Asymmetric Steering of the Mannich Reaction with Phthaloyl Amino Acids

Roland Müller,[b] Herbert Röttele,[b] Henning Henke,[c] and Herbert Waldmann*[a]

Abstract: Mannich-type reactions are powerful methods for the efficient synthesis of β-amino carbonyl compounds that are valuable intermediates for the construction of natural products, β-peptides, and peptidomimetics. For the efficient steric steering of Mannich reactions a method was developed that consists in the treatment of imines with *N*-protected amino acid chlorides to give *N*-acyliminiumion intermediates that are subsequently attacked with silylketene acetals. The reactions are run best at room temperature and in the absence of any Lewis acid. The highest stereoselectivity is observed if *N*,*N*-phthaloyl *tert*-leucine is employed as chiral auxiliary and if *N*-aryl,*C*-aryl Schiffs bases are used that carry two *ortho*-substituents in either aromatic ring. Under these conditions the Mannich adducts are formed in preparatively useful yields and with excellent stereoselectivity (diastereomer ratio in general $>99:1$). The chiral auxiliary group is readily removed by 1) cleavage of the phthaloyl imide via reduction with $NaBH_4$ and acid hydrolysis followed by 2) Edman degradation.

Keywords: amino acids · asymmetric synthesis · β-amino acids · chiral auxiliaries · Mannich reaction

Introduction

Numerous biologically active natural products embody the β-aminocarbonyl substructure and biological activity often is associated with the absolute configuration of this structural subunit.[1] For instance, the tumor-suppressing drug Taxol carries phenylisoserine as side chain, and the antitumor activity of the natural product is correlated with the correct absolute configuration of this β-amino acid.[2c,d] In addition, β-amino acids have recently gained increasing interest as building blocks for β-peptides, a class of novel and promising peptide analogues.[2a,b] Furthermore, enantiomerically pure β-aminocarbonyl compounds are valuable intermediates and reagents for the construction of natural products and analogues thereof. Due to this importance, the development of efficient methods for the synthesis of enantiomerically pure β-aminocarbonyl compounds is of great importance to organic synthesis.

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A particularly efficient transformation that can be employed to achieve this goal is the Mannich reaction. Consequently, the development of diastereo- and enantioselective Mannich reactions has been the focus of numerous research enterprises.[3] However, unlike the development of for example asymmetric aldol reactions, these investigations have met with only limited success. In general, in these transformations either a chiral nucleophile or electrophile was employed to steer the steric course of the reaction, or chirality was introduced by activation of an imine with a chiral Lewis acid. However, in an alternative variant of the Mannich reaction a Schiff base is activated by treatment with an acid chloride giving rise to an *N*-acyliminium intermediate which then is attacked by the nucleophile, for example a silylketene acetal.[4] Thus, the use of chiral acid chlorides in this transformation opens up alternative opportunities for the development of asymmetric Mannich-type reactions. We have recently shown that *N*-acyliminium intermediates generated in situ from *N*-protected amino acid chlorides and indolylethyl imines undergo highly stereoselective Pictet–Spengler reactions.[5] In this paper we report in full detail on the development of amino acid derived acid chlorides as efficient mediators of chirality in Mannich-type processes.[6]

Results

Treatment of Schiff bases with acid chlorides leads to rapid formation of α-chloroalkylamides, from which *N*-acyliminium ions are generated by means of Lewis acids.[7] Therefore, in a

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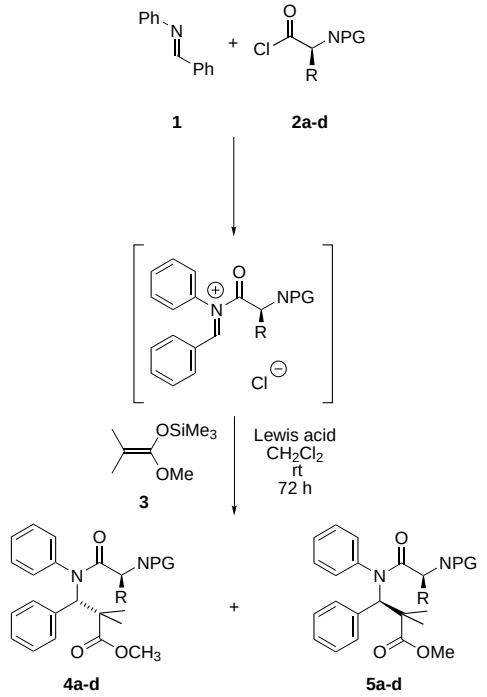
first series of experiments the influence of Lewis acids, the size of the amino acid side chain and the protecting group on the reaction between Schiffs base **1**, acid chlorides **2**, and silylketene acetal **3** were investigated (Scheme 1, Table 1). If



Scheme 1. Asymmetric Mannich reactions via *N*-acyliminium intermediates employing different *N*-protected amino acids as chiral auxiliaries.

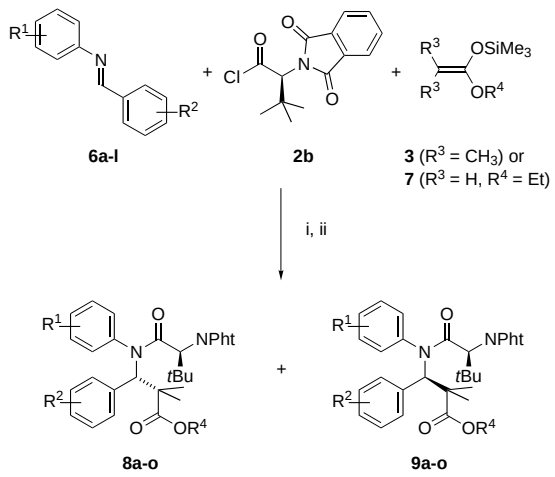
Table 1. Results of the Mannich reactions between imine **1**, *N*-protected amino acid chlorides **2** and silylketene acetal **3**.

Entry	**2**	R	PG[a]	*t* [h]	Yield [%]	*dr*[b]	**4/5**
1	**a**	*i*Pr	Pht	22	17[c]	90:10	**a**
2	**a**	*i*Pr	Pht	73	13[d]	90:10	**a**
3	**a**	*i*Pr	Pht	20	80	87:13	**a**
4	**b**	*t*Bu	Pht	72	54	93:7	**b**
5	**c**	$(CH_2)_3$	Z	72	69	53:47	**c**
6	**d**	*i*Pr	Fmoc	72	–	–	**d**

[a] PG = Protective group. [b] Determined by HPLC from the crude reaction mixture. [c] 1 equiv $BF_3 \cdot OEt_2$ was used as Lewis acid. [d] 0.05 equiv $BF_3 \cdot OEt_2$ were used as Lewis acid.

Lewis acids such as $SnCl_4$, $TiCl_4$, BCl_3, $ZnCl_2$, or $BF_3 \cdot OEt_2$ were employed and *N*,*N*-phthaloyl valine chloride was used, in the majority of the cases the desired β-amino acid esters **4** and **5** could not be detected. The products were formed in 13–17% with a diastereomer ratio of 90:10 only in the presence of $BF_3 \cdot OEt_2$ (Table 1, entries 1 and 2). In the absence of any Lewis acid, however, the β-aminocarbonyl compounds **4** and **5** were obtained in 80% yield and with a diastereomer ratio of 87:13 (Table 1, entry 3). Increasing the size of the amino acid side chain led to a significant enhancement of the stereoselectivity, but also to a decrease in yield (Table 1, entries 3 and 4). The use of proline resulted in decreased stereoselectivity and application of a different *N*-protecting group gave inferior results as well (Table 1, entries 5 and 6). Notably, the best results were obtained by running the reaction at room temperature, lowering the temperature led to a decrease in yield but not to an increase in stereoselectivity.

α-Chloroalkylamides and *N*-acyliminium ions are in equilibrium with each other. The position of the equilibrium and the reactivity of the iminium ions are strongly influenced by the substituents of the imine.[7] Therefore, the *N*- and the *C*-substituents of the Schiff bases were varied in a second series of experiments. If imines **6** with two aromatic substituents were treated with *N*,*N*-phthaloyl *tert*-leucine chloride (**2b**) and silylketene acetals **3** or **7** the desired Mannich adducts **8** and **9** were formed in moderate to high yield and with high to excellent diastereomer ratio in the majority of the cases (Scheme 2, Table 2). The highest yields were recorded if the



Scheme 2. Asymmetric steering of the Mannich reaction with *N*,*N*-phthaloyl *tert*-leucine as chiral auxiliary. i) CH_2Cl_2, rt, 72 h; ii) 10% aq. $NaHCO_3$.

Table 2. Results of the Mannich reactions employing imines **6**, *N*,*N*-phthaloyl *tert*-leucine chloride (**2b**) and silylketene acetals **3** and **7**.

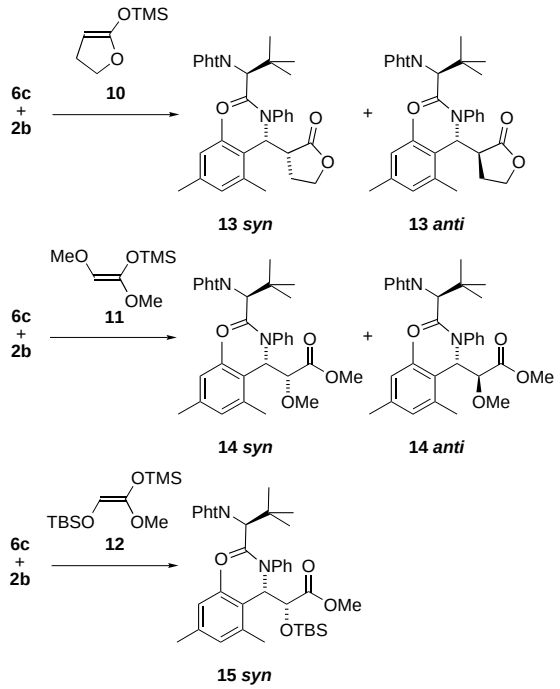
Entry	R^1	R^2	**6**	Nu	Yield [%]	*dr*[a]	**8/9**
1	H	3-NO_2	**a**	**3**	–	–	**a**
2	H	4-Cl	**b**	**3**	44	92:8	**b**
3	H	2,4,6-Me_3	**c**	**3**	46	> 99:1	**c**
4	H	4-NMe_2	**d**	**3**	81	91:9	**d**
5	H	4-OMe	**e**	**3**	84	91:9	**e**
6	4-NO_2	H	**f**	**3**	–	–	**f**
7	4-OMe	H	**g**	**3**	82	91:9	**g**
8	2-OMe-6-Me	H	**h**	**3**	50	> 99:1	**h**
9	H	2-OMe	**i**	**3**	91	92:8	**i**
10	2-OMe-6-Me	4-Cl	**j**	**3**	13	> 99:1	**j**
11	2-OMe-6-Me	2-OMe	**k**	**3**	59	> 99:1	**k**
12	2-OMe-6-Me	4-OMe	**l**	**3**	75	> 99:1	**l**
13	2-OMe-6-Me	H	**h**	**7**	34	97:3	**m**
14	2-OMe-6-Me	4-OMe	**l**	**7**	51	> 99:1	**n**
15	2-OMe-6-Me	2-OMe	**k**	**7**	68	> 99:1	**o**

[a] Determined by HPLC from the crude reaction mixture.

aromatic rings carried electron-donating substituents. If either one of the aromatic ring was nitro-substitued the Mannich products were not formed (Table 2, entries 1 and 6). If the aromatic rings carried only one substituent either in the *ortho*- or the *para*-position, diastereomer ratios of 91:9 → 92:8 were determined (Table 2, entries 2, 4, 5, 7, and 9). If, however, either one of the two aryl rings carried two *ortho*-substituents

the isomer ratio was >99:1 (Table 2, entries 3, 8, 10–12, 14, and 15; for entry 13, a somewhat lower selectivity was determined). Treatment of *N*-alkyl,*C*-aryl imines or *N*-aryl,*C*-alkyl imines with acid chloride **2b** and silylketene acetal **3**, in general, did not lead to Mannich products **8** and **9**. Only the imine formed from benzylamine and benzaldehyde gave β-amino acid esters isolated in 27% yield with an isomer ratio of 83:17. In all other cases *N*-protected amino acid amides were isolated resulting from hydrolysis of the intermediary formed iminium ions.

The substituents at the α-position of the silylketene acetals were varied in a third series of experiments. Replacement of dimethyl-substituted nucleophile **3** (Scheme 2, $R^3 = CH_3$) by methylene silylketene acetal **7** (Scheme 2, $R^3 = H$) influenced yield and selectivity of the asymmetric transformation only to a minor extent (Table 2, compare entries 8, 11, and 12 with entries 13–15). In the case of Mannich adducts **8n** and **8o** only one diastereomer could be detected. In the reactions between imine **6c**, acid chloride **2b**, and silylketene acetals **10–12**, four diastereomers can be formed in each case since two new stereogenic centres are generated (Scheme 3, Table 3). In all three cases, the face selectivity of the imine was complete. For (*E*)-substitued cyclic ketene acetal **10**, the two possible *syn*/*anti* isomers **13*syn*** and **13*anti*** were formed in a ratio of 61:39. (*Z*)-Configured silylketene acetal **11** gave *syn*/*anti* isomers **14*syn*** and **14*anti*** in a ratio of 83:17, and (*Z*)-OTBS silylketene acetal **12** yielded exclusively *syn* isomer **15*syn***.



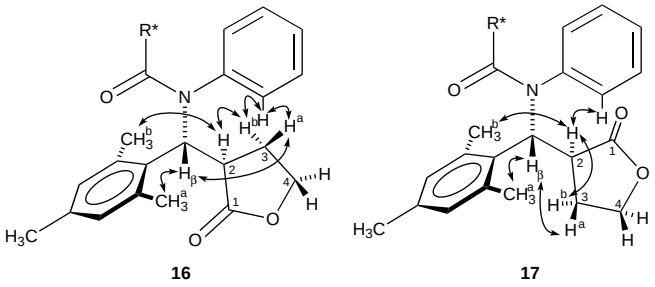
Scheme 3. Asymmetric Mannich reactions with α-monosubstitued silylketene acetals.

