DIPLOMARBEIT

Titel der Diplomarbeit

„Synthetic Efforts Towards a Synthesis of the Tetracyclic Core of (-)-Lemonomycin"

Verfasser

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dedicated to my family

TABLE OF CONTENTS

iv

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Of course I have want to thank my parents, not only for financial support, but also for their patience and confidence that I will pursue my academical education as serious as possible. I want to thank my mother for her thoroughgoing love and support until the last day of her life as well as my father for being my guide, who knows how to reach his goals.

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LIST OF SCHEMES

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AIBN	2,2'-azobis(2-methylpropionitrile)
aq.	aqueous
BHT	2,6-di-*t*-butyl-4-methylphenol
Boc	*t*-butoxycarbonyl
calc.	calculated
CAN	ceric ammonium nitrate
cat.	catalytic
Cbz	benzyloxycarbonyl
conc.	concentrated
CSA	(±)-10-camphersulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBALH	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	*N*,*N*-dimethyl-4-aminopyridin
DMDO	2,2-dimethyldioxirane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
EA	ethyl acetate
EDCI	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide
ee	enantiomeric excess
et al.	*et alii*
fcc	flash column chromatography
Fmoc	9-fluorenylmethoxycarbonyl
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate
HOBt	1-hydroxybenzotriazol
HRMS	high resolution mass spectroscopy
IC_{50}	50% inhibitory concentration
LAH	lithium aluminum hydride
LDA	lithium diisopropylamine

*m*CPBA	*meta*-chloroperbenzoic acid
MIC	minimum inhibitory concentration
MOM	methoxy methyl
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
*p*TSA	*para*-toluene sulfonic acid
Py.	pyridine
r.t.	room temperature
rf.	reflux
sat.	saturated
TEMPO	tetramethyl piperidine oxide
TES	triethylsilyl
TMS	trimethylsilyl
TBAF	tetra-*n*-butylammonium fluoride
TBS	*t*-butyldimethylsilyl
TFA	tetrafluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
tlc	thin layer chromatography

ABSTRACT

Numerous tetrahydroisoquinoline alkaloids such as our target substance (-)-lemonomycin were found to show antimicrobial, antibiotical as well as cytotoxic activity against a versatile pool of microorganisms respectively tumor cell lines. As these potent therapeutics are found at a very low abundance in various natural resources, fermentation is not regarded as an acceptable source. The goal of synthetic chemists is to provide the scientific medicinal community with short and cheap approaches to the desired compounds. Not only the low availability of these substances but also the opportunity to create a diversity of structural derivatives have been a reason for numerous chemists to work on this challenging research topic.

Within this thesis our recent synthetic efforts are reported. Based on a former synthetic approach we started our investigation ending with an alternative route which allowed us to gain a highly functionalized intermediate of lemonomycin. The derived tetrahydroisoquinoline building block was established by an enantioselective alkylation reaction *via* Corey-Lygo phase transfer catalyst followed by a substrate controlled stereoselective Pictet-Spengler cyclization as key steps of this synthesis. All present stereogenic centers were set correctly in the regard of the corresponding chiral centers in the natural compound.

ZUSAMMENFASSUNG

Zahlreiche Vertreter der Tetrahydroisoquinoline Alkaloide, wie auch Lemonomycin selbst, zeigen sowohl antimikrobielle, antibiotische als auch cytotoxische Eigenschaften. Auf Grund ihrer medizinischen Wirksamkeit sind diese Substanzen für die Medizin und somit auch für den Chemiker von großer Wichtigkeit. Ihre Konzentration in der Biomasse ist äußerst gering, weswegen Fermentation zu ihrer Gewinnung nicht in Frage kommt und somit nur ein synthetischer Zugang zu den potentiellen Therapeutika in Frage kommt. Aufgabe der Chemie ist es, möglichst kurze und kostengünstige Synthesen zu entwickeln um genügend Material für pharmakologische Test und zur späteren Medikamentierung bereitstellen zu können. Besonders ist darauf hinzuweisen, dass es durch den synthetischen Zugang möglich ist, Derivate zu erzeugen, deren Wirksamkeit oft höher ist als die des jeweiligen Naturstoffs selbst.

In dieser Arbeit sind kürzlich errungene Fortschritte im Bezug auf die Totalsynthese von Lemonomycin dokumentiert. Ausgehend von billigen Startsubstanzen war es möglich ein hochfunktionalisiertes Intermediat des Naturstoffs herzustellen, in dem alle Stereozentern, die auch später in der Zielsubstanz enthalten sind, die korrekte Konfiguration besitzen. Als Schlüsselschritte dieser Synthese wurde eine enantioselective Alkylierung eines aromatische Bausteins mit dem heterogenen Phasentransferkatalysator nach Corey-Lygo als auch, die für die Substanzklasse der Tetrahydroisoquinoline typische, Pictet-Spengler Zyklisierung gewählt. Das zur weiteren Verarbeitung angedachte Produkt wurde mit guter Ausbeute und exzellenter optischer Reinheit hergestellt.

GRAPHICAL ABSTRACT

(-)-Lemonomycin (1)

glycosylation

Pictet-Spengler cyclization

Strecker like couplig

N-acyliminium cyclization

173

111

156

+

73

67 + **193**
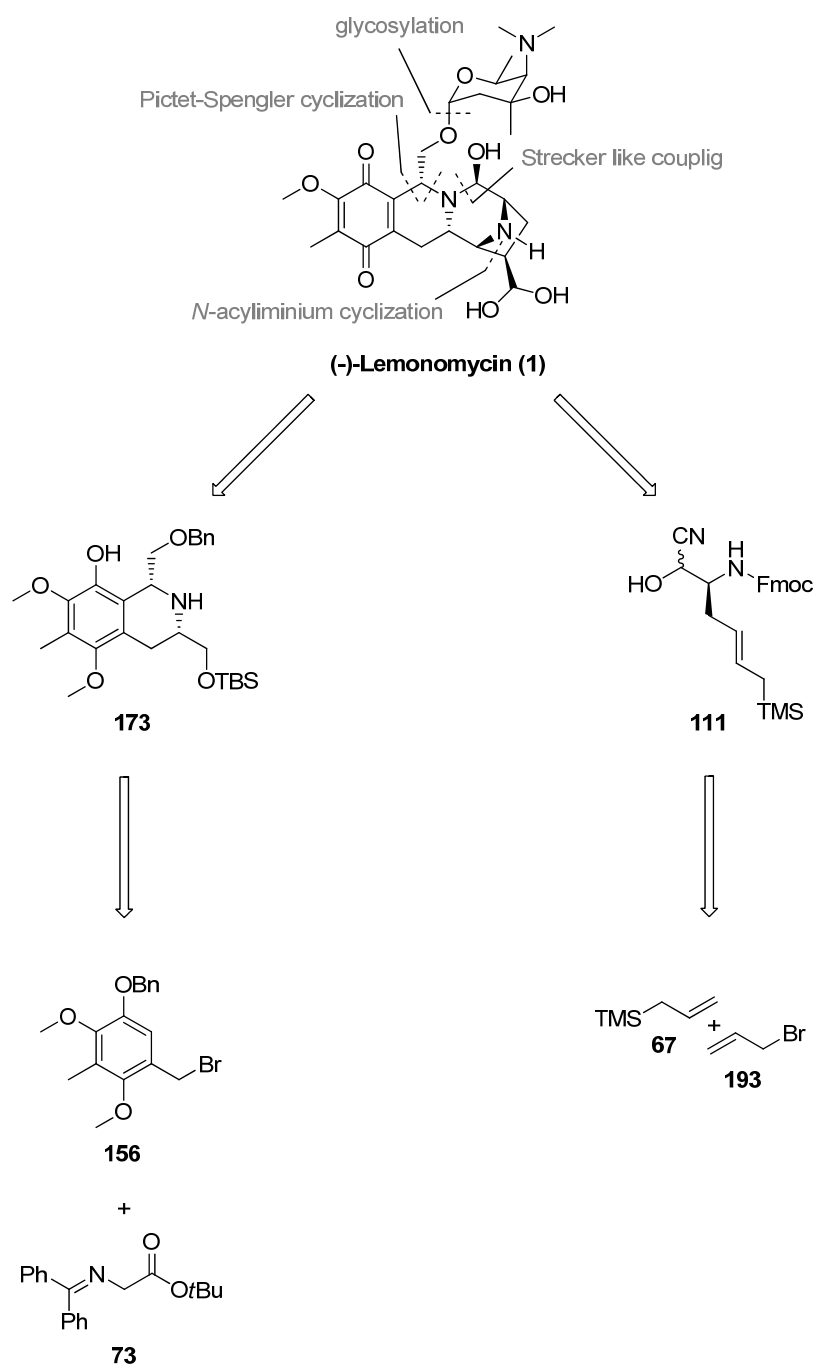
INTRODUCTION

Since the isolation and structure elucidation of naphthyridinomycin in 1974, tetrahydroisoquinoline antitumor antibiotics have been under intense investigation. Today about 60 compounds of this substance class have been isolated. This natural occurring alkaloids form three families, according to their specific structural features; the saframycin, the naphthyridinomycin/bioxalomycin and the quinocarcin/tetrazomine family.

Besides their fascinating and challenging structural characteristics, the antitumor and antimicrobial behavior of numerous potent cytotoxic tetrahydroisoquinolines have been reason enough for these substances to serve as attractive synthetic drug targets during the last three decades.

Chemistry, biology and syntheses of members of the quinocarcin family are topic of this work with an emphasis on the efforts towards an enantioselective total synthesis of (-)-lemonomycin.
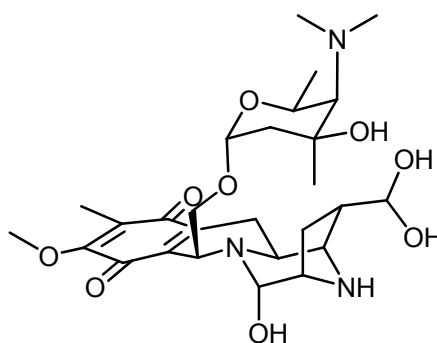
(-)-Lemonomycin (**1**)

Figure 1. (-)-Lemonomycin

Tetrahydroisoquinoline Antitumor Antibiotics

As already mentioned in the introduction, the tetrahydroisoquinoline alkaloids consist of three families. The largest is the saframycin family, containing the saframycins (**2**), renieramycins (**3**), safracins (**4**) and ecteinascidines (**5**).[1,2] Five condensed six-membered rings form the common pentacyclic framework of this subgroup. The two terminating rings either exist as quinones and/or hydroquinones, additional common structural features are a tetrahydroisoquinoline moiety and a piperazine ring, sharing one of its nitrogens with the neighboring piperidine subunit (**Figure 2**). Fukuyama and Sachleben were the first chemists to publish a total synthesis of a saframycin congener with racemic saframycin B in 1982.[3]

Saframycins (**2**)

Renieramycins (**3**)

Safracins (**4**)

Ecteinascidines (**5**)
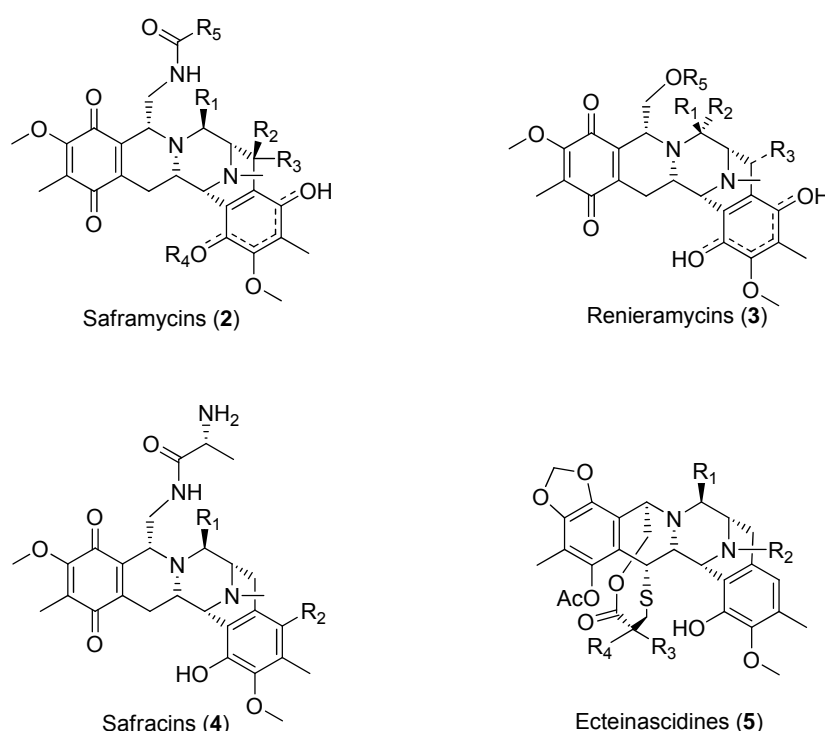
Figure 2. The Saframycin Family

A second very important family is the naphthyridinomycin family. Naphthyridinomycin itself was long believed to be a natural occurring tetrahydroisoquinoline alkaloid as it was isolated by Kluepfel *et al.* in 1974 from *Sreptomyces lusitanus*,[4] but repeated attempts to isolate this compound under the original as well as under milder conditions failed and only a congener

bioxalomycin β_2 was isolated,[5] indicating that naphthyridinomycin might only arise from the opening of the labile oxazolidine moiety due to a too harsh isolation procedure. Treatment of the fermentation broth of *Streptomyces lustianus* with sodium cyanide led to a more stable congener of naphthyridinomycin, cyanocycline A,[6] an old acquaintance in the research group of Mulzer.[2] Together with the dnacins and aclindomycins this family is complete, containing a main carbon frame work of five to seven condensed rings, four of which are six-membered and one to three five-membered ones (**Figure 3**).

Naphthyridinomycin and Cyanocyclines (**6**)   Bioxalomycins (**7**)
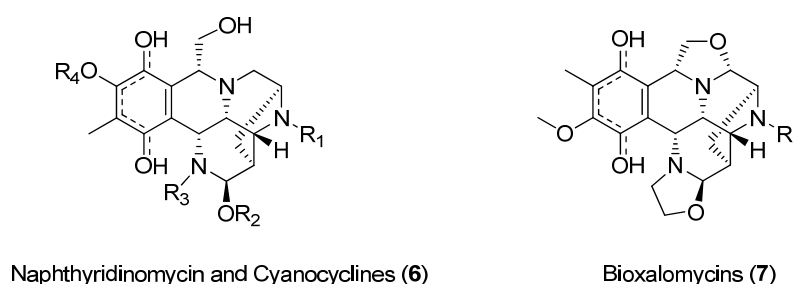
Figure 3. The Naphthyridinomycin Family

The quinocarcin family is the third and last family of this exciting alkaloid pool, with quinocarcin (**8**) itself, quinocarcinol (**10**), tetrazomine (**9**) and lemonomycin (**1**) found as natural occurring congeners (**Figure 4**). A penta- or tetracyclic main carbon core is present, bearing the characteristic isoquinoline moiety, whose aromatic ring can either exist as hydroquinone or quinone ring, condensed to a pyridine moiety. Isolation, structure elucidation and biological activity of lemonomycin will be discussed in more detail within the next pages.

Quinocarcin (**8**)   Tetrazomine (**9**)   Lemonomycin (**1**)
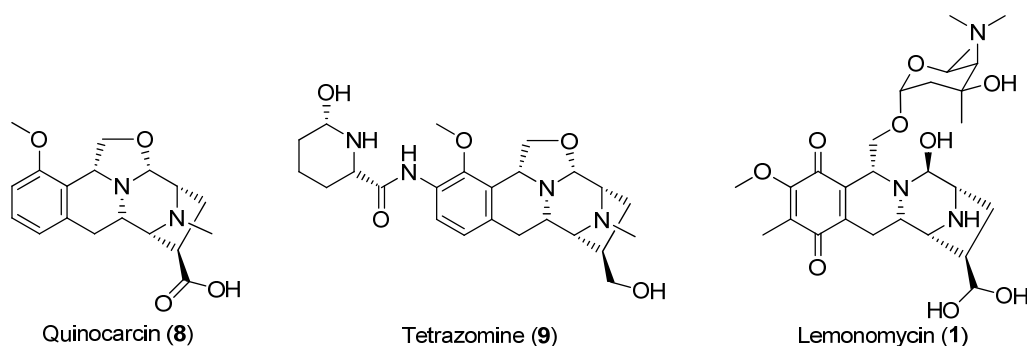
Figure 4. The Quinocarcin Family

A large number of the above mentioned natural products and some of their derivatives show potent cytotoxic, antibiotic and antimicrobial activities and are

therefore of big interest for medicinal and synthetic chemists. Tetrahydroisoquinoline antitumor antibiotics themselves and related synthetic products may serve as various therapeutics.

The Quinocarcin Family

Isolation and Structure Elucidation

Quinocarcin (**8**) and quinocarcinol (**10**) (**Figure 5**) were both isolated from *Streptomyces melanovinaceus* nov. sp. by Tomita *et al.* in 1983.[7] Quinocarcin was found to have in *vitro* activity against Gram-positive bacteria and even showed antitumor activity against murine tumors. X-ray crystallography was used to determine the structure of qinocarcinol,[8] whereas the structure of quinocarcin was determined by comparison of the NMR-data of both natural products,[9] which could be confirmed by reductive conversion of the natural product into quinocarcinol. Nine years later, when Garner's asymmetric total synthesis of (-)-quinocarcin was published,[10] scientists were able to determine the absolute configuration. Through its isolation, many chemists such as Danishefsky,[11] Fukuyama[12] and Weinreb,[13] just to mention a few of them, have contributed efforts and total syntheses to this research topic. Some years ago, the sole total synthesis of this potent broad spectrum antibiotic was published by Stoltz *et al.*,[14] affirming, that this group of natural products still is in the aim of the scientific society.

Quinocarcin (**8**)   Quinocarcinol (**10**)
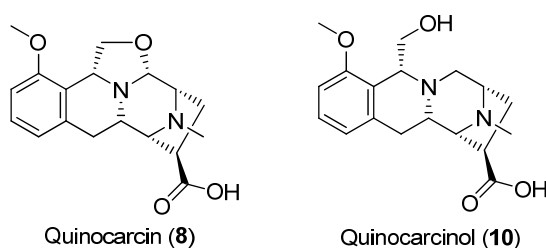
Figure 5. Quinocarcin and Quniocarcinol

Eight years after the isolation of quinocarcin, Suzuki *et al.* reported the isolation of tetrazomine (**9**) (**Figure 6**) from *Saccharothrix mutabilis* subsp. *chichijimaensis* in 1991.[15] Its structure was elucidated by spectroscopic methods, mainly relying on two dimensional NMR-data.[16] The pentacyclic core framework is very similar to the carbon skeleton of quinocarcin, but the unusual substitution on C10', an amino acid(3-hydroxy pipecolic acid), is unique for tetrazomine. The relative and absolute configuration of the tetrazomine and its aminosugar moiety[17] were determined by Williams *et al.*, within the invention of the first total synthesis[18,19] of this quinocarcin congener.
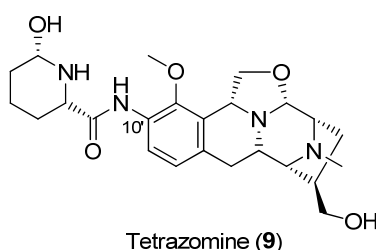
Tetrazomine (**9**)

Figure 6. Tetrazomine

Besides two other antibiotic compounds, lemonomycin hydrochloride was isolated from 2000 liters of fermentation broth from *Streptomyces candidus* (LL-AP191). Treatment with aqueous sodium hydroxide revealed the natural product, which was extracted with chloroform. Finally, lemonomycin was precipitated from acetone as "lemon-yellow spheres", bringing its discoverers to baptize it lemonomycin. Although lemonomycin (**1**) was already isolated in 1964 from *Streptomyces candidus* (LL-AP191) and some of its structural features, such as the quinone moiety, could be affirmed by IR- and NMR-spectra,[20] its structure was determined by He *et al.* in 2000.[21]

Lemonomycin (**1**)   Lemonomycin Aglycon (**11**)   Lemonose (**12**)
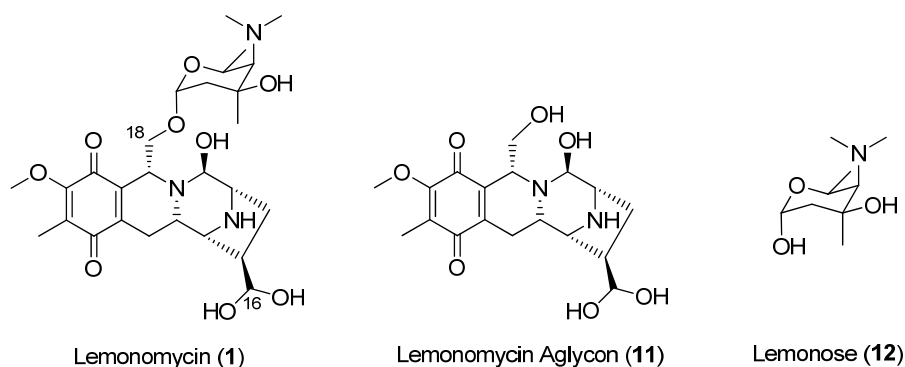
Figure 7. Lemonomycin and Fragments

Belonging to the quinocarcin family of tetrahydroisoquinoline antitumor antibiotics, lemonomycin aglycon (**11**) contains the typical tetracyclic core framework. The substitution pattern of the quinone moiety equals the one of naphthyridinomycin. One of the four core rings, a pyrrolidine, is new to this pool of alkaloids. Additional remarkable structural features are the unusually stable geminal diol at C16 and the 2,6-dideoxo-4-aminosugar (**12**) (**Figure 7**). This moiety at C18 is unique in this class of alkaloids and very scarce in nature as it only serves glycothiohexide α,[22-24] nocathiacin I,[25] and MJ347-81F4 A[26] as substituent. It was given the name lemonose by Stoltz *et al.*, as they were the first ones to synthesize the alkaloid as well as the pyranose[27] and lemonomycin was the first natural product known to bear this structure. The sugar moiety seems to have an important effect on the biotic activity of these compounds, as all of them show similar antibiotic behavior.[28] The research group around He also reported a derivatization of the natural compound to the corresponding cyano compound (**14**) *via* the intermediary formation of an iminium ion acetal (**13**), upon treatment with acidic *i*-propanol, to which was finally added sodium cyanide (**Scheme 1**).[21]
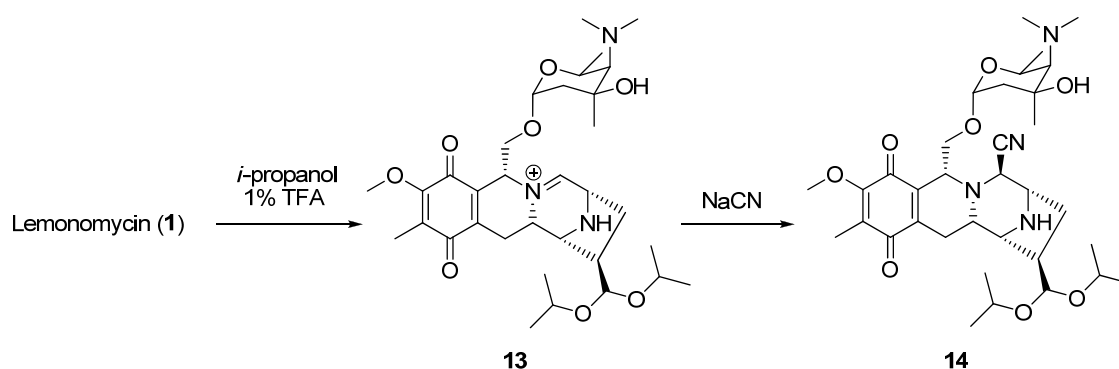
Scheme 1. Conversion of Lemonomycin to the Corresponding Nitrile

Biological Activity

Naphthyridinomycin has shown strong activity against both Gram-positive and Gram-negative bacteria. It was observed, that at low concentration the natural product irreversibly inhibited DNA synthesis in *Escherichia coli* by avoiding the incorporation of ^{14}C-thymidine; whereas at higher concentrations

RNA and protein synthesis were inhibited. Several derivatives and their biological activity were under intense investigation; therefore, 3H-naphthyridinomycin was proved to partially form covalent bonds to DNA, and the reduction of the quinone moiety by dithiothreitol DNA bindings occur irreversibly and at a by far higher extent. Strong indication exists, that naphthyridinomycin binds to GC-rich DNA sequences, as alkylation by poly(dG)-poly(dC) and poly(dA)-poly(dT) polydeoxyribonucleic acids no longer affected the DNA, as guanine was replaced by inosine.

Bioxalomycin α_2 (**15**), unlike naphthyridinomycin and cyanocylcline A - whose biological activities are almost the same - bears significantly higher activity against Gram-positive bacteria, due to double alkylation of the N2 of guanine in duplex DNA. It has been proposed, that the interaction mechanism proceeds *via* *o*-quinone methide intermediate **16** and subsequent oxidation of the *bis*-DNA product to the corresponding quinone **17** (**Scheme 2**).
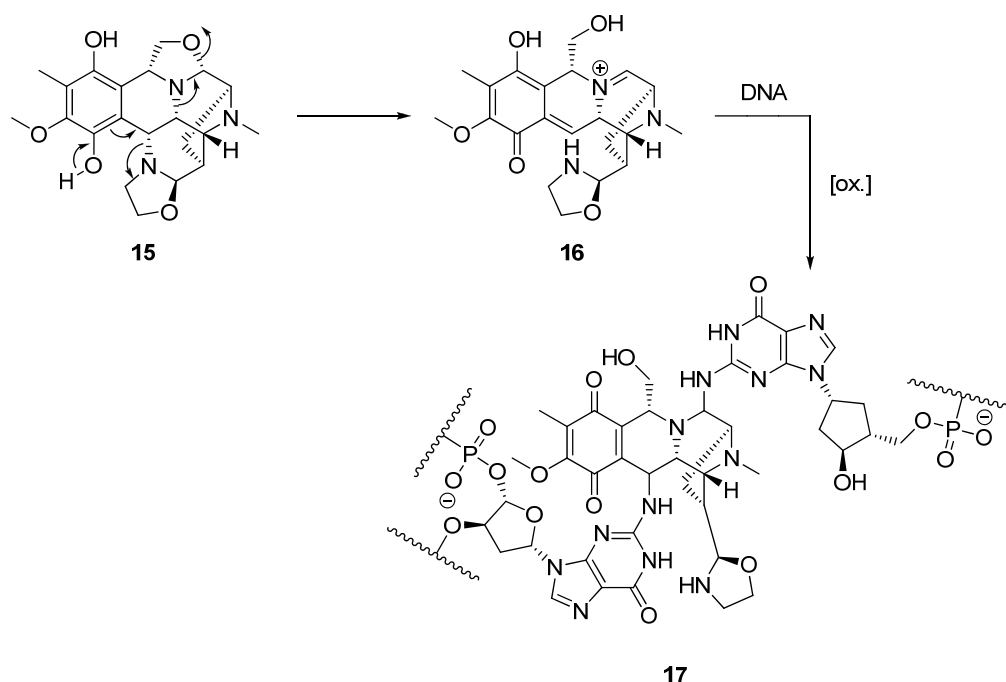
Scheme 2. DNA Interaction of Bioxalomycin α_2

Bioxalomycin α_2 (**15**) is effective by a much higher extent than any other tetrahydroisoquinoline antibiotic, thought to arise from its two oxazolidine moieties and the redox-labile hydroquinone ring. Just like its congeners

quinocarcin and tetrazomine it shows the ability to convert oxygen into its superoxide.[2]

Lemonomycin was found to have antimicrobial activity against strains of *Staphylococcus aureus* and *Bacillus subtilis* with MIC's of 0.4 respectively 0.2 µg/mL. The antibiotic was administered either orally or subcutaneously to mice, showing resistance to above mentioned bacteria but unfortunately at amounts slightly above the therapeutic dose the medication ended lethal for the test animal.[20] Furthermore, antibiotic activity of lemonomycin (**1**) and its cyano-derivative **14** against methicillin resistant *Staphylococcus aureus* and vancomycin resistant *Enterococcus faecium* with MIC's of 0.4 and 0.2 µg/mL, as well as in *vitro* cytotoxicity against a human colon cell tumor line (HCT116), with IC_{50}'s at 0.36 and 0.26 µg/mL, were reported by He *et al.*[21]

As lemonomycin and saframycin A (**18**) show similar structural composition, they probably obey similar biological interaction mechanisms. In **Figure 8** the results of extensive studies on the toxicity of saframycin are visualized. Under mild acidic conditions (pH 5 to 6) hydrogen bonds are established between the minor groove of DNA. Due to calculations of the interplay between the natural product and the DNA duplex oligomer $d(GATGCATC)_2$, indicating, that the proton of the ammonium atom N12 forms a hydrogen bond with the corresponding nitrogen N2 of adenine and the oxygen of the quinone moiety at C8 forms another one with the amine of a guanine.[28]
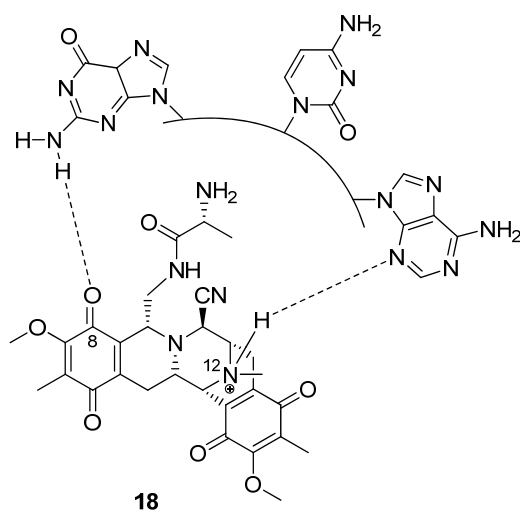
Figure 8. DNA Interaction of Saframycin A[28]

