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ASYMMETRIC SYNTHESES VIA HETEROCYCLIC INTERMEDIATES—XXII[1]

ENANTIOSELECTIVE SYNTHESIS OF α-ALKENYL GLYCINE METHYL ESTERS AND α-ALKENYL GLYCINES (β,γ-UNSATURATED AMINO ACIDS)

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Abstract—Enantioselective syntheses of α-alkenyl glycines of type **10** and of type **23** are described that provide these uncommon amino acids with predictable configuration and with ee-values of >95%. Both approaches are based on the bislactim ether method developed by Schöllkopf *et al.* As for **10**: The lithiated bis-lactim ether **6** of cyclo(L-val-gly) is reacted with 2-[(dimethyl t-butyl)silyl]alkanals **2** to give the addition products **7** with de > 95%. These on acid hydrolysis afford L-valinate **8** and the methyl (2*R*)-2-amino-4-(dimethyl t-butyl)silyl-3-hydroxyalkanoates **9** which are convertible into the (*R*)-α-alkenyl glycines of type **10**. The scope of this synthesis is limited by the fact that the compounds **9** are thermolabile when disubstitued at C-4. As for **23**: The lithiated bis-lactim ether **6** is reacted with thioketones **14** to give the addition products **15** with de > 95%. The *S*-methyl compounds **16** undergo elimination to give regioselectively the olefins **18** when treated with Raney-Ni. Alternatively, the olefins **18** are obtained from the sulfonium salts **24** by dimethyl sulfide elimination, although this route is less regiospecific. The compounds **18** are cleaved by dilute hydrochloric acid, liberating L-valinate **8** and (*R*)-α-alkenyl glycine methyl esters **21**, which on further hydrolysis yield (*R*)-α-alkenyl glycines **23**. This synthesis is limited only by the availability of thioketones **14**.

Optically active, non-proteinogenic amino acids deserve attention because of their documented or potential biological activity. Some are valuable pharmaceuticals, such as L-Dopa, (*S*)-α-Methyldopa, D-Penicillamine, or D-Cycloserine. Others are components of pharmaceuticals, for instance D-phenylglycine or D-(*p*-hydroxy-phenylglycine) in the semisynthetic penicillines Ampicillin or Amoxycillin.

In biochemistry, they are valuable tools to investigate the mechanism of enzyme reactions.[2,3] In fact, enzyme inhibition studies with non-proteinogenic amino acids have furnished valuable information about the mode of action of certain enzymes.[2,3]

Obviously, there is a demand for optically active—if possible optically pure-uncommon amino acids both for pure and applied organic or bioorganic chemistry. Since asymmetric synthesis[4] is—at least in principle—the shortest and most economic way to optically active compounds, it is a challenge for the synthetic organic chemist, to develop asymmetric syntheses of amino acids.[5]

Over the past four years our group has tried to elaborate asymmetric syntheses of uncommon amino acids. Our approach is based on heterocyclic chemistry and on the following concept.[6] (1) From a racemic lower amino acid and a chiral auxiliary an heterocycle is built up, that is CH-acidic adjacent to the potential amino group and that contains two sites susceptible to hydrolysis. (2) An electrophile is introduced diastereoselectively via the anion of the heterocycle. (3) Subsequently the heterocycle is cleaved by hydrolysis to liberate the chiral auxiliary and the new optically active amino acid.

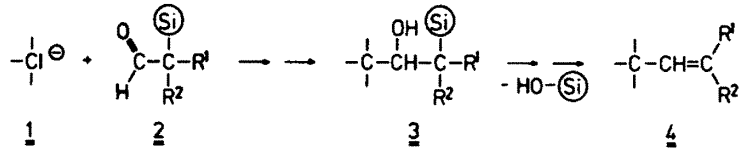
In this strategy the heterocycle merely serves as a vehicle to construct finally an acyclic molecule with the proper structure and proper configuration. It makes use of the obvious fact, that an heterocyclic intermediate is necessarily more rigid than it's open chain analog, hence a higher degree of asymmetric induction can be expected.

This communication describes the asymmetric synthesis of α-alkenyl glycines of type **10** and of type **23** (or their methyl esters **21**, respectively). These non-proteinogenic amino acids deserve attention, because they are potential "suicide inhibitors"[7] of certain pyridoxal phosphate depending enzymes. The asymmetric syntheses described here are based on the fact, that the lithiated bis-lactim ether **6** of cyclo(L-val-gly) reacts both with carbonyl compounds[8,9] and with thioketones with exceptionally high asymmetric induction (de = diastereomeric excess).

α-Alkenyl glycines of type **10** *from* **6** *and* 2-[*(dimethyl t-butyl)silyl*]*alkanals* **2**

2-[(Dimethyl t-butyl)silyl]alkanals **2** are masked alkenyl groups and allow the electrophilic introduction of alkenyl groups into carbanions **1**, according to the following scheme.[10]

The silylated aldehydes **2** add to the lithiated bis-lactim ether **6**—obtained from the bislactim ether **5** of cyclo(L-val-gly) and butyllithium—to give (after protonation) the aldol-type addition products **7a–c**. Like other aldehydes or ketones,[8,9], the incoming aldehyde **2** enters *trans* to the isopropyl group at the

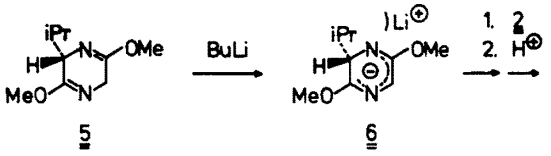


1 2 3 4

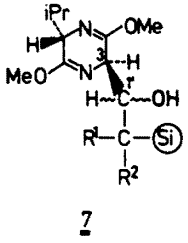
2	a	b	c
R^1	H	H	Me
R^2	H	Me	Me

(Si): tert.butyl(dimethyl)silyl

chiral inducing center C-6, i.e. the (3*R*) configuration is induced. The asymmetric induction is >95%; only (3*R*)-isomers are detectable in the ^{1}H- or ^{13}C-NMR-spectrum. The enantioface selection at the CO group of **2** is less pronounced (see de at C-1'). Very likely the (3*R*,1'*S*)-diastereomers are formed predominantely.[8]



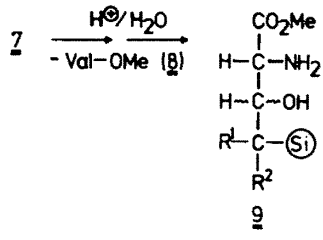
5 6



7

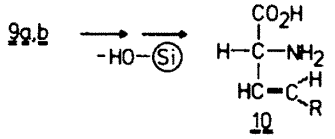
7	R^1	R^2	de(%) C-3	de(%) C-1'
a	H	H	>95	58
b	H	Me	>95	0
c	Me	Me	>95	25

On acid hydrolysis—two equivalents of 0.25 N HCl at room temp—the products **7** are cleaved at the two imino ether groups liberating L-valine methyl ester **8** and methyl (2*R*)-2-amino-4-(dimethyl t-butyl)silyl-3-hydroxy-alkanoates **9**. The esters **8** and **9** are separable by chromatography. However, the rather thermolabile **9c** suffers retro-aldol cleavage and uncontrolled silanol elimination during hydrolysis and chromatography. Probably, due to ground state strain, all 4,4-dialkylated substituted esters **9** will be unstable.



9	R^1	R^2
a	H	H
b	H	Me
c	Me	Me

The esters **9a** and **b** were converted into the (*R*)-α-alkenyl glycines **10a** and **b** by refluxing with 5 N HCl. Alternative methods tried for silanol elimation **9**→**10** gave less good results. (*R*)-(−)-vinyl glycine **10a** was obtained with $[\alpha]_D^{20} = -81.1°$ ($c = 0.2$; H_2O). As the rotation indicates[11] **10a** has the (*R*)-configuration and is of rather high optical purity, although—if the reported rotation of $[\alpha]_D^{20} = -93.8°$ ($c = 1.5$; H_2O)[11] for optically pure (*R*)-**10a** is correct—some racemisation has taken place in going from **7a** to **10a**. *R*-(−)-Propen-1-yl glycine **10b**[12] was obtained as a 1:1-*E*/*Z*-mixture with $[\alpha]_D^{20} = -153.8°$ ($c = 1.2$; H_2O).



10	a	b
R	H	Me

The 2-(dimethyl t-butyl)silyl aldehydes **2a** and **b** were prepared according to lit.[10] The aldehyde **2c** was obtained by the following route. 2-[(dimethyl t-butyl)silyl]propyliden-cyclohexylimine **11** was treated with t-butyllithium to give the Li derivative **12**, which on addition of methyl iodide furnished **13**. This on hydrolysis gave cyclohexylamine and the aldehyde **2c**.

