Tetrahedron 70 (2014) 2982–2991

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total synthesis of reblastatin: convenient preparation of coupling partners and scaled assembly

Chuancai Bian, Rui Yan, Xiaoming Yu *

State Key Laboratory of Bioactive Substance and Function of Natural Medicine, Institute of Materia Medica, Peking Union Medical College & Chinese Academy of Medical Sciences, No. 1 Xiannongtan St., Beijing 100050, China

ARTICLE INFO

Article history:
Received 8 January 2014
Received in revised form 25 February 2014
Accepted 6 March 2014
Available online 14 March 2014

Keywords:
Benzenoid/benzoquinone ansamycin
Reblastatin
Total synthesis
Hsp90 inhibitor

ABSTRACT

Potentially scalable total synthesis of reblastatin was achieved based on Panek's previous study. Novel and convenient synthetic routes were developed for the known C8–C20 and C1–C7 coupling partners. The challenging C8–C20 fragment was prepared from TBS protected (*S*)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (**6**) in nine steps (20% overall yield), and the C1–C7 fragment was synthesized from commercially available 3,4,6-tri-*O*-acetyl-D-glucal (**9**) in eight steps (35% overall yield). On a larger scale, Panek's eight-step assembly of the target molecule from the two partners was also slightly modified, giving 45 mg reblastatin (19% overall yield) in the first batch synthesis. Notable feature of our study is the settlement of the C14 chirality through a diastereoselective α-alkylation of **6** followed by a three-step full reduction of the lactone carboxyl, making vastly available **6** a universally applicable C11–C14 synthon for benzenoid/benzoquinone ansamycins.

1. Introduction

Benzenoid ansamycin reblastatin (**1**, Fig. 1) was first isolated from the culture of *Streptomyces hygroscopicus* sub sp. *hygroscopicus SANK 61995* by Takatsu,[1] and then by Stead from that of *Streptomyces* sp. S6699.[2] This compound showed considerable anti-proliferative activity against human histiocytic lymphoma U-937 cells (IC_{50} 0.43 μg/mL or 0.78 μM)[1] and inhibitory effect against Oncostatin M (OSM) mediated pathways in HepG2 B6 cells (IC_{50} 0.16 μM),[2] indicating its potential for treatment of cancer and rheumatoid arthritis. The closely related natural product geldanamycin (**2**, Fig. 1) is a well-known heat shock protein 90 (Hsp90) inhibitor, and several of its semisynthetic derivatives are now clinically investigated as cancer chemotherapeutics.[3] Similar to compound **2**, reblastatin **1** is also an ATPase inhibitor of Hsp90,[4b] but the structural difference between the two molecules are of great pharmaceutical significance. For example, reblastatin **1** should have lower hepatotoxicity because of the embedment of a redox-inactive phenolic aromatic core. And secondly, the saturated C4 and C5 in **1**, which may account for its higher molecular affinity to Hsp90,[5] also make the compound more stable. For these reasons, we became interested in a scalable synthesis of **1** to support in vivo studies on its toxicological profiles and therapeutic effects, and to this end a sub-gram (0.1–1 g) sample is usually required.

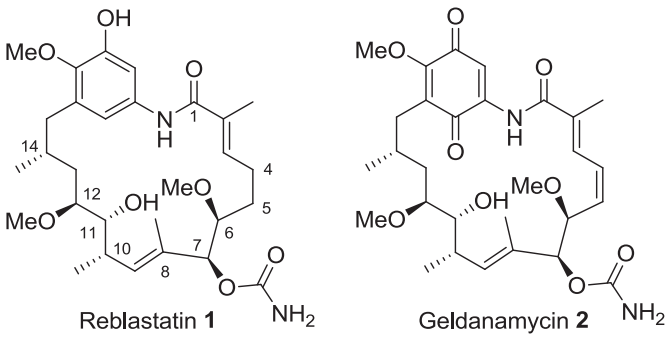
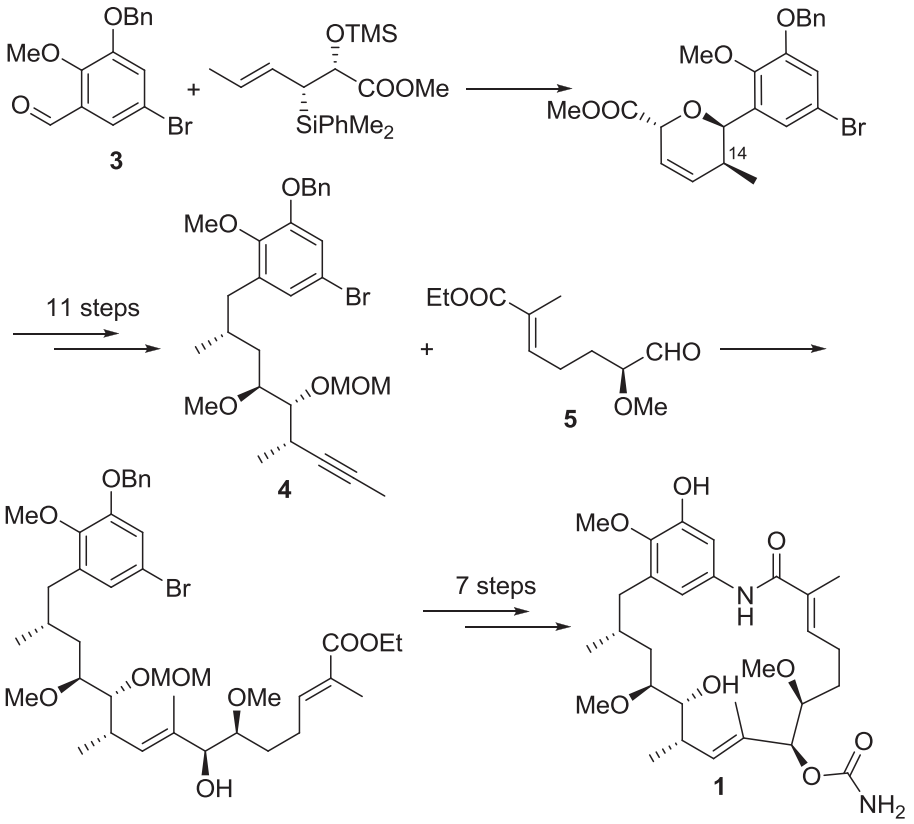


