Technische Universität München
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Total Synthesis of Prezizane-type Sesquiterpenes

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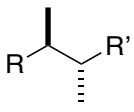
In this thesis, the relative configuration of racemates is represented by straight lines (bold or hashed). The absolute configuration of enantiomerically pure or enriched compounds is represented by wedge-shaped lines (bold or hashed).

Racemate 

enantiomerically pure or
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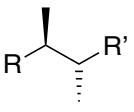

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dedicated to my 16-year-old self.

Abstract

Photochemical cascade reactions offer a strategy for synthesizing complex molecular scaffolds efficiently from simple precursors. A notable example involves the intramolecular *ortho* photocycloaddition of 7-(alkenyloxy)-indanones, which serves as a trigger for a sequence of consecutive reactions. The cascade reaction enables the rapid construction of the complete skeleton of prezizane-type sequiterpene natural products. In this case, the initial *ortho* photocycloaddition is followed by three consecutive transformations, two of which are initiated by a photon. Notably, the reaction cascades exhibit exquisite diastereoselectivity, resulting in the generation of five stereogenic centers for prezizanes. Within the scope of this PhD thesis, a photochemical cascade reaction was utilized as key step for the total synthesis of the prezizane-type sesquiterpenes agarozizanol B, jinkohol II, and jinkoholic acid.

Agarozizanol B was synthesized by utilizing the major diastereoisomeric product of the photochemical cascade reaction. For the precursor, a 1-indanone was tethered to a 1-(chloromethoxy)-olefin, which was derived from prenol. Irradiation over 24 h yielded the major diastereomer, which contained all carbon atoms of the sesquiterpene with the correct relative configuration in 42% yield. The transformation into the tricyclic prezizane skeleton was achieved *via* a strategic cleavage of a cyclopropane bond. Before the opening of the cyclopropane ring, an oxidation was necessary, which could be carried out alongside a reductive resolution step. Following the removal of two functional groups, the natural product was obtained over eleven steps either in racemic form (4%) or, upon resolution, as the (+)-enantiomer (2%), which was demonstrated to be identical to the natural product.

The photochemical cascade reaction, which was utilized in the total synthesis of (+)-agarozianol B was employed for the preparation of (+)-prezizaan-15-ol, (+)-jinkohol II and (+)-jinkoholic acid. While the minor diastereomeric pentacyclic photoproduct with a 2β-Me configuration was converted into (+)-prezizaan-15-ol in twelve steps, the major diastereoisomer with a 2α-Me configuration gave in an analogous route (+)-jinkohol II, which was oxidized at the C13 carbon atom to (+)-jinkoholic acid. The total syntheses provided a means to resolve a previous ambiguity regarding the configuration of the natural products.

Kurzzusammenfassung

Photochemische Kaskadenreaktionen bieten eine Möglichkeit zur effizienten Synthese komplexer molekularer Architekturen aus einfachen Vorläufern. Ein bemerkenswertes Beispiel stellt die Kaskadenreaktion von 7-(Alkenyloxy)-Indanonen dar, welche durch eine intramolekulare *ortho*-Photocycloaddition initiiert wird. Diese Reaktionsabfolge ermöglicht den schnellen Aufbau des vollständigen Skeletts von prezizanartigen Sesquiterpen-Naturstoffen. Hier folgen nach der initialen *ortho*-Photocycloaddition drei weitere Transformationsschritte, von denen zwei durch jeweils ein Photon initiiert werden. Diese Reaktionskaskade zeigt eine hohe Diastereoselektivität und führt zum selektiven Aufbau von fünf stereogenen Zentren. Im Rahmen dieser Doktorarbeit wurde die photochemische Kaskadenreaktion als Schlüsselschritt für die Totalsynthese der Prezizan-Sesquiterpene Agarozizanol B, Jinkohol II und Jinkoholsäure verwendet.

Agarozizanol B wurde aus dem Hauptdiastereomer der photochemischen Kaskadenreaktion synthetisiert. Zur Herstellung des Vorläufers wurde ein 1-Indanon an ein 1-(Chlormethoxy)-Olefin, abgeleitet von Prenol, gebunden. Die Bestrahlung über 24 Stunden lieferte das Hauptdiastereomer, welches alle Kohlenstoffatome des Sesquiterpens mit der korrekten Relativkonfiguration in 42% Ausbeute enthielt. Die Umwandlung in das trizyklische Prezizan-Skelett wurde durch eine strategische Öffnung des Cyclopropanrings erreicht. Vor der Öffnung war eine Anpassung des Oxidationszustands erforderlich, die mit einem enantioselektiven Reduktionsschritt verbunden werden konnte. Nach Entfernung von zwei funktionellen Gruppen wurde der Naturstoff in elf Schritten sowohl in racemischer Form (4%) als auch nach Racemat-Spaltung in Form des (+)-Enantiomers (2%) erhalten, welches sich als identisch mit dem Naturstoff erwies.

Die photochemische Kaskadenreaktion, die bei der Totalsynthese von (+)-Agarozianol B verwendet wurde, wurde zur Herstellung von (+)-Prezizaan-15-ol, (+)-Jinkohol II und (+)-Jinkoholsäure verwendet. Während (+)-Prezizaan-15-ol in zwölf Reaktionsschritten aus dem Nebendiastereomer des pentazyklischen Photoprodukts mit einer 2β-Me-Konfiguration synthetisiert wurde, wurde das Hauptdiastereomer mit einer 2α-Me-Konfiguration auf einem analogen Weg zu (+)-Jinkohol II transformiert. Oxidation am C13 Kohlenstoff führte zu (+)-Jinkoholsäure. Die Totalsynthesen gaben den synthetischen Beweis zur Klärung der Konfiguration der Naturstoffe.

CONTENTS

1. Introduction

1.1. Agarwood as a source of sesquiterpenoids

Aquilaria malaccensis is a species of plant within the *Thymelaeaceae* family and the major source for agarwood (also known as Chen Xiang (沉香)).[1] With a rapidly growing market in several countries,[2] agarwood is a resinous heartwood,[3] which finds its application in perfumes,[4] as incenses in cultural and religious ceremonies,[5] in ornamental displays[6,7] and in medicine. In traditional medicine (e.g. in China) the plant has a history of use for various inflammatory conditions, joint pain, diarrhea, as a stimulant or sedative, and also as a cardioprotective agent.[8,9] The earliest references to agarwood can be traced back to ancient literature and religious scriptures, documenting initial encounters with it. *Kâlidâsa* (*fl*. 4th–5th century CE), considered as one of ancient India's greatest poets and dramatists,[10] wrote:[6]

Beautiful ladies, preparing themselves for the feast of pleasures, cleanse themselves with the yellow powder of sandal, clear and pure, freshen their breast with pleasant aromas, and suspend their dark hair in the smoke of burning aloes.

The word *aloe* in these lines has the same meaning as agarwood.[6] It is crucial to highlight that agarwood is exclusively produced by trees in response to injuries. Consequently, when the tree is wounded, the biosynthetic process is initiated, resulting in the creation of this dark resinous material (Figure 1).[7,11,12]

Figure 1. Cross section of a tree showing resinous agarwood.[13]

The activation of secondary biosynthetic pathways can occur coincidentally through natural processes such as lightning strikes, burning, microbal invasions or fungal infection. However, these defense mechanisms are too slow and insufficient to generate a substantial quantity of agarwood. As a result, the material is produced artificially through methods such as holing, cutting, or intentional fungal infestation of the trees to meet the demand (Figure 2).[12]

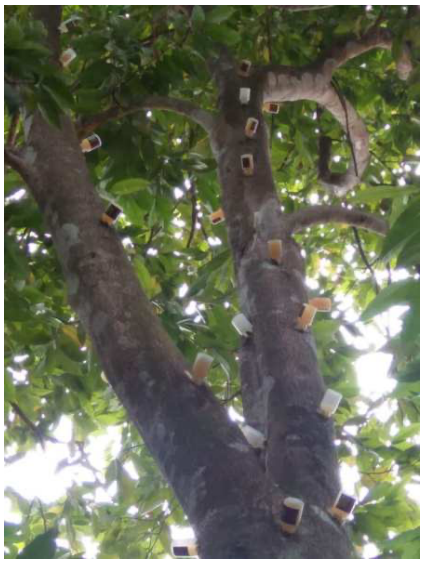
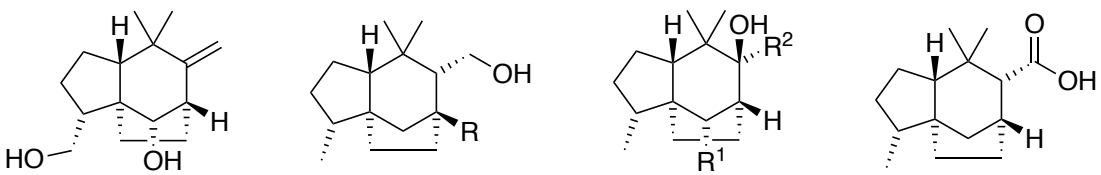


Figure 2. Dispersing wounding of an *aquilaria* tree with 10–20 mL liquid inoculants.[14]

Previous investigations have unveiled that agarwood contains two main aromatic components: sesquiterpenoids and 2-(2-phenylethyl)chromone derivatives. So far, researchers have isolated more than 130 sesquiterpenoids and 120 2-(2-phenylethyl)chromone derivatives from agarwood.[15] Remarkably, many of these compounds have demonstrated diverse pharmacological properties, including antibacterial effects,[16] inhibition of α-glucosidase,[15] cytotoxic activity[15] and antidepressant activities.[17] In 2019, the sesquiterpenoids Agarozizanol A-D (**1**-**4**), Jinkohol II (**5**) and Jinkoholic acid (**6**) (Figure 3) were isolated from agarwood and their structure elucidation, α-glucosidase and tyrosinase inhibitory activities, as well as kinetic and molecular docking studies, were reported by the *Dai* group.[15]



1

2 R = OH
5 R = H

3 R^1 = OH, R^2 = CH_3
4 R^1 = H, R^2 = CH_2OH

6

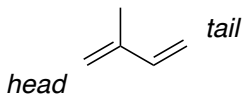
Figure 3. Structures of Agarozizanol A-D (**1**-**4**), Jinkohol II (**5**) and Jinkoholic acid (**6**).

The total synthesis of the isolated prezizane-type sesquiterpenoids agarozizanol B (**2**), jinkohol II (**5**) and jinkoholic acid (**6**), as well as their structural evaluation constitute the fundamental groundwork of this PhD work. The aim was to explore and comprehend the novel reactions that facilitate the efficient construction of intricate structures inherent in small molecules and natural products. The investigated photochemical transformations utilize readily available building blocks, enabling the concise assembly of these complex compounds.

1.2. Terpenes and Terpenoids

1.2.1. Classification

Sesquiterpenes belong to the class of terpenes (Latin = '*turpentine*'), which contains a large number of approximately 55.000 compounds known to date.[18] Generally, terpenes are hydrocarbons, which often undergo oxygenation, hydrogenation, or dehydrogenation to form terpenoids (isoprenoids) with various functional groups.[18,19] All terpenes have at least one isoprene (**7**) unit as their common structural feature and are synthesized by *e.g.* plants. As presented below in Figure 4, each isoprene molecule has a head and a tail. Two or more isoprene units of terpenes are usually connected head to tail.[20]

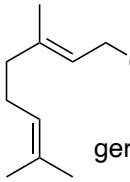
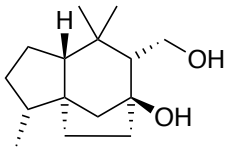
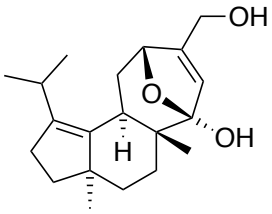
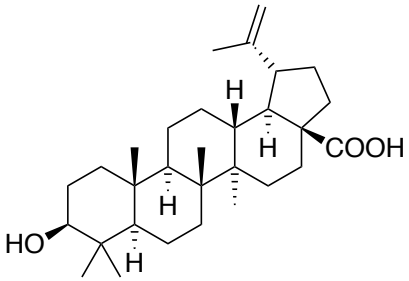
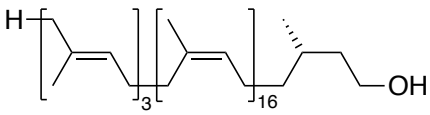


7

Figure 4. Head-to-tail structure of an isoprene unit (**7**).

