Asymmetric Synthesis of Trisubstituted Isoindolines and Tetrahydropalmatine *via* Tandem 1,2-Addition/Cyclisation

Von der Fakultät für Mathematik, Informatik und Naturwissenschaften
der Rheinisch-Westfälischen Technischen Hochschule Aachen
zur Erlangung des akademischen Grades einer Doktorin
der Naturwissenschaften genehmigte Dissertation

vorgelegt von

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The present work has been carried out at the Institute of Organic Chemistry of the Rheinisch-Westfälische Technische Hochschule Aachen under the supervision of Prof. Dr. Dieter Enders between September 2001 and October 2004.

Parts of this work have been published or will be published:

ASYMMETRIC SYNTHESIS OF 3-SUBSTITUTED DIHYDRO-2*H*-ISOQUINOLIN-1-ONES, DIHYDRO- AND TETRAHYDROISOQUINOLINES VIA 1,2-ADDITION/RING CLOSURE
D. Enders, V. Braig, M. Boudou, G. Raabe, *Synthesis* **2004**, 2980-2990.

ASYMMETRIC SYNTHESES OF FOUR-, FIVE- AND SIX-MEMBERED *N*-HETEROCYCLES EMPLOYING THE SAMP/RAMP-HYDRAZONE METHODOLOGY
D. Enders, M. Boudou, J. Gries in *New Methods for the Asymmetric Synthesis of Nitrogen Heterocycles*; J. L. Vicario, D. Badía, J. Carillo, Eds.; Research Signpost: Trivandrum, **2005**, *in press*.

ASYMMETRIC SYNTHESIS OF TETRAHYDROPALMATINE VIA TANDEM 1,2-ADDITION/ CYCLISATION
M. Boudou, D. Enders, *J. Org. Chem.*, *submitted*.

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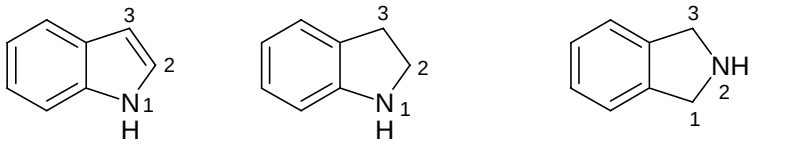
1. INTRODUCTION

1.1 ISOINDOLINES

In the nomenclature, the isoindolines are related to the heterocycle 1*H*-indole (**1**) (benzopyrrole), a fused ring system composed of a 5- and a 6-membered ring. As its dihydrogenated derivative is the 2,3-dihydro-1*H*-indole or indoline (**2**), the dihydrogenated heterocycle possessing the nitrogen in the 2-position is called 2,3-dihydro-1*H*-isoindole or isoindoline (**3**) (Figure 1).



1 1*H*-indole

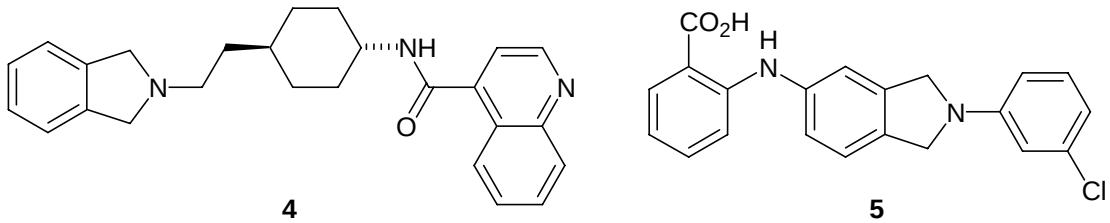
2 indoline or 2,3-dihydro-1*H*-indole

3 isoindoline or 2,3-dihydro-1*H*-isoindole

Figure 1: Nomenclature for the nitrogen heterocycles with a 5,6-fused ring system

1.1.1 STRUCTURE AND BIOLOGICAL ACTIVITY OF ISOINDOLINES

Several patents described the biological activity of *N*-substituted 2,3-dihydro-1*H*-isoindoles. For example the quinoline-containing compound **4** is a potent modulator of dopamine D_3 receptors and could therefore act as an antipsychotic agent,[1] whereas the *N*- and 5-substituted isoindoline **5** was recognised as a potent inhibitor of the amyloid protein aggregation (IC_{50} = 1.1 μM) indicating an eventual capacity in the treatment of *Alzheimer*'s disease (Figure 2).[2]



4 **5**

Figure 2: *N*-substituted isoindolines with significant biological activity

The class of isoindolinones (2,3-dihydro-1*H*-isoindol-1-ones) has also attracted much attention since they represent the core unit of a wide range of naturally occurring and/or bioactive substances.[3] More particularly, enantiopure isoindolinones substituted at C-3 possess various biological properties. For example the thiazoloisoindolones **6** strongly inhibit the HIV-reverse transcriptase (IC_{50} = 16-300 nM),[4] the pazinaclone (**7**) (DN-2327) is an anxiolytic drug candidate[5] and both enantiomers of PD-172938 **8** are antagonists of the dopamine D_4 receptor[6] (Figure 3).

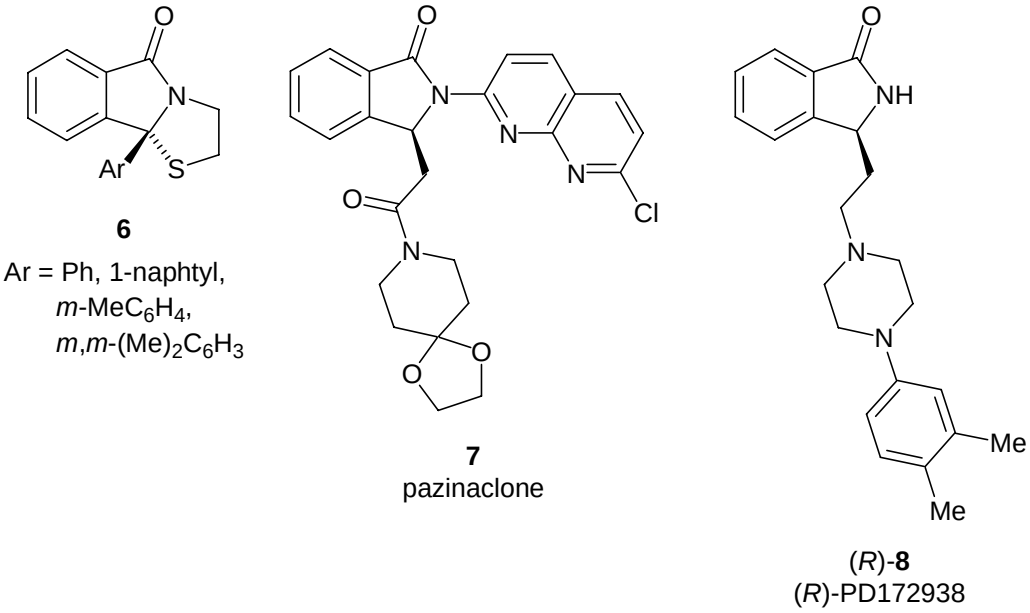
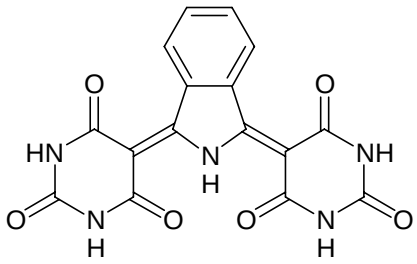
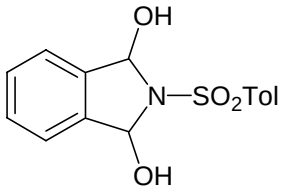


Figure 3: Examples of biologically active 2,3-dihydro-1*H*-isoindol-1-ones

The 1,3-substituted isoindolines, such as the pigment yellow 139 **9**, are mainly used in the industry of organic pigments due to their stability to oxidising and reducing agents, acids, bases and heat. They also display good resistance to light and weather and good migration behaviour.[7] In addition, a patent of the Kodak® company described the isoindoline **10** as additive for a heat developable photoimaging process (Figure 4).[8]



9
pigment yellow 139



10

Figure 4: 1,3-Substituted isoindolines employed in industry

To our knowledge only one 1,3-disubstituted isoindoline compound has been reported to be biologically active so far. In fact the *cis*- and *trans*-isomers of **11** are potent endothelin A (ET_A) receptor antagonists (Figure 5).[9]

The endothelins (ET), peptides consisting of 21 amino acids, are mainly released by vascular endothelial cells. There are three known subtypes, namely ET-1, ET-2, and ET-3, binding to at least two types of receptors, ET_A and ET_B. Elevated levels of ET-1 and of ET_A receptors and down-regulation of ET_B receptors were verified in diseases such as essential and pulmonary hypertension, congestive heart failure, and arteriosclerosis. Therefore, antagonism of the ET_A receptor is expected to be an effective way for treating these disorders.[10]

The indane dicarboxylic compound (*S*,*R*,*S*)-**12** has been described as one of the most potent dual ET_A/ET_B receptor antagonist.[11] Thus, *P. J. Kukkola et al.* envisioned that substitution of the indane ring system with an isoindoline bearing an acidic group attached to the nitrogen atom, should lead to a new class of endothelin antagonists with high affinity for both receptors. These disubstituted isoindolines, missing the chiral centre at the 2-position, should be synthetically more accessible than the indane 2-carboxylic acid analogues. Furthermore, introduction of a basic nitrogen to the backbone of the template might result in compounds with improved bioavailability. Surprisingly, all analogues of *trans*- and *cis*-**11** were both identified as selective ET_A receptor antagonists and both isomers of **11** were found to be the most potent (*trans*-**11**: ET_A-IC_{50} = 5.4 nM; *cis*-**11**: ET_A-IC_{50} = 4.1 nM) (Figure 5).[9b]

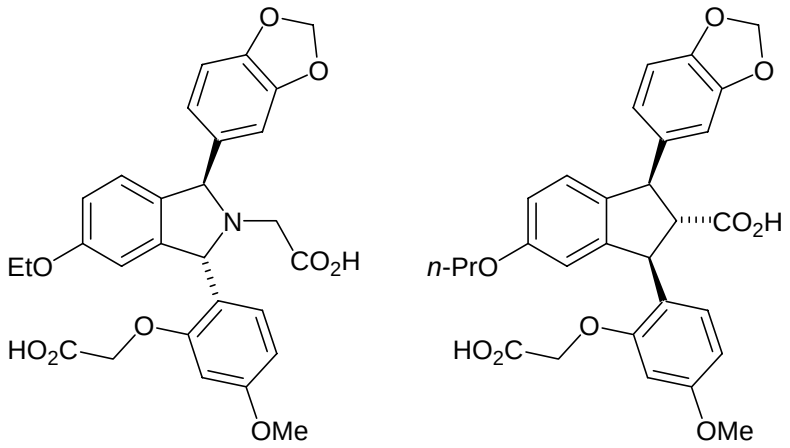
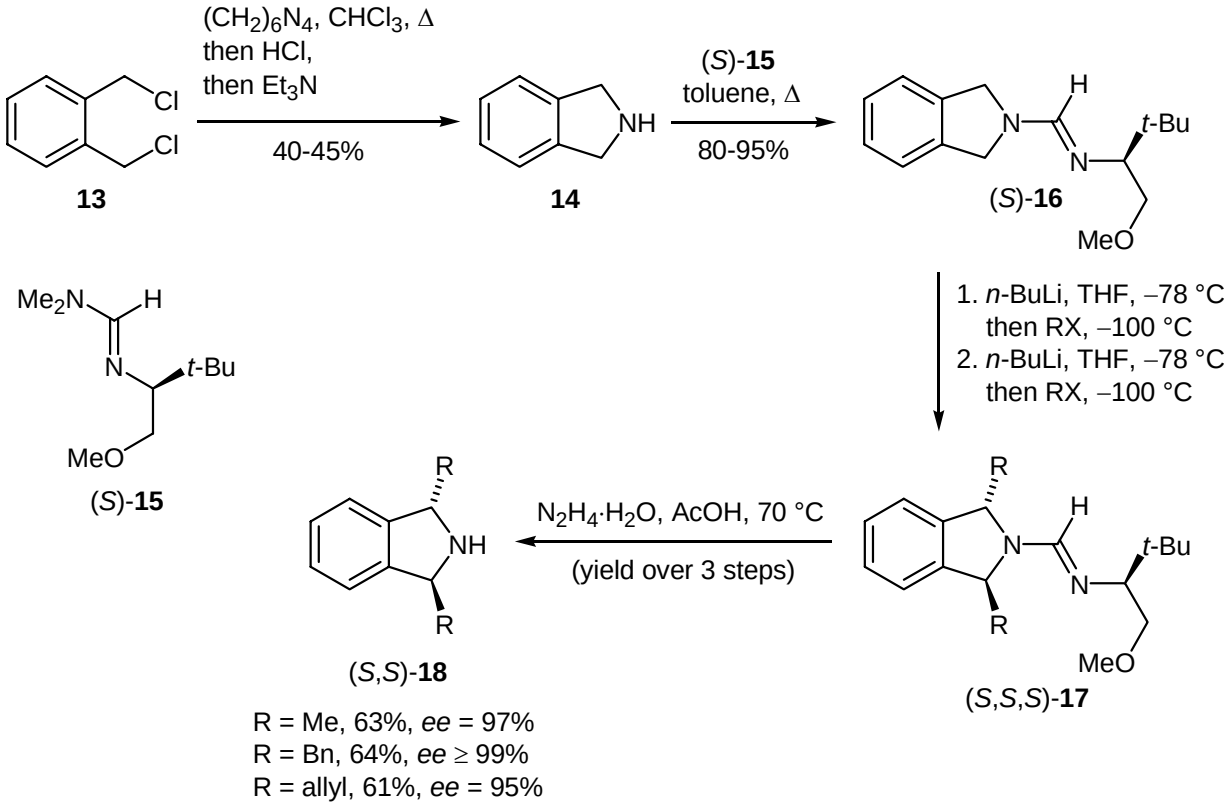


Figure 5: Potent endothelin receptor antagonists *trans*-**11** and (*S*,*R*,*S*)-**12**

1.1.2 SYNTHESIS OF 1,3-DISUBSTITUTED ISOINDOLINES

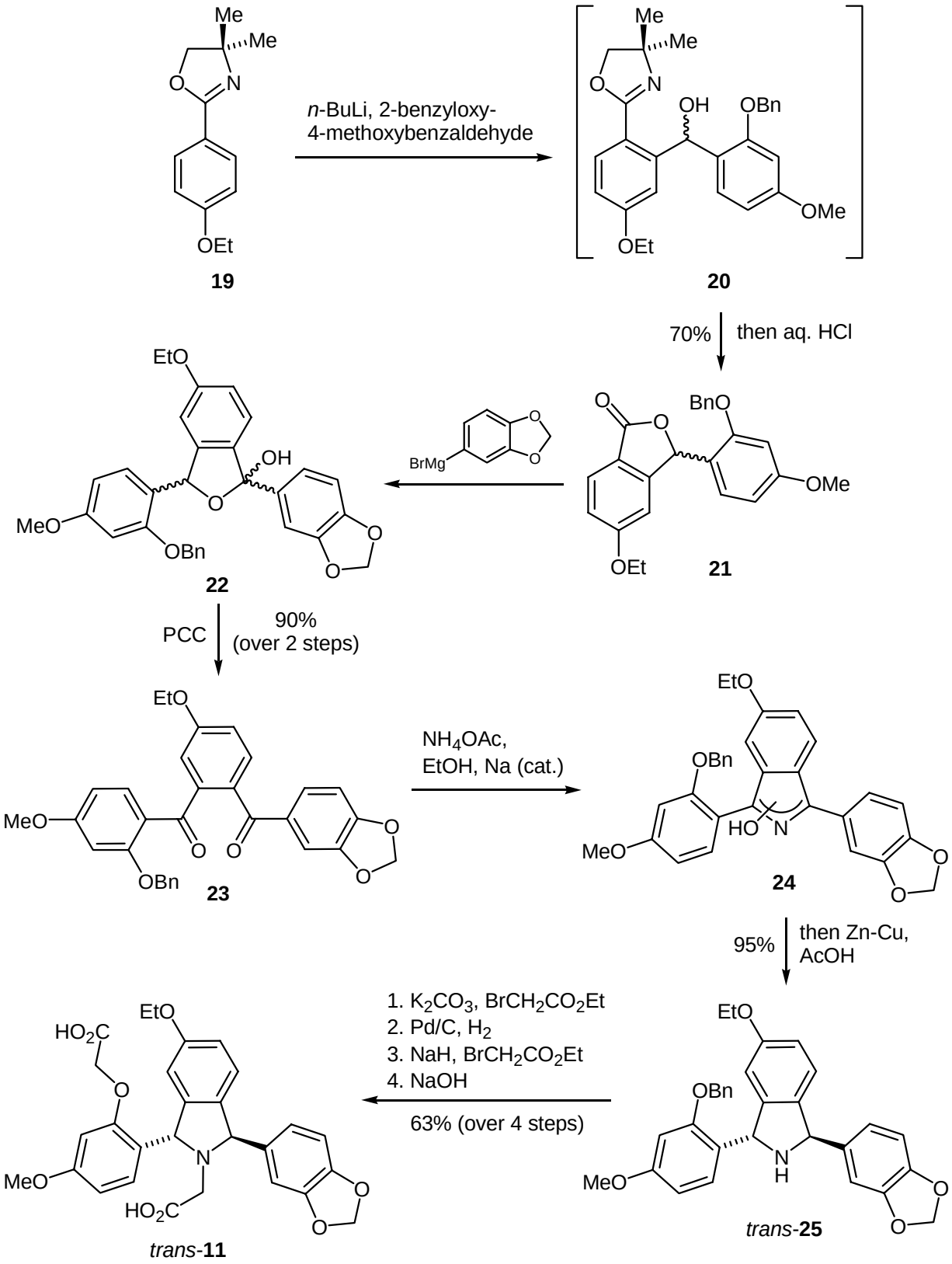
Although several syntheses of racemic 1,3-disubstituted isoindolines were reported[12], to our knowledge only two diastereo- and enantioselective syntheses exist.[13] Only one will be described, the other following the same strategy and differing only in the structure of the chiral auxiliary.

In his goal to realise novel and interesting chiral systems using C_2-symmetrical isoindolines, *A. I. Meyers et al.* reported the synthesis of the 1,3-dialkyl isoindolines (*S*,*S*)-**18**.[13a] The isoindoline **14** was obtained in moderate yield using the *Délepine* reaction with *ortho*-xylenyl dichloride **13** and hexamethylene tetramine after acidic and basic workup. After construction of the chiral compound (*S*)-**16** by refluxing the isoindoline in toluene with the dimethylamino formamidine (*S*)-**15**, metalation of (*S*)-**16** with *n*-butyllithium gave an anion which was cooled to −100 °C and treated with various electrophiles. After chromatography the monoalkylated isoindolines were remetalated in the same conditions to give (*S*,*S*,*S*)-**17**. Hydrazinolysis gave the free chiral C_2-symmetric amines (*S*,*S*)-**18** in good overall yields and very high enantioselectivity (Scheme 1).



Scheme 1: Asymmetric synthesis of 1,3-dialkyl isoindolines (*S*,*S*)-**18** by *A. I. Meyers et al.*[a]

Two diastereoselective syntheses of 1,3-disubstituted isoindolines were also reported.[9b,14] *P. J. Kukkola et al.* described a regioselective route to highly functionalised dibenzoylbenzenes and a methodology for the stereoselective preparation of *trans*- and *cis*-1,3-disubstituted isoindolines *trans*- and *cis*-**11**, two potent selective ET_A receptor antagonists.[9b] Oxazoline directed *ortho*-lithiation of the disubstituted phenyl compound **19** followed by condensation with 2-benzyloxy-4-methoxybenzaldehyde furnished the resulting hydroxyoxazoline intermediate **20**. *In situ* hydrolysis gave the lactone **21** in 70% overall yield and subsequent *Grignard* reaction led to the formation of an unstable hemiketal **22**. Oxidation by treatment with pyridinium chlorochromate (PCC) provided the desired dibenzoylbenzene **23**, which reacted with ammonium acetate and a catalytic amount of sodium ethoxide to afford the hydroxyisoindole derivatives **24** as a 1/1 mixture of regioisomers. This mixture was converted nearly quantitatively to the isoindolines **25** by *in situ* Zn-Cu reduction in the presence of glacial acetic acid. The compounds **25** were obtained exclusively as the *trans*-isomers (Scheme 2).

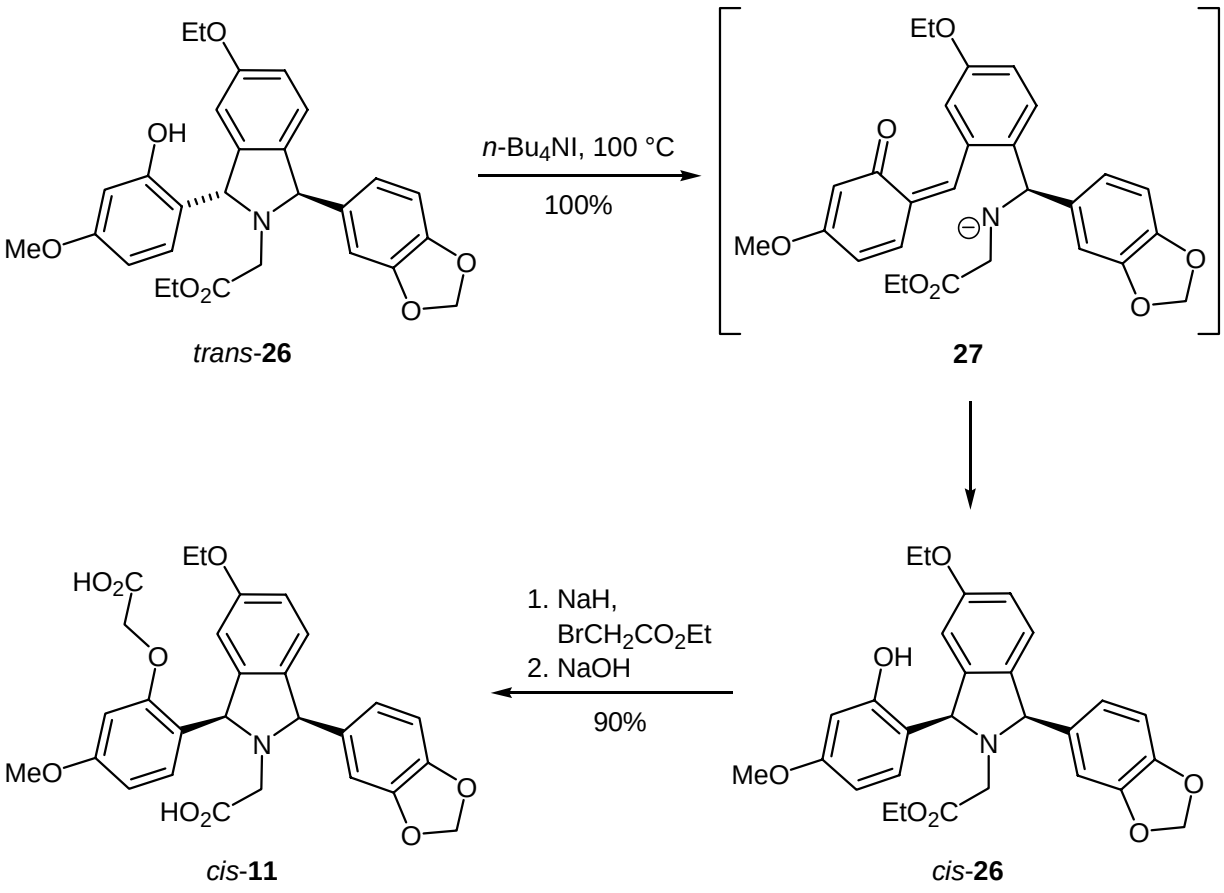


Scheme 2: Synthesis of the endothelin A receptor antagonist *trans*-**11** by *P. J. Kukkola et al.*[9b]

N-alkylation of **25** with ethyl bromoacetate was followed by removal of the benzyl protecting group using catalytic hydrogenation to give the *ortho*-hydroxyaryl isoindolines. Finally, these

compounds were converted to the desired *trans*-dicarboxylic acid **11** in 63% overall yield by an alkylation and hydrolysis sequence (Scheme 2).

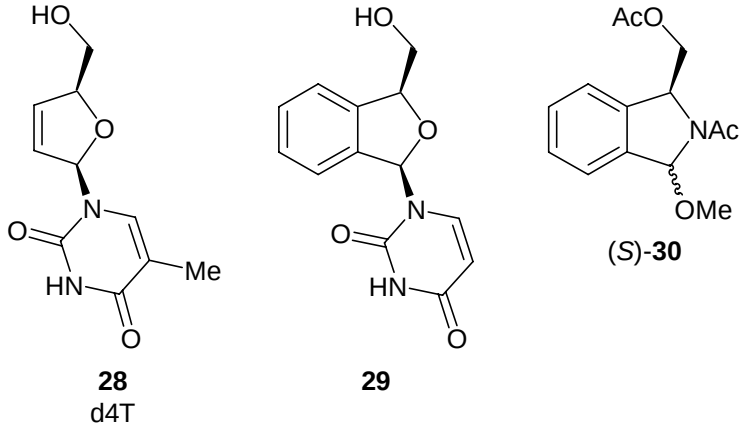
The *o*-hydroxyaryl isoindolines *trans*-**26**, obtained previously, were converted quantitatively to the thermodynamically more stable *cis*-isomers **26** by heating *trans*-**26** at 100 °C with a catalytic amount of tetra-*n*-butylammonium iodide. This reaction likely proceeded through a quinone-methide type intermediate **27** in which the benzylic carbon-nitrogen bond at the isoindoline C-3 had been cleaved. Cyclisation then led to the formation of the more stable *cis*-**26**. Alkylation and hydrolysis under the previously described conditions afforded the *cis*-dicarboxylic acid analogues **11**. However, the authors stated that the *trans*- to *cis*-isomerisation is limited to isoindoline derivatives possessing an *o*- or *p*-hydroxyaryl substituent either at C-1 or C-3 (Scheme 3).



Scheme 3: Synthesis of the endothelin A receptor antagonist *cis*-**11** by *P. J. Kukkola et al.*[b]

The nucleoside analogue **29** with the 2',3' double bond incorporated into a benzene ring has been synthesised as an analogue of d4T (**28**), a commercial anti-HIV nucleoside approved by the US FDA (Food and Drug Administration).[15] Thanks to this modification the substrate

should be more resistant to the hydrolytic process that contributes to the short half-life of d4T *in vivo*. Furthermore, this system is very rigid and it has been speculated that the conformational restriction imposed by the double bond in d4T might be an important factor in its interaction with viral enzymes.[16] Recently, *C. Len et al.* described the diastereoselective synthesis of the *N*-substituted 1,3-disubstituted isoindoline (*S*)-**30**.[14] This azasaccharide mimic could provide an access to a new series of nucleoside analogues with potential as anti retroviral agents (anti-HIV) (Figure 6).



28
d4T

29

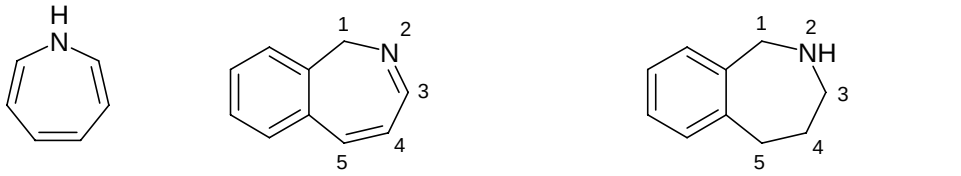
(*S*)-**30**

Figure 6: Commercial anti-HIV d4T (**28**) and nucleoside analogues **29** and (*S*)-**30**

It is interesting to note that some diastereoselective syntheses of 1,1,3,3-tetrasubstituted isoindolines were also reported in the field of radical chemistry.[17]

1.2 TETRAHYDRO-2-BENZAZEPINES

In the nomenclature, the 2-benzazepines are related to the 1*H*-azepine (**31**), a nitrogen-containing seven-membered unsaturated heterocycle. As the fused 6,7-ring system possessing the nitrogen in the 2-position is known as the 1*H*-2-benzazepine (**32**), its tetrahydrogenated derivative is called 2,3,4,5-tetrahydro-1*H*-2-benzazepine (**33**) (Figure 7).



31 1*H*-azepine

32 1*H*-2-benzazepine

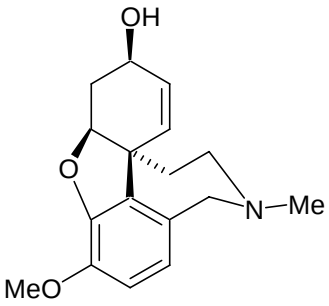
33 2,3,4,5-tetrahydro-1*H*-2-benzazepine

Figure 7: Nomenclature for the azepine and the fused 6,7-ring system of 2-benzazepines

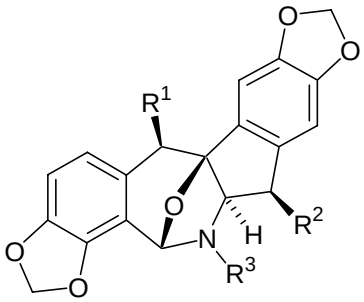
1.2.1 STRUCTURE AND BIOLOGICAL ACTIVITY OF TETRAHYDRO-2-BENZAZEPINES

The tetrahydro-2-benzazepine skeleton is a common structural feature found in a variety of naturally occurring and synthetically produced bioactive compounds. For example the alkaloid from the *Amaryllidaceae* family, galanthamine (**34**),[18] which contains a spiro-linked benzazepine structure, is currently the most effective experimental drug in the treatment of *Alzheimer*'s disease due to its selective inhibiting activity on acetylcholinesterase (Figure 8). An evaluation in the year 2000 showed that the illness is not stopped but the symptoms are efficiently reduced when galanthamine was given to patients with mild to moderate *Alzheimer*'s disease.[19]

Examples are also found in the ribasine-type alkaloids, which possess a indanobenzazepine structure. Ribasine (**35**), isolated independently in 1983 by *L. Castedo et al.*[20] and *M. Shamma et al.*[21] from *Sarcocapnos crassifolia* and *Coryladis claviculata*, is the parent compound of this new class of alkaloids. Other members of this class are the hydroxy ribasines himalayamine (**36**) and ribasidine (**37**), and the *N*-demethyl congener norribasine (**38**) (Figure 8).[22] Although this family of alkaloids is not known to possess any particular medicinal activity so far, the presence of the reactive 8,14-epoxy-indanobenzazepine ring may provide interesting biological responses.



34
galanthamine



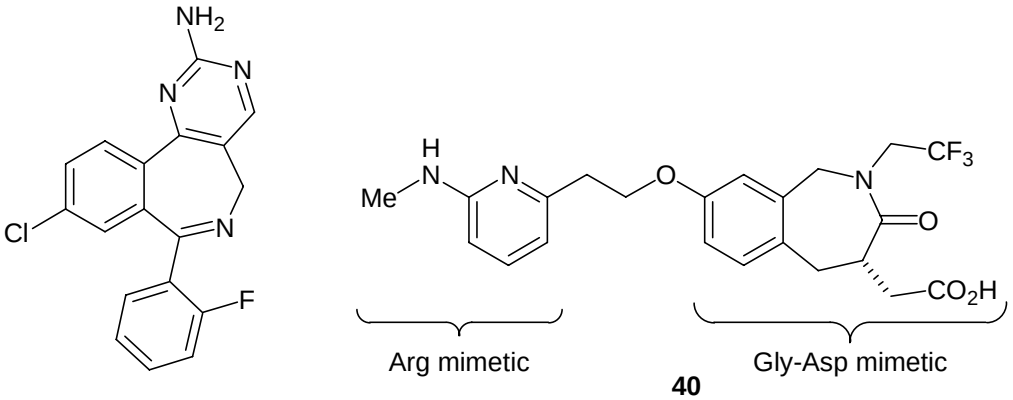
35: R^1, R^2 = H; R^3 = Me; ribasine
36: R^1 = H; R^2 = OH; R^3 = Me; himalayamine
37: R^1 = OH; R_2 = H; R^3 = Me; ribasidine
38: R^1, R^2, R^3 = H; norribasine

Figure 8: Structure of galanthamine and of ribasine-type alkaloids

Another biologically prominent example is the fused 2-amino 9-chloro-7-(2-fluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepine or BBL22 (**39**), that exhibits very promising antitumour activity (Figure 9). In fact in 2000, *N. L. Spector* reported that **39** promotes apoptosis of prostate and certain breast cancer lines (Apoptosis or "programmed cellular death": mechanism responsible for the physiological suppression of the cells, indispensible for the equilibrium of the body. In some cancers, the cell accumulation promoting the tumours could be due to an insufficient apoptosis and not only to an increasing production).[23] In addition, BBL22 exhibited selectivity in targeting tumour cells while sparing the growth and survival of normal cells. The *in vivo* antitumour activity was examined and **39** significantly reduced the growth of prostate tumours without provoking toxicity. The molecule and its analogues were patented one year later.[24]

Integrins are surface molecules found on the exterior of cells helping to bind whole cells together. In particular integrin $\alpha v\beta 3$ has been shown to mediate adhesion of osteoclasts to the bone matrix. An osteoclast is a cell that actively reabsorbs old or fatigued bone so that new bone may be built up by cells which aid the growth and development of bones (osteoblasts). When osteoclasts reabsorb bone faster than the osteoblast cells are producing it, then osteroporosis (bone loss) occurs. Therefore, antagonists of integrin $\alpha v\beta 3$ are expected to be of use in the treatment of several human diseases, including osteoporosis. Integrin $\alpha v\beta 3$ is known to recognise the arginine-glycine-aspartic acid tripeptide sequence. Therefore *W. H. Miller et al.* investigated peptidomimetic approaches to identify $\alpha v\beta 3$ antagonists. In their

structure-activity report, incorporation of the 6-(methyl-amino)pyridine as Arg mimetic has a significant impact on both biological activity and oral bioavailability. Among the new class of 2-benzazepine Gly-Asp mimetics, **40** proved to be the more potent inhibitor of bone resorption *in vitro* and *in vivo* and was active in an animal model of osteoporosis (Figure 9).[25]



39
BBL22

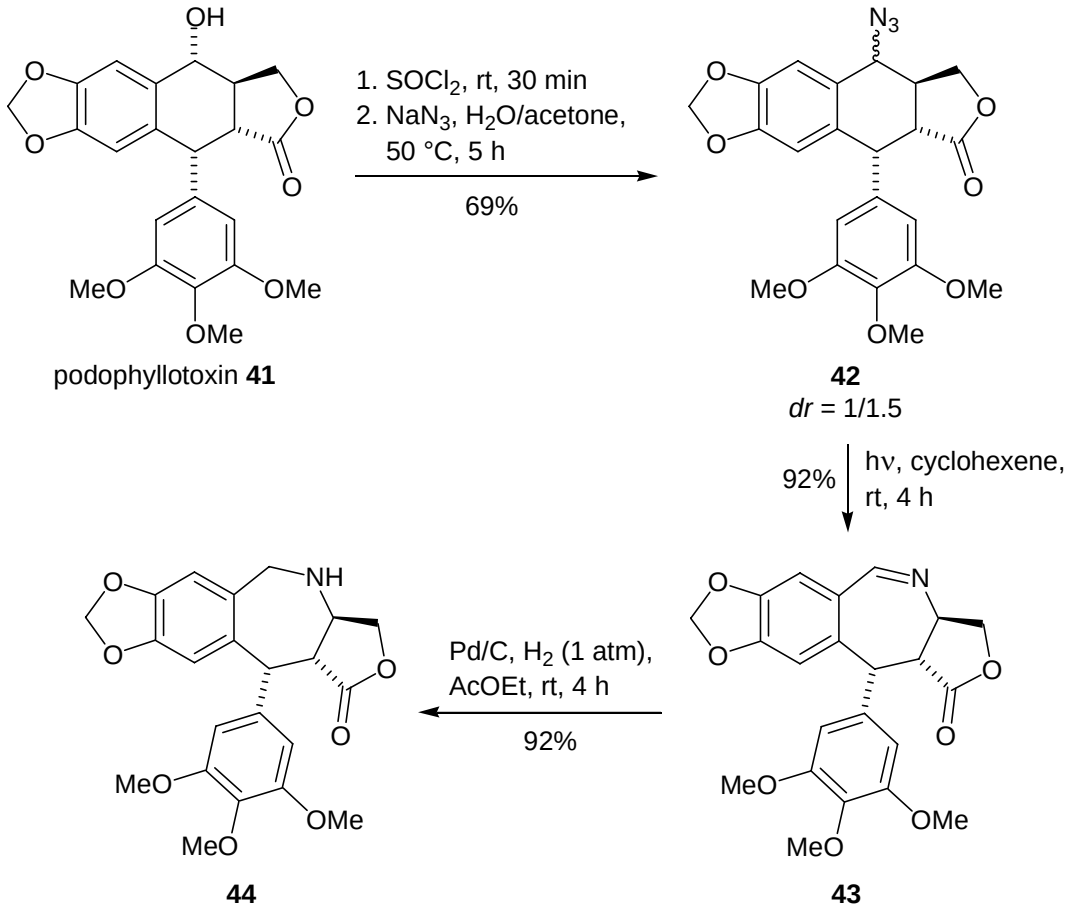
40

Figure 9: Pyrimido-2-benzazepine BBL22 and the Gly-Asp mimetic 2-benzazepine **40**

1.2.2 SYNTHESIS OF SUBSTITUTED TETRAHYDRO-2-BENZAZEPINES

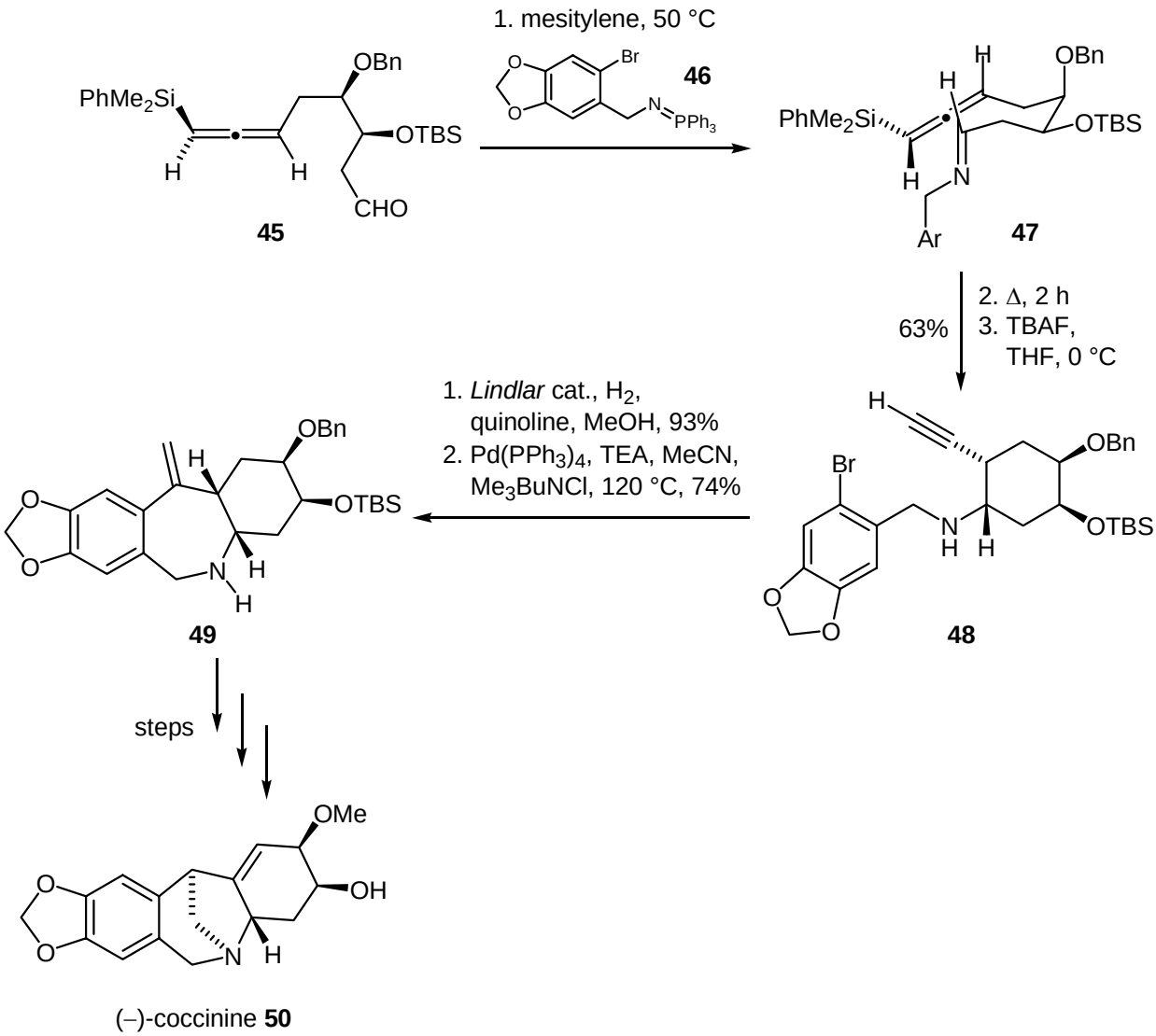
In the literature describing the synthesis of 2-benzazepine derivatives,[26] two major approaches have been employed. One involves the intramolecular cyclisation of appropriately substituted aromatic substrates,[27] and the other follows the expansion of smaller rings.[27p,28] Concerning the 3,4-disubstituted tetrahydro-2-benzazepine derivatives, to our knowledge, only three asymmetric syntheses were reported.

In their search of new podophyllotoxin derivatives, potentially efficient in the treatment of tumours, *H. Laatsch et al.* were interested in the formation of tetrahydro-2-benzazepines by hemisynthesis starting with natural podophyllotoxin (**41**).[29] For example, after alcohol/chloride exchange with thionyl chloride and treatment with two equivalents of sodium azide, a diastereomeric mixture of the 9-azidopodophyllotoxin derivatives **42** was obtained in 69% yield (Scheme 4). At short reaction times and low concentrations 92% of the dihydro-2-benzazepine **43** could be obtained by photochemical ring expansion of the azides **42** in cyclohexene. Final hydrogenation with palladium on charcoal gave the 3,4,5-trisubstituted tetrahydro-2-benzazepine **44** in 92% yield.



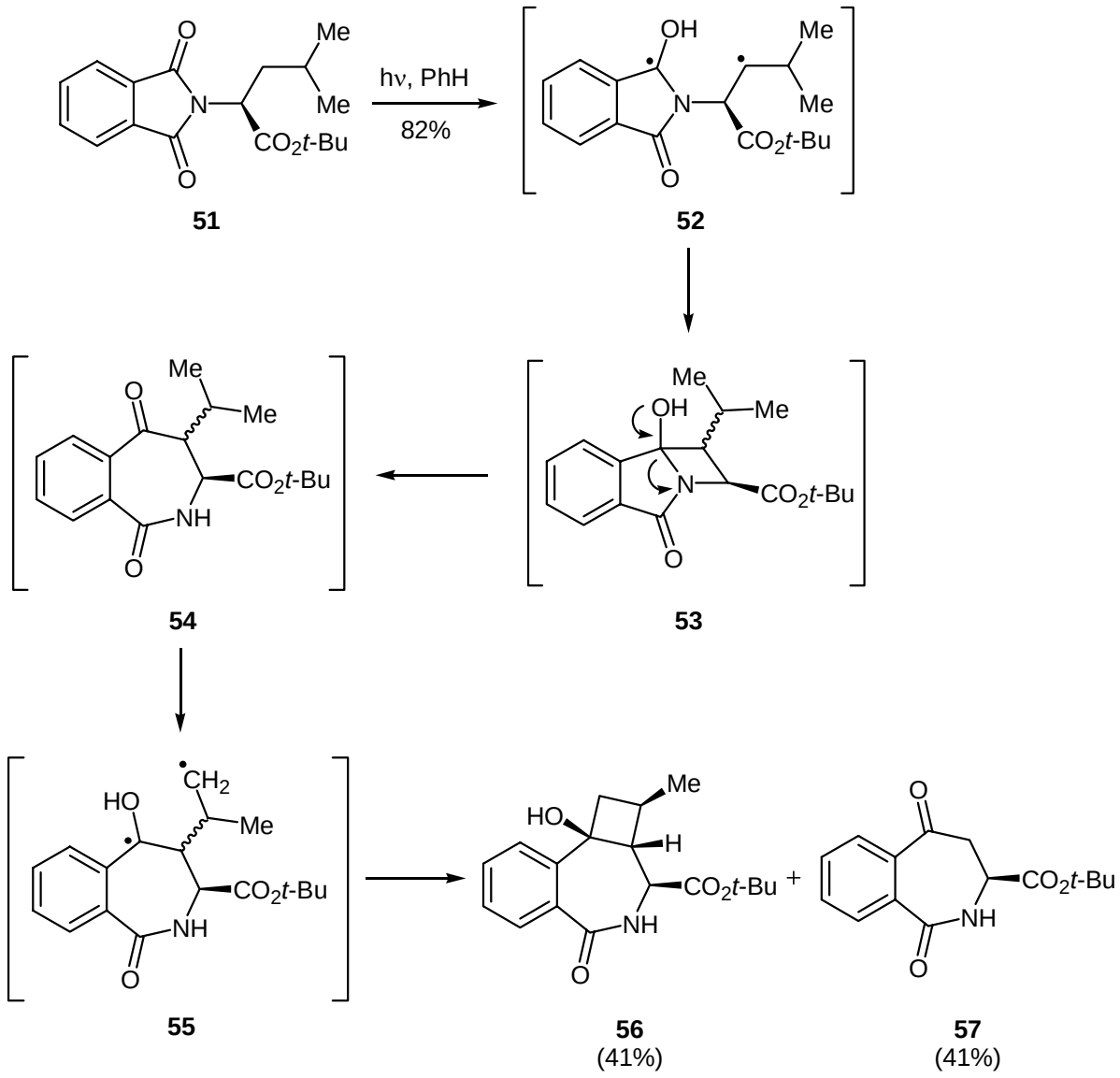
Scheme 4: Hemisynthesis of tetrahydro-2-benzazepine **44** by *H. Laatsch et al.*

In their strategy for the total synthesis of (–)-coccinine (**50**), *S. M. Weinreb et al.* proceeded *via* a diastereo- and enantiomerically pure 3,4,5-trisubstituted tetrahydro-2-benzazepine.[30] The aldehyde functionality of the synthesised building block **45** was condensed with iminophosphorane **46** to form the corresponding imine **47** (Scheme 5). Upon heating to reflux, a stereospecific cyclisation occurred, that is believed to be a thermal imino ene reaction. After alkyne desilation, a single stereoisomer of the amino acetylene **48** was isolated. This pericyclic process can, in principle, proceed through two imine conformations, one of them shown in Scheme 5. However, both lead to the same stereoisomer of the cyclisation product. Alkyne **48** was then partially hydrogenated using *Lindlar*'s catalyst to generate a terminal olefin. This bromoalkene cyclised under *Heck*'s conditions to form the desired tetrahydro-2-benzazepine **49** bearing an exocyclic alkene. From **49** several steps were necessary to reach the natural product (–)-coccinine (**50**).



Scheme 5: Key steps in the total synthesis of (–)-coccinine (**50**) by *S. M. Weinreb et al.*

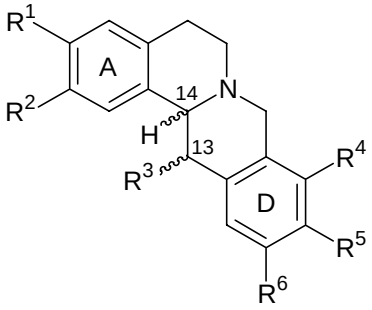
Another example for the asymmetric synthesis of 3,4-disubstituted tetrahydro-2-benzazepine derivatives was realised by *A. G. Griesbeck et al.* using photochemistry (Scheme 6).[31] After photochemical excitation of the phthaloyl leucine ester **51**, the *Norrish* II abstraction of an hydrogen in γ-CH-position led to the intermediate **52**. *Yang* cyclisation formed the azetidinol **53** which opened in a retrotransannular manner to afford the dihydrobenzazepinedione **54**. Again under photochemical excitation, *Norrish* II abstraction of an hydrogen in γ-CH-position led to the intermediate **55**. *Yang* cyclisation led to the formation of 41% of a single tetrahydro-2-benzazepinone enantiomer **56** whereas at the same time *Norrish* II cleavage led to the formation of 41% of the dihydrobenzazepinedione **57**.



Scheme 6: Synthesis of tetrahydro-2-benzazepinone **56** by *A. G. Griesbeck et al.*

1.3 TETRAHYDROPALMATINE

Tetrahydropalmatine belongs to the protoberberine family, a large class of naturally occurring alkaloids possessing antitumour, antimicrobial and other biological activities.[32,33] The tetrahydroprotoberberines **58** are widespread, occurring in at least eight botanical families. They are present most frequently in the various genera of the *Papaveraceae*, but they also appear in the *Berberaceae*, *Menispermaceae*, *Ranunculaceae*, *Rutaceae*, and *Annonaceae* families.[32] They are characterised by a tetracyclic skeleton and an isoquinoline core. Alkoxy or hydroxy substituents are always attached to the A- and D-rings. The protoberberines can have alkyl or hydroxy substitution at the C-13 position, and they all possess a stereogenic centre in C-14 (Figure 10).[34]



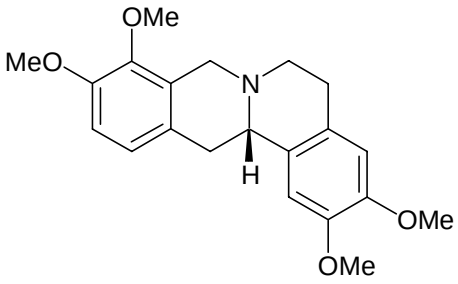
58

R^1 = OH, OMe; R^2 = OMe or R^1 + R^2 = OCH_2O
R^3 = H, OH, Me
R^4 = H, OH, OMe; R^5 = OMe or R^4 + R^5 = OCH_2O
R^6 = H, OH, OMe

Figure 10: Structure of the tetrahydroprotoberberine alkaloids

1.3.1 ISOLATION, STRUCTURE AND BIOLOGICAL ACTIVITY OF TETRAHYDROPALMATINE

Both enantiomers of tetrahydropalmatine as well as the racemate are present in nature. Although (+)-tetrahydropalmatine seems to have been isolated as early as 1903,[35] it was not before 1923 that the structure elucidation of this alkaloid was accomplished by *E. Späth et al.* after its isolation from tubers of *Corydalis Cava* (Figure 11).[36]



59

Figure 11: The protoberberine alkaloid (*S*)-(−)-tetrahydropalmatine (**59**)

In addition to the proof of the structure of tetrahydropalmatine by its oxidation to palmatine and reverse reduction,[36] tetrahydropalmatine was also synthesised from tetrahydroberberine (also known as canadine; Figure 10; $R^1 + R^2 = OCH_2O$; R^3, R^6 = H; R^4, R^5 = OMe).[37] The racemic form was isolated in 1928 from tubers of *Corydalis Ambigua*[38] and the (−)-enantiomer was extracted in 1933 from *Corydalis Aurea*[39] (Figure 12).

Corydalis Aurea

Corydalis Caseana

Figure 12: Examples of plants containing (*S*)-(−)-tetrahydropalmatine[40]

The absolute configuration of tetrahydropalmatine, also called corydalis B, gindarine, caseanine or rotundine,[41] was established in 1956 by *H. Corrodi* and *E. Hardegger*.[42] The absolute configuration of (−)-tetrahydropapaverine (**61**), a 3-phenyl substituted tetrahydroisoquinoline, could be deduced by its oxidation to the L-asparaginic acid derivative (−)-**60**, possessing a known configuration (Figure 13). After reaction of (−)-**61** with two equivalents of methyl iodide and potassium hydroxide, the salt of **61** was found to be the antipode of the salt of (−)-laudanosine. It was concluded that the (−)-tetrahydropapaverine

(**61**) has the same configuration as the natural (+)-laudanosine (**62**). The absolute configuration of many protoberberine alkaloids was finally determined using the known relations with (+)-**62**. Since then, NMR-studies were undertaken to allow the full assignment in tetrahydropalmatine[43] and the (*S*) absolute configuration attributed by X-ray analysis of (–)-tetrahydropalmatine monohydrate[44] confirmed the one reported by *H. Corrodi* and *E. Hardegger* (Figure 11).

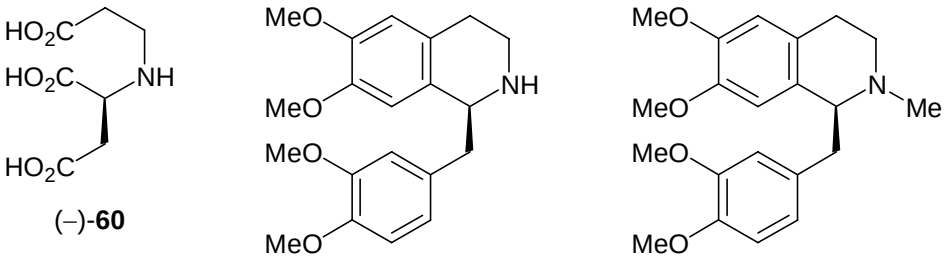


Figure 13: Substances used for the configuration determination of tetrahydropalmatine

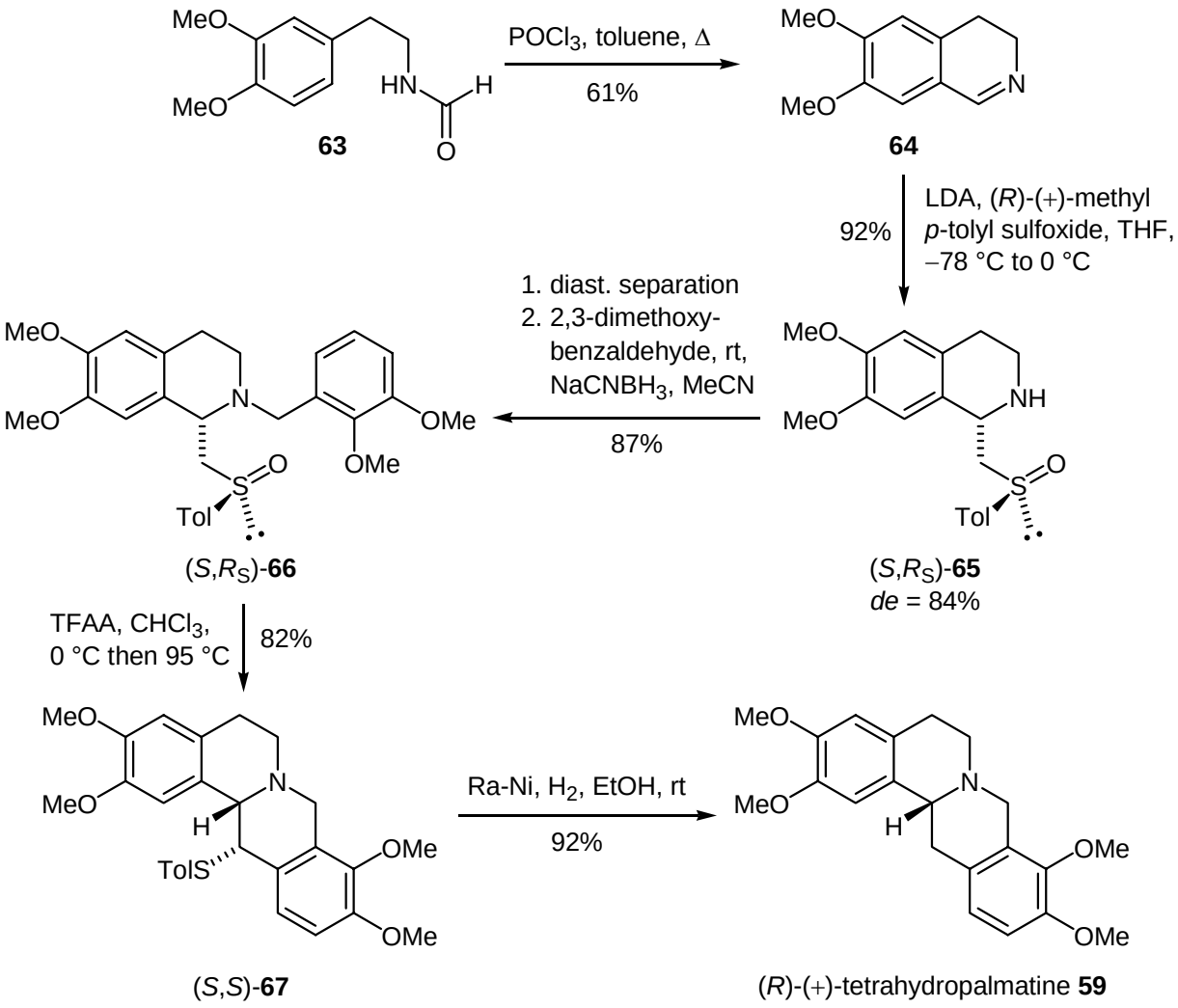
Among all biological activities attributed to tetrahydropalmatine (**59**), only three examples will be shortly detailed here. The racemic form of **59** was shown to possess an insecticidal activity against larvae (LD_{50} > 8.45 µmol/mL of diet) and adults (LD_{50} = 6.5 µg/adults) of *Drosophila melanogaster*.[45] The (*S*) enantiomer might be valuable as anti-tumour promoter (inhibitory effect on *Epstein-Barr* virus).[46]

The (*R*) enantiomer was shown to be an inhibitor by 46% of the activity of GABA-T (*γ*-aminobutyric acid transaminase).[47] GABA is a major inhibitory chemical neurotransmitter in the central nervous system of mammals. When the concentration of GABA in the brain falls below a certain level, various neurological disorders including epilepsy, seizures, convulsions and Parkinsonism may occur. The concentration of GABA in the brain is controlled by two enzymes, one of them being the GABA-T. Therefore, the irreversible inhibition of GABA-T is the basic action mechanism of drugs used in the treatment of convulsive disorders.

1.3.2 ENANTIOSELECTIVE TOTAL SYNTHESES OF TETRAHYDROPALMATINE

Although 13 syntheses of racemic tetrahydropalmatine have been reported,[48] until now only three enantioselective syntheses exist.

S. G. Pyne et al. reported a total synthesis of (*R*)-(+)-tetrahydropalmatine (**59**) as illustration of their methodology based on addition of α-sulfinyl carbanions to imines (Scheme 7).[49] After formation of the 6,7-dimethoxy-3,4-dihydroisoquinoline (**64**) by reaction of *N*-formyl homoveratrylamine **63** with phosphorous oxychloride, the addition of the lithium salt of (*R*)-(+) methyl *p*-tolyl sulfoxide led to a mixture of diastereoisomers (*de* = 84%) in which the thermodynamic (S,R_S)-**65** was favoured. This diastereoselectivity under equilibrium controlled conditions was in contradiction with their former observation of modest to good diastereoselectivities achieved under kinetic control by addition of lithium carbanions of racemic methyl phenyl sulfoxide and (*R*)-(+) methyl *p*-tolyl sulfoxide to aryl imines.



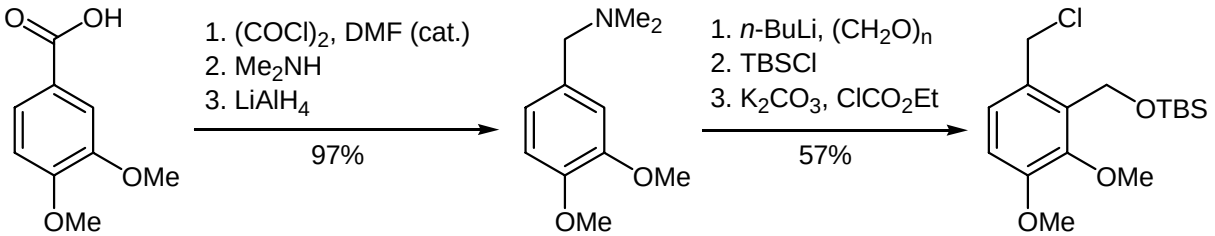
Scheme 7: Total synthesis of (*R*)-(+)-tetrahydropalmatine (**59**) by *S. G. Pyne et al.*

Separation of the diastereoisomers of tetrahydroisoquinoline **65** followed by reductive alkylation with 2,3-dimethoxy-benzaldehyde and sodium cyanoborohydride gave (S,R_S)-**66** in

87% yield. The tetracyclic sulfide (*S*,*S*)-**67** was obtained as a single diastereoisomer in 82% yield by intra-molecular *Pummerer* reaction upon exposure to trifluoroacetic anhydride and subsequent heating. Reductive desulfurisation with *Raney* nickel furnished (*R*)-(+)-**59** in 92% yield (Scheme 7).

In his program towards the asymmetric synthesis of isoquinoline alkaloids *A. I. Meyers et al.* investigated the synthesis of (*S*)-(−)-tetrahydropalmatine (**59**).[50] Due to the C-9 and C-10 D-ring substitution pattern in **59** (see Figure 10), the use of the *Pictet-Spengler* reaction for the formation of the berberine bridge was excluded, although it had been successfully used for the construction of (−)-norcoralydine (*ee* = 98.5%) (Figure 10, R^1, R^2 = OMe, R^3, R^6 = H, R^4, R^5 = OMe).[51] Their strategy was based on an asymmetric alkylation of a tetrahydroisoquinoline where the nitrogen carried a chiral formamidine substituent. However, an *ortho*-substituted electrophile had to be used here to establish the D-ring substitution present in tetrahydropalmatine (**59**).

The synthesis of the electrophile started from the commercially available veratric acid (**68**). After transformation of the carboxylic group into an amide functionality using oxalyl chloride and dimethyl amine, reduction with lithium aluminium hydride led to the benzylic amine **69** in excellent yield. **69** was then subjected to directed lithiation using *n*-butyllithium and the resulting anion was treated with paraformaldehyde. The resulting primary alcohol was then protected to give the silyl ether in 65% over two steps. The substitution of the amine by a chloride using ethyl chloroformate furnished the benzyl chloride **70** in 87% yield (Scheme 8).

