serve to hold the ring in a rigid chair form.

The dipolar-coupled spectrum of cyclohexyltrifluoroacetate contains 12 well-resolved lines. This indicates that the solution was computationally extractable although tedious. The results of these multiple calculations are in Figure 7. It can be seen in this figure that the acetate moiety is in the antipicated, or what may be termed a chemically sensible, location. The rotation about the C1–O bond was well behaved as the *R* factor dropped to a minimum of 40°. A 5° rotation away from this minimum produced a rejectable model at the 99.99% confidence interval. This high precision would indicate that the cyclohexane ring is rather tightly held within the liquid crystal. In contrast to this well-behaved feature, the second rotational mode (around the O—C=O bond) was poorly behaved. The best location was found to be at 50° and could not be fixed closer than 10°. This is the same type of behavior that was found in the acetyl case. Again, we can only rationalize these results on the basis of the small steric size of the trifluoromethyl moiety. As might be expected, the smaller carbon skeleton of the cyclohexane relative to the size of the [2,2,1] allows the liquid crystal to approach more closely the trifluoromethyl moiety. This is indicated by the 10° rotational freedom for the cyclohexyl trifluoroacetate vs. the 20° rotational freedom for acetyl. As was the case before, the averaged coordinates of all the rotational models proved to be unsatisfactory at the 99.95% confidence interval.

Conclusions

An attempt was made to show that the ^{13}C to ^{19}F dipolar coupling experiment is a usable structure determination technique. The ability to use the trifluoromethyl moiety as the source of ^{19}F greatly expands the utility of this technique. It may appear that the application of the technique is extremely tedious but this may be avoided. In the *p*-difluorobenzene experiment, the structural refinement could have been done in less than 2 working days—one to obtain the spectra and the second to preform the calculations. The amount of time required could be even shorter with a wide-bore superconducting NMR. The calculations for the other two examples took considerably longer than 1 working day, due to exploration of the rotational behavior of the functionalities as they were affected by the nematic solvent. This tedious exploration could have been eliminated if potential abnormal behavior had not been investigated. Future users need not be so suspicious.

From these results, it is obvious that this structure determination method cannot be used to determine the rotational populations of a mobile substrate, as the liquid crystal restricts the substrate in what may be an abnormal orientation. This restriction plus the need for a source of ^{19}F are the two major limitations to this technique. On the other hand, the technique produces reproducible, statistically and chemically defendable structures. The technique should find wide applications in the biomedical studies of lipid-bound systems.

Acknowledgment. This work was supported by the National Institutes of Health under the MBRS program, Grant 2 S06 RR08047-13.

Registry No. *p*-Difluorobenzene, 540-36-3; 3-(trifluoroacetyl)camphor, 51800-98-7; cyclohexyl trifluoroacetate, 1549-45-7.

α-Amino Acids as Chiral Educts for Asymmetric Products. Chirospecific Syntheses of the 5-Butyl-2-heptylpyrrolidines from Glutamic Acid

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Received September 10, 1984

Both enantiomers of *trans*-5-butyl-2-heptylpyrrolidine, an active and major component in the repellent venom of the ant *Solenopsis fugax*, have been synthesized with very high diastereomeric and optical purity from glutamic acid. Both enantiomers of the cis isomer also have been synthesized in an extension of our methodology to encompass the preparation of both cis and trans, optically pure, 2,5-disubstituted pyrrolidines and because of their potential entomological interest. Initially, a sulfide contraction process efficiently introduces the first side chain onto a pyroglutamate intermediate. Various strategies to elaborate the second side chain have been developed along with methods to control and establish the relative stereochemistry at C-2 and C-5 of the pyrrolidine ring with high selectivity. 2,5-Dialkyl-1-pyrrolines, which also have been identified in the ant venom, can be prepared by these processes as well with specific absolute stereochemistry.

Various unsymmetrical *trans*-2,5-dialkylpyrrolidines have been identified as the major components in the venom released from a variety of ants in the genus *Solenopsis*.[1] These ants secrete their venom as a powerful repellent to ward off defending host ant species whose nests these thief ants raid for the larvae. Due to this entomological interest, various methods to prepare *trans*-2,5-dialkylpyrrolidines have appeared in the literature. However, these earlier syntheses[2] did not achieve any degree of selectivity in establishing the relative stereochemistry about the pyrrolidine ring. The final mixtures obtained from these routes contained nearly equal amounts

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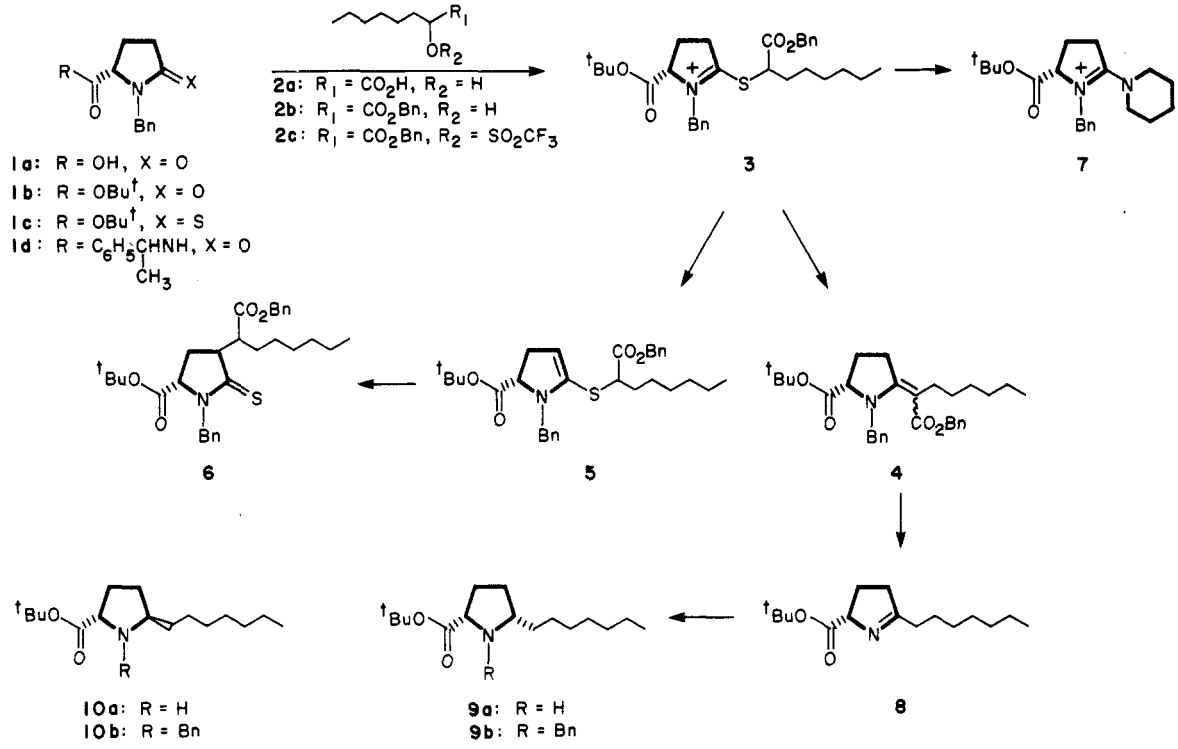
0022-3263/85/1950-1229$01.50/0

Scheme I. Attachment and Stereochemistry of Side Chain at C-5 through Sulfide Contraction and Reduction



of the *cis*- and *trans*-2,5-dialkylpyrrolidines. One recent approach[3] did proceed with a high degree of selectivity in establishing the trans stereochemistry through sequential alkylation of 1-(methyoxycarbonyl)-3-pyrroline but without enantiomeric control.

A continuing question in the structural assignment of these natural dialkylpyrrolidines involves their absolute stereochemistry. It has been suggested that these pyrrolidines exist as single enantiomers; however, lack of material has prevented the determination of any optical properties.[2f] We now report the synthesis of both enantiomers of *trans*-5-butyl-2-heptylpyrrolidine in >99% diastereomeric and >94% enantiomeric purity. This particular pyrrolidine is the major component in the venom of *S. fugax* and its effectiveness as a repellent against competing ant species has been demonstrated.[2f] With both enantiomers now available, evaluating their biological activity should aid in determining the importance, and assignment, of the absolute stereochemistry.

We also report the synthesis of both enantiomers of *cis*-5-butyl-2-heptylpyrrolidine with high diastereomeric and enantiomeric purity. These cis isomers, derived from a common intermediate obtained during the preparation of the trans pyrrolidines, are of some entomological interest themselves as trail pheromones of the pharoh's ant, *Monomorium pharonis*.[2e,4] Additionally, development of a method that can lead to the preparation of either the cis- or trans-2,5-disubstituted pyrrolidines of known absolute stereochemistry from a pivotal intermediate should prove synthetically useful.

Our synthesis to prepare all four possible stereoisomers of a given 2,5-dialkylpyrrolidine exploits glutamic acid as the readily available, optically pure educt. Its ready cyclization to pyroglutamic acid provides a pyrrolidine ring with functional handles at both C-2 and C-5 which can be elaborated into the alkyl side chains. The chiral center at C-2 can be used initially to establish the relative and absolute stereochemistry at C-5, and the newly created C-5 center can then be used to control further stereochemistry at C-2.

Results and Discussion

Establishing the C-5 Center. We planned to develop the C-5 center by converting pyroglutamic acid **1a** to the thiolactam **1c** then introducing the seven-carbon side chain as a single unit through a sulfide-contraction reaction effecting carbon–carbon bond formation. Preparation of the desired thiolactam ester **1c** has been described.[5] To determine the optical integrity of the C-2 center in this first key intermediate, crude thiolactam **1c**, resulting from sulfurization of pyroglutamate **1b** with P_4S_{10} in refluxing THF, was hydrolyzed with HCl to the pyroglutamic acid **1a**. Analysis by HPLC of this regenerated pyroglutamic acid after coupling with optically pure α-phenethylamine indicated the presence of 2% of the undesired enantiomer. The optical purity of the crude thiolactam, thus established as 96% ee, could be improved to >99% by recrystallization. By conducting the sulfurization at room temperature with incremental additions of P_4S_{10}, large quantities of thiolactam **1c** possessing >99% ee could be prepared directly in good yields.

To introduce the seven-carbon side chain through the sulfur-contraction process, the triflate **2c** of 2-hydroxyoctanoate **2b** was required.[6] Cyanide displacement on the bisulfite adduct of heptaldehyde readily afforded the cyanohydrin, which was directly hydrolyzed with acid to yield a mixture of the desired 2-hydroxyoctanoic acid (**2a**) along with various self-condensation products. By employing a vigorous alkaline isolation, these byproducts were hydrolyzed to hydroxy acid **2a**, which was thus obtained

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(4) Ritter, R. J.; Persoons, C. J. *Neth. J. Zool.* **1975**, *25*, 261.
(5) Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539.
(6) Shiosaki, K.; Fels, G.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 3230.

in good overall yield. Esterification with benzyl bromide was followed by conversion to triflate **2c** through reaction of hydroxy ester **2b** with the preformed triflic anhydride–pyridine complex.[7] Alkylation of thiolactam **1c** with triflate **2c** proceeded smoothly at room temperature to thioimidate salt **3**. First triphenylphosphine then triethylamine were introduced at room temperature to form the vinylogous carbamate **4** as a 5/1 mixture of geometrical isomers in 80–85% yields from thiolactam **1c**.

It was imperative that the optical integrity at C-2 be maintained during the sulfide-contraction process. Since electronic effects in the thioimidate ion **3** enhance the acidity of the C-2 hydrogen, the presence of a relatively strong base could lead to the loss of optical purity. Thus it was necessary to evaluate the vinylogous carbamate **4**, preferably by degrading it to the pyroglutamic acid **1a**, which could be analyzed as its α-phenethylamide **1d**. This oxidative cleavage was effected by ozonolysis or better by using $KMnO_4$ under neutral conditions. The resulting pyroglutamic acid **1a**, on HPLC analysis of its α-phenethylamide **1d**, indeed showed the presence of 15% of the opposite enantiomer.

Since 70% ee at this stage of the synthesis was unacceptable, the degree of racemization as a function of base strength and reaction conditions was investigated. Lowering the temperature at which sulfide contraction was conducted from 20 to 0 °C dramatically improved the optical purity from 70% to 90% ee. Decreasing the base strength of the amine also led to improvement of optical purity but at the price of lowered yields of the vinylogous carbamate **4**. The best set of conditions, considering both optical purity and yield, consists in the addition of *N*-methylpiperidine at 0 °C and produces the vinylogous carbamate **4** possessing 96% ee in 70% yield from the thiolactam **1c**.