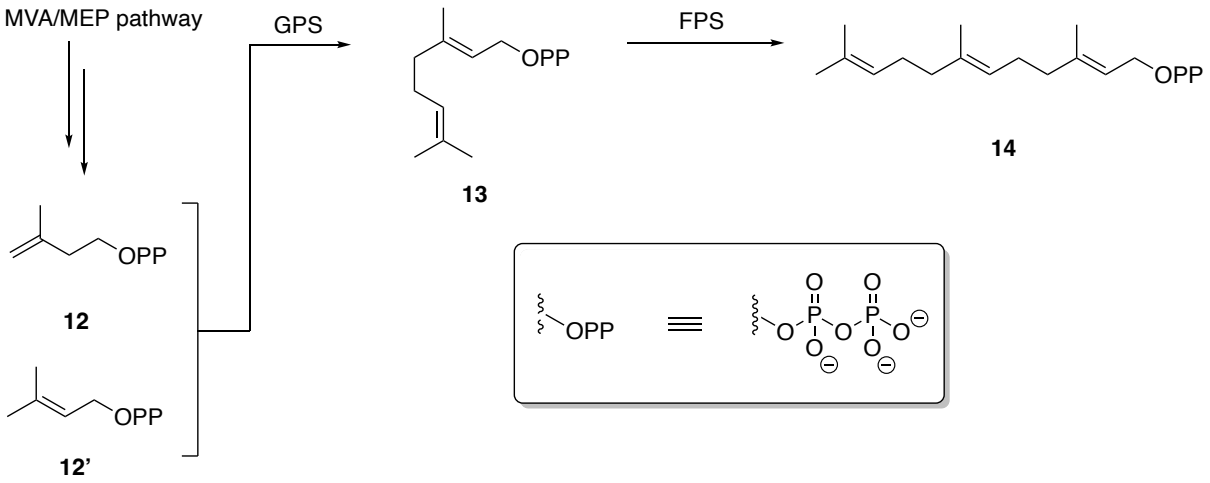
Moreover, terpenes are classified according to the number of isoprene units they contain. Thus, hemiterpenes are the simplest compounds with a single isoprene unit, whereas monoterpenes contain two isoprene units.[20] An important monoterpenoid is for example geraniol (**8**), which is emitted from the flowers of many species of plants (*e.g.* wormwood) and used in cosmetic and perfumery products.[21] Furthermore, terpenoids with three isoprene units are classified as sesquiterpenoids. An example for this is the already mentioned α-glucosidase-inhibitor (+)-agarozizanol B (**2**).[15] An example for a diterpenoid (consisting of four isoprene units) is (–)-cyathin A_3 (**9**), which can be found in fungi, sponges, and fruiting plants and possesses antimicrobial activity.[22] (+)-Betulinic acid (**10**) is a representative of the triterpenoid class (six isoprene units) and displays anti-cancer activity.[23] Terpenoids with more than six isoprene units are polyterpenoids, e.g. (*S*)-(–)-dolichol-20 (**11**), whose structure was also confirmed by total synthesis.[24] The different terpene classes with the aforementioned example molecules are summarized in Table 1. Sesterterpenes (25 carbon atoms) and tetraterpenes (40 carbon atoms), also referred to as carotenoids, exist alongside those listed below.[20]

Table 1. Classification of terpenoids.

# Isoprene units	Terpenoid class	# Carbon atoms	Terpenoid example
2	Monoterpenes/-oids	C_{10}	 geraniol (**8**)[21]
3	Sesquiterpenes/-oids	C_{15}	 (+)-agarozizanol B (**2**)[15]
4	Diterpenes/-oids	C_{20}	 (–)-cyathin A_3 (**9**)[22]
6	Triterpenes/-oids	C_{30}	 (+)-betulinic acid (**10**)[23]
n	Polyterpene/-oids	$(C_5)_n$	 (*S*)-(–)-dolichol-20 (**11**)[24]

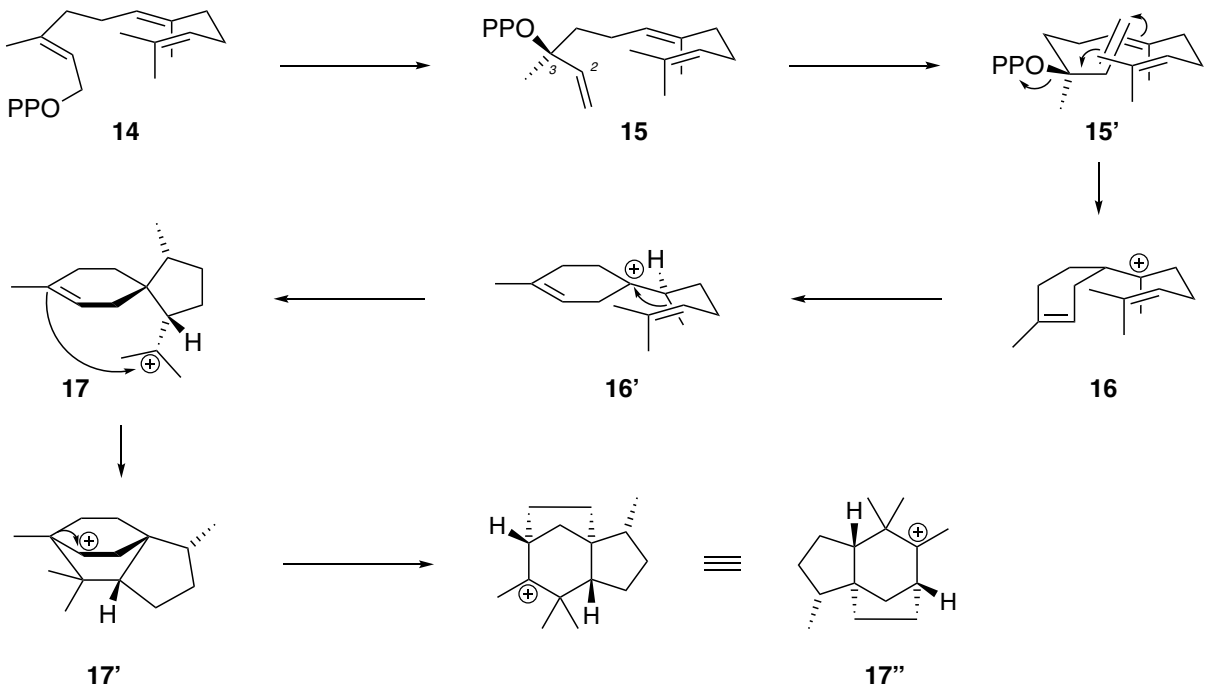
1.2.2. Biosynthetic Pathway of Prezizanes

Nature synthesizes terpenes by coupling of isoprene units in form of isopentyl pyrophosphate (IPP, **12**).[25] The assembly of **12** occurs *via* either the 2-C-methyl-D-erythritol 4-phosphate (MEP) pathway or the mevalonic acid (MVA) pathway, depending on the organism.[25,26,27,28,29] The pathways also deliver dimethylallyl pyrophosphate (DMAPP, **12'**) as an isomerized form of **12**.[25,30] After coupling with an IPP unit geranyl pyrophosphate (GPP, **13**) is formed under activity of geranyl pyrophosphate synthase (GPS). Addition of another IPP unit under farnesyl pyrophosphate synthase (FPS) activity gives farnesyl pyrophosphate (FPP, **14**),[30] from which all sesquiterpenoids are derived (Scheme 1).[31]



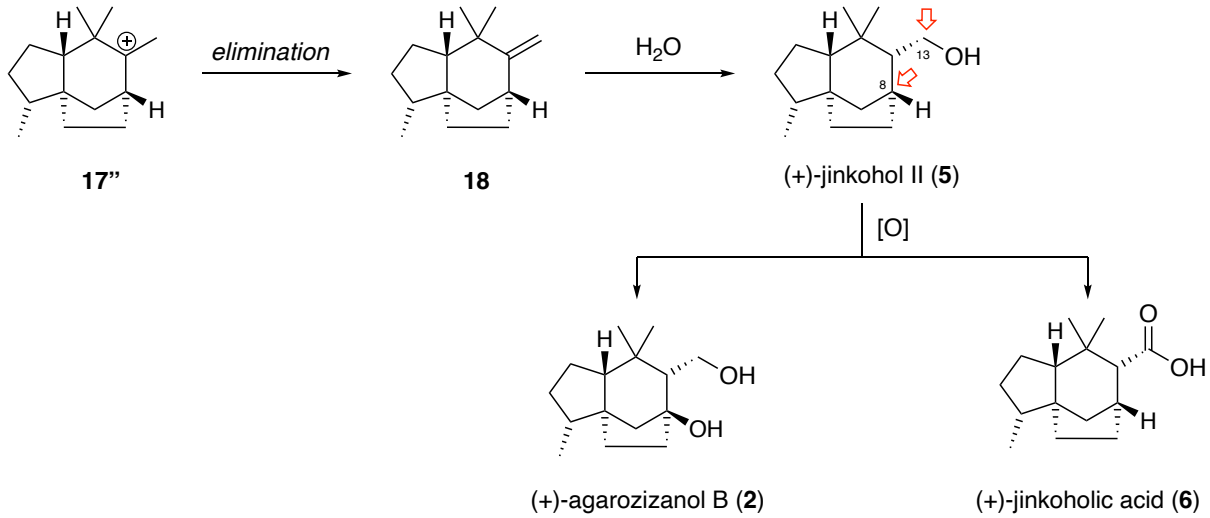
Scheme 1. Biosynthetic pathway of geranyl pyrophosphate (GPP, **13**) and farnesyl pyrophosphate (FPP, **14**).[30]

The group of *Cane* reported the molecular cloning and biochemical characterization of an *S. coelicolor* terpene synthase, which can catalyze the cyclization of farnesyl pyrophosphate (**14**) to a prezizane cation. The description of the postulated subsequent mechanistic steps refers to their work[32] and are fitted to the depicted enantiomer. For a better demonstration of these steps, farnesyl pyrophosphate (**14**) is drawn in a chair like conformation (Scheme 2). FPP (**14**) undergoes isomerization and ionization to yield nerolidyl diphosphate (NPP, **15**), which can form its corresponding *cisoid* conformer **15'** by rotation about the C-2/C-3 bond. Ionization and cyclization give bisabolyl cation **16** and a subsequent 1,2-hydride shift gives **16'**. A spirocyclization of **16'** gives acorenyl cation **17**, which upon further cyclization yields tricyclic cation **17'**, which ring-contracts towards prezizane cation **17"**.



Scheme 2. Mechanism of the cyclization of farnesyl pyrophosphate (**14**) to prezizane cation (**17"**).

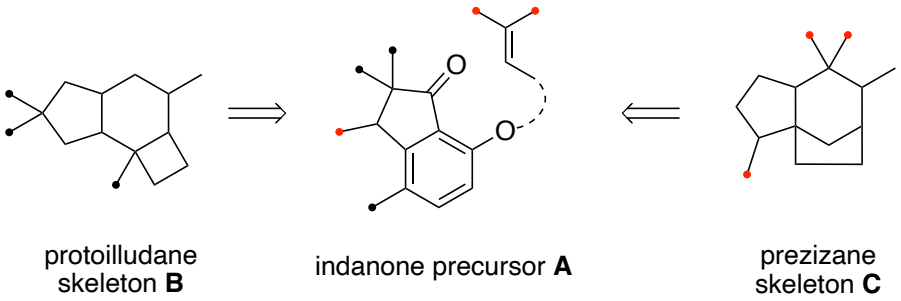
Dai et al. postulated, based on the precedent work of *Cane et al.*,[32] a possible biogenetic pathway for agarozizanol B (**2**), jinkohol II (**5**) and jinkoholic acid (**6**).[15] They referred to the formation of prezizane cation **17"** and continued their postulated mechanism from this point. Elimination of a proton at carbon atom C-13 gives prezizaene (**18**). Addition of water at the newly formed double bond yields jinkohol II (**5**). Oxygenation can take place at either C-13 again to give jinkoholic acid (**6**) or at tertiary carbon atom C-8 to give agarozizanol B (**2**) (Scheme 3).



Scheme 3. Postulated biogenetic pathway to form prezizane-type sesquiterpenes (+)-jinkohol II (**5**), (+)-agarozizanol B (**2**) and (+)-jinkoholic acid (**6**).

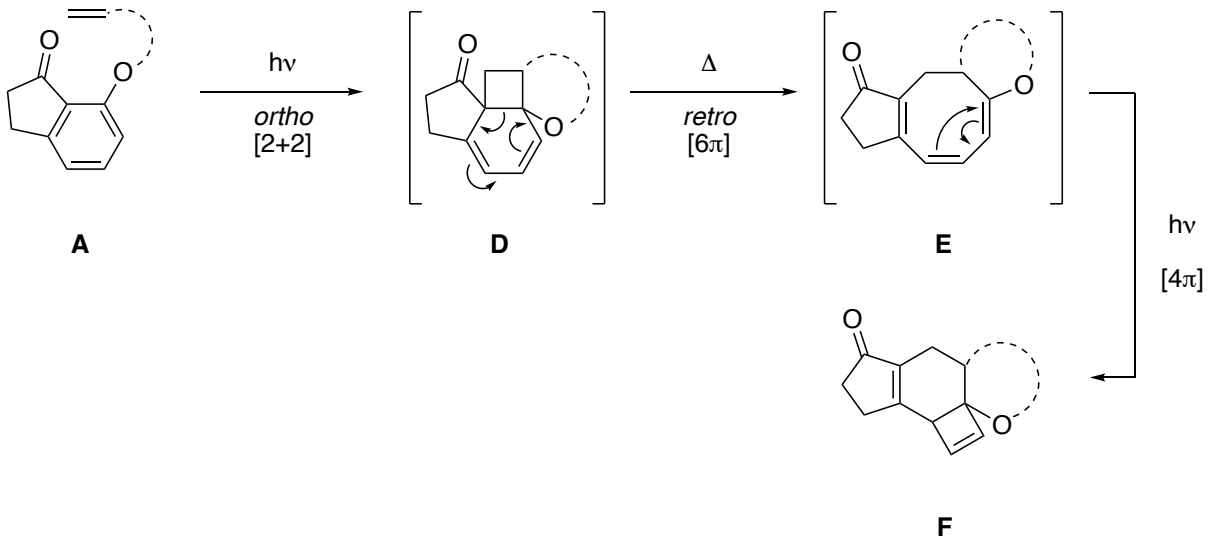
2. The *ortho* Photocycloaddition in the Synthesis of Protoilludane- and Prezizane-Type Sesquiterpene Skeletons

After intensive exploration of the *ortho* photocycloaddition[33] and subsequent photocascade reactions in our group,[34,35] the subsequent phase involved utilizing the complex carbon structure generated in this photochemical reaction cascade to create natural products. Two types of sesquiterpene skeletons were chosen as targets because of their structural similarity to the photocascade adducts: the protoilludanes **B** and the prezizanes **C** (Scheme 4).



