Univerzita Karlova

Přírodovědecká fakulta

Studijní program: Chemie

Studijní obor: Organická chemie

Adam Kurčina

Syntéza kľúčového chevalinulínu A

The synthesis of the key fragment of chevalinulin A

Diplomová práce

Vedoucí závěrečné práce/Školitel: Prof. Jan Veselý

Praha, 2024

Prohlášení:

Prehlasujem, že som záverečnú prácu spracoval samostatne a že som uviedol všetky použité informačné zdroje a literatúru. Táto práca ani jej podstatná časť nebola predložena k získaniu iného alebo rovnakého akademického titulu.

V Praze, 17.8.2024

Podpis

Abstrakt

Chevalinulin A je donedávna neznáma zlúčenina izolovaná v roku 2022 z húb *Aspergillus chevalieri* vyskytujúcich sa v chladných hlbokomorských presakoch. Vykazuje nezvyčajnú a synteticky komplexnú kombináciu štruktúrných motívov; indolový, diketopiperazinový a bicyklo[2.2.2]oktanový motiv. Neobvykle silné proangiogenické účinky naznačujú potenciálne využitie pre liečbu chorôb nedostatočnej cievotvorby vrátane mŕtvice a ischemických chorôb srdca. Totálna syntéza tejto látky predstavuje podstatnú cestu k získaniu tejto látky a jej analógov, podporujúc biologické štúdie a objasnenie vzťahu medzi štruktúrou a biologickou aktivitou. Táto diplomová práca sa zaoberá syntézou kľúčového fragmentu použitelného pre totálnu syntézu chevalinulínu A a jeho analógov.
Klíčová slova: chevalinulin A, syntéza

Abstract

Chevalinulin A is a novel compound obtained from fungal strain *Aspergillus chevalieri* isolated from deep sea cold seeps in 2022. Based on structural characterizations, the compound exhibits an unusual and synthetically challenging combination of structural motifs; indole, diketopiperazine and bicyclo[2.2.2]octane core. This compound demonstrates remarkable proangiogenic properties, suggesting its potential as a therapeutic agent for conditions linked to inadequate angiogenesis, such as ischemic heart disease, coronary artery disease, and stroke. The elaboration of the first total synthesis of this compound is essential for further biological investigations, facilitating studies on structure-activity relationships and the development of its analogues. This diploma thesis focuses on elaboration of the synthesis of the key fragment useful for the total synthesis of chevalinulin A and its analogues.
Key words: chevalinulin A, synthesis

Table of Contents

List of used abbreviations

(+)-CSA – (1*S*)-(+)-10-Camphorsulfonic acid

All – allyl

Bn – benzyl

AQN – anthraquinone-1,4-diyl

BOC – *tert*-butyloxycarbonyl

BOM – benzyloxymethyl

CAN – ceric ammonium nitrate

CBZ – benzyloxycarbonyl

DA – Diels-Alder

DBU – 1,8-diazabicyclo[5.4.0]undec-7-en

DCM – dichloromethane

DHQ – dihydroquinine

DHQD –dihydroquinidine

DIBAL-H – diisobutylaluminiumhydride

DIPEA – *N*,*N*-diisopropylethylamine

DMF – *N*,*N*-dimethylformamide

DMP – Dess–Martin periodinane

DMSO – dimethylsulfoxide

ESI – electrospray ionization

HPLC – high-performance liquid chromatography

INOS – inducible nitric oxide synthase

LA – Lewis acid

LB – Lewis base

MCPBA – *meta*-chloroperoxybenzoic acid

NHC – *N*-heterocyclic carbene

PMB – *para*-methoxybenzyl

PG – protecting group

PHAL – 1,4-phthalazinediyl

PTSA – *p*-toluensulfonic acid

Pybox – 2,6-bis(oxazolinyl)pyridine

Py – pyridine

TBAI – tetrabutylammonium iodide

TBDMS – *tert*-butyldiphenylchlorosilane

TBDMSCl – *tert*-butyldimethylchlorosilane

TBDPS – *tert*-butyldiphenylchlorosilane

TBDPSCl – *tert*-butyldiphenylchlorosilane

TEA – triethylamine

TFA – trifluoroacetic acid

THF – tetrahydrofuran

TLC – thin layer chromatography

TMS – trimethylsilyl

TMSCl – chlorotrimethylsilane

Tf – trifluormethansulfonyl

Ts – *p*-toluensulfonyl

1. Introduction

The sampling of sea sediment in 2022 and the subsequent isolation of a strain of *Aspergillus chevalieri* fungus led to the discovery of a novel natural compound chevalinulin A.[1] In the preliminary biological studies the compound demonstrated strong proangiogenic properties, which are necessary for the treatment of ischemic diseases – such as ischemic heart disease, coronary artery disease and stroke. Structural characterization of this compound revealed a remarkably complex structure, composed of three substituted structural motifs; indole, diketopiperazine and bicyclo[2.2.2]octane core – all with well-defined stereochemistry. Despite the potential of chevalinulin A and its analogues for therapeutic use and to facilitate studies on structure-activity relationships, the total synthesis of chevalinulin A is not known. The unusual combination of structural motifs makes the total synthesis challenging. However, it is essential for providing access to chevalinulin A and its analogues.

This diploma thesis focuses on the synthesis of the key fragment of chevalinulin A, useful for the total synthesis of chevalinulin A and its analogues.

2. Aims of the work

The main goal of this work was to elaborate the synthesis of the key fragment suitable for the preparation of chevalinulin A and its analogues. The goal can be divided into specific aims:

A) Elaboration of detailed retrosynthetic analysis and synthetic plan suitable for preparation of the key fragment of chevalinulin A.

B) Synthesis of the key fragment using chiral D-(-)-quinic acid as a starting material.

C) Synthesis of the key fragment using achiral 1,4-cyclohexadiene as a starting material.

3. State of Art

3.1 Chevalinulins A and B

In 2022, a strain of *Aspergillus chevalieri* fungus was discovered through sea sediment sampling. Chemical analysis of fungus metabolites revealed that the fungus produces two novel compounds, which were named chevalinulin A and B (Figure 1). *In vivo* bioactivity testing demonstrated that both compounds exhibit proangiogenic activity, effectively regenerating inhibited intersegmental blood vessels, suggesting potential applications in treating ischemic heart disease. Among the two, chevalinulin A showed the strongest proangiogenic activity. The structures of chevalinulin A and B were elucidated using standard characterization techniques, supplemented by comparing theoretical (calculated) and experimental specific rotations and NMR shifts. Although the crystallization of chevalinulin A was successful, the X-ray results had large uncertainty, making it challenging to assign the configuration rigorously (Figure 2).[1]

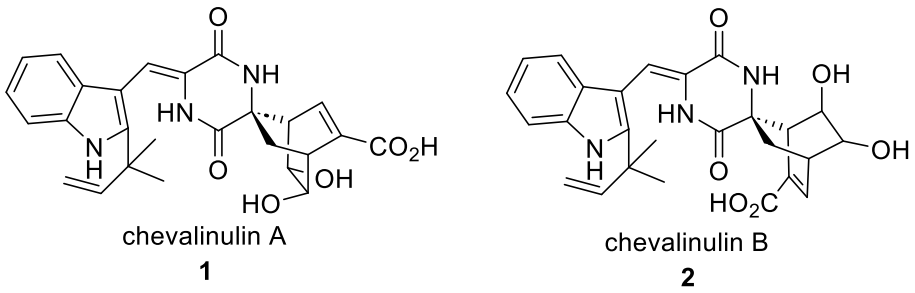


Figure 1: Proposed structure of chevalinulin A and B

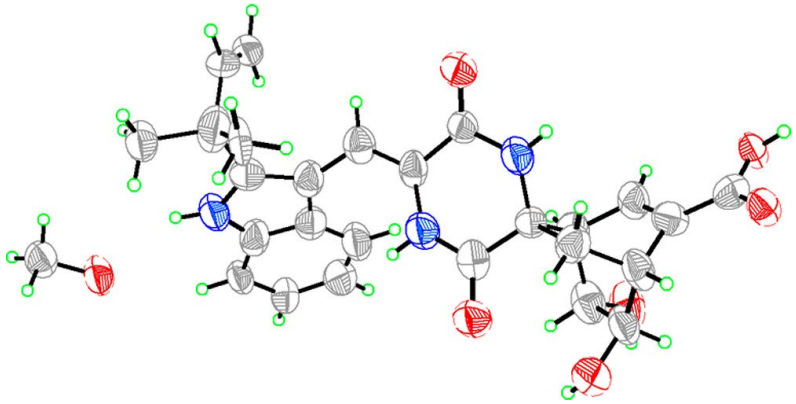
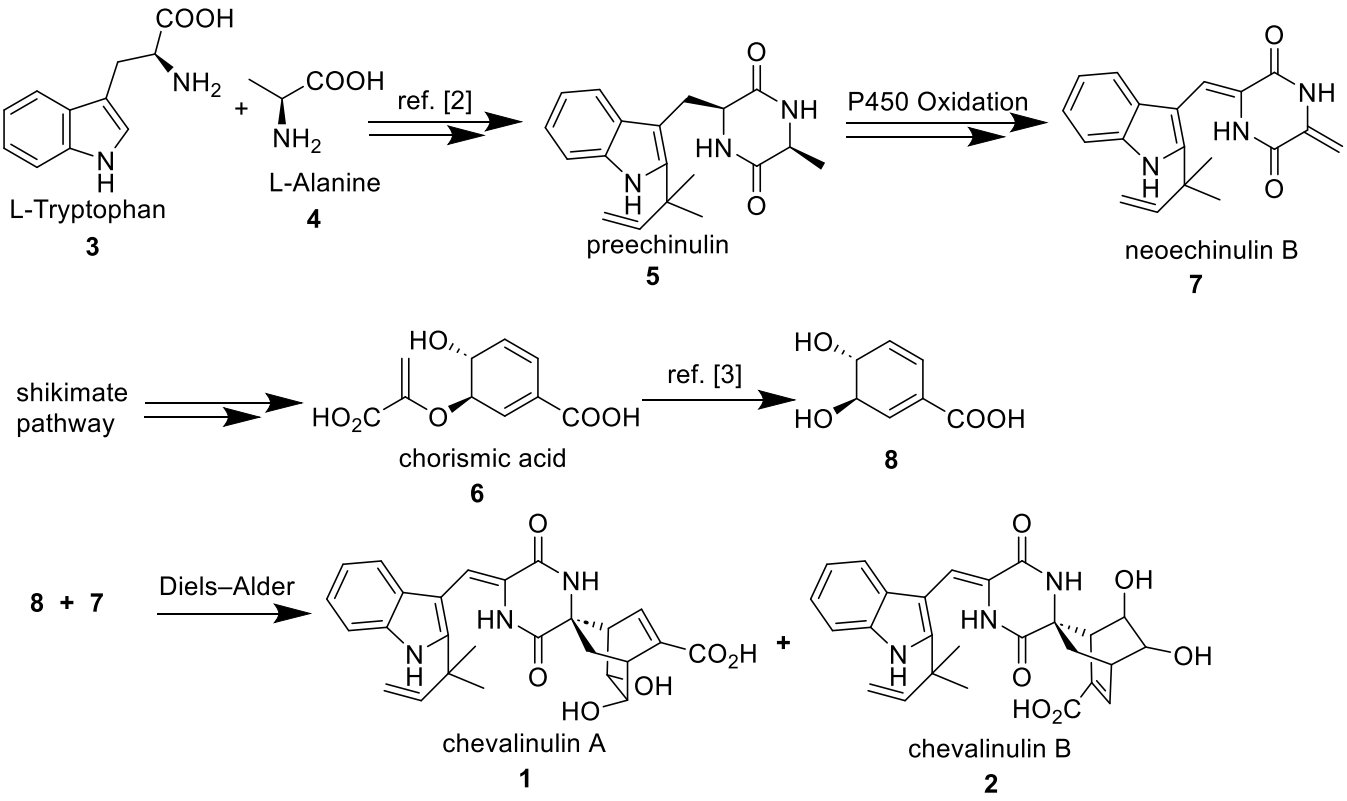


Figure 2: ORTEP (X-ray) structure of chevalinulin A. (CCDC: 2142461)

Li and Wang et al. also proposed a probable biosynthetic pathway (Scheme 1) leading to chevalinulins A and B. The biosynthesis could begin with the biosynthesis of preechinulin (**5**, Scheme 1) *via* known route from L-tryptophan and L-alanine.[2] Preechinulin (**5**) could then be oxidized to neoechinulin B (**7**) mediated by cytochrome P450. This compound contains an

exocyclic double bond, which could react with the hydrolysis product of chorismic acid,[3] a diene **8,** *via* Diels-Alder (DA) reaction to yield chevalinulins A or B.



Scheme 1: Proposed biosynthesis of chevalinulins A and B.

Although detailed disconnection approaches will be discussed in chapter 4.1 Retrosynthetic analysis, this section will provide a brief introduction. The total synthesis of chevalinulin A, in principle, could follow the DA reaction as proposed in biosynthesis; furthermore, the neoechinulin B (**7**) and the diene **8** are known compounds. Apart from the proposed DA reaction, the key structural motifs of chevalinulin A can be built using Strecker synthesis (the construction of green bonds, Figure 3) or aminohydroxylation (violet bonds) from the corresponding bicyclic intermediate **150**. The bicyclic intermediate could be built using DA reaction (red bonds) and functionalized by hydroboration (blue bonds). The synthesis of the indole fragment is known and will be described in Chapter 3.3 Synthesis of neoechinulin B: an indole and diketopiperazine fragment of chevalinulin A. The relevant key reactions will be discussed in the following part of the work, Chapter 3.2 Overview of key reactions.

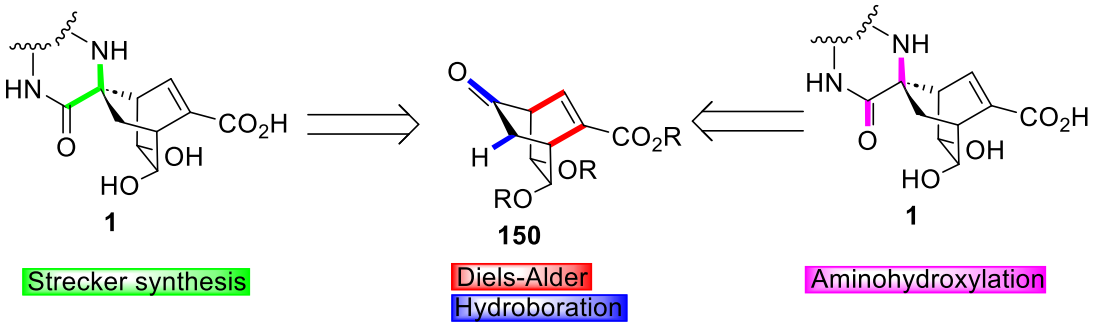


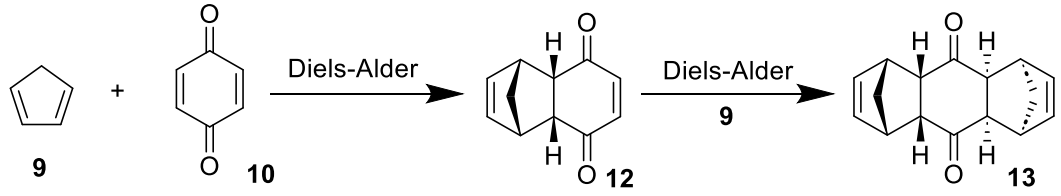
Figure 3: Reactions related to the total synthesis of chevalinulin A.

3.2 Overview of key reactions

This chapter provides an overview of fundamental concepts and advancements in the reactions related to the total synthesis of chevalinulin A.

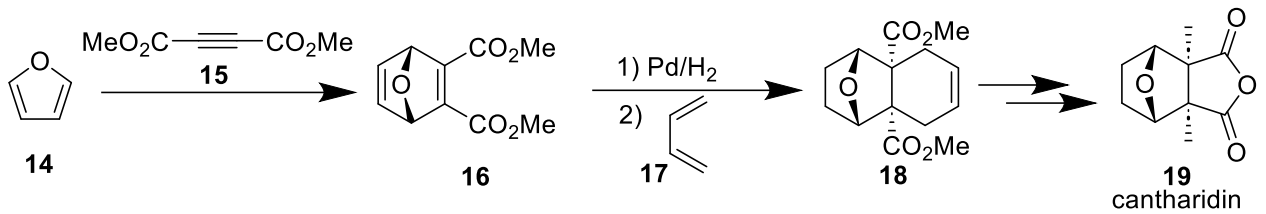
3.3.1 Diels-Alder reaction

The discovery of the Diels-Alder (DA) reaction is a significant historic event in the organic chemistry community. Professor Otto Paul Hermann Diels and his student Kurt Alder discovered the reaction in 1928 by reacting cyclopentadiene (**9**, Scheme 2) with benzoquinone (**10**), successfully identifying the cycloaddition products **12** and **13**.[4] The Diels-Alder reaction is particularly useful because it simultaneously forms two new carbon-carbon bonds through the reaction of a diene with an olefin (or alkyne), leading to substituted cyclohexane arrangement, often with high regio- and stereoselectivity. Its significance was further underscored by the Nobel Prize in Chemistry awarded to Diels and Alder in 1950.



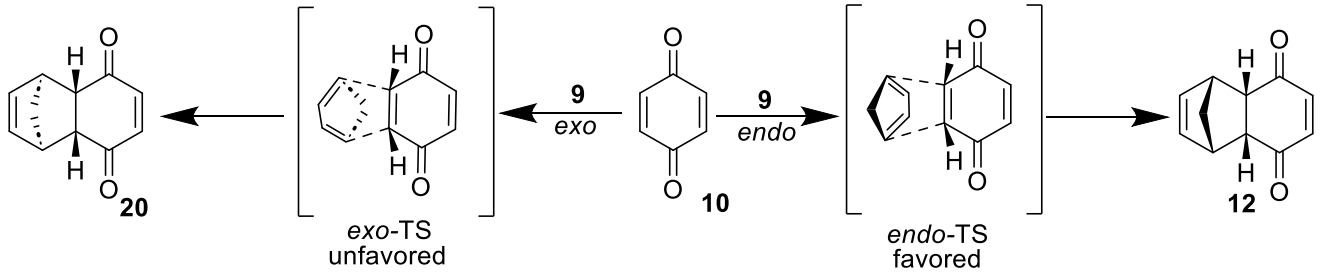
Scheme 2: The historical reaction leading to the discovery of Diels-Alder reaction.

Soon after, the first appearances of the reaction in total synthesis were observed: beginning with Stork's total synthesis of aphrodisiac cantharidin (**19**, Scheme 3) in 1951[5] followed by synthesis of steroid hormone precursor by R. B. Woodward and W. M. McLamore in 1952[6] and Gate's first synthesis of analgesic morphine in 1956.[7]



Scheme 3: An early example of utilization of the Diels-Alder reaction in total synthesis of natural product: the Stork's total synthesis of aphrodisiac cantharidin.

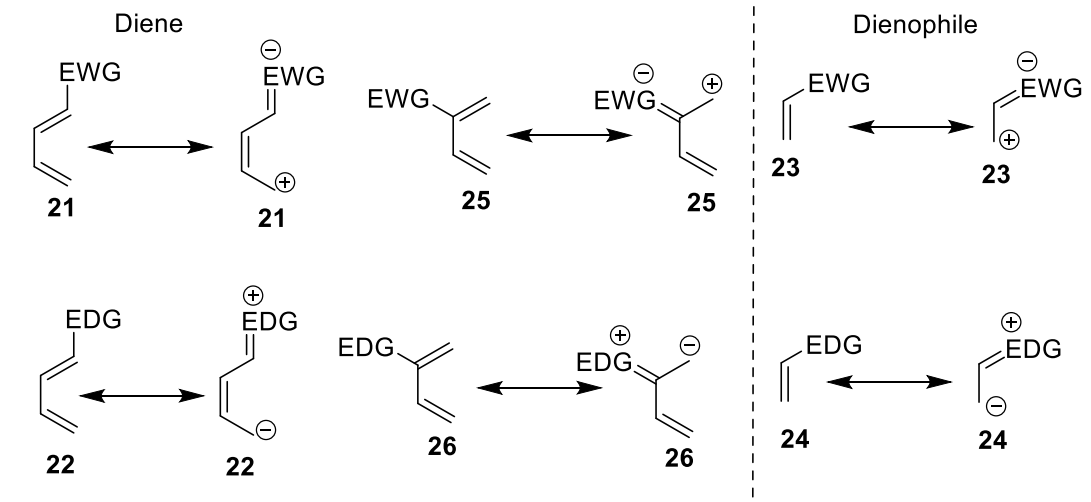
With the growing understanding and experimental advances, empirical rules such as the Alder *endo* rule (Scheme 4) were proposed. This rule concerns the stereochemistry of cycloaddition, stating that the *endo* transition state is favored, leading to the *endo* product (Scheme 4).



Scheme 4: Preference of the *endo* transition state over *endo* led to the formulation of the empirical Alder *endo* rule.

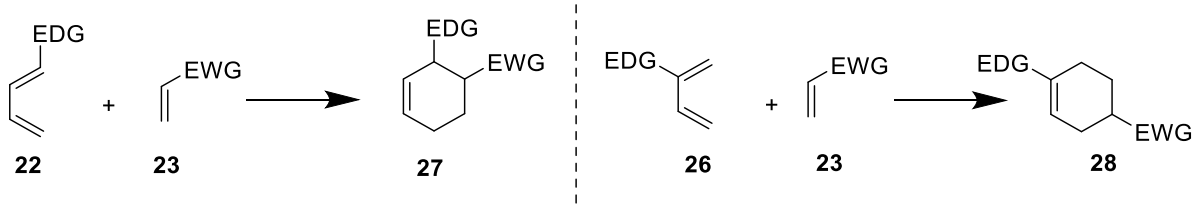
Woodward[8] attempted to rationalize the endo rule by invoking the concept of secondary orbital interactions (SOI). To further support the concept of SOI, advancements to theoretically evaluate and quantify the SOI were made.[9] However, the connection between SOI and the *endo* transition state has been disproved. Instead, the robust energy decomposition analysis predicts that the preference of the *endo* transition state is linked to an unfavorable steric arrangement in the *exo* transition state, meaning the activation energy towards the *endo* transition state is lower.[10,11]

According to the frontier orbital theory, it is generally accepted that the key interaction for Diels-Alder reaction is between the highest occupied molecular orbital (HOMO) of diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile. Consequently, substituting the diene with electron donating group (EDG) increases the diene's HOMO and thus promotes reactivity (and stereoselectivity, as will be shown below). Analogously, the presence of electron-withdrawing groups (EWG) in dienophile increases its LUMO and promotes reactivity and regioselectivity. The orientation of both EWG or EDG on the diene or dienophile affects the coefficients of the frontier orbitals at the respective carbon atoms. This polarization can be illustrated with resonance structures (Scheme 5).



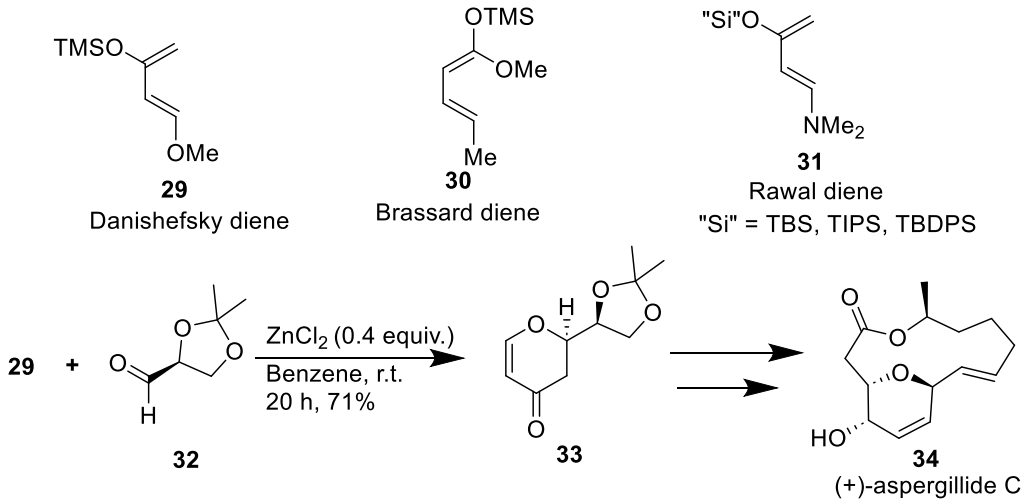
Scheme 5: Resonance structures of corresponding diene and dienophile derivatives.

The polarization of diene/dienophile often results in predictive regiochemical outcome (Scheme 6).



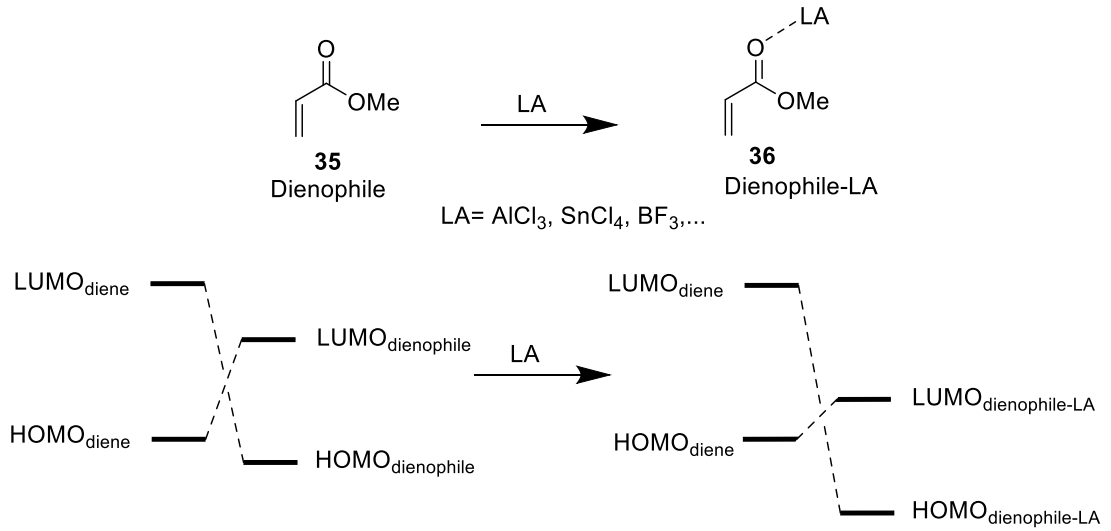
Scheme 6: An example of expected products influenced by the governing effects of substituents on regiochemistry.

Particularly reactive dienophiles contain more EDG groups, for example the widely known Danishefsky's diene[12] (**29**), Brassard's diene[13] (**30**) or Rawal's diene[14] (**31**, Scheme 7). The diene or dienophile containing a heteroatom can be a suitable reaction partner. These reactions of heterodienophile are known as hetero-Diels-Alder reactions. Commonly used heteroatomic dienophiles are carbonyls (oxo-Diels-Alder), leading to substituted dihydropyran derivatives. Dienes or dienophiles containing an imine moiety are analogous, known as aza-Diels-Alder reaction. An example of hetero(oxo)-Diels-Alder reaction is the total synthesis of aspergillide C (Scheme 7), which also utilizes the mentioned Danishefsky's diene (**29**).[15]



Scheme 7: Selected examples of commonly utilized reactive dienes. Total synthesis of the aspergillide C by the hetero-Diels-Alder reaction employing Danishefsky's diene.

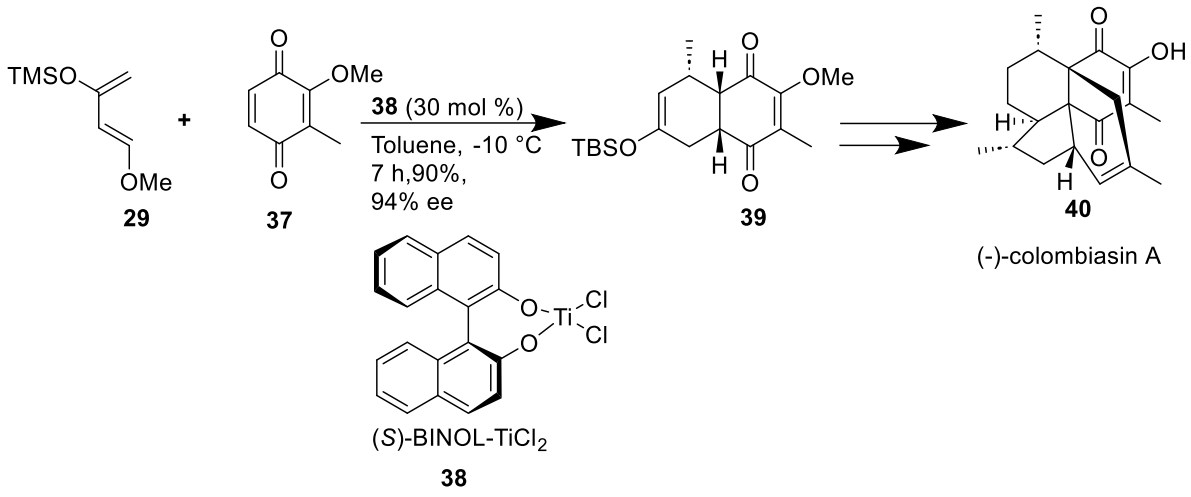
Lewis acids are able to accelerate the DA reaction,[16,17] alter *exo*/*endo* ratio[18] or lead to different regioselectivity.[19] Particularly, the mechanism of acceleration of the reaction is a matter of debate. Coordination of Lewis acid to dienophile, for example to the acrylate ester (**35**, Scheme 8) decreases the $HOMO_{diene}$-$LUMO_{dienophile}$ gap. This is emphasized to enhance orbital interactions, therefore leading to higher reactivity. However, it is mostly forgotten that the $HOMO_{diene}$-$LUMO_{dienophile}$ gap is increased, cancelling the enhanced orbital interactions. As explained by F. M. Bickelhaupt et al. in computational studies,[17] the more likely way how Lewis acids catalyze Diels-Alder reactions is by decreasing the electron repulsion between the π-systems of the dienophile and the incoming diene.



Scheme 8: Lewis acid coordination to the dienophile typically decreases $HOMO_{diene}$-$LUMO_{dienophile}$ gap, but also increases the $HOMO_{dienophile}$-$LUMO_{diene}$ gap, cancelling out the increase in orbital interactions.

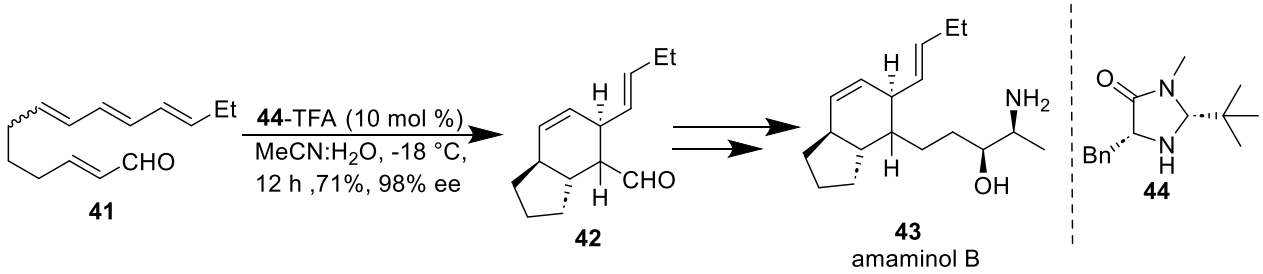
Asymmetric catalysts greatly extend the utility of the DA reaction. Several catalytic systems (mostly chiral Lewis acids) used in asymmetric DA reactions include[20] chiral titanium, boron,

aluminum, indium, copper, zinc, magnesium and rare earth complexes. As demonstrated in the total synthesis of colombiasin A, where BINOL-$TiCl_2$ system (**Scheme** 9) was employed to obtain the intermediate **39** in 90% with 94% ee.[21] The high level of asymmetric induction is attributed to the coordination of BINOL-Ti species to the substrate, effectively guiding the approach of diene **29**.



Scheme 9: Total synthesis of colombiasin A utilizing asymmetric BINOL-$TiCl_2$ catalytic system.

With the growing field of chiral organocatalysts, several organocatalytic systems also emerged: chiral secondary amines, primary amines, Brønsted acids and bifunctional organocatalysts were employed. One selected example is the utilization of MacMillan's imidazolinone catalyst (**44**, Scheme 10) in the total synthesis of amaminol B.[22] The intermediate **41** is activated by the chiral imidazolinone catalyst **44** forming reactive iminium species, resulting in an asymmetric intramolecular Diels-Alder reaction yielding key intermediate **42**.



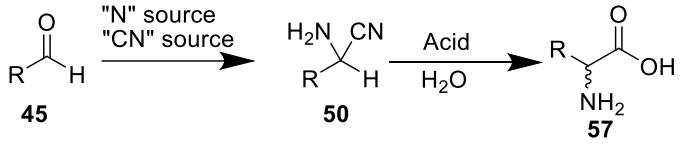
Scheme 10: Organocatalytic synthesis of key intermediate used for the total synthesis of the amaminol B.

3.3.2 Strecker amino acid synthesis and analogous reactions

The occurrence of life on Earth, one of the greatest mysteries of science, can be broken down into several problems. One of these is the formation of amino acids, the building blocks of life. Miller's experiment[23] in 1953 simulated the primordial conditions of prebiotic Earth,[24] particularly the reductive atmosphere containing H_2O, CH_4, NH_3 and H_2, along with cycles of heating, cooling and an electric arc (simulating lightning). After a prolonged time, the formation

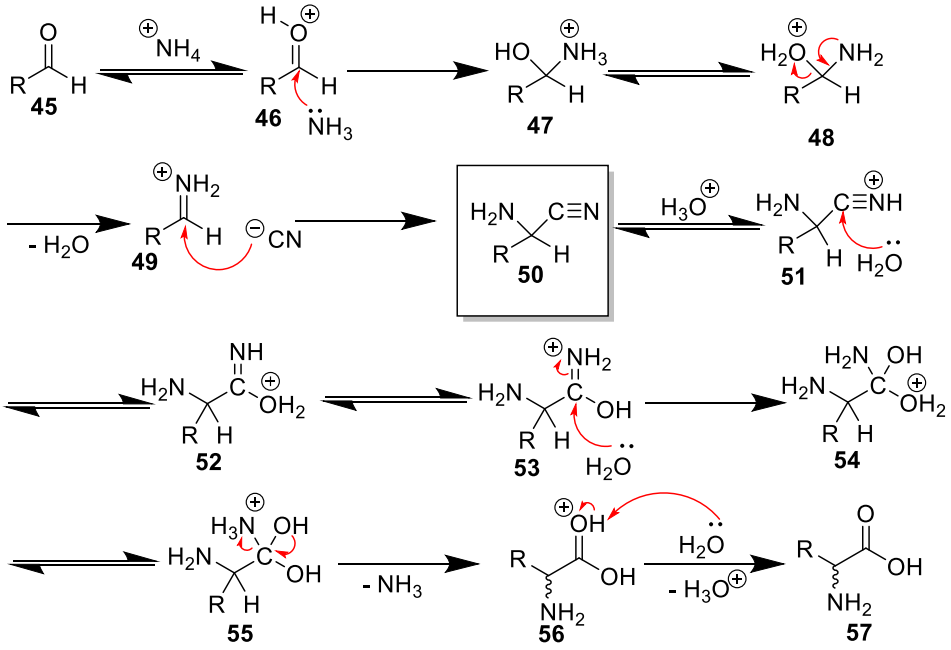
of several amino acids (proteinogenic and non-proteinogenic) was observed. Later, the possible mechanism of amino acid formation was identified as the century-old Strecker amino acid synthesis.[25,26]

In 1850, Strecker synthesized racemic alanine by the hydrolysis of the intermediate formed from acetaldehyde, ammonia and hydrogen cyanide. The methodology became known as Strecker amino acid synthesis. The typical procedure (Scheme 11) encompasses the formation of α-amino nitrile **50** from the starting carbonyl compound **45**, which is subsequently hydrolyzed into α-amino acid **57**.[27]



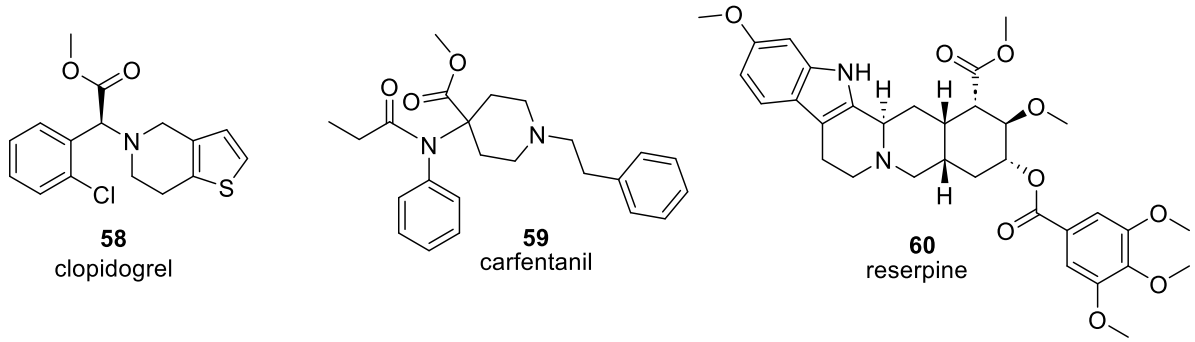
Scheme 11: Reaction scheme of the classical Strecker amino acid synthesis procedure.

