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Rearrangement of α-Hydroxy Imines to α-Amino Ketones : Mechanistic Aspects and Synthetic Applications

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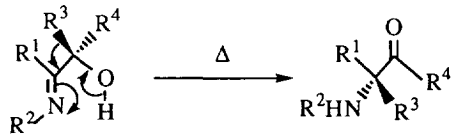
Abstract : In refluxing diglyme, rearrangement of α-hydroxy imines bearing diversely substituted allyl groups or a 3-trimethylsilylpropargyl group on the α-carbon to the nitrogen afforded in good yields α-amino ketones. Migration of allyl or 3-trimethylsilylallyl groups occured without allylic transposition in contrast to the 1-methylallyl group. In the 3 cases studied, the rearrangement of enantioenriched α-hydroxy imines took place with complete 1,2-chirality transfer. The rearrangement was applied to the preparation of (+)-1-benzyl-1-azaspiro[5.5]undecan-7-one, a precursor in the synthesis of (-)-perhydrohistrionicotoxin. Copyright © 1996 Elsevier Science Ltd

Introduction

Thermal rearrangement of α-hydroxy imines is of great synthetic and theoretical interest providing a method for the synthesis of α-disubstituted α-amino ketones which are not readily available by other routes. The benzilic-type mechanism of this rearrangement involves a 1,2-carbon migration accompanied simultaneously by a 1,4-hydrogen migration to the termini of the double bond of the imine (Scheme 1).



Scheme 1

Moreover, rearrangement of α-hydroxyimines derived from 3-hydroxyindolenines is believed to be involved in the biosynthesis of *Aristotelia*-type alkaloids[1] and of naturally occuring 2,5-dioxopiperazine compounds[2]. The total synthesis, based on this biosynthetic scheme of several of these compounds has been reported[3,4].

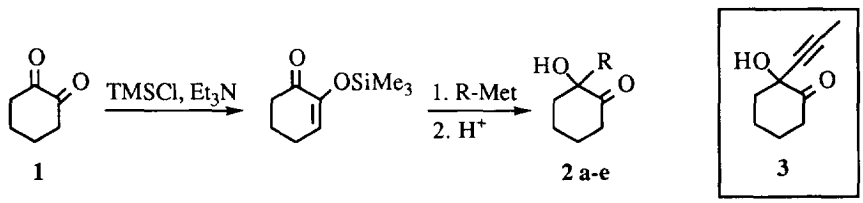
Stevens *et al.* have extensively studied the thermal rearrangement of α-amino ketones and to a less extent of α-hydroxy imines, essentially from a mechanistic point of view[5a-d]. They have investigated the rearrangement of α-hydroxy imines only when migrating groups are aryl groups[5b,c] or with 1-(α-alkyliminobenzyl)cyclopentanols which takes place with ring expansion[5d].

In connection with our efforts devoted to the total synthesis of histrionicotoxins, we studied the rearrangement of α-hydroxy imines bearing α-allyl or 3-trimethylsilylpropargyl groups. In previous communications[6, 7a,b], we have reported that thermal rearrangement of these substrates took place readily giving corresponding α-amino ketones in good yields[6] and with total 1,2-chiral transfer in scalemic series[7a,b].

In this paper, we describe the details of these studies.

Results and Discussion

Synthesis of racemic and enantioenriched α-ketols. Most of the substrates used for the study of the rearrangement are α-substituted α-hydroxycyclohexanones. They are readily available from 1,2-cyclohexanedione **1**, by first monoprotection as a trimethylsilyl enol ether[8] followed by addition of allylic or propargylic Grignard reagents or the lithio derivative of 1-trimethylsilylpropyne[9] (entry 5) to give, after acid treatment, ketols **2a-e** in acceptable yields (47-80%) (Scheme 2). In the case of addition of propargylmagnesium bromide to **1**, the desired compound **2d**, was accompanied by compound **3** (13% yield).

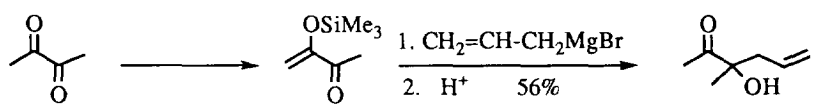


1 **2 a-e** **3**

Entry	R	Product (yield)	Entry	R	Product (yield)
1	CH_2-CH=CH_2	**2a** (80%)	4	CH_2-C≡CH	**2d** (47%)
2	CH_2-C(CH_3)=CH_2	**2b** (75%)	5	CH_2-C≡C-SiMe_3	**2e** (48%)
3	CH(CH_3)-CH=CH_2	**2c** (58%)			

Scheme 2

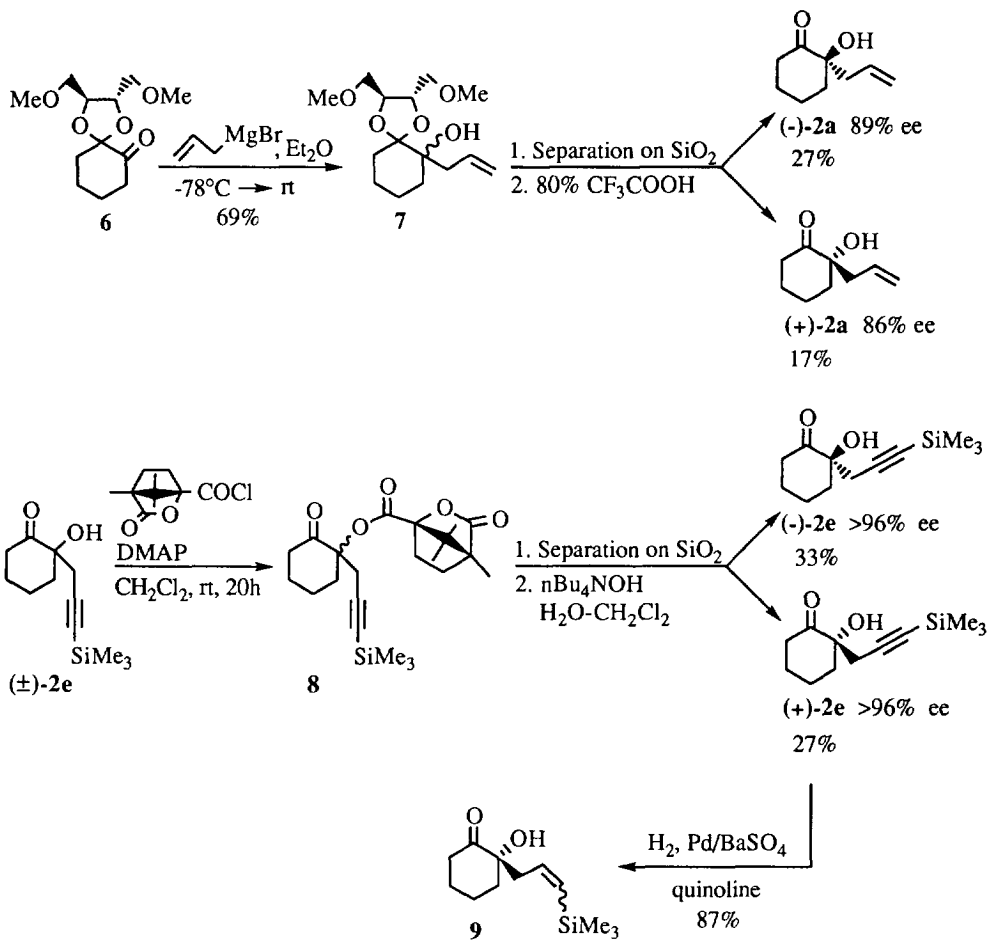
According to the above procedure, the acyclic ketol **5** was obtained in 56% yield from dione **4** (Scheme 3).



