VIP Total Synthesis Very Important Paper

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Concise Total Synthesis of Agarozizanol B via a Strained Photocascade Intermediate

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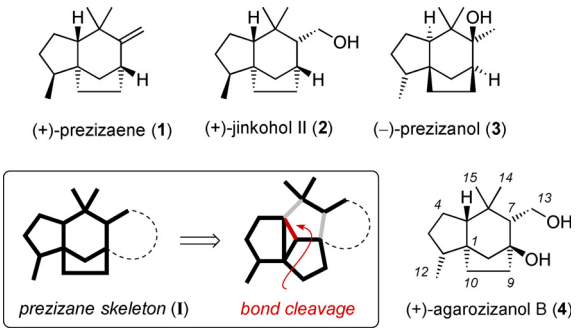
Abstract: *The prezizane-type sesquiterpene agarozizanol B was synthesized employing a photochemical cascade reaction as the key step. Starting from a readily available 1-indanone with a tethered olefin, a strained tetracyclic skeleton was assembled which contained all carbon atoms of the sesquiterpene 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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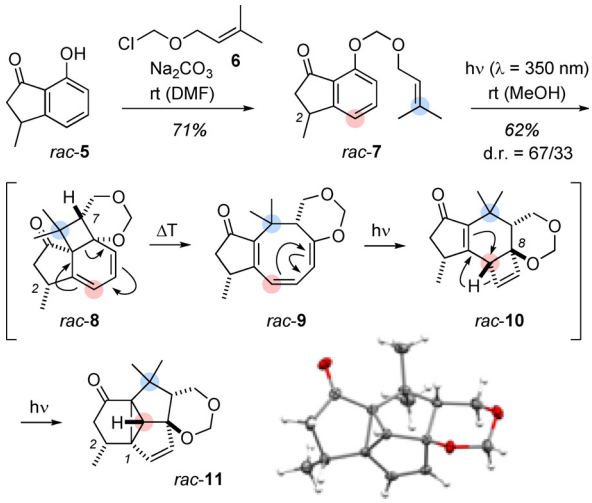
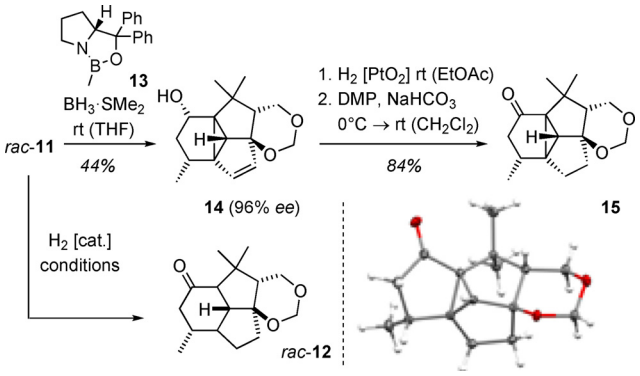
As indicated in Scheme 1, the reaction cascade required to tether the reactive component that brings in carbon atoms C6, C7, and C13-C15 to an existing photoactive building block which carries the remaining ten carbon atoms of the sesquiterpene skeleton. Following our retrosynthetic considerations, the 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, ^{i}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].

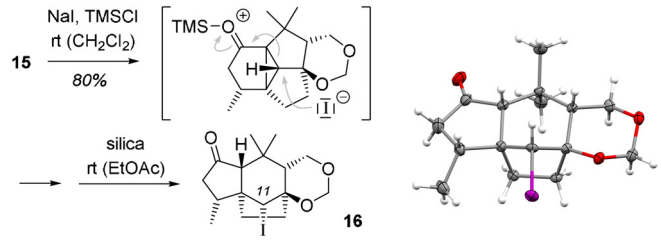


Scheme 3. An undesired cyclopropane ring cleavage occurring upon attempted hydrogenation of compound *rac*-**11** led to product *rac*-**12**. Reduction of the ketone to alcohol **14** allowed for a selective hydrogenation and the desired ketone **15** could be prepared in enantiopure (**15**) or racemic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

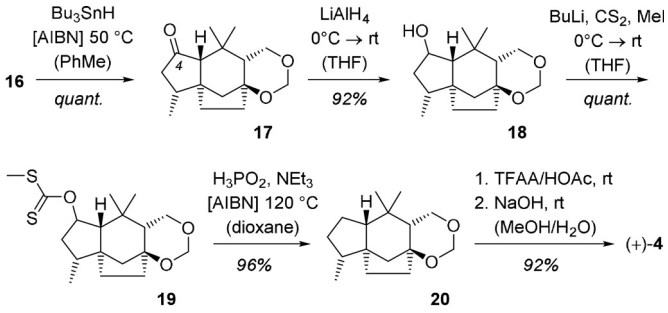
The desired selective opening of the cyclopropane ring as outlined in Scheme 1 was eventually achieved by treatment with sodium iodide and chlorotrimethylsilane (TMSCl).[29] Mechanistically, the opening is suggested to occur by TMS activation of the carbonyl group and substitution by the iodide in an 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.

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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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