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RESOLUTION AND USE IN α-AMINO ACID SYNTHESIS OF IMIDAZOLIDINONE GLYCINE DERIVATIVES

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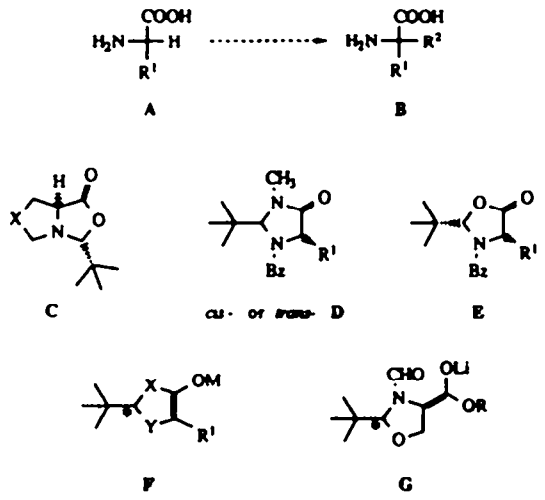
Abstract- The imidazolidinones (*rac.*-1 and *rac.*-2) obtained from pivalaldehyde and glycine amides are resolved efficiently by crystallization of diastereoisomeric ammonium salts with chiral acids (mandelates and a gulonate respectively). The free bases are acylated under *Schotten-Baumann* conditions to give enantiomerically pure 1-Bz-, 1-BOC-, 1-Z- or 1-formyl-2-*t*-butyl-3-methyl- or -3-benzyl-4-imidazolidinones. Diastereoselective alkylation of the 3-methyl derivatives (BMI) with a variety of electrophiles (LDA/THF -70 to + 25°) gives *trans*-disubstituted imidazolidinones exclusively (3 - 22). Some of these are hydrolyzed by a procedure employing excess acidic ion exchange resin to give enantiomerically pure (*R*)- or (*S*)-amino acids. The procedure is compared with other methods of generating chiral glycine enolates.

A) *INTRODUCTION*

In 1981 we first published a method by which an amino acid can be α-alkylated without forming racemic products (A → B in ***Scheme 1***)[2]. This was achieved by converting the amino acid into a cyclic acetal (C, D, E) with diastereoselective formation of a stereogenic acetal center. This in turn directs the steric course of attack at the enolate (F, G) in the subsequent alkylation step. In this way we were able to prepare enantiomerically pure (*R*)- or (*S*)- α-alkylated derivatives of almost all protein amino acids[3-12].

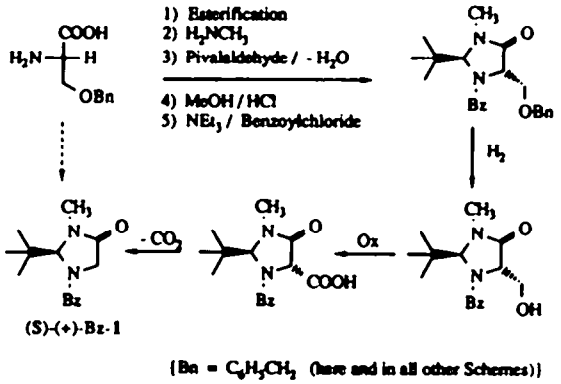
Scheme 1 Enantioselective Branching of Amino Acids through Enolates of Heterocyclic Acetals.



[Bz = C_6H_5CO (here and in all other Schemes)]

Since we noticed the exceptional selectivity of enolates of type F we became convinced that an analogous glycine - derived enolate would lead to non - branched amino acids with similar selectivities. It is important to have a chiral glycine enolate (see also section E) not so much for making protein amino acids as such. Rather, a general method should be available to prepare isotopically labelled amino acids, (*R*)-amino acids, and other natural as well as unnatural non - protein amino acids with special side chains.

Scheme 2 Synthesis of the Chiral Glycine BMI - Derivative (*S*)-Bz-1 by Degradation of Serine.



[Bn = $C_6H_5CH_2$ (here and in all other Schemes)]

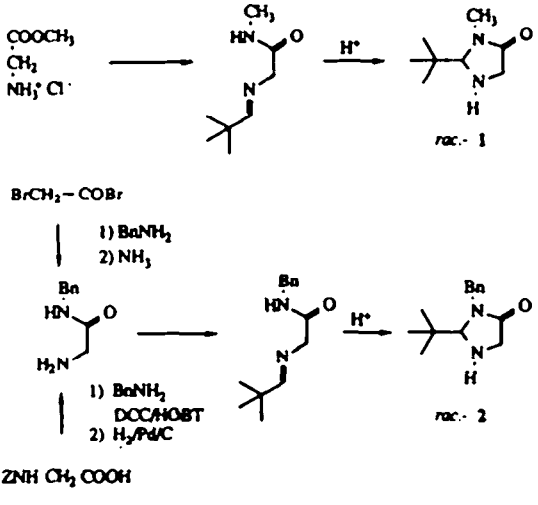
First, we took the hard way and did a multistep degradation of imidazolidinones from amino acids with suitable side chains, such as serine[13] and methionine [7c]. By this route we obtained small amounts of the *t*-butyl-methyl-imidazolidinone

(BMI) (*S*)-Bz-**1** as outlined in ***Scheme 2*** . Indeed, the enolate of this glycine derivative was alkylated with very high selectivity[13]. This result provided strong incentive to search for a simpler way of making enantiomerically pure imidazolidinones of this type[14]. Discarding the notion "that there is a mystique and an aura of art to resolutions", trusting a lifetime experience of Professor *J. Jacques* that "there need be few - if any - failures in intelligently and systematically executed resolutions"[15], and knowing that unprotected BMI derivatives **1** are rather stable[4a], we started a project which led to the results described in the following sections.

B) PREPARATION AND RESOLUTION OF IMIDAZOLIDINONES **1** (BMI) *AND* **2** (BBI).

The racemic imidazolidinones **1** and **2** turned out to be remarkably stable compounds, and thus well suited for resolution experiments. These cyclic aminal derivatives can be handled in open air, they are stable to non - aqueous acidic conditions[16,17], and they can be acylated like simple secondary amines under *Schotten - Baumann* conditions (aqueous NaOH) in high yields. *Rac.*-**1** was prepared from glycine methyl ester hydrochloride as described previously[4a,1b]. The 3-benzyl analogue *rac.*-**2** was chosen as the second subject of our resolution experiments in view of the expected greater ease of conversion to free amino acids in the final stage of its applications. Although Z - protected glycine can be used[18] as a starting material for the preparation of *rac.*-**2** as indicated in ***Scheme3***,

Scheme 3 Preparation of the Glycine Derivatives *rac.*-**1** (BMI) and *rac.*-**2** (BBI).

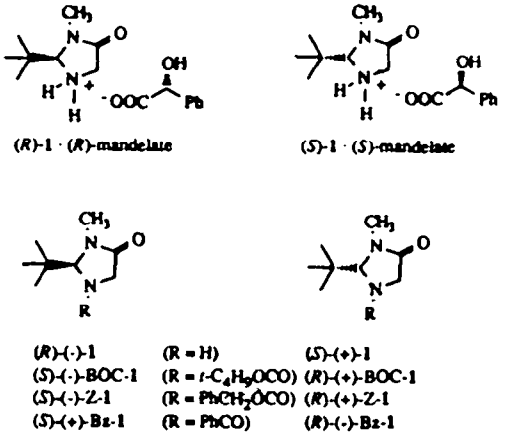


[Z = $C_6H_5CH_2OCO$ (here and in all other Schemes)]

we found that for large - scale preparation bromoacetyl bromide is a far more convenient starting material. *Schiff* base formation and cyclization were achieved as with the methyl derivative **1**. In both cases the crude products of cyclization, which are formed in an exothermic reaction upon treatment of the *Schiff* bases with anhydrous methanolic HCl, were used for the resolution experiments.

Of the dozen or so inexpensive enantiomerically pure acids available mandelic acid[19] quickly turned out to be very efficient for the resolution of **1**.

Scheme 4 Resolution of the *t*-Butyl-methyl-imidazolidinone **1** with Mandelic Acid.



[Ph = C_6H_5 (here and in all other Schemes)]

Solutions of **1** and of mandelic acid in acetone (both saturated at boiling temperature) were combined (1:1 molar ratio of acid and base) and the resulting ammonium salt solution allowed to cool slowly to 5° C in a cold room. The diastereoisomeric salt of *like* - configuration crystallizes and is isolated in ca. 30 % yield (60 % of theory). The free base is recovered from the mother liquor and the crystallization repeated with the enantiomeric mandelic acid, producing ca. 40 % of theory of the enantiomeric salt. Both are of at least 98 % purity. The procedure has been carried out in scales up to many kilograms[20]. From the salts, the enantiomeric imidazolidinones (*R*)-(-)-**1** and (*S*)-(+)-**1** are obtained (≥ 95 %) by treatment with aqueous base in a two - phase system, and the mandelic acids are recovered in high yields.

The BMI derivatives **1** are acylated by di-*t*-butyldicarbonate, benzyloxycarbonylchloride, and benzoylchloride to give BOC-, Z-, and Bz-BMI derivatives, respectively, under *Schotten - Baumann* con-

ditions or with one equivalent of triethylamine (cat. amounts of DMAP[21]) in acetone or acetonitrile. In order to find out whether the racemic mixtures of these BMI derivatives form racemates or conglomerates, and thus whether it might be possible to enrich non-racemic mixtures of enantiomers or even to resolve racemic mixtures by entrainment, melting point diagrams were established.

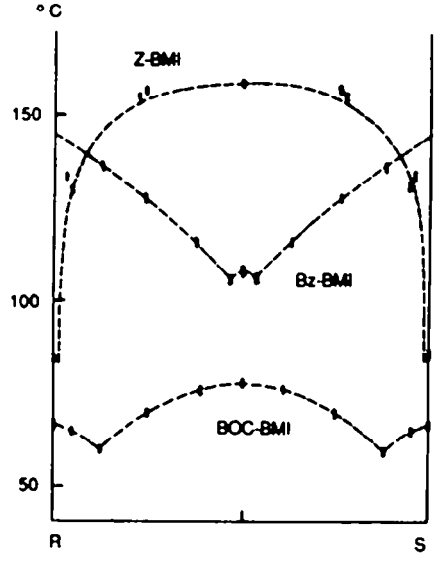
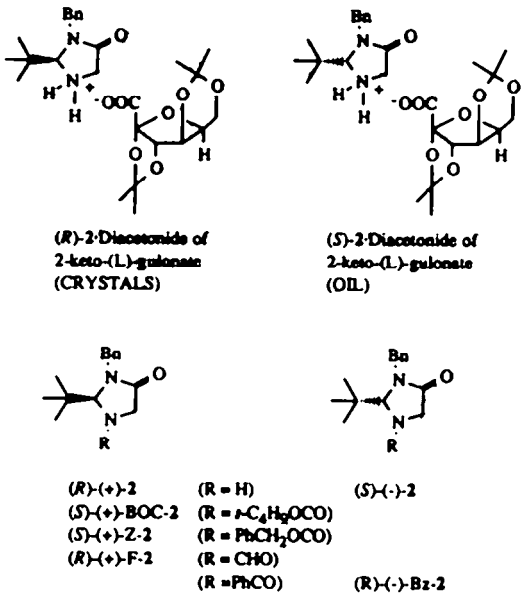


Fig.1. Melting Point Diagrams of the BMI - Derivatives. Mixtures of the enantiomers (*R/S*)- BOC-1 were prepared as described in the experimental section (see also acknowledgement).

Obviously, all three BMI derivatives form racemates. This was confirmed by differences in the solid-state IR spectra of racemic mixtures and pure enantiomers. There is a striking dependence of the melting behaviour of the three derivatives on the N-protecting group: Z-BMI forms a very stable racemate, while the crystals of enantiomerically pure Bz-BMI are much more stable than those of the racemic form. This latter property is a condition for facile enrichment of the excess enantiomer in non-racemic mixtures by crystallization[22].

The benzyl derivative 2 (BBI) can be resolved through a ketogulonate salt[23] (*Scheme 5*), of which one diastereoisomer crystallizes nicely while the other one is an oil. The imidazolidinone freed from the crystalline salt with base was acylated as described above for the BMI analogue to give BOC-, Z-, and F-BBI derivatives 2.

Scheme 5 Resolution of the Benzyl-*t*-butyl-imidazolidinone 2 (BBI) with the Diacetonide of Gulonic Acid.



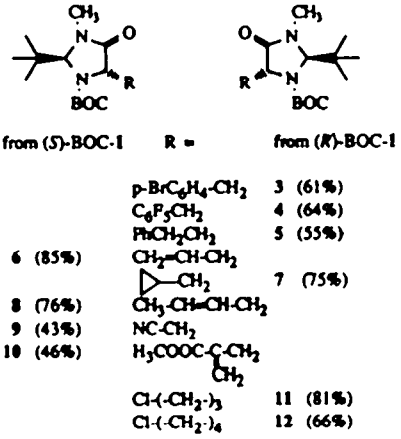
From the oily diasteroisomeric salt the free base BBI 2 of smaller enantiomeric excess was obtained, of which only the benzoyl derivative was suitable for enrichment due to its high crystallization tendency. The chirality senses of the imidazolidinones 2 were proved to be as shown in *Scheme 5* by alkylation to *trans*-substituted heterocycles and subsequent conversion to known amino acid derivatives[18,24].

