DIELS-ALDER, HECK, AND RADICAL CYCLIZATIONS IN APPROACHES TO THE SYNTHESIS OF MORPHINAN SKELETON

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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2003
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[Signature]
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</tr>
<tr>
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</tr>
<tr>
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<td>Pyridinium chlorochromate</td>
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<td>$p$-MBDMA</td>
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<td>Pyridine</td>
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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

DIELS-ALDER, HECK, AND RADICAL CYCLIZATIONS IN APPROACHES TO THE SYNTHESIS OF MORPHINAN SKELETON

By

Josef Zezula

August 2003

Chair: Prof. Tomáš Hudlický
Major Department: Chemistry

This dissertation is composed of two related parts. In part one inter- and intramolecular Diels-Alder reactions of protected enantiomerically pure diene diol (enzymatically derived from 2-azidoethylbenzene) with electron deficient dienophiles are described. Derivatizations of the resulting cycloadducts containing the octahydroisoquinoline core are discussed with the goal to install a second diene unit for further conversion to the morphinan skeleton.

In part two, the required octahydroisoquinoline skeleton is constructed via previously reported cationic cyclization of acyliminium species prepared from diene diol made by biooxidation of 2-bromoethylbenzene. Further conversion of this octahydroisoquinoline skeleton via attachment of an aryl bromide moiety (or its precursor) in stereoselective fashion and subsequent Heck cyclization to establish the C13 center is discussed along with model studies involving Heck and radical cyclizations.
 CHAPTER 1
INTRODUCTION

Morphine 1 (Figure 1) is one of the most commonly known alkaloids isolated from the poppy plant (Papaver somniferum). Its use in medicine can be tracked back to the fourth millennium BC. To this date morphine still plays an irreplaceable role in medicine as an analgesic and an anesthetic in heart surgery.\(^1\) It has remarkably high selectivity for a single receptor, \(\mu\)-receptor, which appears to be responsible for analgesia, euphoria, addiction and respiratory depression.\(^2\) In 2001 global consumption of opiates amounted to 238.3 tons in morphine equivalent. Annual consumption for the next couple of years is extrapolated to be around 245 tons. There are five major legal producers of raw opium: India, Turkey, Australia, Spain and France. In 2001 India produced 85.2 tons in morphine equivalents (28% of global production), followed by Turkey (68.0 t, 22%), Australia (64.3 t, 21%), Spain (37.4 t, 12%) and France (24.8 t, 8%).\(^3\) The still existing demand of morphine justifies attempts to make this alkaloid synthetically with a goal to eventually compete with its isolation from opium and/or its conversion to noroxymorphone and its derivatives.

\[\text{Figure 1: Morphine}\]
Although there are more than 20 reported total syntheses of morphine, none of them have achieved the goal of efficient synthesis. To date the most efficient total synthesis is that of Rice, which yields morphine in 29% overall yield.\textsuperscript{4}

Even though morphine contains three six-membered rings (B, C, D), which possibly could be constructed via Diels-Alder reaction, only a few published syntheses utilize this reaction. In one of the previously reported approaches to morphine, cyclohexadienediol 3 was converted to bridged cycloadduct 4,\textsuperscript{5} which upon conversion to ketone 5 underwent Cope rearrangement to yield partial morphinan skeleton 7 (Scheme 1).

Scheme 1

In the second generation\textsuperscript{6} the necessity of the rearrangement was avoided by reducing dienediol 2 to diol 8, which was further transformed into triene 9. Heating of 9 induced Diels-Alder reaction to yield a truncated morphinan 10, with all five chiral centers of natural morphine correctly set (Scheme 2).

Scheme 2
Inspired by the above-mentioned results novel double Diels-Alder approach to the morphine core was envisioned which is described in more detail in the Discussion Section. Another key issue in approaches to morphine that are based on cyclohexadiene cis-diols is the attachment of the aromatic ring A to the isoquinoline ring system and the establishment of C12-C13 connectivity. In a previously reported study\(^7\) ring A was attached via the sequence of two Mitsunobu reactions and the morphinan skeleton was then constructed via tandem radical cyclization to yield tetracycle 14 (Scheme 3).

![Scheme 3](image)

An alternative synthesis reported in the same paper, relied on a sequence of radical cyclizations to close the isoquinolone system containing rings C and D of morphine.

![Scheme 4](image)

Ring A was then attached via a single Mitsunobu reaction after protective group manipulations. Closure of the ent-morphinan core to give 18 was completed by another radical cyclization (Scheme 4). Radical closure of 16 to the isoquinoline ring system 17 gave a mixture of two isomers (2:1) at carbon 9 (morphine numbering), and this disadvantage was later overcome by utilizing cationic cyclization of acyliminium ion
generated from precursor 19. Ring A was again installed via a single Mitsunobu reaction and the tertiary center was established via Heck coupling\(^8\) on the tetrasubstituted double bond to yield \textit{ent}-morphinan 21 (Scheme 5).

Scheme 5

All of the above approaches used one or even two Mitsunobu reactions for the installation of the ring A, thus carrying out inversion of the chiral center that was correctly set by the microbial oxidation of the corresponding substituted benzenes. The study presented in this thesis seeks to avoid such issues.

In the first part of this thesis, synthesis of bridged isoquinolone synthons 24 will be described via intramolecular Diels-Alder reactions of cyclohexadiene diol derivatives, prepared by biooxidation of corresponding substituted benzene (Scheme 6).

Scheme 6

An alternative route to these synthons via intermolecular Diels-Alder reaction will be discussed as well. These cycloadducts contain rings C and D of morphine, and some of them possess the correct configuration of centers 5, 6 and 14. An additional alternative route towards these synthons via intermolecular cycloaddition will be
discussed. Incorporation of ring A was envisioned via a second Diels-Alder reaction of derivatives such as 25 with tethered furan or methoxyfuran. Such sequence would yield adducts of type 26 which are expected, upon hydrolysis of the ester moiety, to fragment with a loss of carbon dioxide to yield the complete carbon skeleton of morphine (Scheme 7). Further derivatization of cycloadducts 24 with the goal to prepare these intermediates for second intramolecular Diels-Alder reaction will be discussed.

![Scheme 7](image)

The second part of this thesis deals with attempts to improve the synthesis of the previously reported\textsuperscript{10} octahydroisoquinoline synthon 28 (Scheme 8) and its further functionalization, particularly the mechanics of the attachment of ring A or its precursor to the carbon 5 (morphine numbering) while preserving the stereochemistry installed during the biotransformation step at this center.

![Scheme 8](image)

One of the possible routes to attach ring A without inversion of the configuration set by microbial oxidation will be through the opening of epoxide 30, first prepared by Boyd et al.,\textsuperscript{11} with different monoprotected diols 29 as shown in Scheme 9 (route A).
Cyclization of 31 to yield the tetracyclic core of morphinans is envisioned via Heck or radical cyclization.

Scheme 9: Route A

Model study dealing with the opening of epoxide 30 with 2-cyclohexenol and subsequent cyclizations along with attempts to re-oxidize the product of the epoxide opening in order to re-aromatize ring A will be also discussed.

A new alternative to the attachment of ring A via opening of epoxide 33 with bromoguaiacol 34 (or its salts) also will be discussed (Scheme 10). Even though this route B requires the inversion of both stereocenters of diol 28, it offers a great advantage over proposed route A because it avoids possible problems with re-oxidation of the ring A precursor.

Scheme 10: Route B

Establishment of crucial C12-C13 connectivity via Heck coupling to give tetracycle such as 36 will be discussed.
CHAPTER 2
HISTORICAL BACKGROUNDS

Introduction

The opium poppy, *Papaver somniferum*, probably originated from Asia Minor and there are indications that the Sumerians cultivated it to extract opium at least three thousand years BC. The method of extraction of opium practically has not changed since then. Around fifteen days after petals fall, the immature seed capsule of the poppy plant is cut and the fresh opium latex is exuded. The next day the latex, by now black, is scraped off and collected. This procedure is repeated several times to maximize the yield of desired raw material, which is dehydrated by sun baking to remove about 90% of its water content. At this point, the black resinous mass is known commercially as *Indian Opium* and contains approximately 10-15% morphine 1, 3-4% codeine 37, 0.1-2% thebaine 38, 1-7% noscapine (narcotine) 40 and 0.5-1% papaverine 39.\(^\text{13}\)

![Scheme 1: Opium alkaloids](image_url)

Scheme 11: Opium alkaloids
The alkaloid content of the crude opium (approximately 10-20%) consists of more than 40 different alkaloids, however, five of them, namely the morphinans: morphine, codeine, thebaine, benzylisoquinoline papaverine and phthalideisoquinoline noscapine, account for virtually all the mass (Scheme 1). In 1803 Derosne described isolation of "salt of opium" as the first crystalline compound isolated from the crude opium. A year later Armand Séquin also isolated the major constituent of opium.

However it is Friedrich Sertürner who is credited with the isolation of morphine. He began his experimental work on opium in 1803 and published a more detailed paper in 1806. In 1817 he wrote a review paper and a conclusive evaluation of his earlier work. In this particular paper he gave morphine its name ("morphium" after Morpheus, the ancient Greek god of dreams). Following its isolation, morphine was introduced into medical practice to treat a variety of ailments such as asthma, diarrhea, diabetes and ulcers as well as being used as an analgesic.

At the end of the nineteen-century Bayer made commercially available diacetylmorphine (heroin). Heroin was found to be more potent and faster acting than morphine, but also more addictive. It is believed that heroin is rapidly hydrolyzed to morphine in the body, however its more lipophilic nature allows for faster penetration to brain. Another morphine derivative, codeine (3-O-methylmorphine), has much lower potency than morphine itself (approx. one sixth) and it is used as a cough suppressant.

Early studies conducted by Liebig were followed by those of Laurent, who correctly deduced the empirical formula for morphine as $\text{C}_{17}\text{H}_{19}\text{NO}_3$ in 1847. Knorr and Pschorr among others also engaged in experiments to elucidate the structure of morphine via various degradation experiments. The correct structure of morphine was
proposed more than a century after its isolation by Robinson, who noted that morphine is a twisted benzylisoquinoline.\cite{21} An X-ray crystallographic analysis and other evidence allowed for definition of the absolute stereochemistry of morphine.\cite{22,23}

**Morphine Biosynthesis**

Detailed studies on opium alkaloids biosynthesis revealed that morphine and related alkaloids are formed in *P. somniferum* through a series of benzylisoquinoline intermediates which culminate in (R)-reticuline.\cite{24,25} The benzylisoquinoline skeleton is elaborated from two molecules of L-tyrosine 41, which provides the source for all of the non-methyl carbons incorporated into morphine. One molecule of 41 is converted into dopamine 43 in two enzymatic steps via intermediate tyramine 42. A second molecule of L-tyrosine 41 is via action of a transaminase enzyme converted into 4-hydroxyphenylpyruvic acid 44 which is then decarboxylated to yield 4-hydroxyphenylacetaldehyde 45 (Scheme 12).

![Scheme 12: (S)-Norcoclaurine biogenesis](image)

Enzymes: i L-tyrosine decarboxylase; ii phenolase; iii L-tyrosine transaminase; iv p-hydroxyphenylpyruvate decarboxylase; v (S)-norcoclaurine synthase;

Scheme 12: (S)-Norcoclaurine biogenesis

Condensation of 43 and 45 is catalyzed by (S)-norcoclaurine synthase to stereospecifically yield (S)-norcoclaurine 46, which is a precursor of many
benzylisoquinoline alkaloids found in plants including morphine. Two enzyme catalyzed methylations and an aromatic hydroxylation lead to (S)-reticuline 50 (Scheme 13). 26

![Scheme 13: (S)-Reticuline biosynthesis](image)

Curiously (S)-reticuline 50 has the opposite configuration to that found in morphine. Necessary inversion occurs in two steps via dehydroreticuline 51 (Scheme 14). 27 The reductase involved is highly specific and is dependent on NADPH/NADP⁺.

![Scheme 14: Reticuline isomerization](image)

The next step in the morphine biosynthesis is a remarkable oxidative coupling of the two phenolic units of (R)-reticuline 52, where, after cyclization, the top ring re-aromatizes to give salutaridine 53 (Scheme 15). The enzyme catalyzing this
transformation, isolated from microsomal preparations of *P. somniferum*, is a membrane bound cytochrome P 450 protein and its catalytic function is strictly dependent on molecular oxygen and NADPH.28

![Diagram](image)

Scheme 15: Salutaridine formation

The idea that the radical diphenolic coupling reaction is the key step in formation of many C-C and C-O bonds in alkaloids was originated by Barton and Cohen.29 Barton’s idea came from his rejection of the structure assignment of Pummerer’s ketone30 as 57, formed by oxidative dimerization of 4-cresole 54, instead he proposed structure 56 based on the mechanism shown in Scheme 16.31

![Diagram](image)

Scheme 16: Formation of Pummerer's ketone

Barton proved his hypothesis by in vitro conversion of labeled reticuline 52 to salutaridine 53 by treatment with potassium ferricyanide.32

Salutaridine 53 is then stereospecifically converted to salutaridinol 54 by an NADPH-dependent oxidoreductase.33 Enzymatic acetylation gives 55, which
spontaneously cyclizes at slightly alkaline pH to yield opium alkaloid thebaine 38.\textsuperscript{34} To date no enzyme has been found for this conversion (Scheme 17).

\begin{center}
\includegraphics[width=0.9\textwidth]{scheme17.png}
\end{center}

Scheme 17: Thebaine formation

Demethylation of thebaine 38 gives neopinone 56, which is in chemical equilibrium with codeinone 57. A specific oxidoreductase converts 57 into codeine (Scheme 18). Neopinone 56 is not a substrate for this enzyme; it has to be converted to codeinone 57.\textsuperscript{35} A final demethylation of codeine 37 affords morphine 1.

\begin{center}
\includegraphics[width=0.9\textwidth]{scheme18.png}
\end{center}

Scheme 18: Codeine formation

There is some evidence that morphine can be endogenously synthesized in mammals, via a synthetic pathway speculated to be similar to that established in \textit{P. somniferum}.\textsuperscript{1}
Overview of Selected Morphine Syntheses

To date about 20 total syntheses of morphine have been reported, starting with Gates' landmark synthesis published in 1956.\textsuperscript{36} However the first synthesis discussed in this short review will be that of Rice published in 1980, which is currently the shortest and the most efficient.\textsuperscript{4}

The first three steps involve neat condensation of amine 59 with acid 58, followed by a cyclization/reduction sequence to yield the corresponding isoquinoline, which was then reduced under Birch's conditions to compound 60. The cyclization precursor 61 was then prepared in three more steps (Scheme 19).

\begin{center}
\begin{tikzpicture}
  \node[draw] (58) {\includegraphics[width=0.2\textwidth]{58.png}};
  \node[draw, right of=58, xshift=1cm] (59) {\includegraphics[width=0.2\textwidth]{59.png}};
  \node[draw, right of=59, xshift=1cm] (60) {\includegraphics[width=0.2\textwidth]{60.png}};
  \node[draw, right of=60, xshift=1cm] (61) {\includegraphics[width=0.2\textwidth]{61.png}};

  \draw[->] (58) -- node[above] {a-c} (59);
  \draw[->] (59) -- node[above] {3 steps} (60);
  \draw[->] (60) -- node[above] {d-f} (61);

  \node at (0.5,0.1) {3 steps};

  \node[anchor=west] at (4cm,0.3) {Reaction conditions: a) neat/200°C (95%), b) POCl\textsubscript{3}/CH\textsubscript{3}CN then NaCNBH\textsubscript{3} (86% overall), c) Na/NH\textsubscript{3} (90%), d) PhOCHO/EtOAc reflux (94%), e) CH\textsubscript{3}SO\textsubscript{2}H/HOCH\textsubscript{2}CH\textsubscript{2}OH then N-bromoacetamide (88%), f) HCO\textsubscript{2}H/H\textsubscript{2}O (90%)};
\end{tikzpicture}
\end{center}

Scheme 19: Rice's synthesis I

After protection of the secondary amine in 60, the aromatic ring was regioselectively brominated before carrying out a Grewe-type cyclization, which is a key step in Rice's synthesis. Grewe developed his biomimetic approach to morphinans in 1948 by heating the 1-benzyloctahydroisoquinoline derivative 62 in phosphoric acid. Under those conditions cationic cyclization took place to yield morphinan skeleton 63 in good yield (50%) (Scheme 20).\textsuperscript{37}
Scheme 20: Grewe's cyclization

Some 19 years later Grewe applied his cyclization methodology to formal synthesis of morphine via dihydrothebainone 65. Unfortunately byproduct 66 resulting from para coupling was predominant (37% yield vs. 3% of desired 65).\(^\text{38}\)

Rice solved the above problem with a cleverly placed bromine substituent in the para position to the hydroxy group, which prevents formation of para coupling product. When 61 was exposed to 14% NH\(_4\)F*HF in dry CF\(_3\)SO\(_2\)H in a high-density polyethylene vessel, racemic 1-bromo-N-formylnordihydrothebainone 67 was obtained in good yield (60%).

**Reaction conditions:**  g) 37% HCl/MeOH/reflux (84%), h) Br\(_2\)/AcOH, i) Pd/C/H\(_2\)/HCHO (79% overall)

Scheme 21: Rice's synthesis II
After deprotection of the amine under acidic conditions and bromination of the ketone, the phenol intramolecularly displaced bromine to complete construction of the morphine skeleton. The resulting pentacycle 68 was then hydrogenated in presence of HCHO to yield racemic dihydrocodeinone 69 (Scheme 21).

This synthesis starts with readily available starting materials, requires isolation of only six intermediates which are sufficiently pure for further transformations. Codeinone 69 prepared in this way is easily converted in two steps to morphine.

**Approaches Involving Diels-Alder Reaction**

As was mentioned above, Gates in 1956 published the first total synthesis of morphine.\(^{36}\) This synthesis definitely confirmed the structure of morphine proposed by Robinson in 1925.\(^{21}\) 2,6-Dihydroxynaphthalene 70 was first converted into the monobenzoate, which underwent regioselective nitrosylation, followed by reduction-oxidation sequence to yield 6-benzoyloxy-1,2-naphthoquinone (Scheme 22).

![Scheme 22: Gates’ synthesis I](attachment:image.png)

**Reaction conditions:** a) BzCl/Py/dioxane (72%), b) NaNO₂/AcOH (88%), c) Pd/C/H₂ then FeCl₃·6H₂O (85%), d) SO₂/MEOH (91%), e) (MeO)₂SO₂ (88%), f) KOH/H₂O (80%), g) ethyl cyanoacetate/Et₃N then K₃Fe(CN)₆ (84%), h) Claisen’s alkali (97%)

The quinone was then reduced to the corresponding hydroquinone, which after methylation afforded 5,6-dimethoxy-2-naphthol benzoate. After alkaline hydrolysis of the ester, the same sequence of reactions as described above was carried out again to prepare 5,6-dimethoxy-1,2-naphthoquinone which, after condensation with
ethylcyanoacetate and decarboxylation, gave compound 71 (Scheme 22). Synthesis of the phenanthrene core of morphine skeleton was then completed in one step by Diels-Alder reaction of quinone 71 with 1,4-butadiene to yield 72, which underwent reductive cyclization under relatively mild conditions (130 °C/27 atm. H₂) to give 73 possessing a complete carbon skeleton of morphine (Scheme 23).

Scheme 23: Reductive cyclization

The carbonyl groups of racemic 73 were then reduced in two steps to yield rac-β-Δ⁶-dihydropseudoephedrine methyl ether 74, which was then resolved by crystallization with enantiomorphic dibenzooyltartaric acids. The desired d-base was isolated and it was proven to be identical to natural d-β-Δ⁶-dihydropseudoephedrine methyl ether. Thus the rest of the synthesis was carried out using material from natural resources.

Gates then installed oxygen on carbon 6 (morphine numbering) by hydration of the olefin 74 with diluted sulfuric acid (Scheme 24).
Yields of up to 28% were achieved if account was taken of recovered 74. The C3 methoxy group in 75 was then selectively cleaved under Wolff-Kishner conditions and the secondary alcohol was then oxidized by potassium t-butoxide-benzophenone to yield β-dihydrothebainone 76 as its perchlorate (Scheme 24). The next major challenge that Gates had to tackle was inversion of the trans fusion of rings B and C to cis fusion. It was devised that introduction of a α,β-unsaturation in 76 would lead to equilibration at the C14 center to produce appreciable amounts of an α,β-unsaturated ketone of the cis series. Thus compound 76 was dibrominated and the resulting crude product 77 was treated with 2,4-dinitrophenylhydrazine to give cis monobromo α,β-unsaturated 2,4-dinitrophenylhydrazone 78 (Scheme 25).

![Reaction Scheme 25](image)

Scheme 25: Epimerization of C14 center

This short sequence: dibromination of ketone, elimination to give enone, epimerization, with the hydrazone formation elegantly solves the problem of inversion of the B/C ring fusion from trans to cis. Hydrazine 78 was then hydrolyzed and hydrogenated to give the corresponding ketone 79, which was again dibrominated, followed by treatment with 2,4-dinitrophenylhydrazine. The desired 1-bromocodeinone 2,4-dinitrophenylhydrazone was isolated in low yield (26%) (Scheme 26). Total synthesis of morphine 1 was then finished in three steps by hydrolysis of hydrazone 80,
stereospecific reduction of the resulting enone with lithium aluminum hydride and final
demethylation using the method of Rapoport.  

![Chemical structure](image)

**Reaction conditions:** h) 12N HCl (60%), i) H2/Pt02 (80% (hydriodide)), j) Br2/AcOH then ArNHNH2 (26%),
k) 12N HCl (27%), l) LiAlH4 (quant.), m) Pyridine*HCl (34%)

Scheme 26: Closure of the oxide ring between C4 and C5

Ciganek reported another interesting approach to morphinan skeleton via a Diels-
Alder reaction in 1981.  
His design utilized intramolecular cycloaddition of pyrone-
carboxamide tethered to methoxybenzofuran. Heating of 81 in 1,2,4-trichlorobenzene
gave cycloadduct 82 in 53% yield.

![Chemical structure](image)

**Reaction conditions:** a) H2/Pd/C, b) BH3*Me2S, c) n-PrSK/DMF (86% overall from 82)

Scheme 27: Ciganek's cycloaddition approach

After catalytic hydrogenation, which established the *trans* C/D ring junction, the
amide was reduced with borane-methyl sulfide. Final demethylation gave compound 83,
which contains the almost complete carbon skeleton of morphine, lacking only the C-10
carbon (Scheme 27). The stereochemistry of 83 (R= cyclopropylmethyl) was
unambiguously confirmed by single crystal X-ray structure determination. Cycloaddition
of the tethered butadiene 84 in toluene was carried out as well, requiring slightly higher reaction temperature to give cis fused product 85 (10%) isolated by HPLC.

![Chemical structure diagram]

**Scheme 28**

Conversion of 85 to morphinan 86 was carried out as described above (Scheme 28). This report presents a very concise route to an almost complete morphinan skeleton, taking advantage of intramolecular cycloaddition to form two six-membered rings in one step.

Jones reported another interesting model study towards the morphinan skeleton via intramolecular cycloaddition in 1985.\(^{42}\) It is known that 4a-aryloctahydro-isoquinolines such as 89, which are present in the structure of opium alkaloids, do retain some analgesic properties of morphine itself (Scheme 29).\(^{43}\)

![Chemical structure diagram]

**Scheme 29: Jones' cycloaddition approach**

The Jones’ route to this systems starts with the Michael addition of the primary amine to acrylophenone 87, followed by the acylation to install the diene and final Wittig
reaction to prepare triene 88. Heating of triene 88 in DMSO yielded 89, the product of the rearrangement of the double bond in the initially formed cycloadduct, as a single stereoisomer. Hydrogenation of 89 gave trans fused bicycle 90, while similar reduction with LiAlH₄ gave analogous results to yield 91. Thiolactam 92 was also prepared and its single crystal X-ray analysis confirmed cis relationship of C-6 methyl and C-4a aryl groups (Scheme 30).

Scheme 30: Jones' derivatization of the cycloadduct 89

A year after Jones, Kametani⁴⁴ published an approach to the partial morphinan core via intramolecular cycloaddition of benzocyclobutene derivative 95 (Scheme 31).

Scheme 31: Kametani's cycloaddition approach I

When 95 was heated in xylene, the major product was B/C cis fused tricycle 96, whose ring junction has the same stereochemistry as found in natural morphine alkaloids.
Also appreciable amount of \textit{trans} fused tricycle 97 was isolated. Both cycloadducts were further transformed into the corresponding substituted styrenes 98 and 99 via benzylic bromination/elimination sequence (Scheme 32).

\begin{center}
\begin{tabular}{c|c}
98 & 96 \\
\hline
\includegraphics[width=0.2\textwidth]{reaction1.png} & \includegraphics[width=0.2\textwidth]{reaction2.png} \\
\end{tabular}
\end{center}

\textbf{Reaction conditions:} a) NBS/(PhCOO)\textsubscript{2}/CCl\textsubscript{4}/reflux (78\% (98) and 72\% (99))

Scheme 32: Kametani's cycloaddition approach II

The stereochemistry of 99, the derivative of the minor product of cycloaddition, was unambiguously confirmed by X-ray analysis. Based on this finding Kametani assigned the stereochemistry of the major cycloadduct 96 as \textit{cis}.

In 1992 Tius published the synthesis of racemic thebainone, utilizing the Diels-Alder reaction as a pivotal step to form ring B of the morphinan skeleton.\textsuperscript{45} Starting from readily available \textit{o}-vanilin 100, benzoquinone 102 was prepared in 7 steps and in 35\% overall yield (Scheme 33).

\begin{center}
\begin{tabular}{c|c}
100 & 101 \\
\hline
\includegraphics[width=0.2\textwidth]{reaction3.png} & \includegraphics[width=0.2\textwidth]{reaction4.png} \\
\end{tabular}
\end{center}

\textbf{Reaction conditions:} a) MeNO\textsubscript{2}/HOAc/NH\textsubscript{4}OAc (93\%), b) NaBH\textsubscript{4}/THF/MeOH (73\%), c) EVE/TsOH (96\%), d) LiAlH\textsubscript{4}/THF, e) ClCO\textsubscript{2}CH\textsubscript{3}/DIPEA f) TsOH/MeOH (69\% overall), g) O\textsubscript{2}/Salcomine/DMF (78\%)

Scheme 33: Tius' cycloaddition approach I
Diene 103, the precursor of aromatic ring A of morphine, was prepared from commercially available 1,4-cyclohexanedione monoethylene ketal in two steps in 52% overall yield.

Scheme 34: Tius' cycloaddition approach II

Heating of diene 103 and quinone 102 in toluene smoothly gave cycloadduct 104, which was then converted into acyloin 105 in a five steps sequence (Scheme 34). Re-aromatization of ring A in 105 was accomplished in 5 steps to yield anisole 106 (Scheme 35).

Scheme 35: Tius' cycloaddition approach III

In six more steps enone 107 was prepared, which upon reduction with zinc/NH₄Cl system rearranged to form compound 108, which is essentially the complete carbon
skeleton of morphine. Synthesis of racemic thebainone 109 was then completed in three steps (Scheme 36).

Scheme 36

Hudlický published another Diels-Alder reaction-based approach towards partial morphinan skeleton in 1992. The product of the microbial oxidation of toluene 2 was used as a convenient chiral starting material possessing two stereogenic centers of morphine in the correct configuration. The less hindered hydroxyl was protected as a t-hexyldimethylsilyl ether and the alkylation of the remaining free hydroxyl with sorbyl bromide gave tetraene 3 (Scheme 37).

