **23**. Cells were then harvested, and caspase-3-like activity (left), intracellular ceramide content (middle) and GM3 expression (right) were determined.

Finally, as GCS is a key enzyme in membrane sialic acid containing glycosphingolipid biosynthesis, that has long been associated with tumor malignancy and metastasis, we next investigated the effect of **23** on the expression of the monosialoganglioside GM3 at the cell surface. As can be seen in Figure 9 (right-hand graph), the treatment of B16 cells with **23** strongly reduced GM3 expression, which suggests that this compound could interfere in melanoma progression.

Conclusions

The oxirane ring-opening reaction of the pivotal epoxypyrrolidine **1** has proved highly general. It was equally efficient whether a carbon- or a heteroatom-centered nucleophile was used, affording flexible access to a wide range of all-*trans* trisubstituted pyrrolidine derivatives. Notably, the observed level of regiocontrol was also consistently good, the observed ratio between the two isomers always being greater than 90:10. The preponderant formation of the C4 ring-opened product was proved unambiguously by crystallographic analysis of six examples. The reaction mechanism of the oxirane ring-opening reaction with ammonia was investigated by DFT calculations. The nucleophilic attack of C4 was found to be both thermodynamically and kinetically favored and the steric control exerted by the vinyl substituent was confirmed. The synthetic potential of the key oxirane ring-opening reaction of epoxypyrrolidine **1** was illustrated by the straightforward preparation of several five-membered-ring imino sugars devised as sphingolipid mimics. The biological evaluation of five of the derivatives on melanoma cells delineated the structural requirements for activity, that is, the presence of the aliphatic chain, the hydroxymethyl appendage, and the secondary amine. The most potent compound **23**, which displayed pronounced cytotoxicity, was also shown to strongly inhibit GCS activity and to enhance ceramide content, which suggests that it is able to trigger apoptosis by interfering with the sphingolipid metabolism.

Experimental Section

General: Unless otherwise stated, all reactions requiring anhydrous conditions were carried out under nitrogen. The following solvents and reagents were dried prior to use: CH_2Cl_2, MeOH, DMF (from calcium hydride), 1,2-dimethoxyethane, Et_2O, petroleum ether, THF, toluene (freshly distilled from sodium/benzophenone), and Et_3N (from calcium hydride, stored over potassium hydroxide pellets). Analytical thin-layer chromatography (TLC) was performed by using Merck silica gel $60F_{254}$ precoated plates. Chromatograms were observed under UV light and/or were visualized by heating plates that had been dipped in 10% phosphomolybdic acid in ethanol or Dragendorff reagent. Standard column chromatography was performed with SDS 70–200 μm silica gel. Flash column chromatography was carried out with SDS 35–70 μm silica gel. LC–MS analyses and preparative HPLC purifications were performed by using a Waters Autopurif apparatus. Analytical HPLC analyses were performed with an Alliance 2695 pump and a PDA 2996 UV detector. NMR spectroscopic data were obtained with Bruker Advance 300, ARX 400, and Advance 500 spectrometers operating at 300, 400, and 500 MHz, respectively, for ^1H NMR analysis, and at 75, 100, and 125 MHz, respectively, for ^{13}C NMR analysis. Chemical shifts are quoted in parts per million (ppm) relative to the residual solvent peak and coupling constants are given in hertz. Infrared (IR) spectra were recorded with a Perkin-Elmer FT-IR 1725X spectrometer. Mass spectra (MS) were obtained with a ThermoQuest TSQ 7000 spectrometer. High-resolution mass spectra (HRMS) recorded with a ThermoFinnigan MAT 95 XL spectrometer. Optical rotations were measured with a Perkin-Elmer model 241 spectrometer.

(2*S*,3*S*,4*S*)-1-Benzyl-4-butoxy-2-vinylpyrrolidin-3-ol (7): $Yb(CF_3SO_3)_3$ (44.7 mg, 0.04 mmol) was added to a solution of **1** (49.5 mg, 0.25 mmol) in *n*-butanol (1.5 mL). The mixture was stirred at 60 °C for 48 h. The reaction was then quenched by the addition of satu-

rated aqueous NH_4Cl (5.0 mL) and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were then washed with brine, dried with Na_2SO_4, filtered, and the solvents evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 90:10) to give **7** (54.8 mg, 81%) as a pale-yellow oil. R_f = 0.15 (petroleum ether/EtOAc, 90:10). $[\alpha]_D^{25}$ = –12 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 7.3 Hz, 3 H), 1.23–1.37 (m, 2 H), 1.46–1.55 (m, 2 H), 1.92 (br. s, 1 H), 2.52 (dd, ^2J = 10.7, ^3J = 7.6 Hz, 1 H), 2.75 (pseudo-t, $^3J \approx {}^3J \approx$ 8.0 Hz, 1 H), 2.86 (dd, ^2J = 10.7, ^3J = 2.5 Hz, 1 H), 3.14 (d, ^2J = 13.5 Hz, 1 H), 3.38 (AB part of an ABX_2 system, ^2J = 8.0, ^3J = 6.7, δa – δb = 27.0 Hz, 2 H), 4.05 (ddd, ^3J = 7.6, ^3J = 4.0, ^3J = 2.6 Hz, 1 H), 3.90 (dd, ^3J = 7.4, ^3J = 4.0 Hz, 1 H), 3.92 (d, ^2J = 13.5 Hz, 1 H), 5.28 (dd, ^3J = 10.1, ^2J = 1.8 Hz, 1 H), 5.34 (ddd, ^3J = 17.2, ^2J = 1.8, ^4J = 0.5 Hz, 1 H), 5.84 (ddd, ^3J = 17.2, ^3J = 10.1, ^3J = 8.6 Hz, 1 H), 7.28–7.19 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 19.3, 31.9, 56.8, 57.5, 69.5, 74.3, 81.8, 83.8, 119.6, 126.9, 128.1, 128.9, 138.1 ppm. IR (neat): $\tilde{\nu}$ = 3399 (O–H), 1644 (C=C), 1099 (C–O) cm^{-1}. MS (ESI+): m/z (%) = 276 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{17}H_{26}NO_2$ 276.1964; found 276.1967.

(2*S*,3*S*,4*S*)-1-Benzyl-4-(octyloxy)-2-vinylpyrrolidin-3-ol (8): $Yb(CF_3SO_3)_3$ (120 mg, 0.19 mmol) was added to a solution of **1** (100 mg, 0.50 mmol) in *n*-octanol (3 mL). The reaction mixture was stirred at 80 °C for 48 h. The reaction was then quenched by the addition of a saturated aqueous NH_4Cl solution (10.0 mL) and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were then washed with brine, dried with Na_2SO_4, and filtered. The solvent was first evaporated and the excess *n*-octanol was distilled off in a kugelrohr apparatus (T<50 °C/1 mm of Hg). The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 90:10) to give **8** (127.6 mg, 78%) as a pale-yellow oil. R_f = 0.24 (petroleum ether/EtOAc, 90:10). $[\alpha]_D^{25}$ = +8 (c = 1.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, ^3J = 6.7 Hz, 3 H), 1.20–1.28 (m, 10 H), 1.47–1.56 (m, 2 H), 2.28 (br. s, 1 H), 2.51 (dd, ^2J = 10.7, ^3J = 7.5 Hz, 1 H), 2.75 (pseudo-t, $^3J \approx {}^3J \approx$ 8.0 Hz, 1 H), 2.86 (dd, ^2J = 10.7, ^3J = 2.4 Hz, 1 H), 3.13 (d, ^2J = 13.4 Hz, 1 H), 3.37 (AB part of an ABX_2 system, ^2J = 9.2, ^3J = 6.8, δa – δb = 28.5 Hz, 2 H), 3.73 (ddd, ^3J = 7.6, ^3J = 4.0, ^3J = 2.4 Hz, 1 H), 3.90 (dd, ^3J = 7.5, ^3J = 4.0 Hz, 1 H), 3.92 (d, ^2J = 13.4 Hz, 1 H), 5.27 (dd, ^3J = 10.1, ^2J = 1.4 Hz, 1 H), 5.34 (dd, ^3J = 17.2, ^2J = 1.4 Hz, 1 H), 5.84 (ddd, ^3J = 17.2, ^3J = 10.1, ^3J = 8.6 Hz, 1 H), 7.17–7.30 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 26.1, 29.2, 29.4, 29.8, 31.8, 56.8, 57.5, 69.8, 74.3, 81.8, 83.8, 119.4, 126.9, 128.1, 128.9, 138.2 ppm. IR (neat): $\tilde{\nu}$ = 3419 (O–H), 1604 (C=C), 1100 (C–O) cm^{-1}. MS (ESI+): m/z (%) = 332 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{21}H_{34}NO_2$ 332.2590; found 332.2583.

(2*S*,3*R*,4*S*)-1-Benzyl-4-(benzylamino)-2-vinylpyrrolidin-3-ol (9): Benzylamine (81 μL, 0.75 mmol) was added to a solution of **1** (50.0 mg, 0.25 mmol) in water/2-methoxyethanol (1:1; 200 μL). The mixture was allowed to react at 65 °C for 72 h before water (1.0 mL) was added. The aqueous phase was extracted four times with EtOAc. The combined organic phases were then washed with brine, dried with Na_2SO_4, filtered, and the solvents evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (petroleum ether/*i*PrOH, 95:5 to 70:30, 0.15% Et_3N) to give **9** (58.8 mg, 76%) as a white solid. R_f = 0.35 (petroleum ether/*i*PrOH, 80:20, 0.15% Et_3N). $[\alpha]_D^{25}$ = +94 (c = 1.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.48 (dd, ^2J = 10.1, ^3J = 7.9 Hz, 1 H), 2.73 (pseudo-t, $^3J \approx {}^3J \approx$ 7.7 Hz, 1 H), 2.75 (dd, ^2J = 10.1, ^3J = 3.0 Hz, 1 H), 2.96–3.01 (m, 1 H), 3.08 (d, ^2J = 13.3 Hz, 1 H), 3.64 (s, 2 H), 3.72 (dd, ^3J = 7.1, ^3J = 4.6 Hz, 1 H), 3.92 (d, ^2J = 13.3 Hz, 1 H), 5.22 (dd, ^3J = 10.1, ^2J = 1.8 Hz, 1 H), 5.31 (dd, ^3J = 17.2, ^2J = 1.8 Hz, 1 H), 5.77 (ddd, ^3J = 17.2, ^3J = 10.1, ^3J = 8.4 Hz, 1 H), 7.15–7.29 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.0, 56.7, 57.5, 63.3, 74.6, 81.9, 119.0, 126.8, 127.0, 128.1, 128.3, 128.4, 128.7, 138.5, 139.5 ppm. IR (neat): $\tilde{\nu}$ = 3264, 3229 (O–H, N–H), 1644 (C=C), 1601 (aromatic C=C) 1070 (C–O) cm^{-1}. MS (DCI/NH_3): m/z (%) = 309 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{20}H_{25}N_2O$ 309.1967; found 309.1967.

