



# Diastereoselective Synthesis of 2,5-Dimethylpyrrolidines and 2,6-Dimethylpiperidines by Reductive Amination of 2,5-Hexanedione and 2,6-Heptanedione with Hydride Reagents

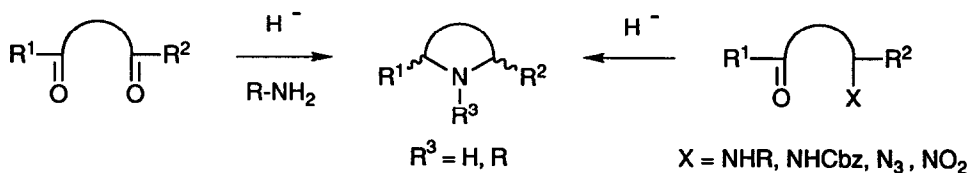
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**Abstract:** The reductive amination of 2,5-hexanedione and 2,6-heptanedione with ammonia and primary amines in the presence of hydride reagents afforded 2,5-dimethylpyrrolidines and 2,6-dimethylpiperidines with variable diastereoselectivity, as the *cis/trans* ratio was affected by the size of the ring formed and the steric and electronic properties of the nitrogen substituent. Increasing the bulkiness of the nitrogen substituent, the *cis* pyrrolidines and the *trans*-piperidines were obtained with enhanced selectivity.

## INTRODUCTION

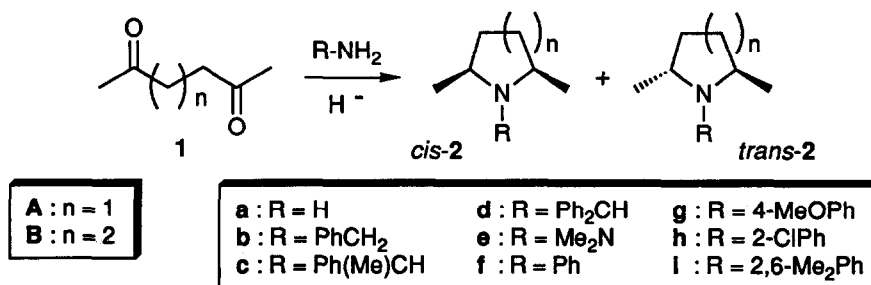
$\alpha,\alpha'$ -Disubstituted cyclic amines have been prepared by the reductive amination<sup>1</sup> of  $\omega$ -diketones with ammonia, ammonium salts or amines in the presence of suitable reducing agents.<sup>2</sup> The intramolecular reductive cyclization of aminoketones formed "*in situ*" from precursors having protected carbonyl or amino function,<sup>3</sup> and the reduction of azidoketones<sup>4</sup> and nitro-ketones<sup>2f,i,l,m,5,6</sup> have been also exploited (Scheme 1). Starting from substrates lacking stereogenic centres in the chain connecting the reactive functions, potentially affecting the relative configuration of the novel stereocentre(s), N-H  $\alpha,\alpha'$ -disubstituted pyrrolidines and piperidines were generally obtained with prevalent or exclusive *cis* configuration, regardless of the nature of the starting compound and the reducing agent (borohydride reagents, electrochemical reduction, catalytic hydrogenation). However, the reaction of ammonium salts with 1,4-diketones in the presence of sodium cyanoborohydride afforded 2,5-disubstituted pyrrolidines as 1:1 mixtures of *cis,trans* isomers<sup>2d</sup> although the *cis*-disubstituted cyclic amines were exclusively obtained from 1,5-diketones<sup>2g</sup> and 1,7-diketones.<sup>2m</sup>



**Scheme 1**

As concerns the preparation of the *N*-substituted cyclic amines, to our knowledge, the reductive amination of diketones with primary amines has been performed only by using potassium tetracarbonylhidydroferrate under an atmosphere of carbon monoxide<sup>2i</sup> and by catalytic hydrogenation.<sup>2a,b,f</sup> However, we could not deduce from these reports the influence of the nitrogen substituent on the *cis:trans* selectivity. The reaction of 2,5-hexanedione with 1,1-dimethylhydrazine and sodium cyanoborohydride has been claimed to afford a 3:1 mixture of *trans*- and *cis*-1-dimethylamino-2,5-dimethylpyrrolidines with modest yield.<sup>2c</sup> On the other hand, indolizidine and pyrrolizidine alkaloids, characterized by the *cis*- $\alpha,\alpha'$ -disubstitution in both rings, were often prepared by applying the intramolecular route, i.e. by reductive cyclization of 2-( $\omega$ -oxoalkyl) cyclic amines.<sup>3,7</sup>

We have examined the reductive amination of 2,5-hexanedione (**1A**) and 2,6-heptanedione (**1B**) with ammonia and primary amines (Scheme 2) by using sodium cyanoborohydride in methanol<sup>8</sup> and sodium triacetoxyborohydride in dichloromethane.<sup>9</sup> By this way we wished to determine the influence of the following factors on the *cis-trans* selectivity: a) the size of the ring formed; b) the nature of the nitrogen substituent; c) the nature of the hydride reagent. The ultimate goal was to find the conditions for the stereoselective synthesis of either the *cis* and *trans* disubstituted cyclic amines, as an alternative route to the reduction of cyclic imines.<sup>10</sup>



**Scheme 2**

## RESULTS AND DISCUSSION

### Reductive Amination of 2,5-Hexanedione (**1A**) and 2,6-Heptanedione (**2B**)

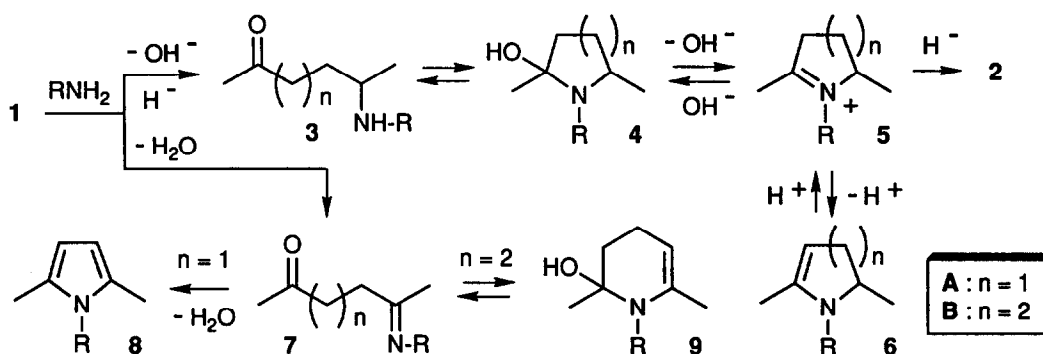
#### Reaction Pathways, Intermediates and Products

The cyclic amines **2** are produced by the consecutive reductive amination steps of the two carbonyl groups of **1**. In the first step are formed the aminoketones **3**, which enter in equilibrium with the cyclic enamines **6** through the cyclic aminol **4** and the iminium ions **5** (Scheme 3). The last species, highly reactive, are most probably the precursors of **2**: in fact, cyclic iminium ions have been detected at high concentrations in the aqueous solutions of 4- and 5-aminoketones, regardless of whether or not the nitrogen atom carried a substituent.<sup>11</sup>

The efficiency of the reaction was found to be dependent principally on the amine. Satisfactory to good yields of **2A,B** were obtained even by using the bulky 1-phenylethylamine and benzhydrylamine and the less nucleophilic aniline and 4-methoxyaniline. Lower yields were obtained by using *N,N*-dimethylhydrazine

(owing to volatility of 2Ae), 2-chloroaniline and 2,6-dimethylaniline. The last two amines were poorly reactive toward 1B and afforded no cyclized product. Furthermore, 4-nitroaniline and O-methylhydroxylamine hydrochloride in the presence of potassium hydroxide did not react with both diketones.

