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TETRAHEDRON: *ASYMMETRY*

First asymmetric nucleophilic displacement reactions on chiral α-substituted aldehyde hydrazones

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Abstract

The first asymmetric nucleophilic substitution reaction on racemic α-substituted aldehydes using enantiomerically pure hydrazines as chiral auxiliaries is presented. The diastereoselectivity of the process is achieved by a dynamic kinetic resolution *via* the 1:1 epimeric mixture of the substrate hydrazones. The a^2-reactivity (Umpolung) of the α-substituted hydrazones is accomplished by complexation with Lewis acids. Several carbon-, sulfur- and oxygen-nucleophiles were shown to readily undergo substitution of the α-leaving group under these conditions, affording the substitution products with good to excellent chemical yields and with low to moderate diastereoselectivities. Two methods for the cleavage of the chiral auxiliary are described.

1. Introduction

Carbonyl compounds bearing a leaving group in the α-position play an important role in modern organic chemistry and their reactivity towards nucleophilic agents has been intensively studied during the last few decades. Since there are several electrophilic sites present in these compounds, the control of the chemoselectivity of the nucleophilic attack is often complicated and the course of the reaction unpredictable. This problem has been well demonstrated for α-halogenated aldehydes and ketones[1] where nucleophilic substitution of the halogen atom (a^2-Umpolung) competes with various other reaction pathways. Besides reduction at C_α or α,β-elimination (dehydrohalogenation), mainly nucleophilic addition to the carbonyl carbon with subsequent epoxide formation or the Favorskii rearrangement can take place, the latter one being due to the high electrophilicity of the carbonyl carbon and the so-caused acidity of the α′-hydrogen, respectively.

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Therefore it seemed likely that the masking of the carbonyl functionality as derivatives with decreased electrophilicity at C-1 constitutes a means to enhance their tendency to give nucleophilic α-substitution. One possibility is to replace the carbonyl oxygen with nitrogen, leading to α-substituted imines. The difference in electronegativity between the two heteroatoms results in a lower electrophilicity of the imino carbon as compared to the carbonyl carbon and the nucleophilic displacement of the α-substituent often becomes more feasible.[1] Moreover, α-halogenated acetals,[2–4] oximes[5–8] and carboxylates,[9] α-[10] and α′-halogenated[11] silyl enol ethers, acetoxy-[12] and alkoxyepoxides[13] and α-substituted esters[14–16] have been reported to readily undergo nucleophilic substitutions.

Particularly interesting in this context are α-substituted hydrazones, since the hydrazone group exhibits an excellent ability to stabilize a positive charge in the α-position (Fig. 1). Of crucial importance is the lone electron pair of the amino group of the hydrazone, which enables the mesomeric stabilization of the cationic structure **A**, a probable intermediate when a S_N1-type reaction mechanism is assumed. Thus, in the case of terminally disubstituted hydrazones an ene-diazenium ion **B**[17–19] is formed, whereas terminally monosubstituted hydrazones undergo deprotonation leading to azoalkenes **C**.[20–23] Both species have been shown to add efficiently nucleophiles to the C_α-position,[17–23] so that the overall result corresponds to a nucleophilic substitution reaction.

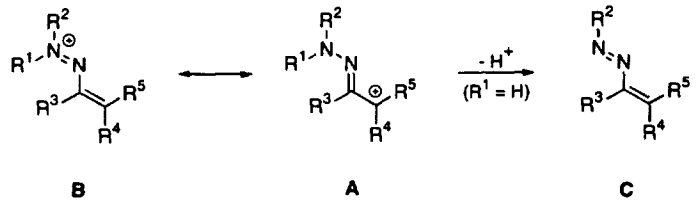


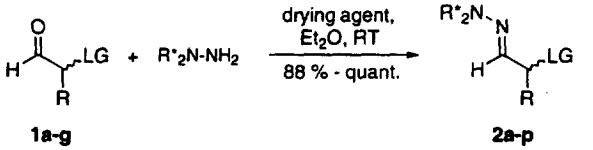
Fig. 1. Stabilization of α-cationic structures in hydrazones

Recently, we have shown the remarkable suitability of 2-acetoxyaldehyde dimethylhydrazones as substrates in the titanium tetrachloride mediated nucleophilic substitution reaction using silyl enol ethers, leading to 4-oxo hydrazones, which are excellent precursors for the pyrrole ring system.[24,25] We wish to present here our efforts towards the development of, to our knowledge, the first asymmetric variant of this type of reaction using chiral α-substituted hydrazones, that are readily available from the corresponding racemic α-substituted aldehydes and enantiomerically pure chiral hydrazines. The closely related reaction of chiral α-halo esters and α-halo amides with a great variety of nucleophiles is already well established in the field of asymmetric organic synthesis.[26–29]

2. Results and discussion

Starting from the racemic aldehydes **1a–g** bearing a leaving group (LG) in the α-position, the hydrazones **2a–p** were readily prepared by condensation with various optically pure chiral hydrazines at room temperature in diethyl ether in the presence of a drying agent (Scheme 1). The products were used without further purification, since both column chromatography and distillation under reduced pressure led to decomposition. Only the less reactive **2a,b** could be obtained in pure form after column chromatography. The enantiomerically pure aldehyde **1b** was chosen for mechanistic studies (see below). Fig. 2 gives a survey of the employed chiral hydrazines and the results are presented in Table 1.

Based on some initial work by our group[30] the reaction of 2-acetoxypropanal SAMP-hydrazone (*R/S,S*)-**2c** with the methyl isobutyrate derived silyl ketene acetal **3b** was first investigated to optimize the reaction conditions (Scheme 2). We examined the dependence of both the diastereoselectivity and the



Scheme 1.

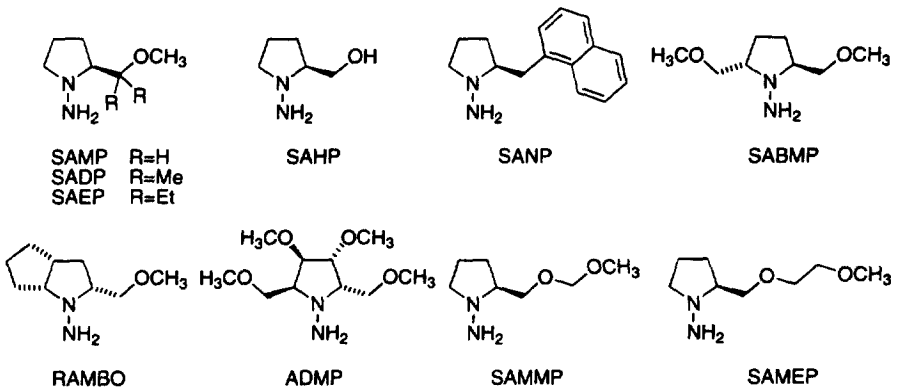


Fig. 2. Auxiliaries used in the model reaction

yield of the model reaction on the reaction temperature, the solvent and the Lewis acid. A remarkably strong influence of the Lewis acid on the diastereoselectivity of the formation of 4-hydrazono ester (*R*/*S*,*S*)-**4a** was observed (entries 7–12, Table 2), whereas the solvent effect was surprisingly low (entries 1–4). The best results were obtained by performing the reaction in diethyl ether at −110°C in the presence of boron trifluoride diethyl ether complex (entry 14).

In order to exclude the possibility of epimerization of the stereogenic center at C_α under the basic work-up conditions, several different work-up procedures were carried out. Using aqueous pH 7 buffer solution, saturated aqueous ammonium chloride solution, saturated aqueous sodium chloride solution and 1 M aqueous K_2HPO_4 solution, respectively, as quenching agents led only to a distinct loss of chemical yield and no detectable increase in the diastereoselectivity of the α-substitution.

For the further refinement of the diastereoselectivity in the model reaction various auxiliaries based on enantiomerically pure substituted 1-aminopyrrolidines were tested. Following the previous procedure, the corresponding 2-acetoxypropanal hydrazones were complexed with 1.1 equiv. of $BF_3 \cdot OEt_2$ in diethyl ether at −78°C and subsequently reacted with 2.0 equiv. of silyl ketene acetal **3b** at −110°C (Scheme 3). The results are presented in Table 3.

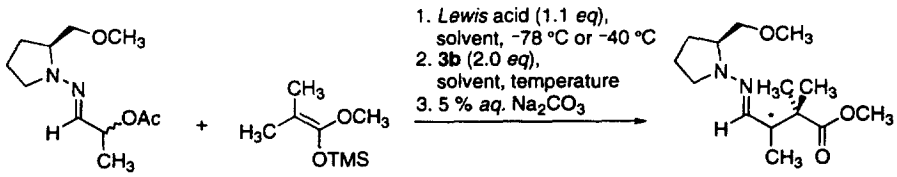
One striking point is that, by increasing the steric demand of the α-substituent of the auxiliary, complete loss of the diastereoselectivity is observed (entries 1–3, Table 3). SANP, which has a very bulky naphthyl-substituent, also exhibits relatively low diastereoselectivity (entry 5). Good results were obtained using 2-(methoxymethyl)-substituted auxiliaries (entries 1, 6–8), of which SAMP turned out to be best concerning both diastereomeric excess and chemical yield of the hydrazonoester **4**. Apparently, the presence of a donor atom in the substituent of the auxiliary as well as its unhindered accessibility by the Lewis acid are essential for an efficient asymmetric induction. This also corresponds to the observation that the diastereoselectivity is strongly influenced by the Lewis acid itself (see above). Therefore, we hoped to achieve further improvement of the stereoselectivity by incorporating additional donor atoms into the pyrrolidine substituent. Unfortunately, this approach was not successful (entries 9–10).

For the evaluation of the suitability of different leaving groups (LG) for the asymmetric nucleophilic

Table 1
Synthesis of α-substituted aldehyde hydrazones **2a–p**

Substrate	Product	R	LG	$R^*_2N\text{-}NH_2$	yield[a] [%]
rac-**1a**	(*S,R/S*)-**2a**	Me	PhSe-	SAMP	91[b]
(*S*)-**1b**	(*S,S*)-**2b**	Me	BnO-	SAMP	91[b,c]
rac-**1c**	(*R/S,S*)-**2c**	Me	AcO-	SAMP	99
rac-**1d**	(*R/S,S*)-**2d**	Et	AcO-	SAMP	95
rac-**1e**	(*R/S,S*)-**2e**	*i*-Pr	AcO-	SAMP	quantitative
rac-**1f**	(*R/S,S*)-**2f**	Me	BzO-	SAMP	quantitative
rac-**1g**	(*R/S,S*)-**2g**	Me	4-NitroBzO-	SAMP	88
rac-**1a**	(*R/S,S*)-**2h**	Me	AcO-	SADP	quantitative
rac-**1a**	(*R/S,S*)-**2i**	Me	AcO-	SAEP	quantitative
rac-**1a**	(*R/S,S*)-**2j**	Me	AcO-	SAHP	quantitative
rac-**1a**	(*R/S,S*)-**2k**	Me	AcO-	SANP	99
rac-**1a**	(*R/S,S,S*)-**2l**	Me	AcO-	SABMP	quantitative
rac-**1a**	(*R/S,R,R,R*)-**2m**	Me	AcO-	RAMBO	quantitative
rac-**1a**	(*R/S,S,R,R,S*)-**2n**	Me	AcO-	ADMP	quantitative
rac-**1a**	(*R/S,S*)-**2o**	Me	AcO-	SAMMP	90
rac-**1a**	(*R/S,S*)-**2p**	Me	AcO-	SAMEP	97

[a] Yield of the crude product
[b] After purification by column chromatography
[c] *de* > 96 % (determined by ^{13}C NMR spectroscopy)
LG = leaving group



(*R/S,S*)-**2c** **3b** (*R/S,S*)-**4a**

Scheme 2. Model reaction for the optimization of the reaction conditions

substitution, we reacted the corresponding propanal SAMP-hydrazones **1a–c,f,g** with silyl ketene acetal **3b** under standard conditions (Scheme 4). Table 4 gives a survey of the results obtained.

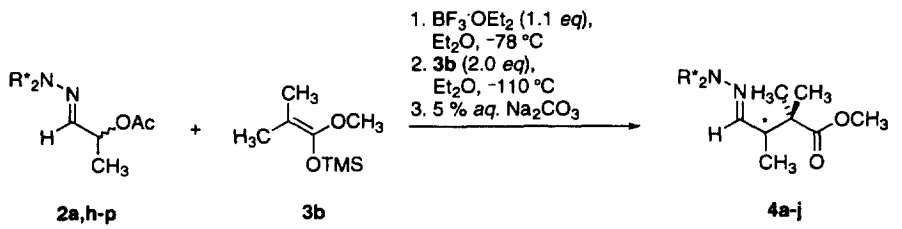
The phenylselenyl-group proved to be unreactive under the chosen reaction conditions. No conversion could be detected, even after warming to room temperature, and the starting material (*S,R/S*)-**2a** was re-isolated after work-up. In contrast, the (4-nitrobenzoate)-substituted hydrazone (*R/S,S*)-**2g** underwent complete decomposition on complexation with the Lewis acid and no substitution product was obtained. By comparison with the other substrates the strong influence of the reactivity of the leaving group on the chemical yield of the substitution reaction is exhibited. The lower yield in the case of the less reactive benzyloxy-group may be due to the increased competition of the α-substitution with side reactions. The more reactive benzoate-group, in contrast, leads to partial decomposition under the reaction conditions. The best chemical yield was obtained using the acetoxy-substituted hydrazone (*R/S,S*)-**2c**.

In addition, a slight decrease of the diastereoselectivity of the substitution reaction with increasing reactivity of the leaving group is observed, as may be expected. The improved diastereoselectivity when changing from the α-epimeric acetoxy-substituted hydrazone (*R/S,S*)-**2c** to the diastereomerically pure 2-

Table 2
Synthesis of 4-hydrazono ester (*R*/*S*,*S*)-**4b** under different reaction conditions

Entry	*Lewis* acid	Solvent	Temperature [°C]	Yield [%]	*de*[a] [%]
1	BF_3·OEt_2	CH_3CN	−40	81	37
2	BF_3·OEt_2	THF	−40	99	35
3	BF_3·OEt_2	CH_2Cl_2	−40	93	40
4	BF_3·OEt_2	Et_2O	−40	39	40
5	$AsCl_3$	CH_2Cl_2	−78	-	-
6	$AlCl_3$	CH_2Cl_2	−78	-	-
7	$ZnCl_2$	Et_2O	−78	53	23
8	*n*-Bu_3B	CH_2Cl_2	−78	64	25
9	$SnCl_4$	CH_2Cl_2	−78	97	40
10	$TiCl_4$	CH_2Cl_2	−78	quantitative	43
11	*n*-Bu_2BOTf	CH_2Cl_2	−78	quantitative	44
12	BF_3·OEt_2	Et_2O	−78	91	50
13	TMSOTf	Et_2O	−110	quantitative	59
14	BF_3·OEt_2	Et_2O	−110	quantitative	60

[a] Determined by ^{13}C NMR spectroscopy



Scheme 3.

benzyloxy hydrazone (*S*,*S*)-**2b** is certainly not due to a chirality transfer process, since the complexation of (*S*,*S*)-**2b** with Lewis acids under the reaction conditions for some minutes and subsequent work-up led to α-epimerized starting material (*R*/*S*,*S*)-**2b**. Moreover, a probable mechanism for a chirality transfer process would be an S_N2-like reaction with inversion of the absolute configuration at C_α. However, the major diastereomer of **4a** is formed with 'retention' of the absolute configuration at C_α, as will be shown later.

In conclusion, the 2-acetoxypropanal SAMP-hydrazone (*R*/*S*,*S*)-**2c** represents a good compromise between the necessary stability of the starting material on the one hand and desired reactivity on the other hand.