(2*S*,3*S*,4*S*)-1-Benzyl-4-bromo-2-vinylpyrrolidin-3-ol (10): $MgBr_2$ was freshly prepared by adding dropwise Mg^0 to a solution of 1,2-dibromoethane (82 mg, 0.44 mmol) in Et_2O (1.3 mL) at room temp. under an inert atmosphere. The reaction mixture was stirred until complete consumption of the metal. The resulting solution of $MgBr_2$ was added to a solution of **1** (49.4, 0.25 mmol) in Et_2O (1.5 mL). The reaction mixture was stirred at room temp. for 2 h and then washed with brine. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were then washed with brine, dried with Na_2SO_4, filtered, and the solvents evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 80:20) to give **10** (64.0 mg, 93%) as a dark-brown oil. R_f = 0.28 (petroleum ether/EtOAc, 80:20). $[\alpha]_D^{25}$ = +91 (c = 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.83 (m, 1 H), 3.03 (AB part of an ABX system, ^2J = 11.6, ^3J = 7.8, ^3J = 3.6, δa – δb = 62.3 Hz, 2 H), 3.23 (d, ^2J = 13.6 Hz, 1 H), 3.96 (d, ^2J = 13.6 Hz, 1 H), 4.05 (ddd, ^3J = 7.8, ^3J = 4.5, ^3J = 3.6 Hz, 1 H), 4.23 (dd, ^3J = 6.7, ^3J = 4.6 Hz, 1 H), 5.29 (dd, ^3J = 10.1, ^2J = 1.6 Hz, 1 H), 5.36 (ddd, ^3J = 17.2, ^2J = 1.6, ^4J = 0.6 Hz, 1 H), 5.84 (ddd, ^3J = 17.2, ^3J = 10.1, ^3J = 8.4 Hz, 1 H), 7.33–7.21 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.6, 56.8, 59.7, 74.2, 84.6, 119.9, 127.1, 128.3, 128.7, 137.2, 137.7 ppm. IR (neat): $\tilde{\nu}$ = 3358 (O–H), 1644 (C=C), 700 (C–Br) cm^{-1}. MS (ESI+): m/z (%) = 282 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{13}H_{17}NOBr$ 282.0494; found 282.0499.

(2*S*,3*R*)-1-Benzyl-2-vinylpyrrolidin-3-ol (11): A solution of **1** (200 mg, 0.99 mmol) in Et_2O (6.0 mL) was added to a suspension of $LiAlH_4$ (119 mg, 2.98 mmol) in Et_2O (19.0 mL) at 0 °C under an inert atmosphere. The reaction mixture was stirred for 2 h at room temperature before being quenched by the sequential addition of water (120 μL), 15% aqueous NaOH (120 μL), and more water (360 μL). The mixture was then filtered through Celite and the solvent evaporated off. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 100:0 to 95:5, 0.15% Et_3N) to give **11** (199 mg, 99%) as a white solid. R_f = 0.20 (CH_2Cl_2/MeOH, 95:5, 0.15% Et_3N). $[\alpha]_D^{25}$ = +64 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.61 (dddd, ^2J = 13.2, ^3J = 8.8, ^3J = 4.3, ^3J = 2.9 Hz, 1 H), 2.12 (pseudo-qd, ^2J = 13.2, $^3J \approx {}^3J \approx {}^3J \approx$ 8.5 Hz, 1 H), 2.34 (br. s, 1 H), 2.38 (pseudo-q, $^2J \approx {}^3J \approx {}^3J \approx$ 8.9 Hz, 1 H), 2.72 (dd, ^3J = 8.4, ^3J = 5.8 Hz, 1 H), 2.83 (td, $^2J = {}^3J$ = 8.9, ^3J = 2.9 Hz, 1 H), 3.17 (d, ^2J = 13.1 Hz, 1 H), 3.91 (d, ^2J = 13.1 Hz, 1 H), 3.97–4.04 (m, 1 H), 5.25 (dd, ^3J = 10.1, ^2J = 1.9 Hz, 1 H), 5.34 (ddd, ^3J = 17.2, ^2J = 1.9, ^4J = 0.7 Hz, 1 H), 5.79 (ddd, ^3J = 17.2, ^3J = 10.1, ^3J = 8.4 Hz, 1 H), 7.18–7.31 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.0, 50.7, 57.8, 76.3 (2 peaks), 118.8, 126.9, 128.1, 128.9, 138.3, 138.5 ppm. IR (neat): $\tilde{\nu}$ = 3367 (O–H), 1641 (C=C), 1604 (aromatic C=C) cm^{-1}. MS (DCI/NH_3): m/z (%) = 204 (100) $[MH]^+$. HRMS (DCI/NH_3): calcd. for $C_{13}H_{18}NO$ 204.1388; found 204.1389.

General Procedure A: The cuprate R_2CuLi was prepared by adding dropwise the alkyllithium solution to a 0.25 M suspension of CuI (0.5 equiv/mmol of RLi) in Et_2O at 0 °C under an inert atmosphere. The solution was then cooled to –20 °C before a 0.4 M solution of

epoxide in Et_2O was added. The reaction mixture was stirred at this temperature, unless otherwise stated, until TLC analysis showed the disappearance of the starting material. The reaction was then quenched by the addition of a saturated aqueous NH_4Cl solution (4.0 mL/mmol of epoxide). The mixture was then allowed to warm to room temp. under vigorous stirring while a 30% ammonium hydroxide solution was added until the aqueous layer had turned dark blue and limpid. The aqueous phase was extracted with Et_2O. The combined organic phases were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure.

(2*S*,3*R*,4*S*)-1-Benzyl-4-methyl-2-vinylpyrrolidin-3-ol (12): Epoxypyrrolidine **1** (100 mg, 0.50 mmol) was treated with Me_2CuLi (2.0 equiv.) according to general procedure A. Me_2CuLi was prepared by using a 1.6 M MeLi solution in Et_2O. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 90:10 to 50:50) to give **12** (83.2 mg, 77%) as a colorless oil. R_f = 0.21 (petroleum ether/EtOAc, 70:30). $[\alpha]_D^{25}$ = +108 (c = 1.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (d, ^3J = 6.9 Hz, 3 H), 1.92–2.02 (m, 1 H), 2.57 (AB part of an ABX system, $^2J \approx {}^3J \approx 9.5$, ^3J = 4.9, δa – δb = 29.9 Hz, 2 H), 2.79–2.83 (m, 1 H), 3.18 (d, ^2J = 13.3 Hz, 1 H), 3.52 (pseudo-t, $^3J \approx {}^3J \approx$ 6.6 Hz, 1 H), 3.91 (d, ^2J = 13.3 Hz, 1 H), 5.25 (dd, ^3J = 10.1, ^2J = 1.8 Hz, 1 H), 5.33 (dd, ^3J = 17.2, ^2J = 1.8 Hz, 1 H), 5.80 (ddd, ^3J = 17.2, ^3J = 10.1, ^3J = 8.5 Hz, 1 H), 7.18–7.29 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6, 39.1, 57.7, 57.9, 76.1, 83.1, 118.9, 126.8, 128.1, 128.8, 138.9, 139.0 ppm. IR (neat): $\tilde{\nu}$ = 3391 (O–H), 1640 (C=C), 1600 (aromatic C=C), 1263 (C–O) cm^{-1}. MS (DCI/NH_3): m/z (%) = 218 (100) $[MH]^+$. HRMS (DCI/NH_3): calcd. for $C_{14}H_{20}NO$ 218.1545; found 218.1544.

(2*S*,3*R*,4*S*)-1-Benzyl-4-butyl-2-vinylpyrrolidin-3-ol (13): Epoxypyrrolidine **1** (100 mg, 0.50 mmol) was treated with nBu$_2$CuLi (1.5 equiv.) according to general procedure A. nBu$_2$CuLi was prepared by using a 1.6 M nBuLi solution in hexane. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 85:15 to 50:50) to give **13** (81.0 mg, 63%) as a white solid. R_f = 0.20 (petroleum ether/EtOAc, 80:20). $[\alpha]_D^{25}$ = +113 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 6.9 Hz, 3 H), 1.24–1.43 (m, 5 H), 1.56–1.64 (m, 1 H), 1.86–1.95 (m, 1 H), 2.59–2.67 (m, 2 H), 2.84–2.88 (m, 1 H), 3.24 (d, ^2J = 13.4 Hz, 1 H), 3.62–3.65 (m, 1 H), 3.98 (d, ^2J = 13.4 Hz, 1 H), 5.31 (dd, ^3J = 10.1, ^2J = 1.8 Hz, 1 H), 5.39 (ddd, ^3J = 17.3, ^2J = 1.8, ^4J = 0.7 Hz, 1 H), 5.85 (ddd, ^3J = 17.3, ^3J = 10.1, ^3J = 8.6 Hz, 1 H), 7.24–7.37 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.8, 30.2, 33.9, 44.5, 56.4, 57.7, 75.9, 81.7, 118.9, 126.7, 128.1, 128.7, 138.8, 139.0 ppm. IR (neat): $\tilde{\nu}$ = 3416 (O–H), 1643 (C=C), 1604 (aromatic C=C), 1265 (C–O) cm^{-1}. MS (DCI/NH_3): m/z (%) = 260 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{17}H_{26}NO$ 260.2014; found 260.2014.