The generally accepted mechanism is depicted in (Scheme 12). The first step is the acid-catalyzed nucleophilic attack of ammonia to the carbonyl atom. Subsequently, proton exchange and protonation occur, which, upon elimination of water gives iminium intermediate **49**. This iminium intermediate is attacked by nitrile anion resulting in aminonitrile **50**, which is often possible to isolate. The nitrile moiety in intermediate **50** is then activated by protonation, leading to a sequence of two nucleophilic additions of water, forming intermediate **54**. Finally, the elimination of ammonia and deprotonation gives the final α-amino acid **57**. It is important to note that ketones can also undergo this reaction, and various sources of nitrile anions or substituted amines can be used.



Scheme 12: Generally accepted mechanism of Strecker amino acid synthesis.

Despite being discovered in 1850, the everlasting importance of the Strecker reaction is underscored by its widespread applications. For example, the synthesis of antiplatelet drug clopidogrel[28,29] (**58**, Scheme 13)**,** extremely potent opioid receptor agonist carfentanil[30] (**59**) and antihypertensive and antipsychotic drug reserpine[31] (**60**). Furthermore, the Strecker reaction provides route to the unnatural amino acids, which are often not available by the chemo-enzymatic approach (**71**, Scheme 15).[32,33]

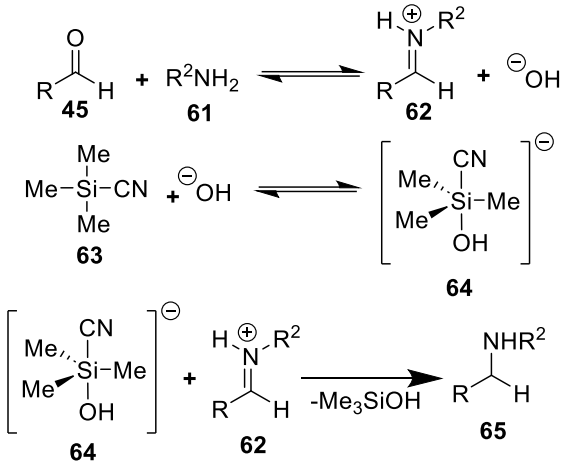


Scheme 13: Examples of drugs synthesized *via* the Strecker reaction.

While one-pot Strecker reactions typically proceed with aldehydes, the reaction with ketones is more challenging, requiring different conditions for respective steps.

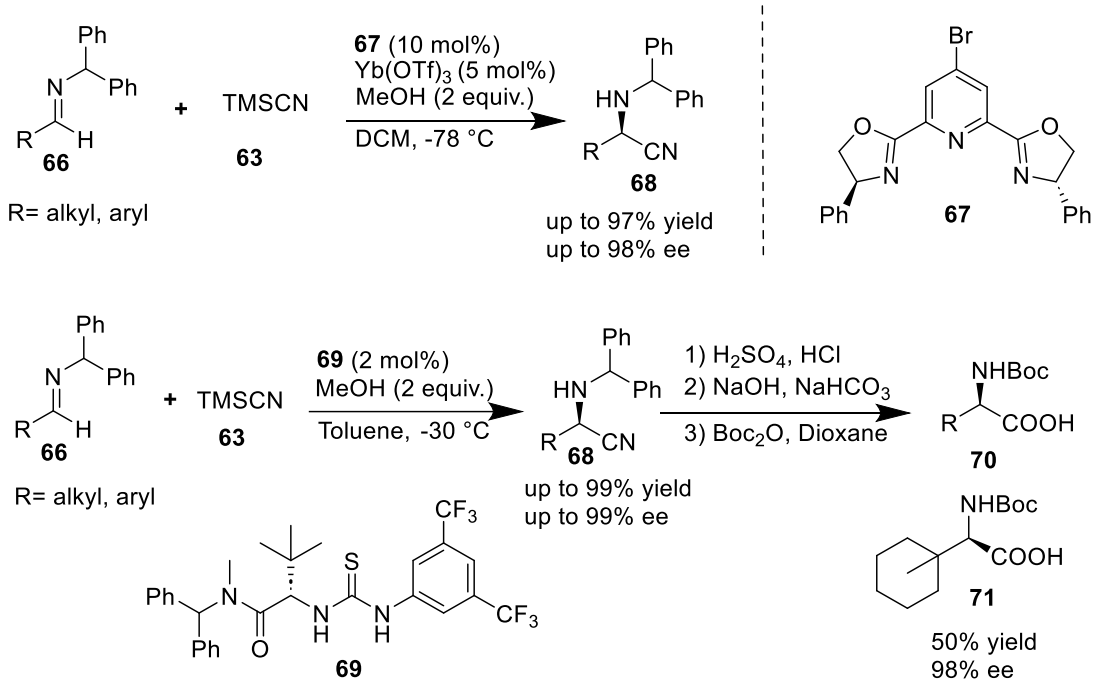
Difficulties arise with usual cyanide anion sources (KCN, NaCN), particularly due to the basic character of cyanide salts, which can cause problems with readily enolisable aldehydes (aldol-type side reactions).[34] Instead, non-alkaline cyanide sources are preferred: diethyl phosphorocyanidate,[35] acetone cyanohydrin,[36] or the most frequently used trimethylsilyl cyanide (TMSCN).[37]

The three-component Strecker reaction of reactive aldehydes, amine and TMSCN is known to proceed without any catalyst. In studies done by M. Yus et al.,[38] it is speculated that the active species is the pentacoordinate silicon species (**64**, Scheme 14), which also has a more nucleophilic character. The possible decomposition of the pentacoordinate species **64** leads to the liberation of the cyanide anion, which leads to the same reaction outcome. Moreover, TMSCN can be used to generate HCN *in situ* adding MeOH.



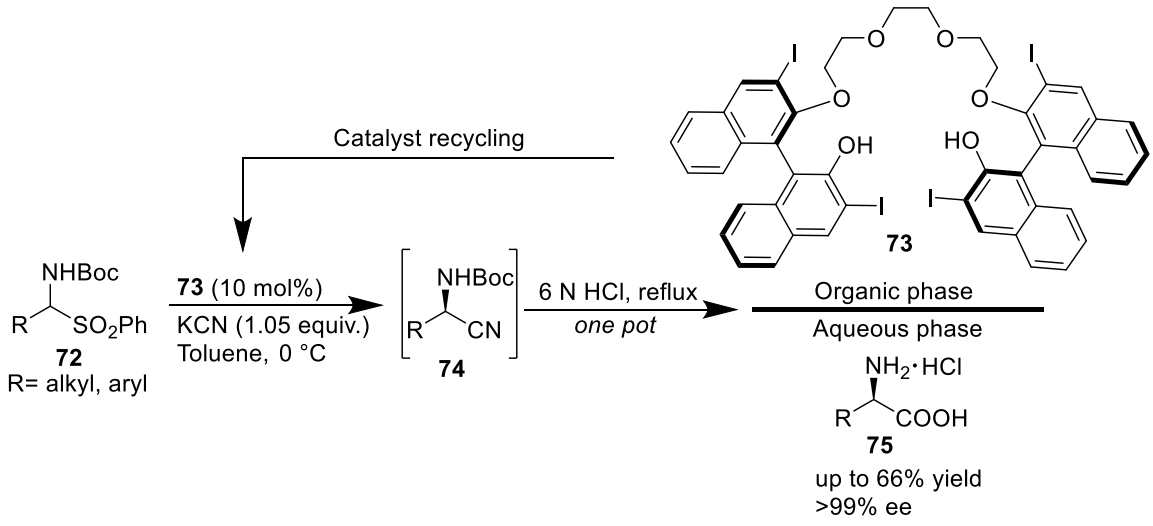
Scheme 14: The proposed formation of pentavalent silicon species in the uncatalyzed three-component Strecker reaction with trimethylsilyl cyanide as a cyanide source.

With less reactive substrates the three-component Strecker reaction with TMSCN is typically catalyzed by a wide variety of Lewis acids, Brønsted acids, and related organocatalysts. In addition to catalyzing the reaction, these catalysts also enable the possibility of asymmetric reactions. An example of homogenous asymmetric Lewis acid catalysis developed by B. Karimi et al.[39] demonstrates the utility of Yb(III)/Pybox complexes in the Strecker reaction of substituted imines (**66**, Scheme 15). The reaction provided α-amino nitriles **68** in good yields and enantioselectivities even with unbranched imines. With a very similar set of substituted imines **66**, E. N. Jacobsen et al.[33] developed an alternative route to α-amino nitriles (**68**, Scheme 15). The method utilizes thiourea organocatalyst with a low catalyst loading (2 mol%), in toluene as a solvent, with excellent yields and enantioselectivities. The catalyst **69** bounds the generated iminium and cyanide ion pair through multiple non-covalent interactions, resulting in a stereocontrolled cyanide attack.[40] The product, amino nitrile **68**, was then readily converted into Boc-protected amino acids **70**.



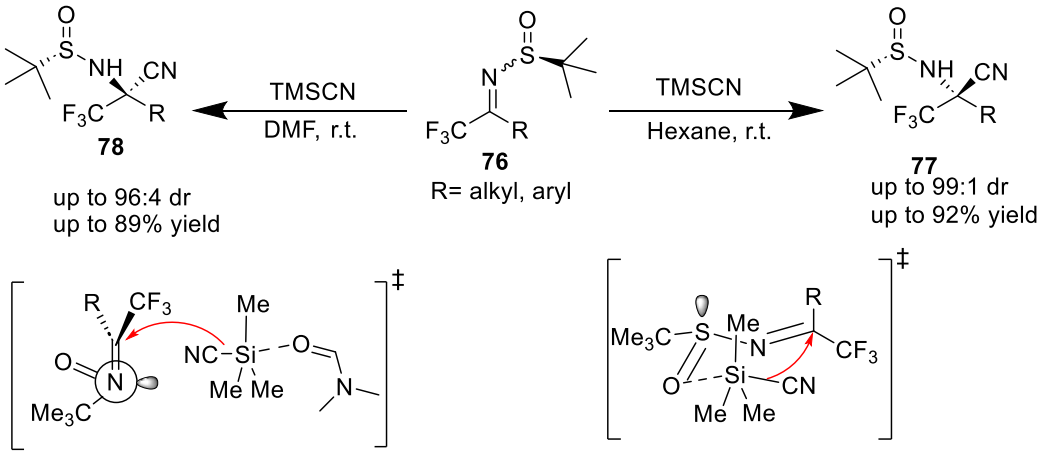
Scheme 15: Yb(III)/Pybox complex and thiourea catalyzed asymmetric Strecker reactions.

A robust, organocatalytic Strecker methodology with polyether-tethered BINOL-based organocatalyst and Boc-aldimine precursors, α-amido sulfones, was developed by H. Yang et al.[41] The method allows an asymmetric formation of α-amino nitriles **74**, which are then hydrolyzed *one pot* to amino acids (**75**, Scheme 16) in good yields with high enantioselectivities. The catalyst is readily recycled, as it remains in the organic phase. It is anticipated that the BINOL-derived organocatalyst **73** activates the KCN and assists in the *in situ* formation of imine, which is then stereoselectively attacked by the delivered cyanide anion.



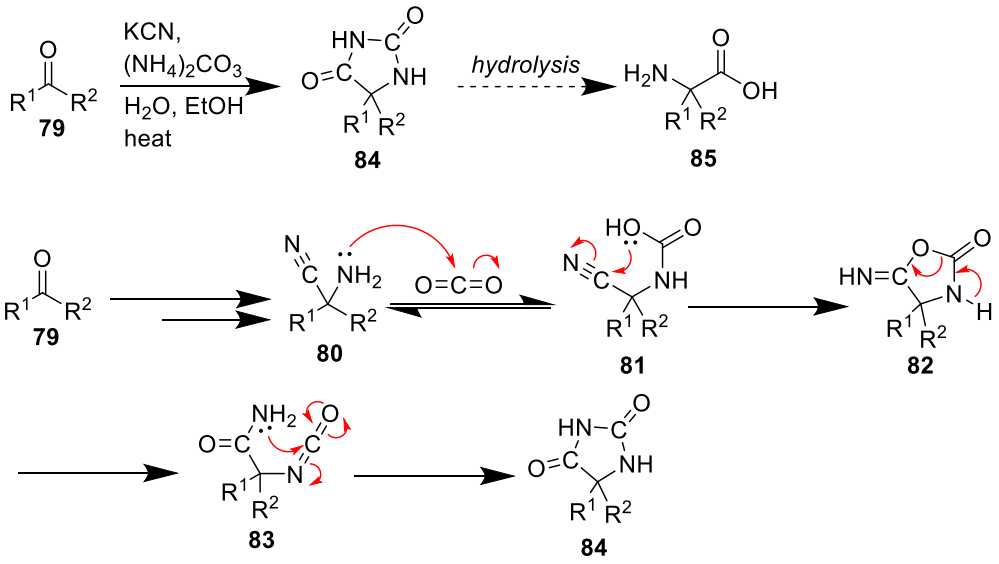
Scheme 16: The robust organocatalytic Strecker methodology suitable for the preparation of α-amino acids.

Apart from the asymmetric catalysts, chiral auxiliaries are also used in the Strecker reaction. Commonly used auxiliaries are, for example, phenylethylamine,[42] phenylglycinol[43] and chiral α-amino acids and their derivatives.[44,45] L. Lu et al.[46] developed a methodology for the synthesis of enantioenriched α-trifluoromethylated α-amino acids from chiral *N-tert*-butylsulfinylimines (Scheme 17). The sulfinyl amide moiety, a chiral auxiliary, in principle, can coordinate with a Lewis acid and direct the stereoselectivity of the reaction. The effect of solvent was crucial in this case: the reaction with hexane resulted in **77**, whereas the reaction in DMF resulted in a product with opposite stereoselectivity **78**. Authors attribute this effect to the different structure of the transition state: six-membered (cyclic) transition state is preferred in hexane, whereas DMF, apart from being a polar solvent, can act as a Lewis base and activate the TMSCN, leading to different transition state and stereoselectivity.



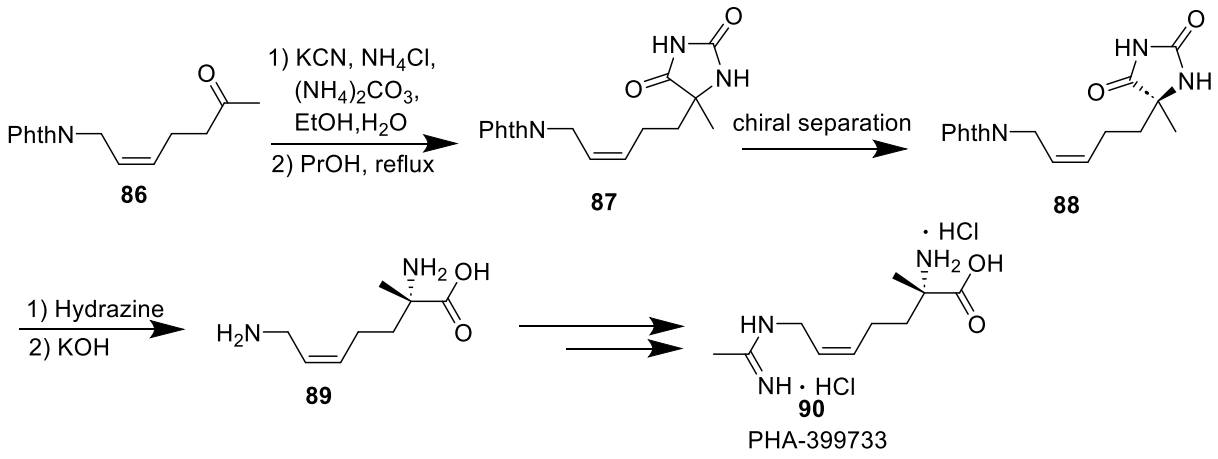
Scheme 17: Strecker reaction with *N-tert*-butylsulfinyl group as a chiral auxiliary, leading to different stereoselectivity depending on the solvent used.

Another approach towards α-amino acids is hydrolysis of hydantoin obtained by the Bucherer-Bergs reaction[47] (Scheme 18). This reaction is principally similar to the Strecker reaction. However, the *in situ* generated α-amino nitrile **80** (analogously as **50**, Scheme 12) reacts with carbon dioxide, forming the carbamate **81**, which, after series of ring closing and opening yields the hydantoin **84**. The reaction usually works very well, especially with structurally less complex aldehydes and ketones. Non-surprisingly, the reaction was proposed as a reliable analytical method for identifying carbonyl compounds. The formed hydantoins are almost always insoluble and crystallize from the mixture.[48]



Scheme 18: Formation of hydantoin 84 from the α-amino nitrile 80 *via* Bucherer-Bergs reaction.

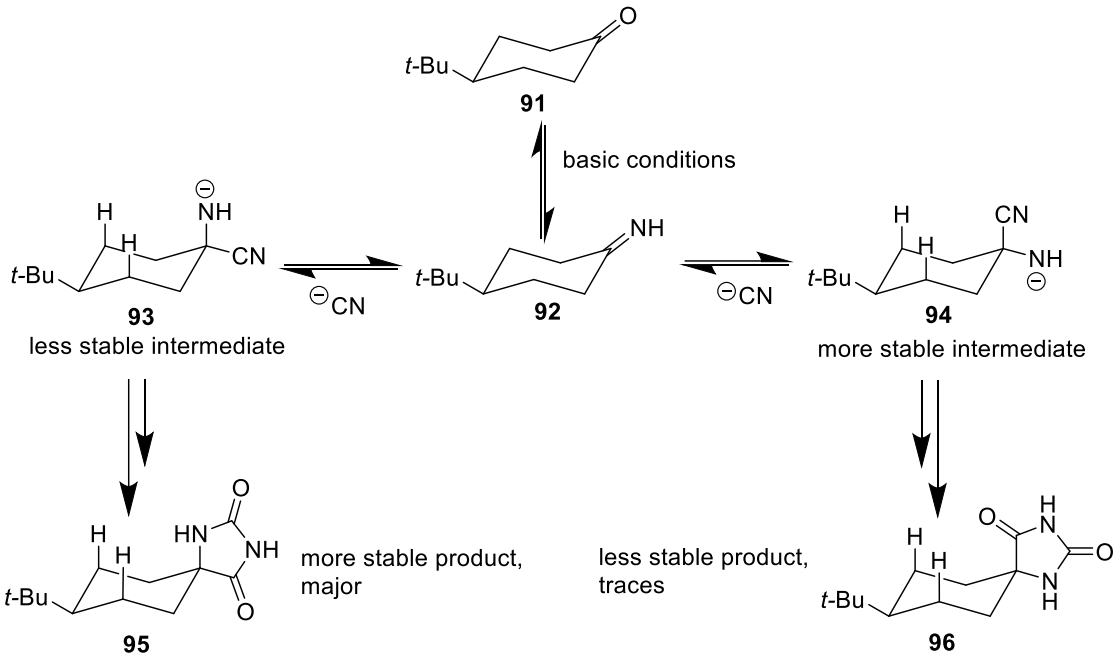
An example of the utilization of Bucherer-Bergs reaction with subsequent hydantoin hydrolysis is the industrial synthesis of INOS inhibitor PHA-399733 (**90**, Scheme 19).[49] The ketone **86** reacted with common conditions: potassium cyanide, ammonium carbonate and ammonium chloride in ethanol/water mixture. Conducting the reaction with basic conditions resulted in the opening of the phthalimide protective group, which was regenerated with reflux in propanol. The racemate was separated using simulated moving bed chiral separation on the chiral column. Finally, the phthalimide protective group was deprotected, and the hydantoin was hydrolyzed using basic conditions, which, after a few reactions, gave the final product.



Scheme 19: Utilization of Bucherer-Bergs reaction with subsequent hydantoin hydrolysis in the synthesis of PHA-399733.

In the Bucherer-Bergs reaction, the thermodynamically more stable product usually predominates. An illustrative example is the Bucherer-Bergs reaction of 4-*tert*-butyl substituted cyclohexanone (**91**, Scheme 20). The imine intermediate **92** can produce either the α-amino nitrile **93** or **94** and is expected to be in equilibrium with these intermediates under basic

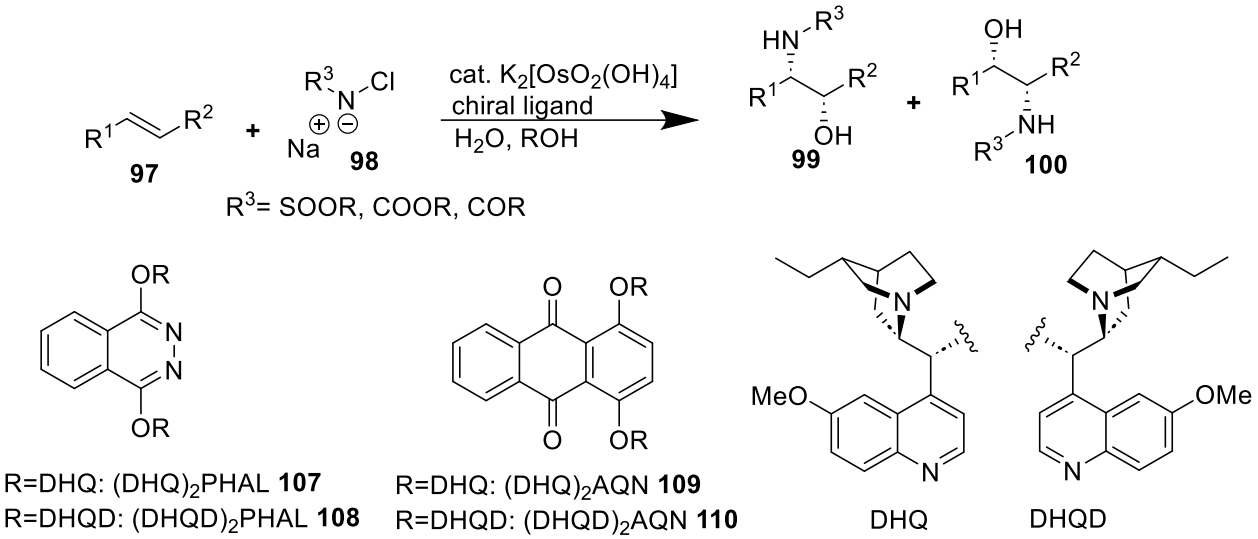
conditions. The intermediate **93** is expected to be less stable, due to energetically unfavorable 1,3-diaxial interactions of the amino group with axial hydrogens. However, the product of the reaction **95** is more stable than the product **96**. This is parallelized by the observed experimental outcome, **95** is the major product with only traces of **96**. However, not all reaction steps are expected to be in equilibrium (for example cyclization **83** → **84**, Scheme 18), therefore certain transition state leading to product **95** over **96** must be favored, in accordance with the Curtin-Hammett principle.[50,51]



Scheme 20: The Bucherer-Bergs reaction is often thermodynamically controlled. The respective reaction steps are expected to be in equilibrium, thus resulting in the thermodynamically most stable product.

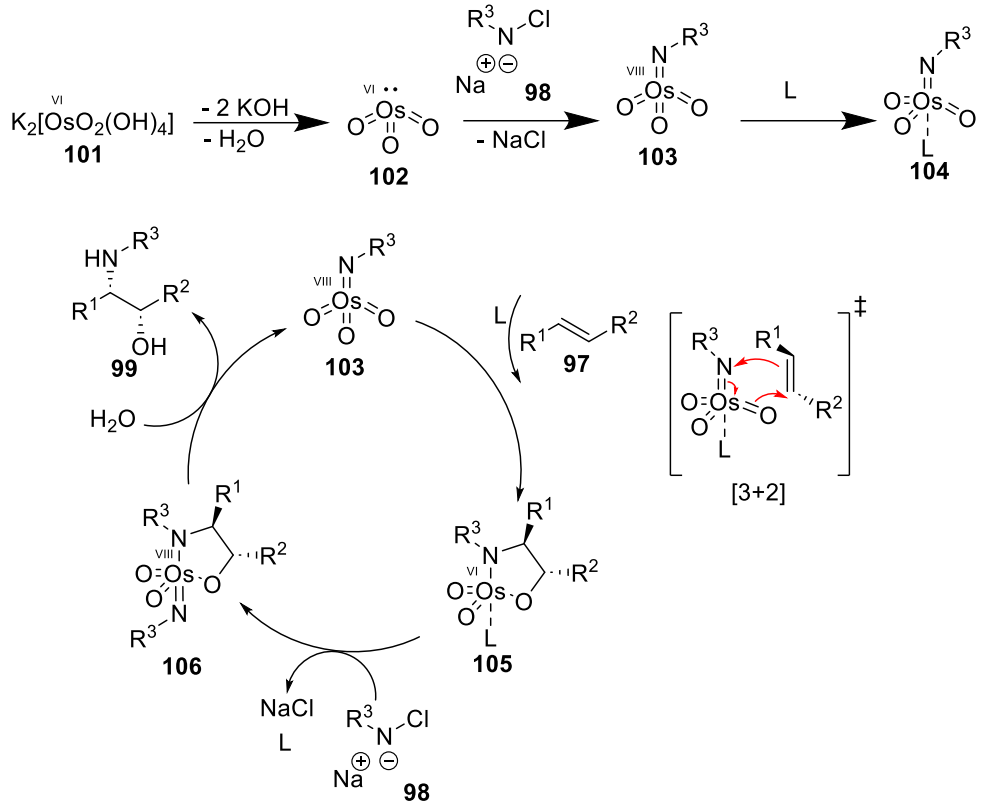
3.3.3 Double bond functionalization

Sharpless asymmetric hydroxylation is a reaction that allows the formation of vicinal amino alcohol (**99**, **100**) from the corresponding alkene (**97**, Scheme 21).[52] The reaction encompasses *in situ* generated osmium (VIII) catalytic species, a DHQD/DHQ-based phthalazine (PHAL) or anthraquinone (AQN) ligand, and an oxidizing nitrogen source, often salts of *N*-halosulfonamides, -amides and -carbamates.



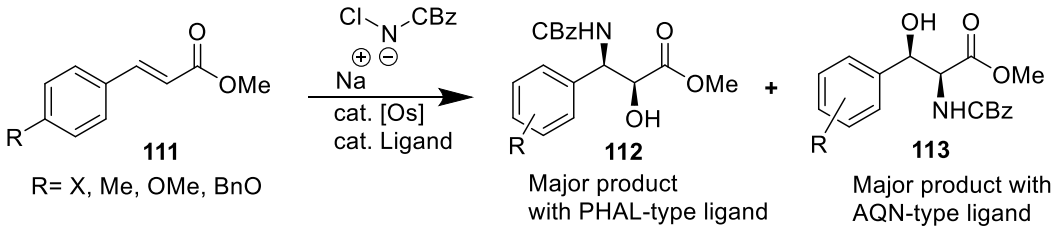
Scheme 21: Typical conditions for Sharpless asymmetric aminohydroxylation reaction.

Opinions on the reaction mechanism vary. However, the depicted version (Scheme 22) is supported by theoretical calculations and kinetic isotope effects.[52] The initial reaction step consists of generating the active osmium (VI) **102** species with subsequent oxidation into imidotrioxoosmium (VIII) **103** species. Subsequent binding with chiral ligand preludes the key reaction step, the [3+2] addition forming cyclic intermediate **105** with osmium (VI). After the release of the ligand and oxidation the osmium (VIII) **106** species is formed. After hydrolysis, the α-amino alcohol **99** is formed, regenerating the catalytic species **103**. The chiral ligands induce enantioselectivity by favoring the addition of the osmium (VIII) **103** species to one face of the prochiral alkene substrate (**97**, Scheme 22).



Scheme 22: Catalytic cycle of the Sharpless aminohydroxylation.

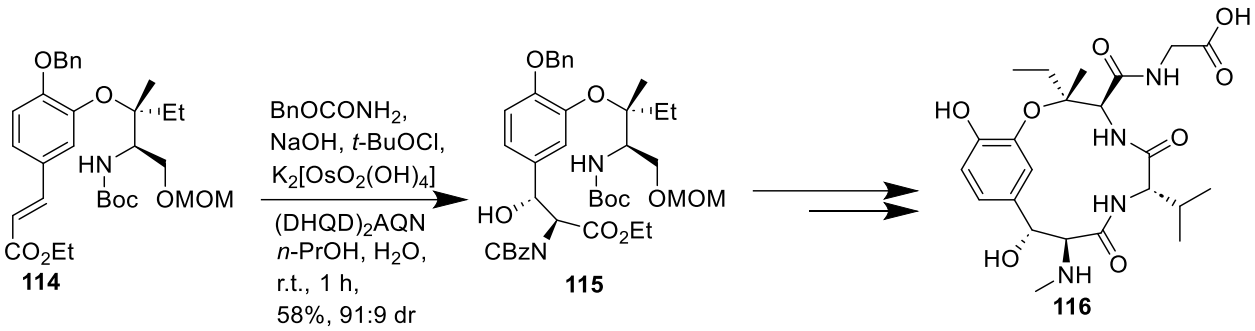
As depicted in Scheme 21, two regioisomeric α-amino alcohols can form: **99** and **100**. The regioselectivity is often substrate-dependent (steric effects and interaction with ligand) and controlled by neighboring moieties (for example, by alkene polarization with electron-withdrawing groups). As demonstrated in K. B. Sharpless's early study,[53] the regioselectivity of aminohydroxylation of series of cinnamate esters **111** can be controlled by proper choice of ligand type. Reaction with the PHAL-type ligand resulted in a major product **112**, whereas the reaction with the AQN-type ligand resulted in a major product **113**.



Scheme 23: Choice of proper ligand-type can result in desired regioselectivity.

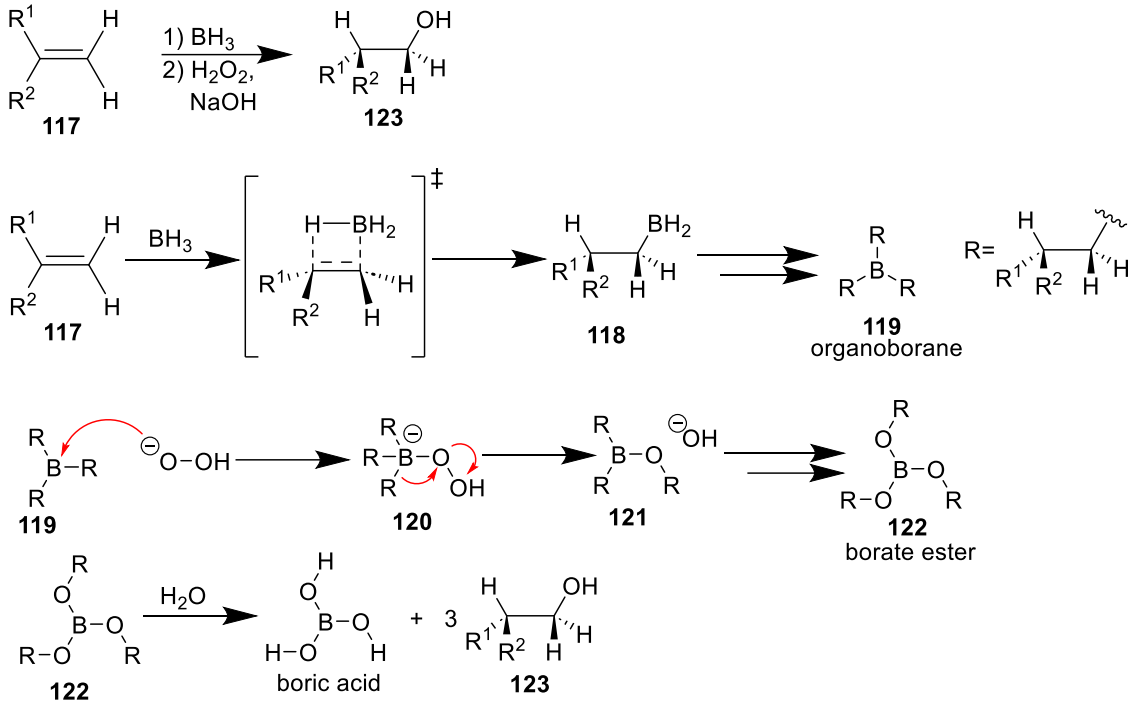
The Sharpless asymmetric aminohydroxylation was utilized in total syntheses of several natural compounds.[54] Selected example is the total synthesis of ustiloxin D.[55] Ustiloxin D (**116**, Scheme 24) is a potent antimitotic agent, inhibiting microtubule assembly, a potential for anticancer drugs. The substituted cinnamate **114** was a substrate for Sharpless asymmetric hydroxylation with regioreversed protocol (using AQN ligands instead of PHAL), yielding the

protected amino alcohol **115** with high stereoselectivity. The alcohol **115** was an important intermediate into the desired product **116.**



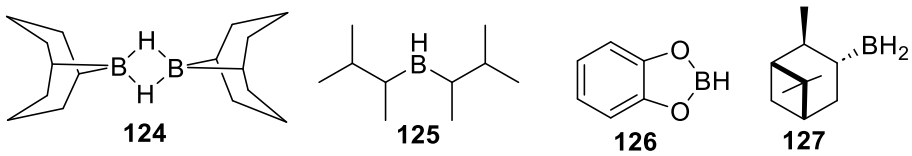
Scheme 24: One of the key steps of the total synthesis of ustiloxin D is Sharpless asymmetric hydroxylation.

Among the revolutionary methods for double bond functionalization is hydroboration. Since its discovery and development by H. C. Brown, [56–58] hydroboration has become widely utilized in organic synthesis, which resulted in Brown's Nobel Prize award (together with G.Wittig). The reaction is well known for its utilization in anti-Markovnikov hydration of alkenes. The typical reaction conditions (Scheme 25) include the reaction with borane (BH_3), followed by the oxidation procedure with basic peroxide. The generally accepted mechanism includes a *cis*-fashion four-centered transition state (**117** → **118**), where the hydride binds to a more substituted carbon atom, whereas the boron binds to less substituted carbon. The result is the formation of mono-alkyl borane **118**, which can undergo up to three same additions to yield the tri-alkyl borane **119.** The second reaction step encompasses borane oxidation by adding peroxide anion to form anionic borane species **120**. The crucial step is the alkyl migration to oxygen with the subsequent elimination of hydroxide anion, forming organoboron species **121**. Subsequently, two peroxide anion additions and alkyl migrations lead to borate ester **122**. After hydrolysis of the borate ester **122**, the resulting products are boric acid and the corresponding alkyl alcohol **123**.