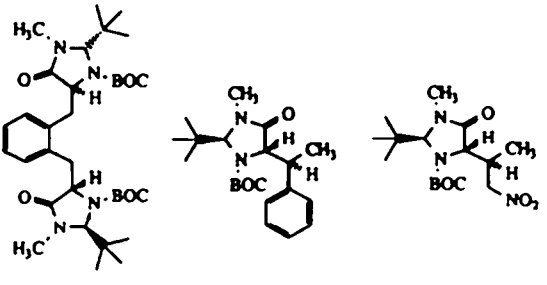
The chiral glycine derivatives BMI and BBI thus available in both enantiomeric forms serve as starting materials for the synthesis of amino acids. BMI is probably going to be more useful than BBI for the following reasons: (i) all derivatives of both enantiomers are equally well available[25], (ii) *rac.*-1 is more easily prepared than *rac.*-2, (iii) the products from BMI can be hydrolysed to the free amino acids directly, (iv) the possible advantage of converting BBI derivatives to free amino acids under milder conditions has to be paid for by a multistep sequence of reactions: dissolving metal reduction for debenzylation, N-protection of the intermediate amino acid amide, and diazotation[18,24].

C) ALKYLATIONS OF BOC-, Z-, AND BZ-BMI LITHIUM ENOLATES.

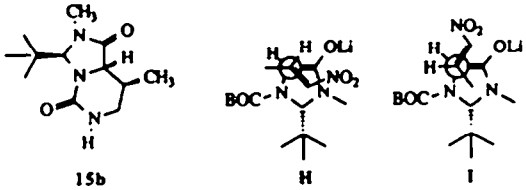
The lithium enolates of the acylated BMI derivatives **1** are generated by treatment with lithium diisopropylamide (LDA). It is possible to prepare 0.2 - 0.5 M enolate solutions in tetrahydrofuran (THF). In the case of BOC- and Bz-BMI, the precursors must be added to LDA solutions at - 50° C, the Z-BMI requires inverse addition[26]. Such enolate solutions from the carbamate protected BMI derivatives are almost colorless, and of *Bordeaux*-red color in the case of Bz-BMI. The products **3** - **22** of alkylation obtained with alkyl halides, acetone and nitropropene are shown in *Schemes* **6** and **7**, along with the yields of analytically pure samples.

Scheme 6 Products of Alkylation of the Lithium BOC-1 Enolates.





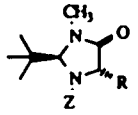
13 (78%) 14 (68%, 85% ds) 15a (73%, 77% ds)



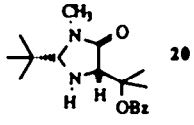
15b H I

Alkylation with the highly reactive halides such as iodomethane, allylic and benzylic chlorides and bromides, cyclopropyl-methyliodide, α-haloacetonitrile and bromoacetic acid esters, as well as the nitroolefin occurs below - 30° C without added activating cosolvents. With the less reactive alkylating reagents longer reaction times and warming up to room temperature (phenylethylbromide → **5**, iodomethyltrimethylsilane → **17**) were applied or the reactions were carried out in the presence of DMPU[27] (bromo-chloroalkanes → **11**, **12**, 2-iodopropane → **16**).

Scheme 7 Products of Alkylation of the Lithium (*S*)-Z-1 and (*R*)-Bz-1 Enolates and a Double-Alkylation Product.



16 : R = CH(CH3)2 (59%)
17 : R = CH2Si(CH3)3 (63%)
18 : R = CH2COOC2H5 (44%)
19 : R = CH2COOCH3 (41%)



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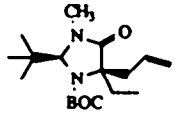
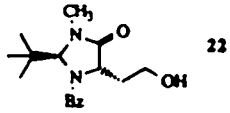


21



22

As with aldehydes[28], the adduct of Bz-BMI enolate to acetone undergoes an acyl shift under acidic conditions (→ **20**). For the preparation of the branched amino acid derivative **21**, it is advantageous to apply the less reactive iodoethane first, and then allyl bromide. For ring opening of oxirane by the Bz-BMI enolate activation with BF_3-etherate is necessary. The homoserine-derived imidazolidinone **22** is thus obtained in good yields[29,30].

All reactions of BMI enolates which occur with formation of only one stereogenic center (→ **3** - **13**, **16** - **22**) give a single diastereoisomer as judged from the high-field NMR spectra of the crude products. Measurements of nuclear *Overhauser* effects (NOE), comparison with BMI derivatives of known configuration, and chemical correlation by hydrolysis to known amino acids (see section D) prove that these alkylation products are *trans*-substituted heterocycles. Thus, electrophilic attack on the enolate double bond occurs with rel. topicity *like* - as with all other imidazolidinone and oxazoli-

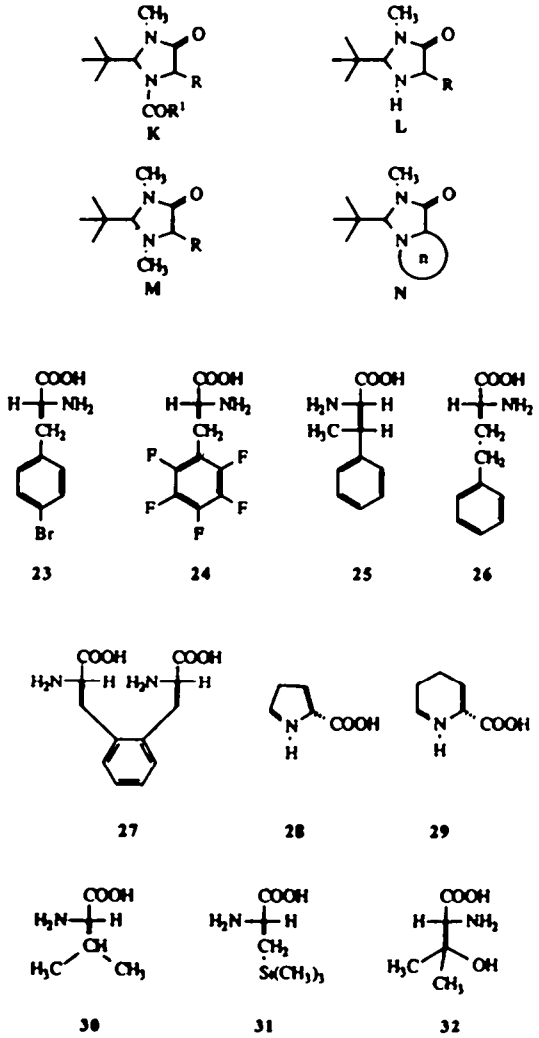
dinone enolates of this type which we have studied so far[12,18], the electrophiles approach the enolate from the face opposite to the *t*-butyl group.

Some of the reactions leading to the products depicted in *Schemes 6* and *7* deserve comment. - The bis (amino acid) derivative **13** was obtained in high yield with dibromoxylene even if the BOC-BMI enolate solution was slowly added to a twofold excess of the dibromide. We speculate that this may be caused by Li-enolate aggregates being involved[31,32]. With the less reactive aliphatic bromo-chloroalkanes (→ **11,12**) this effect was not observed[33]. - The *trans*-butenyl substituted BOC-BMI **8** was obtained in similar yields either from 1-chloro-2-butene (S_N) or from 3-chloro-1-butene ($S_{N'}$). This latter type of reaction has not been observed before with our heterocyclic enolates[12], and is potentially very useful[34]. - The phenyl ethyl derivative **14** is noteworthy because it is formed in good yield and reasonable diastereoselectivity by alkylation with 2.5 equivalents of a racemic secondary bromide, *i.e.* with kinetic resolution[35]. After the usual purification procedure (chromatography of the crude product and recrystallization) the pure diastereoisomer **14** was obtained, the configuration of which was established by hydrolysis to the amino acid (see Section D) and ninhydrin degradation to (*S*)-(+)-2-phenylpropanal (see also experimental section). - The two products obtained in the *Michael* addition of BOC-BMI enolate to nitropropene were epimeric at the β-position. The main product **15a** prevailing by *ca.* 3:1 was separated by crystallization and shown to have *like*-configuration of the newly formed ethane moiety by reduction of the nitro group and cyclization[36] to the urea **15b** which exhibits a typical 10 Hz *trans*-coupling between the bridgehead hydrogen and its neighbour in the NMR spectrum. Thus, the trigonal centers of the enolate and nitroolefin double bonds have combined with rel. topicity *like* (Si,Si), a steric course which had been found before with substituted BMI and similar heterocylcic enolates and nitroolefins[10,37-39], see **H** and **I** in *Scheme 6*. - In comparing the use of BOC- and Z-BMI enolate we have noticed that the former one generally gives very clean "spot--to-spot" conversions, and the latter one furnishes more readily crystallizing products with simple aliphatic alkyl halides.

D) HYDROLYSIS OF BOC- AND Z-BMI DERIVATIVES

In our previous investigations with 5-monosubstituted imidazolidinones **K** (*Scheme 8*) bearing a benzoyl group in the 1-position[4a,13], we found that rather drastic conditions (6 N aqueous HCl, reflux) were necessary to achieve hydrolysis to the free amino acids. These were isolated in partially racemized form. Only the adducts to aldehydes, in which very facile benzoyl shift from N to O, and thus a deprotection to imidazolidinones of type **L** occurs, could be hydrolyzed to threonine analogues without difficulty[28].

Scheme 8 Some Cleavage Intermediates (**K** - **N**) and Amino Acids (**23** - **32**) obtained by Hydrolysis of BMI - Derivatives. Newly formed bonds are marked by heavy lines.



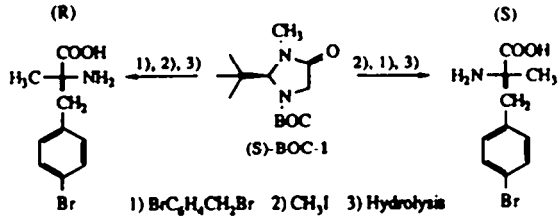
The BOC- and Z-derivatives now available can be deprotected on N(1) under the usual mild anhydrous conditions (trifluoroacetic acid / methylene chloride and H_2/Pd-C / acetic acid, respectively) to give the free bases L. Although these are isolable, and can be used for N-methylations to imidazolidinones M derived from N-methyl amino acids[1a,28], they were hydrolyzed directly to free amino acids in the present study[40]. In the case of the chloroalkylated compounds **11** and **12** the free bases cyclize spontaneously or can be caused to cyclize[41] to bicyclic imidazolidinones of type N which are subsequently hydrolyzed.

Since the aminal moiety of free BMI bases of type L, M and N cleaves most easily in aqueous acid, with formation of pivalaldehyde[42,43] and an amino acid methyl amide, we chose the methyl amide of (*S*)-phenylalanine as a test substance to elaborate a hydrolysis technique with which the racemization in the final step leading to free amino acids could be suppressed. From certain hints in the literature[44,45], we felt that it may be advantageous to do the hydrolysis in the presence of enough acidic ion-exchange resin to bind the entire amount of amino acid and primary amine. Indeed, the phenylalanine amide could be hydrolyzed by simply heating with ion-exchange resin at reflux in water. The reaction was accelerated by employing aqueous ≤ 2 N hydrochloric acid. Since it is known[46,47] that the rate of racemization of amino acids in water is at a minimun slightly below pH 1, we arrived at the following general procedure. The crude free base BMI (type L in ***Scheme 8***) was added to 0.75 N HCl in which freshly activated DOWEX® 50W x 8 (20 - 50 mesh, p.a. quality) was suspended, such that there was a sixfold excess capacity with respect to the imidazolidinone. The mixture was heated[43] at reflux and the reaction was followed by taking samples of the resin[48], eluting and determining the amount of unreacted amide by t.l.c. After complete hydrolysis (18 - 92 hours), the resin was transferred to a column and eluted with aqueous ammonia to give the amino acids in the usual way[49], see the examples in ***Scheme 8***. The allylated free BMI bases from **6**, **8**, **10** and **21** could not be cleanly hydrolyzed to the corresponding amino acids under these standard conditions. Likewise, no free amino acids or only impure samples could be isolated by applying this procedure to the free bases from the cyclopropyl derivative **7**, from the nitrile **9**, the esters **18** and **19**, and from the nitro compound **15a** or the derived amine[50]. So far we have not attempted to develop special procedures for isolating these γ-functionalized amino acids or derivatives thereof.

E) DISCUSSION AND COMPARISON WITH OTHER METHODS.

In summary, the imidazolidinones **1** and **2** can be especially recommended at this stage for the preparation of *either enantiomer* (a) of amino acids with simple aliphatic side chains (including cyclic representatives) {this paper}, (b) of phenylalanines and analogues {this paper}, (c) of threonine-type α-amino-β-hydroxy acids[28], and (d) of α-branched amino acids [2-4,8,9]. The chiral glycine derivatives described here will be useful not only for the preparation of unnatural, non-protein, or labelled amino acids; due to their commercial availability, and due to the fact that it is sometimes not straightforward to convert a given amino acid stereoselectively into either diasteroisomer of a 5-substituted imidazolidinone, they can also be used for preparing branched amino acids which

Scheme 9 Possible Application of a BMI Derivative **1** for the Preparation of two Enantiomeric Branched Alanine Derivatives.