One or more byproducts could be detected by the GC-MS analysis of the reaction mixtures after basic quenching (Scheme 3), although they were never isolated. The nature of the byproducts was dependent on the nature of the starting diketone (i.e. size of the ring formed) and on the nature of the amine. Pyrroles (8) were sometimes obtained from 1A and alkyl or aryl amines, through 7. The reactions with 1B afforded more complex mixtures (especially with 1-phenylethylamine), in which were present variably the mono-imines 7 or (generally) their cyclic tautomers 9, the aminoketones 3B (or 4B) and the cyclic enamines 6B. The reaction of 1A with N,N-dimethylhydrazine was quite complex and gave unexpectedly the bis-hydrazone, together with the mono-hydrazone (7) and the pyrrole (8).



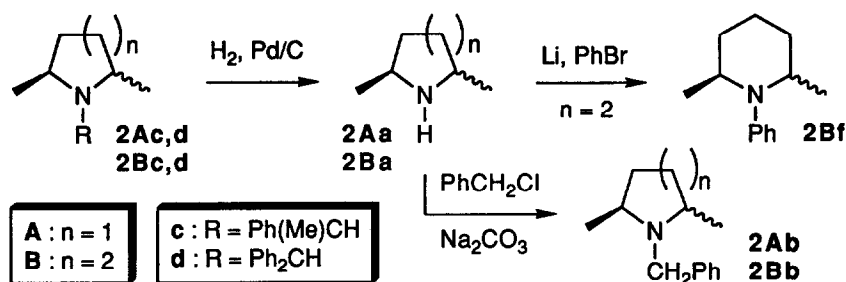
Scheme 3

The influence of the solvent was not examined extensively, but methanol gave usually better results than tetrahydrofuran and dichloromethane when using sodium cyanoborohydride; apart dichloromethane, no other solvent was used for the reactions with sodium triacetoxymethylborohydride, but acetonitrile was the solvent of choice with N,N-dimethylhydrazine.

#### Determination of the Configuration of the Cyclic Amines 2A,B

The *cis/trans* ratio of the products 2A,B was easily determined by glass-capillary GC and GC-MS analysis of the crude reaction mixtures, as it is known that the *cis* isomers of 2,5-dialkylpyrrolidines<sup>10c</sup> and 2,6-dialkylpiperidines<sup>12</sup> have shorter GC retention times than their *trans* isomers. The configuration was then confirmed by <sup>1</sup>H NMR spectroscopy: the ring methine protons of the *trans* pyrrolidines appeared at lower field, as reported for other pyrrolidines,<sup>13</sup> and the methyl protons at higher field with respect to the *cis* isomers. Similarly, the axial methine protons of the *cis* piperidines were observed at higher field than the axial-equatorial methine protons of the *trans* isomers.<sup>14</sup>

The direct comparison with authentic compounds was possible for *cis* and *trans* **2Aa**,<sup>15</sup> **2Ab**,<sup>15b</sup> **2Ac**,<sup>16</sup> **2Ae**,<sup>2c</sup> and **2Af-h**,<sup>17</sup> *trans* **2Ba**,<sup>18</sup> *cis* and *trans* **2Bb**,<sup>15b</sup> and **2Bf,g**.<sup>19</sup> Furthermore, the N-H, N-benzylic, and N-Ph amines could be correlated through interconversion reactions (Scheme 4): catalytic hydrogenation and successive N-benylation was used to convert **2Ac,d** and **2Bc,d** to **2Aa** and **2Ba**, respectively. Commercially available *cis* **2Ba** (95% *cis*) was transformed into *cis* **2Bf** with modest yield (not optimized), by applying a recently reported procedure for the N-phenylation of amines.<sup>20</sup>



Scheme 4

### Influence of the Ring Size and the Nitrogen Substituent on the Diastereoselectivity

**Preparation of 2,5-Dimethylpyrrolidines (2A) from 2,5-Hexanedione (1A).** The pyrrolidines **2Aa,b** (Scheme 2) were obtained with no diastereoselectivity employing ammonium acetate<sup>2d</sup> and benzylamine (Table 1, entries 1, 2), but the prevalence of the *cis* pyrrolidines **2Ac-e** was observed with the more hindered 1-phenylethylamine (entries 3-6), benzhydrylamine (entry 7), and 1,1-dimethylhydrazine (entry 8). In the last case the result contradicted a recent report,<sup>2c</sup> but was consistent with the order of elution (GC-MS) of the diastereoisomers and with the <sup>1</sup>H NMR spectrum of the isolated product (**2Ae**).

The reaction employing 1-phenylethylamine was carried out in different experimental conditions. The *cis:trans* ratio of the pyrrolidine **2Ac** could be only slightly improved by lowering the temperature in experiments with sodium cyanoborohydride, but the reaction was slow at -30° and largely incomplete even after quenching at 0° (entries 3-5). Sodium triacetoxyborohydride afforded only a slightly increased *cis* selectivity (compare entries 3 and 6), but the pyrrole **7c** was formed in a relevant amount (22%). Owing to the stereogenic centre in the nitrogen substituent, two *trans* isomers of **2Ac** were obtained in approximately 2:1 ratio, together with the predominant *cis* isomer, which was eluted first in the glass capillary GC and GC-MS analyses.<sup>16</sup>

The *cis:trans* ratio of the N-aryl pyrrolidines **2Af-i** was affected by the presence of aryl substituents, especially in the *ortho* position(s), as it changed progressively from 30:70 to 64:36 on going from the phenyl to the 2,6-dimethylphenyl substituent (entries 9-12).

