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Asymmetric Syntheses of (+)-Preussin B, the C(2)-Epimer of (−)-Preussin B, and 3-Deoxy-(+)-preussin B

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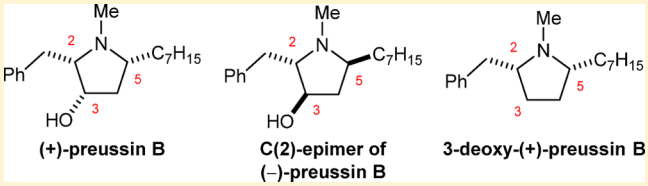
Supporting Information

ABSTRACT: Efficient de novo asymmetric syntheses of (+)-preussin B, the C(2)-epimer of (−)-preussin B, and 3-deoxy-(+)-preussin B have been developed, using the diastereoselective conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to *tert*-butyl 4-phenylbut-2-enoate and diastereoselective reductive cyclizations of γ-amino ketones as the key steps to set the stereochemistry. Conjugate addition followed by enolate protonation generated the corresponding β-amino ester. Homologation using the ester functionality as a synthetic handle gave the corresponding γ-amino ketone. Hydrogenolytic N-debenzylation was accompanied by diastereoselective reductive cyclization in situ; reductive N-methylation then gave 3-deoxy-(+)-preussin B as the major diastereoisomeric product. Meanwhile, the same conjugate addition but followed by enolate oxidation with (+)-camphorsulfonyloxaziridine gave the corresponding *anti*-α-hydroxy-β-amino ester. α-Epimerization by oxidation and diastereoselective reduction then gave access to the corresponding *syn*-α-hydroxy-β-amino ester. Homologation of both of these diastereoisomeric α-hydroxy-β-amino esters gave the corresponding β-hydroxy-γ-amino ketones. N-Debenzylation and concomitant diastereoselective reductive cyclization, followed by reductive N-methylation, provided the C(2)-epimer of (−)-preussin B and (+)-preussin B as the major diastereoisomeric products, respectively. The overall yields (from phenylacetaldehyde) were 19% for 3-deoxy-(+)-preussin B over seven steps, 8% for the C(2)-epimer of (−)-preussin B over nine steps, and 7% for (+)-preussin B over eleven steps.



INTRODUCTION

In 1988, Schwartz et al. reported the isolation of a potent antifungal agent, L-657,398, from fermentation broths of *Aspergillus ochraceus* ATCC22947 and determined its gross structure to be *N*(1)-methyl-2-benzyl-5-(1′-nonyl)pyrrolidin-3-ol.[1,2] Subsequently, in an independent study in 1989, Johnson et al. reported isolation of the same compound from fermentation broths of *Preussia* sp. and named it (+)-preussin (Figure 1).[3] Johnson et al. established the relative configuration within (+)-preussin by NOE experiments, while the absolute (2*S*,3*S*,5*R*)-configuration was assigned using Trost's *O*-methylmandelate ester derivatization technique.[3] (+)-Preussin (L-657,398) displayed antifungal activity against both yeasts and filamentous fungi[1,2] and was later implicated as an antitumor agent[4−6] and antiviral agent.[7] These desirable biological properties, together with the unique structure ("all-*cis*" relative configuration of the three substituents at the stereogenic centers around the pyrrolidine ring) of (+)-preussin, quickly made it a popular target for synthesis: the first total synthesis of (+)-preussin was reported in 1991 (starting from D-glucose),[8] and to date, more than twenty five different routes to (+)-preussin have been developed. A large number of these rely on derivatization of readily available chiral pool materials: elaboration of L-phenylalanine facilitated the second synthesis of (+)-preussin that was reported,[9] and this material (or derivatives thereof) has proven to be the most popular starting material by far in subsequent syntheses,[10−18] although (in chronological order) D-phenylalanine,[19] D-arabinose,[20] L-aspartic acid,[21] L-pyroglutaminol,[22,23] L-serine,[24,25] and (*S*)-malic acid[26,27] (or derivatives thereof) have also been employed as the sources of chirality. Other de novo asymmetric syntheses have been developed,[28−39] along with one formal synthesis of (+)-preussin[40−42] and two syntheses of (−)-preussin.[10,43] Moreover, the synthesis of all eight possible stereoisomers (using an enantiopure phenylalanine derivative as the starting material, proceeding via two nonselective reactions and chromatographic separation) has been reported,[44−46] as well as one synthesis of (±)-preussin.[47,48] The truncated analogue (+)-preussin B, (2*S*,3*S*,5*R*)-*N*(1)-methyl-2-benzyl-5-(1′-heptyl)pyrrolidin-3-ol (Figure 1), was isolated [along with (+)-preussin] in 2014 from *Simplicillium lanosoniveum* TAMA

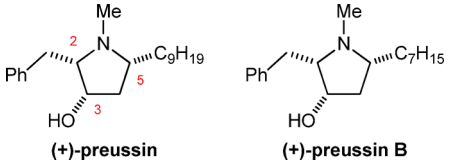


Figure 1. Structures of (+)-preussin and (+)-preussin B.

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173[49] and was shown to exhibit weak antifungal activity.[49] The first and, to date, the only synthesis of (+)-preussin B to be reported is that of Huang et al., who employed (*S*)-malic acid as their starting material.[27] Herein, we report the development of a de novo asymmetric synthesis of (+)-preussin B, and also report for the first time the preparation of the C(2)-epimer of (−)-preussin B, the C(3)-epimer of (+)-preussin B, and the C(3)-deoxy derivative of (+)-preussin B.

RESULTS AND DISCUSSION

Our initial retrosynthetic analysis for the construction of the polysubstituted pyrrolidine scaffold **1** present in (+)-preussin B, its diastereoisomers, and 3-deoxy analogue started by disconnection of the N(1)−C(5) bond to give the corresponding ketone **2**: in the forward sense, the key cyclization step was designed to be a one-pot N-deprotection of **2** and reductive cyclization under hydrogenolysis conditions.[50] Ketone **2** should be easily obtained via addition of *n*-heptylmagnesium bromide to the corresponding nitrile **3**; in turn, **3** could be accessed via Mitsunobu-type displacement of the primary hydroxyl group within **4** by a cyanide ion.[51] Alcohol **4** could arise from the reduction of the corresponding *β*-amino ester **5** (X = H) or the *syn*- or *anti*-diastereoisomeric forms of *α*-hydroxy-*β*-amino ester **5** (X = OH). The conjugate addition of a lithium amide (R_2NLi) to *α*,*β*-unsaturated ester **6** and either enolate protonation (X = H) or oxidation (X = OH) will then be used as the key step to access the *β*-amino ester scaffolds **5**[52] (Figure 2).

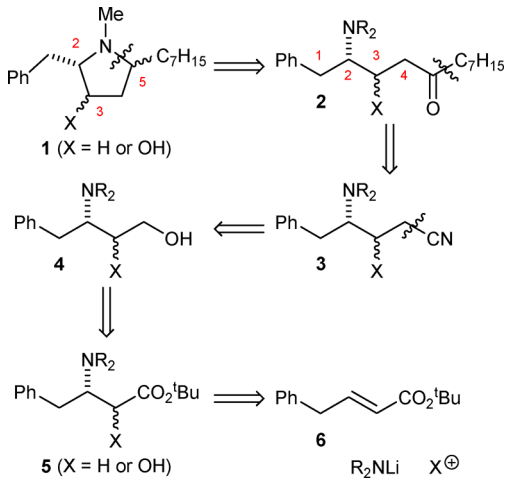

Figure 2. First generation retrosynthetic analysis of (+)-preussin B, its diastereoisomers, and 3-deoxy analogue.

The requisite *α*,*β*-unsaturated ester **6** required for these studies was prepared, as previously described, on a multigram scale via our modified Wadsworth−Emmons reaction using MeMgBr as the base.[53] The use of both lithium (*S*)-*N*-benzyl-*N*-(*α*-methylbenzyl)amide and lithium (*S*)-*N*-methyl-*N*-(*α*-methylbenzyl)amide to facilitate the synthesis of 3-deoxy-(+)-preussin B was assessed. Initially, conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(*α*-methylbenzyl)amide to **6** gave the known *β*-amino ester **7**[54−57] as a single diastereoisomer (>95:5 dr) that was isolated in 73% yield and >99:1 dr. Reduction of **7** using $LiAlH_4$ gave alcohol **9** in 78% yield. Substitution of the hydroxyl group within **9** for a nitrile functionality was achieved using a modified literature procedure for a Mitsunobu-type reaction,[51] using diisopropyl azodicarboxylate (DIAD) and acetone cyanohydrin as the cyanide source, giving nitrile **13** in 88% yield. This outcome is consistent with (i) activation of the alcohol followed by a direct S_N2-type displacement by a cyanide ion; (ii) activation of the alcohol followed by intramolecular attack of the nitrogen atom to form azetidinium ion **11**, which then undergoes regioselective ring opening at the least substituted, primary position (i.e., the lower steric hindrance favors the S_N2-type reaction at this position); or (iii) a mixture of both pathways resulting in the formation of **13**. Addition of *n*-heptylmagnesium bromide to **13** gave ketone **15**, consistent with hydrolysis of the initially formed imine occurring upon aqueous workup; ketone **15** was isolated in 87% yield. The absolute configurations of **9**, **13**, and **15** were confidently assigned from the established absolute (3*S*,*αS*)-configuration of **7**;[54,55] all of these transformations proceeded without any detectable evidence of epimerization of either of the two stereogenic centers, as expected. The final step (one-pot N-debenzylation and reductive cyclization) was next investigated. Treatment of **15** with Pd/C under 1 atm of H_2 for 16 h promoted conversion to a 75:25 mixture of two compounds, assigned as the C(5)-epimeric pyrrolidines **17** and **18**. When this mixture was hydrogenated in the presence of aqueous formaldehyde for 10 min, formation of a 75:25 mixture of pyrrolidines **19** and **20** was observed, with purification giving **19** in 66% yield (from **15**) and **20** in 22% yield (from **15**). The relative configurations within **19** and **20** (and, hence, **17** and **18**) were assigned on the basis of NOE analyses: a strong reciprocal correlation was observed between the C(2)*H* and C(5)*H* protons within **19**, whereas essentially no correlation was observed between these protons within **20**. Thus, **19** was assigned as the 2,5-*cis*-diastereoisomer [3-deoxy-(+)-preussin B], and **20** was assigned as the 2,5-*trans*-diastereoisomer. The formation of the 2,5-*cis*-diastereoisomer **17** (and, hence, **19**) as the major product of the reductive cyclization of ketone **15** is also consistent with the stereochemical outcome of the reductive cyclization of related *γ*-amino ketones.[50] Use of lithium (*S*)-*N*-methyl-*N*-(*α*-methylbenzyl)amide in the conjugate addition step resulted in formation of a 63:24:13 mixture of *β*-amino ester **8** and the corresponding *β*,*γ*-unsaturated esters **21** and **22**, respectively. This mixture proved separable by chromatography, and **8**, **21**, and **22** were isolated in 56, 19, and 10% yield, respectively. The absolute (3*S*,*αS*)-configuration of *β*-amino ester **8** was assigned by analogy to the known absolute configuration of **7**,[54,55] which is consistent with our transition state mnemonic for this class of conjugate addition reaction.[58] The geometries of *β*,*γ*-unsaturated esters **21** and **22** were confidently assigned from the diagnostic values of the ^{1}H NMR ^3J coupling constants [$^3J_{3,4}$ = 15.9 Hz for (*E*)-**21**[54,55] and $^3J_{3,4}$ = 11.6 Hz for (*Z*)-**22**]. The formation of **21** and **22** suggests that a competing deprotonation process is occurring under the basic reaction conditions: deprotonation of the *γ*-carbon atom of *α*,*β*-unsaturated ester **6** leads to a dienolate, which undergoes kinetic protonation of the *α*-carbon upon workup to give *β*,*γ*-unsaturated esters **21** and **22**. Next, reduction of **8** with $LiAlH_4$ gave alcohol **10** in 80% yield; Mitsunobu-type reaction[51] of **10** gave nitrile **14** in 58% yield, and then addition of *n*-heptylmagnesium bromide to **14** gave ketone **16** in 82% yield. Finally, hydrogenolysis of **16** gave 3-deoxy-(+)-preussin B **19** as a single diastereoisomer that was isolated in 78% yield (Scheme 1).

The differing diastereoselectivities of the one-pot N-debenzylation and reductive cyclizations of ketones **15** (R = Bn) and **16** (R = Me) are indicative of the involvement of

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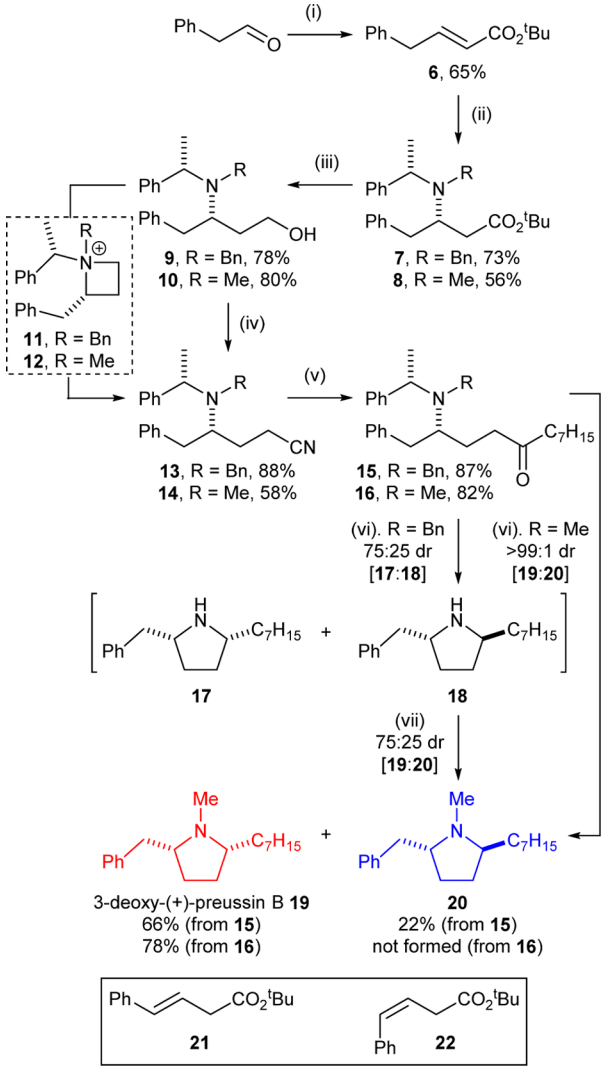
Scheme 1[a]



[a]Reagents and conditions: (i) $(EtO)_2P(O)CH_2CO_2{}^tBu$, MeMgBr, THF, 0 °C to rt, 30 min, then $PhCH_2CHO$, 75 °C, 3 h; (ii) lithium (*S*)-*N*-R-*N*-(α-methylbenzyl)amide, −78 °C, 2 h, then NH_4Cl (saturated aq); (iii) $LiAlH_4$, THF, 0 °C to rt, 2 h; (iv) PPh_3, acetone cyanohydrin, THF, then DIAD, 0 °C to rt, 16 h; (v) $C_7H_{15}MgBr$, Et_2O, rt, 16 h, then H_2O; (vi) H_2, $Pd(OH)_2/C$, MeOH, rt, 16 h; (vii) HCHO (aq), H_2, Pd/C, MeOH, rt, 10 min.

different intermediates on the mechanistic pathways for these reactions. For the transformation of **16** into 3-deoxy-(+)-preussin B **19**, the *N*-α-methylbenzyl group must be cleaved first, giving secondary amine intermediate **25**, which can then undergo intramolecular condensation to form iminium **26**. This would be expected to favor envelope conformation **26A**, with the C(2)-benzyl group adopting a pseudoaxial position in order to minimize 1,2-strain. Reduction of **26** proceeding from this conformation would be expected to occur with high diastereoselectivity from the least hindered face, opposite the C(2)-benzyl group, leading ultimately to 3-deoxy-(+)-preussin B **19**, as observed experimentally. In contrast, the transformation of **15** to a 75:25 diastereoisomeric mixture of **17** and **18** under the same conditions may be rationalized by a mechanism involving initial hydrogenolysis of the *N*-benzyl (rather than the *N*-α-methylbenzyl group) to give secondary amine intermediate **23**. Intramolecular condensation (which was predicted to be faster than loss of the *N*-α-methylbenzyl group) then gives iminium **24**. For **24** in an analogous envelope conformation to **26A** (with the C(2)-benzyl group placed pseudoaxially), it would be anticipated that the preferred conformation of the α-methylbenzyl fragment would be determined by minimization of 1,3-strain, resulting in conformation **24A**. This conformer has the α-methyl group projecting over one face of the iminium and the C(2)-benzyl group projecting over the other, meaning that both faces are somewhat hindered. The diastereoselectivity of the reduction of **24** proceeding from this conformation is not readily predictable, but the formation of a mixture of pyrrolidine products **17** and **18** may be reasonably expected, as observed experimentally (Figure 3).

