Enantioselective Total Synthesis of Either Enantiomer of the Antifungal Antibiotic Preussin (L-657,398) from (S)-Phenylalanine¹

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Abstract: Enantioselective total syntheses of the antifungal agent (+)-preussin (1) and its enantiomer (-)-1 from (S)-phenylalanine are described. The central transformations are protic acid-promoted aza-Cope rearrangement—Mannich cyclization reactions ($12 \rightarrow 19$ and $13 \rightarrow 27$, Schemes 4 and 6). Retro-Mannich fragmentation—Mannich cyclization ($27 \rightarrow 28$, Scheme 6) is key to the formation of (-)-1. This study demonstrates, for the first time, that enantioenriched substituted pyrrolidines can be prepared using the aza-Cope—Mannich rearrangement.

(+)-Preussin (L-657,398, 1), a potent antifungal agent possessing a pyrrolidine skeleton, was isolated from fermentation broths of both Aspergillus ochraceus and Preussia sp. in the late 1980s by scientists at Squibb and Merck.² This antibiotic and its acetate ester 2 show a broader spectrum of antifungal activity against both filamentous fungi and yeasts than the structurally related antibiotic anisomycin 3.2a The structure of (+)-preussin was determined from ¹H and ¹³C NMR spectra and nuclear Overhauser effect experiments, while Trost's O-methylmandelate ester method was employed to establish absolute configuration.^{2b} The first total synthesis of (+)preussin was reported by Pak and co-workers in 1991 and proceeded in 17 steps from D-glucose.³ Recently, concise asymmetric total syntheses of (+)-1 were described by Ohta and co-workers from (R)-phenylalanine,⁴ and by McGrane and Livinghouse and Overhand and Hecht from (S)-phenylalanine.⁵



Investigations in our laboratories over several years have demonstrated the merit of the aza-Cope-Mannich reaction for preparing nitrogen heterocycles and complex alkaloids.^{1,6} This reaction appeared well-suited for the synthesis of **1** and a series of C(5) analogs from (S)-phenylalanine. Herein, we describe in detail enantioselective total syntheses of both enantiomers of preussin, as well as investigations of stereoselection in aza-Cope-Mannich rearrangements of acyclic substrates.⁷



Results

Synthesis Plan. Our strategy was to form the (2S,3S,5R)-3-acetyl-2-benzyl-5-nonylpyrrolidine (4) by rearrangement of iminium cation 6, this latter intermediate being derived from acid-promoted condensation of amino alcohol 7 and decanal (Scheme 1). Analysis of the stereochemical outcome of the pivotal aza-Cope-Mannich rearrangement $(6 \rightarrow 4)$ presupposes a chair topography for the sigmatropic reorganization and preferential rearrangement of an E iminium ion intermediate.⁶⁷ If the product iminium ion signatropic isomer undergoes Mannich cyclization in the chair topography depicted in 5, acylpyrrolidine 4 would result. This cyclization topography has a syn-clinal orientation of the enol and iminium ion groups,8 while the nonyl substituent is oriented in a favored equatorial fashion. The S configuration at C(4) of the starting amino alcohol 7 would derive directly from (S)-phenylalanine. Although not anticipated at the outset of our investigations, it proved feasible to prepare ent-1 also in good efficiency from amino alcohol 7 (vide infra).

Preparation of the Rearrangement Precursors. We initially investigated preparation of the aza-Cope-Mannich rearrangement substrates from the known (S)- α -amino ketone 8, whose preparation from N-Boc-(S)-phenylalanine is described.⁹

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Scheme 2



In our hands, the reaction of N-Boc-(S)-Phe with MeLi only provided 8 in moderate yield (40%) (Scheme 2). However, N-Cbz-(S)-Phe was converted in 89% overall yield to the (S)- α -amino ketone 9 by way of the Weinreb amide intermediate.^{10,11} Subsequent treatment of 9 with vinylmagnesium bromide provided amino alcohol 10 and its diastereomer (ds =5-6:1, GLC or ¹H NMR analysis) in 67-76% yield.¹² Under all conditions examined, this reaction failed to proceed to completion, returning 10-15% of 9. The major stereoisomer 10 was obtained in high isomeric purity by recrystallization of the crude addition product from hexanes-EtOAc. Reduction of 10 with LiAlH₄ then provided the N-methylamino alcohol 11. Alternatively, hydrolysis (KOH, MeOH-H₂O) of 10 afforded the primary amino alcohol 12. Treatment of 10 with KH and benzyl bromide, followed by hydrolysis of the resulting N-benzyloxazolidinone, afforded the N-benzylamino alcohol 13. The enantiomeric excess of 12 and 13 was determined to be >94% by HPLC analysis using a Chiralcel OD column.

Formation of (2S,3S,5R)-3-Acetylpyrrolidine 20 by Aza-Cope-Mannich Rearrangement of Oxazolidine 18. Our initial target was the all-cis *N*-methylpyrrolidine 17, an intermediate that would contain all the functionality of (+)-preussin except for the hydroxy group at C(3). Conversion of amino alcohol 11 to the oxazolidine derivative 14 was readily accomplished by reaction with decanal in refluxing benzene with removal of water using a Dean-Stark trap (Scheme 3). However, aza-Cope-Mannich reorganization of this intermediate in refluxing CF₃CO₂H (TFA) did not afford 17, but rather two stereoisomers 15 (44%) and 16 (38%), each having a trans relationship of the benzyl and acetyl groups. The relative stereochemistry of 15 and 16 was apparent from ¹H NMR





DNOE experiments, and the stereostructure of **15** was confirmed by single-crystal X-ray analysis of the hydrochloride salt.¹³ Pyrrolidines **15** (42%) and **16** (29%) also were obtained when **11** and 1 equiv of decanal were heated in refluxing benzene in the presence of 0.9 equiv of camphorsulfonic acid (CSA). Although the absolute configurations of **15** and **16** were not established, in light of the results obtained in the related *N*-benzyl series (*vide infra*), these pyrrolidines almost certainly have the unnatural *S* configuration at C(5).

Attempted rearrangement of oxazolidine 18, prepared similarly from the primary amino alcohol 12 and decanal, in refluxing TFA led to extensive decomposition (Scheme 4). However, treatment of 18 with 0.9 equiv of CSA in CF₃CH₂-OH at 23 °C yielded the desired all-cis pyrrolidine 19 as the major product (500-MHz ¹H NMR analysis of the crude product mixture). Attempted purification of 19 by chromatography on silica gel led to some epimerization of the acetyl group. Therefore, the crude rearrangement product was treated directly with ethyl chloroformate and NaHCO₃. Rapid chromatography of the derived carbamates on silica gel then provided 20 in 61-68% yield from 12. The three other possible stereoisomeric carbamates were also isolated in a combined yield of 13-26%; spectroscopic and analytical characterization data for these stereoisomers are summarized in the Experimental Section. HPLC analysis of 20 on Chiralcel OD showed that this intermediate had an enantiomeric purity (ee) of $80 \pm 3\%$.

Since the ¹H NMR spectrum of **20** was complicated by carbamate conformational isomerism, the relative stereochemistry of this intermediate was ascertained by ¹H NMR analysis of **19** (Figure 1), which could be isolated by flash chromatography in low yield from the crude aza-Cope-Mannich rearrangement product.¹⁴ Particularly diagnostic were ¹H DNOE data which are summarized in Figure 1. Full assignments of the ¹H NMR signals of **15**, **19**, and **22** were made by ¹H-¹H decoupling and/or ¹H-¹H COSY experiments.

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⁽¹⁴⁾ Carboethoxylation of this sample (EtOCOCl, NaHCO₃, CHCl₃) provided 20.

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Figure 1. Diagnostic NOE Data for pyrrolidines 15, 19, and 22.

Baeyer-Villiger Oxidation of 20 and Completion of the Enantioselective Total Synthesis of (+)-Preussin. We next turned to the Baeyer-Villiger oxidation to introduce the required oxidation at C(3). Our earlier studies had demonstrated that *N*-acyl-(or *N*-alkoxycarbonyl)-protection of the pyrrolidine nitrogen, and the use of a powerful oxidant, would be required for this conversion. For example, oxidation of the *N*-Cbz-protected pyrrolidine 23 (available in two steps from 28, *vide infra*) with trifluoroperoxyacetic acid (TFPAA) provided the corresponding ester 25 in 62% yield (eq 1). In contrast, under similar conditions the *N*-methyl pyrrolidine ketone 16 provided acetate 24 in only 9% yield.



Attempted oxidation of the all-cis N-ethoxycarbonyl-protected pyrrolidine 20 (see Scheme 4) with m-CPBA, MMPP, or TMSOOTMS-TMSOTf¹⁵ returned only starting material. Although 20 underwent Baeyer-Villiger oxidation with 3,5dinitroperoxybenzoic acid,¹⁶ epimerization at C(3) and Baeyer-Villiger oxidation of the resulting epimer was a competing process. Other, less common oxidation conditions examined without success included O₃-vinyl acetate¹⁷ and O₂-PhCHO-Cu(AcO)₂.¹⁸ Trifluoroperoxyacetic acid (TFPAA)¹⁹ was the best reagent found for the conversion of $20 \rightarrow 21$, providing the latter in a disappointing 26-31% yield (Scheme 4).²⁰ Finally, reduction of 21 with LiAlH₄ in refluxing Et₂O provided (+)-preussin (1) in 94% yield. The ¹H and ¹³C NMR spectra of synthetic 1 were in agreement with those reported,² while synthetic (+)-1 exhibited $[\alpha]_D = +18.1^\circ$ (c 0.55, CHCl₃) indicative of an optical purity of $\sim 83\%$.