4 **5**

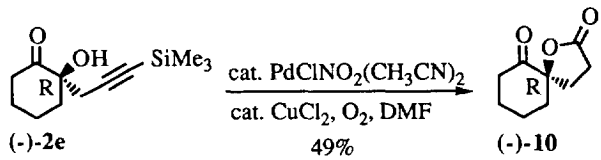
Scheme 3

In Scheme 4 is outlined the synthesis of enantioenriched **2a** , **2e** and **9**. (*R* and *S*)-α-Allyl-α-ketols **2a** were prepared from chiral α-keto acetal **6**[10] by addition of allylmagnesium bromide, at -78°C, to give a diastereomeric mixture of α-hydroxy acetal **7** (8% de). Chromatographic separation on silica gel of the mixture of diastereomers **7** followed by acid deketalization afforded enantioenriched (-) and (+)-**2a**[11] in respectively 15% and 9% from **6**. When applied to **2e**, the resolution method used above was unsuccessful but nevertheless, the racemic mixture of ketol **2e** could be resolved by conversion to diastereomeric camphanate esters **8**[12], easily separable by chromatography on silica gel. Saponification of (+) and (-)-**8** with *n*Bu4NOH in a two-phase system[12] furnished pure (+) and (-)-**2e** respectively in 27% and 33% yield from racemic **2e**. Enantioenriched ketol **9** bearing a 3-trimethylsilylallyl moiety was obtained in 87% yield as a mixture of stereoisomers (Z/E = 4:1) by semi-hydrogenation of (+)-**2e**.



Scheme 4

In order to determine its absolute configuration, (-)-**2e** was transformed to the known γ-butyrolactone **10** using our recently described procedure[14] which involves a Wacker-oxidation type reaction (Scheme 5).



(-)-2e (-)-10

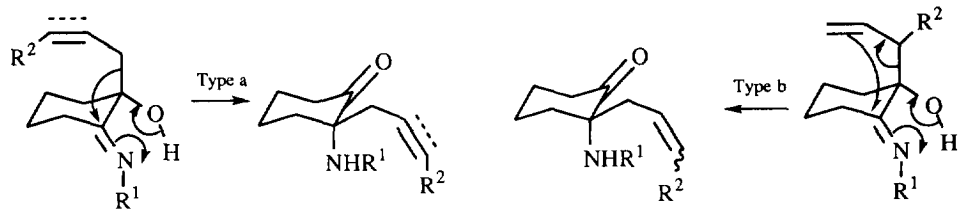
Scheme 5

Thermal rearrangement of α-hydroxyimines 11a-j. In order to gain an insight on the mechanism(s) of this rearrangement and its scope, we used a panel of α-hydroxy imines derived from the previously described α-ketols and five different amines. These α-hydroxy imines were prepared by reaction of 1 equiv of primary amine with α-ketols in refluxing toluene (3 h) with removal of water through Dean-Stark apparatus, except in the case of allylamine where water was trapped with molecular sieves at room temperature. Crude α-hydroxy imines were then heated in refluxing diglyme for 2 to 4 h.

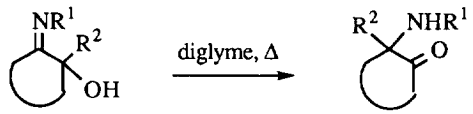
As seen in table 1, the yield of the rearrangement is usually acceptable ranging from 46 to 84 %, except in entries 3 and 9 where α-hydroxy imines bearing a α-propargyl moiety or an ester function are unstable under the reaction conditions giving several by-products or no rearrangement product at all.

Another feature of the rearrangement is that it is equilibrated, as established by Stevens *et al.* [5a] since in every studied case it was impossible to engage completely the α-hydroxy imine in the rearrangement whatever the refluxing time was. The ratio hydroxy imine / amino ketone ranged from 9/1 (in most cases) to 1/1 (entry 6), illustrating that no great difference in thermodynamic stability exists between the equilibrium partners of the rearrangement.

Involvement of the double or triple bond of the migrating group in the rearrangement. Triple bond of compound **2e** (entry 10) does not seem to be involved in the mechanism of the rearrangement because no allenic isomer was observed (Scheme 6, mechanism type a). Participation of the double bond of substituted allylic groups during the rearrangement is function of the position of the unsaturated chain. Indeed, with a methyl group α to the double bond, the rearrangement occurred with complete allylic transposition (entry 8) (mechanism type b). Conversely, with a trimethylsilyl group in terminal position, no participation of a double bond was observed (entry 12) (mechanism type a). As the whole process is equilibrated, the rearrangement product is probably dictated by a thermodynamic control.



Scheme 6

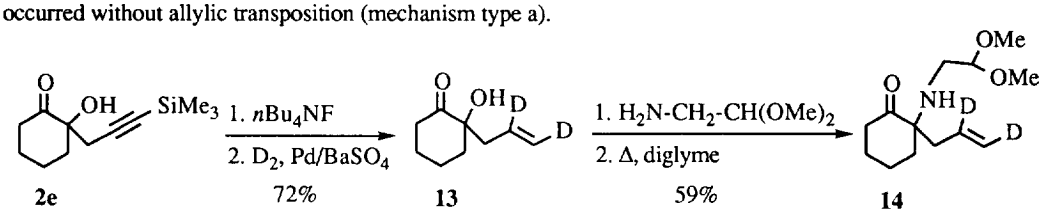


11a-j **12a-j**

Table 1. Thermal rearrangement of α-hydroxy imines 11a-j

Entry	α-Ketol	α-Hydroxy Imine	α-Amino Ketone (isolated yield)
1		**11a** R^1= CH_2Ph	**12a** (62%)
2		**11b** R^1=$CH_2CH{=}CH_2$	**12b** (65%)
3	**2a**	**11c** R^1= CH_2CO_2Me	**12c** (25%)
4		**11d** R^1=$CH_2CH(OMe)_2$	**12d** (69%)
5		**11e** R^1=Cyclohexyl	**12e** (30%)
6	**(-)-2a** (89% ee)	**11d** R^1= $CH_2CH(OMe)_2$	**(-)-12d** (50%) (90% ee)
7	**2b**	**11f** R^1= CH_2Ph	**12f** (53%)
8	**2c**	**11g** R^1= CH_2Ph	**12g** (31%)
9	**2d**	R^1= CH_2Ph, R=H	(0%)
10	**2e**	**11h** R^1= CH_2Ph, R=$SiMe_3$	**12h** (82%)
11	**(-)-2e** (>96% ee)	**11h** R^1= CH_2Ph, R=$SiMe_3$	**(-)-12h** (84%) (>96% ee)
12	**9**	**11i** R^1= CH_2Ph	**(+)-12i** (46%) (>96% ee)
13	**5**	**11j** R^1= CH_2Ph	**12j** (65%)

In order to find out if the double bond of the allylic group was involved in the rearrangement, we synthesized the dideuterio analog of **2a** (Scheme 7). Desilylation of **2e** with nBu4NF in THF followed by semi-hydrogenation with D_2 in the presence of Pd on $BaSO_4$ and quinoline gave **13** in 72 % overall yield (93 % isotopic purity). Imine formation with 1,1-dimethoxyethylamine and thermal rearrangement provided the amino ketone **14** in 59 % yield. The structure and the position of deuterium atoms of compound **14** was determined by analysis of its ^1H broad-band decoupled ^{13}C spectrum where signals for the two ethylenic carbons were diminished significantly and appeared as a triplet ($^1J_{C,D}$ ~ 24 Hz). These signals are shifted upfield by *ca.*0.4 ppm compared to those of the nonlabeled compound **2a**, as a result of the combined α and β effects of deuterium[15]. The absence of deuterium migration during the rearrangement demonstrates that it occurred without allylic transposition (mechanism type a).

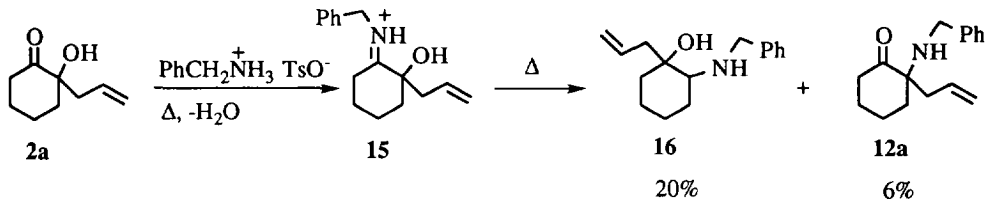


2e **13** **14**

Scheme 7

Stereochemical outcome of the rearrangement[16]. We studied the magnitude of the transfer of stereogenicity during the rearrangement on enantioenriched substrates with three different migrating groups. As seen in table 1 (entries 6,11,12), in all cases the rearrangement occurred with a complete transfer of chirality. Interestingly, rearrangement of the mixture of Z and E isomers of compound **9** bearing a 3-trimethylsilylallyl moiety gave the α-amino ketone **12i** as the pure Z-isomer[17] (entry 12). 1,2-Chirality transfer during the rearrangement of compounds **11d,h,i** is in perfect agreement with the intramolecular cyclic mechanism suggested by Stevens *et al.* [5c].