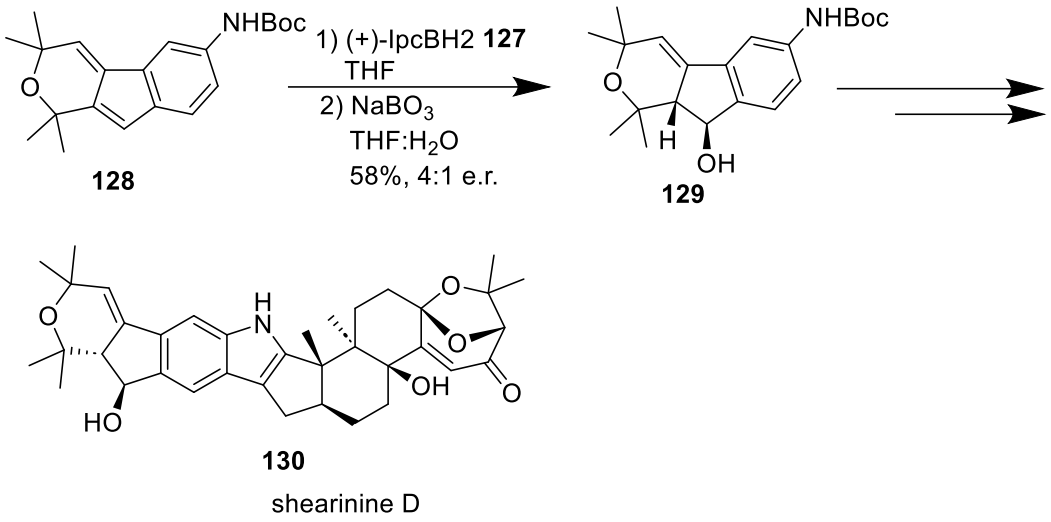
Scheme 25: Hydroboration-oxidation procedure with the generally accepted mechanism.

The regioselectivity and reactivity can be tuned by the proper choice of hydroboration reagent. More sophisticated hydroboration reagents (Scheme 26) are typically disubstituted (HBR_2), carrying sterically dense moiety (such as 9-BBN **124**, disiamylborane **125**) or alkoxy moiety (catecholborane **126**) or chiral moiety (**127**). The common and sterically demanding 9-BBN allows for highly regioselective hydration of alkanes, with the drawback of mild reactivity, often requiring heating. Interestingly, boranes derived from chiral alkyls, such as (+)-monoisopinocampheylborane (**127**) are utilized in enantioselective hydroboration.



Scheme 26: Common hydroboration reagents.

The chiral borane (**127**, Scheme 27) was employed in the total synthesis of shearinine D (**130**), a potential anti-cancer drug.[59] Owing to the chiral nature of borane **127,** the hydroboration-oxidation procedure afforded the formation of the benzylic alcohol **129** in a regioselective and enantioselective manner.



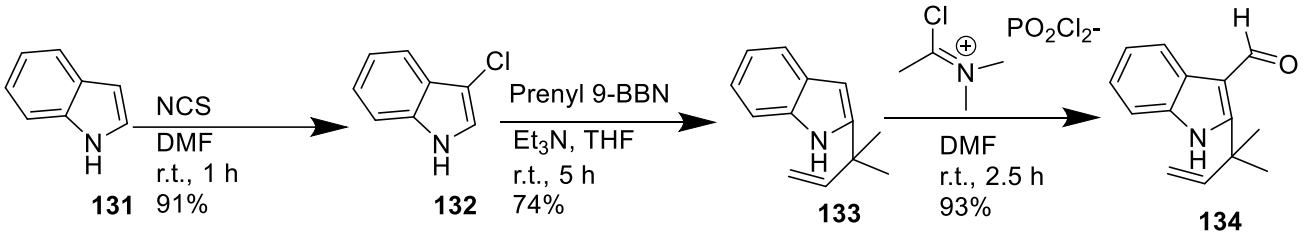
Scheme 27: Synthesis of the shearinine D by utilizing hydroboration-oxidation procedure with chiral hydroboration reagent.

3.3 Synthesis of neoechinulin B: an indole and diketopiperazine fragment of chevalinulin A

As shown in chapter 3.1 Chevalinulins A and B, neoechinulin B appears to be a structural fragment of chevalinulin A and is likely involved in its biosynthesis. In this chapter, the total synthesis of the compound elaborated by D. Trauner et al. will be discussed.[60]

The synthesis is done in a convergent fashion: the last step of the total synthesis is the condensation of two fragments, a formylated indole and a diketopiperazine derivative.

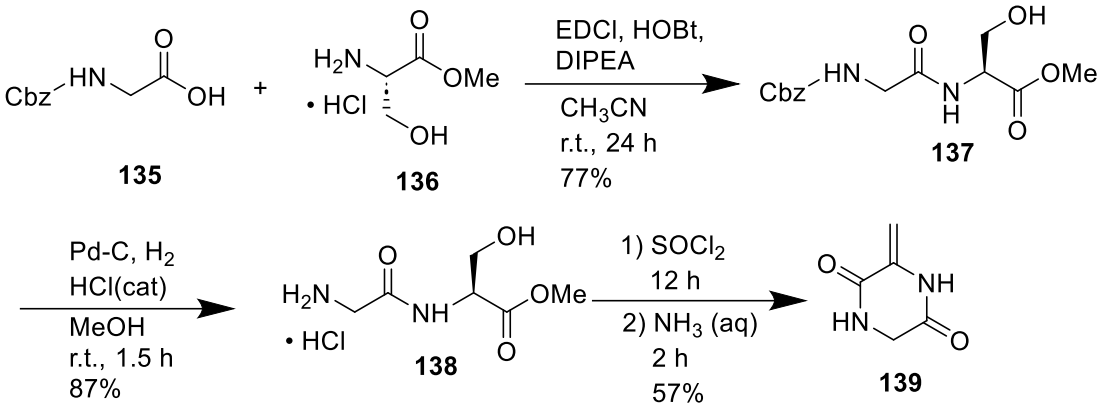
Starting with the synthesis of the formylated indole, the first step is chlorination of the indole (**131**, Scheme 28) followed by the reverse-sense prenylation by using Danishefsky's conditions.[61] The prenylated indole **133** is then subjected to formylation with Vilsmeier–Haack conditions, regioselectively obtaining formylated indole **134**.



Scheme 28: Synthesis of the formylated indole 134 with the key reverse-sense prenylation.

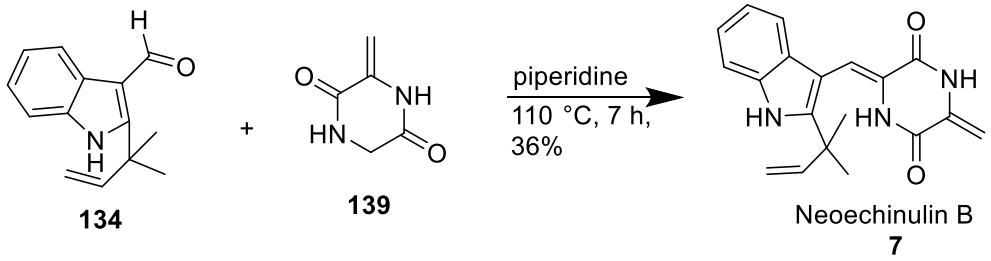
The first step of the synthesis of the second fragment is the condensation of the CBZ-protected glycine (**135**, Scheme 29) with L-serine ester **136** using a common peptide coupling procedure to provide the protected dipeptide **137**. The CBZ-protective group was then reductively cleaved with H_2/Pd-C giving the dipeptide methyl ester **138**. The dipeptide **138** underwent cyclization

by treatment with $SOCl_2$ and with subsequent NH_3 treatment to finally provide the target diketopiperazine **139**.



Scheme 29: Synthesis of the second key fragment, diketopiperazine 136 *via* peptide chemistry and cyclization.

The final step – the Knoevenagel reaction of the two fragments **134** and **139** provided the target compound neoechinulin B (**7**, Scheme 30) in 36% yield. This Knoevenagel reaction served as an inspiration for the first step of our disconnection approach of chevalinulin A, which will be discussed in chapter 4.1 Retrosynthetic analysis.

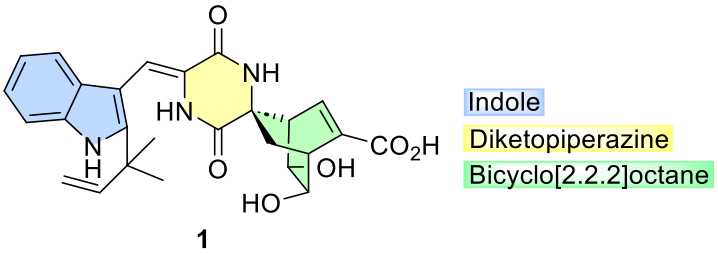


Scheme 30: The final reaction connecting the two fragments – Knoevenagel condensation.

4. Results and discussion

4.1 Retrosynthetic analysis

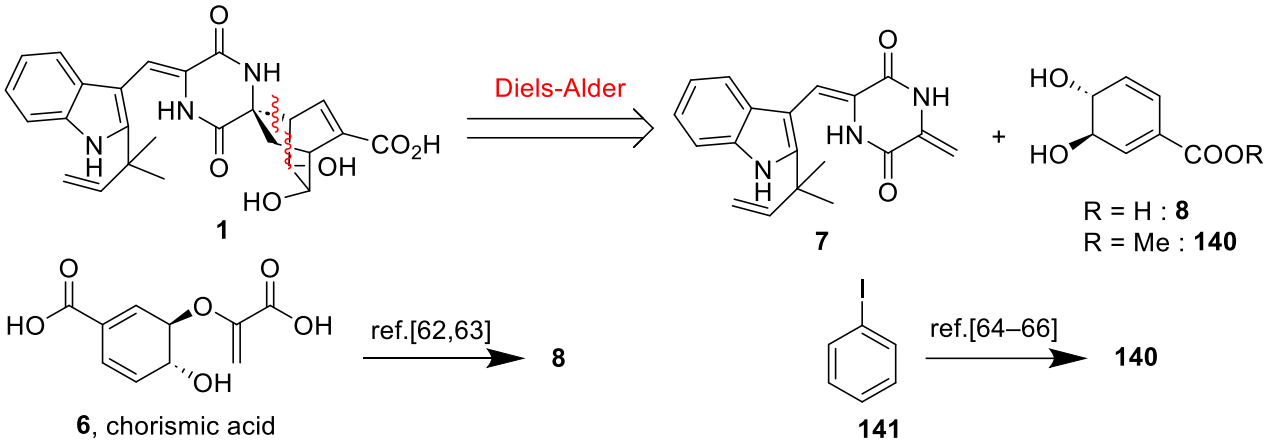
The intricate molecule of chevalinulin A (**1**, Figure 4) exhibits a unique combination of structural motifs; indole, diketopiperazine and bicyclo[2.2.2]octane core (chapter 3.1 Chevalinulins A and B). Within these motifs, the indole moiety features a terpenic (1,1-dimethyl-2-propen-1-yl) unit and a connection to an exocyclic double bond. The exocyclic double bond is a part of the diketopiperazine, which is fused with the bicyclo[2.2.2]octane core in a spirocyclic arrangement. This bicyclic core exhibits remarkable complexity; it features vicinal alcohols, and a carboxylic acid moiety connected to the double bond, all with exactly defined stereochemistry (containing five stereogenic centers). The following retrosynthetic analysis describes the main synthetic approaches, excluding protection/deprotection steps.



1

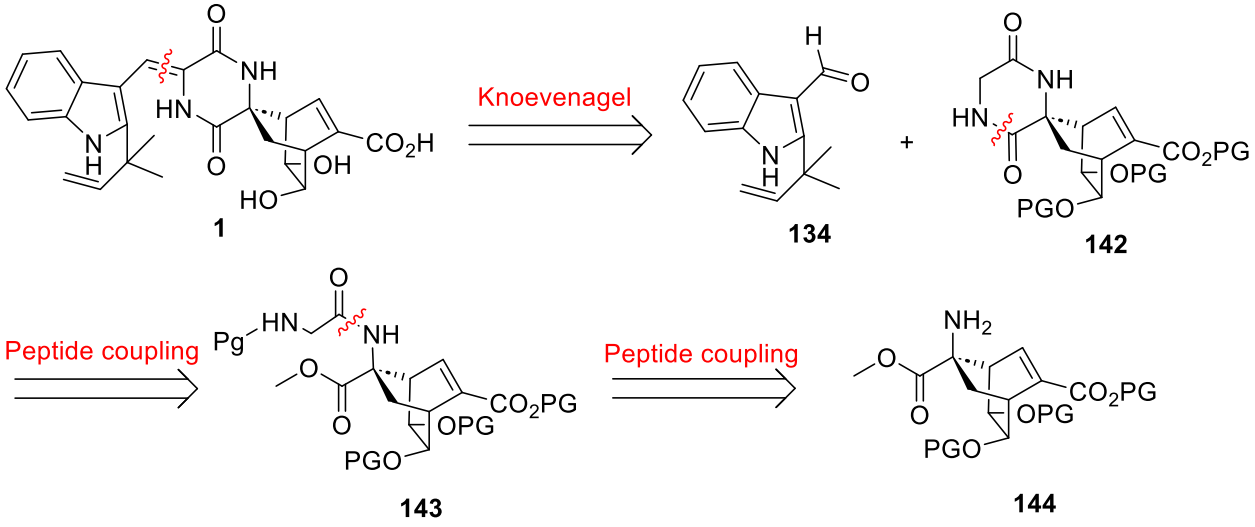
Figure 4: Structure of chevalinulin A and its distinctive structural motifs.

The disconnection of chevalinulin A leading to Diels-Alder reaction (Scheme 31) of fragment **7** and fragments **8** or **140** is in accordance with the proposed biosynthesis of chevalinulin A (chapter 3.1 Chevalinulins A and B). The support of the proposed disconnection is that both fragments are known from previous reports.[60,62,63] The dienophile **7** represents the natural compound neoechinulin B, whose total synthesis was discussed previously (chapter 3.3 Synthesis of neoechinulin B: an indole and diketopiperazine fragment of chevalinulin A). Conversely, the dienes **8** and **140** are not readily available. The free acid **8** is quite expensive (500 mg, 520€, Apollo Scientific), and its laboratory preparation starts from even more expensive chorismic acid (5 mg, 186€, Sigma-Aldrich).[62,63] Preparation of methyl ester **140** is even more complicated, employing not readily available mutated strain of *Pseudomonas putida* bacteria.[64–66]



Scheme 31: Disconnection leading to Diels-Alder reaction of known fragments.

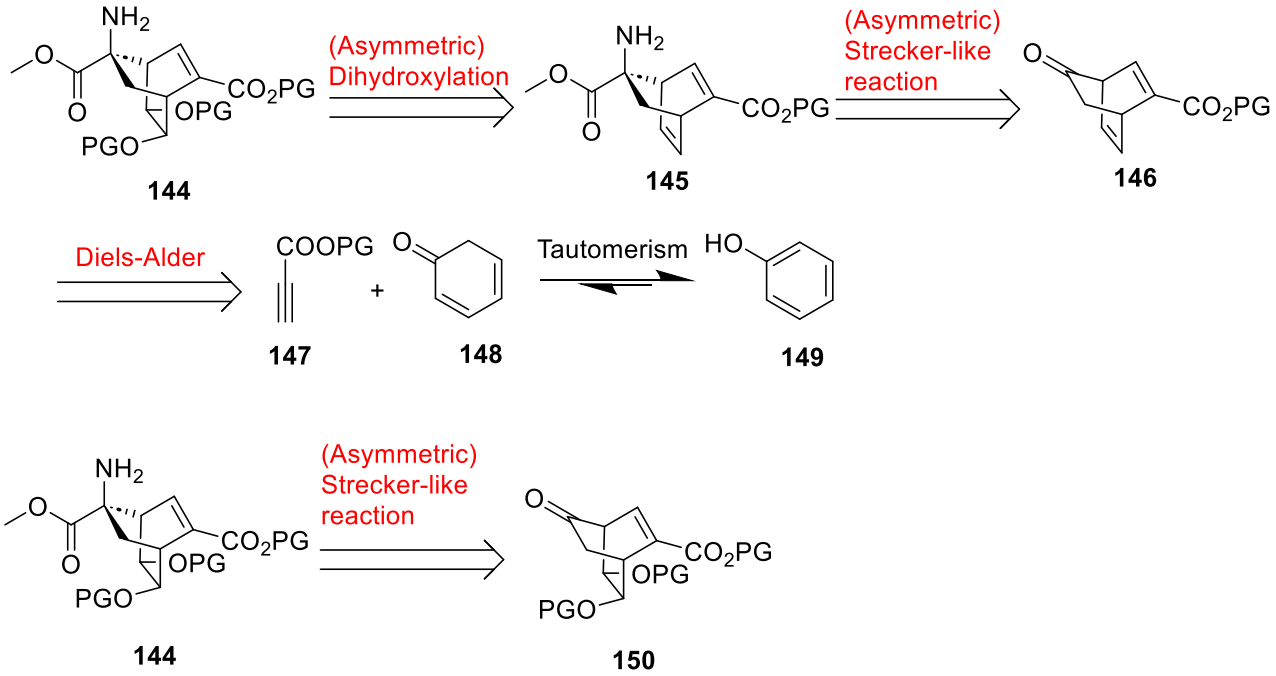
Based on those drawbacks, we proposed an alternative disconnection approach leading to the Knoevenagel reaction of fragments **134** and **142** (Scheme 32). Although fragment **134** is known from the literature literature,[60] the synthesis of the more challenging fragment **142** is not reported. The diketopiperazine core of the fragment **142**, can be disconnected by two peptide couplings leading to a compound with an amino acid arrangement **144**.



Scheme 32: Disconnections leading to Knoevenagel reaction and peptide couplings.

The resulting fragment **144** is an intricate bicyclic compound with exactly defined stereochemistry (Scheme 33). The sequence of further disconnections and corresponding intermediates need to be evaluated carefully. For example, the disconnection of the diol arrangement of intermediate **144** leads to alkene **145** *via* (asymmetric) dihydroxylation. Then, the amino acid arrangement of alkene **145** can be disconnected to the ketone **146** *via* (asymmetric) Strecker reaction. Unfortunately, the bicyclic ketone cannot be disconnected based on Diels-Alder reaction, due to the apparent tautomerization of hypothetical diene **148**.

Alternatively, employing (asymmetric) Strecker reaction for the disconnection of the amino acid arrangement of compound **144** leading to the ketone **150** is reasonable.

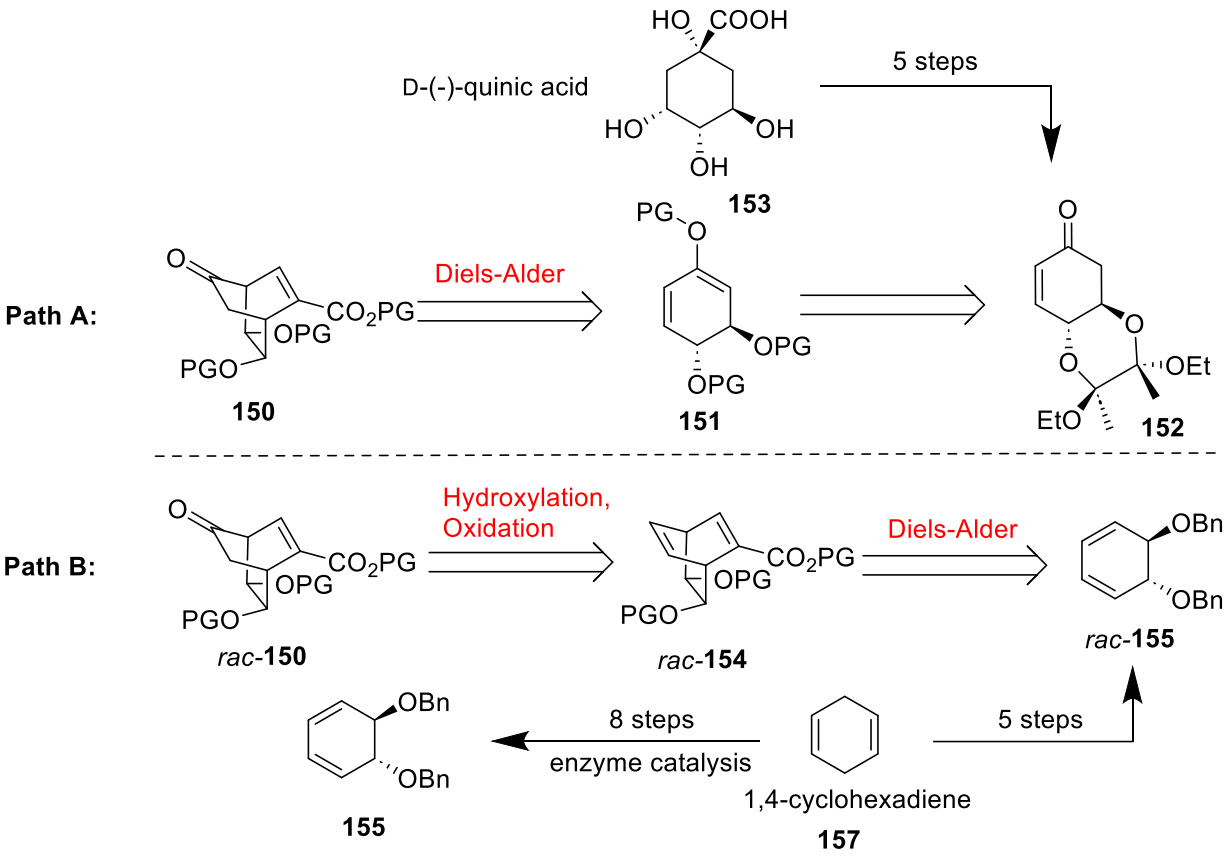


Scheme 33: Retrosynthetic pitfall in the form of tautomerism of starting material.

The retrosynthesis of the key fragment, ketone **150** can be divided into two pathways, **Path A** and **Path B** (Scheme 34).

Path A encompasses disconnection leading to Diels-Alder reaction of diene **151**. The diene could be prepared from enone **152** *via* enolization. This approach (**Path A**) offers the advantage of readily obtaining the enone **152** from natural D-(-)-quinic acid (**153**), which already possesses the desired stereochemistry.[67] Furthermore, the D-(-)-quinic acid (**153**) is readily available (25 g, 58€, Sigma-Aldrich) compared to the chiral diene **8** (Scheme 31).

On the other hand, **Path B** disconnects the ketone moiety by hydroxylation/oxidation procedure. The resulting bicyclic alkene **154** is a product of the Diels-Alder reaction with diene **155**, which can be obtained from cyclohexadiene **157**. The drawbacks of this method include more steps to reach the target ketone **150**, and even more steps to obtain the ketone in enantiomerically enriched form.



Scheme 34: Two retrosynthetic strategies towards the key fragment, ketone 148.

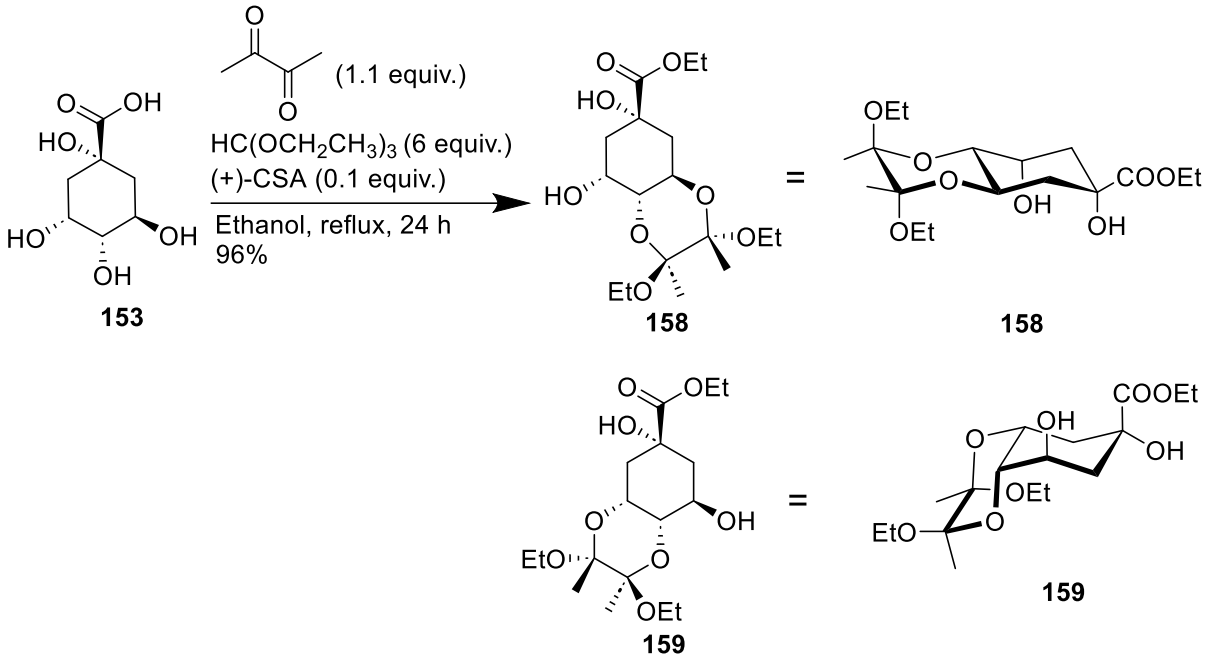
After considering the advantages and drawbacks outlined above, **Path A** was selected as the initial synthetic approach.

4.2 Synthetic Path A

As depicted in Scheme 34, the starting material for synthetic **Path A** is natural and optically pure D-(-)-quinic acid (**153**).

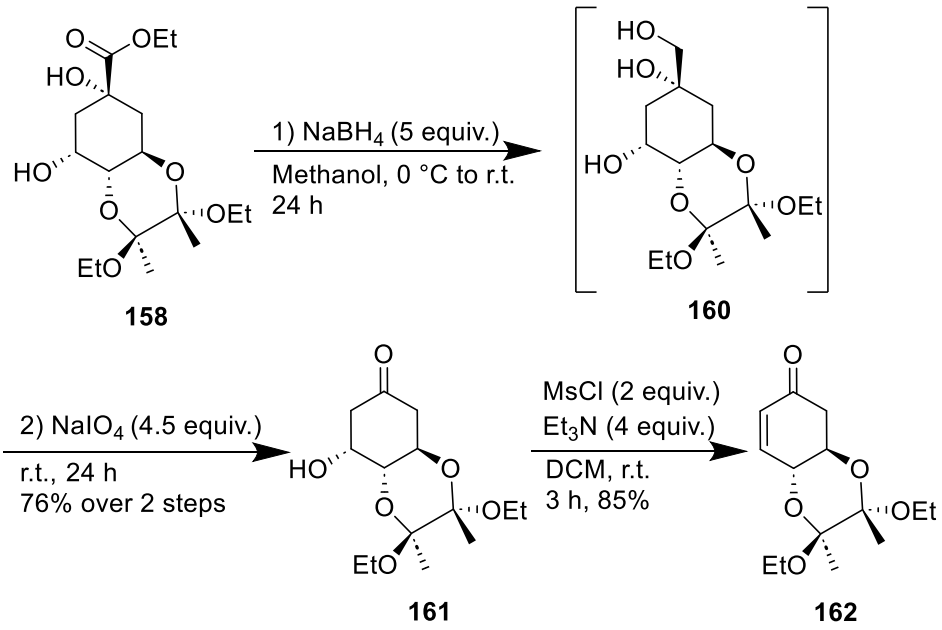
The reaction of D-(-)-quinic acid (**153**) with biacetyl and triethyl orthoformate conducted in the presence of catalytic (+)-CSA resulted in the expected formation of protected ester (**158**, Scheme 35). Despite following the reported procedure, the isolated yield was 34% instead of the reported 97%.[67] NMR analysis of the by-products revealed the formation of mono-acetal, implying the possible presence of water in the reaction mixture. By increasing the amount of water-consuming reagent triethyl orthoformate (from 3.3 to 6 equivalents) the reaction gave exclusively **158** in 96% yield. Biacetyl serves as a protective group for diols, and the molecule of D-(-)-quinic acid (**153**) possesses four free hydroxyl groups, all of which can potentially be protected by various combinations. The probable origin of selectivity is in the preferable

formation of *trans*-decalin arrangement in **158** over the possible formation of a more hindered *cis*-decalin arrangement in **159**.



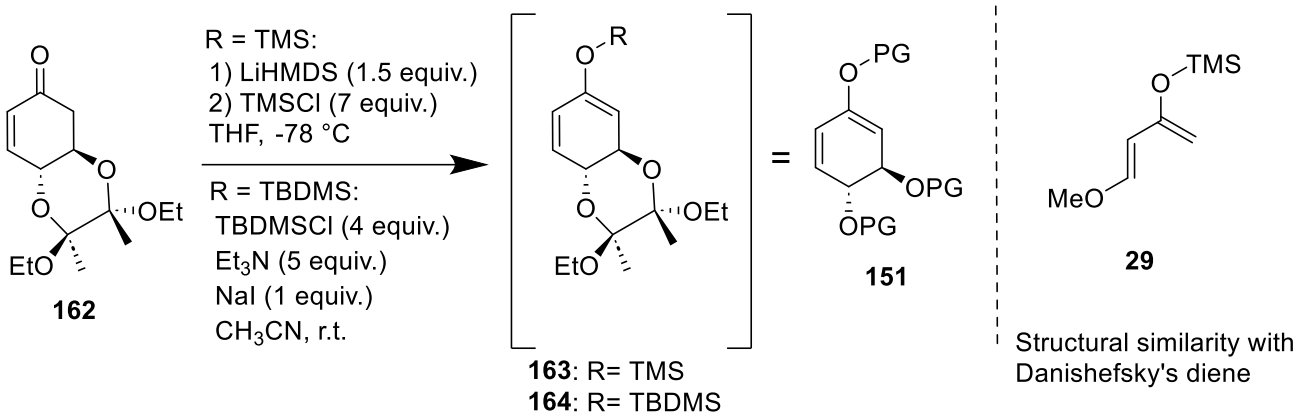
Scheme 35: Selective protection of the *trans* hydroxyl groups.

The ester **158** underwent reduction with $NaBH_4$ to yield the solution of intermediate (**160**, Scheme 36). Subsequently, $NaIO_4$ was added to the reaction mixture to oxidize the resulting diol to ketone **161**. Then, the hydroxyl group of ketone **161** was converted into a better leaving group (trifluoromethanesulfonyl) which underwent elimination to yield enone **162**.



Scheme 36: Further transformations to yield the enone 162.

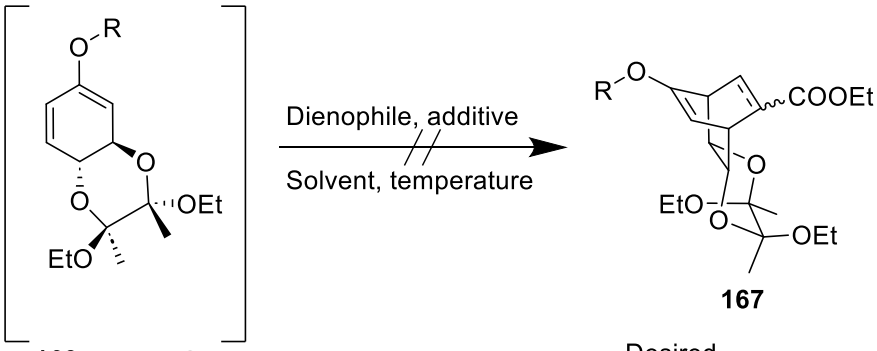
To achieve the desired diene arrangement **151** (Scheme 34, Scheme 37), it was reasonable to transform **162** into the corresponding silyl enol ether. Moreover, the resulting silyl enol ether arrangement closely resembles the well-known and reactive Danishefsky's diene (**29**, Scheme 7). Nearly quantitative conversion (TLC analysis) was obtained by employing a known procedure (TMSCl, LiHMDS in THF)[68] for silylation of almost identical substrate. For TBDMS ether, the highest conversion was achieved with TBDMSCl, Et_3N and NaI in CH_3CN. Other combinations of bases (DBU, LDA), and solvents (DMF, THF, DCM) were also tested. However, they provided worse results. Despite the inherent instability of the crude TMS enol ether, and decomposition into starting material upon standing, NMR measurements conducted in $CDCl_3$ filtered through basic alumina were sufficient to support its presence. In the case of TBDMS enol ether **164** the situation was similar, with an additional supporting measurement ESI-MS.



Scheme 37: Formation of the diene substrate for the subsequent Diels-Alder reaction.

The crude TMS and TBDMS enol ethers (**163**, **164**) were used in subsequent Diels-Alder reactions with ethyl propiolate (**165)**, expecting the formation of the desired bicyclic intermediate (**167**, Table 1). However, no reactivity was observed even under reflux in toluene. Similar results were observed with the more reactive[69] ethyl acrylate (**166**). It is known that Lewis's acids can catalyze the Diels-Alder reaction (Chapter 3.3.1 Diels-Alder reaction).[17] Nevertheless, the addition of Lewis acids such as $AlCl_3$ or $BF_3 \cdot OEt_2$ did not yield the expected product either. Instead, the silyl enol ether completely decomposed back into the enone **162**.

Table 1: Initial attempts for the Diels-Alder reaction with silyl enol ethers.



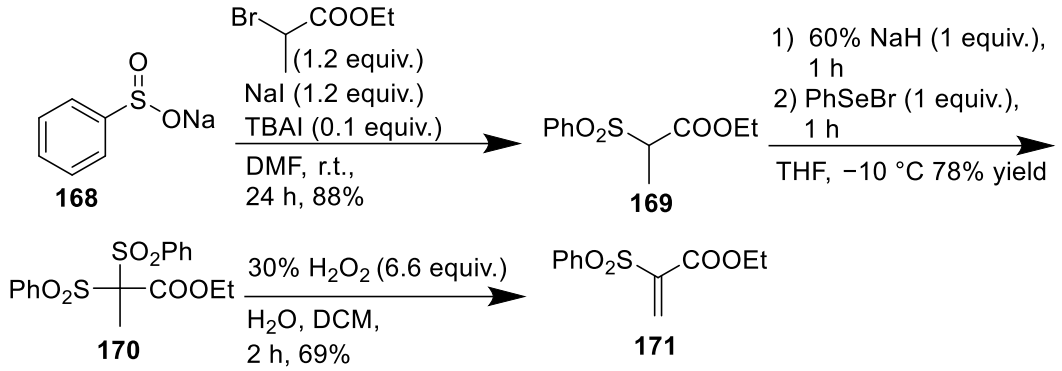
163: R = TMS
164: R = TBDMS

167

Desired Diels-Alder adduct

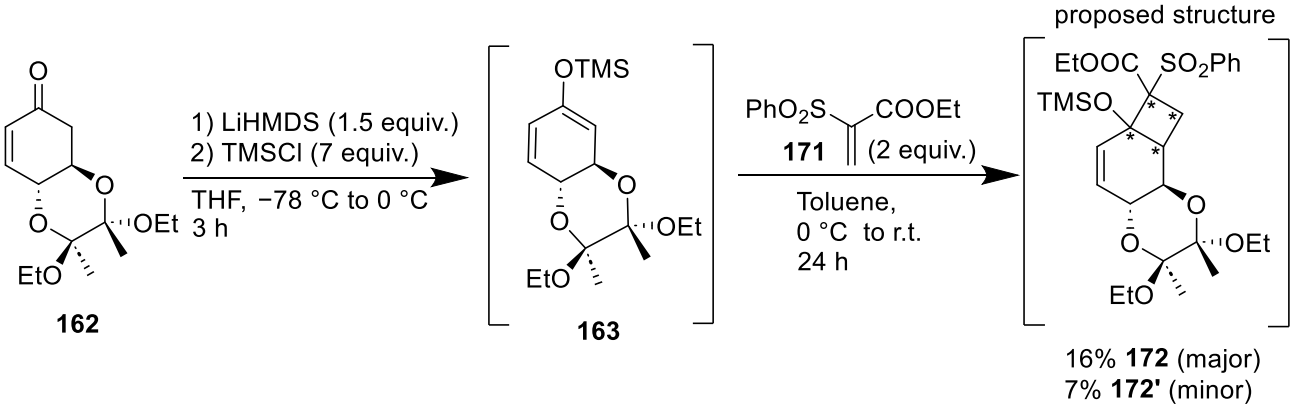
"Si"	Dienophile (equiv.)	Additive (equiv.)	Solvent (anhydrous)	Temperature	Result
TMS	≡—COOEt (2)	$AlCl_3$ (1), 5Å sieves	DCM	0 °C to r.t.	Decomposition
TMS	≡—COOEt (2)		Toluene	110 °C	No reacton
TMS	≡—COOEt (2)	$AlCl_3$ (1), 5Å sieves	Toluene	0 °C to r.t.	No reaction
TBDMS	≡—COOEt (3)	-	Toluene	reflux	No reaction
TMS	COOEt (10)	-	Toluene	reflux	No reaction
TMS	COOEt (10)	$AlCl_3$ (0.05)	Toluene	r.t. to reflux	Decomposition
TMS	COOEt (2)	$BF_3{\cdot}OEt_2$ (0.02), 5Å sieves	DCM	−78 °C to r.t.	Decomposition
TBDMS	COOEt (2.2)	-	Toluene	reflux	No reaction
TBDMS	COOEt (2.2)	-	Acetonitrile	r.t. to 40 °C	No reaction
TMS	COCl (2)	-	Toluene	r.t. to 40 °C	Decomposition

Because the system was apparently not reactive, an alternative dienophile, ethyl 2-(benzenesulfonyl) acrylate (**171**, Scheme 38), was proposed. This dienophile **171** was prepared in three steps according to the literature.[70,71]



Scheme 38: Synthesis of the alternative dienophile 171.

