Enantioselective Total Synthesis of Either Enantiomer of the Antifungal Antibiotic Preussin (L-657,398) from (*S*)-Phenylalanine[1]

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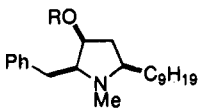
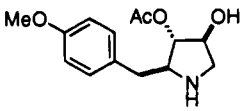
Abstract: Enantioselective total syntheses of the antifungal agent (+)-preussin (**1**) and its enantiomer (−)-**1** from (*S*)-phenylalanine are described. The central transformations are protic acid-promoted aza-Cope rearrangement–Mannich cyclization reactions (**12** → **19** and **13** → **27**, Schemes 4 and 6). Retro-Mannich fragmentation–Mannich cyclization (**27** → **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 ^{1}H and ^{13}C 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]



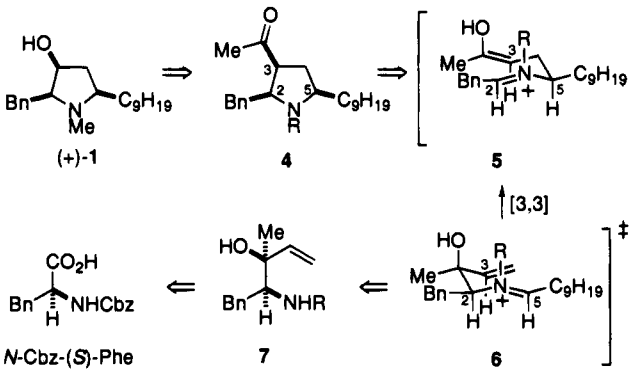
1 R = H (+)-preussin
2 R = Ac



anisomycin (**3**)

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]

Scheme 1. Synthetic Plan



(+)-**1** **4** **5** **6** **7** *N*-Cbz-(*S*)-Phe

Results

Synthesis Plan. Our strategy was to form the (2*S*,3*S*,5*R*)-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** → **4**) presupposes a chair topography for the sigmatropic reorganization and preferential rearrangement of an E iminium ion intermediate.[6,7] If the product iminium ion sigmatropic 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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(1) Publication 27 in the series Synthesis Applications of Cationic Aza-Cope Rearrangements. For part 26, see: Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293.

(2) (a) Schartz, R. E.; Liesch, J.; Hensens, O.; Zitano, L.; Honeycutt, S.; Garrity, G.; Fromtling, R. A.; Onishi; J.; Monaghan, R. *J. Antibiot.* **1988**, 1774. (b) Johnson, J. H.; Phillipson, D. W.; Kahle, A. D. *J. Antibiot.* **1989**, 1184.

(3) Pak, C. S.; Lee, G. H. *J. Org. Chem.* **1991**, *56*, 1128.

(4) Shimazaki, M.; Okazaki, F.; Nakajima, F.; Ishikawa, T.; Ohta, A. *Heterocycles* **1993**, *36*, 1823.

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(6) For brief reviews, see: (a) Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1007–1046. (b) Overman, L. E. *Abstract, 33th National Organic Symposium* **1993**, 96.

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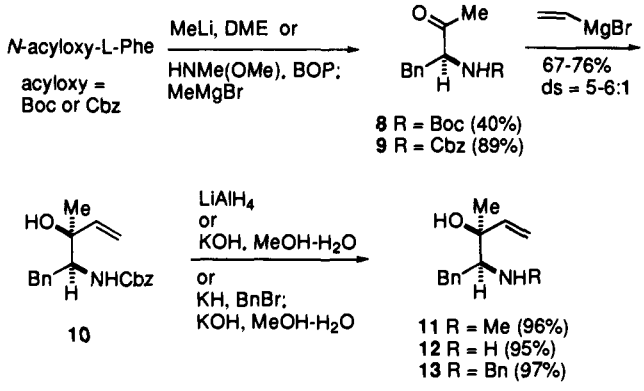
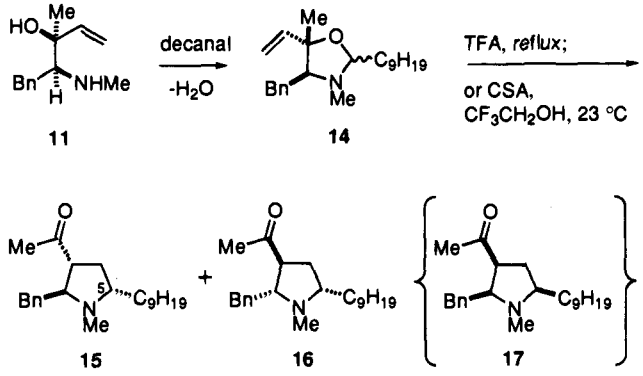
Scheme 2