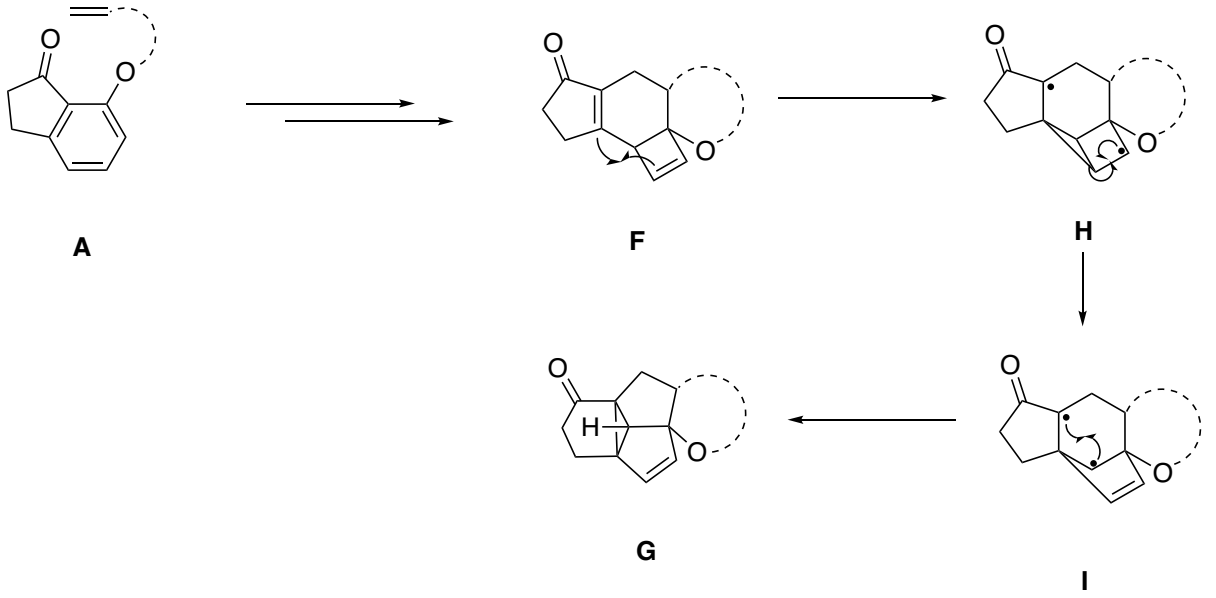
Scheme 4. Accessing the protoilludane skeleton **B** and the prezizane skeleton **C** by transforming simple precursors **A** in photocascade reactions.

What makes this synthetic route so special is that the cascade starts from the same type of simple precursor **A** for the photoreaction, an indanone core linked to a tether bearing an olefin *via* an ether moiety. Substrates **A** were prepared and were found to undergo a photochemical reaction cascade initiated by an *ortho* photocycloaddition. The tetracyclic skeleton **F** (Scheme 5) was obtained after an irradiation time of 20 h ($\lambda \geq 350$ nm),[36] while pentacyclic products **G** (Scheme 6) were obtained upon irradiation times of 16-25 h ($\lambda = 350$ nm).[35] In order to avoid the consecutive reaction from skeleton **F** to **G**, an $Fe_2(SO_4)_3$ solution in aqueous HCl was employed as a filter. The desired wavelength region from fluorescent lamps emitting at a maximum of $\lambda = 350$ nm was filtered successfully and gave the desired effect.[36] As previously mentioned, the sequence of reaction steps starts with an intramolecular *ortho* photocycloaddition, involving the double bond α to the carbonyl and the tethered olefin in precursors **A**, yielding cyclobutanes **D**. A consecutive thermal disrotatory ring opening gives cyclo-octatrienones **E** and a subsequent intramolecular [2+2] photocyclization the desired compounds **F** (Scheme 5) from where you get access to protoilludanes **B**.[34,35,37]



Scheme 5. Three-step photochemical reaction cascade to obtain tetracyclic skeleton **F** from indanone precursor **A**.

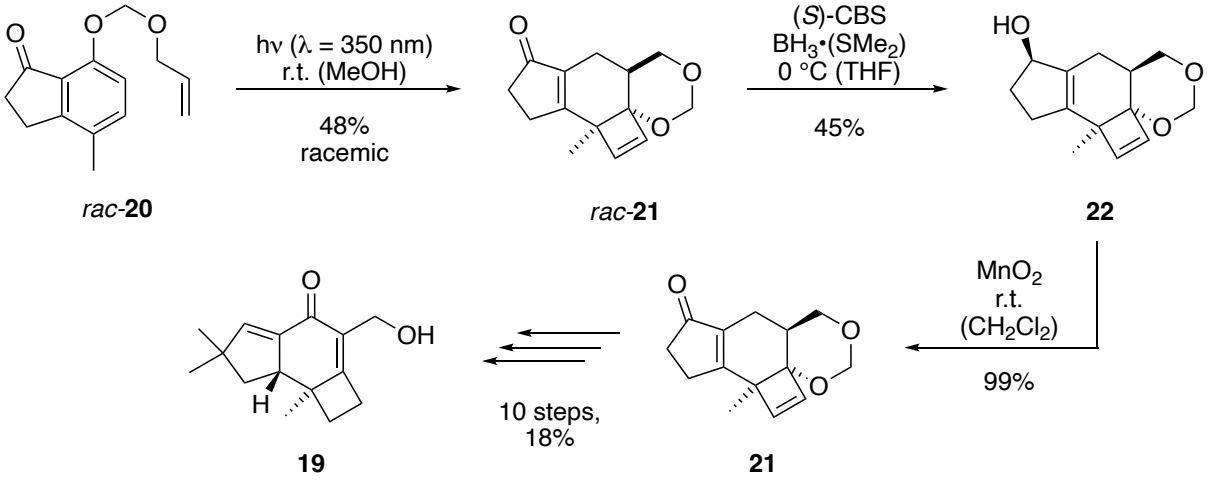
Irradition of **A** over 16+ hours was found to initiate a di-π-methane rearrangement in compound **F** to give skeleton **G**.[35] The rearrangement formally amounts to a 1,2 shift of one of the two *ene* moieties in the 1,4-diene followed by bond formation between the lateral carbon atoms of the non-migrating moiety. A diradical **H** is formed from the 1,4-diene **F** upon further irradiation. Fission of a single bond gives the cyclopentene moiety and diradical **I** is formed.[38,39] A new C-C single bond and a vinylcyclopropane moiety are constructed to finally give skeleton **G** (Scheme 6).



Scheme 6. Mechanism for the di-π-methane-rearrangment in the photochemical reaction cascade to obtain pentacyclic skeleton **G**.

In 2019 and 2020 our group utilized the cascade yielding skeletons **F** for the total synthesis of atlanticone C (**19**) in its racemic[36] and its enantiopure (+)-form.[40] A simple indanone

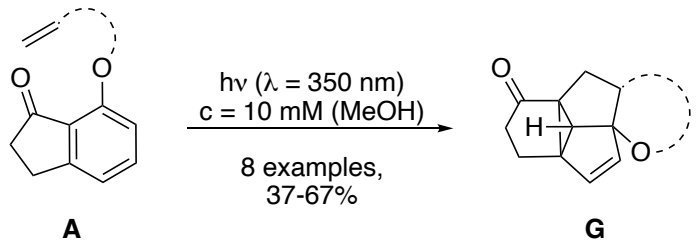
precursor *rac*-**20** was irradiated and transformed by the in Scheme 5 described photocascade reaction, yielding tetracyclic compound *rac*-**21**. An enantiomerically enriched compound **22** was obtained by implementation of a *Corey-Bakshi-Shibata* reduction, and then reoxidized to **21**. The final product was obtained over ten further steps in 18% yield (Scheme 7).[40]



Scheme 7. Basic steps towards the total synthesis of (+)-atlanticone C (**19**).

In another study, the developed cascade including the di-π-methane-rearrangement was further explored and eight racemic, differently substituted products **G** were synthesized from indanones **A** (Scheme 8a). Additionally, it was found that these compounds can be transformed into a compound bearing the tricyclic octahydro-1*H*-3a,6-methanoazulene core exemplified by bromination of **23** to **24** (Scheme 8b). This sets the stage for generating a prezizane skeleton upon modifaction of the starting material.[35]

a)



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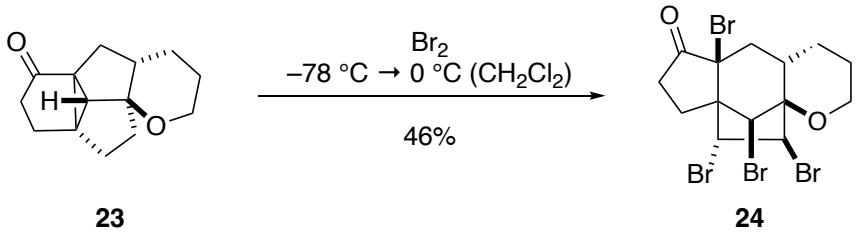


Scheme 8. a) General three-photon photochemical reaction cascade scope. b) Bromination to obtain the tricyclic octahydro-1*H*-3a,6-methanoazulene core present in prezizane skeleton **C**.

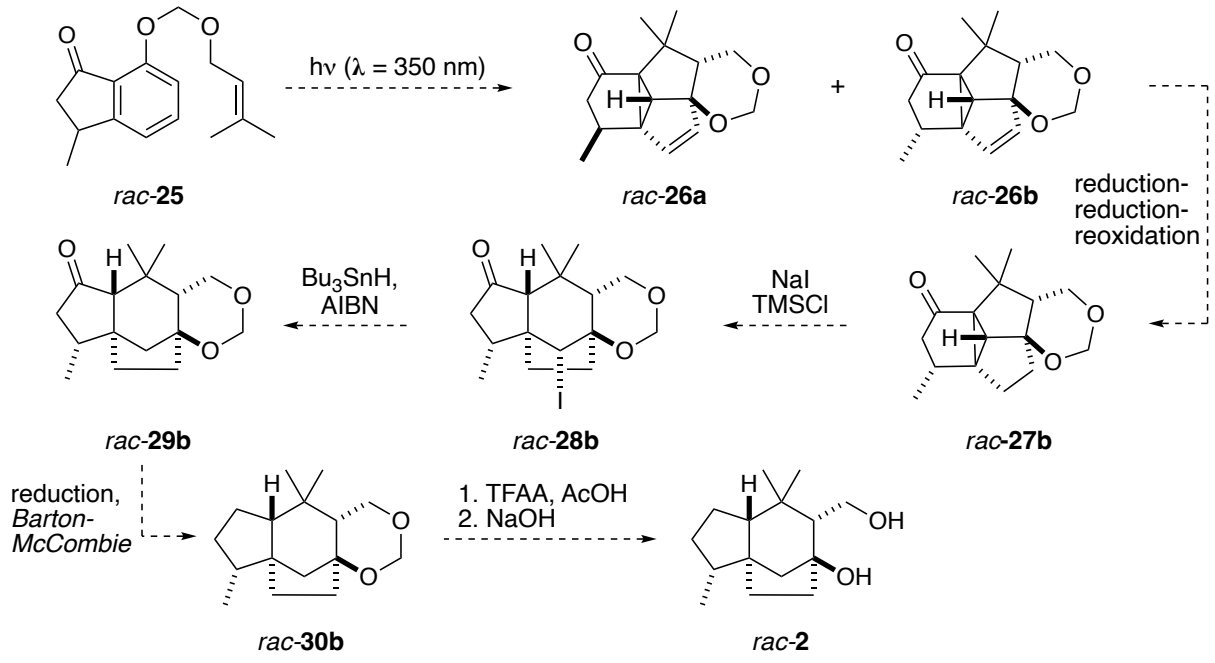
3. Aim of the PhD

Within the scope of this PhD thesis, two projects were defined: a) Utilizing a photochemical reaction cascade for the total synthesis of prezizane-type sesquiterpenoid (+)-agarozizanol B. b) Further application of the photocascade reaction for the total synthesis of prezizane-type sesquiterpenoids (+)-jinkohol II and (+)-jinkoholic acid. Clarification of the absolute configuration in comparison to *epi*-(+)-jinkohol II: (+)-prezizaan-15-ol, whose structure initially was postulated as jinkohol II.

3.1. Towards the total synthesis of (+)-agarozizanol B

As previously mentioned, a photochemical cascade reaction was established to gain access to the tricyclic octahydro-1*H*-3a,6-methanoazulene core of the prezizane skeleton. The aim of this work was to utilize this method to get access to synthetic agarozizanol B, both racemic and enantiopure and to determine the absolute configuration of the natural product.

For this purpose, we envisioned to desgin a specifically modified indanone substrate *rac*-**25**, bearing already all 15 carbon atoms of the final product, including the C-12 carbon atom and the *gem*-dimethyl group. Compound *rac*-**25** should undergo the photoreaction cascade furnishing pentacyclic photocascade adducts *rac*-**26**. Diastereoisomer *rac*-**26b** with correct relative configuration at the C-2 carbon atom was envisioned to be used for further transformations (Scheme 9).