Biosynthesis

Due to their similar structural features, tetrahydroisoquinoline antitumor antibiotics are said to be derived by related biosynthetic pathways with amino acids as major building blocks. The biosynthesis leading to saframycin has been confirmed by isotope labeling experiments, where two tyrosine units condense to build the piperazine moiety and the quinone ring.[29,30] Based on these studies a biosynthetic proposal for lemonomycin has been published in a PhD-thesis at California Institute of Technology (**Scheme 3**).[28] Claiming that the piperazin moiety as well as the quinone ring are installed by condensation of tyrosine (**19**) with ornithine (**20).**
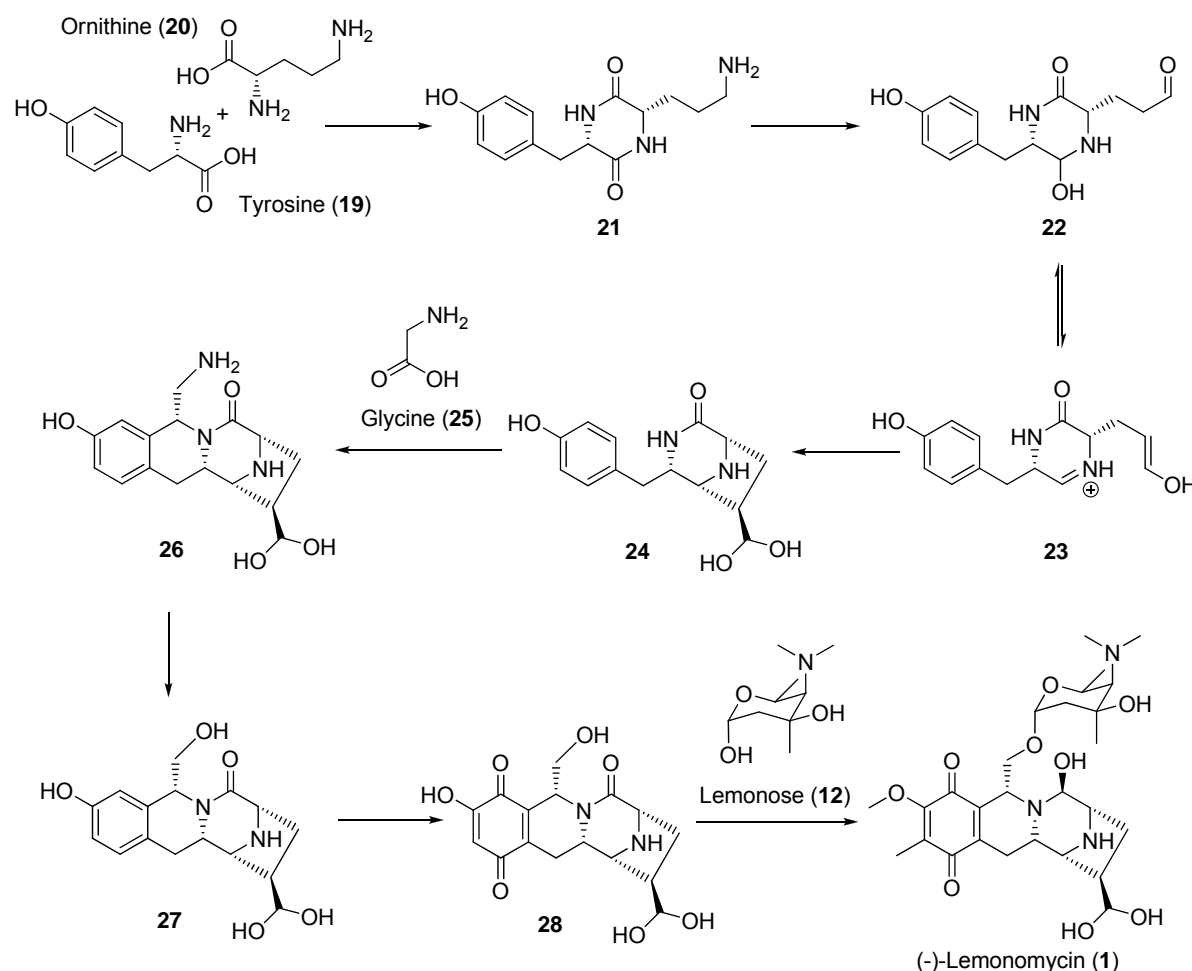
Scheme 3. Proposed Biosynthesis of Lemonomycin

Aldehyde **22** should be derived by oxidation of the primary amine of diketopiperazine **21**. Subsequently, elimination of water and enolization leads to

intermediate **23**, which consecutively undergoes cyclization *via* intramolecular nucleophilic attack of an enol at its electrophile carbon atom, is claimed to furnish **24**. Glycine (**25**) is proposed to deliver the missing carbon atom of the tetrahydroisoquinoline **26**; consecutive oxidation, hydrolysis and reduction should arise in primary alcohol **27**, bearing the tetracyclic carbon core with all five stereogenic centers set correctly. Finally, oxidation of the aromatic ring to the corresponding quinone **28**, methylation *via* the *S*-methyl methionine and glycosylation with lemonose (**12**) should provide (-)-lemonomycin (**1**).

PRELIMINARY SYNTHETIC EFFORTS

The Total Synthesis of Lemonomycin

Today, only one total synthesis of (-)-lemonomycin has been published by Stoltz *et al.* in 2003,[27] 59 years after its isolation. Starting from cheap and readily available material, the desired natural product was obtained in 15 linear steps. According to their retrosynthetic consideration the key steps of the synthetic route are a diastereoselective dipolar Joule reaction to lead to diazabicycle **31**, a Suzuki cross coupling between iodide **32** and boronic ester **33** as well as a diastereoselective Pictet-Spengler cyclization of intermediate **36** and the *α*-glycosylated dideoxysugar **31**. The aminopyranose itself was obtained starting from D-threonine by Felkin-controlled aldol reaction as crucial step.

Diazabicyclo iodide **32** could be obtained in four steps. Therefore, deprotonation of oxidopyrazinium bromide **29** with *N*-methyl morpholine as base and treatment with Oppolzer sultam-derived acrylamide **30** provided a bicyclic product, which under reduction conditions with sodium borohydride gave primary alcohol **31** in high yield (72%) and an excellent enantiomeric excess of 94%. Protection of the alcohol as a silyl ether and iodination gave *Z*-iodoenamine as a single diastereomer. The arising iodide **32** was linked to boronester **33** *via* Suzuki coupling giving enamide **34**. Hydrogenation of the *Z*-double bond with palladium on charcoal was accompanied by cleavage of the nitrogen linked benzyl group providing an amide. Subsequently, the secondary amine was protected as benzyl carbamate and the sulfonate ester was cleaved, obtaining amide **35**. Stoltz *et al.* were not able to perform a Pictet-Spengler cyclization at this stage of the synthesis, as the reactivity of the amide towards aminoglycosyloxy aldehyde **41** was not existent. The more reactive primary amine **36** was established by activation of the secondary amine as *t*-butyl carbamate (the phenol was also affected), followed by reductive opening of the piperazine ring and acidic cleavage of both prior installed Boc groups and the silyl ether (**Scheme 4**).
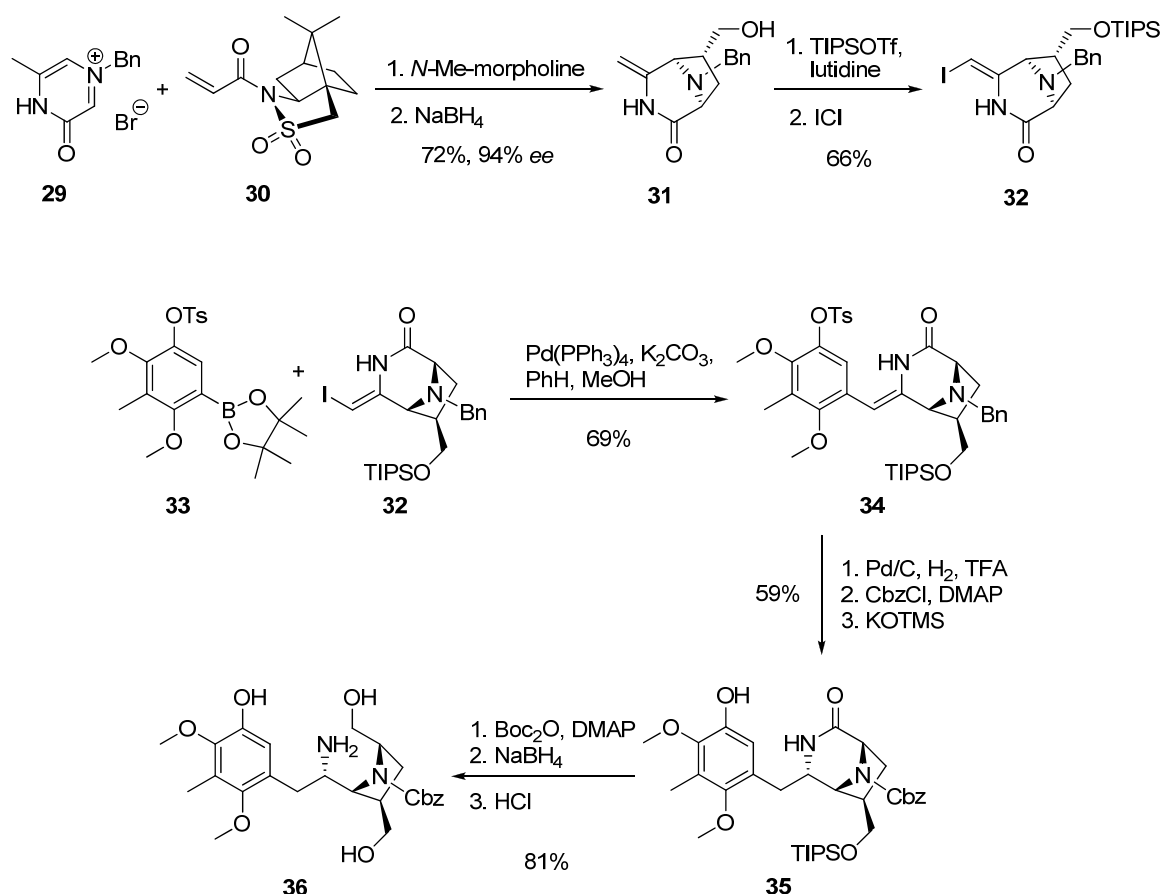
Scheme 4. Synthesis of the Pictet-Spengler Precursor

The aminoglycosyloxy aldehyde itself was provided by conversion of D-threonine (**Scheme 5**). As the only diastereomer, Felkin-controlled aldol product **38** was derived by alkylation of ketone **37** with the in *situ* prepared lithium enolate of ethyl acetate. Acidic opening of the oxazolidine with concomitant formation of a lactone, formation of an oxazolidine, reduction of the prior installed lactone to the lactol and its conversion with allyl alcohol provided bicycle **39**. Later, the oxazolidine together with the sulfonyl group was reductively cleaved and the arising secondary amine was methylated. Finally, to obtain the desired aminopyranose, **41** was derived by glycol cleavage performed with osmium tetroxide in the presence of sodium periodate.
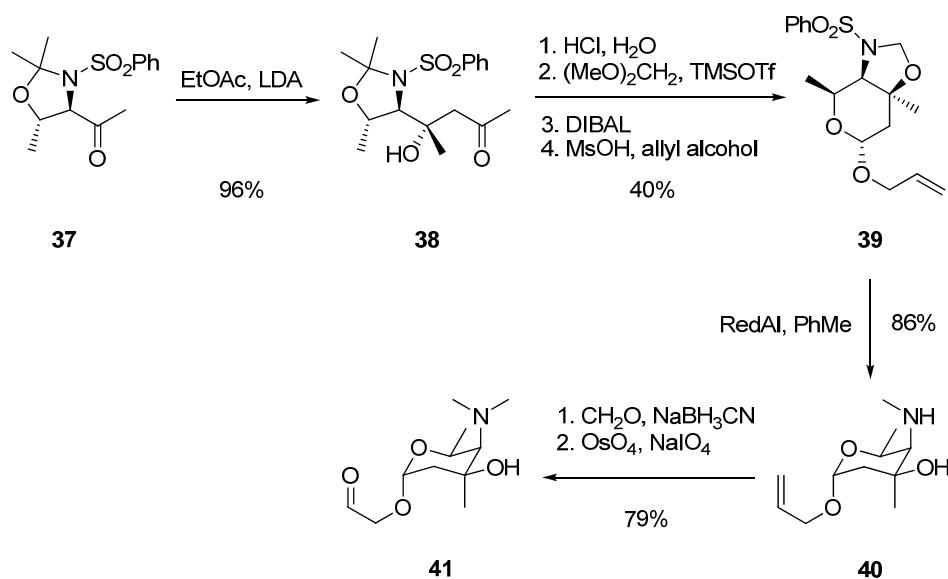
Scheme 5. Synthesis of the Sugar Moiety

Pictet-Spengler reaction of amino alcohol **36** as corresponding TFA salt with aldehyde **41** was diastereoselectively performed by simply mixing both substances in EtOH at room temperature (**Scheme 6**).
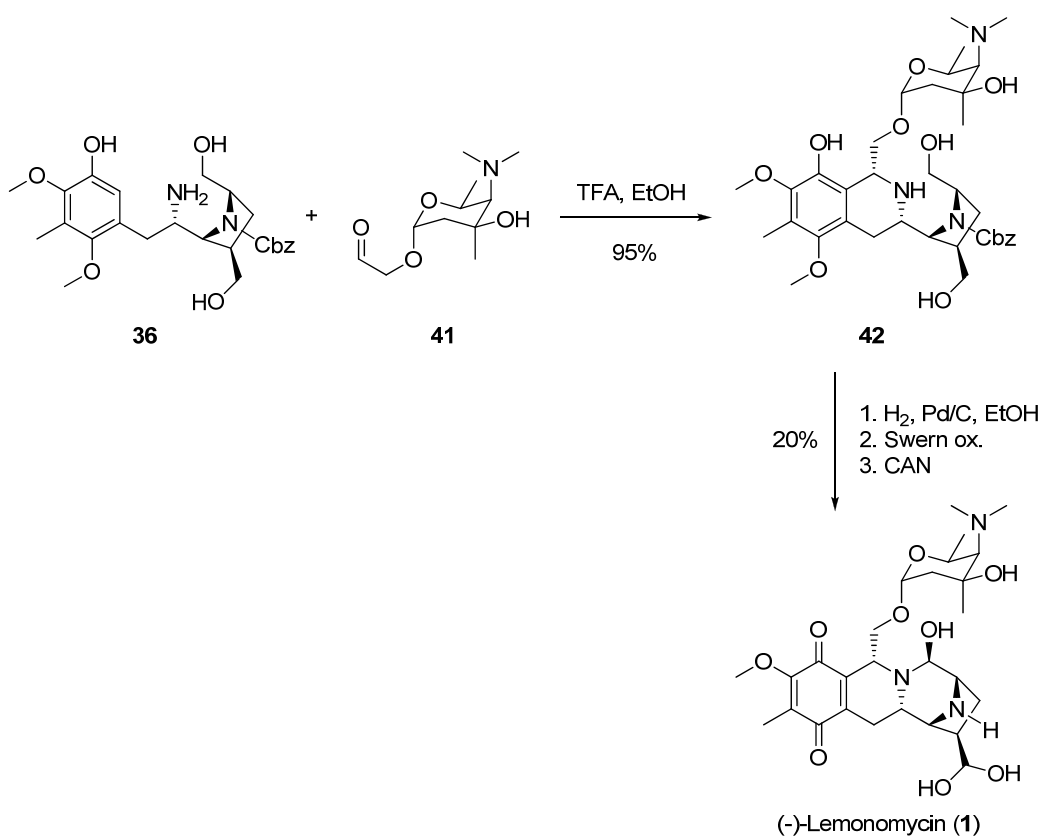
Scheme 6. Endgame of the Total Synthesis

To complete the total synthesis, what was left to do with tetrahydroisoquinoline **42**, was the hydrogenative cleavage of the nitrogen protecting group, Swern oxidation of the primary alcohol followed by immediate closure of the piperazine ring and oxidation of the aromatic ring to provide the natural compound **1**.

Synthetic Contributions Towards a Total Synthesis of Lemonomycin

This section will give a comprehensive chronological overview of synthetic studies and syntheses of lemonomycin derivatives.
Within the last decade several noteworthy achievements toward syntheses of lemonomycin have been published by various research groups.

Magnus' Racemic Synthesis of Advanced Lemonomycinone Amide

In 2005, Magnus *et al.* reported a racemic synthesis of lemonomycin amide **60** and the racemic total synthesis of another tetrahydroisoquinoline alkaloid renieramycin G from a common intermediate, starting from cheap and readily available material.[31] The lemonomycin derivative shows all crucial structural features of the natural compound's aglycon, except that the carbinolamine functionality is present as lactam. Key steps of this synthetic approach are a modified Larock synthesis providing isoquinoline **45**, a silyl activated amide coupling reaction and a thiophile mediated *N*-acyliminium cyclization giving aldehyde **57**.

Linkage of benzylic *o*-iodoimine **43** with triisopropylsilyl protected propargylic alcohol **44** by modified Larock isoquinoline synthesis and subsequent copper mediated ring closure under Castro's conditions gave electronrich isoquinoline **45**. Alkylation of the resulting bicycle with benzyloxymethyl lithium and consecutive treatment with methyl chloroformate gave cyclic tertiary enamine **46**. As direct reduction to intermediate **48** worked unsatisfactory due to degradation of the isoquinoline, the amino alcohol was obtained by conversion of

the silyl ether to oxazolidinone **47**, using TBAF, followed by ionic hydrogenation and hydrazinolysis. Subsequently, treatment with TMSCl leading to protection of the primary alcohol and concomitant activation of the amine, and its coupling with mixed anhydride **49** provided cyclization precursor **50** after acidic workup. The following Swern oxidation was accompanied by direct formation of the piperazine ring resulting in a diastereomeric (3:2) mixture of hemiaminal **51**. The common intermediate **52** on the synthetic routes to renieramycin G and lemonomycin could be generated by substrate controlled diastereospecific conversion to its thioaminal (**Scheme 7**).
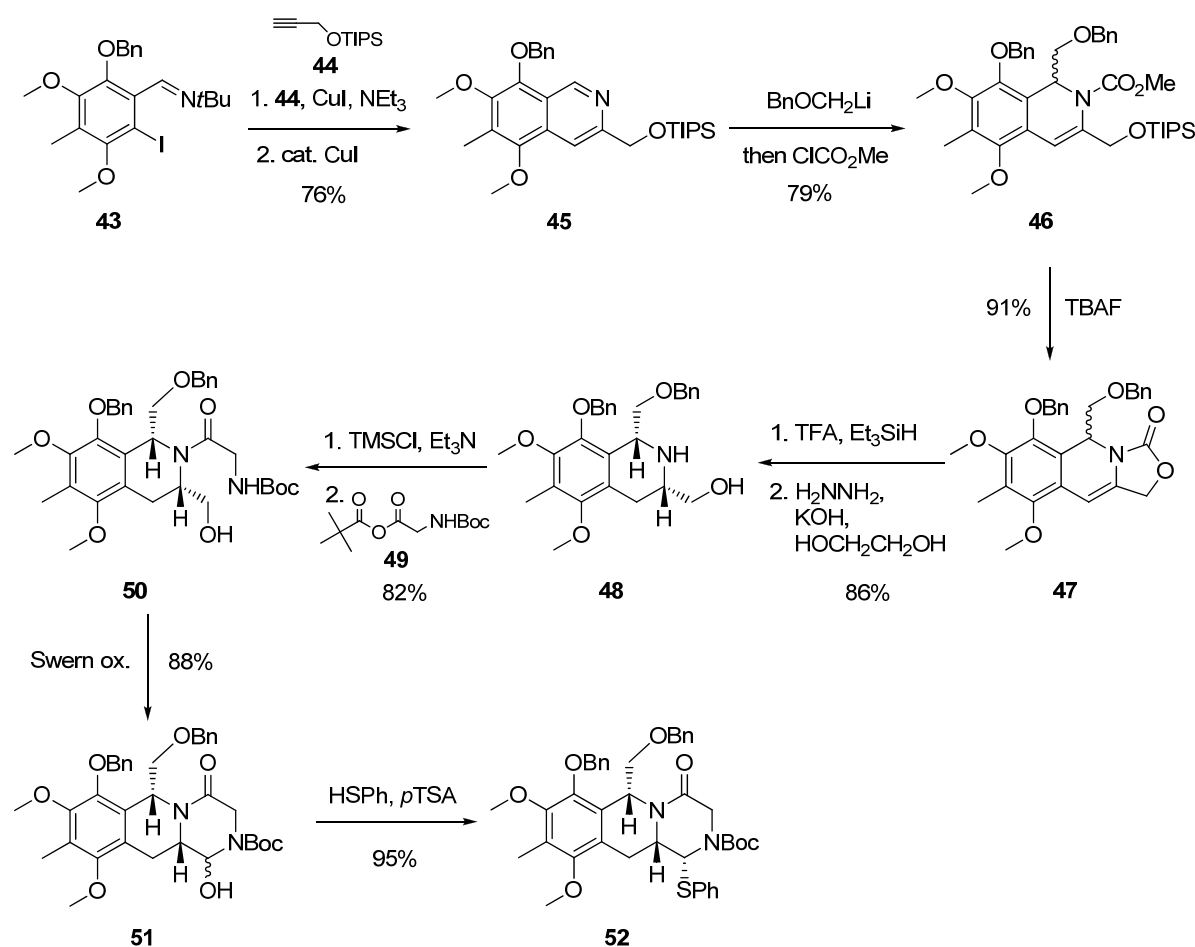
Scheme 7. Route to the Magnus Thioaminal

Following the pathway towards lemonomycin, amide **52** was alkylated with iodide **53** giving the single undesired diastereomer **54**, which was fully converted to the desired one by deprotonation with *t*-BuLi and quenching with BHT. Removal of the silylether under standard conditions gave alcohol **55**. The silyl

enolether **56** was established by Swern oxidation and consecutive treatment with TIPS-triflate. The crucial diastereoselective *N*-acyliminium cyclization was performed in the presence of thiophilic AgBF$_4$ providing intermediate **57** bearing the tetracyclic carbon framework of the natural compound.
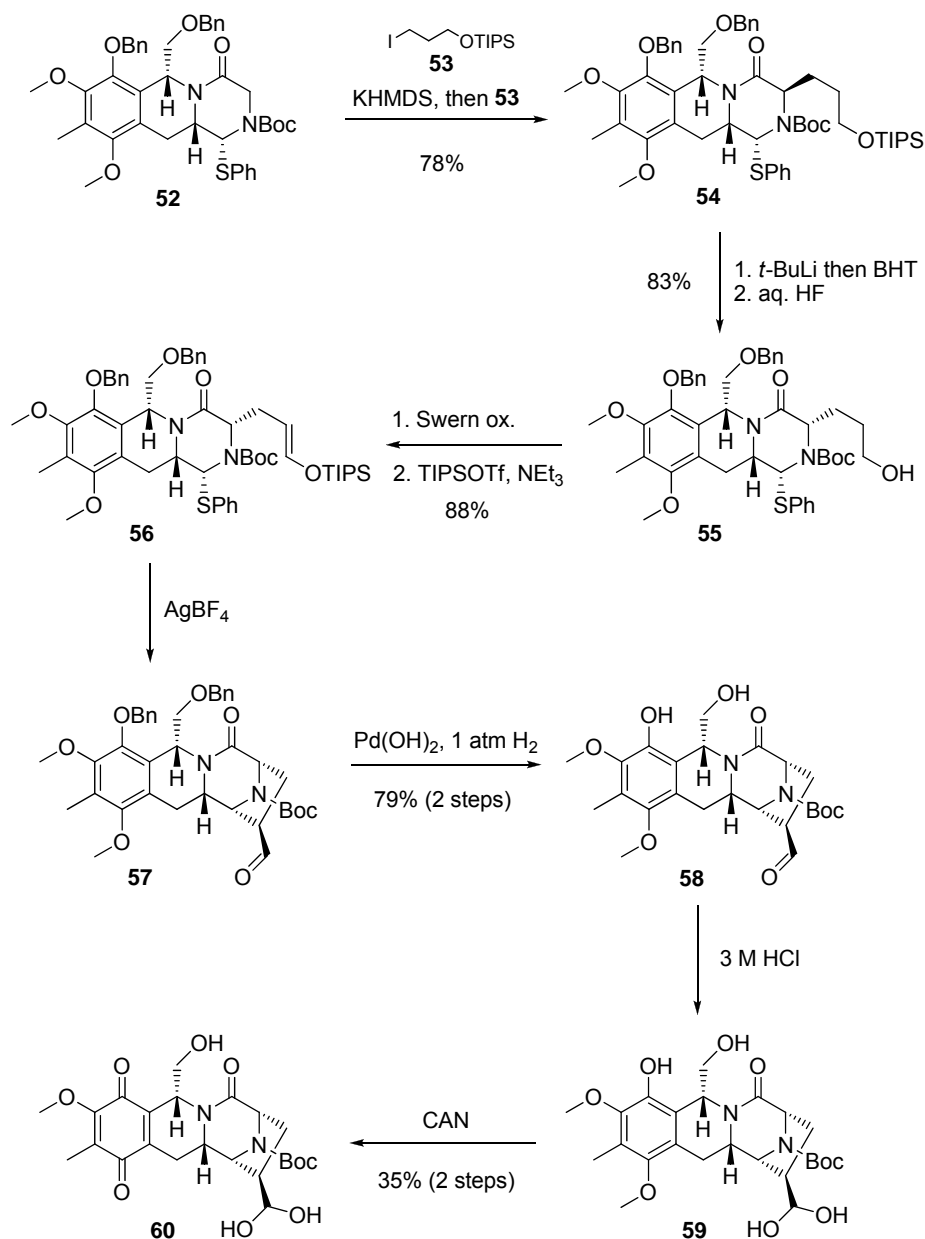
Scheme 8. Endgame to Magnus' Racemic Lemonomycinone Amide

Hydrogenolysis of both present benzyl protection groups gave compound **58**, whose aldehyde functionality was transformed into the unusual hydrate moiety concomitant to the cleavage of the carbamate yielding amine **59** as hydrochloride salt. To complete the endgame of this racemic synthesis, what was

left to do was the oxidation of the hydroquinone to its corresponding quinone **60** with CAN (**Scheme 8**).

Magnus *et al.* managed to synthesize racemic lemonomycin in 19 steps and an overall yield of 5% starting from imine **43**.

Fukuyama's Sterocontrolled Synthesis of the Carbon Skeleton of (-)-Lemonomycin

Fukuyama *et al.* reported a stereocontrolled synthesis of the 3,8-diazabicyclo[3.2.1]octane skeleton of (-)-lemonomycin in 2004.[32] An Ugi reaction using amino acids, a *N*-acyliminium cyclization to form the pyrrolidine moiety and a cross metathesis using 2nd generation Grubbs catalyst were the key steps in their synthesis of advanced precursor **71** of the natural compound.

