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Total Synthesis of the Hsp90 Inhibitor Geldanamycin

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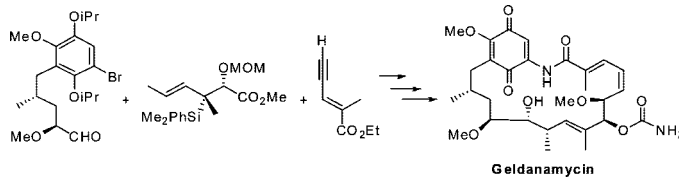
ABSTRACT



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

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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.

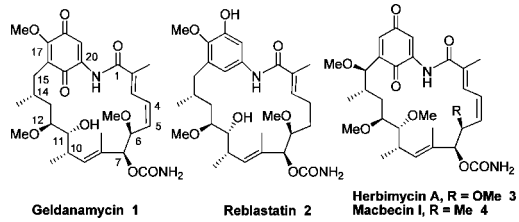
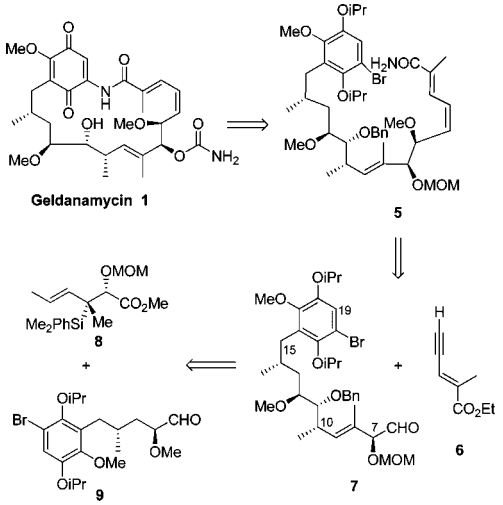


Figure 1. Geldanamycin and related ansamycin antibiotics.

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.

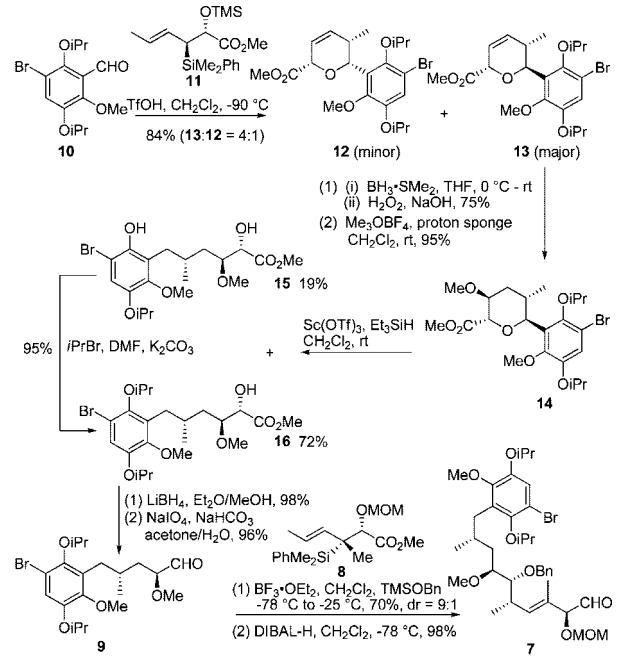
Scheme 1. Retrosynthetic Analysis of Geldanamycin



Recently, we have reported the selective hydridic opening of aryl *C*-glycosides using a $Sc(OTf)_3/Et_3SiH$-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 $Sc(OTf)_3/Et_3SiH$ 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**.

Scheme 2. Synthesis of Aromatic C6−C21 Fragment **7**



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

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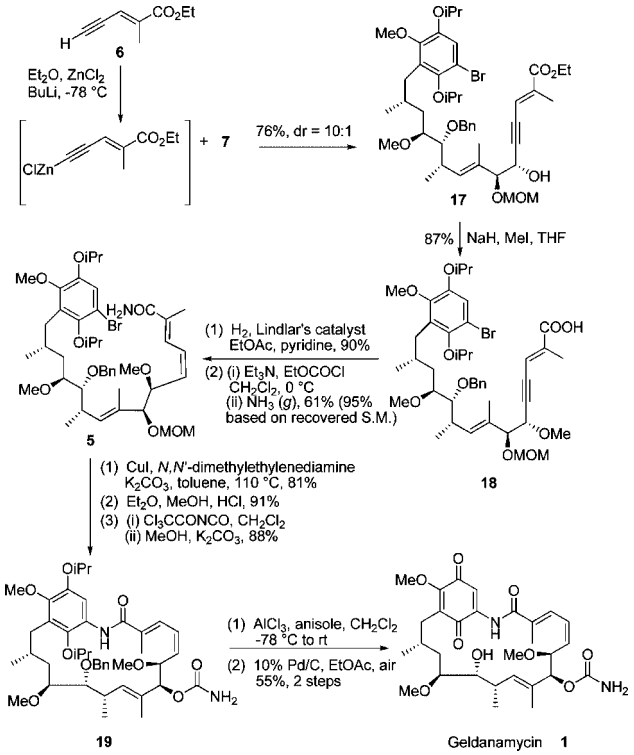
homoallylic ether bearing not only the three desired stereocenters and trisubstituted alkene, but also a benzylic ether protecting group at C11. The reaction proceeded in 70% yield with high selectivity (dr = 9:1). Reduction of the product methyl ester with DIBAL-H yielded aldehyde **7**.

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

Scheme 3. Completion of the Total Synthesis of Geldanamycin



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_2O/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, ^1H 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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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.

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(22) During the review of this work, Belardi and Micalizio reported a related Lindlar reduction to access the E,Z-dienoate of macbecin: Belardi, J. K.; Micalizio, G. C. *Angew. Chem. Int. Ed* **2008**, *47*, Early View.