chloromethylated polymer (10 g, 1.67 mmol of Cl/g) (2) in dry THF (150 mL), giving, after washing and drying, the *trans*-(4*S*,5*S*)-2-ethyl-5-phenyl-2-oxazoline functionalized polymer (10); IR (KBr) 3030, 2910, 1665 (C=N), 1600, 1490, 1450, 1360, 1250, 1180, 1115, 985, 870, 910, 740, 680 cm^{-1}. Anal. Calcd for 90% displacement of Cl and 26% of the repeating units functionalized: C, 85.20; H, 7.30; N, 2.09; Cl, 0.62. Found: C, 85.48; H, 7.65; N, 1.71; Cl, 0.49.

General Procedure for Preparation of Chiral Ester from 10. Preparation of *S*-(+)-Ethyl-2-methyl-3-phenylpropanoate. By use of a procedure identical with that used for alkylation of the achiral oxazolines 3 and 4, the *trans*-(4*S*,5*S*)-2-ethyl-5-phenyl-2-oxazoline functionalized polymer (10; 3.5 g, 1.22 mmol of oxazoline/g) in dry THF (150 mL) was treated stepwise with 12 mL of *n*-butyllithium at -78 °C (in dry ice-acetone) or at -43 °C (in dry ice-monochlorobenzene) and benzyl chloride[10] (10.0 g, 0.79 mol) in dry THF (40 mL), giving the alkylated polymer 12 (3.9 g, theoretical weight is 3.9 g); IR (KBr) 3030, 2910, 1652 (C=N), 1600, 1490, 1445, 1360, 1245, 1170, 1105, 975, 865, 740, 675 cm^{-1}.

By the procedure described for ethanolysis of 6, the sample of optically active benzylated oxazoline polymer (12; 3.7 g) from the -40 °C alkylation was swollen in 100 mL of THF and reacted with 100 mL of ethanolic sulfuric acid at 58 °C for 120 h. Workup provided 2.7 g of a light yellow liquid which contained (by GLC) 0.24 g (48%) of *S*-(+)-ethyl 2-methyl-3-phenylpropanoate. Distillation gave the purified ester: bp 70-80 °C (1.5 mm) [lit.[23] bp 90 °C (4.5 mm)]; $[\alpha]^{22.2}_{589}$ +15.0° (*c* 2.836, EtOH) [lit.[23] $[\alpha]^{18}_{589}$ +26.93° (neat)]; IR (KBr, neat) 3410-3440 (OH, due to impurity), 2980, 2940, 2880, 1730 (C=O), 1600, 1490, 1452, 1375, 1175, 1105, 1055, 735, 690 cm^{-1}; NMR (CD_3COCD_3) δ 7.11 (s, 5 H, Ar H), 3.99 (q, 2 H, OCH_2CH_3), 1.1 (t, 3 H, OCH_2CH_3), 3.75 (m), 1.56 (m). The latter two peaks were tentatively identified as arising from the ethanolysis product of THF, which codistilled with the product (20% by GLC). Subsequent experiments showed that the product could be obtained free of the impurity by preparative GLC. The polymer support which resulted was washed and dried, giving the amino alcohol polymer (13) along with unhydrolyzed or partially hydrolyzed oxazoline polymer; IR (KBr) 3200-3400 (br, OH), 3020-3600, 2920, 1720-1730 (C=O, amino ester), 1660 (C=N, oxazoline), 1660, 1490, 1450, 1362, 1070, 902, 810, 745, 685 cm^{-1}.

Ethanolysis of Tetrahydrofuran. A sample of ethanolic sulfuric acid in THF was prepared identically with the solution used to cleave the oxazoline polymer sample. Refluxing this solution for 336 h, neutralization (Na_2CO_3), and distillation provided a complex mixture collected over the range 30-65 °C (1.85 mm), with the bulk of the material having a boiling range of 54-63 °C (1.85 mm). The principal component, tentatively identified as ethyl 4-hydroxylbutyl ether, had the same IR and NMR spectral characteristics and an identical GLC retention time as the impurity from the ethanolysis experiments above.

Acknowledgment. Partial support of this research was kindly provided by the University of Alabama in Huntsville Research Grants Committee.

Registry No. 1, 39986-37-3; 2, 53416-48-1; 9, 51594-33-3; (*S*)-(+)-ethyl 2-methyl-3-phenylpropanoate, 70878-24-9; polystyrene, 9003-53-6; benzyl chloride, 25168-05-2; methyl iodide, 74-88-4; hydrocinnamic acid, 501-52-0; ethyl 2-methyl-2-phenylpropanoate, 2901-13-5; ethyl hydrocinnamate, 2021-28-5.

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Biomimetic Polyene Cyclizations. Asymmetric Induction during the Acid-Catalyzed Cyclization of Chiral Imines

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This paper reports the details of a basic study showing that an imino function is suitable to initiate acid-catalyzed cyclizations of polyenes, affording high yields of cyclized products. The additional advantage of such a function is to introduce very easily a chirality on the polyene skeleton by the way of a chiral group linked to nitrogen. The extent of asymmetric induction by a chiral phenethyl group on nitrogen is from 36% to 65%, according to the monocyclic or bicyclic nature of the substrate.

The results obtained during the study of the biogenetic synthesis of sterols[1-3] and the stereospecificity of the enzymatic cyclization of epoxysqualene to lanosterol[4] allowed the development of a new strategy for the total synthesis of polycyclic natural products, particularly the steroids and polycyclic triterpenoids usually prepared through step by step annelations.

After a first unsuccessful attempt by Eschenmoser,[5] several biomimetic polyene cyclizations, involving the production of a number of rings stereospecifically in a single step by the ring closure of an acyclic chain having oppositely placed trans olefinic bonds, were reported and demonstrated the aptitude of several functions such as aldehyde,[6-9] carboxylic acids,[10,11] epoxide,[12] or allylic alcohol[13-21] to induce acid-catalyzed cyclizations.

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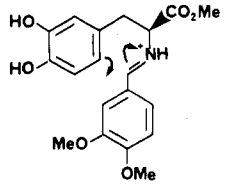
0022-3263/81/1946-3102$01.25/0

Although these cyclizations were stereospecific with respect to the relative configurations of the chiral centers, the products were racemic. Optically active cyclized products could, however, be obtained from optically active polyenes.[22,23] Johnson[22] demonstrated on racemic material that the presence of an asymmetric carbon atom on the polyene chain could result in total asymmetric cyclization, but the difficulty was to prepare such an optically active polyene.

For this reason all the efforts were to use a chiral function to initiate the cyclization. The first report was done by Johnson using a chiral acetal[24,25] which led to 84% of asymmetric induction.