This investigation of the sulfide-contraction process revealed several different reaction paths leading from thioimidate **3** that appeared to be dependent on the nature of the base. The course necessary for sulfide contraction to proceed is initiated by abstraction of the alkyl side-chain α-proton. However, the C-2 methine proton is also acidic and susceptible to abstraction as evidenced by the loss of optical purity. The use of a sterically hindered base, diisopropylethylamine, produced the vinylogous carbamate **4** in lowered yields along with a competing product, which was the α-alkylated thiolactam **6** as a mixture of diastereomers. The formation of **6** probably results from the decreased ability of a sterically hindered base to approach the α-proton in the side chain and the competitive removal of the C-4 proton. The proposed ketene *S,N*-acetal **5** would be generated and undergoes self-alkylation to the observed product **6**. Similar observations have been made in a related example.[5] The use of a secondary amine, piperidine, did not effect proton abstraction but led exclusively to displacement and production of the stable amidinium salt **7** in excellent yield.

Introduction of the heptyl side chain via the sulfide-contraction process brought along a side-chain ester functionality which was now unwanted, and its removal was readily effected through transfer hydrogenolysis.[8] Although the sequence of events is unknown, benzyl ester hydrogenolysis is probably the first step, then decarboxylation of the vinylogous carbamic acid, loss of the nitrogen benzyl group, and isomerization of the enamine to produce the 1-pyrroline ester **8** in 85% yield.

The critical establishment of the stereochemistry at C-5 through transfer of chirality from C-2 was successfully accomplished by catalytic reduction of pyrroline ester **8** to proline ester **9a**, and reprotection of the nitrogen with benzyl bromide was quantitative. The pyrroline ester **8** was also reduced with $NaBH_4$ to afford a 2/1 mixture of cis and trans proline esters **9a** and **10a**. Rebenzylation of the mixture followed by chromatography produced pure samples of the diastereomers **9b** and **10**, which were used to establish analytical HPLC conditions and detection limits. Thus the catalytic reduction of pyrroline ester **8** was shown to proceed with >99% stereoselectivity. The overall conversion of vinylogous carbamate **4** to proline ester **9a** may be accomplished in one pot using ammonium formate as the hydrogen source with the same degree of stereoselectivity.

The chemical shifts of the C-5–H in the ^1H NMR spectra are quite diagnostic in differentiating between the cis and trans prolines. Due to the anisotropic deshielding effect of the carbonyl group, the chemical shift of the C-5–H in the trans proline ester **10b** occurs at δ 3.20 while the C-5–H in the cis ester **9b** is found at 2.65.

Cis Pyrrolidines. Since one of our objectives was to prepare *cis*-5-butyl-2-heptylpyrrolidine (**14b**), the availability of cis proline ester **9b** suggested the possibility of extending the ester functionality into the desired butyl side chain. We planned to introduce the three-carbon unit directly by addition of an organometallic reagent to the cis proline **11**,[9] obtained on hydrolysis of proline ester **9b**. Grignard reagents failed to add to the proline while organolithium reagents did produce the amino ketone **12**. Initial mediocre yields, plagued with the formation of the tertiary carbinol **15**, were significantly improved using ether rather than THF as solvent and maintaining the temperature at 0–5 °C throughout the course of the reaction.

A large excess of propyllithium was necessary to attain a reasonable rate of reaction and this excess was most effectively quenched by the addition of acetone. Subsequent protic workup cleanly released the amino ketone **12**. Quenching with water, on the other hand, led to significant amounts of tertiary carbinol **15**. Amino ketone **12** was immediately reduced with $NaBH_4$ to the diastereomeric amino alcohols **13a**. The diastereomers were produced in a 3/2 ratio and could be chromatographically separated but were carried on as a mixture.

Addition of organometallic reagents to α-amino acids to prepare optically pure amino ketones has been successfully applied to *N*-acetyl, -benzoyl, -(phenylsulfonyl), or -(ethoxycarbonyl) derivatives.[9a] Abstraction of the acidic amide or carbamate proton by the organometallic reagent was postulated as preventing subsequent ionizaton of the α-methine proton, thereby preserving the optical integrity at the α-carbon. Such measures are not possible on a proline derivative; however, we have found that addition of organolithium reagents proceeded to produce a single ketone. The absence of any of the epimeric ketone demonstrated that the optical integrity at C-2 was maintained despite the absence of an adjacent protecting nitrogen anion. Whether addition of organometallic reagents to

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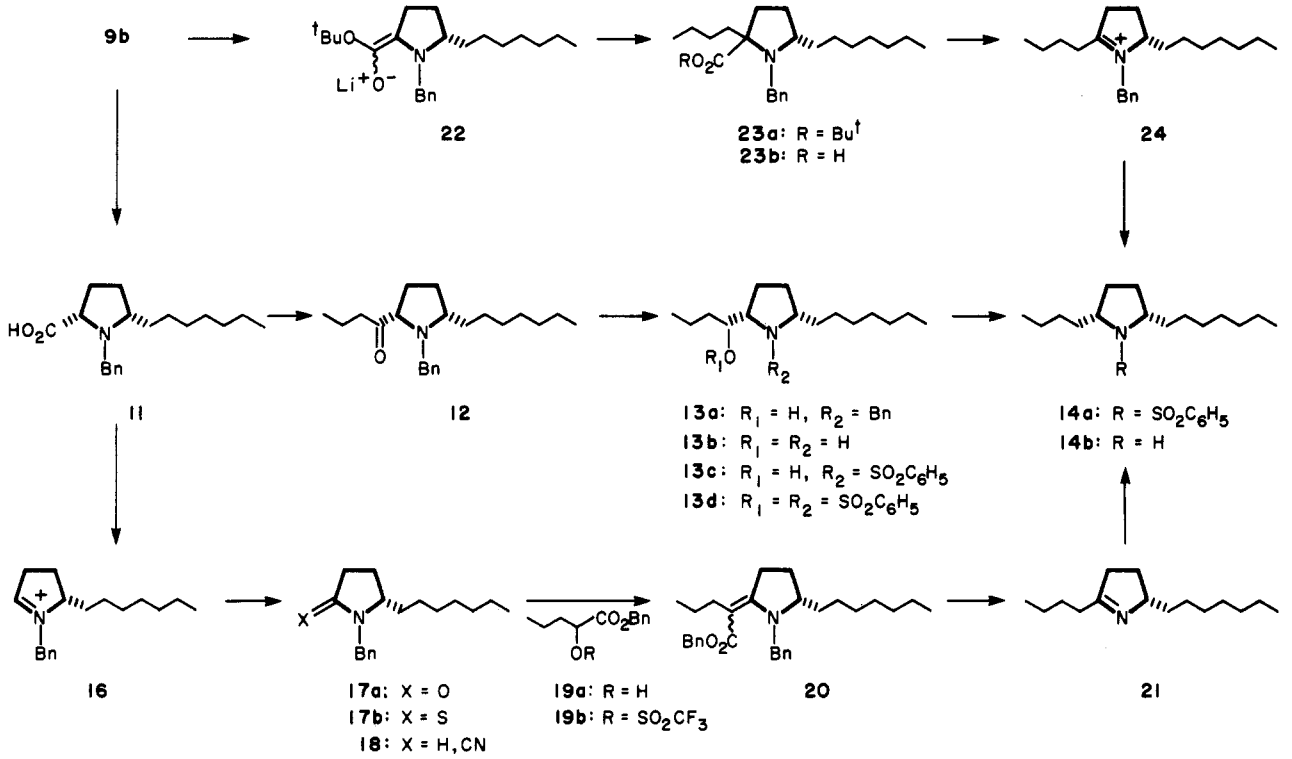
Scheme II. Development of Side Chain at C-2. Synthesis of 2,5-Cis Pyrrolidines



tertiary α-amino acids without racemization is a general reaction has not been determined.

The remaining task of deoxygenating amino alcohol **13a** at first appeared trivial. However, all attempts to convert the alcohol to an appropriate group which in turn could be displaced with hydride or removed through hydrogenolysis failed.[10] Hindered secondary alcohols required fairly vigorous conditions to effect their derivatization and such conditions may have been sufficient to form aziridinium intermediates. Complicated product mixtures were observed possibly owing to ring opening and rearrangement of such intermediates. Conversion of the alcohol to a less easily displaced group which could then be cleaved under radical conditions[11] was also attempted but consistently low yields led to abandonment of this approach. To eliminate these complications, undoubtedly arising from participation of the basic β-nitrogen, the tertiary amine was hydrogenolyzed to the secondary amino alcohol **13b** and converted to the phenylsulfonamide **13c**. As expected, subsequent attempts to derivatize the alcohol proceeded smoothly. The most efficient process was bissulfonation using (phenylsulfonyl)imidazolide activated with trimethyloxonium tetrafluoroborate.[12] The bis-sulfonated products **13d** were isolated in 90% yields and the sulfonates were readily displaced with $NaBH_4$ in Me_2SO.[13] The resulting pyrrolidinylsulfonamide **14a** was deprotected to give the final *cis*-dialkylpyrrolidine **14b** by using 48% HBr with phenol as a bromine scavenger[14] or by a dissolving metal reduction with sodium in liquid ammonia.

The diastereomeric purity of the cis pyrrolidine was assessed at the sulfonamide **14a** stage. Analytical HPLC demonstrated the presence of >99% of the cis pyrrolidine. The optical purity of the final product could not be determined since a number of diastereomeric amides could not be separated either by chromatography or by analysis of the proton or fluorine resonance spectra. However, on the basis of the results with the trans isomers, which could be separated and which were prepared using the same reactions (see below), we conclude that the optical purity is >94%.

The ease and success with which we had introduced the heptyl side chain via the sulfide-contraction process led us to consider applying the same strategy to attach the butyl side chain at C-2. The feasibility of this plan depended on whether the carboxyl group at C-2 of proline **11** could be replaced with a doubly bonded sulfur. The resulting thiolactam **17b** would then be the substrate for sulfide contraction to introduce the butyl chain.

Initially we attempted to oxidize iminium salt **16**, generated from proline **11** by $POCl_3$,[15] to lactam **17a**. Oxidation of azetidinium salts with *m*-CPBA has been reported to produce azetidinone,[16] however, that process failed to oxidize **16**; other peracids as well as peroxides also failed. Oxidation with $KMnO_4$ in acetone did produce lactam **17a** but in inconsistent yields. Trapping the enolate of the proline ester **9b** with di-*tert*-butylmethylsilyl chloride followed by treatment of the ketene acetal with ozone

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or singlet oxygen[16] failed to produce any of the desired lactam **17a**.

An improved route to lactam **17a** was developed on the basis of the efficient trapping of iminium salt **16** with cyanide to produce the amino nitriles **18** together with the application of methods previously used to oxidize α,α-dialkyl nitriles to ketones.[17] Treatment of amino nitriles **18** with LDA followed by sequential reactions of the anion with molecular oxygen, $SnCl_2$, and base produced the lactam **17a** in good yield. As we were ultimately interested in thiolactam **17b** rather than lactam **17a**, a direct conversion of amino nitriles **18** to the former was developed by treatment with LDA followed by the addition of excess sulfur. The excess sulfur was removed by reduction with $NaBH_4$, and thiolactam **17b** was isolated in 73% yield.

Introduction of the butyl side chain onto thiolactam **17b** through alkylation and sulfide contraction using the appropriate triflate **19b** yielded the vinylogous carbamate **20** in 80% yield. Direct conversion to the cis pyrrolidine **14b** then took place with transfer hydrogenolysis–hydrogenation using ammonium formate and palladium/carbon. The reaction proceeds through the intermediate pyrroline **21** on which the critical reduction was performed to reestablish the C-2 asymmetry. Preparation of the *cis*-dialkylpyrrolidine via this double-contraction route represents a reflective transfer of chirality as the original C-2 center is used to establish the C-5 center, which in turn reestablishes the original center, which had been destroyed at an intermediate stage.