Scheme 37: Hudlický’s cycloaddition/Cope rearrangement approach
Heating of 3 yielded the bridged cycloadduct 4, which was converted to ketone 5 in two steps in order to facilitate the subsequent Cope rearrangement. The rearranged product 6 was then reduced under Luche’s conditions to give a truncated morphinan 7. In the second generation of this model study the necessity of the Cope rearrangement was avoided by reducing the less hindered double bond in 2 by diimide, followed by monoprotection and alkylation as described above. Triene 9 underwent the Diels-Alder reaction upon heating supposedly to give cycloadduct 110 (Scheme 38). In the follow-up paper a structure correction was made, where compound 10 is the product of cycloaddition reaction of 9. Stereochemistry of 10 was confirmed by the X-ray crystallography of the corresponding free alcohol.4

Scheme 38

A more advanced model study was carried out, starting from phenethyl bromide 111, which was converted to triene 113 in 7 steps (Scheme 39).

Scheme 39
Cycloaddition proceeded via an exo transition state to yield tricycle 114, which has all the stereocenters of morphine correctly set.\(^6\)

Another interesting model study came from the Hudlický’s research group in 1995, this time focused on the intramolecular cycloadditions of substituted furans as the model study towards noroxymorphone analogues 119. Oxazolidinone 115 was alkylated and triene 116 was either heated in toluene or in water in the presence of β-cyclodextrin. The latter conditions giving much better results in terms of yield. Cycloadduct 117, a highly substituted isoquinoline, was then oxidized to yield diol 118 (Scheme 40).\(^{46}\)

![Scheme 40](image)

**Reaction conditions:** a) NaH/4-bromobut-1-ene/DMF (67%), b) PhMe/200 °C (56%), or β-cyclodextrin/H\(_2\)O (84%), c) OsO\(_4\)/NMO (95%)

The structure of 118 was unambiguously confirmed by X-ray crystallography.

With respect to possible application of this cycloaddition reaction to the synthesis of isoquinoline alkaloids such as morphine or noroxymorphone 120, methoxy furan derivative 121\(^a\) was prepared and subjected to heating in benzene. However, the desired cycloadduct 124 was not isolated.
Reaction conditions: a) Br₂/MeOH (73%) then CSA/PhH/heat (<20%), b) 4-bromobut-1-ene/DMF (66%), c) PhH/120-165 °C, 122 (40%) and 123a (55%)

Scheme 41

Instead a mixture of aromatized product 122 and hydroxy enone 123a were isolated in very good total yield (95%) (Scheme 41). The exact stereochemistry of compound 123a was also confirmed by X-ray crystallography. Cycloadditions of 121b, with a phenyl substituent in the 3-position on the butene side chain (prepared in similar manner as 121a) were investigated as well. Heating of 121b in toluene to 250°C (sealed tube) lead to extensive decomposition. However, cycloadduct 123b was isolated in very low yield (13%).

In 1998 Rodrigo reported a concise route to phenanthrofurans based on intramolecular Diels-Alder reactions. The key step in his approach was the oxidation of substituted guaiacol 126 with bis-(trifluoroacetoxy)iodobenzene in presence of excess of alcohol 125 to yield mixed monoketals 127 which underwent an intramolecular cycloaddition in situ to give tetracycles 128-130 (Scheme 42).
Scheme 42: Rodrigo's cycloaddition approach

The upper ring (A) was re-aromatized easily in two steps by treatment of the endo isomer 129 with TFA, followed by saponification and spontaneous decarboxylation. Alkylation of the resulting ketone afforded 132. The ketal moiety in exo isomer 128 turned out to be stable towards treatment with TFA.

Scheme 43
The bridged cycloadduct 130 was first heated to undergo a Cope rearrangement yielding compound 131, which was converted in two steps to phenanthrofuran 132 (Scheme 43). This approach presents a very concise route to morphinans in just four steps; moreover two out of the three products from the cycloaddition step can be converted into the common intermediate 131.

**Heck Cyclization-based Approaches**

In 1993 Overman reported a relatively short and convergent synthesis featuring an intramolecular Heck coupling as the pivotal step leading to either enantiomer of morphine. Ketone 133 was enantioselectively reduced with catechol borane in the presence of (R)-oxazaborolidine catalyst to yield the corresponding substituted (S)-allylalcohol. After protection of the alcohol, the exocyclic double bond was oxidized and the diol protected as acetonide 134 (Scheme 44).

![Diagram](image)

**Reaction conditions:**
- a) catechol borane/ (R)-oxaborolidine cat. (93%),
- b) PhN=C=O (93%),
- c) OsO₄/R₂NO then MeCOMe/H⁺ (78%),
- d) n-BuLi/Cul(Ph₃P)₂/PhMe₂SiLi (81%),
- e) p-TsOH/MeOH/NaI0₄ then DBS-NH₂/NaCNBH₃ (82%),
- f) n-BuLi/I₂ then HCl (80%),
- g) BnBr/K₂CO₃ (97%),
- h) CH₂SMe₂ (91%),
- i) BF₃*OEt₂/THF (92%)

Scheme 44: Overman's Heck approach I
In two more steps amine 135 was prepared from compound 134 in stereoselective manner. The aromatic component 137, required for the Heck coupling, was prepared from readily available protected isovanillin 136 in four steps. Condensation of allylsilane 135 with arylaldehyde 137 was accomplished in the presence of catalytic amount of ZnI₂ to yield 138. The rather high diastereoelectivity (>20:1) of this reaction is a result of preferential approach of the (E)-iminium intermediate to cyclohexenyl silane from the face opposite to the silyl residue.

Aryl iodide 138 was then subjected to the Heck coupling providing compound 139, which contains the complete carbon skeleton of morphine. After removal of the benzyl protecting group, the double bond in 139 was oxidized to an epoxide, which was intramolecularly opened by free phenol to give the corresponding alcohol, whose oxidation yielded (-)-dihydrocodeinone (91% e.e.) 140 (Scheme 45).

![Chemical structure](image)

**Reaction conditions:**
- a) BF₃·OEt₂/EtSH (79%),
- b) ArCO₂H/CSA/CH₂Cl₂ (60%),
- c) TPAP/NMO (86%)
- d) H₂/Pd(OH)₂/HCHO (80%)

Scheme 45: Overman's Heck approach II

This known compound was converted to morphine via a five-step sequence optimized by Rice. The entire synthesis was also carried out in the ent series using enantiomeric (S)-oxazaborolidine for the reduction of enone 133, to yield enantioenriched (+)-morphine. This work constituted the first total synthesis of morphine, which did not involve resolution of intermediates.
Cheng et al. in 1997 published a very interesting example of Heck coupling between an aryl halide and tetrasubstituted double bond. The starting tetrahydroisoquinoline 141 was converted into aryl bromide 142a in four steps involving a Polonovski rearrangement and Mitsunobu reaction. Subjecting 142a to standard conditions of the Heck coupling yielded the partial morphinan skeleton 143 in moderate yield (Scheme 46). Yield of the Heck coupling was dramatically improved up to 72% under the same cyclization conditions by using aryl iodide 142b. Lactam 144 was also prepared and its Heck reaction proceeded in moderate yield as well to provide morphinan 145 in moderate yield.

![Reaction conditions: a) H₂O₂/HOAc, b)Ac₂O/reflux, c) NaOH/MeOH (43% overall), d) Mel/2-propanol (quant.), e) NaBH₄/MeOH (78%), f) bromoguaiacol/PEt₃/DEAD/THF (77%), g) MnO₂/CH₂Cl₂ (60%), h) NaBH₄/i-PrOH (82%)](image)

Scheme 46: Cheng's Heck approach

In the same paper the synthesis of spirocyclic system 149 via intramolecular Heck coupling was reported as well. It turned out that the protective group on nitrogen was very important in determining the outcome of coupling. The initially installed methyl
group had to be replaced by a carbamate, probably in order to reduce the reactivity of the enamine formed during the Heck coupling (Scheme 47).

Scheme 47: Cheng's Heck approach to spirocycles

Later, Cheng published a total synthesis of racemic desoxycodene based on the above mentioned model study. Starting from 5-acetoxy-5,6,7,8-tetrahydroisoquinoline 150, arylbromide 151 was prepared in 7 steps. It was possible to carry out Heck coupling on unprotected benzyl alcohol, however significantly higher yields of tetracycle 152 were obtained when bulky silyl group was installed (Scheme 48).

Scheme 48: Cheng's synthesis of desoxycodene I
Tetracycle 152 was converted into benzyl chloride 153, which then underwent Pd catalyzed cyclization which surprisingly yielded the product of N-benzylation instead of the desired alkylation of the double bond (Scheme 49).

Scheme 49: Cheng's synthesis of desoxycodeine II

Fortunately the tertiary amine 154 underwent a Stevens’ rearrangement after methylation and treatment with PhLi to give desired tetracycle 155 in good yield, thus successfully completing the total synthesis of racemic desoxycodeine.

In 1999 Hudlický published a model study utilizing the reaction mentioned above as a key step in a synthesis of ent-morphinan. Phenethylbromide 111 was enzymatically oxidized to yield enantiomerically pure dienediol 11 (Scheme 50). The less substituted double bond in 11 was selectively reduced by diimide and the diol was protected as dibenzoate.

Scheme 50: Hudlický’s synthesis of iminium cation precursor 19
The dibenzoate was then used to alkylate oxazolidine-1,4-dione to yield compound 156. The reduction of the more reactive carbonyl in the oxazolidine-1,4-dione moiety gave heminal 19. Acyl iminium cation 157 generated from 19 by treatment with anhydrous aluminum chloride cyclized to give mixture of syn and anti isoquinoline chlorides 159 and 158 in 3.7:1 ratio, respectively (Scheme 51).^10

Scheme 51: Acyl iminium cation cyclization

Elimination of the crude mixture of chlorides 158 and 159 and subsequent saponification gave diol 28. Monoprotection of the less hindered distal alcohol in 28 and subsequent Mitsunobu reaction gave aryl bromide 20, which underwent subsequent Heck coupling to yield ent-morphinan 21 in good yield (Scheme 52).

Scheme 52: Hudlický’s Heck approach
Hudlický investigated a cascade version of the Heck reaction as well. Aryl bromide 160, prepared from phenethylbromide 111 in 5 steps, gave under the conditions of Heck coupling product 161 in very low yield along with recovery of unreacted starting material (Scheme 53).

Scheme 53: Hudlický’s cascade Heck approach

It was suggested that the oxazolidone moiety chelates the palladium catalyst and thus slows the first Heck coupling and prevents the second cyclization as well.\(^\text{52}\)

The latest synthesis of morphine featuring a Heck reaction is that of Trost published in 2002.\(^\text{53}\) The control of stereochemistry is achieved by using chiral bidental diphosphine 162 as ligand in palladium-mediated aryl ether preparation (Scheme 54).

Scheme 54: Chiral ligand used by Trost

Aryl ether 165 was prepared from the substituted guaiacol 164 and ester 163 using palladium catalyst along with a chiral diphosphine ligand 162 in high e.e. (Scheme 55). Aldehyde 165 was then protected as an acetal and the \(\alpha,\beta\)-unsaturated ester was then reduced and converted into the \(\alpha,\beta\)-unsaturated nitrile using the Mitsunobu protocol.
Hydrolysis provided bromide 166 whose Heck coupling stereoselectively gave nitrile 167 in excellent yield (Scheme 55).

![Chemical structure](image)

**Reaction conditions:**
- a) \([h^3-C_3H_3PdCl_2]/Et_3N\), 3% of ligand 162 (72%, 88% e.e.),
- b) p-TsOH/CH(OMe)_3,
- c) DIBAL/PhCH_3 (85% overall),
- d) PPh_3/acetonitrile/DIAD,
- e) p-TsOH/THF/H_2O,
- f) Pd(OAc)_2/dppp/Ag_2CO_3/PhCH_3 (91%)  
  Troc=2,2,2-Trichloroethoxycarbonyl

Scheme 55: Trost's Heck approach I

Benzaldehyde 167 was then converted to (Z)-vinylbromide 168 which smoothly underwent Heck vinylation to close the ring B of morphinan skeleton in 169 (Scheme 56).

![Chemical structure](image)

**Reaction conditions:**
- g) CBr_4/PPh_3 (91%),
- h) Pd(PPh_3)_4/nBu_3SnH/PhCH_3 (88%),
- i) Pd(OAc)_2/dppp/Ag_2CO_3/PhCH_3 (92%),
- j) SeO_2/dioxane then Dess-Martin (58%),
- k) DIBAL/CH_2Cl_2 then NH_2Br, MeNH_2, and then NaBH_4 (89%)

Scheme 56: Trost's Heck approach II

Following adjustments of the oxidation states of ring B, nitrile 169 was converted in a one pot sequence to amine 170. Intramolecular hydroamination of 170 was carried out by treatment with LDA in THF with irradiation of the basic solution with an ordinary
150 W tungsten light bulb to give (-)-codeine 37, which was demethylated using the procedure optimized by Rice\textsuperscript{55} to yield morphine (Scheme 57).

\[
\text{MeO} \quad \text{HO}^{-} \quad \text{H} \quad 170 \quad \xrightarrow{\text{I}} \quad \text{MeO} \quad \text{HO}^{-} \quad \text{N} \quad 37 \quad \xrightarrow{\text{m}} \quad \text{HO}^{-} \quad \text{N} \quad 1
\]

\textit{Reaction conditions:} 1) LDA/THF with tungsten bulb (57%), m) \text{BBR}_3

Scheme 57: Trost's Heck approach III

In summary, compound 167 (Scheme 56) was prepared in 6 steps from 163 and bromovanillin 164 in 44% overall yield and served as a common intermediate for synthesis of \textit{Amaryllidaceae} alkaloid (-)-galanthamine\textsuperscript{54} as well as codeine 37, which was obtained from 168 in six steps and 15% overall yield.

\textbf{Radical Cyclization-based Approaches}

In 1988 Parker published a short model study aimed at the synthesis of morphinans based on tandem radical cyclization.\textsuperscript{56} Cyclization of O-methyloxime 171 was achieved by heating it with 2 eq. of \text{Bu}_3\text{SnH} in benzene. The intermediate aryl radical cyclized in a 5-exo-trig fashion to form a cyclohexyl radical, which was trapped by O-methyloxime group yielding hydrophenanthrenes 172 and 173 (Scheme 58). The stereochemistry of 172 and 173 was determined by nOe experiments.

\[
\text{MeO} \quad \text{N} \quad 171 \quad \xrightarrow{\text{Bu}_3\text{SnH/AIBN}} \quad \text{HO} \quad \text{H} \quad 172 \quad \text{40%} \quad + \quad \text{HO} \quad \text{H} \quad 173 \quad \text{31%}
\]

Scheme 58: Parker's tandem radical cyclization
Utilizing this tandem radical cyclization, Parker reported the synthesis of racemic dihydroisocodeine.\textsuperscript{57} Commercially available \textit{m}-methoxyphenethylamine 174 was converted in 3 steps into enone 175. Following the Luche reduction the allylic alcohol was oxidized to yield epoxide 176 (Scheme 59).

\begin{center}
\includegraphics{path/to/figure.png}
\end{center}

\textbf{Reaction conditions:} a) Li/\text{NH}_2/t-BuOH (97%), b) TsCl/Et_3N/THF (81%), c) MeI/K_2CO_3 (96%), d) NaBH_4/CeCl_3/MeOH (97%), e) m-CPBA/CH_2Cl_2 (92%)

\textbf{Scheme 59: Parker's synthesis of dihydroisocodeine I}

Regioselective isomerization\textsuperscript{58} of epoxide 176 using Sharpless' protocol, followed by monoprotection of the less hindered hydroxyl group and Mitsunobu coupling gave the required substrate for radical cyclization aryl ether 178 (Scheme 60).

\begin{center}
\includegraphics{path/to/figure.png}
\end{center}

\textbf{Reaction conditions:} f) Ti(Oi-Pr)_4/PhH (85%), g) TBSOTri-PrNEt_3 (82%), h) PBu_3/DEAD/THF (83%), i) HF/CH_2CN (98%)

\textbf{Scheme 60: Parker's synthesis of dihydroisocodeine II}

The key tandem radical cyclization sequence was initiated as described above to yield benzylic radical, which after elimination of thiophenoxy radical afforded tetracyclic styrene 179 in moderate yield (Scheme 61).
Scheme 61: Parker's synthesis of dihydroisocodeine III

Reductive cleavage of the tosyl amide 179 with Li/NH$_3$ in presence of $t$-BuOH gave nitrogen radical/anion, which unexpectedly cyclized to yield racemic dihydroisocodeine which was oxidized to dihydroisocodeinone 180 via Swern's protocol.

Cheng also investigated radical cyclizations of aryl radicals as possible routes to morphinan skeleton.$^{59}$ Aryl bromide 142a, prepared from tetrahydroisoquinoline 141 in 6 steps (Scheme 62), was subjected to Bu$_3$SnH/AIBN initiated cyclization (Scheme 63).

Scheme 62

Cyclized products 184 and 185 along with a substantial amount of product 183, resulting from 1,5-hydrogen abstraction process, were isolated in a good total yield (58%) (Scheme 63).
Scheme 63: Cheng's radical approach I

In a similar fashion Cheng also prepared the spirocyclic ring system 189, which contains a partial morphinan structure motif (Scheme 64). In this case the yield of a radical 5-exo-trig cyclization was almost quantitative.

Scheme 64: Cheng's radical approach II

Hudlický also published two radical cyclization-based approaches towards morphinans, one being a cascade process\(^7\) and the other a stepwise approach.\(^{60}\) Synthesis of the substrate for the cascade radical cyclization started from phenethyl bromide 111, which was enzymatically oxidized to the corresponding diene diol in an enantioselective manner.\(^{51}\) After reduction of the less substituted double bond and selective monoprotection of the diol, the first Mitsunobu reaction was carried out to yield a benzoate, which was then used to alkylate 2-oxazolidone to yield compound 191 (Scheme 65).
Scheme 65: Hudlický’s cascade radical cyclization approach

Besides the desired product 191, the alkylation reaction yielded also a substantial amount of elimination product, which was recycled via hydroboration-oxidation-mesylation sequence to improve the overall yield of this sequence. Benzoate 191 was then hydrolyzed and aryl bromide needed for the cyclization was introduced via second Mitsunobu reaction of free alcohol with bromoguaiacol to give compound 13. Exposure of 13 to (TMS)$_3$SiH/AIBN afforded a complex mixture of more than six products, from which morphinan 14 was isolated after extensive chromatography in minute yield. The presence of the other isomer 192 was detected as well, although it was not identified unambiguously (Scheme 65).

In a second generation attempt aimed at improving the stereoselectivity of the radical cyclization the sequence was carried out in a stepwise fashion. Hudlický’s stepwise approach started with the biooxidation of o-bromo-phenethylbromide 193. The resulting corresponding diene diol was reduced, protected as an acetonide and used for
alkylation of 2-oxazolidone to yield compound 16, the same problems with elimination were encountered and solved as described above. Exposure of 16 to Bu$_3$SnH/AIBN yielded mixture of two isomeric octahydroisoquinolines 194 and 195 in 2:1 ratio (Scheme 66).

Scheme 66: Hudlický’s stepwise radical cyclization approach I

Since 194 was more abundant, Hudlický pursued the synthesis of *ent*-morphinan. Deprotection of the acetonide followed by selective monoprotection and Mitsunobu reaction yielded precursor 17, which cyclized upon exposure to Bu$_3$SnH/AIBN to afford pentacycle 18 in moderate yield. Reductive cleavage of the oxazolidone moiety with DIBAL gave alcohol 196 (Scheme 67). Two different routes to close the ring B of morphinan skeleton were then carried out.

Scheme 67: Hudlický's stepwise radical cyclization approach II
Removal of silyl group followed by Swern oxidation gave a ketoaldehyde, which cyclized under acidic catalysis to yield complete carbon skeleton of morphine 197 (Scheme 68).

Scheme 68: Hudlický’s stepwise radical cyclization approach III

Alternative closure was realized by converting alcohol 196 to the corresponding mesylate, its displacement with lithium chloride, and an intramolecular Friedel-Crafts alkylation to afford morphinan 198.

Selected Examples of the Utilization of Cis-diols Metabolites in Synthesis

In 1968 Gibson and colleagues isolated a strain of soil bacteria Pseudomonas putida, which grew on ethyl benzene as a sole source of carbon and energy. This organism also grew on benzene and toluene. Toluene-grown cells did not produced cis-cyclohexadiene diol 2, the corresponding catechol 200 was isolated instead.

Scheme 69: Microbial oxidation of toluene

Further studies lead to the isolation of mutant strain P. putida F1 (strain F39/D), which did not dehydrogenate cis-cyclohexadiene diol to catechol, and thus intermediate enantiopure diene diols could be isolated (Scheme 69). The enzymes carrying out
transformations shown above were named toluene dioxygenase (TDO) and cis-dihydrodiol dehydrogenase. Genes encoding TDO were identified, cloned and expressed in *Escherichia coli*.\textsuperscript{62} Dioxygenase enzyme synthesis in those recombinant strains can be controlled by isopropyl-\(\beta\)-D-thiogalactoside (IPTG)-inducible promoters. These cells also contain multiple copies of dioxygenase genes in their plasmids, which enable overproduction of the desired enzyme.

Even though the first stable *cis*-cyclohexadienediol\textsuperscript{63} derived from \(p\)-chlorotoluene was isolated in 1968 it was not until 1987 when Ley\textsuperscript{64} published his historical synthesis of racemic pinitol utilizing diene diol 202 enzymatically derived from benzene (Scheme 70).

\begin{center}
\includegraphics[width=\textwidth]{Scheme_70.png}
\end{center}

\begin{center}
\textbf{Reaction conditions:} a) *Pseudomonas putida* b) BzCl/Pyridine/DMAP (84%), c) MCPBA (80\%), d) MeOH/CSA (quant.), e) OsO\textsubscript{4}/NMO (58%), f) MeOH/Et\textsubscript{3}N/H\textsubscript{2}O (quant)
\end{center}

Scheme 70: Ley's synthesis of pinitol 207

Diene diol 202 was converted to the corresponding dibenzoate and epoxidized in buffered methylene chloride (pH = 8) to yield easily separable epoxides 203 and 204, whose structures were confirmed by X-ray crystallography. Epoxide 204 was then
opened with methanol to yield mixture of two products 205 as a result of partial benzoyl group migration. Synthesis of racemic pinitol 207 was then completed by dihydroxylation and removal of all protecting groups. After Ley’s first report many other research groups followed and many more examples of the utilization of various diene diols in synthesis were reported since then.

These days many diene diols and their derivatives are commercially available to chemists (e.g. from Sigma Aldrich). A laboratory procedure for the small scale (<1g) oxidation of chlorobenzene to the corresponding diene diol was also published and it is applicable to other volatile aromatic substrates.

Diene diols metabolites are also produced on large scale by whole-cell fermentation process. When cell cultures of recombinant strains of *Escherichia coli* are grown in mineral salts medium and in the presence of an organic substrate (pyruvate or glucose), and certain cell density is reached, inducer is added to the media (i.e. isopropyl-β-D-thiogalactoside (IPTG)). The cells are then allowed to grow and produce the dioxygenase enzyme before the introduction of the aromatic substrate. Those biooxidations require fermentor with carefully regulated oxygen levels, temperature, pH and nutrient/substrate feed. Typically, volume of media is between 10-15 L and amount of dienediol produced can range from 0.2-20 g/L of broth, depending on substrate. A detailed procedure of such fermentation was recently published.

As was mentioned earlier, there are many research groups active in the field of *cis*-hexadiene diols. In this part of thesis only few selected examples of utilization of these metabolites in natural product synthesis with focus on the Diels-Alder reaction are presented, a much more detailed and comprehensive review was published in 1999.
The free cis-diene diols are reasonably stable in crystalline state, however their acetonides undergo Diels-Alder reactions very readily even at (or below) room temperature to give mixture of dimers. For example the acetonide of dihydrostyrenediol 208 dimerizes to three different Diels-Alder products with remarkable regio- and stereoselectivity (Scheme 71).

Scheme 71: Dimerization of diene diol derivatives

Cis-diene diols in general and especially those derived from halobenzenes where diene is quite polarized, are reactive towards various dienophiles (e.g. benzynes, maleic anhydride, acrylate). The diol moiety or side chain in these metabolites offers many possibilities to attach dienophiles and take advantage of the enhanced reactivity and selectivity of intramolecular Diels-Alder reaction.

Hudlický in 1989 published a short enantioselective synthesis of the natural product (-)-zeylena relying on styrene diene diol metabolite 212 as chiral starting material. After protection of the less substituted diene by cycloaddition with bis-(2,2,2-trichloroethyl)azodicarboxylate, and protection of the less hindered alcohol as a silyl ether, the remaining hydroxyl was acetylated. Deprotection of THS group gave alcohol 213, which was acylated using Mitsunobu’s protocol to yield cinnamate 214. Exposure of 214 to Cu/Zn afforded tetraene 215, which upon heating underwent intramolecular Diels-Alder reaction to give adduct 216 in excellent yield (Scheme 72).
Synthesis of zeylena 217 was then completed by ozonolysis of the less substituted double bond followed by reduction and acylation.

Banwell had reported several examples of the creative use of cis-cyclohexadiene diols metabolites (or 1,2-dihydrocatechols) in the synthesis of terpenes and steroids. In 1998 he published an enantioselective synthesis of the AB-ring system of taxoids based on intramolecular Diels-Alder reaction.\textsuperscript{73}

Heating of diene acetal 218 with $\alpha$-chloroacetonitrile afforded a mixture of two cycloadducts 219, which were converted into the same ketone by alkaline hydrolysis. After double geminal methylation, olefination was carried out to give compound 220. In a few more steps 1,5-diene 221 was prepared, and after its deprotonation anionic oxy-Cope rearrangement occurred to yield 222 (Scheme 73).
Scheme 73: Banwell's synthesis of taxoids I

Compound 222 was further converted to the tricyclic alcohol 223 by exposure to Lewis acid. Epoxidation followed by titanium isopropoxide-promoted Eschenmoser-Grob fragmentation afforded the bicyclic compound 224, which contains partial skeleton of ent-taxoids (Scheme 74).

Scheme 74: Banwell's synthesis of taxoids II

Banwell then used compound 222 as a starting material in his short synthesis of sesquiterpene (-)-patchoulen (Scheme 75). After intramolecular Prins reaction catalyzed by tin(II)chloride, tricyclic alcohol 223 was obtained. Catalytic hydrogenation
followed by oxidation gave acyloin 224, which was converted to (-)-patchoulene 228 in three steps.

Scheme 75: Banwell’s synthesis of patchoulene 228

An interesting route towards steroidal skeleton using Diels-Alder reaction of dienediols was reported also by Banwell in 1999. Diels-Alder reaction of cyclopentylidene acetal of bromodiene diol 229 with freshly sublimed $p$-benzoquinone afforded a single endo cycloadduct, which was immediately reduced under Luche’s conditions to prevent aromatization. Ketone 231 was prepared from this cycloadduct in seven more steps (Scheme 76).

Ketone 231 was alkylated in diastereofacial manner by its reaction with excess of organocerium reagent 232 to yield 1,5-diene 233, which readily underwent oxy-Cope rearrangement and subsequent loss of methoxide to give 235. Compound 235 containing the tetracyclic ABCD-ring system of steroids was thus prepared in enantioselective fashion.
Reaction conditions: a) 1,1-dimethoxy cyclopentane (98%), b) p-benzoquinone (55%) c) NaBH₄/CeCl₃·7H₂O, d) Mel/NaH (62% overall), e) HCl/MeCN (72%), f) 4-AcNHTEMPO/TsOH·H₂O (82%), g) Ac₂O/Py, h) SmI₂/AcOH (84%), i) Bu₃SnH/AIBN (84%), j) (80%), k) KHMDS/THF/PhCH₃ (79%)

Scheme 76: Banwell's steroids synthesis

Based on the above brief and by no means comprehensive review it can be said, that cis-diene diols prepared by biooxidation are very valuable starting materials in the synthesis of various targets. Most of these metabolites were used as a dienes in intermolecular Diels-Alder reactions; fewer examples of their intramolecular cycloadditions were reported.