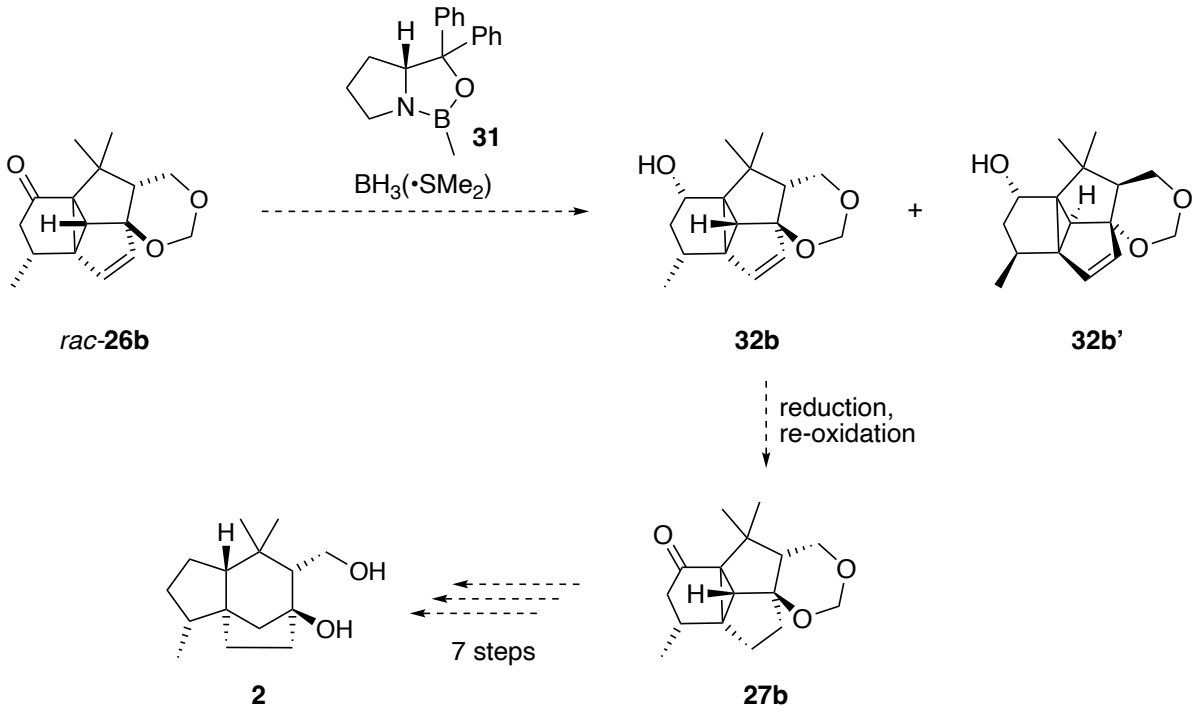


Scheme 9. Envisioned approach for the racemic total synthesis of agarozizanol B (*rac*-**2**).

At first, the double bond of **26b** should be reduced while leaving the cyclopropane ring untouched, yielding compound *rac*-**27b**. This was envisioned to be done either *via* a double-

reduction-reoxidation sequence or directly *via* a one-step transformation. The octahydro-1*H*-3a,6-methanoazulene core was envisioned to be established with a selective ring opening, using sodium iodide and trimethylsilyl chloride,[41] giving compound *rac*-**28b**. The next step was the removal of the introduced iodine under radical conditions to obtain *rac*-**29b**.[42] Reduction and the utilization of a *Barton-McCombie*-type reaction was thought to remove the carbonyl moiety to yield compound *rac*-**30b**.[43] Finally, the desired racemic natural product agarozizanol B (*rac*-**2**) should be obtained by opening of the 1,3-dioxane moiety upon treatment of triflouroacetic anhydride and acetic acid, followed by saponification.[44]

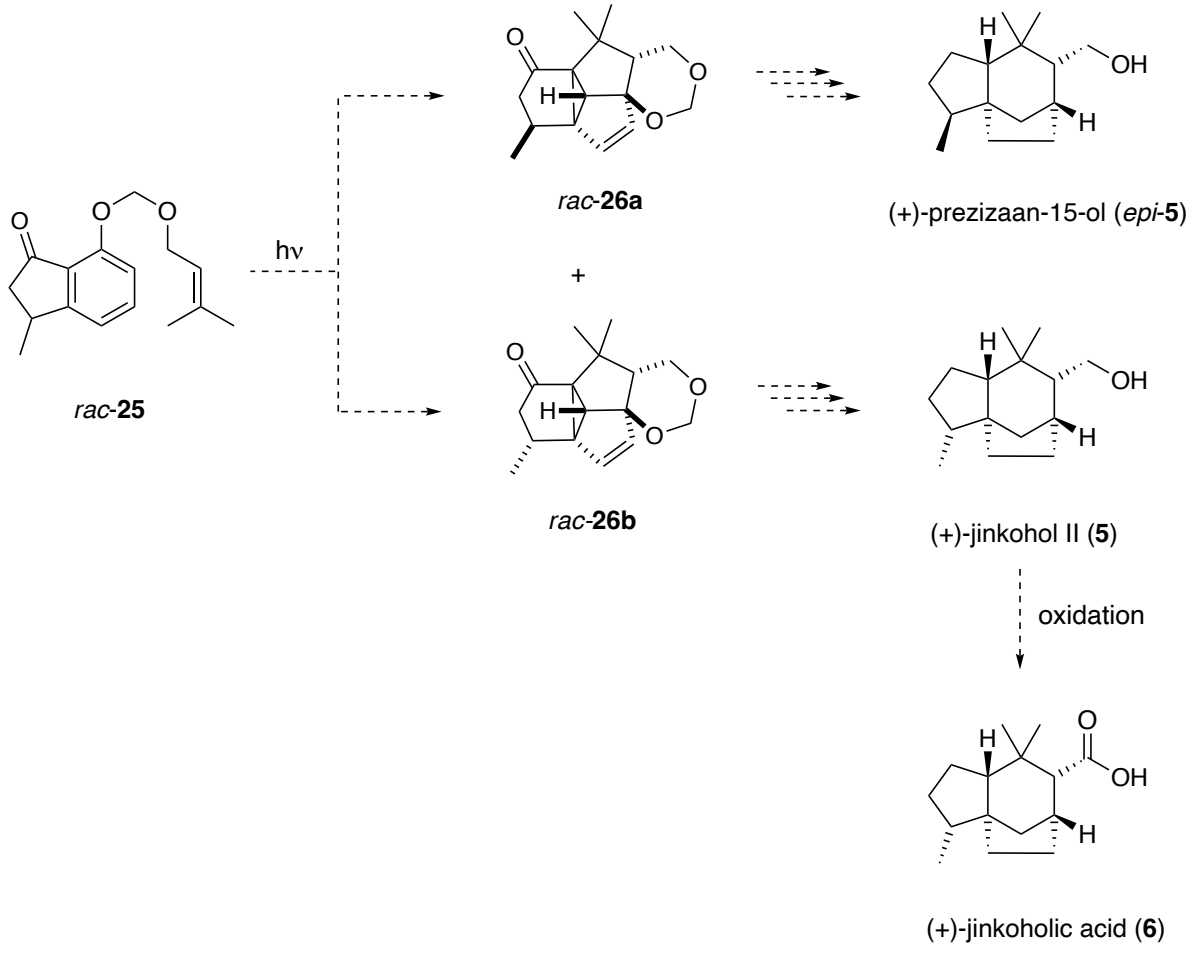
To gain access to enantiomerically enriched material, it was envisioned to employ the sterically approachable carbonyl group as a handle for chiral resolution. Utilizing catalyst **31**, an enantioselective *Corey-Bakshi-Shibata* (CBS) reduction[45] would generate separable diastereoisomers **32b** and **32b'**. A subsequent reduction step and oxidation of the hydroxy group in compound **32b** would yield enantioenriched photoproduct **27b**. The same reaction sequence used for the racemic route would give access to (+)-agarozizanol B (**2**) (Scheme 10).



Scheme 10. Envisioned synthetic strategy to obtain enantiopure (+)-agarozizanol B (**2**).

3.2. Towards the total synthesis of (+)-prezizaan-15-ol, (+)-jinkohol II and (+)-jinkoholic acid

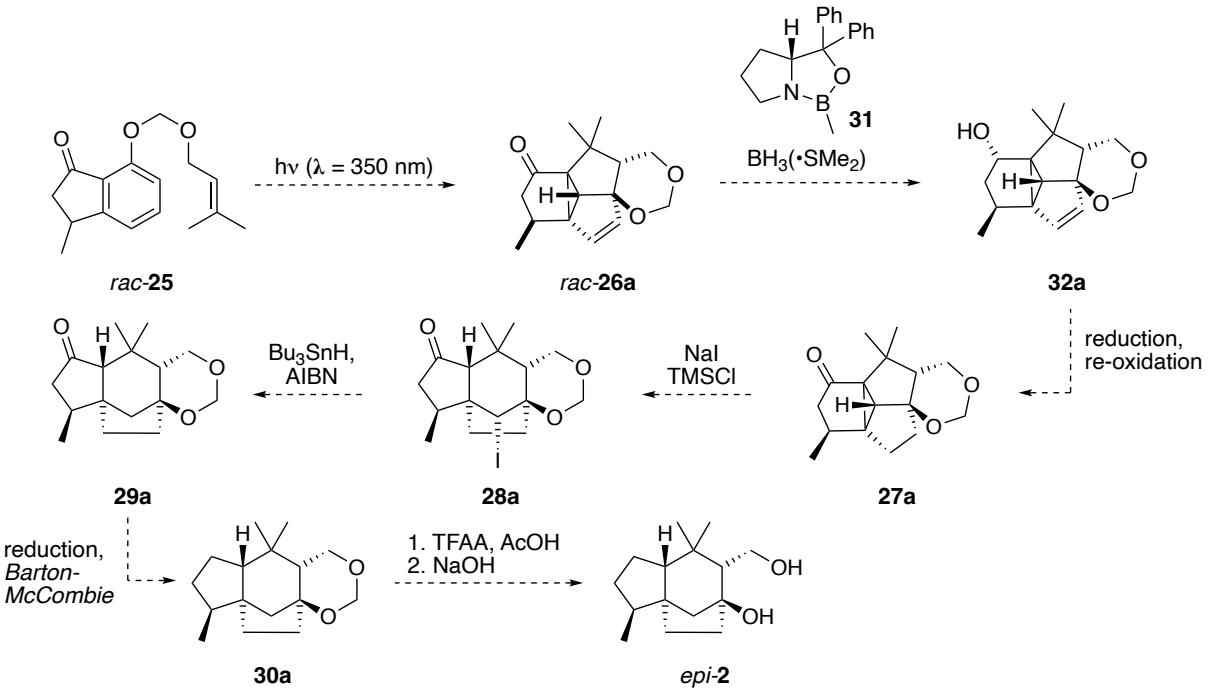
After a successful total synthesis of agarozizanol B (**2**), the developed synthetic strategy was envisioned to be applied for obtaining additional prezizane-type sesquiterpenoids. The natural products were envisioned to be synthesized from racemic photocascade products *rac*-**26**, which should be obtained *via* a photocascade reaction sequence.[35] Racemic photoprecursor *rac*-**25** therefore was envisioned to be transformed in a photocascade reaction to a mixture of racemic diastereoisomers. While minor diastereomer *rac*-**26a** could be utilized to synthesize (+)-prezizaan-15-ol (*epi*-**5**) whose structure was previously assigned to jinkohol II,[46] major diastereomer *rac*-**26b** could be utilized to synthesize (+)-jinkohol II (**5**) and after oxidation to obtain (+)-jinkoholic acid (**6**) (Scheme 11).



Scheme 11. Envisioned general synthetic sequence for the preparation of the prezizane-type natural products, starting from photocascade precursor *rac*-**25**.

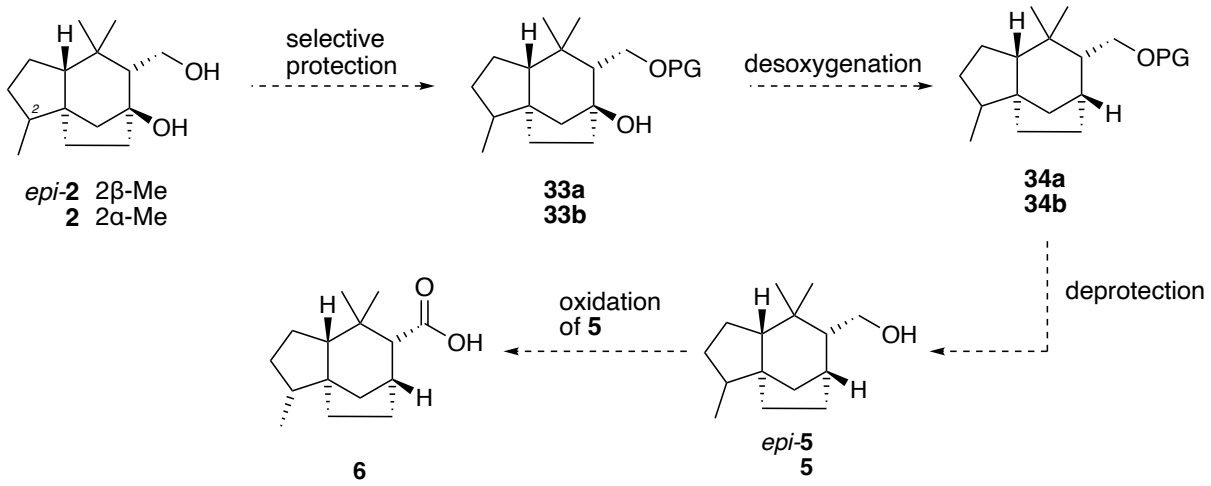
A sequence similar to the (+)-agarozizanol B approach was envisioned to obtain enantiopure compounds with prezizane skeletons. In this regard, the major diastereoisomer *rac*-**26b** was anticipated to be transformed into enantiomerically pure (+)-agarozizanol B (**2**) (as discussed

in Chapter 3.1), while the minor diastereoisomer *rac*-**26a** would yield its epimer *epi*-agarozizanol B (*epi*-**2**) (Scheme 12). The application of the *Corey-Bakshi-Shibata* method[45] was considered for this pathway as well, aiming to yield **32a**. Subsequently, the double bond in the photocascade adduct *rac*-**26a** would be hydrogenated and the hydroxy group oxidized to obtain compound **27a**. Selective ring opening under analogous conditions applied to the major isomer (e.g. NaI/TMSCl) would afford compound **28a**.[41] The removal of the introduced iodide under radical conditions,[42] followed by a reduction and a defunctionalization *via* the *Barton-McCombie* approach,[43] was envisioned to afford **30a** *via* **29a**. Ultimately, the targeted intermediate, *epi*-agarozizanol B (*epi*-**2**), was anticipated to be obtained through a opening of the 1,3-dioxane moiety.[44]



Scheme 12. Envisioned strategy to obtain enantiopure *epi*-agarozizanol B (*epi*-**2**), precursor towards the total synthesis of (+)-prezizaan-15-ol (*epi*-**5**).

