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ASYMMETRIC SYNTHESES OF AMINO ACIDS VIA METALATED BIS-LACTIM ETHERS OF 2,5-DIKETOPIPERAZINES

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Abstract - Metalated Bis-lactim ethers **3** of 2,5-diketopiperazines **1** react with electrophiles highly diastereoselectively to give the adducts **4**. $E^{\oplus}$ enters trans to the inducing chiral center C-6. Acid hydrolysis of **4** liberates the optically active amino acid ester **6**, the target molecule, and the amino acid ester **5** [$R^1CH(NH_2)CO_2Me$)] that functions as the chiral auxiliary in the synthesis of **1**. Examples are described with $E^{\oplus}$ = alkyl halides, carbonyl compounds and thioketones leading to the corresponding amino acid methyl esters **6**. In many cases these are obtained essentially optically pure form. - After exchange of lithium in **3** for tris(dimethylamino)titanium aldehydes react with **28** with exceedingly high diastereoselectivity to give essentially enantiomerically and diastereomerically pure products [(3R,3'S)-**26**], the precursors of 3-substitued (2R)-threoserines **27**.

1 INTRODUCTION

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 mechnism of enzyme reactions (1). In fact, enzyme inhibition studies with non-proteinogenic amino acids have furnished valuable information about the mode of action of certain enzymes.

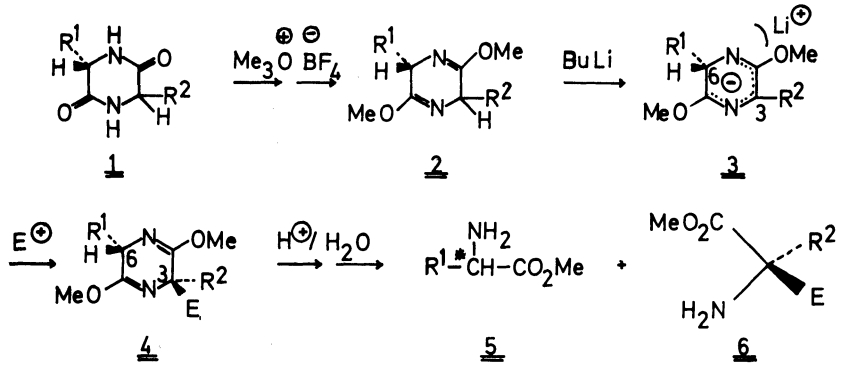
Obviously, there is a demand for optically active-if possible optically pure-uncommon amino acids both for pure and applied organic or bioorganic chemistry. Since asymmetric synthesis (2) is - at least in principle - the shortest and most economic way to optically active compounds, it is a challenge for the synthetic organic chemist, to develop asymmetric syntheses of amino acids.

2 STRATEGY

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 ist 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.

This lecture deals with the use of metalated bis-lactim ethers **3** of 2,5-diketopiperazines **1** according to scheme 1 (3). The bis-lactim ether **2** (prepared from **1** and Meerwein's salt (or methyl triflate)) reacts with butyllithium or LDA (THF, -70 °C) to give the lithium compounds **3**. Theses contain a delocalized diazapentadienyl anion and might be best described as ion pairs. A second metallation at C-6 (which would destroy the chiral information) is unlikely, since it would lead to an antiaromatic 8π-electron system. Electrophiles react with **3** to give the adducts **4**, whereby chirality is transfered from C-6 to C-3. $E^{\oplus}$ enters at C-3 trans to R^1 at C-6. The diastereomer-ratio of **4** can be determined either by ^1H- or ^{13}C-NMR or by capillary GC. The degree of asymmetric induction (= de = diastereomeric excess = $(D_1-D_2)/(D_1+D_2) \cdot 100$) exeeds in many cases 95 % and reaches up to 99 % (> 95 % is assumed if only one stereoisomer is detectable in the NMR-spectrum). The products **4** can be hydrolyzed at the imino ether groups liberating the optically active amino acid methyl esters **6**, the target molecules, and the amino acid methyl esters **5**, that serve as chiral auxiliaries in the synthesis of **1**. The two amino acid esters (**5** and **6**) are separable either by fractional distillation or - eventually after further hydrolysis to the amino acids - by chromatography. The ee-values of **6** are determinable by ^1H-NMR using chiral shift reagents.