The absolute configuration of the stereogenic centre in the benzylic position was determined by X-ray analysis. The α-C of the *tert*-leucine auxiliary served as reference. Analysis of compounds **8c**[9] and **8h**[9] revealed that the stereogenic centre was (*S*)-configured. Thus, the silylketene acetal must have attacked the *Re*-face of the imine double bond (see the Discussion and Scheme 9). The configuration of the second stereogenic centre in compounds **13**, **14**, and **15** was assigned based on analysis of NOESY spectra recorded for compounds **13*syn*** (major diastereomer) and **13*anti*** (minor diastereomer) and on the assumption that these nucleophiles attack the imines predominantly from the *Re*-face as well. Both diastereomers showed a set of common NOE signal enhancements between an *ortho*-H of the *N*-aryl substituent and 2-H, between 2-H and 3-H^b as well as 2H and an *ortho*-CH_3 of the mesityl substituent, 3-H^a and β-H, and between β-H and the other *ortho*-$CH_3{}^a$ (Scheme 4). However, in the major diastereomer **16** ($\cong$**13*syn***) additional characteristic NOE signal enhancements between an *ortho*-H of the *N*-aryl substituent and 3-H^a as well as 3-H^b were detected. In the minor diastereomer **17** ($\cong$**13*anti***) the 3-CH_2-group and the *ortho*-positions of the *N*-aryl ring are not in close poximity. The specific pattern of NOEs can be explained by the conformations and absolute configurations of **16** for the major diastereomer and **17** for the minor diastereomer. Thus, in the Mannich reaction with the cyclic silylketene acetal *syn* diastereomer **13*syn*** was predominantly formed. The relative configuration of the diastereomers **14*syn*/*anti*** and **15*syn*** were assigned based on the assumption that for all three α-substituted silylketene acetals similar transition states are passed (see the Discussion and Scheme 9).

Table 3. Results of the Mannich reactions employing imine **6c**, *N*,*N*-phthaloyl *tert*-leucine chloride (**2b**) and silylketene acetals **10–12**.

Entry	Silylketene acetal	Product	Yield [%]	*syn*/*anti*[a]
1	**10**	**13**	78	61:39
2	**11**	**14**	77	83:17
3	**12**	**15**	66	>99:1

[a] Determined by HPLC from the crude reaction mixture.



Scheme 4. Determination of the relative configuration of Mannich adducts **13*syn*** (=**16**) and **13*anti*** (=**17**) by means of NOE measurements.

Removal of the chiral auxiliary group was achieved in a two-step procedure. Reduction of the phthaloyl group present in compounds **8c**, **8g**, **8h** and subsequent hydrolysis with dilute HCl[10] yielded *N*-terminally deprotected *tert*-leucine amides **18a**, **18c**, and **18**/**19b** (synthesized as a 92:8 mixture of diastereomers **18b** and **19b**; Scheme 5, Table 4). From these amino acid amides *tert*-leucine was cleaved by Edman degradation with phenylisothiocyanate and hydrolysis in

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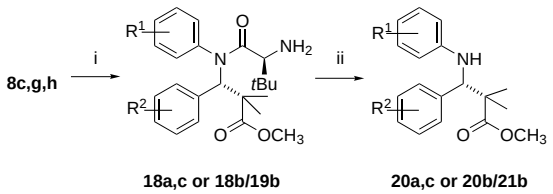
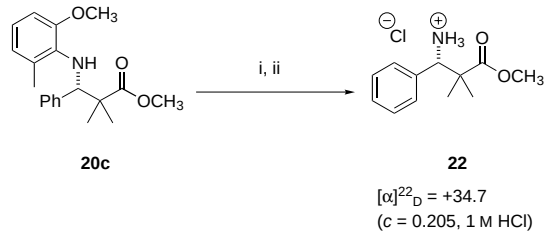


Scheme 5. Cleavage of the phthaloyl groups from Mannich adducts **8c, g, h.** i) 1) 5 equiv $NaBH_4$, *i*PrOH/H_2O 7:1, rt, 2) 18 equiv conc. HCl, 80 °C; ii) 1) 2 equiv PhNCS, 1 equiv NaOH (0.2 M), pyridine/H_2O 1:1, rt, 3 h, 2) 20 % TFA in CH_2Cl_2, reflux.

Table 4. Results of the removal of the chiral auxiliary groups from the Mannich adducts.

Entry	R^1	R^2	**8**	Yield [%]	**18**	Yield [%]	**19**
1	H	2,4,6-Me_3	**c**	88	**a**	59	**a**
2	4-OMe	H	**g**	97	**b**	84	**b**
3	2-OMe-6-Me	H	**h**	65	**c**	45	**c**

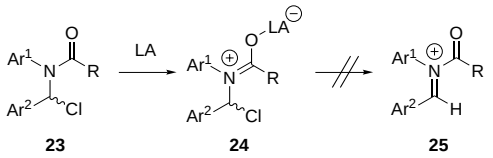
20 % trifluoroacetic acid[12] to give *N*-aryl β-amino acid esters **20a**, **20c**, and **20b**/**21b** (Scheme 5, Table 4). All attempts to remove the chiral auxiliary by hydrolysis under basic or acidic conditions failed, e. g. by hydrolysis in concentrated mineral acids, by treatment with peroxide anions[13], with KO*t*Bu[14] or by *O*-alkylation of the amide group with Meerwein's salt and subsequent aqueous hydrolysis. From compound **20c** the *ortho*-methoxy substituted *N*-aryl group was removed by oxidation with cerium ammonium nitrate (CAN).[16] β-Amino acid methyl ester hydrochloride **22** was obtained in 56 % yield (Scheme 6).



Scheme 6. Oxidative cleavage of the *N*-aryl substituent from β-amino acid **20c**. i) 5 equiv CAN, 0 °C to 22 °C; ii) Et_2O, 56 % HCl.

Discussion

The results given in Table 1 clearly demonstrate that the Mannich reactions studied here are best carried out in the absence of any Lewis acid. Although in the presence of $BF_3 \cdot OEt_2$ the stereoselectivity is somewhat higher, under these conditions the yield is not in the preparatively useful range (Table 1, compare entries 1–3). A possible explanation is that the α-chloroalkylamides **23** formed from the imines and the acid chlorides may react with the Lewis acid to give imidates **24** which can not be converted to the reactive *N*-acyliminium ions **25** (Scheme 7). This would explain the result recorded in the presence of 1 equiv $BF_3 \cdot OEt_2$; it does, however, not account for the fact that in the presence of 5 mol % of this Lewis acid the yield is even lower (Table 1, entries 1 and 2). This low yield may be rationalised based on the assumption



Scheme 7. Possible reaction of intermediary formed α-chloralkyl amides with Lewis acids.

that the Lewis acid does not only activate the electrophile, but that it also may activate the silylketene acetal. In this case a low concentration of the Lewis acid would result in a decreased reaction rate.

The efficiency of the stereoselection is influenced by the size of the amino acid side chain and the nature of the protecting group. Thus, *tert*-leucine gives a significantly higher diastereomer ratio than valine. Use of the cyclic amino acid proline which had proven to be a more advantageous auxiliary in other asymmetric syntheses[17] led to nearly equal amounts of the two diastereomers. Since *tert*-leucine is the most bulky of the commercially readily available amino acids it was used in all further Mannich reactions. If the phthalide is replaced by an urethane, the Mannich adducts are not formed at all. A similar behavior was observed in the application on *N*-masked amino acid chlorides as mediators of chirality in Pictet–Spengler reactions with indolylethylamines.[5] Therefore, we have not investigated further *N*-blocking groups in the Mannich-type transformations and used the phthaloyl protecting group in all further experiments.

The type of the substituent linked to the imine carbon and/or nitrogen and its electronic properties determine whether the Mannich adducts are formed or not. Thus, if either one of the two substituents is aliphatic and the other one is aromatic, the reaction does not proceed. Also, the desired products are not formed, if two aromatic substituents are present and one of them carries an electron-withdrawing nitro group. On the contrary, the Mannich adducts are obtained in preparatively useful yields if at least one of the two aryl substituents is equipped with an electron-donating functional group, in particular a methoxy function. We assume that the Mannich reactions only proceed smoothly if the acyliminium intermediates are stabilised by an electron-donating group that partially delocalises the positive charge. Also, an aromatic substituent next to the α-chloroamide may favor the elimination of the chloride by neighboring-group assistance.[18] This effect should be particularly pronounced in the presence of +M substituents.

The efficiency of the stereoselection is decisively influenced by the substitution pattern of the *N*- or *C*-aryl group. If either one of the two aromatic groups is monosubstituted the isomer ratio consistently is between 91:9 and 92:8, irrespective of the precise nature and the position of the substituent (Table 2, entries 2, 4, 5, 7, and 9). However, if in the imine either the former aniline aryl group or the former aromatic aldehyde embodies two *ortho*-substituents the diastereomer ratio increases dramatically. In nearly all cases investigated with α-disubstituted silylketene acetals **3** and **7** only one diastereomer could be detected by HPLC and NMR (Table 2, entries 3, 8, and 10–15).

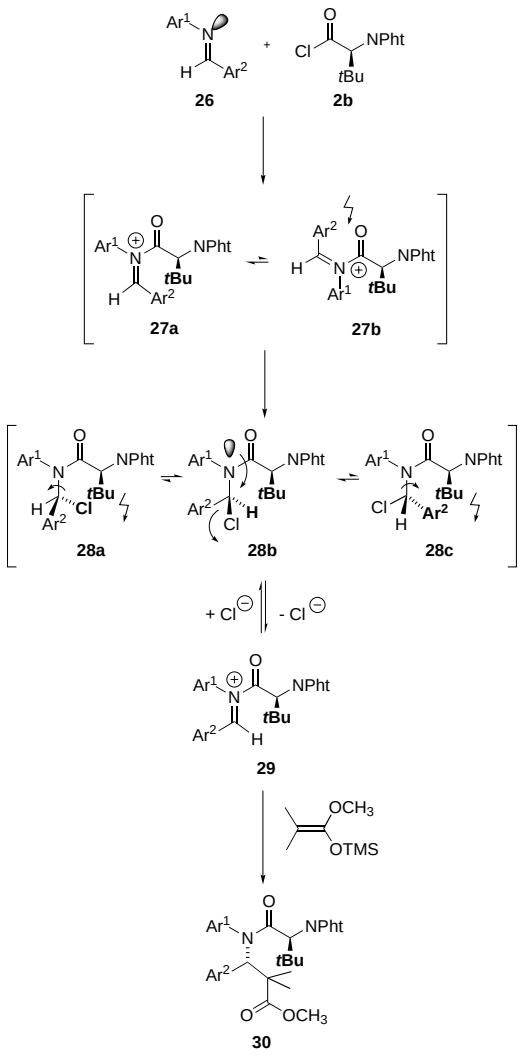
This extremely high selectivity for stereogenic centre at the benzylic carbon atom corresponding to the former imine C is also observed if silylketene acetals are employed that carry one substituent in the α-position. In these cases four diastereomers may be formed, that is two *syn*- and two *anti* isomers. However, in all three cases examined, only one *syn*- and one *anti* diastereomer were detected. Thus, in these cases, too, the imine was only attacked from one of its diastereotopic faces. The *syn*/*anti* selectivity depends on the steric demand of the substituent in the α-position of the nucleophile. Thus, with increasing size of the α-substituent (from CH_2 via OCH_3 to OTBS) the diastereomer ratio increases (Table 3) independently whether an (*E*)- or an (*Z*)-silylketene acetal is employed. In all cases the reaction with the silylketene acetals **10, 11**, and **12** gave predominantly or exclusively *syn* diastereomers.

The chiral auxiliary group can be removed from the Mannich adducts by means of a straightforward two-step procedure. In the first step one of the carbonyl groups of the phthalide is reduced to the alcohol, which readily hydrolyses the remaining amide in the presence of diluted HCl. The resulting amino acid amide is then cleaved by means of Edman degradation. All attempts to cleave the *tert*-leucine amide directly under strongly acidic or basic conditions or by means of a supernucleophile completely failed. The amino acid C=O group is surrounded by bulky groups and obviously no longer accessible for an externally approaching nucleophile. However, if the nucleophile is generated intramolecularly, as is the case in the Edman degradation, attack on the tertiary amide becomes possible and the bond between the chiral auxiliary and the β-amino acid ester is cleaved smoothly.

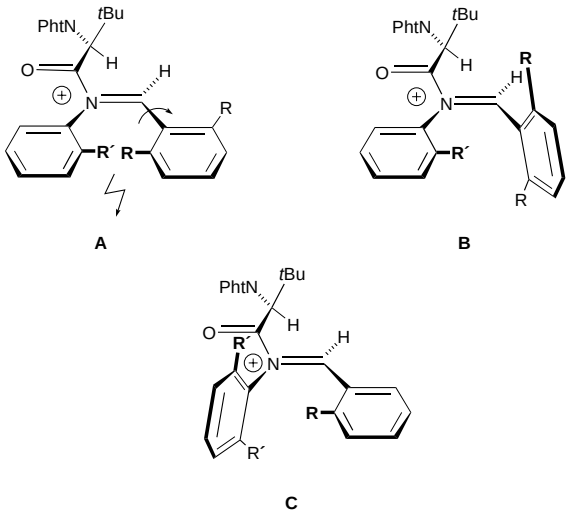
The presence of an *ortho*-methoxy substituent in the *N*-aryl group does not only guarantee high yields and excellent stereoselectivity. It also provides an opportunity for the removal of the aryl group. Thus, upon treatment of **20c** with cerium ammonium nitrate the *N*-aryl bond was cleaved oxidatively and the desired β-amino acid ester **22** was obtained in good yield as the corresponding hydrochloride. The specific rotation recorded for this compound was in good agreement with literature data[3g, 3m] and indicated that the (*R*)-enantiomer had been formed.

However, determination of the absolute configuration of Mannich adducts **8c** and **8h** by X-ray crystallography clearly and unambiguously had proven that the configuration of the newly formed stereogenic centre was (*S*).[9] Since the data reported in the literature were based on an assignment of the absolute configuration by chemical correlation (see[3g] and[3m] and the references therein) but not on X-ray analysis, we suggest that the published assignments of the absolute configuration of **22** should be revised.

