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Diastereoselective synthesis of β-amino acid derivatives from dihydropyridones

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To the memory of A. I. Meyers

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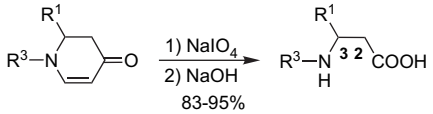
ABSTRACT

A new method for the diastereoselective preparation of stereoisomeric 2,3-disubstituted β-amino acids is presented. It is based on *trans*- and *cis*-2,3-disubstituted dihydropyridones, which were derived from 2-monosubstituted *N*-acyl dihydropyridone derivatives. Alkylation of the enolates of 2-substituted dihydropyridones gave *trans*-2,3-disubstituted dihydropyridones with high diastereoselectivities. Inversion of the stereocenter at C-3 of the dihydropyridone nucleus by a deprotonation/reprotonation sequence yielded the stereoisomeric *cis*-2,3-disubstituted dihydropyridones in high yields and diastereoselectivities. Following removal of the *N*-acyl protective group, oxidative degradation of the resulting *cis*- or *trans*-2,3-disusbtituted dihydropyridones, respectively, by sodium periodate led to the corresponding diastereomeric β-amino acids.

1. Introduction

β-Amino acid derivatives are important structural motifs in natural products and pharmacologically active compounds.[1] An easy and general access to β-amino acid derivatives with arbitrary substitution pattern is therefore an important issue. As part of our research program aimed at the development of GABA uptake inhibitors[2] we focused on β-amino acid derivatives as potentially bioactive compounds. For a systematic examination of the structure–activity relationship a general method was required, which allows the synthesis of β-amino acid derivatives with various substituents at the 2- and 3-positions as well as at the β-amino group. In the drug development process it is also crucial to possess a general and preferably stereoselective method giving access to all diastereomers of pharmacologically active agents. This is necessary as ligand target interactions are in general highly stereospecific events. Thus, a highly flexible yet diastereoselective method for the synthesis of α,β-disubstituted β-amino acids was needed.

In recent reviews, a number of methods for the synthesis of β-amino acid derivatives were described.[3] But, as several authors pointed out,[3b] there is still a need for more efficient methods for the diversity oriented synthesis of β-amino acids. We have recently published a new method for the preparation of β-amino acid derivatives substituted in the 3-position and optionally also at the amino group (Scheme 1).[4] In this synthetic concept, the dihydropyridone skeleton **1** serves as a masked β-alanine equivalent. For the successful implementation of this concept it was essential to find a suitable method effecting ring cleavage and the extrusion of the two unsaturated carbon atoms present in the starting compound resulting in the formation of the β-alanine skeleton. In the treatment of the respective starting material with sodium periodate and subsequently with sodium hydroxide we found a procedure well suited for this purpose. So far this method has been applied to the synthesis of β-alanine derivatives provided with substituents only in the 3-position, or in the 3-position and at the amino group, like **3** and **4**, employing dihydropyridones **1** and **2** as starting compounds (Scheme 1).[4]



1 (R^3 = H)
2 (R^3 = Me)
R^1 = Me, Ph or -CH=CH_2
3 (R^3 = H)
4 (R^3 = Me)

Scheme 1.

As indicated in Scheme 2, β-amino acids with any arbitrary substitution pattern might be derived from dihydropyridones provided the latter are available in the appropriately substituted

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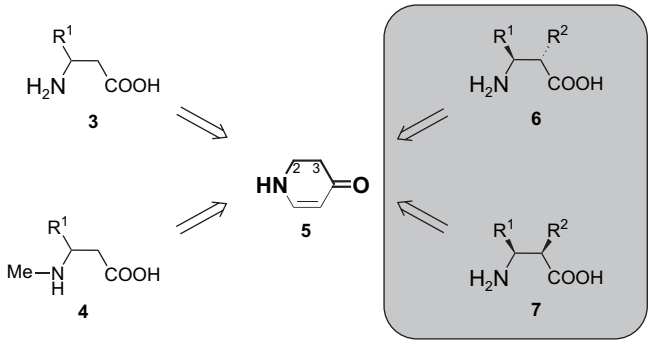
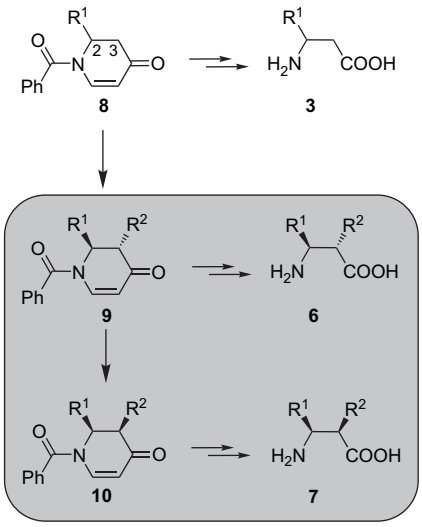
form. In addition the relative, possibly even the absolute stereochemistry should be controllable if appropriate measures are taken for the synthesis of substituted dihydropyridones. When turned into the final compounds these must reflect the stereochemistry of the starting materials as long as no isomerization takes place. In this article, we wish to report the successful expansion of the concept described above to the synthesis of 2,3-disusbtituted β-amino acids in a diastereoselective approach.



Scheme 2.

As a prerequisite for the synthesis of the desired 2,3-disubstiuted β-amino acids an efficient and diastereoselective access to the respective dihydropyridones was needed. The diastereoselective alkylation of the 2-subtituted *N*-benzoyldihydropyridones seemed best suited to achieve this as the alkylation reactions of the enolate of **8** should allow the diastereoselective introduction of substituents in the 3-position (see Scheme 3). The compounds **8** were available to us as they had been used as precursors for the preparation of the monosubstituted β-amino acids **3**.[4] However, regarding the substitution of the 3-position so far only methyl groups had been introduced by alkylation of the enolates of the respective dihydropyridones using methyl iodide furnishing the corresponding *trans*-2,3-disubstituted dihydropyridones **9**.[5a] Now, we wanted to find out whether the known reaction conditions could also be applied to alkylation reactions with other alkyl halides. Furthermore, the *cis*-2,3-disubstituted dihydropyridones **10** were thought to become available from the trans-substituted derivatives **9** by deprotonation of *C-3* of the latter and subsequent diastereoselective reprotonation of the enolate generated this way. As no attempts for diastereoselective epimerisation reactions of dihydropyridones have been published to date we expected that substantial investigations would be necessary, especially as diastereoselective epimerization reactions of α,β-disubstituted ketones are known to be highly dependent on the reaction conditions and the structural properties of the enolates employed.[6]

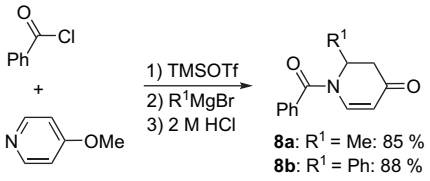


Scheme 3.

In the final step, the diastereomeric pure dihydropyridones **9** and **10** should be converted to the corresponding β-amino acid derivatives **6** and **7** employing the $NaIO_4$ ring cleavage procedure[4] that had proven its worth for the aforementioned synthesis of 3-substituted β-amino acids (Schemes 1 and 2, **3** and **4**). It was of special interest whether these transformations occur without epimerization in the α-position of the carbonyl group of **9** or **10**. If this stereocenter remained unaffected it would be very advantageous for the scope and value of this diversity oriented β-amino acid synthesis.

2. Results and discussion

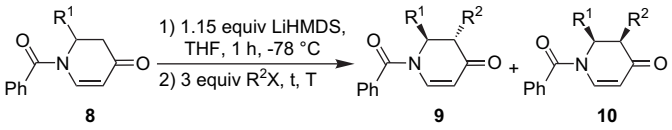
The starting compounds **8a** and **8b** were synthesized as described in literature by treating 4-methoxypyridine with benzoyl chloride and TMSOTf and by subsequently trapping the resulting *N*-acyliminium ion with Grignard reagents (Scheme 4).[4] Of course, these addition reactions could also have been performed in an asymmetric manner by substituting the *N*-benzoyl group with a chiral auxiliary to provide the 2-substituted dihydropyridones in enantiopure form.[7] No asymmetric methods were employed, however, as the main goal of this study was to demonstrate that the concept of utilizing dihydropyridone derivatives in β-amino acid synthesis can also be applied to the preparation of 2,3-disubstituted β-amino acids. Accordingly, all compounds described here are racemic mixtures.



Scheme 4.

