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ASYMMETRIC SYNTHESES VIA METALATED CHIRAL HYDRAZONES

OVERALL ENANTIOSELECTIVE α-ALKYLATION OF ACYCLIC KETONES[1]

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Abstract—A general method is described, which allows the overall enantioselective α-alkylation of acyclic ketones in good overall yields (44–86%, 4 steps) and enantioselectivities ranging routinely from > 94% ee up to virtually complete asymmetric induction (99.5% ee). The acyclic ketones are transformed to their corresponding "*SAMP*-hydrazones" (*S*)-**2** by reaction with the enantiomerically pure hydrazine (*S*)-1-amino-2-methoxymethyl-pyrrolidine [*SAMP*, (*S*)-**1**], readily available from (*S*)-proline. Metalation to form chiral azaenolates (*S*)-**3** of $E_{CC}Z_{CN}$-configuration and then alkylation to product hydrazones **4**, followed by hydrazone cleavage via acidic hydrolysis of methiodides **9** in a two phase system or ozonolysis, leads to α-substituted, enantiomerically enriched, acyclic ketones **5**. In special cases, where a phenyl group is directly attached to the newly generated center of chirality (**5a,o,p**), only low enantiomeric excesses are observed. 17 Examples, including first applications in natural product synthesis (*cf* **5a,b,e**, and **h**) are summarized.

Carbon–carbon bond formations α to the CO group of aldehydes and ketones are among the most important synthetic operations in organic chemistry. Most of the problems of this classical carbonyl chemistry, such as aldol type self condensation, di- and polyalkylation, control of regiochemistry, side reactions of products, and lack of reactivity, have been solved in the past two decades with lithio enolate type reagents. Especially metalated imines, oximes, and hydrazones ("azaenolates") have been used extensively as reactive enolate equivalents in recent years.[2]

Although it is evident from the general Scheme 1 demonstrating the "hydrazone method"[3] that this strategy requires two additional steps to carry out the desired electrophilic substitution—introduction ① and removal ④ of the control group—this more circuitous route has many advantages. Among the most important of these is the ability to introduce a "chiral information" via an enantiomerically pure hydrazine, thus enabling an enantioselective control of the C–C bond forming process.

In view of the often different biological activity of enantiomers, the synthesis of pharmaceuticals, pesticides, food additives, pheromones, etc of high enantiomeric purity is of considerable significance and a challenge in synthetic chemistry. With this in mind and based on the above mentioned hydrazone methodology, our group has been able in the past seven years to develop an efficient, overall enantioselective version of the classical electrophilic substitution α to the CO group of aldehydes and ketones.[4] Utilizing (*S*)- or (*R*)-1-amino-2-methoxymethyl-pyrrolidine (*SAMP*[5] or *RAMP*[6]) as the chiral auxiliary, this approach has turned out to be very successful and experimental details of α-alkylation of cyclic ketones

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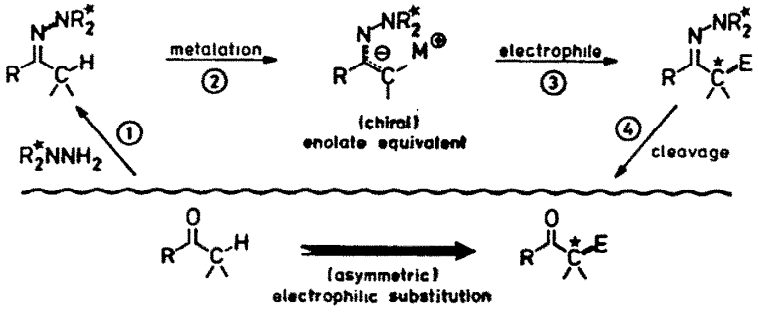


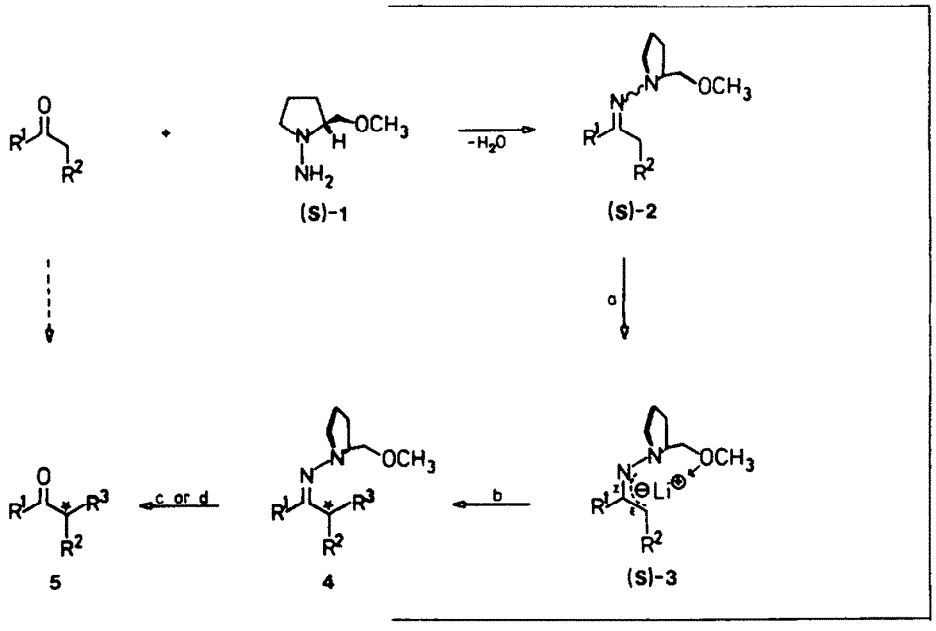
Scheme 1.

and aldehydes† have already been published.[5] In this communication we wish to report in full our results concerning a large number of α-alkylations of acyclic ketones.

According to the general Scheme 1, acyclic ketones are transformed to their corresponding *SAMP*-hydrazones (*S*)-**2** by reaction with the enantiomerically pure hydrazine *SAMP* [(*S*)-**1**], easily prepared in four steps and *ca* 50% overall yield from (*S*)-proline. Metalation with lithium diisopropylamide in ether at 0° to form the chiral azaenolates (*S*)-**3**, followed by alkylation with various iodides and bromides at −110°, furnishes the product hydrazones **4**. Finally, hydrazone cleavage, either by acidic hydrolysis of the methiodides in a two phase system of 3N HCl/n-pentane or by ozonolysis in n-pentane at −78°, leads to the α-substituted acyclic ketones **5** in good overall yields of 44–86% and enantiomeric excesses ranging routinely from >94% up to 99.5% ee.

in a refrigerator. Characteristic spectroscopic features are the methoxy singlet at 3.2–3.4 ppm (^{1}H-NMR), the IR-absorption band of the CN-double bond at 1600-1645 cm^{-1}, and a base peak at $M^+-CH_2OCH_3$ in the mass spectra (Experimental). In the case of unsymmetrical ketones, *E*/*Z*-mixtures of geometrical isomers are obtained. Some data are summarized in Table 1.

In asymmetric electrophilic substitutions α to the CO group, the overall enantioselectivity and thus the enantiomeric excess of the final products **5** depends on three of the four steps of the procedure—the stereoselectivity of the deprotonation ②, the stereoselectivity of the alkylation ③, and the mildness of the hydrazone cleavage ④. In the deprotonation step ② four different anionic species, the $E_{CC}E_{CN}$, $E_{CC}Z_{CN}$, $Z_{CC}E_{CN}$, and $Z_{CC}Z_{CN}$ geometrical isomers can theoretically be generated. Whereas in small to normal ring ketones the C_1–C_2 geometry of the intermediate azaenolates of type (*S*)-**3** must be *E*, in metalations of



a: LiN(i-Pr)$_2$, Et$_2$O, 0°; *b*: R^{3}X (X = Br, I), −110°; *c*: 1. exc. MeI, 60°, 2. 3N HCl, n-pentane; *d*: O$_3$, n-pentane, −78°.

The *SAMP*-hydrazones (*S*)-**2** are usually prepared in excellent yields by simply mixing the ketone and *SAMP* and stirring at 60° for a few hr. In the case of aromatic ketones ($R^1 = C_6H_5$) with lower CO reactivity, longer reaction times are necessary and the reaction water has to be removed azeotropically by refluxing in benzene using a Dean-Stark trap. After purification by distillation or chromatography, the hydrazones (*S*)-**2** are isolated as colorless to pale yellow oils, which can be safely stored under Argon

conformationally much more flexible acyclic systems, C_1–C_2-*E*/*Z* mixtures might be formed and therefore, assuming a uniform mechanism, the maximum overall enantioselectivity would be limited to this *E*/*Z*-ratio. Another problem would be the stereoselective formation of one of the four possible anionic species which shows a low alkylation selectivity. Indeed, such problems exist in Meyers' successful imine method (phenylalaninol methylether as chiral auxiliary), but could be solved very elegantly by thermally equilibrating the azaallyllithium intermediates in refluxing THF.[8]

Fortunately, under the standard deprotonation conditions (LDA, THF or Et$_2$O, 0°), lithiated *SAMP*-hydrazones (*S*)-**3** are stereoselectively generated as $E_{CC}Z_{CN}$-species exclusively. This has been confirmed by numerous trapping experiments,[1b,5,7,10] which reflect the C–N stereochemistry of the "anions" (the *Z*-product hydrazones are formed under mild work up conditions, *cf* *ZSS*-**4b**, Fig. 1, *vide infra*), and NMR spectroscopic investigations,[10,11] allowing the assignment of the C_1–C_2 geometry of the

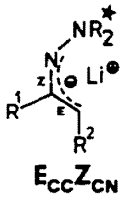
†In the meantime the reported asymmetric inductions in the aldehyde alkylations of up to 86% ee have been optimized using ether instead of THF as solvent during C–C bond formation and enantiomeric excesses of >90% are now routinely reached, see Ref.[4b,c]

Table 1. *SAMP*-hydrazones (*S*)-**2** prepared from ketones and (*S*)-**1**

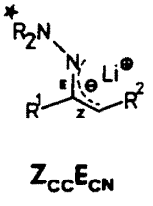
(S)-2	R^1	R^2	$[\alpha]_D^{20}$ (c, C_6H_6) [α_D^{20} (neat)]	reaction time [h] [a]	yield [%] crude [b]	pure [c]
a [7]	C_2H_5	CH_3	+297° (1.0) [+223°]	20	95	87
b	n-C_3H_7	C_2H_5	+243° (3.2) [+203.5°]	11	91	75
c	n-C_4H_9	n-C_3H_7	+209° (2.6) [+175.3°]	12	90	76
d	C_6H_5	CH_3	+733° (1.3) [+710°]	72 [d]	88	74
e	C_6H_5	C_2H_5	+640° (2.1) [+623°]	144 [d]	100	87
f	CH_3	C_6H_5	+284.6° (1.98) [+280.4°]	5	97	80
g	$C_6H_5CH_2$	C_6H_5	+146° (1.0) [+150°]	6	95	88
h	C_6H_5	C_6H_5	+746.7° (0.6) [+709°] [e]	24 [d]	>95	93

a. Ketone and (S)-1 are stirred at 60° . b. The crude products are usually pure by IR, NMR and TLC. c. After short path distillation over glasswool or column chromatography. d. In refluxing benzene and separation of the reaction water using a Dean-Stark trap. e. Corresponds to $[\alpha]_D^{20}$ = +678° (c=1, C_6H_6) of a separate preparation.

azaallyl anion moiety. For instance, in the case of aldehyde hydrazones the C_1–C_2 configuration can easily be determined by directly measuring the ^{1}H NMR spectra of the metalation solution and inspection of the coupling constant of the formyl proton.[10] The ^{13}C NMR spectra were measured in the same manner.[11] Since the interesting C_1/C_2 signals appear at low field and do not overlap with the strong solvent peaks, the use of ^{13}C-enriched starting materials is not necessary.[12,13] For instance, the lithiated *SAMP*-hydrazone $E_{CC}Z_{CN}$-(*S*)-**3a** displays signals at 158.3 ppm (C_1), 70.0 ppm (C_2), and 79.4 ppm (OCH_2) (THF-metalation solution plus HMPA to dissolve the precipitate, −30°). However, when (*S*)-**2a** is deprotonated in THF in the presence of 2.2 equivalents of HMPA, $Z_{CC}E_{CN}$-(*S*)-**3a** is formed predominantly [$Z_{CC}E_{CN}$-: $E_{CC}Z_{CN}$-(*S*)-**3a** = *ca* 3.5:1], showing signals at 163.6 ppm (C_1), 72.3 ppm (C_2), and 79.4 ppm (OCH_2). Thus, in principle it should also be possible to achieve opposite enantioselectivity in acyclic ketone alkylations by simply modifying the deprotonation conditions, while employing a chiral auxiliary of the same configuration. This was demonstrated for the first time through α-alkylations of n-propanal.[10]



$E_{CC}Z_{CN}$



$Z_{CC}E_{CN}$

Although the configuration of the lithiated *SAMP*-hydrazones (*S*)-**3** can be determined by combinations and correlations of trapping experiments and NMR spectroscopic measurements as described, as well as the existence of an intramolecular chelation of Li by the OMe group indicated in the formula,[14] not very much is known about the N–N conformation and the molecular aggregation. Consequently, the specific position of the metal in these species is uncertain and thus, the drawing of (*S*)-**3** in the specific N–N conformation shown and as a monomer is hypothetical.