Since 20 can be epimerized in 94% yield by exposure to DBU in acetone at room temperature (Scheme 5), Baeyer-Villiger oxidation of this epimer (*ent*-29), followed by reduction with LiAlH₄ and inversion of the derived α alcohol by way of the C(3) ketone, would provide (+)-1 in higher overall yield from 20. The latter steps in this sequence were specifically optimized in the enantiomeric series leading to *ent*-preussin (*vide infra*).







Aza-Cope-Mannich Rearrangement of Amino Alcohol 13 Leading to the Formation of the (2S.3R.5S)-3-Acetylpyrrolidine 27 and Ultimately ent-Preussin. The oxazolidine derivative 26 of the N-benzylamino alcohol 13 was produced in quantitative crude yield by condensation with decanal (Scheme 6). Aza-Cope-Mannich rearrangement of this intermediate in refluxing TFA provided two pyrrolidine products, 27 (68-78%) and 28 (6-10%). The enantiomeric excess, determined by HPLC analysis, of the major 2,5-trans product 27 ranged from 78-88% over various runs, while the ee of the 2,5-cis isomer 28 was 79 \pm 1%. Aza-Cope-Mannich reorganization of oxazolidine 26 could also be effected by treatment of 26 with 0.5 equiv of Et₂AlCl in toluene at temperatures from 23 to 85 °C. Results of these experiments are summarized in Table 1. At room temperature, 27 was formed predominantly and in high ee (97%), while the enantiopurity of 28 was low (28% ee). Diastereoselection was reversed at 85 °C and notably

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Table 1. Acid-Promoted Rearrangement of Oxazolidine 26

			products			
reaction conditions			27		28	
acid (equiv)	solvent	temp, °C	yield, %	ee, %ª	yield, %	ee, % ^b
CSA (0.95)	CF ₃ CH ₂ OH	23	60	86	7	nd ^c
TFA	TFA	72	68-78	78-88	6-10	78-80
$Et_2AlCl(0.5)$	PhMe	23	48	97	15	28
$Et_2AlCl(0.5)$	PhMe	85	16	85	67	62

^a HPLC analysis on Chiralcel OJ (98:2 hexane-EtOH). ^b HPLC analysis on Chiralcel OJ (99:1 hexane-EtOH). ^c Not determined.

28 was produced in higher enantiopurity (62% ee). These results suggest that 28 is formed both directly from 26 (in low ee) and from 27 (in high ee). This hypothesis was confirmed by exposure of a sample of 27 (86% ee) to 0.1 equiv of Et₂-AlCl in toluene at 85 °C for 1 h, which provided pyrrolidine 28 (70% yield, 86% ee) and 7–9% of recovered 27.²¹ Following this two-step sequence, enantioenriched 28 (87 \pm 1% ee) could be prepared from 26 in 61% overall yield.

The stereochemistry of **28** was confirmed by ultimate conversion of this intermediate to *ent*-preussin (*vide infra*). The relative stereochemistry of pyrrolidine **27** was established by single crystal X-ray analysis of derivative **33**, which was obtained from **27** in three steps and 55% overall yield (eq 2).¹³



The absolute configuration of 27 was determined by ¹H-NMR analysis of the (R)- and (S)-O-methylmandelate esters 35 and 36 of pyrrolidinol 34 (eq 3).²² Details of this analysis are provided in the Experimental Section.



The synthesis of *ent*-preussin was readily accomplished from pyrrolidine ketone **28** as follows (Scheme 6). Debenzylation of **28**, followed by ethoxycarbonylation, provided the pyrrolidine carbamate **29** in 87% yield. Baeyer-Villiger oxidation of this intermediate, which has a trans arrangement of the vicinal acetyl and benzyl groups, proceeded smoothly with trifluoroperoxyacetic acid to provide acetate **30** in 66% yield. Reduction of **30** with LiAlH₄ provided 3-epi *ent*-preussin **31** in quantitative yield. Oxidation of **31** by the Swern procedure ($-66 \rightarrow -40$ °C),²³ followed by reduction of ketone **32** with LiAlH₄ at -40 °C in THF (ds = 12:1), provided *ent*-preussin in 90% yield. *ent*-1 exhibited a specific rotation, $[\alpha]_D = -21.6^\circ$ (c 1.0, CHCl₃), of similar magnitude, but opposite in sign, to that of natural (+)-preussin, $[\alpha]_D = +22.0^\circ$ (c 1.0, CHCl₃).^{2b,24}

Discussion

Synthetic Aspects. Both (+)- and (-)-preussin have been synthesized from the readily available (S)-ketone 9; the natural dextrorotatory isomer was obtained in five steps and 11% overall yield, while levorotatory ent-preussin was obtained in nine steps and 18% overall yield. Aza-Cope-Mannich rearrangement of the primary amino alcohol 12 and decanal proceeds with $\sim 80\%$ retention of absolute chirality to afford, after ethoxycarbonylation, the all-cis acetylpyrrolidine carbamate 20. This intermediate is transformed to (+)-preussin in two additional steps. The efficiency of this latter conversion is only moderate due to the poor yield realized in the Baeyer-Villiger oxidation of 20. In contrast, aza-Cope-Mannich rearrangement of decanal and the N-benzylamino alcohol 13 affords the 2,5-trans acetylpyrrolidine 27 in $\sim 87\%$ enantiopurity. Since this product can be equilibrated to the 2,5-cis isomer 28, without loss of enantiomeric purity, ent-preussin is available in five additional steps. By changing the aldehyde component of the aza-Cope-Mannich rearrangement step, a wide variety of C(5) analogs of (+)- or (-)-preussin should be readily available.

Mechanistic Aspects. This study raises two interrelated questions: First, why does aza-Cope-Mannich rearrangement of oxazolidine 18 having an NH substituent preferentially form the all-cis acetylpyrrolidine 19, while similar rearrangements of the N-substituted oxazolidines 14 and 26 afford predominantly acetylpyrrolidine products (15 and 27) having a trans relationship of the C(2) benzyl and C(5) nonyl substituents? Second, why is enantiopurity partially eroded in the aza-Cope-Mannich reorganization? To address these questions we make several assumptions, some of which derive experimental support from our earlier mechanistic investigations of the aza-Cope-Mannich reaction.^{7,8} We assume that (a) the [3,3]-reorganization occurs by a chair topography,⁷ (b) intramolecular Mannich cyclization takes place preferentially with a synclinal orientation of the donor and acceptor π -systems,⁸ (c) intramolecular Mannich cyclization is more rapid than stereomutation of the enol and iminium groups, and (d) pyrrolidines having a cis relationship of the acetyl and benzyl groups epimerize at C(3)under the reaction conditions. As outlined in Scheme 7, even with the first three simplifying assumptions, all eight possible stereoisomeric acetylpyrrolidine products (four enantiomer pairs) can be formed.

Acid-promoted ring opening of oxazolidine 37 provides the stereoisomeric iminium ions 38 and 42, which are interconvertable by way of 37 (Scheme 7). In the primary amine series (R = H), the *E* stereoisomer 38 would be highly favored at equilibrium. Aza-Cope rearrangement of 38 provides 39, which could directly cyclize to 40, the major product observed in the NH series. Alternative Mannich cyclization of rotamer 46 \rightarrow ent-44 should be less favorable due to the quasi-axial orientation of the nonyl substituent.

The reason for the preferential formation of acetylpyrrolidine 27 (equivalent to 44, R = Bn, in Scheme 7) in high enantiopurity from protic and Lewis acid-promoted aza-Cope-Mannich rearrangement of the *N*-benzyloxazolidine precursor is less clear.

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⁽²⁴⁾ This comparison undoubtedly over-estimates the enantiomeric purity of *ent-1. ent*-Preussin prepared as summarized in Scheme 6 should have an enantiomeric purity of \sim 87%, since no crystalline intermediates intervene between **28** and *ent-1*.

Scheme 7. Formation of All Eight Possible Stereoisomeric 3-Acetylpyrrolidines from aza-Cope-Mannich Rearrancement of Oxazolidine 37



In the N-benzyl series, iminium ion stereoisomers 38 and 42 would be of comparable stability. Since, 38 is expected to undergo chair topography [3,3]-sigmatropic rearrangement more rapidly than 42,67 the preferential formation of acetylpyrrolidine 44 (R = Bn) suggests that iminium ions 38 (R = Bn) and 42 (R = Bn) are not in rapid equilibrium. Possibly in the N-benzyl series, the Z iminium ion 42 is formed preferentially from ring opening of oxazolidine 37 (R = Bn) and subsequently undergoes aza-Cope-Mannich rearrangement more rapidly than it equilibrates with 38. Sigmatropic rearrangement of 42 would yield 43, which upon direct Mannich cyclization and epimerization at C(3) would provide the major observed product 45 (R =Bn). In this mechanistic scenario, C–C σ -bond rotation of 43 must be slower than Mannich cyclization, since cyclization of rotamer $47 \rightarrow ent-40$ would appear to be more favorable. This latter supposition contrasts with one conclusion of our earlier mechanistic investigation of the aza-Cope-Mannich reaction.8 In this previous study, the product of aza-Cope rearrangement contained no stereogenic centers, and the complete racemization observed required that Mannich cyclization was slower than C-C σ -bond rotation (Scheme 8). It should be noted that in this former study a CH₂CH₂ fragment connects the iminium and enol groups,⁸ suggesting that the barrier for conformational equilibration could have been lower than in the present series.25,26

Scheme 8



Why might the Z iminium ion 42 be formed preferentially from the N-benzyloxazolidine precursor? In the NH series, oxazolidine 18 is a \sim 3:1 mixture of stereoisomers, whose stereostructures could be assigned by ¹H NMR DNOE experiments (Figure 2). Particularly diagnostic was the large (5%)



Figure 2. ¹H NMR DNOE of oxazolidines 18a, 18b, and 26.

