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ENANTIOSELECTIVE SYNTHESIS OF NON-PROTEINOGENIC AMINO ACIDS VIA METALLATED *BIS*-LACTIM ETHERS OF 2,5-DIKETOPIPERAZINES

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Abstract—*Bis*-lactim ethers **1** of 2,5-diketopiperazines contain a chiral inducing center, an acidic CH-bond and two sites susceptible to hydrolysis. They react with BuLi to give Li compounds of type **4,15,29** or **32**, which possess a prochiral C atom. They readily add electrophiles (such as alkylating agents or carbonyl compounds) with unusually high diastereoface differentiation. In many cases the d.e.-value (d.e. = diastereomeric excess = asymmetric induction) of the adduct exceeds 95%. On hydrolysis the adducts are cleaved liberating the chiral auxiliary (used to build up the *bis*-lactim ether **1**) and the target molecules, the optically active amino acid methyl esters of type **8,19,25** or **36**. The two amino acid esters are separable either by fractional distillation or (eventually after further hydrolysis to amino acids) by chromatography. Transition state models are discussed that could explain the exceptionally high asymmetric induction and the predictability of the induced configuration.

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*-hydroxyphenylglycine) in the semisynthetic penicillines Ampicillin or Amoxycillin.

In biochemistry, they are valuable tools to investigate the mechanism of enzyme reactions.[1,2] In fact, enzyme inhibition studies with non-proteinogenic amino acids have furnished valuable information about the mode of action of certain enzymes.[1,2]

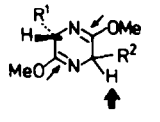
Obviously, there is a demand for optically active—if possible optically pure—uncommon amino acids both for pure and applied organic or bioorganic chemistry. Since asymmetric synthesis[3] is—at least in principle—the shortest and most economic way to optically active compounds, it is a challenge for the synthetic organic chemist, to develop asymmetric syntheses of amino acids.[4]

1. *Strategy*

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. (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 its open chain analog, hence a higher degree of asymmetric induction can be expected.

This paper describes some results achieved with 2,5-dimethoxy-3,6-dihydropyrazines **1**, the *bis*-lactim ethers of cyclic dipeptides (2,5-diketopiperazines). The bold arrow points to the acidic hydrogen; the thin arrows indicate the two sites susceptible to hydrolysis, where the molecule is cleaved after introduction of the electrophile. De-values (de = diastereomeric excess = asymmetric induction) were determined either by ^{1}H- or



	a	b	c	d	e
R^1	CH_3	iPr	iPr	tBu	iPr
R^2	CH_3	CH_3	H	H	C_6H_5

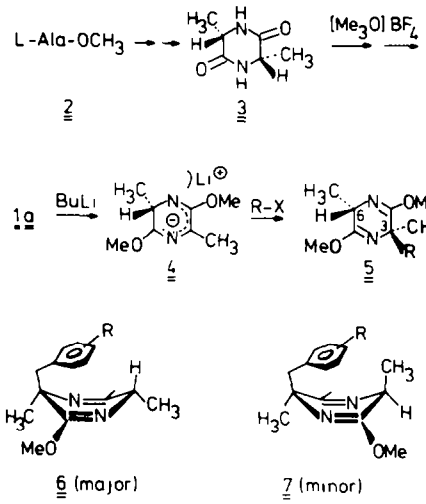
^{13}C-NMR-spectroscopy or by capillary gas chromatography. Ee-values (ee = enantiomeric excess) were determined mainly by ^{1}H-NMR-spectroscopy using chiral shift reagents. > 95% de or ee was assumed if only one stereoisomer is detectable in the NMR-spectrum. For the sake of simplicity of the NMR-spectra all studies were performed with the *bis*-methoxy lactim ethers although the *bis*-ethoxy lactim ethers are cheaper and more readily prepared from the 2,5-diketopiperazines.[5]

2. *Enantioselective synthesis of α-methyl amino acids*

As α-methyldopa, an antihypertensive drug, proves, α-methyl amino acids are of interest in medicinal chemistry. In biochemistry, they are believed to be competitive inhibitors of those enzymes that metabolize the corresponding α-unsubstituted proteinogenic amino acids.[6] Moreover, isovaline has been found as a constituent of antibiotically active peptides.[7]

