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Total Synthesis of Herbimycin A

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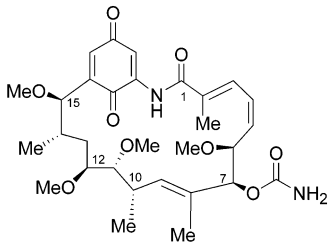
ABSTRACT



Herbimycin A (1)

Herbimycin A (HA) belongs to a class of antibiotics known as the benzoquinoid ansamycins. Members of this class have shown promising biological activity as Hsp90 inhibitors. An enantioselective synthesis of HA is described, employing asymmetric *syn*-crotylation methodology to introduce the C10, C11, C14, and C15 stereocenters. The C6–C7 stereocenters were introduced using Brown's α-pinene-derived γ-methoxy allylborane reagent. The C12 stereocenter was established by diastereoselective hydroboration.

In 1979, herbimycin A (HA) was isolated from the fermentation broth of *Streptomyces hygroscopicus* strain AM-3672.[1a] The structure and absolute configuration of herbimycin A was based on ^{1}H and ^{13}C NMR spectroscopic analysis and single-crystal X-ray analysis.[1] The natural product possesses seven stereocenters, a carbamate, an (*E*,*Z*)-diene, and a 19-membered macrocyclic lactam. Herbimycin A is a member of the ansamycin benzoquinone class of natural products, which possesses an aliphatic ansa bridge connecting two nonadjacent positions of a benzoquinone or naphthoquinone ring system.[2] The biological activity[3] of herbimycin A has been shown to reduce radial tumor, bacterial, herbicidal, and fungal cell growth.

Herbimycin A (**1**) was first synthesized by Tatsuta in 1991, by a strategy that established three of the seven stereocenters (C11, C12, and C14) from a derivative of D-mannose.[4] Other members of the ansamycin benzoquinone family that have been synthesized include macbecin I and geldanamycin.[5]

Our synthetic plan for HA, illustrated in Scheme 1, involved bond disconnection at C1 of the lactam to give the seco acid **2**. Further simplification led to a disconnection of the C4−C5 (*Z*)-olefin and the C5−C21 aromatic fragment, from which the (*E*,*Z*)-dienoate would be established by a

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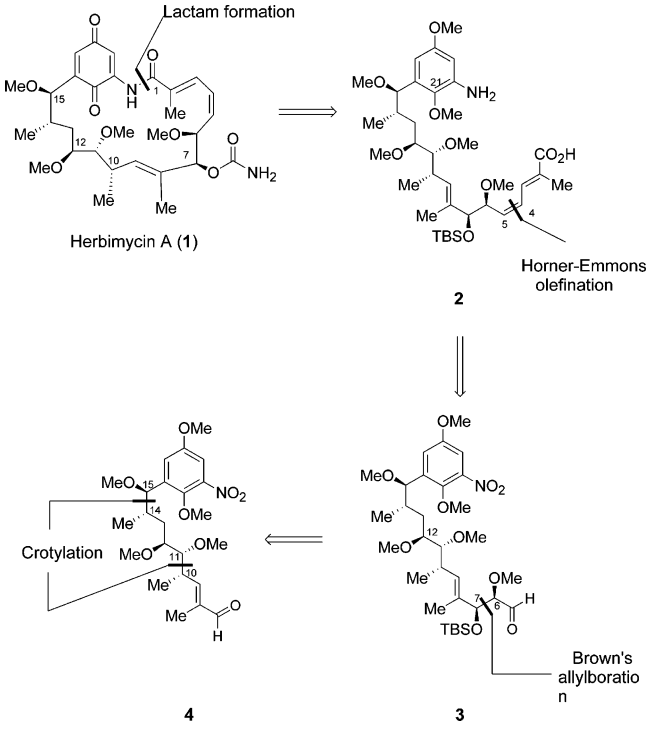
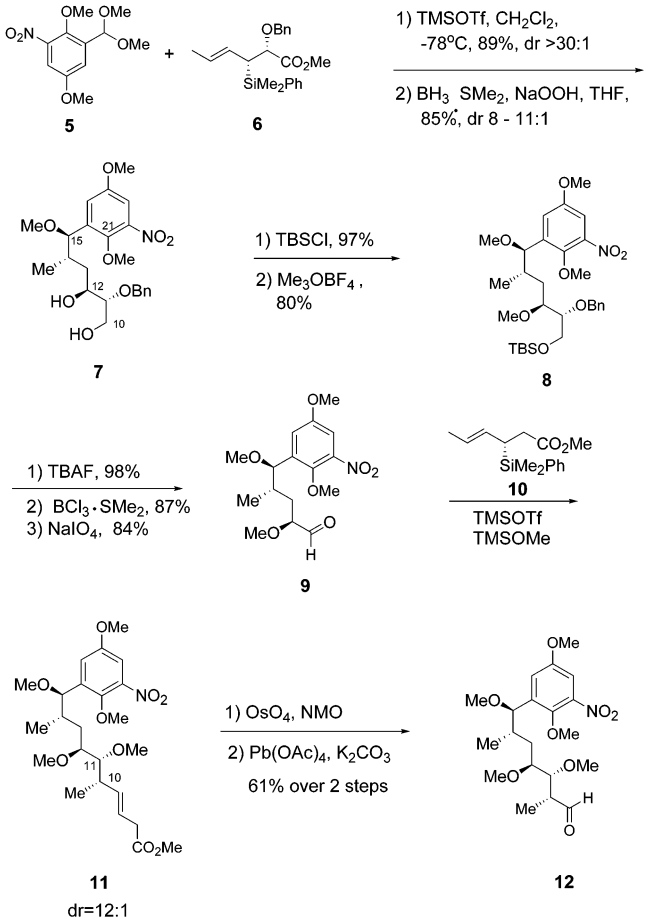
Scheme 1