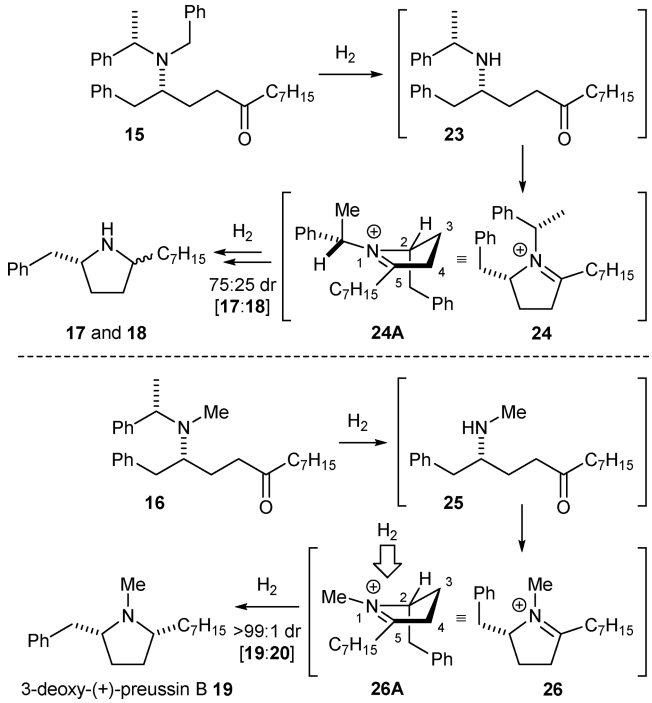


Figure 3. Mechanistic rationale for the differing diastereoselectivities observed in the one-pot N-debenzylation and reductive cyclizations of γ-amino ketones **15** and **16**.

The viability of this approach for construction of 3-deoxy-(+)-preussin B **19** from the corresponding β-amino esters **7** and **8** was now established. The synthesis of **19** from **8** [derived from conjugate addition of lithium (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amide] ultimately resulted in a more highly diastereoselective reductive cyclization, although the overall yield of **19** from **7** [derived from conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide] was higher. It was therefore resolved to investigate the use of both alternative N-substituents for the development of asymmetric syntheses of (+)-preussin B and its diastereoisomers; this entailed use of analogous procedures, but starting from the corresponding *anti*- and *syn*-α-hydroxy-β-amino esters. Thus, following our established procedure for aminohydroxylation of α,β-unsaturated ester **6**,[54,55] conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to **6** and in situ enolate oxidation with (+)-camphorsulfonyloxaziridine (CSO) gave the known α-hydroxy-β-amino ester **27**,[54,55] which was isolated in 71% yield as a single diastereoisomer (>99:1 dr). Reduction of **27** with

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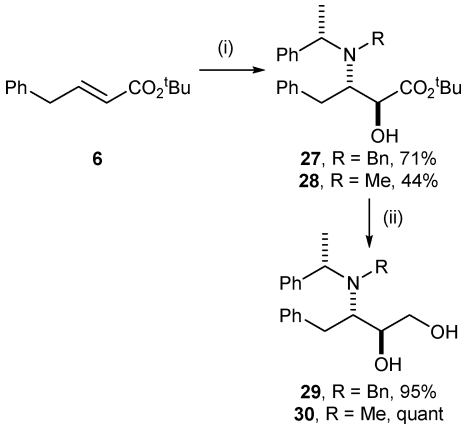
$LiAlH_4$ gave the corresponding diol **29** in 95% yield. Use of lithium (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amide in the conjugate addition/enolate oxidation step resulted in the isolation of α-hydroxy-β-amino ester **28** in 44% yield as a single diastereoisomer; the absolute (2*S*,3*S*,α*S*)-configuration of **28** was assigned by analogy to the known absolute configuration of **27**,[54,55] which is consistent with both the transition state mnemonic for this class of conjugate addition reaction[58] and the established stereochemical outcome of this tandem conjugate addition/enolate oxidation procedure applied to a range of achiral α,β-unsaturated esters.[52] Reduction of **28** with $LiAlH_4$ gave the corresponding diol **30** in quantitative yield (Scheme 2).

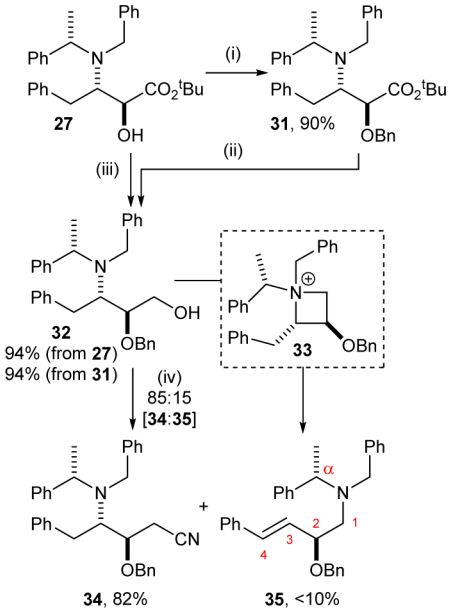
Scheme 2[a]



[a]Reagents and conditions: (i) lithium (*S*)-*N*-R-*N*-(α-methylbenzyl)-amide, −78 °C, 2 h, then (+)-CSO, −78 °C to rt, 12 h; (ii) $LiAlH_4$, THF, rt, 2 h.

Attempted chemoselective displacement of the primary hydroxyl group within **29** by a cyanide ion under the conditions for a Mitsunobu-type reaction[51] proceeded with incomplete consumption of starting material to give a complex mixture of chromatographically inseparable products. The use of a protecting group strategy was therefore implemented. Treatment of **27** with NaH followed by BnBr gave the corresponding *O*-benzyl ether **31** in 90% yield. Reduction of **31** with $LiAlH_4$ gave mono-*O*-benzyl-protected diol **32** in 94% yield. As both of these transformations were carried out in THF, the sequential addition of NaH, BnBr, and $LiAlH_4$ to a solution of **27** in the same reaction flask was investigated and delivered **32** in a great 94% yield. Mitsunobu-type reaction[51] of **32** gave an 85:15 mixture of nitrile **34** and olefin **35**. Chromatography enabled separation, and **34** was isolated in 82% yield along with an impure sample of **35**. Nonetheless, the structure of **35** could be confidently assigned by 2D NMR spectroscopic analyses of this sample, and its formation in this reaction indicts the involvement of azetidinium ion **33**: a plausible mechanism involves activation of the hydroxyl group within **32** followed by intramolecular attack of the nitrogen atom to form azetidinium ion **33**; opening of the strained four-membered ring to give the corresponding secondary carbocation and subsequent regioselective loss of a proton gives olefin **35** (i.e., azetidinium **33** undergoes E1-type elimination). It is on the basis of this mechanism that the absolute (2*S*,α*S*)-configuration of **35** was assigned (i.e., these stereocenters have not changed during conversion of **32** into **35**), with the (*E*)-olefin geometry following from the diagnostic value of the ^{1}H NMR ^3J coupling constant ($^3J_{3,4}$ = 16.0 Hz). However, as with the conversion of alcohols **9** and **10** into the corresponding nitriles **13** and **14**, the conversion of alcohol **32** into nitrile **34** is consistent with several mechanistic scenarios, not all of which necessarily involve the intermediacy of azetidinium ion **33** (Scheme 3).

Scheme 3[a]



[a]Reagents and conditions: (i) NaH, THF, 0 °C to rt, 45 min, then BnBr, rt, 2 h; (ii) $LiAlH_4$, THF, 0 °C to rt, 2 h; (iii) NaH, THF, 0 °C to rt, 45 min, then BnBr, rt, 2 h, then $LiAlH_4$, 0 °C to rt, 2 h; (iv) PPh_3, acetone cyanohydrin, THF, then DIAD, 0 °C to rt, 16 h.

Addition of *n*-heptylmagnesium bromide to nitrile **34** (under the same conditions used successfully for the conversion of nitriles **13** and **14** to the corresponding ketones **15** and **16**) resulted in formation of an approximately 50:50 mixture of α,β-unsaturated ketone **38** and β-benzyloxyketone **39**. Chromatography enabled isolation of **38** in 45% yield and an impure sample of **39** (containing **38** alongside other unknown species) in ∼25% yield. Reaction of **34** with vinylmagnesium bromide was also investigated (as it was envisaged that the incorporation of a vinyl group may enable the long alkyl chain to be introduced in a subsequent step), although this did not result in any addition at all, instead forming a 55:45 mixture of α,β-unsaturated nitriles **36** and **37**, respectively; these diastereoisomers proved inseparable by chromatography and were isolated in 38% combined yield. The formation of the α,β-unsaturated compounds **36**, **37**, and **38** is indicative of a competing elimination process, which may occur during aqueous workup, upon purification, or under the reaction conditions themselves: deprotonation of the α-carbon atom of nitrile **34** by the Grignard reagent and subsequent $E1_{CB}$-type elimination of benzyloxide from the resultant anion would give **36** and/or **37**; subsequent regioselective 1,2-addition of *n*-heptylmagnesium bromide to **36** would then lead to **38** after workup. In order to test this hypothesis, the 55:45 mixture of **36** and **37** was treated with *n*-heptylmagnesium bromide, which did indeed result in the formation of **38**, albeit in only 22% isolated yield. Presumably, however, **38** arises only from 1,2-addition to **36**, and so the fate of **37** under these conditions is

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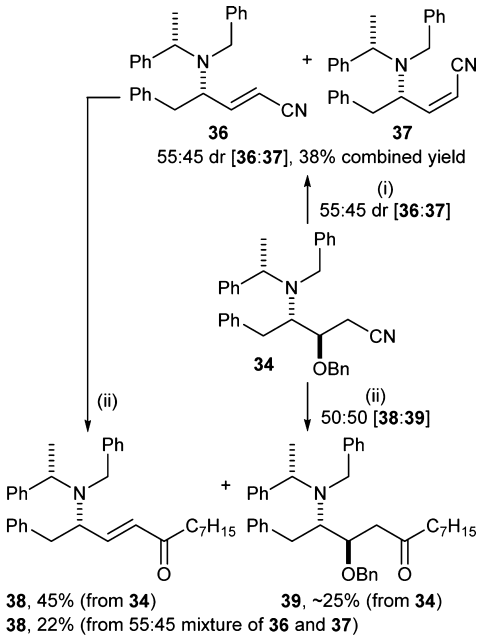
unknown. Based on this result, the effect of inclusion of various additives in the reaction of nitrile **34** with *n*-heptylmagnesium bromide was investigated, in the hope that this would promote the nucleophilic character of the Grignard reagent over its basic character, but unfortunately, the use of LiCl, $MgBr_2$, or $CeCl_3$[59] under a range of conditions did not allow for an efficient addition reaction to take place, and competing elimination remained problematic (Scheme 4).

Scheme 4[a]



[a]Reagents and conditions: (i) $H_2C{=}CHMgBr$, Et_2O, rt, 16 h, then H_2O; (ii) $C_7H_{15}MgBr$, Et_2O, rt, 16 h, then H_2O.

As conversion of nitrile **34** to ketone **39** was proving problematic, investigations were halted at this juncture and an alternative strategy was proposed. Returning to the retrosynthetic analysis, rather than effecting a disconnection of ketone **2** at the C(5)−C(6) bond to give the corresponding nitrile **3**, initial FGI of ketone **2** to the corresponding dithioacetal was considered, such that disconnection of the C(4)−C(5) bond could be effected, giving **4** and an anion of a 1,3-dithiane,[60,61] thus allowing nitrile **3** to be bypassed. In the forward direction, an activated version of **4** would be required, such that overall substitution of the hydroxyl group by the 1,3-dithiane anion could be achieved. To facilitate the synthesis of (+)-preussin B and its diastereoisomers, it was anticipated that diol **4** (X = OH) could be selectively converted into the corresponding epoxide,[62] which would then undergo regioselective ring opening upon attack of the 1,3-dithiane anion at the least hindered (terminal) position.[63] As such, investigations were directed toward this end (Figure 4).

The use of diols **29** (R = Bn) and **30** (R = Me) as substrates for elaboration via the proposed pathway was explored. Given the absolute configurations of both **29** and **30**, it was anticipated that their elaboration would culminate in the preparation of the C(2)-epimer of (−)-preussin B and/or the C(3)-epimer of (+)-preussin B, depending on the diastereoselectivity of the final reductive cyclization step. Reaction of **29** (R = Bn) with 1.05 equiv of methanesulfonyl chloride (MsCl) followed by treatment with K_2CO_3 in MeOH gave a

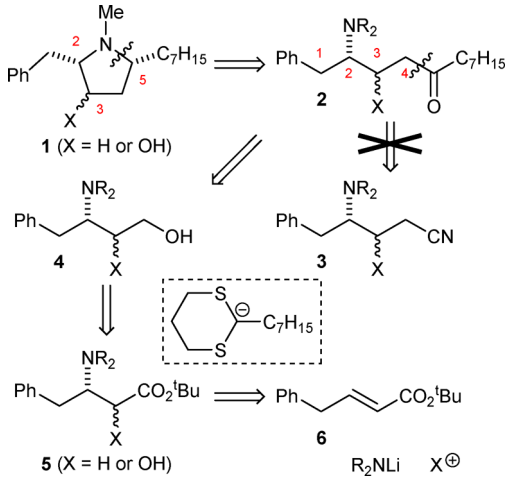


Figure 4. Second generation retrosynthetic analysis of (+)-preussin B, its diastereoisomers, and 3-deoxy analogue.

mixture of products containing epoxide **44** and olefin **45** in the ratio 90:10, respectively. Chromatography allowed isolation of **44** in 62% yield and an impure sample of **45**. The structure of **44** was confidently established with the aid of 2D NMR spectroscopic analyses, and the absolute configuration of the C(2)-stereogenic center was subsequently assigned unambiguously by chemical correlation. The formation of **44** as the major product in this reaction is thus consistent with the dominant pathway being chemoselective mesylation of the primary (rather than the secondary) hydroxyl group within **29**, as expected,[62] to give the intermediate monomesylate **40**, followed by epoxide formation from **40** upon exposure to base. The structure of **45** was also established using 2D NMR spectroscopic analyses and is consistent with involvement of the corresponding aziridinium ion **42** (which can form from **40**), in direct analogy with the formation of olefin **35** from monoprotected diol **32**. When **30** (R = Me) was subjected to the same reaction conditions, incomplete consumption of starting material to form a mixture of products was observed. When the reaction time was increased from 1 to 3 h, a major species containing an olefin was formed; this was tentatively assigned as **47**, although it was not isolated. These results suggested that the elimination pathway from the intermediate monomesylate **41** (proceeding via azetidinium ion **43**) is more facile than for the case of **40**, potentially due to the decreased steric hindrance around the nitrogen atom allowing faster intramolecular reaction. As such, the route employing **30** was not pursued further at this juncture, and attention turned toward effecting the regioselective ring opening of **44** with the requisite 1,3-dithiane anion. Treatment of 2-*n*-heptyl-1,3-dithiane (prepared from condensation of propane-1,3-dithiol with octanal in the presence of $ZnCl_2$)[64] with *n*-BuLi was followed by addition to **44**; workup after 1 h gave **48** as a single product, which was isolated in 86% yield. The identity of **48** was determined by 2D NMR spectroscopic analyses, establishing that **44** had undergone ring opening upon attack of the dithiane anion at the least hindered, terminal position, again as expected.[63] Treatment of **48** with [bis(trifluoroacetoxy)iodo]-benzene (PIFA) in aqueous MeOH[65] gave ketone **49** in 59% isolated yield. Hydrogenolysis of **49** then gave a 25:75 mixture of two compounds, assigned as the C(5)-epimeric pyrrolidines **50** and **51**. Hydrogenation of this mixture in the presence of aqueous formaldehyde gave a 25:75 mixture of pyrrolidines **52**

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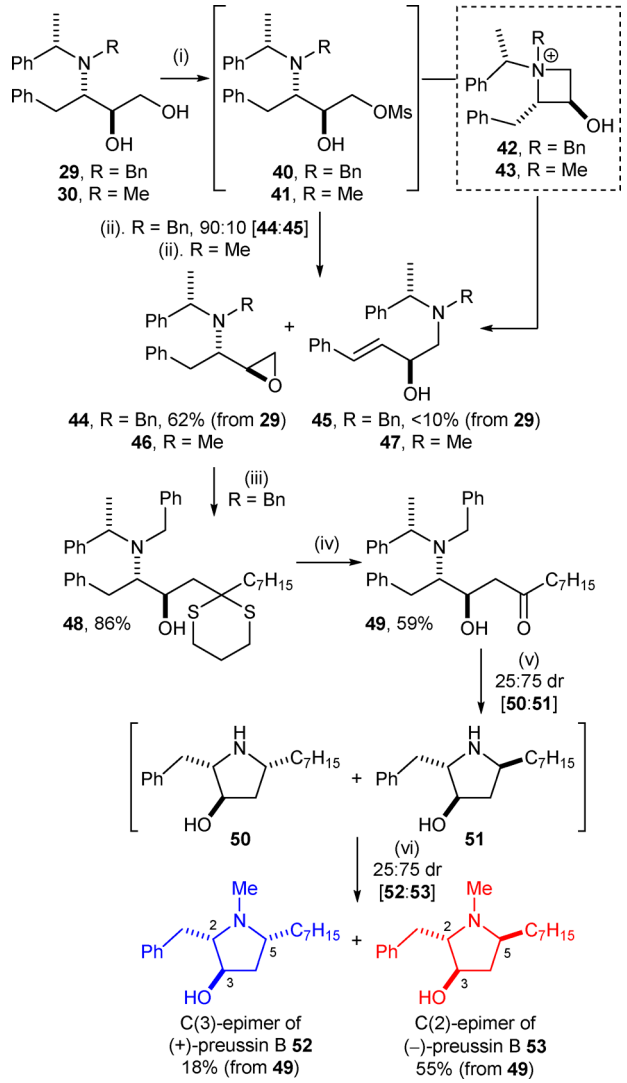
and **53**, with purification giving the minor product **52** in 18% yield and the major product **53** in 55% yield. Both **52** and **53** could be readily assigned the gross structure of *N*(1)-methyl-2-benzyl-5-(1′-heptyl)pyrrolidin-3-ol on the basis of 2D NMR spectroscopic analyses, although the 1D ^{1}H and ^{13}C NMR spectroscopic data of neither **52** nor **53** matched those reported for (+)-preussin B (as expected from the absolute configuration of *α*-hydroxy-*β*-amino ester **27**, from which both **52** and **53** are ultimately derived). As (+)-preussin B is hitherto the only diastereoisomer of *N*(1)-methyl-2-benzyl-5-(1′-heptyl)-pyrrolidin-3-ol to be reported, the relative configurations within **52** and **53** were assigned by comparison of their ^{1}H and ^{13}C NMR spectroscopic data to the ^{1}H and ^{13}C NMR spectroscopic data reported for the homologous compound (+)-preussin [(2*S*,3*S*,5*R*)-*N*(1)-methyl-2-benzyl-5-(1′-nonyl)pyrrolidin-3-ol] and all of its possible diastereoisomers. Thus, the minor product **52** was identified as the C(3)-epimer of (+)-preussin B, and the major product **53** was identified as the C(2)-epimer of (−)-preussin B: in each case, and with the obvious exception of the resonances corresponding to methylene groups in the C(5)-*n*-alkyl chains, the deviation from the chemical shift values compared to the corresponding diastereoisomer of *N*(1)-methyl-2-benzyl-5-(1′-nonyl)pyrrolidin-3-ol was minimal and sufficiently unique to allow for a confident stereochemical assignment. The configurations of all the intermediates **44** and **48**−**51** could thus be confidently inferred on the basis that the overall transformation of *anti*-*α*-hydroxy-*β*-amino ester **27** into a mixture of **52** and **53** corresponds to retention of the configuration of the hydroxyl-bearing stereocenter (Scheme 5).