(2*S*,3*R*,4*S*)-1-Benzyl-4-octyl-2-vinylpyrrolidin-3-ol (14): Epoxypyrrolidine **1** (100 mg, 0.50 mmol) was treated with n-Oct$_2$CuLi (2 equiv.) according to general procedure A. A freshly prepared 0.3 M n-OctLi solution in Et_2O was used for the preparation of n-Oct$_2$CuLi. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 90:10 to 80:20) to give **14** (94.5 mg, 60%) as a white solid. R_f = 0.23 (petroleum ether/EtOAc, 90:10). $[\alpha]_D^{25}$ = +90 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 7.0 Hz, 3 H), 1.22–1.41 (m, 13 H), 1.52–1.64 (m, 1 H), 1.77–1.95 (m, 2 H), 2.55–2.66 (m, 2 H), 2.79–2.85 (m, 1 H), 3.21 (d, ^2J = 13.4 Hz, 1 H), 3.62 (pseudo-t, $^3J \approx {}^3J \approx$ 6.6 Hz, 1 H), 3.97 (d, ^2J = 13.4 Hz, 1 H), 5.30 (dd, ^3J = 10.1, ^2J = 1.8 Hz, 1 H), 5.38 (dd, ^3J = 17.2, ^2J = 1.8 Hz, 1 H), 5.83 (ddd, ^3J = 17.2, ^3J = 10.1, ^3J = 8.5 Hz, 1 H), 7.22–7.36 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.0, 29.3, 29.5, 29.7, 31.9, 34.2, 44.5, 56.5, 57.7, 76.0, 81.8, 118.9, 126.7, 128.1, 128.7, 138.9, 139.0 ppm. IR (neat): $\tilde{\nu}$ = 3219 (O–H), 1641 (C=C), 1091 (C–O) cm^{-1}. MS (DCI/NH_3): m/z (%) = 316 (100) $[MH]^+$. HRMS (DCI/NH_3): calcd. for $C_{21}H_{34}NO$ 316.2640; found 316.2639.

(2*S*,3*R*,4*S*)-1-Benzyl-2,4-divinylpyrrolidin-3-ol (15): Dimethyl sulfide (2.0 mL) and vinylmagnesium bromide (4.5 mL of a 1 M solution in THF, 4.50 mmol) were successively added to a suspension of CuBr·Me_2S (370 mg, 1.80 mmol) in Et_2O (10.0 mL) at –23 °C under an inert atmosphere. After stirring for 10 min, **1** (100 mg, 0.50 mmol) in Et_2O (1.0 mL) was added. The black heterogeneous mixture was allowed to react for 12 h whilst stirring at –23 °C. It was then poured into a saturated aqueous NH_4Cl solution (30.0 mL) at 0 °C, which had been adjusted to pH 8.5 by adding a 30% ammonium hydroxide solution. The aqueous layer was extracted with Et_2O and the combined organic phases were then washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 80:20 to 60:40) to give **15** (58.2 mg, 57% based on starting material recovering at 88% conversion) as a white solid. R_f = 0.19 (petroleum ether/EtOAc, 80:20). $[\alpha]_D^{25}$ = +114 (c = 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56–2.64 (m, 1 H), 2.76 (AB part of an ABX system, $^2J \approx {}^3J \approx 9.8$, ^3J = 5.1, δa – δb = 36.1 Hz, 2 H), 2.92 (pseudo-t, $^3J \approx {}^3J \approx$ 7.8 Hz, 1 H), 3.27 (d, ^2J = 13.4 Hz, 1 H), 3.77 (pseudo-t, $^3J \approx {}^3J \approx$ 6.9 Hz, 1 H), 3.99 (d, ^2J = 13.4 Hz, 1 H), 5.03 (ddd, ^3J = 10.1, ^2J = 1.7, ^4J = 0.8 Hz, 1 H), 5.12 (ddd, ^3J = 17.1, ^2J = 1.7, ^4J = 1.0 Hz, 1 H), 5.33 (dd, ^3J = 10.1, ^2J = 1.8 Hz, 1 H), 5.42 (ddd, ^3J = 17.2, ^2J = 1.8, ^4J = 0.7 Hz, 1 H), 5.81–5.90 (m, 2 H), 7.25–7.36 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.2, 55.7, 57.5, 75.0, 80.9, 115.4, 119.3, 126.9, 128.1, 128.8, 138.4 (2 peaks), 139.6 ppm. IR (neat): $\tilde{\nu}$ = 3358 (O–H), 1640 (C=C), 1604 (aromatic C=C) cm^{-1}. MS (DCI/NH_3): m/z (%) = 230 (100) $[MH]^+$. HRMS (DCI/NH_3): calcd. for $C_{15}H_{20}NO$ 230.1545; found 230.1544.

(2*S*,3*R*,4*S*)-1-Benzyl-4-phenyl-2-vinylpyrrolidin-3-ol (16): Epoxypyrrolidine **1** (50.2 mg, 0.25 mmol) was treated with Ph_2CuLi (5 equiv.) according to general procedure A at 0 °C. Ph_2CuLi was prepared by using a 1.9 M PheLi solution in dibutyl ether. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 90:10) to give **16** (41.2 mg, 59%) as a yellow oil. R_f = 0.20 (petroleum ether/EtOAc, 90:10). $[\alpha]_D^{25}$ = +89 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.81 (pseudo-t, $^2J \approx {}^3J \approx$ 9.9 Hz, 1 H), 2.99 (m, 3 H), 3.18 (d, ^2J = 13.4 Hz, 1 H), 3.92 (pseudo-t, $^3J \approx {}^3J \approx$ 6.9 Hz, 1 H), 4.01 (d, ^2J = 13.4 Hz, 1 H), 5.28 (ddd, ^3J = 10.4, ^2J = 1.6, ^4J = 0.4 Hz, 1 H), 5.38 (ddd, ^3J = 17.2, ^2J = 1.6, ^4J = 0.6 Hz, 1 H), 5.84 (ddd, ^3J = 17.2, ^3J = 10.1, ^3J = 8.4 Hz, 1 H), 7.31–7.20 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.7, 57.8, 58.4, 75.8, 84.0, 119.4, 126.4, 126.8, 127.4, 128.2, 128.5, 128.7, 138.6, 138.7, 144.0 ppm. IR (neat): $\tilde{\nu}$ = 3355 (O–H), 1602, 1643 (C=C) cm^{-1}. MS (ESI+): m/z (%) = 280 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{19}H_{22}NO$ 280.1701; found 280.1698.

(2*S*,3*R*,4*S*)-1-Benzyl-4-(trimethylsilylethynyl)-2-vinylpyrrolidin-3-ol (17): nBuLi (1.1 mL of a 1.3 M solution in hexane, 1.4 mmol), THF (1.3 mL), and $AlMe_3$ (0.28 mL of a 2.0 M solution in toluene, 0.56 mmol) were successively added to a cooled solution (ice/NaCl slurry) of trimethylsilylacetylene (0.19 mL, 1.4 mmol) in toluene (2 mL). The resulting mixture was treated with a solution of **1** (93.1 mg, 0.46 mmol) in toluene (1 mL) and heated to 65 °C for

48 h. A saturated aqueous NH_4Cl solution (5.0 mL) was then added and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and the solvents evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 98:2 to 95:5) to give **17** (41.3 mg, 30%) as an amorphous yellow solid. R_f = 0.25 (petroleum ether/EtOAc, 90:10). $[\alpha]_D^{25}$ = +60 (*c* = 1.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.1 (m, 9 H), 2.69–2.87 (m, 3 H), 2.92 (dd, ^3J = 8.4, ^3J = 4.1 Hz, 1 H), 3.23 (d, ^2J = 13.5 Hz, 1 H), 3.90 (d, ^2J = 13.5 Hz, 1 H), 3.99 (pseudo-t, $^3J \approx {}^3J \approx$ 6.2 Hz, 1 H), 5.27 (dd, ^3J = 10.1, ^2J = 1.4 Hz, 1 H), 5.33 (dd, ^3J = 17.2, ^2J = 1.4 Hz, 1 H), 5.82 (ddd, ^3J = 17.2, ^3J = 10.1, ^3J = 8.5 Hz, 1 H), 7.17–7.30 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.1, 37.5, 56.5, 57.0, 74.6, 81.8, 86.0, 107.5, 119.7, 127.0, 128.2, 128.8, 137.6, 138.2 ppm. IR (neat): $\tilde{\nu}$ = 3435 (O–H), 2166 (C≡C), 1603 (C=C) cm^{-1}. MS (ESI+): *m*/*z* (%) = 300 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{18}H_{26}NOSi$ 300.1784; found 300.1796.

Oxirane Ring-Opening Reaction with Ammonia: A solution of epoxypyrrolidine **1** (100.0 mg, 0.50 mmol) in NH_3-saturated methanol (1.5 mL) was heated at 55 °C in a sealed reaction vessel for 1 week. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (EtOAc/MeOH, 90:10, 0.8% NH_4OH) to give the starting epoxide **1** (12.2 mg, 0.06 mmol), the minor compound **21** (11.4 mg, 12% based on starting material recovering at 88% conversion), and a mixture of the regioisomers **19** and **20** (64.0 mg, 67% based on starting material recovering at 88% conversion).

Bis[(2*S*,3*R*,4*S*)-1-benzyl-3-hydroxy-2-vinylpyrrolidin-4-yl]amine (21): R_f = 0.40 (EtOAc/MeOH, 92:8, 0.8% NH_4OH). $[\alpha]_D^{25}$ = +124 (*c* = 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.90–2.18 (br. s, 3 H), 2.53–2.56 (m, 2 H), 2.72 (pseudo-t, $^3J \approx {}^3J \approx$ 8.1 Hz, 1 H), 3.02 (d, ^2J = 13.2 Hz, 1 H), 3.15–3.20 (m, 1 H), 3.77 (dd, ^3J = 7.5 Hz, 1 H), 3.88 (d, ^2J = 13.2 Hz, 1 H), 5.25 (dd, ^3J = 10.1, ^2J = 1.8 Hz, 1 H), 5.32 (dd, ^3J = 17.1, ^2J = 1.8 Hz, 1 H), 5.76 (ddd, ^3J = 17.1, ^3J = 10.1, ^3J = 8.4 Hz, 1 H), 7.13–7.24 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 57.6, 57.9, 60.6, 75.0, 81.1, 119.7, 127.0, 128.2, 128.9, 138.1, 138.2 ppm. IR (neat): $\tilde{\nu}$ = 3367 (O–H, N–H), 1643 (C=C), 1601 (aromatic C=C) 1073 (C–O) cm^{-1}. MS (DCI/CH_4): *m*/*z* (%) = 448 (24) $[MC_2H_5]^+$, 420 (100) $[MH]^+$. HRMS (CI+): calcd. for $C_{26}H_{34}N_3O$ 420.2651; found 420.2635.

