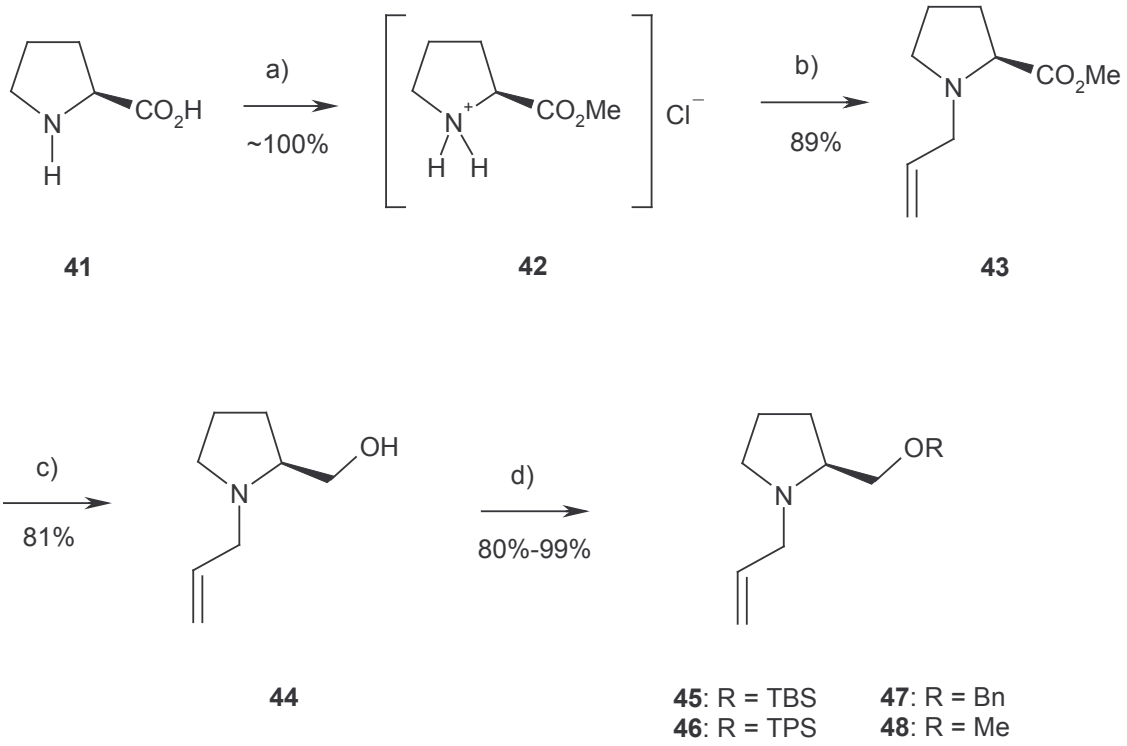
2 Results and Discussion

2.1 Syntheses of *N*-Allylpyrrolidines

N-allylpyrrolidines are important reactants, which are used for the construction of *N*-substituted or *N*-protected *C*-allylglycyl amides by an auxiliary-controlled zwitterionic aza-Claisen rearrangement. Especially, the optical activity of the allylglycine has been introduced by means of a chiral auxiliary, such as (*S*)-proline **41** and (2*S*,4*R*)-4-hydroxyproline **51** and their derivatives, respectively. The following four schemes represent the synthesis of some *N*-allylpyrrolidines to be used as precursors for the aza-Claisen rearrangement.

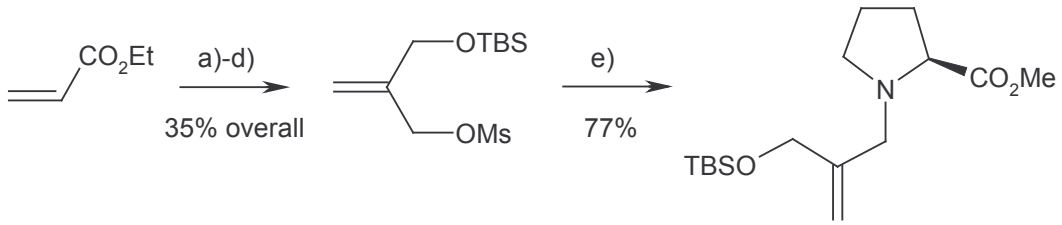


Scheme 15: Synthesis of optical active *N*-allylpyrrolidines

Reagents and Conditions: a) $SOCl_2$, MeOH, rfl., 3h., ~100%; b) allyl bromide, K_2CO_3, DMF, r.t., 16h., 89%; c) DIBAL-H, THF, 0°C, 3h., 81%; d) TBSCl, imid., DMAP (cat.), THF, r.t., 3h., 98% (**45**); or TPSCl, imid., DMAP (cat.), THF, r.t., 3h., 99% (**46**); or NaH, THF, then BnBr, 0°C to r.t., 20h., 84% (**47**); or NaH, THF, then MeI, 0°C to r.t., 20 h., 80% (**48**)

The starting material (*S*)-proline **41** was esterified[1] quantitatively to give proline methyl ester hydrochloride **42**, which was then treated with allyl bromide in dimethyl formamide in the presence of a base[2] to obtain *N*-allylproline methyl ester **43**. The yield was 89% after a kugelrohr distillation, but only 45% after column chromatography (n-hexane / ethyl acetate / triethylamine = 66 : 33 : 1). The ester **43** was reduced with DIBAL-H[3] to form the *N*-allylprolinol **44**.[4] The protection of the alcohol as silyl ether **45** and **46**[5], as a benzyl ether **47**[6] and as a methyl ether **48** was performed using standard reaction conditions (Scheme 15).

The preparation of *N*-allylpyrrolidine **50** (Scheme 16) started with a Baylis-Hillman reaction[7] of ethyl acrylate to furnish ethyl α-(hydroxymethyl) acrylate. Subsequent silylation[38], ester reduction with DIBAL-H[36,8] and sulfonation of the OH-group with methanesulfonyl chloride generated the TBS ether **49**. A final allylation of proline methyl ester hydrochloride **42** in the presence of triethyl amine afforded *N*-allylpyrrolidines **50**.

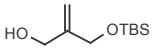


49 **50**

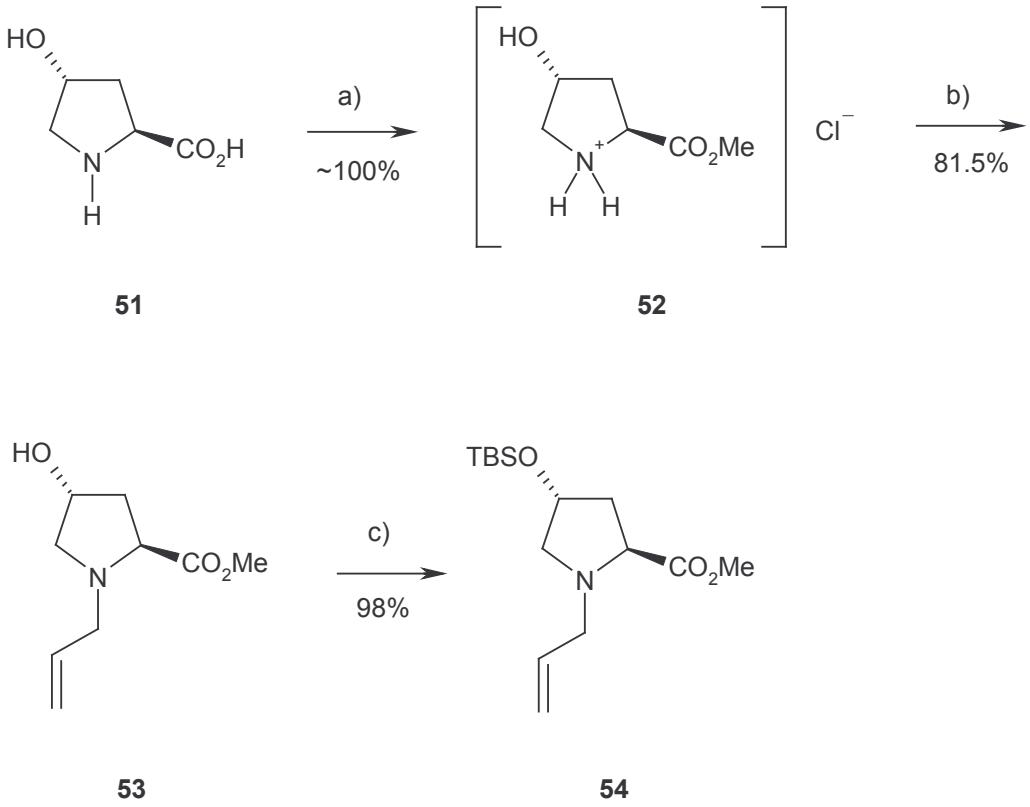
Scheme 16: Synthesis of *N*-allylpyrrolidines **50**

Reagents and Conditions: a) HCHO, DABCO, THF/H_2O (1:1), r.t., 20h., 60%; b) TBSCl, imid., DMAP (cat.), THF, r.t., 3h., 98%; c) DIBAL-H, THF, 0°C, 3h., 85%; d) MsCl, Et_3N, THF, 0°C, 3h., 71%; e) **42**, Et_3N, DMF, 0°C to r.t., 16h., 77%.

[1] Tietze, L.F.; Eicher, T. *Reaktionen and Synthesen im Organisch-Chemischen Praktikum*, 2nd ed.; Thieme: Stuttgart, **1991**, p. 135.
[2] Monlander, G.A.; McKie, J.A. *J. Org .Chem.* **1993**, *58*, 7216.
[3] Winterfeldt, E. *Synthesis* **1975**, 617.
[4] (a) Aurich, H.G.; Frenzen, G.; Gentes, C. *Chem. Ber*. **1993**, *126*, 787. (b) Sandrine, L.-A.; Savignac, M.; Dupuis, C.; Genet, J.P. *Bull. Soc. Chim. Fr.* **1995**, *132*, 1157.
[5] Corey, E.J.; Venkatesvarlu, A. *J. Am. Chem. Soc*. **1972**, *94*, 6190.
[6] Taniguchi, T.; Ogasarawa, K. *Tetrahedron Lett.* **1998**, *39*, 4679.
[7] Reviews on Baylis-Hillman reaction, see: Byun, H.-S.; Reddy, K.C.; Bittman, R. *Tetranhedron Lett*. **1994**, *35*, 1371.

[8] For the molecule 

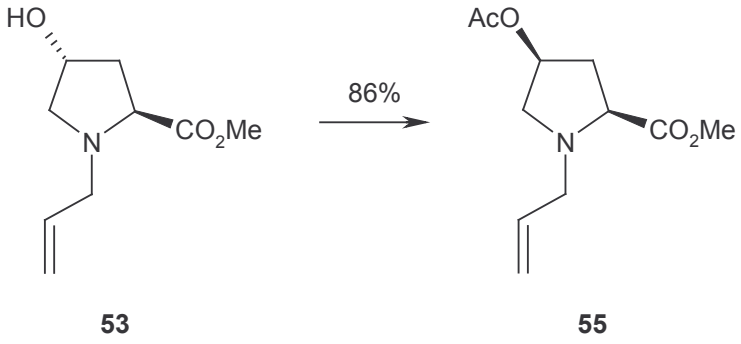
see: (a) Danishefsky, S.J.; Mantlo, N. *J. Am. Chem. Soc*. **1988**, *110*, 8129. (b) Nave, J-F.; Casara, P.J.; Taylor, D.L.; Tyms, A.S.; Kenny, M.; Halazy, S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 179.



Scheme 17: Synthesis of optical active *N*-allyl-4-silyloxypyrrolidine **54**

Reagents and Conditions: a) $SOCl_2$, MeOH, rfl., 3h., ~100%; b) allyl bromide, Et_3N, CH_2Cl_2, r.t. 16h., 81.5%; c) TBSCl, imid., DMAP (cat.), THF, 3h., r.t., 98%.

Allylamine **54** was generated via a three-step sequence starting from (2*S*,4*R*)-4-hydroxyproline **51**. After esterification,[34] the allyl group was introduced by treatment with allyl bromide in the presence of triethyl amine in dry dichloromethane. The alcohol was finally protected as a TBS ether by using standard silylation conditions[38] (Scheme 17).



Scheme 18: Synthesis of *cis*- *N*-allyl-4-acetoxypyrrolidine **55**

Reagents and Conditions: AcOH, DEAD, PPh_3, Et_2O, 0°C to 20°C, 20h., 86%.

Alternatively, the secondary alcohol at C-4 of **53** was cleanly inverted by means of a Mitsunobu reaction[9] (Scheme 18). Treatment of a solution of compound **53** in dry diethyl ether with triphenyl phosphine, diethyl azodicarboxylate (DEAD) and anhydrous acetic acid formed the inverted C-4 acetic acid ester **55**. The relative configuration was proven by NOE analysis (Figure 2.1).

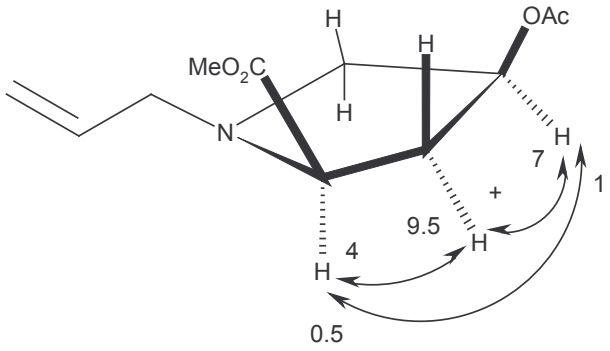


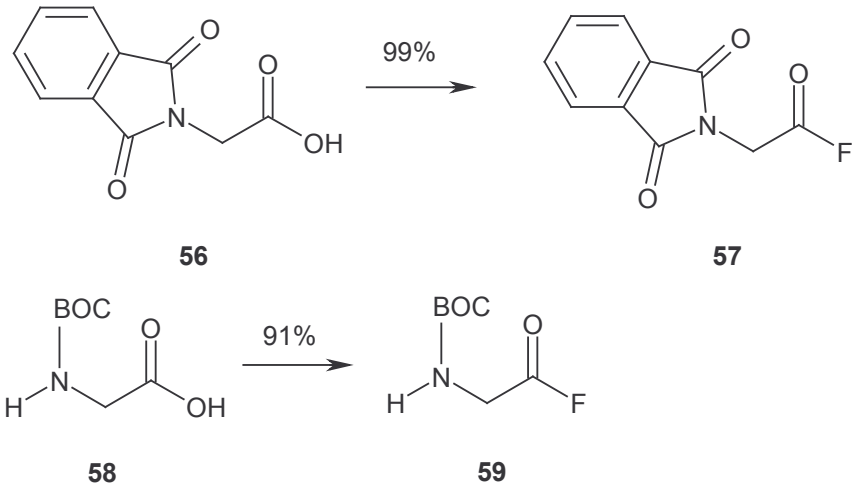
Figure 2.1: NOE data for **55**

[9] (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Barrett, Pilipauskas, *J. Org. Chem*. **1991**, *56*, 2787.

2.2 Syntheses of Carboxylic Acid Fluorides

The carboxylic acid fluorides represented the second key reactants for the zwitterionic aza-Claisen rearrangements. They could be prepared from carboxylic acids and cyanuric fluoride in the presence of pyridine by using standard reactions conditions.[10] Generally, the carboxylic acid fluorides prepared were used as crude compounds, no extensive purification was necessary to obtain satisfactory reactive material.

N-Phthaloylglycinyl fluoride **57** and *N*-Boc-glycinyl fluoride **59** were prepared from *N*-Phthaloylglycine **56** and *N*-Boc-glycine **58** with high yield following Carpino's procedure[43(b)] (Scheme 19). Instead of employing an excess of 3 equivalents of cyanuric fluoride and pyridine, we found that only 0.6 equivalents enabled to achieve best results and less waste.



56 **57**

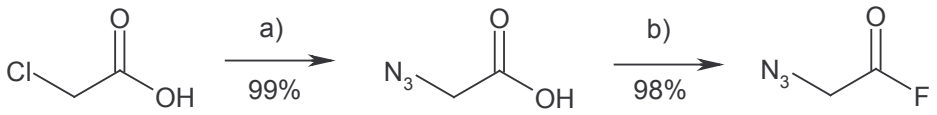
58 **59**

Scheme 19: Syntheses of carboxylic acid fluorides **57** and **59**

Reagents and Conditions: 0.6 eq. cyanuric fluoride, pyridine, dry CH_2Cl_2, 0°C, 1.5 h.

Azidoacetic acid **61**[11] was formed with a yield of 99% upon heating a solution of chloroacetic acid **60** and 3.3 M sodium hydroxide to 60°C for 3 days. Azidoacetic acid **61** might be explosive when raising the temperature to about 90°C. Azidoacetyl fluoride **62** was obtained as a yellow oil under standard reactions conditions (Scheme 20). Because of its instability, it was immediately used in the next step.

[10] (a) Groß, S.; Laabs, S.; Scherrmann, A.; Sudau, A.; Zhang, N.; Nubbemeyer, U. *J. Prak. Chem*. **2000**, *342*, 711. (b) Carpino, L.A.; Mansour, E.-S.M.E.; Sadat-Alaee, D. *J. Org. Chem*. **1991**, *56*, 2611.
[11] Dyke, J.M.; Gores, A.P.; Morris, A.; Odgen, J.S.; Dias, A.A. *J. Am. Chem. Soc.* **1997**,*119*, 6883

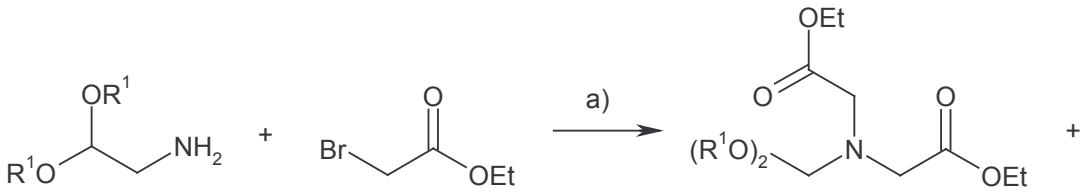


60 **61** **62**

Scheme 18: Synthesis of azidoacetyl fluoride **62**

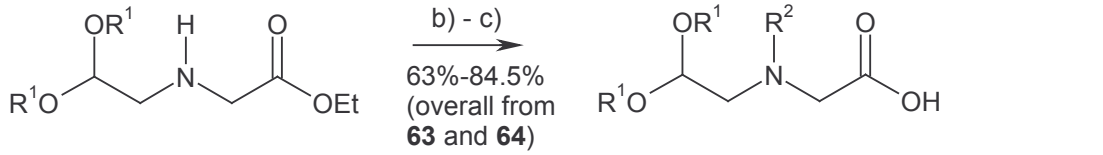
Reagents and Conditions: a) 3.3 M NaOH, NaN_3, 60°C, 3 days, then 2 M H_2SO_4, 99%; b) 0.6 eq. cyanuric fluoride, pyridine, CH_2Cl_2, 0°C, 1.5 h, 98%.

The *N*-functionalized glycinyl fluorides **72-75** were generated via a four-step sequence (Scheme 21). Treatment of 2-aminoacetaldehyde diethylacetal **63** (R^1 = Et) and 2-amino-acetaldehyde dimethylacetal **64** (R^1 = Me) with ethyl bromoacetate **65** provided the mono-



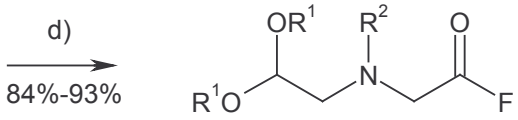
63: R^1 = Et
64: R^1 = Me

65 **66**



67

68: R^1 = Et, R^2 = BOC **70**: R^1 = Me, R^2 = BOC
69: R^1 = Et, R^2 = Cbz **71**: R^1 = Et, R^2 = Bn

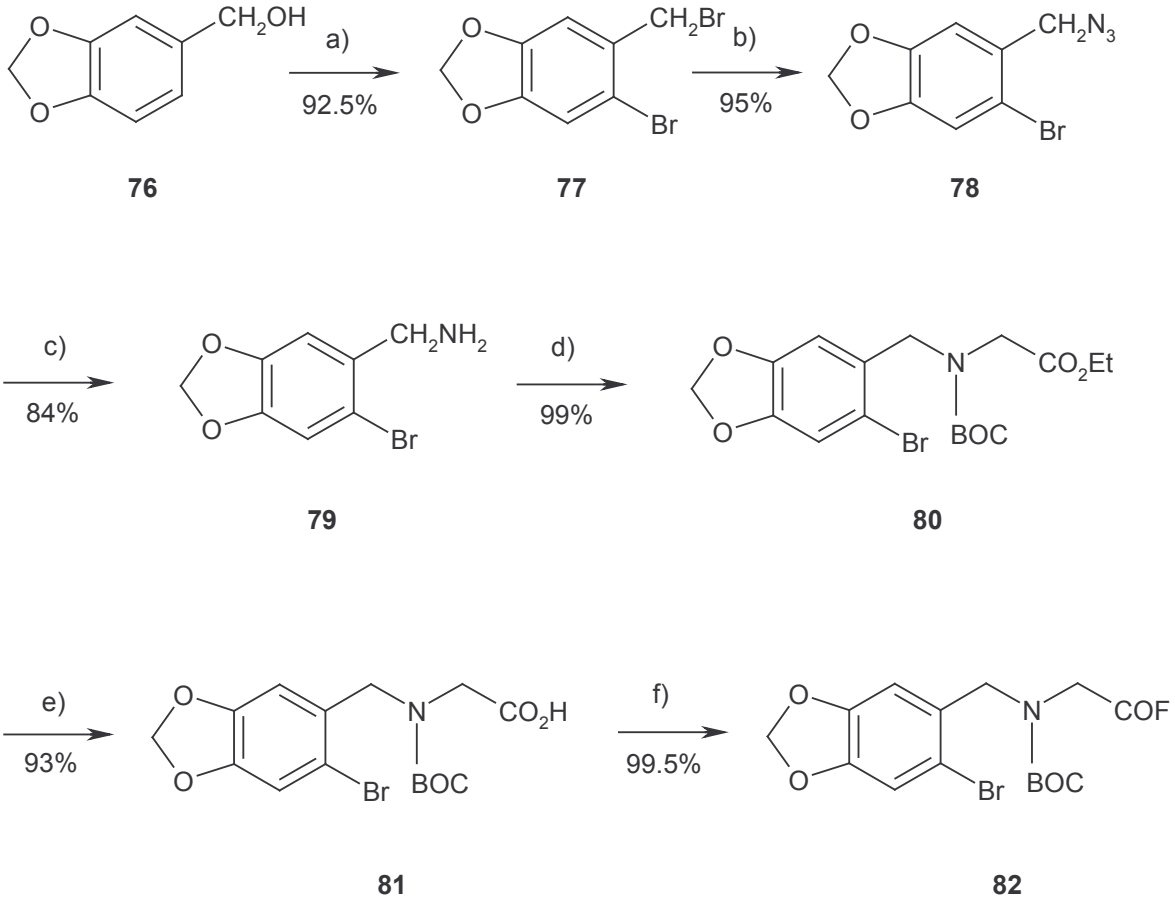


72: R^1 = Et, R^2 = BOC **74**: R^1 = Me, R^2 = BOC
73: R^1 = Et, R^2 = Cbz **75**: R^1 = Et, R^2 = Bn

Scheme 21: Synthesis of *N*-protected glycinyl fluorides

Reagents and Conditions: a) Et_3N, Et_2O, 0°C, 24 h. ; b) Boc_2O or CbzCl or BnCl; c) 1 M NaOH, LiCl, 80°C, then aq. $KHSO_4$, 84.5% (**68**); 63% (**69**); 66% (**70**); 65% (**71**); d) 0.6 eq. cyanuric fluoride, pyridine, dry CH_2Cl_2, 0°C, 1.5 h., 93% (**72**); 89% (**73**); 94.5% (**74**); 84% (**75**).

substituted 2-amino ester **67**[12] as the major product and double substituted 2-amino diester **66** as the minor product. After protection of the secondary amine **67** as a *tert*-butylcarbamate, benzylcarbamate and benzylamine,[13] respectively, the ester was cleaved with aqueous sodium hydroxide and lithium chloride to generate the carboxylic acids **68**, **69**, **70** and **71** with high yields. It is worth to be noted that the cleavage of the ester group with sodium hydroxide only would have taken a long time resulting poor yields. Finally, the activation was carried out with cyanuric fluoride and pyridine in dichloromethane at 0°C to synthesize the acyl fluorides.

