28. Addition of Chiral Glycine, Methionine, and Vinylglycine Enolate Derivatives to Aldehydes and Ketones in the Preparation of Enantiomerically Pure α-Amino-β-hydroxy Acids

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Chiral enolates of imidazolidinones and oxazolidinones from the title amino acids react with carbonyl compounds to afford the corresponding alcohols in excellent yields (see *Scheme 5*). Furthermore, the addition to aldehydes proceeds with high diastereoselectivity to give, after acid hydrolysis, *threo*-α-amino-β-hydroxy acids of high enantiomeric purity. Some of the *threo*-α-amino-β-hydroxy acids prepared in this work are the proteinogenic (*S*)-threonine (**26**), the naturally occurring (*S*)-3-phenylserine (**28**), and (*S*)-3-hydroxyleucine (**27**) as well as the unnatural (*S*)-4,4,4-trifluorothreonine (**30**) and (*S*)-3-(4-pyridyl)serine (**31**). The *N*-methylamide of (2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid (**32**), the unique amino acid in the immunosuppressive cyclosporine, was prepared by the new method. This report presents also information suggesting that both steric and stereoelectronic effects are responsible for the good stereoselectivities observed.

Introduction. – In addition to their fundamental biochemical and physiological significance[6]), amino acids are important in human and animal nutrition and as flavorings, taste enhancers, and sweeteners [1]. Both natural[7]) and unnatural amino acids are also components of many therapeutic agents, agrochemicals, and cosmetics, and in basic research some of them are valuable tools to elucidate the mechanism of enzyme reactions [3]. As a result of the wide spectrum of the applications of amino acids, their economic impact is quite significant and has accordingly led to the development of a variety of procedures for their extraction from natural sources and for their chemical synthesis [1]. The synthetic organic chemist must face the fact that most amino acids are biologically active only in one enantiomeric form. Desired amino acids must, therefore, be synthesized as enantiomerically pure compounds (EPC). Indeed, several methods are now available for the preparation of amino acids of high enantiomeric purity [4–6].

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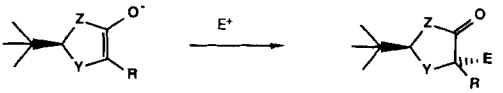
[6]) Amino acids serve as starting materials for the synthesis of proteins and other nitrogen-containing compounds such as the purine and pyrimidine bases in nucleic acids.

[7]) In addition to the 22 protein-forming α-amino acids, nearly 500 naturally occurring amino acids are now known [2].

An important class of amino acids is that of α-amino-β-hydroxy acids, which are ubiquitous in nature and play essential physiological roles, *e.g.* as fundamental components of peptidases [7]. However, only a few α-amino-β-hydroxy acids have been prepared in enantiomerically pure form, either by resolution of a racemic mixture [8], by the chemical modification of a sugar (pool of chiral substrates) [9], or *via* stereoselective reactions [10–12].

Several recent developments in our laboratory permitted the elaboration of a general method for the preparation of enantiomerically pure α-amino-β-hydroxy acids. First of all, it was found that the enolates of the 5-substituted 2-(*tert*-butyl)-1,3-dioxolanones (see **A**) [13], the 4-substituted 2-(*tert*-butyl)-*N*-benzoyl-1,3-oxazolidinones (**B**) [14] [15], and the 5-substituted 2-(*tert*-butyl)-1,3-imidazolidinones (**C**) [15–17] are alkylated highly stereoselectively to afford the products of electrophile approach from the side opposite to the *t*-Bu group *(Scheme 1)*.

Scheme 1[a])

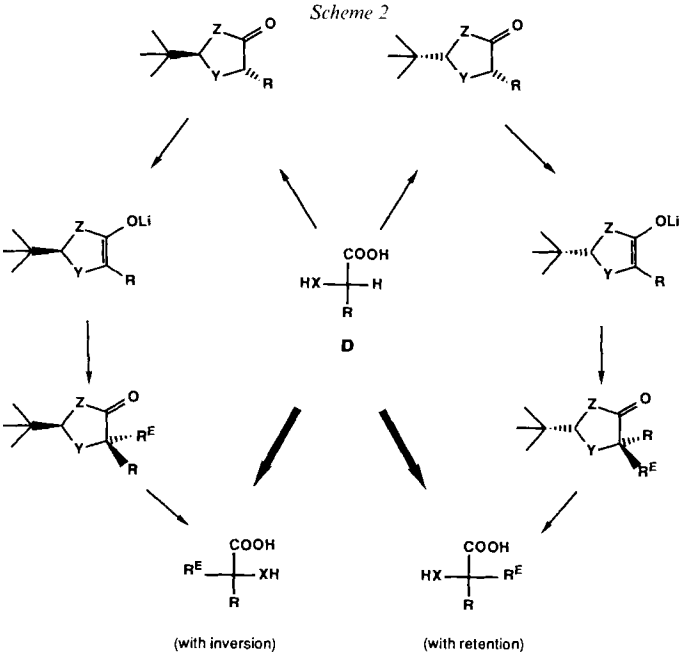


A Z = Y = O; R = CH_3, $C_6H_5CH_2$, $(CH_3)_2CH$, $CH_2CO_2^-$
B Z = O; Y = $NCOC_6H_5$; R = CH_3, $C_6H_5CH_2$, $(CH_3)_2CH$, $CH_3SCH_2CH_2$
C Z = NCH_3; Y = $NCOC_6H_5$; R = CH_3, $C_6H_5CH_2$, $(CH_3)_2CH$, $CH_3SCH_2CH_2$, C_6H_5

[a]) Only one of the enantiomers is shown.

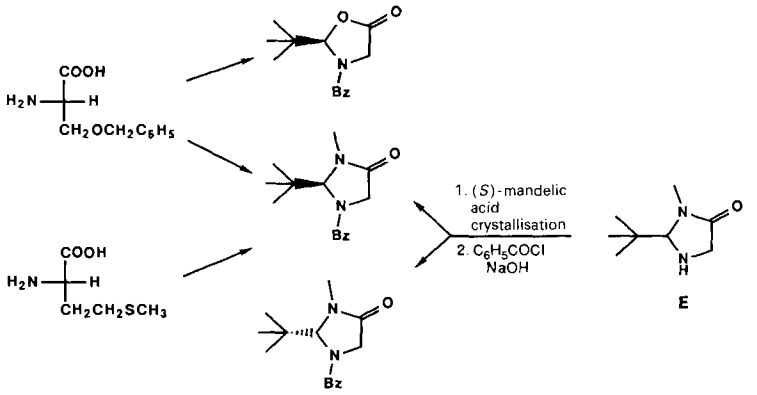
When the acetals were prepared from enantiomerically pure α-heterosubstituted carboxylic acids **D**, it was usually possible to isolate both (either) the *cis*- and (or) the *trans*-diastereoisomer. Although the original stereogenic center is lost during enolate formation (tetrahedral→trigonal), the stereogenic acetal center 'provides for chirality'

Scheme 2



and, thus, for diastereoselectivity of the reactions with electrophiles. Subsequent cleavage of the acetal moiety produces α-branched carboxylic acids in which the incorporation of the electrophile proceeded with retention or inversion of configuration, depending on the configuration (*cis* or *trans*) of the acetal employed *(Scheme 2)*. Since the sequence of reactions is carried out without employing chiral auxiliary reagents, the transformation takes place with self reproduction of the stereogenic center [18] [19].

Scheme 3

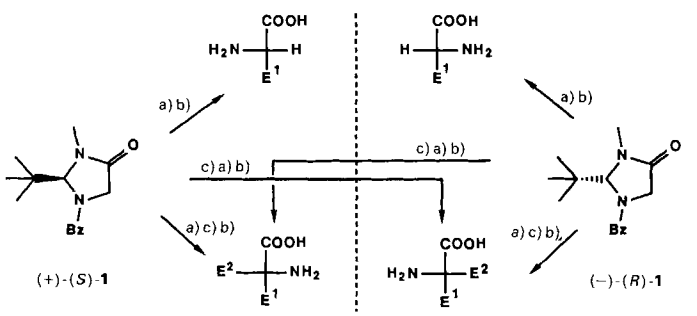


Bz = C_6H_5CO

In a second series of experiments, the preparation *(Scheme 3)* and stereoselective alkylation of chiral N,O- and N,N-acetals formally derived from glycine was achieved. The flexibility of our method was thus substantially increased because not only could α-amino- and α-hydroxy acids be branched without racemization *(Scheme 2)*, but now also the preparation of mono- and disubstituted *unnatural* amino acids became feasible [6] [17] [20] *(Scheme 4)*.

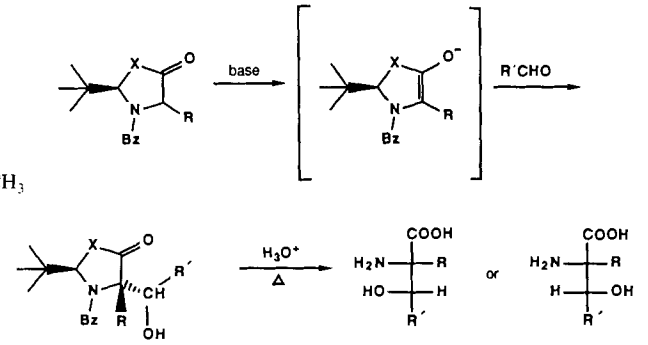
Of course, the full potential of the method is realized only when both enantiomers of the starting chiral acetal are readily available. This is indeed the case: most recently, the non-benzoylated imidazolidinone **E**, prepared from glycine, methylamine, and pivalaldehyde, could be resolved by crystallization of the mandelate salts [20] *(Scheme 3)*. As outlined in *Scheme 4*, this resolution makes possible the synthesis of branched and of unbranched α-amino acids of (*R*)- or (*S*)-configuration!

Scheme 4



a) Addition of E^1. b) Hydrolytic cleavage. c) Addition of E^2.

Scheme 5



It was the main goal of this work to study the addition of the enolates from imidazolidinones and oxazolidinones to aldehydes. The information at hand *(vide supra)* suggested that addition should take place on the enolate face opposite to the *t*-Bu group, leading to precursors of (*S*)-amino acids through the enolate shown in *Scheme 5*. The configuration at C(*β*) of the final α-amino-*β*-hydroxy acid would be determined by the relative topicity of addition.

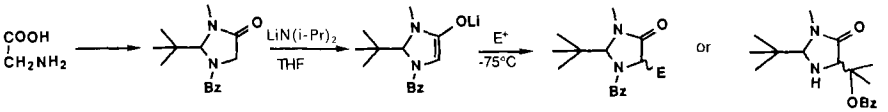
Results and Discussion. – A) *Stereochemical Course of the Alkylation of the Glycine Enolate Derived from 1-Benzoyl-2-(* tert-*butyl)-3-methylimidazolidin-4-one.* As indicated in the *Introduction,* enantiomerically pure *cis*- or *trans*-heterocycles **A**–**C** have been alkylated *via* their enolates to give, without racemization, derivatives with a tetrasubstituted C(α)atom *(Scheme 1)*. The almost exclusive approach of the electrophile from the face opposite to the *t*-Bu group of **C** (relative topicity *lk* [21]) has been applied, for example, to the preparation of either (*S*)- or (*R*)-α-methyldopa from (*S*)-alanine [22].

To prepare enantiomerically pure, non-branched amino acids (see *Scheme 4*), it was necessary that the monosubstituted heterocycle (*S*)- or (*R*)-**1** could also be stereoselectively alkylated, through the chiral glycine enolate **1**-Li, to give after hydrolysis the desired amino acids. Although we are aware of the fact that a racemic Li enolate does not necessarily react with the same selectivity as an enantiomerically pure one [23], due to aggregate formation[8]), we first sought information about the reactivity of the glycine-derived enolate **1**-Li from the racemic 1-benzoyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one (*rac*-**1**) with alkyl halides and symmetric (possessing homotopic faces) ketones.

The imidazolidinone *rac*-**1** was prepared from glycine by initial conversion of its methyl ester to the corresponding N^1-methylamide, which formed a *Schiff* base with pivalaldehyde (azeotropic removal of H_2O); the imine cyclized under acidic conditions, and the product was then treated with benzoyl chloride (BzCl)/Et_3N. The alkylation products **2**–**5** and the hydroxyalkylation product **6** of *rac*-**1** are formed with at least 95:5 preference for the *trans*-isomers, according to ^{13}C-NMR integration *(Scheme 6)*. The relative configuration of the main products **2**–**6** was assigned by NMR spectroscopy. In particular, NOE experiments showed that irradiation of the *t*-Bu group resulted in

[8]) Thus, a dimeric aggregate can be formed from two homochiral units [24] or from a pair of enantiomers. If the resulting diastereoisomers are involved in product-forming steps, they give rise to different ratios of isomeric products [23]!

Scheme 6



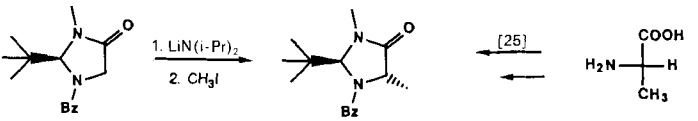
rac-**1** *rac*-**1**-Li **2–5** **6**

Product	E^+ (halide or ketone used)	Yield [%]	ds [%]	M.p. [°C]
2	CH_3I	90	95	145.6–146.2
3	$C_6H_5CH_2Br$	83	> 95	151.0–151.8
4	BuI	89	> 95	118.4–119.0
5	i-PrI	27	> 95	148.0–148.6
6	CH_3COCH_3	89	> 95	133.2–133.8

significant enhancement of the signal of H–C(5). These assignments could be confirmed in the case of **2–4** by comparison with the previously prepared optically active samples [25].

Methylation and benzylation of enantiomerically pure (*S*)-**1** (see *Scheme 3*) under the conditions employed for *rac*-**1** gave (2*S*,5*S*)-**2** and (2*S*,5*S*)-**3**, respectively, in $\geq 95\%$ ds. The product (2*S*,5*S*)-**2** was identified by comparison (NMR and $[\alpha]_D$) with an authentic sample prepared from (*S*)-alanine [25] *(Scheme 7)*.

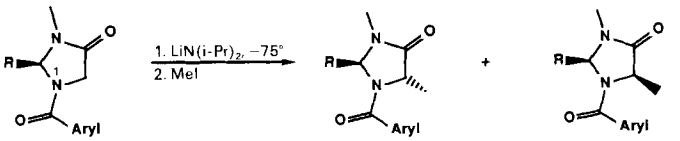
Scheme 7



(*S*)-**1** (2*S*,5*S*)-**2** (*S*)-alanine

B) *Concerning the Effects Determining the Stereoselectivity in the Addition of Electrophiles to the Lithium Enolate of* **1**. While it is obvious to explain the high *trans*/*cis*-ratio in the products **2–6** with the steric requirements of the *t*-Bu group, hindering approach to the *cis*-face and favoring attack of electrophiles with relative topicity *lk*-1,3 (*R*/*Re*, *S*/*Si*) [21], it is noteworthy that the imidazolidinone **10** (see *Scheme 8*), in which the bulky *t*-Bu

Scheme 8

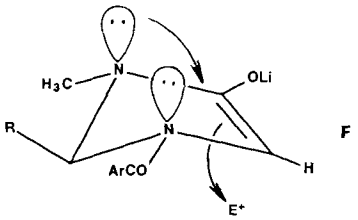


1, 7–11[a]) **2, 12–16**[a])

	R	Aryl	Colour of enolate solution	*trans*/*cis*-ratio in product	
1	*t*-Bu	C_6H_5	orange	19 : 1	**2**
7	*t*-Bu	*p*-CH_3O–C_6H_4	yellow	24 : 1	**12**
8	*t*-Bu	$C_6H_5CH_2O$	slightly yellow	32 : 1	**13**
9	i-Pr	*p*-C_6H_5–C_6H_4	deep red	2.8 : 1	**14**
10	i-Pr	C_6H_5	orange	6 : 1	**15**
11	i-Pr	*p*-CH_3O–C_6H_4	yellow	9 : 1	**16**

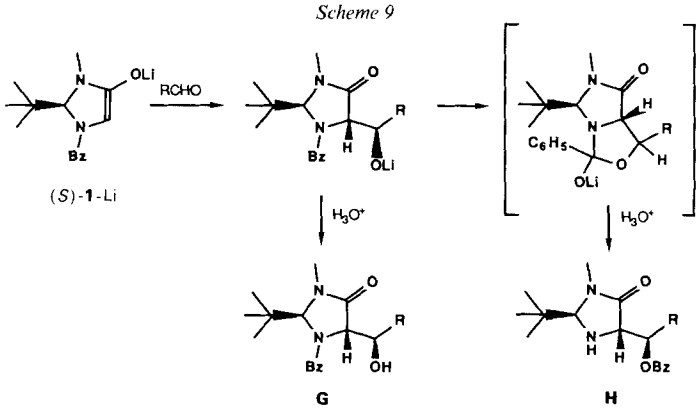
[a]) Compounds **7–16** are racemic mixtures; for convenience, only the formula of one enantiomer is given.

group has been substituted by the much smaller i-Pr group[9]), also reacted with good *lk*-selectivity. This result hinted to the possible involvement of stereoelectronic effects [27] [29a] lowering the transition-state energy of the *lk*-approach[10]) (see **F**) and led to the investigation of the additions **7**→**12**, **8**→**13**, **9**→**14**, and **11**→**16** *(Scheme 8)*.



