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Total Synthesis of the Hsp90 Inhibitor Geldanamycin

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Abstract

An enantioselective synthesis of the Hsp90 inhibitor geldanamycin was achieved in 20 linear steps and 2.0% overall yield from 2-methoxyhydroquinone. The synthesis is highlighted by a regio- and stereoselective hydroboration reaction; a $Sc(OTf)_3/Et_3SiH$-mediated pyran ring-opening reaction; an enantioselective crotylation to simultaneously install the C8–C9 (*E*)-trisubstituted olefin, the C10 and C11 stereocenters; a chelation-controlled asymmetric metallated acetylide addition; and an intramolecular copper(I)-mediated aryl amidation reaction to close the 19-membered macrolactam.

Heat shock protein 90 (Hsp90) is a molecular chaperone that regulates folding, transport, and degradation of client proteins. It also plays a key role in the conformational maturation of oncogenic signaling proteins.[1] Hsp90 ATPase binding region's role in cancer and protein maintenance as well as its broad range of functions make it a significant therapeutic target for anticancer drug development.[1d,e]

Geldanamycin, a natural product isolated from *Streptomyces hygroscopicus* var. *geldanus* var. *nova* in 1970,[2] is the first reported Hsp90 inhibitor. It is currently under development as a therapeutic agent for cancers associated with abnormally elevated levels of receptor tyrosine kinase activity.[3a] Studies have shown that the Hsp90 client proteins can be destabilized when geldanamycin binds to the ATP-binding site of Hsp90 and inhibits the chaperone activity of the protein.[3] Accordingly, several geldanamycin analogues are in various stages of development as novel antitumor agents and as chemotherapeutic agents in a number of diseases.[4]

Geldanamycin, together with herbimycin A,[5] macbecin I,[6] and reblastatin,[7] are members of the ansamycin class of natural products (Figure 1). Geldanamycin differs at C6, C11, C15, and C17 from macbecin I and herbimycin A. Presently, one total synthesis of geldanamycin has been described.[8] Herein, we report the total synthesis of geldanamycin as part of our ongoing studies of ansamycins.

Our strategy for the synthesis of geldanamycin (**1**) is shown in Scheme 1. We envisioned the 19-membered macrocycle would be formed from the acylic amide **5** through an intramolecular aryl amidation reaction similar to that described in our synthesis of reblastatin.[7,9] The (*E*,*Z*)-diene could be installed by reduction of the enyne from alkynylation of precursors **6** and **7** which could be generated from easily accessible aldehyde **9** and chiral silane reagent **8**. Organosilane **8** has unique features as it establishes the C10–C11 syn stereochemistry while simultaneously creating the C8–C9 (*E*)-trisubstituted olefin.

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Supporting Information Available: Experimental details and selected spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Recently, we have reported the selective hydridic opening of aryl *C*-glycosides using a Sc(OTf)$_3$/Et$_3$SiH-mediated reduction of the benzylic C-O σ-bond resulting in the formation of a stereochemically well-defined acyclic system.[10]

The synthesis of the C6–C21 fragment **7** (Scheme 2) started from functionalized aromatic aldehyde **10**, which was easily obtained in three steps from commercially available 2-methoxyhydroquinone in 55% overall yield. [4 + 2]-Annulation of this aldehyde with silane **11** provided a mixture of dihydropyrans **12** and **13** in 84% yield (*trans*/*cis*: 4:1).[11] Regio- and stereoselective hydroboration of the pyran double bond provided the secondary alcohol, which was subsequently methylated with Meerwein's reagent to provide tetrahydropyran **14** in good yield and excellent selectivity (dr > 20:1). Reductive opening of pyran **14** with Sc(OTf)$_3$/Et$_3$SiH gave a mixture of **15** (which was easily converted to **16** in 95% yield) and **16** in excellent yield, essentially deoxygenating C15 (cf. macbecin). Reduction of ester **16** with $LiBH_4$ afforded the 1,2-diol, which was subjected to oxidative cleavage using sodium periodate to furnish the α-methoxyaldehyde **9**.

At this point, we turned toward the generation of the C7, C10, and C11 stereocenters and the installation of the trisubstituted alkene. Gratifyingly, after a variety of conditions were explored, a double-stereodifferentiating crotylation[12] of silane **8** and aldehyde **9** promoted by $BF_3{\cdot}OEt_2$ provided benzyloxy homoallylic ether bearing not only the three desired stereocenters and trisubstituted alkene, but also a benzylic ether protecting group at C11. The reaction proceeded in 70% yield with high selectivity (dr = 9:1). Reduction of the product methyl ester with DIBAL-H yielded aldehyde **7**.