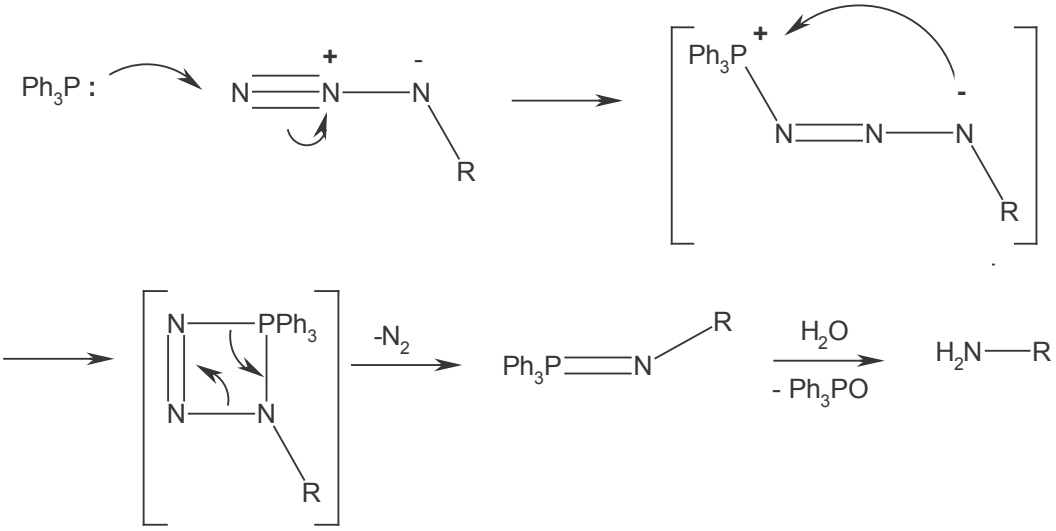


Scheme 22: Synthesis of bromopiperonyl acetyl fluoride **82**

Reagents and Conditions: a) Br_2, AcOH, 0°C, 1 h., 92.5%; b) NaN_3, NaI (cat.), acetone, 20°C, 18 h., 95%; c) PPh_3, THF-H_2O (20:1), 20°C, 4 d., 84%; d) ethyl bromoacetate, Et_3N, Et_2O, 0°C, 16 h., then Boc_2O, 99%; e) 1 M NaOH, LiCl, 80°C, 3 h., then $KHSO_4$, 93%; f) 0.6 eq. cyanuric fluoride, pyridine, 0°C, 1.5 h., 99.5%.

[12] (a) Loeppky, R.N.; Xiong, H. *J. Labelled Compd. Radiopharm*. **1994**, *34*, 1099. (b) Elsworth, J.F.; Msimang, L.N.; Jackson, G.E.S. *Afr. J. Chem*. **1996**, *49*, 35.
[13] Valls, N.; Segarra, V.M.; Maillo, L.C.; Bosch, J. *Tetrahedron* **1991**, *47*, 1065.

Preparation of bromopiperonyl-α-aminoacetyl fluoride **82** commenced with the treatment of piperonyl alcohol **76** with bromine in anhydrous acetic acid at 0°C [14] (Scheme 22). A Finkelstein-type reaction enabled to convert benzyl bromide into benzyl azide **78**; treatment of bromopiperonyl bromide **77** with sodium azide and a catalytic amount of sodium iodide in anhydrous acetone furnished bromopiperonyl azide **78**. Then, a Staudinger reaction[15] (for the mechanism see Scheme 23) completed the synthesis of bromopiperonyl amine **79**. Subjection of **78** to triphenylphosphine in THF-H_2O (20:1) gave amine **79**. The reaction sequence **79** to **82** was similar to that outlined above in Scheme 21. Gratifyingly, no corresponding diester could be detected.



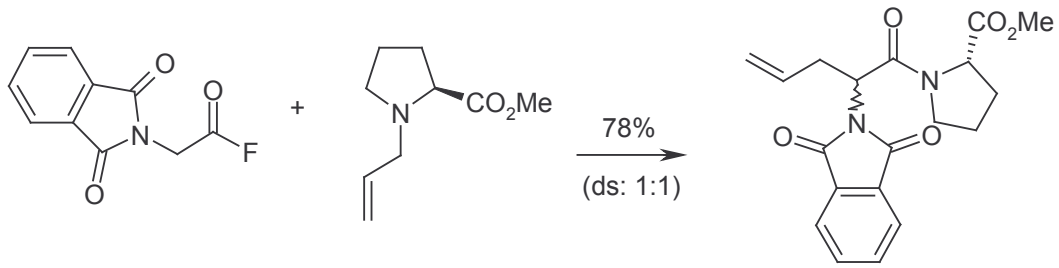
Scheme 23: Mechanism of Staudinger reaction: the four membered ring is the key intermediate

A subsequent carbamate protection of the nitrogen and a final hydrolysis afforded the primary amine, which was then converted into the fluoride as described above.

[14] Padwa, A.; Cochran, J.E.; Kappe, O. *J. Org. Chem.* **1996**, *61*, 3706-3714.
[15] Staudinger, H.; Meyer, J. *Helv. Chim. Acta*. **1919**, *2*, 635-646.

2.3 Zwitterionic Aza-Claisen Rearrangement and Evidence of the Absolute Configuration

The first series of zwitterionic aza-Claisen rearrangement was run with *N*-allylproline methyl ester **43** as the chiral C-3 fragment.[16] The allylamine **43** was treated with freshly prepared phthaloylglycyl fluoride **57**. In the presence of Me_3Al in a suspension of K_2CO_3 in anhydrous CH_2Cl_2 at 0°C, the α-*N*-phthalimidopent-4-enoic acid amides **83** and **84** were obtained in 78% yield (Scheme 22). As known in the literature tertiary amines and acid fluorides do not react spontaneously[17], therefore the trimethyl aluminium was used to activate the acid fluorides and to start the reaction. The determination of the diastereoselectivity of the present reactions turned out to be difficult. The ^{1}H-NMR as well as ^{13}C-NMR spectra were always characterized by a double set of peaks caused by the non-symmetric amide subunit. The partial double bound between carboxyl C and N effected the coexistence of an *E*- and a *Z*-form with diastereomeric properties. These two conformers were found in varying concentrations depending on the configurations of the stereogenic centers and the substitution pattern of the molecules. In our hands coalescence could not be achieved even by heating to about 120°C. In the case of the *N*-phthalimido amides **83**/**84** the NMR spectra proved the unselective generation of the material: three or four sets of peaks indicated the coexistence of two diastereomers **83** and **84** (each adopting two conformers), which could be separated by means of column chromatography.



57 **43** **83**, **84**

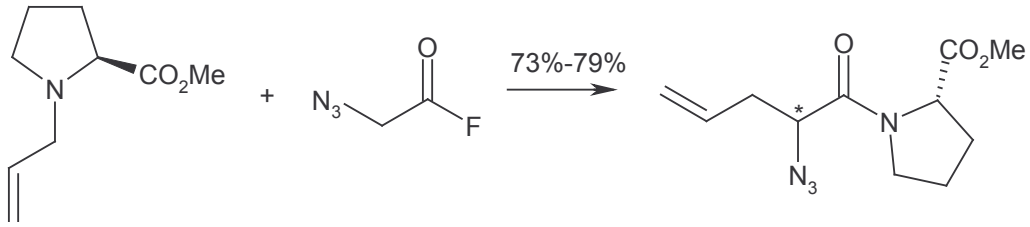
Scheme 24: Synthesis of α-*N*-phthalimidopent-4-enoic acid amides **83** and **84**

Reagents and Conditions: K_2CO_3, $AlMe_3$, CH_2Cl_2, 0°C, 16 h. 78%

[16] (a) Laabs, S.; Scherrmann, A.; Sudau, A.; Diederich, M.; Kierig, C.; Nubbemeyer, U. *Synlett* **1999**, 25. (b) Sudau, A.; Muench, W.; Bats, J.W.; Nubbemeyer, U. *J. Org. Chem*. **2000**, *65*, 1710.

[17] (a) Granitza, D.; Beyermann, M.; Wenschuh, H.; Haber, H.; Carpino, L.A.; Truran, G.A.; Bienert, M. *J.Chem. Soc., Chem. Commun*. **1995**, 2223. (b) Carpino, L.A.; Mansour, E.-S.M.E.; ElFaham, A. *J. Org. Chem*. **1993**, *58*, 4162. (c) Carpino, L.A.; Sadat-Aalace, D.; Chao, H.G.; DeSelms, R.H. *J. Am. Chem. Soc*. **1990**, *112*, 9651.

Because of the disappointing stereoselectivity of α-*N*-phthalimidopent-4-enoic acid amides **83** and **84**, azidoacetyl fluoride **62** was chosen for the rearrangement (Scheme 25).



43 **62** **85**, **86**

Scheme 25: Synthesis of α-azidopent-4-enoic acid amides **85** and **86**

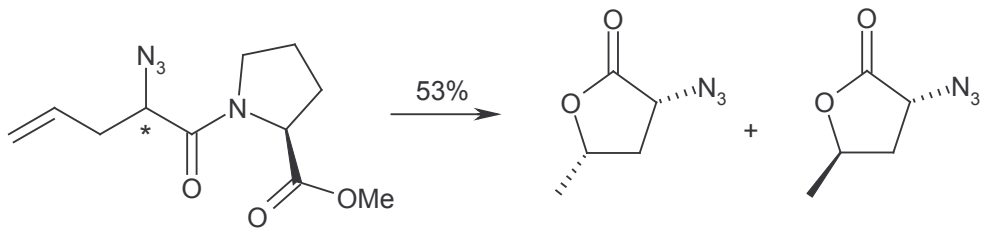
Reagents and Conditions: K_2CO_3, $AlMe_3$, CH_2Cl_2, 3 h. (a) 20°C, 73% (b) 0°C, 77% (c) –20°C, 79%

The reaction was run at different temperatures, 20°C, 0°C and –20°C resulting good yields. Upon isolating **85**/**86**, as expected, the rearrangement with azidoacetyl fluoride **62** and allylamine **43** proceeded in the desired direction to give a higher stereoselectivity (detail see page 29-32). The two diastereomers **85**/**86** were difficult to separate via column chromatography, the structure had to be proven by means of other methods.

First of all, the auxiliary of the α-azidoamides **85**/**86** was removed, and the α-azidoamides were transformed into ester and acids. The data of the so obtained *C*-allylglycine and its derivatives should be compared to literature data to prove the absolute configuration.

The first attempt removed the auxiliary under hash acidic conditions. The α-azidoamides **85**/**86** were heated in 6 N HCl to give a mixture of *cis*-α-azidolactones **87** and *trans*-α-azidolactones **88**[18] in 53% yield (Scheme 26), the ratio was about 1:1.

[18] (a) Ariza, J.; Font, J.; Ortuno, R.M. *Tetrahedron* **1990**, *46*, 1931-1942 (b) White, J.D.; Badger, R.A.; Kezar, H.S.I.I.I.; Pallenberg, A.J.; Schiehser, G.A. *Tetrahedron* **1989**, *45*, 6631 (c) Kraatz, U.; Hasenbrink, W.; Wamhoff, H.; Korte, F. *Chem. Ber*. **1971**, *104*, 2458.



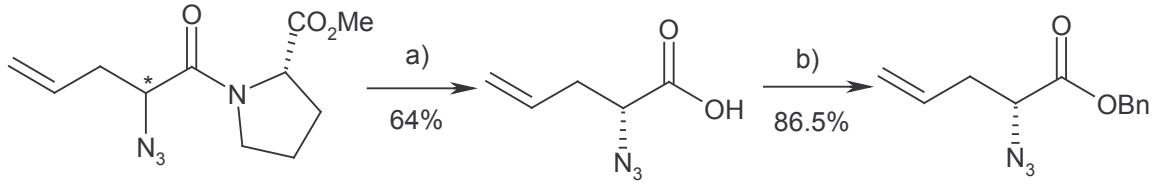
85, **86** **87** **88**

Scheme 26: Lactonization of α-azidoamides **87**/**88**

Reagents and Conditions: 6 N HCl, 80°C, 20 h. 26% of **87**, 27% of **88**

Obviously, the cleavage of the auxiliary was accompanied by the electrophilic regioselective addition of the carboxylic acid function to the double bond, the diastereoselectivity of this final step was low. The comparison of the spectral data and the specific optical rotation (literature value: $[\alpha]_D^{20}$ +221.0°, c = 3.48 in $CHCl_3$; value of **88**: $[\alpha]_D^{20}$ +192.7°, c = 0.5 in $CHCl_3$) of the *trans*-lactone **88** with that published in the literature[17(a)] undoubtedly proved the *R*-configuration of the predominant by formed allylglycine function during the course of the rearrangement.

Because there was no exact ratio of the diastereomers **85**/**86** determined after the first reaction, the next attempt to remove the auxiliary was run under mild conditions. The α-azidoamides **85**/**86** were heated with 2 M H_2SO_4 to give α-azido pent-4-enoic acid **89** in 64% yield (Scheme 27). The consecutive direct reduction of the azide to the amine with PPh_3 was



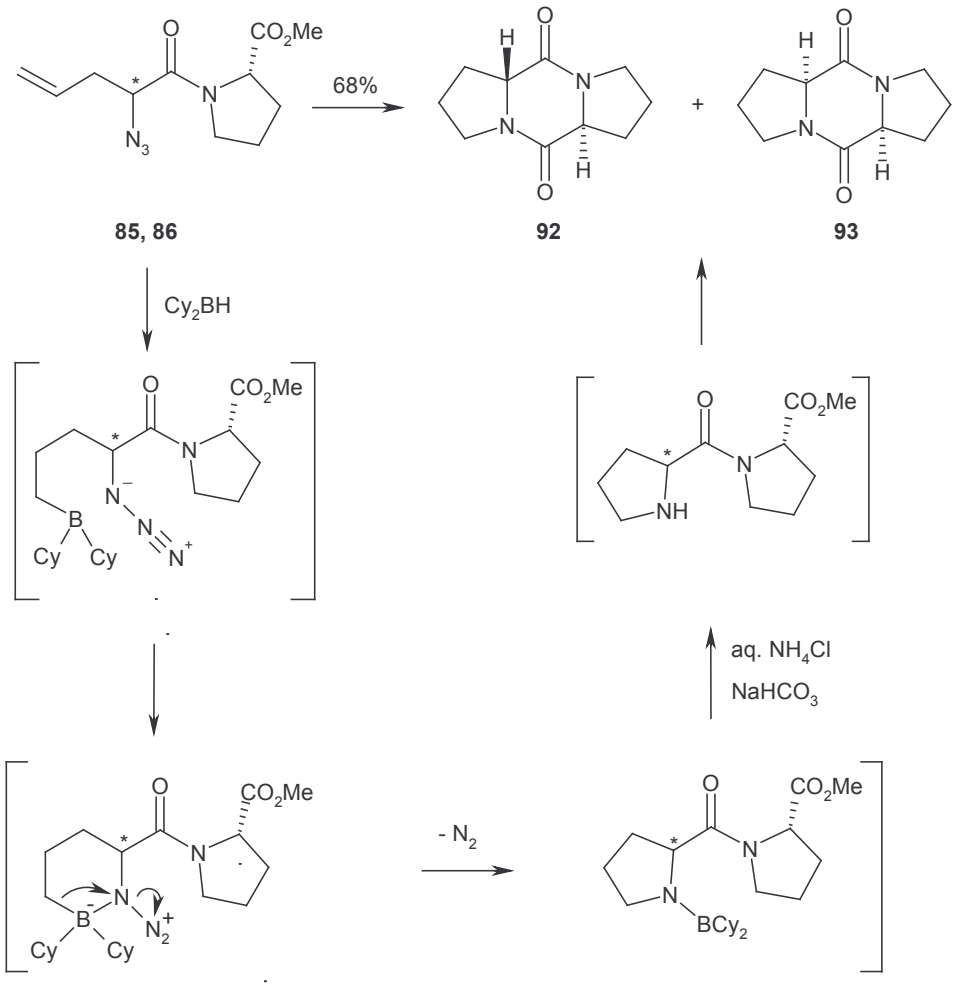
85, **86** **89** **90**

Scheme 27: Synthesis of α-azido pent-4-enoic acid derivative

Reagents and Conditions: a) 2 M H_2SO_4, 80°C, 20 h., 64% b) *N,N'*-diisopropyl-*O*-benzylisourea **91**, THF, 3 days, 86.5%

not successful. Therefore the benzylester **90** was introduced with *N*,*N*'-diisopropyl-*O*-benzylisourea **91** with 86.5% yield.[19] Again, the reduction of the azide to the amine with PPh_3 failed, and disappointingly, no literature data concerning the α-azido pent-4-enoic acid benzyl ester **90** could be found.

Another approach to check the stereochemical outcome of the azidoacetyl fluoride **61** rearrangement turned to be successful. The mixture of diastereomers **85**/**86** was subjected to the reductive alkylation conditions developed by Evans and Sabol.[20] The unsaturated amides were treated with freshly prepared dicyclohexylborane to achieve a smooth hydroboration of the olefin as the initial step (Scheme 28). The so formed trialkylborane underwent an



Scheme 28: Synthesis of piperazinediones **92** and **93**

Reagents and Conditions: dicyclohexylborane, CH_2Cl_2, NH_4Cl, $NaHCO_3$, 68%

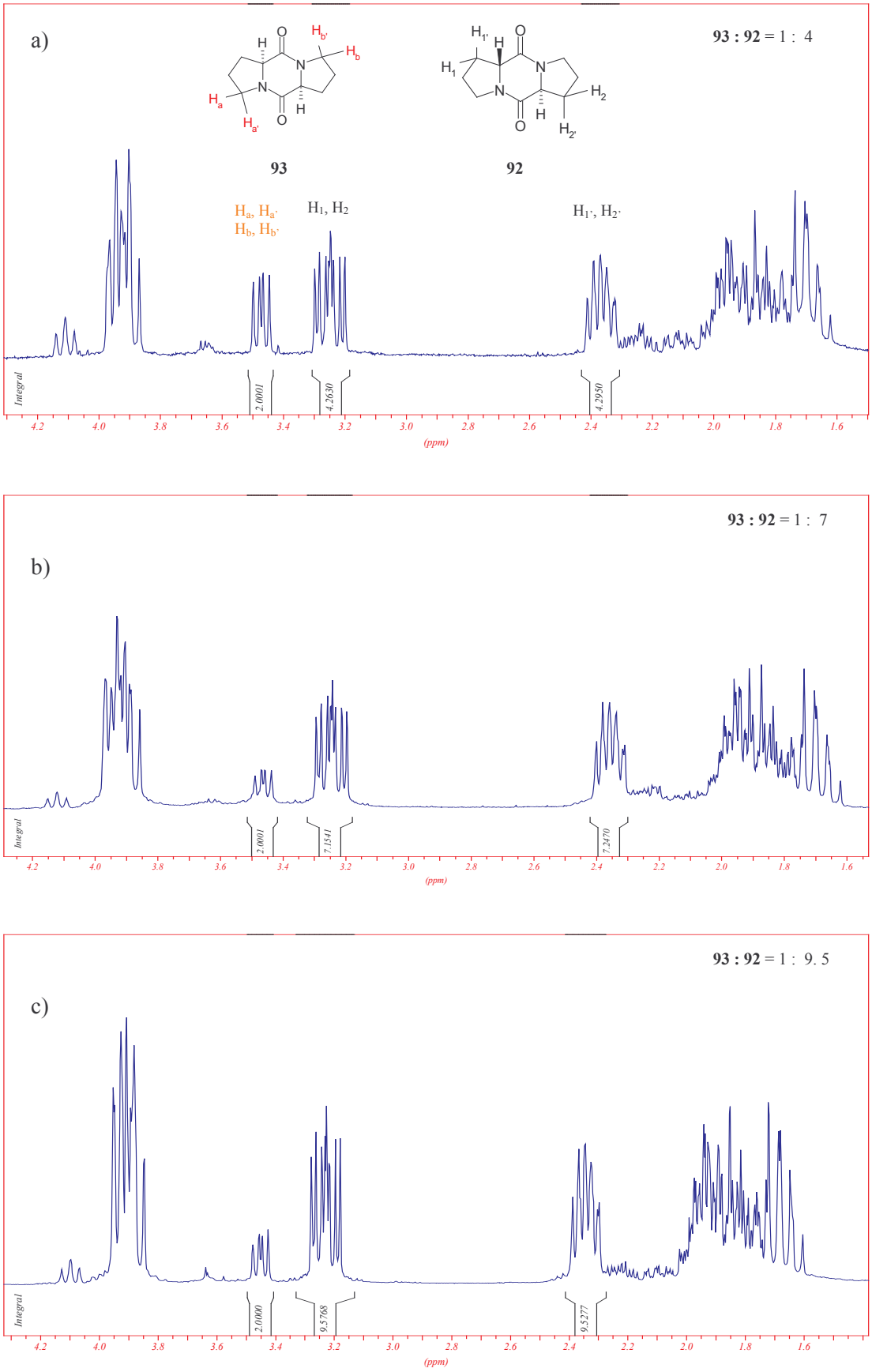
[19] Mathias, L.J. *Synthesis* **1979**, 561

[20] (a) Evans, D.A.; Weber, A.E. *J. Am. Chem. Soc*. **1987**, *109*, 7151 (b) Sabol, J.S.; Flynn, G.A.; Friedrich, D.; Huber, E.W. *Tetrahedron Lett*. **1997**, *38*, 3687 (c) Waid, P.P.; Flynn, G.A.; Huber, E.W.; Sabol, J.S. *Tetrahedron Lett*. **1996**, *37*, 4091

immediate cyclization with the nucleophilic center of the azide. After elimination of N_2 and ring contraction a new proline unit was formed, which underwent a final intramolecular amination of the auxiliary ester function to build up the tricyclic piperazinediones **92** and **93** in about 68% yield.[21] The ^{1}H-NMR spectra and the specific rotation of the two diastereomers **92**/**93** were compared with that published in the literature[54(c), (d)]. It could be proven that the mixture of tricyclic products contained one major meso species **92** originating from the (*R*)-allylglycine subunit in amide **85** and the minor C-2 symmetric diastereomer **91** originating from the (*S*)-configured diastereomer **86**.