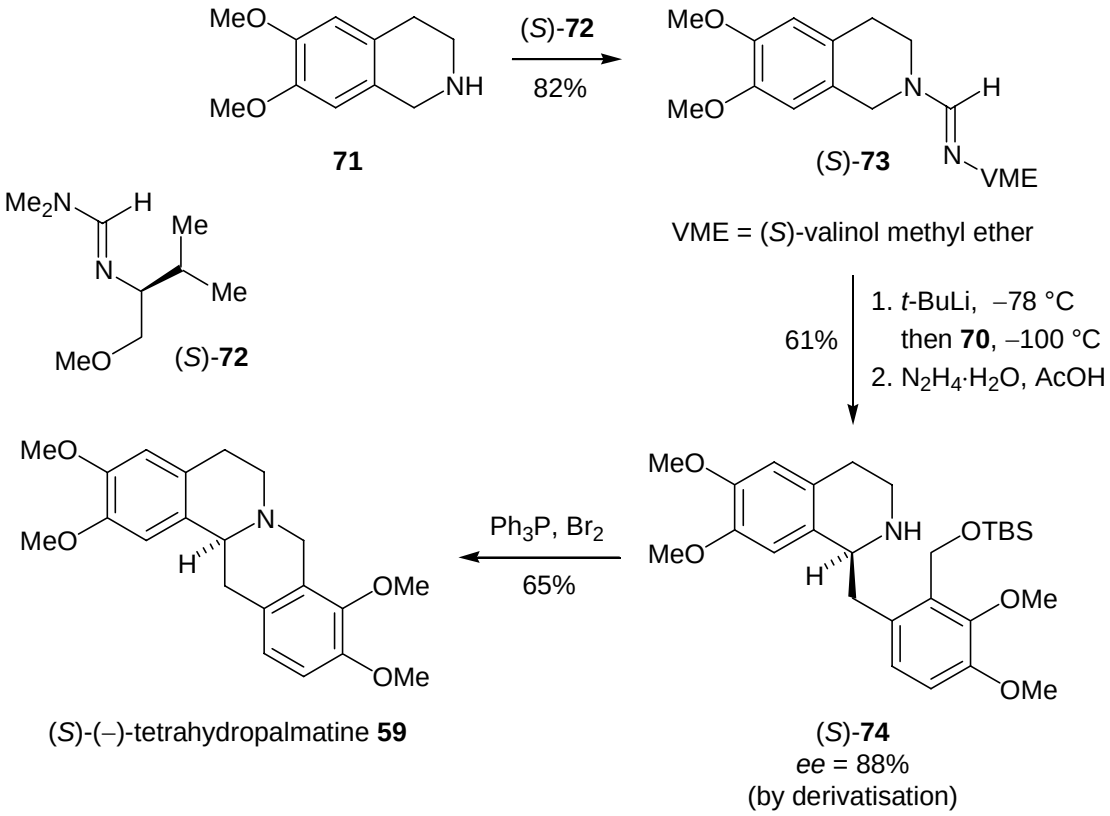


68 **69** **70**

Scheme 8: Synthesis of the benzyl chloride electrophile **70**

The chiral formamidine (*S*)-**73** was constructed from the tetrahydroisoquinoline **71** by formamidine exchange with the (*S*)-valinol derived chiral auxiliary (*S*)-**72**. Lithiation of **73** was effected with *tert*-butyllithium at −78 °C. The solution was then cooled to −100 °C and treated with electrophile **70**. Subsequent removal of the formamidine with hydrazine hydrate

gave the protected amino alcohol (*S*)-**74** in 61% yield. The enantiomeric excess was found to be 88% after derivatisation with 1-naphtoylchloride. Final closure of the berberine bridge was accomplished with triphenylphosphine and bromine to give (*S*)-(−)-tetrahydropalmatine (**59**) in 65% yield (the *ee* was not determined) (Scheme 9). The disappointing low enantioselectivity, compared to those generally obtained in alkylations of chiral formamidines, was explained by a disruption in the formamidine chelate due to chelation of the oxygen lone pairs of the silyl ether. It should be noted that prior to **70** another electrophile was tested and that delivered a nearly racemic product.



Scheme 9: Total synthesis of (*S*)-(−)-tetrahydropalmatine (**59**) by *A. I. Meyers et al.*

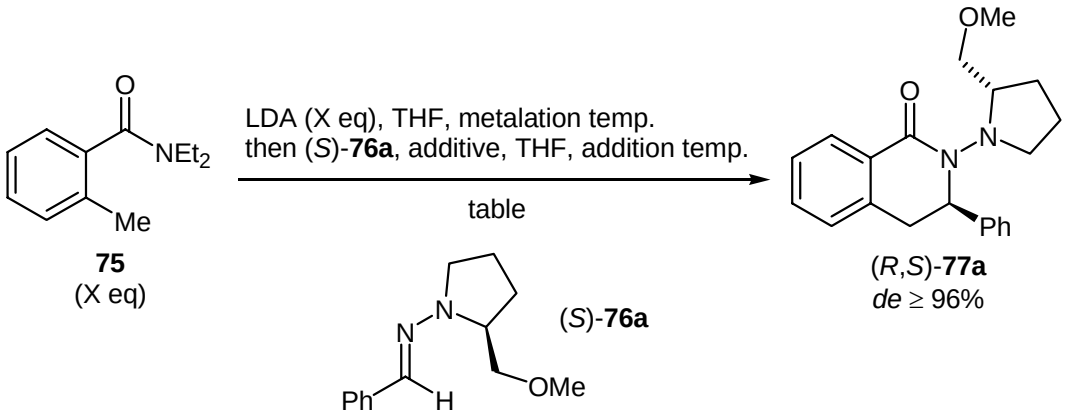
In 2002, an enantioselective synthesis of (*S*)-(−)-tetrahydropalmatine, based on the strategy of *A. I. Meyers et al.* but using a silyl-directed *Pictet-Spengler* cyclisation for the formation of the berberine bridge, was described, but the natural product was obtained in only moderate enantioselectivity (*ee* = 55%) in 22% overall yield over 5 steps.[52]

1.3.3 TANDEM 1,2-ADDITION/RING CLOSURE SEQUENCE

An important entry to the isoquinoline heterocycles is the general concept of nucleophilic addition/cyclisation first outlined by *D. B. McLean et al.* in 1983, who obtained 13-hydroxy-8-oxoprotoberberines from lithiated phthalide anions and 3,4-dihydroisoquinolines.[53] In a related approach, *R. D. Clark et al.* pioneered a non-stereoselective tandem addition/cyclisation of lithiated 2-methyl-benzamides with imines to yield 3-substituted dihydro-2*H*-isoquinolin-1-ones with low to moderate yields.[54] Since then, the lateral metalation methodology[55] has been applied stereoselectively in moderate yields using enantiopure imines,[56] or in low yields and good enantioselectivities using racemic imines and (–)-sparteine.[57] Good overall yields and high enantioselectivities were obtained in a three step process using chiral sulfinimines.[58] Later, these two concepts were combined and 8-oxoprotoberberines were assembled upon condensation of *ortho*-toluamides incorporating chiral auxiliaries with 3,4-dihydroisoquinoline in moderate yields and high enantiomeric excesses.[59] (–)-Sparteine has also been used instead of an auxiliary giving moderate yield and low to good enantioselectivity.[60]

Recently, *D. Enders* and *V. Braig* reported on the first asymmetric synthesis of 3-aryl-substituted 2,3-dihydro-1*H*-isoindol-1-ones by 1,2-addition of *ortho*-lithiated benzamides to aldehyde SAMP/RAMP hydrazones.[61]

Later it was found that the asymmetric synthesis of the *N*-amino-substituted 3-phenyl-3,4-dihydro-2*H*-isoquinolin-1-one (*R*,*S*)-**77a** was possible by nucleophilic addition of lithiated *N*,*N*-diethyl-2-methylbenzamide (**75**) to benzaldehyde SAMP-hydrazone (*S*)-**76a**.[62] A first approach employed 3.5 equivalents of lithiated **75** and the addition to (*S*)-**76a** yielded 37% of (*R*,*S*)-**77a** (Scheme 10, Table 1, entry 1). The open-chain product resulting from a mere 1,2-addition reaction could not be detected, indicating that the reaction took place in a tandem 1,2-addition/ring closure process. As shown in Table 1, the reaction conditions were optimised varying the number of equivalents of **75**, the metalation and addition temperatures and the additive. A large excess of lithiated *ortho*-toluamide **75** slightly improved the yield (entry 1 vs. 2). Various additives like $BF_3{\cdot}OEt_2$, LiCl and LiI were examined, but none of them was found to have a significant effect on the reaction (entry 3 to 5). When the metalation and the addition were conducted at a temperature of –40 °C, the yield could be increased to 52% (entry 6 vs. 2). By comparison with positive effects during nucleophilic 1,2-addition of organolithiums to enantiomerically pure *N*-sulfinyl ketimines,[63] trimethylaluminium as *Lewis* acid was then envisaged. Its presence resulted in the best yield so far (70%, entry 7).



Scheme 10: Optimisation of the synthesis of (*R*,*S*)-**77a** by *V. Braig*

Entry	X (eq)	Metalation temp.	Additive	Addition temp.	Yield
1	3.5	–78 °C	-	–78 °C to rt	37%
2	10	–78 °C	-	–78 °C to rt	46%
3	7	–78 °C	$BF_3{\cdot}OEt_2$	–78 °C to rt	21%
4	5	–78 °C	LiCl	–78 °C to rt	43%
5	5	–78 °C	LiI	–78 °C to rt	31%
6	7	–40 °C	-	–40 °C	52%[a]
7	7	–40 °C	$AlMe_3$	–40 °C	70%

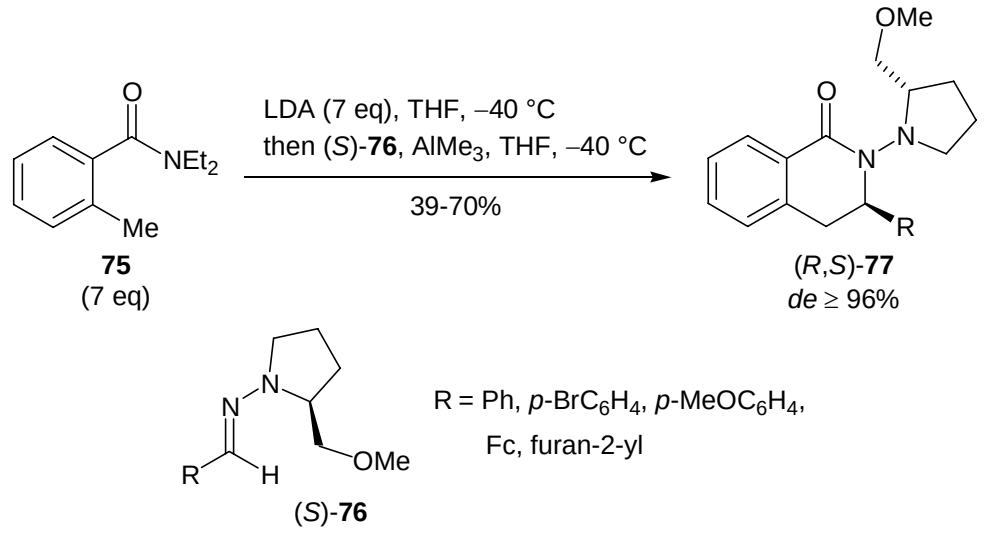
[a] With RAMP as auxiliary

Table 1: Variation of the conditions for the synthesis of (*R*,*S*)-**77a** by *V. Braig*

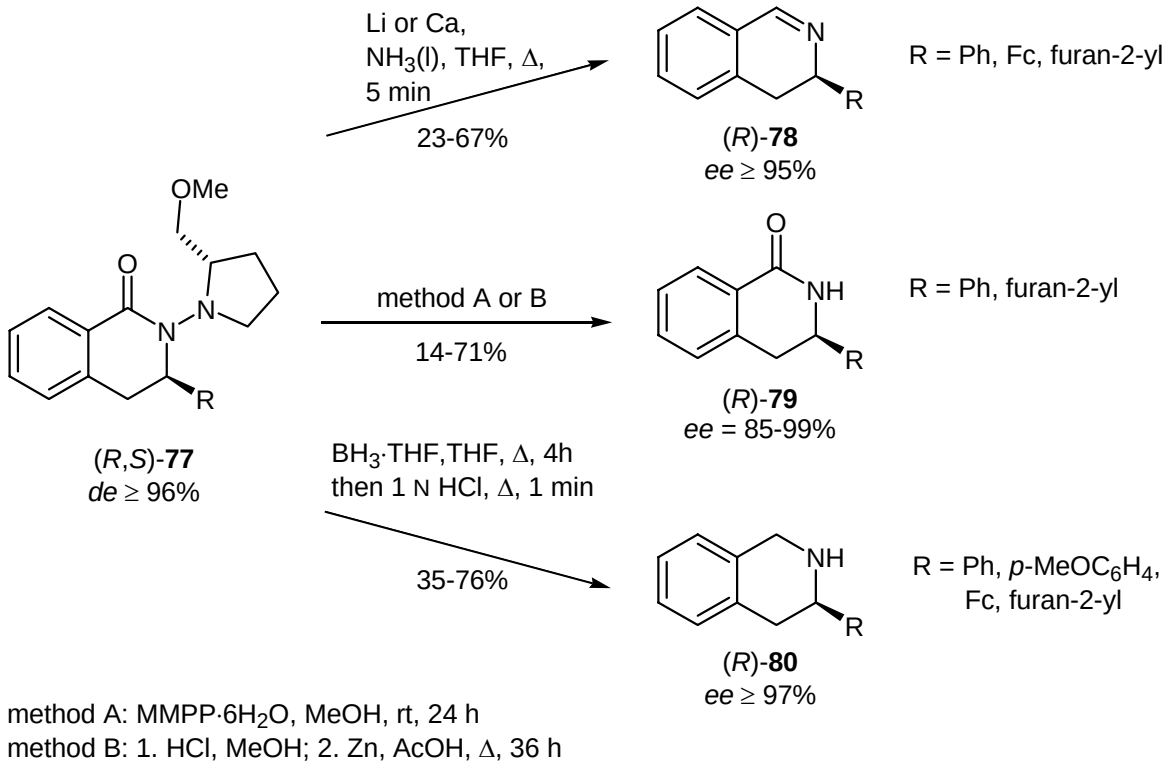
Consequently, the 3,4-dihydro-2*H*-isoquinolin-1-ones (*R*,*S*)-**77** were then synthesised under the optimised conditions employing the aromatic aldehyde SAMP-hydrazones (*S*)-**76** (Scheme 11). Moderate to good yields were obtained but the diastereoselectivity of this tandem process was always excellent.

Methods for the N–N bond cleavage of the auxiliary were then investigated. The use of lithium or calcium in liquid ammonia led to the formation of 3,4-dihydroisoquinolines (*R*)-**78** (probably after reduction of the carbonyl group and subsequent dehydration) in moderate to good yields and in excellent enantiomeric excesses (ee ≥ 95%). In order to obtain 3-substituted 3,4-dihydro-2*H*-isoquinolin-1-ones (*R*)-**79**, another cleavage method was employed that used either magnesium monoperoxyphthalate hexahydrate (MMPP·$6H_2O$) or zinc in acetic acid after prior activation of the hydrazine with a methanolic solution of hydrochloric acid. The yields were moderate to good for (*R*)-**79**, although displaying high

enantioselectivity. Access to 3-substituted 1,2,3,4-tetrahydroisoquinolines (*R*)-**80** was easily accomplished using an excess of the borane-tetrahydrofuran complex. Every hydrazine (*R*,*S*)-**77** was successfully cleaved in moderate to good yields without racemisation. The results are summarised in Scheme 12.



Scheme 11: Tandem 1,2-addition/ring closure providing the dihydroisoquinolinones (*R*,*S*)-**77**

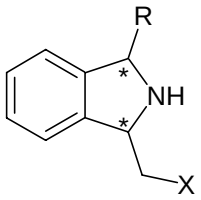


Scheme 12: Conversion to isoquinoline derivatives (*R*)-**78**, (*R*)-**79** and (*R*)-**80** by *V. Braig*

2. OBJECTIVES

The projects of the present work are based on three points.

1. A straightforward asymmetric synthesis of 1,3-disubstituted 2,3-dihydro-1*H*-isoindoles **81** should be undertaken (Figure 14). Due to their potential as bioactive substances, the preparation should allow flexibility in the different substitutions.

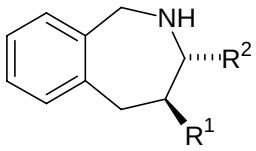


81

R = alkyl
X = electron-withdrawing group

Figure 14: 1,3-disubstituted 2,3-dihydro-1*H*-isoindoles **81**

2. The first diastereo- and enantioselective synthesis of 3,4-disubstituted 2,3,4,5-tetrahydro-1*H*-2-benzazepines **82** was to be performed (Figure 15). Our synthetic strategy should allow various 3- and 4-substitutions.



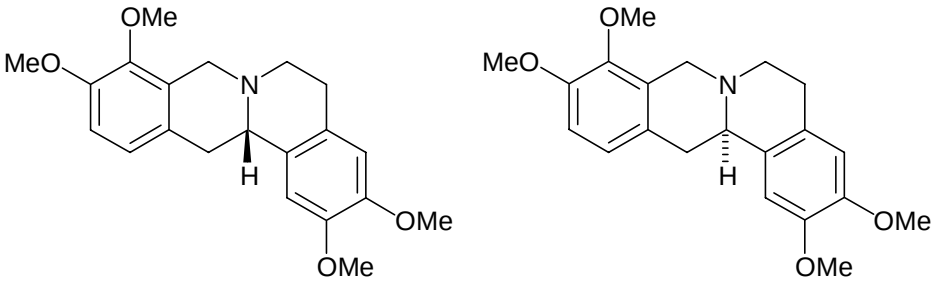
82

R^1, R^2 = alkyl

Figure 15: 3,4-disubstituted 2,3,4,5-tetrahydro-1*H*-2-benzazepines **82**

The construction of both heterocycles was intended to base on a tandem 1,2-addition/cyclisation process. This should permit to create the two stereogenic centres of the isoindolines **81** and the creation of the second chiral centre in the tetrahydro-2-benzazepines **82** after formation of the first centre in a previous alkylation step.

3. Both enantiomers of the protoberberine alkaloid tetrahydropalmatine ((*S*)-(−)-**59**) and ((*R*)-(+)-**59**) were meant to be prepared in enantiomerically pure form by asymmetric synthesis (Figure 16). The synthetic strategy should give access to the asymmetric total synthesis of most of the protoberberines. The formation of the stereogenic centre of the target molecule would proceed *via* the tandem 1,2-addition/ring closure methodology previously developed in our group.[62]



(*S*)-(−)-**59** (*R*)-(+)-**59**

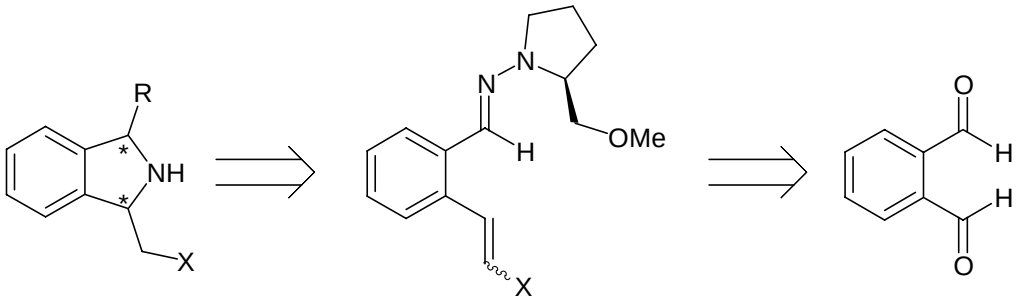
Figure 16: (*S*)-(−)-and (*R*)-(+)-tetrahydropalmatine (**59**)

3. RESULTS AND DISCUSSION

3.1 ASYMMETRIC SYNTHESIS OF ISOINDOLINES

3.1.1 RETROSYNTHETIC CONCEPT

An efficient diastereo- and enantioselective access to isoindolines must be straightforward and substitution diversity should be permitted without changing the entire synthetic strategy. Taking into account these two parameters, the different diastereomeric 2,3-dihydro-1*H*-isoindoles **81** are meant to be accessible in a tandem process from the hydrazones (*S*)-**83**. In the first step of this sequence the 1,2-addition of an organometallic reagent on the SAMP-hydrazone would allow the introduction of the first stereogenic centre. A subsequent *Michael*-addition of the formed anion onto an olefin, bearing an electron-withdrawing group, should promote the ring closure and the formation of the second stereogenic centre. A final N─N cleavage of the auxiliary would then lead to the isoindolines **81**. The generation of the olefin of (*S*)-**83** would be achieved from an aldehyde precursor using the *Horner-Wadsworth-Emmons* (*HWE*) reaction. This will allow tuning either towards the (*E*)- or the (*Z*)-isomer to detect an eventual difference in behaviour and stereoselectivity. As the hydrazone functionality should also be installed on an aldehyde precursor the cheap and commercially available *o*-phthalic dicarboxaldehyde (**84**) will be used as starting material (Scheme 13).



81
R = alkyl
X = electron-withdrawing group

(*S*)-**83**
(*E*) or (*Z*)

84

Scheme 13: Retrosynthetic consideration for the asymmetric synthesis of the isoindolines **81**

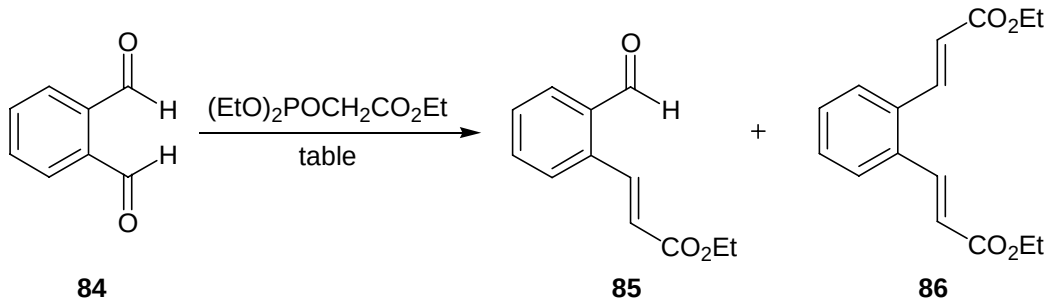
3.1.2 SYNTHESIS OF THE TANDEM ADDITION PRECURSOR

3.1.2.1 FIRST APPROACH: OLEFIN FORMATION FIRST

At the beginning, the combination of steps generating the *Michael* acceptor first and then introducting the SAMP-hydrazone was chosen for the synthesis of the compounds (*S*)-**83**. Indeed, the chiral auxiliary, more expensive than the phosphonate, should preferentially be employed as late as possible.

In comparison with the *Wittig* reaction[64] and the *Horner* reaction[65], the *Horner-Wadsworth-Emmons* reaction[66] has several preparative advantages. First, the isolation of the product is facilitated by the water solubility of the phosphate by-product. Furthermore, reaction conditions are often available for the preparation of olefin mixtures enriched with either the (*Z*)-[67] or (*E*)-isomers.[68] The variety of possible products is large due to a stabilisation of the negative charge of the phosphonate carbanion by delocalisation on the P(O) group. In addition, the phosphonates react with a wide variety of aldehydes and ketones under mild conditions and are also less sensitive to the nature of the base or to atmospheric oxygen.

Standard *HWE*-conditions (1.7 eq of the phosphonoacetate, 1.5 eq of NaH, 0 °C to rt) were first applied to the *o*-phthalic dicarboxaldehyde (**84**) as it was shown to yield ethyl cinnamate quantitatively and with complete (*E*)-selectivity when benzaldehyde and ethyl diethyl phosphonoacetate were employed.[69] As anticipated, a mixture of monoolefin **85** and diolefin **86** was obtained when we employed this method to the dialdehyde. However, to our surprise the disubstituted compound was the major product formed and the mixture proved to be very difficult to separate by column chromatography (Scheme 14, Table 2).

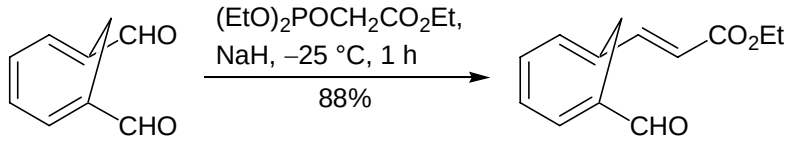


84 **85** **86**

Scheme 14: Attemps for the synthesis of the monoolefin **85** by *HWE* reaction

R. Neidlein et al. described the synthesis of the monosubstituted alkene **88** from diethylphosphono acetic acid ethyl ester and 1,3,5-cycloheptatriene-1,6-dicarbaldehyde (**87**)

(Scheme 15).[70] They showed that lowering the temperature to –25 °C was the decisive factor for a successful monoolefination. They also stated that, when 0.9 equivalents of the phosphonate was used, the yield was reduced to 80% but the monoolefinated product was not contamined with the disubstituted product.



87 **88**

Scheme 15: Monoolefination of cycloheptatriene dicarbaldehyde by *R. Neidlein et al.*

When these conditions were applied to our system, an improvement in the ratio of the monoolefinated/diolefinated products in favour of the former was observed allowing a better separation. However, only small amounts of the desired product were obtained pure (19% yield) showing that the carbonyl groups of *o*-phthalic dicarboxaldehyde (**84**) were more reactive than in cycloheptatriene dicarbaldehyde **87** (Table 2). Lowering the temperature to –40 °C was also attempted to decrease the reactivity even further, but NMR analysis of the crude mixture showed no improvements in the ratio of the monoolefinated/diolefinated products.

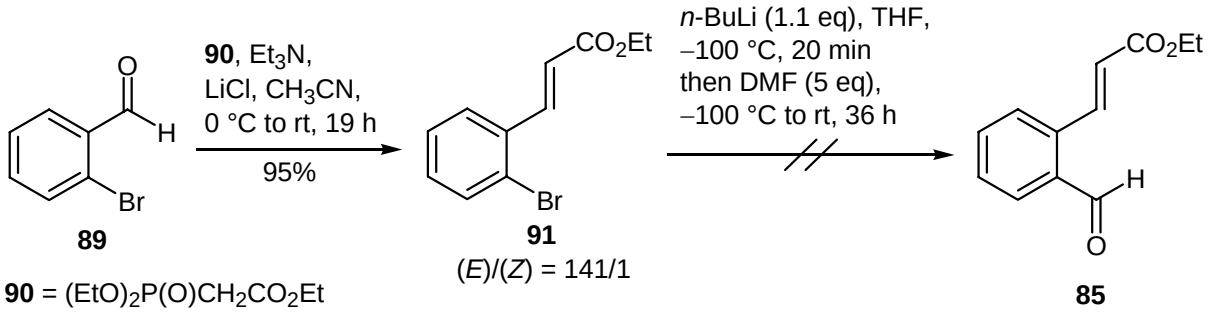
Conditions	Results
$(EtO)_2P(O)CH_2CO_2Et$ (1.7 eq), NaH (1.5 eq), THF, 0 °C to rt, 17 h	inseparable mixture of **85**/**86**
$(EtO)_2P(O)CH_2CO_2Et$ (0.9 eq), NaH (1.0 eq), THF, –20 °C, 1 h	19% of **85**

Table 2: Attempts for the synthesis of the monoolefin **85** by *HWE* reaction

Pursuing this strategy would only be possible with a protection of one aldehyde functionality prior to the *HWE*-reaction to ensure the formation of a monoolefin. A deprotection would then liberate the aldehyde suitable for the formation of the hydrazone (*S*)-**83**. However, in order to avoid a four step protocol alternative strategy was envisaged: the bromo ethyl cinnamate **91** should be formed starting from 2-bromobenzaldehyde (**89**). Transformation of the bromide functionality into an aldehyde should lead to the monoolefin **85**.

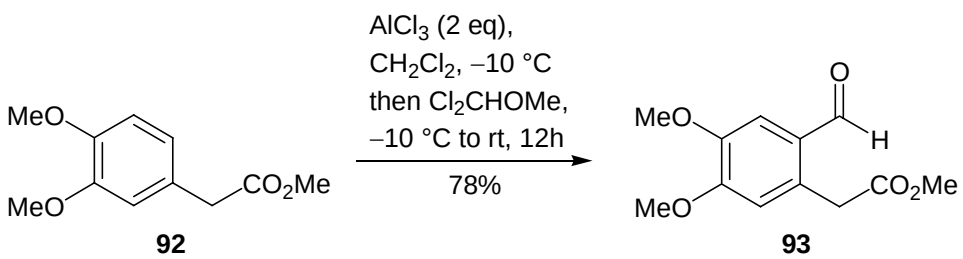
For the formation of the 2-bromo-phenyl acrylic acid ethyl ester (**91**) a variant of the *HWE*-olefination, by *W. R. Roush* and *S. Masamune*[71] and *M. W. Rathke*[72], was used. In the classic reaction a strong base such as sodium hydride, potassium *tert*-butylate or *n*-butyllithium is employed. In the modified procedure, the phosphonate carbanion is produced with the help of amine bases in addition to lithium or magnesium salts (chloride or bromide). As base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), diisopropylethylamine or triethylamine can be used. The addition of a chelating *Lewis* acid induces the formation of a metal enolate and increases the C-H acidity of the methylene group of the phosphonate. The chemical yields obtained by this mild method are generally high and a very good (*E*)-selectivity could be reached. In fact the desired product **91** was formed in an excellent yield and with an excellent (*E*)/(*Z*)-diastereoselectivity (Scheme 16).

The transformation of the bromide functionality by lithium/halogen exchange followed by attack on *N*,*N*-dimethyl-formamide was attempted to obtain the aldehyde **85**. However, none of the desired product could be isolated (Scheme 16).



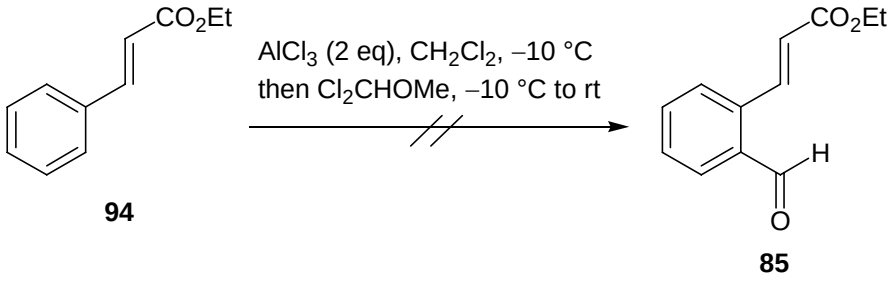
Scheme 16: Attempts for the synthesis of the monoolefin **85** by formylation

Another way of inserting an aldehyde functionality was described by *M. R. Bryce et al.* who suceeded in the formylation of the activated methyl ester **92** by *Friedel-Crafts* reaction with aluminium chloride and dichloromethyl methyl ether to form **93** in good yield (Scheme 17).[73]



Scheme 17: Introduction of an aldehyde functionality by *M. R. Bryce et al.*

Unfortunately when these reaction conditions were applied on the deactivated ethyl cinnamate (**94**) to form the desired monoolefinated product, no formation of the desired aldehyde **85** was detected (Scheme 18).

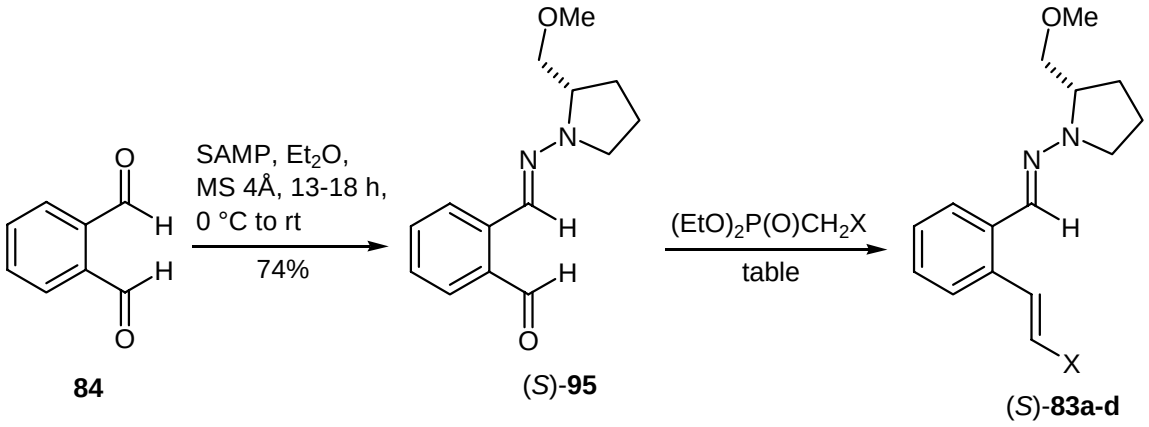


Scheme 18: Attempts for the synthesis of **85**

3.1.2.2 SECOND APPROACH: HYDRAZONE FORMATION FIRST

Our attempts to synthesise the compounds (*S*)-**83** by forming the *Michael* acceptor first and then introducing the SAMP-hydrazone have failed. We thought that the order for the insertion of both functionalities could simply be inverted. An advantage of this combination would be that a large quantity of the hydrazone could be prepared and then be transformed into the different desired alkenes.

In this second approach, the SAMP-hydrazone (*S*)-**95** was easily prepared using the standard conditions developed in our group.[74] The condensation of SAMP with *o*-phthalic dicarboxaldehyde (**84**) in Et_2O at 0 °C, using molecular sieves to remove water, furnished (*S*)-**95** in good yield. The aldehyde functionality was then elaborated into the different alkenes (*S*)-**83a-d** by *HWE*-reaction with the corresponding phosphonates using either the standard conditions or the alternative protocol described above (Scheme 19).



Scheme 19: Synthesis of the starting material (*S*)-**83a-d** for the synthesis of isoindolines

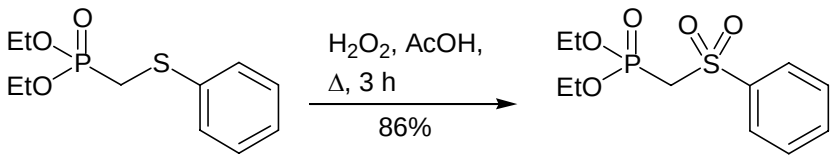
The yields were good to excellent and the (*E*)-selectivity was satisfactory except for the acrylonitrile where the system triethylamine/lithium chloride should have probably been used. The results are summarised in Table 3.

X	Conditions	Product	Yield	(*E*)/(*Z*)[a]
CO_2Et	$(EtO)_2P(O)CH_2CO_2Et$ (1.7 eq), *t*-BuOK (1.5 eq), THF, rt, 14 h	(*S*)-**83a**	quant.	54/1
CO_2t-Bu	$(EtO)_2P(O)CH_2CO_2t$-Bu (1.9 eq), Et_3N (1.7 eq), LiCl (1.7 eq), CH_3CN, 0 °C to rt, 16 h	(*S*)-**83b**	81%[b]	182/1
CN	$(EtO)_2P(O)CH_2CN$ (1.7 eq), *t*-BuOK (1.5 eq), THF, rt, 14 h	(*S*)-**83c**	74%	4.2/1
SO_2Ph	$(EtO)_2P(O)CH_2SO_2Ph$ (1.7 eq), Et_3N (1.5 eq), LiCl (1.5 eq), CH_3CN, 0 °C to rt, 21 h	(*S*)-**83d**	67%	56/1

[a] Determined by ^{1}H-NMR
[b] Over 2 steps

Table 3: Synthesis of the starting material (*S*)-**83a-d** for the synthesis of isoindolines

For the synthesis of the phenylsulfonyl vinyl derivative (*S*)-**83d**, the preparation of the not commercially available phenylsulfonylmethyl-phosphonic acid ethyl ester (**97**) had to be performed before. After oxidation of commercial phenylsulfanylmethyl-phosphonic acid diethyl ester (**96**) with H_2O_2 in AcOH using the protocol described by *S. Müller*[75] the desired phosphonate **97** was obtained in good yield after 3 h reflux (Scheme 20).



96 **97**

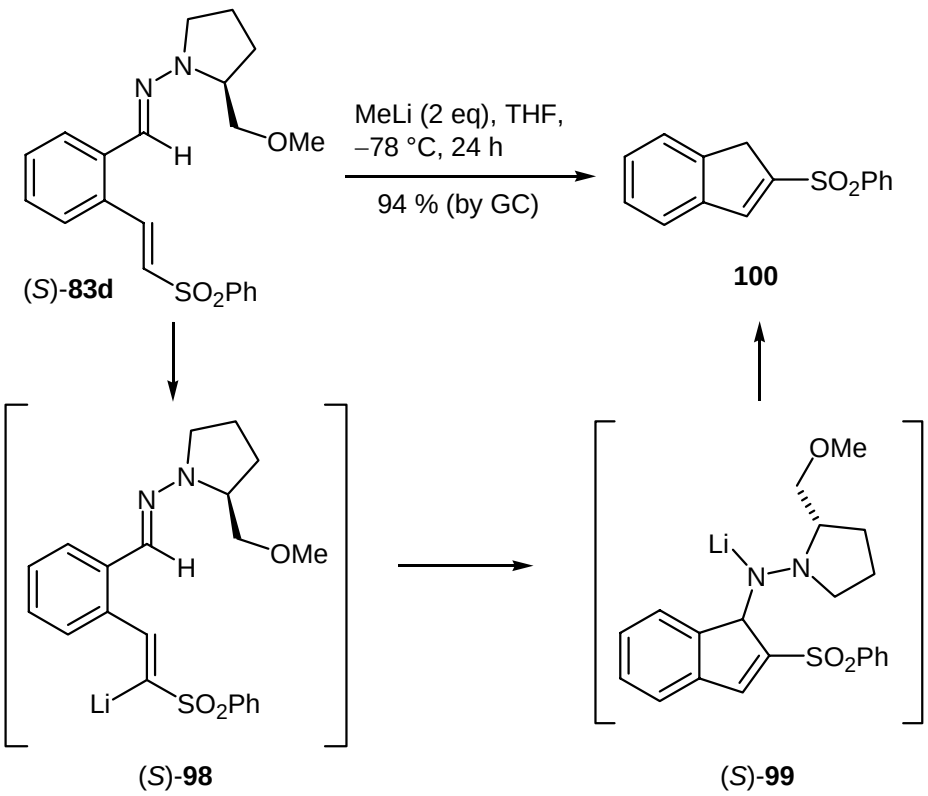
Scheme 20: Preparation of the sulfone phosphonate **97**

3.1.3 SYNTHESIS OF 1,2,3-SUBSTITUTED DIHYDRO-1*H*-ISOINDOLES

The tandem reaction to synthesise substituted 2,3-dihydro-1*H*-isoindoles was first attempted with the phenylsulfonyl vinyl SAMP-hydrazone (*S*)-**83d**. In fact, the risk of a 1,4-addition remains the same for the substrates (*S*)-**83d**, the acrylic acid ester (*S*)-**83a-b** and the

acrylonitrile (*S*)-**83c**. However, the use of the latter compounds could lead to a 1,2-addition to the ester or the nitrile moiety competing with the desired 1,2-addition to the hydrazone.

It had been shown that SAMP-hydrazones derived from aldehydes react with organolithium reagents in a highly stereoselective manner.[76] Our first experiment was performed with methyllithium, small enough to avoid any hindrance problems. Two equivalents were used as usual in literature[76] and a low temperature was maintained to ensure the best diastereoselectivity possible (Scheme 21). The analysis of the crude mixture (^{1}H-NMR and GC) revealed that the reaction led to the formation of only one product. Purification of a small portion of the crude mixture, analysis by NMR- and mass-spectroscopy (*m/z* (%) = 257 ($M^{\bullet+}$+1, 100), 256 ($M^{\bullet+}$, 5)) and comparison with the spectroscopic data available in the literature[77] allowed the identification of the product as 2-benzenesulfonyl-1*H*-indene (**100**). In 1979, *J. J. Eisch et al.* reported the regioselective generation of *α*-lithiated phenyl vinylic sulfone species with methyllithium and without any competing *Michael* additions of methyllithium occurring.[78] The formation of **100** could thus probably be explained by the formation of an intermediate (*S*)-**98** after deprotonation in the *α*-position of the sulfone, 1,2-addition of this lithiated species to the hydrazone to give the intermediate (*S*)-**99** and cleavage of the C─N bond of the hydrazine (Scheme 21).



Scheme 21: Suggested mechanism for the formation of **100**

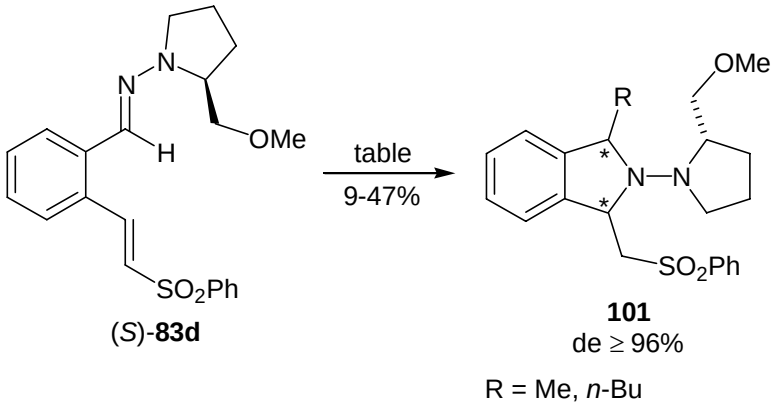
Classical organolithium reagents were thus too basic and promoted the abstraction of the α-vinyl proton of the sulfone. *T. Imamoto et al.* were the first to recognise that organocerium reagents show a lower basicity than organolithium and *Grignard* reagents.[79] In addition organocerium reagents derived from organolithium or organomagnesium reagents have already been used in the past for the highly diastereoselective 1,2-addition to aldehyde SAMP- or related hydrazones to form chiral hydrazines in moderate to good yields.[80] *S. E. Denmark et al.* studied the effect of reagent stoichiometry on efficiency and selectivity in the addition of the methyllithium/cerium chloride system to the chiral hydrocinnamaldehyde SAMEMP-hydrazone. They found that the 1/1 reagent showed the highest selectivities and yields for all equivalents of available methyl nucleophiles.[80f] Furthermore, it was postulated that one equivalent of the organocerium species chelates with the methoxy group of the pyrrolidin ring of the SAMP moiety and the imino nitrogen atom of the hydrazone while another equivalent effectively adds to the CN double bond of the hydrazone.[81]

According to these results, two equivalents of the methyllithium/cerium chloride system (1/1) were added at −100 °C to a solution of the phenylsulfonyl vinyl SAMP-hydrazone (*S*)-**83d**. We were pleased to see that 9% of the desired *N*-substituted isoindoline **101a** could be obtained even if together with 59% of recovered starting material (Scheme 22, Table 4, entry 1). In the molecule (*S*)-**83d**, in addition to the imino nitrogen atom and the methoxy group of the SAMP-hydrazone, the oxygen atoms of the sulfone group were two other potential cerium coordination sites, due to the high oxophilicity of cerium,[79b] and this could explain that starting material was recovered. The amount of the lanthanide nucleophile was then increased to five equivalents which increased the yield to 32% (Entry 2). Although it was impossible to determine the diastereoselectivity of these reactions by analysis of the crude mixture it should be noted that the presence of a diastereoisomer was detected when **101a** was purified by column chromatography. Nevertheless, both diastereoisomers were separable and **101a** could be obtained in high diastereoselectivity.

Organoytterbium reagents have shown an improvement in the yield and diastereoselectivity for certain nucleophile/substrate combinations compared to organolithium or organocerium reagents.[82] Three equivalents of the methyllithium/ytterbium chloride system (1/1) were employed in our reaction system but starting material was entirely recovered suggesting that the organoytterbium species was too big and blocked the nucleophilic attack (Entry 3). Another possible explanation was that the '$RYbCl_2$' species did not add to the hydrazone CN double bond. In fact, *J. Tiebes* reported that species of the type 'YbR_3' were needed for the 1,2-addition in his system.[82a]

In 1997, *S. Kobayashi* reported preferential nucleophilic additions (silyl enol ethers, ketene silyl acetals, allyltributylstannane or cyanotrimethylsilane) to aldimines in the presence of aldehydes with catalytic amounts of ytterbium triflate by selective formation of an aldimine-$Yb(OTf)_3$ complex.[83] It was also shown that silyl enol ethers or tetraallyltin add to benzoyl hydrazones with a catalytic amount of scandium triflate to furnish the corresponding hydrazines in moderate to excellent yields.[84] Moreover, scandium triflate also catalysed the addition of organomagnesium to aldimines[85]. A catalytic amount of ytterbium triflate could selectively complex to the imino nitrogen atom of the hydrazone (*S*)-**83d** and promote the addition of one equivalent of methyllithium. In our plan, a future experiment was also in perspective with the olefin substituted by an ester functionality as in (*S*)-**83a** and (*S*)-**83b**. Since the addition of the nucleophile could occur to several reactive sites in those substrates, the presence of $Yb(OTf)_3$ could help to direct the attack to the hydrazones of those substrates. The addition of methyllithium in presence of a catalytic amount of ytterbium triflate did not lead to any addition after 3 hours at −78 °C in toluene[85] and interestingly **100** could not be detected (Entry 4).

The use of an organocerium species derived from ethyl magnesiumbromide was also tested but led to a complex mixture of products lacking the desired product (Entry 5). To evaluate the range of substituents tolerated by this tandem process two other alkyllithiums in conjunction with cerium chloride were tested. With *tert*-butyllithium the starting material was recovered quantitatively suggesting that the organocerium reagent was too bulky to perform a 1,2-addition (Entry 6). For *n*-butyllithium 47% of the desired isoindoline **101b** was obtained in excellent diastereomeric excess (Entry 7). Due to decomposition during the GC analysis only a purity of 77% could be found. No other estimation of the purity was undertaken.



(*S*)-**83d** → **101**, de ≥ 96%

R = Me, *n*-Bu

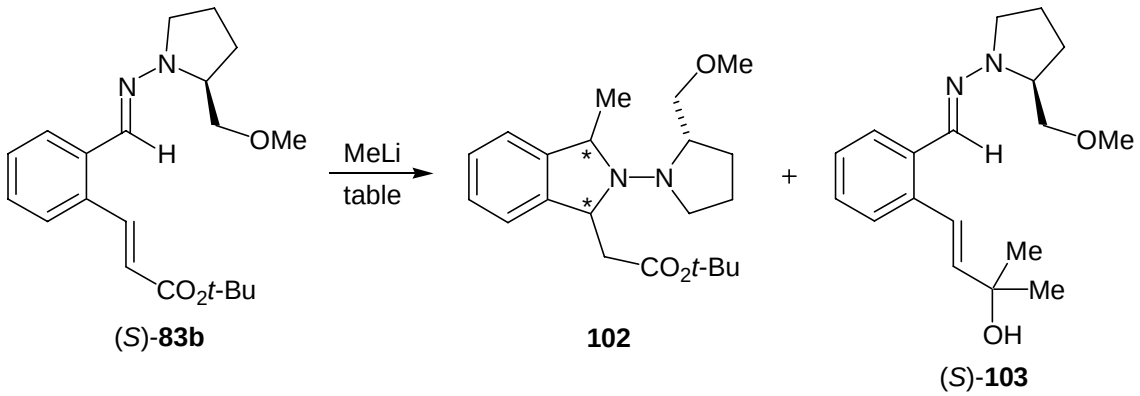
Scheme 22: Synthesis of *N*-substituted 1,3-disubstituted 2,3-dihydro-1*H*-isoindoles **101**

Entry	R	Conditions	Product	Yield	*de*[a]
1	Me	MeLi/$CeCl_3$ (2 eq), THF, −100 °C to rt, 22 h	(*S*)-**101a**	9% + 59% (*S*)-**83d**	≥ 96%
2	Me	MeLi/$CeCl_3$ (5 eq), THF, −100 °C to rt, 40 h	(*S*)-**101a**	32%	≥ 96%
3	Me	MeLi/$YbCl_3$ (3 eq), THF, −100 °C to rt, 22 h	-	starting material	-
4	Me	MeLi (1 eq), $Yb(OTf)_3$ (0.2 eq), toluene, −78 °C, 3 h	-	starting material	-
5	Et	EtMgBr/$CeCl_3$ (3 eq), THF, −100 °C to rt, 18 h	-	complex mixture of products	-
6	*t*-Bu	*t*-BuLi/$CeCl_3$ (3 eq), THF, −100 °C to rt, 41 h	-	starting material	-
7	*n*-Bu	*n*-BuLi/$CeCl_3$ (3 eq), THF, −50 °C to rt, 18 h	(*R*)-**101b**[b]	47% (min.)	≥ 96%

[a] Determined by ^{1}H-NMR after column chromatography
[b] With RAMP as auxiliary

Table 4: Tandem 1,2-addition/*Michael*-addition/ring closure for the formation of **101**

To widen the scope of the substituents at the olefin, the combination methyllithium/cerium chloride was applied to the acrylic acid *tert*-butyl ester SAMP-hydrazone (*S*)-**83b**, less prompted to a 1,2-addition to the ester moiety than the ethyl ester **83a** (Scheme 23). After reaction with 5 equivalents of this system, the isoindoline **102** was not formed but the product (*S*)-**103** was obtained in 63% yield (from GC analysis) (Table 5). This product, identified from the NMR-analysis of the crude mixture, resulted from a double addition of 2 methyl groups to the ester functionality. In fact, *T. Imamoto* showed that the strong carbonylophilicity of the organocerium reagents results in the exclusive formation of 1,2-addition products with *α,β*-unsaturated carbonyl compounds.[79d] In addition, an attempt using a catalytic amount of ytterbium triflate in combination with methyllithium was performed. A selective complexation of the triflate with the hydrazone was expected to promote the 1,2-addition of methyllithium to the hydrazone. This experiment mostly left (*S*)-**83b** untouched (Table 5).



(*S*)-**83b** **102** (*S*)-**103**

Scheme 23: Attempted formation of the isoindoline **102**

Conditions	Results[a]
MeLi/$CeCl_3$ (5 eq), THF, –100 °C, 3 h	63% of (*S*)-**103**
MeLi (1 eq), $Yb(OTf)_3$ (0.2 eq), THF, –100 °C to –78 °C, 17 h	81% of (*S*)-**83b** + 7% of (*S*)-**103**

[a] Determined by GC analysis of the crude mixture

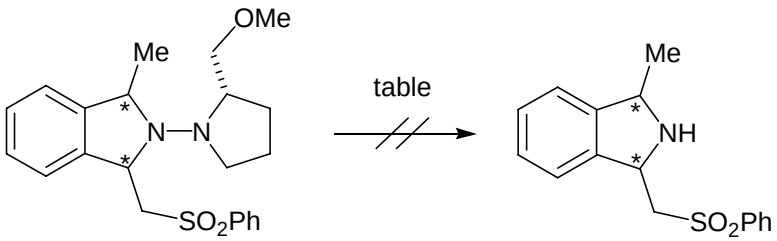
Table 5: Conditions of the attempts for the formation of isoindoline **102**

3.1.4 TOWARDS THE SYNTHESIS OF 1,3-SUBSTITUTED DIHYDRO-1*H*-ISOINDOLES

After the 1,2-addition/ring closure only the cleavage of the chiral auxiliary remained to accomplish the synthesis of the desired 1,3-disubstituted 2,3-dihydro-1*H*-isoindoles **81**. It is noteworthy that among the large variety of methods offered to cleave the N─N bond, some of the procedures are efficient exclusively with an *α*-carbonyl hydrazine or, if there is no carbonyl group, with an hydrazine activated by a carbamate function (cleavage by samarium diiodide,[86] magnesium monoperoxyphtalate hexahydrate,[61,87] lithium in liquid ammonia).[76a,f,80a-c,g,88]

For our synthesis the methods allowing the cleavage of hydrazines without neighbouring carbonyl group should be used (Scheme 24). The cleavage of tetrasubstituted hydrazines using an excess of borane-THF complex was published by *C. Kibayashi*.[89] However, in our case only starting material was recovered when quenching the reaction with methanol as well as with hydrochloric acid (Table 6). Following the procedure described by *M. Klatt*[90] a reductive cleavage by means of *Raney* nickel was also attempted as it was shown to cleave

inactivated tri- and tetrasubstituted hydrazines.[76d,g,80d,91] Unfortunately, probably due to the mild conditions, the starting material stayed untouched (Table 6).



101a
de ≥ 96%

81a

Scheme 24: Attempted N─N cleavage of the auxiliary

Conditions	Results
BH_3·THF (10 eq), THF, Δ, 4 h then MeOH, Δ, 2 h	starting material
BH_3·THF (20 eq), THF, Δ, 20 h then 1 N HCl, Δ, 1 h	starting material
Ra-Ni, H_2,))), MeOH, rt, 24 h	starting material

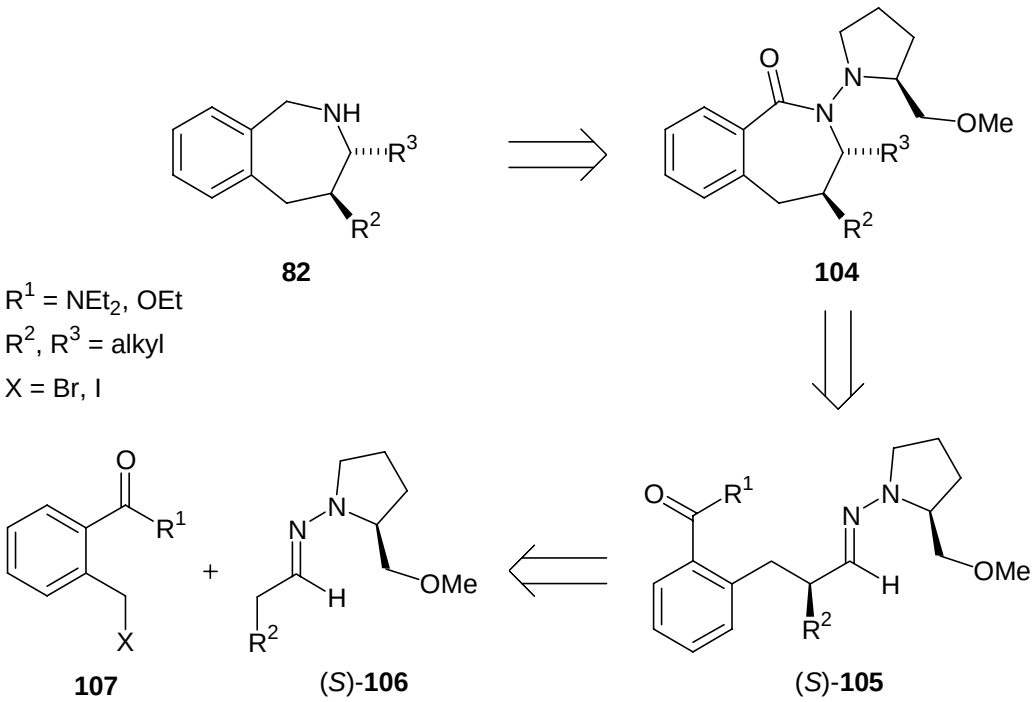
Table 6: Conditions of the attempts for the N─N cleavage of the auxiliary

For time reasons the attempts for the cleavage of the chiral auxiliary were abandoned. However, some possibilities for this step remained, e. g. zinc in acetic acid[92] or a preactivation of the hydrazines with methoxycarbonyl chloride before using standard conditions such as *Raney* nickel.[93]

3.2 TOWARDS THE ASYMMETRIC SYNTHESIS OF TETRAHYDRO-2-BENZAZEPINES

3.2.1 RETROSYNTHETIC CONCEPT

The aim of this project was the first diastereo- and enantioselective synthesis of 3,4-disubstituted 2,3,4,5-tetrahydro-1*H*-2-benzazepines **82**. Our synthetic strategy should allow a broad range in the 3- and 4-substitution. The desired tetrahydro-2-benzazepines **82** could result from reduction and N─N bond cleavage of the chiral auxiliary of the *N*-substituted tetrahydro-2-benzazepinone **104**. The construction of this precursor should rely on a tandem 1,2-addition/ring closure sequence. Thus, the 1,2-addition of an organometallic reagent to SAMP-hydrazone (*S*)-**105**, bearing a stereogenic centre in *α*-position, would introduce the second stereogenic centre in the molecule. The anion generated in this process should promote a subsequent ring closure with an amide or an ester functionality installed on the phenyl ring. The precursor **105** should be formed by *α*-alkylation of an aliphatic aldehyde SAMP-hydrazone (*S*)-**106** with a benzyl halide **107** substituted in *ortho*-position by an ester or an amide (Scheme 25).

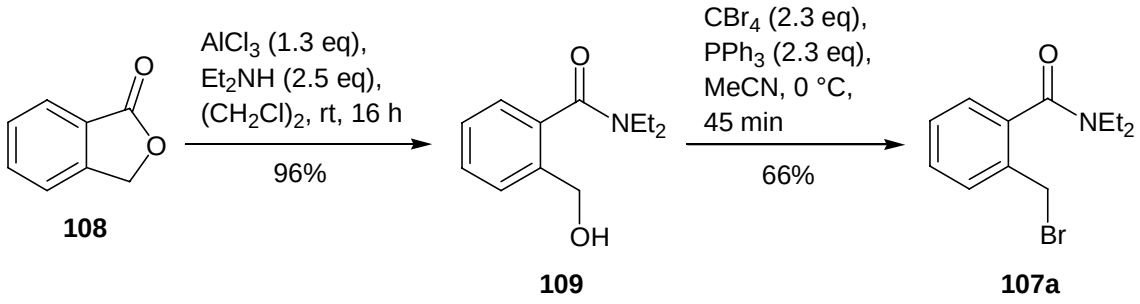


Scheme 25: Retrosynthetic analysis for disubstituted tetrahydro-2-benzazepines synthesis

3.2.2 SYNTHESIS OF THE ELECTROPHILES

For the first step in the synthesis of our first electrophile a protocol developed by *D. C. H. Bigg et al.* for the aluminium chloride mediated aminolysis of lactones was repeated.[94] The authors reported that for optimal yields at least one equivalent of aluminium chloride and two equivalents of the amine have to be employed, consistent with a mechanism involving the formation of an amine-aluminium chloride complex which activates the lactone towards an attack by the second equivalent of the amine. Phthalide (**108**) was reacted with an excess of aluminium chloride and diethylamine to give the desired 2-hydroxymethyl benzamide **109** in a excellent yield of 96% representing an improvement of 15% compared to the reported yield (Scheme 26).

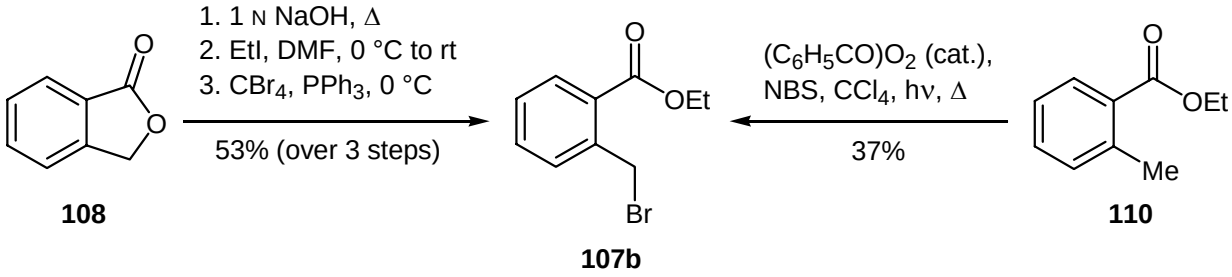
Replacement of the hydroxyl group with a bromine functionality was accomplished using the carbon tetrabromide/triphenylphosphine system,[95] an extension of the method described by *R. Appel*.[96] The 2-hydroxymethyl benzamide **109** was allowed to react with 2.3 equivalents of triphenylphosphine and carbon tetrabromide to give the desired 2-bromomethyl benzamide **107a** in 66% yield (Scheme 26). This relatively low yield, compared to the high yields generally obtained with the *Appel*'s method, could be explained by the fact that the benzylbromide **107a** slowly transforms, even at –25 °C, into the corresponding imidate salt. However, as the salt is insoluble in THF, **107a** can be obtained in pure form.



Scheme 26: Synthesis of the bromomethyl benzamide electrophile **107a**

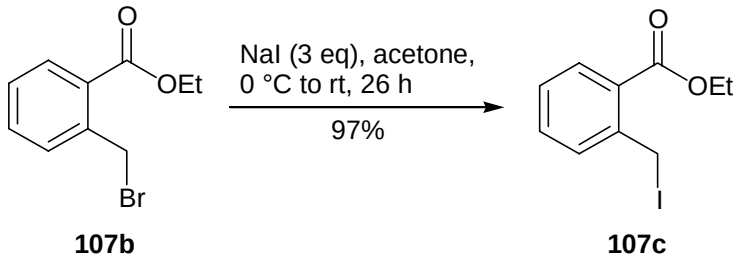
The synthesis of the second electrophile also started from the commercially available phthalide (**108**). After transformation into its corresponding sodium 2-hydroxymethyl benzoate by reflux with an aqueous solution of NaOH and drying under high vacuum, the salt of was converted to an ester using ethyl iodide. Alcohol/bromide exchange was readily achieved using the *Appel*'s conditions detailed above. The desired electrophile **107a** was obtained in good yield (53%) for this three step sequence (Scheme 27).

We also tried to reduce the synthesis of this electrophile to only one step by repeating the protocol of *R. F. Pratt et al.* describing the radical bromination of the ethyl *o*-toluate (**110**) in a *Wohl-Ziegler*-type reaction.[97] Thus, a catalytic amount of dibenzoyl peroxide was used as initiator and the benzylic radical derived from **110** reacted with *N*-bromosuccinimide to give the benzylbromide **107b**. The flask was irradiated with visible light from a 150 W tungsten lamp while the mixture was heated under reflux to prolong the propagation of the reaction. However, we were unable to reproduce the literature result and **107b** was only obtained in 37% yield (Scheme 27).