Indeed, variation of the substitution in the arylcarbonyl moiety in such a way that delocalization of the lone pair of electrons at N(1) (see **1**) is increased resulted in decreased *lk*-selectivity, while substitution by an electron-donating group such as OR (see **7**, **11**)

Scheme 9



Aldehyde	Product of type **H**	ds [%]	Isolated yield [%]	$[\alpha]_D^{r.t.}$ [°]	M.p. [°C]
CH_3CHO	**17**	86[a])	75[b])	+85.7[a])	[c])
CF_3CHO	**18**	63	41	+10.8	103
$(CH_3)_2CHCHO$	**19**	95	79	+10.2	110
C_6H_5CHO	**20**	92	85	+24.6	151
o-CH_3–C_6H_4–CHO	**21**	88	81	+63.3	[c])
3,4-$(OCH_2O)C_6H_3CHO$	**22**	96	77	+16.5	[c])
p-C_6H_5–C_6H_4–CHO	**23**	93	79	+ 6.9	170
2-Furfuraldehyde	**24**	86	78[a])	−62.5	111
4-$(CHO)C_5H_4N$	**25**	89	71	+33.8	177

[a]) ds and $[\alpha]_D^{r.t.}$ of unrearranged hydroxyamide of type **G** (R = CH_3).
[b]) Combined yield of products of type **G** and **H**.
[c]) Non-crystalline material.

[9]) While the '*A*-value' of the *t*-Bu group is > 5 kcal/mol, that for an i-Pr is only *ca.* 2.1 kcal/mol, fairly close to that of Me (1.74 kcal/mol) [26].

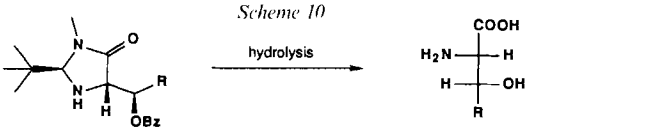
[10]) Structural information about imidazolidinones [28] indicates substantial degrees of non-planarity of the five-membered ring and of pyramidalization of the benzoyl-substituted N-atom. In [15], crystal structure of an oxazolidinone, the substituents on C(2), N(3), and C(4) have a *trans,trans*-arrangement.

led to higher selectivites[11]) *(Scheme 8)*. Nevertheless, it must be realized that, in addition to steric (*van der Waals* repulsion) and stereoelectronic effects, the aggregation state of the reagent and chelation of the metal may play important roles in controlling the course of the reaction; in the absence of detailed structural information about the lithium enolates involved, it is impossible to draw a definitive conclusion at this time.

C) *Reaction of the Enolate (S)-***1***-Li with Aldehydes: Coupling of Two Trigonal Centers.* In additions of the chiral glycine-enolate derivative of (*S*)-**1** to aldehydes, four diastereoisomers can be formed. However, when (*S*)-**1** was treated with $LiN(i\text{-}Pr)_2$/THF at −78° and then with the aldehyde at −100°, one of the possible diastereoisomeric products was formed, usually to the extent of 90% or more *(Scheme 9)*. Unexpectedly, the carbonyl adducts gave problems for another reason: low-temperature quenching of the reaction mixtures gave two isomers, initially thought to be diastereoisomers, until we discovered that one of them was the expected hydroxyamide **G**, and the other one the amino ester **H**, a constitutional isomer. The benzoyl group had shifted from the N- to the O-atom, probably through a tetrahedral intermediate [31] [32], the opening of which may be subject to stereoelectronic control[12]) [27] [33]. In most instances, room temperature quenching of the reaction mixtures afforded almost exclusively the rearranged products **H** (see **17**–**25**; *Scheme 9*).

D) *Stereochemical Course of the Addition of (S)-***1** *to Aldehydes.* The hydrolysis of the adducts **17**, **19**, and **20** afforded the known (2*S*,3*R*)-2-amino-3-hydroxy acids **26**–**28**, respectively, (*Scheme 10*, **H**→**I**; see *Section F*). That the reaction follows the same

Scheme 10

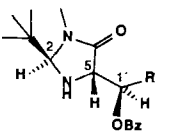


H **I** (2*S*,3*R*), L-*threo*, or *u*

17 R = CH_3
19 R = $(CH_3)_2CH$
20 R = C_6H_5

26 R = CH_3
27 R = $(CH_3)_2CH$
28 R = C_6H_5

Table 1. *^{1}H-NMR* (300 MHz) *Chemical Shifts of the Protons at the Stereogenic Centers C(2), C(5), and C(1′) in Adducts* **H**



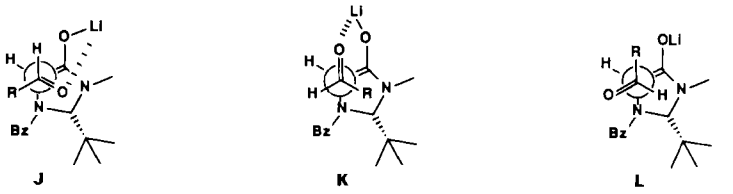
	Adduct **H**	H–C(2)	H–C(5)	H–C(1′)
R = aliphatic	**17**	4.21	3.73	5.38
	19	4.14	3.85	5.34
R = CF_3	**18**	4.17	4.17	5.98
R = aromatic	**20**	4.17	4.07	6.33
	21	4.24	4.00	6.51
	22	4.20	4.01	6.22
	23	4.22	4.11	6.37
	24	4.27	4.20	6.40
	25	4.19	4.08	6.25

[11]) Very recent results of *Hosomi et al.* [30] have also shown the importance of such 'stereoelectronic' effects in acyclic stereoselection.

[12]) So that the ester group is preferentially formed over the thermodynamically more stable amide function, see also the discussion in *Section E*.

stereochemical course in the case of imidazolidinones **18** and **21–25** is seen from the similarity in the ^{1}H-NMR chemical shifts for the protons at the stereogenic centers C(2), C(5), and C(1') *(Table 1)*. As expected *(vide supra)* the imidazolidinone enolate reacts with aldehydes from the side opposite to the *t*-Bu group: *lk*-1,3-induction [21]. *Scheme 11* shows the three staggered approaches of the two trigonal centers leading to the *threo*-product. We assume that the additions take place *via* the transition-state orientation **J** in which *a)* the double bonds of the donor and of the acceptor are synclinal and not antiperiplanar as in **L** [29b] [34], preventing the separation of opposite developing charges and still allowing for O–Li···O chelation (twist-boat arrangement), *b)* H–C(5) of the enolate is antiperiplanar to the acceptor carbonyl bond and not the electronegative *N*-benzoyl group as in **K** [29], and *c)* there is a maximum overlap of the donor and acceptor π-systems.

Scheme 11

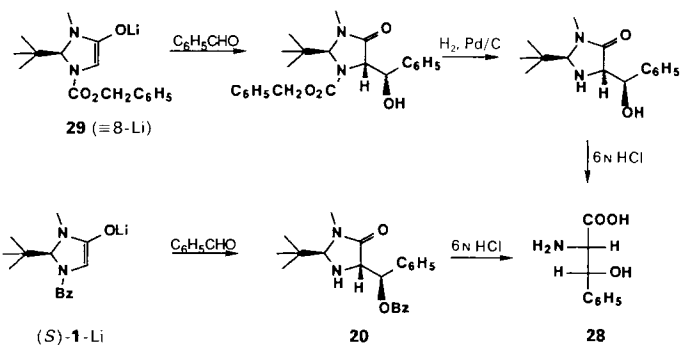


Si,Si (Relative topicity *lk*)

The result (relative topicity *lk* of coupling of the trigonal centers, *Scheme 11*) is opposite to what might have been expected in analogy with the addition of Li enolates of cyclic ketones (such as cyclohexanone) to aldehydes [23] [35–37]. Exchange of lithium for boron (by addition of BCl_3), magnesium (addition of $MgBr_2 \cdot Et_2O$) or titanium (combination with equimolar amounts of $Ti(i\text{-}PrO)_3Cl$, $Ti(NMe_2)_3Cl$) did not alter the relative topicity of the approach; lower yields of the desired aldol products were observed in these cases.

E) *Stereochemical Course of the 1,4-Benzoyl Migration.* As mentioned already *(Scheme 9)*, after the addition of (*S*)-**1**-Li to aldehydes, the amino esters **H** were usually isolated instead of the expected hydroxyamides **G**. To gain information about the stereo-

Scheme 12[a])



[a]) The transformation **29**→→**28** was performed with a racemic mixture.

chemical course of the rearrangement, the *N*-benzyloxycarbonyl-protected glycine derivative **29** (≡**8**-Li) was added to benzaldehyde; no rearrangement took place. After removal of the benzyloxycarbonyl group and subsequent hydrolysis, *threo*-phenylserine **28** was isolated, just like in the case of **1**, when rearrangement occurred *(Scheme 12)*. These results strongly suggest that the 1,3-benzoyl migration *(Scheme 9)* proceeds with retention of configuration at the LiO-substituted C-atom.

We observed that the minor diastereoisomer of addition (relative topicity of coupling of the trigonal centers *ul*) rearranges less readily than the major isomer (because of *'endo'*-substitution on the bicyclic intermediate (?), see *Scheme 9*).

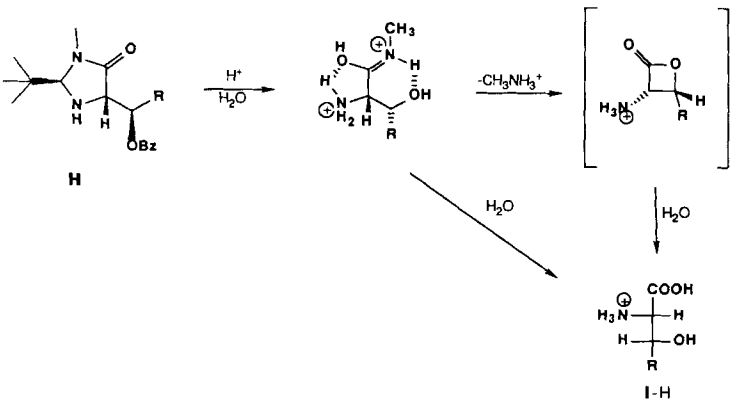
F) *Hydrolysis of the Imidazolidinone/Aldehyde Adducts to Give the α-Amino-β-hydroxy Acids.* The final step of the overall conversions outlined in *Scheme 2* is the hydrolysis of the heterocyclic products with cleavage of the ring and regeneration of a carboxylic acid. Hydrolysis is best achieved under acidic conditions. Although drastic conditions are required for derivatives geminally disubstituted in the position α to the carbonyl group (6N HCl, 160–180°, sealed tube) [22], monosubstituted, hydroxyalkylated imidazolidinones are much easier to cleave[13]). *Table 2* shows the results of hydrolysis of adducts **17**–**20** and **25**, carried out by heating to reflux the hydroxyalkylated product in 6N HCl (see *Schemes 9* and *10*).

The more facile hydrolysis of the hydroxyalkylated materials, as compared to simple alkyl derivatives which tend to give N^1-methyl-amino acid amides, might be due to anchimeric assistance as indicated in *Scheme 13*.

Table 2. *Hydrolysis of Products* **H** *to the α-Amino-β-hydroxy Acids* **I** *with 6N HCl at* ca. *100°*

Adduct **H**	Product **I**	R	Reaction time [h]	Yield [%]	M.p. [°C]	$[\alpha]_D^{r.t.}$ [°]
17	**26**	CH_3	8	> 98	236	−27.9
18	**30**	CF_3	24	> 98	211	−12.4
19	**27**	$(CH_3)_2CH$	12	68	215	− 3.5
20	**28**	C_6H_5	8	54	182	−34.3
25	**31**	4-Pyridyl	24	81	221	−38.0

Scheme 13

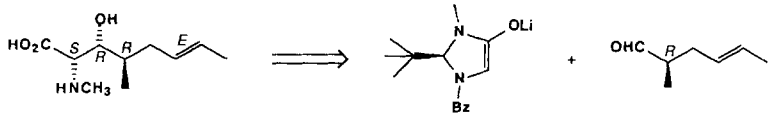


[13]) Also, the O,O-acetal derivatives *(Scheme 2)* are cleaved more readily than the N,O- and N,N-analogues [6].

(*S*)-Threonine (**26**), (2*S*,3*R*)-3-phenylserine (**28**) and (2*S*,3*R*)-3-hydroxyleucine (**27**) and the unnatural α-amino-β-hydroxy acids (2*S*,3*R*)-3-furanylserine (from **24**), (2*S*,3*R*)-3-(biphenyl-4-yl)serine (from **23**), (2*S*,3*R*)-3-(*o*-tolyl)serine (from **21**), (2*S*,3*R*)-3-(4-pyridyl)serine (**31**), (*S*)-β-hydroxydopa, and (*S*)-4,4,4-trifluorothreonine (**30**), and many others are thus available. The unnatural amino-hydroxy acids are expected to possess interesting biological activity and to be of use for the study of the mechanism of enzymic action.

G) *'Multiple Stereoselection': Approach to the Synthesis of (2*S*,3*R*,4*R*,6*E*)-3-Hydroxy-4-methyl-2-(methylamino)-6-octenoic Acid* (**32**), *the C_9 Amino Acid from Cyclosporines.* Because the reaction of the Li enolate of (*S*)-**1** with aldehydes provides α-amino-β-hydroxy acids of absolute configurations (2*S*,3*R*) *(vide supra)*, the synthesis of the important amino acid **32** in the undecapeptide cyclosporine [38] was deemed within reach[14]) *(Scheme 14)*.

Scheme 14



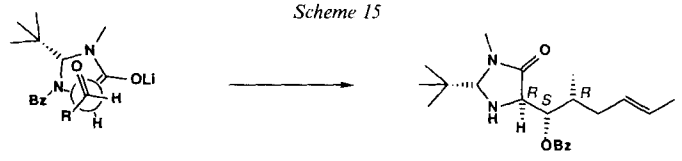
32
amino acid No. 1
in cyclosporine

(*S*)-**1**

(*R*)-**33**

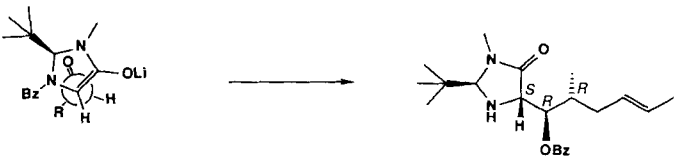
The availability of aldehyde **33**[15]) as well as of both enantiomers of the imidazolidinone **1** [20] offered also an opportunity to examine the degree of stereoselectivity of a process in which two new chiral centers are formed in a reaction of two chiral precursors [6] [39]. In the system at hand, the combination (*R*)-**1**-Li/(*R*)-**33** allows for *lk*-1,3-induction by the chiral center of the enolate, relative topicity *lk* in the approach of the two trigonal centers, and *lk*-1,2-induction by the chiral center of the aldehyde (*Cram's* rule [40]). Indeed, this favorable (*R*)-**1**-Li/(*R*)-**33** pair afforded the adduct **34** in *ca.* 96% ds.

Scheme 15



(*R*)-**1**-Li/(*R*)-**33**

34; 96% ds



(*S*)-**1**-Li/(*R*)-**33**

35; 93% ds

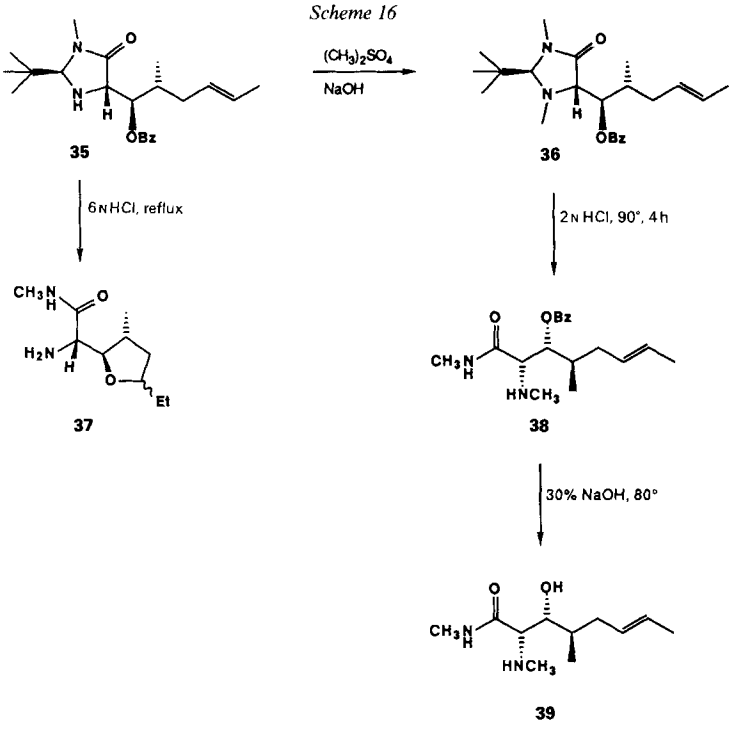
[14]) Synthesis of the so-called C_9 amino acid **32** (MeBmt): see [12] [38].