Rearrangement in the presence of acids or bases. It has been reported that acids or bases catalyzed the rearrangement of α-hydroxy imines, shortening to a certain extent the reaction time and increasing the yield[5d,18a-c]. Hydroxyimine **11a** in the presence of various acids ($BF_3.Et_2O$, APTS, Et_2AlCl, Et_3Al) or NaH did not rearrange at room temperature and gave an untractable mixture of products when heated in refluxing diglyme. Nevertheless, reaction of the ketol **2a** with benzylammonium 4-toluenesulfonate in refluxing xylene and with constant removal of water produced along with the desired product **12a** (6 % yield), a more polar product identified by ^1H and ^{13}C NMR as being the amino alcohol **16** (20 % yield) (Scheme 8). Based on the literature precedents[19], we assume that compound **16** can result from the reduction of the iminium salt **15** by nucleophilic attack of a hydride ion coming probably from the α-carbon of the secondary amine **12a**.

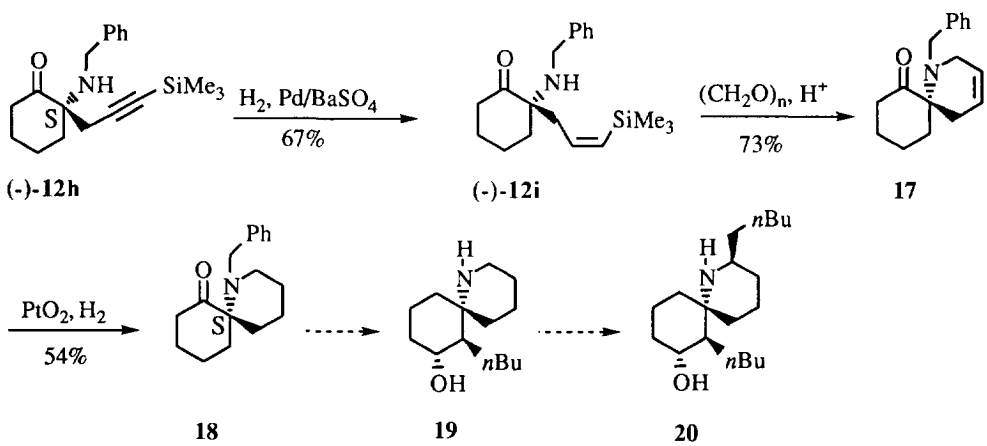


Scheme 8

Application of the rearrangement to the formal synthesis of (-) - perhydrohistrionicotoxin. In order to determine the absolute configuration of the amino ketone (-)-**12h** as well as to confirm that the rearrangement was suprafacial, compound (-)-**12h** was converted in three steps to the known levorotatory spiropiperidine **18** (Scheme 9).

First, compound **12h** was semi-hydrogenated to the Z-vinylsilane **12i** in the presence of Pd on $BaSO_4$ and quinoline (67 % yield). Then, iminium-vinysilane cyclization[20] was effected by treatment of (-) - **12i** by an excess of paraformaldehyde, in the presence of 1 equiv of camphorsulfonic acid in acetonitrile at 70°C, to give the spiroamine **17** in 73 % yield.

Chemoselective hydrogenation of the double bond of **17** in the presence of Adam's catalyst gave (+) - **18** in 54 % yield identical in all respects ($[\alpha]_D$, ^1H and ^{13}C NMR) to an authentic sample[21,25b]. The sense of chirality of the spiropiperidine **18** shows that the rearrangement of enantioenriched α-hydroxyimines **11h,i** is suprafacial and proceed heterofacially[22]. Since 1-benzyl-1-azaspiro [5,5] undecan-7-one **18** can be converted to **19**[23] thence **20**[24], we achieved the formal synthesis of (-) - perhydrohistrionicotoxin[25], an important biochemical tool for studying the mechanism of action of cholinergic agonists in the neuromuscular system[26].



Scheme 9

In summary, the conversion of α-hydroxy imines to α-amino ketones with 1,2-suprafacial shift of substituted or unsubstituted allyl groups as well as a silylated propargyl group proceeds in general without double or triple bond migration (except in one case). Moreover, this rearrangement allows the preparation of enantiopure

α-amino ketones which is not the case of other existing synthetic methods of this class of compounds[27]. The synthetic value of the rearrangement was demonstrated by the efficient and enantioselective synthesis of the spiropiperidine **18**, a precursor of the alkaloid, (-) - perhydrohistrionicotoxin.

Experimental section

General. ^1H NMR spectra were recorded at ambient probe temperatures on the following Fourier transform instruments : Bruker WP 80 (80MHz), AC 200 (200MHz) or AC 300 (300 MHz). The following internal references were used for the residual protons in the following solvents : $CDCl_3$ (δ_H = 7.25), C_6D_6 (δ_H = 7.20). Data are presented as follows : chemical shift (in ppm on the δ scale relative to δ_{TMS} = 0), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constant and interpretation. ^{13}C NMR spectra were recorded at ambient probe temperatures on Bruker AC 200 (50.3 MHz) or AC 300 (75.4 MHz) Fourier transform instrument and are reported in ppm on the δ scale. The following references were used : $CDCl_3$ (δ_c 77.0), C_6D_6 (δ_c 128.0). IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer calibrated relative to polystyrene, using 5mm sodium chloride plates. Wavelenghts of maximum absorbance (νmax) are quoted in cm^{-1}. Mass spectra were carried out on a Nermag R10-10S quadrupole mass spectrometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter at the sodium D line (589 mm). Combustion analyses were performed by the Service Central de Microanalyse, CNRS, Solaise. Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} with visualisation by ultraviolet and/or anisaldehyde dip[28]. Evaporative bulb-to-bulb distillations were done with a Büchi-Kugelrohr at the indicated oven temperature.

Reagents and solvents were purified by standard means. Dichloromethane, acetonitrile, toluene, triethylamine were distilled from calcium hydride ; diethyl ether, tetrahydrofuran and diglyme were distilled from sodium wire / benzophenone and stored under a nitrogen atmosphere. All other chemicals were used as received. Unless otherwise stated, all experiments were performed under anhydrous conditions in an atmosphere of nitrogen.

General procedure for the preparation of α-ketols (2a-e, 5)

To a solution of 1,2-dione **1** or **4** (10 mmol) in 10 ml of CH_2Cl_2 were added dropwise, at room temperature, chlorotrimethylsilane (1.45 ml, 11.4 mmol) followed by triethylamine (1.37 ml, 10.4 mmol). The reaction mixture was stirred at room temperature for 2 h and diluted with Et_2O. After filtration of salts on a cintered funnel, the filtrate was evaporated to dryness. The crude material was used for the next step without any further purification. To a solution of the monoenol silylether of **1** or **4** (10 mmol) in 10 ml of Et_2O, cooled to -40°C, was added 1.5 equiv of the Grignard or the lithium reagents. The reaction mixture was allowed to warm up to 0°C and quenched with an excess of 2N HCl in order to hydrolyze the enol ether. The aqueous phase was extracted twice with Et_2O. The combined etheral extracts were washed with water, dried (Na_2SO_4) and concentrated *in vacuo*.

2-Allyl-2-hydroxycyclohexanone (2a). Purified by distillation (bp 35-40°C, 10^{-2} mmHg) : 80% yield. Spectroscopic data of **2a** are identical with those reported in the literature[29].

2-Hydroxy-2-(2-methylprop-2-enyl)cyclohexanone (2b). Purified by flash chromatography (Et_2O-petroleum ether, 1:4) ; 75% yield. Spectroscopic and physical data of **2b** are in agreement with those described in the literature[27a].