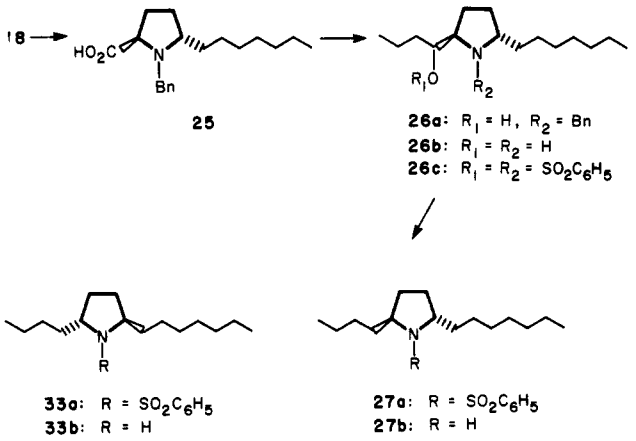
Isolation of pyrroline **21** can be achieved by conducting the transfer hydrogenolysis with cyclohexene as the hydrogen donor. A variety of the 2,5-dialkyl-1-pyrrolines have been identified as components of ant venoms along with the trans pyrrolidines.[1] The current method[2c] for preparing these 1-pyrrolines relies on treatment of 2,5-dialkylpyrrolidines with NaOCl followed by NaOH to produce an inseparable isomeric mixture of pyrrolines. Our method allows the preparation of isomerically pure 2,5-dialkyl-1-pyrroline of known structure as well as known absolute stereochemistry at C-5.

The final *cis*-dialkylpyrrolidine **14b** was converted to the phenylsulfonamide **14a** for analysis of diastereomeric purity. Analysis by HPLC revealed that reduction of pyrroline **21** had proceeded to yield a 98/2 mixture of the cis and trans pyrrolidines.

Another point of interest was whether alkylation of proline ester enolate **22** would occur with any degree of stereoselectivity. We anticipated that approach of the alkylating agent to the enolate would be directed by the heptyl chain to yield predominately the *trans*-dialkylproline ester **23a**. Reduction of the ester to the aldehyde followed by decarbonylation with retention of configuration using rhodium[18] would constitute an entry into the *trans*-dialkylpyrrolidines.

The enolate prepared from the proline ester **9b** with LDA was quenched with butyl bromide to produce in 90% yield an 8/1 mixture of easily separable diastereomers. We had expected to assign stereochemistry to the diastereomers by observation of anisotropic deshielding effects on the C-5 methine proton as in the trans isomer of the 5-heptylproline series. However, the chemical shifts for the methine protons of both diastereomers occurred in the same region. Comparison of the ^1H NMR spectra of the dialkylprolines **23b** also did not differentiate between the methine protons.

Scheme III. Synthesis of 2,5-Trans Pyrrolidines



Steric assignments were subsequently pursued through chemical means as described above. The major diastereomer of **23a** was converted to the dialkylprolinal by first reducing to the dialkylprolinol with LAH followed by oxidizing to the aldehyde with Me_2SO/oxalyl chloride/TEA.[19] The decarbonylation was done with tris(triphenylphosphine)rhodium(I) chloride in refluxing toluene[18] and yielded the dialkylpyrrolidine which was identified as the cis isomer. This unexpected result may be due to participation of the *N*-benzyl group in directing the alkylation. The phenyl ring resides in the plane of the ring opposite the heptyl side chain, thereby directing the approaching alkylating agent to yield the *cis*-dialkyl compound as the major isomer.

Although this method did not result in an entry into the trans pyrrolidine series, the mixture of proline esters can be efficiently taken on to the cis pyrrolidine. Treatment of the mixed esters **23a** with TFA gave the dialkylprolines **23b**, which with $POCl_3$ produced the iminium salt intermediate **24**. Catalytic reduction yielded *cis*-dialkylpyrrolidine **14b**, and formation of phenylsulfonamide **14a** followed by HPLC analysis revealed a 95/5 mixture of cis and trans isomers. This method represents the most direct and efficient preparation of the *cis*-dialkylpyrrolidine although with slightly decreased diastereomeric purity.

Trans Pyrrolidines. Synthesis of the *trans*-dialkylpyrrolidines represented the more difficult task. Early attempts involved directly adding various organometallic reagents containing the four-carbon side chain to iminium salt **16**.[20] Irrespective of the nature of the organometallic reagent (Grignard, alkyllithium) or the substituent on nitrogen (benzyl, methyl), the addition proceeded with poor stereoselectivity, a 2/3, cis/trans mixture representing a typical result. The use of active methylene compounds was considered in the hope of conducting the addition under equilibrating conditions;[21] however, β-keto esters and 1,3-diketones failed to add to our iminium species.

Equilibration of the cis proline ester **9b** was also attempted as the separation of the *cis*-**9b** and *trans*-**10b** isomers could be readily achieved. Thus the cis proline ester **9b** was subjected to heating with *t*-BuOK in *t*-BuOH, but after 1 day, the isomer ratio stabilized as a 3/2, cis/trans mixture.

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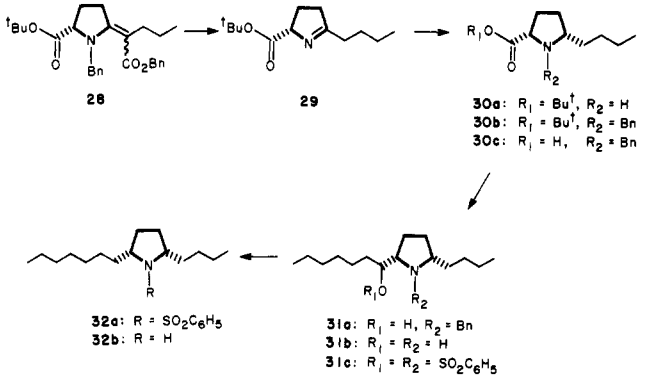
Scheme IV. Synthesis of Enantiomeric Cis Pyrrolidine from L-Glutamic Acid



Entry into the trans series of pyrrolidines was efficiently achieved by equilibration of the amino nitrile **18**. On trapping iminium salt **16** with cyanide, the kinetic addition product was a 1/3 mixture of the cis and trans isomers. This kinetic mixture was then equilibrated in a silica gel slurry to produce a 1/9, cis/trans mixture of amino nitriles **18**. Hydrolysis with strong mineral acid led to the same isomeric mixture of cis and trans prolines, and trans proline **25** was readily isolated by crystallization. The crystalline material was >99% trans proline **25**[22] and was produced in 50% yield over three steps from the cis proline **11**. The isolated yield of the trans proline **25** could be improved by recycling the mother liquor through the treatment with $POCl_3$, trapping the pyrrolinium salt **16** with cyanide, and then equilibrating again to the 1/9, cis/trans mixture.

Elaboration of the butyl side chain at C-2 employed the methodology developed earlier in the preparation of cis pyrrolidines. Propyllithium addition to trans proline **25** under controlled conditions followed by an acetone quench yielded the amino ketone which was immediately reduced with $NaBH_4$ to the diastereomeric amino alcohols **26a**. Hydrogenolysis to the secondary amino alcohol **26b** followed by bissulfonation yielded sulfonate/sulfonamide **26c** from which the sulfonate was removed with $NaBH_4$ in Me_2SO. Sulfonamide **27a** was >99% trans isomer as shown by HPLC. Deprotection with sodium in liquid ammonia or 48% HBr produced trans pyrrolidine **27b**. The enantiomeric purity was assessed through formation of the MTPA amides. HPLC analysis indicated the presence of 3% of the opposite enantiomer thereby establishing a 94% ee in our final compound.

Enantiomers. Our final objective was to synthesize the enantiomers of the cis and trans pyrrolidines. The enantiomeric cis pyrrolidine **32b** was prepared from L-glutamic acid by reversing the order of side-chain introduction into thiolactam **1c**. The butyl side chain was introduced at the C-5 center through the sulfide-contraction process and the heptyl side chain was extended from the C-2 carboxyl via hexyllithium addition to the *cis*-5-butylproline **30c**. The remaining chemistry was directly analogous to the preparation of the original enantiomer. The diastereomeric purity of pyrrolidine **32a** was >99% cis.

The only isomer that required D-glutamic acid as educt was the enantiomeric trans pyrrolidine **33b**. Its synthesis followed exactly that described for the original enantiomer, and the results and purities (diastereomeric and enantiomeric) obtained were identical except for the direction of rotation.

(22) The diastereomeric purity was determined by ^1H NMR where the limit of detection of the cis proline was <1%.

Experimental Section

General Methods. Tetrahydrofuran and ether were distilled from sodium benzophenone; acetonitrile, ethyl acetate, and Me_2SO were distilled from CaH_2; methylene chloride was distilled from P_2O_5. All amine reagents were refluxed and distilled from CaH_2 and all final organic solutions were dried over Na_2SO_4. Propyllithium and hexyllithium were prepared according to Gilman[23] by using an argon atmosphere. Total organolithium content was determined by the double-titration method.[24] Boiling and melting points (Buchi melting point apparatus) are uncorrected. IR spectra were determined on the neat compound and NMR spectra were recorded in $CDCl_3$ in parts per million (δ) downfield from Me_4Si for ^1H and relative to $CDCl_3$ at 77.0 ppm for ^{13}C. HPLC analyses were performed using a Microsorb 5-μm column (3.2 × 250 mm).

2-Hydroxyoctanoic Acid (2a). To $NaHSO_3$ (156 g) in H_2O (300 mL) was added heptaldehyde (114 g, 1.0 mol) while vigorously shaking for 30 min; then a solution of NaCN (64 g, 1.3 mol) in H_2O (160 mL) was added and shaken for 15 min. The upper layer upon separation of phases was poured directly into a solution of 40% sulfuric acid (330 mL) and heated at 125 °C for 3 h, then poured into 6 N NaOH (1 L) and stirred overnight. The alkaline solution was washed with Et_2O (2 × 250 mL) then acidified with 1 N HCl and extracted with Et_2O (3 × 250 mL) which was washed with brine (150 mL), dried, and evaporated. Recrystallization from benzene gave **2a**: 92.5 g, 58% yield; mp 70–71 °C (lit.[25] mp 69 °C); ^1H NMR δ 0.89 (t, 3 H, J = 5.9 Hz), 1.2–2.0 (m, 10 H), 4.2–4.3 (m, 1 H); IR 3440, 2980, 2950, 2880, 1735 cm^{-1}.

Benzyl 2-Hydroxyoctanoate (2b). A solution of 2-hydroxyoctanic acid (98.0 g, 0.61 mol), triethylamine (62.0 g, 0.61 mmol), and benzyl bromide (99.0 g, 0.58 mol) in EtOAc (300 mL) was refluxed for 7 h. After the white precipitate was filtered off, the filtrate was concentrated to a residue which was dissolved in Et_2O (900 mL). Washing with H_2O (250 mL), aqueous $NaHCO_3$ (3 × 100 mL), 1 M HCl (1 × 100 mL), and brine (1 × 100 mL), drying, and evaporating left a residue which was distilled [bulb to bulb, 110 °C (400 mHg)] to afford **2b**: 120 g, 83% yield; ^1H NMR δ 0.87 (br t, 3 H, J = 6.5 Hz), 1.2–1.9 (m, 10 H), 2.83 (d, 1 H, J = 5.8 Hz, exchangeable proton), 4.2–4.3 (m, 1 H), 5.19 (d, 1 H, J = 12.2 Hz), 5.22 (d, 1 H), 7.36 (br s, 5 H); IR 3400, 2850, 1620 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_3$: C, 72.0; H, 8.9. Found: C, 71.7; H, 8.7.

Benzyl 2-([(Trifluoromethyl)sulfonyl]oxy)octanoate (2c). To a solution of pyridine (14.7 g, 186 mmol) in CH_2Cl_2 (500 mL), cooled to −22 °C under a nitrogen atmosphere, was added triflic anhydride (50.0 g, 177 mmol) over 15 min while maintaining vigorous mechanical stirring to form a white slurry. The mixture was stirred an additional 15 min at 22 °C and to it was added a solution of hydroxy ester **2b** (35.5 g, 142 mmol) in CH_2Cl_2 (15 mL) over 2 min. The reaction mixture was allowed to warm to room temperature, vigorously stirred for 1 h, and filtered, and the precipitate was washed with CH_2Cl_2. Filtrate and washings were concentrated then passed through a short column of silica gel (40 g), eluting with hexane. Evaporation left a residue of **2c**: 46.7 g, 86% yield; ^1H NMR δ 0.87 (br t, 3 H, J = 6.5, Hz), 1.2–1.5 (m, 8 H), 1.9–2.1 (m, 2 H), 5.14 (t, 1 H, J = 6.1 Hz), 5.24 (d, 1 H, J = 12.2 Hz), 5.26 (d, 1 H), 7.37 (br s, 5 H); IR 2900, 1760, 1410 cm^{-1}. Anal. Calcd for $C_{16}H_{21}F_3SO_5$: C, 50.3; H, 5.5. Found: C, 49.9; H, 5.6.

