Journal de la Société Chimique de Tunisie, **2004**, *6*, 139-146

EFFICIENT SYNTHESIS OF NEW CHIRAL SECONDARY AMINES DERIVED FROM (-)- MENTHONE

R. El Abed, R. Touati, M. M'saddak, B. Ben Hassine*

Laboratoire de Synthèse Organique Asymétrique et Catalyse Homogène,
Faculté des Sciences de Monastir, Avenue de l'Environnement, 5019 Monastir, Tunisie.

(Reçu le 24 Avril 2004, accepté le 28 Mai 2004)

ABSTRACT: New chiral imines **2a-i** were prepared by condensation of (2S,5R)-(-)-2-isopropyl-5-methyl-cyclohexanone ((-)-menthone) **1** with primary amines. Diastereoselective reduction of these imines with $NaBH_4$ leads to the corresponding chiral secondary amines **3a-i** with diastereomeric excess ranging from 46 to 98%.

Keywords : Menthone / Ketimines / Secondary amines / Diastereoselectivity

RESUME: De nouvelles imines chirales **2a-i** ont été préparées par condensation du (2S,5R)-(-)-2-isopropyl-5-méthyl-cyclohexanone ou (-)-menthone **1** avec des amines primaires. La réduction diastéréosélective de ces imines par $NaBH_4$ conduit aux amines secondaires chirales correspondantes **3a-i** avec des excès diastéréoisomèriques compris entre 46 et 98%.

Mots clés : Menthone / Cétimines / Amines secondaires / Diastéréoselectivité

1. INTRODUCTION

The preparation of chiral secondary amines was of interest in synthetic and pharmaceutical chemistry due to the significant role of these amines as intermediates for biologically active substances [1,2], as resolving agents [3] and as chiral auxiliaries for asymmetric synthesis [4,5].

Reductive amination of aldehydes or ketones constitutes the more used method in the synthesis of chiral secondary amines by reduction of the corresponding imines with chiral catalysts [6] or achiral reagents [7]. However, it has been postulated that reducing agents such as sodium borohydride [8] or sodium cyanoborohydride [9] provided chiral secondary amines from chiral imines with good yields.

In the present study, the commercially available (-)-menthone **1** ((2S,5R)-(-)-2-isopropyl-5-methyl-cyclohexanone; Fluka, $[\alpha]_D^{20} = 26$; e.e = 98%) was used as chiral auxiliary . Several reports on the use of (-)-menthone **1** in asymmetric synthesis like new chiral pyrazoles ligands [10], resolution of racemic 1,3-alcanediols [11], preparation of new α-fluoro-β-cetoacides [12], synthesis of new chiral calix[n]arenes [13] or as synthon for the preparation of (+)- and (-)-5,6-dihydroxy-3,7-dimethyl-octanal intermediates of didemnaketal analogue which exhibited significant inhibition of HIV-1 protease [14] were reported in the literature.

We report here the synthesis of new chiral secondary amines in two steps from (-)-menthone and primary amines. The first step consists of the condensation of (-)-menthone **1** with primary amines in order to obtain the corresponding optically pure ketimines **2a-i** (Schiff bases). In a second stage, ketimines **2a-i** were reduced by sodium borohydrure to give the chiral secondary amines **3a-i** with a diastereoselectivity ranging from 46% to 98%.

2. RESULTS AND DISCUSSION

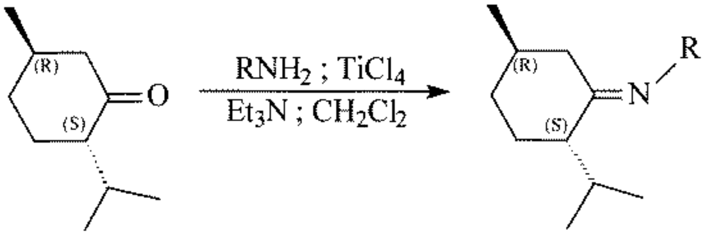
2.1 Synthesis of Ketimines 2

---

* corresponding author, e-mail : Bechir. Hassine@fsm.rnu.tn

The preparation of imines from ketones is well documented [15] but many methods were not applied to very hindered ketones. While traditional methods [16] were successful in some instances, in many other cases long times reactions were necessary to achieve reasonable yields of the desired imines. For example, the preparation of imine **2a** from (-)-menthone **1** and aniline can be achieved via an azeotropic removal of water, but the reaction requires around one week in refluxing toluene (Table I). To facilitate the synthesis of imines **2a-i**, a dehydrating reagent like potassium hydroxide [15a], dry magnesium sulfate [17], titanium tetrachloride [8a] or molecular sieves [7d] were necessary.