2-Hydroxy-2-(1-methylprop-2-enyl)cyclohexanone (2c). Purified by flash chromatography (Et_2O-petroleum ether, 1:4) ; 58% yield ; IR (neat) 3480, 3070, 1710, 1640 cm^{-1}. ^1H NMR (80MHz, $CDCl_3$) (mixture of diastereomers) 0.82 (d, 1.35H, J=7Hz, CH_3), 1.16 (d, 1.65H, J=7Hz, CH_3), 1.39-1.97 (m, 6H), 1.97-2.97 (m, 3H), 3.85 (s, 0.55H, OH), 3.95 (s, 0.45H, OH), 4.97 (dd, 0.55H, J=11 and 1.5Hz, CH=C$\underline{H}_2$), 5.0 (dd, 0.45H, J=16 and 1.5Hz, CH=C$\underline{H}_2$), 5.15 (dd, 0.55H, J=16 and 1.5Hz, CH=C$\underline{H}_2$), 5.17 (dd, 0.45H, J=11 and 1.5Hz, CH=C$\underline{H}_2$), 5.45-6.07 (m, 1H, C$\underline{H}$=CH_2) ; Anal.Calcd for $C_{10}H_{16}O_2$: C, 71.39 ; H, 9.59 ; O, 19.03. Found : C, 71.20 ; H, 9.56 ; O, 19.21.

2-Hydroxy-2-(prop-2-ynl)cyclohexanone (2d) and 2-Hydroxy-2-(prop-1-ynl)cyclohexanone (3). Separation by flash chromatography (Et_2O-petroleum ether, 1:3.5) of the two isomers gave first **3** (13% yield) ; IR (neat) 3460, 2230, 2250, 1725 cm-1 ; ^1H NMR (300MHz, $CDCl_3$), 1.58-1.70 (m, 2H), 1.76-1.87 (m, 1H), 1.89 (s, 3H, CH_3), 1.93-2.17 (m, 2H), 2.53 (m, 2H), 2.94 (td, 1H, J=14,6Hz, H_6 axial), 4.20 (s, 1H, OH) ; Anal. Calcd for $C_{19}H_{12}O_2$: C, 71.02 ; H, 7.95 ; 0, 21.03. Found : C, 70.48 ; H, 8.13 ; O, 21.00. Compound **2d** was then eluted (47% yield) ; IR (neat) 3470, 3280, 2120, 1715 cm^{-1} ; ^1H NMR (300MHz, $CDCl_3$) 1.57-1.90 (m, 6H), 2.06 (t, 1H, J=2.5Hz, C=C$\underline{H}$), 2.08-2.16 (m, 1H), 2.2-2.29 (m, 1H), 2.41-2.64 (m, 3H, C$\underline{H}_2$ C=O, C$\underline{H}$-C ≡C), 2.77 (dd, 1H, J=17, 2.5Hz, C$\underline{H}$-C ≡C), 4.22 (s, 1H, OH) ; Anal. Calcd for $C_9H_{12}O_2$: C, 71.02 ; H, 7.95 ; O, 21.03. Found : C, 70.96 ; H, 7.71 ; O, 21.21.

2-Hydroxy-2-(3-trimethylsilylprop-2-ynyl)cyclohexanone (2e). The crude monoenol silylether of 1,2-cyclohexanedione **1** (1.40 g, 12.5 mmol) in Et_2O (20 ml) was slowly added at -78°C, to an etheral solution of the lithium salt of 1-trimethylsilylpropyne (2.8 ml, 1.5 equiv) containing TMEDA (2.8 ml)[9]. The reaction mixture was allowed to warm up to -40°C and acetic acid (20 ml) then Et_2O were added. The layers were separated and the aqueous phase was dissolved in THF (10 ml) and 0.7 N HCl solution (3 ml) was added. After stirring the solution for 30 min at room temperature, the mixture was extracted three times with Et_2O, washed successively with $NaHCO_3$ and water. The etheral layer was dried (Na_2SO_4) an concentrated *in vacuo*. The residue was purified by flash chromatography (Et_2O-petroleum ether, 1:4) to give **2e** (1.35 g, 48% yield) : IR (neat) 3480, 2180, 1725, 1710 cm^{-1} ; ^1H NMR (300MHz, $CDCl_3$) 1.63-1.92 (m, 4H), 2.01-2.15 (m, 1H), 2.20-2.28 (m, 1H), 2.58 (d,1H, J=17Hz, C$\underline{H}$-C≡C), 2.46-2.62 (m, 2H, C$\underline{H}_2$CO), 2.83 (d, 1H, C$\underline{H}$-C≡C), 4.14 (s, 1H, OH) ; ^{13}C NMR (75.4 MHz) : 0.1, 22.6, 27.6, 29.6, 38.05, 39.9, 77.8, 88.7, 100.7, 211.2 ; MS *m/z* (relative intensity) 224 (0.75)M^+, 206 (0.75) $(M-H_2O)^+$; Anal. Calcd for $C_{12}H_{20}O_2Si$: C, 64.23 ; H, 8.98. Found : C, 64.29 ; H, 9.11.

3-Hydroxy-3-methylhex-5-en-2-one (5). Purified by distillation under reduced pressure (bp 80°C, 12 mmHg) ; 56% yield ; IR (neat) 3470, 3080, 1710, 1640 cm-1 ; ^1H NMR (80MHz, $CDCl_3$) 1.40 (s, 3H,

CH_3), 2.22 (s, 3H, CH_3), 2.47 (d, 2H, J=7Hz, $C\underline{H}_2$-CH=CH_2), 5.03 (br, s, 1H, OH), 4.92-5.3 (m, 2H, CH=$C\underline{H}_2$), 5.77 (m, 1H, $C\underline{H}$=CH_2) ; MS *m/z* (relative intensity) 109 (1.6) $(M-H_2O)^+$; Anal. Calcd for $C_7H_{12}O_2$: C, 65.57 ; H, 9.45. Found : C, 65.56 ; H, 9.19.

Synthesis of enantioenriched (+)-and (-)-2-allyl-2-hydroxycyclohexanone (2a)

(2S, 3S, 6S and 6R)-6-Allyl-2,3-dimethoxy-6-hydroxy-1,4-dioxaspiro[4.5]decane (7). To a solution of the α-ketoacetal **6** [10] (0.88 g, 3.6 mmol) in Et_2O (14 ml), cooled to -78°C, was added a THF solution of allylmagnesium bromide (74 ml of 0.95M solution, 2 equiv). The reaction mixture was allowed to warm up to 0°C and stirred for 30 min at this temperature. At 0°C, the reaction was quenched with water and diluted with Et_2O. The layers were separated and the aqueous layer was extracted twice with Et_2O. The combined etheral extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was filtered on a bed of silica gel to give the mixture of diastereomers (0.705 g, 69% yield). Diastereomers of **7** were separated by flash chromatography using petroleum ether - Et_2O-CH_2Cl_2 (2:1:1) as eluant. Compound(+) **7** was first eluted (0.28 g, 27%) ; $[\alpha]_D$+20.1 (*c* 1.52, $CHCl_3$) ; IR (neat) 3480, 3070, 1640, 1450, 1100 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) 1.43-1.65 (m, 5H), 1.44-1.85 (m, 3H), 2.30 (ddt, 1H, J=15, 6, 1Hz, C$\underline{H}$-CH=CH_2), 3.01 (brs, 1H, OH), 3.39 (s, 3H, OMe), 3.41 (s, 3H, OMe), 3.45-3.67 (m, 3H, $C\underline{H}_2$OMe), 3.72 (dd, 1H, J=10, 3Hz, C$\underline{H}$OMe), 4.1 (dt, 1H, J=10, 3Hz, C$\underline{H}$-CH_2OMe), 4.25 (quint, 1H, J=9, 4.5Hz, C$\underline{H}$-CH_2OMe), 5.05 (brd, 1H, J=11Hz, CH=C$\underline{H}_2$), 5.08 (brd, 1H, J=16Hz, CH=C$\underline{H}_2$), 5.82-6.06 (m, 1H, C$\underline{H}$=CH_2). The next fraction was a mixture of the two diastereomers (0.261 g). The third fraction was constituted of pure (-)-**7** (0.165 g, 17% yield) ; $[\alpha]_D$ -39.3 (*c* 0.84, $CHCl_3$) ; IR (neat) 3480, 3070, 1640, 1450, 1100 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) 1.46-1.73 (m, 7H), 1.77-1.93 (m, 1H), 2.35 (ddt, 1H, J=15, 6.6, 1Hz, C$\underline{H}$-CH=CH_2), 2.39 (ddt, 1H, C$\underline{H}$-CH=CH_2), 3.40 (s, 3H, OMe), 3.41 (s, 3H, OMe), 3.48-3.55 (m, 2H, $C\underline{H}_2$OMe), 3.55-3.62 (m, 2H, $C\underline{H}_2$OMe), 3.94-4.11 (m, 2H, 2C$\underline{H}$-CH_2OMe), 5.09 (brd, 1H, J=16Hz, CH=C$\underline{H}_2$), 5.11 (brd, 1H, J=11Hz, CH=C$\underline{H}_2$), 5.82-6.02 (m, 1H, C$\underline{H}$=CH_2). Anal. Calcd for $C_5H_{26}O_5$ (mixture of diastereomers) : C, 62.91 ; H, 9.15; Found : C, 62.98 ; H, 9.30.

