Pergamon

Tetrahedron 58 (2002) 1317–1334

TETRAHEDRON

Auxiliary controlled enantioselective synthesis of 3-aryl-prolines

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Received 19 July 2001; revised 7 December 2001; accepted 10 December 2001

Abstract—The synthesis of optically active *cis* 3-aryl proline derivatives was achieved in a five-step sequence involving an enantioselective aza-Claisen rearrangement as the key step. Initially, suitable cinnamyl amines were generated via a Pd(0) catalyzed amination of the corresponding *N*-allyl mesylates using optically active proline derivatives as chiral auxiliaries. The zwitterionic aza-Claisen rearrangement with azidoacetyl fluoride gave the corresponding α-azido-γ,δ-unsaturated amides with a complete simple and a moderate to high induced diastereoselectivity. The so formed unsaturated azides were subjected to a reductive cyclization developed by Evans and Sabol to generate the 2,3-*cis*-3-arylproline amides with high yields. The absolute configuration of one representative compound was proven by X-ray analysis. The removal of the auxiliary was difficult but succeeded at the stage of the unsaturated amide by treatment with acid without decrease of the diastereoselectivity. The so obtained 3-arylprolines are useful key fragments in biologically interesting (cyclo-) peptides and peptidomimetics. © 2002 Published by Elsevier Science Ltd.

1. Introduction

During the past years, the synthesis of optically active 3-aryl prolines gained an increasing interest. These non-natural amino acids have been introduced in a range of biologically interesting peptides as substance P analogs, anti-inflammatory cyclopeptides and non-peptidomimics of sandostatin/somatostatin.[1]

Focusing on the syntheses of optically active 3-aryl prolines as key compounds in *oligo* peptides, three major strategies were developed to obtain the desired material.[2] The first one used *S*-pyroglutamate **A** as starting compound involved in an ex chiral pool sequence:[3] The unsaturated amide **B** was generated in six standard steps, an aryl Gilman cuprate addition introduced the aromatic substituent. Likewise a final five or a seven-step sequence was used to synthesize the 2,3-*trans* and the 2,3-*cis* products, respectively. The second strategy employed a 2+3 cycloaddition[4] of azomethinylides and styrenes or a cyclocondensation[5] of 2-aminomalonic acid **C** derivative and a suitable cinnamaldehyde **D** building-up the pyrrolidine system **E**. Though only five steps overall were necessary to synthesize the proline derivative, the stereogenic centers were generated unselectively. Further separations of the diastereomers and optical resolutions allowed to obtain enantiomerically pure material. The third pathway could be subdivided in two sequences:[6,7] Firstly an open chain material **H** or **K** bearing all stereogenic centers was generated, which was subjected to a suitable cyclization as the second key step. Always the stereochemical information was introduced by means of a chiral auxiliary **G** and **I**.

The anion of Schöllkopf's bislactim ether **G** underwent a Michael addition with a cinnamic ester **F** to generate iminoester **H**.[6] A subsequent cyclization in presence of HCl gave exclusively the corresponding 2,3-*trans* proline after reduction of the intermediately formed pyrrolidone (five steps overall). Alternatively, 2,3-*cis* and 2,3-*trans* 3-aryl prolines had been synthesized via Sabols procedure, respectively.[7] A six-step sequence allowed to generate the oxazolidinone **J** from **F** and **I** (incl. optical resolution). After an electrophilic azidation (trisylazide) to **K** and removal of the chiral auxiliary (three steps), the cyclization was achieved via a hydroboration amine insertion sequence published by Evans[8] in 1990. Though the first sequence was found to be the more straight forward one (five steps only, 2,3-*trans* product) the latter seems to be more flexible because of the formation of the 2,3-*cis* and the 2,3-*trans* prolines, respectively. As a matter of principle, the *cis* material was epimerizable to give the thermodynamically more stable *trans* product (Fig. 1).

With the intention to synthesize the *cis* series via a straight forward stereoselective sequence we chose a zwitterionic aza-Claisen rearrangement of an appropriate allylamine and an α-amino acid fluoride fragment. The introduction of the chiral information should succeed incorporating an enantiomerically pure amine function as a chiral auxiliary. In analogy to the Evans/Sabol protocol we planned to involve the reductive cyclization to generate the 3-aryl prolines.

Keywords: 3-aryl-prolines; aza-Claisen rearrangement; zwitterion; chiral auxiliary; enantioselective synthesis; amino acids; allylamines; azides.

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0040–4020/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4020(01)01233-9

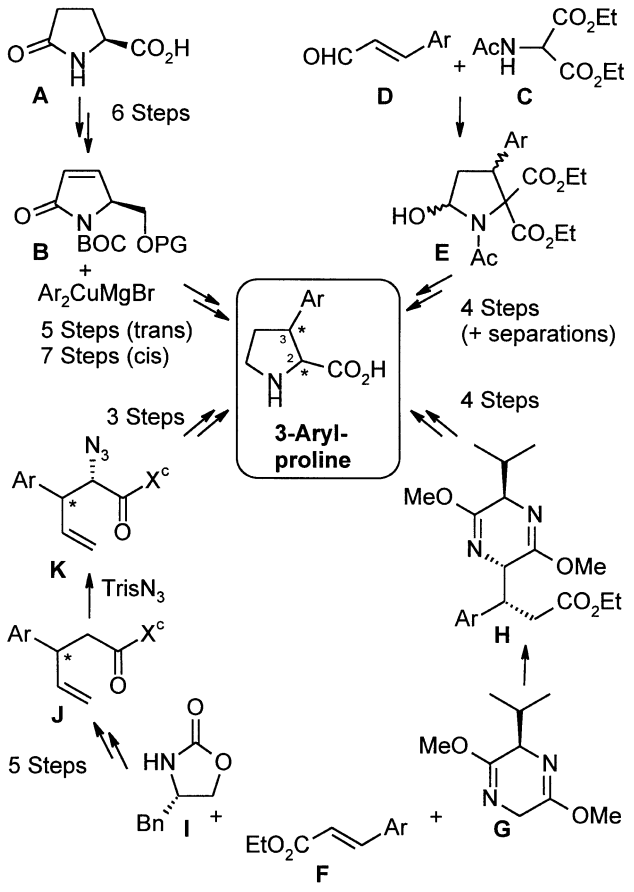
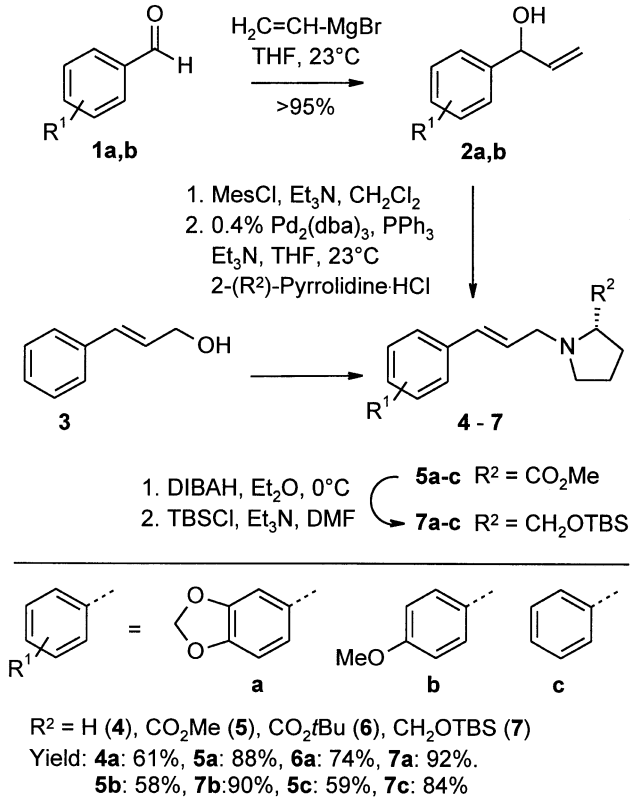


Figure 1. Syntheses of 3-aryl proline derivatives: literature strategies.



Scheme 1.

2. Results and discussion

The syntheses of the allylamines **4**–**7** started from commercially available piperonal **1a**, *p*-anisaldehyde **1b** and cinnamyl alcohol **3**, respectively. In the first step, the aldehydes **1** were subjected to a vinyl Grignard addition to generate the homologous allylalcohols **2** with high yield.[9] A sequence of an activation of the OH group of **2** and **3** as a mesylate and a consecutive Pd(0)-catalyzed substitution[10] by pyrrolidine, proline methylester and *t*-butylester[11] led to the cinnamyl amines **4**–**6**, respectively (Scheme 1). Four aspects were noteworthy to obtain maximal yields of the allylamines **4**–**6**. (1) The allyl mesylates should be subjected to the amination reaction as crude materials. Especially the electron rich systems tended to undergo fast decomposition during purification via column chromatography.[12] (2) The nucleophilic amine was found to attack exclusively the least hindered terminal position of the allyl palladium complex. Only 3-aryl allylamines bearing *E*-double bonds could be isolated. (3) The amount of the Pd catalyst involved could be decreased on increasing the batch. Reacting about 2 mmol cinnamyl alcohol, about 2 mol% were found to be necessary to achieve a satisfactory conversion. In contrast, the transformation of 20 mmol alcohol into the corresponding amine required only 0.2 mol% of the catalyst. Generally, the more electron rich systems gave higher yields with shorter reaction times and lower catalyst concentrations. (4) Handling the electron-rich systems, type **a** and **b**, strong acidic conditions should be avoided during work-up to suppress any cleavage of the intermediately formed ammonium salts (formation of highly stabilized cinnamyl cations).

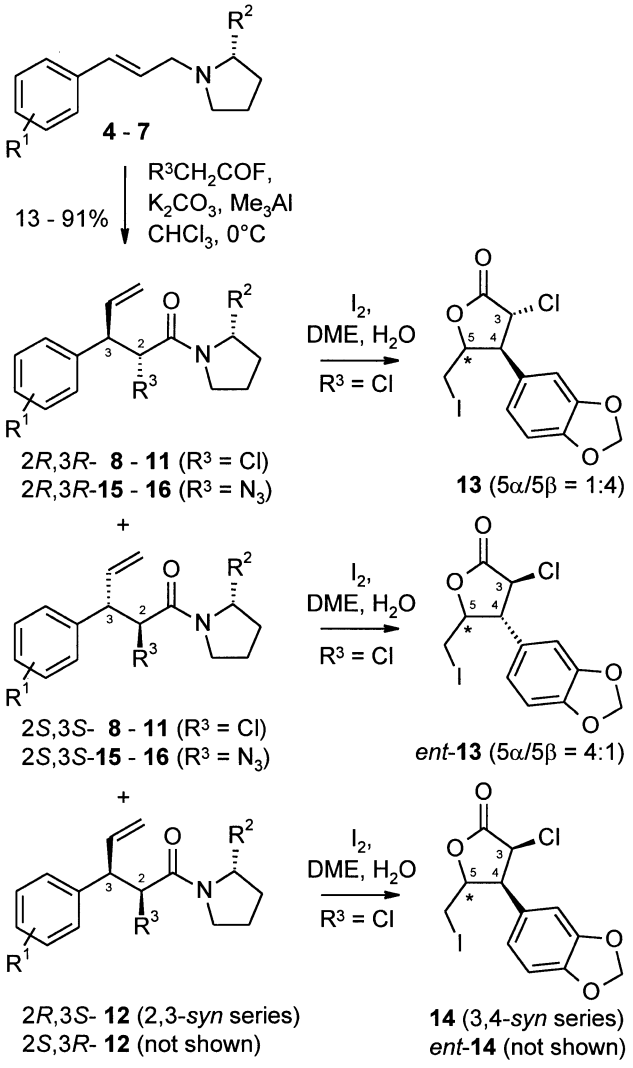
On one hand, the optically active proline derivatives used for the amination in **5** and **6** were generated via standard literature procedures.[10,11] On the other hand, several derivatizations were carried out starting from the methyl esters **5**: after an initial DIBAL-H reduction of the ester function,[13] the primary carbinols had been immediately converted into the corresponding TBS ethers **7** with high yields (Scheme 1).[14]

With the intention to set the benchmark on investigating the stereodirecting properties of the chiral auxiliaries in **5**–**7** during the course of the zwitterionic aza-Claisen rearrangement[15,16] we firstly treated the achiral *N*-allylpyrrolidine **4a** (R^2=H) with an excess of freshly prepared highly reactive chloroacetyl fluoride (R^3=Cl).[17,18] In presence of Me_3Al in a suspension of Na_2CO_3 in CH_2Cl_2 at 0°C, the racemic γ,δ-unsaturated amide **8** was obtained in 36% yield (not optimized) as a single diastereomer. The relative configuration of the stereogenic centers of the racemic material had been unequivocally proven after a final iodo lactonization.[18] Amide **8** was treated with I_2 in DME/H_2O to give the lactones **13** and *ent*-**13** in 88% yield (**13**/ent-**13**=1:1, racemate) as a mixture of two diastereomers (C5 α,β). These diastereomers were separated by means of HPLC, the ratio of **13** (C4–C5 *cis*/C4–C5 *trans*) was 4:1 pointing out, that the diastereoselectivity of the iodolactonization was moderate. The NOE analyses of both lactones **13** (C4–C5 *cis* and C4–C5 *trans*) gave the exclusive *trans* arrangement of C3 and C4.[19] Obviously these new stereogenic centers were generated with excellent

diastereoselectivity during the course of the Claisen rearrangement. No C3–C4 *cis* lactone **14** originating from the iodocyclization of the *syn*-amide series **12** was found. Furthermore both lactones **13** (C4–C5 *cis* and C4–C5 *trans*) were subjected to chiral HPLC analyses.[20] Always, two baseline-separated peaks of the enantiomers **13** and *ent*-**13** were found using a vancomycin precoated silicagel column, respectively.

With such suitable analytic in the hands we now tested the optically active *N*-allylproline derivatives **5**–**7** concerning their stereodirecting properties. Again, initial investigations were carried out employing the chloroacetyl fluoride.[17] The rearrangements of the allylamines **5a**, **6a** and **7a** gave the corresponding amides **9**–**11** with satisfactory yields (50–72%). The determination of the diastereoselectivities of the present reactions turned to be difficult: Always, at least a doubled set of peaks occurred in the NMR spectra of the rearrangement products **9**–**11**. The conversion of allylamine **5a** was found to be non-selective, three sets of peaks could be identified. The ratio was about 4:2:1, extensive HPLC analyses (→ two compounds) prove a difficult separation of the diastereomers.[21] In contrast, the spectra of the amides **10** and **11** showed a doubled set of peaks.[22] The ratio varied between 1:1 and about 1:4, which were found to be inseparable by means of HPLC methods. A subsequent iodolactonization[18] of the amides **9** and **10** clarified the situation. Again, exclusively the lactones **13** and/or *ent*-**13** (C3–C4 *trans*) were isolated with high yields (74–88%) and with moderate diastereoselectivity concerning the construction of C5. No corresponding C3–C4 *cis* material **14** originating from the *syn*-amide series **12** had been found improving the high *anti* selectivity of the Claisen rearrangement on generating the amides **8**–**11**.[19] Furthermore, the lactones were analyzed by means of chiral HPLC as described for the racemic material.[20] Presently, predominantly one enantiomer had been generated with moderate to high selectivity, the enantiomeric excess obtained varied between 50% (from R^2=CO_2Me) and 95% (from R^2=CO_2*t*Bu, CH_2OTBS) analyzing the lactones **13**. Obviously, all chiral proline auxiliaries in **5**–**7** allowed the generation of the new chiral centers of the amides **9**–**11** with a high *anti* selectivity and a variable chiral induction (auxiliary control). The doubled set of peaks analyzing the NMR spectra of **9**–**11** originated from the non-symmetric amide function causing the coexistence of different arrangements of the substituents at the partial C=N double bond. Furthermore, the occurrence of a third set clearly indicated an unselective aza-Claisen rearrangement generating the amides (→9).[21] However, the direct determination of the diastereoselectivity of the Claisen rearrangement analyzing the amides suffered from some uncertainties because of the potential superposition of the key peaks in the NMR spectra.

The allylamines **5** and **7** were chosen to investigate the azidoacetyl fluoride rearrangements to generate the optically active 2-azidoamides **15** and **16**, respectively, as suitable precursors for 3-arylproline syntheses.[23] Furthermore, the absolute configuration of the new centers C3 and C4 of the amides **15/16** had to be determined. Thus, the allylamine **5a** (R^2=CO_2Me) was treated with freshly prepared azidoacetyl fluoride to give amide **15a** in 77%



Scheme 2.

yield.[17,24] As expected, the analysis of the NMR spectra gave a third set of peaks indicating an incomplete diastereoselection during the course of the zwitterionic aza-Claisen rearrangement. The ratio of the three species was about 3:1:1. In addition to the major compound causing two sets of NMR peaks about 20–25% of a second diastereomer had been formed which could hardly been separated by means of HPLC. A preliminary analytical scale experiment starting from allylamine **5b** gave the amides **15b** (at least two diastereomers) in a poor yield of only 13% and a ratio of nearly 1:1 (purified compounds) which had been separated via preparative HPLC.[25] Obviously, the rearrangements incorporating the *N*-allylproline methylesters **5** (R^2=CO_2Me) and azidoacetyl fluoride led to mixtures of products turning this series less useful with regard to the 3-arylproline syntheses (Scheme 2).

Fortunately, the rearrangement series involving the

allylamines **7** (R^2=CH_2OTBS) gave the expected results: Treating the allylamines **7a–c** with azidoacetyl fluoride? a smooth reaction allowed to isolate the corresponding γ,δ-unsaturated amides **16** with satisfactory to high yields, respectively [57% (**16b**), 87% (**16a**) and 91% (**16c**)]. Again, the NMR spectra showed a doubled set of peaks (→non-symmetric amide, coexistence of two conformations), but the rearrangement was found to be diastereoselective (vide supra, Scheme 2).

