Tetrahedron 71 (2015) 7539–7549

Contents lists available at ScienceDirect

Tetrahedron

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

Studies directed towards the total synthesis of polyether antibiotic ionomycin: asymmetric synthesis of fragments C(24)–C(32) and C(1)–C(23)

J.S. Yadav *, Nagendra Nath Yadav, B.V.Subba Reddy

Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

Article history:
Received 24 June 2015
Received in revised form 1 August 2015
Accepted 3 August 2015
Available online 7 August 2015

Keywords:
Polyether antibiotic
Ionomycin
Desymmetrization
Sharpless asymmetric epoxidation and regeoselective opening of epoxide
Julia-Kocienski olefination

ABSTRACT

A convergent and stereoselective approach for the synthesis of C1–C23 and C24–C32 segments of polyether antibiotic, ionomycin has been achieved. The key steps involved in this approach are the elaboration of two advanced fragments from a common precursor using enzymatic desymmetrization to create two methyl chiral centers, desymmetrization of the bicyclic olefin to introduce two methyl and two hydroxyl chiral centers, the use of Evans auxiliary to introduce another methyl group and the creation of four chiral centers in *bis*-tetrahydrofuran ring by Sharpless asymmetric epoxidation and the regioselective opening of epoxide with methyl sulphone. The coupling of C11–C16 with C17–C23 was achieved through a Julia-Kocienski olefination and directed Aldol reaction. Oxidation of C9 alcohol facilitates the coupling of C10–C23 with C1–C9.

1. Introduction

Ionomycin (**1**, Fig. 1) is one of the important polyether antibiotics, which was isolated by Meyers and co-workers from fermentation broths of *Streptomyces congoblatus* in 1978.[1] It has the ability to chelate various inorganic cations so as to transport them across lipid membranes. Ionomycin has a unique feature that distinguishes it from all other ionophores. In particular, it chelates slectively with calcium (and other divalent) ions as a *dibasic acid* in an octahedral coordination array,[2] while other ionophores exhibit their chelating property as monobasic acids.

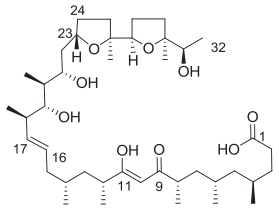


Fig. 1. Chemical structure of ionomycin (**1**).

The X-ray structure and absolute stereochemistry of calcium and cadmium complexes of ionomycin were established by Gougoutas and co-workers in 1979.[3] The main structural feature of this ionophore includes the presence of substituted bis-tetrahydrofuran ring, 14 stereogenic centers and a β-dicarbonyl moiety, which is rare in these natural products. The presence of β-dicarbonyl moiety is responsible for ionomycin's intense ultraviolet absorption at 280 nm and also provides two of the six metal ligation points. Because of its broad range of therapeutic potentials and unique structural features, ionomycin has attracted the attention of many synthetic organic chemists.

A few total syntheses[4–7] and many formal synthetic approaches[8] have been reported in the literature. The retrosynthesis of all the previously published total syntheses of ionomycin employs similar strategies. Hanessian et al.[4] and Evans[5] et al. reported the identical disconnections for the construction of ionomycin backbone but used different strategies for the synthesis of polypropionate and deoxypolypropionate fragments. Hanessian et al. used the chiron approach using L-glutamic acid and Evans et al. reported convergent asymmetric synthesis of ionomycin using chiral enolate chemistry. Lautens[6] applied ring opening strategy for the synthesis of polypropionate and deoxypolypropionate subunits, while *Trans*-tetrahydrofuran motif was prepared via Sharpless asymmetric epoxidation and $VO(acac)_2$ catalyzed epoxidation protocol. Recently, Kocienski et al.[7] reported the total synthesis of

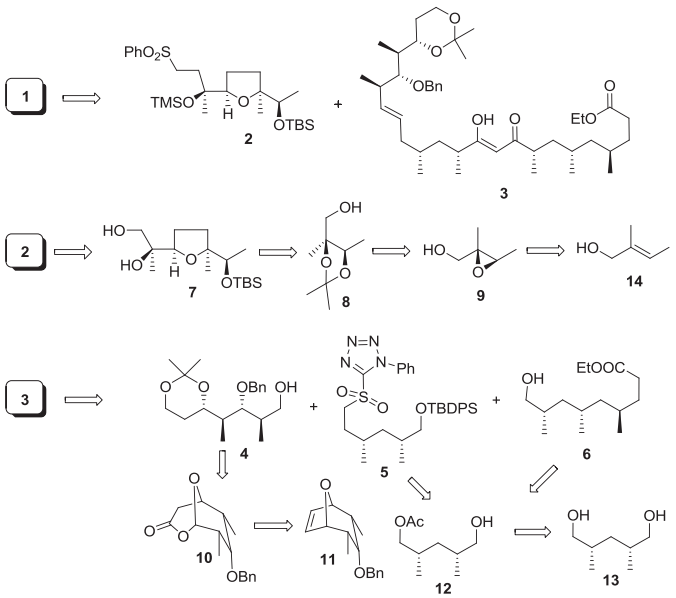
* Corresponding author. Fax: +91 40 27160512; e-mail address: yadavpub@iict.res.in (J.S. Yadav).