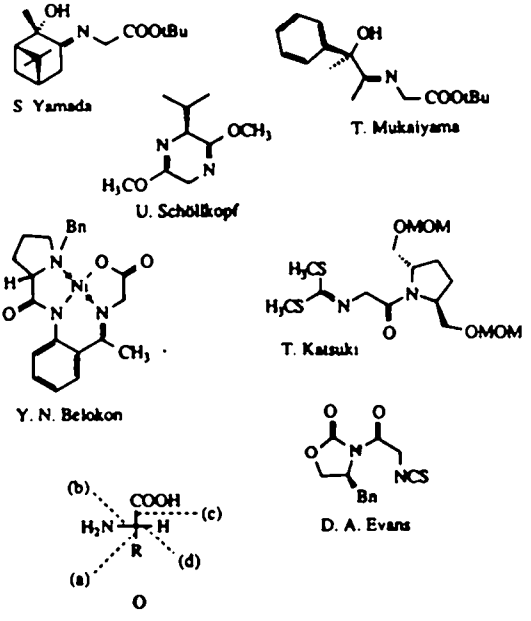
are formally derived from a protein amino acid (such as alanine, see ***Scheme 9***).

Many other chiral non-racemic glycine derivatives have been found to be useful for the amino acid synthesis[51,52]. Of the glycine derivatives which can be used as *nucleophiles*[52], those shown in Scheme **10** react with diastereoselectivities around or above 90 %. As can be seen, these reagents all rely on the use of chiral auxiliaries which are introduced through covalent bonds and which have to be recycled. In contrast, the auxiliary for making our BMI dervatives is the mandelic acid used and recycled in the resolution[1b].

Finally, it is important to point out that the "glycine approach" is only one of four possible ways to form the stereogenic center of an amino acid selectively

(see O in *Scheme 10*). In addition to using a C,C bond formation with the side-chain carbon as the key step (a), the C,N bond (b), the C,C bond involving the carboxyl group (c), and the α-C,H bond (d) can be made by addition to an appropriate trigonal center. We trust that these other possibilities will be presented in other chapters of this symposium-in-print and refrain from discussing and comparing. The reader should do so. Undoubtedly, the chemical community will decide over the years to come which approach is the most generally useful one.

Scheme 10 Chiral Glycine Derivatives for Amino Acid Synthesis by Reaction with Electrophiles (see ref 52).



F) ACKNOWLEDGEMENTS

Ph. Ineichen carried out many of the experiments described here as part of his education to become a chemical technician. Miss *B. Brandenberg*, Mr. *M. Welti* and Dr. *B. Jaun* have measured numerous high-field NMR spectra (including NOEs). Mlle. Dr. *M. J. Brienne* of the Collège de France (F-Paris) investigated the melting behaviour of the BMI derivatives (*Fig.1*).The collaboration with Drs. *H. Lotter* and *K. Drauz* of the DEGUSSA (D-Hanau) for large-scale resolutions and generous gifts of BMI samples from DEGUSSA AG are gratefully acknowledged. BASF AG (D-Ludwigshafen) provided us with ample supplies of pivalaldehyde, and the SANDOZ AG (CH-Basel) provided financial support to do the investigations described here.

G) EXPERIMENTAL PART

General remarks.
Melting points are uncorrected and were determined on a Büchi 510 m.p. apparatus in open capillaries and for amino acids in sealed ones. For the melting point diagrams all mixtures were prepared by dissolving appropriate amounts of one enantiomer and of the racemate (or both enantiomers for Bz-BMI) in a few drops of CH_2Cl_2. Then the solvent was evaporated under an air stream. The solid residue was left on a hot plate at ≈ 45 - 50° C for Z- and Bz-BMI for varying time periods (from a few hours up to 9 days) before measurement.
IR spectra were measured in $CHCl_3$ on a Perkin-Elmer 782 or in KBr on a Perkin-Elmer 283 spectrometer. 90 MHz ^{1}H-NMR spectra were recorded on a Varian EM 390, 300 MHz on a Bruker WM-300 or on a Varian VXR-300 spectrometer. TMS was used as internal standard with $CDCl_3$ or DMSO-d_6 as solvent.With D_2O DSS (3-(trimethylsilyl)-1-propanesulfonic acid (sodium salt, hydrate)) was used as internal standard. For the ^{19}F-NMR spectra $CFCl_3$ was used as external standard and it was recorded on the Varian VXR-300. The MS spectra were recorded on a Hitachi- Perkin-Elmer RMU-6M. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. The diastereoisomeric compositions (% ds = diastereoselectivity) were determined by ^{1}H-NMR (300 MHz) of crude products. Flash chromatography was performed according to the method described by *Still* et al.[53]

Preparation of (S)-2-t-butyl-3-methyl-4-imidazolidinone- (S)-mandelate ((*S*)-1·(*S*)-mandelate).
A hot solution of (*S*)-mandelic acid (180 g, 1.18 mol) in acetone (300 ml, distilled over calcium chloride) was added to a hot stirred solution of free base (*R/S*)-1 (180.2 g, 1.153 mol)[1,4a,17] in acetone (100 ml). After seeding and stirring the solution was allowed to cool down very slowly to 4° C by insulating the flask. The crystals were filtered off, suspended in acetone (290 ml) and stirred under reflux for one hour. After cooling slowly the crystals were collected and treated as above in acetone (170 ml). Colorless crystals (108 g, 60 %, $[\alpha]_D$ + 88, c 1.1 in EtOH) were filtered off. Analysis was performed on a sample, which was recrystallized twice from EtOH.
M.p. 115.5 - 116.5 ° C (Found: C, 62.2; H, 7.7; N, 9.0. $C_{16}H_{24}N_2O_4$ requires C, 62.3; H, 7.8; N, 9.1 %); $[\alpha]_D$ + 89 (c 1.0 in EtOH); ν_{max} ($CHCl_3$) 2960, 1685, 1480, 1450, 1400, 1320, 1255, 1185 and 1060 cm^{-1}; δ_H (90 MHz; DMSO-d_6) 0.88 (9 H, s), 2.80 (3 H, s), 3.22 (2 H, s), 4.03 (1 H, s), 4.98 (1 H, s), 6.16 (3 H, br. s), 7.17 - 7.50 (5 H, m).

Preparation of (R)-2-t-butyl-3-methyl-4-imidazolidinone- (R)-mandelate ((*R*)-1·mandelate).
The first mother liquor of the above crystallizations was concentrated, the residue suspended in CH_2Cl_2 (1200 ml) and washed with 2 N NaOH (600 ml). The organic phase was concentrated to a yellow oil. A hot solution of (*R*)-mandelic acid (120 g, 0.789 mol) in acetone (200 ml) was added with stirring. After seeding and stirring the solution was allowed to cool very slowly to 4° C. The crystals were filtered off and stirred again for one hour in refluxing acetone (175 ml). After cooling colorless crystals (81.1 g, 44 %, m.p. 115 - 116 ° C, $[\alpha]_D$ - 89, c 1.0 in EtOH) were collected.

Preparation of (S)-2-t-butyl-1-t-butyloxycarbonyl-3-methyl-4-imidazolidinone ((*S*)-BOC-1).
A suspension of diastereoisomeric salt ((*R*)-1·(*R*)-mandelate) (73.3 g, 238 mmol) in CH_2Cl_2 was washed with 2 N NaOH (180 ml). After drying ($MgSO_4$) CH_2Cl_2 was evaporated. To the remaining oil a solution of di-*t*-butyldicarbonate (65.9 g, 302 mmol) and *p*-dimethylaminopyridine (2.8 g, 22.9 mmol) in acetone (400 ml) was added with cooling. After stirring for 8 h at ambient temperature, triethylamine (32.4 ml, 232 mmol) was added and after two hours stirring 20 ml of water were added and the solution stirred again for 2 h. The acetone was then distilled off and the residue extracted with ether. The extract was washed twice with 1 N HCl and with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated to a yellow oil (45.5 g, 74 %) which crystallized.
M.p. 68 - 70° C (Found: C, 60.8; H, 9.8; N, 10.8. $C_{13}H_{24}N_2O_3$ requires C, 60.9; H, 9.4; N, 10.9 %); $[\alpha]_D$ -14.6 (*c* 1.18 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1695, 1480, 1450, 1405, 1380, 1370, 1310, 1255, 1160, 1110 and 1030 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 1.00 (9 H, s), 1.49 (9 H, s), 2.99 (3 H, s), 3.72 (1 H, d, *J* 16 Hz, 1/2 ABq), 4.15 (1 H, d, *J* 16 Hz, 1/2 ABq), 4.91 (1 H, s); m/z 199 (M^+ - 57, 39), 183 (17), 143 (100), 99 (44), 57 (96) and 41 (21).

Preparation of (R)-2-t-butyl-1-carbobenzyloxy-3-methyl-4-imidazolidinone ((*R*)-Z-1).
A suspension of diastereoisomeric salt ((*S*)-1·(*S*)-mandelate) (27.8 g, 90 mmol) in CH_2Cl_2 (250 ml) was washed with 2 N NaOH (70 ml). The organic phase was dried ($MgSO_4$) and then benzyloxycarbonylchloride (13.2 ml, 88 mmol) and 2 N NaOH (50 ml, 0.1 mol) were added simultaneously with stirring and ice cooling. After 2 h stirring at ambient temperature the organic phase was washed twice with 1 N HCl and with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated to a yellow oil which crystallized. The crystals were treated with a little pentane, crushed, filtered off, washed with pentane and dried to afford a white powder (22.9 g, 88 %) of product (*R*)-Z-1.
M.p. 84 - 85° C (Found: C, 66.15; H, 7.9; N, 9.4. $C_{16}H_{22}N_2O_3$ requires C, 66.2; H, 7.6; N, 9.65 %); $[\alpha]_D$ + 12 (*c* 1.0 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1705, 1480, 1450, 1410, 1395, 1370, 1360, 1300, 1255 and 1105 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 1.00 (9 H, s), 2.98 (3 H, s), 3.80 (1 H, d, *J* 16 Hz, 1/2 ABq), 4.21 (1 H, d, *J* 16 Hz, 1/2 ABq), 4.97 (1 H, s), 5.12 (2 H, s), 7.33 (5 H, s); m/z 233 (M^+ - 57, 26), 189 (11), 92 (8), 91 (100), 65 (3), 57 (3), 42 (3) and 41 (3).

Preparation of (R/S)-3-benzyl-2-t-butyl-4-imidazolidinone ·hydrochloride (*rac.*-2·hydrochloride).
To a stirred mixture of conc. NH_3 (600 ml) and EtOH (600 ml) bromoacetic acid benzylamide[54] (92.3 g, 0.405 mol) was added in portions. The mixture was stirred for 4 h at ambient temperature and kept then for 12 h at 4° C. After concentration to 300 ml and addition of 2 N NaOH (200 ml) the mixture was extracted with CH_2Cl_2 (1000 ml). The organic phase was refluxed together with pivalaldehyde (60 ml, 0.545 mol) for 7 h at a *Dean-Stark* trap. The solution was concentrated and the remaining oil (79.3 g) quickly distilled through a short connection tube ($4 \cdot 10^{-3}$ torr/ 160° C bath temperature). A solution of the destillate in ethanol (200 ml) was then added slowly to stirred HCl-saturated methanol (250 ml) at - 5° C (exothermic!). The mixture was allowed to warm up to ambient temperature with stirring, then cooled again before filtering off the solid which was washed with a little cold ethanol and ether and dried to give colorless crystals of *rac.*-2-hydrochloride (32.7 g, 30 %).
M.p. 182.5 - 184° C (Found: C, 62.5; H, 8.0; N, 10.3. $C_{14}H_{21}ClN_2O$ requires C, 62.6; H, 7.9; N, 10.4 %); ν_{max} (KBr) 1730, 1430, 1410, 1380, 1360, 1330, 1315, 1305, 1285, 1170, 730 and 700 cm^{-1}; δ_H (90 MHz, d_6-DMSO) 0.97 (9 H, s), 3.81 (1 H, d, *J* 15 Hz, 1/2 ABq), 4.01 (1 H, d, *J* 15 Hz, 1/2 ABq), 4.40 (1 H, d, *J* 16 Hz, 1/2 ABq), 4.67 (1 H, s), 4.82 (1 H, d, *J* 16 Hz, 1/2 ABq), 7.26 (5 H, s); m/z 176 (7), 175 (59), 149 (43), 106 (7), 98 (17), 91 (100), 84 (14), 69 (9), 65 (11), 57 (6), 56 (8), 41 (17), 39 (7), 36 (13) and 28 (42).

Enantiomer separation of (R/S)-3-benzyl-2-t-butyl-4-imidazolidinone (*rac.*-2).
A suspension of BBI-derivative *rac.*-2·hydrochloride (32.6 g, 0.122 mol) in ether (200 ml) was washed with 2 N NaOH (70 ml). The organic phase was dried ($MgSO_4$) and concentrated to a yellow oil which was dissolved in acetone (15 ml). A hot solution of (-)-diacetone-2-keto-(L)-gulonic acid hydrate (34.5 g, 0.118 mol) in acetone (80 ml) was added with stirring to effect immediate crystallization. The suspension was allowed to cool down slowly and was then kept for 12 h at 4° C. The solid was filtered off and dried to give colorless crystals of the (*R*)-2·gulonate salt (28.4 g, 92 %).