The α-azido amides **15a** (mixture of diastereomers) and **16a–c** were subjected to the reductive cyclization (cycloalkylation) as described by Sabol and Evans.[7,8] A solution of dicyclohexyl borane in THF had been freshly prepared by an in situ hydroboration of cyclohexene.[26] Then, the appropriate amide **15** or **16** was added to induce an immediate regioselective hydroboration of the olefin generating the hypothetical intermediate **17**. A subsequent N_2 elimination—ring contraction led to the 3-aryl proline amides **11a** and **12a–c** as amine borane adducts. It should be pointed out that neither the amide functions nor the ester group of the auxiliary in **15a** had been effected by the reductive conditions. A careful final cleavage of the N–B bond with an excess of saturated aqueous NH_4Cl was mandatory to achieve a complete removal of the boron. The 3-arylprolines **19** were isolated with 62–75% yield, respectively. Again, the NMR spectra showed doubled sets of peaks (→non-symmetric amide, coexistence of two conformations).

In contrast, the cleavage of the boron-complex of proline **18a** (mixture of diastereomers) took another course: the so deprotected secondary amine function of the 3-arylproline sub-unit of **18a** underwent an intramolecular attack at the ester group to generate the corresponding pyrazinedione **20** in 62% yield as a white crystalline material.[27] The tricycle **20** was investigated via NOE analysis to improve the relative configuration of the stereogenic centers. While the *cis* arrangement of aryl and amide function of the new proline sub-unit could be confirmed undoubtedly, any save correlation with the stereogenic center with the auxiliary proline failed.[28] An X-ray analysis[29] of appropriate crystals of **20** gave the ultimate proof of the structure indicating the formation of the 2*R*,3*R* configuration of the 3-arylproline in **18a** (Fig. 2). Unless a mixture of diastereomers had been employed as the starting material of the cyclization, the yield of 62% improved, that the major diastereomer had given the isolated material bearing the present configuration. The minor compound could not be isolated as a pure crystalline material circumventing the correct analysis of this compound (probably 2*S*, 3*S*). However, the rearrangement using the *S*-proline derivatives as chiral amine auxiliaries in **5–7** obviously induced the moderate to highly selective formation of 2*R*,3*R* azido amides **9–11**, which represented useful precursors for non-natural amino acids syntheses (Scheme 3).

An asymmetric synthesis using chiral auxiliaries must be characterized by an easy introduction of the chiral

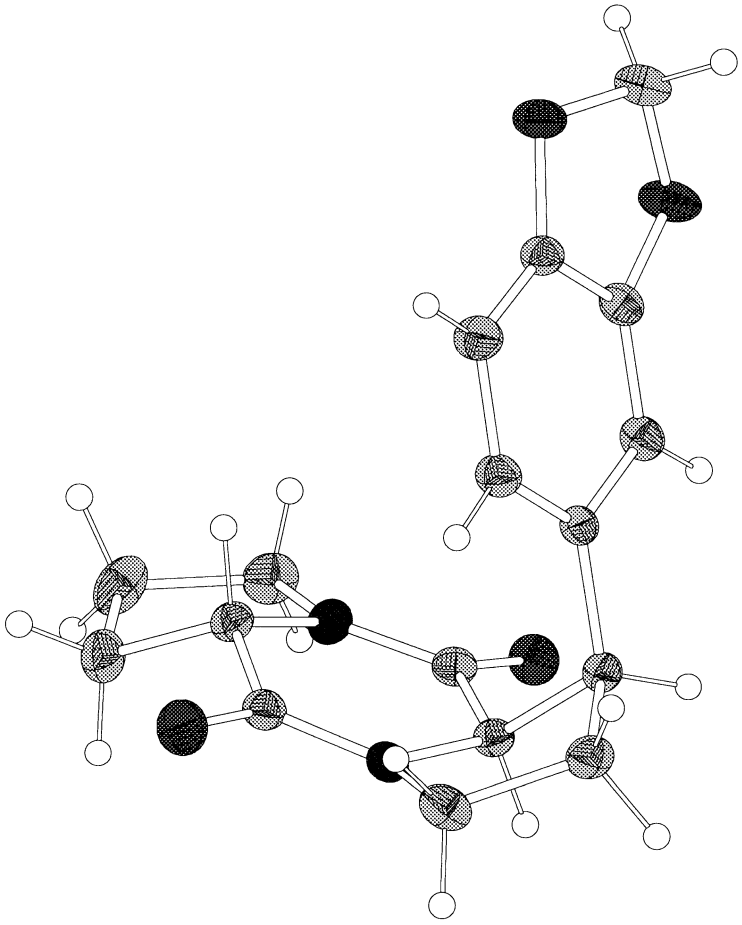
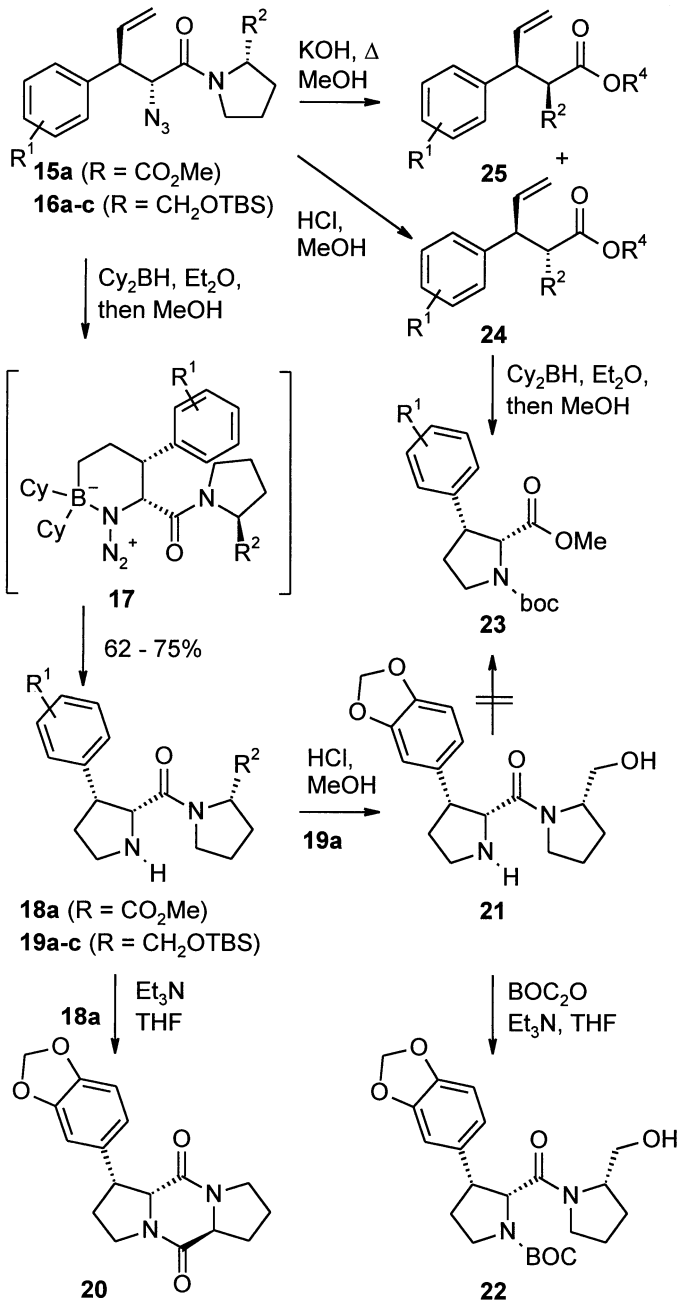


Figure 2. ORTEP plot of tricycle **20**.



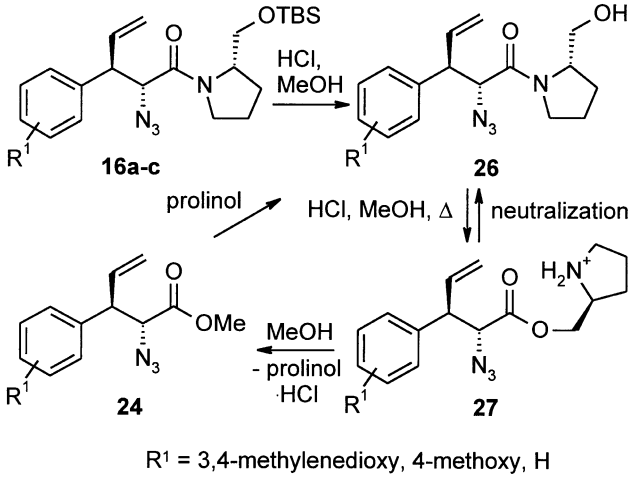
Scheme 3.

sub-unit, an highly asymmetric induction on generating the new framework and, of course, an efficient removal of the auxiliary.

The cleavage of the amide bond of the 3-arylprolines **19** gave only disappointing results. The removal of the chiral auxiliary under nucleophilic, acidic, basic and reductive conditions, respectively, failed.[30] In presence of proton or Lewis acids, the TBS group was easily removed to give the corresponding aminoalcohol **21** (>90% yield), which could be isolated as *N*-BOC-amide **22** after treatment of the crude **21** with BOC_2O in 87% yield overall. Again, the cleavage of the amide failed under extensively varied reaction conditions. Using acidic peptide cleavage conditions, the aminoalcohol **21** suffered from the exclusive protonation of the secondary amine, hence the amide group had not been activated. Obviously, the *N*-protected **22** suffered from an efficient shielding of both faces of the carboxyl

group by the bulky adjacent substituents (*N*-BOC and 3-aryl) suppressing any attack of a range of reagents at the amide function. So far as several intramolecular directed transformations failed, the removal of the auxiliary to achieve the desired 3-arylproline **23** was abandoned at this stage of the synthesis (Scheme 3).

Generally, the cleavage of the amides **15** and **16**, respectively, could be achieved following the Metz protocol.[18] An initial iodo lactonization would have given the lactones **13** as described above (Scheme 2), a final reductive work-up (Zn/HOAc) should regenerate the olefin as well as the carboxylic acid without effecting the stereogenic centers (→**24**, **25**, R^4=H). In presence of the azide (R^3=N_3) in the amides **15** and **16** as a sensitive functional group against reductive conditions an alternative path was mandatory. Aspiring the synthesis of prolines via the efficient one-pot procedure of the reductive cyclization[7,8] the removal of the auxiliary was investigated under basic and acidic conditions. Treating the amide **16a** with KOH in MeOH with heating, the cleavage was found to be successful.[30a–c] After about 12 h, the corresponding carboxylic acids **24** and **25** (R^4=H) occurred, which were likewise converted into the methylesters (R^4=Me) with diazomethane in Et_2O in >80% yield. Unfortunately, the stereogenic α-center (C2 in **15**, **16**) suffered from the complete equilibration, the NMR spectra showed a doubled set of peaks resulting from the ester *syn*-**25** and *anti*-**24**. In contrast, the cleavage under acidic conditions by treating with 1N HCl in MeOH did not effect the stereogenic centers (Scheme 4): Running the reaction at rt, the TBS group was removed in a first step (→**26**). On heating the mixture to about 60°C for 48 h, a slow conversion was observed to give exclusively the ester *anti*-**24**, which could be isolated in >80% yield (+10 to 15% amide recycled). The isolation was found to be somewhat tricky: according to tlc analysis, the reactant hydroxyamide **26** disappeared smoothly to give the ammonium ester **27** as an intermediate.[31] Any work-up with neutralization at this stage of the reaction regenerated the hydroxy amide **26** via an highly efficient intramolecular ester–amide conversion suppressing any removal of the auxiliary. Obviously, the *trans*esterification of the intermediate ammonium ester **27** needed a significantly longer time to achieve a complete conversion into *anti*-**24**. The ester **24** had been purified without neutralization to avoid any amide regeneration. In contrast to the cleavage product mixture obtained under basic conditions, the present reaction generated a single diastereomer according to NMR analyses improving again the *anti* selectivity of the Claisen rearrangement (Scheme 4).[32]



Scheme 4.

3. Mechanistic conclusions

Analyzing the stereochemical outcome of the products **8**–**11** and **15**, **16** of the zwitterionic aza-Claisen rearrangement, two general aspects had to be considered. The simple diastereoselectivity (internal asymmetric induction) and the auxiliary-induced selectivity (Fig. 3).[15e–j,17,34]

Recapitulating the pathway of the process starting from the allylamines **5**–**7** and the acylfluoride,[33] the first step was thought to be the addition of a ketene equivalent at the nucleophilic nitrogen to generate the hypothetical intermediate zwitterion which underwent the 3,3 sigmatropic process. The charge neutralization served as an highly efficient driving force.[16] Consistently with well known acyclic Claisen rearrangements, the highly ordered transition state passed should have adopted a chair-like arrangement to minimize repulsive 1,3 interactions.[34] In combination with a defined *Z*-enolate structure of the amide sub-unit,[35] the relative configuration of the nascent stereogenic centers must be *anti* as found on synthesizing 2-azido-3-vinyl amides **8**–**10**, **15** and **16** (high internal asymmetric induction/simple diastereoselectivity).

The outcome of the auxiliary induced diastereoselectivity can be interpreted as a combination of a diastereoselective acylation of the amino group and the passing of a defined transition state conformation. The high asymmetric induction observed analyzing the products **10**, **11** and **16** implied the more or less exclusive passing of a single transition state. In contrast, the mixtures of diastereomeric amides **9** and **15** pointed out, that obviously one of the directing effects had turned to be inefficient. With regard to a chair-like transition state conformation, the intermediately formed quartery ammonium center should have always arranged the small CH_2 part of the proline ring in an axial, the bulky chain branched function bearing the stereogenic center in the equatorial position. Consequentially, the *syn* acylation-rearrangement sequence gave the 2*R*,3*R* configuration of the nascent stereogenic centers. In contrast, the *anti* acylation-rearrangement had generated the inverted 2*S*,3*S* situation (complete 1,3-chirality transfer via the enolate sub-unit). The crucial step was thought to be the acylation of the teritary amine **5**–**7**.

This first step effecting the formation of the hypothetical acylammonium enolate must have been diastereoselective rearranging the allylamines **6** and **7**. Probably, the bulky R^2 substituents (CO_2tBu, CH_2OTBS) decreased the rate of the nitrogen inversion (**A**⇔**B** via **C**) or fixed the amine in a conformation that arranged the allyl system and the side chain in a quasi equatorial position of the envelope structure **A** inducing a diastereoselective acylation of the 'axial' lone pair (→*syn* acylation). In contrast, the less bulky R^2 (CO_2Me) in amine **5** underwent a fast flipping of

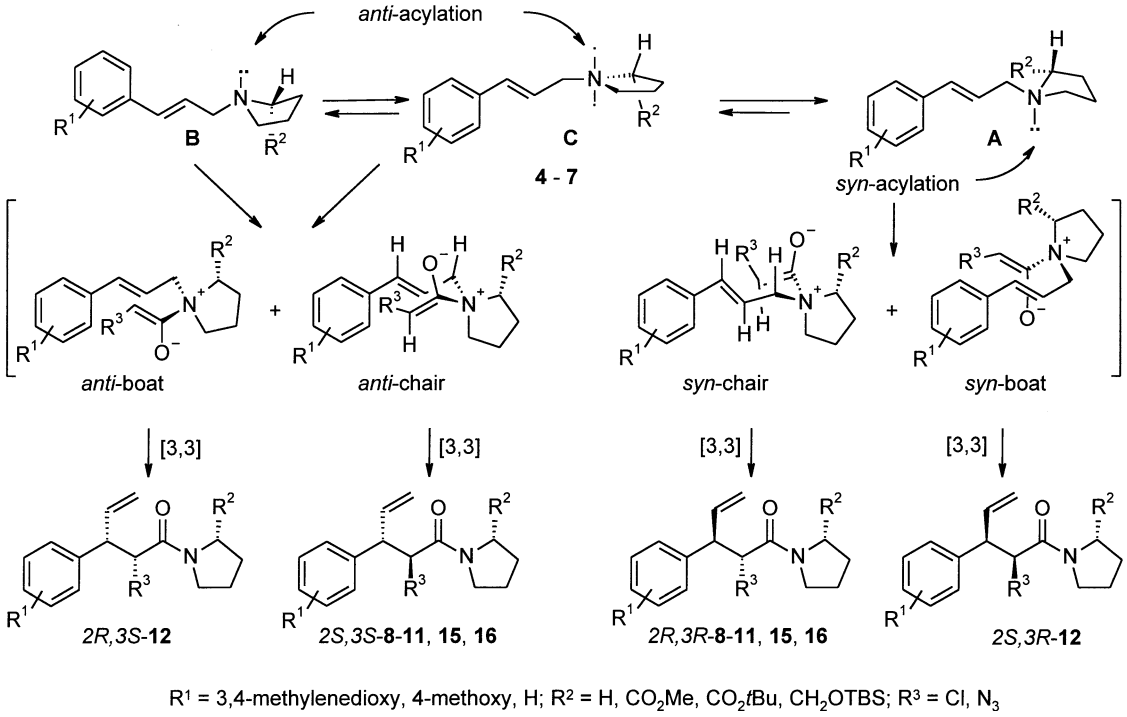


Figure 3. Stereochemical reaction pathways of the zwitterionic aza-Claisen rearrangement: allylamine reactants, hypothetical zwitterionic intermediates and product amides.

the nitrogen during the course of the reaction (**A**⇔**B** via **C**), though the most stable arrangement should have been the envelope **A**. Consequentially, the highly reactive chloroacetyl fluoride attacked the less stable amine **5** adopting the conformations **B** (and **C** as the result of a fast nitrogen inversion: shielded α face→*anti* acylation) as well as **A** (→*syn* acylation) producing a 2:1 mixture of diastereomers **9**. The somewhat less reactive azidoacetyl fluoride rearranged with amine **5** to give amide **15** in a 3–4:1 (2*R*,3*R*/2*S*,3*S*) ratio. Furthermore, the decrease of the reaction temperature led to increasing diastereoselectivities in favor of the 2*R*,3*R* amides **9** and **15** but the effect was not such high to be of preparative use (Fig. 3).

Summing up the results, the stereochemical outcome of the auxiliary controlled aza-Claisen rearrangement strongly depended on the chiral substituent involved in the process. While the enolate structure and the chair-like conformation of the hypothetical zwitterionic transition state were thought to be formed as usual, the acylation of the amine generating a new chiral ammonium center was crucial because of its influence on the consecutive 1,3 chirality transfer (via the vinyl system). Aspiring a selective reaction the fast inversion of the nitrogen had to be taken in account complicating the situation. However, the use of a bulky proline solved the problem of the diastereoselective acylation.[36] Thus, high auxiliary controlled asymmetric inductions had been achieved allowing the enantioselective synthesis of 2*R*,3*R* 3-aryl proline derivatives after the final reductive cyclization (cycloalkylation).