[15]) Kindly provided by Dr. *W. Langer* of *Sandoz AG*, CH-4002 Basel.

On the other hand, the desired product **35** was obtained from the (*S*)-**1**-Li/(*R*)-**33** pair in *ca.* 93% ds *(Scheme 15)*. Clearly, the selectivity induced by the stereogenic center of the aldehyde is smaller than that induced by the stereogenic center of the enolate.

Final purification of **35** was done by recrystallization from Et_2O/hexane; *ca.* 82% of the pure adduct was obtained. Because the target amino acid, (2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid (C_9 amino acid (MeBmt)) occurs in cyclosporine as the *N*-methyl derivative, methylation of **35** was carried out with dimethyl sulfate in the presence of NaOH; the expected product **36** was isolated in 84% yield after flash chromatography (see *Exper. Part*). While the normal hydrolytic procedure to convert adducts **H** into amino acids **I** (6N HCl, reflux) led, in the case of **35**, instead to the tetrahydrofuran derivative **37** *(Scheme 16)*, milder acidic conditions (2N HCl, 90°, 4 h) afforded the carbamoyl-methylamino benzoate **38** in essentially quantitative yield from **36**. Hydrolysis of the benzoate group (**38**→**39**) was also quantitatively achieved by 30% NaOH at 80° *(Scheme 16)*.

Scheme 16



Final hydrolysis of the *secondary* amide group in **39** has proved difficult. The desired conversion **39**→**32** was attempted with sodium peroxide [41] and with hydrazine [42]; over-oxidation with loss of the amino group was observed in the first case, and recovery of the starting material resulted from the latter. Alternative methods are being explored at the present time.

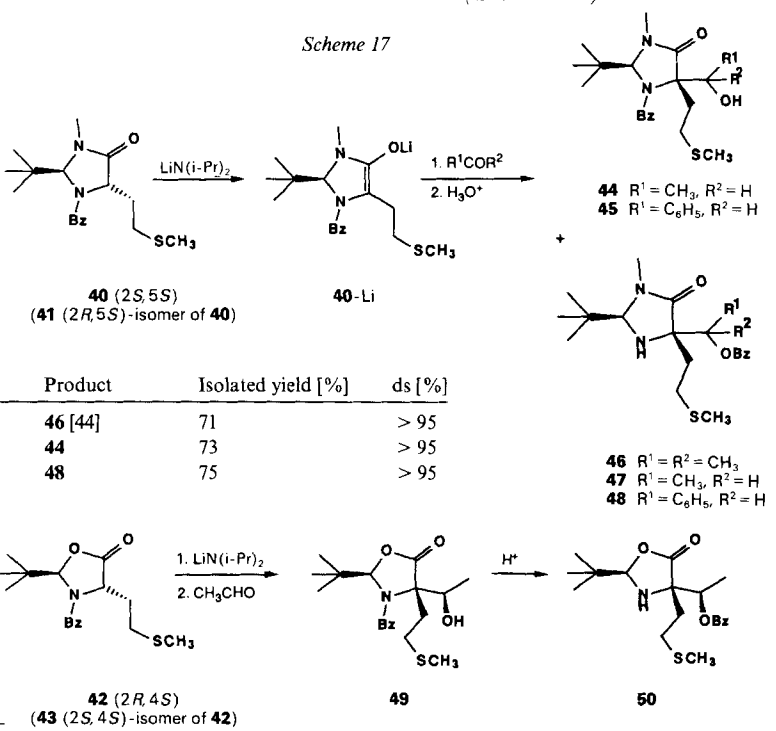
H) *Addition of Chiral Methionine-Enolate Derivatives to Aldehydes and Ketones.* In *Scheme 3* it was shown that (*S*)-methionine is a convenient starting material for the preparation of the enantiomerically pure imidazolidinone (*S*)-**1**. The intermediate cyclic

acetals **40** and **41** as well as their N,O-analogs **42** and **43** are at the same time useful precursors of other amino-acid derivatives. The imidazolidinones **40** and **41** are prepared from (*S*)-*N*^{1}-methylmethionineamide [25], and the oxazolidinones **42** and **43** are obtained through the Na salt of the imine from pivalaldehyde and methionine [14] [15] [43].

Deprotonation of imidazolidinone **40** with 1.1 equiv. of LiN(i-Pr)$_2$ in THF at −75° afforded the characteristic orange solution of the corresponding enolate **40**-Li *(Scheme 17)*. Treatment with acetone resulted in rapid decolourization of the solution, which was then quenched with AcOH and worked up in the usual way to give the diastereoisomerically pure amino ester **46** in 71% yield[16]). Hydroxyamide **44** was obtained from **40**-Li, when acetaldehyde was used as the electrophile; it crystallized as a single diastereoisomer from the crude product. Finally, the reaction of **40**-Li with benzaldehyde yielded a mixture of isomers **45** and **48**; the former rearranged to the amino benzoate upon standing at room temperature. The migration of the benzoyl group (**44**→**47** and **45**→**48**) could be catalyzed in MeOH/HCl or MeOH/TsOH. As it was already discussed (see *Section E*), this 1,4-benzoyl migration most likely takes place with retention of configuration at the O-substituted C-atom; the amides and the esters are, therefore, assigned the same configuration.

The oxazolidinone enolate **42**-Li reacted also diastereoselectively with acetaldehyde; the hydroxyamide **49** could be isolated in this case, and subsequent treatment with MeOH/HCl afforded the acid-sensitive amino ester **50** *(Scheme 17)*.

Scheme 17



40 (2*S*,5*S*) (**41** (2*R*,5*S*)-isomer of **40**)

40-Li

44 $R^1 = CH_3$, $R^2 = H$
45 $R^1 = C_6H_5$, $R^2 = H$

46 $R^1 = R^2 = CH_3$
47 $R^1 = CH_3$, $R^2 = H$
48 $R^1 = C_6H_5$, $R^2 = H$

Electrophile	Product	Isolated yield [%]	ds [%]
Acetone	**46** [44]	71	> 95
Acetaldehyde	**44**	73	> 95
Benzaldehyde	**48**	75	> 95

42 (2*R*,4*S*) (**43** (2*S*,4*S*)-isomer of **42**)

49

50

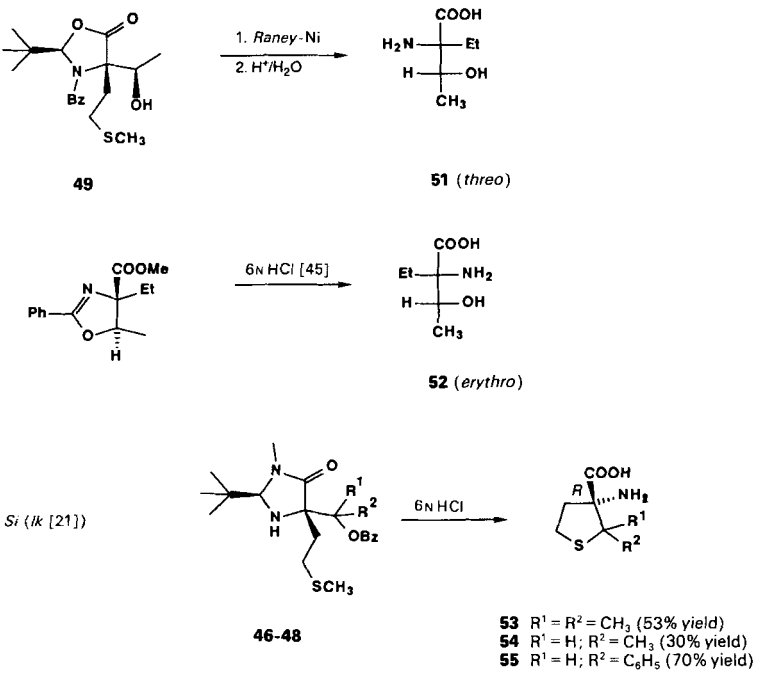
[16]) We had reported [22] that the enolates from the imidazolidinones (**C** in *Scheme 1*) are too basic to add to enolizable carbonyl compounds such as acetone. This is incorrect: the reaction mixture had been warmed too high too long, so that *retro*-aldol addition occurred which eventually gave rise to proton transfer.

The configuration of the hydroxyalkylated imidazolidinones **44**–**48** and of the oxazolidinone **49** was determined by NOE measurements in the ^{1}H-NMR spectrum [44]. It is clear then that hydroxyalkylations of enolates **40**-Li and **42**-Li proceed from the side opposite to the *t*-Bu group, both with N,N- and N,O-heterocycles. The tetrasubstituted C-atoms in the heterocyclic rings of **44**–**50** are thus assigned (*S*)-configuration.

The absolute configuration of the newly formed O-substituted stereogenic center was determined in the case of the hydroxyamide **49** by desulfurization and hydrolysis, which yielded (−)-2-ethylthreonine **51**; its *threo*-configuration could be ascertained by NMR comparison with the known [45] (+)-(2*R*,3*R*)-2-ethylallothreonine (**52**; *Scheme 18*). The (2*R*,4*S*,1′*R*)-configuration was, therefore, assigned to the main product **49** from the hydroxyethylation of **42**. The reaction between the trigonal centers of the enolate **42**-Li and of the acetaldehyde takes place with relative topicity *lk*. We assume that the reactions of imidazolidinone **40**-Li with carbonyl electrophiles *(Scheme 17)* also proceed with the same *lk*-topicity.

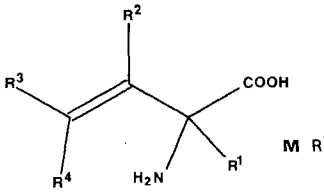
The hydrolysis of the aldol products **46**–**48** was effected as in the case of adducts **H** *(Section F)* with 6N HCl. However, heating to *ca.* 150° for 2–3 h in a *Bombenrohr* was required. The crystalline tetrahydrothiophenes **53**–**55** were isolated in diastereoisomerically pure form[17] *(Scheme 18)*. Because the stereochemical course of the ring closure is not known[18], the *Formulae* **53**–**55** in *Scheme 18* indicate only the absolute configuration at C(3); *i.e. R*.

Scheme 18



[17]) These cyclic amino-acid derivatives may act as inhibitors in the enzymatic synthesis of *S*-adenosyl-(*s*)-methionine [46].

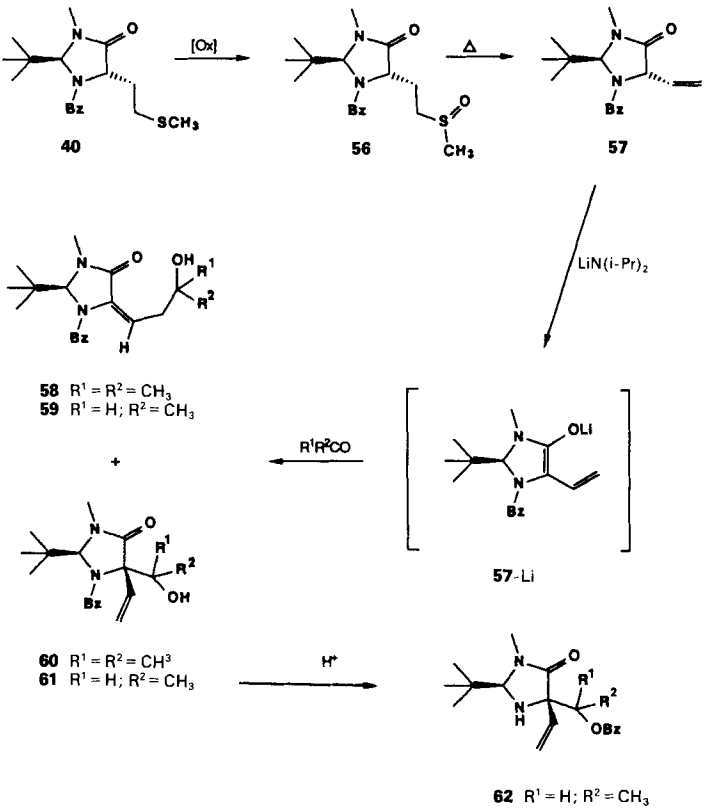
[18]) We assume that the O/S substitution upon ring closure occurs with inversion at the stereogenic center.



M R^1 = H, alkyl; R^2 to R^4 = H, alkyl, XR (X = heteroatom)

I) *Preparation of α-Branched Vinylglycine Derivatives from Methionine.* β,γ-Unsaturated amino-acid derivatives **M** are important enzyme inhibitors [47]. The simplest example of this type of amino acids, *i.e.* vinylglycine (**M**, R^1–R^4 = H), was obtained for the first time in enantiomerically pure form by *Ardakani* and *Rapoport* [48]. More recently, several optically active vinylglycine derivatives (**M**, $R^1 = R^3 = H$; $R^2 = R^4$ = alkyl) have been prepared by *Schöllkopf et al.* [49].

Scheme 19



Electrophile	Enolate	α/γ Ratio	Product	Isolated yield [%]	ds [%]
Acetone	**57**-Li	5:95	**58** [44]	35	> 95
Acetaldehyde	**57**-Li	3:2	**62**	40	> 90
Acetaldehyde	**57**-MgBr	> 95:5	**62**	55	> 90
Acetaldehyde	**57**-Ti(NMe_2)$_3$	> 95:5	**62**	48	> 90

Following the same principle that *Ardakani* and *Rapoport* developed for the synthesis of (*S*)-2-vinylglycine [48], the imidazolidinone **40** was converted to the vinylglycine derivative **57** *via* sulfoxides **56** *(Scheme 19)*. The oxidation step was carried out with H_2O_2/AcOH or $NaIO_4$/MeOH[19]); the pyrolysis was effected at 210°.

Deprotonation of the vinyl-substituted imidazolidinone **57** with 1.1 equiv. of LiN-(i-Pr)$_2$ in THF at −78° afforded a deep-red solution containing the dienolate **57**-Li, which can react with electrophiles in the α- or γ-position. While the alkylation of **57**-Li with alkyl halides took place in a highly regioselective fashion at the α-position [15], addition of **57**-Li to acetone as the electrophile afforded exclusively the γ-hydroxyalkylation product **58** *(Scheme 19)*; no α-hydroxyalkyl derivative **60** was detected. With acetaldehyde as the electrophile, a 2:5 mixture of the constitutional isomers **59** and **61**, both diastereoisomerically pure, was obtained. The main product **61** was isolated in *ca.* 40% yield as an oil, it rearranged slowly at room temperature to the crystalline, diastereoisomerically pure amino ester **62**; this rearrangement can be induced by HCl in MeOH (*Scheme 19;* see also *Section E*). The (*E*)-configuration is tentatively assigned to the α,β-unsaturated carbonyl derivatives **58** and **59**.

The effect of the metal in this C–C bond forming reaction was studied. The Mg derivative **57**-MgBr was formed upon addition of $MgBr_2$ to the THF solution of **57**-Li [50]. The Ti derivative **57**-Ti(NMe$_2$)$_3$ was similarly prepared by the addition of chlorotris(dimethylamino)titanium [11] [51] to **57**-Li/THF. The reaction of acetaldehyde with **57**-MgBr or **57**-Ti(NMe$_2$)$_3$ was regioselective, producing the product from α-hydroxyalkylation as a mixture of hydroxyamide **61** and amino ester **62.** The best yield (55%) was observed with the magnesium enolate **57**-MgBr (see *Scheme 19;* the diastereoselectivities were determined by ^{1}H-NMR spectroscopy of the crude products).

This work was possible thanks to the support of *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung, Sandoz AG* (Basel, Switzerland), *Degussa AG* (West Germany), *Consejo del Sistema Nacional de Educación Tecnológica y Consejo Nacional de Ciencia y Tecnologia* (Mexico).

Experimental Part

General. Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organolithiums were dried for *ca.* 12 h at 120° and allowed to cool in a desiccator over anh. $CaSO_4$. Anh. solvents were obtained by distillation from benzophenone ketyl [53]. The BuLi employed was titrated according to the method of *Juaristi et al.* [54].

