

# Synthesis of Angiolam A

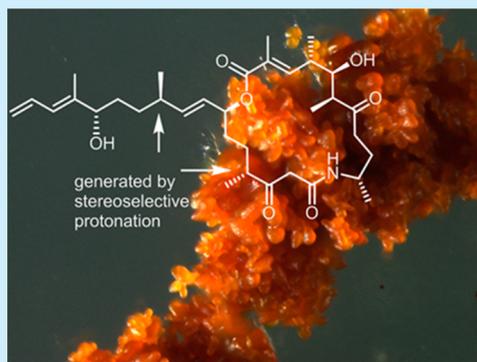
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## S Supporting Information

**ABSTRACT:** The first total synthesis of angiolam A has been accomplished in 18 steps. Key steps include vinylogous Mukaiyama aldol reactions of aldehyde-derived dienol ethers, conjugate reduction of the resulting double bond followed by diastereoselective protonation and the Witzeman protocol for macrolactamization. Comparison of the optical rotation of the synthesized material with the isolation data established that the absolute configuration of angiolam A is opposite from the proposed structure.



In 1985, Höfle and Reichenbach reported on the isolation and structural elucidation of angiolam A (Scheme 1), a new antibiotic from *Angiococcus disciformis*.<sup>1</sup> However, there was uncertainty about the C2–C3 double bond geometry and additionally, the absolute configuration was not determined. Angiolam A exhibits notable antibacterial activity against Gram-positive bacteria (MIC 0.78  $\mu\text{g}/\text{mL}$ ) with no acute toxicity in mice with concentrations of up to 300 mg/kg. So far, there are no reports on the synthesis or biology of angiolam A. Our interest in this natural product originated from the possibility to construct the 1,4-*anti* relationship (5) of hydroxyl and methyl groups through enolate protonation generated by 1,4-reduction of unsaturated aldehydes (Scheme 1).<sup>2</sup> This highly selective process occurs with diastereomeric ratios of up to 20:1 and provides the product as its hemiacetal which serves to protect the  $\alpha$ -position from epimerization. The corresponding precursors for such asymmetric protonations are easily accessible by vinylogous Mukaiyama aldol reactions (VMAR).<sup>3</sup> We recently developed a protocol which takes advantage of silyldienol ether 11 as a redox-economic<sup>4</sup> reagent to access  $\delta$ -hydroxy- $\alpha,\beta$ -unsaturated aldehydes with high enantioselectivities in one step (Scheme 1).<sup>5</sup>

The synthesis presented herein demonstrates the practicability of the vinylogous Mukaiyama aldol reaction followed by internal protonation to construct complex polyketides. It additionally confirms the C2–C3 double bond of angiolam to be *E*-configured. Our retrosynthetic analysis disconnects angiolam into three fragments (Scheme 1).

Fragment 2 contains the phosphonium salt required for olefination to the northern segment, 3. As we will point out below, our initial strategy to establish the macrocyclization through ester formation failed and we therefore decided to use the described olefination to join both segments.