4. Summary

An efficient five (seven) step sequence to synthesize optically active 3-arylproline derivatives had been developed starting from aromatic aldehydes **1** and alcohol **3** and L-proline derivatives as chiral auxiliaries. A Pd(0) catalyzed allylation of the proline amino function allowed an efficient regio- and stereoselective coupling of the chiral auxiliary. The zwitterionic aza-Claisen rearrangement served as the first key step to introduce the stereogenic centers with a high internal and a moderate to high auxiliary mediated diastereoselectivity to give the *anti* γ,δ unsaturated amides **9**–**11** and **15**, **16**. The reaction was thought to undergo a diastereoselective *syn* acylation of the allylamines (**5**) **6** and **7**, the consecutive 3,3 sigmatropic process should have passed a highly ordered chair-like transition state with minimized repulsive interactions generating the products (1,3 chirality transfer via the vinyl system). The cyclization of the amides **15**, **16** to give the desired 3-aryl proline amides **18** and **19** succeeded via the hydroboration—azide insertion—rearrangement sequence as the second key step described by Sabol (cycloalkylation). The present procedure led exclusively to the 2,3 *syn* products, the absolute and the relative configuration of the newly formed pyrrolidine ring had been proven by an X-ray analysis of tricycle **20**. The removal of the chiral auxiliary failed at the stage of the proline amides **19** but succeeded subjecting the unsaturated amides **16** to an acid mediated amide–ester conversion. The so formed esters **24** can be transformed into the proline esters **23** as demonstrated by Evans and Sabol.

The resulting optically active 3-aryl proline derivatives serve as versatile amino acids in peptide, pharmaceutical and natural product syntheses. Further investigations concerning scope and limitations of the auxiliary controlled aza-Claisen rearrangement are in progress.

5. Experimental

For general experimental data see Ref. 37. The ^{1}H NMR spectra of **19a**, **20** and the NOEDS analyses of **13** were recorded on a 500 MHz spectrometer. NOE data are given as irradiation at *x* ppm⇒amplification at *y* ppm (%) Satisfactory HRMS data (±0.4%) are reported for all new compounds. X-Ray analysis was performed using Mo Kα-radiation (λ=0.71073 Å). The structure was determined by direct methods using program SHELXS. The H atoms were taken from a difference Fourier synthesis and were refined with isotropic thermal parameters. The non-H atoms were refined with anisotropic thermal parameters. The structure was refined on F^2 values using program SHELXL-96. The final difference density was between −0.21 and +0.31 e/Å.

5.1. Standard procedure for the Grignard addition

Under argon, the benzaldehyde **1** (33 mmol) in dry Et_2O (250 mL) was treated slowly with vinyl magnesium chloride (36 mL, 36 mmol, 1 M in THF) to avoid any refluxing of the mixture. The reaction mixture muddied because of some precipitating magnesium alcoholate. After about 2 h, a second amount of vinyl magnesium chloride (18 mL, 18 mmol, 1 M in THF) was added. Stirring was continued until no remaining reactant could be detected by tlc analysis. Then, the mixture was poured into ice water, after stirring for some minutes to complete the hydrolysis the organic layer was decanted and dried ($MgSO_4$). After removal of the solvent the remaining allyl alcohol was found to be pure enough for further transformations. Likewise, purification was achieved via column chromatography on silica gel.

5.1.1. 1-((3,4-Methylendioxy)-phenyl)-2-propenol (2a). Reaction with 5.0 g (33.3 mmol) piperonal **1a** following the standard procedure. (Purification by column chromatography on silica gel [*n*-hexane/EtOAc 10:1, R_f=0.2 in *n*-hexane/EtOAc 4:1].) Yield: 5.6 g (31.8 mmol, 95 %) allylalcohol **2a** as clear oil. ^{1}H NMR (270 MHz): δ=3.05 (s, br, 1H, OH); 5.02 (d, br, 1H, *J*=5.9 Hz, 1-H); 5.14 (dt, 1H, *J*=1.5, 10.3 Hz, *cis*-3-H); 5.27 (dt, 1H, *J*=1.5, 17.1 Hz, *trans*-3-H); 5.88 (s, 2H, 10-H); 5.94 (ddd, 1H, *J*=5.9, 10.3, 17.1 Hz, 2-H); 6.72 (d, 1H, *J*=7.8 Hz, 8-H); 6.77 (dd, 1H, *J*=1.5, 8.3 Hz, 9-H); 6.81 (d, 1H, *J*=1.5 Hz, 5-H) ppm. ^{13}C NMR (68 MHz): δ=74.8 (C-1); 101.0 (C-10); 107.0 (C-5); 108.1 (C-8); 114.8 (C-3); 119.8 (C-9); 136.8 (C-4); 140.3 (C-2); 146.9 (C-7); 147.7 (C-6) ppm. IR (film): ν_{max}=3369 s, br, 3077 m, 3011 m, 2979 m, 2892 s, 2778 m, 1855 s, 1641 m, 1609 m, 1503 s, 1488 s, 1443 s, 1374 m, br, 1247 s, 1185 m, 1125 m, 1093 m, 1040 s, 990 s, 933 s, 811 s, 794 s. MS (EI, 80 eV, 40°C): *m*/*z*=178 (M^+, 100%), 161 (M−OH), 151 (M−CH=CH_2), 149 (M−CHO after Claisen rearrangement), 135 (M−CH_2CHO after Claisen rearrangement), 123, 91 ($C_6H_3O^+$), 65. HRMS (EI, 80 eV, 40°C) [$C_{10}H_{10}O_3$] Calcd: 178.06299, 178.0638.

5.1.2. 1-(Methoxy-phenyl)-2-propenol (2b). Reaction with 5.0 g (37.0 mmol, 4.5 mL) anisaldehyde **1b** following the standard procedure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 10:1, R_f=0.5 in *n*-hexane/EtOAc 3:1). Yield: 6.03 g (36.7 mmol, 99%) allylalcohol **2b** as clear oil. ^{1}H NMR (270 MHz): δ=2.32 (s, 1H, OH); 3.79 (s, 3H, 8-H); 5.13 (d, 1H, *J*=6.8 Hz, 1-H); 5.17 (dt, 1H, *J*=1.5, 10.3 Hz, *E*-3-H); 5.32 (dt, 1H, *J*=1.5, 17.2 Hz, H-9); 6.03 (ddd, 1H, *J*=6.8, 10.3, 17.2 Hz, 2-H); 6.88 (d, 2H, *J*=8.8 Hz, 6-H and 6′-H); 7.28 (d, 2H, *J*=8.8 Hz, 5-H and 5′-H) ppm. ^{13}C NMR (63 MHz): δ=55.3 (C-8); 74.8 (C-1); 113.9 (C-6 and C-6′); 114.7 (C-3); 127.7 (C-5 and C-5′); 134.9 (C-4); 140.4 (C-2); 159.1 (C-7) ppm. IR (film): ν_{max}=3429 (s, br, OH), 3073 (m, Ar-H), 2934 (s, CH), 1610 (s, C=C), 1284 (s, Ar-OCH_3), 1105 (m, C–OH), 991 m, 925 (m, R–CH–CH_2). MS (EI, 80 eV, 40°C): *m*/*z*=164 (100%, M^+), 147 (M−OH), 137 (M−C_2H_3), 135 (M−CHO after Claisen rearrangement), 121 (M−CH_2–CHO), 109, 94, 77. HRMS (EI, 80 eV, 40°C) [$C_{10}H_{12}O_2$] Calcd: 164.08373. Found: 164.08633.

5.2. Standard procedure for the allylation of the proline derivatives

Mesylation. Under argon, the allylalcohol **2** or **3** (12 mmol) and Et_3N (4.8 g, 6.6 mL, 48 mmol) were dissolved in dry THF (270 mL). MesCl (1.5 g, 1.02 mL, 13.12 mmol) in dry THF (16 ml) was added dropwise, with stirring. The resulting suspension of Et_3N HCl in THF was stirred at rt for 30 min.

Amination. Pyrrolidine or proline ester hydrochloride (13.12 mmol) was dissolved in dry MeCN (21 mL), with heating. After cooling to 0°C Et_3N (4.8 g, 6.6 mL, 48 mmol) was added and a suspension of ammonium salts was formed, which was immediately poured into the solution of the freshly prepared mesylate. Pd_2dba_3 $CHCl_3$ (0.31 g, 3 mmol, 0.025 equiv.) and PPh_3 (0.64 g, 2.39 mmol) were added, the color changed from deep purple to yellow. After about 2 h, the reaction was found to be complete (tlc analysis). Work-up started by filtration off the ammonium salts. The organic filtrate was washed with H_2O (150 mL), the aqueous layer was re-extracted with Et_2O (3×45 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed and the crude allylamine was purified by column chromatography on silica gel.

5.2.1. *N*-(3-(3,4-Methylenedioxy)-phenyl-2-propenyl)-(*S*)-pyrrolidine (4a). Under argon, alcohol **2a** (2.01 g, 11.3 mmol) and PPh_3 (3.23 g, 12.4 mmol) in dry CCl_4 (35 mL) were heated to reflux for 17 h. After a few minutes, the white precipitate occurred. Work-up started by dilution with *n*-hexane (100 mL), then, the precipitate was filtered off. The crude chloride was purified by Kugelrohr distillation (160°C/0.02 Torr). The chloride would be destroyed by chromatography on silica gel. Yield: 1.39 g (7.1 mmol, 63 %) allylchloride as clear pale yellow oil. Data of the allylchloride: ^{1}H NMR (250 MHz): δ=4.20 (d, 2H, *J*=6.2 Hz, 1-H); 5.90 (s, 2H, 10-H); 6.10 (dt, 1H, *J*=6.2, 16.0 Hz, 2-H); 6.55 (d, 1H, *J*=16.0 Hz, 3-H); 6.75 (d, 1H, *J*=8.3 Hz, 8-H); 6.80 (dd, 1H, *J*=1.5, 8.3 Hz, 9-H); 6.95 (d, 1H, *J*=1.5 Hz, 5-H) ppm. ^{13}C NMR (63 MHz): δ=45.6 (C-1); 101.2 (C-10); 105.8 (C-8); 108.3 (C-5); 121.7 (C-2); 123.1 (C-9); 130.3 (C-4); 133.9 (C-3); 147.1 (C-6); 147.8 (C-7) ppm. IR (film): ν_{max}=2900 (m, CH), 1646 (m, C=C), 1500 (s, C=C Ar), 1448 (s, CH), 1254 (s C–O-Ar), 1039 (s, O–CH_2), 968 (s, *E*-CH=CH). MS (80 eV, 50°C): *m*/*z*=196 (M^+), 161 (M−Cl), 131 (100%), 103, 77. HRMS

(EI, 80 eV, 50°C) [$C_{10}H_9ClO_2$] Calcd: 196.02910. Found: 196.03550.

Amination. Reaction with 1.38 g (7.05 mmol) chloride and pyrrolidine (2.14 g, 2.95 mL, 21.16 mmol) following the standard procedure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1, R_f=0.05 in *n*-hexane/EtOAc 4:1). Yield: 1.44 g (6.23 mmol, 88%) allylamine **4a** as clear pale yellow oil, which was air sensitive (darkening by storing in presence of oxygen). ^{1}H NMR (250 MHz): δ=1.76 (m, 4H, 3-H and 4-H); 2.50 (m, 4H, 2-H and 5-H); 3.18 (d, 2H, *J*=6.0 Hz, 6-H); 5.88 (s, 2H, 15-H); 6.11 (dt, 1H, *J*=6.0, 15.2 Hz, 7-H); 6.38 (d, 1H, *J*=15.2 Hz, 8-H); 6.68 (d, 1H, *J*=8.3 Hz, 13-H); 6.74 (dd, 1H, *J*=1.5, 8.3 Hz, 14-H); 6.88 (d, 1H, *J*=1.5 Hz, 10-H) ppm. ^{13}C NMR (63 MHz): δ=23.3 (C-3 and C-4); 53.9 (C-2 and C-5); 58.2 (C-6); 100.8 (C-15); 105.5 (C-10); 108.0 (C-14); 119.0 (C-8); 125.8 (C-13); 131.3 (C-7); 131.5 (C-9); 146.8 (C-11); 147.8 (C-12) ppm. IR (film): ν_{max}=2949 (s, CH), 2775 (s, N–C), 1607 (w, C=C), 1504 s, 1488 (s C=C Ar), 1446 (s, CH), 1252 (s, Ar-O), 1039 (s, *E*-CH=CH). MS (EI, 80 eV, 90°C): *m*/*z*=231 (M^+), 161 ($M-C_4H_8N$), 131 ($161-CH_2O$), 103 (100%), 96, 77. HRMS (EI, 80 eV, 80°C) of [$C_{14}H_{17}NO_2$] Calcd: 231.12592. Found: 231.12483.

5.2.2. *N*-(3-(3,4-Methylenedioxy)-phenyl-2-propenyl)-(*S*)-proline methylester (5a). Reaction with 2.0 g (11.2 mmol) **2a** and proline methylester following the standard procedure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1, R_f=0.2 in *n*-hexane/EtOAc 1:1). Yield: 2.85 g (9.85 mmol, 88%) aminoester **5a** as a clear pale yellow oil, which was air sensitive (darkening by storing in presence of oxygen). $[\alpha]_D^{23}=-27.9$ (*c*=4.6, $CHCl_3$). ^{1}H NMR (270 MHz): δ=1.77 (m, 1H, 4^1-H); 1.89 (m, 2H, 3^1-H and 4^2-H); 2.08 (m, 1H, 3^2-H); 2.34 (q, 1H, *J*=8.3 Hz, 5^1-H); 3.10 (dd, 1H, *J*=6.4, 8.8 Hz, 2-H); 3.14 (m, 1H, 5^2-H); 3.21 (dd, br, 1H, *J*=6.8, 13.2 Hz, 6^1-H); 3.32 (dd. br, 1H, *J*=6.8, 13.2 Hz, 6^2-H); 3.59 (s, 3H, 17-H); 5.87 (s, 2H, 15-H); 6.08 (dt, 1H, *J*=6.8, 15.6 Hz, 7-H); 6.35 (d, 1H, *J*=15.6 Hz, 8-H); 6.67 (d, 1H, *J*=7.8 Hz, 13-H); 6.72 (dd, 1H, *J*=1.5, 7.8 Hz, 14-H); 6.84 (d, 1H, *J*=1.5 Hz, 10-H) ppm. ^{13}C NMR (68 MHz): δ=23.1 (C-4); 29.5 (C-3); 51.8 (C-17); 53.7 (C-5); 57.0 (C-6); 65.4 (C-2); 100.9 (C-15); 105.6 (C-10); 108.1 (C-14); 120.8 (C-8); 125.0 (C-13); 131.3 (C-9); 132.0 (C-7); 147.0 (C-11); 147.9 (C-12); 174.6 (C-16) ppm. IR (film): ν_{max}=2951 (s, CH), 2800 (s, N–C), 1743 (s, C=O), 1606 (w, C=C), 1503 s, 1489 s, 1445 (s, C=C aryl), 1250 (s, Ar-O), 1039 (s, C–O), 967 (m, *E*-CH=CH). MS (EI, 80 eV, 90°C): *m*/*z*=289 (M^+), 230 ($M-CO_2CH_3$), 161 (100, $230-C_4H_7N$), 131 ($161-CH_2O$), 103, 83, 77. HRMS (EI, 80 eV, 40°C) [$C_{16}H_{19}NO_4$] Calcd: 289.13207. Found: 289.13649.

5.2.3. *N*-(3-(4-Methoxyphenyl)-2-propenyl)-(*S*)-proline methylester (5b). Reaction with 2.49 g (15 mmol) **2b** and proline methylester following the standard procedure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1, R_f=0.2). Yield: 2.4 g (8.73 mmol, 58%) aminoester **5b** as a clear pale yellow oil, which was air sensitive (darkening by storing in presence of oxygen). $[\alpha]_D^{23}=-22.5$ (*c*=1.6, $CHCl_3$). ^{1}H NMR (270 MHz): δ=1.81 (m, 1H, 4^1-H); 1.92 (m, 2H, 3^1-H and 4^2-H); 2.12 (m, 1H, 3^2-H); 2.32 (q, 1H, *J*=8.3 Hz, 5^1-H); 3.3 (m, 2H, 2-H and 5^2-H); 3.28 (dd, br, 1H, *J*=6.4, 13.5 Hz, 6^1-H); 3.32 (dd. br, 1H, *J*=6.4, 13.5 Hz, 6^2-H); 3.51 (s, 3H, 14-H); 3.65 (s, 3H, 15-H); 6.13 (dt, 1H, *J*=6.4, 16.7 Hz, 7-H); 6.43 (d, 1H, *J*=16.7 Hz, 8-H); 6.83 (d, 2H, *J*=8.3 Hz, 10-H and 10′-H); 7.22 (d, 2H, *J*=8.3 Hz, 11-H and 11′-H) ppm. ^{13}C NMR (63 MHz): δ=23.0 (C-4); 29.5 (C-3); 51.7 (C-14); 53.7 (C-5); 55.1 (C-15); 57.1 (C-2); 65.3 (C-6); 113.8 (C-11 and C-11′); 124.5 (C-8); 127.3 (C-10 and C-10′); 131.9 (C-9); 134.8 (C-7); 159.0 (C-12); 17.6 (C-13) ppm. IR (film): ν_{max}=2195 (m, CH), 2836 (m, N–C), 1741 (s, CC=O), 1511 (s, CC=C aryl) 1250 (s, Ar-O), 1174 (s, O–CH_3), 969 (m, CH=CH). MS (EI, 80 eV, 90°C): *m*/*z*=275 (M^+), 216 ($M-CO_2CH_3$), 190, 154, 147 (100, $216-C_4H_8N$), 121 (CH_2O_2=$C_6H_3^+$), 91, 70. HRMS (EI, 80 eV, 90°C) [$C_{16}H_{21}NO_3$] Calcd: 275.152144. Found: 275.15564.