The reaction with dienophile **171** (Scheme 39) resulted in full conversion and yielded two unstable compounds (**172** and **172'**), which upon isolation with silica gel column chromatography decomposed considerably. The proposed structure of the products depicted in Scheme 39 was rationalized using 2D NMR analysis and MS of the major isomer. The isomers decomposed prior to further characterization. The [2+2] cycloadditions involving silyl enol ethers and Michael acceptors are known.[72,73] However, Lewis acid catalysis is usually needed. It is hypothesized that traces of TMSCl could be present in the crude silyl enol ether, facilitating the reaction.

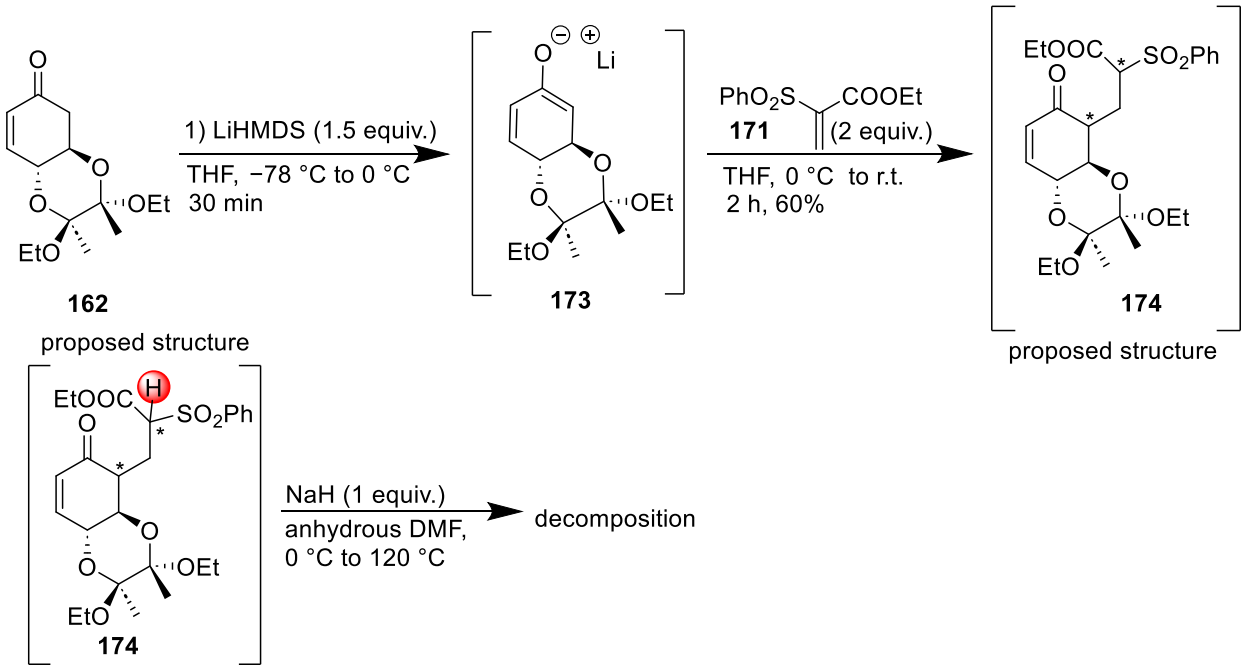


Scheme 39: Reaction of the crude TMS enol ether 163 with alkene 171.

Because of the above considerations, it was reasonable to form the enolate *in situ* without the formation of TMS-enol ether **163** (Scheme 40). The reaction of the *in situ* generated enolate resulted in full conversion and formation of four isomers with proposed structure **174**. The proposed structure was supported by NMR analysis; the presence of four isomers was especially

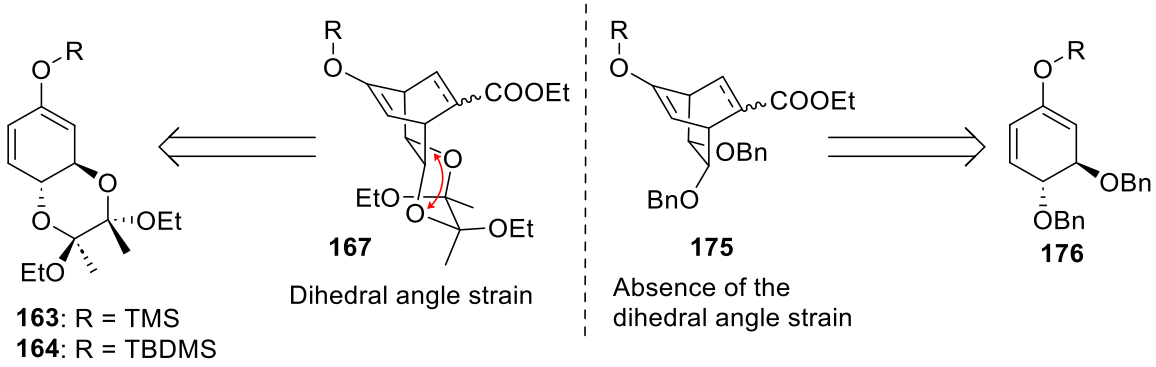
notable in the ^{13}C NMR spectra, where nearly every peak was split into four when zoomed in. Furthermore, MS analysis provided additional support for the proposed structure.

The proposed structure of the intermediate **174** opens the possibility for intramolecular Michael addition. The depicted α-hydrogen is likely the most acidic (two neighboring electron withdrawing groups), and its deprotonation would form carbanion, which could then react with the conjugated ketone *via* the intramolecular Michael addition. Consequently, the reaction was tested with DBU and NaH bases in DMF. The reaction temperature was gradually increased from 0 °C in 10 – 20 °C increments until the disappearance of the starting material was observed. Unfortunately, in both cases, the reaction resulted in a complex mixture, and crude NMR analysis did not indicate the presence of the desired product.



Scheme 40: Attempt for anionic/formal Diels-Alder reaction.

To advance in the synthesis, it was necessary to evaluate why the apparently reactive silyl enol ether (**163**, **164**) or enolate **173** failed to react as expected. One potential reason could be the presence of dihedral angle strain in the product (as depicted in Scheme 41, **167**). This issue could be addressed by changing the protective group with one that does not introduce dihedral angle strain. Benzyl groups are particularly appealing in this regard because they are also stable in the presence of Lewis acids (potential catalysts for the Diels-Alder reaction) and under acidic/basic conditions that may be encountered later in the synthesis.[74] The benefit of benzyl groups was also supported by preliminary calculations (Figure 5), showing that the reaction barrier of Diels-Alder reaction of ethyl propiolate with **176** is about 6 kcal/mol lower than in the reaction with diacetal-protected diene **(163)**.



Scheme 41: Presence of dihedral angle stain in the product and proposed change of protecting group.

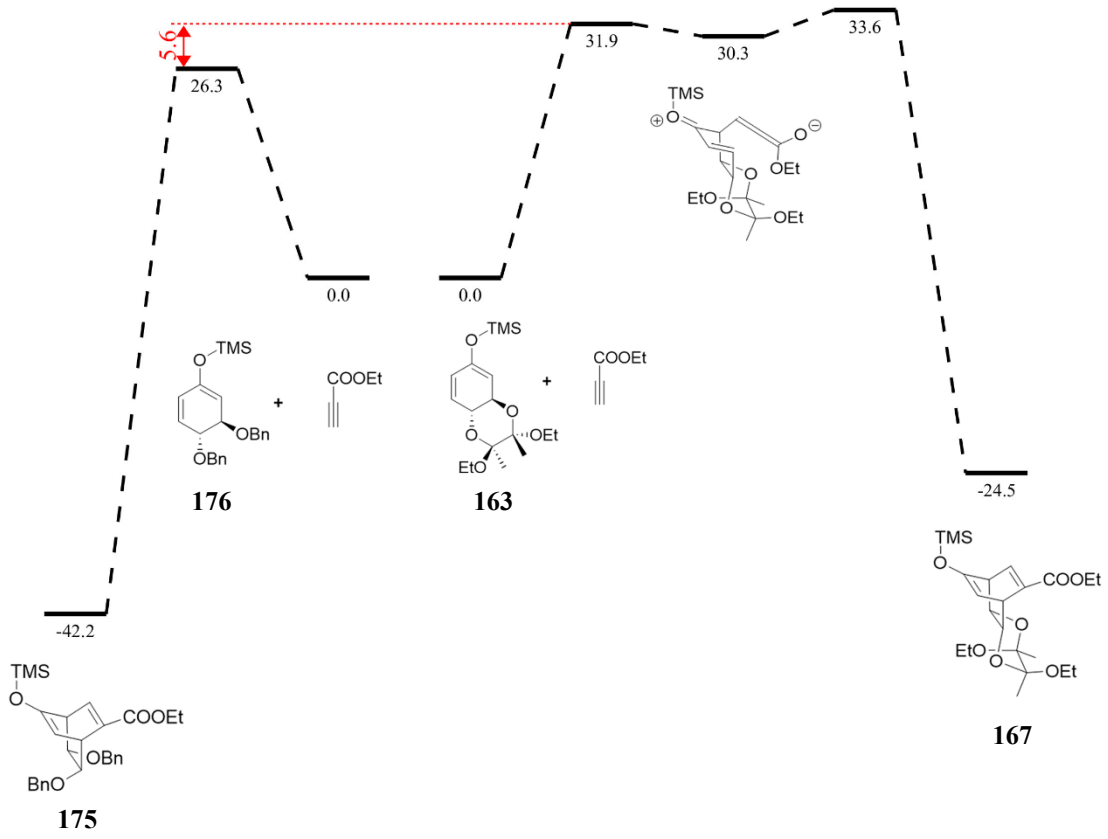
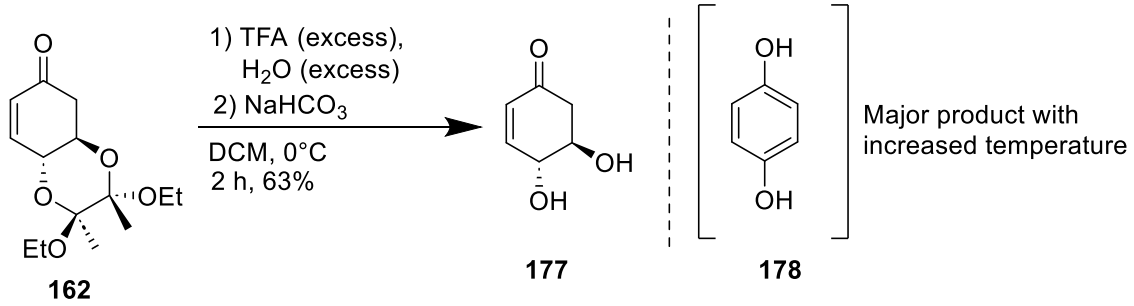


Figure 5: Free energy profile of the Diels-Alder reaction with corresponding dienes in kcal/mol units. Performed at M06-2X/6-311+G*//M06-2X/6-31+G* level of theory. The free energies of 176 and 163 were set to zero for better clarification.

In order to obtain the benzylated intermediate **176**, it was necessary to hydrolyze the biacetal **162** into diol (**177**, Scheme 42). Synthesis of the target diol **177** *via* hydrolysis of similar acetal is known in the literature.[75] However, heating the reaction mixture during concentration under reduced pressure (using a rotary evaporator) resulted in the decomposition of diol **177** into hydroquinone **178**. Thus, the reactant equivalents were modified (inspired by literature),[67] and

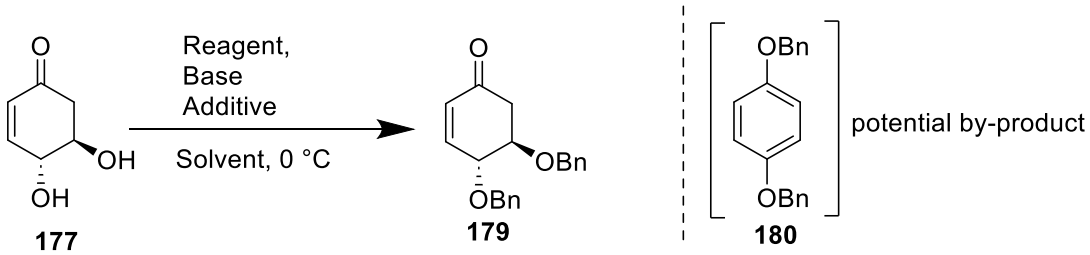
the TFA was quenched with sodium bicarbonate instead of evaporating under reduced pressure, providing the target diol **177** in 63% yield. Additional tested conditions included catalytic PTSA in water/methanol (1:1) and in dioxane. However, these conditions yielded an unreactive system at room temperature and a mixture of products at elevated temperature.



Scheme 42: Acidic hydrolysis of the biacetal 162.

Benzylation of the diol **177** (Table 2) with conventional benzylation procedure (NaH / DMF) resulted in a complex mixture, which upon NMR analysis showed no trace of the desired product. Consequently, alternative base (Ag_2O), additive (TBAI), solvent (DCM) and alternative protecting group reagent (BOMCl) were tested: all yielding the same outcome – a complex mixture. All the used methods shared a common feature: the presence of a base. Even the reaction with benzyl 2,2,2-trichloroacetimidate (**181,** Figure 6), a commonly used benzylation reagent in carbohydrate chemistry requiring the catalytic amount of acid,[76] resulted in the same outcome. Isolation of pure compounds from the complex mixture(s) was not successful. However, NMR analysis revealed the potential presence of dibenzylated hydroquinone (**180**) and other aromatic compounds. The apparent aromatization is supported by the observation of acetal hydrolysis (Scheme 42), wherein aromatization occurred at elevated temperature under acidic conditions.

Table 2: Attemps to protect the diol 177.



Reagent	Base	Additive	Solvent[a]	Result
BnBr	NaH/Ag_2O	-	DMF	Complex mixture
BnBr	NaH/Ag_2O	TBAI	DMF	Complex mixture
BnBr	Ag_2O	TBAI	DCM	Complex mixture
181	-	TsOH	DCM, Pentane	Complex mixture
BOMCl	DIPEA		DCM	Complex mixture

[a]anhydrous

Similar analogy was found in literature, where the direct benzylation of diol (**182**, Figure 6) provided complex mixture.[77]

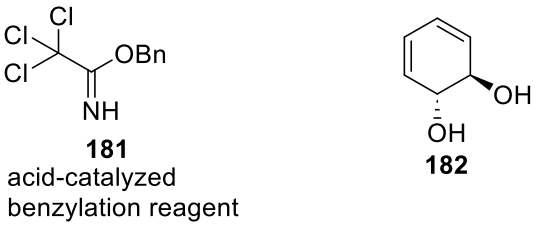
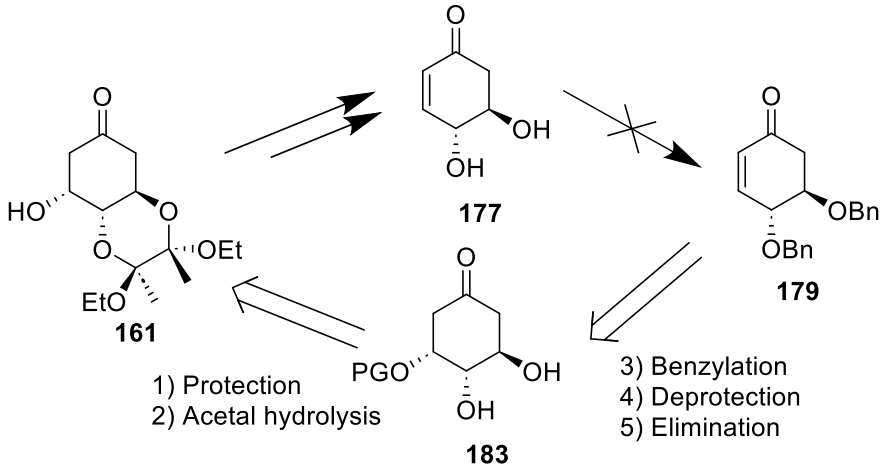


Figure 6 Structure of the acid-catalyzed benzylation reagent 181 and diol 182.

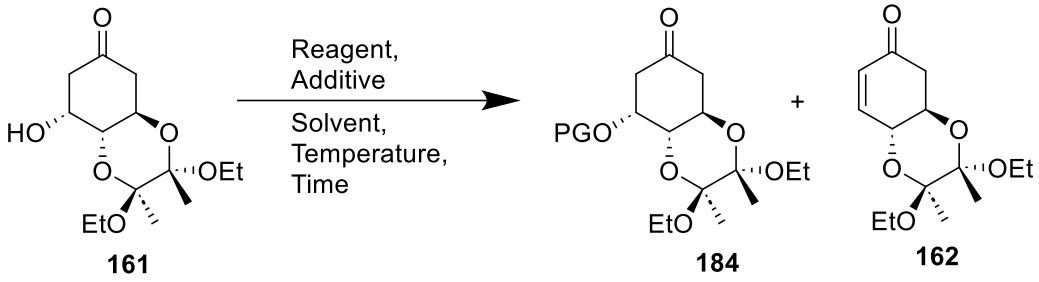
Due to the challenges in protecting diol **177**, an alternative strategy was evaluated (Scheme 43). The concept involves taking two steps back: first, protecting the free hydroxyl group in substrate **161**, and then hydrolyzing the acetal to yield diol **183**. Although the diol **183** has a similar arrangement, it lacks a double bond. Hypothetically, the arrangement lacking a double bond is one step farther from aromatization, implying successful benzylation may occur. Subsequent steps would involve deprotection and elimination of the free hydroxyl.



Scheme 43: Alternative route to benzylated intermediate 179.

Suitable protective groups for the free hydroxyl of **161** are groups capable of withstanding acidic acetal hydrolysis conditions while being easily deprotected. For this reason, acetyl (Ac) and *tert*-butyldiphenylsilyl (TBDPS) were chosen as the best candidates (Table 3). Acetylation with conventional procedure resulted in an exclusive formation of enone (**162**). This could be explained by elimination owing to the good leaving group character of acetate. Therefore, the focus shifted to the TBDPS protective group. Silylation with a common procedure resulted in no reactivity at room temperature. Full conversion was observed at 70 °C, resulting in a mixture of the desired compound **184** and elimination product enone (**162**). By decreasing the temperature to 60 °C and shortening reaction time the exclusive formation of silylated compound **184** was observed.

Table 3: Protection of the free hydroxyl group of 161.

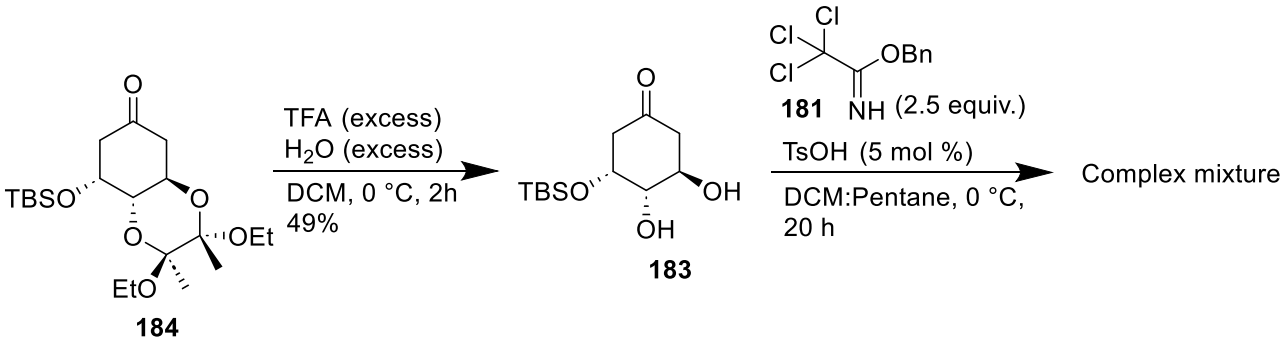


161 **184** **162**

PG donor (equiv.)	Reagents (equiv.)	Solvent (anhydrous)	Temperature	Time	Product
Ac_2O (2)	DMAP (0.1)	Pyridine	r.t.	2 h	78% **162**
TBDPSCl (5)	Imidazole (10)	DMF	70 °C	48 h	**184**:**162** = 2.5:1[a]
TBDPSCl (5)	Imidazole (10)	DMF	60 °C	20 h	73% **184**

[a]**1H NMR ratio**

Hydrolysis of the diacetal **184** using an analogous procedure as before (Scheme 42) provided diol **183** (Scheme 44). Interestingly, even the arrangement of diol **183** provided a complex mixture after treatment with the benzylating trichloroacetimidate reagent **181**.



184 **183** **181**

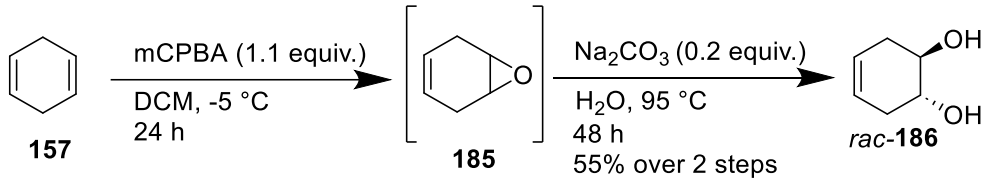
Scheme 44: Biacetal hydrolysis and an attempt to benzylate the diol 183.

Following the unsuccessful Diels-Alder reactions involving silyl enol ethers **163** and **164**, the focus shifted towards structural modification of the substrate. The objective was to facilitate its reactivity in the Diels-Alder reaction, particularly targeting the diacetal protective group. Several synthetic strategies were evaluated, however, none proved successful. The common difficulty was the formation of a complex mixture lacking the desired compound. Consequently, this synthetic pathway was abandoned in favor of pursuing the alternative synthetic **Path B**.

4.3 Synthetic Path B

This section will focus on an alternative synthetic strategy, the racemic version of **Path B**. This approach involves a Diels-Alder reaction utilizing an alternative, structurally less complex diene substrate *rac*-**155** (Scheme 34). The drawback of the proposed synthetic path is the increased number of potential steps necessary to synthesize ketone *rac*-**193**. Additionally, achieving the diene substrate **155** in optically pure form utilizes various strategies published in the literature, such as employing NHC[78] or enzymatic synthesis.[79,80]

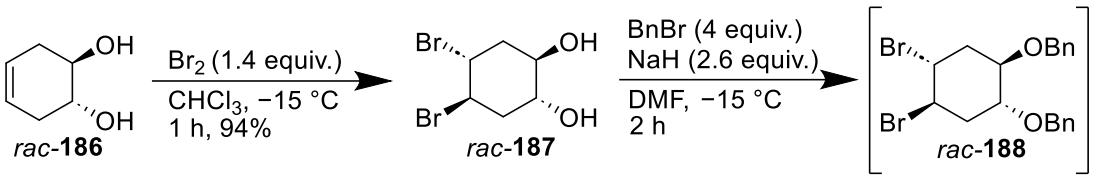
The first step of synthetic **Path B** includes oxidation of 1,4 cyclohexadiene (**157,** Scheme 45)**,** and subsequent basic opening of the epoxide to obtain the racemic diol *rac*-**186** in 55% yield over two steps.[81]



Scheme 45: Epoxidation of cyclohexadiene 157 with the subsequent basic opening.

Then, the diol *rac*-**186** (Scheme 46) was brominated, yielding compound *rac*-**187** in 94% yield.[80] To confirm the literature-reported relative configuration of *rac*-**187**, the compound was crystallized from methanol. X-ray analysis of the crystal confirmed the relative configuration (Figure 7).

Following the synthesis strategy from literature,[77] the subsequent step involves benzylation of the brominated diol *rac*-**187** followed by elimination of the bromide to achieve the diene *rac*-**155**. To achieve successful benzylation of the brominated diol (*rac*-**187**, Scheme 46), the conditions from the literature[77] had to be changed. The reported procedure encompasses benzylation at room temperature for 5 hours; however, it results in a complex mixture. By benzylating at −15 °C for 2 hours the target compound *rac*-**188** was obtained without side products. The compound *rac*-**188** is particularly non-polar, having $R_f \approx 0.5$ (TLC Hexane: EtOAc = 20:1). Subsequently, it proved to be difficult to separate unreacted benzyl bromide from the product, the isolated product *rac*-**188** always showed traces of benzyl bromide. Consequently, compound *rac*-**188** was used directly in the next step and not characterized as a pure compound.



Scheme 46: Bromination and subsequent benzylation *en route* to the Diels-Alder substrate.

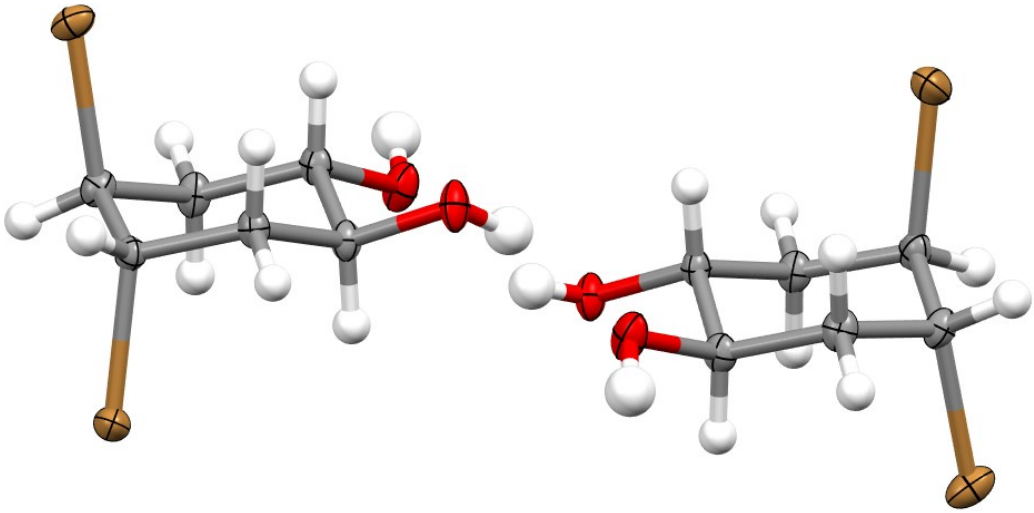
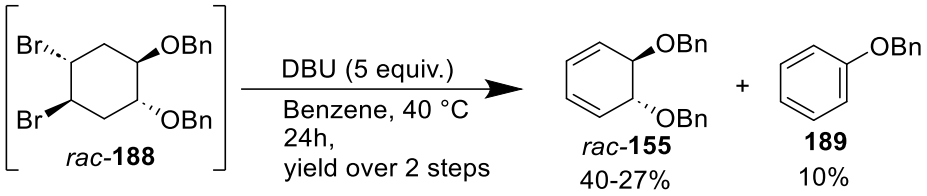


Figure 7: Crystal structure of the racemate 187, confirming the relative configuration. CCDC: 2352199.

The next step encompassed the formation of diene *rac*-**155** (Scheme 47) *via* basic elimination of bromide. The yield of diene *rac*-**155** varied, ranging from 27% to 40%. The presence of aromatization product **189** was observed in every case as a major byproduct.

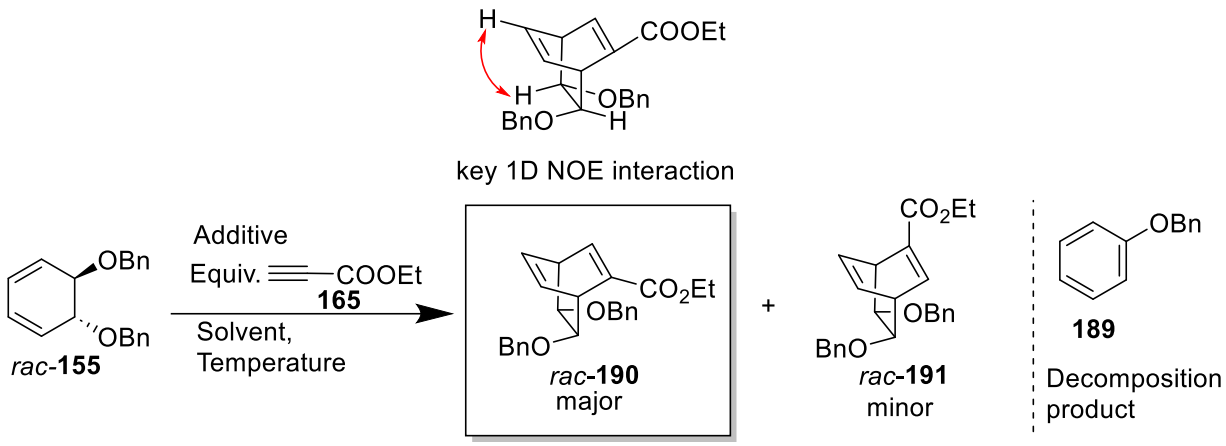


Scheme 47: Synthesis of the Diels-Alder substrate 155 together with byproduct 189.

Surprisingly, the diene *rac*-**155** was reactive with ethyl propiolate (**165)** in Diels-Alder cycloaddition (Table 4). Among the conditions tested, the best results were obtained under neat conditions, which provided a regioisomeric mixture of *rac*-**190** and *rac*-**191** in 80% yield. The separation of the two regioisomers *via* column chromatography was not achieved. The regioisomeric ratio was thus determined through ^{1}H NMR analysis, revealing a 5:1 ratio. The influence of several solvents (toluene, hexafluorobenzene, and DMF) on the regioisomeric ratio was examined, however, none of the reactions yielded an improved ratio. In contrast, reactions conducted with the tested solvents provided a lower yield compared to the neat reaction. Lewis

acid catalysis with $AlCl_3$ in DCM was also tested. However, the complete decomposition of the diene *rac*-**155** into aromatization product **189** was observed. The structure of the major isomer was elucidated with 2D NMR and 1D NOE NMR experiments.

Table 4: Reactivity of the diene *rac*-155 in Diels-Alder cycloaddition.



Solvent	Equiv. of 165	Reaction time	Temp.	Additive	Yield	Ratio[b]
Toluene	3+2[a]	48 hours	75 °C	-	30%	5:1
Hexafluorobenzene	3+2[a]	48 hours	75 °C	-	30%	5:1
DMF	3+2[a]	48 hours	75 °C	-	69%	5:1
anhydrous DCM	3	2 hours	r.t.	$AlCl_3$ [d]	Decomp.[c]	-
Neat	30	24 hours	75 °C	-	80 %	5:1

[a]Addition after 24 hours in order to achieve full conversion observed by TLC.

[b]NMR ratio

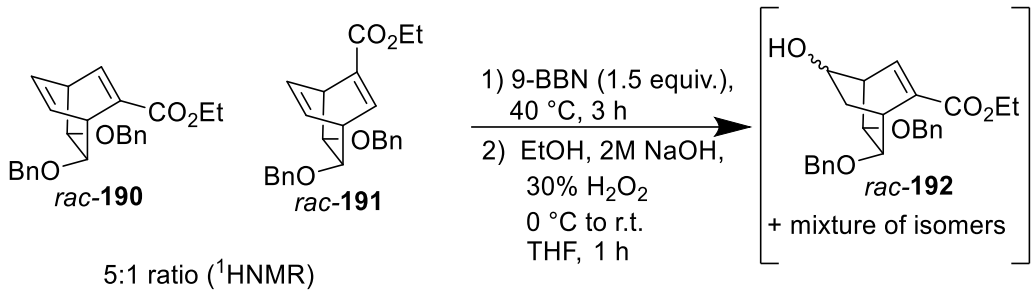
[c]Decomposition of diene *rac*-**155** into **189**

[d]0.2 equiv.

A brief temperature study of the reaction with neat conditions was also undertaken. The reaction temperature was set to 40 °C and raised in 5-10 °C increments over the period of several hours. Below 75 °C, the system was practically unreactive and the NMR ratio of the regioisomers remained unchanged.

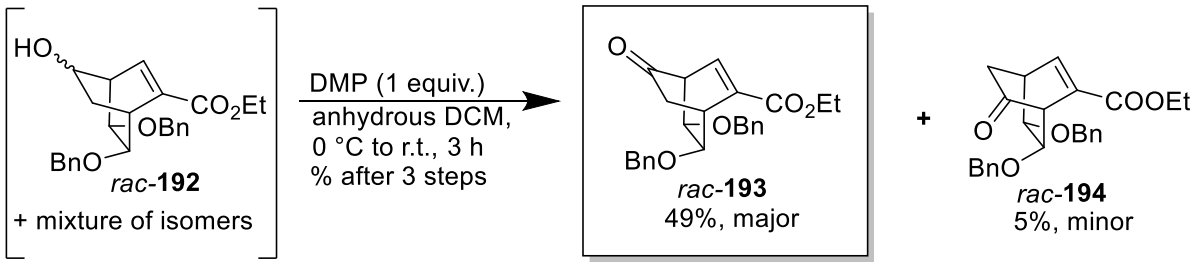
In order to obtain the desired ketone arrangement *rac*-**150** (Scheme 34), an olefin hydroxylation followed by oxidation was a reasonable strategy. Compound *rac*-**190** possesses two double bonds, with one being electron-poor. Furthermore, the carbon atoms in the more electron-rich double bond have different steric environments. These factors were employed in

hydroboration/oxidation procedure with 9-BBN (Scheme 48). The reaction conditions were inspired by literature,[82] however, heating to 40 °C was necessary for reactivity. After the hydroboration-oxidation procedure and column chromatography, a mixture of inseparable alcohols was isolated. The mixture was not characterized but used in the next step instead.



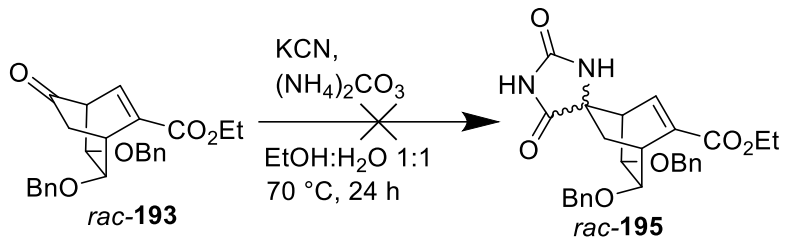
Scheme 48: Hydroboration/oxidation reaction yielding a mixture of isomers.