Attention now turned toward elaboration of the diastereoisomeric diols **58** and **59** according to the same sequence of reactions. In order to prepare **58** and **59**, the corresponding *syn*-*α*-hydroxy-*β*-amino esters **56** and **57** were required; this necessitated inversion of the configuration of the hydroxyl-bearing stereocenter within *anti*-*α*-hydroxy-*β*-amino esters **27** and **28**. These transformations were achieved via a known oxidation/reduction protocol.[66−68] Oxidation of **27** (R = Bn) under Swern conditions gave quantitative conversion to the corresponding ketone **54**, and reduction using $NaBH_4$ at −20 °C gave a 90:10 mixture of **56** and **27**, respectively, which proved chromatographically inseparable; **56** and **27** were thus isolated as a 90:10 mixture in 85% combined yield. Reduction of this mixture using $LiAlH_4$ gave a 90:10 mixture of **58** and **29**, with subsequent chromatography allowing isolation of **58** as a single diastereoisomer in 77% yield. The relative configuration within **58** was unambiguously confirmed by single-crystal X-ray diffraction analysis.[69] Meanwhile, oxidation of **28** (R = Me) gave quantitative conversion to ketone **55**, with subsequent reduction giving a 92:8 mixture of **57** and **28**, respectively. In this case, however, chromatography gave **57** as a single diastereoisomer in 90% yield. Reduction of **57** using $LiAlH_4$ then gave **59** in 84% yield (Scheme 6).

Based upon the relative *syn*-configuration of the amino- and hydroxyl-bearing stereocenters, it was anticipated that elaboration of both diols **58** and **59** would culminate in the preparation of the C(5)-epimer of (+)-preussin B and/or (+)-preussin B itself, depending on the diastereoselectivity of the reductive cyclization. Treatment of **58** (R = Bn) with MsCl then K_2CO_3 in MeOH gave a mixture of products which contained epoxide **64** and olefin **65** in the ratio 85:15, respectively, from which **64** was isolated in 64% yield (∼95% purity) and **65** in 10% yield. Reaction of diol **59** (R = Me) under the same conditions resulted in formation of a complex

Scheme 5[a]



[a]Reagents and conditions: (i) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h; (ii) K_2CO_3, MeOH, rt, 1 h; (iii) 2-*n*-heptyl-1,3-dithiane, *n*-BuLi, THF, rt, 1 h, then **44**, rt, 1 h; (iv) PIFA, MeOH/H_2O (9:1), rt, 2 h; (v) H_2, $Pd(OH)_2$/C, MeOH, rt, 16 h; (vi) HCHO (aq), H_2, Pd/C, MeOH, rt, 10 min.

mixture of products containing an olefin, tentatively assigned as **67**, as a major component; purification and separation of this mixture was not, however, attempted. Nonetheless, treatment of **64** with the lithium anion of 2-*n*-heptyl-1,3-dithiane gave **68**, which was isolated in 83% yield; 2D NMR spectroscopic analyses were used to establish the structure of **68**, which in turn established the regioselectivity of the ring opening of **64**. Hydrolysis of **68** gave ketone **69** in 58% isolated yield, and hydrogenolysis of **69** gave an 85:15 mixture of two compounds, assigned as the C(5)-epimeric pyrrolidines **70** and **71**; hydrogenation of this mixture in the presence of aqueous formaldehyde gave an 85:15 mixture of pyrrolidines **72** and **73**, with purification giving the major product **72** in 75% yield (from **69**), although only an impure sample of **73** was isolated. In this instance, the spectroscopic data of **72** matched perfectly with those reported for the sample of (+)-preussin B isolated from the natural source by Igarashi et al.[49] and those of the synthetic sample prepared by Huang et al.[27] Furthermore, the

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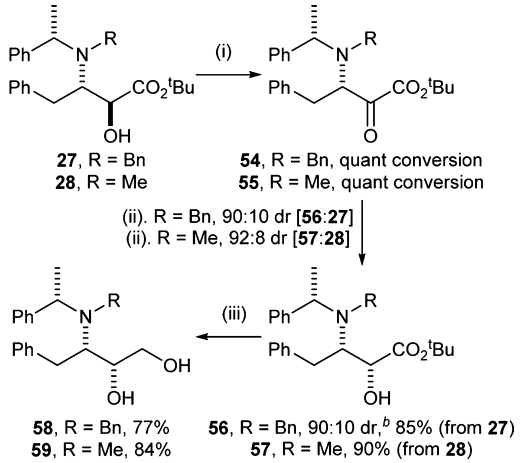
Scheme 6[a]

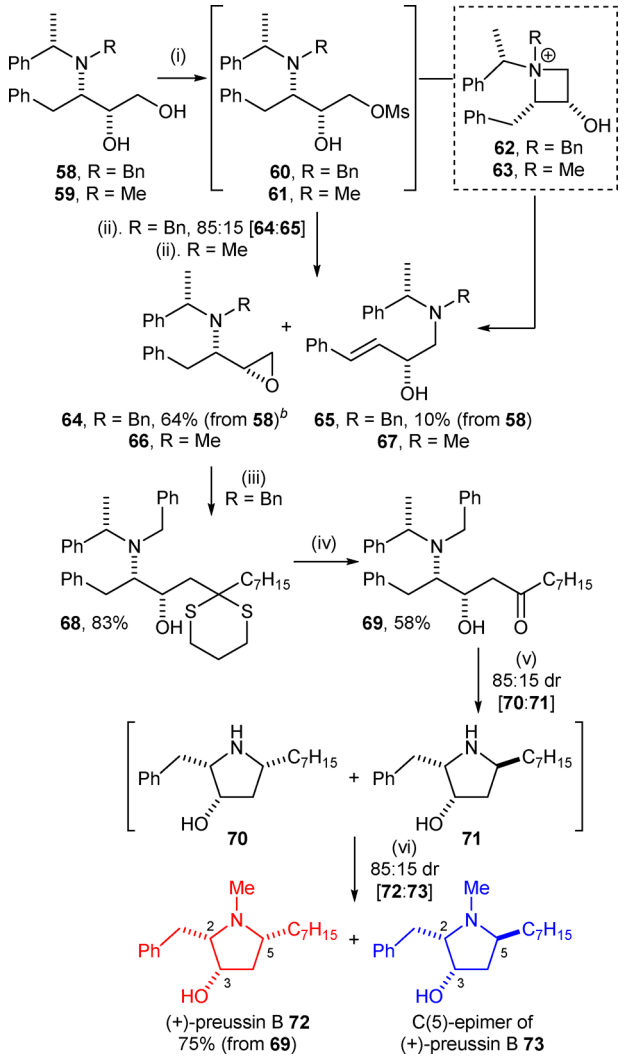


[a]Reagents and conditions: (i) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 5 min, then **27** or **28**, −78 °C, 30 min, then Et_3N, −78 °C to rt, 10 min; (ii) $NaBH_4$, MeOH, −20 °C, 2 h; (iii) $LiAlH_4$, THF, 0 °C to rt, 2 h. [b]The minor diastereoisomer was **27**.

specific rotation value of our sample of **72** {$[\alpha]_D^{25}$ +22.9 (*c* 1.0 in $CHCl_3$)} was also in excellent agreement with the values reported for these samples {Igarashi et al. report $[\alpha]_D^{26}$ +22 (*c* 0.19 in $CHCl_3$)[49] for the sample isolated from the natural source; Huang et al. report $[\alpha]_D^{26}$ +23.1 (*c* 0.19 in $CHCl_3$)[27] for their synthetic sample}. On this basis, the configurations of all the intermediates **64** and **68**−**71**, as well as the regiochemistry of monomesylate **60**, could be confidently inferred, and **73** was therefore identified as the C(5)-epimer of (+)-preussin B (Scheme 7).

It is instructive to compare the diastereoselectivities observed upon tandem N-debenzylation and reductive cyclization of the structurally related ketones **15**, **49**, and **69**, which result in the formation of diastereoisomeric mixtures of the corresponding pyrrolidines: ketone **15** gives a 75:25 mixture of **17** and **18**; ketone **49** gives a 25:75 mixture of **50** and **51**; ketone **69** gives an 85:15 mixture of **70** and **71**, respectively. Thus, reaction of the "parent" system **15** gives the corresponding 2,5-*cis*-diastereosiomer **17** as the major product, and the presence of the hydroxyl group within **69** results in a slight enhancement of this diastereoselectivity in favor of the corresponding 2,5-*cis*-diastereoisomer **70**. In contrast, the presence of the hydroxyl group within **49** results in the opposite diastereoselectivity, forming the corresponding 2,5-*trans*-pyrrolidine **51** as the major product. By direct analogy with the reaction of **15**, the most likely mechanistic pathways for the reactions of **49** and **69** involve initial hydrogenolyses of the *N*-benzyl groups to give the corresponding secondary amines **74** and **75**, which undergo intramolecular condensations to form the corresponding iminiums **76** and **77**. These species are likely to favor envelope conformations **76A** and **77A**, with the C(2)-benzyl substituent placed pseudoaxial. This results in the hydroxyl group within **77A** being placed pseudoequatorially, so it does not significantly project over either face of the iminium; its presence would therefore be anticipated to have little effect on the diastereoselectivity of iminium reduction proceeding from this conformer when compared to that of the parent system (i.e., reduction of **24** proceeding from conformation **24A**). In contrast, the hydroxyl group within **76A** is placed pseudoaxially and projects over one face of the iminium; it is

Scheme 7[a]



[a]Reagents and conditions: (i) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h; (ii) K_2CO_3, MeOH, rt, 1 h; (iii) 2-*n*-heptyl-1,3-dithiane, *n*-BuLi, THF, rt, 1 h, then **64**, rt, 1 h; (iv) PIFA, $MeOH/H_2O$ (9:1), rt, 2 h; (v) H_2, $Pd(OH)_2/C$, MeOH, rt, 16 h; (vi) HCHO (aq), H_2, Pd/C, MeOH, rt, 10 min. [b]Approximately 95% purity.

therefore likely to play a more decisive role in determining the overall diastereoselectivity of the reduction. However, given that **76A** has the C(2)-benzyl group projecting over one face of the iminium and both the C(α)-methyl and C(3)-hydroxyl projecting over the other face, it is again not easy to predict the major stereochemical course of the reduction proceeding from this conformer. However, in comparison with the diastereoselectivity of the reduction of the parent system proceeding from conformation **24A**, the presence of the pseudoaxial C(3)-hydroxyl group within **76A** would be expected to favor production of a higher proportion of the corresponding 2,5-*trans*-diastereoisomer **51**, which is in fact the major product observed experimentally (Figure 5).

CONCLUSION

In conclusion, efficient de novo asymmetric syntheses of 3-deoxy-(+)-preussin B, the C(2)-epimer of (−)-preussin B, and (+)-preussin B itself have been developed, using a diastereoselective hydroamination or aminohydroxylation of *tert*-butyl

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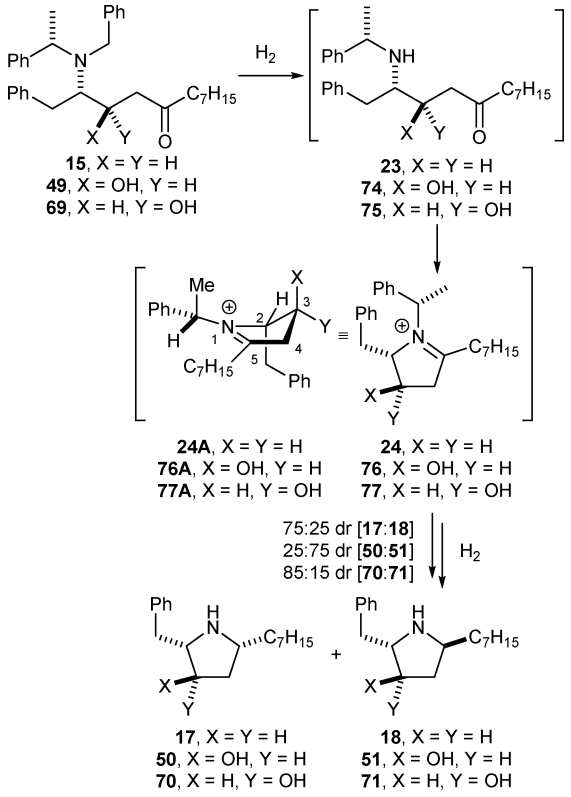

Figure 5. Mechanistic rationale for the differing diastereoselectivities observed in the one-pot N-debenzylation and reductive cyclizations of γ-amino ketones **15**, **49**, and **69**.

4-phenylbut-2-enoate and diastereoselective reductive cyclizations of γ-amino ketones as the key steps to set the stereochemistry. Conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzyl)amide to *tert*-butyl 4-phenylbut-2-enoate followed by enolate protonation gave a β-amino ester. Homologation using the ester functionality as a synthetic handle gave the corresponding γ-amino ketone. Hydrogenolytic N-debenzylation was accompanied by diastereoselective reductive cyclization in situ; reductive N-methylation then gave 3-deoxy-(+)-preussin B. Meanwhile, conjugate addition followed by enolate oxidation gave the corresponding *anti*-α-hydroxy-β-amino ester. An oxidation and diastereoselective reduction then gave access to the corresponding *syn*-α-hydroxy-β-amino ester. Homologation of both of these diastereoisomeric α-hydroxy-β-amino esters gave the corresponding γ-amino ketones. As before, N-debenzylation was accompanied by diastereoselective reductive cyclization; reductive N-methylation then gave the C(2)-epimer of (−)-preussin B and (+)-preussin B, respectively, as the major diastereoisomeric products of these reaction sequences [the minor products were identified as the C(3)-epimer of (+)-preussin B and the C(5)-epimer of (+)-preussin B, respectively]. The overall yields (from phenylacetaldehyde) were 19% for 3-deoxy-(+)-preussin B over seven steps, 8% for the C(2)-epimer of (−)-preussin B over nine steps, and 7% for (+)-preussin B over eleven steps.

EXPERIMENTAL SECTION

General Experimental Details. Reactions involving moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame-dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[70] Organic layers were dried over Na_2SO_4. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points are uncorrected. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. ^{1}H−^{1}H COSY and ^{1}H−^{13}C HMQC analyses were used to establish atom connectivity. Accurate mass measurements were run on a MicroTOF instrument internally calibrated with polyalanine.

X-ray Crystal Structure Determination.[69] Data were collected using graphite-monochromated Mo Kα radiation via standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined using CRYSTALS.[71]

***tert*-Butyl (*E*)-4-Phenylbut-2-enoate 6.** MeMgBr (3.0 M in Et_2O, 33.0 mL, 99 mmol) was added dropwise over 15 min to a stirred solution of *tert*-butyl diethylphosphonoacetate (23.3 mL, 99 mmol) in THF (500 mL) at 0 °C, and the resultant solution was stirred at rt for a further 30 min. Phenylacetaldehyde (13.3 mL, 114 mmol) was then added dropwise via syringe, and the resultant solution was heated at reflux for 3 h and allowed to cool to rt. Saturated aq NH_4Cl (800 mL) was added, and the resultant mixture was extracted with Et_2O (3 × 400 mL). The combined organic extracts were washed with brine (600 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 5:1) gave **6** as a light yellow oil (14.1 g, 65%, >99:1 dr [(*E*):(*Z*) ratio]):[53] δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, CMe_3), 3.50 (2H, dd, *J* = 6.7, 1.6, C(4)H_2), 5.74 (1H, dt, *J* = 15.6, 1.6, C(2)*H*), 7.00 (1H, dt, *J* = 15.6, 6.7, C(3)*H*), 7.17−7.36 (5H, m, *Ph*).