Scheme 27: Syntheses of the electrophile 2-bromomethyl benzoic acid ethyl ester (**107b**)

The synthesis of the third electrophile simply consisted in a bromide/iodine exchange using *Finkelstein*'s reaction on the bromide **107b**. Thus, the benzylbromide was reacted with an excess of NaI in acetone and the benzyliodide **107c** was obtained in nearly quantitative yield (Scheme 28).

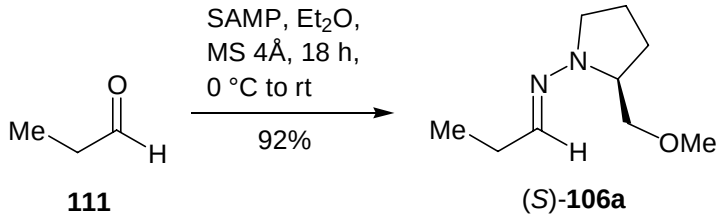


Scheme 28: Synthesis of the electrophile 2-iodomethyl benzoic acid ethyl ester (**107c**)

3.2.3 FORMATION OF THE TANDEM PRECURSOR BY *α*-ALKYLATION

To evaluate our synthetic strategy, the propanal SAMP-hydrazone (*S*)-**106a** was chosen as model nucleophile in the *α*-alkylation to form the tandem precursor **105**. In fact its easy access and its good 'behaviour' in standard *α*-alkylations[74] make it the reagent of choice for the

optimisation of the reaction. (*S*)-**106a** was obtained in excellent yield by condensation of propanal and SAMP using the conditions described above (3.1.2.2) (Scheme 29).



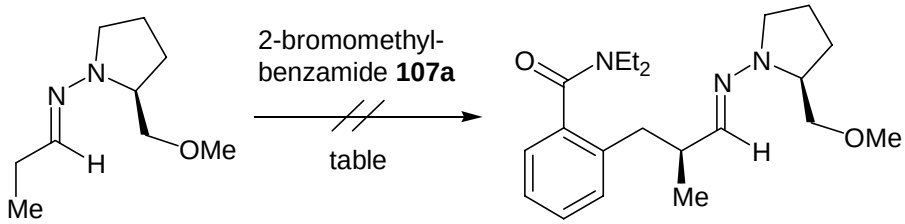
111 (*S*)-**106a**

Scheme 29: Synthesis of the propanal SAMP-hydrazone (*S*)-**106a**

3.2.3.1 ATTEMPTS OF AN *α*-ALKYLATION USING ELECTROPHILE 107a

The *α*-alkylation was first attempted with the 2-bromomethyl benzamide **107a**. The propanal SAMP-hydrazone (*S*)-**106a** was deprotonated with LDA at 0 °C within 4 h before two equivalents of the electrophile were added at −100 °C. The temperature was allowed to warm up to room temperature during the 20 hours of reaction time. A complex mixture of products was obtained in which starting materials and traces of the desired product (*S*,*S*)-**105a** could be identified (Scheme 30, Table 7).

In order to increase the yield we thought to let the lithiation of (*S*)-**106a** be followed by the addition of a supplementary equivalent of *n*-butyllithium in order to deprotonate the formed diisopropylamine. The advantage of this protocol was reported by *J. Tiebes* who demonstrated that the yield of the alkylation of the TBS-protected 5-hydroxy pentanal SAMP-hydrazone with methyl iodide could be increased from 58% to 78% when changing from a simple lithiation to an additional deprotonation.[88b] Unfortunately this protocol did not lead to further improvements (Table 7).



(*S*)-**106a** (*S*,*S*)-**105a**

Scheme 30: Attempted formation of (*S*,*S*)-**105a**

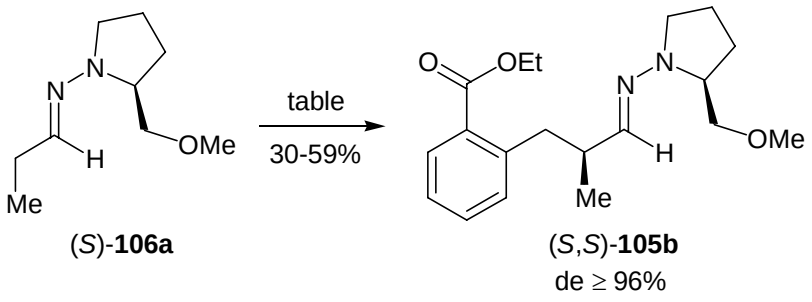
Conditions	Results
LDA (1.1 eq), 0 °C, 4 h then **107a** (2.0 eq), −100 °C to rt, 20 h	traces of (*S*,*S*)-**105a**
LDA (1.1 eq), 0 °C, 4 h then *n*-BuLi (1.1 eq), 0 °C, 1 h then **107a** (2.0 eq), −78 °C, 16 h	traces of (*S*,*S*)-**105a**

Table 7: Conditions attempted for the synthesis of (*S*,*S*)-**105a**

3.2.3.2 SYNTHESIS OF THE *α*-ALKYLATED PRODUCT

It was obvious that the access to the bromide was hindered by the presence of the *N*,*N*-diethyl amide group and that the two electrophiles **107b** and **107c,** only substituted by a ethyl ester group, had now to be tested then.

After deprotonation of (*S*)-**106a** with LDA at 0 °C, 1.4 equivalents of the benzylbromide **107b** were added keeping the reaction at −78 °C for 8 hours. Under these conditions 32% yield of the desired product (*S*,*S*)-**105b** was obtained with an excellent diastereomeric excess of 96% (Scheme 31, Table 8). We then turned to the electrophile **107c** to see if the iodide was more reactive towards the *α*-alkylation. By using nearly the same conditions for the *α*-alkylation as for the benzylbromide **107b** the yield was very close (30%) showing that in these conditions the reactivity of the halide functionality did not play a key role (Table 8). The temperature was also a parameter to vary in order to increase the yield of the alkylation. The reaction was then performed with the benzyliodide at −100 °C and the temperature was slowly increased overnight. An improved yield (59%) was observed with no change concerning the excellent diastereoselectivity (Table 8).



(*S*)-**106a** (*S*,*S*)-**105b**
de ≥ 96%

Scheme 31: Synthesis of the tandem reaction precursor (*S*,*S*)-**105b**

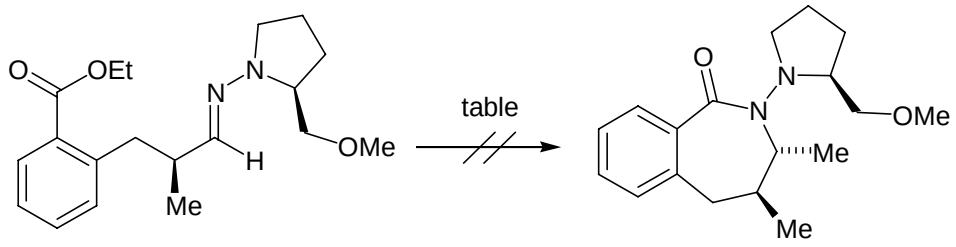
Electrophile	Conditions	Yield	*de*[a]
107b	LDA (1.0 eq), 0 °C, 17 h then **107b** (1.4 eq), −78 °C, 8 h	32%	≥ 96%
107c	LDA (1.0 eq), 0 °C, 19 h then **107c** (1.1 eq), −78 °C, 21 h	30%	n. d.
107c	LDA (1.1 eq), 0 °C, 18 h then **107c** (1.05 eq), −100 °C, 4 h then −100 °C to rt, 18 h	59%	≥ 96%

[a] Determined by ^{1}H-NMR after column chromatography

Table 8: Conditions for the synthesis of the tandem precursor (*S*,*S*)-**105b**

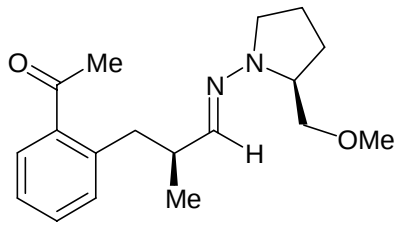
3.2.4 ATTEMPTS FOR THE TANDEM 1,2-ADDITION/RING CLOSURE SEQUENCE

A first experiment, using the tandem precursor (*S*,*S*)-**105b** and two equivalents of methyllithium at −100 °C and warming up the reaction overnight, did not give any of the desired product (*R*,*S*,*S*)-**104a** (Scheme 32). Instead 41% of ketone (*S*,*S*)-**112** and 29 % of alcohol (*S*,*S*)-**113** could be isolated showing that the ester functionality on the phenyl ring was more reactive than the hydrazone (Figure 17, Table 9). In a second test reaction the use of an organocerium reagent was investigated as it could activate the hydrazone compared to the ester. Two equivalents of a methyllithium/cerium chloride system were used maintaining the temperature at −100 °C over 5 h. Unfortunately, only starting material and alcohol (*S*,*S*)-**113** could be isolated showing that the cerium, due to its oxophilicity, preferentially activates the ester to allow a double addition of the nucleophile (Figure 17, Table 9).

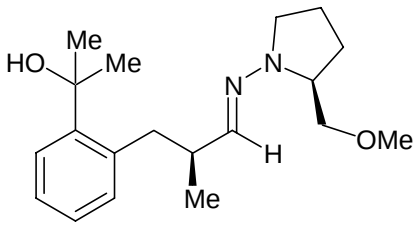


(*S*,*S*)-**105b** (*R*,*S*,*S*)-**104a**

Scheme 32: Attempts for the synthesis of (*R*,*S*,*S*)-**104a**



(*S*,*S*)-**112**



(*S*,*S*)-**113**

Figure 17: Products obtained in the 1,2-addition of (*S*,*S*)-**105b**

Conditions	Results
MeLi (2.0 eq), THF, −100 °C, 5 h then −100 °C to rt, 16 h	41% of (*S*,*S*)-**112** + 29% of (*S*,*S*)-**113**
MeLi/$CeCl_3$ (2.0 eq), THF, −100 °C, 5 h	40% of (*S*,*S*)-**113** + 20% starting material

Table 9: Conditions of the attempts for the synthesis of (*R*,*S*,*S*)-**104a**

Taking into account that a tandem 1,2-addition/ring closure sequence could not be perfomed on our precursor (*S*,*S*)-**105b**, only a complete change in the synthetic strategy could lead to the synthesis of 3,4-disubstituted 2,3,4,5-tetrahydro-1*H*-2-benzazepines **82**. Our project was then abandoned.

3.3 ASYMMETRIC SYNTHESIS OF TETRAHYDROPALMATINE

In the protoberberine family the substitutions of the A ring are always situated at the same positions whereas the substitution pattern of the D ring can slightly vary. In many reported formal or total syntheses the ring closure was effected between the isoquinoline core, containing the A ring, and the D ring using for example a *Pictet-Spengler* reaction. Thus, the synthesis of the tetrahydropalmatine was rendered difficult, the positions of the methoxy substituents favoring another product in this type of ring closure reactions (see 1.3.2).

Our initial thought was to design the synthetic strategy in a way that the asymmetric total synthesis of most of the protoberberines was possible. To achieve this goal, the ring closure should be done between the isoquinoline core with the D ring bearing the correct methoxy substitution pattern, and the A ring. First the total synthesis of tetrahydropalmatine was chosen to show that this molecule was also accessible by our synthesic strategy (Figure 18).

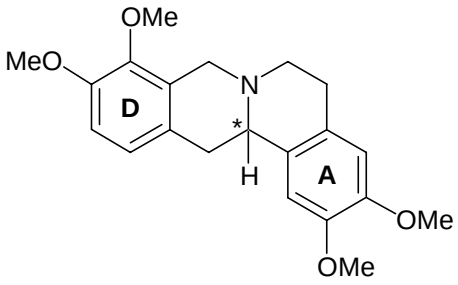
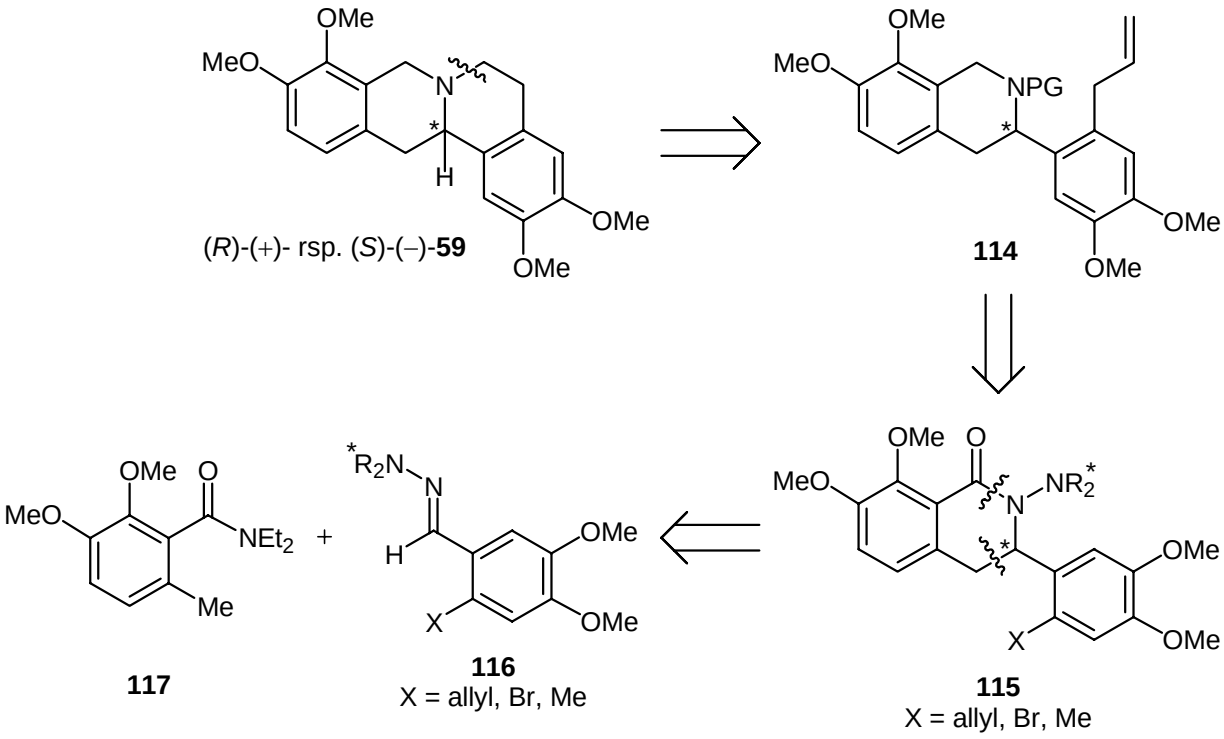


Figure 18: (*R*)-(+)- respectively (*S*)-(−)-tetrahydropalmatine

3.3.1 RETROSYNTHETIC CONCEPT: REDUCTIVE AMINATION

The target molecules (*R*)-(+)- and (*S*)-(−)-tetrahydropalmatine (**59**) should be obtained after ozonolysis, deprotection and reductive amination of the precursor **114**. This protected tetrahydroisoquinoline should be substituted in the 3-position by a phenyl bearing an allyl chain in *ortho*-position. The correct methoxy substitution pattern in **59** would be assured by this fixed substitution during the ring closure. The construction of **114** could derive from the *N*-substituted 3-phenyl substituted dihydroisoquinolinone **115** after N─N cleavage of the chiral auxiliary, reduction of the amide functionality and protection of the resulting free amine. However, in order to introduce the allyl chain the protected amine derived from **115**, substituted by a bromide, would have to be submitted to an additional *Stille*-coupling with allyltributylstannane. As a supplementary option the allyl chain could also be introduced into

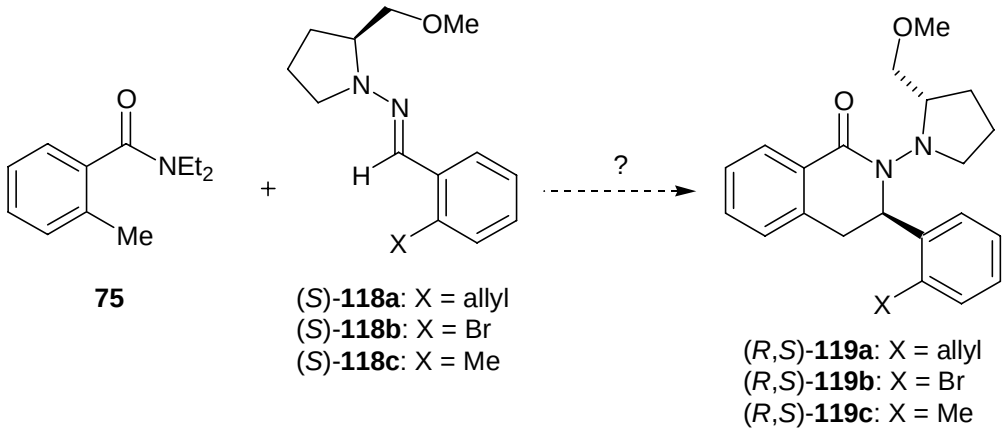
the protected amine derived from **115** and substituted by a methyl group, which should first be transformed into a benzylic bromide by radical bromination in order to be submitted to a *Stille*-coupling with vinyltributylstannane. The generation of the dihydroisoquinolinone precursor **115** should be based on the tandem 1,2-addition/ring closure methodology developed by *V. Braig*[62] leading to the 2,3-dimethoxy-6-methyl-benzamide **117** and the 3,4-dimethoxy benzaldehyde SAMP- rsp. RAMP-hydrazone **116** *ortho*-substituted either by an allyl chain, a bromide or a methyl group (Scheme 33).



Scheme 33: Retrosynthetic concept for (*R*)-(+)- and (*S*)-(–)-**59** by reductive amination

3.3.1.2 MODEL STUDY: SYNTHESIS OF THE STARTING MATERIALS FOR THE TANDEM PROCESS

Our retrosynthetic strategy was based on the tandem 1,2-addition/ring closure process as key step. It was then necessary to evaluate in a model study the possibilities in terms of yield and diastereoselectivity offered by a reaction between the simple 2-methyl benzamide **75** and the 2-substituted benzaldehyde SAMP-hydrazone (*S*)-**118a**, (*S*)-**118b** or (*S*)-**118c** (Scheme 34).

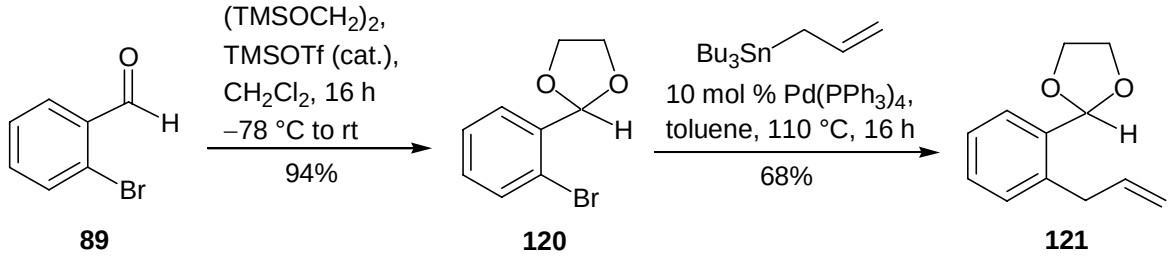


Scheme 34: Model study for the evaluation of the synthetic strategy

As 2-allyl benzaldehyde is not commercially available it was necessary to synthesise it in the shortest possible route to minimize the number of steps of our future total synthesis.

The ethylene glycol acetal **120** was formed, using the *Noyori* variant[98], by reaction of the 2-bromo-benzaldehyde (**89**) with TMS-protected ethylene glycol catalysed by trimethylsilyl trifluoromethanesulfonate (TMSOTf). The very good yield of 94% represented a slight improvement of the reaction described in the literature with *p*-toluenesulfonic acid and ethylene glycol under azeotropic removal of the water formed during the reaction.[99]

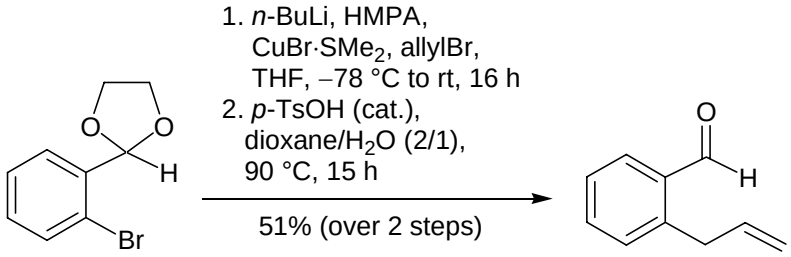
We then thought to use palladium catalysis to introduce the allyl chain. The bromide **120** was submitted to a *Stille*-coupling with allyltributylstannane and a catalytic amount of active tetrakistriphenylphosphinepalladium(0) in hot toluene. A yield of 68% was obtained for the desired compound **121** (Scheme 35).



Scheme 35: Synthesis of the allyl-substituted acetal **121**

For comparison, the synthesis of the 2-allyl benzaldehyde (**122**) was achieved repeating a protocol that *J. A. Kampeier et al*. had described.[99] After lithium/halogen exchange of the bromide **120** with *n*-butyllithium at −78 °C, a stoichiometric amount of HMPA was added.

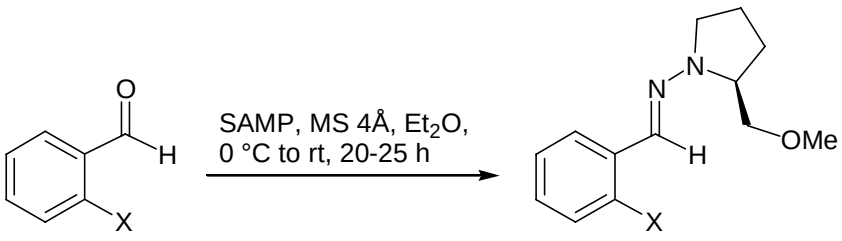
The lithiated species was then transmetalated at –50 °C with the copper bromide-dimethyl sulfide complex. The reductive elimination was performed with allyl bromide at –20 °C. The deprotection of the crude allyl compound was realised using a catalytic amount of *para*-toluene sulfonic acid in a hot mixture of 1,4-dioxane and water. The pure 2-allylbenzaldehyde (**122**) was obtained in a moderate yield of 51% and despite several attempts we were not successful to reproduce the yield of 80% described by the authors (Scheme 36).



120 **122**

Scheme 36: Synthesis of 2-allyl benzaldehyde (**122**)

The synthesis of the SAMP-hydrazones (*S*)-**118a**, (*S*)-**118b** and (*S*)-**118c** were achieved in excellent yield by condensation of SAMP with the corresponding benzaldehydes **122**, **89** and **123** in Et_2O using molecular sieves to remove the water formed during the reaction (Scheme 37).



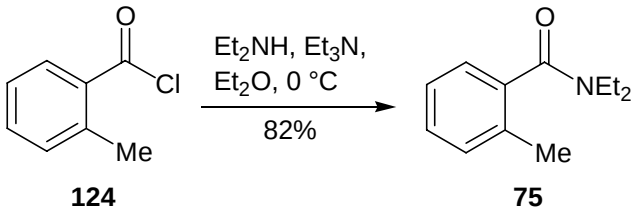
122: X = allyl
89: X = Br
123: X = Me

(*S*)-**118a**: X = allyl; 95%
(*S*)-**118b**: X = Br; 92%
(*S*)-**118c**: X = Me; 90%

Scheme 37: Synthesis of the 2-substituted benzaldehyde SAMP-hydrazones

The 2-methylbenzamide **75** required for the tandem 1,2-addition/ring closure was synthesised using the protocol developed by *V. Braig*.[62] Diethylamine was added to the commercially available 2-methyl benzoyl chloride (**124**) using triethylamine as a proton sponge that formed

a salt with the HCl gas formed during the reaction. The reaction occured immediately and yielded the desired product in 82% yield (Scheme 38).



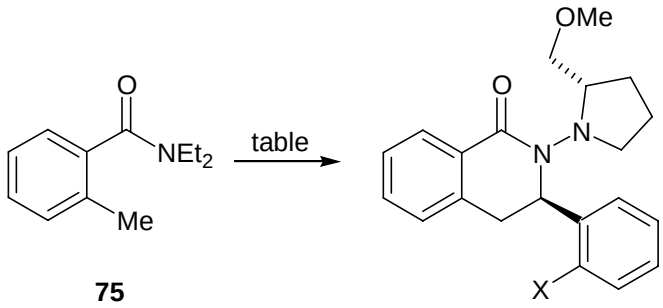
124 **75**

Scheme 38: Synthesis of the 2-methyl benzamide **75**

3.3.1.2 MODEL STUDY: ATTEMPTS FOR THE TANDEM 1,2-ADDITION/RING CLOSURE SEQUENCE

Having in hand all necessary components, we performed the tandem reaction process. 7 equivalents of the 2-methyl benzamide **75** were deprotonated using an equimolar amount of LDA at –45 °C or –78 °C to minimise the risk of self condensation.[55a] The lithiated species was then reacted with the 2-substituted benzaldehyde SAMP-hydrazones (*S*)-**118a**, (*S*)-**118b** or (*S*)-**118c** previously complexed with $AlMe_3$ at –40 °C (Scheme 39, Table 10).

However, even under optimised conditions,[62] we could not detect the dihydroisoquinolinone (*R*,*S*)-**119a**. Instead we isolated a complex mixture of products containing some starting material together with its isomer the (2*E*)-2-propenyl benzaldehyde SAMP-hydrazone. For the bromide substituted SAMP-hydrazone (*S*)-**118b**, only 11% of the dihydroisoquinolone (*R*,*S*)-**119b** could be isolated in an excellent diastereoselectivity of 96%. By comparing this result with the 65% yield previously obtained[62] with the *para*-bromobenzaldehyde SAMP-hydrazone (*S*)-**76** (see 1.3.3), we conclude that the bromide was too bulky as *ortho*-substituent and that we should obtain a better result using a smaller substituent. In fact a slight increase in the yield of this reaction was observed switching from the bromide to the methyl substituent. This time the tandem 1,2-addition/ring closure between 2-methyl benzamide **75** and the 2-methylbenzaldehyde SAMP-hydrazone (*S*)-**118c** gave 27% of the desired dihydroisoquinolone (*R*,*S*)-**119c** with a diastereomeric excess beyond 96%.



75
(7.0 eq)

(*R*,*S*)-**119a**: X = allyl
(*R*,*S*)-**119b**: X = Br
(*R*,*S*)-**119c**: X = Me

Scheme 39: Synthesis of the *N*-substituted 3-substituted dihydroisoquinolinone (*R*,*S*)-**119**

X	Conditions	Product	Yield	*de*[a]
allyl	LDA (7.0 eq), THF, –45 °C then (*S*)-**118a**, $AlMe_3$ (1.1 eq), THF, –40 °C, 17 h	-	complex mixture	-
Br	LDA (7.0 eq), THF, –45 °C then (*S*)-**118b**, $AlMe_3$ (1.1 eq), THF, –40 °C, 16 h	(*R*,*S*)-**119b**	11%	≥ 96%
Me	LDA (7.0 eq), THF, –78 °C then (*S*)-**118c**, $AlMe_3$ (1.1 eq), THF, –40 °C, 20 h	(*R*,*S*)-**119c**	27%	≥ 96%

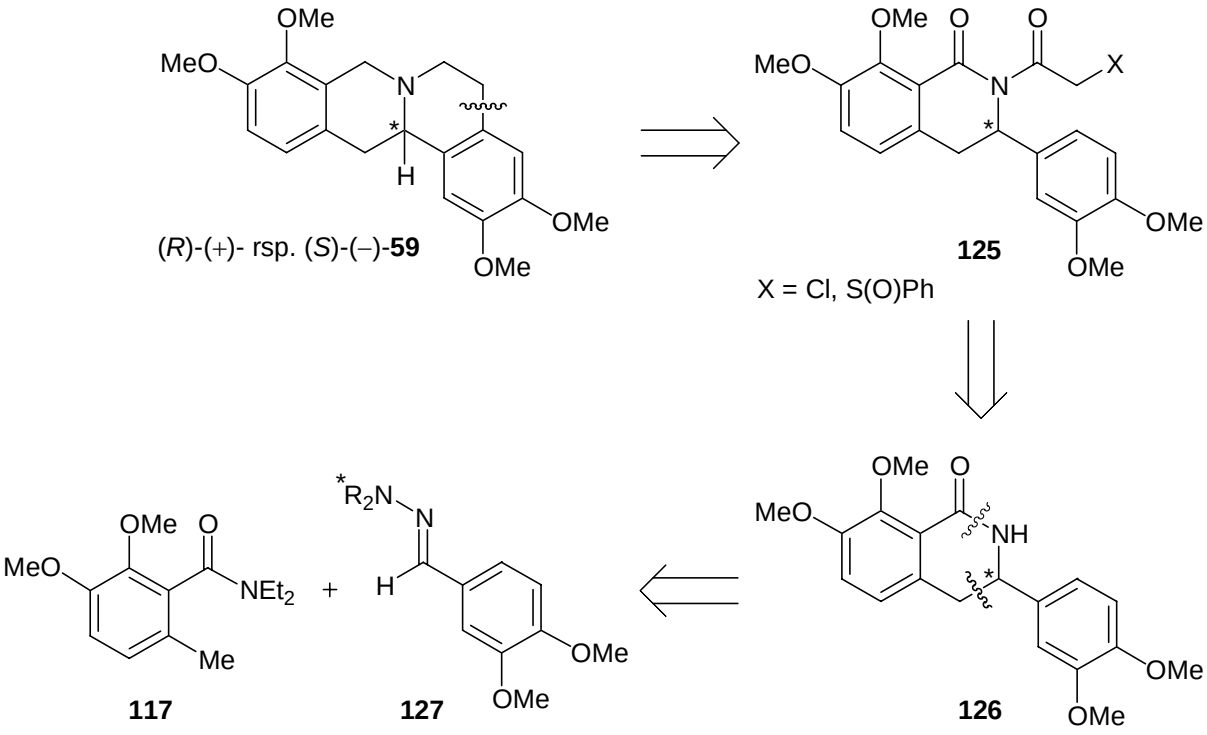
[a] Determined by ^{1}H-NMR after column chromatography

Table 10: Conditions for the synthesis of the dihydroisoquinolinones (*R*,*S*)-**119b-c**

This series of reactions showed that the system did not tolerate any *ortho*-substitution on the benzaldehyde SAMP-hydrazone. The best yield, obtained for the methyl substituent (27%) in our model system, was far too low as second and key step in a total synthesis. Our synthesis strategy should be reviewed and include a ring closure of the tetrahydropalmatine core which did not require the help of an *ortho*-substituent on the phenyl ring of our 3-substituted dihydroisoquinolone system.

3.3.2 RETROSYNTHETIC CONCEPT: NITROGEN FUNCTIONALISATION-RING CLOSURE-REDUCTION

In this approach, the target molecules (*R*)-(+)-**59** or (*S*)-(–)-**59** should be obtained from a dihydroisoquinolinone precursor **125** bearing on the nitrogen an acetyl group substituted with a chloride or a sulfoxide. After a *Friedel-Crafts* or a *Pummerer* reaction, securing the correct position of the methoxy substitution pattern during the ring closure, the reduction of the two carbonyl groups present in the molecule should lead to **59**. The introduction of the acetyl chain could be done in a nitrogen functionalisation of the dihydroisoquinolinone **126** with the corresponding acetyl chloride. The 3-phenyl substituted dihydroisoquinolin-1-one **126** would be obtained using the tandem 1,2-addition/ring closure between the 2-methyl benzamide **117** and the benzaldehyde SAMP- or RAMP-hydrazone **127**, lacking *ortho*-substitution, both bearing the correct methoxy substitution patterns. Subsequent removal of the chiral auxiliary should lead to **126** (Scheme 40).

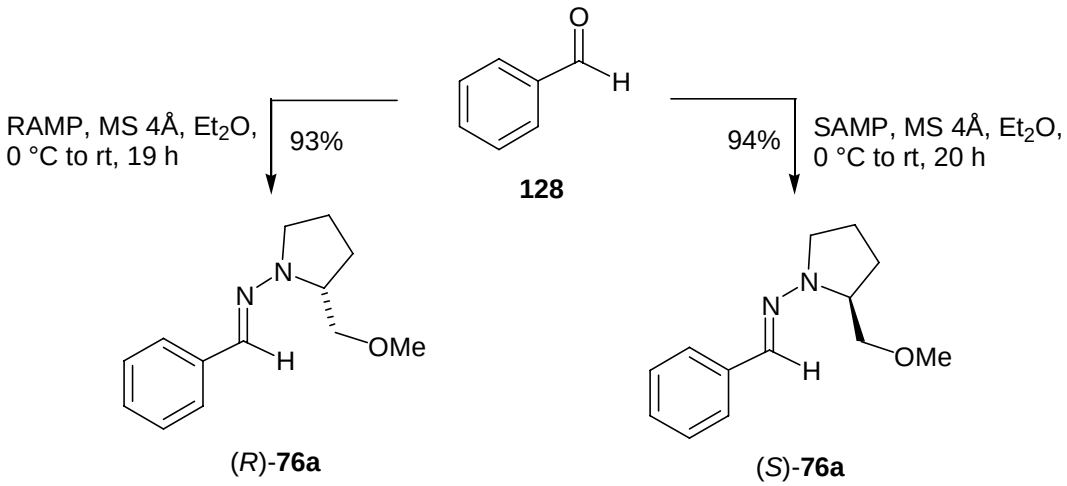


Scheme 40: Retrosynthetic concept *via* nitrogen functionalisation-ring closure-reduction

Again the feasibility of our synthetic strategy was first tested by performing all reactions without the methoxy substituents on the aromatic rings.

3.3.2.1 MODEL STUDY: OPTIMISATION OF THE TANDEM 1,2-ADDITION/RING CLOSURE SEQUENCE

Already having in hands the necessary 2-methyl-benzamide **75** we only needed to synthesise the benzaldehyde SAMP- and RAMP-hydrazones, respectively (*S*)-**76a** and (*R*)-**76a** to perform the tandem reaction. This was easily achieved, using the same conditions as described above (see 3.1.2.2), by condensation of SAMP respectively RAMP with benzaldehyde **128**. Both enantiomers were obtained in excellent yields (Scheme 41)

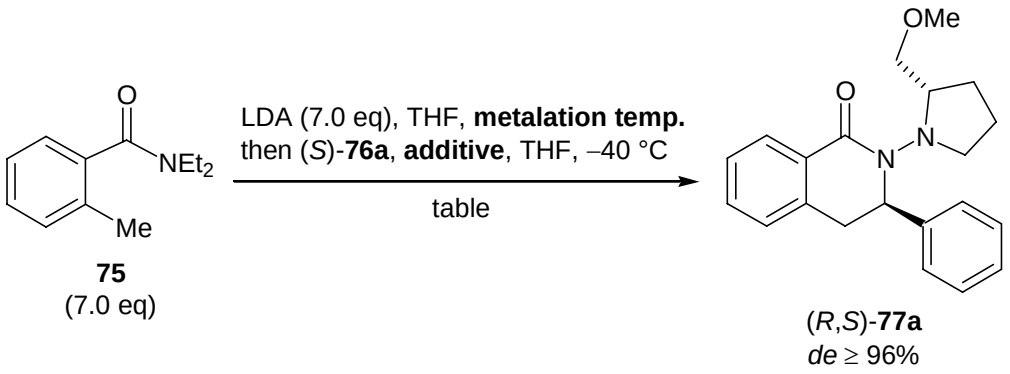


Scheme 41: Synthesis of the SAMP- and RAMP-hydrazones (*S*)-**76a** and (*R*)-**76a**

At this point an optimisation of the tandem process was necessary to ensure the best yield in our key step. When performing the reaction several times we noticed that the yield was hardly reproducible. Until now only the number of equivalents of 2-methyl benzamide **75** had been optimised and some *Lewis* acids had been tested but a rational variation of some parameters such as temperature or solvent had not been realised yet.[62]

First the metalation temperature as well as some new additives were evaluated in the tandem reaction (Scheme 42, Table 11). A slightly increased yield was observed in the reaction with the trimethylaluminium *Lewis* acid by switching the metalation temperature of the 2-methyl benzamide **75** from –45 °C to –78 °C (Entry 1 vs. 2, Table 11). We first thought that the differences in the yield were due to an addition of a methyl group of the trimethylaluminium to the hydrazone during the complexation period consistent with the gas emission observed during the addition of the *Lewis* acid. Therefore, Al(*i*-Bu)$_3$, was chosen for its bulkiness in order to prevent any addition to the hydrazone during the complexation. This attempt only gave rise to 16% of the desired product. In spite of our expectations, a bubbling and an

exothermic reaction during its addition showed its even bigger reactivity towards the hydrazone (Entry 3). Two other *Lewis* acids which should not add to the hydrazone were tested but trimethylsilyltriflate (TMSOTf) gave only 31% of the product (Entry 4) and ytterbium triflate ($Yb(OTf)_3$) led to a yield of 50% (Entry 5). As the yields with trimethyl aluminium and ytterbium triflate were similar, both were evaluated in the variation of the next parameter.



75
(7.0 eq)

(*R*,*S*)-**77a**
de ≥ 96%

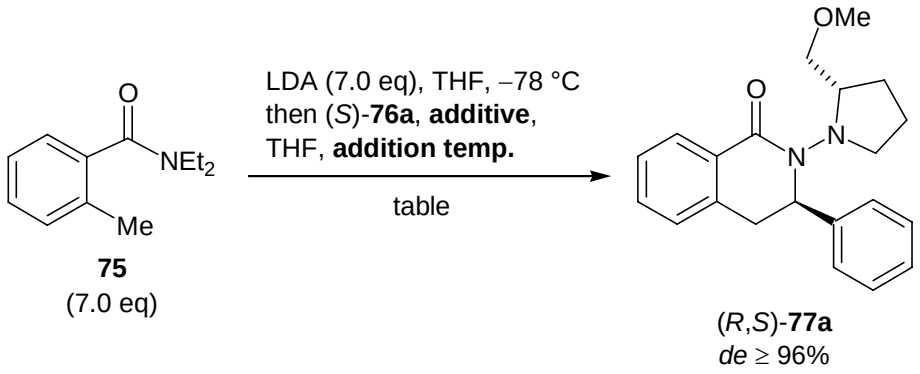
Scheme 42: Variation of the metalation temperature and the additive

Entry	Metalation Temp.	Additive	Yield	*de*[a]
1	–45 °C	$AlMe_3$	30-56%	≥ 96%
2	**–78 °C**	**$AlMe_3$**	**52-61%**	**≥ 96%**
3	–45 °C	$Al(i\text{-}Bu)_3$	16%	≥ 96%
4	–45 °C	TMSOTf	31%[b]	≥ 96%
5	**–78 °C**	**$Yb(OTf)_3$**	**50%**	**≥ 96%**

[a] Determined by ^{1}H-NMR after column chromatography
[b] With RAMP as auxiliary

Table 11: Variation of the additive and the metalation temperature.

The tendancies observed for the addition temperature of the hydrazone were similar for both *Lewis* acids: the yield decreased when we either increased the temperature to –20 °C or decreased it to below –60 °C (Scheme 43, Table 12). As no further improvements had been established for the ytterbium triflate only the trimethyl aluminium was tested for the solvent variation.



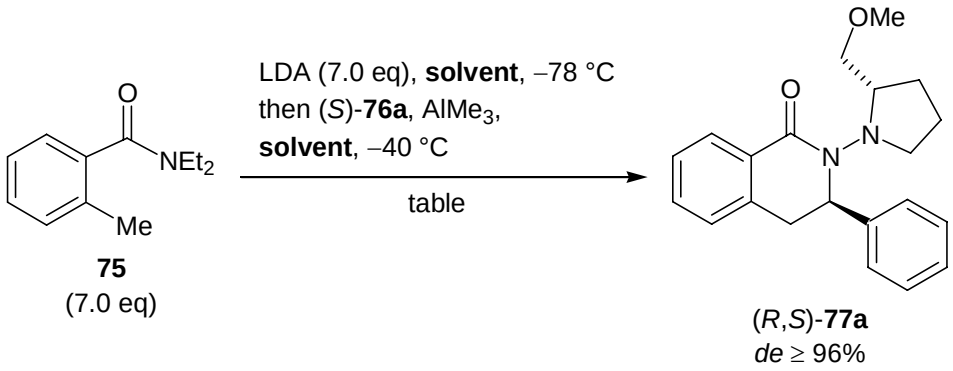
Scheme 43: Variation of the addition temperature

Additive	Addition Temp.	Yield	*de*[a]
$AlMe_3$	–20 °C	45%	≥ 96%
$AlMe_3$	**–40 °C**	**52-61%**	**≥ 96%**
$AlMe_3$	–60 to –78 °C	25%	≥ 96%
$Yb(OTf)_3$	–20 °C	35%	≥ 96%
$Yb(OTf)_3$	–40 °C	50%	≥ 96%
$Yb(OTf)_3$	–78 °C	18%	≥ 96%

[a] Determined by ^{1}H-NMR

Table 12: Variation of the addition temperature

The solvent was varied and to our surprise the reaction performed in unpolar toluene gave the product in a 71% yield with an excellent diastereoselectivity. We then moved to polar diethyl ether and the yield climbed to 80%. Two other tests reactions were performed in dichloromethane and in 1,2-dimethoxyethane but no further improvements were observed (Scheme 44, Table 13). It is noteworthy that the reaction was then performed several times in diethyl ether and a yield close to 80% was always obtained proving a well reproducible reaction.



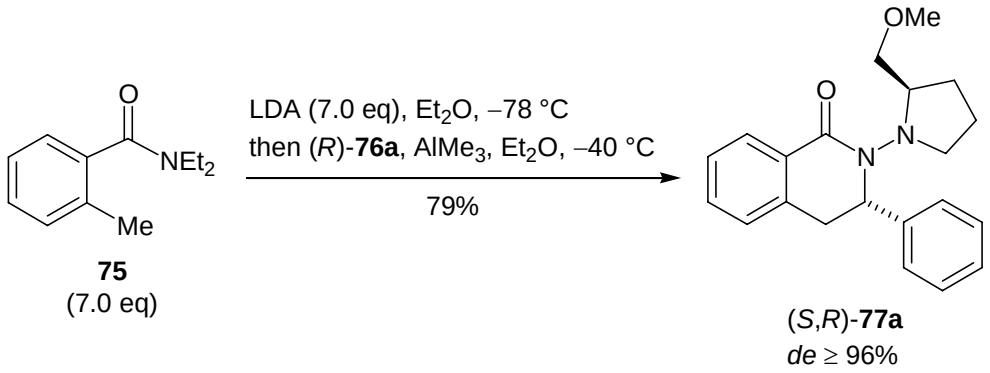
Scheme 44: Variation of the solvent

Solvent	Yield	*de*[a]
THF	52-61%	≥ 96%
PhMe	71%	≥ 96%
Et_2O	**80%**	**≥ 96%**
CH_2Cl_2	0%	-
DME	27%	≥ 96%

[a] Determined by ^{1}H-NMR after column chromatography

Table 13: Variation of the solvent

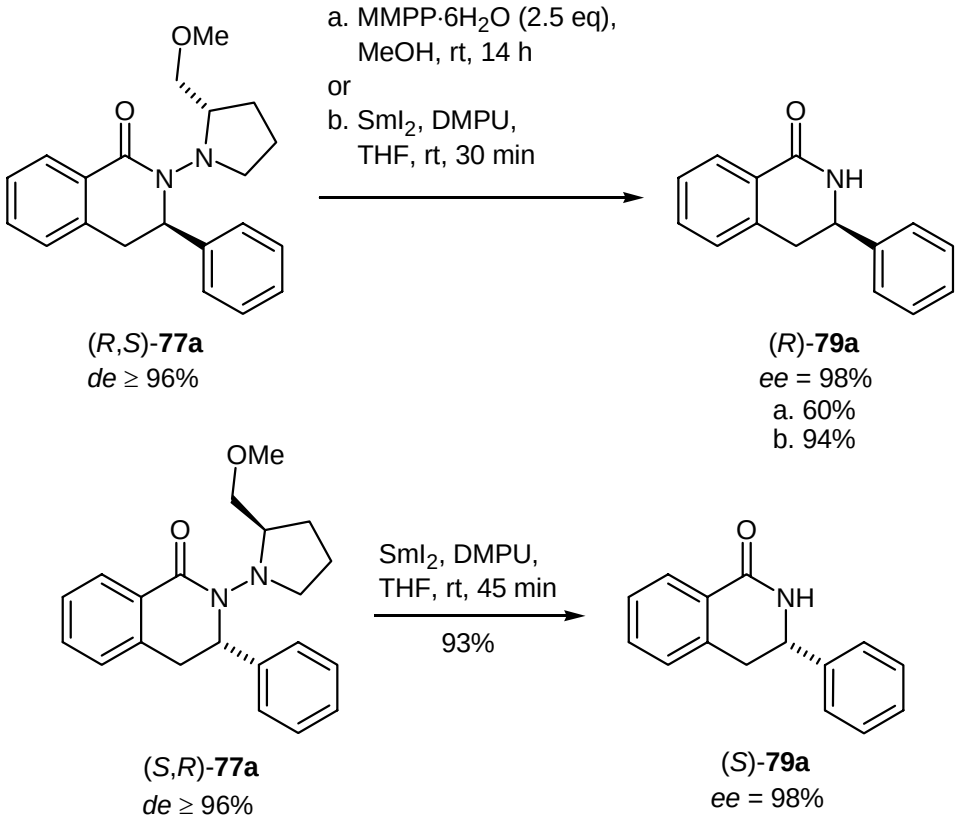
The synthesis of the other enantiomer of the *N*-substituted 3-substituted dihydroisoquinolinone (*S*,*R*)-**77a** was achieved using the optimised conditions and the product was obtained in 79% yield and a diastereomeric excess of 96% (Scheme 45).



Scheme 45: Synthesis of *N*-substituted 3-phenyl substituted dihydroisoquinolinone (*S*,*R*)-**77a**

3.3.2.2 MODEL STUDY: CLEAVAGE OF THE AUXILIARY

The synthesis of the 3-phenyl substituted dihydroisoquinolone **79a** was first realised using magnesium monoperoxyphthalate hexahydrate (MMPP·$6H_2O$) as it was reported to give 71% of **79a** in excellent enantioselectivity.[62] Unfortunately, we could not reproduce the result obtained by *V. Braig* and we then opted for SmI_2, efficient for the cleavage of hydrazines activated by a benzoyl function.[86] Indeed, a carbonyl group was adjacent to the hydrazine. The results were highly satisfying as the yield was high, the reaction was reproducible and the enantioselectivity obtained was excellent (*ee* = 98%, determined by chiral stationary phase HPLC) (Scheme 46).



Scheme 46: N─N cleavage of the chiral auxiliary

Recrystallisation of (*R*)-**79a** from diethyl ether provided single crystals to perform an X-ray structure analysis (Figure 19). Though, the assignment of the absolute configuration of the new stereocentre was not possible: due to a large standard deviation the result of an attempted determination using *Flack*'s method[100] turned out to be insignificant. However, *Davis et al.* reported the asymmetric synthesis of (*S*)-**79a** ($[\alpha]_D^{20}$= –203.4 (c = 1.03, $CHCl_3$)).[58b] By comparison with the optical rotation of (*R*)-**79a** ($[\alpha]_D^{23}$ = +195.3 (c = 1.05, $CHCl_3$)) the

stereogenic centre could be assigned as (*R*). This configuration also correlated with the relative topicity previously observed in our group in the asymmetric synthesis of 2,3-dihydro-1*H*-isoindol-1-ones employing a related methodology.[87d] Moreover, a crystal structure of the *N*-substituted 3-ferrocenyl substituted dihydroisoquinolinone (*R*,*S*)-**77** (see 1.3.3) was previously obtained by *V. Braig*. The absolute configuration was determined with certainty, but the quality of the crystals did not allow a further refinement of the crystallographic data.[62]

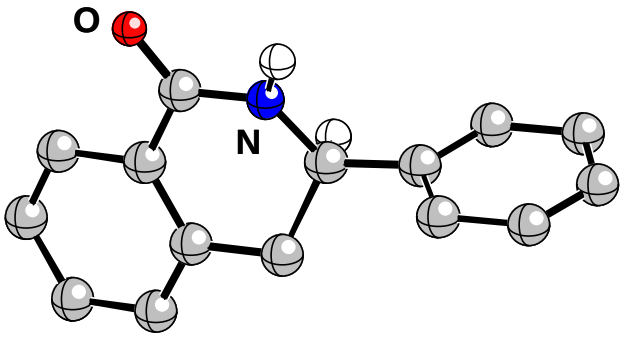
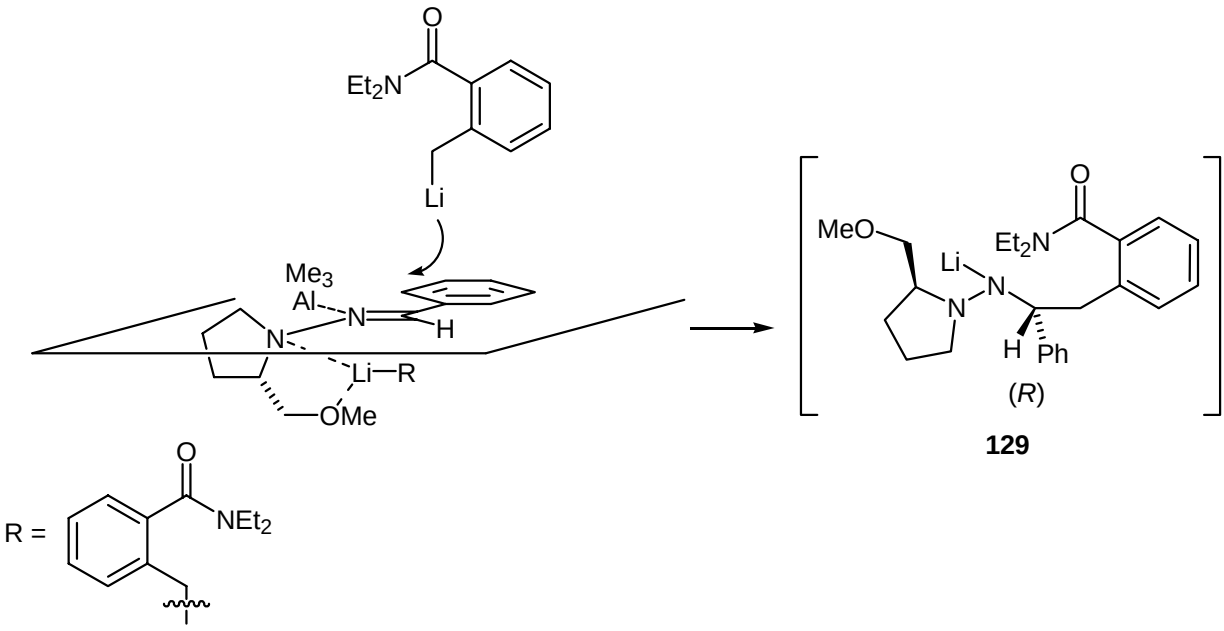


Figure 19: X-ray structure of (*R*)-**79a**

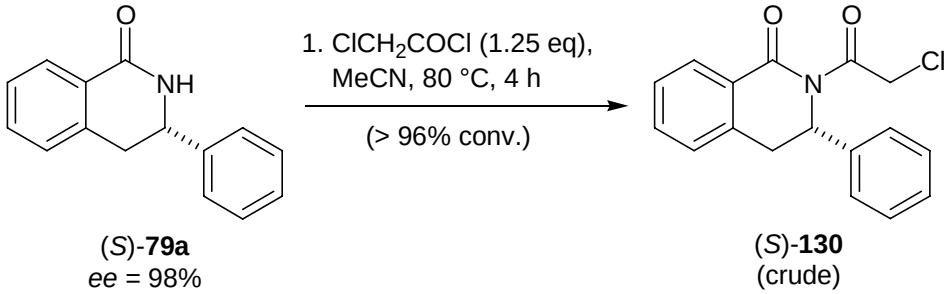
The absolute configuration of the centre being assigned, a mechanism can then be proposed to explain the diastereoselectivity of the reaction. A complexation would take place between one molecule of the lithiated 2-methyl benzamide, the methoxy group and the nitrogen of the pyrrolidine ring forcing the pyrrolidin ring to turn by 90°. Another equivalent of lithiated 2-methyl benzamide would then add to the CN double bond of the hydrazone, activated by complexation with one equivalent of trimethyl aluminium, on the less hindered *Re* face. A short-lived intermediate **129** possessing a (*R*) configuration at the new stereocentre would then be obtained before the ring closure (Scheme 47). This proposed mechanism is supported by the fact that one untouched equivalent of 2-methyl benzamide **75** can always be isolated after the 1,2-addition/ring closure process independent of the time of the reaction and in spite of the self-condensation.



Scheme 47: Proposed mechanism for the formation of (*R*,*S*)-**79a**

3.3.2.3 MODEL STUDY: ATTEMPTS FOR THE *FRIEDEL-CRAFTS* REACTION

The free amide (*S*)-**79a** was transformed into the *Friedel-Crafts* precursor (*S*)-**130** by reaction with a slight excess of chloroacetyl chloride in hot acetonitrile (Scheme 48). Unhappily, the product was very unstable over silica or aluminium oxide and reverted to the dihydroisoquinolinone (*S*)-**79a**. By ^{1}H-NMR spectroscopy analysis of the crude mixture no more starting material could be detected and a minimal conversion of 96% into the chloroacetyl (*S*)-**130** was established. This precursor was then directly subjected to the next step.



Scheme 48: Synthesis of the *Friedel-Crafts* precursor (*S*)-**130**

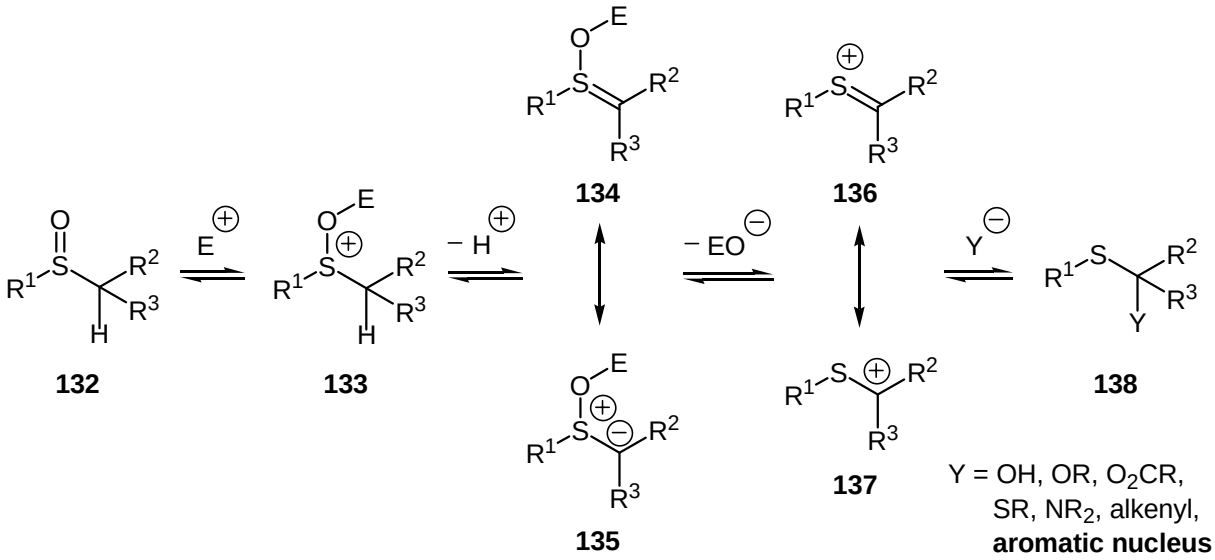
The *Friedel-Crafts* reaction was performed with three equivalents of aluminium chloride in nitrobenzene maintaining the temperature at 130 °C for 17 h. The presence of the free amide

(*S*)-**79a** in the NMR analysis of the crude mixture was mainly detected and after isolation of the other products of the reaction, none was found to be the desired product (*S*)-**131** (Scheme 49).

Scheme 49: Attempts for the *Friedel-Crafts* reaction with the precursor (*S*)-**130**

3.3.2.4 MODEL STUDY: ATTEMPTS FOR THE *PUMMERER* REACTION

We then turned our attention to the *Pummerer* reaction. This reaction is the formation of an *α*-functionalised sulfide **138** from a sulfoxide **132** bearing at least one *α*-hydrogen atom (Scheme 50).[101]

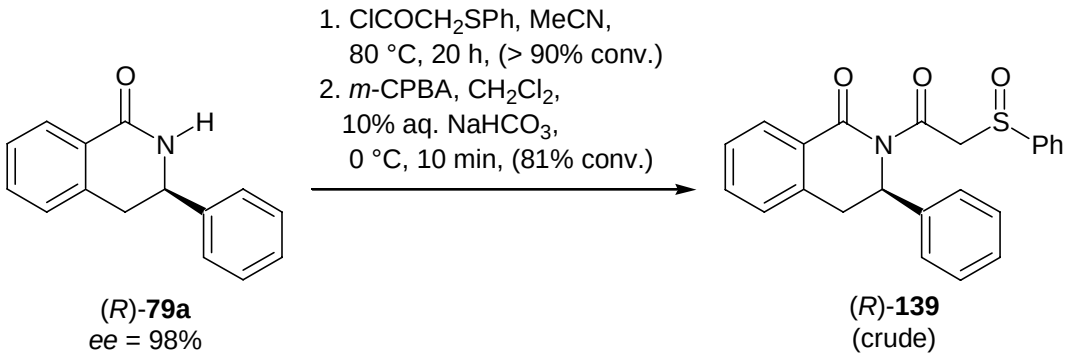


Scheme 50: Mechanism of the *Pummerer* reaction

It requires an electrophile (E^+) to activate the sulfoxide and a base to abstract the *α*-hydrogen atom and to produce the two mesomeric species **134** and **135**. These species will eliminate the oxygen atom of the former sulfoxide now bonded to the electrophile (EO^-) to give rise to two

more stable mesomeric species **136** and **137**. A nucleophile (Y^-) will then be incorporated leading to the final α-functionalised sulfide **138**. The advantage of this process is that several nucleophiles such as hydroxy, alkoxy, carboxylate, sulfide, amine and alkenyl groups can be used or, more interesting in our case, an aromatic nucleus (Scheme 50).

The phenylsulfanyl acetyl substituted compound was prepared analogously to the chloroacetyl (*S*)-**130** by reaction of the free amide (*R*)-**79a** with 1.05 equivalent of (phenylthio)acetyl chloride in hot acetonitrile for 20 h, and it proved to be equally unstable over silica or aluminium oxide. A conversion of at least 90% was determined by ^{1}H-NMR analysis of the crude mixture (Scheme 51) and the crude sulfide was directly subjected to oxidation with *meta*-chloroperbenzoic acid in a two phase system composed of dichloromethane and a 10% aqueous solution of $NaHCO_3$. The sulfoxide (*R*)-**139** was obtained as a mixture of diastereoisomers with a conversion of 81% (determined by ^{13}C-NMR analysis), and it was directly subjected to the *Pummerer* reaction without further purification (Scheme 51).

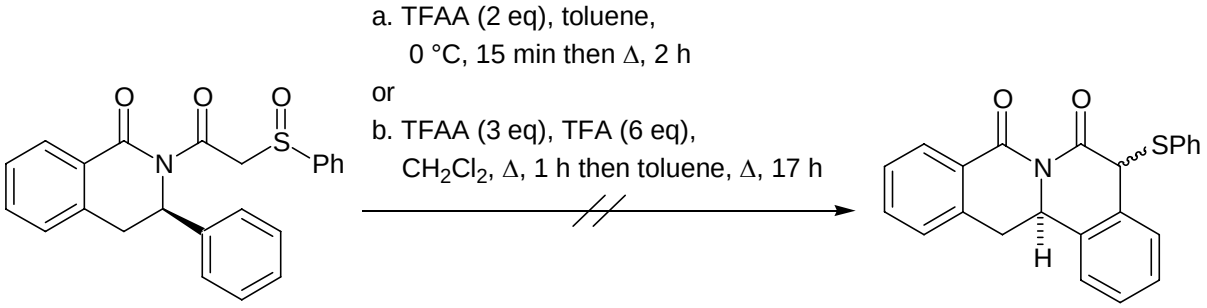


(*R*)-**79a**
ee = 98%

(*R*)-**139**
(crude)

Scheme 51: Synthesis of the *Pummerer* precursor (*R*)-**139**

For the next step, two equivalents of trifluoroacetic anhydride were used to form the sulfonium ion in toluene for 15 min. TLC plates analysis revealed the complete consumption of the starting material. The reaction was then heated to reflux for 2 hours but isolation of the different products formed in the reaction did not indicate presence of the desired product (*R*)-**140** (Scheme 52). The *Pummerer* reaction was then attempted with three equivalents of trifluoroacetic anhydride and six equivalents of trifluoroacetic acid but here again, in spite of the disappearance of the starting material (*R*)-**139**, no product could be isolated (Scheme 52).