In order to obtain better yields and reducing reaction time, we have efficiently prepared all chiral ketimines **2a-i** by the use of titanium tetrachloride in the presence of triethylamine (Scheme1, Table I). The addition of $TiCl_4$ to a mixture of a primary amine and Et_3N in dichloromethane was carried out at 0°C under argon atmosphere then (-)-menthone **1** was added to the mixture at reflux [8a].



1 **2a-i**

Scheme 1

Table I: Synthesis of ketimines **2a-i** from (-)-menthone and primary amines $R\text{-}NH_2$

R	Ketimines	yield %
Ph	2a	85/40^a
o-Cl-Ph	2b	76
$Ph\text{-}CH_2$	2c	70
1-Naph	2d	80
Furfuryl	2e	75
^{i}Bu	2f	72
^{t}Bu	2g	70
^{i}Pr	2h	75
$c\text{-}C_6H_{11}$	2i	68

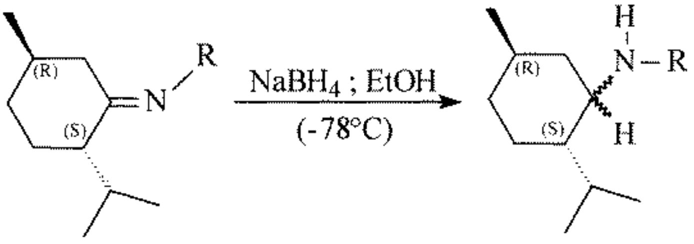
a- Yield obtained by azeotropic removal of water in toluene

All ketimines **2a-i** were obtained as one isomer having the *E* configuration based on GC-MS analysis, steric arguments and H^1 NMR experiments [18-20]. The stability of these ketimines was not extensively investigated, but they were stable for several days when they are stored under anhydrous conditions at low temperature.

2.2 Synthesis of secondary amines 3

N.Moss et al. [8a] showed that the reducing agent had a small influence on the stereochemistry progress, whereas temperature and solvent play an important roles. In this work, we have prepared a new secondary amines of N-menthylarylamines (entry **3a-e**) and N-menthylalkylamines (entry

3f-i) by reduction of the corresponding chiral imines with $NaBH_4$ at low temperature (-78°C) in absolute ethanol (Scheme 2).



2a-i **3a-i**

Schema 2

Good chemicals yields and moderate to good diastereoselectivities were obtained (Table II and experimental section).

Table II: Preparation of secondary amines **3a-i** by reduction of ketimines **2a-i**

Entry	R	yield% of 3a-i	Diastereomeric ratio of 3a-i	d.e^b(%) of 3a-i
a	Ph	94	79/21	58
b	o-Cl-Ph	92	77/23	54
c	Ph-CH_2	88	86/14	72
d	1-Naph	90^a	73/27	46
e	Furfuryl	90	21/79	58
f	^{i}Bu	83	13/87	74
g	^{t}Bu	86	85/15	70
h	^{i}Pr	85	98/2	96
i	c-C_6H_{11}	80	99/1	98

a- m.p = 70-71°C.

b- d.e was determinated by GC-MS analysis.

