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Six-Step Synthesis of Alcyopterosin A, a Bioactive Illudalane Sesquiterpene with a *gem*-Dimethylcyclopentane Ring

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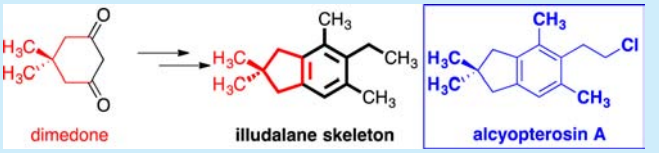
Supporting Information

ABSTRACT: Strategic pairing of ring openings and cycloisomerization provides rapid and efficient "open and shut" entry into sparsely functionalized illudalanes, as exemplified here in the context of a six-step synthesis of alcyopterosin A. Key steps include a tandem ring-opening fragmentation/olefination process for preparing a neopentyl-tethered 1,6-enyne, ring-opening olefination telescoped with alkyne homologation, and Rh-catalyzed oxidative cycloisomerization.



The alcyopterosins are a family of illudalane sesquiterpene natural products isolated from *Alcyonium paessleri*[1] and *Alcyonium grandis*,[2] soft coral species found in frigid waters off the coast of Antarctica. *Alcyonium* soft corals reportedly produce the alcyopterosins as antifeedants, to deter predation by the sea star *Odontaster validus* and other predators.[3] Alcyopterosin A (Figure 1) is cytotoxic at 10 μg/mL to HT-29 cells (human colon carcinoma),[1] and it binds DNA with "excellent" affinity.[4] Such bioactivity is impressive when balanced against its low molecular weight and relative dearth of functional groups. Considering its limited chemical functionality, the bioactivity of alcyopterosin A may be a function of hydrophobic interactions with a sterically complementary binding site or sites. Therefore, the illudalane topology may be worth incorporating into drug fragment screening libraries.[5] However, the particular three-dimensional steric contours of this system include a *gem*-dimethylcyclopentane ring, which has been a nontrivial structural motif to incorporate using modern organic reactions.

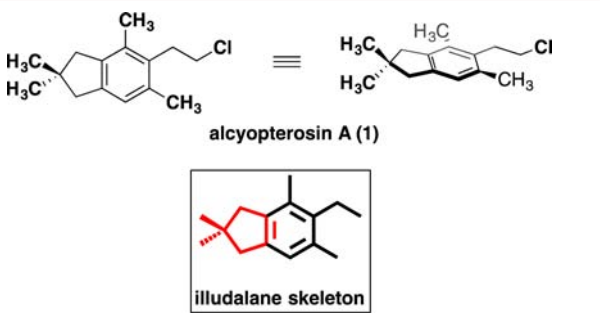


Figure 1. (Top) Alcyopterosin A, including perspective side view to illustrate topology. (Bottom) Illudalane sesquiterpene skeleton.

We aim to develop and advance new strategies for preparing *gem*-dimethylcyclopentanes, which are ubiquitous in Nature but largely absent from synthetic pharmaceutical screening libraries. The objective of the present study is to develop a concise and efficient synthesis of alcyopterosin A, by taking advantage of (1) our recent methodology for preparing neopentyl-tethered 1,6-enynes[6] and (2) extensive prior and emerging knowledge in the area of enyne cycloisomerization and annulation technologies.[7]

The two previous syntheses of alcyopterosin A reflect the challenges associated with the synthesis of *gem*-dimethylcyclopentanes (Figure 2, top). The first synthesis, in 2002,[8] took advantage of state-of-the-art alkyne cyclotrimerization methodology,[9] but it required production of neopentyl-tethered diyne **2** in eight steps (undisclosed yield) from isophorone. The second synthesis features classic aromatic substitution chemistry centered around bromo-indanone **3**,[4] the ketone and bromine of which provide tactical advantages but must be removed in the latter stages of the synthesis. The challenges posed by crafting a synthetic *gem*-dimethyl-cyclopentane are further underscored by noting that other, more highly

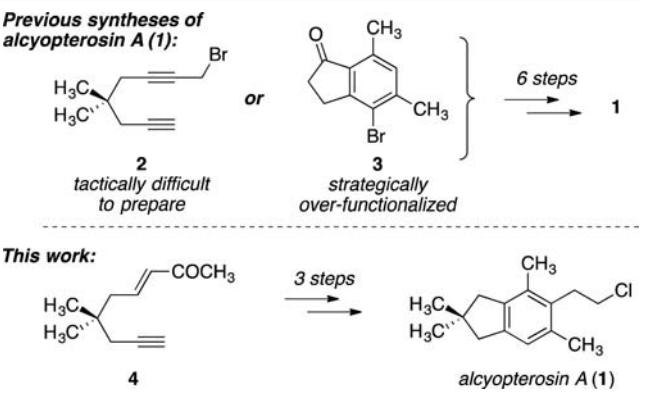


Figure 2. (Top) Previous syntheses of alcyopterosin A reflect the challenges of installing the *gem*-dimethylcyclopentane. (Bottom) Overview of the synthesis reported herein.