(*R*)-**139**
(crude)

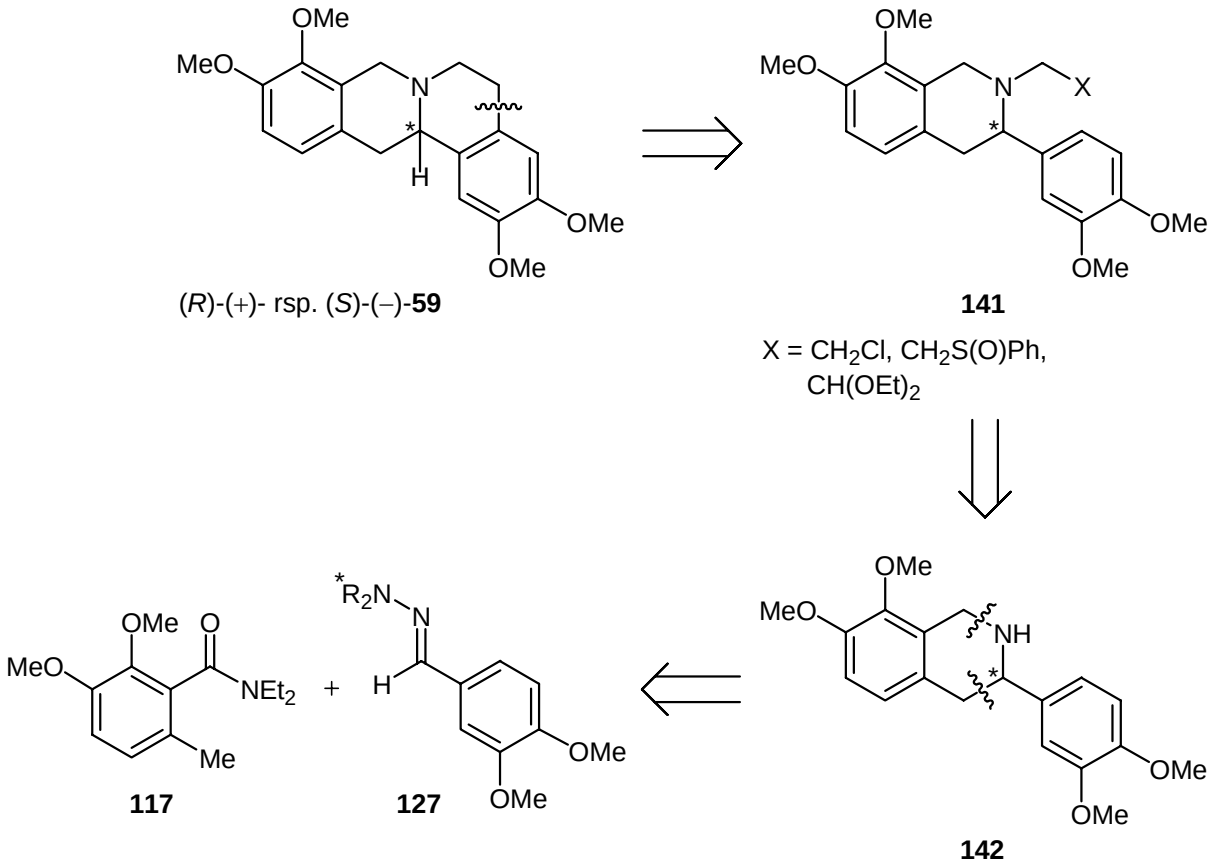
(*R*)-**140**

Scheme 52: Attempts for the *Pummerer* reaction with the precursor (*R*)-**139**

At this point it was clear that the precursors that had been prepared for the *Friedel-Crafts* as well as the *Pummerer* reaction were far too unstable, and it was impossible to determine whether the reaction did not take place or whether the precursors decomposed under the reaction conditions. The strategy should remain globally the same considering the nitrogen functionalisation and the reactions used to perform the ring closure but the nitrogen substituent of the precursors should be exchanged.

3.3.3 RETROSYNTHETIC CONCEPT: REDUCTION-NITROGEN FUNCTIONALISATION-RING CLOSURE

The target molecule (*R*)-(+)- and (*S*)-(−)-tetrahydropalmatine (**59**) should result from the ring closure of a tetrahydroisoquinoline **141** in a *Friedel-Crafts*, a *Pummerer* or a *Pomeranz-Fritsch* reaction. To achieve this goal **141** should be obtained by functionalising the nitrogen position of the tetrahydroisoquinoline **142** with a chain containing respectively a chloride, a sulfoxide or a diethyl acetal. This precursor should be the product of the N─N cleavage of the chiral auxiliary and reduction of the carbonyl function of the *N*-substituted 3-phenyl substituted dihydroisoquinolinone obtained by the tandem process between 2-methyl benzamide **117** and benzaldehyde SAMP- respectively RAMP-hydrazone **127** (Scheme 53).

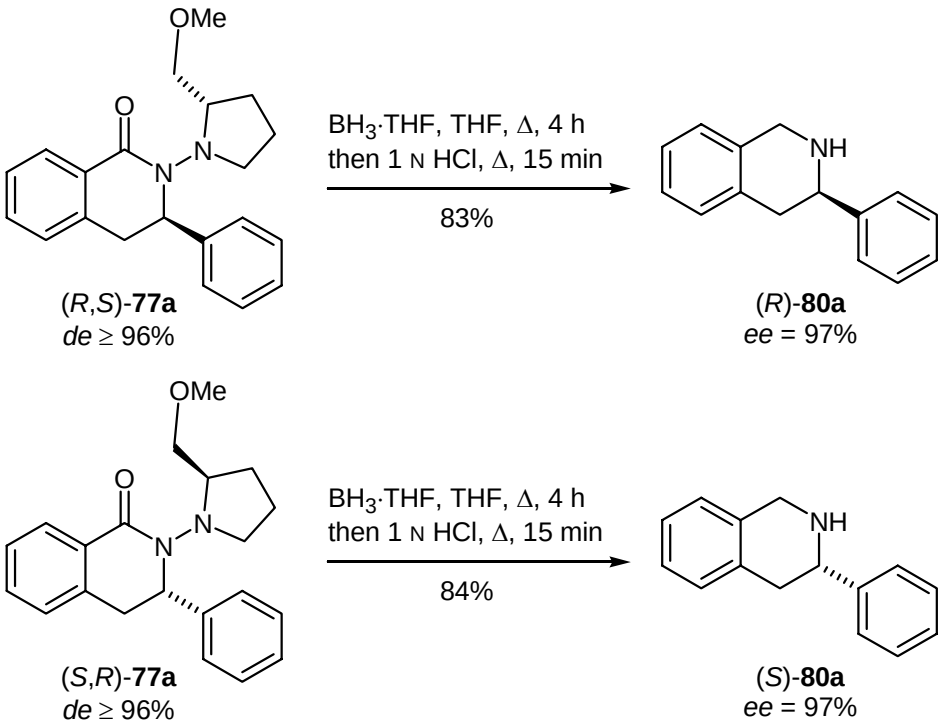


Scheme 53: Retrosynthetic concept *via* reduction-nitrogen functionalisation-ring closure

3.3.3.1 MODEL STUDY: SYNTHESIS OF THE TETRAHYDROISOQUINOLINE

The access to the 1,2,3,4-tetrahydroisoquinolines **80a** was easily accomplished using the protocol developed by *V. Braig*.[62] By using an excess of THF-borane complex on the

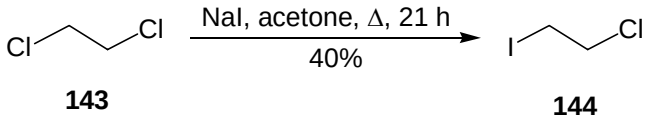
previously synthesised *N*-substituted 3-phenyl substituted dihydroisoquinolinones **77a** the reaction allowed the N─N cleavage of the chiral auxiliary and the reduction of the amide moiety in the same step. The yields obtained for the two enantiomers were slightly higher than the one previously reported[62] and the enantiomeric excess (determined by chiral stationary phase HPLC) remained excellent (Scheme 54).



Scheme 54: Synthesis of the 1,2,3,4-tetrahydroisoquinolines **80a**

3.3.3.2 MODEL STUDY: ATTEMPTS FOR THE *FRIEDEL-CRAFTS* REACTION

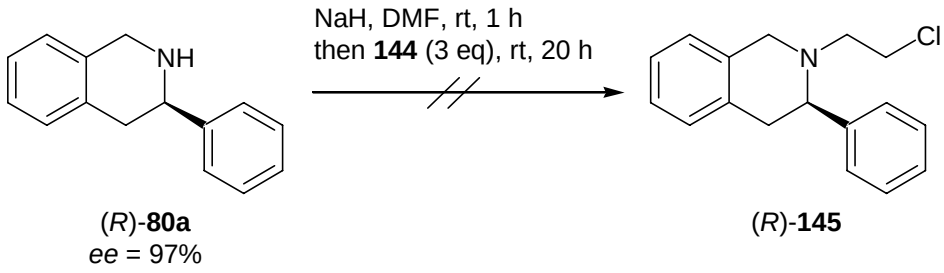
The synthesis of the precursor (*R*)-**145**, for the *Friedel-Crafts* reaction, was attempted in one step starting from our tetrahydroisoquinoline (*R*)-**80a**. We thought of the use of 1-chloro-2-iodo ethane (**144**) to functionalise the nitrogen. Therefore 1,2-dichloroethane (**143**) was subjected to *Finkelstein*'s conditions to give **144** in 40% yield. Although the yield was moderate, it represented an improvement of about 20% compared to the yield described in the literature[102] (Scheme 55).



143 **144**

Scheme 55: Synthesis of 1-chloro-2-iodo ethane (**144**)

Having in hands 1-chloro-2-iodo ethane (**144**) the reaction was performed by subjecting the tetrahydroisoquinoline (*R*)-**80a** to sodium hydride in dimethyl formamide. After 1 h at room temperature three equivalents of **144** were added to the reaction mixture (Scheme 56). Unfortunately, only starting material was recovered from this reaction and **144**, as a conclusion from other experiments not described in this work, could not be exposed to harsher conditions which only promoted its decomposition.

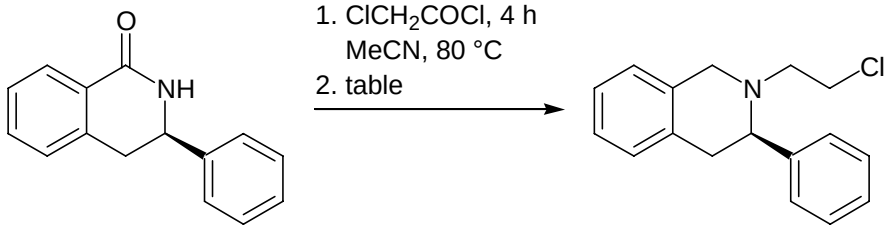


(*R*)-**80a**
ee = 97%

(*R*)-**145**

Scheme 56: Attempts for the synthesis of the *Friedel-Crafts* precursor (*R*)-**145**

Taking into account this result, the idea came forth that we could use the chloroacetyl-dihydroisoquinolinone enantiomer (*R*)-**130** of the previously synthesised (*S*)-**130**. The crude (*R*)-**130** was refluxed for 18 hours with 10 equivalents of lithium aluminium hydride (Scheme 57, Table 14). Only an equal amount of the free amine **80a** and the *N*-ethyl substituted tetrahydroisoquinoline **147** was detected by NMR analysis of the crude reaction mixture. The formation of **147** can be explained by considering the nucleophilic attack of a hydride source on the ammonium salt **146** that is formed due to the anchimeric assistance inherent to the tetrahydroisoquinoline nitrogen atom of **145**, aggravated by the harsh reaction conditions employed (Scheme 58). Milder conditions were then applied by exposing (*S*)-**130** to 6 equivalents of lithium aluminium hydride at room temperature for 2 hours. No more formation of the *N*-ethyl tetrahydroisoquinoline **147** was observed. Instead an equal amount of free amine **80a** and the desired chloroethyl tetrahydroisoquinoline (*S*)-**145** was detected in the NMR of the crude mixture. We were pleased to see that **145** could be isolated however, with slight racemisation. The very moderate yield was also due to the unstability of **145** promoted by the anchimeric effect (Scheme 57, Table 14). We then switched to borane-THF complex and only a slight excess was used refluxing the reaction mixture for 2 hours. (*R*)-**145** was obtained in a 60% yield with an enantiomeric excess of 95%.



(*R*)-**79a**
ee = 98%

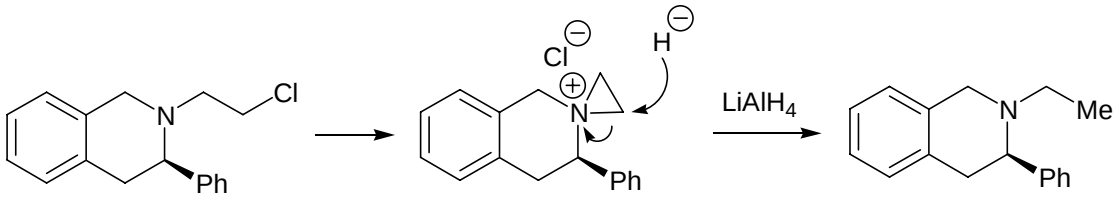
(*R*)-**145**

Scheme 57: Synthesis of the chloroethyl tetrahydroisoquinoline (*R*)-**145**

Starting material	Conditions	Yield[a]	*ee*[b]
(*R*)-**79a**	$LiAlH_4$ (10 eq), THF, Δ, 18 h	**80a** + **147**	-
(*S*)-**79a**	$LiAlH_4$ (6 eq), THF, rt, 2 h	31%	93%
(*R*)-**79a**	BH_3·THF (4.5 eq), THF, Δ, 2 h	60%	95%

[a] Over two steps [b] Determined by chiral stationary phase HPLC

Table 14: Conditions for the synthesis of the chloroethyl tetrahydroisoquinoline (*R*)-**145**

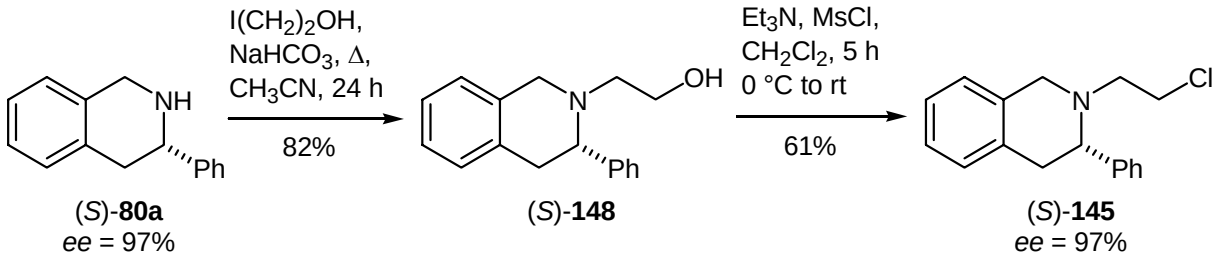


145 **146** **147**

Scheme 58: Possible mechanism for the formation of the *N*-ethyl tetrahydroisoquinoline **147**

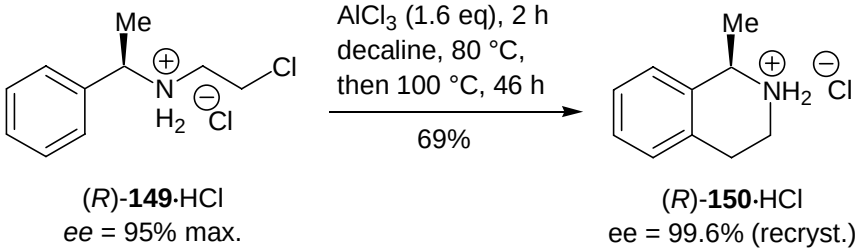
In order to prevent the racemisation we decided to exploit the anchimeric effect exerted by the nitrogen atom to optimise the synthesis of **145**. (*S*)-**80a** was first transformed into the alcohol (*S*)-**148** using 1.1 equivalent of both iodoethanol and sodium hydrogenocarbonate in refluxing acetonitrile for 24 h (Scheme 59). The alcohol (*S*)-**148** was then deprotonated with triethylamine and transformed into the corresponding mesylate by the use of methanesulfonyl chloride. The chloride anion produced during the reaction attacked the ammonium salt formed by anchimeric assistance of the nitrogen atom. After 5 hours at room temperature 61% of the desired product (*S*)-**145** were obtained with an enantiomeric excess of 97% (determined by chiral stationary phase HPLC) showing that no racemisation took place here (Scheme 59). It

should be noted that in a second attempt four additional equivalents of lithium chloride were also added to determine if the yield of the reaction could be further increased. The reaction was stirred longer (in total 20 hours), but the yield of 63% showed that the effect of the additional lithium chloride was negligeable.



Scheme 59: Optimisation of the synthesis of the chloroethyl tetrahydroisoquinoline (*R*)-**145**

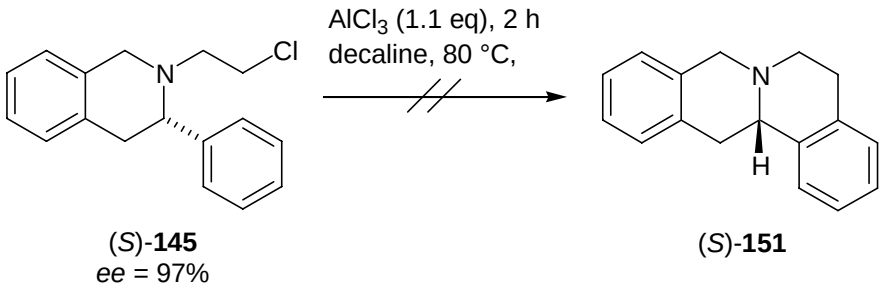
In 2002, a patent reported the transformation of the *N*-(2-chloroethyl)-*α*-methylbenzylamine hydrochloride into the (*R*)-1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride ((*R*)-**150**·HCl) using a *Friedel-Crafts* reaction.[103] (*R*)-**149**·HCl was added to a suspension of 1.6 equivalents of aluminium chloride in decaline at 80 °C. After 2 hours at this temperature an amine-aluminium chloride layer flowed over the decaline and the reaction mixture was heated to 100 °C for 46 hours. After cooling to room temperature, water was added, the decaline layer discarded and the aqueous phase basified. After extraction with dichloromethane the organic layer was acidified and 69% of the hydrochloride (*R*)-**150**·HCl was obtained with an enantiomeric excess of 99.6% after recrystallisation (Scheme 60).



Scheme 60: Synthesis of the (*R*)-**150**·HCl by *Friedel-Crafts* reaction

Motivated by this example, we applied this conditions on our newly formed chloroethyl tetrahydroisoquinoline (*S*)-**145**. Unfortunately the starting material remained as a gum on the wall of the reaction flask and we only assisted to its decomposition when the reaction mixture was heated (Scheme 61). A hydrochloride salt of (*S*)-**145** would probably have been more

resistant to the reaction conditions and eventually have led to the product. However, even if we could have obtained the tertiary salt of the tetrahydrodibenzoquinolizine system, its stability would have made it very difficult to return to the free base (*S*)-**151**.



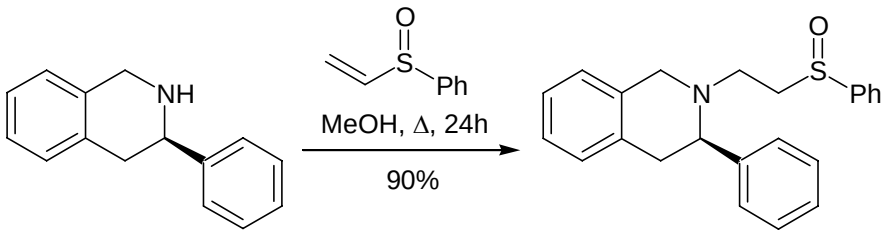
(*S*)-**145**
ee = 97%

(*S*)-**151**

Scheme 61: Attempts for the synthesis of (*S*)-**151** by *Friedel-Crafts* reaction

3.3.3.3 MODEL STUDY: ATTEMPTS FOR THE *PUMMERER* REACTION

To synthesise the precursor for the *Pummerer* reaction a minimal number of steps was desirable. An oxidation of a sulfide to a sulfoxide, as previously used (see 3.3.2.4), should be avoided. The direct installation was fulfilled by performing a *Michael* reaction of 1.5 equivalents of vinyl sulfoxide and the 3-phenyl substituted tetrahydroisoquinoline (*R*)-**80a**. The *N*-phenylsulfinylethyl tetrahydroisoquinoline (*R*)-**152** was obtained in an excellent yield as a mixture of diastereoisomers (ratio of 57/43 determined by HPLC) after 24 hours reflux in methanol without any need of a base to activate the nitrogen atom of the tetrahydroisoquinoline moiety (Scheme 62).



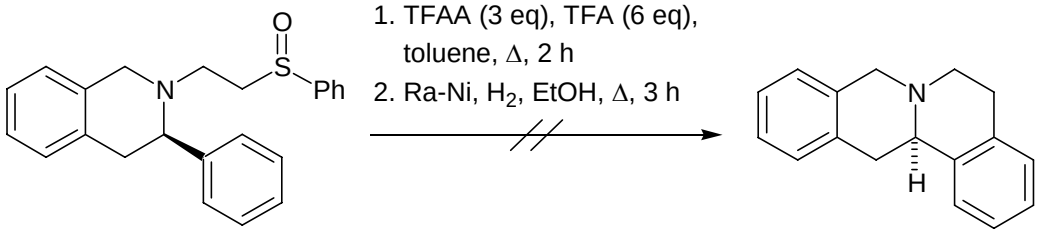
(*R*)-**80a**
ee = 97%

(*R*)-**152**
dr = 57/43

Scheme 62: Synthesis of the *Pummerer* precursor (*R*)-**152**

The *Pummerer* reaction was then attempted employing three equivalents of trifluoroacetic anhydride and additional six equivalents of trifluoroacetic acid to prevent the formation of a vinyl sulfide (Scheme 63).[104] After 2 hours reflux in toluene a NMR analysis of the crude

mixture showed that all starting material had disappeared. Instead, a complex mixture of products was observed in which an aldehyde peak and some vinylic protons could be seen. Probably hydrolysis of the sulfonium ion led to the formation of an aldehyde, and the vinylic protons can be explained with the formation of a vinyl sulfide derivative. Unable to know if the phenylsulfanyl tetrahydrodibenzoquinolizine had been formed, the crude mixture was refluxed in ethanol with *Raney* nickel under hydrogen atmosphere to perform the cleavage of the eventual sulfide. Although each product of the reaction was isolated, the presence of the tetracyclic ring skeleton of (*R*)-**151** could not be detected (Scheme 63).



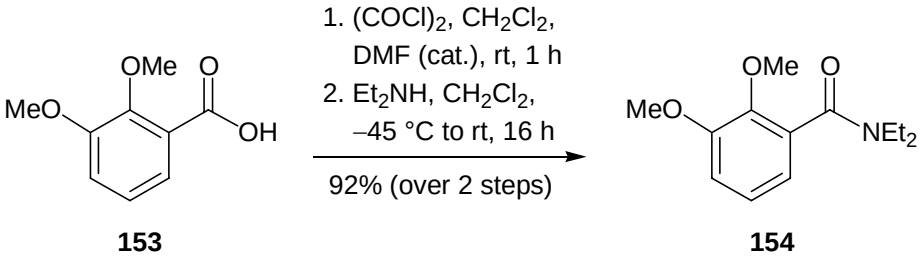
(*R*)-**152** (*R*)-**151**

Scheme 63: Attempts for the *Pummerer* reaction on (*R*)-**152**

The failure of our attempts for the *Friedel-Crafts* as well as for the *Pummerer* reaction could have been caused by the absence of methoxy substituents on the aromatic ring. Indeed those can represent a necessary activation for this kind of ring closure reactions. We decided to switch to the corresponding methoxy-substituted starting materials.

3.3.3.4 SYNTHESIS OF THE STARTING MATERIALS FOR THE TOTAL SYNTHESIS OF TETRAHYDROPALMATINE

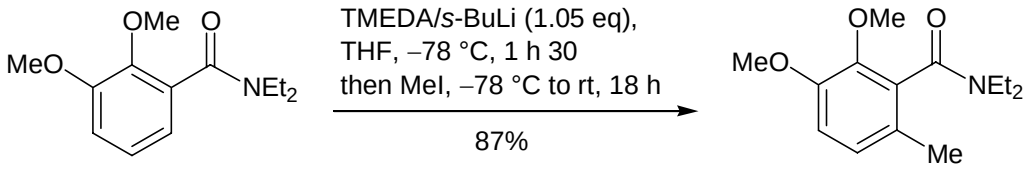
The 2,3-dimethoxy-6-methyl-benzamide **117** is not commercially available. One possibility was to start from the accessible 2,3-dimethoxybenzoic acid (**153**) and to introduce the amide functionality before using its directing effect to install the methyl substituent in *ortho*-position. A protocol described by *L. Zhuang et al.* was followed for the synthesis of the 2,3-dimethoxy-benzamide **154**.[105] After transformation of the carboxylic acid group into an acyl chloride with oxalyl chloride and a catalytic amount of dimethyl formamide, diethylamine was added at low temperature to give after workup the desired product **154** in an excellent yield (Scheme 64).



153 **154**

Scheme 64: Synthesis of 2,3-dimethoxy-benzamide **154**

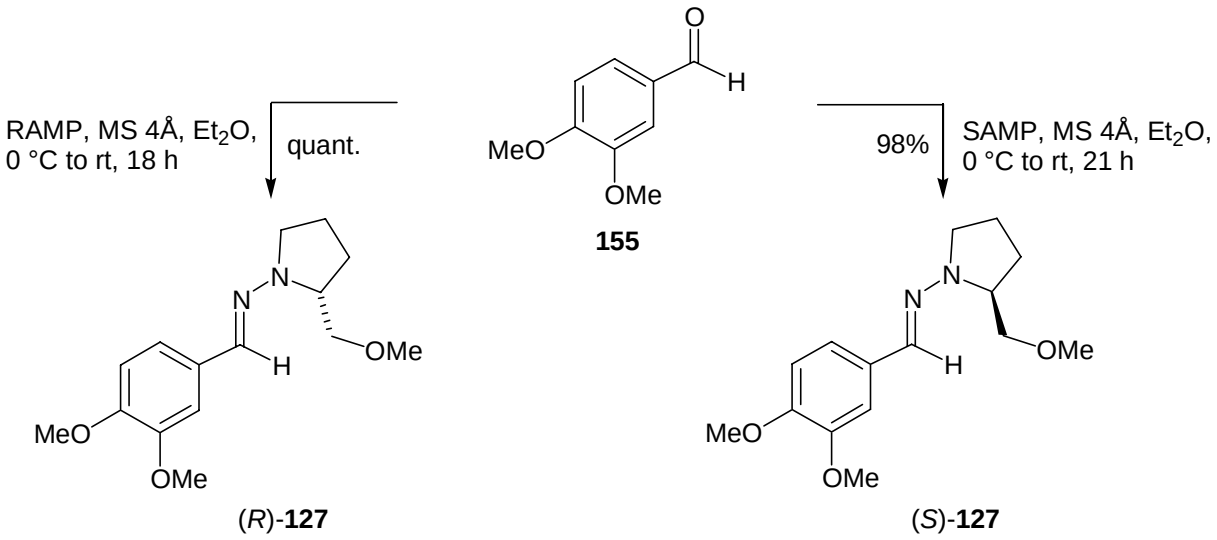
The initial protocol of *L. Zhuang* was transformed to perform the synthesis of the 2,3-dimethoxy-6-methyl-benzamide **117** that is to say that a methyl group was introduced instead of an iodide.[105] After deprotonation of the benzamide moiety in *ortho*-position with 1.05 equivalents of *s*-butyllithium coordinating to an equimolar amount of tetramethylethylenediamine, a stoichiometric amount of methyl iodide was added before slowly warming up the reaction mixture to room temperature (Scheme 65). A good yield of the desired product **117** could be reached taking into account that this product must be absolutely free of any traces of non-methylated and dimethylated benzamide which could react in the next step.



154 **117**

Scheme 65: Synthesis of the 2,3-dimethoxy-6-methyl-benzamide **117**

The next goal was the preparation of 3,4-dimethoxybenzaldehyde SAMP- respectively RAMP-hydrazone **127**. The hydrazones were easily synthesised, by condensation of the commercial 3,4-dimethoxybenzaldehyde and SAMP respectively RAMP. Both SAMP-hydrazone (*S*)-**127** and RAMP-hydrazone (*R*)-**127** were obtained in virtually quantitative yield and the comparison of these results to the precedent yields obtained for the synthesis of the benzaldehyde SAMP- and RAMP-hydrazone **76a** (93-94%) suggests an activating effect of the methoxy substituents on the aromatic ring (Scheme 66).



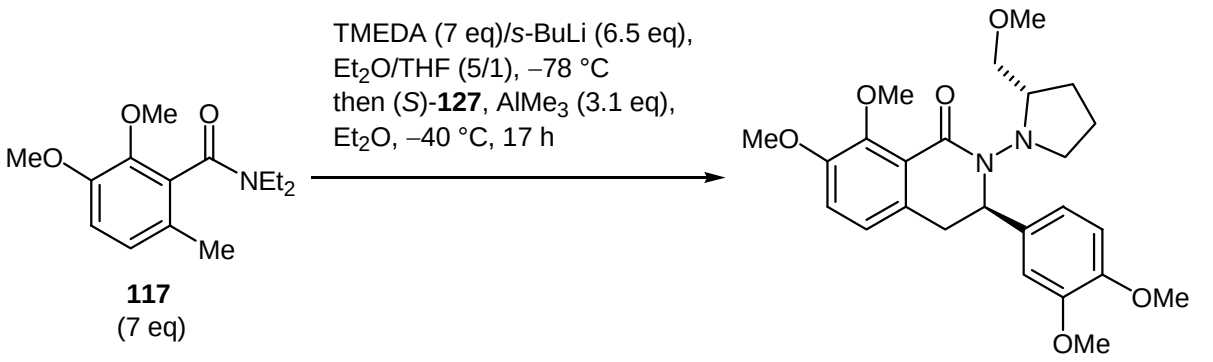
Scheme 66: Synthesis of the 3,4-dimethoxy-benzaldehyde SAMP- and RAMP-hydrazone **127**

3.3.3.5 SYNTHESIS OF THE TETRAHYDROISOQUINOLINE *VIA* 1,2-ADDITION/RING CLOSURE PROCESS

Having now all necessary materials in hands, the tandem process was attempted first with LDA in diethyl ether to deprotonate the methyl group of the 2,3-dimethoxy-6-methyl benzamide **117**. To our surprise the solution did not turn to burgundy red, a typical colour for the lithiated species of the 2-methyl benzamide. Literature already has precedence for the deprotonation of two equivalents of 2,4-dimethoxy-6-methylbenzamide with three equivalents of LDA before the addition to acetylidene-*p*-toluenesulfinamide.[58a] Assuming that LDA probably formed a chelate with the methoxy groups of the aromatic ring and the amide group, we performed another experiment using three equivalents of LDA compared to the benzamide. The reaction mixture turned to a bright orange and as the reaction was worked up no product could be observed.

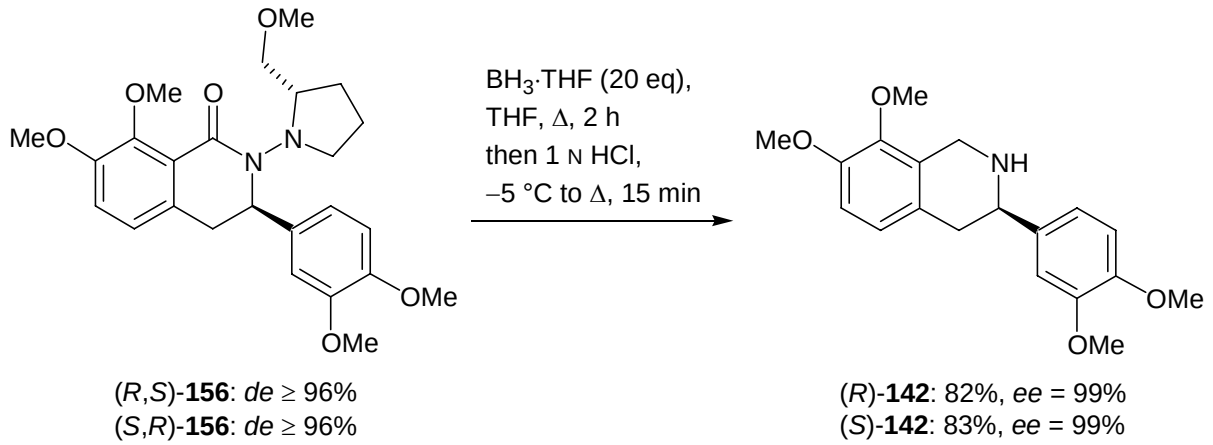
We decided to employ the same system used before for the installation of the methyl substituent (see Scheme 65) and we turned ourselves to the use of 7 equivalents of an equimolar amount of *s*-butyllithium and tetramethylethylenediamine. Taking into account that the methoxy substituents can play an important role in this reaction the amount of trimethyl aluminium was increased to 3.1 equivalents for the complexation with the hydrazone **127**. In addition to this, a small amount of THF has to be used in order to maintain a good solubility of the lithiated species when deprotonating the 2,3-dimethoxy-6-methyl benzamide **117**. Finally, the cyclised product (*R*,*S*)-**156** was obtained with excellent diastereoselectivity and

reasonable yield taking into account the complex functionalities built up in one step. Analogously (*S*,*R*)-**156** could also be obtained with a similar yield demonstrating the reproducibility of the reaction (Scheme 67).



Scheme 67: Synthesis of the *N*-substituted 3-phenyl substituted dihydroisoquinolinone **156**

Starting from the dihydroisoquinolinone (*R*,*S*)-**156**, 20 equivalents of the borane-THF complex were used to cleave the N─N bond of the chiral auxiliary and to reduce the carbonyl group of the amide moiety in the same step (Scheme 68). After hydrolysis of the borane using a 1 N aqueous solution of hydrochloric acid the tetrahydroisoquinoline (*R*)-**142** was obtained in an excellent yield of 82% and an enantiomeric excess of 99% (determined by chiral stationary phase HPLC), better than the one previously observed for **80a** (97% *ee*). Analogously (*S*)-**156** was obtained in the same enantiomeric purity and a reproducible yield of 83%.

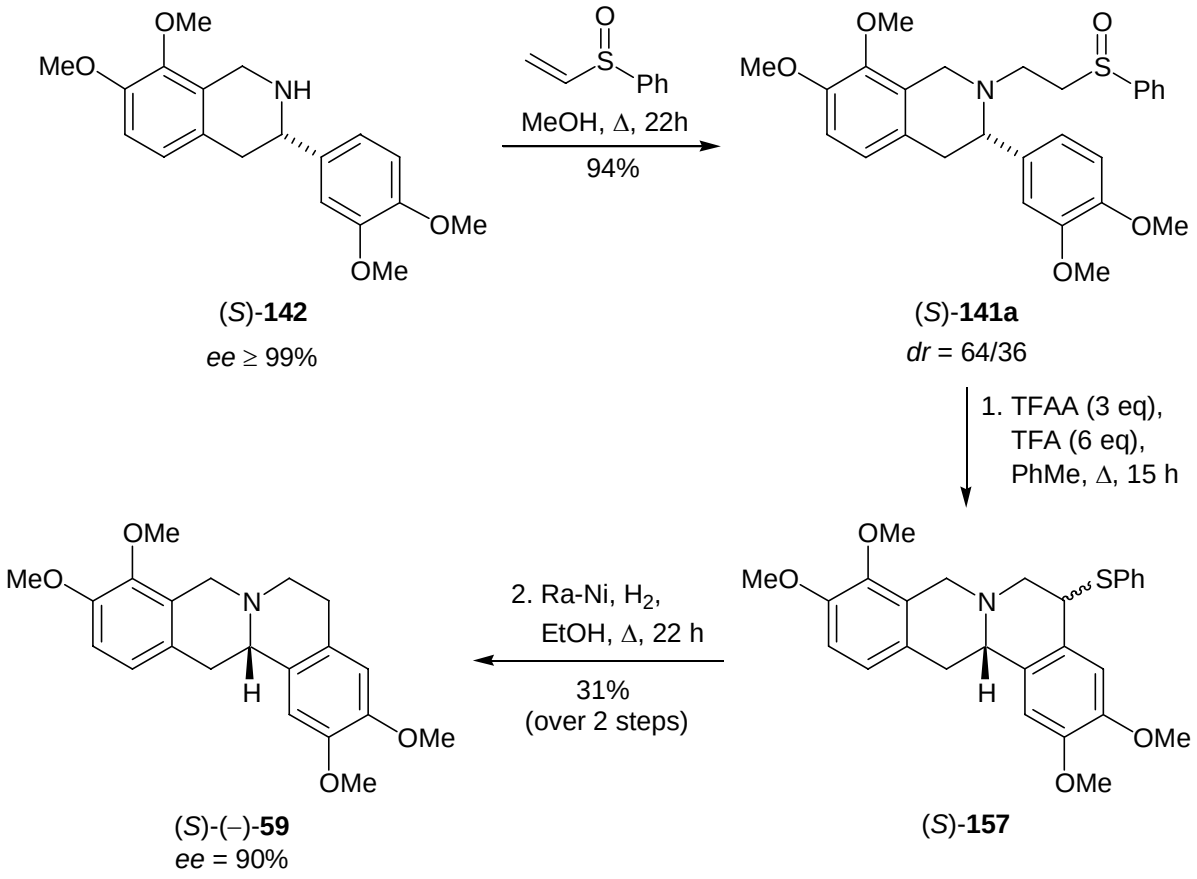


Scheme 68: Synthesis of the 1,2,3,4-tetrahydroisoquinolines **142**

3.3.3.6 SYNTHESIS OF (*S*)-(−)-TETRAHYDROPALMATINE *VIA PUMMERER* REACTION

The synthesis of the *Pummerer* precursor was conducted as before in a *Michael* reaction of the vinyl sulfoxide acceptor and the tetrahydroisoquinoline (*S*)-**142** within 22 hours reflux in methanol. A diastereoisomeric mixture of (*S*)-**141a** (ratio of 64/36 determined by HPLC) was obtained in 94% yield.

The synthesis of the phenylsulfanyl tetrahydrodibenzoquinolizine by *Pummerer* reaction was realised by subjecting (*S*)-**141a** to three equivalents of trifluoroacetic anhydride and six equivalents of trifluoroacetic acid in refluxing toluene. Although the compound could not be detected by NMR analysis, a small amount of the crude mixture was purified using preparative thin layer chromatography. A fraction being identified as the desired sulfide (*S*)-**157**, the rest of the crude mixture was roughly purified by column chromatography and then directly subjected to the next step (Scheme 69).



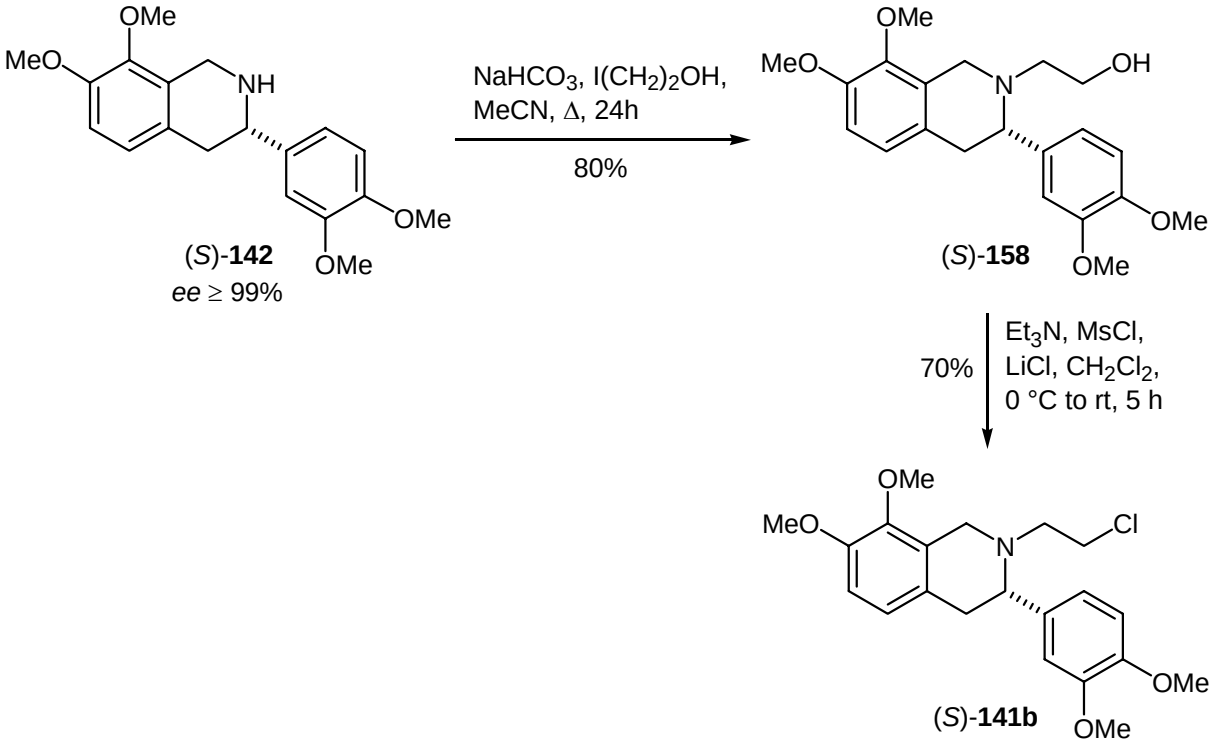
Scheme 69: Synthesis of (*S*)-(−)-tetrahydropalmatine (**59**) by *Pummerer* reaction

We were pleased to see that, after reductive desulfurisation with *Raney* nickel, 31% yield of the (*S*)-(−)-tetrahydropalmatine (**59**) could be obtained after two steps (Scheme 69). However,

slight racemisation occurred during this sequence (*ee* = 90% determined by chiral stationary phase HPLC) which can probably be assigned to the strong trifluoroacetic acid necessary for this transformation.

3.3.3.7 ATTEMPTS FOR THE SYNTHESIS OF (*S*)-(−)-TETRAHYDROPALMATINE *VIA FRIEDEL-CRAFTS* REACTION

The tetrahydroisoquinoline (*S*)-**142** was transformed into the chloride (*S*)-**141b** using the racemisation-free protocol established before (see 3.3.3.2). After reflux with iodoethanol in presence of sodium hydrogenocarbonate the alcohol (*S*)-**158** was obtained in 80% yield. The exchange of the alcohol functionality to chloride took place after mesylation and nucleophilic attack of the intermediate anion in presence of four equivalents of LiCl unlike stated before. A yield of 70% of the desired chloroethyl tetrahydroisoquinoline (*S*)-**141b** was found (Scheme 70).



Scheme 70: Synthesis of the *Friedel-Crafts* precursor (*S*)-**141b**

In 1999 *T. Hudlicky* registered a patent stating the final closure of a morphinane derivative by *Friedel-Crafts* reaction with aluminium chloride in refluxing benzene.[106] However, a mixture

of the desired product and a free phenol resulting from an aluminium chloride catalysed demethylation was obtained.

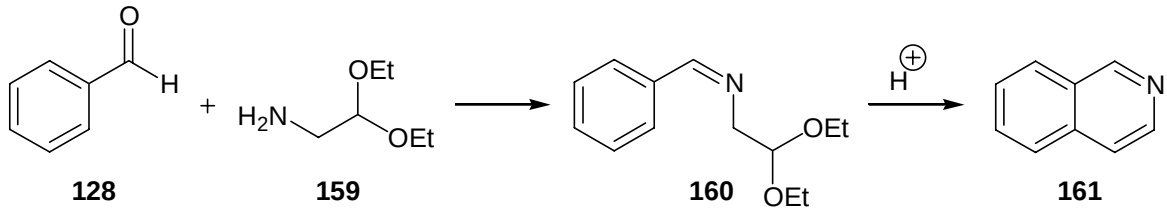
Nevertheless, thinking that our system would perhaps act differently, we conducted an experiment with only 1.1 equivalent of the aluminium chloride to prevent a possible demethylation of our methoxy substituents. After refluxing 28 hours only starting material was recovered. Demethylation had obviously not taken place. Assuming that aluminium chloride might complex with the methoxy substituents, four more equivalents of aluminium chloride were added to our reaction mixture and after 7 hours reflux the workup was performed. Unfortunately no tetrahydropalmatine could be observed in the NMR analysis of the crude mixture and it seemed that the main products were starting material and a phenol derivative (Scheme 71).

(*S*)-**141b** (*S*)-(–)-**59**

Scheme 71: Attempts for the *Friedel-Crafts* reaction with the precursor (*S*)-**141b**

3.3.3.8 SYNTHESIS OF (*S*)-(–)- AND (*R*)-(+)-TETRAHYDROPALMATINE *VIA POMERANZ-FRITSCH* REACTION

The original procedure, independently conceived by *C. Pomeranz*[107] and *P. Fritsch*[108], involved the formation of isoquinoline (**161**) in an acid-catalysed cyclisation of the benzyliminoacetal **160** prepared from benzaldehyde and aminoacetaldehyde diethyl acetal (**159**) (Scheme 72).



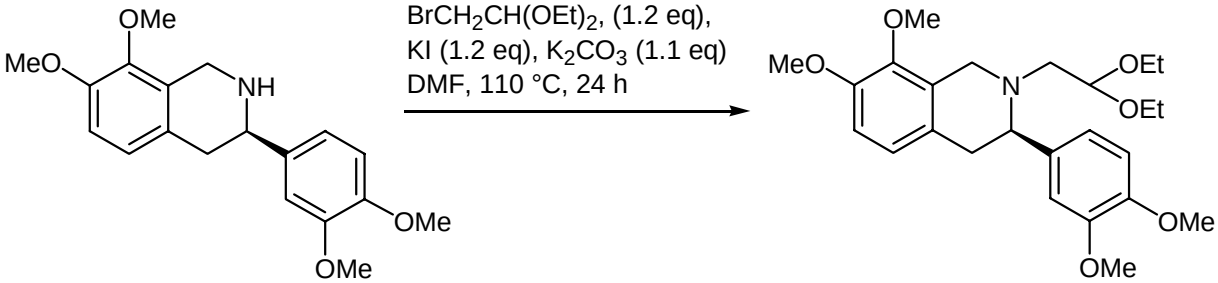
128 **159** **160** **161**

Scheme 72: Formation of isoquinoline (**161**) by *C. Pomeranz* and *P. Fritsch*

In later works the procedure was modified and hydrogenation of the benzyliminoacetal prior to cyclisation allowed to form saturated tetrahydroisoquinolines in a *Pomeranz-Fritsch*-type reaction.[109] In addition, the formation of quinolizin-5-ol was achieved either by formation of an aminoacetaldehyde dihydroxy acetal (glycol) oxidised to the aminoaldehyde and then submitted to acid-catalysed cyclisation[110] or by formation of an aminoacetaldehyde diethyl acetal directly cyclised under acidic conditions[111]. The second method was also applied to the synthesis of quinolizin-5-ol as a mixture of diastereoisomers starting from *N*-alkylated chiral tetrahydroisoquinolines.[112]

In addition it should be noted that for a mild ring closure without epimerisation, electron-donating *ortho*- or *para*-substituents of the cyclisation site are required.[113]

First the synthesis of the *Pomeranz-Fritsch* precursor was attempted on (*R*)-**142** in the presence of bromoacetaldehyde diethyl acetal and potassium carbonate in refluxing acetonitrile. Only 33% of the desired diethyl acetal (*R*)-**141c** could be obtained. In comparison with the yield obtained in the reaction with iodoethanol and sodium hydrogenocarbonate (80%, see 3.3.3.7) it was clear that the bromide was not reactive enough for the nucleophilic substitution. In a second attempt a stoichiometric amount of potassium iodide was employed to perform a bromide-iodide exchange *in situ* before the attack. We were pleased to see that 75% of the product could be isolated (Scheme 73). The reaction was repeated under the same conditions for the other enantiomer, but we obtained only 63% of (*S*)-**141c**. For time reasons this reaction could not be optimised and the next step was directly tested. The enantiomeric excess for both enantiomers of **141c** remained excellent (*ee* = 99% determined by chiral stationary phase HPLC).



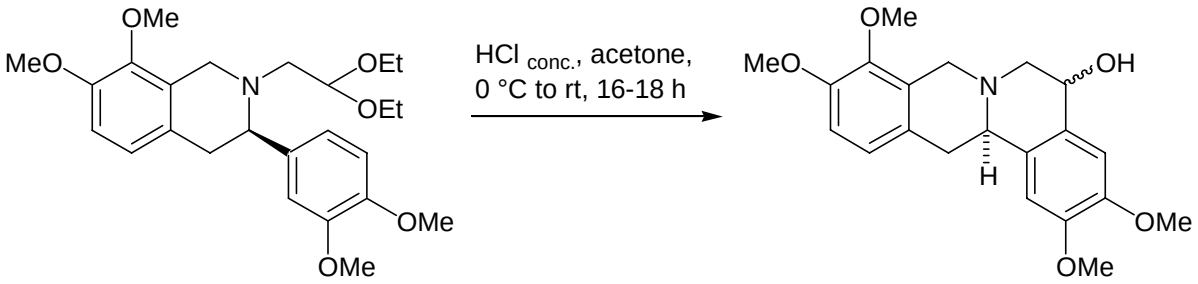
(*R*)-**142**: *ee* ≥ 99%
(*S*)-**142**: *ee* ≥ 99%

(*R*)-**141c**: 75%, *ee* ≥ 99%
(*S*)-**141c**: 63%, *ee* ≥ 99%

Scheme 73: Synthesis of the diethyl acetal **141c**

Slightly modifying a protocol described by *D. Badía* and *E. Domínguez*,[112a] the diethyl acetal **141c** was exposed to concentrated hydrochloric acid in acetone overnight to perform the

Pomeranz-Fritsch-type cyclisation. The quinolizin-5-ols **162** were obtained in very good yield as a mixture of diastereoisomers (ratio determined by chiral stationary phase HPLC) (Scheme 74).



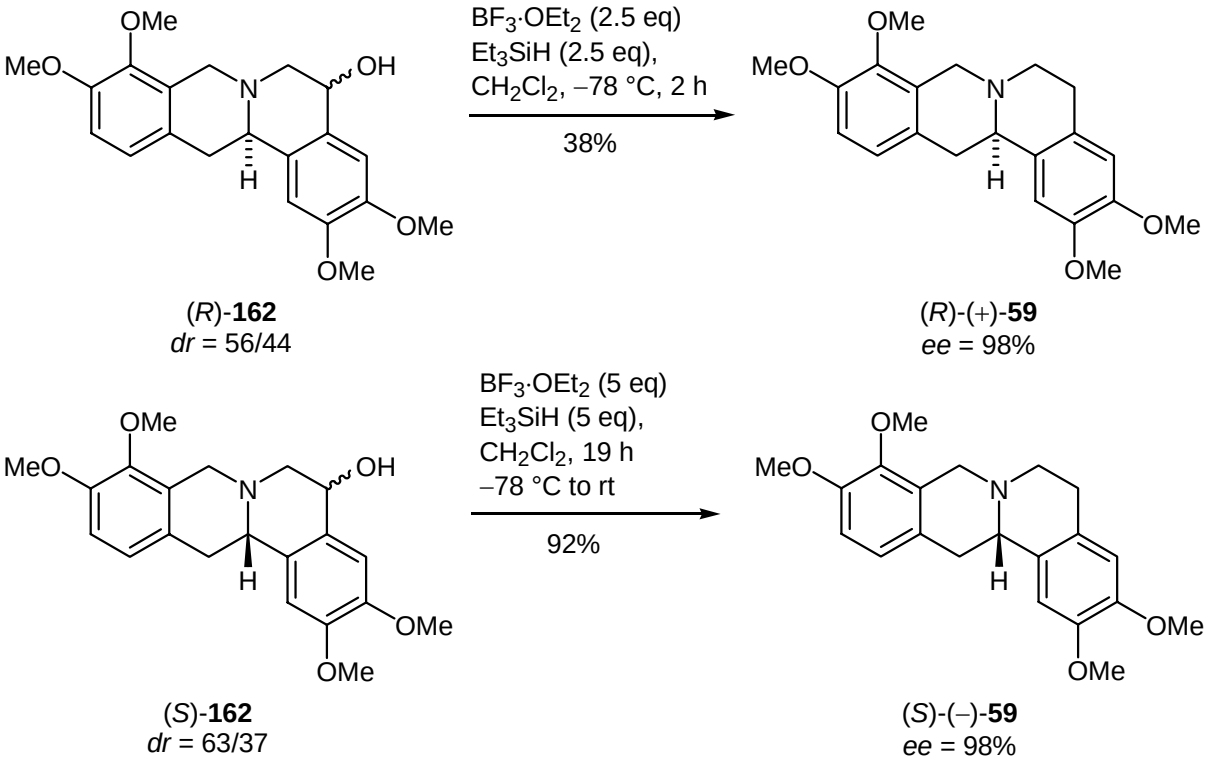
(*R*)-**141c**: *ee* ≥ 99%
(*S*)-**141c**: *ee* ≥ 99%

(*R*)-**162**: 88%, *dr* = 56/44
(*S*)-**162**: 83%, *dr* = 63/37

Scheme 74: Synthesis of the quinolizin-5-ol **162**

The deoxygenation of the alcohols **162** still had to be accomplished to obtain both enantiomers of the target molecule tetrahydropalmatine (**59**). Many examples described the formation of quinolizin-5-ol (see above), but to our knowledge no examples other that dehydrations are reported in the literature for the removal of the hydroxy group.[110a,112b]

First a combination of 2.5 equivalents of trifluoroborane-etherate complex and triethylsilane was applied to the diastereoisomeric mixture of the quinolizin-5-ol (*R*)-**162** for 2 hours at −78 °C. The choice of these smooth conditions proved to be appropriate as the (*R*)-(+)-tetrahydropalmatine (**59**) was obtained in excellent enantiomeric purity, yet in a low yield (Scheme 75). Possible reasons could be that either the number of equivalents of both reagents had to be higher, as often employed in the literature for this combination, or that the *Lewis* acid promoted the demethylation of the methoxy substituents. As no traces of eventual phenol could be detected in the NMR spectra of the crude mixture, another attempt was made with five equivalents of both reagents slowly warming up to room temperature overnight. The isolated yield for the (*S*)-(−)-tetrahydropalmatine (**59**) improved to 92%, in excellent enantiopurity (determined by chiral stationary phase HPLC) (Scheme 75).



Scheme 75: Synthesis of (*R*)-(+)- and (*S*)-(−)-tetrahydropalmatine (**59**)

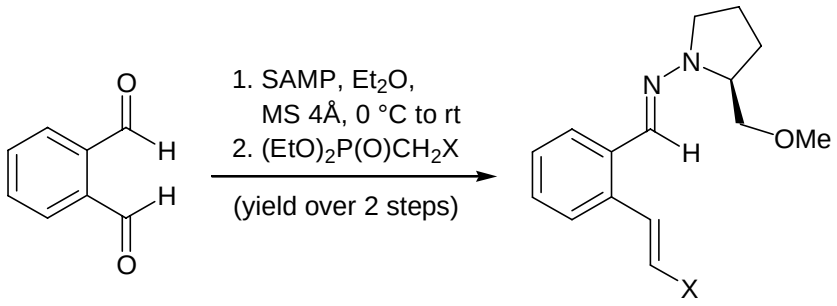
To summarise, the enantioselective synthesis of both enantiomers of tetrahydropalmatine was achieved in seven steps (including the synthesis of the 2,3-dimethoxy-6-methyl benzamide **117**). The overall yield amounted to 9% for the (*R*)-(+)-tetrahydropalmatine (*ee* = 98%) respectively 17% for the (*S*)-(−)-tetrahydropalmatine (*ee* = 98%). For comparison, *S. G. Pyne et al.*[49] obtained the (*R*)-(+)-tetrahydropalmatine with an overall yield of 31% over five steps (key step: 84% *de*, then diastereoisomeric separation) and *A. I. Meyers et al.*[50] obtained (*S*)-(−)-tetrahydropalmatine in five steps with an overall yield of 16% (88% *ee*).

4. SUMMARY

4.1 ASYMMETRIC SYNTHESIS OF ISOINDOLINES

We have demonstrated a straightforward and highly diastereoselective access to 1,2,3-trisubstituted isoindolines *via* a tandem 1,2-addition/cyclisation process.

Attempts to synthesise the tandem precursors (*S*)-**83** by first generating the *Michael* acceptor and then installing the SAMP-hydrazone were not successful. In a second approach, the SAMP-hydrazone was easily prepared by condensation of SAMP with the *o*-phthalic dicarboxaldehyde (**84**) in Et_2O at 0 °C in presence of molecular sieves. The aldehyde functionality was then transformed into the different alkenes (*S*)-**83a-d** by *HWE*-reaction with the corresponding phosphonates. The yields obtained over two steps were moderate to good and the (*E*)-selectivity was excellent except for the acrylonitrile (Scheme 76).



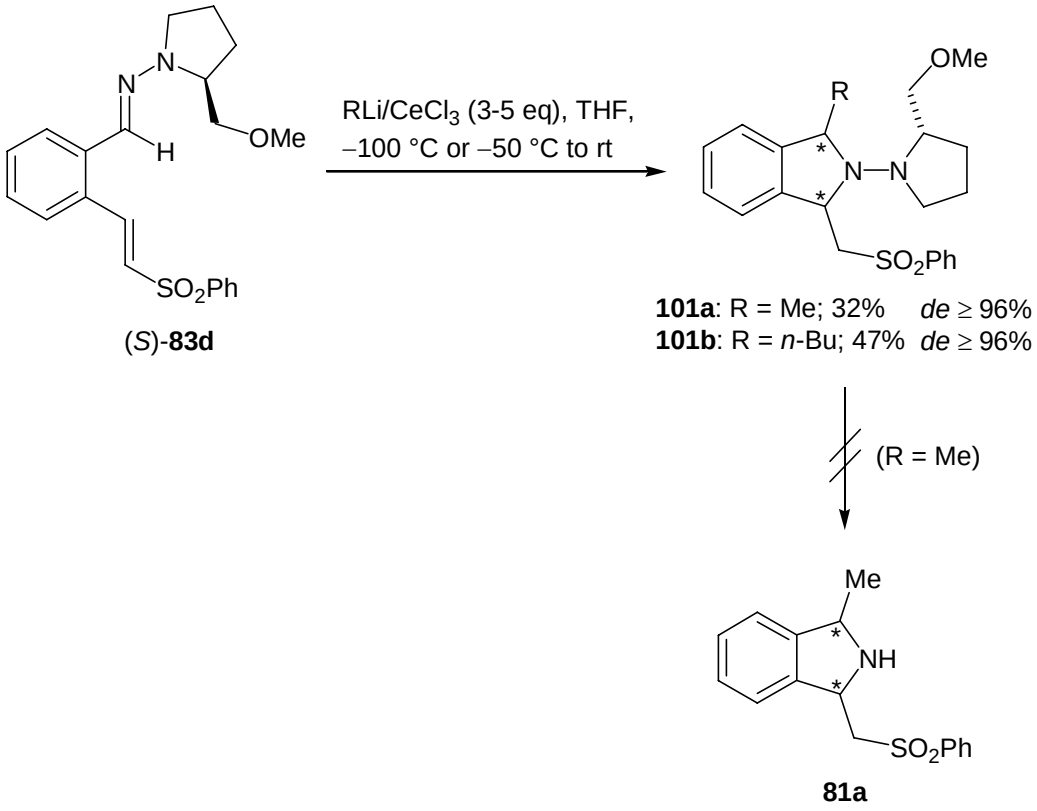
84 (*S*)-**83**

(*S*)-**83a**: X = CO_2Et; 74% (*E*)/(*Z*) = 54/1
(*S*)-**83b**: X = CO_2t-Bu; 81% (*E*)/(*Z*) = 182/1
(*S*)-**83c**: X = CN; 55% (*E*)/(*Z*) = 4.2/1
(*S*)-**83d**: X = SO_2Ph; 50% (*E*)/(*Z*) = 56/1

Scheme 76: Synthesis of the precursors (*S*)-**83**

Our first experiment to perform the tandem reaction used two equivalents of methyllithium and only led to the formation of 2-benzenesulfonyl-1*H*-indene. Among all combinations of organometallic/lanthanide reagents tested, the organolithium/cerium chloride (1/1) system was found to be the most efficient. When three equivalents of methyllithium/cerium chloride were added at −100 °C to a solution of the phenylsulfonyl vinyl SAMP-hydrazone (*S*)-**83d** a yield of 32% of the methyl substituted isoindoline **101a** could be obtained. Five equivalents of *n*-butyllithium/cerium chloride led to the formation of the *n*-butyl substituted dihydro-1*H*-

isoindole **101b** in 47% yield. Both **101a** and **101b** were obtained in excellent diastereoselectivity. However, until now, the cleavage of the auxiliary to synthesise the 1,3-disubstituted 2,3-dihydro-1*H*-isoindole **81a** could not be achieved in spite of several attempts (Scheme 77).

