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Total Synthesis of Pericoannosin A

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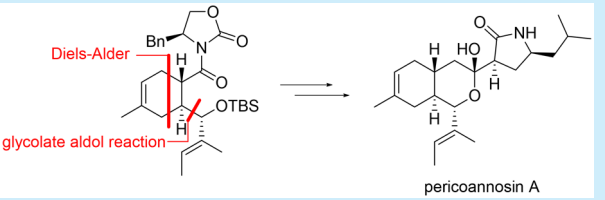
Supporting Information

ABSTRACT: The first total synthesis of pericoannosin A (**1**) containing 15 steps in the longest linear sequence with an overall yield of 5.5% is reported. The hybrid peptide−polyketide was isolated from the endophytic fungus *Periconia* sp. F-31 and bears a unique tricyclic core structure. The key steps are a glycolate aldol reaction and a Diels−Alder reaction utilizing an Evans auxiliary for controlling the stereochemistry. Furthermore, a late-stage equilibration was employed.



During the last ten years, the endophytic fungus *Periconia* sp. F-31, isolated from the medicinal plant *Annona muricata*, turned out to be a rich source of natural products showing a variety of structural motives as well as different biological properties, such as anticancer and anti-inflammatory activities.[1] In 2015 and 2016, Dai and co-workers reported the isolation of two diastereomeric natural products named pericoannosin A (**1**)[2] and pericoannosin B (**2**)[3] (Figure 1),

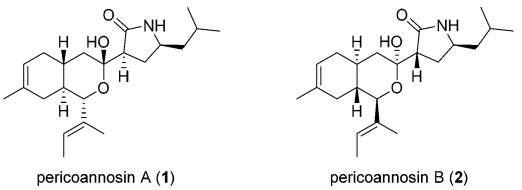
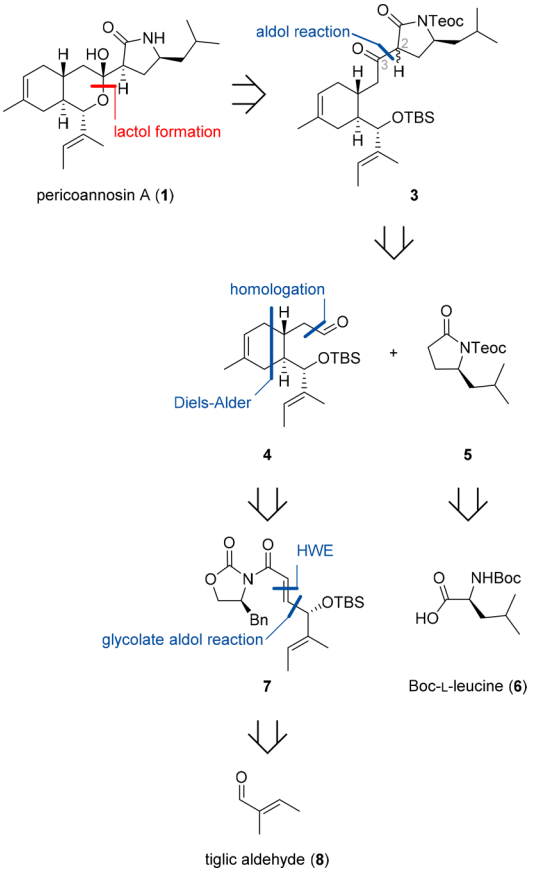


Figure 1. Structures of pericoannosin A (**1**) and B (**2**).

exhibiting a hexahydro-1*H*-isochromen-5-isobutylpyrrolidin-2-one skeleton that has not been found in any other natural product so far. In addition to its interesting structural motif, pericoannosin A (**1**) shows a moderate anti-HIV activity (IC_{50} = 69.9 μM)[2] and is being screened for its applications in pharmaceutical research.[4]