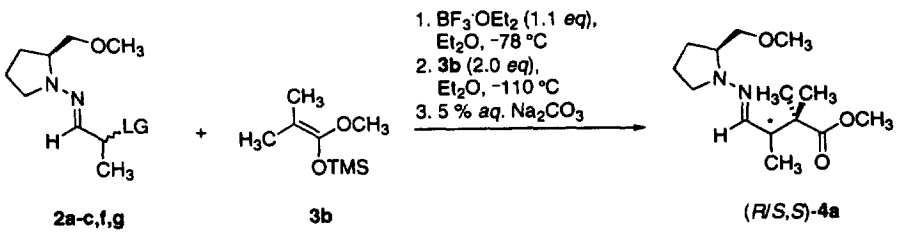
Based on these results, various silyl ketene acetals were tested as nucleophiles in the substitution reaction with α-acetoxyaldehyde SAMP-hydrazones under the optimized reaction conditions (Scheme 5). Only silyl ketene acetals with a symmetrical substitution pattern at C-2 were employed, thus generating only one stereogenic centre. This also circumvents the problem of controlling *E*/*Z*-geometry of the nucleophile during formation. The results are summarized in Table 5.

The 4-hydrazono esters (*R*/*S*)-**4a**,**k**–**p** were obtained in good to excellent chemical yields and with mostly moderate diastereomeric excesses. HPLC enrichment of the major diastereomer failed in all cases except compound (*R*/*S*)-**4m**, which could be further purified affording the major diastereomer with a *de* of 96% and the minor diastereomer with a *de* of 90%. The methyl diphenylacetate derivative **3g** gave

Table 3
Results employing different auxiliaries in the model reaction

Entry	Substrate	Product	$R^*_2N\text{-}NH_2$	Yield [%]	*de*[a] [%]
1	(*R/S,S*)-**2c**	(*R/S,S*)-**4a**	SAMP	quantitative	60
2	(*R/S,S*)-**2h**	(*R/S,S*)-**4b**	SADP	91	<2
3	(*R/S,S*)-**2i**	(*R/S,S*)-**4c**	SAEP	69	<2
4	(*R/S,S*)-**2j**	(*R/S,S*)-**4d**	SAHP	38	<2
5	(*R/S,S*)-**2k**	(*R/S,S*)-**4e**	SANP	70	15
6	(*R/S,S,S*)-**2l**	(*R/S,S,S*)-**4f**	SABMP	39	60
7	(*R/S,R,R,R*)-**2m**	(*R/S,R,R,R*)-**4g**	RAMBO	44	46
8	(*R/S,S,R,R,S*)-**2n**	(*R/S,S,R,R,S*)-**4h**	ADMP	48	53
9	(*R/S,S*)-**2o**	(*R/S,S*)-**4i**	SAMMP	64	22
10	(*R/S,S*)-**2p**	(*R/S,S*)-**4j**	SAMEP	50	35

[a] Determined by ^{13}C NMR spectroscopy



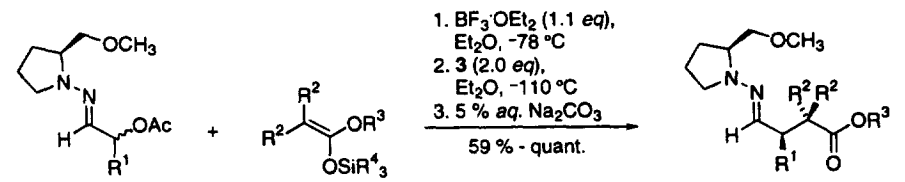
2a-c,f,g **3b** (*R/S,S*)-**4a**

Scheme 4. Study of different leaving groups (LG) in the model reaction

Table 4
Synthesis of 4-hydrazono ester (*R/S,S*)-**4a** by using different leaving groups

Substrate	Leaving Group (LG)	yield [%]	*de*[a] [%]
(*S,R/S*)-**2a**	PhSe-	-[b]	-
(*S,S*)-**2b**	BnO-	62	62
(*R/S,S*)-**2c**	AcO-	quantitative	60
(*R/S,S*)-**2f**	BzO-	51	57
(*R/S,S*)-**2g**	4-NitroBzO-	-[c]	-

[a] Determined by ^{13}C NMR spectroscopy
[b] No reaction, -78 °C - RT
[c] Complete decomposition



(*R/S,S*)-**2c-e** **3a-g** (*R,S*)-**4a,k-p**

de = 12 - 69 %

Scheme 5.

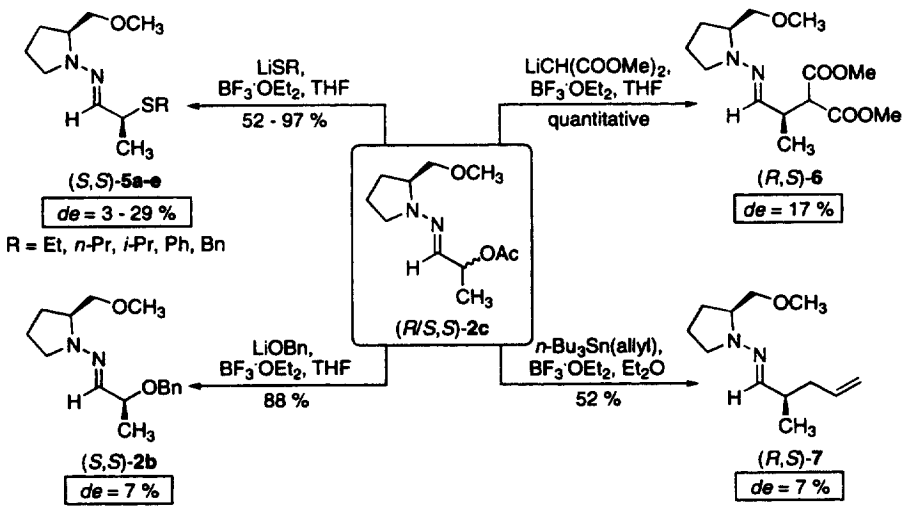
Table 5
Synthesis of 4-hydrazono esters (*R,S*)-**4a,k–p**

Substrate	Nucleophile	Product	R^1	R^2	R^3	R^4	yield [%]	*de*[a] [%]
(*R/S,S*)-**2c**	**3a**	(*R,S*)-**4k**	Me	H	Et	Me	quantitative	12
(*R/S,S*)-**2c**	**3b**	(*R,S*)-**4a**	Me	Me	Me	Me	quantitative	60
(*R/S,S*)-**2d**	**3b**	(*R,S*)-**4l**	Et	Me	Me	Me	59	66
(*R/S,S*)-**2e**	**3b**	(*R,S*)-**4m**	*i*-Pr	Me	Me	Me	90	69 (96[b])
(*R/S,S*)-**2c**	**3c**	(*R,S*)-**4a**	Me	Me	Me	Et	64	46
(*R/S,S*)-**2c**	**3d**	(*R,S*)-**4n**	Me	Me	Et	Me	85	45
(*R/S,S*)-**2c**	**3e**	(*R,S*)-**4o**	Me	Me	*i*-Pr	Me	75	39
(*R/S,S*)-**2c**	**3f**	(*R,S*)-**4p**	Me	Et	Me	Me	76	53
(*R/S,S*)-**2c**	**3g**	-	Me	Ph	Me	Me	-	-

[a] Determined by ^{13}C NMR spectroscopy
[b] After separation of the minor diastereomer by HPLC

no reaction, which may be due to the high steric demand of the phenyl substituents and their electron withdrawing effect reducing the nucleophilicity of the silyl ketene acetal.

Besides the silyl ketene acetals, several other carbon-, sulfur- and oxygen-nucleophiles were successfully employed in our asymmetric nucleophilic displacement reaction on α-acetoxyaldehyde SAMP-hydrazones (Scheme 6). These compounds required higher reaction temperatures and, especially for the lithiated species, the use of THF as solvent turned out to be advantageous concerning the chemical yield of the substitution product. Table 6 gives a survey of the results obtained.



Scheme 6.

The 2-thiolated hydrazones (*S,S*)-**5a–e** were obtained in good to excellent yields but with only low diastereoselectivities. Since these compounds can be expected to be even more susceptible to α-epimerization under basic work-up conditions than the 4-hydrazono esters **4**, additional work-up experiments were carried out using saturated aqueous sodium chloride solution and aqueous pH 7 buffer solution as quenching agent. As before, no improvement of the diastereoselectivity of the substitution could be achieved.

The reaction of (*R/S,S*)-**2c** with lithium benzyloxide afforded the 2-benzyloxypropanal SAMP-

Table 6
Reaction of (*R/S,S*)-**2c** with different nucleophiles

Product	Nucleophile	Reaction conditions	yield [%]	*de*[a] [%]
(*S,S*)-**5a**	EtSLi	A (B)	52 (85)	13 (10)
(*S,S*)-**5b**	*n*-PrSLi	A (B)	65 (82)	13 (9)
(*S,S*)-**5c**	*i*-PrSLi	A (B)	59 (91)	6 (3)
(*S,S*)-**5d**	PhSLi	A	97	29
(*S,S*)-**5e**	BnSLi	A	92	11
(*S,S*)-**2b**	BnOLi	A	88	7
(*R,S*)-**6**	$LiCH(COOMe)_2$	B	quantitative	17
(*R,S*)-**7**	*n*-Bu_3Sn(allyl)	B	52	7

A Reaction temperature: –78 °C
B Reaction temperature: –78 to –20 °C
[a] Determined by ^{13}C NMR spectroscopy

hydrazone (*S,S*)-**2b** in 88% yield but with only 7% diastereomeric excess. As has been mentioned previously, complexation of **2b** with Lewis acids under the reaction conditions effects efficient α-epimerization. Therefore it had to be investigated whether the slight excess of Lewis acid in the reaction mixture is responsible for the low diastereomeric excess of the product. Performing the substitution reaction in the presence of only 0.5 equiv. $BF_3 \cdot OEt_2$ yielded (*S,S*)-**2b** with almost exactly half of the chemical yield (45%) but with an identical *de* of 7%, thus rendering an α-epimerization of the product during the reaction time very unlikely.

Likewise, the use of lithium dimethylmalonate and allyl tributyl stannane, respectively, yielded the α-substituted products in moderate to excellent yields and with low diastereoselectivities. In the case of (*R,S*)-**7** an unidentified by-product was formed, which could only be separated by HPLC. However, no diastereomeric enrichment of the product could be achieved.

For the evaluation of the relative and absolute configuration of the substitution products two methods were employed. The first method consisted of a comparison of the NMR spectra of the substitution products with compounds of known relative and absolute configuration, the latter ones being synthesized from chiral pool starting materials. Thus, the 2-benzyloxypropanal SAMP-hydrazone (*S,S*)-**2b** could be obtained with a *de* of 7% by substitution of the acetoxy group of (*R/S,S*)-**2c** with lithium benzyloxide in the presence of $BF_3 \cdot OEt_2$ (Table 6). On the other hand, this compound was accessible with a *de*>96% starting from ethyl lactate (*S*)-**8**.[31] Fig. 3 shows part of the ^{13}C NMR spectra of the respective compounds. The arrows mark the signals of the α-carbon, indicating the (*S*)-configuration of the newly generated stereogenic centre for the major diastereomer.

Moreover, NOE experiments were carried out on both diastereomers of **4m**, which are available by HPLC purification of the substitution product (Table 5). Fig. 4 shows the characteristic NOE enhancements observed on the major diastereomer.

The missing NOE between H^1 and H^2 and the observed coupling constant of 8.2 Hz indicate the *anti*-position of these protons and therefore unequivocally determine the conformation of the C(1)–C(2) bond. The shown conformation of the N–N bond and the (*E*)-configuration of the C=N double bond follow the observed NOE between H^1 and the protons of the α-methylene group of the pyrrolidine moiety, which can be clearly distinguished by their ^1H NMR chemical shift and which are labelled as H_c and H_t according to their *cis*- and *trans*-position relative to H_s. The crucial point for the assignment of the relative and absolute configuration of the α-centre is the detected NOE between one of the methyl groups of the isopropyl-moiety and H_c, stipulating the (*R*)-configuration at C_α. The minor diastereomer instead

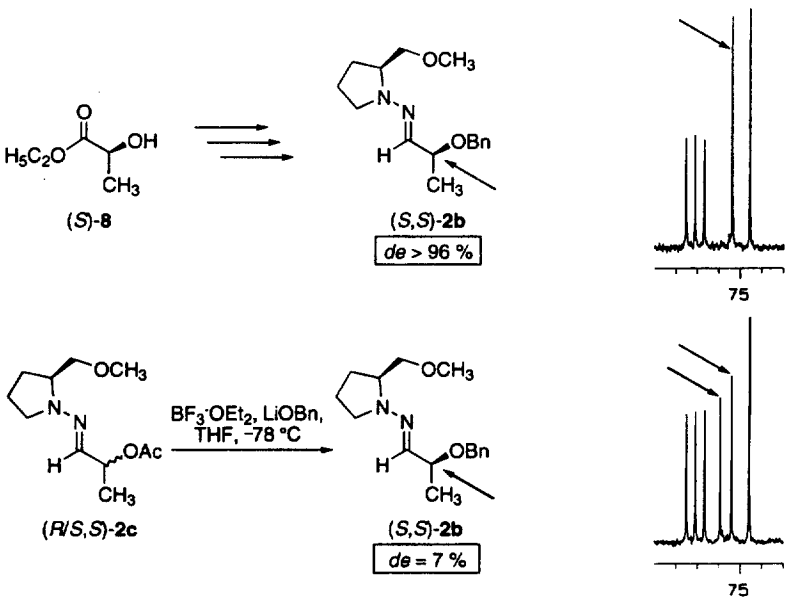


Fig. 3. Determination of the absolute configuration of **2b**

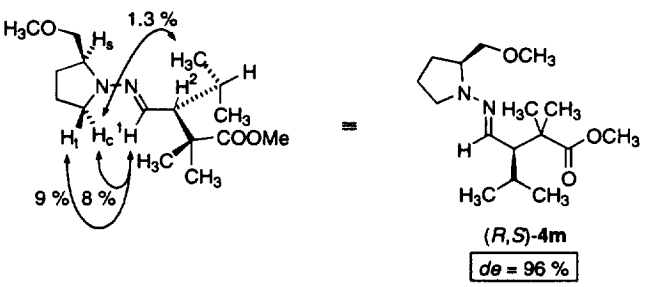
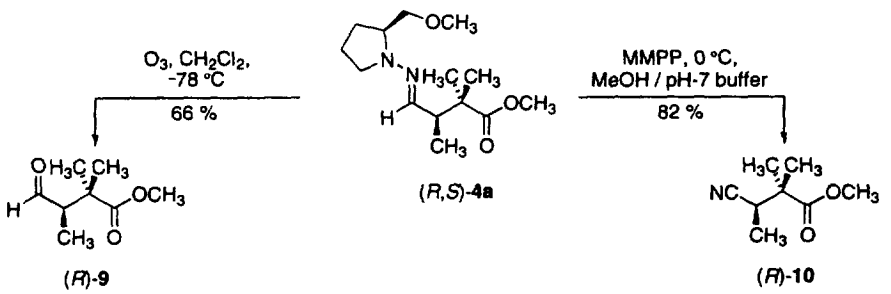


Fig. 4. NOE enhancements observed on the major diastereomer of **4m**

exhibits an NOE between one of the methyl groups adjacent to the ester moiety and H_c, thus confirming the assignment of the absolute configuration of the major diastereomer.

Based on these results, a uniform reaction mechanism for the $BF_3 \cdot OEt_2$ mediated substitution reaction of the 2-acetoxyaldehyde SAMP-hydrazones with the different nucleophiles may be postulated. Supposing an S_N2-like mechanism, the experimental results may be explained by a kinetic preference of the displacement of the acetoxy group on the (*R*,*S*)-diastereomer of **2c–e** in relation to the (*S*,*S*)-diastereomer, rendering the whole process a dynamic kinetic resolution[32–34] of the 1:1 epimeric mixture of the substrate hydrazones. The existence of an efficient α-epimerization under the reaction conditions, which is essential for this type of process, has been shown for the 2-benzyloxy hydrazone **2b** (see above) and may therefore be assumed in particular for the more reactive 2-acetoxy hydrazones **2c–e**. Since all efforts to elucidate the structure of the complexed substrate hydrazones have so far failed, the reason for the different reaction rates of the starting material diastereomers can only be speculated upon.