In order to rationalise the excellent stereoselectivity recorded for the Mannich reactions we propose that the transformations proceed by the mechanism shown in Scheme 8 and via the transition states shown in Schemes 9 and 10. The Schiff bases **26** react with *N*,*N*-phthaloyl *tert*-leucine chloride (**2b**) to form (*Z*)–*trans* acyliminium salts **27**. Chloride then adds *anti* to the *tert*-butyl group of **27a** to the C=N double bond yielding α-chloromethyl amide **28a**. In **27a** and **28a** the Ar^2 group is in close proximity to the bulky amino



Scheme 8. Proposed intermediates and (*E*)–(*Z*)-isomerisation of the C=N bond in the Mannich reaction with *N*,*N*-phthaloyl *tert*-leucine chloride.



Scheme 9. Proposed tilting of aromatic rings in the *N*-acyliminium intermediates due to unfavored steric interactions.

acid side chain. This unfavorable steric interaction is relieved by rotation around the C–N single bond. Thereby, conformers **28a** are converted into conformers **28b** which eliminate

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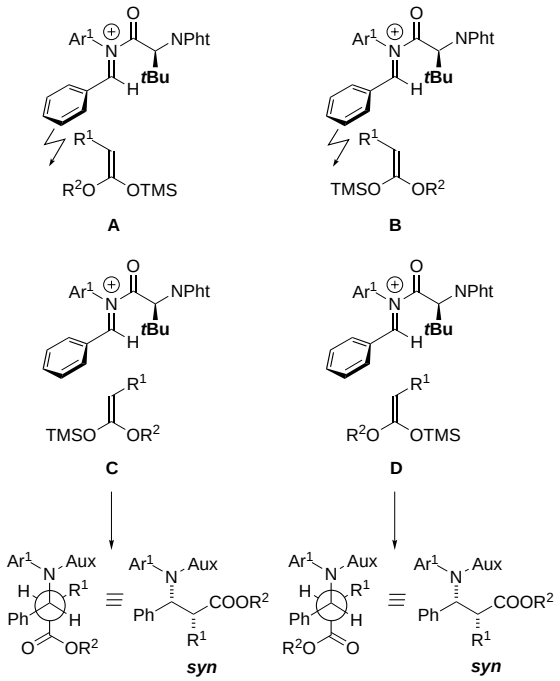
chloride to yield (*E*)–*trans* iminium intermediates **29**. The silylketene acetals then attack the C=N double bond of **29** from the face opposite to the bulky amino acid side chain. This explains the increase of the stereoselectivity with increasing steric demand of the amino acid side chain.

The imine carbon is converted into a stereocenter with (*S*)-configuation, thus the C=N bond must have been attacked from the *Re*-face. This is the case if the nucleophile approaches intermediate **29** *anti* to the *tert*-butyl group. Alternatively, a *Re*-face attack *anti* to the amino acid side chain would be possible if (*Z*)–*cis* rotamer **27b** would be the decisive intermediate (Scheme 8). However, in **27b** the aryl ring Ar^1 is unfavorably close to the *tert*-butyl group of the amino acid, and Ar^2 points towards the C=O group. Thus **27b** is higher in energy than **27a**.

In (*E*)-*trans* conformation **29** the *ortho*-substituents of the two adjacent phenyl groups can point directly towards each other giving rise to disturbing steric interactions (Scheme 9, **A**). These can be compensated by tilting one aryl group out of the plane of the C=N bond (Scheme 9, **B** and **C**). This effect should be particularly pronounced if either one of the two aryl groups embodies *ortho*-substituents. One *ortho*-substituent of the tilted ring would additionally shield the sterically less accessible face of the C=N bond and thereby enhance the stereodiscrimination. This proposal accounts for the observation that the stereoslectivity dramatically increases if one of the two aryl groups of the imine is di-*ortho*-substituted.

In order to explain the stereoselectivity for the reactions with the silylketene acetals carrying only one substituent at the α-carbon, we assume that they also attack the C=N bond at the face opposite to the amino acid side chain (Scheme 10). In this case for (*E*)-silylketene acetals **10** and **12** transition state **C** shown in Scheme 10 may be passed predominantly, leading to *syn* isomers. In **A** and **B** unfavorable interactions between α-substituents R^1 and the tilted aromatic ring have to be expected. In **A** substituent R^1 is in proximity to the two aryl groups of the imine. Transition states **C** leading to *syn* isomers for **10** and **12** appear to determine the steric course of the transformations. Obviously the interactions between the bulky R^1 and the aryl group of the imine in transition state **A** are more severe than the interactions of the OTMS group with the tilted aromatic ring. For the same reason, the use of the (*Z*)-silylketene acetal **11** leads to predominant formation of the *syn* diastereomer via transition state **D**. Thus, the orientation of R^1 and not the silyl group relative to the *N*-acyliminium ion is the decisive factor.



Scheme 10. Proposed transition states for the reactions between the *N*-acyliminium intermediates with (*E*)- and (*Z*)-silylketene acetals.

Conclusion

We have developed a method for the steric steering of the Mannich reaction via *N*-acyliminium intermediates. The best chiral auxiliary, *N*,*N*-phthaloyl *tert*-leucine, is readily available in both enantiomeric forms and the asymmetric transformations are easily carried out. In particular, a Lewis acid is not needed and the reactions are run best at room temperature. The Mannich adducts are obtained in acceptable to high yields and with excellent diastereomer ratios. The chiral auxiliary group is readily removed via a simple two-step process. By means of this method various β-amino acids are available that can find numerous applications, for example in the synthesis of β-peptides, peptidomimetics, and natural products.

Experimental Section

General procedures: Melting points were determined in open capillaries using a Büchi 535 apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC250, AM400, or DRX500 spectrometer at room temperature. IR spectra were recorded on a Bruker IFS88 spectrometer. Mass spectra and high-resolution mass spectra (HR-MS) were measured on a Finnigan MAT MS70 spectrometer. Elementary analyses were performed on a Heraeus CHN-Rapid apparatus. HPLC was performed on a Spherisorb ODS II 250/4/5 analytical column (Bischoff) and methanol/water as eluent at a flow rate of 0.6 mL min^{-1} and on a LiChrosorb RP-18 250/25/7 semipreparative column (MERCK).

Materials: Solvents were dried by standard methods and stored over molecular sieves. Deuterochloroform was carefully degassed prior to use by three times freezing under argon atmosphere and warming up under reduced pressure. For column chromatography silica gel (40–60 μm, Baker) was used. Commercial reagents were used without further purification. Where indicated the reactions were performed under nitrogen or argon. Several compounds were prepared according to literature methods: *N*-phenyl-3-nitrobenzylidene amine (**6a**);[20] *N*-phenyl-4-chlorobenzylidene amine (**6b**);[21] *N*-phenyl-2,4,6-trimethylbenzylidene amine (**6c**);[21] *N*-phenyl-4-dimethylaminobenzylidene amine (**6d**);[22] *N*-phenyl-4-methoxybenzylidene amine (**6e**);[20] *N*-(4-nitrophenyl)-benzylidene amine (**6f**);[21] *N*-(4-methoxyphenyl)-benzylidene amine (**6g**);[21] *N*-phenyl-2-methoxybenzylidene amine (**6i**);[23] *N*,*N*-phthaloyl valine chloride (**2a**);[24] *N*,*N*-pthaloyl *tert*-leucine chloride (**2b**);[24] Z-proline chloride (**2c**);[25] Fmoc-valine chloride (**2d**);[26] 1-ethoxy-1-trimethylsiloxy-ethene (**7**);[27] 3,4-dihydro-1-trimethylsiloxy-furan (**10**);[28] (*Z*)-1,2-dimethoxy-1-trimethylsiloxy-ethene (**11**);[29] (*E*)-2-(dimethyl-*tert*-butyl)-siloxy-1-methoxy-1-trimethylsiloxy-ethene (**12**).[1g]

Preparation of *N*-(2-methoxy-6-methylphenyl)-benzylidene amines (6h, 6j–k). General procedure: A neat mixture of 2-methoxy-6-methylaniline

(1.38 g, 10 mmol) and the corresponding aldehyde (10 mmol) was heated at 80 °C for several hours. The resulting red oil was dissolved in diethyl ether (10 mL) and washed with acetic acid (5 % aqueous). The combined organic layers were dried over K_2CO_3 and concentrated under reduced pressure.

***N*-(2-Methoxy-4-methylphenyl)-benzylidene amine (6h)**: The product was obtained as a yellow solid after recrystallization from ethanol (85 % aqueous). Yield: 50 %; m.p.: 47 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.40$ (s, 1H), 7.92 (dd, $J = 5$, 5 Hz, 2H), 7.47 (d, $J = 5$ Hz, 1H), 7.47 (dd, $J = 2$, 5 Hz, 2H), 6.99 (dd, $J = 8$, 8 Hz, 1H), 6.84 (d, $J = 8$ Hz, 1H), 6.82 (d, $J = 8$ Hz, 1H), 3.75 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta =$ 163.91 (CH), 149.54 (q), 140.54 (q), 136.51 (q), 131.19 (CH), 131.12 (q), 128.62 (CH), 128.57 (CH), 124.37 (CH), 122.64 (CH), 109.52 (CH), 55.86 (CH_3), 18.09 (CH_3); MS (70 eV, EI): *m*/*z* (%): 225 (100), 210 (27), 194 (7), 148 (20), 104 (11), 91 (11), 77 (15); $C_{15}H_{15}NO$ (225.29): calcd C 79.97, H 6.71, N 6.22; found: C 80.00, H 6.69, N 6.11; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 225.1154, found: 225.1143.

***N*-(2-Methoxy-6-methylphenyl)-4′-chlorobenzylidene amine (6j)**: The product was obtained as an orange oil after removing the unreacted starting materials by Kugelrohr distillation. Although the ^{1}H NMR still showed some traces of the unreacted amine, the product was used for the next reaction without further purification (73 %). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.42$ (s, 1H), 7.89 (d, $J = 9$ Hz, 2H), 7.47 (d, $J = 9$ Hz, 2H), 7.04 (dd, $J = 8$, 8 Hz, 1H), 6.88 (d, $J = 8$ Hz, 1H), 6.86 (d, $J = 8$ Hz, 1H), 3.78 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100.4 MHz, $CDCl_3$): $\delta = 162.44$ (CH), 149.52 (q), 140.04 (q), 137.19 (q), 135.07 (q), 131.43 (q), 129.73 (CH), 128.94 (CH), 124.69 (CH), 122.72 (CH), 109.55 (CH), 55.86 (CH_3),18.15 (CH_3); MS (70 eV, EI): *m*/*z* (%): 259 (36), 244 (9), 209 (3), 137 (94), 122 (100); HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 259.0764, found: 259.0747.

***N*-(2-Methoxy-4-methylphenyl)-2′-methoxybenzylidene amine (6k)**: The product was obtained as a yellow solid after recrystallization from ethanol (85 % aqueous). Yield 83 %; m.p.: 86 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 8.79 (s, 1H), 8.25 (dd, $J = 2$, 7 Hz, 1H), 7.41 (ddd, $J = 2$, 7, 7 Hz, 1H), 7.04 (dd, $J = 7$, 7 Hz, 1H), 6.96 (dd, $J = 8$, 8 Hz, 1H), 6.91 (d, $J = 8$ Hz, 1H), 6.82 (d, $J = 8$ Hz, 1H), 6.79 (d, $J = 8$ Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 160.01$ (CH), 159.39 (q), 149.65 (q), 141.57 (q), 132.46 (CH), 130.64 (q), 127.25 (CH), 124.93 (q), 124.03 (CH), 122.57 (CH), 120.76 (CH), 111.08 (CH), 109.46 (CH), 55.87 (CH_3), 55.49 (CH_3), 18.10 (CH_3); MS (70 eV, EI): *m*/*z* (%): 255 (79), 240 (4), 225 (18), 148 (5), 137 (100), 122 (49); $C_{16}H_{17}NO_2$ (255.32): calcd C 75.27, H 6.71, N 5.49; found: C 75.17, H 6.68, N 5.45; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 255.1259; found: 255.1247.

***N*-(2-Methoxy-4-methylphenyl)-4′-methoxybenzylidene amine (6l)**: The product was obtained as a red oil after removing the unreacted starting materials by Kugelrohr distillation (53 %). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.30$ (s, 1H), 7.86 (d, $J = 9$ Hz, 2H), 6.97 (d, $J = 9$ Hz, 2H), 6.97 (dd, $J =$ 8, 8 Hz, 1H), 6.83 (d, $J = 8$ Hz, 1H), 6.79 (d, $J = 8$ Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 163.06$ (CH), 162.12 (q), 149.69 (q), 140.97 (q), 130.98 (q), 130.19 (CH), 129.50 (q), 124.04 (CH), 122.60 (CH), 114.00 (CH), 109.48 (CH), 55.82 (CH_3), 55.35 (CH_3), 18.08 (CH_3); MS (70 eV, EI): *m*/*z* (%): 255 (52), 240 (10), 136 (70), 135 (100), 122 (60); $C_{16}H_{17}NO_2$ (255.32): calcd C 75.27, H 6.71, N 5.49; found: C 75.48, H 6.79, N 5.45; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 255.1259, found: 255.1248.

Amidoalkylation of 1-methoxy-2-methyl-1-trimethylsiloxypropene (3) with *N*-phenylbenzylideneamine (1) and the amino acid chlorides 2a–d. General procedure: Acid chloride **2** (1.5 mmol) in dry CH_2Cl_2 (3 mL) was added under argon at 0 °C to a solution of the Schiff base **1** (181 mg, 1 mmol) in dry CH_2Cl_2 (3 mL). The mixture was kept at 0 °C for 10 min and then warmed to room temperature over 30 min. After cooling the solution to 0 °C, silylketene acetal **3** (261 mg, 1.5 mmol) was added over 5 min. The solution was kept at room temperature for an additional 72 h. After addition of CH_2Cl_2 (10 mL), the mixture was washed with 10 % aq. $NaHCO_3$ (10 mL) and brine (10 mL), and dried over Na_2SO_4. After evaporation to dryness, the residue was purified by chromatography on silica gel.