Preparation of (R)-1-benzoyl-3-benzyl-2-t-butyl-4-imidazolidinone ((*R*)-Bz-2).
The motherliqour from the enantiomer separation was concentrated and the residue dissolved in ether (150 ml). After washing with 2 N NaOH (35 ml) the solution was concentrated and the residue taken up in CH_2Cl_2 (100 ml). With stirring and ice cooling 1 N NaOH (50 ml) and benzoylchloride (5.5 ml, 47 mmol) were added simultaneously. After stirring at ambient temperature for an additional hour the organic phase was dried ($MgSO_4$) and the solvent evaporated. Recrystallization from ethanol yielded colorless crystals of (*R*)-Bz-2 (13.1 g, 64 %; theoretical yield from the original 32.6 g *rac.*-2·hydrochloride).
M.p. 164 - 165° C (Found: C, 74.7; H, 7.2; N, 8.0. $C_{21}H_{24}N_2O_2$ requires C, 75.0; H, 7.2; N, 8.3 %); $[\alpha]_D$ -178 (*c* 0.89 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1700, 1655, 1480, 1445, 1420, 1380, 1365, 1300, 1250, 1140, 1025, 1000 and 995 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 1.05 (9 H, m), 3.92 (1 H, d, *J* 16 Hz, 1/2 ABq), 4.20 (1 H, d, *J* 16 Hz, 1/2 ABq), 4.20 (1 H, d, *J* 16 Hz, 1/2 ABq), 5.21 (1 H, d, *J* 16 Hz, 1/2 ABq), 5.60 (1 H, s), 7.04 - 7.67 (10 H, m); m/z 280 (5), 279 (24), 106 (7), 105 (100), 91 (15), 77 (27), 65 (5), 57 (3), 51 (4), 41 (6), 32 (8), 28 (34).

Preparation of (S)-3-benzyl-2-t-butyl-1-t-butyloxycarbonyl-4-imidazolidinone ((*S*)-BOC-2).
A suspension of diastereoisomeric salt from the enantiomer separation (5.8 g, 11.5 mmol) in ether (50 ml) was washed with 1 N NaOH (20 ml). The organic phase was dried ($MgSO_4$), concentrated and the remaining oil dissolved in acetonitrile (30 ml). Di-*t*-butyl-dicarbonate (2.6 g, 11.9 mmol), triethylamine (1.52 ml, 10.9 mmol) and a trace of dimethylaminopyridine were added and the solution stirred for 12 h at ambient temperature under argon. After evaporation of the solvent a solution of the residue in ether was washed twice with 1 N HCl and twice with 1 N NaOH, dried ($MgSO_4$) and concentrated to a slightly yellow oil of (*S*)-BOC-2 (2.6 g, 74 %) which crystallized.
M.p. 78.0 - 79.5° C (Found: C, 68.55; H, 8.6; N, 8.4. $C_{19}H_{28}N_2O_3$ requires C, 68.65; H, 8.5; N, 8.4 %); $[\alpha]_D$ + 32 (*c* 1.05 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1695, 1480, 1425, 1380, 1365, 1305, 1250, 1160, 1110 and 1025 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 0.96 (9 H, s), 1.38 (9 H, s), 3.78 (1 H, d, *J* 16 Hz, 1/2 ABq), 4.32 (1 H, d, *J* 16 Hz, 1/2 ABq), 4.09 (1 H, d,

J 16 Hz, 1/2 ABq), 4.81 (1 H, s), 5.29 (1 H, d, *J* 16 Hz, 1/2 ABq), 7.03 - 7.45 (5 H, m); m/z 275 (18), 220 (9), 219 (17), 175 (31), 92 (5), 91 (62), 57 (100), 41 (21), 29 (10) and 28 (23).

Preparation of (S)-3-benzyl-2-t-butyl-1-carbobenzyloxy-4-imidazolidinonone ((S)-Z-2) and recovery of the ketogulonic acid derivative.
A suspension of diastereoisomeric salt from the enantiomer separation (22.3 g, 39.8 mmol) in ether (150 ml) was washed with 2 N NaOH (30 ml). Ethyl acetate (150 ml) was added immediately to the water phase, which was then acidified with 6 N HCl. The ethyl acetate phase was concentrated and the residue dissolved in a little acetone and brought to crystallization by the addition of water. The solid was filtered off, washed with a little cold acetone and dried to give colorless crystals of the gulonic acid derivative (6.95 g, 60 %), m.p. 98 - 99° C, $[\alpha]_D$ - 20.5 (c 2.2 in methanol), (lit.[55], - 21 ± 1 (c 2 in methanol)).
The ether phase containing the BBI base was dried ($MgSO_4$) and concentrated to an oil, which was dissolved in CH_2Cl_2 (100 ml). With stirring and ice cooling 1 N NaOH (45 ml) and benzyloxycarbonylchloride (5.6 ml, 39 mmol) were added simultaneously. After stirring for an hour the organic phase was dried ($MgSO_4$) and the solvent evaporated. The residue was recrystallized from ethanol to afford colorless crystals (23 g, 73 %) of (*S*)-Z-2.
M.p. 118 - 119° C (Found: C, 72.2; H, 7.2; N, 7.55. $C_{22}H_{26}N_2O_3$ requires C, 72.1; H, 7.15; N, 7.6 %); $[\alpha]_D$ + 56 (c 1.0 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1705, 1430, 1400, 1360, 1300, 1250, 1105 and 1030 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 0.95 (9 H, s), 3.86 (1 H, d, *J* 16 Hz, 1/2 ABq), 4.34 (1 H, d, *J* 16 Hz, 1/2 ABq), 4.09 (1 H, d, *J* 15 Hz, 1/2 ABq), 5.27 (1 H, d, *J* 15 Hz, 1/2 ABq), 4.94 (1 H, s), 5.09 (2 H, s), 7.00 - 7.45 (10 H, m); m/z 309 (14), 308 (68), 264 (40), 92 (44), 91 (100), 65 (41), 57 (28), 41 (31), 39 (13), 29 (13), 28 (33).

Preparation of (R)-3-benzyl-2-t-butyl-1-formyl-4-imidazolidinone ((R)-F-2).
A suspension of diastereoisomeric salt from the enantiomer separation (4.7 g, 9.2 mmol) in ether (70 ml) was washed with 1 N NaOH (20 ml). The organic phase was dried ($MgSO_4$) and concentrated. A solution of the remaining oil in formic acid (17.6 ml) was treated with acetic acid anhydride (6.2 ml, 65.6 mmol) with stirring and ice cooling[56]. After 2 h ice water (8 ml) was added and the solution stirred for another 15 min. The formic acid was evaporated, the residue dissolved in ether and washed with 1 N HCl and with 1 N NaOH. The ether phase was concentrated and the residue recrystallized from methanol. Precipitation from a concentrated CH_2Cl_2 solution with pentane and drying yielded a colorless powder (1.24 g, 52 %) of (*R*)-F-2.
M.p. 108 - 111° C (Found: C, 69.0; H, 8.0; N, 10.8. $C_{15}H_{20}N_2O_2$ requires C, 69.2; H, 7.7; N, 10.8 %); $[\alpha]_D$ + 76 (c 1.0 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1710, 1680, 1480, 1420, 1405, 1385, 1350, 1085, 1025, 990, 950 and 880 cm^{-1}; δ_H (300 MHz, $CDCl_3$) main conformer: 1.00 (9 H, s), 3.79 (1 H, d, *J* 16 Hz, 1/2 ABq), 4.49 (1 H, d, *J* 16 Hz, 1/2 ABq), 4.11 (1 H, d, *J* 15 Hz, 1/2 ABq), 5.46 (1 H, d, *J* 15 Hz, 1/2 ABq), 4.59 (1 H, s), 7.12 - 7.42 (5 H, m), 8.06 (1H, s); minor conformer: 1.01 (9 H, s), 4.07 (1 H, d, *J* 16 Hz, 1/2 ABq), 4.17 (1 H, d, *J* 16 Hz, 1/2 ABq), 4.27 (1 H, d, *J* 15 Hz, 1/2 ABq), 5.30 (1 H, d, *J* 15 Hz, 1/2 ABq), 5.16 (1 H, s), 7.12 - 7.42 (5 H, m), 8.20 (1H, s); m/z 217 (7), 204 (11), 203 (83), 175 (6), 92 (13), 91 (100), 58 (6), 57 (9), 41 (15), 39 (7) and 29 (9).

General procedure for the alkylation of t-butyloxycarbonyl derivative BOC-1.
All operations were performed in well dried glassware under an argon atmosphere with complete exclusion of moisture.
To a stirred solution of LDA in hexane / THF (15.5 ml, 15.5 mmol) a solution of imidazolidinone BOC-1 (3.85 g, 15 mmol) in THF (20 ml) was added dropwise at - 50° C. After stirring for 30 minutes the electrophile (16 - 20 mmol) was added in one portion. For very reactive electrophiles (e.g. methyl bromomethylacrylate, nitroprop-2-ene) the enolate solution was cooled to - 100° C before the addition of the electrophile. On the other hand DMPU[27] (5 ml) was added after the addition of a very unreactive electrophile (e.g. 2-iodobutane).
The liquid electrophiles were filtered through Alox-N before neat use and solids were carefully dried at high vacuum and then used as a concentrated THF solution. The reactions were followed by t.l.c. (visualized by development in an alcoholic solution of anisaldehyde and sulfuric acid) during slow warming up of the mixture (ca. 10° C per h) and quenched with saturated NH_4Cl (3 ml) after completion. THF was distilled off, the residue suspended in Et_2O (150 ml) and washed with 2 N citric acid, saturated $NaHCO_3$ and water. After drying ($MgSO_4$) the solvent was evaporated and the product chromatographed on silica gel and then recrystallized from diisopropyl ether / hexane.
Only *trans*-substituted imidazolidinones were formed (by high-field NMR of the crude products). In cases in which a stereogenic center was established in the β-position of the carbonyl group the diastereoselectivities were not as high and will be mentioned on the individual procedures below.

Preparation of (2R,5R)-5-p-bromobenzyl-2-t-butyl-1-t-butyloxycarbonyl-3-methyl-4-imidazolidinone (3).
Imidazolidinone (*R*)-BOC-1 (4.90 g, 19.1 mmol) was alkylated according to the general procedure. 4-Bromo-benzylbromide (5.5 g, 22 mmol) was added at - 75° C and the reaction mixture quenched at 0° C. The usual work up gave a crude brownish crystalline material which was chromatographed and recrystallized to give colorless crystals (4.8 g, 61 %).
M.p. 135 - 136° C (Found: C, 56.4; H, 7.0; N, 6.5. $C_{20}H_{29}BrN_2O_3$ requires C, 56.5; H, 6.9; N, 6.6 %); $[\alpha]_D$ - 44 (c 1.28 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1695, 1485, 1480, 1410, 1380, 1365, 1250, 1170, 1130 and 1010 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 0.94 (9 H, s), 1.50 (9 H, s), 2.80 (3 H, s), 3.13 (1 H, dd, J_1 14 Hz, J_2 3 Hz, 1/2 ABq), 3.76 (1 H, dd, J_1 14 Hz, J_2 5 Hz, 1/2 ABq), 4.29 (1 H, m), 4.55 (1 H, s), 7.02 (2 H, d, *J* 11 Hz, 1/2 ABq), 7.29 (2 H, d, *J* 11 Hz, 1/2 ABq); m/z 370 (M^++2 - 57, 1), 369 (M^++1 - 57, 7), 368 (M^+ - 57, 1), 367(M^+-1 - 57, 7), 314 (3), 313 (23), 312 (3), 311 (23), 57 (100).

Preparation of (2R,5R)-2-t-butyl-1-t-butyloxycarbonyl-3-methyl-5-pentafluorobenzyl-4-imidazolidinone (4)
The alkylation of heterocycle (*R*)-BOC-1 (2.6 g, 10.1 mmol) was carried out according to the general procedure. Pentafluorobenzylbromide (1.5 ml, 11 mmol) was added at - 60° C and was quenched after slowly warming up the raction mixture to ambient temperature. Chromatography and recrystallization of the crude product gave colorless crystals (2.9 g, 64 %) of 4.
M.p. 97.5 - 98.5 ° C (Found: C, 54.6; H, 5.5; N, 6.2. $C_{20}H_{25}F_5N_2O_3$ requires C, 55.0; H, 5.8; N, 6.4 %); $[\alpha]_D$ + 9.0 (c 1.0 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1705, 1700, 1520, 1500, 1405, 1380, 1365, 1250, 1165

and 1125 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 0.92 (9 H, s), 1.45 (9 H, s), 2.88 (1 H, d, *J* 14 Hz, 1/2 ABq), 2.93 (3 H, s), 3.86 (1 H, d, *J* 14 Hz, 1/2 ABq), 4.19 (1 H, dd, J_1 9 Hz, J_2 4.5 Hz), 4.95 (1 H, s); m/z 379 (M^+ - 57, 8), 323 (29), 279 (26), 57 (100), 42 (15), 41 (13).