**Preparation of 2,6-Dimethylpiperidines (2B) from 2,6-Heptanedione (1B).** The formation of the 2,6-dimethylpiperidines **2Ba-g** (Scheme 2) was characterized by the different or opposite diastereoselectivity with respect to that observed for the corresponding pyrrolidines **2A** (Table 2). The reaction with ammonium bromide and sodium cyanoborohydride afforded a mixture of 83:17 mixture of *cis* and *trans* **2Ba** (entry 13), as

determined by conversion to the known *cis,trans* 2Bb<sup>15b</sup> by Schotten-Baumann N-benzylation. Noteworthy, exclusively *cis* N-H piperidines were obtained applying the same method to unsymmetrically substituted 1,5-diketones.<sup>2g</sup>

Interestingly, we observed that by using benzylic amines and 1,1-dimethylhydrazine the relative amount of the *trans* isomer in the piperidines 2Bb-e increased with increasing the size of the nitrogen substituent (entries 2-7). The diastereoselectivity was affected by the hydride reagent: the use of sodium cyanoborohydride allowed to achieve the highest *trans* selectivity (95%) in the reaction with benzhydrylamine (compare entries 5 and 6), but with 1-phenylethylamine sodium triacetoxyborohydride was the reagent of choice (entries 3, 4). Using 1-phenylethylamine the two *trans* isomers of 2Bc were obtained with a moderate asymmetric induction<sup>21</sup> (entries 3,4). The reaction with N,N-dimethylhydrazine afforded 2Be with moderate *trans*-selectivity (entry 7), whereas aniline and 4-methoxyaniline afforded prevalently the *cis*-piperidines 2Bf,g (entries 8,9). Hence, the observed trend was opposite to that found for the corresponding pyrrolidines.

**Table 1. Preparation of 2,5-Dimethylpyrrolidines (2A) from 2,5-Hexanedione (1A).<sup>a</sup>**

| Entry | R-NH <sub>2</sub>                      | Hydride                             | Solvent                         | Temp.(°C) | Products (Yield %)                           | <i>cis/trans</i> <sup>b</sup> |
|-------|----------------------------------------|-------------------------------------|---------------------------------|-----------|----------------------------------------------|-------------------------------|
| 1     | NH <sub>4</sub> OAc <sup>c</sup>       | NaBH <sub>3</sub> CN                | MeOH                            | 20        | 2Aa (62) <sup>d</sup>                        | 50 : 50                       |
| 2     | PhCH <sub>2</sub> -NH <sub>2</sub>     | NaBH <sub>3</sub> CN                | MeOH                            | -10 to 0  | 2Ab (90) <sup>b</sup> , 7b (9) <sup>b</sup>  | 50 : 50                       |
| 3     | Ph(Me)CH-NH <sub>2</sub>               | NaBH <sub>3</sub> CN                | MeOH                            | 20        | 2Ac (99) <sup>b</sup>                        | 70 : 30 <sup>e</sup>          |
| 4     | Ph(Me)CH-NH <sub>2</sub>               | NaBH <sub>3</sub> CN                | MeOH                            | -10 to 0  | 2Ac (95) <sup>b</sup> , (85) <sup>d</sup>    | 77 : 23 <sup>e</sup>          |
| 5     | Ph(Me)CH-NH <sub>2</sub>               | NaBH <sub>3</sub> CN                | MeOH                            | -30 to 0  | 2Ac (50) <sup>b</sup>                        | 80 : 20 <sup>e</sup>          |
| 6     | Ph(Me)CH-NH <sub>2</sub>               | NaBH(OAc) <sub>3</sub> <sup>f</sup> | CH <sub>2</sub> Cl <sub>2</sub> | 20        | 2Ac (76) <sup>b</sup> , 7c (22) <sup>b</sup> | 76 : 24 <sup>g</sup>          |
| 7     | Ph <sub>2</sub> CH-NH <sub>2</sub>     | NaBH <sub>3</sub> CN                | MeOH                            | -10 to 20 | 2Ad(72) <sup>d</sup> , 7d (4) <sup>b</sup>   | 75 : 25                       |
| 8     | Me <sub>2</sub> N-NH <sub>2</sub>      | NaBH <sub>3</sub> CN                | MeCN                            | 20        | 2Ae (65) <sup>b,h</sup> (35) <sup>d</sup>    | 80 : 20                       |
| 9     | Ph-NH <sub>2</sub> (1)                 | NaBH <sub>3</sub> CN                | MeOH                            | -10 to 20 | 2Af (99) <sup>b</sup> (95) <sup>i</sup>      | 30 : 70                       |
| 10    | 4-MeOPh-NH <sub>2</sub>                | NaBH <sub>3</sub> CN                | MeOH                            | -10 to 20 | 2Ag (83) <sup>i</sup> , 7g (4) <sup>b</sup>  | 40 : 60                       |
| 11    | 2-ClPh-NH <sub>2</sub>                 | NaBH <sub>3</sub> CN                | MeOH                            | -10 to 20 | 2Ah (28) <sup>b</sup>                        | 55 : 45                       |
| 12    | 2,6-Me <sub>2</sub> Ph-NH <sub>2</sub> | NaBH <sub>3</sub> CN                | MeOH                            | 20        | 2Ai (35) <sup>b</sup>                        | 64 : 36                       |

(a) Unless otherwise indicated the reactions were performed by stirring overnight equimolar amounts of reagents and acetic acid, and 0.25 equiv. KOH. (b) Determined by GC-MS analysis of the reaction mixture after basic quenching. (c) From ref. 2d: reaction performed with 1.1 equiv. NH<sub>4</sub>OAc and 0.25 equiv. KOH. (d) Yield of product isolated by chromatography or distillation. (e) Two *trans* isomers were produced (*ca.* 1:2 ratio). (f) 3 equiv. (g) Two *trans* isomers were produced (1:3 ratio). (h) The reaction mixture contained also the pyrrole and the mono- and bis-hydrazones. (i) Yield of crude isolated product.