TLC: *Merck-DC-F$_{254}$* plates; detection by UV light, I_2, or ninhydrine. Flash column chromatography (FC) [52]: *Merck* silica gel (0.040–0.063 mm). M.p.: *Tottoli (Büchi)* apparatus; not corrected. $[\alpha]_D$ r.t.: *Perkin-Elmer 241* polarimeter. IR spectra: *Perkin-Elmer 297* spectrometer. ^{1}H- and ^{13}C-NMR spectra: *Varian EM-390, AH-100,* or XL-100, as well as *Bruker-300* or *-360-*MHz spectrometer; chemical shifts (δ) in ppm downfield from the internal reference TMS, the coupling constants *J* in Hz. MS: *Hitachi-Perkin-Elmer RMU-6 M* or *Varian MAT-111* (GC/MS system); *m/z* values with relative intensities (%) in parenthesis. ds = diastereoselectivity, ee = enantiomeric excess.

General Procedure 1: Reaction of Imidazolidinone Enolates with Aldehydes. A soln. of (i-Pr)$_2$NH (5.5 mmol) in 75 ml of THF[20]) was cooled down to −75° (dry-ice/acetone bath; *Pt-100* thermometer) before the slow addition of 5.5 mmol of BuLi (in hexane; *ca.* 1.58M). The resulting soln. was stirred at −75° during 20 min, and then treated with 5 mmol of the imidazolidinone in 25 ml of THF. The highly coloured soln. formed (yellow to deep-red,

[19]) A *ca.* 1:1 diastereoisomeric mixture of sulfoxides **56** was obtained.

[20]) Smaller amounts of THF are not convenient because the enolate produced tends to precipitate.

depending on the substituents at the ring) was cooled down to −100° (liquid N_2/Et_2O bath) and stirred at −100° for 20 min. The aldehyde (8–10 mmol) in 10–15 ml of THF was added (concomitant decolouration of the soln.) and stirred for 30 min at −100° and then for 30 additional min at r.t. Then the mixture was transferred *via* cannula into 50–70 ml of sat. aq. NH_4Cl soln. The aq. phase was separated and extracted 3 times with Et_2O. The combined Et_2O extracts were dried (anh. $MgSO_4$), filtered, and evaporated to give the crude product.

General Procedure 2: Hydrolysis of the Hydroxyalkylated Imidazolidinones (**H**→**I**, *Scheme 10* and *Table 2*). A suspension of 1.0 mmol of adduct **H** in 10 ml of 6N HCl was heated to reflux for several h[21]) (exact conditions and reaction times below). The soln. was then allowed to cool to r.t. and extracted 3 times with Et_2O. The aq. phase was evaporated to afford the **I**·HCl, which was adsorbed to acidic ion-exchanger resine *Dowex SOWX8*. The resine was washed with distilled H_2O till the washings came out neutral, and then the free amino acid **I** was recovered with 1.5M aq. NH_3. Evaporation afforded the crystalline **I**, which was dried under high vacuum at 110° for 15 h.

*(S)-1-Benzoyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one* ((*S*)-**1**). Prepared by benzoylation of (*R*)-2-(*tert*-butyl)-3-methylimidazolidin-4-one, itself obtained by the resolution procedure of *Fitzi* and *Seebach* [20].

*1-1-Benzoyl-2-(*tert*-butyl)-3,5-dimethylimidazolidin-4-one* (**2**). A 0.710M soln. of LiN(i-Pr)$_2$ (7.75 ml, 5.5 mmol) was slowly added to a stirred soln. of *rac*-**1** (1.3 g, 5 mmol) in THF (50 ml) at −78°, and stirring was continued for 45 min. MeI (0.373 ml, 6 mmol) was slowly added, and after 1 h at −78°, the temp. was allowed to rise overnight to *ca.* 0°. The reaction was then quenched with half-sat. NH_4Cl soln. (50 ml) and Et_2O (50 ml). The aq. phase was separated and extracted with Et_2O (3 × 50 ml). The combined org. phases were washed with H_2O (2 × 25 ml), dried ($MgSO_4$), and evaporated to give an off-white solid (95% ds (^{13}C-NMR)). FC (Et_2O/petroleum ether/MeOH 60:35:5) gave pure **2** (1.24 g, 90%), which was crystallized from AcOEt/petroleum ether; m.p. 145.6–146.2°. IR: 2982*m*, 1697*s*, 1633*s*, 1380*s*, 1260*s*. ^{1}H-NMR: 7.63–7.26 (*m*, 5 arom. H); 5.67 (*s*, H–C(2)); 4.26 (*q*, *J* = 6.6, H–C(5)); 3.08 (*s*, CH_3N); 1.07 (*s*, *t*-Bu); 0.98 (*d*, *J* = 6.6, CH_3–C(5)). ^{13}C-NMR: 172.25; 170.99; 137.14; 131.42; 128.87; 127.67; 79.88; 57.30; 40.72; 32.00; 26.34; 19.41. MS: 217 (100, $M^{+\cdot}$ − 57), 106 (72), 105 (98), 84 (11), 77 (95). Anal. calc. for $C_{16}H_{22}N_2O_2$: C 70.04, H 8.08, N 10.21; found: C 69.93, H 8.05, N 10.23.

*(2S,5S)-1-Benzoyl-2-(*tert*-butyl)-3,5-dimethylimidazolidin-4-one* ((2*S*,5*S*)-**2**). From (*S*)-**1** and MeI (1.2 equiv.), yield 51%, 95% ds; m.p. 184° (from CH_2Cl_2/pentane); $[\alpha]_D$ = +45° ($CHCl_3$, *c* = 1).

*1-1-Benzoyl-5-benzyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one* (**3**). A 0.750M soln. of LiN(i-Pr)$_2$ (14.7 ml, 11 mmol) was slowly added to a stirred soln. of *rac*-**1** (2.6 g, 10 mmol) in THF (100 ml) at −78°, and stirring was continued for 45 min. Benzyl bromide (1.43 ml, 12 mmol) was slowly added, and after 30 min at −78°, the temp. was allowed to rise over 2 h to *ca.* 0°, and the reaction was then quenched with half-sat. NH_4Cl soln. (100 ml) and Et_2O (100 ml). The aq. phase was separated and extracted with Et_2O (3 × 50 ml). The combined org. phases were washed with H_2O (2 × 50 ml), dried ($MgSO_4$), and evaporated to an off-white solid (> 95% ds (^{13}C-NMR)). FC (AcOEt/petroleum ether 1:1) gave pure **3** (2.9 g, 83%), which was crystallized from AcOEt; m.p. 151.0–151.8°. IR: 2975*m*, 1695*s*, 1640*s*, 1377*s*, 1263*m*. ^{1}H-NMR: 7.50–6.95 (*m*, 10 arom. H); 5.18 (br., H–C(2)); 4.66 (*m*, H–C(5)); 3.18–2.66 (*m*, PhCH_2); 2.86 (*s*, CH_3N); 0.94 (*s*, *t*-Bu). ^{13}C-NMR: 171.08; 170.66; 136.61; 135.00; 131.54; 129.82; 129.19; 128.75; 128.56; 128.31; 128.07; 126.84; 81.17; 62.05; 41.36; 35.90; 31.88; 26.46. MS: 293 (32, $M^{+\cdot}$ − 57), 106 (8), 105 (100), 91 (5), 77 (24). Anal. calc. for $C_{22}H_{26}N_2O_2$: C 75.40, H 7.48, N 7.99; found: C 75.18, H 7.37, N 7.92.

*(2S,5S)-1-Benzoyl-5-benzyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one* ((2*S*,5*S*)-**3**). From (*S*)-**1** and benzyl bromide, yield 45%, > 95% ds; m.p. 148° (from CH_2Cl_2/pentane); $[\alpha]_D$ = +121° ($CHCl_3$, *c* = 1).

*1-1-Benzoyl-5-butyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one* (**4**). A 0.710M soln. of LiN(i-Pr)$_2$ (7.75 ml, 5.5 mmol) was slowly added to a stirred soln. of *rac*-**1** (1.3 g, 5 mmol) in THF (50 ml) at −78°, and stirring was continued for 45 min. Iodobutane (2.85 ml, 25 mmol) was slowly added, and, after 1 h at −78°, the temp. was allowed to rise overnight to *ca.* 0° and the reaction was then quenched with half-sat. NH_4Cl soln. (50 ml) and Et_2O (50 ml). The aq. phase was separated and extracted with Et_2O (3 × 50 ml). The combined org. phases were washed with H_2O (2 × 25 ml), dried ($MgSO_4$), and evaporated to a yellow solid (> 95% ds (^{13}C-NMR)). FC (Et_2O/petroleum ether 70:30) gave pure **4** (1.42 g, 89%), which was crystallized from AcOEt/petroleum ether; m.p. 118.4–119.0°. IR: 2961*m*, 2932*m*, 1703*s*, 1625*s*, 1386*m*, 1368*m*. ^{1}H-NMR: 7.63–7.42 (*m*, 5 arom. H); 5.64 (*s*, H–C(2)); 4.34 (*m*, H–C(5)); 3.08 (*s*, CH_3N); 1.06 (*s*, *t*-Bu); 1.19–0.67 (*m*, *n*-Bu). ^{13}C-NMR: 171.52; 171.33; 136.85; 131.53; 128.80; 127.57; 80.16; 61.50; 41.00; 31.78; 30.41; 26.41; 24.32; 22.16; 13.67. MS: 259 (30, $M^{+\cdot}$ − 57), 106 (8), 105 (100), 77 (19). Anal. calc. for $C_{19}H_{28}N_2O_2$: C 72.12, H 8.92, N 8.85; found: C 72.04, H 8.97, N 8.85.

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[21]) Most commonly, the original suspension vanished upon heating; however, a precipitate formed after a few min, redissolved, and then gave rise to a second precipitate: benzoic acid. The first precipitate could be characterized in one case as the N^1-methylamide of the final amino acid.

l-*1-Benzoyl-2-(*tert-*butyl)-3-methyl-5-isopropylimidazolidin-4-one* (**5**). A 0.720M soln. of LiN(i-Pr)$_2$ (7.64 ml, 5.5 mmol) was slowly added to a stirred soln. of *rac*-**1** (1.3 g, 5 mmol) in THF (50 ml) and *N,N'*-dimethylpropyleneurea (20 ml) at −78°, and stirring was continued for 45 min. 2-Iodopropane (2.49 ml, 25 mmol) was slowly added, and after being maintained at −78° overnight the temp. was allowed to rise to *ca.* 0°, and the reaction was then quenched with half-sat. NH_4Cl soln. (50 ml) and Et_2O (250 ml). The aq. phase was separated and extracted with Et_2O (3 × 50 ml). The combined org. phases were washed with H_2O (3 × 50 ml), dried ($MgSO_4$), and evaporated to a yellow oil (> 95% ds (^{13}C-NMR)). FC (Et_2O/petroleum ether 70:30) gave *rac*-**1** (0.74 g, 57%) and pure **5** (0.41 g, 27%), which was crystallized from Et_2O; m.p. 148.0–148.6°. IR: 2963*m*, 1704*s*, 1632*s*, 1407*m*, 1378*s*, 1365*s*. ^{1}H-NMR: 7.67–7.41 (*m*, 5 arom. H); 5.67 (*s*, H–C(2)); 4.22 (*s*, H–C(5)); 3.04 (*s*, CH_3N); 1.78–1.56 (br., $(CH_3)_2CH$); 1.04 (*s*, *t*-Bu); 0.96, 0.62 (*dd*, *J* = 6.7, $(CH_3)_2CH$). ^{13}C-NMR: 171.29; 170.46; 137.07; 131.64; 128.96; 127.21; 79.95; 65.57; 41.21; 31.44; 30.74; 26.42; 18.11; 14.32. MS: 245 (57, $M^{+\cdot}$ − 57), 106 (12), 105 (100), 77 (35). Anal. calc. for $C_{18}H_{26}N_2O_2$: C 71.49, H 8.67, N 9.26; found: C 71.52, H 8.54, N 9.26.

u-*5-(1'-Benzoyloxy-1'-methylethyl)-2-(*tert-*butyl)-3-methylimidazolidin-4-one* (**6**). A 0.720M soln. of LiN(i-Pr)$_2$ (7.64 ml, 5.5 mmol) was slowly added to a stirred soln. of *rac*-**1** (1.3 g, 5 mmol) in THF (50 ml) at −78°, and stirring was continued for 45 min. Acetone (0.73 ml, 10 mmol) was slowly added and, after 9 h at −78°, the reaction was quenched with 5M AcOH in THF (5 ml), the temp. was allowed to rise to r.t., and then half-sat. NH_4Cl soln. (50 ml) and Et_2O (50 ml) were added. The aq. phase was separated and extracted with Et_2O (3 × 50 ml). The combined org. phases were washed with 2N Na_2CO_3 (25 ml) and H_2O (25 ml), dried ($MgSO_4$), and evaporated to a white solid (> 95% ds (^{13}C-NMR)). FC (Et_2O/petroleum ether 60:40) gave pure **6** (1.42 g, 89%), which was crystallized from AcOEt/petroleum ether; m.p. 133.2–133.8°. IR: 3380*m*, 2952*m*, 1690*s*, 1394*s*, 1281*s*, 1103*s*. ^{1}H-NMR: 7.98–7.94, 7.55–7.38 (2*m*, 5 arom. H); 4.27, 4.17 (2*d*, *J* = 2, H–C(2), H–C(5)); 2.97 (*s*, CH_3N); 2.20 (*s*, NH); 1.78 (*s*, CH_3); 1.58 (*s*, CH_3); 0.97 (*s*, *t*-Bu). ^{13}C-NMR: 172.40; 165.76; 132.61; 131.69; 129.48; 128.25; 84.76; 83.14; 64.40; 37.49; 30.96; 25.43; 23.33; 21.72. MS: 261 (56, $M^{+\cdot}$ − 57), 203 (22), 179 (11), 155 (27), 140 (46), 139 (93), 138 (12). Anal. calc. for $C_{18}H_{26}N_2O_3$: C 67.90, H 8.23, N 8.80; found: C 67.91, H 8.36, N 8.81.

*(±)-2-(*tert-*Butyl)-1-(4-methoxybenzoyl)-3-methylimidazolidin-4-one* (**7**). A soln. of 4-methoxybenzoyl chloride (3.96 g, 6.84 ml of a 58% toluene soln., 23 mmol) in 33 ml of CH_2Cl_2 was cooled to 0° under Ar. (±)-2-(*tert*-Butyl)-3-methylimidazolidin-4-one [25] in 20 ml CH_2Cl_2 was then added dropwise, followed by neat Et_3N (3.3 ml, 23 mmol). The mixture was stirred at 0° for 1 h and at r.t. for an additional h. H_2O (*ca.* 80 ml) was added, and the org. phase separated, dried ($MgSO_4$), filtered, and evaporated to give 6.4 g (100% yield) of crude **7**, which was recrystallized from EtOH (83% yield); m.p. 172.0–173.5°. IR (KBr): 3400*w*, 2980*m*, 1720*s*, 1648*s*, 1380*s*, 1250*s*, 1040*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.08 (*s*, *t*-Bu); 3.04 (*s*, CH_3N); 3.85 (*s*, CH_3O); 3.89 (*A* of *AB*, *J* = 15.6, H–C(5)); 4.15 (*B* of *AB*, *J* = 15.5, H–C(5)); 5.62 (*d*, *J* = 1.1, H–C(2)); 6.93 (distorted *d*, *J* = 8.9, 2 H_{meta}); 7.56 (distorted *d*, *J* = 8.9, 2 H_{ortho}). ^{13}C-NMR ($CDCl_3$): 27.40; 32.95; 41.07; 54.62; 56.82; 82.19; 115.26; 127.73; 131.61; 163.61; 170.83; 172.69. MS: 233 (81, $M^{+\cdot}$ − 57), 135 (100), 107 (26), 92 (29), 77 (45), 57 (10). Anal. calc. for $C_{16}H_{22}N_2O_3$: C 66.18, H 7.64, N 9.65; found: C 66.22, H 7.63, N 9.62.

