ORGANIC LETTERS

2007
Vol. 9, No. 1
145−148

Total Synthesis of Herbimycin A

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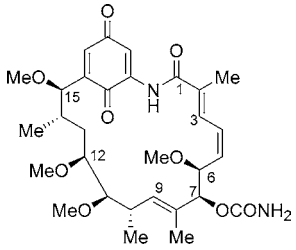
Received October 27, 2006

ABSTRACT



Herbimycin A

Hsp90 has recently emerged as a promising biological target for treatment of cancer. Herbimycin A and other members of the benzoquinoid ansamycin class of natural products are known to inhibit Hsp90 activity. The total synthesis of herbimycin A was achieved from the commercially available Roche ester 1 by using allylmetals to control the stereogenic centers at C6, C7, C10, C11, and C12 and a ring-closing metathesis to control the (*Z*)-double bond of the (*E*,*Z*)-dienic moiety.

Heat shock protein 90 (Hsp90) is an essential protein that chaperones multiple growth-regulatory signaling proteins, including protein kinases[1] and transcription factors.[2,3] The benzoquinoid ansamycins, such as herbimycin A and geldanamycin (Figure 1), have recently been identified as inhibitors of the Hsp90 folding process. This leads to disruption of the Hsp90 client protein complexes and subsequent ubiquitination and degradation by the proteosome of the client proteins. Moreover, a number of known oncogenic proteins are Hps90 client proteins. As a result, Hsp90 is a promising biological target for treatment of cancer, and geldanamycin and herbimycin A as well as their analogues have the potential of serving as chemotherapeutic agents in a number of diseases. Consequently, these compounds are attractive targets for synthetic chemists. Here, we report the total synthesis of herbimycin A.

Herbimycin A was isolated in 1979 from the fermentation broth of *Streptomyces hygroscopicus* strain AM-3672 and exhibits a broad spectrum of biological activities including herbicidal, antifungal, antiangiogenic, and antitumor properties.[4] The structure and absolute configuration of herbimycin A was based on ^{1}H and ^{13}C NMR spectroscopic analysis and X-ray analysis.[4b,c] Herbimycin A is a 19-membered macrocyclic lactam which possesses seven stereogenic centers, a carbamate, an isolated trisubstituted (*E*)-double bond, an (*E*,*Z*)-diene, and a benzoquinone ring system. Despite its interesting properties, only two total syntheses of herbimycin A are described in the literature.[5] One formal synthesis and the synthesis of advanced fragments have also

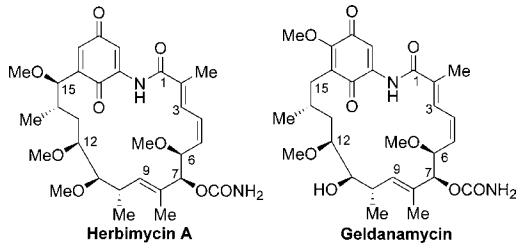


Figure 1. Two inhibitors of Hsp90: herbimycin A and geldanamycin.

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[‡] Sanofi-Aventis.

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10.1021/ol062642i CCC: $37.00
Published on Web 12/05/2006

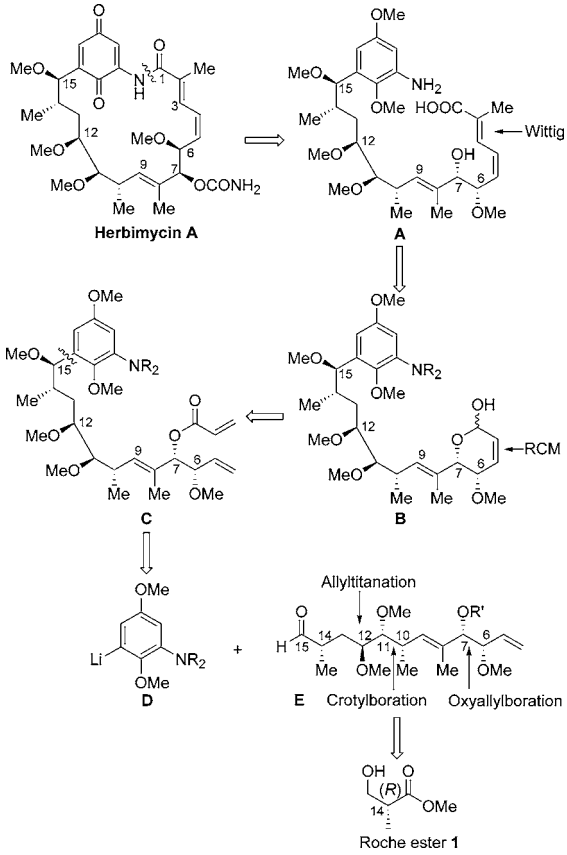
been reported.[6] Other members of the ansamycin benzoquinone class of natural products have been synthesized, including macbecin I[7] and geldanamycin.[8]