5.2.4. *N*-(3-Phenyl-2-propenyl)-(*S*)-proline methylester (5c). Reaction with 2.0 g (15 mmol) **3** and proline methylester following the standard procedure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 1:1, R_f=0.3). Yield: 0.85 g (3.45 mmol, 23%) aminoester **5c** as a clear pale yellow oil, which was air sensitive (darkening by storing in presence of oxygen). $[\alpha]_D^{23}=-36.5$ (*c*=1.0, $CHCl_3$). ^{1}H NMR (270 MHz): δ=1.81 (m, 1H, 4^1-H); 1.92 (m, 2H, 3^1-H and 4^2-H); 2.12 (m, 1H, 3^2-H); 2.41 (q, 1H, *J*=8.1 Hz, 5^1-H); 3.18 (dd, 1H, *J*=5.9, 8.8 Hz, 2-H); 3.20 (m, 1H, 5^2-H); 3.28 (dd, br, 1H, *J*=6.6, 13.2 Hz, 6^1-H); 3.32 (dd. br, 1H, *J*=6.6, 13.2 Hz, 6^2-H); 3.62 (s, 3H, 14-H); 6.27 (dt, 1H, *J*=6.6, 16.2 Hz, 7-H); 6.47 (d, 1H, *J*=16.2 Hz, 8-H); 7.28 (m, 5H, Ar-H) ppm. ^{13}C NMR (63 MHz): δ=23.1 (C-4); 29.5 (C-3); 51.8 (C-14); 53.6 (C-5); 56.9 (C-2); 65.3 (C-6); 126.3 (C-10 and C-10′); 126.7 (C-8); 127.4 (C-12); 128.5(C-11 and C-11′); 132.6 (C-7); 136.9 (C-9); 174.0 (C-13). IR (film): ν_{max}=3025 (m, Ar-H), 2951 (m, CH), 2799 (m, N–C), 1747 (s, CC=O), 1448 (m; CH), 1197 s, 1171 (s, O–CH_3), 968 (s, CH=CH). MS (EI, 80 eV, 40°C): *m*/*z*=245 (M^+), 186 ($M-CO_2Me$), 117 (100, Ph-CH=$CHCH_2^+$), 91. HRMS (EI, 80 eV, 40°C) [$C_{15}H_{19}NO_2$] Calcd: 245.141579. Found: 245.14433.

5.2.5. *N*-(3-(3,4-Methylenedioxy)-phenyl-2-propenyl)-(*S*)-proline *t*-butylester (6a). Reaction with 1.16 g (5.9 mmol) **2a** and *S*-proline *t*-butylester (1.21 g, 7.07 mmol) following the standard procedure. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1, R_f=0.2 in *n*-hexane/EtOAc 4:1). Yield: 1.44 g (4.35 mmol, 74%) aminoester **6a** as a clear pale yellow oil, which was air sensitive (darkening by storing in presence of oxygen). $[\alpha]_D^{23}=21.0$ (*c*=0.4, $CHCl_3$). ^{1}H NMR (250 MHz): δ=1.4 (s, 9H, 18-H); 1.75 (m, 1H, 4^1-H); 1.9 (m, 2H, 3^1-H and 4^2-H); 2.1 (m, 1H, 3^2-H); 2.4 (q, 1H, *J*=8.5 Hz, 5^1-H); 3.05 (dd, 1H, *J*=6, 9 Hz, 2-H); 3.1 (m, 1H, 5^2-H); 3.2 (dd, br, 1H, *J*=7, 13.5 Hz, 6^1-H); 3.45 (dd. br, 1H, *J*=7, 13.5 Hz, 6^2-H); 5.9 (s, 2H, 15-H); 6.1 (dt, 1H, *J*=7, 16 Hz, 7-H); 6.4 (d, 1H, *J*=16 Hz, 8-H); 6.7 (d, 1H, *J*=8 Hz, 13-H); 6.8 (dd, 1H, *J*=1.5, 8 Hz, 14-H); 6.9 (d, 1H, *J*=1.5 Hz, 10-H) ppm. ^{13}C NMR (68 MHz): δ=22.9 (C-4); 28.0 (C-18); 29.3 (C-3); 53.5 (C-5); 56.6 (C-6); 65.6 (C-2); 100.9 (C-15); 105.6 (C-10); 108.1 (C-14); 120.8 (C-8);

125.6 (C-13); 131.5 (C-9); 131.6 (C-7); 146.9 (C-11); 147.8 (C-12); 173.3 (C-16) ppm. IR (film): ν_{max}=2975 (s, CH), 1737 (s, CC=O), 1366 s, 1353 (m, $C(CH_3)_3$), 1249 (s, Ar-O), 1039 (s, C–O), 966 m, 931 (m, *E*-CH=CH_2). MS (EI, 80 eV, 90°C): *m/z*=331 (M^+), 274 (M−^{t}Bu), 230 (274−CO^2), 161 (Pip-CH=CH–CH_2^+), 131 (161−CH_2O), 115, 103, 77, 57. HRMS (EI, 80 eV, 40°C) of [$C_{19}H_{25}NO_4$] Calcd: 331.17836. Found: 331.17844.

5.3. Standard procedure for the conversion of the proline esters into the OTBS prolinols

DIBALH reduction. Under argon, the *N*-allyl proline methylester **5** (5 mmol) in dry Et_2O (65 mL) was treated with DIBALH (11.9 mL, 14.2 mmol, 1.2 M in toluene) at 0°C with stirring. After 30 min, the ice bath was removed and the mixture was stirred overnight at rt. Work-up started by a dropwise addition of H_2O (2.6 mL) and saturated aqueous K–Na tatrate until the white Al_2O_3 precipitated. Na_2SO_4 was added and the organic layer was decanted. The solid residue was extracted with Et_2O (4×20 mL), the organic solution was dried and the solvent was removed. The crude product was directly used for the final silylation, or, likewise, purified via chromatography on silica gel.

Silylation. The crude carbinol (5 mmol) was dissolved in dry DMF (19 mL) and treated subsequently with Et_3N (0.52 g, 5.15 mmol, 0.71 mL) and TBSCl (0.79 g, 5.23 mmol). The mixture was stirred at rt for 12 h. Work-up started by quenching with aqueous $NaHCO_3$ (5%, 40 mL), then, the mixture was extracted with Et_2O (3×90 mL). Remaining DMF was removed by washing with H_2O, the organic layers were dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified via column chromatography on silica gel.

5.3.1. 1-(3-((3,4-Methylenedioxy)-phenyl)-2-propenyl)-2(*S*)-(*t*-butyldimethylsiloxymethyl)-pyrrolidine (7a). Reaction with 2.72 g (9.4 mmol) *N*-allylproline methylester **5a** following the standard procedure. Carbinol: purification by column chromatography on silica gel (EtOAc/MeOH 3:1, R_f=0.1). Yield: 2.33 g (8.9 mmol, 95%) carbinol as clear pale yellow oil. Silyl ether: purification by column chromatography (*n*-hexane/EtOAc 1:1, R_f=0.4). Yield: 3.23 g (8.65 mmol, 92%, two steps) silyl ether **7a** as a clear pale yellow oil. Data carbinol: $[\alpha]_D^{23}$=−31.0 (*c*=2.1, $CHCl_3$). ^{1}H NMR (270 MHz): δ=1.71 and 1.85 (2 m, 1 and 3H, 3-H and 4-H); 2.30 (dd, br, 1H, *J*=8.3, 17.6 Hz, 5^1-H); 2.61(m, 1H, 2-H); 3.01 (dd, 1H, *J*=7.8, 13.2 Hz, 6^1-H); 3.15 (dd, br, 1H, *J*=5.4, 8.3 Hz, 5^2-H); 3.17 (s, br, 1H, OH); 3.42 (dd, 1H, *J*=2.9, 10.7 Hz, 16^1-H); 3.50 (ddd, 1H, *J*=1.5, 5.9, 13.2 Hz, 6^2-H); 3.61 (dd, 1H, *J*=3.9, 10.7 Hz, 16^2-H); 5.89 (s, 2H, 15-H); 6.07 (ddd, 1H, *J*=15.6, 7.8, 5.9 Hz, 7-H); 6.39 (d, br, 1H, *J*=15.6 Hz, 8-H); 6.70 (d, 1H, *J*=8.3 Hz, 13-H); 6.75 (dd, 1H, *J*=1.5, 8.3 Hz, 14-H); 6.88 (d, 1H, *J*=1.5 Hz, 10-H) ppm. ^{13}C NMR (68 MHz): δ=23.4 (C-4); 27.8 (C-3); 54.4 (C-5); 56.5 (C-6); 62.4 (C-2); 64.1 (C-16); 101.0 (C-15); 105.6 (C-10); 108.2 (C-13); 120.8 (C-14); 125.7 (C-8); 131.5 (C-15); 131.5 (C-9); 147.0 (C-11); 148.0 (C-12) ppm. IR (film): ν_{max}=3403 (m, br, OH), 2962 (s, CH), 2804 (s, C–N), 1606 (s, CC=C), 1503 (s, CC=C aryl), 1250 (s, Ar-O), 1040 (s, C–O), 966 (s, *E*-CH=CH). MS (EI, 80 eV, 80°C): *m/z*=261 (M^+), 230 (M−CH_2OH), 204 (M−C_3H_5O), 161 (100, 230−C_4H_7N), 131 (161−CH_2O), 103, 83, 77, 70. HRMS (EI, 80 eV, 40°C) [$C_{15}H_{19}NO_3$] Calcd: 261.13648. Found: 261.13221. Data of silylether **7a**: $[\alpha]_D^{23}$=−43.9 (*c*=1.8, $CHCl_3$). ^{1}H NMR (270 MHz): δ=0.04 (s, 6H, 17-H); 0.88 (s, 9H, 19-H); 1.59, 1.72 and 1.90 (3 m, 1H, 2H and 1H, 3-H and 4-H); 2.28 (q, 1H, *J*=8.3 Hz, 5^1-H); 2.61 (ddd, 1H, *J*=5.7, 6.8, 13.9 Hz, 2-H); 3.08 (m, 2H, 5^2-H and 6^1-H); 3.45 (dd, 1H, *J*=6.8, 9.8 Hz, 16^1-H); 3.67 (m, 2H, 6^2-H, 16^2-H); 5.92 (s, 2H, 15-H); 6.14 (ddd, 1H, *J*=6.3, 7.8, 16.1 Hz, 7-H); 6.41 (d, 1H, *J*=16.1 Hz, H-8); 6.72 (d, 1H, *J*=7.8 Hz, 13-H); 6.78 (dd, 1H, *J*=1.5, 7.8 Hz, 14-H); 6.91 (d, 1H, *J*=1.5 Hz, 15-H) ppm. ^{13}C NMR (68 MHz): δ=−5.4 (C-17); 18.2 (C-18); 22.8 (C-4); 25.9 (C-19); 28.3 (C-3); 54.7 (C-5); 57.7 (C-6); 64.7 (C-2); 67.0 (C-16); 100.9 (C-15); 105.5 (C-10); 108.1 (C-13); 120.7 (C-8); 126.0 (C-14); 131.4 (C-7); 131.6 (C-9); 146.9 (C-11); 147.9 (C-12) ppm. IR (film): ν_{max}=2954 (s, CH), 2865 s, 2791 (m, C–N), 1503 (s, CC=C aryl), 1250 (s, Ar-O), 1098 (s, br, OTBS), 1041 (s, C–O), 964 (m, *E*-CH=CH), 837 (s, OTBS). MS (EI, 80 eV, 95°C): *m/z*=375 (M^+), 360 (M−CH_3), 318 (M−C_4H_9), 260 (M−TBS), 230 (M−CH_2OTBS), 161 (230−C_4H_7N), 131 (161−CH_2O), 103, 73. HRMS (EI, 80 eV, 80°C) [$C_{21}H_{33}NO_3Si$] Calcd: 375.22295. Found: 375.22045.

5.3.2. 1-(3-(4-Methoxy)-phenyl-2-propenyl)-2(*S*)-(*t*-butyldimethylsiloxymethyl)-pyrrolidine (7b). Reaction with 0.95 g (3.45 mmol) *N*-allylproline methylester **5b** following the standard procedure. Carbinol: purification by column chromatography on silica gel (EtOAc, R_f=<0.05). Yield: 0.83 g (3.17 mmol, 92%) carbinol as clear pale yellow oil. Silyl ether: purification by column chromatography (*n*-hexane/EtOAc 1:1, R_f=<0.1 in EtOAc). Yield: 1.13 g (3.11 mmol, 90%, two steps) silyl ether **7b** as a clear pale yellow oil. Data carbinol: $[\alpha]_D^{23}$=−27 (*c*=1.3, $CHCl_3$). ^{1}H NMR (270 MHz): δ=1.73 and 1.88 (2 m, 3 and 1H, 3-H and 4-H); 2.37 (q, br, 1H, *J*=8.3 Hz, 5^1-H); 2.69 (m, 1H, 2-H); 2.72 (s, br, 1H, OH); 3.07 (ddd, 1H, *J*=1.0, 7.3, 13.7 Hz, 6^1-H); 3.14 (dd, br, 1H, *J*=4.4, 9.3 Hz, 5^2-H); 3.43 (dd, 1H, *J*=2.4, 10.7 Hz, 13^1-H); 3.54 (ddd, 1H, *J*=1.5, 5.9, 13.7 Hz, 6^2-H); 3.66 (dd, 1H, *J*=3.9, 10.7 Hz, 13^2-H); 3.78 (s, 3H, 14-H); 6.12 (ddd, 1H, J=5.9, 7.3, 15.6 Hz, 7-H); 6.46 (d, br, 1H, *J*=15.6 Hz, 8-H); 6.83 (d, 2H, *J*=8.8 Hz, 10-H and 10′-H); 7.22 (d, 2H, *J*=8.8 Hz, 11-H and 11′-H) ppm. ^{13}C NMR (63 MHz): δ=23.5 (C-4); 27.8 (C-3); 54.3 (C-5); 55.3 (C-14); 56.6 (C-6); 62.2 (C-2); 64.1 (C-13); 113.9 (C-11 and C-11′); 125.0 (C-8); 127.4 (C-10 and C-10′); 131.7 (C-9); 132.2 (C-7); 153.6 (C-12) ppm. IR (film): ν_{max}=3359 (s, br, OH), 2936 (s, CH), 2816 (s, C–N), 1606 (s, CC=C), 1510 (s, CC=C aryl), 1252 (s, Ar-O), 1032 (m, C–OH), 975 (s, *E*-CH=CH). MS (EI, 80 eV, 95°C): *m/z*=247 (M^+), 216 (M−CH_3O), 190 (M−C_3H_5O), 147 (100, 216−C_4H_7N), 121 (CH_3O–Ph-CH_2), 112, 91, 70. HRMS (EI, 80 eV, 40°C) [$C_{14}H_{18}NO_2$ (M^+−CH_3)] Calcd: 216.138829. Found: 216.13644. Data of silylether **7b**: $[\alpha]_D^{23}$=−42 (*c*=1.9, $CHCl_3$). ^{1}H NMR (270 MHz): δ=0.00 (s, 6H, 14-H); 0.85 (s, 9H, 16-H); 1.68 and 1.88 (2 m, 3 and 1H, 3-H and 4-H); 2.28 (q, br, 1H, *J*=8.3 Hz, 5^1-H); 2.61 (m, 1H, 2-H); 3.05 (m, 1H, 5^2-H); 3.09 (dd, 1H, *J*=7.3, 13.2 Hz,

6^1-H); 3.45 (dd, 1H, J=7.3, 10.3 Hz, 13^1-H); 3.70 (m, 2H, 6^2-H and 13^2-H); 3.77 (s, 3H, 14-H); 6.18 (ddd, 1H, J=5.9, 7.3, 16.1 Hz, 7-H); 6.45 (d, br, 1H, J=16.1 Hz, 8-H); 6.82 (d, 2H, J=8.8 Hz, 10-H and 10′-H); 7.29 (d, 2H, J=8.8 Hz, 11-H and 11′-H) ppm. ^{13}C NMR (63 MHz): δ=−5.4 (C-14); 18.2 (C-15); 22.8 (C-4); 25.9 (C-16); 28.4 (C-3); 54.7 (C-5); 55.1 (C-17); 57.8 (C-6); 64.7 (C-2); 67.0 (C-13); 113.8 (C-11 and C-11′); 125.7 (C-8); 127.3 (C-10 and C-10′); 131.1 (C-9); 131.1 (C-7); 158.9 (C-12) ppm. IR (film): ν_{max}=2954 (s, CH), 2856 s, 2795 (m, C–N), 1608 (s, CC=C), 1511 (s, CC=C aryl), 1250 (s, br, Ar-O), 1106 (s, br, OTBS), 1038 (s, C-O), 967 (m E-CH=CH), 836 (s, OTBS). MS (80 eV, 70°C): m/z=361 (M^+), 346 ($M-CH_3$), 304 ($M-C_4H_9$), 216 ($M-CH_2OTBS$), 147 (100, 216−C_4H_7N), 121 ($CH_3OPhCH_2^+$), 70. HRMS (EI, 80 eV, 40°C) [$C_{21}H_{35}NO_2Si$] Calcd: 361.243708. Found: 361.24722.

