17. α-Alkylation of Amino Acids without Racemization. Preparation of Either (*S*)- or (*R*)-α-Methyldopa from (*S*)-Alanine

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Enantiomerically pure *cis*- and *trans*-5-alkyl-1-benzoyl-2-(*tert*-butyl)-3-methylimidazolidin-4-ones (**1**, **2**, **11**, **15**, **16**) and *trans*-2-(*tert*-butyl)-3-methyl-5-phenylimidazolidin-4-one (**20**), readily available from (*S*)-alanine, (*S*)-valine, (*S*)-methionine, and (*R*)-phenylglycine are deprotonated to chiral enolates (*cf.* **3**, **4**, **12**, **21**). Diastereoselective alkylation of these enolates to 5,5-dialkyl- or 5-alkyl-5-arylimidazolidinones (**5**, **6**, **9**, **10**, **13a–d**, **17**, **18**, **22**) and hydrolysis give α-alkyl-α-amino acids such as (*R*)- and (*S*)-α-methyldopa (**7** and **8a**, resp.), (*S*)-α-methylvaline (**14**), and (*R*)-α-methyl-methionine (**19**). The configuration of the products is proved by chemical correlation and by NOE ^{1}H-NMR measurements (see **23**, **24**). In the overall process, a simple, enantiomerically pure α-amino acid can be α-alkylated with retention or with inversion of configuration through pivalaldehyde acetal derivatives. Since no chiral auxiliary is required, the process is coined 'self-reproduction of a center of chirality'. The method is compared with other α-alkylations of amino acids occurring without racemization. The importance of enantiomerically pure, α-branched α-amino acids as synthetic intermediates and for the preparation of biologically active compounds is discussed.

In [1], we have shown that simple amino acids such as (*S*)-alanine, (*S*)-valine, (*R*)-phenylglycine, (*S*)-phenylalanine, and (*S*)-methionine can be converted selectively to imidazolidinones such as **1** and **2** of either *cis*- or *trans*-configuration. We now show that these imidazolidinones are deprotonated to synthetically useful chiral enolates.

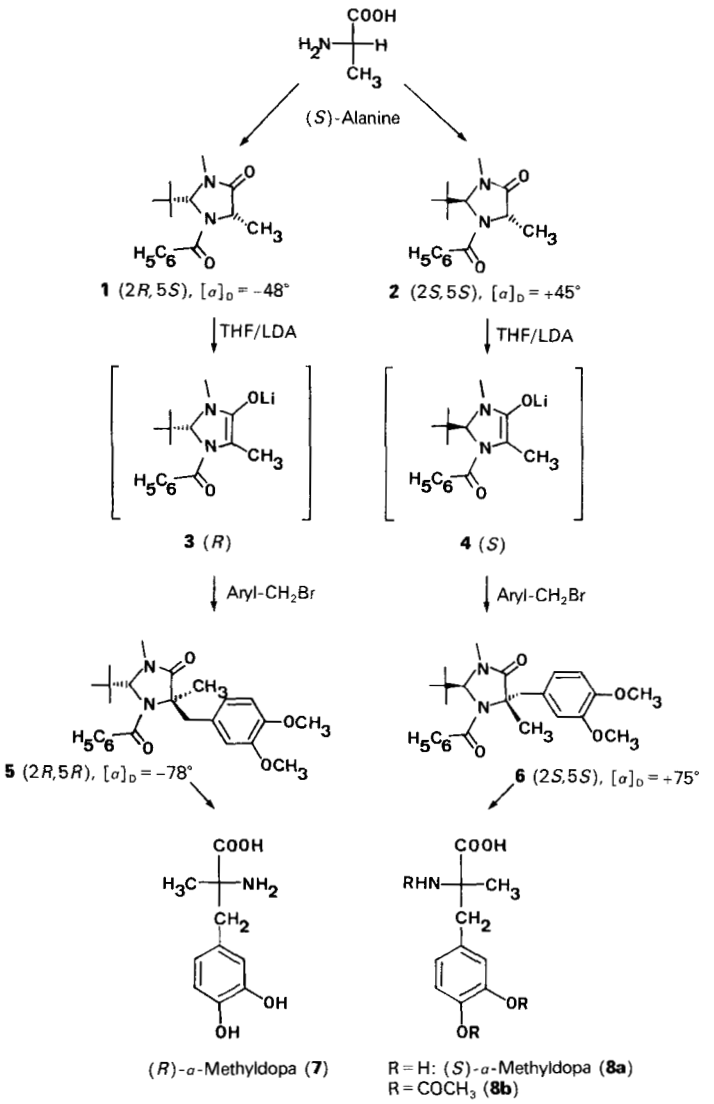
A) Reactions of the Chiral Imidazolidinone Enolates with Electrophiles. – As a first example, the preparation of (*R*)- or (*S*)-α-methyldopa (= 2-amino-2-methyl-3-(3,4-dihydroxyphenyl)propionic acid) from (*S*)-alanine is described *(Scheme 1)*. Solutions of the imidazolidinones (**1** or **2**) in THF were treated at dry-ice temperature with a slight excess of lithium diisopropylamide (LDA). Bright orange-red-colored solutions of the enantiomeric enolates (**3**, **4**) were formed, which were combined with 3,4-dimethoxybenzyl bromide. Rapid decolorization indicated the progress of the alkylation step furnishing the enantiomeric 5,5-disubstituted imidazolidinones (**5**, **6**, *ca.* 60%). We did not detect more than one diastereoisomer by HPLC of the crude products. Within experimental error, the two isomers **5** and **6** had identical physical properties such as melting points, IR, and NMR spectra, but an opposite sense of specific rotation.