Our synthetic plan for herbimycin A is depicted in Scheme 1 and involved a macrolactamization applied to seco acid **A** at the end of the synthesis. In order to control the (*Z*)-double bond of the dienic system of herbimycin A, a ring-closing metathesis of the dienic ester **C** was considered. The formation of the (*E*,*Z*)-diene should then be completed by a Wittig reaction applied to lactol **B**. Further simplification of **C** led to a disconnection of the C15−C16 bond giving fragments **D** and **E**. The C12 center in **E** should be controlled by using an enantioselective allyltitanation, and the C10,C11 and C6,C7 stereogenic centers would be controlled by employing a *syn*-crotylboration and a *syn*-γ-alkoxyallylboration, respectively. The synthesis will begin from the commercially available Roche ester **1** possessing the (*R*) configuration corresponding to the C14 stereogenic center of herbimycin A.

Hydroxyester **1** was transformed to aldehyde **2** in four steps with an overall yield of 80%. After protection of the primary alcohol as a TBDPS ether (TBDPSCl, imidazole, rt, quant), the ester function was reduced by DIBAL-H (Et_2O, −78 °C, 1.5 h, 93%) to yield the corresponding aldehyde directly, which was then homologated to **2** in two steps using the methoxymethylphosphonium ylide followed by an acidic hydrolysis of the enol ether intermediately formed. Aldehyde **2** was then subjected to an enantioselective allyltitanation[9] with the highly face-selective (*S*,*S*)-**I** complex (Et_2O, −78 °C, 5 h) to afford the homoallylic alcohol **3** in 96% yield (dr >95/5). After methylation of the secondary alcohol in **3** (KH, MeI, 97% yield), the terminal double bond of **4** was isomerized[10] by treatment with the second-generation Grubbs' catalyst **GII**[11] in the presence of the *N*-allyl-*N*-tritylamine and diisopropylethylamine (toluene, reflux, 1.5 h) resulting in the formation of allylic ether **5** in 98% yield.

After oxidative cleavage of olefin **5** (OsO_4, NMO then $NaIO_4$), treatment of the obtained aldehyde with the (*Z*)-crotylboronate[12] **6** allowed the control of the C10 and C11 stereocenters. Alcohol **7** was isolated in 70% yield, and after methylation (KH, MeI, 92%) and oxidative cleavage (OsO_4, NMO then $NaIO_4$), the resulting aldehyde was submitted to the Corey−Schlessinger olefination conditions[13] to afford the α,β-unsaturated aldehyde **9** in 93% yield (*E*/*Z* = 4/1). At this stage, the control of the C6−C7 stereocenters was examined. Addition of the (*Z*)-γ-methoxy allylborane **10**, derived from (−)-α-pinene and developed by Brown,[14]