Methyl 2,2-dimethyl-(*S*)-3-phenyl-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloylvalyl)]-amino-propionate (4a): The products were obtained from *N*,*N*-phthaloyl valine chloride (**2a**, 265 mg, 1 mmol) after chromatography with hexane/acetone 9:1 as a colorless oil (80 %) in a 87:13 mixture of diastereomers. TLC: $R_f = 0.14$ (hexane/acetone 9:1); HPLC: $t_R = 82'28''$ (methanol/H_2O 62:38); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.64$ (s, 4H), 7.36–7.44 (m, 2H), 7.11–7.26 (m, 6H), 6.57 (dd, $J = 8$, 7 Hz, 1H), 6.19 (s, 1H), 5.80 (d, $J = 8$ Hz, 1H), 4.38 (d, $J = 10$ Hz, 1H), 3.63 (s, 3H), 2.85 (dqq, $J = 7$, 7, 10 Hz, 1H), 1.35 (s, 3H), 1.22 (s, 3H), 1.11 (d, $J = 7$ Hz, 3H), 0.71 (d, $J =$ 7 Hz, 3H); MS (70 eV, EI): *m*/*z* (%): 512 (2), 481 (2), 411 (35), 282 (4), 230 (14), 202 (100); $C_{31}H_{32}N_2O_5$ (512.60): calcd C 72.64, H 6.29, N 5.47; found: C 72.56, H 6.29, N 5.50; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 512.2311, found: 512.2322.

Methyl 2,2-dimethyl-(*S*)-3-phenyl-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloylvalyl)]-amino-propionate (5a): Characteristic analytical data for the minor product. HPLC: $t_R = 92'25''$ (methanol/H_2O 62:38); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 5.88$(s, 1H), 4.24 (d, $J = 10$ Hz, 1H), 3.61 (s, 3H).

Methyl 2,2-dimethyl-(*S*)-3-phenyl-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (4b): The products were obtained from *N*,*N*-phthaloyl-*tert*-leucylchloride **2b** (209 mg, 0.75 mmol), *N*-phenylbenzylidene amine **1** (91 mg, 0.5 mmol) and silylketene acetal **3** (131 mg, 0.75 mmol) in CH_2Cl_2 (4 mL) after chromatography with hexane/acetone 3:1 as a colorless oil (54 %) in a 93:7 mixture of diastereomers. TLC: $R_f =$ 0.20 (hexane/acetone 8:1); HPLC: $t_R = 13'32''$ (methanol/H_2O 80:20); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.62$ (m, 4H), 7.51 (d, $J = 8$ Hz, 1H), 7.40 (dd, $J = 8$, 8 Hz, 1H), 7.14–7.19 (m, 5H), 7.09 (d, $J = 7$ Hz, 1H), 6.36 (s, 1H), 6.31 (dd, $J = 8$, 8 Hz, 1H), 5.43 (d, $J = 8$ Hz, 1H), 4.48 (s, 1H), 3.63 (s, 3H), 1.34 (s, 3H), 1.22 (s, 3H), 1.12 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta =$ 176.86 (q), 167.08 (q), 166.73 (q), 139.01 (q), 137.45 (q), 133.72 (CH), 131.47 (CH), 131.43 (CH), 131.26 (CH), 130.31 (CH), 129.22 (CH), 128.02 (CH), 127.69 (CH), 127.60 (CH), 127.48 (CH), 122.94 (CH), 65.35 (CH), 58.02 (CH), 51.96 (CH_3), 47.58 (q), 37.15 (q), 27.70 (CH_3), 24.74 (CH_3), 24.28 (CH_3); MS (70 eV, EI): *m*/*z* (%): 526 (3), 425 (46), 282 (8), 244 (33), 216 (100); $C_{32}H_{34}N_2O_5$ (526.63): calcd C 72.98, H 6.51, N 5.32; found: C 72.80, H 6.80, N 5.28; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 526.2468, found: 526.2485.

Methyl 2,2-dimethyl-(*R*)-3-phenyl-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (5b): Characteristic analytic data for the minor product. HPLC: $t_R = 14'49''$ (methanol/H_2O 80:20); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.30$ (s, 1H), 3.65 (s, 3H), 1.07 (s, 9H).

Methyl 3-[*N*-(*S*)-benzyloxycarbonyl-prolyl-*N*-phenyl]-amino-2,2-dimethyl-(*S*)-3-phenyl-propionate (4c) and methyl 3-[*N*-(*S*)-benzyloxycarbonyl-prolyl-*N*-phenyl]-amino-2,2-dimethyl-(*R*)-3-phenyl-propionate (5c): The products were obtained from *N*-benzyloxycarbonyl-prolylchloride (**2c**, 348 mg, 1.3 mmol) after chromatography with hexane/acetone 12:1 as a colorless oil (69 %) in a 53:47 mixture of diastereomers. The ^{1}H- and ^{13}C-NMR spectra showed not only the two diastereomers but also rotamers. The assignment of the signal groups was made by analysis of the ^{1}H/^{1}H- and ^{1}H/^{13}C-COSY spectra. TLC: $R_f = 0.16$ (hexane/acetone 8:1); HPLC: $t_R =$ 23′51″ major product **4c** and 22′16″ minor product **5c** (methanol/H_2O 75:25); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ {7.44, 7.61 (d, $^3J = 8$ Hz; *o-phenyl*-H)}, 6.96–7.39 (m; arom. CH), 6.98 (d, $^3J = 7$ Hz; *o-phenyl*-H), 6.77 (d, $^3J =$ 7 Hz; *o-phenyl*-H), 6.70 (ddd, $^4J = 1$ Hz, $^3J_1 = {}^3J_2 = 8$ Hz; *m-phenyl*-H), {5.85, 6.50, 6.54 (d, $^3J = 8$ Hz; *o-phenyl*-H)}, {5.72, 6.06, 6.13 (s, 1H; PhCHN)}, {5.07, 5.15 (d, $^2J = 5$ Hz, 1H; CH_2-*benzyl*)}, {4.76, 4.94, 5.04, 5.32 (d, $^2J = 12$ Hz, 1H, CH_2-*benzyl*)}, {3.79, 3.98, 4.01, 4.15 (ddd, $^3J_1 = 4$ Hz, $^3J_2 = 8$ Hz, 1H; αH)}, 3.62–3.70 (m, 1H; 5H-*proline*), {3.54, 3.57, 3.65 (s, 3H; OCH_3)}, 3.42–3.51 (m, 1H; 5H-*proline*), 1.95–2.05 (m, 1H; 4H-*proline*), 1.81–1.87 (m, 1H; 3H-*proline*), 1.70–1.76 (m, 1H; 3H-*proline*), 1.62–1.69 (m, 1H; 4H-*proline*), {1.17, 1.20, 1.25, 1.30, 1.31, 1.35, 1.38 (s, 6H; $(CH_3)_2$C)}; ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta =$ {176.67, 176.89, 176.93, 177.03 (q; CO_2CH_3)}, {173.54, 173.71 (q; C(O)-*proline*)}, {154.00, 154.08, 154.52, 154.59 (q; C(O)-*Z*)}, {128.64, 128.88, 130.49, 130.71, 131.03, 131.24, 131.41, 131.82, 132.45 (CH; arom. CH)}, {127.56, 136.10, 136.41, 136.68, 136.85, 136.95, 137.60, 137.67, 139.76, 140.62, 140.71, 140.90 (q; arom. C)}, {127.54, 127.66, 127.70, 127.75, 127.80, 127.89, 127.93, 128.18, 128.22, 128.33, 128.38, 128.47, 128.81, 129.12, 130.25, 130.63, 130.98, 132.38 (CH; arom. CH)}, {67.36, 68.98 (CH; PhCHN)}, {57.58, 57.63, 58.12, 58.28 (CH; αC)}, {65.64, 66.68, 66.90, 67.09, 67.20 (CH_2; CH_2Ph)}, {51.76, 51.88, 51.96 (CH_3; OCH_3)}, {47.51, 47.62, 47.79, 47.83 (q; $(CH_3)_2$C)}, {46.95, 47.01, 47.46, 47.55 (CH_2; 5C-*proline*)}, {30.38, 31.00,31.42 (CH_2; 3C-*proline*)}, {23.24, 23.30, 24.22, 29.93 (CH_2; 4C-*proline*)}, {22.94, 23.56, 24.29, 24.77, 24.86, 24.93, 25.06, 25.13, 25.36 (CH_3; $(CH_3)_2$C)}; MS (70 eV, EI): *m*/*z* (%): 514 (3), 413 (22), 232 (9), 204 (22), 91 (100); HR-MS (70 eV, EI): *m*/*z*: calcd for ($C_{31}H_{34}N_2O_5$): 514.2468, found: 514.2485.

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Mannich reaction of *N*,*N*-phthaloyl-*tert*-leucylchloride (2b), the Schiff bases 6a–l and 1-methoxy-2-methyl-1-trimethylsiloxy propene (3). General procedure: Acid chloride **2b** (336 mg, 1.2 mmol) in dry CH_2Cl_2 (3 mL) was added under argon at 0 °C to a solution of *N*-aryl-arylidene amine **6** (1 mmol) in dry CH_2Cl_2 (3 mL). The mixture was kept at 0 °C for 10 min and then warmed to room temperature over 30 min. After cooling the solution to 0 °C silylketene acetal **3** (261 mg, 1.5 mmol) was added over 5 min. The solution was kept at room temperature for an additional 72 h. After addition of CH_2Cl_2 (10 mL), the mixture was washed with 10% aq. $NaHCO_3$ (10 mL) and brine (10 mL), and dried over Na_2SO_4. After evaporation to dryness, the residue was purified by chromatography on silica gel.

Methyl (*S*)-3-(4-chlorophenyl)-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-2,2-dimethyl-propionate (8b): The products were obtained from acid chloride **2b** (168 mg, 0.6 mmol), *N*-(4-chlorophenyl)-benzylidene amine (**6b**, 108 mg, 0.5 mmol) and silylketene acetal **3** (131 mg, 0.75 mmol) in CH_2Cl_2 (4 mL) after chromatography with hexane/ethyl acetate 3:1 as a colorless oil (44%) in a 92:8 mixture of diastereomers. TLC: $R_f = 0.25$ (hexane/acetone 6:1); HPLC: $t_R = 13'55''$ (methanol/H_2O 80:20); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.63$ (m, 4H), 7.44 (ddd, $J = 2, 8, 8$ Hz, 1H), 7.40 (ddd, $J = 2, 8, 8$ Hz, 1H), 7.12 (m, 5H), 6.38 (ddd, $J = 2, 8, 8$ Hz, 1H), 6.31 (s, 1H), 5.51 (d, $J = 8$ Hz, 1H), 4.45 (s, 1H), 3.61 (s, 3H), 1.30 (s, 3H), 1.21 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 176.63$ (q), 167.18 (q), 166.80 (q), 138.86 (q), 136.09 (q), 133.88 (CH), 133.66 (q), 132.63 (CH), 131.43 (q), 131.35 (CH), 130.12 (CH), 129.49 (CH), 128.28 (CH), 127.88 (CH), 127.78 (CH), 123.08 (CH), 64.73 (CH), 58.00 (CH), 52.09 (CH_3), 47.50 (q), 37.23 (q), 27.70 (CH_3), 24.61 (CH_3), 24.49 (CH_3); MS (70 eV, EI): *m*/*z* (%): 560 (3), 459 (8), 316 (6), 244 (25), 216 (100); $C_{32}H_{33}ClN_2O_5$ (561.07): calcd C 68.50, H 5.93, N 4.99; found: C 68.64, H 6.17, N 4.67; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 560.2078, found: 560.2095.

Methyl (*R*)-3-(4-chlorophenyl)-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-2,2-dimethyl-propionate (9b): Characteristic analytic data for the minor product. HPLC: $t_R = 14'41''$ (methanol/H_2O 80:20); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.69$ (m, 4H), 4.30 (s, 1H), 3.65 (s, 3H), 1.06 (s, 9H).

Methyl 2,2-dimethyl-(*S*)-3-(2,4,6-trimethylphenyl)-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (8c): The product was obtained from acid chloride **2b** (210 mg, 0.75 mmol), *N*-phenyl-2,4,6-trimethylbenzylidene amine (**6c**, 112 mg, 0.5 mg) and silylketene acetal **3** (131 mg, 0.75 mmol) in CH_2Cl_2 (3 mL) after chromatography with hexane/acetone 15:1 as a colorless solid (46%). M.p.: 237 °C; TLC: $R_f = 0.30$ (hexane/acetone 6:1); HPLC: $t_R = 24'45''$ (methanol/H_2O 80:20); $[\alpha]_D^{22} = -86.8$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.63$ (s, 4H), 7.20 (ddd, $J = 2, 8, 8$ Hz, 1H), 7.04 (dd, $J = 8, 8$ Hz, 1H), 6.99 (dd, $J = 8, 8$ Hz, 1H), 6.69 (s, 1H), 6.40 (ddd, $J = 2, 8, 8$ Hz, 1H), 6.59 (s, 1H), 6.19 (d, $J = 8$ Hz, 1H), 6.20 (s, 1H), 4.43 (s, 1H), 3.84 (s, 3H), 2.16 (s, 3H), 2.12 (s, 3H), 1.77 (s, 3H), 1.54 (s, 3H), 1.12 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 178.08$ (q), 166.70 (q), 165.73 (q), 140.81 (q), 139.91 (q), 139.15 (q), 136.71 (q), 133.63 (CH), 131.02 (q), 130.36 (q), 130.34 (CH), 130.31 (CH), 129.93 (CH), 129.27 (CH), 129.14 (CH), 128.10 (CH), 127.54 (CH), 123.01 (CH), 66.68 (CH), 58.57 (CH), 52.17 (CH_3), 48.53 (q), 37.32 (q), 27.85 (CH_3), 23.71 (CH_3), 22.11 (CH_3), 21.89 (CH_3), 20.67 (CH_3); MS (70 eV, EI): *m*/*z* (%): 568 (1), 537 (1), 467 (45), 324 (3), 244 (27), 216 (100); $C_{35}H_{40}N_2O_5$ (568.71): calcd C 73.92, H 7.09, N 4.93; found: C 73.99, H 7.18, N 4.83; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 568.2937, found: 568.2960.