*(±)-1-Benzyloxycarbonyl-2-(*tert-*butyl)-3-methylimidazolidin-4-one* (**8**). Benzyloxycarbonyl chloride (3.55 ml, 25 mmol) was added slowly to a stirred suspension of (±)-2-(*tert*-butyl)-3-methylimidazolidin-4-one hydrochloride (3.85 g, 20 mmol) in CH_2Cl_2 (40 ml) at 0° under Ar. After 15 min, Et_3N (6.96 ml, 50 mmol) was slowly added and the mixture was stirred overnight, under warming from 0° to r.t. Precipitated $Et_3N \cdot HCl$ was filtered off, the filtrate diluted with CH_2Cl_2 (40 ml), washed with 1N HCl (2 × 20 ml), H_2O (10 ml), sat. $NaHCO_3$ soln. (2 × 20 ml), and H_2O (10 ml), and dried ($MgSO_4$). Evaporation gave 4.75 g (82%) of white solid **8**, which was crystallized from CH_2Cl_2/pentane (4.05 g, 70%); m.p. 157.7–158.4°. IR: 3400*w*, 2950*m*, 1710*s*, 1688*s*, 1407*s*, 1356*s*, 1249*s*. ^{1}H-NMR: 7.35 (distorted *s*, 5 arom. H); 5.19, 5.13 (*AB*, *J* = 12.2, $PhCH_2$); 4.99 (br., H–C(2)); 4.20 (br. *d*, *J* = 16.2, H–C(5)); 3.80 (*d*, *J* = 16.2, H–C(5)); 2.99 (*s*, CH_3N); 0.98 (*s*, *t*-Bu). MS: 233 (12, $M^{+\cdot}$ − 57), 189 (8), 149 (29), 111 (10), 97 (16), 91 (100). Anal. calc. for $C_{16}H_{22}N_2O_3$: C 66.18, H 7.64, N 9.65; found: C 65.94, H 7.76, N 9.56.

(±)-2-Isopropyl-3-methylimidazolidin-4-one. N^1-Methyl-N^2-(2'-methylpropyliden)glycinamide (2.6 g, 18.3 mmol; prepared according to [25], with isobutyraldehyde instead of pivalaldehyde) was dissolved in 30 ml of dry MeOH and heated to reflux for 4 h, after the addition of a few crystals of TsOH. TLC (MeOH/CH_2Cl_2 4:1) indicated essentially complete consumption of the starting material (R_f 0.31) with formation of a single product (R_f 0.57). The mixture was evaporated and redissolved in $CHCl_3$, washed with aq. $NaHCO_3$ soln. and water, dried (anh. $MgSO_4$), filtered, and evaporated to afford 2.01 g (77% yield) of the desired product as a clear yellowish oil. ^{1}H-NMR ($CDCl_3$, 90 MHz): 0.81 (*d*, *J* = 6.9, 3 H, $(CH_3)_2CH$); 1.01 (*d*, *J* = 6.9, 3 H, $(CH_3)_2CH$); 1.90 (br., NH); 2.05 (*m*, $(CH_3)_2CH$); 2.81 (*s*, CH_3N); 3.49 (*s*, 2 H–C(5)); 4.40 (br., H–C(2)).

(±)-2-Isopropyl-3-methyl-1-(4-phenylbenzoyl)imidazolidin-4-one (**9**). 4-Phenylbenzoyl chloride (1.52 g, 7.01 mmol, 5% excess) was dissolved in 20 ml of CH_2Cl_2 and cooled to 0° before the addition of 0.95 g (6.68 mmol) of (±)-2-isopropyl-3-methylimidazolidin-4-one in 10 ml of CH_2Cl_2. Et_3N (0.98 ml, 7.01 mmol) was then added

dropwise and the mixture was stirred at 0° for 1 h and at r.t. for an additional h. The solvent was evaporated and the residue partitioned between H_2O and $CHCl_3$; the org. layer was washed with aq. $NaHCO_3$ soln. and H_2O, dried (anh. $MgSO_4$), filtered, and evaporated. Recrystallization of the crude product from Et_2O afforded 1.82 g (85%) of pure **9**; m.p. 133–134°. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.01 (*d*, *J* = 6.9, 3 H, $(CH_3)_2CH$); 1.09 (*d*, *J* = 6.9, 3 H, $(CH_3)_2CH$); 2.33 (*m*, $(CH_3)_2CH$); 2.95 (*s*, CH_3N); 3.97 (*A* of *AB*, *J* = 15.6, H–C(5)); 4.16 (*B* of *AB*, *J* = 15.6, H–C(5)); 5.74 (br., H–C(2)); 7.35–7.70 (*m*, 9 arom. H). ^{13}C-NMR ($CDCl_3$): 15.89; 17.65; 27.95; 32.28; 52.79; 77.69; 127.18; 128.04; 128.38; 128.91; 133.21; 139.84; 144.22; 167.60; 170.80. MS: 322 (0.6, $M^{+\cdot}$), 279 (43.3), 181 (100), 152 (55.2). Anal. calc. for $C_{20}H_{22}N_2O_2$: C 74.51, H 6.88, N 8.69; found: C 74.61, H 6.84, N 8.73.

(±)-1-Benzoyl-2-isopropyl-3-methylimidazolidin-4-one (**10**). (±)-2-Isopropyl-3-methylimidazolidin-4-one (4.5 g, 31.65 mmol) was dissolved in 40 ml of CH_2Cl_2 and cooled to 0° before the dropwise addition of 3.2 g (4.4 ml, 1 equiv.) of Et_3N and then 5.0 g (1.1 equiv.) of benzoyl chloride. The mixture was stirred at 0° for 1 h and then at r.t. overnight. The precipitated $Et_3N \cdot HCl$ was filtered, and the filtrate evaporated to afford 7.8 g (quant. yield) of crude **10**, which was purified by FC [52] (AcOEt/hexane 2:1) and recrystallized from Et_2O to give 3.74 g (48%) white needles; m.p. 102–103°. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.00 (*d*, *J* = 6.9, 3 H, $(CH_3)_2CH$); 1.08 (*d*, *J* = 6.9, 3 H, $(CH_3)_2CH$); 2.32 (*m*, $(CH_3)_2CH$); 2.94 (*s*, CH_3N); 3.89 (*A* of *AB*, *J* = 15.4, H–C(5)); 4.10 (*B* of *AB*, *J* = 15.4, H–C(5)); 5.71 (br., H–C(2)); 7.40 7.57 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 15.91; 17.62; 27.97; 32.29; 52.71; 77.72; 127.78; 128.60; 131.33; 134.71; 167.66; 171.03. MS: 246 (0.5, $M^{+\cdot}$), 203 (100), 149 (35), 105 (41). Anal. calc. for $C_{14}H_{18}N_2O_2$: C 68.27, H 7.37, N 11.37; found: C 68.14, H 7.21, N 11.33.

(±)-2-Isopropyl-1-(4-methoxybenzoyl)-3-methylimidazolidin-4-one (**11**). Same procedure as for **7**. The crude product was purified by FC [52] (AcOEt/Et_2O 2:1) to afford **11** in 60% yield; m.p. 114–115°. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.98 (*d*, *J* = 6.9, 3 H, $(CH_3)_2CH$); 1.06 (*d*, *J* = 6.9, 3 H, $(CH_3)_2CH$); 2.29 (*m*, $(CH_3)_2CH$); 2.93 (*s*, CH_3N); 3.85 (*s*, CH_3O); 3.95 (*A* of *AB*, *J* = 15.4, H–C(5)); 4.14 (*B* of *AB*, *J* = 15.4, H–C(5)); 5.74 (br., H–C(2)); 6.93 (distorted *d*, *AA'* of *AA'BB'*, *J* = 8.9, 2 H_{meta}); 7.55 (distorted *d*, *BB'* of *AA'BB'*, *J* = 8.9, 2 H_{ortho}). Anal. calc. for $C_{15}H_{20}N_2O_3$: C 65.20, H 7.90, N 10.14; found: C 65.37, H 7.40, N 10.15.

*1-2-(*tert*-Butyl)-1-(4-methoxybenzoyl)-3,5-dimethylimidazolidin-4-one* (*trans*-**12**). $(i\text{-Pr})_2NH$ (112 mg, 1.1 mmol, 10% excess) was dissolved in 10 ml of dry THF and cooled to −75° before the addition of 0.7 ml of 1.58M BuLi (1.1 mmol). The resulting soln. was stirred at −78° for 20 min, and then 246 mg (1 mmol) of **7** was added in 5 ml of THF. The orange-red soln. was stirred at −75° for 1 h before the addition of 75 µl (1.2 mmol, 20% excess) of neat MeI. The mixture was stirred at −75° for 1 h and then at r.t. for an additional h; the orange colour fades away during this process. Quenching with half-sat. NH_4Cl soln. and normal workup afforded crude **12** in 99% yield. ^{1}H-NMR (300 MHz): integration of the CH_3N signals showed *trans*/*cis*-**12** 96:4. Recrystallization from Et_2O afforded pure *trans*-**12**; m.p. 123–124°. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.05 (*s*, *t*-Bu); *ca.* 1.06 (*d*, *J* = 6.7, CH_3–C(5)); 3.07 (*s*, CH_3N); 4.26 (*q*, *J* = 6.7, H–C(5)); 5.67 (*s*, H–C(2)); 6.93 (distorted *d*, *J* = 8.7, 2 H_{meta}); 7.58 (distorted *d*, *J* = 8.7, 2 H_{ortho}).

*1-1-(Benzyloxycarbonyl)-2-(*tert*-butyl)-3,5-dimethylimidazolidin-4-one* (**13**). A 0.746M soln. of $LiN(i\text{-Pr})_2$ (2.95 ml, 2.2 mmol) was slowly added to a stirred soln. of **8** (0.58 g, 2 mmol) in THF (25 ml) at −78°, and stirring was continued for 30 min. MeI (0.31 ml, 5 mmol) was slowly added, and after 2 h at −78° the temp. was allowed to rise to *ca.* 0° within 20 min. After quenching with half-sat. NH_4Cl (20 ml) soln. and Et_2O (20 ml). The aq. phase was separated and extracted with Et_2O (3 × 20 ml), the combined org. phases were washed with H_2O (10 ml), dried ($MgSO_4$), and evaporated: **13** (0.61 g, 100%) as a pale yellow solid (97% ds (^{1}H-NMR)). ^{1}H-NMR: 7.39–7.32 (*m*, 5 arom. H); 5.21–5.04 (*m*, $PhCH_2$, H–C(2)); 4.04 (*q*, *J* = 6.6, H–C(5)); 3.00 (*s*, CH_3N); 1.54 (*d*, *J* = 6.6, CH_3–C(5)); 0.95 (*s*, *t*-Bu).

1-2-Isopropyl-3,5-dimethyl-1-(4-phenylbenzoyl)imidazolidin-4-one (**14**). Same procedure as for **12**, starting from **9**. Quant. yield of crude **14**; *trans*/*cis*-**14** 2.8:1 (by ^{1}H-NMR (300 MHz)). ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.04 (*d*, *J* = 7.3, 3 H, $(CH_3)_2CH$); 1.07 (*d*, *J* = 7.3, 3 H, $(CH_3)_2CH$); 1.41 (*d*, *J* = 7.0, CH_3–C(5)); 2.49 (*m*, $(CH_3)_2CH$); 2.99 (*s*, CH_3N); 4.37 (*q*, *J* = 7.0, H–C(5)); 5.65 (br., H–C(2)); 7.4–7.7 (*m*, 5 arom. H).

1-1-Benzoyl-2-isopropyl-3,5-dimethylimidazolidin-4-one (**15**). Same procedure as for **12**, starting from **10**: crude **15** (quant. yield); *trans*/*cis*-**15** 85:15 (by ^{1}H-NMR (300 MHz)). ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.90–1.10 (*m*, $(CH_3)_2CH$, CH_3–C(5)); 2.49 (*m*, $(CH_3)_2CH$); 2.98 (*s*, CH_3N); 4.32 (*q*, *J* = 6.7, H–C(5)); 5.62 (br., H–C(2)); 4.4–4.6 (*m*, 5 arom. H).

1-2-Isopropyl-1-(4-methoxybenzoyl)-3,5-dimethylimidazolidin-4-one (**16**). The same procedure as for **12**, starting from **11**: crude **16** (quant. yield); *trans*/*cis*-**16** 9:1 (by ^{1}H-NMR (300 MHz)). ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.9–1.1 (*m*, $(CH_3)_2CH$, CH_3–C(5)); 2.42 (*m*, $(CH_3)_2CH$); 2.97 (*s*, CH_3N); 3.86 (*s*, CH_3O); 4.34 (*q*, *J* = 7.0, H–C(5)); 5.62 (br., H–C(2)); 6.94 (distorted *d*, *J* = 8.9, 2 H_{meta}); 7.54 (distorted *d*, *J* = 8.9, 2 H_{ortho}).

*(2S,5S,1'R)-1-Benzoyl-2-(*tert*-butyl)-5-(1'-hydroxyethyl)-3-methylimidazolidin-4-one* (**G**, R = CH_3). A 0.746M soln. of $LiN(i\text{-Pr})_2$ (7.37 ml, 5.5 mmol) was slowly added to a stirred soln. of (*S*)-**1** (1.3 g, 5 mmol) in THF

(50 ml) at −78°, and stirring was continued for 15 min. The temp. was then lowered to −100° for 30 min, and acetaldehyde (1.41 ml, 25 mmol) was added. After 1 min, the reaction was quenched with half-sat. NH_4Cl soln. (50 ml) and Et_2O (50 ml). After warming to r.t., the phases were separated, the aq. layer was extracted with Et_2O (3 × 50 ml), the combined org. phases were washed with H_2O (20 ml), dried ($MgSO_4$), and evaporated to a white solid (86% ds (^{1}H-NMR)). Crystallization from CH_2Cl_2/pentane gave pure **G** (0.452 g, 30%); m.p. 165.9–166.8°. $[\alpha]_D = +85.7°$ ($c = 1.03$, $CHCl_3$). IR: 3440*w*, 1686*s*, 1630*s*, 1378*s*, 1092*m*. ^{1}H-NMR: 7.65–7.43 (*m*, 5 arom. H); 5.68 (*s*, H–C(2)); 4.46 (*d*, $J = 4$, H–C(5)); 4.42 (*d*, $J = 11.6$, OH); 3.22 (*m*, H–C(1')); 3.11 (*s*, CH_3N); 1.07 (*s*, *t*-Bu); 0.87 (*d*, $J = 6.4$, $CH_3C(1')$). MS: 247 (25, $M^{+\cdot} - 57$), 203 (11), 125 (49), 105 (100), 77 (36). Anal. calc. for $C_{17}H_{24}N_2O_3$: C 67.08, H 7.95, N 9.20; found: C 66.88, H 8.21, N 9.18.

*(2*R*,5*S*,1'*R*)-5-(1'-Benzoyloxyethyl)-2-(*tert*-butyl)-3-methylimidazolidin-4-one* (**17**). The evaporated residues from the mother liquor of the crystallization in the above experiment were dissolved in THF (25 ml) and AcOH (5 ml) and heated to reflux for 2 h. The cooled soln. was evaporated to a brown oil and residual AcOH was removed by azeotropic evaporation with toluene (3 × 20 ml). FC (Et_2O/pentane 80:20) gave pure **17** as a clear oil (0.689 g, 45%). Overall yield of (5*S*,1'*R*)-isomers: 75%.

Racemic material: IR: 3320*w*, 1700*s*, 1680*s*, 1280*s*, 715*s*. ^{1}H-NMR: 7.98–7.95, 7.54–7.39 (*m*, 5 arom. H); 5.38 (*dq*, $J = 6.5, 4.3$, H–C(1')); 4.21 (*d*, $J = 2$, H–C(2)); 3.73 (*m*, H–C(5)); 2.93 (*d*, $J = 0.4$, CH_3N); 1.48 (*d*, $J = 6.5$, $CH_3C(1')$); 0.99 (*s*, *t*-Bu).

*(2*R*,5*S*,1'*R*)-5-(1'-Benzoyloxy-2',2',2'-trifluoroethyl)-2-(*tert*-butyl)-3-methylimidazolidin-4-one* (**18**). *General Procedure 1* was followed with 1.301 g (5 mmol) of (*S*)-**1** and trifluoroacetaldehyde (obtained from its hydrate by treatment with P_2O_5 [55]; gaseous trifluoroacetaldehyde was condensed at −78° and then transferred into the reaction mixture). ^{1}H-NMR (300 MHz) of crude product: 63% ds. Purification by FC and a final recrystallization from CH_2Cl_2/pentane afforded 0.75 g (41%) of pure **18**; m.p. 102.6–102.8°. $[\alpha]_D = +10.8°$ ($c = 1$, CH_2Cl_2). IR (KBr): 3395*m*, 3065*w*, 2990*m*, 1740*s*, 1690*s*, 1600*w*, 1475*m*, 1250*s*, 1030*m*, 710*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.99 (*s*, *t*-Bu); 2.34 (br., NH); 2.86 (*s*, CH_3N); 4.14–4.20 (*m*, H–C(2), H–C(5)); 5.98 (*dq*, $J = 7.5, 1.5$, H–C(1')); 7.42–7.64 (*m*, 2 H_{meta}, H_{para}); 8.0–8.06 (*m*, 2 H_{ortho}). MS: 301 (51, $M^{+\cdot} - 57$), 179 (77), 105 (100), 77 (27). Anal. calc. for $C_{17}H_{21}F_3N_2O_3$: 56.98, H 5.91, N 7.82; found: C 57.08, H 6.01, N 7.86.