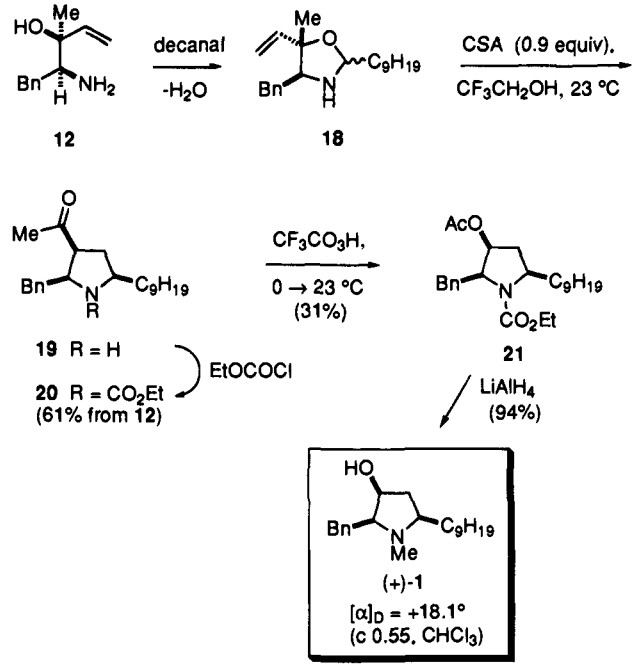
Scheme 3



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 ^{1}H 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 $LiAlH_4$ then provided the *N*-methylamino alcohol **11**. Alternatively, hydrolysis (KOH, MeOH−H_2O) 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 (2*S*,3*S*,5*R*)-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 CF_3CO_2H (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 ^{1}H NMR

Scheme 4. Total Synthesis of (+)-Preussin from Amino Alcohol **12**



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 CF_3CH_2OH at 23 °C yielded the desired all-cis pyrrolidine **19** as the major product (500-MHz ^{1}H 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 $NaHCO_3$. 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 ± 3%.

Since the ^{1}H NMR spectrum of **20** was complicated by carbamate conformational isomerism, the relative stereochemistry of this intermediate was ascertained by ^{1}H 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 ^{1}H DNOE data which are summarized in Figure 1. Full assignments of the ^{1}H NMR signals of **15**, **19**, and **22** were made by ^{1}H−^{1}H decoupling and/or ^{1}H−^{1}H COSY experiments.

(10) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(11) Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676.
(12) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Chem. Pharm. Bull.* **1988**, *36*, 3341.

(13) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request, from the director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
(14) Carboethoxylation of this sample (EtOCOCl, $NaHCO_3$, $CHCl_3$) provided **20**.

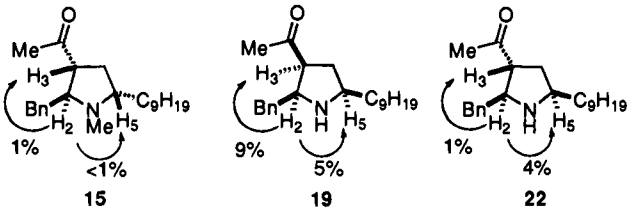
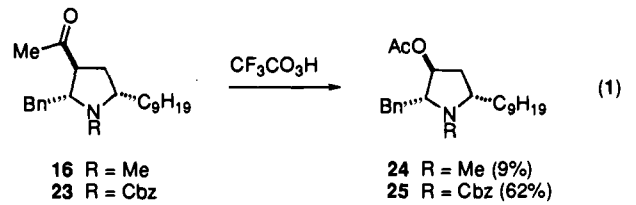


Figure 1. Diagnostic NOE Data for pyrrolidines **15**, **19**, and **22**.

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–TMSOTf[15] returned only starting material. Although **20** underwent Baeyer–Villiger oxidation with 3,5-dinitroperoxybenzoic 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 O_3-vinyl acetate[17] and O_2-PhCHO–$Cu(AcO)_2$.[18] Trifluoroperoxyacetic acid (TFPAA)[19] was the best reagent found for the conversion of **20** → **21**, providing the latter in a disappointing 26–31% yield (Scheme 4).[20] Finally, reduction of **21** with $LiAlH_4$ in refluxing Et_2O provided (+)-preussin (**1**) in 94% yield. The ^1H and ^{13}C NMR spectra of synthetic **1** were in agreement with those reported,[2] while synthetic (+)-**1** exhibited $[\alpha]_D = +18.1°$ (*c* 0.55, $CHCl_3$) indicative of an optical purity of ~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 $LiAlH_4$ 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*).