Our approach to this problem was to use an imino group to induce the cyclization in order to introduce the chirality α to the nitrogen atom.

Several literature reports already showed the potentiality of the iminium group to induce cationic cyclizations during several syntheses of heterocyclic compounds. Yamada[26] obtained a 40% asymmetric induction during a synthesis of (+)-laudanosine from L-dopa involving the formation of the chiral iminium 1. Similarly, Corey[27] prepared the



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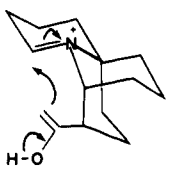

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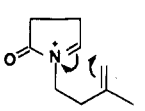


3

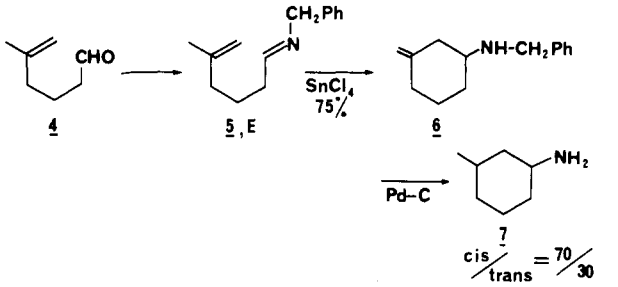
alkaloid porantherine from the intermediate 2. More recently, Speckamp[28] published the results of a study of cationic heterocyclizations through acyl iminium ions 3.

A closely related study was reported by Yamada[29] which used chiral enamines to induce the cyclization with moderate extent of asymmetric induction (12–33%).

We present in this paper a full account of our study of asymmetric synthesis of mono- and bicyclic compounds by acid-catalyzed cyclizations of chiral imines, results partially already reported in two short communications.[30,31]

Cyclization of Imines Derived from 5-Methyl-5-hexenal.

To explore the possibility of using the imino group to initiate polyene cyclization, we first considered the aldimine (*E*)-5[32] derived from benzylamine and 5-methyl-5-hexenal (4).[34] When a solution of this aldimine

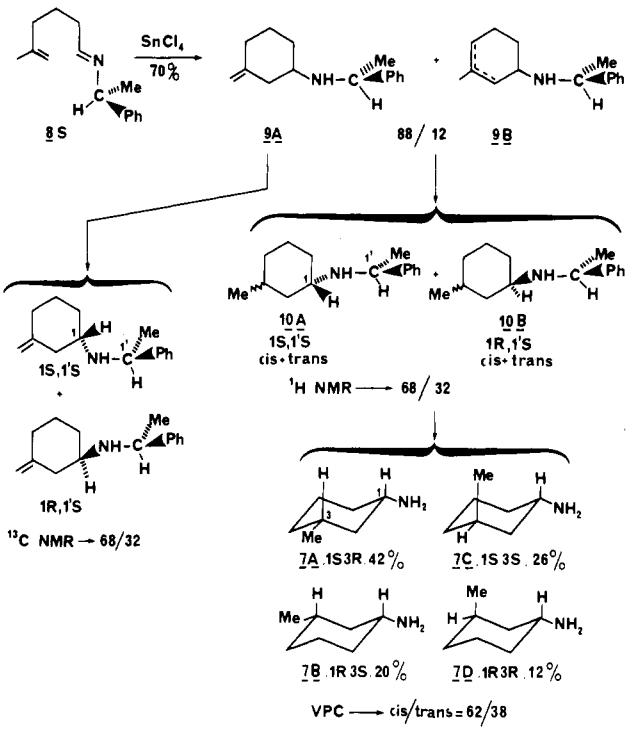


in benzene was allowed to stand in the dark at room temperature in presence of stannic chloride during 24 h, the cyclic secondary amine 6 was obtained with a 75% yield and shown by NMR of the crude product to be free of the isomer having an endocyclic double bond. After debenzylation and hydrogenation of the ethylenic bond, a mixture of *cis*- and *trans*-3-methylcyclohexylamine (7) was obtained and easily identified by comparison (VPC) with authentic samples.[35]

In view of these promising results, we turned our attention to the possibility of using chiral imines for the aforementionned objective of producing optically active cyclized compounds.

The cyclization of imine (*S*)-8 with stannic chloride afforded a 70% yield of cyclic amines 9 (Scheme I) which were shown by NMR to be a mixture of isomers having an endocyclic double bond (vinylic methyl at 1.6 ppm) and an exocyclic double bond (2 vinylic H at 4.6 ppm) in the ratio 12/88 (determined by VPC). The major isomer **9A**,

Scheme I



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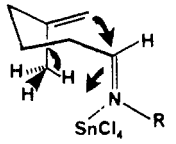
easily separated by column chromatography, was indeed a mixture of two diastereoisomers in the ratio 68/32 as determined by ^{13}C NMR (from the splitting of the carbon atoms adjacent to the created chiral center signals: C_2, $\Delta\delta$ = 29.5 Hz; C_6, $\Delta\delta$ = 37.0 Hz). Therefore, the asymmetric induction was 36%. This enantiomeric excess was also determined by use of the ^1H NMR of the hydrogenated amines **10** (the benzylic proton showing, after spin decoupling, two singlets in the ratio 68/32).

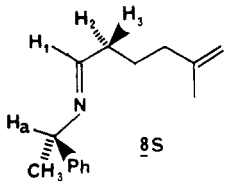
Finally, after debenzylation the cis/trans stereochemistry of the amines **7** was determined by VPC and comparison with authentic samples, while the absolute configuration of the major cis isomer was deduced from the optical rotations of the known acetamide derivatives.[35]

These results show first of all a strong regioselectivity during the double bond formation, the exocyclic location being strongly favored (88% in one case and 100% in the other). This result could hardly be rationalized by the formation of a terminal tertiary carbenium ion which would afford preferentially the thermodynamicly more stable endocyclic double bond. This regioselectivity is better understood in terms of a wholly concerted mechanism already proposed by Andersen[36,37] for cationic cyclizations of aldehydes and applied to our case in **11**. The