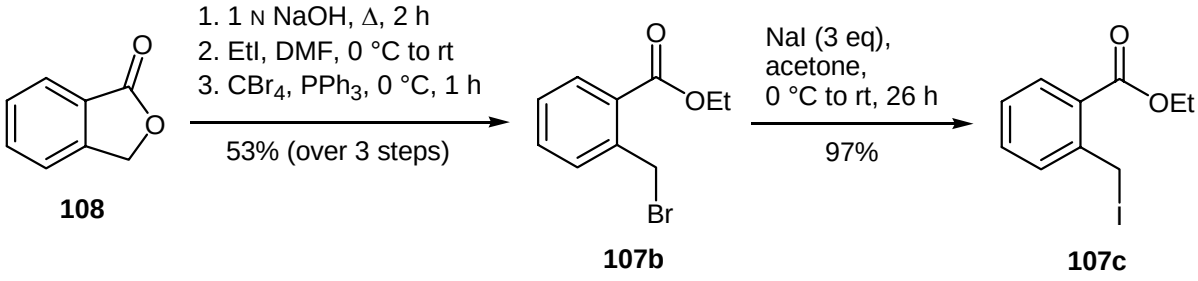


Scheme 77: Synthesis of 1,2,3-trisubstituted 2,3-dihydro-1*H*-isoindoles **101**

4.2 TOWARDS THE ASYMMETRIC SYNTHESIS OF TETRAHYDRO-2-BENZAZEPINES

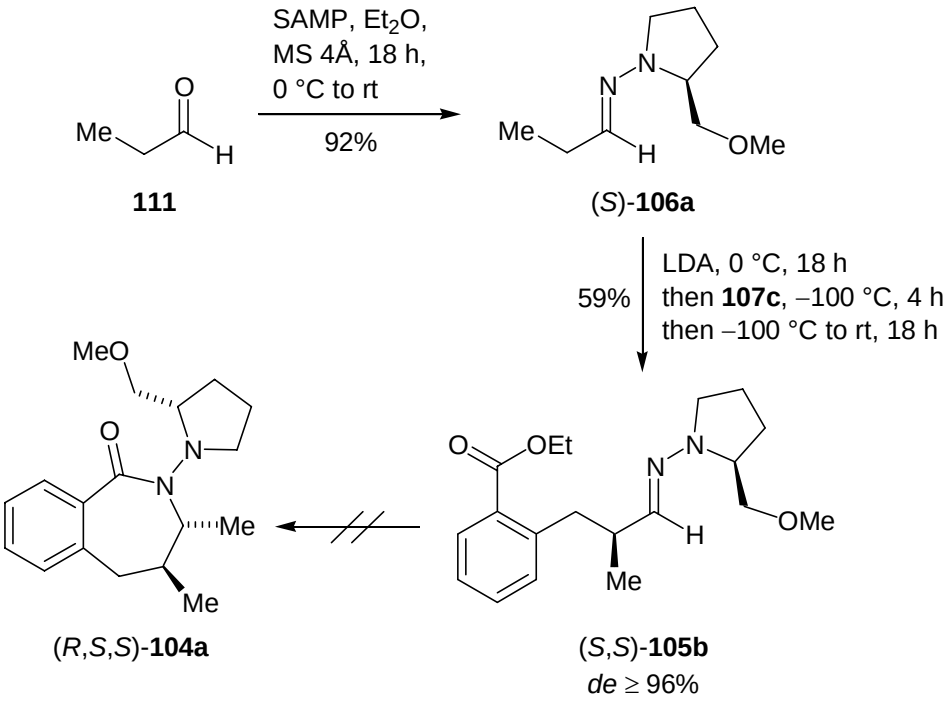
The first diastereo- and enantioselective synthesis of 3,4-disubstituted 2,3,4,5-tetrahydro-1*H*-2-benzazepines in a tandem 1,2-addition/ring closure sequence was attempted.

The necessary tandem precursor was obtained by *α*-alkylation of propanal-SAMP hydrazone (*S*)-**106a** with the electrophile **107c**. The synthesis of **107c** started with the commercially available phthalide **108**. After transformation in its corresponding sodium 2-hydroxymethyl benzoate with an aqueous solution of NaOH under reflux, the salt was converted into an ester by treatment with ethyl iodide. Alcohol/bromide exchange was achieved using carbon tetrabromide and triphenylphosphine and the benzylbromide **107b** was obtained with an overall yield of 53% over three steps. **107b** was reacted with an excess of sodium iodide in acetone giving rise to the electrophile **107c** nearly quantitatively (Scheme 78).



Scheme 78: Synthesis of the electrophile **107c**

Propanal SAMP-hydrazone (*S*)-**106a**, obtained by condensation of propanal and SAMP, was chosen as model nucleophile in the *α*-alkylation to form the tandem precursor (*S*,*S*)-**105b**. After deprotonation of (*S*)-**106a** with LDA at 0°C, the benzyliodide **107c** was added keeping the reaction at −100 °C for 4 hours. By slowly increasing the temperature overnight a yield of 59% and an excellent diastereomeric excess could be obtained for the precursor (*S*,*S*)-**105b**. Two attempts for the tandem 1,2-addition/ring closure sequence were made, one with two equivalents of methyllithium, the other with two equivalents of the methyllithium/cerium chloride system but none of them led to the formation of the desired trisubstituted tetrahydro-2-benzazepine (*R*,*S*,*S*)-**104a** (Scheme 79).

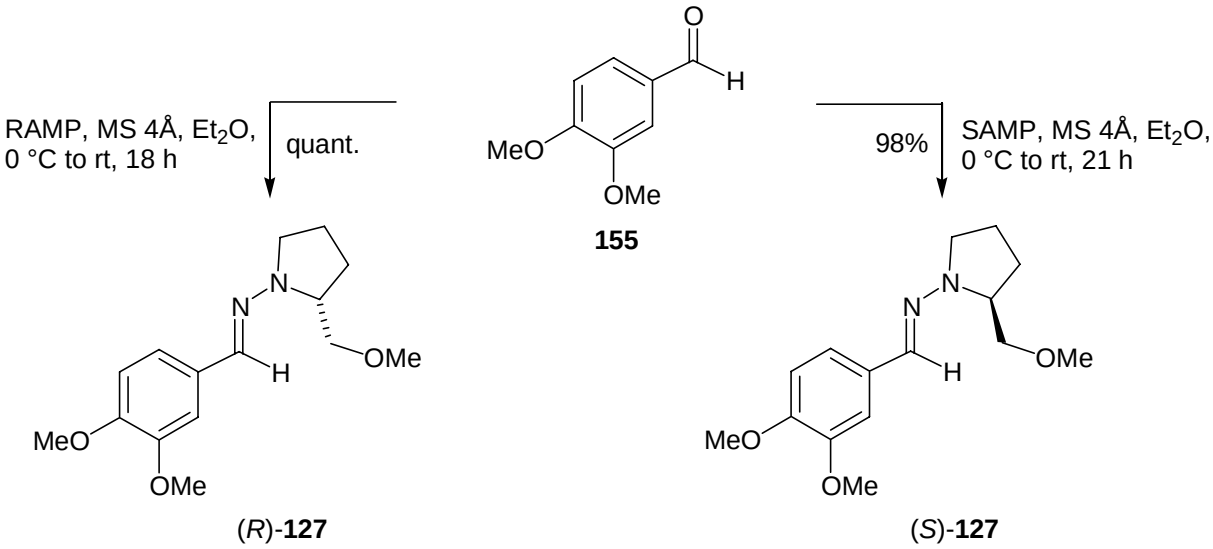


Scheme 79: Synthesis and attempted cyclisation of the tandem precursor (*S*,*S*)-**105b**

4.3 ASYMMETRIC SYNTHESIS OF TETRAHYDROPALMATINE

Within the context of this work, the asymmetric synthesis of both enantiomers of tetrahydropalmatine (*S*)-(−)- and (*R*)-(+)-**59** using a tandem 1,2-addition/ring closure sequence could be achieved.

The synthesis concept started with the preparation of the SAMP-hydrazone (*S*)-**127** and the RAMP-hydrazone (*R*)-**127**. The condensation of the commercially available 3,4-dimethoxy-benzaldehyde with the respective chiral auxiliary led to the formation of the hydrazones in virtually quantitative yield (Scheme 80).



Scheme 80: Synthesis of the 4,5-dimethoxy-benzaldehyde SAMP/RAMP-hydrazones **127**

Transformation of the carboxylic acid group of the commercially available 2,3-dimethoxybenzoic acid **153** into an acyl chloride was achieved by treatment with oxalyl chloride and a catalytic amount of dimethyl formamide. Diethylamine was then added at low temperature and gave the desired product **154** in an excellent yield. Deprotonation with *s*-butyllithium, coordinated to an equimolar amount of tetramethylethylenediamine, took place in *ortho*-position because of the directing effect of the amide moiety. A stoichiometric amount of methyl iodide was then added letting the temperature slowly warm up to room temperature and a good yield of 2,3-dimethoxy-6-methyl benzamide **117** could be reached.

For the tandem reaction, an equimolar amount of *s*-butyllithium and tetramethylethylenediamine had to be employed to deprotonate the methyl group of **117**. As revealed by optimisation of the reaction conditions, Et_2O was found to be the best solvent and

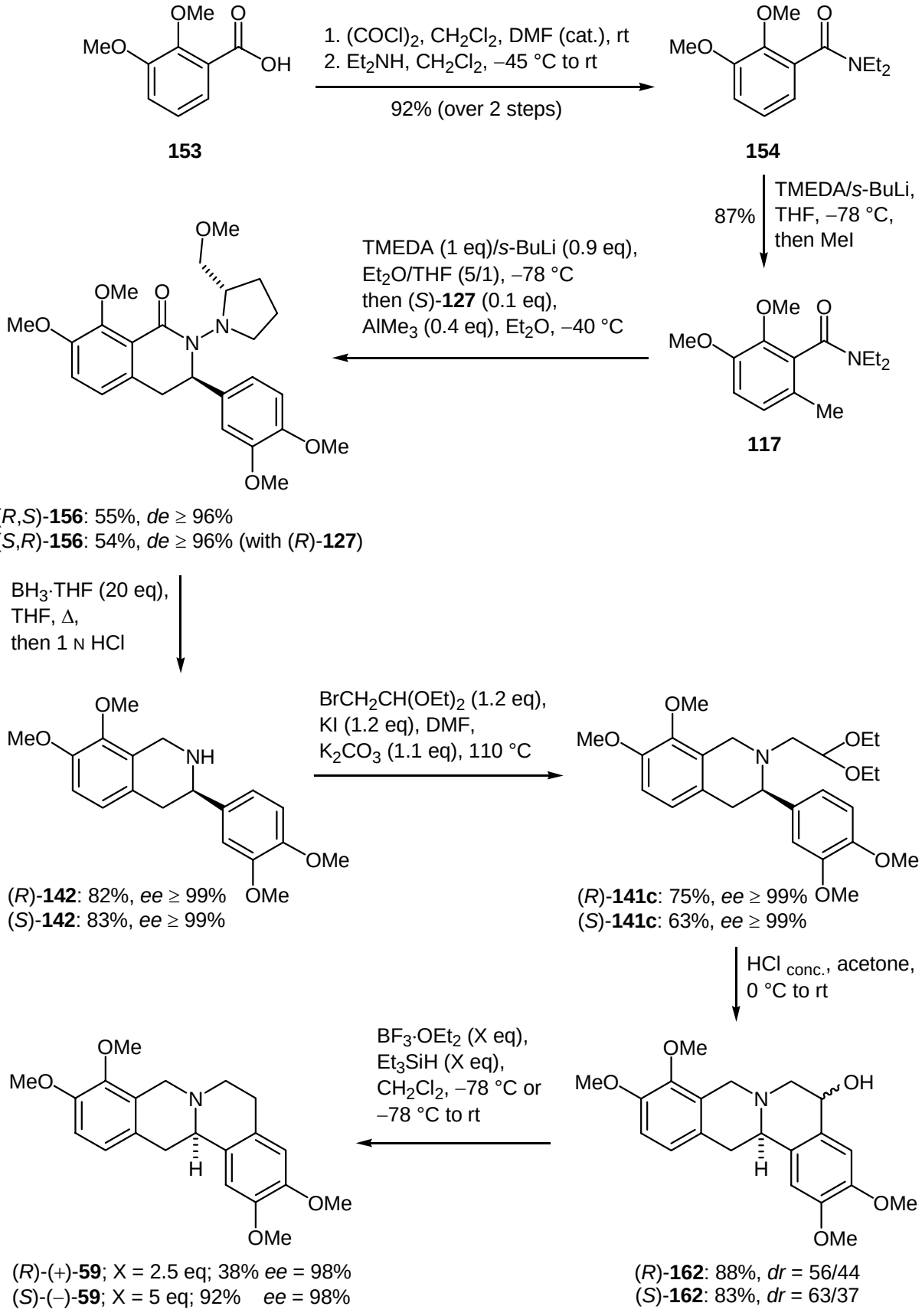
a small amount of THF was necessary to ensure for guarantee a good solubility of the lithiated species. The hydrazone (*S*)- or (*R*)-**127**, complexed before with trimethyl aluminium, was then added at –40 °C. The cyclised product (*R*,*S*)-**156** was obtained with excellent diastereoselectivity and reasonable yield taking into account the various functionalities built up in one step. Analogously the dihydroisoquinolone (*S*,*R*)-**156** could also be obtained with a similar yield showing the reproducibility of the reaction.

An excess of the borane-THF complex was used to cleave the N─N bond of the chiral auxiliary and to reduce the carbonyl group of the amide moiety of (*R*,*S*)-**156** in the same step. After hydrolysis of the borane using an aqueous solution of hydrochloric acid, the tetrahydroisoquinoline (*R*)-**142** was isolated in an excellent yield of 82% and an enantiomeric excess of 99%. Analogously (*S*)-**142** was obtained in the same enantiomeric purity and with a reproducible yield of 83%.

(*R*)-**142** was then heated in presence of bromoacetaldehyde diethyl acetal and potassium carbonate. Additional potassium iodide was employed to perform a bromide/iodide exchange *in situ* before the attack on the amine. The *Pomeranz-Fritsch* precursor (*R*)-**141c** could be obtained in 75% yield. In the same conditions, only 63% of (*S*)-**141c** was obtained. The enantiomeric excess obtained for both enantiomers of **141c** remained excellent (*ee* = 99%).

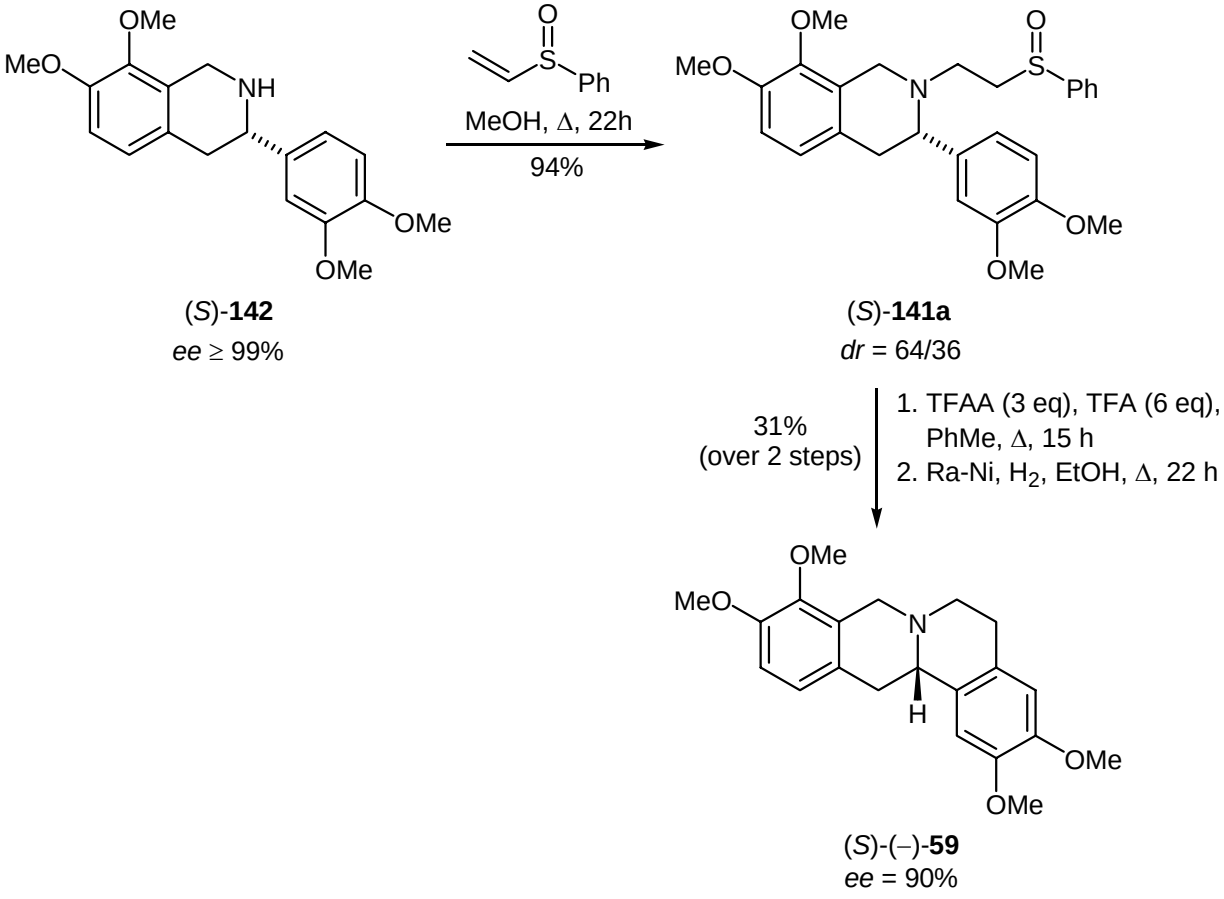
The diethyl acetals **141c** were submitted to concentrated hydrochloric acid in acetone overnight to perform the *Pomeranz-Fritsch*-type cyclisation. Each quinolizin-5-ol **162** was obtained in good yield as a mixture of diastereoisomers.

To our knowledge, the removal of the hydroxy group of a quinolizinol other than by dehydration was accomplished for the first time. First a combination of 2.5 equivalents of trifluoroborane-etherate complex and triethylsilane were employed together with the diastereoisomeric mixture of the quinolizin-5-ol (*R*)-**162** for 2 hours at –78 °C. (*R*)-(+)-tetrahydropalmatine (**59**) was obtained in excellent enantiomeric purity. Another attempt was then made with 5 equivalents of both reagents warming up to room temperature overnight. The yield for the (*S*)-(–)-tetrahydropalmatine (**59**) increased to 92% together with an excellent enantiopurity. The results are summarised in Scheme 81.



Scheme 81: Asymmetric synthesis of tetrahydropalmatine *via Pomeranz-Fritsch* cyclisation

Alternatively, the synthesis of tetrahydropalmatine could be achieved *via Pummerer* reaction. The synthesis of the *Pummerer* precursor was done by *Michael* reaction between the vinyl sulfoxide acceptor and the tetrahydroisoquinoline (*S*)-**142** after 22 hours reflux in methanol. A diastereoisomeric mixture of (*S*)-**141a** was obtained in 94% yield. The *Pummerer* reaction was performed by treatment of (*S*)-**141a** with an excess of trifluoroacetic acid and trifluoroacetic anhydride. The roughly purified phenylsulfanyl tetrahydrodibenzoquinolizine was directly subjected to the next step. Reductive desulfurisation with *Raney* nickel gave 31% of (*S*)-(–)-tetrahydropalmatine **59** after two steps. However, during this sequence a slight racemisation occurred (*ee* = 90%) which can probably be attributed to the strong trifluoroacetic acid that was necessary for this transformation.



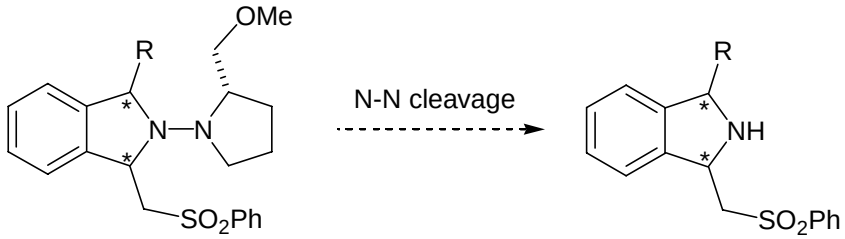
Scheme 82: Asymmetric synthesis of (*S*)-(–)-tetrahydropalmatine (**59**) *via Pummerer* reaction

The enantioselective synthesis of both enantiomers of tetrahydropalmatine was achieved in seven steps (counting as well the synthesis of the 2,3-dimethoxy-6-methyl benzamide **117**). The overall yield amounted to 9% for the (*R*)-(+)-tetrahydropalmatine (*ee* = 98%) and 17% for the (*S*)-(–)-tetrahydropalmatine (*ee* = 98%). For comparison, *S. G. Pyne et al.*[49] obtained

the (*R*)-(+)-tetrahydropalmatine with an overall yield of 31% over five steps (key step: 84% *de*, then diastereoisomeric separation) and *A. I. Meyers et al.*[50] synthesised (*S*)-(−)-tetrahydropalmatine in five steps with an overall yield of 16% (88% *ee*).

5. OUTLOOK

1. To accomplish the synthesis of the 1,3-disubstituted isoindolines **81**, other methods for the cleavage of the chiral auxiliary should be investigated. For example, the use of zinc in acetic acid[92] or a preactivation of the hydrazines with methoxycarbonyl chloride before using standard conditions such as *Raney* nickel[93] could be tested on the *N*-substituted isoindolines **101** (Scheme 83).



101
de ≥ 96%

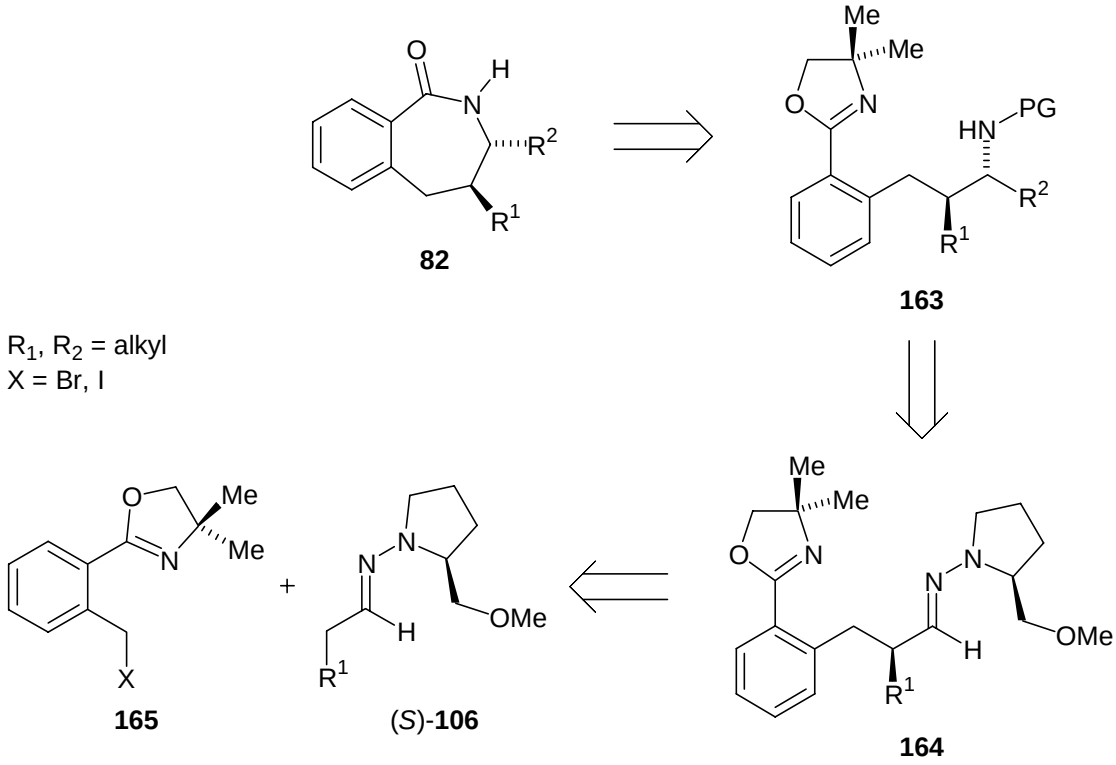
81

Scheme 83: Final synthetic step for the synthesis of disubstituted isoindolines **81**

The absolute configuration of the two stereogenic centres formed in this process still have to be determined.
The tandem reaction should also be performed with the (*Z*)-isomer of the *Michael* acceptor in order to detect an eventual difference in behaviour and stereoselectivity (see 3.1.1).

2. The tandem 1,2-addition/ring closure sequence for the synthesis of 3,4-disubstituted tetrahydro-2-benzazepines was unsuccessful. However, a 1,2-addition and a cyclisation could be performed in two separated steps to realize the synthesis of the desired products. The disubstituted tetrahydro-2-benzazepines **82** should be obtained by spontaneous cyclisation after hydrolysis of the oxazoline **163** under acidic conditions and deprotection of the resulting amide. The construction of the precursor **163** should proceed *via* 1,2-addition of an organometallic reagent to the hydrazone functionality of **164**, protection of the generated hydrazine and cleavage of the chiral auxiliary. The oxazoline moiety should stay intact as similar compounds are reported to be inert towards *Grignard* reagents.[114] The compound **164** should be formed by *α*-

alkylation of an aliphatic aldehyde SAMP-hydrazone (*S*)-**106** with an *ortho*-oxazoline-substituted benzyl halide **165**[115] (Scheme 84).

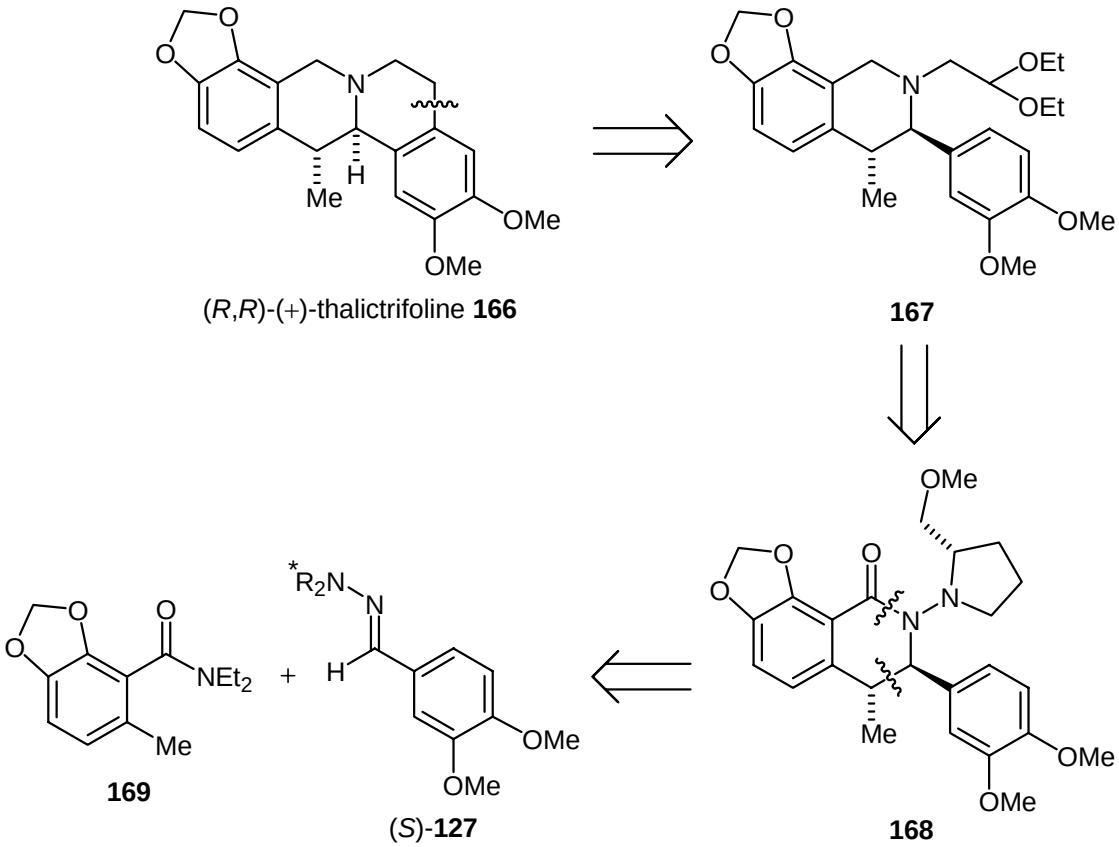


Scheme 84: Retrosynthetic concept for the synthesis of tetrahydro-2-benzazepines **82**

3. As the asymmetric synthesis of (*R*)-(+)- and (*S*)-(−)-tetrahydropalmatine was accomplished, the established methodology could now be applied to all protoberberines lacking substitution at the C-13 position (see Figure 10) as, for example, to the naturally occurring alkaloids (*S*)-(−)-canadine, (*S*)-(−)-isocorypalmine and (*S*)-(−)-stylopine.[34]

   Another aspect of the tandem addition process is that one equivalent of a strong base (lithium diethyl amide) is formed after the attack of the intermediate nitrogen anion on the amide carbonyl group. The generated dialkyl amide deprotonates the 3-substituted dihydroisoquinolinone at the benzylic position. Subsequent treatment of the anion of a racemic cyclic adduct with various electrophiles was shown to yield exclusively the *trans*-isomers of 3,4-disubstituted dihydroisoquinolinones.[54d] It would be interesting to apply this characteristic reaction to the total synthesis of the naturally occurring (*R*,*R*)-(+)-thalictrifoline (**166**), where the hydrogen atoms at C-13 and C-14 are *trans*.[116] This 13-methyl-tetrahydroprotoberberine could result from the acetal **167** in a

Pomeranz-Fritsch-type cyclisation followed by the removal of the hydroxy group. This precursor could be generated from the dihydroisoquinolinone **168** by N─N cleavage of the auxiliary, reduction of the carbonyl group and nitrogen functionalisation with bromoacetaldehyde diethyl acetal. The tandem 1,2-addition/ring closure sequence of lithiated 2-methyl benzamide **169** and SAMP-hydrazone (*S*)-**127** followed by trapping with methyl iodide between should furnish the *N*-substituted *trans*-3,4-disubstituted dihydroisoquinolinone **168** in high diastereoselectivity (Scheme 85).



Scheme 85: Retrosynthetic analysis for the synthesis of (*R*,*R*)-(+)-thalictrifoline (**166**)

6. EXPERIMENTAL PART

At this point I would like to thank all the people without whom this work could not have been realised:

First I would like to express my gratitude to the Graduiertenkolleg 440 and its former director Prof. Dr. Carsten Bolm for attributing me a grant. It gave me the opportunity to discover the high quality of education and working conditions of the institute and to enjoy the nice spirit of Aachen.

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For new ideas for my subjects and interesting discussions in chemistry I warmly thank Dr. André Ridder, Dr. Michael Moser, Miss Antje Hieronymi and Mr. Karsten Lüttgen.

For his contribution to my second project I would like to acknowledge my research student Mr. Bernhard Rußbüldt.

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6.1 PREPARATIVE WORK

6.1.1 WORKING UNDER PROTECTIVE ATMOSPHERE

All reactions involving air- or moisture-sensitive compounds were carried out in a Schlenk flask previously heated in high vacuum, filled with argon and closed by a septum. During the course of the reaction a permanent pressure of argon (approximately 0.1 bar) was applied. The addition of solvents, liquids or dissolved substances was performed with the help of a syringe fitted with a needle through the septum. Solid reagents were added using a flow of argon.
Column chromatography was performed with a pressure of nitrogen (approximately 0.2 bar).

6.1.2 WORKING AT LOW TEMPERATURE

In order to perform a reaction at low temperature, the reaction vessel was cooled in a Dewar containing the following cooling mixtures:

- 0 °C: ice/water
- –5 °C: acetone/ice
- –40 °C: cooled *iso*-propanol bath of a cryostat
- –78 °C: acetone/dry ice
- –100 °C: acetone/liquid nitrogen

6.1.3 SOLVENTS

Acetone	Technical grade
Acetonitrile	Biosolve, anhydrous
1,2-Dichloroethane	Technical grade
Dichloromethane	2 h reflux over CaH_2 and subsequent distillation through a column of packings
1,4-Dioxane	Aldrich, pure
Abs. dichloromethane	Extraction of distilled dichloromethane with conc. HCl until the aqueous phase remains clear. Neutralisation, drying over $MgSO_4$ and distillation over CaH_2 under an argon atmosphere
Diethylether	Distillation over KOH through a column of packings

Abs. diethylether	Passage through a basic aluminium oxide column and distillation over Na-Pb alloy/benzophenone under an argon atmosphere
DMF	Acros, anhydrous
Ethanol	Merck, anhydrous
n-Hexane	Distillation over CaH_2
Methanol	2 h reflux over Mg/MgOMe and subsequent distillation
Abs. methanol	2 h reflux over Mg/MgOMe and subsequent distillation under an argon atmosphere
n-Pentane	Distillation over CaH_2 through a column of packings
Petroleum ether	Technical grade
Tetrahydrofurane	2 h reflux over KOH and subsequent distillation through a column of packings
Abs. tetrahydrofurane	Passage through a basic aluminium oxide column and distillation over Na-Pb alloy/benzophenone under an argon atmosphere
Abs. toluene	Distillation over Na-Pb alloy/benzophenone under an argon atmosphere

6.1.4 CHEMICALS

Chemicals were purchased from commercial suppliers (Acros, Aldrich, Fluka, Lancaster and Merck) or were available in the group. They were used from freshly opened containers or purified according to standard laboratory methods.[117]

Other chemicals were prepared using the following procedures:

pH 7 buffer	11.64 g NaOH, 68.0 g KH_2PO_4 and 1000 mL H_2O
Raney-nickel (W2)	*Raney*-nickel was prepared according to the literature[118]
RAMP	RAMP was gently donated by Dr. A. Ridder and Dr. D. Steinbusch
SAMP	SAMP was prepared according to the literature in 6 steps from (*S*)-(−)-proline[119]

6.1.5 REACTION CONTROL

The course of the reactions was monitored by thin layer chromatography using silica gel 60 with fluorescence indicator F_{254} coated on glass plates from Merck-Schuchardt. The detection of UV-active substances was realised using a UV lamp (λ = 254 nm). UV-inactive substances could be detected by dipping the plates in one of the following solutions and subsequent heating using a hot air flow:

- 50 mg of $KMnO_4$ and 100 mL of H_2O
- 5 g of $H_3[P(Mo_3O_{10})_4]\cdot xH_2O$ and 100 mL of EtOH
- 25 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 10 g of $(NH_4)_4Ce(SO_4)_4$, 100 mL of H_2SO_4 and 900 mL of H_2O

6.1.6 PREPARATIVE COLUMN CHROMATOGRAPHY

For the chromatographic purification of products, glass columns of different widths and lengths were used depending on the purification problem. Silica gel 60 (0.040-0.063 nm) (Merck) as stationnary phase and acid washed sea sand (Riedel de Haën) were used as filling material. The eluent was chosen after preliminary thin layer chromatography experiments. For the separation a light pressure (max. 0.2 bar) was applied. After isolation of the fractions, the solvents were evaporated under reduced pressure, and the resulting purified product, if not volatile, was dried under high vacuum.

6.1.7 PREPARATIVE THIN LAYER CHROMATOGRAPHY

The crude mixture of reaction products was dissolved in a minimum amount of solvent (CH_2Cl_2 or Et_2O) and was carefully placed via a capillary on the concentration zone of a glass plate coated with silica gel 60 with fluorescence indicator F_{254} (Merck). This plate was then treated as for normal thin layer chrompatography. By means of a UV lamp the desired product was detected and the silica was scratched where the product was present. The silica was then poured in a Büchner funnel and the product was extracted several times with CH_2Cl_2 or Et_2O. The solvent was then concentrated under reduced pressure.

6.1.8 STORAGE OF SYNTHESISED SUBSTANCES

All synthesised solid, liquid and oily substances were kept under argon in the freezer at –25 °C and were stable for several months unless otherwise indicated.

6.1.9 SPECIAL APPARATUS

Syringe pump:	Bioblock Scientific, Modell A-99
Lyophilisator:	Christ, Alpha 1-2
Cryostat:	Julabo FPW 90
Ultrasound tank:	Bandelin Sonorex TK 52

6.2 CHARACTERISATION OF THE PRODUCTS

6.2.1 APPARATUS AND MEASUREMENT TECHNIQUES

^{1}H-NMR spectroscopy	Varian Inova 400 (400 MHz), Mercury 300 (300 MHz), Gemini 300 (300 MHz); internal standard: tetramethylsilane
^{13}C-NMR spectroscopy	Varian Inova 400 (100 MHz), Mercury 300 (75 MHz), Gemini 300 (75 MHz); internal standard: tetramethylsilane; ^{1}H-Broad Band Decoupling; J-modulated Spin-Echo-Recording (Waltz-16-Decoupler Programm)
^{31}P-NMR spectroscopy	Varian Mercury 300 (121.5 MHz); internal standard: tetramethylsilane; ^{1}H-Broad Band Decoupling; external standard: phosphoric acid (80%)
Mass spectroscopy	GC-MS: Varian 3400 (Sil-8, 25 m × 0.25 mm, ID); MS: Finnigan SSQ 7000 (EI 70 eV; CI 100 eV); HR-MS: Finnigan MAT 95
IR spectroscopy	Perkin Elmer FT/IR 1760
Elementary analysis	Heraeus CHN-O-Rapid; Elementar Vario EL
Gas chromatography	Varian CP3800; detector: FID; column: Sil-8 (fused silica, 25 m × 0.25 mm, ID); gas: nitrogen (p = 1 bar)
Analytical HPLC	Hewlett Packard 1050; columns: Chiralpak AD2 (250 mm × 4.6 mm, 10 µm), Chiralcel OD (250 mm × 4.6 mm, 10 µm), Chiralpak AD (250 mm × 4.6 mm, 10 µm), Chiralcel OJ (250 mm × 4.6 mm, 10 µm), Lichrosorb Si 60 (250 mm × 4.6 mm, 7 µm), Spherical silica (150 mm × 3.9 mm, 5 µm); DAD-detector
Polarimetry	Perkin-Elmer Polarimeter P 241; Merck Uvasol chloroform
Melting point	Tottoli melting point apparatus; Büchi 510

6.2.2 REMARKS ON THE ANALYTICAL DATA

Yield	The yield given is referred to the purified substance (≥ 95%) and is, if necessary, corrected after GC-analysis.

Gas chromatography	The retention time (in min) of the product is given followed by the used conditions: column, starting temperature-gradient of temperature-ending temperature (in °C).
Boiling point, pressure	The boiling temperature (in °C) is measured by means of a mercury thermometer in the apparatus and is uncorrected. For distillation under vacuum, the reduced pressure is measured by a sensor.
Melting point	The melting point is determined in an open capillary using a mercury thermometer and is uncorrected.
Polarimetry	The optical rotation is measured at the indicated temperature with the sodium-D-line (λ = 589 nm) in a cell of length l = 1 dm. The concentration is given in g/dl.
Analytical HPLC	The enantiomeric purity is given followed by the column and the eluent used for the measurements, the retention time (in min) of the differents enantiomers and the wavelenght used for their detection.
^{1}H-NMR spectroscopy	The chemical shifts δ are given in ppm relative to the internal standard tetramethylsilane (TMS). *J* is the value of the coupling constant in Hz. For the description of the multiplicity of the signal the following abbreviations are used: s = singulet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br = broad. The proton belonging to this signal is marked in italics in the added structure section. The measurements are done at room temperature.
^{13}C-NMR spectroscopy	The chemical shifts δ are given in ppm relative to the internal standard tetramethylsilane (TMS). The signals are assigned to the numbered carbon atoms of the structure drawing (arbitrary numbering). The measurements are done at room temperature.
^{31}P-NMR spectroscopy	The chemical shifts δ are given in ppm relative to the external standard phosphoric acid (80%).
Mass spectroscopy	The mass of the fragments (*m/z*) is given using a number without dimension with the structure element and the peak intensity (proportional to the peak basis) added in brackets.

	Only signals with an intensity ≥ 10% or caracteristic peaks are reported.
IR spectroscopy	The measurements are taken as film between 2 plates of KBr for liquids, in $CHCl_3$ for oils and using KBr pills for solids. The position of the absorption signals are given in cm^{-1}. Only peaks with a transmission ≤ 80% are reported. The peak intensity is characterised using the following abbreviations: vs = very strong (0-20% T), s = strong (21-40% T), m = middle (41-60% T), w = weak (61-80% T).
Elementary analysis	A sample is considered as authentic when $\Delta_{C,H,N} \leq 0.5\%$ or when the HRMS data are accurate within 5 ppm.

6.3 GENERAL PROCEDURES

GP-1 SYNTHESIS OF HYDRAZONES

In a Schlenk flask under argon, SAMP or RAMP (1.0 eq) was added to a suspension of crushed molecular sieves (4Å, 0.1 g/mmol hydrazine) and freshly distillated aldehyde (0.8-1.4 eq) in Et_2O (1.35-1.61 mL/mmol hydrazine) at 0 °C. At the end of the addition, the reaction mixture was warmed up to room temperature and stirred overnight (12-20 h). After dilution with Et_2O and filtration over Celite, the solvent was evaporated under reduced pressure. The crude hydrazone was then purified by distillation or by column chromatography.

GP-2 SYNTHESIS OF ALKENES WITH *t*-BuOK

In a Schlenk flask under argon, phosphonate (1.7 eq) was added to a solution of *t*-BuOK (1.5 eq) in THF (2.35 mL/mmol *t*-BuOK) at 0 °C. The solution was warmed up to room temperature and stirred for 3 h. A solution of pure or crude benzaldehyde-SAMP/RAMP-hydrazone (*R*)/(*S*)-**95** (1.0 eq) in THF (1.4 mL/mmol hydrazone) was then added dropwise over 2-3 h. At the end of the addition the reaction mixture was stirred overnight (13 h). The reaction was hydrolysed by H_2O (0.018 mL/mmol *t*-BuOK), diluted with brine (9 mL/mmol hydrazone) and extracted 3 times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by column chromatography.

GP-3 SYNTHESIS OF ALKENES WITH LiCl/Et_3N

To a suspension of LiCl (1.1-1.5 eq) in anhydrous CH_3CN (1 mL/mmol LiCl) in a Schlenk flask under an argon atmosphere cooled to 0 °C was added successively phosphonate (1.3-1.7 eq) and Et_3N (1.1-1.5 eq). After stirring 1 h at 0 °C, a solution of the substituted benzaldehyde (1.0 eq) in CH_3CN (1 mL/mmol aldehyde) was added over 45 min. At the end of the addition, the temperature was increased directly to room temperature and the reaction mixture was stirred for further 19 h. The reaction was then diluted with H_2O (1.35 mL/mmol aldehyde) and extracted 3 times with Et_2O. The combined organic phases were washed with brine and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the crude alkene was purified by column chromatography.

GP-4 3,4-DIHYDRO-2*H*-ISOQUINOLIN-1-ONES THROUGH 1,2-ADDITION/RING CLOSURE

In a 250 mL Schlenk flask under argon, *n*-BuLi (6.6 mL, 10.50 mmol, 1.59 M in hexane) was added to a solution of (*i*-Pr)$_2$NH (1.5 mL, 10.50 mmol) in abs. THF or Et$_2$O (50 mL) cooled to 0 °C. The solution was stirred 15 min at 0 °C and cooled to −78 °C before a solution of *N*,*N*-diethyl-2-methyl-benzamide (**75**) (10.50 mmol) in abs. THF or Et$_2$O (10 mL) was added dropwise. The temperature was increased to −40 °C and a solution of the SAMP/RAMP-hydrazone (1.50 mmol) in abs. THF or Et$_2$O (6 mL), previously complexed with AlMe$_3$ (0.83 mL, 1.65 mmol, 2 M in heptane) for at least 1 h, was added dropwise over 30 min. The reaction mixture was stirred overnight (~ 18 h) at −40 °C. The reaction was quenched with 10% aqueous potassium and sodium tartrate (5 mL) and sat. aqueous NH$_4$Cl (10 mL). After warming up to room temperature and phase separation, the aqueous layer was extracted 3 times with Et$_2$O (30 mL). The combined organic phases were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography.

GP-5 ACETYLATION OF THE 3-PHENYL-3,4-DIHYDRO-2*H*-ISOQUINOLIN-1-ONES

In a flask under argon, chloroacetyl chloride (1.25 eq) or (phenylthio)acetyl chloride (1.05 eq) was added to a solution of 3-phenyl-3,4-dihydro-2*H*-isoquinolin-1-one ((*R*)-**79a**) or ((*S*)-**79a**) (1.0 eq) in anhydrous CH$_3$CN (2 mL/mmol amide) and the reaction mixture was heated to 80 °C for 4 or 20 h. The volatiles were then removed under reduced pressure. The residue was diluted and extracted with CH$_2$Cl$_2$ (20 mL/mmol amide) and H$_2$O (20 mL/mmol amide) and the organic layer was washed with sat. aqueous Na$_2$CO$_3$ (20 mL/mmol amide). After drying over MgSO$_4$, filtration and concentration under reduced pressure the resulting crude mixture was used directly in the next step.

GP-6 1,2,3,4-TETRAHYDROISOQUINOLINES THROUGH N—N CLEAVAGE WITH BH$_3$·THF

In a Schlenk flask under argon fitted with a reflux condenser, BH$_3$·THF (20 eq, 1 M in THF) was added to a solution of the hydrazine (1.0 eq) in abs. THF (40 mL/mmol hydrazine) and the reaction mixture was heated to reflux for 4 h. After cooling the solution to 5 °C, 1 N aqueous HCl (7.7 mL/mmol hydrazine) was cautiously added. After 1 min reflux, the solvent and most of the water were evaporated under reduced pressure and sat. aqueous NaHCO$_3$ was added to the residue until no evolution of gas could be observed any more. The mixture was extracted 3 times with Et$_2$O. The combined organic phases were dried over MgSO$_4$, filtered

and evaporated under reduced pressure. The resulting crude mixture was purified by column chromatography.

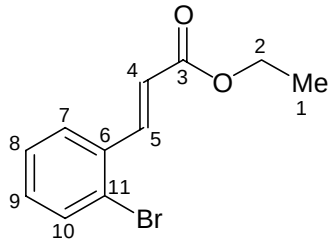
GP-7 REACTION OF THE 1,2,3,4-TETRAHYDROISOQUINOLINES WITH IODOETHANOL

In a flask under argon, a suspension of 1,2,3,4-tetrahydroisoquinoline (1.0 eq), anhydrous CH_3CN (8.8 mL/mmol amine), 2-iodoethanol (1.1 eq) and $NaHCO_3$ (1.1 eq) was heated to reflux overnight (24 h). After being cooled to room temperature, the reaction mixture was filtered with CH_3CN or CH_2Cl_2 and the volatiles were evaporated under reduced pressure. The resulting crude mixture was purified by column chromatography.

6.4 DESCRIPTION OF THE EXPERIMENTS, ANALYTICAL DATA

6.4.1 THE PROJECT ISOINDOLINES

(*E*)-3-(2-Bromo-phenyl)-acrylic acid ethyl ester [91]



According to the general procedure GP-3, LiCl (0.233 g, 5.50 mmol), triethyl phosphonoacetate (1.3 mL, 6.50 mmol), Et_3N (0.78 mL, 5.50 mmol) and 2-bromobenzaldehyde (0.58 mL, 5.00 mmol) were reacted overnight. After purification by column chromatography (*n*-pentane/Et_2O = 18/1 to 13/1) **91** was obtained as a pale yellow liquid.

Yield:	m = 1.206 g (4.73 mmol)	95%
GC:	R_t = 9.46 min	(Sil-8, 100-10-300)
TLC:	R_f = 0.54	(*n*-pentane/Et_2O = 12/1)
(*E*)/(*Z*) Ratio:	141/1	(^{1}H-NMR)

^{1}H-NMR (300 MHz, $CDCl_3$, major isomer):
δ = 1.34 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 4.27 (q, *J* = 7.2 Hz, 2H, C*H*$_2$), 6.37 (d, *J* = 16.0 Hz, 1H, C*H*CO), 7.19 (td, *J* = 1.7 Hz, *J* = 7.9 Hz, 1H, BrCCHC*H* or CCHC*H*) 7.29 (m, 1H, BrCCHC*H* or CCHC*H*), 7.55-7.60 (m, 2H, BrCC*H*, CC*H*), 8.03 (d, *J* = 16.0 Hz, 1H, C*H*=CHCO) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$, major isomer):
δ = 14.31 (C-1), 60.69 (C-2), 121.14 (C-4), 125.29 (C-11), 127.69, 127.76 (C-7/C-8/C-9), 131.14 (C-8/C-9), 133.42 (C-10), 134.55 (C-6), 142.90 (C-5), 166.38 (C-3) ppm.

MS (EI):

m/z (%) = 256 ($M^{\bullet+}$, 16), 254 ($M^{\bullet+}$, 16), 211 (18), 209 (18), 175 ($M^{\bullet+}$–Br, 37), 148 (10), 147 ($M^{\bullet+}$–C_2H_5Br, 100), 103 (14), 102 (32), 101 (12), 75 (10), 51 (11).

IR (capillary):

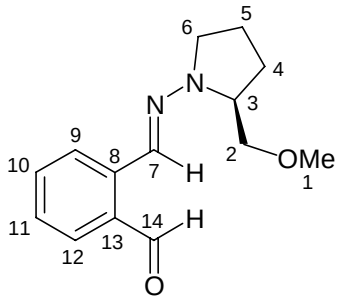
ν = 3413 (vs), 3064 (vs), 2981 (m), 2937 (w), 1714 (vs), 1637 (s), 1562 (w), 1467 (s), 1440 (m), 1367 (m), 1315 (vs), 1284 (s), 1268 (vs), 1245 (m), 1203 (vs), 1180 (vs), 1096 (w), 1028 (s), 977 (m), 872 (w), 760 (vs), 735 (w), 659 (w), 583 (w).

Elementary analysis:

Anal. Calcd. for $C_{11}H_{11}BrO_2$:	C = 51.79	H = 4.35
Found:	C = 51.87	H = 4.47

The NMR spectroscopic data are in agreement with those previously reported.[120]

2-{[(1'*E*)-(2'*S*)-2'-Methoxymethyl-pyrrolidin-1'-ylimino]-methyl}-benzaldehyde [(*S*)-95]



According to the general procedure GP-1, *o*-phthalic dicarboxaldehyde (1.000 g, 7.46 mmol) and SAMP (0.930 g, 6.21 mmol, 87% purity (GC)) were reacted overnight. The crude mixture was purified by column chromatography (*n*-pentane/Et_2O = 6/1 to 2/1 + 3% Et_3N) to yield (*S*)**-95** as a yellow syrup. Alternatively, it can be used directly for the next step without purification.

Yield:	m = 1.137 g (4.62 mmol)	74%
GC:	R_t = 14.02 min	(Sil-8, 100-10-300)
TLC:	R_f = 0.52	(*n*-pentane/Et_2O = 2/1 + 3% Et_3N)
Optical rotation:	$[\alpha]_D^{25}$ = –169.9	(c = 0.93, $CHCl_3$)

ee: 98.5% (Chiralpak AD2, *n*-heptane/*i*-PrOH = 98/2, R_t = 17.73 min, λ = 254 nm)

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 1.85-2.12 (m, 4H, $NCH_2CH_2CH_2$), 3.12-3.23 (m, 1H, NCH_2), 3.39 (s, 3H, OCH_3), 3.44-3.57 (m, 2H, NCH_2, OCH_2), 3.64 (dd, *J* = 3.6 Hz, *J* = 9.3 Hz, 1H, OCH_2), 3.71-3.75 (m, 1H, NC*H*), 7.25-7.32 (m, 1H, C*H*CHCCO), 7.44-7.50 (m, 1H, C*H*CHCCN), 7.72 (dd, *J* = 1.6 Hz, *J* = 7.6 Hz, 1H, C*H*CCO), 7.86 (d, *J* = 8.1 Hz, 1H, C*H*CCN), 7.93 (s, 1H, N=C*H*), 10.25 (s, 1H, O=C*H*) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = 22.65 (C-5), 27.28 (C-4), 49.01 (C-6), 59.60 (C-1), 63.29 (C-3), 74.55 (C-2), 126.29, 126.45 (C-9/C-11), 128.21 (C-7), 132.10 (C-13), 132.47 (C-12), 133.32 (C-10), 139.05 (C-8), 193.58 (C-14) ppm.

MS (EI):

m/z (%) = 246 ($M^{\bullet+}$, 11), 202 (13), 201 ($M^{\bullet+}$–CH_2OCH_3, 100), 132 (39), 70 (30).

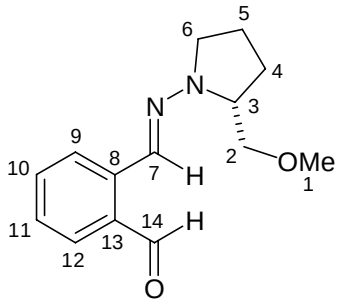
IR (capillary):

ν = 2974 (m), 2926 (m), 2877 (s), 2830 (m), 2734 (w), 1687 (vs), 1597 (m), 1568 (m), 1537 (vs), 1477 (m), 1449 (m), 1374 (s), 1342 (s), 1325 (m), 1308 (m), 1273 (m), 1252 (m), 1186 (s), 1155 (s), 1122 (s), 973 (w), 897 (w), 853 (w), 823 (w), 760 (s), 660 (w), 529 (w).

Elementary analysis:

Anal. Calcd. for $C_{14}H_{18}N_2O_2$:	C = 68.27	H = 7.37	N = 11.37
Found:	C = 68.16	H = 7.42	N = 11.70

2-{[(1'*E*)-(2'*R*)-2'-Methoxymethyl-pyrrolidin-1'-ylimino]-methyl}-benzaldehyde [(*R*)-95]

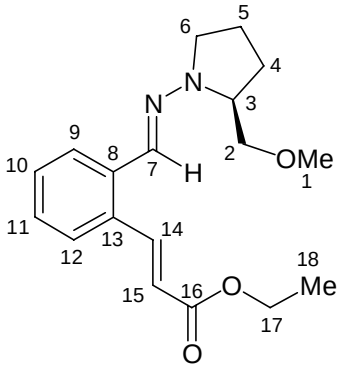


According to the general procedure GP-1, *o*-phthalic dicarboxaldehyde (2.000 g, 14.91 mmol) and RAMP (1.618 g, 10.77 mmol, 87% purity (GC)) were reacted overnight. The crude mixture can be purified by column chromatography (*n*-pentane/Et_2O = 6/1 to 1/1 + 3% Et_3N) to yield (*R*)-**95** as a yellow syrup. Alternatively, it can be used directly for the next step without purification.

Yield:	m = 2.385 g (9.68 mmol)	90%
Optical rotation:	$[\alpha]_D^{25}$ = +168.8	(c = 0.81, $CHCl_3$)
ee:	98.5%	(Chiralpak AD2, *n*-heptane/*i*-PrOH = 98/2, R_t = 19.47 min, λ = 254 nm)

All other analytical data correspond to those of the enantiomer (*S*)-**95**.

(2*E*)-3-(2-{[(1'*E*)-(2'*S*)-2'-Methoxymethyl-pyrrolidin-1'-ylimino]-methyl}-phenyl)-acrylic acid ethyl ester [(*S*)-83a]



According to the general procedure GP-2, *t*-BuOK (2.391 g, 21.3 mmol) was reacted with diethoxyphosphoryl-acetic acid ethyl ester (4.8 mL, 24.2 mmol) and SAMP-hydrazone (*S*)-**95**

(3.499 g, 14.2 mmol). After purification by column chromatography (*n*-pentane/Et_2O = 8/1 to 2/1 + 3% Et_3N) (*S*)-**83a** was obtained as a yellow oil.

Yield:	m = 4.490 g (14.2 mmol)	quant.
GC:	R_t = 17.71 min	(Sil-8, 100-10-300)
TLC:	R_f = 0.31	(*n*-pentane/Et_2O = 5/1 + 3% Et_3N)
Optical rotation:	$[\alpha]_D^{25.5}$ = –160.2	(c = 1.17, $CHCl_3$)
(*E*)/(*Z*) Ratio:	54/1	(^{1}H-NMR)

^{1}H-NMR (400 MHz, $CDCl_3$, major isomer):
δ = 1.34 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.86-2.11 (m, 4H, $NCH_2CH_2CH_2$), 3.10-3.17 (m, 1H, NCH_2), 3.40 (s, 3H, OCH_3), 3.46-3.59 (m, 2H, NCH_2, OCH_2), 3.68 (dd, *J* = 3.6 Hz, *J* = 9.3 Hz, 1H, OCH_2), 3.70-3.76 (m, 1H, NC*H*), 4.26 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 6.32 (d, *J* = 15.9 Hz, 1H, C*H*CO), 7.16 (m, 1H, C*H*CHCCN), 7.29-7.34 (m, 1H, C*H*CHCCHCHCO), 7.41 (s, 1H, N=C*H*), 7.47 (m, 1H, C*H*CCN), 7.72 (dd, *J* = 1.4 Hz, *J* = 8.0 Hz, 1H, C*H*CCHCHCO), 8.25 (d, *J* = 15.9 Hz, 1H, C*H*=CHCO) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, major isomer):
δ = 11.99 (C-18), 22.62 (C-5), 27.21 (C-4), 49.11 (C-6), 59.57 (C-1), 60.68 (C-17), 63.45 (C-3), 74.66 (C-2), 119.44 (C-15), 126.65 (C-12), 126.93 (C-10), 127.40 (C-9), 129.11 (C-7), 129.91 (C-11), 131.71 (C-13), 136.36 (C-8), 143.44 (C-14), 167.26 (C-16) ppm.

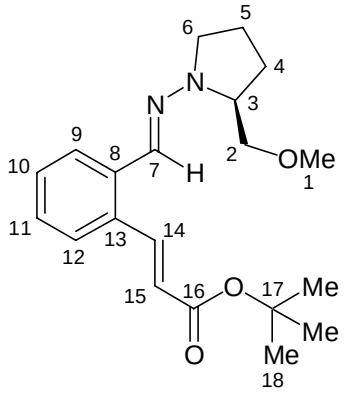
MS (EI):
m/z (%) = 316 ($M^{\bullet+}$, 10), 272 (18), 271 ($M^{\bullet+}$–C_2H_5O, 100), 243 (31), 156 (11), 130 (16), 70 (34).

IR (capillary):
ν = 3060 (w), 2977 (s), 2931 (s), 2878 (s), 2828 (s), 1711 (vs), 1629 (vs), 1573 (m), 1545 (s), 1477 (s), 1459 (s), 1386 (m), 1368 (m), 1342 (w), 1317 (s), 1264 (m), 1174 (vs), 1121 (m), 1039 (m), 976 (s), 883 (w), 858 (w), 763 (s), 543 (w), 476 (w).

Elementary analysis:

Anal. Calcd. for $C_{18}H_{24}N_2O_3$:	C = 68.33	H = 7.65	N = 8.85
Found:	C = 67.90	H = 7.92	N = 9.24

(2*E*)-3-(2-{[(1'*E*)-(2'*S*)-2'-Methoxymethyl-pyrrolidin-1'-ylimino]-methyl}-phenyl)-acrylic acid *tert*-butyl ester [(*S*)-83b]



According to the general procedure GP-1, *o*-phthalic dicarboxaldehyde (1.000 g, 7.46 mmol) and SAMP (0.809 g, 5.41 mmol, 87% purity (GC)) were reacted overnight. The crude mixture was used directly in the next step without further purification.

According to the general procedure GP-3 LiCl (0.395 g, 9.32 mmol), diethoxyphosphoryl-acetic acid *tert*-butyl ester (2.5 mL, 10.56 mmol), Et_3N (1.3 mL, 9.32 mmol) and crude SAMP-hydrazone (max. 5.41 mmol) were reacted overnight. After purification by column chromatography (*n*-pentane/Et_2O = 10/1 to 4/1 + 3% Et_3N) (*S*)**-83b** was obtained as a yellow syrup.

Yield:	m = 1.501 g (4.36 mmol)	81% (over 2 steps)
GC:	R_t = 14.07 min	(Sil-8, 140-10-300)
TLC:	R_f = 0.45	(*n*-pentane/Et_2O = 5/1 + 3% Et_3N)
Optical rotation:	$[\alpha]_D^{24} = -120.8$	(c = 0.71, $CHCl_3$)
(*E*)/(*Z*) Ratio:	182/1	(^{1}H-NMR)

^{1}H-NMR (400 MHz, $CDCl_3$, major isomer):

δ = 1.53 (s, 9H, C(CH_3)$_3$), 1.84-2.09 (m, 4H, NCH$_2$CH_2CH_2), 3.05-3.13 (m, 1H, NCH_2), 3.39 (s, 3H, OCH_3), 3.42-3.57 (m, 2H, NCH_2, OCH_2), 3.64-3.75 (m, 2H, OCH_2, NC*H*), 6.26 (d, *J* = 15.9 Hz, 1H, C*H*CO), 7.16 (t, *J* = 7.4 Hz, 1H, C*H*CHCCN), 7.26-7.31 (m, 1H, C*H*CHCCHCHCO), 7.41 (s, 1H, N=C*H*), 7.47 (d, *J* = 7.7 Hz, 1H, C*H*CCN), 7.77 (d, *J* = 8.0 Hz, 1H, C*H*CCHCHCO), 8.16 (d, *J* = 15.9 Hz, 1H, C*H*=CHCO) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, major isomer):

δ = 22.17 (C-5), 26.77 (C-4), 28.15 (C-18), 48.62 (C-6), 59.08 (C-1), 63.00 (C-3), 74.22 (C-2), 80.05 (C-17), 120.83 (C-15), 126.08 (C-12), 126.47 (C-10), 126.85 (C-9), 128.62 (C-7), 129.27 (C-11), 131.37 (C-13), 135.81 (C-8), 141.71 (C-14), 166.08 (C-16) ppm.

MS (EI):

m/z (%) = 344 ($M^{\bullet+}$, 10), 300 (10), 299 (54), 244 (16), 243 ($M^{\bullet+}$–$CO_2(CH_3)_3$, 100), 130 (13), 70 (26).

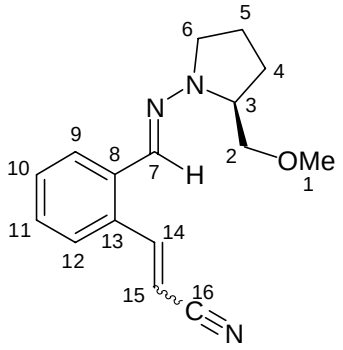
IR (in $CHCl_3$):

ν = 3060 (w), 2976 (s), 2929 (s), 2881 (s), 2829 (m), 1706 (vs), 1629 (s), 1573 (w), 1546 (m), 1477 (m), 1456 (m), 1389 (m), 1369 (w), 1323 (s), 1286 (w), 1252 (w), 1198 (s), 1152 (vs), 978 (m), 867 (w), 758 (vs).

Elementary analysis:

Anal. Calcd. for $C_{20}H_{28}N_2O_3$:	C = 69.74	H = 8.19	N = 8.13
Found:	C = 69.65	H = 7.82	N = 8.66

3-(2-{[(1'*E*)-(2'*S*)-2'-Methoxymethyl-pyrrolidin-1'-ylimino]-methyl}-phenyl)-acrylonitrile [(*S*)-83c]



According to the general procedure GP-2, *t*-BuOK (2.391 g, 21.3 mmol) was reacted with cyanomethyl-phosphonic acid ethyl ester (3.9 mL, 24.2 mmol) and SAMP-hydrazone (*S*)-**95** (3.499 g, 14.2 mmol). After purification by column chromatography (*n*-pentane/Et_2O = 5/1 to 1/3 + 3% Et_3N) and recrystallisation from petroleum ether (*S*)-**83c** was obtained as a yellow solid.