2.1 Bis-*lactim ether* **1a** *of Cyclo(L-Ala-L-Ala) as starting material.* On heating of methyl L-alaninate **2** two molecules condense to give the diketopiperazine **3** [cyclo(L-Ala-L-Ala), ≈ 93% enantiomerically pure after crystallization from water].[5] **3** is converted into the *bis*-methoxy lactim ether **1a** with trimethyloxonium tetrafluoroborate[5]. Compound **1a** reacts smoothly with BuLi or LDA (THF or Glyme, − 78°) to give the lithium derivative **4** which contains a resonance stabilized diazapentadienyl anion and is regarded as an ion pair. A

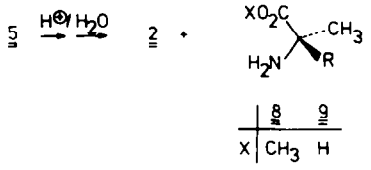
second metallation at C-3 is prohibited, for this would lead to an anti-aromatic 8π-electron system. The Li compound **4** reacts with alkyl halides in good chemical yields to give the adducts **5**. The residue R enters trans to the Me group at C-6, i.e. the (3*R*)-configuration is induced at the new chiral center. The asymmetric induction is generally > 90% (Table 1)[5].



6 (major) **7** (minor)

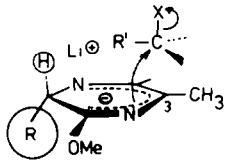
For halides R–X of the benzyl type, the (3*R*)-configuration of **5** can be derived unambigously from the ^{1}H-NMR-spectrum. As depicted in **7** for the minor isomer (obtained with benzylbromide) the heterocycle has a boat shape and the benzyl residue adopts the "folded" conformation, where the aryl ring faces the heterocycle. Hence the C-6-Me group suffers an upfield shift of $\delta \sim 0.75$ ppm (compared to the major isomer **6** or to **1a**).

On hydrolysis (0.25 N HCl, room temp) the adducts **5** are cleaved to (*R*)-α-methyl amino acid methyl esters **8** and methyl L-alaninante **2**. Under these conditions practically no 2,5-diketopiperazines are formed. If **8** and **2** differ sufficiently in bp, the esters can be separated by bulb-to-bulb distillation.[5] Otherwise they can be separated by chromatography, eventually after further hydrolysis to the amino acids. The ee-values of the esters **8**—determined by ^{1}H-NMR-spectroscopy with chiral shift reagents[5]—correspond with the de-values of the adducts **5**.



	8	9
X	CH_3	H

The stereochemical outcome of the alkylation **4**→**5** can be rationalized by the transition state model **10a**. Here, a planar anion is postulated, of which the diastereotopic faces are differently shielded (H vs Me). The alkyl halide enters predominantly from the "top side" affording the (3*R*)-configuration. The incoming alkyl residue presumably adopts the "*R*'-inside" conformation. This brings *R*' close to the chiral center, rendering $\Delta\Delta G^{\neq}$ for the two competing pathways relatively large. The "folded" conformation might be stabilized—in case of *R*' = Aryl or Heteroaryl—by HOMO–LUMO- or charge transfer- or pole-induced dipole-attraction, in case of *R*' = Alkyl by Van der Waals nonbonded attraction forces. Unclear is the role of the Li atom. Noteworthily, another set of experiments—employing the *bis*-lactim ether **1e** of cyclo(L-Val-Phenylgly)—revealed that the nature of the metal cation (M = Li, Na, K) does not influence the de-values significantly.[8]



10	a	b
R	CH_3	iPr

In spite of all shortcomings the model provided a valuable working hypothesis. It suggested, that replacement of the Me group in **10a** by a sterically more demanding group should enhance the diastereoface differentiation. In fact, this proved to be the case (see below).