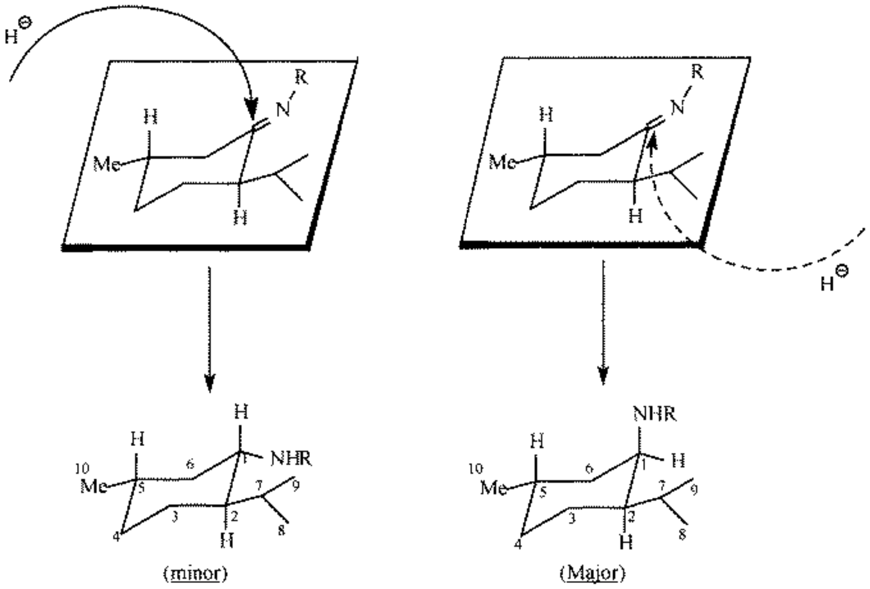


Fig.1: Stereochemical procedure for the attack of hydride.

The diastereoselectivity observed during these reactions is probably due to the initially present asymmetric carbons in the imine. The (2S)-configuration carbon can play a decisive role because of its proximity from the new formed stereogenic center. Y. Hashimoto et al. [7a] showed that nucleophilic attack occurs preferentially from the less hindered side of imine ("*re*" side in this case) (Fig.1).

We have observed that the diastereoselectivity decreases when the chiral secondary amines was derived from an aromatic imine (entry **3a-e**) (Fig.2) except amine **3c** (72% d.e), whereas the chiral secondary aliphatic amines (entry **3f-i**) were obtained with good diastereomeric excess (70% to 98%) (Fig.3). All d.e were determined by gas chromatography coupled to mass spectroscopy.

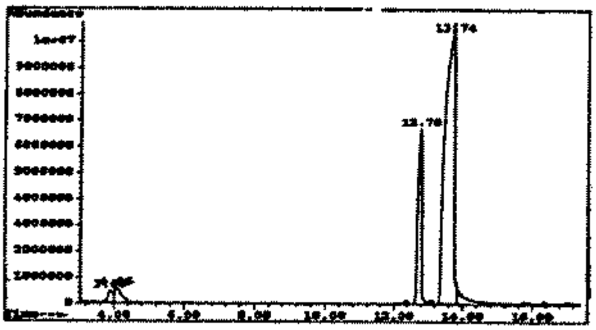


Fig.2. GC of the diastereoisomeric mixture 3c.

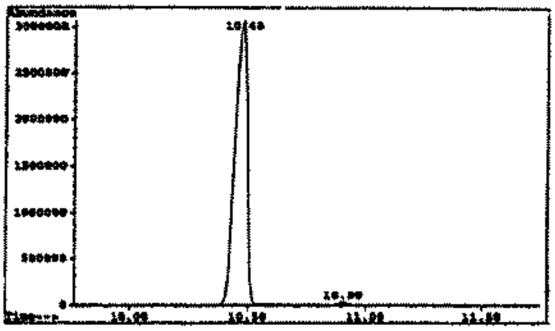


Fig.3. GC of the diastereoisomeric mixture 3i

3. CONCLUSION

In summary, we have prepared a new chiral secondary amines from (-)-menthone via the corresponding optically pure ketimines. These secondary amines were obtained with good chemicals yields and moderate to good diastereoselectivities. Optimization and applications as resolving agents and chiral auxiliaries for asymmetric synthesis are in progress.

4. EXPERIMENTAL SECTION

4.1 General:

All reactions were run under a positive pressure of dry argon. NMR spectra were recorded at 200 or 300 MHz for proton and 50 or 75 MHz for carbon , using TMS as an internal standard and $CDCl_3$ as solvent. IR measurements spectra were determined on a BIO-RAD 6000 spectrometer FT-IR. All GC analyses were carried out with a Hewlett- Packard 5792 gas chromatograph equiped with a Hewlett- Packard 5890 A. Optical purities (de,%) were determined by capillary GC analysis using a Hewlett- Packard 5792 gas chromatograph equiped with a 25 m/ Φ_{int} = 0,25 mm/ e = 0,53 µm capillary column (5% diphenyl, 95% dimethylpolysiloxane). TLC plates were made of E-Merk AG, Darmstad, silica gel PF-254.

4.2 Synthesis of imines 2a-i:

Imines **2a-i** were prepared according to the procedure developed by N.Moss et al.[8a].

N-menthylidenephenylamine 2a

The product was obtained as an oil (85%).

IR (KBr, cm^{-1}): $\nu_{C=N}$ = 1658, $\nu_{C=C}$ = 1597, ν_{C-H} = 2868.