NOE observed between the cis methine hydrogens at C(2) and C(4) of the major stereoisomer **18a**. In contrast, in the *N*-benzyl

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⁽²⁶⁾ To further pursue effects of substitution in the tether on the stereochemical outcome of aza-Cope-Mannich reactions, we plan to study a transformation analogous to that depicted in Scheme 8⁸ with an acetone-derived iminium cation.



Figure 3. Molecular mechanics (MM2*) estimates of the lowest energy conformations of 48 and 49. An ethyl group is employed to model the nonyl side chain. Conformer 48A is 2.2 kcal/mol lower in energy than 49A.

Scheme 9



series only a single oxazolidine stereoisomer is apparent in the 500-MHz ¹H NMR spectrum of **26**; the large NOE for the methine hydrogens flanking nitrogen signals the configuration depicted in Figure 2. Stereoelectronic considerations require that oxazolidine **26** adopt a conformation having an antiperiplanar orientation of the nonbonded electron pair on nitrogen and the oxygen prior to opening of the oxazolidine ring. As depicted in Scheme 9, pyramidal inversion of **26** would form **48**, which could fragment to the *E* iminium ion **38** (R = Bn). Alternatively, pseudorotation of **26** could provide a twist conformation represented by **49**, which upon ring opening would form the *Z* iminium ion **42** (R = Bn).

To pursue what might be required for the $26 \rightarrow 49 \rightarrow 42$ pathway to be favored, we evaluated the relative energies of oxazolidine conformers 48 and 49 by molecular mechanics calculations using the MM2* force field. Fixing the dihedral angle between the nitrogen nonbonded electron pair and the C-O σ bond at $180 \pm 5^{\circ}$, Still's internal coordinate Monte Carlo search method was utilized to search for the lowest energy conformations.²⁷ These minimum energy conformations, 48A and 49A, are shown in Figure 3.²⁸ As one might anticipate the nonbonded interaction between the benzyl and ethyl (nonyl) substituents in 49A is sufficient to make this conformation slightly higher in energy (2.2 kcal/mol) than conformer 48A. Thus, if 42 is formed preferentially, the kinetic bias must reside in the ring-opening step.

The mechanistic analysis depicted in Scheme 7 highlights how easily enantiomeric purity can be eroded in aza-Cope-Mannich rearrangements that form substituted pyrrolidines. All



that is required is for the aza-Cope rearrangement to take place from the alternate iminium ion stereoisomer, which "epimerizes" C(5), and the Mannich cyclization to occur from the alternate stereoface of the rearranged iminium cation, which "epimerizes" C(2) and C(3). This is exemplified by the formation of the enantiomer of 44 following the sequence $38 \rightarrow 39 \rightarrow 46 \rightarrow$ *ent*-44.^{27,28} The opportunities for racemization are even greater than depicted in Scheme 7. For example, aza-Cope rearrangement of 38 in a boat topography (which although disfavored, nonetheless must occur to a certain extent⁷) would yield 43. Also, retro-Mannich fragmentation-Mannich cyclization (as observed for the conversion of $27 \rightarrow 28$) could also epimerize carbons 2 and 3.²⁹

The transformation of acetylpyrrolidine $27 \rightarrow 28$ requires brief comment (Scheme 6). This isomerization, which takes place without loss of enantiomeric purity, undoubtedly results from a retro-Mannich–Mannich sequence (Scheme 10). As shown in Scheme 10, molecular mechanics calculations (with Et used to model the nonyl substituent) support the notion that **28** would be thermodynamically favored in such an equilibration.^{28,30}

Conclusion

The aza-Cope-Mannich reaction has been used to synthesize (+)-preussin, and its enantiomer, from commercially available *N*-(benzyloxycarbonyl)-L-phenylalanine by short (7–11 steps), reasonably efficient (~8% overall yield) sequences. This preparative approach would appear to be particularly attractive for preparing C(5) side chain analogs of preussin. Moreover, this study for the first time shows that enantioenriched pyrrolidines can be prepared using the aza-Cope-Mannich rearrangement. Prior to this demonstration, the aza-Cope-Mannich rearrangement had been employed exclusively for the enantioselective synthesis of more complex nitrogen heterocycles, where racemization is less likely or impossible.^{1,6}

Experimental Section³¹

(35,45)-4-(*N*-(Benzyloxycarbonyl)amino)-3-methyl-5-phenyl-1penten-3-ol (10). To a solution of (*S*)-3-(*N*-(benzyloxycarbonyl)amino)-4-phenyl-2-butanone (9, 8.60 g, 28.9 mmol; prepared in 89% yield from *N*-Cbz-phenylalanine)¹¹ and dry THF (200 mL) cooled to 0 °C was added dropwise over 1.5 h a THF solution of vinylmagnesium bromide (1.0 M, 170 mL). The reaction solution was maintained at

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⁽²⁸⁾ Calculations employed the Monte Carlo search routine of Macro-Model V3.5X. The nitrogen was allowed to freely invert. There were several structures with the same nitrogen configuration within 2.0 kcal/mol of the minimum energy conformers shown in Figure 3.

⁽²⁹⁾ For other reports of partial racemization in Mannich cyclizations resulting from aza-Cope equilibration, see: (a) Meyers, A. I.; Miller, D. B.; White, F. H. J. Am. Chem. Soc. **1988**, 110, 4778. (b) Guiles, J. W.; Meyers, A. I. J. Org. Chem. **1991**, 56, 6873.

⁽³⁰⁾ The relative energies for compounds **27** and **28** were found using the MM2* force field in the Monte Carlo search routine of MacroModel V3.5X. Five hundred structures were searched for each compound and the energies for the global minima are displayed in Scheme 10.

23 °C for 21 h, at which time it was poured into ice-cooled saturated aqueous NH4Cl (400 mL). The aqueous layer was separated and extracted with EtOAc (3×400 mL), and the combined organic phases were washed with brine (2 \times 600 mL), dried over Na₂SO₄, and concentrated. Purification of the residue (silica gel, 5:1 hexanes-EtOAc) provided 10, which was recrystallized (hexanes-EtOAc) to provide 7.12 g (76%, 86% based on consumed starting material) of isomerically pure 10 as colorless needles, mp 99.5-102 °C, and 1.02 g (12%) of recovered ketone. 10: ¹H NMR (500 MHz, CDCl₃) δ 7.30-7.12 (m, 5H), 5.97 (dd, J = 17.2, 10.7 Hz, 1H), 5.32 (d, J = 11.2 Hz, 1H), 5.12 (dd, J = 10.7, 1.1 Hz, 1H), 4.96 (d, J = 12.1 Hz, 1H), 4.91 (d, J = 12.1 Hz, 1H), 4.82 (d, J = 10.9 Hz, 1H), 3.87-3.82 (m, 1H),3.12 (dd, J = 14.5, 2.8 Hz, 1H), 2.71 (br s, 1H), 2.58 (dd, J = 14.0)11.7 Hz, 1H), 1.35 (s, 3H) ppm; 13 C NMR (75 MHz, CDCl₃) δ 156.8, 142.5, 138.5, 136.5, 129.0, 128.3, 127.9, 127.7, 126.3, 113.7, 75.6, 66.6, 60.0, 35.6, 24.9 ppm; IR (KBr) 3452, 3383, 1672, 1545, 1261, 747 cm⁻¹; HRMS (CI, isobutane) m/z 326.1771 (326.1756 calcd for $C_{20}H_{24}NO_3$, MH); $[\alpha]^{28}D = -87.3^{\circ}$, $[\alpha]^{28}D^{77} = -90.9^{\circ}$, $[\alpha]^{28}D^{48} = -87.3^{\circ}$ -104° , $[\alpha]^{28}_{435} = -188^{\circ}$, $[\alpha]^{28}_{405} = -230^{\circ}$ (c 1.0, CHCl₃). Anal. calcd for C₂₀H₂₃NO₃: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.69; H, 7.16; N, 4.23