(15) Suzuki, M.; Takada, H.; Noyori, R. *J. Org. Chem.* **1982**, *47*, 902.
(16) Rastetter, W. H.; Richard, T. J.; Lewis, M. D. *J. Org. Chem.* **1978**, *43*, 3163.
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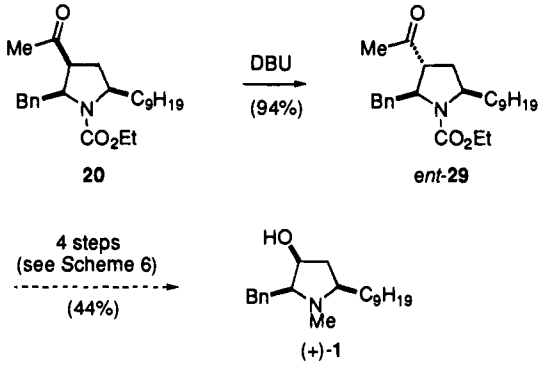
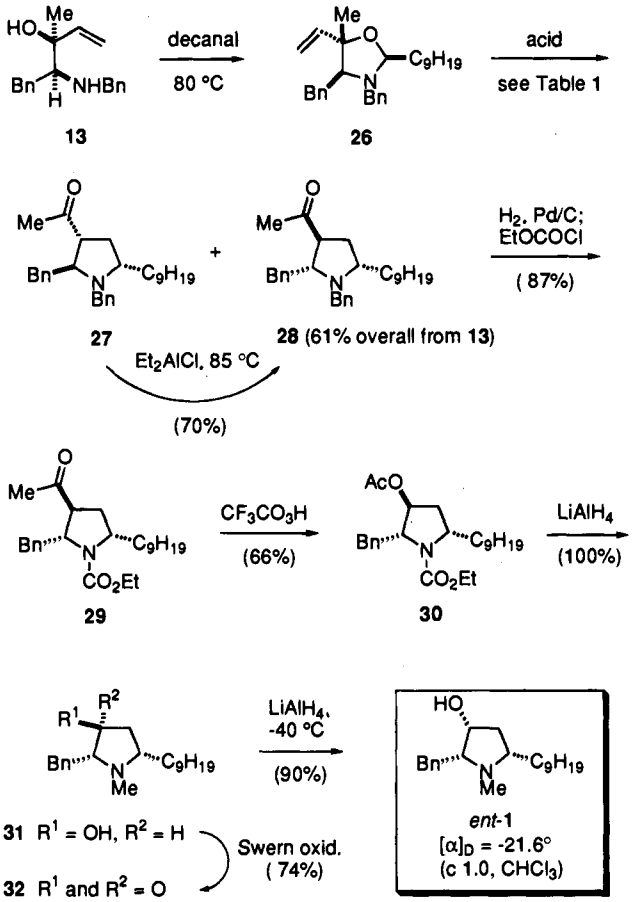
(18) Bolm, C.; Schlingloff, G.; Weickhardt, K. *Tetrahedron Lett.* **1993**, *34*, 3405.
(19) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533.
(20) Attempts to improve the introduction of the C(3) hydroxyl functionality by changing the nitrogen protecting group to Cl_3CCH_2OCO, $Cl_3CC(Me)_2OCO$, Me_3COCO, PhOCO, CF_3CO, CF_3SO_2, $MeSO_2$, $(i\text{-}Pr)_3Si$, or 9-phenylfluorenyl provided derivatives that underwent Baeyer–Villiger oxidation with TFPAA less efficiently than **20**.

Scheme 5. Alternate Endplay to (+)-Preussin



Scheme 6. Total Synthesis of (−)-Preussin from Amino Alcohol **13**



Aza-Cope–Mannich Rearrangement of Amino Alcohol 13 Leading to the Formation of the (2*S*,3*R*,5*S*)-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 ± 1%. Aza-Cope–Mannich reorganization of oxazolidine **26** could also be effected by treatment of **26** with 0.5 equiv of Et_2AlCl 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

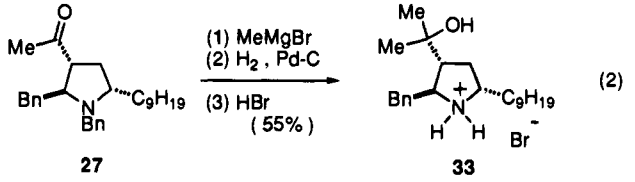
Table 1. Acid-Promoted Rearrangement of Oxazolidine **26**

reaction conditions			products			
			27		**28**	
acid (equiv)	solvent	temp, °C	yield, %	ee, %[a]	yield, %	ee, %[b]
CSA (0.95)	CF_3CH_2OH	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.

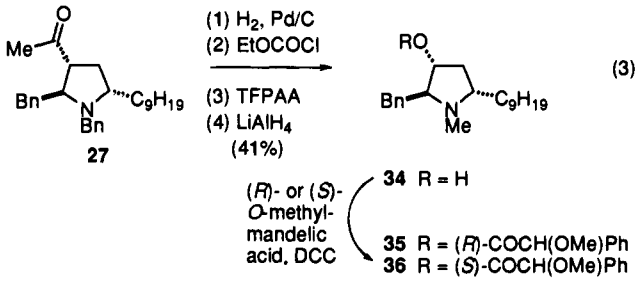
28 was produced in higher enantiopurity (62% ee). These results suggest that **28** is formed both directly from **26** (in low ee) and from **27** (in high ee). This hypothesis was confirmed by exposure of a sample of **27** (86% ee) to 0.1 equiv of Et_2AlCl in toluene at 85 °C for 1 h, which provided pyrrolidine **28** (70% yield, 86% ee) and 7–9% of recovered **27**.[21] Following this two-step sequence, enantioenriched **28** (87 ± 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]



27 **33** (2)

The absolute configuration of **27** was determined by ^{1}H-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.



27 (3)

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 $LiAlH_4$ provided 3-epi *ent*-preussin **31** in quantitative yield. Oxidation of **31** by the Swern procedure (−66 → −40 °C),[23] followed by reduction of ketone **32** with $LiAlH_4$ at −40 °C in THF (ds = 12:1), provided *ent*-preussin in 90% yield. *ent*-**1** exhibited a specific rotation, $[\alpha]_D = -21.6°$ (*c* 1.0, $CHCl_3$), of similar magnitude, but opposite in sign, to that of natural (+)-preussin, $[\alpha]_D = +22.0°$ (*c* 1.0, $CHCl_3$).[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 ~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 ~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** → *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.