The cleavage of the chiral auxiliary in the case of the 4-hydrazono esters **4a,k–p** was investigated using **4a** as an example. Ozonolysis of (*R*,*S*)-**4a** in methylene chloride at −78°C afforded the corresponding 4-oxoester (*R*)-**9** without racemization in 66% yield (Scheme 7). Moreover, reaction of (*R*,*S*)-**4a** with magnesium monoperoxyphthalate in methanol aq. pH 7 buffer at 0°C led to the racemization free formation of 3-cyano ester (*R*)-**10** in 82% yield (Scheme 7).[35,36]



Scheme 7. Cleavage of the chiral auxiliary

The ozonolytic cleavage of the chiral auxiliary in 2-thiolated aldehyde SAMP-hydrazones and the problem of controlling the chemoselectivity of the oxidation of the C=N double bond in the presence of the thioether function have already been studied intensively in our group.[37]

In conclusion, the Lewis acid mediated substitution reaction of 2-acetoxyaldehyde SAMP-hydrazones with different carbon-, sulfur- and oxygen-nucleophiles provides an efficient entry to different α-substituted aldehydes and constitutes a promising contribution to the growing field of dynamic kinetic resolutions *via* diastereomeric mixtures. The substitution products are obtained in good to excellent chemical yields but with only low to moderate diastereoselectivities so far. The further optimization of the stereoselectivity of this process is currently under continuing investigation within our laboratory.

3. Experimental

3.1. General remarks

All reactions were carried out under argon using standard Schlenk techniques unless stated otherwise. Solvents were dried and purified by conventional methods prior to use. Diethyl ether was freshly distilled from sodium, tetrahydrofuran from potassium and dichloromethane and acetonitrile from calcium hydride under argon. Reagents of commercial quality were used from freshly opened containers or purified by common methods. *rac*-2-Phenylselenylpropanal *rac*-**1a** is available by oxidative selenylation of propanal,[38] (*S*)-2-benzyloxypropanal (*S*)-**1b** was obtained from a two step synthesis starting from ethyl (*S*)-lactate.[31] *rac*-2-Acetoxypropanal *rac*-**1c** was kindly donated by BASF AG. Other 2-acetoxyaldehydes *rac*-**1d,e** were available from their corresponding silyl enol ethers.[39] *rac*-2-Benzoyloxypropanal *rac*-**1f** and *rac*-2-(4′-nitrobenzoyloxy)propanal *rac*-**1g** were obtained from *rac*-1-buten-3-ol.[40,41] Silyl ketene acetals **3a–g**,[42] (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP),[43,44] (*S*)-1-amino-2-(1′-methoxy-1′-methylethyl)pyrrolidine (SADP),[45] (*S*)-1-amino-2-(1′-ethyl-1′-methoxypropyl)pyrrolidine (SAEP),[45] (*S*)-1-amino-2-(hydroxymethyl)pyrrolidine (SAHP),[46] (*S*)-1-amino-2-(naphth-1′-ylmethyl)pyrrolidine (SANP),[47] (2*S*,5*S*)-1-amino-2,5-bis(methoxymethyl)pyrrolidine (SABMP),[48] and (2*S*,3*R*,4*R*,5*S*)-1-amino-3,4-dimethyl-2,5-bis(methoxymethyl)pyrrolidine (ADMP)[49] were prepared according to literature procedures. (2*R*,3a*R*,6a*R*)-1-Amino-2-(methoxymethyl)perhydrocyclopenta[*b*]pyrrol (RAMBO)[50] was obtained analogous to the SAMP procedure starting from benzyl (2*R*,3a*R*,6a*R*)-perhydrocyclopenta[*b*]pyrrol-2-carboxylate hydrochloride, which was kindly donated by Hoechst AG. (*S*)-1-Amino-2-[(methoxymethoxy)methyl]pyrrolidine[51] (SAMMP) and (*S*)-1-amino-2-[(2′-methoxyethoxy)methyl]pyrrolidine[51] (SAMEP) were available analogous to the SAMP procedure except using triethyl(methoxymethyl)ammonium chloride[52] and sodium hydride/2-methoxyethylchloride, respectively, for the *O*-protection of the intermediate *N*-formylprolinol. Analytical TLC: Merck

glass-backed silica gel 60 F_{254} plates. Column chromatography: Merck silica gel 60, 0.040–0.063 mm (230–400 mesh) (flash). Analytical GC: Siemens Sichromat 2 or 3 equipped with a SE-54-CB, OV-1-CB or OV-17 column (25 m×0.25 mm), nitrogen carrier gas, operated at temperature programs as indicated, FID. IR: Perkin–Elmer 1420 and Perkin–Elmer FT/IR 1750. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz): Varian VXR 300 or Gemini 300 (TMS as internal standard). MS: Varian MAT 212 or Finnigan SSQ 7000 (EI, 70 eV). Elemental analyses: Heraeus CHN–O-Rapid or elementar vario EL. Diastereomeric excesses were determined by ^{13}C NMR spectroscopy. For 1:1 diastereomeric mixtures the individual diastereomers are not assigned.

3.2. *General procedure for the condensation of 2-substituted aldehydes with chiral hydrazines*

A solution of the 2-substituted aldehyde **1** (1.0 equiv.) in diethyl ether in the presence of a drying agent was cooled to 0°C. Then the chiral hydrazine (1.0 equiv.) was added dropwise with stirring and the resulting reaction mixture was warmed to room temperature. Stirring was continued until the reaction was complete (TLC control, 1.5–2.5 h). After filtration and evaporation of the solvent the crude product was used without further purification or was purified by column chromatography (pentane:Et_2O=2:1).

3.3. *(2S,2′R/S)-[2-(Methoxymethyl)pyrrolidin-1-yl]-[2′-(phenylselenyl)propyliden]amine* **2a**

Scale: 4 mmol, 35 ml Et_2O. Drying agent: 3.5 g magnesium sulfate. Purification by column chromatography. Yield: 91%. Yellow oil. R_f=0.48 (pentane:Et_2O=2:1). R_t=12.4 min (OV-17; 120-10-260; slight decomposition). IR (capillary, ν cm^{-1}): 3069, 3055 (m), 2970, 2921, 2875, 2825, 1579, 1476, 1448, 1438 (vs), 1374, 1341 (s), 1324 (m), 1303 (s), 1283 (m), 1197, 1121 (vs), 1073, 1055, 1022, 1008, 1001 (s), 972, 902, 874 (m), 740, 692 (vs), 671 (w). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52, 1.54 (d, *J*=7.1 Hz, 3H, $CHCH_3$), 1.68–1.94 (m, 4H, $NCH_2CH_2CH_2$), 2.50–2.60, 2.70–2.80 (m, 1H, NC*H*H), 3.15–3.50 (m, 4H, NCH*H*, NC*H*C*H*HO), 3.31, 3.33 (s, 3H, CH_2OCH_3), 4.10, 4.12 (quin, *J*=7.1 Hz, 1H, $CHCH_3$), 6.48, 6.50 (d, *J*=7.1 Hz, 1H, HC=N), 7.20–7.30 (m, 3H, $CH_{meta/para}$), 7.50–7.60 (m, 2H, CH_{ortho}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 19.5 ($CHCH_3$), 22.1, 22.2 (NCH_2CH_2), 26.5, 26.7 ($NCH_2CH_2CH_2$), 41.0, 41.1 ($CHCH_3$), 49.6, 49.8 (NCH_2), 59.2 (CH_2OCH_3), 62.9, 63.3 (NCH), 74.5, 74.6 (CH_2OCH_3), 127.4, 127.5 (C_{para}), 128.6, 128.7 (CH_{meta}), 129.3, 129.5 (C_{ipso}), 135.0, 135.4 (CH_{ortho}), 136.9, 137.4 (HC=N). MS (EI, 70 eV): *m/z* (%) 169 (100) [$M^+-C_6H_5Se$], 157 (17), 123 (89) [$M^+-CH_2OCH_3-C_6H_5Se$], 77 (21) [$C_6H_5^+$], 70 (21) [$C_4H_8N^+$], 55 (10), 51 (10), 45 (16). EA $C_{15}H_{22}N_2OSe$ (325.31): calcd C 55.38, H 6.82, N 8.61; found C 54.83, H 6.97, N 8.93.

3.4. *(2S,2′S)-[2-(Benzyloxy)propyliden]-[2′-(methoxymethyl)pyrrolidin-1′-yl]amine* **2b**

Scale: 3 mmol, 20 ml Et_2O. Drying agent: 5 g magnesium sulfate. Purification by column chromatography. Yield: 91%. Colourless liquid, *de*=96%. R_f=0.43 (pentane:Et_2O=2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (d, *J*=6.3 Hz, 3H, $CHCH_3$), 1.75–2.03 (m, 4H, $NCH_2CH_2CH_2$), 2.77–2.86 (m, 1H, NC*H*H), 3.25–3.60 (m, 4H, NCH*H*, NC*H*C*H*HO), 3.38 (s, 3H, CH_2OCH_3), 4.07 (quint, *J*=6.6 Hz, 1H, $CHCH_3$), 4.46 (d, *J*=12.1 Hz, 1H, CHOC*H*H), 4.58 (d, *J*=12.1 Hz, 1H, CHOCH*H*), 6.41 (d, *J*=6.9 Hz, 1H, HC=N), 7.21–7.37 (m, 5H, aromatic CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.2 ($CHCH_3$), 22.2 (NCH_2CH_2), 26.6 ($NCH_2CH_2CH_2$), 49.4 (NCH_2), 59.2 (CH_2OCH_3), 62.9 (NCH), 70.0 ($CHOCH_2$), 74.5 (CH_2OCH_3), 75.4 ($CHOCH_2$), 127.3 (CH_{para}), 127.8 (CH_{ortho}), 128.3 (CH_{meta}), 137.0 (HC=N), 138.8 (C_{ipso}). For GC, IR and MS data see Section 3.41.

3.5. (1R/S,2′S)-2-{[2′-(Methoxymethyl)pyrrolidin-1′-yl]imino}-1-methylethyl acetate **2c**

Scale: 10 mmol, 40 ml Et_2O. Drying agent: 8 g magnesium sulfate. Crude product was used without further purification. Yield: 95%. Yellowish oil.

3.6. (1R/S,2′S)-1-({[2′-(Methoxymethyl)pyrrolidin-1′-yl]imino}methyl)propyl acetate **2d**

Scale: 10 mmol, 40 ml Et_2O. Drying agent: 8 g magnesium sulfate. Crude product was used without further purification. Yield: 99%. Yellowish oil.

3.7. (1R/S,2′S)-1-({[2′-(Methoxymethyl)pyrrolidin-1′-yl]imino}methyl)-2-methylpropyl acetate **2e**

Scale: 5 mmol, 20 ml Et_2O. Drying agent: 8 g magnesium sulfate. Crude product was used without further purification. Yield: quantitative. Yellowish oil.

3.8. (1R/S,2′S)-2-{[2′-(Methoxymethyl)pyrrolidin-1′-yl]imino}-1-methylethyl benzoate **2f**

Scale: 1 mmol, 10 ml Et_2O. Drying agent: 2 g sodium sulfate. Crude product was used without further purification. Yield: quantitative. Yellowish oil.

3.9. (1R/S,2′S)-2-{[2′-(Methoxymethyl)pyrrolidin-1′-yl]imino}-1-methylethyl 4-nitrobenzoate **2g**

Scale: 1.1 mmol, 20 ml Et_2O. Drying agent: 2 g molecular sieves 4 Å. Crude product was used without further purification. Yield: 88%. Yellowish oil.

3.10. (1R/S,2′S)-2-{[2′-(1′-Methoxy-1′-methylethyl)pyrrolidin-1′-yl]imino}-1-methylethyl acetate **2h**

Scale: 5 mmol, 20 ml Et_2O. Drying agent: 4 g magnesium sulfate. Crude product was used without further purification. Yield: quantitative. Yellowish oil.

3.11. (1R/S,2′S)-2-{[2′-(1′-Ethyl-1′-methoxypropyl)pyrrolidin-1′-yl]imino}-1-methylethyl acetate **2i**

Scale: 1 mmol, 20 ml Et_2O. Drying agent: 4 g magnesium sulfate. Crude product was used without further purification. Yield: quantitative. Yellowish oil.

3.12. (1R/S,2′S)-2-{[2′-(Hydroxymethyl)pyrrolidin-1′-yl]imino}-1-methylethyl acetate **2j**

Scale: 1 mmol, 20 ml Et_2O. Drying agent: 4 g magnesium sulfate. Crude product was used without further purification. Yield: quantitative. Yellowish oil.

3.13. (1R/S,2′S)-2-{[2′-(Naphth-1′-ylmethyl)pyrrolidin-1′-yl]imino}-1-methylethyl acetate **2k**

Scale: 7 mmol, 30 ml Et_2O. Drying agent: 6 g magnesium sulfate. Crude product was used without further purification. Yield: 99%. Yellowish oil.

3.14. (1R/S,2′S,5′S)-2-{[2′,5′-Bis(methoxymethyl)pyrrolidin-1′-yl]imino}-1-methylethyl acetate **2l**

Scale: 1 mmol, 20 ml Et_2O. Drying agent: 4 g magnesium sulfate. Crude product was used without further purification. Yield: quantitative. Yellowish oil.

3.15. (1R/S,2′R,3a′R,6a′R)-2-{[2′-(Methoxymethyl)perhydrocyclopenta[b]pyrrol-1′-yl]imino}-1-methylethyl acetate **2m**

Scale: 6 mmol, 30 ml Et_2O. Drying agent: 6 g magnesium sulfate. Crude product was used without further purification. Yield: quantitative. Yellowish oil.

3.16. (1R/S,2′S,3′R,4′R,5′S)-2-{[3′,4′-Dimethoxy-2′,5′-bis(methoxymethyl)pyrrolidin-1′-yl]imino}-1-methylethyl acetate **2n**

Scale: 2 mmol, 40 ml Et_2O. Drying agent: 5 g magnesium sulfate. Crude product was used without further purification. Yield: quantitative. Yellowish oil.

3.17. (1R/S,2′S)-2-({2′-[(Methoxymethoxy)methyl]pyrrolidin-1′-yl}imino)-1-methylethyl acetate **2o**

Scale: 10 mmol, 40 ml Et_2O. Drying agent: 8 g magnesium sulfate. Crude product was used without further purification. Yield: 90%. Yellowish oil.

3.18. (1R/S,2′S)-2-({2′-[(2′-Methoxyethoxy)methyl]pyrrolidin-1′-yl}imino)-1-methylethyl acetate **2p**

Scale: 10 mmol, 30 ml Et_2O. Drying agent: 8 g magnesium sulfate. Crude product was used without further purification. Yield: 97%. Yellowish oil.

3.19. General procedure for the α-substitution reaction

A solution of the 2-substituted hydrazones **2** (1.0 mmol) in 15 ml of the respective solvent was cooled to −78°C and $BF_3 \cdot OEt_2$ (1.1 mmol) was added dropwise with stirring. After stirring for 15 min at −78°C, the reaction mixture was cooled to the respective reaction temperature and the nucleophile (2.0 mmol) was added dropwise. Stirring was continued until the reaction was complete (TLC control after work-up of a small sample of the reaction mixture, 1.5–3.5 h). Then the reaction mixture was poured into 5% aqueous Na_2CO_3 (15 ml) solution with vigorous stirring and the resulting mixture was extracted with diethyl ether (3×25 ml). The combined organic layers were dried over magnesium sulfate. After filtration and evaporation of the solvent the crude product was purified by column chromatography (for eluent composition see TLC conditions).