Fig. 1. Structures of reblastatin **1** and geldanamycin **2**.

Panek and co-workers accomplished so far the only total synthesis of reblastatin (Scheme 1),[4] which also stands for the first example of convergent synthesis within the benzenoid/benzoquinone ansamycin family.[6] Their synthesis started with an enantioselective formal [4+2] cycloaddition of benzaldehyde **3** and a chiral crotylsilane developed in the authors' own laboratory.[4b] This robust method helped address the challenging C14 configuration with high efficiency and enabled construction of the four-chiral-centered C8–C20 fragment **4** in 12 steps. More remarkable to us, however, is the late stage assembly of the target molecule. Two key steps, namely a ZrH/Zn mediated highly diastereoselective reductive

* Corresponding author. Tel.: +86 10 63165259; fax: +86 10 63017757; e-mail address: mingxyu@imm.ac.cn (X. Yu).

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.03.020

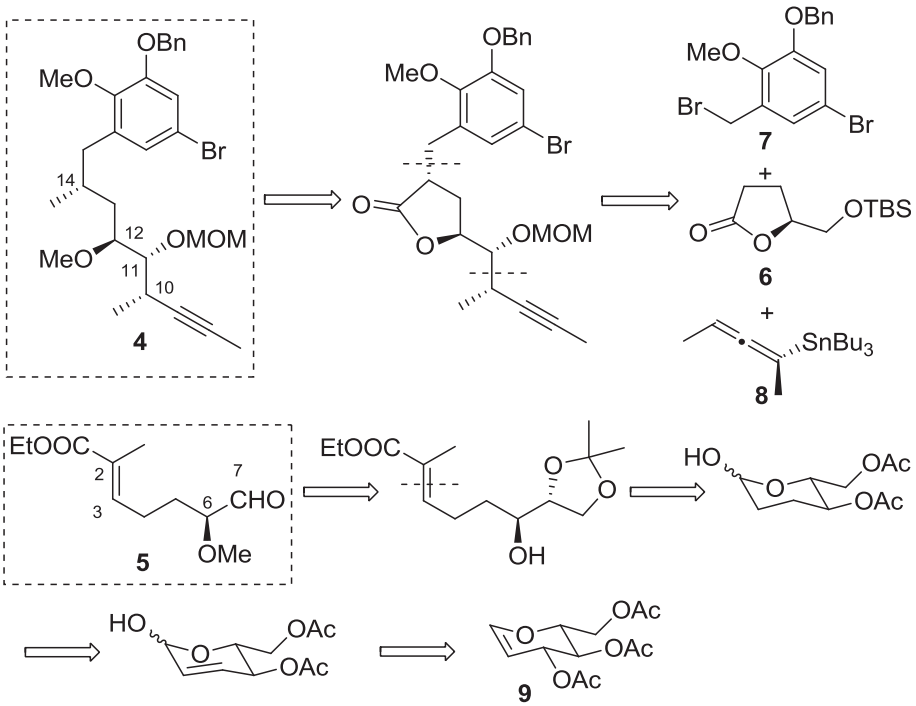


Scheme 1. Panek's total synthesis of reblasatin.

coupling of alkyne **4** and aldehyde **5**, and an unprecedented Hartwig–Buchwald type macrolactam ring-closure, were included in the eight-step sequence that finally delivered reblastatin **1** in 13% overall yield. These excellent achievements undoubtedly formed solid foundation for a scalable synthesis, but we were in short of the supply of Panek's crotylsilane. We therefore developed an alternative approach to **4** and **5** that may feature the easy availability of starting material. In addition, the reported method for assembly **4** and **5** to reblastatin **1** was also slightly modified.

2. Results and discussion

As shown in Scheme 2, we planned to start our synthesis of **4** with a substrate-induced trans-selective α-alkylation of chiral γ-lactone



Scheme 2. The retro-synthetic analysis of **4** and **5**.