Preparation of (2R,5R)-2-t-butyl-1-t-butyloxycarbonyl-3-methyl-5-(2-phenylethyl)-4-imidazolidinone (5).
Imidazolidinone (*R*)-BOC-1 (4.9 g, 19.1 mmol) was alkylated according to the general procedure. 2-Phenylethylbromide (5.4 g, 40 mmol) was added at - 70° C and the reaction mixture was quenched after 19 h stirring at ambient temperature. Chromatographic purification and recrystallization of the crude product gave 5 (3.8 g, 55 %) as colorless crystals.
M.p. 115 -116° C (Found: C, 69.8; H, 9.2; N, 7.7. $C_{21}H_{32}N_2O_3$ requires C, 70.0; H, 8.95; N, 7.8 %); $[\alpha]_D$ - 6.7 (*c* 0.85 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1695, 1480, 1455, 1410, 1380, 1365, 1250, 1175, 1130 and 990 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 0.99 (9 H, s), 1.51 (9 H, s), 2.00 - 2.90 (4 H, m), 2.97 (3 H, s), 4.11 (1 H, m), 4.98 (1 H, s), 7.00 - 7.33 (5 H, m); m/z 303(M^+ - 57, 32), 248 (22), 247 (99), 203 (100), 134 (23), 98 (36), 91 (26), 57 (98) and 41 (10).

Preparation of (2S,5S)-5-allyl-2-t-butyl-1-t-butyloxycarbonyl-3-methyl-4-imidazolidinone (6).
Alkylation of imidazolidinone (*S*)-BOC-1 (5.1 g, 19.9 mmol) was accomplished following the general procedure. Allyl bromide (2 ml, 24 mmol) was added at - 70° C and the reaction mixture quenched at ambient temperature. Chromatography and recrystallization gave pure product 6 (5.01 g, 85 %).
M.p. 45 - 46° C (Found: C, 64.7; H, 9.5; N, 9.5. $C_{16}H_{28}N_2O_3$ requires C, 64.8; H, 9.5; N, 9.45 %); $[\alpha]_D$ - 10 (*c* 1.0 in CH_2Cl_2); ν_{max} ($CHCl_3$) 2970, 1690, 1480, 1405, 1380, 1365, 1305, 1250, 1165 and 1130 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 0.97 (9 H, s), 1.49 (9 H, s), 2.48 - 2.78 (1 H, m), 3.00 (3 H, s), 3.05 -3.45 (1 H, m), 4.08 (1 H, m), 4.92 (1 H, s), 4.87 - 5.67 (3 H, m); m/z 239 (M^+ - 57, 10), 183 (58), 139 (34), 79 (13), 57 (100), 42 (19) and 41 (25).

Preparation of (2R,5R)-2-t-butyl-1-t-butyloxycarbonyl-5-cyclopropylmethyl-3-methyl-4-imidazolidinone (7).
(*R*)-BOC-1 (2.56 g, 10 mmol) was alkylated according to the general procedure. Bromomethylcyclopropane[37] (2 g, 14.8 mmol) was added at - 70° C and the reaction mixture quenched at ambient temperature. Chromatography and recrystallization of the crude product gave heterocycle 7 (2.39 g, 75 %) as colorless crystals.
M.p. 66 - 67° C (Found: C, 65.9; H, 9.9; N, 9.05. $C_{17}H_{30}N_2O_3$ requires C, 65.8; H, 9.7; N, 9.0 %); $[\alpha]_D$ + 7 (*c* 1.0 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1690, 1480, 1405, 1380, 1365, 1310, 1250, 1170 and 1125 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.04 - 0.51 (4 H, m), 0.98 (9 H, s), 1.50 (9 H, s), 1.54 (1 H, br. s), 2.68 (1 H, m), 3.04 (3 H, s), 4.06 (1 H, m), 5.04 (1 H, s); m/z 253 (M^+ - 57, 20), 198 (11), 197 (199), 153 (35), 84 (15), 57 (88), 42 (12) and 41 (21).

Preparation of (2S,5S)-5-(E-but-2-enyl)-2-t-butyl-1-t-butyloxycarbonyl-3-methyl-4-imidazolidinone (8).
Following the general procedure imidazolidinone (*S*)-BOC-1 (3.85 g, 15 mmol) was alkylated with (*R/S*)-3-chlorobutene (3.8 ml, 37.5 mmol) which was added at - 84° C. The reaction mixture was quenched after warming up to room temperature. The crude product was recrystallized from a little pentane to give colorless crystals of product 8 (3.53 g, 76 %).
M.p. 95.5 - 96.5° C (Found: C, 65.6; H, 9.8; N, 9.0. $C_{17}H_{30}N_2O_3$ requires C, 65.8; H, 9.7; N, 9.0 %); $[\alpha]_D$ + 3.6 (*c* 0.8 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1690, 1490, 1410, 1380, 1365, 1305, 1250, 1170 and 1130 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.95 (9 H, s), 1.48 (9 H, s), 1.59 (3 H, dd, J_1 6.5 Hz, J_2 1 Hz), 2.58 (1 H, m), 2.99 (3 H, s), 3.16 (1 H, br. s), 4.05 (1 H, s), 4.94 (1 H, br. s), 5.04 (1H, m), 5.55 (1 H, m); m/z 253 (M^+ - 57, 19), 197 (65), 153 (31), 98 (8), 84 (11), 57 (100), 42 (13), 41 (20) and 29 (13).

Preparation of (2S,5S)-2-t-butyl-1-t-butyloxycarbonyl-5-cyanomethyl-3-methyl-4-imidazolidinone (9).
Following the general procedure imidazolidinone (*S*)-BOC-1 (2.56 g, 10 mmol) was alkylated with chloroacetonitrile (0.75 ml, 12 mmol), which was added at - 60° C forming a black solution. The reaction was quenched after warming up to ambient temperature. The oil obtained by the usual work up was chromatographed on silica gel and the product recrystallized from diisopropyl ether to give fine colorless crystals of 9 (1.26 g, 43 %).
M.p. 114 - 115° C (Found: C, 60.9; H, 8.7; N, 14.3. $C_{15}H_{25}N_3O_3$ requires C, 61.0; H, 8.5; N, 14.2 %); $[\alpha]_D$ + 30 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$) 1710, 1480, 1410, 1380, 1365, 1300, 1250, 1165, 1135 and 950 cm^{-1}; δ_H (300 MHz; DMSO-d_6) 0.92 (9 H, s), 1.46 (9 H, s), 2.94 (1H, br. s), 2.99 (3 H, s), 3.52 (1 H, br. s), 4.30 (1 H, d, *J* 6 Hz), 5.12 (1 H, s); m/z 238 (M^+ - 57, 14), 182 (26), 139 (8), 138 (100), 57 (99), 42 (21) and 41 (22).

Preparation of (2S,5S)-2-t-butyl-1-t-butyloxycarbonyl-5-(2-carbomethoxy-2-propenyl)-3-methyl--4-imidazolidinone (10).
Imidazolidinone (*S*)-BOC-1 (3.84 g, 15 mmol) was alkylated according to the general procedure. Methyl 2-bromomethylacrylate (3 ml) was added at - 90° C and the reaction quenched two minutes later. Two recrystallizations of the crude product from diisopropyl ether / hexane gave product 10 (2.43 g, 46 %) as colorless crystals.
M.p. 92 - 93° C (Found: C, 61.2; H, 8.85; N, 7.9. $C_{18}H_{30}N_2O_5$ requires C, 61.0; H, 8.5; N, 7.9 %); $[\alpha]_D$ - 1.7 (*c* 1.0 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1700, 1480, 1440, 1410, 1380, 1370, 1300, 1255, 1170 and 1130 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.98 (9 H, s), 1.45 (9 H, s), 3.00 (3 H, s), 3.11 (1 H, d, *J* 16 Hz, 1/2 ABq), 3.26 (1 H, dd, J_1 16Hz, J_2 7 Hz, 1/2 ABq), 3.76 (3 H, s), 4.23 (1 H, m), 4.96 (1 H, s), 5.33 (1 H, s), 6.17 (1 H, s); m/z 297 (M^+ - 57, 11), 197 (100), 165 (9), 96 (14), 57 (98), 41 (17) and 29 (12).

Preparation of (2R,5R)-2-t-butyl-1-t-butyloxycarbonyl-5-(3-chloropropyl)-3-methyl-4-imidazolidinone (11).
According to the general procedure heterocycle (*R*)-BOC-1 (2.56 g, 10 mmol) was alkylated with 1-bromo-3-chloropropane (1.2 ml, 12 mmol). The electrophile was added at - 90° C and the reaction quenched after warming up to ambient temperature. Recrystallization of the crude product from diisopropyl ether / hexane gave pure 11 (2.71 g, 81 %) as colorless crystals.
M.p. 95 - 96° C (Found: C, 57.5; H, 9.2; N, 8.4. $C_{16}H_{29}ClN_2O_3$ requires C, 57.7; H, 8.8; N, 8.4 %); $[\alpha]_D$ + 2.5 (*c* 1.0 in CH_2Cl_2); ν_{max} ($CHCl_3$) 2970, 1690, 1480, 1410, 1380, 1365, 1320, 1250, 1165 and 1130 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.97 (9 H, s), 1.50 (9 H, s), 1.36 - 1.58 (2 H, m), 2.01 (1 H, m), 2.59 (1 H, br. s), 3.02 (3 H, s), 3.50 (2 H, m), 4.09 (1 H, m), 4.99 (1 H, s); m/z 275 (M^+ - 57, 10), 221 (16), 219 (21), 177 (14), 175 (42), 57 (100), 42 (16) and 41 (17).

Preparation of (2R,5R)-2-t-butyl-1-t-butyloxycarbonyl-5-(4-chlorobutyl)-3-methyl-4-imidazolidinone (12).
Imidazolidinone (*R*)-BOC-1 (3.8 g, 14.8 mmol) was alkylated according to the general procedure. 1-Bromo-4-chlorobutane (2.1 ml, 18 mmol) was added at - 70° C and the reaction mixture quenched at ambient temperature. By chromatographic purification and recrystallization of the crude material pure product 12 (3.4 g, 66 %) was obtained.
M.p. 83 - 84° C (Found: C, 58.8; H, 8.9; N, 8.0. $C_{17}H_{31}ClN_2O_3$ requires C, 58.9; H, 9.0; N, 8.1 %); $[\alpha]_D$ + 5.7 (c 1.0 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1690, 1480, 1450, 1410, 1380, 1365, 1250, 1165 and 1130 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 0.97 (9 H, s), 1.49 (9 H, s), 0.70 - 2.55 (6 H, m), 3.00 (3 H, s), 3.47 (2 H, t, *J* 6.5 Hz,), 4.05 (1 H, m), 4.96 (1 H, s); m/z (no M^+) 298 (12), 235 (28), 233 (85), 191 (21), 89 (58), 57 (100), 42 (17) and 41 (19).

Preparation of α,α'-bis[(2S,5S)-2-t-butyl-1-t-butyloxycarbonyl-3-methyl-4-imidazolidinon-5-yl]-o-xylol (13).
Imidazolidinone (*S*)-BOC-1 (2.56 g, 10 mmol) was alkylated according to the general procedure. α,α'-Dibromo-o-xylol (1.6 g, 6 mmol) was added in THF (5 ml) at - 80° C. The reaction mixture was quenched at - 40° C. Two recrystallizations of the crude product from diisopropyl ether / hexane gave pure product 13 (2.39 g, 78 %) as colorless crystals.
M.p. 125 -128° C (Found: C, 66.5; H, 9.1; N, 8.5. $C_{34}H_{54}N_4O_6$ requires C, 66.4; H, 8.85; N, 9.1 %); $[\alpha]_D$ + 9 (c 1.0 in CH_2Cl_2); ν_{max} ($CHCl_3$) 2970, 1700, 1480, 1455, 1410, 1380, 1365, 1255, 1165 and 1125 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.95 (18 H, s), 1.40 (18 H, s), 2.81 (6H, s), 3.46 (2 H, dd, J_1 16 Hz, J_2 6 Hz), 3.57 (2 H, dd, J_1 16 Hz, J_2 3 Hz), 4.30 (2 H, m), 4.88 (2 H, s), 6.88 - 7.10 (4 H, m); m/z 557 (M^+ - 57, 6), 457 (20), 299 (10), 57 (49), 43 (100).

Preparation of (2S,5S,1'S)-2-t-butyl-1-t-butyloxycarbonyl-3-methyl-5-(1-methyl-benzyl)-4-imidazolidinone (14).
For the alkylation of imidazolidinone (*S*)-BOC-1 (3.8 g, 15 mmol) according to the general procedure racemic 1-phenyl-ethylbromide (5.2 ml, 37.5 mmol) was added at - 60° C. After quenching the reaction mixture at ambient temperature the usual work up gave the pure product 14 (3.16 g, 58 %) as colorless crystals (ds of crude product 85 %; by high field ^{1}H-NMR).
M.p. 82.5 - 83.5° C (Found: C, 69.7; H, 8.8; N, 7.7. $C_{21}H_{32}N_2O_3$ requires C, 70.0; H, 8.95; N, 7.8 %); $[\alpha]_D$ + 65 (c 1.1 in CH_2Cl_2); ν_{max} ($CHCl_3$) 2970, 1690, 1480, 1450, 1405, 1375, 1365, 1250, 1165 and 1125 cm^{-1}; δ_H (90 MHz; DMSO-d_6) 0.81 (9 H, s), 1.46 (9 H, s), 1.51 (3 H, d, *J* 5 Hz), 2.52 (3 H,s), 4.10 (1 H, s), 4.13 (1 H, br. s), 4.43 (1 H, s), 6.96 - 7.30 (5 H, m); m/z 303 (M^+ - 57, 23), 247 (65), 203 (22), 105 (20), 99 (25), 57 (100).