Preparation of metalated nucleophiles: A solution of the the X–H acidic compound (2 mmol, X=S,O) in THF (5 ml) was cooled to 0°C and *n*-BuLi (2.0 mmol, 1.6 M solution in hexane) was added dropwise under stirring. Stirring was continued for 15 min at 0°C. After cooling to −78°C, the solution of the nucleophile was added to the complexed hydrazone *via* a double ended needle.

3.20. Methyl (3R,2′S)-4-{[2′-(methoxymethyl)pyrrolidin-1′-yl]imino}-2,2,3-trimethylbutanoate **4a**

(a) Substrate: (*S,S*)-**2b**. Nucleophile: **3b**. Solvent: Et_2O. Yield: 62%, *de*=62%.

(b) Substrate: (*R/S,S*)-**2c**. Nucleophile: **3b**. Solvent: Et_2O. Yield: quantitative, *de*=60%
(c) Substrate: (*R/S,S*)-**2c**. Nucleophile: **3c**. Solvent: Et_2O. Yield: 64%, *de*=46%.
(d) Substrate: (*R/S,S*)-**2d**. Nucleophile: **3b**. Solvent: Et_2O. Yield: 51%, *de*=57%.

Colourless liquid. R_f=0.33 (pentane:Et_2O=2:1). R_t=9.2 min (OV-1 CB; 100-10-300). IR (capillary, ν cm^{-1}): 2974 (vs), 2949, 2877 (s), 2826 (m), 1733 (vs), 1598 (w), 1460 (s), 1389, 1341 (m), 1256, 1194 (s), 1130 (vs), 1067 (m), 1039, 974 (w). ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, *J*=7.1 Hz, 3H, $CHCH_3$), 1.15 [1.16], 1.17 [1.16] [s, 2×3H, $C(CH_3)_2$], 1.74–2.02 (m, 4H, $NCH_2CH_2CH_2$), 2.65 [2.64] (quin, *J*=6.7 Hz, 1H, $CHCH_3$), 2.68–2.81 (m, 1H, NC*H*H), 3.26–3.47 (m, 3H, NCH*H*, NC*H*C*H*HO), 3.36 [3.37] (s, 3H, CH_2OCH_3), 3.51–3.61 (m, 1H, NCHCH*H*O), 3.66 [3.65] (s, 3H, $COOCH_3$), 6.48 [6.50] (d, *J*=6.7 Hz, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 [14.1] ($CHCH_3$), 21.9, 23.1 [22.9] [$C(CH_3)_2$], 22.1 [22.0] (NCH_2CH_2), 26.6 ($NCH_2CH_2CH_2$), 44.2 [44.3] ($CHCH_3$), 45.5 [45.4] [$C(CH_3)_2$], 50.0 [50.4] (NCH_2), 51.6 ($COOCH_3$), 59.2 (CH_2OCH_3), 63.3 [63.6] (NCH), 74.6 [74.7] (CH_2OCH_3), 139.1 [139.6] (HC=N), 177.9 [177.8] ($COOCH_3$). MS (EI, 70 eV): *m/z* (%) 270 (11) [M^+], 239 (4) [M^+-OCH_3], 225 (100) [$M^+-CH_2OCH_3$], 169 (16) [$M^+-(H_3C)_2CCOOCH_3$], 156 (5) [M^+−SMP], 128 (7) [M^+−SMP−HCNH], 96 (14) [M^+−SMP−HCNH−CH_3OH], 73 (19), 70 (78) [$C_4H_8N^+$], 55(9), 41 (11). EA $C_{14}H_{26}N_2O_3$ (270.37): calcd C 62.19, H 9.69, N 10.36; found C 62.56, H 9.82, N 10.68.

3.21. Methyl (3R/S,2′S)-4-{[2′-(1′-methoxy-1′-methylethyl)pyrrolidin-1′-yl]imino}-2,2,3-trimethylbutanoate ***4b***

Yield: 91%. Colourless liquid, *de*=2%. R_f=0.46 (pentane:Et_2O=2:1). R_t=6.53/6.64 min (OV-1 CB; 140-10-300). IR (capillary, ν cm^{-1}): 2973 (vs), 2947 (s), 2826 (m), 1733 (vs), 1597 (w), 1461 (s), 1379, 1365 (m), 1255, 1192 (s), 1146 (vs), 1076 (s), 1050 (m), 1001, 988, 917, 848 (w). ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (d, *J*=6.9 Hz, 3H, $CHCH_3$), 1.13–1.22 [m, 12H, $C(CH_3)_2OCH_3$, $C(CH_3)_2C$=O], 1.74–2.01 (m, 4H, $NCH_2CH_2CH_2$), 2.62, 2.63 (quin, *J*=6.9 Hz, 1H, $CHCH_3$), 2.64–2.75 (m, 1H, NC*H*H), 3.23 [s, 3H, $C(CH_3)_2OCH_3$], 3.34–3.44 (m, 2H, NCH, NCH*H*), 3.65, 3.66 (s, 3H, $COOCH_3$), 6.47, 6.52 (d, *J*=6.6 Hz, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 14.2 ($CHCH_3$), 21.0, 21.8, 22.0, 22.9, 23.0, 23.0, 23.3 [$C(CH_3)_2OCH_3$, $C(CH_3)_2C$=O], 23.9 (NCH_2CH_2), 24.7, 24.8 ($NCHCH_2$), 44.0, 44.2 ($CHCH_3$), 45.5, 45.6 [$C(CH_3)_2C$=O], 49.5, 49.6, 51.5, 51.6 [$COOCH_3$, $C(CH_3)_2OCH_3$], 51.8. 52.1 (NCH_2), 71.5, 71.7 (NCH), 77.8 (NCHC), 137.8, 137.9 (HC=N), 177.9, 178.0 ($COOCH_3$). MS (EI, 70 eV): *m/z* (%) 298 (4) [M^+], 267 (3) [M^+-OCH_3], 225 (100) [$M^+-(H_3C)_2COCH_3$)], 165 (6), 156 (9) [M^+−SDP], 128 (15) [M^+−SDP−HCNH], 125 (10), 124 (13), 111 (11), 110 (11), 109 (11), 96 (26) [M^+−SDP−HCNH−CH_3OH], 91 (8), 81 (13), 70 (29) [$C_4H_8N^+$], 57 (25), 55 (28), 43 (31), 41 (57). EA $C_{16}H_{30}N_2O_3$ (298.42): calcd C 64.40, H 10.13, N 9.39; found C 64.64, H 10.32, N 9.63.

3.22. Methyl (3R/S,2′S)-4-{[2′-(1′-ethyl-1′-methoxypropyl)pyrrolidin-1′-yl]imino}-2,2,3-trimethylbutanoate ***4c***

Yield: 69%. Colourless liquid, *de*=2%. R_f=0.40 (pentane:Et_2O=2:1). R_t=8.09/8.20 min (OV-1 CB; 140-10-300). IR (capillary, ν cm^{-1}): 2969, 2943 (vs), 2880 (s), 2825 (m), 1734 (vs), 1596 (w), 1460 (s), 1434, 1378 (m), 1345, 1321 (w), 1255, 1191 (s), 1141 (vs), 1086 (s), 1045 (m), 1003, 990 (w), 917 (m), 888, 847 (w). ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 [q, *J*=7.4 Hz, 6H, $C(CH_2CH_3)_2$], 0.99, 1.00 (d, *J*=7.1 Hz, 3H, $CHCH_3$), 1.14, 1.15, 1.16, 1.17 [s, 6H, $C(CH_3)_2$], 1.45–2.02 [m, 8H, $NCH_2CH_2CH_2$, $C(CH_2CH_3)_2$], 2.56–2.74 (m, 2H, $CHCH_3$, NC*H*H), 3.25 [s, 3H, $C(C_2H_5)_2OCH_3$], 3.29–3.35 (m, 1H, NCH*H*), 3.44–3.58 (m, 1H, NCH), 3.66, 3.67 (s, 3H, $COOCH_3$), 6.38, 6.43 (d, *J*=6.7 [6.0] Hz, 1H,

HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.9, 8.6 [$C(CH_2CH_3)_2$], 13.9, 14.2 ($CHCH_3$), 21.7, 21.9, 22.9, 23.3 [$C(CH_3)_2$], 23.8, 23.9 [$C(CH_2CH_3)_2$], 24.4, 24.5 (NCH_2CH_2), 26.2, 26.3 ($NCHCH_2$), 43.9, 44.2 ($CHCH_3$), 45.6, 45.7 [$C(CH_3)_2$], 50.4, 50.5, 51.5, 51.6 [$COOCH_3$, $C(C_2H_5)_2OCH_3$], 51.4, 51.5 (NCH_2), 68.9, 69.0 (NCH), 80.4, 80.5 [$C(C_2H_5)_3$], 136.4, 136.6 (HC=N), 178.0, 178.1 ($COOCH_3$). MS (EI, 70 eV): *m/z* (%) 326 (1) [M^+], 295 (2) [M^+-OCH_3], 225 (89) [$M^+-(H_5C_2)_2COCH_3$], 156 (11) [M^+−SEP], 145 (5), 128 (13) [M^+−SEP−HCNH], 124 (13), 109 (11), 96 (39) [M^+−SEP−HCNH−CH_3OH], 83 (20), 81 (20), 73 (27), 70 (100) [$C_4H_8N^+$], 57 (41), 55 (41), 43 (56), 41 (64). EA $C_{18}H_{34}N_2O_3$ (326.48): calcd C 66.22, H 10.50, N 8.58; found C 66.89, H 10.75, N 8.93.

3.23. *Methyl (3R/S,2′S)-4-{[2′-(hydroxymethyl)pyrrolidin-1′-yl]imino}-2,2,3-trimethylbutanoate* **4d**

Yield: 38%. Colourless liquid, *de*=2%. R_f=0.40 (pentane:Et_2O=1:2). R_t=7.5 min (SE-54; 140-10-300). IR ($CHCl_3$, ν cm^{-1}): 3431 (m, br.), 2972 (vs), 2949, 2876 (s), 1731 (vs), 1598 (w), 1460, 1434 (s), 1390, 1379, 1342, 1326, 1295 (m), 1258 (vs), 1192 (s), 1146 (vs, br.), 1066 (m), 1041 (s), 1005, 987, 912, 850 (w). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (d, *J*=6.9 Hz, 3H, $CHCH_3$), 1.16 [s, 6H, $C(CH_3)_2$], 1.44–1.58 (m, 1H, NCH_2CHH), 1.80–2.03 (m, 3H, NCH_2CHHCH_2), 2.65, 2.66 (quin, *J*=6.9 Hz, 1H, $CHCH_3$), 2.67–2.81 (m, 1H, $NCHH$), 3.24–3.45 (m, 2H, NCH*H*, NCH), 3.64–3.86 (m, 2H, CH_2OH), 3.67, 3.68 (s, 3H, $COOCH_3$), 9.46, 9.48 (d, *J*=6.3 Hz, *J*=6.6 Hz, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 13.8 ($CHCH_3$), 21.6, 21.7 (NCH_2CH_2), 22.2, 22.4, 22.5, 22.6 [$C(CH_3)_2$], 25.4, 25.5 ($NCH_2CH_2CH_2$), 44.0, 44.1 ($CHCH_3$), 45.5, 45.6 [$C(CH_3)_2$], 49.1, 49.2 (NCH_2), 51.7 ($COOCH_3$), 64.1, 64.4 (NCH), 66.9, 67.0 (CH_2OH), 139.6, 140.1 (HC=N), 177.7, 177.8 ($COOCH_3$). MS (EI, 70 eV): *m/z* (%) 256 (12) [M^+], 225 (100) [M^+-CH_2OH], 155 (47) [M^+−SHP], 128 (13) [M^+−SHP−HCNH], 124 (9), 100 (9), 96 (21) [M^+−SHP−HCNH−CH_3OH], 82 (5), 73 (16), 70 (66) [$C_4H_8N^+$], 55 (9), 41 (17). EA $C_{13}H_{24}N_2O_3$ (256.34): calcd C 60.91, H 9.44, N 10.93; found C 61.02, H 9.47, N 11.09.

3.24. *Methyl (3R/S,2′S)-4-{[2′-(naphth-1′-ylmethyl)pyrrolidin-1′-yl]imino}-2,2,3-trimethylbutanoate* **4e**

Yield: 70%. Colourless liquid, *de*=15%. R_f=0.43 (pentane:Et_2O=5:1). R_t=12.6 min (SE-54; 180-10-300). IR (capillary, ν cm^{-1}): 3042 (w), 2971 (vs), 2947, 2876 (s), 2838 (m), 1731 (vs), 1596 (m), 1510 (w), 1459 (s), 1433, 1396, 1390, 1378, 1366, 1339, 1328 (m), 1293 (w), 1257, 1191 (s), 1138 (vs, br.), 1065 (m), 1037, 1016, 916, 850 (w), 792, 778 (vs). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 [1.12] (d, *J*=6.9 [7.1] Hz, 3H, $CHCH_3$), 1.18–1.26 [m, 6H, $C(CH_3)_2$], 1.56–2.00 (m, 4H, $NCH_2CH_2CH_2$), 2.64–2.88 (m, 3H, $NCHH$, $CHCH_3$, $NCHCHHC$), 3.25–3.64 (m, 2H, NCH*H*, NCH), 3.69 [3.68] (s, 3H, $COOCH_3$), 3.90–4.08 (m, 1H, $NCHCHHC$), 8.27 [8.30] (d, *J*=6.3 [6.6] Hz, 1H, HC=N), 7.31–7.42 (m, 2H, CH_2CCHCH), 7.43–7.56 (m, 2H, $CH_2CCCHCHCH$), 7.69–7.74 (m, 1H, $CH_2CCCHCHCHCH$), 7.81–7.86 (m, 1H, $CH_2CCHCHCH$), 8.26–8.31 (m, 1H, CH_2CCCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 [13.9] ($CHCH_3$), 21.3 [21.2] (NCH_2CH_2), 22.0 [22.2], 23.0 [22.8] [$C(CH_3)_2$], 28.7 [28.9] ($NCH_2CH_2CH_2$), 37.5 [37.8] ($NCHCH_2C$), 44.1 [44.2] ($CHCH_3$), 45.6 [45.5] [$C(CH_3)_2$], 49.1 [49.4] (NCH_2), 51.7 (OCH_3), 64.9 [65.9] (NCH), 124.6 [124.7], 125.4, 125.5, 125.8 [125.7], 126.8, 127.2 [127.1] 128.6 (aromatic CH), 132.4 [132.3], 133.9, 136.2 [136.3] (aromatic C), 139.1 [139.6] (HC=N), 178.1 ($COOCH_3$). MS (EI, 70 eV): *m/z* (%) 366 (0.1) [M^+], 335 (2) [M^+-OCH_3], 225 (100) [$M^+-CH_2C_{10}H_7$], 156 (5) [M^+−SNP], 141 (16) [$CH_2C_{10}H_7^+$], 128 (19), [M^+−SNP−HCNH], 115 (8), 96 (14) [M^+−SNP−HCNH−CH_3OH], 73 (11), 70 (31) [$C_4H_8N^+$]. EA $C_{23}H_{30}N_2O_2$ (366.50): calcd C 75.38, H 8.25, N 7.64; found C 75.63, H 8.58, N 7.43.