X	11	12	13
	H	Li	Me

Synthesis of α-alkenyl glycine methyl esters of type **21** *and α-alkenyl glycines of type* **23**

Addition of thioketones **14** *to the lithiated bis-lactim ester* **6**

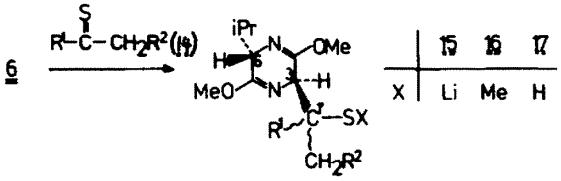
As studied so far, thioketones **14** react with the lithiated bis-lactim ether **6** to give in good chemical yields the addition products **15**. Due to our experience in the field we can safely assume, that—like other electrophiles such as ketones and aldehydes[8,9] or alkyl halides[6]—also thioketones **14** enter in *trans* position to the iso-propyl group at C-6 of **6**, i.e. that the (3*S*)-configuration is induced at C-3 in **15**. Moreover, the coupling constant $J_{3\text{-H}/6\text{-H}}$ in the ^{1}H-NMR-spectrum of **16** is *ca* 1–3 Hz, typical for a *trans* relation between H-3 and H-6 assuming a boat shape of the diaza-hexadienyl heterocycle.[13] The de-values of **15** exceed 95%. For instance, the ^{1}H-NMR spectrum of **16b**, obtained from **15b** by *S*-

Table 1. Compounds **16**

16	R^1	R^2	Yield %	Config. C-3	de (%) C-3	
a	Et	Me	76	S	>95	a)
b	$-(CH_2)_4-$		40	S	≈97	
c	nPr	Et	36	S	>95	
d	Me	Me	52	S	>95	

a) (3S,1'S):(3S,1'R) ≈ 1:1

methylation, was carefully scrutinized and a *ca* 60:1 diastereomer ratio was found (tantamount to de ca 97%). As for the **16a,c** and **d** (Table 1) only (3*S*)-diastereomers were detectable in the ^{1}H- and ^{13}C-NMR spectrum.†

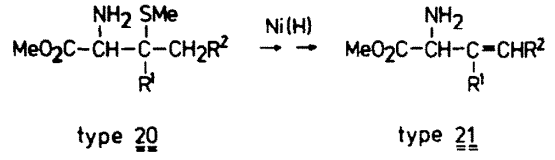


Usually, metallation of **5** to give **6** and addition of the thioketone **14** were performed at −70° (in THF). In one experiment with pentane-3-thione both reactions were carried out at room temp in hexane, whereby **16a** was obtained with de *ca* 69%. Hence, the reaction **6** + **14** → **15** should be performed at low temps.

Hofmann olefins **18** *by elimination of methylthiol from the compounds* **16**. Attempts to replace the methylthio group in **16** by hydrogen by the usual Raney–Ni treatment[14] gave a surprising result. Nearly quantitatively, methylthiol elimination took place with virtually complete regioselectivity to give the Hofmann olefins **18**. Olefin formation during a Raney–Ni treatment of thioethers has previously been observed occasionally, but only as a minor side reaction.[14] The Ni was prepared from a commercial alloy[15] according to a standard procedure.[16] An excess of Raney–Ni was used and the mixture refluxed in ethanol for *ca* 3 hr. As for **18a**, **16a** with SBz instead of SMe was employed. With **16d** the regio isomer **19** was formed as the main product besides the two *E*/*Z*-isomers of **18d**.

The *E*/*Z*-assignments are based on the ^{1}H-NMR spectra of the isomers. In one of the diastereomers the 3-H suffers an upfield shift of $\Delta\delta \approx 0.5$ ppm. Obviously, in this isomer the 3-H is located within the shielding cone of the double bond. Models indicate, that this is more likely for the *Z*- than for the *E*-isomer.

Noteworthyly, according to preliminary results, 3-methyl-thio amino acid esters of type **20** also undergo methylthiol elimination to give β,γ-unsaturated amino acid esters of type **21** when treated with Raney–Ni.

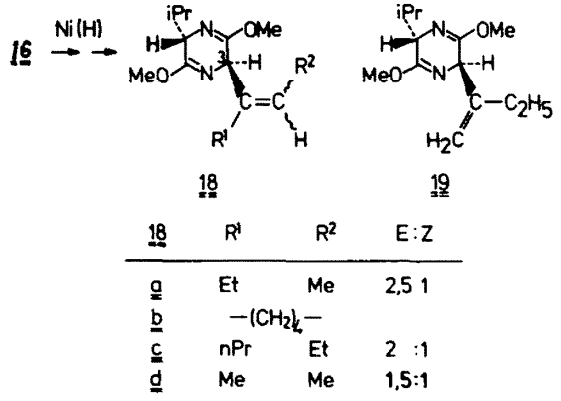


On hydrogenation (Pd/C, ethanol, 1 at H_2, room temp) **18a** afforded (3*R*,6*S*)-2,5-dimethoxy-3-(1'-ethylprop-1'-yl)-6-isopropyl-3,6-dihydropyrazine (yield: 90%), the precursor of (*R*)-2-amino-3-ethyl-pentanoic acid.

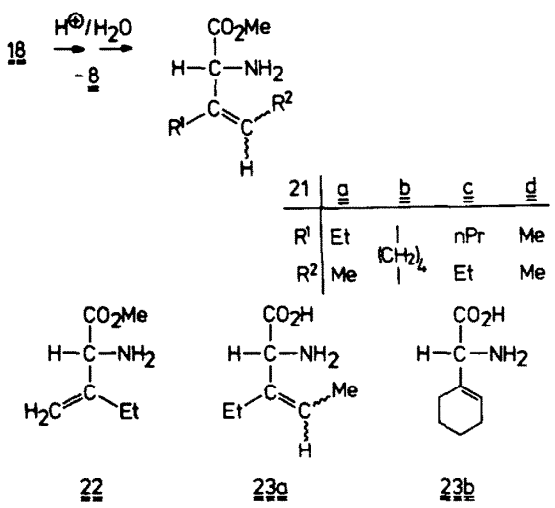
Hydrolysis of **18**; (R)-α-*alkenyl glycine methyl esters* **21** *and* α-*alkenyl glycines* **23**

Hydrolysis of the bis-lactim ethers **18** proceeds under very mild conditions—two equivalents of 0.1 N HCl, room temp—to give methyl L-Valinate **8** and the (*R*)-α-alkenyl glycine methyl esters **21**. L-Valinate **8** could be separated (as forerun) by fractional bulb-to-bulb distillation. Alternatively, it should be possible to remove the valinate **8** by chromatography. The (*R*)-amino acid esters **21** obtained were essentially enantiomerically pure; only the (*R*)-enantiomers were detectable in the ^{1}H-NMR spectrum [Eu(hfc)$_3$ as chiral shift reagent]. The **19**/**18d** mixture gave a mixture of **22** and **21d**.

On further hydrolysis—2 N HCl 90°—the esters **21a** and **b** afforded (*R*)-α-2-amino-3-ethyl-pentenoic acid **23a** (*E*/*Z*-mixture) and (*R*)-(cyclohex-1'-en-1'-yl)glycine **23b** respectively.



18	R^1	R^2	E:Z
a	Et	Me	2,5 1
b	$-(CH_2)_4-$		
c	nPr	Et	2 :1
d	Me	Me	1,5:1

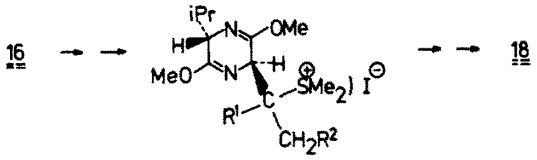


†After preparation of the manuscript, a capillary-GC analysis of **16a** revealed a diastereomer ration of *ca* 98:2, tantamount to *ca* 96% de.

Hofmann olefins **18** *by dimethyl sulfide elimination from the sulfonium salts* **24**

As an alternative method to accomplish the transformation **16**→**18** we tried the dimethyl sulfide elimination from the sulfonium salts **24**. When the bis-lactim ethers **16** were heated with methyl iodide in acetonitrile—heating was required to accomplish methylation—dimethylsulfide elimination took place from the intermediate sulfonium salts **24** to give as major products the Hofmann olefins **18** and as minor products the Saytzeff olefins **25** (*ca* 90:10 ratio). As for the olefins **18a** and **c**, the *Z*-isomers are formed predominantely. If one compares both elimination methods, the Raney-Ni induced elimination **16**→**18** (see above) is the method of choice, since it affords the olefins **18** regiospecifically.

On acid hydrolysis the **18**/**25**-mixtures gave (besides L-valinate **8**) the α-alkenyl glycine esters **21** and (from **25**) the α-keto esters **26**. The latter could be extracted from the acid aqueous solution with ether.