In addition to the virtually complete deprotonation selectivities, excellent diastereoselectivites are observed in the alkylation step. This is evident from the diastereomeric excess (de) of the product hydrazones

Table 2. α-Alkylations of *SAMP*-hydrazones (*S*)-**2** to form product hydrazones **4**

(S)-4	R^1	R^2	R^3	prepared from (S)-2 + R^3X	yield [%] crude	pure [a]
a	C_2H_5	CH_3	C_2H_5	(S)-2a + C_2H_5I	~100	82
b	C_2H_5	CH_3	n-C_3H_7	(S)-2a + n-C_3H_7I	~100	91
c	C_2H_5	CH_3	n-C_6H_{13}	(S)-2a + n-$C_6H_{13}Br$	~100	87.5
d	C_2H_5	CH_3	c-$C_6H_{11}CH_2$	(S)-2a + c-$C_6H_{11}CH_2Br$	~100	95
e[7]	C_2H_5	CH_3	$H_3COCH{=}^{E}C(CH_3)CH_2$	(S)-2a + R^3Br	~100	85
	C_2H_5	CH_3	$H_3COCH{=}^{E}C(CH_3)CH_2$	(R)-2a + R^3Br	~100	85
f	C_2H_5	CH_3	t-$C_4H_9OCOCH_2$	(S)-2a + t-$C_4H_9OCOCH_2Br$	93	65
g	C_2H_5	CH_3	$C_2H_5O_2CCH{=}^{E}C(OC_2H_5)CH_2$	(S)-2a + R^3Br	~100	78
h[15]	C_2H_5	CH_3	$C_2H_5CH(OR)CH(CH_3)CH_2$	(S)-2a + R^3I		
i	n-C_3H_7	C_2H_5	CH_3	(S)-2b + CH_3I	99	83
j	n-C_3H_7	C_2H_5	n-C_3H_7	(S)-2b + n-C_3H_7I	99	85
k	n-C_4H_9	n-C_3H_7	CH_3	(S)-2c + CH_3I	~100	82
l	n-C_4H_9	n-C_3H_7	C_2H_5	(S)-2c + C_2H_5I	97	82
m	C_6H_5	CH_3	C_2H_5	(S)-2d + C_2H_5I	95	88
m'	C_6H_5	C_2H_5	CH_3	(S)-2e + CH_3I	100	90
n	CH_3	C_6H_5	CH_3	(S)-2f + CH_3I	~100	93 [b]
o	$C_6H_5CH_2$	C_6H_5	CH_3	(S)-2g + CH_3I	98	77
p	C_6H_5	C_6H_5	CH_3	(S)-2h + CH_3I	98	68

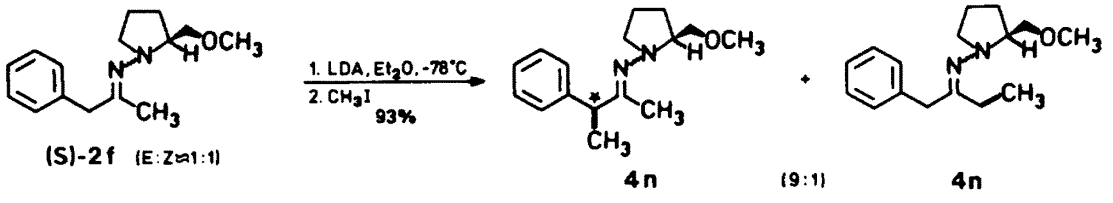
a. After purification by short path distillation or column chromatography.

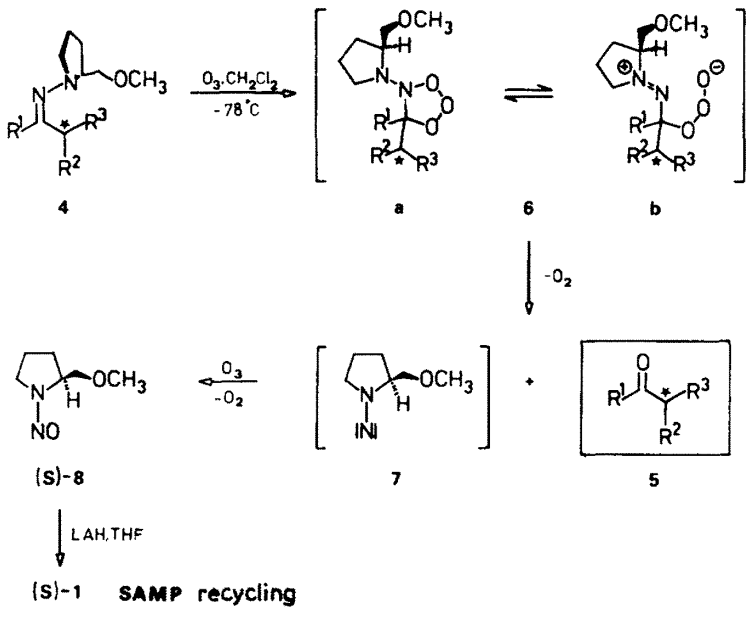
b. Contaminated by ca. 10% of the regioisomer (S)-4n' (^{1}H NMR: t at 0.95 ppm).

4, which are easily determined by ^{1}H NMR shift experiments (e.g. **4b**, Fig. 2, *vide infra*) and further confirmed by the enantiomeric excess of the final products **5**. As can be seen from the crude yields given in Table 2, the ether suspensions of (*S*)-**3** usually can be "titrated" with a variety of reactive bromides and iodides almost quantitatively. In all cases tested so far, the C–C bond formation takes place exclusively at the carbon terminus of the ambident azaallyl anion system and not even a trace of an N-alkylation isomer or di- and polyalkylation side products could be detected. The crude product hydrazones **4** are usually clean enough to be cleaved in the final step without further purification. They are colorless to pale yellow oils, which can be distilled or chromatographed without epimerization. Upon storage in a refrigerator, no change of optical rotations could be observed over a period of several months. Thus, they constitute protected α-chiral acyclic ketones, which can be safely stored over an extended period of time. The sensitive optically active carbonyl compounds may be regenerated for further use whenever the need arises.

Since most of the starting ketones used in this work were either symmetrical or R^1 possessed no α-hydrogens (e.g. R_1 = phenyl), the formation of regioisomers was not a problem. Only in the alkylation of (*S*)-**2f** to form **4n** could a small amount of the regioisomer **4n'** be detected. All α-alkylations of *SAMP*-hydrazones (*S*)-**2**, including a very elegant application in natural product synthesis by Mori *et al.*,[15] are summarized in Table 2.

In order not to lose any optical activity, the regeneration of the α-substituted, enantiomerically enriched ketones **5** from the product hydrazones **4** must take place without any epimerization and/or racemization at the newly generated chiral center. Classical cleavage procedures, such as heating with





acid or base,[16] can not be used, since the sensitive "α-chiral" ketones rapidly racemize under these harsh conditions. Fortunately, a wide palette of relatively mild cleavage procedures, some 40 different methods, are presently at our disposal.[17] In the special case of *SAMP/RAMP*-hydrazones, two variants have proven to be practically useful and mild enough to regenerate the very sensitive, optically active, "α-chiral" aldehydes and ketones.[5]

Oxidative cleavage of **4** by ozonolysis (method A) in methylene chloride at −78° is a very clean reaction, and the only products formed are the desired ketones **5** and one equivalent of the nitrosoamine (*S*)-**8** in quantitative yield. The latter allows a recycling of the chiral auxiliary after separation by distillation or flash chromatography, followed by lithium aluminiumhydride reduction. While the chemical yield of the recycling step is good (*ca* 80%), a loss of up to 10% of the optical activity was observed in some cases.

Although the mechanism of the ozonolysis is not yet exactly known, it is conceivable that the oxidative CN-bond cleavage, as for dimethylhydrazones,[18] starts with intermediates of type **6a** and/or **b**, which can directly decompose to the carbonyl compounds **5**, oxygen and an aminonitrene **7**. Under the reaction conditions **7** can be oxidized with a second equivalent of ozone to the nitrosoamine (*S*)-**8**. A Criegee type mechanism via an azaozonide seems unlikely, since (a) nitrosoamines are not good dipolarophiles, (b) two equivalents of ozone are consumed,[18] and (c) external water must be present, which is not the case.

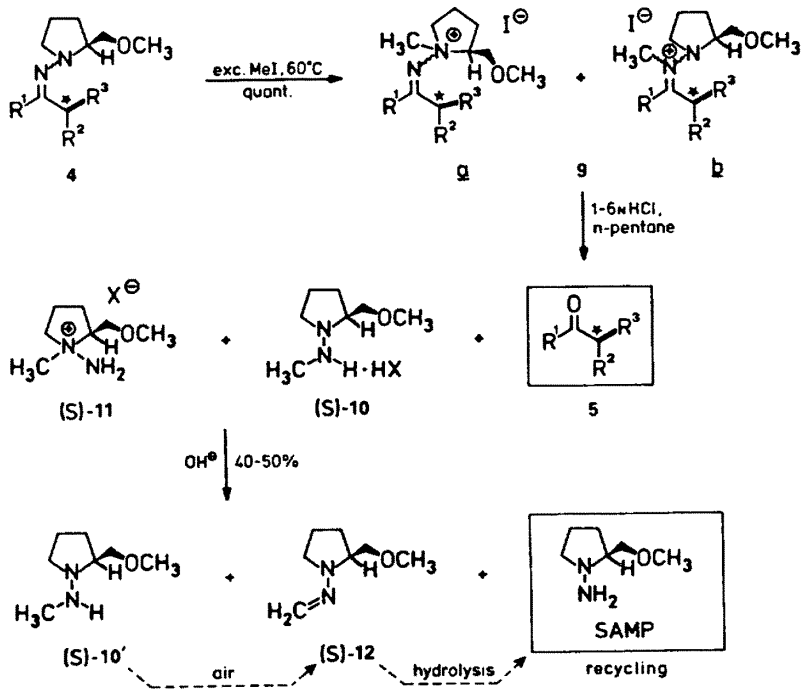
Advantages of the oxidative cleavage by ozonolysis are the extremely mild reaction conditions, low temperature (−78°), neutral milieu and short reaction times (15–30 min in a 10 mmole experiment), the ease of detecting the end of the reaction (appearance of a green colored mixture of yellow nitrosoamine and blue ozone), the excellent, almost quantitative yields and last but not least, the lack of any racemization of the sensitive ketones during the operation.

Of course, method A cannot be applied in the presence of other functional groups which are not compatible with ozone under the reaction conditions. In this case method B ("salt method") may be applied.

According to Levisalles *et al.*,[19] dimethylhydrazones can be hydrolyzed under much milder conditions, if they are transformed to their corresponding trimethylhydrazonium iodides. For the conversion of *SAMP/RAMP*-hydrazones to optically active carbonyl products, an even milder two phase variant was developed.[5]

Treatment of **4** with excess methyl iodide at 60° leads quantitatively to a mixture of the methiodides **9a** and **b**, which are hydrolyzed without further purification in a two phase system (3–4 N HCl/n-pentane) to afford the ketones **5** in good to excellent yields and short reaction times (15–60 min). By comparison of the percent de in **4** and the percent ee in **5** (*cf* **4b/5b**), it was evident that this two phase procedure also occurred without any racemization. Obviously the carbonyl products **5** are rapidly transferred with vigorous stirring into the pentane phase, which is free of acid. For instance, solutions of optically active ketones in n-pentane can be stirred for one hour in the presence of 3N HCl without any change in their optical rotations. Against the prevailing opinion and in agreement with similar observations by S. Yamada *et al.*[20] and later Meyers *et al.*,[21] α-chiral ketones and aldehydes are unexpectedly resistant against racemization in an acidic environment. Traces of base however, lead to complete racemization within seconds.