**Table 2.** Preparation of 2,6-Dimethylpiperidines (2B) from 2,6-Heptanedione (1B).<sup>a</sup>

| Entry | R-NH <sub>2</sub>                  | Hydride                             | Solvent                         | Temp.(°C) | Products (Yield %)                                                   | <i>cis:trans</i> <sup>b</sup> |
|-------|------------------------------------|-------------------------------------|---------------------------------|-----------|----------------------------------------------------------------------|-------------------------------|
| 1     | NH <sub>4</sub> Br                 | NaBH <sub>3</sub> CN                | MeOH                            | 20        | 2Ba (70) <sup>c</sup>                                                | 83 : 17 <sup>c</sup>          |
| 2     | PhCH <sub>2</sub> -NH <sub>2</sub> | NaBH <sub>3</sub> CN <sup>d</sup>   | MeOH                            | -10 to 20 | 2Bb (98) (95) <sup>e</sup>                                           | 18 : 82                       |
| 3     | Ph(Me)CH-NH <sub>2</sub>           | NaBH <sub>3</sub> CN <sup>d</sup>   | MeOH                            | -10 to 20 | 2Bc (80) <sup>b</sup> 6c (10) <sup>b</sup>                           | 30 : 70 <sup>f</sup>          |
| 4     | Ph(Me)CH-NH <sub>2</sub>           | NaBH(OAc) <sub>3</sub> <sup>g</sup> | CH <sub>2</sub> Cl <sub>2</sub> | 20        | 2Bc (85) <sup>e</sup> , 6c (5) <sup>b</sup>                          | 18 : 82 <sup>h</sup>          |
| 5     | Ph <sub>2</sub> CH-NH <sub>2</sub> | NaBH <sub>3</sub> CN <sup>d</sup>   | MeOH                            | -10 to 20 | 2Bd (77) <sup>i</sup> , 9d (7) <sup>b</sup>                          | 05 : 95                       |
| 6     | Ph <sub>2</sub> CH-NH <sub>2</sub> | NaBH(OAc) <sub>3</sub> <sup>g</sup> | CH <sub>2</sub> Cl <sub>2</sub> | 20        | 2Bd (77) <sup>b</sup><br>9d (10) <sup>b</sup> , 3d (12) <sup>b</sup> | 10 : 90                       |
| 7     | Me <sub>2</sub> N-NH <sub>2</sub>  | NaBH(OAc) <sub>3</sub> <sup>g</sup> | MeCN                            | 20        | 2Be (75) <sup>b,j</sup> (35) <sup>i</sup><br>9e (15%) <sup>b</sup>   | 30 : 70                       |
| 8     | Ph-NH <sub>2</sub>                 | NaBH <sub>3</sub> CN <sup>d</sup>   | MeOH                            | 20        | 2Bf (97) <sup>b</sup> , (94) <sup>e</sup>                            | 65 : 35                       |
| 9     | 4-MeOPh-NH <sub>2</sub>            | NaBH(OAc) <sub>3</sub> <sup>g</sup> | CH <sub>2</sub> Cl <sub>2</sub> | 20        | 2Bg (92) <sup>b</sup> , (68) <sup>h</sup><br>9g (5) <sup>b</sup>     | 70 : 30                       |

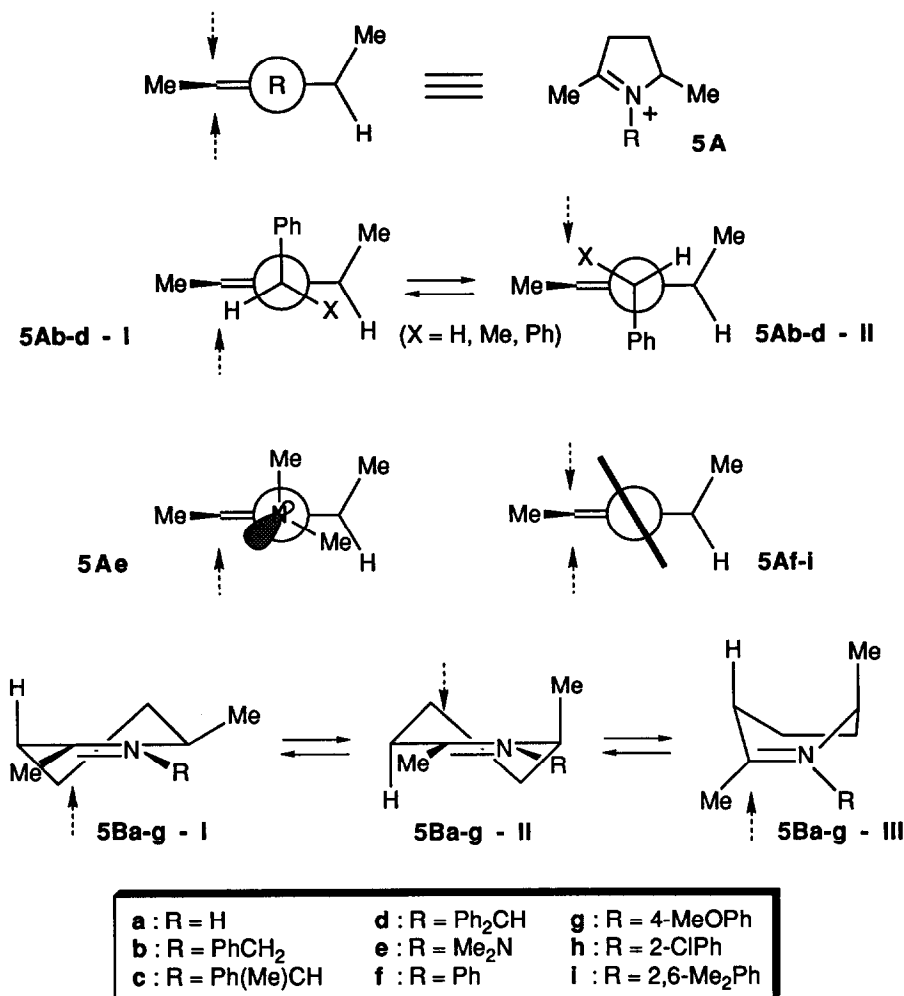
(a) All the reactions were carried out by stirring overnight equimolar amounts of the reagents. (b) Determined by GC-MS analysis of the reaction mixture after basic quenching. (c) The yield and *cis/trans* ratio refer to the N-benzyl derivative 2Bb isolated after treatment of the reaction mixture with benzyl chloride and sodium carbonate in acetone-water. (d) The reaction was performed in the presence of acetic acid (1 equiv.) and potassium hydroxide (0.25 equiv.). (e) Yield of crude isolated product. (f) Two *trans* isomers were produced in 70:30 ratio. (g) The reaction was carried out with 3 molar equiv. of hydride and 1 equiv. of acetic acid. (h) Two *trans* isomers were produced in 73:27 ratio. (i) Yield of product isolated by chromatography or distillation. (j) 3-Methylcyclohex-2-en-1-one (ca 10%) was produced.

### Stereochemical Models

We have made attempts to rationalize the stereoselectivity observed by examining stereochemical models for the hydride addition to the cyclic iminium ions **5A,B** (Figure 1).

The five-membered ions **5A** have a substantially planar ring. The *cis,trans* selectivity is affected by the steric and stereoelectronic effects operating in the hydride addition to the many conformations that are obtained by rotation around the N-R bond. When the nitrogen substituent R is a hydrogen atom or a small alkyl group, the addition can occur from either above and below the plane of **5A**. By considering the N-benzylic salts **5Ab-d**, the relative stability of the conformations **I** and **II** is affected by the substituent X at the benzylic carbon: apart when X=H, **I** is apparently more stable than **II**, which suffers from the non bonded interaction of X and the methyl substituent at the C<sub>2</sub> ring carbon.

Stereoelectronic effects direct the addition of the hydride ion *anti* to the phenyl group in either the conformations **I** and **II** of **5Ab-d**, since by this way the overlap of the parallel C=N  $\pi^*$  and C-Ph  $\sigma^*$  orbitals allows to attain the most favourable transition states, according to the Felkin-Anh model for the nucleophilic addition to  $\alpha$ -chiral carbonyl groups.<sup>22</sup> The hydride additions to **I** and **II** provide the opposite configurations of the amines **2A**, so that *cis* pyrrolidines can be obtained only with bulky benzylic amines.



**Figure 1.** Stereochemical models for the hydride addition to iminium ions **5A,B**.

The prevalent formation of *cis* 1-dimethylaminopyrrolidine **2Ae** suggested that only the steric properties of the dimethylamino group were important, as the +M electronic effect does not stabilize the iminium ion **5Ae**. The hydride addition should occur preferentially from below the plane to the conformation shown in Figure 1.

