Communication

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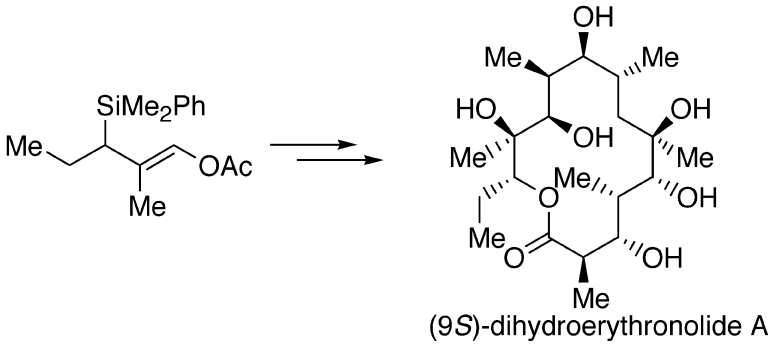
J. Am. Chem. Soc., **2003**, 125 (20), 6018-6019• DOI: 10.1021/ja034865z • Publication Date (Web): 25 April 2003



(9*S*)-dihydroerythronolide A

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[3 + 2] Annulation of Allylic Silanes in Acyclic Stereocontrol: Total Synthesis of (9*S*)-Dihydroerythronolide A

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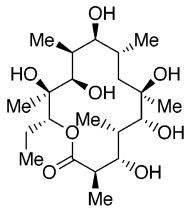
The [3 + 2] annulation reactions of allylic silanes are powerful methods for the stereoselective preparation of cyclopentanes and five-membered ring heterocycles.[1] These reactions have been used as key transformations for the syntheses of five-membered ring-containing natural products.[2,3] While evidently useful for the formation of cyclic compounds, these annulation reactions are not obviously suited for the synthesis of acyclic compounds.[4] In this communication, we demonstrate that annulation reactions of allylic silanes can be used in acyclic stereocontrol. We use this method as a key step in an enantioselective total synthesis of (9*S*)-dihydroerythronolide A (**1**), a molecule that has stimulated the development of a host of new reactions and concepts for C−C bond construction.[5,6]



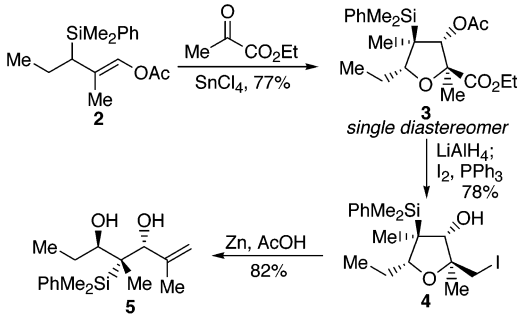
1
(9*S*)-dihydroerythronolide A

To demonstrate the transfer of the stereochemical information introduced by the annulation reaction to an acyclic system, we performed a ring-opening reaction of the highly substituted tetrahydrofuran **3**. This heterocycle was obtained as a single diastereomer from the annulation reaction of allylic silane **2** with ethyl pyruvate (Scheme 1).[2b] Conversion of the carboethoxy group in **3** to the iodomethyl group followed by elimination formed the highly functionalized acyclic intermediate **5**.

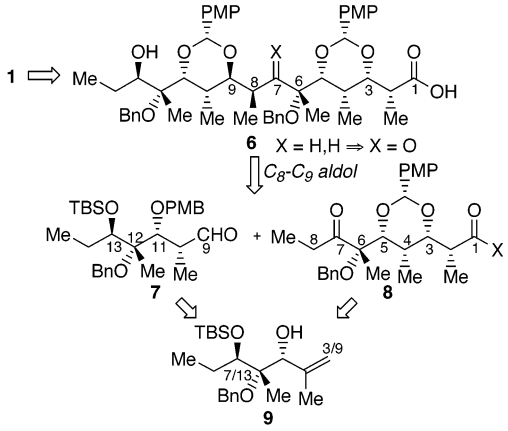
If the tertiary silyl group, which was established during the annulation reaction, is considered as a tertiary hydroxyl group,[7] the synthetic utility of **5** becomes immediately apparent. This silane represents a motif that can be found twice in the natural product (9*S*)-dihydroerythronolide A (**1**). Disconnection of the seco acid **6** by an aldol reaction between the C8−C9 bond gives two similarly sized fragments **7** and **8** (Scheme 2).[8] These two fragments could be prepared from alkene **9**, which closely resembles silane **5**.

While the synthetic plan outlined in Scheme 2 was appealing in principle, the success of the aldol disconnection about the C8−C9 bond was not assured. Although the requisite stereochemistry of the aldol adduct can be anticipated from an α-chelation-controlled aldol reaction of the (*Z*)-enolate of α-benzyloxy ethyl ketone **8**, only a few examples of this transformation were reported with simple α-oxygenated ethyl ketones.[9] Model studies with analogous substituted aldol partners suggested, however, that the key aldol reaction of **7** and **8** would proceed according to plan. Addition of the tin(II) enolate of the model ethyl ketone **10** to the model chiral aldehyde **11** proceeded with high diastereoselectivity, favoring the