Initial experiments for the alkylation of **8a** and **8b** via their enolates were performed following a literature procedure employing methyl iodide as electrophile that had been proven to be successful in methylation reactions of related systems[5a,8] (Table 1). When the reaction was performed that way, i.e., the starting material was treated with LiHMDS at −78 °C followed by methyl iodide, and the mixture was subsequently allowed to warm to rt, in both cases, using the dihydropyridones **8a** and **8b** the methylated products **9a** and **9c**, respectively, were obtained in very high yields and in diastereomeric pure form (Table 1, entries 1 and 4), as indicated by ^1H NMR spectra. However, the analogously performed syntheses of **9b** and **9d** using benzyl bromide as alkylating agent gave less satisfying results (Table 1, entries 2 and 5). Even though **9b** was obtained in diastereomeric pure form it was accompanied by the dibenzylation product **11** (Fig. 1) that had formed in a yield of 10% (Table 1, entry 2 and Fig. 1). In the case of **9d**, the situation was even worse as a mixture of the desired trans-derivative and its cis-diastereomer formed (Table 1, entry 5). In the course of the subsequently performed optimization of the benzylation reactions of **8a** and **8b** some quench experiments with D_2O were also carried out. These indicated that even when applied in excess LiHMDS is not capable of deprotonating the once 3-alkylated dihydropyridones, i.e., **9**, as long as the temperature is kept at −78 °C. This changed, however, when the temperature was raised. Accordingly, the undesired side reactions, such as epimerization and

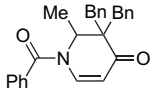
Table 1
Diastereoselective synthesis of *trans*-2,3-disubstituted dihydropyridones **9**



8 **9** **10**

Entry	**8**	R^1	R^2	X	*t* (h)	*T*	Product		
							9	Yield (%)	dr[a] (**9**/**10**)
1	**a**	Me	Me	I	2	−78 °C→rt	**a**	91	>99:1
2	**a**	Me	Bn	Br	1.25	−78 °C→rt	**b**	81[b]	>99:1
3	**a**	Me	Bn	I	29	−78 °C	**b**	96	>99:1
4	**b**	Ph	Me	I	3	−78 °C→rt	**c**	90	>99:1
5	**b**	Ph	Bn	Br	2	−78 °C→rt	**d**	91	94:6
6	**b**	Ph	Bn	I	24	−78 °C	**d**	92	>99:1

[a] Assigned from ^{1}H NMR spectra.
[b] Compound **11** (Fig. 1) was isolated with a yield of 10%.

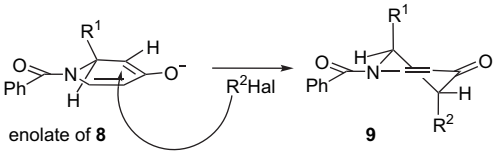


11

Figure 1. Over-alkylation product **11**.

over-alkylation, must take place during the warm up of the reaction mixture. Consequently we examined whether it was necessary to raise the temperature from −78 °C to a higher temperature to accomplish the alkylation reaction or whether it could be affected even at −78 °C. With benzyl bromide no alkylation of the enolate of **8a** occurred at −78 °C or at −60 °C for instance. However, with the more reactive benzyl iodide the enolates of **8a** and **8b** underwent a smooth reaction at −78 °C which, to our delight, then provided the *trans*-2,3-disubstituted dihydropyridones **9b** and **9d** in high yields and without the formation of the side products observed before resulting from epimerization (*cis*-dihydropyridone) or over-alkylation (**11**) (Table 1, entries 3 and 6). As a consequence, all the dihydropyridones **9** were accessible with high diastereoselectivities and in high yields (Table 1, entries 1, 3, 4, and 6).

The high diastereoselectivity observed in the alkylation reactions of the dihydropyridones **8** is easily explained by the geometry of their enolates (Scheme 5). As doubly unsaturated piperidine derivatives, the enolates of **8** must be almost planar.[5] As a result of the $A^{(1,3)}$ strain arising from the benzamide moiety R^1 is forced into a pseudo axial position. With the 'upper' face being shielded, the electrophile will enter the molecule from the opposite, less hindered side that is also favored for stereoelectronic reasons and leads to the trans-configuration found in product **9**.

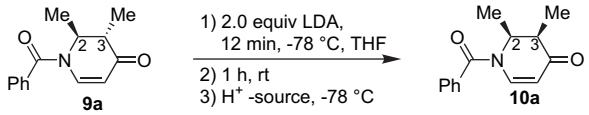


enolate of **8** **9**

Scheme 5.

As this study was aimed at the diastereoselective preparation of the different diastereomers of the final amino acids the *cis*-2,3-disubstituted dihydropyridones were required as well. A diastereoselective epimerisation of the *trans*-2,3-disubstituted dihydropyridones **9** (Table 2) by deprotonation of **9** at 3-position and subsequent diastereoselective reprotonation with inversion of the stereoconfiguration was considered the most promising method. To optimize the reaction conditions, the dihydropyridones **9a** and **9d** were selected. The steric demand of their substituents is quite

Table 2
Diastereoselective epimerisation of the *trans*-2,3-methyl-dihydropyridone **9a** employing LDA as base



9a **10a**

Entry	H^+-source	Yield[d] [%]	dr[a] (**10a**/**9a**)
1	Ethyl salicylate[b]	82	>99:1
2	2 M HCl[c]	83	99:1

[a] Determined via ^{1}H NMR spectra.
[b] The enolate of **9a** was added to a precooled solution (−78 °C) of the H^+-source in THF.
[c] Addition of the H^+-source to the solution of the enolate of **9a** at −78 °C.
[d] The yield refers to both diastereomers, if a mixture of diastereomers was obtained.

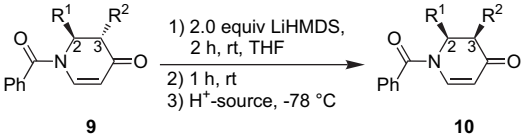
different and therefore a method that is suitable for these substrates, **9a** and **9d,** should work in almost all other cases as well.

Unfortunately, the quantitative deprotonation of **9a**, an indispensable prerequisite for the intended stereoinversion, proved to be difficult. Of the various bases that were tried out LDA appeared to be best suited. It was, however, crucial to add the ketone **9a** slowly to LDA, and to apply a significant excess of LDA (in total 2.0 equiv of LDA, Table 2), as otherwise **9a** underwent a rapid and extensive decomposition that could easily be spotted by the discoloration of the reaction mixture. For the reprotonation of the enolate of **9a** ethyl salicylate was applied, which is common for diastereoselective epimerization reactions of cyclic ketones having small substituents in the α- and β-position of the carbonyl group.[6] Under these conditions, the inversion reaction proceeded with high diastereoselectivity providing the *cis*-2,3-disubstituted dihydropyridone **10a** in a high yield and diastereomerically pure form (Table 2, entry 1). A further experiment with aqueous hydrogen chloride revealed that this reagent produces a very high diastereoselectivity in the reprotonation step of the enolate of **9a** as well (Table 2, entry 2). This shows that nature and structural properties of the proton source do not have a significant influence on the diastereoselectivity of the reprotonation process of the enolate of **9a**. But obviously the use of hydrochloric acid has a clear advantage over that of ethyl salicylate, as no additional organic compound is introduced in the reaction mixture that needs to be separated from the final product.

When applied to **9d**, the results of the reaction conditions optimized for a stereoinversion of **9a** were utterly disappointing. The reaction only led to a mixture of a vast number of unidentified products. After extensive experimentation, we were very pleased to discover that this problem could be solved by using LiHMDS as base. As mentioned above, LiHMDS does not deprotonate dihydropyridones such as **9d** at −78 °C. However, we found that a clean deprotonation can be effected when this step is performed at higher temperatures, i.e., at rt. After treatment of **9d** with 2.0 equiv of LiHMDS at rt (3 h at total) and subsequent reprotonation reaction by addition of the enolate to a precooled solution (−78 °C) of ethyl salicylate the cis-isomer **10b** was obtained in a large excess over the trans-isomer (92:8, 80% combined yield, Table 3, entry 3). The yield and diastereoselectivity were even improved (94:6, 83% combined yield, Table 3, entry 4) when the solution of ethyl salicylate was added to the precooled solution of the analogously generated enolate of **9d**. Interestingly, the *cis*-2,3-dihydropyridone **10b** was formed with a still higher diastereoselectivity when hydrochloric acid was used instead of ethyl salicylate as the proton source (97:3, Table 3, entry 5).

Fortunately, the new method based on LiHMDS proved suitable for the diastereoselective epimerization of **9a**, as well. When

Table 3
Diastereoselective epimerisation of the *trans*-2,3-disubstituted dihydropyridones **9a** and **9d** employing LiHMDS as base



9 **10**

Entry	9	R^1	R^2	H^+-source	Product		
					10	Yield[d] (%)	dr[a] (10/9)
1	**a**	Me	Me	Ethyl salicylate[b]	**a**	85	>99:1
2	**a**	Me	Me	2 M HCl[c]	**a**	81	99:1
3	**d**	Ph	Bn	Ethyl salicylate[b]	**b**	80	92:8
4	**d**	Ph	Bn	Ethyl salicylate[c]	**b**	83	94:6
5	**d**	Ph	Bn	2 M HCl[c]	**b**	78	97:3

[a] Determined via ^{1}H NMR spectra.
[b] The enolate of **9a** and **9d**, respectively, was added to a precooled solution (−78 °C) of the H^+-source in THF.
[c] Addition of the H^+-source to the solution of the enolate of **9a** and **9d**, respectively, at −78 °C.
[d] The yield refers to both diastereomers, if a mixture of diastereomers was obtained.

applied to **9a** with either reprotonation agent, ethyl salicylate or aqueous hydrogen chloride, the diastereoselectivity actually not only surpassed that of the transformation of **9d** into **10b**, the result was also as excellent as with the above described method applying LDA as base (Table 2).

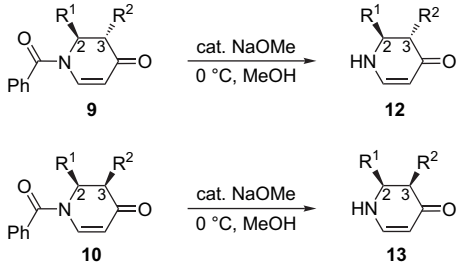
We therefore had successfully developed a highly efficient protocol for the synthesis of *cis*-2,3-disubstituted dihydropyridones **10** from the respective trans-configurated dihydropyridones **9** that tolerates substrates of quite different steric demands.