Yield:		m = 2.842 g (10.6 mmol)	74%
GC:	(*E*)	R_t = 10.44 min	(Sil-8, 160-10-300)
	(*Z*)	R_t = 10.25 min	(Sil-8, 160-10-300)
TLC:	(*E*)	R_f = 0.17	(*n*-pentane/Et_2O = 5/1 + 3% Et_3N)
	(*Z*)	R_f = 0.12	(*n*-pentane/Et_2O = 5/1 + 3% Et_3N)
mp:		54 °C	
Optical rotation:		$[\alpha]_D^{25.5}$ = –230.7	(c = 0.93, $CHCl_3$)
(*E*)/(*Z*) Ratio:		4.2/1	(^{1}H-NMR)

^{1}H-NMR (400 MHz, $CDCl_3$, (*E*)/(*Z*) mixture):
δ = 1.86-2.14 (m, 4H, $NCH_2CH_2CH_2$), 3.06-3.18 (m, 1H, NCH_2), 3.40 (s, 3H, OCH_3 (*Z*)), 3.43 (s, 3H, OCH_3 (*E*)), 3.44-3.69 (m, 3H, NCH_2, OCH_2), 3.69-3.77 (m, 1H, NC*H*), 5.46 (d, *J* = 11.8 Hz, 1H, C*H*CN (*Z*)), 5.73 (d, *J* = 16.5 Hz, 1H, C*H*CN (*E*)), 7.15-7.23 (m, 1H, CH_{arom}), 7.27 (s, 1H, N=C*H*), 7.33-7.41 (m, 2H, CH_{arom}), 7.55-7.62 (m, 1H, CH_{arom}), 7.73 (d, *J* = 11.8 Hz, 1H, C*H*=CHCN (*Z*)), 7.79 (d, *J* = 7.7 Hz, 1H, CH_{arom} (*Z*)), 8.10 (d, *J* = 16.5 Hz, 1H, C*H*=CHCN (*E*)) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, (*E*)/(*Z*) mixture):
δ = 22.20 (C-5), 26.78 (C-4), 48.47 (C-6), 59.28 (C-1), 63.00 (C-3), 74.06 (C-2 (*E*)), 74.21 (C-2 (*Z*)), 95.65 (C-15 (*Z*)), 96.14 (C-15 (*E*)), 118.55 (C-16), 126.46 (CH_{arom} (*E*)), 126.53 (CH_{arom} (*E*)), 126.88 ((CH_{arom} (*Z*)), 127.30 (CH_{arom} (*E*)), 128.43 (C-7 (*E*)), 129.01 (C-7 (*Z*)), 129.96 (CH_{arom} (*Z*)), 130.29 (CH_{arom} (*E*)), 135.68 (C-8), 149.58 (C-15 (*Z*)), 150.31 (C-15 (*E*)) ppm. (The missing peaks are covered by other peaks).

MS (EI):
m/z (%) = 270 ($M^{\bullet+}$+1, 18), 225 (16), 224 ($M^{\bullet+}$–CH_2OCH_3, 100), 155 (17), 154 (10), 70 (29).

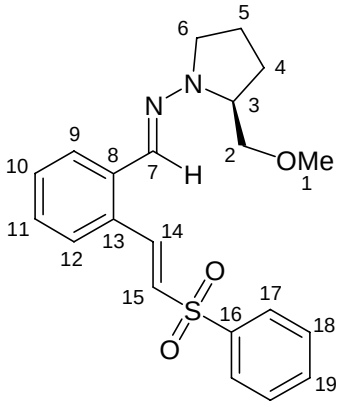
IR (KBr):
ν = 3058 (m), 3026 (w), 2974 (vs), 2927 (vs), 2894 (vs), 2816 (vs), 2620 (vs), 2209 (vs), 1963 (w), 1605 (vs), 1572 (vs), 1544 (vs), 1458 (vs), 1379 (vs), 1341 (vs), 1306 (vs), 1251 (vs), 1195 (vs), 1108 (vs), 1044 (m), 956 (vs), 902 (s), 881 (vs), 816 (s), 756 (vs), 703 (m), 619 (w), 551 (s), 516 (s), 500 (m).

HRMS:

m/z Calcd. for $C_{16}H_{19}N_3O$ ($M^{\bullet+}$): 269.1528

Found: 269.1528

[1-[2'-((1''*E*)-2''-phenylsulfonyl-vinyl)-phenyl]-meth-(1*E*)-ylidene]-((2'''*S*)-2'''-methoxymethyl-pyrrolidin-1'''-yl)-amine [(*S*)-83d]



According to the general procedure GP-3 LiCl (0.361 g, 8.51 mmol), phenylsulfonylmethyl-phosphonic acid diethyl ester (**97**) (2.820 g, 9.65 mmol), Et_3N (1.2 mL, 8.51 mmol) and SAMP-hydrazone (*S*)-**95** (1.000 g, 5.68 mmol) were reacted overnight. After column chromatography (*n*-pentane/Et_2O = 1/1 to 1/3 + 3% Et_3N then Et_2O/MeOH = 80/1 to 60/1 + 3% Et_3N) (*S*)-**83d** was obtained as a yellow foam.

Yield:	m = 1.456 g (3.79 mmol)	67%
GC:	decomposition	
HPLC:	R_t = 12.61 min	(Sil-5, *n*-heptane/ *i*-PrOH = 99/1, λ = 254 nm)
TLC:	R_f = 0.66	(*n*-pentane/Et_2O = 1/2 + 3% Et_3N)
Optical rotation:	$[\alpha]_D^{25}$ = –119.7	(c = 0.76, $CHCl_3$)
(E)/(Z) Ratio:	56/1	(^{1}H-NMR)

^{1}H-NMR (400 MHz, $CDCl_3$, major isomer):

δ = 1.90-2.14 (m, 4H, $NCH_2CH_2CH_2$), 3.08-3.17 (m, 1H, NCH_2), 3.41 (s, 3H, OCH_3), 3.46-3.53 (m, 1H, NCH_2), 3.59 (dd, *J* = 6.6 Hz, *J* = 9.3 Hz, 1H, OCH_2), 3.75 (dd, *J* = 3.6 Hz, *J* = 9.3 Hz, 1H, OCH_2), 3.76-3.83 (m, 1H, NC*H*), 6.73 (d, *J* = 15.4 Hz, 1H, C*H*SO_2), 7.12-7.18 (m, 1H, C*H*CHCCN), 7.33 (s, 1H, N=C*H*), 7.31-7.36 (m, 1H, C*H*CHCCH=CHSO_2), 7.38 (d,

J = 8.0 Hz, 1H, C*H*CCN), 7.51-7.63 (m, 4H, C*H*CCH=CHSO$_2$, SO$_2$CCHC*H*, SO$_2$CCHCHC*H*), 7.96 (m, 2H, SO$_2$CC*H*), 8.42 (d, *J* = 15.4 Hz, 1H, C*H*=CHSO$_2$) ppm.

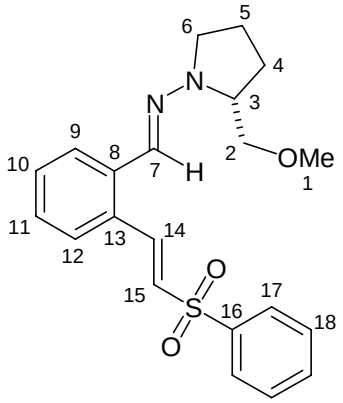
^{13}C-NMR (100 MHz, $CDCl_3$, major isomer):
δ = 22.66 (C-5), 27.18 (C-4), 49.00 (C-6), 59.58 (C-1), 63.52 (C-3), 74.53 (C-2), 126.74 (C-10), 127.50 (C-15), 127.77, 127.82, 127.092 (C-18/C-17/C-9), 129.04 (C-7), 129.315 (C-13), 129.46 (C-19), 130.69 (C-11), 133.36 (C-12), 136.86 (C-8), 141.29 (C-16), 142.36 (C-14) ppm.

MS (EI):
m/z (%) = 384 ($M^{\bullet+}$, 9), 340 (21), 339 ($M^{\bullet+}$–C_2H_5O, 100), 243 (15), 197 (16), 70 (11).

IR (in $CHCl_3$):
ν = 3060 (m), 2974 (s), 2927 (s), 2878 (s), 2829 (m), 1609 (s), 1595 (s), 1572 (s), 1545 (s), 1479 (s), 1447 (s), 1384 (m), 1341 (s), 1307 (vs), 1252 (m), 1224 (m), 1197 (s), 1146 (vs), 1122 (s), 1086 (vs), 970 (m), 885 (w), 854 (m), 799 (m), 755 (vs), 735 (s), 717 (m), 689 (s), 620 (s), 585 (s), 565 (s), 540 (s), 482 (w).

HRMS:
m/z Calcd. for $C_{19}H_{19}N_2O_2S$ ($M^{\bullet+}$–C_2H_5O): 339.1167
Found: 339.1168

[1-[2'-((1''*E*)-2''-Phenylsulfonyl-vinyl)-phenyl]-meth-(*E*)-ylidene]-((2'''*R*)-2'''-methoxymethyl-pyrrolidin-1'''-yl)-amine [(*R*)-83d]

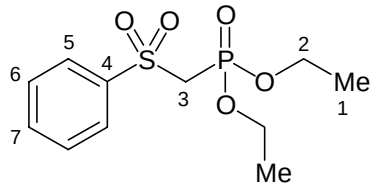


According to the general procedure GP-3, LiCl (0.361 g, 8.51 mmol), phenylsulfonylmethyl-phosphonic acid diethyl ester (**97**) (2.820 g, 9.65 mmol), Et_3N (1.2 mL, 8.51 mmol) and RAMP-hydrazone (*R*)-**95** (1.000 g, 5.68 mmol) were reacted overnight. After column chromatography (*n*-pentane/Et_2O = 1/1 to 1/3 + 3% Et_3N then Et_2O/MeOH = 80/1 to 60/1 + 3% Et_3N) (*R*)-**83d** was obtained as a yellow foam.

Yield:	m = 1.570 g (4.08 mmol)	72%
Optical rotation:	$[\alpha]_D^{25}$ = +132.1	(c = 1.57, $CHCl_3$)

All other analytical data correspond to those of the enantiomer (*S*)-**83d**.

Phenylsulfonylmethyl-phosphonic acid diethyl ester [97]



In a 100 mL 3-necked flask fitted with a reflux condenser, an inner thermometer and an addition funnel, phenylsulfanylmethyl-phosphonic acid diethyl ester (10.00 g, 38.4 mmol) and acetic acid (40 mL) were mixed together. Hydrogen peroxide (12 mL, 30% in H_2O) was added slowly in order to maintain the inner temperature below 75 °C. The reaction mixture was then heated to reflux for 3 h, cooled to room temperature, poured into a large beaker and diluted with 200 mL H_2O. A conc. aqueous solution of NaOH was slowly added until the pH reached 8-9. The reaction mixture was then extracted 5 times with CH_2Cl_2. The combined organic phases were washed with 10% aqueous $NaHSO_3$ (the absence of peroxide was tested using KI paper), dried over $MgSO_4$, filtered and concentrated under reduced pressure. After purification by column chromatography (Et_2O/MeOH = 60/1 to 5/1) **97** was obtained as a colorless solid.

Yield:	m = 9.69 g (33.2 mmol)	86%
GC:	R_t = 13.37 min	(Sil-8, 10 0-10-300)
TLC:	R_f = 0.34	(Et_2O/MeOH = 60/1)
mp:	47 °C	(Lit.[121] 59 °C (benzene/*n*-heptane))

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 1.30 (td, J = 0.5 Hz, $J_{H\text{-}P}$ = 7.0 Hz, 6H, CH_2CH_3), 3.77 (d, $J_{H\text{-}P}$ = 17 Hz, 2H, CH_2S), 4.16 (m, 4H, CH_2CH_3), 7.55-7.62 (m, 2H, *m*-CH_{arom}), 7,65-7,72 (m, 1H, *p*-CH_{arom}), 7,98-8.03 (m, 2H, *o*-CH_{arom}) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):

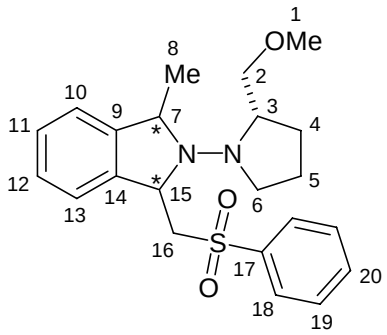
δ = 16.23 (d, $J_{C\text{-}P}$ = 6.0 Hz, C-1), 53.81 (d, $J_{C\text{-}P}$ = 137.7 Hz, C-3), 63.41 (d, $J_{C\text{-}P}$ = 6.6 Hz, C-2), 128.34 (C-5), 129.15, 134.12 (C-6/C-7), 140.02 (C-4) ppm.

^{31}P-NMR (121.5 Hz, $CDCl_3$):

δ = 11.22 ppm.

All other analytical data correspond to those of the literature.[122]

1-Phenylsulfonylmethyl-2-((2'*S*)-2'-methoxymethyl-pyrrolidin-1'-yl)-3-methyl-2,3-dihydro-1*H*-isoindole [(*S*)-101a]



A 250 mL Schlenk flask containing $CeCl_3 \cdot H_2O$ (1.863 g, 5.00 mmol) was heated under high vacuum at 140 °C for 2 h. The temperature was then decreased to room temperature and abs. THF (50 mL) was added under argon. The suspension was sonicated for 15 h and then cooled to −78 °C. MeLi (3.1 mL, 5.00 mmol, 1.59 M in Et_2O) was added dropwise and the reaction mixture was stirred for 2 h 30. At the end of the addition, the temperature was decreased to −100 °C and a solution of SAMP-hydrazone (*S*)-**83d** (0.384 g, 1.00 mmol) in abs. THF (20 mL) was added dropwise. The reaction was stirred for 4 h before increasing the temperature to −78 °C. After 14 h the temperature was allowed to reach room temperature slowly for further 22 h. The reaction was hydrolysed with 0.1 mL H_2O, diluted with 70 mL H_2O and extracted 3 times with Et_2O. The combined organic phases were washed with brine,

dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography (*n*-pentane/Et_2O = 5/1 to 1/2 + 3% Et_3N) to give (*S*)-**101a** as a pale pink oil.

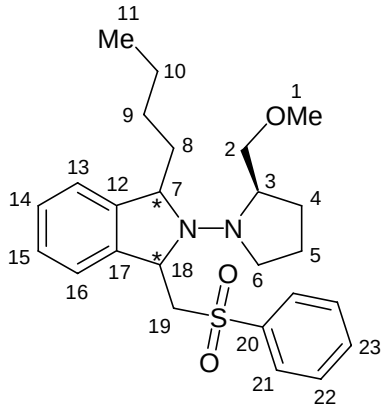
Yield:	m = 0.135 g (0.32 mmol)	32%
GC:	decomposition	
HPLC:	R_t = 5.14 min	(Spherical silica, *n*-heptane/*i*-PrOH = 95/5, λ = 230 nm)
TLC:	R_f = 0.35	(*n*-pentane/Et_2O = 2/1)
de:	≥ 96%	(^{1}H-NMR)

^{1}H-NMR (400 MHz, $CDCl_3$):
δ = 1.36 (d, *J* = 6.3 Hz, 3H, CHC*H*$_3$), 1.43-1.69 (m, 3H, NCH$_2$C*H*$_2$C*H*$_2$), 1.75-1.87 (m, 1H, NCH$_2$CH$_2$C*H*$_2$), 2.72-2.80 (m, 1H, NC*H*$_2$), 2.87-2.93 (m, 1H, NC*H*$_2$), 2.97-3.03 (m, 1H, OC*H*$_2$), 3.13-3.22 (m, 1H, NC*H*), 3.24 (s, 3H, OC*H*$_3$), 3.27-3.33 (m, 1H, OC*H*$_2$), 3.51 (dd, *J* = 8.0 Hz, *J* = 14.8 Hz, 1H, C*H*$_2$SO$_2$), 3.89 (dd, *J* = 1.4 Hz, *J* = 14.8 Hz, 1H, C*H*$_2$SO$_2$), 4.29 (q, *J* = 6.3 Hz, 1H, C*H*CH$_3$), 4.78 (d, *J* = 8.0 Hz, 1H, C*H*CH$_2$SO$_2$), 7.05-7.09 (m, 1H, C*H*$_{arom}$), 7.23-7.28 (m, 2H, C*H*$_{arom}$), 7.58-7.63 (m, 3H, C*H*$_{arom}$), 7.66-7.71 (m, 1H, C*H*$_{arom}$), 7.99-8.03 (m, 2H, SO$_2$CC*H*) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):
δ = 21.07 (C-8), 21.11 (C-5), 27.84 (C-4), 48.39 (C-6), 58.29 (C-3), 58.58 (C-15), 59.28 (C-1), 60.09 (C-7), 63.22 (C-16), 75.95 (C-2), 121.66, 123.39, 127.69, 127.82 (C_{arom}), 128.53 (C-18), 129.57 (C-19), 133.91 (C_{arom}), 139.91, 140.12 (C-14/C-17), 142.82 (C-9) ppm.

MS (CI):
m/z (%) = 402 (26), 401 ($M^{\bullet+}$+1, 100), 400 ($M^{\bullet+}$, 11).

1-Phenylsulfonyl-3-butyl-2-((2'*R*)-2'-methoxymethyl-pyrrolidin-1'-yl)-2,3-dihydro-1*H*-isoindole [(*R*)-101b]



A Schlenk flask containing $CeCl_3 \cdot H_2O$ (1.863 g, 5.00 mmol) was heated under high vacuum at 140 °C for 2 h. The temperature was then decreased to room temperature and abs. THF (50 mL) was added under argon. The suspension was sonicated for 16 h and cooled to −78 °C. *n*-BuLi (3.1 mL, 5.00 mmol, 1.59 M in hexanes) was then added dropwise. At the end of the addition the reaction was stirred for 3 h before increasing the temperature to −50 °C. A solution of RAMP-hydrazone (*R*)-**83d** (0.344 g, 0.89 mmol) in abs. THF (20 mL) was added dropwise. The reaction was stirred for 16 h while warming up slowly to room temperature. The reaction was hydrolysed with 0.1 mL H_2O, diluted with 50 mL H_2O and extracted 3 times with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography (*n*-pentane/Et_2O = 8/1 to 2/1 + 3% Et_3N) to yield impure (*R*)-**101b** (77% purity min. after GC-analysis).

Yield:	m = 0.184 g (0.42 mmol)	47% (min. after GC-analysis)
GC:	R_t = 17.11 min (decomposition)	(Sil-8, 160-10-300)
TLC:	R_f = 0.42	(*n*-pentane/Et_2O = 2/1 + 3% Et_3N)
de:	≥ 96%	(^{1}H-NMR)

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 0.82-0.90 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.00-1.80 (m, 10H, $NCH_2CH_2CH_2$, $CH_2CH_2CH_2CH_3$), 2.52-2.64 (m, 1H, NCH_2), 2.72-2.80 (m, 1H, NCH_2), 2.98-3.08 (m, 1H, NCH), 3.12-3.21 (m, 1H, OCH_2), 3.26 (s, 3H, OCH_3), 3.32-3.41 (m, 1H, OCH_2), 3.43 (dd, *J* =

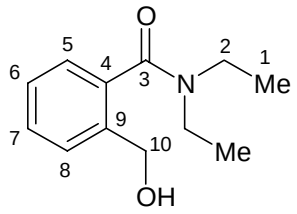
7.7 Hz, *J* = 14.6 Hz, 1H, C*H*$_2$SO$_2$), 3.84 (dd, *J* = 1.7 Hz, *J* = 14.6 Hz, 1H, C*H*$_2$SO$_2$), 4.31 (t, *J* = 4.5 Hz, 1H, C*H*CH$_2$CH$_2$), 4.91 (d, *J* = 7.7 Hz, 1H, C*H*CH$_2$SO$_2$), 7.04-7.11 (m, 1H, C*H*$_{arom}$), 7.19-7.27 (m, 2H, C*H*$_{arom}$), 7.55-7.70 (m, 4H, C*H*$_{arom}$), 7.98-8.30 (m, 2H, SO$_2$CC*H*) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 14.09 (C-11), 20.54 (C-5), 22.92 (C-10), 26.33, 26.85 (C-4/C-9), 34.19 (C-8), 46.01 (C-6), 56.99 (C-18), 58.46 (C-3), 58.82 (C-1), 64.31 (C-19), 66.32 (C-7), 75.04 (C-2), 121.69, 123.02 (C-14/C-15), 127.15, 127.35 (C-13/C-16), 127.99 (C-21), 129.12 (C-22), 133.45 (C-23), 139.74, 140.24, 141.63 (C-12/C-17/C-20) ppm.

6.4.2 THE PROJECT TETRAHYDRO-2-BENZAZEPINES

_N_,_N_-Diethyl-2-hydroxymethyl-benzamide [109]



In a 50 mL Schlenk flask under argon, a suspension of $AlCl_3$ (4.330 g, 32.5 mmol) in 1,2-dichloroethane (22.5 mL) was cooled to 0 °C. A solution of Et_2NH (6.5 mL, 62.5 mmol) in 1,2-dichloroethane (7.5 mL) was added over 20 min (the evolving HCl gas was removed by means of a needle through the septum). At the end of the addition the temperature was increased directly to room temperature and the reaction mixture was stirred for 15 min. Phthalide (3.353 g, 25.0 mmol) was then added in one portion and the reaction was stirred overnight (16 h). The flask was cooled to 0 °C and 10 mL of H_2O were slowly added. After warming up to room temperature the reaction mixture was filtered over a pad of celite. The filter cake was washed successively with H_2O (20 mL) and 1,2-dichloroethane (50 mL) and discarded. The organic phase was washed with H_2O (100 mL) and brine (100 mL). After drying over $MgSO_4$, filtration and concentration under reduced pressure, the resulting red-brown oil was purified by column chromatography (*n*-pentane/Et_2O = 1/5 then pure Et_2O then Et_2O/MeOH = 60/1) to yield **109** as a colourless oil.

Yield:	m = 4.949 g (23.9 mmol)	96%
GC:	R_t = 13.55 min	(Sil-8, 60-10-300)
TLC:	R_f = 0.09	(*n*-pentane/Et_2O = 1/4)

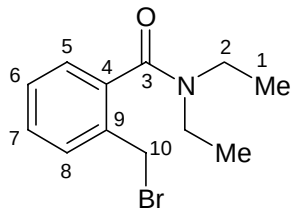
^{1}H-NMR (400 MHz, $CDCl_3$, mixture of rotamers):
δ = 1.05 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.25 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 3.18 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 3.55 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 4.16 (br s, 1H, O*H*), 4.49 (s, 2H, CH_2OH), 7.19 (dd, *J* = 1.1 Hz, *J* = 7.4 Hz, 1H, C*H*CCO), 7.28 (dt, *J* = 1.4 Hz, *J* = 7.4 Hz, 1H, C*H*CHCCO), 7.35 (dt, *J* = 1.4 Hz, *J* = 7.7 Hz, 1H, C*H*CHCCH$_2$), 7.43 (d, *J* = 7.7 Hz, 1H, C*H*CCH$_2$) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, mixture of rotamers):
δ = 12.86 (C-1), 14.10 (C-1'), 39.32 (C-2), 43.41 (C-2'), 63.12 (C-10), 125.55 (C-5), 127.25 (C-6), 129.18, 129.30 (C-7/C-8), 135.71 (C-9), 138.36 (C-4), 171.10 (C-3) ppm.

MS (EI):
m/z (%) = 207 ($M^{\bullet+}$, 48), 206 (15), 178 (10), 135 ($M^{\bullet+}$–NEt_2, 92), 134 (83), 133 (37), 118 (19), 106 (13), 105 (50), 90 (14), 79 (24), 77 (57), 74 (100), 58 (95), 51 (16).

The other analytical data are in agreement with those previously reported.[123]

2-Bromomethyl-*N*,*N*-diethyl-benzamide [107a]



In a 250 mL Schlenk flask under argon, a solution of alcohol **109** (2.073 g, 10.00 mmol) in anhydrous CH_3CN (80 mL) was cooled to 0 °C. PPh_3 (6.033 g, 23.00 mmol) was added in one portion and the mixture was stirred for 15 min. CBr_4 (7.628 g, 23.00 mmol) was added in one portion and the mixture was stirred for 45 min before sat. aqueous $CuSO_4$ was added (50 mL). The reaction was then diluted successively with Et_2O (60 mL) and H_2O (60 mL) and the organic phase was kept. The aqueous phase was extracted 2 times with Et_2O (60 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude red oil was purified by column chromatography (*n*-pentane/Et_2O = 2/1 to 1/4) to yield **107a** as a yellow liquid.

Remark: upon standing, even at –25°C, **107a** slowly transforms into the corresponding imidate salt. However, in THF, **107a** is soluble whereas the salt remains insoluble, a separation is then possible.

Yield:	m = 1.786 g (6.61 mmol)	66%
GC:	R_t = 12.45 min	(Sil-8, 80-10-300)
TLC:	R_f = 0.25	(*n*-pentane/Et_2O = 2/1)

^{1}H-NMR (400 MHz, $CDCl_3$, mixture of rotamers):

δ = 1.44 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.56 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 3.16 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 3.20-4.00 (br, 2H, CH_2CH_3), 4.20-4.90 (br, 2H, CH_2Br), 7.21 (m, 1H, C*H*=CCO), 7.27-7.35 (m, 2H, C*H*CH=CCO, C*H*CH=CCH_2), 7.42 (d, *J* = 7.1 Hz, 1H, C*H*=CCH_2) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, mixture of rotamers):

δ = 12.58 (C-1), 13.97 (C-1'), 30.52 (C-10), 38.82 (C-2), 43.38 (C-2'), 125.74 (C-5), 128.31, 129.17 (C-6/C-7), 130.79 (C-8), 134.41 (C-4), 137.38 (C-9), 169.36 (C-3) ppm.

MS (EI):

m/z (%) = 271 ($M^{\bullet+}$, 37), 270 (76), 269 ($M^{\bullet+}$, 17), 268 (48), 199 ($M^{\bullet+}$–NEt_2, 73), 198 (46), 197 ($M^{\bullet+}$–NEt_2, 86), 196 (47), 190 (50), 188 (18), 176 (46), 174 (30), 162 (17), 160 (16), 146 (16), 134 (12), 125 (12), 119 (49), 118 ($M^{\bullet+}$–$BrNEt_2$, 100), 116 (11), 91 (25), 90 (74), 89 (54), 63 (18), 51 (10).

IR (in $CHCl_3$):

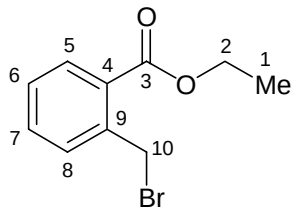
ν = 3456 (m), 3409 (m), 3060 (w), 2973 (m), 2935 (m), 1766 (w), 1671 (s), 1628 (vs), 1494 (w), 1436 (vs), 1382 (m), 1362 (w), 1287 (s), 1223 (m), 1185 (w), 1101 (m), 1076 (m), 980 (w), 948 (w), 866 (w), 818 (w), 785 (m), 762 (m), 741 (s), 631 (w), 609 (m).

Elementary analysis:

Anal. Calcd. for $C_{12}H_{16}BrNO$:	C = 53.35	H = 5.97	N = 5.18
Found:	C = 53.02	H = 5.69	N = 5.41

The ^{1}H-NMR spectrum is in agreement with the one previously reported.[124]

2-Bromomethyl-benzoic acid ethyl ester [107b]



In a 100 mL flask phthalide (5.365 g, 40.0 mmol) was suspended in 1 N aqueous NaOH (40 mL) and heated to reflux for 2 h. After cooling, most of the water was evaporated under reduced pressure and the remaining syrup was coevaporated 2 times with toluene. The white crystalline powder was dried in a lyophilisator overnight. The sodium salt was dissolved in abs. DMF (50 mL) under argon and cooled to 0 °C. Ethyl iodide (4.8 mL, 60.0 mmol) was added dropwise and the temperature was slowly increased to room temperature. The reaction mixture was stirred for 24 h and then hydrolysed with pH 7 phosphate buffer (50 mL). The aqueous phase was extracted 2 times with Et_2O (100 mL) and the combined organic phases were washed with a sat aqueous solution of NaCl (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting 2-hydroxymethyl-benzoic acid ester, obtained as a colourless liquid, was used directly in the next step without further purification.

TLC: R_f = 0.20 (*n*-pentane/Et_2O = 2/1)

^{1}H-NMR (400 MHz, $CDCl_3$):
δ = 1.40 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 4.11 (br s, 1H, O*H*), 4.38 (q, *J* = 7.2 Hz, 2H, CH_2CH_3), 4.80 (s, 2H, CH_2OH), 7.32-7.37 (m, 1H, CH_{arom}), 7.46-7.55 (m, 2H, CH_{arom}), 7.96-8.02 (m, 1H, CH_{arom}) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):
δ = 14.23, 61.39, 64.43, 127.60, 128.99, 129.81, 130.98, 132.84, 143. 16, 167.95 ppm.

In a 500 mL Schlenk flask a solution of crude alcohol (max. 40.0 mmol) in anhydrous CH_3CN (200 mL) was cooled to 0 °C. PPh_3 (24.131 g, 92.0 mmol) was added in one portion and the reaction mixture was stirred for 15 min. CBr_4 was added in one portion (30.512 g, 92.0 mmol), and after 1 h, sat. aqueous $CuSO_4$ (200 mL) was added. Upon dilution with Et_2O (280 mL) and H_2O (280 mL), the organic phase was kept. The aqueous phase was extracted 2 times with Et_2O (200 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was absorbed in silica and purified by column chromatography (pure *n*-pentane then *n*-pentane/Et_2O = 9/1 to 6/1) providing **107b** as a pale yellow oil.

Yield: m = 5.145 g (21.2 mmol) 53% (over 3 steps)
GC: R_t = 9.66 min (Sil-8, 80-10-300)

TLC: R_f = 0.53 (*n*-pentane/Et_2O = 9/1)

^{1}H-NMR (300 MHz, $CDCl_3$):
δ = 1.42 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 4.41 (q, *J* = 1.2 Hz, 2H, CH_2CH_3), 4.95 (s, 2H, CH_2Br), 7.31-4.39 (m, 1H, CH_{arom}), 7.41-7.51 (m, 2H, CH_{arom}), 7.94-7.98 (m, 1H, CHCCO) ppm.

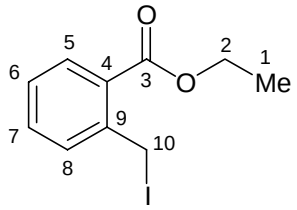
^{13}C-NMR (75 MHz, $CDCl_3$):
δ = 14.23 (C-1), 31.57 (C-10), 61.30 (C-2), 128.49 (C_{arom}), 129.52 (C-4), 131.22, 131.61 (C-5/C_{arom}), 132.36 (C_{arom}), 139.05 (C-9), 166.61 (C-3) ppm.

Elementary analysis:

Anal. Calcd. for $C_{10}H_{11}BrO_2$:	C = 49.41	H = 4.56
Found:	C = 49.42	H = 4.61

All other analytical data correspond to those described in the literature.[125]

2-Iodomethyl-benzoic acid ethyl ester [107c]



In a 250 mL Schlenk flask under argon, a solution of NaI (2.698 g, 18.00 mmol) in dry acetone (70 mL) was cooled to 0 °C. A solution of bromide **107b** (1.459 g, 6.00 mmol) in dry acetone (14 mL) was added dropwise over 1 h. At the end of the addition the temperature was increased to room temperature and the reaction was stirred for 26 h. The reaction mixture was then diluted with H_2O (140 mL) and extracted 4 times with Et_2O (40 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product **107c** obtained as a brownish liquid was used without further purification (97% purity by GC).

Yield:	m = 1.691 g (5.83 mmol)	97%
GC:	R_t = 10.75 min	(Sil-8, 80-10-300)
TLC:	R_f = 0.32	(*n*-pentane/Et_2O = 30/1)

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 1.43 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 4.42 (q, J = 7.1 Hz, 2H, CH_2CH_3), 4.93 (s, 2H, CH_2I), 7.29-7.34 (m, 1H, CH_{arom}), 7.39-7.46 (m, 2H, CH_{arom}), 7.92-7.96 (m, 1H, CHCCO) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 4.02 (C-10), 14.30 (C-1), 61.18 (C-2), 127.76 (C_{arom}), 128.55 (C-4), 131.04, 131.25 (C-5/C_{arom}), 132.25 (C_{arom}), 140.83 (C-9), 166.42 (C-3) ppm.

MS (EI):

m/z (%) = 290 ($M^{\bullet+}$, 3), 245 (10), 163 (78), 135 ($M^{\bullet+}$–C_2H_5I, 100), 118 (18), 90 (14), 89 (12).

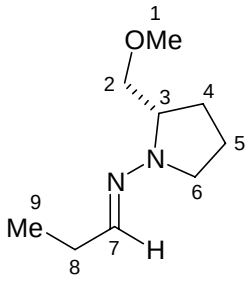
IR (in $CHCl_3$):

ν = 3064 (w), 2980 (m), 2935 (w), 2903 (w), 1765 (w), 1715 (vs), 1598 (w), 1575 (w), 1487 (w), 1447 (m), 1366 (m), 1296 (s), 1264 (vs), 1166 (s), 1103 (vs), 1070 (m), 1016 (w), 758 (s), 707 (m), 572 (m).

Elementary analysis:

Anal. Calcd. for $C_{10}H_{11}IO_2$:	C = 41.40	H = 3.82
Found:	C = 41.43	H = 3.91

((2'*S*)-2'-Methoxymethyl-pyrrolidin-1'-yl)-prop-(1*E*)-ylidene-amine [(*S*)-106a]



According to the general procedure GP-1, propanal (2.788 g, 48.0 mmol) and SAMP (5.528 g, 40.0 mmol, 94% purity (GC)) were reacted overnight. After distillation under reduced pressure (*S*)-**106a** was obtained as a colourless oil.

Yield:	m = 6.241 g (36.7 mmol)	92%
GC:	R_t = 7.38 min	(Sil-8, 60-10-300)

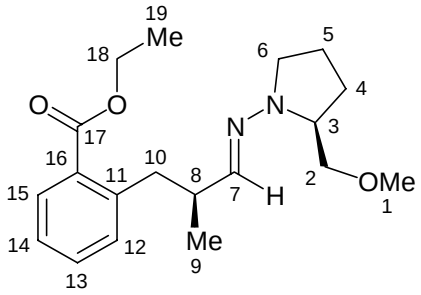
bp:	68-72 °C/3 mbar	(Lit.[126] 73-74 °C/1 Torr)
Optical rotation:	$[\alpha]_D^{24} = -126.9$	(c = 1.42, $CHCl_3$) (Lit.[119] $[\alpha]_D^{22}$ = −150.2 (neat))

^{1}H-NMR (400 MHz, $CDCl_3$):
δ = 1.06 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.74-1.99 (m, 4H, $NCH_2CH_2CH_2$), 2.23 (dq, *J* = 5.5 Hz, *J* = 7.4 Hz, 2H, CH_2CH_3), 2.67-2.75 (m, 1H, NCH_2), 3.38 (s, 3H, OCH_3), 3.33-3.45 (m, 3H, NCH_2, NCH, OCH_2), 3.57 (dd, *J* = 3.6 Hz, *J* = 8.8 Hz, 1H, OCH_2), 6.66 (t, *J* = 5.5 Hz, 1H, N=CH) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):
δ = 12.12 (C-9), 22.14 (C-5), 26.38 (C-8), 26.58 (C-4), 50.41 (C-6), 59.11 (C-1), 63.42 (C-3), 74.79 (C-2), 140.34 (C-7) ppm.

All other analytical data correspond to those reported in the literature.[119]

2-{(2'*S*)-3'-[(1''*E*)-(2''*S*)-2''-Methoxymethyl-pyrrolidin-1''-ylimino]-2'-methyl-propyl}-benzoic acid ethyl ester [(2'*S*,2''*S*)-105b]



In a 25 mL Schlenk flask under argon, a solution of $(i\text{-Pr})_2NH$ (0.23 mL, 1.65 mmol) in abs. THF (8 mL) was cooled to 0 °C. *n*-BuLi (1.2 mL, 1.65 mmol, 1.39 M in hexanes) was added dropwise and the reaction mixture was stirred for 15 min. Propanal SAMP-hydrazone (*S*)-**106a** (0.255 g, 1.50 mmol) was added dropwise and the reaction was stirred for 21 h at 0 °C. The temperature was decreased to −100 °C and 2-iodomethyl-benzoic acid ethyl ester (**107c**) (0.457 g, 1.58 mmol) was added dropwise over 15 min. The solution was stirred for 4 h and the temperature was slowly increased to room temperature overnight (18 h). The reaction was quenched with 10 mL of H_2O and extracted 4 times with Et_2O (20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced

pressure. The resulting crude yellow-brown oil was purified by column chromatography (*n*-pentane/Et_2O = 4/1 to 3/1) to give (2'*S*,2''*S*)-**105b** as a yellow liquid.

Yield:	m = 0.292 g (0.88 mmol)	59%
GC:	R_t = 19.85 min	(Sil-8, 60-10-300)
TLC:	R_f = 0.19	(*n*-pentane/Et_2O = 4/1)
Optical rotation:	$[\alpha]_D^{24} = -15.3$	(c = 2.47, $CHCl_3$)
de:	≥ 96%	(^{1}H-NMR)

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 1.05 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 1.39 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.69-1.96 (m, 4H, $NCH_2CH_2CH_2$), 2.56-2.73 (m, 2H, C*H*CH_3, NC*H*$_2$), 3.02 (dd, *J* = 7.4 Hz, *J* = 13.2 Hz, 1H, CH_2CHCH_3), 3.17 (dd, *J* = 7.4 Hz, *J* = 13.2 Hz, 1H, CH_2CHCH_3), 3.21-3.34 (m, 2H, NC*H*, NC*H*$_2$), 3.36 (s, 3H, OC*H*$_3$), 3.37-3.41 (m, 1H, OC*H*$_2$), 3.53 (dd, *J* = 3.9 Hz, *J* = 9.1 Hz, 1H, OC*H*$_2$), 4.35 (qd, *J* = 0.5 Hz, *J* = 7.1 Hz, 2H, CH_2CH_3), 6.58 (d, *J* = 6.1 Hz, 1H, N=C*H*), 7.21-7.26 (m, 2H, C*H*$_{arom}$), 7.36-7.41 (m, 1H, C*H*$_{arom}$), 7.85-7.89 (m, 1H, C*H*CO) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 14.30 (C-19), 18.58 (C-9), 22.05 (C-5), 26.48 (C-4), 38.77 (C-8), 39.50 (C-10), 50.14 (C-6), 59.08 (C-1), 60.74 (C-18), 63.38 (C-3), 74.64 (C-2), 125.71 (C-14), 130.17 (C-16), 130.41, 131.15, 131.78 (C-12/C-13/C-15), 141.89 (C-11), 142.61 (C-7), 167.67 (C-17) ppm.

MS (EI):

m/z (%) =332 ($M^{\bullet+}$, 13), 288 (19), 287 (20), 287 (81), 173 (11), 172 (100), 169 (30), 145 (14), 131 (10), 117 (13), 71 (14), 70 (45), 69 (16), 57 (11), 55 (10), 51 (14), 45 (19).

IR (capillary):

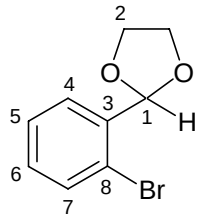
ν = 3064 (w), 2970 (vs), 1718 (vs), 1602 (m), 1577 (w), 1454 (s), 1369 (w), 1258 (vs), 1198 (m), 1092 (vs), 874 (w), 750 (s), 716 (m), 536 (w).

Elementary analysis:

Anal. Calcd. for $C_{19}H_{28}N_2O_3$:	C = 68.65	H = 8.49	N = 8.43
Found:	C = 68.85	H = 8.95	N = 8.00

6.4.3 THE PROJECT TETRAHYDROPALMATINE

2-(2'-Bromo-phenyl)-1,3-dioxolane [120]



In a 25 mL Schlenk flask under argon, a solution of 1,2-bis-(trimethylsilyloxy)-ethane (3.0 mL, 12.00 mmol) and trimethylsilyl trifluoromethanesulfonate (0.19 mL, 1.00 mmol) in abs. CH_2Cl_2 (5 mL) was cooled to −78 °C. 2-Bromobenzaldehyde (1.2 mL, 10.00 mmol) was added rapidly and the reaction mixture was stirred overnight (16 h) at −78 °C. The reaction was hydrolysed with 3.5 mL of pH 7 puffer and extracted 3 times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude product was distilled in high vacuum to yield **120** as a colourless liquid

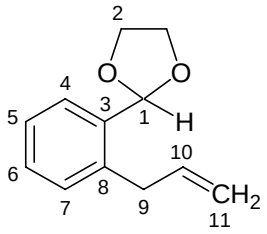
Yield:	m = 2.154 g (9.41 mmol)	94%
GC:	R_t = 9.00 min	(Sil-8, 80-10-300)
bp:	57-65 °C/0.1-0.01 mbar	(Lit.[127] 78-80 °C/0.15 Torr)

^{1}H-NMR (400 MHz, $CDCl_3$):
δ = 4.01-4.20 (m, 4H, C*H*$_2$C*H*$_2$), 6.10 (s, 1H, C*H*), 7.22 (td, *J* = 1.6 Hz, *J* = 7.7 Hz, 1H, C*H*CHCBr), 7.34 (t, *J* = 7.7 Hz, 1H, C*H*CHCCH), 7.56 (d, *J* = 8.0 Hz, 1H, C*H*CBr), 7.61 (dd, *J* = 1.4 Hz, *J* = 7.7 Hz, 1H, C*H*CCH) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):
δ = 65.39 (C-2), 102.48 (C-1), 122.77 (C-8), 127.24 (C-5), 127.63 (C-4), 130.42 (C-6), 132.78 (C-7), 136.42 (C-3) ppm.

All other analytical data correspond to those of the literature.[127,128]

2-(2'-Allyl-phenyl)-1,3-dioxolane [121]



Method A:

In a 250 mL Schlenk flask under argon, *s*-BuLi (8.5 mL, 11.00 mmol, 1.3 M in hexane) was added dropwise to a solution of bromoacetal **120** (2.291 g, 10.00 mmol) in abs. THF (100 mL) cooled to −78 °C. After 2 h 30 min at −78 °C, hexamethylphosphoramide (1.7 mL, 10.00 mmol) was added and the solution was transferred via a double ended needle into a solution of $CuBr{\cdot}SMe_2$ (2.056 g, 10.00 mmol) in abs. THF (50 mL) at −50 °C. After 30 min at −50 °C, the solution was warmed up to −20 °C and allyl bromide (5.6 mL, 65.00 mmol) was added rapidly. The temperature was slowly increased to room temperature (13 h). The reaction mixture was then hydrolysed with sat. aqueous NH_4Cl (150 mL) and extracted 4 times with Et_2O. The combined organic phases were washed 2 times with conc. aqueous NH_4OH (250 mL) and once with H_2O. After drying over $MgSO_4$, filtration and concentration under reduced pressure, the crude product was used directly in the next step.

Method B:

In a 25 mL Schlenk flask under argon, bromoacetal **120** (0.687 g, 3.00 mmol) and allyltributylstannane (1.02 mL, 3.30 mmol) were successively added to a suspension of $Pd(PPh_3)_4$ (0.347 g, 0.30 mmol) in abs. toluene (6 mL). The reaction mixture was then heated to reflux for 16 h and the reaction was filtered through a pad of celite using Et_2O (360 mL). The combined organic phases were succesively washed with sat. aqueous $Na_2S_2O_3$ (240 mL), with H_2O (120 mL) and brine. After drying over $MgSO_4$, filtration and concentration under reduced pressure, the crude mixture was purified by column chromatography (*n*-pentane/Et_2O = 25/1 to 6/1) providing **121** as a colourless liquid.

Yield:	m = 0.387 g (2.03 mmol)	68%
GC:	R_t = 6.76 min	(Sil-8, 100-10-300)
TLC:	R_f = 0.47	(*n*-pentane/Et_2O = 40/1)

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 3.55 (d, *J* = 6.2 Hz, 2H, CC*H*$_2$CH=CH$_2$), 3.98-4.19 (m, 4H, C*H*$_2$C*H*$_2$), 4.97-5.10 (m, 2H, CCH$_2$CH=C*H*$_2$), 5.99 (s, 1H, C*H*(OCH$_2$)$_2$), 5.94-6.08 (m, 1H, CCH$_2$C*H*=CH$_2$), 7.17-7.34 (m, 3H, C*H*$_{arom}$), 7.57 (dd, *J* = 1.5 Hz, *J* = 7.4 Hz, 1H, C*H*CCH(OCH$_2$)$_2$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = 36.48 (C-9), 65.24 (C-2), 101.63 (C-1), 115.85 (C-11), 126.12 (C-4), 126.34, 129.19, 129.90 (C-5/C-6/C-7), 135.27 (C-3), 137.19 (C-10), 138.42 (C-8) ppm.

MS (EI):

m/z (%) = 190 ($M^{\bullet+}$, 18), 189 (18), 175 (13), 163 (11), 162 ($M^{\bullet+}$–C_2H_4, 97), 147 (14), 146 (11), 145 (28), 133 (12), 131 (19), 130 (27), 129 (100), 128 (90), 127 (12), 118 (14), 117 (37), 116 (12), 115 (37), 105 (44), 91 (21), 73 (31), 45 (13).

IR (capillary):

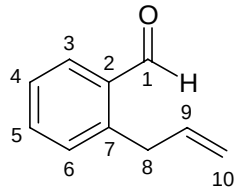
ν = 3073 (m), 2976 (s), 2886 (vs), 1638 (m), 1606 (w), 1486 (m), 1452 (m), 1395 (s), 1287 (w), 1223 (s), 1183 (w), 1073 (vs), 970 (vs), 946 (vs), 917 (vs), 760 (vs), 632 (w).

HRMS:

m/z Calcd. for $C_{12}H_{14}O_2$ (M^+):	190.0994
Found:	190.0994

The ^{1}H-NMR spectrum is in accordance with the one reported in the literature.[99]

2-Allyl-benzaldehyde [122]



In a 100 mL Schlenk flask, the crude acetal **121** (max. 10.00 mmol) was dissolved in a mixture of dioxane (30 mL) and H_2O (15 mL). *p*-TsOH (0.190 g, 1.00 mmol) was added and the reaction mixture was heated to 90 °C for 15 h. Brine (150 mL) was added and the solution

was extracted 4 times with Et_2O. The combined organic phases were washed 2 times with H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was distilled in high vacuum using a microdistillation apparatus to give **122** as a colourless liquid.

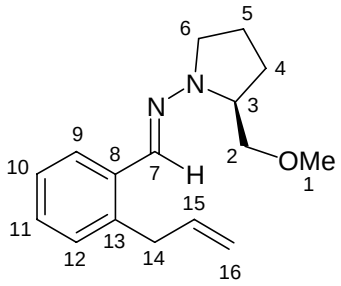
Yield:	m = 0.743 g (5.08 mmol)	51% (over 2 steps)
GC:	R_t = 5.32 min	(Sil-8, 80-10-300)
bp:	75-78 °C/2 Torr	(Lit.[99] 51-52 °C/0.35 Torr)

^{1}H-NMR (400 MHz, $CDCl_3$):
δ = 3.82 (d, *J* = 6.0 Hz, 2H, C*H*$_2$CH=CH$_2$), 4.98 (dq, *J* = 1.7 Hz, *J* = 17.0 Hz, 1H, CH$_2$CH=C*H*$_2$), 5.09 (dq, *J* = 1.7 Hz, *J* = 10.2 Hz, 1H, CH$_2$CH=C*H*$_2$), 6.04 (tdd, *J* = 6.0 Hz, *J* = 10.2 Hz, *J* = 17.0 Hz, 1H, CH$_2$C*H*=CH$_2$), 7.29 (d, *J* = 7.7 Hz, 1H, C*H*CCH$_2$), 7.39 (td, *J* = 1.1 Hz, *J* = 7.4 Hz, 1H, C*H*CHCCO), 7.53 (td, *J* = 1.4 Hz, *J* = 7.7 Hz, 1H, C*H*CHCCH$_2$), 7.84 (dd, *J* = 1.4 Hz, *J* = 7.7 Hz, 1H, C*H*CCO), 10.25 (s, 1H, C*H*O) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):
δ = 36.47 (C-8), 116.22 (C-10), 126.72 (C-4), 130.87 (C-6), 131.39 (C-3), 133.66 (C-2), 133.76 (C-5), 136.73 (C-9), 142.03 (C-7), 192.02 (C-1) ppm.

All other analytical data correspond to those reported in the literature.[99,129]

[1-(2'-Allyl-phenyl)-meth-(1*E*)-ylidene]-((2''*S*)-2''-methoxymethyl-pyrrolidin-1''-yl)-amine [(*S*)-118a]



According to the general procedure GP-1, 2-allyl-benzaldehyde (**122**) (1.038 g, 7.10 mmol) and SAMP (1.079 g, 7.81 mmol, 94% purity (GC)) were reacted overnight. After purification by column chromatography (*n*-pentane/Et_2O = 20/1 to 3/1 + 2% Et_3N) (*S*)-**118a** was obtained as a pale yellow liquid.

Yield:	m = 1.747 g (6.76 mmol)	95%
GC:	R_t = 10.98 min	(Sil-8, 120-10-300)
TLC:	R_f = 0.60	(*n*-pentane/Et_2O = 15/1 + 2% Et_3N)
Optical rotation:	$[\alpha]_D^{24.5}$ = –156.2	(c = 1.84, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 1.84-2.09 (m, 4H, $NCH_2CH_2CH_2$), 2.98-3.06 (m, 1H, NCH_2), 3.40 (s, 3H, OCH_3), 3.41-3.56 (m, 4H, NCH_2, $CH_2CH{=}CH_2$, OCH_2), 3.64-3.70 (m, 2H, NCH, OCH_2), 4.99 (dq, *J* = 1.7 Hz, *J* = 17.0 Hz, 1H, $CH_2CH{=}CH_2$), 5.05 (dq, *J* = 1.7 Hz, *J* = 10.1 Hz, 1H, $CH_2CH{=}CH_2$), 5.92 (tdd, *J* = 6.0 Hz, *J* = 10.1 Hz, *J* = 17.0 Hz, *J* = 17.0 Hz, 1H, $CCH_2CH{=}CH_2$), 7.10-7.22 (m, 3H, CH_{arom}), 7.39 (s, 1H, N=CH), 7.81 (dd, *J* = 1.4 Hz, *J* = 7.7 Hz, 1H, CHCCH=N) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 22.20 (C-5), 26.79 (C-4), 37.50 (C-14), 49.04 (C-6), 59.20 (C-1), 63.08 (C-3), 74.50 (C-2), 115.43 (C-16), 124.86 (C-9), 126.33, 126.84, 129.77 (C-10/C-11/C-12), 130.73 (C-7), 134.81 (C-8), 135.88 (C-13), 136.98 (C-15) ppm.

MS (EI):

m/z (%) = 258 ($M^{\bullet+}$, 17), 214 (17), 213 ($M^{\bullet+}$–CH_2OCH_3, 100), 144 (16), 130 (13), 129 (33), 116 (12), 115 (17), 114 (10), 85 (22), 70 (44).

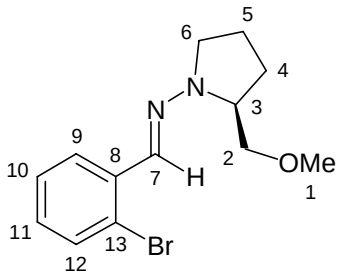
IR (in $CHCl_3$):

ν = 3062 (m), 2974 (vs), 2880 (vs), 2827 (vs), 1636 (m), 1580 (vs), 1552 (vs), 1477 (s), 1450 (vs), 1382 (s), 1342 (s), 1305 (m), 1285 (m), 1248 (m), 1197 (vs), 1119 (vs), 995 (m), 975 (m), 911 (vs), 756 (vs), 645 (w), 560 (w), 480 (w).

Elementary analysis:

Anal. Calcd. for $C_{16}H_{22}N_2O$:	C = 74.38	H = 8.58	N = 10.84
Found:	C = 74.14	H = 8.09	N = 11.18

[1-(2'-Bromo-phenyl)-meth-(1*E*)-ylidene]-((2''*S*)-2''-methoxymethyl-pyrrolidin-1''-yl)-amine [(*S*)-118b]



According to the general procedure GP-1, 2-bromo-benzaldehyde (1.17 mL, 10.00 mmol) and SAMP (1.658 g, 12.00 mmol, 94% purity (GC)) were reacted overnight. After distillation under high vacuum (*S*)-**118b** was obtained as a yellow liquid.

Yield:	m = 2.743 g (9.23 mmol)	92%
GC:	R_t = 15.89 min	(Sil-8, 80-10-300)
bp:	115-122 °C/0.1-0.01 mbar	
Optical rotation:	$[\alpha]_D^{25} = -132.6$	(c = 2.47, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$):
δ = 1.85-2.11 (ca, 4H, $NCH_2CH_2CH_2$), 3.11-3.17 (m, 1H, NCH_2), 3.40 (s, 3H, OCH_3), 3.45-3.52 (m, 1H, NCH_2), 3.53 (dd, *J* = 6.6 Hz, *J* = 9.3 Hz, 1H, OCH_2), 3.67 (dd, *J* = 3.9 Hz, *J* = 9.3 Hz, 1H, OCH_2), 3.70-3.77 (m, 1H, NC*H*), 6.99-7.05 (m, 1H, CH_{arom}), 7.21-7.26 (m, 1H, CH_{arom}), 7.42 (s, 1H, N=C*H*), 7.48 (dd, *J* = 1.1 Hz, *J* = 8.0 Hz, 1H, CH_{arom}), 7.89 (dd, *J* = 1.7 Hz, *J* = 8.0 Hz, 1H, C*H*CCH=N) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):
δ = 22.24 (C-5), 26.88 (C-4), 48.81 (C-6), 59.23 (C-1), 62.93 (C-3), 74.39 (C-2), 121.95 (C-13), 125.67 (C-9), 127.05, 127.64 (C-10/C-11), 130.16 (C-7), 132.54 (C-12), 135.73 (C-8) ppm.

MS (EI):
m/z (%) =298 ($M^{\bullet+}$, 10), 296 ($M^{\bullet+}$, 13), 254 (12), 253 ($M^{\bullet+}$–CH_2OCH_3, 100), 251 ($M^{\bullet+}$–CH_2OCH_3, 98), 70 (37).

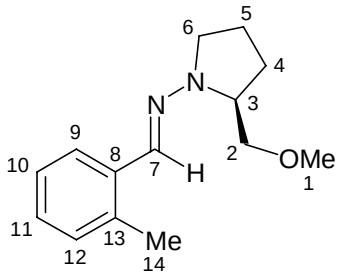
IR (capillary):

ν = 3060 (w), 2972 (vs), 2924 (vs), 2878 (vs), 2826 (vs), 2736 (w), 1568 (vs), 1544 (vs), 1463 (vs), 1436 (s), 1375 (vs), 1342 (vs), 1308 (s), 1284 (m), 1248 (s), 1197 (vs), 1156 (s), 1114 (vs), 1042 (w), 1019 (vs), 974 (m), 900 (w), 870 (m), 851 (m), 753 (vs), 651 (w), 545 (m), 530 (m).

Elementary analysis:

Anal. Calcd. for $C_{13}H_{17}BrN_2O$:	C = 52.54	H = 5.77	N = 9.43
Found:	C = 52.10	H = 6.16	N = 9.92

((2'*S*)-2'-Methoxymethyl-pyrrolidin-1'-yl)-[1-*o*-tolyl-meth-(1*E*)-ylidene]-amine [(*S*)-118c]



According to the general procedure GP-1, 2-methyl-benzaldehyde (1.39 mL, 12.00 mmol) and SAMP (1.382 g, 10.00 mmol, 94% purity (GC)) were reacted overnight. After distillation under high vacuum with the help of a microdistillation apparatus (*S*)-**118c** was obtained as a yellow liquid.

Yield:	m = 2.088 g (8.99 mmol)	90%
GC:	R_t = 12.23 min	(Sil-8, 100-10-300)
bp:	84 °C/0.1-0.01 mbar	
Optical rotation:	$[\alpha]_D^{25} = -158.9$	(c = 1.23, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 1.84-2.09 (m, 4H, $NCH_2CH_2CH_2$), 2.39 (s, 3H, CCH_3), 2.99-3.07 (m, 1H, NCH_2), 3.40 (s, 3H, OCH_3), 3.45-3.58 (m, 2H, NCH_2, OCH_2), 3.64-3.71 (m, 2H, OCH_2, NCH), 7.09-7.18 (m, 3H, CH_{arom}), 7.38 (s, 1H, N=CH), 7.75 (d, *J* = 7.4 Hz, 1H, CHCCH=N) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 19.69 (C-14), 22.20 (C-5), 26.76 (C-4), 49.00 (C-6), 59.19 (C-1), 63.15 (C-3), 74.50 (C-2), 124.62 (C-9), 125.78, 126.59, 130.26 (C-10/C-11/C-12), 130.92 (C-7), 134.20, 134.89 (C-8/C-13) ppm.

MS (EI):

m/z (%) = 232 ($M^{\bullet+}$, 13), 188 (12), 187 ($M^{\bullet+}$–CH_2OCH_3, 100), 70 (34).

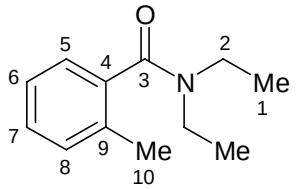
IR (capillary):

ν = 3057 (m), 2879 (vs), 1697 (m), 1670 (w), 1579 (vs), 1553 (vs), 1458 (vs), 1379 (s), 1342 (s), 1305 (w), 1284 (w), 1248 (m), 1198 (vs), 1154 (s), 1120 (vs), 973 (m), 879 (m), 755 (vs), 719 (m), 560 (w), 539 (w), 499 (m).

Elementary analysis:

Anal. Calcd. for $C_{14}H_{20}N_2O$:	C = 72.38	H = 8.68	N = 12.06
Found:	C = 71.96	H = 8.21	N = 12.07

***N*,*N*-Diethyl-2-methyl-benzamide [75]**



To a solution of Et_2NH (10.3 mL, 100.0 mmol) and Et_3N (13.9 mL, 100.0 mmol) in Et_2O (350 mL) at 0 °C, 2-methylbenzoyl chloride (13.0 mL, 100.0 mmol) was slowly added. Upon completion of the addition the precipitate was filtered off, washed with Et_2O (75 mL) and discarded. The combined organic layers were concentrated under vacuum and the crude product was recrystallized from petroleum ether to yield **75** as a colourless crystalline solid.

Yield:	m = 15.715 g (82.2 mmol)	82%
GC:	R_t = 11.14 min	(Sil-8, 60-10-300)
mp:	48 °C	(Lit.[130] 49-50 °C)

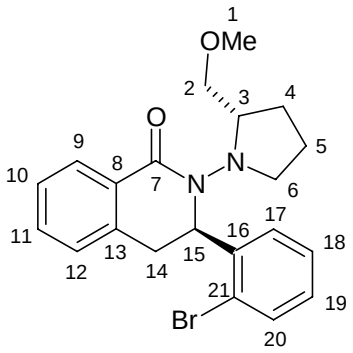
^{1}H-NMR (300 MHz, $CDCl_3$, mixture of rotamers):
δ = 1.03 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.26 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 2.29 (s, 3H, CCH_3), 3.12 (q, *J* = 7.2 Hz, 2H, CH_2CH_3), 3.20-3.85 (br, 2H, CH_2CH_3), 7.13-7.29 (m, 4H, CH_{arom}) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$, mixture of rotamers):
δ = 12.88 (C-1), 13.99 (C-1'), 18.79 (C-10), 38.66 (C-2), 42.59 (C-2'), 125.44, 125.77, 128.51, 130.29 (C_{arom}), 133.84 (C-4), 137.17 (C-9), 170.87 (C-3) ppm.

MS (EI):
m/z (%) =191 ($M^{\bullet+}$, 20), 190 (26), 176 (29), 119 ($M^{\bullet+}$–NEt_2, 100), 118 (15), 91 (43), 65 (15).

All other analytical data correspond to those reported in the literature.[130,131]

(3*R*)-3-(2'-Bromo-phenyl)-2-((2''*S*)-2''-methoxymethyl-pyrrolidin-1''-yl)-3,4-dihydro-2*H*-isoquinolin-1-one [(3*R*,2''*S*)-119b]



According to the general procedure GP-4, 2-methyl benzamide **75** and SAMP-hydrazone (*S*)-**118b** were reacted overnight in abs. THF. After purification by column chromatography (*n*-pentane/Et_2O = 8/1 to 1/3) (3*R*,2''*S*)-**119b** was obtained as a yellow syrup.