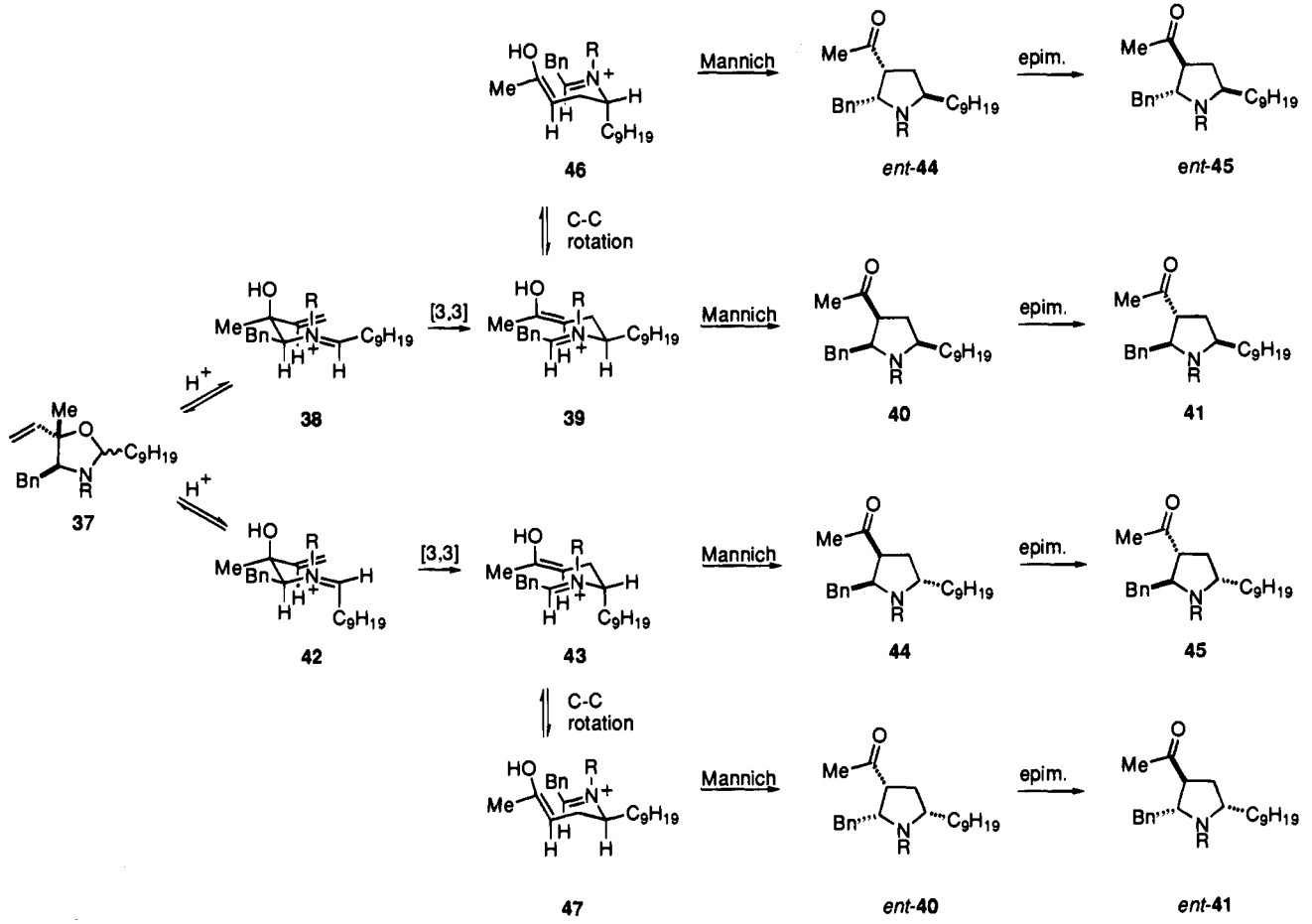
(21) This isomerization can be accomplished using 0.1–0.5 equiv of Et_2AlCl; 0.1 equiv was optimal.

(22) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

(23) Mancuso, A. J.; Huang, S. -L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(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 ~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**

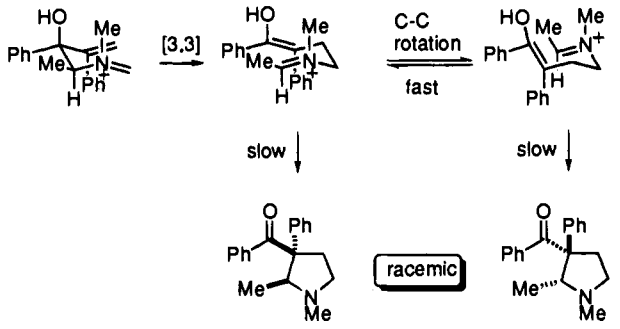


In the *N*-benzyl series, iminium ion stereoisomers **38** and **42** would be of comparable stability. Since, **38** is expected to undergo chair topography [3,3]-sigmatropic rearrangement more rapidly than **42**,[6,7] the preferential formation of acetylpyrrolidine **44** (R = Bn) suggests that iminium 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** → *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 CH_2CH_2 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]

(25) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Interscience: New York, 1965; Chapter 1.

(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 8[8] with an acetone-derived iminium cation.

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 ~3:1 mixture of stereoisomers, whose stereostructures could be assigned by ^{1}H NMR DNOE experiments (Figure 2). Particularly diagnostic was the large (5%)

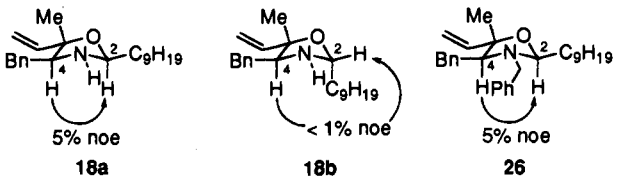


Figure 2. ^{1}H NMR DNOE of oxazolidines **18a**, **18b**, and **26**.