The diastereoselectivity observed in the addition to the N-aryl iminium ions is more difficult to rationalize, owing to the particular steric and electronic properties of the aryl groups. When *ortho*-substituents are not present in the aryl group, i.e. in the case of **5Af,g**, the addition takes place apparently from above the plane, affording the *trans* isomers **2Af-i**. Perhaps in such conformations the non bonded interactions of the R (Ar) and C<sub>2</sub> methyl group are reduced by N-aryl twisting, despite the loss of the C=N-Ph resonance stabilization. This assumption is supported by the calculations and X-ray crystal structures reported for N-methylacetanilides, where twist angles approach 90°. <sup>23</sup> However, the presence of *ortho*-substituents in the N-aryl substituent constituted a serious obstacle to the addition from above the plane and causes a slight preference for the alternative addition from below the plane, producing the *cis* isomers **2Ah,i**.

The *cis/trans* selectivity in the formation of the piperidines **2B** from **5B** was also the result of an interplay of steric and stereoelectronic effects. The conformations **I-III** should be considered (Figure 1). The hydride addition to **I** and **II** should take place from below and above the ring plane, respectively, in order to provide chair-like transition states. <sup>3b,24</sup> The preferred conformation is **I** when the nitrogen substituent R is hydrogen, owing to the equatorial disposition of the C<sub>6</sub> methyl group: in fact, *cis* **2Ba** was preferentially obtained by using ammonium bromide. However, the reactions with benzylic amines and N,N-dimethylhydrazine gave instead **2Bb-e** with prevalent *trans* configuration through the addition to **II**, because the steric interactions between the bulky R group and the C<sub>6</sub> methyl substituent are too severe in **I**. This interpretation is analogous to that proposed to explain the inversion of stereoselectivity observed in the hydride reduction of 2,6-dialkyl-3,4,5,6-tetrahydropyridines, when trimethylaluminum, acting as a nitrogen substituent, was added. <sup>10d,e,h,i</sup>

To explain the moderate *cis* selectivity in the formation of the 1-arylpiperidines **2Bf,g** we suppose that the iminium ions **5Bf,g** exist preferentially in the conformation **I** (R=Ar), where the steric interactions could be reduced by twisting the planar aryl group. Alternatively, the *cis* isomers might derive through the addition of the hydride to the boat-like conformation **III** from below the plane, *anti* to the axial "allylic" C-H and C-Me bonds. An analogous boat conformation has been proposed to explain the *cis* selective reduction of 1-Boc-2-methyl-4-chloro-6-undecyl-3,6-dihydropyridinium ion. <sup>10k</sup>

## CONCLUSIONS

The reductive amination of 2,5-hexanedione (**1A**) and 2,6-heptanedione (**1B**) with ammonium salts and primary amines by using borohydrides as reducing agents, allowed to prepare 2,5-dimethylpyrrolidines (**2A**) and 2,6-dimethylpiperidines (**2B**) having H, alkyl, aryl, and dimethylamino substituents at nitrogen. It was established that the nature of the diketone and the amine had a marked influence on the *cis:trans* ratio of **2A,B**. Increasing the size of the nitrogen substituent, the *cis* pyrrolidines and the *trans* piperidines were produced with enhanced diastereoselectivity. The prevalent diastereoisomers could be generally isolated with high purity by chromatography or crystallization of the picrate or hydrochloride salts.

The use of bulky benzylic amines, followed by hydrogenolysis of the benzylic group, allowed to prepare the N-H amines, i.e. *cis*-2,5-dimethylpyrrolidine (**2Aa**) and *trans*-2,6-dimethylpiperidine (**2Ba**) from **1A** and **1B**, respectively (Scheme 4). On the other hand, *cis*-**2Ba** is available from **1B** by using ammonium bromide.

## EXPERIMENTAL SECTION

## General Information

$^1\text{H}$  NMR spectra were recorded on a Varian ET90 (90 MHz) or a Varian Gemini 300 (300 MHz) instruments in deuteriochloroform.  $^{13}\text{C}$  NMR spectra were taken on the latter instrument. IR spectra were recorded on Perkin-Elmer 682. Capillary gas chromatography was performed on a Carlo Erba HRGC 5300 Mega Series apparatus using an OV1 column (15 m, 0.1  $\mu\text{m}$  film thickness) or a Supelcowax column (30 m, 0.25  $\mu\text{m}$  film thickness). GC-MS analysis were performed on a Hewlett Packard 5890 spectrometer (70 eV) connected with a Hewlett Packard 5970B gaschromatograph by using a HP-1 column.

2,5-Hexanedione (**1A**), all the amines, sodium cyanoborohydride, and sodium triacetoxyborohydride were purchased from Aldrich. 2,6-Heptanedione (**1B**) was prepared by following a literature procedure.<sup>25</sup> The amines were purified by distillation prior to use.

**Reductive Amination with Sodium Cyanoborohydride (Typical Procedure). Preparation of 1-(1-Phenylethyl)-2,5-*cis*-dimethylpyrrolidine (2Ac):** To a magnetically stirred solution of 1-phenylethylamine (1.28 mL, 10 mmol), acetic acid (0.66 g, 1.1 mmol), and potassium hydroxide (0.1 g, 0.25 mmol) in methanol (5 mL), cooled at ca  $-10^\circ$  by immersion in a bath of ice and hydrochloric acid, was added **1A** (1.2 mL, 10 mmol) and sodium cyanoborohydride (0.63 g, 10 mmol). After stirring overnight the temperature spontaneously raised to  $20^\circ$ , and the reaction mixture was quenched with 4 N hydrochloric acid (10 mL). Methanol was removed under reduced pressure and the aqueous solution was washed with diethyl ether (10 mL). The aqueous solution was made basic by careful addition of potassium carbonate, and the organic bases were extracted with diethyl ether (3 X 10 mL), washed with brine, dried with sodium sulphate and concentrated at reduced pressure to leave **3c** as an oil (1.72 g (85%). GC-MS analysis showed that the product **2Ac** was a mixture of three diastereoisomers (A, B, C) in a ratio 77:14:9, in the order of increasing retention times. Two successive flash-chromatographies on silica gel column, preliminarily doped with triethylamine (10 mL for 100 g of  $\text{SiO}_2$ ) in cyclohexane solution, allowed to separate partially the isomers. One fraction (1.1 g) was a mixture of the three isomers in a ratio 93.5:2.5:4; formation of the picrate from diethyl ether, recrystallization from diethyl ether-ethyl acetate, and basic treatment afforded a sample (0.80 g) of the isomer A (*cis*, 98% pure by GC-MS) identified as *cis* **2Ac**<sup>16</sup>;  $^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.1-7.5 (m, 5 H, Ph), 3.95 (q, 1 H, PhCHMe), 2.90 (m, 2 H, CHMe), 1.20-1.90 (m, 4 H,  $\text{CH}_2$ ), 1.43 (d, 3 H, PhCHMe, J 6 MHz), 1.05 and 0.87 ppm (2d, J 6 Hz, 6 H, CHMe). Another chromatographic fraction (80 mg) was a 5:95 mixture of isomers A and C, the last being one of the *trans* isomers;<sup>16</sup>  $^1\text{H}$  NMR (90 MHz) of C:  $\delta$  7.1-7.5 (m, 5 H, Ph), 3.72 (q, 1 H, PhCH), 3.23 (m, 2 H, CHMe), 1.2-2.3 (m, 4 H,  $\text{CH}_2$ ), 1.40 (d, J 6 Hz, 3 H, PhCHMe), 0.70 ppm (d, J 6 Hz, 6 H, CHMe). GC-MS m/e (relative intensity) 203 ( $\text{M}^+$ , 12), 84 (100), 188 (95), 105 (76), 106 (18) 77 (15), 79 (14), 189 (13), 126 (10).