Hydrolysis of the acetal function of (+)-and(-)- (7)

A solution of (+)-**7** (0.27 g, 0.94 mmol) in 80% trifluoroacetic acid solution was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (Et_2O-petroleum ether, 1:3) to give compound (-)-**2a** (0.078 g, 54% yield) ; colorless oil ; $[\alpha]_D$ -139.2 (*c* 1.2, $CHCl_3$). Its spectroscopic data were identical with those of racemic **2a**.

Determination of the enantiomeric purity of compound (-)- (2a)

To a solution of the ketol (-)-**2a** (0.03 g, 0.2 mmol) in CH_2Cl_2 (2 ml) was added methoxyacetyl chloride (70 µl, 0.7 mmol) and DMAP (0.003 g, 0.025 mmol). After stirring 5 days at room temperature, water was added. The layers were separated and the aqueous phase was extracted twice with Et_2O. The combined organic extracts were washed with $NaHCO_3$ solution followed by water and finally dried (Na_2SO_4). Flash chromatography of the residue (Et_2O-petroleum ether, 1:2) gave the O-methoxyacetate derivative of (-)-**2a** (0.031 g, 70% yield). The enantiomeric excess of (-)-**2a** ester was determined by ^1H

NMR of a 0.2M solution in $CDCl_3$ from the methoxy signal which appeared as a singlet at 3.45 ppm whereas in the presence of 0.2 equiv of Eu(Hfc)3 gave two distincts signals at 5.02 (94%) and 5.05 ppm (5%).

Using the same experimental procedure, hydrolysis of (-)-**7** afforded (+)-**2a**, $[\alpha]_D$ +136.6 (*c* 2, $CHCl_3$), enantiomeric excess 86%, determined by NMR-Lanthanide Induced Shift (LIS) experiments.

(±)-2-Hydroxy-2(3-trimethylsilylprop-2-ynyl)cyclohexanone camphanyl ester (8). To a solution of the α-ketol **8** (1.5 g, 6.7 mmol) in CH_2Cl_2 (40 ml), cooled to 0°C, was successively added (-)-camphanic acid chloride (1.75 g, 8.1 mmol) and DMAP (1.95 g, 16 mmol, 2.4 equiv). The reaction mixture was allowed to warm up to room temperature and stirred for 20 h. The solvent was evaporated until the solution became cloudy and was filtered on a bed of silica gel. After concentration *in vacuo* of the filtrate, the residue was purified by chromatography on silica gel (petroleum ether - EtOAc-CH_2Cl_2, 7:1:1). (+)-**8** Camphanate ester was first eluted (1.12 g, 41% yield) ; white solid ; $[\alpha]_D$ + 26.3 (*c* 1.06, $CHCl_3$) ; IR (KBr) 2960, 2170, 1795, 1755, 1735, 1265, 845, 745 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) 0.13 (s, 9H, $Si(CH_3)_3$), 1.09 (s, 6H, $2CH_3$), 1.14 (s, 3H, CH_3), 1.50-2.05 (m, 10H), 2.15-2.60 (m, 2H, $C\underline{H}_2CO$), 2.64 (d, 1H, J=18Hz, $C\underline{H}$-C≡C), 3.0 (d, 1H, $C\underline{H}$-C≡C) ; ^{13}C NMR (50.3 MHz, $CDCl_3$) 0.02, 9.8, 16.8, 17.1, 21.2, 25.2, 28.1, 28.8, 30.8, 37.4, 40.0, 54.4, 55.0, 85.2, 88.8, 91.0, 100.4, 166.8, 178.2, 205.9. The second fraction was constituted by the pure (-)-8 camphanate ester, obtained as a white solid (0.89 g, 33%) ; $[\alpha]_D$ -47.8 (*c* 0.9, $CHCl_3$) ; IR (KBr) 2960, 2170, 1785, 1745, 1725, 1260, 840, 735 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) 0.14 (s, 9H, $Si(C\underline{H}_3)_3$), 1.05 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.40-2.05 (m, 10H), 2.15-2.55 (m, 2H, $C\underline{H}_2CO$), 2.62 (d, 1H, J=18Hz, $C\underline{H}$-C≡C), 2.98 (d, 1H, $C\underline{H}$-C≡C) ; ^{13}C NMR (50.3 MHz, $CDCl_3$) -0.005, 9.7, 16.6, 16.9, 21.3, 25.3, 28.0, 30.9, 37.3, 39.0, 54.3, 54.9, 85.0, 88.9, 90.7, 100.5, 166.3, 177.9, 205.9 ; Anal. Calcd for $C_{22}H_{32}O_5Si$ (mixture of diastereomers) : C, 65.31 ; H, 7.97. Found : C, 65.21 ; H, 7.85.

Typical procedure for saponification of (+) and (-)- (8)

To a well-stirred solution of (+)-**8** (0.77 g, 1.9 mmol) in a 1:1 mixture of water-CH_2Cl_2 (40 ml) was added 0.1 N *n*Bu_4NOH solution in a 1:1 mixture of EtOH-*i*PrOH (28.5 ml, 2.85 mmol, 1.5 equiv). After stirring the reaction mixture for 15 min, 0.1N HCl solution (35 ml) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3x40 ml). The combined organic extracts were washed once with saturated NaCl solution and dried (Na_2SO_4). Flash chromatography of the residue (petroleum ether - Et_2O, 5:1) afforded (-)-**2e** as a colorless oil (0.346 g, 81% yield) ; $[\alpha]_D$ - 93 (*c* 1.3, $CHCl_3$). Its spectroscopic data were found identical with those of racemic **2e**. By the same procedure effected on 1.4 mmol scale, the dextrorotatory **2e** was obtained in 83% yield ; $[\alpha]_D$ - 93 (*c* 2.0, $CHCl_3$).

(Z,E)-2-Hydroxy-2-(3-trimethylsilylallyl)cyclohexanone (9). A solution of (+)-**2e** (0.25 g, 1.13 mmol) in absolute ethanol (5 ml) was stirred under hydrogen atmosphere, in the presence of Pd on $BaSO_4$ (0.03 g) and quinoline (1 drop). After consumption of 1.05 equiv of hydrogen, the mixture was filtered on celite and evaporated *in vacuo*. Flash chromatography of the residue (petroleum ether - Et_2O, 8:1) afforded **9** as an oil (0.22 g, 87% yield) obtained as a mixture of isomers (Z/E = 4:1) ; IR (neat) 3490, 2950, 2860, 1715, 860, 840, 765 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) 0.11 (s, 9H, $Si(CH_3)_3$), 1.46-1.95 (m, 4H), 1.98-2.28 (m, 2H), 2.32-2.60 (m, 3.25 H, $C\underline{H}_2CO$, $C\underline{H}$-CH=CH), 2.68 (ddd, 0.75H, J=15, 7, 1.5 Hz,

CH-CH=CH), 3.92 (s, 0.75H, OH), 3.97 (s, 0.25H, OH), 5.65 (dt, 0.75H, J=14.2, 1.4Hz, CH=CHSiMe3), 5.73 (d, 0.25H, J=18.5Hz, CH=CHSiMe3), 5.9 (dt, 0.25H, J=18.5, 6Hz, CH=CHSiMe3), 6.12 (quint, 0.75H, J=14.2, 7Hz, CH=CHSiMe3). ^{13}C NMR (50.3 MHz, $CDCl_3$) : *Z* isomer 0.2, 22.7, 27.7, 38.3, 40.2, 40.3, 78.5, 133.4, 140.4, 213.4 ; *E* isomer -1.3, 22.5, 27.9, 38.3, 40.2, 78.8, 135.5, 139.3, 213.3.

