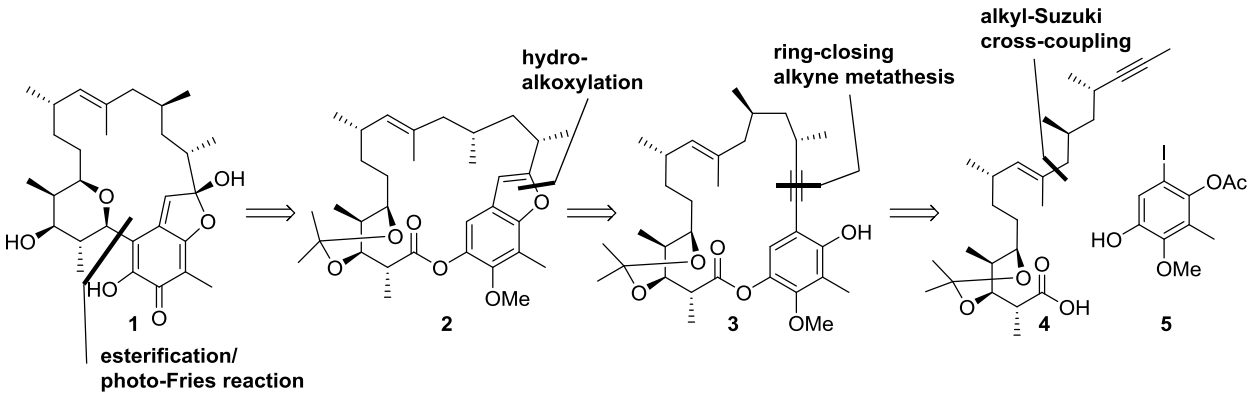
Summary

Formal Total Synthesis of Kendomyicn via Ring-Closing Alkyne Metathesis

Kendomycin **1** [(**–**)-TAN 2162] occurs as a metabolite of the species *Streptomyces violaceoruber.* The multifarious biological profile of this compound comprises activity as endetholin receptor agonist, exeptional antiosteoporotic and antibiotic properties and a remarkable cytotoxicity. The polyketidic 18-membered macrocycle exhibits a *para*-quinone methide core and a highly substituted tetrahydropyran. The versatile pharmacological activity and the unique structural features have prompted several research groups to pursue a synthesis of kendomycin **1**.



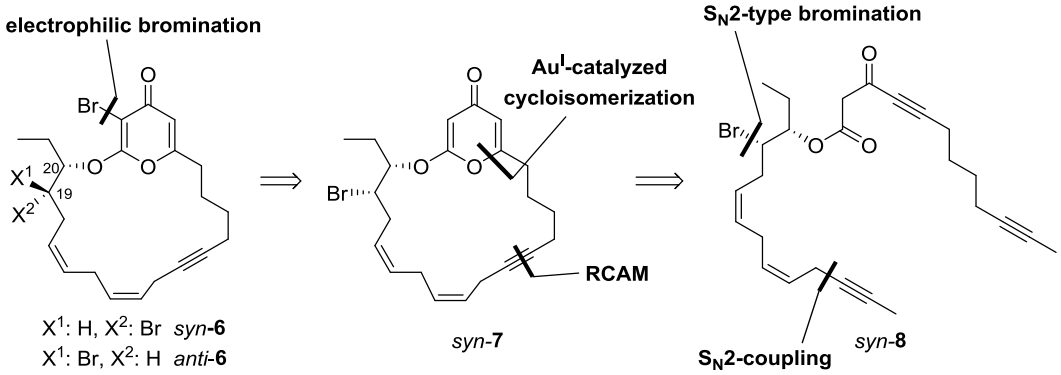
Scheme 1: Retrosynthetic analysis of kendomycin **1**.

A ring-closing alkyne metathesis (RCAM) and a subsequent postmetathetic transformation of the cycloalkyne to the benzofuran by π-acid catalyzed hydroalkoxylation were designed to be the key steps of our total synthesis.

The required polyketide fragment **4** (12 steps) was constructed by an alkyl-Suzuki cross-coupling of a vinyl iodide and an alkyl iodide. The resulting fragment was esterified with phenol **5** (3 steps) before the second alkyne was introduced by another variant of the Suzuki-Miyaura coupling to yield the RCAM precursor. Ring-closure of the obtained diyne was achieved under mild conditions using a molybdenum alkylidyne catalyst. After deprotection of the phenol group, the heterocycle was quickly formed in the presence of catalytic amounts of an electrophilic gold-catalyst, whereas it could not be assembled by simple platinum(II)- oder gold(I/III) chlorides. Furthermore, a ring-contraction by photo-Fries rearrangement gave the desired hexasubstituted cyclophane. Finally, the natural product was obtained after the remaining redox and protecting group manipulations had been carried out according to a literature precedent.

Total Synthesis of a Polyunsaturated, Marine 4-Pyrone Derivative

In the further course of this PhD thesis, the marine 4-pyrone derivative **6** from the red alga of the species *Phacelocarpus labillardieri* was selected for a total synthesis. This compound displayed an impressive inhibitory activity of the phospholipase A_2 in preliminary biological tests (IC_{50} < 4,4 μM).



Scheme 2: Retrosynthetic strategy for the marine natural product **6**.

The polyunsaturated metabolite **6** is a representative of a family of compounds that exhibit a dibrominated, keteneacetal-comprising macrocycle as an extraordinary structural feature. The unknown relative configuration of **6** was to be elucidated by the total syntheses and comparison of the two possible diastereomers *syn*-**6** and *anti*-**6**.

The key transformation of the synthesis was a π-acid catalyzed cycloisomerization of a corresponding β-ketoester to the 4-pyrone and a RCAM to construct the cycloalkyne. At first, the required alcohol fragment (8 steps) was brominated at C19 with inversion of configuration, deprotected and esterified with the corresponding β-ketoacid (6 steps). The formation of the 4-pyrone and the subsequent macrocyclization by RCAM proceeded very efficiently. At last, the second bromine atom on the 4-pyrone was installed under electrophilic bromination conditions. However, the desired bromination competed significantly with the *cis*/*trans* isomerization of the (*Z*)-olefins. Starting from a late-stage intermediate of the alcohol fragment, the diastereomeric compound *anti*-**6** was prepared by twofold inversion of the stereogenic center at C19. By comparison of the NMR data of *syn*- and *anti*-**6** to the data of the natural product, the relative configuration of the substituents at C19 and C20 was determined to be *syn*. Thus, the relative stereochemistry of the natural product **6** was elucidated.