The following cyclic amines were prepared (Tables 1 and 2):

**1-Benzyl-2,5-dimethylpyrrolidine (2Ab):**<sup>15b</sup> GC-MS m/e (relative intensity) 189 ( $\text{M}^+$ , 5), 91 (100), 174 (76), 65 (11), 175 (9), 92 (7), 41 (6), 42 (4).  $^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.30 (m, Ph), 3.70 (AB q, PhCH<sub>2</sub>, *trans* isomer) 3.74 (s, PhCH<sub>2</sub>, *cis*), 3.05 (m, CHMe, *trans*), 2.62 (m, CHMe, *cis*), 1.20-2.0 (m,  $\text{CH}_2$ ), 1.04 (d, J 6 Hz, CHMe, *cis*), 0.97 ppm (d, J 6 Hz, CHMe, *trans*).

**1-Diphenylmethyl-2,5-dimethylpyrrolidine (2Ad):** GC-MS *m/e* (relative intensity) 265 ( $M^+$ , 3), 167 (100), 1165 (26), 250 (18), 168 (14), 152 (12), 166 (9), 188 (8), 55 (8). The *cis* and *trans* isomers were separated by flash-chromatography, but the *trans* isomer was not obtained pure.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.15-7.50 (m, 10 H, Ph), 4.92 (s, 1 H,  $\text{Ph}_2\text{CH}$ ), 2.98 (m, 2 H,  $\text{CHMe}$ ), 1.85 (m, 2 H,  $\text{CH}_2$ ), 1.46 (m, 2 H,  $\text{CH}_2$ ), 0.97 (d, J 6 Hz,  $\text{CHMe}$ ) (*cis* isomer); 4.70 (s,  $\text{Ph}_2\text{CH}$ ), 3.23 (m, 2 H,  $\text{CHMe}$ ), 0.65 ppm (d, J 6 Hz,  $\text{CHMe}$ ) (*trans* isomer). Found: C 84.62, H 9.60, N 5.78 %;  $\text{C}_{17}\text{H}_{23}\text{N}$  requires: C 84.59, H 9.61, N 5.80 %.

**1-Dimethylamino-2,5-dimethylpyrrolidine (2Ae):**<sup>2c</sup> GC-MS *m/e* (relative intensity) 142 ( $M^+$ , 59), 127 (100), 85 (33), 58 (16), 55 (13), 59 (11), 84 (10), 87 (10), 71 (10), 70 (10).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.43 (m,  $\text{CHMe}$ , *trans*), 2.91 (m,  $\text{CHMe}$ , *cis*), 2.59 (s,  $\text{NMe}_2$ , *trans*), 2.52 (s,  $\text{NMe}_2$ , *cis*), 1.25-2.1 (m,  $\text{CH}_2$ ), 1.14 (d, J 6 Hz,  $\text{CHMe}$ , *cis*), 1.11 ppm (d, J 6 Hz,  $\text{CHMe}$ , *trans*).

**1-Phenyl-2,5-dimethylpyrrolidine (2Af):**<sup>17</sup> GC-MS *m/e* (relative intensity) 175 ( $M^+$ , 18), 160 (100), 77 (25), 104 (15), 161 (12), 118 (11), 51 (11), 119 (7), 41 (6).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.20 (m, Ph), 6.60 (m, Ph), 3.98 (m,  $\text{CHMe}$ , *trans*), 3.75 (m,  $\text{CHMe}$ , *cis*), 1.5-2.3 (m,  $\text{CH}_2$ ), 1.27 (d, J 6 Hz,  $\text{CHMe}$ , *cis*), 1.08 ppm (d, J 6 Hz,  $\text{CHMe}$ , *trans*).

**1-(4-Methoxyphenyl)-2,5-dimethylpyrrolidine (2Ag):**<sup>17</sup> GC-MS *m/e* (relative intensity) 205 ( $M^+$ , 22), 190 (100), 134 (16), 191 (13), 149 (12), 77 (10), 122 (9), 41 (7).  $^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  6.4-7.0 (m, aryl), 3.5-4.2 (m,  $\text{CHMe}$ ), 3.75 (s, OMe), 1.4-2.5 (m,  $\text{CH}_2$ ), 1.22 (d, J 6 Hz,  $\text{CHMe}$ , *cis*), 1.07 ppm (d, J 6 Hz,  $\text{CHMe}$ , *trans*).

**1-(2-Chlorophenyl)-2,5-dimethylpyrrolidine (2Ah):**<sup>17</sup> was not isolated: GC-MS *m/e* (relative intensity) 209 ( $M^+$ , 11), 194 (100), 196 (33), 138 (16), 11 (12), 195 (12), 75 (9), 140 (8), 41 (8), 152 (6).

**1-(2,6-Dimethylphenyl)-2,5-dimethylpyrrolidine (2Ai)** was not isolated: GC-MS *m/e* (relative intensity) 203 ( $M^+$ , 14), 188 (100), 132 (19), 189 (15), 77 (12), 79 (11), 202 (10), 105 (9), 148 (9), 117 (7).

**2,6-Dimethylpiperidine (2Ba):**<sup>18</sup> GC-MS *m/e* (relative abundance) 113 ( $M^+$ , 7), 98 (100), 70 (31), 56 (20), 55 (12), 11 (6), 99 (6), 84 (4), 81 (4). The compound was not isolated, but converted to **4b**.

**1-Dimethylamino-2,6-dimethylpiperidine (2Be)** GC-MS *m/e* (relative intensity) 156 ( $M^+$ , 88), 141 (100), 59 (58), 87 (32), 85 (16), 58 (15), 55 (15), 60 (12), 157 (11), 71 (9), 86 (9). The two isomers could be separated in part by flash-chromatography ( $\text{SiO}_2$ , hexane-ether).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  2.55 (m, 8 H, *CHMe* and *NMe*<sub>2</sub>), 1.2-1.8 (m, 6 H,  $\text{CH}_2$ ), 1.10 ppm (d, *J* 6 Hz, 6 H, *CHMe*) (*cis* isomer); 3.25 (m, 2 H, *CHMe*), 2.57 (s, 6 H, *NMe*<sub>2</sub>), 1.25-1.75 (m, 6 H,  $\text{CH}_2$ ), 1.10 ppm (d, *J* 6 Hz, 6 H, *CHMe*) (*trans* isomer).