SM: m/z = 229 ($M^{+\cdot}$, 27%); m/z = 187 ($C_{13}H_{17}N^+$, 100%); m/z = 77 ($C_6H_5^+$, 48%).

^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.87 (d, *J*= 7.1 Hz, 3H, 9-H), 0.92 (d, *J*= 6.9 Hz, 3H, 8-H), 0.97 (d, *J*= 6.4 Hz, 3H, 10-H), 1.05-2.72 (m, 9H), 6.65- 7.34 (m, 5H, Arom.); ^{13}C-NMR (50MHz, $CDCl_3$) δ: 119.3, 119.7, 122.4, 128.6 (4C, Arom.), 151.5 (C=N), 175 (C, sp).

N-menthylidene-2-chlorophenylamine 2b
The product was obtained as an oil (76%).
IR (KBr, cm^{-1}): $\nu_{C=N}$ = 1661, $\nu_{C=C}$ = 1589, $\nu_{C\text{-}H}$ = 2955.
SM: m/z = 263 ($M^{+\cdot}$, 25%); m/z = 248 ($C_{15}H_{19}NCl^+$, 52.5%); m/z = 221 ($C_{13}H_{16}NCl^+$, 100%).
^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.82 (d, *J*= 6.8 Hz, 3H, 9-H), 0.88 (d, *J*= 7 Hz, 3H, 8-H), 0.95 (d, *J*= 6.4 Hz, 3H, 10-H), 1.11-2.63 (m, 9H), 6.98-7.08 (m, 2H), 7.47 (d, *J*= 8.2 Hz, 1H), 7.84 (d, J= 7.8 Hz, 1H).

N-menthylidenebenzylamine 2c
The product was obtained as an oil (70%).
IR (KBr, cm^{-1}): $\nu_{C=N}$ = 1656, $\nu_{C=C}$ = 1580, $\nu_{C\text{-}H}$ = 2969.
SM: m/z = 243 ($M^{+\cdot}$, 29%); m/z = 228 ($C_{16}H_{22}N^+$, 36%); m/z = 91 ($C_7H_7^+$, 69%); m/z = 200 ($C_{14}H_{18}N^+$, 100%).
^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.79 (d, *J*= 7.1 Hz, 3H, 9-H), 0.83 (d, *J*= 6.8 Hz, 3H, 8-H), 0.91 (d, *J*= 6.4 Hz, 3H, 10-H), 1.02-2.35 (m, 9H), 2.52 (d, *J*= 13.4Hz, 2H: CH_2-Ph), 6.3-7.02 (m, 5H, Arom.).

N-menthylidenenaphtylamine 2d
The product was obtained as an oil (80%).
IR (KBr, cm^{-1}): $\nu_{C=N}$ = 1660, $\nu_{C=C}$ = 1593, $\nu_{C\text{-}H}$ = 2881.
SM: m/z = 279 ($M^{+\cdot}$, 46.6%); m/z = 237 ($C_{17}H_{19}N^+$, 100%).
^{1}H-NMR (300MHz, $CDCl_3$) δ: 0.85 (d, *J*= 6.8 Hz, 3H, 9-H), 0.90 (d, *J*= 6.9 Hz, 3H, 8-H), 0.96 (d, *J*= 6.2 Hz, 3H, 10-H), 1.02-2.34 (m, 9H), 7.34-7.82 (m, 7H, Arom.); ^{13}C-NMR (50MHz, $CDCl_3$) δ: 113.3, 122.5, 123.6, 125.1, 125.8, 126.8, 127.9 (7C, Arom.), 148.0 (C=N), 176.3 (C, sp).

N-menthylidenefurfurylamine 2e
The product was obtained as an oil (75%).
IR (KBr, cm^{-1}): $\nu_{C=N}$ = 1655, $\nu_{C=C}$ = 1600, $\nu_{C\text{-}H}$ = 2950.
SM: m/z = 233 ($M^{+\cdot}$, 11%), m/z = 218 ($C_{14}H_{10}NO^+$, 40.5%), m/z = 191 ($C_{12}H_{16}NO^+$, 100%).
^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.83 (d, *J*= 6.8 Hz, 3H, 9-H), 0.89 (d, *J*= 7.1 Hz, 3H, 8-H), 0,97 (d, *J*= 6.1 Hz, 3H, 10-H), 1.09-2.68 (m, 9H), 2.89 (d, *J*= 13Hz, 2H: R-CH_2-N), 6.91-7.22 (m, 3H, Arom.).