In most of these intramolecular reactions the dienophiles were attached via the ether or ester linkage to one of oxygens introduced by microbial oxidation. In the following section of this dissertation novel intramolecular Diels-Alder cycloadditions of diene diol derived from 2-azidoethylbenzene where the dienophiles are attached via side chain will be discussed.
CHAPTER 3
RESULTS AND DISCUSSION

Double Diels-Alder Approach to Morphine

Introduction

The isoquinoline ring system is the essential part of the morphine skeleton (rings C and D). It contains five chiral centers, two of which (C5, C6) could be set by using enantiopure metabolite 22 as starting material. We envisioned that closure of both rings C and D could be simultaneously realized by an intramolecular Diels-Alder reaction of the triene of type 237, which would also set C13 center correctly since such cycloaddition would most likely occur to less hindered face of the diene (Scheme 77).

Scheme 77: Retrosynthetic analysis

For our cycloaddition studies the acetonide of dienediol 22, enzymatically derived from β-azidoethylbenzene,76 was chosen because the azide moiety can be easily reduced under very mild condition and the resulting amine could be used for attachment of activated dienophile (e.g. monoalkylester of fumaric acid) to yield a triene such as 23. Intramolecular cycloaddition of 23 was expected to give bridged isoquinolines synthons of type 24. The second approach to those synthons was via intermolecular cycloaddition of acetonide of diol 22 with maleic anhydride to give compounds 238 followed by
reduction of azide to the amine, which was expected to intramolecularly open anhydride moiety giving the isoquinolines skeleton. Two different possible routes (A and B) towards desired bridged isoquinoline synthons 24 starting from diol 22 are shown in retrosynthetically in Scheme 78.

Scheme 78: Intra- and intermolecular Diels-Alder cycloadditions

The retrosynthetic plan of converting the isoquinoline synthons 240 to morphinan skeleton is shown in Scheme 79. The lactam moiety would be selectively converted into the more reactive group, e.g. iminoether, and the furfuryl moiety would be installed to prepare system 25 for the second Diels-Alder cycloaddition.

Scheme 79: Double Diels-Alder approach

Compound 239 would be expected from such cycloaddition. Another projected crucial step is the fragmentation of 26, which should occur after hydrolysis of ester 239,
with the loss of carbon dioxide and rearrangement of the carbon skeleton as shown in Scheme 80. Dehydration of the product of the fragmentation would give morphinan skeleton 242 with the control of stereochemistry.

Scheme 80: Designed fragmentation

**Intermolecular Cycloadditions**

The required azidoethyl diene diol 22 was prepared in two steps from commercially available phenethylbromide, which was converted to the corresponding azide. Whole-cell fermentation of azidoethylbenzene then yielded desired diol 22, which was protected as acetonide 243.

In the first round of experiments, intermolecular cycloadditions of acetonide 243 with maleic anhydride and 1,4-benzoquinone were investigated. Reaction of diene 243 and maleic anhydride 244 in benzene either at room temperature or at reflux gave a mixture of two cycloadducts 245 and 246 (46-58% combined yield) in a 1:1.6 ratio ($^1$H-NMR) (Scheme 81). Surprisingly the exo-cycloadduct 246 predominated. The cycloadducts were readily separated by column chromatography; the exo-cycloadduct 246 was the less polar component of mixture. The most striking difference observed in $^1$H-NMR spectra of 245 and 246 was the extent of separation of the signals of the acetonide methyl groups. In the case of exo-adduct 246 these singlets are 0.14 ppm apart, in case of endo-adduct 245 separation is only 0.02 ppm.
Scheme 81: Intermolecular cycloadditions with maleic anhydride

Stereochemistry of endo and exo cycloadducts 245 and 246 respectively was also confirmed by advanced 2D-NMR techniques (COSY, NOESY, HMBC, HMQC). A complete chemical shifts assignment for endo cycloadduct 245 is shown in Figure 2. Strong nOe interactions between the protons at 3.11 ppm and 4.33 ppm were observed along with nOe of similar intensity between the protons at 3.08 ppm and 4.20 ppm.

Figure 2: Chemical shift assignment for endo cycloadduct 245

In order to convert cycloadducts to isoquinoline synthons, reduction of the azide moiety with triphenylphosphine was carried out using Staudinger’s protocol. Reduction proceeded smoothly at elevated temperature (refluxing wet tetrahydrofuran), and the in situ generated amine cyclized onto the anhydride. In order to avoid handling the free
acids, the resulting crude carboxylates were treated directly with diazomethane and the corresponding methylesters 247 and 248 were isolated in good yields (Scheme 82).

![Scheme 82: Reduction/cyclization of cycloadducts 245 and 246](image)

Banwell has carried out cycloadditions on similar diene systems (e.g., the diene diol derived from toluene), with \( p \)-benzoquinone\(^75 \) (refluxing benzene) or with maleic anhydride\(^78 \) (in methylene chloride at 0–18 °C) as a dienophiles. He observed an outcome different from ours; in both cases he reported a single isomer resulting from the endo process (55% and 68% yields, respectively).

With the possibility of the preparation of interesting bridged tricyclic structures such as 252 in mind, the cycloaddition of diene 243 with 1,4-benzoquinone 249 using Banwell’s conditions (benzene, r.t. or reflux) was attempted, but the reaction produced complex mixtures. However, the expected cycloadduct 250 was isolated along with aromatized hydroquinone product 251 in very low yields by preparative TLC (Scheme 83).
Scheme 83: Intermolecular cycloadditions of 243 with 1,4-benzoquinone

During the reaction of 243 with 249 extensive decomposition was observed; as the reaction mixture turned dark after a few hours at room temperature. Compounds 243 and 249 were separately heated in benzene to reflux; quinone seemed to be stable, diene 243 quickly decomposes and/or oligomerizes as expected.

To prevent aromatization, reduction of the crude reaction mixture under Luche conditions\(^\text{79}\) following cycloaddition was attempted. The reduction product 253 was isolated in low yield (Scheme 84).

Scheme 84: Cycloaddition-Luche reduction sequence

Because side reactions (such as 1,3-dipolar cycloaddition) of the azide moiety were suspected, the azide 243 was reductively acylated\(^\text{80}\) to acetamide 254, which was then used for cycloaddition with 1,4-benzoquinone. A cleaner reaction was observed as
judged by TLC analysis. The isolated product appeared as a single spot on TLC; however, the $^1$H-NMR spectrum showed that it was actually a mixture of isomers 255 and 256 with a ratio of ca. 2:1. The yield in this case was good (54%) in comparison to cycloadditions of azide. The endo cycloadduct 255 predominated, in contrast to our observations of the cycloaddition with maleic anhydride. Further attempts to separate these compounds were not successful (Scheme 85). Given the low yields and difficult separation of products of reaction of 243 or 254 with 1,4-benzoquinone, this route was abandoned.

Scheme 85: Reduction cycloaddition sequence

**Intramolecular Cycloadditions**

With the results of the intermolecular cycloadditions in hand we decided to investigate analogous intramolecular processes. Azide 243 was first reduced at room temperature using Staudinger protocol. The crude amine was used for DCC coupling with either the monoethyl esters of maleic acid or fumaric acid to yield amides 257 and 258, respectively (Scheme 86).

Scheme 86: Preparation of trienes
In the first case the overall yields of the reduction/coupling sequence were rather modest (26-34%), in the latter case overall yields were satisfactory (58-72%). Maleamide 257 was heated in refluxing benzene to yield mixture of cycloadducts 259 and 260. Heating for up to six days was necessary to complete the reaction (Scheme 87). The ratio of exo to endo cycloadducts (259 to 260) was determined from $^1$H-NMR spectra to be 1:2. Surprisingly this ratio is exactly opposite to exo to endo ratio (1.6:1) observed in intermolecular cycloaddition reaction of 243.

Scheme 87: Intramolecular cycloadditions I

Separation of these cycloadducts was difficult because of extremely small difference in $R_f$ values, however, analytically pure samples of each compounds were isolated, for example heating of 257 (0.087g) in benzene for 6 days gave pure 259 (0.017g, 20%), mixtures of 259:260 = 1:5 (0.018g, 21%) and 1:8.8 (0.017g, 20%), and pure 260 (0.022g, 25%) after column chromatography.

Cycloaddition of 258 possessing trans dienophile in benzene at reflux proceeded much faster than the reaction of maleamide 257; as one day of heating afforded a mixture of the cycloadducts 261 and 262 in 68-85% total yield. Cycloaddition of fumaramide 258 also proceeds even at low temperature. However, there is almost no selectivity; the ratio of 261 to 262 was found to be approximately 1.3:1 as determined from $^1$H-NMR spectra. Separation of 261 and 262 was also complicated by extremely low difference in $R_f$ values (approximately 0.06; adduct 261 is slightly less polar than 262) (Scheme 88).
Scheme 88: Intramolecular cycloadditions II

However, pure samples of each isomer were isolated, for example from the reaction of 258 (0.141g, 27 hours in refluxing benzene) pure 261 (0.033g, 23%) and pure 262 (0.018g, 13%) were isolated along with mixtures of 261:262 = 1:1 (0.023g, 16%), 1:2 (0.012g, 9%). Absolute stereochemistry of 261 and 262 was established by 2D-NMR experiments (NOESY, COSY, HMQC and HMBC). A complete assignment of chemical shifts for the cycloadduct 261 is shown in Figure 3.

Figure 3: Chemical shift assignment for endo cycloadduct 261

The large nOe's of the protons at 1.91, 4.03 and 2.73 ppm, comparable in intensity with the one between 4.03 and 4.24, confirmed the stereochemistry of 261 as shown.

This cycloadduct was of particular interest because it has the correct configuration of four centers of morphine (C5, C6, C13, C14; see Figure 3 above) and possesses the trans
relationship of lactam and carboxylate required for the proposed double Diels-Alder synthetic design.

**Further Functionalization of Cycloadducts**

In order to attach the second diene (i.e. furan) to 261, lactam 261 was converted into imino ether 263 by reaction with freshly prepared\textsuperscript{82} triethylxonium tetrafluoroborate in good yield (Scheme 89). Literature reports indicate that it is possible to exchange the ethoxy group in simple cyclic iminoethers, derived from \( \gamma \)- or \( \delta \)-lactams, with an alkyl group by reaction with Grignard reagent\textsuperscript{83} or alkyl/aryl lithium\textsuperscript{84} to yield the corresponding cyclic imines.

![Scheme 89](image)

**Scheme 89: Preparation of iminoether 263**

Attempts to generate Grignard reagent from freshly prepared\textsuperscript{85} furfuryl bromide 265 failed, probably because of its extremely high electrophilicity. Therefore known phenylsulfone\textsuperscript{86} 266 was prepared by reaction of furfuryl bromide with sodium phenylsulfinate (Scheme 90).

![Scheme 90](image)

**Scheme 90: Preparation of phenylsulfone 266**

Sulfone 266 was then deprotonated with n-butyllithium and the thus formed carbanion reacted with iminoether 263. However, no reaction was observed even in
presence of excess lithium salt of sulfone, and only starting iminoether was isolated. The same result was obtained using excess of phenyl lithium (Scheme 91).

Scheme 91: Attempted alkylation of iminoether 263

The extent of deprotonation of sulfone 266 was checked by D$_2$O quench. After 30 minutes at -78 °C, 60% of sulfone is deprotonated as judged by $^1$H-NMR of quenched sample. Reactivity of this salt was probed by reaction with cyclohexanone, and the expected adduct 267 was isolated in low yield (Scheme 92).

Scheme 92: Model alkylation

Suspecting poor reactivity of iminoether 263 towards nucleophiles, we have attempted to reduce this moiety to an amine by literature procedure (NaBH$_4$/EtOH), however only unreacted starting material was recovered. The use of LiAlH$_4$ in ether or tetrahydrofuran lead to fast reduction of ester however, the iminoether moiety still proved resistant to reduction (r.t. to reflux) as observed by IR spectroscopy. Reduction of the corresponding lactam gave similar results, and the lactam seemed to survive reduction with LiAlH$_4$ in refluxing 1,4-dioxane (IR monitoring). Speculating that the influence of bridgehead double bond prevented the approach of the nucleophile, we reduced mixture of lactams 261 and 262 by catalytic hydrogenation over Pd/C in ethanol (Scheme 93).
Scheme 93: Reduction experiments

The reduced compound 269 (characterized by \(^1\)H-NMR and IR) was subjected to reduction with LiAlH\(_4\), first in refluxing THF, where reduction of ester was easily achieved, then in refluxing 1,4-dioxane after the addition of fresh LiAlH\(_4\). As judged by IR monitoring of reaction progress, reduction of lactam was successful after reducing the bridgehead double bond in 261/262. This result supports our hypothesis, that the bridge double bond in compound 263 does prevent nucleophilic attack on the iminoether moiety, presumably by the repulsions between its \(\pi\)-system and nonbonding electron pairs of iminoether oxygen.

We investigated another possibility via alkylation of lactam 261 by the Eschenmoser's method.\(^{88}\) Required thiolactam 272 was first prepared by reaction of 261 with P\(_4\)S\(_{10}\) in THF in the presence of Na\(_2\)CO\(_3\), however yields were rather low (25-29%) contrary to the literature reports (>80%).\(^{89}\)

Scheme 94: Preparation and alkylation of thiolactam 272
The yield was greatly improved by using Lawesson’s reagent 271 (Scheme 94). Thiolactam 272 was then alkylated with furfuryl bromide in presence of Hunig’s base to yield thioiminoether 273 in modest to good yields (43-78%). This compound turned out to be stable in refluxing C₆D₆, and no sign of cycloaddition was observed by NMR spectroscopy. A sample was sent out to Dr. Kerr (WOU, London, Ontario) for high pressure experiments. Unfortunately no cycloaddition was observed and only unreacted starting material was recovered.

In order to carry out Eschenmoser’s sulfide contraction the acidity of protons on α-carbon of thioether needed to be increased. Therefore bromosulfone 274 was prepared by a modified literature procedure via deprotonation of corresponding phenylsulfone 266 with n-butyl lithium followed by quench with BrCN. This reaction yielded an inseparable mixture of the starting material and the desired bromo sulfone 274, which was used directly in an attempt to alkylate thiolactam 272. Unfortunately no alkylation was observed (Scheme 95).

Scheme 95: Attempted alkylation with bromosulfone 274

As a last set of experiments, intermolecular cycloadditions of lactams 261 and 262 with 2-methoxyfuran or furan were attempted, however, only unreacted starting material was recovered as proven by ¹H-NMR spectra of dried crude reaction mixtures. Conditions are shown in Scheme 96.
Scheme 96: Attempted intermolecular cycloadditions

At this point we decided to abandon this approach and switch to a Heck /radical cyclization based approach to the synthesis of the morphinan skeleton as will be discussed in the next part of this thesis. In conclusion, the syntheses of the bridged isoquinoline synthons by either intermolecular Diels-Alder reaction/reduction/cyclization sequence or by intramolecular Diels-Alder reactions were accomplished in good yields. Stereochemistry of these cycloadducts was determined using 2D-NMR techniques.

Several derivatives of one cycloadduct (261) such as iminoether 263 and thiolactam 272 were prepared. However, further functionalization by reactions with nucleophiles failed, presumably because of stereoelectronic influence of the bridge double bond in these rigid bicyclooctene ring systems. Attempts to affect intermolecular Diels-Alder reaction at the bridge double bond with excess of furans even at harsh conditions were not successful, yielding the recovery of unreacted starting materials.

Heck and Radical Cyclization Approaches

As mentioned in the review part of this thesis, there are many literature precedents for the Heck coupling to establish the C12-C13 connection of rings A and C in the morphine skeleton (Cheng,49 Hudlicky8) and also for analogous radical cyclization closure (Parker,57 Hudlický,7,60 Cheng59).
Scheme 97: Heck and radical cyclization precursors summary

However, most of these syntheses use racemic material or unnatural enantiomer on C5 as cyclization precursors. It is also noteworthy that all the above authors utilized the Mitsunobu reaction as a tool to prepare the required aryl ether. The overview of precursors is shown in Scheme 97. One of the key problems about which this part of the dissertation is concerned is the attachment of aromatic ring A, or its precursor containing a vinylbromide moiety, as a route to isoquinoline synthons of type 20 possessing the natural configuration at the C5 center in a stereoselective manner (i.e. establishment of C-O bonds labeled on the structure of morphine with arrows in Figure 4 below).

Figure 4
Two different routes to stereoselectively establish those C-O bonds, marked in Figure 4 above, were envisioned. Route A relies on the opening of the epoxide 30 with monoprotected isoquinoline diol such as 29, thus preserving configuration of the stereocenter on the C5 installed by the biotransformation.

![Chemical diagram](image)

Scheme 98: Retrosynthetic scheme of investigated routes A and B

The product of epoxide opening 31 could be either oxidized prior to Heck coupling/radical closure or protected and re-oxidized later on (Scheme 98). The C12-C13 connectivity would be then established by Heck coupling or the radical cyclization.

Route B mirrors route A in that the synthesis of isoquinoline epoxide 33 from cis diol 28 in stereoselective fashion is required, which necessitates carrying out the inversion of either stereocenter (either C5 or C6). However, opening of this epoxide with
bromoguaiacol 34 or its salt would install the complete ring A without the need for further manipulation. This represents an advantage over route A, where oxidation of 31 to ketone 276, with probable shift of the double bond into conjugation, is necessary. Enolization and subsequent dehydrogenation would be then required to adjust the oxidation state of ring A (Scheme 99).

Scheme 99: Route A: re-aromatization of precursor

Two possible closures of C12-C13 bond either by Heck coupling or by the radical cyclization of the product of route B are shown in Scheme 100. Heck coupling closure seems to be more attractive from the perspective of morphine synthesis because its product 279 has ring C in the correct neopine oxidation state.

Scheme 100: Planned C12-C13 Closure

Product of the radical closure 278 would have a fully saturated C ring, but the stereochemistry at C14 would be hard to predict. Also a literature reports indicate that a complex mixture of products result from the radical cyclization on substrates very similar to 35.  

7
Synthesis of Octahydroisoquinoline Intermediate

Octahydroisoquinolines can be valuable intermediates in the synthesis of various alkaloids (e.g. morphine\textsuperscript{48}). The most common method of their preparation is the cationic cyclization of an acyliminium ion onto a double bond or aromatic ring.\textsuperscript{92} The 1999 synthesis of compound 28, which was chosen as a convenient starting material for advanced synthetic studies towards morphine, was reported by Hudlický.\textsuperscript{93} The synthesis starts with phenethyl bromide 111, which is oxidized by whole-cell fermentation to yield diene diol, which was selectively reduced by diimide to give compound 280 (Scheme 101).

![Scheme 101: Previously reported synthesis of compound 28](image)

After protection of the alcohols as benzoates in 281, nucleophilic substitution with oxazolidine-1,4-dione was carried out to give the desired product 156 in good yield (50-77\%) along with varying amounts of a byproduct, most probably resulting from the nucleophilic displacement of bromine by benzoate. It turns out that benzoic anhydride is present as an impurity in dibenzoate 281, since an excess of benzoic acid is used in the DCC coupling reaction (2.5-3.0 eq.). Reduction of the more reactive carbonyl with sodium borohydride in methanol gave heminal 19 in good yield. The key ring-forming cationic cyclization was achieved by reaction of 19 with Lewis acids (AlCl\textsubscript{3}, BF\textsubscript{3}•Et\textsubscript{2}O, AlBr\textsubscript{3}) in methylene chloride.
Best yields of the cyclization were obtained using AlCl₃, followed by BF₃·Et₂O. The poorest results were obtained using AlBr₃, where formation of a large amount of black tar was observed. Results of cyclizations are shown in Scheme 102 (literature yields⁹³ are in brackets); ratios of syn and anti isomers were determined by integration of ¹H-NMR spectra of crude mixtures.

A detailed account of the assignments of chemical shifts and the absolute stereochemistry of chlorides 282 and similar compounds by advanced 2D-NMR techniques was published in 1999 by Ghiviriga.⁹⁴

Scheme 102: Lewis acids catalyzed cyclizations

The most problematic step in the synthesis of the desired tetrasubstituted olefin 285 is the elimination of chlorides 282a and 283a (Scheme 103).

Scheme 103: Crucial elimination step
Published yield for this reaction using mixture of syn and anti chlorides is in the range of 40-60%. Both, syn and anti isoquinoline halides 282 and 283 were separated and treated individually with DBU in DMSO (at ca. 70-100°C).

The anti chloride 282a yielded tetrasubstituted olefin 285 in moderate yields (25-45%) as the major product. Elimination proceeds well at 70 °C; lower yields were achieved at 100°C. Changing the concentration of the anti chloride by running the reaction in neat DBU with only a few drops of DMSO added did not affect the yield significantly. The anti bromide 282b under similar conditions smoothly eliminated to yield olefin 285, as the only observed product in moderate yield (Scheme 104).

Scheme 104: Eliminations of separated octahydoisoquinoline halides

The syn isoquinoline chloride 283a was also subjected to the same elimination conditions; however the desired olefin 285 was isolated in very low yield. When the reaction was run at 70 °C, olefin 286 was isolated by preparative HPLC along with unreacted starting material (inseparable on silica gel) and traces of olefin 285. By increasing the reaction temperature to 100 °C mass recovery drops significantly, probably
because of the decomposition of elimination products. Elimination of the syn isoquinoline bromide 283b gave similar results, however yields were even lower. When the elimination was carried out under the same conditions on a pre-purified mixture of chlorides 282/283 yields of 285 were in 10-20% range, which is consistent with results of elimination of separated syn and anti chlorides, where anti chloride gives significantly higher yield of the desired product.

Unfortunately the anti chloride 282 is the minor constituent in the mixture of chlorides obtained by cyclization. Another reaction system, KHMDS/DME/18-crown-6, was tried with both syn and anti chlorides, however decomposition occurred in both cases and poor mass recoveries despite of exhaustive extraction work up were observed.

The reaction of hydroxyisoquinoline 284, the only isomer from the BF₃-catalyzed cyclization reaction, with Burgess’ reagent 287 in benzene either under reflux or at room temperature was also investigated (Scheme 105).

Scheme 105: Reactions of hydroxyisoquinoline 284
Reaction at room temperature was very slow and yielded only one isolated product, which was assigned as adduct 288 based on NMR and IR data. When the reaction was run in refluxing benzene elimination did proceed, however a complex and hard to separate mixture of products was obtained. Along with olefins 285 and 286, an interesting compound displaying three olefinic hydrogens in its NMR spectrum was isolated. This compound turned out to be the product of ring cleavage 289, as determined by comparison of its spectra to published data.95 Isolated adduct 288 did decompose at room temperature over a period of time to yield mixture of above mentioned products (Scheme 105). Conversion of 284 to corresponding mesylate was attempted (MsCl (excess)/Pyridine/DMAP, r.t. to reflux), however, no reaction was observed.

Given the yields of cyclization and elimination of hydroxyisoquinoline 284 using Burgess’ reagent we concluded that this route offered no advantage over elimination of isoquinoline chlorides with DBU with respect to the yield of the desired olefin 285. In conclusion, the best yields of 285 were obtained by elimination of anti chloride or bromide 282a,b (41 and 45% respectively), while the syn halides 283a,b gave only low yields of the desired product under the same conditions. In terms of efficiency, elimination of chlorides 282/283a, which can be obtained by AlCl₃-catalyzed cyclization of 19 in good yield, is still the best route to 284, since yields of analogous bromides 282/283b are rather low.

Following the published procedure, 285 was deprotected with LiOH (MeOH/H₂O) and isolated by column chromatography (silica/ethylacetate), albeit in slightly lower yields than reported.95 Therefore the procedure was modified by using methanolic
sodium methoxide in tetrahydrofuran and the chromatography was carried out with ethylacetate:ethanol (9:1) to achieve the high yield (>85%) reported.

Scheme 106: Deprotection of 285

Given the difficulties associated with accumulation of large quantities of diol 28 we decided to first carry out simple model study for the route A (see Scheme 98), where commercially available racemic 2-cyclohexenol was used as a model of monoprotected diol 28 for the opening of epoxide 30.

Model Study of Epoxide Opening and Cyclization

Chiral epoxide 30, first reported\(^{11}\) by Boyd et al., was chosen as a convenient precursor of aromatic ring A of morphine. Preparation of this epoxide starts with microbial oxidation of bromobenzene to give the corresponding diene diol,\(^{96}\) which is then selectively reduced by diimide. The resulting diol 291 is then subjected to \(\alpha\)-acetoxyisobutyrylbromide to yield bromoacetate 292. Interestingly, the allylic alcohol is replaced by the bromide with inversion of configuration, whereas the homoallylic alcohol is just acetylated.

Scheme 107: Preparation of epoxide 30
This general reaction was first described by Moffatt on nucleosides and simple vicinal diols. Bromoacetate 292 is then subjected to methanolic sodium methoxide in tetrahydrofuran to yield the desired epoxide 30 (Scheme 107).

Having the epoxide 30 in hand we decided to try its opening with a simple allylic alcohol such as racemic 1-cyclohexenol 293 as a model substrate before attempting the reaction with the hard-to-prepare monoprotected isoquinoline diol synthons. Opening proceeded readily at low temperatures using boron trifluoride etherate in methylene chloride as catalyst to give expected products 294 along with variable amount of oligomeric species (Scheme 108).

Scheme 108: Model epoxide opening

Selective opening at the allylic position was confirmed by simple D₂O quench experiment (in CDCl₃/ 300 MHz). The change of the chemical shift of the doublet of the allylic hydrogen (3.85 ppm) is much smaller (Δ= 0.050 ppm) than that of the multiplet of homoallylic hydrogen on carbon 1 (3.95 ppm), which shifts more visibly (Δ= 0.010 ppm) after hydrogen-deuterium exchange.

Attempts were made to optimize this reaction. Combinations of three solvents (methylen chloride, tetrahydrofuran, 1,4-dioxane) and four catalysts (BF₃*Et₂O, Yb(OTf)₃, CSA, CeCl₃) were probed at different temperatures (r.t. to reflux) using TLC analysis for monitoring. We took advantage of a minireactor system (6x4 wells for 12x95 mm screw cap tubes) generously donated by Dr. Venit (Bristol-Myers Squibb).
This reactor system consists of two hollow aluminum blocks fitted with self-closing quick-release tubing fittings. The bottom block can be heated (cooled) either by circulating a tempered liquid medium or simply by placing in on the hot plate. The top block serves as a cooling jacket efficient enough to reflux even small volumes (0.2 mL) of methylene chloride, when ice cold water was circulated through the block using a pump submerged in an ice slurry.

The first two catalysts were efficient in all solvents, however extensive oligomerization and/or decomposition of epoxide were already observed at r.t. The latter two catalysts were much less active, an unreacted epoxide was observed even after prolonged reaction times.

To be useful in the approach towards the morphinan skeleton, conditions for rendering the bromocyclohexene ring aromatic had to be discovered. Oxidation of the mixture of secondary alcohols 294 using Swern’s conditions\(^98\) yielded enone 295 (Scheme 109).