(2*S*)-1-Benzyl-5-(1-[(benzyloxy)carbonyl]heptylidene)-proline *tert*-Butyl Ester (4). To a solution of triflate **2c** (8.15 g, 21.3 mmol) in CH_3CN (3 mL) was added a solution of thiolactam **1c** (5.88 g, 20.2 mmol) in CH_3CN (8 mL), prepared from lactam **1b**.[4] After stirring at 0 °C for 15 min, the solution was allowed to warm to room temperature. After 4 h to complete the formation of thioiminium salt **3**, the solution was diluted with CH_2Cl_2 (125 mL), triphenylphosphine (6.35 g, 24.2 mmol) was added in one portion, and the mixture was stirred for 30 min. It was cooled to 0 °C and a solution of 1-methylpiperidine (3.61 g, 36.4 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added dropwise over 30 min. The

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mixture was stirred at 0 °C for 5 h, diluted with CH_2Cl_2 (100 mL), washed with cold 1 M H_3PO_4 (2 × 150 mL), aqueous $NaHCO_3$ (1 × 150 mL), and brine (200 mL), and then dried. The residue after evaporating the CH_2Cl_2 was dissolved in EtOAc (50 mL) and hexane added until slight cloudiness persisted. Precipitation was completed by cooling, the mixture was filtered, and the filtrate was evaporated to an oil which was passed through a silica gel column (250 g). Elution with 1% EtOAc in CH_2Cl_2 gave the vinylogous carbamate **4** as a viscous 5/1 mixture of geometrical isomers: 6.93 g, 70% yield; ^1H NMR δ, major isomer, 0.80 (3 H, t, J = 6.5 Hz), 1.1–1.5 (10 H, m), 1.42 (9 H, s), 1.9–2.5 (2 H, m), 3.0–3.3 (2 H, m), 3.86 (1 H, dd, J = 4.7, 8.4 Hz), 4.32 (1 H, d, J = 16.8 Hz), 4.90 (1 H, d), 5.13 (2 H, s), 7.1–7.4 (10 H, m), minor isomer, 0.84 (3 H, m), 1.1–1.5 (10 H, m), 1.43 (9 H, s), 1.9–2.5 (2 H, m), 3.0–3.3 (2 H, m), 3.90–3.95 (1 H, m), 4.24 (1 H, d, J = 15.2 Hz), 4.72 (1 H, d), 5.03 (1 H, d, J = 12.7 Hz), 5.13 (1 H, d), 7.1–7.4 (10 H, m); IR 2900, 1725, 1680, 1550 cm^{-1}; UV (CH_3CN) λ_{max} 290 nm (ε 14 800). Anal. Calcd for $C_{31}H_{41}NO_4$: C, 75.7; H, 8.4; N, 2.8. Found: C, 75.7; H, 8.3; N, 2.8.

(2*S*)-1-Benzyl-4-(1-[(benzyloxy)carbonyl]heptyl)-5-thioxoproline *tert*-Butyl Ester (6). To a solution of triflate **2c** (3.02 g, 7.9 mmol) in CH_3CN (3.0 mL) at 0 °C was added a solution of thiolactam **1c** (2.09 g, 7.2 mmol).[4] After stirring 30 min at 0 °C, the solution was allowed to warm to room temperature and stirred for 16 h, diluted with CH_2Cl_2 (35 mL) containing triphenylphosphine (2.25 g, 8.6 mmol), and after 30 min cooled to 0 °C. A solution of diisopropylethylamine (14.0 g, 19.8 mmol) in CH_2Cl_2 (3.0 mL) was added dropwise over several minutes, the solution was stirred at 0 °C for 6 h, and then it was diluted with CH_2Cl_2 (30 mL), which was washed with 1 M H_3PO_4 (3 × 20 mL), saturated bicarbonate, (2 × 20 mL), and brine (50 mL), then dried, and evaporated. The residue was chromatographed eluting with 1/1 isooctane/CH_2Cl_2 followed by 100% CH_2Cl_2 and finally 5% EtOAc in CH_2Cl_2 to yield **4** (1.10 g, 31%) and **6**: 1.21 g, 33% yield; R_f (CH_2Cl_2) 0.51, 0.46. Faster eluting isomer: ^1H NMR δ 0.8–0.9 (m, 3 H), 1.42 (s, 9 H), 1.2–1.9 (m, 10 H), 2.1–2.2 (m, 1 H), 2.5–2.7 (m, 1 H), 3.1–3.3 (m, 1 H), 3.5–3.6 (m, 1 H), 4.1–4.2 (m, 1 H), 4.27 (d, 1 H, J = 15 Hz), 5.06 (s, 2 H), 7.60 (d, 1 H), 7.27.4 (7, 10 H); IR 2950, 1745, 1485 cm^{-1}. Slower eluting isomer: ^1H NMR δ 0.86 (br t, 3 H, J = 6.3 Hz). 1.41 (s, 9 H), 1.1–1.7 (m, 10 H), 2.1–2.2 (m, 2 H), 3.3–3.5 (m, 2 H), 4.0–4.1 (m, 1 H), 4.21 (d, 1 H, J = 14.6 Hz), 5.14 (d, 1 H, J = 12.3 Hz), 5.18 (d, 1 H), 5.84 (d, 1 H), 7.2–7.4 (m, 10 H); IR 2950, 2880, 1745, 1735, 1460 cm^{-1}. Mass Spectrum, calcd for $C_{31}H_{41}NO_4S$, m/z 523.7333, found 523.7754. Anal. Calcd for $C_{31}H_{41}NO_4S$: C, 71.1; H, 7.9; N, 2.7. Found: C, 71.4; H, 7.9; N, 2.6.

(5*S*)-1-Benzyl-5-[(*tert*-butyloxy)carbonyl]-2-(1-piperidinyl)-1,2-dehydropyrrolidinium Trifluoromethanesulfonate (7). A solution of triflate **2c** (3.00 g, 7.8 mmol) in CH_3CN (3.0 mL) at 0 °C to which was added a solution of thiolactam (2.08 g, 7.1 mmol) in CH_3CN (3.0 mL) was allowed to stir at 0 °C for 0.5 h then stirred at room temperature for 16 h. After the solution was diluted with CH_2Cl_2 (35 mL), triphenylphosphine (2.25 g, 8.6 mmol) was added, stirring was continued for 30 min, then it was cooled to 0 °C, and a solution of piperidine (1.00 g, 11.7 mmol) in CH_2Cl_2 (3.0 mL) was added over 2 min and stirred for 6 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with 1 M H_3PO_4 (3 × 20 mL), saturated $NaHCO_3$ (2 × 20 mL), and brine (50 mL), then dried, and evaporated. The residue was chromatographed eluting with 100% CH_2Cl_2 then 10% CH_3OH in CH_2Cl_2 to yield **7** which was crystallized from EtOAc/hexane: 2.63 g, 86% yield; mp 103–104 °C; ^1H NMR δ 1.36 (s, 9 H), 1.72 (br s, 6 H), 2.0–2.1 (m, 1 H), 2.6–2.8 (m, 1 H), 2.9–3.0 (m, 1 H), 3.45–3.6 (m, 1 H), 3.72 (br s, 4 H), 4.3 (m, 1 H), 4.78 (d, 1 H, J = 16.1 Hz), 4.91 (d, 1 H), 7.3–7.5 (m, 5 H). Anal. Calcd for $C_{22}H_{31}N_2SF_3O_5$: C, 53.7; H, 6.3; N, 5.7. Found: C, 53.9; H, 6.3; N, 5.7.

(2*S*)-5-Heptyl-Δ⁴-dehydroproline *tert*-Butyl Ester (8). To a solution of vinologous carbamate **4** (5.00 g, 10.2 mmol) in methanol (30 mL) were added 10% Pd/charcoal (3.75 g) and cyclohexene (8.35 g, 0.10 mol). The reaction mixture was refluxed for 15 min, cooled, and filtered and the catalyst was digested with CH_3OH (50 mL). The combined filtrate and digest were evaporated and the residue was dissolved in CH_2Cl_2 (30 mL), washed with aqueous $NaHCO_3$ (2 × 15 mL), dried, and evaporated. Bulb-to-bulb distillation of the residue yielded imine **8**: bp 105 °C (250 μmHg); 2.35 g, 86% yield; ^1H NMR δ 4.56 (1 H, br t, J = 7.3 Hz), 1.9–2.7 (6 H, m), 1.2–1.7 (10 H, m), 1.47 (9 H, s), 0.87 (3 H, br t, J = 6.5 Hz); ^{13}C NMR δ 181.70, 172.55, 80.83, 74.76, 37.42, 33.80, 31.68, 29.36, 28.02, 28.00, 26.64, 26.46, 22.60, 14.04; IR 2850, 1720, 1630 cm^{-1}; $[\alpha]^{20}_D$ +78.3° (c 6.8, EtOH). Anal. Calcd for $C_{16}H_{29}NO_2$: C, 71.9; H, 10.9; N, 5.2. Found: C, 71.8; H, 10.8; N, 5.2.

(2*S*)-*cis*-5-Heptylproline *tert*-Butyl Ester (9a). (A) From Vinylogous Carbamate 4. To a solution of **4** (1.35 g, 2.75 mmol) and ammonium formate (1.73 g, 27.5 mmol) in methanol (10 mL) and acetic acid (10 mL) was added 10% Pd/charcoal (0.67 g). The reaction mixture was agitated by sonication and vibro-mixing while the bath temperature was maintained between 20 and 25 °C. After 1.5 h, the reaction mixture was filtered, the catalyst was washed with methanol (35 mL), the filtrate and washings were evaporated, and the residue was diluted with water (60 mL), made alkaline with $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was shaken with brine (25 mL), dried, and distilled (bulb to bulb, 110 °C (200 μHg)) to give **9a**: 630 mg, 86% yield; ^1H NMR δ 0.88 (m, 3 H), 1.2–2.2 (m, 17 H), 1.46 (s, 9 H), 2.90–3.05 (m, 1 H), 3.55–3.65 (m, 1 H); IR 3400, 2950, 1680, 1420 cm^{-1}; $[\alpha]^{20}_D$ −14.4° (c 11.3, EtOH). Anal. Calcd for $C_{16}H_{31}NO_2$: C, 71.3; H, 11.6; N, 5.2. Found: C, 71.2; H, 11.4; N, 5.2.

(B) From Imine 8. A solution of pyrroline **8** (10.9 g, 40.8 mmol) and PtO_2 (0.55 g) in ethanol (100 mL) was hydrogenated under a 50 psi of H_2 atmosphere for 4.5 h. After filtering the mixture and washing the catalyst the solvent was evaporated to a residue which was distilled as above to give 10.9 g, 99% yield, of **9a**, identical with the material prepared above.

(2*S*)-*cis*-1-Benzyl-5-heptylproline *tert*-Butyl Ester (9b). To proline ester **9a** (1.50 g, 5.58 mmol) and calcined K_2CO_3 (3.08 g, 22.3 mmol) in dry CH_3CN (15 mL) cooled to 0 °C was added a solution of benzyl bromide (0.95 g, 5.58 mmol) in CH_3CN (5 mL). After it was stirred at 0 °C for 30 min, the mixture was allowed to warm to room temperature, stirred for 16 h, and then diluted with CH_2Cl_2 (25 mL) and H_2O (25 mL). The phases were separated and the aqueous layer extracted further with CH_2Cl_2 (5 mL). The combined organic phase was shaken with brine (25 mL), dried, and evaporated to a residue which was chromatographed on silica, eluting with 5/1 isooctane/EtOAc and kugelrohr distilled (110 °C (300 μmHg)) to give 1.94 g, 97% yield, of **9b**: ^1H NMR δ 0.88 (br t, J = 6.9 Hz), 1.2–2.0 (m, 16 H), 1.33 (s, 9 H), 2.6–2.7 (m, 1 H), 3.15–3.20 (m, 1 H), 3.72 (d, 1 H, J = 14.0 Hz), 3.90 (d, 1 H), 7.2–7.3 (m, 5 H); IR 2960, 2940, 1745, 1450, 1360, 1150 cm^{-1}; $[\alpha]^{20}_D$ −0.03° (c 6.1, EtOH). Anal. Calcd for $C_{23}H_{37}NO_2$: C, 76.8; H, 10.4; N, 3.9. Found: C, 76.8; H, 10.3; N, 3.8.