The Ugi reaction of isocyanide **64**, dimethyl carbonate **63**, amino acid **62** and benzylic amine **61** in trifluoroethanol established diamido acetal **65**. Closure of the piperazine ring with CSA and consecutive formation of an oxazolidinone with potassium *t*-butanol provided intermediate **66**. *N*-Acyliminium cyclization precursor **68** was derived by reductive cleavage of the oxazolidinone, acetylation of the arising alcohol, concomitant deprotection and reprotection of the former silyl ether as acetate and final cross metathesis with allyltrimethylsilane (**67**). The following cyclization by cleavage of the carbon-silicon bond was carried out with boron trifluoride etherate as Lewis acid providing tricycle **69**. A protection reprotection sequence, affecting the Boc protected amine and the acetate, followed by a DMDO oxidation gave hemiaminal ether **70**. Finally, acyliminium mediated reduction, occurring from the less hindered *exo*-face, change of the phenol protecting group, Dess-Martin oxidation and TFA mediated cyclization gave amide **71**, completing the synthetic studies of Fukuyama and coworkers.
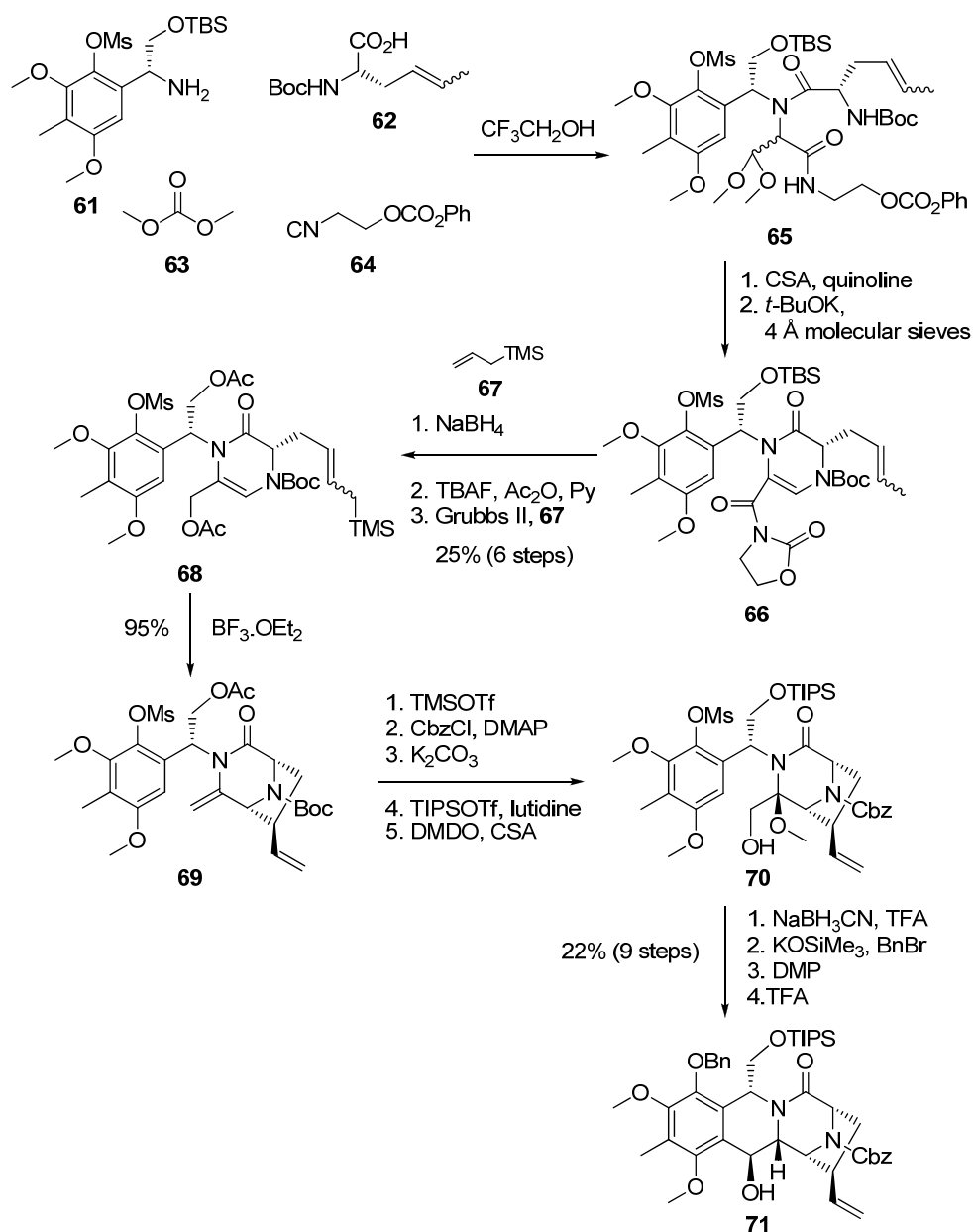
Scheme 9. Fukuyama's Contribution

This stereocontrolled synthesis of an advanced precursor of lemonomycin was preformed in 16 steps and an overall yield of 5% from readily available starting materials.

Zhu's First Synthetic Efforts Towards a Total Synthesis of Lemonomycin

Two years later, in 2006, pursuing the total synthesis of (-)-lemonomycin, after they finished a total synthesis of the congener ecteinascidine 743, J. Zhu and coworkers reported the synthesis of an advanced tricyclic intermediate of **1**.[33]

The first key step of this approach, the enantioselective alkylation of *N*-(diphenylmethylene)glycine *t*-butyl ester **73**, with literature known benzylic bromide **72**, in the use of *O*-(9)-allyl-*N*-(9'-anthracenylmethyl) cinchonidium bromide **74** provided tyrosine related ester **75** with an *ee* of higher than 90%. Subsequently, protection of the primary amine as carbamate, saponification of the ester under mild acidic conditions and coupling with 2,2-dimethoxy ethanol (**76**) gave cyclization precursor **77**. After oxidation of the acetal to the corresponding aldehyde, intramolecular Pictet-Spengler cyclization, consecutive cleavage of the benzylcarbamate and change of silyl ether protection group to benzyl, lactone-bridged tetrahydroisoquinoline **78** was obtained. In two more steps lactol **80** was afforded, by coupling of the isoquinoline with L-5,5'-dimethyl-*N*-Cbz-4-carboxy-glutamate (**79**) and subsequent chemoselective reduction of the lactone.
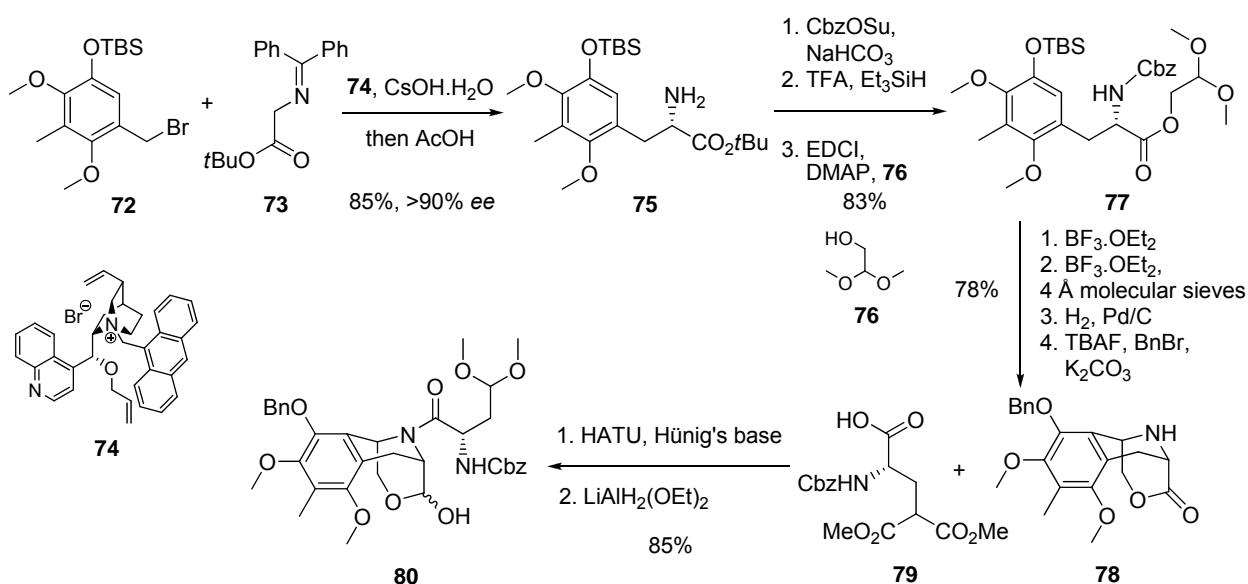
Scheme 10. Synthesis of Zhu's Lactol Bridged Intermediate

Piperazine derivative **81** was derived under Lewis acidic conditions as iminium ion intermediate. Unluckily, the desired intramolecular nucleophilic addition onto the present electrophilic center was not successful, thus the initially desired tetracyclic compound **82** could not be isolated. Iminium ion **81**, finally shifted the double bond, *via* its enamine tautomer, into the favored conjugated position, providing product **83**. Exposure to Krapcho conditions, concomitant reduction of the ester and amide functionalities and consecutive cyclization of the free alcohol onto the carbinol moiety gave an unstable amine **84**, which finally turned into enamine **85** upon impact of air-oxygen.
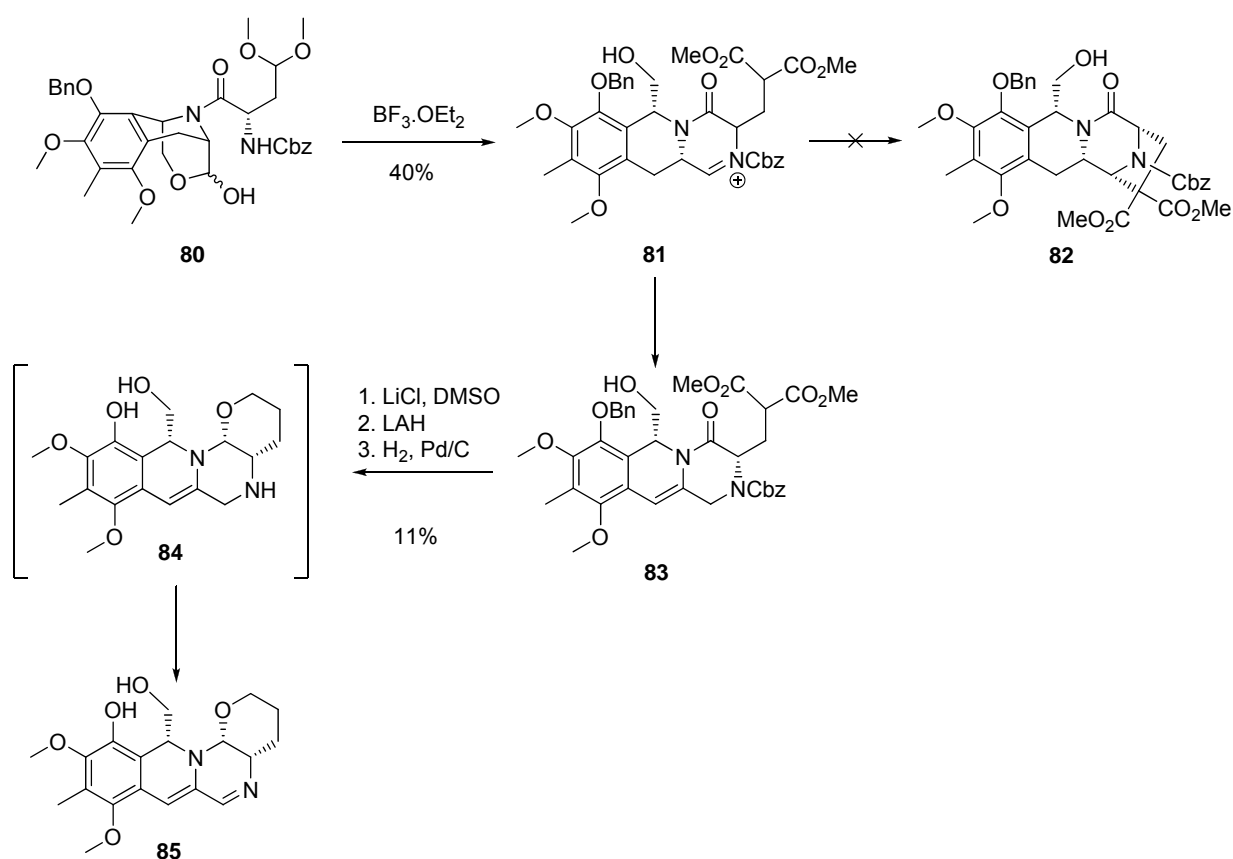
Scheme 11. Zhu's Endgame Towards the Enamine Intermediate

William's Synthesis of an Advanced Intermediate of Lemonomycin

Williams *et al.* synthetic efforts towards lemonomycin, based on a [1,3]-dipolar cycloaddition and an intramolecular condensation reaction, were published in 2007.[34]

Tetrahydroisoquinoline **88** was derived from iodide **86** and compound **87**, achieved from glycine, as main building blocks. After the coupling, protection group manipulation, concomitant partial cleavage of the auxiliary, reductive treatment of mixed anhydride intermediate and consecutive Pictet-Spenlger cyclization with ethylglyoxylate afforded the tetrahydroisoquinoline intermediate **88** as a single diastereomer. Subsequently, the free phenol was acetylated, the auxiliary was cleaved off and the freed secondary amine was subject of coupling with 2-(benzyl(Boc)amino)acetic acid (**89**). Amino aldehyde **90**, as precursor for the closure of the piperazine ring, was obtained after removal of the silyl protecting group and consecutive Swern oxidation. Cleavage of the Boc protecting group led to the desired ring closure providing an iminium ion **91**, which, similar to Zhu's former approach[33] (*vide supra*), tautomerized to the favored conjugated olefin **92**. Consecutive TEMPO oxidation gave iminium ion **93**, which underwent [1,3]-dipolar cycloaddition under treatment with triethylamine and *tert*-butyl acrylate forming tetracyclic compound **94** *via* an initial azomethine ylide.
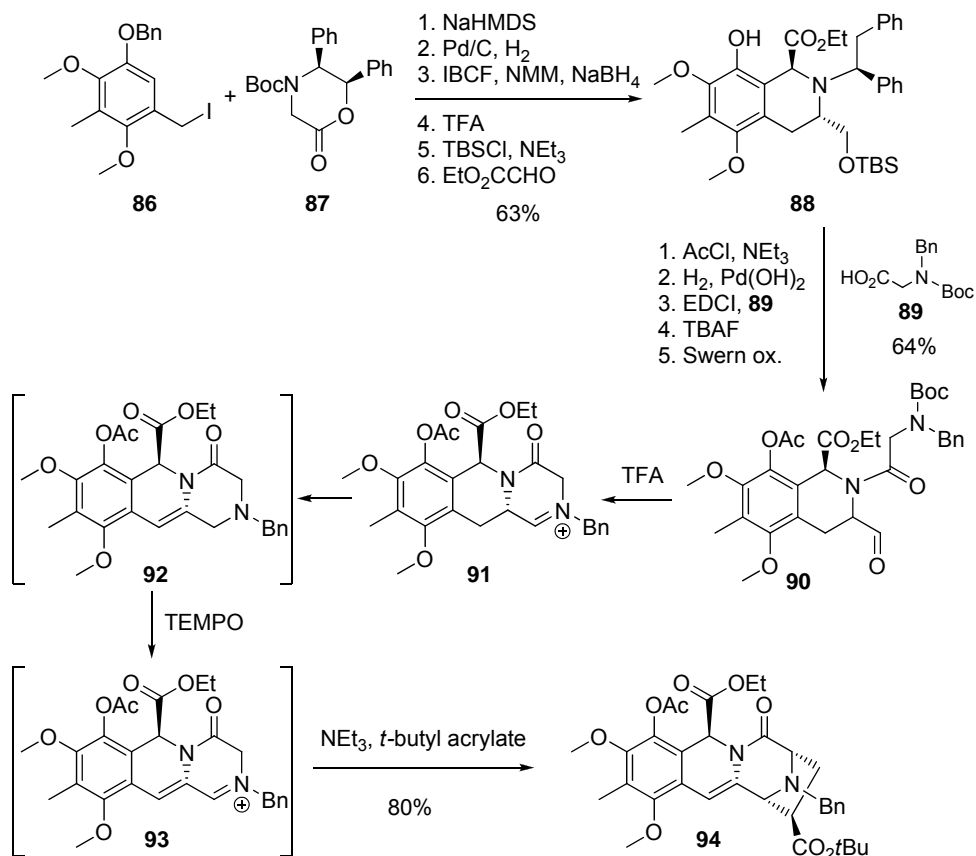
Scheme 12. Williams' Contribution

The configuration of the benzylic stereogenic center is the opposite as in the natural product, the hemiaminal moiety is present as an amide and the achieved advanced intermediate bears an undesired double bond in the isoquinoline core fragment.

Mulzer *et al.* were the next scientist to contribute a report containing synthetic efforts towards an advanced precursor of lemonomycin in 2008.[35] This publication will be discussed later on in the *Results and Discussion* section, as it will directly lead to our recent work.

Zhu's Second Contribution; Synthesis of an Advanced Lemonomycinone Amide

The most recently published report of the synthesis of an lemonomycin-aglycon derivative was edited by Zhu and coworkers.[36] The synthesis of lemonomycinone amide (**107**) started from a common point of their former publication, even with the tyrosine related intermediate **75**, derived by enantioselective alkylation as already mentioned (*vide supra*).[33] Cleavage of the silyl ether and consecutive diastereoselective Pictet-Spengler cyclization with benzyloxy acetaldehyde (**99**) gave tetrahydroisoquinoline **100**. Subsequently, protection of the free phenol and the secondary amine and consecutive transesterification of the *t*-butyl ester to the corresponding methyl ester provided suitable intermediate **101** for the peptide coupling with amino acid **98**.

The amino acid itself was obtained in seven steps starting with L-glutamic acid **95** as described in **Scheme 13**.
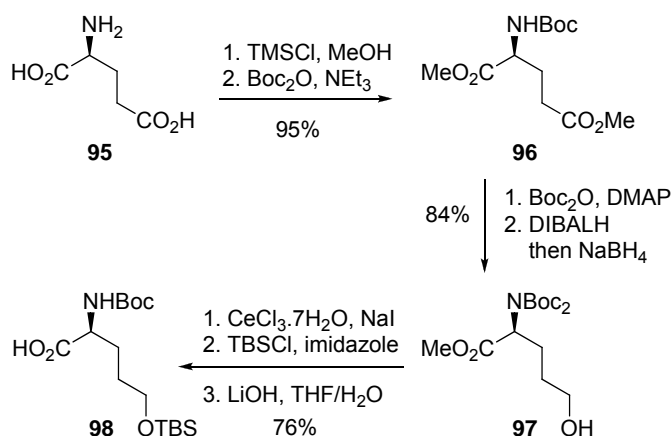
Scheme 13. Zhu's Side Chain

The linear synthesis was further prosecuted by reduction of the ester functionality of **102**, oxidation of the newly formed alcohol to the aldehyde, which cyclized upon cleavage of the carbamate protection group affording tricyclic intermediate **103** as a mixture of diastereomers.
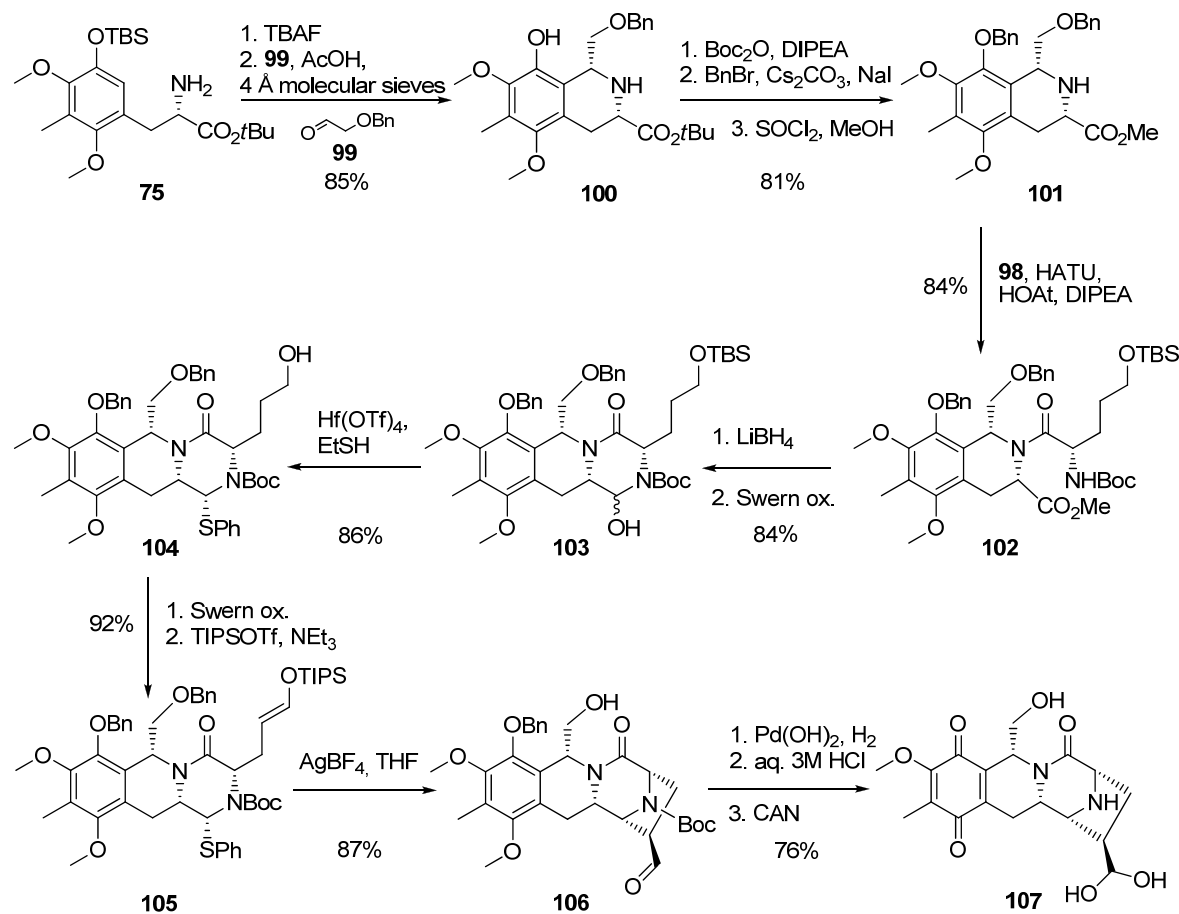
Scheme 14. Zhu's Second Approach towards an Advanced Intermediate of Lemonomycin

Treatment of the mixture of diastereomers with EtSH, as noted in **Scheme 14**, and concomitant cleavage of the TBS group provided thioaminal **104** as single diastereomer. Intramolecular Mannich reaction, promoted by silver tetrafluoroborate, of **105** was carried out after conversion of the free alcohol to TIPS trapped enol. Hydrogenolysis of the benzyl protecting group, cleavage of the Boc group with accompanied hydration of the aldehyde functionality and oxidation of the aromatic system to the corresponding quinone, converted **106** into the desired amide. The product **107**, with all stereogenic centers in the carbon core framework set correctly, was derived with an overall yield of 12% starting form cheap 2,6-dimethoxytoluene.

Short Summary of Synthetic Approaches

As outlined in this section only one total synthesis of (-)-lemonomycin is known to this very date. This enantioselective synthesis was published in 2003, although the natural compound was isolated in 1964 and its structure was elucidated in 2000. The enantioselective total synthesis of this tetrahydroisoquinoline antitumor antibiotic was performed with an overall yield of 3%. Among to date known seven synthetic efforts towards lemonomycin, it is the only approach not starting from an aromatic moiety, which later on is converted into a quinone, but with a piperazine precursor; and with the longest linear sequence of 15 steps it is definitely straight forward.

RESULTS AND DISCUSSION

Preliminary Synthetic Efforts and the Arising Strategy

In 2008 Mulzer and coworkers, published their stereocontrolled synthesis of the tetracyclic core frame work of (-)-lemonomycin (**1**).[35]

According to extensively investigated options to synthesize cyanocycline A (**115**), which shows a partially similar carbon core, we based our retrosynthetic analysis on former studies on this natural product. As outlined in **Scheme 15**, both synthetic approaches have advanced key intermediate **112** in common, with rings B, C and D already closed.
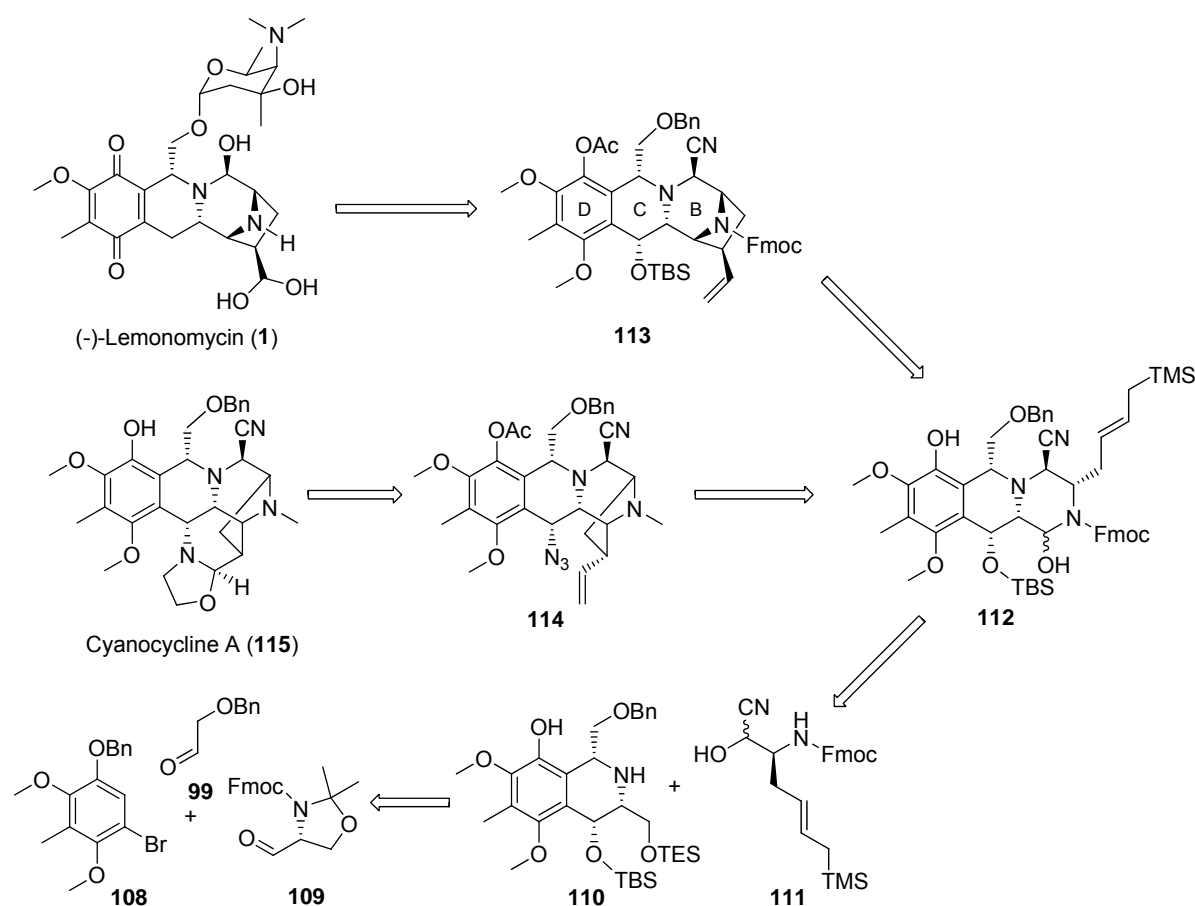
Scheme 15. Retrosynthetic Analysis of Lemonomycin and Cyanocycline A

Installation of the labile quinone and unusual hydrate moiety, as well as the glycosylation with the amino sugar was thought to be elaborated at a later stage of the synthesis. Linkage of readily available starting materials, **108** and **109**, Pictet-Spengler cyclization to install ring C, a Strecker-like reaction of cyanohydrin side chain **111** and tetrahydroisoquinoline **110** and finally a *N*-acyliminium cyclization to form the pyrrolidine ring were thought to be the key steps, leading towards lemonomycin. The synthetic efforts towards a total synthesis of cyanocycline A will not be discussed in further detail.[37]

In 2008, Mulzer *et al.* published the synthesis of advanced lemonomycinone nitrile **121**, starting with the alkylation of Fmoc protected Garner's aldehyde **109** with bromide **108**, providing **116**, favoring the desired diastereomer at a ratio of 5:2. Within an oxidation reduction sequence the mixture of diastereomer was converted into the *syn* product using PCC and DIBALH, and subsequently the alcohol was protected as silyl ether. The oxazolidine intermediate **117** was opened concomitant to the cleavage of the carbamate protection group. The arising primary alcohol was protected with TESCl and the benzyl group linked to the phenol was cleaved by hydrogenation, providing cyclization precursor **118**.
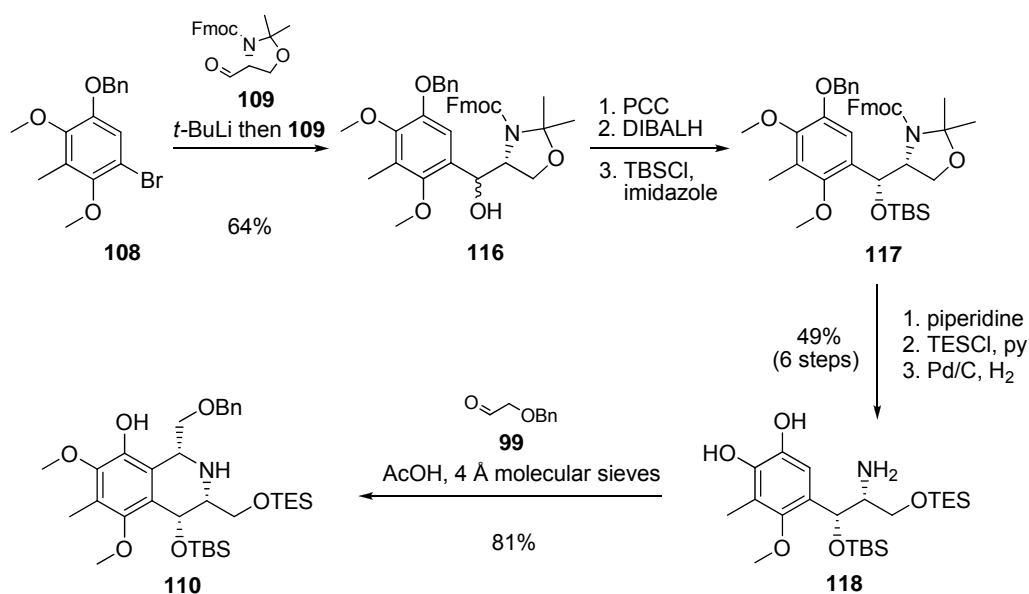
Scheme 16. Mulzer's Synthesis of the Tetrahydroisoquinoline Intermediate

The Pictet-Spengler reaction with benzyloxy acetaldehyde (**99**) was elaborated by the use of a catalytic amount of acetic acid and crushed 4 Å molecular sieves. Tetrahydroisoquinoline **110** was obtained as a single diastereomer in high yield. The cyanohydrine side chain **102** was provided by cross metathesis of allytrimethylsilane and allylbromide followed by Myers' enantioselective alkylation reaction and four consecutive literature known steps.[38,39]