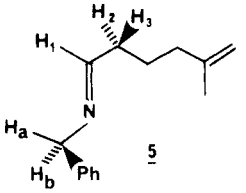


11

enantioselectivity of the cyclization of aldimine (*S*)-**8** can

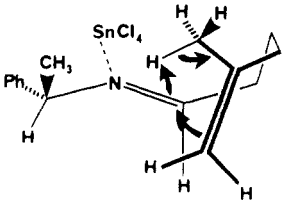


8S



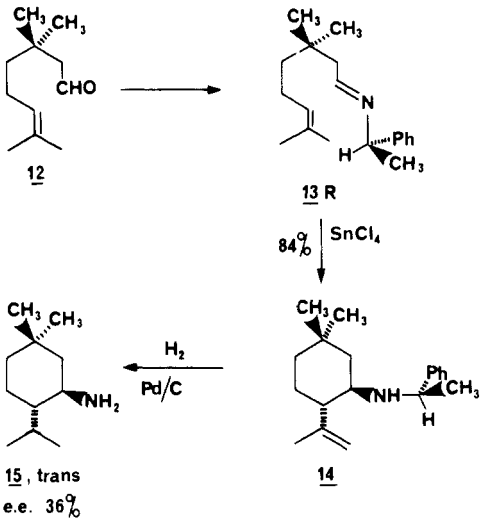
5

be now explained by a stereochemical model by using this concerted pericyclic mechanism and the preferred conformation of the starting imine, having H_1 coplanar with H_A. This conformation, deduced from ^1H NMR spectra,[38] is consistent with the conformational study of Karabatsos.[33] In such a conformation the two diastereotopic faces of the iminodouble bond are distinguishable by the presence of a methyl group or a phenyl group, the concerted cyclization occurring preferentially on the methyl group side.



Cyclization of Imine Derived from 3-Methylcitronellal. The next step in our approach was to study the formation of two chiral centers during the cyclization process.

Scheme II

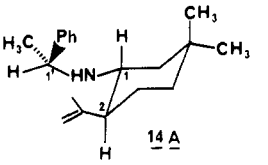


The cyclization of imine (*R*)-**13**, derived from 3-methylcitronellal (**12**), afforded a 84% yield of cyclic amines **14** (Scheme II) having a methylenic double bond, characterized in NMR by two vinylic protons at 4.76 and 4.84 ppm (without any evidence of the presence of the tetrasubstituted double bond isomer).

The debenzylated amine **15** was shown to be the pure trans isomer by VPC and comparison with authentic cis and trans amines. Finally, the secondary amines **14** being only a mixture of two diastereoisomers, it was possible to determine that these stereoisomers were present in the ratio 68:32 by 90-MHz ^1H NMR (from the signals corresponding to the gemdimethyl group and the vinylic protons) as well as by ^{13}C NMR (from the terminal vinylic carbon signals).

The absolute configuration of the major enantiomer **15**, 1*R*, was deduced from the application of Horeau's method.[39,40]

Therefore, the acid-catalyzed cyclization of imine (*R*)-**13** afforded only the trans isomer having a methylenic double bond and an enantiomeric purity of 36%, the predominant diastereoisomer obtained being (1*R*, 1′*R*, 2*S*) **14A**. We



14A

have already pointed out that the regioselectivity in the double bond formation is consistent with a concerted mechanism. In addition, in this case the exclusive formation of the trans isomer is another point in favor of such a mechanism. As a matter of fact, Oshima[43] reported in this context an interesting result. He actually observed the exclusive formation of the cis isomer by acidic cyclization of aldehyde **16**. In this case, the ability of sulfur and silicon to stabilize a positive charge led to a nonconcerted mechanism proceeding by open transition states,

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(38) In imine (*S*)-**8**, the proton H_1 gives a large triplet at 7.8 ppm (J = 4.5 Hz), the coupling constant with H_a being close to zero, while in imine **5**, H_1 gives a multiplet at 7.7 ppm resulting of a ^3J coupling with H_2 and H_3 and also a ^4J coupling with H_b.
(39) (a) Horeau, A. *Bull. Soc. Chim. Fr.* **1967**, 2673. (b) Weidmann, R.; Horeau, A. *Ibid.* **1967**, 117.
(40) Although some primary amines exhibit anomalous behavior with this method,[41] we have demonstrated by ORD in a similar case[42] that the result was reliable.
(41) Horeau, A. In "Stereochemistry"; Georg Thieme Verlag: Stuggart, 1977; Vol. 3.
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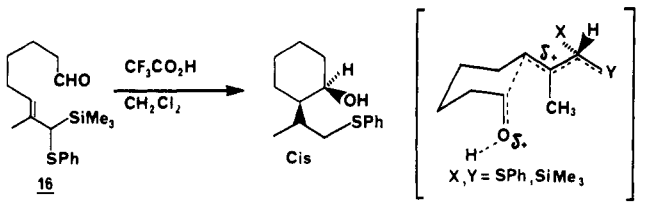
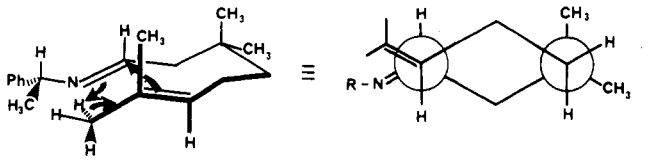


the cis isomer being favored by smaller dipole–dipole interactions.

In our case, a model very similar to the one developed for the imine(*S*)-8 and involving a concerted pericyclic mechanism can rationalize the exclusive formation of the trans isomer as well as the enantiomeric recognition.



In this quasi-chair conformation, the formation of the cis isomer would require either the azomethine double bond or the isopropylidene group in a pseudoaxial orientation, leading to unfavorable interactions (an isopropyl group in an axial position in a monosubstituted cyclohexane is destabilized by about 2 kcal/mol with respect to the equatorial orientation).

The asymmetric induction is exactly the same as in the preceeding case, 36%. In the preferred conformation, already discussed, of the imino moiety, the cyclization on the face of the azomethine double bond bearing the methyl group is favored by about 0.4 kcal/mol.

It is important to point out that the stereochemistry of the two chiral centers created during the cyclization is not dependent on the same factors. The chirality of the nitrogen-substituted carbon atom is governed by the nature of the nonequivalence of the two diastereotopic faces of the double bond while the chirality of the second center is much more dependent on the interactions in the quasi-chair conformation.

Cyclization of Imines Derived from Citronellal. The results obtained during the cyclization of imines prepared from citronellal afforded complementary information about the importance of this quasi-chair conformation. In this case there is a chiral center on the olefinic chain.

Cyclization of imine **17**, prepared from benzylamine and (+)-(*R*)-citronellal gave a 75% yield of cyclized product **18** (methylenic double bond, characterized in NMR by two vinylic protons at 4.82 ppm) which after reduction and debenzylation led to a mixture of the known amines **19–21** (Scheme III) identified by VPC and comparison with authentic material. The absolute configuration of the major isomer **19** was deduced from the optical rotations of the known chlorohydrates.[44]

The results are listed in Table I as well as those from imines having an additional chiral center on the nitrogen.

In each case menthylamine is the predominant isomer. The presence of a second chiral center on nitrogen does not change significantly the diastereoisomeric ratio. The asymmetric induction is therefore totally controlled by the chiral center on the chain and is independent of the chirality of the substituent linked to nitrogen.