![Scheme 109: Oxidation and protection of alcohol 294](image)

The expected double bond migration into conjugation with the ketone that was formed was evident from the proton NMR spectrum: signals for only two olefinic protons along with just one -CH-O- proton were observed. Two triplets (2.93 and 2.53 ppm) corresponding to two protons each (methylenes in positions 4 and 6) and a multiplet centered on 2.01 ppm (8 protons) were also present. The selective decoupling
experiments showed that the two triplets do not couple with each other but do couple to the same methylene group at 2.00 ppm. When the multiplet at 2.00 ppm was selectively irradiated both triplets at 2.93 and 2.53 ppm were reduced to singlets. Having the structure of enone 295 firmly established, it could be envisioned that aromatization could be achieved by an enolization/dehydrogenation sequence performed at the appropriate time.

A mixture of enantiomeric alcohols 294 was protected as dimethyl thexyl silyl ethers 296 in good yield for use in the cyclization attempts. Bromide 296 was then subjected to conditions of radical closure (i.e. excess of Bu₃SnH with AIBN as initiator) in refluxing benzene under high dilution conditions. The intermediate vinyl radical readily cyclized onto the double bond, yielding easily separable mixture of diastereomeric products 297 and 298 (Scheme 110).

Scheme 110: Model radical cyclization

The exact stereochemistry of cyclized products was tentatively assigned based on chemical shifts of -CH-O- protons. Chemical shifts of the multiplets of the selected protons on carbons 4, 5 and 6 (Scheme 110), designed as Ha, Hb and Hc, were assigned based on their multiplicity and selective decoupling experiments. From the stereochemistry assignment point of view, proton Ha is not interesting, since it has virtually same chemical shift in both compounds 297 and 298. However the chemical
shifts of the protons Hc and Hb are dramatically different because of the *cis* or *trans* fusion of rings B and C in compounds 297 and 298, respectively. Pertinent expansions of proton NMR spectra of 297 and 298 to support this argument are shown below along with proposed structures.

Figure 5: Partial spectra of radical cyclization products with tentative assignment

We were satisfied with the results of radical closure, and turned to the investigation of possibility of Heck coupling on substrate 296. Initially the reaction was run in toluene at 110 °C (sealed tube) using Pd(PPh₃)₄ as catalyst in the presence of N,N,N',N'-tetramethylnaphtalene-1,10-diamine (commercially available as Proton Sponge™) as a strong base to help reductive elimination (Scheme 111). However very slow progress was observed after a few days, therefore the temperature was raised to 130 °C. The reaction was complete after prolonged period of heating to yield a mixture of two products, 299 and 300, which were separated using preparative TLC.
Scheme 111: Model Heck coupling

Multiplets of three olefinic protons were observed in $^1$H-NMR spectra. Stereochemistry of cyclized materials were tentatively assigned as shown below based on the same argument used for the products of radical cyclization. The reason why the absolute stereochemistry of 297/298 and 299/300 was not investigated in more detail, and only tentative assignments were made, is that these reaction served only as models to establish whether the corresponding radical or Heck cyclizations proceed or not.

![Diagram of Heck cyclization products](image)

Figure 6: Partial spectra of Heck cyclization products with tentative assignments

Given the results above, precedents for radical and Heck cyclization of vinylbromide 296 (prepared by opening of epoxide 30 with rac-2-hexenol 293), to give corresponding deca- or octahydrodibenzofurans (297/298 or 299/300), were reasonably
established. Next we turned our attention to the application of the knowledge acquired from the above model study to the opening of epoxide 30 with octahydroisoquinolines 29.

**Epoxide Opening Attempts Using Hydroxyoctahydroisoquinolines**

Because monoprotected isoquinoline diols 29 could be prepared in one step from known diol 28 we investigated the retrosynthetic route A first (Scheme 112).

![Scheme 112: Retrosynthetic route A]

Monoprotection of diol 28 with TBSOTf in the presence of base at -78°C gave alcohol 300 as reported previously. Attempts to use this alcohol in the opening of the epoxide using BF₃·Et₂O as catalyst in methylene chloride within range of temperatures of -75°C to r.t. were not successful; extensive decomposition of the epoxide was observed and starting TBS ethers were recovered. Other conditions investigated, which were reported to work well even with highly functionalized epoxides, involved using Yb(OTf)₃ as catalyst and 1,4-dioxane or toluene (r.t. to reflux) as solvent. Unfortunately, the same negative result was obtained even in the presence of excess of epoxide. When toluene was used, loss of TBS group was observed at high temperatures (Scheme 113).
Speculating that steric hindrance by the bulky TBS group was responsible for the lack of reactivity we prepared monobenzyl derivatives 302 of diol 28 by reaction of 28 with benzyl bromide in the presence of silver oxide in methylene chloride. These conditions were reported to give selective monobenzylation of symmetrical diols in excellent yields. However in case of 28, reaction progress was rather slow and the expected mixture of monobenzyl ethers was isolated in low yield (32%). Better yields (61-79%) were obtained using cesium carbonate as a base in refluxing acetone (Scheme 114).

A mixture of monobenzylethers 302a,b, inseparable by chromatography, was isolated. Their ratio was determined by integration of $^1$H-NMR spectra as 2:1. The major isomer 302a was isolated by recrystallization of the mixture from ethyl acetate.

Opening of epoxide 30 with monobenzyl ethers 302 was attempted using similar conditions to the attempted openings with TBS ether derivatives mentioned previously.
Firstly, reaction of 302 with the epoxide in CH₂Cl₂ (-3°C to r.t.) with BF₃•Et₂O as catalyst, was investigated. Under these conditions fast decomposition of the epoxide was observed and starting alcohol was recovered. Attempt to use epoxide itself as a solvent (at 100°C) was also unsuccessful: unreacted starting materials were recovered. Reaction of monobenzylether 302a with epoxide 30 in 1,4-dioxane using Yb(OTf)₃ as a catalyst again lead to fast deterioration of the latter and unreacted alcohol was recovered even after prolonged heating to reflux. Attempts were also made to generate sodium salts of monobenzyl derivatives 302 and use these for epoxide opening; however no product formation was observed. Finally, reaction in toluene with Yb(OTf)₃ at high temperatures led to the loss of the benzyl group.

Monocinnamyl derivatives of 28 (characterized by NMR and IR) were also prepared in similar fashion, because we suspected possible problems with removal of the benzyl group later in the reaction sequence. Those problems could be avoided by utilization of the selective method for removal of the cinnamyl groups via mild electrochemical reduction recently developed in Hudlický's research group. Unfortunately, similar discouraging results of the epoxide opening under Lewis acid catalysis were obtained: epoxide rapidly decomposed and unreacted monocinnamates were recovered. Given the negative results of the Lewis catalyzed reactions, it seems that the monoprotected isoquinolines are poor nucleophiles towards activated bromoepoxide, perhaps because of the steric hindrance imposed by the protecting group. We decided to abandon this approach and switch to the investigation of the remaining retrosynthetic route B, which is described in the following part of the dissertation.
Synthesis and Opening of Octahydroisoquinoline Epoxide

Unable to achieve the opening of the epoxide precursor of the aromatic ring A of morphine (compound 30) with the monoprotected octahydroisoquinoline diols 29, we redesigned our strategy and set out to prepare octahydroisoquinoline epoxide 33. We hoped that the opening of 33 with the bromoguaiacol 34 would be the solution to the problem of the installment of the aromatic ring A of morphine in enantioselective fashion. Even though this route involves double inversion of the C5 center, originally correctly installed by microbial oxidation, and inversion of the stereocenter on C6 into the wrong configuration, the paradigm issue (i.e. installment of arylbromide via ether linkage on C5 in correct absolute stereochemistry) would be resolved (Scheme 115).

Configuration of the C5 center is of utmost importance since it controls delivery of the organopalladium intermediate during Heck coupling to one face of the tetrasubstituted double bond in 35 and thus predetermines the configuration of the tertiary C13 center. First, selective monoprotection of diol 28 to convert one of the hydroxyls to a leaving group was required, then Mitsunobu reaction was envisioned to occur on the remaining alcohol with inversion of that stereocenter giving the desired isoquinoline epoxide precursor.
After searching through literature reports, e.g. Sharpless et al.\textsuperscript{102} and references therein, selective arenesulfonylation of diol 28 to the corresponding monosulfonate 304 seemed a good first approach to differentiate one hydroxyl group of a diol. Exposure of diol 28 to tosyl chloride in pyridine at low temperatures yielded mixture of 3 products in addition to a substantial amount of unreacted diol. Surprisingly, only two of those products contained tosyl group and in both cases only the homoallylic alcohol was tosylated (Scheme 116).

Based on NMR data, the identities of the byproducts were established as tosylate chloride 303 and chlorohydrin 305 both resulting from nucleophilic substitution of allylic hydroxyl. This observation is in agreement with reports of Orsini who observed similar results from tosylation of enantiopure (1R,2S)-1,2-dihydroxy-1,2,3,4-tetrahydronaphtalene.\textsuperscript{103} Desired monotosyl alcohol 304a was isolated in moderate yields (20-26%), which could be increased by recycling of recovered starting material (Scheme 116).
Formation of chlorohydrin 305 and tosylate chloride 303 byproducts could be suppressed by using 2,4,5-triisopropylbenzenesulfonyl chloride, whose increased steric bulk improved selectivity. Unfortunately, yields of the desired monosulfonate were about the same as those from the tosylation reaction.

Having successfully differentiated homoallylic hydroxyl in diol 28 we attempted to carry out the substitution of the allylic hydroxyl with inversion of the C5 center and thus establish the trans relationship between the nucleophile (alkoxide) and the leaving group (sulfonate). To our satisfaction, Mitsunobu reaction of monotosylate with benzoic acid ran smoothly to give high yields (>80%) of expected tosylate benzoate 306a (Scheme 117).

![Scheme 117: Preparation of the epoxide precursor 306](attachment:image.png)

The sterically more encumbered sulfonate 304b also smoothly reacted under these conditions to give the corresponding sulfonate-benzoate 306b, however, the chromatographic isolation of 306b was complicated by its co-elution with the by-product of Mitsunobu reaction (i.e., EtCO₂NHNHCO₂Et). This set back was partially alleviated by recrystallization of purified 305b from ethyl acetate-hexane mixture, where most of the byproduct crystallizes and can be removed by filtration.

Encouraged by these results, we attempted generation of the required epoxide 33 by the deprotection of benzoate ester 306a,b by its exposure to 1.0 equivalent of freshly
prepared methanolic sodium methoxide, resulting in alkoxide, which was expected to
displace tosylate and close the oxirane ring. The reaction was run in tetrahydrofuran at
0°C, to give a very clean, spot-to-spot conversion as observed by TLC. Initially, aqueous
work up (sat. aq. NH₄Cl) was carried out, which lead to formation of noticeable amount
of by-product (presumably the product of acid catalyzed epoxide rearrangement). Pure
epoxide 33 could be isolated by column chromatography in good yield (60-69%),
(Scheme 118).

\[
\begin{align*}
\text{ArSO}_2\text{O,} & \quad \text{Bz} \\
\text{306} & \quad \text{a} \\
& \quad \text{b}
\end{align*}
\]

\text{Reaction conditions: a) MeONa/MeOH/THF}

Scheme 118: Preparation of octahydroisoquinoline epoxide 33

An alternative non-aqueous work up was discovered when we tried to evaporate the
reaction mixture to dryness and then re-dissolve the crude epoxide in a different solvent
for the opening reaction. When the crude solid residue resulting from the evaporation
was treated with dry 1,2-dimethoxy ethane (or 1,4-dioxane) and immersed in ultrasonic
bath for few minutes, a fine yellow precipitate separated. It was removed by filtration,
and identified by NMR as a salt of the corresponding sulfonic acid generated as leaving
group. The filtrate contained purified epoxide, which upon evaporation and drying in
vaccuo gave an oily residue shown by NMR to be almost pure epoxide in quantitative
yield.
After gaining access to desired isoquinoline epoxide 33, we advanced to study its opening with bromoguaiacol 34 prepared by bromination of commercially available 2-methoxyphenol utilizing a procedure reported by Hoshino. Initial attempts to open this epoxide with bromoguaiacol 34 either in solution catalyzed by Lewis acid (i.e. Yb(OTf)₃) or in a phenol melt resulted in complex mixtures of products. However, when epoxide was reacted with the large excess (4 to 9 equivalents) of carefully dried potassium salt of the bromoguaiacol 307 in refluxing DME in the presence of catalytic 18-crown-6-ether, very slow, but clean conversion to one product was observed.

The desired aryl ether 308 was isolated in good yields (56-80%) by the removal of solvent under reduced pressure, the residue (usually brown or black in color, probably a result of partial oxidation of guaiacol salt) was taken up in a large volume of ethyl ether and excess bromoguaiacol was removed by repetitive extraction with diluted aqueous sodium or potassium hydroxide. The organic layer was then dried, the ether removed, and the residue purified by column chromatography (Scheme 119).

Scheme 119: The key epoxide opening

It was later found that the addition of substoichiometric 18-crown-6-ether (> 0.3 eq. to epoxide) to generate a higher concentration of “naked” phenoxide anion (by the removal of potassium countercation by the strong complexation), and increased reaction
temperature (110°C/sealed tube) can shorten reaction times from more than week to two or three days.

This successful epoxide opening finally presents a novel solution to the enantioselective introduction of the arylbromide on carbon 5 (morphine numbering) of octahydroisoquinoline in 4 steps from the previously reported cis diol 28. The next key step in our approach to morphine skeleton was the intramolecular Heck coupling to establish the tertiary C13 center which is discussed below.

**Heck Coupling and Further Advances towards Synthesis of Morphinans**

Alcohol 308 was protected prior to coupling as its silyl ether 309 by reaction with a slight excess of TBSOTf (1.5 eq.) at -78°C in the presence of base. Maintaining the low temperature is necessary since 308 decomposes when subjected to an excess of TBSOTf at room temperature (Scheme 120).

![Scheme 120: Protection of alcohol 308](image)

TBS- ether 309 was characterized and compared to its presumed enantiomer 17, first reported in 1996 by Hudlický: the full experimental data were published in 1998. The proton and carbon NMR data were found to be virtually identical, as expected, and the measurement of the specific rotation showed the same magnitude but opposite sign, proving that those two compounds are enantiomers (Figure 7).
Figure 7: Optical rotation comparison

Confident of the absolute stereochemistry of 309, we moved on to the next key step, the Heck coupling. The initial experiment was carried out using catalytic Pd(PPh₃)₄ in toluene reported previously to work well on a similar compound with opposite stereochemistry at C5 and C6. Product formation was observed, however, catalyst seemed to be consumed during reaction, as black palladium precipitated during the course of the reaction. In order to complete this transformation, stoichiometric amount of Pd(PPh₃)₄ had to be used (Scheme 121).

Scheme 121: Establishment of C12-C13 connectivity via Heck coupling

Desired product 310 was isolated in good yield. Another catalytic system was investigated, Pd(OAc)₂ (5 mol%)/PCy₃ (20 mol%)/ Et₃N (5 eq.) (acetonitrile, 120°C, sealed tube), but it proved to be inefficient. Reaction progress was minor even after 7 days of heating. The addition of an extra catalyst and ligand was necessary to drive the reaction closer to completion. Extensive precipitation of black palladium was observed
as well. The optimization of catalyst/ligand system will be subject of further investigation.

In 2000 Eastwood\textsuperscript{106} reported a very efficient catalytic system (PdCl\textsubscript{2}dppf(3mol%)/dppf(3mol%)/KOAc/1,4-dioxane) for Suzuki couplings. The bidentate 1,1'-Bis(diphenylphosphino)ferrocene ligand (dppf) used, might help to overcome the problems with the precipitation of palladium from the reaction mixture.

Having successfully established the tertiary Cl\textsubscript{3} center via the Heck coupling as described above, we turned our attention to investigation of the conditions for the closure of the last ring of the morphinan skeleton. Reductive cleavage of the oxazolidone moiety in compound 310 by DIBAL-H resulted in the corresponding alcohol 311 in good yield (57-69%). Two possible routes from 311 were considered based on previously reported results on a similar system.\textsuperscript{7} Following the first route, primary alcohol 311 was converted to chloride 312 via mesylation of 311 in the presence of anhydrous lithium chloride (Scheme 122).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme122.png}
\caption{Scheme 122: Preparation of chloride 312}
\end{figure}

Attempts to close ring B of morphine skeleton by intramolecular Friedel-Crafts alkylation of aromatic ring in 311 using anhydrous aluminum chloride as catalyst in refluxing benzene or toluene were not successful. Presumably unreacted starting material was recovered along with a compound in which the dihydrofuran ring was opened, as
indicated by the dramatic up field shift of the doublet of proton on the carbon next to the tertiary carbon centre. Full characterization was prevented by the small scale of these reactions (2-3 mg of chloride 312). Attempts to deprotect the methyl ether moiety in 312 using lithium chloride in DMF (100°C/ sealed tube), and thus generate the phenoxide which was expected to cyclize more readily, led to two compounds. Unfortunately no cyclization was observed as judged by 1H-NMR analysis of isolated materials (<0.5 mg each).

Those negative results could be explained in terms of the ring C unsaturation. The triple substituted endocyclic double bond in ring C makes tetracycle 312 very rigid and might prevent the proper alignment of carbon 10 with carbon 11 of the aromatic ring A (morphine numbering) for cyclization to occur (see Scheme 122).

The second route involving oxidation accompanied by a shift of the double bond into conjugation with ketone formed was envisioned to solve this problem. Alcohol 311 was first treated with TBAF in order to remove the silyl protective group from the C6 hydroxyl, the resulting diol 313 was then subjected to double Swern oxidation to presumably give enone-aldehyde 314. This reaction was carried out on very small scale (< 2 mg) and based on NMR spectra of the crude mixture; the migration of double bond into conjugation with the ketone did occur (Scheme 123).

Scheme 123: Double Swern oxidation
Crude enone-aldehyde 314 was then dissolved in neat trifluromethanesulfonic acid in an attempt to close ring B.

Scheme 124: Attempted acid catalyzed cyclization of enone-aldehyde 314

The minute scale of this reaction prevented unambiguous characterization of the products, so the presence of the desired product 315 can neither be confirmed nor ruled out at this point.

Currently work is underway to repeat this sequence on a larger scale to obtain more material for complete characterization of the alcohol 313 and enone-aldehyde 314 and for repetition of the key cyclization shown above.
CHAPTER 4
CONCLUSIONS

Summary and Conclusions

Inter and intramolecular Diels-Alder reactions of the derivatives of enantiopure dienediol 22 with electron poor dienophiles were successfully carried out to yield highly substituted bridged octahydroisoquinoline synthons. More than twelve new derivatives were isolated and characterized. In particular cycloadduct 261, prepared by intramolecular cycloaddition of 258, was in two steps converted to compound 273, bearing the second diene, intended for second Diels-Alder reaction with bridge double bond (Scheme 125).

Scheme 125: Summary of double Diels-Alder approach

Unfortunately, no cycloaddition was observed even under high pressure conditions. Similarly, attempts to carry out intermolecular Diels-Alder reactions of compounds 261/262 with furan or 2-methoxyfuran were not successful: only unreacted starting material was recovered. The bridge double bond in 261 is probably not a very good dienophile, probably because of unfavorable stereoelectronic factors. Results of this cycloaddition study were published as full paper in 2001.\textsuperscript{107}
After abandoning the double Diels-Alder approach we turned our attention to optimization of the synthesis of the previously reported\textsuperscript{10} octahydroisoquinoline synthon 28. The bottle neck step in the synthesis, the elimination reaction to obtain tetrasubstituted olefin 285, was investigated in detail (Scheme 126).

![Scheme 126: Elimination reaction](image)

It was found that the best yields of olefin 285 (41-45\%) were obtained when \textit{anti} 316a or \textit{anti} 316b were used. Corresponding \textit{syn} chloride or bromide 316a,b gave negligible yields of desired product. Attempts to achieve a better yield of 285 by elimination of the \textit{syn} hydroxy derivative 316c with Burgess’ reagent were not successful.

Next, the model study of the opening of epoxide 30\textsuperscript{11} with racemic 2-cyclohexenol was carried out to yield the expected products, which were protected as corresponding thexyldimethylsilyl ethers (THS-ethers) 296 (Scheme 127).

![Scheme 127: Model study of the epoxide opening/cyclization](image)
Cyclization under radical or Heck coupling cyclization conditions gave the mixtures of expected products 317 or 318, respectively.

Next, the monobenzyl ethers of diol 28 were prepared along with the known mono TBS-derivative and were used in attempts to open epoxide 30. However only decomposition of the epoxide was observed and starting materials were recovered. The reason for this outcome is probably a mismatch between the very low nucleophilicity of alcohols 29a,b caused by steric hindrance, and extremely high reactivity of epoxide 30, activated by Lewis acid (e.g. BF₃·Et₂O) (Scheme 128).

Scheme 128: Unsuccessful epoxide opening

In the last part of this thesis, successful preparation of isoquinoline epoxide 33 in three steps from diol 28 was described. Opening of this epoxide with the potassium salt of bromoguaiacol yielded the desired alcohol, which was protected as t-butyl-dimethyldimethylsilyl ether (TBS-ether) 309. Compound 309 has the C5 and C9 centers of morphine in the correct configuration (Scheme 129).

Scheme 129: Epoxide opening and Heck coupling
Heck coupling of 309 required stoichiometric amount of palladium catalyst to yield tetracyclic morphinan 310 in good (74%) yield. Tetracycle 309, prepared from commercially available phenethylbromide in 14 steps, presents the advanced intermediate towards the synthesis of natural (-)-morphine. The key stereocenters of morphine (C5, C13 and C9) are correctly set, adjustment of the C6 center has precedence in the literature. Attempts were made to establish C10-C11 connectivity and thus close ring B of morphine, however the minute scale of these reactions prevented characterization of products.

**Future Work**

Larger quantities of chloride 312 will be prepared to repeat Lewis acid (e.g. AgBF₄) catalyzed alkylation again so products can be fully characterized.

![Scheme 130: Key intermediates](image)

Also preparation of aldehyde enone 314 on larger scale (ca. 20-30 mg) is planned, at this time it was prepared only on minute scale (<1 mg) and the only evidence we have is proton NMR spectra of the crude material.

![Scheme 131: Future work](image)
Exposure of 314 to neat trifluoromethanesulfonic acid is hoped to yield pentacycle 315, which could, upon reduction with lithium aluminum hydride, yield codeine 37 (Scheme 131).

Other future research will address the preparation of the key intermediate epoxide 33 by shorter routes, starting from commercially available materials. Racemic tetrahydroisoquinoline 320 can be prepared in two steps from compounds 194 and 319. Biooxidation of 320 (e.g. by recombinant strains of *E. coli* JM109 pDTG 601) might yield a diol such as 321, which could be converted to epoxide 33 in 4 steps (Scheme 132). Another possibility is Birch reduction of 320 to possibly yield diene 322.

Scheme 132: Alternative routes to epoxide 33
APPENDIX A
EXPERIMENTAL

General Methods and Instrumentation

All non-hydrolytic reactions were carried out under an argon atmosphere, with standard techniques to exclude moisture. Analytical and preparative TLC was performed on Silicycle silica gel 60A plates. Flash chromatography was performed on chromatographic silica gel, 230-400 mesh (Lagand Chemicals). Infrared spectra were recorded on Perkin-Elmer “Spectrum One” FT-IR instrument. Proton and carbon NMR spectra were obtained on a Varian 300 MHz or on a Varian Inova 500 MHz spectrometer with CDCl₃/TMS as a solvent. Proton chemical shifts (δ) are reported in parts per million (ppm) relative to TMS (0.0 ppm). Carbon chemical shifts are reported in parts per million (ppm) relative to the central line of the CDCl₃ triplet (77.23 ppm). Coupling constants (J) are reported in Hz. Optical rotations were recorded on a Perkin-Elmer 241 digital polarimeter (10⁻¹ deg. cm² g⁻¹). Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. High-resolution mass spectra and elemental analyses were performed at the University of Florida and Atlantic Microlab, Inc., respectively.

Experimental Procedures and Data

[3aR,7aS]-4-(2-Azido-ethyl)-2,2-dimethyl-3a,7a-dihydro-benzo[1,3]dioxole (243):

To a solution of the crude diene diol 22 (0.88 g, 4.9 mmol) (containing small amount of the corresponding phenol) in methylene chloride (6 mL) and 2,2-dimethoxy-
propane (6 mL, 49 mmol, 10 eq.) was added a catalytic amount of p-toluenesulfonic acid. The reaction mixture was stirred at room temperature for 45 min with monitoring by TLC. Upon completion, the reaction mixture was treated with 5% wt solution of sodium hydroxide (10 mL), followed by extraction with methylene chloride (4 x 20 mL). The organic layers were combined and washed with brine (10 mL) and dried over sodium sulfate. After filtration and removal of solvent the oily residue was purified by column chromatography (Hex-EtOAc, 95:5). Acetonide 243 was obtained as yellow oil in 46% yield (0.50 g). 1H NMR and IR data were in agreement with previously published data for this compound.76

\[
\text{[1S,2R,6S,7R,8R,12S]-1-(2-Azidoethyl)-4,4-dimethyl-3,5,10-trioxa-9,11-dioxo-tetracyclo[5.5.2.2.0.2^6,0^8.12]tetradec-13-ene (245)}
\]

\[
\text{and}
\]

\[
\text{[1S,2R,6S,7R,8S,12R]-1-(2-Azidoethyl)-4,4-dimethyl-3,5,10-trioxa-9,11-dioxo-tetracyclo[5.5.2.2.0.2^6,0^8.12]tetradec-13-ene (246):}
\]

To a solution of diene 243 (0.212 g, 0.96 mmol) in benzene (7 mL) was added maleic anhydride (0.099 g, 1.0 mmol, 1.05 eq.). The reaction mixture was stirred under argon atmosphere at room temperature for 68 hours, and the reaction progress was monitored by TLC. Benzene was then evaporated under reduced pressure, and the resulting oily residue was purified by column chromatography (Hexanes-EtOAc, 80:20) to yield the expected cycloadducts 245 as a white solid (0.051 g, 17%) and 246 as a yellow oil (0.121 g, 39%). The ratio of the cycloadducts (by integration of the 1H-NMR spectrum of the crude mixture) was 1.6:1 (246:245). The reaction was also carried out at reflux temperature with similar results.
245 (for the complete chemical shifts assignment see Figure 2, p. 59): \( R_f \) (hexanes–EtOAc, 70:30) = 0.33; m.p. 116–117 °C, \( \alpha_D^{29} +2.3^\circ \) (c = 0.0104 g/mL, CHCl₃), \(^1\)H-NMR: \( \delta \): 6.18 (dd, 1 H, \( J = 8.3 \) Hz, 6.2 Hz), 5.91 (d, 1 H, \( J = 8.4 \) Hz), 4.33 (dd, 1 H, \( J = 7.2 \) Hz, 3.3 Hz), 4.20 (d, 1 H, \( J = 7.1 \) Hz), 3.67 (m, 2 H), 3.48 (m, 1 H), 3.10 (m, 2 H), 2.39 (m, 2 H), 1.31 and 1.29 (s, 6 H). \(^{13}\)C-NMR: \( \delta \): 171.0, 169.9, 134.5, 129.8, 110.4, 78.2, 77.2, 47.3, 43.1, 42.2, 36.2, 30.0, 25.3, 25.0. IR (KBr): \( \nu \) (cm\(^{-1}\)): 2979.0, 2105.0, 1846.9, 1776.1. HRMS: \( C_{15}H_{18}N_3O_5 \) calculated ([M+H]⁺) 320.1246 found 320.1244. CH analysis calculated: C 56.42%, H 5.37% found C 56.84% and H 5.66%.