N-menthylidenisobutylamine 2f
The product was obtained as an oil (72%).
IR (KBr, cm^{-1}): $\nu_{C=N}$ = 1663, $\nu_{C\text{-}H}$ = 2907.
SM: m/z = 209 ($M^{+\cdot}$, 10%), m/z = 194 ($C_{13}H_{24}N^+$, 49.5%), m/z = 167 ($C_{11}H_{21}N^+$, 89%), m/z = 124 ($C_8H_{14}N^+$, 100%).
^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.81 (d, *J*= 7.1 Hz, 3H, 9-H), 0.87 (d, *J*= 6.9 Hz, 3H, 8-H), 0.97 (d, *J*= 6.1 Hz, 3H, 10-H), 1.04 (d, J= 6.6 Hz, 6H), 1.13-3.32 (m, 12H).

N-menthylidenetertiobutylamine 2g
The product was obtained as an oil (70%).
IR (KBr, cm^{-1}): $\nu_{C=N}$ = 1659, $\nu_{C\text{-}H}$ = 2913.
SM: m/z = 209 ($M^{+\cdot}$, 17%), m/z = 194 ($C_{13}H_{24}N^+$, 41%), m/z = 167 ($C_{11}H_{21}N^+$, 71%), m/z = 124 ($C_8H_{14}N^+$, 100%).
^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.88 (d, *J*= 7.2 Hz, 3H, 9-H), 0.94 (d, *J*= 7.1 Hz, 3H, 8-H), 1.02 (d, *J*= 6.4 Hz, 3H, 10-H), 1.15 (s, 9H, 3 Me), 1.23-2.96 (m, 9H).

N-menthylidenisopropylamine 2h
The product was obtained as an oil (75%).
IR (KBr, cm^{-1}): $\nu_{C=N}$ = 1658, ν_{C-H} = 2953.
SM: m/z = 195 ($M^{+\cdot}$, 11%), m/z = 43 ($C_3H_7^+$, 31%), m/z = 152 ($C_{10}H_{18}N^+$, 86%), m/z = 110 ($C_7H_{12}N^+$, 100%).
^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.80 (d, *J*= 7.1 Hz, 3H, 9-H), 0.87 (d, *J*= 7.1 Hz, 3H, 8-H), 0.96 (d, *J*= 6.2 Hz, 3H, 10-H), 1.12 (d, *J*= 6.6Hz, 6H), 1.20-2.39 (m, 9H), 2.92 (h, 1H).

N-menthylidenecyclohexylamine 2i
The product was obtained as an oil (68%).
IR (KBr, cm^{-1}): $\nu_{C=N}$ = 1662, ν_{C-H} = 2943.
SM: m/z = 235 ($M^{+\cdot}$, 9.7%), m/z = 220 ($C_{15}H_{25}N^+$, 42.7%), m/z = 193 ($C_{13}H_{22}N^+$, 100%).
^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.78 (d, *J*= 6.9 Hz, 3H, 9-H), 0.85 (d, *J*= 6.9 Hz, 3H, 8-H), 0.93 (d, *J*= 6.4 Hz, 3H, 10-H), 1.18-3.13 (m, 20H)

4.3 Preparation of amines 3a-i:

General procedure

To a solution of imine **2** (5 mmol) in absolute ethanol (20 mL) at –78°C was added sodium boroydride (2.5 mmol). After one hour, the reaction mixture was allowed to warm to 0°C and treated with HCl (6M). The ethanol was removed and the residue was diluted with water and basified (10% aqueous Na_2CO_3). The mixture was extracted with EtOAc and the organic layer was washed with brine, dried and concentrated to provide crude **3**.

N-menthylphenylamine 3a
The product was obtained as an oil (94%).
IR (KBr, cm^{-1}): ν_{N-H} = 3431, ν_{C-H} = 2953, ν_{C-N} = 1370.
SM: m/z = 231 ($M^{+\cdot}$, 26.2%), m/z = 216 ($C_{15}H_{22}N^+$, 6.8%), m/z = 146 ($C_{10}H_{12}N^+$, 100%).
^{1}H-NMR (300MHz, $CDCl_3$) δ: 0.79 (d, *J*= 6.8 Hz, 3H, 9-H), 0.83 (d, *J*= 7.1 Hz, 3H, 8-H), 0.88 (d, *J*= 6.2 Hz, 3H, 10-H), 2.33 (ddd, *J*= 2.3; 4.5; 11.2 Hz, 1H, 1-H), 0.95-2.71 (m, 9H), 6.54-7.17 (m, 5H, Arom.).