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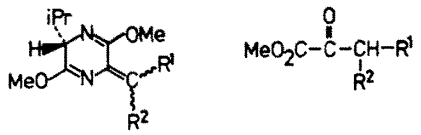


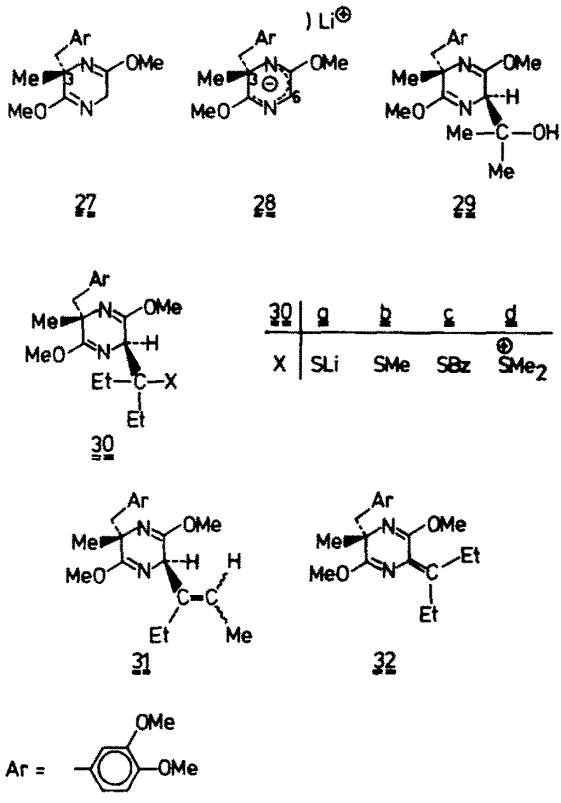
25 **26**

Synthesis of methyl (R)-2-*amino*-3-*ethyl-pentenoate* **21a** *via the bis-lactim ether* **27**

As described previously,[18] the lithiated bis-lactim ether **28**—obtained from **27**[18] and butyllithium—reacts with acetone with de ≈94% to give the addition product **29** with (6*R*)-configuration.[9] The chiral auxiliary in **27** (providing C-3) is (*S*)-O,O-dimethyl-α-methyldopa, the precursor of the antihypertensive drug (*S*)-α-methyldopa.[19] Analogously, **28** reacted with pentane-3-thione to give the addition product **30a** with de >95%; only one diastereomer was detectable in the ^{1}H- and ^{13}C-NMR spectrum. The exceedingly high diastereoface differentiation in the addition of the thioketone is surprising. To us it indicates that the anion of **28** has a folded conformation; the dimethoxybenzyl group is "turned inside" and the dimethoxyphenyl group faces the heterocyclic anion providing efficient shielding for the Si-site of the prochiral C-6 in **28**.

On dimethyl sulfide elimination the sulfonium salt **30d** furnished a 76:24-mixture of the Hofmann olefin **31** (*Z*:*E* = 4) and the Saytzeff olefin **32**. On hydrolysis, this mixture afforded the amino acid methyl ester **21a** (*E*:*Z* = 4), which was enantiomerically pure by NMR standard [Eu(hfc)$_3$ as chiral shift reagent].

Addendum: Starting with **15a** (R^1=Et, R^2=Me), (*S*)-(−)-2-amino-3-ethyl-3-thio-pentanoic acid ((*S*)-(−)-β,β-diethylcysteine) ($[\alpha]_D^{22} = -83.0°$ (*c* = 1.0, 1N HCl)) has been prepared, the bishomolog of D-penicillamine.



EXPERIMENTAL

α-Alkenyl glycines of type **10**

2-[(Dimethyl t-butyl)silyl]alkanals **2**. **2a** and **2b** were prepared according to lit.[10]

Compound **2c**: (a) 2-(*Dimethyl t-butyl*)*silyl*-2-*methyl-propyliden-cyclohexylimine* (**13**). 3 mmol t-BuLi (1.7 ml of a 1.8 N soln in pentane) was added at −70° to a soln of 0.58 g (2.3 mmol) freshly distilled **11** in 7 ml THF and stirred for 2 hr at −70° (formation of **12**!). A soln of 0.57 g (4 mmol) MeI in 5 ml THF was added and stirring continued for 30 min at −70° and for 4 hr at 0°. After warming to room temp the solvent was removed *in vacuo*, the residue shaken with *ca* 30 ml ether and twice with phosphate buffer soln (pH = 7). The ether soln was dried with $MgSO_4$. Usual workup gave 0.48 g (78%) **13** that was used without further purification. ^{1}H-NMR($CDCl_3$): δ = 1.16 (s; CH_3), 0.80–1.90 (2m; C_6H_{11}), 7.65 (s; CH=N).

(b) 2-(*Dimethyl t-butyl*)*silyl*-2-*methyl-propanal* (**2c**). The soln of 0.13 g (2.1 mmol) glacial AcOH in 2.5 ml water was added to a soln of 0.56 g (2.1 mmol) **13** in 5 ml CH_2Cl_2 and stirred for 1 hr; 20 ml ether was added and the organic layer separated. The aqueous layer was shaken with water, $NaHCO_3$ aq soln and again with water. The organic layer was dried with $MgSO_4$. Usual workup gave 0.31 g (79%) **2c**; b.p. 80–90°/0.5 torr (bulb-to-bulb-distillation)- IR(film): ν = 1710 cm^{-1} (C=O). ^{1}H-NMR($CDCl_3$): δ = 1.24 (s; CH_3), 9.63 (s; CHO). (Found: C, 64.40; H, 11.95. Calc for $C_{10}H_{22}OSi$ (186.4): C, 64.45: H, 11.90%).

Compounds **7** (*General Procedure*)

BuLi (11 mmol; 6.5 ml of a 1.7 N soln in hexane) was added (syringe!) at −70° to a soln of 1.84 g (10 mmol) ether **5**[20] in 20 ml THF. After 10 min stirring, the soln of 10 mmol **2** in 15 ml THF was added and stirred for 3–4 hr at −70°.

A soln of 0.66 g (11 mmol) glacial AcOH in 5 ml THF was added. After warming to room temp the solvent was evaporated *in vacuo* and the residue shaken with 30 ml ether and 20 ml water. After separation, the water layer was extracted twice with 10 ml ether. The ether layers were dried with $MgSO_4$. Usual workup. The crude compounds **7** were bulb-to-bulb distilled.

(3R,6S,1'R,S) - 2,5 - *Dimethoxy* - 3 - [1' - *hydroxy* - 2' - (*dimethyl t - butyl*)*silyl* - *eth* - 1' - *yl*] - 6 - *isopropyl* - 3,6 - *dihydropyrazine* (**7a**)

Compound **5** (1.75 g; 9.5 mmol) and **2a** (1.50 g; 9.5 mmol). Workup after 3 hr, yield: 2.46 g (76%) **7a**; b.p. 120–130°/0.2 torr; (3*R*,6*S*,1'*S*):(3*R*,6*S*,1'*R*) *ca* 3.8; no (3*S*)-diastereomers detectable in the ^{13}C-NMR spectrum. De at C-3 > 95%.

IR(film): ν = 3500–3200 (OH), 1690 cm^{-1} (N=C). ^{1}H-NMR ($CDCl_3$): $\delta = -0.04$ and -0.01 (2s; 6H, $Si(CH_3)_2$), 0.67 and 0.99 (2d, J = 7 Hz; 6H, $CH(CH_3)_2$), 0.80 (s; 9H, $C(CH_3)_3$), 3*R*,6*S*,1'*R*), 0.84 (s; 9H, $C(CH_3)_3$), 3*R*,6*S*,1'*S*), 0.91 (d, J = 7 Hz; 2H, $SiCH_2$), 2.21 (dsp, J = 3 and 7 Hz; $CH(CH_3)_2$), 2.00–2.50 br.; 1H, OH), 3.63 and 3.66 (2s; 6H, OCH_3), 3.86 and 3.93 (2dd, J = 3 Hz, ^{3}J = 3 Hz; 2H, 3- and 6-H), 4.11 (br. dt, J = 3 and 7 Hz; 1H, CHOH). ^{13}C-NMR($CDCl_3$): (3*R*,6*S*,1'*S*): $\delta = -5.89$ and -4.95 ($Si(CH_3)_2$), 16.56 and 17.66 ($CH_2SiC(CH_3)_3$), 16.78 and 19.04 ($CH(CH_3)_2$), 26.50 ($C(CH_3)_3$), 31.98 ($CH(CH_3)_2$), 52.50 and 52.55 (OCH_3), 60.99 and 61.52 (3- and 6-CH), 70.81 (C–OH), 162.29 and 165.41 (C=N). (3*R*,6*S*,1'*R*): $\delta = -6.07$ and -4.65 ($Si(CH_3)_2$), 15.11 and 17.66 ($CH_2SiC(CH_3)_3$), 16.74 and 19.04 ($CH(CH_3)_2$), 26.50 ($C(CH_3)_3$), 32.24 ($CH(CH_3)_2$), 52.29 and 52.63 (OCH_3), 61.21 and 61.25 (3- and 6-CH), 69.52 (C–OH), 162.02 and 165.04 (C=N). (Found: C, 59.74; H, 9.85. Calc. for $C_{17}H_{34}N_2O_3Si$ (342.6): C, 59.61; H, 10.00%).

(3R,6S,1'R,S,2'R,S) - 2,5 - *Dimethoxy* - 3 - [1' - *hydroxy* - 2' - (*dimethyl t - butyl*)*silyl* - *prop* - 1' - *yl*] - 6 - *isopropyl*-3,6 - *dihydropyrazine* (**7b**)

Compound **5** (0.37 g; 2 mmol) and **2b** (0.34 g; 2 mmol). Workup after 4 hr, yield: 0.57 g (80%) **7b**; b.p. 110–120°/0.1 torr; (3*R*,6*S*,1'*S*,2'*S*) : (3*R*,6*S*,1'*S*,2'*R*) : (3*R*,6*S*,1'*R*,2'*S*) : (3*R*,6*S*,1'*R*,2'*R*) = 2.6:2.6:1:1; no (3*S*)-diastereomers detectable in the ^{13}C-NMR spectrum.