***tert*-Butyl (3*S*,α*S*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-4-phenylbutanoate 7.** *n*-BuLi (2.5 M in hexanes, 2.84 mL, 7.10 mmol) was added dropwise via syringe to a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.55 g, 7.33 mmol, >99% ee) in THF (10 mL) at −78 °C. The resultant solution was stirred at −78 °C for 30 min. A solution of **6** (1.00 g, 4.58 mmol, >99:1 dr [(*E*):(*Z*) ratio]) in THF (10 mL) at −78 °C was added, and the resultant solution was stirred at −78 °C for a further 2 h. Saturated aq NH_4Cl (0.5 mL) was added, and the reulstant mixture was allowed to warm to rt over 15 min and concentrated in vacuo. The residue was partitioned between H_2O (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 15:1 → 10:1) gave **7** as a colorless oil (1.44 g, 73%, >99:1 dr):[55] +8.1 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* = 7.0, C(α)*Me*), 1.41 (9H, s, CMe_3), 1.97 (1H, dd, *J* = 14.8, 4.6, C(4)H_A), 2.03 (1H, dd, *J* = 14.8, 8.3, C(4)H_B), 2.64 (1H, dd, *J* = 13.7, 5.8, C(2)H_A), 2.76 (1H, dd, *J* = 13.7, 8.2, C(2)H_B), 3.62 (1H, d, *J* = 15.0, NCH_AH$_B$Ph), 3.66−3.74 (1H, m, C(3)*H*), 3.81 (1H, q, *J* = 7.0, C(α)*H*), 3.93 (1H, d, *J* = 15.0, NCH_AH$_B$Ph), 7.14−7.39 (15H, m, *Ph*).

***tert*-Butyl (3*S*,α*S*)-3-[*N*-Methyl-*N*-(α-methylbenzyl)amino]-4-phenylbutanoate 8.** *n*-BuLi (2.5 M in hexanes, 0.57 mL, 1.45 mmol) was added dropwise via syringe to a stirred solution of (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amine (200 mg, 1.48 mmol, >99% ee) in THF (3 mL) at −78 °C. The resultant solution was stirred at −78 °C for 30 min. A solution of **6** (202 mg, 0.92 mmol, >99:1 dr [(*E*):(*Z*) ratio]) in THF (3 mL) at −78 °C was added, and the resultant solution was stirred at −78 °C for a further 2 h. Saturated aq NH_4Cl (0.5 mL) was added, and the reulstant mixture was allowed to warm to rt over 15 min and concentrated in vacuo. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried, and concentrated in vacuo to give a 63:24:13 mixture of **8**, **21**, and **22**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 20:1) gave **22** as a colorless oil (20 mg, 10%): R_f 0.53 (30−40 °C petrol/Et_2O, 10:1); δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, CMe_3), 3.25 (2H, dd, *J* =

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7.3, 2.0, C(2)H_2), 5.87 (1H, dt, J = 11.6, 7.3, C(3)H), 6.60 (1H, dt, J = 11.6, 2.0, C(4)H), 7.23−7.36 (5H, m, *Ph*). Further elution gave a 67:33 mixture of **21** and **22** (11 mg, 5%). Further elution gave **21** as a colorless oil (38 mg, 19%):[55] R_f 0.43 (30−40 °C petrol/Et_2O, 10:1); δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, CMe_3), 3.16 (2H, dd, J = 7.1, 1.5, C(2)H_2), 6.29 (1H, dt, J = 15.9, 7.1, C(3)H), 6.47 (1H, dt, J = 15.9, 1.5, C(4)H), 7.20−7.39 (5H, m, *Ph*). Further elution gave **8** as a white solid (183 mg, 56%); R_f 0.23 (30−40 °C petrol/Et_2O, 20:1); mp 55−56 °C; $[\alpha]_D^{25}$ −19.3 (c 1.0 in $CHCl_3$); ν_{max} 1727 (C═O); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, J = 6.6, C(α)*Me*), 1.42 (9H, s, CMe_3), 2.19 (1H, dd, J = 14.0, 6.7, C(2)H_A), 2.20 (3H, s, N*Me*), 2.40 (1H, dd, J = 14.0, 7.9, C(2)H_B), 2.47 (1H, dd, J = 13.3, 8.3, C(4)H_A), 2.79 (1H, dd, J = 13.3, 6.1, C(4)H_B), 3.52−3.61 (1H, m, C(3)H), 3.65 (1H, q, J = 6.6, C(α)H), 7.06−7.30 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.9 (C(α)*Me*), 28.1 (CMe_3), 32.1 (N*Me*), 35.8 (*C*(4)), 37.3 (*C*(2)), 58.1 (*C*(3)), 62.2 (*C*(α)), 79.9 (*C*Me$_3$), 125.8, 126.6 (*p-Ph*), 127.3, 128.1, 128.2, 129.3 (*o,m-Ph*), 140.0, 146.0 (*i-Ph*), 172.1 (*C*(1)); m/z (ESI$^+$) 354 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{32}NO_2^+$ ([M + H]$^+$) requires 354.2428; found 354.2429.

(3*S*,α*S*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-4-phenylbutan-1-ol 9. $LiAlH_4$ (1.0 M in THF, 4.89 mL, 4.89 mmol) was added dropwise via syringe to a stirred solution of **7** (1.40 g, 3.26 mmol, >99:1 dr) in THF (25 mL) at 0 °C, and the resultant solution was allowed to warm to rt over 2 h. The resultant solution was then cooled to 0 °C, and 1 M aq NaOH (25 mL) was added. The resultant mixture was heated at reflux for 1 h, allowed to cool to rt, and filtered through Celite (eluent EtOAc), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 3:1 → 1:1) gave **9** as a colorless oil (914 mg, 78%, >99:1 dr): $[\alpha]_D^{25}$ +13.0 (c 1.0 in $CHCl_3$); ν_{max} 3389 (O−H); δ_H (400 MHz, $CDCl_3$) 1.32−1.42 (1H, m, C(2)H_A), 1.50 (3H, d, J = 7.1, C(α)*Me*), 1.52−1.67 (1H, m, C(2)H_B), 2.53 (1H, dd, J = 12.8, 10.5, C(4)H_A), 2.73 (1H, m, O*H*), 3.01−3.22 (3H, m, C(1)H_A, C(3)H, C(4)H_B), 3.28−3.40 (1H, m, C(1)H_B), 3.71−3.85 (1H, m, NC$H_A$$H_B$Ph), 3.95−4.12 (2H, m, C(α)H, NCH$_A$$H_B$Ph), 7.07−7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 32.7 (*C*(2)), 39.1 (*C*(4)), 50.0 (NCH_2Ph), 56.3 (*C*(α)), 57.4 (*C*(3)), 61.8 (*C*(1)), 126.0, 127.0, 127.1 (*p-Ph*), 128.0, 128.2, 128.4, 128.5, 129.1 (*o,m-Ph*), 140.1, 140.3, 143.5 (*i-Ph*); m/z (ESI$^+$) 360 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{30}NO^+$ ([M + H]$^+$) requires 360.2322; found 360.2323.

(3*S*,α*S*)-3-[*N*-Methyl-*N*-(α-methylbenzyl)amino]-4-phenylbutan-1-ol 10. $LiAlH_4$ (1.0 M in THF, 0.40 mL, 0.40 mmol) was added dropwise via syringe to a stirred solution of **8** (100 mg, 0.28 mmol, >99:1 dr) in THF (3 mL) at 0 °C, and the resultant solution was allowed to warm to rt over 2 h. The resultant solution was then cooled to 0 °C, and 1 M aq NaOH (3 mL) was added. The resultant mixture was heated at reflux for 1 h, allowed to cool to rt, and filtered through Celite (eluent EtOAc), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 1:1) gave **10** as a colorless oil (64 mg, 80%, >99:1 dr): R_f 0.13 (30−40 °C petrol/Et_2O, 1:1); $[\alpha]_D^{25}$ −94.8 (c 1.0 in $CHCl_3$); ν_{max} 3403 (O−H); δ_H (400 MHz, $CDCl_3$) 1.40−1.48 (1H, app dq J = 14.8, 2.9, C(2)H_A), 1.55 (3H, d, J = 6.6, C(α)*Me*), 1.86 (1H, dddd, J = 14.8, 11.1, 9.6, 5.3, C(2)H_B), 2.15 (3H, s, N*Me*), 2.37 (1H, dd, J = 13.0, 11.1, C(4)H_A), 2.89 (1H, dd, J = 13.0, 2.9, C(4)H_B), 3.51 (1H, app tt, J = 11.1, 2.9, C(3)H), 3.71−3.83 (3H, m, C(1)H_2, C(α)H), 5.95 (1H, br s, O*H*), 7.13−7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.8 (C(α)*Me*), 29.9 (*C*(2)), 32.8 (N*Me*), 34.0 (*C*(4)), 62.5, 62.7 (*C*(3), *C*(α)), 64.3 (*C*(1)), 126.1 (*p-Ph*), 127.2 (*o,m-Ph*), 127.2 (*p-Ph*), 128.5, 128.7, 129.2 (*o,m-Ph*), 140.0, 144.6 (*i-Ph*); m/z (ESI$^+$) 284 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{26}NO^+$ ([M + H]$^+$) requires 284.2009; found 284.2010.

(4*R*,α*S*)-4-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-phenylpentanenitrile 13. A solution of DIAD (1.25 mL, 6.34 mmol) in THF (7 mL) was added dropwise via syringe to a stirred solution of **9** (760 mg, 2.11 mmol, >99:1 dr), PPh_3 (1.66 g, 6.34 mmol), and acetone cyanohydrin (0.58 mL, 6.34 mmol) in THF (28 mL) at 0 °C, at such a rate as to maintain the temperature at 0 °C (approximately 15 min addition time). The resultant solution was stirred for 30 min, allowed to warm to rt, stirred at rt for 16 h, and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 5:1 → 2:1) gave **13** as a white solid (681 mg, 88%, >99:1 dr): mp 72−74 °C; $[\alpha]_D^{25}$ +16.4 (c 1.0 in $CHCl_3$); ν_{max} 2244 (C≡N); δ_H (400 MHz, $CDCl_3$) 1.45−1.58 (3H, m, C(2)H_A, C(3)H_2) overlapping 1.53 (3H, d, J = 7.0, C(α)*Me*), 2.17−2.25 (1H, m, C(2)H_B), 2.54 (1H, dd, J = 13.2, 10.6, C(5)H_A), 2.84−2.93 (1H, m, C(4)H), 3.19 (1H, dd, J = 13.2, 3.3, C(5)H_B), 3.84 (1H, d, J = 13.8, NC$H_A$$H_B$Ph), 3.94 (1H, d, J = 13.8, NCH$_A$$H_B$Ph), 4.05 (1H, q, J = 7.0, C(α)H), 7.12−7.43 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3 (*C*(2)), 15.2 (C(α)*Me*), 27.3 (*C*(3)), 38.4 (*C*(5)), 49.9 (NCH_2Ph), 56.3 (*C*(α)), 57.8 (*C*(4)), 120.1 (*C*(1)), 126.2, 127.0, 127.1, (*p-Ph*), 127.7, 128.2, 128.4, 128.5, 128.8, 128.9 (*o,m-Ph*), 139.6, 140.3, 143.8 (*i-Ph*); m/z (ESI$^+$) 369 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{28}N_2Na^+$ ([M + Na]$^+$) requires 391.2145; found 391.2145.

(4*R*,α*S*)-4-[*N*-Methyl-*N*-(α-methylbenzyl)amino]-5-phenylpentanenitrile 14. A solution of DIAD (313 μL, 1.59 mmol) in THF (2 mL) was added dropwise via syringe to a stirred solution of **10** (150 mg, 0.53 mmol, >99:1 dr), PPh_3 (417 mg, 1.59 mmol), and acetone cyanohydrin (145 μL, 1.59 mmol) in THF (13 mL) at 0 °C, at such a rate as to maintain the temperature at 0 °C (approximately 15 min addition time). The resultant solution was then allowed to warm to rt and stirred at rt for 16 h and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 3:1) gave **14** as a colorless oil (90 mg, 58%, >99:1 dr): $[\alpha]_D^{25}$ −16.6 (c 1.0 in $CHCl_3$); ν_{max} 2245 (C≡N); δ_H (400 MHz, $CDCl_3$) 1.44 (3H, d, J = 6.7, C(α)*Me*), 1.65−1.72 (2H, m, C(3)H_2), 2.08 (3H, s, N*Me*), 2.27−2.47 (3H, m, C(2)H_2, C(5)H_A), 2.98 (1H, dd, J = 13.0, 3.5, C(5)H_B), 3.22−3.31 (1H, m, C(4)H), 3.74 (1H, q, J = 6.7, C(α)H), 7.12−7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.5 (*C*(2)), 21.7 (C(α)*Me*), 26.4 (*C*(3)), 32.3 (N*Me*), 34.2 (*C*(5)), 58.4 (*C*(4)), 62.2 (*C*(α)), 120.3 (*C*(1)), 126.2, 126.9 (*p-Ph*), 127.1, 128.4, 128.6, 129.1 (*o,m-Ph*), 139.6, 146.1 (*i-Ph*); m/z (ESI$^+$) 293 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{24}N_2Na^+$ ([M + Na]$^+$) requires 315.1832; found 315.1831.

(2*R*,α*S*)-1-Phenyl-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-dodecan-5-one 15. *n*-Heptylmagnesium bromide (1.0 M in Et_2O, 3.66 mL, 3.66 mmol) was added dropwise via syringe to a stirred solution of **13** (450 mg, 1.22 mmol, >99:1 dr) in Et_2O (10 mL) at rt, and the resultant solution was stirred at rt for 16 h. Saturated aq NH_4Cl (0.5 mL) and H_2O (0.5 mL) were then added sequentially. The aqueous layer was extracted with Et_2O (3 × 2 mL), and the combined organic extracts were washed sequentially with saturated aq $NaHCO_3$ (10 mL) and brine (10 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 7:1 → 3:1) gave **15** as colorless oil (501 mg, 87%, >99:1 dr): $[\alpha]_D^{25}$ −5.3 (c 1.0 in $CHCl_3$); ν_{max} 1710 (C═O); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, J = 6.9, C(12)H_3) 1.10−1.55 (12H, m, C(3)H_2, C(7)H_2−C(11)H_2) overlapping 1.42 (3H, d, J = 6.9, C(α)*Me*), 1.76 (1H, ddd, J = 17.2, 10.0, 5.9, C(4)H_A), 1.98−2.14 (2H, m, C(6)H_2), 2.28 (1H, ddd, J = 17.2, 10.0, 4.7, C(4)H_B), 2.53 (1H, dd, J = 13.1, 9.6, C(1)H_A), 2.79−2.88 (1H, m, C(2)H), 3.10 (1H, dd, J = 13.1, 4.1, C(1)H_B), 3.82 (1H, d, J = 14.2, NC$H_A$$H_B$Ph), 3.92 (1H, d, J = 14.2, NCH$_A$$H_B$Ph), 4.02 (1H, q, J = 6.9, C(α)H), 7.10−7.38 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(12)), 16.1 (C(α)*Me*), 22.6, 23.9, 25.0, 29.1, 29.2, 31.7 (*C*(3), *C*(7)−*C*(11)), 39.2 (*C*(1)), 40.3 (*C*(4)), 42.7 (*C*(6)), 50.0 (NCH_2Ph), 56.2 (*C*(α)), 58.3 (*C*(2)), 125.9, 126.7, 126.8 (*p-Ph*), 127.9, 128.0, 128.2, 128.3, 128.8, 129.2 (*o,m-Ph*), 140.6, 141.3, 144.6 (*i-Ph*), 211.7 (*C*(5)); m/z (ESI$^+$) 470 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{44}NO^+$ ([M + H]$^+$) requires 470.3417; found 470.3421.

(2*R*,α*S*)-1-Phenyl-2-[*N*-methyl-*N*-(α-methylbenzyl)amino]-dodecan-5-one 16. *n*-Heptylmagnesium bromide (1.0 M in Et_2O, 0.72 mL, 0.72 mmol) was added dropwise via syringe to a stirred solution of **14** (70 mg, 0.24 mmol, >99:1 dr) in Et_2O (2 mL) at rt, and the resultant solution was stirred at rt for 16 h. Saturated aq NH_4Cl (0.5 mL) and H_2O (0.5 mL) were then added sequentially. The aqueous layer was extracted with Et_2O (3 × 2 mL), and the combined organic extracts were washed sequentially with saturated aq $NaHCO_3$ (10 mL) and brine (10 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 7:1 → 3:1) gave **16** as a colorless oil (77 mg, 82%, >99:1

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dr): $[\alpha]_D^{25}$ −18.4 (*c* 1.0 in $CHCl_3$); ν_{max} 1713 (C═O); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* = 6.8, C(12)H_3), 1.19−1.40 (8H, m, C(8)H_2−C(11)H_2) overlapping 1.35 (3H, d, *J* = 6.6, C(*α*)*Me*), 1.46−1.65 (3H, m, C(3)H_A, C(7)H_2), 1.66−1.75 (1H, m, C(3)H_B), 2.08 (3H, s, N*Me*), 2.27−2.41 (4H, m, C(1)H_A, C(4)H_A, C(6)H_2), 2.52 (1H, ddd, *J* = 16.9, 8.7, 5.5, C(4)H_B), 2.87 (1H, dd, *J* = 13.0, 4.1, C(1)H_B), 3.01−3.10 (1H, m, C(2)*H*), 3.69 (1H, q, *J* = 6.6, C(*α*)*H*), 7.11−7.30 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(12)), 22.0 (C(*α*)*Me*), 22.6 (*C*(8)−*C*(11)), 23.9 (*C*(7)), 24.4 (*C*(3)), 29.1, 29.2, 31.7 (*C*(8)−*C*(11)), 32.3 (N*Me*), 35.1 (*C*(1)), 40.2 (*C*(4)), 42.9 (*C*(6)), 59.2 (*C*(2)), 62.0 (*C*(*α*)), 125.7, 126.6 (*p*-*Ph*), 127.2, 128.2, 128.3, 129.2 (*o*,*m*-*Ph*), 140.6, 146.6 (*i*-*Ph*), 211.6 (*C*(5)); *m*/*z* (ESI$^+$) 394 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{40}NO^+$ ([M + H]$^+$) requires 394.3104; found 394.3101.