The next step was the oxidation of the inseparable mixture of alcohols *rac*-**192** into ketones (Scheme 49). The reaction resulted in full conversion with common DMP oxidation conditions,[83] yielding a separable mixture of a major (*rac*-**193)** and a minor product (*rac*-**194**) in 49% and 5% yield over 3 steps, respectively. The structures of the products were determined by 2D-NMR experiments and additionally confirmed by 1D-NOE experiments, revealing that the major isomer is the desired key fragment of chevalinulin A, *rac*-**193.**



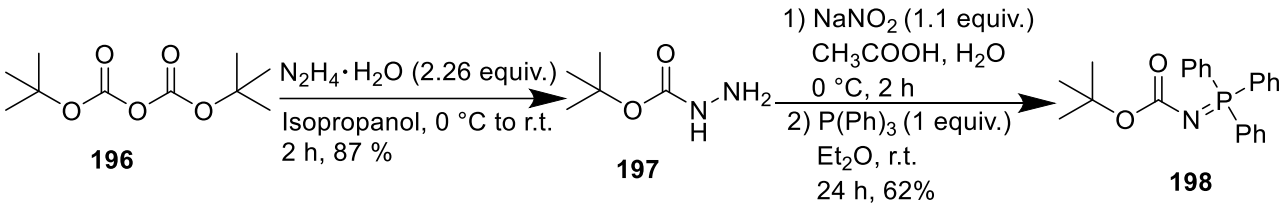
Scheme 49: Oxidation with DMP.

Having obtained the key fragment of chevalinulin A, the ketone *rac*-**193**, further synthetic transformations were also tested. The next synthetic step encompasses the construction of the α-amino acid skeleton. An appealing choice is the Bucherer-Bergs reaction, (Scheme 50) which comprises the formation of hydantoin. The formed hydantoin can then be hydrolyzed into the corresponding α-amino acid arrangement.[49,84] The reaction is known to proceed with many substrates.[85] Unfortunately, the successful outcome was not achieved; the desired product *rac*-**195** was not observed (Scheme 50).



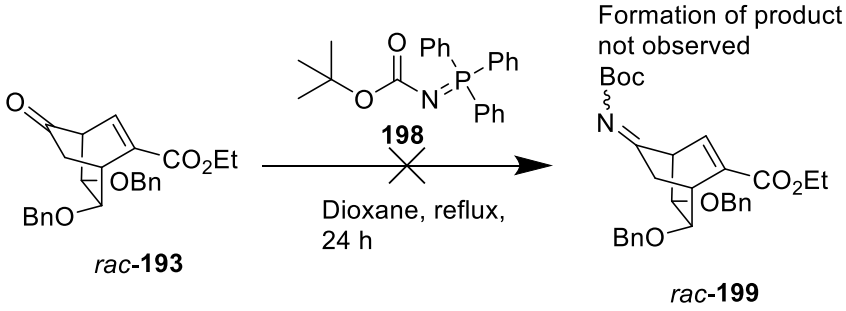
Scheme 50: Unsuccessful formation of hydantoin *via* Bucherer-Bergs reaction.

An alternative strategy to obtain the α-amino acid skeleton comprises the formation of protected imine and the subsequent addition of a suitable nucleophile. Examples of suitable nucleophiles include nitrile (Strecker reaction) or nitromethane (aza-Henry and subsequent Nef reaction). The initial idea was to generate a BOC-protected imine *via* aza-Wittig reaction[86] with reagent **198** (prepared in three steps, Scheme 51),[87] which would subsequently undergo nucleophilic addition.



Scheme 51: Preparation of the aza-Wittig reagent

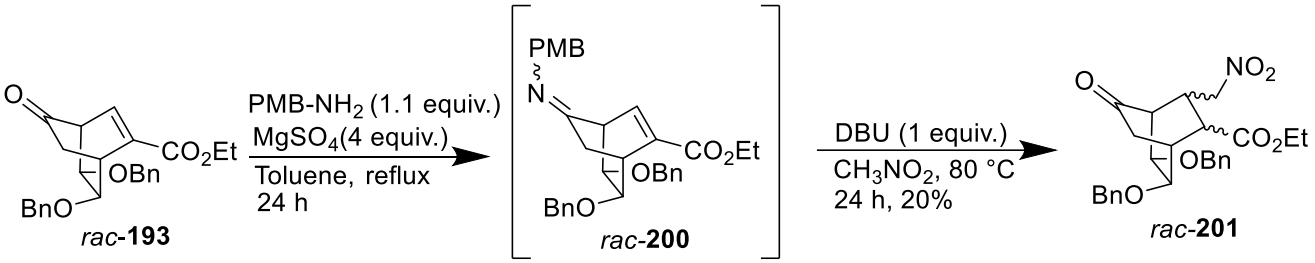
Unfortunately, the reaction of ketone *rac*-**193** and Aza-Wittig reagent (**198**, Scheme 52) did not occur even after 24 h reflux (determined by TLC and NMR of the reaction mixture).



Scheme 52: Unsuccessful formation of BOC-imine *via* aza-Wittig reaction.

On the other hand, the formation of PMB-protected imine was supported by ^{1}H and ^{13}C NMR measurements of the reaction mixture and by MS (Scheme 53). Isolation of the pure imine was not achieved, as the imine decomposed into ketone *rac*-**193** upon isolation with silica gel column chromatography. Accordingly, TMSCN and Et_3N were added to the crude imine to carry out nucleophilic nitrile addition.[88] Although a full conversion was observed (using TLC, and 1H NMR), the mixture decomposed back into starting material upon isolation, implying reversibility or instability of the potential product. The alternative strategy involved nucleophilic addition of nitromethane to imine, an aza-Henry reaction.[89] No reactivity was

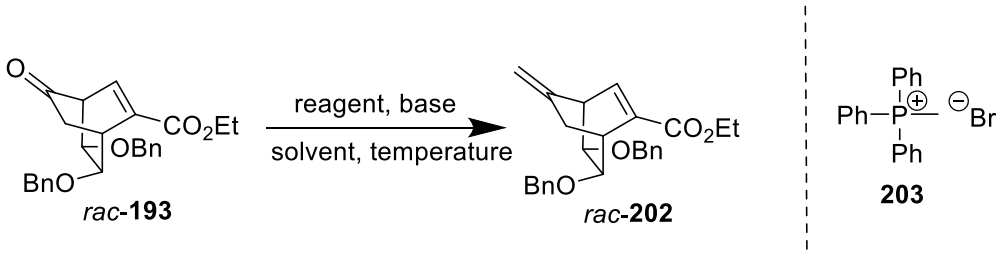
observed when 0.1 equiv. of DBU and 1 equiv. of nitromethane were added to the crude imine. When 1 equiv. of DBU, heating and nitromethane as a solvent was employed, the full conversion of starting imine *rac*-**200** was observed. After isolation, the reaction product was identified as a 1,4–conjugated addition product (*rac*-**201**, Scheme 53).



Scheme 53: Attempt for nucleophilic addition on imine provided the unwanted conjugate addition product.

Consequently, the new strategy involved the transformation of ketone into methylidene derivative (Table 5). The initial (Wittig-based) approach consisted of generating triphenyl phosphonium ylide with *n*-BuLi in THF. However, this resulted in decomposition into unidentified products. Next, Lombardo's reagent[90,91] and analogue[92] were tested. Unfortunately, no desired reactivity was observed. Surprisingly, generating the triphenyl phosphonium ylide with *t*-BuOK and conducting the reaction in toluene resulted in the formation of the desired product.

Table 5: Methylidenation of the ketone *rac*-193.



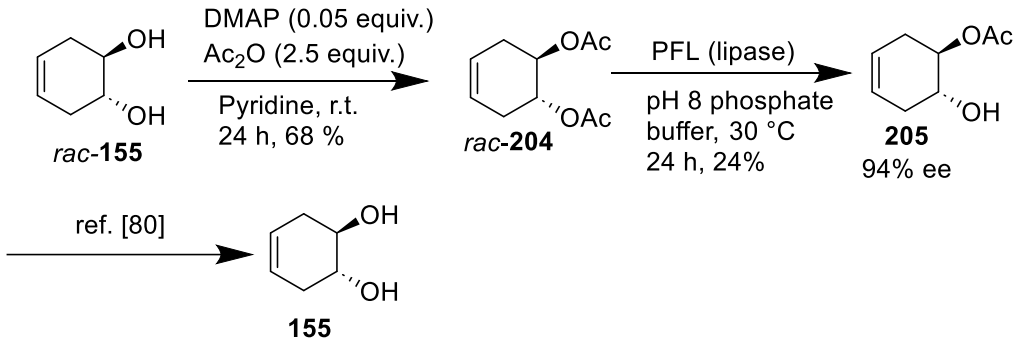
Reagents (equiv.)	Base (equiv.)	Solvent	Temperature	Result
rac-**203** (1.5)	*n*-BuLi (1.5)	THF	−78 °C to r.t.	Decomposition
$TiCl_4$ (10), CH_2Br_2 (10), Zn (10)	-	THF	0 °C to r.t.	No reaction
$TiCl_4$ (2), Mg (8)	-	THF/DCM	0 °C to r.t.	Decomposition
rac-**203** (3.75)	*t*-BuOK (3.6)	Toluene	80 °C	*rac*-**202**- 80%

The alternative synthetic Path B successfully led to the synthesis of the key fragment of chevalinulin A, the ketone *rac*-**193**, in 9 steps. The reactivity of the ketone was challenging,

particularly with nucleophiles. Fortunately, the methylidenation of the ketone was successful. The compound *rac*-**202** with the exocyclic double bond is therefore anticipated to be the precursor for the α-amino acid arrangement.

4.4 Future prospectives

Following the chiral outlook mentioned in chapter 4.3 Synthetic Path B, the route to optically pure **155** was preliminarily tested (Scheme 54). Following the acetylation of diol *rac*-**155**, the enzymatic hydrolysis with PFL (*Pseudomonas fluorescens* lipase)[79] provided the monoacetate **205** in 24% yield with 94% ee. The obtained monoacetate can then be hydrolyzed to yield the diol.[80]



Scheme 54: Preliminary test of the enzymatic hydrolysis.

After the successful synthesis of a racemic key fragment of chevalinulin A, the strategy towards an enantiomerically enriched form was addressed. The synthetic strategy utilizing enzymatic hydrolysis was demonstrated in this section.

Future experimentation will consist of attempts to obtain the α-amino acid **144**. The proposed way is to functionalize the intermediate **202**, *via* aminohydroxylation such as Sharpless asymmetric aminohydroxylation.[52] Benefit of this approach is that the regioselectivity can be tuned by the proper choice of *N*-haloamide and ligand. An alternative approach would consist of epoxide formation and subsequent opening with a suitable nitrogen donor (such as azide); however, the stereochemistry would be harder to control.

Thus, the journey towards the total synthesis of chevalinulin A continues.

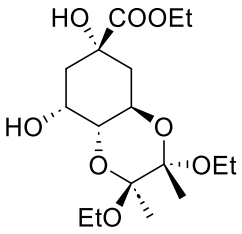
5. Experimental procedure

5.1 General procedure and chemicals

All chemicals used in this work were obtained from commercially available sources (BLDpharm, Acros organics, Sigma-Aldrich, Lach-Ner, Fluorochem). Ethyl acetate, toluene, hexane, chloroform and DCM were purified by distillation. Anhydrous DCM was obtained by reflux with calcium hydride and distillation under nitrogen atmosphere. Anhydrous THF and anhydrous toluene were obtained by reflux with sodium/benzophenone and distillation under nitrogen atmosphere. Unless stated otherwise, other reagents and solvents were not further dried or purified. The pH was analyzed using universal pH indicator strips (obtained from Lach-Ner). The thin layer chromatography (TLC) analysis was done using Kieselgel 60 F 254 TlC plates obtained from Merck. The TLC plates were analyzed using UV lamp (NU – 6KL, λ = 254 nm) and then developed by dipping the plate into AMC or vaniline solution and then applying heat with heat gun. The AMC solution was prepared by mixing 10 g of ceriuim(IV) sulfate dihydrate and 25 g of phosphotungstic acid in 1 liter of 1M sulfuric acid solution. The vaniline solution was prepared by mixing 12 g of vaniline and 2.5 ml of concentrated sulfuric acid in 200 ml of absolute ethanol. The compounds were concentrated *in vacuo* using rotary evaporator Heidolph LABOROTA 4000. Synthesized substances were vacuum dried using oil pump Vacuubrand RZ 2. NMR spectra of the synthesized compounds were measured using Bruker AVANCE III Spectrometer, ^{1}H at 400 MHz and ^{13}C at 100 MHz. When deuterated chloroform was used as a solvent, ^{1}H chemical shifts were referenced to the $CDCl_3$ residual peak (δ 7.26) and ^{13}C were referenced to $CDCl_3$ (δ 77.16) peak. When deuterated methanol was used as a solvent, ^{1}H chemical shifts were referenced to the MeOD residual peak (δ 4.87) and ^{13}C were referenced to MeOD (δ 49.00) peak. Molecular mass was analyzed with HRMS technique using Q-TOP COMPACT BRUKER. Unless stated otherwise, the ionization method was ESI. IR spectra were measured by Nicolet Avatar 370 FTIR machine with ATR method. Silica-gel column chromatography was performed with Fluka 60 (40-63 μm) silica gel. The enantiomeric excess of product **205** was determined by HPLC (SHIMADZU) using a Chiralpak® IC column. The melting point analysis was performed using the Büchi Melting Point B-545 machine. Specific rotation analysis was performed using the AUTOMATIC POLARIMETER Autopol III.

5.2 Synthesis of intermediates

Ethyl (2*S*,3*S*,4a*R*,6*S*,8*R*,8a*R*)-2,3-diethoxy-6,8-dihydroxy-2,3-dimethyloctahydrobenzo[*b*][1,4]dioxine-6-carboxylate (158)



The compound was prepared by modified described procedure.[67] The vacuum-dried D-(−)-quinic acid (5.00 g, 26.0 mmol, 1 equiv.), (+)-CSA (0.60 g, 2.6 mmol, 0.1 equiv.), triethyl orthoformate (21.7 ml, 130 mmol, 5 equiv.) and diacetyl (2.48 ml, 28.6 mmol, 1.1 equiv) were dissolved in ethanol (anhydrous, 40 ml) under argon atmosphere. The resulting solution was then refluxed at 100 °C overnight with stirring. TLC analysis the next day showed full conversion. The mixture was allowed to cool to room temperature and TEA was added (0.67 ml, 4.8 mmol, 0.18 equiv.) and stirred for 10 minutes. The resulting mixture was concentrated *in vacuo* and silica gel column chromatography (Hexane: EtOAc, 3:1 → 1:1) was done affording yellowish oil, which upon vacuum drying gave amorphous solid (9.10 g, 96%). $R_f \approx$ 0.4 (TLC Hexane: EtOAc = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (m, 1H), 4.28 – 4.18 (m, 2H), 4.15 (q, J = 3.0 Hz, 1H), 3.62 – 3.44 (m, 5H), 2.16 (dt, J = 14.8, 3.0 Hz, 1H), 2.09 – 2.00 (m, 2H), 1.91 (t, J = 12.5 Hz, 1H), 1.36 (s, 3H), 1.31 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.24 – 1.17 (m, 6H) ppm

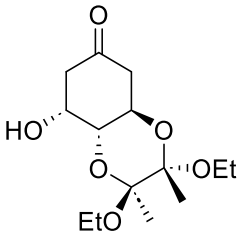
^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 100.47, 99.86, 75.8, 73.0, 69.4, 62.5, 62.1, 56.0, 55.9, 38.8, 37.5, 18.7, 18.7, 15.7, 15.7, 14.2 ppm.

The spectra are consistent with literature.[67]

HRMS-ESI (m/z) for $C_{17}H_{30}O_8$ (M + Na) calcd: 385.1832 found: 385.1835.

$[\alpha]_D^{23}$ = + 100 (*c* 0.90, $CHCl_3$) (lit. + 78, *c* 0.90, $CHCl_3$).

(2*S*,3*S*,4a*R*,8*R*,8a*R*)-2,3-diethoxy-8-hydroxy-2,3-dimethylhexahydrobenzo[*b*][1,4]dioxin-6(5*H*)-one (161)



The compound was prepared by modified described procedure.[67] The vacuum-dried compound **158** (6.89 g, 19.0 mmol, 1 equiv.), was dissolved in methanol (anhydrous, 100 ml) under argon atmosphere. The resulting solution was then cooled to 0 °C. Then sodium borohydride (3.60 g, 95.1 mmol, 5 equiv.) was added in two portions over the period of 30 minutes. After one hour of stirring at 0 °C the mixture was allowed to warm to room temperature and react overnight. The next day, TLC analysis showed full conversion. Subsequently, the mixture was cooled to 0 °C and water (130 ml) was added slowly. After 10 minutes of stirring, sodium periodate (18.03 g, 85.5 mmol, 4.5 equiv.) was added and the mixture was allowed to warm to room temperature. The reaction was left to react overnight. The next day, the mixture was filtered through Celite®, and the filtrate was concentrated *in vacuo*. Concentrated ammonium chloride solution (150 ml) was then added to the resulting residue and the mixture was extracted with DCM (3 × 50 ml). The combined organic phases were dried with anhydrous sodium sulfate and then concentrated *in vacuo.* After that, silica gel column chromatography (Hexane: EtOAc, 5:1 → 1:1) was done, affording a white amorphous solid, which was then vacuum dried yielding the target compound (2.19 g, 76%). $R_f \approx 0.6$ (TLC Hexane: EtOAc = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 – 4.24 (m, 1H), 4.23 – 4.19 (m, 1H), 3.88 (dd, J = 9.9, 2.5 Hz, 1H), 3.63 – 3.41 (m, 4H), 2.68 – 2.58 (m, 2H), 2.52 – 2.43 (m, 2H), 1.36 (s, 3H), 1.32 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H) ppm.

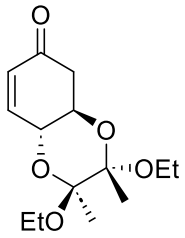
^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8, 100.3, 99.2, 72.4, 67.9, 63.3, 56.2, 55.9, 46.2, 44.9, 18.6, 18.6, 15.7, 15.5 ppm.

HRMS-ESI (m/z) for $C_{14}H_{24}O_6$ (M + Na) calcd: 311.1465 found: 311.1465.

The spectra are consistent with literature.[67]

$[\alpha]_D^{23}$ = + 103 (*c* 1.0, $CHCl_3$) (lit. + 106, *c* 1.0, $CHCl_3$).

(2*S*,3*S*,4a*R*,8a*R*)-2,3-diethoxy-2,3-dimethyl-2,3,4a,8a-tetrahydrobenzo[*b*][1,4]dioxin-6(5*H*)-one (162)



The compound was prepared by modified described procedure.[67] The vacuum-dried compound **161** (0.56 g, 1.94 mmol, 1 equiv.), was dissolved in DCM (anhydrous, 20 ml) under argon atmosphere. The resulting solution was then cooled to 0 °C. After that, mesyl chloride (0.30 ml, 3.87 mmol, 2 equiv.) and TEA (1.1 ml, 7.90 mmol, 4 equiv.) were added. After 2 hours the reaction was allowed to warm to room temperature and stirred at this temperature for an additional hour. After that, the reaction mixture was washed with water (3 × 20 ml) and the organic phase was collected. The combined water phases were additionally extracted with DCM (3 × 20 ml). The combined organic phases were then dried with anhydrous sodium sulfate and concentrated *in vacuo*. Silica gel column chromatography (Hexane: EtOAc, 4:1 → 3:1) afforded white amorphous solid, which was then vacuum dried yielding the target compound (0.44 g, 85%).

R_f ≈ 0.6 (TLC Hexane: EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (dd, *J* = 10.1, 1.8 Hz, 1H), 5.99 (ddd, *J* = 10.1, 2.7, 1.2 Hz, 1H), 4.51 (ddd, *J* = 9.0, 2.7, 1.7 Hz, 1H), 4.06 (ddd, *J* = 13.7, 9.0, 4.8 Hz, 1H), 3.65 – 3.45 (m, 4H), 2.71 (ddd, *J* = 16.4, 4.9, 1.2 Hz, 1H), 2.47 (dd, *J* = 16.4, 13.5 Hz, 1H), 1.39 (s, 3H), 1.35 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm.

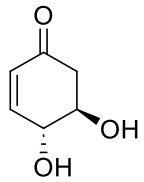
^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 149.0, 130.1, 100.9, 99.7, 69.4, 68.3, 56.3, 56.2, 42.2, 18.6, 18.6, 15.6, 15.5 ppm.

The spectra are consistent with literature.[67]

HRMS-ESI (m/z) for $C_{14}H_{22}O_5$ (M + Na) calcd: 293.1359 found: 293.1363.

$[\alpha]_D^{23}$ = + 26 (*c* 1.0, $CHCl_3$) (lit. + 29, *c* 1.0, $CHCl_3$).

(4*R*,5*R*)-4,5-dihydroxycyclohex-2-en-1-one (177)



The preparation of this compound was inspired by the deprotection procedure in literature.[67] The compound **162** (100 mg, 0.37 mmol, 1 equiv.) was dissolved in DCM (10 ml) and the resulting solution was then cooled to 0 °C. After that, water (0.42 ml, 23.3 mmol, 63 equiv.) and TFA (1.28 ml, 16.6 mmol, 45 equiv.) were added. After 3 hours the reaction was allowed to warm to room temperature and stirred at this temperature for an additional hour. Then, the mixture was cooled to 0 °C and the acid was quenched with sodium bicarbonate (approx. 2.1 g), until a slightly basic pH was observed (indicated by pH strips). After that, the mixture was concentrated *in vacuo*. Then silica gel column chromatography (Hexane: EtOAc, 1:1 → 1:3) was done affording yellowish oil, which was then vacuum dried, yielding the target compound as an oil (29.7 mg, 63%). $R_f \approx 0.1$ (TLC Hexane: EtOAc = 1:1).

^{1}H NMR (400 MHz, CD_3OD) δ 6.92 (dd, J = 10.2, 2.3 Hz, 1H), 5.97 (ddd, J = 10.2, 2.2, 1.1 Hz, 1H), 4.28 (dt, J = 7.8, 2.2 Hz, 1H), 3.88 (ddd, J = 11.4, 7.8, 4.6 Hz, 1H), 2.72 (ddd, J = 16.2, 4.6, 1.2 Hz, 1H), 2.46 (dd, J = 16.2, 11.4 Hz, 1H) ppm.

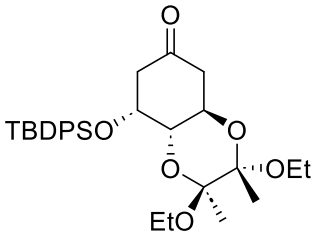
^{13}C NMR (100 MHz, CD_3OD) δ 200.3, 153.5, 129.7, 73.4, 73.1, 45.5 ppm.

HRMS-ESI (m/z) for $C_6H_8O_3$ (M + H) calcd: 129.0546 found: 129.0544.

The spectra are consistent with literature.[67]

$[\alpha]_D^{23} = -210$ (*c* 1.0, MeOH).

(2*S*,3*S*,4a*R*,8*R*,8a*S*)-8-((*tert*-butyldiphenylsilyl)oxy)-2,3-diethoxy-2,3-dimethylhexahydrobenzo[*b*][1,4]dioxin-6(5*H*)-one (184)



The vacuum-dried compound **161** (100 mg, 0.34 mmol, 1 equiv.) was dissolved in DMF (anhydrous, 2 ml). After that, imidazole (0.23 g, 3.37 mmol, 10 equiv.) and TBDPSCl (0.45 ml, 1.75 mmol, 5 equiv.) were added. The solution was heated to 60 °C and left to react overnight. The next day, the reaction was monitored using TLC analysis showing full conversion. The solution was diluted with EtOAc (15 ml) and washed with water (2 × 10 ml) and NaCl solution (1 × 10 ml). The combined organic phases were dried using anhydrous sodium sulfate and concentrated *in vacuo*. Then silica gel column chromatography (Hexane: EtOAc, 10:1 → 5:1) was done, affording a white amorphous solid, which was then vacuum dried, yielding the target compound (0.133 g, 73%). $R_f \approx 0.5$ (TLC Hexane: EtOAc = 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.86 (m, 2H), 7.72 – 7.67 (m, 2H), 7.45 – 7.34 (m, 6H), 4.59 (ddd, J = 12.4, 9.9, 5.5 Hz, 1H), 4.16 (q, J = 2.8 Hz, 1H), 3.80 (dd, J = 9.9, 2.3 Hz, 1H), 3.60 – 3.50 (m, 3H), 3.47 – 3.38 (m, 1H), 2.71 (ddd, J = 14.2, 5.6, 2.4 Hz, 1H), 2.50 (dd, J = 14.2, 12.4 Hz, 1H), 2.34 (dt, J = 15.1, 2.9 Hz, 1H), 2.27 (dd, J = 15.0, 2.9 Hz, 1H), 1.41 (s, 3H), 1.37 (s, 3H), 1.31 – 1.15 (m, 6H), 1.06 (s, 9H) ppm.

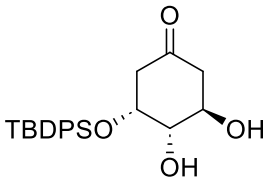
^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 136.8 (2C), 136.1 (2C), 133.7, 132.9, 129.8, 129.6, 127.7 (2C), 127.3 (2C), 100.0, 99.0, 72.8, 69.8, 64.0, 55.9, 55.8, 48.3, 45.2, 26.9 (3C), 19.5, 18.6, 18.6, 15.7, 15.4 ppm.

HRMS-ESI (m/z) for $C_{30}H_{42}O_6Si$ (M + Na) calcd: 549.2642 found: 549.2636.

$[\alpha]_D^{23}$ = + 64 (*c* 1.0, $CHCl_3$).

IR (KBr) νmax 2931, 2887, 2858, 1722, 1472, 1122, 1105, 700, 507, 486 cm^{-1}.

(3*R*,4*S*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-4,5-dihydroxycyclohexan-1-one (183)



The preparation of this compound was inspired by the deprotection procedure in literature.[67] The compound **184** (133 mg, 0.25 mmol, 1 equiv.) was dissolved in DCM (10 ml) and the resulting solution was then cooled to 0 °C. After that, water (0.42 ml, 23.3 mmol, 60 equiv.) and TFA (1.28 ml, 16.6 mmol, 40 equiv.) were added. After 3 hours, the reaction was allowed to warm to room temperature and stirred at this temperature for an additional hour. Then the mixture was cooled to 0 °C and the acid was quenched with sodium bicarbonate (approx. 2.1 g), until slightly basic pH was observed (indicated by pH strips). After that, the mixture was concentrated *in vacuo*. Then, silica gel column chromatography (Hexane: EtOAc, 1:1 → 1:3) was done, affording yellowish oil, which was then vacuum dried yielding the target compound as an oil (48.4 mg, 49%). $R_f \approx 0.3$ (TLC Hexane: EtOAc = 1:1).

^{1}H NMR (400 MHz, CD_3OD) δ 7.77 – 7.73 (m, 2H), 7.69 – 7.66 (m, 2H), 7.47 – 7.36 (m, 6H), 4.30 (ddd, J = 7.9, 4.1, 2.6 Hz, 1H), 4.19 (td, J = 6.6, 4.6 Hz, 1H), 3.88 (dd, J = 6.5, 2.6 Hz, 1H), 2.75 (ddd, J = 14.6, 4.6, 1.7 Hz, 1H), 2.52 (ddd, J = 14.3, 7.8, 1.6 Hz, 1H), 2.37 – 2.25 (m, 2H), 1.07 (s, 9H) ppm.

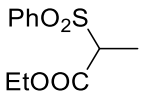
^{13}C NMR (100 MHz, CD_3OD) δ 210.3, 137.1 (2C), 137.0 (2C), 134.9, 134.5, 130.9, 130.9, 128.7 (2C), 128.6 (2C), 74.6, 72.2, 70.2, 47.2, 46.2, 27.4 (3C), 20.0 ppm.

HRMS-ESI (m/z) for $C_{22}H_{28}O_4Si$ (M + Na) calcd: 407.1649 found: 407.1653.

$[\alpha]_D^{23} = -15$ (*c* 1.0, MeOH).

IR (KBr) νmax 3417, 2929, 2856, 1709, 1427, 1103, 700, 503, 486 cm^{-1}.

Ethyl 2-(phenylsulfonyl)propanoate (169)



The compound was prepared by modified described procedure.[71] Sodium benzenesulfinate (0.82 g, 5.0 mmol, 1 equiv.), sodium iodide (0.90 g, 6.0 mmol, 1.2 equiv.) and TBAI (0.184 g, 0.5 mmol, 0.1 equiv.) were dissolved in DMF (30 ml). To this solution ethyl 2-bromopropionate (0.78 ml, 6 mmol, 1.2 equiv.) was added. TLC analysis after 2 hours of reaction time showed full conversion, concentrated sodium bicarbonate solution (10 ml) was added, and the mixture was stirred for 10 minutes. Then, the mixture was washed with DCM (3 × 20 ml) and the combined organic phases were additionally washed with brine (1 × 10 ml). The organic phases were dried with anhydrous sodium sulfate and concentrated *in vacuo*. Silica gel column chromatography (Hexane: EtOAc, 3:1 → 2:1) afforded the target compound as a colorless oil (1.069 g, 88%). $R_f \approx 0.50$ (TLC Hexane:EtOAc = 2:1).

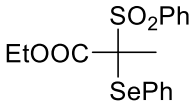
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.86 (m, 2H), 7.70 – 7.65 (m, 1H), 7.59 – 7.53 (m, 2H), 4.09 (dd, J = 7.2, 0.6 Hz, 2H), 4.04 (q, J = 7.2 Hz, 1H), 1.57 (d, J = 7.2 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 137.1, 134.3, 129.4 (2C), 129.1 (2C), 65.5, 62.3, 13.9, 11.8 ppm.

The spectra are consistent with literature.[71]

HRMS-ESI (m/z) for $C_{11}H_{14}O_4S$ (M + H) calcd: 243.0685 found: 243.0683.

***rac*-Ethyl 2-(phenylselanyl)-2-(phenylsulfonyl)propanoate (170)**



The compound was prepared by modified described procedure.[70] The vacuum-dried compound **169** (1.07 g, 4.42 mmol, 1 equiv.) was dissolved in THF (4 ml) under argon atmosphere. NaH (60% suspension in oil, 0.18 g, 4.42 mmol, 1 equiv.) was added to a separate flask with THF (12 ml) under argon atmosphere. Both flasks were cooled to −10 °C with ice/salt bath. After that, solution of starting material in THF was slowly added to the NaH suspension. Immediately after addition, dense suspension was formed. This suspension was diluted with additional THF (5 ml). After 1 hour of stirring, PhSeBr (1.04 g, 4.42 mmol, 1 equiv.) was added. The mixture was stirred for 1 hour. After that, TLC analysis showed full conversion, concentrated NH_4Cl solution (15 ml) was added to quench the reaction. After 5 minutes of stirring, the mixture was concentrated *in vacuo* to remove THF and the residue was extracted with Et_2O (3 x 35 ml). The combined organic phases were dried with anhydrous sodium sulfate and concentrated *in vacuo*. Then, silica gel column chromatography (Hexane: EtOAc, 3:1 → 2:1) was done, affording colorless amorphous solid, which after vacuum drying provided the target compound (1.37 g, 78%). $R_f \approx 0.7$ (TLC Hexane:EtOAc = 2:1).

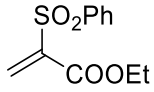
^{1}H NMR (400 MHz, $CDCl_3$) 8.02 – 7.94 (m, 2H), 7.75 – 7.62 (m, 3H), 7.60 – 7.50 (m, 2H), 7.47 – 7.38 (m, 1H), 7.37 – 7.28 (m, 2H), 4.07 (q, J = 7.1 Hz, 2H), 1.65 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) 167.0, 138.7 (2C), 136.1, 134.3, 131.3 (2C), 130.4, 129.1 (2C), 128.6 (2C), 126.0, 71.3, 63.0, 20.1, 13.8 ppm.

The spectra are consistent with literature.[70]

HRMS-ESI (m/z) for $C_{17}H_{18}O_4SSe$ (M + Na) calcd: 420.9983 found: 420.9977.

Ethyl 2-(phenylsulfonyl)acrylate (171)



The compound was prepared by modified described procedure.[70] The vacuum-dried compound **170** (0.11 g, 0.27 mmol, 1 equiv.) was dissolved in DCM (0.5 ml) and cooled to 0 °C. In separate flask, solution of H_2O_2 (30 %, 0.18 ml, 1.8 mmol, 6.63 equiv.) and H_2O (0.38 ml) was made. This solution was then slowly added to the reaction mixture. After one hour, the TLC analysis showed complete conversion, saturated sodium bicarbonate solution (10 ml) was slowly added and stirred for 5 minutes. Then, the mixture was diluted with DCM (10 ml) and washed with water (3 × 10 ml) and brine (1 × 10 ml). The organic phase was dried with anhydrous sodium sulfate and concentrated *in vacuo,* which after vacuum drying, afforded the target compound as a slightly yellow oil (0.046 g, 69%). $R_f \approx 0.55$ (TLC Hexane:EtOAc = 2:1).

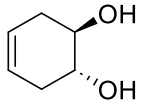
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.92 (m, 2H), 7.64 – 7.59 (m, 1H), 7.55 – 7.48 (m, 2H), 7.12 (s, 1H), 7.00 (s, 1H), 4.16 (q, J = 7.2 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 143.5, 139.1, 137.5, 133.8, 129.0 (2C), 128.9 (2C), 62.3, 13.8 ppm.

The spectra are consistent with literature.[70]

HRMS-ESI (m/z) for $C_{11}H_{12}O_4S$ (M-CH3OH + H) calcd: 273.0791 found: 273.0793.

***rel*-(1*R*,2*R*)-cyclohex-4-ene-1,2-diol (186)**



The compound was prepared by modified described procedure.[81] 1,4-Cyclohexadiene **157** (7.50 ml, 79.2 mmol, 1 equiv.) was dissolved in DCM (7.5 ml) and cooled to −5 °C. Then, mCPBA (77%, 19.5 g, 87.0 mmol, 1.1 equiv.) was dissolved in DCM (150 ml) and this solution was slowly added to the reaction mixture. After the addition, the mixture was allowed to warm to

room temperature and stirred for a day. The next day, the mixture was cooled to 0 °C and Na_2CO_3 (100 ml, 2.5M solution, 3 equiv.) was added and stirred for 15 minutes. After that, the mixture was extracted with DCM (3 × 75 ml). The combined organic phases were then washed with water (40 ml) and brine (2 × 40 ml). The combined organic phase was then carefully concentrated *in vacuo*. Na_2CO_3 (80 ml, 0.2M solution, 0.2 equiv.) was then added to the residue and the mixture was heated to 95 °C for 2 days. After that, the TLC analysis showed full conversion. The mixture was allowed to cool to room temperature and HCl (1M) was added to quench the base, until the pH was slightly acidic (measured by pH strips). Then, the mixture was concentrated *in vacuo* and silica gel column chromatography (Hexane: EtOAc, 1:1 → 1:2) was done affording colorless crystalline solid, which after vacuum drying gave the target compound (4.808 g, 53%). $R_f \approx 0.2$ (TLC Hexane: EtOAc = 1:1).

^{1}H NMR (400 MHz, CD_3OD) δ 5.55 – 5.51 (m, 2H), 3.65 – 3.57 (m, 2H), 2.47 – 2.38 (m, 2H), 2.05 – 1.96 (m, 2H) ppm.

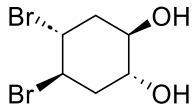
^{13}C NMR (100 MHz, CD_3OD) δ 125.4, 72.4, 34.2 ppm.