(2*S*)-*trans*-1-Benzyl-5-heptylproline *tert*-Butyl Ester (10b). To a solution of pyrroline **8** (170 mg, 0.63 mmol) in methanol (10 mL) was added $NaBH_4$ (119 mg, 3.15 mmol) and the mixture stirred for 30 min, then concentrated, dissolved in saturated $NaHCO_3$ (25 mL), and stirred for 15 min. The aqueous mixture was extracted with CH_2Cl_2 (1 × 10 mL, 3 × 5 mL) which was washed with brine (15 mL), dried, and evaporated to a residue which was distilled (bulb to bulb, 75–80 °C (200 μmHg)) to yield 157 mg (93%) of a mixture of cis and trans proline esters **9a** and **10a**. This mixture (115 mg, 0.43 mmol) was N-benzylated as above. The product mixture (142 mg, 92% yield) was separated on a Chromatotron (2 mm, 10 mL/min, 2% EtOAc/isooctane), HPLC (7% Et_2O in isooctane, 1.0 mL/min) **10b** t_R 4.1 min, **9b** t_R 5.3 min. Trans proline ester **10b**: ^1H NMR δ 0.88 (t, 3 H, J = 6.3 Hz), 1.2–2.2 (m, 16 H), 1.44 (s, 9 H), 3.1–3.3 (m, 1 H), 3.4–3.5 (m, 1 H), 3.73 (d, 1 H, J = 13.6), 3.94 (d, 1 H), 7.2–7.4 (m, 5 H); IR 2940, 2880, 1730 cm^{-1}. Anal. Calcd for $C_{23}H_{37}NO_2$: C, 76.8; H, 10.4; N, 3.9. Found: C, 76.8; H, 10.0; N, 3.8.

(2*S*)-*cis*-1-Benzyl-5-heptylproline (11). A solution of amino ester **9b** (8.33 g, 23.2 mmol) in propanol (80 mL), H_2O (80 mL), and acetic acid (16 mL) was refluxed for 6 h, then it was evaporated, and the residue was dissolved in CH_2Cl_2 (50 mL) which was washed with pH 7 phosphate buffer (2 × 25 mL) and brine (25 mL), dried, and evaporated. The residue was further dried (40 °C (250 μmHg)) for 18 h to give proline **11**: 6.82 g, 97% yield; ^1H NMR δ 0.88 (t, 3 H, J = 6.6 Hz), 1.2–1.8 (m, 12 H), 2.0–2.4 (m, 4 H), 3.10–3.25 (m, 1 H), 3.8–3.9 (m, 1 H), 4.17 (d, 1 H, J = 13.2 Hz), 4.27 (d, 1 H), 7.3–7.5 (m, 5 H); ^{13}C NMR δ 13.98, 22.48,

26.15, 28.91, 29.18, 30.09, 31.55, 32.77, 57.34, 66.92, 67.94, 129.06, 129.15, 130.06, 131.98, 171.82; IR 3400, 2850, 2800, 1700, 1620 cm^{-1}. Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.2; H, 9.6; N, 4.6. Found: C, 75.1; H, 9.7; N, 4.7.

(2*S*)-*cis*-1-Benzyl-2-(1-hydroxybutyl)-5-heptylpyrrolidine (13a) was prepared as described below for the corresponding trans amino alcohols **26a**: 75% yield; R_f (1/1, isooctane/EtOAc) 0.52, 0.42; ^1H NMR (faster eluting isomer) δ 0.8–1.9 (m, 26 H), 2.7–2.8 (m, 2 H), 3.4–3.5 (m, 1 H), 3.75 (s, 2 H), 7.2–7.3 (m, 5 H); ^1H NMR (slower eluting isomer) δ 0.8–1.9 (m, 26 H), 2.7–2.85 (m, 2 H), 3.0–3.1 (m, 1 H), 3.78 (s, 2 H), 7.2–7.3 (m, 5 H); IR 3000, 2950, 2850 cm^{-1}. Anal. Calcd for $C_{22}H_{37}NO$: C, 79.7; H, 11.2; N, 4.2. Found: C, 79.8; H, 11.1; N, 4.2.

(2*S*)-*cis*-2-(1-Hydroxybutyl)-5-heptylpyrrolidine (13b). A solution of the amino alcohols **13a** (526 mg, 1.6 mmol) and 10% Pd/carbon (250 mg) in acetic acid (10 mL) was shaken at room temperature for 10 h under a 55 psi of H_2 atmosphere. The reaction mixture was filtered, the catalyst was washed with methanol, and the filtrate and washings were evaporated to a residue which was dissolved in CH_2Cl_2 (20 mL) and washed with aqueous $NaHCO_3$ (2 × 10 mL) and brine (15 mL) and dried. Evaporation followed by bulb-to-bulb distillation (80 °C (200 μmHg)) yielded the secondary amino alcohols **13b**: 374 mg, 98% yield; ^1H NMR δ 0.8–1.0 (m, 6 H), 1.2–2.0 (m, 20 H), 3.0–3.4 (m, 2 H), 3.7–4.0 (m, 3 H); IR 3150, 2850, 1430 cm^{-1}. Anal. Calcd for $C_{15}H_{31}NO$: C, 74.6; H, 12.9; N, 5.8. Found: C, 74.8; H, 13.0; N, 5.9.

(2*S*)-*cis*-1-(Phenylsulfonyl)-2-(1-hydroxybutyl)-5-heptylpyrrolidine (13c). To a vigorously stirred solution of secondary amino alcohols **13b** (276 mg, 1.14 mmol) in $CHCl_3$ (7 mL) at 0 °C were added phenylsulfonyl chloride (217 mg, 1.23 mmol) in $CHCl_3$ (4 mL) and a 20% solution of NaOH (0.46 mL, 2.3 mmol) over 5 min. The mixture was stirred for 1 h at 0 °C then 2 h at room temperature followed by dilution with CH_2Cl_2 (25 mL) and H_2O (15 mL). The aqueous phase was further extracted with CH_2Cl_2 (5 mL) and the combined organic layer washed with 1 M H_3PO_4 (2 × 15 mL) and brine (15 mL) and dried. The residue after solvent evaporation was chromatographed (Chromatotron, 2-mm plate, flow 10 mL/min, 15% EtOAc in isooctane) to yield the mixture of alcohols **13c**: 399 mg, 92% yield; R_f 0.38 and 0.45 (1/1, EtOAc/isooctane); ^1H NMR (faster eluting isomer) δ 0.8–1.0 (m, 6 H), 1.1–2.0 (m, 20 H), 2.26 (d, 1 H, J = 3.8 Hz), 3.4–3.5 (m, 1 H), 3.6–3.75 (m, 1 H), 4.0–4.1 (m, 1 H), 7.3–7.6 (m, 3 H), 7.8–7.9 (m, 2 H); (slower eluting isomer) δ 0.8–1.0 (m, 6 H), 1.1–1.9 (m, 20 H), 3.35–3.55 (m, 3 H), 3.65–3.75 (m, 1 H), 7.2–7.6 (m, 3 H), 7.8–8.9 (m, 2 H); IR 3600, 2900, 1430 cm^{-1}. Anal. Calcd for $C_{21}H_{35}NO_3S$: C, 66.1; H, 9.3; H, 3.7. Found: C, 66.1; H, 9.3; N, 3.7.

(2*S*)-*cis*-1-(Phenylsulfonyl)-2-(1-[(phenylsulfonyl)oxy]-butyl)-5-heptylpyrrolidine (13d). To a solution of (phenylsulfonyl)imidazolide (1.51 g, 7.27 mmol) in dry CH_2Cl_2 (75 mL) was added trimethyloxonium tetrafluoroborate (1.07 g, 7.26 mmol) and the mixture was stirred at room temperature for 3 h. Stirring was continued for 18 h after *N*-methylimidazole (1.19 g, 14.5 mmol) and amino alcohol **13b** (250 mg, 1.04 mmol) were added. Saturated $NaHCO_3$ (50 mL) was poured into the reaction mixture which was vigorously stirred for 30 min, the phases were separated, the aqueous layer was further extracted with CH_2Cl_2 (5 mL), and the combined organic extracts were washed with 1 M H_3PO_4 (3 × 30 mL) then brine (50 mL) and dried. The residue upon evaporation was chromatographed (Chromatotron, 2-mm plate, flow 10 mL/min, 1/1 CH_2Cl_2/isooctane) to yield the bis(phenylsulfonyl) derivatives **13d**: 503 mg, 93% yield; R_f 0.61, 0.58 (CH_2Cl_2); ^1H NMR (faster eluting isomer) δ 0.7–2.0 (m, 26 H), 3.5–3.6 (m, 1 H), 3.9–4.0 (m, 1 H), 5.0–5.1 (m, 1 H), 7.5–8.1 (m, 10 H); (slower eluting isomer) δ 0.7–2.0 (m, 26 H), 3.4–3.5 (m, 1 H), 3.6–3.7 (m, 1 H), 5.0–5.1 (m, 1 H), 7.5–8.1 (m, 10 H); IR 3100, 2980, 2050, 2890, 1380, 1350, 1190, 1170 cm^{-1}. Anal. Calcd for $C_{27}H_{39}NO_5S_2$: C, 62.2% H, 7.5; N, 2.7. Found: C, 62.5; H, 7.6; N, 2.7.

(2*S*)-*cis*-5-Butyl-2-heptyl-1-(phenylsulfonyl)pyrrolidine (14a). A solution of the bis(sulfonyl) derivatives **13d** (310 mg, 0.50 mmol) and $NaBH_4$ (180 mg, 4.8 mmol) in Me_2SO (8 mL) was heated at 80–85 °C for 30 h. The reaction mixture was cooled to room temperature, poured into saturated $NaHCO_3$ (50 mL), vigorously stirred for 1 h, then diluted with H_2O (25 mL), and extracted with CH_2Cl_2 (1 × 15, 2 × 10 mL). The combined organic phase was washed with brine (25 mL), dried, and evaporated to an oil which was chromatographed (Chromatotron, 2-mm plate, flow 10 mL/min, 1/1, isooctane/CH_2Cl_2) then distilled (120 °C (250 μmHg)) to yield **14a**: 163 mg, 75% yield; ^1H NMR δ 0.9–1.9 (m, 28 H), 3.5–3.7 (m, 2 H), 7.5–7.6 (m, 3 H), 7.8–7.9 (m, 2 H); ^{13}C NMR δ 183.10, 138.29, 132.31, 128.89, 127.48, 61.70, 44.68, 37.23, 36.93, 31.82, 29.64, 29.50, 29.26, 28.45, 26.30, 22.64, 14.10; IR 2950, 1340, 1150 cm^{-1}; HPLC (4% EtOAc in isooctane, 1.0 mL/min) t_R 7.8 min; $[\alpha]^{20}_D$ +0.47° (*c* 1.7, CH_2Cl_2). Anal. Calcd for $C_{21}H_{35}NO_2S$: C, 69.0; H, 9.6; N, 3.8. Found: C, 68.8; H, 9.6; N, 3.8.

(2*S*)-*cis*-5-Butyl-2-heptylpyrrolidine (14b). (A) By HBr/Phenol Cleavage of 14a. A solution of *cis*-sulfonamide **14a** (66 mg, 0.18 mmol) and phenol (66 mg, 0.70 mmol) in freshly distilled 48% HBr (5.0 mL) was refluxed for 1 h. After cooling to room temperature, the solution was basified with 12 M NaOH (5 mL) and extracted with CH_2Cl_2 (1 × 10 mL, 3 × 5 mL of CH_2Cl_2). The organic phase was washed with 6 N NaOH (5 mL) and brine (10 mL), dried, and evaporated to a residue which was chromatographed (silica gel, 10% CH_3OH in $CHCl_3$) and distilled (70–80 °C (200 μmHg)) to yield 33 mg (81%) of **14b**. The hydrochloride salt was prepared by dissolving **14b** in 1 M HCl and extracting with 25% isopropyl alcohol in $CHCl_3$. Drying and evaporating the organic extracts left **14b**·HCl, which was recrystallized from Et_2O/CH_3OH: melting point over a wide range with decomposition ^1H NMR δ 0.8–1.0 (6 H), 1.2–2.2 (m, 22 H), 3.4–3.6 (m, 2 H); $[\alpha]^{26}_D$ 0° (*c* 0.5, CH_3OH). Anal. Calcd for $C_{15}H_{32}ClN$: C, 68.8; H, 12.3; N, 5.3. Found: C, 69.0; H, 11.9; N, 5.2.