Scheme 1



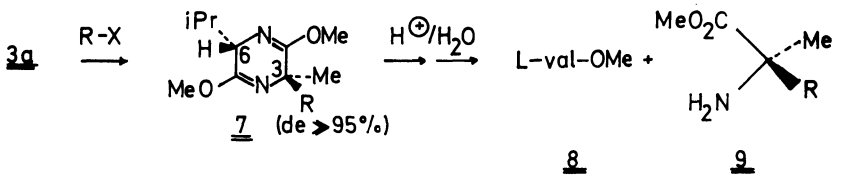
1, 2, 3	a	b	c	d	e
R^1	iPr	iPr	tBu	iC_4H_9	CH_3
R^2	Me	H	H	H	H

3 (R)-α-METHYL AMINO ACID ESTERS 9 FROM 3a AND ALKYL HALIDES

3.1 Results

The bis-lactim ether **2a** yields with butyllithium (or LDA) regiospecifically **3a**. This reacts with alkyl halides with virtually complete asymmetric inductions to give the (3R)-addition products **7**. In the ^{1}H-NMR only (6S,3R)-diastereomers are detectable. Capillary GC analysis reveals diastereomer ratios in the order of $\geq 98:2$. Acid hydrolysis of **7** liberates (besides methyl L-valinate **8**) the α-methyl amino acid methyl esters **9** which are enantiomerically pure by ^{1}H-NMR-standard (scheme 2) (4).

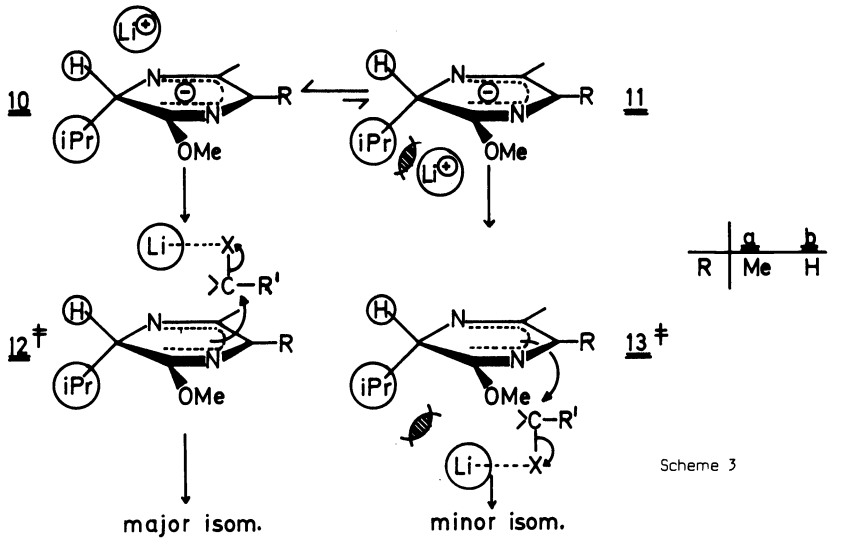
Scheme 2



3.2 Interpretation

We assume that the ion pairs **3** contain a planar anion with the lithium cation situated near N-1. Furthermore, we postulate a mobile equilibrium between two diastereomeric ion pairs **10** and **11**, which lies far on the left side because of steric reasons. Due to attractive complexation between $Li^{\oplus}$ and X-R', **10a** reacts via **12a**$^{\mp}$ to (3R,6S)-**7** and **11a** via **13a**$^{\mp}$ to (3S,6S)-**7**. **10a** reacts faster than **11a**, since **12a**$^{\mp}$ is relatively strain free, wheras **13a**$^{\mp}$ is strained due to steric congestion "at the bottom side" (scheme 3).