When the aqueous acidic layer, expected to contain the chiral auxiliary in the form of salts (*S*)-**10** and (*S*)-**11**, is neutralized and extracted, the hydrazine (*S*)-**10′**, formaldehyde-*SAMP*-hydrazone (*S*)-**12**, and *SAMP* were isolated in a ratio of 1:7:2 (40–50% yield). While the ammonium salt (*S*)-**11** remains in the aqueous phase, trisubstituted hydrazines such as (*S*)-**10′** are known to easily undergo air oxidation to



formaldehyde hydrazones like (*S*)-**12**, which itself is hydrolyzed to *SAMP*. In this way, at least a partial recycling of *SAMP* or *RAMP* is possible.

The method is best exemplified with the asymmetric synthesis of (+)-(*S*)-4-methyl-3-heptanone (**5b**), the principal alarm pheromone of the leaf-cutting ant *Atta texana*, which is 400 times more active than its optical antipode.[16,22] **5b** has also been identified as an alarm pheromone in three other ant genera of the subfamily *Myrmicinae*,[23] as well as a component of the defensive secretion of *Leiobunum vittatum*.[7,24] Pentane-3-one is converted into the corresponding *SAMP*-hydrazone (*S*)-**2a**, which is metalated with LDA in ether at 0° followed by treatment of the suspension of the lithiated intermediate (*S*)-**3a** with n-propyl iodide at −110°. The resulting diastereomerically pure product hydrazone (*ZSS*)-**4b** is subjected to acid cleavage *via* method B, affording the pheromone (*S*)-**5b** in an overall chemical yield of 60% by this three-step procedure. The optical purity consistently exceeded 99% in several preparations, which demonstrates complete acyclic stereochemical control of the three critical operations: metalation, alkylation, and cleavage. In other words, the (*pro*-*S*)-H of the two enantiotopic hydrogens of diethyl ketone is enantiospecifically replaced by the propyl group and thus, *this classical electrophilic substitution of an acyclic ketone occurs with virtually complete asymmetric induction!*

One advantage of the *SAMP*/*RAMP*-method is

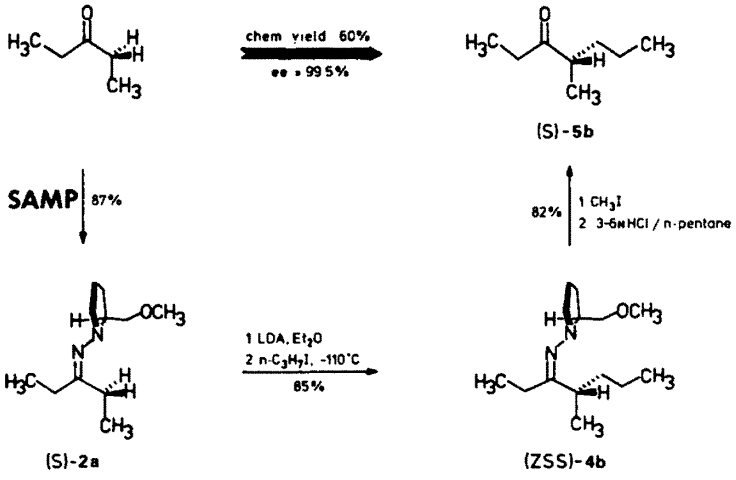


Fig. 1. Asymmetric synthesis of the alarm pheromone of the leaf-cutting ant *Atta texana*. Virtually complete acyclic asymmetric induction.

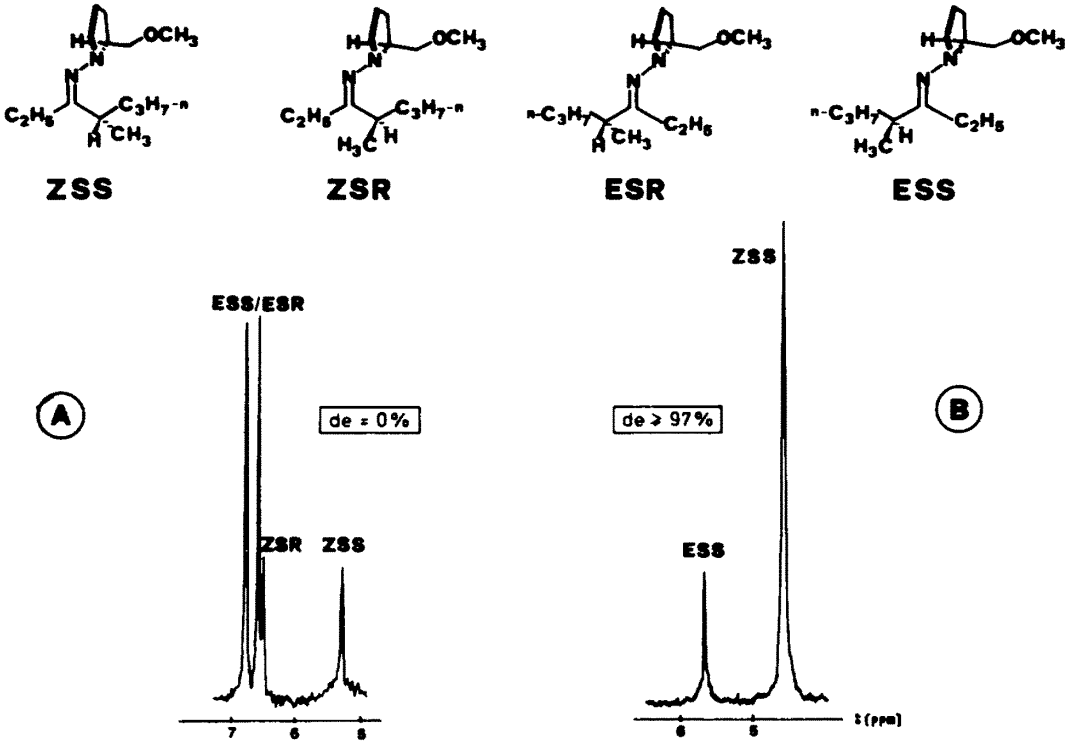


Fig. 2. Simple and reliable determination of the diastereomeric excess (de) by ^{1}H NMR shift experiments [100 MHz, $CDCl_3$, Eu (fod)$_3$].

the fact that the ratio of product diastereomers **4** present in the crude products, and thus the degree of asymmetric induction, can easily be measured by simple ^{1}H NMR shift experiments. After addition of a small amount of shift reagent [e.g. Eu(fod)$_3$], the sharp methoxy singlet at *ca* 3.2–3.4 ppm is strongly shifted to lower field by about 1–4 ppm, usually does not overlap with other signals, and thus can serve as an ideal intramolecular probe for the presence of each single diastereomer formed during asymmetric C–C bond formation. For instance, a 1:1 diastereomeric mixture of *SAMP*-hydrazones **4b** starting from racemic 4-methyl-3-heptanone† was prepared (*E*:*Z* *ca* 70:30). As is demonstrated in Fig. 2, all four possible diastereomers are detectable by their sharp methoxy singlets (A). Inspection of the crude product of an asymmetric synthesis of the same hydrazone, prepared from (*S*)-**2a** and propyl iodide, showed that only the *ZSS*-isomer of **4b** was present (B). During measurement a slow isomerization to the thermodynamically more stable *ESS*-isomer took place, but within the limit of detection of a 100 MHz-spectrometer no *SR*-diastereomer could be seen (diastereomeric excess de $\geq$ 97%).

In most cases the enantiomeric excesses of the ketones **5** could also be determined by ^{1}H NMR shift experiments using the enantiomerically pure reagent Eu(hfc)$_3$ (Aldrich). In order to confirm the ee-determination, the racemic ketone is usually prepared, either via the DMH-method,[3] or more conveniently, by racemizing a small amount of the final product (Al_2O_3, basic, Et_2O, 1d), and again applying the LIS-technique (1:1 ratio detectable).

As is evident from Table 3, the method has a rather broad applicability and a variety of simple acyclic ketones, including another ant alarm pheromone (**5a**, genus *manica*[1b,25]), the defensive substance of "daddy longlegs" (**5e**, *Leiobunum vittatum*[7,24] and *L.calcar*[7,26]), and the sex pheromone of the cigarette beetle (serricornin **5h**, *Lasioderma serricorne F.*, Mori *et al.*[15]), could be synthesized at the >95% ee-level. The asymmetric syntheses of **5f**, **g** and **h** demonstrate that polyfunctional electrophiles may also be used very successfully. Of interest to note is that the oxidative cleavage of (*S*)-**4g** to form **5g** by ozonolysis occurs chemoselectively at the CN-double bond of the hydrazone, leaving the enolether function untouched.

Due to the uniform diastereoface differentiation common for all asymmetric *SAMP/RAMP*-hydrazone alkylations, the absolute configuration which will predominate in the final product can safely be predicted. Of course, it is also possible to prepare both enantiomers of a single ketone in excess using *SAMP* as auxiliary, simply by changing the Cahn-Ingold-Prelog (CIP) priority of R^2 and R^3 and thus

†Prepared from pentane-3-one and propyl iodide using the dimethylhydrazone method.[3]

Table 3. α-Chiral acyclic ketones **5** prepared by asymmetric synthesis via *SAMP/RAMP*-hydrazones

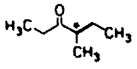
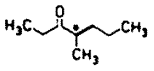
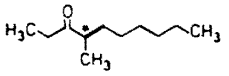
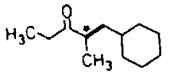
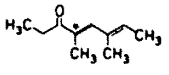
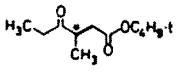
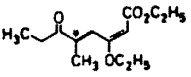
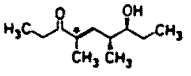
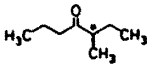
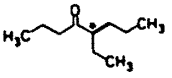
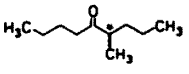
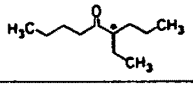
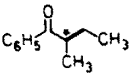
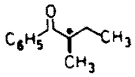
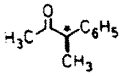
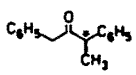
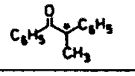
5	acyclic ketone 5	cleavage [a]	yield [%] [b]	$[\alpha]_D^T$ (c, solvent) [c] $[\alpha]_D$ (lit.)	ee [%] [d] (config.)
a		B	61	+30.2[23] (3.7, Et_2O) +32.18[20] (2.5, Et_2O)[e]	94 (S)
b		B	60	+22.0[22] (1.8, n-hexane) +22.1[25] (1.0, n-hexane)[29]	99.5 (S)
c		B	60	+20.4[22] (2.0, n-hexane) [f]	≥97 (S)
d		B	77	+22.7[22] (2.4, n-hexane) [f]	≥97 (S)
e [7]		B	61	+31.6[20] (1.4, n-hexane) [f]	≥97 (S)
		B	62	-33.0[20] (1.95, n-hexane) [f]	≥97 (R)
f		A	62	-25.5[20] (1.3, n-hexane) [f]	≥94 (S)
g		A	86	+5.7[20] (1.0, acetone)[g] [f]	≥95 (S)
h [15]		B	53	-16.7[23] (n-hexane) -17.7[23] (n-hexane)	≥99 (S)[h]
i		B	55	-20.9[22] (1.6, Et_2O) +17.5[20] (1.8, Et_2O)[27]	≥98 (R) [i]
j		B	50	+1.11[22] (2.0, Et_2O) [j]	(S)
k		B	54	-17.7[22] (2.6, Et_2O) [k]	≥98 (R)
l		B	55	-1.14[22] (1.4, Et_2O) [f]	(R)

Table 3. (*Contd*)