After successful synthesis of *epi*-agarozizanol B (*epi*-**2**) and agarozizanol B (**2**), the compunds were envisioned to be transformed to prezizaan-15-ol (*epi*-**5**) and jinkohol II (**5**), respectively (Scheme 13). Hence, a three-step procedure was conceived. Initially, the primary hydroxy group should be protected to obtain compounds **33**. Subsequently, a desoxygenation process, such as employing e.g. a *Barton-McCombie* sequence,[43] should afford compounds **34**. Finally, the removal of the introduced protecting group would yield compounds **5** and *epi*-**5**. Oxidation of jinkohol II (**5**) should yield jinkoholic acid (**6**).



Scheme 13. Envisioned reaction sequence to obtain (+)-prezizaan-15-ol (*epi*-**5**), (+)-jinkohol II (**5**), and (+)-jinkoholic acid (**6**) from compounds **2**.

4. Concise Total Synthesis of Agarozizanol B via a Strained Photocascade Intermediate

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Authors: Niklas Rauscher, Line Naesborg, Christian Jandl, Thorsten Bach

Content: The prezizane-type sesquiterpene agarozizanol B was synthesized employing a photochemical cascade reaction as the key step. Starting from a readily available 1-indanone with a tethered olefin, a strained tetracyclic skeleton was assembled which contained all carbon atoms of the sesquiterpene with the correct relative configuration. The conversion into the tricyclic prezizane skeleton was accomplished by a strategic cyclopropane bond cleavage. Prior to the cyclopropane ring opening an adaption of the oxidation state was required, which could be combined with a reductive resolution step. After removal of two functional groups, the natural product was obtained both in racemic form or, if resolved, as the (+)-enantiomer which was shown to be identical to the natural product.

Author contributions: The conceptual contribution was made by T. Bach and L. Naesborg. Initial test reactions were executed by L. Naesborg. N. Rauscher planned, performed, and analyzed the synthetic steps in this total synthesis. For determination of the absolute configuration, N. Rauscher planned and performed the necessary reactions including the preparation of crystalline material. C. Jandl conducted the X-ray crystallographic analysis. N. Rauscher and T. Bach wrote the manuscript.

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Concise Total Synthesis of Agarozizanol B via a Strained Photocascade Intermediate

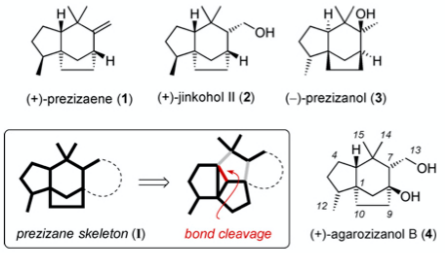
*Niklas Rauscher, Line Næsborg, Christian Jandl, and Thorsten Bach**

Abstract: *The prezizane-type sesquiterpene agarozizanol B was synthesized employing a photochemical cascade reaction as the key step. Starting from a readily available 1-indanone with a tethered olefin, a strained tetracyclic skeleton was assembled which contained all carbon atoms of the sesquiterpene with the correct relative configuration. The conversion into the tricyclic prezizane skeleton was accomplished by a strategic cyclopropane bond cleavage. Prior to the cyclopropane ring opening an adaption of the oxidation state was required, which could be combined with a reductive resolution step. After removal of two functional groups, the natural product was obtained both in racemic form or, if resolved, as the (+)-enantiomer which was shown to be identical to the natural product.*

The plethora of products originating from farnesyl pyrophosphate impressively demonstrates the enormous structural diversity, that nature achieves from simple precursors.[1] In multiple reaction sequences, molecular skeletons are created with a highly diversified set of C–C bonds and carbocyclic rings. In fact, sesquiterpenes represent the structurally most complex class of all terpenoids and have provided organic chemists with an abundant playground to probe new synthetic methods and strategies.[2] In the present study, the focus is on the synthesis of sesquiterpenes with a prezizane skeleton. Members of this family such as (+)-prezizaene (Scheme 1, **1**), and (+)-jinkohol II (**2**) were isolated from vetiver roots (vetiver oil) and from agarwood.[3] The enantiomeric (−)-form of **1** and (−)-prezizanol (**3**) were found in the oil of *Eremophila georgei*, a flowering plant of the figwort family.[4,5] More recently, di- and trioxygenated sesquiterpenes with a prezizane skeleton (agarozizanols,[6] aquilarenes[7]) were isolated from agarwood and arose some interest due to their activity as α-glucosidase inhibitors.

The key element of the prezizane skeleton is the tricyclo[6.2.1.$0^{1,5}$]undecane core which carries the remaining four carbon atoms of the sesquiterpene unit at carbon atoms C2, C6 (twice), and C7. Apart from the construction of the existing stereogenic centers, the formation of the bonds at the quaternary carbon atom C1 and the introduction of the bridging carbon atoms C9 and C10 pose structural challenges which need to be met by total synthetic efforts. Followed by the first total synthesis of (−)-prezizaene and (−)-prezizanol by Vettel and Coates,[8] syntheses of compounds **1**–**3** were achieved by the groups of Piers,[9] Mori,[10] and Rao.[11] All syntheses had to pay tribute to the complexity of the molecules by a relative large number of steps (>15) in the longest linear sequence. Banwell and co-workers reported an elegant approach to (−)-prezizaene based on a cationic rearrangement of khusiol.[12] However, khusiol was prepared in a 17-step sequence starting from a chiral 1,2-dihydrocatechol.[13] The more highly oxygenated prezizane skeletons of the agarozizanols and aquilarenes have not yet been approached by total synthesis.

We envisaged a facile and concise access to compounds with a prezizane skeleton **I** (Scheme 1) from a strained tetracyclic precursor which we hoped to access by a recently discovered photochemical cascade reaction.[14,15] Cleavage of the indicated bond[16] would allow for immediate formation of the skeleton with all 15 carbon atoms already present in the key intermediate. We now report the successful implementation of this strategy which allowed us to access agarozizanol B (**4**)[6] both in racemic and in enantiopure form. The absolute configuration of its naturally occurring (+)-enantiomer (+)-**4** could be established.



Scheme 1. Structure of the naturally occurring prezizane-type sesquiterpenes (+)-prezizaene (**1**), (+)-jinkohol II (**2**), (−)-prezizanol (**3**), (+)-agarozizanol B (**4**), and retrosynthetic access to the tricyclic prezizane skeleton **I** by bond cleavage from a strained tetracyclic precursor. The bond set for the precursor (new bonds in gray) requires to bring in carbon atoms C6, C7, and C13-C15 by a tethered trisubstituted olefin (tether indicated as dashed line).

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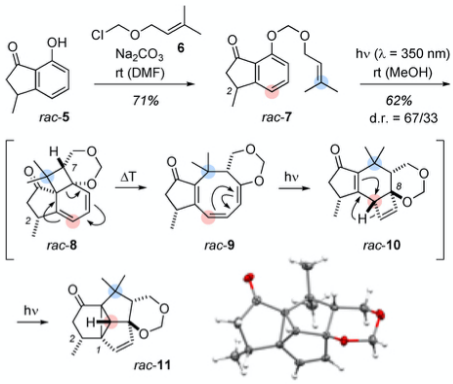
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202110009.

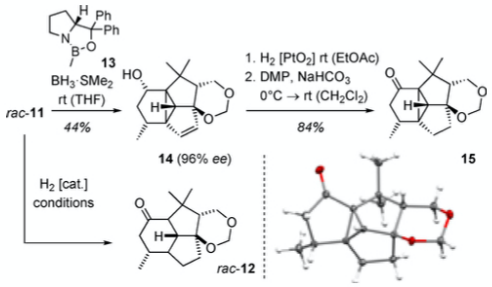
As indicated in Scheme 1, the reaction cascade required to tether the reactive component that brings in carbon atoms C6, C7, and C13-C15 to an existing photoactive building block which carries the remaining ten carbon atoms of the sesquiterpene skeleton. Following our retrosynthetic considerations, the latter building block is represented by an indanone with a methyl substituent at the carbon atom which would be C2 in the natural product. Gratifyingly, an access to this starting material in racemic form (*rac*-**5**, Scheme 2) has been reported and relies on a tandem Friedel–Crafts acylation/alkylation of phenol with γ-butyrolactone.[17] Compound *rac*-**5** required attachment of an olefin component representing the above mentioned carbon atoms. Initial attempts to employ a carbonate (-OCOO-) or a dioxysilyl (-OSiR$_2$O-; R = Me, Ph, ^{t}Pr) linker remained unsuccessful due to the insufficient reactivity of the compounds in the ensuing photochemical reaction. Instead, alkylation of phenol *rac*-**5** with the chloromethylether **6** (CAUTION!)[18] delivered in reasonable yield the precursor *rac*-**7** for the photochemical cascade reaction. It should be noted that the combination of the dioxymethyl (-OCH$_2$O-) linker with a trisubstituted alkene and a chiral indanone is without precedence. We were consequently pleased to note that irradiation at $\lambda = 350$ nm for 24 h led to the desired product *rac*-**11** with exquisite control of the constitution and relative configuration.

The course of the reaction can be understood by an initial *ortho* photocycloaddition[19–21] which sets up the relative configuration between carbon atoms C2 and C7 (prezizane numbering). The approach of the olefin[22] to the top face of the benzene ring is preferred which accounts for the observed facial diastereoselectivity (d.r. = diastereomeric ratio). Although intermediate *rac*-**8** could not be isolated, it appears likely that the cyclobutane ring and the 1,3-dioxane ring are *cis*- but not *trans*-connected. Disrotatory ring opening produces cyclooctatriene *rac*-**9** which undergoes the second photochemical step, a disrotatory [4π] cyclization. The cascade can be interrupted at the stage of cyclobutene *rac*-**10** and compounds of this type have been shown to be useful for total synthesis.[23] However, continued irradiation induces a di-π-methane rearrangement[24] which generates the final product with the correct relative configuration at carbon atoms C1 and C8. The formation of the quaternary carbon atom C1 with correct relative configuration to C2 in a single step is particularly notable. As a result of the photochemical reaction cascade, the desired diastereoisomer *rac*-**11** was isolated in a remarkable yield of 42%. Its constitution and relative configuration was proven by single crystal X-ray crystallography.[25] The minor diastereoisomer isolated in 20% yield was not further studied but it likely stems from a bottom face attack in the *ortho* photocycloaddition step. Attempted hydrogenation reactions performed with compound *rac*-**11** led under a variety of conditions to concomitant cleavage of the cyclopropane ring and the unwanted product *rac*-**12** was obtained (Scheme 3, see the Supporting Information for details).

The synthesis of the required ketone **15** was accomplished by a sequence of reduction-hydrogenation-oxidation. The reduction could be performed with NaBH$_4$ in MeOH to generate a diastereomeric mixture of racemic alcohols in 96% yield. However, it was found that the reduction step can also be combined with a resolution step employing chiral oxazaborolidine **13** in a Corey–Bakshi–Shibata (CBS) reaction.[26] Under the given conditions the reduction is known to occur from the *Re* face[27] delivering compound **14** with the depicted absolute and relative configuration. Double bond hydrogenation and oxidation with the Dess–Martin periodinane (DMP)[28] delivered ketone **15**. All subsequent steps were performed both with racemic ketone *rac*-**15** and with the enantiopure compound **15** derived from alcohol **14** (96% *ee*). The relative configuration of ketone *rac*-**15** was secured by single crystal X-ray crystallography.[25]



Scheme 2. Synthesis of photosubstrate *rac*-**7** and formation of the desired product *rac*-**11** in a cascade reaction that includes three photochemical steps. Two carbon atoms are marked to facilitate a better understanding of the skeletal rearrangements. The relative configuration of three new stereogenic centers (at C1, C7, C8) present in agarozizanol B is correctly established in this transformation based on the existing stereogenic center at C2. The relative configuration was proven by single crystal X-ray crystallographic analysis of product *rac*-**11**.[25].

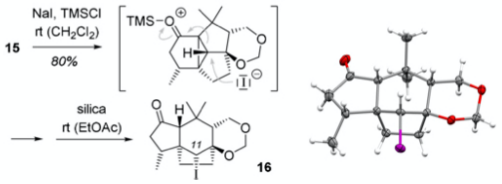


Scheme 3. An undesired cyclopropane ring cleavage occurring upon attempted hydrogenation of compound *rac*-**11** led to product *rac*-**12**. Reduction of the ketone to alcohol **14** allowed for a selective hydrogenation and the desired ketone **15** could be prepared in enantiopure (**15**) or racemic (*rac*-**15**, crystal structure shown[25]) form (for details see the narrative).