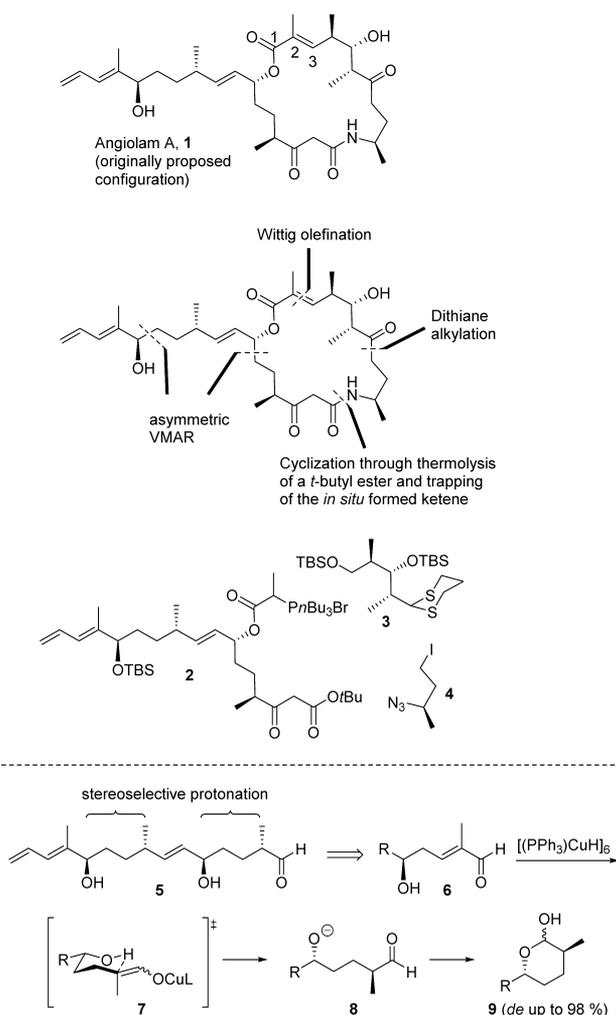
The eastern fragment can be constructed from dithiane 3 and iodide 4. The four chiral centers of segment 2 are generated by two identical sequences of vinylogous Mukaiyama aldol reaction of an aldehyde-derived silyl enol ether followed by direct reduction of the  $\alpha,\beta$ -unsaturated aldehyde with Stryker's reagent to generate the corresponding enolate which is protonated by the previously established secondary alcohol to generate the desired 1,4-*anti* relationship (Scheme 1).

The synthesis commenced with a stereoselective vinylogous Mukaiyama aldol reaction using OXB1<sup>5</sup> as the chiral Lewis acid, aldehyde 10 and the aldehyde-derived dienol ether 11 to yield alcohol 12 with an enantiomeric access of 91% (Scheme 2). The VMAR was directly followed by Stille coupling (13), 1,4-reduction and  $\alpha$ -protonation using Stryker's reagent.<sup>6</sup>

This transformation is believed to occur through conjugate reduction followed by intramolecular protonation by the secondary alcohol (6–9, Scheme 1). The resulting aldehyde forms hemiacetal 14, which can be directly converted to the corresponding unsaturated ester through an olefination with the tributylphosphine-derived Wittig reagent 15.<sup>7</sup> Other olefination strategies such as HWE-olefination only yielded the corresponding oxa-Michael product or resulted in diminished yields. Established oxidation state changes gave access to aldehyde 16, which was subjected again to a sequence of vinylogous aldol reaction (OXB2, 17)<sup>5</sup> followed by Stryker reduction and stereoselective protonation which proceeds with a diastereomeric ratio of >20:1. Here, it should be pointed out that the two VMA reactions proceed with different selectivities and different catalysts were used. We realized that the addition

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Scheme 1. Originally Proposed Configuration of Angiolam A and Retrosynthetic Disconnection

