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Application of Tandem Ring-Closing Enyne Metathesis: Formal Total Synthesis of (−)-Cochleamycin A

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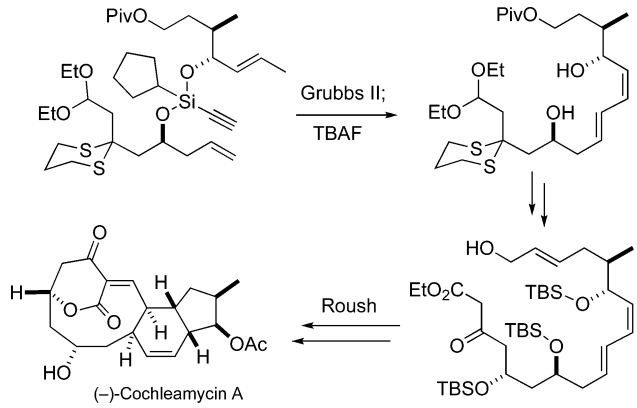
ABSTRACT



A tandem ring-closing metathesis of a silaketal-based dienyne substrate proceeded efficiently to provide a bicyclic siloxane, which upon removal of the silicon tether afforded an (*E*,*Z*)-1,3-dienediol. Further manipulation of this key functional motif rendered synthesis of the entire C1−C19 linear skeleton of (−)-cochleamycin A, a late-stage intermediate employed in the previous total synthesis of (+)-cochleamycin A by Roush and co-workers.

Cochleamycin A was isolated in 1992 by a team headed by Shindo and Kawai during a screening program for antitumor antibiotics from a cultured broth of *Streptomyces* DT136.[1] Subsequently, they reported significant antimicrobial activity against Gram-positive bacteria and cytotoxicity against P388 leukemia cells (IC_{50} = 1.6 μg/mL) for cochleamycin A.[2] The relative stereochemistry and the 5,6-fused and 10,6-bridged tetracyclic core were later revealed by them from exhaustive NMR studies.[3] Not surprisingly, the combination of architectural complexity and favorable biological activity led to a number of impressive initital synthetic studies,[4] finally resulting in the first total synthesis and establishment of the absolute configuration of naturally occurring (+)-cochleamycin A by Tatsuta and co-workers.[5] Soon after, Roush and Dineen also reported their total synthesis of (+)-cochleamycin A.[6] These synthetic studies were based on the proposed biosynthetic pathway of cochleamycins involving a putative transannular Diels−Alder reaction of (*E*,*Z*,*E*)-1,6,8-nonatrienes to construct the cochleamycin A skeleton.[7]

We envisioned that the prowess of enyne metathesis[8] to form 1,3-dienes can be implemented in the synthesis of