(2*R*,5*R*)-*N*(1)-Methyl-2-benzyl-5-(heptan-1′-yl)pyrrolidine [3-Deoxy-(+)-preussin B] 19 and (2*R*,5*S*)-*N*(1)-Methyl-2-benzyl-5-(heptan-1′-yl)pyrrolidine 20. *Method A (from **15**).* Step 1. Pearlman's catalyst (50% w/w substrate, 250 mg) was added to a degassed solution of **15** (500 mg, 1.06 mmol, >99:1 dr) in MeOH (10 mL), and the resultant suspension was stirred vigorously under H_2 (5 atm) for 16 h. The resultant suspension was filtered through Celite (eluent MeOH) and concentrated in vacuo to give a 75:25 mixture of **17** and **18**, respectively (288 mg).

Step 2. Pd/C (50% w/w substrate, 144 mg) and formaldehyde (37 wt % aq solution, 159 μL, 2.13 mmol) were added sequentially to a degassed solution of the residue from the previous step in MeOH (10 mL), and the resultant suspension was stirred vigorously under H_2 (1 atm) for 10 min. The resultant suspension was filtered through Celite (eluent MeOH) and concentrated in vacuo to give a 75:25 mixture of **19** and **20**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 10:1 → 3:1) gave **19** as a colorless oil (192 mg, 66% from **15**, >99:1 dr): $[\alpha]_D^{25}$ +9.6 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* = 7.0, C(7′)H_3), 1.16−1.51 (13H, m, C(3)H_A, C(4)H_A, C(1′)H_A, C(2′)H_2−C(6′)H_2), 1.57−1.85 (3H, m, C(3)H_B, C(4)H_B, C(1′)H_B), 2.08−2.17 (1H, m, C(5)*H*), 2.32−2.48 (2H, m, C(2)*H*, C(2)C$H_A$$H_B$Ph) overlapping 2.36 (3H, s, N*Me*), 3.09 (1H, dd, *J* = 12.4, 3.2, C(2)CH$_A$$H_B$Ph), 7.17−7.31 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(7′)), 22.7, 26.7 (*C*(2′)−*C*(6′)), 28.8, 28.9 (*C*(3), C(4)), 29.3, 30.0, 31.8 (*C*(2′)−*C*(6′)), 34.6 (*C*(1′)), 39.2 (N*Me*), 41.1 (C(2)CH_2Ph), 67.7 (*C*(5)), 69.1 (*C*(2)), 125.9 (*p*-*Ph*), 128.2, 129.2 (*o*,*m*-*Ph*), 140.1 (*i*-*Ph*); *m*/*z* (ESI$^+$) 274 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{32}N^+$ ([M + H]$^+$) requires 274.2529; found 274.2530. Further elution gave **20** as a pale yellow oil (64 mg, 22%, >99:1 dr); $[\alpha]_D^{25}$ +61.8 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* = 7.0, C(7′)H_3), 1.10−1.35 (11H, m, C(1′)H_A, C(2′)H_2−C(6′)H_2), 1.44−1.82 (4H, m, C(3)H_2, C(4)H_A, C(1′)H_B), 1.95−2.04 (1H, m, C(4)H_B), 2.30−2.37 (1H, m, C(2)C$H_A$$H_B$Ph), 2.48 (3H, s, N*Me*), 2.78−2.84 (1H, m, C(5)*H*), 3.04 (1H, dd, *J* = 12.4, 3.2, C(2)CH$_A$$H_B$Ph), 3.12−3.19 (1H, m, C(2)*H*), 7.15−7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(7′)), 22.7, 26.8 (*C*(2′)−*C*(6′)), 27.8 (*C*(3)), 28.5 (*C*(4)), 29.3, 30.0 (*C*(2′)−*C*(6′)), 31.5 (*C*(1′)), 31.8 (*C*(2′)−*C*(6′)), 35.4 (N*Me*), 36.1 (C(2)CH_2Ph), 63.2 (*C*(5)), 65.3 (*C*(2)), 125.8 (*p*-*Ph*), 128.3, 129.2 (*o*,*m*-*Ph*), 140.3 (*i*-*Ph*); *m*/*z* (ESI$^+$) 274 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{32}N^+$ ([M + H]$^+$) requires 274.2529; found 274.2532.

*Method B (from **16**).* Pearlman's catalyst (50% w/w substrate, 13 mg) was added to a degassed solution of **16** (26 mg, 0.07 mmol) in MeOH (2 mL), and the resultant suspension was stirred vigorously under H_2 (5 atm) for 16 h. The resultant suspension was filtered through Celite (eluent MeOH) and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 10:1 → 3:1) gave **19** as a colorless oil (14 mg, 78%, >99:1 dr).

***tert*-Butyl (2*S*,3*S*,*αS*)-2-Hydroxy-3-[*N*-benzyl-*N*-(*α*-methylbenzyl)amino]-4-phenylbutanoate 27.** *n*-BuLi (2.5 M in hexanes, 11.4 mL, 28.4 mmol) was added dropwise via syringe to a stirred solution of (*S*)-*N*-benzyl-*N*-(*α*-methylbenzyl)amine (6.20 g, 29.3 mmol, >99% ee) in THF (40 mL) at −78 °C. The resultant solution was stirred at −78 °C for 30 min. A solution of **6** (4.00 g, 18.3 mmol, >99:1 dr [(*E*):(*Z*) ratio]) in THF (40 mL) at −78 °C was added, and the resultant solution was stirred at −78 °C for a further 2 h. (+)-CSO (8.78 g, 29.3 mmol) was added, and the reulstant mixture was allowed to warm to rt over 12 h. Saturated aq NH_4Cl (2 mL) was added, and the resultant mixture was concentrated in vacuo. The residue was partitioned between H_2O (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (30 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 15:1 → 3:1) gave **27** as a light yellow oil (5.80 g, 71%, >99:1 dr):[55] R_f 0.50 (30−40 °C petrol/Et_2O, 3:1); $[\alpha]_D^{25}$ +46.5 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* = 7.0, C(*α*)*Me*), 1.38 (9H, s, CMe_3), 2.70 (1H, dd, *J* = 14.0, 6.3, C(4)H_A), 2.90 (1H, dd, *J* = 14.0, 7.9, C(4)H_B), 2.96 (1H, d, *J* = 5.7, OH), 3.62 (1H, ddd, *J* = 7.9, 6.3, 1.4, C(3)*H*), 3.80 (1H, d, *J* = 15.4, NC$H_A$$H_B$Ph), 3.89 (1H, dd, *J* = 5.7, 1.4, C(2)*H*), 3.94 (1H, q, *J* = 7.0, C(*α*)*H*), 4.35 (1H, d, *J* = 15.4, NCH$_A$$H_B$Ph), 7.11−7.44 (15H, m, *Ph*).

***tert*-Butyl (2*S*,3*S*,*αS*)-2-Hydroxy-3-[*N*-methyl-*N*-(*α*-methylbenzyl)amino]-4-phenylbutanoate 28.** *n*-BuLi (2.5 M in hexanes, 0.57 mL, 1.43 mmol) was added dropwise via syringe to a stirred solution of (*S*)-*N*-methyl-*N*-(*α*-methylbenzyl)amine (200 mg, 1.48 mmol, >99% ee) in THF (3 mL) at −78 °C. The resultant solution was stirred at −78 °C for 30 min. A solution of **6** (202 mg, 0.92 mmol, >99:1 dr [(*E*):(*Z*) ratio]) in THF (3 mL) at −78 °C was added, and the resultant solution was stirred at −78 °C for a further 2 h. (+)-CSO (339 mg, 1.48 mmol) was added, and the resultant mixture was allowed to warm to rt over 12 h. Saturated aq NH_4Cl (0.5 mL) was added, and the reulstant mixture was concentrated in vacuo. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 15:1 → 3:1) gave **28** as a white solid (149 mg, 44%, >99:1 dr): R_f 0.45 (30−40 °C petrol/Et_2O, 3:1); mp 37−38 °C; $[\alpha]_D^{25}$ +60.8 (*c* 1.0 in $CHCl_3$); ν_{max} 3504 (O−H), 1719 (C═O); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* = 6.7, C(*α*)*Me*), 1.34 (9H, s, CMe_3), 2.47 (3H, s, N*Me*), 2.54 (1H, dd, *J* = 13.8, 6.2, C(4)H_A), 2.82 (1H, dd, *J* = 13.8, 8.5, C(4)H_B), 3.14 (1H, br s, O*H*), 3.32 (1H, ddd, *J* = 8.5, 6.2, 1.8, C(3)*H*), 3.67 (1H, q, *J* = 6.7, C(*α*)*H*), 4.31 (1H, app br s, C(2)*H*), 7.00−7.26 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.9 (C(*α*)*Me*), 27.9 (CMe_3), 32.6 (*C*(4)), 33.6 (N*Me*), 62.8 (*C*(*α*)), 63.5 (*C*(3)), 69.6 (*C*(2)), 82.4 (CMe_3), 125.7, 126.5 (*p*-*Ph*), 127.4, 127.9, 128.0, 129.6 (*o*,*m*-*Ph*), 139.8, 145.2 (*i*-*Ph*), 174.4 (*C*(1)); *m*/*z* (ESI$^+$) 392 ([M + Na]$^+$, 3%), 370 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{32}NO_3^+$ ([M + H]$^+$) requires 370.2377; found 370.2379.

(2*S*,3*S*,*αS*)-3-[*N*-Benzyl-*N*-(*α*-methylbenzyl)amino]-4-phenylbutane-1,2-diol 29. $LiAlH_4$ (1.0 M in THF, 0.34 mL, 0.34 mmol) was added dropwise via syringe to a stirred solution of **27** (100 mg, 0.22 mmol, >99:1 dr) in THF (2 mL) at 0 °C, and the resultant solution was stirred at rt for 2 h. The resultant solution was then cooled to 0 °C, and 1 M aq NaOH (2 mL) was added. The resultant mixture was heated at reflux for 1 h, allowed to cool to rt, and filtered through Celite (eluent EtOAc), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 3:1 → 1:1 → neat Et_2O) gave **29** as a colorless oil (80 mg, 95%, >99:1 dr): $[\alpha]_D^{25}$ +14.4 (*c* 1.0 in $CHCl_3$); ν_{max} 3371 (O−H); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* = 7.0, C(*α*)*Me*), 1.83 (2H, br s, O*H*), 2.91 (1H, dd, *J* = 14.0, 8.9, C(4)H_A), 3.14 (1H, dd, *J* = 14.0, 4.7, C(4)H_B), 3.22 (1H, app dt, *J* = 8.9, 4.7, C(3)*H*), 3.38−3.48 (2H, m, C(1)H_A, C(2)*H*), 3.51 (1H, dd, *J* = 9.2, 1.5, C(1)H_B), 3.93 (1H, d, *J* = 14.2, NC$H_A$$H_B$Ph), 4.00 (1H, q, *J* = 7.0, C(*α*)*H*), 4.02 (1H, d, *J* = 14.2, NCH$_A$$H_B$Ph), 7.20−7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3 (C(*α*)*Me*), 35.1 (*C*(4)), 51.8 (NCH_2Ph), 56.9 (*C*(*α*)), 59.0 (*C*(3)), 64.1 (*C*(1)), 72.7 (*C*(2)), 126.2, 127.2, 127.3 (*p*-*Ph*), 127.8, 128.5, 128.5, 128.7, 129.0 (*o*,*m*-*Ph*), 140.3, 140.4, 143.6 (*i*-*Ph*); *m*/*z* (ESI$^+$) 376 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{30}NO_2^+$ ([M + H]$^+$) requires 376.2271; found 376.2274.

(2*S*,3*S*,*αS*)-3-[*N*-Methyl-*N*-(*α*-methylbenzyl)amino]-4-phenylbutane-1,2-diol 30. $LiAlH_4$ (1.0 M in THF, 7.31 mL, 7.31 mmol) was added dropwise via syringe to a stirred solution of **28** (900 mg, 2.44 mmol, >99:1 dr) in THF (25 mL) at 0 °C, and the resultant

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solution was stirred at rt for 2 h. The resultant solution was then cooled to 0 °C, and 1 M aq NaOH (25 mL) was added. The resultant mixture was heated at reflux for 1 h, allowed to cool to rt, and filtered through Celite (eluent EtOAc), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 3:1 → 1:1 → neat Et_2O) gave **30** as a light yellow solid (727 mg, quant, >99:1 dr); mp 80−82 °C; $[\alpha]_D^{25}$ −101.2 (*c* 1.0 in $CHCl_3$); ν_{max} 3370 (O−H); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* = 6.7, C(*α*)*Me*), 2.20 (3H, s, N*Me*), 2.60−3.20 (2H, br s, O*H*) overlapping 2.84 (1H, dd, *J* = 13.9, 6.9, C(4)H_A) and 2.91 (1H, dd, *J* = 13.9, 6.4, C(4)H_B), 3.41 (1H, app q, *J* = 6.7, C(3)*H*), 3.51 (1H, q, *J* = 6.7, C(*α*)*H*), 3.62−3.82 (3H, m, C(1)H_2, C(2)*H*), 7.11−7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.3 (C(*α*)*Me*), 33.1 (*C*(4)), 34.7 (N*Me*), 63.0 (*C*(*α*)), 63.6 (*C*(3)), 66.4 (*C*(1)), 71.9 (*C*(2)), 126.2, 127.2 (*p-Ph*), 127.2, 128.5, 129.2 (*o,m-Ph*), 140.4, 144.5 (*i-Ph*); *m*/*z* (ESI$^+$) 300 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{26}NO_2^+$ ([M + H]$^+$) requires 300.1958; found 300.1960.

***tert*-Butyl (2*S*,3*S*,*αS*)-2-Benzyloxy-3-[*N*-benzyl-*N*-(*α*-methylbenzyl)amino]-4-phenylbutanoate 31.** NaH (60% dispersion in mineral oil, 28 mg, 0.69 mmol) was stirred in 30−40 °C petrol (1 mL) for 10 min; then the solvent was removed via cannula, and THF (1 mL) was added to the residue. The resultant slurry was cooled to 0 °C. A solution of **27** (300 mg, 0.66 mmol, >99:1 dr) in THF (1 mL) was added dropwise via syringe, and the resultant slurry was allowed to warm to rt over 45 min. BnBr (86 μL, 0.73 mmol) was added, and resultant solution was stirred for a further 2 h at rt, diluted with Et_2O (3 mL), and washed with saturated aq $NaHCO_3$ (2 × 5 mL). The combined aqueous washings were extracted with Et_2O (2 × 10 mL). The combined organic layers were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 9:1) gave **31** as a colorless oil (318 mg, 90%, >99:1 dr): $[\alpha]_D^{25}$ −21.9 (*c* 1.0 in $CHCl_3$); ν_{max} 1737 (C═O); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* = 6.9, C(*α*)*Me*), 1.42 (9H, s, C*Me*$_3$), 2.81 (1H, dd, *J* = 14.5, 4.0, C(4)H_A), 2.91 (1H, dd, *J* = 14.5, 9.8, C(4)H_B), 3.55 (1H, d, *J* = 15.9, NCH_AH$_B$Ph), 3.66−3.73 (2H, m, C(2)*H*, C(3)*H*), 3.79 (1H, q, *J* = 6.9, C(*α*)*H*), 4.17 (1H, d, *J* = 11.0, OCH_AH$_B$Ph), 4.50 (1H, d, *J* = 15.9, NCH$_A$$H_B$Ph), 4.61 (1H, d, *J* = 11.0, OCH$_A$$H_B$Ph), 7.08−7.38 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.1 (C(*α*)*Me*), 28.1 (C*Me*$_3$), 34.3 (*C*(4)), 50.8 (NCH_2Ph), 58.4, 60.6 (*C*(3), *C*(*α*)), 72.3 (OCH_2Ph), 79.2 (*C*(2)), 81.3 (*C*Me$_3$), 125.8, 126.2, 126.8, 127.7 (*p-Ph*), 127.8, 127.9, 128.0, 128.1, 128.3, 129.8 (*o,m-Ph*), 137.7, 140.5, 142.3, 142.8 (*i-Ph*), 171.3 (*C*(1)); *m*/*z* (ESI$^+$) 536 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{42}NO_3^+$ ([M + H]$^+$) requires 536.3159; found 536.3159.