Methyl 2,2-dimethyl-(*S*)-3-[4′-(*N*,*N*-dimethylaminophenyl)]-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (8d): The products were obtained from of *N*-phenyl-4-dimethylaminobenzylidene amine (**6d**, 224 mg, 1 mmol) after chromatography with hexane/ethyl acetate 3:1 as a yellow oil (91%) as a 91:9 mixture of diastereomers. To determine the optical rotation, an analytical sample was obtained after separation by HPLC. The major product **8d** was obtained as a pure diastereomer. TLC: $R_f = 0.18$ (hexane/acetone 6:1); HPLC: $t_R = 19'2''$ (methanol/H_2O 75:25); $[\alpha]_D^{22} = -206.1$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.61$ (s, 4H), 7.56 (d, $J = 8$ Hz, 1H), 7.40 (ddd, $J = 1, 8, 8$ Hz, 1H), 7.08 (dd, $J = 7, 7$ Hz, 1H), 6.90 (d, $J = 9$ Hz, 2H), 6.46 (d, $J = 9$ Hz, 2H), 6.35 (ddd, $J = 1, 7, 8$ Hz, 1H), 6.24 (s, 1H), 5.50 (d, $J = 8$ Hz, 1H), 4.46 (s, 1H), 3.64 (s, 3H), 2.88 (s, 6H), 1.30 (s, 3H), 1.19 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 177.12$ (q), 166.77 (q), 149.63 (q), 139.02 (q), 133.64 (CH), 132.21 (CH), 131.55 (CH), 130.99 (CH), 129.02 (CH), 127.81 (CH), 127.29 (CH), 124.66 (q), 122.97 (CH), 111.25 (CH), 64.87 (CH), 57.98 (CH), 51.91 (CH_3), 47.95 (q), 40.27 (CH_3), 37.14 (q), 27.73 (CH_3), 24.87 (CH_3), 23.92 (CH_3); MS (70 eV, EI): *m*/*z* (%): 569 (3), 468 (68), 225 (25), 234 (17), 216 (100); $C_{34}H_{39}N_3O_5$ (569.70): calcd C 71.68, H 6.90, N 7.38; found: C 71.63, H 6.91, N 7.28; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 569.2890, found: 569.2878.

Methyl 2,2-dimethyl-(*R*)-3-[4′-(*N*,*N*-dimethylaminophenyl]-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (9d): Characteristic analytic data for the minor product. HPLC: $t_R = 21'6''$ (methanol/H_2O 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.71$ (s, 4H), 4.26 (s, 1H), 3.63 (s, 3H), 2.92 (s, 6H), 1.08 (s, 9H).

Methyl 2,2-dimethyl-(*S*)-3-(4′-methoxyphenyl)-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (8e): The products were obtained from acid chloride **2b** (169 mg, 0.6 mmol), *N*-(4-methoxyphenyl)-benzylidene amine (**6e**, 105 mg, 0.5 mmol) and silylketene acetal **3** (131 mg, 0.75 mmol) in CH_2Cl_2 (4 mL) after chromatography with hexane/ethyl acetate 3:1 as a colorless oil (84%) in a 92:8 mixture of diastereomers. TLC: $R_f = 0.18$ (hexane/acetone 6:1); HPLC: $t_R = 17'24''$ (methanol/H_2O 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.53–7.62$ (m, 4H), 7.51 (d, $J = 9$ Hz, 1H), 7.39 (ddd, $J = 1, 8, 8$ Hz, 1H), 7.08 (dd, $J = 8, 8$ Hz, 1H), 7.02 (d, $J = 9$ Hz, 2H), 6.65 (dd, $J = 9, 9$ Hz, 2H), 6.32 (ddd, $J = 1, 8, 8$ Hz, 1H), 6.31 (s, 1H), 5.43 (d, $J = 9$ Hz, 1H), 4.44 (s, 1H), 3.73 (s, 3H), 3,62 (s, 3H), 1.30 (s, 3H), 1.19 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 176.94$ (q), 166.94 (q), 166.75 (q), 158.84 (q), 138.87 (q), 133.73 (CH), 132.51 (CH), 131.46 (CH), 130.59 (CH), 129.41 (q), 129.20 (CH), 127.99 (CH), 127.43 (CH), 122.99 (CH), 112.85 (CH), 64.59 (CH), 57.97 (CH), 55.04 (CH_3), 51.98 (CH_3), 47.76 (q), 37.15 (q), 27.69 (CH_3), 24.71 (CH_3), 24.16 (CH_3); MS (70 eV, EI): *m*/*z* (%): 556 (4), 455 (19), 336 (6), 244 (15), 216 (100); $C_{33}H_{36}N_2O_6$ (556.66): calcd C 71.20, H 6.52, N 5.03; found: C 71.15, H 6.61, N 4.84; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 556.2573, found: 556.2593.

Methyl 2,2-dimethyl-(*R*)-3-(4-methoxyphenyl)-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (9e): Characteristic analytic data for the minor product. HPLC: $t_R = 18'34''$ (methanol/H_2O 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.69$ (m, 4H), 5.68 (s, 1H), 4.26 (s, 1H), 3.77 (s, 3H), 3,63 (s, 3H), 1.04 (s, 9H).

Methyl 2,2-dimethyl-(*S*)-3-phenyl-3-[*N*-(4′-methoxy-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (8g): The products were obtained from acid chloride **2b** (230 mg, 0.82 mmol), *N*-(4-methoxyphenyl)-benzylidene amine (**6g**, 158 mg, 0.75 mmol) and silylketene acetal **3** (195 mg, 1.12 mmol) in CH_2Cl_2 (4 mL) after chromatography with hexane/acetone 10:1 as a colorless oil (82%) in a 91:9 mixture of diastereomers. To determine the optical rotation, an analytical sample was obtained after separation by HPLC. The major product **8g** was obtained as a pure diastereomer. TLC: $R_f = 0.23$ (hexane/acetone 3:1); HPLC: $t_R = 17'43''$ (methanol/H_2O 75:25); $[\alpha]_D^{22} = -64.0$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.61$ (s, 4H), 7.43 (dd, $J = 3, 9$ Hz, 1H), 7.16–7.19 (m, 5H), 6.88 (dd, $J = 3, 9$ Hz, 1H), 6.35 (s, 1H), 5.78 (dd, $J = 3, 9$ Hz, 1H), 5.27 (dd, $J = 3, 9$ Hz, 1H), 4.45 (s, 1H), 3.68 (s, 3H), 3.64 (s, 3H), 1.33 (s, 3H), 1.20 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 176.94$ (q), 167.36 (q), 166.75 (q), 158.91 (q), 137.32 (q), 133.68 (CH), 132.43 (CH), 131.59 (CH), 131.48 (q), 131.36 (CH), 127.66 (CH), 127.59 (CH), 122.91 (CH), 113.90 (CH), 113.02 (CH), 64.87 (CH), 57.95 (CH), 55.31 (CH_3), 52.02 (CH_3), 47.57 (q), 37.14 (q), 27.70 (CH_3), 24.79 (CH_3), 24.06 (CH_3); MS (70 eV, EI): *m*/*z* (%): 556 (5), 455 (40), 312 (4), 244 (26), 216 (100); $C_{33}H_{36}N_2O_6$ (556.66): calcd C 71.20, H 6.52, N 5.03; found: C 71.06, H 6.69, N 5.01; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 556.2573, found: 556.2556.

Methyl 2,2-dimethyl-(*R*)-3-phenyl-3-[*N*-(4-methoxyphenyl)-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (9g): Characteristic analytic data for the minor product. HPLC: $t_R = 19'57''$ (methanol/H_2O 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.61$ (s, 4H), 7.41 (dd, $J = 3, 9$ Hz, 1H), 4.27 (s, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 1.05 (s, 9H).

Methyl 2,2-dimethyl-(*S*)-3-phenyl-3-[*N*-(2′-methoxy-6′-methylphenyl)-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (8h): The product was obtained from acid chloride **2b** (838 mg, 3 mmol), *N*-(2-methoxy-6-methylphenyl)-benzylidene amine (**6h**, 451 mg, 2 mmol) and silylketene acetal **3** (523 mg, 3 mmol) in CH_2Cl_2 (12 mL) after chromatography with hexane/acetone 10:1 as a colorless solid (50%). M.p.: 197 °C; TLC: $R_f = 0.22$ (hexane/acetone 6:1); HPLC: $t_R = 17'52''$ (methanol/H_2O 80:20); $[\alpha]_D^{22} = -79.9$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.73$ (d, $J = 7$ Hz, 1H), 7.61 (dd, $J = 7, 7$ Hz, 2H), 7.49 (d, $J = 7$ Hz, 1H), 7.06 (dd, $J = 8, 8$ Hz, 2H), 6.96 (dd, $J = 8, 8$ Hz, 2H), 6.85 (s, 2H), 6.83 (s, 1H), 6.37 (s,

1H), 6.05 (d, $J=8$ Hz, 1H), 4.33 (s, 1H), 3.92 (s, 3H), 3.59 (s, 3H), 1.54 (s, 3H), 1.16 (s, 3H), 1.09 (s, 9H), 0.65 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta=177.25$ (q), 167.68 (q), 166.32 (q), 155.91 (q), 140.92 (q), 136.12 (q), 133.59 (CH), 132.32 (q), 131.95 (CH), 130.74 (q), 129.19 (CH), 127.47 (CH), 127.35 (q), 127.01 (CH), 123.02 (CH), 122.78 (CH), 122.41 (CH), 109.59 (CH), 66.76 (CH), 58.50 (CH), 54.74 (CH_3), 51.78 (CH_3), 49.91 (q), 37.40 (q), 27.93 (CH_3), 24.39 (CH_3), 22.33 (CH_3), 17.55 (CH_3); MS (70 eV, EI): *m*/*z* (%): 570 (0.4), 539 (1), 469 (38), 326 (4), 244 (11), 226 (37), 216 (100); $C_{34}H_{38}N_2O_6$ (570.68): calcd C 71.56, H 6.71, N 4.91; found: C 71.56, H 6.75, N 4.82; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 570.2730, found: 570.2753.

Methyl 2,2-dimethyl-(*S*)-3-(2′-methoxyphenyl)-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (8i): The products were obtained after chromatography with hexane/acetone 12:1 as a colorless oil (91%) in a 92:8 mixture of diastereomers. To determine the optical rotation, an analytical sample was obtained after separation by HPLC. The major product **8i** was obtained as a pure diastereomer. TLC: $R_f=0.16$ (hexane/acetone 6:1); HPLC: $t_R=19'43''$ (methanol/H_2O 77:23); $[\alpha]_D^{22}=-122.0$ ($c=0.5$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.63$ (br, 4H), 7.45 (d, $J=8$ Hz, 1H), 7.35 (ddd, $J=1$, 8, 8 Hz, 1H), 7.14 (ddd, $J=1$, 8, 8 Hz, 1H), 7.06 (dd, $J=8$, 8 Hz, 1H), 6.81 (ddd, $J=1$, 8, 8 Hz, 1H), 6.79 (d, $J=8$ Hz, 1H), 6.58 (dd, $J=8$, 8 Hz, 1H), 6.57 (s, 1H), 6.35 (ddd, $J=1$, 8, 8 Hz, 1H), 5.68 (d, $J=8$ Hz, 1H), 4.42 (s, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 1.35 (s, 3H), 1.29 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (125.6 MHz, $CDCl_3$): $\delta=177.27$ (q), 166.75 (q), 166.58 (q), 158.20 (q), 139.82 (q), 133.68 (CH), 132.03 (CH), 131.62 (q), 131.19 (CH), 130.81 (CH), 129.05 (CH), 128.84 (CH), 127.76 (CH), 127.46 (CH), 125.87 (CH), 122.95 (CH), 119.14 (CH), 110.86 (CH), 58.35 (CH), 56.02 (CH_3), 51.88 (CH_3), 47.87 (q), 37.24 (q), 27.81 (CH_3), 25.13 (CH_3), 24.56 (CH_3); MS (70 eV, EI): *m*/*z* (%): 556 (1), 525 (2), 455 (46), 312 (5), 244 (20), 216 (100); $C_{33}H_{36}N_2O_6$ (556.66): calcd C 71.20, H 6.52, N 5.03; found: C 71.17, H 6.49, N 4.89; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 556.2573, found: 556.2590.

Methyl 2,2-dimethyl-(*R*)-3-(2′-methoxyphenyl)-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (9i): Characteristic analytic data for the minor product. HPLC: $t_R=17'3''$ (methanol/H_2O 77:23); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.69$ (br, 4H), 6.20 (s, 1H), 4.33 (s, 1H), 3.72 (s, 3H), 3.54 (s, 3H), 1.09 (s, 9H).

Methyl (*S*)-3-(4′-chlorophenyl)-3-[*N*-(2′-methoxy-6′-methylphenyl)-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-2,2-dimethyl-propionate (8j): The product was obtained from *N*-(2-methoxy-6-methylphenyl)-4′-chlorobenzylidene amine (**6j**, 260 mg, 1 mmol) after chromatography with hexane/ethyl acetate 3:1 as a colorless solid (26%). TLC: $R_f=0.22$ (hexane/ethyl acetate 3:1); HPLC: $t_R=14'46''$ (methanol/H_2O 82:18); $[\alpha]_D^{22}=-87.9$ ($c=0.5$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.77$ (d, $J=7$ Hz, 1H), 7.67 (ddd, $J=1$, 7, 7 Hz, 1H), 7.63 (ddd, $J=1$, 7, 7 Hz, 1H), 7.52 (d, $J=7$ Hz, 1H), 7.09 (dd, $J=8$, 8 Hz, 1H), 6.98 (d, $J=8$ Hz, 2H), 6.88 (d, $J=8$ Hz, 2H), 6.84 (d, $J=8$ Hz, 1H), 6.19 (s, 1H), 6.15 (d, $J=8$ Hz, 1H), 4.34 (s, 1H), 3.87 (s, 3H), 3.61 (s, 3H), 1.52 (s, 3H), 1.23 (s, 3H), 1.11 (s, 9H), 0.81 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta=176.87$ (q), 167.87 (q), 167.44 (q), 166.18 (q), 155.69 (q), 140.13 (q), 134.89 (q), 133.94 (CH), 133.63 (CH), 133.41 (q), 133.18 (CH), 132.17 (q), 130.62 (q), 129.29 (CH), 127.27 (q), 127.04 (CH), 122.95 (CH), 122.76 (CH), 122.54 (CH), 109.69 (CH), 66.65 (CH_3), 58.36 (CH_3), 54.64 (CH), 51.75 (CH), 49.63 (q), 37.28 (q), 27.83 (CH_3), 24.67 (CH_3), 22.32 (CH_3), 17.70 (CH_3); MS (70 eV, EI): *m*/*z* (%): 604 (1), 573 (2), 545 (1), 503 (43), 360 (6), 244 (25), 216 (100); $C_{34}H_{37}N_2O_6$ (604.13): calcd C 67.49, H 6.16, N, 4.63; found: C 67.22, H 6.29, N 4.85; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 604.2340, found: 604.2356.