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

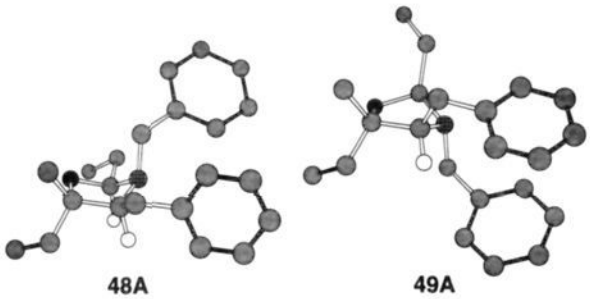
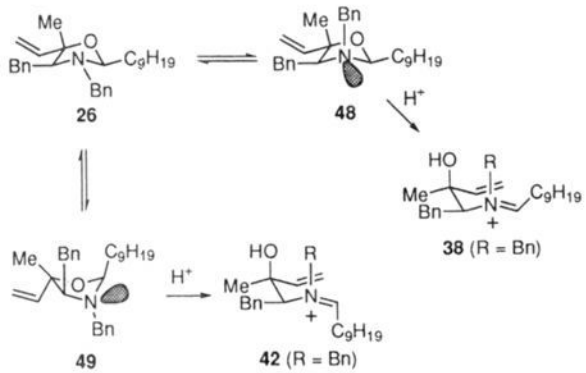


Figure 3. Molecular mechanics (MM2*) estimates of the lowest energy conformations of **48** and **49**. An ethyl group is employed to model the nonyl side chain. Conformer **48A** is 2.2 kcal/mol lower in energy than **49A**.

Scheme 9

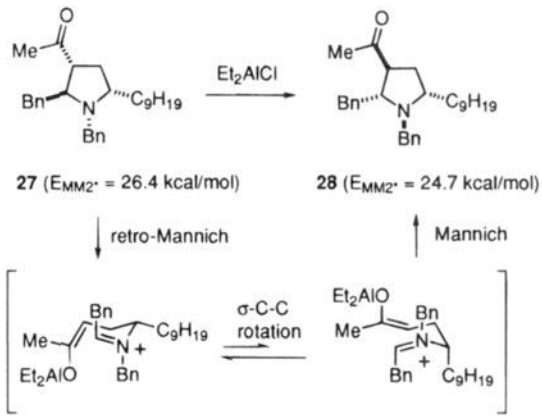


series only a single oxazolidine stereoisomer is apparent in the 500-MHz ^{1}H NMR spectrum of **26**; the large NOE for the methine hydrogens flanking nitrogen signals the configuration depicted in Figure 2. Stereoelectronic considerations require that oxazolidine **26** adopt a conformation having 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** → **49** → **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 ± 5°, 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

Scheme 10



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** → **39** → **46** → *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 extent[7]) would yield **43**. Also, retro-Mannich fragmentation−Mannich cyclization (as observed for the conversion of **27** → **28**) could also epimerize carbons 2 and 3.[29]

The transformation of acetylpyrrolidine **27** → **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 Section[31]

(3*S*,4*S*)-4-(*N*-(Benzyloxycarbonyl)amino)-3-methyl-5-phenyl-1-penten-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

(27) (a) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379. (b) Saunders, M.; Houk, K. N.; Wu, Y.-D.; Still, W. C.; Lipton, M.; Chang, G.; Guida, W. C. *J. Am. Chem. Soc.* **1990**, *112*, 1419.

(28) Calculations employed the Monte Carlo search routine of MacroModel 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 NH_4Cl (400 mL). The aqueous layer was separated and extracted with EtOAc (3 × 400 mL), and the combined organic phases were washed with brine (2 × 600 mL), dried over Na_2SO_4, 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**: ^{1}H NMR (500 MHz, $CDCl_3$) 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, $CDCl_3$) 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°, $[\alpha]^{28}_{577}$ = −90.9°, $[\alpha]^{28}_{546}$ = −104°, $[\alpha]^{28}_{435}$ = −188°, $[\alpha]^{28}_{405}$ = −230° (*c* 1.0, $CHCl_3$). Anal. calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.69; H, 7.16; N, 4.23.

(3*S*,4*S*)-4-(*N*-Methylamino)-3-methyl-5-phenyl-1-penten-3-ol (11). To a suspension of $LiAlH_4$ (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 H_2O (0.35 mL), 15% NaOH (0.35 mL), and H_2O (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 pale-yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) 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 = 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; ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{13}H_{20}NO$, MH); $[\alpha]^{28}_D$ = 7.8°, $[\alpha]^{28}_{577}$ = 4.4°, $[\alpha]^{28}_{546}$ = 4.2°, $[\alpha]^{26}_{435}$ = 10.2°, $[\alpha]^{26}_{405}$ = 10.1° (*c* 1.0, $CHCl_3$).