3.25. Methyl (3R/S,2′S,5′S)-4-{[2′,5′-bis(methoxymethyl)pyrrolidin-1′-yl]imino}-2,2,3-trimethylbutanoate ***4f***

Yield: 39%. Colourless liquid, *de*=60%. R_f=0.28 (pentane:Et_2O=2:1). R_t=7.13 [6.97] min (OV-1 CB; 140-10-300). IR (capillary): 2976 (vs), 2950, 2931 (s), 2879 (vs), 2827 (mt), 1733 (vs), 1596 (w), 1460 (s), 1389 (m), 1338, 1324 (w), 1303 (m), 1256 (s), 1195 (vs), 1118 (vs, br.), 1066 (m), 1040, 988 (w), 970 (m), 941, 920, 875, 848 (w). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 [0.99] (d, *J*=7.1 Hz, 3H, CHC*H*$_3$), 1.14, 1.15 [1.16, 1.18] [s, je 3H, C(C*H*$_3$)$_2$], 1.74–1.88 (m, 2H, NCHC*H*HCH*H*), 1.94–2.07 (m, 2H, NCHCH*H*CH*H*), 2.65 [2.63] (quin, *J*=6.7 Hz, 1H, C*H*CH$_3$), 3.21–3.28 (m, 2H, 2×NCHC*H*HO), 3.32 [3.33] (s, 6H, 2×CH$_2$OC*H*$_3$), 3.44–3.51 (m, 2H, 2×NCHCH*H*O), 3.67 (s, 3H, COOC*H*$_3$), 6.55 [6.56] (d, *J*=6.7 Hz, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 [14.3] (*C*HC*H*$_3$), 21.8 [22.0], 23.2 [23.3] [C(*C*H$_3$)$_2$], 25.8 (2×NCH*C*H$_2$), 44.4 [44.6] (*C*HCH$_3$), 45.6 [*C*(CH$_3$)$_2$], 51.6 (COO*C*H$_3$), 59.1 (2×CH$_2$O*C*H$_3$), 60.3 [60.1] (2×NCH), 73.0 [72.9] (2×*C*H$_2$OCH$_3$), 136.4 [136.6] (HC=N), 177.9 (*C*OOCH$_3$). MS (EI, 70 eV): *m/z* (%) 314 (8) [M$^+$], 269 (100) [M$^+$−CH$_2$OCH$_3$], 213 (6), 156 (4) [M$^+$−SBMP], 128 (6) [M$^+$−SBMP−HCNH], 123 (6), 114 (36) [SMP$^+$], 96 (11) [M$^+$−SBMP−HCNH−CH$_3$OH], 82 (16), 71 (14), 55 (13), 45 (14), 41 (16). EA $C_{16}H_{30}N_2O_4$ (314.42): calcd C 61.12, H 9.62, N 8.91; found C 61.54, H 9.73, N 9.37.

3.26. Methyl (3R/S,2′R,3a′R,6a′R)-4-{[2′-(methoxymethyl)perhydrocyclopenta[b]pyrrol-1′-yl]imino}-2,2,3-trimethylbutanoate ***4g***

Yield: 44%. Colourless liquid, *de*=46%. R_f=0.44 (pentane:Et_2O=2:1). R_t=13.8 min (OV-17; 100-10-260). IR (capillary, ν cm^{-1}): 2965, 2948 (vs), 2893 (s), 2865, 1733 (vs), 1601 (w), 1460 (s), 1389, 1343, 1325 (m), 1254, 1192 (vs), 1126 (vs, br.), 1095 (vs), 1068, 1039, 975 (m), 880, 848 (w). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 [1.03] (d, *J*=6.9 [7.1] Hz, 3H, CHC*H*$_3$), 1.15, 1.17 [1.16] [s, 2×3H, C(CH$_3$)$_2$], 1.23–1.37 (m, 1H, NCHCHC*H*HCH$_2$), 1.45–1.70 (m, 6H, NCHC*H*HC*H*$_2$CH*H*CHC*H*$_2$), 2.15 (ddd, *J*=12.4/9.1/5.8 Hz, 1H, NCHCH*H*CH$_2$), 2.59–2.73 (m, 2H, C*H*CH$_3$, NCHC*H*), 3.12–3.25 (m, 1H, NC*H*CH$_2$O), 3.25–3.34 (m, 1H, NC*H*CH), 3.38 (s, 3H, CH$_2$OC*H*$_3$), 3.40–3.52 (m, 1H, NCHC*H*HO), 3.63–3.72 (m, 2H, 2×NCH), 3.66 [3.65] (s, 3H, COOCH$_3$), 3.75–3.83 (m, 1H, NCHCH*H*O), 6.57 [6.58] (d, *J*=6.0 Hz, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 [13.7] (CH*C*H$_3$), 22.2 [22.3], 22.9 [22.6] [C(*C*H$_3$)$_2$], 24.2 (NCH*C*H$_2$CH), 32.4, 33.3 [33.4], 34.2 (NCH*C*H$_2$*C*H$_2$*C*H$_2$), 40.4 (NCH*C*H), 44.2 (*C*HCH$_3$), 45.6 [45.4] [*C*(CH$_3$)$_2$], 51.6 (COO*C*H$_3$), 59.4 [59.3] (CH$_2$O*C*H$_3$), 65.6 [65.8] (N*C*HCH$_2$O), 67.0 [67.5] (N*C*HCH), 75.2 (*C*H$_2$OCH$_3$), 139.0 [139.6] (HC=N), 177.9 (*C*OOCH$_3$). MS (EI, 70 eV): *m/z* (%) 310 (3) [M$^+$], 279 (1) [M$^+$−OCH$_3$], 265 (100) [M$^+$−CH$_2$OCH$_3$], 209 (27) [M$^+$−(H$_3$C)$_2$CCOOCH$_3$], 163 (61) [M$^+$−CH$_2$OCH$_3$−(H$_3$C)$_2$CCOOCH$_3$], 151 (30), 110 (13) [(H$_6$C$_3$)C$_4$H$_6$N$^+$], 73 (12), 67 (19), 45 (5). EA $C_{17}H_{30}N_2O_3$ (310.44): calcd C 65.77, H 9.74, N 9.02; found C 66.14, H 10.18, N 9.24.

3.27. Methyl (3R/S,2′S,3′R,4′R,5′S)-4-{[3′4′-dimethoxy-2′,5′-bis(methoxymethyl)pyrrolidin-1′-yl]-imino}-2,2,3-trimethylbutanoate ***4h***

Yield: 48%. Colourless liquid, *de*=53%. R_f=0.32 (pentane:Et_2O=1:1). R_t=8.99 [8.83] min (SE-54; 160-10-300). IR (neat, ν cm^{-1}): 2979, 2930, 2895 (s), 2827 (m), 1733 (vs), 1601 (w), 1460 (s), 1390 (m), 1326, 1298 (w), 1256 (s), 1195 (vs), 1115 (vs, br.), 1029, 985 (w). ^{1}H NMR (300 MHz, C_6D_6): δ 1.17 [1.11] (d, *J*=7.1 Hz, 3H, CHC*H*$_3$), 1.25 [1.27], 1.28 [s, 2×3H, C(CH$_3$)$_2$], 2.92 (quin, br., *J*=6.5 Hz, 1H, C*H*CH$_3$), 3.15 [3.16] (s, 6H, 2×CH$_2$OC*H*$_3$), 3.26 [3.27] (s, 6H, 2×CHOC*H*$_3$), 3.42 (s, 3H, COOCH$_3$), 3.49–3.55 (m, 2H, 2×C*H*HOCH$_3$), 3.73–3.80 (m, 2H, 2×CH*H*OCH$_3$), 3.90–3.99 (m, 2H, 2×NCH),

3.99–4.06 (m, 2H, 2×NCHC*H*), 6.86 [6.84] (d, *J*=5.8 [6.9] Hz, 1H, HC=N). ^{13}C NMR (75 MHz, C_6D_6): δ 14.0 [14.4] (CH*C*H$_3$), 22.1 [22.2], 23.3 [23.4] [C(*C*H$_3$)$_2$], 44.7 [45.0] (*C*HCH$_3$), 45.9 [46.0] [*C*(CH$_3$)$_2$], 51.3 (COO*C*H$_3$), 58.5 [58.6], 58.7 (2×CH$_2$O*C*H$_3$, 2×CHO*C*H$_3$), 62.2 [62.0] (2×NCH), 69.8 [69.7] (2×*C*H$_2$OCH$_3$), 83.1 [83.2] (2×NCH*C*H), 135.5 [135.9] (HC=N), 177.4 (*C*OOCH$_3$). MS (EI, 70 eV): *m/z* (%) 374 (8) [M$^+$], 343 (2) [M$^+$−OCH$_3$], 329 (100) [M$^+$−CH$_2$OCH$_3$], 297 (3), 273 (8), 172 (9), 156 (2), 140 (12), 128 (4), 110 (12), 101 (13), 71 (8), 55 (5), 45 (24). EA $C_{18}H_{34}N_2O_6$ (374.48): calcd C 57.73, H 9.15, N 7.48; found C 57.83, H 9.10, N 7.80.

3.28. Methyl (3R/S,2′S)-4-({2′-[(methoxymethoxy)methyl]pyrrolidin-1′-yl}imino)-2,2,3-trimethylbutanoate ***4i***

Yield: 64%. Colourless liquid, *de*=22%. R_f=0.28 (pentane:Et$_2$O=2:1). R_t=8.9 min (OV-17; 140-10-260). IR (capillary, ν cm^{-1}): 2972, 2949 (vs), 2879 (s), 2822 (m), 1732 (vs), 1598 (w), 1461 (s), 1389, 1379, 1342, 1324, 1294 (m), 1256 (vs), 1212, 1191 (s), 1149, 1114, 1047 (vs), 1004, 967 (m), 919 (s), 849 (w). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 [1.01] (d, *J*=7.2 [6.9] Hz, 3H, CHC*H*$_3$), 1.14 [1.15], 1.17 [1.16] [s, 2×3H, C(CH$_3$)$_2$], 1.76–2.05 (m, 4H, NCH$_2$C*H*$_2$C*H*$_2$), 2.65 [2.64] (quin, *J*=6.9 Hz, 1H, C*H*CH$_3$), 2.70–2.82 (m, 1H, NC*H*H), 3.28–3.45 (m, 2H, NCH*H*, NCH), 3.36 (s, 3H, CH$_2$OC*H*$_3$), 3.55–3.62 (m, 1H, NCHC*H*HO), 3.66 [3.65] (s, 3H, COOC*H*$_3$), 3.68–3.74 (m, 1H, NCHCH*H*O), 4.64 (s, 2H, C*H*$_2$OCH$_3$), 6.49 [6.47] (d, *J*=6.6 Hz, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 [14.1] (CH*C*H$_3$), 21.9 (NCH$_2$*C*H$_2$), 22.2 [22.0], 23.1 [22.9] [C(*C*H$_3$)$_2$], 26.6 [26.5] (NCH$_2$CH$_2$*C*H$_2$), 44.2 [44.3] (*C*HCH$_3$), 45.5 [45.4] [*C*(CH$_3$)$_2$], 49.9 [50.2] (NCH$_2$), 51.6 [51.5] (COO*C*H$_3$), 55.1 (CH$_2$O*C*H$_3$), 63.3 [63.5] (NCH), 69.5 (NCH*C*H$_2$O), 96.8 (*C*H$_2$OCH$_3$), 139.0 [139.4] (HC=N), 177.9 [177.8] (*C*OOCH$_3$). MS (EI, 70 eV): *m/z* (%) 300 (5) [M$^+$], 269 (3) [M$^+$−OCH$_3$], 239 (1) [M$^+$−OCH$_2$OCH$_3$], 225 (74) [M$^+$−CH$_2$OCH$_2$OCH$_3$], 199 (12), 156 (7) [M$^+$−SMMP], 128 (18) [M$^+$−SMMP−HCNH], 124 (11), 123 (10), 112 (10), 96 (32) [M$^+$−SMMP−HCNH−CH$_3$OH], 82 (14), 73 (39), 70 (100) [C$_4$H$_8$N$^+$], 55 (26), 45 (43). EA $C_{15}H_{28}N_2O_4$ (300.40): calcd C 59.98, H 9.40, N 9.33; found C 59.65, H 9.34, N 9.70.

3.29. Methyl (3R/S,2′S)-4-({2′-[(2′-methoxyethoxy)methyl]pyrrolidin-1′-yl}imino)-2,2,3-trimethylbutanoate ***4j***

Yield: 50%. Colourless liquid, *de*=35%. R_f=0.33 (pentane:Et$_2$O=1:1). R_t=10.1 min (OV-17; 140-10-260). IR (capillary, ν cm^{-1}): 2973 (vs), 2948, 2876 (s), 1732 (vs), 1597 (w), 1460 (s), 1389, 1365, 1341, 1325, 1294 (w), 1255, 1194 (s), 1138 (vs), 1067, 1039 (m), 1003, 987, 917, 885, 850 (w). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, *J*=7.1 Hz, 3H, CHC*H*$_3$), 1.14 [1.15], 1.17 [1.16] [s, je 3H, C(CH$_3$)$_2$], 1.76–2.00 (m, 4H, NCH$_2$C*H*$_2$C*H*$_2$), 2.64 [2.63] (quin, *J*=6.9 [7.1] Hz, 1H, C*H*CH$_3$), 2.69–2.82 (m, 1H, NC*H*H), 3.25–3.72 (m, 8H, NCH*H*, NC*H*CH$_2$OCH$_2$CH$_2$), 3.37 [3.38] (s, 3H, CH$_2$OC*H*$_3$), 3.66 [3.65] (s, 3H, COOC*H*$_3$), 6.46 [6.48] (d, *J*=6.6 [6.1] Hz, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 [14.1] (CH*C*H$_3$), 21.9, 23.1 [23.0] [C(*C*H$_3$)$_2$], 22.0 [22.1] (NCH$_2$*C*H$_2$), 26.8 (NCH$_2$CH$_2$*C*H$_2$), 44.1 [44.2] (*C*HCH$_3$), 45.5 [45.4] [*C*(CH$_3$)$_2$], 50.0 [50.3] (NCH$_2$), 51.6 (COO*C*H$_3$), 59.0 (CH$_2$O*C*H$_3$), 63.2 [63.4] (NCH), 70.7 (NCH*C*H$_2$O), 72.0 (*C*H$_2$OCH$_3$), 73.4 [73.5] (*C*H$_2$CH$_2$OCH$_3$), 138.6 [139.1] (HC=N), 177.9 [177.8] (*C*OOCH$_3$). MS (EI, 70 eV): *m/z* (%) 314 (5) [M$^+$], 283 (1) [M$^+$−OCH$_3$], 225 (100) [M$^+$−CH$_2$OCH$_2$CH$_2$OCH$_3$], 213 (9), 156 (10) [M$^+$−SMEP], 137 (4), 128 (14) [M$^+$−SMEP−HCNH], 124 (9), 123 (7), 96 (24) [M$^+$−SMEP−HCNH−CH$_3$OH], 73 (24), 70 (70) [C$_4$H$_8$N$^+$], 59 (28), 55 (16), 45 (11). EA $C_{16}H_{30}N_2O_4$ (314.42): calcd C 61.12, H 9.62, N 8.91; found C 60.67, H 9.53, N 9.36.

3.30. Ethyl (3R,2′S)-4-{[2′-(methoxymethyl)pyrrolidin-1′-yl]imino}-3-methylbutanoate **4k**

Yield: quantitative. Colourless liquid, *de*=12%. R_f=0.29 (pentane:Et_2O=2:1). R_t=5.0 min (OV-1 CB; 140-10-300). IR (capillary, ν cm^{-1}): 2974 (vs), 2930, 2876, 2827 (s), 1736 (vs), 1603 (w), 1460 (s), 1372, 1340, 1302 (m), 1281, 1248 (s), 1180, 1121 (vs, br.), 1098, 1031 (s), 973, 926, 904, 876, 848 (w). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (d, *J*=6.9 Hz, 3H, $CHCH_3$), 1.26 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.72–2.00 (m, 4H, $NCH_2CH_2CH_2$), 2.24–2.33 (m, 1H, CHHCOO), 2.52–2.62 (m, 1H, CHHCOO), 2.64–2.75 (m, 1H, NCHH), 2.86 (quin, br., *J*=6.9 Hz, 1H, $CHCH_3$), 3.28–3.47 (m, 3H, NCHH, NCHCHHO), 3.37 [3.38] (s, 3H, CH_2OCH_3), 3.53–3.61 (m, 1H, NCHCHHO), 4.13 [4.12] (q, *J*=7.1 Hz, 2H, CH_2CH_3), 6.55–6.58 (m, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 ($CHCH_3$), 18.7 [18.6] (CH_2CH_3), 22.1 [22.0] (NCH_2CH_2), 26.6 [26.5] ($NCH_2CH_2CH_2$), 33.8 ($CHCH_3$), 39.7 [39.6] (CH_2COO), 49.9 [49.8] (NCH_2), 59.2 (CH_2OCH_3), 60.1 (CH_2CH_3), 63.4 (NCH), 74.6 [74.5] ($NCHCH_2O$), 140.3 [140.2] (HC=N), 172.7 [172.8] (CH_2COO). MS (EI, 70 eV): *m/z* (%) 256 (11) [M^+], 225 (4) [M^+-OCH_3], 211 (100) [$M^+-CH_2OCH_3$], 183 (3), 169 (5), 142 (9) [M^+−SMP], 137 (5), 123 (6), 114 (23) [M^+−SMP−HCNH], 96 (55), 86 (15), 83 (11), 70 (94) [$C_4H_8N^+$], 57 (14), 55 (15), 45 (24), 43 (43), 41 (32). EA $C_{13}H_{24}N_2O_3$ (256.34): calcd C 60.91, H 9.44, N 10.93; found C 60.86, H 9.63, N 11.03.

