Tetrahedron 73 (2017) 1358–1366

Contents lists available at ScienceDirect

Tetrahedron

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

Stereoselective total synthesis of 10-*epi*-tirandamycin E

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ARTICLE INFO

Article history:
Received 29 August 2016
Received in revised form
16 January 2017
Accepted 23 January 2017
Available online 26 January 2017

Keywords:
Tirandamycins
Desymmetrization protocol
Ring-closing metathesis
Acid catalyzed ketalization
Substrate-controlled dihydroxylation
Horner-Wadsworth-Emmons olefination

ABSTRACT

A stereoselective total synthesis of 10-*epi*-tirandamycin E is described, employing desymmetrization protocol, ring-closing metathesis (RCM), acid-catalyzed ketalization, substrate controlled dihydroxylation and Horner-Wadsworth-Emmons olefination as key reactions.

1. Introduction

The tirandamycins belong to a small group of naturally occurring dienoyl tetramic acids with diverse molecular architecture, are an important class of compounds in medicinal chemistry. Compounds containing a tetramic acid structural unit exhibit broad biological activities such as antibacterial, antiviral, anti-HIV-1, cytotoxicity, mycotoxicity, antitumor, and antimicrobial activities.[1] In 1970s tirandamycin A (**1**) and tirandamycin B (**2**), two of the more well-known members of this family, were isolated from *Streptomyces species* (Fig. 1).[2] In 2011, tirandamycin G (**6**), a novel dienoyl tetramic acid with inhibitory activity against the *B. Malayi* AsnRS was isolated by Shen and co-workers[3] from *Streptomyces* sp.; 17944 along with two known tirandamycin A (**1**) and tirandamycin B (**2**). Tirandamycins also exhibited antibacterial activity against Gram-positive bacteria and in vitro activity against bacterial DNA-directed RNA polymerase.[4] Previously, tirandamycins have not been identified for the use in the prevention and treatment of lymphatic filariasis (LF). Consequently, tirandamycins represent a new lead structure for the discovery and development of antifilarial drugs. In addition to the dienoyl tetramic acid moiety, tirandamycins possess another fascinating structural element, the 2,6-dioxabicyclononane skeleton. In the tirandamycin family, two types of 2,6-dioxabicyclononane structures are known. One is the oxabicyclononane structure with an epoxy ketone moiety (tirandamycin A and B) and the other incorporates a double bond (tirandamycin C, D and E),[5] but tirandamycin G contains vicinal dihydroxy in 2,6-dioxabicyclononane skeleton (Fig. 1).

The complex molecular architecture and potent pharmacological properties render this family of antibiotics worthy targets for their biosynthetic[6] and synthetic exploration.[7] The most significant challenging feature of the tirandamycins synthesis is the *anti, anti*-dipropionate stereotriad unit which is used for the construction of 2,6-dioxabicyclononane skeleton. Recently, we have successfully employed our own developed desymmetrization protocol for the synthesis of 2,6-dioxabicyclononane skeleton of tirandamycin C (**3**).[8] To further demonstrate the utility of desymmetrization protocol, we tried to synthesize tirandamycin G that led to the synthesis of 10-*epi*-tirandamycin E, which is described in this manuscript.

Our retrosynthetic analysis for the synthesis of tirandamycin G (**6**) is illustrated in Scheme 1. We envisioned that tirandamycin G (**6**) could be assembled from the bicyclic aldehyde **7** and Schlessinger's phosphonate **8**[7a,7c] *via* Horner-Wadsworth-Emmons olefination. Aldehyde **7** in turn could be accessible from an advanced 2,6-dioxabicyclononane intermediate **9** *via* substrate controlled dihydroxylation. The bicyclic framework of **9** could be prepared by elaboration of lactone **10**, which in turn would arise from esterification of acid **12** with diol **11**, followed by ring-closing metathesis

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http://dx.doi.org/10.1016/j.tet.2017.01.057
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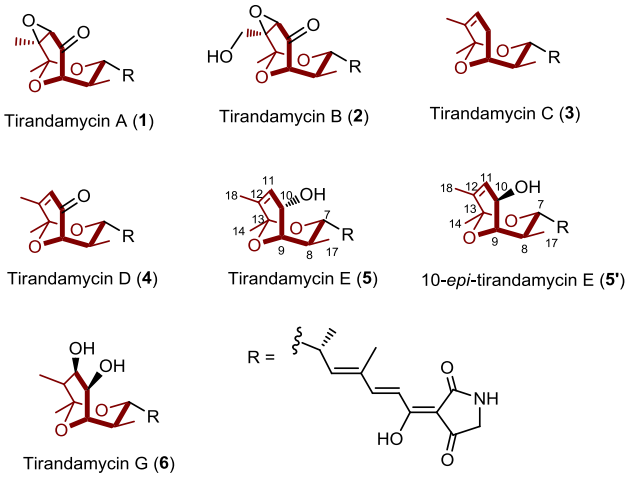
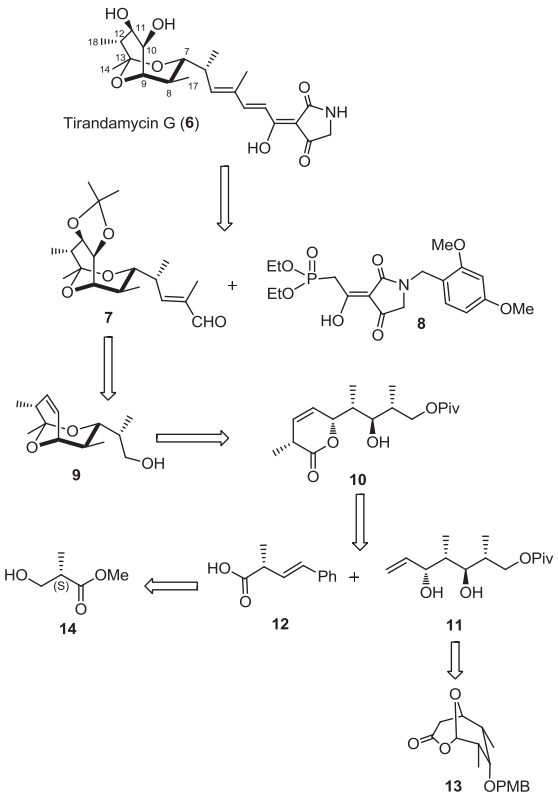