(3S.4S)-4-(N-Methylamino)-3-methyl-5-phenyl-1-penten-3-ol (11). To a suspension of LiAlH₄ (350 mg, 9.23 mmol) in dry THF (4 mL) was added dropwise at 0 °C over 10 min a solution of 10 (1.00 g, 3.08 mmol) and dry THF (4 mL). The reaction mixture was allowed to warm to 23 °C, and the resulting slurry was heated at reflux for 18 h. The reaction mixture then was cooled in an ice bath, and H₂O (0.35 mL), 15% NaOH (0.35 mL), and H₂O (1.05 mL) were added sequentially with stirring. The heterogeneous mixture was maintained at 23 °C for 1 h, at which time the solid was removed by filtration. The filtrate was concentrated and the residue chromatographed (silica gel, 1:1 hexanes-EtOAc) to afford 608 mg (96%) of 11 as a paleyellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.30-7.20 (m, 5H), 5.97 (dd, J = 17.6, 10.8 Hz, 1H), 5.36 (dd, J = 17.6, 1.3 Hz, 1H), 5.14 (dd, J = 10.8, 1.3 Hz, 1H), 3.03 (dd, J = 14.2, 3.3 Hz, 1H), 2.56 (dd, J = 14.2, 3.3 Hz, 1H) 10.4, 3.4 Hz, 1H), 2.38 (dd, J = 14.2, 10.5 Hz, 1H), 2.13 (s, 3H), 1.22 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 144.3, 139.7, 129.8, 128.5, 126.2, 113.4, 73.8, 69.2, 37.4, 22.5 ppm; IR (film) 3418, 3343, 1500, 1456, 1106 cm⁻¹; HRMS (CI, isobutane) m/z 206.1557 (206.1545 calcd for C₁₃H₂₀NO, MH); $[\alpha]^{28}_{D} = 7.8^{\circ}$, $[\alpha]^{28}_{577} = 4.4^{\circ}$, $[\alpha]^{28}_{546} = 4.2^{\circ}$, $[\alpha]^{26}_{435} = 10.2^{\circ}, \ [\alpha]^{26}_{405} = 10.1^{\circ} \ (c \ 1.0, \ CHCl_3).$

(35, 45)-4-Amino-3-methyl-5-phenyl-1-penten-3-ol (12). A mixture of 10 (1.00 g, 3.08 mmol), KOH (20.7 g), MeOH (24 mL), and H₂O (8 mL) was heated at reflux for 12 h, cooled in a water bath to 23 °C, and extracted with Et₂O (3 × 70 mL). The combined extracts were washed with brine (2 × 100 mL), dried over MgSO₄, and concentrated. Purification of the residue on silica gel (2:1 hexanes– EtOAc and then EtOAc) provided 12 (586 mg, 100%, 94% ee³⁴) as a pale-yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.32–7.16 (m, 5H),

5.92 (dd, J = 17.3, 10.7 Hz, 1H), 5.37 (dd, J = 17.3, 1.5 Hz, 1H), 5.16 (dd, J = 10.9, 1.5 Hz, 1H), 3.02 (dd, J = 13.5, 2.6 Hz, 1H), 2.92 (dd, J = 11.3, 2.7 Hz, 1H), 2.35 (dd, J = 13.5, 11.3 Hz, 1H), 1.30 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 144.0, 139.5, 129.1, 128.6, 126.3, 113.5, 73.7, 59.0, 37.4, 22.5 ppm; IR (film) 3453, 2978, 2929, 1496, 1455, 999, 734 cm⁻¹; HRMS (EI) m/z 192.1393 (192.1388 calcd for C₁₂H₁₈NO, MH). $[\alpha]^{26}_{D} = -64.2^{\circ}$, $[\alpha]^{26}_{577} = -65.9^{\circ}$, $[\alpha]^{26}_{546} =$ -77.9° , $[\alpha]^{26}_{435} = -141.3^{\circ}$, $[\alpha]^{26}_{405} = -174.4^{\circ}$ (c 1.0, CHCl₃). Benzoyltartaric acid salt: mp 162–163 °C; Anal. Calcd for C₃₀H₃₁-NO₉: C, 65.55; H, 5.69; N, 2.55. Found: C, 65.35; H, 5.73; N, 2.48.

(3S,4S)-4-(N-Benzylamino)-3-methyl-5-phenyl-1-penten-3-ol (13). To a suspension of oil-free KH (2.2 g, 55 mmol) in 9:1 Et₂O-DMSO (38 mL) was added dropwise a solution of 10 (3.60 g, 11.1 mmol) and dry Et₂O (151 mL) over 30 min at 0 °C. The resulting mixture was allowed to warm to 23 °C and was maintained at this temperature for 1.5 h. The reaction mixture was then cooled in an ice bath, neat benzyl bromide (9.47 g, 55.4 mmol) was added dropwise over 10 min, and after 10 additional min the cooling bath was removed. Water (5.5 mL) then was added, the reaction was maintained at 23 °C for 1 h, and Et₂O then was removed in vacuo at 23 °C. Solid KOH (74 g, 120 equiv), MeOH (82 mL), and H₂O (27 mL) were added, and the resulting mixture was heated at reflux for 16 h. After cooling to 23 °C, the reaction mixture was extracted with Et₂O (3 \times 200 mL), and the combined organic layers were washed with brine (2×500 mL), dried over MgSO₄, and concentrated. Purification of the residue on silica gel (5:1 hexanes-EtOAc) provided 3.02 g (97% yield, 97% ee³⁴) of 13 as a light yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.39–6.97 (m, 10H), 6.05 (dd, J = 17.3, 10.8 Hz, 1H), 5.44 (dd, J = 17.3, 1.4 Hz, 1H), 5.21 (dd, J = 10.8, 1.4 Hz, 1H), 4.03 (br s, 1H), 3.51 (d, J =12.2 Hz, 1H), 3.27 (d, J = 12.2 Hz, 1H), 3.12 (dd, J = 13.9, 3.4 Hz, 1H), 2.80 (dd, J = 10.8, 3.4, Hz, 1H), 2.42 (dd, J = 13.9, 10.8 Hz, 1H), 1.29 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 144.3, 139.9, 139.5, 129.0, 128.6, 128.3, 128.2, 128.1, 127.0, 126.4, 113.5, 73.8, 66.8, 54.5, 37.6, 22.4 ppm; IR (film) 3421, 3388, 3003, 2978, 2860, 1495, 1454, 1102, 922, 741 cm⁻¹; HRMS (CI, isobutane) m/z 282.1845 (282.1850 calcd for C₁₉H₂₄NO, MH). $[\alpha]^{25}_{D} = -42.2^{\circ}, \ [\alpha]^{26}_{577} =$ $-41.5^{\circ}, \ [\alpha]^{25}_{546} = -48.9^{\circ}, \ [\alpha]^{25}_{435} = -93.9^{\circ}, \ [\alpha]^{25}_{405} = -119^{\circ} \ (c \ 1.0, \ c \ 1.0, \ c \ 1.0)$ CHCl₃). Hydrochloride salt: mp 156-158 °C; Anal. Calcd for C₁₉H₂₄ClNO: C, 71.89; H, 7.63; N, 4.42. Found: C, 71.74; H, 7.64; N, 4.44.

Camphorsulfonic Acid (CSA)-Promoted Aza-Cope-Mannich **Reaction of 11 and Decanal. Preparation of Acetylpyrrolidines 15** and 16. A solution of 11 (500 mg, 2.44 mmol), freshly distilled decanal (380 mg, 2.44 mmol), CSA (99%, 509 mg, 2.19 mmol), and dry benzene (20 mL) was heated at reflux using a Dean-Stark H₂O separator for 24 h. After cooling to 23 °C, the reaction mixture was quenched with 1 N NaOH (30 mL), and the organic layer was separated, washed with water (2 x 80 mL) and brine (2 \times 80 mL), dried over Na₂CO₃, and concentrated. Purification of the residue on silica gel (10:1 to 5:1 hexanes-EtOAc) provided pure samples of acetylpyrrolidines 15 (354 mg, 42%) and 16 (246 mg, 29%). 15: ¹H NMR (500 MHz, C₆D₆) δ 7.10–6.90 (m, 5H), 3.54 (ddd, J = 10.2, 4.2, 3.3 Hz, 1H), 2.83 (dd, J = 14.5, 5.5 Hz, 1H), 2.74–2.68 (m, 1H), 2.50 (ddd, J = 9.5, 4.9, 3.3 Hz, 1H), 2.30 (s, 3H), 2.19 (dd, J = 14.5, 9.9 Hz, 1H), 2.00–1.85 (m, 1H), 1.83–1.75 (m, 1H), 1.50 (s, 3H), 1.35–1.25 (m, 16H), 0.90 (t, J = 7.0 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 208.9, 139.2, 129.3, 128.5, 126.2, 67.9, 62.7, 53.8, 35.5, 35.1, 31.9, 31.8, 30.0, 29.6, 29.6, 29.3, 28.6, 26.6, 22.7, 14.1 ppm; IR (film) 2927, 2855, 1714, 1486, 1357, 700 cm⁻¹; HRMS (CI, isobutane) m/z 344.2949 $(344.2875 \text{ calcd for } C_{23}H_{38}NO, MH)$. $[\alpha]^{23}_{D} = 12.4^{\circ}, [\alpha]^{23}_{577} = 10.4^{\circ},$ $[\alpha]^{23}_{546} = 11.7^{\circ}, \ [\alpha]^{23}_{435} = 19.3^{\circ}, \ [\alpha]^{23}_{405} = 13.7^{\circ} \ (c \ 1.2, \ CHCl_3).$ Hydrochloride salt: mp 145-6 °C; Anal. Calcd for C23H38NOC1: C, 72.70; H, 10.08; N, 3.69. Found: C, 72.48; H, 10.04; N, 3.64. 16: ¹H NMR (300 MHz, CDCl₃) δ 7.25–7.15 (m, 5H), 3.11 (dd, J = 13.9, 5.5 Hz, 1H), 2.90 (m, 1H), 2.78 (m, 1H), 2.52 (dd, J = 13.9, 9.7 Hz, 1H), 2.37 (s, 3H), 2.30 (m, 1H), 1.75-1.86 (m, 1H), 1.65 (s, 3H), 1.30 (m, 17H), 0.90 (t, J = 7.0 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃)