5	acyclic ketone 5	cleavage [a]	yield [%] [b]	$[\alpha]_D^T$ (c, solvent) [c] $[\alpha]_D$ (lit.)	ee [%] [d] (config.)
m		B	44	+36.6^{20} (4.7, Et_2O) l	≥97 (S)
m'		B	48	-27.9^{20} (1.0, Et_2O) l	≥74 (R)
n		B	57	-73.2^{22} (1.9, C_6H_6) +368^{24} (1.76, C_6H_6) [32]	20 (R) [m]
o		A	70	+88.0^{20} (1.0, C_6H_6) f,n	30 (S) [o]
		B	45	-32.4^{20} (1.76, C_6H_6) -26.0^{20} (1.1, EtOH) [39]	11 (R) [o]
p		A	72	+257^{20} (1.4, EtOH)	10 (R) [m]

a. A: Oxidative cleavage by ozonolysis. B: Two phase acidic hydrolysis. b. Overal chemical yield. c. First row: rotations of the distilled ketones shown to be pure by IR, NMR and VPC (15m, OV 101 capillary column). Second row: maximum rotation reported in the literature (in degrees). d. Determined by polarimetry and/or ^{1}H NMR shift experiments using Eu(hfc)$_3$ (Aldrich). e. Lit.[27]; rotation of pure 5a: $[\alpha]_D^{20}$= +32.2° (neat)[23]. f. Not previously reported; % ee determined by using Eu(hfc)$_3$, postulated configuration. g. Rotation of 5g obtained using THF as solvent during C-C bond formation (ee ≥50%); the ee-value given in the table is that of the ether-experiment, estimated max. rotation: $[\alpha]_D^{20}$ ≥ 11° (acetone). h. Rotations of the acetate; (4R, 6R, 7R)-5h was also synthesized using RAMP[15]. i.% de of the corresponding SAMP-hydrazone precursor 4i determined by using Eu(fod)$_3$ as NMR shift reagent. j. Meyers et al.[8] report -0.914° (3.60, Et_2O) for the R enantiomer, % ee unknown. k. Meyers et al.[8] report +14.8° (3.0, Et_2O) for the S enantiomer of 94% ee (NMR shift experiment). l. Estimated max. rotation: α_D^{25}= 40.6° (neat)[30], $[\alpha]_n$= 44° (c= 5, Et_2O)[31]. m. THF was used as solvent during C-C bond formation. n. absolute configuration assigned according to Meyers et al.[8]. o. Metalation of (S)-2g with n-BuLi/THF. p. Metalation of (S)-2g with LDA, ether.

the building blocks used as nucleophile and electrophile. This "opposite enantio-selectivity through synthon control" is demonstrated in the case of **5m**.

It should be noted that the extent of asymmetric induction varies considerably depending on the solvent used during C–C bond formation. The use of diethylether is essential to reach the ≧90% ee level; in THF, for instance, the enantiomeric excesses are considerably lower (e.g. **5a**: 60% ee vs 94% ee, **5b**: 85% ee vs 99.5% ee, **5g**: ≧50% ee vs ≧95% ee).

In special cases however, with a phenyl group directly attached to the newly formed center of chirality (e.g. **5n, o**, and **p**, $R^2 = C_6H_5$), the enantiomeric purities drop drastically to 10–30%. This phenomenon is also seen in Meyers' technique, using phenylalaninol-methylether as the chiral auxiliary.[8] Whether these poor results are more or less due to the formation of a mixture of $E_{CC}Z_{CN}/Z_{CC}E_{CN}$ isomers of the azaallyl Li intermediates (*S*)-**3f, g**, and **h**, i.e. a low deprotonation selectivity, or more a low alkylation selectivity, is not yet known. Although the "hydrazone anions" (*S*)-**3** are stable enough to survive for one hour in refluxing THF, an attempted equilibration did not result in much change in the overall stereochemical outcome. How sensitive these electrophilic substitutions of phenyl substituted ketones are towards slightly different reaction conditions is demonstrated in the case of the asymmetric methylation of dibenzyl ketone. Metalation with n-butyllithium in THF gave rise to (*S*)-**5o** of 30% ee, while metalation with LDA in ether resulted in a 11% ee of the other enantiomer, (*R*)-**5o**. All acyclic ketones **5** are summarized in Table 3.

Besides the *SAMP/RAMP*-hydrazone method and Meyers' technique an alternative asymmetric synthesis of simple acyclic ketones via alkylation of ephedrine amides, followed by reaction with alkyllithium compounds (44–81% ee), was recently reported.[34]

In summary, the *SAMP/RAMP*-hydrazone method as a modern version of the classical enolate chemistry, allows α-alkylations of aldehydes and ketones in excellent enantioselectivities and good overall chemical yields.[35]

EXPERIMENTAL

1. SAMP-*Hydrazones* (*S*)-**2** (*general procedure*)

(a) A mixture of 1 equiv of (*S*)-**1** and 0.98-1.02 equivs of ketone is stirred for 5–20 hr at 60° in a round bottom flask topped by a reflux condenser. After the reaction is complete (determined by TLC or IR), the mixture is poured into CH_2Cl_2–H_2O (6:1). The organic layer is separated, dried over Na_2SO_4, and concentrated *in vacuo*, delivering a spectroscopically clean crude product, usually in quantitative yield. Purification by short path distillation or column chromatography (silica gel, Et_2O) affords colorless to light yellow oils, which are stored in a refrigerator under Argon. [Note: volatile ketones should be added dropwise to (*S*)-**1** as the reaction is exothermic.]

(b) For cases (*S*)-**2d, e** and **h**, the ketone is dissolved in benzene (70 ml/50 mmol) and the mixture is refluxed while the reaction water is removed via a Dean Stark trap. After the reaction is complete (followed by TLC), the benzene phase is dried over $MgSO_4$ and concentrated *in vacuo*. For purification of the crude product see (a).

2. SAMP-*hydrazones* **4** (*general procedure*)

(a) A soln of n-BuLi in n-hexane (1.05 eq, 1.6M) is added dropwise via syringe to a soln of diisopropylamine in ether (1.05 eq, 0.25–0.5 M) under Argon at 0° and stirred for 15 min to generate a soln of LDA (1.05 eq). After dropwise addition of 1.0 eq of (*S*)-**2**, the mixture is stirred at 0° for 4 hr, cooled to −110°, and 1.05 eq of the electrophile (dissolved in 3–5 ml ether/10 mmol) is added. Stirring is continued at this temp for 1–3 hr, after which the mixture is allowed to warm up to room temp within 4–12 hr. The mixture is then poured into ether/H_2O (2:1) and the inorganic salts are thoroughly washed out with water. After drying the organic layer over $MgSO_4$ and concentrating *in vacuo*, the crude oily product is purified by short path distillation, Kugelrohr distillation or by column chromatography on silica gel (Et_2O).

(b) In the case of **4g**, the lithiated species is formed as in (a), inside a dropping funnel, cooled to −78° and added slowly into a cooled (−110°) soln of 0.95 eq of the electrophile in ether. Work up as in a).

3. *Cleavage to form ketones* **5** (*general procedure*)

Method A (*ozonolysis*). 1 equiv of **4** is dissolved in CH_2Cl_2 (30 ml/10 mmol) and cooled to −78°. A gentle stream of O_3 is flushed through the soln. The color of the soln turns green to blue (indicating excess O_3), when the reaction has run to completion. Argon is then flushed through the soln as it warms up to room temp. The soln is concentrated *in vacuo*, and the ketone is separated from the nitrosoamine (*S*)-**8** by either distillation or flash chromatography (silica gel, Et_2O).

Method B ("*salt method*"). 1 equiv of **4** is dissolved in 5 equiv MeI and the soln is heated to 60° (reflux condenser). After 20–48 hr the reaction is complete (TLC control), and excess MeI is removed *in vacuo*. The remaining methiodide **9** (viscous brown oil) is dissolved in 3-4N HCl (50 ml/10 mmol) and stirred for 5 min at room temp. n-Pentane (200 ml/10 mmol) is then added and the two phase system is vigorously stirred for 30 min. The organic layer is separated, washed with a few ml of a $NaHSO_3$-soln and pH 7-buffer soln, and dried over Na_2SO_4. The solvent is removed *in vacuo* and the remaining crude product is purified by short path or Kugelrohr-distillation.

(+)-(S)-2-*Methoxymethyl*-1-(1-*propylbutylideneamino*)-*pyrrolidine* [(*S*)-**2b**]: 2.6 g (20 mmol) (*S*)-**1** and 2.8 ml (20 mmol) heptane-4-one. Yield of crude product 4.13 g (91%); 3.41 g (75%) of a colorless oil after short path distillation, b.p. 61–64°/0.07 torr.

IR (film): ν = 2970, 2940, 2880, 2835, 1632 (CN), 1460, 1380, 1350, 1198, 1125, 1100, 1056, 970, 920 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.80–1.06 (t, 6H, CH_3), 1.30–2.66 (compl. mult., 13H, β-ring CH_2, chain CH_2, NCHH), 2.90-3.50 (compl.mult., 4H, NCHH, OCH_2, NCH), 3.36 (s, 3H, OCH_3); MS: *m/e* (rel.int.): 227 (M^+ + 1, 7), 226 (M^+, 27), 182 (63), 181 (M^+-CH_2OCH_3, 100 = b.p.), 141 (9), 112 (14), 83 (13), 82 (13), 71 (50), 70 (50), 69 (12), 68 (23), 57 (13), 55 (21), 45 (40), 42 (34). (Found: C, 68.89; H, 11.52; N, 12.56. Calc for $C_{13}H_{26}N_2O$ (226.4): C, 68.97; H, 11.58; N, 12.38%).

(+)-(S)-1-(1-*n*-*Butylpentylideneamino*)-2-*methoxymethyl-pyrrolidine* [(*S*)-**2c**]: 2.6 g (20 mmol) (*S*)-**1** and 3.62 ml (21 mmol) nonane-5-one. Yield of crude product 4.59 g (90%); 3.88 g (76%) of a colorless oil after short path distillation, b.p. 102°/0.5 torr.

IR (film): ν = 2960, 2940, 2880, 2830, 2730, 1630 (CN), 1460, 1379, 1340, 1280, 1195, 1125, 1095, 1045, 967, 915, 740, 730 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.80-1.08 (*t*, 6H, CH_3), 1.4 (compl. mult., 8H, chain CH_2), 1.8 (m, 4H, β-ring CH_2), 2.1–2.6 (compl. mult., 5H, N=CCH_2, NCHH), 2.88–3.52 (compl.mult., 4H, NCHH, OCH_2, NCH), 3.36 (s, 3H, OCH_3); MS: *m/e* (rel.int.): 255 (M^+ + 1, 2), 254 (M^+, 9), 210 (38), 209 (M^+-CH_2OCH_3, 100 = b.p.), 140 ($C_9H_{18}N$, 7), 85 (27), 84 (96), 82 (16), 70 (38), 68 (16), 67 (18), 57 (51), 55 (32), 54 (14), 45 (33), 43 (33), 42 (32).(Found: C, 70.80; H, 11.90; N, 11.08 Calc for $C_{15}H_{30}N_2O$ (254.4): C, 70.81; H, 11.89; N, 11.01%).

(+)-(S)-2-*Methoxymethyl*-1-(1-*phenylpropylideneamino*)-*pyrrolidine* [(*S*)-**2d**]. 5.1 g (39.7 mmol) (*S*)-**1** and 5.4 g (40 mmol) 1-phenylpropane-2-one. Yield of crude

product 8.56 g (88%); 7.2 g (74%) after short path distillation, b.p. 112°/0.05 torr.

IR (film): ν = 3070, 3000–2800, 2740, 1615 (CN), 1565, 1550, 1500, 1495, 1380, 1350, 1345, 1325, 1309, 1285, 1245, 1205, 1130, 1110, 1075, 1060, 1030, 1020, 975, 950, 915, 890, 775, 750, 705 cm^{-1}; ^1H NMR (CCl_4): δ = 0.98 and 1.08 (2t, 3H, CH_3-*E*/*Z*), 1.31–2.13 (m, 4H, β-ring CH_2), 2.13–2.98 (compl.mult., 3H, CH_2, NC<u>H</u>H), 2.98–3.9 (compl.mult., 4H, NCH<u>H</u> NCH, OCH_2), 3.22 and 3.26 (2s, 3H, OCH_3-E/Z), 7.16 (m, 3H, m-, p-C_6H_5), 7.56 (m, 2H, o-C_6H_5). (Found: C, 72.61; H, 8.91; N, 11.21 Calc for $C_{15}H_{22}N_2O$ (246.34): C, 73.13; H, 9.00; N, 11.37%).

