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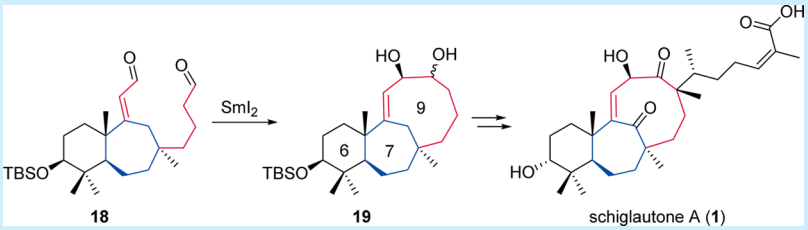
# Pinacol Coupling Strategy for the Construction of the Bicyclo[6.4.1]tridecane Framework of Schiglautone A

Bettina Werner[†] and Markus Kalesse*[,†,‡]

[†]Institute for Organic Chemistry, Leibniz Universität Hannover, Schneiderberg 1B, D-30167 Hannover, Germany

[‡]Helmholtz Centre for Infection Research (HZI), Inhoffenstrasse 7, D-38124 Braunschweig, Germany

Supporting Information




**ABSTRACT:** The synthesis of the tricyclic carbon framework of schiglautone A (**1**) is reported herein. The generation of the bicyclo[6.4.1]tridecane **19** was accomplished via a $SmI_2$-mediated pinacol coupling of dialdehyde **18**. The side chain in **18** was introduced using a selective 1,4-addition. A further key step of the synthesis was the homologation of a Wieland−Miescher ketone derivative to establish the 7-membered ring.

Several plants from the Schisandraceae family have been widely used in traditional Chinese medicine to treat a variety of different diseases, such as cough, premature ejaculation, chronic dysentery, and insomnia.[1] Their remarkable biological activity has been assigned to lignans[3] and terpenoids.[4] To date, the triterpenoids isolated from Schisandraceae species exhibit around 35 different and unprecedented skeletons.[5] One of them is schiglautone A (**1**), first isolated from *Schisandra glaucescens* by Ruan et al. in 2011.[1] Its structure (Figure 1) was elucidated via NMR spectroscopy and X-ray crystallography. Schiglautone A (**1**) belongs to the lanostane group (**3**) with the carbon scaffold shown in Figure 1.[5]

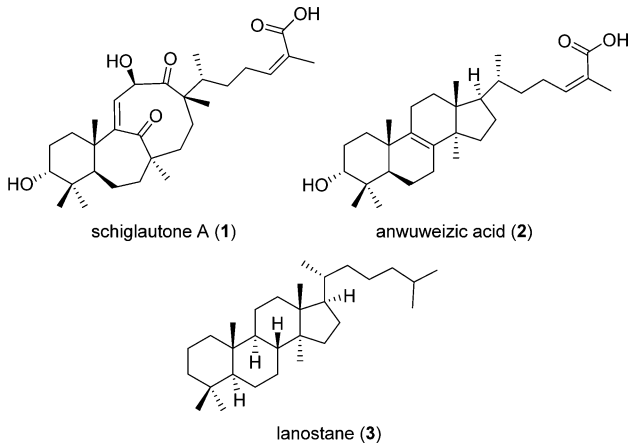



**Figure 1.** Structure of schiglautone A (**1**), anwuweizic acid (**2**) and carbon framework of the lanostanes (**3**).

Ruan et al. proposed a biosynthetic pathway starting from anwuweizic acid (**2**), which was isolated in large amounts from the same plant source and reported weak cytotoxic activities against HeLa, Hep G2, and SGC-7901 cell lines.[1]

Our interest in this natural product was caused by its novel tricyclic skeleton, which consists of a bicyclo[6.4.1]tridecane framework with an annulated six membered ring and offers a unique synthetic challenge. No example of such a carbon framework has been published so far. Additionally, the three quaternary stereogenic centers and the uncommon $sp^2$-carbon atom at the bridged position make schiglautone A (**1**) a fascinating target for total synthesis.[2]

Our retrosynthetic considerations are depicted in Scheme 1. We decided to introduce the C20−C26 side chain at the end of the synthesis through asymmetric alkylation strategies, even though such transformation which establish a quaternary center in the $\alpha$-position of a carbonyl group and a chiral center next to it have not been described yet and are the subject of additional investigations. For the construction of the nine-membered ring, we envisioned a pinacol coupling of dialdehyde **6**. This transformation would result in a diol so that both oxygens of the final product would already be in place and one hydroxyl group could remain unchanged in further transformations. Dialdehyde **6**, in turn, should be accessible from ketone **5** by Grignard addition, oxidative rearrangement, as well as oxidative cleavage of the pentenyl side chain. The transformation of **16** to **17** seemed to be particularly attractive since not only the desired aldehyde could be introduced but it also would allow stereoselective construction of the C9−C11 trisubstituted