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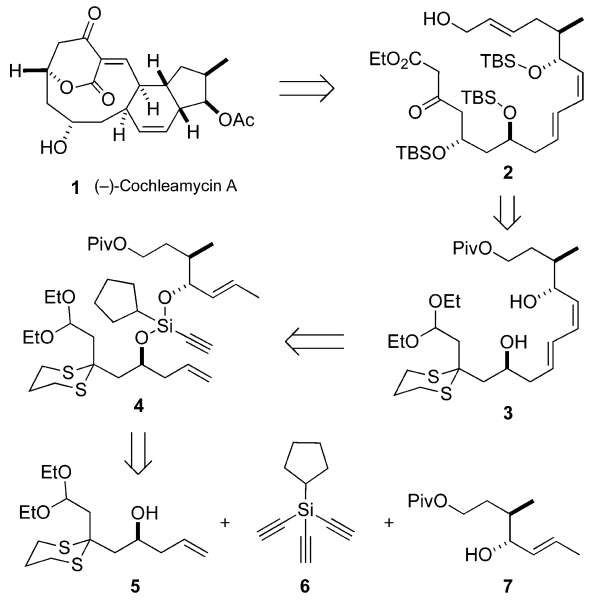
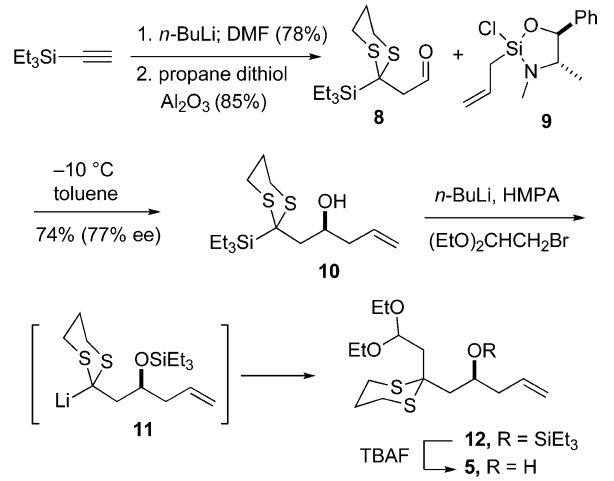
cochleamycin A if we can effectively control the *E*/*Z* stereochemistry of 1,3-diene. Previously, we reported on a tandem dienyne ring-closing metathesis (RCM) of alkynyl silaketals to generate bicyclic siloxanes[9] in the presence of Grubbs NHC−ruthenium catalyst.[10] Removal of the silicon tether through protodesilylation allowed for the generation of stereochemically defined 1,4-substituted (*E*,*Z*)-1,3-dienes. The group selectivity (ring closure from right to left vs that from left to right) in tandem RCM to obtain only the desired regioisomer would be achieved by differential substitution on the alkene as demonstrated in the construction of the carbon framework of tatrolon B.[11] Herein, we report a formal total synthesis of (−)-cochleamycin A by intercepting the Roush advanced synthetic intermediate.

Scheme 1. Retrosynthetic Analysis for (−)-Cochleamycin A



As shown in the retrosynthetic analysis in Scheme 1, *β*-keto ester **2**, an advanced intermediate employed in the Roush total synthesis of (+)-cochleamycin A,[6] would be derived from dienediol precursor **3**. The tandem RCM[12] of silaketal **4** followed by desilylation would deliver dienediol **3**. Silaketal **4** could be obtained from the base-catalyzed stepwise alcoholysis of cyclopentyltrialkynylsilane **6** with alcohols **5** and **7**. The key intermediate **5** was prepared by utilizing the anion relay chemistry developed by Smith and co-workers.[13] A general route to a precursor of **5** was developed starting with the formylation of the lithium (triethylsilyl)acetylide,[14] which afforded the known 3-triethylsilylpropynal[15] in 78% yield (Scheme 2). This aldehyde

Scheme 2



was then subjected to double Michael addition of 1,3-propanedithiol in the presence of basic alumina to give dithiane aldehyde **8** in 85% yield.[16] Asymmetric allylation utilizing the pseudoephedrine-derived strained silacycle **9** developed by Leighton and co-workers afforded homoallylic alcohol **10** in 74% yield and 77% enantiomeric excess (ee).[17] Many other conventional aymmetric allylation protocols including Brown's allylation,[18] Roush allylation,[19] Keck

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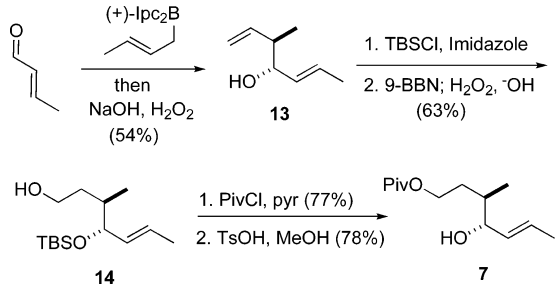
allylation,[20] or Loh's indium mediated allylation[21] failed to provide acceptable yields or enatiomeric excess. We suppose this should be caused by possible chelation of the dithiane moiety to the allylating agents disabling the complexation of the aldehyde. The lithium alkoxide generated from alcohol **10** with butyllithium induced a solvent (HMPA)-controlled 1,4-Brook rearrangement to provide intermediate dithiane anion **11**, which was reacted with the diethyl acetal bromoacetaldehyde to afford triethylsilyl ether **12**.[13] Removal of the silyl group with TBAF afforded alcohol **5** in 64% yield over two steps.