⁽³¹⁾ General experimental details: tetrahydrofuran (THF) and Et₂O were distilled from Na and benzophenone. Dimethylformamide (DMF) was distilled from CaH₂ at 20 mm, while CH₂Cl₂, benzene, toluene, and diisopropylamine were distilled from CaH2 at atmospheric pressure. The molarities indicated for organolithium reagents were established by titration with 2,5-dimethoxybenzyl alcohol.³² ¹H NMR and ¹³C NMR were measured at 300 and 75, and 500 and 125 MHz, respectively, with Nicolet Omega 500, Nicolet GN-500, Varian AC 300, or Nicolet QE 300 spectrometers. ¹H NMR chemical shifts are reported as δ values in ppm relative to TMS. ¹H NMR coupling constants are reported in hertz and refer to apparent multiplicities and not true coupling constants. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), etc. Mass spectra were measured using a VG Analytical 7070E or Fisons Autospec spectrometer. Infrared spectra were recorded with a Nicolet 5DBX FTIR spectrometer. Optical rotations were measured with a JASCO DIP-360 digital polarimeter; concentration c is reported in g/100 mL. Microanalyses were performed by Atlantic Microlab, Atlanta, GA. TLC and column chromatography were typically performed as described by Still³³ using E. Merck silica gel. Radial chromatography was done with a Harrison Research Chromatotron. All reactions were conducted under nitrogen or argon and concentrations were performed under reduced pressure using a Büchi rotary evaporator.

⁽³²⁾ Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. J. Chem. Soc., Chem. Commun. 1980, 87.

⁽³³⁾ Still, W. C.; Kahn, M.; Mitra, A. J. Org. Chem. 1978, 43, 2923.

⁽³⁴⁾ HPLC conditions: stationary phase-Chiralcel OD, mobile phase = 99:1 (90:10 for 13) hexane-*i*-PrOH, flow rate = 1.0 mL/min (0.6 mL/min for 13), detection UV detection at 254 NM. Reference samples of *ent*-12 and *ent*-13 were prepared from (*R*)-phenylalanine following the same procedure used to prepare 12 and 13.

δ 210.1, 138.8, 129.5, 128.2, 126.2, 70.4, 66.2, 53.4, 40.5, 38.8, 34.1, 33.8, 31.8, 29.9, 29.4, 29.2, 26.2, 22.6, 14.0 ppm; IR (film) 2926, 2855, 1711, 1496, 1353, 700 cm⁻¹; HRMS (CI, isobutane) *m/z* 344.2942 (344.2953 calcd for C₂₃H₃₈NO, MH); $[\alpha]^{22}_{D} = -1.2^{\circ}, [\alpha]^{22}_{577} = -5.0^{\circ}, [\alpha]^{22}_{435} = -5.4^{\circ}, [\alpha]^{22}_{435} = -3.1^{\circ}, [\alpha]^{22}_{405} = -0.8^{\circ}$ (*c* 1.2, CHCl₃).

(2S,3S,5R)-3-Acetyl-2-benzyl-1-(ethoxycarbonyl)-5-nonylpyrrolidine (20). A mixture of amino alcohol 12 (300 mg, 1.57 mmol), freshly distilled decanal (258 mg, 1.57 mmol), and dry benzene (2 mL) was heated at reflux for 2 h in a Soxhlet apparatus containing CaC2. Concentration at 23 °C provided the crude oxazolidine 18 as a 3:1 mixture of stereoisomers: ¹H NMR (500 MHz, CDCl₃) & 7.41-7.25 (m, major and minor), 5.85 (dd, J = 17.9, 10.7 Hz, minor), 5.83 (dd, J = 17.3, 10.7 Hz, major), 5.31 (dd, J = 7.2, 1.5, Hz, minor), 5.28 (dd, J = 16.1, 1.4 Hz, major), 5.08 (dd, J = 10.7, 1.2 Hz, major andminor), 4.85 (t, J = 5.7 Hz, minor), 4.57 (t, J = 5.3 Hz, major), 3.31 (dd, J = 9.5, 4.8 Hz, major and minor), 2.84-2.71 (m, major and minor), 2.53 (broad s, major and minor), 1.72-1.66 (m, major and minor), 1.50-1.42 (m, major and minor), 1.38-1.26 (m, major and minor), 0.93 (t, J = 7.0 Hz, minor), 0.92 (t, J = 6.9 Hz, minor) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 143.4 (minor), 142.5 (major), 139.2 (minor), 138.9 (major), 129.0 (minor), 128.8 (major), 128.5 (major), 128.3 (minor), 126.4 (major), 126.2 (minor), 113.0 (minor), 112.8 (major), 90.7 (major), 90.4 (minor), 82.5 (minor), 81.4 (major), 68.3 (major), 66.0 (minor), 43.9, 36.3, 35.5, 35.4, 35.2, 31.9, 29.6, 29.55, 29.5, 29.4, 29.35, 29.3, 29.27, 29.2, 29.1, 25.4, 25.0 (major), 22.6 (major), 22.0 (minor), 19.8 (minor), 14.1 ppm.

A solution of this sample of 18, CF₃CH₂OH (4 mL), and camphorsulfonic acid (99%, 350 mg, 1.49 mmol) was maintained at 23 °C for 40 h. After concentration, the residue was dissolved in CHCl₃ (100 mL) and then washed with 1 N NaOH (2 \times 50 mL) and brine (50 mL). This solution was then dried over MgSO₄ and concentrated, and the crude pyrrolidine products were dissolved in CHCl₃ (16 mL). Ethyl chloroformate (0.23 mL, 2.4 mmol) and solid NaHCO₃ (1.3 g, 15 mmol) were added. The resulting mixture was stirred at 23 °Cfor 2 h and then filtered. The concentrated filtrate was purified on silica gel (15:1 hexanes-EtOAc) to provide pyrrolidine 20 (383 mg, 61% yield, 77% ee³⁵), a mixture of three additional stereoisomers (26%), and recovered oxazolidine 18 (2%). 20: ¹H NMR (500 MHz, C₆D₅CD₃, 100 °C)δ 7.17-6.96 (m, 5H), 4.53 (dd, J = 13.3, 7.1 Hz, 1H), 3.96 (m, 2H), 3.65 (m, 1H), 2.72 (dd, J = 13.8, 5.8 Hz, 1H), 2.61 (dd, J = 13.8, 7.5 Hz, 1H)Hz, 1H), 2.53 (dt, J = 12.7, 7.0 Hz, 1H), 2.22 (m, 1H), 1.82 (dt, J =13.0, 7.0 Hz, 1H), 1.46 (s, 3H), 1.36–1.26 (m, 15H), 1.01 (t, J = 7.0 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H) ppm; ¹³C NMR (125 MHz, C₆D₅-CD₃, 100 °C) & 203.8, 155.2, 139.3, 130.6, 128.5, 126.7, 61.6, 60.9, 58.1, 54.6, 39.3, 37.2, 32.5, 32.2, 30.3, 30.2, 30.0, 29.9, 26.7, 23.1, 20.0, 14.8, 14.2 ppm; IR (film) 2954, 1708, 1686, 1410, 1281 cm⁻¹; HRMS (CI, isobutane) m/z 402.3001 (402.3008 calcd for C₂₅H₄₀NO₃, MH); $[\alpha]^{25}_{D} = -26.7^{\circ}$, $[\alpha]^{25}_{577} = -26.1^{\circ}$, $[\alpha]^{25}_{546} = -29.0^{\circ}$, $[\alpha]^{25}_{435}$ $= -34.2^{\circ}$, $[\alpha]^{25}_{405} = -29.7^{\circ}$ (c 1.0, CHCl₃). Anal. Calcd for C₂₅H₃₉-NO3: C, 74.76; H, 9.79; N, 3.49. Found: C, 74.67; H, 9.83; N, 3.43.