2.2 Bis-*lactim ether* **1b** *of cyclo* (L-Val-Ala) *as starting material.* "Symmetrical" *bis*-lactim ethers of type **1a**—build up from two identical amino acids—do have one disadvantage, inherent in the system: only half of the chiral auxiliary—in this case L-alanine ester **2**—is recovered; the other half is incorporated in the product. This disadvantage is avoided by employing "mixed" *bis*-lactim ethers, i.e. those, build up from two different amino acids. The "mixed" *bis*-lactim ether **1b** of cyclo(L-val-D,L-ala) is a suitable candidate for the highly enantioselective synthesis of α-methyl amino acids **9**. The 2,5-diketopiperazine **14**, the precursor of **1b**, is best prepared via the Leuch's anhydride **12** of L-valine—the chiral auxiliary—according to the route outlined below without comments.[9]

The *bis*-lactim ether **1b** is metallated by BuLi (THF, −70°) regiospecifically in the alanine part of the molecule to give **15**. This reacts with alkyl halides with de > 95% (*cf* Table 2) to give the (3*R*)-adducts **16**. These on hydrolysis (0.25 N HCl, room temp, eventually for many hours) are cleaved to methyl L-) valinate **17** and the (*R*)-α-methyl amino acid esters **8**.[9] In all cases (*cf* Table 2) their ee-values are > 95%, i.e. they are practically optic-

Table 1. (3*R*)-Dihydropyrazines **5**

5[a]	a	b	c	d	e	f	g	h
R	Bzl	2-naphthyl-CH_2	2-chinolyl-CH_2	3-pyridyl-CH_2	Allyl	iPr	n-C_8H_{17}	cinnamyl
≈ De (%)	92	95	95	95	92	92	92	91

a) Chemical Yield 80–92 %.

Table 2. (3*R*)-Dihydropyrazines **16** and (*R*)-amino acid methyl esters **8** from **16**

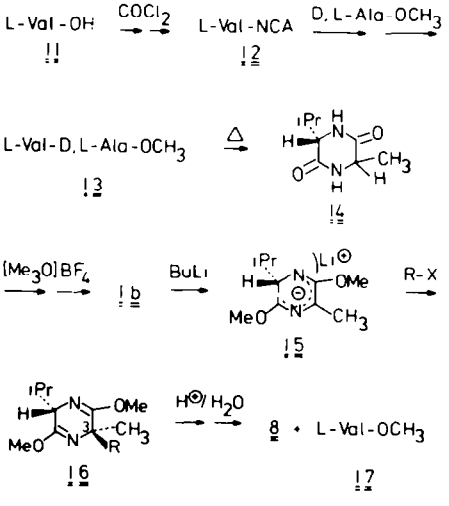
	R	(3R)-16 de (%)	$[\alpha]_D^{20°}$	(R)-8 (in EtOH)	ee (%)[a]
a	$C_6H_5CH_2$	> 95	- 2.8o	(c=1.o)	> 95
b	$(3,4\text{-}OCH_3)_2C_6H_3CH_2$	> 95	- o.7o	(c=1.1)	> 95
c	$C_6H_5CH{=}CHCH_2$	> 95	-13.2o	(c=1.1)	> 95
d	n-C_3H_7	> 95	-12.9o	(c=0.6)	> 95
e	$CH_2{=}CHCH_2$	> 95	+ 2.33	(c=o.4)	> 95
f	$CH{\equiv}CCH_2$	> 95	+ 2.o8	(c=o.8)	> 95
g	$(CH_3)_2C{=}CHCH_2$	> 95			
f	$BzSCH_2CH_2$	> 95	+1o.o	(c=o.56)	> 95
g	$tBuO_2CCH_2$	> 95	-26.o	(c=1.14)	> 95
h	$BzOCH_2CH_2$	> 95	+ 1.o	(c=1.o)	> 95
i	$BzOCH_2$	> 95	+ 4.7	(c=1.4)	> 95[b]

a) Determined with chiral shift reagents.

b) With 6 N HCl transformed in (R)-α-methyl serine, optically pure by rotation.

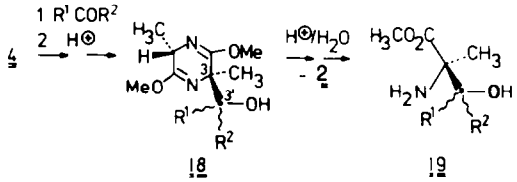
ally pure. With D-valine as chiral auxiliary the (*S*)-enantiomers of **8** would be formed.

The exceptionally high level of diastereoface selection in the formation of **16**—in one case examined, capillary GC revealed de ≥ 98%—can best be explained on the basis of the transition state model **10b** with the bulky isopropyl group at the "bottom side" of the anion.