1-Oxaspiro[4,5]decan-2,6-dione (10). To a solution of α-ketol (-)-**2e** (0.09 g, 0.4 mmol) in DMF (1 ml) containing water (1%, v/v), under air atmosphere, was successively added $PdClNO_2(CH_3CN)_2$ (0.009 g, 8 mole %) and $CuCl_2$ (0.011 g, 20 mole %). The mixture was stirred at room temperature for 66 h and diluted with CH_2Cl_2. The organic phase washed with 0.5 NHCl solution followed by water and dried (Na_2SO_4). After concentration *in vacuo*, flash chromatography of the residue (hexane-EtOAc, 1:1) gave (-)-**10** as a solid (0.033 g, 49% yield) ; $[\alpha]_D$ - 44.3 (*c* 1.65, EtOAc) (lit.[30] $[\alpha]_D$ - 44 (*c* 6, EtOAc).

General procedure for the preparation of α-amino ketones (12a-j) from their corresponding α-ketols.

A solution of α-ketol (1 mmol) and amine (1.15 mmol) in toluene was heated for 3 h under reflux with removal of water by azeotropic distillation through Dean-Stark apparatus. Completion of the imine formation was determined by IR spectroscopy by the disappearance of the carbonyl band (1710 cm^{-1}). The solution was evaporated to dryness and heated to 50°C under reduced pressure (10^{-2} mmHg) to remove excess of amine. The residue was dissolved in 3 ml of diglyme and refluxed for 2-4 h. Diglyme was then removed by bulb to bulb distillation (80°C, 12 mmHg) and the residue was dissolved in Et_2O. Amino ketone was extracted from the etheral solution with 0.1 HCl solution. The aqueous phase was washed once with Et_2O, basified with saturated $NaHCO_3$ solution and extracted twice with Et_2O. The combined etheral extracts were washed with water and dried (Na_2SO_4). The residue was purified by flash chromatography (petroleum ether - Et_2O, 3:1 ; except for **12d**, 1:1).

2-Allyl-2-benzylaminocyclohexanone (12a). Yellow oil (62% yield) ; IR (neat) 1710, 1640, 1605 cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$) 1.07-1.26 (m, 1H), 1.07-1.65 (m, 7H, $3CH_2$,NH), 2.07 (dt, 1H, J=14, 6Hz, CH_eCO), 2.23 (dd, 1H, J=14, 7Hz, CH-CH=CH_2), 2.42-2.62 (m, 2H, CH-CH=CH_2, CH_aCO), 3.32 (d, 1H, J=12Hz, CHPh), 3.58 (d, 1H, CHPh), 5.01 (brd, 1H, J=15Hz, CH=CH_2), 5.02 (brd, J=11Hz, CH=CH_2), 5.61-5.78 (m, 1H, CH=CH_2), 7.06-7.4 (m, 5H, Ph) ; ^{13}C NMR (75.4 MHz, C_6D_6) 20.9, 27.4, 37.4, 38.2, 38.9, 46.7, 65.6, 118.7, 126.9, 128.0, 128.3, 132.8, 140.5, 213.4 ; Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97 ; H, 8.70 ; N, 5.76 ; O, 6.58. Found : C, 78.68 ; H, 8.59 ; N, 5.71 ; O, 6.81.

2-Allyl-2-(allylaminocyclohexanone) (12b). In this case, imine **11b** was prepared at room temperature with an excess of allylamine (5 equiv) and 4Å molecular sieves (0.5 g/1 mmol) as a watertrap (reaction time ~48 h). Compound **12b** was obtained as a light yellow oil (65% yield) ; IR (neat) 3080, 1710, 1640 cm^{-1} ; ^{1}H NMR (80 MHz, $CDCl_3$) 1.5-2.06 (m, 7H, $3CH_2$, NH), 2.1-2.8 (m, 4H, CH_2CO, CH_2-CH=CH_2), 2.93 (qt, 1H, J=14, 6, 1.5Hz, NHCH), 3.21 (qt, 1H, NHCH), 4.92-5.43 (m, 4H, 2CH=CH_2), 5.43-6.22 (m, 2H, 2CH=CH_2) ; ^{13}C NMR (75.4 MHz, $CDCl_3$) 21.1, 27.3, 37.3, 38.5, 38.9, 45.2, 65.5,

115.6; 118.7, 132.7, 137.0, 213.2 ; Anal. Calcd for $C_{12}H_{19}NO$: C, 74.56 ; H, 9.91 ; N, 7.24 ; O, 8.28. Found : C, 74.28 ; H, 10.05 ; N, 7.10 ; O, 8.38.

Ethyl N-(1-hydroxy-2-oxocyclohexyl)glycinate (12c). Rearrangement of the α-hydroxy imine **11c** was effected in refluxing xylene for 14 h. Compound **12c** was obtained as a yellow oil (25% yield) ; IR (neat) 3080, 1710, 1640 cm^{-1} ; ^1H NMR (80 MHz, $CDCl_3$) 1.25 (t, 3H, J=7Hz, CH_3), 1.52-2.06 (m, 7H), 2.06-2.8 (m, 4H, CH_2CO, CH_2-CH=CH_2), 3.17 (d, 1H, J=17Hz, $CHCO_2Et$), 3.40 (d, 1H, $CHCO_2Et$), 4.18 (q, 2H, J=7Hz, $CO_2CH_2CH_3$), 4.9-5.31 (m, 2H, CH=CH_2), 5.37-6.0 (m, 1H, CH=CH_2) ; ^{13}C NMR (75.4 MHz, $CDCl_3$) 14.2, 21.1, 27.0, 36.9, 38.7, 38.9, 61.0, 65.1, 118.9, 132.3, 172.1, 212.5 ; MS *m/z* (relative intensity) 239 (0.1)M^+ ; Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24 ; H, 8.84 ; N, 5.85 ; O, 20.05. Found : C, 64.82 ; H, 8.66 ; N, 6.00 ; O, 20.19.

2-Allyl-2-(3,3-dimethoxyethylamino)cyclohexanone (12d). Yellow oil (69% yield) ; IR (neat) 3080, 1710, 1640 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) 1.63-1.93 (m, 6H, $3CH_2$), 2.21-2.37 (m, 2H, CH_2CO), 2.45 (dd, 1H, J=12, 5.6Hz, $CHCH(OMe)_2$), 2.55 (ddt, 1H, J=15, 6, 1Hz, CH-CH=CH_2), 2.60 (ddt, 1H, CH-CH=CH_2), 2.68 (dd, 1H, $CHCH(OMe)_2$), 3.37 (s, 3H, OMe), 3.38 (s, 3H, OMe), 4.42 (t, 1H, J=5.6Hz, $CH(OMe)_2$, 5.05-5.17 (m, 2H, CH=CH_2), 5.55-5.72 (m, 1H, CH=CH_2) ; ^{13}C NMR (75.4 MHz, $CDCl_3$) 21.1, 27.3, 37.3, 38.3, 38.8, 43.6, 53.4, 53.9, 64.8, 104.3, 118.6, 132.8, 212.9 ; Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.7 ; H, 9.60 ; N, 5.80 ; O, 19.90. Found : C, 64.59 ; H, 9.64 ; N, 5.88 ; O, 20.17.

Starting from enantioenriched levorotatory **2a** (89% ee), α-aminoketone **12d** was obtained in 50% yield (90% ee) ; $[\alpha]_D$-15.1 (*c* 1.47, $CHCl_3$). The enantiomeric excess was determined by ^1H NMR spectroscopy using 0.2 M solution of (-)-2 in $CDCl_3$, in the presence of 25 mole % Eu(Hfc)3. The four methyl signals were completely separated and appeared for the major enantiomer at 4.18 and 4.71 ppm and at 4.13 and 4.80 ppm for the minor enantiomer.