The hydroboration of the amide **85**/**86** could also prove that the temperature of the rearrangement influenced the stereoselectivity. Running the rearrangement at 20°C, a 4:1 mixture of two diastereomers **92**/**93** was obtained. Decreasing the temperature to about 0°C, the ratio increased to 7:1, at –20°C the ratio of tricyclic piperazinediones **92**/**93** increased again to about 9.5:1 (Scheme 29). The chemical shifts of the four protons of the two methylene groups adjacent to the two nitrogens of the (*S*,*S*)-tricyclic piperazinedione **93**, occurred at about 3.4 ppm. The chemical shifts of the corresponding protons of the two methylene units adjacent to the two stereogenic center of the (*R*,*S*)-tricyclic piperazinediones **92** were found at about 2.3 ppm, the other two protons were identified at about 3.1-3.2 ppm. The ratio of the two compounds **92**/**93** could be clearly determined integrating the peaks of the four protons of the compound **91** and comparing the value to that obtained from the compound **90**. The calculated specific rotation of the compound **91** ($[\alpha]_D^{20}$ -144.4°, c = 0.2 in H_2O) was consistent with the value of the literature[54(c)] ($[\alpha]_D^{36}$ -149.5°, c = 1 in H_2O; the specific rotation of the compound **90**: $[\alpha]_D^{36}$ 0, c = 1 in H_2). The spectra are outlined in Scheme 29.

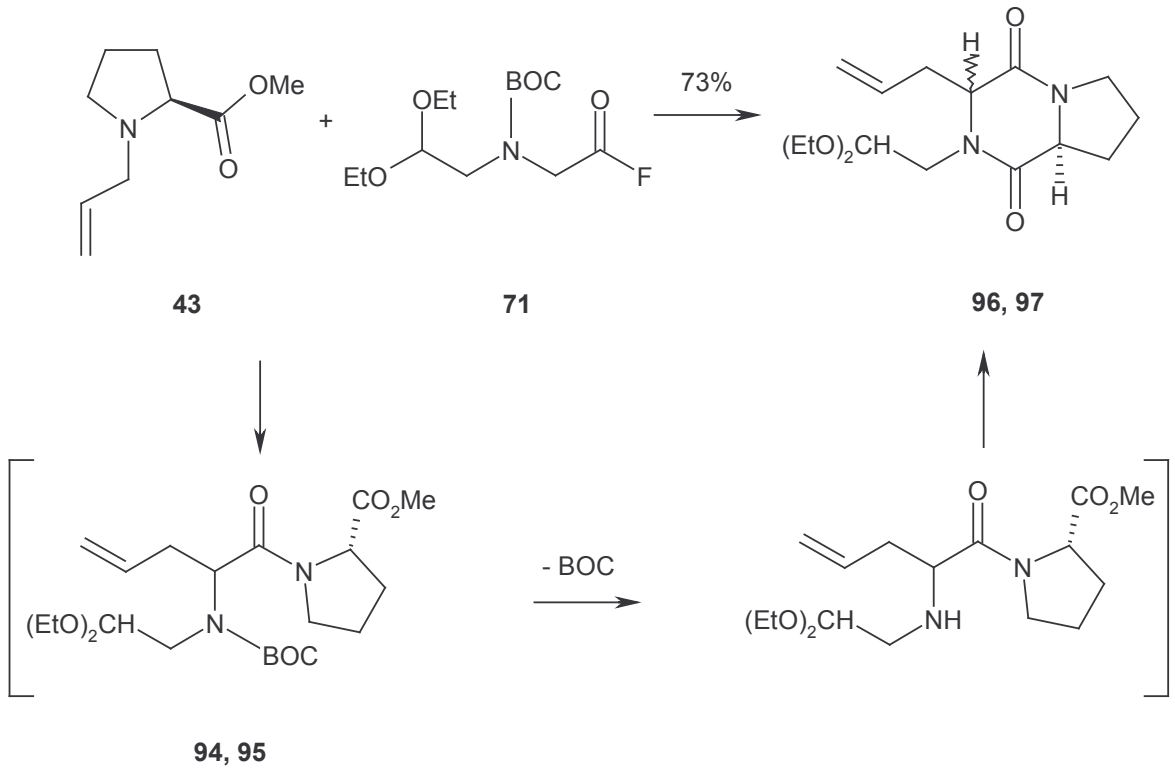
[21] (a) Ueda, T.; Saito, M.; Kato, T.; Izumiya, N. *Bull. Chem. Soc. Jpn*. **1983**, *56*, 568 (b) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem*. **1996**, *61*, 4196 (c) Eguchi, C.; Kakuta, A. *Bull. Chem. Soc. Jpn*. **1974**, *47*, 2277 (d) Young, P.E.; Madison, V.; Blout, E.R. *J. Am. Chem. Soc*. **1973**, *95*, 6142



Scheme 29: ^{1}H-NMR spectra of the tricyclic piperazinediones **92**/**93**
temperature of the aza-Claisen rearrangement of **85**/**86** a) 20°C b) 0°C c) –20°C

In the next series, sterically more encumbered glycine fluorides were tested. Disappointingly, the rearrangement with the *N*-benzylglylcinyl fluoride **74** gave no corresponding α-aminopentenoic acid amides. Some degradation product could be isolated.

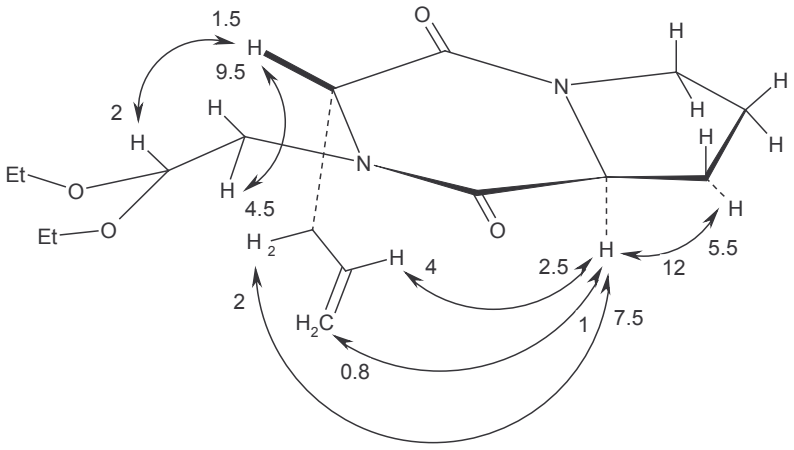
The most bulky glycinyl fluoride derivate bearing an acceptor protected nitrogen center was found to react highly diastereoselective. The rearrangement was run with *N*-Boc-glycinyl fluoride derivative **71** and allylamine **43** in the presence of $AlMe_3$ in a suspension of K_2CO_3 in anhydrous CH_2Cl_2 at 0°C (Scheme 30). The *N*-Boc amides **94**/**95** were found to be



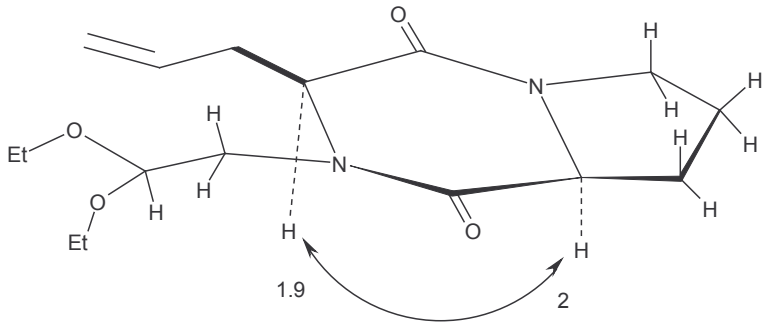
Scheme 30: Synthesis of the bicyclic piperazinediones **96**/**97**

Reagents and Conditions: K_2CO_3, $AlMe_3$, CH_2Cl_2, 0°C, 16 h. 73%

unstable under the workup conditions. The *N*-Boc group was completely removed passing the reaction mixture through a short silica gel column. The in situ formed secondary amine underwent immediate cyclization with the methyl ester of the auxiliary group generating the bicyclic piperazinediones **96** and **97** in 73% overall yields, the ratio of the diastereomers **96**/**97** was determined to be about 15:1 according to HPLC and NMR-analyses. The NOE analysis of the major product **96** proved undoubtedly the *R*-configuration of the new stereogenic center in the allylglycine subunit while the minor compound **97** was shown to be *S*-configured (Figure 2.2).



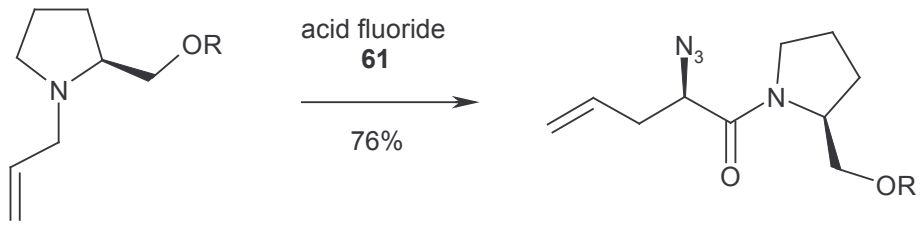
major compound **96**



minor compound **97**

Figure 2.2: NOE data and structure determination of the bicyclic compounds **96** and **97**

Aspiring more selective rearrangements and milder cleavage conditions we investigated the *N*-allylprolinol reactants **45** and **46**. The treatment of **45** and **46** with azidoacetyl fluoride **61** under standard conditions led to the formation of the α-azidoamides **98** and **99** with 76% yield as single diastereomers (according NMR) (Scheme 31).



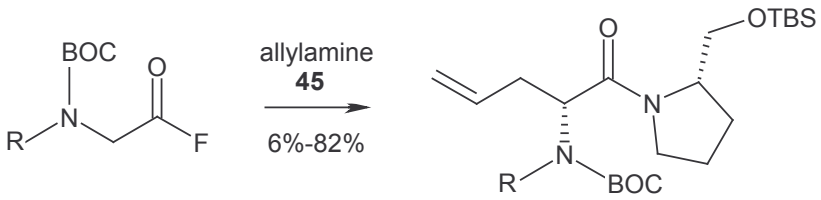
45: R = TBS
46: R = TPS

98: R = TBS
99: R = TPS

Scheme 31: Synthesis of the α-azidoamides **98** and **99**

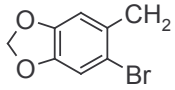
Reagents and Conditions: K_2CO_3, $AlMe_3$, CH_2Cl_2, 0°C, 3 h. **98** 76%; **99** 76%.

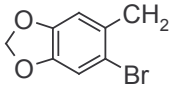
As expected, the reaction of the *N*-Boc protected glycine derivatives **71**, **73** and **81** gave the α-aminopent-4-enoic acid amides **101**, **102** and **103** with high yields as single diastereomers (Scheme 18), but the Boc-group was found again to be unstable and the silyl ether of the



58: R = H
71: R = $(EtO)_2CHCH_2$
73: R = $(MeO)_2CHCH_2$

100: R = H
101: R = $(EtO)_2CHCH_2$
102: R = $(MeO)_2CHCH_2$

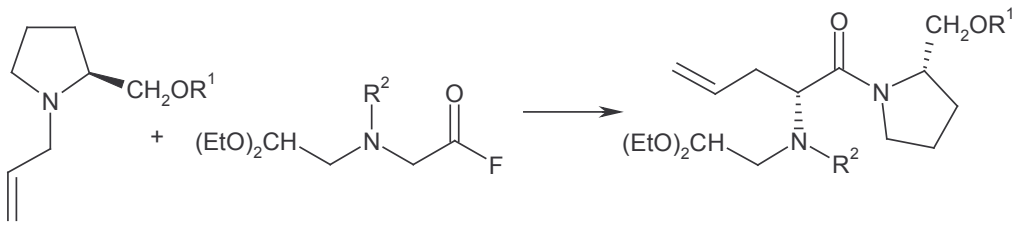
81: R = 

103: R = 

Scheme 32: rearrangement with *N*-Boc protected glycine derivatives

Reagents and Conditions: **45**, K_2CO_3, $AlMe_3$, CH_2Cl_2, 0°C, 20 h. **100** 6%; **101** 80%; **102** 74%; **103** 82%.

amide were partly removed under the workup conditions. Hence, the rearrangement with *N*-Boc-glycinyl fluoride **58** (R = H) gave **100** only 6% yield. In contrast, subjecting the more stable Cbz-protected acid fluoride **72** to the allylation reaction with amine **45**, and the Boc-protected acid fluoride **71** to the allylation with amine **47** (Scheme 33), the corresponding amides **104** and **105** could be isolated in 75% and 82% as single diastereomers, respectively.



47: R^1 = Bn
45: R^1 = TBS

71: R^2 = BOC
72: R^2 = Cbz

104: R^1 = Bn, R^2 = BOC, (82%)
105: R^1 = TBS, R^2 = Cbz, (75%)

Scheme 33: Synthesis of amides **104** and **105**

Reagents and Conditions: K_2CO_3, $AlMe_3$, CH_2Cl_2, 0°C, **104** 20 h. 82%; **105** 16 h. 75%

After the workup of the rearrangement employing *N*-Boc protected glycine derivatives **71**, **73**, **81** and allylamine **45**, **47**, some deprotection was detected of amide **101**-**104**. Consequently, it was crucial to treat the crude mixture once again with $(Boc)_2O$ intending to achieve maximal yields.

2.4 Rationalization of the Stereochemical Outcome

Analyzing the stereochemical outcome of the *C*-allylglycine derivates **85**/**86**, **98-105** originating from zwitterionic aza-Claisen rearrangement, three aspects have to be considered: 1) the enolate geometry, 2) the transition state conformation (simple diastereoselectivity, internal asymmetric introduction), and 3) the auxiliary-induced selectivity.[22, 23]

Considering the pathway of the process starting from the allylamines **43**, **45**, **46**, **47** and acetyl fluorides **61**, **71-74**, **81** the first step was thought to be addition of a ketene, which was produced from trimethyl aluminum and acetyl fluorides, at the nucleophilic nitrogen to generate the hypothetical intermediate zwitterions. In this special case, such addition led to the construction of a stereogenic ammonium center (*syn* or *anti* with respect to the adjacent *C*-center). The diastereoselectivity of the process depends on the efficency of the auxiliary. Generally, a tertiary amine should suffer from a fast nitrogen inversion **A** ⇔ **B** (Figure 2.3), but here, the substitution pattern of the pyrrolidine should decelerate the rate. The conformation **A** should predominate, (quasi equatorial arrangement of the allyl side chain and the substituent at the chiral center) causing the *syn*-adduct formation of the ketene equivalent. At ambient temperature, the flipping of the nitrogen should not be suppressed. Consequently, less bulky, reactive ketene fragments and auxiliaries bearing stereogenic centers with less bulky substituents also allow addition starting from the conformation **B** resulting the *anti*-adducts (Figure 2.3). However, the so generated zwitterions must be characterized by a defined Z-enolate geometry of the amide subunit as is known for all related systems.[24] Finally, the acylammonium enolate undergoes the [3,3]-sigmatropic process. The charge neutralization serves as a highly efficient driving force. Consistent with well known acyclic Claisen rearrangements, the highly ordered transition state should have adopted a chair-like arrangement to minimize repulsive 1,3 interactions. The small CH_2 part of the proline ring

[22] Reviews on Claisen Rearrangements: (a) Ziegler, F.E. *Chem.Rev*. **1988**, *88*, 1423. (b) Frauenrath, H. In *Houben Weyl: Stereoselective Synthesis*, Vol. E21d; Helmchen, G.; Hoffmann, R.W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, **1995**, 3301-3756. (c) Wipf, P. In *Comprehensive organic Synthesis*, Vol. 5; Trost, B.M., Flemming, I., Paquette, L.A., Eds.; Pergamon: New York, **1991**, 827-873. (d) Hill, R.K. In *Asymmetric Synthesis*, Vol. 3; Morrison, J.D., Ed.; Academic Press: New York, **1984**, 503-572.

[23] For enantioselective Claisen rearrangement, see: (a) Enders, D.; Knopp, M.; Schiffers, R. *Tetahedron: Asymmetry* **1996**, *7*, 1847. (b) Clayden, J.; Helliwell, M.; McCarthy, C.; Westlund, N. *J. Chem. Soc., Perkin Trans.1* **2000**, 3232. (c) Lemieux, R.M.; Devine, P.N.; Mechelke, M.F.; Meyers, A.I. *J. Org. Chem*. **1999**, *64*, 3585. (d) Lemieux, R.M.; Meyers, A.I. *J. Am. Chem. Soc*. **1998**, *120*, 5453. (e) Metz, P.; Hungerhoff, B. *J. Org. Chem*. **1997**, *62*, 4442. (f) Roush, W.R.; Works, A.B. *Tetrahedron lett*. **1997**, *38*, 351. (g) Yoon, T.P.; MacMillan, D.W.C. *J. Am. Chem. Soc*. **2001**, *123*, 2911.

[24] (a) Evans, D.A.; Bartoli, J.; Shih, T.L. *J. Am. Chem. Soc*. **1981**, *103*, 2127. (b) Richter, W.; Sucrow, W. *Chem. Ber*. **1971**, *104*, 3679.

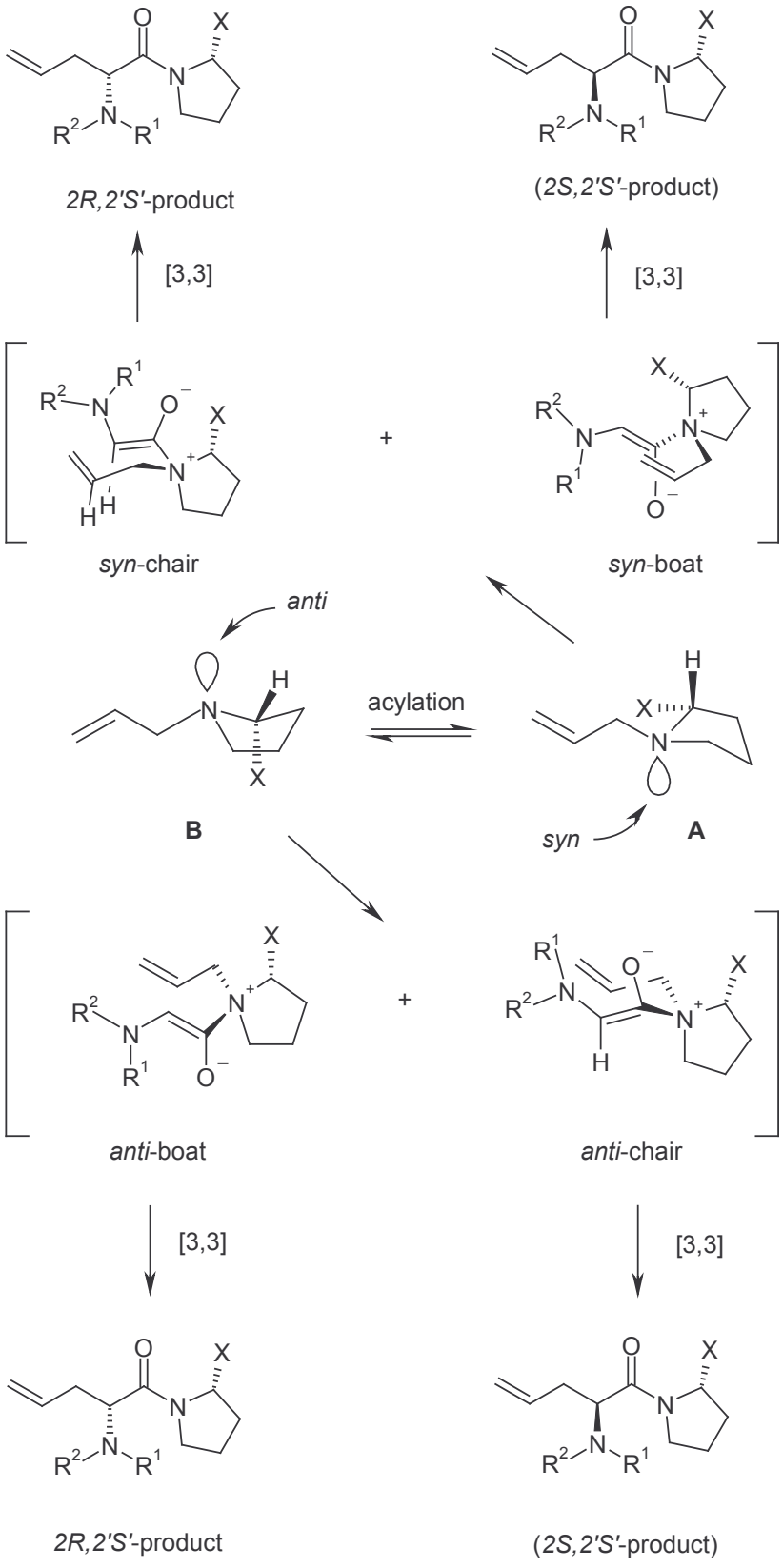
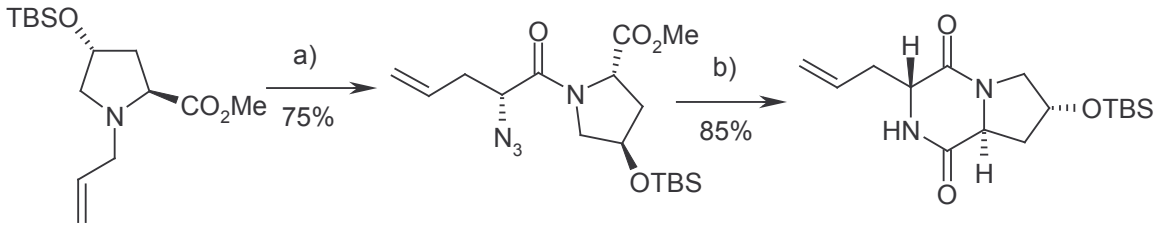


Figure 2.3: Stereochemistry of the *C*-allylation: working hypothesis

should have been placed in an axial position and the bulky chain branched function bearing the stereogenic center in the equatorial position.[25] In combination with a *Z*-enolate structure the configuration of the nascent stereogenic center must be *R* originating from the *syn* adduct and *S* resulting from the *anti* analog. The diastereoselectivity of the auxiliary induced acylation directly determines the stereochemical outcome of the process. Expecting selective reactions with highly reactive small glycinyl fluorides **61**, the use of bulky auxiliaries (TBS-prolinol, **45**) was mandatory, the rearrangement of less reactive bulky glycine derivatives **71**, **72** can involve the small proline methyl ester substituent like **43** to achieve satisfactory results.[26]

In conclusion, the main reaction path could be described as the *syn*-acylation of the allylamine conformation **A**, the formation of the *Z*-enolate, and the passing of a chair-like transition state to generate the (*2R*)-*C*-allylglycine derivatives **82**, **85** and **98**-**105**. Obviously this hypothesis presents a Claisen rearrangement proceeding with the well known 1,3 chirality transfer, shifting the chiral information via the heteroatom containing fragment.