N-menthyl-2-chlorophenylamine 3b
The product was obtained as an oil (92%).
IR (KBr, cm^{-1}): ν_{N-H} = 3434, ν_{C-H} = 2921, ν_{C-N} = 1371.
SM: m/z = 265 ($M^{+\cdot}$, 21.4%), m/z = 250 ($C_{15}H_{21}NCl^+$, 5.3%), m/z = 180 ($C_{10}H_{11}NCl^+$, 100%).
^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.82 (d, J= 6.9 Hz, 3H, 9-H), 0.85 (d, *J*= 7.1 Hz, 3H, 8-H), 0.90 (d, *J*= 6.4 Hz, 3H, 10-H), 2.38 (ddd, *J*= 2.5; 4.7; 11.4 Hz, 1H, 1-H), 1.02-2.83 (m, 9H), 6.46-6.57 (m, 2H), 6.83 (d, *J*= 8.8 Hz, 1H), 7.06 (d, J= 8.2 Hz, 1H).

N-menthylhenzylamine 3c
The product was obtained as an oil (88%).
IR (KBr, cm^{-1}): ν_{N-H} = 3433, ν_{C-H} = 2950, ν_{C-N} = 1369.
SM: m/z = 245 ($M^{+\cdot}$, 4%), m/z = 91 ($C_7H_7^+$, 74.8%), m/z = 160 ($C_{11}H_{14}N^+$, 100%).
^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.85 (d, *J*= 7 Hz, 3H, 9-H), 0.90 (d, *J*= 6.8 Hz, 3H, 9-H), 0.96 (d, *J*= 6.4 Hz, 3H, 10-H), 2.42 (ddd, *J*= 2.7; 4.5; 11.3 Hz, 1H, 1-H), 1,15-2.94 (m, 9H), 3.64 (d, *J*= 12.8Hz, 2H, Ph-CH_2-N), 6.29-7.12 (m, 5H, Arom.).

N-menthylnaphtylamine 3d
The product was obtained as a white solid (90%), mp = 70-71°C, (petroleum ether).
IR (KBr, cm^{-1}): ν_{N-H} = 3450, ν_{C-H} = 2954, ν_{C-N} = 1371.

SM: m/z = 281 ($M^{+\cdot}$, 71.8%), m/z = 266 ($C_{19}H_{24}N^+$, 8.3%), m/z = 196 ($C_{14}H_{14}N^+$, 100%).
^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.91 (d, J= 7.2 Hz, 3H, 9-H), 0.94 (d, J= 7,1 Hz, 3H, 8-H), 0,99 (d, J= 6.4 Hz, 3H, 10-H), 2.31 (ddd, J= 2.4; 4.8; 11.2 Hz, 1H, 1-H), 1.10-2.54 (m, 9H), 6.65-7.81 (m, 7H, Arom.).

N-menthylfurfurylamine 3e
The product was obtained as an oil (90%).
IR (KBr, cm^{-1}): ν_{N-H} = 3440, ν_{C-H} = 2953, ν_{C-N} = 1371.
SM: m/z = 235 ($M^{+\cdot}$, 2%), m/z = 150 ($C_9H_{12}NO^+$, 48.6%), m/z = 81 ($C_5H_5O^+$, 100%).
^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.82 (d, J= 7.1 Hz, 3H, 9-H), 0.86 (d, J= 7.1 Hz, 3H, 8-H), 0.92 (d, J= 6.4 Hz, 3H, 10-H), 2.28 (ddd, J= 2.7; 4.6; 11.2 Hz, 1H, 1-H), 1.01-2.45 (m, 9H), 2.79 (d, J= 13.6Hz, 2H), 7.01-7.26 (m, 3H, Arom.).

N-menthylisobutylamine 3f
The product was obtained as an oil (83%).
IR (KBr, cm^{-1}): ν_{N-H} = 3437, ν_{C-H} = 2912, ν_{C-N} = 1368.
SM: m/z = 211 ($M^{+\cdot}$, 6%), m/z = 168 ($C_{11}H_{22}N^+$, 41.7%), m/z = 126 ($C_8H_{16}N^+$, 100%).
^{1}H-NMR (300MHz, $CDCl_3$) δ: 0.79 (d, J= 6.9 Hz, 3H, 9-H), 0.84 (d, J= 6.8 Hz, 3H, 8-H), 0.91 (d, J= 6.2 Hz, 3H, 10-H), 0.98 (d, J= 6.8 Hz, 6H), 2.44 (ddd, J= 2.5; 4.6; 11.4 Hz, 1H, 1-H), 1.13-3.38 (m, 12H).