(3*S*, 4*S*)-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 H_2O (8 mL) was heated at reflux for 12 h, cooled in a water bath to 23 °C, and extracted with Et_2O (3 × 70 mL). The combined extracts were washed with brine (2 × 100 mL), dried over $MgSO_4$, and concentrated. Purification of the residue on silica gel (2:1 hexanes–EtOAc and then EtOAc) provided **12** (586 mg, 100%, 94% ee[34]) as a pale-yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) 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; ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{12}H_{18}NO$, MH). $[\alpha]^{26}_D$ = −64.2°, $[\alpha]^{26}_{577}$ = −65.9°, $[\alpha]^{26}_{546}$ = −77.9°, $[\alpha]^{26}_{435}$ = −141.3°, $[\alpha]^{26}_{405}$ = −174.4° (*c* 1.0, $CHCl_3$). Benzoyltartaric acid salt: mp 162–163 °C; Anal. Calcd for $C_{30}H_{31}NO_9$: C, 65.55; H, 5.69; N, 2.55. Found: C, 65.35; H, 5.73; N, 2.48.

(3*S*,4*S*)-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 Et_2O–DMSO (38 mL) was added dropwise a solution of **10** (3.60 g, 11.1 mmol) and dry Et_2O (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 Et_2O then was removed *in vacuo* at 23 °C. Solid KOH (74 g, 120 equiv), MeOH (82 mL), and H_2O (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 Et_2O (3 × 200 mL), and the combined organic layers were washed with brine (2 × 500 mL), dried over $MgSO_4$, and concentrated. Purification of the residue on silica gel (5:1 hexanes–EtOAc) provided 3.02 g (97% yield, 97% ee[34]) of **13** as a light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) 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; ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{19}H_{24}NO$, MH). $[\alpha]^{25}_D$ = −42.2°, $[\alpha]^{26}_{577}$ = −41.5°, $[\alpha]^{25}_{546}$ = −48.9°, $[\alpha]^{25}_{435}$ = −93.9°, $[\alpha]^{25}_{405}$ = -119° (*c* 1.0, $CHCl_3$). Hydrochloride salt: mp 156–158 °C; Anal. Calcd for $C_{19}H_{24}ClNO$: 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 H_2O 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 × 80 mL), dried over Na_2CO_3, 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**: ^{1}H NMR (500 MHz, C_6D_6) 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; ^{13}C NMR (75 MHz, $CDCl_3$) 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 calcd for $C_{23}H_{38}NO$, MH). $[\alpha]^{23}_D$ = 12.4°, $[\alpha]^{23}_{577}$ = 10.4°, $[\alpha]^{23}_{546}$ = 11.7°, $[\alpha]^{23}_{435}$ = 19.3°, $[\alpha]^{23}_{405}$ = 13.7° (*c* 1.2, $CHCl_3$). Hydrochloride salt: mp 145–6 °C; Anal. Calcd for $C_{23}H_{38}NOCl$: C, 72.70; H, 10.08; N, 3.69. Found: C, 72.48; H, 10.04; N, 3.64. **16**: ^{1}H NMR (300 MHz, $CDCl_3$) 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; ^{13}C NMR (75 MHz, $CDCl_3$)

(31) General experimental details: tetrahydrofuran (THF) and Et_2O were distilled from Na and benzophenone. Dimethylformamide (DMF) was distilled from CaH_2 at 20 mm, while CH_2Cl_2, benzene, toluene, and diisopropylamine were distilled from CaH_2 at atmospheric pressure. The molarities indicated for organolithium reagents were established by titration with 2,5-dimethoxybenzyl alcohol.[32] ^{1}H NMR and ^{13}C 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. ^{1}H NMR chemical shifts are reported as δ values in ppm relative to TMS. ^{1}H 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 Still[33] 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 $C_{23}H_{38}NO$, MH); $[\alpha]^{22}_D = -1.2°$, $[\alpha]^{22}_{577} = -5.0°$, $[\alpha]^{22}_{546} = -5.4°$, $[\alpha]^{22}_{435} = -3.1°$, $[\alpha]^{22}_{405} = -0.8°$ (*c* 1.2, $CHCl_3$).

(2*S*,3*S*,5*R*)-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 CaC_2. Concentration at 23 °C provided the crude oxazolidine **18** as a 3:1 mixture of stereoisomers: ^1H NMR (500 MHz, $CDCl_3$) δ 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 and minor), 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; ^{13}C NMR (125 MHz, $CDCl_3$) 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**, CF_3CH_2OH (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 $CHCl_3$ (100 mL) and then washed with 1 N NaOH (2 × 50 mL) and brine (50 mL). This solution was then dried over $MgSO_4$ and concentrated, and the crude pyrrolidine products were dissolved in $CHCl_3$ (16 mL). Ethyl chloroformate (0.23 mL, 2.4 mmol) and solid $NaHCO_3$ (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% ee[35]), a mixture of three additional stereoisomers (26%), and recovered oxazolidine **18** (2%). **20**: ^1H NMR (500 MHz, $C_6D_5CD_3$, 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), 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; ^{13}C NMR (125 MHz, $C_6D_5CD_3$, 100 °C) δ 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 $C_{25}H_{40}NO_3$, MH); $[\alpha]^{25}_D = -26.7°$, $[\alpha]^{25}_{577} = -26.1°$, $[\alpha]^{25}_{546} = -29.0°$, $[\alpha]^{25}_{435} = -34.2°$, $[\alpha]^{25}_{405} = -29.7°$ (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{25}H_{39}NO_3$: 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 follows. (2*S*,3*R*,5*R*)-3-Acetyl-2-benzyl-1-ethoxycarbonyl-5-nonylpyrrolidine: ^1H NMR (500 MHz, $C_6D_5CD_3$, 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 $C_{25}H_{40}NO_3$, MH). (2*R*,3*S*,5*R*)-3-Acetyl-2-benzyl-1-(ethoxycarbonyl)-5-nonylpyrrolidine: ^1H NMR (500 MHz, $C_6D_5CD_3$, 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 $C_{25}H_{40}NO_3$, MH). (2*R*,3*R*,5*R*)-3-Acetyl-2-benzyl-1-(ethoxycarbonyl)-5-nonylpyrrolidine: ^1H NMR (500 MHz, $C_6D_5CD_3$, 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 $C_{25}H_{40}NO_3$, 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 $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, 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: $[\alpha]^{24}_D = -23.2°$, $[\alpha]^{24}_{577} = -26.1°$, $[\alpha]^{24}_{546} = -26.5°$, $[\alpha]^{24}_{435} = -54.5°$, $[\alpha]^{24}_{405} = -66.7°$ (*c* 0.70, $CHCl_3$).