The results obtained with the conversions of **9** with LDA on one side and LiHMDS on the other gave an interesting insight into the chemical behavior of 2,3-disubstituted *N*-acyl dihydropyridones. At first, it is not astonishing that a kinetically inhibited reaction can be initiated by raising the temperature, as was the case in the deprotonation reaction of **9d** with LiHMDS that could not be effected at −78 °C but proceeded smoothly at rt. But, kinetic hindrance may usually also be overcome by employing a stronger base instead of increasing the temperature. However, LDA, a stronger base than LiHMDS, did not only fail to accomplish the desired enolate formation of **9d** it also led to the decomposition of the starting compound **9d** at −78 °C as well as at higher temperature such as 0 °C. As known from literature[9] or from Table 2, LDA is usually a strong enough base for the deprotonation of ketones at low temperature (like −78 °C). The failure of LDA in the present case might be attributed to the position of the equilibrium between the different conformers of **9d** and the kinetics of their equilibration. In the major conformer of **9d**, the substituents at the 2- and 3-position adopt each an pseudo axial orientation due to the strong $A^{(1,3)}$ strain arising from the benzamide moiety R^1 as discussed above (Scheme 5). Accordingly, the proton at the 3-position of the major conformer is in an equatorial position, e.g., roughly in plane with the carbonyl function, and is therefore expected to show a low kinetic acidity. The equilibration between the major conformer and the minor conformer, having both hydrogen atoms in a pseudo axial position and therefore being more susceptible to deprotonation, will proceed slowly at low temperatures as well. Depending on the substituents, the equilibration between the conformers may be much slower than the deprotonation reaction of the minor conformer. As a consequence, the minor conformer of **9d**, i.e., the conformer more reactive toward deprotonation reactions, is lacking. In the case of **9d**, LDA seems not to be appropriate to deprotonate the major conformer in the 3-position as desired, but instead, since the minor conformer is almost absent from the reaction mixture, initiates side reactions leading to the decomposition of **9d**. In the case of **9a**, with only methyl groups in 2- and 3-position of the dihydropyridone ring, the strain between the substituents will be lower and the kinetics of the aforementioned equilibration will therefore be faster. According to the successful transformation of **9a** to its enolate by LDA (see Table 2) the equilibration between the conformers seems to be fast enough in this case for the deprotonation to take place at a sufficient rate to avoid the side reactions observed with **9d**. But still, the kinetics of the equilibration of the conformers of **9a** are also of importance in this case since the velocity of the addition of the **9a** to LDA proved to be crucial to obtain good yields of **10a**, as mentioned above.

It is worth noting that the protonation of the enolates of **9a** and **9d** with either hydrochloric acid or ethyl salicylate resulted in a high cis-stereoselectivity (Table 3). It is known from the diastereoselective epimerization of *trans*-2,3-disubstituted cyclic ketones that the proton source has a crucial influence on the diastereoselectivity of epimerization reactions. Particularly, if the substituent at the 3-position of the keto group is small and, as consequence, the substrate control is low. Then, specific reagents for protonation, like ethyl salicylate, are required to gain high cis-stereoselectivity.[6] Interestingly, for the epimerization reactions of the dihydropyridones **9** no substantial influence of the proton sources on the diastereoselectivity was observed.

As precursors for our synthesis of β-amino acids, the *N*-unprotected dihydropyridones **12** and **13** were required (Table 4). Therefore, the *N*-benzoyl group present in **9** and **10** had to be removed. This transformation had to be performed under carefully controlled conditions to avoid epimerization of the stereocenter in the α-position of the carbonyl group. At first, according to standard procedures for such cleavage reactions, **9a** was treated with 3.5 equiv of NaOMe at rt for 3.5 h.[7a,b,10] This procedure, however, yielded a mixture of **12a** and its diastereomer **13a**. As the methanolysis of **9a** turned out to be distinctly faster than the epimerization reaction only catalytic amounts of NaOMe were employed in further experiments. Additionally, the reaction temperature was lowered to 0 °C, and the reaction was immediately stopped when TLC indicated completion of the conversion. Under these modified reaction conditions no epimerization occurred and the final product could be obtained in a high yield (94%, Table 4, entry 1). These reaction conditions also worked well for all other derivatives **9** and **10**, providing the dihydropyridones **12b–d** and **13a** and **13b** in diastereomeric pure form (^{1}H NMR) and in almost quantitative yields (94–98%, Table 4, entries 2–6).

Table 4
Synthesis of *N*-unprotected dihydropyridones **12** and **13**



9 **12**

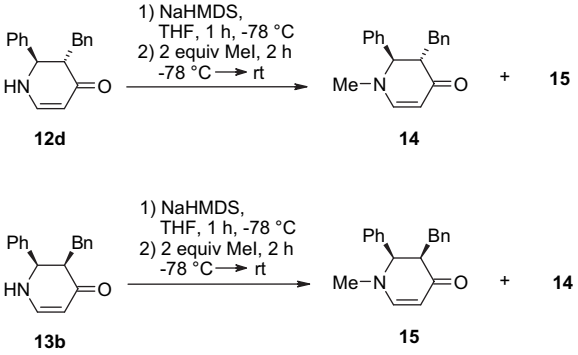
10 **13**

Entry	Educt	R^1	R^2	NaOMe (equiv)	*t* (min)	Product	
							Yield (%)
1	**9a**	Me	Me	0.3	30	**12a**	94
2	**9b**	Me	Bn	0.5	35	**12b**	98
3	**9c**	Ph	Me	0.5	40	**12c**	95
4	**9d**	Ph	Bn	0.5	70	**12d**	95
5	**10a**	Me	Me	0.3	45	**13a**	96
6	**10b**	Ph	Bn	0.5	75	**13b**	95

The relative configurations of **9**, **10**, **12**, and **13** were determined by their ^{1}H NMR spectra. As mentioned above it is a general phenomenon that substituents in the 2-position of 2-substituted *N*-acyl-2,3-dihydropyridones adopt an axial orientation which is due to the $A^{(1,3)}$ strain arising from the *N*-acyl group. As a consequence, the J_{H2-3} coupling constants observed for hydrogen atoms in the 2- and 3-positions of *trans*-2,3-disubstituted dihydropyridones adopting an equatorial orientation are small (<1.2 Hz).[11] The J_{H2-3} coupling constants found for **9a–d** were between 0.0 and 1.3 Hz providing clear evidence that these compounds possess trans-configuration. For compounds **10a** and **10b** as epimers of **9a** and **9d**, respectively, significantly larger J_{H2-3} coupling constants (5.6 Hz) were observed, which is in accord with published data, confirming the cis-configuration of these compounds.[12] In the case of the *N*-unprotected *trans*-2,3-disubstituted dihydropyridones **12**, freed from the *N*-acyl group and from the $A^{(1,3)}$ strain, the J_{H2-3} coupling constants increased as expected to a significant extent. The dihydropyridones **12a–c** showed J_{H2-3} coupling constants between 11.0 and 13.7 Hz, typical values for trans-substituted compounds.[13] The J_{H2-3} coupling constant of **12d** was somewhat lower (6.1 Hz), which is likely to be the result of a ring distortion due to sterical interactions as two large substituents in 2- and 3-position are present in this case. Finally, **13a–b** showed J_{H2-3} coupling constants between 4.5 and 5.4 Hz, which are typical values for cis-substituted compounds.[13] The configurations assigned by ^{1}H NMR spectroscopy were further confirmed by the structure of the β-amino acids **6** and **7**, which were obtained from **12** and **13** in the subsequent transformation reactions (see below, Table 6), which are well known in literature.[14–17]

The transformation of dihydropyridones into β-amino acids had already been applied successfully to compounds **2** being methylated at the nitrogen atom (Scheme 1).[4] Therefore, it was interesting to include the higher substituted *N*-methyl derivatives **14** or **15** in this study as well. For the synthesis of **14** and **15**, by N-methylation, compounds **12d** and **13b** were treated with a slight excess of NaHMDS at −78 °C and subsequently with methyl iodide following standard reaction conditions.[15] At −78 °C no reaction occurred, however, in additional experiments the reaction mixtures, with **12d** and **13b**, respectively, were therefore allowed to warm to rt after methyl iodide had been added (Table 5, entries 1 and 3). A product was then formed, but it was a mixture of the diastereomers **14** and **15**, which most astonishingly, contained the trans-diastereomer **14** as the clearly predominating species in both cases (Table 5, entries 1 and 3).

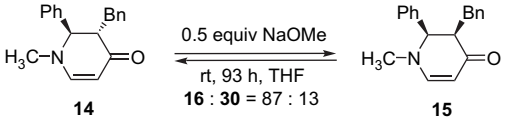
Table 5
Synthesis of **14** and **15** via N-methylation of **12d** and **13b**



Entry	Educt	NaHMDS (equiv)	Product	
			Yield[b] (%)	**14**/**15**[a]
1	**12d**	1.15	92	93:7
2	**12d**	0.85	80[c]	>99:1
3	**13b**	1.15	88	82:18
4	**13b**	0.85	81[d]	5:95

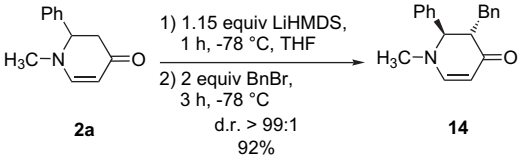
[a] Assigned from ^{1}H NMR spectra.
[b] The yield refers to both diastereomers, if a mixture of diastereomers was obtained.
[c] Starting material **12d** (13%) was reisolated.
[d] Starting material **13b** (12%) was reisolated.

