Abstract

Total synthesis of Cruentaren A and Analogues

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Development of new Molybdenum-Nitride-Catalysts for Alkyne Metathesis

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The very potent myxobacterium metabolite cruentaren A (**10**) was the target of this total synthesis. A combination of ring-closing alkyne metathesis (RCAM) and Lindlar reduction was chosen for the construction of the *Z*-configured double bond embedded in the 12-membered benzolactone moiety of **10**. This methodology allows the compound to be divided up into building blocks of similar size and complexity.

The total synthesis of **10** commenced with the acylation of the known fragment **52** and Weinreb amide **58** to furnish ketone **59**. The CBS methodology developed by Corey was used to reduce ketone **59** to the corresponding secondary alcohol, which was then protected as a robust *tert*-butyldiphenylsilyl (TBDPS) ether. Concomitant cleavage of the trimethylsilylethyl group with TASF furnished the desired acid **66**. The preparation of alcohol **95** started with an asymmetric alkylation/Evans-aldol strategy, which gave after some routines operations, exclusively the *Z*-configured aldehyde **82** in an efficient manner. The final stereogenic centre was generated by using the chiral borane (*S*)-**87** recently developed by Soderquist. The desired propargylic alcohol **91** was obtained in good yield and with excellent diastereocontrol. Finally, conversion of **91** to the corresponding triethylsilyl ether, methylation of the terminal alkyne and selective cleavage of the TES group with HF-pyridine buffered in pyridine delivered subunit **95**.

After considerable experimentation, trying a wide range of activating agents commonly used in peptide coupling, esterification could only be achieved with *acid fluoride* **102** which reacted with alcohol **95** to ester **103** in very good yield. Ring-closing alkyne metathesis using the molybdenum-based complex **106** followed by Lindlar reduction delivered the desired *Z*-configured double bond of cycloalkene **107**. Deprotection of the THP group, formation of the corresponding azide and Staudinger reaction furnished amine **110** as a precursor for the peptide coupling with acid **115**. Regioselective cleavage of the methyl ether was carried out with boron trichloride. Removal of all silyl groups failed when applying standard fluoride sources like TBAF, TASF or HF/pyridine because of the stable TBDPS group and the translactonization tendency of the 9-OH functionality. Fortunately, this problem could be solved with aqueous HF ($pK_a \approx 3.14$), which gave cruentaren A (**10**) in 7% overall yield. The described synthesis blueprint provided a library of analogues with structural and configurational changes that are otherwise inaccessible.

Development of new Molybdenum-Nitride-Catalysts for Alkyne Metathesis

The molybdenum nitride complex $[(Me_3SiO)_2((Me_3Si)_2N)Mo{\equiv}N]$ (**166**), which can be conveniently prepared from commercial available and inexpensive sodium molybdate (**164**), in combination with Ph_3SiOH (**186**) exhibit excellent catalytic activity in alkyne metathesis reactions. This new system is compatible with a wide range of functional groups, including esters, alkenes, carbamates, THP acetals, silyl ethers, ketones, thiophenes, thiazoles, thiazolidinones, nitro groups, ethers and even thioethers and protected propargyl alcohols are accepted as substrates. It has been applied for the synthesis of key intermediates of potent bioactive natural products such as homoepilachnene, epothilone A, cruentaren A and a synthetic latrunculin B analogue. In addition, **166** reacts with aldehydes to give the corresponding nitrile derivates.