Natural Products

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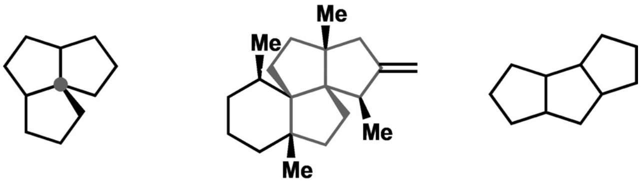
Total Synthesis of the Diterpene Waihoensene

Lisa-Catherine Rosenbaum[+], *Maximilian Häfner*[+], *and Tanja Gaich**

Abstract: *A racemic and scalable enantioselective total synthesis of (+)-waihoensene was accomplished. (+)-Waihoensene belongs to the diterpene natural product family, and it features an angular triquinane substructure motif. Its tetracyclic [6.5.5.5]backbone is all-cis-fused, containing six contiguous stereocenters, four of which are quaternary. These structural features were efficiently installed by means of a diastereoselective radical cyclization, followed by an intramolecular Pauson–Khand reaction, a diastereoselective α-alkylation, and a diastereoselective 1,4-addition reaction. Enantioselectivity was introduced at an early stage, by an asymmetric palladium catalyzed decarboxylative allylation reaction on gram scale.*

Terpene natural products containing polyquinane structure motifs constitute a diverse structural subclass prominent in sesqui- and di-, as well as sesterterpenes, and ever since have attracted great attention from the synthetic community.[1] Angular triquinanes **2** in particular pose a synthetic challenge, since their principal structure element implies the existence of a quaternary stereocenter[2] (blue dot structure **2** in Figure 1), as opposed to linear triquinanes **3**, where a quaternary stereocenter is not a prerequisite.



angular triquinane **2**

(+)-waihoensene (**1**)

linear triquinane **3**

Figure 1. Comparison of the linear and angular triquinane structure element.

Waihoensene (**1**) harbors such an angular triquinane substructure, and moreover contains altogether four quaternary stereocenters which are aligned in a contiguous fashion across the carboskeleton. The diterpene waihoensene (**1**) has been isolated from the plant *Podocarpus totara var. waihoensis* native to New Zealand in 1997 by the Weavers group.[3] Structural analysis of waihoensene (**1**) reveals a tetracyclic fused ring-skeleton with six stereocenters embedded of which four are quaternary stereocenters. All stereocenters are contiguously arranged, making it a very densely packed molecule sterically utmost encumbered. In addition, waihoensene (**1**) does not contain any functional groups beside a single double bond thus representing a pure hydrocarbon. This specific feature might look innocent in the first place, but upon synthetic planning it turns out to represent one of the greatest synthetic obstacles for an efficient synthesis, besides the four quaternary stereocenters present in the natural product. Since most C−C bond forming reactions require functional groups, the lack of functionalization (or in biosynthetic terms—lack of oxygenation of the natural product) inevitably entails over-functionalization of synthetic intermediates (overshooting molecular complexity), and eventually requires application of additional de-functionalization reactions (FGIs), lengthening the overall synthetic route. Waihoensene (**1**) has been synthesized previously by three groups, who devised different synthetic strategies depicted in Figure 2.[4–7] The first accomplished total synthesis in racemic form followed a tandem [3+2] cycloaddition