(2*S*,3*S*,*αS*)-2-Benzyloxy-3-[*N*-benzyl-*N*-(*α*-methylbenzyl)-amino]-4-phenylbutan-1-ol 32. *Method A (One-Pot Protocol from 27).* Step 1. NaH (60% dispersion in mineral oil, 14 mg, 0.35 mmol) was stirred in 30−40 °C petrol (1 mL) for 10 min; then the solvent was removed via cannula, and THF (1 mL) was added to the residue. The resultant slurry was cooled to 0 °C. A solution of **27** (150 mg, 0.33 mmol, >99:1 dr) in THF (1 mL) was added dropwise via syringe, and the resultant slurry was allowed to warm to rt over 45 min. BnBr (43 μL, 0.36 mmol) was added, and resultant solution was stirred for a further 2 h at rt and cooled to 0 °C. $LiAlH_4$ (1.0 M in THF, 0.50 mL, 0.50 mmol) was added dropwise via syringe, and the resultant solution was allowed to warm to rt over 2 h. The resultant solution was then cooled to 0 °C, and 1 M aq NaOH (2 mL) was added. The resultant mixture was heated at reflux for 1 h, allowed to cool to rt, and filtered through Celite (eluent EtOAc), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 3:1 → 1:1) gave **32** as a colorless oil (204 mg, 94%, >99:1 dr): $[\alpha]_D^{25}$ −30.5 (*c* 1.0 in $CHCl_3$); ν_{max} 3450 (O−H); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* = 7.0, C(*α*)*Me*), 1.86 (1H, app t, *J* = 5.5, O*H*), 2.95−3.06 (2H, m, C(4)H_2), 3.28 (1H, app q, *J* = 5.0, C(2)*H*), 3.35−3.42 (2H, m, C(1)H_A, C(3)*H*), 3.46−3.54 (1H, m, C(1)H_B), 3.82 (1H, d, *J* = 14.7, NCH_AH$_B$Ph), 3.90 (1H, q, *J* = 7.0, C(*α*)*H*), 4.13 (1H, d, *J* = 14.7, NCH$_A$$H_B$Ph), 4.38 (1H, d, *J* = 11.4, OCH_AH$_B$Ph), 4.45 (1H, d, *J* = 11.4, OCH$_A$$H_B$Ph), 7.12−7.39 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.4 (C(*α*)*Me*), 35.0 (*C*(4)), 51.3 (NCH_2Ph), 57.7 (*C*(*α*)), 59.6 (*C*(3)), 63.1 (*C*(1)), 72.0 (OCH_2Ph), 80.8 (*C*(2)), 125.7, 126.8, 127.0, 127.6 (*p-Ph*), 127.7, 128.0, 128.1, 128.2, 128.3, 128.6, 129.4 (*o,m-Ph*), 138.2, 141.0, 141.3, 143.6 (*i-Ph*); *m*/*z* (ESI$^+$) 466 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{36}NO_2^+$ ([M + H]$^+$) requires 466.2741; found 466.2743.

Method B (from 31). $LiAlH_4$ (1.0 M in THF, 0.70 mL, 0.70 mmol) was added dropwise via syringe to a stirred solution of **31** (250 mg, 0.22 mmol, >99:1 dr) in THF (5 mL) at 0 °C, and the resultant solution was stirred at rt for 2 h. The resultant solution was then cooled to 0 °C, and 1 M aq NaOH (5 mL) was added. The resultant mixture was heated at reflux for 1 h, allowed to cool to rt, and filtered through Celite (eluent EtOAc), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 3:1 → 1:1) gave **32** as a colorless oil (204 mg, 94%, >99:1 dr).

(3*R*,4*S*,*αS*)-3-Benzyloxy-4-[*N*-benzyl-*N*-(*α*-methylbenzyl)-amino]-5-phenylpentanenitrile 34. A solution of DIAD (127 μL, 0.64 mmol) in THF (1 mL) was added dropwise via syringe to a stirred solution of **32** (100 mg, 0.22 mmol, >99:1 dr), PPh_3 (169 mg, 0.64 mmol), and acetone cyanohydrin (59 μL, 0.64 mmol) in THF (7 mL) at 0 °C, at such a rate as to maintain the temperature at 0 °C (approximately 15 min addition time). The resultant solution was then allowed to warm to rt and stirred at rt for 16 h and concentrated in vacuo to give an 85:15 mixture of **34** and **35**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 5:1 → 3:1) gave an impure sample of **35** as a colorless oil (<10%, >95:5 dr): δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.39 (3H, d, *J* = 6.9, C(*α*)*Me*), 2.74 (1H, dd, *J* = 13.5, 5.7, C(1)H_A), 2.84 (1H, dd, *J* = 13.5, 6.9, C(1)H_B), 3.59 (1H, d, *J* = 14.1, NCH_AH$_B$Ph), 3.72 (1H, d, *J* = 14.1, NCH_AH$_B$Ph), 3.90−3.97 (2H, m, C(2)*H*, C(*α*)*H*), 4.35 (1H, d, *J* = 12.0, OCH_AH$_B$Ph), 4.57 (1H, d, *J* = 12.0, OCH$_A$$H_B$Ph), 6.09 (1H, dd, *J* = 16.0, 7.8, C(3)*H*), 6.49 (1H, d, *J* = 16.0, C(4)*H*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 16.3 (C(*α*)*Me*), 54.9 (*C*(1)), 55.7 (NCH_2Ph), 59.0 (*C*(*α*)), 70.2 (OCH_2Ph), 79.4 (*C*(2)), 129.8 (*C*(3)), 132.6 (*C*(4)); HRMS (ESI$^+$) $C_{32}H_{34}NO^+$ ([M + H]$^+$) requires 448.2635; found 448.2638. Further elution gave **34** as a colorless oil (84 mg, 82%, >99:1 dr): $[\alpha]_D^{25}$ −27.0 (*c* 1.0 in $CHCl_3$); ν_{max} 2247 (C≡N); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* = 7.0, C(*α*)*Me*), 2.15 (1H, dd *J* = 17.0, 6.7, C(2)H_A), 2.41 (1H, dd, *J* = 17.0, 4.6, C(2)H_B), 2.96−3.08 (2H, m, C(5)H_2), 3.30 (1H, app q, *J* = 5.9, C(4)*H*), 3.34−3.40 (1H, m, C(3)*H*), 3.81 (1H, d, *J* = 14.5, NCH_AH$_B$Ph), 3.86 (1H, q, *J* = 7.0, C(*α*)*H*), 4.04 (1H, d, *J* = 14.5, NCH$_A$$H_B$Ph), 4.37 (1H, d, *J* = 11.0, OCH_AH$_B$Ph), 4.57 (1H, d, *J* = 11.0, OCH$_A$$H_B$Ph), 7.18−7.37 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.5 (C(*α*)*Me*), 21.3 (*C*(2)), 34.0 (*C*(5)), 51.2 (NCH_2Ph), 57.8 (*C*(*α*)), 61.2 (*C*(4)), 72.7 (OCH_2Ph), 118.4 (*C*(1)), 126.0 127.0, 127.2 (*p-Ph*), 127.8 (*o,m-Ph*), 127.9 (*p-Ph*), 128.0, 128.3, 128.4, 128.5, 129.4 (*o,m-Ph*), 137.2, 140.5, 140.6, 143.5 (*i-Ph*);[72] *m*/*z* (ESI$^+$) 475 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{35}N_2O^+$ ([M + H]$^+$) requires 475.2744; found 475.2749.

(4*S*,*αS*,*E*)- and (4*S*,*αS*,*Z*)-4-[*N*-Benzyl-*N*-(*α*-methylbenzyl)-amino]-5-phenylpent-2-enenitrile 36 and 37. Vinylmagnesium bromide (1.0 M in THF, 0.64 mL, 0.64 mmol) was added dropwise via syringe to a stirred solution of **34** (100 mg, 0.21 mmol, >99:1 dr) in Et_2O (2 mL) at rt, and the resultant solution was stirred at rt for 16 h. Saturated aq NH_4Cl (0.5 mL) and H_2O (0.5 mL) were sequentially added. The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed sequentially with saturated aq $NaHCO_3$ (10 mL) and brine (10 mL), dried, and concentrated in vacuo to give a 55:45 mixture of **36** and **37**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 5:1 → 1:1) gave a 55:45 mixture of **36** and **37** as a yellow oil (43 mg, 38%). Data for mixture: ν_{max} 2222 (C≡N); *m*/*z* (ESI$^+$) 367 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{26}N_2Na^+$ ([M + Na]$^+$) requires 389.1988; found 389.1986. Data for **36**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.29 (3H, d, *J* = 7.0, C(*α*)*Me*), 2.73 (1H, dd, *J* = 13.5, 9.1, C(5)H_A), 3.09 (1H, dd, *J* = 13.5, 5.4, C(5)H_B), 3.55−3.64 (1H, m, C(4)*H*), 3.78 (1H, d, *J* = 15.1, NCH_AH$_B$Ph), 3.95 (1H, q, *J* = 7.0, C(*α*)*H*), 4.10 (1H, d, *J* = 15.1, NCH$_A$$H_B$Ph), 5.05 (1H, dd, *J* = 16.4, 1.2, C(2)*H*), 6.45 (1H, dd, *J* = 16.4, 7.2, C(3)*H*); δ_C (100 MHz,

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$CDCl_3$) [selected peaks] 19.5 (C(α)*Me*), 38.8 (C(5)), 50.7 (NCH_2Ph), 59.0 (C(α)), 61.6 (C(4)), 101.0 (C(2)), 117.2 (C(1)), 154.4 (C(3)). Data for **37**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.26 (3H, d, J = 7.0, C(α)*Me*), 2.70 (1H, dd J = 13.6, 7.5 C(5)H_A), 3.05 (1H, dd, J = 13.6, 7.2, C(5)H_B), 3.77 (1H, d, J = 15.1, NCH_AH_BPh), 3.94 (1H, q, J = 7.0, C(α)*H*), 4.06 (1H, d, J = 15.1, NCH_AH_BPh), 4.13−4.21 (1H, m, C(4)*H*), 5.06 (1H, d, J = 11.0, C(2)*H*), 6.26 (1H, dd, J = 11.0, 9.9, C(3)*H*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 19.6 (C(α)*Me*), 39.9 (C(5)), 50.5 (NCH_2Ph), 58.9 (C(α)), 61.1 (C(4)), 100.0 (C(2)), 115.3 (C(1)), 153.4 (C(3)).

(2*S*,α*S*,*E*)-1-Phenyl-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-dodec-3-en-5-one 38 and (2*S*,3*R*,α*S*)-1-Phenyl-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-benzyloxydodecan-5-one 39. *n*-Heptylmagnesium bromide (1.0 M in Et_2O, 0.64 mL, 0.64 mmol) was added dropwise via syringe to a stirred solution of **34** (100 mg, 0.21 mmol, >99:1 dr) in Et_2O (2 mL) at rt, and the resultant solution was stirred at rt for 16 h. Saturated aq NH_4Cl (0.5 mL) and H_2O (0.5 mL) were then added sequentially. The aqueous layer was extracted with Et_2O (3 × 2 mL), and the combined organic extracts were washed sequentially with saturated aq $NaHCO_3$ (10 mL) and brine (10 mL), dried, and concentrated in vacuo to give a 50:50 mixture of **38** and **39**. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 5:1 → 1:1) gave an impure sample of **39** as colorless oil (34 mg, ∼25%, >90:10 dr): ν_{max} 1713 (C═O); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J = 6.9, C(12)H_3) 1.09−1.35 (11H, m, C(8)H_2−C(11)H_2, C(α)*Me*), 1.35−1.45 (2H, m, C(7)H_2), 2.20−2.18 (2H, m, C(6)H_2), 2.28 (1H, dd, J = 16.7, 7.0, C(4)H_A), 2.40 (1H, dd, J = 16.7, 4.7, C(4)H_B), 2.94−3.08 (3H, m, C(1)H_2, C(2)*H*), 3.80 (1H, d, J = 15.0, NCH_AH_BPh), 3.94 (1H, q, J = 6.9, C(α)*H*), 4.04−4.12 (1H, m, C(3)*H*), 4.16 (1H, d, J = 15.0, NCH_AH_BPh), 4.35 (2H, app s, OCH_2Ph), 7.12−7.38 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (C(12)), 18.4 (C(α)*Me*), 22.6 (C(8)−C(11)), 23.6 (C(7)), 29.1, 31.7 (C(8)−C(11)), 34.7 (C(1)), 43.9 (C(6)), 46.7 (C(4)), 51.0 (NCH_2Ph), 58.3 (C(α)), 62.4 (C(2)), 71.9 (OCH_2Ph), 76.9 (C(3)), 125.7, 126.5, 126.7, 127.4 (*p-Ph*), 127.6, 127.9, 128.1, 128.2, 128.3, 129.4 (*o,m-Ph*), 138.5, 141.3, 142.0, 144.6 (*i-Ph*), 210.1 (C(5)); m/z (ESI$^+$) 576 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{40}H_{49}NNaO_2^+$ ([M + Na]$^+$) requires 598.3656; found 598.3653. Further elution gave **38** as a colorless oil (44 mg, 45%, >99:1 dr): $[\alpha]_D^{25}$ −15.9 (*c* 1.0 in $CHCl_3$); ν_{max} 1699 (C═O); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, J = 6.9, C(12)H_3), 1.16−1.35 (11H, m, C(8)H_2−C(11)H_2, C(α)*Me*), 1.43−1.54 (2H, m, C(7)H_2), 2.20−2.35 (2H, m, C(6)H_2), 2.79 (1H, dd, J = 13.6, 8.2, C(1)H_A), 3.06 (1H, dd, J = 13.6, 6.5, C(1)H_B), 3.66 (1H, app q, J = 7.5, C(2)*H*), 3.74 (1H, d, J = 15.3, NCH_AH_BPh), 3.97 (1H, q, J = 6.9, C(α)*H*), 4.11 (1H, d, J = 15.3, NCH_AH_BPh), 5.75 (1H, dd, J = 16.0, 1.0, C(4)*H*), 6.51 (1H, dd, J = 16.0, 7.8, C(3)*H*), 6.98−7.40 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (C(12)), 20.5 (C(α)*Me*), 22.6 (C(8)−C(11)), 24.3 (C(7)), 29.1, 29.2, 31.7 (C(8)−C(11)), 39.2 (C(1)), 40.0 (C(6)), 50.7 (NCH_2Ph), 59.2 (C(α)), 61.2 (C(2)), 126.2, 126.6, 127.0 (*p-Ph*), 127.6, 127.9, 128.2, 128.3, 128.4, 129.4 (*o,m-Ph*), 131.3 (C(4)), 138.7, 141.6, 144.4 (*i-Ph*), 145.0 (C(3)), 200.8 (C(5)); m/z (ESI$^+$) 468 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{41}NNaO^+$ ([M + Na]$^+$) requires 490.3080; found 490.3081.

(2*S*,3*S*,α*S*)-1,2-Epoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-4-phenylbutane 44. Et_3N (333 μL, 2.40 mmol) and MsCl (65 μL, 0.84 mmol) were sequentially added dropwise to a stirred solution of **29** (300 mg, 0.80 mmol, >99:1 dr) in CH_2Cl_2 (3 mL) at 0 °C. The resultant solution was stirred for 1 h at rt, and then H_2O (10 mL) was added. The resultant mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried and concentrated in vacuo. The residue was dissolved in MeOH (3 mL), and K_2CO_3 (552 mg, 4.00 mmol) was added. The resultant mixture was stirred at rt for 1 h and filtered through Celite (eluent MeOH), and the filtrate was concentrated in vacuo. The residue was partitioned between H_2O (10 mL) and Et_2O (10 mL), and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (40 mL), dried, and concentrated in vacuo to give a 90:10 mixture of **44** and **45**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 10:1) gave **44** as a colorless oil (177 mg, 62%, >99:1 dr): $[\alpha]_D^{25}$ −29.0 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, J = 6.9, C(α)*Me*), 2.19 (1H, dd, J = 4.9, 2.9, C(1)H_A), 2.41 (1H, dd, J = 4.9, 4.3, C(1)H_B), 2.65−2.78 (2H, m, C(2)*H*, C(4)H_A), 2.82−2.92 (2H, m, C(3)*H*, C(4)H_B), 3.85 (1H, d, J = 15.0, NCH_AH_BPh), 3.99 (1H, q, J = 6.9, C(α)*H*), 4.05 (1H, d, J = 15.0, NCH_AH_BPh), 7.03−7.28 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.0 (C(α)*Me*), 35.6 (C(4)), 46.0 (C(1)), 51.1 (NCH_2Ph), 53.1 (C(2)), 58.1 (C(α)), 60.4 (C(3)), 126.0, 126.7, 126.9 (*p-Ph*), 127.7, 128.1, 128.2, 129.5 (*o,m-Ph*), 139.8, 141.4, 144.3 (*i-Ph*); m/z (ESI$^+$) 358 ([M + H]$^+$), 100%; HRMS (ESI$^+$) $C_{25}H_{28}NO^+$ ([M + H]$^+$) requires 358.2165; found 358.2165. Further elution gave an impure sample of **45** as a colorless oil (28 mg, <10%, >95:5 dr): δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, J = 6.8, C(α)*Me*), 2.40 (1H, dd, J = 12.9, 10.2, C(1)H_A), 2.57 (1H, dd, J = 12.9, 3.4, C(1)H_B), 3.25 (1H, br s, O*H*), 3.53 (1H, d, J = 13.4, NCH_AH_BPh), 3.70 (1H, d, J = 13.4, NCH_AH_BPh), 3.96 (1H, q, J = 6.8, C(α)*H*), 4.12−4.20 (1H, m, C(2)*H*), 5.90 (1H, dd, J = 16.0, 6.5, C(3)*H*), 6.47 (1H, d, J = 16.0, C(4)*H*), 7.09−7.30 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.5 (C(α)*Me*), 54.7 (NCH_2Ph), 55.4 (C(1)), 56.9 (C(α)), 68.4 (C(2)), 126.4 (*o,m-Ph*), 127.2, 127.3, 127.5 (*p-Ph*), 127.9, 128.3, 128.5, 128.6, 129.0 (*o,m-Ph*), 129.8 (C(3)), 131.0 (C(4)), 136.7, 139.4, 142.8 (*i-Ph*); HRMS (ESI$^+$) $C_{25}H_{28}NO^+$([M + H]$^+$) requires 358.2165; found 358.2167.