Yield:	m = 0.066 g (0.16 mmol)	11%
GC:	R_t = 13.65 min	(Sil-8, 160-10-300)
TLC:	R_f = 0.45	(petroleum ether/Et_2O = 2/3)
Optical rotation:	$[\alpha]_D^{27}$ = +62.3	(c = 0.83, $CHCl_3$)
de:	≥ 96%	(^{1}H-NMR)

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 1.37-1.47 (m, 1H, $NCH_2CH_2CH_2$), 1.57-1.68 (m, 1H, $NCH_2CH_2CH_2$), 1.92-2.02 (m, 1H, $NCH_2CH_2CH_2$), 2.05-2.14 (m, 1H, $NCH_2CH_2CH_2$), 2.78-2.85 (dt, *J* = 4.4 Hz, *J* = 7.7 Hz, 1H, NCH_2), 3.05 (dd, *J* = 1.7 Hz, *J* = 15.9 Hz, 1H, O=CNCHCH_2), 3.40-3.47 (m, 2H, OCH_2), 3.42 (s, 3H, OCH_3), 3.69-3.78 (m, 2H, O=CNCHCH_2, NCH_2), 4.00-4.10 (m, 1H, NC*H*), 5.53 (dd, *J* = 1.7 Hz, *J* = 7.4 Hz, 1H, O=CNC*H*CH_2), 6.93-6.98 (m, 2H, CH_{arom}), 7.01-7.06 (m, 2H, CH_{arom}), 7.29-7.34 (m, 2H, CH_{arom}), 7.51-7.56 (m, 1H, CH_{arom}), 8.05-8.11 (m, 1H, O=CCC*H*) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 23.20 (C-5), 26.95 (C-4), 34.15 (C-14), 51.56 (C-6), 58.89 (C-1), 60.66 (C-3), 64.98 (C-15), 77.30 (C-2), 122.54 (C-21), 126.82, 126.85, 127.13, 127.48, 127.67, 128.55 (C_{arom}), 130.08 (C-8), 131.77, 132.98 (C_{arom}), 134.56 (C-13), 139.49 (C-16), 163.46 (C-7) ppm.

MS (EI):

m/z (%) =417 ($M^{\bullet+}$+1, 5), 415 ($M^{\bullet+}$+1, 6), 372 (20), 371 ($M^{\bullet+}$–CH_2OCH_3, 100), 370 (24), 369 ($M^{\bullet+}$–CH_2OCH_3, 99), 304 (14), 303 (16), 302 (16), 206 (25), 178 (13), 114 (72), 113 (18), 68 (10).

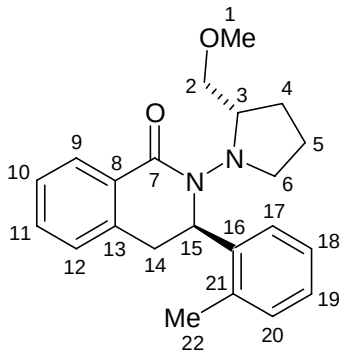
IR (in $CHCl_3$):

ν = 3065 (w), 2925 (s), 2875 (s), 1653 (vs), 1604 (m), 1462 (s), 1406 (vs), 1329 (s), 1249 (s), 1102 (s), 1025 (s), 964 (w), 754 (vs), 694 (w), 665 (w), 587 (w), 488 (w).

Elementary analysis:

Anal. Calcd. for $C_{21}H_{23}BrN_2O_2$:	C = 60.73	H = 5.58	N = 6.74
Found:	C = 60.27	H = 5.42	N = 7.06

(3*R*)-2-((2'*S*)-2'-Methoxymethyl-pyrrolidin-1'-yl)-3-*o*-tolyl-3,4-dihydro-2*H*-isoquinolin-1-one [(3*R*,2'*S*)-119c]



According to the general procedure GP-4, 2-methyl benzamide **75** and SAMP-hydrazone (*S*)**-118c** were reacted overnight in abs. THF. After purification by column chromatography (*n*-pentane/Et_2O = 4/1) (3*R*,2'*S*)**-119c** was obtained as a pale pink crystalline solid.

Yield:	m = 0.142 g (0.41 mmol)	27%
GC:	R_t = 16.88 min	(Sil-8, 120-10-300)
TLC:	R_f = 0.40	(petroleum ether/Et_2O = 2/3)
mp:	88 °C	
Optical rotation:	$[\alpha]_D^{21}$ = +7.7	(c = 0.65, $CHCl_3$)
de:	≥ 96%	(^{1}H-NMR)

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 1.36-1.48 (m, 1H, $NCH_2CH_2CH_2$), 1.54-1.64 (m, 1H, $NCH_2CH_2CH_2$), 1.87-2.01 (m, 1H, $NCH_2CH_2CH_2$), 2.04-2.16 (m, 1H, $NCH_2CH_2CH_2$), 2.44 (s, 3H, CCH_3), 2.73 (dt, *J* = 4.2 Hz, *J* = 7.9 Hz, 1H, NCH_2), 2.86 (dd, *J* = 1.7 Hz, *J* = 15.6 Hz, 1H, O=CNCHCH_2), 3.39-3.43 (m, 2H, OCH_2), 3.40 (s, 3H, OCH_3), 3.66 (dt, *J* = 7.9 Hz, *J* = 7.9 Hz, 1H, NCH_2), 3.77 (ddd, *J* = 0.7 Hz, *J* = 7.7 Hz, *J* = 15.6 Hz, 1H, O=CNCHCH_2), 4.01-4.12 (m, 1H, NC*H*), 5.38 (dd, *J* = 1.7 Hz, *J* = 7.7 Hz, 1H, O=CNC*H*CH_2), 6.85-6.98 (m, 3H, CH_{arom}), 7.07 (td, *J* = 1.7 Hz, *J* = 7.0 Hz, 1H, CH_{arom}), 7.11-7.16 (m, 1H, CH_{arom}), 7.29-7.36 (m, 2H, CH_{arom}), 8.06-8.13 (m, 1H, O=CCC*H*) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 19.28 (C-22), 23.25 (C-5), 27.01 (C-4), 34.59 (C-14), 51.62 (C-6), 58.88 (C-1), 60.43 (C-3), 62.01 (C-15), 77.46 (C-2), 125.69, 126.04, 126.99, 127.06, 127.33, 127.63 (C_{arom}), 130.45 (C-8), 130.66, 131.86 (C_{arom}), 134.57, 135.05 (C-13/C-21), 139.18 (C-16), 163.59 (C-7) ppm.

MS (EI):

m/z (%) =351 ($M^{\bullet+}$+1, 0.4), 306 (24), 305 ($M^{\bullet+}$–CH_2OCH_3, 100), 221 (16), 178 (13), 158 (10), 114 (83), 91 (10), 84 (11).

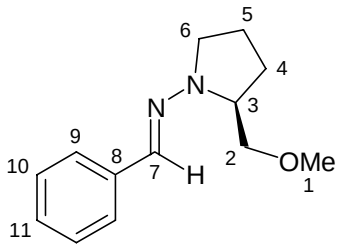
IR (KBr):

ν = 3449 (m), 3066 (w), 3027 (w), 2923 (s), 2875 (s), 2838 (s), 2749 (w), 1648 (vs), 1602 (s), 1488 (m), 1458 (s), 1410 (s), 1385 (s), 1331 (s), 1255 (s), 1201 (w), 1128 (m), 1105 (vs), 1041 (m), 982 (w), 963 (w), 753 (s), 731 (s), 692 (m), 641 (w).

Elementary analysis:

Anal. Calcd. for $C_{22}H_{26}N_2O_2$:	C = 75.40	H = 7.48	N = 7.99
Found:	C = 75.00	H = 7.14	N = 7.78

((2'*S*)-2'-Methoxymethyl-pyrrolidin-1'-yl)-[1-phenyl-meth-(1*E*)-ylidene]-amine [(*S*)-76a]



According to the general procedure GP-1, freshly distilled benzaldehyde (2.4 mL, 24.0 mmol) and SAMP (2.704 g, 20.0 mmol, 96% purity (GC)) were reacted overnight. After distillation under high vacuum with the help of a microdistillation apparatus (*S*)**-76a** was obtained as a yellow liquid.

Yield:	m = 4.125 g (18.9 mmol)	94%
GC:	R_t = 11.20 min	(Sil-8, 100-10-300)
bp:	104 °C/0.1-0.01 mbar	(Lit.[132] 123 °C/0.05 Torr)

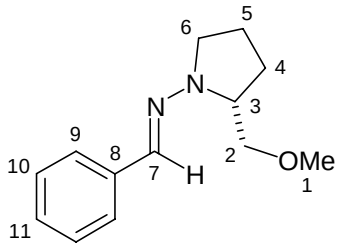
Optical rotation: $[\alpha]_D^{26} = -171.7$ (c = 1.96, $CHCl_3$) (Lit.[132] $[\alpha]_D^{22}$ = −130.8 (neat))

^{1}H-NMR (400 MHz, $CDCl_3$):
δ = 1.82-2.08 (m, 4H, $NCH_2CH_2CH_2$), 3.00-3.08 (m, 1H, NCH_2), 3.40 (s, 3H, OCH_3), 3.43-3.55 (m, 2H, NCH_2, OCH_2), 3.64-3.70 (m, 2H, OCH_2, NC*H*), 7.16-7.21 (m, 1H, *p*-CH_{arom}), 7.21 (s, 1H, N=C*H*), 7.27-7.32 (m, 2H, *m*-CH_{arom}), 7.52-7.56 (m, 2H, *o*-CH_{arom}) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):
δ = 22.20 (C-5), 26.79 (C-4), 48.87 (C-6), 59.19 (C-1), 62.97 (C-3), 74.50 (C-2), 125.12 (C-9), 126.73 (C-11), 128.20 (C-10), 132.22 (C-7), 137.08 (C-8) ppm.

All other analytical data correspond to those reported in the literature.[132]

((2'*R*)-2'-Methoxymethyl-pyrrolidin-1'-yl)-[1-phenyl-meth-(1*E*)-ylidene]-amine [(*R*)-76a]

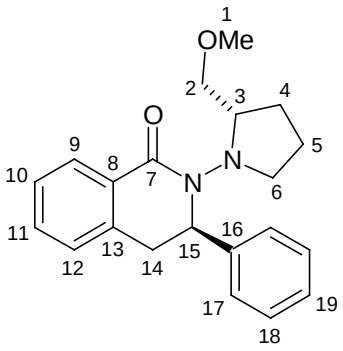


According to the general procedure GP-1, freshly distilled benzaldehyde (2.4 mL, 24.0 mmol) and RAMP (3.038 g, 20.0 mmol, 86% purity (GC)) were reacted overnight. After distillation under high vacuum with the help of a microdistillation apparatus (*R*)**-76a** was obtained as a yellow liquid.

Yield: m = 4.042 g (18.5 mmol) 93%
Optical rotation: $[\alpha]_D^{26} = +169.9$ (c = 2.07, $CHCl_3$) (Lit.[132] $[\alpha]_D^{20}$ = +133.6 (neat))

All other analytical data correspond to those of the other enantiomer (*S*)**-76a**.

(3*R*)-2-((2'*S*)-2'-Methoxymethyl-pyrrolidin-1'-yl)-3-phenyl-3,4-dihydro-2*H*-isoquinolin-1-one [(3*R*,2'*S*)-77a]



According to the general procedure GP-4, 2-methyl benzamide **75** and SAMP-hydrazone (*S*)**-76a** were reacted overnight in abs. Et_2O. After purification by column chromatography (*n*-pentane/Et_2O = 3/2) (3*R*,2'*S*)**-77a** was obtained as a pale yellow oil which crystallised on standing.

Yield:	m = 0.404 g (1.20 mmol)	80%
GC:	R_t = 16.23 min	(Sil-8, 120-10-300)
TLC:	R_f = 0.16	(*n*-pentane/Et_2O = 3/2)
mp:	81 °C	
Optical rotation:	$[\alpha]_D^{24}$ = –29.7	(c = 1.02, $CHCl_3$)
de:	≥ 96%	(^{1}H-NMR)

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 1.39-1.48 (m, 1H, $NCH_2CH_2CH_2$), 1.54-1.66 (m, 1H, $NCH_2CH_2CH_2$), 1.89-2.00 (m, 1H, $NCH_2CH_2CH_2$), 2.04-2.14 (m, 1H, $NCH_2CH_2CH_2$), 2.76 (dt, *J* = 4.4 Hz, *J* = 8.0 Hz, 1H, NCH_2), 2.95 (dd, *J* = 2.5 Hz, *J* = 15.8 Hz, 1H, O=CNCHCH_2), 3.38 (s, 3H, OCH_3), 3.38-3.46 (m, 2H, OCH_2), 3.66 (dt, *J* = 8.0 Hz, *J* = 8.0 Hz, 1H, NCH_2), 3.77 (dd, *J* = 7.2 Hz, *J* = 15.8 Hz, 1H, O=CNCHCH_2), 4.04-4.13 (m, 1H, NC*H*), 5.07 (dd, *J* = 2.5 Hz, *J* = 7.2 Hz, 1H, O=CNC*H*CH_2), 6.63-7.02 (m, 1H, CH_{arom}), 7.10-7.22 (m, 5H, CH_{arom}), 7.29-7.33 (m, 2H, CH_{arom}), 8.06-8.12 (m, 1H, O=CCC*H*) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 23.06 (C-5), 26.98 (C-4), 36.51(C-14), 51.68 (C-6), 58.76 (C-1), 60.10 (C-3), 65.93 (C-15), 77.04 (C-2), 126.44 (C-18), 126.75, 127.05, 127.15, 127.24 (C-9/C-10/C-11/C-12/C-19),

128.01 (C-17), 130.19 (C-8), 131.67 (C-9/C-10/C-11/C-12/C-19), 135.02 (C-13), 141.20 (C-16), 163.07 (C-7) ppm.

MS (EI):

m/z (%) = 336 ($M^{\bullet+}$, 1), 292 (21), 291($M^{\bullet+}$– CH_2OCH_3, 100), 207 (23), 178 (12), 114 (55), 113 (10).

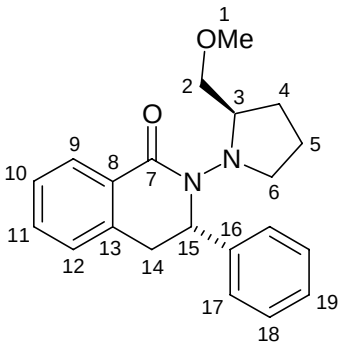
IR (capillary):

ν = 3062 (w), 3029 (w), 2971 (s), 2934 (s), 2873 (s), 2829 (w), 1652 (vs), 1634 (vs), 1603 (s), 1584 (w), 1494 (m), 1458 (vs), 1427 (vs), 1406 (s), 1382 (m), 1364 (m), 1338 (m), 1293 (s), 1280 (m), 1247 (m), 1222 (w), 1189 (w), 1157 (w), 1125 (m), 1099 (s), 1045 (w), 1033 (w), 983 (w), 966 (w), 769 (m), 735 (s), 701 (m), 632 (w).

Elementary analysis:

Anal. Calcd. for $C_{21}H_{24}N_2O_2$:	C = 74.97	H = 7.19	N = 8.33
Found:	C = 74.91	H = 7.33	N = 8.31

(3*S*)-2-((2'*R*)-2'-Methoxymethyl-pyrrolidin-1'-yl)-3-phenyl-3,4-dihydro-2*H*-isoquinolin-1-one [(3*S*,2'*R*)-77a]

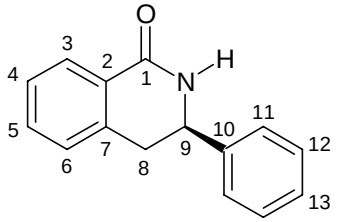


According to the general procedure GP-4, 2-methyl benzamide **75** and RAMP-hydrazone (*R*)**-76a** were reacted overnight in abs. Et_2O. After purification by column chromatography (*n*-pentane/Et_2O = 3/2) (3*S*,2'*R*)**-77a** was obtained as a pale yellow oil.

Yield:	m = 0.397 g (1.18 mmol)	79%
Optical rotation:	$[\alpha]_D^{24}$ = +26.2	(c = 0.39, $CHCl_3$)
de:	≥ 96%	(^{1}H-NMR)

All other analytical data correspond to those of the other enantiomer (3*R*,2'*S*)-**77a**.

(3*R*)-3-Phenyl-3,4-dihydro-2*H*-isoquinolin-1-one [(*R*)-79a]



In a 50 mL Schlenk flask under argon, a THF solution of SmI_2 (14.5 mL, 1.45 mmol, 0.1 M in THF) was added dropwise at room temperature to a solution of dihydroisoquinolinone (3*R*,2'*S*)-**77a** (0.162 g, 0.48 mmol) and DMPU (0.85 mL) in abs. THF (3.5 mL). After 30 min (the solution should remain deep blue otherwise more SmI_2 is needed) the reaction mixture was quenched with 10% aqueous $NaHCO_3$ (80 mL) and diluted with CH_2Cl_2 (33 mL). After phase separation the aqueous phase was extracted 2 times with CH_2Cl_2 (50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-pentane/Et_2O = 1/3) to yield (*R*)-**79a** as a colourless solid.

Yield:	m = 0.100 g (0.45 mmol)	94%
GC:	R_t = 13.64 min	(Sil-8, 120-10-300)
TLC:	R_f = 0.26	(*n*-pentane/Et_2O = 1/2)
mp:	105 °C	(Lit.[54b] 130-131 °C (hexane))
Optical rotation:	$[\alpha]_D^{23}$ = +195.3	(c = 1.05, $CHCl_3$)
ee:	= 98%	(Chiralcel OD, *n*-heptane/*i*-PrOH = 9/1, R_t = 13.06 min, λ = 254 nm)

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 3.12 (dd, *J* = 5.2 Hz, *J* = 15.8 Hz, 1H, NCHC*H*$_2$), 3.21 (dd, *J* = 10.6 Hz, *J* = 15.8 Hz, 1H, NCHC*H*$_2$), 4.86 (ddd, *J* = 1.0 Hz, *J* = 5.2 Hz, *J* = 10.6 Hz, 1H, NC*H*CH$_2$), 6.03 (br, 1H, N*H*), 7.18 (d, *J* = 7.4 Hz, 1H, NCHCH$_2$C=C*H*), 7.31-7.50 (m, 7H, C*H*$_{arom}$), 8.12 (dd, *J* = 1.5 Hz, *J* = 7.7 Hz, 1H, O=CCC*H*) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):

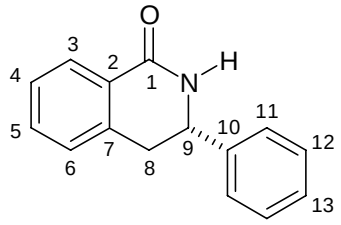
δ = 37.50 (C-8), 56.21 (C-9), 126.43 (C_{arom}), 127.32 (C-6), 128.08 (C_{arom}), 128.42 (C-2), 128.43, 129.03, 132.52 (C_{arom}), 137.57 (C-7), 140.95 (C-10), 166.29 (C-1) ppm. (the missing peaks were covered by other peaks)

MS (EI):

m/z (%) = 224 (13), 223 ($M^{\bullet+}$, 75), 119 (12), 118 ($M^{\bullet+}$–NH_2Bn, 100), 90 (26), 89 (10).

All other analytical data correspond with those reported in the literature.[54d,58b]

(3*S*)-3-Phenyl-3,4-dihydro-2*H*-isoquinolin-1-one [(*S*)-79a]

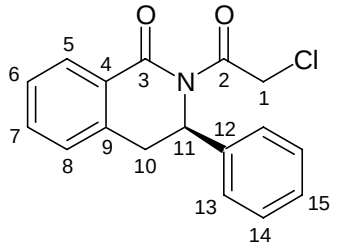


In a 100 mL Schlenk flask under argon, a THF solution of SmI_2 (49 mL, 4.85 mmol, 0.1 M in THF) was added dropwise at room temperature to a solution of dihydroisoquinolinone (3*S*,2'*R*)**-77a** (0.544 g, 1.62 mmol) and DMPU (2.8 mL) in abs. THF (11 mL). After 30 min 30 mL of the THF solution of SmI_2 were added in order to keep the solution deep blue. The reaction mixture was then quenched with 10% aqueous $NaHCO_3$ (280 mL) and diluted with CH_2Cl_2 (110 mL). After phase separation the aqueous phase was extracted 2 times with CH_2Cl_2 (170 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-pentane/Et_2O = 1/3) providing (*S*)**-79a** as a colourless solid.

Yield:	m = 0.335 g (1.50 mmol)	93%
Optical rotation:	$[\alpha]_D^{26} = -191.9$	(c = 1.04, $CHCl_3$) (Lit.[58b] $[\alpha]_D^{20}$ = –203.4 (c = 1.03, $CHCl_3$))
ee:	= 98%	(Chiralcel OD, *n*-heptane/*i*-PrOH = 9/1, R_t = 16.81 min, λ = 254 nm)

All other analytical data correspond to those of the other enantiomer (*R*)**-79a**.

(3*R*)-2-(2'-Chloro-acetyl)-3-phenyl-3,4-dihydro-2*H*-isoquinolin-1-one [(*R*)-130]



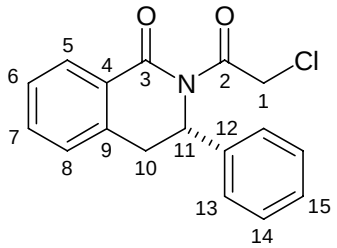
According to the general procedure GP-5, chloroacetyl chloride (20 µL, 0.25 mmol) and dihydroisoquinolinone (*R*)-**79a** (0.044 g, 0.20 mmol) were heated to 80 °C for 4 h. The resulting crude product was used directly in the next step.

Conversion: ≥ 96% (^{1}H-NMR)

^{1}H-NMR (300 MHz, $CDCl_3$):
δ = 3.28 (dd, *J* = 2.0 Hz, *J* = 16.6 Hz, 1H, NCHC*H*$_2$), 3.66 (dd, *J* = 6.2 Hz, *J* = 16.6 Hz, 1H, NCHC*H*$_2$), 4.93 (d, *J* = 16.3 Hz, 1H, C*H*$_2$Cl), 5.03 (d, *J* = 16.3 Hz, 1H, C*H*$_2$Cl), 6.16 (dd, *J* = 2.0 Hz, *J* = 6.2 Hz, 1H, NC*H*CH$_2$), 7.03-7.22 (m, 6H, C*H*$_{arom}$), 7.32-7.39 (m, 1H, C*H*$_{arom}$), 7.48 (td, *J* = 1.5 Hz, *J* = 7.4 Hz, 1H, C*H*$_{arom}$), 8.13 (m, 1H, C*H*$_{arom}$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):
δ = 34.19 (C-10), 47.73 (C-1), 55.35 (C-11), 126.02 (C-13), 127.58, 127.65, 128.17 (C$_{arom}$), 128.59 (C-14), 129.24 (C$_{arom}$), 134.38 (C-7), 137.31 (C-9), 139.15 (C-12), 165.78, 169.88 (C-2/C-3) ppm. (the missing peak was hidden by other peaks).

(3*S*)-2-(2'-Chloro-acetyl)-3-phenyl-3,4-dihydro-2*H*-isoquinolin-1-one [(*S*)-130]

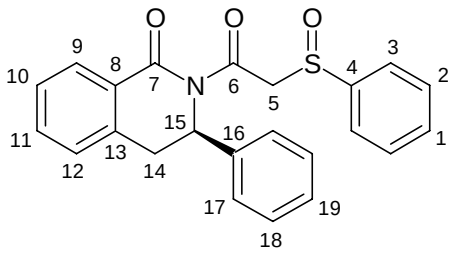


According to the general procedure GP-5, chloroacetyl chloride (47 µL, 0.60 mmol) and dihydroisoquinolinone (*S*)-**79a** (0.107 g, 0.48 mmol) were heated to 80 °C for 4 h. The resulting crude product was used directly in the next step.

Conversion: ≥ 96% (^{1}H-NMR)

The spectroscopic data correspond to those of the other enantiomer (*R*)-**130**.

(3*R*)-2-(2'-Phenylsulfinyl-acetyl)-3-phenyl-3,4-dihydro-2*H*-isoquinolin-1-one [(*R*)-139]



According to the general procedure GP-5, (phenylthio)acetyl chloride (70 µL, 0.47 mmol) and dihydroisoquinolinone (*R*)-**79a** (0.099 g, 0.44 mmol) were heated to 80 °C for 20 h. The resulting crude (3*R*)-3-phenyl-2-(2'-phenylsulfanyl-acetyl)-3,4-dihydro-2*H*-isoquinolin-1-one was used directly in the next step.

Conversion: ≥ 90% (^{1}H-NMR)

^{1}H-NMR (300 MHz, $CDCl_3$):
δ = 3.24 (dd, *J* = 1.7 Hz, *J* = 16.3 Hz, 1H, NCHC*H*$_2$), 3.58 (dd, *J* = 5.8 Hz, *J* = 16.3 Hz, 1H, NCHC*H*$_2$), 4.52 (dd, *J* = 1.5 Hz, 2H, C*H*$_2$S), 6.10 (d, *J* = 5.8 Hz, 1H, NC*H*CH$_2$), 7.06-7.47 (m, 13H, C*H*$_{arom}$), 8.14 (d, *J* = 7.7 Hz, 1H, C*H*CCO) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):
δ = 34.12, 42.38, 54.72, 126.01, 126.75, 126.92, 127.34, 127.50, 128.04, 128.48, 128.72, 128.93, 129.29, 130.26, 134.18, 137.29, 139.41, 165.78, 172.18 ppm.

In a 100 mL flask a solution of (3*R*)-3-phenyl-2-(2'-phenylsulfanyl-acetyl)-3,4-dihydro-2*H*-isoquinolin-1-one (max. 0.44 mmol) in CH_2Cl_2 (10 mL) and 10% aqueous Na_2CO_3 (5 mL)

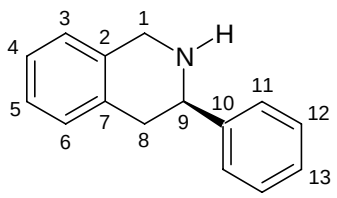
were vigourously stirred at 0 °C. A solution of *m*-CPBA (0.109 g, 0.44 mmol, 70-75% in H_2O) in CH_2Cl_2 (5 mL) was added dropwise over 45 min. After another 10 min at 0 °C, the organic layer was separated and the aqueous phase was extracted once with CH_2Cl_2 (10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was used in the next step without further purification.

Conversion: ~ 81% (^{13}C-NMR)

^{1}H-NMR (300 MHz, $CDCl_3$, mixture of diastereomers):
δ = 3.22 (dd, *J* = 1.6 Hz, *J* = 18.7 Hz, 1H, NCHC*H*$_2$ (min.)), 3.25 (dd, *J* = 1.6 Hz, *J* = 16.8 Hz, 1H, NCHC*H*$_2$ (maj.)), 3.55 (dd, *J* = 5.8 Hz, *J* = 18.7 Hz, 1H, NCHC*H*$_2$ (min.)), 3.60-3.69 (m, 1H, NCHC*H*$_2$ (maj.)), 4.52-4.65 (m, 3H, C*H*$_2$SO), 4.82 (d, *J* = 14.3 Hz, 1H, C*H*$_2$SO), 6.06 (d, *J* = 5.8 Hz, 1H, NC*H* (min.)), 6.15 (d, *J* = 6.1 Hz, 1H, NC*H* (maj.)), 7.02-7.52 (m, 23H, C*H*$_{arom}$), 7.71-7.78 (m, 3H, C*H*$_{arom}$), 8.02-8.08 (m, 1H, C*H*$_{arom}$), 8.08-8.14 (m, 1H, C*H*$_{arom}$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$, mixture of diastereomers):
δ = 33.91 (C-14 (min.)), 34.01 (C-14 (maj.)), 54.96 (C-15), 67.64 (C-5), 124.26 (C$_{arom}$ (maj.)), 124.44 (C$_{arom}$ (min.)), 125.94 (C$_{arom}$), 127.47 (C$_{arom}$ (maj.)), 127.50 (C$_{arom}$ (min.)), 127.54, 128.53 (C$_{arom}$), 129.23 (C$_{arom}$ (maj.)), 129.29 (C$_{arom}$ (min.)), 131.28 (C$_{arom}$ (maj.)), 131.38 (C$_{arom}$ min.)), 137.38 (C$_{arom}$ (min.)), 134.44 (C$_{arom}$ (maj.)), 137.39, 137.53 (C-8/C-13), 138.98 (C-16 (min.)), 139.05 (C-16 (maj.)), 143.38 (C-4 (maj.)), 143.69 (C-4 (min.)), 165.86 (C-7), 167.70 (C-6 (min.)), 168.06 (C-6 (maj.)) ppm. (the missing peaks were covered by the other peaks).

(*R*)-3-Phenyl-1,2,3,4-tetrahydroisoquinoline [(*R*)-80a]



According to the general procedure GP-6, dihydroisoquinolinone (3R,2'*S*)-**77a** (0.381 g, 1.13 mmol) was reacted with BH_3·THF (23 mL, 22.65 mmol, 1 M in THF). After purification by column chromatography (*n*-pentane/Et_2O = 7/3) (*R*)-**80a** was obtained as a pale yellow oil.

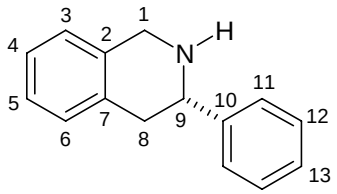
Yield:	m = 0.197 g (0.94 mmol)	83%
GC:	R_t = 8.13 min	(Sil-8, 140-10-300)
TLC:	R_f = 0.10	(*n*-pentane/Et_2O = 1/1)
Optical rotation:	$[\alpha]_D^{23.5}$ = +112.9	(c = 1.39, $CHCl_3$)
ee:	= 97%	(Chiralcel OJ, *n*-heptane/*i*-PrOH = 98/2, R_t = 38.45 min, λ = 214 nm)

^{1}H-NMR (300 MHz, $CDCl_3$):
δ = 2.15 (br, 1H, N*H*), 2.94 (d, *J* = 7.1 Hz, 2H, NCHCH_2), 3.98 (t, *J* = 7.1 Hz, 1H, NC*H*CH_2), 4.14 (d, *J* = 15.7 Hz, 1H, NCH_2CCH), 4.24 (d, *J* = 15.7 Hz, 1H, NCH_2CCH), 7.03-7.18 (m, 4H, CH_{arom}), 7.23-7.45 (m, 5H, CH_{arom}) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):
δ = 37.65 (C-8), 49.17 (C-1), 58.53 (C-9), 125.84, 126.12, 126.20, 126.49, 127.34 (C_{arom}), 128.57 (C-12), 129.04 (C_{arom}), 134.82, 134.91 (C-2/C-7), 144.22 (C-10) ppm.

All other analytical data correspond to those reported in the literature.[133]

(3*S*)-3-Phenyl-1,2,3,4-tetrahydroisoquinoline [(*S*)-80a]



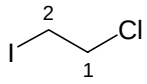
According to the general procedure GP-6, dihydroisoquinolinone (3*S*,2'*R*)-**77a** (0.809 g, 2.41 mmol) was reacted with BH_3·THF (48 mL, 48.09 mmol, 1 M in THF). After purification by column chromatography (*n*-pentane/Et_2O = 7/3) (*S*)-**80a** was obtained as a pale yellow oil.

Yield:	m = 0.428 g (2.04 mmol)	84%

Optical rotation:	$[\alpha]_D^{25} = -137.5$	(c = 1.03, $CHCl_3$)
ee:	= 97%	(Chiralcel OJ, *n*-heptane/*i*-PrOH = 98/2, R_t = 43.44 min, λ = 214 nm)

All other analytical data correspond to those of the other enantiomer (*R*)-**80a**.

1-Chloro-2-iodo-ethane [144]



Sodium iodide (30.0 g, 200.0 mmol) was placed in a Soxhlet socket and extracted with the condensate from the vapours of a boiling mixture of 1,2-dichloroethane (500 mL) and acetone (200 mL) during 21 h. The acetone was distilled from the reaction mixture which was then washed 2 times with sat. aqueous $Na_2S_2O_5$ (500 mL), dried over $MgSO_4$ and filtered. The solution was fractionally distilled to yield **144** as a brown liquid.

Yield:	m = 15.387 g (80.8 mmol)	40%
GC:	R_t = 3.08 min	(Sil-8, 40-10-300)
bp:	133 °C	(Lit.[134] 137-139 °C)

^{1}H-NMR (300 MHz, $CDCl_3$):
δ = 3.38-3.45 (m, 2H, C*H*$_2$I), 3.78-3.86 (m, 2H, C*H*$_2$Cl) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):
δ = 2.35 (C-2), 43.73 (C-1) ppm.

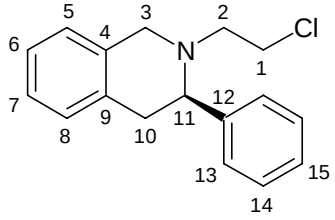
MS (EI):
m/z (%) = 192 ($M^{\bullet+}$, 10), 190 ($M^{\bullet+}$, 34), 65 (28), 63 (100).

IR (capillary):
ν = 2970 (w), 1434 (s), 1276 (m), 1234 (s), 1163 (vs), 1047 (m), 906 (w), 822 (s), 708 (vs), 659 (m), 576 (vs).

Elementary analysis:

Anal. Calcd. for C_2H_4ClI:	C = 12.62	H = 2.12
Found:	C = 12.65	H = 2.51

(3*R*)-2-(2'-Chloro-ethyl)-3-phenyl-1,2,3,4-tetrahydroisoquinoline [(*R*)-145]



In a 5 mL flask under argon, BH_3·THF (0.89 mL, 0.89 mmol, 1 M in THF) was added to a solution of crude chloroacetyl (*R*)-**130** (max. 0.20 mmol) in abs. THF (2 mL). The reaction mixture was heated to reflux for 2 h and then cooled to 0 °C. MeOH (1.5 mL) was carefully added and the mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The organic phase was kept and the remaining aqueous phase was extracted 2 times with CH_2Cl_2 (10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was absorbed over silica and purified by column chromatography (*n*-pentane/Et_2O = 15/1) to give (*S*)-**145** as a colourless syrup.

Yield:	m = 0.032 g (0.12 mmol)	60%
GC:	R_t = 12.76 min	(Sil-8, 120-10-300)
TLC:	R_f = 0.46	(*n*-pentane/Et_2O = 15/1)
Optical rotation:	$[\alpha]_D^{20}$ = +69.1	(c = 0.49, $CHCl_3$)
ee:	= 95%	(Chiralpak AD, *n*-heptane/*i*-PrOH = 98/2, R_t = 9.75 min, λ = 214 nm)

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 2.58 (dt, *J* = 6.6 Hz, *J* = 13.5 Hz, 1H, NC*H*$_2$CH$_2$Cl), 2.92 (dt, *J* = 7.4 Hz, *J* = 13.5 Hz, 1H, NC*H*$_2$CH$_2$Cl), 3.03 (dd, *J* = 4.7 Hz, *J* = 16.5 Hz, 1H, NCHC*H*$_2$), 3.13 (dd, *J* = 9.1 Hz, *J* = 16.5 Hz, 1H, NCHC*H*$_2$), 3.54 (t, *J* = 7.4 Hz, 2H, NCH$_2$C*H*$_2$Cl), 3.75-3.82 (m, 2H, NC*H*CH$_2$, NC*H*$_2$CCH), 4.11 (d, *J* = 15.4 Hz, 1H, NC*H*$_2$CCH), 7.06-7.11 (m, 2H, C*H*$_{arom}$), 7.14-7.18 (m, 2H, C*H*$_{arom}$), 7.26-7.38 (m, 5H, C*H*$_{arom}$) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 36.82 (C-10), 41.51 (C-1), 54.70 (C-3), 55.51 (C-2), 63.95 (C-11), 125.77, 126.05, 126.27, 127.42 (C_{arom}), 127.70 (C-13), 128.01, 128.26 (C_{arom}), 128.46 (C-14), 133.67, 133.90 (C-4/C-9), 141.85 (C-12) ppm.

MS (EI):

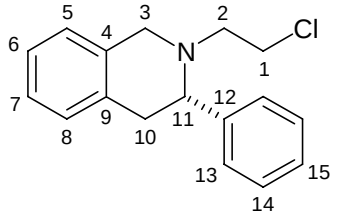
m/z (%) = 271 ($M^{\bullet+}$, 8), 223 (16), 222 ($M^{\bullet+}$–$COCH_2Cl$, 100), 194 (17), 193 (42), 115 (13), 104 (33).

IR (in $CHCl_3$):

ν = 3062 (w), 3027 (m), 2925 (m), 2836 (w), 2794 (w), 1715 (w), 1659 (m), 1604 (w), 1495 (m), 1452 (s), 1379 (w), 1316 (w), 1257 (w), 1219 (w), 1134 (w), 1105 (w), 754 (vs), 702 (s), 666 (w).

A correct elementary analysis could not be obtained due to the insufficient stability of the product.

(3*S*)-2-(2'-Chloro-ethyl)-3-phenyl-1,2,3,4-tetrahydroisoquinoline [(*S*)-145]



Method A:

In a 10 mL Schlenk flask under argon, a solution of crude chloroacetyl (*S*)-**130** (max. 0.48 mmol) in abs. THF (2 mL) was added dropwise to a suspension of $LiAlH_4$ (0.109 g, 2.87 mmol) in abs. THF (4 mL). After 2 h at room temperature, the reaction was carefully quenched with H_2O (1.5 mL). The organic phase was washed successively with 10% aqueous NaOH (2.5 mL) and H_2O (2.5 mL). The combined aqueous phases were then extracted with $CHCl_3$ (10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was absorbed in silica and purified by column chromatography (*n*-pentane/Et_2O = 15/1) to yield (*S*)-**145** as a colourless syrup.

Yield:	m = 0.040 g (0.15 mmol)	31%
ee:	= 93%	(Chiralpak AD, *n*-heptane/*i*-PrOH = 98/2, R_t = 12.04 min, λ = 214 nm)

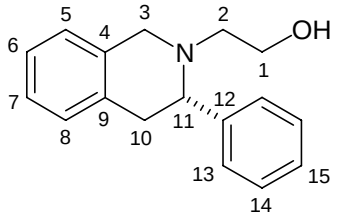
Method B:

In a 25 mL Schlenk flask under argon, a solution of alcohol (*S*)-**148** (0.101 g, 0.40 mmol) in abs. CH_2Cl_2 (13 mL) was cooled to 0 °C. Et_3N (61 µL, 0.44 mmol) and methanesulfonyl chloride (34 µL, 0.44 mmol) were successively added. After 5 min at 0 °C the temperature was increased to room temperature and the reaction mixture was stirred for 5 h. The reaction was then diluted with CH_2Cl_2 and the organic phase was washed 2 times with sat. aqueous $NaHCO_3$ and 2 times with H_2O. After drying over $MgSO_4$, filtration and concentration under reduced pressure, the residue was absorbed in silica and purified by column chromatography (*n*-pentane/Et_2O = 20/1) to yield (*S*)-**145** as a colourless syrup.

Yield:	m = 0.066 g (0.24 mmol)	60%
Optical rotation:	$[\alpha]_D^{24}$ = –61.6	(c = 0.88, $CHCl_3$) (*ee* = 97%)
ee:	= 97%	(Chiralpak AD, *n*-heptane/*i*-PrOH = 98/2, R_t = 12.21 min, λ = 254 nm)

All other analytical data correspond to those of the other enantiomer (*R*)-**145**.

2-((3'*S*)-3'-Phenyl-3',4'-dihydro-1*H*-isoquinolin-2'-yl)-ethanol [(*S*)-148]



According to the general procedure GP-7, tetrahydroisoquinoline (*S*)-**80a** (0.238 g, 1.14 mmol), 2-iodoethanol (0.10 mL, 1.25 mmol) and $NaHCO_3$ (0.105 g, 1.25 mmol) were heated to reflux for 24 h. The resulting crude mixture was purified by column chromatography (*n*-pentane/Et_2O = 1/2) to yield (*S*)-**148** as a colourless syrup.

Yield:	m = 0.239 g (0.94 mmol)	82%

GC:	R_t = 10.64 min	(Sil-8, 140-10-300)
TLC:	R_f = 0.18	(*n*-pentane/Et_2O = 1/2)
Optical rotation:	$[\alpha]_D^{26}$ = –42.6	(c = 0.35, $CHCl_3$)
ee:	≥ 97%	(deduced from the *ee* obtained for the corresponding chloride (*S*)**-145)**

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 2.32 (dt, *J* = 4.7 Hz, *J* = 12.6 Hz, 1H, NC*H*$_2$CH$_2$OH), 2.61 (br, 1H, O*H*), 2.71-2.79 (m, 1H, NC*H*$_2$CH$_2$OH), 3.06-3.19 (m, 2H, NCHC*H*$_2$), 3.50 (dt, *J* = 4.7 Hz, *J* = 11.0 Hz, 1H, NCH$_2$C*H*$_2$OH), 3.63 (d, *J* = 15.4 Hz, 1H, NC*H*$_2$CCH), 3.63-3.73 (m, 1H, NCH$_2$C*H*$_2$OH), 3.82 (dd, *J* = 5.5 Hz, *J* = 8.0 Hz, 1H, NC*H*CH$_2$), 4.2 (d, *J* = 15.4 Hz, 1H, NC*H*$_2$CCH), 7.05-7.13 (m, 2H, C*H*$_{arom}$), 7.15-7.20 (m, 2H, C*H*$_{arom}$), 7.24-7.36 (m, 5H, C*H*$_{arom}$) ppm

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 36.09 (C-10), 53.24 (C-3), 54.76 (C-2), 58.19 (C-1), 63.75 (C-11), 125.74, 126.13, 126.28, 127.34 (C_{arom}), 127.82 (C-13), 128.04 (C_{arom}), 128.42 (C-14), 133.79, 133.98 (C-4/C-9), 141.50 (C-12) ppm.

MS (EI):

m/z (%) = 253 ($M^{\bullet+}$, 4), 223 (18), 222 ($M^{\bullet+}$–CH_2CH_2OH, 100), 193 (49), 178 (10), 115 (19).

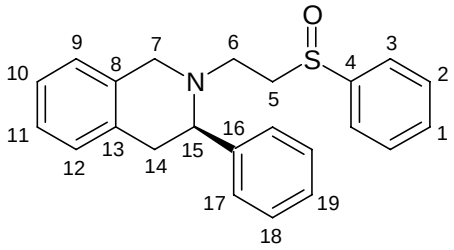
IR (in $CHCl_3$):

ν = 3400 (w), 3063 (w), 3011 (w), 2926 (m), 2829 (w), 1495 (w), 1452 (m), 1376 (w), 1217 (w), 1132 (w), 1102 (w), 1060 (m), 1034 (m), 973 (w), 754 (vs), 703 (m), 667 (w).

HRMS:

m/z Calcd. for $C_{17}H_{19}NO$ ($M^{\bullet+}$):	253.1466
Found:	253.1466

(3*R*)-2-(2'-Phenylsulfinyl-ethyl)-3-phenyl-1,2,3,4-tetrahydroisoquinoline [(*R*)-152]



In a 10 mL flask under argon, a solution of tetrahydroisoquinoline (*R*)-**80a** (0.161 g, 0.77 mmol) and phenyl vinyl sulfoxide (0.15 mL, 1.15 mmol) in abs. MeOH (2.7 mL) was heated to reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (*n*-pentane/Et_2O = 1/3 then pure Et_2O) to yield (*R*)-**152** as a pale yellow oil.

Yield:		m = 0.248 g (0.69 mmol)	90%
HPLC:	(maj.)	R_t = 13.12 min	(LiChrosorb Si 60 7µ; pure Et_2O; λ = 254 nm)
	(min.)	R_t = 15.03 min	(LiChrosorb Si 60 7µ; pure Et_2O; λ = 254 nm)
TLC:		R_f = 0.15	(*n*-pentane/Et_2O = 1/3)
dr:		= 57/43	(LiChrosorb Si 60 7µ; pure Et_2O; λ = 254 nm)

^{1}H-NMR (400 MHz, $CDCl_3$, mixture of diastereomers):
δ = 2.46-2.53 (m, 1H, CH_2SO), 2.70-3.15 (m, 11H, CH_2CH$_2$SO, CH_2SO, NCHCH_2), 3.67 (d, *J* = 15.2 Hz, 1H, NCH_2C), 3.69-3.78 (m, 3H, NCH_2C, NC*H*), 3.97 (d, *J* = 15.2 Hz, 1H, NCH_2C), 3.98 (d, *J* = 15.2 Hz, 1H, NCH_2C), 7.01-7.09 (m, 4H, CH_{arom}), 7.12-7.16 (m, 4H, CH_{arom}), 7.23-7.32 (m, 10H, CH_{arom}), 7.39-7.48 (m, 8H, CH_{arom}), 7.50-7.54 (m, 2H, CH_{arom}) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, mixture of diastereomers):
δ = 36.51 (C-14 (min.)), 36.69 (C-14 (maj.)), 47.06 (C-5 (maj.)), 47.41 (C-5 (min.)), 53.90 (C-7 (maj.)), 53.99 (C-7 (min.)), 55.28 (C-6 (maj.)), 55.33 (C-6 (min.)), 63.60 (C-15 (min.)), 63.75 (C-15 (maj.)), 123.68 (C-3 (maj.)), 123.72 (C-3 (min.)), 125.67, 126.00 (C_{arom}), 126.20

(C_{arom} (maj.)), 126.23, 127.33 (C_{arom} (min.)), 127.41 (C_{arom} (maj.)), 127.73 (C_{arom}), 127.88 (C_{arom} (min.)), 127.94 (C_{arom} (maj.)), 128.31 (C_{arom} (min.)), 128.39 (C_{arom} (maj.)), 128.90 (C-2), 130.57 (C-1), 133.56, 133.86 (C-8/C-13), 141.30 (C-4 (maj.)), 141.35 (C-4 (min.)), 143.60 (C-16 (min.)), 143.88 (C-16 (maj.)) ppm.

MS (EI):

m/z (%) = 345 (23), 344 ($M^{\bullet+}$–OH, 100), 235 (12), 234 (16), 193 (14), 137 (35), 115 (14), 104 (19).

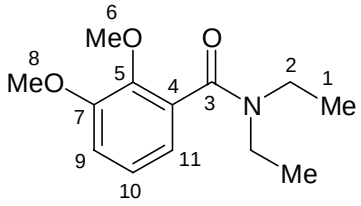
IR (capillary):

ν = 3058 (s), 3028 (m), 2921 (s), 2793 (m), 2723 (w), 1588 (w), 1494 (s), 1448 (s), 1377 (w), 1134 (w), 1097 (s), 1043 (vs), 966 (w), 746 (vs), 700 (vs), 556 (w).

HRMS:

m/z Calcd. for $C_{23}H_{22}NS$ ($M^{\bullet+}$–OH):	344.1473
Found:	344.1472

***N*,*N*-Diethyl-2,3-dimethoxy-benzamide [154]**



In a 500 mL flask oxalyl chloride (13 mL, 150.0 mmol) was added dropwise to a solution of 2,3-dimethoxybenzoic acid (18.218 g, 100.0 mmol) and anhydrous DMF (0.77 mL, 10.0 mmol) in CH_2Cl_2 (200 mL). The reaction mixture was stirred 1 h at room temperature and the solvent was evaporated under reduced pressure. The residue was coevaporated 2 times with benzene. The crude acyl chloride was dissolved in CH_2Cl_2 (200 mL) and the temperature was decreased to –45 °C. Et_2NH (41 mL, 400.0 mmol) was added dropwise and the temperature was allowed to increase slowly to room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 and the organic phase was washed successively with H_2O, 1 N aqueous HCl and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated

under reduced pressure. The resulting crude mixture was purified by column chromatography (*n*-pentane/Et_2O = 1/2) to give **154** as a pale yellow liquid.

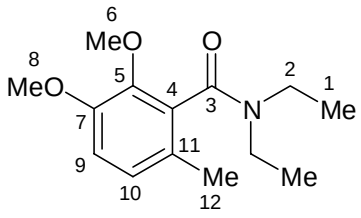
Yield:	m = 21.818 g (91.9 mmol)	92%
GC:	R_t = 9.98 min	(Sil-8, 100-10-300)
TLC:	R_f = 0.22	(*n*-pentane/Et_2O = 1/2)

^{1}H-NMR (300 MHz, $CDCl_3$, mixture of rotamers):
δ = 1.04 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.25 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 3.16 (qd, *J* = 2.5 Hz, *J* = 7.2 Hz, 2H, CH_2CH_3), 3.35-3.57 (br, 1H, CH_2CH_3), 3.64-3.78 (br, 1H, CH_2CH_3), 3.85 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.78-6.83 (m, 1H, CH_3OCCH), 6.92 (dd, *J* = 1.5 Hz, *J* = 8.2 Hz, 1H, O=CCCH), 7.07 (dd, *J* = 8.2 Hz, 1H, $CH_3OCCHCH$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$, mixture of rotamers):
δ = 12.81 (C-1'), 13.99 (C-1), 38.91 (C-2'), 43.01 (C-2), 55.82 (C-8), 61.53 (C-6), 112.59 (C-11), 118.85 (C-9), 124.62 (C-10), 132.48 (C-4), 144.79 (C-5), 152.70 (C-7), 168.39 (C-3) ppm.

All other analytical data correspond to those reported in the literature.[135]

***N*,*N*-Diethyl-2,3-dimethoxy-6-methyl-benzamide [117]**



In a 500 mL Schlenk flask under argon, a solution of TMEDA (7.9 mL, 52.5 mmol) in abs. THF (200 mL) was cooled to −78 °C. *s*-BuLi (40.4 mL, 52.50 mmol, 1.3 M in hexane) was rapidly added and the reaction mixture was stirred at −78 °C for 15 min. A solution of 2,3-dimethoxy benzamide **154** (11.865 g, 50.0 mmol) in abs. THF (50 mL) was added and the reaction was stirred for 1 h 30 min. Methyl iodide (15.6 mL, 250.0 mmol) was rapidly added and the reaction was warmed up slowly overnight. The reaction was quenched with H_2O and the organic layer was kept. The aqueous phase was extracted 2 times with Et_2O and the

combined organic layers were washed with H_2O and brine. After drying over $MgSO_4$, filtration and concentration under reduced pressure, the resulting crude mixture was purified by column chromatography (*n*-hexane/acetone = 4/1) providing **117** as a pale yellow oil.

Remark: in order to obtain a good yield in the next step (formation of the dihydroisoquinolinone **156**), **117** should be absolutely free of the non-substituted and the dimethyl-substituted benzamide. An appropriate 60 cm column filled with silica should be used for the purification.

Yield:	m = 10.926 g (43.5 mmol)	87%
GC:	R_t = 11.95 min	(Sil-8, 100-10-300)
TLC:	R_f = 0.20	(*n*-pentane/Et_2O = 1/1)

^{1}H-NMR (400 MHz, $CDCl_3$):
δ = 1.04 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.26 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 2.19 (s, 3H, CCH_3), 3.03-3.23 (m, 2H, CH_2CH_3), 3.47-3.72 (m, 2H, CH_2CH_3), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.80 (d, *J* = 8.4 Hz, 1H, CH_3OCCH), 6.89 (d, *J* = 8.4 Hz, 1H, CH_3CCH) ppm.

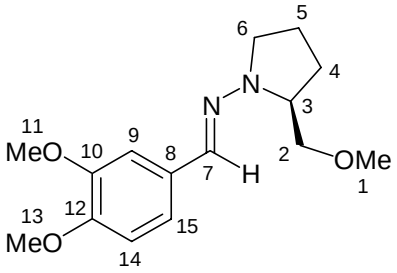
^{13}C-NMR (100 MHz, $CDCl_3$):
δ = 12.71 (C-1), 13.81 (C-1'), 17.97 (C-12), 38.54 (C-2), 42.61 (C-2'), 55.72 (C-8), 61.39 (C-6), 111.99 (C-9), 125.49 (C-10), 126.42 (C-4), 132.11 (C-11), 144.37 (C-5), 150.34 (C-7), 167.63 (C-3) ppm.

Elementary analysis:

Anal. Calcd. for $C_{14}H_{21}NO_3$:	C = 66.91	H = 8.42	N = 5.57
Found:	C = 66.72	H = 8.80	N = 5.87

All other analytical data correspond to those of the literature.[135a]

[1-(3',4'-Dimethoxy-phenyl)-meth-(1*E*)-ylidene]-((2''*S*)-2''-methoxymethyl-pyrrolidin-1''-yl)-amine [(*S*)-127]



According to the general procedure GP-1, 3,4-dimethoxybenzaldehyde (3.988 g, 24.0 mmol) and SAMP (2.791 g, 20.0 mmol, 93% purity (GC)) were reacted overnight. After distillation under high vacuum using a microdistillation apparatus (*S*)-**127** was obtained as an orange syrup.

Yield:	m = 5.466 g (19.6 mmol)	98%
GC:	R_t = 15.67 min	(Sil-8, 100-10-300)
bp:	136 °C/0.1-0.01 mbar	
Optical rotation:	$[\alpha]_D^{25} = -114.7$	(c = 0.89, $CHCl_3$)

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 1.78-2.08 (m, 4H, $NCH_2CH_2CH_2$), 2.94-3.05 (m, 1H, NCH_2), 3.40 (s, 3H, CH_2OCH_3), 3.42-3.53 (m, 2H, NCH_2, OCH_2), 3.59-3.72 (m, 2H, OCH_2, NCH), 3.86 (s, 3H, $COCH_3$), 3.92 (s, 3H, $COCH_3$), 6.80 (d, *J* = 8.2 Hz, 1H, $CH_3OCCHCH$), 6.96 (dd, *J* = 1.8 Hz, *J* = 8.2 Hz, 1H, N=CHCCHCH), 7.20 (s, 1H, N=CH), 7.25 (d, *J* = 1.8 Hz, 1H, N=CHCCHCO) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = 22.23 (C-5), 26.83 (C-4), 49.37 (C-6), 55.78, 55.89 (C-11/C-13), 59.26 (C-1), 63.18 (C-3), 74.77 (C-2), 107.17 (C-9), 110.04 (C-14), 119.04 (C-15), 130.59 (C-8), 133.05 (C-7), 148.59, 149.19 (C-10/C-12) ppm.

MS (EI):

m/z (%) = 278 ($M^{\bullet+}$, 32), 234 (16), 233 ($M^{\bullet+}$–CH_2OCH_3, 100), 70 (18).

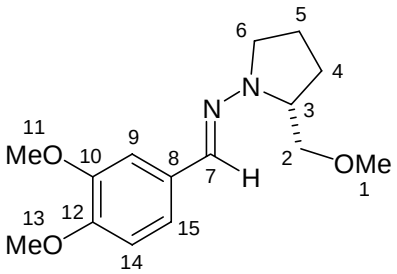
IR (capillary):

ν = 3075 (w), 2933 (vs), 2833 (vs), 1597 (vs), 1563 (s), 1513 (vs), 1461 (s), 1416 (s), 1379 (m), 1342 (m), 1268 (s), 1229 (w), 1166 (w), 1118 (s), 1028 (vs), 973 (m), 885 (s), 807 (s), 758 (vs), 668 (w), 626 (m), 607 (m), 565 (w), 528 (w), 480 (w).

Elementary analysis:

Anal. Calcd. for $C_{15}H_{22}N_2O_3$:	C = 64.73	H = 7.97	N = 10.06
Found:	C = 64.91	H = 7.52	N = 10.26

[1-(3',4'-Dimethoxy-phenyl)-meth-(1*E*)-ylidene]-((2''*R*)-2''-methoxymethyl-pyrrolidin-1''-yl)-amine [(*R*)-127]

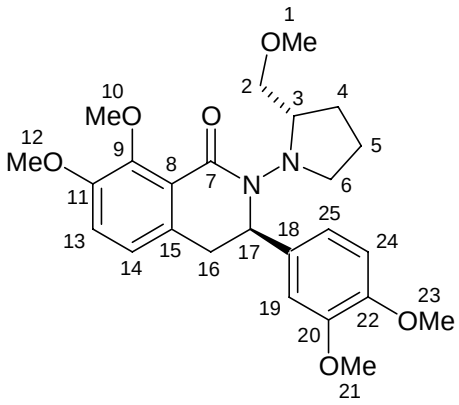


According to the general procedure GP-1, 3,4-dimethoxybenzaldehyde (3.988 g, 24.0 mmol) and RAMP (3.493 g, 20.0 mmol, 75% purity (GC)) were reacted overnight. After distillation under high vacuum using a microdistillation apparatus (*R*)**-127** was collected as a pale yellow syrup.

Yield:	m = 5.539 g (19.9 mmol)	quant.
Optical rotation:	$[\alpha]_D^{28}$ = +114.1	(c = 1.27, $CHCl_3$)

All other analytical data correspond to those of the other enantiomer (*S*)**-127**.

(3*R*)-3-(3',4'-Dimethoxy-phenyl)-7,8-dimethoxy-2-((2''*S*)-2''-methoxymethyl-pyrrolidin-1''-yl)-3,4-dihydro-2*H*-isoquinolin-1-one [(3*R*,2''*S*)-156]



In a 250 mL Schlenk flask under argon, *s*-BuLi (7.5 mL, 9.75 mmol, 1.3 M in hexane) was added to a solution of TMEDA (1.59 mL, 10.50 mmol) in abs. THF (10 mL) and abs. Et_2O (50 mL) at −78 °C. After 15 min a solution of 2,3-dimethoxy-6-methyl benzamide **117** (2.639 g, 10.50 mmol) in abs. Et_2O (10 mL) was added dropwise. The temperature was increased to −40 °C and a solution of SAMP-hydrazone (*S*)**-127** (0.418g, 1.50 mmol) in abs. Et_2O (6 mL), previously complexed with $AlMe_3$ (2.3 mL, 4.65 mmol, 2 M in heptane) for at least 1 h, was added dropwise over 45 min. The reaction mixture was stirred overnight (17 h) at −40 °C. The reaction was quenched with 10% aqueous potassium and sodium tartrate (10 mL) and sat. aqueous NH_4Cl (10 mL). After phase separation, the aqueous layer was extracted 4 times with Et_2O (30 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography (*n*-pentane/AcOEt = 1/2) to yield (3*R*,2''*S*)**-156** as a pale yellow syrup.

Yield:	m = 0.375 g (0.82 mmol)	55%
GC:	R_t = 15.64 min	(Sil-8, 180-10-300)
TLC:	R_f = 0.24	(pure Et_2O)
Optical rotation:	$[\alpha]_D^{24}$ = +21.18	(c = 1.67, $CHCl_3$)
de:	≥ 96%	(^{1}H-NMR)

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 1.40-1.53 (m, 1H, $NCH_2CH_2CH_2$), 1.56-1.72 (m, 1H, $NCH_2CH_2CH_2$), 1.88-2.02 (m, 1H, $NCH_2CH_2CH_2$), 2.06-2.20 (m, 1H, $NCH_2CH_2CH_2$), 2.83 (dd, *J* = 2.2 Hz, *J* = 15.3 Hz, 1H,

O=CNCHC*H*$_2$), 2.95 (dt, *J* = 3.7 Hz, *J* = 7.7 Hz, 1H, NC*H*$_2$), 3.40 (s, 3H, CH$_2$OC*H*$_3$), 3.38-3.50 (m, 2H, OC*H*$_2$), 3.65-3.91 (m, 2H, NC*H*$_2$, O=CNCHC*H*$_2$), 3.73 (s, 3H, COC*H*$_3$), 3.78 (s, 3H, COC*H*$_3$), 3.81 (s, 3H, COC*H*$_3$), 3.98 (s, 3H, COC*H*$_3$), 4.10-4.22 (br, 1H, NC*H*), 4.98 (dd, *J* = 2.2 Hz, *J* = 6.2 Hz, 1H, O=CNC*H*CH$_2$), 6.62-6.69 (m, 4H, C*H*$_{arom}$), 6.84 (d, *J* = 8.4 Hz, 1H, C*H*$_{arom}$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = 22.89 (C-5), 26.83 (C-4), 36.99 (C-16), 51.70 (C-6), 55.67, 55.75, 56.12 (C-10/C-12/C-21/C-23), 58.90 (C-1), 59.85 (C-3), 61.61 (C-10/C-12/C-21/C-23), 65.82 (C-17), 77.17 (C-2), 109.83, 110.77, 115.30, 118.73, 122.84 (C_{arom}), 124.56 (C-8), 128.93 (C-15), 133.38 (C-18), 147.56, 148.52, 149.81, 152.70 (C-9/C-11/C-20/C-22), 161.81 (C-7) ppm.

MS (EI):

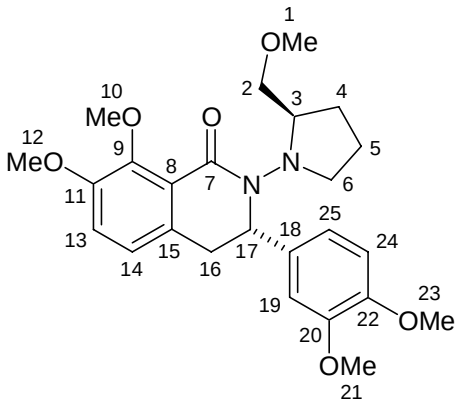
m/z (%) =456 ($M^{\bullet+}$, 1), 412 (24), 411 ($M^{\bullet+}$–CH_2OCH_3, 87), 344 (24), 343 ($M^{\bullet+}$–SMP+1, 100), 342 (14), 327 (15), 325 (18), 324 (12), 312 (17), 205 (15), 192 (10), 178 (11), 166 (11), 151 (46).

IR (in $CHCl_3$):

ν = 3001 (s), 2937 (vs), 2876 (s), 2836 (s), 1653 (vs), 1581 (m), 1516 (vs), 1484 (vs), 1455 (vs), 1419 (vs), 1389 (m), 1351 (w), 1302 (s), 1265 (vs), 1140 (s), 1102 (m), 1064 (m), 1033 (vs), 1002 (m), 956 (w), 906 (w), 855 (w), 810 (w), 792 (m), 755 (vs), 666 (w).

A correct elementary analysis could not be obtained.