3. *On the enantioselective synthesis of α-methyl serines and α-alkenyl alanines*

3.1 Bis-*lactim ether* **1a** *of cyclo*(L-*ala*-L-*ala*) *as starting material.* The lithiated *bis*-lactim ether **4** reacts with ketones and aldehydes with rather high diastereoface selection to give (after protonation) the adducts **18** (3*R*)-configuration (Table 3)[10] i.e. also the CO group enters trans to the Me group at the chiral C-6 center. For aromatic ketones and aldehydes the (3*R*)-configuration can be derived from the ^{1}H-NMR-spectrum. Also in the aldol type adducts the aryl ring faces the heterocycle—*cf* **6** or **7** for analogy—and consequently in the minor (6*S*,3*S*)-isomer the C-6-Me group suffers an upfield shift.[10] Expectedly, with unsymmetrically substituted ketones or with aldehydes, the CO group enantioface selection is poorer than the diastereoface selection at the anion. The "induced configuration" at C-3' (in the major (3*R*)-isomer) is also listed in Table 3.[10]



Surprisingly (*cf* Table 3) the degree of asymmetric induction at C-3 does not depend very much on the size of the groups R^1 or R^2 of the carbonyl compound. Obviously, the interaction of these groups with the heterocyclic anion **15** is not a decisive factor in the transition state of the CO addition. The decisive factor seems to be the interaction with the CO oxygen, the functional atom common to all carbonyl compounds. Hence, the transition state has the "oxygen inside" con-

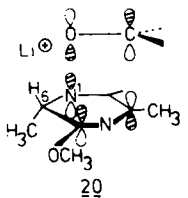
Table 3. Aldol-type adducts **18** from **4**

			C-3		C-3' [a]	
			de (%)	Config.	de (%)	Config.
a	H	H	81	R		
b	CH_3	CH_3	85[b]	77[c]		
c	C_6H_5	C_6H_5	> 95[c]			
d	C_6H_5	H	88[b]	80[c]	52[b]	R
e	C_6H_5	CH_3	> 95[b]	86[c]	41[b]	R

a) For the (6S,3R)-isomers. b) Glyme as solvent.

c) THF as solvent.

formation, depicted in the models **20** or **21** and **22**, respectively. In **20** an HOMO(anion)—LUMO(carbonyl) attraction is supposed to stabilize this conformation, the Li cation playing a minor role. In the alternative models **21** and **22** the chelating power of the Li atom is supposed to be the dominating factor. The latter models are based on the chair-like transition state models accepted nowadays for the related aldol addition.[11] Both models—**20** and **21/22**—have practically the same geometry. According to MO calculations, N-1 is the atom with the biggest coefficient in the HOMO and at the same time with the highest electron density. Hence, in both models the CO oxygen can be assumed to be located above N-1.



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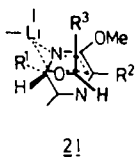

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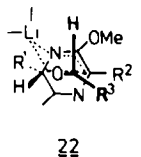


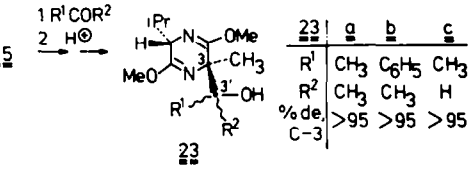
22

	a	b	c
R^1	CH_3	iPr	iPr
R^2	CH_3	CH_3	H

Models **21** and **22** differ in the configuration at C-3'. The preferred formation of the (3'*R*)-isomers with, for instance, aldehydes, can be rationalized by comparing the magnitude of two nonbonded repulsions, namely the diaxial $R^3 \leftrightarrow$ OMe interaction in **21** and the gauche $R^3 \leftrightarrow R^2$ interaction in **22**. In **21a/22a** obviously the latter outweighs the former, i.e. **21a**, leading to (3'*R*), is of lower energy than **22a**.

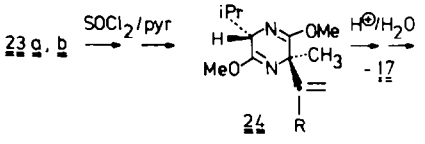
On hydrolysis (0.25 N HCl, room temp) the adducts **18** are cleaved to **17** and (*R*)-α-methyl serine methyl esters **19**. As discussed elsewhere,[10] isolation of **19** might be a problem, for α-methyl serine esters are rather thermolabile compounds.

