Tetrahedron 67 (2011) 10281–10286

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Stereoselective synthesis of a fully protected C_{13}–C_{23} fragment of tedanolide

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ARTICLE INFO

Article history:
Received 30 July 2011
Received in revised form 7 October 2011
Accepted 10 October 2011
Available online 18 October 2011

Keywords:
Non-aldol aldol
Semipinacol rearrangement
Stannylcupration
Dienylstannane

ABSTRACT

The combination of a high-yielding dienyllithium addition and a highly diastereoselective 1,2-reduction allows the preparation of the completely protected C_{13}–C_{23} fragment **3** of the potent cytotoxic agent tedanolide **1**. A convergent approach was used, namely a late stage coupling of the dienyllithium **16** with the selectively protected aldehyde **5** followed by oxidation–reduction and final epoxidation to give **3**. The dienylstannane **4** was prepared from the dibromide **6** in five steps, the key step being the highly regio- and stereoselective stannylcupration of the alkyne **7**. The commercially available hydroxy ester **10** was converted in 11 steps to the aldehyde **5**. The compound **3** could potentially be a key intermediate for the synthesis of tedanolide **1**.

1. Introduction

Schmitz and co-workers isolated the macrolide tedanolide **1** in 1984 from the Caribbean sponge *Tedania ignis*.[1] This lactone epoxide exhibits very potent cytotoxicity, with ED_{50}s of 250 pg/mL against human nasopharynx carcinoma and 16 pg/mL against in vitro lymphocytic leukemia. Because of its excellent antitumor activity and its intriguing structural features (18-membered macrocyclic lactone with a polypropionate skeleton, an internal trisubstituted *E* olefin, and 13 stereocenters), tedanolide has generated considerable synthetic interest. Three total syntheses[2] have resulted as well as a significant amount of synthetic work.[3]

2. Background

In our attempts to synthesize this molecule, our group has employed over the last few years the non-aldol aldol process, a reaction that we developed for the preparation of aldol natural products.[4,5] Recently we reported two approaches for the preparation of the C_1–C_{12} fragment of tedanolide **2** using an alkenyllithium addition followed by a reductive hydroboration methodology[6a] and the combination of aldol and non-aldol aldol methodology,[6b] respectively. We report herein the efficient preparation of the fully protected C_{13}–C_{23} fragment of tedanolide **3** by a convergent synthetic method that involves a dienyllithium addition and a highly diastereoselective reduction of an enone as the key steps. Our proposed retrosynthesis for tedanolide **1** using these fragments is shown in Fig. 1. We designed the synthetic route for fragment **3** from the dienylstannane **4** via nucleophilic addition of the derived dienyllithium to the selectively protected aldehyde **5**. Although this addition would be expected to give the undesired stereochemistry at C_{17} due to Cram–Felkin–Anh control,[7] the stereochemistry at C_{17} could be easily changed via a simple oxidation–reduction protocol using a bulky hydride agent, again via Cram–Felkin–Anh control.

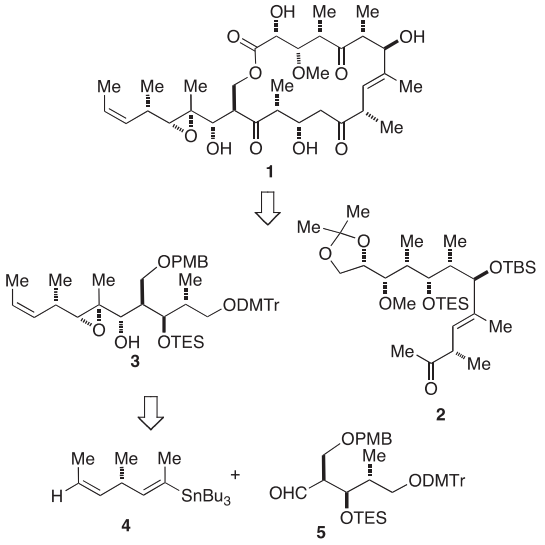

Fig. 1. Retrosynthesis of tedanolide **1**.

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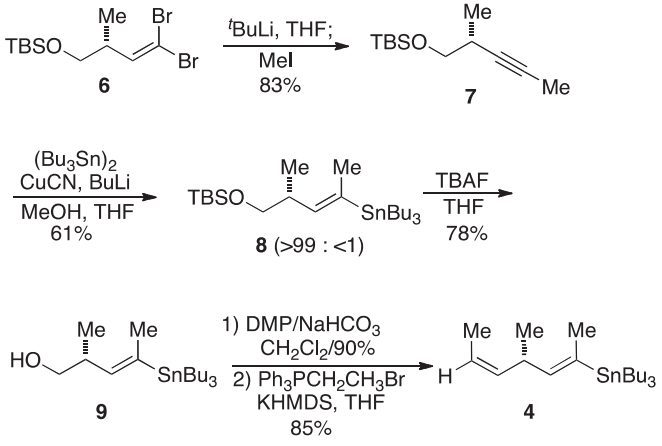
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.10.024