5.3.3. 1-(3-Phenyl-2-propenyl)-2(*S*)-(*t*-butyldimethylsiloxymethyl)-pyrrolidine (7c). Reaction with 0.94 g (3.83 mmol) *N*-allylproline methylester **5c** following the standard procedure. Carbinol: purification by column chromatography on silica gel (EtOAc, R_f=<0.05). Yield: 0.70 g (3.21 mmol, 84%) carbinol as a clear pale yellow oil. Silyl ether: purification by column chromatography (*n*-hexane/EtOAc 1:1, R_f=0.1). Yield: 1.01 g (3.06 mmol, 80%, two steps) silyl ether **7c** as clear pale yellow oil. Data carbinol: $[\alpha]_D^{23}$=−28 (c=1.6, $CHCl_3$). ^{1}H NMR (270 MHz): δ=1.77 and 1.88 (2 m, 3 and 1H, 3-H and 4-H); 2.37 (q, br, 1H, J=8.3 Hz, 5^1-H); 2.67 (m, 1H, 2-H); 2.85 (s, br, 1H, OH); 3.03 (ddd, 1H, J=1.0, 7.3, 13.7 Hz, 6^1-H); 3.12 (dd, br, 1H, J=4.4, 9.3 Hz, 5^2-H); 3.41 (dd, 1H, J=2, 10.8 Hz, 13^1-H); 3.54 (ddd, 1H, J=1.5, 5.4, 13.7 Hz, 6^2-H); 3.66 (dd, 1H, J=3.9, 10.8 Hz, 13^2-H); 6.26 (ddd, 1H, J=5.4, 7.3, 15.6 Hz, 7-H); 6.52 (d, br, 1H, J=15.6 Hz, 8-H); 7.30 (m, 5H, Ar-H) ppm. ^{13}C NMR (63 MHz): δ=23.5 (C-4); 27.8 (C-3); 54.4 (C-5); 56.5 (C-6); 62.2 (C-2); 64.0 (C-13); 126.3 (C-10 and C-10′); 127.4 (C-8); 127.6 (C-12); 128.5 (C-11 and C-11′); 131.9 (C-7); 137.0 (C-9) ppm. IR (film): ν_{max}=3380 (s, br, OH), 2950 (s, CH), 2800 (s, C–N), 1601 (s, CC=C), 1496 (s, CC=C aryl), 1035 (m, C–OH), 969 (s, E-CH=CH). MS (EI, 80 eV, 95°C): m/z=217 (M^+), 187 ($M-CH_2O$), 160 ($M-C_3H_5O$), 118 (100, 187−C_4H_7N), 70. HRMS (EI, 80 eV, 40°C) [$C_{14}H_{19}NO$] Calcd: 217.14665. Found: 217.14136. Data of silyl ether **7c**: $[\alpha]_D^{23}$=−59 (c=0.8, $CHCl_3$). ^{1}H NMR (270 MHz): δ=0.05 (s, 6H, 14-H); 0.89 (s, 9H, 16-H); 1.61, 1.73 and 1.90 (3 m, 1H, 2H and 1H, 3-H and 4-H); 2.31 (q, br, 1H, J=8.3 Hz, 5^1-H); 2.65 (ddd, 1H, J=5.9, 8.3, 13.7 Hz, 2-H); 3.11 (m, 1H, 5^2-H); 3.14 (dd, 1H, J=7.8, 13.7 Hz, 6^1-H); 3.47 (dd, 1H, J=6.8, 9.8 Hz, 13^1-H); 3.71 (dd, 1H, J=5.4, 9.8 Hz, 13^2-H); 3.73 (m, 1H, 6^2-H); 6.34 (ddd, 1H, J=5.9, 7.8, 16.1 Hz, 7-H); 6.52 (d, 1H, J=16.1 Hz, H-8); 7.30 (m, 5H, Ar-H) ppm. ^{13}C NMR (63 MHz): δ=−5.3 (C-14); 18.3 (C-15); 22.9 (C-4); 25.9 (C-16); 28.4 (C-3); 54.8 (C-5); 57.9 (C-6); 64.8 (C-2); 67.1 (C-13); 126.2 (C-10 and C-10′); 127.2 (C-8); 128.0 (C-12); 128.5 (C-11 and C-11′); 131.7 (C-7); 137.2 (C-9) ppm. IR (film): ν_{max}=3025 (m, ArH), 2954 (s, CH), 2790 (s, N–C), 1091 (s, br, OTBS), 965 (m, E-CH=CH), 836 (s, br, OTBS). MS (EI, 80 eV, 50°C): m/z=331 (M^+), 316 ($M-CH_3$), 274 ($M-C_4H_9$), 226, 216, 186 (100, $M-CH_2OTBS$), 117 (186−C_4H_7N), 70. HRMS (EI, 80 eV, 40°C) [$C_{20}H_{33}NOSi$] Calcd: 331.233143. Found: 331.23098.

5.4. Standard procedure for the zwitterionic aza-Claisen rearrangement

Under argon, dry Na_2CO_3 (1.65 g, 15.9 mmol) was suspended in dry CH_2Cl_2 (12 mL) and cooled to 0°C. *N*-Allylpyrrolidine **4**–**7** (2 mmol) and freshly prepared α-azidoacetyl fluoride (0.41 g, 4 mmol) or α-chloroacetyl fluoride (0.41 g, 4 mmol) were added subsequently by means of a syringe. After about 15 min of stirring at 0°C, a solution of Me_3Al (1.0 mL, 2 mmol, 2 M in *n*-heptane) was added via syringe, CH_4 evolved. The mixture was allowed to warm up to rt, the color changed from pale yellow to light brown. The reaction was completed within 30 min. In several attempts the addition of a second amount of acid fluoride and Me_3Al was necessary to achieve a complete conversion of the reactant. Work-up was started by a dropwise addition of H_2O until the Al_2O_3 precipitated. The solids were removed by filtration through a short silica gel column, careful washing with CH_2Cl_2 was mandatory to obtain maximal yields. Finally, the solvent was removed and the crude product was purified by column chromatography.

5.4.1. 2-Chloro-3-((3,4-methylenedioxy)-phenyl)-4-pentenoic acid pyrrolidine amide (8a). Reaction with 0.38 g (1.64 mmol) *N*-allylproline methylester **4a** and chloroacetyl fluoride (0.24 mL, 3.46 mmol) following the standard procedure. Purification by column chromatography on silica gel (hexane/EtOAc 1:1, R_f=0.25). Yield: 0.19 g (0.62 mmol, 37%) amide **8a** as a clear pale yellow oil. ^{1}H NMR (270 MHz): δ=1.75 and 1.80 (2 m, 4H, 3′-H and 4′-H); 3.45 (m, 4H, 2′-H and 5′-H); 3.90 (dd, br, 1H, J=7.5, 10 Hz, 3-H); 4.45 (d, 1H, J=10 Hz, 2-H); 4.90 (d, br, 1H, J=17.5 Hz, Z-5-H); 5.05 (d, 1H, J=10 Hz, E-5-H); 5.90 (ddd, 1H, J=7.5, 10, 17.5 Hz, 4-H); 5.90 (s, 2H, 12-H); 6.70 (dd, 1H, J=1.5, 8.3 Hz, 10-H); 6.75 (d, 1H, J=8.3 Hz, 11-H); 6.80 (d, 1H, J=1.5 Hz, 7-H) ppm. ^{13}C NMR (68 MHz): δ=24.2 and 26.0 (C-3′ and C-4′); 46.6 and 46.3 (C-2′ and C-5′); 52.1 (C-3); 58.1 (C-2); 101.0 (C-12); 108.3 and 108.6 (C-7 and C-10); 118.1 (C-5); 121.9 (C-11); 133.2 (C-6); 136.7 (C-4); 146.6 (C-9); 147.9 (C-8); 166.1 (C-1) ppm. IR (film): ν_{max}=2957 s, 2930 s, 2890 s, 2866 s, 1645 s, 1510 s, 1488 s, 1469 m, 1437 s, 1348 m, 1265 s, 1170 m, 1107 s, 1043 s, 1010 w, 931 m. MS (80 eV, 90°C): m/z=307 (M^+), 273, 238, 187, 162 (100%), 147, 71. HRMS (EI, 80 eV, 80°C), [$C_{16}H_{18}ClNO_3$] Calcd: 307.09751. Found: 307.09337.

5.4.2. 2-Chloro-3-((3,4-methylenedioxy)-phenyl)-4-pentenoic acid (*S*-proline methylester) amide (9a). Reaction with 0.7 g (2.4 mmol) *N*-allylproline methylester **5a** and chloroacetyl fluoride (0.34 mL, 4.8 mmol) following the standard procedure. Purification by column chromatography on silica gel (hexane/EtOAc 4:1, R_f=0.05). Yield: 0.61 g (1.67 mmol, 69%) amide **9a** (mixture of diastereomers) as a clear pale yellow oil. (potential separation of the diastereomers via HPLC). ^{1}H NMR (250 MHz, major diastereomer and amide conformer 2:1): δ=1.8–2.3 (m, 4H, 3′-and 4′-H); 3.50 (m, 2H, 5′-H); 3.70 (s, 3H, 7′-H); 3.75 (s, 3H, 7′-H amide conformer); 3.80 (m, 2H, 5′-H amide

conformer); 4.90 (dd, 1H, *J*=7.5, 10 Hz, 3-H); 4.95 (dd, 1H, *J*=7.5, 10 Hz, 3-H, amide conformer); 4.30 (d, 1H, *J*=10 Hz, 2-H, amide conformer); 4.40 (dd, 1H, *J*=4, 7 Hz, 2′-H); 4.50 (d, 1H, *J*=10 Hz, 2-H); 4.55 (dd, 1H, *J*=4, 7 Hz, 2′-H, amide conformer); 5.00 (d, 1H, *J*=17 Hz, *Z*-5-H); 5.05 (d, 1H, *J*=10 Hz, *E*-5-H); 5.80 (ddd, 1H, *J*=7.5, 10, 17 Hz, 4-H, amide conformer); 5.90 (ddd, 1H, *J*=7.5, 10, 17 Hz, 4-H); 5.90 (s, 2H, 12-H); 6.60 (s, 1H, 7-H); 6.60 (d, 8 Hz, 11-H); 6.65 (d, 8 Hz, 10-H) ppm. ^{13}C NMR (63 MHz, major diastereomer and amide conformer ca. 2:1): δ=22.6 (C-4′, amide conformer); 24.7 (C-4′); 29.0 (C-3′); 30.9 (C-3′, amide conformer); 46.8 (C-5′, amide conformer); 47.0 (C-5′); 52.2 (C-3); 52.4 (C-7′); 57.7 (C-2′); 59.2 (C-2); 101.0 (C-12); 108.4 (C-7); 108.7 (C-10); 118.3 (C-5); 122.0 (C-11); 133.2 (C-6); 136.7 (C-4); 146.7 (C-8); 147.8 (C-9); 166.7 (C-6′); 171.9 (C-1) ppm. ^{1}H NMR (250 MHz, minor diastereomer and amide conformer): δ=1.95 (m, 3H, 3′- and 4′-H); 2.2 (m, 1H, 3′- or 4′-H); 3.65 (m, 2H, 5′-H); 3.65 (s, 3H, 7′-H); 3.95 (dd, 1H, *J*=6.5, 10 Hz, 3-H); 4.4 (d, 1H, *J*=10 Hz, 2-H amide conformer); 4.4 (d, 1H, *J*=10 Hz, 2-H); 4.5 (dd, 1H, *J*=5, 8.5 Hz, 2′-H); 4.95 (d, 1H, *J*=17 Hz, *Z*-5-H); 5.1 (d, 1H, *J*=10.5 Hz, *E*-5-H); 5.9 (s, 2H, 12-H); 5.9 (ddd, 1H, *J*=6.5, 10.5, 17 Hz, 4-H); 6.7 (d, br, 1H, *J*=8.5 Hz, 11-H); 6.75 (s, 1H, 7-H); 6.8 (d, 1H, *J*=8.5 Hz, 10-H) ppm. IR (film): ν_{max}=3078 w, 2954 (s, CH), 1744 (s, ester-CC=O), 1659 (s, amide-CC=O), 1246 (s, Ar-O), 1039 (s, C-O). MS (EI, 80 eV, 150°C): *m*/*z*=365 (M^+), 329 (M−HCl), 306 (M−CO_2Me), 270 (306−HCl), 201 (100%, 270−C_4H_4N), 161, 131, 115, 103. HRMS (EI, 80 eV, 110°C) [$C_{18}H_{20}ClNO_5$] Calcd: 365.103002. Found: 365.10318.

5.4.3. 2-Chloro-3-((3,4-methylenedioxy)-phenyl)-4-pentenoic acid (*S*-proline *t*-butylester) amide (10a). Reaction with 1.14 g (3.44 mmol) *N*-allylproline methylester **6a** and chloroacetyl fluoride (0.66 g, 6.88 mmol) following the standard procedure. Purification by column chromatography on silica gel (hexane/EtOAc 8:1, R_f=0.2 in *n*-hexane/EtOAc 4:1). Yield: 0.71 g (1.73 mmol, 50%) amide **10a** as a clear pale yellow oil. The first fractions contained some minor diastereomer, which was separated via preparative HPLC: 2% *i*-PrOH in *n*-hexane, flow 2 mL/min; minor diastereomer: 1.9 min retention time; major diastereomer: 2.7 min. Separation of 120 mg material gave 110 mg of the major and 10 mg of the minor diastereomer. ^{1}H NMR (250 MHz, major diastereomer and amide conformer 2:1): δ=1.4 (s, 9H, 8′-H); 1.5 (s, 9H, 8′-H, amide conformer); 1.7–2.1 (m, 4H, 3′- and 4′-H); 3.45 (m, 1H, $5^{1\prime}$-H); 3.55 (m, 1H, $5^{2\prime}$-H); 3.8 (m, 2H, 5′-H amide conformer); 4.0 (dd, 1H, *J*=7.5, 10 Hz, 3-H); 4.0 (dd, 1H, *J*=7.5, 10 Hz, 3-H, amide conformer); 4.2 (d, 1H, *J*=10 Hz, 2-H, amide conformer); 4.3 (dd, 1H, *J*=4, 8 Hz, 2′-H); 4.5 (d, 1H, *J*=10 Hz, 2-H); 4.5 (dd, 1H, *J*=4, 8 Hz, 2′-H, amide conformer); 5.0 (d, 1H, *J*=17 Hz, *Z*-5-H); 5.05 (d, 1H, *J*=10 Hz, *E*-5-H); 5.85 (ddd, 1H, *J*=7.5, 10, 17 Hz, 4-H, amide conformer); 5.9 (ddd, 1H, *J*=7.5, 10, 17 Hz, 4-H); 5.9 (s, 2H, 12-H); 6.6 (s, 1H, 7-H); 6.6 (d, *J*=8 Hz, 11-H); 6.65 (d, *J*=8 Hz, 10-H) ppm. ^{13}C NMR (63 MHz, major diastereomer and amide conformer ca. 2:1): δ=22.4 (C-4′, amide conformer); 24.4 (C-4′); 27.8 (C-8′); 29.0 (C-3′); 31.1 (C-3′, amide conformer); 46.8 (C-5′, amide conformer); 47.0 (C-5′); 52.2 (C-3); 57.2 (C-2′); 57.8 (C-2′, amide conformer); 59.9 (C-2); 81.4 (C-7′); 82.6 (C-7′, amid conformer); 101.0 (C-12); 108.2 (C-7); 108.6 (C-10); 118.2 (C-5); 121.9 (C-11); 133.2 (C-6); 133.4 (C-6, amide conformer); 136.7 (C-4); 136.8 (C-4, amide conformer); 146.7 (C-8); 147.8 (C-9); 166.0 (C-6′); 166.4 (C-6′, amide conformer); 170.4 (C-1); 171.1 (C-1, amide conformer) ppm. ^{1}H NMR (250 MHz, minor diastereomer): δ=1.4 (s, 9H, 8′-H); 1.9–2.2 (m, 4H, 3′- and 4′-H); 3.65 (m, 2H, 5′-H); 3.95 (dd, 1H, *J*=6.5, 10 Hz, 3-H); 4.4 (dd, 1H, *J*=4.5, 8 Hz, 2′-H); 4.45 (d, 1H, *J*=10 Hz, 2-H); 4.95 (d, 1H, *J*=17 Hz, *Z*-5-H); 5.1 (d, 1H, *J*=10.5 Hz, *E*-5-H); 5.9 (s, 2H, 12-H); 5.9 (ddd, 1H, *J*=6.5, 10.5, 17 Hz, 4-H); 6.7 (d, br, 1H, *J*=8.5 Hz, 11-H); 6.75 (s, 1H, 7-H); 6.8 (d, 1H, *J*=8.5 Hz, 10-H) ppm. ^{13}C NMR (63 MHz, minor diastereomer): δ=24.8 (C-4′); 27.9 (C-8′); 29.2 (C-3′); 47.1 (C-5′); 52.1 (C-2); 57.8 (C-2′); 60.3 (C-3); 81.3 (C-7′); 101.0 (C-12); 108.2 (C-7); 108.9 (C-10); 118.4 (C-5); 122.3 (C-11); 133.1 (C-6); 136.5 (C-4); 146.1 (C-8); 146.7 (C-9); 166.3 (C-1); 170.1 (C-6′) ppm. IR (film): ν_{max}=3082 w, 2979 (s, CH), 1736 (s, Ester-CC=O), 1659 (s, Amid-CC=O), 1246 (s, Ar-O), 1040 (s, C−O). MS (EI, 80 eV, 150°C): *m*/*z*=407 (M^+), 371 (M−HCl), 315 (371−C_4H_8), 306 (M−$CO_2{}^t$Bu), 270 (306−HCl), 201 (100%, 270−C_4H_4N), 161, 131, 115, 103, 70. HRMS (EI, 80 eV, 110°C) [$C_{21}H_{26}ClNO_5$] Calcd: 407.149952. Found: 407.14983.

5.5. Standard procedure for the iodocyclization

The amide (2 mmol) was dissolved in DME (5 mL) and H_2O (5 mL) and cooled to 0°C. With exclusion of light, I_2 (1.0 g, 4 mmol) was added. The mixture was vigorously stirred at rt, until the reaction was found to be complete (~30 min). Then, the excess of I_2 was reduced with saturated aq. $Na_2S_2O_3$ (5 mL). The mixture was extracted with Et_2O (4×15 mL), the organic layers were dried ($MgSO_4$) and the solvent was removed. The crude material was purified and the diastereomers were separated by column chromatography on silica gel, EtOAc/hexanes 1:4, (EtOAc/hexanes 1:2, R_f=0.35: 5β-**13a**, R_f=0.25: 5α-**13a**; ratio: 4–5:1).

Analytical chiral HPLC: Column: Chirobiotic V (Astec), 4.6×250 mm,10% EtOH in *n*-hexane, flow: 1 mL/min, UV detection (254 nm). Major 4,5-*syn* lactone: peaks at 10.1 (a) and 10.8 min (b). Minor 4,5-*anti* lactone: peaks at 17.7 (a) and 18.5 min (b).

Reaction with amide **8a** (0.1 g, 0.32 mmol) following the standard procedure, reaction time: 12 h. Yield: 0.11 g (0.29 mmol, 88%) of **13a** (mixture of diastereomers, racemate). Chiral HPLC: 13-5α (a/b=1:1); 13-5β (a/b=1:1).

Reaction with amide **9a** (0.53 g, 1.4 mmol) following the standard procedure, reaction time: 12 h. Yield: 0.38 g (1.0 mmol, 70%) of **13a** (mixture of diastereomers). Chiral HPLC: 13-5α (a/b=2:1); 13-5β (a/b=2:1).