246: \( R_f \) (hexanes–EtOAc, 70:30) = 0.55; \( \alpha_D^{31} +44.5^\circ \) (c = 0.0121 g/mL, CHCl₃); \(^1\)H-NMR data: \( \delta \): 6.26 (dd, 1 H, \( J = 8.3 \) Hz, 6.5 Hz), 6.04 (d, 1 H, \( J = 8.3 \) Hz), 4.19 (dd, 1 H, \( J = 8.2 \) Hz, 3.9 Hz), 4.01 (d, 1 H, \( J = 8.3 \) Hz), 3.6 (m, 3 H), 3.42 (m, 2 H), 2.32 (m, 2 H), 1.48 (s, 3 H), 1.35 (s, 3 H). \(^{13}\)C-NMR: \( \delta \): 173.2, 172.1, 136.2, 131.7, 113.1, 76.6, 74.4, 47.5, 43.6, 41.9, 39.9, 37.0, 32.0, 26.5, 24.4. IR (KBr): \( \nu \) (cm\(^{-1}\)): 2986.0, 2095.8, 1841.6, 1770.4. HRMS: \( C_{15}H_{18}N_3O_5 \) calculated ([M+H]⁺) 320.1246 found 320.1235. CH analysis calculated: C 56.42%, H 5.37% found C 57.06% and H 5.46%.

\[[1S,2R,6S,7R,8R,9S]-4,4-Dimethyl-11-aza-3,5-dioxa-10-oxo-tetracyclo-[5.4.2.2.0^{26}.0^{19}]-pentadec-14-ene-8-carboxylic acid-8-methylester (247):\]

To a solution of compound 245 (0.083 g, 0.26 mmol) in tetrahydrofuran (3 mL) was added triphenylphosphine (0.072 g, 0.27 mmol, 1.05 eq.) and water (5 \( \mu \)L, 0.52 mmol, 2.0 eq.). The reaction mixture was heated to approximately 60 °C for 54 h (monitored by TLC) (a white precipitate forms during the reaction). The solvent was evaporated under reduced pressure, and the residue treated with a cold solution of
diazomethane in ether (3 mL). During the reaction initially insoluble residue dissolves. After stirring at room temperature for 30 min, more of the diazomethane solution (3 mL) was added, and stirring was continued for 17 h. Methanol (1 mL) was then added and solvents were removed under reduced pressure. The residue was purified by column chromatography (EtOAc–hexanes, 3:1, with 0.5% Et₃N). Product 247 was obtained as a white crystalline material (0.050 g, 63%); m.p. 172–173 °C, Rᵣ (EtOAc)= 0.39, αᵣ²⁷ +19.9° (c= 0.0122 g/mL, CHCl₃), ¹H-NMR: δ: 6.16 (bs, 1 H), 5.99 (m, 2 H), 4.34 (dd, 1 H, J=7.2 Hz, 3.3 Hz), 4.18 (d, 1 H, J= 7.2 Hz), 3.71 (s, 3 H), 3.56 (m, 1 H), 3.47 (m, 1 H), 3.30 (m, 1 H), 3.04 (dd, 1 H, J= 6.2 Hz, 1.5 Hz), 2.77 (d, 1 H, J= 6.0 Hz), 2.37 (m, 1 H), 2.14 (m, 1 H), 1.32 and 1.26 (s, 6 H). ¹³C-NMR: δ: 174.0, 172.8, 136.4, 129.2, 109.5, 78.4, 76.1, 52.7, 45.5, 41.1, 38.9, 38.7, 27.2, 25.6, 25.3. IR (KBr): ν (cm⁻¹): 3416.7, 3224.8, 1744.6, 1648.2, 1195.2. HRMS: calculated for C₁₆H₂₂NO₅ ([M+H]+): 308.1498 found 308.1496. CH analysis calculated: C 62.53%, H 6.89% found C 62.84% and H 6.80%.

[1S,2R,6S,7R,8S,9R]-4,4-Dimethyl-11-aza-3,5-dioxo-tetracyclo-[5.4.2.2.0²⁶.0¹⁹]-pentadec-14-ene-8-carboxylic acid-8-methylester (248):

To a solution of compound 246 (0.48 g, 1.5 mmol) in tetrahydrofuran (30 mL) was added triphenylphosphine (0.41 g, 1.57 mmol, 1.05 eq.) and water (54 µL, 3 mmol, 2 eq.). The reaction mixture was heated to approximately 60 °C for 72 h (monitored by TLC) (a white precipitate forms during the reaction). Solvent was then evaporated under reduced pressure, and the residue treated with a cold solution of diazomethane in ether (20 mL). During the reaction the initially insoluble residue dissolves. After stirring at
room temperature for 60 min, more of the diazomethane solution (5 mL) was added, and stirring was continued for 17 h. Methanol (3 mL) was added and solvents were removed under reduced pressure. The residue was purified by column chromatography (silica, EtOAc with 0.5% Et$_3$N). Product 248 was obtained as a white crystalline material (0.31 g, 70%), m.p. 173–174 °C; R$_f$ (EtOAc)= 0.18; $\alpha^D$ +48.6° (c= 0.0107 g/mL, CHCl$_3$), $^1$H-NMR: $\delta$: 6.34 (t, 1 H, $J$= 7.2 Hz), 6.11 (d, 1 H, $J$= 8.4 Hz), 6.01 (bs, 1 H), 4.15 (dd, 1 H, $J$=8.0 Hz, 4.3 Hz), 3.82 (d, 1 H, $J$= 8.1 Hz), 3.64 (s, 3 H), 3.56 (m, 1 H), 3.36 (m, 1 H) 3.24 (d, 1 H, $J$= 10.2 Hz), 3.09 (m, 2 H), 2.03 (m, 2 H), 1.85 (m, 1 H), 1.52 and 1.34 (s, 6 H). $^{13}$C-NMR: $\delta$: 174.6, 172.8, 134.0, 132.4, 113.0, 78.8, 75.0, 51.9, 41.4, 41.1, 41.0, 38.6, 29.9, 26.9, 26.5, 24.6. IR (KBr): $\nu$ (cm$^{-1}$): 3354.1, 3060.3, 2931.0, 1736.9, 1660.5, 1208.0. HRMS: calculated for C$_{16}$H$_{22}$N0$_5$ ([M+H]$^+$): 308.1498 found: 308.1497.

CH analysis: calculated C 62.53%, H 6.89% Found C 62.65% and H 6.88%.

$$\text{[1S,2R,6S,7R,8S,13R]-1-(2-Azidoethyl)-4,4-dimethyl-3,5-dioxa-9,12-dioxo-tetracyclo[5.4.2.0.^{2.6}.0.8]pentadec-10,14-diene (250) and}$$

$$\text{[1S,2R,6S,7R]-1-(2-Azidoethyl)-4,4-dimethyl-3,5-dioxa-tetracyclo[5.4.2.0.^{2.6}.0.8]pentadec-8,10,12,14-tetraene-10,13-diol (251):}$$

To a solution of diene 243 (0.12 g, 0.53 mmol) in benzene (3 mL) was added freshly sublimed 1,4-benzoquinone (0.058 g, 0.47 mmol, 1.1 eq.), and the reaction mixture was stirred at room temperature for 3 days. A black precipitate formed during reaction. Reaction mixture was evaporated, and the residue was purified on preparative TLC (hexanes–EtOAc 9:1, 3 elutions). The aromatized product 251 was isolated (oil, 0.013 g, 7.6%) along with expected exo cycloadduct 250 (oil, 0.015 g, 8.6%).
250: \(R_f\) (hexanes–EtOAc 70:30)= 0.35; \(^1\)H-NMR: \(\delta\): 6.69 (d, 1 H, \(J= 10.5\) Hz), 6.65 (d, 1 H, \(J= 10.5\) Hz), 6.19 (t, 1 H, \(J= 8.1\) Hz), 6.20 (dd, 1 H, \(J= 8.3\) Hz, 8.1 Hz), 5.91 (d, 1 H, \(J= 7.8\) Hz), 4.15 (dd, 1 H, \(J= 8.1\) Hz, 3.9 Hz), 3.90 (d, 1 H, \(J= 8.7\) Hz), 3.68 (m, 1 H), 4.50 (m, 2 H), 3.42 (d, 1 H, \(J= 8.7\) Hz), 2.16 (m, 1 H), 1.86 (m, 1 H), 1.35 (s, 3 H), 1.25 (s, 3 H). \(^{13}\)C-NMR: \(\delta\): 143.2, 141.9, 136.2, 132.1, 129.6, 127.9, 115.9, 114.8, 112.4, 82.0, 79.3, 50.0, 49.7, 38.3, 31.2, 29.1, 25.7. IR (neat): \(\nu\) (cm\(^{-1}\)): 2982.9, 2928.3, 2097.0, 1688.3, 1682.8, 1606.9.

251: \(R_f\) (hexanes–EtOAc 60:40)= 0.27; \(^1\)H-NMR: \(\delta\): 6.50 (d, 1 H, \(J= 8.7\) Hz), 6.48 (t, 1 H, \(J= 7.5\) Hz), 6.39 (d, 1 H, \(J= 8.7\) Hz), 6.21 (dd, 1 H, \(J= 7.8\) Hz, 1.2 Hz), 4.48 (m, 1 H), 4.28 (dd, 1 H, \(J= 7.2\) Hz, 3.3 Hz), 4.08 (d, 1 H, \(J= 6.9\) Hz), 3.81 (m, 1 H), 3.61 (m, 1 H), 2.71 (m, 2 H), 1.38 (s, 3 H), 1.26 (s, 3 H). \(^{13}\)C-NMR: \(\delta\): 146.2, 145.1, 135.7, 132.6, 129.6, 127.9, 115.9, 114.8, 112.4, 82.0, 79.3, 50.0, 49.7, 38.3, 31.2, 29.1, 25.7. IR (neat): \(\nu\) (cm\(^{-1}\)): 3426.3, 2977.8, 2930.1, 2094.5, 1642.0. HRMS: calculated for C\(_{17}\)H\(_{20}\)N\(_{3}\)O\(_{4}\) ([M+H]\(^{+}\)): 330.1454, found: 330.1476.

1-(2-Azidoethyl)-4,4-dimethyl-3,5-dioxa-tetracyclo[5.4.2.2.0\(^{26}\)0.8]pentadec-10,14-diene 9,12-diol (253):

![Diagram](image)

To a solution of acetonide 243 (0.076 g, 0.34 mmol) in benzene (5 mL) was added freshly sublimed benzoquinone (0.038 g, 0.34 mmol, 1.1 eq.), and reaction mixture was heated to reflux for 18 h under argon atmosphere. The resulting dark brown mixture containing a black precipitate was concentrated, and residue was dissolved in 5 mL of a 1:1 mixture of methylene chloride and methanol mixture. Ceric (III) chloride heptahydrate (0.129 g, 1 eq.) was added, and after 5 min at ambient temperature sodium
borohydride (0.013 g, 1 eq.) was added in one portion. After stirring for an additional 30 min at ambient temperature, the pH was adjusted to neutral with dilute hydrochloric acid. Water (10 mL) was added, and the mixture was extracted with ether (4 × 15 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc 1:1).

Product 252 was obtained as oil (0.028 g, 25%, containing a trace of aromatized product). $R_f$ (hexanes–EtOAc 1:1) = 0.3; $^1$H-NMR: $\delta$: 6.47 (m, 2 H), 6.12 (t, 1 H, $J$=7.5 Hz), 5.87 (d, 1 H, $J$= 7.8 Hz), 4.26 (m, 2 H), 4.03 (d, 1 H, $J$= 7.2 Hz), 3.57 (m, 2 H), 2.87 (m, 1 H), 2.59 (d, 1 H, $J$= 8.7 Hz), 2.25 (m, 1 H), 2.05 (m, 1 H), 1.91 (dd, 1 H, $J$= 11.1 Hz, 3.9 Hz), 1.68 (dd, 1H, $J$= 10.8 Hz, 4.2 Hz), 1.33 (s, 3H), 1.27 (s, 3H). $^{13}$C-NMR: $\delta$: 136.6, 136.3, 132.2, 128.2, 109.0, 81.3, 79.7, 65.2, 61.9, 48.0, 46.0, 43.0, 41.1, 31.4, 30.9, 29.7, 29.6. IR (neat): $\nu$ (cm$^{-1}$): 3358.8, 3052.97, 2978.7, 2924.1, 2855.0, 2096.7, 1661, 1208.3, 1066.3. HRMS: calculated for $C_{17}$H$_{24}$N$_{3}$O$_{4}$ ([M+H]$^+$): 334.1767, found: 334.1742.

N-[2-(2,2-Dimethyl-3a,7a-dihydro-benzo[1,3]dioxol-4-yl-ethyl]-acetamide (254):

Compound 243 (0.25 g, 1.1 mmol) in thioacetic acid (0.4 mL, 4.4 mmol, 4 eq.) was stirred at 0 °C for 1 h, and then allowed to warm to room temperature. Stirring was continued for 17 h, then the mixture was concentrated under reduced pressure and the residue purified by column chromatography (EtOAc). Product 254 was obtained as yellow oil (0.12 g, 46%). $R_f$(EtOAc) = 0.33; $^1$H-NMR: $\delta$: 6.21(bs, 1 H), 5.96 (m, 1 H);
5.80 (m, 2 H), 4.72 (dd, 1 H, J= 8.7 Hz, 3.3 Hz), 4.52 (d, 1 H, J= 8.7 Hz), 3.45 (m, 2 H), 2.48 (m, 1 H), 2.36 (m, 1 H), 1.96 (s, 3 H), 1.41 (s, 6 H). $^{13}$C-NMR: δ: 170.0, 134.5, 123.8, 123.7, 121.0, 104.9, 72.9, 71.5, 37.7, 37.1, 26.7, 24.7, 23.1. IR (neat): ν (cm$^{-1}$): 3298.4, 3087.9, 2985.7, 2935.0, 1651.5, 1557.1434.3.

[1S,2R,6S,7R,8R,13S]-1-(2-Acetamidoethyl)-4,4-dimethyl-3,5-dioxa-tetracyclo[5.4.2.2.0.2.6.0.8.9]pentadec-10,14-diene 9,12-diol (255) and [1S,2R,6S,7R,8S,13R]-1-(2-Acetamidoethyl)-4,4-dimethyl-3,5-dioxa-tetracyclo[5.4.2.2.0.2.6.0.8.9]pentadec-10,14-diene 9,12-diol (256):

To a stirred solution of 254 (0.048 g, 0.2 mmol) in benzene (7 mL) was added p-benzoquinone (0.033 g, 0.3 mmol, 1.5 eq.). The reaction mixture was stirred at ambient temperature for 4 days (with monitoring by TLC). After removal of the solvent under reduced pressure, the residue was purified by column chromatography (EtOAc). The isolated compound (0.047 g) was shown by $^1$H-NMR to be a mixture of the two isomers 255 and 256 (ca. 2:1 ratio). Further attempt to separate the isomers by column chromatography (hexanes–acetone, 2:1) was unsuccessful.

Partial $^1$H-NMR (300 MHz) of the mixture (signals belonging to the exo adduct (256) are underlined): δ: 6.60 (s, 2 H), 6.65 (s, 2 H), 6.28 (bs, 1 H), 6.19 (dd, 1 H, J= 6.3 Hz, 8.1 Hz), 6.09 (t, 1 H, J= 8.1 Hz), 5.99 (bs, 1 H), 5.91 (d, 1 H, J= 8.1 Hz), 5.73 (d, 1 H, J= 8.4 Hz), 1.98 (s, 3 H), 1.97 (s, 3 H), 1.51 and 1.35 (s, 6 H), 1.30 and 1.28 (s, 6 H). IR (neat): ν (cm$^{-1}$): 3106.9, 2982.9, 2929.3, 1667.0, 1659.2, 1652.0, 1265.1, 1208.8. HRMS: calculated for C$_{19}$H$_{24}$NO$_5$ ([M-H]$^-$): 346.1654 found 346.1618.
(Z)-[3aR,7aS]-3-[2-(2,2-Dimethyl-3a,7a-dihydro-benzo[1,3]dioxole-4-yl)-ethylcarbamoyl] acrylic acid ethylester (257):

To a solution of the azidoethyl diene 243 (0.496 g, 2.24 mmol) in tetrahydrofuran (15 mL) was added triphenylphosphine (0.882 g, 3.36 mmol, 1.05 eq.). The resulting mixture was stirred at room temperature for 3 h then water (120 µL, 6.7 mmol, 3.0 eq.) was added. After 26 hours the solution was dried over sodium sulfate. Following filtration and removal of solvent, the crude residue was used for the next step.

To a solution of monoethyl maleic acid (0.649 g, 4.48 mmol, 2.0 eq.) in methylene chloride (15 mL) was added dicyclohexylcarbodiimide (DCC) (0.924 g, 4.48 mmol, 2.0 eq.) (white precipitate forms) and a catalytic amount of a DMAP. The reaction mixture was stirred at 0 °C for five minutes, then a solution of the crude amine (ca. 0.44 g, 2.24 mmol) in the methylene chloride (10 mL) was added. After stirring at 0 °C for 1 hour, the reaction mixture was allowed to warm to room temperature, and stirring was continued for 4 hours. The white precipitate was filtered and the solvent evaporated. The remaining dark brown oil was trituated with ether (20 mL), the precipitate filtered and the filtrate was evaporated to dryness. The residue was then purified by column chromatography (hexanes–EtOAc, 60:40). Pure 257 was obtained as oil (0.248 g, 34%) and was stored under argon in the freezer. 

\[ R_f \text{ (EtOAc)} = 0.74; \ \alpha_{D}^{29} +71.6^\circ; (c= 0.0145 g/mL, CHCl}_3) \]

\[ ^1H-\text{NMR: } \delta: 8.19 \text{ (bs, 1 H), 6.30 and 6.10 (2 d, 2 H, } J= 12.9 \text{ Hz), 5.96 (m, 1 H), 5.81 (m, 2 H), 4.71 (dd, 1 H, } J= 3.0 \text{ Hz, 8.6 Hz), 4.56 (d, 1 H, } J= 8.4 \text{ Hz), 4.23 (q, 2 H, } J= 7.2 \text{ Hz), 3.56 (q, 2 H, } J= 6.3 \text{ Hz), 2.51 (m, 2 H), 1.40 and 1.39 (2 s, 6 H), 1.31 (t, 6 H).} \]
3 H, \( J = 7.2 \) Hz. \(^{13}\)C-NMR: \( \delta \): 166.2, 164.2, 138.3, 134.9, 125.5, 124.3, 123.8, 121.0, 105.3, 73.1, 71.6, 61.7, 38.0, 33.8, 27.0, 25.2, 14.2. IR (neat): \( \nu (\text{cm}^{-1}) \): 3300.3, 3047.5, 2985.2, 2935.1, 1729.4, 1661.7, 1629.6, 1211.4, 1027.4. HRMS: calculated for \( \text{C}_{17}\text{H}_{24}\text{O}_{5}\text{N} [\text{M+H}^+] \): 322.1654 found 322.1689.

(E)-[3aR,7aS]-3-[2-(2,2-Dimethyl-3a,7a-dihydro-benzo[1,3]dioxole-4-yl) ethylcarbamoyl] acrylic acid ethylester (258):

To a solution of the azide 243 (0.270 g, 1.22 mmol) in tetrahydrofuran (2 mL) was added triphenylphosphine (0.336 g, 1.36 mmol, 1.05 eq.) and water (33 \( \mu \)L, 1.8 mmol, 1.5 eq.). The resulting mixture was stirred at room temperature. After 29 hours methylene chloride (10 mL) was added, and solution was dried over sodium sulfate. Following filtration and removal of solvent, the crude residue was used for the next step. To a solution of monoethyl fumaric acid (0.147 g, 0.97 mmol, 1.05 eq.) in methylene chloride (3 mL) was added dicyclohexylcarbodiimide (DCC) (0.220 g, 1.07 mmol, 1.1 eq.) (a white precipitate forms) and a catalytic amount of DMAP. The reaction mixture was stirred at 0 °C for 5 min, and then a solution of the crude amine (ca. 0.2 g, 0.92 mmol) in the methylene chloride (3 mL) was added. After stirring at 0 °C for 1 hour, the reaction mixture was allowed to warm to room temperature, and stirring was continued for 18 hours. The white precipitate was filtered and the solvent evaporated. The remaining dark brown oil was triturated with ether (15 mL), and the resulting solid was separated by filtration. Silica was added to the filtrate, and solvent was removed under
reduced pressure. The crude product thus adsorbed on silica was then purified by column chromatography (hexanes–EtOAc, 60:40, 50:50, 40:60).

Product 257 was obtained as semi crystalline oil (0.174 g, 59%) and was stored under argon in the freezer (it easily undergoes Diels–Alder reaction at r.t.). \( R_f \) (hexanes–EtOAc, 1:1) = 0.41; \( \alpha_d^{29} = -14.6^\circ \) (c = 0.0308 g/mL, CHCl\(_3\)); \( ^1H\)-NMR: \( \delta \): 6.84 and 6.77 (d, 2 H, \( J = 15.6 \) Hz), 6.44 (bs, 1 H), 5.95 (m, 1 H), 5.82 (m, 2 H), 4.76 (d, 1 H, \( J = 8.4 \) Hz), 4.49 (d, 1 H, \( J = 8.4 \) Hz), 4.24 (q, 2 H, \( J = 6.9 \) Hz), 3.57 (m, 2 H), 2.59 (m, 1 H), 2.38 (m, 1 H), 1.43 (s, 6 H), 1.31 (t, 3 H, \( J = 7.2 \) Hz). \( ^{13}C\)-NMR: \( \delta \): 165.7, 163.7, 136.7, 134.2, 130.1, 124.4, 123.7, 121.9, 105.27, 71.3, 71.9, 61.3, 38.5, 34.3, 27.0, 25.0, 14.3. IR (neat): \( \nu \) (cm\(^{-1}\)): 3287.2, 3074.9, 3049.4, 2985.1, 2934.1, 1724.8, 1667.5, 1651.8, 1298.9, 1031.2. HRMS: calculated for \( C_{17}H_{24}O_5N \) ([M+H]\(^+\)): 322.1654, found: 322.1652.

\[ [1S,2R,6S,7R,8R,9S]-4,4-Dimethyl-11-aza-3,5-dioxa-10-oxo-tetracyclo-\[5.4.2.0^{2.6}.0^{1.9}\]-pentadec-14-ene-8-carboxylic acid-8-ethylester (259) \]

and

\[ [1S,2R,6S,7R,8S,9R]-4,4-Dimethyl-11-aza-3,5-dioxa-10-oxo-tetracyclo-\[5.4.2.0^{2.6}.0^{1.9}\]-pentadec-14-ene-8-carboxylic acid-8-ethylester (260): \]

A solution of triene 257 (0.1 g, 0.3 mmol) in benzene (7 mL) was heated at reflux for 5 days. The solvent was evaporated, and the residue purified by column chromatography (hexanes–EtOAc, 20:80, EtOAc) to provide pure 260 (0.010 g, 10%) and pure 259 (0.010 g, 10%) and a mixture of both isomers (0.026 g, 26%, \( 260:259 = 4:1 \)) as oils. The overall yield of the reaction was 46%. The ratio of cycloadducts (by integration of the \(^1H\)-NMR spectrum of the crude mixture) was 2:1 (260:259).
259: \( R_f (\text{CHCl}_3-\text{MeOH}, 9:1) = 0.56, \alpha_D^{30} +38.58^\circ (c = 0.0092 \text{ g/mL, CHCl}_3) \); \(^1\)H-NMR: \( \delta: 6.32 (t, 1 \text{ H}, J= 7.5 \text{ Hz}), 6.10 (d, 1 \text{ H}, J= 8.4 \text{ Hz}), 5.83 (bs, 1 \text{ H}), 4.16 (dd, 1 \text{ H}, J= 8.1 \text{ Hz}, 4.2 \text{ Hz}), 4.09 (q, 2 \text{ H}, J= 7.0 \text{ Hz}), 3.82 (d, 1 \text{ H}, J= 8.1 \text{ Hz}), 3.62 (dd, 1 \text{ H}, J= 10.2 \text{ Hz}, 2.7 Hz), 3.54 (dd, 1 \text{ H}, J= 12.3 \text{ Hz}, 4.2 Hz), 3.36 (m, 1 \text{ H}), 3.24 (d, 1 \text{ H}, J= 10.2 \text{ Hz}), 3.11 (m, 1 \text{ H}), 2.02 (dt, 1 \text{ H}, J= 13.3 \text{ Hz}, 6.1 \text{ Hz}), 1.84 (dd, 1 \text{ H}, J= 13.1 \text{ Hz}, 3.6 \text{ Hz}), 1.53 (s, 3 \text{ H}), 1.35 (s, 3 \text{ H}), 1.25 (t, 3 \text{ H}, J= 7.1 \text{ Hz}). \(^{13}\)C-NMR: \( \delta: 174.0, 173.0, 133.9, 132.5, 113.1, 78.9, 74.9, 60.6, 41.3, 41.1, 41.1, 38.7, 38.6, 26.9, 26.5, 24.6, 14.3. \) IR (neat): \( \nu (\text{cm}^{-1}): 3306.3, 3046.5, 2928.2, 2856.1, 1731.9, 1666.5, 1175.7. \) HRMS: calculated for \( \text{C}_{17}\text{H}_{24}\text{O}_5\text{N} ([\text{M}+\text{H}]^+): 322.1654, \) found 322.1637. CH analysis calculated: C 63.54%, H 7.21%, found C 63.05% and H 7.31%.

260: \( R_f (\text{CHCl}_3-\text{MeOH}, 9:1) = 0.51; \alpha_D^{25} -29.58^\circ (c = 0.0100 \text{ g/mL, CHCl}_3) \); \(^1\)H-NMR: \( \delta: 6.23 (t, 1 \text{ H}, J= 7.3 \text{ Hz}), 6.01 (d, 1 \text{ H}, J= 8.4 \text{ Hz}), 5.80 (bs, 1 \text{ H}), 4.31 (dd, 1 \text{ H}, J= 2.8 \text{ Hz}, 7.1 \text{ Hz}), 4.22 (dd, 1 \text{ H}, J= 3.8 \text{ Hz}, 6.3 \text{ Hz}), 4.10 (q, 2 \text{ H}, J= 7.1 \text{ Hz}), 3.93 (d, 1 \text{ H}, J= 7.2 \text{ Hz}), 3.61 (dt, 1 \text{ H}, J= 12.6 \text{ Hz}, 3.8 \text{ Hz}), 3.39 (m, 1 \text{ H}), 3.10 (m, 2 \text{ H}), 2.32 (m, 2 \text{ H}), 1.33 (s, 3 \text{ H}), 1.28 (s, 3 \text{ H}), 1.25 (t, 3 \text{ H}, J= 7.1 \text{ Hz}). \(^{13}\)C-NMR: \( \delta: 172.7, 171.0, 131.9, 129.7, 110.1, 83.0, 78.6, 60.9, 45.1, 43.5, 41.2, 39.4, 39.1, 28.4, 25.6, 25.4, 14.3. \) IR (neat): \( \nu (\text{cm}^{-1}): 3310.5, 2927.5, 2855.7, 1731.9, 1666.9. \) HRMS: calculated for \( \text{C}_{17}\text{H}_{24}\text{O}_5\text{N} ([\text{M}+\text{H}]^+): 322.1654, \) found: 322.1628. CH analysis calculated: C 63.54%, H 7.21%, found C 63.18% and H 7.13%.
[1S,2R,6S,7R,8S,9S]-4,4-Dimethyl-11-aza-3,5-dioxa-10-oxo-tetracyclo-
[5.4.2.02,6.019]-pentadec-14-ene-8-carboxylic acid-8-ethylester (261)
and
[1S,2R,6S,7R,8R,9R]-4,4-Dimethyl-11-aza-3,5-dioxa-10-oxo-tetracyclo-
[5.4.2.02,6.019]-pentadec-14-ene-8-carboxylic acid-8-ethylester (262):

A solution of triene 258 (0.13 g, 0.4 mmol) in benzene (10 mL) was heated to
reflux for 21 h; then the solvent was evaporated. Column chromatography (Hex–EtOAc,
20:80) yielded pure 261 (0.030 g, 23%), pure isomer 262 (0.020 g, 15%), and a mixture
of both isomers (0.048 g, 37%). The overall yield of the reaction was 75%.