The heterocyclic ring *and* the phenolic methyl-ether groups of the enantiomer **6** were cleaved by heating for 4 hours in 6N HCl at 180° in a sealed tube. Isolation of the α-methyldopa thus produced caused considerable problems due to the known [2a] sen-

[1]) Part of the projected Ph. D. theses of *J. D. A.* and *Th. W.*, ETH Zürich.

[2]) Part of the Dissertation No. 7442 of *R. N.*, ETH Zürich, 1983.

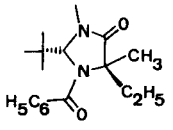
Scheme 1



sitivity of this substance towards oxygen (air!), especially under basic conditions. It appeared that the $MeNH_2$ formed in the ring cleavage as a by-product catalyzed decomposition of α-methyldopa. Therefore, the crude product **8a** was acetylated to the crystalline *N,O,O*-triacetyl derivative **8b**.

The enantiomer of **6** was also cleaved to give (*R*)-α-methyldopa (**5**→**7**). The specific rotations of **5** and **6**, and the comparison of the specific rotation of **8b** with that of authentic material [2b] are definitive proof for the diastereoisomeric and enantiomeric purities of the imidazolidinones **1** and **2**. Thus, the overall conversion of (*S*)-alanine to

methyldopa has been achived with retention[3]) of configuration through the *cis*-isomer and with inversion[3]) through the *trans*-isomer. The enolates (**3, 4**) were alkylated from the face opposite to the *t*-Bu group (relative topicity *lk* [4])[4]).



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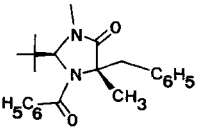

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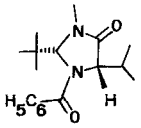

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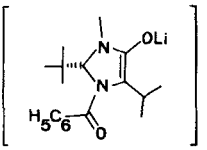
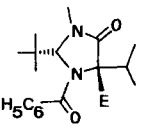
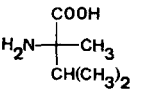


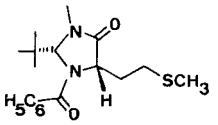
12 (*R*)



13a E = D
13b E = CH_3
13c E = C_2H_5
13d E = CH_2–CH=CH_2



14 (*S*)



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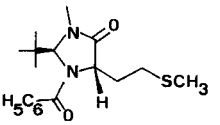

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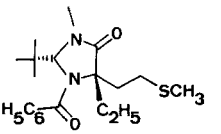

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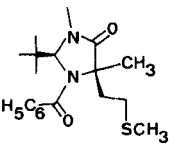

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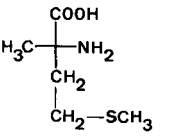

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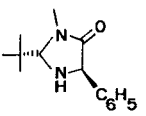

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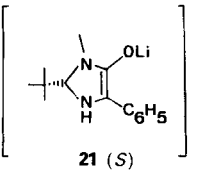
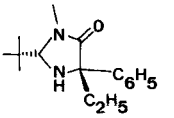


21 (*S*)



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[3]) For the definition of the use of the terms inversion and retention of configuration in cases like this, see [3a], especially footnote 21 therein (the paper mentioned has appeared in the meantime, *cf.* [3b]).

[4]) It is probably also possible to prepare **5** and **6**, and thus α-methyldopa by methylation of dopa itself. The *cis*-imidazolidinone (**1**, $C_6H_5CH_2$ instead of CH_3) from (*S*)-phenylalanine could be prepared, albeit with *ca.* 50% racemization (enantiomerically pure (2*R*,5*S*)-1-benzoyl-5-benzyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one has an $[\alpha]_D^{25} = -27°$, m.p. 193°). A partially racemized sample was allylated (CH_2=CH–CH_2Br) in 81% yield to give diastereomerically pure *u*-1-benzoyl-5-benzyl-2-(*tert*-butyl)-3-methyl-5-(2-propen-1-yl)imidazolidin-4-one.

The (*R*)-enolate **3** derived from (*S*)-alanine was also ethylated (→**9**), and its enantiomer **4** benzylated (→**10**). Of the other imidazolinones reported in [1], we have alkylated[4]) those derived from (*S*)-valine (see **11**), (*S*)-methionine (see **15**, **16**), and (*R*)-phenylglycine (see **20**). In the case of the derivative **11**, we first determined the stereochemical course of the deprotonation/deuteration by quenching the lithium enolate **12** with CH_3OD at −78°. This gave the deuterated product **13a** with retention of configuration (*ca.* 70% yield, ≥ 90% D-incorporation, ≥ 95% (*R*,*S*)-diastereoisomer (by ^{1}H-NMR)). Thus, again, the attack of the electrophile D^+ has taken place cleanly from the (*Re*)-face of the enolate **12** double bond, opposite to the *t*-Bu group. Methylation, ethylation, and allylation of **12** gave single diastereomers **13b**, **13c**, and **13d**, respectively, which are drawn with (5*S*)-configuration in the *Formulae*, and of which **13b** was hydrolyzed to (*S*)-α-methylvaline (**14**) by heating its solution in 20% aq. HCl to 180° in a sealed tube for 4 hours. For configurational assignments, see *Section B*. The *cis*- and *trans*-substituted heterocycles **15** and **16** from (*S*)-methionine were deprotonated to the enantiomeric enolates and alkylated to give the geminally disubstituted derivatives **17** and **18**, respectively; hydrolysis of **18** as described above furnished (*R*)-α-methylmethionine (**19**).

A special case is that of the non-acylated *trans*-substituted heterocycle **20**, obtained from (*R*)-phenylglycine. Due to the additionally acidifying effect of the phenyl group of **20**, and hence the increased stability of the enolate, it was possible to deprotonate this imidazolidinone without 'protection' of the NH-group and to ethylate the resulting enolate **21** in 80% yield and with high diastereoselectivity (→**22**)[5]).