The spectra are consistent with literature.[93]

HRMS-ESI (m/z) for $C_6H_{10}O_2$ (M + Na) calcd: 137.0573 found: 137.0574.

Melting point = 99 – 102 °C (lit. 100 – 102 °C).[78]

***rel*-(1*R*,2*R*,4*R*,5*R*)-4,5-dibromocyclohexane-1,2-diol (187)**



The compound was prepared by modified described procedure.[80] The vacuum-dried compound **186** (2.50 g, 21.9 mmol, 1 equiv.) was suspended in chloroform (125 ml). The suspension was then cooled to −15 °C with ice/salt bath. Then Br_2 (1.58 ml, 30.6 mmol, 1.4 equiv.) was added dropwise over the course of 5 minutes. After one hour, TLC analysis showed full conversion. Sodium thiosulfate solution was added until the precipitation of sulfur stopped. The mixture was then washed with DCM (3 × 30 ml) and EtOAc (1 × 30 ml) and the combined organic

phases were filtered through Celite®, dried with anhydrous sodium sulfate and concentrated *in vacuo*. Then silica gel column chromatography (Hexane: EtOAc, 1:2 → 1:3) was done, which after vacuum drying provided the target compound as a colorless amorphous solid (5.62 g, 94%). $R_f \approx 0.65$ (TLC Hexane:EtOAc = 1:3). A small amount of the compound was then crystallized from methanol and crystal data (Table 6) were obtained.

^{1}H NMR (400 MHz, CD_3OD) δ 4.62 (s, 2H), 3.88 – 3.81 (m, 2H), 2.48 – 2.40 (m, 2H), 2.35 – 2.25 (m, 2H) ppm.

^{13}C NMR (100 MHz, CD_3OD) δ 71.5 (2C), 53.3 (2C), 38.2 (2C) ppm.

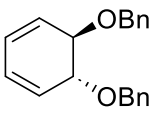
The spectra are consistent with the literature.[80]

Melting point (crystal): 119 – 121 °C (lit. 118 – 120 °C).[80]

HRMS-ESI (m/z) for $C_6H_{10}Br_2O_2$ (M + Na) calcd: 294.8939 found: 294.8941.

IR (KBr) νmax 3323, 2910, 2887, 1439, 1176, 1053, 935, 548 cm^{-1}.

***rel*-(5*R*,6*R*)-5,6-Bis(benzyloxy)cyclohexa-1,3-diene (155)**



The compound was prepared by modified described procedure.[77] The vacuum-dried compound **187** (2.00 g, 7.35 mmol, 1 equiv.) was dissolved in DMF (anhydrous, 20 ml) under argon atmosphere. Then, BnBr (3.5 ml, 29.4 mmol, 4 equiv.) was added. To a separate vacuum-dried flask was added NaH (60%, 0.770 g, 19.2 mmol, 2.6 equiv.) and DMF (anhydrous, 40 ml) under argon atmosphere and cooled to −15 °C with ice/salt bath. Then, the solution of starting material **187** and BnBr was added dropwise to the NaH solution. After 1 hour of stirring the TLC analysis (Hexane:EtOAc = 20:1) showed complete conversion. NH_4Cl solution (30 ml) was added, and the mixture was extracted with Et_2O (3 × 30 ml). The combined organic phases were then additionally washed with brine (1 × 30 ml), dried with anhydrous sodium sulfate and concentrated *in vacuo.* The obtained residue was purified using silica gel column chromatography (Hexane:EtOAc 30:1 → 20:1), giving compound with $R_f \approx 0.4$

(Hexane:EtOAc = 20:1). The obtained compound was dissolved in benzene (30 ml) and DBU (5.50 ml, 36.7 mmol, 5 equiv.) was added. The mixture was heated to 40 °C and stirred for 48 hours. After the noted duration, H_2O (distilled, 30 ml) was added and the mixture was stirred for 15 minutes. The resulting mixture was extracted with Et_2O (3 × 50 ml). Combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified using silica gel column chromatography (Hexane:EtOAc 30:1 → 20:1). Subsequent vacuum drying provided of the title compound as a colorless oil (0.778 g, 36% over 2 steps). $R_f \approx 0.25$ (Hexane:EtOAc = 20:1).

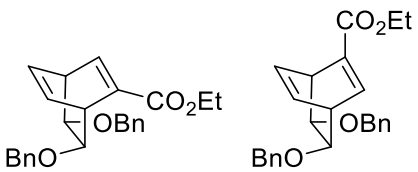
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 10H), 6.00 – 5.92 (m, 4H), 4.66 (dd, J = 15.5, 11.9 Hz, 4H), 4.44 (s, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6 (2C), 128.5 (4C), 128.0 (4C), 127.8 (2C), 127.7 (2C), 124.7 (2C), 78.3 (2C), 71.0 (2C) ppm.

Spectra are consistent with literature.[77]

HRMS-ESI (m/z) for $C_{20}H_{20}O_2$ (M + Na) calcd: 315.1355 found: 315.1357.

Mixture of *rel*-ethyl (1*R*,4*S*,7*R*,8*R*)-7,8-bis(benzyloxy)bicyclo[2.2.2]octa-2,5-diene-2-carboxylate (190) and *rel*-ethyl (1*R*,4*S*,7*S*,8*S*)-7,8-bis(benzyloxy)bicyclo[2.2.2]octa-2,5-diene-2-carboxylate (191)



190 **191**

To a vacuum-dried **155** (0.141 g, 0.482 mmol, 1 equiv.) under argon atmosphere was added ethyl propiolate (1.50 ml, 14.7 mmol, 30 equiv.). The neat mixture was heated to 75 °C and stirred overnight. The next day, TLC analysis (Hexane:EtOAc = 10:1) showed full conversion. The reaction mixture was concentrated *in vacuo* and the obtained residue was purified using silica gel column chromatography (Hexane:EtOAc 15:1 → 10:1). Subsequent vacuum drying

provided colorless oil containing the title compound as a unseparable mixture with corresponding regioisomer (0.151 g, 80%, **190**/**191** = 5/1). $R_f \approx 0.2$ (Hexane:EtOAc = 10:1).

Compound **190** (Major):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 11H, overlapping with isomer), 6.48, (t, *J* = 6.2 Hz, 1H), 6.33 (ddd, *J* = 7.4, 6.1, 1.6 Hz, 1H), 4.80 – 4.42 (m, 5H, overlapping with isomer), 4.30 – 4.16 (m, 2H, overlapping with isomer), 3.96 (tdd, *J* = 6.3, 3.2, 1.2 Hz, 1H), 3.52 – 3.46 (m, 2H, overlapping with isomer), 1.33 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 145.4, 138.2, 138.2, 136.7, 134.3, 130.6, 128.5 (2C), 128.5 (2C), 128.0 (2C), 127.9 (2C), 127.8, 127.8, 84.4, 83.6, 71.3, 71.2, 60.7, 43.0, 40.8, 14.4 ppm.

Compound **191** (Minor):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 11H, overlapping with isomer), 6.45 – 6.41 (m, 2H), 4.80 – 4.42 (m, 5H, overlapping with isomer), 4.30 – 4.16 (m, 2H, overlapping with isomer), 3.88 (ddt, *J* = 7.2, 5.1, 2.6 Hz, 1H), 3.50 – 3.44 (m, 2H, overlapping with isomer), 1.30 (t, *J* = 7.1 Hz, 3H) ppm.

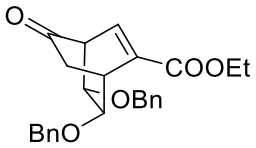
^{13}C NMR (100 MHz, $CDCl_3$) 165.1, 141.5, 138.8, 138.3, 133.2, 131.7, 128.5 (2C), 128.4 (2C), 128.0 (2C), 127.9 (2C), 127.8, 127.7, 83.7, 82.7, 71.4, 70.8, 60.6, 42.7, 40.3, 14.1 ppm.1 carbon peak was not found.

Mixture **190**/**191** = 5/1:

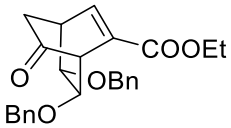
HRMS-ESI (m/z) for $C_{25}H_{26}O_4$ (M + H) calcd: 391.1903 found: 391.1908.

IR (KBr) νmax 3030, 2979, 2870, 1705, 1633, 1599, 1454, 1352, 1068, 764, 739, 694, 606, 461 cm^{-1}.

***rel*-Ethyl (1*R*,4*S*,5*R*,6*R*)-5,6-Bis(benzyloxy)-8-oxobicyclo[2.2.2]oct-2-ene-2-carboxylate (193) and *rel*-ethyl (1S,4R,5R,6R)-5,6-Bis(benzyloxy)-7-oxobicyclo[2.2.2]oct-2-ene-2-carboxylate (194)**



193



194

The vacuum-dried mixture of compounds **190** and **191** (0.524 g, 1.34 mmol, 1 equiv.) was dissolved in THF (anhydrous, 7 ml) under argon atmosphere. The resulting solution was cooled to 0 °C and 9-BBN solution (0.5M in THF, 4.02 ml, 2.01 mmol, 1.5 equiv.) was added. After 10 minutes of stirring the solution was heated to 40 °C. After three hours, TLC analysis (Hexane:EtOAc = 10:1) showed complete conversion. The solution was cooled to 0 °C and EtOH (1.46 ml, 25 mmol, 18.6 equiv.), NaOH (2M, 1.75 ml, 3.5 mmol, 2.61 equiv.), and H_2O_2 (30%, 1.75 ml, 17.15 mmol, 12.8 equiv.) were added in that order. After 30 minutes of stirring the mixture was allowed to heat to room temperature and stirred at this temperature for an additional 30 minutes. Subsequent TLC analysis (Hexane:EtOAc = 2:1) showed full conversion. The mixture was cooled to 0 °C and sodium thiosulfate solution (3 ml) was added to quench the peroxide and stirred for 15 minutes. Then, the resulting mixture was extracted with EtOAc (3 × 15 ml), dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified using silica gel column chromatography (Hexane:EtOAc 2:1 → 1:1) giving compound with $R_f \approx 0.2$ (Hexane:EtOAc = 2:1). The obtained colorless oil was vacuum dried, providing a mixture of alcohols (0.375 g, 0.91 mmol). The mixture of alcohols was dissolved in DCM (anhydrous, 8 ml) under argon atmosphere and cooled to 0 °C. DMP (0.468 g, 1.10 mmol, 1.2 equiv.) was added and stirred at this temperature for 3 hours. After that, the reaction was allowed to heat to room temperature and stirred at this temperature for an additional 30 minutes. Subsequent TLC analysis (Hexane:EtOAc 2:1) showed full conversion. Subsequently, $NaHCO_3$ solution (5 ml) was added and stirred for 15 minutes. The mixture was then washed with EtOAc (3 × 15 ml), dried with anhydrous sodium sulfate and concentrated *in vacuo*. The obtained residue was purified using silica gel column chromatography (Hexane:EtOAc 15:1 → 10:1), isolating major and minor stereoisomer. Subsequent vacuum drying provided the major stereoisomer (0.265 g, 49% over 2 steps) and minor stereoisomer (38 mg 5% over 2 steps) as a colorless oil. R_f(major) ≈ 0.75 (Hexane:EtOAc = 2:1). R_f(minor) ≈ 0.6 (Hexane:EtOAc = 2:1).

Compound **193** (Major):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 10H), 7.11 (ddt, *J* = 6.4, 1.8, 0.8 Hz, 1H), 4.64 (d, J = 11.7 Hz, 1H), 4.54 (d, J = 11.8 Hz, 1H), 4.50 (d, J = 11.8 Hz, 1H), 4.46 (d, J = 11.8 Hz, 1H), 4.24 (m, 2H), 3.85 – 3.90 (m, 2H), 3.72 (dt, *J* = 3.8, 2.0 Hz, 1H), 3.66 (dd, *J* = 6.3, 2.6 Hz, 1H), 2.49 (ddd, *J* = 18.7, 2.0, 0.4 Hz, 1H), 1.95 (ddd, *J* = 18.7, 3.2, 1.9 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 164.0, 137.7, 137.4, 137.3, 137.2, 128.7 (2C), 128.6 (2C), 128.2, 128.0, 128.0 (2C), 127.9 (2C), 81.9, 80.7, 71.3 (2C), 61.2, 56.1, 35.3, 32.5, 14.3 ppm.

HRMS-ESI (m/z) for $C_{25}H_{26}O_5$ (M + Na) calcd: 429.1672 found: 429.1668.

IR (KBr) νmax 2987, 2879, 2837, 1728, 1709, 1616, 1498, 1454, 1252, 1086, 733, 694 cm^{-1}

Compound **194** (Minor):

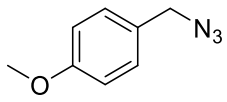
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dt, *J* = 6.6, 1.0 Hz, 1H), 7.40 – 7.28 (m, 10H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.52 (d, *J* = 2.0 Hz, 2H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.34 – 4.17 (m, 3H), 3.88 – 3.86 (m, 1H), 3.75 (dt, *J* = 3.8, 1.4 Hz, 1H), 3.41 – 3.33 (m, 1H), 2.12 (dd, *J* = 6.5, 2.9 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 163.7, 145.5, 137.7, 137.3, 129.9, 128.6 (2C), 128.2 (2C), 128.2 (2C), 128.1, 128.1, 127.9 (2C), 83.4, 81.6, 71.0, 70.9, 61.3, 52.0, 37.3, 34.2, 14.3. ppm.

HRMS-ESI (m/z) for $C_{25}H_{26}O_5$ (M + Na) calcd: 429.1672 found: 429.1674.

IR (KBr) νmax 2979, 2904, 2871, 1732, 1709, 1626, 1496, 1454, 1228, 1065, 737, 696 cm^{-1}.

1-(Azidomethyl)-4-methoxybenzene (209)



The compound was prepared by described procedure.[94] 4-Methoxybenzyl chloride (0.56 g, 3.56 mmol) was dissolved in DMF (anhydrous, 2 ml) under argon atmosphere. Then, sodium azide (0.23 g, 3.55 mmol) was added at room temperature and the mixture was stirred overnight. The next day, water (distilled, 5 ml) was added to the reaction mixture, followed by extraction with EtOAc (3 × 15 ml). The organic layer was then washed with brine (5 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to yield the title compound (0.397 g, 68%) as a colorless oil.

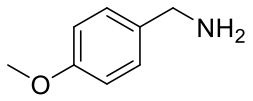
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 6.98 – 6.87 (m, 2H), 4.29 (s, 2H), 3.84 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 129.8, 127.5, 114.3, 55.4, 54.5 ppm.

The spectra are consistent with literature.[95]

HRMS-ESI (m/z) for $C_8H_9N_3O$ (M - N_2 + H) calcd: 136.0756 found: 136.0754

4-Methoxybenzylamine (210)



The compound was prepared by described procedure.[96] The vacuum-dried 4-methoxybenzyl azide **209** (0.502 g, 3.08 mmol, 1 equiv.) and $NaBH_4$ (0.350 g, 9.25 mmol, 3 equiv.) were dissolved in THF (anhydrous, 8 ml) under argon atmosphere. The mixture was brought to reflux and methanol (anhydrous, 2 ml) was slowly added over the course of 1 hour. After an additional three hours of refluxing, the reaction was let to cool to room temperature and HCl (1M, 4 ml) was slowly added. The resulting organic and aqueous phases were separated. The aqueous layer was washed with hexane (3 × 10 ml). The combined organic layers were extracted with HCl (1M, 3 × 10 ml). A concentrated NaOH solution was added to the combined aqueous phases to

make pH > 12, as observed with pH indicator strips. The basic aqueous solution was extracted with DCM (3 x 20 ml) and dried with anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* and further vacuum drying provided the title compound as yellowish oil (0.120 g, 29%).

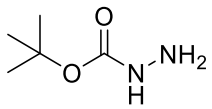
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.18 (m, 2H), 6.87 – 6.83 (m, 2H), 3.77 (s, 5H), 1.52 (s, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 135.7, 128.4 (2C), 114.0 (2C), 55.4, 46.0 ppm.

HRMS-ESI (m/z) for $C_8H_{11}NO$ (M + H) calcd: 138.0913 found: 138.0912.

Spectra are consistent with literature.[97]

***tert*-Butyl hydrazinecarboxylate (197)**



The compound was prepared by described procedure.[87] Hydrazine monohydrate (1.00 ml, 20.58 mmol, 2.25 equiv.) was dissolved in isopropanol (4 ml) and cooled to 0 °C. Solution of Boc_2O (2.0 g, 9.16 mmol, 1 equiv.) in isopropanol (3 ml) was made in a separate flask. The Boc_2O solution was slowly added to the reaction mixture. The mixture was heated to room temperature after addition and stirred for 2 hours. After that, the solvent was evaporated *in vacuo* and the residue was dissolved in 15 ml DCM. The organic phase was then dried with anhydrous magnesium sulfate, filtered, and evaporated *in vacuo* providing the title compound (1.05 g, 87%) as a colorless oil.

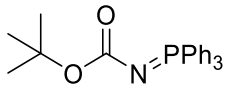
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (bs, 1H), 3.80 (bs, 2H), 1.46 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 80.7, 28.4 (3C) ppm.

HRMS-ESI (m/z) for $C_5H_{12}N_2O_2$ (M + Na) calcd: 155.0791 found: 155.0791.

Spectra are consistent with literature.[98]

***tert*-Butyl (triphenyl-phosphanylidene)carbamate (198)**



The compound was prepared by described procedure.[87] The compound **197** (1.05 g, 7.94 mmol, 1 equiv.) was dissolved in H_2O (distilled, 6.38 ml) and acetic acid (3.2 ml). The solution was then cooled to 0 °C and $NaNO_2$ (0.60 g, 8.69 mmol, 1.1 equiv.) was slowly added. After 30 minutes of stirring the reaction was heated to room temperature. After 1 hour, the reaction mixture was extracted with Et_2O (2 x 10 ml). The combined organic phases were washed with H_2O (distilled, 10 ml), $NaHCO_3$ solution (20 ml) and brine (20 ml). Then, the combined organic phases were dried with anhydrous sodium sulfate and filtered. The resulting Et_2O solution was cooled to 0 °C and PPh_3 (2.08 g, 7.94 mmol, 1 equiv.) was slowly added. The mixture was left to stir overnight. The next day, the resulting crystalline precipitate was filtered, washed with cold Et_2O and vacuum dried, providing the title compound as a colorless crystalline powder (1.85 g, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.69 (m, 6H), 7.57 – 7.51 (m, 3H), 7.47 – 7.41 (m, 6H), 1.37 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 133.23 (d, J = 10.0 Hz, 6C), 132.05 (d, J = 2.7 Hz, 3C), 129.3 (d, J = 12.4 Hz 105.9 Hz, 3C), 128.66 (d, J = 12.4 Hz, 6C), 77.3, 28.4 (3C). ppm.

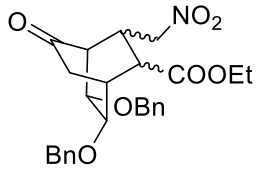
^{31}P NMR (162 MHz, $CDCl_3$) δ 20.4 ppm.

Spectra are consistent with literature.[99]

HRMS-ESI (m/z) for $C_{23}H_{24}NO_2P$ (M + H) calcd: 378.1617 found: 378.1619.

Melting point = 146 – 148 °C (lit. 146 – 148 °C)[100]

***rel*-Ethyl (1R,4S,5R,6R)-5,6-Bis(benzyloxy)-3-(nitromethyl)-8-oxobicyclo[2.2.2]octane-2-carboxylate (201)**



The solution of imine **200** (0.1 mmol, 1 equiv.) was concentrated *in vacuo* and dissolved in nitromethane (1 ml). Subsequently DBU (15 µl, 1 equiv.) was added, and the reaction was stirred for 2 hours at 80 °C. After the noted duration, the TLC analysis showed a complete disappearance of starting material. The reaction mixture was concentrated *in vacuo* and purified using silica gel column chromatography (Hexane:EtOAc = 3:1). Subsequent vacuum drying provided the title compound as a colorless oil (9 mg, 6%). $R_f \approx 0.1$ (Hexane:EtOAc = 5:1).

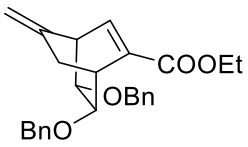
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 10H), 4.60 – 4.24 (m, 6H) 4.20 (q, *J* = 7.1 Hz, 2H), 3.87 (q, *J* = 2.7 Hz, 1H), 3.76 (t, *J* = 3.0 Hz, 1H), 3.54 (tdd, *J* = 8.2, 6.3, 1.8 Hz, 1H), 2.90 (dt, *J* = 4.9, 2.5 Hz, 1H), 2.75 (dd, *J* = 2.8, 1.8 Hz, 1H), 2.67 (dd, *J* = 19.2, 2.4 Hz, 1H), 2.42 (dd, *J* = 8.3, 2.2 Hz, 1H), 2.09 (ddd, *J* = 19.2, 3.5, 2.0 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 171.3, 137.8, 137.4, 128.7 (2C), 128.6 (2C), 128.2, 128.1 (2C), 128.0, 127.9 (2C), 78.9, 78.8, 77.8, 77.4, 71.2, 61.9, 51.5, 44.3, 38.5, 34.7, 30.9, 14.2. ppm.

HRMS-ESI (m/z) for $C_{26}H_{29}NO_7$ (M + Na) calcd: 490.1836 found: 490.1833.

IR (KBr) νmax 2906, 2871, 1724, 1610, 1552, 1454, 1369, 1306, 1198, 1093, 1028, 698, 459 cm^{-1}.

***rel*-Ethyl (1*R*,4*R*,5*R*,6*R*)-5,6-Bis(benzyloxy)-8-methylenebicyclo[2.2.2]oct-2-ene-2-carboxylate (202)**



To a vacuum-dried flask, methyltriphenylphosphonium bromide (115.4 mg, 0.32 mmol, 3.75 equiv.) was added. Then, toluene (anhydrous, 0.6 ml) followed by potassium tert-butoxide (34.8 mg, 0.31 mmol, 3.6 equiv.) were added. The suspension was stirred under reflux for 1 hour, resulting in a yellow solution. To this solution, a solution of ketone **193** (35 mg, 0.086 mmol, 1 equiv., in 0.2 ml of anhydrous toluene) was added. The resulting solution was stirred overnight at 80 °C. The next day, the TLC analysis showed full conversion. Brine (1 × 10 ml) was added to the solution and the mixture was extracted with EtOAc (3 × 10 ml). The combined organic phases were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (Hexane:EtOAc 10:1 → 5:1). Subsequent vacuum drying provided the title compound as a colorless oil (24.8 mg, 71%). $R_f \approx 0.6$ (Hexane:EtOAc = 5:1).

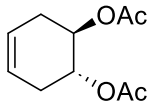
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 10H), 7.23 (dt, J = 6.5, 1.3 Hz, 1H), 4.97 (d, J = 2.9 Hz, 1H), 4.81 (td, J = 2.1, 1.1 Hz, 1H), 4.65 – 4.44 (m, 4H), 4.24 – 4.16 (m. 2H), 3.66 – 3.61 (m, 2H), 3.50 – 3.46 (m, 2H), 2.65 (dq, J = 16.8, 2.3 Hz, 1H), 1.94 – 1.85 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 143.7, 142.1, 138.2, 138.1, 134.8, 128.4 (2C), 128.3 (2C), 127.8 (2C), 127.8 (2C), 127.7, 127.7, 109.1, 83.6, 82.9, 70.9, 70.7, 60.6, 47.6, 34.9, 26.1, 14.3. ppm.

IR (KBr) νmax 2979, 2870, 1709, 1653, 1454, 1392, 1250, 1070, 733, 696 cm^{-1}.

HRMS-ESI (m/z) for $C_{26}H_{28}O_4$ (M + Na) calcd: 427.1879 found: 427.1879.

***rel*-(1*R*,2*R*)-cyclohex-4-ene-1,2-diyl diacetate (204)**



The compound was prepared by modified literature procedure.[79] The diol **186** (0.10 g, 0.87 mmol, 1 equiv.) was dissolved in pyridine (anhydrous, 3 ml). Then, Ac_2O (0.21 ml, 2.18 mmol, 2.5 equiv.) was added dropwise. After 5 minutes of stirring DMAP (5.3 mg, 0.043 mmol, 0.05 equiv.) was added. After stirring overnight, the TLC analysis (Hexane:EtOAc = 1:1) showed full conversion. EtOAc (20 ml) was added to the reaction mixture and the mixture was washed with NaCl (conc.solution, 2 × 10 ml), HCl (1 M, 35 ml) and $NaHCO_3$ (conc.solution, 10 ml). The organic phase was then dried with anhydrous sodium sulfate and concentrated *in vacuo.* Further vacuum drying provided the title compound as a colorless oil (0.117 g, 68%). $R_f \approx 0.9$ (Hexane:EtOAc = 1:1).

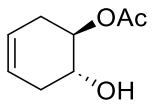
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 – 5.52 (m, 2H), 5.08 (ddt, J = 6.7, 3.7, 1.7 Hz, 2H), 2.56 (ddt, J = 17.0, 3.9, 1.9 Hz, 2H), 2.24 – 2.10 (m, 2H), 2.04 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 123.8, 70.1, 30.1, 21.2 ppm.

Spectra are consistent with literature.[79]

HRMS-ESI (m/z) for $C_{10}H_{14}O_4$ (M + Na) calcd: 221.0784 found: 221.0785.

(1*R*,6*R*)-6-hydroxycyclohex-3-en-1-yl acetate (205)



The compound was prepared by modified described procedure.[79] The pH 8 buffer was prepared by mixing Na_2HPO_2 (dodecahydrate, 33.63 g), NaH_2PO_4 (dihydrate, 0.934 g) and H_2O (100 ml). To a flask with diacetate **204** (117 mg, 0.59 mmol, 1 equiv.) pH 8 buffer (12 ml) was added. To this mixture, Amano Lipase from *Pseudomonas fluorescens* (58.5 mg) was added. The resulting suspension was heated to 30 °C and stirred overnight. The next day, TLC analysis showed full conversion. The mixture was extracted with EtOAc (4 × 10 ml). The combined organic phases

were washed with brine (1 × 10 ml), dried with anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (Hexane:EtOAc = 1:1). Subsequent vacuum drying provided the title compound as a colorless oil (22.5 mg, 24%). $R_f \approx 0.5$ (Hexane:EtOAc = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 – 5.48 (m, 2H), 4.85 (ddd, J = 9.4, 8.6, 5.9 Hz, 1H), 3.89 (td, J = 9.0, 5.8 Hz, 1H), 2.64 – 2.46 (m, 2H), 2.19 – 1.98 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 124.4, 123.9, 74.5, 69.0, 33.1, 30.4, 21.4 ppm.

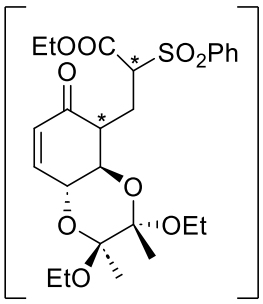
Spectra are consistent with literature.[79]

HRMS-ESI (m/z) for $C_8H_{12}O_3$ (M + Na) calcd: 179.0678 found: 179.0676.

$[\alpha]_D^{23}$ = - 120 (*c* 1.0, $CHCl_3$) (lit. - 121, c = 0.86).[79]

Er = 97:3 (*ee* = 94%), the enantiomeric excess of product **205** was determined by HPLC using a Chiralpak® IC column (*n*-heptane/*i*-PrOH - 80:20, flow rate = 1.0 ml/min, λ = 205 nm, t = 25 °C): t_R = 6.5 min (minor), t_R = 7.7 min (major).

Mixture of four stereoisomers of ethyl 3-((2*S*,3*S*,4a*R*,8a*R*)-2,3-diethoxy-2,3-dimethyl-6-oxo-2,3,4a,5,6,8a-hexahydrobenzo[*b*][1,4]dioxin-5-yl)-2-(phenylsulfonyl)propanoate (174)



The vacuum-dried enone **162** (0.100 g, 0.37 mmol, 1 equiv.) was dissolved in freshly distilled THF (2.5 ml) under argon atmosphere and cooled to −78 °C. Then, LiHMDS solution (1M in THF, 0.56 ml, 0.56 mmol, 1.5 equiv.) was added. After 30 minutes of stirring alkene **171** (0.116 g, 0.48 mmol, 1.3 equiv.) was added. After 1 hour of stirring the mixture was allowed to heat to room temperature and stirred at this temperature for an additional 1 hour. After that,

the reaction was quenched with a concentrated ammonium chloride solution (5 ml). The resulting mixture was subsequently diluted with EtOAc (30 ml) and washed with distilled water (3 × 10 ml). The organic phase was dried using anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (Hexane:EtOAc 5:1 → 2:1), which after vacuum drying provided the isomeric mixture (80 mg, 42%). $R_f \approx 0.2$ (Hexane:EtOAc = 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.83 (m, 8H), 7.71 – 7.76 (m, 4H), 7.60 – 7.53 (m, 8H), 6.87 – 6.74 (m, 4H), 5.98 – 5.87 (m, 4H), 4.76 – 4.59 (m, 5H), 4.54 – 4.49 (m, 1H), 4.27 – 4.22 (m, 1H), 4.2 – 3.98 (m, 12H), 3.82 – 3.71 (m, 1H), 3.64 – 3.28 (m, 17H), 2.82 – 2.69 (m, 3H), 2.61-2.50 (m, 4H), 2.45 – 2.38 (m, 1H), 2.23 – 2.10 (m, 3H), 1.38 – 1.28 (m, 28H), 1.27 – 1.09 (m, 32H) ppm.

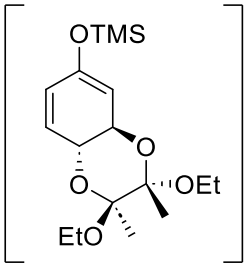
^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 198.5, 197.8, 197.1, 165.9, 165.8, 165.2, 165.2, 149.0, 148.4, 148.3, 148.1, 137.5 (3C), 137.2 (2C), 134.2 (2C), 134.1, 133.8, 129.5 (2C), 129.4, 129.3, 129.2, 129.1, 129.0 (3C), 128.9 (2C), 128.8, 128.7, 100.7, 100.6 (2C), 100.5, 99.9 (2C), 99.8, 99.8, 77.3, 72.8, 71.5, 70.1, 69.5, 69.4 (2C), 69.0, 68.8, 68.6, 68.3, 67.5, 64.6, 62.2 (2C), 62.1, 62.0, 56.2 (2C), 56.1 (5C), 56.0, 48.1, 47.7, 47.3, 47.0, 24.0, 23.0, 22.6, 21.0, 18.4 (3C), 18.3, 15.5 (2C), 15.4 (2C), 13.9, 13.8 (4C), 13.7 ppm. Note: Peaks of 4 carbon atoms were not found.

HRMS-ESI (m/z) for $C_{25}H_{34}O_9S$ (M + Na) calcd: 533.1815 found: 533.1818.

IR (KBr) νmax 2978, 2931, 2889, 1736, 1680, 1446, 1392, 1323, 1146, 1130, 1115, 1082, 1047, 995, 920, 688, 530 cm^{-1}.

5.3 Synthesis of unstable intermediates without full characterization

(((2*S*,3*S*,4a*R*,8a*R*)-2,3-diethoxy-2,3-dimethyl-2,3,4a,8a-tetrahydrobenzo[*b*][1,4]dioxin-6-yl)oxy)trimethylsilane (163)



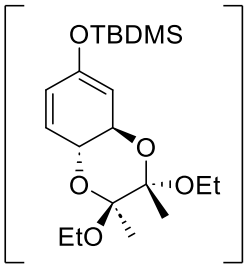
The crude silyl enol ether was prepared by literature procedure with similar substrate.[101] The vacuum-dried enone **162** (0.100 g, 0.37 mmol, 1 equiv.) was dissolved in freshly distilled THF (2.5 ml) under argon atmosphere and cooled to −78 °C. Then, LiHMDS solution (1M in THF, 0.56 ml, 0.56 mmol, 1.5 equiv.) was added. After 30 minutes of stirring, TMSCl (0.27 ml, 2.12 mmol, 5.7 equiv.) was added. After 1 hour of stirring the mixture was carefully concentrated *in vacuo*.

Crude ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (dt, *J* = 10.0, 1.5 Hz, 1H), 5.65 (dt, *J* = 10.0, 2.6 Hz, 1H), 4.91 (t, *J* = 2.1 Hz, 1H), 4.62 (ddd, *J* = 15.2, 1.8, 0.9 Hz, 1H), 4.52 (dddd, *J* = 15.0, 2.9, 1.9, 1.0 Hz, 1H), 3.60 – 3.43 (m, 4H), 1.34 (s, 6H), 1.22 – 1.16 (m, 6H), 0.19 (s, 9H) ppm.

Crude ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 130.8, 127.1, 104.8, 100.2, 99.8, 71.3, 70.7, 56.0, 55.9, 18.9, 18.8, 15.7, 15.6, 0.2 (3C) ppm.

Further characterization of this compound is incomplete due to its instability. Note: The $CDCl_3$ was filtered through basic alumina and potassium carbonate before dissolving the sample.

***tert*-Butyl(((2*S*,3*S*,4a*R*,8a*R*)-2,3-diethoxy-2,3-dimethyl-2,3,4a,8a-tetrahydrobenzo [*b*][1,4]dioxin-6-yl)oxy)dimethylsilane (164)**



The vacuum-dried enone **162** (26 mg, 0.1 mmol, 1 equiv.), TEA (0.08 ml, 0.6 mmol, 6 equiv.), NaI (28 mg, 0.2 mmol, 2 equiv.) and TBDMSCl (72.5 mg, 0.5 mmol, 5 equiv.) were dissolved in acetonitrile (anhydrous, 0.5 ml). After 12 hours of stirring at room temperature, the mixture was concentrated *in vacuo.*

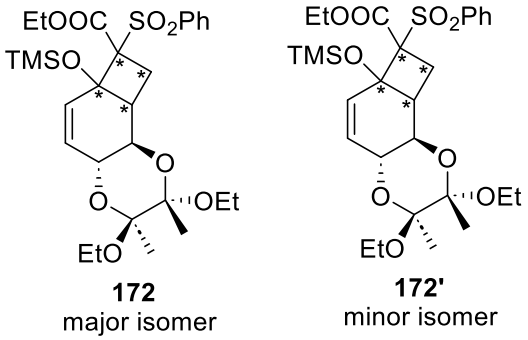
Crude ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 10.1, 1.6 Hz, 1H), 5.64 (dt, *J* = 10.0, 2.6 Hz, 1H), 4.91 (q, *J* = 2.1 Hz, 1H), 4.60 (ddd, *J* = 15.1, 2.1, 1.0 Hz, 1H), 4.50 (dddd, *J* = 15.1, 3.0, 1.9, 1.0 Hz, 1H), 3.53 – 3.42 (m, 4H), 1.32 (s, 6H), 1.20 – 1.14 (m, 6H), 0.88 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H) ppm.

Crude ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 130.7, 127.0, 105.0, 100.1, 99.7, 71.2, 70.6, 55.9, 55.8, 25.6 (3C), 18.8, 18.7, 18.0, 15.5, 15.5, -4.4, -4.5 ppm.

HRMS-ESI (m/z) for $C_{20}H_{36}O_5Si$ (M + Na) calcd: 407.2224 found: 407.2225.

Further characterization of this compound is incomplete due to its instability. Note: The $CDCl_3$ was filtered through basic alumina and potassium carbonate before dissolving the sample.