Scheme 3

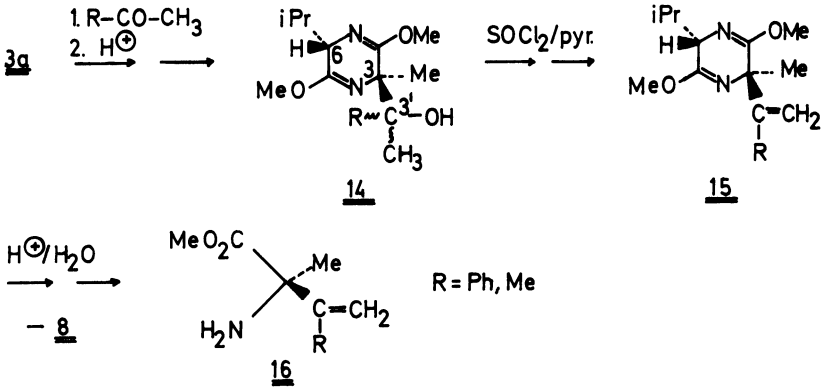


Scheme 3

4 (R)-α-ALKENYL ALANINE METHYL ESTERS **16** FROM **3a** AND KETONES

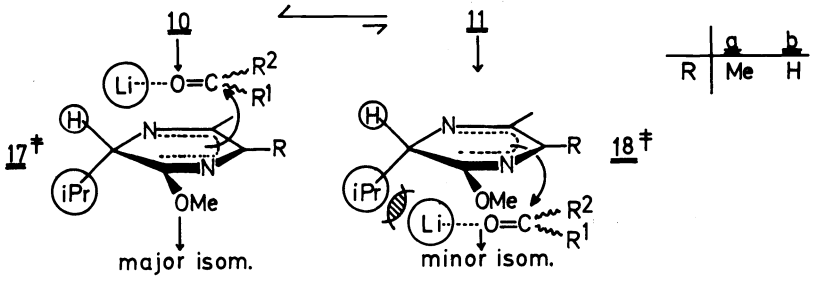
Like alkyl halides, ketones add to **3a** with exceedingly high diastereoface selection to give the (R)-adducts **14** (d.e. >95 %). With acetophenone C-3' becomes also a chiral center, although the enantioface selection at the carbonyl group is relatively poor(5). Hydrolysis of **14** is not a clear reaction, due to retro aldol reactions. However, after dehydratation **14** ⟶ **15**, hydrolysis of **15** yields the (R)-α-alkenyl alanine esters **16**. These are enantiomerically pure by ^{1}H-NMR standard (5) (scheme 4).

Scheme 4



The diastereofacial bias of **3a** toward carbonyl compounds can be explained by a model concept analogous to the one put forward in 3.2. TS **17a**‡, leading to the major isomer, is of lower energy than TS **18a**‡ which is strained due to steric hindrance at "the bottom side" (scheme 5).

Scheme 5

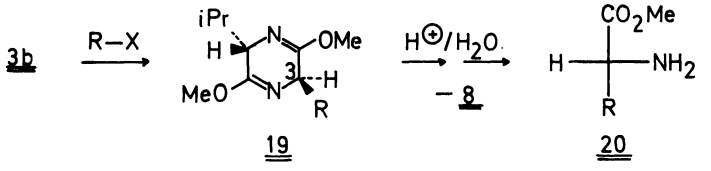


5 (α-UNSUBSTITUTED) AMINO ACID METHYL ESTERS **20** FROM **3b** AND ALKYL HALIDES

In general, enantioselective hydrogenation of dehydro amino acids seems to be an elegant route to α-unsubstituted amino acids of type **20** (6). However, not all dehydroamino acids react properly with hydrogen and for each case the suitable catalyst and conditions must be found in preliminary studies. Furthermore, the method is limited to those dehydroamino acids that do not carry additional functional groups susceptible to hydrogenation, such as double bonds, triple bonds, carbonyl groups, nitro groups, etc.. Hence, also in the field of α-unsubstituted amino acids **20** an efficient stoichiometric asymmetric synthesis is useful.

As expected, the bis-lactimether **2b** of cyclo(L-val-gly) **1b** is lithiated by butyllithium regiospecifically in the glycine part to give **3b**. This reacts with alkyl halides to afford the (3R)-products **19** with de-values from 70 - > 95 % (scheme 6) (7). On hydrolysis, the products **19** are cleaved to methyl L-valinate **8** and (R)-amino acid methyl esters **20** (7). A comparison of the results depicted in scheme 6 with those reported in 3.1 reveals that a methyl group at the prochiral center C-3 in **3** is beneficial to the degree of asymmetric induction. The results are rationalized on the basis of the TSs **12b‡** and **13b‡** (scheme 3), although it is hard to explain, why the induction is in general higher with R=Me than with R=H.