(2*S*,3*R*,α*S*)-1-Phenyl-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-hydroxydodecan-5-one (1′,3′-Propylene)dithioacetal 48. *n*-BuLi (0.57 mL, 1.42 mmol) was added dropwise via syringe to a stirred solution of 2-*n*-heptyl-1,3-dithiane[64] (193 mg, 0.95 mmol) in THF (0.8 mL) at 0 °C, and the resultant solution was stirred at rt for 1 h. A solution of **44** (170 mg, 0.46 mmol, >99:1 dr) in THF (0.2 mL) was then added dropwise; the resultant solution was stirred at rt for 1 h, and then H_2O (10 mL) was added. The resultant mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed sequentially with H_2O (30 mL), 2 M aq NaOH (30 mL), and H_2O (30 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol) gave recovered 2-*n*-heptyl-1,3-dithiane (96 mg, 50%). Further elution (eluent 30−40 °C petrol/Et_2O, 10:1 → 5:1) gave **48** as a colorless oil (226 mg, 86%, >99:1 dr): $[\alpha]_D^{25}$ −4.0 (*c* 1.0 in $CHCl_3$); ν_{max} 3408 (O−H); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, J = 7.0, C(12)H_3), 1.20 (3H, d, J = 6.9, C(α)*Me*) overlapping 1.14−1.53 (11H, m, C(4)H_A, C(7)H_2−C(11)H_2), 1.62−1.84 (3H, m, C(6)H_2, C(2′)H_A), 1.84−1.96 (2H, m, C(4)H_B, C(2′)H_B), 2.46−2.69 (3H, m, C(1′)H_2, C(3′)H_A), 2.81 (1H, ddd, J = 13.7, 10.5, 2.9, C(3′)H_B), 2.95−3.11 (3H, m, C(1)H_2, C(2)*H*), 3.50 (1H, d, J = 2.6, O*H*), 3.95 (1H, d, J = 15.1, NCH_AH_BPh), 4.02−4.11 (2H, m, C(3)*H*, C(α)*H*), 4.25 (1H, d, J = 15.1, NCH_AH_BPh), 7.16−7.45 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (C(12)), 18.0 (C(α)*Me*), 22.7, 23.9 (C(7)−C(11)), 24.7 (C(2′)), 25.7 (C(1′)), 26.3 (C(3′)), 29.1, 29.8, 31.9 (C(7)−C(11)), 34.2 (C(1)), 39.4 (C(6)), 42.6 (C(4)), 51.2 (NCH_2Ph), 52.3 (C(5)), 58.0 (C(α)), 63.7 (C(2)), 69.9 (C(3)), 125.7, 126.5, 126.8 (*p-Ph*), 127.7, 128.1, 128.2, 129.7 (*o,m-Ph*), 141.3, 142.2, 144.7 (*i-Ph*); m/z (ESI$^+$) 576 ([M + H]$^+$), 100%; HRMS (ESI$^+$) $C_{36}H_{50}NOS_2^+$ ([M + H]$^+$) requires 576.3328; found 576.3329.

(2*S*,3*R*,α*S*)-1-Phenyl-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-hydroxydodecan-5-one 49. PIFA (2.24 g, 5.21 mmol) was added to a stirred solution of **48** (1.00 g, 1.74 mmol) in MeOH/H_2O (v/v, 9/1, 20 mL) at rt. The resultant solution was stirred at rt for 2 h; then saturated aq $NaHCO_3$ (1 mL) was added, and the resultant mixture was concentrated in vacuo. The residue was partitioned between Et_2O (20 mL) and H_2O (20 mL), and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (60 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 10:1 → 5:1 → 3:1) gave **49** as a colorless oil (500 mg, 59%, >99:1 dr): $[\alpha]_D^{25}$ +5.8 (*c* 1.0 in $CHCl_3$); ν_{max} 3502 (O−H), 1703 (C═O); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, J = 6.9, C(12)H_3), 1.15−1.38 (11H, m, C(8)H_2−C(11)H_2, C(α)*Me*), 1.38−1.50 (2H, m, C(7)H_2), 2.06−2.23 (3H, m, C(4)H_A, C(6)H_2), 2.44 (1H, dd, J = 16.5, 2.1, C(4)H_B), 2.78 (1H, br s, O*H*), 2.92−3.12 (3H, m, C(1)H_2, C(2)*H*), 3.85−3.93 (1H, m, C(3)*H*), 3.94 (1H, d, J = 14.8, NCH_AH_BPh), 4.00 (1H, q, J = 6.9, C(α)*H*), 4.10 (1H, d, J = 14.8, NCH_AH_BPh), 7.18−7.40 (15H, m, *Ph*);

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δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(12)), 16.5 (C(*α*)*Me*), 22.6 (*C*(8)−*C*(11)), 23.6 (*C*(7)), 29.0, 29.1, 31.6 (*C*(8)−*C*(11)), 34.6 (*C*(1)), 43.3 (*C*(6)), 46.9 (*C*(4)), 51.5 (NCH_2Ph), 57.3 (*C*(*α*)), 61.6 (*C*(2)), 69.0 (*C*(3)), 125.9, 126.8, 127.0 (*p-Ph*), 127.8, 128.2, 128.3, 128.5, 129.3 (*o,m-Ph*), 141.1, 141.2, 144.0 (*i-Ph*), 212.4 (*C*(5)); *m*/*z* (ESI^+) 486 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{33}H_{43}NNaO_2^+$ ($[M + Na]^+$) requires 508.3186; found 508.3187.

(2*S*,3*R*,5*R*)-*N*(1)-Methyl-2-benzyl-5-(heptan-1′-yl)pyrrolidin-3-ol [C(3)-Epimer of (+)-Preussin B] 52 and (2*S*,3*R*,5*S*)-*N*(1)-Methyl-2-benzyl-5-(heptan-1′-yl)pyrrolidin-3-ol [C(2)-Epimer of (−)-Preussin B] 53. Step 1. Pearlman's catalyst (50% w/w substrate, 35 mg) was added to a degassed solution of **49** (70 mg, 0.14 mmol, >99:1 dr) in MeOH (1 mL), and the resultant suspension was stirred vigorously under H_2 (5 atm) at rt for 16 h. The resultant suspension was filtered through Celite (eluent MeOH) and concentrated in vacuo to give a 25:75 mixture of **50** and **51**, respectively (48 mg).

Step 2. Pd/C (50% w/w substrate, 24 mg) and formaldehyde (37 wt % aq solution, 22 μL, 2.13 mmol) were added sequentially to a degassed solution of the residue from the previous step in MeOH (1 mL), and the resultant suspension was stirred vigorously under H_2 (1 atm) for 10 min. The resultant suspension was filtered through Celite (eluent MeOH) and concentrated in vacuo to give a 25:75 mixture of **52** and **53**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 10:1 → 5:1 → 3:1 → 1:1 → neat EtOAc) gave **52** as a light yellow oil (8 mg, 18% from **49**, >99:1 dr): $[\alpha]_D^{25}$ +1.7 (*c* 1.0 in $CHCl_3$); ν_{max} 3365 (O−H); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* = 7.0, C(7′)H_3), 0.94 (1H, d, *J* = 3.3, O*H*), 1.12−1.35 (11H, m, C(1′)H_A, C(2′)H_2−C(6′)H_2), 1.60−1.72 (2H, m, C(4)H_2), 1.77 (1H, ddd, *J* = 13.3, 6.7, 2.8, C(1′)H_B), 2.36 (3H, s, N*Me*), 2.40−2.51 (2H, m, C(2)*H*, C(5)*H*), 2.55 (1H, dd, *J* = 13.3, 9.6, C(2)C$H_A$$H_B$Ph), 3.06 (1H, dd, *J* = 13.3, 4.5, C(2)C$H_A$$H_B$Ph), 3.98−4.04 (1H, m, C(3)*H*), 7.18−7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(7′)), 22.7, 26.4, 29.3, 29.9, 31.8 (*C*(2′)−*C*(6′)), 33.9 (*C*(1′)), 39.1 (N*Me*), 39.1 (*C*(4)), 39.4 (C(2)CH_2Ph), 64.9 (*C*(5)), 74.8 (*C*(3)), 77.2 (*C*(2)), 126.4 (*p-Ph*), 128.6, 129.3 (*o,m-Ph*), 138.9 (*i-Ph*); *m*/*z* (ESI^+) 290 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{32}NO^+$ ($[M + H]^+$) requires 290.2478; found 290.2479. Further elution gave **53** as a light yellow oil (25 mg, 55% from **49**, >99:1 dr): $[\alpha]_D^{25}$ +53.3 (*c* 1.0 in $CHCl_3$); ν_{max} 3318 (O−H); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* = 7.0, C(7′)H_3), 1.17−1.38 (11H, m, C(1′)H_A, C(2′)H_2−C(6′)H_2), 1.52 (1H, app dd, *J* = 14.5, 4.7, C(4)H_A), 1.63−1.74 (1H, m, C(1′)H_B), 2.04 (1H, s, O*H*), 2.20 (1H, dd, *J* = 13.3, 10.8, C(2)C$H_A$$H_B$Ph), 2.38 (1H, ddd, *J* = 14.5, 8.8, 6.5, C(4)H_B), 2.46 (3H, s, N*Me*), 2.60−2.71 (1H, m, C(5)*H*), 2.98 (1H, dd, *J* = 13.3, 4.1, C(2)C$H_A$$H_B$Ph), 3.16 (1H, dd, *J* = 10.8, 4.1, C(2)*H*), 3.90 (1H, app s, C(3)*H*), 7.12−7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(7′)), 22.6, 26.3, 29.3, 29.9 (*C*(2′)−*C*(6′)), 31.5 (C(2)CH_2Ph), 31.8 (*C*(2′)−*C*(6′)), 33.6 (*C*(1′)), 35.1 (N*Me*), 38.9 (*C*(4)), 61.3 (*C*(5)), 73.3 (*C*(3)), 73.9 (*C*(2)), 126.1 (*p-Ph*), 128.6, 129.0 (*o,m-Ph*), 139.4 (*i-Ph*); *m*/*z* (ESI^+) 290 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{32}NO^+$ ($[M + H]^+$) requires 290.2478; found 290.2478.

***tert*-Butyl (2*R*,3*S*,*αS*)-2-Hydroxy-3-[*N*-benzyl-*N*-(*α*-methylbenzyl)amino]-4-phenylbutanoate 56.** Step 1. DMSO (3.99 mL, 56.1 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (950 μL, 11.2 mmol) in CH_2Cl_2 (14 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 5 min. A solution of **27** (2.50 g, 5.61 mmol, >99:1 dr) in CH_2Cl_2 (14 mL) at −78 °C was added dropwise, and the resultant solution was stirred for 30 min. Et_3N (3.13 mL, 22.4 mmol) was added; the resultant solution was allowed to warm to rt over 10 min, and then H_2O (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were dried and concentrated in vacuo to give **54** as a yellow oil (3.30 g): δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, CMe_3), 1.42 (1H, d, *J* = 6.9, C(*α*)*Me*), 2.83 (1H, dd, *J* = 13.5, 4.3, C(4)H_A), 3.19 (1H, dd, *J* = 13.5, 9.5, C(4)H_B), 3.93 (2H, app s, NCH_2Ph), 4.04 (1H, q, *J* = 6.9, C(*α*)*H*), 4.52 (1H, dd, *J* = 9.5, 4.3, C(3)*H*), 7.07−7.28 (15H, m, *Ph*).

Step 2. $NaBH_4$ (212 mg, 5.61 mmol) was added to a stirred solution of the residue **54** from the previous step in MeOH (10 mL) at −20 °C. The resultant solution was stirred at −20 °C for 2 h, then concentrated in vacuo. The residue was partitioned between H_2O (10 mL) and Et_2O (10 mL) and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried and concentrated in vacuo to give a 90:10 mixture of **56** and **27**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 20:1 → 5:1) gave a 90:10 mixture of **56** and **27**, respectively, as a colorless oil (2.13 g, 85%). Data for mixture: ν_{max} 3650 (O−H); *m*/*z* (ESI^+) 446 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{35}NNaO_3^+$ ($[M + Na]^+$) requires 468.2509; found 468.2507. Data for **56**: δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* = 7.0, C(*α*)*Me*), 1.35 (9H, s, CMe_3), 2.69 (1H, dd, *J* = 13.2, 4.4, C(4)H_A), 2.93 (1H, dd, *J* = 13.2, 10.2, C(4)H_B), 3.01 (1H, d, *J* = 4.4, O*H*), 3.42 (1H, dt, *J* = 10.2, 4.4, C(3)*H*), 3.79 (1H, app t, *J* = 4.4, C(2)*H*), 3.83 (1H, d, *J* = 14.8, N$CH_A$$H_B$Ph), 4.06 (1H, d, *J* = 14.8, N$CH_A$$H_B$Ph), 4.16 (1H, q, *J* = 7.0, C(*α*)*H*), 7.09−7.29 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.7 (C(*α*)*Me*), 27.9 (CMe_3), 33.8 (*C*(4)), 50.4 (NCH_2Ph), 61.1 (*C*(*α*)), 63.0 (*C*(3)), 72.6 (*C*(2)), 82.0 (CMe_3), 126.0, 126.5, 127.0 (*p-Ph*), 128.1, 128.4, 128.5, 129.4 (*o,m-Ph*), 139.8, 141.6, 143.4 (*i-Ph*), 173.3 (*C*(1)). Data for **27**:[55] δ_C (100 MHz, $CDCl_3$) 18.5 (C(*α*)*Me*), 27.9 (CMe_3), 34.1 (*C*(4)), 51.0 (NCH_2Ph), 58.0 (*C*(*α*)), 61.0 (*C*(3)), 71.3 (*C*(2)), 82.5 (CMe_3), 125.9, 126.4, 126.8 (*p-Ph*), 127.9, 128.0, 128.1, 129.6 (*o,m-Ph*), 139.8, 141.9, 143.2 (*i-Ph*), 173.9 (*C*(1)).

***tert*-Butyl (2*R*,3*S*,*αS*)-2-Hydroxy-3-[*N*-methyl-*N*-(*α*-methylbenzyl)amino]-4-phenylbutanoate 57.** Step 1. DMSO (2.88 mL, 40.6 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (686 μL, 8.11 mmol) in CH_2Cl_2 (10 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 5 min. A solution of **28** (1.50 g, 4.06 mmol, >99:1 dr) in CH_2Cl_2 (10 mL) at −78 °C was added dropwise, and the resultant solution was stirred for 30 min. Et_3N (2.26 mL, 16.2 mmol) was added; the resultant solution was allowed to warm to rt over 10 min, and then H_2O (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were dried and concentrated in vacuo to give **55** as a yellow oil (1.81 g): δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* = 6.7, C(*α*)*Me*), 1.55 (9H, s, CMe_3), 2.10 (3H, s, N*Me*), 2.61 (1H, dd, *J* = 13.6, 3.9, C(4)H_A), 3.04 (1H, dd, *J* = 13.6, 9.2, C(4)H_B), 3.77 (1H, q, *J* = 6.7, C(*α*)*H*), 4.54 (1H, dd, *J* = 9.2, 3.9, C(3)*H*), 7.12−7.35 (10H, m, *Ph*).

Step 2. $NaBH_4$ (153 mg, 4.06 mmol) was added to a stirred solution of the residue **55** from the previous step in MeOH (7.5 mL) at −20 °C. The resultant solution was stirred at −20 °C for 2 h and concentrated in vacuo. The residue was partitioned between H_2O (10 mL) and Et_2O (10 mL), and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried and concentrated in vacuo to give a 92:8 mixture of **57** and **28**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 20:1 → 5:1) gave **57** as a colorless oil (1.35 g, 90%, >99:1 dr): $[\alpha]_D^{25}$ −87.5 (*c* 1.0 in $CHCl_3$); ν_{max} 3501 (O−H), 1725 (C═O); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* = 6.8, C(*α*)*Me*), 1.49 (9H, s, CMe_3), 2.30 (3H, s, N*Me*), 2.59 (1H, dd, *J* = 13.2, 5.0, C(4)H_A) 2.91 (1H, dd, *J* = 13.2, 9.8, C(4)H_B), 3.48−3.55 (2H, m, C(3)*H*, O*H*), 3.67 (1H, q, *J* = 6.8, C(*α*)*H*), 3.91 (1H, d, *J* = 4.7, C(2)*H*), 7.17−7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.6 (C(*α*)*Me*), 28.2 (CMe_3), 31.2 (*C*(4)), 34.2 (N*Me*), 62.6 (*C*(3)), 63.3 (*C*(*α*)), 72.6 (*C*(2)), 82.0 (CMe_3), 126.0, 126.9 (*p-Ph*), 127.3, 128.3, 128.4, 129.4 (*o,m-Ph*), 139.9, 144.7 (*i-Ph*), 173.6 (*C*(1)); *m*/*z* (ESI^+) 370 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{31}NNaO_3^+$ ($[M + Na]^+$) requires 392.2196; found 392.2191.