3.31. Methyl (3R,2′S)-3-({[2′-(methoxymethyl)pyrrolidin-1′-yl]imino}methyl)-2,2-dimethylpentanoate **4l**

Yield: 59%. Colourless liquid, *de*=66%. R_f=0.34 (pentane:Et_2O=2:1). R_t=7.5 min (SE-54; 140-10-300). IR (capillary, ν cm^{-1}): 2966, 2934, 2875 (vs), 2827 (s), 1734 (vs), 1597 (w), 1461 (s), 1434, 1388, 1368, 1341, 1304 (m), 1249, 1193 (vs), 1147, 1125 (vs, br.), 1011 (w), 973 (m), 947, 904, 865 (w). ^{1}H NMR (300 MHz, C_6D_6): δ 0.96 [0.95] (t, *J*=7.4 Hz, 3H, CH_2CH_3), 1.23, 1.26 [s, 2×3H, $C(CH_3)_2$], 1.38–1.83 (m, 6H, CH_2CH_3, $NCH_2CH_2CH_2$), 2.52–2.68 (m, 2H, $CHCH_2CH_3$, NCHH), 3.01–3.09 (m, 1H, NCHH), 3.16 (s, 3H, CH_2OCH_3), 3.40 [3.39] (s, 3H, $COOCH_3$), 3.39–3.46 (m, 1H, NCHCHHO), 3.52–3.61 (m, 1H, NCH), 3.66–3.73 (m, 1H, NCHCHHO), 6.31 [6.33] (d, *J*=7.4 Hz, 1H, HC=N). ^{13}C NMR (75 MHz, C_6D_6): δ 13.1 [13.0] (CH_2CH_3), 22.0, 24.3 [24.2] [$C(CH_3)_2$], 22.2, 22.3 (NCH_2CH_2, CH_2CH_3), 27.2 [27.3] ($NCH_2CH_2CH_2$), 46.2 [46.0] [$C(CH_3)_2$], 49.6 [49.8] (NCH_2), 51.2 ($CHCH_2CH_3$), 52.3 [52.4] ($COOCH_3$), 58.9 (CH_2OCH_3), 63.5 [63.7] (NCH), 75.5 (CH_2OCH_3), 135.9 [136.3] (HC=N), 177.4 ($COOCH_3$). MS (EI, 70 eV): *m/z* (%) 284 (5) [M^+], 239 (67) [$M^+-CH_2OCH_3$], 183 (18) [$M^+-(H_3C)_2CCOOCH_3$], 170 (6) [M^+−SMP], 142 (8) [M^+−SMP−HCNH], 138 (9), 114 (8) [SMP$^+$], 110 (32) [M^+−SMP−HCNH−CH_3OH], 96 (5), 83 (17), 82 (16), 73 (18), 70 (100) [$C_4H_8N^+$], 55 (25), 45 (27), 43 (24), 41 (40). EA $C_{15}H_{28}N_2O_3$ (284.40): calcd C 63.35, H 9.92, N 9.85; found C 63.69, H 9.99, N 10.04.

3.32. Methyl (3R,2′S)-3-({[2′-(methoxymethyl)pyrrolidin-1′-yl]imino}methyl)-2,2,4-trimethylpentanoate **4m**

Yield: 90%. Colourless liquid, *de*=69%. $[\alpha]_D^{22}$=−75.4 (*c* 1.12, $CHCl_3$). R_f=0.38 (pentane:Et_2O=2:1). R_t=10.3 min (OV-17; 120-10-260). IR (capillary, ν cm^{-1}): 2960 (vs), 2876 (s), 2827 (m), 1731 (vs), 1595 (w), 1434 (s), 1388, 1369, 1340, 1304 (m), 1248 (vs), 1194 (s), 1145, 1126 (vs, br.), 1015, 975, 925, 904, 874 (w). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 [d, *J*=6.6 Hz, 3H, $CH(CH_3)CH_3$], 0.88 [d, *J*=6.9 Hz, 3H, $CH(CH_3)CH_3$], 1.16, 1.19 [1.21] [s, je 3H, $C(CH_3)_2$], 1.76–2.04 [m, 5H, $NCH_2CH_2CH_2$, $CH(CH_3)_2$], 2.39 [dd, *J*=8.3/5.0 Hz, 1H, $CHCH(CH_3)_2$], 2.78–2.87 (m, 1H, NCHH), 3.36 [3.37] (s, 3H,

CH_2OCH_3), 3.33–3.50 (m, 3H, NCH*H*, NC*H*C*H*HO), 3.52–3.59 (m, 1H, NCHCH*H*O), 3.66 [3.65] (s, 3H, $COOCH_3$), 6.56 [6.59] (d, *J*=8.5 Hz, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.2 [19.9], 22.0 [22.4], 22.8 [22.9], 26.1 [25.9] [$CH(CH_3)_2$, $C(CH_3)_2$], 22.1 (NCH_2CH_2), 26.5 ($NCH_2CH_2CH_2$), 28.2 [28.4] [$CH(CH_3)_2$], 45.1 [44.9] [$C(CH_3)_2$], 50.7 (NCH_2), 51.6 ($COOCH_3$), 55.2 [55.3] [$CHCH(CH_3)_2$], 59.2 (CH_2OCH_3), 63.4 (NCH), 74.8 ($NCHCH_2O$), 137.8 [137.9] (HC=N), 178.5 [178.4] ($COOCH_3$). MS (EI, 70 eV): *m/z* (%) 299 (13) [MH^+], 298 (18) [M^+], 253 (94) [$M^+-CH_2OCH_3$], 197 (100) [$M^+-(H_3C)_2CCOOCH_3$], 184 (6) [M⁺−SMP], 156 (12) [M⁺−SMP−HCNH], 151 (39), 137 (17), 124 (10) [M⁺−SMP−HCNH−CH_3OH], 114 (26) [SMP^+], 109 (16), 97 (12), 82 (51), 73 (17), 70 (84) [$C_4H_8N^+$], 55 (24), 45 (18). EA $C_{16}H_{30}N_2O_3$ (298.42): calcd C 64.40, H 10.13, N 9.39; found C 64.36, H 10.16, N 9.12. After separation of the diastereomers by HPLC:

*3.32.1. Methyl (3R,2′S)-3-({[2′-(methoxymethyl)pyrrolidin-1′-yl]imino}methyl)-2,2,4-trimethylpentanoate (3R,2′S)-**4m***

De=96%. $[\alpha]_D^{22}=-92.9$ (*c* 1.16, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6): δ 0.95 [d, *J*=6.7 Hz, 3H, $CH(CH_3)CH_3$], 1.00 [d, *J*=6.7 Hz, 3H, $CH(CH_3)CH_3$], 1.26, 1.29 [s, 2×3H, $C(CH_3)_2$], 1.48–1.57 (m, 1H, NCH_2CHH), 1.66–1.84 (m, 3H, $NCH_2CHHCHH$), 1.90 [sept d, *J*=6.7/4.9 Hz, 1H, $CH(CH_3)_2$], 2.62 (br. q, *J*=8.5 Hz, 1H, NC*H*H), 2.69 [dd, *J*=8.2/4.9 Hz, 1H, $CHCH(CH_3)_2$], 3.06–3.14 (m, 1H, NCH*H*), 3.15 (s, 3H, CH_2OCH_3), 3.39 (s, 3H, $COOCH_3$), 3.43 (dd, *J*=9.0/7.1 Hz, 1H, NCHC*H*HO), 3.56–3.62 (m, 1H, NCH), 3.69 (dd, *J*=9.0/3.5 Hz, 1H, NCHCH*H*O), 6.49 (d, *J*=8.2 Hz, 1H, HC=N). ^{13}C NMR (125 MHz, C_6D_6): δ 20.4 [$CH(CH_3)CH_3$], 22.4 [NCH_2CH_2, $C(CH_3)CH_3$], 23.2 [$CH(CH_3)CH_3$], 26.4 [$C(CH_3)CH_3$], 27.3 ($NCH_2CH_2CH_2$), 28.6 [$CH(CH_3)_2$], 45.4 [$C(CH_3)_2$], 49.8 (NCH_2), 51.2 ($COOCH_3$), 55.7 [$CHCH(CH_3)_2$], 58.9 (CH_2OCH_3), 63.5 (NCH), 75.6 ($NCHCH_2O$), 135.2 (HC=N), 177.9 ($COOCH_3$).

*3.32.2. Methyl (3S,2′S)-3-({[2′-(methoxymethyl)pyrrolidin-1′-yl]imino}methyl)-2,2,4-trimethylpentanoate (3S,2′S)-**4m***

De=90%. $[\alpha]_D^{22}=-19.4$ (*c* 1.09, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6): δ 0.94 [d, *J*=6.7 Hz, 3H, $CH(CH_3)CH_3$], 1.02 [d, *J*=6.7 Hz, 3H, $CH(CH_3)CH_3$], 1.25, 1.30 [s, 2×3H, $C(CH_3)_2$], 1.48–1.57 (m, 1H, NCH_2CHH), 1.64–1.84 (m, 3H, $NCH_2CHHCHH$), 1.90 [sept d, *J*=6.7/4.9 Hz, 1H, $CH(CH_3)_2$], 2.65 (br. q, *J*=8.5 Hz, 1H, NC*H*H), 2.70 [dd, *J*=8.2/4.9 Hz, 1H, $CHCH(CH_3)_2$], 3.06–3.12 (m, 1H, NCH*H*), 3.16 (s, 3H, CH_2OCH_3), 3.37 (s, 3H, $COOCH_3$), 3.44 (dd, *J*=9.1/7.3 Hz, 1H, NCHC*H*HO), 3.57–3.63 (m, 1H, NCH), 3.72 (dd, *J*=9.1/3.5 Hz, 1H, NCHCH*H*O), 6.51 (d, *J*=8.2 Hz, 1H, HC=N). ^{13}C NMR (125 MHz, C_6D_6): δ 20.3 [$CH(CH_3)CH_3$], 22.3 (NCH_2CH_2), 22.6 [$C(CH_3)CH_3$], 23.3 [$CH(CH_3)CH_3$], 26.3 [$C(CH_3)CH_3$], 27.3 ($NCH_2CH_2CH_2$), 28.9 [$CH(CH_3)_2$], 45.1 [$C(CH_3)_2$], 49.8 (NCH_2), 51.2 ($COOCH_3$), 55.7 [$CHCH(CH_3)_2$], 58.9 (CH_2OCH_3), 63.5 (NCH), 75.6 ($NCHCH_2O$), 135.3 (HC=N), 177.9 ($COOCH_3$).

*3.33. Ethyl (3R,2′S)-4-{[2′-(methoxymethyl)pyrrolidin-1′-yl]imino}-2,2,3-trimethylbutanoate **4n***

Yield: 85%. Colourless liquid, *de*=45%. R_f=0.38 (pentane:Et_2O=2:1). R_t=9.9 min (OV-17; 120-10-260). IR (capillary, ν cm^{-1}): 2976 (vs), 2936, 2877 (s), 2826 (m), 1728 (vs), 1598 (w), 1462 (s), 1387, 1365, 1341 (m), 1323 (w), 1295 (m), 1253, 1197, 1175 (s), 1129 (vs, br.), 1067, 1028 (m), 973, 926, 903, 883, 861 (w). ^1H NMR (300 MHz, C_6D_6): δ 1.00 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.14 [1.11] (d, *J*=7.1 Hz, 3H, $CHCH_3$), 1.23 [1.25], 1.27 [s, 2×3H, $C(CH_3)_2$], 1.44–1.82 (m, 4H, $NCH_2CH_2CH_2$), 2.51–2.61 (m, 1H, NC*H*H), 2.93 (quin, *J*=6.9 Hz, 1H, $CHCH_3$), 3.00–3.12 (m, 1H, NCH*H*), 3.17 [3.16] (s, 3H, CH_2OCH_3), 3.37–3.45 (m, 1H, NCHC*H*HO), 3.51–3.62 (m, 1H, NCH), 3.69–3.75 (m,

1H, NCHCH*H*O), 4.01 [3.99, 4.00] (q, *J*=7.1 Hz, 2H, C*HH*CH$_3$), 6.46 (d, *J*=6.3 Hz, 1H, HC=N). ^{13}C NMR (75 MHz, C_6D_6): δ 14.3, 14.4 (CHCH$_3$, CH$_2$CH$_3$), 22.2 [22.3], 23.4 [23.3] [C(CH$_3$)$_2$], 22.4 [22.3] (NCH$_2$CH$_2$), 27.3 [27.4] (NCH$_2$CH$_2$CH$_2$), 44.5 [44.6] (CHCH$_3$), 45.7 [45.6] [C(CH$_3$)$_2$], 49.5 [49.7] (NCH$_2$), 58.9 (CH$_2$OCH$_3$), 60.2 (CH$_2$CH$_3$), 63.5 [63.6] (NCH), 75.5 [75.6] (NCHCH$_2$O), 136.9 [137.1] (HC=N), 176.8 (COOC$_2$H$_5$). MS (EI, 70 eV): *m/z* (%) 284 (6) [M$^+$], 253 (5) [M$^+$−OCH$_3$], 239 (65) [M$^+$−CH$_2$OCH$_3$], 169 (17) [M$^+$−SMP], 142 (34) [M$^+$−SMP−HCNH], 124 (14), 114 (10) [SMP$^+$], 96 (22), 82 (10), 70 (100) [C$_4$H$_8$N$^+$], 58 (18), 55 (13), 45 (20), 43 (20), 41 (27). EA C$_{15}$H$_{28}$N$_2$O$_3$ (284.40): calcd C 63.35, H 9.92, N 9.85; found C 63.70, H 10.01, N 10.24.