N-menthyltertiobutylamine 3g
The product was obtained as an oil (86%).
IR (KBr, cm^{-1}): ν_{N-H} = 3436, ν_{C-H} = 2953, ν_{C-N} = 1365.
SM: m/z = 211 ($M^{+\cdot}$, 20%), m/z = 196 ($C_{13}H_{26}N^+$, 55.3%), m/z = 126 ($C_8H_{16}N^+$, 100%).
^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.81 (d, J= 7.1 Hz, 3H, 9-H), 0.86 (d, J= 7.2 Hz, 3H, 8-H), 0.92 (d, J= 6.2 Hz, 3H, 10-H), 1.03 (s, 9H, 3Me), 2.48 (ddd, J= 2.5; 4.7; 11.2 Hz, 1H, 1-H), 1.12-2.61 (m, 9H).

N-menthylisopropylamine 3h
The product was obtained as an oil (85%).
IR (KBr, cm^{-1}): ν_{N-H} = 3438, ν_{C-H} = 2957, ν_{C-N} = 1377.
SM: m/z = 197 ($M^{+\cdot}$, 6.3%), m/z = 182 ($C_{12}H_{24}N^+$, 15%), m/z = 112 ($C_7H_{14}N^+$, 100%).
^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.79 (d, J= 6.9 Hz, 3H, 9-H), 0.84 (d, J= 6.8 Hz, 3H, 8-H), 0.89 (d, J= 6.1 Hz, 3H, 10-H), 0.96 (d, J= 6.8 Hz, 6H), 2.42 (ddd, J= 2.6; 4.7; 11.3 Hz, 1H, 1-H), 1.08-2.46 (m, 9H), 2.89 (h, 1H).

N-menthylcyclohexylamine 3i
The product was obtained as an oil (80%).
IR (KBr, cm^{-1}): ν_{N-H} = 3433, ν_{C-H} = 2935, ν_{C-N} = 1366.
SM: m/z = 237 ($M^{+\cdot}$, 4.5%), m/z = 222 ($C_{15}H_{28}N^+$, 9%), m/z = 152 ($C_{10}H_{18}N^+$, 100%).
^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.86 (d, J= 7.1 Hz, 3H, 9-H), 0.90 (d, J= 6.9 Hz, 3H, 8-H), 0.96 (d, J= 6.4 Hz, 3H, 10-H), 2.45 (ddd, J= 2.6; 4.7; 11.3 Hz, 1H, 1-H), 1.10-2.87 (m, 20H).

Acknowledgments

We wish to thank "la Direction Générale de la Recherche Scientifique et Technique" and "Ministère de l'enseigement Superieur Tunisien" for their support of our program. The authors thank also Professor M. Hammami "Faculté de Médecine de Monastir-Tunisie" for GC-SM analysis.