Mixture of two unassigned stereoisomers of ethyl (2*S*,3*S*,4a*R*,8b*R*)-2,3-diethoxy-2,3-dimethyl-7-(phenylsulfonyl)-6a-((trimethylsilyl)oxy)-2,3,4a,6a,7,8,8a,8b-octahydrocyclobuta[3,4]benzo[1,2-*b*][1,4]dioxine-7-carboxylate (172) and (172')



The crude trimethylsilyl enol ether **163** (0.55 mmol, 1 equiv.) was dissolved in toluene (anhydrous, 5 ml) under argon atmosphere. The solution was then cooled to −10 °C and alkene **171** (421 mg, 1.71 mmol, 3.1 equiv.) was added. After 4 hours the mixture was allowed to heat to room temperature and stirred at this temperature overnight. The next day, the mixture was diluted with EtOAc (30 ml) and washed with distilled water (3 × 15 ml) and brine (1 × 15 ml). The organic phase was dried using anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography (Hexane:EtOAc 5:1), providing major stereoisomer of **172** (51 mg, 16%) and minor stereoisomer of **172** (21 mg, 6.5%). R_f(major) ≈ 0.3 (Hexane:EtOAc = 5:1). R_f(minor) ≈ 0.4 (Hexane:EtOAc = 5:1).

Compound **172** (Major stereoisomer):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.84 (m, 2H), 7.62-7.57 (m, 1H), 7.49-7.43 (m, 2H), 5.74 (dd, *J* = 10.3, 1.5 Hz, 1H), 5.58 (ddd, *J* = 10.3, 2.7, 1.4 Hz, 1H), 4.34 (ddd, *J* = 9.1, 2.6, 1.5 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.78 (dd, *J* = 9.1, 4.6 Hz, 1H), 3.53-3.40 (m, 4H), 3.33 (td, *J* = 10.2, 4.7 Hz, 1H), 2.71 (dd, *J* = 14.3, 10.6 Hz, 1H), 2.33 (dd, *J* = 14.3, 9.7 Hz, 1H), 1.32 (s, 3H), 1.30 (s, 3H), 1.19-1.10 (m, 9H), 0.20 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 138.6, 133.8, 130.3, 130.2 (2C), 129.73, 128.5 (2C), 100.4, 100.0, 79.9, 79.5, 65.5, 65.1, 62.0, 55.8, 55.7, 41.2, 20.9, 18.7, 18.6, 15.6, 15.5, 14.08, 2.2 (3C) ppm.

HRMS-ESI (m/z) for $C_{28}H_{42}O_9SSi$ (M + Na) calcd: 605.2211 found: 605.2220.

Further characterization of this compound is incomplete due to its instability. Note: The $CDCl_3$ was filtered through basic alumina and potassium carbonate before dissolving the sample.

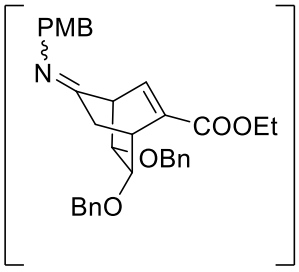
Compound **172'** (Minor stereoisomer):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.75 (m, 2H), 7.65 – 7.54 (m, 1H), 7.54 – 7.43 (m, 2H), 6.13 – 6.00 (m, 2H), 4.63 (dt, *J* = 9.0, 2.1 Hz, 1H), 4.04 – 3.86 (m, 2H), 3.82 (dd, *J* = 9.1, 4.9 Hz, 1H), 3.68 – 3.40 (m, 4H), 2.85 (ddt, *J* = 10.4, 5.6, 3.1 Hz, 1H), 2.78 – 2.61 (m, 2H), 1.37 (s, 3H), 1.34 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 0.11 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 140.0, 133.5 (2C), 131.7 (2C), 128.7, 128.5, 127.6, 100.3, 100.0, 81.8, 80.4, 65.7, 65.5, 62.2, 55.9, 55.6, 41.5, 21.6, 18.7, 18.6, 15.6, 15.4, 13.9, 1.8 (3C). ppm.

Further characterization of this compound is incomplete due to its instability. Note: The $CDCl_3$ was filtered through basic alumina and potassium carbonate before dissolving the sample.

***rel*-Ethyl (1*R*,4*R*,5*R*,6*R*)-5,6-Bis(benzyloxy)-8-((4-methoxybenzyl)imino) bicyclo[2.2.2]oct-2-ene-2-carboxylate (200)**



To a solution of vacuum-dried ketone **193** (40.0 mg, 0.1 mmol, 1 equiv.) in toluene (anhydrous, 0.5 ml) was added anhydrous $MgSO_4$ (47.4 mg, 0.4 mmol, 4 equiv.) and *para*-methoxybenzyl amine (14.9 mg, 1.1 mmol, 1.1 equiv.) under argon atmosphere. The solution was heated to reflux and let to stir overnight. Next day the crude NMR showed full conversion.

Crude ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 – 4.55 (m, 2H), 4.53 – 4.44 (m, 2H), 4.35 – 4.27 (m, 2H), 4.27 – 4.18 (m, 2H), 3.87 (dd, *J* = 6.5, 2.7 Hz, 1H), 3.87 – 3.83 (m, 2H), 3.78 (s, 3H), 3.64 (s, 1H), 2.62 (d, *J* = 17.5 Hz, 1H), 2.01 (d, *J* = 17.5 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H) ppm. Peaks of olefinic hydrogen atoms were not assigned due to overlap with residual toluene peaks.

Crude ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 164.4, 158.7, 140.5, 136.1, 131.9, 128.6 (2C), 128.5 (2C), 128.0 (2C), 127.9 (2C), 127.8 (2C), 114.1, 82.6, 82.3, 71.2, 71.0, 60.9, 56.2, 55.7,

51.3, 35.3, 25.7, 14.3 ppm. Peaks of 5 carbon atoms were not assigned due to the complexity of crude NMR and/or overlap with residual toluene peaks.

HRMS-ESI (m/z) for $C_{33}H_{35}NO_5$ (M + H) calcd: 526.2588 found: 526.2591.

Further characterization of this compound is incomplete due to its instability. Note: The $CDCl_3$ was filtered through basic alumina and potassium carbonate before dissolving the sample.

6. Conclusion

This diploma thesis focused on preparation of the key fragment of chevalinulin A. The retrosynthetic analysis was done, providing insights into the synthesis plan. Two synthesis pathways were elaborated; synthesis path A starting from natural and chiral D-(-)-quinic acid, and synthesis path B starting from 1,4-cyclohexadiene. Initially, synthesis path A was chosen because fewer steps were theoretically needed to obtain the crucial intermediate with the advantage that the starting material was chiral – thus eliminating the need for chiral resolution. However, this path presented challenges. The desired Diels-Alder product was not formed; instead, unreactivity or the formation of an undesired product was observed. It was hypothesized that changing the protective group to benzyl – and thus reducing the sterical demand could lead to the desired Diels-Alder product. However, the necessary step – the benzylation resulted in complex mixtures. Therefore, the focus switched to synthesis path B. This synthetic plan started with 1,4-cyclohexadiene. The racemic key fragment of chevalinulin A was obtained in 9 steps and 8.1% total yield. Further synthetic transformations on the way to chevalinulin A were tested, revealing a new strategy for the synthesis of chevalinulin A. Additionally, the utility of path B on the synthesis of the optically pure key fragment was demonstrated.

7. Acknowledgement

Foremost, I would like to express my sincere gratitude to my supervisor Prof. RNDr. Jan Veselý, Ph.D. for invaluable chemical insights, encouraging discussions, and for making this thesis possible. I am deeply grateful to RNDr. Vojtěch Dočekal, Ph.D, for his insightful opinions and comments on my work. Special appreciation goes to my fumehood neighbor, Bc. Daniel Čermák, for our enriching philosophical discussions ranging from chemical curiosities to existential crisis. I am grateful to my fellow lab mates for their help with lab matters. I also thank RNDr. Simona Petrželová, Ph.D. for measurements of advanced NMR experiments together with assistance with interpretation, Mgr. Bohunka Šperlichová for optical rotatory power and melting point measurements, RNDr. Martin Štícha, Ph.D. for mass spectrometry measurements and Mgr. Michal Urban, Ph.D. for IR spectra measurements. I am grateful to my girlfriend for support. Finally, my deepest gratitude goes to my loving and always supportive parents.

8. References

(1) Yan, L.-H.; Li, P.-H.; Li, X.-M.; Yang, S.-Q.; Liu, K.-C.; Wang, B.-G.; Li, X. Chevalinulins A and B, Proangiogenic Alkaloids with a Spiro[Bicyclo[2.2.2]Octane-Diketopiperazine] Skeleton from Deep-Sea Cold-Seep-Derived Fungus *Aspergillus Chevalieri* CS-122. *Org. Lett.* **2022**, *24*, 2684–2688. https://doi.org/10.1021/acs.orglett.2c00781.

(2) Wohlgemuth, V.; Kindinger, F.; Xie, X.; Wang, B.-G.; Li, S.-M. Two Prenyltransferases Govern a Consecutive Prenylation Cascade in the Biosynthesis of Echinulin and Neoechinulin. *Org. Lett.* **2017**, *19*, 5928–5931. https://doi.org/10.1021/acs.orglett.7b02926.

(3) Franke, D.; Sprenger, G. A.; Müller, M. Easy Access to (*R* , *R*)-3,4-Dihydroxy-3,4-dihydrobenzoic Acid with Engineered Strains of *Escherichia Coli*. *ChemBioChem* **2003**, *4*, 775–777. https://doi.org/10.1002/cbic.200300601.

(4) Diels, O.; Alder, K. Synthesen in Der Hydroaromatischen Reihe. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98–122. https://doi.org/10.1002/jlac.19284600106.

(5) Stork, G.; Tamelen, E. E. V.; Friedman, L. J.; Burgstahler, A. W. CANTHARIDIN. A STEREOSPECIFIC TOTAL SYNTHESIS. *J. Am. Chem. Soc.* **1951**, *73*, 4501–4501. https://doi.org/10.1021/ja01153a552.

(6) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. The Total Synthesis of Steroids [1]. *J. Am. Chem. Soc.* **1952**, *74*, 4223–4251. https://doi.org/10.1021/ja01137a001.

(7) Gates, M.; Tschudi, G. The Synthesis of Morphine. *J. Am. Chem. Soc.* **1956**, *78*, 1380–1393. https://doi.org/10.1021/ja01588a033.

(8) Hoffmann, R.; Woodward, R. B. Orbital Symmetries and Endo-Exo Relationships in Concerted Cycloaddition Reactions. *J. Am. Chem. Soc.* **1965**, *87*, 4388–4389. https://doi.org/10.1021/ja00947a033.

(9) Arrieta, A.; Cossío, F. P.; Lecea, B. Direct Evaluation of Secondary Orbital Interactions in the Diels−Alder Reaction between Cyclopentadiene and Maleic Anhydride. *J. Org. Chem.* **2001**, *66*, 6178–6180. https://doi.org/10.1021/jo0158478.

(10) Fernández, I.; Bickelhaupt, F. M. Origin of the “Endo Rule” in Diels-Alder Reactions. *J. Comput. Chem.* **2014**, *35*, 371–376. https://doi.org/10.1002/jcc.23500.

(11) García, J. I.; Mayoral, J. A.; Salvatella, L. The Source of the *Endo* Rule in the Diels−Alder Reaction: Are Secondary Orbital Interactions Really Necessary? *Eur. J. Org. Chem.* **2005**, *2005*, 85–90. https://doi.org/10.1002/ejoc.200400424.

(12) Danishefsky, S.; Kitahara, T. Useful Diene for the Diels-Alder Reaction. *J. Am. Chem. Soc.* **1974**, *96*, 7807–7808. https://doi.org/10.1021/ja00832a031.

(13) Savard, J.; Brassard, P. Regiospecific Syntheses of Quinones Using Vinylketene Acetals Derived from Unsaturated Esters. *Tetrahedron Lett.* **1979**, *20*, 4911–4914. https://doi.org/10.1016/S0040-4039(01)86747-2.

(14) Kozmin, S. A.; Rawal, V. H. Preparation and Diels−Alder Reactivity of 1-Amino-3-Siloxy-1,3-Butadienes. *J. Org. Chem.* **1997**, *62*, 5252–5253. https://doi.org/10.1021/jo970438q.

(15) Panarese, J. D.; Waters, S. P. Enantioselective Formal Total Synthesis of (+)-Aspergillide C. *Org. Lett.* **2009**, *11*, 5086–5088. https://doi.org/10.1021/ol902154p.

(16) Yates, P.; Eaton, P. Acceleration of the diels-alder reaction by aluminum chloride. *J. Am. Chem. Soc.* **1960**, *82*, 4436–4437. https://doi.org/10.1021/ja01501a085.

(17) Vermeeren, P.; Hamlin, T. A.; Fernández, I.; Bickelhaupt, F. M. How Lewis Acids Catalyze Diels–Alder Reactions. *Angew. Chem. Int. Ed.* **2020**, *59*, 6201–6206. https://doi.org/10.1002/anie.201914582.

(18) Sakata, K.; Fujimoto, H. Roles of Lewis Acid Catalysts in Diels-Alder Reactions between Cyclopentadiene and Methyl Acrylate. *ChemistryOpen* **2020**, *9*, 662–666. https://doi.org/10.1002/open.202000112.
(19) Yin, D.; Yin, D.; Fu, Z.; Li, Q. The Regioselectivity of Diels–Alder Reaction of Myrcene with Carbonyl-Containing Dienophiles Catalysed by Lewis Acids. *J. Mol. Catal. Chem.* **1999**, *148*, 87–95. https://doi.org/10.1016/S1381-1169(99)00113-2.
(20) *Handbook of Cyclization Reactions*; Ma, S., Ed.; Wiley-VCH: Weinheim, 2010.
(21) R. Kranich, K. C. N. Total Synthesis of Colombiasin A and Determination of Its Absolute Configuration. **2001**, No. 113, 2543–2547. https://doi.org/10.1002/1521-3765(20011217)7:24%3C5359::AID-CHEM5359%3E3.0.CO;2-Z.
(22) Jacobs, W.; Christmann, M. Synthesis of Amaminol B. *Synlett* **2008**, *2008*, 247–251. https://doi.org/10.1055/s-2007-1000935.
(23) Miller, S. L. A Production of Amino Acids Under Possible Primitive Earth Conditions. *Science* **1953**, *117*, 528–529. https://doi.org/10.1126/science.117.3046.528.
(24) Urey, H. C. On the Early Chemical History of the Earth and the Origin of Life. *Proc. Natl. Acad. Sci.* **1952**, *38*, 351–363. https://doi.org/10.1073/pnas.38.4.351.
(25) Bada, J. L. New Insights into Prebiotic Chemistry from Stanley Miller's Spark Discharge Experiments. *Chem. Soc. Rev.* **2013**, *42*, 2186. https://doi.org/10.1039/c3cs35433d.
(26) Miller, S. L. The Mechanism of Synthesis of Amino Acids by Electric Discharges. *Biochim. Biophys. Acta* **1957**, *23*, 480–489. https://doi.org/10.1016/0006-3002(57)90366-9.
(27) Strecker, A. Ueber Die Künstliche Bildung Der Milchsäure Und Einen Neuen, Dem Glycocoll Homologen Körper; *Justus Liebigs Ann. Chem.* **1850**, *75*, 27–45. https://doi.org/10.1002/jlac.18500750103.
(28) Metil, D. S.; Sampath, A.; Reddy, C. V. R.; Bandichhor, R. Synthesis and Characterization of Potential Related Substances of the Antiplatelet Agent Clopidogrel Bisulfate. *ChemistrySelect* **2018**, *3*, 100–104. https://doi.org/10.1002/slct.201702605.
(29) Sashikanth, S.; Raju, V.; Somaiah, S.; Rao, P.; Reddy, K. An Asymmetric Synthesis of Clopidogrel Hydrogen Sulfate. *Synthesis* **2013**, *45*, 621–624. https://doi.org/10.1055/s-0032-1316852.
(30) Feldman, P. L.; Brackeen, M. F. A Novel Route to the 4-Anilido-4-(Methoxycarbonyl)Piperidine Class of Analgetics. *J. Org. Chem.* **1990**, *55*, 4207–4209. https://doi.org/10.1021/jo00300a047.
(31) Stork, G. The Stereospecific Synthesis of Reserpine. *Pure Appl. Chem.* **1989**, *61*, 439–442. https://doi.org/10.1351/pac198961030439.
(32) Bommarius, A. S.; Schwarm, M.; Drauz, K. Comparison of Different Chemoenzymatic Process Routes to Enantiomerically Pure Amino Acids. *CHIMIA* **2001**, *55* (1–2), 50. https://doi.org/10.2533/chimia.2001.50.
(33) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. Scaleable Catalytic Asymmetric Strecker Syntheses of Unnatural α-Amino Acids. *Nature* **2009**, *461*, 968–970. https://doi.org/10.1038/nature08484.
(34) Kouznetsov, V. V.; Galvis, C. E. P. Strecker Reaction and α-Amino Nitriles: Recent Advances in Their Chemistry, Synthesis, and Biological Properties. *Tetrahedron* **2018**, *74*, 773–810. https://doi.org/10.1016/j.tet.2018.01.005.
(35) Harusawa, S.; Shioiri, T. Diethyl Phosphorocyanidate (DEPC): A Versatile Reagent for Organic Synthesis. *Tetrahedron* **2016**, *72*, 8125–8200. https://doi.org/10.1016/j.tet.2016.09.070.
(36) Sipos, S.; Jablonkai, I. One-Pot Synthesis of α-Aminonitriles from Alkyl and Aryl Cyanides: A Strecker Reaction via Aldimine Alanes. *Tetrahedron Lett.* **2009**, *50*, 1844–1846. https://doi.org/10.1016/j.tetlet.2009.02.004.

(37) Shen, K.; Liu, X.; Cai, Y.; Lin, L.; Feng, X. Facile and Efficient Enantioselective Strecker Reaction of Ketimines by Chiral Sodium Phosphate. *Chem. – Eur. J.* **2009**, *15*, 6008–6014. https://doi.org/10.1002/chem.200900210.
(38) Martínez, R.; Ramón, D. J.; Yus, M. Catalyst-Free Multicomponent Strecker Reaction in Acetonitrile. *Tetrahedron Lett.* **2005**, *46*, 8471–8474. https://doi.org/10.1016/j.tetlet.2005.10.020.
(39) Karimi, B.; Maleki, A. Catalytic Asymmetric Strecker Hydrocyanation of Imines Using Yb(OTf)3–Pybox Catalysts. *Chem. Commun.* **2009**, No. 34, 5180. https://doi.org/10.1039/b908854g.
(40) Zuend, S. J.; Jacobsen, E. N. Mechanism of Amido-Thiourea Catalyzed Enantioselective Imine Hydrocyanation: Transition State Stabilization via Multiple Non-Covalent Interactions. *J. Am. Chem. Soc.* **2009**, *131*, 15358–15374. https://doi.org/10.1021/ja9058958.
(41) Yan, H.; Suk Oh, J.; Lee, J.-W.; Eui Song, C. Scalable Organocatalytic Asymmetric Strecker Reactions Catalysed by a Chiral Cyanide Generator. *Nat. Commun.* **2012**, *3*, 1212. https://doi.org/10.1038/ncomms2216.
(42) Harada, K. Asymmetric Synthesis of α-Amino-Acids by the Strecker Synthesis. *Nature* **1963**, *200*, 1201–1201. https://doi.org/10.1038/2001201a0.
(43) Dave, R. H.; Hosangadi, B. D. A Simple and Efficient Diastereoselective Strecker Synthesis of Optically Pure α-Arylglycines. *Tetrahedron* **1999**, *55*, 11295–11308. https://doi.org/10.1016/S0040-4020(99)00673-0.
(44) Boesten, W. H. J.; Seerden, J.-P. G.; De Lange, B.; Dielemans, H. J. A.; Elsenberg, H. L. M.; Kaptein, B.; Moody, H. M.; Kellogg, R. M.; Broxterman, Q. B. Asymmetric Strecker Synthesis of α-Amino Acids via a Crystallization-Induced Asymmetric Transformation Using (*R*)-Phenylglycine Amide as Chiral Auxiliary. *Org. Lett.* **2001**, *3*, 1121–1124. https://doi.org/10.1021/ol007042c.
(45) Ohfune, Y.; Shinada, T. Asymmetric Strecker Route toward the Synthesis of Biologically Active α,α-Disubstituted α-Amino Acids. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1115–1129. https://doi.org/10.1246/bcsj.76.1115.
(46) Wang, H.; Zhao, X.; Li, Y.; Lu, L. Solvent-Controlled Asymmetric Strecker Reaction: Stereoselective Synthesis of *α* -Trifluoromethylated *α* -Amino Acids. *Org. Lett.* **2006**, *8*, 1379–1381. https://doi.org/10.1021/ol0601186.
(47) Ware, Elinor. The Chemistry of the Hydantoins. *Chem. Rev.* **1950**, *46*, 403–470. https://doi.org/10.1021/cr60145a001.
(48) Henze, H. R.; Speer, R. J. Identification of Carbonyl Compounds through Conversion into Hydantoins [1]. *J. Am. Chem. Soc.* **1942**, *64*, 522–523. https://doi.org/10.1021/ja01255a014.
(49) Wuts, P. G. M.; Ashford, S. W.; Conway, B.; Havens, J. L.; Taylor, B.; Hritzko, B.; Xiang, Y.; Zakarias, P. S. A Scalable Synthesis of the INOS Inhibitor PHA-399733. *Org. Process Res. Dev.* **2009**, *13*, 331–335. https://doi.org/10.1021/op8002745.
(50) Munday, L. 861. Amino-Acids of the Cyclohexane Series. Part I. *J. Chem. Soc. Resumed* **1961**, 4372. https://doi.org/10.1039/jr9610004372.
(51) Edward, J. T.; Jitrangsri, C. Stereochemistry of the Bucherer–Bergs and Strecker Reactions of 4- *Tert* -Butylcyclohexanone. *Can. J. Chem.* **1975**, *53*, 3339–3350. https://doi.org/10.1139/v75-477.
(52) Bodkin, J. A.; McLeod, M. D. The Sharpless Asymmetric Aminohydroxylation. *J. Chem. Soc. Perkin 1* **2002**, No. 24, 2733–2746. https://doi.org/10.1039/b111276g.
(53) Tao, B.; Schlingloff, G.; Sharpless, K. B. Reversal of Regioselection in the Asymmetric Aminohydroxylation of Cinnamates. *Tetrahedron Lett.* **1998**, *39*, 2507–2510. https://doi.org/10.1016/S0040-4039(98)00350-5.

(54) Heravi, M. M.; Lashaki, T. B.; Fattahi, B.; Zadsirjan, V. Application of Asymmetric Sharpless Aminohydroxylation in Total Synthesis of Natural Products and Some Synthetic Complex Bio-Active Molecules. *RSC Adv.* **2018**, *8*, 6634–6659. https://doi.org/10.1039/C7RA12625E.
(55) Cao, B.; Park, H.; Joullié, M. M. Total Synthesis of Ustiloxin D. *J. Am. Chem. Soc.* **2002**, *124* (4), 520–521. https://doi.org/10.1021/ja017277z.
(56) Brown, H. C. Hydroboration—a Powerful Synthetic Tool. *Tetrahedron* **1961**, *12*, 117–138. https://doi.org/10.1016/0040-4020(61)80107-5.
(57) Brown, H. C.; Zweifel, G. A stereospecific cis hydration of the double bond in cyclic derivatives. *J. Am. Chem. Soc.* **1959**, *81*, 247–247. https://doi.org/10.1021/ja01510a059.
(58) Brown, H. C.; Rao, B. C. S. A new technique for the conversion of olefins into organoboranes and related alcohols. *J. Am. Chem. Soc.* **1956**, *78*, 5694–5695. https://doi.org/10.1021/ja01602a063.
(59) Hauser, N.; Imhof, M. A.; Eichenberger, S. S.; Kündig, T.; Carreira, E. M. Total Synthesis of Shearinines D and G: A Convergent Approach to Indole Diterpenoids. *Angew. Chem.* **2022**, *134*, e202112838. https://doi.org/10.1002/ange.202112838.
(60) Kuttruff, C. A.; Zipse, H.; Trauner, D. Concise Total Syntheses of Variecolortides A and B through an Unusual Hetero-Diels–Alder Reaction. *Angew. Chem. Int. Ed.* **2011**, *50*, 1402–1405. https://doi.org/10.1002/anie.201006154.
(61) Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. Total Synthesis of Gypsetin, Deoxybrevianamide E, Brevianamide E, and Tryprostatin B: Novel Constructions of 2,3-Disubstituted Indoles. *J. Am. Chem. Soc.* **1999**, *121*, 11964–11975. https://doi.org/10.1021/ja9925249.
(62) Hubrich, F.; Juneja, P.; Müller, M.; Diederichs, K.; Welte, W.; Andexer, J. N. Chorismatase Mechanisms Reveal Fundamentally Different Types of Reaction in a Single Conserved Protein Fold. *J. Am. Chem. Soc.* **2015**, *137*, 11032–11037. https://doi.org/10.1021/jacs.5b05559.
(63) Young, I. G.; Gibson, F. The Enzymic and Chemical Formation of 3,4-Dihydro-3,4-Dihydroxybenzoic Acid: A New Compound Derived from Chorismic Acid. *Biochim. Biophys. Acta BBA - Gen. Subj.* **1969**, *177*, 182–183. https://doi.org/10.1016/0304-4165(69)90088-9.
(64) Boyd, D. R.; Sharma, N. D.; O'Dowd, C. R.; Hempenstall, F. Enantiopure Arene Dioxides: Chemoenzymatic Synthesis and Application in the Production of Trans-3,4-Dihydrodiols. *Chem. Commun.* **2000**, No. 21, 2151–2152. https://doi.org/10.1039/b006837n.
(65) Boyd, D. R.; Sharma, N. D.; Llamas, N. M.; O'Dowd, C. R.; Allen, C. C. R. Chemoenzymatic Synthesis of the Trans-Dihydrodiol Isomers of Monosubstituted Benzenes Viaanti-Benzene Dioxides. *Org. Biomol. Chem.* **2006**, *4*, 2208. https://doi.org/10.1039/b603928f.
(66) Boyd, D. R.; Sharma, N. D.; Byrne, B.; Hand, M. V.; Malone, J. F.; Sheldrake, G. N.; Blacker, J.; Dalton, H. Enzymatic and Chemoenzymatic Synthesis and Stereochemical Assignment of Cis-Dihydrodiol Derivatives of Monosubstituted Benzenes. *J. Chem. Soc. Perkin 1* **1998**, No. 12, 1935–1944. https://doi.org/10.1039/a800809d.
(67) Tharra, P. R.; Mikhaylov, A. A.; Švejkar, J.; Gysin, M.; Hobbie, S. N.; Švenda, J. Short Synthesis of (+)-Actinobolin: Simple Entry to Complex Small-Molecule Inhibitors of Protein Synthesis. *Angew. Chem. Int. Ed.* **2022**, *61*, e202116520. https://doi.org/10.1002/anie.202116520.
(68) Murray, L. M.; O'Brien, P.; Taylor, R. J. K. Stereoselective Reactions of a (−)-Quinic Acid-Derived Enone: Application to the Synthesis of the Core of Scyphostatin. *Org. Lett.* **2003**, *5*, 1943–1946. https://doi.org/10.1021/ol034521d.

(69) Tang, S.-Y.; Shi, J.; Guo, Q.-X. Accurate Prediction of Rate Constants of Diels–Alder Reactions and Application to Design of Diels–Alder Ligation. *Org. Biomol. Chem.* **2012**, *10*, 2673. https://doi.org/10.1039/c2ob07079k.
(70) Yamazaki, S.; Yanase, Y.; Tanigawa, E.; Yamabe, S.; Tamura, H. [2 + 1] Cycloaddition Reactions of a 1-Seleno-2-Silylethene to 2-Sulfonylacrylates: Stereoselective Synthesis of Sulfone-Substituted Cyclopropanes. *J. Org. Chem.* **1999**, *64*, 9521–9528. https://doi.org/10.1021/jo9911591.
(71) Gao, Y.; Qin, W.; Tian, M.; Zhao, X.; Hu, X. Defluorinative Alkylation of Trifluoromethyl Alkenes with Soft Carbon Nucleophiles Enabled by a Catalytic Amount of Base. *Adv. Synth. Catal.* **2022**, *364*, 2241–2247. https://doi.org/10.1002/adsc.202200328.
(72) Takasu, K.; Ueno, M.; Inanaga, K.; Ihara, M. Catalytic (2 + 2)-Cycloaddition Reactions of Silyl Enol Ethers. A Convenient and Stereoselective Method for Cyclobutane Ring Formation. *J. Org. Chem.* **2004**, *69*, 517–521. https://doi.org/10.1021/jo034989u.
(73) Hata, K.; Arichi, N.; Yamaoka, Y.; Yamada, K.; Takemoto, Y.; Takasu, K. Equilibration of the [2+2] Cycloaddition of Silyl Enol Ethers Catalyzed by Ethylaluminium Dichloride: Diastereoselectivity Switch in the Synthesis of Fused Cyclobutanes. *Asian J. Org. Chem.* **2014**, *3*, 706–710. https://doi.org/10.1002/ajoc.201402042.
(74) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 1st ed.; Wiley, 2006. https://doi.org/10.1002/0470053488.
(75) Ran, N.; Knop, D. R.; Draths, K. M.; Frost, J. W. Benzene-Free Synthesis of Hydroquinone. *J. Am. Chem. Soc.* **2001**, *123*, 10927–10934. https://doi.org/10.1021/ja016460p.
(76) Boa, A. N.; Jenkins, P. R.; Li, C.; Wang, J. Benzyl 2,2,2-Trichloroacetimidate. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd, Ed.; John Wiley & Sons, Ltd: Chichester, UK, 2011; p rb076. https://doi.org/10.1002/047084289X.rb076.
(77) Watanabe, A.; Kamahori, T.; Aso, M.; Suemune, H. Asymmetric Synthesis of C2-Symmetric 5,6-Bis(Benzyloxy)Cyclohexa-1,3-Diene and a Tricarbonyliron Complex. *J. Chem. Soc. Perkin 1* **2002**, No. 22, 2539–2543. https://doi.org/10.1039/b205526k.
(78) Kuwano, S.; Harada, S.; Kang, B.; Oriez, R.; Yamaoka, Y.; Takasu, K.; Yamada, K. Enhanced Rate and Selectivity by Carboxylate Salt as a Basic Cocatalyst in Chiral N-Heterocyclic Carbene-Catalyzed Asymmetric Acylation of Secondary Alcohols. *J. Am. Chem. Soc.* **2013**, *135*, 11485–11488. https://doi.org/10.1021/ja4055838.
(79) Suemune, H.; Hizuka, M.; Kamashita, T.; Sakai, K. Preparation of optically active gamma hydroxyethyl alpha beta unsaturated gamma lactone using an enzymatic procedure. *Chem. Pharm. Bull. (Tokyo)* **1989**, *37*, 1379–1381. https://doi.org/10.1248/cpb.37.1379.
(80) Sakai, K.; Suemune, H.; Hasegawa, A. Highly Enantio- and Diastereo-Seleetive Synthesis of C2-Symmetrie 3,5-Cyclohexadiene-l,2-Diol and D2-Symmetric Cyclohexane-l,2,4,5-Tetrol. *Tetrahedron Asymmetry* **1995**, *6*, 55–58.
(81) Michaud, S.; Viala, J. A New Facile Preparation of a Bifunctionalized C6 Homologating Agent from 1,4-Cyclohexadiene. *Tetrahedron* **1999**, *55*, 3019–3024. https://doi.org/10.1016/S0040-4020(99)00077-0.
(82) Lang, J. H.; Jones, P. G.; Lindel, T. Total Synthesis of the Marine Natural Product Hemiasterlin by Organocatalyzed α-Hydrazination. *Chem. – Eur. J.* **2017**, *23*, 12714–12717. https://doi.org/10.1002/chem.201702812.
(83) Da Paixao Soares, F.; Groaz, E.; Herdewijn, P. Phosphorus Pentachloride Promoted Gem-Dichlorination of 2′- and 3′-Deoxynucleosides. *Molecules* **2018**, *23*, 1457. https://doi.org/10.3390/molecules23061457.
(84) Tsang, J. W.; Schmied, B.; Nyfeler, R.; Goodman, M. Peptide Sweeteners. 6. Structural Studies on the C-Terminal Amino Acid of L-Aspartyl Dipeptide Sweeteners. *J. Med. Chem.* **1984**, *27*, 1663–1668. https://doi.org/10.1021/jm00378a023.