261 (for the complete chemical shifts assignment see Figure 3, p. 64): Rf (EtOAc)=
0.46; αD29 +10.7° (c= 0.0138 g/mL, CHCl3); 1H-NMR (500 MHz): δ: 6.30 (ddt, 1 H, J=
8.3 Hz, 6.6 Hz, 0.9 Hz), 6.03 (bs, 1 H), 5.95 (dt, 1 H, J= 8.2 Hz, 1.3 Hz), 4.24 (ddd, 1 H,
J= 7.1 Hz, 3.2 Hz, 1.0 Hz), 4.22 (dq, 1 H, J= 15.8 Hz, 7.2 Hz), 4.20 (dq, 1 H, J= 15.6 Hz,
7.2 Hz), 4.03 (dd, 1 H, J= 7.1 Hz, 2.0 Hz), 3.50 (td, 1 H, J= 12.3 Hz, 4.9 Hz), 3.43 (ddd, 1 H,
J= 12.5 Hz, 6.4 Hz, 2.5 Hz), 3.26 (dtd, 1 H, J= 6.5 Hz, 3.3 Hz, 1.1 Hz), 2.97 (dd, 1 H,
J= 5.9 Hz, 3.0 Hz), 2.73 (d, 1 H, J= 6.0 Hz), 2.29 (ddd, 1 H, J= 13.6 Hz, 4.6 Hz, 1.7 Hz),
1.91 (ddd, 1 H, J= 13.3 Hz, 12.2 Hz, 6.9 Hz), 1.31 (s, 3 H), 1.30 (t, 3 H, J= 7.3 Hz), 1.26
(s, 3 H). 13C-NMR (126 MHz,CDCl3): δ: 173.5, 172.8, 133.4, 130.7, 109.6, 82.0, 76.2,
61.5, 44.3, 43.0, 41.4, 39.3, 38.0, 27.7, 25.4, 25.1, 14.3. IR (neat): ν (cm⁻¹): 3311.84,
3213.3, 3056.6, 2983.5, 2937.2, 1728.1, 1668.2, 1194.7. HRMS: calculated for
C17H24O5N ([M+H]⁺): 322.1654, found 322.1653. CH analysis calculated: C 63.54%, H
7.21%, found C 63.59% and H 7.30%.
**262**: \( R_f (\text{EtOAc}) = 0.40; \alpha_D^{27} + 17.2^\circ \) (c= 0.0181 g/mL, CHCl\(_3\)); \(^1\)H-NMR: \( \delta \): 5.99 (m, 2 H), 5.73 (bs, 1 H), 4.35 (dd, 1 H, \( J = 3.2 \) Hz, 7.0 Hz), 4.18 (m, 3 H), 3.56 (m, 1 H), 3.47 (m, 1 H), 3.32 (m, 1 H), 3.04 (dd, 1 H, \( J = 1.7 \) Hz, 6.3 Hz), 2.79 (d, 1 H, \( J = 5.9 \) Hz), 2.39 (m, 1 H), 2.14 (m, 1 H), 1.32 (s, 3 H), 1.26 (s, 3 H), 1.26 (t, 3 H, \( J = 7.1 \) Hz). \(^{13}\)C-NMR: \( \delta \): 173.5, 172.8, 136.4, 129.2, 109.6, 78.5, 76.2, 61.5, 45.4, 41.3, 41.2, 39.0, 38.9, 27.3, 25.6, 25.3, 14.4. IR (neat): \( \nu (\text{cm}^{-1}) \): 3307.9, 3052.7, 2981.6, 2933.9, 1731.8, 1667.1, 1058.7. HRMS: calculated for C\(_{17}\)H\(_{24}\)O\(_5\)N (\([\text{M+H}]^+\)): 322.1654, found 322.1653.

**Ethyl (1R, 6R, 7S, 8S, 9R, 13S)-11,11-dimethyl-5-ethoxy-10,12-dioxa-4-azatetracyclo[6.5.2.0\(_{1,6}\).0\(_{9,13}\)]pentadec-4,14-diene-7-carboxylate (263):**

To a solution of lactam 261 (0.055g, 0.17 mmol) in methylene chloride (3 mL) was added triethyloxonium tetrafluoroborate (0.048g, 0.25 mmol, 1.5 eq.). The reaction mixture was stirred at r.t. under argon atmosphere for 27 hours. After the dilution of the reaction mixture with methylene chloride (20 mL), it was extracted with sat. aq. K\(_2\)CO\(_3\) (2 x 2 mL) and washed with brine (5 mL) and dried over magnesium sulfate. After filtration and evaporation of solvent, crude product 263 was obtained as colorless oil (0.042 g, 72%). \( R_f (\text{Hex:EtOAc} = 1:1) = 0.5, \alpha_D^{26} + 19.47^\circ \) (c= 0.0100 g/mL, chloroform), \(^1\)H-NMR: \( \delta \) (ppm): 6.30 (t, 1 H, \( J = 7.2 \) Hz), 5.91 (d, 1H, \( J = 8.4 \) Hz), 4.31 (dd, 1 H, \( J_1 = 3.0 \) Hz, \( J_2 = 6.9 \) Hz), 4.22 (m, 2 H), 4.00 (d, 1 H, \( J = 7.2\)Hz), 3.95 (m, 2 H), 3.70 (dd, 1H, \( J_1 = 5.7 \) Hz, \( J_2 = 16.6 \) Hz), 3.57 (m, \( J = 7.2 \) Hz), 3.12 (m, 1 H), 2.60 (m, 2 H), 2.10 (dd, 1 H, \( J_1 = 4.5 \) Hz, \( J_2 = 13.5 \) Hz), 1.66 (m, 2 H), 1.32 (s, 3 H), 1.26 (s, 3H), 1.15 (t, 3H, \( J = 7.2 \) Hz). \(^{13}\)C-NMR: \( \delta \): 173.65, 161.96, 133.03, 131.91, 109.36, 82.56, 76.18, 61.31, 60.55,
45.70, 43.93, 38.79, 38.62, 28.65, 25.60, 25.21, 14.46, 14.31. IR (neat): ν (cm⁻¹):

Ethyl (1R, 6R, 7S, 8S, 9R, 13S)-11,11-dimethyl-5-thio-10,12-dioxo-4-azatetracyclo[6.5.2.0₁,6.0⁹,₁₃]pentadec-4,14-diene-7-carboxylate (272):

To a solution of lactam 261 (0.100 g, 0.31 mmol) in dry benzene (3 mL) was added Lawesson's reagent (0.065 g, 0.16 mmol, 0.5 eq.). The reaction mixture was then heated to reflux under argon atmosphere for 15 hours. Solvent was removed under reduced pressure; the residue was re-dissolved in methylene chloride followed by addition of silica. After the methylene chloride was evaporated, the crude product was purified by column chromatography (silica, Hex:EtOAc = 60:40). Product 271 was obtained as colorless oil (0.092 g, 88%). Rf (Hex:EtOAc 1:1) = 0.42, αD²⁸ = 7.96° (c = 0.0087 g/mL, chloroform), ¹H-NMR: δ (ppm): 8.45 (bs, 1 H), 6.33 (t, 1 H, J = 7.5 Hz), 5.88 (d, 1 H, J = 8.4 Hz), 4.26 (m, 3 H), 4.04 (d, 1 H, J = 7.2 Hz), 3.51 (m, 2 H), 3.36 (dd, 1 H, J₁ = 3.0 Hz, J₂ = 6.2 Hz), 3.24 (m, 1 H), 2.96 (d, 1 H, J = 6.3 Hz), 2.34 (dt, 1 H, J₁ = 3.0 Hz, J₂ = 13.2 Hz), 1.98 (dt, 1 H, J₁ = 9.0 Hz, J₂ = 13.8 Hz), 1.33 (t, 3 H, J = 6.9 Hz), 1.30 (s, 3 H), 1.26 (s, 3 H). ¹³C-NMR: δ: 205.45, 173.52, 133.87, 130.35, 109.90, 82.04, 76.38, 61.67, 49.71, 48.27, 42.06, 40.80, 38.48, 27.39, 25.60, 25.26, 14.44. IR (neat): ν (cm⁻¹): 3297.4, 3182.6, 3071.7, 2980.3, 2934.6, 1725.2, 1539.1, 1193.6. HR MS: calculated for C₁₇H₂₄NO₄S ([M-H]⁺) = 338.1426; found: 338.1466. CH analysis: calculated for C₁₇H₂₃NO₄S: C 60.51%, H 6.87%, found C 60.76% and H 6.87%.
Ethyl (1R, 6R, 7S, 8S, 9R, 13S)-11,11-dimethyl-5-thio(2-furfuryl)-10,12-dioxa-4-azatetracyclo[6.5.2.0\(^{1,6}.0^{9,13}\)]pentadec-4,14-diene-7-carboxylate (273):

![Chemical Structure](image)

To a solution of thiolactam 272 (0.050 g, 0.15 mmol) in dry tetrahydrofuran (2 mL) was added a freshly prepared ethereal solution of furfuryl bromide (0.32 mL, ca. 0.17 mmol, 1.2 eq.) and ethyldiisopropyl amine (0.030 mL, 0.022 g, 0.17 mmol, 1.2 eq.). The reaction mixture was then stirred at r.t.; after one day starting material was still present. The reaction mixture was therefore concentrated to ca. half of its volume under a stream of argon and more furfuryl bromide solution was added (0.2 mL). After stirring for two more days at r.t. the reaction was complete. White precipitate that had formed was filtered and washed with tetrahydrofuran (2 mL). To the filtrate was added silica. After the evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (silica, Hex:EtOAc= 90:10). The product 273 was obtained as a yellow oil (0.049 g, 78%). \( R_f \) (Hex:EtOAc=7:3)= 0.56, \( \alpha_D^{25} +38.10^\circ \) (c= 0.0187 g/mL, chloroform), \(^1\)H-NMR: \( \delta \) (ppm: 7.30 (dd, 1 H, \( J_1=0.9 \) Hz, \( J_2=1.8 \) Hz ), 6.27 (m, 2H), 6.14 (dd, 1 H, \( J_1=0.6 \) Hz, \( J_2=3.0 \) Hz), 5.93 (d, 1 H, \( J=8.1 \) Hz), 4.23 (m, 3 H), 4.18 (d, 1 H, \( J=10.8 \) Hz), 4.12 (d, 1 H, \( J=11.7 \) Hz), 3.98 (m, 2 H), 3.72 (m, 1 H), 3.19 (m, 1 H), 2.72 (m, 2 H), 2.15 (dd, 1 H, \( J_1=4.8 \) Hz, \( J_2=12.3 \) Hz ), 1.74 (m, 1 H), 1.31 (t, 3 H, \( J=6.9 \) Hz), 1.31 (s, 3 H), 1.25 (s, 3 H). \(^{13}\)C-NMR: \( \delta \): 173.11, 165.13, 151.19, 142.06, 132.70, 132.10, 110.66, 109.44, 107.88, 82.14, 76.15, 61.76, 47.64, 46.64, 43.09, 40.76, 39.00, 28.46, 25.96, 25.62, 25.26, 14.43. IR (neat): v (cm\(^{-1}\)): 3117.8, 3049.9, 2981.4, 2934.6,
1727.7, 1629.4, 1180.4. HRMS: calculated for C_{22}H_{28}NO_{5}S ([M-H])^{+} = 418.1688; found: 418.1678.

3-(2-Bromoethyl)-cyclohex-3-ene-1R,2S-diol (280):

![Chemical Structure](image)

Approximately 90 g (0.41 mol) of crude diene diol 11 was dissolved in methanol (500 mL) in three-neck round-bottom flask equipped with mechanical stirrer and bubbler. The solution was cooled to 0°C in an ice bath, and then PAD (135 g, 0.70 mol, 1.7 eq.) portion wise was added under vigorous stirring. To the yellow suspension that resulted was drop wise added glacial acetic acid (96.1 mL, 100.9 g, 1.68 mol, 2.4 eq. to PAD) in methanol (400 mL) over 4 hours while maintaining the temperature of the reaction mixture bellow 0°C. Upon completion of the addition of acetic acid the reaction mixture was allowed to warm up to r.t. overnight. TLC next day showed traces of unreacted material, therefore more PAD (12 g) was added to the cooled reaction mixture to complete reduction. After 3 hours of stirring a TLC indicated complete conversion, so the reaction mixture was concentrated under reduced pressure. Water (300 mL) and sat. aq. solution of sodium bicarbonate was added to residue. Aqueous mixture was extracted with ethyl acetate (7 x 400 mL). Organic layers were dried over MgSO_{4}, filtered and evaporated to dryness. The residue was taken up in ethyl acetate (100 mL) and treated with hexanes (1000 mL). The solution was allowed to stand in the freezer for an hour. The crystals were collected by filtration and dried under vacuum to yield 46.1 g (52%) of 280 as yellow crystals; m.p. 93-94°C (Hex/EtOAc), lit.\textsuperscript{51} m.p. 95-96°C (Hex/CH\textsubscript{2}Cl\textsubscript{2}); \(\alpha_d^{25} \approx 75.6^\circ \) (c = 1.03, CHCl\textsubscript{3}), lit.\textsuperscript{51} \(\alpha_d^{25} \approx 63.6^\circ \) (c = 1.02, CHCl\textsubscript{3}). \textsuperscript{1}H-NMR spectra agreed with the reported data.
(2S, 3R)-Dibenzoyloxy-1-(2-bromoethyl)-cyclohex-1-ene (281):

3-(2-Bromoethyl)-cyclohex-3-ene-1R,2S-diol 280 (20 g, 90.4 mmol) was dissolved in dry methylene chloride (500 mL) then benzoic acid (29.8 g, 244.4 mmol, 2.7 eq.) was added and the reaction mixture was cooled to 0°C. DCC (50.42 g, 244.4 mmol, 2.7 eq.) was added along with a catalytic amount of DMAP. The suspension was stirred under argon atmosphere overnight. Next day more DCC (5.6 g, 27 mmol, 0.3 eq.), benzoic acid (3.32 g, 27 mmol, 0.3 eq.) and DMAP was added. The reaction mixture was stirred for two more days, then the dicyclohexyl urea was filtered off and the filtrate was evaporated to dryness. The residue was triturated with diethyl ether (500 mL), the solid was filtered and the filtrate evaporated under reduced pressure. Purification of the crude residue by column chromatography (silica, Hex:EtOAc 99:1, 97:3, 95:5) yielded 36.9 g (95%) of yellow oil. Rf (hexanes-EtOAc, 2:1)= 0.68; 1H-NMR: δ: 8.05 and 7.85 (2d, 4 H, J= 8.0 Hz), 7.30-7.58 (m, 6 H), 5.94 (t, 1 H, J= 3.9 Hz), 5.91 (d, 1 H, J=3.4 Hz), 5.38 (dt, 1 H, J1= 11.2 Hz, J2= 3.7 Hz), 3.49 (t, 2 H, J= 7.1 Hz), 2.00-2.70 (m, 6 H) agreed with the data reported in the literature.10

3-(2-(5,6-Dibenzoyloxy-(5S,6R)-1-cyclohexenyl)ethyl)[1,3]oxazolidine-2,4-dione (156):

Dibenzoate 281 (30.8 g, 71.8 mmol) was dissolved in dry THF (300 mL), then oxazolidine-1,4-dione95 (7.98 g, 79.0 mmol, 1.10 eq.) was added followed by drop wise addition of tetramethylguanidine (10.4 mL, 9.51 g, 82.6 mmol, 1.15 eq.). The cloudy
reaction mixture was heated to reflux under argon atmosphere for 4 days, then more of oxazolidine-1,4-dione (0.72 g, 7.18 mmol, 0.10 eq.) and tetramethylguanidine (0.9 mL, 0.83 g, 7.18 mmol, 0.10 eq.) were added and the reaction mixture was refluxed for one more day. After cooling to r.t. the solid was filtered and the filtrate evaporated to dryness with silica. Purification by column chromatography (silica, Hex:EtOAc 70:30 then 60:40) yielded 28.2 g (79%) of white solid; m.p. 78-80 °C, lit. m.p. 54-54.5 °C (Hex/EtOAc); α<sub>D</sub><sup>25</sup> – 101.2° (c= 0.40, MeOH), lit.<sup>10</sup> α<sub>D</sub><sup>27</sup> – 124.9° (c= 0.43, MeOH). <sup>1</sup>H-NMR: δ: 8.06 and 7.85 (2 d, 4 H, J= 7.1 Hz), 7.57 (m, 1 H), 7.45 (m, 3 H), 7.29 (m, 2 H), 6.00 (s, 1 H), 5.82 (s, 1 H), 5.37 (dt, 1 H, J<sub>1</sub>= 10.7 Hz, J<sub>2</sub>= 3.7 Hz), 4.66 (s, 2 H), 3.74 (m, 2 H), 2.00-2.50 (m, 6 H), 1.20-1.40 (m, 2 H). <sup>1</sup>H-NMR spectra agreed with the reported data.<sup>10</sup>

1,6-Dibenzoyloxy-2-[2-(4-hydroxy-2-oxo-oxazolidin-3-yl)-ethyl]-cyclohex-2-ene (19):

Oxazolidine-1,4-dione 156 (11.1 g, 24.9 mmol) was dissolved in methanol (240 mL) and THF (40 mL). The solution was cooled to 0°C and sodium borohydride (9.47 g, 249 mmol, 10 eq.) was carefully added in small portions with vigorous stirring. After 40 minutes, when TLC indicated complete conversion, acetone (50 mL) was added to quench the excess of sodium borohydride. The reaction mixture was then evaporated to dryness, and water (200 mL) was added to the residue. Extraction of the residue with methylene chloride (3 x 200 mL) followed. The organic layers were washed with brine (30 mL) and dried over magnesium sulfate. The drying agent was filtered and the filtrate evaporated to dryness and dried under vacuum to yield 11.1 g of the crude product, which was used for next step as reported previously.<sup>10</sup>
Heminal 19 (1.5 g, 3.3 mmol) was dissolved in dry methylene chloride (50 mL) and the solution was cooled to 0°C. Then aluminum chloride (4.43 g, 33.2 mmol, 10 eq.), was then portion-wise added and the reaction mixture was stirred overnight under argon atmosphere. After 20 hours of stirring at r.t. the dark brown reaction mixture was cooled in an ice bath and carefully quenched by slow addition of water (50 mL). The organic layer was separated and the aqueous phase was extracted with methylene chloride (3 x 50 mL), the combined organic layers were washed with brine (20 mL) and dried over sodium sulfate. Filtration and evaporation yielded a brown oil which was purified by column chromatography (silica, Hex:EtOAc 70:30, 60:40).

*Anti* chloride 282a (0.246 g, 16%) was isolated along with *syn* chloride 283a (0.620 g, 40%). 1H-NMR spectra were in agreement with previously reported data.10

6a-Hydroxy-7,8-dibenzoyloxy-(6aR, 7R, 8S, 10aR, 10bS)-perhydro[1,3]oxazolo[4,3-a]isoquinoline-3-one (284):

BF₃·Et₂O (0.32 mL, 0.36 g, 2.55 mmol, 5 eq.) was added to cooled (0°C) solution of the heminal 19 (0.23 g, 0.51 mmol) in dry methylene chloride (20 mL). The reaction mixture was then allowed to slowly warm up to r.t. under argon atmosphere overnight. After 19 hours of stirring at r.t. the reaction mixture was quenched with saturated solution of sodium bicarbonate (10 mL). The organic phase was separated and the aqueous phase
was extracted with methylene chloride (5 x 20 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous sodium sulfate. Filtration, evaporation and column chromatography (silica, Hex:EtOAc 50:50) yielded 0.125 g (54%) of white solid. $^1$H-NMR: $\delta$: 8.01 and 7.94 (2d, 4 H, $J = 7.2$ Hz), 7.62 (t, 1 H, $J = 7.5$ Hz), 7.55 (t, 1 H, $J = 7.5$ Hz), 7.49 (t, 1 H, $J = 8.0$ Hz), 7.38 (t, 1 H, $J = 8.0$ Hz), 5.77 (dd, 1 H, $J_1 = 6.2$ Hz, $J_2 = 3.7$ Hz), 5.53 (d, 1 H, $J = 3.7$ Hz), 4.48 (t, 1 H, $J = 8.5$ Hz), 4.04 (dd, 1 H, $J_1 = 8.8$ Hz, $J_2 = 5.1$ Hz), 3.92 (ddd, 1 H, $J_1 = 12.0$ Hz, $J_2 = 8.0$ Hz, $J_3 = 5.0$ Hz), 3.87 (ddd, 1 H, $J_1 = 14.1$ Hz, $J_2 = 5.4$ Hz, $J_3 = 1.4$ Hz), 3.09 (dt, 1 H, $J_1 = 13.7$ Hz, $J_2 = 3.0$ Hz), 2.45 (m, 1 H), 2.13(m, 1 H), 1.95 (m, 3 H), 1.55 (dt, 1 H, $J_1 = 13.6$ Hz, $J_2 = 5.7$ Hz), 1.42 (bd, 1 H, $J = 14.8$ Hz). $^1$H-NMR data agreed with published data.$^{10}$

7R,8S-Dibenzoyloxy-6a-bromo-3-oxo-decahydro-oxazolo[4,3-a]isoquinolines (282b and 283b):

Heminal 19 (0.29 g, 0.06 mmol) was dissolved in dry methylene chloride (4 mL). The solution was cooled to 0°C then aluminum bromide (4.7 mL of 1M solution in CH$_2$Br$_2$, 1.25 g, 4.7 mmol, 7 eq.) was portion-wise added. The reaction mixture was then stirred overnight under argon atmosphere. After 22 hours of stirring at r.t. the dark reaction mixture was cooled in ice bath and carefully quenched by slow addition of water (20 mL). The organic layer was separated and the aqueous phase was extracted with methylene chloride (7 x 20 mL). The combined organic layers were washed with brine (10 mL) and dried over sodium sulfate. Filtration and evaporation yielded a brown oil which was purified by column chromatography (silica, Hex:EtOAc 7:3, 6:4, 5:5). Anti bromide 282b was isolated (0.032 g, 9%) along with syn bromide 283b (0.077 g, 23%) as
yellow oils. Structure assignment was done by comparison with spectra of the corresponding chlorides.  

\[(7R,8S)\text{-Dibenzoyloxy-1,5,6,7,8,9,10,10b-octahydro-oxazolo[4,3-a]isoquinolin-3-one (285)}: \]

To a solution of purified anti chloride 282a (0.30 g, 0.64 mmol) in dry DMSO (3 mL) was added distilled DBU (0.29 mL, 1.92 mmol, 3 eq., 0.29 g) and the solution was heated to 70 °C under argon atmosphere for 2 days. After cooling to r.t. water (10 mL) was added and the aqueous phase was extracted with ethyl ether (12 x 20 mL). The combined organic layers were then washed with water (20 x 1 mL), brine (5 mL) and dried over anhydrous sodium sulfate. After filtration the filtrate was evaporated to yield 0.22 g of the crude product, which was then purified by column chromatography (silica, Hex:EtOAc 5:5) to yield 0.13 g (45%) of yellow solid. $^1$H-NMR: δ: 7.94 (d, 2 H, $J$= 8.3 Hz), 7.83 (d, 2 H, $J$= 8.6 Hz), 7.49 (m, 2 H), 7.35 (m, 4 H), 5.79 (s, 1 H), 5.50 (m, 1 H), 4.54 (t, 1 H, $J$= 8.8 Hz), 4.31 (t, 1 H, $J$= 7.8 Hz), 4.06 (m, 1 H), 3.95 (dd, 1 H, $J$1= 13.2 Hz, $J_2= 6.6$ Hz), 3.02 (td, 1 H, $J_1= 13.2$ Hz, $J_2= 4.4$ Hz), 2.48 (s, 1 H), 1.89-2.26 (m, 5 H). $^1$H-NMR data agreed with published data.  

\[(7R,8S)\text{-Dibenzoyloxy-1,5,6,8,9,10,10a,10b-octahydro-oxazolo[4,3-a]isoquinolin-3-one (286)}: \]

To a solution of syn chloride 283a (0.3 g, 0.64 mmol) in dry DMSO (3 mL) was added DBU (0.29 mL, 0.292 g, 1.92 mmol, 3 eq.). The reaction mixture was then heated
under argon atmosphere to 70°C for 3 days. After cooling to ambient temperature, water (10 mL) was added, followed by extraction with ether (12 x 20 mL). The combined ether layers were washed with water (20 x 1 mL), brine (5 mL) and dried over anhydrous sodium sulfate. After filtration and removal of solvent under reduced pressure yellow oil (0.15 g) was obtained, which was further purified by column chromatography (silica, Hex:EtOAc 1:1) to yield 0.113 g of a green oil. HPLC analysis (CH$_3$CN:HO 65:35, Prodigy ODS column) determined the oil to be a mixture of product 286 and unreacted starting material 283a. Compound 286 was isolated by preparative HPLC (0.048 g, oil, 17%). Approx. 0.017 g (16%) of white crystalline syn chloride 283a was isolated as well.

286: $^1$H-NMR (300 MHz) $\delta$ (ppm): 8.00 (d, 2 H, $J$ = 7.5 Hz), 7.97 (d, 2 H, $J$ = 7.5 Hz), 7.55 (m, 2 H), 7.40 (m, 4 H), 5.80 (t, 1 H, $J$ = 4.8 Hz), 4.48 (t, 1 H, $J$ = 8.4 Hz), 4.13 (dd, 1 H, $J_1$ = 4.8 Hz, $J_2$ = 9.2 Hz), 3.95 (dd, 1 H, $J_1$ = 5.4 Hz, $J_2$ = 13.2 Hz), 3.62 (m, 1 H), 2.91(dt, 1 H, $J_1$ = 3.6 Hz, $J_2$ = 12.9 Hz), 2.57 (dd, 1H, $J_1$ = 2.4 Hz, $J_2$ = 13.8 Hz), 2.38 (m, 1 H), 2.24 (m, 1 H), 2.11 (m, 1 H), 2.03 (m, 2 H), 1.49 (m, 1 H). $^{13}$C-NMR $\delta$: 166.1, 164.9, 156.9, 140.9, 133.9, 133.3, 130.3, 130.0, 129.8, 128.9, 128.7, 128.5, 128.0, 68.1, 66.7, 58.6, 41.2, 41.0, 26.4, 26.3, 20.2. IR (film): $\nu$ (cm$^{-1}$): 3063, 2926, 2854, 1755, 1721, 1270. HRMS (FAB): calculated for C$_{27}$H$_{24}$N$_2$O$_6$ ([M+H]$^+$): 434.1604, found: 434.1654.