The linkage of tetrahydroisoquinoline **110** and side chain **111** was performed with 2,2,2-trifluoroethanol in high yield. Acetylation of the phenol, selective cleavage of the TES group and consecutive oxidation with Dess-Martin periodinane directly afforded tricyclic substrate **120** bearing the piperazine moiety. Treatment with TFA provided tetracyclic lemonomycin precursor **121** at moderate yield.
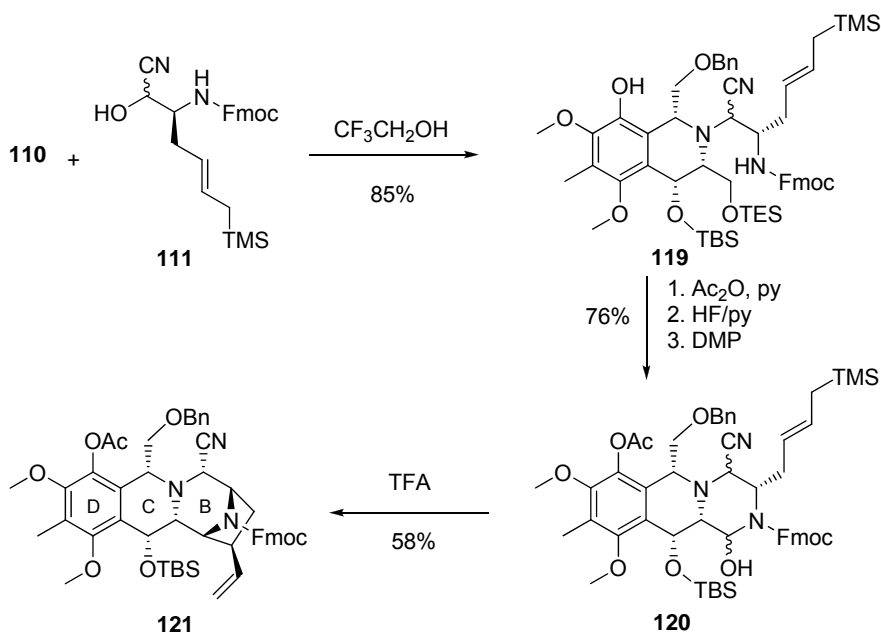
Scheme 17. Mulzer's Endgame Towards Lemonomycinone Nitrile

According to the proposed cascade reaction mechanism the configuration of the nitrile linked stereogenic center at C17 was inverted, forming the less bulky equatorial isomer, subsequent to the iminium ion **122** mediated formation of the pyrrolidine ring.
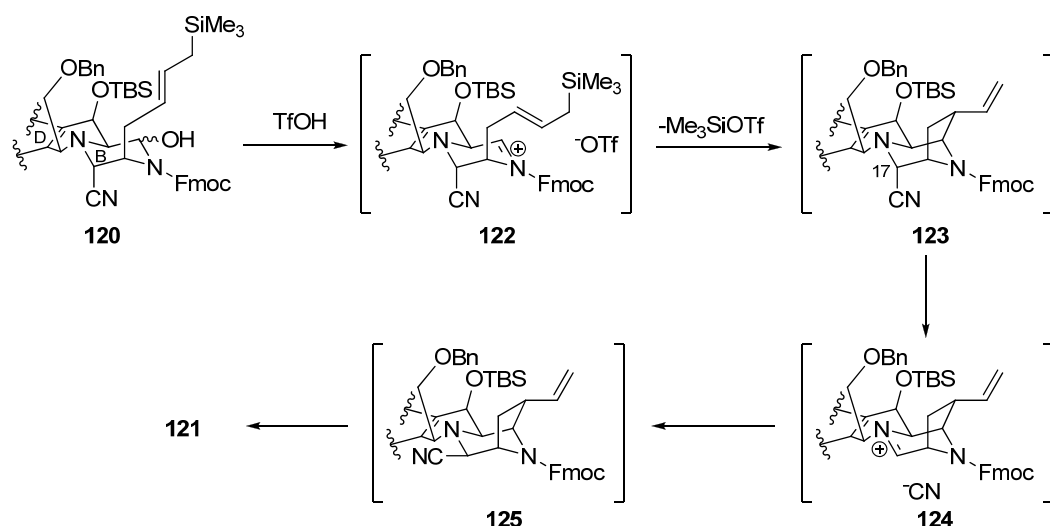
Scheme 18. Mechanistic Proposal for the Cyclization and the Inversion of the Stereogenic Center

Based on this 13 steps lasting approach towards lemonomycin derivative **121**, we developed a new, slightly modified approach. Removal of the benzylic hydroxyl group, arising from the alkylation of Garner's Aldehyde with bromide **108**, should shorten the synthesis by at least one reaction step.

Main Building Blocks

The Aromatic Portion

According to previous synthetic efforts, aromatic bromide **108** was thought to be a suitable building block for the alkylation of Garner's aldehyde (**109**, **134**). Bromide **108** was synthesized from cheap and readily available 2,6-dimethoxytoluene (**126**).[40,41] Friedel-Crafts acylation and consecutive Bayer-Villiger oxidation with *m*CPBA provided acetate **127**. After saponification of the ester functionality and protection of the freed phenol intermediate **128** was obtained. Finally, selective bromination of the *para*, respectively the *ortho* position of both methoxy groups, afforded desired precursor **108**. This five steps lasting reaction sequence was pursued with an overall yield of 50%. The restricting step

was the Bayer-Villiger oxidation as it was performed with a maximum yield of 69%.
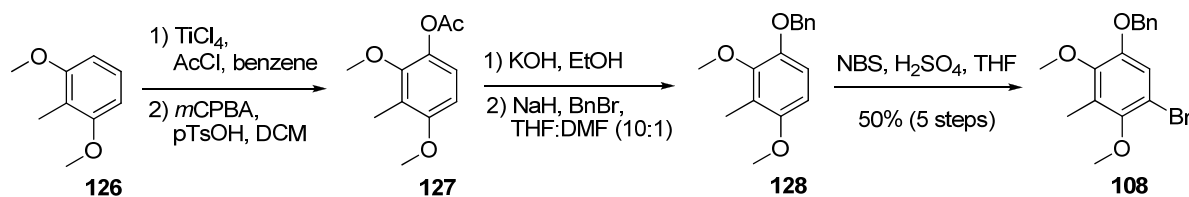
Scheme 19. Synthesis of the Aromatic Building Block

Garner's Aldehyde

Commercially available Garner's aldehyde was synthesized from L-serine in two modifications, either Cbz or Fmoc protected.[42,43] Therefore, the chirality of the later building block was introduced by the starting material itself.
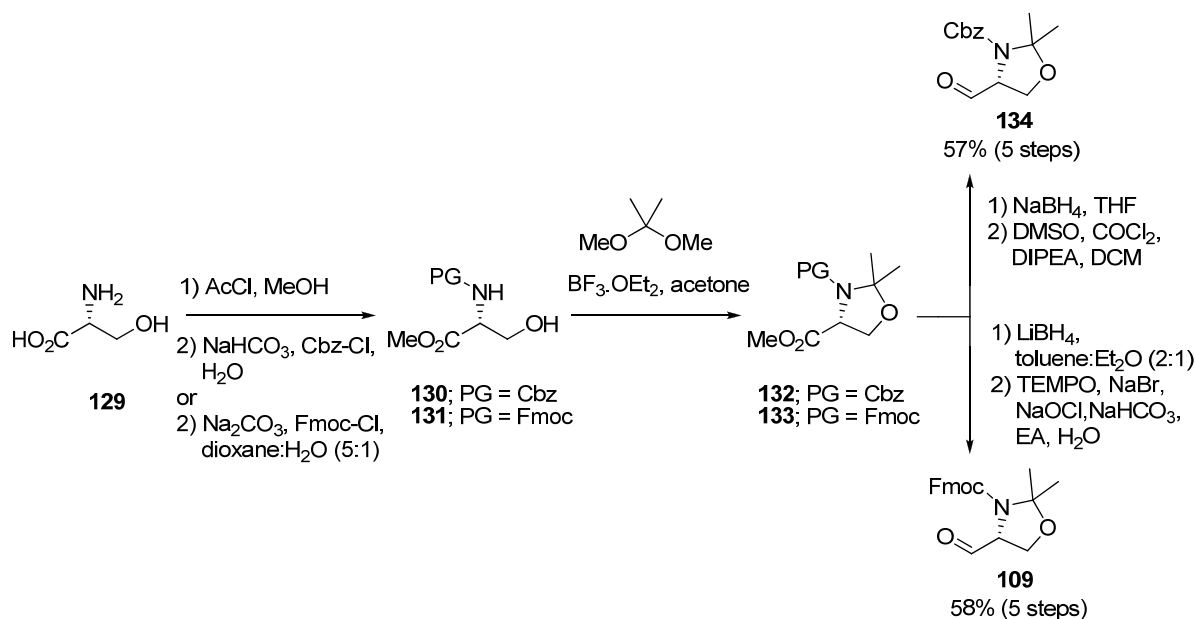
Scheme 20. Synthesis of Garner's Aldehydes

In the first step, the non essential amino acid L-serine (**129**) was converted into its corresponding methyl ester, which was isolated as hydrochloride salt and respectively protected either as benzyl- or 9-fluorenylmethyl carbamate, providing compound **130** and **131**. Formation of an amino acetal with

2,2-dimethoxypropane under Lewis acidic conditions afforded oxazolidine **132**, respectively **133**. Reduction of the ester functionality and consecutive oxidation of the prior installed alcohol gave desired compounds **134** and **109**.[44]

Alkylation Reaction

With both major building blocks in hands the planned alkylation reaction could be performed. Therefore, aromatic bromide **108** was treated with *n*-BuLi at -78 °C, to in *situ* form the lithium species, which then alkylated Garner's aldehydes (**109**, **134**). As the yield and diastereomeric ratio of this reaction varied, some optimization work had to be done at this stage of the reaction sequence (**Scheme 21**, **Table 1**).

134; PG = Cbz
109; PG = Fmoc
conditions

108; R$_1$ = Br, R$_2$ = Bn, R$_3$ = Me
137; R$_1$ = H, R$_2$ = TIPS, R$_3$ = H

135; R$_2$ = Bn, R$_3$ = Me, PG = Cbz
136; R$_2$ = Bn, R$_3$ = Me, PG = Fmoc
138; R$_2$ = TIPS, R$_3$ = H, PG = Fmoc
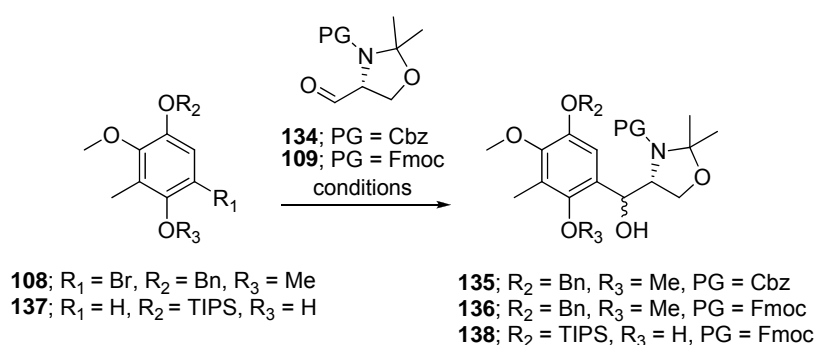
Scheme 21. The Alkylation of Garner's Aldehyde

Changing the solvent from THF to toluene dramatically improved the yield of this reaction. From the reactions in THF, besides the desired product, bromide **108** was isolated as its corresponding alcohol, indicating, that the lithiation of the halide took place, but by some reason, which was not investigated, the alkylation of Garner's aldehyde was unsuccessful.

Reaction No.	R$_1$	R$_2$	PG	Conditions	d.e.	Yield
1	Br	Bn	Cbz	THF, *n*-BuLi, -78 °C	2.3 : 1	23 - 75%
2	Br	Bn	Fmoc	THF, *n*-BuLi, -78 °C	2.1 : 1	20%
3	Br	Bn	Fmoc	THF, *t*-BuLi, -78 °C	X	X
4	Br	Bn	Cbz	THF, *t*-BuLi, -78 °C	X	X
5	Br	Bn	Fmoc	toluene, *n*-BuLi, -78 °C	1.8 : 1	54%
6	**Br**	**Bn**	**Cbz**	**toluene, *n*-BuLi, -78 °C**	**2.7 : 1**	**96%**
7	H	TIPS	Fmoc	THF, MeMgCl, r.t. then 0 °C	2.3 : 1	71%

Table 1. Conditions for the Alkylation of Garner's Aldehyde

Parallel to this effort a second aromatic portion **137**, derived from vanillin (**139**) (**Scheme 22**), was prepared,[45] which should have been a suitable alternative for the alkylation of **109** (reaction No. 7 in **Table 1**), if we would not have been able to solve this problem.
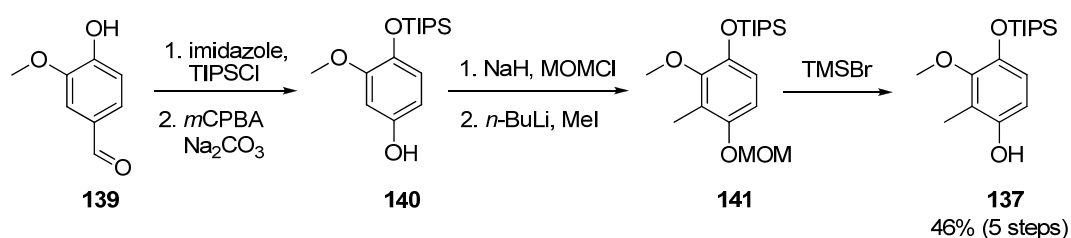
Scheme 22. Synthesis of the Alternative Aromate

Improving the Diastereomeric Ratio

The next goal was to optimize the stereochemical control of this synthesis. Therefore, the most obvious opportunity was to dehydroxylate the benzylic position *via* hydrogenolysis in a Parr-hydrogenation apparatus. Under these conditions the benzylic hydroxyl functionality was not affected at all, but the oxazolidine was opened and - only to a small amount - the benzyl group was cleaved. Different conditions by the use of TMSCl and sodium iodide, were uneffective, resulting in decomposition of the starting material. Desired dehydroxylated product **147** was obtained by the use of the Barton-McCombie

reaction *via* the radical substitution with tributyltin hydride of the prior formed xanthate **146**.

As dehydroxylation with triethylsilane and TFA was accompanied by the cleavage of the oxazolidine moiety and the reaction could be elaborated in much higher yield, it was regarded as the method of choice.
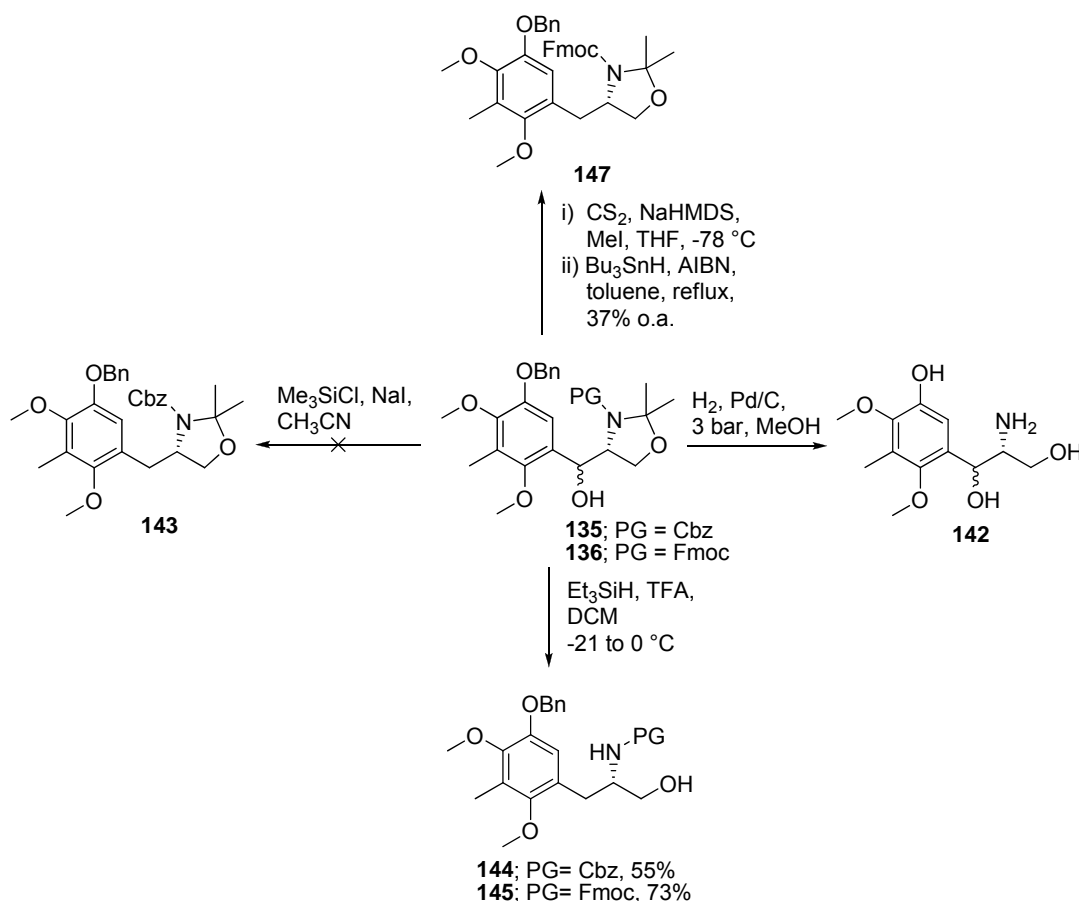
Scheme 23. Strategies to Remove the Benzylic Hydroxy Functionality

At this stage of the synthesis, we were not sure if removal of the stereogenic center in the benzylic position would affect the diastereoselectivity of the planed cyclization, nonetheless we decided to pursue this strategy.

After some protection group operations, product **144**, respectively **145**, should have provided the desired Pictet-Spengler cyclization precursor, but as mentioned in the next section, these steps bared some unexpected problems.

The Benzylic Problem

To perform the Pictet-Spengler reaction, a free phenol group *ortho* to the unsubstituted phenol position was needed. First, cleavage of the benzyl group of **145** with standard hydrogenation conditions was elaborated, which in the former contribution by Mulzer[35] was performed successfully. This deprotection would provide a secondary amino alcohol with a free phenol. But as outlined in **Table 2**, aminophenol **145** was not affected and the starting material could be recovered almost quantitatively.

Therefore, another intermediate (**149**), with a free amine and an alcohol protected as a silyl ether, was tested to investigate if the failure of the prior attempts to cleave the benzyl group was substrate related. But these reactions also failed, as the starting material remained unaffected. The substrates and solvents were inspected for impurities and, if necessary, purified or changed, unfortunately not leading to any result at that time.

The next modification of the starting material, as its amino functionality was left as carbamate and the alcohol in the *α*-position was protected as silyl ether, was expected to deliver better results. Surprisingly, hydrogenation with palladium on charcoal catalyst did not result in the desired deprotected phenol **151**, but the less reactive Lindlar catalyst led to Pictet-Spengler precursor **145** in low yield. With palladium hydroxide better results were obtained, as the benzyl group was cleaved. But probably due to the in *situ* formation of HCl from residual chloride impurities - present in the reagent because of its preparation procedure – lowered the yield to 50%, as the TES group was partially cleaved. As the last experiment indicated, hydrogenative deprotection definitely was possible and to avoid cleavage of the silyl ether, more active palladium on charcoal under much higher hydrogen pressure of 70 bar was suggested to be suitable conditions, but again the starting material was not affected.

In substrate **150** two aromatic rings were present, the benzyl group and the more electron rich and highly substituted one. Lithium was chosen to be the suitable alkali metal for the reductive cleavage of the aromatic protecting group under Birch conditions, as it is less reactive than sodium and therefore it should leave the electron rich aromatic ring unaffected. The reaction was performed in a

maximum yield of 31% providing free phenol **153**. As no other product was isolated and unaffected starting material was recovered this method was performed in a cyclic way and was favored in regard to the hydrogenation reaction.
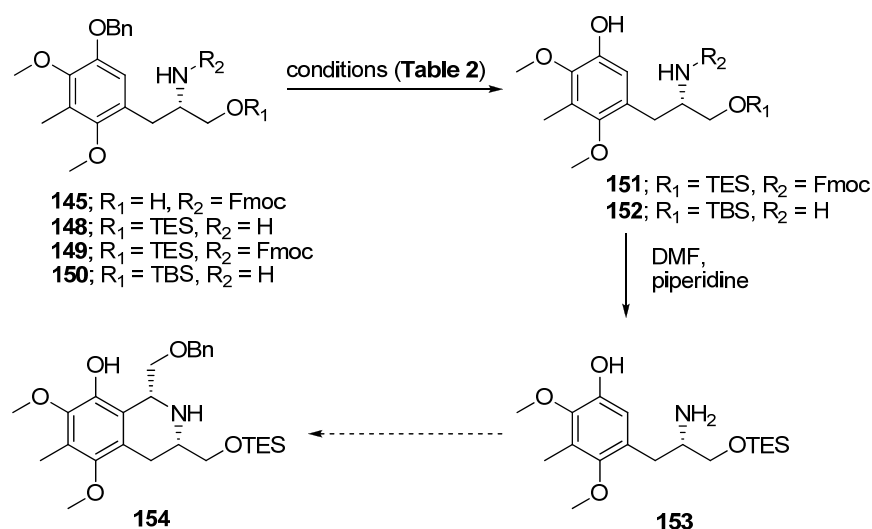
Scheme 24. Elaboration of the Prictet-Spengler Cyclization Precursor

Reaction No.	R_1	R_2	Conditions	Yield
1	H	Fmoc	H_2, Pd/C (5 w%), EA	X
2	H	Fmoc	H_2, Pd/C (5 w%), EA, 3 bar	X
3	H	Fmoc	H_2, Pd/C (5 w%), AcOH, MeOH : EA (3 : 2)	X
4	TES	H	H_2, Pd/C (5 w%), MeOH	X
5	TES	H	H_2, Pd/C (5 w%), MeOH 3 bar	X
6	TES	Fmoc	H_2, Pd/C (5 w%), MeOH : EA	X
7	TES	Fmoc	H_2, Pd/CaCO$_3$ (10 w%), EA, 3 bar	14%
8	*TES*	*Fmoc*	*H_2, Pd(OH)$_2$/C (20 w%), MeOH : EA (3 : 2), 3 bar*	*50%*
9	TES	Fmoc	H_2, Pd/C (5 w%), MeOH : EA (3 : 2), 70 bar	X
10	**TBS**	**H**	**Li, NH$_3$ (l.), THF : *t*-BuOH (3 : 2), -78 °C**	**31%**

Table 2. Conditions for the Benzyl Group Cleavage

Cleavage of the carbamate protecting group was carried out under standard conditions providing cyclization precursor **146**. The Pictet-Spengler

reaction could not be elaborated at his stage of the synthesis, as the amount of obtained cyclization precursor was too small to allow a reproducible reaction procedure.

The dramatical change of reactivity of the benzyl group by modification of the former tetrahydroisoquinoline approach (*vide supra*), wherein the protection group was cleaved by hydrogenation with palladium on charcoal under normal pressure and high yield, was the driving force to investigate other synthetic strategies to obtain a tetrahydroisoquinoline intermediate of lemonomycin.

Alternative Approaches Towards the Tetrahydroisoquinoline Key Intermediate

With the aim to improve the efficiency of the former approach, alternative strategies to provide a suitable tetrahydroisoquinoline for the endgame towards aglycon nitrile **158** were elaborated and the following slightly modified retrosynthetic analysis was proposed.
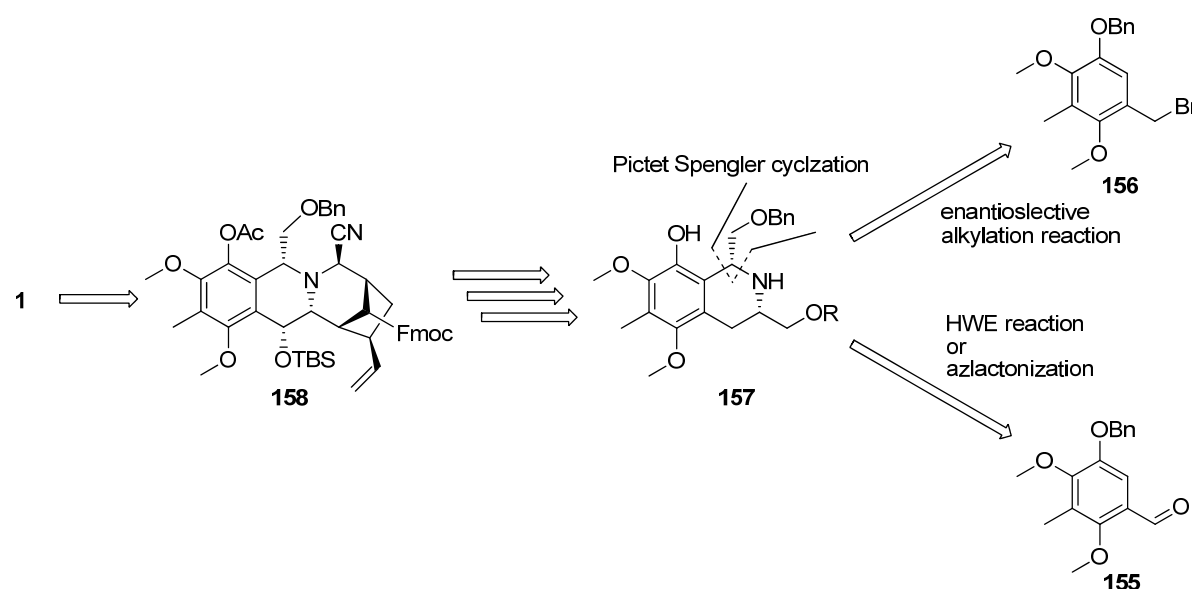
Scheme 25. The Alternative Retrosynthetic Strategy Towards Lemonomycinone Aglycon Nitrile

Benzylic bromide **156** was obtained according to **Scheme 26**. Halide metal exchange and consecutive alkylation of DMF afforded the desired benzaldehyde **155** for the HWE approach. Finally, reductive treatment with sodium borohydride and conversion of the obtained benzylic alcohol into the corresponding bromide *via* Appel reaction provided desired building block **156**.
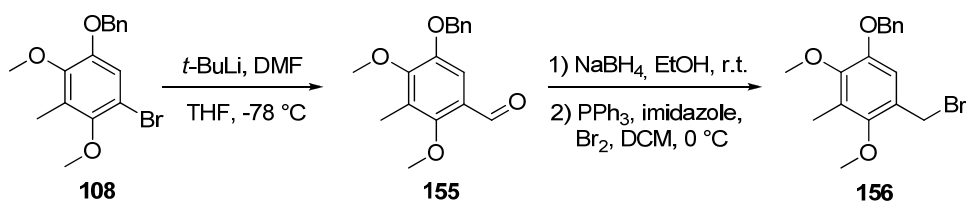
Scheme 26. Synthesis of the Benzylic Aldehyde and Bromide

Aza-lactonization Approach

Similar to the literature known formation of α-acetaminocinnamic acid,[46] compound **161** could be established *via* an aza-lactonization with acetylglycine (**151**) and subsequent hydrolysis. Therefore, a solution of benzaldehyde **147**, acetyl glycine **151** and sodium acetate in acetic anhydride was heated to 140 °C in a sealed tube. Unfortunately aza-lactone **152** could not be derived and this approach was abandoned.
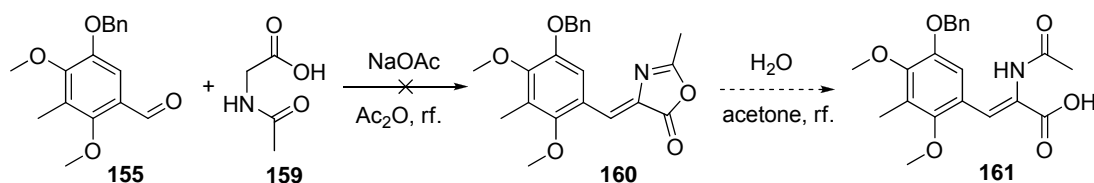
Scheme 27. The Aza-lactonization Approach

The next steps would have been esterification of the amido acid and subsequent reduction to the corresponding alcohol. Protection of the alcohol as silyl ether followed by asymmetric hydrogenation[47] of the enamino silylether and concomitant cleavage of the benzyl group should have provided a suitable precursor for the Pictet-Spengler cyclization.

Horner-Wadsworth-Emmons Approach

According to preliminary retrosynthetic considerations, Horner-Wadsworth-Emmons olefination of benzaldehyde **155** and phosphonate **165** should selectively provide desired *E*-alken **166** in regard to the carbon substituents of the formed double bond.

Initially, phosphonate **165** was derived from glyoxalic acid (**155**) and benzylcarbamate (**154**) by condensation, ester- and etherification and subsequent conversion into phosphonate **165** as outlined in **Scheme 28**.