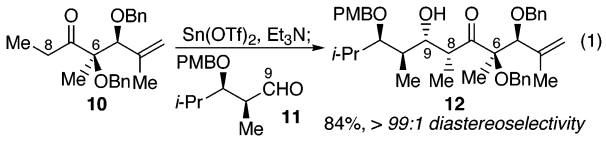
Scheme 1



Scheme 2



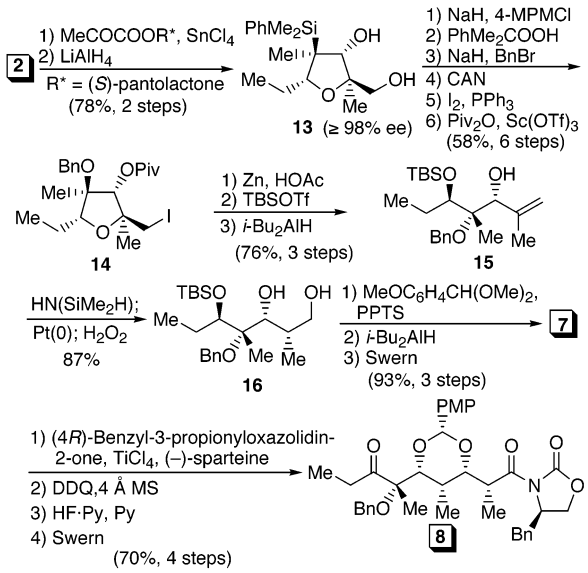
product possessing the relative configuration required to complete the synthesis (eq 1).[10,11]



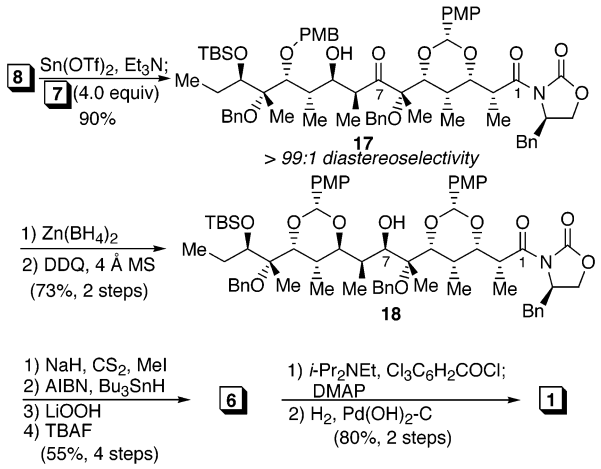
Encouraged by the result on the model aldol reaction, we began the total synthesis of (9*S*)-dihydroerythronolide A by assembling the aldol coupling partners **7** and **8** (Scheme 3). The annulation reaction of the racemic allylic silane **2** with (*S*)-pantolactone pyruvate ester followed by reduction afforded the chiral diol **13** with an ee greater than 98% (Scheme 3).[2b] The same diol **13** could also be obtained with comparable enantiomeric purity from the resolved chiral allylic silane (−)-**2** using (*R*)-pantolactone pyruvate ester.[2b] The derived iodide **14** underwent a ring-opening reaction to afford the key acyclic intermediate **15** after protecting group manipulations. Intramolecular hydrosilylation of allylic alcohol **15** followed by Tamao oxidation provided the desired diol **16** as a single diastereomer.[12] The C9−C15 fragment **7** was obtained from diol **16** in three steps. Condensation of **7** with the titanium enolate

10.1021/ja034865z CCC: $25.00

Scheme 3



Scheme 4



of (*R*)-4-benzyl-3-propionyloxazolidin-2-one afforded the desired aldol adduct as a single diastereomer.[13,14] Protection of the hydroxyl group by an anhydrous DDQ oxidation yielded a 4-methoxybenzylidene acetal, which could be converted to the C1−C8 fragment **8**.

With the two fragments in hand, efforts were focused on the key aldol coupling reaction. In accordance with the model system (eq 1), the aldol reaction of **7** and **8** gave the desired product **17** as a single diastereomer in 90% yield (Scheme 4). Although an excess of the aldehyde **7** (4.0 equiv) was used to consume all the ketone **8**, unreacted aldehyde was easily recovered without epimerization. The C7 oxygen atom was removed by a directed reduction[15] and protection of the C9 hydroxyl group followed by deoxygenation.[6c,16] Unmasking of the carboxylic acid and removal of the silyl group provided the seco-acid **6**. Macrolactonization[17] followed by global deprotection afforded (9*S*)-dihydroerythronolide A (**1**), whose subsequent conversion into erythronolide A and erythromycin A is known.[18,19]

This work demonstrates that the [3 + 2] annulation of allylic silanes can be a powerful method for the synthesis of highly substituted acyclic targets. Using this methodology, a convergent total synthesis of (9*S*)-dihydroerythronolide A has been accomplished with the longest linear sequence of 29 steps and in 5.4% overall yield.

Acknowledgment. This research was supported by a CAREER Award from the National Science Foundation (CHE-9701622). K.A.W. thanks the Camille and Henry Dreyfus Foundation, Johnson & Johnson, and Merck Research Laboratories for awards to support research. We thank Dr. John Greaves and Dr. John Mudd for mass spectrometric data. We thank Professor Kazunobu Toshima (Keio University, Japan) for providing a ^{1}H NMR spectrum of (9*S*)-dihydroerythronolide A for comparison.

Supporting Information Available: Full experimental and analytical data for all new compounds; the chiral HPLC traces of (±)-**13**, (−)-**13**, and (+)-**13**; and ^{1}H and ^{13}C NMR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA034865Z