The major fraction was analyzed by LC–MS (Sunfire C18 column, 5 μm, 4.6 × 150 mm, eluted with a 90:10 to 30:70 gradient of 0.1 aqueous trifluoroacetic acid/0.1 trifluoroacetic acid in CH_3CN at 1 mL/min; t_R = 7.4 min for the minor component and 9.4 min for the major component), which allowed identification of the two isomers at *m*/*z* = 219. A 94:6 ratio was deduced (based on UV absorption at 260 nm) by analytical HPLC of this mixture (Sunfire C18 5 μm 4.6 × 150 mm column, eluted with a 90:10 to 30:70 gradient of 0.1% aqueous trifluoroacetic acid/0.1% trifluoroacetic acid in CH_3CN at 1 mL/min; t_R = 6.3 min for the minor component and 8.6 min for the major component). Preparative HPLC (Sunfire C18 column, 5 μm, 19 × 150 mm, eluted with a 90:10 to 49:51 gradient of 0.1% aqueous trifluoroacetic acid/0.1% trifluoroacetic acid in CH_3CN at 20 mL/min) allowed separation of the two isomers.

(3*S*,4*S*,5*S*)-4-Amino-1-benzyl-5-vinylpyrrolidin-3-ol (20) (Trifluoroacetate Salt): Isolated as the minor product (3.0 mg). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.59 (dd, ^3J = 11.0, ^3J = 5.4 Hz, 1 H), 3.41 (dd, ^3J = 11.1, ^3J = 6.4 Hz, 1 H), 3.56 (dd, ^3J = 6.7, ^3J = 3.9 Hz, 1 H), 3.67 (d, ^2J = 12.9 Hz, 1 H), 3.93 (pseudo-t, $^3J \approx {}^3J \approx$ 7.8 Hz, 1 H), 4.10 (d, ^2J = 13.1 Hz, 1 H), 4.24 (dd, ^3J = 9.9, ^3J = 5.8 Hz, 1 H), 4.75 (br. s, 4 H), 5.51 (d, ^3J = 16.8 Hz, 1 H), 5.52 (d, ^3J = 10.8 Hz, 1 H), 5.78 (pseudo-td, ^3J = 17.7, $^3J \approx {}^3J \approx$ 9.0 Hz, 1 H), 7.23–7.35 (m, 5 H) ppm. MS (ESI+): *m*/*z* (%) = 219 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{13}H_{19}N_2O$ 219.1497; found 219.1494.

(2*S*,3*R*,4*S*)-4-Amino-1-benzyl-2-vinylpyrrolidin-3-ol (19) (Trifluoroacetate Salt): Isolated as the major product 50.0 mg). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.49–2.67 (m, 2 H), 2.78 (pseudo-t, $^3J \approx {}^3J \approx$ 7.7 Hz, 1 H), 3.11 (d, ^2J = 13.2 Hz, 1 H), 3.24–3.34 (m, 1 H), 3.79 (dd, ^3J = 6.8, ^3J = 3.8 Hz, 1 H), 3.92 (d, ^2J = 13.2 Hz, 1 H), 5.29 (dd, ^3J = 10.1, ^2J = 1.4 Hz, 1 H), 5.36 (dd, ^3J = 17.1, ^2J = 1.1 Hz, 1 H), 5.72 (ddd, ^3J = 17.3, ^3J = 10.0, ^3J = 8.5 Hz, 1 H), 5.83 (br. s, 4 H), 7.17–7.33 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.6, 56.6, 56.8, 74.1, 80.3, 116.4 (q, $^1J_{C,F}$ = 292.1 Hz), 127.4, 128.5, 129.0, 136.8, 137.2, 162.4 (q, $^2J_{C,F}$ = 34.7 Hz) ppm.

(2*S*,3*R*,4*S*)-4-Amino-1-benzyl-2-vinylpyrrolidin-3-ol (19): Treatment with Dowex 50WX8–200 ion-exchange resin of the major fraction afforded the free base of **19** (30.0 mg) as a white solid. R_f = 0.24 (EtOAc/MeOH, 90:10, 1.6% NH_4OH). $[\alpha]_D^{25}$ = +118 (*c* = 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.80–2.10 (m, 3 H), 2.61–2.69 (m, 2 H), 2.79 (pseudo-t, $^3J \approx {}^3J \approx$ 7.4 Hz, 1 H), 3.11–3.19 (m, 2 H), 3.66 (dd, ^3J = 6.6, ^3J = 4.3 Hz, 1 H), 3.97 (d, ^2J = 13.3 Hz, 1 H), 5.28 (dd, ^3J = 10.1, ^2J = 1.7 Hz, 1 H), 5.38 (dd, ^3J = 17.2, ^2J = 1.6 Hz, 1 H), 5.85 (ddd, ^3J = 17.2, ^3J = 10.1, ^3J = 8.3 Hz, 1 H), 7.20–7.35 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 57.5, 57.7, 60.1, 75.1, 83.8, 118.8, 126.9, 128.2, 128.8, 138.6 ppm. IR (neat): $\tilde{\nu}$ = 3348, 3287 (O–H, N–H), 1667 (N–H), 1639 (C=C), 1604 (aromatic C=C), 1074 (C–O) cm^{-1}. MS (DCI/NH_3): *m*/*z* (%) = 219 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{13}H_{19}N_2O$ 219.1497; found 219.1517.

General Procedure B – Ozonolysis: A methanolic HCl solution was prepared by the slow addition of acetyl chloride (355 μL, 5.00 mmol) to anhydrous MeOH (5.00 mmol) under an inert atmosphere. A 1 M methanolic HCl solution (10 equiv.) was added to a 0.08 M solution of the vinylpyrrolidine in MeOH under an inert atmosphere at 0 °C. The resulting mixture was then stirred for 30 min at this temperature and the solvents evaporated to dryness. The residue was then taken up in MeOH (17 mL/mmol) and cooled to –78 °C. Ozone was then bubbled into the solution until it became bluish (3–5 min). $NaBH_4$ (20 equiv.) was then added portionwise and the mixture was vigorously stirred for 1 h at –78 °C and then at –10 °C overnight. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution. The MeOH was then evaporated off under reduced pressure before the aqueous phase was extracted with EtOAc. The combined organic phases were dried with Na_2SO_4, filtered, and the solvents evaporated to dryness.

Ozonolysis of Vinylpyrrolidine 11: Olefin **11** (70.0 mg, 0.34 mmol) was treated according to procedure B. The crude product was purified by flash column chromatography on silica gel (petroleum ether/*i*PrOH/Et_3N, 73:25:2) to give a mixture of **24** and byproduct **27**. Reversed-phase HPLC purification (XTerra MSC18 column, 5 μm, 100 × 19, 3 mM Et_3N in water/CH_3CN, 85:15, 15 mL/min) delivered **24** (48.3 mg, 68%) and **27** (1.8 mg, 3%).

(2*S*,3*R*)-1-Benzyl-2-(hydroxymethyl)pyrrolidin-3-ol (24): Colorless oil; R_f = 0.35 (petroleum ether/*i*PrOH/Et_3N, 73:25:2). $[\alpha]_D^{25}$ = +44 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, CD_3OD): δ = 1.68–1.74 (m, 1 H), 1.93–2.02 (m, 1 H), 2.53 (br. s, 2 H), 2.61–2.68 (m, 2 H), 2.96–3.00 (m, 1 H), 3.53 (d, ^2J = 13.0 Hz, 1 H), 3.64 (AB part of an ABX system, ^2J = 11.1, ^3J = 3.7, ^3J = 2.6, $\delta a - \delta b$ = 11.4 Hz, 2 H), 3.97 (d, ^2J = 13.0 Hz, 1 H), 4.31–4.34 (m, 1 H), 7.27–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.8, 52.0, 58.7, 60.5, 73.5, 75.0, 127.2, 128.4, 128.7, 138.6 ppm. IR (neat): $\tilde{\nu}$ = 3387 (O–H), 1645 (C=C) cm^{-1}. MS (DCI/NH_3): *m*/*z* (%) = 208 (100)

[MH]$^+$. HRMS (DCI/NH_3): calcd. for $C_{12}H_{18}NO_2$ 208.1338; found 208.1336.

(*R*)-1-Benzylpyrrolidin-3-ol (27): CAS Number: 775-15-5: R_f = 0.35 (petroleum ether/*i*PrOH/Et_3N, 73:25:2). ^{1}H NMR (300 MHz, CD_3OD): δ = 1.63–1.79 (m, 1 H), 2.07–2.21 (m, 1 H), 2.46 (dd, ^2J = 10.4, ^3J = 3.6 Hz, 1 H), 2.51–2.60 (m, 1 H), 2.68–2.74 (m, 1 H), 2.81 (dd, ^2J = 10.4, ^3J = 6.2 Hz, 1 H), 3.65 (AB system, ^2J = 12.5, δa – δb = 16.2 Hz, 2 H), 4.28–4.41 (m, 1 H), 7.21–7.43 (m, 5 H) ppm. MS (DCI/NH_3): *m*/*z* (%) = 178 (100) [MH]$^+$.

Ozonolysis of Vinylpyrrolidine 13: Olefin **13** (73.7 mg, 0.28 mmol) was treated according to general procedure B. The crude product was purified by flash column chromatography on silica gel (petroleum ether/*i*PrOH, 90:10 to 80:20, 0.15% Et_3N) to give a mixture of **25** and byproduct **28**. Reversed-phase HPLC purification (XTerra MSC18 column, 5 μm, 100 × 19, 3 mM Et_3N in water/CH_3CN, 65:35, 15 mL/min) delivered **25** (52.3 mg, 70%) and **28** (4.50 mg, 7%).