Diagnostic characterization data for the three minor stereoisomers (2S,3R,5R)-3-Acetyl-2-benzyl-1-ethoxycarbonyl-5-nonylfollows. pyrrolidine: ¹H NMR (500 MHz, C₆D₅CD₃, 100 °C) δ 7.10-6.96 (m, 5H), 4.46 (dt, J = 8.9, 4.4 Hz, 1H), 4.12-4.02 (m, 2H), 3.98-3.93 (m, 1H), 3.21 (dd, J = 9.2, 4.1 Hz, 1H), 2.71 (dt, J = 7.0, 4.8 Hz, 1H), 2.66 (dd, J = 13.2, 9.0 Hz, 1H), 1.94 (ddd, J = 11.9, 7.6, 5.2 Hz, 1H), 1.80-1.73 (m, 1H), 1.52 (s, 3H), 1.50 (m, 1H), 1.34-1.24 (m, 15H), 1.10 (t, J = 7.0 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H) ppm; HRMS (CI, isobutane) m/z 402.3009 (402.3008 calcd for C₂₅H₄₀NO₃, MH). (2R,3S,5R)-3-Acetyl-2-benzyl-1-(ethoxycarbonyl)-5-nonylpyrrolidine: ¹H NMR (500 MHz, C₆D₅CD₃, 100 °C) δ 7.11-6.96 (m, 5H), 4.58 (dt, J = 8.2, 3.1 Hz, 1H), 4.18-4.05 (m, 2H), 3.71-3.66 (m, 1H), 3.30-3.24 (m, 1H), 2.56 (dd, J = 13.2, 8.9 Hz, 1H), 2.49 (dt, J= 9.1, 2.4 Hz, 1H), 2.07–2.05 (m, 1H), 1.97 (dt, J = 13.2, 2.4 Hz, 1H), 1.70 (dt, J = 13.0, 4.4 Hz, 1H), 1.54 (s, 3H), 1.34–1.24 (m, 15H), 1.13 (t, J = 7.0 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H) ppm; HRMS (CI, isobutane) m/z 402.3008 (402.3008 calcd for C₂₅H₄₀NO₃, MH). (2R,3R,5R)-3-Acetyl-2-benzyl-1-(ethoxycarbonyl)-5-nonylpyrrolidine: ¹H NMR (500 MHz, C₆D₅CD₃, 100 °C) δ 7.20–6.95 (m, 5H),

4.45-4.40 (m, 1H), 4.10-4.00 (m, 2H), 3.75-3.65 (m, 1H), 3.00-2.88 (m, 1H), 2.86 (dt, J = 13.2, 6.9 Hz, 1H), 2.66 (dd, J = 13.6, 8.5 Hz, 1H), 2.25 (dt, J = 12.7, 8.7 Hz, 1H), 1.42 (dd, J = 12.9, 6.0 Hz, 1H), 1.38 (s, 3H), 1.32-1.24 (m, 16H), 1.11 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H) ppm; HRMS (CI, isobutane) m/z 402.2993 (402.3008 calcd for C₂₅H₄₀NO₃, MH).

Conversion of Acetylpyrrolidine 20 to ent-29. A solution of **20** (27 mg, 0.0673 mmol, 77% ee), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.25 mL), and acetone (1 mL) was maintained at 23 °C for 2 h, at which time 3 N HCl (2 mL) was added. The resulting mixture was extracted with EtOAc (3 × 15 mL), and the combined organic phases were washed with saturated aqueous NaHCO₃ (20 mL) and brine (20 mL), dried over MgSO₄, and concentrated. Purification of the residue by flash chromatography (silica gel, 15:1 hexanes-EtOAc) provided *ent-29* (25.5 mg, 94%) as a light yellow oil: $[\alpha]^{24}_{D} = -23.2^{\circ}$, $[\alpha]^{24}_{577} = -26.1^{\circ}$, $[\alpha]^{24}_{546} = -26.5^{\circ}$, $[\alpha]^{24}_{435} = -54.5^{\circ}$, $[\alpha]^{24}_{405} = -66.7^{\circ}$ (*c* 0.70, CHCl₃).

(25,35,5R)-3-Acetoxy-2-benzyl-1-(ethoxycarbonyl)-5-nonylpyrro**lidine (21)**. To a suspension of urea $-H_2O_2^{19}$ (98%, 1.60 g, 16.7 mmol) in dry CH₂Cl₂ (2 mL) was added dropwise over 5 min at 0 °C trifluoroacetic anhydride (TFAA, 877 mg, 0.590 mL, 4.2 mmol). The resulting mixture was maintained at 0 °C for 30 min before a solution of 3-isobutyl-4-hydroxy-5-methylphenylsulfide (4 mg), acetylpyrrolidine 20 (134 mg, 0.334 mmol, 77% ee) and dry CH₂Cl₂ (1.3 mL) was added. This resulting suspension was allowed to stir at 0 °C for 108 h at which time additional TFAA (0.118 mL) was added. The reaction mixture then was allowed to warm to 23 °C, and after an additional 24 h, was partitioned between H₂O (25 mL) and CH₂Cl₂ (15 mL). Solid NaHCO₃ was added until the pH of the aqueous layer was 7-8. The aqueous layer was separated, extracted with 2:1 CH₂Cl₂-EtOAc (2×60 mL), and the combined organic phases were washed with brine (2 \times 150 mL), dried over MgSO₄, and concentrated to give a thick yellow oil. Chromatography of the residue on silica gel (10:1 hexanes-EtOAc) provided 21 (42.7 mg, 31%), the alcohol resulting from acetate cleavage (4.0 mg, 3.2%), and starting ketone 20 (7.0 mg, 5.2%). 21: ¹H NMR (500 MHz, C₆D₅CD₃, 100 °C) δ 7.20-6.96 (m, 5H), 4.98 (dd, J = 7.6, 7.0 Hz, 1H), 4.39 (dd, J = 12.8, 7.1 Hz, 1H), 3.96 (m, 2H), 3.70 (m, 1H), 3.01 (dd, J = 13.7, 5.2 Hz, 1H), 2.84 (dd, J = 13.7, 8.2 Hz, 1H), 2.13 (m, 1H), 2.03 (dt, J = 13.1, 7.2 Hz, 1H), 1.62 (s, 3H), 1.40-1.23 (m, 16H), 0.99 (t, J = 7.1 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H) ppm; ¹³C NMR (125 MHz, C₆D₅CD₃, 100 °C) δ 169.0, 155.7, 139.8, 130.0, 128.5, 126.4, 73.1, 61.2, 60.9, 56.8, 37.5, 37.1, 35.6, 32.3, 30.1, 29.8, 26.8, 23.1, 20.3, 14.8, 14.2 ppm; IR (film) 3029, 2954, 1744, 1697, 1379, 1237 cm⁻¹; HRMS (CI, isobutane) m/z 418.2955 (418.2976 calcd for C₂₅H₄₀NO₄, MH); $[\alpha]^{25}_{D} = -40.3^{\circ}$, $[\alpha]^{25}_{577} = -45.3^{\circ}$, $[\alpha]^{25}_{546} =$ -51.6° , $[\alpha]^{25}_{435} = -35.7^{\circ}$ (c 1.0, CHCl₃). Anal. Calcd for C₂₅H₃₉-NO4: C, 71.89, H; 9.42; N, 3.36. Found: C, 71.97; H, 9.44; N, 3.30.

Formation of (+)-**Preussin (1) from 21.** A mixture of **21** (30 mg, 0.072 mmol) and LiAlH₄ powder (95%, 14 mg, 0.35 mmol) in dry Et₂O (0.2 mL) was heated at reflux for 2.5 h and then cooled in an ice bath. Ether (5.0 mL) then was added followed by Na₂SO₄·10H₂O (~200 mg), the resulting mixture was stirred at 23 °C for 1 h and filtered, and the filtrate was concentrated. Purification of the residue on silica gel (4:1 hexanes-EtOAc) provided (+)-1 (21.4 mg, 94%) as a yellowish wax: $[\alpha]^{24}{}_{D}$ = +18.1°, $[\alpha]^{24}{}_{577}$ = +14.6°, $[\alpha]^{24}{}_{546}$ = +15.5°, $[\alpha]^{24}{}_{435}$ = +37.1°, $[\alpha]^{24}{}_{405}$ = +49.2° (c 0.55, CHCl₃).

Preparation of (2S,3R,5S)-3-Acetyl-1, 2-dibenzyl-5-nonylpyrrollidine (27) and (2R, 3S, 5S)-3-Acetyl-1, 2-dibenzyl-5-nonylpyrrollidine (28). Method A. Et₂AlCl-Promoted Rearrangement of Oxazolidine 26. A mixture of amino alcohol 13 (342 mg, 1.22 mmol), freshly distilled decanal (199 mg, 1.28 mmol), and 2.4 mL of dry toluene was heated at reflux in a Dean–Stark apparatus for 2 h to form the crude oxazolidine 26: ¹H NMR (500 MHz, CDCl₃) δ 7.35–7.13 (m, 10H), 5.60 (dd, J = 17.3, 10.7 Hz, 1H), 5.17 (dd, J = 17.5, 1.5 Hz, 1H), 4.93 (dd, J = 10.9, 1.5 Hz, 1H), 4.22–4.20 (m, 1H), 3.64 (d, J = 14.3 Hz, 1H), 3.55 (d, J = 14.3 Hz, 1H), 3.10 (t, J = 7.5 Hz, 1H), 2.76 (dd, J = 14.0, 7.0 Hz, 1H), 1.45–1.05 (m, 19H), 0.88 (t, J = 7.0 Hz, 3H) ppm.

Additional dry toluene (13 mL) was added, the resulting solution was cooled in an ice bath, and a toluene solution of Et_2AlCl (1.8 M, 0.338 mL, 0.609 mmol) was added dropwise over 5 min. The reaction mixture then was allowed to warm to 23 °C and was maintained at

⁽³⁵⁾ Same conditions as described in footnote 33 with a flow rate = 0.2 mL/min.

this temperature for 4 h. Half of the reaction solution was removed and quenched with 1 N NaOH (15 mL). The remainder of the reaction solution was heated at 85 °C for 20 min, at which time the reaction was quenched with ice-cooled 1 N NaOH (15 mL). These two portions were worked up identically: the mixture was extracted with Et₂O (3 \times 25 mL), the combined extracts were washed with brine (2 \times 50 mL), dried over MgSO₄, and concentrated, and the residue was purified on silica gel (1:1:0.02 hexanes-CHCl₃-EtOAc). The 23 °C reaction provided 122 mg (48%, 97% ee³⁶) of 27, 37.4 mg (15%, 28% ee) of 28, and 49 mg (19%) of oxazolidine 26. The 85 °C reaction provided 41 mg (16%, 85% ee) of 27, 171 mg (67%, 62% ee³⁶) of 28, and 7 mg (3%) of oxazolidine 26.