The rearrangement with azidoacetyl fluoride **61** and (2*S*,4*R*)-*N*-Allyl-4-*tert*-butyldimethyl-silyloxyproline methyl ester **54** (Scheme 34) under standard conditions generated the amide **106** in 75% yield. Staudinger reaction[15] reduced the azide-group to the amine, which cyclized immediately with the auxiliary ester function to give bicyclic piperazinedione **107** with 85%



54 **106** **107**

Scheme 34: Synthesis of the bicyclic piperazinedione **107**

Reagents and Conditions: a) K_2CO_3, $AlMe_3$, CH_2Cl_2, 0°C, azidoacetyl fluoride **61**, 3 h. 75% b) PPh_3, THF/H_2O (20:1), 16 h, 85%

[25] (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. (b) Vettorelli, P.; Hansen, H.J.; Schmid, H. *Helv. Chim. Acta* **1975**, *58*, 1293. (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. (d) Büchi, G.; Powell, J.E. *J. Am. Chem. Soc*. **1970**, *92*, 3162. (e) Abelmann, M.M.; Funk, R.F.; Munger, J.D. *J. Am. Chem. Soc*. **1982**, *104*, 4030.

[26] As an alternative, the use of C2-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.

yield as a single diastereomer. The NOE analysis (Figure 2.4) of the piperazinedione **107** proved that the new stereogenic center in the allylglycine derivative **106** was *R* configured.

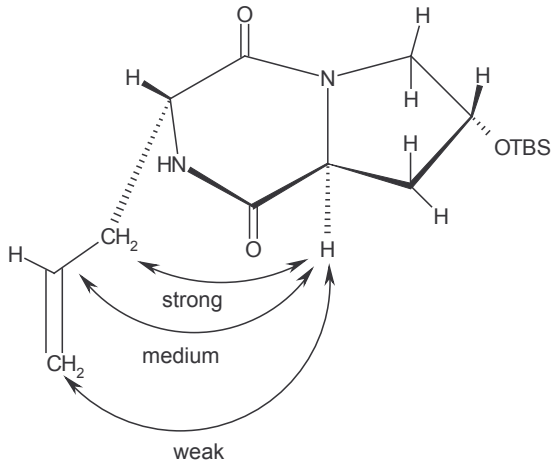


Figure 2.4: relevant NOE's of **107** from NOESY

Because of the large OTBS-group, the *anti*-acylated ammonium enolate occurred disfavoured (Figure 2.5). As expected, the favoured *syn*-acylated ammonium enolate underwent the [3,3]-sigmatropic process via a chair-like transition state to afford (*R*)-α-azidoamide **106**, even at room temperature.

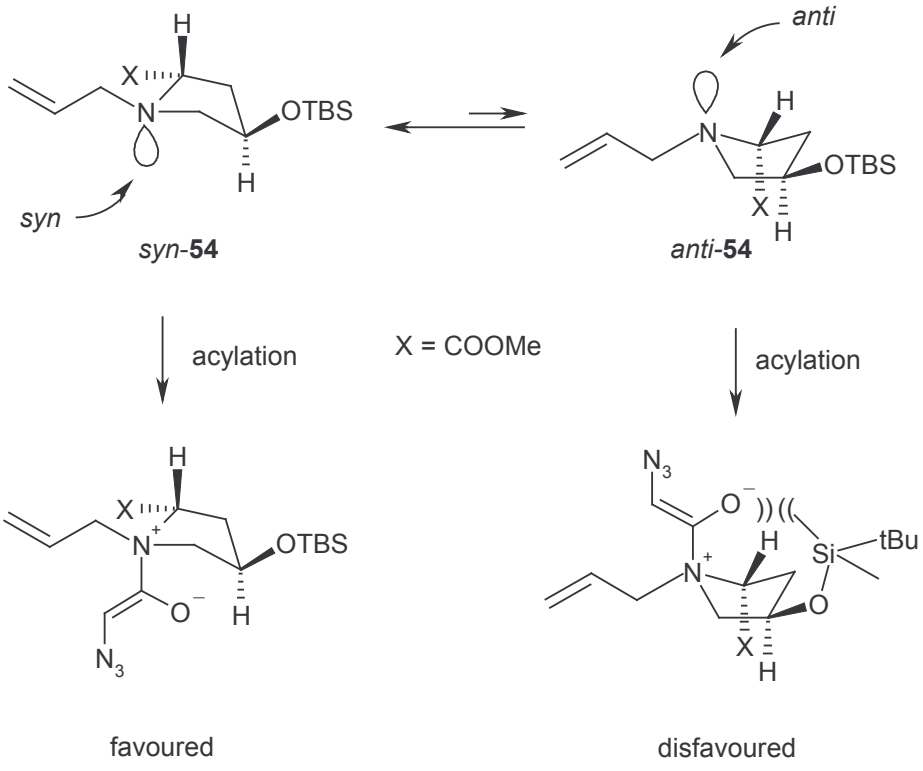
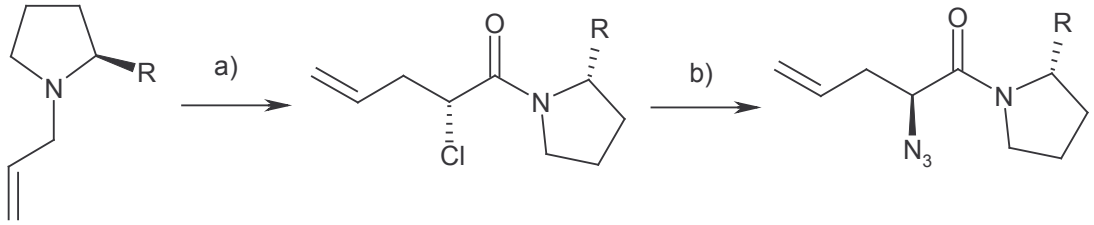


Figure 2.5: *N*-Acylation of compound **54**

The (*S*)-α-Azidoamides **110** and **111** could be synthesized from (*R*)-α-Chloroamide **108** and **109** under standard azide displacement conditions. (*R*)-α-Chloroamides **108** and **109** were generated via the aza-Claisen rearrangement with chloracetyl chloride **112** and allylamine **43** and **45** under standard conditions (Scheme 35).



43: R = COOMe
45: R = CH_2OTBS

108: R = COOMe
109: R = CH_2OTBS

110: R = COOMe
111: R = CH_2OTBS

Scheme 35: Synthesis of (*S*)-α-azidoamides **110** and **111**

Reagents and Conditions: a) chloracetyl chloride **112**, $AlMe_3$, -20°C, 1 h., **108**, 70%; **109** 69%. ds > 20 :1 b) NaN_3, DMF, rt, 20 h., **110** 97%; **111**, 99%.

The (*R*)-α-Chloroamides **108** and **109** were cleanly converted into the (*S*)-α-azidoamides **110** and **111** with NaN_3 in DMF at room temperature for 20 hours. The yields were almost quantitative. The absolute configuration of the inverted stereogenic center was proven by NOESY of the bicyclic piperazinedione **113** (Figure 2.6), which had been prepared from (*S*)-α-Azidoamide **110** via the Staudinger reaction with Ph_3P in THF and H_2O at room temperature for 20 hours (see Scheme 34).

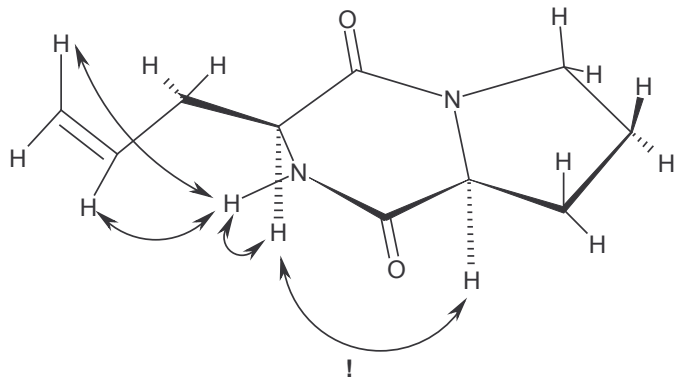
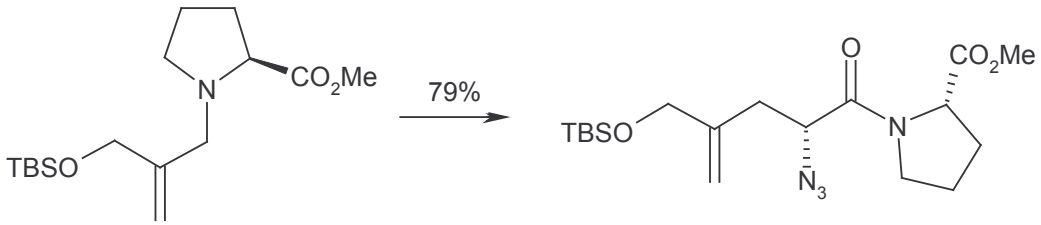


Figure 2.6: relevant NOE's of **113** from NOESY

The treatment of allylamine **50** with azidoacetyl fluoride **61** was carried out at 0°C. After addition of Me_3Al the rearrangement produced the product **114** with 79% yield after 3 hours as a single diastereomer (Scheme 36). Though not proven in detail, the absolute configuration of the new stereogenic center seemed reasonable.

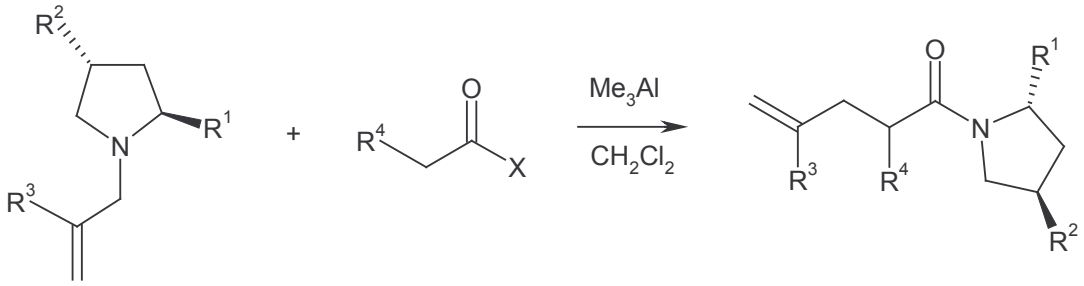


50 **114**

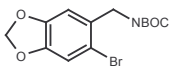
Scheme 36: Synthesis of α-azido amide **114**

Reagents and Conditions: azidoacetyl fluoride **61**, $AlMe_3$, 0°C, 3 h., 79%

The results of the zwitterionic aza-Claisen rearrangements bearing chiral auxiliaries and α-amino acetyl fluoride derivatives and chloracetyl chloride and acetyl chloride are summarized in Table 2.1.



Entry	R^1	R^2	R^3	Amine No	R^4	X	React No	Temp (°C)	Products No	Yield (%)	Ratio (*R*:*S*)
1	CO_2Me	H	H	**43**	PhtN	F	**56**	0	**82**, **83**	78	1:1
2	CO_2Me	H	H	**43**	N_3	F	**61**	20	**85**, **86**	73	4:1
3	CO_2Me	H	H	**43**	N_3	F	**61**	0	**85**, **86**	77	7:1
4	CO_2Me	H	H	**43**	N_3	F	**61**	-20	**85**, **86**	79	9.5:1

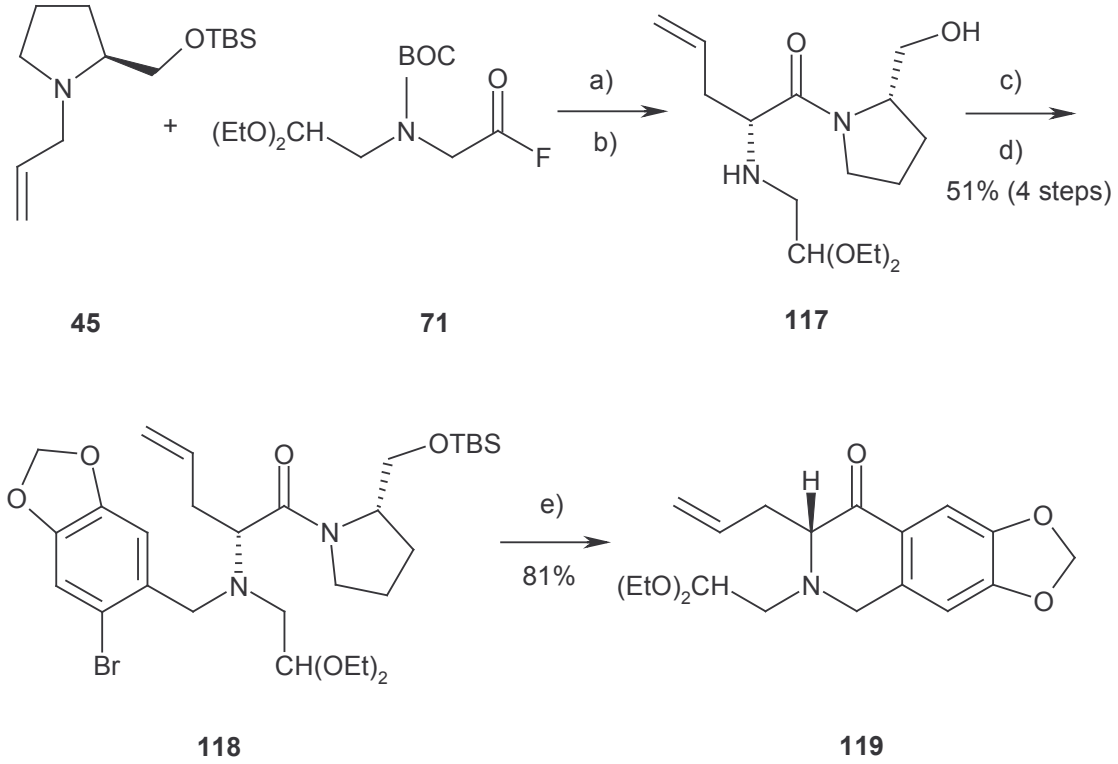
5	CO_2Me	H	H	**43**	$BocNCH_2CH(OEt)_2$	F	**71**	0	**94**, **95**	73[a]	15:1
6	CH_2OTBS	H	H	**45**	N_3	F	**61**	0	**98**	76	>15:1
7	CH_2OTPS	H	H	**46**	N_3	F	**61**	0	**99**	76	>15:1
8	CH_2OTBS	H	H	**45**	BocNH	F	**58**	0	**100**	6	–
9	CH_2OTBS	H	H	**45**	$BocNCH_2CH(OEt)_2$	F	**71**	0	**101**	80	>15:1
10	CH_2OTBS	H	H	**45**	$BocNCH_2CH(OMe)_2$	F	**73**	0	**102**	74	>15:1
11	CH_2OTBS	H	H	**45**		F	**81**	0	**103**	82	>15:1
12	CH_2OBn	H	H	**47**	$BocNCH_2CH(OEt)_2$	F	**71**	0	**104**	82	>15:1
13	CH_2OTBS	H	H	**45**	$CbzNCH_2CH(OEt)_2$	F	**72**	0	**105**	75	>15:1
14	CO_2Me	OTBS	H	**54**	N_3	F	**71**	0	**106**	75	100:0
15	CO_2Me	H	H	**43**	Cl	Cl	**112**	-20	**108**	70	>20:1
16	CH_2OTBS	H	H	**45**	Cl	Cl	**112**	-20	**109**	69	>20:1
17	CO_2Me	H	CH_2OTBS	**50**	N_3	F	**61**	0	**114**	79	>15:1
18	CO_2Me	H	H	**45**	$BnNCH_2CH(OEt)_2$	F	**74**	0	–	–	–
19	CO_2Me	OTBS	H	**54**	H	Cl	**115**	0	**116**	70	–

a: Yield determined after cyclization **96** and **97**

Table 2.1: Synthesis of *C*-allylglycinyl amides

2.5 Consecutive Processes: Introduction of the Piperonyl Group (1)

Envisaging total syntheses of amaryllidaceae alkaloid, the piperonyl subunit had to be introduced in due course. Considering the fact, that the Boc group and the silyl ether of amide were partly removed under non-neutral workup conditions, a complete cleavage could be achieved upon treating the crude material with thionyl chloride in anhydrous ethanol at 0°C to give the amino alcohol **117**. Several attempts to achieve a chemoselective deprotection of the nitrogen in presence of a silyl ether failed. Thus, the TBS group was forced to be reintroduced under standard silylation conditions.[38] The so obtained secondary amine was then benzylated with *o*-bromomethyl-piperonyl bromide **77** in the presence of potassium carbonate in acetonitrile to give the piperonylamine **118**. Starting from allylamine **45** and *N*-Boc glycinyl fluoride **71** the overall yield was about 51% over four steps[27] (Scheme 37).

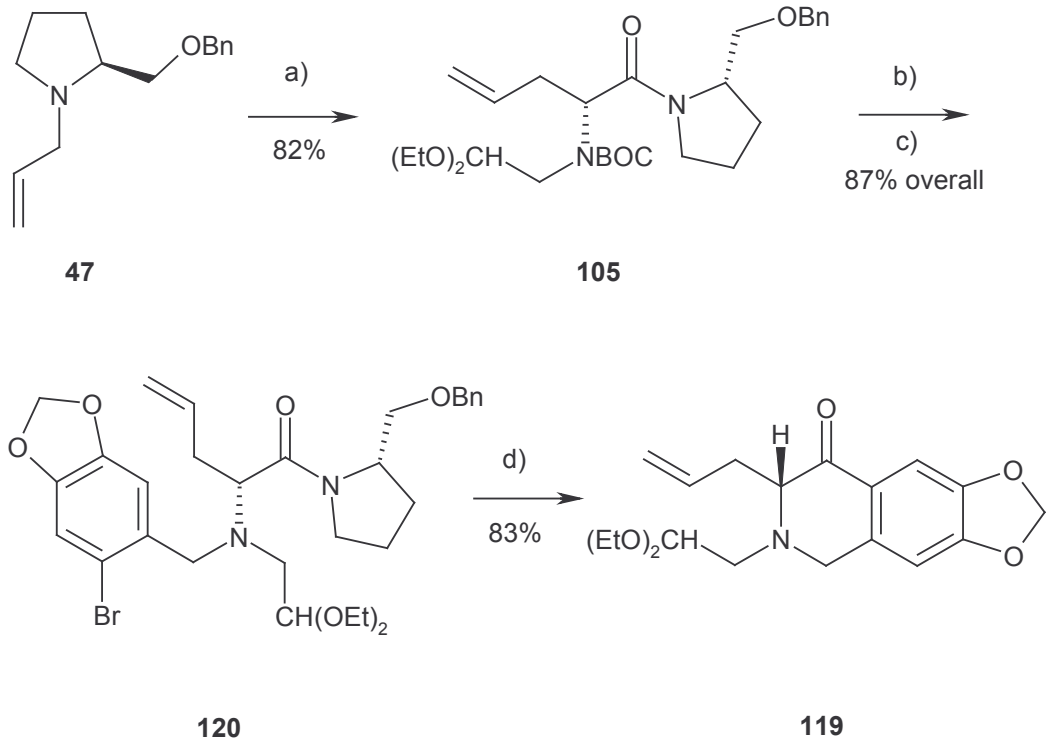


Scheme 37: Synthesis of isoquinolone **119**

Reagents and Conditions: a) K_2CO_3, $AlMe_3$, CH_2Cl_2, 0°C b) $SOCl_2$, EtOH, r.t. 16 h. c) TBSCl, imidazole, CH_2Cl_2, r.t. d) $ArCH_2Br$ **77**, K_2CO_3, MeCN, 80°C, 20 h. 51% 4 steps from **45** and **71**. e) BuLi, THF, -78°C, 3 h. 81%.

[27] Cossy, J. *Eur. J. Org. Chem*. **1999**, 1925.

A final ring closure gave the optically active isoquinolone derivative **119** under mild conditions:[28] the piperonylamine **118** was treated with butyllithium in anhydrous THF at –78°C inducing the bromine-lithium exchange. This in situ formed aryllithium species attacked the amide function resulting in the formation of the ketone **119**. After removal of the auxiliary during the course of the workup neither tertiary alcohol (alkylation of the ketone) nor further side products were detected. An analogous sequence allowed to avoid the use of the unstable silylether **45**. The reaction of allylamine **47** and glycinyl fluoride **71** gave the

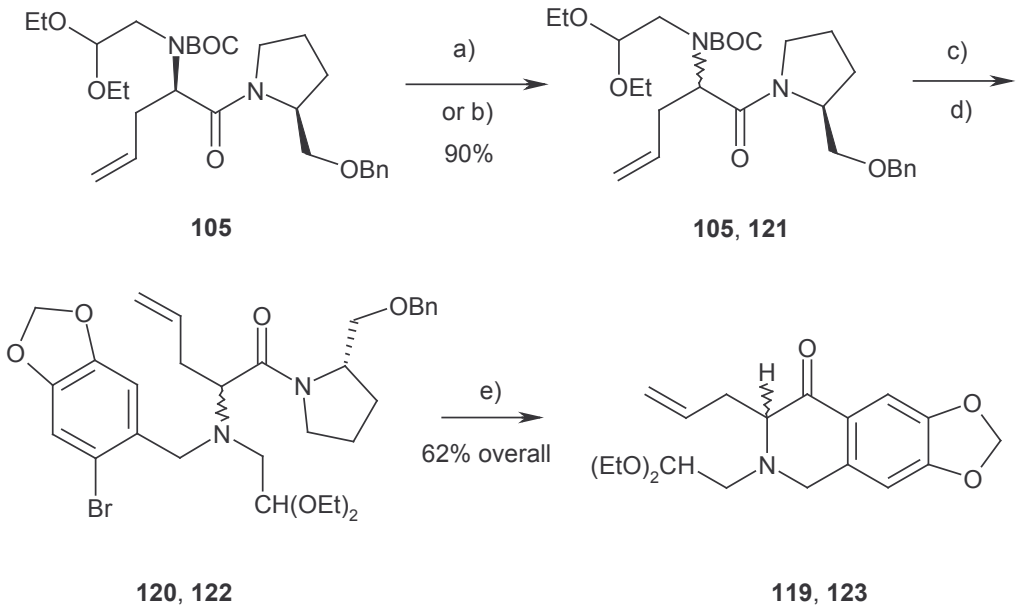


Scheme 38: Synthesis of the isoquinolone **119** with benzyl ether

Reagents and Conditions: a) **71**, K_2CO_3, $AlMe_3$, CH_2Cl_2, 0°C, 20 h. 82% b) $SOCl_2$, EtOH, r.t. 16 h. c) $ArCH_2Br$ **77**, K_2CO_3, MeCN, 80°C, 20 h. 87% for 2 steps d) BuLi, , THF, -78°C, 3 h. 83%

amide **105** in 82% yield. The *N*-Boc group was completely removed by treating with thionyl chloride and ethanol, the crude material was then benzylated with bromomethylpiperonyl bromide **77** in the presence of potassium carbonate in acetonitrile to give compound **120** in 87% yield for 2 steps. The isoquinolone **119** was obtained after subsequent treatment of **120** with butyllithium in THF at –78°C in 83% yield (Scheme 38).