Subsequently, the olefination reaction was carried out with DBU providing enamine **166** as a single diastereomer.
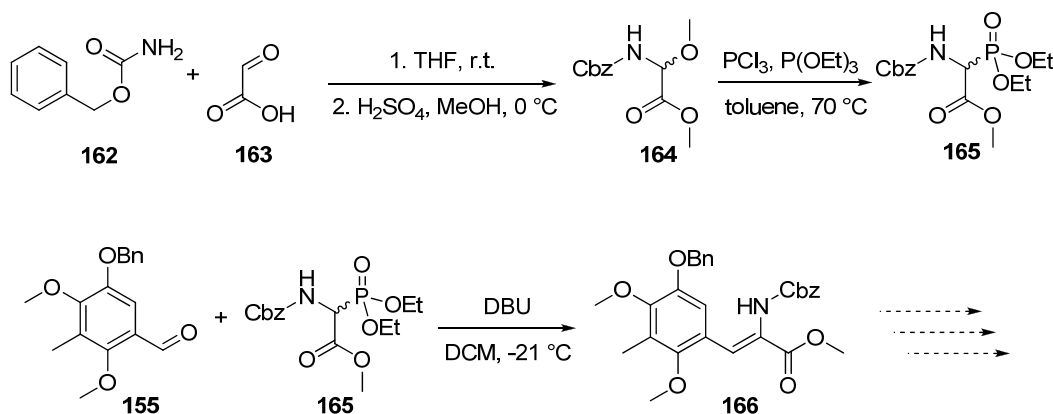
Scheme 28. The Horner-Wadsworth-Emmons Approach

As one of the contemporaneously elaborated alkylation reactions was delivering good results we decided not to pursue further reactions, which would have been enantioselective hydrogenation[47] and concomitant or subsequent removal of the benzyl group, leading to a suitable cyclization precursor.

Myers' Alkylation Approach

Commercially available (-)-pseudoephedrine glycine amide **167**, bearing the chiral auxiliary and therefore controlling the enantioselectivity of this reaction, was alkylated with bromide **156**, providing secondary *α*-amino amide **168**. Consecutive reductive cleavage of the auxiliary afforded amino alcohol **169**. Due to the unsatisfying yield of this reaction and a recent progress with a heterogenic catalyzed alkylation reaction (*vide infra*), the Myers' alkylation approach was abandoned.
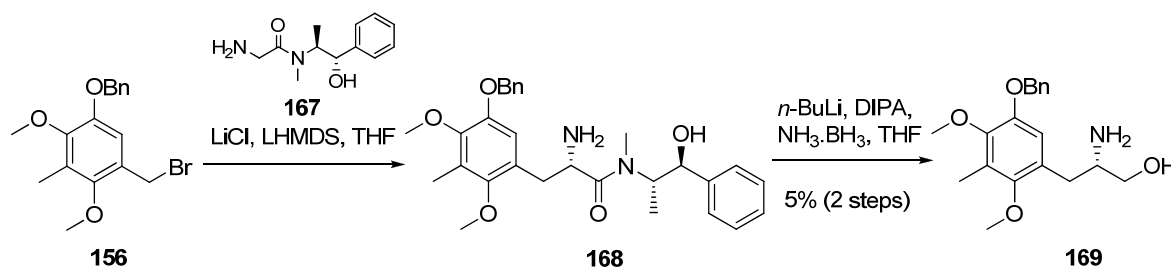
Scheme 29. The Myers' Enantioselective Alkylation Approach

Enantioselective Alkylation via Corey-Lygo's Phase Transfer Catalyst

As the structure of cyclization precursor **153** is strongly related to the amino acid L-tyrosine, two new synthetic suggestions were investigated. The first option would have been to import the correct stereochemistry *via* the amino acid as starting material followed by modification of the aromatic moiety. According to our preliminary retrosynthetic analysis (*vide infra*), we decided to focus our synthetic efforts on the use of the enantioselective alkylation reaction by the use of Corey-Lygo's cinchonidium catylst **74**.[48,49]

Therefore, *N*-diphenylmethylene glycine *t*-butyl ester (**73**)[50] was treated with CsOH.H$_2$O in the presence of catalyst **74**. Subsequently, bromide **156**, as it was used in the former Myers' alkylation approach, was added at low temperature under vigorous stirring, which was reported to be the crucial restricting factor of the reaction time.[51] Imine **170** was provided in excellent yield and was directly

hydrolyzed to the corresponding amino ester **171**. The *ee* of 88% was determined by comparison of the NMR-data of elaborated *S*- and *R*-Mosher amide (**184**, **186**). The present *t*-butyl ester was reduced to the corresponding alcohol and protected as silyl ether. Desired Pictet-Spengler cyclization precursor **152** was derived *via* cleavage of the benzyl group under Birch conditions (*vide supra*). Finally, tetrahydroisoquinoline **173** was obtained in excellent yield by addition of benzyloxy acetaldehyde **99** to a solution of amino phenol **152** under acidic conditions in the presence of crushed 4 Å molecular sieves as single diastereomer.
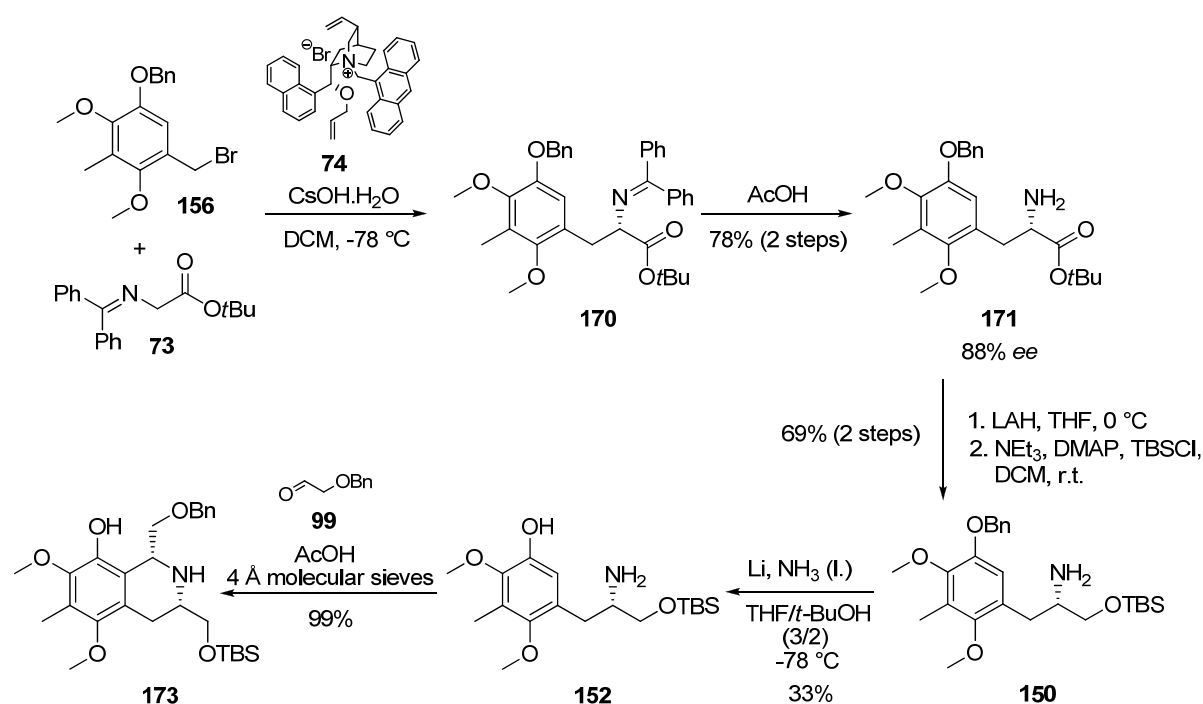
Scheme 30. The Enantioselective Alkylation Approach *via* Corey-Lygo Cinchonidium Catalyst

Zhu and coworkers already adopted Corey-Lygo's phase transfer catalyst in their total synthesis of quinocarcin and in their synthetic studies towards lemonomycin in 2006 (*vide supra*).[33]

As the benzyl group was not the most convenient protection group in this synthesis, it was redesigned for MOM protected analog **168** of benzylic bromide **148** (*vide infra*). Detailed experimental procedures leading to this aromatic building block will be presented in a later section. Again enantioselective

alkylation was used to install the crucial stereocenter in *α*-position to the ester functionality. Reduction of the ester and protection of the prior installed alcohol as silyl ether provided compound **176**.
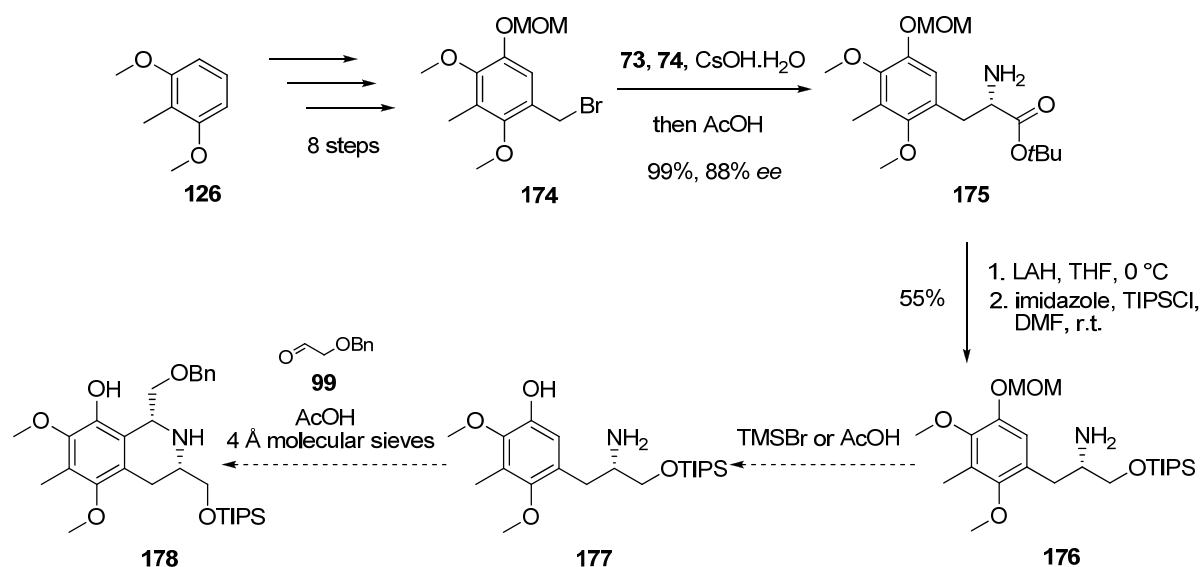
Scheme 31. The Promising Approach with the MOM Analog

Cleavage of the methoxymethyl moiety and consecutive Pictet-Spengler cyclization of compound **171** could not be elaborated at this stage of the synthesis, but the MOM protection group will be easily cleaved by the use of TMSBr or under acidic conditions.

OUTLOOK

The alternative synthetic route *via* the MOM protected aromate is currently topic of our investigation, showing equal enantioselectivity in the heterogeneous alkylation reaction and excellent yields in the already elaborated reaction steps.

With tetrahydroisoquinoline **173**, respectively **178** in hands, the endgame described in **Scheme 17**, which was accomplished with substrate **110**,[35] possessing a similar silyl protection group, should lead us to aglycon nitrile **158**.

CONCLUSION

The rings D and C of (-)-Lemonomycin were installed with all present stereogenic centers set correctly, following a synthetic route containing an enantioselective heterogeneously catalyzed alkylation and the classic Pictet-Spengler reaction as key steps. Tetrahydroisoquinoline **173** was obtained in 8% yield and 14 linear steps starting from inexpensive 2,6-dimethoxytoluene with excellent enantioselectivity.

To increase the yield the analog route with the MOM protected phenol **174**, as the cleavage of the benzyl group was the restricting reaction step in the elaborated synthesis, will be subject of our future work.

EXPERIMENTAL SECTION

General Experimental Procedures:

Synthetic methods

Reaction vessels for moisture- and air-sensitive reactions were flame dried with a heat gun or a Bunsen-burner under vaccum and consecutively purged with argon. Where needed, reactions were performed under slight over pressure of argon (balloon) in dry solvents. Sensitive solvents and reagents were either transferred by double tipped needle or syringe through rubber septa to predried vessels. If not mentioned otherwise, all reactions were stirred magnetically.

Solvents and Reagents

Commercial reagents were checked for impurities by NMR spectroscopy and thin-layer chromatography and were used as delivered unless otherwise noted. Freeze-pump-thaw technique was used to degas reaction mixtures and solvents where needed.

Methanol, dichloromethane (DCM), *N,N*-dimethyl formamide (DMF), acetonitrile, hexane, ethyl acetate (EA), diisopropylamine (DIPA), diisopropylethylamin (DIPEA) and triethylamine (TEA) were distilled form calcium hydride. Tetrathydrofuran (THF), toluene, benzene and diethylether were refluxed with sodium in the presence of benzophenone and were freshly distilled prior to use.

Dry solvents were stored under argon atmosphere over 4 Å molecular sieves in predried vessels.

Analytics and Purification

Thin-layer chromatography (tlc)

Coated aluminum sheets and glass plates, both E. Merck silica gel 60-F_{254} impregnated with a 254 nm fluorescent indicator, were used for reaction control. TLC was usually developed with either a DCM/MeOH or a hexane/EE mixtures mentioned in the respective procedures. UV-active spots were detected at longwave (254 nm) or shortwave UV (180 nm). Additionally most developed tlc-plates were treated with following visualization reagents followed by heating with a heat gun: acidic ninhydrin solution in butanol (dying amines and imines); aqueous ceric ammonium molybdate solution (CAM); acidic vanillin solution in ethanol or anisic aldehyde in acetic anhydride.

Column chromatography

Preparative flash-column-chromatography was carried out using silica gel (Merck KGA, 60 Å pore size, 230-240 mesh). As eluents, mixtures (detailed compositions are reported in the procedures) of either hexane/ethyl acetate or DCM/MeOH were used; in the first case "dry packing" and in the second "wet packing" were chosen as routine conditioning circumstance.

NMR Spectroscopy

^{1}H NMR and ^{13}C NMR spectra were recorded on either Bruker Avance 250 MHz, Avance 400 MHz or Avance III 400 MHz spectrometer. Deuterated chloroform was chosen as the desired solvent for all measurements, also serving as internal reverence with its respective residual signals (^{1}H, δ = 7.26; ^{13}C, δ = 77.0).

Chemical shifts of proton and carbon resonances are given in parts per million (ppm, δ scale) referring to the resonance of trimethylsilane. Coupling constants J are reported in Hz (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet,

br = broad signal). Assignment of proton resonances was, as far as possible, confirmed by 2D spectra (COSY, HSQC, HMQC, NOESY).

Mass Spectroscopy

Mass spectra were measured on *Micro Mass*, *Fissions Instrument* and *Trio200* spectrometers. HRMS were taken with a Finnigan MAT 8230 with a resolution of 10000.

Experimental Procedures

1-(2,4-Dimethoxy-3-methylphenyl)ethanone (179)
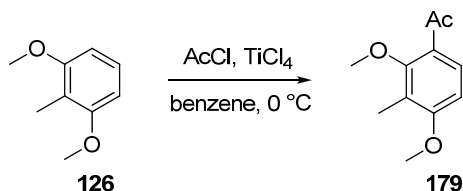
A round-bottomed flask equipped with a reflux condenser was charged with titanium tetrachloride (86.45 mL, 788 mmol, 2 equiv.) and cooled to 0 °C. Upon the drop wise addition of acetyl chloride (56.01 mL, 788 mmol 2 equiv.) *via* dropping funnel the reaction mixture turns orange and solidifies. Subsequently a solution of 2,6-dimethoxytoluene (60.00 g, 394 mmol, 1 equiv.) in benzene (260 mL) was added to the orange residue at 0 °C within 15 min resulting in a deep red solution. After 30 min at that temperature the reaction mixture was quenched by pouring it into ice cold HCl (5%, 100mL). The aq. layer was washed with DCM (4 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated. Purification by distillation under high vacuum gave 30.22g (98 %) **179** as pale yellow oil.

$C_{11}H_{14}O_3$; 194.23 g/mol;

R_f.: 0.64 (hexane : ethyl acetate = 4 : 1);

^1H NMR (CDCl$_3$, 250 MHz): δ [ppm] = 7.62 (d, *J* = 8.8 Hz, 1 H), 6.68 (d, *J* = 8.8 Hz, 1 H), 3.87 (s, 3 H), 3.75 (s, 3 H), 2.62 (s, 3 H), 2.16 (s, 3 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 198.9, 162.1, 159.3, 128.9, 125.5, 120.2, 105.9, 61.8, 55.7, 30.3, 8.9;

HRMS (70 eV, 30 °C) calc.: m/z 194.0943, found 194.0951.

2,4-Dimethoxy-3-methylphenyl acetate (127)
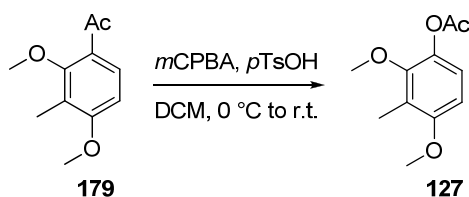
A solution of **179** (30.22 g, 156 mmol, 1 equiv.) and *p*TsOH (208 mg, 1.29 mmol, 0.007 equiv.) in DCM (35 mL) was treated with a suspension of *m*CPBA (57.57 g, 234 mmol, 1.5 equiv.) in DCM (280 mL) at 0 °C *via* dropping funnel within one hour. The resulting yellow suspension was allowed to warm to r.t. over night. After the addition of a saturated $NaHSO_3$ solution (15 mL) the reaction mixture was vigorously stirred for 15 min, followed by the addition of sat. $NaHCO_3$ solution (15 mL) and additional 15 min of stirring. The aq. layer was extracted with DCM (3 x 100 mL). Consecutively the combined organic layers were washed with sat. $NaHCO_3$ solution (100 mL) and water (100 mL), dried with Na_2SO_4. Evaporation of the solvent and purification by high vacuum distillation yielded 22.29 g of **127** (68 %) as pale yellow oil.

$C_{11}H_{14}O_4$; 210.23 g/mol;

R_f: 0.84 (hexane : ethyl acetate = 4 : 1);

^{1}H NMR ($CDCl_3$, 250 MHz): δ [ppm] = 6.87 (d, *J* = 8.8 Hz, 1 H), 6.61 (d, *J* = 8.8 Hz, 1 H), 3.81 (s, 3 H), 3.74 (s, 3H), 2.32 (s, 3 H), 2.15 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ [ppm] = 169.8, 156.3, 150.4, 137.5, 121.2, 119.7, 105.5, 60.8, 55.7, 20.8, 9.18;

HRMS (70eV, 30 °C): calc.: 210.0892, found: 210.0899.

2,4-Dimethoxy-3-methylphenol (180)
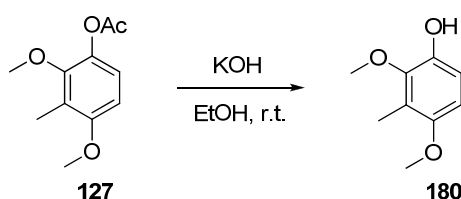
To a solution of **127** (63.0 g, 299 mmol, 1 equiv.) in EtOH (820 mL), aq. KOH (120 mL, 10 M, 4 equiv.) was added accompanied by moderate warming of the reaction mixture. After one hour at room temperature water (400 mL) was added and EtOH was removed under reduced pressure. The resulting aqueous solution was extracted with DCM (100 mL), acidified to pH 1 with conc. HCl and again washed with DCM (3 x 100 mL). The combined organic layers were washed with water (100 mL) and dried over Na_2SO_4. Evaporation of the solvent

and distillation under high vacuum afforded 38.88 g (77 %) of orange phenol **180**, which crystallized on standing.

$C_9H_{12}O_3$; 168.19 g/mol;

R_f.: 0.51 (hexane : ethyl acetate = 4 : 1);

^1H NMR (CDCl$_3$, 250 MHz): δ [ppm] = 6.76 (d, J = 8.8 Hz, 1 H), 6.53 (d, J = 8.8 Hz, 1 H), 5.41 (s, 3 H), 3.77 (s, 3 H), 2.17 (s, 3 H);

^{13}C NMR (CDCl$_3$, 62.5 MHz): δ [ppm] = 152.1, 146.1, 143.1, 120.1, 111.8, 107.0, 60.9, 56.2, 9.4;

HRMS: calc.: 168.1898, found: 168.1894.

1-(Benzyloxy)-2,4-dimethoxy-methylbenzene (128)
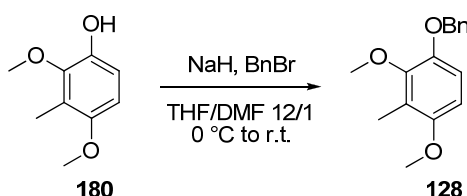
Phenol **180** (1.0 g, 6 mmol, 1 equiv.) was dissolved in a mixture of THF/DMF 12/1 (13.5 mL). The resulting orange solution was cooled to 0 °C. After 15 min sodium hydride (248 mg, 6 mmol, 1.05 equiv.) was added batch-wise under vigorous stirring. Benzyl bromide (740 µL, 6 mmol, 1.05 equiv) was continuously added *via* syringe within 5 min. Over night the reaction mixture was allowed to warm to room temperature, resulting in a beige solution the next day. The reaction was quenched by the addition of water (15 mL) turning the mixture from beige to purple. The aqueous layer was separated and extracted with hexane (3 x 20 mL). The combined organic layers were washed with water, dried over Na$_2$SO$_4$. After filtration and solvent removal *via* evaporation the crude product was purified by flash column chromatography (hexane : ethyl acetate = 19 : 1) to provide 1.45 g (95 %) **128** as yellow oil

$C_{16}H_{18}O_3$; 251.31 g/mol;

R_f.: 0.54 (hexane : ethyl acetate = 9 : 1);

^1H NMR (CDCl$_3$, 62.5 MHz): δ [ppm] = 7.54 (m, 5 H), 6.91 (d, J = 8.9 Hz, 1 H), 6.62 (d, J = 8.9 Hz, 1 H), 5.17 (s, 2 H), 4.03 (s, 1 H), 3.86 (s, 1 H) 2.44 (s, 3 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 153.3, 149.4, 146.6, 138.0, 128.9, 128.1, 127.7, 121.6, 112.5, 105.6, 72.0, 60.9, 56.3;

HRMS (70eV, 50 °C): calc.: 258.1256, found: 258.1261.

1-(Benzyloxy)-5-bromo-2,4-dimethoxy-3methylbenzene (108)
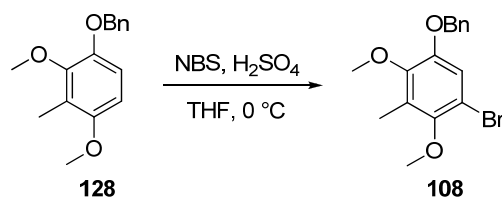
A solution of **128** (17.52 g, 67 mmol, 1 equiv.) in THF (210 mL) was cooled to 0 °C. After 10 min N-bromosuccinimide (15 g, 81 mmol, 1.2 equiv.) was added batch-wise to the vigorously stirred reaction mixture. Conc. sulfuric acid (200 µL) was added, causing the color of the mixture to turn into deep orange. After 90 min the reaction was quenched by addition of sat. aq. NaS$_2$O$_3$ solution in the cold. 15 min later the aq. layer was separated and extracted with hexane (3 x 60 mL). The combined organic layers were washed with brine (100 mL) and water (50 mL) and finally dried over Na$_2$SO$_4$. Removal of the solvent and purification by flash column chromatography (hexane : ethyl acetate = 19 :1) yielded in 21.77 g (95 %) of bromine **108** as yellow oil.

C$_{16}$H$_{17}$BrO$_3$; 337.21 g/mol;

R$_f$.: 0.56 (hexane : ethyl acetate = 9 : 1);

^{1}H NMR (CDCl$_3$, 62.5 MHz): δ [ppm] = 7.38 (m, 5H), 7.00 (s, 1 H), 5.05 (s, 2 H), 3.82 (s, 3 H), 3.76 (s, 3 H), 2.26 (s, 3H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 150.3, 149.3, 148.4, 137.1, 129.0, 128.4, 127.8 127.7, 116.1, 111.0, 71.7, 60.8, 60.7, 10.5;

HRMS (70eV, 50 °C): calc.: 336.0361, found: 336.0358.

1-(Benzyloxy)-5-(bromomethyl)-2,4-dimethoxy-3-methylbenzene (156)
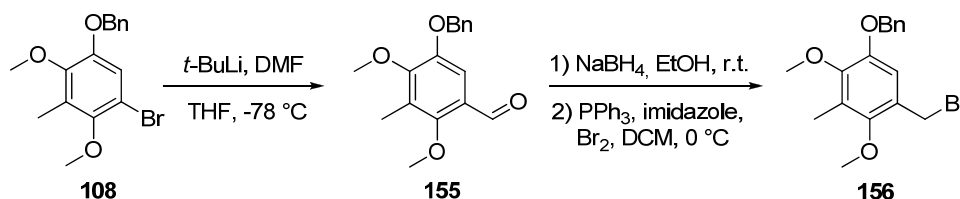
To a solution of bromine **108** (4.21 g, 15 mmol, 1 equiv.) in THF (55 mL) was added drop wise *t*-BuLi (22.7 mL, 1.7 M in hexane) at -78 °C within 30 min. Upon the addition the initially bright yellow solution turned its color from orange over bright green and olive to brown. After 15 min DMF (5.8 mL, 74 mmol, 4.9 equiv.) was added *via* syringe followed by additional 30 min of stirring at -78 °C. The reaction mixture was diluted with ethyl acetate (50 mL) and quenched by the addition of brine (50 mL) at -78 °C. The resulting biphasic mixture was warmed to room temperature. The organic layer was washed with brine (20 mL) and water (20 mL) followed by drying over Na_2SO_4. Removal of the solvent provided 4.21 g of **155** as yellow oil. The crude product, which should be stored at -20 °C and under exclusion of sunlight, was used in the next step without further purification. $C_{17}H_{18}O_4$; 286.32 g/mol;

R_f.: 0.31 (hexane : ethyl acetate = 3 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] =10.28 (s, 1 H), 7.45 (m, 2 H), 7,38 (m, 2 H), 7.33 (m, 1 H), 5.10 (s, 2 H), 3.92 (s, 3 H), 3.83 (s, 3 H), 2.23 (s, 3 H).

Crude aldehyde **155** (3.81 g, 13 mmol, 1 equiv.) was dissolved in ethanol (47 mL) and coled to 0 °C in the dark. Sodium borohydride (511 mg, 13 mmol, 1 equiv) was added batch-wise to the vigorously stirred yellow solution within 15 min. After 30 min at 0 °C the reaction was quenched by cautious addition of sat. aq. ammonium chloride untill no more gas evolved. The resulting mixture was diluted with DCM (30 mL) and water (30 mL) was added 10 min later. The aq. layer was separated and extracted with DCM (3 x 20 mL). The combined organic layer was washed with pH 7 buffer (KH$_2$PO$_4$/Na$_2$HPO$_4$) and water (2 x 20 mL) and finally dried over Na_2SO_4. Filtration and subsequent evaporation of the solvent yielded 3.79 g of the crude alcohol. Exclusion of sunlight and storage at low temperature are necessary to avoid decomposition of the isolated product. $C_{17}H_{20}O_4$; 288.34 g/mol;

R_f: 0.78 (hexane : ethyl acetate = 3 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.45 (m, 2 H), 7.39 (m, 2 H), 7.32 (m, 1 H), 6.84 (s, 1 H), 5.08 (s, 2 H), 4.65 (s, 2 H), 3.84 (s, 3 H), 3.73 (d, J = 0.81 Hz, 3 H), 2.23 (s, 3 H).

Imidazole (600 mg, 8.8 mmol, 1.2 equiv.) and triphenylphosphine (2.1 g, 8.0 mmol, 1.1 equiv.) were dissolved in 24 mL dry DCM and cooled to 0 °C under Ar-atmosphere. Bromine (410 µL, 8.0 mmol, 1.1 equiv.) was added drop wise *via* syringe, allowing the reaction mixture to discolor after each drop. After 15 min the addition was finished and the pale orange reaction mixture was allowed to stir for additional 15 min at 0 °C. Subsequently, a solution of prior obtained alcohol (2.10 g, 7.3 mmol, 1 equiv.) in 24 mL of dry DCM was added within 10 min. After 30 min the alcohol was fully converted and the reaction was quenched with sat. aq. sodium thiosulfate solution (20 mL) and diluted with DCM (20 mL). The separated organic layer was washed with sat. aq. sodium thiosulfate (30mL), brine (30 mL) and finally with water (30 mL) and was dried over Na$_2$SO$_4$. After evaporation of the solvent, the resulting crude mixture was dissolved in a minimum amount of acetone and triphenylphosphine oxide was removed by the addition of hexane and filtration of the suspension through Celite$^®$. Evaporation of the solvent yielded 2.485 g (96%) of bromide **156**.

C$_{17}$H$_{19}$BrO$_3$; 351.24 g/mol;

R_f: 0.75 (hexane : ethyl acetate = 4 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.39 (m, 5 H), 6.84 (s, 1 H), 5.08 (s, 2 H), 4.55 (s, 2 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 2.22 (s, 3 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 152.9, 150.4, 145.6, 138.8, 129.0, 128.3, 127.8, 126.4, 126.0, 113.9, 71.5, 61.5, 60.8, 29.4, 10.1;

HRMS (70eV, 50 °C): calc.: 350.0518, found: 350.0522.