Reaction with amide **10a** (0.71 g, 1.7 mmol) following the standard procedure, reaction time: 12 h. Yield: 0.49 g (1.3 mmol, 74 %) of **13a** (mixture of diastereomers). Chiral HPLC: 13-5α (a/b=>10:1). 13-5β (a/b=>10:1).

5.5.1. (3*R*,4*S*,5*R*) 3-Chloro-4-(3,4-methylenedioxyphenyl)-5-iodomethyl-2(3H)-furanone (13-5α). ^{1}H NMR (250 MHz): δ=3.3 (dd, 1H, *J*=5, 11 Hz, 5^1-H); 3.45 (dd, 1H, *J*=9, 11 Hz, 5^2-H); 3.55 (dd, 1H, *J*=4, 11 Hz); 4.3 (ddd, 1H, *J*=4, 5, 9 Hz, 4-H); 4.7 (d, 1H, *J*=11 Hz); 6.0 (s, 2H, 12-H); 6.75 (d, 1H, *J*=9 Hz, 11-H); 6.8 (s, 1H, 7-H); 6.85 (d, 1H, *J*=9 Hz, 10-H) ppm. NOE analysis: 3.3⇒3.45 (33.0); 3.55 (5.0); 3.45⇒3.3 (31.3); 3.55 (5.0); 3.55⇒3.3 (1.5); 4.3 (1.0); 4.7 (1.5); 4.3⇒3.55 (1.5); 4.7 (4.5); 6.8, 6.85 (11.0); 4.7⇒3.55 (1.6); 4.3 (3.0); 6.8, 6.85 (11.5); 6.8, 6.85⇒4.3 (15.0); 4.7 (10.0). ^{13}C NMR (63 MHz): δ=0.2 (C-5); 57.4 (C-3); 58.0 (C-2); 80.8 (C-4); 101.6 (C-12); 107.3 (C-10); 109.1 (C-7); 121.4 (C-11); 127.0 (C-6); 148.2 (C-8); 148.7 (C-9); 169.4 (C-1) ppm. IR (film): ν_{max}=2961 m, 2900 (m, CH), 1792 (s, br, CC═O), 1256 (s, Ar-O), 1039 (s, C–O). MS (80 eV, 100°C): *m*/*z*=380 (M$^+$), 253 (M−I), 209 (M−I, CO_2), 182, 175, 89. HRMS (EI, 80 eV, 100°C) of [$C_{12}H_{10}ClIO_4$] Calcd: 379.93124. Found: 379.93342.

5.5.2. (3*R*,4*S*,5*S*) 3-Chloro-4-(3,4-methylenedioxyphenyl)-5-iodomethyl-2(3*H*)-furanone (13-5β). ^{1}H NMR (250 MHz): δ=2.9 (dd, 1H, *J*=7.5, 10 Hz, 5^1-H); 3.2 (dd, 1H, *J*=7.5, 10 Hz, 5^2-H); 3.8 (dd, 1H, *J*=4, 6 Hz, 3-H); 4.55 (d, 1H, *J*=4 Hz, 2-H); 5.17 (q, br, 1H, *J*=8.5 Hz, 4-H); 5.9 (s, 2H, 12-H); 6.6 (d, 1H, *J*=9 Hz, 11-H); 6.65 (s, 1H, 7-H); 6.75 (d, 1H, *J*=9 Hz, 10-H) ppm. NOE analysis: 2.9⇒3.2 (34.8), 6.6, 6.65 (4.0); 3.2⇒2.9 (33.6), 4.55 (1.5); 3.8⇒4.55 (4.0), 5.17 (14.0); 4.55⇒3.8 (3.0), 6.6, 6.65 (11.5); 5.17⇒2.9, 3.2 (2.4); 3.8 (12.5); 6.6, 6.65⇒2.9 (2.0); 4.55 (13.0). ^{13}C NMR (63 MHz): δ=0.2 (C-5); 53.6 (C-3); 55.3 (C-2); 81.3 (C-4); 101.5 (C-12); 108.1 (C-10); 108.9 (C-7); 121.5 (C-11); 126.5 (C-6); 147.9 (C-8); 148.4 (C-9); 171.0 (C-1) ppm. IR (film): ν_{max}=2961 m, 2900 (m, CH), 1792 (s, br, CC═O), 1256 (s, Ar-O), 1039 (s, C–O). MS (80 eV, 100°C): *m*/*z*=380 (M$^+$), 253 (M−I), 209 (M−I, CO_2), 182, 175, 89. Calcd: 379.93124. Found: 379.93342.

5.5.3. (2*R*,3*R*)-2-Azido-3-((3,4-methylenedioxy)-phenyl)-4-pentenoic acid-(*S*-proline methylester)-amide (15a). Reaction with 0.91 g (3.14 mmol) *N*-allylproline methylester **5a** following the standard procedure. Purification by column chromatography on silica gel (hexane/EtOAc 10:1, R_f=0.4 in *n*-hexane/EtOAc 4:1). Yield: 0.9 g (2.41 mmol, 77%) amide **15a** (mixture of diastereomers) as a clear pale yellow oil. Potential separation of the diastereomers via HPLC (difficult). Data of the major diastereomer 2*R*,3*R*-**15a** (minor diastereomer probably 2*S*,3*S*-**15a**): [α]$_D^{23}$=−66.0 (*c*=2.8, $CHCl_3$). ^{1}H NMR (270 MHz): δ=2.00 (m, br, 3H, 3-H and 4-H); 2.13 (m, br, 1H, 3-H or 4-H); 3.46 (q, 1H, *J*=6.8 Hz, 5′^{1}-H (minor conformer)); 3.47 (q, 1H, *J*=6.8 Hz, 5′^{1}-H); 3.60 (q, br, 1H, *J*=6.8 Hz, 5′^{2}-H (incl. minor conformer)); 3.71 (s, 3H, 7′-H); 3.65–4.02 (m, 2H, 2-H and 3-H); 4.45 (dd, 1H, *J*=3.9, 7.8 Hz, 2′-H); 4.54 (dd, 1H, *J*=3.9, 7.8 Hz, 2′-H (minor conformer)); 5.02 (m, 1H, 5-H (minor conformer)); 5.08 (d, 1H, *J*=10.3 Hz, *E*-5-H); 5.08 (d, 1H, *J*=17.1 Hz, *Z*-5-H); 5.17 (d, 1H, *J*=10.3 Hz, *E*-5-H (diastereomer)); 5.81 (ddd, 1H, *J*=6.8, 10.3, 17.1 Hz; 4-H (minor conformer)); 5.89 (ddd, 1H, *J*=6.8, 10.3, 17.1 Hz; 4-H); 5.91 (s, 2H, 12-H); 6.01 (ddd, 1H, *J*=6.8, 10.3, 17.1 Hz; 4-H (diastereomer)); 6.73 (m, 3H, 7-H, 10-H and 11-H) ppm. ^{13}C NMR (68 MHz, major conformer): δ=24.6 (C-4′); 29.0 (C-3′); 47.0 (C-5′); 50.9 (C-7′); 52.3 (C-3); 59.0 (C-2′); 63.0 (C-2); 101.1 (C-12); 108.2 (C-7); 108.5 (C-10); 118.2 (C-5); 121.5 (C-11); 132.7 (C-6); 136.2 (C-4); 146.8 (C-9); 148.0 (C-8); 167.2 (C-1); 172.0 (C-6′) ppm (minor conformer): δ=22.3 and 24.8 (C-4′); 29.1 and 31.0 (C-3′); 46.7 and 47.1 (C-5′); 50.2 and 50.6 (C-7′); 52.2 and 52.6 (C-3); 59.0 and 59.10 (C-2′); 62.3 and 63.6 (C-2); 108.3 (C-7); 108.5 (C-10); 117.9 and 118.5 (C-5); 121.7 and 121.9 (C-11); 135.8 and 136.4 (C-4) ppm. IR (film): ν_{max}=3058 (w, ArH), 2982 m, 2954 (m, CH), 2099 (s, N_3), 1744 (s, ester CC═O), 1653 (s, amide CC═O), 1246 (s, Ar-O), 1039 (s, C−O), 996 w, 932 (m, CH═CH_2). **MS** (EI, 80 eV, 130°C): *m*/*z*=372 (M$^+$), 330 (M−N_3^+), 201 (330−MePro), 188, 171, 161 (Ar-CH–CH═CH_2), 148, 131 (100, 161−CH_2O), 128, 103, 77, 70. HRMS (EI, 80 eV, 110°C) [$C_{18}H_{20}N_4O_5$] Calcd: 372.14336. Found: 372.14289.

5.5.4. (2*R*,3*R*)-2-Azido-3-(4-methoxyphenyl)-4-pentenoic acid (*S*-proline methylester) amide (15b). Reaction with 1.0 g (3.6 mmol) *N*-allylproline methylester **5b** following the standard procedure. Purification by column chromatography on silica gel (hexane/EtOAc 10:1, R_f=0.4 in *n*-hexane/EtOAc 4:1). Yield: 0.18 g (0.51 mmol, 14 %) amide **15b** (mixture of diastereomers: 1:1) as a clear pale yellow oil. Separation of the diastereomers via HPLC (20% EtOAc/hexane, difficult). Data of the first diastereomer **15b** (probably 2′*S*,3′*S*), (90 mg): [α]$_D^{23}$=8.0 (*c*=5.6, $CHCl_3$). ^{1}H NMR (270 MHz): δ=2.00 (m, br, 3H, 3-H and 4-H); 2.10 (m, br, 1H, 3-H or 4-H); 3.58 (m, 3H, 3′-H, 5-H); 3.71 (s, 3H, ArOMe); 3.77 (s, 3H, CO_2Me); 4.02 (dd, 1H, *J*=3.9, 7.8 Hz, 2-H); 4.57 (dd, 1H, *J*=3.9, 7.8 Hz, 2′-H); 5.00 (d, 1H, *E*-5′-H); 5.17 (d, 1H, *J*=10.3 Hz, *E*-5′-H); 6.05 (ddd, 1H, *J*=6.8, 10.3, 17.1 Hz; 4′-H); 6.88 (d, br, *J*=6.8, 2H, Ar-H); 7.18 (d, br, *J*=6.8, 2H, Ar-H) ppm. ^{13}C NMR (68 MHz): δ=24.7 (C-4); 29.0 (C-3); 47.1 (C-5); 50.1 (CO_2Me); 52.1 (C-3′); 55.1 (ArOMe); 59.0 (C-2); 62.3 (C-2′); 114.1 (Ar-CH); 118.3 (C-5′); 129.0 (Ar-CH); 130.5 (Ar-C); 136.0 (C-4′); 158.7 (ArO); 167.2 (CON); 171.0 (CO_2) ppm. IR (film): ν_{max} 2954 (m, CH), 2098 (s, N_3), 1745 (s, ester CC═O), 1654 (s, amide CC═O), 925 (m, CH═CH_2). **MS** (EI, 80 eV, 150°C): *m*/*z*=358 (M$^+$), 330 (M−N_2^+), 327 (M−OMe), 316 (M−N_3^+), 147, 128. HRMS (EI, 80 eV, 140°C) [$C_{18}H_{22}N_2O_4$] Calcd: 330.15796. Found: 330.15430. Data of the second diastereomer **15b** (probably 2′*R*,3′*R*), (90 mg): [α]$_D^{23}$=−59.9 (*c*=7.5, $CHCl_3$). ^{1}H NMR (270 MHz): δ=2.00 (m, br, 2H, 3-H and 4-H); 2.15 (m, br, 2H, 3-H and 4-H); 3.45 (m, 2H, 5-H); 3.60 (m, 1H, 3′-H); 3.70 (s, 3H, ArOMe); 3.76 (s, 3H, CO_2Me); 3.92 (dd, 1H, *J*=3.9, 7.8 Hz, 2-H); 4.45 (dd, 1H, *J*=3.9, 7.8 Hz, 2′-H); 5.06 (d, 1H, *J*=17.1 Hz, *Z*-5-H); 5.08 (d, 1H, *J*=10.3 Hz, *Z*-5-H); 5.94 (ddd, 1H, *J*=6.8, 10.3, 17.1 Hz; 4′-H; 6.86 (d, br, *J*=6.8, 2H, Ar-H); 7.16 (d, br, *J*=6.8, 2H, Ar-H) ppm. ^{13}C NMR (68 MHz): δ=24.6 (C-4); 28.9 (C-3); 46.9 (C-5); 50.4 (CO_2Me); 52.2 (C-3′); 55.1 (ArOMe); 58.9 (C-2); 62.9 (C-2′); 114.1 (Ar-CH); 118.0 (C-5′); 129.0 (Ar-CH); 130.9 (Ar-C); 136.3 (C-4′); 158.7 (ArO); 167.3 (CON); 172.0 (CO_2) ppm. IR (film): ν_{max} 2954 (m, CH), 2098 (s, N_3), 1746 (s, ester CC═O), 1654 (s, amide CC═O), 925 (m, CH═CH_2). MS (EI, 80 eV, 135°C): *m*/*z*=358 (M$^+$), 330 (M−N_2^+), 327 (M−OMe), 316 (M−N_3^+), 147, 128. HRMS (EI, 80 eV, 135°C) [$C_{18}H_{22}N_2O_4$] Calcd: 330.15796. Found: 330.16020.

5.5.5. (2*R*,3*R*)-2-Azido-3-((3,4-methylenedioxy)-phenyl)-4-pentenoic acid (2*S*-(*t*-butyldimethylsilyloxymethyl) pyrrolidinyl) amide (16a). Reaction with 0.5 g (1.33 mmol) *N*-allylprolinol silylether **7a** following the standard procedure. Purification by column chromatography on silica gel (hexane/EtOAc 10:1, R_f=0.4 in *n*-hexane/EtOAc 4:1). Yield: 0.53 g (1.15 mmol, 87%) amide **16a** as clear pale yellow oil. $[\alpha]_D^{23}=-83$ (c=1.2, $CHCl_3$). ^{1}H NMR (270 MHz): δ=0.04 (s, 6H, 7′-H); 0.86 (s, 9H, 9′-H); 1.85 and 2.05 (2 m, br, 3H and 1H, 3′-H and 4′-H); 3.46 (m, br, 2H, 5′-H); 3.82 (m, br, 4H, 3-H, 2-H, 6′-H); 4.14 (m, 1H, 2′-H); 5.08 11 (dd, 1H, J=1.46, 17.1 Hz, *Z*-5-H (minor conformer)); 5.11 (d, 1H, J=10.3 Hz, *E*-5-H); 5.11 (dd, 1H, J=1.46, 17.1 Hz, *Z*-5-H); 5.86 (ddd, 1H, J=7.3, 10.3, 17.1 Hz, 4-H (minor conformer)); 5.91 (ddd, 1H, J=7.3, 10.3, 17.1 Hz, 4-H); 5.93 (s, 2H, 12-H); 6.67 (m, 3H, 7-H, 10-H, 11-H) ppm. ^{13}C NMR (68 MHz, major conformer): $\delta=-5.5$ (C-7′); 18.1 (C-8′); 24.1 (C-4′); 25.9 (C-9′); 27.1 (C-3′); 47.6 (C-5′); 51.0 (C-3); 58.9 (C-2′); 62.5 (C-2); 63.1 (C-6′); 101.2 (C-12); 108.2 (C-7); 108.3 (C-10); 118.2 (C-5); 121.5 (C-11); 132.6 (C-6); 136.2 (C-4); 146.7 (C-8); 148.0 (C-9); 167.1 (C-1) ppm. Minor conformer: $\delta=-5.3$ (C-7′); 18.3 (C-8′); 21.7 (C-4′); 25.8 (C-9′); 28.3 (C-3′); 46.1 (C-5′); 50.1 (C-3); 53.4 (C-2′); 65.0 (C-6′); 108.2 (C-7); 108.3 (C-10); 118.2 (C-5); 121.5 (C-11); 132.6 (C-6); 136.2 (C-4); 146.7 (C-8); 148.0 (C-9); 167.1 (C-1) ppm. IR (film): ν_{max}=3081 (w, Ar-H), 2954 s, 2928 (s, CH), 2099 (s, N_3), 1648 (s, CC═O), 1504 (s, CC═C aryl), 1247 (s, Ar-O), 1103 (s, OTBS), 1040 (s, C-O), 1004 w, 931 (m, CH═CH_2), 838 (s, OTBS). MS (EI, 80 eV, 165°C): m/z=458 (M^+), 443 ($M-CH_3$), 430 ($M-N_2$), 416 ($M-N_3$), 401 ($M-C_4H_9$), 373 ($401-N_2$), 358, 242 ($CO-NC_4H_9-OTBS^+$), 211, 201, 184, 161 (100, Ar-$C_3H_4^+$), 131 ($161-CH_2O$), 103, 73. HRMS (EI, 80 eV, 110°C) [$C_{23}H_{34}N_4O_4Si$] Calcd: 458.23492. Found: 458.23673.