To access (*E*,*Z*)-unsaturated macrocycle **19** through the intermediacy of bromo ester **17**, aldehyde **7** was homologated through diastereoselective addition[13] of a metallated acetylide (Scheme 3). Accordingly, fragment **17** was obtained through chelation-controlled coupling of acetylene **6** and aldehyde **7** in 76% yield (dr = 10:1).[14,15]

To complete the synthesis, methylation of propargylic alcohol **17** using NaH and MeI occurred with simultaneous dealkylation of the ester to the corresponding acid[16] and gave the enyne–acid **18** in 87% yield, which was subjected to Lindlar reduction.[17] The resulting acid was subsequently converted to the (*E*,*Z*)-unsaturated amide **5**. The amide **5** was then subjected to an intramolecular copper(I)-mediated aryl amidation reaction to provide the desired macrocyclic lactam in 81% yield. Deprotection of the MOM ether was achieved utilizing anhydrous HCl/Et$_2$O/MeOH to obtain the secondary alcohol in nearly quantitative yield without affecting other protecting groups. The secondary alcohol was then converted to the desired carbamate **19** in 88% yield.[7,18] Finally, deprotection of both the diisopropyl and benzyl ethers was accomplished with $AlCl_3$ in the presence of anisole[19] to generate dihydrogeldanamycin, which was immediately treated with catalytic palladium on carbon[20] (10%) under air atmosphere to give geldanamycin in 55% yield over two steps. The spectroscopic data obtained for synthetic material were in agreement with those for authentic geldanamycin (optical rotation, ^{1}H and ^{13}C NMR, IR, and HRMS).[21]

In summary, we achieved the total synthesis of geldanamycin in 20 linear steps and 2.0% overall yield from commercially available 2-methoxyhydroquinone. Notable features of our synthetic route include the following: a concise synthesis of the C11–C21 fragment through reductive pyran-opening approach; an efficient and selective crotylation with silane **8** that simultaneously set two stereocenters (C10, C11), created an (*E*)-trisubstituted olefin, and put the stereocenter C7 in place; an asymmetric alkynylation to install stereocenter C6; and the first example of synthesis of the *E*,*Z*-diene of ansamycins through Lindlar reduction of the enyne precursor.[22] An intramolecular copper(I)-mediated amidation reaction was used to close the 19-membered macrolactam.

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21. Authentic geldanamycin was provided by Pfizer, and experiments to obtain spectroscopic data were carried out at Boston University Chemical Instrumentation Center.

22. During the review of this work, Belardi and Micalizio reported a related Lindlar reduction to access the E,Z-dienoate of macbecin: Belardi JK, Micalizio GC. Angew Chem Int Ed 2008;47Early View