Scheme 1. Retrosynthetic Analysis



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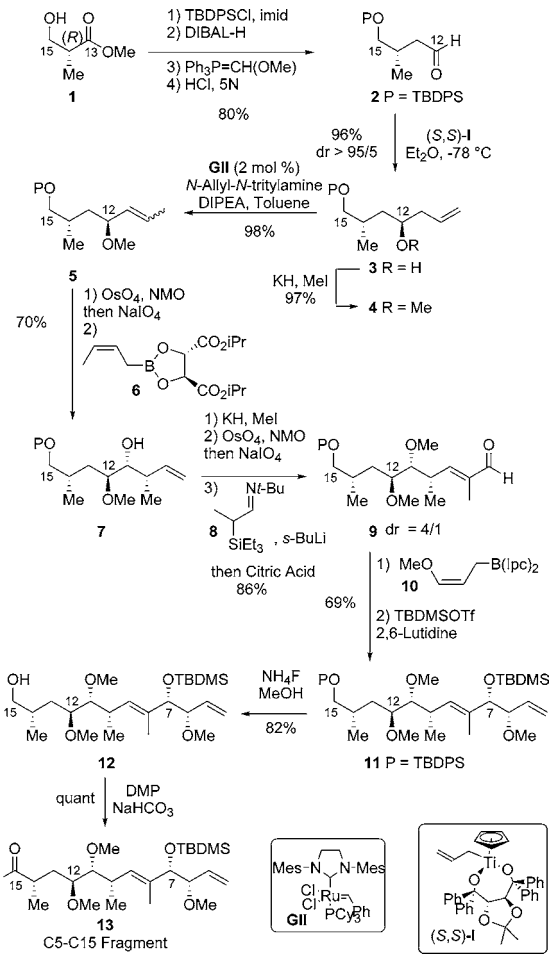
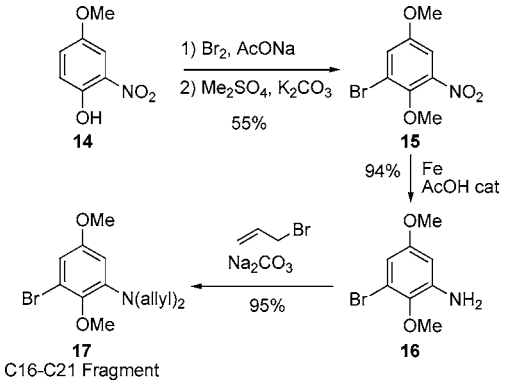
Scheme 2. Synthesis of the C5−C15 Fragment of Herbimycin A



on aldehyde **9** (THF, −50 °C to 0 °C, 6 h) led to the desired *syn*-product (dr = 4/1), which was directly protected to produce the TBDMS ether **11** (TBDMSOTf, 2,6-lutidine) in 69% overall yield for the two steps. The selective deprotection of the primary alcohol, without affecting the secondary TBDMS ether at C7, was achieved by using NH_4F in methanol (reflux, 8 h, 82%), and the primary alcohol in compound **12** was then oxidized to the corresponding aldehyde **13** by using Dess−Martin periodinane (DMP, $NaHCO_3$, rt) in quantitative yield. All data obtained for compounds **12** (^{1}H NMR, ^{13}C NMR, IR, $[\alpha]_D$) and **13** (^{1}H NMR) were in agreement with those reported in the literature.[5b] The known C5−C15 fragment **13** was synthesized in 16 steps with an overall yield of 25% (Scheme 2).

With the C5−C15 fragment in hand, we next turned our attention to the coupling reaction of **13** with the aromatic fragment **17** (C16−C21 fragment). The aromatic fragment **17** was prepared in four steps from the commercially available 4-methoxy-2-nitrophenol **14**. After regioselective *ortho*-bromination of the aromatic ring (Br_2, AcONa, AcOH, 76%), the phenol function was methylated (Me_2SO_4, K_2CO_3, acetone, reflux, 72%) and the nitro group was selectively reduced (Fe, AcOH, H_2O, reflux, 94%). Allylation of the aniline function of **16**[15] (allyl bromide, Na_2CO_3, DMF, reflux, 95%) produced the C16−C21 fragment **17** with an overall yield of 49% from **14** (Scheme 3).