As an excess of NaHMDS (1.15 equiv) had been applied in this reaction it was assumed that the base that had remained after the N-methylation had effected the isomerization. In a further experiment, **12d** was therefore treated with only 0.85 equiv of NaHMDS while retaining all other conditions (treatment with NaHMDS at −78 °C followed by MeI and warming to rt, Table 5, entry 2). This set up yielded the methylated trans-substituted diastereomer **14** in diastereomeric pure form (^{1}H NMR). Using the same method, the 2,3-*cis*-disubstituted compound **13b** could be transformed without a substantial loss of diastereomeric purity to **15** (**14**/**15**=5:95, Table 5, entry 4). To determine whether the 82:18 mixture of **14** and **15** that had been obtained after treatment of **13b** with 1.15 equiv of NaHMDS followed by methyl iodide (Table 5, entry 3), possibly reflects the thermodynamic equilibrium an additional experiment was performed. Compound **14** was treated with 0.5 equiv of NaOMe in THF at rt. After 25 h, the ratio between **14** and **15** was 89:11 and remained almost unchanged after 93 h (87:13, Scheme 6). Therefore, the result observed in the aforementioned N-alkylation experiment (82:18) can be assumed to approximately reflect the thermodynamic equilibrium.



Scheme 6.

2,3-Substituted *N*-methyldihydropyridones are even better accessible via the corresponding 2-substituted *N*-methyl derivative, e.g., **2a**,[4] by introducing the 3-subtituent at the end of the synthetic sequence as exemplified by the preparation of **14** (Scheme 7). Deprotonation of **2a**[4] with a slight excess of LiHMDS at −78 °C, similar to the procedures described for the benzylation of **8** (Table 1), followed by treatment with benzyl bromide (3 h at −78 °C) provided **15** in diastereomeric pure form and in a very high yield (92%).

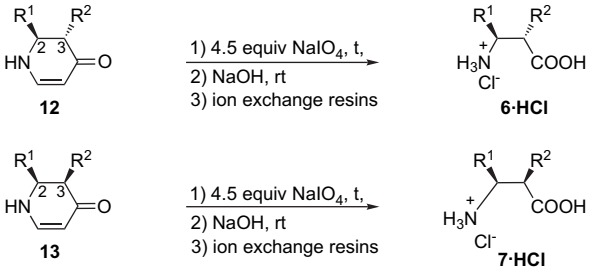


Scheme 7.

For the final step of the proposed β-amino acid synthesis, the dihydropyridones **12–14** described above were subjected to an oxidative ring cleavage procedure based on the use of sodium periodate following our recently published reaction conditions for this type of transformation[4] (Table 6). Accordingly, aqueous solutions of the respective compound, **12** and **13**, were treated first with sodium periodate and subsequently with sodium hydroxide at rt. Purification by anion and subsequently by cation exchange chromatography provided the amino acids **6a–c**·HCl and **7a**·HCl in the form of their hydrochlorides in good to quantitative yields (Table 6, entries 1–3 and 5). The ring cleavage reactions proceeded without any epimerization reaction, thereby yielding the final compounds **6a–c**·HCl and **7a**·HCl in diastereomerically pure form.

However, the situation was completely different when **12d** and **13b** were used as starting compounds. For these compounds, **12d** and **13b**, the reaction rates were distinctly slower, the isolated yields were lower, around 60%, and the obtained product showed

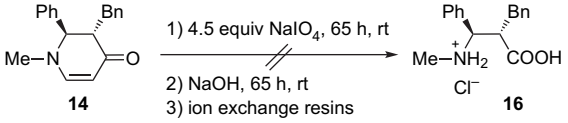
Table 6
Synthesis of β-amino acid derivatives **6**·HCl and **7**·HCl



entry	Educt	R^1	R^2	Reaction times		Product		
				t^a (h)	t^b (h)		Yield[c] (%)	dr[d]
1	**12a**	Me	Me	2	24	**6a**·HCl	94	>99:1
2	**12b**	Me	Bn	22	65	**6b**·HCl	83	>99:1
3	**12c**	Ph	Me	22	65	**6c**·HCl	81	>99:1
4	**12d**	Ph	Bn	65	65	**6d**·HCl	57	87:13
5	**13a**	Me	Me	2	24	**7a**·HCl	94	>99:1
6	**13b**	Ph	Bn	65	65	**7b**·HCl	61	95:5

[a] For oxidation.
[b] For hydrolysis.
[c] The yield refers to both diastereomers, if a mixture of diastereomers was obtained.
[d] Determined via ^{1}H NMR spectra.

some epimerisation (Table 6, entries 4 and 6). Interestingly, the *cis*-2,3-disubstituted dihydropyridone **13b** suffered significantly less epimerisation in this reaction sequence than its trans-diastereomer **12d**. Finally, the trisubstituted *N*-methyl derivative **14** completely failed to undergo the transformation reaction to give the amino acid **16**, which is probably due to the higher substitution of this compound and the steric demand associated with it (Scheme 8).



Scheme 8.

The results indicate the effect of the substitution pattern on the outcome of the transformation reaction of dihydropyridones into β-amino acids employing sodium periodate and sodium hydroxide. When sterically demanding groups are present, the reaction is slowed down and epimerization may occur. The latter is obviously not a result of a reaction mechanism for the conversion of the dihydropyridones into β-amino acids that requires an enol or enolate as intermediate. Otherwise epimerization would occur more extensively and, particularly, would also occur with the less hindered substrates **12a–c** and **13a** (Table 6, entries 1–3 and 5). Therefore, the epimerization in the case of the transformation of **12d** and **13b** (Table 6, entries 4 and 6) is likely to be a competing side reaction, which becomes significant only if the oxidation and saponification sequence is extremely slow.

3. Conclusion

In summary, a synthetic concept for the diastereodivergent synthesis of 2,3-disubstituted β-amino acids that uses dihydropyridone derivatives as a synthetic equivalent for β-amino acids was successfully implemented. In a key step of this new approach, 2-substituted dihydropyridone derivatives are transformed into *trans*-2,3-disubstituted derivatives by enolate alkylation and further into the corresponding cis isomers by stereoinversion. The latter was accomplished by kinetic reprotonation of the enolate formed from the trans-isomer obtained earlier. Importantly, for both steps, the enolate alkylation as well as the stereoinversion, high diastereoselectivities were observed. The oxidative ring opening to give the final β-amino acids could be efficiently effected employing sodium periodate as oxidant that had already proven useful in a related synthesis of 3-monosubstituted β-amino acids. A particular advantage of the method introduced here is that the substituents in the α- and β-position of the β-amino acid can be varied freely. It therefore represents a valuable addition to literature methods.[18] In the present case, the final β-amino acids were prepared as racemates only. But the synthetic concept could be easily turned into an asymmetric version using chiral *N*-acyliminium ion chemistry.

4. Experimental section

4.1. General methods

THF was freshly distilled from sodium benzophenone ketyl under nitrogen prior to use. Methanol was freshly distilled from magnesium prior to use. Solvents for extraction and column chromatography were distilled prior to use. Purchased chemical reagents were used without further purification. The dihydropyridones **2** and **8** were synthesized as described previously.[4] Merck silica gel (mesh 230–400) was used as stationary phase for column chromatography (cc). Melting points: mps (uncorrected) were determined using a Büchi 510 Melting Point apparatus. Elementary analysis: Elementaranalysator Rapid (Heraeus). IR spectroscopy: FT-IR Spectrometer 1600 and Paragon 1000 (Perkin Elmer), oily samples as film, solid samples as pellets for measurements. Mass spectroscopy: Mass Spectrometer 5989 A with 59980 B particle beam LC/MS interface (Hewlett Packard). NMR spectroscopy: NMR spectra were recorded on JNMR-GX (Jeol, 400 MHz and 500 MHz) with TMS as internal standard and integrated with the program of NMR-software Nuts (2D Version 5.097, Acorn NMR, 1995).

4.2. General procedure for the preparation of the *trans*-2,3-disubstituted dihydropyridones 9a–d and 14 (GP1)

A solution of the respective dihydropyridone **2b** or **8a–d** in THF (0.08–0.1 M) was cooled to −78 °C, and a solution of LiHMDS (1.15 equiv, 1 M in THF) was added dropwise. After stirring at the same temperature for 1 h, the alkylating reagent (3 equiv) was added, and the reaction further treated as given. After quenching with saturated brine, the mixture was extracted with EtOAc (3×). The extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by cc to give the respective dihydropyridone.

4.3. General procedure for the preparation of the *N-H*-2,3-disubstituted dihydropyridones 12a–d and 13a–b (GP2)

A solution of NaOMe (0.3–0.5 equiv) in MeOH (0.16–0.35 M) was added dropwise to an ice cooled solution of the respective dihydropyridone **9a–d** or **10a** and **10b** in MeOH (0.16–0.36 M). The solution was stirred at 0 °C for the time given. The solution was neutralized with HCl (2 M) and concentrated in vacuo. The residue was dissolved in brine and extracted with EtOAc (7×). The extract was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by cc to give the respective dihydropyridone **12a–d** or **13a** and **13b**.