Scheme 6



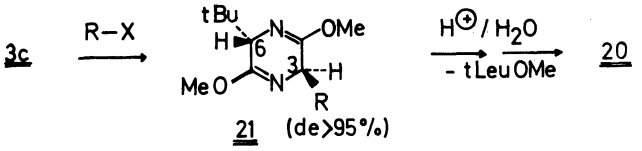
19,20,R	Bz	$CH_2CH{=}CHPh$	$CH_2C{\equiv}CPh$	CH_2OBz	$n\text{-}C_7H_{15}$
% de,ee	92	>95	>95	94	70

6 AMINO ACID METHYL ESTERS **20** FROM **3c** AND ALKYL HALIDES

Bulkier than iso-propyl is tert-butyl. Hence, it is not surprising, that **3c** reacts with all alkyl halides, tried so far - apart from methyl iodide - with de > 95 % (8), i.e. with essentially complete asymmetric induction (scheme 7).

Although this system works exceedingly well - in fact it could be the final solution to the problem as far as the bis-lactim ether approach is concerned - it has the drawback, that tert-leucine, the chiral auxiliary in **2c**, is not available in natures chiral pool. However ist has become commercially available recently (9), both in the (R)-and the (S)-form.

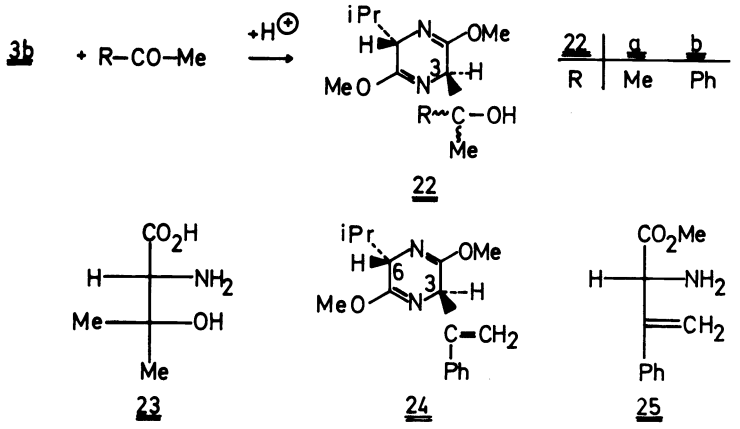
Scheme 7



7 (R)-ß-HYDROXY VALINE **23** AND (R)-ß-METHYLENE PHENYLALANINE ESTER **25** FROM **3b** AND ACETONE, RESP ACETOPHENONE

Ketones such as acetone and acetophenone afford with **3b** the (3R)-adducts **22** with de > 95 %; only (3R)-diastereomers are detectable in the ^{1}H-NMR (scheme 8). From **22a** practically optically pure (R)-ß-hydroxy valine **23** is obtainable (10), from **22b** (R)-ß-methylene phenylalanine methyl ester **25** (via the olefin **24**) (11) (scheme 8).

Scheme 8



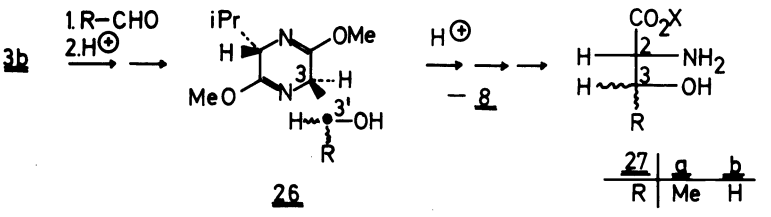
The high diastereoselectivity observed in the addition of ketones to **3b** can be rationalized on the basis of the model concept depicted in scheme 5. TS **17b**$^{\mp}$ is of considerably lower energy than **18b**$^{\mp}$.

8 (2R)-3-SUBSTITUTED SERINES **27**

8.1 Addition of Aldehydes to the Lithium Compound **3b**

Compared with ketones (cf. 7), aldehydes react with the lithium compound **3b** with somewhat lower diastereoselectivity (12). The asymmetric induction at C-3 (de at C-3) are listed in scheme 9 as well as the (3R,3'S) : (3R,3'R)-ratios.