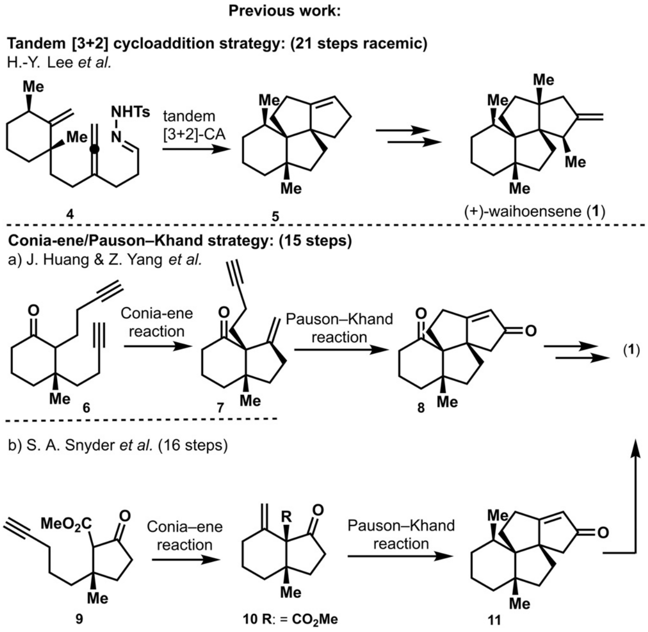


Figure 2. Synthetic strategies of previous syntheses.

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[*] M. Sc. L.-C. Rosenbaum,[+] M. Sc. M. Häfner,[+] Prof. Dr. T. Gaich
Department of Chemistry, University of Konstanz
Universitätsstrasse 10, 78464 Konstanz (Germany)
E-mail: tanja.gaich@uni-konstanz.de

[+] These authors contributed equally to this work.

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strategy, and was published in 2017 by Lee and co-workers.[5] Recently, in 2020 two further syntheses were published involving a Conia–Ene/Pauson–Khand strategy by the groups of Huang & Zhang[6] and the group of Snyder.[7] Both latter synthetic approaches are enantioselective with a step count ranging of 15 and 16 steps. By contrast Lee's racemic synthesis required 21 steps.

Herein we report both, an enantioselective synthesis of waihoensene (**1**) and in racemic form, with an overall step count of 14 (racemic) and 19 (enantioselective) steps. Our strategy was guided by first establishing one of the four quaternary stereocenters via an asymmetric allylation reaction to give compound **27** (Scheme 3).[8] We then assembled the hydrindane part **18** of waihoensene (**1**) by a radical cyclization reaction together with establishing the methyl-group at C7 at the same time.[9] By contrast, all other syntheses do not tie these two transformations together. This bicycle **18** served as rigid template for the Pauson–Khand reaction[10] to give the carboskeleton of **1**. Compound **11** was eventually converted to waihoensene (**1**) in a three-step sequence.

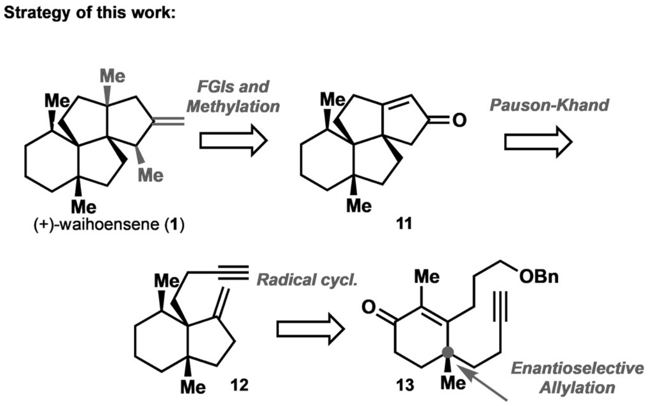
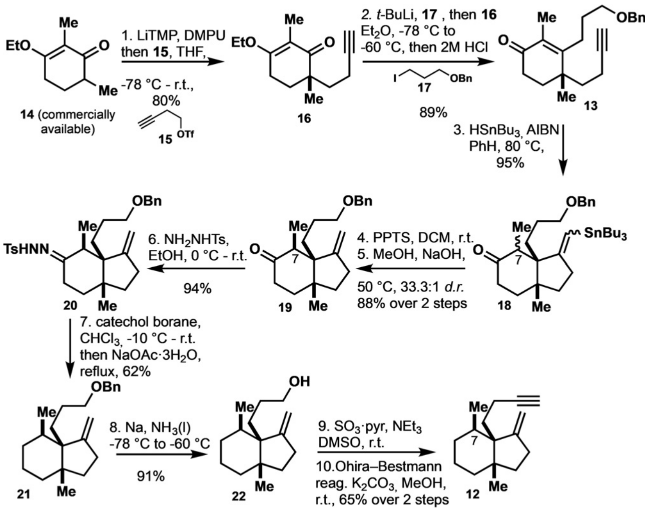