The quasi-chair model shows that the formation of menthylamine is energetically favored: the isopropylidene

Scheme III

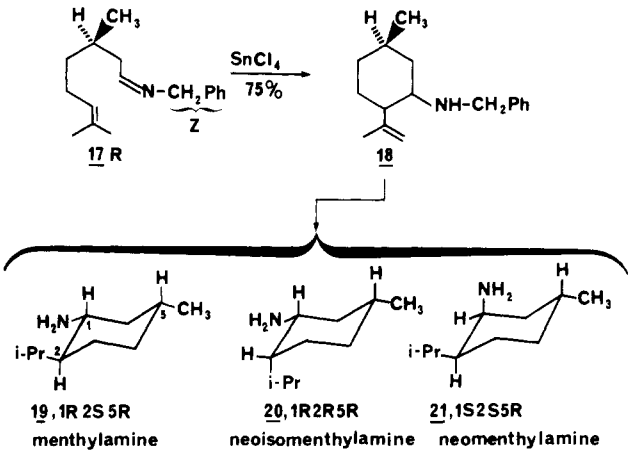
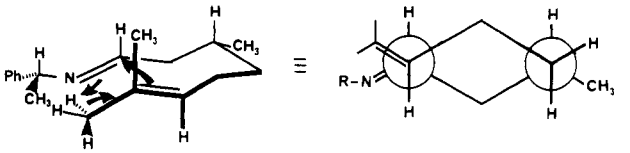


Table I

Z	yield, %	% 19	% 20	% 21	asymmetric induction, % C_1	asymmetric induction, % C_2
CH_2Ph	75	73	9	18	64 (*R*)	82 (*S*)
	70	76	10	14	71 (*R*)	80 (*S*)
	70	75	9	16	68 (*R*)	82 (*S*)

and azomethine groups being in a pseudoequatorial orientation as well as the methyl group of the chiral center.



Any competitive effect of a chiral group on nitrogen to invert the stereochemistry of the cyclization would require an energetically unfavorable axial orientation for the methyl group on the chiral center of the chain.

Another interesting aspect of the results listed in Table I is the formation of about 25% of amines **20** and **21** having a cis configuration between carbon atoms 1 and 2. According to our stereochemical model the formation of these stereoisomers would require either the isopropylidene group or the azomethine function in an axial orientation. This conformation is more stable than that of imine **13**, because of the absence of the *gem*-dimethyl group.

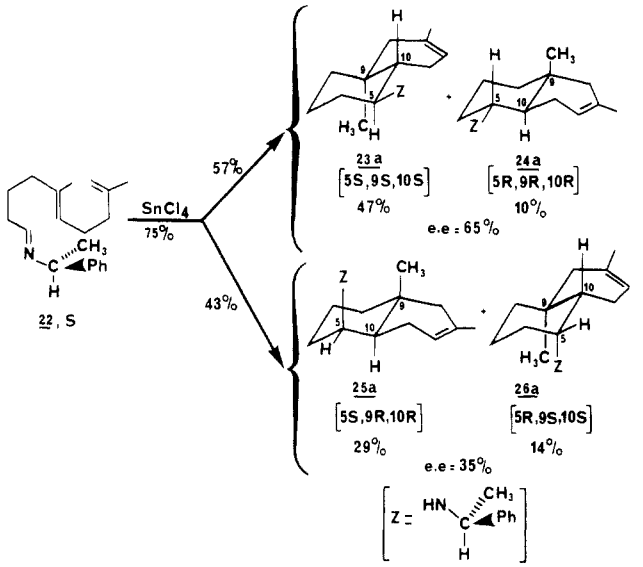
Cyclization of Imine Derived from *trans*-5,9-Dimethyldeca-5,9-dienal. The last part of this work deals with the formation of bicyclic compounds and offers a direct comparison of the extent of asymmetric induction obtained with a chiral imine group and with the chiral ketal described by Johnson.

Cyclization of imine **22** prepared from *trans*-5,9-dimethyldeca-5,9-dienal[24,25] and (–)-(*S*)-α-phenylethylamine with stannic chloride leads to a 75% yield of cyclic secondary amines constituted by 90% of amines **23a** to **26a**[45] (Scheme IV) having an endocyclic double bond (vinylic protons leading at 250 MHz to a multiplet between 5.08

(44) Fellkamp, H.; Koch, F.; Thah, Than Nhut *Justus Liebigs Ann. Chem.* **1967**, *707*, 78.

(45) The endocyclic double bond in compounds **23a** to **26a** was located between carbons 2 and 3 by analogy with the results of Johnson,[24,25] who has shown that less that 1% of the $\Delta^{1,2}$ isomer was present in the cyclization products from acetal **27**.

Scheme IV



and 5.25 ppm) and 10% of amines having an exocyclic methylene group (characterized by a multiplet for the vinylic protons between 4.7 and 4.85 ppm[24,25]) which were easily separated by chromatography on silica gel.

In the mixture of amines **23a–26a**,[46] the diastereoisomers having an equatorial amino group, **23a** and **24a** (57%), and those having an axial amino group, **25a** and **26a** (43%), were easily distinguished by the relative positions of the NMR signals (and their intensities) for the angular methyl group which appeared at 0.78 (47%) and 0.83 (10%) in the case of an equatorial amino group and at 0.90 (14%) and 0.94 ppm (29%) in the case of an axial amino group.[47]

Finally the diastereoisomeric series **23a** plus **25a** and **24a** plus **26a** were distinguished by the two quartets centered at 3.9 (76%) and 4.0 ppm (24%), corresponding to the benzylic proton.

We can conclude from this NMR study that 76% of the reaction mixture has the same chirality at C-5 (47% having an equatorial amino group and 29% an axial one) while 24% have the opposite chirality at C-5 (10% with an equatorial NHR and 14% with an axial one).

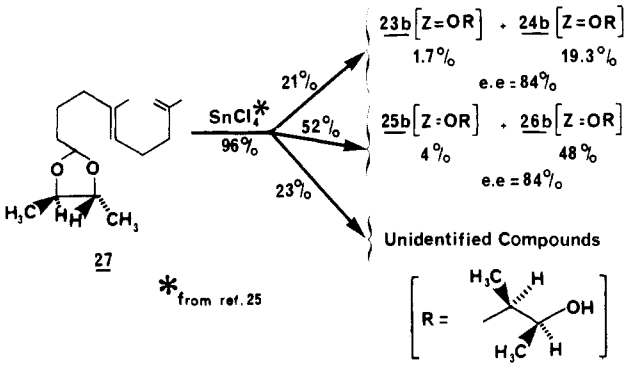
The absolute configuration of C-5 in the major diastereoisomer was determined, after debenzylation on Pd/C, by Horeau's method:[39] the formation of (−)-α-phenylbutyric acid indicated that the C-5 absolute configuration in the predominant diastereoisomers was probably *S*.[40]

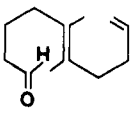
The first comment on these results concerns the location of the terminal double bond which is mainly endocyclic (90%). A wholly concerted mechanism cannot be, of course, involved here, and therefore a terminal tertiary cation must be produced.