IR(film): ν = 3400–3200 (OH), 1685 cm^{-1} (N=C). ^{1}H-NMR($CDCl_3$): $\delta = -0.06$, -0.04, -0.03 and 0.01 (4s; 24H, $Si(CH_3)_2$), 0.64, 0.66, 0.98 and 1.00 (4d, J = 7 Hz; 36H, $CH(CH_3)_2$ and CH_3 CHSi), 0.81, 0.82, 0.85 and 0.87 (4s; 36H, $C(CH_3)_3$), 1.16–1.50 (m; 4H, CH_3CHSi), 2.00–2.30 (m; 4H, $CH(CH_3)_2$), 3.63, 3.65 and 3.66 (3s; 24H, OCH_3), 3.74–4.12 (m; 16H, 3- and 6-CH, CHOH). ^{13}C-NMR($CDCl_3$): (3*R*,6*S*,1'*S*,2'*R*,*S*): δ = 27.12 and 27.63 ($C(CH_3)_3$), 31.77 and 31.94 ($CH(CH_3)_2$), 73.96 and 74.70 (C–OH), 162.93, 163.06, 165.18 and 166.33 (C=N); (3*R*,6*S*,1'*R*,2'*R*,*S*): δ = 26.34 and 27.02 ($C(CH_3)_3$), 31.08 and 31.63 ($CH(CH_3)_2$), 70.83 and 73.05 (C–OH), 162.43, 163.46, 163.84 and 165.71 (C=N). (Found: C, 61.02; H, 10.18. Calc for $C_{18}H_{36}N_2O_3Si$ (356.6): C, 60.63; H, 10.18%).

(3R,6S,1'R,S) - 2,5 - *Dimethoxy* - 3 - [1' - *hydroxy* - 2' - *methyl* - 2' - (*dimethyl t - butyl*)*silyl* - *prop* - 1' - *yl*] - 6 - *isopropyl* - 3,6 - *dihydropyrazine* (**7c**)

Compound **5** (0.18 g; 1 mmol) and **2c** (0.19 g; 1 mmol), yield: 0.26 g (70%) **7c**; b.p. 140–150°/0.1 torr; (3*R*,6*S*,1'*S*):(3*R*,6*S*,1'*R*) *ca* 1.7:1; no 3*S*-diastereomers detectable in the ^{13}C-NMR spectrum.

IR(film): ν = 3500–3200 (OH), 1685 cm^{-1} (N=C). (3*R*,6*S*,1'*S*): ^{1}H-NMR($CDCl_3$): $\delta = -0.06$ (s; 6H, $Si(CH_3)_2$), 0.67 and 0.97 (2d, J = 7 Hz; 6H, $CH(CH_3)_2$), 0.93 (s; 9H, $C(CH_3)_3$), 1.03 and 1.05 (2s; 6H, $(CH_3)_2CSi$), 1.54 (br.s; 1H, OH), 2.06–2.34 (m; 1H, $CH(CH_3)_2$), 3.62 and 3.66 (2s; 6H, OCH_3), 3.84–3.97 and 4.02–4.16 (2m; 2H, 3- and 6-CH), 4.13 (d, J = 3 Hz; 1H, CHOH); ^{13}C-NMR($CDCl_3$): $\delta = -6.12$ and -5.61 ($Si(CH_3)_2$), 16.97 and 19.00 ($CH(CH_3)_2$), 19.00 (CH_3)$_3$), 20.27 and 22.19 (CH_3), 28.53 ($C(CH_3)_3$), 29.25 (C–Si), 32.07 ($CH(CH_3)_2$), 52.50 and 52.67 (OCH_3), 60.53 and 60.72 (3- and 6-CH), 74.99 (C–OH), 162.95 and 165.85 (C=N). (3*R*,6*S*,1'*R*): ^{1}H-NMR($CDCl_3$): $\delta = -0.02$ (s; 6H, $Si(CH_3)_2$), 0.61 and 1.00 (2d, J = 7 Hz; 6H, $CH(CH_3)_2$, 0.92 (s; 9H, $C(CH_3)_3$), 3.64 and 3.65 (2s; 6H,OCH_3), 4.19 (d, J = 3 Hz; 1H, CHOH); ^{13}C-NMR($CDCl_3$): $\delta = -6.22$ and -5.51 ($Si(CH_3)_2$), 16.53 and 19.48 ($CH(CH_3)_2$), 19.00 ($C(CH_3)_3$), 19.10 and 21.77 (CH_3), 28.53 ($C(CH_3)_3$), 30.23 (C–Si), 31.46 ($CH(CH_3)_2$), 52.05 and 52.82 (OCH_3), 59.91 and 60.95 (3- and 6-CH), 76.15 (C–OH), 162.30 and 163.19 (C=N). (Found: C, 61.39; H, 10.14. Calc for $C_{19}H_{38}N_2O_3$ Si (370.6): C, 61.58; H, 10.34%).

Compounds **9**; hydrolysis of compounds **7** (*General Procedure*)

The suspension of 2 mmol **7** in 16 ml (4 mmol) 0.25 N HCl was stirred for 12 hr at room temp. The mixture was extracted with ether which was discharged. The solvent was concentrated *in vacuo* (bath temp 40–60°) to 1–2 ml, 10 ml ether were added and then with shaking conc ammonia till pH 8–10. The ether layer was separated, the water layer saturated with NaCl and three times extracted with 5–10 ml ether. The combined ether layer was dried with $MgSO_4$. Usual workup. The residual mixture of **8** and **9** was chromatographed on silica gel (low pressure) with ether–acetone 4:1. **8** was eluted before **9**.

Methyl(2R,3S,R) - 2 - *amino* - 3 - *hydroxy* - 4 - (*dimethyl t - butyl*) *silyl* - *butanoate* (**9a**)

Compound **7a** (0.68 g; 2 mmol), yield, 0.26 g (53%) **9a**; R_f = 0.66 (R_f for **8** = 0.15); **9a** can be distilled without decomposition; b.p. 110–120°/0.1 torr (bulb-to-bulb); (2R,3*S*):(2*R*,3*R*) *ca* 2.4 (^{1}H-NMR spectroscopically with Eu(fod)$_3$).

IR(film): ν = 3550–3150 (NH_2 and OH), 1740 (C=O), 1640–1680 cm^{-1} (NH_2). ^{1}H-NMR($CDCl_3$): δ = 0.03 and 0.06 (2s; 6H, $Si(CH_3)_2$), 0.78–0.91 (m: 2H, $SiCH_2$), 0.86 (s; 9H, $C(CH_3)_3$), 2.31–2.55 (br.s; 3H, NH_2 and OH), 3.23–3.35 (m; 1H, 2-H), 3.68 (s; 3H, OCH_3), 3.80–4.03 (m; 1H, 3-H). (Found: C, 53.41; H, 10.11. Calc for $C_{11}H_{25}NO_3Si$ (247.4): C, 53.40; H, 10.19%).

Methyl(2R,3S,R,4R,S)2 - *amino* - 3 - *hydroxy* - 4 - (*dimethyl t - butyl*)*silyl pentanoate* (**9b**)

Compound **7b** (0.57 g; 1.6 mmol) and 0.25 N HCl (12.8 ml; 3.2 mmol), yield: 0.24 g (58%) **9b**; R_f = 0.51 (R_f for **8** = 0.15); **9b** can be distilled without decomposition; b-p. 140–150°/0.1 torr (bulb-to-bulb distillation); (2*R*,3*S*, 4*R*):(2*R*, 3*S*, 4*S*):(2*R*, 3*R*, 4*R*):(2*R*, 3*R*, 4*S*) *ca* 2.1:2.1:1:1 (^{1}H-NMR spectroscopically determined, t-Bu and OMe-signals).

IR(film): ν = 3500–3100 (NH_2 and OH), 1740 (C=O), 1630–1670 cm^{-1} (NH_2). ^{1}H-NMR($CDCl_3$): δ = 0.01, 0.03, 0.05 and 0.06 (4s; 12H, $Si(CH_3)_2$), 0.87 and 0.88 (2s; 18H, $C(CH_3)_3$, 2*R*,3*R*,4*R*,*S*), 0.90 and 0.92 (2s; 18H, $C(CH_3)_3$, 2*R*,3*S*,4*R*,*S*), 0.98 (d, J = 7 Hz; 6H, CH_3CH), 1.06–1.39 (m; 2H, CH_3CH), 1.96–2.14 (br.s; 6H, NH_2 and OH), 3.22–3.91 (m; 4H, 2- and 3-H), 3.70 and 3.71 (2s; 6H, OCH_3, 2*R*,3*R*,4*R*,*S*), 3.73 (s; 6H,OCH_3, 2*R*,3*S*,4*R*,*S*). (Found: C, 55.46; H, 10.42. Calc for $C_{12}H_{27}NO_3Si$ (261.4): C, 55.13: H, 10.41%).

(R)-α-*Alkenyl glycines* **10** *from* **9** (*General Procedure*)

The soln of 1 mmol **9** in 10 ml 5 N HCl was refluxed for 1 hr. The solvent was evaporated *in vacuo*, the residue dried for 30 min at 30–40°/0.1 torr. 5–10 ml EtOH were added, the mixture was refluxed, 2–3 ml propene oxide were added and reflux continued for 15 min. After cooling to 0°, the precipitated **10** was isolated by suction, washed on the funnel with ether and dried *in vacuo* over P_4O_{10}.