[28] Rita, P.M. *J. Org. Chem*. **1997**, *62*, 6862.



Scheme 39: Racemization of the amide **105** and synthesis of racemic isoquinolone **119**/**123**

Reagents and Conditions: a) LDA, THF, -78°C to - 40°C, 3 h., then aq. NH_4Cl, 90% b) K_2CO_3, DMF, reflux, 5 h., 90%. c) $SOCl_2$, EtOH, r.t. 16 h. d) $ArCH_2Br$ **77**, K_2CO_3, MeCN, 80°C, 20 h. e) BuLi, THF, -78°C, 3 h., 62% for 3 steps.

The strong basic conditions raised the question concerning the optical purity of the product **119**. Intending to put the analysis on a firm basis it was mandatory to synthesize the racemic isoquinolone **119** and the enantiomer **123**, respectively. The first attempt to obtain the racemate was carried out under standard conditions: a solution of isoquinolone **119** in THF was treated with LDA at – 40°C, after deprotonation for 3 hours, the reaction was quenched with aq. NH_4Cl. To our disappointment, the isoquinolone **119** was decomposed under these conditions. Hence, we checked the precursor **105** concerning the potential equilibration of the stereogenic α-center in the presence of a strong base. Amide **105** was treated with LDA in THF at – 40°C, the proton of the stereogenic center, introduced by the aza-Claisen rearrangement, was removed. Subsequent quenching with aq. NH_4Cl gave the re-protonation. The diastereomers **105** and **121** could be separated by means of HPLC, and the ratio was 1:1. Alternatively, the amide **105** was refluxed with K_2CO_3 in DMF for 5 hours to achieve equilibration, the ratio of the diastereomers **105** and **121** was found to be about 5:1 (Scheme 39). Treatment of the mixture of the diastereomers **105**/**121** (1:1) with thionyl chloride in anhydrous ethanol at 0°C caused the cleavage of the Boc-group, the consecutive reaction with bromomethylpiperonyl bromide **77** afforded the diastereomers **120**/**122** with good yield. The final halide-metal-exchange / cyclization sequence gave rise to the formation of the racemic isoquinolones **119**/**123** with about 62% yield for three steps. High yields for each step were necessary to avoid kinetic resolution!

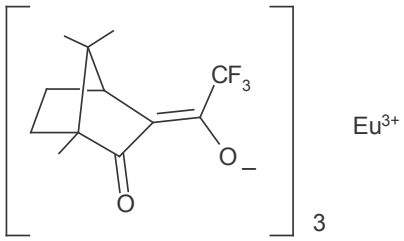
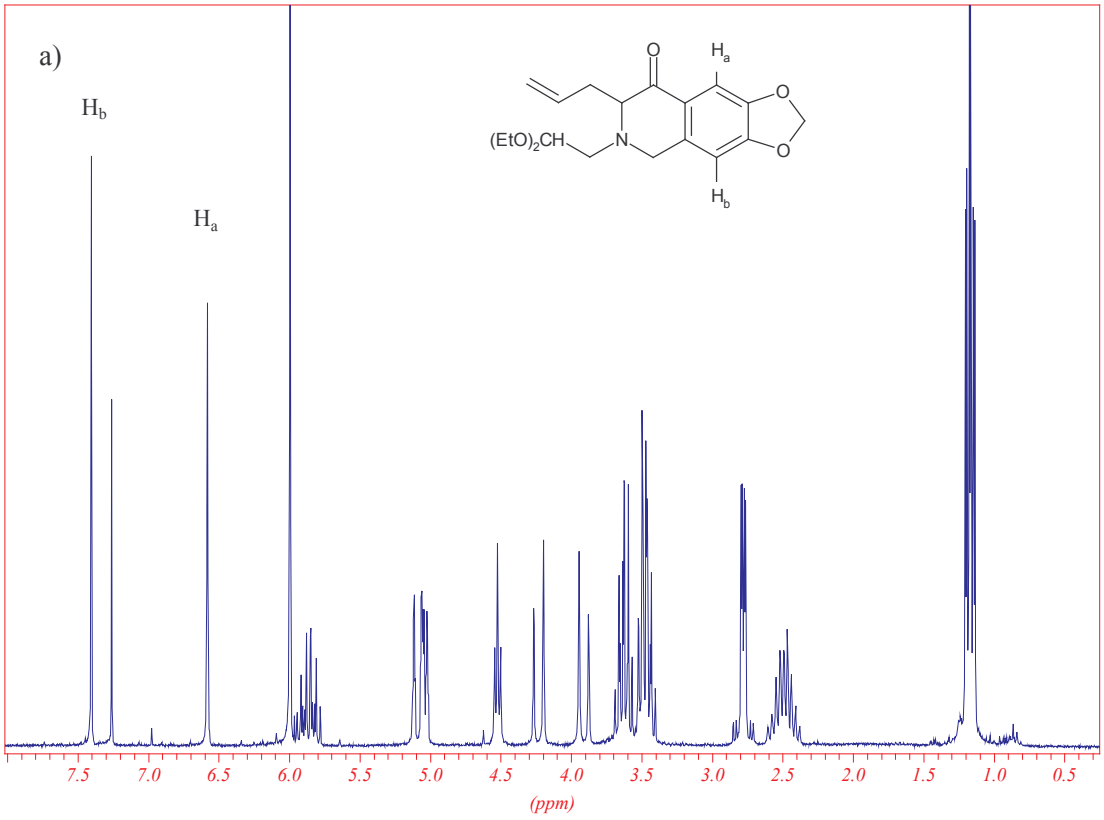
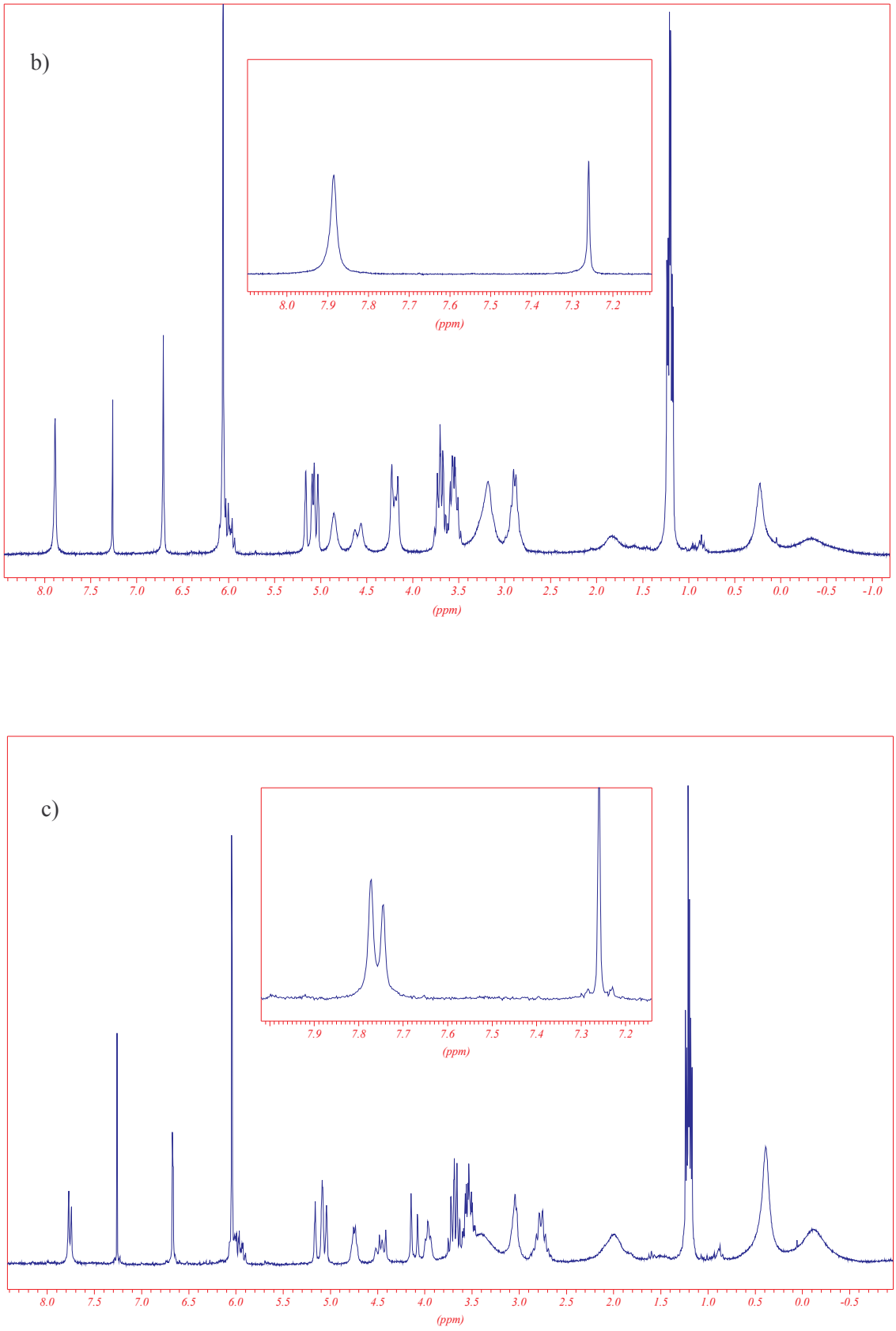


Figure 2.7: Tris[3-(trifluoromethylhydroxymethylene)-(+)-camphoratol]-europium(Ⅲ)

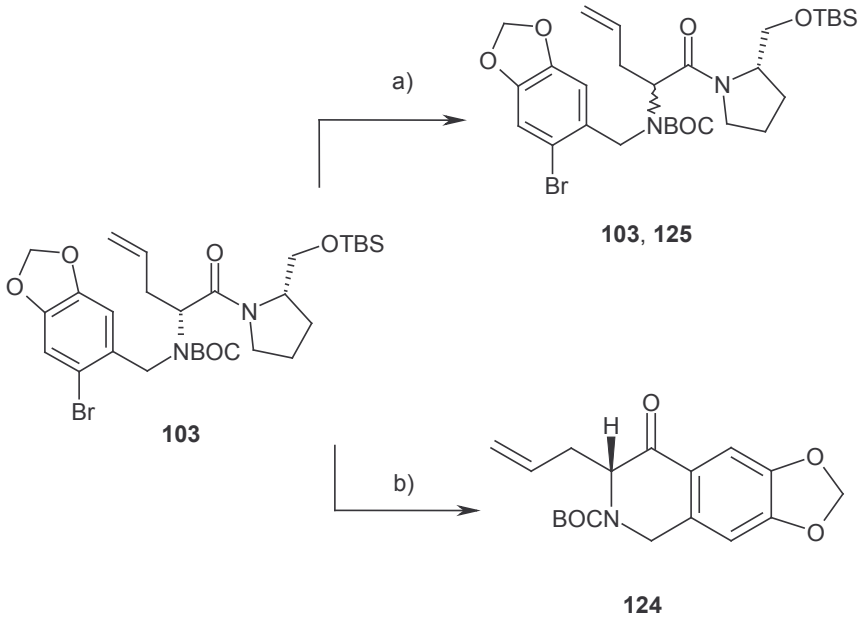
Analyzing the isoquinolone **119** by means of ^{1}H-NMR shift experiments [Eu(tfc)$_3$] (figure 2.7), a single compound was found. In contrast the racemate displayed a double set of peaks (Scheme 40). This fact proved the formation of the optically pure material during the course of the rearrangement and the final ring closure.





Scheme 40: ^{1}H-NMR spectra of the isoquinolone a) without shift reagent Eu(tfc)$_3$ b) optical pure compound **119** with Eu(tfc)$_3$ c) racemic compounds **119**/**123** with Eu(tfc)$_3$

Finally, the amide **103** was treated with K_2CO_3 in DMF. A refluxing for 20 hours gave two diastereomers **103** and **125** in the ratio of 1.5 to 1, which were separated by means of HPLC. Cyclization was achieved by subjecting the amide **103** to halide-metal exchange conditions. The yield of this step was only 41.5% (Scheme 41). The specific rotation of the compound **124** was $[\alpha]_D^{20}$ – 4.7° (c = 1.3 in $CHCl_3$). Any resolution could not be excluded!



Scheme 41: Synthesis of diastereomers **103**/**125** and isoquinolone derivative **124**

Reagents and Conditions: a) K_2CO_3, DMF, reflux, 20 h., **125** 36%, **103** 56% b) BuLi, THF, -78°C, 41.5%

2.6 Removal of the Chiral Auxiliary: Introduction of the Piperonyl Group (2)

A preparatively useful chiral auxiliary controlled reaction requires always a highly efficient auxiliary removal as the last step. Analysing the chiral auxiliary removal processes to be used for zwitterionic aza-Claisen rearrangement products, several processes had to be considered:

a) Acid mediated cleavage (heating in aq. 6 N HCl, in aq. 2 N H_2SO_4 and in anhydrous hydrochloride-methanol-solution[29])

Heating of the rearrangement products in aq. 6 N HCl gave rise to the formation of γ-butyrolactones. Obviously, the intermediately formed γ,δ-unsaturated acid suffered from intramolecular double bond addition with moderate yield. Intending to regenerate the unsaturated acid, the starting from the lactones seemed not recommendable (see chapter 2.3, page 29-32).

In contrast, the cleavage with 2 N H_2SO_4 in methanol gave a smooth formation of the corresponding methyl esters. The same result could be obtained after cleavage with anhydrous HCl-MeOH.

Smooth reactions were obtained in the case of acid stable functional groups. In contrast, the presence of acid labile functions, such as acetals and *N*-Boc subunits forced to develop alternative protocols.

b) Iodolactonization

Iodine in dimethoxyethane and water at 0°C induced a iodolactonization[30] to achieve the cleavage of the auxiliary amides. The so formed iodolactones offered the opportunity to remove the iodine by means of a reduction with zinc dust in acetic acid or methanol to afford pentenoic acid derivative.[31] Disappointingly, the iodolactonization gave no corresponding lactone, some degradation product were isolated.

---

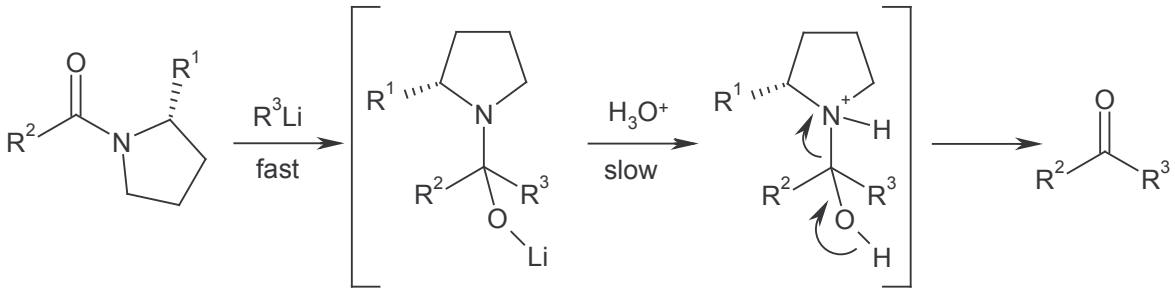
[29] Laabs, S. Dissertation: *Diastereoselektive Synthese von cis-3-Arylprolinderivaten durch auxiliarkontrollierte zwitterionische Aza-Claisen-Umlagerungen*, **2001**, p. 96

[30] (a) Laabs, S.; Münch, W.; Bats, J.W.; Nubbemeyer, U. *Tetrahedron*, **2002**, *58*, 1317 (b) Mulzer, J.; Altenbach, H.J.; Braun, M.; Krohn, K.; Reissig, H.U. *Organic Synthesis Highlights*, VCH Publishers: Weinheim, New York, **1991**, p. 158 (c) Dowle, M.D.; Davies, D.I. *Chem. Soc. Rev*. **1979**, 171 (d) Bartlett, P.A. *Tetrahedron*, **1980**, *36*, 2.

[31] (a) Metz, P.; Hungerhoff, B. *J. Org. Chem*. **1997**, *62*, 4442. (b) Metz, P. *Tetrahedron* **1993**, 49, 6367. (c) Smith, E.H.; Tyrrell, N.D. *J. Chem. Soc. Chem. Commun*. **1983**, *6*, 285. (d) Hatakeyama, S.; Sugawara, M.; Kawamura, M.; Takano, S. *J. Chem. Soc. Chem. Commun*. **1992**, *17*, 1229.

c) Organo-lithium addition

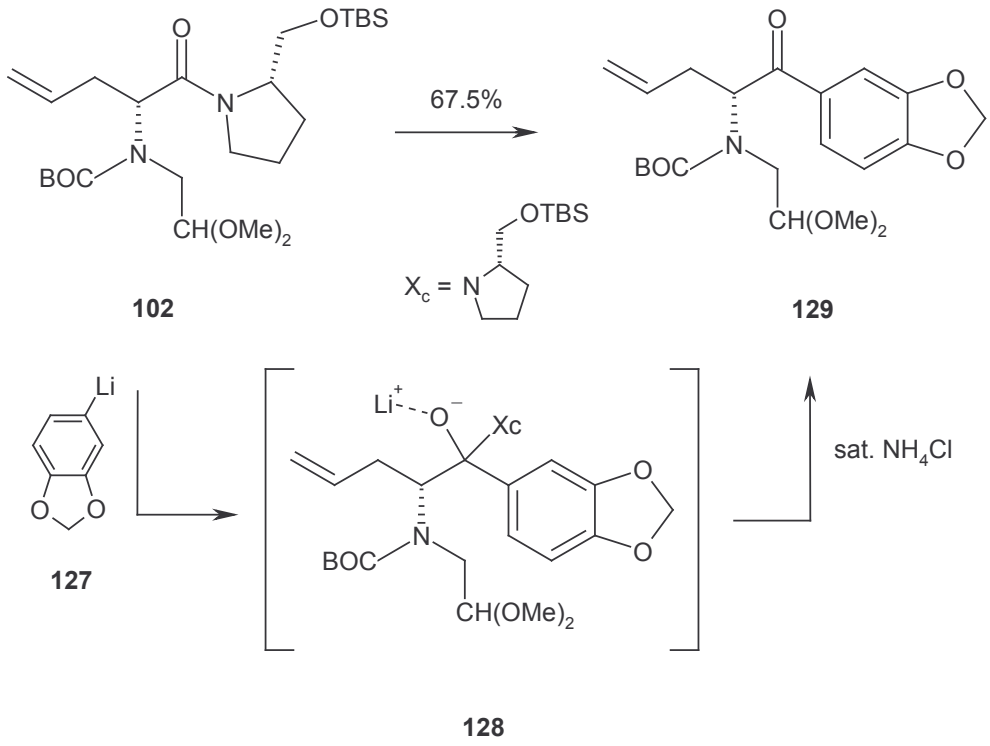
Cleavage of the auxiliary could be run as a new C-C bond forming step. Considering that tertiary amides underwent smoothly organo-lithium additions, but retained amine eliminations, the alkylations should generate defined ketones right after aq. NH_4Cl work-up (Scheme 42).



Scheme 42: Cleavage of the auxiliary with organo-lithium reagents

First successful experiment had been described upon synthesizing isoquinolone, the direct introduction of an aryl moiety furnished the cyclic aryl ketone without lost of the chiral information (see chapter 2.5, page 43-45).

First attempts to remove the chiral auxiliary on synthesizing acyclic α-amino aryl ketone started with α-aminoamide **102** and 1-bromo-3,4-methylendioxybenzene **126**. A cold (−78°C) solution of aryl bromide **126** in THF was treated with one equivalent of n-butyllithium, a halogen-metal exchange took place and furnished aryllithium reagent **127**. Adding α-aminoamide **102**, a selective attack of the amide carbonyl group conceivably furnished organolithium salt **128**. The intermediate **128** was quite stable at low temperature. Finally, Ketone **129** was generated after quenching with saturated NH_4Cl solution with 67.5% yield. The specific rotation was $[\alpha]_D^{20}$ +110.7° (Scheme 43). The optical purity still remained to be proven.



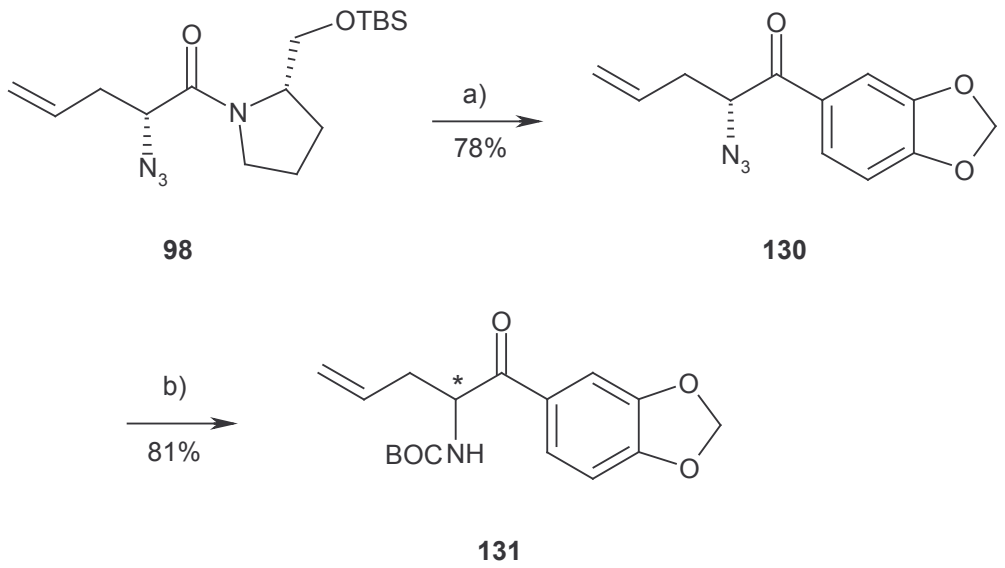
102 **129** **127** **128**

Scheme 43: Synthesis of acyclic α-amino aryl ketone **129**

Reagents and Conditions: 1-Brom-3,4-methylendioxybenzene **126**, n-butyllithium, THF, -78°C, 15 min., then α-amino-amide **102**, 30 min., sat. NH_4Cl, 67.5%

Furthermore, acyclic α-azido aryl ketone **130** could be achieved with α-azidoamide **98** and aryllithium **127** with 78% yield. The transformation of α-azido ketone **130** to the corresponding α-*N*-Boc ketone **131** succeeded under the conditions similar to that suggest by Afonso[32] (Scheme 44). Afonso used n-Bu_3P as reducting reagent in diethyl ether at room temperature to prepare an iminophosphorane. Subsequent $(Boc)_2O$ addition enabled to introduce a protecting group. After a further 18 hours at room temperature the reaction was quenched with aqueous sodium hydrogencarbonate to give product with moderate yield. Subjecting our material to these conditions no product could be isolated. Interestingly, the presence of a catalytical amount of water turned to be extremely helpful. The catalytical amount of water converted the intermediate iminophosphorane into primary amine, the amine and $(Boc)_2O$ combined to afford the product.