The synthesis of another key building block **7** began with the asymmetric (*E*)-crotylboration[22] of *trans*-crotonaldehyde, providing known allyl alcohol **13**[23] in 54% yield with 15:1 *anti*/*syn* selectivity and 95% ee (Scheme 3). TBS-protection

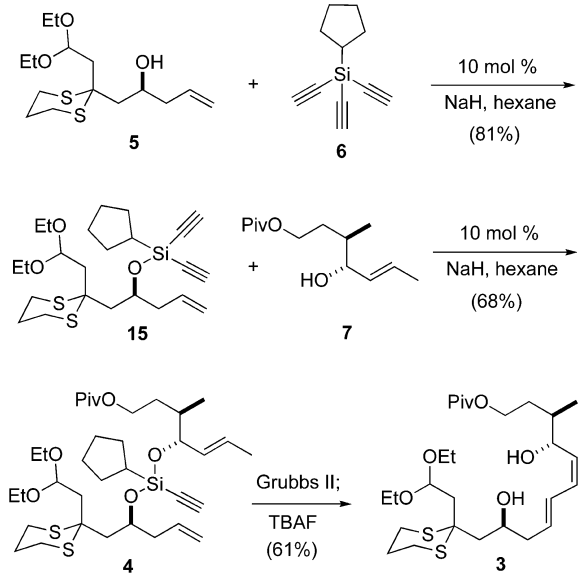
Scheme 3



of the hydroxyl group and regioselective hydroboration−oxidation gave the silyl ether **14** in 63% yield over two steps. Pivalation of the resulting primary hydroxyl group proceeded in 77% yield. This was followed by cleavage of the TBS ether to furnish alcohol **7** in 78% yield.

With all the required building blocks for silaketal **4** in hand, we first silylated alcohol **5** with trialkynylsilane **6**

Scheme 4



in the presence of a catalytic amount (10 mol %) of NaH in hexanes,[24] affording silyl ether **15** in 81% yield (Scheme 4). The reaction proceeded to completion in 15−20 min at room temperature with 1 equiv of **6**, and formation of the symmetrical silaketal was not observed. Subsequent coupling of silyl ether **15** with alcohol **7** required higher reaction temperature (60 °C, toluene) to provide the desired silaketal **4** in 68% yield as a mixture of diastereomers originating from the newly created stereocenter at the silicon. Formation of a symmetrical silaketal by double addition of **7** was also observed, which could not be suppressed even with 1.5 equiv of **15**. Silaketal **4** was designed such that the ring closure can occur in a group-selective manner[25] by initiaing the RCM at the most accessible terminal alkene. Treatment of the bicyclic siloxane RCM product with TBAF in THF under reflux provided dienediol **3** in 61% yield over two steps. Varying amounts of a prematurely terminated monocyclic siloxane, obtained via an RCM from the monosubstituted olefin, was also isolated from the RCM−desilylation reaction sequence. Longer reaction times or higher loading of catalyst did not reduce the formation of this monocylic siloxane.

With dienediol **3** in hand, we proceeded to the synthesis of β-keto ester **2** as shown in Scheme 5. Removal of the dithane using an excess amount of iodomethane in aqueous acetone at 60−65 °C provided ketone **16** in 79% yield.[26] The diastereoselective carbonyl reduction of **16**, according to Paterson's procedure,[27] gave *syn*-1,3-diol **17** in 76% yield, which was then converted to tri-TBS ether **18** in 73% yield. Reduction of the pivaloate in **18** with DIBAL-H gave alcohol **19** in quantitative yield. Oxidation of primary alcohol **19** by using the Parikh−Doering protocol[28] gave the corresponding aldehyde, which was subjected to Horner−Wadsworth−Emmons olefination[29] to give ester **20** in 90% yield for the two steps. Again, reduction of ester **20** with DIBAL-H in 85% yield followed by carbonate protection of the resulting allylic alcohol **21** afforded carbonate **22** in 96% yield. Removal of the acetal group with *p*-TsOH in acetone gave the corresponding aldehyde, which was converted to the β-keto ester **23** (79% over two steps) by subjecting it to ethyl diazoacetate in the presence of catalytic amount (10 mol %) of $SnCl_2$ according to Roskamp's procedure.[30] Finally, we attempted to remove the carbonate group in the presence of 2% K_2CO_3 in methanol to obtain the Roush intermediate **2**. However, methyl β-keto ester **24** was isolated in 82% yield instead of the corresponding ethyl ester **2**, due to a concomitant transesterification. The subtle difference between ethyl and methyl β-keto esters **2** and **24** is inconsequential for the remaining transformations toward a total synthesis