(2*S*,3*R*,4*S*)-1-Benzyl-4-butyl-2-(hydroxymethyl)pyrrolidin-3-ol (25): White solid; R_f = 0.4 (petroleum ether/*i*PrOH, 85:15, 0.15% Et_3N). $[a]_D^{25}$ = +68 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 7.0 Hz, 3 H), 1.23–1.35 (m, 5 H), 1.51–1.61 (m, 1 H), 1.87–1.96 (m, 1 H), 2.39–2.65 (m, 2 H), 2.62 (td, ^3J = 6.5, ^3J = 3.0 Hz, 1 H), 2.71 (AB part of an ABX system, $^2J \approx {}^3J \approx$ 10.1, ^3J = 5.5 Hz, δa – δb = 21.4 Hz, 2 H), 3.40 (d, ^2J = 13.3 Hz, 1 H), 3.74 (d, ^3J = 3.0 Hz, 2 H), 3.90 (pseudo-t, $^3J \approx {}^3J \approx$ 6.5 Hz, 1 H), 3.97 (d, ^2J = 13.3 Hz, 1 H), 7.26–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.8, 30.2, 32.8, 44.4, 57.1, 58.2, 59.0, 72.0, 78.4, 127.1, 128.4, 128.5, 138.5 ppm. IR (neat): $\tilde{\nu}$ = 3378 (O–H), 1643 (C=C), 1043 (C–O) cm^{-1}. MS (DCI/NH_3): *m*/*z* (%) = 264 (100) [MH]$^+$. HRMS (ESI+): calcd. for $C_{16}H_{26}NO_2$ 264.1964; found 264.1963.

(3*R*,4*S*)-1-Benzyl-4-butylpyrrolidin-3-ol (28): Colorless oil; R_f = 0.4 (petroleum ether/*i*PrOH, 85:15, 0.15% Et_3N). $[a]_D^{25}$ = +12 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 6.8 Hz, 3 H), 1.28–1.36 (m, 5 H), 1.47–1.52 (m, 1 H), 1.85–1.90 (m, 1 H), 1.96–2.07 (m, 1 H), 2.13 (br. s, 1 H), 2.47 (dd, ^2J = 10.2, ^3J = 5.5 Hz, 1 H), 2.81 (br. d, ^2J = 10.6 Hz, 1 H), 3.12 (pseudo-t, $^2J \approx {}^3J \approx$ 8.3 Hz, 1 H), 3.61 (s, 2 H), 3.87–3.90 (m, 1 H), 7.24–7.35 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.7, 30.2, 33.2, 48.6, 59.5, 60.2, 62.2, 77.4, 127.1, 128.3, 128.8, 138.5 ppm. MS (DCI/NH_3): *m*/*z* (%) = 234 (100) [MH]$^+$. HRMS (DCI/NH_3): calcd. for $C_{15}H_{24}NO$ 234.1858; found 234.1854.

Ozonolysis of Vinylpyrrolidine 14: Olefin **14** (73.0 mg, 0.23 mmol) was treated according to procedure B. The crude product was purified by flash column chromatography on silica gel (petroleum ether/*i*PrOH, 95:5 to 85:15, 0.15% Et_3N) to give a mixture of **26** and byproduct **29**. Reversed-phase HPLC purification (XTerra MSC18 column, 5 μm, 100 × 19, 3 mM Et_3N in water/CH_3CN, 45:55, 15 mL/min) delivered **26** (38.4 mg, 52%) and **29** (3.1 mg, 5%).

(2*S*,3*R*,4*S*)-1-Benzyl-2-(hydroxymethyl)-4-octylpyrrolidin-3-ol (26): White solid; R_f = 0.27 (petroleum ether/*i*PrOH, 90:10, 0.15% Et_3N). $[a]_D^{25}$ = +53 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79 (t, ^3J = 7.0 Hz, 3 H), 1.13–1.24 (m, 13 H), 1.38–1.53 (m, 1 H), 1.76–1.88 (m, 1 H), 2.50 (dt, ^3J = 6.8, ^3J = 2.7 Hz, 1 H), 2.60 (AB part of an ABX system, $^2J \approx {}^3J \approx$ 10.1, ^3J = 5.7 Hz, δa – δb = 15.9 Hz, 2 H), 2.88–3.04 (m, 2 H), 3.29 (d, ^2J = 13.3 Hz, 1 H), 3.63 (br. d, ^3J = 2.7 Hz, 2 H), 3.77 (pseudo-t, $^3J \approx {}^3J \approx$ 6.6 Hz, 1 H), 3.86 (d, ^2J = 13.3 Hz, 1 H), 7.14–7.26 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.0, 29.2, 29.5, 29.8, 31.8, 33.1, 44.3, 57.0, 58.2, 59.1, 71.9, 78.2, 127.1, 128.3, 128.5, 138.6 ppm. IR (neat): $\tilde{\nu}$ = 3401 (O–H), 1605 (C=C), 1050 (C–O) cm^{-1}. MS (DCI/NH_3): *m*/*z* (%) = 320 (100) [MH]$^+$. HRMS (DCI/NH_3): calcd. for $C_{20}H_{34}NO_2$ 320.2590; found 320.2588.

(3*R*,4*S*)-1-Benzyl-4-octylpyrrolidin-3-ol (29): Colorless oil; R_f = 0.27 (petroleum ether/*i*PrOH, 90:10, 0.15% Et_3N). $[a]_D^{25}$ = +7 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, ^3J = 7.0 Hz, 3 H), 1.15–1.25 (m, 13 H), 1.34–1.45 (m, 1 H), 1.74–1.79 (m, 1 H), 1.85–1.96 (m, 1 H), 2.03 (br. s, 1 H), 2.36 (dd, ^2J = 10.2, ^3J = 5.4 Hz, 1 H), 2.70 (br. d, ^2J = 10.2 Hz, 1 H), 3.02 (pseudo-t, $^2J \approx {}^3J \approx$ 8.3 Hz, 1 H), 3.51 (s, 2 H), 3.76–3.81 (m, 1 H), 7.10–7.25 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.7, 28.0, 29.3, 29.5, 29.7, 31.9, 33.5, 48.6, 59.4, 60.1, 62.1, 77.2, 127.2, 128.3, 128.9, 138.0 ppm. MS (DCI/NH_3): *m*/*z* (%) = 290 (100) [MH]$^+$. HRMS (DCI/NH_3): calcd. for $C_{19}H_{32}NO$ 290.2484; found 290.2484.

General Procedure C – *O*-Benzylation: Molecular sieves (4 Å, 30% w/w), NaI (0.04 equiv.), benzyl bromide (1.2 equiv.), and NaH (1.4 equiv.) were successively added to a 0.2 M solution of secondary alcohol in dry DMF at 0 °C under an inert atmosphere. The mixture was stirred at 0 °C for 10 min and then for 2.5 h at room temp. The reaction was quenched by the addition of water (2 mL/mmol). The aqueous layer was extracted with Et_2O. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and the solvents evaporated to dryness.

(2*S*,3*R*,4*S*)-1-Benzyl-3-(benzyloxy)-4-methyl-2-vinylpyrrolidine (30): Secondary alcohol **12** (93.0 mg, 0.43 mmol) was treated according to general procedure C. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 97:3 to 94:6) to give **30** (112 mg, 85%) as a colorless oil. R_f = 0.36 (petroleum ether/EtOAc, 95:5). $[a]_D^{25}$ = +103 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, ^3J = 7.1 Hz, 3 H), 1.97–2.10 (m, 1 H), 2.42–2.47 (m, 2 H), 2.87–2.92 (m, 1 H), 3.05 (d, ^2J = 13.4 Hz, 1 H), 3.35–3.38 (m, 1 H), 3.90 (d, ^2J = 13.4 Hz, 1 H), 4.49 (AB system, ^2J = 11.8 Hz, δa – δb = 12.8 Hz, 2 H), 5.16 (br. d, ^3J = 10.1 Hz, 1 H), 5.30 (d, ^3J = 17.2 Hz, 1 H), 5.75–5.86 (m, 1 H), 7.12–7.25 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 37.6, 57.3, 58.3, 71.9, 74.6, 91.1, 118.0, 126.7, 127.5, 127.6, 128.1, 128.3, 128.6, 138.5, 139.4, 139.6 ppm. IR (neat): $\tilde{\nu}$ = 1636, 1602 (C=C), 1264 (C–O) cm^{-1}. MS (DCI/NH_3): *m*/*z* (%) = 308 (100) [MH]$^+$. HRMS (DCI/NH_3): calcd. for $C_{21}H_{26}NO$ 308.2014; found 308.2015.

(2*S*,3*R*,4*S*)-1-Benzyl-3-(benzyloxy)-4-butyl-2-vinylpyrrolidine (31): Secondary alcohol **13** (66.3 mg, 0.26 mmol) was treated according to general procedure C. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 97.5:2.5 to 95:5) to give **31** (74.9 mg, 84%) as a colorless oil. R_f = 0.17 (petroleum ether/EtOAc, 95:5). $[a]_D^{25}$ = +90 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78 (t, ^3J = 6.9 Hz, 3 H), 1.05–1.46 (m, 6 H), 1.84–1.96 (m, 1 H), 2.46 (AB part of an ABX system, $^2J \approx {}^3J \approx$ 9.2, ^3J = 2.7 Hz, δa – δb = 37.1 Hz, 2 H), 2.90 (dd, ^3J = 8.2, ^3J = 6.1 Hz, 1 H), 3.06 (d, ^2J = 13.4 Hz, 1 H), 3.42–3.45 (m, 1 H), 3.90 (d, ^2J = 13.4 Hz, 1 H), 4.49 (AB system, ^2J = 11.7 Hz, δa – δb = 23.2 Hz, 2 H), 5.17 (dd, ^3J = 10.1, ^2J = 1.8 Hz, 1 H), 5.31 (dd, ^3J = 17.2, ^2J = 1.8 Hz, 1 H), 5.75–5.87 (m, 1 H), 7.11–7.30 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.7, 30.2, 34.0, 43.2, 56.5, 57.3, 71.9, 74.4, 89.7, 118.1, 126.6, 127.5, 127.7, 128.1, 128.3, 128.6, 138.6, 139.4, 139.8 ppm. IR (neat): $\tilde{\nu}$ = 1643, 1605 (C=C) cm^{-1}. MS (DCI/NH_3): *m*/*z* (%) = 350 (100) [MH]$^+$. HRMS (DCI/NH_3): calcd. for $C_{24}H_{32}NO$ 350.2484; found 350.2481.