*(2*R*,5*S*,1'*R*)-5-(1'-Benzoyloxy-2'-methylpropyl)-2-(*tert*-butyl)-3-methylimidazolidin-4-one* (**19**). *General Procedure 1* was followed with 1.301 g (5 mmol) of (*S*)-**1** and 0.72 g (10 mmol) of isobutyraldehyde. ^{1}H-NMR (300 MHz) of crude product: 95% ds. FC (Et_2O/hexane 2:1) was followed by recrystallization from CH_2Cl_2/pentane to provide pure **19** in 79% yield (1.30 g). M.p. 110.4–110.5° $[\alpha]_D = +10.2°$ ($c = 1$, CH_2Cl_2). IR (KBr): 3325*m*, 3065*w*, 2955*s*, 1725*s*, 1685*s*, 1270*s*, 1025*m*, 1010*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.97 (*s*, *t*-Bu); 1.04 (*d*, $J = 6.9$, $(CH_3)_2CH$); 2.21 (br., NH); 2.31 (*m*, $(CH_3)_2CH$); 2.83 (*s*, CH_3N); 3.85 (*d*, $J = 1.6$, H–C(5)); 4.14 (*d*, $J = 1.6$, H–C(2)); 5.34 (*dd*, $J = 7.2, 3.7$, H–C(1')); 7.41–7.58 (*m*, 2 H_{meta}, H_{para}); 7.98–8.02 (*m*, 2 H_{ortho}). ^{13}C-NMR ($CDCl_3$): 18.08; 18.99; 25.41; 29.75; 31.05; 37.37; 59.74; 77.98; 83.58; 128.20; 129.39; 130.12; 132.76; 165.37; 173.52. MS: 275 (18, $M^{+\cdot} - 57$), 153 (100), 105 (50), 99 (13), 77 (22). Anal. calc. for $C_{19}H_{18}N_2O_3$: C 68.65, H 8.49, N 8.43; found: C 68.39, H 8.43, N 8.33.

*(2*R*,5*S*,α*R*)-4-(α-Benzoyloxybenzyl)-2-(*tert*-butyl)-1-methylimidazolidin-4-one* (**20**). A 0.746M soln. of LiN(i-Pr)$_2$ (7.37 ml, 5.5 mmol) was slowly added to a stirred soln. of (*S*)-**1** (1.3 g, 5 mmol) in THF (50 ml) at −78°, and stirring was continued for 15 min. The temp. was then lowered to −100° for 30 min, and benzaldehyde (1.01 ml, 10 mmol) was added. After 5 min, the reaction was quenched with half-sat. NH_4Cl soln. (50 ml) and Et_2O (50 ml). After warming to r.t., the phases were separated, and the aq. layer was extracted with Et_2O (3 × 50 ml). The combined org. phases were washed with H_2O (20 ml), dried ($MgSO_4$), and evaporated to a yellow solid (95% ds (^{1}H-NMR)). FC (Et_2O/petroleum ether 70:30) gave pure **20** (85%), which was crystallized from CH_2Cl_2/pentane; m.p. 153.2–153.8°. $[\alpha]_D = +24.6°$ ($c = 1.05$, $CHCl_3$). IR: 3350*w*, 1722*s*, 1686*s*, 1270*s*, 710*s*. ^{1}H-NMR: 8.05–8.01, 7.60–7.27 (2*m*, 10 arom.); 6.33 (*d*, $J = 2.8$, H–C(α)); 4.17 (*d*, $J = 2.2$, H–C(2)); 4.07 (*t*, $J = 2.4$, H–C(5)); 2.88 (*s*, CH_3N); 2.09 (br., NH); 0.95 (*s*, *t*-Bu). MS: 309 (24, $M^{+\cdot} - 57$), 203 (28), 187 (100), 155 (29), 149 (29), 130 (29). Anal. calc. for $C_{22}H_{26}N_2O_3$: C 72.11, H 7.15, N 7.64; found: C 72.04, H 7.21, N 7.60.

Racemic compound: 81% yield, 92% ds. M.p. 159.4–160.0°. Spectra identical to those of **20**.

*(2*R*,5*S*,1'*R*)-5-[Benzoyloxy(o-tolyl)methyl]-2-(*tert*-butyl)-3-methylimidazolidin-4-one* (**21**). *General Procedure 1* was followed with 1.301 g (5 mmol) of (*S*)-**1** and 1.16 ml (10 mmol) of 2-methylbenzaldehyde. ^{1}H-NMR (300 MHz) of the crude product: 88% ds. FC (Et_2O/hexane 2:1) afforded 1.54 g (81% yield) of pure **21**; $[\alpha]_D = +63.3°$ ($c = 1$, CH_2Cl_2). IR (KBr): 3380*w*, 3025*w*, 2920*m*, 1730*s*, 1690*s*, 1600*w*, 1450*m*, 1270*s*, 1070*m*, 770*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.95 (*s*, *t*-Bu); 1.90 (br., NH); 2.52 (*s*, $CH_3C_6H_4$); 2.92 (*s*, CH_3N); 4.00 (*dd*, $J = 2.4$, H–C(5)); 4.24 (*d*, $J = 2.2$, H–C(2)); 6.51 (*d*, $J = 2.9$, H–C(1')); 7.15–7.58 (*m*, 7 arom. H); 7.98–8.04 (*m*, 2 H_{ortho} of Bz). ^{13}C-NMR ($CDCl_3$): 19.31; 25.27; 30.98; 36.89; 61.30; 72.53; 83.81; 125.88; 126.14; 127.85; 128.29; 129.46; 130.14;

130.49; 132.92; *ca.* 134.80; 138.96; *ca.* 164.84; 172.53. MS: 323 (13, $M^{+\cdot} - 57$), 203 (43), 201 (100), 155 (53), 105 (83), 77 (29). Anal. calc. for $C_{23}H_{28}N_2O_3$: C 72.61, H 7.42, N 7.37; found: C 72.34, H 7.42, N 7.33.

*(2*R,*5*S,*1'*R*)-5-[Benzoyloxy(3,4-methylenedioxyphenyl)methyl]-2-(*tert*-butyl)-1-methylimidazolidin-4-one* (**22**). *General Procedure 1* was followed with 1.301 g (5 mmol) of (*S*)-**1** and 1.501 g (10 mmol) of piperonal. ^{1}H-NMR (300 MHz) of crude product: 96% ds. The crude product was purified by FC (Et_2O/hexane 2:1) to afford 1.58 g (77%) of pure **22**; $[\alpha]_D = +16.5°$ (*c* = 1, CH_2Cl_2). IR (KBr): 3400*w*, 3040*w*, 2980*w*, 1725*s*, 1695*s*, 1600*w*, 1450*m*, 1250*s*, 1040*m*, 710*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.99 (*s*, *t*-Bu); 2.12 (br., NH); 2.89 (*s*, CH_3N); 4.01 (*dd*, *J* = 2.3, H–C(5)); 4.20 (*d*, *J* = 2.1, H–C(2)); 5.93 (*dd*, *J* = 3.4, 1.4, OCH_2O); 6.22 (*d*, *J* = 2.9, H–C(1')); 6.78 (*d*, *J* = 8.0, H–C(6) of methylenedioxyphenyl); 6.95 (*ddd*, *J* = 8.0, 0.5, H–C(5) of methylenedioxyphenyl); 7.0 (*d*, *J* = 1.7, H–C(2) of methylenedioxyphenyl); 7.4–7.6 (*m*, 2 H_{meta}, H_{para}, H_{ortho} of Bz); 8.00–8.06 (*m*, 2 H_{ortho} of Bz). ^{13}C-NMR ($CDCl_3$): 25.28; 30.98; 37.06; 62.82; 75.27; 83.74; 100.97; 107.22; 108.08; 120.19; 128.26; 129.44; 129.96; 131.37; 132.94; 147.35; 147.67; 164.81; 172.34. MS: 288 (12, $M^{+\cdot} - 122$), 232 (17), 231 (93), 203 (11), 189 (13), 161 (43), 155 (37), 105 (100), 77 (37). Anal. calc. for $C_{23}H_{26}N_2O_5$: C 67.30, H 6.38, N 6.82; found: C 66.84, H 6.39, N 6.82.

*(2*R,*5*S,*1'*R*)-5-[Benzoyloxy(4-biphenylyl)methyl]-2-(*tert*-butyl)-3-methylimidazolidin-4-one* (**23**). *General Procedure 1* was followed with 1.301 g (5 mmol) of (*S*)-**1** and 1.882 g (10 mmol) of 4-phenylbenzaldehyde. ^{1}H-NMR (300 MHz) of the crude product: 93% ds. FC (Et_2O/hexane 2:1) afforded pure **23**, which was recrystallized from CH_2Cl_2/pentane and dried ($MgSO_4$). Diastereoisomerically and enantiomerically pure **23** was isolated in 79% yield (1.75 g). M.p. 169.6–169.8°. $[\alpha]_D = +6.9°$ (*c* = 1, CH_2Cl_2). IR (KBr): 3355*m*, 3030*w*, 2970*m*, 1720*s*, 1690*s*, 1270*s*, 1025*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.97 (*s*, *t*-Bu); 2.14 (br., NH); 2.91 (*s*, CH_3N); 4.11 (br., H–C(5)); 4.22 (*d*, *J* = 2.0, H–C(2)); 6.37 (*d*, *J* = 3.0, H–C(1')); 7.30–7.60 (*m*, 12 arom. H); 8.03–8.06 (*m*, 2 H_{ortho} of Bz). ^{13}C-NMR ($CDCl_3$): 25.36; 31.07, 37.07; 37.12; 62.85; 75.50; 83.87; 127.05; 127.14; 127.28; 128.36; 128.66; 129.59; 130.08; 133.01; 136.58; 140.58; 141.02; 164.94; 172.41. MS: 443 (0.7, $M^{+\cdot}$), 264 (25), 263 (100), 203 (51), 155 (73), 105 (86), 77 (23), 57 (31). Anal. calc. for $C_{28}H_{30}N_2O_3$: C 75.99, H 6.83, N 6.33; found: C 75.93, H 6.81, N 6.28.

*(2*S,*5*S,*1'*R*)-1-Benzoyl-2-(*tert*-butyl)-5-[(2-furanyl)hydroxymethyl]-3-methylimidazolidin-4-one* (**G**, R = 2-furanyl). *General Procedure 1* was followed with 780 mg (3 mmol) of (*S*)-**1** and 0.57 g (6 mmol) of 2-furfuraldehyde. ^{1}H-NMR (300 MHz) of the crude product: 86% ds. FC (Et_2O/hexane 9:1) and recrystallization from Et_2O gave 0.83 g (78%) of pure **G** (R = 2-furanyl); m.p. 126–127°. $[\alpha]_D = +184.1°$ (*c* = 1.35, CH_2Cl_2). IR (KBr): 3340*m*, 2990*m*, 1700*s*, 1658*s*, 1380*s*, 1034*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.04 (*s*, *t*-Bu); 3.01 (*s*, CH_3N); 4.31 (*dd*, *J* = 11.3, 4.9, H–C(1')); 4.64 (*d*, *J* = 4.9, H–C(5)); 5.39 (*d*, *J* = 11.3, OH); 5.41 (br., H–C(2)); 6.07 (*d*, *J* = 2.6, H–C(3) of furanyl); 6.29 (*dd*, *J* = 1.8, 3.0, H–C(4) of furanyl); 7.33 (*dd*, *J* = 0.7, 1.8, H–C(5) of furanyl); 7.4–7.7 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 27.70; 33.56; 42.26; 62.70; 68.64; 81.81; 110.42; 111.85; 129.17; 130.59; 133.57; 137.52; 144.09; 153.21; 171.76; 173.28. MS: 299 (16, $M^{+\cdot} - 57$), 203 (93), 177 (18), 105 (100), 77 (29). Anal. calc. for $C_{20}H_{24}N_2O_4$: C 67.40, H 6.79, N 7.86; found: C 67.28, H 6.67, N 7.83.

*(2*R,*5*S,*1'*R*)-5-[Benzoyloxy(2-furanyl)methyl]-2-(*tert*-butyl)-3-methylimidazolidin-4-one* (**24**). The adduct **G** (R = 2-furanyl) (160 mg, 0.45 mmol) was dissolved in 10 ml of MeOH and heated to reflux for 3 h, after the addition of a few crystals of TsOH. Evaporation of the solvent afforded **24** as a yellow oil (crude product, quant. yield), which was purified by FC [52] (Et_2O/hexane 1:1): 82 mg (51%) of **24**; m.p. 111°. $[\alpha]_D = -62.5°$ (*c* = 1.1, CH_2Cl_2). IR (KBr): 3380*m*, 2940*m*, 1740*s*, 1685*s*, 1265*m*, 1110*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.00 (*s*, *t*-Bu); 2.92 (*s*, CH_3N); 4.19 (*dd*, *J* = 2.6, 2.6, H–C(4)); 4.27 (*d*, *J* = 2.2, H–C(2)); 6.36 (*dd*, *J* = 3.3, 1.9, H–C(4) of furanyl); 6.40 (*d*, *J* = 3.0, H–C(1')); 6.50 (*d*, *J* = 3.3, H–C(3) of furanyl); 7.38–7.47 (*m*, 2 H_{meta}, H–C(5) of furanyl); 7.50–7.60 (*m*, H_{para}); 7.95–8.01 (*m*, 2 H_{ortho}). ^{13}C-NMR ($CDCl_3$): 26.86; 32.71; 38.92; 62.61; 70.45; 85.29; 111.26; 111.92; 129.88; 131.15; 133.94; 134.66; 144.39; 152.03; 166.41; 173.45. MS: 299 (9.6, $M^{+\cdot} - 57$), 203 (17), 177 (100), 155 (21), 120 (44), 105 (39), 99 (25), 77 (19). Anal. calc. for $C_{20}H_{24}N_2O_4$: C 67.40, H 6.79, N 7.86; found: C 67.36, H 6.77, N 7.70.

*(2*R,*5*S,*1'*R*)-5-[Benzoyloxy(4-pyridyl)methyl]-2-(*tert*-butyl)-3-methylimidazolidin-4-one* (**25**). *General Procedure 1* was followed with 1.301 g (5 mmol) of (*S*)-**1** and 1.071 g (10 mmol) of pyridine-4-carbaldehyde. ^{1}H-NMR (300 MHz) of the crude product: 89% ds. FC (AcOEt/hexane 10:1) and recrystallization from Et_2O afforded 1.31 g (71%) of pure **25**; m.p. 176.4–176.8°. $[\alpha]_D = +33.8°$ (*c* = 1, CH_2Cl_2). IR (KBr): 3355*m*, 3040*w*, 2980*m*, 1730*s*, 1690*s*, 1600*m*, 1455*m*, 1030*m*, 710*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.96 (*s*, *t*-Bu); 2.04 (br., NH); 2.89 (*s*, CH_3N); 4.08 (br., H–C(5)); 4.19 (br., H–C(2)); 6.25 (*d*, *J* = 2.8, H–C(1')); 7.35–7.62 (*m*, 5 arom. H); 8.0–8.06 (*m*, 2 H_{ortho} of Bz); 8.57–8.61 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 25.29; 31.09; 37.11; 61.87; 74.48; 84.01; 121.42; 128.47; 129.60; 133.14; 133.31; 146.58; 149.84; 164.85; 171.76. MS: 368 (11, $M^{+\cdot}$), 311 (15), 310 (75), 213 (29), 189 (15), 188 (100), 163 (13), 155 (18), 131 (25), 108 (28), 105 (76), 77 (46), 57 (14). Anal. calc. for $C_{21}H_{15}N_3O_3$: C 68.64, H 6.86, N 11.44; found: C 68.39, H 6.90, N 11.63.

(−)-Threonine (**26**). A mixture of **G** (R = CH_3; 0.304 g, 1 mmol) and 6N HCl (10 ml) was heated to reflux for 8 h. The cooled soln. was extracted with Et_2O (3 × 10 ml) and evaporated. The residue was adsorbed onto a *Dowex-50-WX8* ion-exchange column, and after washing with H_2O till neutrality, elution with dil. NH_3 soln. (200 ml) and evaporation gave pure **26** (0.119 g, quant. yield), which was crystallized from EtOH/H_2O; m.p. 235–237° (dec.); commercial sample *(Degussa)*: 242–245° (dec.); [56]: 255–257° (dec.); $[\alpha]_D = -27.9°$ (*c* = 1.02, H_2O; [56]: $[\alpha]_D = -28.3°$ (*c* = 1.01, H_2O)). ^{1}H-NMR (90 MHz, D_2O): 4.15 (*dq*, *J* = 6.3, 4.5, H–C(3)); 3.47 (*d*, *J* = 4.5, H–C(2)); 1.23 (*d*, *J* = 6.3, CH_3–C(3)).