4.4. General procedure for the purification of the β-amino acid derivatives 6a–d·HCl and 7a,b·HCl (GP3)

The respective neutralized reaction mixture was adsorbed on an acidic ion exchange resin (Amberlite IR 120). The resin was washed

with distilled water until the washings were neutral and the free amino acid was eluted with aqueous NH_3 (20%). Following evaporation, the residue was adsorbed on a basic ion exchange resin (Amberlite IR 410). The resin was first washed with distilled water until the washings were neutral, and then eluted with HCl (2 M). Following evaporation, the respective amino acid hydrochloride **6a–d**·HCl or **7a–b**·HCl was obtained.

4.4.1. (2RS,3RS)-1-Benzoyl-2,3-dimethyl-2,3-dihydro-1H-pyridin-4-one (**9a**)

A solution of **8a**[4] (1.00 g, 4.65 mmol) in 60 mL THF was cooled to −78 °C and a solution of LiHMDS (5.35 mL, 5.35 mmol, 1 M in THF) was added dropwise. After stirring at the same temperature for 1 h, MeI (872 μL, 14.00 mmol) was added. The cooling bath was removed and the reaction mixture was allowed to warm to rt slowly; 2 h after removal of the cooling bath, the reaction mixture was quenched with saturated brine, and the aqueous phase was extracted with EtOAc (3×). The extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The residue contained **9a** with ds>99:1 (^{1}H NMR). Purification by column chromatography on silica gel (cc) (PE/EtOAc 1:1) yielded **9a** (970 mg, 91%, ds>99:1, ^{1}H NMR) as colorless solid: mp 108–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, J=7.4 Hz, 3H), 1.33 (d, J=6.8 Hz, 3H), 2.18 (qt, J=7.4, 1.3 Hz, 1H), 4.66 (qd, J=6.8, 1.3 Hz, 1H), 5.21 (dd, J=8.2, 1.3 Hz, 1H), 7.36 (d, J=8.2 Hz, 1H), 7.45–7.58 (m, 5H); IR (KBr) 2922, 1657, 1636, 1341, 630 cm^{-1}; MS (EI) m/z (rel intensity) 229 (M^+, 14), 124 (8), 105 (100), 77 (34). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.29; H, 6.59; N, 6.15.

4.4.2. (2RS,3RS)-1-Benzoyl-3-benzyl-2-methyl-2,3-dihydro-1H-pyridin-4-one (**9b**)

(*A*) According to GP1 from **8a** (50 mg, 0.23 mmol) in 2.5 mL THF, LiHMDS (246 μL, 0.26 mmol, 1 M in THF), and BnI (150 mg, 0.69 mmol). The alkylation was performed by stirring the reaction mixture at −78 °C for 29 h. The raw product contained **9b** with ds>99:1 (^{1}H NMR). Purification by cc (PE/EtOAc 7:3) yielded **9b** (68 mg, 96%, ds>99:1, ^{1}H NMR) as colorless solid: mp 84–85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (d, J=6.7 Hz, 3H), 2.53 (ddt, J=10.5, 4.8, 1.2 Hz, 1H), 2.77 (dd, J=13.7, 10.5 Hz, 1H), 3.00 (dd, J=13.7, 4.8 Hz, 1H), 4.69 (q, J=6.7 Hz, 1H), 5.29 (dd, J=8.2, 1.2 Hz, 1H), 7.11–7.18 (m, 2H), 7.24 (tt, J=7.4, 1.6 Hz, 1H), 7.30 (tt, J=7.4, 1.6 Hz, 2H), 7.37–7.39 (m, 1H), 7.47–7.53 (m, 4H), 7.57 (m, 1H); IR (KBr) 3070, 3024, 2922, 1658, 1587, 1495, 1450, 1423, 1336, 1276, 1216, 1151, 704 cm^{-1}; MS (CI) m/z (rel intensity) 306 (MH^+, 100), 105 (7). Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.56; H, 6.22; N, 4.62. (*B*) A solution of **8a** (50 mg, 0.23 mmol) in 2.5 mL THF was cooled to −78 °C and a solution of LiHMDS (250 μL, 0.25 mmol, 1 M in THF) was added dropwise. After stirring at the same temperature for 1 h, benzyl bromide (82 μL, 0.69 mmol) was added. The cooling bath was removed and the reaction mixture was allowed to warm to rt slowly; 1.25 h after removal of the cooling bath, the reaction mixture was quenched with saturated brine. The aqueous phase was separated and extracted with EtOAc (3×). The extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The residue contained **9b** with ds>99:1 (^{1}H NMR). Purification by cc (PE/EtOAc 7:3) yielded **9b** (58 mg, 81%, ds>99:1, ^{1}H NMR) and **11** (9 mg, 10%), each as colorless solid. Compound **11**: mp 108–109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (d, J=6.7 Hz, 3H), 2.88 (d, J=15.4 Hz, 1H), 2.96 (d, J=14.1 Hz, 1H), 3.09 (d, J=14.1 Hz, 1H), 3.25 (d, J=15.4 Hz, 1H), 4.99 (q, J=6.7 Hz, 1H), 5.36 (d, J=8.0 Hz, 1H), 7.04–7.10 (m, 2H), 7.20–7.37 (m, 11H), 7.43 (t, J=7.9 Hz, 2H), 7.52 (tt, J=7.5, 1.3 Hz, 1H); IR (KBr) 3060, 3028, 2929, 2851, 1667, 1597, 1494, 1450, 1422, 1335, 1276, 1154, 699 cm^{-1}; MS (EI) m/z (rel intensity): 395 (M^+, 100), 380 (53), 366 (19), 343 (20), 329 (26), 319 (100); HRMS (EI) calcd for $C_{27}H_{25}NO_2$ (M^+) 395.1885, found 395.1874.

4.4.3. (2RS,3SR)-1-Benzoyl-3-methyl-2-phenyl-2,3-dihydro-1H-pyridin-4-one (**9c**)

According to GP1 from **8b** (2.10 g, 7.58 mmol) in 100 mL THF, LiHMDS (8.70 mL, 8.7 mmol, 1 M in THF), and MeI (1.39 mL, 22.75 mmol). After addition of MeI, the cooling bath was removed and the reaction mixture was warmed to rt slowly. The reaction mixture was quenched 2 h after removal of the cooling bath. The raw product contained **9c** with ds>99:1 (^{1}H NMR). Purification by cc (PE/EtOAc 6:4) yielded **9c** (1.98 g, 90%, ds>99:1, ^{1}H NMR) as colorless solid: mp 87–88 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (d, J=7.4 Hz, 3H), 2.94 (qt, J=7.4, 0.9 Hz, 1H), 5.28 (dd, J=8.3, 0.9 Hz, 1H), 5.71 (br s, 1H), 7.24–7.29 (m, 3H), 7.29–7.34 (m, 2H), 7.45–7.50 (m, 2H), 7.51–7.58 (m, 3H), 7.64 (d, J=8.3 Hz, 1H); IR (KBr) 3069, 2924, 2852, 1659, 1594, 1494, 1447, 1423, 1342, 1265, 1215, 1150 cm^{-1}; MS (EI) m/z (rel intensity) 291 (M^+, 23), 186 (22), 105 (100), 77 (33). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.30; H, 5.72; N, 4.78.

4.4.4. (2RS,3SR)-1-Benzoyl-3-benzyl-2-phenyl-2,3-dihydro-1H-pyridin-4-one (**9d**)

A solution of **8b**[4] (1.00 g, 3.60 mmol) in 36 mL THF was cooled to −78 °C and a solution of LiHMDS (4.10 mL, 4.10 mmol, 1 M in THF) was added dropwise. After stirring at the same temperature for 1 h, BnI (2.35 g, 10.8 mmol) was added. After stirring for 24 h at −78 °C, the reaction mixture was quenched with saturated brine and warmed to rt. The aqueous phase was separated and extracted with EtOAc (3×). The extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The residue contained **9d** with ds>99:1 (^{1}H NMR). Purification by cc (PE/EtOAc 7:3) yielded **9d** (1.22 g, 92%, ds>99:1, ^{1}H NMR) as colorless solid: mp 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (dd, J=13.3, 10.8 Hz, 1H), 3.07 (dd, J=10.8, 4.6 Hz, 1H), 3.16 (dd, J=13.3, 4.6 Hz, 1H), 5.37 (d, J=8.4 Hz, 1H), 5.66 (br s, 1H), 7.11 (d, J=7.0 Hz, 2H), 7.19–7.30 (m, 6H), 7.33 (t, J=7.2 Hz, 2H), 7.41–7.60 (m, 5H), 7.63–7.78 (m, 1H); IR (KBr) 3026, 2926, 1680, 1660, 1592, 1494, 1448, 1423, 1345, 1272, 1210, 1148, 699 cm^{-1}; MS (EI) m/z (rel intensity) 367 (M^+, 14), 276 (10), 262 (30), 193 (42), 115 (15), 105 (100), 77 (58). Anal. Calcd for $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.44; H, 5.69; N, 3.74.