(R)-(−)-*Vinyl glycine* (**10a**)

Compound **9a** (0.20 g), yield: *Ca* 50 *mg* (62%) **10a**;

$[\alpha]_D^{20} = -81.1°$ (c = 0.2, H_2O) [lit[11] $[\alpha]_D^{22} = -93.8°$ (*c* = 1.5, H_2O)].

^{1}H-NMR(D_2O): $\delta = 4.27$ (br.d, J = 7 Hz, ^{4}J < 1 Hz; 1H, α-H), 5.46 (br.dd, J = 2 Hz, $J_{trans} = 17$ Hz, ^{4}J < 1 Hz; 1H, *trans*-HC=CH–CH), 5.47 (br.dd, ^{2}J = 2 Hz, $J_{cis} = 10$ Hz, ^{4}J < 1 Hz; 1H, cis-HC = CH – CH), 5.99 (ddd, J = 7 Hz, $J_{cis} = 10$ Hz, $J_{trans} = 17$ Hz; 1H, H_2C=CH–CH). Found: C, 47.64; H, 7.17. Calc for $C_4H_7NO_2$ (101.1): C, 47.52; H, 6.98%).

(R)-(−)-E/Z-2-*Amino*-3-*pentenoic acid* (α-*propenyl glycine*) (**10b**)

Compound **9b** (0.13 g; 0.5 mmol), yield, *ca* 40 mg (70%) **10b**; $[\alpha]_D^{20} = -153.8°$ (*c* = 1.2, H_2O); $[\alpha]_D^{20} = -152.3°$ (*c* = 0.4, 1 N HCl). *E*:*Z* *ca* 1:1.

^{1}H-NMR(D_2O): $\delta = 1.73$ and 1.76 (2dd, J = 7 Hz, ^{4}J = 1.5 Hz; je 3H, CH_3 von *E*- und *Z*-**10b**), 4.15 (br.d, J = 8 Hz, ^{4}J < 1 Hz; 1H, α-H), 5.20–6.16 (m: 2H, CH=CH). (Found: C, 52.60; H, 7.73. Calc for $C_5H_9NO_2$ (115.1): C, 52.16; H, 7.88%).

(R)-α-*Alkenyl glycine methyl esters* **21** *and* (R)-α-*alkenyl glycines* **23** *from the bis-lactim ether* **5**

Compounds **16** (*General Procedure*). A 1.55 N soln of BuLi (2.7 ml) in hexane (4.2 mmol BuLi) were added (syringe!) at −70° to a stirred soln of 0.74 g (4 mmol) bis-lactim ether **5**[20] in 10 ml dry THF. After 10 min (formation of **6**) the soln of 4.2 mmol thioketone (freshly prepared and distilled, see below) in 5 ml THF was added at −70° and stirring continued for 12 hr at −70°. A soln of 0.6 g (4.2 mmol) MeI [in one case 0.72 g (4.2 mmol) benzyl bromide] in 5 ml THF was added. After warming, stirring was continued at room temp for 40 hr. The solvent was evaporated *in vacuo*, the residue shaken with 15 ml ether and 20 ml water, the layers separated and the water layer extracted twice with 10 ml ether. The combined ether soln was dried with $MgSO_4$ with usual workup. The crude compounds **16** were bulb-to-bulb distilled *in vacuo*.

(3S,6S) - 2,5 - *Dimethoxy* - 6 - *isopropyl* - 3 - (1′ - *methylthio* - 1′ - *ethylprop* - 1′ - *yl*) - 3,6 - *dihydropyrazine* (**16a**)

Pentane-2-thione (0.43 g; 4.2 mmol), yield: 0.91 g (76%) **16a**; b.p. 160–170°/10 torr. Only one diastereomer detectable in the ^{1}H- and ^{13}C-NMR spectrum. De > 95%.

IR(film): $\nu = 1695\ cm^{-1}$ (C=N). ^{1}H-NMR($CDCl_3$): $\delta = 0.67$ and 1.10 (2d, J = 7 Hz; 6H, $CH(CH_3)_2$), 0.96 (t, J = 7 Hz; 3H, CH_2CH_3), 0.97 (t, J = 7 Hz; 3H, CH_2CH_3), 1.70 (q; J = 7 Hz; 2H, CH_2), 1.74 (q, J = 7 Hz; 2H, CH_2), 1.86 (s; 3H, S–CH_3), 2.39 (dsp, J = 3 and 7 Hz; 1H, $CH(CH_3)_2$), 3.66 and 3.71 (2s; 6H, 2- and 5-OCH_3), 4.07 (dd, J = 3 Hz, ^{5}J = 3 Hz; 1H, 6-H), 4.13 (d, ^{5}J = 3 Hz; 1H, 3-H). ^{13}C-NMR($CDCl_3$): $\delta = 8.05$, 8.37 and 11.83, 16.43 ($CH(CH_3)_2$ and CH_2–CH_3), 19.41 (S–CH_3), 26.06 and 26.22 (CH_2), 30.35 ($CH(CH_3)_2$), 52.02 and 52.51 (OCH_3), 57.94 (–C–S), 60.63 and 61.27 (3- and 6-CH), 162.65 and 165.23 (C=N). High resolution MS: (Found: 300.1871. Calc for $C_{15}H_{28}N_2O_2S$; 300.1865).

(3S,6S) - 3 - (1′ - *Benzylthio* - 1′ - *ethylprop* - 1′ - *yl*) - 2,5-*dimethoxy* - 6 - *isopropyl* - 3,6 - *dihydropyrazine* (**16a**, SBz *instead of* SMe)

Pentane-2-thione (0.43 g; 4.2 mmol). After 12 hr stirring at −70° addition of 0.72 g (4.2 mmol) benzyl bromide; reflux for 12 hr, yield: 1.07 g (71%) **16a** (SBz instead of SMe); b.p. 120–130°/0.01 torr. Only one diastereomer detectable in the ^{1}H-NMR spectrum. De > 95%.

IR(film): $\nu = 1690\ cm^{-1}$ (C=N). ^{1}H-NMR($CDCl_3$): $\delta = 0.67$ and 1.14 (2d, J = 6.5 Hz; 6H, $CH(CH_3)_2$), 0.98 (t, J = 7 Hz; 3H, CH_2–CH_3), 1.02 (t, J = 7 Hz; 3H, CH_2–CH_3), 1.74 (q, J = 7 Hz; 2H CH_2–CH_3), 1.77 (q, J = 7 Hz; 2H, CH_2–CH_3), 2.39 (dsp, J = 1 und 6 Hz; 1H, $CH(CH_3)_2$), 3.54 (s; 2H, CH_2–Ph), 3.66 and 3.71 (2s; 6H, 2- and 5-OCH_3). (Found: C, 67.77; H, 8.59. Calc for $C_{21}H_{32}N_2O_2S$ (376.6): C, 66.98; H, 8.57%).

(3S,6S) - 2,5 - *Dimethoxy* - 6 - *isopropyl* - 3 - (1′ - *methylthio-cyclohex* - 1′ - *yl*) - 3,6 - *dihydropyrazine* (**16b**)

Cyclohexanethione (0.48 g; 4.2 mmol), yield: 0.5 g (40%) (**16b**); b.p. 170°/8 torr.

Careful examination of the ^{1}H-NMR spectrum revealed a diastereomer ratio of *ca* 60:1 (de *ca* 97%) (SMe signals at $\delta = 1.88$ and 1.89).

IR(film): $\nu = 1685\ cm^{-1}$ (C=N). ^{1}H-NMR($CDCl_3$): (3*S*,6*S*)-diastereomer: $\delta = 0.64$ and 1.09 (2d, J = 6.5 Hz; 6H, $CH(CH_3)_2$), 1.4–2.0 (m: 10 H, C_6H_{10}), 1.88 (s; 3H, S–CH_3), 2.35 (dsp, J = 1.5 and 6.5 Hz; 1H, $CH(CH_3)_2$), 3.65 and 3.68 (2s; 6H, 2- and 5-OCH_3), 4.03 and 4.05 (3-H and 6-H, J = 1.5 Hz, ^{5}J ≤ 1 Hz). (3*R*,6*S*)-diastereomer: 1.89 (s; 3H, S–CH_3). High resolution MS: (Found: 312.1872. Calc for $C_{16}H_{28}N_2O_2S$: 312.1865).

(3S,6S) - 2,5 - *Dimethoxy* - 6 - *isopropyl* - 3 - (1′ - *methylthio* - 1′ - *propylbut* - 1′ - *yl*) - 3,6 - *dihydropyrazine* (**16c**)

Heptane-4-thione (0.55 g; 4.2 mmol), yield, 0.47 g (36%) **16c**; b.p. 170–180°/10 torr. Only one diastereomer detectable in the ^{1}H-NMR spectrum. De > 95%.