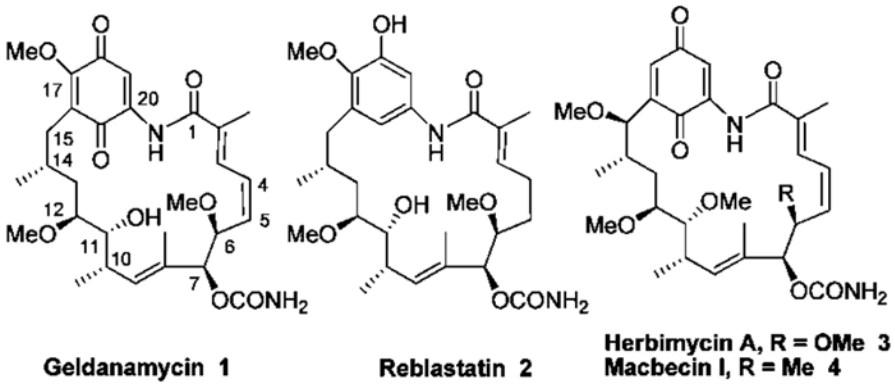
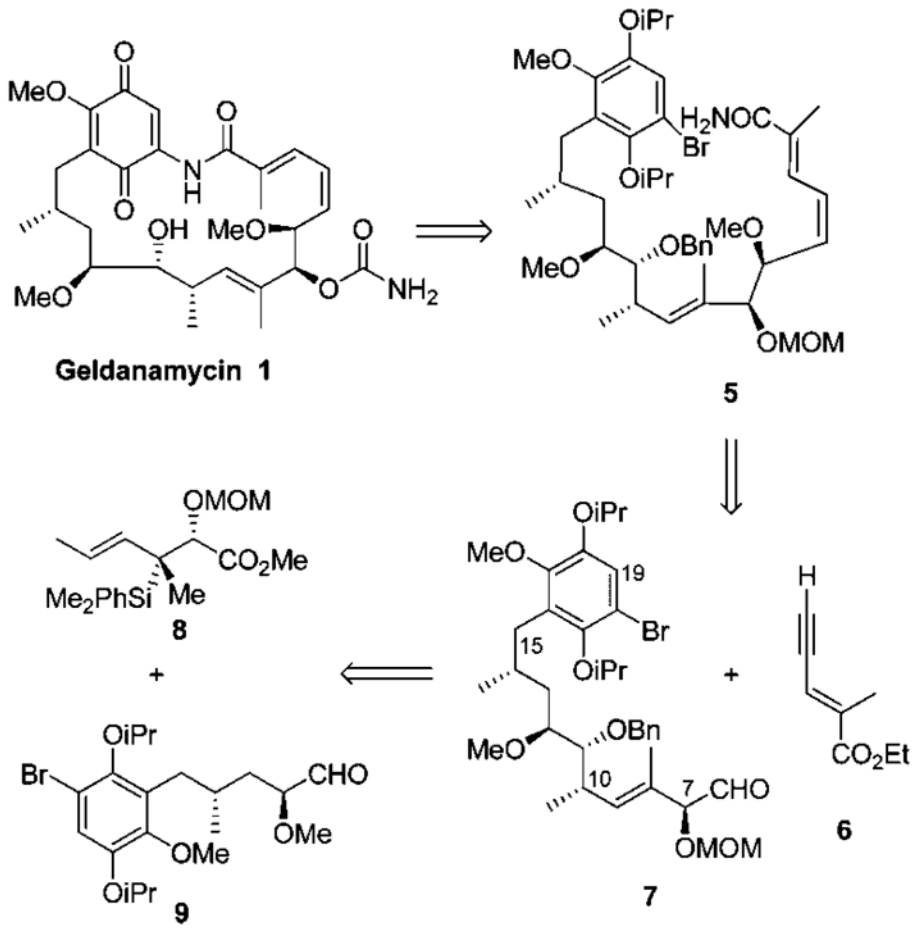
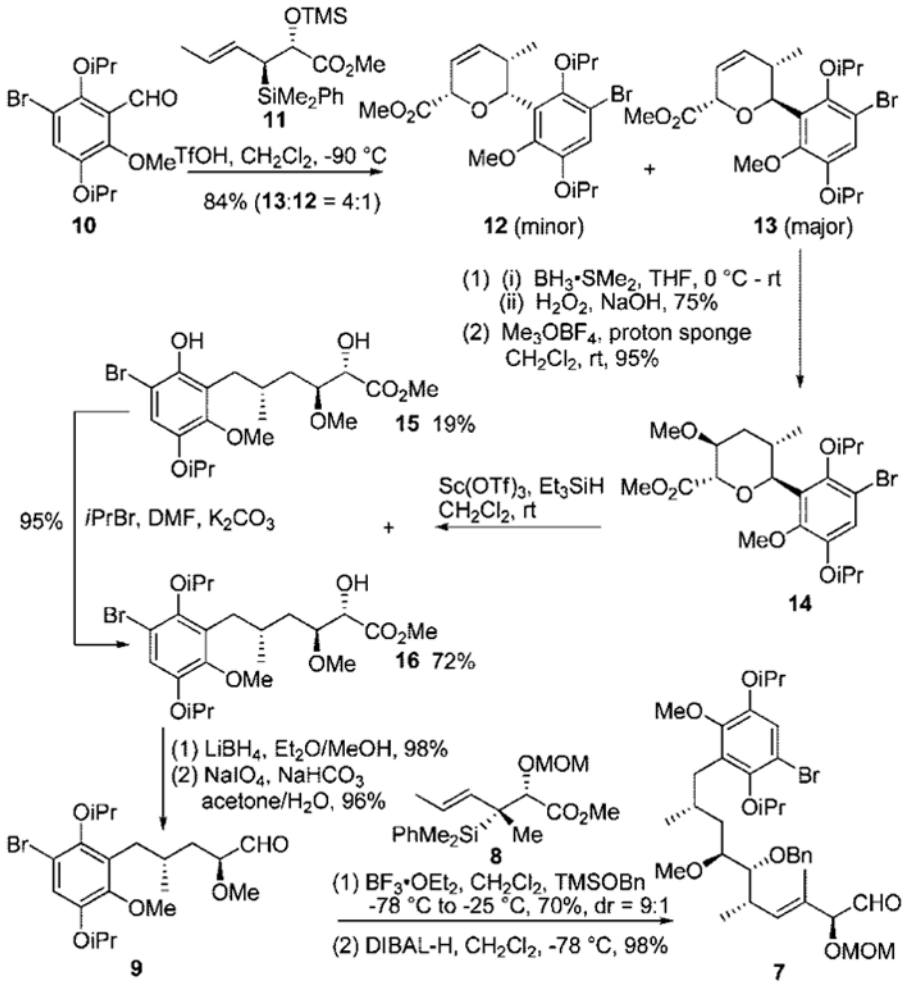