[32] Afonso, C.A.M. *Synth. Commun*. **1998**, *28*, 261

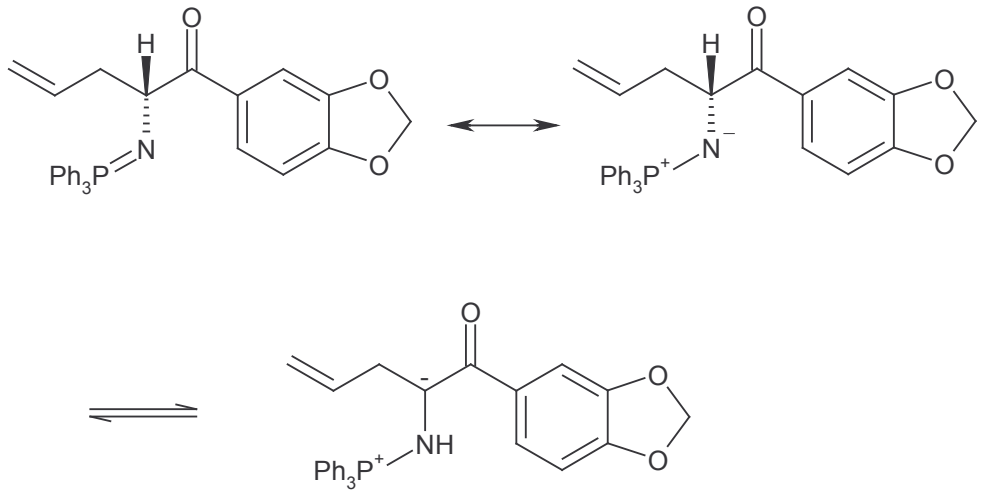


Scheme 44: Synthesis of acyclic α-amino aryl ketone **131** from α-azido amide **98**

Reagents and Conditions: a) 1-Brom-3,4-methylendioxybenzene **126**, n-butyllithium, THF, -78°C, 15 min., then α-azido amide **96**, 30 min., sat. NH_4Cl, 78% b) Ph_3P, $(Boc)_2O$, THF/H_2O (20:1), rt, 16 h. 81%.

Replacing of n-Bu_3P by Ph_3P to reduce the azide in compound **130** was found to be not recommended. THF / H_2O (20:1) was chosen as solvent, and the $(Boc)_2O$ was directly added after Ph_3P. The reaction started spontaneously and was completed at room temperature after 16 hours. Surprisingly, the product was optically inactive $[\alpha]_D^{20}$ 0.

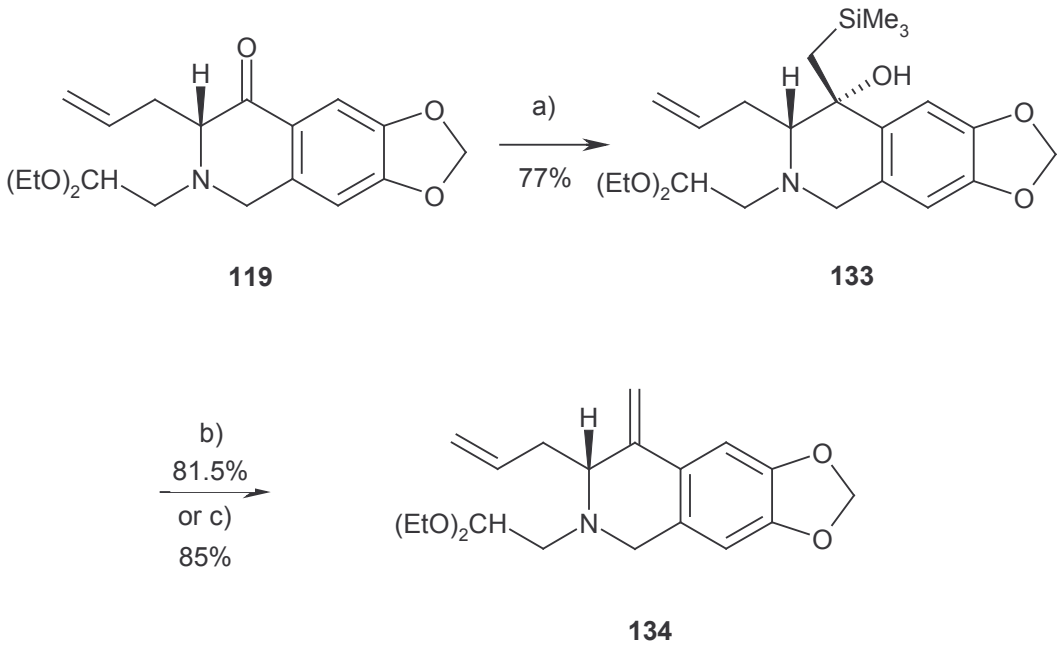
Presumably, the absence of a protic solvent turned the reaction medium too basic causing the racemization of the ketone (Scheme 45).



Scheme 45: Hypothetical racemization of the ketone

2.7 Transformations of the Isoquinolone

Planing the total synthesis of amaryllidaceae alkaloid as a long-term-objektive, the ketone of compound **119** had to be convert into a suitable exomethylene side chain. Several attempts to introduce a nucleophile into isoquinolone **119** to accomplish a carbon-carbon bond failed. Because of the strong + I-effect of the electron rich aromatic group, the activity of the carbonyl group was decreased. No reactions took place, when the isoquinolone **119** was treated with Wittig reagent,[33] Horner-Wadsworth-Emmons reagent,[34] Grignard reagent and Tebbe reagent.[35] Finally, an organyllithium reagent was found to attack the ketone successfully. The first step of a Peterson olefination[36] took place smoothly adding trimethylsilyl methyl lithium **132** to a solution of the isoquinolone **119** in THF at –78°C. Compound **133** could be isolated with 77% yield (Scheme 46).



119 **133** **134**

Scheme 46: Synthesis of exo-methylene isoquinoline **134**

Reagents and Conditions: a) **132**, THF, -78°C, 3 h., then NH_4Cl, 77% (b) NaH, THF, relux, 3 h. then NH_4Cl, 81.5% (c) AcOH, 3 h., 20°C, then K_2CO_3, 85%

[33] For reviews of Wittig reaction, see: (a) Maercker, A. *Org. React*. **1965**, *14*, 270. (b) Gosney, I.; Rowley, A.G.; Cardogan, J.I.G. in *Organophosphorus Reagents in Organic Synthesis*, Academic Press, London, **1979**, p. 17-153. (c) Maryanoff, B.E.; Reitz, A.S. *Chem. Ber*. **1989**, *89*, 863.
[34] For reviews of Horner-Wadsworth-Emmons reaction, see (a) Boutagy, J.; Thomas, R. *Chem. Rev*. **1974**, *74*, 87. (b) Wadsworth, W.S. Jr., *Org. React*. **1977**, *25*, 73. (c) Gross, H.; Keitels, I. *Z. Chem*. **1982**, *22*, 117.
[35] (a) Tebbe, F.N.; Parshall, G.V.; Reddy, G.S. *J. Am. Chem. Soc*. **1978**, *100*, 3611. (b) Prine, S.H.; Petti, R.J.; Geib, G.D.; Gruz, S.G.; Gallego, C.H.; Tujerina, T.; Pine, R.D. *J. Org. Chem*. **1985**, *50*, 1212.
[36] Peterson, D.J. *J. Org. Chem*. **1968**, *33*, 780.

It was noteworthy, that the compound **133** was isolated as a diastereomerically pure substance. It seemed likely, because of steric reasons, that trimethylsilyl methyl lithium **132** attacked the carbonyl group anti with respect to nitrogen (parallel to the H). The NOE analysis had proven this hypothesis (Figure 2.8).

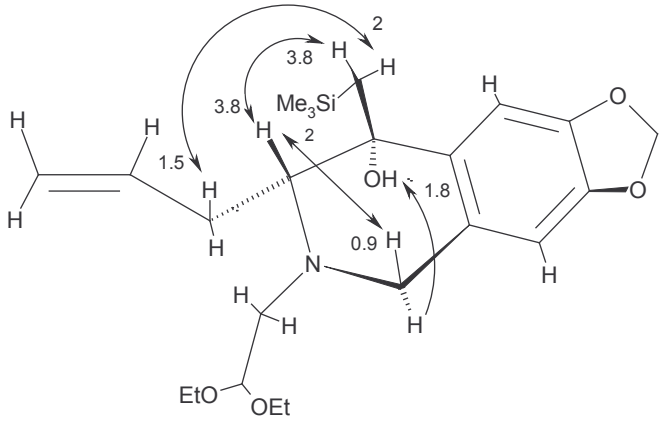


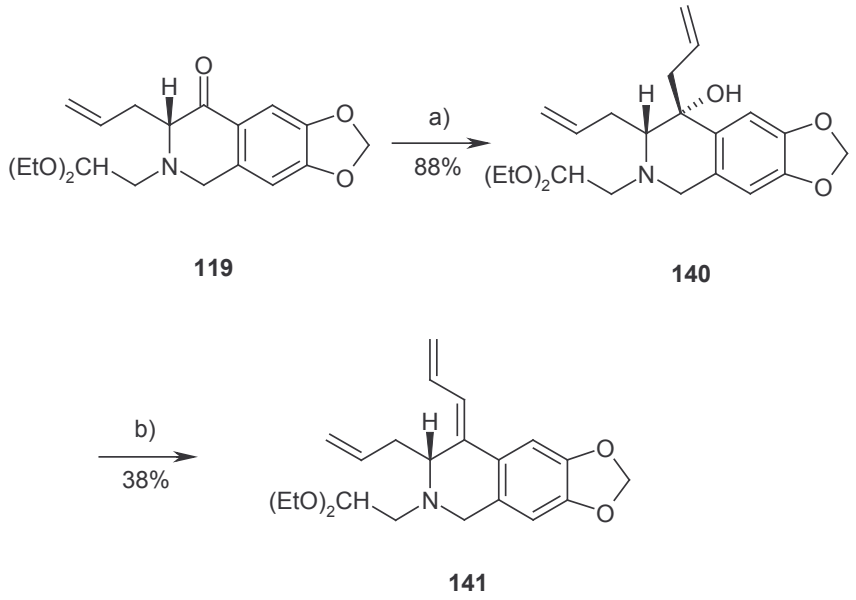
Figure 2.8: NOE data of compound **133**

The second step of a Peterson olefination included the elimination of the trimethylsilyl and hydroxyl group to give exo-methylene isoquinoline **134**. Such conversion could be run under acidic and basic conditions, respectively. In the presence of anhydrous acetic acid, the compound **133** underwent conversion to isoquinoline **134** in 85% yield without cleavage of the acetal group. Alternatively, the compound **133** was subjected to NaH inducing fragmentation to give **134** in 81.5% yield.

As expected the cleavage of the diethyl acetal was turned to be difficult. Treatment of the compound **134** with 3 M HCl at room temperature,[37] 2 M H_2SO_4 under reflux,[38] 50% TFA at 0°C,[39] TsOH in acetone under reflux,[40] $TiCl_4$ in the presence of LiI at room temperature,[41] $SmCl_3$ at room temperature,[42] Me_3SiI at room temperature,[43] and heating in DMSO-H_2O-Dioxane system[44] gave no expected product. Obviously, the basic isoquinoline **134** served as an efficient protective group trapping all proton and Lewis acids. The so formed positively charged intermediate did not suffer from a second activation to enable acetal cleavage.

[37] Wenkert, E.; Goodwin, T.E. *Syn. Commun*. **1977**, *7*, 409.
[38] Cameron, A.F.B.; Hunt, J.S.; Oughton, J.F.; Wilkinson, P.A.; Wilson, B.M. *J. Chem. Soc*. **1953**, 3864.
[39] Ellison, R.A.; Lukenbach, E.R. ; Chiu, C.W. *Tetrahedron Lett*. **1975**, *46*, 499.
[40] Colvin, E.W.; Raphael, R.A.; Roberts, J.S.; *Chem. Commun*. **1971**, 858.
[41] Balme, G.; Gore, J. *J. Org. Chem*. **1983**, *48*, 3336.
[42] (a) Ukaji, Y.; Koumoto, N.; Fujisawa, T. Chem. Lett. 1989, 1623. (b) Wu, S.H.; Ding, Z.B. *Syn. Commun*. **1994**, *24*, 2173.
[43] Jung, M.E.; Andrus, W.A.; Ornstein, P.L. *Tetrahedron Lett*. **1977**, *48*, 4178.
[44] Suzuki, Y.; Mori, W. *Chem. Lett*. **1989**, 901.

Furthermore, allylation of the carbonyl group in isoquinolone **119** with allyllithium **137**, in situ prepared from phenyllithium **135** and allyltriphenyltin **136** in THF at room temperature,[45] succeeded. Compound **140** was isolated as a single diastereomer. The reaction took place smoothly at –78°C. After 1 hour the product was obtained with 88% yield (Scheme 47).



119 **140** **141**

Scheme 47: Synthesis of diallyl isoquinoline **140** and elimination of hydroxyl group

Reagents and Conditions: a) **135** and **136**, THF, rt. 30 min. then **119**, 1 h., -78°C, methanol, 88%. b) MsCl, *t*-BuOK, DMSO, 120°C, 38%.

Intending to complete the synthesis of the exocyclic double bond, the OH-group had to be eliminated. Unfortunately, the butandienyl isoquinoline **141** was as difficult to obtain as worried about. The attempts to eliminate the tertiary hydroxyl group in compound **140** under basic and neutralized conditions failed as well as the protection of the hydroxyl group with TMSCl. Only treatment with MsCl in the presence of *t*-BuOK gave the product with a poor yield (Table 2.2).

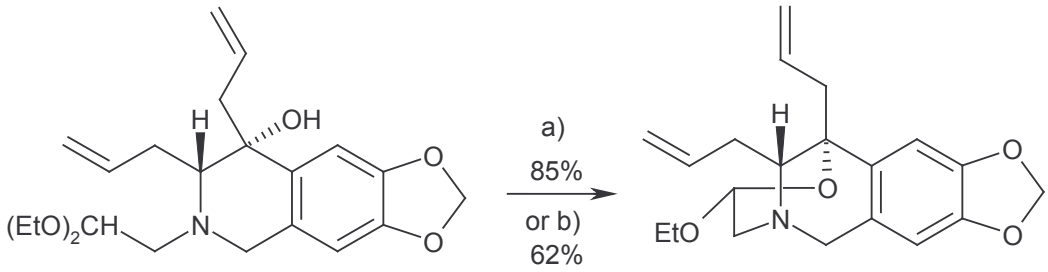
[45] Tamaru, Y.; Harada, T.; Nishi, S.; Yoshida, Z. *Tetrahedron Lett*. **1982**, *23*, 2383.

Reagent	Base / Solvent	Temperature	Time	Result
MsCl	Et_3N / THF	20°C	5 h.	no reaction
MsCl	Pyridine / -	80°C	20 h.	no reaction
MsCl	NaH / THF	0°C to rt	5 h.	decomposed
$SOCl_2$	Pyridine / THF	20 °C	3 h.	decomposed
$SOCl_2$	Et_3N / THF	0°C	3 h.	decomposed
$(CF_3SO_2)_2O$	DBU / THF	20°C	1 h.	decomposed
$(CF_3SO_2)_2O$	Pyridine / THF	0°C	1 h.	decomposed
Burgess[46] reagent	– / CH_3CN	50°C	1 h.	decomposed
MsCl	t-BuOK/DMSO	120°C	20 h.	**141** (38%)
TMSCl	NaH / THF	0°C to rt	20 h.	no reaction

Table 2.2: Reagents were tested to eliminate the tertiary hydroxyl in compound **140**

The failure of the acetal cleavage and OH-elimination using the hard oxygenophilic lewis acids was unexpected. The reaction with $SmCl_3$ in the presence of acetyl chloride induced an intramolecular acetal transformation to give a second six membered ring (Scheme 48). Further attempts to cleave the new ethyl acetal with 3 M HCl was not successful.

[46] Burgess, E.M.; Penton, H.R. J_R.; Taylor, E.A. *J. Org. Chem*. **1973**, *38*, 26.



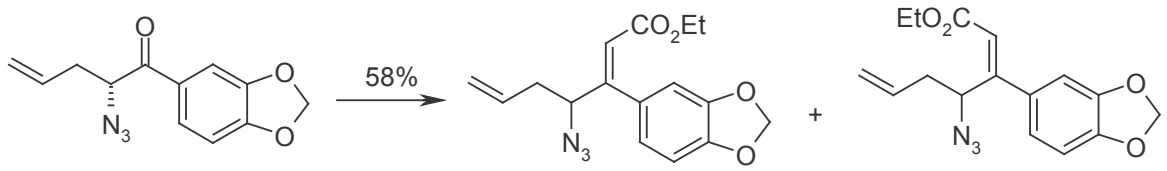
140 **144**

Scheme 48: Intramolecular acetal transformation under acid conditions

Reagents and Conditions: a) $SmCl_3$, acetyl chloride, $CHCl_3$, rt, 30 min, then NaOH, 85%. (b) 1 M HCl, 50°C, 20 h. then NaOH, 62%.

2.8 Transformations of the Acyclic Ketones

Azido ketone **130** could be defined as an acyclic isoquinoline precursor. Intending to convert the ketone moiety into an olefin, several processes had been tested. Initially, Horner reagent[67] (triethyl phosphonoacetate) was deprotonated with LDA in THF at –40°C for 1 hour. Then, a solution of acyclic α-azido ketone **130** was injected, the mixture was then stirred at –20°C to afford two isomers *E*-**145** and *Z*-**145** in a ratio of 2 to 1 in 58% yield (Scheme 49). Disappointingly, the two compounds displayed no optical rotation indicating racemization within the whole sequence.

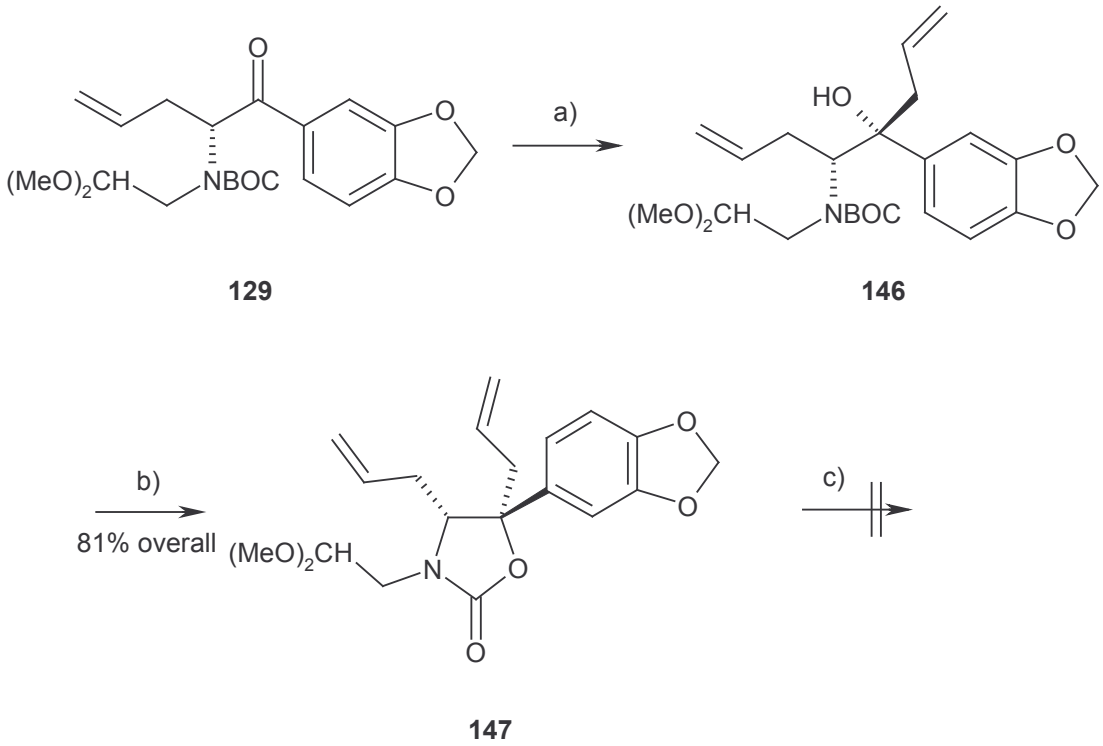


130 *E*-**145** *Z*-**145**

Scheme 49: Synthesis of *E*- and *Z*-**145** from α-azido ketone **130**

Reagents and Conditions: triethyl phosphonoacetate, LDA, -40°C, 1 h., then **130**, -20°C, 20 h., *syn*-**145** 38.8%, *anti*-**145**, 19.4 %.

Alternatively, an allylation elimination sequence should enable to introduce the desired olefin. Thus, diallyl **146** was achieved smoothly after treatment of the α-amino ketone **129** with allyllithium **137** in THF at −78°C (Scheme 50). The avoiding of any transacetalization processes recommended (basic and neutral elimination conditions, see chapter 2.7, page 52). Initially, a leaving group had to be built-up intending to eliminate the tertiary hydroxyl group under basic condition. It was assumed, that the tertiary hydroxyl should have been smoothly deprotonated by means of KHMDS, the deprotonated oxygen would have to attack MsCl to form a good leaving group, and finally, the presence of KHMDS should have induced elimination to construct a conjugated double bond.



129 **146** **147**

Scheme 50: Synthesis of carboxamide **147**

Reagents and Conditions: a) allyllithium **137**, THF, -78°C b) KHMDS, THF, 0°C, 30 min., 81% (2 steps) c) Lawesson's reagent, xylene, reflux.