(3*S*)-3-(3',4'-Dimethoxy-phenyl)-7,8-dimethoxy-2-((2''*R*)-2''-methoxymethyl-pyrrolidin-1''-yl)-3,4-dihydro-2*H*-isoquinolin-1-one [(3*S*,2''*R*)-156]

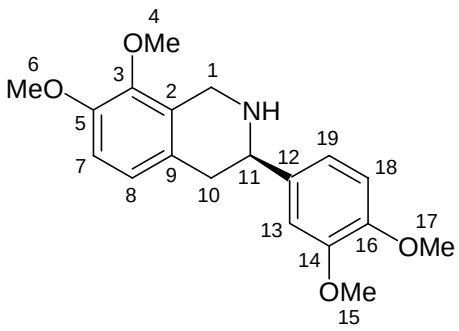


According to the procedure described for (3*R*,2''*S*)-**156**, *s*-BuLi (7.5 mL, 9.75 mmol, 1.3 M in hexane), TMEDA (1.59 mL, 10.50 mmol), 2,3-dimethoxy-6-methyl benzamide **117** (2.639 g, 10.50 mmol), RAMP-hydrazone (*R*)-**127** (0.418 g, 1.50 mmol) and trimethylaluminium (2.3 mL, 4.65 mmol, 2 M in heptane) were reacted overnight (17 h). The crude mixture was purified 2 times by column chromatography (pure Et_2O) to yield (3*S*,2''*R*)-**156** as a pale yellow syrup.

Yield:	m = 0.371 g (0.81 mmol)	54%
Optical rotation:	$[\alpha]_D^{30} = -20.76$	(c = 0.79, $CHCl_3$)
de:	≥ 96%	(^{1}H-NMR)

All other analytical data correspond to those of the other enantiomer (3*R*,2''*S*)-**156**.

(3*R*)-3-(3',4'-Dimethoxy-phenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*R*)-142]



According to the general procedure GP-6, dihydroisoquinolinone (3*R*,2''*S*)-**156** (0.126 g, 0.28 mmol) was reacted with BH_3·THF (5.5 mL, 5.52 mmol, 1 M in THF). After purification by column chromatography (*n*-hexane/acetone = 1/1) (*R*)-**142** was obtained as a champagne-beige solid.

Yield:	m = 0.075 g (0.23 mmol)	82%
GC:	R_t = 13.63 min	(Sil-8, 160-10-300)
TLC:	R_f = 0.09	(Et_2O/MeOH = 20/1)
mp:	103-104 °C	
Optical rotation:	$[\alpha]_D^{30}$ = +81.6	(c = 0.70, $CHCl_3$)
ee:	= 99%	(Chiralpak AD; *n*-heptane/*i*-PrOH = 65/35; R_t = 14.96 min; λ = 214 nm)

^{1}H-NMR (400 MHz, $CDCl_3$):
δ = 1.99 (br, 1H, N*H*), 2.86-2.96 (m, 2H, NCHCH_2), 3.83-3.91 (m, 1H, NC*H*CH_2), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.10 (d, *J* = 16.4 Hz, 1H, NCH_2), 4.36 (d, *J* = 16.4 Hz, 1H, NCH_2), 6.78 (d, *J* = 8.5 Hz, 1H, CH_{arom}), 6.82 (d, *J* = 8.5 Hz, 1H, CH_{arom}), 6.85 (d, *J* = 8.2 Hz, 1H, NCHCCHC*H*), 6.95 (dd, *J* = 1.9 Hz, *J* = 8.2 Hz, 1H, NCHCC*H*CH), 7.02 (d, *J* = 1.9 Hz, 1H, NCHCC*H*$COCH_3$) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):
δ = 37.26 (C-10), 44.75 (C-1), 55.83, 55.86 (C-4/C-6/C-15/C-17), 58.15 (C-11), 60.02 (C-4/C-6/C-15/C-17), 109.44 (C-13), 110.70, 110.91 (C-7/C-8/C-18), 118.50 (C-19), 123.92 (C-7/C-8), 127.99, 128.73 (C-2/C-9), 136.86 (C-12), 145.14, 148.03, 148.91, 150.09 (C-3/C-5/C-14/C-16) ppm. (the missing peak was covered by the other signals).

MS (EI):
m/z (%) = 330 ($M^{\bullet+}$+1, 10), 329 ($M^{\bullet+}$, 49), 328 (11), 165 (14), 164 ($(CH_3O)_2C_6H_3(C_2H_2)^+$, 100), 149 (40).

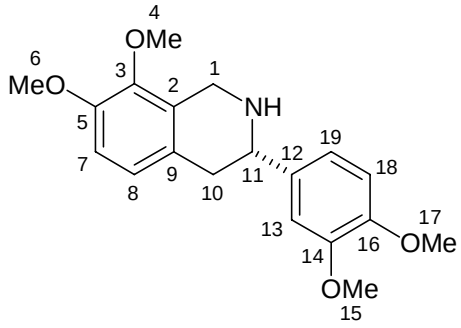
IR (KBr):

ν = 3976 (m), 3948 (w), 3905 (w), 3855 (w), 3459 (vs), 3330 (s), 3236 (s), 2990 (s), 2936 (vs), 2831 (s), 1596 (s), 1515 (vs), 1492 (vs), 1461 (vs), 1421 (vs), 1360 (w), 1323 (m), 1272 (vs), 1228 (vs), 1157 (vs), 1080 (m), 1030 (vs), 869 (s), 800 (vs), 758 (s), 654 (w).

Elementary analysis:

Anal. Calcd. for $C_{19}H_{23}NO_4$:	C = 69.28	H = 7.04	N = 4.25
Found:	C = 69.48	H = 7.36	N = 4.38

(3*S*)-3-(3',4'-Dimethoxy-phenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*S*)-142]

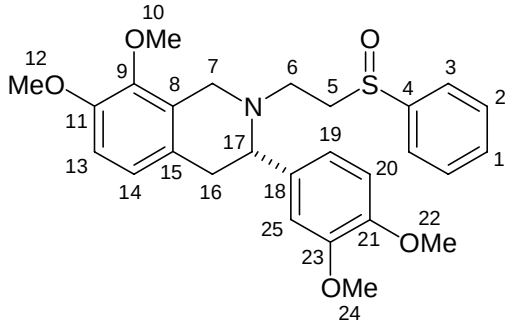


According to the general procedure GP-6, dihydroisoquinolinone (3*S*,2''*R*)-**156** (0.300 g, 0.66 mmol) was reacted with BH_3·THF (13.1 mL, 13.14 mmol, 1 M in THF). After purification by column chromatography (Et_2O/MeOH = 20/1) (*S*)-**142** was obtained as a champagne-beige solid.

Yield:	m = 0.182 g (0.55 mmol)	83%
Optical rotation:	$[\alpha]_D^{27}$ = –94.0	(c = 0.70, $CHCl_3$)
ee:	= 99%	(Chiralpak AD; *n*-heptane/*i*-PrOH = 65/35; R_t = 11.47 min; λ = 214 nm)

All other analytical data correspond to those of the other enantiomer (*R*)-**142**.

(3*S*)-2-(2'-Phenylsulfinyl-ethyl)-3-(3'',4''-dimethoxy-phenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*S*)-141a]



In a 10 mL flask under argon, a solution of tetrahydroisoquinoline (*S*)-**142** (0.109 g, 0.33 mmol) and phenyl vinyl sulfoxide (66 μL, 0.50 mmol) in abs. MeOH (2 mL) was heated to reflux for 22 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (pure Et_2O then Et_2O/MeOH = 20/1) to give (*S*)-**141a** as a yellow syrup.

Yield:		m = 0.150 g (0.31 mmol)	94%
HPLC:	(maj.)	R_t = 21.82 min	(Spherical silica; *n*-heptane/*i*-PrOH = 9/1; λ = 254 nm)
	(min.)	R_t = 27.90 min	(Spherical silica; *n*-heptane/*i*-PrOH = 9/1; λ = 254 nm)
TLC:	(1st diast.)	R_f = 0.56	(Et_2O/MeOH = 20/1)
	(2nd diast.)	R_f = 0.62	(Et_2O/MeOH = 20/1)
dr:		= 64/36	(Spherical silica; *n*-heptane/*i*-PrOH = 9/1; λ = 254 nm)

^{1}H-NMR (400 MHz, $CDCl_3$, mixture of diastereomers):
δ = 2.46-2.54 (m, 1H, C*H*$_2$SO), 2.73-3.18 (m, 11H, NCHC*H*$_2$, C*H*$_2$CH$_2$SO, C*H*$_2$SO), 3.55 (d, *J* = 16.1 Hz, 1H, NC*H*$_2$C (maj.)), 3.58-3.75 (m, 3H, NC*H*$_2$C (min.), NC*H*), 3.78 (s, 3H, OC*H*$_3$), 3.83 (s, 6H, OC*H*$_3$), 3.85 (s, 9H, OC*H*$_3$), 3.88 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 4.06 (d, *J* = 16.2 Hz, 1H, NC*H*$_2$C (min.)), 4.18 (d, *J* = 16.1 Hz, 1H, NC*H*$_2$C (maj.)), 6.75-6.84 (m, 9H, C*H*$_{arom}$), 6.91 (s, 1H, C*H*$_{arom}$), 7.43-7.49 (m, 8H, C*H*$_{arom}$), 7.51-7.55 (m, 2H, C*H*$_{arom}$) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, mixture of diastereomers):

δ = 36.12 (C-16 (min.)), 36.69 (C-16 (maj.)), 47.14 (C-5), 49.36 (C-7 (min.)), 49.54 (C-7 (maj.)), 54.84 (C-6 (min.)), 55.28 (C-6 (maj.)), 55.69, 55.78, 55.83 (C-12/C-22/C-24), 60.11 (C-10 (maj.)), 60.16 (C-10 (min.)), 63.02 (C-17 (min.)), 63.57 (C-17 (maj.)), 110.36, 110.48, 110.62, 110.95 (C-13/C-20/C-25), 119.93 (C-14/C-19 (maj.)), 120.00 (C-14/C-19 (min.)), 123.14 (C-14/C-19), 123.74 (C-3), 127.18 (C-8/C-15 (min.)), 127.29, 127.69 (C-8/C-15 (maj.)), 127.91 (C-8/C-15 (min.)), 128.89 (C-2 (min.)), 128.94 (C-2 (maj.)), 130.64 (C-1), 133.79 (C-18 (min.)), 134.08 (C-18 (maj.)), 143.50 (C-4/C-11/C-21/C-23 (min.)), 143.97 (C-4/C-11/C-21/C-23 (maj.)), 144.97 (C-4/C-11/C-21/C-23), 148.13 (C-4/C-11/C-21/C-23 (min.)), 148.24 (C-4/C-11/C-21/C-23 (maj.)), 148.81 (C-4/C-11/C-21/C-23 (min.)), 149.06 (C-4/C-11/C-21/C-23 (maj.)), 150.07 (C-9) ppm.

MS (EI):

m/z (%) = 466 (10), 465 (31), 464 ($M^{\bullet+}$–OH, 100), 355 (10), 354 (12), 313 (17), 164 (27), 149 (11), 137 (25).

IR (in $CHCl_3$):

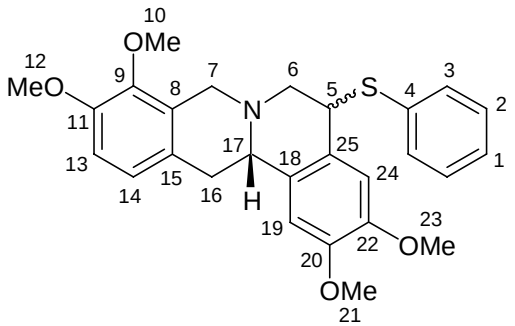
ν = 3013 (m), 2962 (m), 2935 (m), 2836 (w), 1595 (w), 1513 (s), 1497 (s), 1461 (m), 1423 (w), 1263 (s), 1219 (s), 1143 (m), 1083 (m), 1032 (s), 758 (vs), 693 (w), 667 (m).

HRMS:

m/z Calcd. for $C_{27}H_{30}NO_4S$ ($M^{\bullet+}$–OH): 464.1896

Found: 464.1896

(13a*S*)-2,3,9,10-Tetramethoxy-5-phenylsulfanyl-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizine [(*S*)-157]



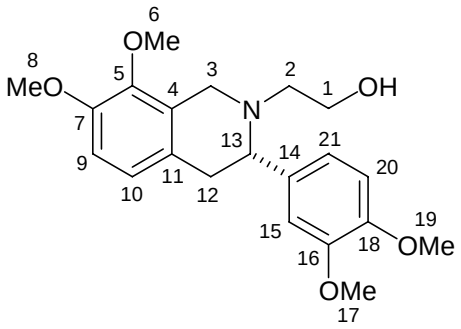
In a 25 mL flask under argon, a solution of sulfoxide (*S*)-**141a** (0.124 g, 0.26 mmol), TFAA (0.11 mL, 0.77 mmol) and TFA (0.12 mL, 1.55 mmol) in abs. toluene (12 mL) was heated to reflux for 15 h. The volatiles were removed under reduced pressure and a part of the resulting crude mixture was purified by preparative TLC (Et_2O/MeOH = 20/1) for analysis whereas the rest was purified by column chromatography (Et_2O/MeOH = 20/1). The combined impure products were then used in this state of purity for the next step.

TLC: R_f = 0.78 (Et_2O/MeOH = 20/1)

^{1}H-NMR (400 MHz, $CDCl_3$, mixture of diastereomers):
δ = 2.71-3.00 (m, 4H, NCHCH_2, NCH_2CHS), 3.18-3.40 (m, 4H, NCHCH_2, NCH_2CHS), 3.42-3.71 (m, 4H, NCH, NCH_2C), 3.78 (s, 3H, OCH_3 (min.)), 3.82 (s, 3H, OCH_3 (maj.)), 3.85 (s, 3H, OCH_3 (maj.)), 3.86 (s, 3H, OCH_3 (min.)), 3.86 (s, 3H, OCH_3 (min.)), 3.89 (s, 3H, OCH_3 (maj.)), 3.90 (s, 3H, OCH_3 (min.)), 3.92 (s, 3H, OCH_3 (maj.)), 4.15 (d, *J* = 15.9 Hz, 1H, NCH_2C (maj.)), 4.21 (d, *J* = 15.9 Hz, 1H, NCH_2C (min.)), 4.36 (s, 1H, CHS (min.)), 4.72 (dd, *J* = 5.2 Hz, *J* = 9.9 Hz, 1H, CHS (maj.)), 6.64 (s, 1H, CH_{arom} (min.)), 6.73 (s, 1H, CH_{arom} (maj.)), 6.75-6.90 (m, 4H, CH_{arom}), 7.24-7.35 (m, 8H, CH_{arom}), 7.42-7.52 (m, 4H, CH_{arom}) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, mixture of diastereomers):
δ = 35.75 (C-16 (maj.)), 36.12 (C-16 (min.)), 45.94 (C-5 (maj.)), 47.68 (C-5 (min.)), 53.06 (C-7 (maj.)), 53.28 (C-7 (min.)), 55.78, 55.83, 55.95 (C-12/C-21/C-23), 57.72 (C-6), 58.93 (C-17 (min.)), 59.09 (C-17 (maj.)), 60.84 (C-10), 107.98 (C-13/C-19/C-24 (min.)), 108.20, 110.68 (C-13/C-19/C-24 (maj.)), 110.77 (C-13/C-19/C-24 (min.)), 110.85 (C-13/C-19/C-24 (maj.)), 111.66 (C-13/C-19/C-24 (min.)), 123.63 (C-14), 126.22 (C-8/C-15/C-18/C-25), 126.98 (C-1), 127.98 (C-8/C-15/C-18/C-25), 128.73 (C-2 (min.)), 128.88 (C-2 (maj.)), 130.81 (C-8/C-15/C-18/C-25), 131.56 (C-3), 132.31 (C-8/C-15/C-18/C-25), 134.51 (C-4), 144.87 (C-11), 147.36, 147.99 (C-20/C-22), 150.10 (C-9) ppm.

2-[(3'*S*)-3'-(3'',4''-Dimethoxy-phenyl)-7',8'-dimethoxy-3',4'-dihydro-1*H*-isoquinolin-2'-yl]-ethanol [(*S*)-158]



According to the general procedure GP-7, tetrahydroisoquinoline (*S*)-**142** (0.097 g, 0.30 mmol), 2-iodoethanol (25 µL, 0.32 mmol) and $NaHCO_3$ (0.027 g, 0.32 mmol) were heated to reflux for 24 h. The resulting crude mixture was purified by column chromatography (Et_2O/MeOH = 80/1 to 20/1) providing (*S*)-**158** as a pale yellow foam.

Yield:	m = 0.089 g (0.24 mmol)	80%
GC:	R_t = 16.93 min	(Sil-8, 140-10-300)
TLC:	R_f = 0.45	(*n*-pentane/Et_2O = 20/1)
Optical rotation:	$[\alpha]_D^{25}$ = –36.9	(c = 0.45, $CHCl_3$)
ee:	n. d.	

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 2.38 (dt, *J* = 4.7 Hz, *J* = 12.9 Hz, 1H, NC*H*$_2$CH$_2$), 2.59 (br, 1H, O*H*), 2.80 (ddd, *J* = 4.7 Hz, *J* = 12.9 Hz, 1H, NC*H*$_2$CH$_2$), 2.99-3.12 (m, 2H, NCHC*H*$_2$), 3.55 (dt, *J* = 4.7 Hz, *J* = 11.0 Hz, 1H, NCH$_2$C*H*$_2$), 3.61 (d, *J* = 16.5 Hz, 1H, NC*H*$_2$C), 3.71-3.78 (m, 2H, NC*H*CH$_2$, NCH$_2$C*H*$_2$), 3.83 (s, 3H, OC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 3.87 (s, 3H, OC*H*$_3$), 4.17 (d, *J* = 16.5 Hz, 1H, NC*H*$_2$C), 6.79-6.88 (m, 5H, C*H*$_{arom}$) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 35.62 (C-12), 48.75 (C-3), 54.68 (C-2), 55.73, 55.77, 55.83 (C-8/C-17/C-19), 58.29 (C-1), 60.12 (C-6), 63.09 (C-13), 110.93, 110.76, 110.93, 120.01, 123.19 (C_{arom}), 127.28, 127.92 (C-4/C-11), 134.14 (C-14), 145.06, 148.09, 148.86, 150.11 (C-5/C-7/C-16/C-18) ppm.

MS (EI):

m/z (%) = 373 ($M^{\bullet+}$, 10), 343 (23), 342 ($M^{\bullet+}$–OCH_3, 100), 314 (11), 313 (49), 282 (13), 175 (12), 164 (16), 151 (12), 149 (16).

IR (in $CHCl_3$):

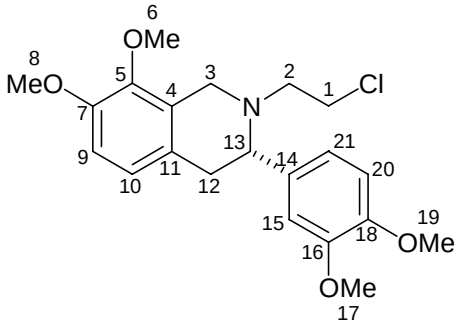
ν = 3971 (w), 3920 (w), 3764 (w), 3698 (w), 3674 (w), 3563 (m), 3536 (m), 3379 (m), 3314 (m), 3234 (w), 3012 (vs), 2936 (vs), 2836 (vs), 1596 (s), 1497 (vs), 1461 (vs), 1423 (s), 1373 (m), 1339 (w), 1263 (vs), 1233 (vs), 1145 (vs), 1087 (vs), 1030 (vs), 986 (s), 915 (w), 877 (m), 756 (vs), 667 (vs), 625 (w), 522 (w), 497 (w).

HRMS:

m/z Calcd. for $C_{21}H_{27}NO_5$ ($M^{\bullet+}$): 373.1889

Found: 373.1890

(3*S*)-2-(2'-Chloro-ethyl)-3-(3'',4''-dimethoxy-phenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*S*)-141b]



In a 25 mL Schlenk flask under argon, a solution of alcohol (*S*)-**158** (0.135 g, 0.36 mmol) in abs. CH_2Cl_2 (12 mL) was cooled to 0 °C. Et_3N (55 µL, 0.40 mmol), methanesulfonyl chloride (31 µL, 0.40 mmol) and LiCl (0.061 g, 1.45 mmol) were successively added and the temperature was increased to room temperature. After 5 h the reaction was diluted with CH_2Cl_2 and the organic phase was washed 2 times with sat. aqueous $NaHCO_3$ and 2 times with H_2O. After drying over $MgSO_4$, filtration and concentration under reduced pressure, the residue was purified by column chromatography (*n*-pentane/Et_2O = 1/1) to yield (*S*)-**141b** as a white solid.

Yield: m = 0.097 g (0.25 mmol) 70%

GC:	R_t = 14.79 min	(Sil-8, 160-10-300)
TLC:	R_f = 0.40	(*n*-pentane/Et_2O = 1/1)
mp:	113-115 °C	
Optical rotation:	n. d.	
ee:	n. d.	

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 2.51-2.62 (m, 1H, NC*H*$_2$CH$_2$), 2.88-3.11 (m, 3H, NC*H*$_2$CH$_2$, NCHC*H*$_2$), 3.53-3.68 (m, 4H, NCH$_2$C*H*$_2$, NC*H*CH$_2$, NC*H*$_2$CCOCH$_3$), 3.85 (s, 3H, OC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 3.88 (s, 3H, OC*H*$_3$), 4.26 (d, *J* = 16.1 Hz, 1H, NC*H*$_2$CCOCH$_3$), 6.85-6.88 (m, 4H, C*H*$_{arom}$) 6.97 (d, *J* = 1.2 Hz, 1H, NCHCC*H*COCH$_3$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = 36.64 (C-12), 41.76 (C-1), 50.24 (C-3), 55.52 (C-2), 55.86, 55.91 (C-8/C-17/C-19), 60.19 (C-6), 63.47 (C-13), 110.54, 110.84, 111.11, 120.06, 123.32 (C_{arom}), 127.46, 128.01 (C-4/C-11), 134.86 (C-14), 145.22, 148.37, 149.23, 150.32 (C-5/C-7/C-16/C-18) ppm. (the missing peak was covered by other signals).

MS (EI):

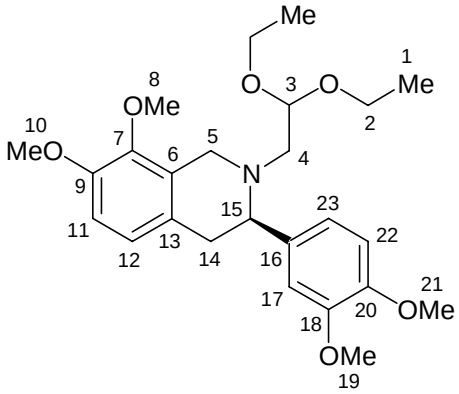
m/z (%) =393 ($M^{\bullet+}$, 22), 392 (18), 391 ($M^{\bullet+}$, 61), 390 (11), 343 (13), 342 (68), 328 (19), 313 (46), 312 (24), 165 (13), 164 ($(CH_3O)_2C_6H_3(C_2H_2)^+$, 100), 149 (36).

IR (KBr):

ν = 2999 (m), 2931 (s), 2831 (s), 2362 (m), 2338 (w), 1596 (m), 1512 (vs), 1458 (vs), 1373 (s), 1340 (w), 1325 (m), 1263 (vs), 1234 (vs), 1153 (vs), 1081 (vs), 1030 (vs), 980 (s), 878 (s), 807 (vs), 761 (s), 741 (s), 660 (w).

A correct elementary analysis could not be obtained.

(3*R*)-2-(2',2'-Diethoxy-ethyl)-3-(3'',4''-dimethoxy-phenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*R*)-141c]



In a 10 mL flask bromoacetaldehyde diethyl acetal (72 µL, 0.48 mmol) was added to a suspension of tetrahydroisoquinoline (*R*)-**142** (0.132 g, 0.40 mmol), K_2CO_3 (0.061 g, 0.44 mmol) and KI (0.080 g, 0.48 mmol) in anhydrous DMF (5 mL). The reaction mixture was heated to 110 °C for 24 h and diluted with H_2O. The organic phase was kept and the aqueous phase was extracted 4 times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (*n*-pentane/Et_2O = 1/3) to yield (*R*)-**141c** as a yellow syrup.

Yield:	m = 0.135 g (0.30 mmol)	75%
GC:	R_t = 15.19 min	(Sil-8, 160-10-300)
TLC:	R_f = 0.51	(*n*-pentane/Et_2O = 1/3)
Optical rotation:	$[\alpha]_D^{24}$ = +46.8	(c = 1.10, $CHCl_3$)
ee:	= 99%	(Chiralpak AD; *n*-heptane/*i*-PrOH = 9/1; R_t = 15.54 min; λ = 230 nm)

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 1.15 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.19 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 2.39 (dd, *J* = 5.2 Hz, *J* = 13.4 Hz, 1H, $CH_2CH(OCH_2CH_3)_2$), 2.76 (dd, *J* = 5.2 Hz, *J* = 13.4 Hz, 1H, $CH_2CH(OCH_2CH_3)_2$), 2.95 (dd, *J* = 4.7 Hz, *J* = 16.3 Hz, 1H, $NCHCH_2$), 3.05 (dd, *J* = 9.2 Hz, *J* = 16.3 Hz, 1H, $NCHCH_2$), 3.38-3.72 (m, 6H, $NCHCH_2CCH$, OCH_2CH_3, NCH_2C), 3.84 (s, 3H, OCH_3), 3.85 (s, 6H, OCH_3), 3.87 (s, 3H, OCH_3), 4.38 (d, *J* = 16.6 Hz, 1H, NCH_2C), 4.64

(t, *J* = 5.2 Hz, 1H, C*H*(OCH_2CH_3)$_2$), 6.74 (m, 3H, CH_{arom}), 6.86 (dd, *J* = 1.7 Hz, *J* = 8.4 Hz, 1H, NCHCC*H*CH), 6.96 (d, *J* = 1.7 Hz, 1H, NCHCC*H*$COCH_3$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = 15.32 (C-1), 36.15 (C-14), 50.82 (C-5), 55.81, 55.90 (C-10/C-19/C-21), 56.34 (C-4), 60.16 (C-8), 61.46 (C-2), 62.24 (C-2'), 63.57 (C-15), 102.44 (C-3), 110.82, 120.26, 123.32 (C_{arom}), 127.65, 128.88 (C-6/C-13), 135.27 (C-16), 145.28, 148.18, 149.07, 150.32 (C-7/C-9/C-18/C-20) ppm. (the missing peaks were hidden by other peaks).

MS (EI):

m/z (%) = 445 ($M^{\bullet+}$, 6), 400 (12), 399 (11), 343 (32), 342 ($M^{\bullet+}$–$CH(OCH_2CH_3)_2$, 100), 329 (13), 314 (20), 313 (50).

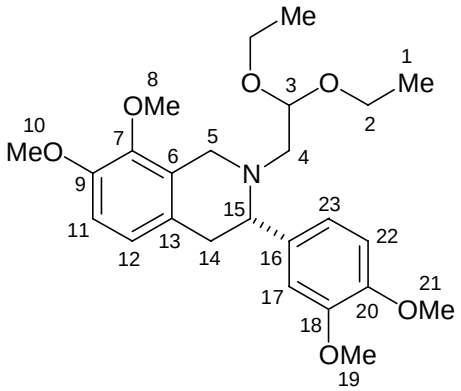
IR (in $CHCl_3$):

ν = 2973 (vs), 2933 (vs), 2903 (vs), 2835 (s), 1594 (m), 1497 (vs), 1460 (vs), 1423 (s), 1373 (m), 1341 (w), 1265 (vs), 1236 (vs), 1138 (vs), 1085 (vs), 1058 (vs), 1030 (vs), 988 (s), 865 (w), 803 (m), 757 (vs), 665 (w).

Elementary analysis:

Anal. Calcd. for $C_{25}H_{35}NO_6$:	C = 67.39	H = 7.92	N = 3.14
Found:	C = 67.22	H = 7.90	N = 2.94

(3*S*)-2-(2',2'-Diethoxy-ethyl)-3-(3'',4''-dimethoxy-phenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*S*)-141c]

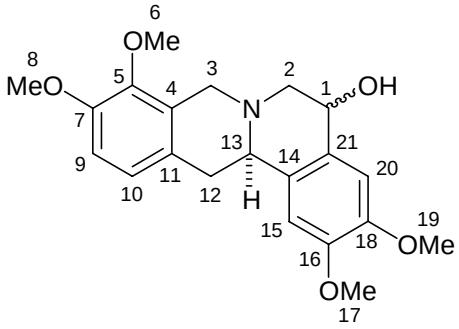


In a 10 mL flask bromoacetaldehyde diethyl acetal (71 µL, 0.47 mmol) was added to a suspension of tetrahydroisoquinoline (*S*)-**142** (0.129 g, 0.39 mmol), K_2CO_3 (0.060 g, 0.43 mmol) and KI (0.078 g, 0.47 mmol) in anhydrous DMF (5 mL). The reaction mixture was heated to 110 °C for 24 h and diluted with H_2O. The organic phase was kept and the aqueous phase was extracted 4 times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (*n*-pentane/Et_2O = 1/3) to give (*S*)-**141c** as a yellow syrup.

Yield:	m = 0.111 g (0.25 mmol)	64%
Optical rotation:	$[\alpha]_D^{23.5} = -51.8$	(c = 0.64, $CHCl_3$)
ee:	= 99%	(Chiralpak AD; *n*-heptane/*i*-PrOH = 9/1; R_t = 14.13 min; λ = 230 nm)

All other analytical data correspond to those of the other enantiomer (*R*)-**141c**.

(13a*R*)-2,3,9,10-Tetramethoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]-quinolizin-5-ol [(*R*)-162]



In a 10 mL flask a solution of acetal (*R*)-**141c** (0.105 g, 0.24 mmol) in acetone (2.6 mL) was cooled to 0 °C. Conc. aqueous HCl (86 µL) was added dropwise and the temperature was increased slowly to room temperature. After 2 h 30 the cooling bath was removed and the reaction mixture was stirred for further 14 h. The temperature was decreased to 0 °C and 1 N aqueous NaOH was carefully added till pH 10. The reaction mixture was extracted 4 times with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (Et_2O/MeOH = 60/1) providing (*R*)-**162** as a yellow solid.

Yield:	m = 0.077 g (0.21 mmol)	88%
HPLC: (min.)	R_t = 18.33 min	(Chiralcel OD; *n*-heptane/*i*-PrOH = 8/2; λ = 230 nm)
(maj.)	R_t = 23.72 min	(Chiralcel OD; *n*-heptane/*i*-PrOH = 8/2; λ = 230 nm)
TLC:	R_f = 0.38	(Et_2O/MeOH = 60/1)
mp:	n. d.	
dr:	44/56	(Chiralcel OD; *n*-heptane/*i*-PrOH = 8/2; λ = 230 nm)

^{1}H-NMR (400 MHz, $CDCl_3$, mixture of diastereomers):
δ = 2.49 (dd, *J* = 8.1 Hz, *J* = 11.0 Hz, 1H, NCH_2CHOH (min.)), 2.72-2.85 (m, 3H, NCH_2CHOH (maj.), NCHCH_2 (maj.), NCHCH_2 (min.)), 3.12 (dd, *J* = 4.0 Hz, *J* = 16.1 Hz, 1H, NCHCH_2 (min.)), 3.24-3.30 (m, 2H, NCH_2CHOH (maj.), NCHCH_2 (maj.)), 3.33 (dd, *J* = 4.9 Hz, *J* = 11.0 Hz, 1H, NCH_2CHOH (min.)), 3.52 (dd, *J* = 3.9 Hz, *J* = 11.2 Hz, 1H, NC*H* (maj.)), 3.58 (d, *J* = 15.9 Hz, 1H, NCH_2C (maj.)), 3.64 (dd, *J* = 4.0 Hz, *J* = 11.8 Hz, 1H, NC*H* (min.)), 3.69 (d, *J* = 16.8 Hz, 1H, NCH_2C (min.)), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.87 (s, 6H, OCH_3), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.15 (d, *J* = 16.5 Hz, 1H, NCH_2C (min.)), 4.19 (d, *J* = 16.8 Hz, 1H, NCH_2C (maj.)), 4.53 (s, 1H, NCH_2CHOH (maj.)), 4.86 (dd, *J* = 4.9 Hz, *J* = 8.1 Hz, 1H, NCH_2CHOH (min.)), 6.69 (s, 1H, NCHCC*H* (min.)), 6.74 (s, 1H, NCHCC*H* (maj.)), 6.78 (d, *J* = 8.2 Hz, 1H, $NCHCH_2CCHCH$ (maj.)), 6.81 (d, *J* = 8.5 Hz, 1H, $NCHCH_2CCHCH$ (min.)), 6.84 (d, *J* = 8.5 Hz, 1H, $NCHCH_2CCH$ (min.)), 6.87 (d, *J* = 8.2 Hz, 1H, $NCHCH_2CCH$ (maj.)), 6.89 (s, 1H, $NCH_2CH(OH)CCH$ (min.)), 7.06 (s, 1H, $NCH_2CH(OH)CCH$ (maj.)) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, mixture of diastereomers):
δ = 34.55 (C-12 (min.)), 36.22 (C-12 (maj.)), 52.97 (C-3 (min.)), 53.47 (C-3 (maj.)), 55.79, 55.82, 55.95 (C-8/C-17/C-19), 58.06 (C-2 (min.)), 58.45 (C-13 (min.)), 58.66 (C-2 (maj.)), 59.06 (C-13 (maj.)), 60.11 (C-6), 66.53 (C-1), 107.81 (C-15 (maj.)), 109.06 (C-15 (min.)), 110.83 (C-9/C-20 (min.)), 110.95 (C-9/C-20 (maj.)), 111.71 (C-9/C-20), 123.60 (C-10 (maj.)), 123.65 (C-10 (min.)), 126.98 (C-4/C-11/C-14/C-21 (min.)), 127.07 (C-4/C-11/C-14/C-21 (maj.)), 127.94 (C-4/C-11/C-14/C-21 (min.)), 128.24 (C-4/C-11/C-14/C-21 (maj.)), 128.67 (C-4/C-11/C-14/C-21 (min.)), 129.77, 130.02 (C-4/C-11/C-14/C-21 (maj.)), 130.07 (C-4/C-11/C-14/C-21 (min.)), 144.79 (C-7 (maj.)), 144.97 (C-7 (min.)), 147.77 (C-16/C-18),

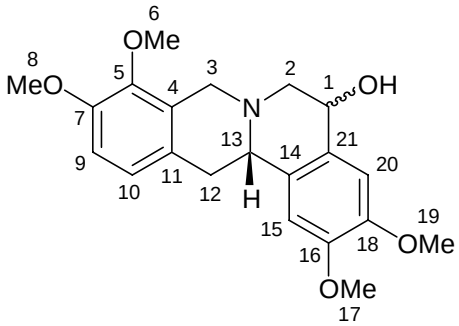
148.21 (C-16/C-18 (min.)), 148.84 (C-16/C-18), 150.11 (C-5 (maj.)), 150.15 (C-5 (min.)) ppm. (the missing peaks were covered by the other signals).

MS (EI):
m/z (%) = 371 ($M^{\bullet+}$, 41), 370 (13), 355 (10), 354 (47), 165 (32), 164 ($(CH_3O)_2C_6H_3(C_2H_2)^+$, 100), 163 (16), 150 (13), 149 (69), 121 (11).

IR (in $CHCl_3$):
ν = 3016 (w), 2937 (w), 2362 (w), 2335 (w), 1612 (w), 1514 (s), 1497 (s), 1460 (m), 1326 (w), 1278 (m), 1261 (m), 1218 (m), 1148 (m), 1106 (w), 1085 (w), 1035 (w), 861 (w), 755 (vs), 667 (w).

HRMS:
m/z Calcd. for $C_{21}H_{25}NO_5$ ($M^{\bullet+}$): 371.1733
Found: 371.1733

(13a*S*)-2,3,9,10-Tetramethoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]-quinolizin-5-ol [(*S*)-162]

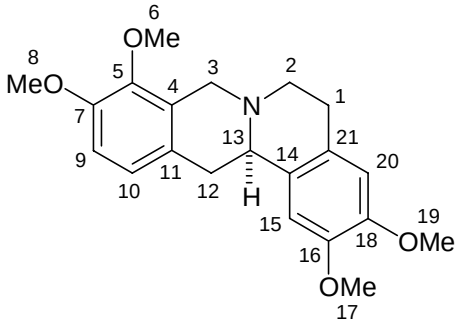


In a 10 mL flask a solution of acetal (*S*)-**141c** (0.105 g, 0.24 mmol) in acetone (2.6 mL) was cooled to 0 °C. Conc. aqueous HCl (86 µL) was added dropwise and the temperature was increased slowly to room temperature. After 2 h 30 the cooling bath was removed and the reaction mixture was stirred for further 14 h. The temperature was decreased to 0 °C and 1 N aqueous NaOH was carefully added until pH 10. The reaction mixture was extracted 4 times with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (Et_2O/MeOH = 60/1) to yield (*S*)-**162** as a yellow solid.

Yield:	m = 0.076 g (0.20 mmol)	83%
dr:	= 63/37	(Chiralcel OD; *n*-heptane/*i*-PrOH = 8/2; λ = 230 nm)

All other analytical data correspond to those of the other mixture of diastereoisomers.

(13a*R*)-2,3,9,10-Tetramethoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizine; (*R*)-(+)-tetrahydropalmatine [(*R*)-(+)-59]



In a 5 mL flask under argon, a solution of alcohol (*R*)-**162** (43 mg, 0.116 mmol) in abs. CH_2Cl_2 (1.5 mL) was cooled to −78 °C. $BF_3{\cdot}OEt_2$ (37 µL, 0.289 mmol) and Et_3SiH (46 µL, 0.289 mmol) were successively added. After 2 h at −78 °C the temperature was increased to room temperature and the reaction mixture was stirred for further 5 h. The solution was then neutralised with sat. aqueous $NaHCO_3$ (~ 0.5-1 mL). The organic phase was kept and the aqueous phase was extracted 4 times with CH_2Cl_2. The combined organic phase were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (*n*-pentane/Et_2O = 1/1 + 5% Et_3N) to yield (*R*)-**59** as a light yellow solid.

Yield:	m = 16 mg (0.044 mmol)	38%
GC:	R_t = 15.47 min	(Sil-8, 160-10-300)
TLC:	R_f = 0.33	(*n*-pentane/Et_2O = 1/2 + 5% Et_3N)
Optical rotation:	$[\alpha]_D^{24.5}$ = +387.6	(c = 0.17, $CHCl_3$) (Lit.[136] $[\alpha]_D^{20}$ = +280 (c = 1.16, $CHCl_3$))
ee:	= 98%	(Chiralpak AD; *n*-heptane/*i*-PrOH = 8/2; R_t = 9.81 min; λ = 230 nm)

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 2.61-2.71 (m, 2H, NC*H*$_2$C*H*$_2$), 2.83 (dd, *J* = 11.4 Hz, *J* = 15.8 Hz, 1H, NCHC*H*$_2$), 3.10-3.24 (m, 2H, NC*H*$_2$C*H*$_2$), 3.27 (dd, *J* = 3.7 Hz, *J* = 15.8 Hz, 1H, NCHC*H*$_2$), 3.51-3.58 (m, 2H, NC*H*$_2$C, NC*H*CH$_2$), 3.56 (s, 6H, OC*H*$_3$), 3.87 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 4.25 (d, *J* = 15.9 Hz, 1H, NC*H*$_2$C), 6.62 (s, 1H, CH$_2$CH$_2$CC*H*), 6.74 (s, 1H, NCHCC*H*), 6.79 (d, *J* = 8.2 Hz, 1H, NCHCH$_2$CCHC*H*), 6.88 (d, *J* = 8.2 Hz, 1H, NCHCH$_2$CC*H*) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 29.10 (C-1), 36.33 (C-12), 51.46 (C-2), 53.95 (C-3), 55.77, 55.80, 56.00 (C-8/C-17/C-19), 59.25 (C-13), 60.10 (C-6), 108.42 (C-15), 110.76, 111.17 (C-9/C-20), 123.68 (C-10), 126.63 (C-21), 127.57 (C-4), 128.54 (C-11), 129.53 (C-14), 144.86 (C-7), 147.21, 147.25 (C-16/C-18), 150.05 (C-5) ppm.

MS (EI):

m/z (%) = 356 (20), 355 ($M^{\bullet+}$, 100), 354 (90), 324 (18), 190 (16), 165 (11), 164 (37), 149 (31).

IR (KBr):

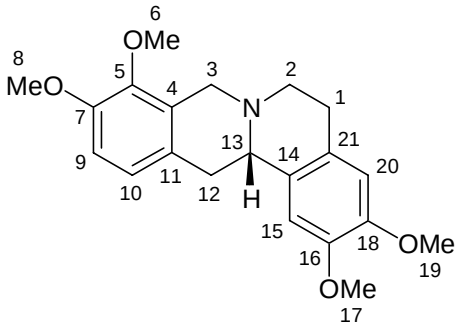
ν = 3464 (vs), 2929 (vs), 2866 (w), 2833 (m), 2800 (w), 2745 (w), 2361 (s), 2338 (s), 1734 (w), 1719 (w), 1652 (m), 1613 (s), 1559 (w), 1514 (vs), 1458 (vs), 1386 (s), 1359 (m), 1335 (s), 1278 (vs), 1259 (vs), 1230 (vs), 1141 (s), 1108 (s), 1083 (vs), 1056 (m), 1025 (s), 858 (s), 823 (w), 786 (m), 500 (w).

Elementary analysis:

Anal. Calcd. for $C_{21}H_{25}NO_4$:	C = 70.96	H = 7.09	N = 3.94
Found:	C = 70.61	H = 7.67	N = 3.56

All analytical data correspond to those reported in the literature.[45,137]

(13a*S*)-2,3,9,10-Tetramethoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizine; (*S*)-(−)-tetrahydropalmatine [(*S*)-(−)-59]



Method A:

In a 25 mL flask under argon, *Raney*-nickel W2 (2 spatulas) was added to a solution of crude sulfide (*S*)-**157** (max. 0.26 mmol) in anhydrous EtOH (10 mL). The argon atmosphere was removed under high vacuum until the EtOH started to bubble and hydrogen gas was added. This operation was repeated 2 times and the reaction mixture was heated to reflux for 22 h. The suspension was then filtered with CH_2Cl_2 over a pad of Celite. After evaporation of the solvents the residue was purified by column chromatography (*n*-pentane/Et_2O = 1/2 to 1/1 + 5% Et_3N) to give (*S*)-**59** as a light yellow solid.

Yield:	m = 0.029 g (0.08 mmol)	31% (over 2 steps)
ee:	= 90%	(Chiralpak AD; *n*-heptane/*i*-PrOH = 8/2; R_t = 13.74 min; λ = 230 nm)

Method B:

In a 5 mL flask a solution of alcohol (*S*)-**162** (60 mg, 0.162 mmol) in abs. CH_2Cl_2 (3 mL) was cooled to −78 °C. $BF_3{\cdot}OEt_2$ (0.10 mL, 0.808 mmol) and Et_3SiH (0.13 mL, 0.808 mmol) were successively added. After 1 h at −78 °C the temperature was increased to room temperature and the reaction mixture was stirred for further 18 h. The solution was then neutralised with sat. aqueous $NaHCO_3$ (~ 1-2 mL). The organic phase was kept and the aqueous phase was extracted 4 times with CH_2Cl_2. The combined organic phase were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (*n*-pentane/Et_2O = 1/1 + 5% Et_3N) providing (*S*)-**59** as a light yellow solid.

Yield:	m = 53 mg (0.149 mmol)	92%

mp:	138 °C	(Lit.[138] 140 °C)
Optical rotation:	$[\alpha]_D^{24.5} = -268.5$	(c = 0.8, $CHCl_3$, *ee* = 98%) (Lit.[139] $[\alpha]_D^{20} = -269$ (c = 0.8, $CHCl_3$))
ee:	= 98%	(Chiralpak AD; *n*-heptane/*i*-PrOH = 8/2; R_t = 13.74 min; λ = 230 nm)

All other analytical data correspond to those of the other enantiomer (*R*)-**59**.

7. ABBREVIATIONS

abs.	absolute
Ac	acetate
Ar	aryl
bp	boiling point
br	broad
BuLi	butyllithium
Bz	benzyl
calcd.	calculated
CI	chemical ionisation
conc.	concentrated
d	doublet
Δ	reflux
de	diastereoisomeric excess
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
ee	enantiomeric excess
EI	electron ionisation
Et	ethyl
Et_2O	diethylether
EtOH	ethanol
eq	equivalent(s)
GC	gas chromatography
GP	general procedure
HMPA	hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
i-	*iso*-
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide

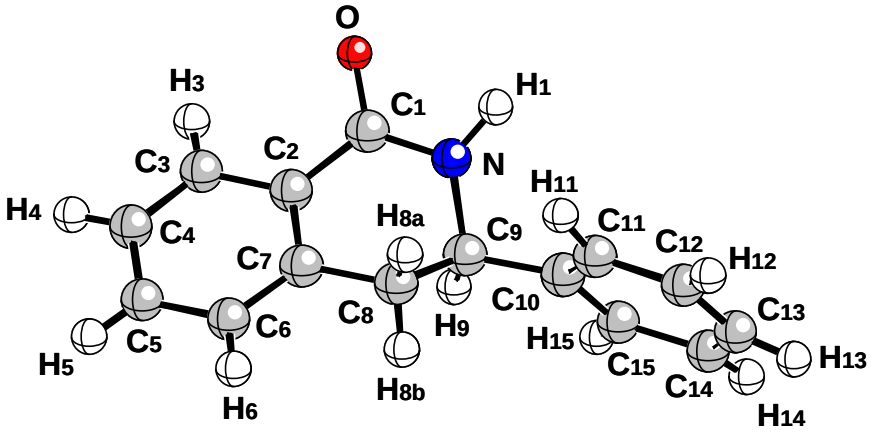
m	multiplet
m-	*meta*-
m-CPBA	3-chloroperbenzoic acid
MHz	Mega-Hertz
M	molecular mass
$M^{\bullet+}$	molecule radical ion
M	molar
max.	maximum
Me	methyl
MeOH	methanol
min	minute(s)
MMPP	magnesium monoperoxyphthalate hexahydrate
mp	melting point
Ms	methanesulfonyl
MS	Mass spectroscopy, mass spectrum
MS	molecular sieves
N	normal
n-	*normal*- (linear)
n. d.	not determined
NMP	1-methyl-2-pyrrolidinone
NMR	Nuclear Magnetic Resonance
o-	*ortho*-
p-	*para*-
PCC	pyridinium chlorochromate
ppm	Parts Per Million
p-TsOH	*para*-toluenesulfonic acid monohydrate
Ph	phenyl
PhMe	toluene
Pr	propyl
q	quartet
quant.	quantitative
R	organic rest
RAMP	(*R*)-1-amino-2-methoxymethyl-pyrrolidin
R_f	ratio of fronts (TLC)

R_t	retention time (GC)
rt	room temperature
s	singulet
s-	*sec*- (secondary)
SAMP	(*S*)-1-amino-2-methoxymethyl-pyrrolidin
sat.	saturated
SMP	(*S*)-2-methoxymethyl-pyrrolidin
t	triplet
t-	*tert*- (tertiary)
T	transmission
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofurane
TLC	Thin Layer Chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
UV	ultraviolet
*	symbol for a stereogenic centre

8. APPENDIX

8.1 STRUCTURE REPORT TO THE X-RAY ANALYSIS

8.1.1 (3*R*)-3-PHENYL-3,4-DIHYDRO-2*H*-ISOQUINOLIN-1-ONE [(*R*)-79a]



Single colorless crystals of (*R*)-**79a** were obtained by recrystallisation from Et_2O. The compound (irregular crystal of about 0.3×0.3×0.3 mm^3) crystallizes in monoclinic space group $P2_1$ (Nr. 4) with two symmetrically independent molecules in the asymmetric unit ($2\times C_{15}H_{13}NO$, M_r = 446.55). The cell dimensions are a = 9.087(1), b = 6.126(1), c = 20.915(3) Å, and β = 91.176(5)°. A cell volume of V = 1164.0(3) $Å^3$ and Z = 2 result in a calculated density of d_{cal} = 1.274 gcm^{-3}. 4959 reflections have been collected in the ω/2Θ mode at T = 298 K on an Enraf-Nonius CAD4 diffractometer employing graphite-monochromated CuK_α-radiation (λ = 1.54179 Å). Data collection covered the range $-11\leq h\leq 11$, $-7\leq k\leq 7$, and $-25\leq l\leq 25$ (Friedel pairs) up to Θ_{max} = 72.77°. μ = 0.63 mm^{-1}, no absorption correction. The structure has been solved by directs methods as implemented in the Xtal3.7 suite of crystallographic routines[140] where GENSIN has been used to generate the structure-invariant relationships and GENTAN for the general tangent phasing procedure. 3771 observed reflections ($I>2\sigma(I)$) have been included in the final full matrix least-squares refinement on F involving 316 parameters and converging at $R(R_w)$ = 0.089 (0.11, w = $1/[18.0\sigma^2(F)]$, S = 1.277, and a residual electron density of -0.36/0.50 $eÅ^{-3}$. Due to a large standard deviation the result of an attempted determination of the absolute configuration using *Flack*'s method[100] turned out to be insignificant. However, based on chemical evidence the

absolute configuration of the molecule could be assigned as shown in Figure 19. The nitrogen-bonded hydrogen atoms could be located and have been refined isotropically. All other hydrogen positions have been calculated in idealized positions, and their *U*s have been fixed at 1.5 times *U* of the relevant heavy atom without refinement of any parameters.

The crystal structure of (*R*)-**79a** has been deposited as supplementary publication no. CCDC-236862 at the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk, or http//www.ccdc.cam.ac.uk).

Fractional atomic positional and isotropic displacement parameters (U). Equivalents isotropic parameters (U_{eq}) for anisotropic refined atoms (shown with *)

Atom	X/a	Y/b	Z/x	U_{eq}/Å^2
O	0.6327(4)	–0.191(2)	0.1994(2)	* 0.060(2)
N	0.4611(4)	0.069(2)	0.1786(2)	* 0.050(2)
C1	0.5823(5)	–0.051(2)	0.1639(2)	* 0.047(3)
C2	0.6541(5)	0.010(2)	0.1044(2)	* 0.046(3)
C3	0.7609(5)	–0.128(2)	0.0790(3)	* 0.057(3)
C4	0.8316(5)	–0.070(3)	0.0243(3)	* 0.069(4)
C5	0.7994(5)	0.125(3)	–0.0071(2)	* 0.066(4)
C6	0.6936(5)	0.262(3)	0.0178(3)	* 0.062(3)
C7	0.6204(5)	0.205(3)	0.0724(2)	* 0.050(3)
C8	0.5016(6)	0.349(2)	0.1001(3)	* 0.061(3)
C9	0.3865(5)	0.205(2)	0.1314(2)	* 0.050(3)
C10	0.2572(5)	0.331(3)	0.1572(2)	* 0.047(3)
C11	0.2769(5)	0.524(3)	0.1909(3)	* 0.057(3)
C12	0.1542(6)	0.645(2)	0.2082(3)	* 0.067(4)
C13	0.0159(6)	0.579(2)	0.1913(3)	* 0.066(4)
C14	–0.0047(5)	0.391(3)	0.1587(3)	* 0.068(4)
C15	0.1159(5)	0.264(2)	0.1419(2)	* 0.057(3)
H1	0.433(4)	0.05(1)	0.215(2)	0.04(1)
H8a	0.5400(-)	0.4528(-)	0.1264(-)	* 0.067(-)
H8b	0.4515(-)	0.4264(-)	0.0627(-)	* 0.067(-)
H3	0.7906(-)	–0.2652(-)	0.0993(-)	* 0.060(-)
H4	0.9060(-)	–0.1741(-)	0.0061(-)	* 0.079(-)
H5	0.8515(-)	0.1534(-)	–0.0465(-)	* 0.078(-)
H11	0.3775(-)	0.5675(-)	0.2086(-)	* 0.060(-)
H6	0.6751(-)	0.4031(-)	–0.0053(-)	* 0.070(-)
H13	–0.0695(-)	0.6753(-)	0.1982(-)	* 0.070(-)
H9	0.3483(-)	0.1009(-)	0.1000(-)	* 0.060(-)
H12	0.1612(-)	0.7838(-)	0.2314(-)	* 0.083(-)
H14	–0.1041(-)	0.3314(-)	0.1512(-)	* 0.065(-)
H15	0.1004(-)	0.1309(-)	0.1158(-)	* 0.062(-)

Atomic displacement parameters

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O	0.070(2)	0.049(2)	0.062(2)	0.017(2)	0.007(2)	0.012(2)
N	0.054(2)	0.047(3)	0.048(2)	0.005(2)	0.008(2)	0.001(2)
C1	0.047(2)	0.044(3)	0.050(3)	0.000(3)	–0.002(2)	–0.004(3)
C2	0.040(2)	0.048(3)	0.051(3)	0.001(2)	–0.006(2)	–0.006(3)
C3	0.054(3)	0.057(4)	0.060(3)	0.011(3)	0.003(2)	–0.003(3)
C4	0.053(3)	0.086(5)	0.069(4)	0.017(4)	0.003(3)	–0.012(4)
C5	0.051(3)	0.092(5)	0.056(3)	–0.011(3)	0.011(2)	–0.005(4)
C6	0.060(3)	0.060(4)	0.065(3)	–0.001(3)	0.011(2)	0.008(3)
C7	0.043(2)	0.051(3)	0.056(3)	–0.001(3)	0.002(2)	0.002(3)
C8	0.066(3)	0.047(3)	0.071(3)	0.007(3)	0.014(3)	0.010(3)
C9	0.051(2)	0.047(3)	0.051(3)	–0.000(2)	0.003(2)	–0.003(3)
C10	0.046(2)	0.048(3)	0.047(3)	0.005(3)	0.000(2)	0.006(3)
C11	0.050(2)	0.057(4)	0.063(3)	–0.003(3)	–0.003(2)	–0.009(3)
C12	0.071(3)	0.054(4)	0.077(4)	0.002(3)	0.008(3)	–0.011(3)
C13	0.055(3)	0.076(5)	0.069(4)	0.020(3)	0.000(3)	0.002(4)
C14	0.043(3)	0.083(5)	0.079(4)	–0.001(3)	0.000(2)	0.000(4)
C15	0.052(3)	0.055(4)	0.064(3)	–0.007(3)	0.001(2)	–0.010(3)
H1	0.04(1)					
H8a	0.067(-)	0.067(-)	0.067(-)	0.000(-)	0.001(-)	0.000(-)
H8b	0.067(-)	0.067(-)	0.067(-)	0.000(-)	0.001(-)	0.000(-)
H3	0.060(-)	0.060(-)	0.060(-)	0.000(-)	0.001(-)	0.000(-)
H4	0.079(-)	0.079(-)	0.079(-)	0.000(-)	0.002(-)	0.000(-)
H5	0.078(-)	0.078(-)	0.078(-)	0.000(-)	0.002(-)	0.000(-)
H11	0.060(-)	0.060(-)	0.060(-)	0.000(-)	0.001(-)	0.000(-)
H6	0.070(-)	0.070(-)	0.070(-)	0.000(-)	0.001(-)	0.000(-)
H13	0.070(-)	0.070(-)	0.070(-)	0.000(-)	0.001(-)	0.000(-)
H9	0.060(-)	0.060(-)	0.060(-)	0.000(-)	0.001(-)	0.000(-)
H12	0.083(-)	0.083(-)	0.083(-)	0.000(-)	0.002(-)	0.000(-)
H14	0.065(-)	0.065(-)	0.065(-)	0.000(-)	0.001(-)	0.000(-)
H15	0.062(-)	0.062(-)	0.062(-)	0.000(-)	0.001(-)	0.000(-)

Bond distances (Å)

Bond	Distance	Bond	Distance
C2-C7	1.40(2)	C5-H5	0.974(6)
C2-C3	1.40(1)	C5-C6	1.38(1)
C2-C1	1.466(8)	C11-H11	1.016(6)
N-H1	0.81(4)	C11-C12	1.39(1)
N-C1	1.36(1)	C11-C10	1.38(2)
N-C9	1.45(1)	C6-H6	1.00(1)
C1-O	1.22(2)	C10-C15	1.378(9)
C7-C6	1.378(9)	C10-C9	1.52(1)
C7-C8	1.51(1)	C13-H13	0.99(1)
C8-H8b	1.016(8)	C13-C12	1.36(1)
C8-H8a	0.91(1)	C13-C14	1.35(2)
C8-C9	1.53(1)	C9-H9	0.97(1)
C3-H3	0.98(1)	C12-H12	0.98(1)
C3-C4	1.370(9)	C14-H14	0.983(8)
C4-H4	1.01(1)	C14-C15	1.39(1)
C4-C5	1.39(2)	C15-H15	0.99(1)

Bond angles (º)

Bond	Angle	Bond	Angle
C7-C2-C3	118.7(6)	H11-C11-C12	119(1)
C7-C2-C1	121.7(9)	H11-C11-C10	121(1)
C3-C2-C1	120(1)	C12-C11-C10	119.5(7)
H1-N-C1	114(4)	H6-C6-C7	122(1)
H1-N-C9	125(3)	H6-C6-C5	116.9(7)
C1-N-C9	121.7(5)	C7-C6-C5	121(1)
O-C1-N	122.6(6)	C11-C10-C15	118.7(9)
O-C1-C2	121.9(7)	C11-C10-C9	121.6(6)
N-C1-C2	115(1)	C15-C10-C9	119(1)
C6-C7-C2	120.3(9)	H13-C13-C12	121(1)
C6-C7-C8	122(1)	H13-C13-C14	118.8(7)
C2-C7-C8	117.6(6)	C12-C13-C14	120.1(9)
H8b-C8-H8a	107(1)	H9-C9-N	104(1)
H8b-C8-C9	107.5(5)	H9-C9-C8	109.1(5)
H8b-C8-C7	106.8(5)	H9-C9-C10	107.8(5)
H8a-C8-C9	113.9(6)	N-C9-C8	108.0(5)
H8a-C8-C7	111.8(6)	N-C9-C10	114.0(5)
C9-C8-C7	109(1)	C8-C9-C10	114(1)
H3-C3-C4	117.1(9)	H12-C12-C13	115.8(9)
H3-C3-C2	122.7(7)	H12-C12-C11	123.2(8)
C4-C3-C2	120(1)	C13-C12-C11	121(1)
H4-C4-C3	119(1)	H14-C14-C15	119(1)
H4-C4-C5	120.0(7)	H14-C14-C13	120.9(9)
C3-C4-C5	121(1)	C15-C14-C13	120.0(7)
H5-C5-C4	117(1)	H15-C15-C14	119.6(6)
H5-C5-C6	124(1)	H15-C15-C10	119.6(9)
C4-C5-C6	118.9(7)	C14-C15-C10	121(1)

Dihedral angles (º)

Bond	Angle	Bond	Angle
C7-C2-C1-N	13(1)	C2-C3-C4-H4	−178.2(8)
C7-C2-C1-O	−163(1)	H3-C3-C4-C5	−178.4(8)
C3-C2-C1-N	−167.8(9)	H3-C3-C4-H4	3(1)
C3-C2-C1-O	16(2)	C3-C4-C5-C6	0(1)
C1-C2-C7-C8	−3(1)	C3-C4-C5-H5	−178.0(8)
C1-C2-C7-C6	177.7(8)	H4-C4-C5-C6	178.0(8)
C3-C2-C7-C8	178.5(7)	H4-C4-C5-H5	0(1)
C3-C2-C7-C6	−1(1)	C4-C5-C6-C7	0(1)
C1-C2-C3-C4	−178.3(8)	C4-C5-C6-H6	178.3(8)
C1-C2-C3-H3	0(1)	H5-C5-C6-C7	177.2(9)
C7-C2-C3-C4	0(1)	H5-C5-C6-H6	−4(1)
C7-C2-C3-H3	179.0(8)	C12-C11-C10-C9	173.7(8)
C9-N-C1-C2	16(2)	C12-C11-C10-C15	0(1)
C9-N-C1-O	−168(1)	H11-C11-C10-C9	−15(1)
H1-N-C1-C2	−168(4)	H11-C11-C10-C15	171.2(8)
H1-N-C1-O	8(4)	C10-C11-C12-C13	−1(1)
C1-N-C9-C8	−51(1)	C10-C11-C12-H12	−178.9(9)
C1-N-C9-C10	−178(1)	H11-C11-C12-C13	−172.9(9)
C1-N-C9-H9	65(1)	H11-C11-C12-H12	9(2)
H1-N-C9-C8	134(5)	C11-C10-C9-N	81(1)
H1-N-C9-C10	6(5)	C11-C10-C9-C8	−43.5(9)
H1-N-C9-H9	−111(5)	C11-C10-C9-H9	−164.4(9)
C2-C7-C8-C9	147.2(8)	C15-C10-C9-N	−105(1)
C2-C7-C8-H8a	94(1)	C15-C10-C9-C8	130.5(9)
C2-C7-C8-H8b	−148.5(9)	C15-C10-C9-H9	10(1)
C6-C7-C8-C9	−32.6(8)	C11-C10-C15-C14	1(1)
C6-C7-C8-H8a	−86(1)	C11-C10-C15-H15	176.8(9)
C6-C7-C8-H8b	31(1)	C9-C10-C15-C14	−172.7(9)
C2-C7-C6-C5	1(1)	C9-C10-C15-H15	3(1)
C2-C7-C6-H6	−177.5(8)	C14-C13-C12-C11	2(1)
C8-C7-C6-C5	−178.6(8)	C14-C13-C12-H12	179.6(9)
C8-C7-C6-H6	3(1)	H13-C13-C12-C11	−171.3(8)
C7-C8-C9-N	56.1(9)	H13-C13-C12-H12	7(1)
C7-C8-C9-C10	−176.5(4)	C12-C13-C14-C15	0(1)
C7-C8-C9-H9	−56.2(9)	C12-C13-C14-H14	172.0(9)
H8a-C8-C9-N	−70(1)	H13-C13-C14-C15	172.6(8)
H8a-C8-C9-C10	58(1)	H13-C13-C14-H14	−15(2)
H8a-C8-C9-H9	178.1(9)	C13-C14-C15-C10	0(1)
H8b-C8-C9-N	171.7(9)	C13-C14-C15-H15	−176.4(9)
H8b-C8-C9-C10	−61(1)	H14-C14-C15-C10	−173.7(8)
H8b-C8-C9-H9	59(1)	H14-C14-C15-H15	11(1)
C2-C3-C4-C5	0(1)		

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