The imidazolidinone enolates described here are surprisingly stable. The orange to dark-red-colored solutions can be briefly warmed up to at least 0° without deterioration. The color of the solutions can be used as an indicator in reactions with electrophiles: it disappears or turns to a light yellow at −75° instantaneously when CD_3OD, CD_3COOD, or benzaldehyde are added, with allyl and benzyl bromides it takes a few minutes that the color fades away at the same temperature, while MeI and EtI require warming to temperatures between −50° and −30°. The yields of the alkylations range from 70 to 90%[6]). The imidazolidinone enolates appear to be more basic and less nucleophilic towards carbonyl derivatives than the corresponding enolates of dioxolanones [8] and oxazolidinones [3a] derived from α-hydroxy acids and from proline, respectively. Thus, the enolate **12** was quantitatively protonated upon addition of acetone, while it gave the adduct with the non-enolizable benzaldehyde[7]) in good yield.

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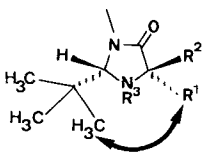
[5]) The benzoylation of the other imidazolidinones **1**, **2**, **11**, **15**, and **16** does not only serve as a protection but should also acidify the neighboring CH-group: it is known that non-enolizable carboxamides with sterically protected but electronically effective carbonyl groups are readily deprotonated at the N–*C*H-position; for reviews, see [5–7].

[6]) Alkylating reagents such as secondary or long chain alkyl halides or sulfonates have not been tested in these reactions, as yet.

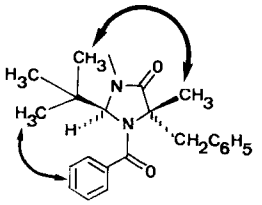
[7]) This and other adducts of imidazolidinone enolates and carbonyl derivatives will be described elsewhere. We expect the enolate **21** to be much less basic than the analogues with *N*-benzoyl groups, because a proline-derived enolate with nonacylated NH_2-group [3a] and dioxolanone enolates bearing atoms with 'free electron pairs' on the enolate β-C-atom [8] are also nonbasic, but highly nucleophilic.

B) Assignment of the Configuration of the Products 9, 10, and 22 by NOE ^{1}H-NMR-Measurements. – The relative and absolute configurations of the α-methyldopa derivatives **5** and **6**, and of the valine derivative **13a** were assigned by chemical correlation (see above). We have determined the relative configuration of three further 5,5-disubstituted imidazolidinones from nuclear *Overhauser* effects (NOE).

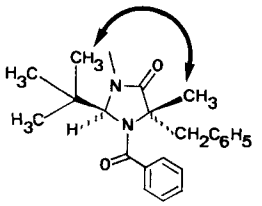
The NOE were preferably measured with a 360-MHz instrument in (D_6)benzene for better separation of the important ^{1}H-NMR signals in these experiments. Thus, upon irradiation of **9** with the resonance frequency of the *t*-Bu group, a positive NOE was observed at the signal of the CH_3-group in 5-position, indicating the *cis*-relationship of these two groups, see **23** ($R^1 = CH_3$). Likewise, in the ^{1}H-NMR spectrum of the phenylglycine-derived compound **22**, the intensity of the signal of the *ortho*-protons in the phenyl group was enhanced by irradiating with the frequency of the *t*-Bu protons, see **23** ($R^1 = C_6H_5$).



23 $R^1 = CH_3$, $R^2 = C_2H_5$, $R^3 = COC_6H_5$ (≡**9**)
$R^1 = C_6H_5$, $R^2 = C_2H_5$, $R^3 = H$ (≡**22**)



24a



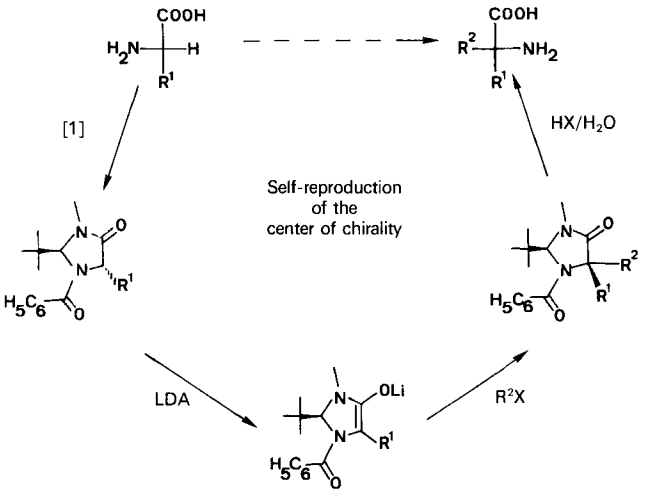
24b

Several of the ^{1}H-NMR spectra of 5,5-disubstituted imidazolidinones appeared very complex at first sight. In some cases, most signals were broad and unresolved, in others, two full sets of signals were present. Thus, a $CDCl_3$ solution of the alanine-derived compound **10**, which is nicely crystalline with a sharp m.p. at 112°, and which was a single, pure compound according to HPLC, was proved to contain two isomers by ^{1}H-NMR spectroscopy. Irradiation with the frequencies of the *t*-Bu protons caused a positive NOE in the signals from *both* CH_3–C(5), but only in those from the *ortho*-protons of phenyl of *one* of the isomers! This indicates that in both isomers, the *t*-Bu and the CH_3-groups are *cis* to each other, and that we are dealing with the (*E*/*Z*)-isomers **24a** and **24b** of the same *l*-diastereoisomer. Indeed, corresponding signals of the spectrum coalesce near the boiling point of (D_6)DMSO (*ca.* 180°).