(2*S*,3*R*,4*S*)-1-Benzyl-3-(benzyloxy)-4-octyl-2-vinylpyrrolidine (32): Secondary alcohol **14** (187.8 mg, 0.59 mmol) was treated according to general procedure C. The crude product was purified by flash

column chromatography on silica gel (petroleum ether/EtOAc, 99:1 to 95:5) to give **32** (203.6 mg, 85%) as a colorless oil. R_f = 0.38 (petroleum ether/EtOAc, 95:5). $[\alpha]_D^{25}$ = +56 (c = 1.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.82 (t, ^3J = 6.8 Hz, 3 H), 1.12–1.46 (m, 14 H), 1.87–1.97 (m, 1 H), 2.48 (AB part of an ABX system, $^2J \approx {}^3J \approx 9.2$, ^3J = 2.8 Hz, δa – δb = 38.8 Hz, 2 H), 2.92 (dd, ^3J = 8.3, ^3J = 6.0 Hz, 1 H), 3.07 (d, ^2J = 13.4 Hz, 1 H), 3.45 (dd, ^3J = 6.0, ^3J = 4.0 Hz, 1 H), 3.91 (d, ^2J = 13.4 Hz, 1 H), 4.51 (AB system, ^2J = 11.7 Hz, δa – δb = 26.2 Hz, 2 H), 5.18 (dd, ^3J = 10.1, ^2J = 1.8 Hz, 1 H), 5.33 (dd, ^3J = 17.2, ^2J = 1.8 Hz, 1 H), 5.82 (ddd, ^3J = 17.2, ^3J = 10.1, ^3J = 8.3 Hz, 1 H), 7.13–7.31 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.0, 29.3, 29.5, 29.6, 31.9, 34.3, 43.2, 56.5, 57.2, 71.9, 74.4, 89.7, 118.1, 126.6, 127.5, 127.7, 128.1, 128.3, 128.6, 138.6, 139.3, 139.8 ppm. IR (neat): $\tilde{\nu}$ = 1654, 1601 (C=C) cm^{-1}. MS (ESI+): m/z (%) = 406 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{28}H_{40}NO$ 406.3110; found 406.3109.

(2*S*,3*R*,4*S*)-1-Benzyl-3-(benzyloxy)-4-phenyl-2-vinylpyrrolidine (18): Secondary alcohol **16** (50.2 mg, 0.18 mmol) was treated according to general procedure C. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 99:1 to 98:2) to give **18** (60.2 mg, 90%) as a white solid. R_f = 0.25 (petroleum ether/EtOAc, 98:2). $[\alpha]_D^{25}$ = –5 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.89 (AB part of an ABX system, ^2J = ^3J = 9.4, ^3J = 3.6 Hz, δa – δb = 38.5 Hz, 2 H), 3.09–3.14 (m, 1 H), 3.15 (d, ^2J = 13.3 Hz, 1 H), 3.28–3.34 (m, 1 H), 3.89 (dd, ^3J = 6.7, ^3J = 4.6 Hz, 1 H), 4.11 (d, ^2J = 13.3 Hz, 1 H), 4.50 (AB system, ^2J = 11.8 Hz, δa – δb = 22.8 Hz, 2 H), 5.31 (dd, ^3J = 10.2, ^2J = 1.8 Hz, 1 H), 5.47 (ddd, ^3J = 17.2, ^2J = 1.8, ^4J = 0.4 Hz, 1 H), 5.95 (ddd, ^3J = 17.2, ^3J = 10.2, ^3J = 8.3 Hz, 1 H), 7.17–7.39 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.7, 57.6, 59.2, 72.2, 74.6, 92.1, 118.7, 126.1, 126.7, 127.4, 127.5, 127.6, 128.1, 128.2, 128.4, 128.6, 138.2, 139.0, 139.1, 145.8 ppm. IR (neat): $\tilde{\nu}$ = 1632, 1598 (C=C) cm^{-1}. MS (ESI+): m/z (%) = 370 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{26}H_{28}NO$ 370.2171; found 370.2151.

(2*S*,3*S*,4*S*)-1-Benzyl-3-(benzyloxy)-4-(octyloxy)-2-vinylpyrrolidine (33): Secondary alcohol **8** (75.6 mg, 0.23 mmol) was treated according to general procedure C. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 99:1 to 95:5) to give **33** (69.1 mg, 79%) as a colorless oil. R_f = 0.48 (petroleum ether/EtOAc, 90:10). $[\alpha]_D^{25}$ = +77 (c = 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.82 (t, ^3J = 7.0 Hz, 3 H), 1.14–1.30 (m, 10 H), 1.42–1.51 (m, 2 H), 2.36 (dd, ^2J = 10.5, ^3J = 6.1 Hz, 1 H), 2.80–2.88 (m, 2 H), 3.05 (d, ^2J = 13.4 Hz, 1 H), 3.20–3.33 (m, 2 H), 3.73–3.75 (m, 2 H), 3.93 (d, ^2J = 13.4 Hz, 1 H), 4.56 (s, 2 H), 5.22 (dd, ^3J = 10.1, ^2J = 1.5 Hz, 1 H), 5.33 (dd, ^3J = 17.3, ^2J = 1.5 Hz, 1 H), 5.85 (ddd, ^3J = 17.3, ^3J = 10.1, ^3J = 8.7 Hz, 1 H), 7.14–7.28 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 26.1, 29.2, 29.4, 29.7, 31.8, 56.7, 57.2, 69.5, 72.1, 72.8, 82.9, 89.2, 119.1, 126.8, 127.5, 127.7, 128.1, 128.2, 128.9, 138.2, 138.3, 138.7 ppm. IR (neat): $\tilde{\nu}$ = 1643, 1605 (C=C), 1099 (C–O) cm^{-1}. MS (ESI+): m/z (%) = 423 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{28}H_{40}NO_2$ 422.3059; found 422.3077.

[(2*S*,3*R*,4*S*)-1-Benzyl-3-(benzyloxy)-4-methylpyrrolidin-2-yl]methanol (36): Vinylpyrrolidine **30** (83.0 mg, 0.27 mmol) was treated according to general procedure B. The crude product was purified by flash column chromatography on silica gel (petroleum ether/*i*PrOH, 95:5 to 90:10, 0.15% Et_3N) to give **36** (53.1 mg, 63%) as a colorless oil. R_f = 0.23 (petroleum ether/*i*PrOH, 90:10, 0.15% Et_3N). $[\alpha]_D^{25}$ = +26 (c = 1.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (d, ^3J = 7.2 Hz, 3 H), 2.17–2.29 (m, 1 H), 2.64–2.79 (m, 3 H), 3.39 (d, ^2J = 13.2 Hz, 1 H), 3.71–3.73 (m, 1 H), 3.72 (AB part of an ABX system, ^2J = 11.3, ^3J = 3.5, ^3J = 1.8 Hz, δa – δb = 32.4 Hz, 2 H), 3.99 (d, ^2J = 13.2 Hz, 1 H), 4.58 (AB system, ^2J = 11.6 Hz, δa – δb = 25.4 Hz, 2 H), 7.28–7.38 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 36.7, 57.9, 59.3 (2 peaks), 71.9, 72.0, 88.3, 127.2, 127.6, 127.7, 128.4 (2 peaks), 128.6, 138.2 ppm. IR (neat): $\tilde{\nu}$ = 3438 (O–H), 1602 (C=C), 1264 (C–O) cm^{-1}. MS (DCI/NH_3): m/z (%) = 312 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{20}H_{26}NO_2$ 312.1964; found 312.1966.

[(2*S*,3*R*,4*S*)-1-Benzyl-3-(benzyloxy)-4-butylpyrrolidin-2-yl]methanol (37): Vinylpyrrolidine **31** (67.5 mg, 0.19 mmol) was treated according to general procedure B. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 90:10 to 60:40, 0.3% NH_4OH) to give **37** (42.0 mg, 63%) as a colorless oil. R_f = 0.26 (petroleum ether/EtOAc, 80:20, 0.8% NH_4OH). $[\alpha]_D^{25}$ = +23 (c = 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 6.9 Hz, 3 H), 1.20–1.53 (m, 6 H), 2.00–2.09 (m, 1 H), 2.67–2.76 (m, 3 H), 3.37 (d, ^2J = 13.2 Hz, 1 H), 3.70 (AB part of an ABX system, ^2J = 11.2, ^3J = 3.5, ^3J = 1.9 Hz, δa – δb = 34.9 Hz, 2 H), 3.76–3.79 (m, 1 H), 3.97 (d, ^2J = 13.2 Hz, 1 H), 4.57 (AB system, ^2J = 11.6 Hz, δa – δb = 23.5 Hz, 2 H), 7.26–7.41 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.7, 30.2, 33.1, 42.6, 57.6, 57.9, 59.3, 71.7, 71.8, 87.0, 127.1, 127.6, 127.7, 128.4 (2 peaks), 128.5, 138.3, 138.7 ppm. IR (neat): $\tilde{\nu}$ = 3440 (O–H), 1605 (C=C), 1071 (C–O) cm^{-1}. MS (DCI/NH_3): m/z (%) = 354 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{23}H_{32}NO_2$ 354.2433; found 354.2432.

[(2*S*,3*R*,4*S*)-1-Benzyl-3-(benzyloxy)-4-octylpyrrolidin-2-yl]methanol (38): Vinylpyrrolidine **32** (203.6 mg, 0.50 mmol) was treated according to general procedure B. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 90:10, 0.4% NH_4OH to 80:20, 1.2% NH_4OH) to give **38** (117.3 mg, 57%) as a colorless oil. R_f = 0.48 (petroleum ether/EtOAc, 80:20, 1.2% NH_4OH). $[\alpha]_D^{25}$ = +16 (c = 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, ^2J = 6.9 Hz, 3 H), 1.10–1.39 (m, 14 H), 1.90–1.98 (m, 1 H), 2.56–2.65 (m, 3 H), 3.26 (d, ^2J = 13.2 Hz, 1 H), 3.54 (dd, ^2J = 11.2, ^3J = 1.8 Hz, 1 H), 3.64–3.68 (m, 2 H), 3.87 (d, ^2J = 13.2 Hz, 1 H), 4.46 (AB system, ^2J = 11.6 Hz, δa – δb = 26.3 Hz, 2 H), 7.15–7.34 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.0, 29.2, 29.5, 29.6, 31.8, 33.4, 42.6, 57.6, 57.9, 59.3, 71.7, 71.8, 87.1, 127.1, 127.6, 127.7, 128.4 (2 peaks), 128.5, 138.3, 138.7 ppm. IR (neat): $\tilde{\nu}$ = 3445 (O–H), 1605 (C=C), 1071 (C–O) cm^{-1}. MS (ESI+): m/z (%) = 410 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{27}H_{40}NO_2$ 410.3059; found 410.3067.