Method B. Trifluoroacetic Acid (TFA)-Promoted Rearrangement of Oxazolidine 26. A crude sample of oxazolidine 26 was prepared identically from 13 (1.14 g, 4.06 mmol) and decanal (633 mg, 4.06 mmol). A solution of this material and TFA (13.5 mL) was heated at reflux for 2 h, allowed to cool to 23 °C, and then concentrated. The residue was dissolved in CH₂Cl₂ (200 mL), and the resulting solution was extracted with 2 N NaOH (2×100 mL). The organic layer was washed with brine (100 mL), dried over MgSO₄, and concentrated. Purification of the crude product as described in method A provided 27 (1.32 g, 78% yield, 86% ee³⁶) and 28 (99 mg, 6% yield, 78% ee³⁶).

27: ¹H NMR (500 MHz, CDCl₃) δ 7.40-6.90 (m, 10H), 3.99 (d, J = 13.8 Hz, 1H), 3.65 (d, J = 13.8 Hz, 1H), 3.40 (ddd, J = 10.5, 6.1, 3.4 Hz, 1H), 3.06 (dd, J = 12.8, 3.4 Hz, 1H), 2.95-2.89 (m, 1H), 2.62 (ddd, J = 9.5, 4.4, 2.4 Hz, 1H), 2.32 (dd, J = 12.8, 10.5 Hz, 1H), 2.10(ddd, J = 13.1, 9.5, 7.8 Hz, 1H), 1.97 (ddd, J = 13.1, 6.7, 4.7 Hz,1H), 1.67 (s, 3H), 1.34-1.20 (m, 16H), 0.88 (t, J = 6.9 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 209.2, 139.8, 139.5, 129.2, 129.1, 128.5, 128.4, 128.3, 128.1, 126.8, 126.1, 64.5, 60.4, 53.2, 51.0, 33.7, 32.7, 31.9, 30.0, 29.7, 29.6, 29.3, 26.2, 22.7, 14.1 ppm; IR (NaCl) 3029, 2955, 2924, 2855, 1712, 698 cm⁻¹; HRMS (CI, isobutane) m/z 420.3244 (420.3266 calcd for C₂₉H₄₂NO, MH); $[\alpha]^{26}_{D} = 25.5^{\circ}$, $[\alpha]^{26}_{577} = 26.6^{\circ}$, $[\alpha]^{26}_{546} = 28.8^{\circ}, \ [\alpha]^{26}_{435} = 26.9^{\circ}, \ [\alpha]^{26}_{405} = 15.8^{\circ} \ (c \ 1.0, \ CHCl_3).$ 28: ¹H NMR (500 MHz, CDCl₃) δ 7.41–7.06 (m, 10H), 3.93 (d, J = 13.9Hz, 1H), 3.75 (d, J = 13.9 Hz, 1H), 3.28 (dt, J = 9.4, 4.7 Hz, 1H), 2.78 (dt, J = 9.4, 4.4 Hz, 1H), 2.73 (dd, J = 13.5, 4.4 Hz, 1H), 2.37 (dd, J = 13.5, 9.4 Hz, 1H), 1.93 (ddd, J = 12.5, 6.4, 3.7 Hz, 1H), 1.68 (s, 3H), 1.66-1.60 (m, 2H), 1.35-1.20 (m, 16H), 0.91 (t, J = 6.9 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 210.2, 140.2, 139.2, 129.5, 129.1, 128.2, 128.1, 128.0, 126.8, 126.2, 68.6, 64.6, 57.8, 54.1, 42.7, 35.2, 33.5, 31.9, 31.6, 29.9, 29.6, 29.5, 29.3, 28.8, 26.2, 22.7, 14.1 ppm; IR (NaCl) 3027, 2954, 2925, 2855, 1710, 1494, 1353, 751, 700 cm⁻¹; HRMS (CI, isobutane) *m/z* 420.3249 (420.3266 calcd for C₂₉H₄₂-NO, MH); $[\alpha]^{25}_{D} = -0.05^{\circ}, [\alpha]^{25}_{577} = -0.7^{\circ}, [\alpha]^{25}_{546} = -1.8^{\circ}, [\alpha]^{25}_{435}$ $= -2.1^{\circ}, \ [\alpha]^{25}_{405} = -0.32^{\circ} \ (c \ 1.0, \ CHCl_3).$

Conversion of Acetylpyrrolidine 27 to 28. A solution of **27** (1.13 g, 2.70 mmol, 86% ee, prepared by method B) in dry toluene (40 mL) was dried by heating for 2 h at reflux through a Soxhlet apparatus containing CaC₂. This solution then was allowed to cool to 23 °C, and a toluene solution of Et₂AlCl (1.8 M, 0.15 mL, 0.270 mmol) was added dropwise. The resulting solution was heated at 85 °C for 1 h, cooled to 23 °C in a water bath, and quenched with 1 N NaOH (50 mL). The aqueous layer was separated and extracted with Et₂O (2 × 100 mL), and the combined organic phases were washed with brine (2 × 100 mL), dried over MgSO₄, and concentrated. Purification of the residue on silica gel (1:1:0.015 hexanes-CHCl₃-EtOAc) gave 794 mg (70%, 86% ee³⁶) of pyrrolidine **28** and 77 mg (7%, 75% ee³⁶) of recovered **27**.

(2R,3S,5S)-3-Acetyl-2-benzyl-1-(ethoxycarbonyl)-5-nonylpyrrolidine (29). A 780 mg sample of 28 (1.86 mmol, 86% ee; prepared by Et₂AlCl-catalyzed rearrangement of 27), Pd/C (78 mg, 10% w/w), MeOH (22 mL), and concentrated HCl (1 mL) was maintained under H₂ (1 atm) at 23 °C for 12 h. After concentration, the residue was dissolved in CHCl₃ (19 mL), solid NaHCO₃ (1.56 g, 10 equiv) was added, and after CO₂ evolution ceased EtOCOCl (0.27 mL, 2.8 mmol) was added dropwise over 1.5 min. The resulting mixture was maintained under N₂ at 23 °C for 1 h and filtered, and the filtrate was concentrated. Purification of the residue on silica gel (5:1 hexanes– EtOAc) provided **29** (651 mg, 87%) as a yellowish oil: ¹H NMR (500 MHz, C₆D₅CD₃, 100 °C) δ 7.30–6.95 (m, 5H), 4.46 (dt, J = 8.9, 4.4 Hz, 1H), 4.07 (m, 2H), 3.95 (m, 1H), 3.21 (dd, J = 13.3, 4.1 Hz, 1H), 2.71 (dt, J = 7.2, 4.8 Hz, 1H), 2.66 (dd, J = 13.3, 9.1 Hz, 1H), 1.93 (m, 1H), 1.75 (m, 1H), 1.52 (s, 3H), 1.40–1.20 (m, 17H), 1.09 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H) ppm; ¹³C NMR (125 MHz, C₆D₅-CD₃, 100 °C) δ 205.3, 155.5, 139.0, 129.3, 128.4, 126.9, 62.5, 61.0, 59.0, 54.3, 42.1, 36.7, 33.4, 32.4, 30.2, 30.1, 29.8, 27.6, 26.9, 23.1, 14.9, 14.2 ppm; IR (film) 2955, 2925, 1716, 1696, 1465, 1347, 1113, 701 cm⁻¹; HRMS (CI, isobutane) m/z 402.3020 (402.3008 calcd for C₂₅H₄₀NO₃, MH); $[\alpha]^{25}{}_{\rm D}$ = 23.5°, $[\alpha]^{25}{}_{577}$ = 25.0°, $[\alpha]^{25}{}_{546}$ = 29.4°, $[\alpha]^{25}{}_{435}$ = 54.1°, $[\alpha]^{25}{}_{405}$ = 72.6° (c 1.0, CHCl₃).