Surprisingly, a cyclic carboxamide **147** was formed indicating the nucleophilic attack of the potassium alcoholate at the carbonyl group of the BOC-function and a subsequent t-BuOH release. A related "basic Boc-cleavage" supported the outcome of the reaction: diallyl **146** was treated with KHMDS in THF at 0°C without MsCl, and after 30 minutes the formation of the carboxamide **147** was completed with good yield. Obviously, the alcoholate induced a rapid five-exo-trig cyclization even with a sterically encumbered system like a Boc-group. The NOESY spectra had shown, that the second allyl chain in compound **147** was arranged anti with respect to the nitrogen (Figure 2.9).

The cyclic carboxamide **147** did not undergo ring opening even upon heating in 2 M NaOH. Furthermore, the treatment of the carboxamide **147** with Lawesson's reagent[47] in xylene under reflux gave no corresponding thionocarbamate.

[47] (a) Shiebye, S.; Pederson, B.S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg*. **1978**, *87*, 229. (b) For a review on the use of Lawesson's reagent, see: Cava, M.; Levinson, M.I. *Tetrahedron* **1985**, *41*, 5061.

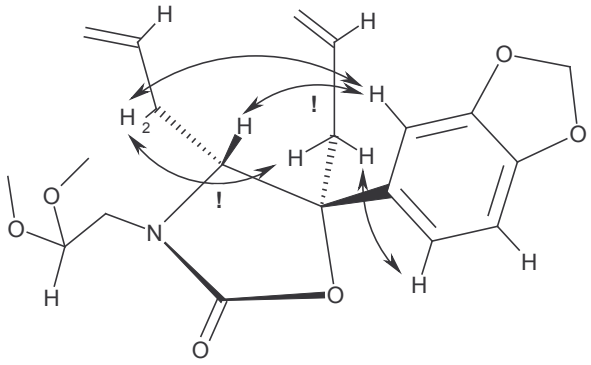
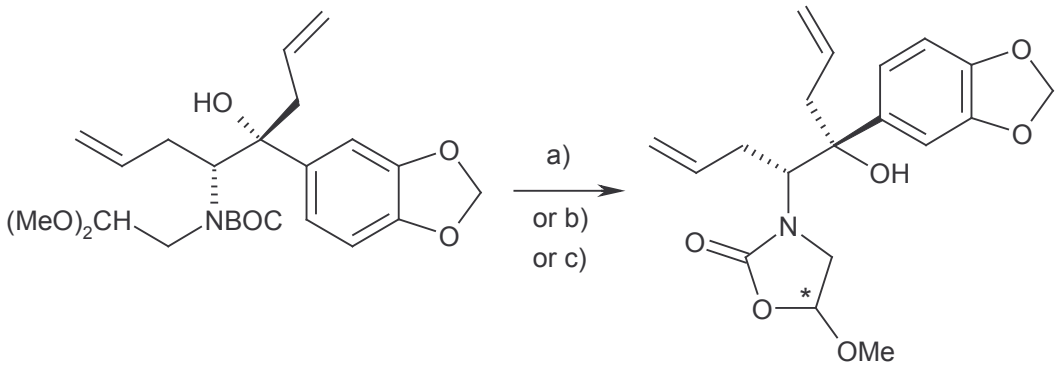


Figure 2.9: relevant NOE's of **147** from NOESY

The failure of the basic OH-elimination forced to test some acid mediated reactions. Again, trans-acetalization proceeded. Alternatively, the diallyl **146** was heated with DMSO-H_2O, and treated with $SmCl_3$ in the presence of acetyl chloride[75 (b)] in $CHCl_3$ at room temperature, and treated with $SOCl_2$ in methanol at 0°C to give cyclic carbamates **150** (Scheme 51), respectively. Always, a smooth conversion into oxazolidinone **150** (mixture of diastereomers) had been observed indicating an overall loss of methanol and 2-methyl propene.



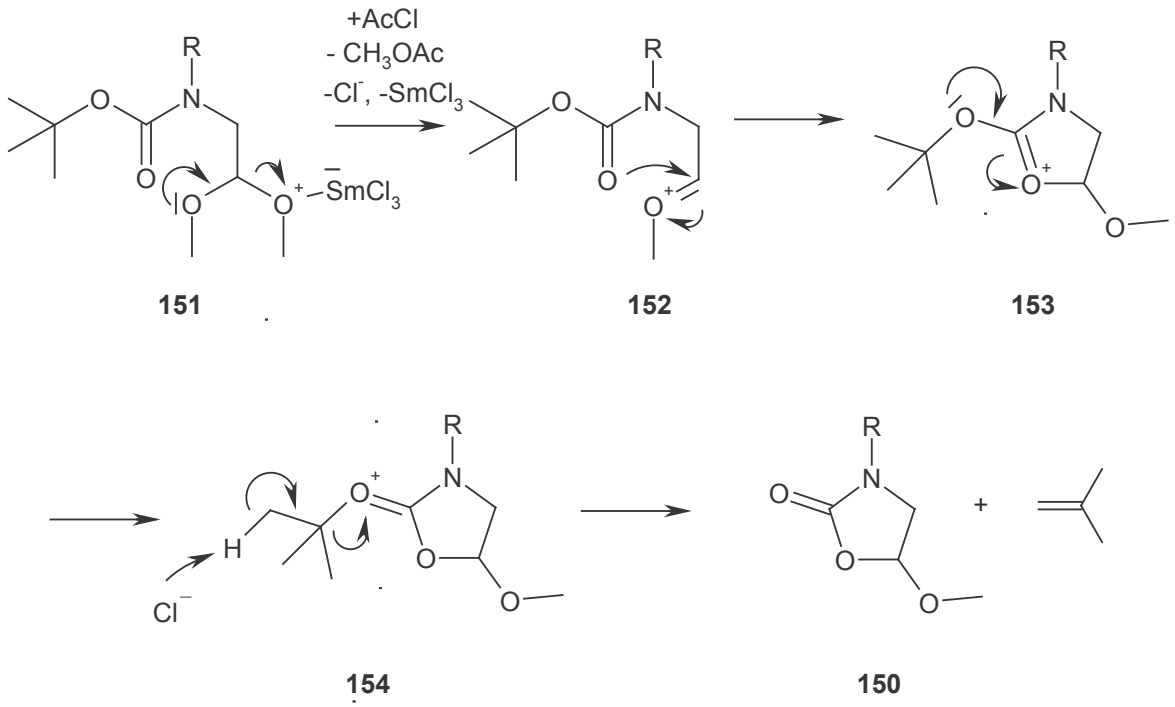
146 **150**

Scheme 51 Intramolecular acetal transformation

Reagents and Conditions: a) DMSO-H_2O, 80-90°C, 20 h., 74%. b) $SmCl_3$, acetyl chloride, rt, 30 min. 66%. c) $SOCl_2$, MeOH, 0°C, 3 h. 57%.

The reaction pathway could be rationalized as depicted in Scheme 52 (example conditions: $SmCl_3$ / AcCl). The initial attack of the oxygen lone pair on the Lewis-acid $SmCl_3$ afforded the intermediate **151**, which should have suffered from an immediate loss of MeO^- to form the oxonium ion **152**. Then, the oxygen of the carbamate attacked oxonium ion to close a five membered ring **153** (and **154** mesomer). Finally, HCl and *iso*-butene had been eliminated to

generate the cyclic carbamate **150**. In the presence of AcCl, the $[MeO\text{-}SmCl_3]^-$ should give AcOMe and regenerated $SmCl_3$ and Cl^-.

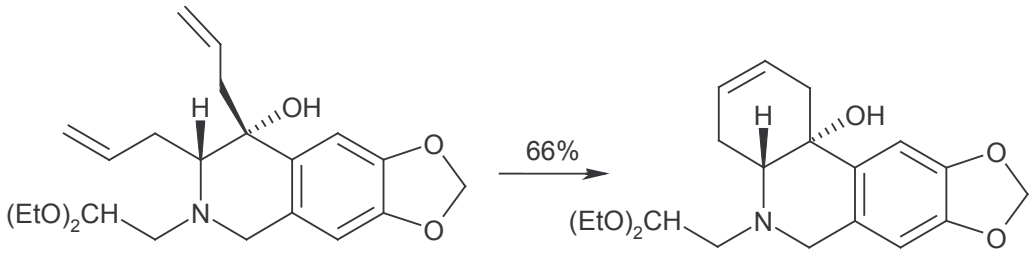


Scheme 52 : Rationalization of the intramolecular acetal transformation

2.9 Ring-Closing Olefin Metathesis with Grubbs Catalyst

Intending to generate suitable precursors of amaryllidaceae alkaloid, six membered ring closures had been testet. The 1,2-diallyl amino alcohol derivatives had been readily prepared to investigate ring-closing metathesis (RCM). Taking into account that the Grubbs I catalyst **40** is air and moisture sensitive, all RCM were carefully run under argon atmosphere.

First test had been performed with compound **140** even though this compound was characterized by a still basic nitrogen function. Such basic nitrogen was known to decelerate RCM. Treatment of compound **140** with 5 mol% Grubbs I catalyst **40** in CH_2Cl_2 upon heating to reflux for 4 hours, TLC of the reaction mixture analysis displayed only some new product in addition to a major reactant **140** spot. Continuing refluxing for another 20 hours resulted only few more conversion. Thus, more catalyst and a prolonged reaction time were found to be necessary to achieve the complete transformation of compound **140** into **141**. Finally, this special reaction required 20 mol% catalyst and a reaction time of at least 96 hours to obtain a satisfying result: compound **142** was formed in 66% yield as a single product (Scheme 53).

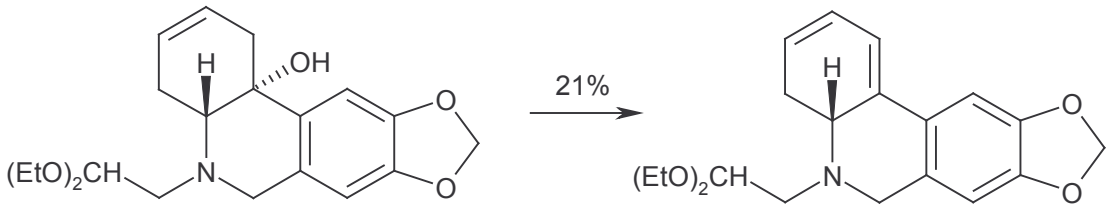


140 **142**

Scheme 53: Synthesis of **142** via RCM

Reagents and Conditions: 20 mol% Grubbs catalyst **40**, CH_2Cl_2, reflux, 96 h., 66%.

The attempts to eliminate the tertiary hydroxyl group in compound **142** under basic and neutralized conditions failed. Only treatment with MsCl in the presence of *t*-BuOK gave the product **143** with a poor yield (Scheme 54).

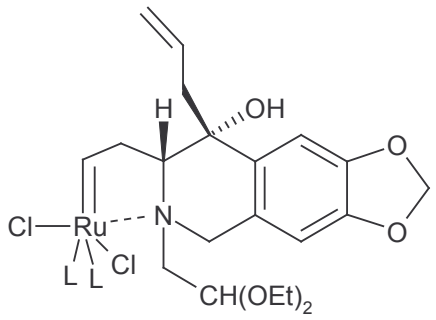


142 **143**

Scheme 54: Elimination of the tertiary hydroxyl group of **142**

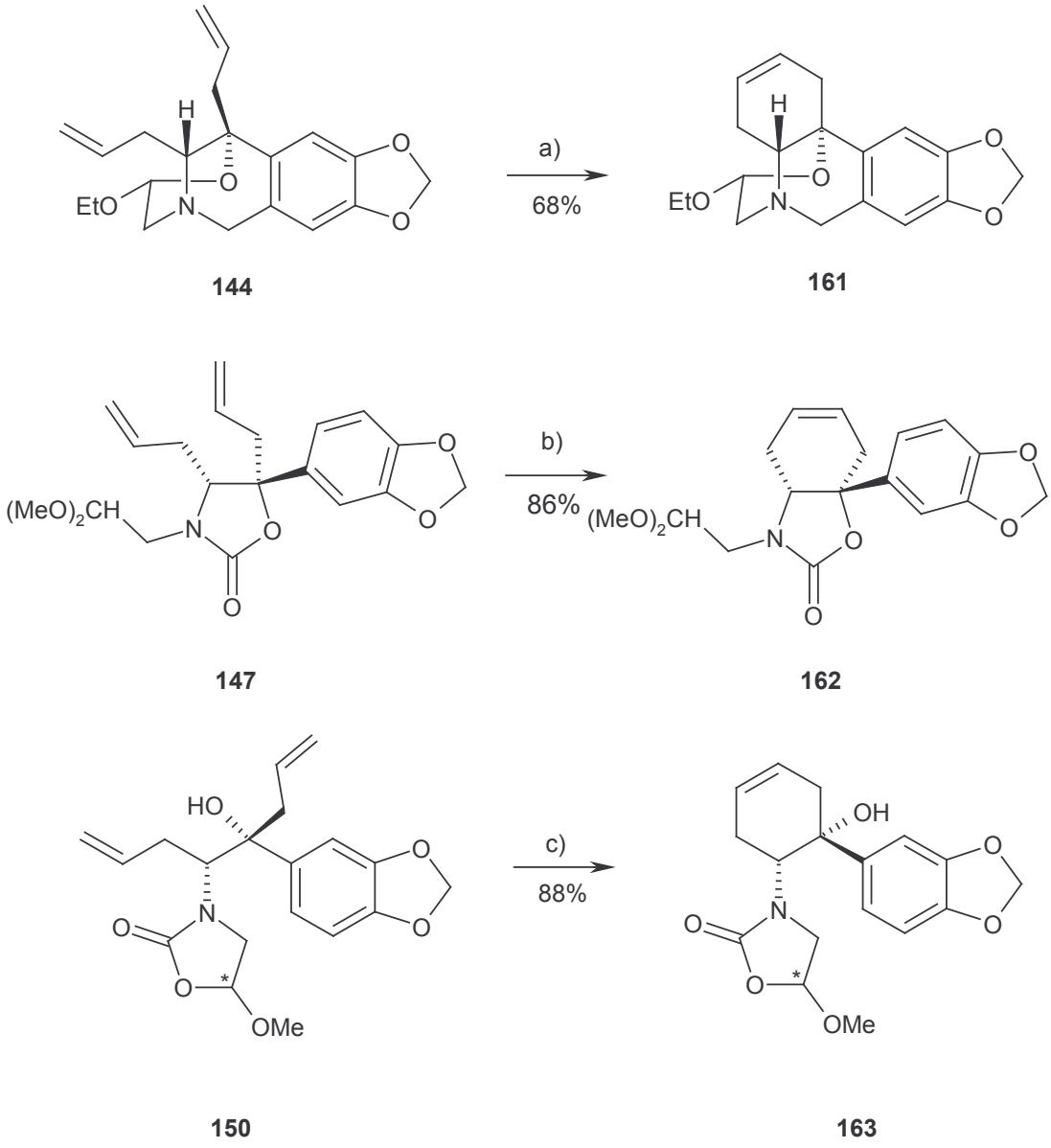
Reagents and Conditions: MsCl, *t*-BuOK, DMSO, 120°C, 21%.

In contrast to well known six membered ring forming RCM, the present reaction was found to be very slow. Presumably, the basic nitrogen served as an efficient ligand to complex the ruthenium-catalyst itself or as a more or less stable five membered ring carbeniod **160** (Figure 2.10). However, the decelerated release of the catalyst was thought to be the result of the slow and moderate yielding RCM reaction.



160

Figure 2.10: Five membered ring **160**



Scheme 55: Ring-closing metathesis of **144**, **147** and **150**

Reagents and Conditions: a) 20 mol% Grubbs catalyst **40**, CH_2Cl_2, reflux, 96 h., 68%. b) 5 mol% Grubbs catalyst **40**, CH_2Cl_2, reflux, 3 h., 86%. c) 5 mol% Grubbs catalyst **40**, CH_2Cl_2, reflux, 3 h., 88%.

A related result had been obtained subjecting compound **144** to the RCM conditions, 20 mol% catalyst and 96 hours refluxing in CH_2Cl_2 gave compound **161** with 68% yield (Scheme 55).

In contrast, carbamate protected nitrogen RCM precursors allowed smooth reactions. Upon treating cyclic carbamates **147** and **150** with 5 mol% catalyst, the reactions were completed within 3 hours to afford the **162** and **163** in 86% and 88% yield (Scheme 55).

However, compounds **141**, **161**, **162** and **163** should serve as useful precursors for amaryllidaceae alkaloid syntheses.

2.10 Summary and Outlook

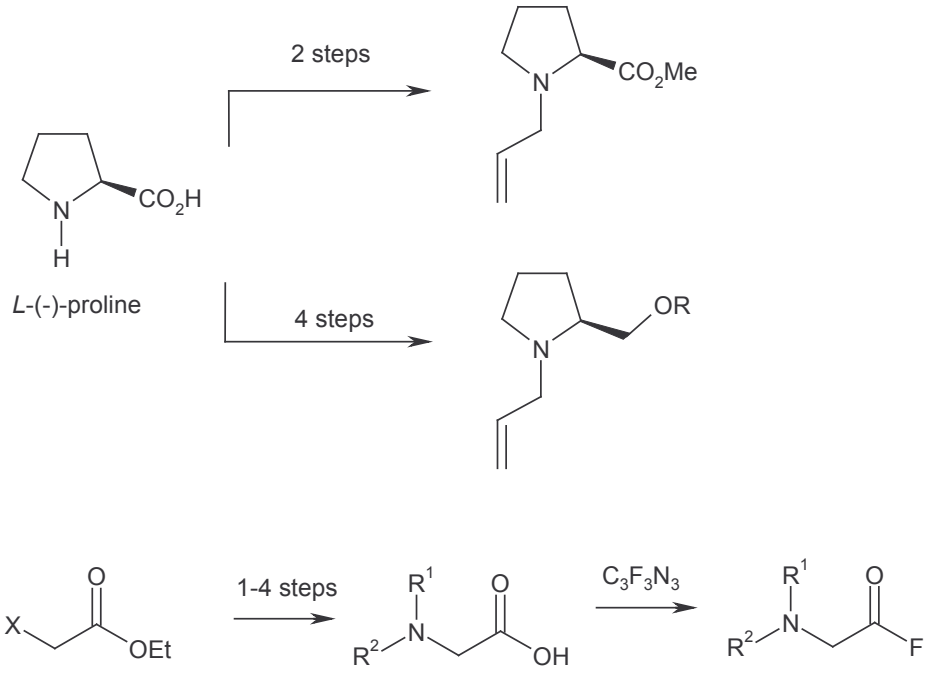
2.10.1 Summary

In this work, a highly flexible and efficient new synthetic route has been developed to generate various optically active *C*-allylglycine derivatives. Likewise, *R* and *S* absolute configurations could be introduced selectively by choosing an appropriate strategy.

An auxiliary directed zwitterionic aza-Claisen rearrangement served as the key reaction to obtain γ,δ-unsaturated α-amino acid amides with acceptable yields and high diastereo-selectivity.

Various *N*-allyl proline derivatives and α-chloro as well as α-amino acetyl fluorides have been synthesized as suitable starting compounds.

Ex-chiral-pool syntheses enable to obtain the optically active *N*-allyl pyrrolidines. Only two to four steps were necessary starting from *L*-(-)-proline, the yields varied between 57%-70% overall. The α-substituted acetyl fluorides have been synthesized starting from glycine and α-halogen acetic acid, respectively. One to four steps allowed to produce the carboxylic acids with high yields. Finally, a very mild cyanuric fluoride mediated conversion enabled to obtain the corresponding acetyl fluorides with sufficient purity and activity (Scheme 56).

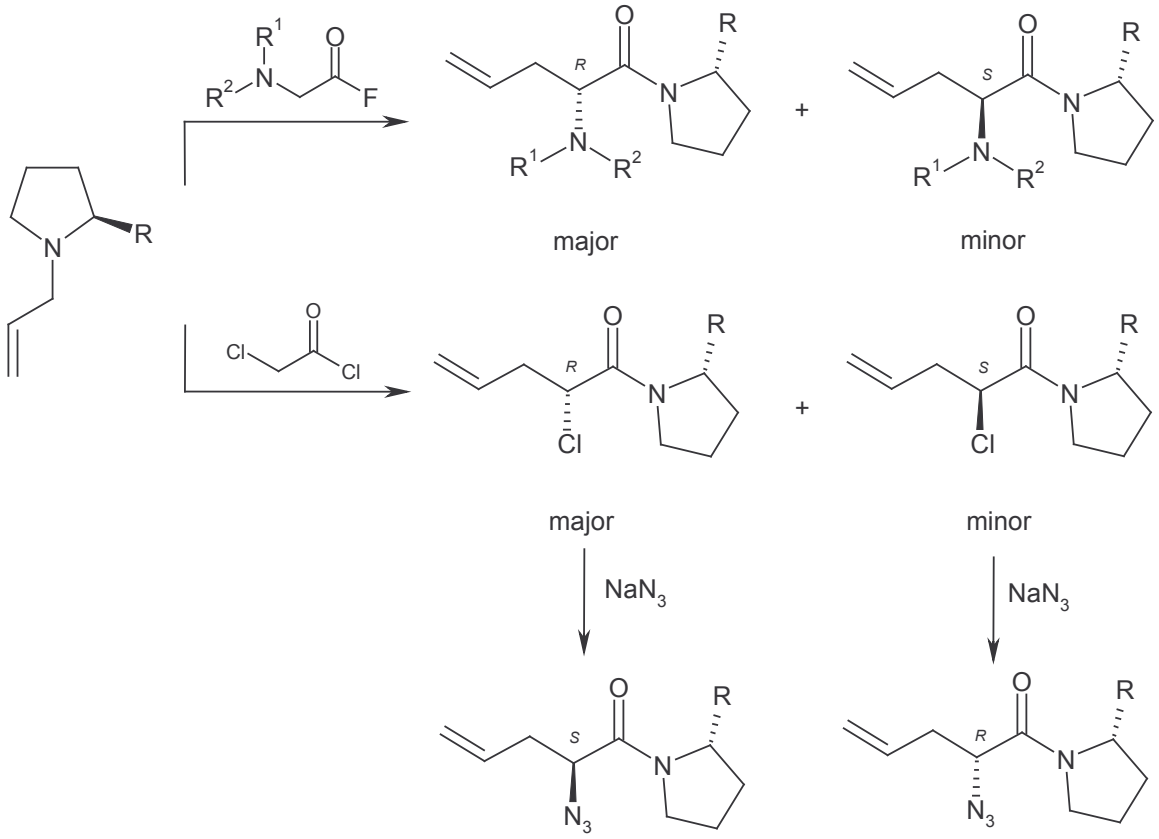


Scheme 56: Syntheses of *N*-allyl proline derivatives and α-amino acetyl fluorides

The zwitterionic aza-Claisen rearrangement can be seen as an auxiliary directed α-allylation of carboxylic acid derivatives. *N*-Allyl pyrrolidines and acid fluorides underwent the addition rearrangement sequence to give the γ,δ-unsaturated amides with moderate to high yields and low to very high diastereoselectivities depending on the substitution patterns of the starting materials. Since the reactions of the ester auxiliaries and acid fluorides bearing small nitrogen substituents gave the product amides with low diastereoselectivity, more bulky amino acid fluorides rearranged with high asymmetric induction. However, the use of the prolinol derivatives enabled to obtain maximal diastereoselectivities independently of the acid fluoride substitution pattern.