[(2*S*,3*R*,4*S*)-1-Benzyl-3-(benzyloxy)-4-phenylpyrrolidin-2-yl]methanol (39): Vinylpyrrolidine **18** (80.8 mg, 0.22 mmol) was treated according to general procedure B. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 90:10, 0.4% NH_4OH) to give **39** (45.1 mg, 56%) as a colorless oil. R_f = 0.37 (petroleum ether/EtOAc, 80:20, 0.8% NH_4OH). $[\alpha]_D^{25}$ = +24 (c = 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.82–2.86 (m, 1 H), 2.97–3.09 (m, 2 H), 3.25–3.32 (m, 1 H), 3.40 (d, ^2J = 13.1 Hz, 1 H), 3.72 (AB part of an ABX system, ^3J = 11.4, ^3J = 3.5 Hz, ^3J = 2.1 Hz, $\Delta\delta$a – δb = 32.8 Hz, 2 H), 4.03 (d, ^2J = 13.1 Hz, 1 H), 4.03 (dd, ^3J = 6.2, ^3J = 4.9 Hz, 1 H), 4.44 (AB system, ^2J = 11.5 Hz, δa – δb = 53.6 Hz, 2 H), 7.14–7.37 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.8, 58.3, 59.3, 59.6, 71.3, 72.4, 88.1, 126.4, 127.3, 127.7, 128.4, 128.5, 128.7, 138.0, 138.2, 144.1 ppm. IR (neat): $\tilde{\nu}$ = 3472 (O–H), 1644, 1605 (C=C), 1071 (C–O) cm^{-1}. MS (ESI+): m/z (%) = 374 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{25}H_{28}NO_2$ 374.2120; found 374.2109.

[(2*S*,3*S*,4*S*)-1-Benzyl-3-(benzyloxy)-4-(octyloxy)pyrrolidin-2-yl]methanol (40): Vinylpyrrolidine **33** (69.0 mg, 0.16 mmol) was treated according to general procedure B. The crude product was purified by

flash column chromatography on silica gel (petroleum ether/EtOAc, 90:10, 0.4% NH_4OH to 80:20, 0.8% NH_4OH) to give **40** (40.8 mg, 59%) as a colorless oil. R_f = 0.22 (petroleum ether/EtOAc, 80:20, 0.8% NH_4OH). $[\alpha]_D^{25}$ = +16 (c = 2.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, ^3J = 6.7 Hz, 3 H), 1.14–1.32 (m, 10 H), 1.44–1.52 (m, 2 H), 2.58 (dd, ^2J = 10.6, ^3J = 5.3 Hz, 1 H), 2.72 (m, 1 H), 2.99 (br. d, ^2J = 10.6 Hz, 1 H), 3.24–3.37 (m, 3 H), 3.62 (AB part of an ABX system, ^2J = 11.1, ^3J = 3.1, ^3J = 1.7 Hz, δa – δb = 30.2 Hz, 2 H), 3.74 (m, 1 H), 3.92–3.97 (m, 2 H), 4.56 (AB system, ^2J = 11.7 Hz, δa – δb = 21.6 Hz, 2 H), 7.18–7.34 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 26.1, 29.2, 29.4, 29.7, 31.8, 57.1, 57.9, 59.7, 69.2, 70.1, 71.9, 81.3, 85.3, 127.1, 127.7, 127.8, 128.3, 128.4, 128.6, 138.0, 138.3 ppm. IR (neat): $\tilde{\nu}$ = 3466 (O–H), 1605 (C=C), 1100 (C–O) cm^{-1}. MS (ESI+): m/z (%) = 427 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{27}H_{40}NO_3$ 426.3008; found 426.3005.

2-[(2*S*,3*R*,4*S*)-1-Benzyl-3-(benzyloxy)-4-octylpyrrolidin-2-yl]ethanol (34): 9-BBn (0.84 mL, 0.42 mmol) was added to a solution of vinylpyrrolidine **32** (85.7 mg, 0.21 mmol) in THF (1 mL) at 0 °C. The reaction mixture was stirred at room temp. for 4 h. A saturated aqueous solution of $NaBO_3$ was added and the resulting mixture was stirred at room temp. for 18 h. The aqueous phase was then extracted three times with EtOAc. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and the solvents evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 80:20, 0.8% NH_4OH) to give **34** (64.9 mg, 73%) as a colorless oil. R_f = 0.26 (petroleum ether/EtOAc, 80:20, 0.8% NH_4OH). $[\alpha]_D^{25}$ = +17 (c = 1.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t, ^2J = 6.7 Hz, 3 H), 1.11–1.43 (m, 14 H), 1.61–1.71 (m, 1 H), 1.90–2.01 (m, 2 H), 2.50 (AB part of an ABX system, ^2J = 10.2, ^3J = 7.3, ^3J = 3.3 Hz, δa – δb = 32.8 Hz, 2 H), 2.80 (dd, ^3J = 9.3, ^3J = 4.6 Hz, 1 H), 3.14 (d, ^2J = 12.7 Hz, 1 H), 3.59–3.81 (m, 3 H), 4.11 (d, ^2J = 12.7 Hz, 1 H), 4.44 (AB system, ^2J = 11.6 Hz, δa – δb = 32.6 Hz, 2 H), 7.16–7.31 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.1, 29.2, 29.5, 29.6, 30.1, 31.8, 33.5, 42.6, 57.0, 58.9, 61.0, 70.8, 71.5, 87.9, 127.2, 127.7, 127.8, 128.4 (2 peaks), 128.9, 138.1, 138.2 ppm. IR (neat): $\tilde{\nu}$ = 3428 (O–H), 1075 (C–O) cm^{-1}. MS (ESI+): m/z (%) = 424 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{28}H_{42}NO_2$ 424.3216; found 424.3224.

General Procedure D – Catalytic Hydrogenation: 10% Pd/C or $Pd(OH)_2$/C (20–30% w/w) and 1–2 drops of a 12 N HCl aqueous solution were successively added to a 0.1 M solution of *N*-benzylpyrrolidine in MeOH. The flask was purged with N_2 and then loaded with H_2 (10–12 bars). The mixture was stirred at room temp. until disappearance of the starting material (24–90 h). The catalyst was then removed by filtration through Celite and the filtrate evaporated to dryness. The intermediate was taken up in MeOH/water (2:1, 25 mL/mmol) and Dowex 50WX8–200 ion-exchange resin (12 g/mmol) was added. After being stirred for 1 h, the resin was successively filtered and washed with water and MeOH. A 3 M ammonium hydroxide solution was then added (50 mL/mmol) and the resin stirred for 1 h before being filtered and rinsed with a 3 M ammonium hydroxide solution (500 mL/mmol). The resulting solution was evaporated to dryness under reduced pressure.

(2*S*,3*R*,4*S*)-4-Butyl-2-(hydroxymethyl)pyrrolidin-3-ol (4): *N*-Benzylpyrrolidine **25** (45.1 mg, 0.17 mmol) was treated according to general procedure D. The crude product was purified by flash column chromatography on silica gel ($MeOH/EtOH/NH_4OH/CH_2Cl_2$, 4:12:6:78 to 6:12:6:76) to give **4** (26.5 mg, 90%) as a white solid. R_f = 0.15 ($MeOH/EtOH/NH_4OH/CH_2Cl_2$, 6:12:6:76). $[\alpha]_D^{25}$ = +11 (c = 1.3, MeOH). ^1H NMR (300 MHz, CD_3OD): δ = 0.92 (t, ^3J = 6.8 Hz, 3 H), 1.25–1.39 (m, 5 H), 1.59–1.67 (m, 1 H), 1.87–2.00 (m, 1 H), 2.59 (dd, ^2J = 10.9, ^3J = 8.0 Hz, 1 H), 2.90 (ddd, ^3J = 7.0, ^3J = 5.8, ^3J = 3.9 Hz, 1 H), 3.14 (dd, ^2J = 10.9, ^3J = 8.1 Hz, 1 H), 3.53 (pseudo-t, $^3J \approx {}^3J \approx$ 7.1 Hz, 1 H), 3.64 (AB part of an ABX system, ^2J = 11.3, ^3J = 5.8, ^3J = 3.9 Hz, δa – δb = 33.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 14.4, 24.0, 31.5, 33.1, 48.4, 50.5, 62.8, 68.0, 79.3 ppm. MS (DCI/NH_3): m/z (%) = 174 (100) $[MH]^+$. HRMS (DCI/NH_3): calcd. for $C_9H_{20}NO_2$ 174.1494; found 174.1495.

(2*S*,3*R*,4*S*)-2-(Hydroxymethyl)-4-octylpyrrolidin-3-ol (23): *N*-Benzylpyrrolidine **26** (40.0 mg, 0.13 mmol) was treated according to general procedure D to give **23** (15.0 mg, 52%) as a yellow oil. $[\alpha]_D^{25}$ = +10 (c = 1.5, $CHCl_3$). ^1H NMR (300 MHz, CD_3OD): δ = 0.90 (t, ^3J = 7.0 Hz, 3 H), 1.26–1.40 (m, 13 H), 1.60–1.72 (m, 1 H), 1.96–2.11 (m, 1 H), 2.73–2.80 (m, 1 H), 3.11–3.16 (m, 1 H), 3.34 (dd, ^2J = 11.2, ^3J = 8.1 Hz, 1 H), 3.64–3.70 (m, 2 H), 3.79 (dd, ^2J = 11.7, ^3J = 3.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.7, 28.2, 29.3, 29.6, 29.9, 31.6, 31.9, 46.3, 48.5, 60.3, 66.4, 76.9 ppm. MS (DCI/NH_3): m/z (%) = 230 (100) $[MH]^+$, 247 (52) $[MNH_4]^+$. HRMS (DCI/NH_3): calcd. for $C_{13}H_{28}NO_2$ 230.2120; found 230.2120. $C_{13}H_{27}NO_2 + 0.9H_2O$: calcd. C 63.58, H 11.82, N 5.70; found C 63.47, H 12.11, N 6.05.