2-Allyl-2-(cyclohexylamino)cyclohexanone (12e). In this case, after evaporation of diglyme under reduced pressure, the residue was purified by flash chromatography (petroleum ether-Et_2O, 3:1) to give a 1:1 mixture of **12e** and **2a**. The mixture was dissolved in dry Et_2O and dry 4-toluene sulfonic acid (1 equiv) in Et_2O was added. The tosylate of **12e** precipitated and was filtered and dried (30% yield) ; ^1H NMR (300 MHz, $CDCl_3$) 1.10-1.40 (m, 3H), 1.52-2.12 (m, 9H), 2.12-2.34 (m, 3H), 2.41 (s, 3H, CH_3), 2.46-2.76 (m, 3H), 2.41 (s, 3H, CH_3), 2.46-2.76 (m, 3H), 2.9-3.22 (m, 3H), 5.24-5.66 (m, 3H, CH=CH_2), 6.51 (brs, 1H, NH), 7.2 (d, 2H, J=7.8Hz, aromatic H), 7.85 (d, 2H, aromatic H), 9.63 (brs, 1H, NH) ; Anal. Calcd for $C_{22}H_{33}NO_4S$: C, 64.83 ; H, 8.17 ; N, 3.44 ; O, 15.70 ; S, 7.87. Found : C, 64.55 ; H, 8.28 ; N, 3.38 ; O, 15.58 ; S, 7.86.

2-Benzylamino-2-(2-methylprop-2-enyl)cyclohexanone (12f). Light yellow oil (53% yield) ; IR (neat) 3080, 3060, 3030, 1710, 1640, 1605 cm^{-1} ; ^1H NMR (80 MHz, $CDCl_3$) 1.72 (s, 3H, CH_3), 1.73-2.11 (m, 7H, $3CH_2$, NH), 2.37 (d, 1H, J=14Hz, CH-C=CH_2), 2.70 (d, 1H, CH-C=CH_2), 2.38-2.88 (m, 2H, CH_2CO), 3.48 (d, 1H, J=12Hz, CHPh), 3.78 (d, 1H, CHPh), 4.76 (brs, 1H, C=CH_2) ; 4.9 (brs, 1H, C=CH_2), 7.12-7.52 (m, 5H, Ph) ; ^{13}C NMR (75.4 MHz, $CDCl_3$) 21.3, 24.7, 37.6, 39.3, 41.6, 46.9,

66.1, 115.1, 126.9, 128.1, 128.3, 140.7, 141.5, 213.4 ; Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33 ; H, 9.0 ; N, 5.44 ; O, 6.21. Found : C, 78.66 ; H, 9.15 ; N, 5.37 ; O, 6.45.

(Z,E)-2-Benzylamino-2-(but-2-en-1-yl)cyclohexanone (12g). Yellow oil (31% yield, Z/E = 45:55) ; IR (neat) 3090, 3060, 3030, 1715, 1610 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) 1.62 (d, 3H, J=6Hz, CH_3), 1.71-2.06 (m, 7H, $3CH_2$, NH), 2.18-2.41 (m, 2H, C<u>H</u>$_2$CO), 2.34-2.76 (m, 2H, C<u>H</u>$_2$-CH=CH), 3.45 (d, 0.45H, J=12Hz, C<u>H</u>Ph), 3.46 (d, 0.55H, C<u>H</u>Ph), 3.64 (d, 0.45H, J=12Hz, C<u>H</u>Ph), 3.65 (d, 0.55H, C<u>H</u>Ph), 5.2-5.4 (m, 1H, CH=C<u>H</u>-CH$_3$), 5.45-5.72 (m, 1H, C<u>H</u>=CH-CH$_3$), 7.20-7.50 (m, 5H, Ph) ; ^{13}C NMR (75.4 MHz, $CDCl_3$) *Z* isomer 13.2, 22.6, 31.2, 37.5 (2C), 38.9, 46.9, 66.0, 126.9, 127.4, 128.1, 128.4, 129.4, 140.8, 213.6 ; *E* isomer 18.2, 22.6, 27.4, 37.3 (2C), 39.1, 46.8, 66.0, 124.1, 124.9, 126.9, 128.1, 128.4, 140.8, 213.5.

2-Benzylamino-2-(3-trimethylsilylprop-2-ynyl)cyclohexanone (12h). Yellow oil (82% yield) ; IR (neat) 3080, 3060, 3025, 2170, 1710, 1605, 1250, 845, 755 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) 0.14 (s, 9H, $Si(CH_3)_3$), 1.5-1.84 (m, 3H), 1.95-2.31 (m, 3H), 2.30 (d, 1H, J=17Hz, C<u>H</u>-C≡C), 2.9-3.04 (m, 1H), 3.09 (d, 1H, C<u>H</u>-C≡C), 3.22 (d, 1H, J=12Hz, C<u>H</u>Ph), 3.7 (d, 1H, C<u>H</u>Ph), 7.20-7.43 (m, 5H, Ph) ; ^{13}C NMR (75.4 MHz, $CDCl_3$) 0.3, 20.5, 25.1, 28.3, 38.6, 39.1, 47.1, 64.8, 83.2, 102.8, 127.0, 128.2, 128.3, 140.2, 212.6 ; MS *m/z* (relative intensity) 313 (1.5)M^+ ; Anal. Calcd for $C_{19}H_{27}NOSi$: C, 72.79 ; H, 8.68 ; N, 4.47 ; O, 5.10. Found : C, 72.55 ; H, 8.53 ; N, 4.58 ; O, 5.04.

Rearrangement effected on enantioenriched (-)-**2e** (>96% ee) gave α-aminoketone **12h** in 84% yield ; $[\alpha]_D$-86 (*c* 1.93, $CHCl_3$). The optical purity and absolute configuration of (-)-**12h** were established by its transformation to the known spiropiperidine (+)-**18**.

(Z)-2-Benzylamino-2-(3-trimethylsilylprop-2-enyl)cyclohexanone (12i). Oil (46% yield) ; $[\alpha]_D$+52 (*c* 2.75, $CHCl_3$) ; IR (neat) 3080, 3060, 3020, 1710, 1600, 1245, 855, 760, 730, 700 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) 0.3 (s, 9H, $Si(CH_3)_3$), 1.55-2.10 (m, 7H, $3CH_2$, NH), 2.28-2.42 (m, 1H, C<u>H</u>CO), 2.45 (ddt, 1H, J=15, 8, 1.2Hz, C<u>H</u>-CH=CH), 2.76 (ddt overlapping m, 2H, J=15, 6, 1.5Hz, C<u>H</u>-CH=CH, C<u>H</u>CO), 3.47 (d, 1H, J=12.3Hz, C<u>H</u>Ph), 3.72 (d, 1H, C<u>H</u>Ph), 5.68 (dt, 1H, J=14, 1.5Hz, CH=C<u>H</u>SiMe3), 6.26 (sept, 1H, J=14, 8, 6Hz, C<u>H</u>=CHSiMe3), 7.20-7.45 (m, 5H, Ph) ; ^{13}C NMR (50.3 MHz, $CDCl_3$) 0.3, 21.1, 26.1, 37.0, 37.6, 38.9, 46.8, 65.5, 127.0, 128.1, 128.4, 132.6, 140.7, 142.3, 213.4 ; Anal. Calcd for $C_{19}H_{29}NOSi$: C, 72.33 ; H, 9.26 ; N, 4.44. Found : C, 72.54 ; H, 9.31 ; N, 4.51.

3-Benzylamino-3-methylhex-5-en-2-one (12j). Colorless oil (65% yield) ; IR (neat) 3080, 3060, 3020, 1710, 1640, 1605, 1350, 920, 740 cm^{-1} ; ^1H NMR (80 MHz, $CDCl_3$) 1.32 (s, 3H, CH_3), 1.73 (s, 1H, NH), 2.25 (s, 3H, CH_3), 2.45 (d, 2H, J=6Hz, C<u>H</u>$_2$-CH=CH$_2$), 3.62 (s, 2H, C<u>H</u>$_2$Ph) 4.95-5.33 (m, 2H, CH=C<u>H</u>$_2$), 5.5-6.07 (m, 1H, C<u>H</u>=CH$_2$), 7.15-7.50 (m, 5H, Ph) ; ^{13}C NMR (75.4 MHz, $CDCl_3$) 21.5, 24.9, 41.2, 47.8, 65.7, 118.8, 127.0, 128.1, 128.3, 132.9, 140.3, 212.5 ; Anal. Calcd for $C_{14}H_{19}NO$: C, 77.37 ; H, 8.81 ; N, 6.64. Found : C, 77.48 ; H, 8.91 ; N, 6.52.