Methyl 2,2-dimethyl-(*S*)-3-(2′-methoxyphenyl)-3-[*N*-(2′-methoxy-6′-methylphenyl)-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (8k): The product was obtained from *N*-(2-methoxy-6-methylphenyl)-2′-methoxybenzylidene amine (**6k**, 255 mg, 1 mmol) after chromatography with hexane/ethyl acetate 3:1 as a colorless solid (59%). TLC: $R_f=0.16$ (hexane/ethyl acetate 3:1); HPLC: $t_R=19'40''$ (methanol/H_2O 77:23); $[\alpha]_D^{22}=-103.4$ ($c=0.5$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.77$ (d, $J=7$ Hz, 1H), 7.65 (ddd, $J=1$, 7, 7 Hz, 1H), 7.61 (ddd, $J=1$, 7, 7 Hz, 1H), 7.50 (d, $J=7$ Hz, 1H), 7.03 (ddd, $J=1$, 8, 8 Hz, 1H), 6.99 (dd, $J=8$, 8 Hz, 1H), 6.84 (d, $J=8$ Hz, 1H), 6.73 (d, $J=8$ Hz, 1H), 6.63 (d, $J=8$ Hz, 1H), 6.59 (s, 1H), 6.52 (dd, $J=8$, 8 Hz, 1H), 6.07 (d, $J=8$ Hz, 1H), 4.34 (s, 1H), 3.81 (s, 3H), 3.66 (s, 3H), 3.65 (s, 3H), 1.47 (s, 3H), 1.21 (s, 3H), 1.11 (s, 9H), 0.96 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta=177.33$ (q), 167.75 (q), 167.34 (q), 166.30 (q), 157.95 (q), 155.69 (q), 140.05 (CH), 133.77 (CH), 133.46 (CH), 132.71 (CH), 132.30 (q), 130.85 (q), 128.61 (CH), 128.28 (CH), 128.06 (q), 125.25 (q), 122.87 (CH), 122.67 (CH), 122.27 (CH), 118.66 (CH), 110.11 (CH), 109.29 (CH), 58.60 (CH), 58.45 (CH), 55.87 (CH_3), 54.57 (CH_3), 51.63 (CH_3), 48.75 (q), 37.26 (q), 27.92 (CH_3), 24.05 (CH_3), 28.85 (CH_3), 17.26 (CH_3); MS (70 eV, EI): *m*/*z* (%): 600 (1), 569 (3), 499 (100), 356 (4), 256 (64), 216 (81); $C_{35}H_{40}N_2O_7$ (600.71): calcd C 69.98, H 6.71, N 4.66; found: C 70.11, H 6.68, N 4.67; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 600.2836, found: 600.2856.

Methyl 2,2-dimethyl-(*S*)-3-(4′-methoxyphenyl)-3-[*N*-(2′-methoxy-6′-methylphenyl)-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (8l): The product was obtained from *N*-(2-methoxy-6-methylphenyl)-4′-methoxybenzylidene amine (**6l**, 257 mg, 1 mmol) after chromatography with hexane/ethyl acetate 3:1 as a colorless solid (75%). TLC: $R_f=0.09$ (hexane/ethyl acetate 3:1); HPLC: $t_R=24'32''$ (methanol/H_2O75:25); $[\alpha]_D^{22}=-98.5$ ($c=0.5$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.74$ (d, $J=7$ Hz, 1H), 7.65 (ddd, $J=1$, 7, 7 Hz, 1H), 7.61 (ddd, $J=1$, 7, 7 Hz, 1H), 7.51 (d, $J=7$ Hz, 1H), 7.08 (dd, $J=8$, 8 Hz, 1H), 6.86 (d, $J=8$ Hz, 1H), 6.71–6.75 (br, 2H), 6.50 (d, $J=8$ Hz, 2H), 6.44 (s, 1H), 6.08 (d, $J=8$ Hz, 1H), 4.34 (s, 1H), 3.95 (s, 3H), 3.67 (s, 3H), 3.60 (s, 3H), 1.54 (s, 3H), 1.16 (s, 3H), 1.11 (s, 9H), 0.65 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta=177.21$ (q), 167.47 (q), 166.27 (q), 158.74 (q), 155.87 (q), 141.07 (q), 133.85 (CH), 133.53 (CH), 132.29 (q), 130.68 (q), 129.12 (CH), 128.29 (q), 127.11 (q), 122.95 (CH), 122.71 (CH), 122.36 (CH), 112.27 (CH), 109.50 (CH), 65.52 (CH), 58.41 (CH), 54.92 (CH_3), 54.69 (CH_3), 51.69 (CH_3), 50.14 (q), 37.32 (q), 27.86 (CH_3), 24.40 (CH_3), 21.34 (CH_3), 17.57 (CH_3); MS (70 eV, EI): *m*/*z* (%): 600 (2), 569 (2), 499 (63), 380 (16), 256 (33), 221 (28), 216 (100); $C_{35}H_{40}N_2O_7$ (600.71): calcd C 69.98, H 6.71, N 4.66; found: C 69.86, H 6.72, N 4.83; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 600.2836, found: 600.2823.

Mannich reaction of *N*,*N*-phthaloyl-*tert*-leucylchloride (2b), the Schiff bases 6h,l,k and 1-ethoxy-1-trimethylsiloxy-ethene (7). General procedure: Acid chloride **2b** (168 mg, 0.6 mmol) was added in dry CH_2Cl_2 (3 mL) to a solution of of the Schiff base (0.5 mmol) in dry CH_2Cl_2 (2 mL) under argon at 0 °C. The mixture was stirred for 10 min and then allowed to warm to room temperature over 30 min. After cooling the solution to 0 °C, silylketene acetal **7** (120 mg, 0.75 mmol) was added over 5 min. The solution was then stirred at room temperature for 72 h. After addition of CH_2Cl_2 (10 mL), the mixture was washed with 10% aq. $NaHCO_3$ (10 mL) and brine (10 mL) and dried over Na_2SO_4. After evaporation to dryness, the residue was purified by chromatography on silica gel with hexane/ethyl acetate 3:1.

Ethyl (*R*)-3-[*N*-(2′-methoxy-6′-methylphenyl)-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-3-phenyl-propionate 8m. The product was obtained from *N*-(2-methoxy-6-methylpheny)-benzylidene amine (**6h**, 113 mg, 0.5 mmol) as a 96:4 mixture of diastereomers (34%). To determine the optical rotation, an analytical sample was obtained after separation by HPLC. The major product **8m** was obtained as a pure diastereomer (colorless oil). TLC: $R_f=0.19$ (hexane/ethyl acetate 3:1); HPLC: $t_R=16''55'$ (minor) 18′21″ (major) (methanol/water 75:25); $[\alpha]_D^{22}=-90.0$ ($c=0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.80$ (d, $J=7$ Hz, 1H), 7.66 (dd, $J=7$, 7 Hz, 1H), 7.64 (dd, $J=7$, 7 Hz, 1H), 7.55 (d, $J=7$ Hz, 1H), 7.06–7.12 (m, 6H), 6.79 (d, $J=8$ Hz, 1H), 6.26 (d, $J=8$ Hz, 1H), 5.62 (dd, $J=5$, 9 Hz, 1H), 4.17 (s, 1H), 3.92 (q, $J=7$ Hz, 2H), 3.68 (s, 3H), 3.30 (dd, $J=16$, 5 Hz, 1H), 3.28 (dd, $J=16$, 9 Hz, 1H), 1.08 (s, 9H), 1.03 (t, $J=7$ Hz, 3H), 0.91 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=171.24$ (q); 168.33 (q), 167.74 (q), 166.53 (q), 155.45 (q), 138.99 (q), 137.91 (q), 133.99 (CH), 133.72 (CH), 132.23 (q), 130.87 (q), 129.90 (CH), 128.99 (CH), 127.58 (CH), 127.53 (CH), 127.29 (q), 123.09 (CH), 122.91 (CH), 122.78 (CH), 109.43 (CH), 60.29 (CH), 60.18 (CH_2), 58.14 (CH), 55.11 (CH_3), 32.00 (CH_2), 37.02 (q), 27.69 (CH_3), 17.01 (CH_3), 13.97 (CH_3), MS (70 eV, EI): *m*/*z* (%): 556 (6), 452 (1), 396 (2), 312 (2), 216 (100); HR-MS (70 eV, EI): *m*/*z*: calcd for ($C_{33}H_{36}N_2O_6$): 556.2573, found: 556.2608.

Ethyl (*S*)-3-(4′-methoxyphenyl)-3-[*N*-(2′-methoxy-6′-methylphenyl)-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (8n): The product was obtained from *N*-(2-methoxy-6-methylphenyl)-4′-methoxybenzylidene amine (**6l**, 128 mg, 0.5 mmol). Colorless solid (68%); m.p.: 192 °C; TLC: $R_f=0.11$ (hexane/acetone 6:1); HPLC: $t_R=20'25''$ (methanol/H_2O 70:30); $[\alpha]_D^{22}=-102.6$ ($c=0.5$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.81$ (d, $J=7$ Hz, 1H), 7.68 (dd, $J=7$, 7 Hz, 1H), 7.64 (dd, $J=7$, 7 Hz, 1H), 7.56 (d, $J=7$ Hz, 1H), 7.09 (dd, $J=8$, 8 Hz, 1H), 6.96 (dd, $J=7$, 2 Hz, 2H), 6.81 (d, $J=8$ Hz, 1H), 6.60 (dd, $J=7$, 2 Hz, 2H), 6.26 (d, $J=8$ Hz, 1H), 5.66 (dd, $J=11$, 4 Hz, 1H), 4.18 (s, 1H), 3.95 (dq, $J=30$, 7 Hz, 1H), 3.93 (dq, $J=30$,

0947-6539/00/0611-2040 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 11

7 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.31 (dd, $J = 16$, 4 Hz, 1H), 3.19 (dd, $J = 16$ Hz, 11 Hz, 1H), 1.09 (s, 9H), 1.06 (ddd, $J = 12$, 7, 7 Hz, 3H), 0.91 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 171.27$ (q), 168.21 (q), 167.74 (q), 166.56 (q), 158.97 (q), 155.52 (q), 139.23 (q), 133.98 (CH), 133.70 (CH), 132.30 (q), 131.09 (CH), 130.92 (q), 130.09 (q), 128.98 (CH), 127.12 (q), 123.11 (CH), 122.93 (CH), 122.81 (CH), 112.85 (CH), 109.40 (CH), 60.18 (CH_2), 59.52 (CH), 58.18 (CH), 55.18 (CH_3), 55.08 (CH_3), 38.23 (CH_2), 37.06 (q), 27.73 (CH_3), 17.15 (CH_3), 14.04 (CH_3); MS (70 eV, EI): m/z (%): 586 (86), 541 (14), 380 (74), 324 (35), 216 (80), 207 (100); $C_{34}H_{38}N_2O_7$ (586.68): calcd C 69.61, H 6.53, N 4.77; found: C 69.64, H 6.49, N 4.85; HR-MS (70 eV, EI): m/z: calcd for $[M]^+$: 586.2679, found: 586.2700.

Ethyl (*R*)-3-(2′-methoxyphenyl)-3-[*N*-(2′-methoxy-6′-methylphenyl)-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (8o): The product was obtained from *N*-(2-methoxy-6-methylphenyl)-2′-methoxybenzylidene amine (**6k**, 128 mg, 0.5 mmol). Colorless solid (51%); m.p.: 172 °C; TLC: $R_f = 0.12$ (hexane/ethyl acetate 3:1); HPLC: $t_R = 20'0''$ (methanol/H_2O 70:30); $[\alpha]_D^{22} = -136.1$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.81 (d, $J = 7$ Hz, 1H), 7.68 (ddd, $J = 1$, 7, 7 Hz, 1H), 7.64 (ddd, $J = 1$, 7, 7 Hz, 1H), 7.57 (d, $J = 7$ Hz, 1H), 7.06 (dd, $J = 8$, 8 Hz, 1H), 7.06 (dd, $J = 8$, 8 Hz, 1H), 6.98 (d, $J = 8$, 8 Hz, 1H), 6.79 (d, $J = 8$ Hz, 1H), 6.64 (d, $J = 8$ Hz, 1H), 6.62 (dd, $J = 8$, 8 Hz, 1H), 6.32 (dd, $J = 4$, 11 Hz, 1H), 6.23 (d, $J = 8$ Hz, 1H), 4.18 (s, 1H), 3.93 (dq, $J = 31$, 7 Hz, 1H), 3.90 (dq, $J = 31$, 7 Hz, 1H), 3.75 (s, 3H), 3.55 (s, 3H), 3.35 (dd, $J = 16$, 4 Hz, 1H), 3.25 (dd, $J = 16$, 11 Hz, 1H), 1.09 (s, 9H), 1.01 (dd, $J = 7$, 7 Hz, 3H), 0.87 (s, 3H):^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 171.39$ (q), 168.30 (q), 167.47 (q), 166.60 (q), 158.28 (q), 155.67 (q), 139.34 (q), 133.91 (CH), 133.62 (CH), 132.33 (q), 131.00 (q), 130.25 (CH), 128.65 (CH), 128.58 (CH), 127.44 (q), 125.97 (q), 122.94 (CH), 122.88 (CH), 122.51 (CH), 119.56 (CH), 109.75 (CH), 108.87 (CH), 59.94 (CH_2), 58.03 (CH), 55.19 (CH_3), 55.06 (CH_3), 52.05 (CH), 37.10 (q), 37.01 (CH_2), 27.75 (CH_3),16.56 (CH_3), 13.93 (CH_3); MS (70 eV, EI): m/z (%): 586 (99), 541 (16), 380 (80), 324 (41), 216 (100), 207 (19); $C_{34}H_{38}N_2O_7$ (586.68): calcd C 69.61, H 6.53, N 4.77; found: C 69.39, H 6.61, N 4.67; HR-MS (70 eV, EI): m/z: calcd for $[M]^+$: 586.2679, found: 586.2664.