3.34. Isopropyl (3R,2′S)-4-{[2′-(methoxymethyl)pyrrolidin-1′-yl]imino}-2,2,3-trimethylbutanoate **4o**

Yield: 75%. Colourless liquid, *de*=39%. R_f=0.43 (pentane:Et$_2$O=2:1). R_t=12.1 min (OV-17; 100-10-260). IR (capillary, ν cm^{-1}): 2977 (vs), 2936, 2876 (s), 2826 (m), 1724 (vs), 1598 (w), 1461, 1386, 1374 (s), 1340 (m), 1321 (w), 1293 (m), 1254 (vs), 1197 (s), 1146, 1108 (vs, br.), 1067 (m), 1039, 1002, 973, 935, 908, 872 (w). ^{1}H NMR (300 MHz, C_6D_6): δ 1.06 [1.05], 1.06 [1.07] [d, *J*=6.3 Hz, 2×3H, CH(C*H*$_3$)$_2$], 1.16 [1.13] (d, *J*=7.2 [6.9] Hz, 3H, CHCH$_3$), 1.23, 1.27 [1.25] [s, 2×3H, C(C*H*$_3$)$_2$], 1.45–1.83 (m, 4H, NCH$_2$C*H*$_2$C*H*$_2$), 2.53–2.61 (m, 1H, NC*H*H), 2.93 (quin, *J*=6.9 Hz, 1H, C*H*CH$_3$), 3.01–3.13 (m, 1H, NCH*H*), 3.17 [3.16] (s, 3H, CH$_2$OC*H*$_3$), 3.38–3.45 (m, 1H, NCHC*H*HO), 3.53–3.63 (m, 1H, NCH), 3.70–3.76 (m, 1H, NCHCH*H*O), 5.04 [5.03] [sept, *J*=6.3 Hz, 1H, C*H*(CH$_3$)$_2$], 6.48 (d, *J*=6.3 Hz, 1H, HC=N). ^{13}C NMR (75 MHz, C_6D_6): δ 14.4 [14.3] (CH*C*H$_3$), 21.7, 21.8 [CH(*C*H$_3$)$_2$], 22.1 [22.2], 23.5 [23.3] [C(*C*H$_3$)$_2$], 22.4 (NCH$_2$*C*H$_2$), 27.3 [27.4] (NCH$_2$CH$_2$*C*H$_2$), 44.4 [44.5] (*C*HCH$_3$), 45.6 [45.5] [*C*(CH$_3$)$_2$], 49.5 [49.7] (NCH$_2$), 58.9 (CH$_2$O*C*H$_3$), 63.5 [63.6] (NCH), 67.2 [*C*H(CH$_3$)$_2$], 75.5 [75.6] (*C*H$_2$OCH$_3$), 137.1 [137.2] (HC=N), 176.3 [176.2] (*C*OOCH). MS (EI, 70 eV): *m/z* (%) 298 (6) [M$^+$], 253 (68) [M$^+$−CH$_2$OCH$_3$], 169 (19), 142 (45), 124 (13), 114 (10) [SMP$^+$], 96 (20), 82 (10), 70 (100) [C$_4$H$_8$N$^+$], 58 (19), 55 (14), 45 (18), 43 (31), 41 (31). EA C$_{16}$H$_{30}$N$_2$O$_3$ (298.42): calcd C 64.40, H 10.13, N 9.39; found C 64.55, H 10.29, N 9.85.

3.35. Methyl (3R,2′S)-4-{[2′-(methoxymethyl)pyrrolidin-1′-yl]imino}-2,2-diethyl-3-methylbutanoate **4n**

Yield: 76%. Colourless liquid, *de*=53%. R_f=0.41 (pentane:Et$_2$O=2:1). R_t=8.9 min (SE-54; 140-10-300). IR (capillary, ν cm^{-1}): 2970, 2947, 2880 (vs), 2827 (m), 1728 (vs), 1599 (w), 1459, 1451 (s), 1382 (m), 1341, 1314, 1280 (w), 1220, 1134 (vs, br.), 1075, 996 (m), 973, 891, 807, 789, 743 (w). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 [0.80], 0.83 [0.82] [t, *J*=7.4 Hz, je 3H, C(CH$_2$C*H*$_3$)$_2$], 1.01 [1.00] (d, *J*=7.1 Hz, 3H, CHC*H*$_3$), 1.49–2.04 [m, 8H, NCH$_2$C*H*$_2$C*H*$_2$, C(C*H*$_2$CH$_3$)$_2$], 2.56 (quin, *J*=7.1 Hz, 1H, C*H*CH$_3$), 2.70–2.83 (m, 1H, NC*H*H), 3.27–3.47 (m, 3H, NCH*H*, NC*H*C*H*HO), 3.37 [3.38] (s, 3H, CH$_2$OC*H*$_3$), 3.53–3.60 (m, 1H, NCHCH*H*O), 3.66 [3.67] (s, 3H, COOCH$_3$), 6.58 [6.60] (d, *J*=7.4 [6.7] Hz, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.4 [8.3], 8.6 [8.7] [C(CH$_2$*C*H$_3$)$_2$], 14.8 [14.7] (CH*C*H$_3$), 22.0 [22.2] (NCH$_2$*C*H$_2$), 23.9 [23.7], 25.2 [25.3] [C(*C*H$_2$CH$_3$)$_2$], 26.6 [26.7] (NCH$_2$CH$_2$*C*H$_2$), 41.8 (*C*HCH$_3$), 50.1 [50.7] (NCH$_2$), 51.2 (COO*C*H$_3$), 52.5 [52.2] [*C*(CH$_2$CH$_3$)$_2$], 59.2 (CH$_2$O*C*H$_3$), 63.3 [63.6] (NCH), 74.8 [74.9] (NCH*C*H$_2$O), 141.0 [141.5] (HC=N), 176.5 (*C*OOCH$_3$). MS (EI, 70 eV): *m/z* (%) 298 (7) [M$^+$], 267 (2) [M$^+$−OCH$_3$], 253 (100) [M$^+$−CH$_2$OCH$_3$], 184 (10) [M$^+$−SMP], 169 (44) [M$^+$−(H$_5$C$_2$)$_2$CCOOCH$_3$], 156 (24) [M$^+$−SMP−HCNH], 124 (20) [M$^+$−SMP−HCNH−CH$_3$OH], 114 (8) [SMP$^+$], 112 (7), 101 (6), 97 (15), 82 (14), 70 (98) [C$_4$H$_8$N$^+$], 55 (27), 45 (25), 41 (44). EA C$_{16}$H$_{30}$N$_2$O$_3$ (298.42): calcd C 64.40, H 10.13, N 9.39; found C 64.48, H 10.38, N 9.58.

3.36. (2S,2′S)-[2-(Ethylsulfanyl)propyliden]-[2′-(methoxymethyl)pyrrolidin-1′-yl]amine **5a**

(a) Reaction temperature: −78°C. Yield: 52%, *de*=13%.
(b) Reaction temperature: −78°C to −20°C. Yield: 85%, *de*=10%.

Colourless liquid. R_f=0.30 (pentane:Et_2O=5:1). R_t=8.50 [8.57] min (SE-54; 100-10-300). IR (capillary, ν cm^{-1}): 2967, 2926, 2873 (vs), 2825, 1591 (s), 1449 (vs, br.), 1374, 1341 (s), 1324, 1303, 1282, 1267 (m), 1197 (vs), 1121 (vs, br.), 1016, 973 (s), 922, 902, 875 (m), 813, 783, 759, 714 (w). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 [1.23] (t, *J*=7.4 Hz, 3H, CH_2CH_3), 1.35 (d, *J*=7.1 Hz, 3H, $CHCH_3$), 1.76–2.04 (m, 4H, $NCH_2CH_2CH_2$), 2.38–2.62 (m, 2H, CH_2CH_3), 2.72–2.85 (m, 1H, NCHH), 3.30–3.59 (m, 5H, $CHCH_3$, NCHH, NCHCHHO), 3.36 [3.38] (s, 3H, CH_2OCH_3), 6.36 [6.40] (d, *J*=7.4 Hz, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.9 (CH_2CH_3), 19.0 [18.9] ($CHCH_3$), 22.1 [22.2] (NCH_2CH_2), 24.5 [24.4] (CH_2CH_3), 26.6 ($NCH_2CH_2CH_2$), 41.6 [41.7] ($CHCH_3$), 49.7 [50.1] (NCH_2), 59.1 [59.2] (CH_2OCH_3), 63.1 [63.6] (NCH), 74.5 [74.6] (CH_2OCH_3), 138.3 [138.7] (HC=N). MS (EI, 70 eV): *m/z* (%) 230 (4) [M^+], 185 (25) [$M^+-CH_2OCH_3$], 169 (100) [$M^+-SCH_2CH_3$], 137 (7), 123 (53) [$M^+-CH_2OCH_3-CH_3CH_2SH$], 116 (13), 112 (10), 89 (19), 85 (14), 83 (21), 82 (17), 80 (13), 71 (30), 70 (25) [$C_4H_8N^+$], 69 (22), 68 (16), 67 (11), 61 (10), 57 (13), 55 (15), 45 (10). EA $C_{11}H_{22}N_2OS$ (230.37): calcd C 57.35, H 9.63, N 12.16; found C 57.70, H 9.78, N 12.09.

3.37. (2S,2′S)-[2-(Methoxymethyl)pyrrolidin-1′-yl]-[2′-(propylsulfanyl)propyliden]amine **5b**

(a) Reaction temperature: −78°C. Yield: 65%, *de*=13%.
(b) Reaction temperature: −78°C to −20°C. Yield: 82%, *de*=9%.

Colourless liquid. R_f=0.39 (pentane:Et_2O=5:1). R_t=9.56 [9.67] min (SE-54; 100-10-300). IR (capillary, ν cm^{-1}): 2962, 2926, 2872 (vs), 2825 (s), 1591 (m), 1451 (vs), 1375, 1341 (s), 1303 (m), 1197, 1121 (vs, br.), 1058, 1019, 973 (m), 922 (w), 900, 875 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 [0.96] (t, *J*=7.4 Hz, 3H, CH_2CH_3), 1.34 (d, *J*=6.9 Hz, 3H, $CHCH_3$), 1.53–1.71 (m, 2H, CH_2CH_3), 1.75–2.03 (m, 4H, $NCH_2CH_2CH_2$), 2.35–2.58 (m, 2H, $CH_2CH_2CH_3$), 2.73–2.83 (m, 1H, NCHH), 3.30–3.59 (m, 5H, $CHCH_3$, NCHH, NCHCHHO), 3.37 [3.38] (s, 3H, CH_2OCH_3), 6.35 [6.39] (d, *J*=7.4 Hz, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6 [13.5] (CH_2CH_3), 19.1 [19.0] ($CHCH_3$), 22.1 [22.2] (NCH_2CH_2), 23.2 [23.1] (CH_2CH_3), 26.6 ($NCH_2CH_2CH_2$), 32.6 [32.5] ($CH_2CH_2CH_3$), 41.9 [42.0] ($CHCH_3$), 49.8 [50.1] (NCH_2), 59.2 (CH_2OCH_3), 63.2 [63.6] (NCH), 74.5 [74.6] ($NCHCH_2O$), 138.5 [138.8] (HC=N). MS (EI, 70 eV): *m/z* (%) 244 (7) [M^+], 199 (24) [$M^+-CH_2OCH_3$], 169 (100) [$M^+-SCH_2CH_2CH_3$], 137 (5), 130 (9), 123 (36) [$M^+-CH_2OCH_3-CH_3CH_2CH_2SH$], 82 (11), 80 (8), 71 (18), 70 (15) [$C_4H_8N^+$], 69 (11), 57 (9), 55 (10). EA $C_{12}H_{24}N_2OS$ (244.40): calcd C 58.97, H 9.90, N 11.46; found C 59.27, H 10.01, N 11.55.

3.38. (2S,2′S)-[2-(Isopropylsulfanyl)propyliden]-[2′-(methoxymethyl)pyrrolidin-1′-yl]amine **5c**

(a) Reaction temperature: −78°C. Yield: 59%, *de*=6%.
(b) Reaction temperature: −78°C to −20°C. Yield: 91%, *de*=3%.

Colourless liquid. R_f=0.34 (pentane:Et_2O=5:1). R_t=8.71 [8.80] min (SE-54; 100-10-300). IR (capillary, ν cm^{-1}): 2966, 2925, 2867 (vs), 2825 (s), 1592 (m), 1450 (vs), 1381, 1373, 1365, 1341 (s), 1324, 1304, 1283 (m), 1247 (s), 1197, 1155, 1121 (vs, br.), 1020, 973 (m), 924, 902 (w), 875 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 [1.22] (d, *J*=6.9 Hz, 3H, $CHCH_3$), 1.26–1.36 [m, 6H, $CH(CH_3)_2$], 1.76–2.03 (m, 4H, $NCH_2CH_2CH_2$), 2.72–2.82 (m, 1H, NCHH), 2.90 [2.86] [sept, *J*=6.9 Hz, 1H, $CH(CH_3)_2$], 3.30–3.48 (m, 3H, $CHCH_3$, NCHH, NCH), 3.36 [3.38] (s, 3H, CH_2OCH_3), 3.50–3.66 (m, 2H, NCHCHHO), 6.36 [6.41]

(d, J=7.7 [7.4] Hz, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 ($CHCH_3$), 22.1 [22.2] (NCH_2CH_2), 23.2 [23.4], 23.9 [23.8] [$CH(CH_3)_2$], 26.5 [26.6] ($NCH_2CH_2CH_2$), 33.9 [34.0] [$CH(CH_3)_2$], 41.1 [41.2] ($CHCH_3$), 49.7 [50.1] (NCH_2), 59.2 (CH_2OCH_3), 63.1 [63.6] (NCH), 74.4 [74.6] (CH_2OCH_3), 138.9 [139.2] (HC=N). MS (EI, 70 eV): *m/z* (%) 244 (9) [M^+], 199 (24) [$M^+-CH_2OCH_3$], 169 (100) [$M^+-SCH(CH_3)_2$], 123 (14) [$M^+-CH_2OCH_3-(H_3C)_2CHSH$], 88 (10), 71 (11), 70 (11) [$C_4H_8N^+$], 61 (9). EA $C_{12}H_{24}N_2OS$ (244.40): calcd C 58.97, H 9.90, N 11.46; found C 59.34, H 10.11, N 11.53.

3.39. (2S,2′S)-[2-(Methoxymethyl)pyrrolidin-1′-yl]-[2′-(phenylsulfanyl)propyliden]amine **5d**

Yield: 97%. Colourless liquid, *de*=29%. R_f=0.24 (pentane:Et_2O=5:1). GC: decomposition. IR (capillary, ν cm^{-1}): 3056 (w), 2971, 2924, 2876 (vs), 2825 (s), 1585, 1478, 1443 (vs), 1373 (m), 1342 (s), 1304, 1284 (m), 1197, 1121 (vs, br.), 1021 (s), 973, 902, 872 (m), 745, 693 (vs). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 [1.44] (d, J=6.9 [7.1] Hz, 3H, $CHCH_3$), 1.67–1.97 (m, 4H, $NCH_2CH_2CH_2$), 2.50–2.61 [2.73–2.82] (m, 1H, NCHH), 3.16–3.50 (m, 4H, NCHH, NCHCHHO), 3.34 [3.31] (s, 3H, CH_2OCH_3), 3.99 [3.98] (quin, J=6.9 Hz, 1H, $CHCH_3$), 6.38 (d, J=6.9 Hz, 1H, HC=N), 7.15–7.29 (m, 3H, $CH_{meta/para}$), 17.37–7.44 (m, 2H, CH_{ortho}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.9 [19.1] ($CHCH_3$), 22.2 [22.1] (NCH_2CH_2), 26.5 [26.7] ($NCH_2CH_2CH_2$), 45.6 [45.4] ($CHCH_3$), 49.9 [49.5] (NCH_2), 59.2 (CH_2OCH_3), 63.4 [62.9] (NCH), 74.5 [74.4] ($NCHCH_2O$), 126.8 [126.6] (CH_{para}), 128.5 [128.6] (CH_{meta}), 132.4 [131.9] (CH_{ortho}), 134.7 [135.0] (C_{ipso}), 136.9 [136.4] (HC=N). MS (EI, 70 eV): *m/z* (%) 233 (2) [$M^+-CH_2OCH_3$], 169 (100) [$M^+-SC_6H_5$], 137 (7), 123 (12) [$M^+-CH_2OCH_3-C_6H_5SH$], 114 (6) [SMP^+], 112 (8), 109 (15), 82 (7), 80 (6), 71 (12), 70 (10) [$C_4H_8N^+$], 55 (5), 45 (5). EA $C_{15}H_{22}N_2OS$ (278.42): calcd C 64.71, H 7.96, N 10.06; found C 65.16, H 8.01, N 10.01.