Elimination of Syn/Anti Chlorides Mixture:

(7R,8S)-Dibenzoyloxy-1,5,6,7,8,9,10,10b-octahydro-oxazolo[4,3-a]isoquinolin-3-one (285):

A crude mixture of chlorides 282a and 283a (8.65 g, 18.4 mmol) was dissolved in dry DMSO (80 mL) and DBU (14.3 mL, 92.0 mmol, 5 eq. 14.01 g). The solution was
heated to 100°C under argon atmosphere for 3 days. After cooling to r.t. water (200 mL) was added and the aqueous phase was extracted with ethyl acetate (5 x 500 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous magnesium sulfate. After filtration the filtrate was evaporated with silica and the crude product was purified by column chromatography (silica, Hex:EtOAc 6:4, 5:5, 4:6) to yield 1.16 g (15%) of 285 (yellow solid).

Elimination of Anti bromide 282b:

To a solution of purified anti bromide 282b (0.032 g, 0.062 mmol) in dry DMSO (0.3 mL) was added distilled DBU (0.029 mL, 0.19 mmol, 3 eq., 0.029 g). The solution was heated to 70°C under argon atmosphere for one day. After cooling to r.t the mixture was treated with water (3 mL) and the aqueous phase was extracted with ethyl ether (4 x 20 mL). The combined organic layers were washed with water (10 x 1 mL), brine (4 mL) and dried over anhydrous magnesium sulfate. After filtration the filtrate was evaporated to yield 0.011 g (41%) of the crude product 285 of high purity (92% by HPLC).

Elimination of Syn Bromide 283b:

To a solution of purified syn bromide 283b (0.077 g, 0.15 mmol) in dry DMSO (0.4 mL) was added distilled DBU (0.069 mL, 0.45 mmol, 3 eq., 0.069 g). The solution was heated to 70°C under argon atmosphere for one day. After cooling to r.t. the reaction mixture was treated with water (4 mL) and the aqueous phase was extracted with ethyl ether (5 x 20 mL). The combined organic layers were washed with water (10 x 1 mL), brine (6 mL) and dried over anhydrous magnesium sulfate. After filtration the filtrate was evaporated to yield 0.008 g (12%) of the crude product which was shown to be
mixture of two products 285 and 286 isolated previously (HPLC, \textsuperscript{1}H-NMR) in 1:3 ratio (HPLC).

Elimination of alcohol 284:

To a solution of alcohol 284 (0.058 g, 0.13 mmol) in dry benzene (3 mL) was added Burgess’s reagent (0.061 g, 0.026 mmol, 2.0 eq.). The reaction mixture was heated to 60°C under argon atmosphere for 4 days. After the reaction mixture cooled to r.t., benzene/ethyl acetate (20 mL/5 mL) was added and the organic layer was then washed with water (3 x 2 mL) and dried over anhydrous sodium sulfate. The aqueous layers, containing white solid, were back extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate. The organic extracts were combined and evaporated to yield 0.060 g of the crude product. Column chromatography (silica, Hex:EtOAc 6:4 then 5:5) yielded product of ring cleavage 289 (0.003 g, 5%), trisubstituted olefin 286 (0.011 g, 20%) and tetrasubstituted olefin 285 (0.009 g, 16%).

3-[2-(5R, 6S-Dibenzoyloxy-cyclohex-1-enyl)-ethyl]-3H-oxazol-2-one (289):

\[ \text{3-[2-(5R, 6S-Dibenzoyloxy-cyclohex-1-enyl)-ethyl]-3H-oxazol-2-one (289):} \]

\[ \begin{align*}
\text{OBz} & \quad \text{BzO} \\
\text{289} & \quad \text{N} \\
\end{align*} \]

\textsuperscript{1}H-NMR: \( \delta \): 8.05 (d, 2 H, \( J = 8.2 \) Hz), 7.85 (d, 2 H, \( J = 8.2 \) Hz), 7.59 (t, 1 H, \( J = 7.4 \) Hz), 7.42 (m, 3 H), 7.27(m, 2 H), 6.74 (d, 1 H, \( J = 1.9 \) Hz), 6.50 (d, 1 H, \( J = 1.9 \) Hz), 5.95 (d, 1 H, \( J = 3.6 \) Hz), 5.87 (s, 1 H), 5.36 (dt, 1 H, \( J_1 = 11.0 \) Hz, \( J_2 = 3.6 \) Hz), 3.72 (m, 2 H), 2.00-2.50 (m, 6 H). \textsuperscript{1}H-NMR data agreed with published data.\textsuperscript{95}
Burgess’ adduct 288:

To stirred solution of hydroxy isoquinoline 284 (0.022 g, 0.05 mmol) in dry benzene (5 mL) was added Burgess’ reagent (0.035 g, 0.15 mmol, 3 eq.). The reaction mixture was stirred at room temperature under argon atmosphere for 3 days (monitored by TLC). Then silica was added and the solvent was removed under reduced pressure. Product 288 was purified by column chromatography (SiO₂, CH₂Cl₂:MeOH 9:1) to yield 0.028 g (97%) of semisolid. 

\(^1\)H-NMR (300 MHz) \(\delta\) (ppm): 8.20 (d, 2 H, \(J= 7.5\) Hz), 7.99 (d, 2 H, \(J= 7.5\) Hz), 7.53 (m, 4 H), 7.35 (t, 2 H, \(J= 7.5\) Hz), 5.70 (s, 1 H), 5.61 (d, 1 H, \(J= 3.6\) Hz), 4.51 (t, 1 H, \(J= 8.4\) Hz), 4.12 (dd, 2 H, \(J_1= 7.2\) Hz, \(J_2= 14.4\) Hz), 4.00 (m, 2 H), 3.53 (s, 3 H), 3.15 (t, 1 H, \(J= 12.9\) Hz), 2.88 (d, 1 H, \(J= 10.2\) Hz), 2.63 (m, 2 H), 2.31 (d, 2 H, \(J= 13.2\) Hz), 1.99 (m, 1 H), 1.47 (d, 1 H, \(J= 13.8\) Hz). 

\(^1^3\)C-NMR: \(\delta\): 171.4, 166.3, 165.7, 157.0, 150.7, 134.0, 134.4, 130.4, 130.3, 130.0, 128.7, 128.58, 93.4, 68.4, 67.2, 66.9, 60.7, 53.8, 53.7, 46.4, 43.6, 38.4, 28.8, 24.4, 21.3, 16.5, 14.4. IR (film): \(v\) (cm\(^{-1}\)): 3071, 2956, 2935, 1759, 1723, 1367, 1279, 1171.

2R,3-Dibromo-cyclohex-3S-enyl acetate\(^1\) (292):

To an ice cold solution of bromodiol 291 (0.25 g, 1.3 mmol) in dry acetonitrile (5 mL) was added drop wise \(\alpha\)-acetoxyisobutyryl bromide (0.38 mL, 0.54 g, 2.0 eq.) using glass pipette. The yellow reaction mixture was stirred at 0°C under argon atmosphere for
one hour, then allowed to slowly warm to room temperature and stirred overnight (approx. 15 h at r.t.). To the orange reaction mixture was added water (2 mL). The volume of liquid was reduced at the rotary evaporator to ca. 3 mL. Ethyl acetate (50 mL) was added and after separation of the aqueous layer, the dark orange organic layer was washed with a saturated solution of sodium bicarbonate (2 x 5 mL, discolors), water (5 mL), brine (5 mL) and dried over anhydrous sodium sulfate. After filtration, removal of solvent under reduced pressure and drying under vacuum, product 292 was obtained as orange oil (0.357 g, 92%). \( \text{R}_f \text{(Hex:EtOAc 9:1)} = 0.42 \), \( \text{H-NMR (300 MHz)} \) \( \delta \) (ppm): 6.27 (dd, 1 H, \( J = 2.7 \) Hz, 4.8 Hz), 5.36 (t, 1H, 2.4 Hz), 4.54 (s, 1H), 2.42 (m, 1H), 2.27 (m, 2H), 2.09 (s, 3H), 1.95 (m, 1H). \( \text{C-NMR} \) \( \delta \): 170.2, 133.8, 119.4, 72.9, 50.5, 23.5, 21.3, 20.0. \( \text{IR (film): } \nu \text{(cm}^{-1}) = 2963, 2935, 1742, 1230. \)

(1S,6S)-2-Bromo-7-oxa-bicyclo[4.1.0]hept-2-ene\(^{11} \) (30):

\[
\begin{array}{c}
\text{Br} \\
\text{30} \\
\end{array}
\]

2R,3-Dibromo-cyclohex-3S-enyl acetate 292 (0.25 g, 0.84 mmol) was dissolved in dry tetrahydrofuran (2 mL) under argon atmosphere. The solution was cooled down to 0 °C and then a freshly prepared solution of sodium methoxide in absolute methanol (ca. 1.08 M, 0.9 mL, 1.0 mmol, 1.2 eq.) was drop wise added with stirring at 0°C for 1 hour (monitored by TLC). Then saturated solution of ammonium chloride (1 mL) was added and a precipitate formed. The reaction mixture was diluted with water (2 mL) and extracted with ether (5 x 10 mL). The combined ether layers were washed with water (10 x 0.5 mL), brine (5 mL) and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under stream of argon. Product 30 was obtained as a colorless oil (ca. 0.120g, 82%).\(^{11} \) \( \text{R}_f \text{(Hex:EtOAc 9:1)} = 0.52 \), \( \text{H-NMR} \)
(300 MHz) δ (ppm): 6.20 (m, 1 H), 3.55 (bs, 1 H), 3.49 (dd, 1 H, J₁ = 2.4 Hz, J₂ = 4.4 Hz), 2.28 (m, 1 H), 2.08 (m, 2 H), 1.67 (td, 1 H, J₁ = 9.3 Hz, J₂ = 14.7 Hz). ¹³C-NMR δ: 131.7, 116.2, 56.6, 53.8, 22.6, 20.5. IR (film): ν (cm⁻¹): 2994, 2936, 823.

3-Bromo-2R-(cyclohex-2-enyloxy)-cyclohex-3R-enol (294):

Epoxide 30 (0.14 g, 0.8 mmol) was dissolved in dry methylene chloride (2 mL) and solution was cooled to 0°C. Then rac-2-cyclohexenol (0.8 mmol, 80 μL, 0.079 g, 1.0 eq.) was added, followed by drop-wise addition of a stock solution of the BF₃·Et₂O in methylene chloride (0.8 M, 100 μL, 0.08 mmol, 0.1 eq.). The reaction mixture was stirred at 0°C for one hour and then allowed to slowly warm to r.t. Saturated sodium bicarbonate solution (1 mL) and water (4 mL) were added, and after separation of the organic layer, the aqueous phase was extracted with methylene chloride (6 × 10 mL). The combined organic layers were washed with water (2 mL), brine (4 mL) and dried over anhydrous magnesium sulfate. Filtration, evaporation of the solvent under a stream of argon and column chromatography (silica, Hex:EtOAc 95:5, 90:10, 80:20) gave product 294 (0.055 g, 25%) as colorless oil. Rf (Hex:EtOAc 50:50) = 0.65; αD²⁹ +70.13° (c= 0.0050 g/mL, CHCl₃), ¹H-NMR: δ (ppm): 6.19 (m, 1 H), 5.90 (m, 1 H), 5.80 (m, 1 H), 4.25 and 4.13 (m, 1 H), 3.95 (m, 1 H), 3.85 (bd, 1 H, J= 5.1 Hz), 2.26 to 1.55 (m, 10 H). ¹³C-NMR δ: 132.7, 132.3, 132.2, 131.2, 127.9, 127.3, 121.8, 121.5, 81.4, 80.4, 74.8, 73.2, 71.1, 70.5, 29.4, 28.7, 25.7, 25.4, 25.2, 25.1, 24.3, 24.0, 19.2, 18.8. IR (film): ν (cm⁻¹): 3417.0, 3027.2, 2932.3, 1066.5. HRMS: calculated for C₁₂H₁₈O₂Br([M+H]+):
273.0490 found 273.0403. CH analysis calculated: C 52.76%, H 6.27% found C 52.75% and H 6.46%.

3-Bromo-2-(cyclohex-2-enyloxy)-cyclohex-2-enone (295):

\[
\begin{array}{c}
\text{Br} \\
\text{O} \\
\text{O} \\
\text{295}
\end{array}
\]

To a cooled (-70°C) solution of oxalyl chloride (143 µL, 0.204 g, 1.61 mmol 1.25 eq.) in dry methylene chloride (5 mL) was added drop-wise dry DMSO (228 µL, 0.251 g, 3.22 mmol, 2.5 eq.). The reaction mixture was then stirred for 20 minutes at -70°C and then a cold solution of 293 (0.350 g, 1.290 mmol) in methylene chloride (5 mL) was added. After 25 additional minutes of stirring, triethyl amine (1.08 mL, 7.72 mmol, 6 eq.) was added and reaction mixture was allowed to slowly warm to r.t. overnight. Water and saturated aq. sodium bicarbonate (5 mL/ 5 mL) was added, and after separation of the layers, the aqueous phase was extracted with methylene chloride (6 x 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate. Filtration, and evaporation of the solvent under reduced pressure and column chromatography (silica, Hex:EtOAc 95:5, 90:10) gave product (0.220 g, 63%) as colorless oil. Rf (Hex:EtOAc 50:50) = 0.78; \(^1\)H-NMR: δ (ppm): 5.89 (m, 2 H), 4.68 (m, 1 H), 2.93 (t, 1 H, J= 6.0 Hz), 2.53 (t, 1 H, J= 6.3 Hz), 2.07 to 1.77 (m, 8 H). \(^{13}\)C-NMR δ: 192.6, 149.5, 135.5, 132.2, 126.8, 75.0, 38.8, 36.3, 29.1, 25.2, 22.9, 18.8. IR (film): ν (cm\(^{-1}\)): 3031.2, 2930.5, 1683.0, 1153.7. HRMS: calculated for C\(_{12}\)H\(_{16}\)O\(_2\)Br ([M+H]\(^{+}\)): 271.0334 found 271.0271, C\(_{12}\)H\(_{16}\)O\(_2^{81}\)Br ([M+H]\(^{+}\)): 273.0315 found 273.0299.
Alcohol 293 (2.65 g, 9.68 mmol) was dissolved in dry dimethylformamide (17 mL), then imidazole (0.92 g, 13.6 mmol, 1.4 eq.) and thexyl chloride (2.67 mL, 2.42 g, 13.6 mmol, 1.4 eq.) were added under an argon atmosphere. The reaction mixture was then stirred at ambient temperature for 21 hours. Reaction was quenched with water (50 mL) and the aqueous phase was extracted with ether (4 x 100 mL), the combined organic layers were washed with brine (100 mL) and dried over anhydrous magnesium sulfate. After filtration and evaporation of solvent under reduced pressure the residue was purified by column chromatography (SiO₂, Hex:EtOAc 98:2, 80:20 then 70:30). The product 296 was obtained as an oil (2.56 g, 64%). \( R_f \) (Hex:EtOAc 98:2) = 0.25; \( \alpha_D^{29} +108.96^\circ \) (c= 0.010 g/mL, CHCl₃), \(^1\)H-NMR \( \delta \) (ppm): 6.21 (m, 1 H), 5.90 (m, 1 H), 5.72 (m, 1 H), 4.18 and 4.03 (m, 1 H), 3.66 (m, 1 H), 2.26 to 1.57 (m, 10 H), 0.89, 0.86 and 0.83 (3s, 12 H), 0.13 and 0.10 (s, 6 H). \(^1^3\)C-NMR: \( \delta \): 133.2, 132.8, 131.9, 130.8, 128.2, 127.9, 121.0, 120.8, 80.8, 80.1, 74.7, 72.8, 70.6, 69.9, 34.5, 30.1, 28.5, 25.4, 25.3, 25.0, 24.3, 23.7, 23.6, 20.5, 20.4, 19.6, 18.8, 18.7, -2.5, -2.6, -2.7. IR (film): \( \nu \) (cm\(^{-1}\)): 3028.0, 2950.1, 1080.3. CH analysis calculated: C 57.82%, H 8.49% found C 57.32% and H 8.36%.
(2,3,4a,5a,6,7,8,9,9a-Decahydro-dibenzofuran-4-yloxy)-dimethyl-(1,1,2-trimethyl-propyl)-silane (297 and 298)

Vinyl bromide 296 (1.64 g, 3.96 mmol) was dissolved in dry benzene (50 mL) and the solution was degassed under stream of argon for 15 minutes, then n-Bu₃SnH (2.13 mL, 2.30 g, 7.92 mmol, 2.0 eq.) was added via glass pipette followed by AIBN (0.13 g, 0.79 mmol, 0.2 eq.). The reaction mixture was heated under argon atmosphere for four hours then more AIBN (0.065 g, 0.39 mmol, 0.1 eq.) was added and the solution was refluxed for 14 hours. After cooling, the benzene was removed under reduced pressure and the residue was purified by column chromatography (SiO₂, CH₂Cl₂:Hex, 2:3, 1:1 then 3:2). The products were obtained as colorless oils (0.86 g, 65% total yield).

297: \( R_f (\text{Hex:EtOAc } 98:2) = 0.28, \alpha_D^{29} +3.49^\circ (c= 0.0100 \text{ g/mL, CHCl}_3) \),

\( ^1H\)-NMR \( \delta (\text{ppm}) \): 5.36 (m, 1 H), 4.22 (m, 1 H), 3.79 (d, 1 H, \( J = 3.3 \text{ Hz} \)), 3.56 (m, 1 H), 2.29 (m, 1 H), 2.15 (m, 2 H), 1.80 (m, 1 H), 1.75 to 1.26 (m, 8 H). \( ^{13}C\)-NMR: \( \delta \): 144.0, 116.9, 80.7, 75.4, 72.7, 43.7, 34.4, 29.6, 28.5, 27.3, 27.0, 25.6, 25.3, 24.3, 20.6, 20.5, 20.2, 18.9, 18.8, 17.5, 13.8, -2.0, -2.8. IR (film): \( \nu (\text{cm}^{-1}) \): 2932.7, 1104.3, HRMS: calculated for C\(_{14}\)H\(_{23}\)O\(_2\)Si ([M-C\(_6\)H\(_{13}\)]\(^+\)): 251.1467 found: 251.1471. CH analysis calculated: C 71.37%, H 10.57% found C 71.13% and H 10.57%.

298: \( R_f (\text{Hex:EtOAc } 98:2) = 0.23, \alpha_D^{29} +0.81^\circ (c= 0.0070 \text{ g/mL, CHCl}_3) \),

\( ^1H\)-NMR: \( \delta (\text{ppm}) \): 5.31 (m, 1 H), 4.04 (m, 2 H), 3.51 (m, 1 H), 2.78 (m, 1 H), 2.22 (m, 2 H), 1.91 to 1.11 (m, 10 H), 0.88 (m, 12 H), 0.16 and 0.13 (s, 6 H). \( ^{13}C\)-NMR: \( \delta \): 139.4, 116.9, 82.4, 76.8, 74.6, 40.5, 34.4, 31.3, 29.9, 28.5, 27.0, 25.7, 25.1, 24.7, 23.2, 21.4,
20.6, 20.5, 20.2, 18.9, 18.8, 17.5, 13.8, -2.0, -2.6. IR (film): ν (cm⁻¹): 3038.4, 2932.3, 1116.8, 1090.6. HRMS: calculated for C₁₄H₂₃O₂Si ([M-C₆H₁₃]⁺): 251.1467 found 251.1472. CH analysis calculated: C 71.37%, H 10.57% found C 70.66% and H 10.79%.

**Dimethyl-(2,3,4,4a,5a,6,7,9a-octahydro-dibenzofuran-4-yloxy)-(1,1,2-trimethyl-propyl)-silane (299 and 300):**

![Diagram of 299 and 300]

In thick-walled threaded tube containing the vinyl bromide 296 (0.163 g, 0.38 mmol) was dissolved in dry toluene (3 mL) was added Pd(PPh₃)₄ (0.027 g, 0.023 mmol, 0.17 eq.) and N,N,N',N'-tetramethylnaphtalene-1,4-diamine (0.100 g, 0.47 mmol, 1.2 eq.). The solution was degassed under a mild stream of argon for 10 minutes. The tube was then capped and the reaction mixture was heated to 110°C on an oil bath for 2 days. After cooling to r.t. TLC analysis revealed the presence of a substantial amount of starting material. The reaction mixture was therefore heated to 130°C for 2 days and 160°C for 3 more days. After cooling to r.t. the reaction mixture was filtered through short celite plug and silica was added to the filtrate. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica, Hex:EtOAc 99:1) to yield 0.109 g of product mixture, which was further purified by preparative TLC (silica, Hex:EtOAc 99:1, eluted three times) to yield product 300 as an off white solid (0.019 g, 15%) and 0.020 g of oil, which turned out to be mixture of the proton sponge and 299. Product 299 was isolated by taking up its mixture with amine in ether (50 mL) and washing it with 1M HCl (7 x 3 mL), sat. NaHCO₃ (4 mL), water (4 mL) and brine (4
mL). After drying the ether solution over magnesium sulfate, filtration and removal of solvent under reduced pressure, product 299 was obtained as a yellow oil (0.009 g, 7%).

300: \( R_f (\text{Hex:EtOAc } 98:2) = 0.32 \); \( \alpha_D^{29} + 100.43^\circ \) (c = 0.0100 g/mL, CHCl₃), \( ^1H\)-NMR: \( \delta \) (ppm): 5.78 (m, 1 H), 5.44 (m, 2 H), 4.19 (m, 2 H), 4.04 (dd, 1 H, \( J_1 = 7.5 \) Hz, \( J_2 = 1.8 \) Hz), 3.53 (m, 1 H), 3.07 (bs, 1 H), 2.14 (m, 2 H), 1.97 to 1.45 (m, 6 H), 0.85 (m, 13 H), 0.16 and 0.12 (s, 6 H). \( ^13C\)-NMR: \( \delta \): 140.0, 128.4, 126.6, 118.4, 81.0, 74.8, 73.6, 43.7, 34.4, 29.6, 26.0, 25.8, 25.2, 20.6, 20.5, 19.4, 18.9, 18.8, -2.1, -2.6. HRMS: calculated for \( C_{14}H_{21}O_2Si([M-C_6H_{13}]^+) \): 249.1310 found 249.1306 (M-H)\(^+\) (m/z = 334) was observed in LR spectra.

299: \( R_f (\text{Hex:EtOAc } 98:2) = 0.27 \); \( ^1H\)-NMR: \( \delta \) (ppm): 5.74 (m, 2 H), 5.31 (m, 1 H), 4.08 (bd, 1 H, \( J = 6.6 \) Hz), 3.45 (m, 1 H), 3.15 (m, 1 H), 2.14 (m, 2 H), 2.05 to 1.40 (m, 6 H), 0.90-0.85 (m, 13 H), 0.16 and 0.12 (2s, 6 H).

7S,8S-Dihydroxy-1,5,6,7,8,9,10,10b-octahydro-oxazolo[4,3-a]isoquinolin-3-one (28):

Dibenzoate 285 (1.16 g, 2.67 mmol) was dissolved in the THF (8 mL) and 1.03 M of methanolic sodium methoxide (7.8 mL, 8.03 mmol, 3 eq.) was added. The reaction mixture was then stirred at r.t. for 8 hours, then saturated ammonium chloride solution (ca. 10 drops) was added along with silica and the reaction mixture was evaporated to dryness. Column chromatography of the residue (silica, EtOAc:EtOH 9:1) yielded 0.53 g (87%) of product as a yellow oil. \( ^1H\)-NMR (300 MHz): \( \delta \) (ppm): 4.48 (t, 1 H, \( J = 8.80 \) Hz), 4.22 (s, 1 H), 4.05-3.88 (m, 3 H), 2.99 (dt, 1 H, \( J_1 = 13.2 \) Hz, \( J_2 = 4.4 \) Hz), 2.8 (bs, 2 H), 2.5 (m, 1 H), 2.15-1.75 (m, 6 H) agreed with the reported data.⁹⁵
8R-((t-Butyl-dimethyl-silanyloxy)-7S-hydroxy-1,5,6,7,8,9,10,10b-octahydro-oxazolo[4,3-a]isoquinolin-3-one\textsuperscript{8} (301):

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\text{Diol 28 (0.130 g, 0.58 mmol) was dissolved in dry methylene chloride (10 mL) under argon atmosphere, and diisopropylethylamine (201 \mu L, 0.149 g, 1.15 mmol, 2.0 eq.) was added. The reaction mixture was cooled to \(-75^\circ C\) and TBSOTf (162 \mu L, 0.183 g, 0.69 mmol, 1.2 eq.) was drop-wise added. The reaction was quenched by the addition of water (1 mL) after it had been stirring at \(-75^\circ C\) for 3 hours. After warming to r.t. the reaction mixture was diluted with brine (5 mL) and extracted with methylene chloride (5 x 10 mL). The combined organic layers were dried over magnesium sulfate. After filtration and removal of solvent under reduced pressure, the residue was purified by column chromatography (SiO\textsubscript{2}, Hex: EtOAc 50: 50, 40:60). Compound 301 was obtained as clear oil (0.077 g, 39%) along with the other mono-TBS ether, di-TBS ether and small amount of starting material. (301): }^1\text{H-NMR (300 MHz): }\delta (ppm): 4.50 (t, 1 H, J= 8.70 Hz), 4.23 (bt, 1 H, J= 8.1 Hz), 3.94 (m, 4 H), 2.99 (m, 1 H), 2.59 (m, 1 H), 2.42 (d, 1 H, J=3.3Hz), 2.05-1.65 (m, 6 H), 0.91 (s, 9 H), 0.12 (s, 6 H).
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8R-Benzylxyloxy-7S-hydroxy-1,5,6,7,8,9,10,10b-octahydro-oxazolo[4,3-a]isoquinolin-3-one (302a):

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\text{To a solution of the diol 28 (0.178 g, 0.787 mmol) in dry acetone (10 mL) was added finely ground cesium carbonate (0.769 g, 2.36 mmol, 3.0 eq.) followed by the addition of benzyl bromide (116 \mu L, 0.944 mmol, 1.2 eq.). The reaction mixture was}
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heated to reflux for 2 days. Upon cooling the solid was filtered and washed with acetone (3 x 10 mL). The solid was then taken up in a mixture of water/sat. NH₄Cl (5 mL/5 mL) and the resulting solution was extracted with ether (3 x 10 mL). The combined extracts were united with acetone filtrate and dried over magnesium sulfate. After filtration, silica was added and the solvents were removed under reduced pressure. Product was purified by the column chromatography (SiO₂, Hex:EtOAc 3:7) to yield a mixture of monobenzyl ethers (2:1 ratio by integration of the ¹H-NMR spectra) as a yellow solid (0.197 g, 79%). The major product could be obtained by the recrystallization of mixture from ethyl acetate to yield pure 302a (m.p. 179-180°C dec). Rₜ (EtOAc) = 0.48, αD²⁷ + 137.47° (c = 0.0100 g/mL, CHCl₃), ¹H-NMR: δ (ppm): 7.36 (m, 5 H), 4.74 (d, 1 H, J= 11.4 Hz), 4.58 (d, 1 H, J= 11.4 Hz), 4.47 (t, 1 H, J= 8.6 Hz), 4.21 (bt, 1 H, J= 6.6 Hz), 4.15 (m, 1 H), 3.99 (d, 1 H, J= 3.3 Hz), 3.95 (t, 1 H, J= 7.8 Hz), 2.94 (ddd, 1 H, J₁= 11.9 Hz, J₂= 9.0 Hz, J₃= 4.2 Hz), 2.56 (m, 1 H), 2.19 (m, 1 H), 2.06 (m, 1 H), 1.79 to 1.61 (m, 4 H). ¹³C-NMR: δ: 157.4, 137.8, 130.5, 128.8, 128.3, 128.2, 127.6, 78.3, 72.4, 67.2, 64.5, 55.3, 38.2, 26.1, 26.0, 21.0. IR (film): ν (cm⁻¹): 3456.1, 2924.9, 1748.5, 1060.0. HRMS: calculated for C₁₈H₂₁N0₄ ([M+H]⁺): 315.1470 found 315.1474. CH analysis calculated: C 68.55%, H 6.71% found C 68.46% and H 6.83%.