Scheme 2



series of Wittig reactions. We anticipated that the C6−C7 *syn*-diol would be introduced by Brown's asymmetric allylboration methodology. In accordance with our previous synthesis of macbecin, the C12 stereocenter would be created by a diastereoselective hydroboration reaction,[6] with the pair of *syn*-methoxy-methyl stereocenters at C10−C11 and C14−C15 being introduced by our organosilane methodology.[7]

Our synthesis began with protection of the known primary alcohol in **7**,[5f] which was followed by methylation of the secondary alcohol using Meerwein's reagent (Me_3OBF_4) to give **8** in 80% yield (Scheme 2).[5f,g] Removal of the silicon protecting group at C10 was followed by debenzylation of the C11 hydroxy group with BCl_3·SMe_2 complex in CH_2Cl_2 at −78 to 0 °C, which gave the diol in 87% yield. The 1,2-diol was subjected to an oxidative cleavage reaction with $NaIO_4$ and $NaHCO_3$ in a 1:1 mixture of acetone and water to yield aldehyde **9**, which was subjected to a second crotylation with silane **10** to afford the *syn*-homoallylic ether **11** in 59% yield (dr = 12:1). This reaction was carried out as a multicomponent process that utilized the in situ generation and trapping of an oxonium ion created by the action of TMSOMe on aldehyde **9** in the presence of catalytic amounts of TMSOTf. This material was subjected to a dihydroxylation reaction with catalytic OsO_4 (35 mol %, NMO 1.08 equiv), and this was followed by cleavage of the intermediate diol with $Pb(OAc)_4$ (1.08 equiv) in buffered (K_2CO_3) benzene to afford the aldehyde **12** in 61% yield for the two steps (Scheme 3). A Wittig reaction with the stabilized ylide $Ph_3P{=}C(Me)CO_2Et$ in toluene gave the (*E*)-olefin in 78% yield (Scheme 3).[8] The ester was reduced with DIBAL-H in THF to the alcohol, which underwent a Swern oxidation to give the aldehyde **4** in 91% yield. Using Brown's allylboration technology, we constructed the C6−C7 *syn*-stereocenters by asymmetric allylboration of **4** with the γ-methoxyallyl organoborane reagent derived from (−)-α-pinene.[9] The corresponding allylation product was obtained in good yield as a single diastereoisomer.

Protection of the C7 hydroxyl group as a TBS ether allowed incorporation of the carbamate toward the end of the synthesis. Using this reaction sequence, we were able to