(2*S*,3*S*,5*R*)-3-Acetoxy-2-benzyl-1-(ethoxycarbonyl)-5-nonylpyrrolidine (21). To a suspension of urea–H_2O_2[19] (98%, 1.60 g, 16.7 mmol) in dry CH_2Cl_2 (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 CH_2Cl_2 (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 H_2O (25 mL) and CH_2Cl_2 (15 mL). Solid $NaHCO_3$ was added until the pH of the aqueous layer was 7–8. The aqueous layer was separated, extracted with 2:1 CH_2Cl_2–EtOAc (2 × 60 mL), and the combined organic phases were washed with brine (2 × 150 mL), dried over $MgSO_4$, 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, $C_6D_5CD_3$, 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; ^{13}C NMR (125 MHz, $C_6D_5CD_3$, 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 $C_{25}H_{40}NO_4$, MH); $[\alpha]^{25}_D = -40.3°$, $[\alpha]^{25}_{577} = -45.3°$, $[\alpha]^{25}_{546} = -51.6°$, $[\alpha]^{25}_{435} = -35.7°$ (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{25}H_{39}NO_4$: 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 $LiAlH_4$ powder (95%, 14 mg, 0.35 mmol) in dry Et_2O (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 $Na_2SO_4{\cdot}10H_2O$ (~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, $CHCl_3$).

Preparation of (2*S*,3*R*,5*S*)-3-Acetyl-1, 2-dibenzyl-5-nonylpyrrolidine (27) and (2*R*, 3*S*, 5*S*)-3-Acetyl-1, 2-dibenzyl-5-nonylpyrrolidine (28). Method A. Et_2AlCl-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, $CDCl_3$) 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 Et_2O (3 × 25 mL), the combined extracts were washed with brine (2 × 50 mL), dried over $MgSO_4$, and concentrated, and the residue was purified on silica gel (1:1:0.02 hexanes–$CHCl_3$–EtOAc). The 23 °C reaction provided 122 mg (48%, 97% ee[36]) 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% ee[36]) 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 CH_2Cl_2 (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 $MgSO_4$, and concentrated. Purification of the crude product as described in method A provided **27** (1.32 g, 78% yield, 86% ee[36]) and **28** (99 mg, 6% yield, 78% ee[36]).

27: ^{1}H NMR (500 MHz, $CDCl_3$) 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; ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{29}H_{42}NO$, MH); $[\alpha]^{26}_D$ = 25.5°, $[\alpha]^{26}_{577}$ = 26.6°, $[\alpha]^{26}_{546}$ = 28.8°, $[\alpha]^{26}_{435}$ = 26.9°, $[\alpha]^{26}_{405}$ = 15.8° (c 1.0, $CHCl_3$). **28**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.06 (m, 10H), 3.93 (d, J = 13.9 Hz, 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; ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{29}H_{42}NO$, MH); $[\alpha]^{25}_D$ = −0.05°, $[\alpha]^{25}_{577}$ = −0.7°, $[\alpha]^{25}_{546}$ = −1.8°, $[\alpha]^{25}_{435}$ = −2.1°, $[\alpha]^{25}_{405}$ = −0.32° (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 CaC_2. This solution then was allowed to cool to 23 °C, and a toluene solution of Et_2AlCl (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 Et_2O (2 × 100 mL), and the combined organic phases were washed with brine (2 × 100 mL), dried over $MgSO_4$, and concentrated. Purification of the residue on silica gel (1:1:0.015 hexanes–$CHCl_3$–EtOAc) gave 794 mg (70%, 86% ee[36]) of pyrrolidine **28** and 77 mg (7%, 75% ee[36]) of recovered **27**.

(2*R*,3*S*,5*S*)-3-Acetyl-2-benzyl-1-(ethoxycarbonyl)-5-nonylpyrrolidine (29). A 780 mg sample of **28** (1.86 mmol, 86% ee; prepared by Et_2AlCl-catalyzed rearrangement of **27**), Pd/C (78 mg, 10% w/w), MeOH (22 mL), and concentrated HCl (1 mL) was maintained under H_2 (1 atm) at 23 °C for 12 h. After concentration, the residue was dissolved in $CHCl_3$ (19 mL), solid $NaHCO_3$ (1.56 g, 10 equiv) was added, and after CO_2 evolution ceased EtOCOCl (0.27 mL, 2.8 mmol) was added dropwise over 1.5 min. The resulting mixture was maintained under N_2 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: ^{1}H NMR (500 MHz, $C_6D_5CD_3$, 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; ^{13}C NMR (125 MHz, $C_6D_5CD_3$, 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 $C_{25}H_{40}NO_3$, MH); $[\alpha]^{25}_D$ = 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, $CHCl_3$).