(−)-(2S,3R)-3-Hydroxyleucine (**27**). *General Procedure 2* was followed with 0.664 g (2 mmol) of **19** in 20 ml of 6N HCl for 12 h. The crude product was recrystallized from MeOH/EtOH to give 0.23 g (68%) of **27**·H_2O; m.p. 213–217° (dec.). $[\alpha]_D = -3.5°$ (*c* = 2.2, H_2O; [57]: $[\alpha]_D = -3.5°$ (*c* = 2, H_2O)). IR (KBr): 3305*s*, 2955*s*, 1670*s*, 1630*s*, 1570*s*, 1515*s*, 1465*s*, 1400*s*, 1355*s*, 1010*s*, 690*m*. ^{1}H-NMR (DMSO, 300 MHz): 0.84 (*d*, *J* = 6.6, CH_3(5)); 0.88 (*d*, *J* = 6.6, CH_3(5')); 1.77 (*m*, H–C(4)); 3.16 (*d*, *J* = 4.1, H–C(2)); 3.57 (*dd*, *J* = 6.7, 4.1, H–C(3)). ^{13}C-NMR (D_2O): 18.14; 19.18; 30.99; 57.64; 75.75; 173.94. MS: 104 (14, $M^{+\cdot}$ − 43), 75 (100), 72 (23), 57 (73), 43 (61). Anal. calc. for $C_7H_{13}NO_3 \cdot H_2O$: C 43.63, H 9.15, N 8.48; found: C 44.02, H 9.03, N 8.26.

(−)-(2S,3R)-3-Phenylserine (**28**). A mixture of **20** (0.366 g, 1 mmol) and 6N HCl (10 ml) was heated to reflux for 8 h. The cooled soln. was extracted with Et_2O (3 × 10 ml) and evaporated. The residue was adsorbed onto a *Dowex-50-WX8* ion-exchange column, and after washing with H_2O till neutrality, elution with dil. NH_3 soln. (200 ml) and evaporation gave pure **28** (0.098 g, 54%), which was crystallized from EtOH/H_2O; m.p. 181–182° (dec.); [58]: 183–186 (dec.); $[\alpha]_D = -34.3°$ (*c* = 1.02, H_2O; [58]: $[\alpha]_D = -32 \pm 2°$ (H_2O)). ^{1}H-NMR (90 MHz, D_2O): 7.32 (*s*, 5 arom. H); 5.13 (*d*, *J* = 4.5, H–C(3)); 3.75 (*d*, *J* = 4.5, H–C(2)).

(−)-(2S,3R)-4,4,4-Trifluorothreonine (**30**). *General Procedure 2* was followed with 0.358 g (1 mmol) of **18** and 10 ml of 6N HCl for 24 h: **30** (0.17 g, quant. yield). Recrystallization from acetone afforded an anal. pure sample, m.p. 209–213° (dec.). $[\alpha]_D = -12.4°$ (*c* = 1, H_2O). IR (KBr): 2500–3400 (br.), 1655*s*, 1575*m*, 1200*s*, 1080*m*, 1040*w*. ^{1}H-NMR (DMSO, 300 MHz): 3.38 (*d*, *J* = 1.6, H–C(2)); 4.68 (*dq*, *J* = 6.8, 1.5, H–C(3)). MS: 128 (59, $M^{+\cdot}$ − 45), 80 (17), 74 (100), 59 (25). Anal. calc. for $C_4H_6F_3NO_3$: C 27.76, H 3.49, N 8.09; found: C 27.79, H 3.58, N 7.65.

(−)-(2S,3R)-3-(4-Pyridyl)serine (**31**). *General Procedure 2* was followed with 0.367 g (1 mmol) of **25** and 10 ml of 6N HCl for 24 h. The crude product was recrystallized from H_2O/acetone to give 0.147 g (81%) of pure **31**; m.p. 219–223° (dec.). $[\alpha]_D = -38.0°$ (*c* = 0.4, H_2O). IR (KBr): 3410*m*, 2500–3300 (br.), 1640*s*, 1610*s*, 1410*s*, 1065*s*, 1050*s*, 815*s*. ^{1}H-NMR (DMSO, 300 MHz): *ca.* 3.3 (*d*, H–C(2)); 5.09 (*d*, *J* = 3.3, H–C(3)); 7.35–7.39 (*m*, 2 arom. H); 8.48–8.52 (*m*, 2 arom. H). MS: 119 (10, $M^{+\cdot}$ − 63), 109 (70), 108 (100), 75 (50), 51 (39). Anal. calc. for $C_8H_{10}N_2O_3$: C 52.74, H 5.53, N 15.38; found: C 52.57, H 5.51, N 15.61.

*(2S,5R,1'S,2'R)-5-[(E)-1'-Benzoyloxy-2'-methyl-4'-hexenyl]-2-(*tert*-butyl)-3-methylimidazolidin-4-one* (**34**). *General Procedure 1* was followed with 260 mg (1 mmol) of (*R*)-**1** and 247 mg (2.2 mmol) of (*R,E*)-2-methyl-4-hexenal ((*R*)-**33**). ^{1}H-NMR (300 MHz): 96% ds.

*(2R,5R,1'S,2'R)-1-Benzoyl-2-(*tert*-butyl)-5-[(E)-1'-hydroxy-2'-methyl-4'-hexenyl]imidazolidin-4-one.* Recrystallization of crude **34** (see above) was accompanied by migration of the Bz group from the O- to the N-atom. The title compound, 'unrearranged' hydroxyamide, was then isolated in 30% yield (113 mg); m.p. 149.0–149.5°. $[\alpha]_D = -95.4°$ (*c* = 0.7, CH_2Cl_2). IR (KBr): 3380*m*, 2960*m*, 1684*s*, 1628*s*, 1380*s*, 1260*m*, 970*m*, 697*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.58 (*d*, *J* = 6.7, CH_3–C(2')); 1.07 (*s*, *t*-Bu); 1.43 (*m*, H–C(2')); 1.55 (*dd*, *J* = 6.5, 1.3, CH_3(6')); 1.55–1.80 (*m*, CH_2(3')); 3.07 (*s*, CH_3N); 3.25 (*m*, H–C(1')); 4.51 (*d*, *J* = 5.9, H–C(5)); 4.66 (*d*, *J* = 11.1, OH); 5.02–5.35 (*m*, H–C(4'), H–C(5')); 5.68 (br., H–C(2)); 7.4–7.7 (*m*, 5 arom. H). MS: 315 (24, $M^{+\cdot}$ − 57), 203 (33), 193 (46), 105 (100), 99 (16), 77 (38), 57 (10). Anal. calc. for $C_{22}H_{32}N_2O_3$: C 70.94, H 8.66, N 7.52; found: C 70.82, H 8.82, N 7.43.

*(2R,5S,1'R,2'R)-5-[(E)-1'-Benzoyloxy-2'-methyl-4'-hexenyl]-2-(*tert*-butyl)-3-methylimidazolidin-4-one* (**35**). *General Procedure 1* was followed with 1.3 g (5 mmol) of (*S*)-**1** and 1.235 g (*ca.* 11 mmol) of (*R*)-**33**. ^{1}H-NMR (300 MHz) 93% ds. Recrystallization from Et_2O/pentane 1:1 yielded 1.53 g (82% yield) of pure **35**; m.p. 122–123°. $[\alpha]_D = +27.4°$ (*c* = 0.94, CH_2Cl_2). IR (KBr): 3322*m*, 3061*w*, 2980*m*, 1727*s*, 1680*s*, 1450*m*, 1270*s*, 1110*m*, 705*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.97 (*s*, *t*-Bu); 1.0 (*d*, *J* = 6.8, CH_3–C(2')); 1.88–2.0 (*m*, H–C(2')); 2.06–2.30 (*m*, CH_2(3'), NH); 2.81 (*s*, CH_3N); 3.87 (br., H–C(5)); 4.13 (*d*, *J* = 1.7, H–C(2)); 5.38–5.46 (*m*, H–C(1'), H–C(4'), H–C(5')); 7.4–7.6 (*m*, 2 H_{meta}, H_{para}); 7.96–8.03 (*m*, 2 H_{ortho}). ^{13}C-NMR ($CDCl_3$): 17.31; 19.34; 27.03; 32.71; 36.35; 37.01; 39.04; 61.24; 78.53; 85.29; 128.39; 129.81; 130.24; 131.02; 131.61; 134.38; 166.77; 175.14. MS: 315 (25, $M^{+\cdot}$ − 57), 193 (100), 138 (14), 105 (80), 99 (43), 77 (34). Anal. calc. for $C_{22}H_{32}N_2O_3$: C 70.94, H 8.66, N 7.52; found: C 70.77, H 8.66, N 7.41.

*(2R,5S,1'R,2'R)-5-[(E)-1'-Benzoyloxy-2'-methyl-4'-hexenyl]-2-(*tert*-butyl)-1,3-dimethylimidazolidin-4-one* (**36**). A soln. of **35** (0.8 g, 2.15 mmol) in 10 ml of acetone was treated with 0.8 ml of 40% aq. NaOH soln. The

mixture was warmed up to 50°, and then 1.8 ml of 40% aq. NaOH soln. and 1.24 ml (12.9 mmol) of Me_2SO_4 were added. The mixture was stirred at 50° for 12 h, allowed to cool to r.t., diluted with H_2O and extracted with CH_2Cl_2. Usual workup afforded crude **36**, which was then purified by FC (Et_2O/hexane 3:2) to give 0.70 g (84%) of **36** as a clear oil. ^{1}H-NMR ($CDCl_3$, 90 MHz): 1.00 (*s*, *t*-Bu); 1.06 (*d*, $J \approx 7.0$, CH_3–C(2')); 1.60 (*d*, $J \approx 4.0$, CH_3(6')); 1.8–2.0 (*m*, H–C(2'), CH_2(3')); 2.70 (*s*, CH_3–N(3)); 2.93 (*s*, CH_3–N(1)); 3.56 (*s*, H–C(2)); 3.98 (*d*, $J = 4.5$, H–C(5)); 5.41 (*m*, H–C(4'), H–C(5')); 5.60 (*dd*, $J = 9.0, 4.5$, H–C(1')); 7.3–7.6 (*m*, 2 H_{meta}, H_{para}); 7.9–8.1 (*m*, 2 H_{ortho}).

(1R,2R,2'S,4E)-1-(N$^{1'}$,N$^{2'}$-Dimethylglycinamid-2'-yl)-2-methyl-4-hexenyl Benzoate (**38**). A soln. of **36** (700 mg, 1.81 mmol) in 10 ml of EtOH was treated with 10 ml of 2N HCl. The resulting soln. was heated to 90° for 4 h and then evaporated, redissolved in $CHCl_3$, washed with aq. $NaHCO_3$ soln., dried ($MgSO_4$), filtered, and evaporated to afford 0.58 g (100%) of spectroscopically (^{1}H-NMR) pure **38** as a clear, slightly yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.99 (*d*, $J = 6.7$, CH_3–C(2)); 1.61 (*d*, $J = 4.0$, CH_3(6)); 1.69 (br., NH); 1.88–2.10 (*m*, H–C(2), H–C(3)); 2.32 (*m*, H–C(3)); 2.41 (*s*, CH_3–N(2')); 2.73 (*d*, $J = 5.0$, CH_3N(1')); 3.29 (*d*, $J = 4.4$, H–C(2')); 5.31 (*dd*, $J = 4.4$, 6.9, 1 H, H–C(1)); 5.38–5.45 (*m*, H–C(4), H–C(5)); 7.16 (br., H–N(1')); 7.4–7.6 (*m*, 2 H_{meta}, H_{para}); 8.0–8.06 (*m*, 2 H_{ortho}).

(2S,3R,4R,6E)-3-Hydroxy-N^1,4-dimethyl-2-(methylamino)-6-octenamide (**39**). A soln. of **38** (0.57 g, 1.8 mmol) in 10 ml of EtOH was treated with 2 ml of 30% aq. NaOH soln. The resulting soln. was heated to 80° for 4 h and then allowed to cool to r.t., diluted with 15 ml of H_2O and extracted with $CHCl_3$. Usual workup yielded 0.38 g (100%) of pure **39**. ^{1}H-NMR ($CDCl_3$, 90 MHz): 0.93 (*d*, $J = 6.9$, CH_3–C(4)); 1.66 (*d*, $J = 4.2$, CH_3(8)); 1.5–2.2 (*m*, H–C(4), CH_2(5)); *ca.* 2.35 (br., NH–C(2), OH); 2.47 (*s*, CH_3N–C(2)); 3.05 (distorted *d*, $J = 3.8$, H–C(2)); 3.71 (*dd*, $J = 7.5, 3.8$, H–C(3)); 5.47 (*m*, H–C(6), H–C(7)); 7.33 (br., NH–C(1)).

*(2S,5S)- and (2R,5S)-1-Benzoyl-2-(*tert*-butyl)-3-methyl-5-(3'-thiabutyl)imidazolidin-4-one* (**40** and **41**, resp.). Prepared according to [25].

40: 32% yield; m.p. 141–142°. $[\alpha]_D = +64.7°$ (*c* = 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.06 (*s*, *t*-Bu); 1.35–2.30 (*m*, 2 CH_2); 3.07 (*s*, CH_3N); 4.35–4.50 (*m*, H–C(5)); 5.62 (*s*, H–C(2)); 7.35–7.78 (*m*, 5 arom. H).

41: 23% yield; m.p. 94.0–94.5°. $[\alpha]_D = +54.2°$ (*c* = 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.10 (*s*, *t*-Bu); 1.91 (*s*, CH_3S); 1.95–2.80 (*m*, 2 CH_2); 3.03 (*s*, CH_3N); 3.92 (*m*, H–C(5)); 5.56 (*s*, H–C(2)); 7.47 (*s*, 5 arom. H).

*(2R,4S)- and (2S,4S)-3-Benzoyl-2-(*tert*-butyl)-4-(3'-thiabutyl)-1,3-oxazolidin-5-one* (**42** and **43**, resp.). NaOH (100 ml of 1N aq. soln.) was added dropwise to 14.9 g (0.1 mol) of (*S*)-methionine in 50 ml of EtOH, and the mixture was stirred for 15 min. After evaporation, the sodium salt of (*S*)-methionine was dried under high vacuum and then suspended in 150 ml of CH_2Cl_2. This suspension was treated with 16.6 ml (0.15 mol) of pivalaldehyde and heated to reflux for 4 h with simultaneous removal of H_2O generated (*Dean-Stark* trap). The solvent was evaporated and the solid residue (*N*-neopentylidene-(*S*)-methionine; 21.82 g, 91%) was dried overnight under high vacuum. The residue was dissolved in 400 ml of dry (filtered through Al_2O_3) CH_2Cl_2. The resulting soln. was cooled to −10° and treated with 15.9 ml (0.137 mol) of benzoyl chloride (dropwise addition *via* syringe). The mixture was stirred at −10° for 7 h and then at r.t. for 17 h, before it was shaked with 2 × 200 ml of aq. $NaHCO_3$, once with 200 ml of aq. $NaHSO_4$ soln., and then twice with 200 ml of H_2O. The org. phase was dried ($MgSO_4$), filtered, and evaporated to give 29.19 g (91%) of the crude product, which was recrystallized from MeOH to afford 19.26 g (60%) of pure **43**. Recrystallization of the solid residue obtained from the concentration of the mother liquid gave pure **42**.

42: M.p. 156.0–156.5°. $[\alpha]_D = +144.2°$ (*c* = 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.07 (*s*, *t*-Bu); 1.84 (*s*, CH_3S); 1.40–2.45 (*m*, 2 CH_2); 4.49 (*m*, H–C(4)); 6.18 (*s*, H–C(2)); 7.35–7.70 (*m*, 5 arom. H).

43: M.p. 126.5–127.5°. $[\alpha]_D = +61.1°$ (*c* = 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.04 (*s*, *t*-Bu); 1.88 (*s*, CH_3S); 1.9–2.7 (*m*, 2 CH_2); 4.16 (*m*, H–C(4)); 6.05 (*s*, H–C(2)); 7.43 (*m*, 5 arom. H).

*(2S,5S)-1-Benzoyl-2-(*tert*-butyl)-5-(1"-hydroxyethyl)-3-methyl-5-(3'-thiabutyl)imidazolidin-4-one* (**44**). According to *General Procedure 1*, **40** (1.66 g, 5 mmol) was reacted with acetaldehyde (1.2 ml, 21 mmol; addition at −78° instead of −100° and quenching with AcOH at −78°). Recrystallization of the crude product from CH_2Cl_2/pentane afforded 1.38 g (73%) of pure **44**; m.p. 119–120°. $[\alpha]_D = -65.6°$ (*c* = 1.32, $CHCl_3$). IR ($CHCl_3$): 3480, 2980, 1660, 1645, 1410, 1370, 1265, 1115, 1070. ^{1}H-NMR ($CDCl_3$): 1.00 (*d*, $J = 6.0$, CH_3–C(1")); 0.85, 1.15 (2*s*, *t*-Bu); 2.00–4.45 (*m*, 12 H, *inter alia* 2.15 (*s*, CH_3S) and 3.12 (*s*, CH_3N)); 5.45, 5.65 (2*s*, H–C(2)); 7.35–7.70 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 15.14; 18.16; 27.24; 27.78; 30.90; 31.20; 38.32; 39.01; 69.03; 73.14; 80.52; 127.44; 128.12; 128.6; 131.5; 137.2; 171.68; 174.46. MS: 199 (46), 173 (10), 151 (15), 125 (12), 106 (18), 105 (100), 77 (49), 42 (12). Anal. calc. for $C_{20}H_{30}N_2O_3S$: C 63.46, H 7.99, N 7.40; found: C 63.66, H 8.17, N 7.48.