5.5.6. (2*R*,3*R*)-2-Azido-3-(4-methoxyphenyl)-4-pentenoic acid (2*S*-*t*-butyldimethylsiloxymethyl) pyrrolidinyl amide (16b). Reaction with 0.44 g (1.22 mmol) *N*-allylprolinol silylether **7b** following the standard procedure. Purification by column chromatography on silica gel (hexane/EtOAc 10:1, R_f=0.1). Yield: 0.31 g (0.69 mmol, 57%) amide **16b** as clear oil. $[\alpha]_D^{23}=-121$ (c=2.1, $CHCl_3$). ^{1}H NMR (270 MHz): δ=0.04 (s, 6H, 7′-H); 0.86 (s, 9H, 9′-H); 1.85 and 2.05 (2 m, br, 4H, 3′-H and 4′-H); 3.45 (m, br, 2H, 5′-H); 3.75 and 3.90 (2 m, 4H, 3-H, 2-H, 6′-H); 3.79 (s, 3H, 12-H); 4.14 (m, 1H, 2′-H); 5.03 (d, br, 2H, J=12.9 Hz, 5-H (minor conformer)); 5.09 (d, br, 2H, J=11.2 Hz, 5-H); 5.91 (ddd, 1H, J=6.9, 10.3, 17.2 Hz, 4-H (minor conformer)); 5.94 (ddd, 1H, J=6.9, 9.5, 17.2 Hz, 4-H); 6.89 (d, 2H, J=8.6 Hz, 7-H and 11′-H); 7.19 (d, 2H, J=8.6 Hz, 8-H and 10′-H) ppm. ^{13}C NMR (68 MHz, major conformer): $\delta=-5.7$ (C-7′); 18.0 (C-8′); 24.0 (C-4′); 25.7 (C-9′); 26.7 (C-3′); 47.5 (C-5′); 50.5 (C-3); 55.0 (C-12); 58.8 (C-2′); 62.4 (C-2); 63.0 (C-6′); 114.0 (C-8 and C-10); 117.9 (C-5); 129.0 (C-7 and C-11); 131.1 (C-6); 136.4 (C-4); 158. 7 (C-9); 167.2 (C-1) ppm. Minor conformer: $\delta=-5.5$ (C-7′); 18.2 (C-8′); 21.6 (C-4′); 25.7 (C-9′); 29.5 (C-3′); 46.0 (C-5′); 49.5 (C-3); 64.9 (C-6′); 118.1 (C-5); 129.3 (C-7 and C-11); 130.7 (C-6); 136.9 (C-4); 166.8 (C-1) ppm. IR (film): ν_{max}=3078 (w, ArH), 2954 s, 2928 (s, CH), 2099 (s, N_3), 1650 (s, br, CC═O), 1611 (m, CC═C), 1513 (s, CC═C aryl), 1250 (s, Ar-O), 1105 (m, br, OTBS), 1036 (m, C-O), 1004 w, 927(m, CH═CH_2), 836 (s, OTBS). MS (80 eV, 125°C): m/z=444 (M^+), 429 ($M-CH_3$), 416 ($M-N_2$), 402 ($M-N_3$), 387 ($M-C_4H_9$), 359 ($387-N_2$), 242 ($CO-NC_4H_9-OTBS^+$), 211, 187, 147 (100, CH_3O–Ph-$C_3H_4^+$), 70. HRMS (EI, 80 eV, 125°C) [$C_{22}H_{33}N_4O_3Si-CH_3$] Calcd: 429.232195. Found: 429.23541.

5.5.7. (2*R*,3*R*)-2-Azido-3-phenyl-4-pentenoic acid (2*S*-*t*-butyldimethylsiloxymethyl) pyrrolidinyl amide (16c). Reaction with 0.5 g (1.5 mmol) *N*-allylprolinol silylether **7c** following the standard procedure. Purification by column chromatography on silica gel (hexane/EtOAc 10:1, R_f=0.1). Yield: 0.57 g (1.38 mmol, 91%) amide **16c** as clear oil. $[\alpha]_D^{23}=-92$ (c=1.8, $CHCl_3$). ^{1}H NMR (270 MHz): δ=0.04 (s, 6H, 7′-H); 0.86 (s, 9H, 9′-H); 1.85 and 2.03 (2 m, br, 4H, 3′-H and 4′-H); 3.48 (m, br, 2H, 5′-H); 3.65 and 3.90 (2 m, 4H, 3-H, 2-H, 6′-H); 4.10 (m, 1H, 2′-H); 5.10 (d, br, 2H, 5-H (minor conformer)); 5.15 (d, br, 2H, J=10.8 Hz, *E*-5-H); 5.15 (d, br, 2H, J=17.3 Hz, *E*-5-H); 5.91 (ddd, 1H, J=6.8, 10.8, 17.3 Hz, 4-H (minor conformer)); 5.94 (ddd, 1H, J=6.8, 10.8, 17.3 Hz, 4-H); 7.35 (m, 5H, Ar-H) ppm. ^{13}C NMR (68 MHz): $\delta=-5.7$ (C-7′); 18.0 (C-8′); 24.2 (C-4′); 25.8(C-9′); 27.1 (C-3′); 47.6 (C-5′); 51.5 (C-3); 59.0 (C-2′); 62.6 (C-2); 63.0 (C-6′); 118.4 (C-5); 127.4 (C-9); 128.2 (C-8 and C-10); 128.5 (C-6); 128.8 (C-7 and C-11); 136.7 (C-4); 167.5 (C-1) ppm. IR (film): ν_{max}=3063 w, 3030 (w, Ar-H), 2955 s, 2928 (s, CH), 2098 (s, N_3), 1650 (s, CC═O), 1104 (s, br, OTBS), 1004 m, 927 (m, CH═CH_2). MS (80 eV, 90°C): m/z=414 (M^+), 399 ($M-CH_3$), 386 ($M-N_2$), 372 ($M-N_3$), 357 (100, $M-C_4H_9$), 329 ($357-N_2$), 269 ($M-CH_2OTBS$), 242 ($CO-NC_4H_9-OTBS$), 227, 211, 186, 156, 117 (Ph-$C_3H_4^+$), 73. HRMS (EI, 80 eV, 100°C) [$C_{22}H_{34}N_4O_2Si$] Calcd: 414.245105. Found: 414.24899.

5.6. Standard procedure for the hydroboration cyclization sequence: 3-aryl proline amides

Under argon, BH_3 SMe_2 (0.46 g, 6 mmol, 10.2 M) was dissolved in dry CH_2Cl_2 (37 mL) and cooled to 0°C. Cyclohexene (0.98 g, 12 mmol, 1.22 mL) was added dropwise via syringe over a period of 15 min. After stirring for 3 h at 0°C the α-azidoamide **15** or **16** (2 mmol) in CH_2Cl_2 was injected and the mixture was allowed to warm-up to rt. After stirring for another 10 h, the resulting clear yellow solution was treated with saturated aqueous NH_4Cl (12 mL) to destroy the amine borane complex. After 5 min saturated aqueous K_2CO_3 was added (caution) until a pH of 10–11 was reached. The mixture was extracted with CH_2Cl_2 (4×20 mL), the combined organic layers were washed with brine (15 mL) and dried ($MgSO_4$). The solvent was removed and the crude material was purified by column chromatography.

5.6.1. (2*R*,3*R*)-3-((3,4-Methylendioxy)-phenyl)-proline (2*S*-(*t*-butyl-dimethylsiloxymethyl)-pyrrolidinyl) amide (19a). Reaction with 2 g (4.36 mmol) α-azidoamide **16a** following the standard procedure. Purification by column chromatography on silica gel (MeOH/EtOAc 1:10, R_f=0.05–0.15 in EtOAc/MeOH 3:1). Yield: 1.42 g (3.28 mmol, 75%) of a clear pale brownish oil.

$[\alpha]_D^{23}=-51.9$ (c=1.8, $CHCl_3$). ^1H NMR (500 MHz): $\delta=-0.01$ (s, 6H, 7′-H); 0.82 (s, 9H, 9′-H); 1.17 (m, 1H, $4^{1\prime}$-H); 1.30 (m, 1H, $3^{1\prime}$-H); 1.69 (m, 1H, $4^{2\prime}$-H); 1.77 (m, 1H, $3^{2\prime}$-H); 2.24 (ddt, 1H, J=7.5, 12.0, 12.0 Hz, 4^1-H); 2.32 (m, 1H, 4^2-H); 2.57 (dt, 1H, J=7.6, 10 Hz, $5^{1\prime}$-H); 3.21 (ddd, 1H, J=4.9, 8.7, 10 Hz, $5^{2\prime}$-H); 3.39 (dd, 1H, J=7.4, 10 Hz, $6^{1\prime}$-H); 3.51 (ddd, 1H, J=6.6, 11.4, 11.4 Hz, 5^1-H); 3.70 (dd, 1H, J=3.4, 10 Hz, 6^2-H); 3.80 (m, 3H, 3-H, 5^2-H and 2′-H); 4.73 (d, 1H, J=9.5 Hz, 2-H); 5.91 (s, 2H, 13-H); 6.72 (m, 3H, 8-H, 11-H and 12-H) ppm. ^{13}C NMR (68 MHz): $\delta=-5.4$ (C-7′); 18.1 (C-8′); 23.0 (C-4′); 25.8 (C-9′); 26.4 (C-3′); 32.3 (C-4); 45.7 (C-5); 46.8 (C-5′); 47.7 (C-3); 59.8 (C-2′); 61.3 (C-2); 62.0 (C-6′); 101.3 (C-13); 108.2 (C-8); 108.3 (C-11); 122.3 (C-12); 129.0 (C-7); 147.5 (C-10); 147.9 (C-9); 165.4 (C-6) ppm. IR (film): ν_{max}=3426 (w, br, NH), 2955 s, 2928 (s, CH), 1649 (s, CC═O), 1254 (s, Ar-O), 1098 (s, OTBS), 1031 (s, C-O), 836 (s, OTBS). MS (EI, 80 eV, 95°C): m/z=432 (M^+), 417 ($M-CH_3$), 390 ($M-C_2H_4N$), 375 ($M-C_4H_9$), 227, 190 (100, Ar-C_4H_7N), 131, 84, 70. HRMS (EI, 80 eV, 110°C) [$C_{23}H_{36}N_2O_4Si$] Calcd: 432.24442. Found: 432.24518.

5.6.2. (2*R*,3*R*)-3-(4-Methoxyphenyl)-proline (2*S*-(*t*-butyl-dimethylsiloxymethyl)-pyrrolidinyl) amide (19b). Reaction with 0.12 g (0.27 mmol) α-azidoamide **16b** following the standard procedure. Purification by column chromatography on silica gel (MeOH/EtOAc 1:10, R_f=<0.05, R_f=0.1 in MeOH/EtOAc (1:10)+1% Et_3N). Yield: 0.07 g (0.17 mmol, 62%) of a clear oil. $[\alpha]_D^{23}=-82$ (c=1.4, $CHCl_3$). ^1H NMR (250 MHz) $\delta=-0.04$ (s, 6H, 7′-H); 0.77 (s, 9H, 9′-H); 1.04 (m, 1H, $4^{1\prime}$-H); 1.18 (m, 1H, $3^{1\prime}$-H); 1.63 (m, 2H, $3^{2\prime}$-H and $4^{2\prime}$-H); 1.94 (m, 1H, 4^1-H); 2.11 (m, 1H, 4^2-H); 2.74 (m, 1H, $5^{1\prime}$-H); 2.91 (m, 1H, $5^{2\prime}$-H); 3.13 (m, 2H, NH and $6^{1\prime}$-H); 3.35–3.67 (m, 5H, 2′-H, 3-H, 5^1-H, 5^2-H, 6^2-H); 3.72 (s, 3H, 13-H); 4.16 (d, 1H, J=8.8 Hz, 2-H); 4.76 (s, br, 1H, NH); 6.74 (d, 2H, J=7.4 Hz, 8-H and 12-H); 7.10 (d, 2H, J=7.4 Hz, 9-H and 11-H) ppm. ^{13}C NMR (68 MHz): $\delta=-5.5$ (C-7′); 18.1 (C-8′); 23.1 (C-4′); 25.8 (C-9′); 26.3 (C-3′); 35.3 (C-4); 46.4 (C-5); 47.0 (C-5′); 48.9 (C-3); 55.3 (C-13); 58.9 (C-2′); 62.4 (C-2); 63.3 (C-6′); 113.5 (C-9, C-11); 129.4 (C-8, C-12); 131.1 (C-7); 158.7 (C-10); 169.6 (C-6) ppm. IR (film): ν_{max}=3291 (w, br, NH), 2952 s, 1644 (s, br, CC═O), 1249 (s, br, Ar-O), 1101 (s, br, OTBS), 1035 (s, C–O), 834 (s, OTBS). MS (EI, 80 eV, 130°C): m/z=418 (M^+), 403 ($M-CH_3$), 389 ($M-CHO$), 376 ($M-C_2H_4N$), 361 ($M-C_4H_9$), 218, 176 (100%, Ar-C_4H_7N), 134, 106, 70. HRMS (EI, 80 eV, 100°C [$C_{22}H_{38}N_2O_3Si$] Calcd: 418.265172. Found: 418.26172.

5.6.3. (2*R*,3*R*)-3-(Phenyl)-proline-(2*S*-(*t*-butyl-dimethyl-siloxymethyl)-pyrrolidinyl) amide (19c). Reaction with 0.53 g (1.28 mmol) α-azidoamide **16c** following the standard procedure. Purification by column chromatography on silica gel (MeOH/EtOAc 1:10, R_f=<0.05, 0.1 in MeOH/EtOAc (1:10)+1% Et_3N). Yield: 0.35 g (0.9 mmol, 71%) of a clear oil. $[\alpha]_D^{23}=-72$ (c=0.7, $CHCl_3$). ^1H NMR (250 MHz) $\delta=-0.02$ (s, 6H, 7′-H); 0.82 (s, 9H, 9′-H); 0.97 (m, 1H, $4^{1\prime}$-H); 1.14 (m, 1H, $3^{1\prime}$-H); 1.62 (m, 2H, $3^{2\prime}$-H and $4^{2\prime}$-H); 1.96 (ddt, 1H, J=7.0, 11.5, 11.5 Hz, 4^1-H); 2.15 (m, 1H, 4^2-H); 2.77 (m, 1H, $5^{1\prime}$-H); 2.88 (m, 1H, $5^{2\prime}$-H); 3.16 (m, 2H, NH and $6^{1\prime}$-H); 3.38–3.64 (m, 5H, 2′-H, 3-H, 5^1-H, 5^2-H, 6^2-H); 4.13 (d, 1H, J=8.83 Hz, 2-H); 7.21 (m, 5H, Ar-H) ppm. ^{13}C NMR (68 MHz): $\delta=-5.5$ (C-7′); 17.1 (C-8′); 22.7 (C-4′); 25.5 (C-9′); 25.9 (C-3′); 35.2 (C-4); 46.2 (C-5); 46.0 (C-5′); 49.5 (C-3); 58.4 (C-2′); 62.1 (C-2); 63.3 (C-6′); 126.7 (C-10); 127.7 (C-9 and C-11); 128.1 (C-8 and C-12); 139.3 (C-7); 169.7 (C-6) ppm. IR (film): ν_{max}=3293 (w, br, NH), 2955 s, 2928 (s, CH), 1639 (s, CC═O), 1103 s, br, 837 (s, br, OTBS). MS (80 eV, 100°C): m/z=388 (M^+), 373 ($M-CH_3$), 346 ($M-C_2H_4N$), 331 ($M-C_4H_9$), 284, 227, 214, 200, 192, 186 ($M-C_4H_7N-CH_2OTBS$), 146 (100, Ph-$C_4H_7N^+$), 70. HRMS (EI, 80 eV, 100°C) [$C_{22}H_{36}N_2O_2Si$] Calcd: 388.254607. Found: 388.25833.

5.6.4. (3*R*,4*R*,9*S*)-((3,4-Methylenedioxy)-phenyl)-octa-hydro-dipyrrolo[1,2-a;1′,2′-d]-pyrazine-2,8-dione (20). Reaction with 0.6 g (1.61 mmol) α-azidoamide **15a** following the standard procedure. Before drying with $MgSO_4$, the clear yellow solution was stirred for another 12 h to complete the formation of the pyrazinedione **20**. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 1:1, R_f=0.2). Yield: 0.31 g (1.0 mmol, 62%) of **20** as a pale yellow oil, which crystallized from Et_2O/hexanes, mp 208–209°C. $[\alpha]_D^{23}=-30.7$ (c=1.1, $CHCl_3$). ^1H NMR (500 MHz, CD_2Cl_2): δ=1.68 (m, 3H, 10^1-H and 11^1-H); 1.87 (m, 1H, 11^2-H); 2.12 (ddd, 1H, J=3.2, 9.6, 12.8 Hz, 5^1-H); 2.22 (m, 1H, 10^2-H); 2.36 (m, 1H, 5^2-H); 3.05 (ddd, 1H, J=3.5, 9.6, 12.1 Hz, 12^1-H); 3.34 (ddd, 1H, J=3.9, 12.6, 11.3 Hz, 6^1-H); 3.37 (dd, br, J=5.9, 10.6 Hz, 1H, 9-H); 3.66 (ddd, 1H, J=8.4, 8.4, 12.1 Hz, 12^2-H); 3.70 (dd, 1H, J=5.4, 7.6 Hz, 4-H); 4.22 (dd, 1H, J=1.7, 5.4 Hz, 3-H); 4.28 (ddd, 1H, J=7.4, 9.6, 12.6 Hz, 6^2-H); 5.92 (s, 2H, 7′-H); 6.48 (dd, 1H, J=1.7, 8.1 Hz, 6′-H); 6.54 (d, 1H, J=1.7 Hz, 2′-H); 6.71 (d, 1H, J=8.1 Hz, 5′-H) ppm. NOE analysis: 2.12⇒2.36 (23.5); 3.34 (1.0); 3.70 (2.0); 4.28 (4.0); 6.48, 6.54 (7.0); 2.36⇒2.12 (25.5); 3.34 (8.0); 3.70 (10.0); 4.22 (4.0); 3.34⇒2.36 (5.0); 4.28 (26.0); 3.70⇒2.36 (2.0); 4.22 (10.5); 6.48, 6.54 (5); 4.22⇒3.70 (12.0); 4.28 (4.0); 4.28⇒2.12 (4.0); 2.36 (1.0); 3.34 (30); 6.48, 6.54 (3.0); 6.48, 6.54⇒2.12 (2.5); 3.70 (5.0); 4.28 (5.0). ^{13}C NMR (68 MHz, CD_2Cl_2): δ=21.3 (C-11); 29.0 (C-10); 29.9 (C-5); 43.8 (C-4); 44.4 (C-6); 45.4 (C-12); 60.1 (C-9); 66.6 (C-3); 101.0 (C-7′); 108.2 (C-5′); 108.3 (C-2′); 120.4 (C-6′); 133.3 (C-1′); 146.7 (C-4′); 147.7 (C-3′); 162.2 (C-2); 165.5 (C-8) ppm. IR (film): ν_{max}=2991 m, 2961 (m, CH), 1665 (s, CC═O), 1648 (s, CC═O), 1237 (s, Ar-O), 1034 (s, C–O). MS (EI, 80 eV, 60°C): m/z=314 (M^+, 100%), 297 ($M-OH$), 244 ($M-C_4H_8N$), 217 ($M-C_5H_7NO$), 127, 189, 175, 166, 162, 138, 131, 122 (Ar-H^+), 103, 70. HRMS (EI, 80 eV, 125°C) [$C_{17}H_{18}N_2O_4$] Calcd: 314.126657. Found: 314.12378.