(+)-(S)-2-*Methoxymethyl*-1-(1-*phenylbutylideneamino*)-*pyrrolidine* [(*S*)-**2e**]: 4.1 g (31.5 mmol) (*S*)-**1** and 5.1 g (34.6 mmol) 1-phenylbutane-1-one. Yield of crude product 8.22 g (100%); 7.15 g (87%) of a pale yellow oil after short path distillation, b.p. 128°/0.05 torr.

IR (film): ν = 3080, 3020, 3000–2800, 2740, 1610 (CN), 1570, 1490, 1460, 1450, 1380, 1340, 1320, 1305, 1280, 1200, 1110, 1070, 1030, 970, 920, 770, 730, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.90 and 0.91 (2t, 3H, CH_3-*E*/*Z*), 1.2-2.2 (compl.mult., 6H, β-ring CH_2, N=CCH$_2$C<u>H</u>$_2$), 2.3–2.9 (compl.mult., 3H, N=CC<u>H</u>$_2$CH$_2$, NC<u>H</u>H), 3.1-3.6 (compl.mult., 4H, NCH<u>H</u>, NCH, OCH_2), 3.34 and 3.38 (2s, 3H, OCH_3-E/Z), 7.28 (m, 3H, m-C_6H_5), 7.59 (m, 2H, o-C_6H_5). (Found: C, 73.57; H, 9.36; N, 10.72. Calc for $C_{16}H_{24}N_2O$ (260.4): C, 73.80; H, 9.29; N, 10.76%).

(+)-(S)-2-*Methoxymethyl*-1-(1-*methyl*-2-*phenylethylideneamino*)-*pyrrolidine* [(*S*)-**2f**]. 6.51 g (50 mmol) (*S*)-**1** and 7.49 ml (50 mmol) 1-phenyl-propane-2-one. Yield of crude product 11.93 g (97%); 9.84 g (80%) of a pale yellow oil after short path distillation, b.p. 103–106°/0.05 torr.

IR (film): ν = 3090, 3065, 3030, 2980, 2920, 2880, 1633 (CN), 1602, 1493, 1453, 1359, 1280, 1246, 1195, 1125, 1079, 1060, 1030, 969, 915, 800, 740, 700, 618 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.80 (m, 4H, β-ring CH_2), 1.81 (s, 3H, CH_3), 2.50 (m, 1H, NC<u>H</u>H), 2.96–4.16 (compl.mult., 4H, NCH<u>H</u>, OCH_2, NCH), 3.37 and 3.39 (2s, 3H, OCH_3-E/Z), 3.55 (s, 2H, $C_6H_5CH_2$), 7.35 (m, 5H, C_6H_5); MS: *m*/*e* (rel.int.): 247 (M^+ + 1, 3), 246 (M^+, 15), 202 (63), 201 (M^+-CH_2OCH_3, 100 = b.p.), 117 (14), 92 (72), 91 (C_7H_7, 96), 83 (14), 70 (25), 65 (33), 45 (43), 42 (31). (Found: C, 73.05; H, 8.87; N, 11.42. Calc for $C_{15}H_{22}N_2O$ (246.4): C, 73.13; H, 9.00; N, 11.37%).

(+)-(S)-1-(1-*Benzyl*-*phenylethylideneamino*)-2-*methoxymethyl pyrrolidine* [(*S*)-**2g**]. 2.6 g (20 mmol) (*S*)-**1** and 5.25 g (25 mmol) 1.3-diphenylpropane-2-one. Yield of crude product 6.12 g (95%); 5.67 g (88%) of a pale yellow oil after short path distillation, b.p. 125°/0.04 torr.

IR (film): ν = 3100–2800, 1625 (CN), 1598, 1579, 1490, 1450, 1423, 1335, 1270, 1240, 1190–1175, 1130–1090, 1070, 965, 918, 749, 726, 696 cm^{-1}; ^1H NMR (CCl_4): δ = 1.80 (m, 4H, β-ring CH_2), 2.55 (m, 1H, NC<u>H</u>H), 2.94-3.65 (compl.mult., 8H, NCH<u>H</u>, CH_2O, NCH, $C_6H_5CH_2$), 3.30 (s, 3H, OCH_3), 7.15 (m, 10H, C_6H_5); MS: *m*/*e* (rel.int.): 322 (M^+, 6), 278 (30), 277 (M^+-CH_2OCH_3, 100 = b.p.), 210 (13), 209 (4), 208 (5), 193 (5), 192 (5), 160 (6), 130 (5), 119 (5), 118 (22), 117 (26), 116 (14), 115 (8), 103 (7), 93 (5), 92 (72), 91 (84), 90 (21), 89 (24), 83 (13), 82 (10), 77 (11), 70 (34), 69 (9), 68 (9), 65 (47), 63 (11), 55 (12), 51 (17), 50 (6), 45 (58), 43 (8). (Found: C, 78.00; H, 8.13; N, 8.62. Calc for $C_{21}H_{26}N_2O$ (322.4): C, 78.22; H, 8.13; N, 8.69%).

(+)-(S)-1-(1,2-*Diphenyl*-*ethylideneamino*)-2-*methoxymethyl*)-*pyrrolidine* [(*S*)-**2h**]. 2.6 g (20 mmol) (*S*)-**1** and 4.9 g (25 mmol) 1,2-diphenylethanone. Yield of crude product 5.9 g (95%); 5.73 g (93%) of a viscous pale yellow oil after column chromatography (SiO_2, Et_2O).

IR (film): ν = 3100–2800, 1600 (CN), 1492, 1450, 1440, 1338, 1300, 1274, 1195–1175, 1140–1080, 1070, 1040, 1025, 1020, 967, 754, 723, 690, 528 cm^{-1}; ^1H NMR (CCl_4): δ = 1.75 (m, 4H, β-ring CH_2), 2.55 (m, 1H, NC<u>H</u>H), 2.95–3.65 (compl.mult., 4H, NCH<u>H</u>, OCH_2, NCH), 3.25 (s, 3H, OCH_3), 4.17 (s, 2H, $C_6H_5CH_2$), 6.95–7.85 (m, 10H, C_6H_5).(Found: C, 78.13; H, 7.76; N, 8.31. Calc for $C_{20}H_{24}N_2O$ (308.4): C, 77.88; H, 7.84; N, 9.09%).

(+)-1-(1-*Ethyl*-2-*methylbutylideneamino*)-2-*methoxymethyl*-*pyrrolidine* (**4a**). 1.98 g (10 mmol) (*S*)-**2a** and 0.91 ml (11.5 mmol) EtI. Yield of crude product 2.25 g (100%); 1.85 g (82%) of a colorless liquid after short path distillation, b.p. 64–65°/0.25 torr; α_D^{22} = + 241.7° (neat), $[\alpha]_D^{22}$ = + 281.8° (*c* = 2.34, C_6H_6).

IR (film): ν = 3000–2800, 1628 (CN), 1460, 1375, 1350, 1200, 1180, 1140–1090, 1050, 1035, 998, 969, 950, 803 cm^{-1}; ^1H NMR (CCl_4): δ = 1.00 (m, 9H, CH_3), 1.30 (m, 2H, CHC<u>H</u>$_2$), 1.75 (m, 4H, β-ring CH_2), 2.15 (m, 2H, C(N)C<u>H</u>$_2$), 2.40 (m, 1H, NC<u>H</u>H), 3.26 (s, 3H, OCH_3), 2.80–3.55 (m, 5H, NCH<u>H</u>, CH_2O, NCH, C(N)CH). (Found: C, 68.00; H, 11.40; N, 12.91. Calc for $C_{13}H_{26}N_2O$ (226.36): C, 68.97; H, 11.58; N, 12.38%).

(+)-1-(1-*Ethyl*-2-*methylpentylideneamino*)-2-*methoxymethyl*-*pyrrolidine* (**4b**). 1.59 g (8 mmol) (*S*)-**2a** and 0.86 ml (8.8 mmol) n-PrI. Yield of crude product 1.91 g (100%), 1.74 g (91%) of a colorless liquid after short path distillation, b.p. 63°/0.1 torr; α_D^{22} = 224.0° (neat).

IR (film): ν = 2960, 2935, 2875, 2825, 1625 (CN), 1455, 1375, 1195, 1180, 1125, 1095, 1030, 988, 967, 912 cm^{-1}; ^1H NMR (CCl_4): δ = 0.76–1.16 (1d, 2t, 9H, 3 CH_3), 1.25 (m, 4H, chain C<u>H</u>$_2$C<u>H</u>$_2$), 1.50–2.48 (compl.mult., 7H, β-ring-CH_3, C(N)C<u>H</u>$_2$, NC<u>H</u>H), 3.27 (s, 3H, OCH_3), 2.88–3.60 (compl.mult., 5H, NCH<u>H</u>, OCH_2, NCH, C(N)CH); MS: *m*/*e* (rel.int.): 240 (M^+, 9), 196 (16), 195 (M^+-CH_2OCH_3, b.p. = 100), 126 (9), 98 (21), 71 (49), 70 (64), 55 (62), 54 (18), 45 (14), 43 (62), 42 (11). (Found: C, 69.69; H, 11.55; N, 11.64. Calc for $C_{14}H_{28}N_2O$ (240.4): C, 69.95; H, 11.74; N, 11.66%).

(+)-1-(1-*Ethyl*-2-*methyloctylideneamino*)-2-*methoxymethyl*-*pyrrolidine* **4c**. 2.97 g (15 mmol) (*S*)-**2a** and 2.12 ml (15 mmol) of 1-bromohexane. Yield of crude product 4.22 g (100%), 3.7 g (87.5%) of a light-yellow colored oil after short path distillation, b.p. 75–80°/0.03 torr; $[\alpha]_D^{22}$ = + 209.5° (*c* = 2.1, C_6H_6).

IR (film): ν = 3000–2800, 1630 (CN), 1465, 1455, 1380, 1200, 1140, 1100, 1040, 1020, 980, 920 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.05 (d, 3H, CH_3), 0.71–2.57 (compl.mult., 23H, 2 CH_3, C(N)C<u>H</u>$_2$, chain CH_2, β-ring CH_2, NC<u>H</u>H), 3.25 (s, 3H, OCH_3), 2.78–3.61 (compl.mult., 5H, NCH<u>H</u>, OCH_2, NCH, C(N)CH); MS: *m*/*e* (rel.int.): 282 (M^+, 7), 238 (20), 237 (b.p. = 100), 168 (5), 140 (8), 71 (48), 70 (30), 57 (54), 56 (52), 55 (12), 54 (5), 49 (8), 43 (29), 42 (8), 41 (19). (Found: C, 72.39; H, 12.35; N, 9.72. Calc for $C_{17}H_{34}N_2O$ (282.5): C, 72.29; H, 12.13; N, 9.92%).

(+)-1-(1-*Ethyl*-3-*cyclohexyl*-2-*methyl*-*propylideneamino*)-2-*methoxymethyl*-*pyrrolidine* (**4d**). 2.97 g (15 mmol) (*S*)-**2a** and 2.1 ml (15 mmol) cyclohexylmethyl bromide. Yield of crude product 4.42 g (100%), 4.2 g (95%) of a light-yellow colored oil after short path distillation, b.p. 89°/0.02 torr; $[\alpha]_D^{22}$ = + 220.9° (*c* = 1.72, C_6H_6).

IR (film): ν = 3000-2860, 1630 (CN), 1465, 1455, 1380, 1350, 1270, 1200, 1140, 1100, 1040, 980, 920, 850 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.97 (d, 3H, CH_3), 1.06 (t, 3H, CH_3), 1.15 (d, 2H, CHC<u>H</u>$_2$), 0.52–2.65 (compl.mult., 18H, C(N)CH_2, c-C_6H_{11}, β-ring CH_2, NC<u>H</u>H), 3.3 (s, 3H, OCH_3), 2.82 – 3.74 (compl.mult., 5H, NCH<u>H</u>, OCH_2, NC<u>H</u>, C(N)CH); MS: *m*/*e* (rel.int.): 294 (M^+, 8), 250 (20), 249 (b.p. = 100), 198 (15), 180 (6), 153 (13), 125 (12), 114 (10), 84 (5), 83 (53), 81 (5), 70 (35), 69 (73), 67 (8), 57 (16), 56 (19), 55 (32), 54 (6), 45 (8), 42 (6), 41 (21). (Found: C, 73.84; H, 11.82; N, 9.40. Calc for $C_{18}H_{34}N_2O$ (294.5); C, 73.42; H, 11.64; N, 9.51%).