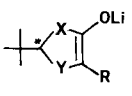
In analogy with the established cases, the absolute and relative configurations of the other 5,5-disubstituted imidazolidinones (and of the products of their hydrolysis) are assumed without proof to be such that the substituent introduced in the reaction of the enolate with the electrophile is in a *trans*-position with respect to the *t*-Bu group, as drawn in the corresponding *Formulae* and as specified in the *Exper. Part.*

C) Discussion and Conclusions. – The present results show that α-amino acids can be α-alkylated without racemization, see *Scheme 2* for the transformation with inversion of configuration[3]); thus, a (*S*)-α-amino acid is, for instance, converted to the *trans*-imidazolidinone [1], a pivalaldehyde N,N-acetal with two asymmetric centers; this acetal is deprotonated to a nonracemic lithium enolate, which in turn reacts with electrophiles highly diastereoselectively, *i.e.* the acetal center exerts a strong asymmetric induction in the formation of the new center of chirality; finally, hydrolysis of the imidazolidinone with cleavage of the acetal and amide bonds completes the overall

Scheme 2



alkylation of the amino acid. Since no chiral auxiliary is employed in the entire sequence, this was called a self-reproduction of the center of chirality. The only nonracemic compound used is the original α-amino acid. It is possible to perform this sequence of reactions also through the less readily available imidazolidinones of *cis*-configuration, *i.e.* with retention of configuration[3]); furthermore, many α-amino acids are now commercially available in both enantiomeric forms. The 'auxiliary' which is necessary for the enantioselective overall conversion is pivalaldehyde, a by-product of the industrial hydroformylation of 2-methylpropene (isobutylene). We have realized similar sequences, using the same auxiliary, for the α-alkylation of α-hydroxy- and α-mercaptocarboxylic acids (see **25** and [8]), of proline (see **26**, X = CH_2, and [3a]), and of cysteine and serine (see **26**, X = S, and **27**, and [9] [10], resp.).



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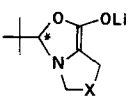

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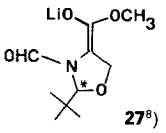

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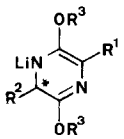

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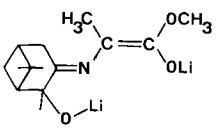
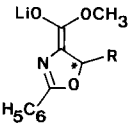


29[8])



30[8])

[8]) The configuration of the enolate double bonds shown in the *Formulae* **27**, **29**, and **30** has not been established; the drawing is arbitrary, as long as structural information is missing; see [14].

Previous methods of preparing enantiomerically pure α-branched α-amino acids had to rely on chiral auxiliaries such as other α-amino acids in *Schöllkopf*'s procedure (see **28** and [11] [12]) or 2-hydroxypinan-3-one as employed by *Viallefont et al.* (see **29** and [13]). For practical purposes and large scale preparations, these auxiliaries would have to be recycled[9]).

We have previously shown that chiral dihydroxy-carboxylic acids such as tartaric acid [15], as well as β-hydroxy α-amino acids such as threonine, allothreonine, and phenylserine (see **30**, R = CH_3 and C_6H_5, resp., and [16]) can also be alkylated stereoselectively. Work on the α-alkylation of other functionalized amino acids (tyrosine, tryptophane, aspartic acid, glutamic acid, lysine, ornithine, arginine, histidine *etc.*) is in progress in our laboratory. Thus, an increasing number of enantiomerically pure compounds (EPC) with persubstituted C-atoms become available as starting materials for EPC-syntheses of natural products and of physiologically active compounds. This is important not only for the synthetic chemist: more and more α-branched α-amino acids are now being discovered as minor components of peptides or are isolated from other natural sources[10]). They have been shown to be biologically active such as (*S*)-α-methyldopa (**8**) which exhibits hypotensive activity and which inhibits the decarboxylation of (*S*)-dopa by mammalian decarboxylase, while the (*R*)-enantiomer is totally inactive [18]. Some hydantoins derived from α-branched amino acids are antiepileptica [19]. On the other hand, the highly toxic α-aminocyclopentanecarboxylic acid has been shown to have carcinostatic properties[11]) while derivatives of α-methylmethionine and ethylalanine trigger tumor growth [21]. Finally, it is to be expected that incorporation of branched amino acids at certain positions of physiologically active oligopeptides will be possible with preservation of activity and simultaneous protection against cleavage by peptidases. Our method provides ready access to a large variety of α-branched amino acids for tests and further elaboration and application.

We thank the same persons, firms, and institutions as stated in [1] for generous help and support during these investigations.

Experimental Part

General. See [1]. Melting points (m.p.) and boiling points (b.p.) are uncorrected. Reagents and solvents were purified in the usual way. THF was distilled under Ar over K. All reactions involving Li derivatives were carried out under anh. conditions in an Ar atmosphere [22]. The diastereoisomeric composition of crude products was determined by ^{1}H-NMR. The anisochronous ^{1}H-NMR signals of the minor diastereoisomer are given in *italics*. Flash chromatography was performed according to the method described by *Still et al.* [23].

A) General Procedure for Reactions of the Enolates 25 with Various Electrophiles. – Unless noted otherwise, 1.1 equiv. of a 1M LDA solution in THF/hexane 1:3 was added to a 0.17M solution of the imidazolidinone derivative in THF at −78° (→deep red). After 30 min, 1.2 equiv. of the electrophile were added, and the temp.

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[9]) This is an especially problematic task in the case of the highly selective reaction used by *Schöllkopf et al.* [11] [12], because two amino-acid esters, the auxiliary one and the branched one, have to be separated from each other; this is done by fractional distillation or by preparative gas chromatography following the final step!

[10]) See the recent reviews [17].

[11]) Leucinostatin A, a novel nonapeptide with antitumor activity, contains three 2-amino-2-methylpropionic-acid units [20].

was allowed to warm to 0° within 2 h. The resulting light yellow solution was poured into half-sat. NH_4Cl soln. and extracted twice with Et_2O (200 ml). The org. phase was washed once with 150 ml of dist. H_2O and dried ($MgSO_4$). The solvent was then removed *in vacuo*.