(7S-Hydroxy-3-oxo-1,5,6,7,8R,9,10,10b-octahydro-oxazolo[4,3-a]isoquinolin-8-yl) toluene-4-sulfonate (304a):

Diol 28 (0.100 g, 0.44 mmol) was dissolved in dry pyridine (1.3 mL). The solution was cooled to -3 °C, then p-toluenesulfonyl chloride (0.089 g, 0.46 mmol, 1.05 mmol)
was added, followed by addition of a catalytic amount of DMAP. The reaction mixture was stirred at -3°C for two hours under an argon atmosphere and then placed in the freezer (-7 °C) for 16 hours. The reaction progress was checked by TLC. Upon observing the presence of starting material, more p-toluenesulfonyl chloride (0.013 g, 0.066 mmol, 0.15 eq.) was added and the reaction mixture was placed back to freezer for 24 hours. The reaction mixture was then stirred at r.t. for an hour. After dilution of the mixture with toluene (ca. 5 mL) silica was added and solvents were removed under reduced pressure. The adsorbed material was purified by column chromatography (silica, 6:4 then 7:3 EtOAc:Hex) to yield 0.015 g of tosylate-chloride 303a, 0.011 g of chlorohydrin 305, 0.055 g (45% based on recovered diol) of monotosylate 304a and 0.027 g (27%) of recovered diol 28.

Monotosylate 304a: m.p.(EtOAc/Hex)= 130–132 °C (dec.), Rf (7:3 EtOAc:Hex)= 0.18, αD 26 +90.56° (c= 0.0100 g/mL, CHCl3), ¹H-NMR: δ: 7.83 (d, 2 H, J= 8.4 Hz), 7.37 (d, 2 H, J= 8.1 Hz), 4.73 (m, 1 H), 4.46 (t, 1 H, J = 8.7 Hz), 4.20 (bt, 1 H, J = 8.1 Hz), 4.08 (bs, 1 H), 3.93 (d, 1 H, J= 6.3 Hz), 3.95 (t, 1 H, J= 8.1 Hz), 2.95 (m, 1 H), 2.54 (m, 1 H), 2.45 (s, 3 H), 2.16 (m, 2 H), 1.88 (m, 2 H), 1.75 (m, 2 H). ¹³C-NMR: δ: 157.2, 145.4, 133.7, 130.2, 130.1, 129.0, 127.9, 79.7, 69.5, 67.0, 54.7, 37.9, 26.2, 23.8, 22.6, 21.9. IR (neat): ν (cm⁻¹): 3419.8, 3065.1, 1748.3, 1174.6. HRMS: calculated for C₁₈H₂₂NSO₆ ([M+H]+): 380.1168 found 380.1187. CH analysis calculated: C 56.98%, H 5.58% found C 57.33% and H 5.76%.
(7S-Hydroxy-3-oxo-1,5,6,7,8R,9,10,10b-octahydro-oxazolo[4,3-a]isoquinolin-8-yl) 2,4,5-triisopropyl-benzenesulfonate (304b):
3-Oxo-8S-(2,4,5-triisopropyl-benzenesulfonyloxy)-1,5,6,7S,8,9,10,10b-octahydro-oxazolo[4,3-a]isoquinolin-7-yl benzoate (306b):

Two solutions were prepared under argon atmosphere: A: monotosylate 303b (0.140 g, 0.280 mmol) and benzoic acid (0.052 g, 0.430 mmol, 1.5 eq.) in dry THF (5 mL) and B: n-Bu$_3$P (220 µL 0.173 g, 0.850 mmol, 3 eq.) in THF (5 mL) cooled down to 0°C. Then solution B was titrated with DEAD (135 µL, 0.149 g, 0.850 mmol, 3 eq.). After stirring at 0°C for 10 minutes, solution B was drop wise added to solution A and the reaction mixture was stirred for an hour in the ice bath, and allowed to warm to r.t. overnight. The reaction mixture was stirred at r.t. for 2 days, then silica was added and solvent was removed under reduced pressure. Column chromatography (silica, Hex: EtOAc 5:5) yielded 0.290 g of oil, which was re-dissolved in a minimal amount of ethyl acetate and excess amount of hexanes was added. White precipitate formed and was removed by filtration and dried to yield 0.145 g of solid; it was shown by H-NMR to be pure byproduct (EtO$_2$CNHNHCO$_2$Et). The mother liquor was evaporated with silica and the residue purified by column chromatography (silica, methylene chloride: MeOH 95:5) to yield desired benzoate 306b (0.071 g, 50%) as colorless oil. R$_f$ (5:5 EtOAc:Hex)= 0.49, $\alpha_D^{25}$ +156.78° (c= 0.0100 g/mL, CHCl$_3$). $^1$H-NMR: δ: 8.01 (d, 2 H, J= 6.9 Hz), 7.59 (t, 1 H, J= 7.2 Hz), 7.44 (t, 2 H, J= 8.1 Hz), 7.18 (s, 2 H), 5.35 (d, 1 , J= 3.3 Hz), 5.06 (m, 1 H), 4.54 (t, 1 H, J= 9.0 Hz), 4.33 (bt, 1 H, J = 6.9 Hz), 4.12 to 3.93 (m, 5 H), 3.07 to 2.86 (m, 2 H), 2.30 to 1.96 (m, 6 H), 1.25 (m, 18 H). $^{13}$C-NMR: δ: 165.6, 157.2,
134.2, 150.6, 133.7, 133.1, 130.3, 130.0, 129.3, 128.7, 125.6, 124.0, 75.2, 69.2, 66.7, 55.3, 38.1, 34.4, 29.9, 24.9, 24.7, 23.7, 23.7, 20.9. IR (neat): ν (cm⁻¹): 3061.3, 1760.7, 1724.9, 1261.9, 1178.2. CH analysis calculated: C 66.53%, H 6.94% found C 62.80% and H 6.78%.

3-Oxo-8S-(toluene-4-sulfonyloxy)-1,5,6,7S,8,9,10,10b-octahydro-oxazolo[4,3-a]isoquinolin-7-yl benzoate (306a):

Two solutions were prepared under argon atmosphere: A: monotosylate 304a (0.055 g, 0.145 mmol) and benzoic acid (0.027 g, 0.217 mmol, 1.5 eq.) in dry THF (3 mL) and B: n-Bu3P (112 μL, 0.088 g, 0.435 mmol, 3 eq.) in THF (1.5 mL) and cooled to 0°C, then the solution B was titrated with DEAD (68 μL, 0.076 g, 0.435 mmol, 3 eq.) and after stirring at 0 °C for 10 minutes, solution B was added drop wise to solution A. The reaction mixture was stirred for an hour in an ice bath and then placed into freezer for 14 hours. After warming the reaction mixture to r.t., silica was added and solvent was removed under reduced pressure. Column chromatography (silica, Hex: EtOAc 6:4 then 5:5) yielded 0.055 g (79%) of white solid, m.p. = 134-136 °C (dec) (CH₂Cl₂/Hex). Rₓ (7:3 EtOAc:Hex)= 0.50, α Dhabi 162.13° (c= 0.0100 g/mL, CHCl₃), ¹H-NMR: δ: 7.92 (d, 2H, J = 7.8Hz), 7.77 (d, 2 H, J= 7.8 Hz), 7.59 (t,1 H, J= 7.2 Hz), 7.43 (t, 2 H, J= 7.8 Hz), 7.26 (d, 2 H, J= 8.4 Hz), 5.29 (d, 1 H, J= 3.0 Hz), 4.86 (m, 1 H), 4.53 (t, 1 H, J= 8.6 Hz), 4.30 (bt, 1 H, J = 8.1 Hz), 4.03 (t, 1 H, J = 8.4 Hz), 3.93 (dd, 1 H, J₁= 13.2 Hz, J₂= 6.3 Hz), 2.97 (ddd, 1 H, J₁= 11.7 Hz, J₂= 8.1 Hz, J₃= 4.8 Hz), 2.39 (s, 3 H), 2.09 (m, 6 H). ¹³C-
NMR: δ: 165.5, 157.2, 145.2, 133.8, 133.7, 130.1, 129.9, 129.2, 128.7, 127.9, 125.5, 77.2, 69.3, 68.8, 55.1, 38.0, 29.9, 24.5, 21.9, 21.1. IR (neat): ν (cm⁻¹): 3064.4, 1756.1, 1723.4, 1189.9, 1176.7. CH analysis calculated: C 62.10%, H 5.21% found C 62.06% and H 5.35%.

1a,2,3,6,6a,7,8,8a-Octahydro-1,5-dioxa-3a-aza-(2S, 9R, 10S)-cyclopenta[a]cyclopropa[f]naphthalene-4-one (33):

To a solution of the benzoate-tosylate 304a (0.055 g, 0.11 mmol) in dry THF (3 mL) was added drop wise 1.03M methanolic MeONa (121 μL, 0.125 mmol, 1.1 eq.) at -3 °C under an argon atmosphere. The reaction mixture was stirred for one hour on an ice bath. When TLC indicated complete conversion, saturated ammonium chloride solution (7 drops) and water (5 mL) were added. The aqueous phase was extracted with ethyl acetate (6 x 10 mL). The combined organic layers were then washed with saturated solution of sodium bicarbonate (3 x 3 mL), water (3 mL), brine (3 mL) and dried over anhydrous magnesium sulfate. Filtration and evaporation of the filtrate yielded crude product, which was purified by column chromatography (silica, Hex:EtOAc 6:4).

Product 33 was obtained as yellow oil (0.016 g, 68%). Rf (EtOAc)= 0.34, αD 26 +20.21° (c= 0.0100 g/mL, CHCl₃), ¹H-NMR: δ: 4.50 (t, 1 H, J= 8.1 Hz), 4.34 (m, 1 H), 4.00 (dd, 1 H, J₁= 13.8 Hz, J₂= 6.9 Hz), 3.93 (dd, 1 H, J₁= 8.1 Hz, J₂= 6.9 Hz), 3.53 (m, 1 H), 3.11 (d, 1 H, J= 4.2 Hz), 3.10 (ddd, 1 H, J₁= 13.5 Hz, J₂= 7.2 Hz, J₃= 4.5 Hz), 2.54 (m, 1 H), 2.34 (m, 1 H), 2.21 (m, 1 H), 2.03 (m, 1 H), 1.66 (m, 2 H). ¹³C-NMR: δ: 157.5, 131.7, 126.3, 66.9, 54.6, 54.4, 50.8, 38.4, 27.1, 21.6, 20.0. IR (neat): ν (cm⁻¹): 1747.7, HRMS: Calculated for C₁₁H₁₃NO₃ ([M+H]⁺): 207.0895 found 207.0896.
Potassium 2-bromo-6-methoxyphenoxide (307):

Bromoguaiacol 34 (0.25 g, 1.2 mmol) was dissolved in abs. ethanol (15 mL) and potassium hydroxide (0.074 g, 1.17 mmol, 0.95 eq.) was added. The reaction mixture was gently heated until all the hydroxide dissolved, then the ethanol was evaporated under reduced pressure on hot water bath. To the solid residue was added dry benzene (10 mL) and the solvents were removed under reduced pressure (repeated 4 times total). The resulting hygroscopic white solid 307 was dried on vacuum at 60°C for 2 days before use.

7R-(2-Bromo-6-methoxy-phenoxy)-8R-hydroxy-1,5,6,7,8,9,10,10b-octahydro-oxazolo[4,3-a]isoquinolin-3-one (308):

Solution of the epoxide 33 (0.036 g, 0.17 mmol) in dry DME (9 mL) was transferred into a flask with 307 (0.220 g, 0.91 mmol, 5.4 eq.) under an argon atmosphere. After complete dissolution of 307, 18-crown-6 ether (small spatula tip) was added and the reaction mixture was heated to reflux under argon atmosphere for 5 days, with one addition of extra 307 (0.1 g, 2.5 eq.) after 4 days of heating. The resulting purple reaction mixture was then cooled to r.t. and solvent was removed under reduced pressure. The residue was taken up in ether (110 mL) and 5% wt aq. sodium hydroxide (5 mL). After separation of the phases, the organic phase was washed with 5% wt aq. sodium hydroxide (5 x 5 mL). The combined aqueous phases were back-extracted with ether (4 x 30 mL) and all organic layers were combined, washed with water (5 mL), brine (5 mL) and dried over anhydrous magnesium sulfate. The drying agent was then filtered
and solvents were removed under reduced pressure. The crude product was purified by column chromatography (silica, Hex: EtOAc 2:8 then 1:9) to yield 0.057 g (80%) of an oil. 308: \( R_f \) (EtOAc)= 0.34, \( \alpha_d^{27} +20.21^\circ \) (c= 0.0100 g/mL, CHCl₃), \(^1\)H-NMR: \( \delta \): 7.14 (dd, 1 H, \( J_1=7.5 \) Hz, \( J_2=1.8 \) Hz), 6.93 (t, 1 H, \( J=8.4 \) Hz), 6.87 (dd, 1 H, \( J_1=8.4 \) Hz, \( J_2=1.8 \) Hz), 4.68 (d, 1 H, \( J=4.2 \) Hz), 4.53 (t, 1 H, \( J=8.1 \) Hz), 4.30 (m, 1 H), 4.20 (m, 1 H), 4.05 (t, 1 H, \( J=8.1 \) Hz), 3.97 (dd, 1 H, \( J_1=13.2 \) Hz, \( J_2=6.0 \) Hz), 3.86 (s, 3 H), 3.03 (ddd, 1 H, \( J_1=16.2 \) Hz, \( J_2=13.2 \) Hz, \( J_3=4.5 \) Hz), 2.62 (m, 1 H), 2.24 (m, 2 H), 2.02 (m, 2 H), 1.90 (m, 1 H), 1.80 (m, 1 H). \(^{13}\)C-NMR: \( \delta \): 157.3, 153.2, 145.0, 131.4, 127.9, 125.4, 125.0, 117.7, 111.9, 83.6, 69.6, 67.4, 55.9, 55.0, 38.1, 26.5, 26.4, 22.3. IR (neat): \( \nu \) (cm\(^{-1}\)): 3430.6, 2928.4, 1738.5, 1732.6, 767.6, 731.5. HRMS: Calculated for C\(_{18}\)H\(_{20}\)NBrO\(_5\) ([M+H])\(^+\): 409.0525 found 409.0596. CH analysis calculated: C 52.70%, H 4.91% found C 52.86% and H 5.10%.

**7R-(2-Bromo-6-methoxy-phenoxy)-8R-(tert-butyl-dimethyl-silanyloxy)-1,5,6,7,8,9,10,10b-octahydro-oxazolo[4,3-a]isoquinolin-3-one (309):**

To a solution of the alcohol 308 (0.041 g, 0.1 mmol) in dry methylene chloride (5 mL) was added diisopropylethyl amine (26 \( \mu \)L, 0.019 g, 0.15 mmol, 1.5 eq.) drop wise at -78°C under argon atmosphere. The resulting solution was stirred for 10 minutes and then tert-butylidemsilyl trifluoromethylsulfonate (34 \( \mu \)L, 0.039 g, 0.015 mmol, 1.5 eq.) was added drop wise. The reaction mixture was stirred at -78°C for an additional 2 hours. Saturated ammonium chloride solution (10 mL) was used to quench reaction at -75°C,
and the reaction mixture was allowed to thaw with stirring. After separation of the layers, the aqueous phase was diluted with water (5 mL) and extracted with methylene chloride (6 x 20 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous sodium sulfate. Filtration, evaporation of solvent and column chromatography (silica, Hex:EtOAc 7:3, then EtOAc) yielded 0.040 g (77%) of clear oil. Rf (50:50, Hex:EtOAc)= 0.61, $\alpha_D^{28} +9.50^\circ$ (c= 0.0100 g/mL, CHCl$_3$), $^1$H-NMR: $\delta$: 7.14 (dd, 1 H, $J_1$= 7.8 Hz, $J_2$= 1.4 Hz), 6.93 (t, 1 H, $J$= 8.1 Hz), 6.86 (dd, 1 H, $J_1$= 8.1 Hz, $J_2$= 1.2 Hz), 4.55 (t, 1 H, $J$= 8.4 Hz), 4.40 (m, 1 H), 4.32 (t, 1 H, $J$= 9.0 Hz), 4.07 (t, 1 H, $J$= 8.1 Hz), 4.08 (d, 1 H), 3.94 (dd, 1 H, $J_1$= 12.9 Hz, $J_2$= 6.6 Hz), 3.85 (s, 3 H), 3.02 (ddd, 1 H, $J_1$= 16.0 Hz, $J_2$= 12.2 Hz, $J_3$= 4.8 Hz), 2.53 (m, 1 H), 2.32 (m, 1 H), 2.17 (m, 1 H), 2.00 (m, 1 H), 1.75 (m, 2 H), 0.78 (s, 9 H), -0.09 (s, 3 H), -0.12 (s, 3 H). $^{13}$C-NMR: $\delta$: 157.4, 153.7, 144.4, 132.7, 126.1, 125.4, 125.2, 118.4, 111.7, 81.9, 67.8, 67.1, 55.9, 54.8, 38.3, 28.1, 25.8, 25.3, 20.7, 18.2, -4.8, -5.0. IR (neat): v (cm$^{-1}$): 2951.9, 1760.4, 836.2, 771.9 HRMS: Calculated for C$_{24}$H$_{35}$NSiBrO$_5$ ([M+H]$^+$): 524.1468 found 524.1489.

10-tert-Butyldimethylsilyloxy-6-methoxy-(1S, 9R, 10R, 14S)-8,16,18-dioxazapentacyclo[11.7.0.0$^{1.9}$,0$^{2.7}$,0$^{14.18}$]icosa-2(7), 3, 5, 12-tetraene-17-one (310):

Aryl bromide 309 (0.068 g, 0.13 mmol) was dissolved in dry toluene (11 mL), to which was added Pd(PPh$_3$)$_4$ (0.180 g, 0.16 mmol, 1.2 eq.) and the Proton Sponge$^\text{TM}$ (0.042 g, 0.19 mmol, 1.5 eq.). The solution was degassed with an argon stream for 30 minutes and then heated to reflux for 21 hours (the originally bright yellow solution turned dark brown). Then an extra amount of catalyst (0.018 g, 0.1 eq.) was added and
reaction mixture was refluxed for additional 2 hours. Upon cooling to r.t., ether (100 mL) was added and the solution was filtered through celite bed and washed with 1M HCl (5 x 5 mL), sat. NaHCO₃ (5 mL), water (5 mL), brine (5 mL) and dried over anhydrous magnesium sulfate. Filtration and evaporation with silica followed by column chromatography (SiO₂, Hex:EtOAc 70:30) gave product as yellowish oil (0.042 g, 74%).

Rf (50:50, Hex:EtOAc)= 0.45, αD²⁶ +15.65° (c= 0.0100 g/mL, CHCl₃), ¹H-NMR: δ: 6.85 (t, 1 H, J= 8.1 Hz), 6.78 (dd, 1 H, J₁= 7.8 Hz, J₂= 0.9 Hz), 6.66 (dd, 1 H, J₁= 7.2 Hz, J₂= 1.5 Hz), 5.49 (m, 1 H), 4.79 (bt, 1 H, J= 9.0 Hz), 4.61 (t, 1 H, J= 8.7 Hz), 4.39 (d, 1 H, J= 4.5 Hz), 4.25 (dd, 1 H, J₁= 8.4 Hz, J₂= 4.2 Hz), 4.00 (t, 1 H, J= 8.4 Hz), 3.87 (s, 3 H), 3.74 (ddd, 1 H, J₁= 12.9 Hz, J₂= 10.2 Hz, J₃= 8.1 Hz), 3.38 (ddd, 1 H, J₁= 12.6 Hz, J₂= 10.1 Hz, J₃= 7.5 Hz), 2.33 to 1.99 (m, 4 H), 0.88 (s, 9 H), 0.10 (s, 3 H), 0.04 (s, 3 H).

¹³C-NMR: δ: 157.5, 146.9, 145.2, 136.4, 132.8, 122.2, 121.9, 117.0, 111.7, 91.3, 69.1, 67.2, 56.0, 54.6, 48.0, 36.8, 33.3, 29.9, 25.9, 18.2, -4.6, -4.9. IR (neat): ν (cm⁻¹): 3055.4, 2952.5, 1760.5, 836.6, 778.6, 735.1. HRMS: Calculated for C₂₄H₃₄NSiO₅ ([M+H]⁺): 444.2206 found 444.2226.

5-Hydroxymethyl-9-tert-butyldimethylsilyloxy-13-methoxy-4-methyl-(1S, 5S, 9R, 10R)-11,4-oxazatetracyclo[8.7.0.0¹,6.0¹₂,17]-heptadeca-6,12(17), 13, 15-tetraene (311):

Amide 310 (0.040 g, 0.09 mmol) was dissolved in dry methylene chloride (7 mL) and the solution was cooled to 0°C under an argon atmosphere. Then DIBAL-H (160 μL, 0.128 g, 0.90 mmol, 10 eq.) was added and the reaction mixture was allowed to slowly warm up to r.t. overnight. After 22 hours of stirring at r.t. the reaction mixture was
quenched by consecutive additions of water (2 mL), methanol (2 mL) and sat. aq. 
NaHCO₃ (2 mL). The solid that formed was filtered on a celite bed and washed with 
methylene chloride (7 x 10 mL). The organic layer was separated and the aqueous layer 
was back-extracted with methylene chloride (3 x 10 mL). The combined organic phases 
were dried over magnesium sulfate. Drying agent was then filtered and the filtrate was 
everoped with silica and purified by column chromatography (SiO₂, EtOAc: EtOH: 
NH₄OH 90:10:0.01). Product was obtained as yellow oil (0.027 g, 69%) Rf (90:10, 
EtOAc:EtOH)= 0.31, αD²⁵ - 78.20° (c= 0.0100 g/mL, CHCl₃), ¹H-NMR: δ: 7.27 (dd, 1 H, 
J₁= 6.9 Hz, J₂= 0.9 Hz), 6.81 (t, 1 H, J= 7.8 Hz), 6.73 (dd, 1 H, J₁= 8.4 Hz, J₂= 1.2 Hz),
5.64 (bd, 1 H, J= 4.5 Hz), 4.47 (dd, 1 H, J₁= 6.3 Hz, J₂= 3.0 Hz), 4.34 (dd, 1 H, J₁= 3.9 
Hz, J₂= 1.2 Hz), 3.86 (dd, 1 H, J₁= 14.7 Hz, J₂= 3.9 Hz), 3.86 (s, 3 H), 3.32 (dd, 1 H, J₁= 
10.8 Hz, J₂= 4.2 Hz), 3.21 (m, 1 H), 3.03 (bt, 1 H, J= 7.8Hz), 2.57 to 2.49 (m, 2 H), 2.48 
(s, 3 H), 2.29 to 2.14 (m, 3 H), 1.80 (m, 1 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H).
¹³C-NMR: δ: 147.1, 144.8, 136.2, 134.1, 124.2, 121.2, 118.7, 111.0, 91.3, 71.5, 66.6,
63.0, 55.9, 48.2, 46.5, 43.5, 33.4, 29.0, 26.0, 18.2, -4.8. IR (neat): v (cm⁻¹): 3399.1,
2951.6, 1098.0, 834.3, 776.2, 735.9. HRMS: Calculated for C₂₃H₃₄NSiO₄ ([M-CH₃]⁺):
416.2257 found 416.2251.

5-Chloromethyl-9-tert-butyldimethylsilyloxy-13-methoxy-4-methyl-(1S, 5S, 9R, 
10R)-11,4-oxazatetracyclo[8.7.0.0¹⁶.0¹².¹⁷]-heptadeca-6,12(17), 13, 15-tetraene (312):

Anhydrous LiCl (0.038 g, 15 eq.) was flame-dried under vacuum. Upon cooling to 
r.t. under argon atmosphere a solution of 311 (0.026 g, 0.060 mmol) in dry methylene
chloride (2 x 2.5 mL) was added via syringe, followed by the addition of dry triethyl amine (42 μL, 0.0307 g, 0.300 mmol, 5 eq.), dry THF (2 mL) and distilled methanesulfonyl chloride (12 μL, 0.0172 g, 0.15 mmol, 2.5 eq.). The reaction mixture was stirred at r.t. under argon atmosphere for 7.5 hours to yield a yellow suspension. The reaction mixture was quenched by the addition of water (5 mL) and brine (5 mL), followed by extraction with methylene chloride (10 x 10 mL). The combined organic layers were dried over magnesium sulfate. The drying agent was then filtered and the filtrate was evaporated with silica and purified by the column chromatography (SiO₂, Hex:EtOAc 90:10). The product was obtained as a yellow oil (0.021 g, 78%).

312: Rf (80:20, Hex:EtOAc)= 0.55, αD²⁶ - 62.07° (c= 0.0100 g/mL, CHCl₃), ¹H-NMR: δ: 7.30 (dd, 1 H, J₁= 7.5 Hz, J₂= 1.2 Hz), 6.81 (t, 1 H, J= 8.4 Hz), 6.73 (d, 1 H, J= 6.9 Hz), 5.70 (bd, 1 H, J= 5.1 Hz), 4.50 (dd, 1 H, J₁= 6.3 Hz, J₂= 3.3 Hz), 4.37 (d, 1 H, J= 3.0 Hz), 3.86 (s, 3 H), 3.63 (dd, 1 H, J₁= 11.1 Hz, J₂= 4.5 Hz), 3.21 (dd, 1 H, J₁= 11.1 Hz, J₂= 7.2 Hz), 3.03 (bt, 1 H, J= 6.6 Hz), 2.88 (m, 1 H), 2.56 to 2.41 (m, 2 H), 2.46 (s, 3 H), 2.21 to 2.14 (m, 4 H), 0.88 (s, 9 H), 0.08 (s, 6 H). ¹³C-NMR: δ: 147.1, 144.7, 136.7, 134.1, 123.3, 121.2, 119.2, 111.0, 91.0, 73.0, 66.0, 56.0, 50.2, 47.5, 45.3, 44.3, 34.7, 29.0, 26.0, 18.2, -4.7, -4.8. IR (neat): ν (cm⁻¹): 2952.7, 1491.0, 1278.0, 1098.60, 834.0, 776.4, 738.3. HRMS: Calculated for C₂₄H₃₇NSiClO₃ ([M+H]⁺): 450.2231 found 450.2225.
APPENDIX B
SELECTED SPECTRA

On the following pages the proton and the carbon NMR spectra of selected compounds are shown along with the proposed structure.
LIST OF REFERENCES


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BIOGRAPHICAL SKETCH

Josef Zezula was born in Jihlava, Czechoslovakia (nowadays Czech Republic), in February, 1976. He grew up in Dobroutov along with his older sister Helena, raised by the parents Josef and Helena. He attended elementary school in nearby Polná and middle school in Jihlava. After graduation with honors he was accepted at the Institute of Chemical Technology, Prague, where he became interested in organic chemistry in particular. In his third year of study he joined the research group of Professor Ivan Stibor, where he worked on the synthesis of calixarene-based macromolecules. He received his MSc. Degree (Ing.) with honors in June 1999, and went on to pursue graduate studies at the University of Florida, where he is currently a fourth year graduate student in Professor Tomáš Hudlický’s group. His research interests involve the use of products of microbial biotransformations in organic synthesis.
I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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August, 2003

Dean, Graduate School