Comparison of our results and those obtained by Johnson during the cyclization of acetal **27** points out several comments.

(1) The main diastereoisomer obtained from the chiral acetal **27** is the axial epimer **26b** (see Scheme V) while the chiral aldimine (*S*)-**22** leads mainly to the equatorial epimer **23a**. Our result is similar to that obtained by Ireland[48] during acid-catalyzed cyclization of aldehyde **28** which afforded mainly the racemic equatorial alcohol.

Scheme V

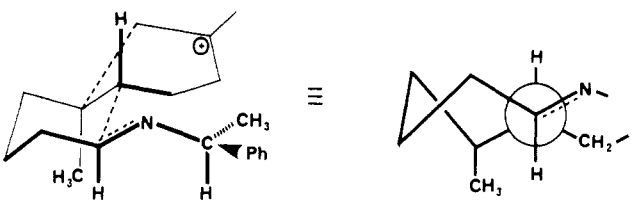




28

(2) A striking difference between the two experiments is also observed in the extent of asymmetric induction. During the acetal cyclization an 84% enantiomeric excess is obtained in both diastereoisomeric series, while in the imine cyclization we observed a 65% enantiomeric excess in the trans–trans series but only a 35% in the cis–trans series, the optical purity at C-5 being 52% in our case and 84% in the acetal case.

The formation of the major isomer **23a** can be rationalized by our stereochemical model, the azomethine group being in an equatorial orientation.



The asymmetric induction (65%) is almost twice as large that observed in the preceeding series (36% from **8** and **12**), the cyclization occurring on the side of the azomethine double bond bearing the methyl group.

The formation of 29% of amine **25a** with an axial amino group required a pseudoaxial orientation of the imino group, which is not very favorable because of a 1,3 interaction with the axial methyl group on carbon 9. The asymmetric induction (35%) is in this case of the same order of magnitude as in the preceeding monocyclic series. Even more difficult to rationalize is the predominant formation of the axial epimer during the acetal cyclization as well as the high asymmetric induction.

In conclusion, this study shows that an imino function is suitable to initiate acid-catalyzed cyclizations and that the reactions give high yield of cyclized products. An additional advantage of such function is to introduce very easily a chirality on a polyene skeleton. The extent of asymmetric induction by the chiral center linked to nitrogen ranges from 36% to 65% according to the monocyclic or bicyclic nature of the substrates. Since, in this domain, the only literature results dealing with optically active material have been until now the acetal cyclization

(46) The absence in this mixture of isomers having an exocyclic double bond was confirmed by ^{13}C off-resonance NMR showing four doublets between 119 and 121.2 ppm, corresponding to vinylic carbons bearing only one hydrogen atom.

(47) The position of the NMR signal for an angular methyl group at C-9 in compounds having an axial substituent at C-5 is shifted downfield relative to the equatorial isomer as a result of 1,3-diaxiaal interactions (see: Zurcher, R. F. *Helv. Chim. Acta* **1963**, *46*, 2054). In compounds **23b** and **24b** having an equatorial hydroxy ether group, the chemical shift of the angular methyl group is 0.80 ppm, meanwhile in compounds **25b** and **26b** having an axial OR group, this chemical shift is 0.92 ppm.[24,25]

(48) Ireland, R. E.; Dawson, M. J.; Kowalski, C. J.; Lipinski, C. A.; Marshall, D. R.; Wiley, J. W.; Bordner, J. *J. Org. Chem.* **1975**, *40*, 973.

(a very recent paper[49] dealing with the use of optically active allylic alcohols to induce polyenic cyclization demonstrated an extensive racemization), chiral imines provide a possible synthetic tool to obtain optically active polycyclic compounds.

Experimental Section

***N*-(5-Methyl-5-hexenylidene)benzylamine (5E).** A 0.55-g (4.9 mmol) sample of 5-methyl-5-hexenal[34] (4) and 0.5 g (4.7 mmol) of benzylamine was diluted by 20 mL of benzene and kept for 1 h at room temperature in presence of 10 g of 4-Å molecular sieves. After the evaporation of the solvent, 1 g of crude imine (*E*)-5 was obtained: IR (benzene) $\nu_{C=N}$ 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.3–2.5 (m, 6 H), 1.70 (s, 3 H, vinylic CH_3), 4.57 (br s, 2 benzylic H), 4.70 (br s, 2 vinylic H), 7.2 (m, 5 aromatic H), 7.7 (m, 1 H, azomethine H).

Cyclization of *N*-(5-Methyl-5-hexenylidene)benzylamine ((*E*)-5) with Stannic Chloride in Benzene. A 1.0-g sample of imine (*E*)-5 was diluted in 1.5 L of anhydrous benzene (distilled over Na) under argon. To this solution, kept in the dark, was added, under vigorous stirring and slowly (over a period of 30 min), 2.5 mL of stannic chloride diluted in 100 mL of benzene. Stirring was continued at room temperature for 24 h. After addition of 100 mL of water, the solution was concentrated, neutralized with a 20% sodium hydroxide solution and extracted with ether. The organic layer was washed twice by 20 mL of hydrochloric acid (10%). The aqueous layer was then neutralized with sodium hydroxide (20%) and extracted with ether. The ether solution was washed with water, dried, and concentrated, giving 0.80 g of amines. A rapid filtration on silica gel (eluant benzene–10% EtOH) removed any trace of benzylamine and gave amine **6**: 0.75 g (75%); NMR ($CDCl_3$) δ 1–3 (m, 10 H), 3.8 (s, 2 benzylic H), 4.7 (s, 2 vinylic H), 7.2–7.3 (m, 5 aromatic H).

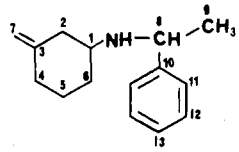
3-Methylcyclohexylamine (7). A 0.7-g (3.5 mmol) sample of amine **6** diluted in 100 mL of ethanol was debenzylated in presence of 200 mg of Pd/C in 3 days under a 3-atm pressure of hydrogen.