B) General Procedure for Hydrolysis of the 5,5-Dialkylated Imidazolidinones. – The purified 5,5-dialkylated imidazolidinone (1 g) was mixed with 20 ml of aq. 6N HCl. The sealed tube was heated at 175–185° for 4 h in a steel tube after which the heterogeneous mixture was washed with 15 ml of CH_2Cl_2. Concentration under reduced pressure gave the crude amino-acid hydrochlorid.

C) General Procedure for Production of the Free Amino Acid. – The salt was dissolved in 10 ml of H_2O and adsorbed on 30 g of acidic *Dowex 50 WX8*. The resin was washed with dist. H_2O until neutral, and then the free amino acid was eluted with 1.3N aq. NH_3. The solvent was removed *in vacuo*. Complete removal of NH_3 was accomplished by redissolving the substance in H_2O and concentrating in a rotatory evaporator. Finally, drying for 24 h under high vacuum (50°) provided pure amino acids.

*(2R,5R)-1-Benzoyl-2-(*tert*-butyl)-5-(3',4'-dimethoxybenzyl)-3,5-dimethylimidazolidin-4-one* (**5**). Following *Procedure A*, 2.74 g (10 mmol) of **1** and 2.8 g (12 mmol) of 3,4-dimethoxybenzyl bromide dissolved in 15 ml of THF provided, after flash chromatography (Et_2O/pentane 5:1), 2,47 g (57%) of **5** as white powder. The following modification improved the yield by 15%: Using a *Teflon* tube as a cannula, the enolate solution (0.1M, −78°) was transferred dropwise to the 0.31M 3,4-dimethoxybenzyl bromide solution (−78°). M.p. 165°, $[\alpha]_D^{25} = -78.0$ ($c = 0.5$, $CHCl_3$). IR (KBr): 2960*m*, 1710*s*, 1640*s*, 1520*m*, 1370*m*, 1260*m*, 1240*m*, 1135*m*. ^{1}H-NMR ($CDCl_3$, mixture of 2 rotamers): 7.80–6.67 (*m*, 8 arom. H); *5.26*/4.92 (*s*, H–C(2)); *3.90*/3.51 (*s*, CH_3O); 3.83 (*s*, CH_3O); 3.80–3.00 (*m*, $C_6H_5CH_2$); 2.97/*2.60* (*s*, CH_3–C(5)); *1.00*/0.77 (*s*, $(CH_3)_3C$). MS: 424 (1, M^+), 367 (12), 151 (18), 105 (100), 77 (22). For the microanalysis, a sample was crystallized from MeOH/Et_2O at −78°. ^{1}H-NMR: presence of 0.5 equiv. of MeOH in the crystal. Anal. calc. for $C_{25.5}H_{34}N_2O_{4.5}$ (440.53): C 69.52, H 7.77, N 6.36; found: C 69.68, H 7.47, N 6.46.

*(2S,5S)-1-Benzoyl-2-(*tert*-butyl)-5-(3',4'-dimethoxybenzyl)-3,5-dimethylimidazolidin-4-one* (**6**). Following *Procedure A*, 2.74 g (10 mmol) of **2** and 2.8 g (12 mmol) of 3,4-dimethoxybenzyl bromid dissolved in 15 ml of THF provided after flash chromatography (Et_2O/pentane 5:1) 2.64 g (61%) of **6** as white powder. $[\alpha]_D^{25} = +74.9$ ($c = 0.4$, $CHCl_3$). Other physical data are identical with those of **5**.

*(2S)-*N*-Acetyl-3-(3',4'-diacetoxyphenyl)-2-methylalanine* (**8b**). Following *Procedure B*, 4.69 g (11.05 mmol) of **6** in 30 ml of aq. 6N HCl provided 3.67 g of a mixture of ammonium salts. To remove the $MeNH_2$ this crude product was dissolved in 20 ml of pyridine and evaporated to dryness *in vacuo* (0.01 Torr). For acetylation of **8a**, the residue was dissolved in 60 ml of Ac_2O/pyridine 2:1 and heated at 95° for 3 h[12]). The dark solution was concentrated *in vacuo*. The residual oil was dissolved in 5 ml of acetone, 10 ml of H_2O and 1 ml of 2.5M HCl[13]). After evaporation, the oil was dissolved in 20 ml of EtOH and poured into 200 ml of H_2O/Et_2O 1:3. The H_2O phase was extracted twice with Et_2O (100 ml). Then, the org. phase was evaporated and dried *in vacuo*. Crystallization from acetone/pentane gave 2.44 g (56%) of **8b**. $[\alpha]_D^{25} = -74.7$ ($c = 0.73$, MeOH)[14]). One further crystallization gave 1.23 g (33%) of pure **8b**. M.p.: 178.0–179.0°. $[\alpha]_D^{25} = -93.9$ ($c = 1.04$, MeOH)[14]) ([2b]: m.p. 180.0–181.0°; $[\alpha]_D^{22} = -94.2$ ($c = 0.716$, MeOH)). ^{1}H-NMR (CD_3OD): 7.20–6.91 (*m*, 3 arom. H); 4.85 (br. *s*, NH, COOH); 3.46, 3.11 (*AB*, $J = 13.5$, 2H–C(3)); 2.21 (*s*, 2 $OCOCH_3$); 1.90 (*s*, $NHCOCH_3$); 1.40 (*s*, CH_3–C(2)).

*(2R)-3-(3',4'-Dihydroxyphenyl)-2-methylalanine (= (*R*)-α-Methyldopa;* **7**). Following *Procedure B*, 0.6 g (1.41 mmol) of **5** in 20 ml of aq. 6N HCl provided 0.47 g of **7** as the methylammonium salt. ^{1}H-NMR (D_2O; HDO = 4.8 ppm): 6.91–6.50 (*m*, 3 arom. H); 3.10, 2.86 (*AB*, $J = 13.5$, 2H–C(3)); 2.53 (*s*, CH_3N); 1.55 (*s*, CH_3–C(2)).