(2*R*,3*S*,5*S*)-3-Acetoxy-2-benzyl-1-(ethoxycarbonyl)-5-nonylpyrrolidine (30). The urea–H_2O_2 complex[19] (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 Et_2O (150 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 40 mL), and the aqueous layers were back-extracted with Et_2O (2 × 50 mL). The combined organic phases were washed with brine (3 × 100 mL), dried over $MgSO_4$, 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**: ^{1}H NMR (500 MHz, $C_6D_5CD_3$, 100 °C) δ 7.16–6.96 (m, 5H, ArH), 5.08 (dt, J = 5.10, 2.4 Hz, 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; ^{13}C NMR (125 MHz, $C_6D_5CD_3$, 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 $C_{25}H_{40}NO_4$, MH); $[\alpha]^{25}_D$ = 38.7°, $[\alpha]^{25}_{577}$ = 40.3°, $[\alpha]^{25}_{546}$ = 46.9°, $[\alpha]^{25}_{435}$ = 80.3°, $[\alpha]^{25}_{405}$ = 96.2° (c 1.13, $CHCl_3$). Anal. Calcd for $C_{25}H_{39}NO_4$: C, 71.89; H, 9.42; N, 3.36. Found: C, 71.99; H, 9.40; N, 3.32.

(2*R*,3*S*,5*S*)-2-Benzyl-3-hydroxyl-1-methyl-5-nonylpyrrolidine (31). A mixture of **30** (300 mg, 0.719 mmol), dry THF (2 mL), and $LiAlH_4$ 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 H_2O (0.14 mL), 15% NaOH (0.14 mL), and H_2O (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: ^{1}H NMR (500 MHz, $CDCl_3$) 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, CH_3N), 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; ^{13}C NMR (125MHz, $CDCl_3$) 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 $C_{21}H_{36}NO$, MH); $[\alpha]^{25}_D$ = −0.5°, $[\alpha]^{25}_{577}$ = −1.6°, $[\alpha]^{25}_{546}$ = −1.5°, $[\alpha]^{25}_{435}$ = −7.2°, $[\alpha]^{25}_{405}$ = −11.4° (c 1.15, $CHCl_3$). Anal. Calcd for $C_{21}H_{35}NO$: C, 79.43; H, 11.12; N, 4.41. Found: C, 79.28; H, 11.11; N, 4.38.

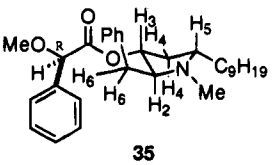
(2*R*,5*S*)-2-Benzyl-1-methyl-5-nonyl-3-oxopyrrolidine (32). Following the general procedure of Swern,[23] a solution of $(COCl)_2$ (0.10 mL, 150 mg, 1.2 mmol) and dry CH_2Cl_2 (3.3 mL) was added dropwise at −66 °C over 5 min to a solution of DMSO (0.170 mL, 187 mg, 2.40 mmol) and dry CH_2Cl_2 (1.1 mL). The resulting solution was maintained at −66 °C for 20 min, and then a solution of **31** (190 mg, 0.600 mmol) and dry CH_2Cl_2 (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 Et_3N (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.

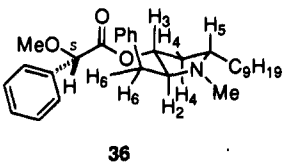
which temperature H_2O (2 mL) was added and the mixture then was allowed to warm to 23 °C. The aqueous layer was separated and back-extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over Na_2CO_3, and concentrated. Purification of the residue on silica gel (10:1 hexanes–EtOAc) provided ketone **32** (140 mg, 74%) as a pale-yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) 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; ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{21}H_{34}NO$, MH); $[\alpha]^{25}_D$ = 29.3°, $[\alpha]^{25}_{577}$ = 29.6°, $[\alpha]^{25}_{546}$ = 34.2°, $[\alpha]^{25}_{435}$ = 26.7°, $[\alpha]^{25}_{405}$ = 38.1° (c 1.02, $CHCl_3$).

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 $LiAlH_4$ 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°, $[\alpha]^{26}_{577}$ = −22.8°, $[\alpha]^{26}_{546}$ = −25.8°, $[\alpha]^{26}_{435}$ = −51.6°, $[\alpha]^{26}_{405}$ = −65.0° (c 1.0, $CHCl_3$).

Determination of the Absolute Configuration of Acetylpyrrolidine 27 by ^{1}H 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 CH_2Cl_2 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**. ^{1}H NMR signals for the key hydrogens of esters **35** and **36** are summarized in the table that follows.[22]



35



36

hydrogen	**35**[a]	**36**[a]
H_2	3.16	3.24
H_4	2.36	2.24
H_6	2.93	3.01, 2.37

[a] In $CDCl_3$, δ.

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Supplementary Material Available: Experimental details for the preparation of **33** and **34**, tables of ^{1}H NMR assignments and decoupling data for **15**, **19**, and **22**, and ^{1}H and ^{13}C 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.