4.4.5. (2RS,3SR)-1-Benzoyl-2,3-dimethyl-2,3-dihydro-1H-pyridin-4-one (**10a**)

(*A*) A solution of **9a** (400 mg, 1.74 mmol) in 14 mL THF was added to a solution of LiHMDS (3.50 mL, 3.50 mmol, 1 M in THF) for 2 h at rt. Following stirring for 1 h, this solution was added to a precooled solution (−78 °C) of ethyl salicylate (1.28 mL, 8.70 mmol, 0.73 M in THF). After stirring for 1 h at −78 °C, glacial acetic acid (400 μL, 6.90 mmol) was added and the reaction mixture was warmed up to rt. On addition of EtOAc, the solution was washed with saturated $NaHCO_3$ and brine. The aqueous layers were extracted with EtOAc (3×). The combined organic layers dried over Na_2SO_4 and evaporated under reduced pressure. The residue contained **10a** with ds>99:1 (^{1}H NMR). The residue was purified by cc (PE/EtOAc 1:1) to give **10a** (340 mg, 85%, ds>99:1, ^{1}H NMR) as colorless solid. (*B*) A solution of **9a** (46 mg, 0.20 mmol) in 1.6 mL THF was added to a solution of LiHMDS (400 μL, 0.40 mmol, 1 M in THF) for 2 h at rt. Following stirring for 1 h, the solution was cooled to −78 °C and quenched with HCl (1.0 mL, 2 M). The reaction mixture was warmed to rt slowly and washed with saturated $NaHCO_3$. The aqueous phase was extracted with EtOAc and dried over Na_2SO_4 as described under (*A*). The residue contained **10a** with ds>99:1 (^{1}H NMR). Purification by cc (PE/EtOAc 1:1) yielded **10a** (37 mg, 81%, ds>99:1, ^{1}H NMR) as colorless solid. (*C*) A solution of **9a** (50 mg, 0.22 mmol) in 1.5 mL THF was added to a solution of LDA [prepared from diisopropylamine (62 μL, 0.44 mmol) and *n*-BuLi (275 μL, 0.44 mmol, 1.6 M in hexane)] in 1 mL THF for 12 min at −78 °C. After stirring for 1 h at −78 °C, the reaction mixture was

added to a precooled solution (−78 °C) of ethyl salicylate (162 μL, 1.10 mmol) in 1.5 mL THF and finally quenched with glacial acetic acid (51 μL, (0.88 mmol) according to (*A*)). After work up as described under (*A*), the raw product contained **10a** with ds>99:1 (^{1}H NMR). After purification of the raw product by cc (PE/EtOAc 1:1) **10a** was obtained (42 mg, 82%, ds>99:1, ^{1}H NMR) as colorless solid. (*D*) A solution of **9a** (50 mg, 0.22 mmol) in 1.5 mL THF was added to a solution of LDA [prepared from diisopropylamine (62 μL, 0.44 mmol) and *n*-BuLi (275 μL, 0.44 mmol, 1.6 M in hexane)] in 1 mL THF for 12 min at −78 °C. After stirring for 1 h at −78 °C, the reaction mixture was quenched with HCl (1.0 mL, 2 M) according to (*B*). After work up as described under (*B*), the raw product contained **10a** with ds>99:1 (^{1}H NMR). After purification of the raw product by cc (PE/EtOAc 1:1) **10a** was obtained (43 mg, 83%, ds=99:1, ^{1}H NMR) as colorless solid: mp 111–112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (d, J=7.0 Hz, 3H), 1.20 (d, J=6.7 Hz, 3H), 2.98 (qd, J=7.0, 5.6 Hz, 1H), 4.83–4.87 (m, 1H), 5.25 (d, J=8.1 Hz, 1H), 7.33 (d, J=8.1 Hz, 1H), 7.44–7.64 (m, 5H); IR (KBr) 3076, 2968, 2931, 2873, 1661, 1592, 1448, 1427, 1349, 1307, 1257, 1212, 1156, 1080 cm^{-1}; MS (CI) m/z (rel intensity) 230 [MH^+] (100), 126 (14), 105 (56). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.42; H, 6.15; N, 6.15.

4.4.6. (2RS,3SR)-1-Benzoyl-3-benzyl-2-phenyl-2,3-dihydro-1H-pyridin-4-one (**10b**)

(*A*) A solution of **9d** (46 mg, 0.13 mmol) in 1.5 mL THF was added to a solution of LiHMDS (250 μL, 0.25 mmol, 1 M in THF) for 2 h at rt. Following stirring for 1 h, the solution was cooled to −78 °C and quenched with ethyl salicylate (92 μL, 0.60 mmol) in 1.0 mL THF. After stirring for 1 h at the same temperature, glacial acetic acid (29 μL, 0.50 mmol) was added and the reaction mixture was warmed up to rt. On addition of EtOAc, the solution was washed with saturated $NaHCO_3$ and brine. The aqueous layers were extracted with EtOAc (3×). The combined organic layers dried over Na_2SO_4 and evaporated under reduced pressure. The residue contained **10b** with ds 94:6 (^{1}H NMR). Purification by cc (PE/EtOAc=7:3) yielded **10b** (38 mg, 83%, ds=94:6, ^{1}H NMR) as colorless solid. (*B*) A solution of **9d** (46 mg, 0.13 mmol) in 1.5 mL THF was added to a solution of LiHMDS (250 μL, 0.25 mmol, 1 M in THF) for 2 h at rt. Following stirring for 1 h, the solution was cooled to −78 °C and quenched with HCl (1.0 mL, 2 M). The reaction mixture was warmed to rt slowly and washed with saturated $NaHCO_3$. The aqueous phase was extracted with EtOAc (3×). The combined organic layers dried over Na_2SO_4 and evaporated under reduced pressure. The raw product contained **10b** with ds>97:3 (^{1}H NMR). Purification by cc (PE/EtOAc 7:3) yielded **10b** (36 mg, 78%, ds=97:3, ^{1}H NMR) as colorless solid: mp 224–225 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (dd, J=14.3, 9.5 Hz, 1H), 3.47–3.59 (m, 2H), 5.44 (d, J=8.3 Hz, 1H), 5.74 (d, J=5.6 Hz, 1H), 7.06 (d, J=7.2 Hz, 2H), 7.17–7.45 (m, 12H), 7.45–7.58 (m, 2H); IR (KBr) 3060, 3027, 2924, 1663, 1596, 1493, 1446, 1422, 1329, 1225, 1147, 697 cm^{-1}; MS (EI) m/z (rel intensity) 367 (M^+, 21), 262 (64), 193 (79), 115 (24), 105 (100), 77 (85). Anal. Calcd for $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.57; H, 5.76; N, 3.74.

4.4.7. (2RS,3RS)-2,3-Dimethyl-2,3-dihydro-1H-pyridin-4-one (**12a**)

A solution of NaOMe in MeOH prepared by addition of Na (15 mg, 0.65 mmol) to 4 mL MeOH was added dropwise to an ice cooled solution of **9a** (500 mg, 2.18 mmol) in 6 mL MeOH. The solution was stirred at 0 °C for 30 min before it was neutralized with HCl (2 M) and concentrated in vacuo. The residue was dissolved in brine and extracted with EtOAc (7×). The extract was dried over Na_2SO_4 and evaporated under reduced pressure. The residue containing **12a** with ds>99:1 (^{1}H NMR) was purified by cc (CH_2Cl_2/MeOH 9.5:0.5) to give **12a** (256 mg, 94%, ds>99:1, ^{1}H NMR) as colorless solid: mp 68–69 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, J=7.0 Hz, 3H), 1.30 (d, J=6.5 Hz, 3H), 2.17 (dq, J=11.0, 7.0 Hz, 1H), 3.38 (dqd, J=11.0, 6.5, 1.5 Hz, 1H), 4.98 (d, J=7.5 Hz, 1H), 5.04 (br s, 1H), 7.10 (t, J=7.5 Hz, 1H); IR (KBr) 3427, 2923, 2854, 1636, 1023 cm^{-1}; MS (EI) m/z (rel intensity) 125 (M^+, 79), 110 (25), 96 (18), 82 (28), 70 (100). Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 66.96; H, 8.87; N, 11.11.

4.4.8. (2RS,3RS)-3-Benzyl-2-methyl-2,3-dihydro-1H-pyridin-4-one (**12b**)

According to GP2 from **9b** (800 mg, 2.62 mmol) in 17 mL MeOH, Na (32 mg, 1.39 mmol) in 4 mL MeOH, reaction time 35 min. The raw product contained **12b** with ds>99:1 (^{1}H NMR). Purification by cc (CH_2Cl_2/MeOH 9.5:0.5) yielded **12b** (517 mg, 98%, ds>99:1, ^{1}H NMR) as colorless solid: mp 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, J=6.7 Hz, 3H), 2.34–2.37 (m, 1H), 2.79 (dd, J=13.8, 10.4 Hz, 1H), 3.00 (dd, J=13.8, 4.5 Hz, 1H), 3.40–3.45 (m, 1H), 4.97 (br s, 1H), 5.01 (d, J=7.4 Hz, 1H), 7.07 (t, J=7.4 Hz, 1H), 7.18–7.24 (m, 3H), 7.26–7.31 (m, 2H); IR (KBr) 3253, 3020, 2967, 2922, 1616, 1573, 1512, 1443, 1401, 1241 cm^{-1}; MS (EI, 70 eV); m/z (rel intensity): 201 (M^+, 88), 186 (21), 158 (13), 124 (31), 117 (100), 110 (59), 91 (69). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.28; H, 7.50; N, 6.93.