References

[1] H. Moser, G. Rihs, H. Sauter, Z. Naturforsch, **1982**, *376*, 451.
[2] Y. Suzuki, H. Takahashi, *Chem. Pharm. Bull.*, **1983**, *31*, 2895.
[3] W. M. Pirkel, T. C. Pochapsky, G. S. Mahler, D. S. Coney, D. S. Reno, D. M. Aessi, *J.Org. Chem.* **1986,** *51*, 4991.
[4] J. K. Whitesell, *Chem. Rev.*, **1989**, *89*, 1581 and references cited therein.
[5] M. Shimizu, T. Iida, T. Fujisawa, *Chem. Lett.*, **1995**, 609.
[6] (a) G. Zhu, X. Zhang, *Tetrahedron: asymmetry*, **1998**, *14*, 2415 and references cited therein.
(b) D. Taniyama, M. Hasegawa, K. Tomioka, *Tetrahedron: asymmetry*, **1999**, *10*, 221.
(c) J. M. Brunel, G. Buono, *Synlett*, **1996**, *2*, 177.
(d) C. Bolm, M. Felder, *Synlett*, **1994**, *8*, 655.
(e) I. Inoue, M. Shindo, K. Koga, M. Kanai, K. Tomioka, *Tetrahedron: asymmetry*, **1995**, *6*, 2527.
(f) I. Inoue, M. Shindo, K. Koga, K. Tomioka, *Tetrahedron: asymmetry*, **1993**, *4*, 1603.
[7] (a) Y. Hashimoto, N. Kobayashi, A. Kai, K. Saigo, *Synlett*, **1995**, *9*, 961.
(b) H. Yamada, T. Kawate, A. Nishida, M. Nakagawa, *J. Org. Chem.*, **1999**, *64*, 8821.
(c) A. H. Vetter, A. Berkessel, *Synthesis*, **1995**, 419.
(d) Y. Ukaji, T. Watai, T. Sumi, T. Fujisawa, *Chemistry Lett.*, **1991**, 1555.
[8] (a) N. Moss, J. Gautier, M. Ferland, *Synlett*, **1995**, 142.
(b) R. O. Hutchins, W. Y. Su, R. Sivakumar, F. Cistone, Y. P. Stercho, *J. Org. Chem.*, **1983**, *48*, 3412.
(c) R. Bolton, T. N. Danks, J. M. Paul, *Tetrahedron Lett.*, **1994**, *35*, 3411.
[9] (a) J. Brusse, R. M. V. Benthem, C. G. Krusse, A. V. D. Gen, *Tetrahedron: asymmetry*, **1990**, *1*, 163.
(b) C. F. Lane, *Synthesis*, **1975**, 135.
(c) R. O. Hutchins, N. R. Natale, *Org. Prep. Proced. Int.*, **1979**, *11*, 201.
[10] A. Heumann, M. Moukhliss, *Synlett*, **1998**, 1211.
[11] (a) T. Harada, H. Kurokawa, Y. Kugamihara, S. Tanaka, I. Inoue, A. Oku, *J. Org. Chem.*, **1992**, *57*, 1412.
(b) T. Harada, S. Tanaka, A. Oku, *Tetrahedron*, **1992**, *48*, 8621.
(c) T. Harada, A. Oku, *Synlett*, **1994**, 95.
[12] (a) T. Iwaoka, T. Murohashi, M. Sato, C. Kaneko, *Tetrahedron: asymmetry*, **1992**, *3*, 1025.
(b) M. Sato, Y. Abe, K. Takayama, K. Sekiguchi, C. Kaneko, T. Inukai, *J. Heterocyclic Chem.*, **1991**, *28*, 241.
[13] A. Soi, J. Pfeiffer, J. Jauch, V. Schurig, *Tetrahedron: asymmetry*, **1999**, *10*, 177.
[14] P. Z. Wang, Y. Q. Tu, L. Yang, C. Z. Dong, W. Kitching, *Tetrahedron: asymmetry*, **1998**, *9*, 3789.
[15] (a) H. Weingarten, J. P. Chupp, W. A. White, *J. Org. Chem.*, **1967**, *32*, 3246.
(b) C. Stetin, B. de Jeso, J. C. Pommier, *Synthetic Commun.*, **1982**, *12*, 495.
(c) R. Carlson, U. Larsson, L. Hansson, *Acta Chem. Scand.*, **1992**, *46*, 1211.
(d) B. E. Love, J. Ren, *J. Org. Chem.*, **1993**, *58*, 5556. (e) R. Bolton, T. N. Danks, J. M. Paul, *Tetrahedron Lett.*, **1994**, *35*, 2411.
[16] (a) S. Dayagi, Y. Degani, "In The Chemistry of the Carbon-Nitrogen Double Bond," S. Patai, Ed., John Wiley and Sons: New York, **1970**, p. 61.
(b) K. Taguchi, F. H. Westheimer, *J. Org. Chem.*, **1971**, *36*, 1570.
(c) J. K. Whitesell, "In Comprehensive Organic Synthesis," E. Winterfeldt, Ed., Pergamon Press: Oxford, **1991**, p. 705.
[17] M. M. Midland, R. W. Koops, *J. Org. Chem.*, **1992**, *57*, 1158.
[18] K. Kloc, E. Kubiz, J. Mlochwski, L. Super, *Synthesis*, **1987**, 1084.
[19] R. Touati, B. Ben Hassine, J. P. Genet, *C. R. Acad. Sci. Série IIc*, **2000**, *3*, 35.
[20] J. Kraeim, Y. Kacem, J. E. Khiari, B. Ben Hassine, *Synthetic Commun.*, **2001**, *31*, 263.