(B) By Na/NH_3 Cleavage of 14a. To sulfonamide **14a** (27 mg, 0.074 mmol) in liquid ammonia was added sodium until a blue color persisted for 1 h. The reaction was quenched with NH_4Cl, the ammonia was allowed to evaporate, and the residue was dissolved in aqueous $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 5 mL). Washing the CH_2Cl_2 with brine (10 mL), drying, and evaporating followed by distillation yielded 12 mg (73%) of **14b**.

(C) By Decarbonylation of Prolines 23b to Iminium Salt 24 and Reduction. A solution of prolines **23b** (37 mg, 0.10 mmol) in $POCl_3$ (165 mg, 1.10 mmol) was heated at 100 °C for 5 min with stirring, then evaporated, and further dried (200 μmHg) for 1 h. The resulting iminium salt **24** was dissolved in CH_3OH to which 25 mg of 10% Pd/carbon was added and the mixture was shaken under H_2 at 55 psi. Filtration and evaporation of the filtrate left a residue which was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ then brine and dried. Evaporation of the CH_2Cl_2 followed by distillation yielded 20 mg (89%) of **14b**.

(D) From Pyrroline 21. A solution of pyrroline **21** (31 mg, 0.14 mmol) and 5 mg of PtO_2 in EtOH (3 mL) was shaken under H_2 at 55 psi. The solution was filtered, the filtrate was evaporated, and the residue was distilled to yield 28 mg (90%) of **14b**.

(5*S*)-1-Benzyl-5-heptyl-2-oxopyrrolidine (17a). To diisopropylamine (72 mg, 0.71 mmol) in THF (10 mL) at 0 °C was added *n*-BuLi in hexane (0.51 mmol). After the mixture was stirred at 0 °C for 30 min then cooled to −78 °C, a solution of amino nitriles **18** in THF (0.5 mL) was added and a stream of dry oxygen was bubbled through the solution for 30 min followed by the addition of 0.5 mL of 1 M $SnCl_2$ in 2 M HCl. The solution was allowed to warm to 0 °C, stirred for 30 min, diluted with H_2O, made alkaline with 2 M NaOH, and then extracted with CH_2Cl_2 (1 × 15, 2 × 5 mL). After shaking with brine and drying, the residue upon concentration was chromatographed (Chromatotron, 2-mm plate, from 10 mL/min, 2% $CH_3OH/CHCl_3$) and distilled (130 °C (250 μmHg)) to give lactam **17a**: 68 mg, 60% yield; ^1H NMR δ 0.87 (t, 3 H, J = 7 Hz), 1.1–2.2 (m, 14 H), 2.3–2.5 (m, 2 H), 3.35–3.5 (m, 1 H), 3.96 (d, 1 H, J = 15 Hz), 4.97 (d, 1 H), 7.2–7.4 (m, 5 H); IR 1690 cm^{-1}; $[\alpha]^{20}_D$ −21.9° (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{18}H_{27}NO$: C, 79.1; H, 10.0; N, 5.1. Found: C, 78.7; H, 10.2; N, 5.1.

(5*S*)-1-Benzyl-5-heptyl-2-thioxopyrrolidine (17b). To diisopropylamine (330 mg, 3.3 mmol) in 25 mL of THF at 0 °C was added *n*-BuLi in hexane (2.55 mmol). After the mixture was cooled to −78 °C, a solution of amino nitriles **18** (631 mg, 2.22 mmol) in 4 mL of THF was added over 5 min and stirred for 30 min; then sublimed sulfur powder (3.55 g, 110 mmol) was added and the mixture was maintained at −78 °C for 1 h then allowed

to warm to room temperature. After 2 h, the mixture was filtered and the filtrate evaporated to a residue which was dissolved in 50 mL of EtOH, and $NaBH_4$ (500 mg, 13.2 mmol) was slowly added. The mixture was stirred for 2 h, additional $NaBH_4$ (250 mg, 6.6 mmol) was added, and the mixture refluxed for 15 min then evaporated. The residue was dissolved in 2 N NaOH (75 mL) and extracted with CH_2Cl_2 (25 mL, 2 × 15 mL, 2 × 10 mL) which was washed with brine and dried. The residue upon evaporation was chromatographed (Chromatotron, 2-mm plate, flow 10 mL/min, starting with 100% isooctane and eluting with 10% EtOAc) and distilled (120 °C (250 μmHg)) to give thiolactam **17b**: 469 mg, 73% yield; ^1H NMR δ 0.88 (t, 3 H, J = 6.6 Hz), 1.1–1.5 (m, 11 H), 1.7–1.8 (m, 2 H), 2.0–2.2 (m, 1 H), 3.0–3.2 (m, 2 H), 3.7–3.8 (m, 1 H), 4.27 (d, 1 H, J = 14.7 Hz), 5.80 (d, 1 H), 7.3–7.4 (m, 5 H); IR 2950, 1480, 1450 cm^{-1}; $[\alpha]^{20}_D$ −107.1° (c 1.3, EtOH). Anal. Calcd for $C_{18}H_{27}NS$: C, 74.7; H, 9.4; N, 4.8. Found: C, 74.9; H, 9.3; N, 5.0.

(5*S*)-1-Benzyl-2-cyano-5-heptylpyrrolidine (18). Cis proline 11 (590 mg, 1.95 mmol) in $POCl_3$ (1.8 mL, 2.96 g, 19.31 mmol) was heated at 100 °C for 5 min with stirring, then excess reagent was evaporated (45 °C (15 mm Hg)), the residue of iminium salt **16** was further dried (200 μmHg) and dissolved in isopropyl alcohol (10 mL), and a solution of KCN (630 mg, 9.8 mmol) was added over 30 min and vigorously stirred for 1 h. The mixture was diluted with aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (1 × 20 mL, 3 × 10 mL), the organic phase was shaken with brine (20 mL), dried, and evaporated, and the residue was distilled (100 °C (200 μmHg)) to afford 480 mg, 87% yield, of nitrile **18** as a 1/3 mixture of cis/trans diastereomers: R_f (5/1, isooctane/EtOAc) 0.23 (cis), 0.32 (trans); ^1H NMR (trans δ 0.85–0.95 (br t, 3 H), 1.2–2.3 (m, 16 H), 2.7–2.8 (m, 1 H), 3.43 (d, 1 H, J = 13.2 Hz), 3.6–3.7 (m, 1 H), 4.09 (d, 1 H), 7.2–7.4 (m, 5 H); ^1H NMR (cis) δ 0.85–0.95 (br t, 3 H), 1.2–2.3 (m, 16 H), 2.7–2.8 (m, 1 H), 3.4–3.5 (m, 1 H), 3.79 (d, 1 H, J = 14.0 Hz), 3.97 (d, 1 H), 7.2–7.4 (m, 5 H); IR 2850, 2200 (w), 1480, 1430 cm^{-1}. Anal. Calcd for $C_{19}H_{28}N_2$: C, 80.2; H, 9.9; N, 9.9. Found: C, 80.1; H, 9.9; N, 9.7.

Benzyl 2-hydroxypentanoate (19a) was prepared as described for the corresponding octanoate **2b**: 80% yield; ^1H NMR δ 0.91 (t, 3 H, J = 7.3 Hz), 1.3–1.9 (m, 4 H), 2.88 (d, 1 H, J = 5.8 Hz, exchangeable proton), 4.20–4.25 (m, 1 H), 5.20 (s, 2 H), 7.35 (br s, 5 H); IR 2950, 1740 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.2; H, 7.7. Found: C, 6.1; H, 7.7.

Benzyl 2-([(Trifluoromethyl)sulfonyl]oxy)pentanoate (19b) was prepared as described for the corresponding octanoate **2c**: 80% yield; ^1H NMR δ 0.95 (t, 3 H, J = 7.3 Hz), 1.4–1.5 (m, 2 H), 1.9–2.0 (m, 2 H), 5.15 (t, 1 H, J = 6.2 Hz), 5.25 (s, 2 H), 7.37 (br s, 5 H); IR 2950, 1740, 1200 cm^{-1}. Anal. Calcd for $C_{13}H_{15}F_3SO_5$: C, 45.9; H, 4.4. Found: C, 45.8; H, 4.4.

(5*S*)-1-Benzyl-2-(1-[(benzyloxy)carbonyl]butylidene)-5-heptylpyrrolidine (20). To a solution of triflate **19b** (250 mg, 0.73 mmol) in CH_3CN (3 mL) at 0 °C was added a solution of thiolactam **17b** (189 mg, 0.65 mmol) in CH_3CN (3 mL). The solution was maintained at 0 °C for 15 min, then allowed to warm to room temperature, stirred for 4 h, and diluted with dry CH_2Cl_2 (10 mL). Triphenylphosphine (200 mg, 0.76 mmol) was added followed after 30 min by a solution of *N*-methylpiperidine (144 mg, 1.45 mmol) in CH_2Cl_2 (0.5 mL) and stirring was continued for 6 h. The mixture was diluted with CH_2Cl_2 (15 mL), and the CH_2Cl_2 was washed with 1 M H_3PO_4 (2 × 10 mL), aqueous $NaHCO_3$ (10 mL) and brine (15 mL), then dried, and evaporated to a residue which was chromatographed (Chromatotron, 2-mm plate, flow 10 mL/min, 100% CH_2Cl_2 then 5% EtOAc in CH_2Cl_2) to **20** as a 2/1 cis/trans mixture: 229 mg, 79% yield; ^1H NMR (major diastereomer) δ 0.7–0.9 (m, 6 H), 1.1–1.7 (m, 13 H), 2.0–2.1 (m, 2 H), 2.2–2.3 (m, 2 H), 3.0–3.4 (m, 4 H), 4.40 (d, 1 H, J = 17.0 Hz), 4.69 (d, 1 H), 5.13 (s, 2 H), 7.2–7.4 (m, 10); ^1H NMR (minor diastereomer) δ 0.7–0.9 (m, 6 H), 1.1–1.7 (m, 13 H), 2.0–2.1 (m, 2 H), 2.2–2.3 (m, 2 H), 2.55–2.65 (m, 2 H), 3.0–3.2 (m, 1 H), 3.5–3.6 (m, 1 H), 4.22 (d, 1 H, J = 15.7 Hz), 4.77 (d, 1 H), 5.06 (d, 1 H, J = 12.7 Hz), 5.11 (d, 1 H), 7.0–7.4 (m, 10 H); IR 2950, 1680, 1560 cm^{-1}. Anal. Calcd for $C_{30}H_{41}NO_2$: C, 80.5; H, 9.2; N, 3.1. Found: C, 80.4; H, 9.2; N, 3.2.

(5*S*)-2-Butyl-5-heptyl-5-pyrroline (21). To vinylogous carbamate **20** (67 mg, 0.15 mmol) and cyclohexene (120 mg, 1.5 mmol) in CH_3OH (5 mL) was added 10% Pd/carbon (50 mg), the mixture was refluxed for 15 min then filtered, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (15 mL) which was washed with aqueous $NaHCO_3$ (2 × 10 mL) and brine (15 mL), dried, evaporated, and distilled (100 °C (200 μmHg)) to give pyrroline **21**: 24 mg, 70% yield; ^1H NMR δ 0.8–1.0 (m, 6 H), 1.2–1.8 (m, 18 H), 1.9–2.1 (m, 1 H), 2.3–2.5 (m, 3 H), 3.8–4.0 (m, 1 H); IR 2950, 1650 cm^{-1}. Anal. Calcd for $C_{15}H_{29}N$: C, 80.6; H, 13.1; N, 6.3. Found: C, 80.4; H, 12.9; N, 6.2.