(2*R*,3*S*,*αS*)-3-[*N*-Benzyl-*N*-(*α*-methylbenzyl)amino]-4-phenylbutan-1,2-diol 58. $LiAlH_4$ (2.4 M in THF, 4.68 mL, 11.2 mmol) was added dropwise via syringe to a stirred solution of a 90:10 mixture of **56** and **27**, respectively (2.50 g, 5.39 mmol) in THF (40 mL) at 0 °C, and the resultant solution was allowed to warm to rt over 2 h. The resultant solution was then cooled to 0 °C, and 1 M aq NaOH (40 mL) was added. The resultant mixture was heated at reflux for 1 h, allowed to cool to rt, and filtered through Celite (eluent EtOAc), and the filtrate was concentrated in vacuo to give a 90:10 mixture of **58** and **29**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 3:1 → neat Et_2O) gave **58** as white solid (1.01 g, 77%, >99:1 dr): mp 136−138 °C; $[\alpha]_D^{25}$ +19.1 (*c* 1.0 in $CHCl_3$);

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ν_{max} 3410 (O−H); δ_H (400 MHz, $CDCl_3$) 1.46 (3H, d, J = 7.1, C(α)*Me*), 1.99 (1H, app t, J = 6.3, O*H*), 2.75 (1H, dt, J = 10.8, 5.3, C(1)H_A), 2.78−2.90 (1H, m, C(4)H_A), 3.15−3.29 (3H, m, C(1)H_B, C(3)*H*, C(4)H_B), 3.39 (1H, app dt, J = 7.1, 3.6, C(2)*H*), 3.82 (1H, d, J = 13.2, NCH_AH_BPh), 3.92 (1H, br s, O*H*), 4.09 (1H, q, J = 7.1, C(α)*H*), 4.11 (1H, d, J = 13.2, NCH_AH_BPh), 7.15−7.42 (15H, m, *Ph*), δ_C (100 MHz, $CDCl_3$) 13.3 (C(α)*Me*), 35.3 (*C*(4)), 51.3 (NCH_2Ph), 56.2 (*C*(α)), 58.0 (*C*(3)), 64.0 (*C*(1)), 71.1 (*C*(2)), 126.4, 127.3, 127.9 (*p-Ph*), 128.1, 128.4, 128.7, 128.9, 129.0, 129.3 (*o,m-Ph*), 139.4, 139.6, 143.0 (*i-Ph*); m/z (ESI$^+$) 376 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{30}NO_2^+$ ([M + H]$^+$) requires 376.2271; found 376.2276.

(2*R*,3*S*,α*S*)-3-[*N*-Methyl-*N*-(α-methylbenzyl)amino]-4-phenylbutan-1,2-diol 59. $LiAlH_4$ (2.4 M, in THF, 5.00 mL, 12.0 mmol) was added dropwise via syringe to a stirred solution of **57** (1.48 g, 4.01 mmol, >99:1 dr) in THF (40 mL) at 0 °C, and the resultant solution was allowed to warm to rt over 2 h. The resultant solution was then cooled to 0 °C, and 1 M aq NaOH (40 mL) was added. The resultant mixture was heated at reflux for 1 h, allowed to cool to rt, and filtered through Celite (eluent EtOAc), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 2:1 → neat Et_2O) gave **59** as white solid (1.01 g, 84%, >99:1 dr): mp 51−53 °C; $[\alpha]_D^{25}$ −112.4 (*c* 1.0 in $CHCl_3$); ν_{max} 3394 (O−H); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, J = 6.6, C(α)*Me*), 2.23 (3H, s, N*Me*), 2.68 (1H, dd, J = 13.8, 6.9, C(4)H_A), 2.87 (1H, dd, J = 13.8, 5.1, C(4)H_B), 3.38 (1H, dd, J = 11.6, 2.6, C(1)H_A), 3.47−3.54 (2H, m, C(2)*H*, C(3)*H*), 3.59 (1H, q, J = 6.6, C(α)*H*), 3.70 (1H, dd, J = 11.6, 2.3, C(1)H_B), 3.84 (2H, br s, O*H*), 7.22−7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.2 (C(α)*Me*), 32.3 (*C*(4)), 33.8 (N*Me*), 60.3 (*C*(3)), 62.9 (*C*(α)), 64.4 (*C*(1)), 70.4 (*C*(2)), 126.4 (*p-Ph*), 127.2 (*o,m-Ph*), 127.3 (*p-Ph*), 128.5, 128.6, 129.1 (*o,m-Ph*), 139.6, 144.4 (*i-Ph*); m/z (ESI$^+$) 300 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{26}NO_2^+$ ([M + H]$^+$) requires 300.1958; found 300.1960.

(2*R*,3*S*,α*S*)-1,2-Epoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-4-phenylbutane 64. Et_3N (319 μL, 2.29 mmol) and MsCl (93 μL, 1.20 mmol) were sequentially added dropwise to a stirred solution of **58** (430 mg, 1.15 mmol) in CH_2Cl_2 (8.5 mL) at 0 °C. The resultant solution was stirred for 1 h at rt, and then H_2O (10 mL) was added. The resultant mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried and concentrated in vacuo. The residue was dissolved in MeOH (2 mL), and K_2CO_3 (792 mg, 5.73 mmol) was added. The resultant mixture was stirred at rt for 1 h and filtered through Celite (eluent MeOH), and the filtrate was concentrated in vacuo. The residue was partitioned between H_2O (10 mL) and Et_2O (10 mL), and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (40 mL), dried, and concentrated in vacuo to give an 85:15 mixture of **64** and **65**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 5:1 → 2:1) gave **64** as a colorless oil (260 mg, ∼95% purity, 64%, >95:5 dr): $[\alpha]_D^{25}$ −36.9 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, J = 7.0, C(α)*Me*), 2.02 (1H, dd, J = 5.1, 2.5, C(1)H_A), 2.41 (1H, dd, J = 5.1, 3.9, C(1)H_B), 2.59−2.74 (1H, m, C(4)H_A) 2.78−2.92 (3H, m, C(2)*H*, C(3)*H*, C(4)H_B), 3.93 (1H, d, J = 15.1, NCH_AH_BPh), 4.07 (1H, d, J = 15.1, NCH_AH_BPh), 4.17 (1H, q, J = 7.0, C(α)*H*), 6.98−7.41 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.1 (C(α)*Me*), 36.7 (*C*(4)), 45.4 (*C*(1)), 50.6 (NCH_2Ph), 52.5 (*C*(2)), 59.2 (*C*(α)), 61.8 (*C*(3)), 126.0, 126.5, 126.7 (*p-Ph*), 127.8, 128.0, 128.1, 128.2, 129.2 (*o,m-Ph*), 139.6, 142.0, 144.8 (*i-Ph*); m/z (ESI$^+$) 358 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{28}NO^+$ ([M + H]$^+$) requires 358.2165; found 358.2166. Further elution gave **65** as a colorless oil (45 mg, 10%, >99:1 dr): $[\alpha]_D^{25}$ −37.2 (*c* 1.0 in $CHCl_3$); ν_{max} 3424 (O−H); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, J = 7.0, C(α)*Me*), 2.34 (1H, dd, J = 13.0, 3.7, C(1)H_A) 2.66 (1H, dd, J = 13.0, 9.8, C(1)H_B), 3.37 (1H, d, J = 13.9, NCH_AH_BPh), 3.56 (1H, s, O*H*), 3.70 (1H, d, J = 13.9, NCH_AH_BPh), 3.90 (1H, q, J = 7.0, C(α)*H*), 4.02−4.14 (1H, m, C(2)*H*), 6.00 (1H, dd, J = 15.9, 6.2, C(3)*H*), 6.51 (1H, d, J = 15.9, C(4)*H*), 7.10−7.30 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.8 (C(α)*Me*), 55.1 (NCH_2Ph), 55.9 (*C*(1)), 58.4 (*C*(α)), 68.4 (*C*(2)), 126.4 (*o,m-Ph*), 127.1, 127.2, 127.5 (*p-Ph*), 128.2, 128.4, 128.5, 128.7 (*o,m-Ph*), 129.9 (*C*(3)), 131.0 (*C*(4)), 136.8, 139.4, 140.6 (*i-Ph*); m/z (ESI$^+$) 358 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{28}NO^+$ ([M + H]$^+$) requires 358.2165; found 358.2167.

(2*S*,3*S*,α*S*)-1-Phenyl-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-hydroxydodecan-5-one (1′,3′-propylene)dithioacetal 68. *n*-BuLi (0.80 mL, 2.02 mmol) was added dropwise via syringe to a stirred solution of 2-*n*-heptyl-1,3-dithiane[64] (279 mg, 1.34 mmol) in THF (1 mL) at 0 °C, and the resultant solution was stirred at rt for 1 h. A solution of **64** (240 mg, ∼95% purity, ∼0.67 mmol, >95:5 dr) in THF (0.5 mL) was then added dropwise; the resultant solution was stirred at rt for 1 h, and then H_2O (10 mL) was added. The resultant mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed sequentially with H_2O (30 mL), 2 M aq NaOH (30 mL), and H_2O (30 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol) gave recovered 2-*n*-heptyl-1,3-dithiane (76 mg, 27%). Further elution (eluent 30−40 °C petrol/Et_2O, 20:1 → 5:1) gave **68** as a colorless oil (321 mg, 83%, >99:1 dr): $[\alpha]_D^{25}$ −3.7 (*c* 1.0 in $CHCl_3$); ν_{max} 3426 (O−H); δ_H (400 MHz, $CDCl_3$) 0.75−0.87 (1H, m, C(7)H_A), 0.92 (3H, t, J = 7.3, C(12)H_3), 0.96−1.24 (8H, m, C(4)H_A, C(7)H_B, C(8)H_2−C(10)H_2), 1.24−1.38 (2H, m, C(11)H_2), 1.45−1.56 (1H, m, C(6)H_A) overlapping 1.52 (3H, d, J = 7.0, C(α)*Me*), 1.64−1.75 (1H, m, C(6)H_B), 1.76−1.97 (2H, m, C(2′)H_2), 2.05 (1H, dd, J = 15.5, 9.4, C(4)H_B), 2.56−2.73 (4H, m, C(1′)H_2, C(3′)H_2), 2.75−2.84 (1H, m, C(2)*H*), 3.10 (1H, dd, J = 13.7, 9.7, C(1)H_A), 3.17 (1H, dd, J = 13.7, 3.9, C(1)H_B), 3.58−3.65 (1H, m, C(3)*H*), 3.68 (1H, d, J = 1.5, O*H*), 3.86 (1H, d, J = 13.4, NCH_AH_BPh), 4.31 (1H, q, J = 7.0, C(α)*H*), 4.34 (1H, d, J = 13.4, NCH_AH_BPh), 7.18−7.50 (15H, m, *Ph*), δ_C (100 MHz, $CDCl_3$) 13.7 (C(α)*Me*), 14.1 (*C*(12)), 22.6 (*C*(11)), 23.6 (*C*(7)), 25.1 (*C*(2′)), 25.9, 26.1 (*C*(1′), *C*(3′)), 29.0, 29.6, 31.7 (*C*(8)−*C*(10)), 34.5 (*C*(1)), 39.5 (*C*(6)), 42.1 (*C*(4)), 51.8 (NCH_2Ph), 52.6 (*C*(α)), 56.2 (*C*(2)), 61.8 (*C*(5)), 68.6 (*C*(3)), 126.0, 126.8, 127.0 (*p-Ph*), 128.0, 128.1, 128.3, 128.5, 129.0, 129.2 (*o,m-Ph*), 140.7, 140.9, 144.4 (*i-Ph*); m/z (ESI$^+$) 576 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{49}NNaOS_2^+$ ([M + Na]$^+$) requires 598.3148; found 598.3146.

(2*S*,3*S*,α*S*)-1-Phenyl-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-hydroxydodecan-5-one 69. PIFA (129 mg, 0.30 mmol) was added to a stirred solution of **68** (69 mg, 0.12 mmol, >99:1 dr) in MeOH/H_2O (v/v, 9/1, 1.5 mL) at rt. The resultant solution was stirred at rt for 2 h, then saturated aq $NaHCO_3$ (1 mL) and the resultant mixture were concentrated in vacuo. The residue was partitioned between Et_2O (5 mL) and H_2O (5 mL), and the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic extracts were washed with brine (15 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 5:1 → 1:1) gave **69** as a colorless oil (34 mg, 58%, >99:1 dr): $[\alpha]_D^{25}$ +3.8 (*c* 1.0 in $CHCl_3$); ν_{max} 3525 (O−H), 1700 (C═O); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J = 7.0, C(12)H_3), 1.12−1.33 (8H, m, C(8)H_2−C(11)H_2), 1.34−1.43 (2H, m, C(7)H_2), 1.46 (1H, dd, J = 17.2, 2.4, C(4)H_A), 1.52 (3H, d, J = 7.0, C(α)Me), 1.98−2.17 (2H, m, C(6)H_2), 2.31 (1H, dd, J = 17.2, 9.5, C(4)H_B), 2.75−2.84 (1H, m, C(2)*H*), 3.06 (1H, dd, J = 13.6, 10.1, C(1)H_A), 3.16 (1H, dd, J = 13.6, 3.5, C(1)H_B), 3.64 (1H, d, J = 1.4, O*H*), 3.79 (1H, d, J = 13.4, NCH_AH_BPh), 3.80−3.85 (1H, m, C(3)*H*), 4.18 (1H, q, J = 7.0, C(α)*H*), 4.28 (1H, d, J = 13.4, NCH_AH_BPh), 7.18−7.43 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.0 (C(α)*Me*), 14.1 (*C*(12)), 22.6 (*C*(8)−*C*(11)), 23.6 (*C*(7)), 29.0, 29.1, 31.6 (*C*(8)−*C*(11)), 34.8 (*C*(1)), 43.6 (*C*(6)), 47.0 (*C*(4)), 51.6 (NCH_2Ph), 56.1 (*C*(α)), 60.7 (*C*(2)), 67.8 (*C*(3)), 126.1, 126.9, 127.1 (*p-Ph*), 128.1, 128.2, 128.4, 128.6, 129.1, 129.3 (*o,m-Ph*), 140.4, 140.7, 144.0 (*i-Ph*), 212.7 (*C*(5)); m/z (ESI$^+$) 486 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{44}NO_2^+$ ([M + H]$^+$) requires 486.3367; found 486.3365.

(2*S*,3*S*,5*R*)-*N*(1)-Methyl-2-benzyl-5-(heptan-1′-yl)pyrrolidin-3-ol [(+)-Preussin B] 72. Step 1. Pearlman's catalyst (50% w/w substrate, 55 mg) was added to a degassed solution of **69** (110 mg, 0.23 mmol, >99:1 dr) in MeOH (5 mL), and the resultant suspension was stirred vigorously under H_2 (5 atm) at rt for 16 h. The resultant suspension was filtered through Celite (eluent MeOH) and concentrated in vacuo to give an 85:15 mixture of **70** and **71**, respectively (78 mg).

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Step 2. Pd/C (50% w/w substrate, 39 mg) and formaldehyde (37 wt % aq solution, 34 μL, 0.45 mmol) were added sequentially to a degassed solution of the residue from the previous step in MeOH (5 mL), and the resultant suspension was stirred vigorously under H_2 (1 atm) for 10 min. The resultant suspension was filtered through Celite (eluent MeOH) and concentrated in vacuo to give an 85:15 mixture of **72** and **73**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 5:1 → neat EtOAc) gave **72** as a colorless oil (47 mg, 75% from **69**, >99:1 dr): $[\alpha]_D^{25}$ +22.9 (*c* 1.0 in $CHCl_3$); ν_{max} 3410 (O−H); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* = 7.0, C(7′)H_3), 1.15−1.37 (11H, m, C(1′)H_A, C(2′)H_2−C(6′)H_2), 1.41 (1H, ddd, *J* = 13.7, 6.3, 1.5, C(4)H_A), 1.67−1.78 (1H, m, C(1′)H_B), 2.03−2.13 (2H, m, C(5)*H*, O*H*), 2.18 (1H, ddd, *J* = 13.7, 9.0, 6.4, C(4)H_B), 2.22−2.28 (1H, m, C(2)*H*), 2.32 (3H, s, N*Me*), 2.79−2.92 (2H, m, C(2)CH_2Ph), 3.76−3.83 (1H, m, C(3)*H*), 7.15−7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(7′)), 22.6, 26.3, 29.3, 29.8, 31.8 (*C*(2′)−*C*(6′)), 33.7 (C(2)CH_2Ph), 35.0 (*C*(1′)) 38.6 (N*Me*), 39.4 (*C*(4)), 65.7 (*C*(5)), 70.4 (*C*(3)), 73.5 (*C*(2)), 126.0 (*p*-*Ph*), 128.3, 129.3 (*o*,*m*-*Ph*), 139.5 (*i*-*Ph*); *m*/*z* (ESI$^+$) 290 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{32}NO^+$ ([M + H]$^+$) requires 290.2478; found 290.2478.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00362.

Copies of ^{1}H and ^{13}C NMR spectra (PDF)
X-ray data for structure CCDC 1454017 (CIF)

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Notes

The authors declare no competing financial interest.
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