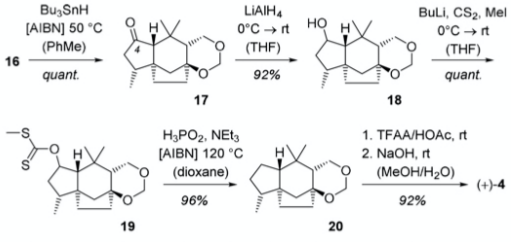
The desired selective opening of the cyclopropane ring as outlined in Scheme 1 was eventually achieved by treatment with sodium iodide and chlorotrimethylsilane (TMSCl).[29] Mechanistically, the opening is suggested to occur by TMS activation of the carbonyl group and substitution by the iodide in an S_N2 fashion (Scheme 4). The intermediate silyl enol ether is hydrolyzed upon work-up and iodide **16** was obtained in 80% yield (7% recovered starting material). At the stage of iodide **16** it was also possible to corroborate the absolute configuration of the carbon skeleton by anomalous X-ray diffraction (see the Supporting Information for details).

The conclusion of the synthesis required removal of the iodide at carbon atom C11 and the oxygen atom at position C4. The steps were performed in successive order and, given the high yields achieved in the individual steps, it was not attempted to combine the deiodination with the deoxygenation event (Scheme 5). The former reaction was performed with tributyltinhydride as the reductant in a radical chain reaction.[30] Reduction of ketone **17** to secondary alcohol **18** set the stage for a Barton-McCombie reaction.[31] Xanthate **19** was preferably reduced with phosphinic acid[32] and delivered in high yield the immediate precursor **20** to agarozizanol B. The deprotection of the latent diol was performed with a mixture of trifluoroacetic anhydride and acetic acid and subsequent saponification.[33]

The relative configuration and constitution of the final product were secured by single-crystal X-ray crystallographic analysis (see the Supporting Information for details). The specific rotation of the final product was determined as $[\alpha]_D^{20} = +15$ ($c = 0.3$, MeOH) and was identical with the specific rotation of naturally occurring agarozizanol B.[6]



Scheme 4. Formation of iodide **16** by regioselective ring opening of cyclopropyl ketone **15**. The indicated S_N2 type pathway was secured by single crystal X-ray crystallographic analysis of product *rac*-**16**.[25]



Scheme 5. Final step of the total synthesis of agarozizanol B (**4**) starting from iodide **16** [AIBN = azobis(isobutyronitril); TFAA = trifluoroacetic anhydride; HOAc = acetic acid].

Since the absolute configuration of the synthetic material is known, the synthesis establishes the absolute configuration of the natural product.

In summary, a concise synthetic route to oxygenated prezizaene sesquiterpenes has been discovered. Starting from commodity chemicals (phenol, γ-butyrolactone, prenol), agarozizanol B has been prepared in eleven steps in racemic (4%) and enantiopure form (2%). The comparably low overall yields are mainly due to the fact that the initial formation of compound *rac*-**5**[16] proceeded in our hands in only 27% yield. The pivotal photochemical reaction cascade holds promise for further applications in the synthesis of natural products. Its compatibility with functional groups needs to be explored and its scope further expanded.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: cycloaddition · diastereoselectivity · domino reactions · photochemistry · terpenoids · total synthesis

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5. Total Synthesis of (+)-Prezizaan-15-ol, (+)-Jinkohol II, and (+)-Jinkoholic acid

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Authors: Niklas Rauscher, Christian Jandl, Thorsten Bach

Content: A recently developed photochemical cascade reaction provides access to diastereomeric pentacyclic products, which display the carbon skeleton of prezizane natural products. The minor diastereoisomer with a 2β-Me configuration was converted in 12 reaction steps into (+)-prezizaan-15-ol. The major diastereoisomer with a 2α-Me configuration gave in an analogous route (+)-jinkohol II, which was oxidized at C13 to (+)-jinkoholic acid. A previous ambiguity regarding the configuration of the natural products could be clarified by total synthesis.

Author contributions: The conceptual contribution was made by T. Bach and N. Rauscher. N. Rauscher planned, performed, and analyzed the synthetic steps in this total synthesis. For determination of the absolute configuration, N. Rauscher planned and performed the necessary reactions including the preparation of crystalline material. C. Jandl conducted the X-ray crystallographic analysis. N. Rauscher and T. Bach wrote the manuscript.

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Total Synthesis of (+)-Prezizaan-15-ol, (+)-Jinkohol II, and (+)-Jinkoholic Acid

Niklas Rauscher, Christian Jandl, and Thorsten Bach*

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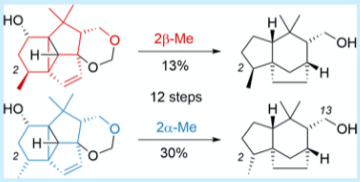
ABSTRACT: A recently developed photochemical cascade reaction provides access to diastereomeric pentacyclic products, which display the carbon skeleton of prezizane natural products. The minor diastereoisomer with a 2β-Me configuration was converted in 12 reaction steps into (+)-prezizaan-15-ol. The major diastereoisomer with a 2α-Me configuration gave in an analogous route (+)-jinkohol II, which was oxidized at C13 to (+)-jinkoholic acid. A previous ambiguity regarding the configuration of the natural products could be clarified by total synthesis.

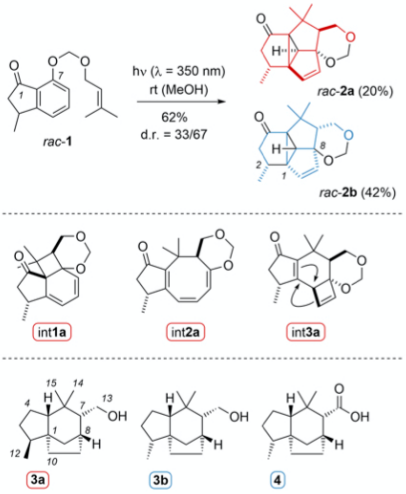


Arene photocycloaddition reactions represent versatile synthetic tools to obtain three-dimensional carbon skeletons from planar precursors.[1] Particularly for benzene and its derivatives, however, the loss of aromaticity comes with an enthalpic penalty which needs to be compensated. Ever since the advent of arene photocycloaddition reactions,[2] it has become evident that the energy of a photon is a suitable currency to pay the prize for the scission of arene bonds. Inspired by the pioneering efforts of Wagner,[3] Gilbert,[4] Hoffmann,[5] and others,[1] our group has studied reaction cascades which are initiated by an *ortho*-photocycloaddition[6,7] to a benzene ring. We found that 7-alkenyloxy-substituted 1-indanones provide a remarkably efficient entry into the protoilludane class of natural products if irradiated at long wavelength (λ > 350 nm).[8] At shorter wavelength (λ = 350 nm), a third photon initiates a di-π-methane rearrangement reaction which eventually delivers a pentacyclic product.[9,10] Compound *rac*-**1** for example gave strained cyclopropanes *rac*-**2a** and *rac*-**2b** in a total yield of 62% (Scheme 1).[11] Putative intermediates of the reaction sequence en route to product *rac*-**2a** derive from initial *ortho*-photocycloaddition (int**1a**), followed by a disrotatory cyclohexadiene ring opening (int**2a**). A photochemically induced, disrotatory [4π] cyclization leads to cyclobutene int**3a**, which finally undergoes the already mentioned di-π-methane rearrangement.

The existing stereogenic center in substrate *rac*-**1** induces a moderate facial diastereoselectivity in favor of product *rac*-**2b**. The diastereoisomers can be separated and were isolated in 20% (*rac*-**2a**) and 42% yield (*rac*-**2b**). The compounds display the complete carbon skeleton of prezizane sesequiterpenes, and compound *rac*-**2b** was employed in the total synthesis of (+)-agarozizanol B.[11]

In 1983, Nakanishi et al. reported on the isolation of a sesquiterpene natural product from agarwood which they called jinkohol II. They assigned the structure **3a** to this compound (Scheme 1), and the specific rotation $[\alpha]_D^{20}$ was

Scheme 1. Synthesis of Complex Pentacyclic Products *rac*-2 from Planar Indanone *rac*-1 in a Three-Photon-Cascade and Structure Correlation to Sesquiterpenes



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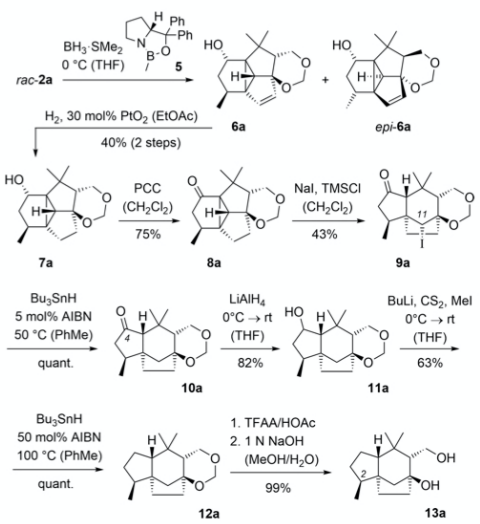
reported as +32.4 (c = 0.26, $CHCl_3$).[12] Later, the relative configuration was allegedly confirmed by a total synthesis of racemic jinkohol II, the spectral data of which were said to be identical with the natural product.[13] In 2020, Weyerstahl et al. pointed out, in a comprehensive publication on sesquiterpenes from Haitian vetiver oil, that the ^{1}H NMR data of compounds **3a** and **3b** are very similar while they differ significantly in their ^{13}C NMR spectra. Based on semisynthetic work, they suggested to assign structure **3b** to jinkohol II and renamed **3a** prezizaan-15-ol.[14] Likewise, the respective jinkoholic acid, which had been previously isolated from *Neocallitropsis pancheri*,[15] was reported to display a specific rotation of $[\alpha]_D^{20}$ = +26 (c = 0.41, $CHCl_3$) and was proposed to be compound **4**. Since our synthesis (*rac*-**1** → *rac*-**2**) had given access to the skeleton of both diastereomeric compound classes, with minor diastereoisomer **2a** corresponding to **3a** and major diastereoisomer **2b** corresponding to **3b** and **4**, we planned to provide further evidence for the assignment by *de novo* synthesis[16] of all three compounds, ideally in enantiomerically pure form.

The major challenge in the approach to all three compounds was the deoxygenation at carbon atom C8. We decided to perform this transformation in the final stages of the synthesis after having adjusted the oxidation state at all other positions. The resolution of product *rac*-**2a** was performed by an enantioselective reduction[17] with borane and (*R*)-configured oxazaborolidine **5**. The protocol had been shown for related compounds to deliver the hydride exclusively from the *Re* face.[11,18] As a consequence, the two epimeric alcohols **6a** and *epi*-**6a** were obtained (Scheme 2). Based on the putative absolute configuration of **3a**, we continued to work with diastereoisomer **6a** which was hydrogenated to deliver alcohol **7a** as an enantiopure compound (>99% *ee*) in 40% yield. Oxidation with pyridinium chlorochromate (PCC)[19] led to ketone **8a** which was the precursor for the pivotal cyclopropane ring opening reaction. Simultaneous activation of the ketone carbonyl group by the silyl Lewis acid and attack of the iodide at the cyclopropane ring[20] enabled the desired bond fission and delivered the desired product **9a**. With the heavy atom iodine present, we attempted to secure the absolute configuration of the compound by anomalous diffraction. Crystallization attempts remained futile, however. Instead, we studied the enantiomeric product *ent*-**9a**, which was obtained by subjecting *epi*-**6a** to the same three-step protocol used for **6a** (see the Supporting Information for details). This compound was crystalline and its absolute configuration could be determined by anomalous X-ray diffraction (Figure 1). Since **9a** represents the enantiomer of *ent*-**9a**, its configuration was confirmed, and the synthesis was continued.

Scheme 2. Synthesis of Enantiopure Diol 13a from Racemic Photocascade Product *rac*-2a



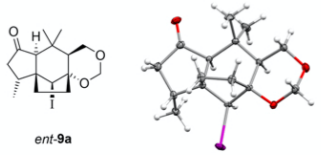


Figure 1. Compound *ent*-**9a** was synthesized from epimer *epi*-**6a**, which in turn was obtained by kinetic resolution of compound *rac*-**2a**. Its absolute configuration was determined by anomalous X-ray diffraction. Ellipsoids in the ORTEP structure are displayed at the 50% probability level.