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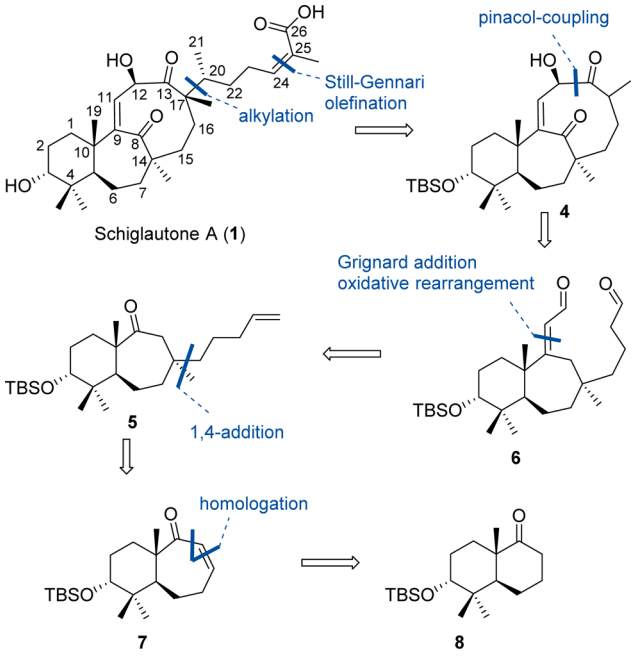
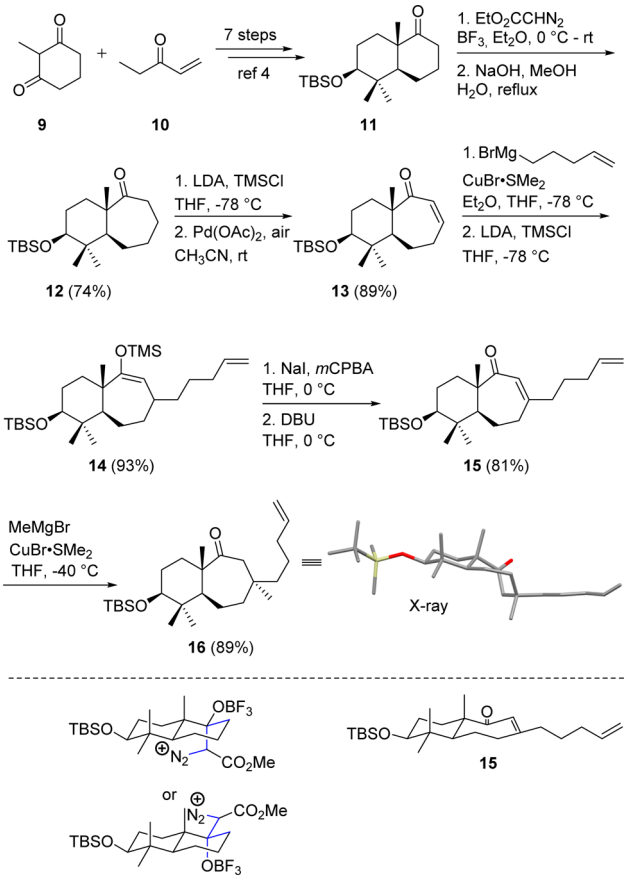
**Scheme 1. Retrosynthetic Analysis of Schiglautone A (1)**




**Scheme 2. Synthesis of Ketone 16**




double bond. The pentenyl side chain in **5** as well as the methyl group should be introduced by two subsequent 1,4-additions of corresponding cuprates to unsaturated ketone **13** or **15**, respectively. 1,4-Additions were chosen for the construction of this quaternary stereocenter as changing the order of addition would allow the formation of both diastereomers. The bicyclic system in **12** finally could be derived via an established homologation from ketone **11**.

Our synthetic efforts started with compound **11**, which was prepared from 2-methyl-1,3-cyclohexanedione (**9**) and ethyl vinyl ketone (**10**) in seven steps using a slightly modified literature-known sequence (Scheme 2).[6] The (*S*)-configured alcohol in **11** was chosen to establish the subsequent transformations due to its easy accessibility and the possibility of inverting its configuration at a later stage.

For the ring-enlargement to construct the seven-membered ring we used a robust and high-yielding two-step sequence as depicted in Scheme 2. Therefore, ketone **11** was treated with $BF_3{\cdot}OEt_2$ and ethyl diazoacetate to furnish an ester[7] which in refluxing aqueous NaOH/methanol underwent decarboxylation and furnished the seven-membered ketone **12**. A conformation with the $N_2$ group pointing inward can be used as a stereoelectronic argument to rationalize the observed selectivity in the ring-enlargement step.