The stereochemistry of the debenzylated 3-methylcyclohexylamine (**7**) was determined by VPC analysis of a solution of 100 mg of amine **7** in 5 mL of acetone (prepared 2 h before the analysis) under the following conditions: 140 °C, Carbowax 20M over Chromosorb W 60-80 treated with KOH (15%). The products were compared with authentic cis and trans isomers prepared by reduction of the corresponding oxime.[35] This analysis demonstrated that the mixture contained 70% of the cis isomer and 30% of the trans isomer.

(*S*)-*N*-(5-Methyl-5-hexenylidene)-α-phenylethylamine ((*S*)-8). Imine (*S*)-8 was obtained as previously from 0.4 g (3.6 mmol) of aldehyde **4** and 0.5 g (4.1 mmol) of (–)-(*S*)-α-phenylethylamine in 50 mL of benzene in presence of molecular sieves: quantitative yield; IR ($CHCl_3$) $\nu_{C=N}$ 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.2–2.5 (m, 12 H), 4.2 (q, J = 7 Hz, 1 benzylic H), 4.7 (br s, 2 vinylic H), 7.2–7.3 (m, 5 aromatic H), 7.8 (t, J = 4 Hz, 1 azomethine H).

Cyclization of (*S*)-*N*-(5-Methyl-5-hexenylidene)-α-phenylethylamine ((*S*)-8) with Stannic Chloride in Benzene. A 0.77-g (3.6 mmol) sample of imine (*S*)-8 diluted in 1000 mL of benzene was cyclized as previously in presence of 2 mL of stannic chloride in 250 mL of benzene. The same workup gave 0.60 g of amines **9** (yield 70%): VPC analysis (same conditions as in the case of amines **7** but a column temperature of 200 °C) 2 peaks in the ratio 88/12.

For determination of the spectral characteristics of the amines **9A** and **9B**, they were separated by column chromatography on silica gel (eluent 10% EtOH–90% benzene).



First fraction (83% of the mixture, **9A**): ^{1}H NMR ($CDCl_3$) δ 1.3 (d, J = 7 Hz, 3 H, CH_3), 1.1–3 (m, 10 H), 3.9 (q, J = 7 Hz, 1 benzylic H), 4.6 (br s, 2 vinylic H), 7.2–7.3 (m, 5 aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz; the signals were assigned by off-resonance spectrum) 24.9 (C_9), 25.07 (C_5), 31.94 and 33.43 (C_6 or C_4), 34.83 (C_4 or C_6), 41.56 and 42.74 (C_2), 54.04 (C_8 or C_1), 54.21 and 54.75 (C_8 or C_1), 108.66 (C_7), 126.64, 126.86 and 128.49 (C_{13}, C_{12} and C_{11}), 146.27 and 147.31 ppm (C_3 and C_{10}). The splitting of C_2 and C_6 signals in the respective ratios 67/33 and 69/31 is due to the presence of two diastereoisomers relative to C_1 and C_8.

Second fraction (14% of the mixture, **9B**): ^{1}H NMR ($CDCl_3$) δ 1.3 (d, J = 7 Hz, 3 H, CH_3), 1.1–3 (m, 8 H), 1.60 (s, 3 H, vinylic CH_3), 3.70 (m, 1 benzylic H), 5.0 (m, 1 vinylic H), 7.2 (m, 5 aromatic H).

(*S*)-[(α-Phenylethyl)amino]-3-methylcyclohexylamine (10A,B). A 0.6-g (2.8 mmol) sample of the mixture of amines **9** diluted by 100 mL of ethanol was hydrogenated in presence of 50 mg of Pd/C during 2 h under 1 atm of hydrogen, yielding the saturated amines **10**: ^{1}H NMR ($CDCl_3$) δ 0.85–1.0 (m, 3 H, CH_3), 1.1–2.5 (m, 14 H), 3.95 (2 q, J = 7 Hz, 1 benzylic H), 7.2–7.3 ppm (m, 5 aromatic H). By spin decoupling the two quartets at 3.95 ppm gave two singlets in the ratio 68/32.

3-Methylcyclohexylamines 7A–D. The mixture of amines **10** gave a mixture of amines **7** after catalytic debenzylation for 3 days under the conditions previously used.

The cis–trans configuration of amines **7** was identified by VPC as previously and by comparison with authentic samples, giving 62% of the cis isomer (**7A** and **7B**) and 38% of the trans isomer (**7C** and **7D**).

The mixture of amines **7** was transformed into the *N*-acetyl derivatives with acetyl chloride in triethylamine and methylene chloride: IR ($CHCl_3$) ν_{NH} 3440, $\nu_{C=O}$ 1680 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (br d, 3 H, CH_3), 1.0–2 (m, 10 H), 1.95 (2 s, 3 H, CH_3 α to carbonyl), 5–5.5 (m, 1 NH); $[\alpha]^{20}_D$ –8° 0.55, benzene). From the literature:[35] *N*-acetyl derivative of (1*S*,3*R*)-*cis*-3-methylcyclohexylamine, $[\alpha]_D$ –43.4°; *N*-acetyl derivative of (1*S*,3*S*)-trans-3-methylcyclohexylamine $[\alpha]_D$ +3.4°.

The NMR spectra indicate that the mixture of amines **7** contains 62% of amine cis and 38% of amine trans and that the enantiomeric purity of C-1 is 36%. Hence, it is possible to calculate the rotatory power of the mixture of the *N*-acetyl derivatives of amines **7**: $[\alpha]_{D,calcd}$ = (–43.4)(0.36)(0.62) + (+3.4)(0.36)(0.38) = –8.7°, a value in good agreement with the experimental value of –8°.

3,3,7-Trimethyl-6-octenal (12; 3-methylcitronellal). To a solution of 3 g of CuI (15.8 mmol) in 60 mL of ether under argon at –20 °C was added 19.7 mL of MeI (0.316 mol). After 0.5 h at –20 °C, 4.5 g (30 mmol) of citral was added. The usual workup yielded after purification by chromatography 2.3 g (45%) of aldehyde **12**:[54] IR (CCl_4) $\nu_{C=O}$ 1720 cm^{-1}; NMR (CCl_4) δ 1.06 (s, 6 H, 2 CH_3), 1.58 (s, 3 H, vinylic CH_3), 1.67 (s, 3 H, vinylic CH_3), 1.2–2.1 (m, 4 H), 2.22 (d, J = 2 Hz, 2 H, CH_2 α to aldehyde), 5.03 (br t, 1 vinylic H), 9.80 (t, J = 1 aldehydic H).