(+)-(Z)-3-*Methyl*-4-*oxo*-(1,1-*dimethylethyl*)-*hexanoate*-*SAMP*-*hydrazone* (**4f**). 0.99 g (5 mmol) (*S*)-**2a** and 0.8 ml (5.5 mmol) bromo-t-butylacetate. Yield of crude product 1.45 g (93%), 1.01 g (65% of a yellow colored oil after Kugelrohr distillation, b.p. 70°/0.09 torr; $[\alpha]_D^{20}$ = + 146.6° (*c* = 1.3, C_6H_6). IR (film): ν = 3000–2800, 1730 (CO), 1640, 1460, 1370, 1280, 1260, 1155, 1035, 975, 920, 850, 760 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.08 (d, 3H, CH_3), 1.1 (t, 3H, CH_3), 1.45 (s, 9H, t-C_4H_9), 1.6–2.03 (m, 4H, β-ring CH_2), 2.03–2.6 (m, 5H, C(N)CH_2, C(O)CH_2, NC<u>H</u>H), 3.3 (s, 3H,

OCH_3), 2.91–3.53 (m, 4H, NCHH, OCH_2, NCH), 3.63–4.1 (m, 1H, C(N)CH-syn); MS: *m/e* (rel.int.): 312 (M^+, 7.2), 268 (4), 267 (80), 239 (10), 212 (14), 211 (100), 114 (11), 87 (9), 70 (18), 69 (17), 57 (18), 41 (23). (Found: C, 66.20; H, 10.80; N, 8.98. Calc for $C_{17}H_{32}N_2O_3$ (312.2): C, 65.35; H, 10.32; N, 8.90%).

(2E, 6Z)-3-*Ethoxy*-5-*methyl*-6-*oxo*-*ethyl*-*oct*-2-*enoate*-SAMP-*hydrazone* (**4g**). 0.99 g (5 mmol) (*S*)-**2a** and 1.16 g (4.9 mmol) (*E*)-4-bromo-3-ethoxy-ethyl-crotonoate.[38] Yield of crude product 1.75 g (100%), 700 mg of which were purified by column chromatography (SiO_2, Et_2O, n-pentane 2:1); yield 550 mg (78%) of a pale yellow oil.

IR (film): ν = 3020, 2980–2820, 1710 (CO), 1640 (C=C, CN), 1460, 1375, 1290, 1140, 1115, 1060, 920, 815, 735 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.1 (2t, 6H, OCH_2CH_3), 1.3 (d, 3H, CH_3), 1.33 (t, 3H, CH_3), 1.5–2.1 (m, 4H, β-ring CH_2), 2.1–2.66 (m, 4H, C(N)CH_2, $CHCH_2$), 3.32 (s, 3H, OCH_3), 2.88–3.46 (m, 5H, NCH_2, OCH_2, NCH), 3.78 (q, m, 3H, enolether-OCH_2, C(N)CH-syn), 4.13 (q, 2H, ester-OCH_2), 4.97 (s, 1H, C=CH); MS: *m/e* (rel.int.): 354 (M^+, 5), 310 (20), 309 (100), 256 (6), 240 (10), 219 (5), 194 (14), 185 (14), 166 (14), 157 (14), 139 (40), 111 (20), 70 (20), 45 (24), 41 (21). (Found: 354.2520. Calc for $C_{19}H_{34}N_2O_4$: 354.2517. High resolution MS).

(+)-2-*Methoxymethyl*-1-(2-*methyl*-1-*n*-*propyl*-*butylideneamino*)-*pyrrolidine* (**4i**). 1.81 g (8 mmol) (*S*)-**2b** and 0.55 ml (8 mmol) MeI. Yield of crude product 1.91 g (99%), 1.60 g (83%) of a colorless oil after short path distillation, b.p. 130°/0.55 torr: $[\alpha]_D^{22}$ = + 167.1° (*c* = 1.13, C_6H_6), $[\alpha]_D^{22}$ = + 136.0°(neat).

IR (film): ν = 2960, 2935, 2875, 2825, 2730, 1628 (CN), 1455, 1376, 1349, 1275, 1195, 1180, 1120, 1035, 993, 967, 915 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.80–1.12 (2t, d, 9H, CH_3), 1.25–2.65 (m, 11H, β-ring CH_2, CH_2CH_3, C(N)CH_2, NCHH), 3.37 (s, 3H, OCH_3), 2.84 – 3.68 (m, 5H, NCHH, OCH_2, NCH, C(N)CH); MS: *m/e* (rel. int.): 241 (M^+ + 1, 6), 240 (M^+, 25), 196 (47), 195 ($M^+ - CH_2OCH_3$, b.p. = 100), 126 (9), 85 (11), 84 (94), 82 (19), 71 (49), 70 (64), 69 (18), 68 (27), 56 (24), 55 (48), 54 (18), 45 (63), 43 (80), 42 (37), 39 (24), 29 (70), 28 (39), 27 (28).(Found C, 69.91; H, 11.79, N, 1165. Calc for $C_{14}H_{28}N_2O$ (240.4): C, 69.95; H, 11.74; N, 11.66%).

(+)-1-(2-*Ethyl*-1-*n*-*propyl*-*pentylideneamino*)-2-*methoxymethyl*-*pyrrolidine* (**4j**) 1.14 g (5.04 mmol) (*S*)-**2b** and 0.59 ml (6 mmol) n-PrI. Yield of crude product 1.34 g (99%), 1.15 g (85%) of a yellow oil after short path distillation, b.p. 98–99°/0.3 torr; $[\alpha]_D^{23}$ = + 204.3° (*c* = 2.35, C_6H_6), $[\alpha]_D^{23}$ = + 174.5° (neat).

IR (film): ν = 2960, 2930, 2870, 2820, 2730, 1625 (CN) 1455, 1375, 1347, 1270, 1248, 1222, 1193, 1177, 1120, 1050, 1035, 993, 966, 915, 770, 740 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.72–1.00 (3t, 9H, CH_3), 1.04–2.50 (m, 15H, β-ring CH_2, chain CH_2, C(N)CH_2, NCHH), 3.28 (s, 3H, OCH_3), 2.76–3.48 (m, 5H, NCHH, OCH_2, NCH, C(N)CH); MS: *m/e* (rel.int.): 269 (M^+ + 1, 10), 268 (M^+, 31), 224 (80), 223 (M^+-CH_2OCH_3, b.p. = 100), 183 (9), 181 (17), 154 (17), 126 (16), 114 (28), 113 (21), 112 (88), 110 (9), 98 (30), 96 (13), 86 (21), 85 (86), 84 (31), 83 (34), 82 (39), 81 (15), 80 (16), 79 (10), 71 (86), 70 (90), 69 (55), 68 (52), 67 (21), 57 (89), 56 (37), 55 (93), 54 (46), 53 (20), 45 (CH_2OCH_3, 88), 44 (26), 43 (90), 42 (68), 41 (93) (Found: C, 71.58; H, 12.15; N, 10.63. Calc. for $C_{16}H_{32}N_2O$ (268.4): C, 71.58; H, 12.02; N, 10.44%).

(+)-2-*Methoxymethyl*-1-(2-*methyl*-1-*nbutyl*-*pentylideneamino*)-*pyrrolidine* (**4k**). 2.04 g (8 mmol) (*S*)-**2c** and 0.55 ml (8.8 mmol) MeI. Yield of crude product 2.15 g (100%), 1.76 g (82%) of a light-yellow colored oil after short path distillation, b.p. 140–160°/0.55 torr; $[\alpha]_D^{22}$ = + 168.5° (*c* = 0.89, C_6H_6), $[\alpha]_D^{22}$ = + 118.0° (neat).

IR (film): ν = 2955, 2925, 2870, 2820, 2730, 1630 (CN), 1455, 1375, 1346, 1275, 1193, 1179, 1120, 1095, 1040, 965, 918, 740 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.72–1.12 (2t, d, 9H, CH_3), 1.15–2.64 (m, 15H, β-ring CH_2, chain CH_2, C(N)CH_2, NCHH), 3.30 (s, 3H, OCH_3), 2.80–3.66 (compl.mult., 5H, NCHH, OCH_2, NCH, C(N)CH; MS: *m/e* (rel.int.): 268 (M^+, 6), 224 (17), 223 (M^+-CH_2OCH_3, b.p. = 100), 154 (3), 114 (7), 98 (54), 85 (21), 84 (99), 82 (10), 71 (55), 70 (56), 69 (9), 68 (13), 67 (11), 57 (37), 56 (11), 55 (31), 54 (14), 45 (31), 43 (82) (Found: C, 71.41; H, 12.03; N, 10.49. Calc. for $C_{16}H_{32}N_2O$ (268.4): C, 71.58; H, 12.02; N, 10.44%).

(+)-1-(2-*Ethyl*-1-*n*-*butyl*-*pentylideneamino*)-2-*methoxymethyl*-*pyrrolidine* (**4l**). 2.54 g (10 mmol) (*S*)-**2c** and 0.91 ml (11.5 mmol) EtI. Yield of crude product 2.73 g (97%), 2.30g (82%) of a yellow oil after short path distillation, b.p. 96–97°/0.1 torr; $[\alpha]_D^{23}$ = + 200.6° (*c* = 2.21, C_6H_6), α_D^{23} = + 163.5° (neat).

IR (film): ν = 2960, 2930, 2870, 2825, 2725, 1625 (CN), 1458, 1375, 1345, 1193, 1178, 1120, 1040, 998, 915, 905, 760, 740 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.66–1.06 (m, 9H, CH_3), 1.06–2.60 (m, 17H, β-ring CH_2, chain CH_2, C(N)CH_2, NCHH), 3.31 (s, 3H, OCH_3), 2.76–3.54 (m, 5H, NCHH, OCH_2, NCH, C(N)CH_2); MS: *m/e* (rel.int.): 283 (M^+ + 1, 4), 282 (M^+, 13), 238 (41), 237 (M^+-CH_2OCH_3, b.p. = 100), 195 (5), 168 (9), 140 (9), 125 (14), 114 (22), 113 (15), 112 (99), 110 (8), 96 (7), 86 (17), 85 (93), 84 (97), 83 (24), 82 (38), 81 (11), 80 (13), 71 (24), 70 (84), 69 (50), 68 (39), 67 (30), 58 (13), 56 (33), 54 (61), 53 (24), 45 (CH_2OCH_3, 74), 44 (24), 40 (14), 39 (44).(Found: C, 71.75; H, 12.12; N, 9.93. Calc for $C_{14}H_{34}N_2O$ (282.5): C, 72.28; H, 12.13; N, 9.92%).

(+)-2-*Methoxymethyl*-1-(2-*methyl*-1-*phenyl*-*butylideneamino*)-*pyrrolidine* (**4m**). 2.95 g (12 mmol) (*S*)-**2d** and 1.01 ml (12.6 mmol) of EtI. Yield of crude product 3.15 g (95%), 2.61 g of which were purified by Kugelrohr-distillation affording 2.40 g (88%) of a clear, yellow liquid, b.p. 145–148°/0.002 torr; $[\alpha]_D^{22}$ = + 432.0° (*c* = 1.7, C_6H_6), α_D^{20} = + 392.6° (neat).

IR (film): ν = 3080, 3000-2800, 2750, 1610 (CN), 1580, 1570, 1500, 1470, 1460, 1450, 1390, 1320, 1210, 1190, 1140, 1120, 1110, 1070, 1020, 980, 960, 920, 780, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.9 (t, 3H, CH_3), 1.1 and 1.3 (2d, 3H, CH_3-*E*/*Z*), 1.4–2.3 (m, 7H, β-ring CH_2, CH_2CH_3, NCHH), 2.6 [m, 1H, C(N)CH], 3.4 (s, 3H, OCH_3), 3.1–3.8 (m, 4H, NCHH, OCH_2, NCH), 7.1–7.5 (m, 5H, C_6H_5). (Found: 74.16; H, 9.96; N, 10.12. Calc. for $C_{17}H_{26}N_2O$ (274.4): C, 74.41; H, 9.55; N, 10.21%).

Compound (+)-(**4m'**). 1.73 g (6.6 mmol) (*S*)-**2e** and 0.44 ml (7 mmol) methyliodide. Yield of crude product 1.83 g (100%), 1.64 g (90%) of a yellow-colored liquid after Kugelrohr-distillation, b.p. 140°/0.001 torr; $[\alpha]_D^{22}$ = + 323° (c = 2.7, C_6H_6), α_D^{22} = +322° (neat). All spectroscopic (IR, NMR) data are in agreement with those of **4m**.