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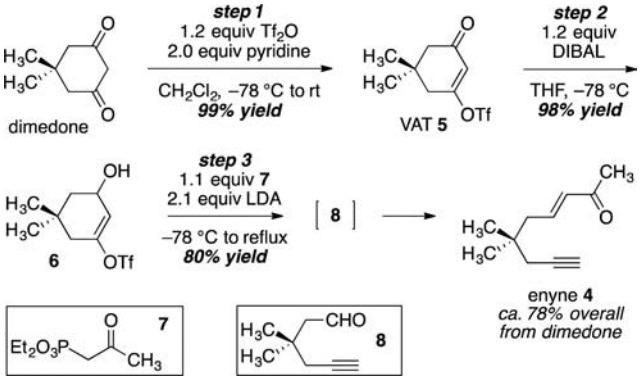
functionalized alcyopterosins can be prepared more efficiently than alcyopterosin A in terms of step count and overall yield.[10]

Here we describe a synthesis of alcyopterosin A in three steps (58% overall yield) from neopentyl-tethered 1,6-enyne **4** (Figure 2, bottom)[6] which itself is available in nearly 80% yield over three steps from commercially available dimedone (*vide infra*). The key steps include a tandem fragmentation/olefination to deliver enyne **4** and, later, a Rh-catalyzed cycloisomerization with *in situ* oxidation to complete the synthesis. This concise and efficient synthesis of alcyopterosin A exemplifies how neopentyl-tethered 1,6-enynes can bridge the gap between enyne cycloisomerization methodologies and the target-oriented synthesis of *gem*-dimethylcyclopentane-containing goal structures.

The synthesis of alcyopterosin A commenced with the condensation of dimedone with trifluoromethanesulfonic anhydride (Tf_2O) to produce vinylogous acyl triflate (VAT) **5** in high yield (Scheme 1). We have been studying the

Scheme 1. Three-Step Synthesis of Enyne 4 from Dimedone, Featuring the Tandem Fragmentation/Olefination (6 → 4) of Triflate 6

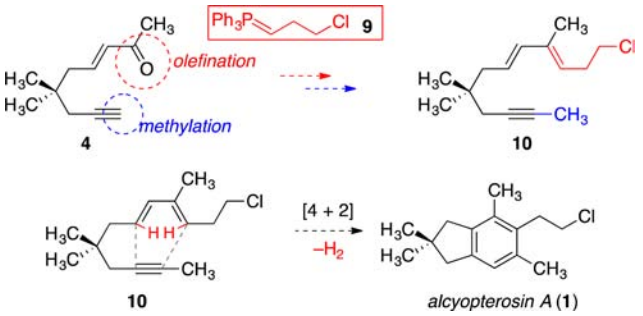


synthesis and reactivity of cyclic vinylogous acyl triflates (VATs),[11] including **5**. Nucleophilic addition to cyclic VATs in many cases triggers ring-opening fragmentation, which can result in the synthesis of alkynes tethered to ketones,[12] alcohols,[13] amides,[14] β-keto esters,[15] etc.[16] However, reaction of VAT **5** with diisobutylaluminum hydride (DIBAL) results in 1,2-reduction of the carbonyl *without* fragmentation to produce alcohol **6**,[6,17] which remains poised for fragmentation.

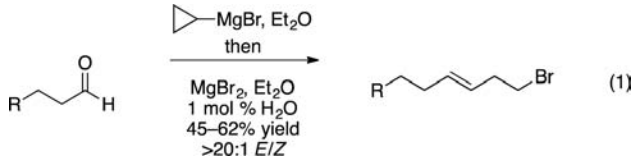
Tandem base-mediated fragmentation/olefination of **6** with β-keto phosphonate **7** can produce neopentyl-tethered enyne **4** in 80% yield (Scheme 1). Base-mediated fragmentation of triflate **6** produces alkyne-tethered aldehyde **8**, but this aldehyde is subject to base-catalyzed condensation processes and cannot be isolated in synthetically reasonable yields. On the other hand, **8** can be trapped *in situ* with external nucleophiles, as we reported previously for Grignard reagents[17] and for lithiated phosphonates (i.e., Horner–Wadsworth–Emmons reagents).[6] Thus, we have prepared enyne **4** in three steps and nearly 80% overall yield from commercially available dimedone, an improvement over our previous report.[6]

Our synthetic approach to alcyopterosin A capitalizes on neopentyl-tethered 1,6-enyne **4** as laid out in Scheme 2. Both ends of enyne **4** must be elongated to set up the final oxidative cycloisomerization reaction. Base-mediated methylation was envisioned for the alkyne terminus. For converting the ketone terminus into the desired homoallyl chloride (cf. **10**), we first

Scheme 2. Hypothesized Synthetic Approach to Alcyopterosin A from Neopentyl-Tethered Enyne 4, including Two Chain Extensions (Top) and Proposed Oxidative Cycloisomerization (Bottom)