5.6.5. *N*-*t*-Butyloxycarbonyl-3*R*-((3,4-methylenedioxy)-phenyl)-*R*-proline (2*S*-(hydroxymethyl)-pyrrolidinyl) amide (22). Acetyl chloride (1 mL) was cleaved with dry MeOH (15 mL) at 0°C to generate methanolic HCl. The cooling bath was removed and proline amide **19a** (0.14 g, 0.32 mmol) in dry MeOH (15 mL) was added dropwise. The solution was stirred for about 30 min until the silylether was found to be completely consumed. Then, aqueous $NaHCO_3$ and a small amount of solid K_2CO_3 was added to raise the pH to about 10. BOC_2O (76 mg, 0.35 mmol) was injected by means of a syringe and the mixture was stirred at rt for 12 h. Work-up started by extraction with CH_2Cl_2 (4×10 mL). The

organic layer was dried ($MgSO_4$) and the solvent was removed. The crude material was purified via column chromatography (EtOAc/MeOH: 10:1, R_f=0.2). Yield: 116 mg (0.28 mmol, 87%) of **22** as a clear colorless oil. $[\alpha]_D^{23}=-62$ (c=1.0, $CHCl_3$). ^1H NMR (270 MHz) δ=1.03, 1.30 and 1.58 (3 m, 1H, 1H and 2H, 3′-H and 4′-H); 1.40 and 1.44 (2 s, 9H, 9′-H); 2.02 (m, 1H, 4^1-H); 2.55 (m, 1H, 4^2-H); 2.82 (m, 1H, 3-H); 3.18 (m, 1H, 2′-H); 3.45 (m, 4H, 5-H and 5′-H); 3.82 (m, 2H, 6′-H); 4.56 and 4.63 (2 d, 1H, J=7.8 Hz, 2-H of 2 amide forms); 5.56 (d, br, 1H, J=7.3 Hz, OH); 5.59 (s, 2H, 13-H); 6.71 (d, 1H, J=8.3 Hz, 11-H); 6.47 (dd, 1H, J=1.0, 8.3 Hz, 12-H); 6.80 (d, 1H, J=1.0 Hz, 8-H) ppm. ^{13}C NMR (68 MHz): doubled set of peaks because two amide forms. δ=23.9 and 24.2 (C-4′); 27.7 and 27.4 (C-3′); 28.2 and 28.4 (C-9′); 29.6 and 30.3 (C-4); 45.7 and 46.2 (C-5′); 47.2 and 48.4 (C-5); 47.4 and 47.5 (C-3); 61.1 and 61.5 (C-2′); 62.4 (C-2); 65.2 and 67.3 (C-6′); 79.8 and 80.0 (C-8′); 101.0 and 101.1 (C-13); 108.0 (C-8); 108.4 and 108.5 (C-11); 121.8 (C-12); 130.7 and 130.8 (C-7); 146.9 (C-10); 147.7 (C-9); 152.7 and 153.5 (C-7′); 171.1 and 172.4 (C-6) ppm. IR (film): ν_{max}=3418 (s, br, OH), 2975 (s, CH); 1697 (s, amide–CC═O), 1629 (urethane–CC═O), 1251 (c, Ar-O), 1039 (s, C–O). MS (EI, 80 eV, 200°C): m/z=418 (M^+), 388 ($M-CH_2O$), 362 ($M-C_4H_8$), 345 ($M-C_4H_9O$), 332, 317 ($362-CO_2H$), 290 ($M-CO-NC_4H_7-CH_2OH$), 262, 234 (100%, Pip-$C_4H_8N-CO_2^+$), 190 (Pip-$C_4H_7N^+$), 128, 70, 57. HRMS (EI, 80 eV, 180°C) of [$C_{22}H_{30}N_2O_6$] Calcd: 418.21038. Found: 418.21551.

5.6.6. 2*R*-Azido-3*R*-((3,4-methylenedioxy)-phenyl)-4-pentenoic acid methylester (24). The amide **16a** (0.45 g, 0.98 mmol) was dissolved in a solution of HCl in dry MeOH (1 M, 12 mL). The mixture was heated to 50–60°C for about 24 h. Then, the solvent was removed in vacuum and the brownish residue was dissolved in H_2O (20 mL) and extracted with Et_2O (4×10 mL) and dried ($MgSO_4$). After removal of the solvent, the crude material was purified by column chromatography on silica gel (EtOAc/hexane 1:4, R_f=0.4). Yield: 0.21 g (0.74 mmol, 76%) of **24** as a pale yellow oil. Remaining desilylated amide **26** could be recycled from the aqueous layer: solid K_2CO_3 was added until the pH reached about 10–12. The mixture was extracted with Et_2O (3×) and dried ($MgSO_4$). The crude material is pure enough for further transformations. If necessary, purification can be carried out via column chromatography (EtOAc, R_f=0.35). Yield: 40–65 mg (0.12–0.19 mmol, 12–19%) of **26**. Data of **24**: $[\alpha]_D^{23}=-8.7$ (c=1.4, $CHCl_3$). ^1H NMR (270 MHz): δ=3.70 (s, 3H, 13-H); 3.7 (t, 1H, J=8.5 Hz, 3-H); 4.1 (d, 1H, J=8.5 Hz, 2-H); 5.2 (d, 1H, J=10.5 Hz, *trans*-5-H); 5.2 (d, 1H, J=17,0 Hz, *cis*-5-H); 5.9 (s, 2H, 12-H); 5.9 (ddd, 1H, J=8.5, 10.5, 17.0 Hz, 4-H); 6.7 (d, br, 1H, J=8.1 Hz, 11-H); 6.7 (s, br, 1H, 7-H); 6.8 (d, 1H, J=8.1 Hz, 10-H) ppm. ^{13}C NMR (68 MHz): δ=51.4 (C-13); 52.4 (C-3); 66.0 (C-2); 101.1 (C-12); 108.3 (C-7); 108.4 (C-10); 117.6 (C-5); 121.5 (C-11); 132.2 (C-6); 136.4 (C-4); 146.9 (C-8); 147.9 (C-9); 169.7 (C-1) ppm. IR (film): ν_{max}=3080 (w, Ar-H), 2953 m, 2897 m, 2109 (s, N_3), 1745 (s, CC═O), 1639 (m, CC═C), 1490 (s, CC═C Ar), 1249 s, br, 933 (s, CH═CH_2). MS (EI, 80 eV, 50°C): m/z=275 (M^+), 161 ($M-N_3CHCO_2CH_3$), 131 (100%, $161-H_2CO$), 103, 77. HRMS (EI, 80 eV, 50°C) of [$C_{13}H_{13}N_3O_4$] Calcd: 275.09061. Found: 275.09366. For X-ray data see: CCDC 163382.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Data Centre as supplementary publication no. CCDC-163382 (**20**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033, e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

We thank the DFG the FCI and the Schering AG for support of this research.

References

1. Haptens on antibodies influencing 2,3 sigmatropic rearrangements: (a) Zhou, Z. S.; Jiang, N.; Hilvert, D. *J. Am. Chem. Soc.* **1997**, *119*, 3623–3624. (b) Zhou, Z. S.; Jiang, N.; Hilvert, D. *J. Am. Chem. Soc.* **1999**, *121*, 8334–8341. Substance P analog with constrained phenylalanine–phenylalanine region: (c) Tong, Y.; Fobian, Y. M.; Wu, M.; Boyd, N. D.; Moeller, K. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1679–1682. Potential anti-inflammatory cyclopeptide: (d) Jackson, D. Y.; Quan, C.; Artis, D. R.; Rawson, T.; Blackburn, B.; Struble, M.; Fitzgerald, G.; Chan, K.; Mullins, S.; Burnier, J. P.; Fairbrother, W. J.; Clark, K.; Berisni, M.; Chui, H.; Renz, M.; Jones, S.; Fong, S. *J. Med. Chem.* **1997**, *40*, 3359–3368. Non-peptidomimics of sandostatin/somatostatin: (e) Damour, D.; Doerflinger, G.; Pantel, G.; Labaudiniere, R.; Leconte, J.-P.; Sablé, S.; Vuilhorgne, M.; Mignani, S. *Synlett* **1999**, 189–192. (f) Damour, D.; Herman, F.; Labaudiniere, R.; Pantel, G.; Vuilhorgne, M.; Mignani, S. *Tetrahedron* **1999**, *55*, 10135–10154.
2. General syntheses of 3-substituted prolines: (a) Sharma, R.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 202–209. (b) Belokon', Y. N.; Bulychev, A. G.; Pavlov, V. A.; Fedorova, E. B.; Tsyryapkin, V. A.; Bakhmutov, V. A.; Belikov, V. M. *J. Chem. Soc. Perkin Trans. 1* **1988**, 2075–2084. (c) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814–3819. For a fourth strategy involving a ring contraction of 3-mesylaxy-piperidines see: (d) Naik, R. G.; Kattige, S. L.; Bhat, S. V.; Alreja, B.; de Souza, N. J.; Rupp, R. H. *Tetrahedron* **1988**, *44*, 2081–2086.
3. (a) Herdeis, C.; Hubmann, H. P.; Lotter, H. *Tetrahedron: Asymmetry* **1994**, *5*, 351–354. (b) Herdeis, C.; Hubmann, H. P. *Tetrahedron: Asymmetry* **1992**, *3*, 1213–1221. (c) Jones, K.; Woo, K.-C. *Tetrahedron Lett.* **1991**, *32*, 6949–6952.
4. (a) Shono, T.; Terauchi, J.; Matsumura, Y. *Chem. Lett.* **1989**, 1963–1966. (b) Chastanet, J.; Roussi, G. *J. Org. Chem.* **1988**, *53*, 3808–3812.
5. Chung, J. Y. L.; Wasicak, J. T.; Arnold, W. A.; May, C. S.; Nadzan, A. M.; Holladay, M. W. *J. Org. Chem.* **1990**, *55*, 270–275.
6. Micheli, F.; DiFabio, R.; Marchioro, C. *Il Farmaco* **1999**, *54*, 461–464.
7. (a) Sabol, J. S.; Flynn, G. A.; Friedrich, D.; Huber, E. W. *Tetrahedron Lett.* **1997**, *38*, 3687–3690. (b) Waid, P. P.;

Flynn, G. A.; Huber, E. W.; Sabol, J. S. *Tetrahedron Lett.* **1996**, *37*, 4091–4094. (c) Evans, M. C.; Johnson, R. L. *Tetrahedron* **2000**, *56*, 9801–9808. (d) Tong, Y.; Fobian, Y. M.; Wu, M.; Boyd, N. D.; Moeller, K. D. *J. Org. Chem.* **2000**, *65*, 2484–2493.

8. Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151–7157.
9. (a) Nakai, T.; Setoi, H.; Kageyama, Y. *Tetrahedron Lett.* **1981**, *22*, 4097–4100. (b) White, W. N.; Fife, W. K. *J. Am. Chem. Soc.* **1961**, *109*, 3846–3853. (c) Jurd, L.; Roitman, J. N. *Tetrahedron* **1978**, *34*, 57–62. (d) Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170–1186.
10. Gatti, R. G. P.; Larsson, A. L. E.; Bäckvall, J.-E. *J. Chem. Soc. Perkin Trans. 1* **1997**, 577–584.
11. Proline methylester: (a) Montgomery, J.; Chevliakov, M. V.; Brielmann, H. L. *Tetrahedron* **1997**, *53*, 16449–16462. Proline *t*-butylester: (b) Gibson, F. S.; Bergmeier, S. C.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3216–3218. TBS-prolinol: (c) Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1995**, *117*, 891–900.
12. Alternatively, the alcohol **2a** had been activated as the corresponding chloride (Appel, R. *Angew. Chem.* **1975**, *87*, 863). However, the yield of the allylamine **4a** was found to be somewhat lower. For details and data see Section 5.
13. Winterfeldt, E. *Synthesis* **1975**, 617–630.
14. Corey, E. J.; Venkatesvarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.
15. Reviews on Claisen rearrangements: (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423–1452. (b) Frauenrath, H. In *Houben Weyl, Vol. E21d: Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, New York, 1995; pp 3301–3756. (c) Wipf, P. *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Paquette, L. A., Eds.; Pergamon: New York, 1991; Vol. 5, pp 827–873. (d) Hill, R. K. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, pp 503–572. For enantioselective Claisen rearrangements see: (e) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847–1882. Additional references: (f) Clayden, J.; Helliwell, M.; McCarthy, C.; Westlund, N. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3232–3249. (g) Lemieux, R. M.; Devine, P. N.; Mechelke, M. F.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 3585–3591. (h) Lemieux, R. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1998**, *120*, 5453–5457. (i) Roush, W. R.; Works, A. B. *Tetrahedron Lett.* **1997**, *38*, 351–354. (j) Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2911–2912. (k) Furthermore Refs. 16,18,34.
16. (a) Laabs, S.; Scherrmann, A.; Sudau, A.; Diederich, M.; Kierig, C.; Nubbemeyer, U. *Synlett* **1999**, 25–28. (b) Sudau, A.; Münch, W.; Nubbemeyer, U.; Bats, J. W. *J. Org. Chem.* **2000**, *65*, 1710–1720.
17. Preparation of the carboxylic acid fluorides: (a) Groß, S.; Laabs, S.; Scherrmann, A.; Sudau, A.; Zhang, N.; Nubbemeyer, U. *J. Prak. Chem.* **2000**, *342*, 711–714. (b) Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, 487–488. (c) Olah, G. A.; Kuhn, S.; Beke, S. *Chem. Ber.* **1956**, *89*, 862–864.
18. (a) Metz, P.; Hungerhoff, B. *J. Org. Chem.* **1997**, *62*, 4442–4448. (b) Nubbemeyer, U. *J. Org. Chem.* **1996**, *61*, 3677–3686. (c) Metz, P. *Tetrahedron* **1993**, *49*, 6367–6374. (d) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079–1085.
19. NOE analyses of both lactones gave unequivocally the anti-arrangement of chloro and aryl substituents, respectively. For details see Section 5.
20. Chiral HPLC was carried out on a chirobiotic V column 4.6×250 mm with 10% EtOH in hexane, flow 1 mL/min. For detailed data see Section 5.
21. The minor diastereomer in **9a** had been separated by means of HPLC in an analytical scale. Again, the NMR spectra of this compound were characterized by a doubled set of peaks, but the present ratio was about 10:1 preventing the determination of the minor set in the spectra of the non-separated rearrangement products **9a** (triple instead of quadruple set of peaks).
22. Chlorolactone **11a** has only been prepared in an analytical scale, any pure compound was not isolated. The stereochemical outcome of the rearrangement has been proven in the azidoseries **15a/16a**.
23. Preliminary investigations using *N*-phthaloyl glycinoyl fluoride (Refs. 15,16) gave the corresponding amides with low yields and disappointing diastereoselectivities.
24. Preparation of α-azido acetic acid: (a) Wieland, T.; Henning, H. J. *Chem. Ber.* **1960**, *93*, 1236–1246. (b) Dyke, J. M.; Gores, A. P.; Morris, A.; Odgen, J. S.; Dias, A. A. *J. Am. Chem. Soc.* **1997**, *119*, 6883–6887.
25. HPLC nucleosil 50-5, column 32×110 mm, 2% *i*-PrOH in *n*-hexane, flow 64 mL/min.
26. Synthesis of Cy_2BH:Brown, H. C.; Mandal, A. K.; Kularni, S. U. *J. Org. Chem.* **1977**, *42*, 1392–1398.
27. For an analogous cyclization see: (a) Eguchi, C.; Kakuta, A. *Bull. Chem. Soc. Jpn* **1974**, *47*, 2277–2282. (b) Young, P. E.; Madison, V.; Blount, E. R. *J. Am. Chem. Soc.* **1973**, *95*, 6143–6145.
28. NOE analyses of tricycle **20a** gave unequivocally the *syn*-arrangement of carboxyl and aryl substituent. Any safe correlation with the stereogenic center of the auxiliary failed. For details see Section 5.
29. X-Ray data of **20**: colorless, transparent block, dimensions 0.27×0.60×0.65 mm^3, crystallized from Et_2O/*n*-hexane at 20°C, $C_{17}H_{18}N_2O_4$ (M_r=314.33); crystal data: orthorhombic; $P2_12_12_1$. For further data see CCDC 163382 and Fig. 2.
30. Various amide cleavage reactions had been investigated by Myers: (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511. (b) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656–673. (c) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361–9362. Reductions: (d) Charette, A. B.; Chua, P. *Synlett* **1998**, 163–165. (e) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623–3626. (f) Brown, H. C.; Kim, S. C. *Synthesis* **1977**, 635–636.
31. Phillips, A. P.; Baltzly, R. *J. Am. Chem. Soc.* **1947**, *69*, 200–204.
32. For analytical purposes the ester **24** can be converted again into the corresponding proline amide **15a** by treatment with proline methylester.
33. As known in the literature tertiary amines and acid fluorides do not react spontaneously: (a) Granitza, D.; Beyermann, M.; Wenschuh, H.; Haber, H.; Carpino, L. A.; Truran, G. A.; Bienert, M. *J. Chem. Soc., Chem. Commun.* **1995**, 2223–2224. (b) Carpino, L. A.; Mansour, E.-S. M. E.; El-Faham, A. *J. Org. Chem.* **1993**, *58*, 4162–4164. (c) Carpino, L. A.;

Sadat-Aalaee, D.; Chao, H.-G.; DeSelms, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 9651–9652.

34. (a) Johnson, W. S.; Bauer, V. J.; Margrave, J. L.; Frisch, M. A.; Dreger, L. H.; Hubbard, W. N. *J. Am. Chem. Soc.* **1961**, *83*, 606–614. (b) Vittorelli, P.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1975**, *58*, 1293–1309. (c) Vance, R. L.; Rondan, N. G.; Houk, K. N.; Jensen, F.; Borden, W. T.; Komornicki, A.; Wimmer, E. *J. Am. Chem. Soc.* **1988**, *110*, 2314–2315. (d) Büchi, G.; Powell, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 3126–3133. (e) Abelmann, M. M.; Funk, R. F.; Munger, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 4030–4032.
35. (a) Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129. (b) Richter, W.; Sucrow, W. *Chem. Ber.* **1971**, *104*, 3679–3682.
36. As an alternative, the use of *C*2-symmetric pyrrolidine derivatives should generate the corresponding amides with high auxiliary controlled chiral induction: He, S.; Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 190–191.
37. Nubbemeyer, U. *Synthesis* **1993**, 1120–1128.