(85) Kalník, M.; Gabko, P.; Bella, M.; Koóš, M. The Bucherer–Bergs Multicomponent Synthesis of Hydantoins—Excellence in Simplicity. *Molecules* **2021**, *26*, 4024. https://doi.org/10.3390/molecules26134024.
(86) Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; De Los Santos, J. M. The Aza-Wittig Reaction: An Efficient Tool for the Construction of Carbon–Nitrogen Double Bonds. *Tetrahedron* **2007**, *63*, 523–575. https://doi.org/10.1016/j.tet.2006.09.048.
(87) Urban, M.; Franc, M.; Hofmanová, M.; Císařová, I.; Veselý, J. The Enantioselective Addition of 1-Fluoro-1-Nitro(Phenylsulfonyl)Methane to Isatin-Derived Ketimines. *Org. Biomol. Chem.* **2017**, *15*, 9071–9076. https://doi.org/10.1039/C7OB02408H.
(88) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. A Facile Synthesis of Cyanohydrin Trimethylsilyl Ethers by the Addition Reaction of Trimethylsilyl Cyanide with Aldehydes under Basic Condition. *Chem. Lett.* **1991**, *20*, 537–540. https://doi.org/10.1246/cl.1991.537.
(89) Kutovaya, I. V.; Shmatova, O. I.; Nenajdenko, V. G. Aza-Henry Reaction with Trifluoropiruvate Ketimines. *Mendeleev Commun.* **2018**, *28*, 133–134. https://doi.org/10.1016/j.mencom.2018.03.006.
(90) Lombardo, L. Methylenation of Carbonyl Compounds with Zn ,CH2Br2, TiCl4. Application to Gibberellins. *Tetrahedron Lett.* **1982**, *23*, 4293–4296. https://doi.org/10.1016/S0040-4039(00)88728-6.
(91) Ding, X.; Xu, Y.; Yan, L.; Chen, L.; Lu, Z.; Ge, C.; Zhao, X.; Wang, Z.; Lu, A.; Wang, Q. Marine Sesquiterpenes for Plant Protection: Discovery of Laurene Sesquiterpenes and Their Derivatives as Novel Antiviral and Antiphytopathogenic Fungal Agents. *J. Agric. Food Chem.* **2022**, *70*, 6006–6014. https://doi.org/10.1021/acs.jafc.2c00664.
(92) Yan, T.-H.; Tsai, C.-C.; Chien, C.-T.; Cho, C.-C.; Huang, P.-C. Dichloromethane Activation. Direct Methylenation of Ketones and Aldehydes with CH_2Cl_2 Promoted by $Mg/TiCl_4$ /THF. *Org. Lett.* **2004**, *6*, 4961–4963. https://doi.org/10.1021/ol0478887.
(93) Zhao, L.; Han, B.; Huang, Z.; Miller, M.; Huang, H.; Malashock, D. S.; Zhu, Z.; Milan, A.; Robertson, D. E.; Weiner, D. P.; Burk, M. J. Epoxide Hydrolase-Catalyzed Enantioselective Synthesis of Chiral 1,2-Diols via Desymmetrization of *m Eso* -Epoxides. *J. Am. Chem. Soc.* **2004**, *126*, 11156–11157. https://doi.org/10.1021/ja0466210.
(94) Michalska, K.; Gruba, E.; Mizera, M.; Lewandowska, K.; Bednarek, E.; Bocian, W.; Cielecka-Piontek, J. Application of Spectroscopic Methods (FT-IR, Raman, ECD and NMR) in Studies of Identification and Optical Purity of Radezolid. *Spectrochim. Acta. A. Mol. Biomol. Spectrosc.* **2017**, *183*, 116–122. https://doi.org/10.1016/j.saa.2017.04.038.
(95) Mayer, J. C. P.; Pereira, P. C.; Sagrilo, P. L.; Iglesias, B. A.; Back, D. F.; Da Rocha, V. N.; Köhler, M. H.; Rodrigues, O. E. D.; Dornelles, L. Synthesis, Spectroscopic, Electrochemistry and Antioxidant Properties of Benzofuroxan and 2H-Benzimidazole 1,3-Dioxide Derivatives: Effects of Conjugation with Electron-Acceptor 1,2,3-Triazolyl-1,2,4-Oxadiazole. *J. Mol. Struct.* **2024**, *1311*, 138420. https://doi.org/10.1016/j.molstruc.2024.138420.
(96) Bandini, M.; Bottoni, A.; Eichholzer, A.; Miscione, G. P.; Stenta, M. Asymmetric Phase-Transfer-Catalyzed Intramolecular N-Alkylation of Indoles and Pyrroles: A Combined Experimental and Theoretical Investigation. *Chem. – Eur. J.* **2010**, *16*, 12462–12473. https://doi.org/10.1002/chem.201000560.
(97) Szostak, M.; Sautier, B.; Spain, M.; Procter, D. J. Electron Transfer Reduction of Nitriles Using SmI_2 –Et_3N–H_2O: Synthetic Utility and Mechanism. *Org. Lett.* **2014**, *16*, 1092–1095. https://doi.org/10.1021/ol403668e.
(98) Das, M.; Yang, T.; Dong, J.; Prasetya, F.; Xie, Y.; Wong, K. H. Q.; Cheong, A.; Woon, E. C. Y. Multiprotein Dynamic Combinatorial Chemistry: A Strategy for the Simultaneous Discovery of Subfamily-Selective Inhibitors for Nucleic Acid Demethylases

FTO and ALKBH3. *Chem. – Asian J.* **2018**, *13*, 2854–2867. https://doi.org/10.1002/asia.201800729.
(99) Han, W.; Su, J.; Mo, J.-N.; Zhao, J. Photoredox Catalytic Phosphine-Mediated Deoxygenation of Hydroxylamines Enables the Construction of *N* -Acyliminophosphoranes. *Org. Lett.* **2022**, *24*, 6247–6251. https://doi.org/10.1021/acs.orglett.2c02226.
(100) Čmelová, P.; Šramel, P.; Zahradníková, B.; Modrocká, V.; Szabados, H.; Mečiarová, M.; Šebesta, R. Pro-Pro Dipeptide-Thiourea Organocatalyst in the Mannich Reaction between α-Imino Esters and Pyruvates. *Eur. J. Org. Chem.* **2022**, *2022*, e202200106. https://doi.org/10.1002/ejoc.202200106.
(101) Arthurs, C. L.; Morris, G. A.; Piacenti, M.; Pritchard, R. G.; Stratford, I. J.; Tatic, T.; Whitehead, R. C.; Williams, K. F.; Wind, N. S. The Synthesis of 2-Oxyalkyl-Cyclohex-2-Enones, Related to the Bioactive Natural Products COTC and Antheminone A, Which Possess Anti-Tumour Properties. *Tetrahedron* **2010**, *66*, 9049–9060. https://doi.org/10.1016/j.tet.2010.08.072.
(102) Neese, F. Software Update: The ORCA Program System—Version 5.0. *WIREs Comput. Mol. Sci.* **2022**, *12*, e1606. https://doi.org/10.1002/wcms.1606.
(103) Pracht, P.; Bohle, F.; Grimme, S. Automated Exploration of the Low-Energy Chemical Space with Fast Quantum Chemical Methods. *Phys. Chem. Chem. Phys.* **2020**, *22*, 7169–7192. https://doi.org/10.1039/C9CP06869D.
(104) Bannwarth, C.; Caldeweyher, E.; Ehlert, S.; Hansen, A.; Pracht, P.; Seibert, J.; Spicher, S.; Grimme, S. Extended TIGHT-BINDING Quantum Chemistry Methods. *WIREs Comput. Mol. Sci.* **2021**, *11*, e1493. https://doi.org/10.1002/wcms.1493.
(105) Ásgeirsson, V.; Birgisson, B. O.; Bjornsson, R.; Becker, U.; Neese, F.; Riplinger, C.; Jónsson, H. Nudged Elastic Band Method for Molecular Reactions Using Energy-Weighted Springs Combined with Eigenvector Following. *J. Chem. Theory Comput.* **2021**, *17*, 4929–4945. https://doi.org/10.1021/acs.jctc.1c00462.
(106) Grimme, S.; Brandenburg, J. G.; Bannwarth, C.; Hansen, A. Consistent Structures and Interactions by Density Functional Theory with Small Atomic Orbital Basis Sets. *J. Chem. Phys.* **2015**, *143*, 054107. https://doi.org/10.1063/1.4927476.
(107) Wheeler, S. E.; Houk, K. N. Integration Grid Errors for Meta-GGA-Predicted Reaction Energies: Origin of Grid Errors for the M06 Suite of Functionals. *J. Chem. Theory Comput.* **2010**, *6*, 395–404. https://doi.org/10.1021/ct900639j.
(108) Gaussian 16, Revision C.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.

9. Appendix

9.1 Crystallographic data

Table 6: Summary of crystallographic data and structure refinement parameters.

Compound	**187**
Formula	C12H20Br4O4
M	547.92
Crystal system	monoclinic
Space group	*P 1 21/n 1*
T/K	120(2)
a/Å	7.1207(3)
b/Å	10.3796(3)
c/Å	23.0378(9)
α/°	90
β/°	92.983(2)
γ/°	90
V/Å^3	1700.42(11)
Z	4
μ(Mo Kα)/mm^{-1}	9.475
Diffrns collected	69660
Independent diffrns	4579
Observed[b] diffrns	4204
R_{int}[c]/%	0.0421
No. of parameters	191
R[c] obsd diffrns/%	0.0239
R, *wR*[c] all data/%	0.0274, 0.0668
Δρ/e Å^{-3}	0.876, -0.680
CCDC entry	2352199

[a] The range of transmission factors. [b] Diffractions with $I > 2\sigma(I)$. [c] Definitions: $R_{int} = \Sigma \left| F_o^2 - F_o^2(\text{mean}) \right| / \Sigma F_o^2$, where F_o^2(mean) is the average intensity of symmetry-equivalent diffractions. $R = \Sigma \left| \left| F_o \right| - \left| F_c \right| \right| / \Sigma \left| F_o \right|$, $wR = [\Sigma\{w(F_o^2 - F_c^2)^2\}/\Sigma w(F_o^2)^2]^{1/2}$.

9.2 Computational methods

Calculations were performed using Orca 5.0.4[102], Gaussian 16[108], Crest 2.12[103] and xTB 6.6.0[104] software. The relevant conformers for each product were generated by the default Crest/xTB procedure at the GFN2-xTB/ALPB (toluene) level. The corresponding transition states were found using Nudged elastic band (NEB-TS, as implemented in Orca 5.0.4)[105] method at PBEh-3c[106] level of theory. The stationary points were reoptimized and characterized by full

calculation of vibrational frequencies carried out at the M06-2X/6-311+G*//M06-2X/6-31+G* level of theory (at 298.15 K), including an implicit description of toluene solvent using conductor-like PCM (CPCM) method as implemented in Gaussian 16. Because the M06 functional is known to be more sensitive to the integration grid[107] a dense integration grid was used specifying the grid=ultrafine keyword.

Table 7 XYZ of ethyl propiolate (165)

6	-1.307202000	-0.778656000	0.066573000
6	-0.501443000	0.116981000	0.043564000
1	-2.021270000	-1.575451000	0.087116000
8	0.084425000	2.396020000	0.061765000
6	0.429427000	1.238181000	0.018862000
8	1.691923000	0.821158000	-0.056013000
6	2.694175000	1.860423000	-0.085169000
1	4.113225000	0.571950000	-1.074719000
1	4.831530000	1.933649000	-0.191811000
1	4.203015000	0.533901000	0.700042000
6	4.041041000	1.178399000	-0.168010000
1	2.499229000	2.500629000	-0.949935000
1	2.589371000	2.463281000	0.821051000

Table 8 XYZ of diene (176)

6	-0.294567000	0.203653000	-0.222439000
6	-0.093011000	1.016530000	0.830273000
6	-0.558367000	2.445743000	0.767922000
8	0.434977000	3.324660000	0.217921000
6	-1.787873000	2.673002000	-0.130634000
8	-3.023251000	2.660253000	0.580007000
6	-1.801733000	1.768044000	-1.339342000
6	-1.078790000	0.645147000	-1.385240000
6	1.469446000	-3.525421000	-0.282410000
1	3.103306000	-4.197663000	1.026241000
1	3.348228000	-2.716964000	-1.078910000
6	2.170541000	-4.576752000	0.590778000
1	2.426857000	-5.457097000	-0.015129000
1	1.928361000	-2.363419000	-2.081286000

6	2.630173000	-1.064464000	1.223316000
1	3.427286000	-1.769467000	1.489339000
1	2.987273000	-0.453777000	0.386062000
8	0.148630000	-1.066901000	-0.337169000
1	2.479930000	-0.399359000	2.080236000
1	-0.846702000	-2.995057000	2.000335000
1	0.634222000	-2.979128000	2.974443000
1	-3.001320000	-3.017213000	0.221662000
1	-0.805367000	2.806257000	1.778568000
1	-1.101374000	-0.022702000	-2.242521000
1	3.209734000	0.772791000	-2.825302000
1	-0.299201000	-1.492928000	2.769256000
14	1.072617000	-1.992582000	0.746193000
1	2.621343000	-3.996704000	-2.066082000
1	1.528085000	-4.918609000	1.411340000
6	2.394748000	-3.121312000	-1.440910000
6	0.037765000	-2.401911000	2.258029000
1	-1.705452000	3.708507000	-0.476115000
1	-0.360010000	-3.401514000	-1.479528000
1	0.406143000	-5.003712000	-1.467918000
6	0.174302000	-4.123184000	-0.851929000
1	-0.506389000	-4.450223000	-0.056036000
6	-3.334559000	1.510427000	1.356744000
6	-5.019425000	-0.703177000	-1.241109000
1	-2.501903000	1.256838000	2.026934000
1	1.609110000	2.912243000	1.875646000
6	3.435435000	1.194422000	-1.849523000
1	2.049127000	4.319934000	0.904952000
1	-5.755158000	-0.605985000	-2.034557000
6	3.994228000	2.272051000	0.651723000
6	2.457898000	1.922890000	-1.169428000
6	2.728203000	2.460888000	0.089256000
6	-3.726174000	0.294078000	0.547147000
1	-5.134971000	1.372328000	-0.668158000
1	-2.448882000	2.052153000	-2.165273000
6	-4.679425000	0.404843000	-0.469457000
6	-4.413195000	-1.938475000	-0.998349000
1	1.474639000	2.069703000	-1.606650000
6	-3.139758000	-0.945744000	0.797539000

1	5.951640000	1.408274000	0.424113000
1	-4.177717000	1.831123000	1.977280000
6	-3.477552000	-2.059604000	0.027935000
6	1.699336000	3.282319000	0.843530000
6	4.695853000	1.006051000	-1.282723000
6	4.973983000	1.550635000	-0.027757000
1	-4.672681000	-2.801503000	-1.604733000
1	5.455284000	0.438424000	-1.812776000
1	-2.389127000	-1.033058000	1.580042000
1	4.214190000	2.689231000	1.633221000
1	0.466199000	0.687810000	1.701718000

Table 9 XYZ of diene (163)

6	-1.452723000	0.915878000	2.100989000
6	-0.130886000	1.118350000	2.168437000
6	0.168938000	-0.429584000	0.274453000
8	0.915213000	-0.657634000	-0.914850000
1	0.324570000	-1.282675000	0.958807000
1	1.691351000	-5.149392000	0.552036000
14	-4.471906000	0.057695000	-0.418965000
6	2.300495000	-0.837492000	-0.660380000
6	0.694418000	0.815521000	0.951816000
1	0.352461000	1.557206000	3.036880000
1	-2.124187000	1.175592000	2.914036000
6	-2.061632000	0.348284000	0.878661000
8	2.062367000	0.632823000	1.284176000
1	0.602878000	1.654319000	0.238589000
6	-1.293915000	-0.275552000	-0.034033000
8	-3.407377000	0.506087000	0.824712000
6	2.866532000	0.382301000	0.139923000
6	4.272947000	0.147777000	0.664216000
8	2.793406000	1.463652000	-0.757555000
8	2.508460000	-1.944591000	0.183889000
6	2.953878000	-1.008250000	-2.021470000
1	4.009161000	-1.269626000	-1.904453000
1	2.448809000	-1.807942000	-2.569414000
1	2.869136000	-0.083895000	-2.592700000
1	4.977512000	0.062197000	-0.167556000

1	4.570682000	0.988231000	1.296533000
1	4.299401000	-0.765299000	1.258721000
6	3.240244000	2.723985000	-0.268362000
6	2.053118000	-3.203726000	-0.299722000
1	4.337260000	2.739956000	-0.230958000
6	2.724219000	3.788494000	-1.216467000
1	2.858196000	2.884581000	0.747486000
1	1.630504000	3.780258000	-1.242656000
1	3.058543000	4.778352000	-0.891643000
1	3.095832000	3.611044000	-2.229921000
6	2.018930000	-4.157666000	0.878082000
1	1.056020000	-3.092338000	-0.743770000
1	2.736631000	-3.573335000	-1.075220000
1	3.013056000	-4.249410000	1.325286000
1	1.327010000	-3.795492000	1.644243000
1	-1.688771000	-0.757041000	-0.922800000
6	-6.128318000	0.652487000	0.205821000
1	-6.385822000	0.167874000	1.153492000
1	-6.118140000	1.735248000	0.369032000
1	-6.919611000	0.425409000	-0.517183000
1	-5.311159000	-2.104018000	-1.262718000
1	-3.553992000	-2.187499000	-1.084811000
6	-4.470539000	-1.806120000	-0.624820000
1	-4.595389000	-2.300677000	0.344731000
1	-3.924533000	2.014284000	-1.840847000
6	-3.995616000	0.933552000	-2.005243000
1	-3.039420000	0.589700000	-2.411158000
1	-4.764375000	0.760057000	-2.767487000

Table 10 XYZ of DA product (167)

6	-0.147196000	-3.424440000	-1.893268000
6	-0.493886000	-2.427526000	-0.800396000
8	-1.809777000	-2.573723000	-0.323377000
6	-2.848005000	-2.607170000	-1.296459000
6	-4.163032000	-2.443570000	-0.561020000
6	0.408435000	-2.616177000	0.492282000
6	-0.053251000	-3.774613000	1.359241000
8	1.707337000	-2.816500000	-0.014814000

6	2.756509000	-2.958410000	0.940303000
6	4.061143000	-2.649540000	0.231767000
8	0.384106000	-1.465698000	1.340867000
6	0.697112000	-0.324416000	0.557140000
6	-0.457314000	-0.132498000	-0.405934000
8	-0.337783000	-1.134682000	-1.404558000
6	-0.488516000	1.362447000	-0.837677000
6	-1.051499000	1.998677000	0.443490000
8	-2.219766000	2.687269000	0.383864000
14	-3.744052000	1.940053000	0.350434000
6	-3.947571000	1.059872000	-1.294303000
6	-3.851225000	0.750738000	1.793365000
6	-4.952188000	3.352920000	0.510840000
6	-0.321399000	1.772762000	1.539174000
6	0.977517000	1.029463000	1.259529000
1	-0.334991000	-4.446505000	-1.552594000
1	0.902341000	-3.322690000	-2.164927000
1	-0.760329000	-3.223396000	-2.775182000
1	-2.826900000	-3.566086000	-1.829752000
1	-2.697975000	-1.804512000	-2.029713000
1	-4.179105000	-1.500299000	-0.007068000
1	-4.307310000	-3.262513000	0.149850000
1	-4.996380000	-2.445264000	-1.270488000
1	-1.069564000	-3.599677000	1.709897000
1	0.609936000	-3.858139000	2.224236000
1	-0.019975000	-4.710029000	0.794211000
1	2.761124000	-3.983733000	1.332001000
1	2.594070000	-2.267561000	1.775632000
1	4.204361000	-3.320996000	-0.620015000
1	4.902775000	-2.775019000	0.919509000
1	4.062676000	-1.617978000	-0.133945000
1	1.589956000	-0.571956000	-0.023938000
1	-1.389210000	-0.328703000	0.135421000
1	-0.597327000	2.111844000	2.531219000
1	-3.198039000	0.272696000	-1.436223000
1	-3.851713000	1.770263000	-2.123355000
1	-4.936623000	0.591600000	-1.363061000
1	-4.835225000	0.268027000	1.821821000
1	-3.711029000	1.286579000	2.738940000

1	-3.091445000	-0.037960000	1.740824000
1	-4.809961000	3.882514000	1.458518000
1	-5.984597000	2.987979000	0.476346000
1	-4.819382000	4.071608000	-0.304691000
6	1.678922000	1.756536000	0.110263000
1	-1.124548000	1.543691000	-1.705568000
6	0.930513000	1.883484000	-0.993113000
1	1.623264000	0.919703000	2.131277000
1	1.288820000	2.310217000	-1.923562000
6	3.114574000	2.094190000	0.210409000
8	3.564864000	2.775536000	-0.852962000
8	3.813092000	1.783894000	1.155028000
6	4.966566000	3.104074000	-0.862458000
1	5.716196000	1.093746000	-0.596806000
1	5.480595000	1.573114000	-2.295508000
1	6.854287000	2.212599000	-1.371366000
6	5.802042000	1.918476000	-1.308734000
1	5.042242000	3.934455000	-1.566050000
1	5.254424000	3.446138000	0.134346000

Table 11 XYZ of DA product (175)

6	2.287931000	-0.448919000	1.025161000
6	1.115745000	-1.414523000	1.004397000
6	0.422093000	-1.175802000	-0.365469000
8	-0.664019000	-2.080629000	-0.444049000
6	-0.036646000	0.298339000	-0.449719000
8	0.479202000	0.860025000	-1.641261000
6	0.440876000	1.039082000	0.839395000
6	1.941851000	0.840094000	0.939525000
6	5.374411000	-0.105807000	-0.989542000
1	3.295814000	0.302186000	-1.579613000
1	4.451989000	-2.014005000	-1.546631000
6	4.288775000	0.760292000	-1.646295000
1	4.522983000	0.901794000	-2.711512000
1	6.204609000	-2.115091000	-1.287071000
6	5.194271000	1.293378000	1.795887000
1	4.855805000	2.158178000	1.216060000
1	4.618783000	1.260569000	2.727681000

8	3.508852000	-1.024636000	1.071251000
1	6.245553000	1.462167000	2.057797000
1	6.032268000	-1.660782000	2.697320000
1	5.968630000	-2.610432000	1.203251000
1	0.148984000	2.090167000	0.830722000
1	1.138664000	-1.370925000	-1.176469000
1	1.443971000	-2.450226000	1.096417000
1	-6.700311000	-1.367964000	-0.998355000
1	7.230902000	-1.383199000	1.423318000
14	5.045851000	-0.329345000	0.861212000
1	5.569263000	-1.356836000	-2.755996000
1	4.224588000	1.756499000	-1.190458000
6	5.400774000	-1.479281000	-1.676678000
6	6.177173000	-1.616492000	1.612397000
1	-1.133735000	0.318341000	-0.479220000
1	7.555124000	-0.003095000	-0.719934000
1	6.965254000	0.693387000	-2.235748000
6	6.739353000	0.579198000	-1.166147000
1	6.753480000	1.580566000	-0.718503000
6	-0.100082000	2.114935000	-1.995265000
6	-3.840978000	2.353774000	-1.297734000
1	-5.801606000	-2.341603000	-3.104546000
1	-1.186729000	-2.954493000	-2.228853000
6	-4.753067000	-1.153163000	-0.099896000
1	-1.023338000	-1.192403000	-2.281186000
1	-5.437266000	1.473833000	-2.446638000
6	-3.753659000	-2.235341000	-2.455714000
6	-3.377518000	-1.334994000	-0.253199000
6	-2.867093000	-1.872013000	-1.437011000
6	-1.599633000	2.018909000	-2.158154000
1	-1.465275000	0.892493000	-3.986845000
1	-0.341111000	-1.709578000	2.738748000
6	-2.462366000	2.542054000	-1.192023000
6	-4.366145000	1.637397000	-2.371641000
1	-2.991675000	0.085977000	5.331332000
6	-2.135692000	1.308703000	-3.236915000
1	-4.500771000	2.752551000	-0.532181000
1	-2.696013000	-1.073517000	0.553241000
6	-3.511237000	1.116803000	-3.344323000

6	-1.380747000	-2.031563000	-1.666817000
6	-5.630270000	-1.508791000	-1.122291000
6	-5.125748000	-2.053259000	-2.304116000
1	-2.052374000	3.076180000	-0.336731000
1	-3.363423000	-2.663879000	-3.377302000
1	-3.917594000	0.553430000	-4.179503000
1	0.154955000	2.878812000	-1.248446000
1	0.381800000	2.386520000	-2.938167000
6	0.097705000	-0.999884000	2.045859000
6	-0.255463000	0.287600000	1.955188000
1	-2.825785000	1.711197000	4.619411000
6	-1.348293000	0.930687000	2.713136000
8	-1.769988000	2.044680000	2.469042000
8	-1.840820000	0.148930000	3.685096000
6	-2.983835000	0.652994000	4.399376000
1	-4.380398000	-0.632719000	3.374668000
1	-5.121184000	0.766772000	4.178388000
1	-4.224408000	0.993868000	2.663407000
6	-4.254866000	0.430513000	3.600460000
1	-5.140292000	-0.732579000	0.823949000
1	2.628945000	1.675521000	0.881074000

Table 12 XYZ of DA reaction intermediate

6	-0.670530000	-4.061902000	-1.724950000
6	-0.550606000	-3.234987000	-0.457229000
8	-1.422779000	-3.653312000	0.562047000
6	-2.806031000	-3.704879000	0.227888000
6	-3.583609000	-3.813391000	1.524668000
6	0.874764000	-3.301013000	0.181184000
6	1.201441000	-4.653687000	0.786896000
8	1.741222000	-2.934658000	-0.854859000
6	3.129890000	-2.834123000	-0.535378000
6	3.779427000	-1.994400000	-1.616876000
8	0.953334000	-2.363272000	1.254247000
6	0.692567000	-1.049307000	0.796288000
6	-0.710026000	-0.977691000	0.219636000
8	-0.845553000	-1.894923000	-0.841847000
6	-0.982737000	0.445679000	-0.280478000

6	-0.781304000	1.388558000	0.849020000
8	-1.387746000	2.510623000	0.918045000
14	-2.615193000	3.336383000	-0.046533000
6	-2.160498000	3.300729000	-1.848223000
6	-4.204970000	2.448148000	0.360856000
6	-2.522527000	5.042444000	0.686070000
6	0.140383000	1.093658000	1.913364000
6	0.837745000	-0.065209000	1.899482000
1	-0.597143000	-5.126992000	-1.489037000
1	0.122571000	-3.785982000	-2.420065000
1	-1.636226000	-3.868432000	-2.198960000
1	-3.001407000	-4.574197000	-0.412980000
1	-3.087686000	-2.799598000	-0.325080000
1	-3.397123000	-2.941064000	2.158327000
1	-3.285487000	-4.710133000	2.075524000
1	-4.656452000	-3.872737000	1.318516000
1	0.436135000	-4.934430000	1.511123000
1	2.167344000	-4.598301000	1.295747000
1	1.258304000	-5.412128000	0.001739000
1	3.568110000	-3.839872000	-0.493490000
1	3.250397000	-2.361325000	0.447273000
1	3.626991000	-2.452082000	-2.598971000
1	4.855163000	-1.914411000	-1.432114000
1	3.352558000	-0.986511000	-1.620001000
1	1.422457000	-0.775196000	0.017666000
1	-1.423263000	-1.236470000	1.018345000
1	0.272483000	1.844416000	2.685169000
1	-2.369623000	2.336837000	-2.320831000
1	-1.099876000	3.525992000	-1.996337000
1	-2.754352000	4.067266000	-2.361360000
1	-5.045462000	2.972337000	-0.108240000
1	-4.378383000	2.433678000	1.441643000
1	-4.212938000	1.416458000	-0.005246000
1	-2.711157000	5.020990000	1.763964000
1	-3.266921000	5.698006000	0.221473000
1	-1.533000000	5.479556000	0.516654000
6	1.151575000	1.357458000	-1.504642000
1	-2.025421000	0.516127000	-0.615205000
6	-0.069815000	0.845864000	-1.501620000

1	1.555849000	-0.288783000	2.685566000
1	-0.604380000	0.620355000	-2.426891000
6	2.001627000	1.725721000	-0.434207000
8	1.715000000	2.988691000	0.051329000
8	2.955872000	1.083453000	0.021460000
6	2.629345000	3.524245000	1.009109000
1	4.414711000	3.309687000	-0.181451000
1	3.584945000	4.870235000	-0.384043000
1	4.526917000	4.548575000	1.087695000
6	3.866230000	4.098703000	0.339070000
1	2.063798000	4.304976000	1.525947000
1	2.901192000	2.745141000	1.728287000

Table 13 XYZ of transition state (163 → intermediate)

6	-0.564024000	-3.934769000	-1.746303000
6	-0.527152000	-3.111867000	-0.470542000
8	-1.444218000	-3.560383000	0.497061000
6	-2.810164000	-3.614954000	0.099772000
6	-3.645057000	-3.742148000	1.358876000
6	0.865726000	-3.156700000	0.246611000
6	1.153651000	-4.493296000	0.907573000
8	1.784998000	-2.834450000	-0.762318000
6	3.150615000	-2.682590000	-0.377381000
6	3.881797000	-2.088833000	-1.563678000
8	0.902615000	-2.190431000	1.293924000
6	0.635817000	-0.888664000	0.790773000
6	-0.766429000	-0.875030000	0.225642000
8	-0.835719000	-1.776538000	-0.863121000
6	-1.176617000	0.526879000	-0.182487000
6	-1.013567000	1.468200000	0.851428000
8	-1.644893000	2.620909000	0.920955000
14	-3.001812000	3.224961000	0.039732000
6	-2.590882000	3.281606000	-1.782586000
6	-4.456814000	2.114771000	0.423963000
6	-3.206610000	4.929094000	0.761975000
6	0.008515000	1.260670000	1.859271000
6	0.781528000	0.154849000	1.848658000
1	-0.456138000	-4.997589000	-1.513153000

1	0.242556000	-3.623625000	-2.409868000
1	-1.518969000	-3.777873000	-2.254581000
1	-2.971848000	-4.477970000	-0.558934000
1	-3.072078000	-2.704762000	-0.454689000
1	-3.493956000	-2.874712000	2.008468000
1	-3.365208000	-4.642116000	1.914101000
1	-4.707065000	-3.807118000	1.103827000
1	0.349896000	-4.748580000	1.598342000
1	2.090904000	-4.427045000	1.465766000
1	1.246572000	-5.275417000	0.149430000
1	3.569767000	-3.659860000	-0.104588000
1	3.220361000	-2.016178000	0.491045000
1	3.799688000	-2.746580000	-2.434414000
1	4.941101000	-1.957303000	-1.322385000
1	3.460514000	-1.109485000	-1.806245000
1	1.360735000	-0.670915000	-0.005655000
1	-1.452084000	-1.224722000	1.014768000
1	0.149852000	2.049508000	2.591368000
1	-2.715397000	2.312545000	-2.276521000
1	-1.561126000	3.618234000	-1.942740000
1	-3.261255000	3.993644000	-2.278374000
1	-5.360354000	2.515900000	-0.049531000
1	-4.634632000	2.070394000	1.503580000
1	-4.317645000	1.092429000	0.057911000
1	-3.360549000	4.879904000	1.844714000
1	-4.071819000	5.432787000	0.317399000
1	-2.320742000	5.542891000	0.569177000
6	1.229577000	1.476594000	-1.334655000
1	-2.117764000	0.570448000	-0.729709000
6	0.022888000	1.122474000	-1.502837000
1	1.578321000	0.026151000	2.578046000
1	-0.627598000	1.038940000	-2.364067000
6	2.305911000	1.694308000	-0.430590000
8	2.309963000	2.964785000	0.057728000
8	3.175441000	0.875534000	-0.143889000
6	3.380259000	3.295329000	0.951920000
1	5.011965000	2.766164000	-0.360545000
1	4.472960000	4.456442000	-0.503241000
1	5.432591000	3.944497000	0.900250000

6	4.653216000	3.634946000	0.196401000
1	3.010435000	4.158474000	1.509836000
1	3.539573000	2.462831000	1.643514000

Table 14 XYZ of transition state (intermediate → 167)

6	-0.448966000	-3.814654000	-1.736592000
6	-0.488402000	-2.929769000	-0.503680000
8	-1.508179000	-3.292823000	0.395526000
6	-2.836199000	-3.301093000	-0.118454000
6	-3.783683000	-3.278162000	1.065072000
6	0.836918000	-2.999143000	0.342333000
6	0.964774000	-4.292211000	1.129827000
8	1.858221000	-2.832756000	-0.604887000
6	3.194358000	-2.729616000	-0.113850000
6	4.077091000	-2.382714000	-1.294689000
8	0.870019000	-1.952939000	1.313658000
6	0.709089000	-0.685739000	0.674360000
6	-0.674130000	-0.672854000	0.075717000
8	-0.713537000	-1.603624000	-0.986959000
6	-1.082047000	0.739896000	-0.329837000
6	-1.142912000	1.560221000	0.872347000
8	-1.984065000	2.557960000	1.029878000
14	-3.427627000	2.960412000	0.167926000
6	-2.991582000	3.349908000	-1.608130000
6	-4.599430000	1.513108000	0.341009000
6	-4.023663000	4.467843000	1.082789000
6	-0.105504000	1.407066000	1.825252000
6	0.857164000	0.452994000	1.638352000
1	-0.377229000	-4.865935000	-1.444908000
1	0.408023000	-3.549960000	-2.355093000
1	-1.363050000	-3.668974000	-2.318149000
1	-2.994274000	-4.203698000	-0.722600000
1	-2.990990000	-2.424902000	-0.760688000
1	-3.638659000	-2.368019000	1.655258000
1	-3.608097000	-4.141537000	1.713348000
1	-4.821403000	-3.308395000	0.719371000
1	0.096602000	-4.423528000	1.775370000
1	1.862548000	-4.250667000	1.751159000

1	1.044002000	-5.142695000	0.447438000
1	3.498590000	-3.682840000	0.337220000
1	3.249256000	-1.944723000	0.649934000
1	4.008261000	-3.155112000	-2.066997000
1	5.119385000	-2.304915000	-0.969963000
1	3.774083000	-1.419243000	-1.711807000
1	1.477149000	-0.613916000	-0.101773000
1	-1.376687000	-1.006237000	0.853202000
1	-0.011221000	2.157398000	2.603976000
1	-2.837132000	2.454772000	-2.219063000
1	-2.085131000	3.962737000	-1.660464000
1	-3.808697000	3.922511000	-2.062611000
1	-5.562605000	1.759901000	-0.120195000
1	-4.780513000	1.291301000	1.398169000
1	-4.226992000	0.602171000	-0.139330000
1	-4.192486000	4.243370000	2.140782000
1	-4.966377000	4.827147000	0.655965000
1	-3.290784000	5.278495000	1.016868000
6	1.279237000	1.641991000	-0.938159000
1	-2.013184000	0.728712000	-0.899174000
6	0.044913000	1.471962000	-1.262932000
1	1.740570000	0.446543000	2.274657000
1	-0.421149000	1.792649000	-2.195040000
6	2.547479000	1.657402000	-0.354432000
8	2.835919000	2.852794000	0.252389000
8	3.362509000	0.725586000	-0.393051000
6	4.149306000	2.972770000	0.808351000
1	5.253087000	2.500587000	-0.985684000
1	4.897789000	4.232391000	-0.778039000
1	6.159941000	3.459488000	0.203564000
6	5.177640000	3.311674000	-0.257192000
1	4.062068000	3.779015000	1.540670000
1	4.410720000	2.046217000	1.326853000

Table 15 XYZ of transition state (176 → 175)

6	2.049029000	-0.481791000	0.980829000
6	1.203284000	-1.338541000	0.298276000
6	0.247475000	-0.770288000	-0.717334000

8	-0.744419000	-1.745700000	-0.971670000
6	-0.350187000	0.590757000	-0.297636000
8	-0.146835000	1.496527000	-1.387210000
6	0.310014000	1.164787000	0.935621000
6	1.569289000	0.806678000	1.326511000
6	5.128326000	-0.460309000	-0.600828000
1	3.315587000	0.609583000	-1.244011000
1	3.601446000	-1.945065000	-1.109268000
6	4.404960000	0.661038000	-1.363473000
1	4.622829000	0.580822000	-2.438035000
1	5.154050000	-2.657383000	-0.635022000
6	4.920621000	1.380102000	1.893472000
1	4.291814000	2.088168000	1.344249000
1	4.653516000	1.433607000	2.954860000
8	3.187039000	-0.967065000	1.542499000
1	5.960530000	1.714241000	1.795243000
1	5.477968000	-1.591618000	3.281540000
1	5.823155000	-2.553445000	1.834750000
1	-0.137485000	2.067229000	1.348140000
1	0.818915000	-0.587841000	-1.644147000
1	1.554125000	-2.348195000	0.096197000
1	-6.776780000	-2.408310000	-1.094475000
1	6.873359000	-1.190290000	2.266293000
14	4.757084000	-0.377946000	1.256668000
1	4.976835000	-1.895291000	-2.224267000
1	4.732093000	1.654154000	-1.034123000
6	4.688366000	-1.818473000	-1.166347000
6	5.835216000	-1.539165000	2.247477000
1	-1.428572000	0.465173000	-0.129476000
1	7.206366000	-1.119364000	-0.334125000
1	6.884134000	-0.303093000	-1.871928000
6	6.645326000	-0.300066000	-0.799133000
1	7.018059000	0.645033000	-0.384233000
6	-1.098087000	2.560329000	-1.441463000
6	-4.715550000	1.362952000	-1.660480000
1	-5.884142000	-2.646473000	-3.403033000
1	-1.205303000	-2.076472000	-2.955563000
6	-4.860177000	-1.888815000	-0.252230000
1	-1.474906000	-0.420398000	-2.387643000

1	-5.794474000	0.796182000	-3.433838000
6	-3.867574000	-2.152549000	-2.837027000
6	-3.507044000	-1.667248000	-0.504122000
6	-3.002837000	-1.792181000	-1.801200000
6	-2.431257000	2.106521000	-1.989024000
1	-1.748198000	2.125211000	-4.031600000
1	-0.162762000	-2.742389000	1.802258000
6	-3.505353000	1.828551000	-1.141042000
6	-4.857455000	1.170342000	-3.031350000
1	-1.476532000	2.251616000	5.286042000
6	-2.583995000	1.912474000	-3.367648000
1	-5.538442000	1.134445000	-0.989578000
1	-2.836904000	-1.394097000	0.306928000
6	-3.787394000	1.444926000	-3.887533000
6	-1.557765000	-1.477983000	-2.103981000
6	-5.722559000	-2.235530000	-1.292440000
6	-5.221596000	-2.369150000	-2.587623000
1	-3.391367000	1.956031000	-0.065899000
1	-3.479696000	-2.257073000	-3.848658000
1	-3.894616000	1.295518000	-4.958363000
1	-1.227801000	3.009070000	-0.447609000
1	-0.647712000	3.310104000	-2.097414000
6	-0.259399000	-1.671962000	1.796584000
6	-0.825966000	-0.639550000	2.178546000
1	-2.402564000	2.541269000	3.791189000
6	-1.704179000	0.364923000	2.710206000
8	-2.674047000	0.807218000	2.116908000
8	-1.318478000	0.782352000	3.927053000
6	-2.134691000	1.796277000	4.544439000
1	-3.076831000	0.428969000	5.922820000
1	-3.932140000	1.969454000	5.708819000
1	-4.012987000	0.732508000	4.438910000
6	-3.365482000	1.189164000	5.191423000
1	-5.241426000	-1.784362000	0.760104000
1	2.103153000	1.381165000	2.078251000