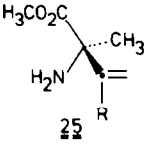
3.2 Bis-*lactim ether* **1b** *of cyclo*(L-*val*-D,L-*ala*) *as starting material.* Like alkyl halides (*cf* 2.2), carbonyl compounds react with **15** with exceptionally high diastereoface differentiation. With acetone, acetophenone or acetaldehyde, only the (3*R*)-diastereomers of the adducts **23** are detectable in the ^{1}H- and ^{13}C-NMR-spectrum.[12]



23	a	b	c
R^1	CH_3	C_6H_5	CH_3
R^2	CH_3	CH_3	H
% de, C-3	>95	>95	>95

When treated with thionyl chloride/pyridine the adducts **23a,b** afford the corresponding olefins **24a,b**, which on hydrolysis give the α-alkenyl alanine methyl esters **25a,b** which are enantiomerically pure by NMR-standard.[12]





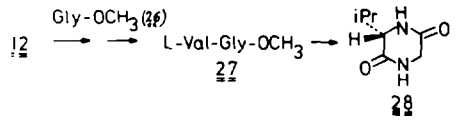
25

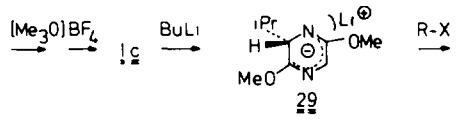
24, 25	a	b
R	CH_3	C_6H_5

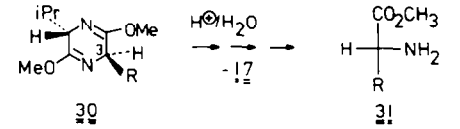
4. Enantioselective synthesis of α-unsubstituted amino acids

In general, enantioselective hydrogenation of N-acyl α-dehydroamino acids seems to be a promising and elegant route to α-unsubstituted amino acids.[13] However, not all dehydroamino acids are readily prepared and react properly with hydrogen. In each case the suitable catalysts and reaction conditions must be explored in preliminary studies. Moreover, the method is limited to those dehydroamino acids that do not carry additional functional groups susceptible to hydrogenation. Hence, also in the field of α-unsubstituted amino acids efficient stoichiometric asymmetric syntheses are desirable.

4.1 Bis-*lactim ether* **1c** *of cyclo*(L-*val-gly*) *as starting material.* The synthesis of cyclo(L-val-gly) **28**, the precursor of the *bis*-lactim ether **1c** follows the pattern outlined above for the synthesis of **14**.[14]





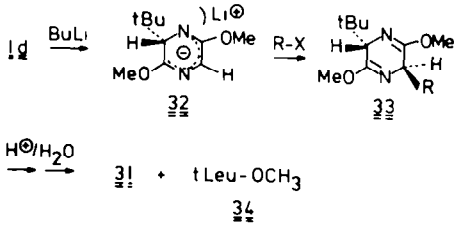


Compound **1c** reacts regioselectively with BuLi in the glycine part of the molecule to give **29**, which affords with alkyl halides the adducts **30** with (3*R*)-configuration.[14] The asymmetric induction—determined either by NMR-spectroscopy on the adducts **30** and/or indirectly from the ee-values of **31**—is in the range of 75 – > 95%. With *R* groups containing extended π-systems high de-values are observed (*cf* Table 4). For *R* = benzyl or methylnaphthyl the adducts **30** adopt the "folded" conformation—analogs to **6** or **7** (see above).

A comparison of the results listed in Tables 2 and 4 indicates, that a Me group at the prochiral anionic center in the lithiated heterocycle is beneficial to asymmetric induction. With **15** *all* alkyl halides react with ⩾ 95% asymmetric induction, but not with **29**.

Hydrolysis of **30** proceeds smoothly (0.25 N HCl, room temp) liberating methyl valinate **17** and the (*R*)-α-amino acid methyl esters **31**. In most cases, esters **17** and **31** can be separated by bulb-to-bulb distillation. The ee-values of **31**—determined by ^{1}H-NMR-spectroscopy using chiral shift reagents—are listed in Table 4.[14] They correspond with the de-values of adducts **30**, as far as these were determined. Hence, hydrolysis conditions are sufficiently mild to avoid significant racemization.