(5*S*)-1-Benzyl-2-butyl-5-heptylproline *tert*-Butyl Ester (23a). To diisopropylamine (200 mg, 1.99 mmol) in THF (25 mL) at 0 °C was added a 1.5 M solution of BuLi in hexane (0.97 mL, 1.45 mmol). The solution was cooled to −78 °C and proline ester **9b** (479 mg, 1.33 mmol) in THF (2.0 mL) was added over 15 min and stirred for 45 min; then to this mixture was added a solution of butyl bromide (636 mg, 4.64 mmol) in THF (2.0 mL). The reaction mixture was stirred at −78 °C for 20 min, at 0 °C for 2 h, and at room temperature for 2.5 h, then it was diluted with CH_2Cl_2 (30 mL). The CH_2Cl_2 was washed with 1 M H_3PO_4 (2 × 15 mL), aqueous $NaHCO_3$ (2 × 20 mL), and then brine (25 mL) and dried. Evaporation yielded a residue which was chromatographed (Chromatotron, 2-mm plate, flow 10 mL/min, 100% isooctane to 10% EtOAc in isooctane) to yield 310 mg of the pure faster eluting major isomer along with 137 mg of a 60/40 mixture of isomers which could be recycled on the Chromatotron to obtain a pure sample of the minor isomer: combined yield, 447 mg, 80%; bp 120 °C (200 μmHg); ^1H NMR (major isomer) δ 0.85 (br t, 3 H, J = 6.6 Hz), 0.8–2.2 (m, 25 H), 1.50 (s, 9 H), 2.9–3.0 (m, 1 H), 3.51 (d, 1 H, J = 15.6 Hz), 4.10 (d, 1 H), 7.1–7.4 (m, 5 H); (minor isomer) δ 0.90 (br t, 3 H, J = 6.7 Hz), 0.8–2.4 (m, 25 H), 2.9–3.0 (m, 1 H), 3.86 (d, 1 H, J = 15.5), 4.14 (d, 1 H), 7.1–7.4 (m, 1 H); ^{13}C NMR (major isomer) δ 174.21, 143.01, 127.86, 127.77, 126.10, 80.41, 73.11, 65.71, 53.16, 36.67, 36.04, 32.92, 31.76, 29.72, 29.26, 28.93, 28.35, 26.76, 25.95, 23.24, 22.36, 22.58, 14.97; IR 3000, 1730 cm^{-1}; $[\alpha]^{19}_D$ (major isomer) +2.70° (c 2.6, EtOH). Anal. Calcd for $C_{27}H_{45}NO_2$: C, 78.0; H, 10.9; N, 3.4. Found: C, 78.1; H, 10.7; N, 3.4.

(5*S*)-1-Benzyl-2-butyl-5-heptylproline (23b). After a solution of proline esters **23a** (136 mg, 0.33 mmol) in trifluoroacetic acid (3.0 mL) was stirred at room temperature for 10 h, the trifluoroacetic acid was evaporated and the residue was dissolved in CH_2Cl_2 (15 mL) which was washed with 0.2 M pH 7 phosphate buffer (15 mL) then brine (15 mL) and dried. Evaporation left acids **23b**: 112 mg, 95% yield; ^1H NMR (major isomer) δ 0.7–2.1 (m, 27 H), 2.3–2.4 (m, 1 H), 3.1–3.2 (m, 1 H), 3.84 (d, 1 H, J = 14.5 Hz), 4.0–4.2 (m, 1 H), 7.2–7.4 (m, 5 H); ^1H NMR (minor isomer) δ 0.6–2.1 (m, 27 H), 2.7–2.8 (m, 1 H), 3.1–3.3 (m, 1 H), 3.70 (d, 1 H, J 12.8 Hz), 4.42 (d, 1 H), 7.3–7.5 (m, 5 H); IR 3400, 2950, 1710, 1630 cm^{-1}.

(2*R*)-*trans*-1-Benzyl-5-heptylproline (25). The mixture of cis/trans amino nitriles **18** (1.26 g, 4.43 mmol) was stirred in a slurry of silica gel (25 g) in 1/1 isooctane/EtOAc, for 18 h. After filtration and concentration, the equilibrated 1/9, cis/trans mixture of diastereomeric amino nitriles **18** was stirred with concentrated HCl (30 mL) for 18 h at room temperature then refluxed for 2 h. The mixture was neutralized with aqueous $NaHCO_3$ (200 mL) and extracted with CH_2Cl_2 (1 × 30 mL, 2 × 15 mL). The combined organic phase was shaken with pH 7 phosphate buffer (50 mL), dried, and evaporated to a residue which was dissolved in hot EtOAc, and petroleum ether was added until coudiness persisted. Two crystallizations gave the pure trans proline **25**: 0.65 g, 50% yield; mp 95–97 °C; ^1H NMR δ 0.87 (m, 3 H, J = 6.5 Hz), 1.1–2.5 (m, 16 H), 3.60–3.76 (m, 1 H), 3.80–3.87 (m, 1 H), 4.03 (d, 1 H, J = 13.3 Hz), 4.25 (d, 1 H), 7.2–7.5 (m, 5 H); ^{13}C NMR δ 14.02, 22.52, 26.30, 26.52, 27.38, 29.01, 29.22, 31.60, 52.14, 63.91, 65.79, 128.85, 129.56, 132.32, 132.34, 171.71; IR (CCl_4) 2970, 2500, 1710, 1600 cm^{-1}; $[\alpha]^{20}_D$ +52.8° (c 2, EtOH). Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.2; H, 9.6; N, 4.6. Found: 74.9; H, 9.6; N, 4.6.

(2*R*)-*trans*-1-Benzyl-2-(1-hydroxybutyl)-5-heptylpyrrolidine (26a). To trans proline **25** (718 mg, 2.37 mmol) in Et_2O (70 mL) cooled to −78 °C was added PrLi (9.51 mmol) over 15 min, and the mixture was stirred at −78 °C for 1 h then warmed to 0 °C where it was kept for 12 h. The mixture was cooled to −78 °C, acetone (0.5 mL) was added, and after 15 min it was warmed to 0 °C and stirred for 30 min. The mixture was then poured into pH 7 phosphate buffer (200 mL) and extracted with CH_2Cl_2 (1 × 100 mL, 3 × 25 mL) which was shaken with brine

(100 mL), dried, and evaporated to yield the intermediate amino ketone: ^{1}H NMR δ 0.8–2.3 (m, 26 H), 3.2–3.3 (m, 1 H), 3.5–3.6 (m, 1 H), 3.76 (d, 1 H, J = 13 Hz), 3.83 (d, 1 H), 7.2–7.3 (m, 5 H). To the residue dissolved in absolute EtOH (50 mL) and cooled to 0 °C was added $NaBH_4$ (500 mg, 13.2 mmol) in four portions over 15 min; the solution was then allowed to stir for 1 h at 0 °C. The mixture was warmed to room temperature and stirred for 5 h, then the EtOH was evaporated and the residue was stirred with saturated $NaHCO_3$ (150 mL) for 30 min then extracted with CH_2Cl_2 (2 × 25 mL, 3 × 10 mL). The CH_2Cl_2 was washed with brine (50 mL), dried, and evaporated to an oil which was chromatographed (Chromatotron, 2 mm, flow 10 mL/min, 10% EtOAc in isooctane) to yield the diastereomeric mixture of amino alcohols **26a**: bp 120 °C (250 μmHg); 545 mg, 70% yield; R_f (5/1, octane/EtOAc) 0.36, 0.17; ^{1}H NMR (faster eluting isomer) δ 0.9–1.9 (m, 26 H), 2.7–2.8 (m, 1 H), 2.95–3.05 (m, 1 H), 3.65–3.75 (m, 1 H), 3.69 (d, 1 H, J = 13.6 Hz), 3.84 (d, 1 H), 7.2–7.3 (m, 5 H); (slower eluting isomer) δ 0.8–2.1 (m, 26 H), 2.7–2.8 (m, 1 H), 2.95–3.05 (m, 1 H), 3.2–3.3 (m, 1 H), 3.40 (d, 1 H, J = 13.3 Hz), 3.90 (d, 1 H), 7.2–7.3 (m, 5 H); IR 3450, 2980, 2960, 2880 cm^{-1}. Anal. Calcd for $C_{22}H_{37}NO$: C, 79.7; H, 11.3; N, 4.2. Found: C, 79.8; H, 11.3; N, 4.1.

(2*R*)-*trans*-2-(1-Hydroxybutyl)-5-heptylpyrrolidines (26b) were prepared as described for the corresponding cis amino alcohols **13b**: yield, 95%; bp 120 °C (200 μmHg); ^{1}H NMR δ 0.8–2.0 (m, 26 H), 3.0–3.9 (3 H); IR 3310, 2950, 2870, 2800, 2540 cm^{-1}.

(2*R*)-*trans*-1-(Phenylsulfonyl)-2-(1-[(phenylsulfonyl)-oxy]butyl)-5-heptylpyrrolidines (26c) were prepared according to the procedure described for sulfonamides **13c**: yield, 85%; R_f (CH_2Cl_2) 0.71, 0.60; ^{1}H NMR (faster eluting diastereomer) δ 0.6–2.2 (m, 26 H), 4.0–4.2 (m, 2 H), 5.15–5.25 (m, 1 H), 7.5–8.1 (m, 10 H); (slower eluting diastereomer) δ 0.5–2.1 (m, 26 H), 3.25–3.30 (m, 1 H), 3.75 (d, 1 H, J = 8.4 Hz), 5.44 (t, 1 H, J = 6.4 Hz), 7.5–8.1 (m, 10 H); IR 2980, 2940, 2880, 1360, 1165 cm^{-1}. Anal. Calcd for $C_{27}H_{39}NO_5S_2$: C, 62.2; H, 7.5; N, 2.7. Found: C, 61.8; H, 7.6; N, 2.9.

(2*S*)-*trans*-5-Butyl-2-heptyl-1-(phenylsulfonyl)-pyrrolidine (27a) was prepared as described for the corresponding cis pyrrolidine **14a**: yield, 80%; ^{1}H NMR δ 0.8–2.0 (m, 28 H), 3.8–3.9 (m, 2 H), 7.2–7.4 (m, 3 H), 7.8–7.9 (m, 2 H); ^{13}C NMR δ 142.00, 131.83, 128.71, 136.77, 60.95, 33.88, 33.62, 31.75, 20.40, 20.21, 28.55, 27.96, 26.41, 22.60, 22.55, 14.07, 14.00; IR 2980, 2950, 2880, 1330, 110 cm^{-1}; HPLC (4% EtOAc in isooctane, 1.0 mL/min) t_R 6.6 min; $[\alpha]^{20}_D$ +59.7° (*c* 1.8, CH_2Cl_2). Anal. Calcd for $C_{21}H_{35}NO_2S$: C, 69.0; H, 9.6; N, 3.8. Found: C, 69.2; H, 9.6; N, 3.8.

(2*S*)-*trans*-5-Butyl-2-heptylpyrrolidine (27b) was prepared by method A or B as described for pyrrolidine **14b**: yield, 80%; ^{1}H NMR δ 0.8–1.0 (m, 6 H), 1.1–2.0 (m, 20 H), 3.0–3.2 (m, 2 H); $[\alpha]^{20}_D$ +60.1° (*c* 1.5, CH_3OH). Anal. Calcd for $C_{15}H_{31}N$: C, 79.9; H, 13.9; N, 6.2. Found: C, 79.6; H, 13.9; N, 6.1.

(2*S*)-1-Benzyl-5-(1-[(benzyloxy)carbonyl]butylidene)-proline *tert*-butyl ester (28) was prepared as described for the corresponding heptylidene analogues **4**: yield, 70%; ^{1}H NMR δ (major isomer) 0.80 (t, 3 H, J = 7.4 Hz), 1.42 (s, 9 H), 1.4–1.6 (m, 2 H), 1.9–2.5 (m, 4 H), 3.1–3.3 (m, 2 H), 3.75–3.80 (m, 1 H), 4.32 (d, 1 H, J = 16.4 Hz), 4.89 (d, 1 H), 5.14 (s, 2 H), 7.2–7.4 (m, 10 H); (minor isomer) δ 0.86 (t, 3 H, J = 7.3 Hz), 1.43 (s, 9 H), 1.4–1.6 (m, 2 H), 1.9–2.5 (m, 4 H), 3.1–3.3 (m, 2 H), 3.8–3.9 (m, 1 H), 4.26 (d, 1 H, J = 15.1 Hz), 4.72 (d, 1 H), 5.05 (d, 1 H, J = 12.7 Hz), 5.12 (d, 1 H), 7.2–7.4 (m, 10 H); IR 2950, 1730, 1680, 1560, cm^{-1}. UV (CH_3CN) λ_{max} 290 nm (ε 21 300). Anal. Calcd for $C_{28}H_{35}NO_4$: C, 74.8; H, 7.8; N, 3.1. Found: C, 74.6; H, 7.8; N, 3.1.

(2*S*)-5-Butyl-Δ^4-dehydroproline *tert*-butyl ester (29) was prepared as described for the corresponding heptyl analogue **8**: yield, 87%; bp 90 °C (250 μmHg); ^{1}H NMR δ 0.92 (m, 3 H, J = 7.3 Hz), 1.3–1.5 (m, 2 H), 1.47 (s, 9 H), 1.5–1.7 (m, 2 H), 1.9–2.2 (m, 2 H), 2.4–2.7 (m, 2 H), 4.5–4.6 (m, 1 H); ^{13}C NMR δ 13.68, 22.33, 26.52, 27.85, 28.39, 33.30, 37.28, 74.56, 80.70, 172.38, 181.56; IR 2000, 1730, 1650 cm^{-1}; $[\alpha]^{20}_D$ +90.8° (*c* 5.1, EtOH). Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.3; H, 10.3; N, 6.2. Found: C, 69.1; H, 10.2; N, 6.2.