*(2R,5R)-1-Benzoyl-2-(*tert*-butyl)-5-ethyl-3,5-dimethylimidazolidin-4-one* (**9**). Following *Procedure A*, 2.74 g (10 mmol) of **1** and 1 ml (12 mmol) of EtI provided, after flash chromatography (Et_2O/pentane 2:1), 2.72 g (90%) of **9** as colorless crystals. For analytical purposes **9** crystallized from Et_2O/pentane (ds > 95%). M.p. 122.5–123.5°. $[\alpha]_D^{25} = +16.5$ ($c = 1.43$, $CHCl_3$). IR ($CHCl_3$): 2970*m*, 1680*s*, 1630*s*, 1355*s*, 1090*w*. ^{1}H-NMR ($CDCl_3$): 7.66–7.36 (*m*, 5 arom. H); 5.74 (*s*, H–C(2)); 3.10 (*s*, CH_3N); 1.67–1.56 (*q*, $J = 9$, CH_3CH_2); 1.53 (*s*,

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[12]) All manipulations were carried out under an Ar [2].

[13]) The acid was added to accelarate hydrolysis of the azalactone.

[14]) The ^{1}H-NMR spectra shows that 1 equiv. of acetone is present in the crystal. For anal. measurements, the crystals were dissolved several times in CH_2Cl_2 and the solvent evaporated. Finally, **8b** was precipitated with pentane and dried *in vacuo*.

CH_3–C(5)); 1.10 (*s*, $(CH_3)_3C$); 0.60 (*t*, $J = 9$, CH_3CH_2–C(5)). MS: 287 (1, $M^+ - 15$), 245 (25), 105 (100), 77 (27), 42 (10). Anal. calc. for $C_{18}H_{26}N_2O_2$ (302.34): C 71.49, H 8.67, N 9.26; found: C 71.38, H 8.57, N 9.38.

*(2S,5S)-1-Benzoyl-5-benzyl-2-(*tert*-butyl)-3,5-dimethylimidazolidin-4-one* (**10**). Following *Procedure A*, 2.74 g (10 mmol) of **2** and 1.5 ml (12 mmol) of benzyl bromide provided, after flash chromatography (Et_2O/pentane 5:1), 2.65 g (73%) of **10** as colorless crystals (ds > 95%). M.p.: 112°. $[\alpha]_D^{25} = +67.7$ ($c = 1.0$, $CHCl_3$). IR (KBr): 2990*m*, 1700*s*, 1642*s*, 1400*m*, 1375*s*. ^{1}H-NMR (C_6D_6; mixture of two rotamers): 7.50–6.90 (*m*, 10 arom. H); *5.17*/4.66 (*s*, H–C(2)); *3.98*, *3.34*/2.61, 2.53 (*AB*, $J = 14$, $C_6H_5CH_2$); 2.49/*2.28* (*s*, CH_3N); 1.91/*1.44* (*s*, CH_3–C(5)); *0.76*/0.42 (*s*, $(CH_3)_3C$). MS: 349 (1, $M^+ - 15$), 307 (100), 306 (33), 305 (94), 77 (90), 57 (22). Anal. calc. for $C_{23}H_{28}N_2O_2$ (364.45): C 75.79, H 7.74, N 7.68; found: C 75.71, H 7.86, N 7.57.

*(2R,5S)-1-Benzoyl-2-(*tert*-butyl)-5-isopropyl-3-methyl-(5-^{2}H)imidazolidin-4-one* (**13a**). Following *Procedure A*, 2.74 g (10 mmol) of **11** and 1.7 ml (30 mmol) of CH_3COOD provided a max. deuteration of 20%. At –30°, the enolate-solution of **12** was evaporated under high vacuum, and the resinous residue was washed several times with hexane yielding **12** as powdery, orange solid. A sample was quenched in the NMR tube at 0° with CD_3OD. The degree of deuteration was ≥95% (79% ds). The molar ratio of imidazolidinone **13a** to THF was exactly 1:1. The main part of **12** was suspended at –78° in hexane and quenched with CH_3OD. Workup as described in *Procedure A* gave 2.05 g (68%) of **13a** with a degree of deuteration of ≥90% (ds > 95%). M.p. 116°. $[\alpha]_D^{25} = +24.8$ ($c = 1.2$, $CHCl_3$). ([1]: m.p. 112°; $[\alpha]_D^{25} = +22.4$ ($c = 1.7$, $CHCl_3$)). IR ($CHCl_3$): 2965*m*, 1685*s*, 1635*s*, 1362*s*, 1295*w*. ^{1}H-NMR (CCl_4): 7.46–7.13 (*m*, 5 arom. H); 5.33 (*s*, H–C(2)); 3.86 (< 10%, *d*, $J = 10$, H–C(5)); 2.97 (*s*, CH_3N); 2.06–1.46 (*m*, $(CH_3)_2CH$); 1.03 (*s*, $(CH_3)_3C$); 1.00 (*d*, $J = 6$, CH_3CHCH_3); 0.66 (*d*, $J = 6$, CH_3CHCH_3). Anal. calc. for $C_{18}H_{25}DN_2O_2$ (303.38): C 71.26, H 8.96, N 9.32; found: C 71.47, H 8.70, N 9.23.