3-Methoxy-4-(triisopropylsilyloxy)benzaldehyde (181)
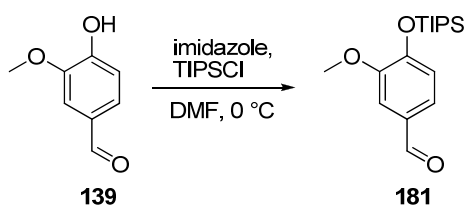
DMF (1.3 mL) was added to a mixture of vanillin (**139**) (250 mg, 1.64 mmol, 1 equiv.) and imidazole (336 mg, 4.9 mmol, 3 equiv.). At 0 °C triisopropylsilyl chloride (520 mL, 2.46 mmol, 1.5 equiv.) was added drop wise *via* syringe. After 5 min the ice bath was removed and the reaction mixture was stirred at room temperature for 2 hours. DCM (10 mL) was added and the resulting organic layer was washed with water (3 x 10 mL) and brine (10 mL) and was dried with Na_2SO_4. After filtration, evaporation of the solvent, and purification by flash column chromatography (hexane : ethyl acetate = 9 : 1) 487 mg (96%) of silyl ether **181** were obtained as yellow oil.

$C_{17}H_{28}O_3Si$; 308.49 g/mol;

R_f.: 0.39 (hexane : ethyl acetate = 5 : 1);

^{1}H NMR ($CDCl_3$, 250 MHz): δ [ppm] = 9.83 (s, 1 H), 7.39 (d, *J* = 1.80 Hz, 1 H), 7.35 (dd, *J* = 7.96 Hz, 1 H), 6.98 (d, *J* = 7.96 Hz, 1 H), 3.87 (s, 3 H), 1.27 (m, 3 H), 1.08 (m, 18 H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ [ppm] = 191.4, 152.3, 152.0, 131.0, 126.6, 120.6, 110.5, 55.8, 18.22, 13.3;

HRMS (70 eV, 30 °C): calc.: 108.1808, found: 108.1811.

3-Methoxy-4-(triisopropylsilyloxy)phenol (140)
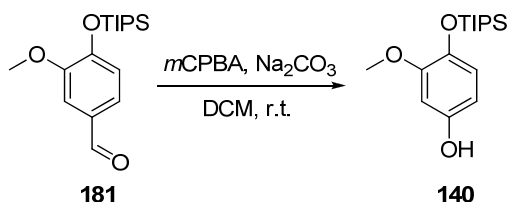
To a solution of aldehyde **181** (9.833 g, 31.8 mmol, 1 equiv.) in DCM (60 mL) was added batch-wise *m*CPBA (9.168 g, 48 mmol, 1.5 equiv.) at room temperature within 15 min, increasing the temperature of the reaction mixture to

approximately 40 °C. After 30 min of reaction time the starting material was fully consumed and the solvent was removed under reduced pressure. The resulting yellow residue was redissolved in 50 mL of ethyl acetate, washed with sat. *aq.* sodium bicarbonate solution (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered and again evaporated. The resulting yellow oil was dissolved in methanol (40 mL) and treated with sodium carbonate (675 mg, 6.4 mmol, 0.2 equiv.), whereby the reaction mixture turned its appearance from a yellow solution to a pink suspension. Again, the solvent was evaporated after 45 min under vigorous stirring. The pink residue was dissolved in water (50 mL) and neutralized with 5% HCl followed by extraction with ethyl acetate (3 x 50 mL). The combined organic layer were dried with Na_2SO_4, filtered and concentrated under reduced pressure yielding 9.11 g (97 %) crude white crystals of desired phenol **140** after purification by flash column chromatography (hexane : ethyl acetate = 9 : 1).

$C_{16}H_{28}O_3Si$; 296.48 g/mol;

R_f.:0.39 (hexane : ethyl acetate = 5 : 1);

^1H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 6.71 (d, *J* = 8.5 Hz, 1 H), 6.40 (d, *J* = 2.9 Hz, 1 H), 6.24 (dd, *J* = 8.5, 2.9 Hz, 1H), 4.35 (br, 1 H), 3.77 (s, 1 H), 1.22 (m, 3 H), 1.09 (br, 10 H), 1.07 (br, 8 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 185.9, 150.5, 148.6, 129.9, 120.7, 106.5, 101.0, 55.8, 18.3, 13.2;

HRMS (70 eV, 30 °C): calc.: 296.1808, found: 296.1806.

Triisopropyl(2-methoxy-4-(methoxymethoxy)phenoxy)silane (182)
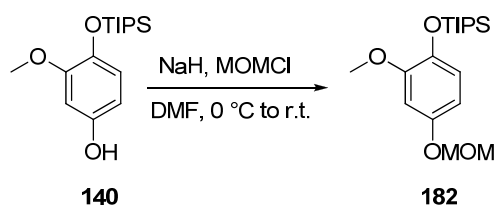
Phenol **140** (222 mg, 0.75 mmol, 1 equiv.) was dissolved in DMF (3 mL) and sodium hydride (60 w% suspension in mineral oil, 45 mg , 1.13 mmol, 1.5 equiv.) was added at room temperature. The two necked round-bottomed flask was equipped with a septum and cooled to 0 °C. After 15 min at that temperature

methoxymethyl chloride (90 μL, 1.13 mmol, 1.5 equiv.) was added within 5 min. The resulting reaction mixture was warmed to room temperature and stirred for another 7 hours. The reaction was quenched by the addition of pH 7 buffer (KH_2PO_4/Na_2HPO_4, 5 mL) and diluted with hexane (10 mL). The aqueous layer was extracted with hexane (3 x 10 mL). The combined organic layer was washed with brine (10 mL), water (10 mL) and was dried over Na_2SO_4. After filtration, removal of the solvent and purification by flash column chromatography (hexane : ethyl acetate = 5 : 1) 184 mg (72%) **182** were obtained as yellow oil.

$C_{18}H_{32}O_4Si$; 340.53 g/mol;

R_f.: 0.64 (hexane : ethyl acetate = 5 : 1);

^1H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 6.76 (d, J = 8.7 Hz, 1 H), 6.57 (d, J = 2.8 Hz, 1 H), 6.48 (dd, J = 8.7, 2.8 Hz, 1 H), 5.10 (s, 2 H), 3.78 (s, 3 H), 3.02 (s, 3 H), 1.23 (m, 3 H), 1.11 (br, 10 H), 1.08 (br, 8 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 152.4, 151.7, 140.9, 120.5, 107.6, 102.6, 95.7, 56.3, 55.8, 18.3, 13.2;

HRMS (70eV, 30 °C): calc.: 340.2070, found: 340.2073.

Triisopropyl(2-methoxy-4-(methoxymethoxy)-3-methylphenoxy)silane (141)
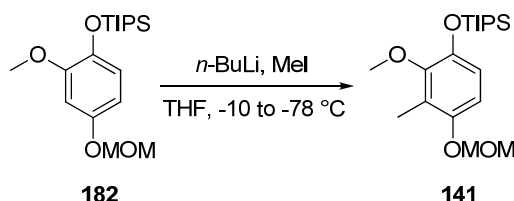
Methyl ether **182** (6.346 g, 18.6 mmol, 1.0 equiv.) dissolved in THF (90 mL) was cooled to -10 °C; *n*-BuLi (22.4 mL, 2.5 M in hexane, 5.0 equiv.) was added drop wise to the vigorously stirred solution, accompanied by changing from a colorless to a yellow solution. The resulting reaction mixture was stirred at -10 °C for one hour and was subsequently cooled to -78 °C followed by continuous addition of methyl iodide (4.7 mL, 74.5 mmol, 4.0 equiv.) within 10 min resulting in a yellow solution. After 30 min -78 °C the reaction was warmed to room temperature. Finally sat. aq. ammonium chloride (20 mL) was added and

the separated organic layer was washed with brine (20 mL) and water (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography gave 5.768 g (87%) of the desired methylated species **141**.

$C_{19}H_{34}O_4Si$; 344.56 g/mol;

R_f.: 0.77 (hexane : ethyl acetate = 5 : 1);

^1H NMR ($CDCl_3$, 400 MHz): δ [ppm] = 6.67 (d, J = 9.0 Hz, 1 H), 6.63 (d, J = 9.0 Hz, 1 H), 5.11 (s, 2 H), 3.78 (s, 3 H), 3.49 (s, 3 H), 2.17 (s, 3 H), 1.26 (m, 3 H), 1.12 (br, 10 H), 1.10 (br, 8 H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ [ppm] = 150.4, 150.0, 144.6, 117.6, 110.4, 102.6, 95.8, 60.5, 56.4, 18.3, 13.2, 9.7;

HRMS (70 eV, 30 °C): calc.: 354.2226, found: 354.2230.

3-Methoxy-2-methyl-4-(triisopropylsilyloxy)phenol (137)
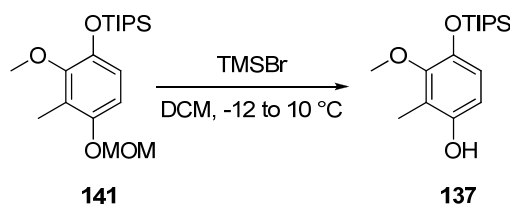
Compound **141** (1.02g, 2.9 mmol, 1.0 equiv.) was dissolved in dry DCM (12 mL) and cooled to -12 °C. Trimethylsilyl bromide (1.5 mL, 11.5 mmol, 4.0 equiv.) was added within 5 min. After additional 30 min at -12 °C the reaction mixture was allowed to warm to 10 °C and was stirred at that temperature for another 90 min. The clear orange solution was quenched with sat. aq. sodium bicarbonate solution (20 mL) and was diluted with ethyl acetate 20 mL. The organic layer was again washed with bicarbonate solution (30 mL), dried over Na_2SO_4 and after removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography (hexane : ethyl acetate = 19 : 1) providing 0.675 g (76%) desired deprotected phenol **137** as pale yellow oil which crystallized on standing.

$C_{17}H_{30}O_3Si$; 310.50 g/mol;

R_f.: 0.77 (hexane : ethyl acetate = 5 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 6.59 (d, J = 8.7 Hz, 1 H), 6.41 (d, J = 8.7 Hz, 1 H), 4.46 (s, 1 H), 3.78 (s, 3 H), 2.17 (s, 3 H), 1.27 (m, 3 H), 1.11 (br, 10 H), 1.10 (br, 8 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 150.0, 148.6, 143.5, 119.1, 117.6, 110.26, 60.6, 18.3, 13.2, 9.4;

HRMS (70 eV, 30 °C): calc.: 310.1964, found: 310.1965.

Fmoc and Cbz-protected Garner's Aldehyde were prepared according to literature from readily available L-serine over 5 steps with high yield. [42,43,44]

(R)-(9H-Fluoren-9-yl)methyl 4-(hydroxyl(2-hydroxy-4-methoxy-3-methyl-5-(triisopropylsilyloxy)phenyl)methyl)-2,2-dimethyloxazolidine-3-carboxylate (138)
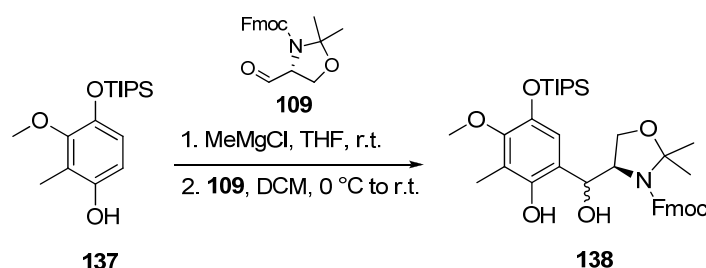
Methylmagnesium chloride (57 µL, 3.0 M in THF, 1.3 equiv.) was added to a vigorously stirred solution of **137** (50 mg, 0.16 mmol, 1.2 equiv.) in THF (300 µL) within 5 min at room temperature. The resulting reaction mixture was cooled to 0 °C and Fmoc-protected Garner's aldehyde **109** (47 mg, 0.13 mmol, 1.0 equiv.) in DCM (200 µL) was added drop wise. The ice bath was removed and the reaction was stirred at room temperature over night. After 12 hours the reaction was diluted with DCM (5 mL) and quenched with sat. aq. ammonium chloride solution (5 mL). The aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layer was washed with brine (10 mL) and water (10 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification by flash column chromatography (gradient, hexane : ethyl acetate = 7:1 to 4:1)

yielded 63 mg (71 %) of desired product **138** as pale yellow foam at a diastereomeric ratio of 2.3:1 (according to NMR data).

$C_{38}H_{51}NO_7Si$; 661.90 g/mol;

R_f: 0.18 (hexane : ethyl acetate = 2 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.77 (m; 2 H), 7.59 (m, 2 H), 7.37 (m, 4 H), 6.27 (s, 1 H), 4.84 (dd, J = 28.3, 9.0 Hz, 2 H), 4.48 (d, J = 7.0 Hz, 1 H), 4,25 (t, J = 3.6 Hz, 1 H), 4.2 (m, 1 H), 3.73 (s, 3 H), 3.48 (br, 2 H), 2.12 (s, 3 H), 1.22 (m, 3 H), 1.06 (dd, J = 7.25, 3.6 Hz, 18 H), 0.86 (br, 3 H), 0.77 (br, 3 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 168.5, 156.3, 149.7, 148.4, 148.4, 143.6, 143.5, 141.7, 141.6, 127.8, 126.0, 124.3, 124.1, 121.0, 120.1, 120.0, 118.3, 117.0, 95.0, 80.3, 67.1, 65.3, 62.8, 60.0, 47.2, 25.7, 23.5, 17.9, 12.7, 8.9;

HRMS (70 eV, 150 °C): calc.: 661.3435, found: 661.3412.

(R)-Benzyl 4-((5-(benzyloxy)-2,4-dimethoxy-3-methylphenyl)(hydroxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (135)
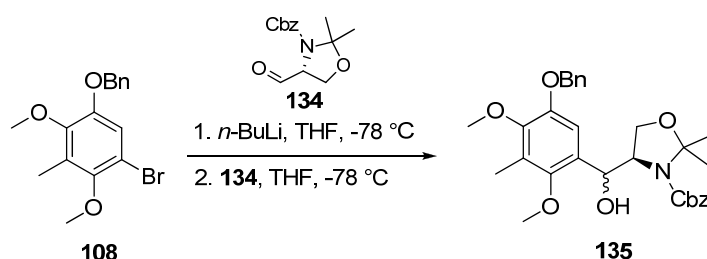
To a solution of aromatic bromide **108** (300 mg, 0.9 mmol, 1.25 equiv.) in THF (7 mL) *n*-BuLi was added drop wise (360 µL, 2.5 M in hexane, 1.3 equiv.) at -78 °C whereby the color of the reaction mixture changed from dark red to foggy yellow. After 30 min at low temperature the solution was transferred to a solution of Cbz-protected Garner's aldehyde **134** (188 mg, 0.7 mmol, 1.0 equiv.) in THF (7 mL) *via* syringe within 10 min. After full consumption of the aldehyde, DCM (20 mL) and sat. aq. ammonium chloride solution (20 mL) were added to the reaction -78 °C. The separated aq. layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic layer was washed with brine (20 mL) and water (20 mL). The organic layer was treated with Na$_2$SO$_4$, filtered and concentrated under

reduced pressure. The crude product was purified by flash column chromatography (gradient, hexane : ethyl acetate = 7:1 to 2:1) providing 279 mg (75%) **135** at a diastereomeric ratio of 2.1:1 (according to NMR-data) as pale yellow foam.

$C_{30}H_{35}NO_7$; 521.6014 g/mol;

R_f.: 0.33, 0.32* (hexane : ethyl acetate = 2 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.44 (dd, J = 7.9, 1.1 Hz, 2 H), 7.34 (m, 8 H), 7.01 (s, 1 H), 5.39* (br, 1 H), 5.25 (br, 1 H), 5.22 (d, J = 10.7 Hz, 2 H), 5.11* (d, J = 12.7 Hz, 2 H), 5.07 (br, 2 H), 5.05* (br, 2 H), 4.45* (br, 1 H), 4.33 (br, 1 H), 3.85 (br, 2 H), 3.83 (s, 3 H), 3.35 (br, 3 H), 2.18 (br, 3 H), 1.73 (br, 3 H), 1.48 (br, 3 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 148.2, 147.9, 137.1, 128.5, 128.4, 128.2, 127.8, 127.4, 125.5, 110.1, 71.0, 69.6, 67.2, 63.6, 60.7, 60.2, 32.2, 26.0, 23.6, 9.5;

(*) denotes the minor diastereomer

HRMS (70 eV, 140 °C): calc.: 521.2415, found: 521.2424.

(R)-(9H-Fluoren-9-yl)methyl 4-((5-(benzyloxy)-2,4-dimethoxy-3methylphenyl)(hydroxyl)methyl)-2,2-dimethyloxazolidine-3-carboxylate (136)
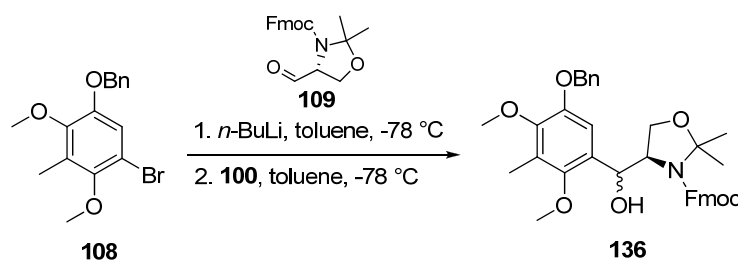
136 was prepared according to the experimental procedure for **135** except the solvent was changed from THF to toluene. Oxazoldine **136** was obtained with excellent yield (96%) at a diastereomeric ratio of 2.7 : 1 according to NMR data.

$C_{37}H_{39}NO_7$; 609.71 g/mol;

Diastereomer A:

R_f.: 0.32 (hexane : ethyl acetate = 2 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.76 (d, *J* = 7.5 Hz, 2 H), 7.56 (m, 2 H), 7.44 (m, 2 H), 7.38 (m, 4 H), 7.31 (m, 2 H), 6.96 (br, 1 H), 5.28 (br, 1 H), 5.06 (m, 2 H), 4.79 (br, 1 H), 4.31 (br, 1 H), 4.24 (br, 1 H), 3.89 (m, 1 H), 3.81 (s, 3 H), 3.74 (br, 2 H), 3.61 (m, 1 H), 3.36 (br, 1 H), 3.23 (br, 1 H), 2.18 (s, 3 H), 1.72 (m, 2 H), 1.53 (m, 1 H), 0.75 (s, 3 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 149.8, 148.2, 147.9, 143.8, 141.5, 137.2, 128.5, 128.4, 127.8, 127.7, 127.3, 127.1, 125.4, 124.2, 119.9, 110.1, 71.0, 69.1, 66.6, 66.4, 64.3, 63.4, 62.1, 60.6, 60.4, 60.3, 47.3, 30.6, 25.2, 23.0, 19.1, 9.5.

Diastereomer B:

R$_f$.: 0.30 (hexane : ethyl acetate = 2 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.77 (dd, *J* = 7.3, 2.1 Hz, 2 H), 7.60 (dd, *J* = 10.9, 7.3, 2 H), 7.43 (m, 2 H), 7.37 (m, 4 H), 7.31 (m, 2 H), 6.82 (s, 1 H), 5.05 (m, 2 H), 4.83 (m, 3 H), 4.27 (br, 1 H), 4.16 (br, 1 H), 3.81 (m, 3 H), 3.70 (br, 3 H), 3.44 (m, 2 H), 2.19 (s, 3 H), 0.96 (br, 3 H), 0.79 (br, 3 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 151.2, 148.9, 148.8, 144.2, 144.1, 142.1, 142.0, 137.6, 129.7, 128.9, 128.2, 127.9, 127.7, 127.6, 126.2, 124.8, 124.6, 120.5, 120.4, 111.3, 95.3, 73.8, 71.5, 67.5, 65.4, 64.2, 61.7, 60.7, 47.6, 26.6, 23.8, 10.1

HRMS (70 eV, 80 °C): calc.: 609.2727, found: 609.2719.

(S)-(9H-Fluoren-9-yl)methyl 1-(5-(benzyloxy)-2,4-dimethoxy-3-methylphenyl)-3-hydroxypropan-2-ylcarbamate (145)
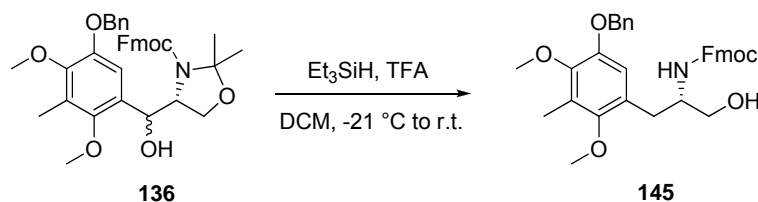
A round bottomed flask was charged with a solution of **136** (18 mg, 0.03 mmol, 1.0 equiv.) in DCM (0.5 mL). Triethylsilane (27 µL, 0.16 mmol, 5.7 equiv) was added at room temperature and the resulting reaction mixture was cooled to -21 °C. Subsequently trifluoroacetic acid (13 µL, 0.16 mmol, 5.7 equiv.) was added drop wise *via* syringe and the reaction was stirred for 30 min at -21 °C.

After 4 hours at room temperature the starting material was fully consumed; the reaction was diluted with DCM (3 mL) and quenched with sat. aq. sodium bicarbonate solution (3 mL). The aq. layer was extracted with DCM (3 x 6 mL) and the resulting organic layer was dried over Na_2SO_4. After filtration, removal of the solvent under reduced pressure and purification by flash column chromatography (hexane:ethyl acetate = 4:1) 16 mg (98%) **145** were obtained as colorless foam.

$C_{34}H_{35}NO_6$; 553.65 g/mol;

R_f.: 0.23 (hexane : ethyl acetate = 1 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.76 (m, 2 H), 7.56 (dd, J = 22.5, 7.4 Hz, 2 H), 7.39 (m, 5 H), 7.30 (m, 3 H), 6.69* (s, 1 H), 6.60 (s, 1 H), 5.57 (m, 2 H), 5.05* (s, 2 H), 5.03 (s, 2 H), 4.44 (m, 2 H), 4.35 (m, 2 H), 4.21 (m, 1 H), 4.14 (m, 1 H), 3.84* (s, 3 H), 3.83 (s, 3 H), 3.74* (br, 3 H), 3.71 (br, 3 H), 2.83 (m, 2 H), 2.25 (s, 3 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 156.5, 155.9, 151.1, 148.5, 143.9, 141.3, 137.0, 128.5, 127.9, 127.8*, 127.7, 127.4*, 127.3, 127.0, 125.1, 125.0*, 120.0, 113.7, 113.6, 113.5*, 71.1, 71.0, 68.0, 66.9, 66.8*, 60.6*, 60.3, 54.3, 51.1, 47.3*, 47.2, 31.7, 31.3, 9.8;

(*) denotes the minor rotamer;

HRMS (70 eV, 150 °C): calc.:576.2362, found: 576.2350.

(S)-(9H-Fluoren-9-yl)methyl 1-(5-(benzyloxy)-2,4-dimethoxy-3-methylphenyl)-3-(triethylsilyloxy)propan-2-ylcarbamate (149)
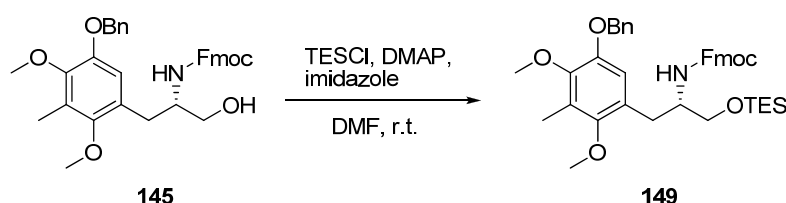
Primary alcohol **145** (97 mg, 0.18 mmol, 1.0 equiv.) was dissolved in dry DMF (1 mL) and DMAP (22 mg, 0.18 mmol, 1.0 equiv.) together with imdazole (30 mg, 0.44 mmol, 2.5 equiv.) were added at room temperature. Subsequently, triethylsilyl chloride (40 µL, 0.22 mmol, 1.25 equiv.) was added. The resulting reaction mixture was quenched with pH 7 phosphate buffer (5 mL,

KH$_2$PO$_4$/Na$_2$HPO$_4$) after complete consumption of starting material. The aq. layer was washed with DCM (3 x 10). Hereafter, the combined organic layer was dried over Na$_2$SO$_4$, filtered and evaporated. Purification by flash column chromatography (hexane : ethyl acetate = 2 : 1) gave 84 mg (73%) desired silyl ether **149**.

C$_{40}$H$_{49}$NO$_6$Si; 667.91 g/mol;

R$_f$.: 0.71 (hexane : ethyl acetate = 1 : 1);

NMR-data considers only the major rotamer;

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.75 (d, J = 7.4 Hz, 2 H), 7.54 (dd, J = 7.4, 1.6 Hz, 2 H), 7.42 (m, 2 H), 7.37 (m, 4 H), 7.29 (m, 2 H), 6.72 (s, 1 H), 5.03 (s, 2 H), 4.28 (m, 2 H), 4.19 (m, 1 H), 3.89 (br, 1 H), 3.80 (s, 3 H), 3.73 (br, 3 H), 3.62 (m, 2 H), 2.87 (m, 2 H), 2.25 (s, 3 H), 0.99 (m, 9 H), 0.63 (m, 6 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 156.4, 144.4, 141.7, 137.7, 128.9, 128.2, 128.0, 127.8, 127.6, 127.4, 126.4, 125.6, 120.3, 114.2, 71.5, 67.0, 64.1, 61.0, 60.7, 54.2, 47.6, 10.2, 7.2, 4.8;

HRMS: calc.: 690.3227, found: 690.3222.

(S)-1-(5-(Benzyloxy)-2,4-dimethoxy-3-methylphenyl)-3-(triethylsilyloxy)propan-2-amine (148)
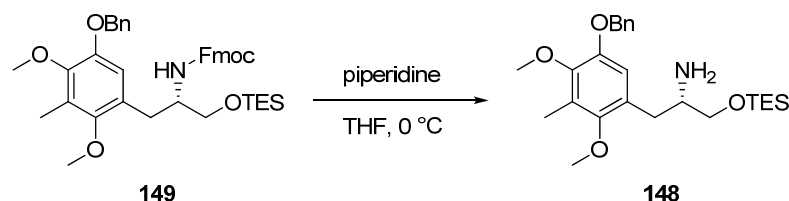
Compound **149** (17 mg, 0.03 mmol, 1.0 equiv.) in THF (0.3 mL) was treated with piperidine (0.1 mL) at 0 °C, resulting in a 20 vol% piperidine solution. Within two hours the starting material was completely consumed, the reaction was diluted with ethyl acetate (5 mL) and quenched by the addition of pH 7 phosphate buffer (10 mL, KH$_2$PO$_4$/Na$_2$HPO$_4$); the aq. layer was separated and extracted four times with ethyl acetate (10 mL). The combined organic layers was washed with brine (5 mL) and water (5 mL), dried with Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification by flash column

chromatography (hexane : ethyl acetate = 1:1) gave 8 mg (100%) secondary amine **148** as colorless residue.

$C_{25}H_{39}NO_4Si$; 445.67 g/mol;

R_f.: 0.18 (hexane : ethyl acetate = 1 : 1);

^1H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.44 (dd, *J* = 7.3, 1.3 Hz, 2 H), 7.38 (dd, *J* = 7.3, 7.2 Hz, 2 H), 7.31 (m, 1 H), 6.66 (s, 1 H), 5.06 (s, 2 H), 3.83 (s, 3 H), 3.67 (s, 3 H), 3.59 (dd, *J* = 9.8, 4.5 Hz, 1 H), 3.47 (dd, *J* = 9.8, 6.6 Hz, 1 H), 3.13 (m, 1 H), 2.76 (dd, *J* = 13.5, 5.0 Hz, 1 H), 2.52 (dd, *J* = 13.5, 8.4 Hz, 1 H), 2.22 (s, 3 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 0.61 (q, *J* = 0.79 Hz, 6 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 151.8, 151.2, 148.5, 136.9, 128.9, 128.2, 127.8, 127.05, 126.0, 114.2, 71.5, 67.5, 61.0, 60.7, 54.2, 34.7, 10.1, 7.2, 4.8;

HRMS: calc.: 445.2648, found: 445.2653.

(S)-(9H-Fluoren-9-yl)methyl 1-(5-hydroxy-2,4-dimethoxy-3-methylphenyl)-3-(triethylsilyloxy)propan-2-ylcarbamate (151)
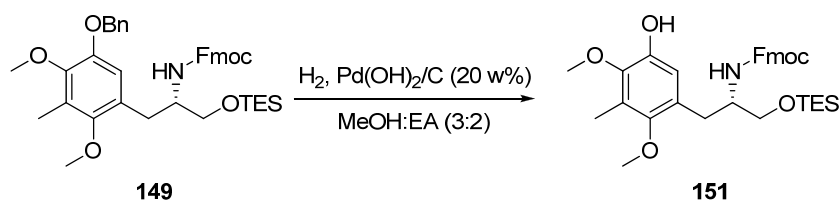
Silyl ether **149** (60 mg, 0.09 mmol, 1.0 equiv.) was dissolved in a 3:2 methanol:ethyl acetate mixture (5 mL) before palladium hydroxide on charcoal (10 mg, 20 w%) was added to a Parr hydrogenation apparatus. The resulting black suspension was treated for two days under 3.4 bar hydrogen pressure. The catalyst was removed by filtration over a bulk of Celite$^®$, removal of the solvent under reduced pressure followed by flash column chromatography (gradient, hexane : ethyl acetate = 5:1 to 1:1) yielded 31 mg (60%) of the desired product **159** as colorless residue.