In light of our ongoing work with hybrid peptide−polyketide natural products,[5] we focused our efforts on the total synthesis of pericoannosin A (**1**) aiming for the first synthetic approach toward its unique tricyclic core structure. In our retrosynthetic analysis (Scheme 1), we envisioned lactol formation via nucleophilic attack of an alcohol to a ketone as one of the last steps of our synthesis. Based on the assumption of the natural product as the thermodynamically most stable diastereomer, we expected the stereogenic centers at C2 and C3 to either adopt the desired configuration during cyclization or be easily equilibrated afterward. The required precursor, β-keto amide **3**, should be obtained from an aldol reaction of aldehyde **4** and Teoc-lactam **5**. While the lactam can be derived from Boc-L-

Scheme 1. Retrosynthetic Analysis



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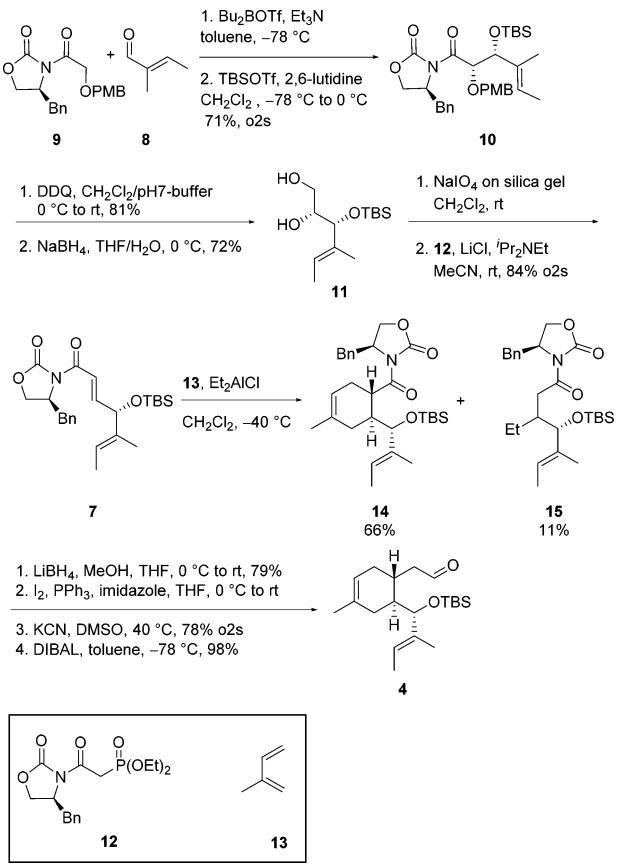
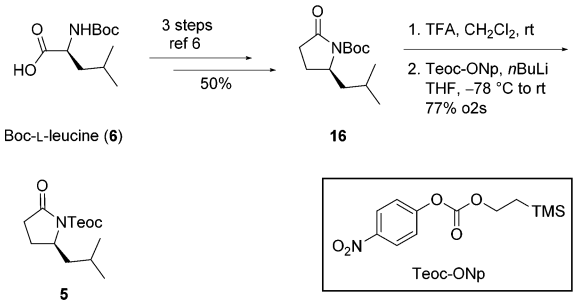
leucine (**6**),[6] a sequence composed of a Diels–Alder reaction[7] and subsequent homologation starting from dienophile **7** was planned for the synthesis of aldehyde **4**. Dienophile **7** itself can be traced back to commercially available tiglic aldehyde (**8**) with an olefination and a glycolate aldol reaction[8] in mind as the key transformations.