(2*S*)-*cis*-5-Butylproline *tert*-butyl ester (30a) was prepared as described for the corresponding heptyl analogue **9a**: yield, 96%; bp 100 °C (250 μmHg); ^{1}H NMR (0.90 (br t, 3 H, J = 7.0 Hz), 1.2–1.6 (m, 4 H), 1.46 (s, 9 H), 1.8–1.9 (m, 2 H), 2.0–2.1 (m, 2 H), 2.90–3.05 (m, 1 H), 3.60–3.65 (m, 1 H); IR 3000, 1740 cm^{-1}; $[\alpha]^{20}_D$ −16.8° (*c* 3.4, EtOH). Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.7; H, 11.1; N, 6.2. Found: C, 68.7; H, 11.0; N, 6.2.

(2*S*)-*cis*-1-Benzyl-5-butylproline *tert*-butyl ester (30b) was prepared as described for the corresponding heptyl analogue **9b**: yield, 92%; bp 110 °C (300 μmHg); ^{1}H NMR δ 0.87 (br t, 3 H, J = 6.6 Hz), 1.2–2.0 (m, 10 H), 1.33 (s, 9 H), 2.6–2.7 (m, 1 H), 3.15–3.25 (m, 1 H), 3.72 (d, 1 H, J = 14.0 Hz), 3.90 (d, 1 H), 7.2–7.4 (m, 5 H); IR 3000, 1740 cm^{-1}; $[\alpha]^{20}_D$ −1.6° (*c* 5.3, EtOH). Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.7; H, 9.8; N, 4.4. Found: C, 75.6; H, 9.7; N, 4.4.

(2*S*)-*cis*-1-Benzyl-5-butylproline (30c) was prepared as described for proline **11**: 81% yield; ^{1}H NMR δ 0.86 (br t, 3 H), 1.2–2.3 (m, 10 H), 3.1–3.3 (m, 1 H), 3.8–3.9 (m, 1 H), 4.17 (d, 1 H, J = 13 Hz), 4.32 (d, 1 H), 7.3–7.4 (m, 5 H); IR 1690, 1620 cm^{-1}.

(2*S*)-*cis*-1-Benzyl-5-butyl-2-(1-hydroxyheptyl)pyrrolidines (31a) were prepared as described for the trans amino alcohols **26a**: yield, 70%; bp 130 °C (250 μmHg); R_f (1/1, isooctane/EtOAc) 0.55, 0.45; ^{1}H NMR (faster eluting diastereomer) δ 0.8–2.0 (m, 26 H), 2.7–2.85 (m, 2 H), 3.4–3.5 (m, 1 H), 3.75 (s, 2 H), 7.2–7.3 (m, 5 H); (slower eluting diastereomer) δ 0.8–2.0 (m, 26 H), 2.7–2.85 (m, 2 H), 3.0–3.1 (m, 1 H), 3.78 (s, 2 H), 7.2–7.3 (m, 5 H). Anal. Calcd for $C_{22}H_{37}NO$: C, 79.7; H, 11.2; N, 4.2. Found: C, 79.8; H, 11.2; N, 4.2.

(2*S*)-*cis*-2-(1-Hydroxyheptyl)-5-butylpyrrolidines (31b) were prepared as described for the corresponding cis amino alcohols **13b**: yield, 99%; R_f (10% $CH_3OH/CHCl_3$, ninhydrin activation) 0.27, 0.11; ^{1}H NMR δ 0.8–1.0 (m, 6 H), 1.2–1.9 (m, 20 H), 3.0–3.2 (m, 2 H), 3.5–2.6 (m, 1 H).

(2*S*)-*cis*-1-(Phenylsulfonyl)-5-butyl-2-(1-[(phenylsulfonyl)oxy]heptyl)pyrrolidines (31c) were prepared according to the procedure described for the diastereomers **13d**: yield, 88%; R_f (CH_2Cl_2) 0.53, 0.45; ^{1}H NMR (faster eluting diastereomer) δ 0.7–2.0 (m, 26 H), 3.5–3.6 (m, 1 H), 3.9–4.0 (m, 1 H), 5.0–5.1 (m, 1 H), 7.5–8.1 (m, 10 H); (slower moving diastereomer) δ 0.7–2.0 (m, 26 H), 3.4–3.5 (m, 1 H), 3.6–3.7 (m, 1 H), 5.0–5.1 (m, 1 H), 7.5–8.1 (m, 10 H); IR 3090, 2980, 2940, 2880, 1360, 1190, 1160 cm^{-1}. Anal. Calcd for $C_{27}H_{39}NO_5S_2$: C, 62.2; H, 7.5; N, 2.7. Found: C, 62.1; H, 7.5; N, 2.6.

(2*R*)-*cis*-5-Butyl-2-heptyl-1-(phenylsulfonyl)pyrrolidine (32a) was prepared in 75% yield as described for the corresponding 2*S*-cis pyrrolidine **14a**. The chromatographic and spectral properties were identical with those of enantiomer **14a**, $[\alpha]^{20}_D$ −9.5° (*c* 1.0, CH_2Cl_2).

(2*R*)-*cis*-5-Butyl-2-heptylpyrrolidine (32b) was prepared as described for pyrrolidine **14b** by method B in 80% yield. The chromatographic and spectral properties were identical with those of the enantiomer **14b**, $[\alpha]^{20}_D$ 0° (*c* 1, CH_3OH).

Determination of Diastereomeric Purities. The diastereomeric purities of the trans pyrrolidines were established by HPLC analysis (4% EtOAc/isooctane) of sulfonamides **27a** and **33a** obtained from hydride displacement on the preceding sulfonates. The diastereomeric purities of the cis pyrrolidines were determined as described for the trans sulfonamides or by treatment of the pyrrolidine **14b** (obtained from hydrogenation of **21** or **24**) in $CHCl_3$ at 0 °C with phenylsulfonyl chloride (105 mol %) and 15% NaOH (200 mol %). After 1 h of stirring at 0 °C, the reaction was allowed to warm to room temperature, stirred an additional 2 h, then washed with brine, and dried. The residue upon concentration was chromatographed as described above.

Determination of Optical Purity of Vinylogous Carbamate 4. To a solution of **4** (113 mg, 0.25 mmol) in acetone (10 mL) and 1 M pH 7 phosphate buffer (2 mL) was added $KMnO_4$ (50 mg, 0.32 mL). After stirring for 1.5 h, another portion of $KMnO_4$ (20 mg, 0.13 mmol) was added and the solution was stirred further for 2 h. To the reaction mixture was added saturated aqueous $NaHSO_3$ (35 mL); then it was extracted with CH_2Cl_2 (2 × 10 mL, 1 × 20 mL) which was dried and evaporated. The residue was dissolved in CH_2Cl_2 (1.0 mL) and an equal volume of trifluoroacetic acid was added. After stirring for 3.5 h, the mixture was evaporated and the residue was dissolved in saturated $NaHCO_3$ (20 mL) and washed with Et_2O (2 × 10 mL). The organic phase was extracted with saturated $NaHCO_3$ (5 mL), and the combined aqueous phases were acidified with HCl then extracted with CH_2Cl_2 (1 × 10, 2 × 5 mL). Drying and evaporation gave pyroglutamic acid (**1a**), 40 mg, 73% yield. The enantiomeric

excess of the **1a** thus obtained was >98% as determined by HPLC of the (+)-(1-phenylethyl)amide **1d**.[4]

Determination of Optical Purities of Pyrrolidines. To the trans pyrrolidines **27b** or **33b**, dissolved in THF and triethylamine (120 mol %), was added MTPA acid chloride (200 mol %). The reaction mixture was refluxed (1 h) then diluted with CH_2Cl_2 which was washed successively with 1 M H_3PO_4, saturated $NaHCO_3$ solution, and brine. Drying and evaporating left a residue which was directly separated by HPLC (4% EtOAc/isooctane).

Synthesis of Optically Pure Pipecolates from L-Asparagine. Application to the Total Synthesis of (+)-Apovincamine through Amino Acid Decarbonylation and Iminium Ion Cyclization

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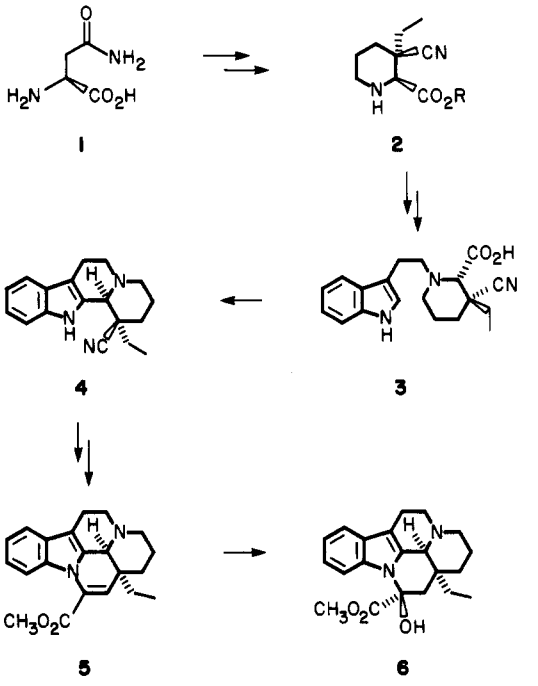
Received October 26, 1984

Pipecolic acid derivatives have been examined as intermediates in a synthesis of apovincamine (**5**). First, the racemic pipecolate **10** was elaborated to the pentacyclic β-keto ester **14**. Ethylation of **14** gave eburnane **15**, with the incorrect relative stereochemistry, and test experiments established that this route would be unsuitable for a chirospecific synthesis since it would lead to a racemic product. Therefore, in a second approach, the optically pure 3-cyano-3-ethylpipecolate (**2**) was synthesized from L-asparagine. The new phenylfluorenyl N-protecting group served to direct both enolate formation and alkylation stereochemistry. Pipecolate **2**, by a sequence including iminium ion formation via amino acid decarbonylation, was used to make the octahydroindolo[2,3-*a*]quinolizine **4** which was elaborated to (+)-apovincamine.

Recent work has demonstrated the usefulness of α-amino acids as educts for chirospecific alkaloid synthesis. Thus, the neurotransmitter anatoxin a[1] and ant trail pheromones[2] have been synthesized from glutamic acid. Also, we have investigated the use of pipecolic acid derivatives as precursors in indole alkaloid syntheses.[3]

In this report we combine these two concepts for the synthesis of an optically pure indole alkaloid (Scheme I). Specifically, L-asparagine (**1**) has been used to synthesize the optically pure pipecolate **2**. Further synthetic development proceeded through the decarbonylation of the tertiary amino acid **3** and cyclization to give the octahydroindolo[2,3-*a*]quinolizine **4**, which was elaborated to apovincamine (**5**), a known synthetic precursor to the antihypertensive agent vincamine (**6**).[4]

Scheme I. General Course for the Synthesis of Apovincamine (5) from Asparagine (1)



1 2 3 4 5 6

Results and Discussion

Attempted Synthesis Using Piperidine Diester 10. Initially we investigated an apovincamine synthesis as an extension of the earlier work on octahydroindolo[2,3-*a*]-quinolizines. The easily available racemic piperidine diester **10**[3] was used as a model pending developments toward optically active pipecolates. We also desired the modified tryptophyl bromide **9**, in which the *N*-[(methoxycarbonyl)methyl] substituent would be incorporated into the last ring. Compound **9** was made from tryptophyl bromide (**7**) by base-induced (K_2CO_3) formation of the spiroindolenine **8**,[3] followed by in situ alkylation with methyl bromoacetate. The proof of **8** as an intermediate in this reaction is based on experiments showing that **8** is formed by treating tryptophyl bromide (**7**) with K_2CO_3, that **8** is converted to **9** upon treatment with methyl bromoacetate, and that indole is not converted to *N*-[(methoxycarbonyl)methyl]indole under these conditions.

Alkylation of piperidine diester **10** with bromide **9** produced the tertiary indole amine **11**, which was hydrolyzed to amino acid **12** and then cyclized through the iminium ion produced by $POCl_3$ decarbonylation to give only the [1(*S*,*R*),12b(*S*,*R*)] diastereomer **13**. A small amount (10%) of enamine **16** was produced as a side product and was the sole product when acid **12** was treated with

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