$C_{33}H_{43}NO_6Si$; 577.78 g/mol;

R_f.: 0.25 (DCM : MeOH = 12 : 1);

^1H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.75 (d, *J* = 7.5 Hz, 2 H), 7.54 (d, *J* = 7.4 Hz, 2 H), 7.39 (dddd, *J* = 7.5, 7.4, 2.5, 0.8 Hz, 2 H), 7.29 (ddd, *J* = 7.5, 2.5, 1.2 Hz, 2 H), 6.7 (s, 1H), 5.53 (d, *J* = 7.6 Hz,1 H), 5.39 (s, 1 H), 4.32 (dd,

J = 9.0, 6.2 Hz, 1 H), 4.20 (m, 2 H), 3.89 (br, 1 H), 3.74 (s, 3 H), 3.73 (s, 3H), 3.69 (dd, *J* = 10.2, 2.6 Hz, 1 H), 3.59 (dd, *J* = 9.8, 5.2 Hz, 1 H), 2.85 (m, 1 H), 2.26 (s, 3 H), 0.98 (t, *J* = 7.9 Hz, 9 H), 0.63 (q, *J* = 7.9 Hz, 6 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 156.0, 150.5, 145.1, 144.4, 144.1, 144.0, 141.2, 127.6, 127.4, 127.0, 125.2, 125.1, 124.1, 119.9, 114.4, 66.6, 63.7, 60.7, 60.6, 53.7, 47.2, 31.7, 29.7, 9.9, 6.8, 4.4;

HRMS (eV, °C): calc.: 600.2757, found: 600.2748 (M + Na$^+$).

(S)-(9H-Fluoren-9-yl)methyl 4-(5-(benzyloxy)-2,4-dimethoxy-3-methylbenzyl)-2,2-dimethyloxazolidine-3-carboxylate (147)

a) NaHMDS, CS$_2$, MeI, THF, -78 °C; b) Bu$_3$SnH, AIBN, toluene, rf.
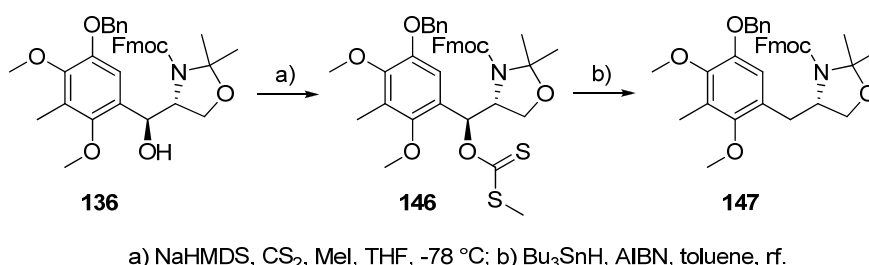
Pure minor diastereomer B **136** (138 mg, 0.23 mmol, 1.0 equiv) together with carbon disulfide (270 µL, 4.47 mmol, 19.8 equiv.), dissolved in dry THF (5 mL), was cooled to -78°C. After 15 min NaHMDS (270 µL, 0.27 mmol, 1.2 equiv.) was added drop wise and the resulting reaction mixture was stirred for an additional hour at -78 °C. Subsequently methyl iodide (140 µL, 0.23 mmol, 1.0 equiv.) was added at -78 °C. After two hours the reaction mixture was quenched with sat. aq. ammonium chloride (5 mL); the aq. layer was extracted with ethyl acetate (3 x 5 mL). The separated and combined organic layer was washed with brine (10 mL) and water (10 mL), dried over Na$_2$SO$_4$ and evaporated under reduced pressure to afford 124 mg (80%) **146** as white foam after purification by flash column chromatography (hexane : ethyl acetate = 6 : 1).

C$_{39}$H$_{41}$NO$_7$S$_2$; 699.88 g/mol;

R$_f$.: 0.52 (hexane : ethyl acetate = 2 : 1);

HRMS: calc.: 722.222, found: 722.2216 (M + Na$^+$).

The resulting white residue was dissolved (99 mg, 0.14 mmol, 1.0 equiv.) in toluene (5 mL), treated with tributyltin hydride (80 µL, 0.28 mmol, 2.0 equiv.) and AIBN (5 mg, 0.03 mmol, 0.2 equiv.) at room temperature. The mixture was

degassed by three pump-freeze-thaw cycles and heated to reflux for 16 hours. After concentration of the mixture at reduced pressure and purification by flash column chromatography (hexane : ethyl acetate = 20 : 1 and 2 : 1) 39 mg (46%) **147** was obtained as white foam.

$C_{37}H_{39}NO_6$; 593.71 g/mol;

R_f.: 0.51 (hexane : ethyl acetate = 2 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.75 (dd, J = 8.4, 8.3 Hz, 2 H), 7.63 (m, 2 H), 7.37 (m, 8 H), 6.62* (s, 1 H), 5.02* (s, 2 H), 4.98 (d, J = 1.8 Hz, 2 H), 4.77* (d, J = 2.1 Hz, 2 H), 4.49 (ddd, J = 35.0, 10.8, 6.0 Hz, 2 H), 4.26 (m, 1H), 4.09 (m, 1 H), 3.82 (s, 3 H), 3.81* (s, 3 H), 3.72 (d, J = 2.6 Hz, 2H), 3.70* (s, 3 H), 3.61* (ddd, J = 22.2, 8.8, 6.0 Hz, 2 H), 3.55 (s, 3 H), 3.04* (dd, J = 12.9, 1.9 Hz, 1 H), 2.81 (dd, J = 13.3, 3.9 Hz, 1 H), 2.64 (dd, J = 12.9, 10.5 Hz, 1 H), 2.53* (dd, J = 12.3, 11.3 Hz, 1 H), 2.19 (s, 3 H), 1.66 (s, 3 H), 1.50* (s, 3 H), 0.96 (s, 3 H), 0.82* (s, 3 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 153.5, 152.8, 152.4, 151.6, 148.1, 147.5, 144.1, 141.6, 141.5* 141.4, 141.3*, 137.2, 128.4, 127.8, 127.7, 127,4, 127.2, 127.1, 126.0, 125.8, 125.7, 125.1, 124.9*, 124.3, 124.2*, 120.0, 114.0, 113.9*, 94.3, 93.6*, 71.2, 71.1*, 66.6, 66.4*, 66.0, 65.9*, 60.6*, 60.4, 60.3, 58.5*, 57.7, 47.5, 47.3*, 33.5, 32.9*, 27.8, 26.8, 26.7, 26.6, 23.5*, 23.2*, 9.7;

(*) denotes the minor rotamer;

HRMS: calc.: 616.2675, found: 616.2681 (M + Na$^+$).

Phosphinate **165** was prepared in three steps according to literature, starting from readily available glyoxylic acid monohydrate.[52]

(Z)-Methyl 3-(5-(benzyloxy)-2,4-dimethoxy-3-methylphenyl)-2-(benzyloxycarbonylamino)acrylate (166)
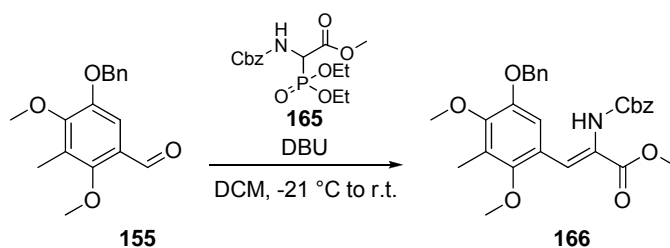
Phosphinate **165** (130 mg, 0.23 mmol, 1.1 equiv.) in DCM (0.5 mL) was cooled to -21 °C followed by the drop wise addition of DBU (33 µL, 2.2 mmol, 1.05 equiv.) within 2 min. A solution of benzaldehyde **155** (60 mg, 0.21 mmol, 1.0 equiv.) in DCM (0.5 mL) was added after 10 min at -21 °C. After one hour at -21°C the reaction mixture was warmed to room temperature for two hours before it was diluted with ethyl acetate (10 mL), quenched with sat aq. ammonium chloride solution (5 mL), dried (MgSO$_4$) and concentrated under vacuum providing 43 mg (41 %) of the desired enamine **166** as white crystals.

C$_{28}$H$_{29}$NO$_7$; 491.53 g/mol;

R$_f$.: 0.43 (hexane : ethyl acetate = 2 : 2);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.38 (m, 4 H), 7.31 (m, 6 H), 7.21 (s, 1 H), 7.15 (br, 1 H), 6.93 (s, 1 H), 5.09 (s, 2 H), 4.97 (s, 2 H), 3.87 (s, 3 H), 3.81 (br, 3 H), 3.61 (br, 3 H), 2.22 (s, 3 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 165.8, 153.8, 151.3, 149.6, 148.3, 136.8, 135.9, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.3, 126.0, 125.7, 124.3, 121.9, 111.8, 70.9, 67.4, 66.9, 61.6, 60.4, 52.5, 9.5;

HRMS: calc.: 514.1842, found: 514.1845 (M + Na$^+$).

N-(Diphenylmethylene)-glycine *t*-butyl ester (**73**) was prepared according to literature,[50] except for the installation of the *t*-butyl ester, which was carried out in DCM with isobutene and cat. conc. H$_2$SO$_4$ from readily available L-glycine.

(S)-t-Butyl 2-amino-3-(5-(benzyloxy)-2,4-dimethoxy-3-methylphenyl)propanoate (171)
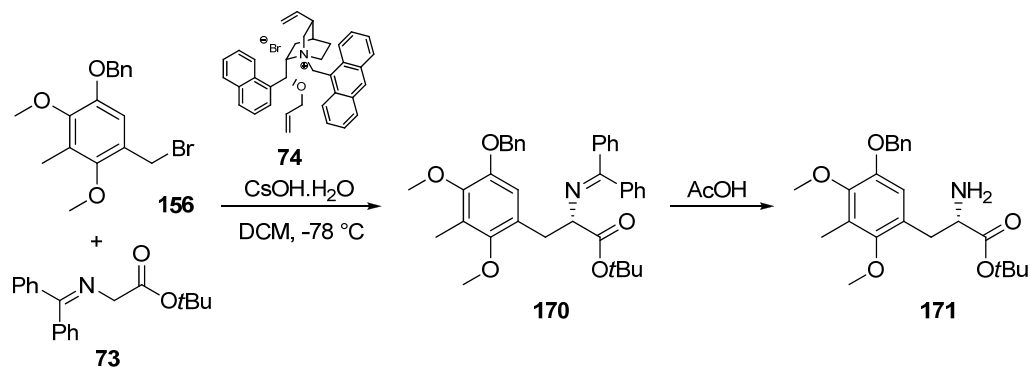
N-(Diphenylmethylene)-glycine *tert*-butyl ester (**73**) (400 mg, 1.35 mmol, 1.0 equiv.), O-allyl-N-(9-anthracenylmethyl)cinchonidinium bromide (**74**) (82 mg, 0.14 mmol, 0.1 equiv.) and cesium hydroxide monohydrate (2.497 g, 14.87 mmol, 10.0 equiv.) were suspended in DCM (1.8 mL) in a three necked round-bottomed flask equipped with a large magnetic stirring bar under Ar-atmosphere, resulting in a bright yellow cake. The vigorously stirred reaction mixture was cooled to -78 °C for 10 min before a solution of benzylic bromide **156** (522 mg, 1.48 mmol, 1.1 equiv.) in DCM (1.8 mL) was added within 10 min. The reaction was warmed to -10 °C over 14 hours. Diethylether (10 mL) and water (10 mL) were added. The separated aq. layer was extracted with diethylether (3 x 10 mL) containing the product, and DCM (3 x 10 mL), only containing phase transfer catalyst **74**. The combined ethereal layer was washed with brine (10 mL) and water (10 mL), dried and concentrated under vacuum, giving crude imine **170**. To the resulting oil, diethylether (4 mL) and a 1 : 1 mixture of water and acetic acid (10 mL), was added. The organic layer was washed with water several times until no more amine was in the acidic aq. layer. The combined aq. layer was transferred to an Erlenmeyer flask and cautiously adjusted to pH 12 with solid sodium carbonate. The crude product precipitated as orange oil on the surface upon neutralization, DCM (30 mL) was added and the layers separated. The aqueous layer was extracted with DCM (3 x 30 mL). The combined organic layer was finally dried (MgSO$_4$), filtered and concentrated under vacuum. Purification by flash column chromatography (DCM : methanol = 12 : 1 to 6:1) gave 469 mg (78%) of the desired secondary amine **171** of 88% *ee* (according to NMR data of Mosher's amide **184**, **186**) as yellow oil.

Imine **170**:

$C_{36}H_{39}NO_5$; 565.70 g/mol;

R_f.: 0.60 (hexane : ethyl acetate = 4 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.64 (m, 2 H), 7.46 (m, 2 H), 7.31 (m, 9 H), 7.23 (m, 2 H), 6.58 (s, 1 H), 4.75 (d, *J* = 11.6 Hz, 1 H), 4.63 (d, *J* = 11.6 Hz, 1 H), 4.17 (dd, *J* = 10.0, 3.5 Hz, 1 H), 3.79 (s, 3 H), 3.45 (s, 3 H), 3.32 (dd, *J* = 13.3, 3.5 Hz, 1 H), 3.02 (dd, *J* = 13.3, 10.1 Hz, 1 H), 2.17 (s, 3 H), 1.46 (s, 9 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 171.0, 169.9, 151.5, 147.7, 147.0, 139.5, 137.3, 136.2, 130.1, 128.7, 128.4, 128.0, 127.8, 127.7, 127.2, 126.2, 125.1, 114.3, 81.1, 70.7, 66.9, 60.7, 60.3, 33.5, 28.1, 9.5;

HRMS: calc.: 566.2906, found: 566.2902 (M + H$^+$).

Amine **171**:

$C_{23}H_{31}NO_5$; 401.50 g/mol;

R_f.: 0.42 (DCM : MeOH = 12 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.44 (dd, *J* = 7.4, 1.1 Hz, 2 H), 7.34 (ddd, *J* = 7.4, 7.0, 0.8 Hz, 2 H), 7.31 (ddd, *J* = 7.0, 1.3, 0.8 Hz, 1 H), 6.67 (s, 1 H), 5.05 (s, 2 H), 3.83 (s, 3 H), 3.69 (s, 3 H), 3.62 (dd, *J* = 8.6, 5.5 Hz, 1 H), 3.00 (dd, *J* = 13.5, 5.5 Hz, 1 H), 2.70 (dd, *J* = 13.5, 8.6 Hz, 1 H), 2.22 (s, 3 H), 1.47 (br, 2 H),1.42 (s, 9 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 174.6, 151.6, 148.0, 147.4, 137.3, 132.1, 132.1, 128.5, 127.8, 127.4, 125.7, 125.6, 113.9, 80.9, 71.1, 60.6, 60.3, 55.7, 36.1, 28.0, 9.7;

HRMS: calc.: 401.2202, found: 401.2207.

(S)-t-Butyl 3-(5-(benzyloxy)-2,4-dimethoxy-3-methylphenyl)-2-((S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamido)propanoate (184)
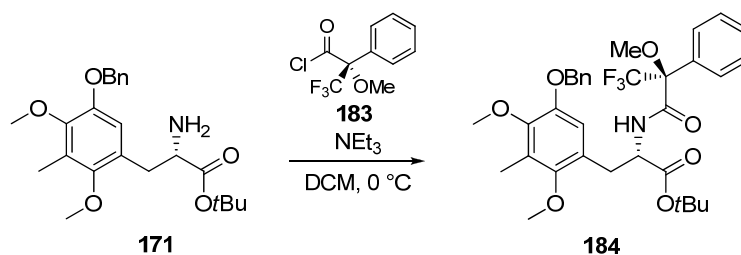
Secondary amine **171** (10 mg, 0.025 mmol, 1.0 equiv.) was suspended in DCM and cooled to 0 °C. Triethylamine (8 µL, 0.055 mmol, 2.2 equiv.) was added drop wise and 10 min later (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride **183** (5 µL, 0.028 mmol, 1.1 equiv.). The reaction mixture was warmed to room temperature and stirred for 15 min. Removal of the solvent and base under vacuum gave 14 mg (91%) of crude corresponding Mosher amide **184**.

$C_{33}H_{38}F_3NO_7$; 617.65 g/mol;

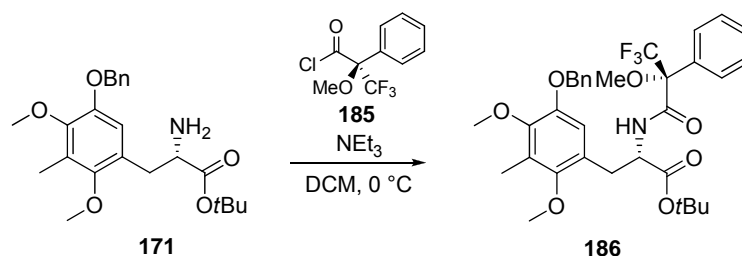R_f.: 0.33 (hexane : ethyl acetate = 2 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.74 (d, *J* = 7.7 Hz, 2 H), 7.56 (m, 2 H), 7.38 (m, 6 H), 6.69 (s, 1 H), 5.03 (s, 2 H), 4.63 (m, 1 H), 3.81 (s, 3 H), 3.67 (s, 3 H), 3.25 (s, 3 H), 3.07 (dd, *J* = 13.9, 8.5 Hz, 1 H), 3.00 (dd, *J* = 13.9, 5.5 Hz, 1 H), 2.21 (s, 3 H), 1.38 (s, 9 H);

NMR data only considers the major diastereomer.

HRMS: calc.: 640.2498, found: 640.2409.

(R)-t-Butyl 3-(5-(benzyloxy)-2,4-dimethoxy-3-methylphenyl)-2-((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamido)propanoate (186)

186 was synthesized according to the procedure for **184** except (+)-Mosher chloride **185** was used instead of (-)-enantiomer. The reaction yielded 15 mg (97%) crude product **186** as colorless oil.

$C_{33}H_{38}F_3NO_7$; 617.65 g/mol;
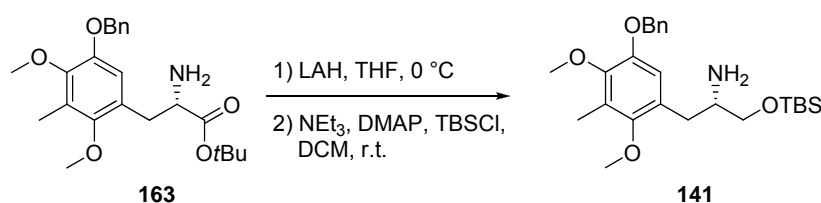
R_f.: 0.33 (hexane : ethyl acetate = 2 : 1);

^{1}H NMR (CDCl$_3$, 100 MHz): δ [ppm] = 7.81 (d, *J* = 7.2 Hz, 2 H), 7.61 (m, 2 H), 7.36 (m, 6 H), 6.62 (s, 1 H), 4.94 (s, 2 H), 4.64 (m, 1 H), 3.81 (s, 3 H), 3.58 (s, 3 H), 3.44 (s, 3 H), 3.12 (ddd, *J* = 14.0, 7.1, 2.2 Hz, 2 H), 2.13 (s, 3 H), 1.41 (s, 9 H);

NMR data only considers the major diastereomer.

HRMS: calc.: 640.2498, found: 640.2411.

(S)-1-(5-(Benzyloxy)-2,4-dimethoxy-3-methylphenyl)-3-(t-butyldimethylsilyloxy)propan-2-amine (150)

To amine **171** (389 mg, 1.0 mmol, 1.0 equiv) in THF (10 mL) was added LAH (480 µL, 4.0 M in THF, 2.0 equiv) at 0 °C within 5 min. The resulting pale yellow reaction mixture was quenched by addition of sat. aq. sodium thiosulfate solution (10 mL) after 15 min and complete consumption of starting material. The aq. layer was extracted with DCM (4 x 10 mL) and the combined organic layer was washed with brine (10 mL) and water (10 mL), dried ($MgSO_4$), filtered and concentrated under vacuum, affording 338 mg of crude alcohol.

The crude product was dissolved in DCM (6 mL) and triethylamine (170 µl, 2.1 mmol, 2.2 equiv.) was added at room temperature. DMAP (194 µL, 0.2 mmol, 0.22 equiv.) and a solution of TBSCl (165 mg, 1.1 mmol, 1.1 equiv.) in DCM (6 mL) were added consecutively under vigorous stirring. The resulting reaction mixture was stirred for 14 hours, quenched by the addition of water (10 mL) and the aq. layer was washed with DCM (3 x 10 mL). The combined organic layer was washed with brine (15 mL), dried ($MgSO_4$), filtered and evaporated. Purification by flash column chromatography (gradient, DCM : MeOH = 39 : 1 to 10 : 1) yielded 299 mg (69%) of **150** as pale yellow oil.

$C_{25}H_{39}NO_4Si$; 445.67 g/mol;

R_f.: 0.68 (DCM : MeOH = 12 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.46 (m, 2 H), 7.37 (m, 2 H), 7.31 (m, 1 H), 6.66 (s, 1 H), 6.62* (s, 1 H), 5.06 (s, 2 H), 5.02* (s, 2 H), 3.83 (s, 3 H), 3.82* (s, 3 H), 3.69* (s, 3 H), 3.67 (s, 3 H), 3.56 (dd, J = 9.7, 4.6 Hz, 1 H), 3.45 (dd, J = 9.7, 6.3 Hz, 1 H), 3.08 (m, 1 H), 2.74 (dd, J = 13.4, 5.0 Hz,1 H), 2.46 (dd,
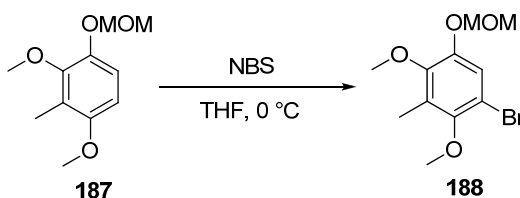
J = 13.4, 8.6 Hz, 1 H), 2.22 (s, 3 H), 2.20* (s, 3 H), 1.58 (br, 2 H), 0.91 (s, 9 H), 0.88* (s, 9 H), 0.06 (d, J = 1.6 Hz, 6 H),

(*) denotes the minor rotamer;

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 151.4, 148.0, 147.1, 137.3, 128.5, 127.8, 127.3, 127.0, 125.6, 113.8, 71.1, 67.8, 60.6, 60.3, 53.7, 34.7, 25.9, 18.3, 9.7, -5.3;

HRMS: calc.: 446.2727, found: 446.2721 (M + H$^+$).

1-Bromo-2,4-dimethoxy-5-(methoxymethoxy)-3-methylbenzene (188)

187 (1.50 g, 7.0 mmol, 1.0 equiv) was dissolved in acetonitrile (35 mL) and *N*-bromosuccinimide (1.32 g, 7.4 mmol, 1.05 equiv.) was added batch-wise at 0 °C. The reaction mixture was stirred at 0°C for three hours, diluted with ethyl acetate (10 mL) and quenched with aq. sat. sodium thiosulfate solution (20 mL). The separated organic layer was washed with water (10 mL) and brine (10 mL), dried (MgSO$_4$) and concentrated under reduced pressure to yield 2.038g (99 %) of **188** after purification by flash column chromatography (hexane : ethyl acetate = 10 : 1).

C$_{11}$H$_{15}$BrO$_4$; 291.14 g/mol;

R$_f$.: 0.50 (hexane : ethyl acetate = 4 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.19 (d, J = 0.4 Hz, 1 H), 5.15 (s, 2 H), 3.80 (s, 3 H), 3.75 (s, 3 H), 3.51 (s, 3 H), 2.24 (d, J = 0.4 Hz, 3 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 151.0, 148.7, 147.6, 127.7, 118.5, 111.3, 96.0, 60.8, 60.7, 56.7, 10.5;

HRMS (70 eV, 30 °C): calc.: 290.0154, found: 290.0148.

2,4-Dimethoxy-5-(methoxymethoxy)-3-methylbenzaldehyde (189)
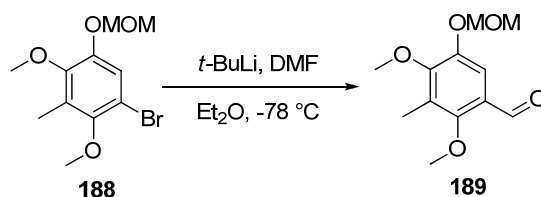
Bromide **188** (2.038 g, 7.0 mmol, 1 equiv.) was dissolved in diethyl ether (24 mL), cooled to -78 °C and *t*-BuLi (10.3 mL, 1.7 M in hexane, 2.5 equiv.) was added within 15 min, where upon the reaction mixture turned its appearance from a blue solution to a beige suspension. After additional 30 min at -78 °C DMF (2.6 mL, 33.6 mmol, 4.8 equiv.) was added drop wise resulting in a grey suspension which was stirred for additional 60 min; sat. aq. ammonium chloride solution (15 mL) was added and the aq. layer was washed with DCM (3 x 20 mL). The combined organic layer was dried (MgSO$_4$) and concentrated under vacuum providing 1.618 g (96 %) of **189** after purification by flash column chromatography (hexane : ethyl acetate = 14 : 1).

C$_{12}$H$_{16}$O$_5$; 240.25 g/mol;

R$_f$.: 0.54 (hexane : ethyl acetate = 4 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 10.1 (s, 1 H), 7.09 (s, 1 H), 5.03 (s, 2 H), 3.73 (s, 3 H), 3.66 (s, 3 H), 3.33 (s, 3 H), 2.05 (s, 3 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 189.0, 158.0, 154.8, 147.1, 126.4, 124.8, 112.3, 95.3, 63.5, 60.5, 56.3, 9.1;

HRMS (70 eV, 30 °C): calc.: 240.0998, found: 240.0991.

(2,4-Dimethoxy-5-(methoxymethoxy)-3-methylphenyl)methanol (190)
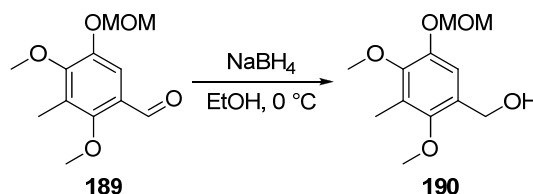
Sodium borohydride (290 mg, 7.4 mmol, 1.1 equiv.) was added batch-wise to a solution of **189** (1.618 g, 6.6 mmol, 1.0 equiv) in ethanol (80 mL) at 0 °C. The resulting reaction mixture was stirred at 0 °C for two hours, diluted with diethyl ether and quenched with sat aq. ammonium chloride solution (30mL). The aq.

layer was extracted with diethyl ether (3 x 20 mL). The combined organic layer was dried (MgSO$_4$), filtered and concentrated under reduced pressure. After purification by flash column chromatography (gradient, hexane : ethyl acetate = 7 : 1 to 2:1) 1.593 g (98 %) benzylic alcohol **190** were obtained as yellow oil.
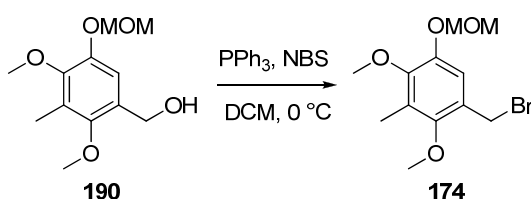
C$_{12}$H$_{18}$O$_5$; 242.27 g/mol;

R$_f$.: 0.22 (hexane : ethyl acetate = 2 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 6.98 (s, 1 H), 5.17 (s, 2 H), 4.64 (d, J = 5.7 Hz, 2 H), 3.81 (s, 3 H), 3.73 (s, 3 H), 3.51 (s, 3 H), 2.21 (s, 3 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 151.7, 148.6, 146.7, 129.1, 125.8, 114.4, 95.5, 61.3, 61.1, 60.4, 56.2, 9.4;

HRMS (70 eV, 30 °C): calc.: 242.1154, found: 242.1130.

1-(Bromomethyl)-2,4-dimethoxy-5-(methoxymethoxy)-3-methylbenzene (174)

Primary alcohol **190** (300 mg, 1.24 mmol, 1equiv.) and triphenylphosphine (373 mg, 1.42 mmol, 1.15 equiv.) were dissolved in DCM (13 mL) at room temperature and cooled to 0 °C. *N*-Bromosuccinimide (242 mg, 1.36 mmol, 1.10 equiv.) was added in one portion. After 10 min the reaction was warmed to room temperature for 2 hours. Finally DCM (15 mL) and water (15 mL) were added. The organic layer was washed with brine (15 mL), filtered and concentrated under vacuum. The resulting residue was dissolved in a minimum amount of acetone, cold hexane was added to precipitate triphenylphosphine oxide, which was removed by filtration over a bulk of Celite$^®$. Removal of the solvent resulted in 357 mg (94%) benzylic bromide **174**.
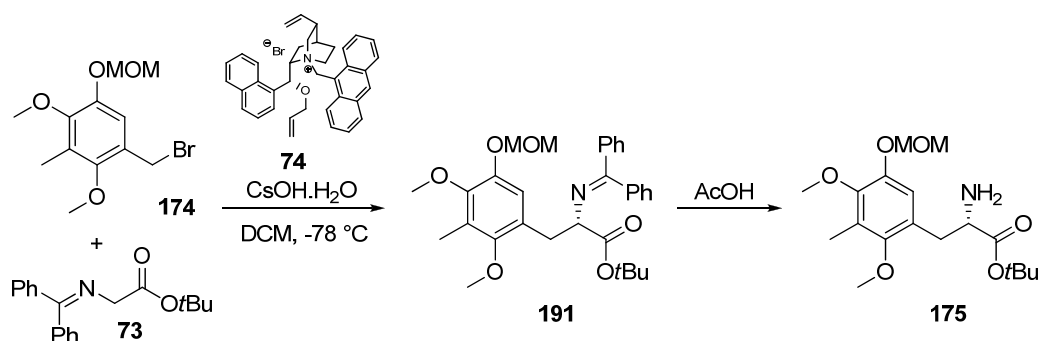
C$_{12}$H$_{17}$BrO$_4$; 305.17 g/mol;

R$_f$.: 0.79 (hexane : ethyl acetate = 2 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.01 (s, 1 H), 5.18 (s, 2 H), 4.54 (s, 2 H), 3.82 (s, 3 H), 3.52 (s, 3 H), 2.21 (s, 3 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 152.2, 149.7, 146.8, 126.3, 126.1, 116.1, 95.6, 61.0, 60.4, 56.3, 28.8, 9.7;

HRMS: calc.: 446.2727, found: 446.2721 (M + H$^+$).