IR(film): $\nu = 1690\ cm^{-1}$ (C=N). ^{1}H-NMR($CDCl_3$): $\delta = 0.68$ and 1.12 (2d, J = 6.5 Hz; 6H, $CH(CH_3)_2$), 0.94 and 0.97 (2t, J = 4 Hz; 6H, $[(CH_2)_2$–$CH_3]_2$), 1.23–1.76 (m; 8H, $[(CH_2)_2$–$CH_3]_2$), 1.88 (s; 3H, S–CH_3), 2.37 (dsp, J = 3 and 6.5 Hz; 1H, $CH(CH_3)_2$), 3.70 and 3.72 (2s; 6H, 2- and 5-OCH_3), 4.09 (dd, J = 3 Hz, ^{5}J = 3 Hz; 1H, 6-H), 4.14 (d, J = 3 Hz; 1H, 3-H). High resolution MS: Found: 328.2185. Calc for $C_{17}H_{32}N_2O_2S$ (328.5): 328.2177.

(3S,6S,1′S,R) - 2,5 - *Dimethoxy* - 6 - *isopropyl* - 3 - (1′ - *methylthio* - 1′ - *methyl* - *prop* - 1′ - *yl*) - 3,6 - *dihydropyrazine* (**16d**)

Butane-2-thione (0.37 g; 4.2 mmol), yield: 0.60 g (52%) **16d**; b.p. 140°/8 torr. (3*S*,6*S*,1′*S*):(3*S*,6*S*,1′*R*) = 1.05:1 (determined by ^{1}H-NMR, signals at $\delta = 1.33$ and 1.37 or 1.94 and 1.97). (3*R*,6*S*)-diastereomers were not detectable in the ^{1}H-NMR spectrum, even not with Eu(fod)$_3$.

IR(film): $\nu = 1690\ cm^{-1}$ (C=N). ^{1}H-NMR($CDCl_3$): (3*S*,6*S*,1′*S*)-diastereomer: $\delta = 0.68$ and 1.13 (2d, j = 7 Hz; 6H, $CH(CH_3)_2$, 1.05 (t, J = 7 Hz; 3H, CH_2–CH_3), 1.33 (s; 3H, 1′–C–CH_3), 1.78 (q, J = 7 Hz; CH_2–CH_3), 1.97 (s; S–CH_3), 2.38 (dsp, J = 3 and 7 Hz; $CH(CH_3)_2$), 3.71 and 3.73 (2s; 2- and 5-OCH_3), 4.01 (dd, J = 3 Hz, ^{5}J = 3 Hz; 1H, 6-H), 4.12 (d, J = 3 Hz; 1H, 3-H); (3*S*,6*S*,1′*R*)-diastereomer: 1.37 (s; 3H, 1′–C–CH_3), 1.75 (q, J = 7 Hz; CH_2–CH_3), 1.94 s; CH_3). High resolution MS: Found: 286.1715. Calc for $C_{14}H_{26}N_2O_2S$: 286.1709.

Compounds **18** *and* **19**; *methylthiol elimination with Raney*–Ni (*General Procedure*)

A suspension of Raney–Ni prepared from 6 g Raney–Ni alloy[15] according to lit[16] in 20 ml 75% EtOH was added to the soln of 3 mmol **16** in 30 ml 75% EtOH and the mixture refluxed for 3 hr. The catalyst was filtered off when still hot and washed three times with hot EtOH. The solvent was evaporated *in vacuo* and the residual compounds **18** bulb-to-bulb distilled.

E/Z-(3R,6S) - 2,5 - *Dimethoxy* - 3 - (1′ - *ethylprop* - 1′ - *en*-1′ - *yl*) - 6 - *isopropyl* - 3,6 - *dihydropyrazine* (**18a**)

Compound **16a** (SBz instead of SMe) (1.13 g; 3 mmol), yield, 0.67 g (88%) *E*/*Z*-**18a** (*E*:*Z* = 1.3:1); b.p. 130°/1 torr.

IR(film): $\nu = 1620$ (C=C), $1695\ cm^{-1}$ (C=N). ^{1}H-NMR ($CDCl_3$): *Z*-**18a**: $\delta = 0.72$ and 1.09 (2d; 6H, $CH(CH_3)_2$), 0.96 (t, J = 7 Hz; 3H, CH_2–CH_3), 1.68 (d, J = 7 Hz; 3H, C=C–CH_3), 1.95 (q, J = 7 Hz; 2H, C=C–CH_2), 2.32 (dsp, J = 3 and 7 Hz; 1H, $CH(CH_3)_2$), 3.66 and 3.67 (2s; 6H, 2- and 5-OCH_3), 3.96 (dd, J = 3 Hz, ^{5}J = 3 Hz; 1H, 6-H), 4.48 (d, J = 3 Hz; 1H, 3-H), 5.47 (q, J = 7 Hz; 1H, C=C–H). *E*-**18a**: $\delta = 0.76$ and 1.09 (2d; 6H, $CH(CH_3)_2$), 0.98 (t, J = 7 Hz; 3H, CH_2–CH_3), 1.78 (d, J = 7 Hz; 3H, C=C–CH_3),

1.95 (q, J = 7 Hz; 2H, C=C–CH_2), 2.32 (dsp, J = 3 and 7 Hz; 1H, $CH(CH_3)_2$), 3.70 and 3.71 (2s; 6H, 2- and 5-OCH_3), 4.04 (dd, J = 3 Hz, ^{5}J = 4 Hz; 1H, 6-H), 5.02 (d, J = 4 Hz; 1H, 3-H), 5.47 (q, J = 7 Hz; 1H, C=C–H). High resolution MS: Found: 252.1838. Calc for $C_{14}H_{24}N_2O_2$: 252.1832.

(3R,6S) - 3 - (1′ - *Cyclohex* - 1′ - *en* - 1′ - *yl*) - 2,5 - *dimethoxy* - 6 - *isopropyl* - 3,6 - *dihydropyrazine* (**18b**)

Compound **16b** (0.94 g; 3 mmol), yield, 0.74 g (93%) **18b**; b.p. 160°/10 torr.

IR(film): ν = 1620 (C=C), 1685 cm^{-1} (C=N). ^{1}H-NMR ($CDCl_3$): δ = 0.72 and 1.09 (2d, J = 7 Hz; 6H, $CH(CH_3)_2$), 1.40–2.20 (m; 8H, –$(CH_2)_4$), 2.32 (dsp, J = 3 and 7 Hz; 1H, $CH(CH_3)_2$), 3.68 and 3.70 (2s; 6H, 2- and 5-OCH_3), 3.93 (dd, J = 3 Hz, ^{5}J = 3 Hz; 1H, 6-H), 4.41 (d, J = 3 Hz; 1H, 3-H), 5.68 (m; 1H, C=C–H). High resolution MS: Found: 264.1838. Calc for $C_{15}H_{25}N_2O_2$: 264.1832.

E/Z - (3R,6S) - 2,5 - *Dimethoxy* - 6 - *isopropyl* - 3 - (1′ - *propylbut* - 1′ - *en* - 1′ - *yl*) - 3,6 - *dihydropyrazine* (**18c**)

Compound **16c** (0.99 g; 3 mmol), yield, 0.71 g (84%) **18c**; b.p. 180°/8 torr.

IR(film): ν = 1620 (C=C), 1690 cm^{-1} (C=N). ^{1}H-NMR ($CDCl_3$): *Z*-**18c**: δ = 0.72 and 1.09 (2d, J = 7 Hz; 6H, $CH(CH_3)_2$), 0.85 and 1.02 (2t, J = 7 Hz; 6H, CH_2–CH_3 and $(CH_2)_2$–CH_3), 1.30 (m; 2H, –CH_2–CH_2–CH_3), 1.86 and 2.20 (2m; 4H, –CH_2–CH_2–CH_3 and –CH–CH_3), 2.30 (dsp, J = 3 and 7 Hz; 1H, $CH(CH_3)_2$), 3.69 and 3.73 (2s; 6H, 2- and 5-OCH_3), 4.08 (dd, J = 3 Hz, ^{5}J = 3.5 Hz; 1H, 6-H), 4.43 (d, J = 3.5 Hz; 1H, 3-H), 5.36 (t, J = 7.5 Hz; 1H, C=C–H). *E*–**18c**: δ = 0.71 and 1.07 (2d, J = 7 Hz; 6H, $CH(CH_3)_2$), 0.92 and 0.97 (2t, J = 7 Hz; 6H, CH_2–CH_3 and $(CH_2)_2$–CH_3), 2.45 (m; 2H, –CH_2CH_2–CH_3), 1.88 and 2.23 (2m; 4H, –CH_2–CH_2–CH_3 and –CH_2–CH_3), 2.30 (dsp, J = 3 and 7 Hz; 1H, $CH(CH_3)_2$), 3.66 and 3.69 (2s; 6H, 2- and 5-OCH_3), 3.98 (dd, J = 3 Hz, ^{5}J = 3.5 Hz;1H, 6-H), 4.93 (d, J = 3.5 Hz; 1H, 3-H), 5.36 (t, J = 7.5 Hz; 1H, C=C–H). High resolution MS: Found: 280.2151. Calc for $C_{16}H_{28}N_2O_2$: 280.2144.

(3R,6S) - 2,5 - *Dimethoxy* - 3 - (1′ - *ethyl* - *ethenyl*) - 6 - *isopropyl* - 3,6 - *dihydropyrazine* (**19**) *and* Z/E - (3R,6S) - 2,5-*dimethoxy* - 6 - *isopropyl* - 3 - (1′ - *methyl* - *prop* - 1′ - *en*-1′ - *yl*) - 3,6 - *hydropyrazine* (**18d**)

Compound **16d** (0.86 g; 3 mmol), yield, 0.61 g (86%) 74:16:10-mixture of **19**:*Z*-**18d**:*E*-**18d**; b.p. 130–140°/8 torr.