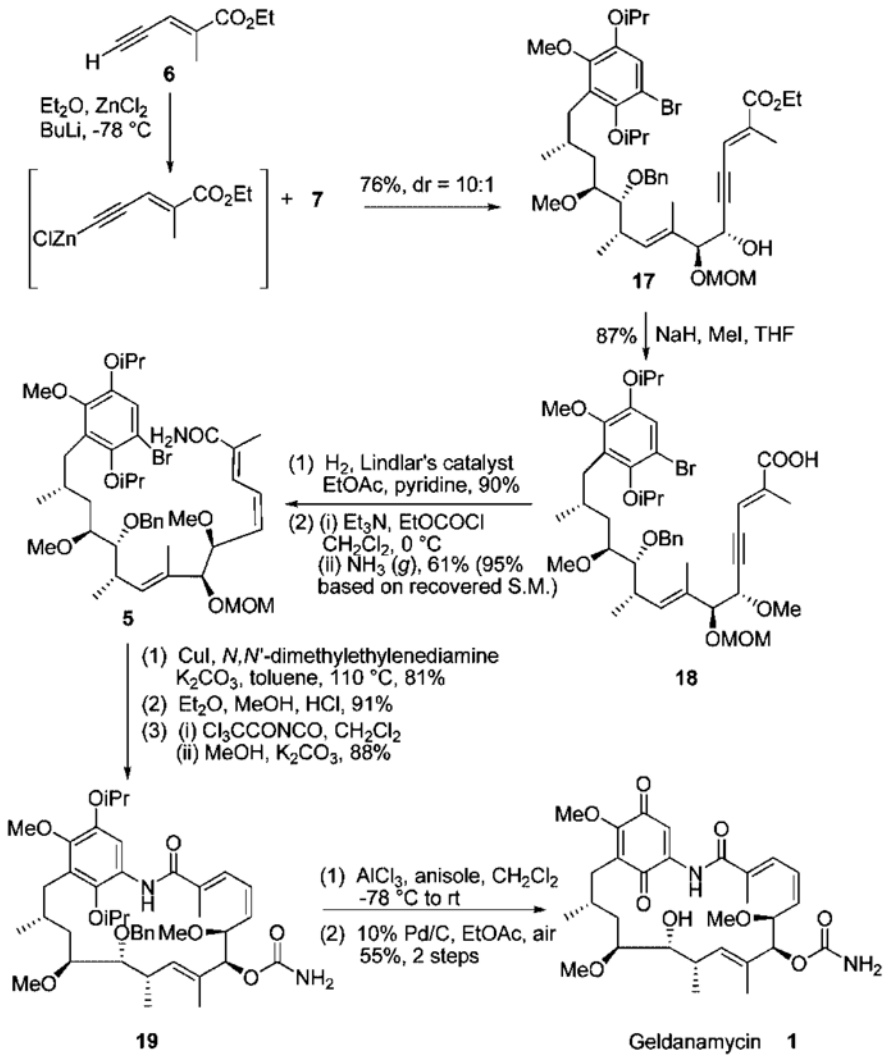
Figure 1.
Geldanamycin and related ansamycin antibiotics.



Scheme 1.
Retrosynthetic Analysis of Geldanamycin



Scheme 2.
Synthesis of Aromatic C6–C21 Fragment 7



Scheme 3.
Completion of the Total Synthesis of Geldanamycin