*(2R,5S)-1-Benzoyl-2-(*tert*-butyl)-5-isopropyl-3,5-dimethylimidazolidin-4-one* (**13b**). Following *Procedure A*, 3.02 g (10 mmol) of **11** and 0.75 ml (12 mmol) of MeI provided, after flash chromatography (Et_2O/pentane 5:1), 2.18 g (70%) of **13b** as colorless crystals (ds > 95%). M.p. 95.0–97.5°. $[\alpha]_D^{25} = +38.7$ ($c = 1.38$, $CHCl_3$). IR ($CHCl_3$): 2955*m*, 2895*w*, 1695*s*, 1650*s*, 1410*s*, 1271*m*, 1122*m*, 1102*m*, 1036*w*, 935*w*, 708*w*. ^{1}H-NMR ($CDCl_3$): 7.43 (*s*, 5 arom. H); 5.46 (*s*, H–C(2)); 3.03 (*s*, CH_3N); 2.26–1.76 (*m*, $(CH_3)_2CH$); 1.37 (*s*, CH_3C–C(5)); 1.15 (*d*, $J = 7$, CH_3CHCH_3); 1.12 (*d*, $J = 7$, CH_3CHCH_3); 1.02 (*s*, $(CH_3)_3C$). MS: 301 (0.3, $M^+ - 15$), 260 (6), 259 (32), 106 (8), 105 (100), 77 (14), 42 (5). Anal. calc. for $C_{19}H_{28}N_2O_2$ (316.45): C 72.11, H 8.92, N 8.85; found: C 72.25, H 8.76, N 8.84.

*(2R,5S)-1-Benzoyl-2-(*tert*-butyl)-5-ethyl-5-isopropyl-3-methylimidazolidin-4-one* (**13c**). Following *Procedure A*, 3.02 g (10 mmol) of **11** and 1 ml (12 mmol) of EtI provided, after one crystallization (Et_2O/pentane), 2.67 g (81%) of diastereoisomerically pure **13c** as white crystals. M.p. 112°. $[\alpha]_D^{25} = +39.9$ ($c = 1.3$, $CHCl_3$). IR ($CHCl_3$): 2960*s*, 1675*s*, 1630*s*, 1450*m*, 1350*s*, 1090*m*. ^{1}H-NMR ($CDCl_3$; mixture of two rotamers): 7.43 (*s*, 5 arom. H); 5.56/*5.43* (*s*, H–C(2)); 3.03 (*s*, CH_3N); 2.20–1.70 (*m*, $(CH_3)_2CH$); 1.33–0.56 (*m*, $(CH_3)_2CH$, $(CH_3)_3C$, CH_3CH_2). MS: 331 (46, $M^+ + 1$), 274 (74), 273 (95), 105 (90), 77 (100), 57 (15). Anal. calc. for $C_{20}H_{30}N_2O_2$ (330.44): C 72.69, H 9.15, N 8.48; found: C 72.57, H 9.02, N 8.39.

*(2R,3S)-5-Allyl-1-benzoyl-2-(*tert*-butyl)-5-isopropyl-3-methylimidazolidin-4-one* (**13d**). Following *Procedure A*, 3.02 g (10 mmol) of **11** and 1 ml (12 mmol) of allyl bromide provided, after a bulb-to-bulb distillation, 3.05 g (89%) of diastereoisomerically pure **13d** as a colorless resin. B.p. 190°/0.1 Torr. $[\alpha]_D^{25} = -5.94$ ($c = 0.41$, $CHCl_3$). IR ($CHCl_3$): 2970*m*, 1690*s*, 1635*s*, 1365*m*, 1090*w*. ^{1}H-NMR (CCl_4): 7.34 (*s*, 5 arom. H); 5.73–4.86 (*m*, CH_2=$CHCH_2$, H–C(2)); 2.83 (*s*, CH_3N); 2.80–2.43 (*m*, $(CH_3)_2CH$); 2.33–1.56 (*m*, CH_2=$CHCH_2$); 1.40–0.66 (*m*, $(CH_3)_2CH$, $(CH_3)_3C$). MS: 341 (2, $M^+ - 1$), 285 (15), 105 (100), 77 (25). Anal. calc. for $C_{21}H_{30}N_2O_2$ (342.45): C 73.65, H 8.83, N 8.18; found: C 73.25, H 8.70, N 8.25.

(2S)-2-Amino-2,3-dimethylbutanoic Acid (= *(S)-α-methylvaline*; **14**). Following *Procedure B*, 1.36 g (4.3 mmol) of **13b** in 30 ml of aq. 6N HCl provided the crude hydrochloride of **14**. Cation-exchange chromatography by *Procedure C* gave 0.564 g (95%) of **14** as colorless crystals. Dec. 215°. $[\alpha]_D^{25} = -4.6$ ($c = 1.15$, 0.2N HCl). IR (KBr): 3440*m* (br.), 3300–2200*s* (br.), 1610*s*, 1530*m*, 1465*m*, 1405*s*, 1370*s*, 1335*s*, 1320*s*, 1251*w*, 1230*w*, 1175*w*, 1160*m*, 1078*w*, 902*m*, 861*m*, 790*w*, 768*m*, 631*w*. ^{1}H-NMR (D_2O, HDO = 4.8 ppm): 2.19 (*sept.*, $J = 6.3$, H–C(3)); 1.50 (*s*, CH_3–C(2)); 1.04 (*d*, $J = 6.3$, CH_3–C(3)); 1.00 (*d*, $J = 6.3$, 3H–C(4)). MS: 132 (1, $M^+ + 1$), 131 (0.5, M^+), 89 (7), 88 (100), 87 (5), 86 (74), 72 (6), 71 (11), 70 (14), 69 (19), 43 (18), 42 (59), 41 (19). Anal. calc. for $C_6H_{13}NO_2$ (131.18): C 54.94, H 9.99, N 10.68; found: C 54.85, H 10.02, N 10.57.