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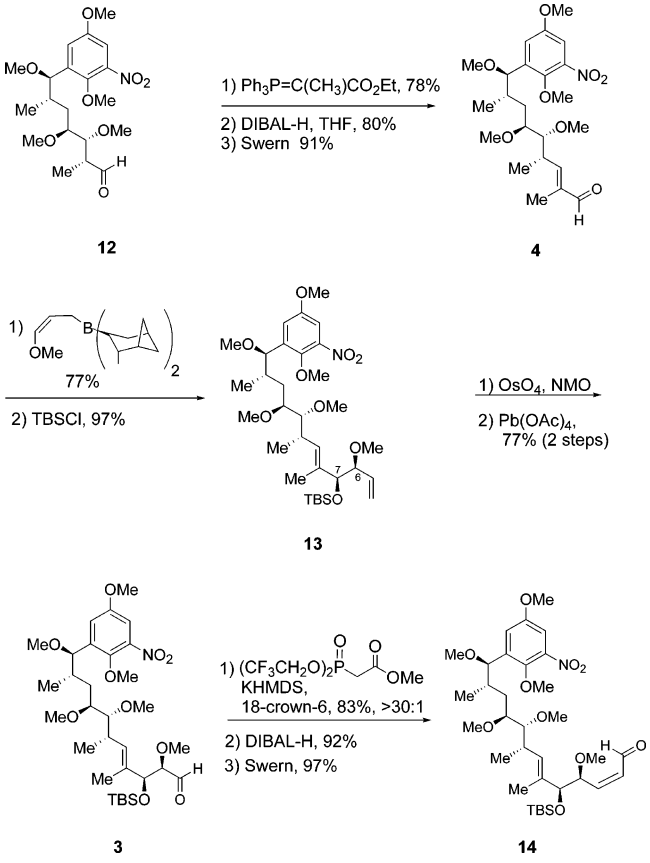
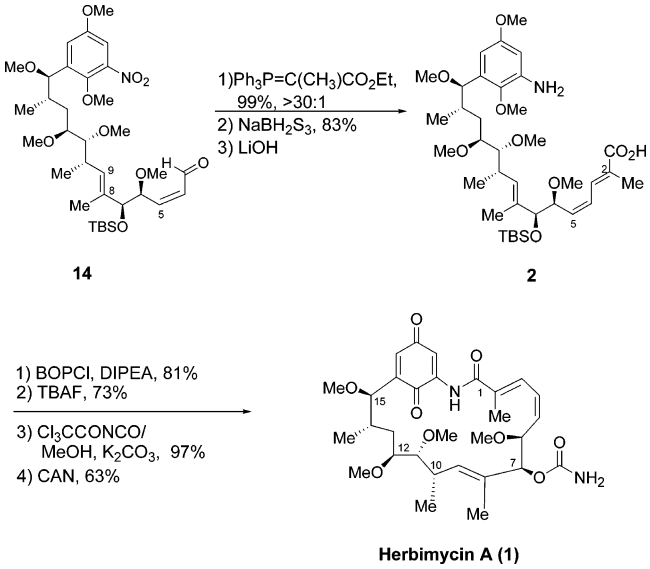
Scheme 3



Scheme 4



establish the C6,C7 stereochemical relationship and complete the synthesis of the C5−C21 fragment **13** in 97% yield. The installation of the C2−C5 (*E*,*Z*)-dienoate began with transformation of the terminal olefin in **13** to the aldehyde **3**. In a two-step reaction sequence, the aldehyde **3** was obtained after an oxidative cleavage of the terminal olefin with a catalytic amount of OsO_4 followed by treatment of the intermediate diol with $Pb(OAc)_4$ in benzene buffered with K_2CO_3. The C4−C5 (*Z*)-olefin was then established by a Horner−Emmons olefination reaction using the Still−Gennari phosphonate to afford the (*Z*)-α,*β*-unsaturated ethyl ester in 83% yield as a single isomer.[10] Reduction of the ester with DIBAL-H followed by Swern oxidation provided the α,*β*-unsaturated aldehyde **14** with an 89% overall yield. The synthesis of the (*E*,*Z*)-dienoate was completed by installation of the C2−C3 trisubstituted (*E*)-olefin employing similar conditions used earlier to install the C8−C9 trisubstituted (*E*)-olefin (Scheme 4). Accordingly, the (*E*,*Z*)-dienoate was synthesized in quantitative yield as a single isomer. The aryl nitro group was reduced under the mild conditions developed by Lalancette,[11] and this was followed by saponification of the ester to give the advanced intermediate **2**. As initially reported by Baker and Castro,[5a,b] treatment of the unpurified seco acid with BOPCl and DIPEA gave the macrocycle in 81% yield.[12]

Completion of the synthesis of **1** was accomplished by a few well-documented transformations. Deprotection of the C7-silyl ether with TBAF in THF at ambient temperature for 52 h gave the secondary alcohol in 73% yield. Formation of the carbamate with trichloroacetylisocyanate[13] and K_2CO_3/MeOH gave the desired urethane product in 97% yield; this was followed by oxidation of the dimethoxy aromatic core to the quinone with CAN, which gave synthetic herbimycin A in 63% yield. The spectroscopic and physical properties were identical in all respects with those of natural herbimycin A.

The present synthesis of herbimycin A uses chiral organosilanes to establish four (C10, C11, C14, and C15) of the seven stereocenters, a diastereoselective hydroboration to establish the C12 stereocenter, and Brown's allylboration methodology to install the C6−C7 stereocenters. Our synthesis documents the reliability and high levels of stereoselectivity that can be obtained using our chiral organosilane technology. The synthesis was accomplished in 27 steps beginning with the crotylation reaction between the acetal **5** and the (*E*)-crotylsilane **6** with an overall yield of 1.09%. Further studies on the chemistry and biology of this and other members of this class of natural products are underway in our laboratory and will be reported at a later time.

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

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