The first step of our synthesis was a glycolate aldol reaction of tiglic aldehyde (**8**) and PMB-oxazolidinone **9**.[9] Subsequently, a three-step sequence consisting of TBS protection, PMB deprotection, and reductive removal of the Evans auxiliary led to diol **11**, which was cleaved using silica gel-supported sodium periodate.[10] The obtained aldehyde was submitted to a Horner–Wadsworth–Emmons (HWE) olefination with phosphonate **12**[11] utilizing Masamune–Roush conditions[12] yielding dienophile **7** in a good overall yield of 84%. The following Diels–Alder reaction of dienophile **7** and isoprene (**13**) gave the desired product **14** in the expected dia- and regioselectivity.[7] To our regret, Diels–Alder product **14** was obtained in an inseparable mixture with the 1,4-adduct **15** arising from the addition of an ethyl moiety.[7b] Fortunately, this impurity could be removed over the course of the following four-step homologation process consisting of reductive removal of the Evans auxiliary, an Appel reaction,[13] S_N2 displacement with potassium cyanide, and DIBAL reduction to give aldehyde **4** in a good overall yield of 60% (Scheme 2). Our initial plan was to use Boc-lactam **16**[6] for the ensuing aldol reaction, but we experienced the acid-mediated elimination of the C11 TBS-ether. Thus, a protecting group switch to the 2-(trimethylsilyl)ethyl (Teoc) carbamate **5** was performed (Scheme 3).

Scheme 2. Synthesis of Aldehyde 4



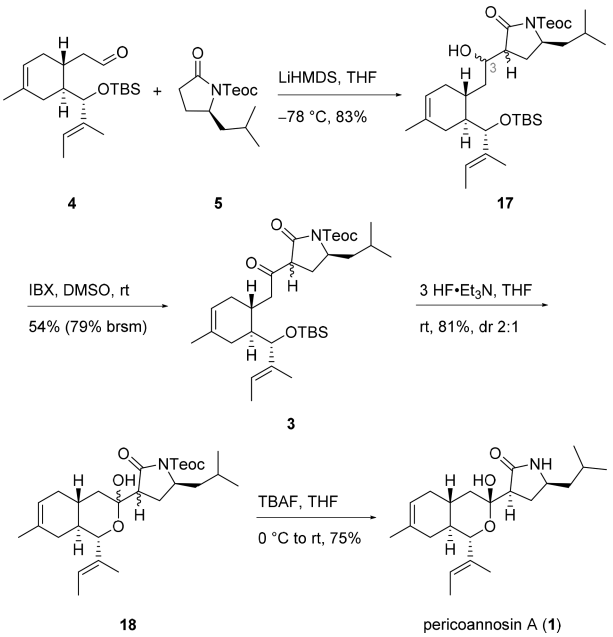
Scheme 3. Synthesis of Teoc Lactam 5



Obtained Teoc-lactam **5** and aldehyde **4** were subjected to an aldol reaction leading to the desired aldol product **17** in a mixture of four diastereomers. With the entire carbon skeleton in place, the last transformation before removal of the protecting groups was oxidation of the newly formed alcohol at C3. Though no full conversion could be achieved, 2-iodoxybenzoic acid (IBX) gave the best results in comparison to other screened conditions (Dess–Martin, Ley–Griffith, Swern). Nevertheless, most of the starting material could be recovered. With β-keto amide **3** in hand, global deprotection inducing the cyclization remained as the last challenge. During our attempts to address this problem, it turned out that the TBS ether could only be cleaved by using hydrogen fluoride, whereas Teoc deprotection worked only using TBAF. Therefore, we had to perform a stepwise deprotection approach starting with removal of the TBS group. The use of triethylamine trihydrofluoride cleaved the TBS ether and induced the cyclization yielding lactol **18** in a 2:1 mixture of two diastereomers. This mixture was treated with an excess of TBAF cleaving the Teoc carbamate and equilibrating both diastereomers to a single compound, pericoannosin A (**1**, Scheme 4).

In summary, we accomplished the first total synthesis of pericoannosin A (**1**) in the longest linear sequence of 15 steps with an overall yield of 5.5% starting from commercially

Scheme 4. Endgame of the Synthesis



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available tiglic aldehyde (**8**). The key steps of our synthesis were a stereoselective glycolate aldol reaction and a stereoselective Diels–Alder reaction. Furthermore, it is worth noting that our expectation of the natural product as the thermodynamically most stable compound could be proven by late-stage equilibration.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01768.

Experimental procedures and spectral data for the compounds described herein (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Dr. Dieter Schinzer (Otto-von-Guericke-Universität Magdeburg) on the occasion of his 65th birthday.

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