IR(film); δ = 1635 (C=C), 1695 cm^{-1} (C=N). ^{1}H-NMR($CDCl_3$): **19**: δ = 0.66 and 0.71 (2d, J = 7 Hz; 6H, $CH(CH_3)_2$), 1.04 (t, J = 7 Hz; 3H, CH_2–CH_3), 1.68 (q, J = 7 Hz; 2H, CH_2–CH_3), 2.30 (dsp, J = 3 and 7 Hz; 1H, $CH(CH_3)_2$), 3.70 (2s; 6H, 2- and 5-OCH_3), 3.70–4.20 (m: 4H, 3-H, 6-H, =CH_2). *Z*-**18d**: δ = 0.72 and 0.95 (2d, J = 7 Hz; 6H, $CH(CH_3)_2$), 1.52 (d, ^{4}J = 1 Hz; 3H, HC=C–CH_3), 1.77 (d, J = 7 Hz; 3H, =CH–CH_3), 2.02 (dsp, J = 3 and 7 Hz; 1H, $CH(CH_3)_2$), 3.68 (2s; 6H, 2- and 5-OCH_3), 4.42 (d, J = 3 Hz; 1H, 3-H), 5.54 (q, J = 7 Hz, ^{4}J = 1 Hz; 1H, C=C–H). *E*-**18d**: δ = 0.74 and 0.90 (2d, J = 7 Hz; 6H, $CH(CH_3)_2$), 1.48 (d, ^{4}J = 1 Hz; 3H, HC=C–CH_3), 1.79 (d, J = 7 Hz; 3H, =CH–CH_3), 2.02 (dsp, J = 3 and 7 Hz; 1H, $CH(CH_3)_2$), 3.68 (2s; 6H, 2- and 5-OCH_3), 4.97 (d, J = 3Hz; 1H, 3-H), 5.54 (q, J = 7 Hz, ^{4}J = 1 Hz; 1H, C=C–H). (Found: C, 65.48; H, 9.53. Calc for $C_{13}H_{22}N_2O_2$ (238.3): C, 65.52; H, 9.30%).

Compounds **18a–c** *and* **25a–c** *from the sulfonium salts* **24** (*General Procedure*)

MeI (1.42 g; 10 mmol) was added to a soln of 3 mmol **16** in 15 ml dry acetonitrile. The mixture was refluxed for 12–14 hr. The solvent was evaporated *in vacuo* and the residue shaken with 20 ml water and 10 ml ether. The layers were separated and the water layer extracted twice with 10 ml ether. The combined ether layer was dried with $MgSO_4$ with usual workup. The crude products **18/25** were purified by bulb-to-bulb distillation. The product ratios were analyzed by ^{1}H-NMR spectroscopy.

Compounds **18a** and (6*S*)-**25a**: 0.9 g (3 mmol) **16a**, yield, 0.55 g (73%) 88:12-mixture of *Z*/*E*-**18a** and **25a**.. *Z*:*E* = 2.5; b.p. 130°/1 torr.

Spectra of *Z*/*E*-**18a** see above.

Compound **25a**: ^{1}H-NMR($CDCl_3$): δ = 0.84 (d, J = 7 Hz; 3H, CH_3–CH–CH_3), 3.75 and 3.76 (2s; 6H, 2- and 5-OCH_3).

Compound **18b** *and* (6S) - 3 - *Cyclohexylidene* - 2,5 - *dimethoxy* - 6 - *isopropyl* - 3,6 - *dihydropyrazine*(**25b**)

Compound **16b** (0.94 g; 3 mmol), yield 0.53 g (67%) 90:10-mixture of **18b** and **25b**; b.p. 160°/10 torr.

IR(film): ν = 1620 (C=C), 1685 cm^{-1} (C = N). ^{1}H-NMR($CDCl_3$) for **25b** (for **18b** see above): δ = 0.93 and 1.22 (2d, $CH(CH_3)_2$), 3.74 and 3.76 (2s, 2- and 5-OMe). High resolution MS: Found: 264.1838. Calc for $C_{15}H_{24}N_2O_2$: 264.1832.

Compound **18c** *and* (6S) - 2,5 - *Dimethoxy* - 6 - *isopropyl* - 3 - (1′ - *propylbutylidene*) - 3,6 - *dihydropyrazine* (**25c**)

Compound **16d** (0.99 g; 3 mmol), yield, 0.67 g (80%) 87:13-mixture of *E*/*Z*-**18c** and **25c**. *Z*:*E* = 2.

IR(film): ν = 1620 (C=C), 1690 cm^{-1} (C=N). ^{1}H-NMR($CDCl_3$) for **25c** (for **18c** see above): δ = 0.70 (d, –CH–CH_3), 3.64 and 3.65 (2s, 2- and 5-OMe). High resolution MS: Found: 280.2151. Calc for $C_{16}H_{28}N_2O_2$: 280.2144.

(R)-α-*Alkenyl glycine methyl esters* **21** *and* α-*alkenyl glycines* **23**

Hydrolysis of **18** *or* **18/25**-*mixtures* (*General Procedure*). 2 mmol **18** (or the mixture of **18** and **25**, see above) were suspended in 40 ml 0.1 N HCl and vigorously stirred for 40–60 hr at room temp. The aqueous layer was extracted twice with 30 ml ether which was discarded (in case of the **18/25**-mixture it contained **26**). The solvent was evaporated *in vacuo* (bath temp 40–60°); *ca* 15 ml water and 20 ml ether were added to the residue and with vigorous shaking conc. ammonia till pH 8. The ether layer was separated and the water layer extracted three times with 15 ml ether. The combined ether layer was dried with $MgSO_4$ with usual workup. The crude mixture of **21** and valinate **8** was bulb-to-bulb distilled and **8** removed as forerun.

E/Z - *Methyl*(R) - 2 - *amino*-3 - *ethyl* - 3 - *pentenoate* (**21a**)

Compound **18a** (0.5 g; 2 mmol). Workup after 40 hr, yield: 0.23 g (73%) *E*/*Z*-**21a** (*E*:*Z* = 1.3:1); b.p. 130°/5 torr; $[\alpha]_D^{20}$ = −150.6° (*c* = 1.0, $CHCl_3$).

IR(film): ν = 1740 (C=O, 3200–3500 cm^{-1} (NH_2). ^{1}H-NMR($CDCl_3$): *E*-**21a**: δ = 1.04 (t, J = 7 Hz; 3H, CH_2–CH_3), 1.75 (d, J = 6 Hz; 3H, =CH–CH_3), 1.93 (s; 2H, NH_2), 2.16 (q, J = 7 Hz; 2H, CH_2–CH_3), 3.72 (s; 3H, OCH_3), 4.49 (s; 1H, α-H), 5.49 (q, J = 6 Hz; 1H, =CH). *Z*-**21a**: δ = 1.02 (t, J = 7 Hz; 3H, CH_2–CH_3), 1.67 (d, J = 6 Hz; 3H, =CH–CH_3), 1.93 (s; 2H, NH_2), 2.16 (q, J = 7 Hz; 2H, CH_2–CH_3), 3.72 (s; 3H, OCH_3), 3.99 (s; 1H, α-H), 5.49 (q, J = 6 Hz, =CH). (Found: C, 60.98; H, 9.92. Calc for $C_8H_{15}NO_2$ (157.2): C, 61.12; H, 9.62%).

Methyl (R) - (*cyclohex* - 1′ - *ene* - 1 - *yl*)*glycinate* (**21b**)

Compound **18b** (0.53 g; 2 mmol). Workup after 40 hr, yield: 0.26 g (76%) **21b**; b.p. 140–150°/10 torr. Enantiomerically pure by ^{1}H-NMR. $[\alpha]_D^{20}$ = −89.4° (*c* = 1.0,$CHCl_3$).

IR(film): ν = 1740 (C=O), 3200–3500 cm^{-1} (NH_2). ^{1}H-NMR($CDCl_3$): δ = 1.50–2.20 (m; 8H, –$(CH_2)_4$–), 1.78 (s; 2H, NH_2), 3.72 (s; 3H, OCH_3), 3.93 (s; 1H, α-H), 5.70 (m; 1H, =CH). (Found: C, 64.00; H, 8.95. Calc for $C_9H_{15}NO_2$ (169.2): C, 63.88; H, 8.93%).

Methyl(R) - 2 - *amino* - 3 - *ethyl* - 3 - *butenoate* (**22**) *and* Z/E-*methyl* (R) - 2 - *amino* - 3 - *methyl* - 3 - *pentenoate* (**21d**)

A mixture of **19** and *E*/*Z*-**18d** (0.48 g; 2 mmol). Workup

after 40 hr, yield, 0.18 g (64%) 74:16:10-mixture of **22** and *Z/E*-**21d**; b.p. 110°/8 torr. Contaminated with *ca* 20% of **8**.