3.40. (2S,2′S)-[2-(Benzylsulfanyl)propyliden]-[2′-(methoxymethyl)pyrrolidin-1′-yl]amine **5e**

Yield: 92%. Colourless liquid, *de*=11%. R_f=0.27 (pentane:Et_2O=5:1). R_t=13.2 min (SE-54; 120-10-300). IR (capillary, ν cm^{-1}): 3084 (w), 3060, 3027 (m), 2970, 2924, 2875, 2825 (vs), 1589 (s), 1495 (s), 1453 (vs), 1418 (w), 1374 (m), 1341 (s), 1323, 1304, 1283 (m), 1197 (vs), 1121 (vs, br.), 1073, 1021 (s), 973, 917, 903, 874, 770 (m), 703 (vs). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 [1.33] (d, J=7.1 [6.9] Hz, 3H, $CHCH_3$), 1.76–2.03 (m, 4H, $NCH_2CH_2CH_2$), 2.61–2.81 (m, 1H, NCHH), 3.28–3.75 (m, 7H, $CHCH_3$, SCHH, NCHH, NCHCHHO), 3.37 [3.38] (s, 3H, CH_2OCH_3), 6.35 [6.36] (d, J=7.7 Hz, 1H, HC=N), 7.16–7.38 (m, 5H, aromatic H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.8 [18.7] ($CHCH_3$), 22.0 [22.1] (NCH_2CH_2), 26.6 ($NCH_2CH_2CH_2$), 34.9 [35.1] (SCH_2), 41.6 [42.0] ($CHCH_3$), 49.6 [49.9] (NCH_2), 59.3 (CH_2OCH_3), 63.1 [63.6] (NCH), 74.5 [74.6] ($NCHCH_2O$), 126.7 (CH_{para}), 128.4, 129.1 ($CH_{ortho/meta}$), 138.0 [138.2] (HC=N), 139.1 [139.2] (C_{ipso}). MS (EI, 70 eV): *m/z* (%) 292 (6) [M^+], 247 (22) [$M^+-CH_2OCH_3$], 169 (100) [$M^+-SCH_2C_6H_5$], 123 (13) [$M^+-CH_2OCH_3-C_6H_5CH_2SH$], 114 (5) [$SMP^+$], 112 (5), 91 (45) [$C_6H_5CH_2^+$], 82 (5), 80 (4), 71 (9), 70 (10) [$C_4H_8N^+$], 65 (5), 55 (4), 45 (8). EA $C_{16}H_{24}N_2OS$ (292.44): calcd C 65.71, H 8.27, N 9.58; found C 66.08, H 8.41, N 9.59.

3.41. (2S,2′S)-[2-(Benzyloxy)propyliden]-[2′-(methoxymethyl)pyrrolidin-1′-yl]amine **2b**

Yield: 88%. Colourless liquid, *de*=7%. R_f=0.43 (pentane:Et_2O=2:1). GC: decomposition. IR (capillary, ν cm^{-1}): 3087, 3063 (w), 3029 (m), 2973, 2928, 2875, 2827 (vs), 1593 (s), 1496 (m), 1454 (vs), 1384 (m), 1370, 1341 (s), 1324, 1305, 1290 (m), 1198 (vs), 1118, 1089, 1073 (vs, br.), 1028 (s), 974, 935, 903, 875 (m), 737, 698 (vs). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (d, J=6.6 Hz, 3H, $CHCH_3$), 1.75–2.03 (m, 4H, $NCH_2CH_2CH_2$), 2.77–2.87 [2.67–2.77] (m, 1H, NCHH), 3.25–3.62 (m, 4H, NCHH,

NC*H*C*H*HO), 3.38 [3.37] (s, 3H, CH_2OCH_3), 4.07 [4.08] (quint, *J*=6.6 Hz, 1H, C*H*CH_3), 4.46 [4.47] (d, *J*=12.1 [11.8] Hz, 1H, CHOC*H*H), 4.58 [4.56] (d, *J*=12.1 Hz, 1H, CHOCH*H*), 6.42 [6.41] (d, *J*=6.9 Hz, 1H, HC=N), 7.21–7.37 (m, 5H, aromatic CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3 [20.2] (CH*C*H_3), 22.2 (NCH_2*C*H_2), 26.6 [26.7] (NCH_2CH_2*C*H_2), 49.4 [49.6] (NCH_2), 59.3 [59.2] (CH_2OCH_3), 62.9 [63.1] (NCH), 70.0 [70.1] (CHO*C*H_2), 74.5 [74.6] (*C*H_2OCH_3), 75.4 [75.9] (*C*HOCH_2), 127.4 [127.3] (CH_{para}), 127.9 [127.8] (CH_{ortho}), 128.3 (CH_{meta}), 137.1 [137.4] (HC=N), 138.9 [139.1] (C_{ipso}). MS (EI, 70 eV): *m/z* (%) 276 (5) [M^+], 231 (63) [$M^+-CH_2OCH_3$], 170 (10), 168 (9), 123 (38) [$M^+-CH_2OCH_3-C_6H_5CH_2OH$], 108 (5), 91 (100) [$C_6H_5CH_2^+$], 79 (13), 77 (9) [$C_6H_5^+$], 71 (5), 70 (11) [$C_4H_8N^+$], 69 (6), 68 (7), 65 (8), 55 (6), 51 (4), 45 (12). EA $C_{16}H_{24}N_2O_2$ (276.38): calcd C 69.53, H 8.75, N 10.14; found C 69.21, H 8.44, N 10.62.

3.42. Dimethyl (1′R,2″S)-2-(2′-{[2″-(methoxymethyl)pyrrolidin-1″-yl]imino}-1′-methyl-ethyl)-malonate **6**

Yield: quantitative. Colourless liquid, *de*=17%. R_f=0.30 (pentane:Et_2O=2:1). R_t=10.5 min (SE-54; 120-10-300). IR (capillary, ν cm^{-1}): 2953 (s), 2878, 2829 (m), 1758, 1737 (vs), 1601 (w), 1459 (m), 1435 (s), 1381 (w), 1340 (m), 1280, 1253 (s), 1198 (vs), 1155, 1140 (s, br.), 1023 (m), 973, 904 (w). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (d, *J*=6.9 Hz, 3H, CHC*H*$_3$), 1.71–2.00 (m, 4H, NCH_2C*H*$_2$C*H*$_2$), 2.64–2.73 (m, 1H, NC*H*H), 3.08–3.21 (m, 1H, C*H*CH_3), 3.23–3.39 (m, 2H, NCH*H*, NCH), 3.36 [3.37] (s, 3H, CH_2OCH_3), 3.41 [3.44] [d, *J*=6.6 Hz, 1H, C*H*$(COOCH_3)_2$], 3.50–3.64 (m, 2H, NCHC*H*$_2$O), 3.71 [3.70], 3.73 [3.74] (s, 2×3H, 2×$COOCH_3$), 6.56 (d, *J*=4.4 Hz, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.7 [16.5] (CH*C*H_3), 22.0 [21.9] (NCH_2*C*H_2), 26.6 [26.5] (NCH_2CH_2*C*H_2), 36.8 [36.9] (*C*HCH_3), 49.6 [49.5] (NCH_2), 52.3 [52.2], 52.3 [52.4] (2×COO*C*H_3), 55.9 [55.8] [*C*$H(COOCH_3)_2$], 59.2 (CH_2OCH_3), 63.4 [63.5] (NCH), 74.5 [74.3] (*C*H_2OCH_3), 137.6 [137.5] (HC=N), 169.0 [169.1], 169.2 (2×*C*$OOCH_3$). MS (EI, 70 eV): *m/z* (%) 300 (2) [M^+], 269 (1) [M^+-OCH_3], 255 (55) [$M^+-CH_2OCH_3$], 186 (1) [M^+−SMP], 169 (4) [$M^+-CH(COOCH_3)_2$], 154 (24) [M^+−SMP−CH_3OH], 137 (6), 122 (12) [M^+−SMP−2×CH_3OH], 82 (9), 80 (7), 71 (14), 70 (100) [$C_4H_8N^+$], 69 (67), 68 (16), 59 (35), 55 (10), 45 (19). EA $C_{14}H_{24}N_2O_5$ (300.35): calcd C 55.99, H 8.05, N 9.33; found C 56.13, H 8.12, N 9.16.

3.43. (2S,2′R)-[2-(Methoxymethyl)pyrrolidin-1-yl]-(2′-methylpent-4′-enylidene)amine **7**

Yield: 52% (after HPLC). Colourless liquid, *de*=7%. R_f=0.41 (pentane:Et_2O=4:1). R_t=6.4 min (SE-54; 100-10-300). IR (capillary, ν cm^{-1}): 3075 (m), 2972, 2926, 2876, 2827 (vs), 1641 (s), 1603 (m), 1458 (vs), 1416 (m), 1377, 1339, 1301 (s), 1282 (m), 1197 (vs), 1122 (vs, br.), 994, 973 (s), 911 (vs), 876 (m). ^{1}H NMR (300 MHz, C_6D_6): δ 1.09 [1.10] (d, *J*=6.9 [6.6] Hz, 3H, CHC*H*$_3$), 1.44–1.57 (m, 1H, NCH_2C*H*H), 1.63–1.83 (m, 3H, NCH_2CH*H*C*H*$_2$), 2.02–2.14 (m, 1H, C*H*HCH=CH_2), 2.23–2.35 (m, 1H, CH*H*CH=CH_2), 2.43–2.57 (m, 2H, C*H*CH_3, NC*H*H), 3.01–3.13 (m, 1H, NCH*H*), 3.16 (s, 3H, CH_2OCH_3), 3.39–3.46 (m, 1H, NCHC*H*HO), 3.52–3.62 (m, 1H, NCH), 3.76 (dd, *J*=9.1/3.6 Hz, 1H, NCHCH*H*O), 4.98–5.10 (m, 2H, CH_2CH=CH_2), 5.84 (dd t, *J*=17.0/10.2/7.1 Hz, 1H, CH_2C*H*=CH_2), 6.37 [6.38] (d, *J*=5.5 [5.2] Hz, 1H, HC=N). ^{13}C NMR (75 MHz, C_6D_6): δ 18.7 [18.6] (CH*C*H_3), 22.4 (NCH_2*C*H_2), 27.4 (NCH_2CH_2*C*H_2), 37.1 [37.0] (*C*HCH_3), 40.3 (*C*H_2CH=CH_2), 49.8 [49.7] (NCH_2), 58.9 (CH_2OCH_3), 63.7 (NCH), 75.7 (*C*H_2OCH_3), 116.0 [116.1] (CH_2CH=*C*H_2), 137.4 [137.3] (HC=N), 140.2 [140.1] (CH_2*C*H=CH_2). MS (EI, 70 eV): *m/z* (%) 210 (2) [M^+], 169 (6) [M^+-CH_2CH=CH_2], 165 (100) [$M^+-CH_2OCH_3$], 123 (10) [$M^+-CH_2OCH_3-CH_2CH$=CH_2−H], 114 (7) [SMP$^+$], 109 (6), 96 (6) [M^+−SMP], 84 (4), 82 (6), 70 (36) [$C_4H_8N^+$], 69 (13), 68 (9), 67 (5), 55 (7),

53 (5), 45 (13). EA: $C_{12}H_{22}N_2O$ (210.32): calcd C 68.53, H 10.54, N 13.32; found C 68.21, H 10.61, N 13.25.

3.44. *Methyl (R)-2,2,3-trimethyl-4-oxobutanoate* **9**

A solution of 4-hydrazono ester (*R,S*)-**4a** (1 mmol) in methylene chloride (40 ml) was cooled to −78°C and ozone was bubbled through this solution until the cleavage of the hydrazone was complete (carefully followed by TLC; any excess of ozone has to be avoided). Then the reaction mixture was flushed with argon and allowed to warm to room temperature. After evaporation of the solvent the crude product was purified by column chromatography (pentane:Et_2O=2:1) to afford 104 mg of compound (*R*)-**9** (66% yield) as a colourless oil.

R_f=0.47 (pentane:Et_2O=2:1). R_t=3.9 min (OV-17; 80-10-260). IR (capillary, ν cm^{-1}): 2982 (s), 2953 (m), 2883, 2843 (w), 1728 (vs), 1462 (s), 1436, 1392 (m), 1260, 1193 (s), 1146 (vs), 1042, 1007, 985, 948, 914, 880, 838, 773 (w). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, *J*=7.4 Hz, 3H, $CHCH_3$), 1.25, 1.27 [s, je 3H, $C(CH_3)_2$], 2.68 (qd, *J*=7.4/1.6 Hz, 1H, $CHCH_3$), 3.71 (s, 3H, $COOCH_3$), 9.72 (d, *J*=1.6 Hz, 1H, HC=O). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.3 ($CHCH_3$), 22.0, 23.9 [$C(CH_3)_2$], 43.9 [$C(CH_3)_2$], 52.1 ($CHCH_3$), 52.6 ($COOCH_3$), 177.1 ($COOCH_3$), 203.4 (HC=O). MS (EI, 70 eV): *m/z* (%) 143 (4) [M^+-CH_3], 128 (4) [MH^+-OCH_3], 115 (9) [$M^+-CO-CH_3$], 102 (18) [$(H_3C)_2CHCOOCH_3^+$], 101 (26) [$(H_3C)_2CCOOCH_3^+$], 87 (7), 74 (17), 73 (19) [$(H_3C)_2COCH_3^+$], 70 (42) [$C_5H_{10}^+$], 69 (24) [$C_5H_9^+$], 59 (100), 57 (85), 55 (27), 45 (13), 43 (16), 41 (59), 39 (24). EA $C_8H_{14}O_3$ (158.20): calcd C 60.74, H 8.92; found C 60.32, H 8.85.

3.45. *Methyl (R)-3-cyano-2,2-dimethylbutanoate* **10**

A solution of 4-hydrazono ester (*R,S*)-**4a** (1 mmol) in methanol (1 ml) was added dropwise under stirring to a suspension of magnesium monoperoxyphthalate (2.5 mmol) in a mixture of methanol (4 ml) and aqueous pH 7 phosphate buffer solution (4 ml) at 0°C. Stirring was continued for 1.5 h and the reaction mixture was partitioned between methylene chloride (25 ml) and water (25 ml). After separation of the layers, the organic layer was washed with saturated aqueous sodium chloride solution (2×25 ml) and dried over magnesium sulfate. After filtration and evaporation of the solvent the crude product was purified by column chromatography (pentane:Et_2O=2:1) to afford 127 mg of compound (*R*)-**10** (82% yield) as a colourless oil.

R_f=0.44 (pentane:Et_2O=2:1). R_t=5.8 min (OV-17; 60-10-260). IR (capillary, ν cm^{-1}): 2987 (s), 2955 (m), 2884, 2847, 2242 (w), 1736 (vs), 1463 (s), 1436 (m), 1395, 1384, 1372, 1318, 1303 (w), 1264 (vs), 1194 (s), 1142 (vs), 1091 (m), 1067, 1029, 1004, 985, 883, 834, 775 (w). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (d, *J*=7.1 Hz, 3H, $CHCH_3$), 1.30, 1.37 [s, 2×3H, $C(CH_3)_2$], 3.09 (q, *J*=7.1 Hz, 1H, $CHCH_3$), 3.73 (s, 3H, $COOCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 ($CHCH_3$), 20.5, 24.6 [$C(CH_3)_2$], 34.1 ($CHCH_3$), 44.5 [$C(CH_3)_2$], 52.5 ($COOCH_3$), 120.9 (CHCN), 175.2 ($COOCH_3$). MS (EI, 70 eV): *m/z* (%) 124 (15) [M^+-OCH_3], 102 (69) [$(H_3C)_2CHCOOCH_3^+$], 101 (93) [$(H_3C)_2CCOOCH_3^+$], 96 (100) [$M^+-COOCH_3$], 73 (58) [$(H_3C)_2COCH_3^+$], 70 (40) [$C_5H_{10}^+$], 69 (69) [$C_5H_9^+$], 59 (28), 57 (20), 55 (62), 43 (33), 42 (33), 41 (93), 39 (38). EA $C_8H_{13}NO_2$ (155.20): calcd C 61.91, H 8.44, N 9.03; found C 62.19, H 8.58, N 8.98.

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