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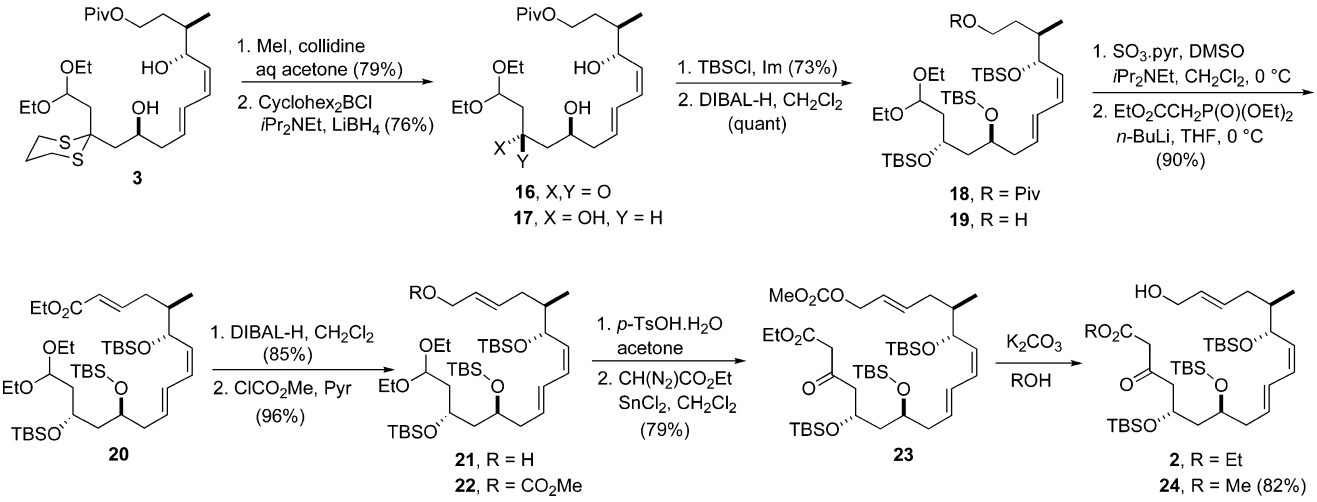
Scheme 5. Elaboration of Intermediates and the Completion of a Formal Total Synthesis of (−)-Cochleamycin A



of cochleamycin A. Nevertheless, we decided to synthesize ethyl ester **2** to directly compare its spectroscopic data to that reported by Roush. The carbonate deprotection was attempted again using K_2CO_3 in ethanol. The reaction was much slower than in methanol and thus required longer reaction time or higher temperature. This led to significant decomposition as evident from the ^{1}H NMR of the isolated crude products. Other stronger bases such as sodium ethoxide reduced the overall reaction time, but increased amounts of unidentified byproducts were generated. Trimethyltin hydroxide mediated hydrolysis of methyl ester according to Nicolaou's procedure[31] resulted in deesterification−decarboxylation of the β-keto ester moiety. However, ethyl ester **2** could be isolated in fairly high purity (~90%) by stopping the reaction at low conversion (30−40%) of **24** with K_2CO_3 in ethanol. The ^{1}H and ^{13}C NMR and optical rotation of **2** were in good agreement with that reported by Roush, except for the opposite sign in optical rotation.[6]

In conclusion, we have achieved a formal total synthesis of (−)-cochleamycin A. The key feature of the synthesis is to form a silaketal from two alkenyl alcohols and trialkynyl silane followed by tandem enyne RCM to establish the (*E*,*Z*)-1,3-diene moiety required for a Diels−Alder reaction. Further development and application of this silaketal-based enyne RCM will be reported in due course.

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Supporting Information Available: General procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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