Preparation of (2S,5S,1'S)-2-t-butyl-1-t-butyloxycarbonyl-3-methyl-5-(nitroprop-2-yl)-4-imidazolidinone (15a).
Alkylation of heterocycle (*S*)-BOC-1 (3.8 g, 14.8 mmol) was effected according to the general procedure. E-1-Nitropropene (1.6 ml) was added at - 100° C. The reaction mixture was quenched 10 minutes later. Four recrystallizations from diisopropyl ether gave pure 15a (2.9 g, 57 %) as colorless crystals (ds of crude product 77 % by high field ^{1}H-NMR).
M.p. 109.5 - 111° C (Found: C, 55.7; H, 8.7; N, 12.1. $C_{16}H_{28}N_3O_5$ requires C, 56.0; H, 8.5; N, 12.2 %); $[\alpha]_D$ - 15 (c 1.1 in CH_2Cl_2); ν_{max} ($CHCl_3$) 2970, 1700, 1550, 1410, 1380, 1370, 1255, 1170 and 1130 cm^{-1}; δ_H (90 MHz; DMSO-d_6) 0.64 (3 H, d, *J* 7 Hz), 0.87 (9 H, s), 1.42 (9 H, s), 2.89 (3 H, s), 3.40 - 4.00 (1 H, br. m), 4.10 (1 H, m), 4.60 (1 H, dd, J_1 13 Hz, J_2 8.5 Hz, 1/2 ABq), 4.98 (1 H, dd, J_1 13 Hz, J_2 5 Hz), 5.03 (1 H, s); m/z 286 (M^+ - 57, 11), 239 (18), 187 (8), 186 (92), 125 (7), 57 (100), 42 (16) and 41 (19).

General procedure for the alkylation of the carbobenzyloxy derivative Z-1.
All operations were performed in well dried glassware under an argon atmosphere with complete exclusion of moisture.
To a stirred solution of imidazolidinone Z-1 (4.36 g, 15.0 mmol) in THF (20 ml) a solution of LDA in THF / hexane (15.5 ml, 15.5 mmol) was added dropwise at - 50° C. When the enolate formation is complete a green color develops (presumed to be the dianion derivative) and LDA addition should be stopped. After stirring for 30 minutes the electrophile was added in one portion. The reaction was monitored by t.l.c. (with fluorescence indicator) during slow warming up and quenched after completion by the addition of saturated NH_4Cl (3 ml). THF was evaporated and the residue extracted with ether. After washing with 1 N HCl, saturated $NaHCO_3$ and water the solution was dried ($MgSO_4$) and evaporated to dryness. Chromatography on silica gel and recrystallization from diisopropyl ether / hexane gave pure products.

Preparation of (2S,5S)-1-benzyloxycarbonyl-2-t-butyl-3-methyl-5-(prop-2-yl)-4-imidazolidinone (16).
The enolate of imidazolidinone (*S*)-Z-1 (2.90 g, 10 mmol) was produced according to the general procedure. After the addition of 2-iodopropane (2 ml, 20 mmol) the mixture was cooled again to - 70° C and then treated with DMPU[27] (5 ml, 41.5 mmol). The solution was allowed to warm slowly to room temperature and stirred for an additional 4 h. After quenching the usual work up gave a slightly yellow solid which was recrystallized twice from diisopropyl ether / hexane to give colorless crystals of product 16 (1.97 g, 59 %).
M.p. 108 - 109 ° C (Found: C, 68.5; H, 8.5; N, 8.3. $C_{19}H_{28}N_2O_3$ requires C, 68.65; H, 8.5; N, 8.4 %); $[\alpha]_D$ - 34 (c 1.0 in CH_2Cl_2); ν_{max} ($CHCl_3$) 2960, 1700, 1450, 1410, 1390, 1360, 1340, 1250 and 1115 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.64 (3 H, br. s), 0.94 (9 H, s), 1.18 (3 H, d, *J* 6 Hz), 2.65 - 3.25 (1 H br. s), 2.97 (3 H, s), 3.99 (1 H, br. s), 5.05 (1 H, br. s), 5.12 (1 H, d, *J* 12 Hz, 1/2 ABq), 5.19 (1 H, d, *J* 12 Hz, 1/2 ABq), 7.36 (5 H, s); m/z 275 (M^+ - 57, 18), 231 (9), 91 (100), 65 (5), 57 (6), 42 (6) and 41 (5).

Preparation of (2S,5R)-1-benzyloxycarbonyl-2-t-butyl-3-methyl-5-trimethylsilylmethyl-4-imidazolidinone (17).
Following the general procedure imidazolinone (*S*)-Z-1 (2.7 g, 9.3 mmol) was alkylated with iodomethyltrimethylsilane (1.6 ml, 11.1 mmol). After warming up to ambient temperature the solution was stirred for additional 15 h at room temperature. The usual work up gave a pale yellow solid which was chromatographed on silica gel and recrystallized from diisopropyl ether / hexane to give product 17 (1.8 g, 51 %) as colorless crystals.
M.p. 91 - 92° C (Found: C, 63.5; H, 8.7; N, 7.4. $C_{20}H_{32}N_2O_3Si$ requires C, 63.8; H, 8.6; N, 7.4 %); $[\alpha]_D$ - 1.2 (c 1.0 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1700, 1450, 1415, 1395, 1355, 1300, 1250, 1125 and 1035 cm^{-1}; δ_H (300 MHz; $CDCl_3$) - 0.04 (9 H, s), 0.95 (9 H, s), 1.50 (2 H, d, *J* 5 Hz), 2.99 (3 H, s), 4.27 (1 H, m), 5.01 (1 H, s), 5.06 (1 H, d, *J* 12 Hz, 1/2 ABq), 5.21 (1 H, d, *J* 12 Hz, 1/2 ABq), 7.38 (5 H, m); m/z 319 (M^+ - 57, 21), 275 (9), 91 (100), 73 (8), 68 (6) and 57 (6).

Preparation of (2S,5S)-1-benzoyloxycarbonyl-2-t-butyl-5-carboethoxymethyl-3-methyl-4-imidazolidinone (**18**).
The Alkylation of heterocycle (*S*)-Z-**1** (4.4 g, 17.2 mmol) was carried out according to the general procedure. Ethyl bromoacetate (2.1 ml, 18.9 mmol) was added at - 70° C and the reaction mixture quenched at - 40° C. The usual work up yielded crude product **18** (5.15 g, 91 %) which was recrystallized twice from diisopropyl ether / hexane to give colorless crystals (2.3 g, 41 %).
M.p. 97 - 98° C (Found: C, 63.8; H, 7.4; N, 7.45. $C_{20}H_{28}N_2O_5$ requires C, 63.8; H, 7.5; N, 7.4 %); $[\alpha]_D$ - 15 (c 0.9 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1700, 1480, 1450, 1415, 1395, 1355, 1250, 1175 and 1125 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 0.96 (9 H, s), 1.16 (3 H, t, *J* 7 Hz), 2.94 (1 H, m), 3.02 (3 H, s), 3.10 - 3.70 (1 H, br. m), 3.98 (2 H, q, *J* 7 Hz), 4.23 (1 H, m), 4.94 (1 H, d, *J* 12 Hz, 1/2 ABq), 5.00 (1 H, s), 5.17 (1 H, d, *J* 12 Hz, 1/2 ABq), 7.32 (5 H, m); m/z 320 (4), 319 (M^+ - 57, 24), 275 (24), 91 (100), 65 (4), 57 (5) and 42 (6).

Preparation of (2S,5S)-1-benzyloxycarbonyl-2-t-butyl-5-carbomethoxymethyl-3-methyl-4-imidazolidinone (**19**).
In a similar procedure to that described for imidazolidinone **18** carbomethoxymethyl derivative **19** could be prepared in 44 % yield with methyl bromoacetate as electrophile.
M.p. 94 - 96° C (Found: C, 62.7; H, 7.4; N, 7.7. $C_{19}H_{26}N_2O_5$ requires C, 63.0; H, 7.2; N, 7.7 %); $[\alpha]_D$ -17 (c 1.0 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1735, 1700, 1440, 1415, 1395, 1365, 1360, 1250, 1180 and 1125 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.96 (9 H, s), 2.90 (1 H, d, *J* 16 Hz, 1/2 ABq), 3.04 (3 H, s), 3.40 (1 H, br. m, 1/2 ABq), 3.55 (3 H, br. s), 4.30 (1 H, m), 5.01 (1 H, d, *J* 12 Hz, 1/2 ABq), 5.05 (1 H, br. s), 5.20 (1 H, d, *J* 12 Hz, 1/2 ABq), 7.35 (5 H, s); m/z 305 (M^+ - 57, 17), 261 (15), 92 (8), 91 (100), 65 (6), 57 (6), 42 (10) and 41 (6).

Preparation of (2S,5R)-5-(O-benzoyl-1-methyl-1-hydroxyethyl)-2-t-butyl-3-methyl-4-imidazolidinone (**20**).
The general techniques used for the alkylation of *t*-butyloxycarbonyl derivative BOC-**1** were also applied in this case.
Thus a solution of (*R*)-1-benzoyl-2-*t*-butyl-3-methyl-4-imidazolidinone[1b] (2.6 g, 10 mmol) in THF (40 ml) was added dropwise to a stirred solution of LDA in THF / hexane (10.5 ml, 10.5 mmol). The solution was cooled to - 100° C, acetone was added (1.5 ml, 20 mmol) and after one min. a solution of acetic acid (3.5 ml, 61 mmol) in THF (6.5 ml) was added. After warming, the THF was evaporated, the residue stirred for 10 h in acetic acid (10 ml). The solution was concentrated, the residue dissolved in Et_2O washed with 1 N NaOH, dried ($MgSO_4$) and concentrated to a yellow oil. Chromatography and recrystallization of the product gave heterocycle **20** (1.97 g, 62 %) as colorless crystals.
M.p. 74 -75° C; $[\alpha]_D$ + 19 (c 1.0 in CH_2Cl_2); the analytical data were in accordance with those described in the literature[28] for the racemic product.

Preparation of (2S,5R)-2-t-butyl-1-t-butyloxycarbonyl-5-ethyl-3-methyl-5-(2-propenyl)-4-imidazolidinone (**21**).
Alkylation product **6** (2.1 g, 7.1 mmol) was alkylated a second time according to the general procedure for the alkylation of *t*-butyloxycarbonyl derivative BOC-**1**. Ethyliodide (1.1 ml, 13.6 mmol) was added at - 70° C and then immediately DMPU (5 ml). The reaction was quenched after warming up to room temperature. The usual work up gave a yellow oil which was chromatographed on silica gel to give the 5-disubstituted imidazolidinone **21** (0.83 g, 36 %) as an amorphous solid.
M.p. 77 - 78° C (Found: C, 66.4; H, 10.2; N, 8.4. $C_{18}H_{32}N_2O_3$ requires C, 66.6; H, 9.9; N, 8.6 %); $[\alpha]_D$ - 59 (c 1.0 in CH_2Cl_2); ν_{max} ($CHCl_3$) 2970, 1690, 1480, 1455, 1365, 1355, 1310, 1250 and 1165 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 0.57 (3 H, t, *J* 7 Hz), 1.02 (9 H, s), 1.50 (9 H, s), 1.63 - 2.05 (1 H, m), 2.10 - 2.50 (1 H, m), 2.64 (2 H, d, *J* 7 Hz), 3.00 (3H, s), 5.03 (2 H, m), 5.13 (1 H, br. s), 5.72 - 6.33 (1 H, m); m/z 267 (M^+ - 57,13), 211 (100), 167 (40), 98 (6), 81 (8), 57 (95), 42 (18) and 41 (23).

Preparation of (2S,5S)-1-benzoyl-2-t-butyl-5-(2-hydroxyethyl)-3-methyl-4-imidazolidinone (**22**).
The general techniques used for the alkylation of *t*-butyloxycarbonyl derivative BOC-**1** were also applied in this case.
In detail a solution of (*S*)-Bz-**1** (1.90 g, 7.3 mmol) in THF (14 ml) was added at - 50° C to a stirred LDA/THF/hexane solution (14.6 ml, 7.3 mmol). After the addition of ethylene oxide (1 ml, 20 mmol) BF_3 - etherate (1.0 ml, 8 mmol, carefully distilled over CaH_2) was added dropwise and the solution stirred for an additional hour. The usual work up (see general procedure for the alkylation of BOC-**1**; chromatography on silica gel) gave colorless crystals of product **22** (1.24 g, 56 %).
M.p. 204 - 205° C (Found: C, 67.1; H, 7.9; N, 9.2. $C_{17}H_{24}N_2O_3$ requires C, 67.1; H, 7.95; N, 9.2 %); $[\alpha]_D$ - 27 (c 1.0 in CH_2Cl_2); ν_{max} ($CHCl_3$) 1695, 1640, 1480, 1450, 1410, 1400, 1375, 1260, 1175, 1155, 1110, 1075 and 1025 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 1.09 (9 H,s), 1.29 - 2.17 (2 H, m), 2.75 (1 H, s), 3.08 (3 H, s), 3.42 (2 H, t, *J* 6 Hz), 4.42 (1 H, m), 5.62 (1 H, s), 7.26 - 7.73 (5 H, m); m/z 248 (11), 247 (73), 125 (6), 106 (8), 105 (100), 77 (37), 57 (5), 51 (6), 42 (13) and 29 (5).