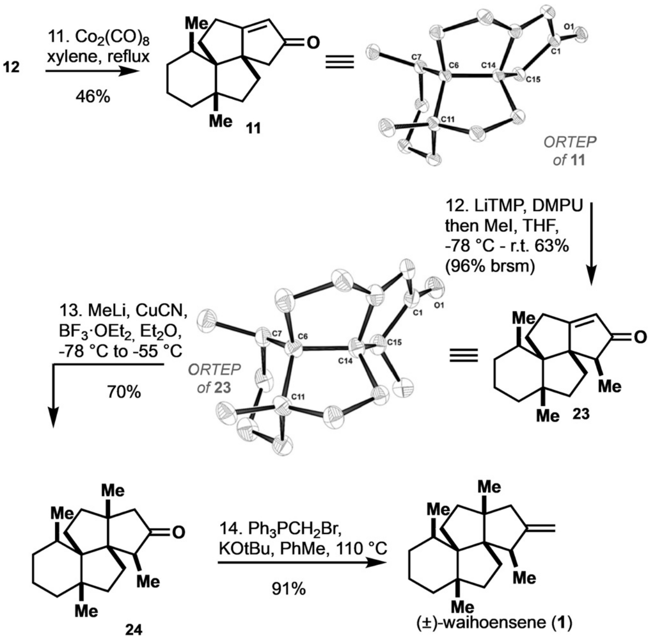
Figure 3. Retrosynthetic analysis this work's synthesis.

On the outset, we started our synthetic racemic sequence from commercially available compound **14** (Scheme 1). Introduction of the quaternary center to **14** was accomplished by an alkylation reaction with homopropargylic triflate to yield **16** in 80%. This was followed by an addition of lithiated **17** to the vinylogous ester in **16** and in situ elimination reaction to afford enone **13** in 89% yield. At this point the radical cyclization reaction established the desired hydrindane scaffold **18** in 95% yield as an inconsequential diastereomeric mixture at C7. Destannylation of **18** and consecutive treatment with sodium hydroxide in methanol established the desired configuration of the C7 methyl group by equilibration to give 97% of desired all-*cis* **19** in 88% yield. The correct configuration of the methyl-group and the *cis*-fusion of the hydrindane system was confirmed by single crystal X-ray analysis after converting the ketone into the 2,4-di-nitrophenyl hydrazone.[11]

The high preference for the desired configuration of the C7 methyl group in **19** is attributed to minimization of 1,3-allyl-strain. Defunctionalization of the ketone in **19** was accomplished by conversion to hydrazone **20** followed by reduction with catechol borane to give compound **21**. This was converted to alkyne **12** by deprotection under Birch conditions, Parikh–Doering oxidation to the corresponding aldehyde, and Ohira-Bestmann alkynylation. The intermediate aldehyde tends to undergo acid-mediated Prins cyclization and was therefore used in the next step without purification. Alkyne **12** poses the precursor for the Pauson–Khand reaction, and it was treated with dicobalt-octacarbonyl to give the corresponding cobalt-alkyne complex. This intermediate underwent cyclization and CO-insertion under forcing conditions to yield 46% of the desired product **11**, and thus delivering the fully established core of waihoensene (**1**; Scheme 2). Fortuitously, we obtained a single crystal[12] of this



Scheme 1. Synthesis of the Pauson–Khand precursor **12**.



Scheme 2. Pauson–Khand reaction of **12** and endgame to waihoensene (**1**).