For the introduction of the double bond we chose the Saegusa–Ito oxidation. The required silyl enol ether of ketone **12** was obtained by deprotonation with LDA and trapping the enolate with TMSCl. Subsequent treatment with $Pd(OAc)_2$ delivered unsaturated ketone **13** in 89% yield.[8] The next steps contained two 1,4-additions to install the methyl group as well as the pentenyl side chain. In our case, the C5 side chain was introduced first, using the freshly prepared corresponding Grignard reagent[9] and $CuBr{\cdot}SMe_2$ complex. Unfortunately it was not possible to directly trap the in situ generated enolate as its TMS-enol ether. Therefore, deprotonation with LDA and treatment with TMSCl was necessary to generate the TMS-enol ether. This enol ether was transformed into the $\alpha$-iodide via treatment with sodium iodide and *m*-chloroperoxybenzoic acid.[10] The following elimination with DBU provided the desired product **15** in good yields. (It is also noteworthy that, in this case, oxidation to the unsaturated ketone with $Pd(OAc)_2$ gave only low yields.) This 1,4-addition precursor was converted with methyl cuprate to saturated ketone **16**, which was possible by warming the reaction mixture from −78 to −40 °C. The configuration of the newly formed quaternary stereocenter in compound **16** was determined via X-ray crystallography (Scheme 2) and can be rationalized by attack at the convex side of the C8–C16 double bond as depicted in the conformational drawing of compound **16** (Scheme 2). Under the given conditions, we observed the formation of the product, and in order to maintain this good selectivity we decided to retain the configuration of the alcohol.

To obtain the precursor for the pinacol coupling, ketone **16** was treated with vinylmagnesium bromide, and the resulting tertiary alcohol underwent an oxidative rearrangement with PCC forming unsaturated aldehyde **17**. The second aldehyde group of compound **18** was introduced via dihydroxylation of the terminal double bond with $OsO_4$ and subsequent glycol cleavage with $NaIO_4$[11] (Scheme 3). In the presence of $SmI_2$, compound **18** underwent pinacol coupling, forming the nine membered ring and giving diol **19** in a diastereomeric ratio of 2:1.[12]

The allylic alcohol was selectively protected with TBSCl, and the free alcohol oxidized with IBX. At this stage, a single diastereomer was obtained, indicating that the pinacol coupling was stereoselective with regard to the allylic position. Further NOE experiments confirmed that compound **20** with the desired stereochemistry was formed. As shown in Figure 2,



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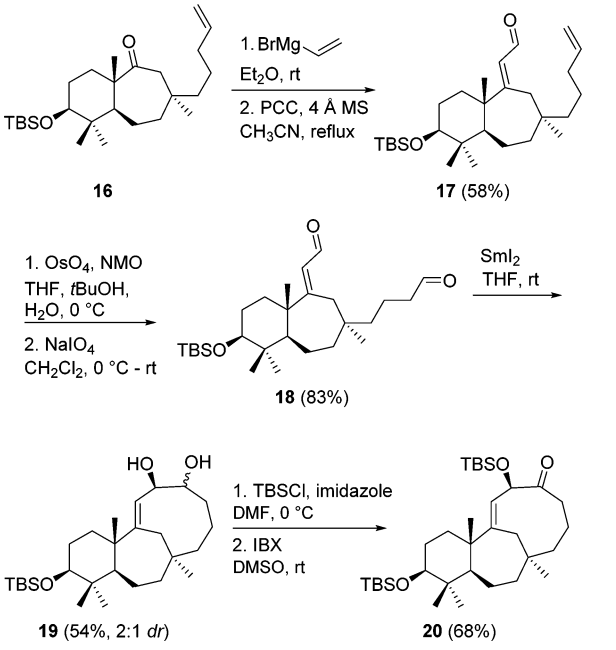
**Scheme 3. Synthesis of Tricyclic Compound 20**



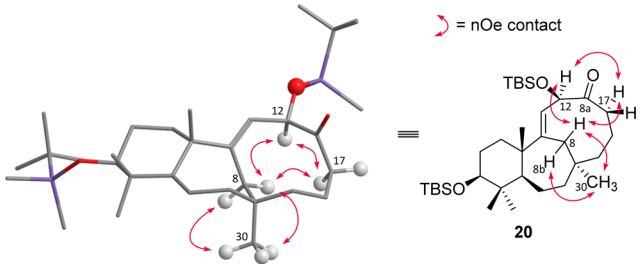




**Figure 2.** Configurational assignment of compound **20** via NOE experiments.

proton 8a gave NOE contacts to the proton of interest (H12) as well as to protons at C30 and C17. H12 showed cross signals to the same proton at C17 and H8a. Due to the fixed conformation of the tricyclic framework, the configuration at C12 was confirmed as *R*. With compound **20** in hand, the complex tricyclic framework of the natural product has been successfully prepared; to complete the total synthesis of the natural product, it is still needed to oxidize the bridgehead carbon, install the side chains to the C ring, and invert the stereochemistry of the oxygen in the A ring.

In conclusion, we have accomplished a route to a new tricyclic carbon scaffold. As key steps, ring expansion and pinacol coupling were used to build up these rings. Four of the seven stereogenic centers of schiglautone A (**1**) were installed in the desired configuration, and one secondary alcohol requires inversion at the end of the synthesis. This core structure of schiglautone A (**1**) was synthesized in a linear sequence of 16 steps and 7.7% overall yield from building block **11**. Further experiments to complete the total synthesis are currently under investigation.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00288.

X-ray data for **16** (CIF)
Experimental procedures and spectral data of compounds described herein (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: markus.kalesse@oci.uni-hannover.de.

### ORCID

Markus Kalesse: 0000-0003-4858-3957


### Notes

The authors declare no competing financial interest.

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