Scheme 3. Synthesis of the C16−C21 Fragment



The organolithium reagent issued from **17** was obtained by halogen−metal exchange using *n*-BuLi (−78 °C then rt, 30 min) and was then reacted with aldehyde **13** (Et_2O, −78 °C, 1.5 h) to produce the two epimers at C15, **18** and **18′**, in a 1.6/1 ratio,[16] in 87% yield. After separation, the major epimer **18** (the Felkin−Anh adduct, 54% yield) was methylated at C15 (NaH, MeI, DMF, quant) and *N*-deprotected [$Pd(PPh_3)_4$, *N*,*N*-dimethylbarbituric acid (NDMBA), 97%] to give aniline **19**. This latter compound was then transformed to the desired unsaturated lactone **21** in four steps. In order to perform the RCM, the aniline function should be protected with a deactivating group, and the synthesis of the *N*,*N*-biscarbamate from **19** was performed (Boc_2O, Et_3N, DMAP, THF, reflux, 75%). After deprotection of the hydroxy group at C7 (TBAF, THF) and esterification using acryloyl chloride (DIPEA, CH_2Cl_2, 89%), the obtained dienic ester **20** was subjected to RCM using the second-generation Grubbs' catalyst (**GII** 20 mol %, PhMe, c = 5.10^{-3} M), and the unsaturated lactone **21** was isolated in 72% yield. The transformation of **21** to the (*E*,*Z*)-conjugated diene **23** was achieved in two steps. At first, the lactone was reduced to the corresponding lactol using DIBAL-H (Et_2O, −78 °C), and the resulting lactol was treated with the stabilized Wittig reagent PPh_3=C(Me)CO_2Et **22** in toluene to produce the (*E*,*Z*)-diene **23** (dr >9/1) in 85% yield (Scheme 4).[17]

After deprotection of the aniline, and saponification of the ester, the treatment of the nonpurified seco acid with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl) and DIPEA gave the macrocycle **24** in 77% yield. Completion of herbimycin A synthesis was accomplished by formation

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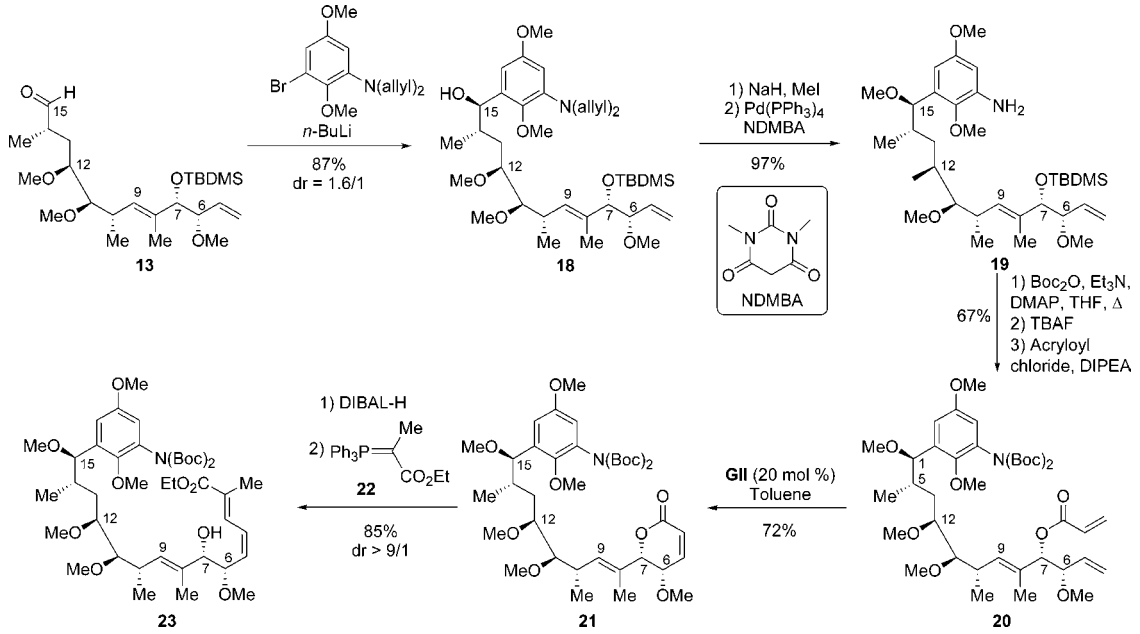
(15) The synthesis of compound **16** is described in the literature. See: Guay, V.; Brassard, P. *J. Heterocycl. Chem.* **1987**, *24*, 1649−1652.