General procedure for the hydrolysis of t-butyloxycarbonyl- and benzyloxycarbonyl- protected 4-imidazolidinones.
In a typical procedure a solution of a t-butyloxycarbonyl protected imidazolidinone (4 mmol) in CH_2Cl_2 (10 ml) was treated with trifluoroacetic acid (3 ml, 39.2 mmol) and stirred overnight under an argon atmosphere. The solvent was then evaporated under reduced pressure.
Benzyloxycarbonyl protected imidazolidinones (4 mmol) were deprotected by catalytic hydrogenation in methanol / acetic acid 4 : 1 (20 ml) in the presence of 10 % Pd/C (0.1 g) at normal pressure overnight. The catalyst was subsequently filtered off and the solvent evaporated at reduced pressure.
The residue was transferred with a little acetic acid (max. 5 ml) and with 0.75 N HCl (40 ml) (only doubly de-ionised water was used in this procedure) into an Erlenmeyer flask (Pyrex glass, Sovirel stopper). After the addition of cation exchange resin (17 ml wet DOWEX 50 W x 8, 20 - 50 mesh p.a., activated with 10 % HCl) the mixture was kept in the stoppered flask at 100° C (!) for 18 to 92 h. Hydrolysis was followed by t.l.c.: Small samples of the resin were washed in a pipette to neutrality and eluted with a little 10 % NH_3. t.l.c.'s were developed with EtOH / H_2O / NH_3 conc. 7:2:1 and sprayed with 3 % ethanolic ninhydrin. When the upper spot of amino acid methylamide had almost disappeared the whole resin was applied to a column, the solution concentrated, the residue taken

up in a little water and also applied to the ion exchanger. After washing with EtOH (200 ml) and water to neutrality (ca. 100 ml) the resin was eluted with 10 % NH_3 until the fractions were free of amino acid (tested by spotting on a silica gel plate, drying and spraying with ninhydrin). Water was evaporated under reduced pressure, the residue dissolved twice in a little water and concentrated again in each case. Then the solid was stirred twice in a little refluxing acetone which was decanted after cooling each time. The enantiomeric purity was checked by chiral t.l.c.[58]. Finally the amino acids were dried at high vacuum over P_2O_5.

Preparation of (R)-p-bromophenylalanine (23)
Alkylation product **3** (1.82 g, 4.28 mmol) was deprotected and then hydrolysed for 44 h as described in the general procedure to give amino acid **23** (0.732 g, 61 %) as a white amorphous solid, m.p. 250 - 260° C (d) (lit.[59], 256° C); $[\alpha]_D$ + 1.4 (c 0.98 in 1 N HCl) (lit.[59] + 1.0, c 1.0 in 1 N HCl); ν_{max} (KBr) 1740, 1665, 1490, 1405, 1225, 1210, 1195, 1135, 1110, 1075 and 1010 cm^{-1}; δ_H (300 MHz, 1 N DCl / D_2O) 2.98 (2 H, m), 4.10 (1 H, t, *J* 7 Hz), 6.94 (2 H, d, *J* 8 Hz, 1/2 ABq), 7.27 (2 H, d, *J* 8 Hz, 1/2 ABq).

Preparation of (R)-2-amino-3-pentafluorophenyl-propionic acid (24).
The pentafluoro derivative **4** (1.3 g, 2.98 mmol) was deprotected and then hydrolysed for 18 h following the general procedure to give amino acid **24** (0.21 g, 25 %) as colorless amorphous crystals. For analytical purposes amino acid **24** (0.2 g, 6.71 mmol) was recrystallized by dissolving in 2 N HCl (0.5 ml) and neutralizing the solution with 5 % NH_3. The very fine crystals were filtered off and dried over P_2O_5 to give pure amino acid **24** (0.12 g, 14 %).
M.p. 236 - 238° C (d) (lit.[60], 261° C); $[\alpha]_D$ - 21 (c 0.65 in H_2O) (lit.[60], + 22.4, c 1.0 in H_2O for the (*S*)-enantiomer); ν_{max} (KBr) 1625, 1525, 1505, 1415, 1355, 1330, 1300, 1125, 1065, 1000, 970 and 930 cm^{-1}; δ_H (300 MHz, 1 N DCl / D_2O) 3.10 (2 H, m), 4.06 (1 H, t, *J* 7 Hz); δ_F (280 MHz, 1 N DCl / D_2O) - 142.6 (2 F, m), - 154.91 (1 F, t, *J* 21 Hz), - 162.53 (2 F, m).

Preparation of (2S,3S)-2-amino-3-phenylbutyric acid (25).
Imidazolidinone **14** (1.1 g, 3 mmol) was deprotected and then hydrolysed for 92 h according to the general procedure to give amino acid **25** (0.293 g, 54 %) as a white amorphous solid.
For the analysis amino acid **25** (0.107 g, 0.6 mmol) was dissolved in 1 N HCl (1 ml) and crystallization was effected by raising the pH of the solution to 6 by the addition of 5 % NH_3 (0.4 ml).
M.p. 195 - 200° C (d); $[\alpha]_D$ + 13 (c 0.78 in 5 N HCl); ν_{max} (KBr) 1605, 1580, 1545, 1495, 1450, 1400, 1360, 1340, 1320, 805, 765 and 700 cm^{-1}; δ_H (300 MHz, 1 N DCl / D_2O) 1.10 (3 H, d, *J* 7 Hz), 3.20 (1 H, quintett, *J* 7 Hz), 3.96 (1 H, d, *J* 6 Hz), 7.05 (5 H, m).
To determine the configuration of the β-centre amino acid **25** (70 mg, 0.39 mmol) and ninhydrin (69.5 mg, 0.39 mmol) were dissolved in water (10 ml) and benzene was added (6 ml). The mixture was warmed to 80° C and shaked for 10 minutes. The benzene phase was separated, dried ($MgSO_4$) and used directly for optical rotation measurement : α_D + 28 (according to lit.[61] (*S*)-2-phenylpropanal has a specific rotation $[\alpha]_D$ of + 314.6 with c 0.45 in benzene).

Preparation of (R)-2-amino-4-phenylbutyric acid (26).
Alkylation product **5** (2.0 g, 5.55 mmol) was deprotected and hydrolysed then for 50 h according to the general procedure to give (*R*)-2-amino-4-phenylbutyric acid (0.60 g, 60 %).
M.p. 265 - 267° C (d); $[\alpha]_D$ - 46 (c 1.0 in 1 N HCl) (lit.[62] - 48.8, c 1.0 in 1 N HCl); ν_{max} (KBr) 1580, 1620, 1450, 1410, 1150, 1120, 750, 700 and 490 cm^{-1}; δ_H (300 MHz, 1 N DCl / D_2O) 2.00 (2 H, m), 2.55 (2 H, m), 3.86 (1 H, t, *J* 6 Hz), 7.10 (5 H, m).

Preparation of (S,S)-α,α'-bis(glycin-2-yl)-o-xylol (27).
Bis-heterocycle **13** (1.31 g, 2.13 mmol) was deprotected and then hydrolysed for 48 h according to the general procedure but with double amount of ion exchange resin to afford 0.459 g of colorless crystals. This were dissolved in 2 N HCl (2.3 ml) and crystallization was effected by addition of 5 % NH_3 (1.4 ml, solution reached pH 6). The crystals were filtered off and dried over P_2O_5 to afford pure amino acid **27** (0.325 g, 61 %).
M.p. 295 - 300° C (d) (Found: C, 57.2; H, 6.8; N, 10.4. $C_{12}H_{16}N_2O_4$ requires C, 57.1; H, 6.4; N, 11.1 %); $[\alpha]_D$ + 21 (c 1.15, 5 N HCl); ν_{max} (KBr) 1625, 1495, 1410, 1355, 1315, 1210, 1165, 960, 850 and 780 cm^{-1}; δ_H (300 MHz, 1 N DCl / D_2O) 2.96 (2 H,m), 3.12 (2 H,m), 4.02 (2 H, t, *J* 7 Hz), 7.08 (4 H, s).

Cyclization of imidazolidinone **11** *and hydrolysis to (R)-Proline* (28).
Chloride **11** (1.29 g, 3.87 mmol) was dissolved in CH_2Cl_2 (10 ml) and stirred with trifluoroacetic acid (2 ml) for 12 h at ambient temperature. The solvent was evaporated, the residue dissolved in ether and washed with saturated $NaHCO_3$. After evaporation of the ether, the semi-crystalline residue was stirred for 48 h in methanol (10 ml) at room temperature. The solvent was removed to yield an amorphous solid (0.6 g) which was hydrolysed for 72 h in HCl/DOWEX 50 mixture following the general procedure to afford (*R*)-proline (0.25 g, 70 %) m.p. 200 - 210° C (lit.[63], 215 - 220 (d)); $[\alpha]_D$ + 79 (c 1.0 in H_2O) (lit.[55], + 84.8, c 5.0 in H_2O).

Cyclization of imidazolidinone **12** *and hydrolysis to (R)-pipecolic acid* (29).
A Solution of heterocycle **12** (1.4 g, 4.0 mmol) in CH_2Cl_2 (12 ml) was treated with trifluoroacetic acid (3 ml) and stirred for 5 h at 30° C. After concen- tration CH_2Cl_2 (30 ml) was added and the solution washed with saturated $NaHCO_3$. The solvent was evaporated, the residue dissolved in methanol (10 ml). After stirring for 6 h at ambient temperature triethylamine (0.2 ml, 1.43 mmol) was added and the solution stirred for 24 h at 60° C, then con- centrated, the residue dissoved in ether (150 ml) and the solution washed twice with saturated $NaHCO_3$. After drying ($MgSO_4$) the solvent was removed to afford 1.3 g crude product which was chromato- graphed on silica gel to yield 0.34 g (41 %) colorless crystals.
The product was hydrolyzed for 70 h in the DOWEX 50/HCl mixture according to the general procedure to give (*R*)-pipecolic acid (121 mg, 22%) as slightly yellow crystals.
M.p. 263 - 267° C (lit.[64], 270° C); $[\alpha]_D$ + 24.4 (c 0.76 in H_2O) (lit.[65], - 25.4 for the other enantiomer)

Hydrolysis of imidazolidinone **16** *to (S)-valine* (**30**).
Imidazolidinone **16** (1.3 g, 3.92 mmol) was deprotected and then hydrolysed for 48 h according to the general procedure to give (*S*)-valine (0.19 g, 42 %), m.p. 300-305° C (d) (lit.[64] 315° C); $[\alpha]_D$ + 27 (c 1.0 in 5 N HCl) (lit.[55] $[\alpha]_D$ + 27.0, c 5.0 in 5 N HCl).

Preparation of (R)-2-amino-3-trimethylsilylpropionic acid (**31**).
Imidazolidinone **17** (1.0 g, 5.65 mmol) was deprotected and subsequently hydrolyzed for 47 h following the general procedure to give silyl amino acid **31** (0.172 g, 40 %).
M.p. 256 - 260° C (Found: C, 44.6; H, 9.7; N, 8.7. $C_6H_{15}NO_2Si$ requires C, 44.7; H, 9.4; N, 8.7 %); $[\alpha]_D$ + 31 (c 0.5) in 4 N HCl); ν_{max} (KBr) 1620, 1525, 1495, 1430, 1350, 1320, 1250, 1185, 840 and 770 cm^{-1}; δ_H (300 MHz, 1 N DCl / D_2O) - 0.17 (9 H, s), 0.96 (2 H, m), 3.85 (1 H, m); data for *rac.*-**31** see ref. 66.

Hydrolysis of imidazolidinone **20** to *(R)-β-hydroxy-valine* (**32**).
Alkylation product **20** (1.34 g, 4.20 mmol) was directly hydrolyzed (deprotection not necessary) according the the general procedure to afford (*R*)-β-hydroxy-valine (0.57 g, 30 %) as a white amorphous solid.
M.p. 180 - 185° C (d) (lit.[66], 200 - 201° C); $[\alpha]_D$ -11 (c 0.74 in 5 N HCl) (lit.[66], -11.2, c 2 in 5 N HCl).

G) REFERENCES

[1a] Part of the Ph. D. thesis of R. F., ETH Zürich 1988.

[1b] For a preliminary account of part of this work see: R. Fitzi, D. Seebach, Angew. Chem. 1986, 98, 363; Berichtigung: ibid 1986, 98, 842; Angew. Chem. Int Ed. 1986, 25, 345; Erratum: ibid 1986, 25, 766.

[2] D. Seebach, R. Naef, Helv. Chim. Acta 1981, 64, 2704.