4.2 Bis-*lactim ether* **1d** *of cyclo*(L-*tleu-gly*) *as starting material.* As expected from the results with **29**, the Li derivative **32** of the *bis*-lactim ether **1d** of cyclo(L-tleu-gly) reacts with alkyl halides with exceptionally high diastereoselection (*cf* Table 5). With exception of methyl iodide, only the (3*R*)-diastereomers of **33** are formed. The ee-values of the (*R*)-amino acid esters **31**—isolated after hydrolysis of **33** followed by separation of methyl tertiary leucinate **34**—correspond within experimental error with the optical purity of the *bis*-lactim ether **33**.[15] The synthesis of **1d** is analogous to the one of **1c**[15] (see above).



Although this system works exceedingly well—in fact, it could be the final solution to the problem as far as this approach is concerned—, it has one disadvantage. Tertiary leucine (= tertiary butyl glycine) is not available in nature's chiral pool; it has to be synthesized. There is an efficient method for the synthesis of the racemic compound,[16] but resolution by the conventional method

Table 4. (*R*)-Amino acid methyl esters **31** from the adducts **30**

31	**a**	**b**	**c**	**d**	**e**	**f**
R	Bzl	(3,4-OCH_3)$_2$-$C_6H_3CH_2$	2-naphthyl-CH_2	cinnamyl	$PhC{\equiv}CCH_2$	CH_2OBzl
ee (%)[a]	92	92	92	>95	>95	93

a) Determined with chiral shift reagents.

Table 5. (3*R*)-Dihydropyrazines **33** from **32**

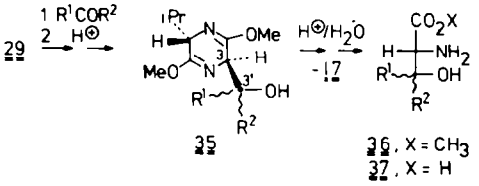
33	**a**	**b**	**c**	**d**	**e**
R	CH_3	$CH_2CH{=}CH_2$	$CH_2C{\equiv}CH$	C_7H_{15}	CH_2CO_2tBu
De (%)[a]	≈80	>95	>95	>95	>95

a) Determined indirectly via ee of **31** obtained after hydrolysis.

(crystallisation of the brucine salt) is very tedious, if optically pure material is required.[17] There is an efficient enzymatic resolution which provides practically optically pure tertiary leucine,[18] but the enzyme (a penicillin amidase) is not available in any laboratory.

5. Enantioselective synthesis of (R)-serines with bis-*lactim ether* 1c *of cyclo(*L*-val-gly) as starting material.*

As observed with **4** or **15** (see above), carbonyl compounds add to lithiated *bis*-lactim ethers generally with relatively high diastereoface selection. This is also true for **29**. With, for instance, acetone, acetophenone, isobutyraldehyde or t-butyldimethylsilyl acetaldehyde only the (3)-adducts **35** can be detected either in the ^{1}H- or ^{13}C-NMR-spectrum.[19] With acetaldehyde or benzaldehyde diastereoface selection is somewhat lower but still fairly high (*cf* Table 6).

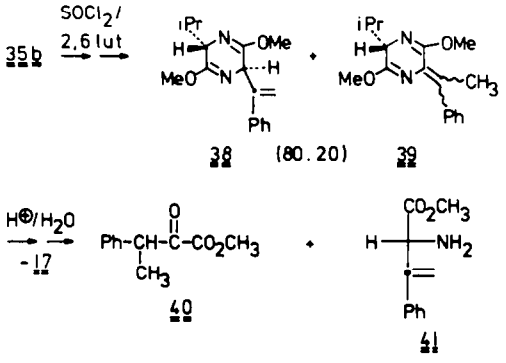


The CO enantioface selection [for the (*R*)-diastereomers] is also listed in Table 6. Contrary to the results observed with **4**, here the (3'*S*)-configuration is formed predominantly.[19] Obviously, transition state **22b** is of lower energy than transition **21b**. This is plausible; with R^2 = hydrogen the gauche interaction $R^3 \leftrightarrow$ H is of subordinate importance and the $R^3 \leftrightarrow$ OMe repulsion is the dominating factor.

Hydrolysis of the aldol-type adducts **35** occurs smoothly (dilute HCl, room temp) liberating methyl L-valinate **17** and the (*R*)-serine methyl esters **36**. However, hydrolysis might require carefully controlled conditions.