(2*S*,3*R*)-2-(Hydroxymethyl)pyrrolidin-3-ol (41): *N*-Benzylpyrrolidine **24** (32.0 mg, 0.15 mmol) was treated according to general procedure D. The crude product was purified by flash column chromatography on silica gel ($MeOH/EtOH/NH_4OH/CH_2Cl_2$, 15:20:10:55) to give **41** (15.0 mg, 82%) as a yellow oil. R_f = 0.21 ($MeOH/EtOH/NH_4OH/CH_2Cl_2$, 15:20:10:55). $[\alpha]_D^{25}$ = –36 (c = 1.1, water). ^1H NMR (300 MHz, CD_3OD): δ = 1.71 (dddd, ^2J = 13.2, ^3J = 7.1, ^3J = 4.6, ^3J = 3.8 Hz, 1 H), 1.94 (dtd, ^2J = 13.2, ^3J = 8.2, ^3J = 6.5 Hz, 1 H), 2.92–3.06 (m, 3 H), 3.53 (AB part of an ABX system, ^2J = 11.3, ^3J = 5.8, ^3J = 5.2 Hz, δa – δb = 14.1 Hz, 2 H), 4.06 (dt, ^3J = 6.5, ^3J = 3.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 35.5, 45.3, 62.8, 69.1, 74.1 ppm. MS (DCI/NH_3): m/z (%) = 118 (100) $[MH]^+$. HRMS (DCI/NH_3): calcd. for $C_5H_{12}NO_2$ 118.0868; found 118.0869.

(2*S*,3*R*,4*S*)-2-(Hydroxymethyl)-4-phenylpyrrolidin-3-ol (42): *N*-Benzylpyrrolidine **39** (50.6 mg, 0.14 mmol) was treated according to general procedure D. The crude product was purified by flash column chromatography on silica gel ($MeOH/EtOH/NH_4OH/CH_2Cl_2$, 6:6:3:85) to give **42** (21.3 mg, 81%) as a white solid. R_f = 0.19 ($MeOH/EtOH/NH_4OH/CH_2Cl_2$, 6:6:3:85). $[\alpha]_D^{25}$ = +29 (c = 1.1, MeOH). ^1H NMR (300 MHz, CD_3OD): δ = 3.09–3.28 (m, 3 H), 3.47 (dd, ^3J = 10.4, ^3J = 8.1 Hz, 1 H), 3.81 (AB part of an ABX system, ^3J = 11.5, ^3J = 5.5, ^3J = 3.5 Hz, δa – δb = 28.8 Hz, 2 H), 4.11 (pseudo-t, $^3J \approx {}^3J \approx$ 8.2 Hz, 1 H), 7.20–7.40 (m, 5 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 51.5, 53.7, 61.8, 67.3, 79.3, 128.1, 128.7, 129.7, 141.3 ppm. IR (neat): $\tilde{\nu}$ = 3300 (O–H), 1635, 1603 (C=C), 1066 (C–O) cm^{-1}. MS (ESI+): m/z (%) = 374 (100) $[MH]^+$. HRMS (ESI+): calcd. for $C_{11}H_{16}NO_2$ 194.1181; found 194.1181.

(2*S*,3*S*,4*S*)-2-(Hydroxymethyl)-4-(octyloxy)pyrrolidin-3-ol (43): *N*-Benzylpyrrolidine **40** (39.0 mg, 0.09 mmol) was treated according to general procedure D. The crude product was purified by flash column chromatography on silica gel ($MeOH/EtOH/NH_4OH/CH_2Cl_2$, 6:12:6:76) to give **43** (18.6 mg, 82%) as a white solid. R_f = 0.22 ($MeOH/EtOH/NH_4OH/CH_2Cl_2$, 6:12:6:76). $[\alpha]_D^{25}$ = +13 (c = 1.1, MeOH). ^1H NMR (300 MHz, CD_3OD): δ = 0.90 (t, ^3J = 6.7 Hz, 3 H), 1.28–1.40 (m, 10 H), 1.51–1.60 (m, 2 H), 2.93 (m, 2 H), 3.08 (dd, ^2J = 12.1, ^3J = 5.4 Hz, 1 H), 3.49 (AB part of an ABX_2 system, ^2J = 9.2, ^3J = 6.5 Hz, δa – δb = 30.3 Hz, 2 H), 3.65 (AB part of an ABX system, ^2J = 11.2, ^3J = 5.9, ^3J = 5.0 Hz, δa –

δb = 23.6 Hz, 2 H), 3.76 (dt, ^3J = 5.4, ^3J = 2.6 Hz, 1 H), 3.90 (dd, ^3J = 5.0, ^3J = 2.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 14.5, 23.8, 27.4, 30.5, 30.6, 31.1, 33.1, 51.1, 62.9, 68.4, 70.4, 78.5, 87.7 ppm. IR (neat): ṽ = 3440 (O–H), 1640 (N–H), 1075 (C–O) cm^{-1}. MS (ESI+): *m*/*z* (%) = 246 (100) [MH]$^+$. HRMS (ESI+): calcd. for $C_{13}H_{28}NO_3$ 246.2069; found 246.2067.

(2*S*,3*R*,4*S*)-2-(2-Hydroxyethyl)-4-octylpyrrolidin-3-ol (35): *N*-Benzylpyrrolidine **34** (33.3 mg, 0.08 mmol) was treated according to general procedure D. The crude product was purified by flash column chromatography on silica gel ($MeOH/EtOH/NH_4OH/CH_2Cl_2$, 6:12:6:76) to give **35** (10.9 mg, 57%) as a white solid. R_f = 0.21 ($MeOH/EtOH/NH_4OH/CH_2Cl_2$, 12:6:6:76). $[\alpha]_D^{25}$ = +15 (*c* = 0.8, MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ = 0.91 (t, ^2J = 6.7 Hz, 3 H), 1.21–1.41 (m, 13 H), 1.60–1.71 (m, 2 H), 1.82–1.97 (m, 2 H), 2.59 (dd, ^2J = 11.0, ^3J = 7.6 Hz, 1 H), 2.81–2.88 (m, 1 H), 3.14 (dd, ^2J = 10.9, ^3J = 8.7 Hz, 1 H), 3.32–3.36 (m, 1 H), 3.62–3.76 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 23.8, 29.3, 30.5, 30.7, 31.0, 33.1, 34.0, 37.0, 47.8, 50.1, 61.2, 64.4, 83.5 ppm. IR (neat): ṽ = 3283 (O–H), 1060 (C–O) cm^{-1}. MS (ESI+): *m*/*z* (%) = 244 (100) [MH]$^+$. HRMS (ESI+): calcd. for $C_{14}H_{30}NO_2$ 244.2277; found 244.2301.

(2*S*,3*R*,4*S*)-2-(Hydroxymethyl)-1-methyl-4-octylpyrrolidin-3-ol (44): $Pd(OH)_2/C$ (7.3 mg, 30% w/w), formaldehyde (54 mg of a 37% aqueous solution, 1.8 mmol), and 1 drop of 12 N HCl were added to a solution of *N*-benzylpyrrolidine **38** (24.2 mg, 0.06 mmol) in methanol (0.8 mL). The flask was purged with N_2 and then loaded with H_2 (12 bars). The mixture was stirred at room temp. until disappearance of the starting material (96 h). The catalyst was then removed by filtration through Celite and the filtrate was evaporated to dryness. The resulting crude mixture was taken up in MeOH/water (2:1) (2.6 mL) and Dowex 50WX8–200 ion-exchange resin (1.2 g) was added. After stirring for 1 h, the solution was filtered and the resin was successively washed with water (52 mL) and MeOH (15 mL). A 30% ammonium hydroxide solution was then added (5.2 mL) and the resin was stirred for 1 h before being filtered and rinsed with a 30% ammonium hydroxide solution (52 mL). The resulting solution was then evaporated to dryness under reduced pressure. The crude product was purified by flash column chromatography on silica gel ($MeOH/EtOH/NH_4OH/CH_2Cl_2$, 6:6:3:85) to give **44** (11.2 mg, 77%) as a white solid. R_f = 0.25 ($MeOH/EtOH/NH_4OH/CH_2Cl_2$, 6:6:3:85). $[\alpha]_D^{25}$ = +27 (*c* = 0.9 in MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ = 0.90 (t, ^2J = 6.6 Hz, 3 H), 1.22–1.42 (m, 13 H), 1.48–1.60 (m, 1 H), 1.79–1.91 (m, 1 H), 2.18–2.24 (m, 1 H), 2.37 (s, 3 H), 2.67 (AB part of an ABX system, $^2J \approx {}^3J \approx$ 9.8, ^3J = 3.9 Hz, δa – δb = 32.3 Hz, 2 H), 3.60 (dd, ^3J = 7.1, ^3J = 5.2 Hz, 1 H), 3.69 (AB part of an ABX system, ^2J = 11.6, ^3J = 4.9, ^3J = 3.8 Hz, δa – δb = 31.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 14.5, 23.8, 29.3, 30.5, 30.7, 30.9, 33.1, 34.8, 42.1, 46.0, 61.3, 62.1, 76.0, 79.8 ppm. IR (neat): ṽ = 3436 (O–H), 1076 (C–O) cm^{-1}. MS (ESI+): *m*/*z* (%) = 243 (100) [MH]$^+$. HRMS (ESI+): calcd. for $C_{14}H_{30}NO_2$ 244.2277; found 244.2325.

Computational Details: Geometries were fully optimized at the B3LYP/6-31G** level of theory using the Gaussian 03 software package.[28] Vibrational analysis was performed at the same level of theory as the geometry optimization in order to identify the nature of the stationary points obtained on the potential energy surfaces (minima or first-order saddle points). The connections between transition states and minima were checked by optimization of the structures distorted along the intrinsic reaction coordinate, namely the C4–N or the C3–N distance. The implicit solvation by methanol (ε = 32.63) was performed with the polarizable continuum model (PCM) implemented in Gaussian 03.[28] AIM (Atoms in Molecules) analysis was performed with the TopMoD program.[29]

CCDC-710252 (for **2**), -710253 (for **9**), -710254 (for **14**), -710255 (for **15**), -710256 (for **18**), and -710257 (for **19**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): Selected crystallographic data for **2**, **9**, **14**, **15**, **18**, and **19**, selected NMR spectroscopic data for **7**–**11**, **13**–**17**, **19**–**21**, **23**–**26**, **28**, **29**, and **43**, LC–MS and HPLC analyses of the mixture of **19** and **20**, and biological evaluation protocols.

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