**1-Phenyl-2,6-dimethylpiperidine (2Bf):**<sup>19</sup> GC-MS *m/e* (relative intensity) 189 ( $M^+$ , 13), 174 (100), 77 (24), 104 (16), 175 (13), 132 (10), 120 (10), 119 (10), 118 (10), 51 (9).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.9-7.4 (m, Ph), 3.50 (m, *CHMe*, *trans*), 2.95 (m, *CHMe*, *cis*), 1.3-2.0 (m,  $\text{CH}_2$ ), 0.93 (d, *J* 6 Hz, *CHMe*, *trans*), 0.80 ppm (d, *J* 6 Hz, *CHMe*, *cis*).

**1-(4-Methoxyphenyl)-2,6-dimethylpiperidine (2Bg):**<sup>19</sup> GC-MS *m/e* (relative intensity) 219 ( $M^+$ , 16), 204 (100), 134 (20), 149 (19), 205 (12), 77 (9), 41 (8), 162 (5).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.8-7.3 (m, Ar), 3.80 (s, OMe, *cis*), 3.79 (s, OMe, *trans*), 3.40 (m, *CHMe*, *trans*), 2.75 (m, *CHMe*, *cis*), 1.25-1.95 (m,  $\text{CH}_2$ ), 0.90 (d, *J* 6 Hz, *CHMe*, *trans*), 0.73 ppm (d, *J* 6 Hz, *CHMe*, *cis*).

**Preparation of 2Aa and 2Ab from 2Ac:** A mixture of 2Ac (*cis:trans* 90:10, 2.14 g, 10.5 mmol) and 10% palladium hydroxide on carbon (1 g) in diethyl ether (20 mL) was shaken in a Parr apparatus at the pressure of 30 psi of  $\text{H}_2$  for 28 h. The organic solution was filtered, then added to a saturated solution of hydrogen chloride in diethyl ether at 0°, obtaining a white precipitate of 2Aa hydrochloride (0.88 g, 63%): m.p. 178-182°; lit.<sup>16b</sup> 202-203° (*cis*), 187-188° (*trans*); lit.<sup>16d</sup> 187-189° (2*R*,5*R trans*); lit.<sup>15e</sup> 197-200° (2*R*,5*R trans*); lit.<sup>16f</sup> 200-203° (2*R*,5*R trans*); lit.<sup>16g</sup> 200-201° (2*S*,5*S trans*).  $^1\text{H}$  NMR (60 MHz,  $\text{CDCl}_3$ )  $\delta$  9.6 (br s, 2 H,  $\text{NH}_2^+$ ), 3.70 (m, 2 H, *CHMe*), 1.7-2.4 (m, 4 H,  $\text{CH}_2\text{CH}_2$ ), 1.60 ppm (d, *J* 6 Hz, 6 H, *CHMe*).  $^{13}\text{C}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  17.91 (Me), 30.77 ( $\text{C}_3$  and  $\text{C}_4$ ), and 56.25 ppm ( $\text{C}_2$  and  $\text{C}_5$ ) attributed to the *cis* isomer; minor absorptions at  $\delta$  18.13, 32.31, and 55.01 ppm were assigned to *trans* salt.<sup>15c</sup> Treatment of 2Aa hydrochloride with potassium carbonate (3 equiv.) and benzyl chloride (1 equiv.) in water-acetone mixture (1:1) with magnetic stirring overnight gave *cis* 2Ab as an oil, identified by the  $^1\text{H}$  NMR spectrum.<sup>15b</sup>

**Preparation of 2Ba from 2Bd:** A mixture of 2Bd (*trans:cis* 90:10, 4.3 g, 15.4 mmol) and 10% Pd/C (0.2 g) in diethyl ether (20 mL) was

1.20 g (32 %). The GC-MS analysis showed a *cis/trans* ratio 96:4, the *cis* isomer being eluted first. The 300 MHz  $^1\text{H}$  NMR spectrum confirmed the absorptions previously assigned to the *cis* and *trans* isomers.  $^{13}\text{C}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.65, 23.50, 34.80, 56.85, 124.37, 125.97, 128.55 ppm (*cis* isomer).

**Acknowledgement:** The authors are grateful to MURST (Roma) for financial support.

## REFERENCES AND NOTES

- (a) Emerson, W. F. *Org. React. (N. Y.)* **1948**, *IV*, 174. (b) Moore, M. L. *Org. React. (N. Y.)* **1949**, *V*, 301. (c) Klyuev, M. V.; Khidekel, M. L. *Russ. Chem. Rev. (Engl. Transl.)* **1980**, *49*, 14.
- (a) Skita, A.; Keil, F. *Chem. Ber.* **1929**, *62*, 1142. (b) Schwogler, E. J.; Adkins, H. *J. Am. Chem. Soc.* **1939**, *61*, 399. (c) Nelsen, S. F.; Weisman, G. R. *Tetrahedron Lett.* **1973**, 2321. (d) Jones, T. H.; Franko, J. B.; Blum, M. S.; Fales, H. M. *Tetrahedron Lett.* **1980**, *21*, 789. (e) Jones, T. H.; Blum, M. S.; Fales, H. M.; Thompson, C. R. *J. Org. Chem.* **1980**, *45*, 4778. (f) Baliah, V.; Jeyaraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379. (g) Abe, K.; Okumura, H.; Tsugoshi, T.; Nakamura, N. *Synthesis* **1984**, 597. (h) Abe, K.; Tsugoshi, T.; Nakamura, N. *Bull. Chem. Soc. Jpn* **1984**, *57*, 3351. (i) Shim, S. C.; Huh, K. T.; Kim, K. D.; Oh, D. H.; Kim, W. S. *Taehan Hwahakhoe Chi* **1986**, *30*, 389; *C.A.* **1987**, *106*, 138194e. (j) Pienemann, T.; Schafer, H.-J. *Dechema Monogr.* **1988**, *112*, 367. (k) Whitesell, J. K.; Minton, M. A.; Chen, K.-M. *J. Org. Chem.* **1988**, *53*, 5384. (l) Janowitz, A.; Vavrecka, M.; Hesse, M. *Helv. Chim. Acta* **1991**, *74*, 1352. (m) Vavrecka, M.; Janowitz, A.; Hesse, M. *Tetrahedron Lett.* **1991**, *32*, 5543. (n) Reitz, A. B.; Baxter, E. W. *Tetrahedron Lett.* **1991**, *47*, 6777. (o) Zou, W.; Szarek, W. A. *Carbohydr. Res.* **1993**, *242*, 311. (p) Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1542.
- (a) Takano, S.; Otaki, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1983**, 1172. (b) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289. (c) Royer, J.; Husson, H.-P. *J. Org. Chem.* **1985**, *50*, 670. (d) Iida, H.; Watanabe, Y.; Kibayashi, C. *Tetrahedron Lett.* **1986**, *27*, 5513. (e) Yamaguchi, R.; Hata, E.; Matsuki, T.; Kawanisi, M. *J. Org. Chem.* **1987**, *52*, 2094. (f) Ryckman, D. M.; Stevens, R. V. *J. Org. Chem.* **1987**, *52*, 4274. (g) Ohta, T.; Sato, N.; Kimura, T.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 4305. (h) Jegham, S.; Das, B. C. *Tetrahedron Lett.* **1989**, *30*, 2801. (i) Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396. (j) Watanabe, Y.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 4088. (k) Nagasaka, T.; Kato, H.; Shioda, M.; Hikasa, H.; Hamaguchi, F. *H*