2-([2,3-$^2H_1$]allyl)-2-hydroxycyclohexanone (13). To a solution of ketol **12e** (0.2 g, 0.09 mmol) in THF (4 ml) was added *n*-Bu4NF solution ((1M in THF, 1.1 ml, 1.2 equiv). After stirring for 30 min, the solution was filtered on a bed of silica gel and the filtrate concentrated *in vacuo*. The residue (0.095 g) was dissolved in EtOH (3 ml) and stirred under D_2 atmosphere, in the presence of Pd on $BaSO_4$ (0.03 g) and quinoline (1 drop). After consumption of 1 equiv of D_2, the reaction mixture was filtered on a bed of celite and washed with EtOH. After concentration *in vacuo*, the residue was purified by flash chromatography (petroleum ether-Et_2O, 5:1) to give the deuterio compound **13** (0.07 g, 72% yield) as an oil ; IR (neat) 3480, 3020, 1710, 1600 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) 1.50-1.95 (m, 4H, $2CH_2$), 2.05-2.34 (m, 2H, CH_2), 2.35-2.65 (m, 4H, $C\underline{H}_2CO$, $C\underline{H}_2$-CH=CH_2), 3.95 (s, 1H, OH), 5.10 (brs, 1H, CD=C$\underline{D}$H) ; ^{13}C NMR (50.3 MHz, $CDCl_3$) 22.6, 28.0, 38.3, 40.3, 41.6, 78.8, 118.3 (t, J_{CD}=24Hz), 131.2 (t, J_{CD}=24Hz), 213.5.

2-([2,3-$^2H_1$]allyl)-2-(3,3-dimethoxyethylamino)cyclohexanone (14). Amino ketone **14** was obtained from ketol **13** in 59% yield following the general procedure ; IR (neat) 3350, 3020, 1710, 1600 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) 1.62-2.0 (m, 7H, $3CH_2$, NH), 2.15-2.40 (m, 2H, $C\underline{H}_2CO$), 2.45 (dd, 1H, J=12, 5.5Hz, C$\underline{H}$CH$(OMe)_2$), 2.68 (dd, 1H, C$\underline{H}$-CH$(OMe)_2$), 2.48-2.7 (m, 2H, $C\underline{H}_2$-CD=CHD), 3.37 (s, 6H, $2OCH_3$) 4.42 (t, 1H, J=5.5Hz, C$\underline{H}(OCH_3)_2$), 5.08 (brs, 1H, CD=C$\underline{H}$D) ; ^{13}C NMR (50.3 MHz, $CDCl_3$) 21.1, 27.3, 37.3, 38.2, 38.9, 43.6, 53.4, 54.0, 64.9, 104.3, 118.3 (t, J=24Hz), 132.3 (t, J=24Hz), 214.8 ; Anal. Calcd for $C_{13}D_2H_{21}NO_3$: C, 64.17 ; H, 8.70 ; N, 5.76. Found : C, 64.27 ; H, 8.51 ; N, 5.77.

1-Allyl-2-benzylaminocyclohexan-1-ol (16). To a suspension of 4-toluenesulfonic acid monohydrate (0.246 g, 1.3 mmol) in toluene (5 ml) was added benzylamine (0.15 ml, 1.37 mmol). After stirring the mixture for 10 min at room temperature, α-ketol **2a** (0.2 g, 1.3 mmol) was added and the reaction mixture was refluxed with removal of water through Dean-Stark apparatus. After 48 h of reflux, the mixture was cooled down to room temperature and diluted with Et_2O. The organic phase was extracted twice with 0.1 N HCl solution. The aqueous layer was basified with saturated $NaHCO_3$ solution and extracted twice with Et_2O. The etheral extracts were washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (petroleum ether-Et_2O, 3:1) to give compound **12a** (0.019 g, 6% yield) which are spectral data identical to an authentic sample. Elution with a mixture of (petroleum ether : Et_2O, 1:2) afforded amino alcohol **16** [0.064 g, 20% yield ; one major diastereomer (90% de)] ; IR (neat) 3470, 3060, 3020, 1640, 1605, 1450, 1120, 910, 740, 705 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) 1.05-1.27 (m, 4H), 1.50-1.67 (m, 1H), 1.67-1.78 (m, 1H), 1.81-1.92 (m, 1H), 1.95-2.08 (m, 1H), 2.26 (dd, 1H, J=14, 7Hz, C$\underline{H}$-CH=CH_2), 2.30 (dd, 1H, C$\underline{H}$-CH=CH_2), 2.48 (dd, 1H, J=12, 4Hz, CH_aNH), 3.64 (d, 1H, J=13Hz,C$\underline{H}$Ph), 3.92 (d, 1H, C$\underline{H}$Ph), 5.08 (brd, 1H, J=16Hz, CH=C$\underline{H}_2$), 5.10 (brd, 1H, J=8Hz, CH=C$\underline{H}_2$), 5.83-6.02 (m, 1H, C$\underline{H}$=CH_2), 7.18-7.38 (m, 5H, Ph) ; ^{13}C NMR (75.4 MHz, $CDCl_3$) 22.4, 24.8, 27.9, 35.2, 36.8, 46.5, 65.1, 73.4, 117.7, 127.0, 128.1, 128.4, 134.2, 140.6 ; MS *m/z* (relative intensity) 245 (1) M^+ ; Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32 ; H, 9.45 ; N, 5.71. Found : C, 78.20 ; H, 9.39 ; N, 5.66.

(+)-1-Benzyl-1-azaspiro[5.5]undec-3-en-7-one (17). To a solution of amino ketone (-)-**12i** (0.15 g, 0.47 mmol) in CH_3CN (2.5 ml) were added paraformaldehyde (0.036 g, 1.2 mmol) and camphorsulfonic acid (0.11 g, 0.47 mmol). The reaction mixture was heated at 70°C for 4 h. After concentration *in vacuo*, the residue was dissolved in CH_2Cl_2 and added to a mixture of CH_2Cl_2-saturated $NaHCO_3$ solution (30 ml, 2:1). The aqueous phase was extracted with CH_2Cl_2 (3x20 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (petroleum ether-Et_2O, 95:5) to give **17** (0.088 g, 73% yield) as a colorless oil ; $[\alpha]_D$+ 11 (c 1.88, $CHCl_3$) ; IR (neat) 3080, 3060, 3020, 1710, 1650, 1600, 1585, 730, 695, 650 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) : 1.21-1.40 (m, 1H), 1.45-1.82 (m, 3H), 2.09-2.35 (m, 3H), 2.38 (dq, 1H, J=14.4, 2.9Hz), 2.67 (quint d, 1H, J=18.3, 2.9Hz), 2.89 (brd, 1H, J=18.2Hz), 3.08-3.27 (m, 2H), 3.28 (d, 1H, J=14.3Hz, C<u>H</u>Ph), 3.71 (d, 1H, C<u>H</u>Ph), 5.45 (dm, 1H, J=10Hz, C<u>H</u>=CH), 5.82 (dm, 1H, J=10Hz, CH=C<u>H</u>), 7.18-7.42 (m, 5H, Ph) ; ^{13}C NMR (50.3 MHz, $CDCl_3$) 20.1, 25.9, 29.8, 37.8, 38.3, 44.0, 52.4, 66.7, 122.9, 124.6, 126.9, 128.1, 128.4, 139.8, 215.5 ; Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96 ; H, 8.29 ; N, 5.49. Found : C, 80.16 ; H, 8.40 ; N, 5.63.

(+)-1-Benzyl-1-azaspiro[5.5]undecan-7-one (18). To a solution of compound **17** (0.075 g, 0.29 mmol) in EtOAc (10 ml) was added PtO_2 (0.034 g). The suspension was vigorously stirred under hydrogen atmosphere at room temperature. After consumption of 1.15 equiv of H_2 (7.6 ml) in 10 min, the reaction mixture was filtered on celite. After concentration *in vacuo* the residue was purified by flash chromatography (petroleum ether-Et_2O, 95:5) to give **18** as a colorless oil (0.041 g, 54% yield) ; $[\alpha]_D$ + 15 (c 2.06, $CHCl_3$) ; (lit[21] $[\alpha]_D$ + 15 (c 1.57, $CHCl_3$). Its spectroscopic data (^1H and ^{13}C NMR, IR) were identical with those of an authentic sample[31].

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