Mannich reaction with *N*,*N*-phthaloyl-*tert*-leucylchloride (2b), *N*-phenyl-2,4,6-trimethylbenzylidene amine (6c), and the silylketene acetals 10, 11 and 12. General procedure: Acid chloride **2b** (168 mg, 0.6 mmol) in dry CH_2Cl_2 (3 mL) was added under argon at 0 °C to a solution of of Schiff base **6c** (112 mg, 0.5 mmol) in dry CH_2Cl_2 (2 mL). The mixture was kept at 0 °C for 10 min and then warmed to room temperature over 1 h. After cooling the solution to 0 °C the silylketene acetal (0.75 mmol) was added over 5 min. The solution was then stirred at room temperature for 72 h. After addition of CH_2Cl_2 (10 mL), the mixture was washed with 10% aq. $NaHCO_3$ (10 mL) and brine (10 mL) and dried over Na_2SO_4. After evaporation to dryness, the residue was purified by chromatography on silica gel.

(*R*)-2-{(*R*)-[*N*-Phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-(2′,4′,6′-trimethylphenyl)-methyl}-butano-4-lactone (13*syn*): The product was obtained from Schiff base **6c** (223 mg, 1 mmol), acid chloride **2b** (308 mg, 1.1 mmol) and 2-trimethylsiloxydihydrofuran (**10**, 237 mg, 0.75 mmol) after chromatography with hexane/acetone 12:1). Colorless solid (47%); m.p.: 186 °C; TLC: $R_f = 0.06$ (hexane/acetone 6:1); HPLC: $t_R = 15'22''$ (methanol/H_2O 72:28); $[\alpha]_D^{22} = -82.9$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.63$ (br, 4H), 7.42 (ddd, $J = 8$, 8, 1 Hz, 1H), 7.23 (d, $J = 8$ Hz, 1H), 7.15 (dd, $J = 8$, 8 Hz, 1H), 6.81 (s, 1H), 6.65 (d, $J = 10$ Hz, 1H), 6.39 (ddd, $J = 8$, 8, 1 Hz, 1H), 6.38 (s, 1H), 4.45 (d, $J = 8$ Hz, 1H), 4.58 (ddd, $J = 16$, 8, 6 Hz, 1H), 4.46 (s, 1H), 4.30 (ddd, $J = 16$, 8, 6 Hz, 1H), 3.46 (ddd, $J = 10$, 16, 8 Hz, 1H), 2.60–2.70 (m, 1H), 2.53–2.59 (m, 1H), 2.50 (s, 3H), 2.12 (s, 3H), 1.27 (s, 3H), 1.11 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 175.85$ (q), 166.49 (q), 139.52 (q), 138.94 (q), 137.30 (q), 137.21 (q), 133.93 (CH), 130.67 (CH), 130.45 (CH), 130.13 (q), 129.77 (CH), 129.35 (CH), 128.62 (CH), 128.55 (CH), 123.16 (CH), 66.09 (CH_2), 57.80 (CH), 55.66 (CH), 41.95 (CH), 37.13 (q), 27.78 (CH_2), 27.67 (CH_3), 21.62 (CH_3), 21.28 (CH_3), 20.76 (CH_3); MS (70 eV, EI): m/z (%): 552 (18), 496 (6), 336 (20), 308 (27), 280 (14), 216 (100); $C_{34}H_{36}N_2O_3$ (552.67): calcd C 73.89, H 6.57, N 5.07; found: C 73.60, H 6.40, N 4.93; HR-MS (70 eV, EI): m/z: calcd for $[M]^+$: 552.2624, found: 552.2607.

(*S*)-2-{(*R*)-[*N*-Phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-(2′,4′,6′-trimethylphenyl)-methyl}-butano-4-lactone (13*anti*): colorless solid (28%); m.p.: 174 °C; TLC: $R_f = 0.11$ (hexane/acetone 6:1); HPLC: $t_R = 20'44''$ (methanol/H_2O 72:28); $[\alpha]_D^{22} = -77.4$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.11$ (d, $J = 8$ Hz, 1H), 7.62 (br, 4H), 7.47 (ddd, $J =$ 8, 8, 1 Hz, 1H), 7.13 (dd, $J = 8$, 8 Hz, 1H), 6.92 (s, 1H), 6.81 (d, $J = 12$ Hz, 1H), 6.40 (s, 1H), 6.35 (ddd, $J = 8$, 8, 1 Hz, 1H), 5.42 (d, $J = 8$ Hz, 1H), 4.50 (ddd, $J = 10$, 9, 7 Hz, 1H), 4.59 (s, 1H), 4.32 (ddd, $J = 10$, 9, 3 Hz, 1H), 3.30 (ddd, $J = 12$, 9, 3 Hz, 1H), 2.59 (s, 3H), 2.30 (ddd, $J = 9$, 10, 13 Hz, 1H), 2.17 (s, 3H), 1.70 (ddd, $J = 3$, 7, 13 Hz, 1H), 1.12 (s, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 177.27$ (q), 166.30 (q), 140.82 (q), 138.26 (q), 137.57 (q), 137.50 (q), 133.69 (CH), 130.94 (CH), 130.42 (CH), 130.25 (CH), 130.18 (CH), 130.08 (CH), 129.60 (q), 128.30 (CH), 128.13 (CH), 123.00 (CH), 66.34 (CH_2), 57.49 (CH), 54.50 (CH), 39.34 (CH), 37.25 (q), 27.80 (CH_3), 27.37 (CH_2), 21.68 (CH_3), 20.67 (CH_3); MS (70 eV, EI): m/z (%): 552 (22), 496 (6), 336 (20), 308 (30), 280 (15), 216 (100); HR-MS (70 eV, EI): m/z: calcd for $[M]^+$: 552.2624, found: 552.2626.

Methyl (*S*)-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-3-(2,4,6-trimethylphenyl)-(*R*)-2-methoxy-propionate (14*syn*): The product was obtained from the same reaction mixture as **14*anti*** after additional chromatography with hexane/dichloromethane 1:6. Colorless solid (70%); m.p.: 235 °C; TLC: $R_f = 0.29$ (hexane/ethyl acetate 3:1); HPLC: $t_R = 18'58''$ (methanol/H_2O 75:25); $[\alpha]_D^{22} = -98$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.86$ (d, $J = 8$ Hz, 1H), 7.61 (br, 4H), 7.45 (ddd, $J = 2$, 8, 8 Hz, 1H), 7.12 (dd, $J = 8$, 8 Hz, 1H), 6.85 (s, 1H), 6.67 (d, $J = 11$ Hz, 1H), 6.37 (s, 1H), 6.32 (ddd, $J = 2$, 8, 8 Hz, 1H), 5.37 (d, $J = 8$ Hz, 1H), 4.46 (s, 1H), 4.36 (d, $J = 11$ Hz, 1H), 3.93 (s, 3H), 3.24 (s, 3H), 2.51 (s, 3H), 2.15 (s, 3H), 1.13 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 172.58$ (q), 166.13 (q), 140.51 (q), 139.14 (q), 137.77 (q), 137.06 (q), 133.71 (CH), 130.49 (CH), 130.46 (CH), 130.19 (CH), 129.88 (CH), 129.86 (CH), 129.28 (q), 128.30 (CH), 128.00 (CH), 123.06 (q), 79.52 (CH), 57.83 (CH_3), 57.58 (CH), 56.62 (CH), 52.54 (CH_3), 37.23 (q), 27.90 (CH_3), 21.43 (CH_3), 20.75 (CH_3), 19.84 (CH_3); MS (70 eV, EI): m/z (%): 570 (0.1), 539 (0.4), 511 (1), 467 (48), 244 (23), 216 (100); $C_{34}H_{38}N_2O_6$ (570.682): calcd C 71.56, H 6.71, N 4.91; found: C 71.18, H 6.67, N 4.73; HR-MS (70 eV, EI): m/z: calcd for $[M]^+$: 570.2730, found: 570.2755.

Methyl (*S*)-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-3-(2,4,6-trimethylphenyl)-(*S*)-2-methoxy-propionate (14*anti*): The product was obtained from (*Z*)-1,2-dimethoxy-1-trimethyl siloxy-ethene **11** (132 mg, 0.75 mmol) after chromatography with hexane/ethyl acetate 4:1. Colorless oil (7%); TLC: $R_f = 0.23$ (hexane/ethyl acetate 3:1); HPLC: $t_R = 18'2''$ (methanol/H_2O 75:25); $[\alpha]_D^{22} = -21$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.62$ (s, 4H), 7.45 (ddd, $J = 1$, 8, 8 Hz, 1H), 7.29 (d, $J = 8$ Hz, 1H), 7.16 (dd, $J = 8$, 8 Hz, 1H), 6.84 (d, $J = 10$ Hz, 1H), 6.81 (s, 1H), 6.46 (ddd, $J = 1$, 8, 8 Hz, 1H), 6.38 (s, 1H), 5.64 (d, $J = 8$ Hz, 1H), 4.47 (d, $J = 10$ Hz, 1H), 4.46 (s, 1H), 3.54 (s, 3H), 3.52 (s, 3H), 2.51 (s, 3H), 2.13 (s, 3H), 1.23 (s, 3H), 1.12 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta =$ 170.66 (q), 166.84 (q), 165.61 (q), 140.70 (q), 138.64 (q), 138.35 (q), 137.24 (q), 133.67 (CH), 131.52 (q), 130.63 (CH), 130.49 (CH), 130.07 (CH), 129.86 (CH), 129.62 (CH), 129.12 (q), 128.60 (CH), 128.35 (CH), 123.07 (CH), 80.99 (CH), 57.99 (CH), 57.85 (CH_3), 51.86 (CH_3), 37.11 (q), 27.60 (CH_3), 21.79 (CH_3), 20.77 (CH_3); MS (70 eV, EI): m/z (%): 570 (0.1), 539 (0.5), 511 (1), 467 (48), 244 (21), 216 (100); HR-MS (70 eV, EI): m/z: calcd for $[M]^+$: 570.2730, found: 570.2748.

Methyl (*S*)-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-3-(2,4,6-trimethylphenyl)-(*R*)-2-(*tert*-butyl-dimethyl)-siloxy-propionate (15*syn*): The product was obtained from (*E*)-1-(dimethyl-*tert* butylsiloxy)-2-methoxy, 2-trimethylsiloxy-ethene **12** (207 mg, 0.75 mmol) after chromatography with hexane/ethyl acetate 10:1. Colorless solid (66%); m.p.: 197 °C; TLC: $R_f = 0.17$ (hexane/ethyl acetate 10:1); HPLC: $t_R = 11'13''$ (methanol/H_2O 75:25); $[\alpha]_D^{22} = -91.8$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.62$ (s, 4H), 7.34 (d, $J = 8$ Hz, 1H), 7.29 (ddd, $J = 1$, 8, 8 Hz, 1H), 7.07 (dd, $J = 7$, 7 Hz, 1H), 6.67 (s, 1H), 6.49 (s, 1H), 6.44 (ddd, $J = 1$, 8, 8 Hz, 1H), 6.08 (d, $J = 10$ Hz, 1H), 6.00 (d, $J = 8$ Hz, 1H), 5.12 (d, $J = 10$ Hz, 1H), 4.37 (s, 1H), 3.88 (s, 3H), 2.16 (s, 3H), 2.13 (s, 3H), 1.64 (s, 3H), 1.07 (s, 9H), 0.55 (s, 9H), −0.06 (s, 3H), −0.31 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 172.54$ (q), 166.72 (q), 165.87 (q), 140.41 (q), 139.52 (q), 138.15 (q), 136.74 (q), 133.68 (CH), 131.54 (q), 130.23 (CH), 130.19 (CH), 130.06 (q), 129.82 (CH), 129.61 (CH), 129.09 (CH), 128.29 (CH), 128.01 (CH), 123.05 (q), 72.31 (CH), 61.67 (CH), 57.94 (CH), 51.90 (CH_3), 37.14 (q), 27.86 (CH_3), 25.31 (CH_3), 21.25 (CH_3), 20.69 (CH_3), 20.36 (CH_3), 17.87 (q), −4.79 (CH_3), −5.19 (CH_3); MS (70 eV, EI): m/z (%): 670 (0.3), 613 (16), 585 (5), 467 (78), 244 (28), 216 (100); $C_{39}H_{50}N_2O_6Si$ (670.92): calcd C 69.82, H 7.51, N 4.18; found: C 69.83, H 7.42, N 4.05; HR-MS (70 eV, EI): m/z: calcd for $[M]^+$: 670.3438, found: 670.3422.

Modified procedure for the cleavage of the *N,N*-phthaloyl group. General procedure: $NaBH_4$ (4 mg, 0.1 mmol) was added to a solution of of methyl-(*S*)-3-aryl-3-[*N*-aryl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-2,2-dimethyl-propionate (0.09 mmol) in isopropanol/water 7:1 (1.6 mL). The reaction mixture was stirred at room temperature until a TLC showed the consumption of the starting material. By addition of concentrated HCl (aqueous, 0.36 mmol, 30 μL) the pH of the solution was adjusted to pH 1. After stirring at 80 °C until a TLC showed the consumption of the intermediate product, the solution was neutralised with aq. $NaHCO_3$ and extracted with CH_2Cl_2 (5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed in vacuo. The residue was added onto a plug of silica gel, washed with hexane/acetate 3:1 and eluted with pure ethyl acetate.