Removal of the iodine substituent with tributyltinhydride [AIBN = azobis(isobutyronitrile)] set the stage for the deoxgenation at carbon atom C4.[21] Ketone **10a** was first reduced to a mixture of diastereomeric alcohols **11a** which were converted into the respective xanthates. A Barton–McCombie reaction[22] delivered product **12a**, the 1,3-dioxane ring of which was cleaved under acidic conditions (TFAA = trifluoroacetic anhydride; HOAc = acetic acid). Saponification gave diol **13a** which is the C2-epimer of (+)-agarozizanol B (**13b**).[11]

The following steps were performed with both the 2β-Me and the 2α-Me epimer of prezizane diols **13**. The former was expected to produce alcohol **3a**, the latter **3b**. Selective protection of the primary alcohol at C13 was facile with several protecting groups and delivered products with a free tertiary alcohol at carbon atom C8. The ensuing deoxygenation reaction was attempted under a broad variety of conditions reported for related substrates (see the Supporting Information for a compilation of all attempted reactions). Eventually, it was found that only the conversion of the alcohol to a chloride and reductive chlorine removal gave reproducibly the desired compounds. A benzyl (Bn) group at the C13 alcohol was found to be the most suitable protecting group to execute this protocol (Scheme 3). It was introduced by Williamson ether synthesis with benzyl chloride and the resulting benzyloxy-substituted alcohols **14** were converted into the tertiary chlorides by treatment with phosphorus pentachloride at elevated temperature.[23] Reductive hydro-dechlorination was accomplished by treating chlorides **15** with tributyltinhydride and AIBN under reflux.[21] In either case, a single diastereoisomer **16a** (2β-Me) or **16b** (2α-Me) resulted with the desired prezizane skeleton. The reaction sequence was concluded by hydrogenolysis of the benzyl ether delivering the desired products **3a** and **3b**.

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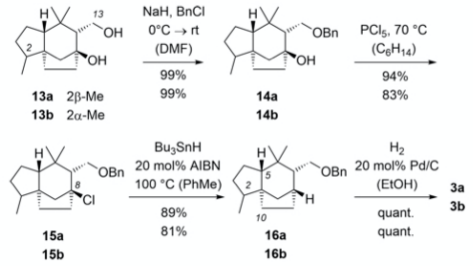
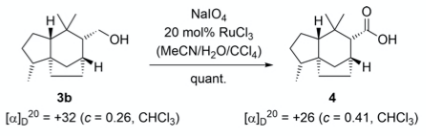
Scheme 3. Deoxygenation of Enantiopure Diols 13 at Position C8 Giving Access to (+)-Prezizaan-15-ol (3a) and (+)-Jinkohol II (3b)



A detailed analysis of the one- and two-dimensional NMR spectra (see the Supporting Information for a more elaborate discussion) revealed clear differences between the two diastereoisomers **3a** and **3b**. The observations of Weyerstahl and co-workers regarding the ^{1}H NMR spectra were confirmed.[14] The spectra are indeed very similar and it is mainly the ^{13}C NMR spectra that display distinct differences. The differences are most significant for carbon atoms close to the epimeric stereogenic center at C2. For example, the signals of carbon atom C5 appear at 55.3 ppm for **3a** and at 59.5 ppm for **3b**. The carbon atoms at C10 resonate at 33.6 ppm for **3a** and at 21.2 ppm for **3b**. The difference for the methyl (C12) group at C2 is 20.1 (**3a**) vs 14.5 ppm (**3b**). Gratifyingly, the data found for the synthetic material matched extremely well with the data reported for the natural products. Most importantly, the relative configuration of (+)-jinkohol II could be revised to be **3b** but not **3a** as originally proposed.[12] The NMR data of the natural product as provided by Nakanishi et al.[12] match perfectly with the synthetic product **3b** but not with the compound with structure **3a**. The latter compound was confirmed to be (+)-prezizaan-15-ol.[14] The specific rotation of **3b** was determined as +32 (c = 0.26, $CHCl_3$) and was identical with the reported value for (+)-jinkohol II. The specific rotation determined for (+)-prezizaan-15-ol (**3a**) was determined as +23 (c = 0.26, $CDCl_3$) and was significantly lower than that for **3b**.

As a final exercise of the prezizane synthesis campaign we aimed to access (+)-jinkoholic acid (**4**) from (+)-jinkohol II (**3b**). After some optimization, the direct Ru-catalyzed oxidation of the alcohol to the carboxylic acid[24] proved to be the most reliable and highest yielding procedure (Scheme 4). The spectral data obtained for the synthetic material matched the reported ^{13}C NMR data[15] with all carbon signals displaying a chemical shift difference $\Delta\delta \leq 0.3$ ppm. The specific rotation was identical with the reported value.

Scheme 4. Synthesis of (+)-Jinkoholic Acid (4) by Oxidation of (+)-Jinkohol II (3b) and their Specific Rotations



In summary, the total synthesis of three prezizane-type natural products has been accomplished. The starting material was in all cases a pentacyclic precursor (*rac*-**2a** or *rac*-**2b**), which was accessible in a single step by a photochemical cascade reaction and which displayed the tricyclo[6.2.1.0^{1,5}]-undecane core of the natural products with the correct relative configuration. The racemic products were resolved employing an enantioselective Corey–Bakshi–Shibata reduction. Starting from diastereoisomer *rac*-**2a**, the sequence enabled the total synthesis of (+)-prezizaan-15-ol (**3a**), while (+)-jinkohol II (**3b**) and (+)-jinkoholic acid (**4**) were synthesized from diastereoisomer *rac*-**2b**. The total syntheses established the correct absolute and relative configuration of the three natural products. While prezizaan-15-ol had been prepared previously, there had been no precedence for a total synthesis of compounds with the correct structure of jinkohol II and jinkoholic acid.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01184.

Materials and methods, optimization of reaction conditions (desoxygenation step at C8), synthetic procedure, NMR spectra in $CDCl_3$ of new compounds **3a**, **3b**, **4**, **6a**, **8a**–**16a**, and **14b**–**16b**, NMR comparison tables for **3a**, **3b**, and **4**, HPLC traces of **2a**, *rac*-**2a**, **2b**, and *rac*-**2b**, stereochemical assignments of compounds **6**, and X-ray crystallographic details (structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments) (PDF)

FAIR data, including the primary NMR FID files, for compound(s) **3a**, **3b**, and **4**. (ZIP)

Accession Codes

CCDC 2250216–2250218 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

The abstract graphic was corrected on June 7, 2023.

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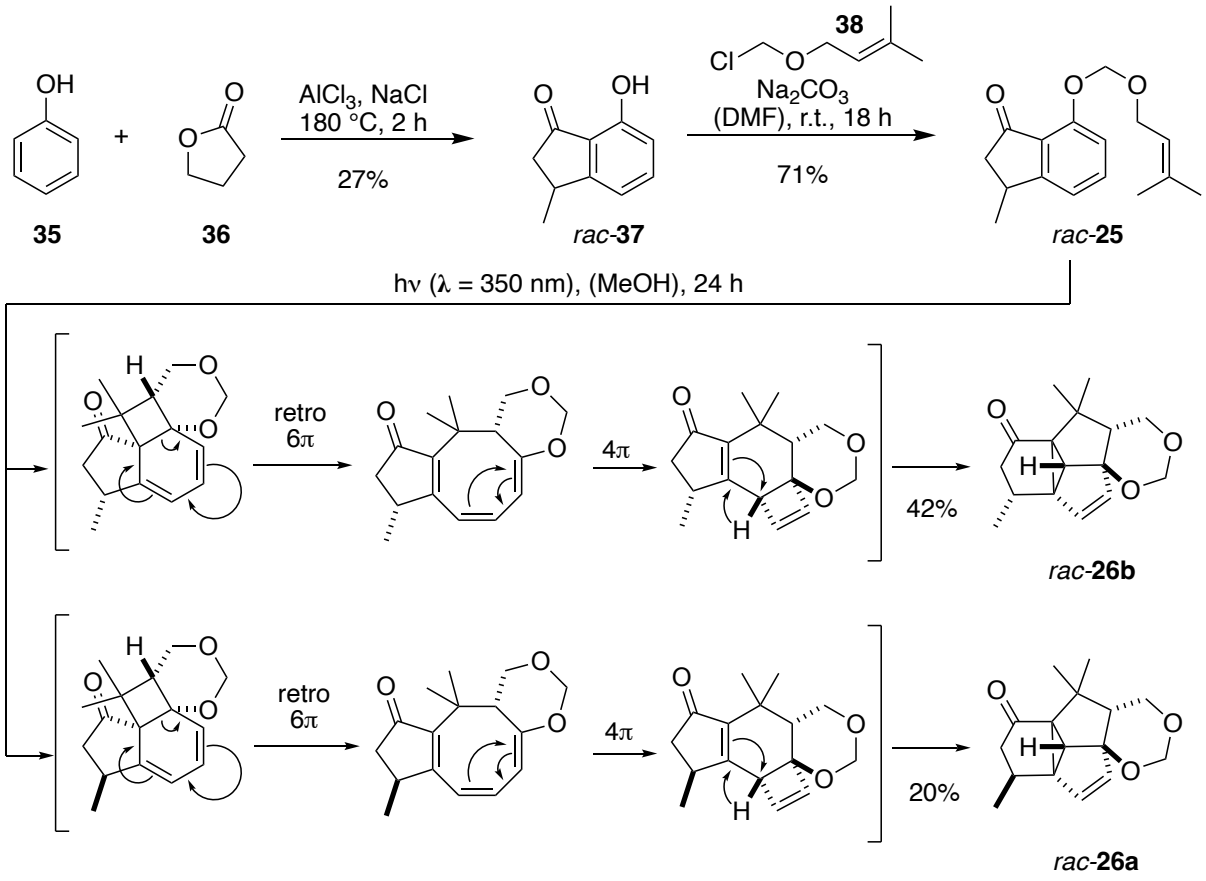
6. Summary

Within this PhD work, two main projects were completed. a) The total synthesis of agarozizanol B was achieved in its racemic, as well as in its enantiopure (+)-form. The synthetic applicability of the employed *ortho* photocycloaddition-induced reaction cascade that includes the di-π-methane rearrangement was proven. The absolute configuration was determined by X-ray crystallography. b) The total syntheses of (+)-prezizaan-15-ol, (+)-jinkohol II and (+)-jinkoholic acid were completed, applying the same photochemical reaction cascade. The absolute configuration of (+)-prezizaan-15-ol was proven by X-ray crystallography.

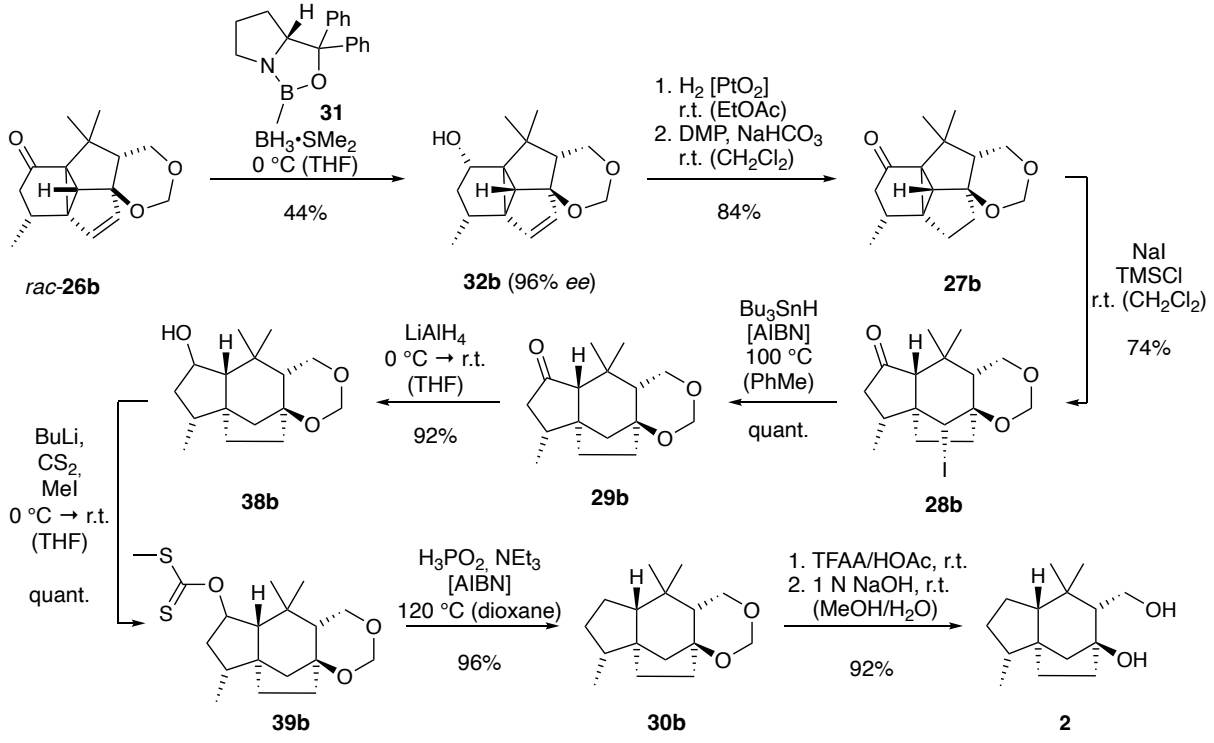
A) Racemic and enantioselective total synthesis of agarozizanol B

The initial reaction of the synthetic route, a tandem *Friedel-Crafts* reaction with starting materials phenol (**35**) and γ-butyrolactone (**36**) gave access to indanone **37**,[47] which was alkylated with chloromethoxyether **38**[48] in a *Williamson* ether synthesis[35,49] to afford compound *rac*-**25**. Subsequently, the photo-induced reaction cascade was carried out successfully at 350 nm, in MeOH with a reaction time of 24 h yielding 42% of major diastereoisomer *rac*-**26b** and 20% of minor diastereoisomer *rac*-**26a**, with a *d.r.* of 67/33 (Scheme 14).



Scheme 14. Synthetic sequence towards photocascade adducts *rac*-**26**.