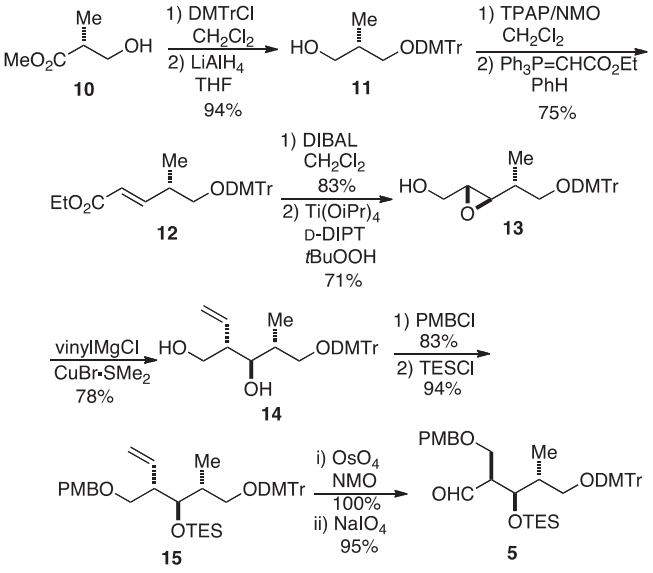
3. Results and discussion

In order to prepare the fully protected C_{13}–C_{23} fragment of tedanolide **3**, efficient syntheses of both the dienylstannane **4** and the protected aldehyde **5** were required. The synthesis of the dienylstannane with high *E*-selectivity was difficult to achieve. Finally we developed a method that utilized a regio- and stereoselective hydrostannylation of a substituted alkyne to prepare the desired vinylstannane, which could then be converted into the dienylstannane without any loss of the tin component. Thus the alkyne **7** was prepared from the dibromoolefin **6**, prepared by a Corey–Fuchs reaction on the known aldehyde, in 83% yield via lithium–halogen exchange followed by trapping with iodomethane (Scheme 1). Initially we explored the palladium-catalyzed hydrostannylation using Yamamoto's procedure.[8] However the desired vinylstannane **8** was obtained in only 13% yield along with a small amount of the undesired regioisomer (6:1 ratio). When a larger amount of the palladium catalyst and tributyltin hydride was used, the yield of the vinylstannane increased while the regioselectivity unfortunately decreased. However, when stannylcupration[9] of the alkyne **7** was carried out, the desired vinylstannane **8** was isolated in good yield and with superb regioselectivity (>99:1). Desilylation of **8** with TBAF gave the primary alcohol **9**. Oxidation of this alcohol using Dess–Martin periodinane (DMP)[10] afforded in 90% yield the somewhat unstable aldehyde, which was immediately subjected to the Wittig olefination with ethyltriphenylphosphonium bromide using potassium hexamethyldisilazide (KHMDS) in THF to afford the desired dienylstannane **4** in 85% yield. All of the vinylstannanes—**4**, **8**, and **9**—are unstable on normal silica gel chromatography. Therefore, either adding triethylamine in the eluent or chromatography on neutral alumina is preferred for purification of these compounds.



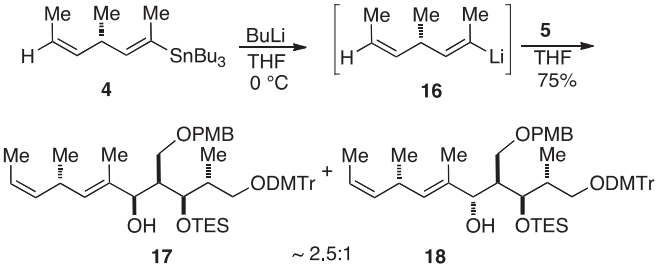
Scheme 1.

The coupling partner for the dienylstannane, the aldehyde **5**, was prepared from the commercially available methyl (*R*)-3-hydroxy-2-methylbutanoate **10** by a short sequence (Scheme 2). Protection of the alcohol as the 4,4′-dimethoxytrityl (DMTr) ether followed by reduction of the ester gave the known[4d] alcohol **11** in 94% yield. Oxidation with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO)[11] afforded the aldehyde, which was immediately subjected to the Wittig reaction with (ethoxycarbonylmethylidene)triphenylphosphorane to give the desired *E*-enoate **12** in 75% yield for the two steps. Reduction of the ester **12** with DIBAL furnished, in 83% yield, the allylic alcohol, which upon Sharpless asymmetric epoxidation[12] afforded the β-epoxy alcohol **13** in 71% yield and >90% ee. The epoxide was opened regio- and stereoselectively by treatment of vinylmagnesium chloride and copper(I) bromide–dimethyl sulfide complex[13] to give the diol **14**. Selective protection of the primary alcohol of this diol as the *p*-methoxybenzyl (PMB) ether proceeded in 83% yield. Final protection of the secondary alcohol as the triethylsilyl (TES) ether afforded the selectively protected alkene **15** in 94% yield. Finally dihydroxylation with catalytic osmium tetroxide/NMO gave in quantitative yield the expected diol mixture, which underwent oxidative cleavage using sodium periodate to afford the desired aldehyde **5**.



Scheme 2.

With both the dienylstannane **4** and the aldehyde **5** in hand, we next explored the coupling reaction (Scheme 3). Lithium–tin exchange of **4** was achieved with *n*-butyllithium at 0 °C within 10 min to give the dienyllithium **16**. Carrying out this exchange reaction at −78 °C resulted in no significant exchange of tin for lithium. Addition of the dienyllithium **16** to the aldehyde **5** afforded an approximately 2.5:1 mixture of the two diastereomeric allylic alcohols **17** (β-OH) and **18** (α-OH) in 75% yield. To confirm the stereochemistry at the newly generated chiral center, the major diastereomer **17** was transformed to the corresponding acetonide **19** by removal of the silyl ether with TBAF and acetonide formation (Fig. 2). The stereochemistry was confirmed via coupling constant (small *J* values) and NOE analysis.



Scheme 3.

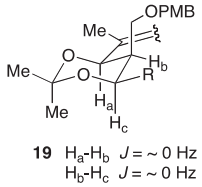


Fig. 2. NMR data of **19** for structure determination of **17**.