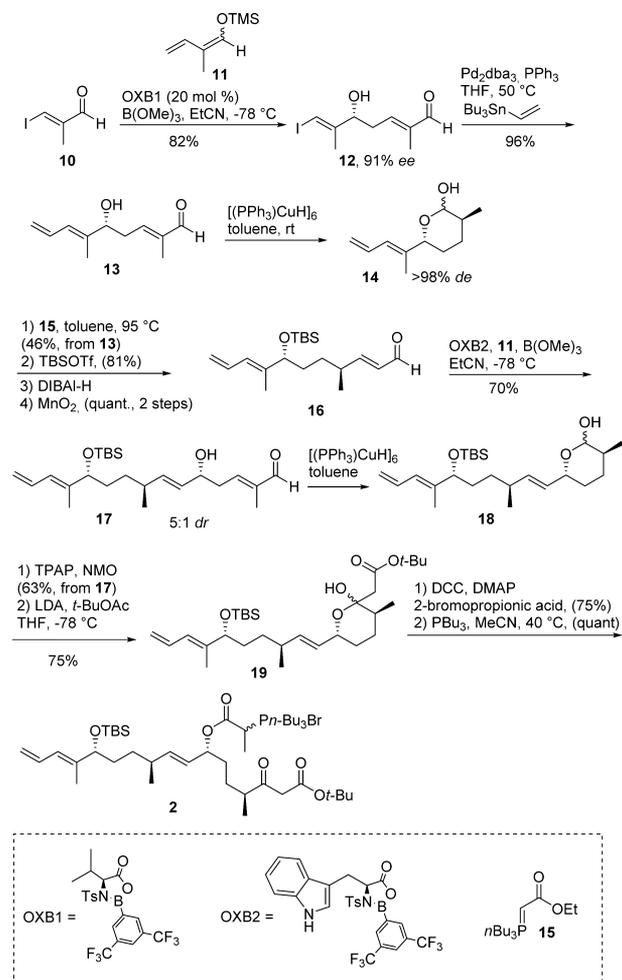


of  $\text{B}(\text{OMe})_3$ <sup>8</sup> as competitor for binding of the product to the chiral Lewis acid led to improved turnover numbers.

Even though we proposed that the secondary alcohol generated during the vinylogous Mukaiyama aldol only serves as intramolecular proton source, it is additionally required for the activation of the Stryker's reagent. Experiments with protected alcohols did not perform the conjugate addition at all. This parallels the observation that transformations with Stryker's reagent usually require catalytic quantities of water. The synthesis continues with oxidation of hemiacetal **18** and addition of *t*-butyl acetate in a Claisen condensation to generate **19**. Although by <sup>1</sup>H NMR only the cyclic acetal of **19** can be detected it is possible to esterify the secondary alcohol with bromopropionic acid under Steglich conditions,<sup>9</sup> which was a prerequisite for its further functionalization. Substitution of bromide by tributylphosphane established segment **2** that was the pivotal segment for the construction of angiolam A (Scheme 2).

The synthesis of the northern fragment started with Roche ester-derived aldehyde **20**, which was converted to aldehyde **22** using reagent **21** in an Evans aldol reaction. Transformation of this aldehyde to its corresponding dithiane (**3**) and subsequent alkylation with **24**,<sup>10</sup> provided the desired product (**26**). After removal of the PMB group and transformation of the resulting alcohol to its mesylate the azide was introduced through

Scheme 2

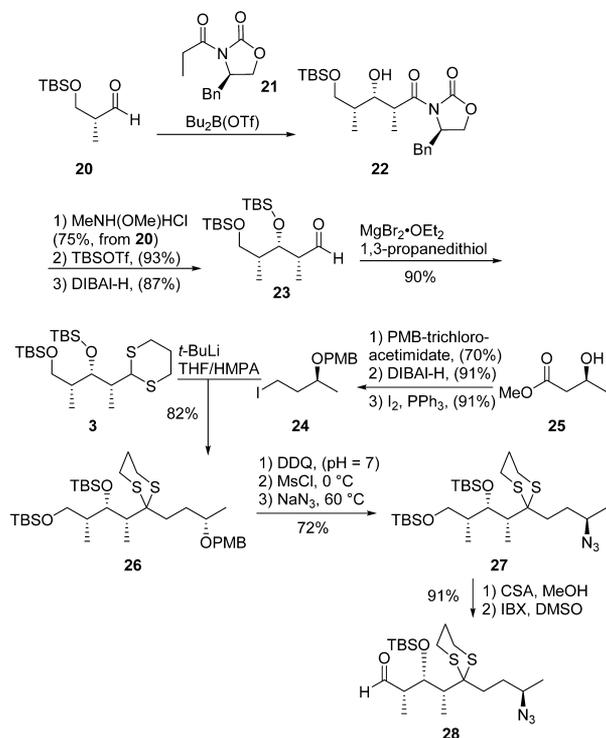


displacement with sodium azide. In order to allow conjunction of fragments through the above-mentioned Wittig olefination, the primary TBS group in compound **27** was removed and the alcohol oxidized to aldehyde **28** (Scheme 3).