IR(film): $\nu = 1730$ (C=O), 3200–3400 cm^{-1} (NH_2). ^{1}H-NMR($CDCl_3$): **22**: $\delta = 0.84$ (t, J = 7 Hz; 3H, CH_2–CH_3), 1.65 (s; 2H, NH_2), 1.75 (q, J = 7 Hz; 2H, CH_2–CH_3), 3.65 (s; 3H, OCH_3), 3.70–4.00 (m; 3H, =CH_2, α-H). *Z*-**21d**: $\delta = 1.60$ (s; 3H, CH_3), 1.65 (s; 2H, NH_2), 1.70 (d, J = 6 Hz; 3H, =$CHCH_3$), 3.65 (s, 3H, OCH_3), 3.84 (s; 1H, α-H), 5.39 (q, J = 6 Hz; 1H, =CH). *E*-**21d**: $\delta = 1.60$ (s; 3H, CH_3), 1.65 (s; 2H, NH_2), 1.70 (d, J = 6 Hz; 3H, =$CHCH_3$), 3.65 (s; 3H, OCH_3), 4.35 (s; 1H, α-H), 5.39 (q, J = 6 Hz; 1H, =CH).

α-Alkenyl glycines **23** (*General Procedure*)

Compound **21** (1 mmol) was refluxed for 3 hr with 10 ml 2 N HCl. The soln was evaporated *in vacuo* to dryness, 5 ml dry EtOH and 2 ml propylene oxide added and the mixture refluxed for 20 min. After cooling to room temp the precipitated **23** was isolated by suction, washed with some cold acetone and dried several days at room temp at 10 torr.

Z/E-(R)-2-Amino-3-ethyl-3-pentenoic acid (**23a**)

Compound *E/Z*-**21a** (0.16 g; 1 mmol) (obtained from the sulfonium salt **25**), yield, 0.10 g (72%) *Z/E*-**23a** (*Z* : *E* = 2.5); m.p. 164° (dec) $[\alpha]_D^{20} = -113.1°$ (*c* = 1.0; 1 NHCl).

IR(KBr): $\nu = 1620$ (CO_2^-), 3050 cm^{-1} (NH_3^+, br.). ^{1}H-NMR (D_6–DMSO/D_2O): *Z*-**23a**: $\delta = 0.95$ (t, J = 7.5 Hz; 3H, CH_2CH_3), 1.64 (d, J = 6.5 Hz; 3H, =$CHCH_3$), 2.08 (q, J = 7.5 Hz; 2H, CH_2–CH_3), 3.85 (s; 1H, α-H), 5.54 (q, J = 6.5 Hz; 1H, =CH). *E*-**23a**: $\delta = 0.98$ (t, J = 7.5 Hz; 3H, CH_2–CH_3), 1.67 (d, J = 6.5 Hz; 3H, =$CHCH_3$), 2.08 (q, J = 7.5 Hz; 2H, CH_2–CH_3), 5.54 (q, J = 6.5 Hz; 1H, =CH). (Found: C, 56.42; H, 9.19. Calc for $C_{17}H_{13}NO_3$ (143.2): C, 58.72; H, 9.15%).

(R)-(*Cyclohex-1'-en-1'-yl*)*glycine* (**23b**)

Compound **21b** (0.17 g; 1 mmol), yield, 0.12 g (76%) **23b**; m.p. 154° (dec) $[\alpha]_D^{21} = -96.8°$ (*c* = 0.5; 1 N HCl).

IR(KBr): $\nu = 1600$ (CO_2^-), 3050 cm^{-1} (NH_3^+ br.). ^{1}H-NMR(D_2O): $\delta = 1.25 - 2.15$ (m; 8H, –$(CH_2)_4$–), 4.03 (s; 1H, α-H), 5.83 (m; 1H, =CH). (Found: C, 61.57; H, 8.39. Calc for $C_8H_{13}NO_2$ (155.2): C, 61.91; H, 8.44%).

Compound **21a** *from the bis-lactim ether* **27**

(3*S*) - 2,5 - Dimethoxy - 3 - (3,4 - dimethoxybenzyl) - 3-methyl - 3,6 - dihydropyrazine (**27**) was obtained according to lit.[18]

(3S,6S) - 2,5 - *Dimethoxy* - 3 - (3,4 - *dimethoxybenzyl*) - 3-*methyl* - 6 - (1' - *methylthio* - 1' - *ethylprop* - 1' - *yl*) - 3,6-*dihydropyrazine* (**30b**)

A soln of 4.2 mmol BuLi (2.7 ml of a 1.55 N soln in hexane) was added at −70° to the soln of 1.23 g (4 mmol) **27**. After stirring for 20 min, the soln of 0.43 g (4.2 mmol) pentane-3-thione in 5 ml dry THF was added. After 12 hr stirring at −70° the soln of 0.60 g (4 mmol) MeI was added. After stirring at room temp for 40 hr workup as described above for **18**, yield: 0.91 g (54%) **30b**; b.p. 180°/0.005 torr (bulb-to-bulb distillation).

IR(film): $\nu = 1696$ cm^{-1} (C=N). ^{1}H-NMR($CDCl_3$): $\delta = 0.87$ and 0.92 (2t, J = 7 Hz; 6H, (CH_2–CH_3)$_2$), 1.60 (s; 3H, 3-CH_3), 1.62 and 1.74 (2q, J = 7 Hz; 4H, (CH_2–CH_3)$_2$), 1.82 (s; 3H, S–CH_3), 2.85 and 2.98 (AB, C_6H_3–CH_2; J = 13 Hz). 3.59 (s; 1H, 6-H), 3.65 and 3.66 (2s; 6H, 2- and 5-OCH_3), 3.80 and 3.83 (2s; 6H, C_6H_3–(OCH_3)$_2$), 6.61 (m; 3H, C_6H_3). High resolution MS: Found: 422.2239. Calc for $C_{22}H_{34}N_2O_4S$: 422.2231.

Z/E - (3S,6R) - 2,5 - *Dimethoxy* - 3 - (3,4 - *dimethoxybenzyl*)-6 - (1' - *ethylprop* - 1' - *en* - 1' - *yl*) - 3 - *methyl* - 3,6 - *dihydropyrazine* (**31**) *and* (3S) - 2,5 - *dimethoxy* - 3 - (3,4 - *dimethoxybenzyl*) - 6 - (1' - *ethyl* - *propyliden*) - 3 - *methyl*-3,6 - *dihydropyrazine* (**32**)

Elimination via the sulfonium salt as described above. Compound **30b** (1.2 g; 3 mmol); reflux with MeI in acetonitrile for 14 hr, yield: 0.97 g (86%) *Z/E*-**31** and **32** (76:24); *Z* : *E* = 4; b.p. 130–140°/0.04 torr (bulb-to-bulb distillation).

IR(film): $\nu = 1620$ (C=C), 1680 cm^{-1} (C=N). *Z*-**31**: ^{1}H-NMR($CDCl_3$): $\delta = 0.89$ (t, J = 7 Hz; 3H, CH_2–CH_3), 1.52 (s; 3H, 3-CH_3), 1.61 (d, J = 6 Hz; 3H, C=C–CH_3), 1.86 (q, J = 7 Hz; 2H, C=C–CH_2), 2.83 and 2.97 (AB, C_6H_3–CH_2; J = 13 Hz), 3.65 (2s; 6H, 2- und 5-OCH_3), 3.79 and 3.80 (2s; 6H, C_6H_3(OCH_3)$_2$), 4.05 (s; 1H, 6-H), 5.33 (q, J = 6 Hz; 1H, CC–H), 6.59 (m; 3H, C_6H_3). *E*-**31**: ^{1}H-NMR($CDCl_3$): $\delta = 0.87$ (t, J = 7 Hz; 3H, CH_2–CH_3), 1.49 (s; 3H, 3-CH_3), 1.59 (d, J = 6 Hz; 3H, C=C–CH_3), 1.86 (q, J = 7 Hz; 2H, C=C–CH_2), 2.83 and 2.97 (AB, C_6H_3–CH_2; J = 13 Hz), 3.65 (2s; 6H, 2- and 5-OCH_3), 3.77 and 3.78 (2s; 6H, C_6H_3–(OCH_3)$_2$), 4.05 (s; 1H, 6-H), 5.27 (q, J = 6 Hz; 1H, C=C–H), 6.59 (m; 3H, C_6H_3). Compound **32**: ^{1}H-NMR($CDCl_3$): $\delta = 0.79$ and 0.94 (2t, J = 7 Hz; 6H, –(CH_2CH_3)$_2$), 1.46 (s; 3H, 3-CH_3), 3.82 (2s; 6H, C_6H_3–(OCH_3)$_2$). High resolution MS: Found: 374.2206. Calc for $C_{21}H_{30}N_2O_4$: 374.2198.

Compound **21a**. Hydrolysis of 0.75 g (2 mmol) **31/32**-mixture according to hydrolysis **18**→**21** (see above) for 60 hr, yield: 0.16 g (52%) *Z/E*-**21a** (*Z* : *E* = 4); $[\alpha]_D^{20} = -104°$ (*c* = 1.0, $CHCl_3$); physical data and spectra see above.

Thioketones **14**

The thioketones **14** were basically prepared according to lit.[21], the procedure modified according to lit.[22]: Through the soln of the dimethyl ketals in AcOH, that contained some hydrochinone and a catalytic amount of conc H_2SO_4, a rather strong stream of H_2S was passed. For further information about the preparation of thioketones, see lit.[23]

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