(S)-t-Butyl 2-amino-3-(2,4-dimethoxy-5-(methoxymethoxy)-3-methylphenyl)propanoate (175)

The asymmetric alkylation of benzylic bromide **174** and hydrolysis of the intermediary imine was performed according to the procedure for **171**.

The desired amine **175** was obtained at a yield of 99% and 88% *ee* (according to NMR data of the corresponding Mosher's amide).

Imine **191**:

C$_{31}$H$_{37}$NO$_6$; 519.63 g/mol;

R$_f$.: 0.49 (hexane :ethyl acetate = 4 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] =7.49 (m, 6H), 7.30 (m, 4 H), 6.71 (s, 1 H), 4.91 (s, 2 H), 4.16 (dd, *J* = 9.9, 3.5 Hz, 1 H), 3.77 (s, 3 H), 3.45 (s, 3 H), 3.29 (dd, *J* = 13.3, 3.5 Hz, 1 H), 3.26 (s, 3 H), 3.01 (dd, *J* = 13.3, 9.9 Hz, 1 H), 2.17 (s, 3 H), 1.45 (s, 9 H);

HRMS: calc.: 542.2519, found: 542.2527 (M + Na$^+$).

Amine **175**:

C$_{18}$H$_{29}$NO$_6$; 355.43 g/mol;

R$_f$.: 0.39 (DCM : MeOH = 12 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 6.82 (s, 1 H), 5.15 (dd, *J* = 7.6, 6.6 Hz, 2 H), 3.80 (s, 3 H), 3.69 (s, 3 H), 3.65 (dd, *J* = 8.6, 5.6 Hz, 1 H), 3.51 (s, 3 H), 2.98 (dd, *J* = 13.6, 5.6 Hz, 1 H), 2.74 (dd, *J* = 13.6, 8.6 Hz, 1 H), 2.21 (s, 3 H), 1.52 (br, 2 H), 1.42 (s, 9 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 174.6, 152.4, 147.9, 146.5, 126.2, 125.6, 116.2, 95.7, 80.9, 60.5, 60.4, 56.2, 56.7, 36.1, 28.0, 9.7;

HRMS: calc.: 355.1995, found: 355.1988.

(S)-5-(2-Amino-3-(t-butyldimethylsilyloxy)propyl)-2,4-dimethoxy-3-methylphenol (152)
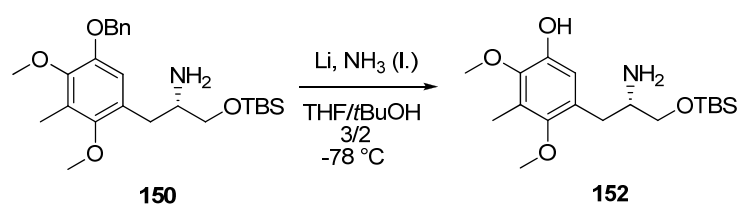
Secondary amine **150** (238 mg, 0.5 mmol, 1.0 equiv.) and *t*-butanol (0.8 mL, 8.4 mmol, 15.7 equiv.) were dissolved in 1.2 mL THF. At -78 °C approximately 8 mL ammonia were condensed to the reaction mixture. Lithium (8 mg, 1.2 mmol, 2.2 equiv.) was added to the vigorously stirred solution. After one hour solid ammonium chloride was added and the reaction mixture was allowed to warm to room temperature. The resulting solution was concentrated and the resulting residue was purified by flash column chromatography (gradient, DCM : methanol = 24 : 1 to 3 : 1). The purification gave 70 mg (31 %) of the desired compound **152** and starting material (69%) was recovered.

C$_{18}$H$_{39}$NO$_4$Si; 355.54 g/mol;

R$_f$.: 0.37 (DCM : MeOH = 12 : 1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 6.65 (s, 1 H), 3.78 (s, 3 H), 3.66 (d, 3 H), 3.60 (dd, *J* = 9.8, 4.8 Hz, 1 H), 3.48 (dd, *J* = 9.8, 6.3 Hz, 1H), 3.12 (m, 1 H), 2.73 (dd, *J* = 13.5, 5.1 Hz, 1 H), 2.50 (dd, *J* = 13.5, 8.6 Hz, 1 H), 2.23 (s, 3 H), 0.91 (s, 9 H), 0.64 (d, *J* = 2.7 Hz, 6 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 150.5, 145.2, 144.4, 128.1, 124.4, 114.1, 67.6, 60.7, 60.6, 53.6, 34.3, 25.9, 16.9, 9.9, -5.4;

HRMS: calc.: 356.2257, found: 356.2249 (M + H$^+$).

***(1R,3S)-1-(Benzyloxymethyl)-3-((t-butyldimethylsilyloxy)methyl)-5,7-dimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinolin-8-ol* (173)**
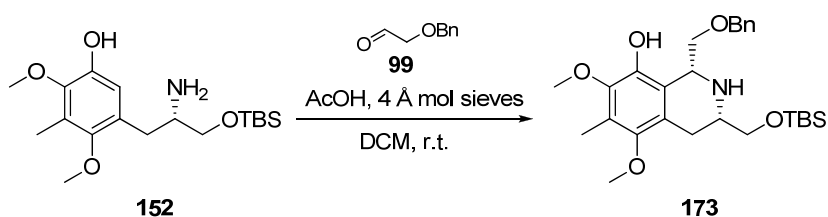
A suspension of amino phenol **152** (60 mg, 0.17 mmol, 1.0 equiv.), crushed 4 Å molecular sieves (20 mg) and acetic acid (2.4 µL, 0.04 mmol, 0.25 equiv.) in DCM (2 mL) was degassed by four freeze-pump-thaw cycles. Benzyloxy acetaldehyde **99** (29 mg, 0.19 mmol, 1.1 equiv.) dissolved in degassed DCM (1 mL) was added to the vigorously stirred suspension *via* syringe pump within 8 hours at room temperature. The reaction was stirred for 24 hours, whereupon its color changed from beige to dark brown. The suspension was diluted with DCM (4 mL), filtered and cautiously treated with sat. aq. sodium bicarbonate solution (5 mL). The aq. layer was washed with DCM (4 x 5 mL). The combined organic layer was dried (MgSO$_4$), filtered and concentrated under vacuum. Purification by flash column chromatography (DCM : MeOH : 60 : 1 to 20 : 1) yielded 82 mg (99%) of tetrahydroisoquinoline **173**.

C$_{27}$H$_{41}$NO$_5$Si; 487.70 g/mol;

R$_f$.: 0.45 (DCM : MeOH = 12 :1);

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm] = 7.30 (m, 5 H), 4.58 (dd, *J* = 20.0, 12.0 Hz, 2 H), 4.50 (t, *J* = 4.5 Hz, 1 H), 4.13 (dd, *J* = 9.1, 4.7 Hz, 1 H), 3.77 (dd, *J* = 10.5, 4.7 Hz, 1 H), 3.76 (s, 3 H), 3.69 (dd, *J* = 9.1, 6.0 Hz, 1 H), 3.65 (s, 3H), 3.63 (dd, *J* = 10.5, 6.9 Hz, 1 H), 2.86 (m, 1 H), 2.81 (dd, *J* = 15.3, 2.5 Hz, 1 H), 2.28 (dd, *J* = 15.3, 11.5 Hz, 1 H), 2.22 (s, 3 H), 1.27 (br, 1 H), 0.90 (s, 9 H), 0.08 (s, 6 H);

^{13}C NMR (CDCl$_3$, 100 MHz): δ [ppm] = 149.2, 144.0, 143.0, 138.1, 128.3, 127.6, 127.5, 125.9, 122.0, 74.5, 73.2, 67.1, 60.6, 60.2, 53.7, 27.1, 25.9, 18.3, 9.5, -5.3;

HRMS: calc.: 487.2754, found: 487.2758.

SELECTED SPECTRA

145

7.305

4.576
4.499
4.131
3.781
3.765
3.687
3.653
3.630
2.858
2.813
2.283
2.217
0.905
0.084

4.67
2.12
0.98
1.00
3.50
1.08
3.21
0.97
0.66
1.40
1.33
3.07
9.28
6.04

9 8 7 6 5 4 3 2 1 0 ppm

149.19
144.04
143.05
138.06
128.30
127.64
127.55
125.90
122.00
74.53
73.25
67.14
60.62
60.20
53.71
27.12
25.94
18.33
9.50
−5.28

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
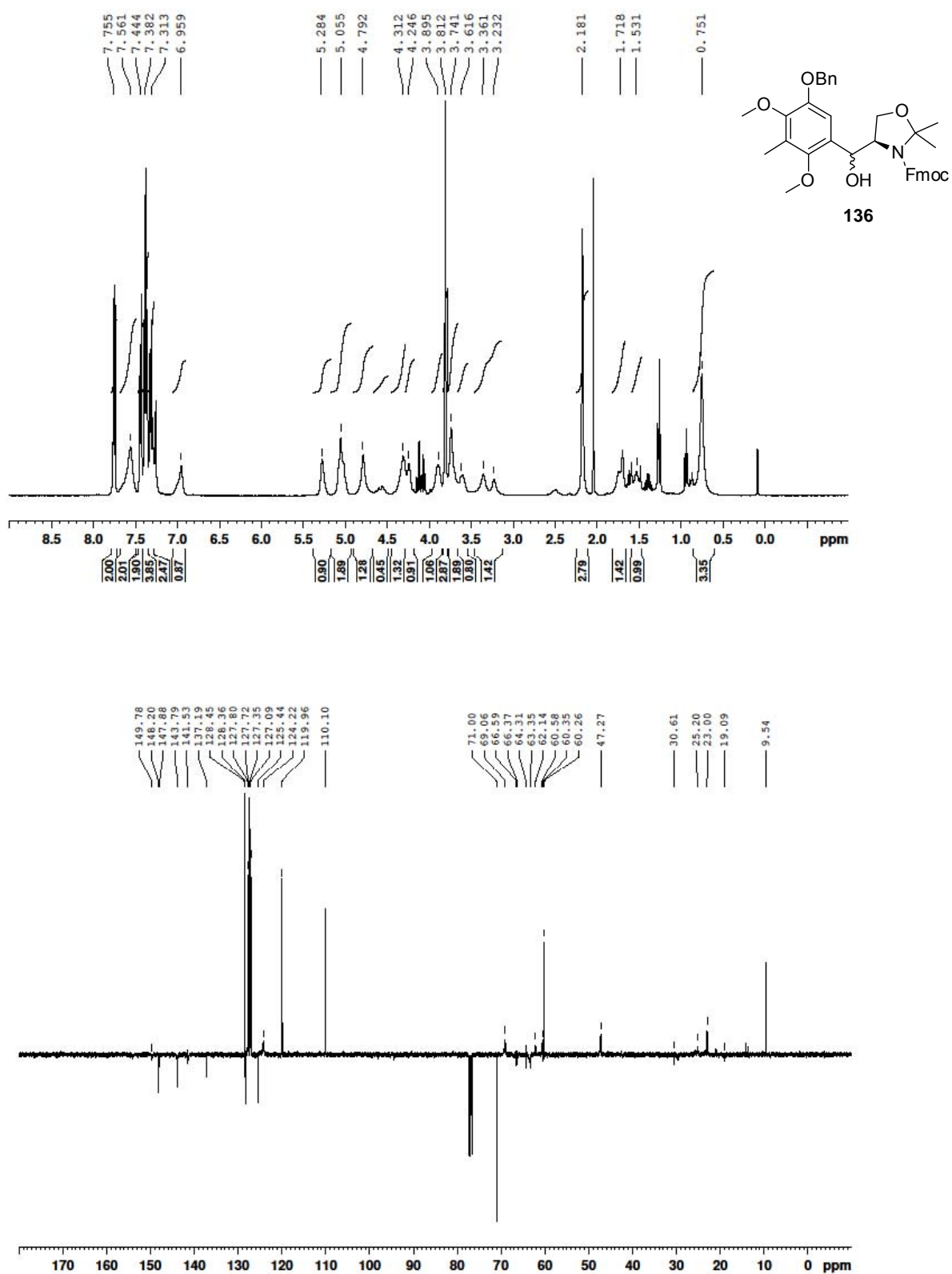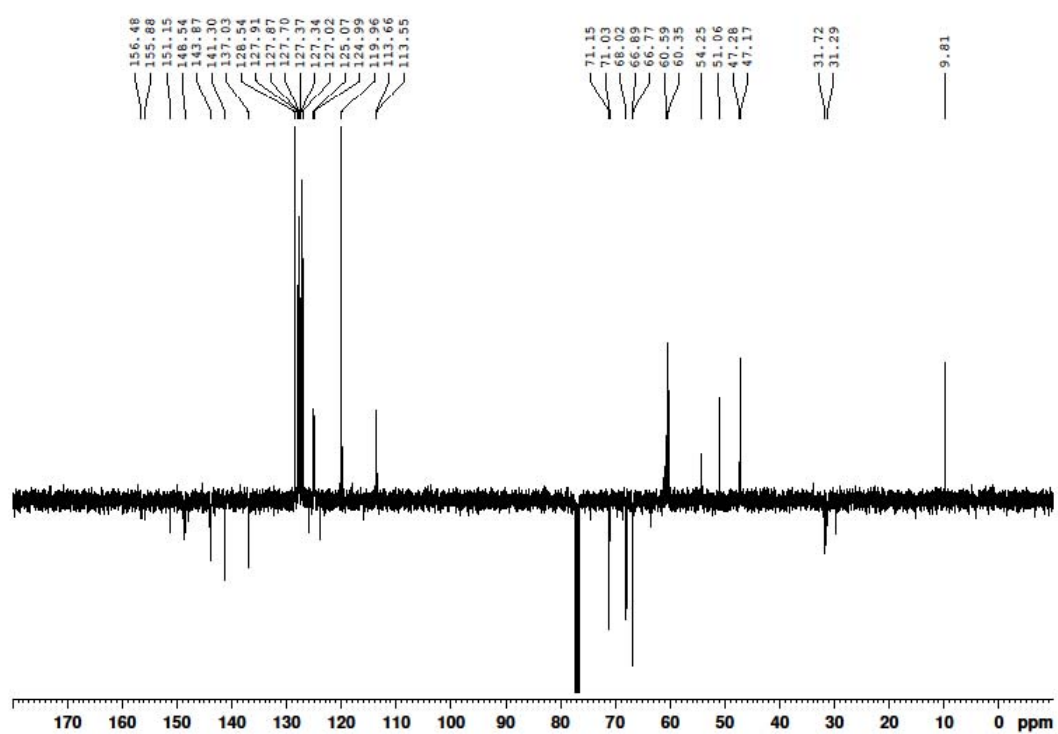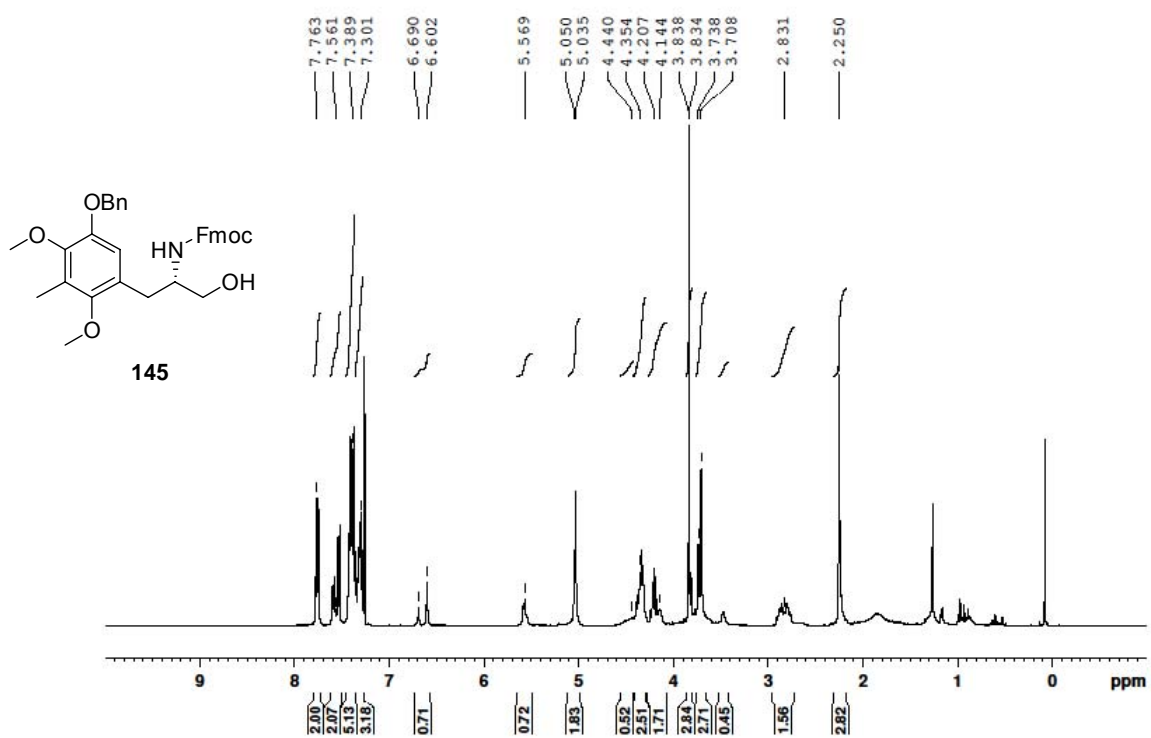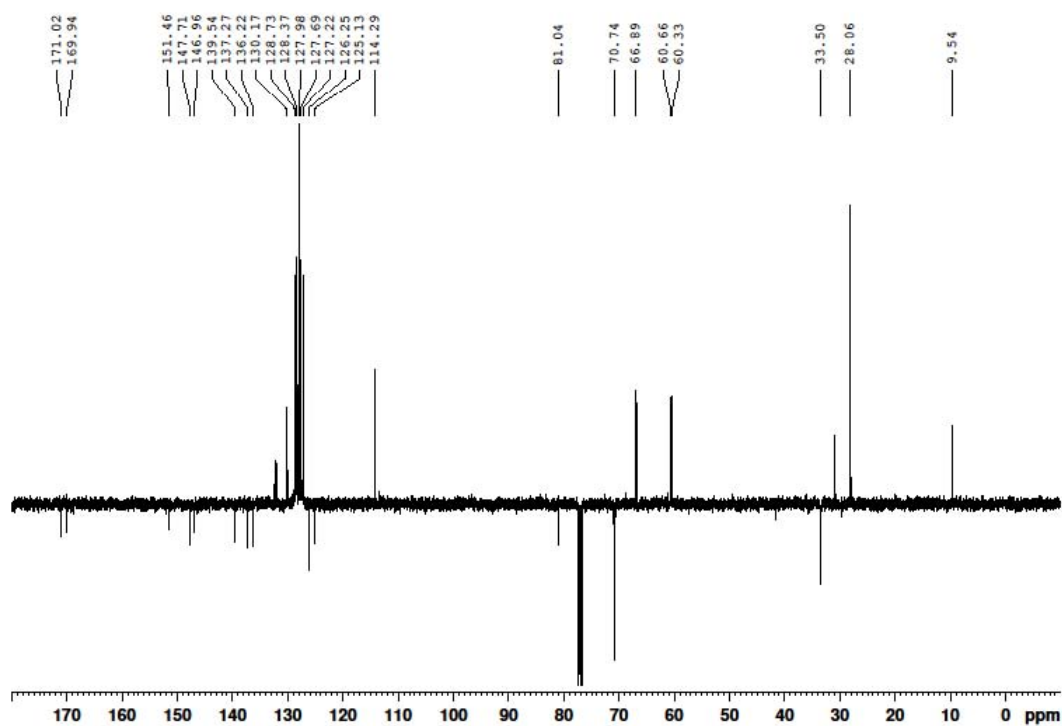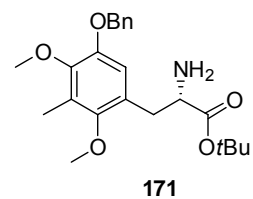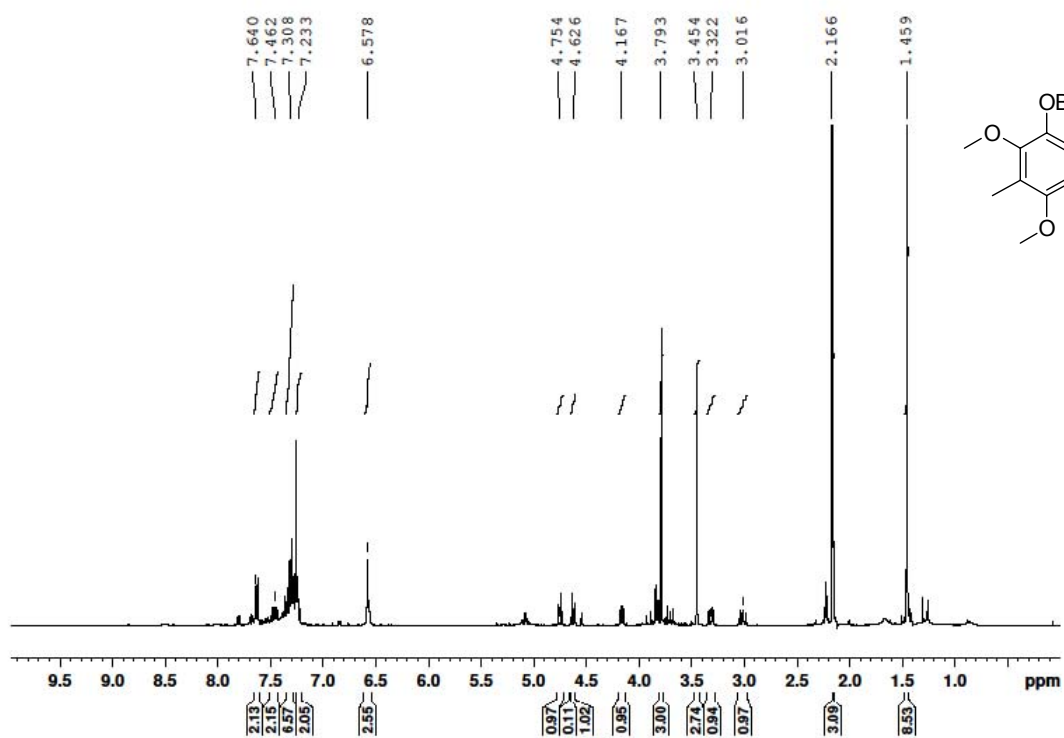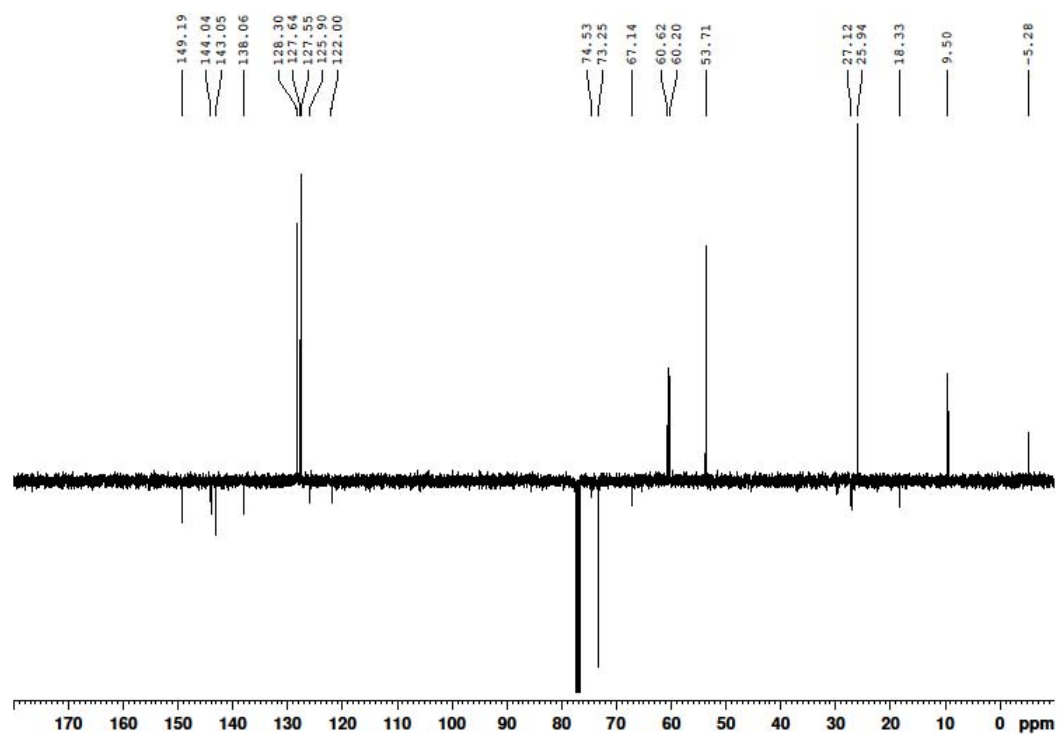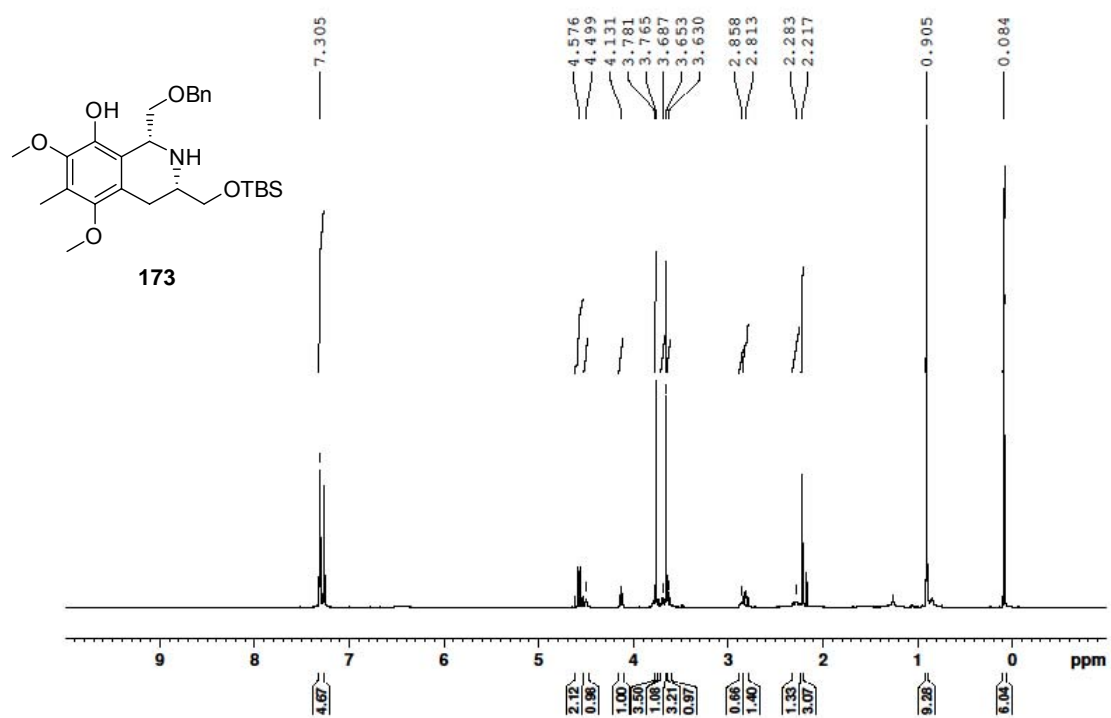
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Nationality	Austrian

Education

1993 - 2001	Grammar School at the BRG 1 Linz (Fadingerstraße), with an emphasis on natural science and mathematics
June 2001	Final exam (Matura) of Grammar School
2002	Military Service at Austrian Guards Division
	Study of chemistry at the University of Vienna
2006	Finished the general part of undergraduate chemistry and specialization in "Organic Chemistry, Spectroscopy and Material Chemistry"
2008 - present	Diploma Thesis "Synthetic Efforts Towards a Synthesis of the Tetracyclic Core of (-)-Lemonomycin" at the Institute of Organic Chemistry under the supervision of Prof. Mulzer

Employments

Summer 2001	Population Census, coworker
Winter 2001	Landesverlag (now Thalia), Linz; salesman
Summer 2003	Bar-Cafe Schumanski, Gramastetten (Upper Austria); waiter
2004 – 2007	Nycomed Austria GmbH; trainee from September to October
2008 – present	University of Vienna; tutor of undergraduate students

Publications

2008	EuCheMS2008, Turin; "Towards the Stereocontrolled Synthesis of the Tetracyclic Core Framework of (-)-Lemonomycin"; poster presentation
2009	ESPCI workshop, Paris; "Towards a Synthesis of Lemonomycin"; poster presentation