Cyclization of (*R*)-*N*-(3,3,7-Trimethyl-6-octenylidene)-α-phenylethylamine (14) with Stannic Chloride in Benzene. A 1.2 g (4.3 mmol) sample of imine **13** [prepared as usual from 0.73 g (4.3 mmol) of aldehyde **12** and 0.57 g of (+)-(*R*)-α-phenylethylamine] diluted in 1500 mL of benzene was cyclized at room temperature in 24 h in the presence of 3 mL of stannic chloride diluted in 200 mL of benzene (84% yield in amines **14**).

In order to characterize the two diastereoisomers of amine **14** by NMR, they were separated by column chromatography (eluent 10% EtOH–90% benzene): NMR of one diasteroisomer (CCl_4)

(49) Peters, J. A. M.; Posthumus, T. A. P.; Van Vliet, N. P.; Zeelen, F. J.; Johnson, W. S. *J. Org. Chem.* **1980**, *45*, 2208.

(50) By analogy with the synthesis of *cis*- and *trans*-isopropyl-2-cyclohexylamine,[51] the cis isomer of amine **15** was prepared by hydrogenation of the corresponding oxime in presence of PtO_2, while a mixture of the two isomers (80% trans, 20% cis) was prepared by oxime reduction with Na/EtOH.

(51) Booth, H.; Gidley, G. C.; Franklin, W. C. *Tetrahedron Lett.* **1967**, 2421.

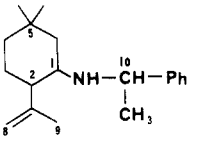
(52) (a) Bose, A. K.; Kistner, J. F.; Farber, L. *J. Org. Chem.* **1962**, *27*, 2925. (b) Bose, A. K.; Morrison, S.; Farber, L. *Ibid.* **1963**, *28*, 1223.

(53) Read, J.; Robertson, G. J. *J. Chem. Soc.* **1927**, 2168.

(54) Sathe, W. M.; Rao, A. S. *Curr. Sci.* **1967**, *36*, 431; *Chem. Abstr.* 1968, *68* 2998.

δ 0.82 (br s, 6 H, 2 CH_3), 1.23 (d, J = 7 Hz, 3 H, CH_3), 1.70 (s, 3 H, vinylic CH_3), 1.0–2.4 (m, 9 H), 3.76 (q, J = 7 Hz, 1 benzylic H), 4.84 (br s, 2 vinylic H), 7.2 (m, 5 aromatic H); NMR of the second diastereoisomer (CCl_4) δ 0.70 (s, 3 H, CH_3), 0.90 (s, 3 H, CH_3), 1.32 (d, J = 7 Hz, 3 H, CH_3), 1.0–2.4 (m, 12 H), 3.80 (q, J = 7 Hz, 1 benzylic H), 4.76 (br s, 2 vinylic H), 7.2 (m, 5 aromatic H); 90-MHz ^1H NMR of the diastereoisomeric mixture of amines **14** ($CDCl_3$) δ 0.71, 0.82, 0,92 (3 s, 6 H, 2 CH_3), 1.1–2.4 (m, 15 H), 3.76 and 3.80 (2 q, J = 7 Hz, 1 benzylic H), 4.75 and 4.85 (2 m, 2 vinylic H), 7.2 (m, 5 aromatic H).

From the two singlets at 0.71 and 0.92 corresponding to the nonequivalent CH_3 at C-5 in one diastereoisomer and the singlet at 0.82 ppm corresponding to the accidental equivalence of these CH_3 groups in the other diastereoisomer, it can be calculated that the relative ratio of these two stereoisomers is 68:32. The same value is calculated from the two multiplets at 4.75 and 4.85 ppm: ^{13}C NMR (90 MHz) of the diastereoisomeric mixture of amines **14** ($CDCl_3$; the signals were assigned by the off-resonance technic; three sets of signals allowed the determination of the diastereoisomeric ratio): 112.47 and 112.79 (C_8, ratio 68/32) 53.75 and 53.35 (C_2 or C_1 or C_{10}, ratio 66/34), 52.49 and 52.69 (C_2 or C_3 or C_4, ratio 68/32).



***trans*-2-Isopropyl-5,5-dimethylcyclohexylamine (15).** The mixture of amines **14** was reduced and debenzylated over Pd/C as usual, giving a quantitative yield in amine **15** which was analyzed by VPC with the same conditions used for the analysis of amine **9** and compared with synthetic *cis*- and *trans*-2-isopropyl-5,5-dimethylcyclohexylamine (**50**). Amine **15** was shown to be the pure trans isomer. For the *N*-acetyl derivative of amine **15**: $[\alpha]_D$ −19.4° (*c* 1.8, CCl_4); IR (CCl_4) $\nu_{C=O}$ 1640 cm^{-1}; NMR (CCl_4) δ 0.7–0.9 (m, 12 H), 1.0–1.70 (m, 9 H), 1.80 (s, 3 H, CH_3) 3.2 (m, 1 NH).

Determination of the Absolute Configuration of Amine 15 by Horeau's Method. A 54-mg (0.3 mmol) sample of amine **15** was added to a solution of 250 mg (0.8 mmol) of α-phenylbutyric anhydride in 4 mL of pyridine. After the mixture was stirred 2 h at room temperature, 10 mL of benzene and 5 mL of water were added, and the mixture was heated under reflux for 2 h. The excess of α-phenylbutyric acid was carefully neutralized by 14.6 mL of a N/10 sodium hydroxide solution in presence of phenol–phthalin. The aqueous layer was acidified by 15% hydrochloric acid and extracted three times with 10 mL of benzene. After evaporating the solvent, we recovered 183 mg of α-phenylbutyric acid: $[\alpha]_D$ +0.60° *C* 3.7, benzene); esterification yield 54%; optical yield 5.7%.

Imine 17 from (+)-(*R*)-Citronellal and Benzylamine. Imine **17** was prepared as usual from 1.1 g (7.1 mmol) of (+)-(*R*)-citronellal and 0.80 g (7.5 mmol) of benzylamine in 50 mL of benzene in presence of molecular sieves: quantitative yield; NMR ($CDCl_3$) δ 0.90 (d, 3 H, CH_3), 1.56 (s, 3 H, vinylic CH_3), 1.64 (s, 3 H, vinylic CH_3), 1.0–2.5 (m, 7 H), 4.47 (s, 2 benzylic H), 5.05 (br t, 1 vinylic H), 7.20 (m, 5 aromatic H), 7.75 (m, 1 azomethine H).

Cyclization of Imine 17 with Stannic Chloride in Benzene. A 1.4-g (5.8 mmol) sample of imine **17** diluted in 1500 mL of benzene was cyclized in presence of 4 mL of stannic chloride in 100 mL of benzene at room temperature as usual for 24 h. The usual workup gave 1.05 g of amines **18**: 75% yield; NMR ($CDCl_3$) δ 0.91 (d, 3 H, CH_3), 1–3 (m, 13 H), 3.72 (AB system, 2 benzylic H), 4.82 (br s, 2 vinylic H), 7.25 (m, 5 aromatic H).