[3] Proline: M. Boes, R. Naef, W. B. Schweizer, J. Am. Chem. Soc. 1983, 105, 5390.

[4] Neutral open chain amino acids:

[a] R. Naef, D. Seebach, Helv. Chim. Acta 1985, 68, 135.

[b] D. Seebach, J. D. Aebi, R. Naef, Th. Weber, Helv. Chim. Acta 1985, 68, 144.

[5] Serine and threonine: D. Seebach, J. D. Aebi, Tetrahedron Lett. 1983, 24, 3311; D. Seebach, J. D. Aebi, Tetrahedron Lett. 1984, 25, 2545; D. Seebach, J. D. Aebi, M. Gander-Coquoz, R. Naef, Helv. Chim. Acta 1987, 70, 1194.

[6] Hydroxyproline: Th. Weber, D. Seebach, Helv. Chim. Acta 1985, 68, 155.

[7] Cysteine and methionine:

[a] D. Seebach, Th. Weber, Tetrahedron Lett. 1983, 24, 3315;

[b] D. Seebach, Th. Weber, Helv. Chim. Acta 1984, 67, 1650;

[c] Th. Weber, R. Aeschimann, Th. Maetzke, D. Seebach, Helv. Chim. Acta 1986, 69, 1365.

[8] Acidic amino acids: J. D. Aebi, D. Seebach, Helv. Chim. Acta 1985, 68, 1507.

[9] Basic amino acids: M. Gander-Coquez, D. Seebach, Helv. Chim. Acta 1988, 71, in print.

[10] Addition of amino acid enolates to nitroolefins: G. Calderari, D. Seebach, Helv. Chim. Acta 1985, 68, 1592, and ref. 37.

[11] Oxazolidinone enolates: D. Seebach, A. Fadel, Helv. Chim. Acta 1985, 68, 1243.- *cf.* also: S. Karady, J. S. Amato, L. M. Weinstock, Tetrahedron Lett. 1984, 39, 4337; A. Fadel, J. Salaün, Tetrahedron Lett. 1987, 28, 2243.

[12] Review article: D. Seebach, R. Imwinkelried, Th. Weber, "Modern Synthetic Methods 1986", Vol 4, Ed. R. Scheffold, Springer Verlag Berlin, 1986.

[13] D. Seebach, D. D. Miller, S. Müller, Th. Weber, Helv. Chim. Acta 1985, 68, 949.

[14] The corresponding glycine-derived oxazolidinones (*cf.* ref. 11) could neither be obtained by degradation nor by the method described here: R. Fitzi, S. Müller, Ph. D. theses hitherto unpublished results, ETH Zürich 1985 - 88.

[15] J. Jaques, A. Collet, S. H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley and Sons, Inc., New York 1981, p. 378.

[16] A Solution of (*R*)-**1** in anhydrous methanol containing ca. 3 % HCl did not loose more than 1 % of its optical activity in 2 h at room temperature.

[17] Upon vacuum distillation (135° C / 0.05 torr) partial ring opening to the precursor *Schiff* base occurs. Therefore we used the crude product of cyclisation for the resolution.

[18] R. Polt hitherto unpublished results, ETH Zürich 1987.

[19] Both enantiomers are equally available, *ca.* 80 SFR/mol from commercial laboratory suppliers.

[20] A practical laboratory scale ranges from 0.1 to 1 mol. Large-scale resolutions have been carried out by Dr. Lotter of DEGUSSA AG (D - Hanau).

[21] Reviews: G. Höfle, W. Steglich, H. Vorbrüggen, Angew. Chem. 1978, 90, 602; Angew. Chem. Int. Ed. 1978, 17, 569; A. Hassner, R. L. Krepski, V. Alexanian, Tetrahedron 1978, 34, 2069; E. F. Scriven, Chem. Soc. Rev. 1983, 12, 129.

[22] Indeed, *ca.* 80 % ee samples of Bz-BMI as obtained from the non-purified first crop mandelate salt gave better than 98 % ee samples by two crystallizations from acetone (see ref. 1b).

[23] The diacetonide of 2-keto-L-gulonic acid is an intermediate of an industrial ascorbic acid synthesis and is available at *ca.* 150 SFR/mol from commercial laboratory chemical suppliers.

[24] G. Rumpf masters' thesis (Diplomarbeit), ETH Zürich 1987.

[25]If only one enantiomer is desired there is probably the possibility of recycling the other one by racemization. As mentioned in footnote 16 this is not readily achieved by treatment with non-aqueous acid. Without having done a systematic investigation, we assume that heating of the free bases **1** and **2** and subsequent treatment with anhydrous acid will cause racemization (see footnote 17 and procedures for cyclization of the *Schiff* bases in the experimental section).

[26]If Z-BMI is added to an excess of LDA, olive green solutions are formed. We assume that this color arrises from benzylic deprotonation; the yields of products are much lower than with inverse addition.

[27]T. Mukhopadhyay, D. Seebach, Helv. Chim. Acta 1982, 65, 385.

[28]D. Seebach, E. Juaristi, D. D. Miller, Ch. Schickli, Th. Weber, Helv. Chim. Acta 1987, 70, 237; and Ch. Schickli masters' thesis, ETH Zürich 1986.

[29]No benzoyl migration from N to O was observed in this case (*cf.* **20** and ref 28). Reactions of oxirane with other BMI derivatives were not carried out. Due to the more facile cleavage the Z-BMI enolate would be preferable.

[30]Other epoxides such as the one derived from *trans*-butene and propene gave poorer yields of ring opening products with Bz-BMI enolate (10 and 30 % respectively).

[31]Review: D. Seebach, "The Robert A. Welch Foundation Conference on Chemical Research. XXVII. Stereospecificity in Chemistry and Biochemistry", Houston, Texas Nov. 7-9, 1983, published in the proceedings of the above conference, Welch Foundation, Houston 1984.

[32]Indeed, Schöllkopfs glycine enolate reagent gives a monoalkylation product with the same electrophile, and it is known that lithiated bislactim ethers are present mainly as monomers under the reaction conditions:
D. Seebach, J. Hansen, T. Laube, W. B. Schweizer, J. D. Dunitz, J. Chem. Soc., Chem. Comm. 1984, 853;
W. Bauer, D. Seebach, Helv. Chem. Acta 1984, 67, 1972;
W. Bauer, T. Laube, D. Seebach, Chem. Ber. 1985, 118, 764;
U. Schöllkopf, R. Hinrichs, R. Lonsky, Angew. Chem. 1987, 99, 137.

[33]With dibromides we got more of the 2:1 adduct (two enolates ot one dibromide) than the desired 1:1 product (according to t.l.c. analysis).

[34]Allylic halides with terminal double bonds are readily available. In principle allylations of BMI enolates may preferably be done by this very facile alkylation with subsequent hydrogenation.

[35]This effect was also observed with enolates of chiral oxazolines: A. I. Meyers, K. Kamata, J. Am. Chem. Soc. 1976, 98, 2290.

[36]Imidazolidinone **15a** was converted to the bicyclic product **15b** by: (i) Zn / HOAc (ii) benzyloxycarbonylchloride / CH_2Cl_2 / 2 N NaOH (iii) trifluoroacetic acid / CH_2Cl_2 (iv) phenyloxycarbonylchloride / NEt_3 / DMAP / acetonitrile (v) H_2 / Pd-C / ethanol / 20 h room temperature.

[37]G. Calderari, Diss. No 7841, ETH Zürich 1985.

[38]Another *Michael* acceptor to which the Bz-BMI enolate added in high yield to give two products (1:1 epimeric at the lactone) is methylene-valerolactone.

[39]We did not notice oxidative dimerization of the BOC-BMI enolate by the nitroolefin. Iodine, however, dimerizes Bz-BMI enolate to a statistical mixture (1:2:1) of the diastereoisomers; derivatives of 2,3-diamino-succinic acid {M. Rouilly, masters' thesis (Diplomarbeit), ETH Zürich 1986}.

[40]The BOC-BMI derivatives shown in ***Scheme 6*** can even be directly hydrolyzed to free amino acids under the conditions described here but we found the yields were not as good as with the two-step procedure.

[41]Compare: J. Bajgrowicz, A. El Achquar, M.-L. Roumestant, Ch. Pigière, Ph. Viallefont, Heterocycles 1986, 24, 2165;
U. Schöllkopf, R. Hinrichs, R. Lonsky, Angew. Chem. 1987, 99, 137.

[42]Under the usual acidic hydrolysis conditions pivalaldehyde derivatives (black droplets) separate on top of the aqueous layer in the case of all types of imidazolidinones (BOC-, Z-, Bz-BMI and BBI) . We have never tried to recover the aldehyde as such.

[43]We noticed that addition of some toluene to the hydrolysis mixture in the presence of ion exchange resin as described here prevented darkening of the resin, probably due to removal of pivalaldehyde derived products into the organic phase.

[44]Hydrolysis of acetamide and acetanilide with ion exchange resin: P. D. Bolton, T. Henshall, J. Chem. Soc. 1962, 3369.

[45]Enantioselective hydrolysis of esters and amides of amino acids catalysed by polymer-bound chiral complexes of Cu(II) and Ni(II): I. A. Yamskov, B. B. Berezin, V. A. Danankov, Katal. Sonderzh. Nanesennye Kompleksy 1980, 51; CA 95:43612e.

[46]G. C. Barrett, "Chemistry and Biochemistry of Amino Acids", Chapman and Hall, London, New York 1985, p. 401.

[47]See ref. 15. on page 414 in ref.[46].

[48]Less than 5 % of the organic material is in the aqeuous phase under these conditions.

[49]The methylamine is removed with the ammonia upon concentration of the eluent.

[50]Compare: U. Schöllkopf, W. Kühnle, E. Egert, M. Dyrbusch, Angew. Chem. 1987, 99, 480.

[51a]Some electrophilic chiral glycine derivatives are: Methyl iminoacetates, R. Kober, K. Papadopoulos, W. Miltz, D, Enders, W. Steglich, H. Reuter, H. Puff, Tetrahedron 1985, 41, 1693; Chlorobislactim ether: U. Schöllkopf, S. Güttner, R. Anderskewitz, E. Egert, M. Dyrbusch, Angew. Chem. 1987, 99, 717; A bromomorpholine: P. J. Sinclair, D. Zhai, J. Reibenspies, R. M. Williams, J. Am. Chem Soc. 1986, 108, 1103

[b]The BOC- and the Bz-BMI derivatives 1 can be diastereoselectively brominated to give highly reactive electrophilic glycine derivatives: J. Zimmermann, D. Seebach, Helv. Chim. Acta 1987, 70, 1104; Ch. Schickli hitherto unpublished results and part of the projected Ph. D. thesis, ETH Zürich.

[52]T. Oguri, N. Kawai, T. Shioiri, S.-I. Yamada, Chem. Pharm. Bull. 1978, 26, 803.
T. Nakatsuka, T. Miwa, T. Mukaiyama, Chemistry Lett. 1981, 279.
U. Schöllkopf, U. Groth, C. Deng, Angew. Chem. 1981, 93, 793.
Y. N. Belokon, A. G. Bulychev, S. V. Vitt, Y. T. Struchkov, A. S. Batsanov, T. V. Timofeeva, V. A.Tsyryapkin, M. G. Ryzhov, L. A. Lysova, V. I. Bakhmutov, V. M. Belikov, J. Am. Chem. Soc. 1985, 107, 4252.
S. Ikegami, T. Hayama, T. Katsuki, M. Yamaguchi, Tetrahedron Lett. 1986, 27, 3403.
D. A. Evans, A. E. Weber, J. Am. Chem. Soc. 1986, 108, 6757.

[53]W. C. Still, M. Kahn, A. Mitra, J. Org. Chem. 1978, 43, 2923.

[54]S. Kushner, R. I. Cassell, J. Morton, J. H. Williams, J. Org. Chem. 1951, 16, 1283.

[55]Value taken from the Fluka Katalog 15, 1986/87, Fluka AG (CH - Buchs).

[56]J. C. Sheehan, D.-D. H. Yang, J. Am. Chem. Soc. 1958, 80, 1154.

[57]L. I. Smith, Sc McKenzie, Jr., J. Org. Chem. 1950, 15, 74.

[58]T.l.c. on "CHIRALPLATE" (MACHERY-NAGEL, D - Düren), lit., K. Günther, M. Schickedanz, Naturwissenschaften 1985, 72, 149.

[59]H. Faulstich, H. O. Smith, S. Zobeley, Liebigs Ann. Chem. 1973, 765.

[60]J. L. Fauchère, R. Schwyzer, Helv. Chim. Acta 1971, 54, 2078.

[61]D. Enders, W. Mies, J. Chem. Soc., Chem. Comm. 1984, 1221.

[62]H. Schutt, G. Schmidt-Kastner, A. Arens, M. Preiss, Biotechnol. Bioing. 1985, 27, 420.

[63]"Handbook of Chemistry and Physics", 56th edition, CRC - press.

[64]"Merck Index", 10th edition, Merck & Co., Rahway 1983.

[65]R. I. Morrison, Biochem. J. 1953, 53, 474.

[66]T. H. Porter, W. Shive, J. Med. Chem. 1968, 11, 402

[67]U. Schöllkopf, J. Nozulak, U. Groth, Synthesis 1982, 868.