(+)-2-*Methoxymethyl*-1-(1-*methyl*-2-*phenylpropylidene*-*amino*)-*pyrrolidine* (**4n**). 2.46 g (10 mmol) (*S*)-**2f** and 0.71 ml (11.5 mmol) MeI. Yield of crude product 2.60 g (100%), 2.41 g (93%) of a yellow oil after distillation, b.p. 101–103°/0.08 torr; $[\alpha]_D^{23}$ = + 279.7° (*c* = 2.73, C_6H_6), α_D^{23} = + 267° (neat).

IR (film): ν = 3080, 3060, 3030, 2970, 2925, 2875, 2825, 2730, 1630 (CN), 1600, 1490, 1449, 1368, 1356, 1275, 1193, 1120, 1067, 1040, 1025, 965, 904, 755, 696 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.64 and 1.66 (2s, 3H, CH_3, *E*/*Z* = 1:1), 1.80 (m, 4H, β-ring CH_2), 2.40 (m, 1H, NCHH), 2.84–3.80 (compl.mult., 5H, NCHH, OCH_2, NCH, C(N)CH), 3.32(s, 3H, OCH_3), 7.22 (m, 5H, C_6H_5); MS: *m/e* (rel.int.): 261 (M^+ + 1, 2), 260 (M^+, 10), 216 (30), 215 (M^+-CH_2OCH_3, b.p. = 100), 143 (10), 130 (6), 116 (7), 106 (54), 105 (92), 104 (52), 103 (35), 91 ($C_7H_7^+$, 60), 83 (18), 82 (12), 80 (9), 79 (36), 78 (37), 77 (47), 71 (12), 70 (84), 69 (12), 68 (26), 55 (22), 52 (17), 51 (40), 50 (12), 45 (CH_2OCH_3, 76), 43 (11), (Found: C, 74.24; H, 9.30; N, 10.82. Calc. for $C_{16}H_{24}N_2O$ (260.4): C, 73.80; H, 9.29; N, 10.76%).

(+)-1-(1-*Benzyl*-2-*phenylpropylideneamino*)2-*methoxy*-*methyl*-*pyrrolidine* (**4o**). 3.22 g (10 mmol) (*S*)-2g and 0.71 ml (11.5 mmol) MeI. Yield of crude product 3.29 g (98%), 2.58 g (77%) after chromatographic purification (SiO_2, Et_2O) of a yellow oil; $[\alpha]_D^{22}$ = + 144° (*c* = 1, C_6H_6).

IR (film): ν = 3080–2800, 1628 (CN), 1597, 1579, 1490, 1449, 1366, 1190, 1130–1090, 1023, 965, 908, 755, 696,

548 cm^{-1}; ^{1}H NMR (CCl_4): δ = 1.30 (d, 3H, CH_3), 1.80 (m, 4H, β-ring CH_2), 2.65 (m, 1H, NC$\underline{H}$H), 2.87–3.65 (m, 4H, NCH$\underline{H}$, CH_2O, CH), 3.21 (s, 2H, $C_6H_5C\underline{H}_2$), 3.29 (s, 3H, OCH_3), 4.30 (q, 1H, $C_6H_5C\underline{H}$), 7.15 (m, 10H, C_6H_5). (Found: C, 78.55; H, 8.69; N, 8.33. Calc. for $C_{22}H_{28}N_2O$ (336.5): C, 78.53; H, 8.39; N, 8.33%).

(+)-1-(1,2-*Diphenyl-propylideneamino*)-2-*methoxymethyl-pyrrolidine* (**4p**). 3.08 g (10 mmol) (*S*)-**2h** and 0.75 ml (12 mmol) MeI. Yield of crude product 3.15 g (98%), 2.19 g (68%) after chromatographic purification (SiO_2, Et_2O) of a yellow oil; $[\alpha]_D^{20}$ = + 523° (*c* = 1, C_6H_6).

IR (film): ν = 3100–2800, 1600, 1570, 1492, 1440, 1371, 1300, 1195, 1180, 1140–1090, 1067, 1048, 1026, 1015, 968, 950, 910, 771, 755, 694 cm^{-1}; ^{1}H NMR (CCl_4): δ = 1.45 (d, 3H, CH_3), 1.75 (m, 4H, β-ring CH_2), 2.60 (m, 1H, NC$\underline{H}$H), 3.28 (s, 3H, OCH_3), 2.95–3.69 (m, 4H, NCH$\underline{H}$, CH_2O, NCH), 5.23 (q, 1H, $C_6H_5C\underline{H}$), 6.90–7.50 (m, 10H, C_6H_5). (Found: C, 77.86; H, 8.19; N, 8.18. Calc for $C_{21}N_{26}N_2O$ (322.44): C, 78.22; H, 8.13; N, 8.69%).

(+)-(S)-4-*Methyl-hexane*-3-*one* [(*S*)-**5a**]. Hydrolysis (method B) of 1.34 g (5.92 mmol) of **4a** and distillation afforded 0.47 g (70%) of a colorless liquid, b.p. 80–100°/150 torr (lit.[38]: 134–135°/760 torr). IR (film): ν = 2980, 2944, 2895, 1722 (CO), 1468, 1420, 1385, 1270, 1179, 1116, 1037, 981, 815 cm^{-1}; ^{1}H NMR (CCl_4): δ = 0.76–1.3 (overlapping mult., 9H, CH_3), 2.22–2.52 (compl.mult., 4H, CH_2), 3.26–3.54 (m, 1H, CH).

(+)-(S)-4-*Methyl-heptane*-3-*one* [(*S*)-**5b**]. Hydrolysis (method B) of 1.24 g (5.16 mmol) of **4b** and distillation afforded 0.45 g (69%) of a colorless liquid. All spectroscopic data (^{1}H NMR, IR) are in agreement with lit. values.[36]

(+)-(S)-4-*Methyl-decane*-3-*one* [(*S*)-**5c**]. Hydrolysis (method B) of 3.7 g (13.1 mmol) of **4c** and distillation afforded 1.55 g (69%) of a colorless oil, b.p. 95°/13 torr.

IR (film): ν = 3000–2860, 1720 (CO), 1460, 1415, 1380, 1110, 1030, 980, 805, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.91 (t, 3H, CH_3), 1.08 (t, 3H, CH_3), 1.09 (d, 3H, CH_3), 1.14–1.47 (compl.mult., 10H, CH_2), 2.53 (overlapping mult., 3H, CH, $C(O)CH_2$); MS: *m/e* (rel.int.): 170 (M^+, 3), 141 (3), 133 (6), 99 (8), 86 (100 = b.p.), 71 (72), 57 (98), 55 (13), 43 (53), 41 (27). (Found: C, 77.53; H, 13.15. Calc. for $C_{11}H_{22}O$ (170.3): C, 77.58; H, 13.02%).

(+)-(S)-4-*Methyl*-4-*cyclohexyl-pentane*-3-*one* [(*S*)-**5d**]. Hydrolysis (method B) of 4.2 g (14.3 mmol) of **4d** and distillation afforded 2.3 g (88%) of a colorless oil, b.p. 115°/13 torr. IR (film): ν = 3000–2860, 1710 (CO), 1460, 1450, 1415, 1380, 1270, 1210, 1190, 1170, 1110, 1030, 980, 960, 900, 890, 850, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.11 (t, 3H, CH_3), 1.12 (d, 3H, CH_3), 0.58–2.14 (overlapping mult., 13H, c-C_6H_{11}, $CHCH_2$), 2.62 (q, 2H, CH_2CH_3), 2.83 (m, 1H, $C\underline{H}CH_3$); MS: *m/e* (rel.int.): 182 (M^+, 0.3), 153 (43), 125 (20), 97 (39), 86 (100 = b.p.), 83 (48), 69 (66), 57 (72), 55 (71), 41 (27). High resolution MS, Found: 182.1683. Calc for $C_{12}H_{22}O$: 182.1670.

(−)-(S)-3-*Methyl*-4-*oxo*-(1,1-*dimethylethyl*)-*hexanoate* [(*S*)-**5f**]. Ozonolysis (method A) of 0.62 g (2 mmol) of **4f** and purification of 0.40 g of the product mixture by chromatography on 40 g silica-gel (Et_2O) afforded 0.23 g (98%), after distillation 0.18 g (77%) of a colorless oil, b.p. 70°/0.3 torr. IR (film): ν = 300–2860, 1710 (CO), 1450, 1360, 1250, 1150, 1100, 1015, 792 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.06 (t, 3H, CH_3), 1.1 (d, 3H, CH_3), 1.41 (d, 9H, t-C_4H_9), 2.06–3.1 (compl. mult., 5H, $C(O)CH_2$, CH, $CHCH_2$); MS: *m/e* (rel.int.): 200 (M^+, 5), 171 (5), 142 (10), 127 (52), 115 (25), 87 (14), 75 (37), 70 (26), 57 (100 = b.p.), 56 (52), 43 (42), 41 (92). High resolution MS, Found: 200.1390. Calc for $C_{11}H_{20}O_3$; 200.1411. The racemic ketone (±)-**5f** was prepared from pentane-3-one and bromo-t-butylacetate via the dimethylhydrazone method.[3]

3-*Methyl*-4-*oxo*-(1,1-*dimethylethyl*)-*hexanoate-dimethylhydrazone*. 0.64 g (5 mmol) of pentane-3-one-dimethylhydrazone and 0.84 ml (5.5 mmol) bromo-t-butylacetate. Yield of crude product 1.27 g (100%), 0.73 g (60%) of a pale yellow oil after distillation, b.p. 70°/0.4 torr.

IR (film): ν = 2980, 2860, 2820, 2780, 1730 (CO), 1635 (CN), 1460, 1390, 1365, 1350, 1280, 1255, 1215, 1155, 1085, 1022, 960, 850, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.07 (d, 3H, CH_3), 1.09 (t, 3H, CH_3), 1.45 (s, 9H, t-C_4H_9), 1.8–2.8 (compl.mult., 5H, N=CC$\underline{H}_2$, N=CC$\underline{H}$, CHC$\underline{H}_2$), 2.4 (s, 6H, NMe_2); MS: *m/e* (rel.int.): 243 (M^+ + 1, 4), 242 (M^+, 25), 194 (15), 186 (20), 179 (5), 169 (19), 165 (7), 142 (5), 127 (25), 126 (13), 124 (19), 99 (8), 98 (17), 57 (65), 45 (100 = b.p.), 44 (81), 41 (27). (Found: 64.72; H, 10.86; N, 11.51. Calc for $C_{11}H_{24}N_2O_2$ (242.3): C, 64.42; H, 10.81; N, 11.55%).

(+)-(E, S)-3-*Ethoxy*-5-*methyl*-6-*oxo*-*ethyl*-*oct*-2-*enoate* [(*S*)-**5g**]. Ozonolysis (method A) of 0.36 g (1.0 mmol) of **4g** with two equivs. O_3 afforded 0.39 g (100%) of crude (*S*)-**5g** and (*S*)-**8**. Purification of 0.11 g of this mixture by column chromatography [SiO_2, Et_2O, separation of (*S*)-**8**] afforded 68 mg (99%) of a colorless oil.

IR (film): ν = 3040, 2995–2895, 1710, 1620, 1460, 1380, 1285, 1145, 1060, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.04 (t, 3H, CH_3), 1.09 (d, 3H, CH_3), 1.25 (t, 3H, CH_3), 1.28 (t, 3H, CH_3), 2.51 (q, 2H, $C(O)CH_2$), 2.71–3.28 (compl.mult., 3H, CH, $CHCH_2$), 3.79 (q, 2H, enolether-OCH_2), 4.15 (q, 2H, ester-OCH_2), 5.0 (s, 1H, C=CH); MS: *m/e* (rel.int.): 242 (M^+, 9), 238 (12), 236 (15), 197 (19), 196 (28), 185 (60), 157 (12), 140 (14), 139 (100), 127 (14), 125 (11), 123 (28), 115 (16), 111 (43), 87 (20), 69 (21), 57 (47), 43 (21). High resolution MS (Calc. for $C_{13}H_{22}O_4$: 242.1516. Found: 242.1519. The racemic ketone **5g** was prepared from pentane-3-one and (*E*)-4-bromo-3-ethoxy-ethylcrotonoate via the dimethylhydrazone method.[3]

(2E, 6Z)-3-*Ethoxy*-5-*methyl*-6-*oxo*-*ethyl*-*oct*-2-*enoate*-*dimethylhydrazone*. 0.64 g (5.0 mmol) of pentane-3-one-dimethylhydrazone and 1.06 g (4.47 mmol) of (*E*)-4-bromo-3-ethoxy-ethylcrotonoate. Yield of crude product 1.27 g (100%), 330 mg of which were purified by column chromatography [Al_2O_3 (neutral, activity III), Et_2O-n-pentane (1:3] to give 200 mg (60%) of a pale yellow oil.