Hydrogenation of Amines 18. Hydrogenation and debenzylation of amines **18** over Pd/C in EtOH gave a mixture of amines **19–21**: chlorohydrate derivative $[\alpha]_D$ −19.8° ($CHCl_3$, *c* 1.2, $CHCl_3$). The analysis of this mixture was done by VPC with the same conditions as in the case of amines **9**, and the components were identified by comparison with synthetic samples of these amines prepared according to literature procedures: menthylamine[44] (**19**) chlorohydrate, $[\alpha]_D$ −39° (*c* 0.84, $CHCl_3$); neomenthylamine[52] (**21**) chlorohydrate, $[\alpha]_D$ −+19.4° (*c* 2.8, $CHCl_3$); neoisomenthylamine[44,53] (**20**) chlorohydrate $[\alpha]_D$ +20.9°.

The VPC analysis showed the following percentages: 73% of **19**, 9% of **20**, and 18% of **21**.

Imine from (+)-(*R*)-Citronellal and (−)-(*S*)-α-phenylethylamine: NMR of the imine ($CDCl_3$) δ 0.92 (d, 3 H, CH_3), 1–3 (m, 16 H), 4.16 (q, 1 benzylic H), 5.05 (t, 1 vinylic H), 7.25 (m, 5 aromatic H), 7.68 (t, J = 4.5 Hz, 1 azomethine H).

Cyclization of Imine Derived from (+)-(*R*)-Citronellal and (−)-(*S*)-α-Phenylethylamine with Stannic Chloride in Benzene. The cyclization of 1.3 g of imine with stannic chloride under the same conditons gave 0.90 g (70% yield) of cyclic amines: NMR ($CDCl_3$) δ 0.7–2.5 (m, 19 H), 3.83 (q, 1 benzylic H), 4.75 (m, 2 vinylic H), 7.2 (m, 5 aromatic H).

Hydrogenation of *N*-(*S*)-(α-Phenylethyl)-3(*R*)-methyl-6-isopropenylcyclohexylamine. Hydrogenation and debenzylation over Pd/C of the preceding secondary amines gave a mixture of amines **19–21** which was analyzed and identified by VPC as previously: 76% of **19**, 10% of **20**, and14% of **21**.

Imine from (+)-(*R*)-Citronellal and (+)-(*R*)-α-Phenylethylamine. No difference in the NMR spectrum with respect to the preceeding imine.

Cyclization of Imine Derived from (+)-(*R*)-Citronellal and (+)-(*R*)-α-Phenylethylamine with Stannic Chloride in Benzene. NMR of the cyclized product: δ 0.75–2.5 (m, 19 H), 3.75 (q, 1 benzylic H), 4.80 (m, 2 vinylic H), 7.2 (m, 5 aromatic H).

Hydrogenation of *N*-(*R*)-(α-Phenylethyl)-3(*R*)-methyl-6-isopropenylcyclohexylamine. After hydrogenation and debenzylation, the products composition was shown to be: 75% of **19**, 9% of **20**, and 16% of **21**.

Imine (*S*)-22 Derived from *trans*-5,9-Dimethyldeca-5,9-dienal and (−)-(*S*)-α-Phenylethylamine. Imine (*S*)-**22** was prepared as usual from *trans*-5,9-dimethyldeca-5,9-dienal[24,25] and (−)-(*S*)-α-phenylethylamine in a quantitative yield.

Cyclization of Imine (*S*)-22 with Stannic Chloride in Benzene. Cyclization under the usual conditions of 0.95 g (3.3 mmol) of imine **22** yielded 0.670 g (2.4 mmol) of secondary amines **23a–26a**: 250-MHz ^1H NMR δ 3.9–4.0 (2 q in the ratio 77/23, 1 benzylic H), 4.7–4.85 (m, 0.2 H, $=CH_2$), 5.08–5.25 (m, 0.9 H, vinylic H), 7.2 (m, 5 aromatic H); ^{13}C NMR (250 MHz), between 100 and 125 ppm, four signals corresponding to vinylic carbon atoms: 119.3 (14%), 119.4 (51%), 119.92 (25%), 121.22 ppm (10%).

Application of Horeau's Method to the Debenzylated Amines 23α–26α (Z = NH_2). To a solution of 155 mg (0.5 mmol) of α-phenylbutyric anhydride was added, as in the case of amine **15**, 50 mg (0.27 mmol) of the mixture of debenzylated amines. After the hydrolysis of the excess of anhydride, the α-phenylbutyric acid was neutralized with 8.1 mL of N/10 NaOH, and finally 120 mg of this acid was recovered: $[\alpha]_D$ −1.2° (*c* 2.4, benzene); esterification yield 70%; optical yield 5.3%.

Registry No. 4, 64825-78-1; (*E*)-**5**, 77495-26-2; **6**, 77495-27-3; *cis*-**7**, 1193-16-4; *trans*-**7**, 1193-17-5; **7A**, 64869-63-2; **7B**, 64869-65-4; **7C**, 64869-64-3; **7D**, 64869-66-5; (*S*)-**8**, 64825-72-5; **9A** (isomer 1), 64825-75-8; **9A** (isomer 2), 64825-74-7; **9B**, 64808-94-2; *cis*-**10A**, 64869-67-6; *trans*-**10A**, 64869-69-8; *cis*-**10B**, 64869-70-1; *trans*-**10B**, 64869-68-7; **12**, 17920-90-0; (*R*)-**13**, 77495-28-4; (1*R*,1'*R*,2*S*)-**14**, 77495-29-5; (*R*)-*trans*-**15**, 77495-30-8; (*R*)-*trans*-**15** *N*-acetyl derivative, 77495-31-9; (*R*)-**17**, 64825-71-4; **18**, 64825-73-6; **19**, 2216-54-8; **20**, 16934-77-3; **21**, 7231-40-5; (*S*)-(*E*)-**22**, 77495-32-0; **23a**, 77495-33-1; **24a**, 77495-34-2; **25a**, 77495-35-3; **26a**, 77495-36-4; *N*-(3(*R*),7-dimethyl-6-octenylidene)-(*S*)-α-phenylethylamine, 64825-76-9; *N*-(α-phenylethyl)-3-methyl-6-isopropenylcyclohexylamine, 77495-37-5; *N*-(3(*R*),7-dimethyl-6-octenylidene)-(*R*)-α-phenylethylamine, 64825-77-0.