- B. *J. Am. Chem. Soc.* **1992**, *114*, 7321; (f) Takaoka, Y.; Kajimoto, T.; Wong, C.-H. *J. Org. Chem.* **1993**, *58*, 4809.
5. (a) Kloetzel, M. C. *J. Am. Chem. Soc.* **1947**, *69*, 2271. (b) Brown, E.; Dhal, R.; Casals, P. F. *Tetrahedron* **1972**, *28*, 5607. (c) Brown, E.; Bonte, A. *Tetrahedron Lett.* **1975**, 2881. (d) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 103. (e) Cariou, M. Hazard, R.; Jubault, M.; Tallec, A. *Can. J. Chem.* **1983**, *61*, 2359. (f) Vavrecka, M.; Hesse, M. *Helv. Chim. Acta*, **1989** *72*, 847. (g) Paterne, M.; Dhal, R.; Brown, E. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1321. (h) Vavrecka, M.; Hesse, M. *Helv. Chim. Acta* **1991**, *74*, 438.
6. A related approach involves the reduction of keto-nitronates and keto-oximes: (a) Miyashita, M.; Awen, B. Z. E.; Yoshikoshi, A. *Chem. Lett.* **1990**, 239. (b) Tronchet, J. M. J.; Zosimo-Landolfo, G.; Balkadjian, M.; Ricca, A.; Zsély, M.; Barbalat-Rey, F.; Cabrini, D.; Lichtle, P.; Geoffroy, M. *Tetrahedron Lett.* **1991**, *32*, 4129. (c) Oppolzer, W.; Merifield, E. *Helv. Chim. Acta* **1993**, *76*, 957.
7. The pyrrolizidine alkaloid *xenovenine* could be obtained with the *trans,trans* configuration by the reaction of 5-nitro-2,8-pentadecanedione with ammonium acetate and hydride reagents,<sup>2k</sup> as well as by the reaction of 2,5,8-pentadecanetrione with ammonium acetate and sodium cyanoborohydride.<sup>2e,l,m</sup>
8. Lane, C. F. *Synthesis* **1975**, 135.
9. Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595.
10. The reduction of isolated  $\alpha,\alpha'$ -disubstituted cyclic imines and enamines allows the selective preparation of either *cis* and *trans* pyrrolidines or piperidines by the proper choice of the reducing agents and reaction conditions: (a) Hill, R. K.; Yuri, T. *Tetrahedron* **1977**, *33*, 1569. (b) Astier, A.; Plat, M. M. *Tetrahedron Lett.* **1978**, 2051. (c) Jones, H. T.; Blum, M. S.; Fales, H. M. *Tetrahedron Lett.* **1979**, 1031. (d) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831. (e) Nakazono, Y.; Yamaguchi, R.; Kawanisi, M. *Chem. Lett.* **1984**, 1129. (f) Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229. (g) Marco, J. L. *J. Heterocyclic Chem.* **1986**, *23*, 1059. (h) Yamaguchi, R.; Nakazono, Y.; Matsuki, T.; Hata, E.; Kawanisi, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 215. (i) Wasserman, H. H.; Rusiecki, V. *Tetrahedron Lett.* **1988**, *29*, 4977. (j) Bacos, D.; Célérier, J. P.; Marx, E.; Saliou, C.; Lhommet, G. *Tetrahedron Lett.* **1989**, *30*, 1081. (k) Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1991**, *56*, 2506. (l) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 2911. Furthermore, the presence of a hydroxy group in the ring substituent allowed the preparation of *trans* 2,5-disubstituted pyrrolidines.<sup>3a,r,10g</sup>
11. (a) Brandange, S.; Lindblom, L.; Pilotti, A.; Rodriguez, B. *Acta Chem. Scand.* **1983**, *B 37*, 617. (b) Brandange, S.; Rodriguez, B. *Acta Chem. Scand.* **1983**, *B 37*, 643. (c) Mohrle, H.; Dwuletzki, H. Z. *Naturforsch.* **1986**, *41b*, 1323. (d) McClelland, R. A

15. *Cis* and racemic *trans* 3a: (a) Overberger, C.G.; Palmer, L. C.; Marks, B. S.; Byrd, N. R. *J. Am. Chem. Soc.* **1955**, *77*, 4100. (b) Hill, R. K.; Chan, T.-H. *Tetrahedron* **1965**, *21*, 2015. (c) Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1981**, *46*, 3920. *Trans*-(*-*)-2R,5R 3a: (d) Perrone, R.; Tortorella, V. *Tetrahedron* **1978**, *34*, 2533. (e) Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, 28 2083. (f) Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755. *Trans*-(*+*)-2S,5S-3a: (g) Yamazaki, T.; Gimi, R.; Welch, J. T. *Synlett* **1991**, 573.
16. Zwaagstra, M. E.; Meetsma, A.; Feringa, B. *Tetrahedron: Asymmetry* **1993**, *4*, 2163.
17. Barluenga, J.; Najera, C.; Yus, M. *J. Heterocyclic Chem.* **1981**, *18*, 1297.
18. Hill, R. K.; Chan, T. H.; Joule, J. A. *Tetrahedron* **1965**, *21*, 147.
19. Barluenga, J.; Najera, C.; Yus, M. *Synthesis* **1979**, 896.
20. Kanth, J. V. B.; Periasamy, M. *J. Org. Chem.* **1993**, *58*, 3156.
21. The distribution of the diastereoisomers was similar by using (S)-valine methyl ester, although a good level of asymmetric induction was obtained on 4- and 5-ketoaldehydes<sup>2p</sup>
22. (a) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145. The asymmetric induction in the nucleophilic addition to homochiral cyclic iminium ions was similarly explained: (c) Polniaszek, R. P.; Kaufman, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 4859. (d) Polniaszek, R. P.; Dillard, L. W. *Tetrahedron Lett.* **1990**, *31*, 797. (e) Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. *J. Org. Chem.* **1990**, *55*, 215. (f) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. (g) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868.
23. Curran, D. P.; DeMello, N. C. *J. Chem. Soc., Chem. Commun.* **1993**, 1314.
24. Deslongchamp, P. "Stereo-electronic effects in organic synthesis", Pergamon Press, Oxford, 1983.
25. Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M.A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675.

(Received in UK 1 October 1993; revised 31 January 1994; accepted 4 February 1994)