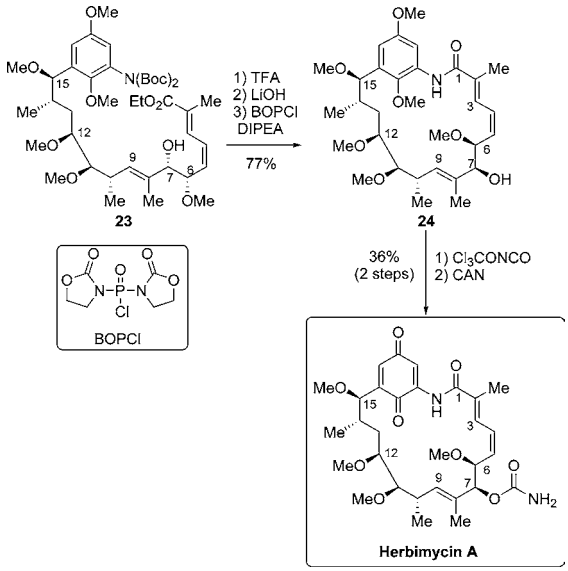
(16) Configuration of the major isomer **18** was verified by formation in two steps of *N*-trityl compound already described by Nakata and Tatsuta (ref 5b).

Scheme 4



of the carbamate at C7 with trichloroacetylisocyanate and K_2CO_3/MeOH followed by oxidation of the dimethoxy aromatic core to the quinone ring system with CAN. Herbimycin A was produced in 36% overall nonoptimized yield for the last two steps (Scheme 5). The spectroscopic

Scheme 5. Synthesis of Herbimycin A



and physical properties were identical in all respects with those of natural herbimycin A purchased from Sigma-Aldrich. Optical rotations of our herbimycin A sample and of the commercially available one were respectively $[\alpha]^{20}_D$ +223 (*c* 0.14, $CHCl_3$) and $[\alpha]^{20}_D$ +231 (*c* 0.05, $CHCl_3$).[18]

The synthesis of herbimycin A was achieved from the commercially available Roche ester **1** by using allylmetals to control the stereogenic centers at C6, C7, C10, C11, and C12. The synthesis of the C5−C15 fragment of herbimycin A is shorter and more efficient than the synthesis of the same fragment reported previously.[5a,b] Furthermore, the (*Z*)-double bond of the (*E*,*Z*)-dienic moiety was formed, with excellent control of configuration, by using ring-closing metathesis.

The total synthesis of herbimycin A was accomplished in 30 steps from **1** with a nonoptimized overall yield of 1.5%. In terms of steps and overall yield, our synthesis of herbimycin A was comparable to the shortest of the two previous reported syntheses.[5]

Acknowledgment. We thank Sanofi-Aventis and the Centre National de la Recherche Scientifique (CNRS) for a grant (S.C.). We are indebted to Prof. J. S. Panek (Boston University) for providing spectra of natural and synthetical herbimycin A. This paper is dedicated to the memory of Guy Ourisson.

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

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(18) The ^{1}H NMR spectrum of our synthetical herbimycin A was identical to those provided by Prof. Panek (natural and synthetical) and identical to the spectrum of commercial herbimycin A purchased from Sigma-Aldrich. Optical rotations of our herbimycin A sample and of the commercially available one were respectively $[\alpha]^{20}_D$ +223 (*c* 0.14, $CHCl_3$) and $[\alpha]^{20}_D$ +231 (*c* 0.05, $CHCl_3$). These values are significantly higher than those described in the literature (ref 1a: $[\alpha]^{20}_D$ +137 (*c* 1.0, $CHCl_3$); ref 5a: $[\alpha]^{25}_D$ +122 (*c* 0.20, $CHCl_3$); ref 5c: $[\alpha]^{23}_D$ +127 (*c* 0.15, $CHCl_3$)).