(2R,3S,5S)-3-Acetoxy-2-benzyl-1-(ethoxycarbonyl)-5-nonylpyrrolidine (30). The urea $-H_2O_2$ complex¹⁹ (98%, 6.59 g, 68.7 mmol) was added in one portion to a stirring solution of 29 (551 mg, 1.37 mmol) and dry CH_2Cl_2 (9.6 mL). The resulting mixture was cooled to -4°C, TFAA (0.81 mL, 5.7 mmol) was added dropwise over 8 min, and the resulting yellow-colored heterogeneous mixture was stirred at -4 °C for 24 h. A second portion (0.81 mL) of TFAA then was added, the reaction mixture was stirred at -4 °C for 24 h, a final portion (0.81 mL) of TFAA was added, and the reaction mixture again stirred at -4 °C for 24 h. The reaction mixture then was diluted with Et₂O (150 mL) and washed with saturated aqueous NaHCO₃ (3 \times 40 mL), and the aqueous layers were back-extracted with Et₂O (2 \times 50 mL). The combined organic phases were washed with brine $(3 \times 100 \text{ mL})$, dried over MgSO₄, and concentrated. Purification of the residue on silica gel (15:1 hexanes-EtOAc) provided 30 (377 mg, 66%) as a yellowish oil and 17.6 mg (3%) of recovered ketone 29. 30: ¹H NMR (500 MHz, $C_6D_5CD_3$, 100 °C) δ 7.16-6.96 (m, 5H, ArH), 5.08 (dt, J = 5.10, 2.4Hz, 1H), 4.25 (m, 1H), 4.01 (m, 2H), 3.95, (m, 1H), 2.98 (dd, J =13.6, 4.8 Hz, 1H), 2.66 (dd, J = 13.6, 8.4 Hz, 1H), 2.03 (m, 1H), 1.95 (m, 1H), 1.67 (m, 1H), 1.55 (s, 3H), 1.32-1.16 (m, 19 H), 1.03 (t, J = 7.0 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H) ppm; ¹³C NMR (125 MHz, C₆D₅CD₃, 100 °C) δ 169.4, 155.8, 138.6, 130.1, 127.9, 126.8, 76.8, 66.4, 61.0, 58.0, 36.7, 32.4, 30.3, 30.14, 30.10, 29.8, 26.6, 23.1, 19.9, 14.8, 14.2 ppm; IR (film) 3028, 2925, 2856, 1744, 1701, 1496, 1411, 1238, 1114 cm⁻¹; HRMS (CI, isobutane) m/z 418.2940 (418.2957 calcd for C₂₅H₄₀NO₄, MH); $[\alpha]^{25}_{D} = 38.7^{\circ}, [\alpha]^{25}_{577} = 40.3^{\circ}, [\alpha]^{25}_{546} = 46.9^{\circ},$ $[\alpha]^{25}_{435} = 80.3^{\circ}, \ [\alpha]^{25}_{405} = 96.2^{\circ} \ (c \ 1.13, \ CHCl_3).$ Anal. Calcd for C₂₅H₃₉NO₄: C, 71.89; H, 9.42; N, 3.36. Found: C, 71.99; H, 9.40; N, 3.32.

(2R,3S,5S)-2-Benzyl-3-hydroxyl-1-methyl-5-nonylpyrrolidine (31). A mixture of 30 (300 mg, 0.719 mmol), dry THF (2 mL), and LiAlH₄ powder (95%, 0.137 g, 3.60 mmol) was stirred at 23 °C for 7 h. The reaction mixture then was cooled in an ice bath, and H₂O (0.14 mL), 15% NaOH (0.14 mL), and H₂O (0.42 mL) were added. The resulting rapidly stirred mixture was allowed to warm to 23 °C. After 1 h, the mixture was filtered and the filtrate was concentrated. Purification of the residue on silica gel (4:1 hexanes-EtOAc) provided 31 (227 mg, 100%) as a yellowish wax: ¹H NMR (500 MHz, CDCl₃) δ 7.37-7.21 (m, 5H), 4.01 (m, 1H), 3.06 (dd, J = 13.4, 4.6 Hz, 1H), 2.54 (dd, J =13.4, 9.7 Hz, 1H), 2.48-2.38 (m, 2H), 2.35 (s, 3H, CH₃N), 1.76 (ddd, J = 13.2, 6.7, 2.9 Hz, 1H), 1.71 - 1.61 (m, 2H), 1.32 - 1.13 (m, 16H), 0.88 (t, J = 6.9 Hz, 3H) ppm; ¹³C NMR (125MHz, CDCl₃) δ 139.0, 129.2, 128.6, 126.3, 74.6, 64.8, 39.4, 39.2, 39.1, 33.9, 31.9, 29.9, 29.6, 29.5, 29.3, 26.4, 22.6, 14.1 ppm; IR (film) 3396, 2955, 2855, 1464, 1455, 1056 cm⁻¹; HRMS (CI, isobutane) m/z 318.2770 (318.2796 calcd for C₂₁H₃₆NO, MH); $[\alpha]^{25}_{D} = -0.5^{\circ}$, $[\alpha]^{25}_{577} = -1.6^{\circ}$, $[\alpha]^{25}_{546} = -1.5^{\circ}$, $[\alpha]^{25}_{435} = -7.2^{\circ}, \ [\alpha]^{25}_{405} = -11.4^{\circ} \ (c \ 1.15, \text{CHCl}_3).$ Anal. Calcd for C₂₁H₃₅NO: C, 79.43; H, 11.12; N, 4.41. Found: C, 79.28; H, 11.11; N. 4.38

(2*R*,5*S*)-2-Benzyl-1-methyl-5-nonyl-3-oxopyrrolidine (32). Following the general procedure of Swern,²³ a solution of (COCl)₂ (0.10 mL, 150 mg, 1.2 mmol) and dry CH₂Cl₂ (3.3 mL) was added dropwise at -66 °C over 5 min to a solution of DMSO (0.170 mL, 187 mg, 2.40 mmol) and dry CH₂Cl₂ (1.1 mL). The resulting solution was maintained at -66 °C for 20 min, and then a solution of **31** (190 mg, 0.600 mmol) and dry CH₂Cl₂ (3.3 mL) was added dropwise over 5 min. The resulting solution was maintained at -40 to -55 °C for 30 min, cooled to -66 °C, and dry Et₃N (0.50 mL, 3.60 mmol) was added over 2 min. The reaction mixture was allowed to warm to 0 °C at

⁽³⁶⁾ HPLC conditions: Chiralcel OJ, 99:1 or 98:2 hexane-EtOH, 0.2 or 0.3 mL/min.

which temperature H₂O (2 mL) was added and the mixture then was allowed to warm to 23 °C. The aqueous layer was separated and backextracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine $(2 \times 100 \text{ mL})$, dried over Na₂CO₃, and concentrated. Purification of the residue on silica gel (10:1 hexanes-EtOAc) provided ketone 32 (140 mg, 74%) as a pale-yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.25-7.16 (m, 5H), 3.05 (dd, J = 14.3, 4.7 Hz, 1H), 2.85 (dd, J = 14.3, 5.1 Hz, 1H), 2.75 (t, J = 5.1 Hz, 1H), 2.47 (m, 1H), 2.37 (dd, J = 18.0, 6.1 Hz, 1H), 2.31 (s, 3H), 1.76 (dd, J = 18.0, 10.8 Hz, 1H), 1.32-1.20 (m, 16H), 0.88 (t, J = 6.9 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 214.9, 154.5, 138.5, 129.7, 128.0, 126.1, 74.4, 62.5, 42.8, 39.3, 35.9, 32.9, 31.9, 29.8, 29.6, 29.3, 25.6, 22.7, 14.1 ppm; IR (film) 2955, 2926, 2855, 1757, 1455, 1156, 898 cm⁻¹; HRMS (CI, isobutane) m/z 316.2614 (316.2632 calcd for C₂₁H₃₄-NO, MH); $[\alpha]^{25}{}_{D} = 29.3^{\circ}$, $[\alpha]^{25}{}_{577} = 29.6^{\circ}$, $[\alpha]^{25}{}_{546} = 34.2^{\circ}$, $[\alpha]^{25}{}_{435}$ = 26.7°, $[\alpha]^{25}_{405}$ = 38.1° (*c* 1.02, CHCl₃).

Preparation of *ent*-**Preussin from 32.** To a solution of **32** (50 mg, 0.159 mmol) and 1 mL of dry THF at -45 °C was added LiAlH₄ powder (18 mg, 98%, 0.476 mmol) in one portion. The resulting slurry was maintained at -45 to -35 °C for 4 h and then worked up as described for the preparation of **31**. Purification of the crude product by chromatography on silica gel (6:1 hexanes-EtOAc) provided *ent*-1 (45 mg, 90%) as a yellowish wax-like solid and **35** (4.4 mg, 9%) as a yellow oil. *ent*-1: $[\alpha]^{26}_{D} = -21.6^{\circ}$, $[\alpha]^{26}_{577} = -22.8^{\circ}$, $[\alpha]^{26}_{546} = -25.8^{\circ}$, $[\alpha]^{26}_{435} = -51.6^{\circ}$, $[\alpha]^{26}_{405} = -65.0^{\circ}$ (*c* 1.0, CHCl₃).

Determination of the Absolute Configuration of Acetylpyrrolidine 27 by ¹H NMR Analysis of the (R)- and (S)-O-Methylmandelate Esters 35 and 36. The preparation of alcohol 34 from 27 is detailed in supplementary material. A solution of 34 (8 mg, 0.02 mmol), (R)or (S)-O-methylmandelic acid (5 mg, 0.02 mmol), DCC (5 mg, 0.02 mmol), and 0.25 mL of CH₂Cl₂ was maintained at 23 °C for 24 h. After filtration, the filtrate was concentrated and the residue purified on silica gel (4:1 hexanes-EtOAc) to give ~3 mg (~45%) of 35 or 36 as well as recovered 34. ¹H NMR signals for the key hydrogens of esters 35 and 36 are summarized in the table that follows.²²



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Supplementary Material Available: Experimental details for the preparation of 33 and 34, tables of ¹H NMR assignments and decoupling data for 15, 19, and 22, and ¹H and ¹³C NMR spectra of 11, 16, 27–29, and 32 (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.