The *d.r.* (diastereomeric ratio) is determined by the initial *ortho* photocycloaddition step, in which the internal olefin approaches the less hindered face of the indanone core. Additionally, it was possible to confirm the relative configuration of major diastereoisomer *rac*-**26b** by X-ray crystallography. This diastereoisomer was utilized to carry out further reactions. A *Corey-Bakshi-Shibata* reduction afforded enantiomerically enriched compound **32b** in a 44% yield (Scheme 15).[45] For the racemic route sodium borohydride was used, yielding 96% of a racemic mixture of diastereomeric alcohols.[50] Consecutive reactions were carried out with racemic material as well as enantiomerically enriched material. Reduction of the double bond and re-oxidation with *Dess-Martin* periodinane gave compound **27b** with 84% yield over two steps.[51] Ring opening with sodium iodide and trimethylsilyl chloride as *Lewis* acid gave compound **28b** in 74% yield.[41] Removal of iodide under radical conditions[42] gave **29b** and a carbonyl reduction[52] with $LiAlH_4$ followed by a *Barton-McCombie* sequence[43] (*via* **38b** and **39b**) utilitzing phosphinic acid[53] gave compound **30b** with 88% yield over additional four steps. Dioxane ring opening with trifluoro acetic anhyhdride/acetic acid and further saponification[44] yielded desired natural product (+)-agarozizanol B (**2**).



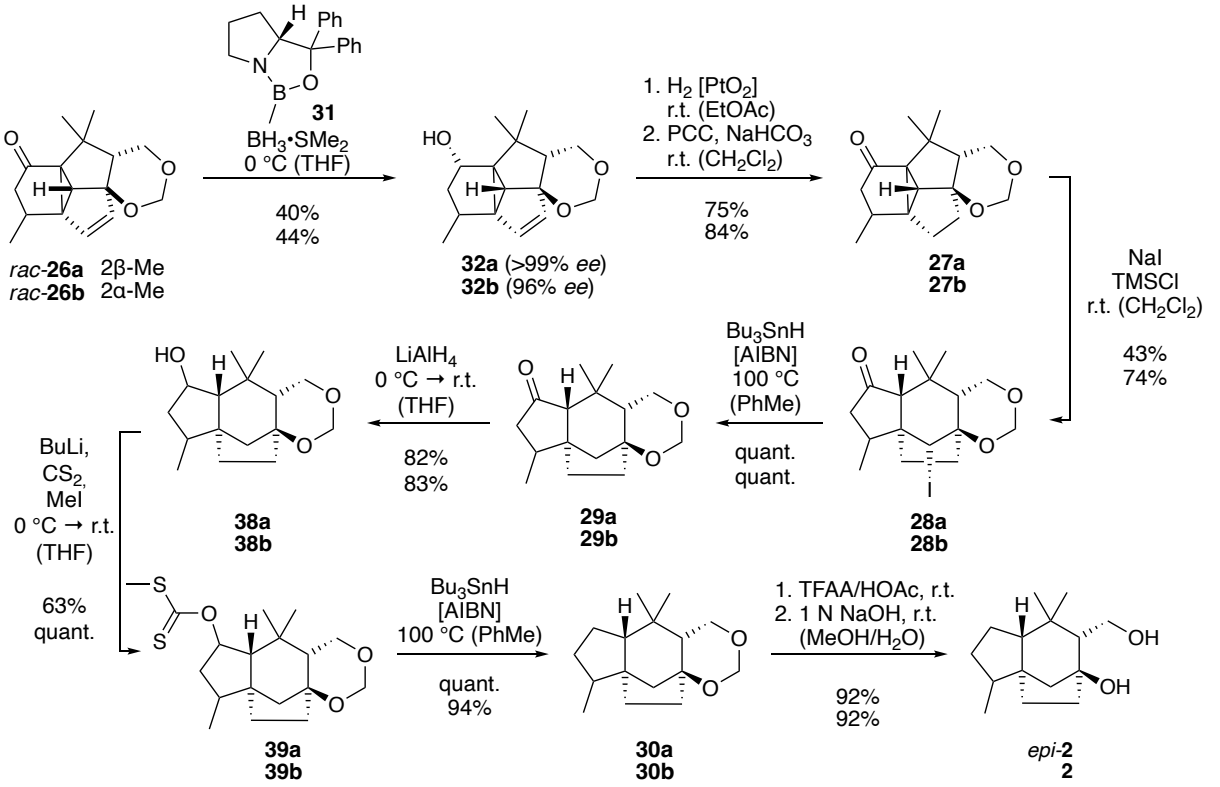
Scheme 15. Synthetic sequence towards (+)-agarozizanol B (**2**) from photocascade adduct *rac*-**26b**.

To confirm the absolute conformation, compound **28b** was analyzed by single crystal X-ray crystallography. A crystal structure was obtained of its epimer, due to epimerization in α-position to the carbonyl moiety. Since the compound displays the same absolute configuration

as **28b**, except for the single stereogenic center in α-position to the carbonyl group, the anomalous X-ray diffraction data for the epimer confirmed the absolute configuration of **28b**.

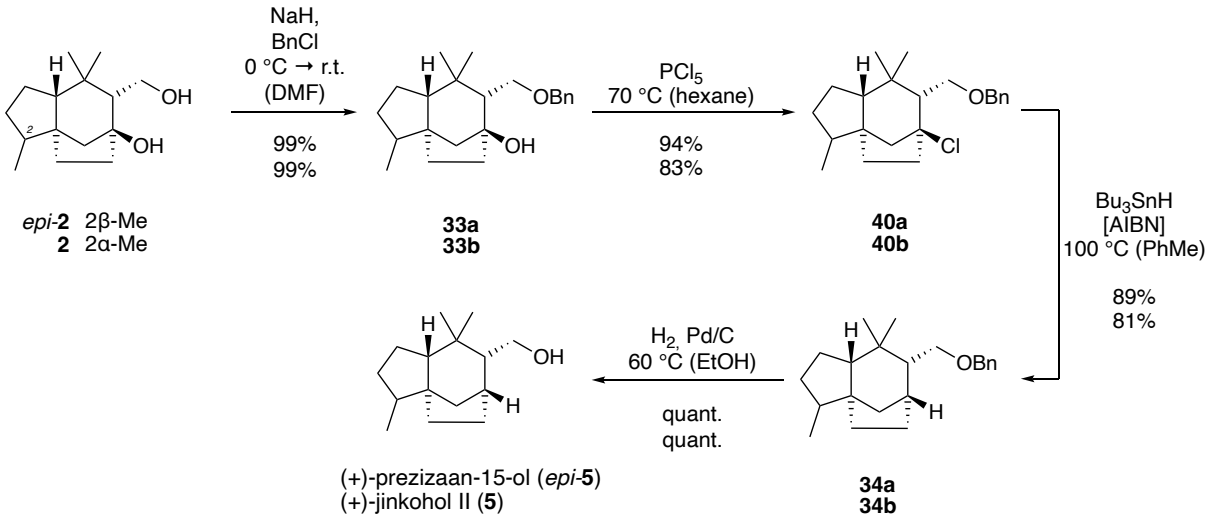
B) Total Synthesis of (+)-Prezizaan-15-ol, (+)-Jinkohol II, and (+)-Jinkoholic acid

While the minor diastereoisomer *rac*-**26a** from the photocascade reaction was used for the total synthesis of (+)-prezizaan-15-ol (*epi*-**5**), the major diastereoisomer *rac*-**26b** was utilized for the total synthesis of (+)-jinkohol II (**5**) and (+)-jinkoholic acid (**6**), respectively. Enantiopure material was gained utilizing *Corey-Bakshi-Shibata* catalyst **31**,[45] which was used before for the total synthesis of (+)-agarozizanol B, yielding compounds **32** (Scheme 16). For the subsequent reduction/re-oxidation sequence, pyridinium chloro chromate (PCC) was used instead of *Dess-Martin* periodinane,[54] since more reproducable yields were obtained for the synthesis of ketones **27**. Ring opening was conducted with NaI/TMSCl[41] as in the agarozizanol B-synthesis. Compound **28a** was only obtained in 43% yield because of the enhanced steric shielding of the methyl group in the cylcopentane ring. The sequence of the removal of the iodine[42] and the carbonyl remained the same, only differing in the conditions for the xanthate removal.[43,55] This time, tributyl tinhydride/AIBN gave more reliable yields than the previously used phosphinic acid/triethylamine/AIBN protocol[53] for obtaining compounds **30**. Finally, dioxane-ring opening[44] gave compounds *epi*-**2** and **2**.



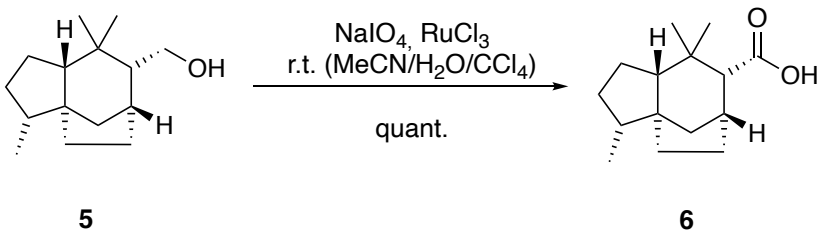
Scheme 16. Synthetic route towards compounds *epi*-**2** and **2**.

The crucial transformation to obtain the target molecules was the desoxygenation of the tertiary C-8 carbon atom. Twenty-three different conditions were tested for this reaction. To obtain (+)-prezizaan-15-ol (*epi*-**5**) and (+)-jinkohol (**5**) from compounds *epi*-**2**/**2**, the primary hydroxy group at the C-13 carbon atom was protected with a benzyl group in 99% for both cases (Scheme 17).[56] Afterwards, the actual desoxygenation step was carried out. First, phosphorus pentachloride was added, and stirring overnight at 70 °C in dry hexane gave chlorides **40** with 94% and 83% yield, respectively.[57] Afterwards, adding Bu_3SnH/AIBN afforded the desired alkyl skeletons in compounds **34** with 89% and 81% yield, respectively.[42] Deprotection of the primary alcohol under hydrogen atmosphere and palladium on carbon catalysis[58] gave the desired compounds *epi*-**5**/**5** quantitatively.



Scheme 17. Reaction sequence towards the synthesis of (+)-prezizaan-15-ol (*epi*-**5**) and (+)-jinkohol II (**5**) starting from diols *epi*-**2**/**2**.

To finally get hands on (+)-jinkoholic acid (**6**), (+)-jinkohol II (**5**) was oxidized using sodium periodate and ruthenium(III)-chloride[59] in quantitative yield (Scheme 18).



Scheme 18. Oxidation of (+)-jinkohol II (**5**) to (+)-jinkoholic acid (**6**).

Detailed analysis of the 1D- and 2D-NMR spectra of the synthetic material showed noticeable differences between the two epimers **5** and *epi*-**5**, especially in their ^{13}C NMR data. The observations of the *Weyerstahl* group regarding the relative configuration of (+)-jinkohol II in

favor of **5** were confirmed.[46] Single X-ray crystallography also cleared the absolute configuration of (+)-prezizaan-15-ol (*epi*-**5**).

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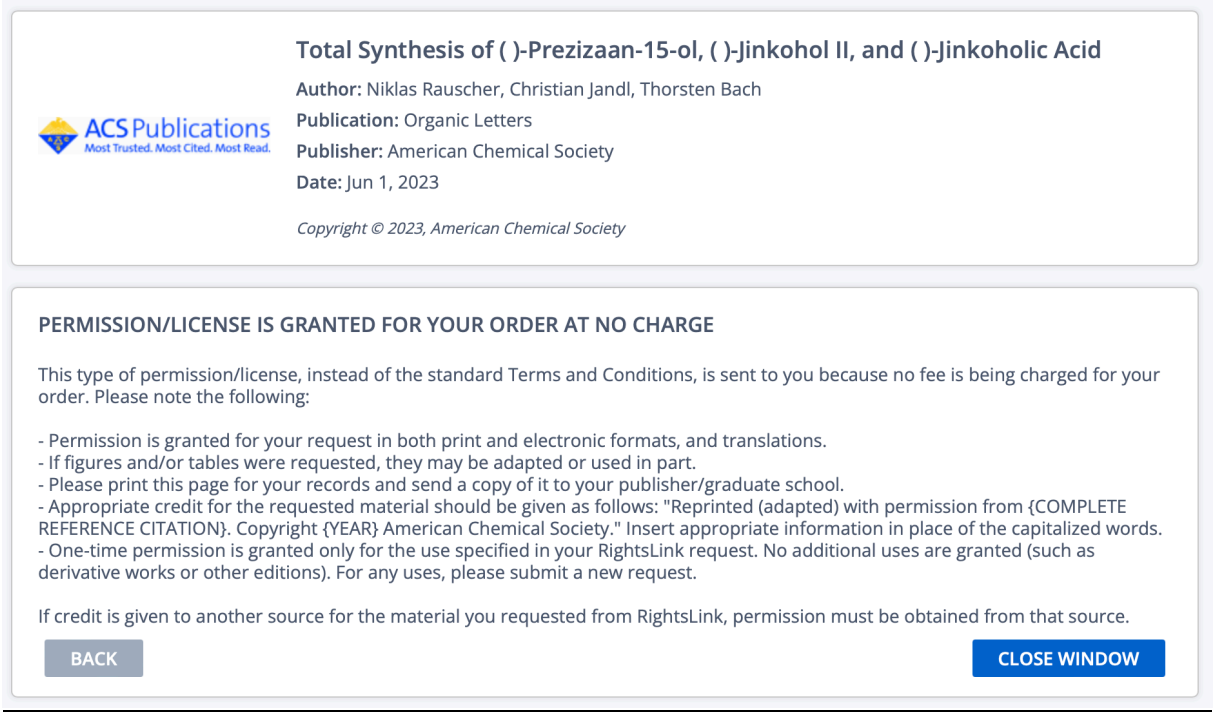

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