*(2R,5S)-1-Benzoyl-2-(*tert*-butyl)-5-ethyl-3-methyl-5-(3'-thiabutyl)imidazolidin-4-one* (**17**). Following *Procedure A*, 3.34 g (10 mmol) of **15** and 1 ml (12 mmol) of EtI provided, after flash chromatography (Et_2O/pentane 5:1), 3.04 g (84%) of **17** as colorless crystals (ds > 95%). M.p. 86°. $[\alpha]_D^{25} = +81.3$ ($c = 1.0$, $CHCl_3$). IR (KBr): 2975*m*, 1695*s*, 1640*s*, 1350*m*, 1330*m*, 1265*m*. ^{1}H-NMR ($CDCl_3$): 7.50 (br. *s*, 5 arom. H); 5.70 (*s*, H–C(2)); 3.06 (*s*, CH_3N); 3.00–1.50 (*m*, 3 CH_2); 2.03 (*s*, CH_3S); 1.10 (*s*, $(CH_3)_3C$); 0.66 (*t*, $J = 6$,

CH_3–C–C(5)). ^{13}C-NMR ($CDCl_3$): 174.26 (*s*); 170.95 (*s*); 137.37 (*s*); 130.34 (*d*); 127.63 (*d*); 126.71 (*d*); 79.38 (*d*); 67.85 (*s*); 40.05 (*t*); 37.70 (*s*); 30.66 (*q*); 29.82 (*t*); 28.68 (*t*); 26.51 (*q*); 14.64 (*q*); 6.94 (*q*). MS: 362 (1, M^+), 306 (71), 305 (92), 111 (34), 106 (100), 105 (91), 77 (89), 42 (59), 41 (39). Anal. calc. for $C_{20}H_{30}N_2O_2S$ (362.44): C 66.26, H 8.34, N 7.73; found: C 66.07, H 8.25, N 7.70.

*(2S,5R)-1-Benzoyl-2-(*tert*-butyl)-3,5-dimethyl-5-(3'-thiabutyl)imidazolidin-4-one* (**18**). Following *Procedure A*, 3.34 g (10 mmol) of **16** and 0.9 ml (15 mmol) of MeI provided, after one crystallization ($CHCl_2$/pentane), 2.36 g (66%) of **18** as slightly yellow crystals (ds > 95%). M.p. 99–107°. $[\alpha]_D^{25} = -76.1$ (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): 2970*s*, 1690*s*, 1640*s*, 1400*m*, 1300*m*, 1260*m*, 1115*m*, 1075*m*, 870*m*, 650*m*. ^{1}H-NMR ($CDCl_3$): 7.50 (*s*, 5 arom. H); 5.83 (*s*, H–C(2)); 3.84 (*s*, CH_3N); 3.00–2.00 (*m*, CH_2CH_2); 2.03 (*s*, CH_3S); 1.10 (*s*, CH_3–C(5), $(CH_3)_3C$). MS: 291 (100), 112 (10), 106 (29), 105 (86), 77 (64), 42 (15), 41 (11). Anal. calc. for $C_{19}H_{28}NO_2S$ (348.51): C 65.48, H 8.09, N 8.03; found: C 65.35, H 8.04, N 8.12.

(2R)-2-Amino-2-methyl-5-thiahexanoic Acid (= (R)-α-Methylmethionine; **19**). Following the *Procedures B* and *C*, 1 g (2.8 mmol) of **18** in 25 ml of aq. 6N HCl provided 0.324 g (72%) of **19** as colorless crystals. M.p. 265–270°. $[\alpha]_D^{25} = -17.9$ (*c* = 0.7, 0.2N HCl). IR (KBr): 3450 (br.), 3300–2000*s* (br.), 1600*s*, 1455*m*, 1435*m*, 1400*s*, 1370*m*, 1305*m*, 1250*m*, 1120*w*, 890*w*, 550*m*. ^{1}H-NMR (D_2O, HDO = 4.80 ppm): 2.73–2.46 (*m*, 2H–C(4)); 2.22–1.93 (*m*, 2H–C(3)); 2.13 (*s*, CH_3S); 1.53 (*s*, CH_3–C(2)). MS: 163 (63, M^+), 146 (16), 118 (41), 89 (20), 88 (29), 75 (21), 71 (18), 70 (36), 61 (42), 57 (26), 46 (28), 45 (64), 43 (27), 42 (28), 41 (17), 31 (100), 27 (22), 18 (21). Anal. calc. for $C_6H_{13}NO_2S$ (163.24): C 44.14, H 8.02, N 8.58; found: C 43.98, H 7.97, N 8.77.

*(2S,5S)-2-(*tert*-Butyl)-5-ethyl-3-methyl-5-phenylimidazolidin-4-one* (**22**). Following *Procedure A*, 2.23 g (10 mmol) of **20** and 1 ml (12 mmol) of EtI provided, after one crystallization at −20° (Et_2O/pentane), 2.08 g (80%) of **22** as slightly yellow crystals (ds > 95%). Addition of tris(*d,d*-dicampholylmethanato)europium(III) did not split signals in ^{1}H-NMR. M.p. 129°. $[\alpha]_D^{25} = -6.76$ (*c* = 2.2, $CHCl_3$). IR ($CHCl_3$): 3450*m* (br.), 2960*s*, 1670*s*, 1390*m*, 1075*m*. ^{1}H-NMR ($CDCl_3$): 7.81–7.20 (*m*, 5 arom. H); 4.25 (*s*, H–C(2)); 2.99 (*s*, CH_3N); 2.11–1.30 (*m*, CH_2); 2.05 (br. *s*, NH); 0.93 (*s*, $(CH_3)_3C$); 0.85 (*t*, *J* = 6, CH_3–C–C(5)). MS: 259 (1, $M^+ - 1$), 203 (100), 134 (44), 104 (10), 42 (17). Anal. calc. for $C_{16}H_{24}N_2O$ (260.35): C 73.81, H 9.29, N 10.76; found: C 73.86, H 9.37, N 10.83.

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