Methyl 2,2-dimethyl-(*S*)-3-(2′,4′,6′-trimethylphenyl)-3-[*N*-phenyl-*N*-((*S*)-*tert*-leucyl)]-amino-propionate (18a): The product was obtained from of methyl 2,2-dimethyl-(*S*)-3-(2′,4′,6′-trimethylphenyl)-3-[*N*-phenyl-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-propionate (**8c**, 60 mg, 0.11 mmol) in isopropanol/water 7:1 (12 mL) as a colorless oil (88%); TLC: $R_f = 0.08$ (hexane/ethyl acetate 4:1); $[\alpha]_D^{22} = -38$ ($c = 1.31$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.46$ (d, $J = 8$ Hz, 1H), 7.34 (ddd, $J = 1, 7, 7$ Hz, 1H), 7.23 (dd, $J = 7, 7$ Hz, 1H), 7.08 (ddd, $J = 1, 8, 8$ Hz, 1H), 6.63 (s, 1H), 6.81 (s, 1H), 6.57 (d, $J = 8$ Hz, 1H), 5.63 (s, 1H), 3.75 (s, 3H), 2.74 (s, 1H), 2.28 (s, 3H), 2.12 (s, 3H), 1.80 (s, 3H), 1.56 (s, 3H), 1.50 (br, 2H), 1.16 (s, 3H), 0.87 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 177.62$ (q), 175.35 (q), 144.09 (q), 139.16 (q), 139.08 (q), 136.72 (q), 130.79 (CH), 130.41 (q), 130.30 (CH), 129.69 (CH), 129.02 (CH), 128.93 (CH), 128.30 (CH), 127.80 (CH), 69.19 (CH), 59.89 (CH), 51.87 (CH_3), 49.23 (q), 34.28 (q), 29.20 (CH_3), 27.72 (CH_3), 23.62 (CH_3), 22.17 (CH_3), 21.66 (CH_3), 20.68 (CH_3); MS (70 eV, EI): *m*/*z* (%): 438 (0.2), 407 (1), 338 (7), 264 (7), 147 (6), 86 (100); HR-MS (70 eV, EI): *m*/*z*: calcd for ($C_{27}H_{38}N_2O_3$): 438.2882, found: 438.2898.

Methyl 2,2-dimethyl-(*S*)-3-[*N*-(4′-methoxyphenyl)-*N*-((*S*)-*tert*-leucyl)]-amino-3-phenyl-propionate (18b) and methyl 2,2-dimethyl-(*R*)-3-[*N*-(4′-methoxyphenyl)-*N*-((*S*)-*tert*-leucyl)]-amino-3-phenyl-propionate (18b): The product was obtained from of a 92:8 mixture (11 mg, 0.02 mmol) of the diastereomers methyl 2,2-dimethyl-(*S*)-3-[*N*-(4′-methoxyphenyl)-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-3-phenyl-propionate (**8g**) and methyl 2,2-dimethyl-(*R*)-3-[*N*-(4′-methoxyphenyl)-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-3-phenyl-propionate (**9g**) as a colorless oil (97%) as a 92:8 mixture of the diastereomers **18b** and **19b**. TLC: $R_f = 0.17$ (hexane/acetone 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.28$ (dd, $J = 3$, 9 Hz, 1H), 7.11 (m, 2H), 6.88 (dd, $J = 3$, 9 Hz, 1H), 6.63 (dd, $J = 3$, 9 Hz, 1H), 6.38 (dd, $J = 3$, 9 Hz, 1H), 3.79 (s, 3H), 6.15 (s, 1H), 3.64 (s, 3H), 2.74 (s, 1H), 1.27 (s, 3H), 1.21 (s, 3H), 0.88 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 177.02$ (q), 176.74 (q), 159.08 (q), 136.84 (q), 133.53 (q), 132.48 (CH), 132.31 (CH), 131.41 (CH), 127.73 (CH), 127.59 (CH), 113.32 (CH), 66.06 (CH), 58.99 (CH), 55.35 (CH_3), 51.99 (CH_3), 47.45 (q), 34.73 (q), 26.45 (CH_3), 26.14 (CH_3), 23.27 (CH_3); MS (70 eV, EI): *m*/*z* (%): 426 (1), 395 (2), 369 (2), 341 (23), 212 (36), 86 (100); $C_{25}H_{34}N_2O_4$ (426.55): calcd C 70.40, H 8.03, N 6.57; found: C 70.32, H 7.86, N 6.53; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 426.2519, found: 426.2527. Characteristic data of the minor diastereomer **19b**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.78$ (s, 3H), 3.61 (s, 3H), 2.89 (s, 1H), 0.77 (s, 9H).

Methyl 2,2-dimethyl-(*S*)-3-[*N*-(2′-methoxy-6′-methylphenyl)-*N*-((*S*)-*tert*-leucyl)]-amino-3-phenyl-propionate (18c): The product was obtained from of methyl 2,2-dimethyl-(*S*)-3-[*N*-(2′-methoxy-6′-methylphenyl)-*N*-((*S*)-*N*′,*N*′-phthaloyl-*tert*-leucyl)]-amino-3-phenyl-propionate (**8h**, 174 mg, 0.31 mmol) in isopropanol/water 7:1 (25 mL) after column chromatography with hexane/ethyl acetate 3:1 as a colorless oil (65%). TLC: $R_f = 0.11$ (hexane/ethyl acetate 3:1); $[\alpha]_D^{22} = +78$ ($c = 0.55$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.17$ (dd, $J = 8$, 8 Hz, 1H), 7.15 (dd, $J = 7$, 7 Hz, 1H), 7.05 (dd, $J = 7$, 7 Hz, 2H), 6.99 (d, $J = 7$ Hz, 2H), 6.75 (d, $J = 8$ Hz, 1H), 6.56 (d, $J = 8$ Hz, 1H), 6.54 (s, 1H), 3.82 (s, 3H), 3.64 (s, 3H), 2.63 (s, 1H), 1.47 (s, 3H), 1.38 (s, 3H), 1.07 (s, 3H), 0.93 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 177.58$ (q), 177.48 (q), 156.30 (q), 140.92 (q), 135.94 (q), 131.74 (CH), 129.18 (CH), 128.77 (q), 127.54 (CH), 127.21 (CH), 122.92 (CH), 108.33 (CH), 65.84 (CH), 60.10 (CH), 54.15 (CH_3), 51.86 (CH_3), 48.78 (q), 34.67 (q), 26.55 (CH_3), 24.56 (CH_3), 22.80 (CH_3), 18.35 (CH_3); MS (70 eV, EI): *m*/*z* (%): 440 (1), 409 (1), 383 (3), 308 (3), 254 (3), 226 (22), 86 (100); HR-MS (70 eV, EI): *m*/*z*: calcd for ($C_{26}H_{36}N_2O_4$): 440.2675, found: 440.2689.

Modified procedure for carrying out the Edman degradation. General procedure: Phenylisothiocyanate (25 mg, 0.183 mmol) was added to a solution of one of the above mentioned amines (0.091 mmol) in water/pyridine 1:1 (5 mL). To this solution was slowly added 1 equivalent of aqueous NaOH (0.2 M, 0.9 mL) at room temperature. After stirring for 3 h, the reaction mixture was extracted with toluene and the organic solvent removed in vacuum. The residue was dissolved in a mixture of CH_2Cl_2 (5 mL) and TFA (1 mL) and refluxed until a TLC: of the reaction mixture showed the disappearance of the starting material. After neutralisation with aq. $NaHCO_3$ and extraction with CH_2Cl_2 (10 mL) the combined organic layers were dried over Na_2SO_4. After filtration the solution was evaporated to dryness and the amine was obtained by column chromatography on silica gel.

Methyl 2,2-dimethyl-(*S*)-3-phenyl-amino-3-(2′,4′,6′-trimethylphenyl)-propionate (20a): The product was obtained after hydrolysis of methyl 2,2-dimethyl-(*S*)-3-[*N*-(*tert*-leucyl)-*N*-phenyl]-amino-3-(2′,4′,6′-trimethylphenyl)-propionate (**18a**, 66 mg, 0.151 mmol) in a mixture of CH_2Cl_2 (8 mL) and TFA (2.3 mL). Column chromatography with hexane/actone 40:1 afforded the product as a yellow oil (59%). TLC: $R_f = 0.51$ (hexane/acetone 4:1); $[\alpha]_D^{22} = -69.4$ ($c = 1.13$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.04$ (ddd, $J = 2, 7, 7$ Hz, 2H), 6.85 (s, 1H), 6.68 (s, 1H), 6.58 (ddd, $J = 1, 7, 7$ Hz, 1H), 6.40 (dd, $J = 1, 9$ Hz, 2H), 5.03 (s, 1H), 4.61 (br, 1H), 3.68 (s, 3H), 2.56 (s, 3H), 2.29 (s, 3H), 2.21 (s, 3H), 1.33 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 177.58$ (q), 147.16 (q), 137.90 (q), 137.05 (q), 136.19 (q), 132.04 (CH), 131.23 (q), 129.89 (CH), 129.10 (CH), 116.80 (CH), 112.37 (CH), 60.61 (CH_3), 52.33 (CH), 48.55 (q), 25.61 (CH_3), 22.33 (CH_3), 22.08 (CH_3), 21.46 (CH_3), 20.62 (CH_3); IR (KBr, drift): $\tilde{\nu} = 3408, 2955, 1719, 1518, 1499, 1432, 1389, 1367, 1273, 1254, 1074, 852, 751, 723$ cm^{-1}, MS (70 eV, EI): *m*/*z* (%): 325 (3), 224 (100), 104 (7); $C_{21}H_{27}NO_2$ (325.45): calcd C 77.50, H 8.36, N 4.30; found: C 77.37, H 8.18, N 4.25; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 325.2042, found: 325.2032.

Methyl 2,2-dimethyl-3-(4′-methoxyphenyl)-amino-3-phenyl-propionate (20b): The product was obtained from methyl 2,2-dimethyl-3-[*N*-(*tert*-leucyl)-*N*-(4′-methoxyphenyl)]-amino-3-phenyl-propionate (**18b**, 39 mg, 0.091 mmol) as a pale yellow oil after column chromatography with hexane/acetone 30:1 and gave correct analytical data according to the literature.[30] Yield 84%; TLC: $R_f = 0.36$ (hexane/acetone 3:1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.27$ (s, 5H), 6.62 (d, $J = 9$ Hz, 2H), 6.43 (d, $J = 9$ Hz, 2H), 4.44 (s, 1H), 3.66 (s, 3H), 2.18 (s, 1H), 1.25 (s, 3H),1.16 (s, 3H); IR (KBr, drift): $\tilde{\nu} = 3368, 3070, 3028, 2834, 1733, 1715, 1617, 1514, 1391, 1035, 824, 806, 764$ cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 313 (8), 212 (100), 196 (3), 168 (3); HR-MS (70 eV, EI): *m*/*z*: calcd for ($C_{19}H_{23}NO_3$):313.1678, found: 313.1689.

Methyl 2,2-dimethyl-(*S*)-3-(2′-methoxy-6′-methylphenyl)-amino-3-phenyl-propionate (20c): The product was obtained after hydrolysis of methyl 2,2-dimethyl-(*S*)-3-[*N*-(*tert*-leucyl)-*N*-(2′-methoxy-6′-methylphenyl)]-amino-3-phenyl-propionate (**18c**, 66 mg, 0.150 mmol) in a mixture of CH_2Cl_2 (7.8 mL) and TFA (1.6 mL). Column chromatography with hexane/ethyl acetate 25:1 gave the product as a colorless oil (45%). TLC: $R_f = 0.13$ (hexane/ethyl acetate 25:1); $[\alpha]_D^{22} = -46.3$ ($c = 1.045$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.11 - 7.19$ (m, 5H), 6.61 (dd, $J = 7, 7$ Hz, 1H), 6.56 (dd, $J = 2, 7$ Hz, 2H), 5.02 (s, 1H), 4.84 (s, 1H), 3.81 (s, 3H), 3.65 (s, 3H), 2.25 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 177.27$ (q), 149.93 (q), 139.76 (q), 135.40 (q), 128.34 (CH), 127.55 (q), 127.44 (CH), 126.99 (CH), 123.89 (CH), 119.84 (CH), 108.35 (CH), 66.28 (CH), 55.71 (q), 51.78 (CH_3), 47.42 (CH_3), 24.68 (CH_3), 19.95 (CH_3), 19.48 (CH_3); IR (KBr, drift): $\tilde{\nu} = 3387, 3067, 3027, 2950, 2838, 1734, 1608, 1587, 1506, 1467, 1429, 1388, 1377, 764, 704$ cm^{-1}, MS (70 eV, EI): *m*/*z* (%): 237 (6), 226 (100), 210 (5); $C_{20}H_{25}NO_3$ (327.42): calcd C 73.37, H 7.70, N 4.28, found: C 73.36, H 7.60, N 4.25; HR-MS (70 eV, EI): *m*/*z*: calcd for $[M]^+$: 327.1834, found: 327.1849.

Methyl (*S*)-3-amino-2,2-dimethyl-3-propionate hydrochloride (22): A solution of cerium ammonium nitrate (CAN) (163 mg, 0.3 mmol) in water (0.95 mL) was added to a solution of 33 mg methyl 2,2-dimethyl-(*S*)-3-(2′-methoxy-6′-methylphenyl)-amino-3-phenyl-propionate (**20c**, 33 mg, 0.1 mmol) in acetonitrile (2 mL) at 0 °C. After vigorous stirring for 1 h, a solution of CAN (109 mg, 0.2 mmol) in water (0.3 mL) was added and the mixture was stirred for an additional hour at room temperature. The mixture was then diluted with water (8 mL) and extracted with diethyl ether (5 mL). The aqueous layer was set to pH 8 to 9 and extracted a second time with ether (5 mL). After drying the combined organic layers over

0947-6539/00/0611-2042 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 11

Na_2SO_4 and addition of a saturated solution of HCl in ether (2 mL), the solvent was removed in vacuo. Colorless solid (56%); $[\alpha]_D^{22} = +34.7$ ($c = 0.21$ in 1M HCl) {Lit.: $[\alpha]_D^{23} = -32.8$ ($c = 1.1$, 1N HCl) (*S*)-compound,[3g] $[\alpha]_D^{26} = +34.6$ ($c = 0.17$, 1M HCl) (*R*)-compound[3m]}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.41-7.50$ (m, 3H; *o*H, *p*H), 7.34–7.60 (m, 2H; *m*H), 4.54 (s, 1H; PhCHN), 3.76 (s, 3H; OCH_3), 1.28 (s, 3H; CH_3), 1.24 (s, 3H; CH_3); MS (70 eV, EI): *m*/*z* (%): 206 (0.02), 176 (0.06), 146 (0.31), 132 (0.75), 106 (100); HR-MS (70 eV, EI): *m*/*z*: calcd for $[M - H_2Cl]^+$: 206.1181, found: 206.1200.

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