*(2R,5S)-5-(1"-Benzoyloxyethyl)-2-(*tert*-butyl)-3-methyl-5-(3'-thiabutyl)imidazolidin-4-one* (**47**). A soln. of **44** (0.377 g, 1 mmol) in 10 ml of MeOH was treated with 2–3 ml of MeOH sat. with HCl and stirred at r.t. for 1 h. The mixture was then evaporated and redissolved in 20 ml of CH_2Cl_2 before extraction with sat. aq. $NaHCO_3$ and

NaCl solns. The org. phase was dried ($MgSO_4$), filtered, and concentrated to afford the crude product which was purified by FC (Et_2O): **47** in 87% yield (0.33 g); m.p. 93.5°. $[\alpha]_D = -45.1°$ ($c = 0.94$, $CHCl_3$). IR ($CHCl_3$): 3400, 2980, 1710, 1700, 1400, 1270, 1110, 1070. ^{1}H-NMR ($CDCl_3$): 1.07 (*s*, *t*-Bu); 1.42 (*d*, $J = 6.0$, CH_3–C(1″)); 1.70–2.90 (*m*, 8 H); 2.90 (*s*, CH_3N); 4.32 (*d*, $J = 6.0$, H–C(2)); 5.30 (*q*, $J = 7.0$, H–C(1″)); 7.30–8.15 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 14.73; 15.58; 25.65; 29.00; 30.56; 32.82; 35.39; 66.43; 74.14; 81.51; 128.50; 129.59; 130.15; 133.18; 165.63; 174.29. MS: 321 (64, $M^{+\cdot} - 56$), 230 (14), 229 (100), 199 (65), 173 (70), 151 (26), 125 (31), 124 (13), 111 (23), 105 (81), 77 (28). Anal. calc. for $C_{20}H_{30}N_2O_3S$: C 63.46, H 7.99, N 7.40; found: C 63.74, H 8.24, N 7.30.

*(2R,5S)-5-(1″-Benzoyloxybenzyl)-2-(*tert*-butyl)-3-methyl-5-(3′-thiabutyl)imidazolidin-4-one* (**48**). Prepared according to the procedure used for **44** with 1.66 g (5 mmol) of **40** and 0.55 ml (5.44 mmol) of benzaldehyde. The crude product was purified by FC (Et_2O/pentane 1:1) to yield 1.64 g (75%) of pure **48**; m.p. 138–140°. $[\alpha]_D = +35.3°$ ($c = 1.1$, $CHCl_3$). IR ($CHCl_3$): 2600–3100, 1725, 1695, 1600, 1475, 1395, 1315, 1265, 1110, 1070, 1025, 925, 875. ^{1}H-NMR ($CDCl_3$): 0.93 (*s*, *t*-Bu); 1.50–2.70 (*m*, CH_2CH_2, OH); 2.05 (*s*, CH_3S); 2.75 (*s*, CH_3N); 3.63–3.83 (*m*, H–C(1″)); 5.97 (*s*, H–C(2)); 7.27–8.20 (*m*, 10 arom. H). ^{13}C-NMR ($CDCl_3$): 15.48; 25.58; 28.80; 30.51; 34.35; 35.21; 66.80; 79.83; 82.02; 127.78; 128.36; 128.46; 128.70; 129.78; 130.07; 133.15; 136.46; 164.89; 174.13. MS: 441 (1, $M^{+\cdot} + 1$), 261 (35), 230 (22), 229 (100), 174 (10), 173 (98), 125 (18), 111 (22), 105 (60), 77 (22), 42 (25).

*(2R,4S)-3-Benzoyl-2-(*tert*-butyl)-4-(1″-hydroxyethyl)-4-(3′-thiabutyl)oxazolidin-5-one* (**49**). Prepared according to the procedure used for **44** with 1.602 g (5 mmol) of **42** and 1.21 ml (21 mmol) of acetaldehyde. The product was purified by crystallization from MeOH. Yield: 78% (1.42 g); m.p. 95° (dec.). $[\alpha]_D = -10.0°$ ($c = 1.42$, $CHCl_3$). IR ($CHCl_3$): 3550 (br.), 2970, 1770, 1650, 1375, 1340, 1310, 1180, 1150, 1110, 1080, 1060, 1020. ^{1}H-NMR ($CDCl_3$): 1.00 (*s*, *t*-Bu); 1.22 (*d*, $J = 7.0$, CH_3–C(1″)); 2.0–3.1 (*m*, 9 H); 3.85 (br., H–C(1″)); 6.07 (*s*, H–C(2)); 7.30–7.70 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 14.94; 18.28; 25.51; 29.61; 35.97; 38.16; 70.09; 71.18; 95.12; 127.36; 128.39; 131.51; 136.14; 172.13; 192.16. MS: 199 (11, $M^{+\cdot} - 166$), 142 (96), 122 (42), 115 (18), 105 (100), 96 (19), 95 (39), 77 (53). Anal. calc. for $C_{19}H_{27}NO_4S$: C 62.44, H 7.45; N 3.83; found: C 62.62, H 7.35, N 3.62.

(2S,3R)-2-Ethylthreonine Hydrate (**51**·½ H_2O). A soln. of **49** (0.918 g, 2.5 mmol) in 50 ml of EtOH and warmed up to 70° before the rapid addition of 7.5 g (*ca.* 15 equiv.) of *Raney*-Ni (*W-2*) in 50 ml of H_2O. The mixture was stirred for 15 min, allowed to cool to r.t., filtered through *Celite* and evaporated. The residue in 10 ml of 6N HCl was then heated to reflux for 16 h and allowed to cool to r.t. The resulting aq. soln. was extracted with CH_2Cl_2 and evaporated to afford crude **51**·HCl. This product in 2 ml of H_2O was adsorbed onto 20 g of acidic ion exchanger (*Dowex-50-W X 8*), and, after washing with H_2O till neutrality, elution with dil. NH_3 soln., and evaporation, the free amino acid was recrystallized from EtOH/H_2O to afford 0.15 g (40%) of **51**·½ H_2O[22]); m.p. 240° (dec.). $[\alpha]_D = -1.7°$ ($c = 0.3$, H_2O). IR (KBr): 3700–2000, 1630, 1615, 1525, 1390, 1380, 1290, 1110. ^{1}H-NMR (D_2O): 0.89–0.95 (*m*, CH_3CH_2); 1.22 (*d*, $J = 6.5$, CH_3–C(3)); 1.5–2.0 (*m*, CH_3CH_2); 4.24 (*q*, $J = 6.5$, H–C(3)). ^{13}C-NMR (D_2O): 10.05; 18.64; 27.54; 71.50; 177.25. MS: 149 (3), 103 (58), 102 (77), 85 (37), 57 (97), 56 (100), 43 (30). Anal. calc. for $C_6H_{13}NO_3$: C 48.97, H 8.90, N 9.52; found: C 46.67, H 8.83, N 8.93.

(2R,3R)-2-Ethylallothreonine Hydrate (**52**·½ H_2O). Methyl (4*R*,5*R*)-4-ethyl-5-methyl-2-phenyl-1,3-oxazoline-4-carboxylate [45] (0.591 g, 2.38 mmol) was heated to reflux in 10 ml of 6N HCl for 16 h and then allowed to cool to r.t. The soln. was extracted with CH_2Cl_2 and concentrated. The residue was then adsorbed onto 20 g of acidic ion exchanger (*Dowex-50-W X 8*), washed with H_2O till neutrality, eluted with dil. NH_3 soln., and evaporated. Recrystallization from EtOH/H_2O afforded 0.24 g (68%) of pure **52**·½ H_2O[22]); m.p. 229–231° (dec.). $[\alpha]_D = +11.3°$ ($c = 0.48$, H_2O). IR (KBr): 3700–2300, 1640, 1610, 1580, 1520, 1460, 1390, 1280, 1100. ^{1}H-NMR (D_2O): 0.92–0.97 (*m*, CH_3–C(1′)); 1.23 (*d*, $J = 6.5$, CH_3–C(3)); 1.87–2.00 (*m*, CH_2(1′)); 4.10 (*q*, $J = 6.5$, H–C(3)). ^{13}C-NMR (D_2O): 10.09; 19.54; 29.51; 71.79; 72.44; 176.83. MS: 148 (17), 103 (46), 102 (73), 85 (26), 57 (75), 56 (100), 43 (24). Anal. calc. for $C_6H_{13}NO_3$: C 48.97, H 8.90, N 9.52; found: C 45.81, H 8.86, N 8.71.

(+)-3-Amino-2,2-dimethyl-2,3,4,5-tetrahydro-3-thiophenecarboxylic Acid (**53**). A mixture of 0.264 g (0.7 mmol) of **46** and 25 ml of 6N HCl was heated to 150° for 4 h in a *Bombenrohr*. The aq. soln. was extracted with CH_2Cl_2 and then concentrated to afford **53**·HCl, which was adsorbed onto *ca.* 10 g of *Dowex-50-W X 8* ion-exchange resin, washed with H_2O till neutral, eluted with dil. NH_3 soln., and evaporated to give 61 mg (53%) of **53**·⅛ H_2O; m.p. > 310°. $[\alpha]_D = +168°$ ($c = 0.2$, H_2O). IR (KBr): 3700–1900, 1630, 1595, 1505, 1460, 1325, 1210, 1150, 1120, 655. ^{1}H-NMR (D_2O): 147 (*s*, 2 CH_3); 2.41–2.48 (*m*, 1 H); 2.90–3.06 (*m*, 2 H); 3.16–3.22 (*m*, 1 H). MS: 175 (52), 101 (55), 100 (54), 88 (94), 83 (98), 69 (48), 57 (29), 55 (100), 41 (53). Anal. calc. for $C_7H_{13}NO_2S$: C 47.98, H 7.48, N 7.99; found: C 47.34, H 7.40, N 7.87.

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[22]) It is suggested by the anal. data that these crystals contain approximately 0.5 equiv. of H_2O.

(+)-3-Amino-2-phenyl-2,3,4,5-tetrahydro-3-thiophenecarboxylic Acid (**55**). As for **53**, with 0.595 g (1.35 mmol) of **48** and *ca.* 20 ml 6N HCl (3 h at 180°): **55** in 70% yield (0.19 g); m.p. 269–271° (dec.). $[\alpha]_D = +157°$ (*c* = 0.55, AcOH). IR (KBr): 3700–2000, 1640, 1500, 1450, 1370, 1240, 700. ^{1}H-NMR (CD_3COOD): 2.61–2.70 (*m*, 1 H); 2.95–3.06 (*m*, 1 H); 3.15–3.25 (*m*, 2 H); 5.35 (*s*, H–C(2)); 7.30–7.52 (*m*, 5 arom. H). ^{13}C-NMR (CD_3OD): 27.80; 39.08; 49.00; 57.20; 71.26; 128.57; 129.07; 129.45; 129.71; 171.21. MS: 223 (24), 206 (52), 136 (55), 135 (100), 101 (28), 100 (73), 91 (35), 55 (51). Anal. calc. for $C_{11}H_{13}NO_2S$: C 59.17, H 5.87, N 6.27, S 14.36; found: C 59.00, H 5.90, N 6.34, S 14.09.

*(2S,5S)-1-Benzoyl-2-(*tert*-butyl)-3-methyl-5-vinylimidazolidin-4-one* (**57**). Aq. H_2O_2 (0.6 g of 35% soln., 6.4 mmol) was added to a soln. of 10 ml of AcOH and 1.68 g (5 mmol) of **40**. The resulting mixture was stirred at r.t. for 4 h, treated with 100 ml of CH_2Cl_2, the org. phase extracted with sat. aq. Na_2CO_3 and sat. NaCl soln. and H_2O, dried ($MgSO_4$), and evaporated. The solid residue was dissolved in 20 ml of xylene and heated to 200–210° in a *Bombenrohr* for 2 h. The solvent was distilled to give the crude product, which was purified by FC (Et_2O/CH_2Cl_2 8:1) to afford 0.78 g (55%) of **57**; m.p. 167–169°. $[\alpha]_D = +104.1°$ (*c* = 1, $CHCl_3$). IR ($CHCl_3$): 2990, 1710, 1650, 1380. ^{1}H-NMR ($CDCl_3$): 1.08 (*s*, *t*-Bu); 3.08 (*s*, CH_3N); 4.55–5.37 (*m*, H–C(5), CH_2=CH); 5.70 (*s*, H–C(2)); 7.20–7.60 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 26.29; 32.21; 40.59; 65.62; 79.58; 120.40; 128.16; 128.35; 131.34; 132.94; 136.71; 169.56; 171.28. MS: 229 (57), 136 (96), 119 (39), 118 (66), 105 (100), 91 (94), 77 (33). Anal. calc. for $C_{17}H_{22}N_2O_2$: C 71.30, H 7.74, N 9.78; found: C 71.06, H 7.72, N 9.68.

*(2S,5S)-1-Benzoyl-2-(*tert*-butyl)-5-(1'-hydroxyethyl)-3-methyl-5-vinylimidazolidin-4-one* (**61**). The procedure used for **44** was followed with 1.14 g (4 mmol) of **57** and 1.2 ml (21 mmol) of acetaldehyde. FC (Et_2O) afforded 0.49 g (38%) of **61**, 0.25 g (19%) of **59**, and 0.13 g (10%) of **62**.

*(2S)-1-Benzoyl-2-(*tert*-butyl)-5-(3'-hydroxybutylidene)-3-methylimidazolidin-4-one* (**59**): M.p. 107°. R_f (Et_2O): 0.09. $[\alpha]_D = +50.0°$ (*c* = 0.7, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.95–1.15 (*m*, *t*-Bu, CH_3–C(3')); 2.20–3.10 (*m*, 3 H); 3.08 (*s*, CH_3N); 5.30–5.65 (*m*, H–C(3')); 5.05 (*t*, *J* = 9.0, H–C(1')); 5.40 (*s*, H–C(2)); 7.25–7.47 (*m*, 5 arom. H).

61: R_f (Et_2O): 0.29. $[\alpha]_D = -50.3°$ (*c* = 0.92, $CHCl_3$). IR ($CHCl_3$): 3460, 2990, 1690, 1645, 1405, 1365, 1330, 1310, 1265, 1120, 1090, 940, 894. ^{1}H-NMR ($CDCl_3$): 1.00–1.15 (*m*, *t*-Bu, CH_3–C(1')); 3.13 (*s*, CH_3N); 3.36–3.62 (*m*, H–C(1')); 4.05 (*d*, *J* = 12.0, OH); 5.40–5.50 (*m*, CH_2=CH); 5.75 (*s*, H–C(2)); 5.96–6.10 (*m*, CH_2=CH); 7.3–7.7 (*m*, 5 arom. H). MS: 273 (35), 229 (70), 151 (37), 105 (93), 77 (100), 42 (22). Anal. calc. for $C_{19}H_{29}N_2O_3$: C 69.06, H 7.93, N 8.48; found: C 68.92, H 7.99, N 8.35.

*(2R,5S)-4-(1'-Benzoyloxyethyl)-2-(*tert*-butyl)-1-methyl-4-vinylimidazolidin-4-one* (**62**). M.p. 137°. $[\alpha]_D = -9.5°$ (*c* = 0.265, $CHCl_3$). IR ($CHCl_3$): 3420, 2980, 1720, 1700, 1455, 1405, 1275, 1120. ^{1}H-NMR ($CDCl_3$): 1.00 (*s*, *t*-Bu); 1.32 (*d*, *J* = 6.0, CH_3–C(1')); 2.12 (*s*, NH); 2.84 (*s*, CH_3N); 4.34 (*d*, *J* = 6.0, H–C(2)); 5.31–5.41 (*m*, 2 H); 5.55–5.61 (*m*, CH_2=CH); 6.0–6.1 (*m*, CH_2=CH); 7.25–8.05 (*m*, 5 arom. H). MS: 331 (4), 273 (63), 229 (23), 181 (59), 151 (60), 125 (40), 105 (100), 77 (35), 42 (38). Anal. calc. for $C_{19}H_{26}N_2O_3$: C 69.06, H 7.93, N 8.48; found: C 68.96, H 8.15, N 8.41.

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