Scheme 9



26	R	(3R,3'S)	(3R,3'R)	(3S,3'S)	(3S,3'R)	% de C-3	u : l [a]
a	Ph	16	13	1	1	86	1,2:1
b	iPr	55	10	1	1	94	5,5:1
c	tBu	35	18	2	1	85	2 : 1
d	Me	19,5	4,7	1	1	85	4 : 1

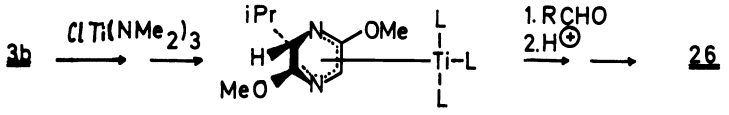
a) (3R,3'S):(3R,3'R)

The diastereoface selection with regard to the anion of **3b** is best explained on the basis of the TS **17b**$^{\mp}$ and **18b**$^{\mp}$ (scheme 5). The enantioface selection at the carbonyl group can be rationalized on the basis of the chair like TSs **29a**$^{\mp}$ and **30a**$^{\mp}$ (13) (scheme 11). The (3R,3'S)-epimers are formed predominantly, probably because the 1,3 diaxial R ⟷ OMe - and the R ⟷ Li-repulsion in **30a**$^{\mp}$ outweighs the 1,2 R ⟷ H-repulsion (in **29a**$^{\mp}$) (scheme 11). However, the low u:l-ratio in the benzaldehyde adduct **26a** is somewhat puzzling. It could be due to some kind of stabilizing charge transfer attraction between $Li^{\oplus}$ and the phenyl ring in **30a**$^{\mp}$. - As described in ref. (12), (2R)-3-substituted serine methyl esters **27a** or -serines **27b** can be obtained from the compounds **26**.

8.2 Addition of Aldehydes to a Titanium Derivative of **2b**

All factors, that render the TSs **17b**$^{\mp}$, **18b**$^{\mp}$, **29**$^{\mp}$ and **30**$^{\mp}$ more compact should enhance both the diastereoface selection with respect to the anion and the enantioface selection with regard to the carbonyl group. Consequently, exchange of lithium for metals with shorter metal-oxygen- and metal-nitrogen-bonds should lead to an higher degree of de at C-3 and to an higher (3R,3'S) : (3R,3'R)-ratio in **26**. This working hypothesis seems to be correct. Exchange of lithium for tris(dimethylamino)titanium - for example - has a dramatic effect as can be seen by comparing the data in scheme 9 with those in scheme 10. The titanium compound **28** yields with aldehydes essentially diastereomerically pure (3R,3'S)-adducts **26**. These are suitable precursors of the corresponding (2R)-threo-serines **27b** (12).

Scheme 10



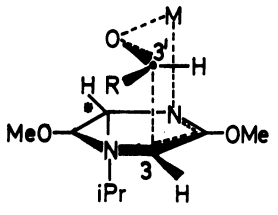
28

26	R	(3R,3'S)	(3R,3'R)	(3S,3'S)	(3S,3'R)	% de C-3	u:l [b]
a	Ph	32	1	—[a]	—[a]	>99	32:1
b	iPr	151	2,3	1	1	97	65:1
c	Me	88	0,6	1	1	95,6	146:1

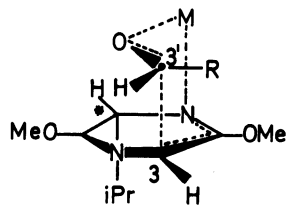
a) Not detectable any more with capillary GLC. b) (3R,3'S):(3R,3'R)

Scheme 11 depicts the TSs **29**$^{\mp}$ and **30**$^{\mp}$. With M = $Ti(NMe_2)_3$, the TSs are more compact than with M = Li. Hence, **29b**$^{\mp}$ and **30b**$^{\mp}$ differ more in energy than **29a**$^{\mp}$ and **30a**$^{\mp}$.