IR (film): ν = 3040, 3000–2780, 1715 (CO), 1625, 1470, 1460, 1450, 1380, 1290, 1150, 1120, 1060, 970, 820, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.12 (2t, 6H, CH_3), 1.29 (d, 3H, CH_3), 1.31 (t, 3H, CH_3), 2.24 (q, 2H, $C(N)CH_2$-anti), 2.35 (s, 6H, NMe_2), 2.66 (dd, 1H, $CHC\underline{H}H$, ^2J = 13.5 Hz, ^3J = 7.5 Hz), 3.16 (dd, 1H, $CHC\underline{H}H$, ^2J = 13.5 Hz, ^3J = 7.5 Hz), 3.78 (q, 2H, enolether-OCH_2), 3.82 (m, 1H, C(N)C$\underline{H}$-syn), 4.16 (q, 2H, ester-OCH_2), 5.0 (s, 1H, C=C$\underline{H}$); MS: *m/e* (rel.int.): 285 (M^+ + 1,6), 284 (M^+, 27), 255 (19), 240 (46), 225 (3), 223 (3), 212 (9), 197 (25), 196 (33), 194 (33), 185 (7), 166 (53), 157 (12), 151 (14), 139 (100 = b.p.), 127 (65), 111 (45), 99 (16), 84 (25), 72 (25), 69 (37), 56 (46), 42 (92). High resolution MS (Calc for $C_{15}H_{28}N_2O_3$: 284.2099. Found: 284.2106).

(±)-(*E*)-3-*Ethoxy*-5-*methyl*-6-*oxo*-*ethyl*-*oct*-2-*enoate* [(±)-**5g**]. Cleavage of 0.34 g (1.19 mmol) of the corresponding dimethyl hydrazone with $NaIO_4$[3] and workup afforded 0.33 g (100%) crude product, which was purified by Kugelrohr distillation, yield 0.19 g (66%), b.p. 95°/0.4 torr. All spectroscopic data (IR, NMR) were in agreement with those of (*S*)-**5g**. (Found: C, 64.32; H, 9.15. Calc for $C_{13}H_{22}O_4$ (242.3): C, 64.43; H, 9.15%).

(−)-(R)-3-*Methyl-heptane*-4-*one* [(**R**)-**5i**]. Hydrolysis (method B) of 1.38 g (5.74 mmol) of **4i** and distillation afforded 0.54 g (74%) of a colorless liquid, b.p. 100–120°/70 torr (lit.: 154–155°/760 torr[27]).

IR (film): ν = 1711 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.72–1.13 (2t, d, 9H, CH_3), 1.16–1.85 (m, 4H, CH_2), 2.20–2.57 (m, 3H, $C(O)CH_2$, CH).

(+)-(S)-5-*Ethyl-octane*-4-*one* [*S*]-**5j**]: Hydrolysis (method B) of 0.98 g (3.65 mmol) of **4j** and distillation afforded 0.38 g (67%) of a colorless liquid, b.p. 110–130°/30 torr.

IR (film): ν = 2965, 2940, 2880, 1710 (CO), 1460, 1405, 1378, 1265, 1160, 1118, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.72–1.12 (3t, 9H, CH_3), 1.12–1.84 (m, 8H, CH_2), 2.25–2.60 (m, 3H, $C(O)CH_2$, CH); MS: *m/e* (rel.int.): 157 (M^+ + 1, 1), 156 (M^+, 2), 115 (7), 114 (52), 113 (12), 99 (12), 86 (22), 85 (C_6H_{13}, 100 = b.p.), 84 (8), 72 (8), 71 (C_4H_7O, 99), 70 (9), 69 (8), 57 (38), 56 (11), 55 (27), 44 (11),

43 (C_3H_7, 99). (Calc for $C_{10}H_{20}O$ (156.3): C, 76.86; H, 12.90%). Found: C, 76.87; H, 13.11.

(−)-(R)-4-*Methyl-nonane-5-one* [(*S*)-**5k**]. Hydrolysis (method B) of 1.51 g (5.62 mmol) of **4k** and distillation afforded 0.62 g (71%) of a colorless liquid, b.p. 130°/13 torr.

IR (film): ν = 2955, 2925, 2860, 1710 (CO), 1455, 1401, 1370, 1250, 1230, 1155, 1115, 1035, 980, 960, 910 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.72–1.12 (2t, d, 9H, CH_3), 1.12–1.80 (m, 8H, CH_2), 2.2–2.68 (m, 3H, C(O)CH_2, CH).

(−)-(R)-4-*Ethyl-nonane-5-one* [(*S*)-**5l**]. Hydrolysis (method B) of 1.80 g (6.37 mmol) of **4l** and distillation afforded 0.81 g (75%) of a colorless oil, b.p. 140°/7 torr.

IR (film): ν = 2970, 2940, 2880, 1712 (CO), 1462, 1407, 1380, 1255, 1150, 1120, 1040 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.72–1.08 (3t, 9H, CH_3), 1.08–1.90 (m, 10H, CH_2), 2.24–2.60 (m, 3H, C(O)CH_2, CH); MS: *m/e* (rel.int.): 171 (M^+ + 1, 1), 170 (M^+, 2), 141 (5), 129 (5), 128 (54), 113 (26), 86 (90), 85 (C_6H_{13}, 100 = b.p.), 84 (12), 71 (18), 69 (12), 58 (21), 57 (89), 56 (15), 55 (31), 43 (90), 42 (12), 41 (81). (Found: C, 77.60; H, 13.14. Calc for $C_{11}H_{22}O$ (170.3): C, 77.58; H, 13.02%).

(+)-(S)-1-*Phenyl-2-methyl-butane-1-one* [(*S*)-**5m**]. Hydrolysis (method B) of 0.50 g (1.8 mmol) of **4m** and Kugelrohr-distillation of 0.10 g of the crude product afforded 83 mg (63%) of a colorless liquid, b.p. 40–45°/0.01 torr. All spectroscopic data (IR, NMR) are in agreement with literature values.[30,31]

(−)-(R)-1-*Phenyl-2-methyl-butane-1-one* [(*R*)-**5m**]. Hydrolysis (method B) of 0.95 g (3.44 mmol) of **4m′** and Kugelrohr distillation of the crude product afforded 0.30 g (55%). All spectroscopic data (IR, NMR) are identical with those of (*S*)-**5m**.

(−)-(R)-3-*Phenyl-butane-2-one* [(*R*)-**5n**]. Hydrolysis (method B) of 1.04 g (4 mmol) of **4n** and distillation afforded 0.42 g (71%) of a colorless oil, b.p. 100–120°/6 torr (lit.[32]: 102.5–103.5°/15 torr).

IR (film): ν = 3080, 3060, 3030, 2980, 2935, 2870, 1710 (CO), 1600, 1581, 1489, 1449, 1420, 1370, 1350, 1313, 1243, 1190, 1160, 1064, 1025, 943, 906, 800, 760, 732, 695, 630, 585, 540 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.37 (d, 3H, CH_3), 2.03 (s, 3H, CH_3), 3.72 (q, 1H, CH), 7.30 (m, 5H, C_6H_5).

(+)-(S)-1,3-*Diphenyl-butane-2-one* [(*S*)-**5o**]. Ozonolysis (method A) of 1.68 g (5 mmol) of **4o** and distillation afforded 0.91 g (81%) of a colorless oil, b.p. 120–140°/0.02 torr (lit.[39]: 152–153°/2 torr).

IR (film): ν = 3100–2900, 1720 (CO), 1606, 1590, 1500, 1460, 1380, 1340, 1130, 1075, 1038, 768, 705 cm^{-1}; ^1H NMR (CCl_4): δ = 1.28 (d, 3H, CH_3), 3.48 (s, 2H, $C_6H_5CH_2$), 3.72 (q, 1H, C_6H_5CH), 6.92–7.32 (m, 10H, C_6H_5).

(−)-(R)-1,3-*Diphenyl-butane-2-one* [(*R*)-**5o**]. Hydrolysis (method B) of 3.36 g (10 mmol) of **4o′** (Table 3) and distillation afforded 1.14 g (51%) of a colorless oil, b.p. 130–140°C/0.07 torr (lit.[39]: 152–153°/2 torr). All spectroscopic data (IR, NMR) are identical with those of (*S*) **5o**.

(−)-(R)-1,2-*Diphenyl-propane-1-one* [*R*)-**5p**]. Ozonolysis (method A) of 1.61 g (5 mmol) of **4p** and purification of the product by column chromatography (SiO_2, Et_2O/ n-pentane 1:10) afforded 0.83 g (79%).

IR (film): ν = 3080–2840, 1960, 1890, 1810, 1680 (CO), 1595, 1580, 1490, 1445, 1370, 1340, 1305, 1248, 1217, 1172, 1155, 1094, 1067, 1025, 1000, 949, 840, 754, 740, 695, 652, 615, 560, 509 cm^{-1}; ^1H NMR (CCl_4): δ = 1.40–1.60 (d, 3H, CH_3), 4.44–4.76 (q, 1H, C_6H_5CH), 7.12–8.00 (m, 10H, C_6H_5).

(S)-1-*Amino-2-methoxymethyl-1-methyl-pyrrolidinium-iodide* [(*S*)-**11**]. 0.65 g (5 mmol) (*S*)-**1** are dissolved in 25 ml ether. 0.30 ml (5 mmol) MeI are added at room temp and a white ppt is formed after a short time. Stirring is continued for 26 hr, after which the solvent is removed *in vacuo*, and the residue is treated with acetone, leaving 0.77 g (57%) of a colorless, crystalline solid, m.p. 114°; $[\alpha]_D^{25} = -24.3°$ (c = 1.67, $CHCl_3$).

IR (film): ν = 3280, 3260, 3140, 3020, 3000, 2970, 2930, 2875, 2825, 2800, 1630, 1465, 1420, 1395, 1345, 1277, 1222, 1192, 1123, 1092, 1045, 975, 950, 920, 833, 740, 696 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.80–2.60 (m, 4H, β-ring CH_2), 3.35–4.60 (m, 5H, NCH_2, OCH_2, CH), 3.44 (s, 3H, OCH_3), 3.60 (s, 3H, NCH_3), 6.09 (s, 2H, NH_2). (Found: C, 30.98; H, 6.14; N, 10.13. Calc for $C_7H_{17}IN_2O$ (272.1): C, 30.89; H, 6.30; N, 10.30%).

(S)-2-*Methoxymethyl-1-methylideneamino-pyrrolidine* [(*S*)-**12**]. The aqueous phase remaining from the cleavage by method B ("salt method"), is treated with Na_2CO_3 until pH > 7 is attained. Following extraction with CH_2Cl_2, the organic layer is separated and dried over Na_2SO_4. Removal of the solvent *in vacuo* affords a pink oil, which is purified by distillation (colorless oil), b.p. 50°/0.2 torr; $[\alpha]_D^{25} = -104.8°$ (c = 0.52, C_6H_6).

IR (film): ν = 3070, 2970, 2940, 2870, 2820, 1565 (CN), 1455, 1428, 1380, 1338, 1300, 1280, 1191, 1150, 1113, 966, 865 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.60 (m, 4H, β-ring CH_2), 2.55 (m, 1H, NCHH), 2.76–3.40 (m, 4H, NCHH, OCH_2, CH), 3.02 (s, 3H, OCH_3), 5.72 (d, 2H, N=CH_2, ^2J = 8 Hz). (Found: C, 59.36; H, 9.77; N, 18.94. Calc for $C_7H_{14}N_2O$ (142.2): C, 59.12; H, 9.92; N, 19.70%). (*S*)-**12** was independently prepared from formaldehyde and *SAMP*, the spectroscopic data were identical. (*S*)-**10′** was identified by ^1H NMR and MS.

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