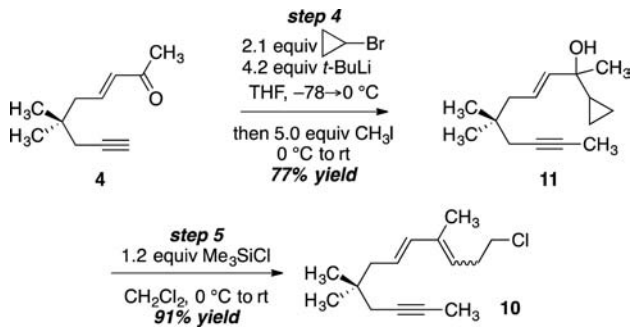


considered the possibility of a one-step Wittig-type olefination using a triphenylphosphine-based reagent exemplified by **9** (Scheme 2, inset box). However, Wittig olefination was tactically unappealing to us, in part because the molecular weight of the usual byproduct (triphenylphosphine oxide, 278.29 g/mol) exceeds that of our desired product (dienyne **10**, 238.80 g/mol).We have previously made use of various two-step olefination protocols[18,19] as alternatives to traditional stoichiometric phosphorus-mediated olefination. For example, a two-step (one-pot) conversion of an aldehyde into a homoallylic bromide outlined in eq 1 was a key sequence in our recent synthesis of progesterone,[19a] and we envisioned an analogous tactic for olefination of **4**.



The double elongation of enyne **4** (methylation of the terminal alkyne and olefination of the ketone) was accomplished in parallel by a two-step protocol (Scheme 3). In the

Scheme 3. Double Chain-Extension of Enyne 4



first step, cyclopropyllithium serves both as a nucleophile, for 1,2-addition to the ketone carbonyl, and as a base, for metalation of the terminal alkyne: enyne **4** was added to a roughly 2-fold excess of cyclopropyllithium (generated *in situ* by bromine–lithium exchange). After a warming period, the resulting solution was treated with excess iodomethane to methylate the (presumed) lithium acetylide, leading to homologated enyne **11**.[20] The second step takes advantage of cyclopropane ring strain to complete the olefination: treatment

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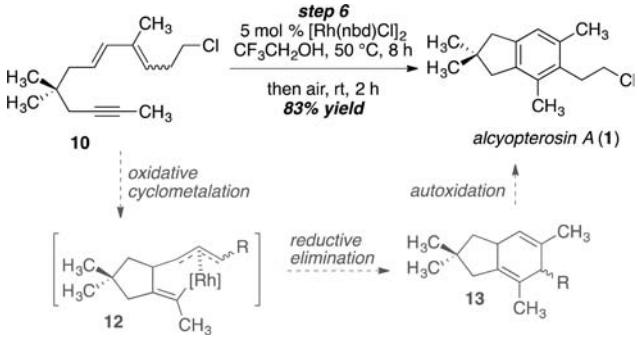
of tertiary, allylic cyclopropyl-carbinol **11** with trimethylsilyl chloride results in an S_N1-type substitution reaction coupled with cyclopropyl → homoallyl rearrangement to produce homoallyl chloride **10** chemoselectively as an inconsequential mixture of olefin stereoisomers.

A formal intramolecular Diels–Alder (IMDA) cycloaddition was envisioned for generating the illudalane bicyclic skeleton (cf. Scheme 2, top), with a net loss of hydrogen being required to complete the process and deliver alcyopterosin A. Rhodium redox catalysis proved to be competent to these ends.[21] In our initial screening experiments, homoallyl chloride stereoisomers **10** gave way to mixtures of bicyclic structures upon heating in the presence of various rhodium(I) salts. These mixtures of bicyclic structures presumably comprised the two expected stereoisomeric dihydroindanes (**13**, Scheme 4) admixed with

Scheme 4. Oxidative Cycloisomerization of Dienyne 10 to Alcyopterosin A



various levels of alcyopterosin A from autoxidation. The autoxidation was ascribed to trace levels of oxygen in the reaction environment.[22] Indeed, subsequent bubbling of air through the reaction mixture converted these mixtures into a single product, alcyopterosin A.

Optimized conditions are outlined in Scheme 4. A solution of homoallyl chlorides **10** and a 2,5-norbornadiene–rhodium(I) chloride dimer in trifluoroethanol (TFE) was heated at 50 °C for 8 h under nitrogen, albeit without any special precautions taken to exclude oxygen. The system was allowed to cool to room temperature, after which time air was bubbled through the solution, which still contains rhodium salts, for 2 h to complete the process and produce alcyopterosin A.

In conclusion, the synthesis of alcyopterosin A has been achieved in six steps from dimedone (ca. 45% overall yield). This is the shortest and highest yielding synthesis of any illudalane sesquiterpene of which we are aware, which illustrates the utility of neopentyl-tethered 1,6-enynes as building blocks for synthesis of important goal structures that contain the *gem*-dimethyl-cyclopentane structural motif. This relatively concise and efficient synthesis more broadly highlights the strategic pairing[23] of fragmentation[24] and cycloisomerization[7] processes for preparing challenging ring systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01665.

Experimental procedures, characterization data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ISSUE PUBLICATION

Author Nicholas J. Kramer's middle initial was corrected on August 30, 2016. An Addition and Correction is published in volume 18, issue 18.

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