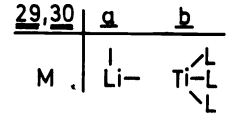
Scheme 11



29$^{\mp}$ (3R,3'S)



30$^{\mp}$ (3R,3'R)

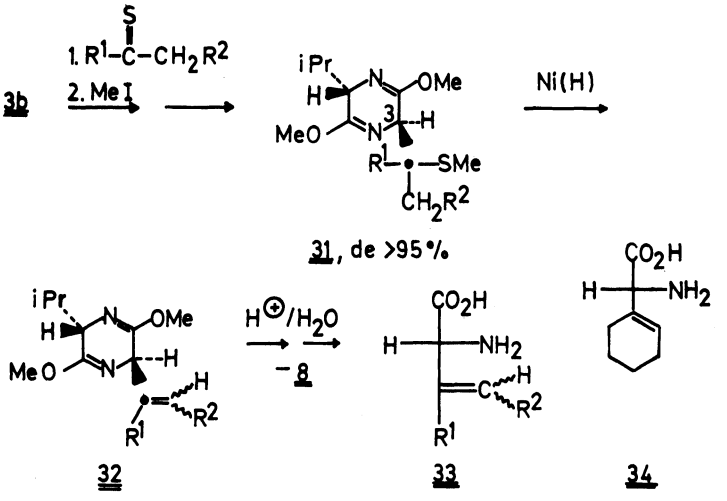


L = NMe_2

9 (R)-α-ALKENYL GLYCINES **33** (α-VINYL GLYCINES, β,γ-UNSATURATED AMINO ACIDS) FROM **3b** AND THIOKETONES

As studied so far, thioketones add to **3b** with de-values in the order of 96-98 % (determined at the stage of **31** after S-methylation). When treated with Raney-nickel, the compounds **31** suffer a regiospecific methylthio-elimination yielding the Hofmann-olefins **32**. From these, (R)-α-alkenyl glycines of type **33** are obtainable (14) (scheme 12); (R)-α-(cyclohexenyl)glycine **34** is a concrete example (scheme 12). Amino acids of type **33** deserve attention as potential suicide inhibitors of pyridoxalphosphate dependant enzymes (15).

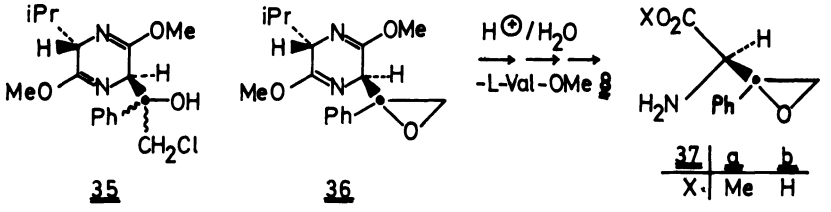
Scheme 12



10 EPOXY AMINO ACID ESTER **37a** FROM **3b** AND CHLORO ACETOPHENONE

Like other ketones (cf. 7) chloro acetophenone adds to **3b** with de > 95 % at C-3 to give (after protonation) the addition product **35**. This, when treated mit sodium hydroxide, affords the epoxy compound **36** from which the (2R)-α-epoxy amino acid ester **37a** can be obtained (mild acid hydrolysis, followed by removal of **8** at 0.01 Torr in vacuo) (16) (scheme 13). α-Epoxy amino acids of type **37b** are so far unknown. Like α-vinyl amino acids they are potential suicide inhibitors of pyridoxalphosphate dependant enzymes. However, it remains to be seen, whether the free amino acids **37b** can be obtained from **37a** and whether it is a stable compound or not.

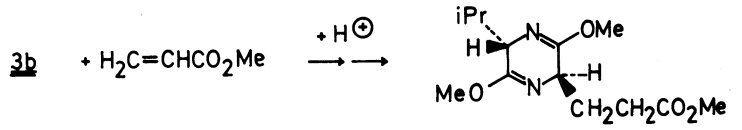
Scheme 13



11 ADDITION OF METHYL ACRYLATE TO **3b**

According to preliminary results (17), Michael addition of methyl acrylate to **3b** proceeds with de > 99 % (capillary GC) to give the adduct **38** (scheme 14). Further experiments will have to show whether all Michael additions occur with this exceptionally high level of diastereoselection. Methyl vinyl ketone reacts with **3b** in a 1,2-fashion (17).

Scheme 14



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