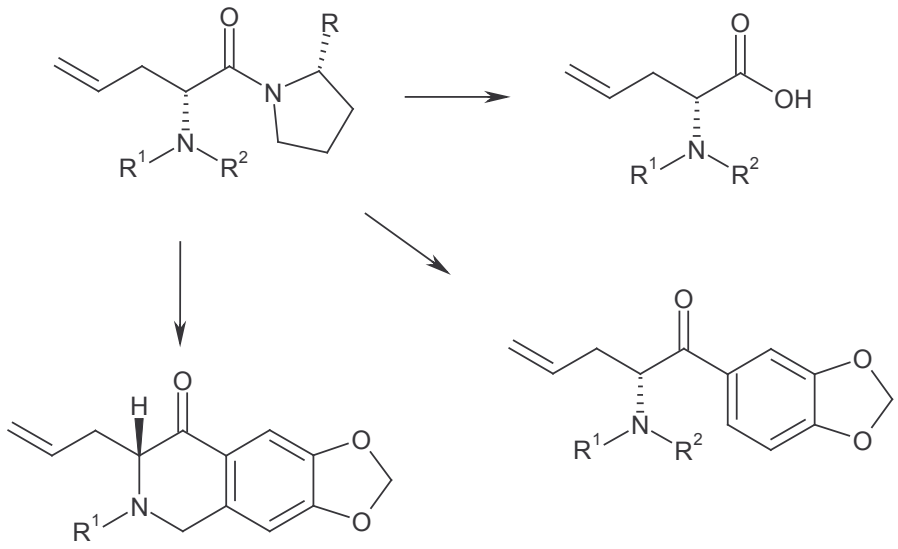
Several independent sequences allowed to prove the absolute configuration of the new stereogenic center: The *S*-proline derivatives caused the formation of (*R*)-*C*-allylglycines.

The generation of (*R*)-2-chloropentenioc acid amides allowed to obtain the (*S*)-*C*-allylglycine series after a S_N2-reaction with NaN_3 with complete inversion of the configuration (Scheme 57).



Scheme 57: Zwitterionic aza-Claisen rearrangement and inversion of the new stereogenic center

Finally, the chiral auxiliary could be removed by means of an acid mediated solvolysis and a organolithium addition leading to α-amino ketones, respectively (Scheme 58). This latter method enable to combine auxiliary removal and C-C bond formation in a single step. It should be pointed out, that the strong basic conditions of the Grignard type reaction risked a potential racemization of the stereogenic center, careful optimization of the reaction conditions and structural proofs were mandatory!



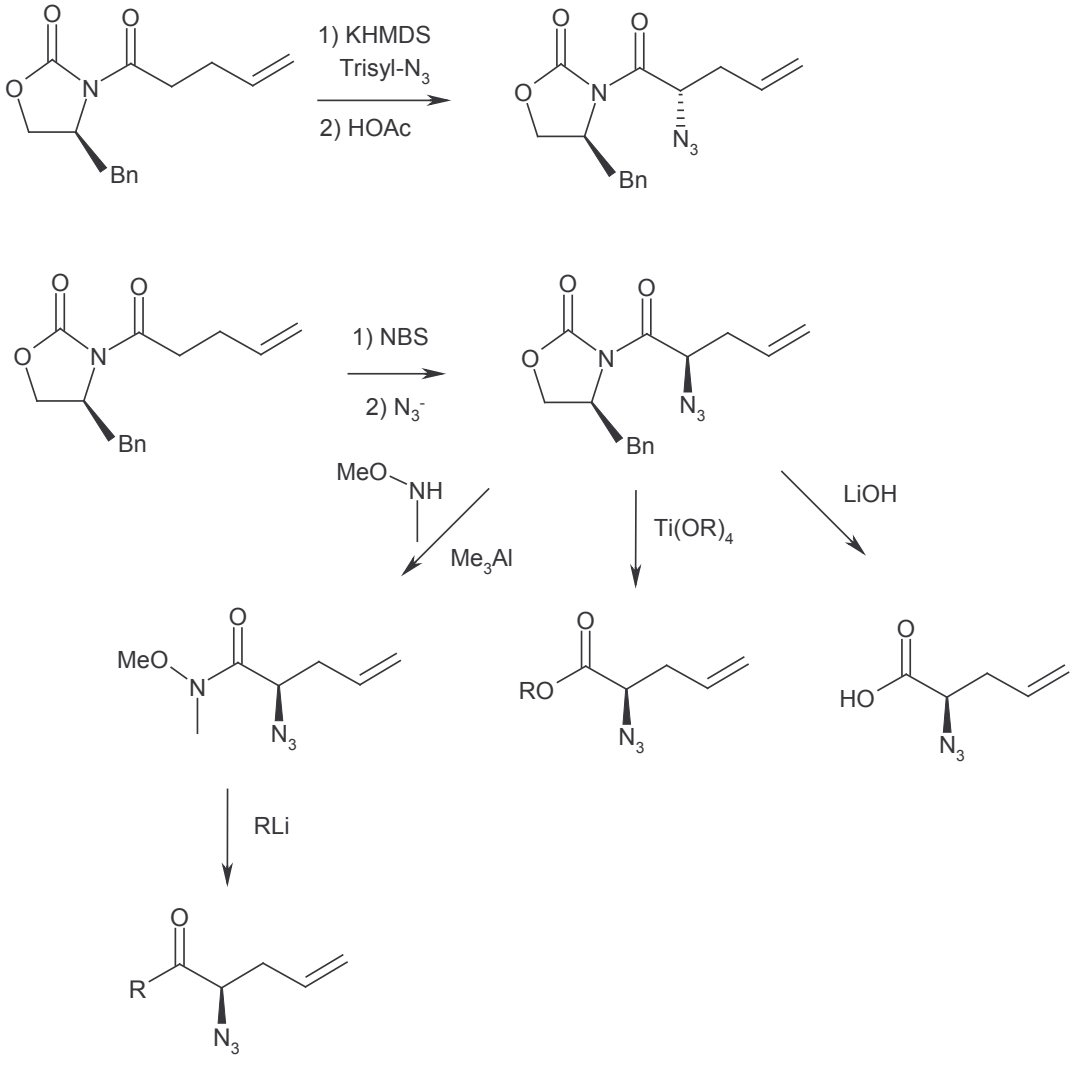
Scheme 58: Cleavage of the auxiliary

Intending to rank the new C-allyl glycine synthesis among the well known procedures, a direct comparison with the broadly applied Evans variant should be presented in Table 2.3.

	Zwitterionic aza-Claisen rearrangement	**Evans Variant** (Scheme 59)
Yield: α–azido	76%-79%	78%
BOCNR, CbzNR	73%-82%	–
α–halogen and azide displacement (2 steps)	69% (should be optimized)	83%
Diasteroselectivity: α–azido	9.5:1	97:3
BOCNR	> 15:1	–

α–halogen	> 20:1	94:6
azide displacement	> 99:1	> 99:1
Substitution patterns	N_3, Cl, PhtN, BocNR, CbzNR	N_3, Cl, Br
Cleavage of the auxiliary	a) 2M H_2SO_4 → acid b) CH_3COCl, ROH[62] → ester c) organolithium → ketone	a) LiOH → acid b) $Ti(OR)_4$ → ester c) 2 steps to ketone
Auxiliary recycling	not investigated but potentially not so easy	easy

Table 2.3: Comparison of the zwitterionic aza-Claisen rearrangement with the synthesis of *C*-allylglycine derivatives by Evans (chapter 1.1.3, page 5-6)



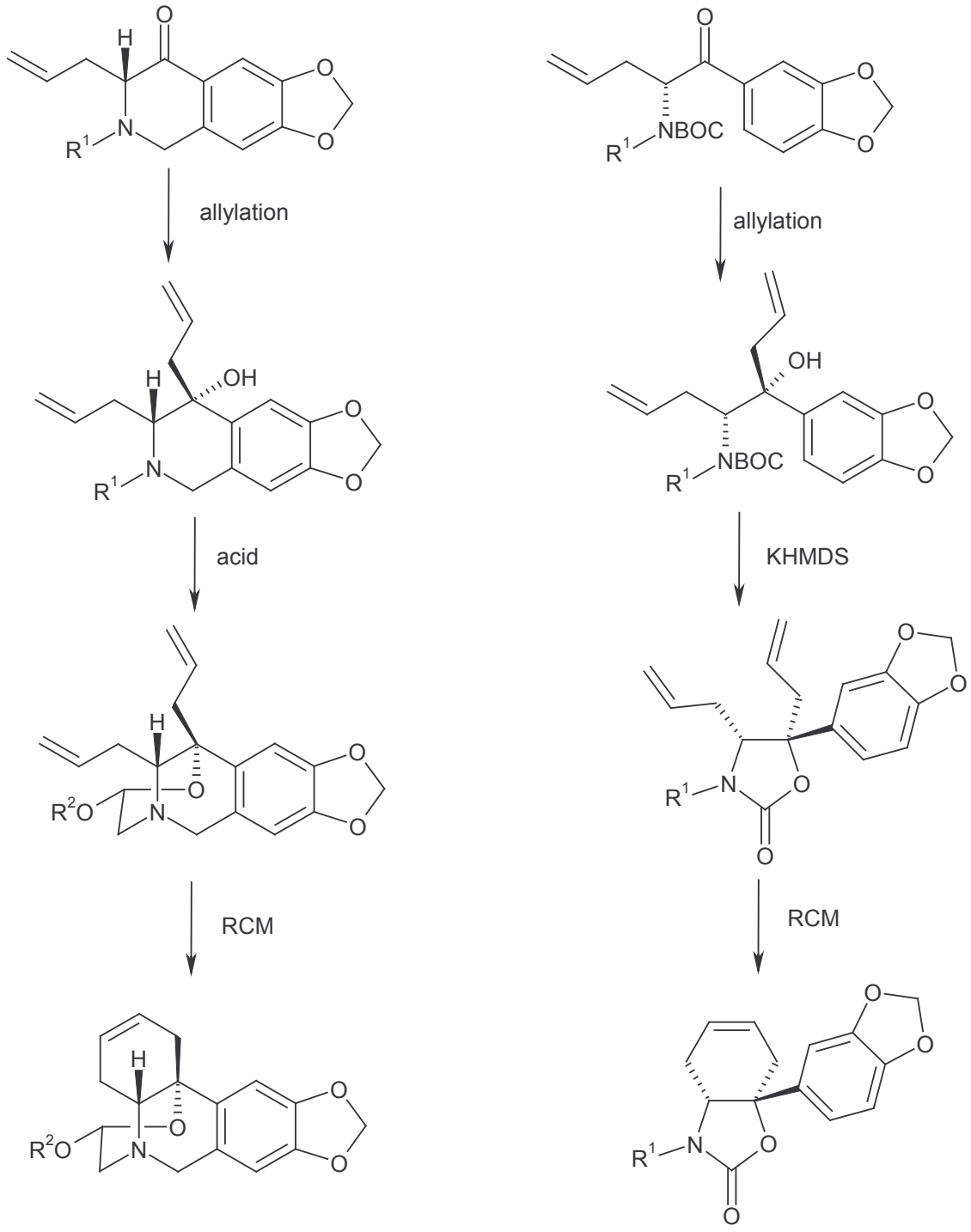
Scheme 59: Evans variant and auxiliary cleavage

As shown in Table 2.3, the yield of the zwitterionic aza-Claisen rearrangement with azidoacetyl fluoride and tertiary allylamine was as good as the synthesis of *C*-allylglycine derivatives by Evans. The diastereoselectivities obtained via the Evans variant seemed slightly better. Building-up α-halogen amide derivatives, the zwitterionic aza-Claisen rearrangement was characterized by a higher diastereoselectivity, however, the yield was somewhat lower in comparison to the Evans protocol.

In addition to the α-azido and α-halogen amide derivatives, the zwitterionic aza-Claisen rearrangement could also afford *C*-allylglycine derivatives with various functional groups on the nitrogen. Thus, numerous *C*-allylglycine derivatives could be synthesized via the zwitterionic aza-Claisen rearrangement without further modifications of the nitrogen.

The chiral auxiliary could be removed under acidic conditions to generate carboxylic acids or esters in one step. Furthermore, the chiral auxiliary could be removed by treating the amides with organolithium reagents. Auxiliary cleavage and C-C bond formation could be combined in a single step. An analogous formation starting from Evans intermediates required at least two steps: The first step was imide weinreb amide transformation, the second was the generation of the corresponding ketone.

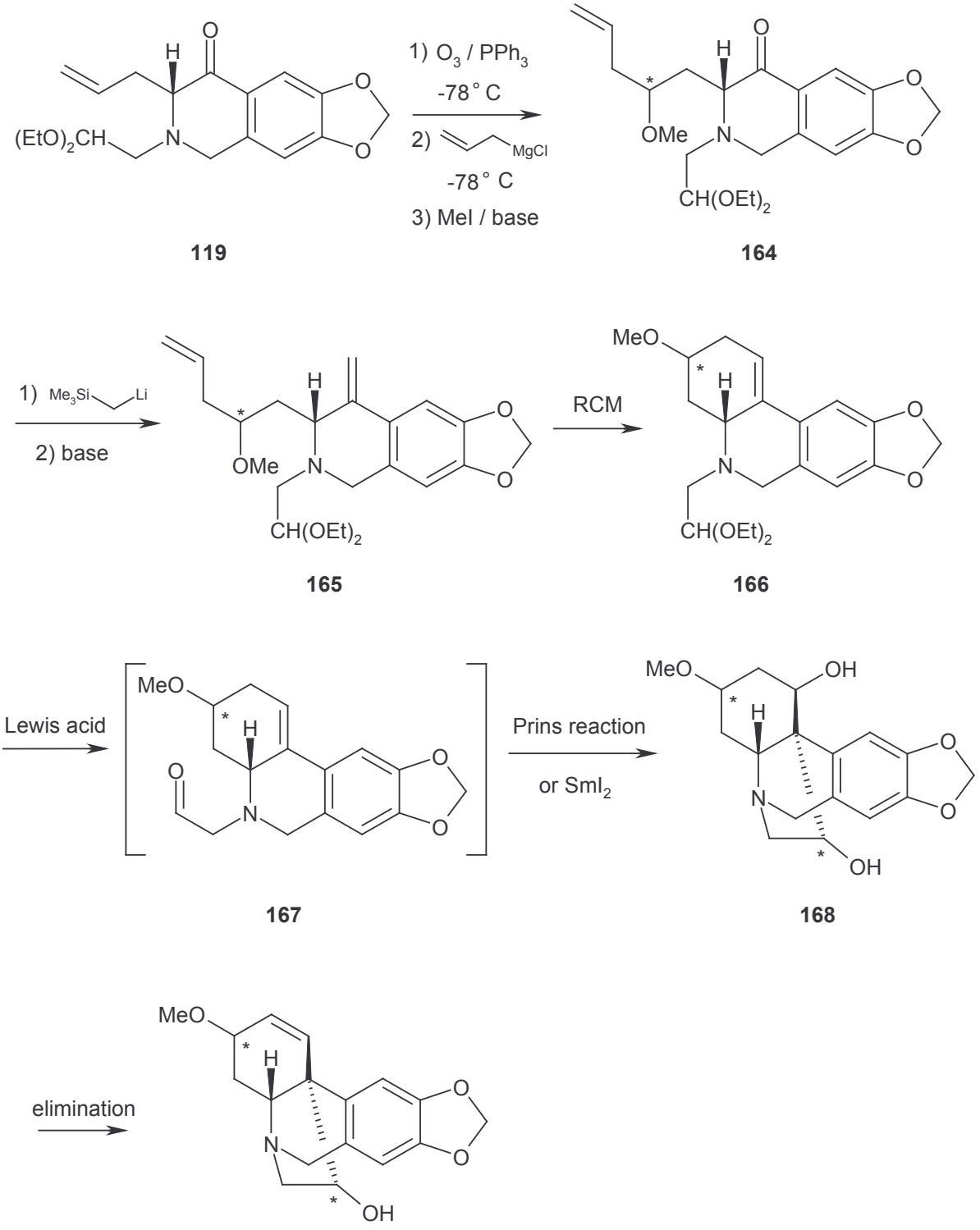
Intending to use the rearrangement products for amaryllidaceae alkaloid total syntheses, the introduction of the piperonyl substituent and first ring closure have been investigated. The isoquinolone and acyclic piperonyl ketone, prepared from the products of the zwitterionic aza-Claisen rearrangement could be introduced with allyllithium reagent to generate diallyl compound, which could be converted into a six membered ring via ring-closing metathesis (Scheme 60).



Scheme 60: Allylation and RCM of isoquinolone and acyclic piperonyl ketone

2.10.2 Outlook

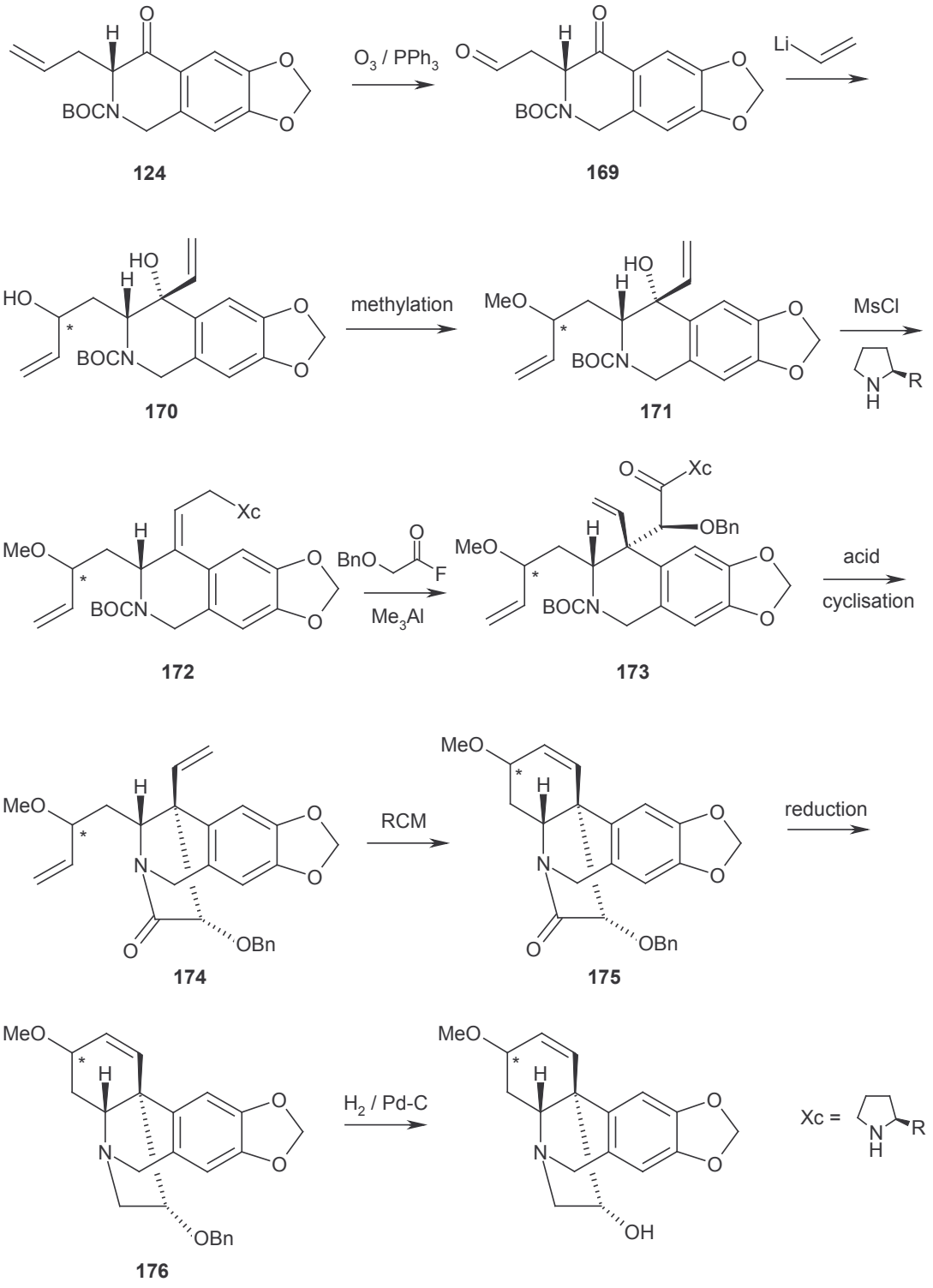
Especially, the bicyclic quinolizidinone derivatives should represent useful key intermediate to start amaryllidaceae alkaloid total syntheses.



Scheme 61: Possible synthesis route of (±)-Crinamine from compound **119**

Starting from the isoquinolone **119**, double bond ozonolysis should deliver the corresponding aldehyde. A subsequent allylation with allyl magnesium chloride and *O*-methylation with methyl iodide should generate the compound **164**. The keto-function could be converted into exo-methylene isoquinoline **165** via Peterson-olefination. The second six-membered ring should be obtained smoothly by RCM. After treatment of compound **166** with a suitable Lewis acid, the acetal-group should be cleaved to achieve aldehyde **167**. A Prins-type cyclization should enable to generate the tricycle amine **168**. Alternatively, a SmI_2-induced radical cyclization should also accomplish this task. The Crinamine should be generated by a regio-selective OH-group elimination. Overall, eight steps seem to be necessary to complete the enantioselective total synthesis of the crinamine (Scheme 61).

Alternatively, *N*-BOB-isoquinolone **124** should serve as a starting compound. After ozonolysis of the double bond (to aldehyde **169**) a double vinyl lithium addition should generate diol **170**. The less hindered OH-group should be protected as a methyl ether **171**. After treatment of **171** with mesyl chloride and a chiral pyrrolidine, a S_N2' reaction should take place to give the compound **172**. Then zwitterionic aza-Claisen rearrangement should be run under standard conditions with benzoxyl acetyl fluoride to generate the compound **173**. After acidic cleavage of the Boc-group, a subsequent intramolecular cyclization should take place to obtain the amide **174**. The taking six-membered ring should be built-up by ring-closing metathesis. Final reduction of the amide and cleavage of the benzyl-group should allow to complete the Crinamine total synthesis (Scheme 62).



(±)-Crinamine

Scheme 62: Possible synthesis route of (±)-Crinamine from compound **124**