Fig. 1. Structures of tirandamycins (**1**–**6**).

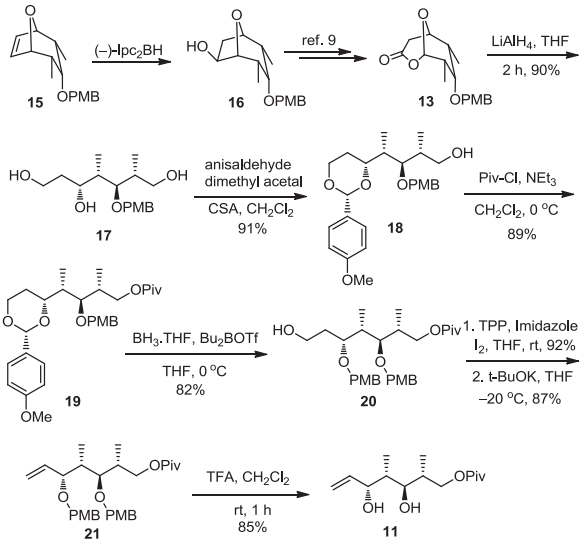
(RCM) reaction. Diol **11** in turn could be achieved from a known bicyclic lactone **13**.[9]

2. Result and discussion

Our first objective focused on the stereoselective synthesis of the 2,6-dioxabicyclic skeleton **9**. As outlined in Scheme 2, the fragment **11** was prepared following a desymmetrization of bicylic olefin **15** using Brown's chiral hydroboration followed by oxidation *via* known lactone **13**, which was widely used as a building block for the synthesis of polypropionated natural products in our group.[10] Lithium aluminum hydride reduction of **13** afforded triol **17** in 90% yield. The conversion of triol **17** to PMB acetal **18** was carried out using anisaldehyde dimethyl acetal[11] and substoichiometric amount of camphorsulfonic acid (CSA). The primary hydroxyl group of compound **18** was protected as pivaloyl ester with PivCl and Et_3N in anhydrous CH_2Cl_2 to obtain compound **19** in good yield. Regioselectively reductive opening of PMB acetal with BH_3.THF and Bu_2BOTf led to the primary alcohol **20**.[12] The hydroxy was converted to its iodo, followed by elimination with *t*-BuOK in THF smoothly afforded olefin **21** (80% yield over two steps). The di-PMB protecting group in the resulted olefin **21** were removed using TFA in CH_2Cl_2 at room temperature to furnish the diol **11** in good yield (Scheme 2).



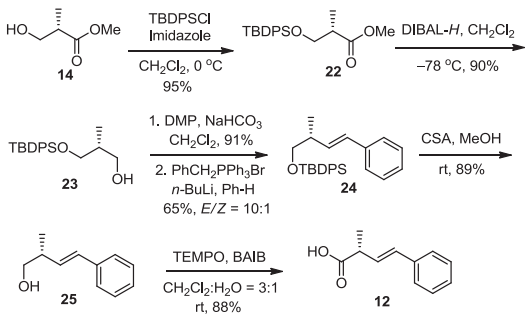
Scheme 1. Retrosynthetic analysis.



Scheme 2. Synthesis of the fragment **11**.

Preparation of the acid **12** began with protection of the Roche's ester as its TBDPS ether with TBDPS-Cl and imidazole in CH_2Cl_2 at 0 °C. DIBAL-*H* reduction of **22** afforded corresponding alcohol which on treatment with the Dess-Martin periodinane[13] reagent gave aldehyde. The aldehyde was immediately subjected to Wittig olefination with benzyltriphenylphosphonium bromide and *n*-BuLi in benzene at 0 °C to furnish olefin **24** as a 10:1 ratio of *E*/*Z* isomers (53% yield over three steps). The TBDPS group present in compound **24** was deprotected with CSA in MeOH to obtain alcohol **25**. TEMPO-BAIB[14] mediated oxidation of the resulting alcohol in CH_2Cl_2-water (3:1) afforded the acid **12** in 88% yield (Scheme 3).

Having diol **11** and acid fragment **12** in hand, our next objective was to couple both the fragments. Initially, esterification of acid **12** with alcohol **11** was performed activatin with dicyclohexyl carbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine



Scheme 3. Synthesis of the fragment **12**.