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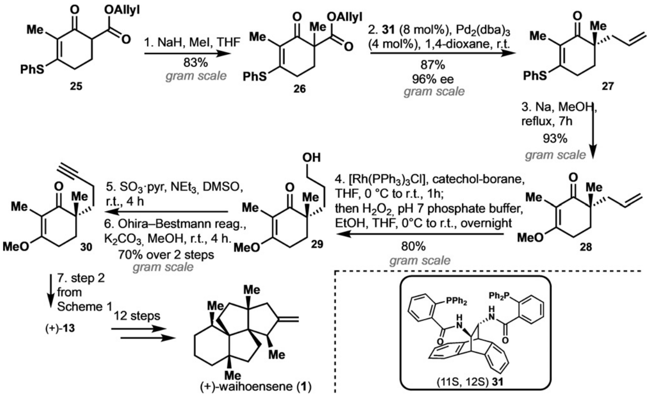
key intermediate and therefore we were able to unambiguously establish the correct configuration of **11**.

The endgame of the synthesis consisted of a three-step sequence starting with α-alkylation of Pauson–Khand product **11** to give **23** as a single diastereomer. From this point onward, our synthesis deviates from all previously published ones, who share a common endgame consisting sequentially of a 1,4-addition of the methyl-group to enone **11**, subsequent α-alkylation, and final olefination to give waihoensene (**1**). By contrast to these reports,[5] we encountered no difficulties upon first performing an α-alkylation of **11**, and were able to confirm the desired stereochemistry of the newly formed stereocenter by single crystal X-ray analysis of product **23**.[13] The choice of base and additive in this α-alkylation of **11** is crucial with regard to the competing formation of kinetic and thermodynamic enolates. Strong bases, that is, LDA (lithium diisopropylamide), LiTMP (lithium 2,2,6,6-tetramethylpiperidid) and LiICA (lithium isopropylcyclohexylamide) in combination with DMPU give desired methylated **23** as the only product, however incomplete conversion lead to concurrent re-isolation of starting material in all cases. The use of weaker bases such as LiHMDS lead to the formation of the thermodynamic enolate (deprotonation in γ-position of the enone moiety). 1,4-Addition of methyl cuprate to **23** delivered **24** in 70 % yield, and again exclusively gave a single stereoisomer. The synthesis was concluded by Wittig olefination to deliver the natural product waihoensene (**1**) in 91 % yield and a very concise overall 14 step sequence. For obtaining optically active material, we decided to proceed via an enantioselective allylation reaction[14] to introduce the first of the four quaternary stereocenters (Scheme 3). We thereby started from vinylogous thioester **25**,[15] which was required in order to obtain excellent enantioselectivity. Quaternarization of **25** with methyl iodide delivered **26**[14] and palladium catalyzed decarboxylative allylation using Trost's ligand[16] furnished the desired optically active **27** with 96 % *ee* and 87 % yield. Conversion of the vinylogous thioester to its corresponding methylester, manipulation of the allyl side chain in three steps (hydroboration/oxidation and Ohira–Bestman reaction), and addition elimination reaction of **30** gave synthetic intermediate (+)-**13** in full accordance with the racemic route. The enantioselective route is very robust and was executed on gram scale with no loss of yields and optical activity. Therefore, the enantioselective material was funneled into the racemic route and eventually delivered (+)-waihoensene (**1**) in analogous fashion and 19 overall steps.



Scheme 3. Enantioselective approach to (+)-waihoensene (**1**) by an asymmetric allylation reaction.

In conclusion, we have developed the so far shortest route to (±)-waihoensene (**1**) consisting of only 14 steps and delivering racemic material. For the enantioselective route we require 19 steps and are able to produce optical active material **30** on gram scale. Our synthetic strategy to assemble the carboskeleton features a radical cyclization to form the hydrindane part **18** of waihoensene as a rigid template for further C–C-bond forming reactions. The skeleton is constructed via the Pauson–Khand reaction to deliver the final product (+)-waihoensene (**1**) in a three-steps containing endgame which introduces two additional stereocenters.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: natural products · Pauson–Khand reaction · radicals · terpenes · total synthesis

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[11] Deposition Number 2016640 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures. For an X-ray data analysis, see experimental section.

[12] Deposition Number 2016641 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures. For an X-ray data analysis, see experimental section.

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