4.4.9. (2RS,3SR)-3-Methyl-2-phenyl-2,3-dihydro-1H-pyridin-4-one (**12c**)

According to GP2 from **9c** (1.00 g, 3.43 mmol) in 21 mL MeOH, Na (40 mg, 1.74 mmol) in 5 mL MeOH, reaction time 40 min. The raw product contained **12c** with ds>99:1 (^{1}H NMR). Purification by cc (CH_2Cl_2/MeOH 9.5:0.5) yielded **12c** (610 mg, 95%, ds>99:1, ^{1}H NMR) as colorless solid: mp 174–175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, J=6.9 Hz, 3H), 2.63–2.70 (m, 1H), 4.29 (d, J=13.7 Hz, 1H), 4.96 (br s, 1H), 5.12 (dd, J=7.3, 1.2 Hz, 1H), 7.21 (t, J=7.3 Hz, 1H), 7.33–7.41 (m, 5H); IR (KBr) 3303, 3060, 3032, 2967, 2926, 1558, 1231, 1183, 768, 700 cm^{-1}; MS (EI) m/z (rel intensity) 187 (M^+, 66), 118 (100), 117 (87), 91 (21). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.76; H, 6.95; N, 7.55.

4.4.10. (2RS,3SR)-3-Benzyl-2-phenyl-2,3-dihydro-1H-pyridin-4-one (**12d**)

According to GP2 from **9d** (400 mg, 1.09 mmol) in 7 mL MeOH, Na (13 mg, 0.56 mmol) in 3 mL MeOH, reaction time 70 min. The raw product contained **12d** with ds>99:1 (^{1}H NMR). Purification by cc (CH_2Cl_2/MeOH 9.5:0.5) yielded **12d** (274 mg, 95%, ds>99:1, ^{1}H NMR) as colorless solid: mp 129–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.85–2.93 (m, 2H), 2.97–3.03 (m, 1H), 4.38 (dd, J=6.1, 2.4 Hz, 1H), 5.10 (d, J=7.5 Hz, 1H), 5.22 (br s, 1H), 7.07–7.32 (m, 11H); IR (KBr) 3222, 3025, 2922, 1621, 1564, 1521, 1211, 1174, 698 cm^{-1}; MS (EI) m/z (rel intensity) 263 (M^+, 100), 193 (30), 172 (53), 115 (42), 106 (66), 91 (53), 77 (20). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.88; H, 6.52; N, 5.28.

4.4.11. (2RS,3SR)-2,3-Dimethyl-2,3-dihydro-1H-pyridin-4-one (**13a**)

According to GP2 from **10a** (230 mg, 1.00 mmol) in 6.5 mL MeOH, Na (7 mg, 0.30 mmol) in 1.6 mL MeOH, reaction time 45 min. The raw product contained **13a** with ds>99:1 (^{1}H NMR). Purification by cc (CH_2Cl_2/MeOH 9.5:0.5) yielded **13a** (120 mg, 96%, ds>99:1, ^{1}H NMR) as colorless solid: mp 74–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, J=7.3 Hz, 3H), 1.20 (d, J=6.6 Hz, 3H), 2.22 (qd, J=7.3, 4.5 Hz, 1H), 3.74–3.80 (m, 1H), 4.91 (d, J=7.3 Hz, 1H), 5.26 (br s, 1H), 7.10 (t, J=7.3 Hz, 1H); IR (KBr) 3278, 2925, 1618, 1238 cm^{-1}; MS (CI) m/z (rel intensity) 126 (MH^+, 100). Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.16; H, 8.87; N, 11.13.

4.4.12. (2RS,3RS)-3-Benzyl-2-phenyl-2,3-dihydro-1H-pyridin-4-one (**13b**)

According to GP2 from **10b** (200 mg, 0.54 mmol) in 3.5 mL MeOH, Na (6 mg, 0.26 mmol) in 1.5 mL MeOH, reaction time 75 min. The

raw product contained **13b** with ds>99:1 (^{1}H NMR). Purification by cc (CH_2Cl_2/MeOH 9.5:0.5) yielded **13b** (135 mg, 95%, ds>99:1, ^{1}H NMR) as colorless solid: mp 141–142 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (dd, J=14.2, 7.1 Hz, 1H), 2.92–2.99 (m, 1H), 3.08 (dd, J=14.2, 7.6 Hz, 1H), 4.77 (dd, J=5.4, 1.4 Hz, 1H), 5.05 (br s, 1H), 5.12 (d, J=7.4 Hz, 1H), 6.91–6.95 (m, 2H), 7.13 (tt, J=7.3, 1.3 Hz, 1H), 7.15–7.19 (m, 2H), 7.19–7.24 (m, 1H), 7.31–7.40 (m, 5H); IR (KBr) 3190, 3021, 2926, 1623, 1565, 1214, 699 cm^{-1}; MS (EI) m/z (rel intensity) 263 (M^+, 100), 193 (33), 179 (24), 172 (52), 158 (16), 144 (12), 130 (20), 115 (43), 106 (77), 91 (65), 77 (21). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.84; H, 6.43; N, 5.29.

4.4.13. (2RS,3SR)-3-Benzyl-1-methyl-2-phenyl-2,3-dihydro-1H-pyridin-4-one (**14**)

(*A*) NaHMDS (48 μL, 0.10 mmol, 2 M in THF) was added to a solution of **12d** (30 mg, 0.11 mmol) in 1.5 mL THF at −78 °C. Following stirring for 1 h, methyl iodide (14 μL, 0.33 mmol) was added, the cooling bath was removed, and the mixture was stirred for 2 h. The reaction mixture was quenched with 2 M NaOH. The aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue contained **14** and **12d** each with ds>99:1 (^{1}H NMR). Purification by cc (CH_2Cl_2/MeOH 9.5:0.5) yielded **14** (25 mg, 80%, ds>99:1, ^{1}H NMR) and **12d** (4 mg, 13%, ds>99:1, ^{1}H NMR) as colorless solid. (*B*) According to GP1 from **2b** (300 mg, 1.60 mmol) in 21 mL THF, LiHMDS (1.85 mL, 1.85 mmol, 1 M in THF) and BnBr (580 μL, 4.80 mmol). The alkylation was performed by stirring the reaction mixture at −78 °C for 2 h. The raw product contained **14** with ds>99:1 (^{1}H NMR). Purification by cc (CH_2Cl_2/MeOH, 9.5:0.5) yielded **14** (408 mg, 92%, ds>99:1, ^{1}H NMR) as colorless solid: mp 77–78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67 (dddd, J=11.3, 4.2, 1.9,[†] 0.9 Hz, 1H), 2.77 (dd, J=13.6, 11.3 Hz, 1H), 2.99 (s, 3H), 3.15 (dd, J=13.6, 4.2 Hz, 1H), 4.06 (d, J=1.9 Hz,[†] 1H), 4.97 (dd, J=7.5, 0.9 Hz, 1H), 6.96–7.00 (m, 2H), 7.13 (dd, J=7.5 Hz, 1H), 7.18–7.29 (m, 6H), 7.35 (t, J=7.3 Hz, 2H); IR (KBr) 3028, 2949, 2905, 1641, 1594, 1490, 1448, 1422, 1344, 1173, 781, 750, 703 cm^{-1}; MS (EI) m/z (rel intensity) 277 (M^+, 100), 200 (14), 193 (43), 186 (36), 178 (20), 146 (25), 115 (49), 91 (60). Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 81.93; H, 7.20; N, 5.06.

4.4.14. (2RS,3RS)-3-Benzyl-1-methyl-2-phenyl-2,3-dihydro-1H-pyridin-4-on (**15**)

NaHMDS (39 μL, 0.08 mmol, 2 M in THF) was added to a solution of **13b** (25 mg, 0.09 mmol) in 1.5 mL THF at −78 °C. Following stirring for 1 h, methyl iodide (12 μl, 0.28 mmol) was added, the cooling bath was removed, and the mixture was stirred for 2 h. The reaction mixture was quenched with 2 M NaOH. The aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue contained **15** with ds>95:5 and **13b** with ds>99:1 (^{1}H NMR). Purification by cc (CH_2Cl_2/MeOH 9.5:0.5) yielded **15** (21 mg, 81%, ds=95:5, ^{1}H NMR) and **13b** (3 mg, 12%, ds>99:1, ^{1}H NMR) as colorless solid. Compound **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.07 (dd, J=14.7, 10.9 Hz, 1H), 2.84 (s, 3H), 3.49 (ddd, J=10.9, 7.6,[†] 3.8 Hz, 1H), 3.58 (dd, J=14.7, 3.8 Hz, 1H), 4.06 (d, J=7.6 Hz,[†] 1H), 5.00 (d, J=7.5 Hz, 1H), 6.90 (d, J=7.5 Hz, 1H), 7.00 (d, J=7.5 Hz, 2H), 7.19–7.36 (m, 8H).

4.4.15. Equilibration between (2RS,3SR)-3-benzyl-1-methyl-2-phenyl-2,3-dihydro-1H-pyridin-4-one (**14**) and (2RS,3RS)-3-benzyl-1-methyl-2-phenyl-2,3-dihydro-1H-pyridin-4-on (**15**)

A solution of MeOH (4 μL, 0.10 mmol) and NaHMDS (25 μL, 0.05 mmol, 2 M in THF) in 1 mL THF was added to a solution of **14** (30 mg, 0.10 mmol) in 1 mL THF at rt. After stirring for 93 h, the reaction mixture was quenched with 2 M NaOH. The aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue contained **14** and **15** in a ratio of 87:13 (^{1}H NMR).