The method has been used, for example, to prepare essentially enantiomerically pure (*R*)-(−)-β-hydroxyvaline **37** (*R* = Me).[20] Subsequent to hydrolysis of **35a** the esters **17** and **36** further hydrolyzed to **37** (*R* = Me).[20] Earlier, (+)-β-hydroxyvaline was isolated from an antibiotically active peptide and its configuration assigned as (*S*).[21] Since the enantioselective synthesis via **29** occurs with predictable configuration and affords (*R*)-(−)-β-hydroxyvaline, the synthesis proves, that the natural product does indeed have the (*S*)-configuration.

The exceptionally high diastereoface differentiation in the reaction of **29** with carbonyl compounds can be exploited for the synthesis of optically active α-vinylamino acids. These deserve attention in biochemistry, for they possess the structural features required for "suicide inhibitors[22]" of certain (pyridoxal phosphate dependant) enzymes. An example is the enantioselective synthesis of (*R*)-β-methylene phenylalanine methyl ester **41**.[23] The adduct **35b** when treated with thionyl chloride/2,6-lutidine gives a 80:20-mixture of the "Hoffmann-olefin" **38** and the "Saytzeffolefin" **39**, which on hydrolysis afford a mixture of methyl L-valinate **17**, the keto ester **40**, and the target molecule **41**. The mixture can be readily separated and **41** is obtained in enantiomerically pure form (by NMR-standard).[23] The racemic compound was recently prepared in a fairly lengthy synthesis; no resolution was reported.[24]



Another example is the synthesis of (*R*)-(−)-vinyl glycine **43**.[25] The adduct **35d** is hydrolyzed to liberate **17** and **42** which can be separated by bulb-to-bulb distillation. The ester **42** is subsequently converted[26] into the target molecule **43** which is enantiomerically pure (by NMR-standard).

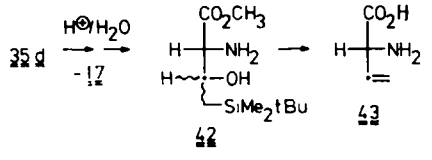


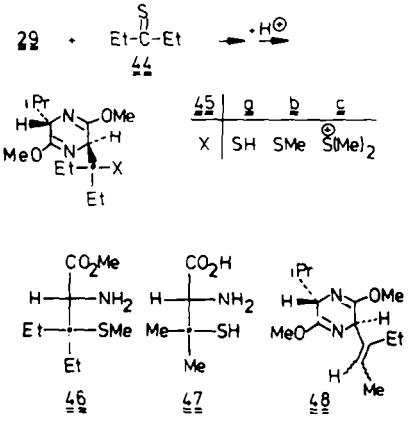
Table 6. Aldol-type adducts **35** from **29**

			C-3		C-3'	
35	R^1	R^2	de(%)	Config.	de(%)	Config.
a	CH_3	CH_3	>95	R		
b	C_6H_5	CH_3	>95	R	≈30	S
c	$CH(CH_3)_2$	H	>95	R	≈85	S
d	CH_2SiMe_2tBu	H	>95	R		
e	C_6H_5	H	≈80	R	≈10	S[a]
f	CH_3	H	≈84	R	≈60	S[a]

a) For the (3R)-isomer.

6. *Enantioselective synthesis of* (R)-*cystein derivatives with the* bis-*lactim ether of cyclo*(L-*val-gly*) *as starting material*

As studied so far, also thioketones react with the lithiated *bis*-lactim ether **29** [of cyclo(L-val-gly)] with practically complete asymmetric induction.[27] For instance, diethyl thioketone **44** affords in good chemical yield a single diastereomer, probably the (3*R*)-isomer **45a**. After *S*-methylation to give **45b**, hydrolysis (0.25 N HCl, r.t.) affords a mixture of methyl L-valinate **17** and methyl (*R*)-2-amino-2-ethyl-3-methylthiopentanoate **46**, which is readily separated by fractional distillation.[27] Compound **46** is a structural variant of D-penicillamine **47**. Moreover, **45b** is easily converted into the sulfonium salt **45c** which on Hofmann-elimination affords the olefin **48**,[27] the precursor of the corresponding α-vinyl amino acid. This seems to be[27] a promising and general route to optically pure α-vinyl amino acids such as cyclohexenyl glycine etc.



Note added in proof: After exchange of the lithium cation in **29** for the tris(dimethylamino)titanium cation acetaldehyde gave **35F** with de at C-3 *ca* 95.6% and at C-3' *ca* 96.5% (See Ref. 19).

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