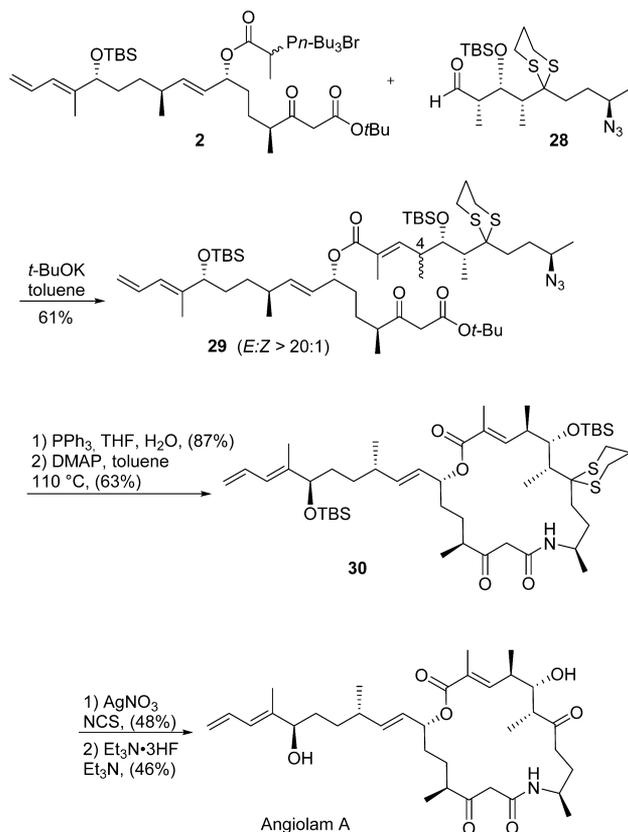
As shown in Scheme 4, the endgame starts with a Wittig olefination between compounds **2** and **28**. It should be pointed out that this reaction proved to be a challenging transformation that failed when other olefination conditions were employed. For instance, the use of triphenylphosphine for the construction of the Wittig reaction as well as Horner–Wadsworth–Emmons conditions failed to generate any detectable product in the subsequent olefination reaction. Furthermore, all attempts to introduce the entire northern segment through an ester formation failed as well. The difficulties associated with this transformation became apparent by the fact that the  $\alpha$ -stereocenter at C4 exhibited substantial epimerization (1:1) during the olefination reaction. Fortunately, we were able to separate these isomers during the purification of the final product.

With **29** in hand, the Staudinger reaction liberated the amine and upon heating in toluene in the presence of DMAP the desired macrocyclization product **30** was obtained in 63% yield. The cyclization is believed to occur according to the Witzman protocol<sup>11</sup> via an acylketene intermediate which is liberated from the *t*-butyl ester and then trapped by the free amine. The dithiane could be removed with  $\text{AgNO}_3$  and  $\text{NCS}$ <sup>12</sup> and finally  $\text{Et}_3\text{N}\cdot 3\text{HF}$  at elevated temperature removed both TBS groups

Scheme 3



Scheme 4



to generate angiolam A. The synthetic compound was obtained as isomerically homogeneous material after HPLC purification and exhibited NMR spectra identical to the authentic material. However, the  $\alpha$ -D-value was opposite to the reported value, and

we therefore conclude that authentic angiolam A is the opposite enantiomer with respect to our synthetic material (authentic: +24.8; synthetic: -25.0).

In summary, we have developed a sequence of stereoselective vinylogous Mukaiyama aldol reaction and subsequent conjugate reduction followed by stereoselective protonation to provide rapid access to polyketides with two new stereocenters. Here, all four configurations of the southern fragment are constructed in this way, and we see the synthesis of angiolam A as prime example of the construction of this particular motif found in polyketides. Additionally, the Witzeman protocol was established for the macrolactamization. The synthetic material also established that the absolute configuration of angiolam A is opposite from the proposed structure and confirms the C2–C3 double bond to be *E*-configured (Figure 1).

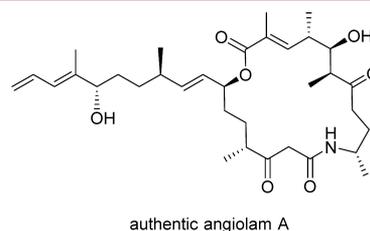


Figure 1. Configuration of authentic angiolam A.

## ■ ASSOCIATED CONTENT

### Supporting Information

Detailed synthetic information as well as spectroscopic characterization of all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest

## ■ ACKNOWLEDGMENTS

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