4.4.16. (2RS,3RS)-3-Amino-2-methylbutyric acid hydrochloride (**6a**·HCl)

$NaIO_4$ (376 mg, 1.76 mmol) was added to a solution of **12a** (50 mg, 0.38 mmol) in H_2O (3.0 mL) at rt and after stirring for 2 h, NaOH (3.0 mL, 15.7 M) was added. After stirring for 24 h at rt, the reaction mixture was neutralized with HCl (6 M) and adsorbed on an acidic ion exchange resin (Amberlite IR 120). The resin was washed with distilled water until the washings were neutral and the free amino acid was eluted with aqueous NH_3 (20%). Following evaporation, the residue was adsorbed on a basic ion exchange resin (Amberlite IR 410). The resin was first washed with distilled water until the washings were neutral, and then eluted with HCl (2 M). Following evaporation, the amino acid hydrochloride **6a**·HCl (55 mg, 94%, ds>99:1, ^{1}H NMR) was obtained as colorless solid: mp 207–209 °C (lit. mp[16] 221–222 °C); ^{1}H NMR (400 MHz, D_2O) δ 1.09 (d, J=7.2 Hz, 3H), 1.12 (d, J=6.6 Hz, 3H), 2.59–2.63 (m, 1H), 3.43–3.46 (m, 1H); IR (KBr) 1655, 1618, 1406, 1338 cm^{-1}; MS (CI) m/z (rel intensity) 118 ($M-Cl^-$, 100). The analytical data are in accord with published data.[16]

4.4.17. (2RS,3RS)-3-Amino-2-benzylbutyric acid hydrochloride (**6b**·HCl)

$NaIO_4$ (213 mg, 1.00 mmol) was added to a solution of **12b** (40 mg, 0.19 mmol) in H_2O (1.4 mL) at rt and after stirring for 22 h, aqueous NaOH (0.65 mL, 12.6 M) was added. After stirring for 65 h at rt, the reaction mixture was neutralized with HCl (6 M) and purified according to GP3 yielding the amino acid hydrochloride **6b**·HCl (35 mg, 83%, ds>99:1, ^{1}H NMR) as colorless solid. The amino acid hydrochloride **6b**·HCl was transformed to the corresponding free amino acid using the acidic ion exchange resin Amberlite IR 120 for comparison with the published analytical data of the free amino acid of **6b**·HCl: mp 219–222 °C (lit. mp[16] 218–219 °C); ^{1}H NMR (500 MHz, D_2O) δ 1.39 (d, J=6.8 Hz, 3H), 2.70 (dt, J=9.5, 5.6 Hz, 1H), 2.93 (dd, J=13.6, 9.5 Hz, 1H), 2.99 (dd, J=13.6, 5.6 Hz, 1H), 3.48–3.52 (m, 1H), 7.28–7.33 (m, 3H), 7.36–7.41 (m, 2H); IR (KBr) 1650, 1632, 1432 cm^{-1}; MS (CI) m/z (rel intensity) 194 (MH^+, 100). The analytical data are in accord with published data.[16]

4.4.18. (2RS,3SR)-3-Amino-2-methyl-3-phenylpropionic acid hydrochloride (**6c**·HCl)

$NaIO_4$ (214 mg, 1.00 mmol) was added to a solution of **12c** (40 mg, 0.21 mmol) in 1.4 mL H_2O and 0.7 mL THF at rt and after stirring for 22 h, aqueous NaOH (0.90 mL, 10.0 M) was added. After stirring for 65 h at rt, the reaction mixture was neutralized with HCl (6 M) and purified according to GP3 yielding the amino acid hydrochloride **6c**·HCl (31 mg, 81%, ds>99:1, ^{1}H NMR): mp 242–244 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 1.04 (d, J=7.1 Hz, 3H), 3.08 (dq, J=9.9, 7.1 Hz, 1H), 4.24 (d, J=9.9 Hz, 1H), 7.41–7.53 (m, 5H); IR (KBr) 1721, 1595, 1514, 1204 cm^{-1}; MS (CI) m/z (rel intensity) 180 ($M-Cl^-$, 100), 163 (92), 107 (23). The NMR and IR data are in accord with data published for the respective enantiomeric pure product.[14]

4.4.19. (2RS,3SR)-3-Amino-2-benzyl-3-phenylpropionic acid hydrochloride (**6d**·HCl)

$NaIO_4$ (223 mg, 1.08 mmol) was added to a solution of **12d** (60 mg, 0.22 mmol) in 1.5 mL H_2O and 1.5 mL THF at rt and after stirring for 65 h, aqueous NaOH (0.65 mL, 16.9 M) was added. After stirring for 65 h at rt, the reaction mixture was neutralized with HCl (6 M) and purified with a acidic ion exchange resin (Amberlite IR

[†] Compound should adopt a bisaxial conformation due to the $A^{(1,2)}$ strain between substituents in 1- and 2-position.

120) as described in GP3. The residue of the eluate with aqueous NH_3 (20%) was dissolved in HCl (1 M) and washed with EtOAc (5×). The aqueous phase was neutralized and further purified on Amberlite IR 410 as described in GP3. The amino acid hydrochlorides **6d**·HCl and **7a**·HCl were obtained in a ratio of 87:13 (^{1}H NMR) (31 mg, 57% referring to **6d**·HCl and **7a**·HCl) as a colorless solid (31 mg, 57%, ds=87:13, ^{1}H NMR): mp 224–226 °C (lit.[19] mp 227 °C); ^{1}H NMR (400 MHz, D_2O) δ 2.56 (dd, J=13.9, 9.3 Hz, 1H), 2.62 (dd, J=13.9, 4.8 Hz, 1H), 3.17–3,22 (m, 1H), 4.37 (d, J=9.7 Hz, 1H), 6.88–6.91 (m, 2H), 7.03–7.12 (m, 3H), 7.25–7.36 (m, 5H); IR (KBr) 1755, 1618, 1512 cm^{-1}; MS (CI) m/z (rel intensity) 256 (M−Cl$^-$, 75), 161 (81), 106 (100). The NMR and IR data are in accord with data published for the respective enantiomeric pure product.[14]

4.4.20. (2RS,3SR)-3-Amino-2-methylbutyric acid hydrochloride (*7a*·HCl)

$NaIO_4$ (1.18 g, 5.52 mmol) was added to a solution of **13a** (150 mg, 1.20 mmol) in 9.1 mL H_2O at rt and after stirring for 2 h, aqueous NaOH (1.15 mL, 18.5 M) was added. After stirring for 24 h at rt, the reaction mixture was neutralized with HCl (6 M) and purified according to GP3 yielding the amino acid hydrochloride **7a**·HCl (173 mg, 94%, ds>99:1, ^{1}H NMR). The amino acid hydrochloride **7a**·HCl was transformed to the corresponding free amino acid using the acidic ion exchange resin Amberlite IR 120 for comparison purpose with the published analytical data of the free amino acid of **7a**·HCl: mp 226–228 °C; ^{1}H NMR (500 MHz, D_2O) δ 1.19 (d, J=7.3 Hz, 3H), 1.29–132 (m, J=6.7 Hz, 3H), 2.50–2.52 (m, 1H), 3.46–3.49 (m, 1H); IR (KBr) 1723, 1633, 1470, 1206 cm^{-1}; MS (CI) m/z (rel intensity) 118 (MH$^+$, 100). The NMR and IR data are in accord with data published for the respective enantiomeric pure product.[20]

4.4.21. (2RS,3RS)-3-Amino-2-benzyl-3-phenylpropionic acid hydrochloride (*7b*·HCl)

$NaIO_4$ (223 mg, 1.08 mmol) was added to a solution of **13b** (60 mg, 0.22 mmol) in 1.5 mL H_2O and 1.5 mL THF at rt. After stirring for 65 h, NaOH (0.65 mL, 16.9 M) was added and the reaction mixture was subsequently stirred for another 65 h at rt. The reaction mixture was neutralized with HCl (6 M) and adsorbed on an acidic ion exchange resin (Amberlite IR 120). The resin was washed with distilled water until the washings were neutral and the free amino acid was eluted with aqueous NH_3 (20%). The eluate was concentrated, dissolved in HCl (1 M), and washed with EtOAc (5×). The aqueous solution was neutralized and adsorbed on a basic ion exchange resin (Amberlite IR 410). The resin was first washed with distilled water until the washings were neutral, and then eluted with HCl (2 M). Following evaporation, the amino acid hydrochlorides **7b**·HCl and **6a**·HCl were obtained in a ratio of 95:5 (^{1}H NMR) (31 mg, 61% referring to **7b**·HCl and **6a**·HCl) as colorless solid (31 mg, 61%, ds=95:5, ^{1}H NMR): mp 230–233 °C (lit. mp[21] 236–237 °C); ^{1}H NMR (500 MHz, D_2O) δ 2.77 (dd, J=13.6, 10.7 Hz, 1H), 2.92 (dd, J=13.6, 5.2 Hz, 1H), 3.24 (ddd, J=10.7, 8.6, 5.2 Hz, 1H), 4.42 (d, J=8.6 Hz, 1H), 7.07–7.31 (m, 10H); IR (KBr) 1720, 1620, 1525 cm^{-1}; MS (CI) m/z (rel intensity) 256 (M−Cl$^-$, 84), 161 (60), 106 (100). The NMR and IR data are in accord with data published for the respective enantiomeric pure product.[17]

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References and notes

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