http://dx.doi.org/10.1016/j.tet.2015.08.011
0040-4020/

ionomycin using gold(III)-catalyzed cycloisomerization of α-hydroxyallene and rhodium-catalyzed rearrangement reaction to generate the β-diketone moiety.

Following our interest in the total synthesis of biologically active natural products by desymmetrization strategy[9,10] and inspiring biological activity combined with fascinating structural features of ionomycin (**1**), we herein report a convergent stereoselective method for the synthesis of C24–C32 (**2**) and C1–C23 (**3**) fragments of ionomycin. This method involves Sharpless asymmetric epoxidation to generate tetrahydrofuran ring, desymmetrization strategy, Evans alkylation, Julia-Kocienski olefination and directed Aldol reaction.

Retrosynthetically, ionomycin **1** (Scheme 1) can be synthesized from four key fragments, **6** (C1–C9), **5** (C11–C16), **4** (C17–C23) and **2** (C24–C32), which is similar to Lautens approach.[6] *Trans*-Tetrahydrofuran **2** was proposed to be synthesized via the Sharpless epoxidation of a suitable allylic alcohol followed by regioselective ring opening of the epoxide.



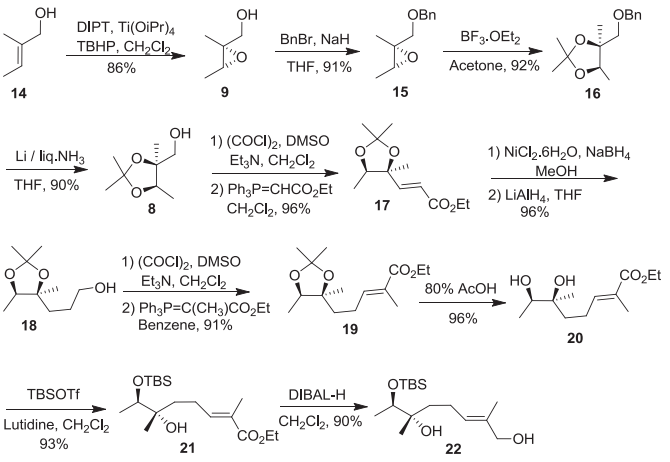
Scheme 1. Retrosynthetic analysis of C24–C32 (**2**) and C1–C23 (**3**) segments of ionomycin (**1**).

Polypropionate fragment (**4**) can be obtained through desymmetrization of bicyclic olefin developed previously by us.[9] Deoxypolypropionate segment can be achieved through a common precursor **12**, which in turn can be synthesized by desymmetrization of *meso*-diol[9k,10] and Evan's asymmetric alkylation. The three fragments could be connected through a modified Julia olefination followed by base catalyzed directed Aldol reaction, while fragment (**2**) can be coupled with fragment **4** via sulphone addition to aldehyde corresponding to alcohol fragment (**4**) to finish the total synthesis.

2. Results and discussion

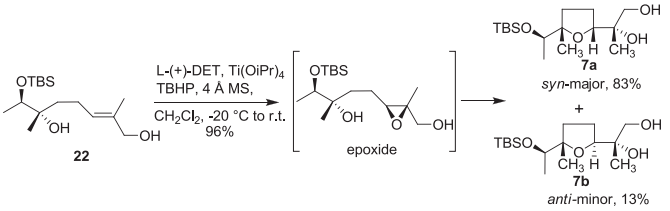
2.1. Stereoselective synthesis of C24–C32 furanoid fragment of ionomycin (2)

Accordingly, the synthesis of C24–C32 fragment (**2**) began from the readily available starting material tiglic acid. The requisite allylic alcohol **14** was prepared from tiglic acid by esterification[11] followed by reduction of the ethyl tiglate.[12] Sharpless asymmetric epoxidation of allylic alcohol **14** using D-DIPT, Ti(O*i*Pr)$_4$ and TBHP in dry CH_2Cl_2 afforded the epoxy alcohol **9** in 86% yield with 92% *ee*. The analytical data of **9** was found to be identical with the data reported in literature.[13] The free hydroxy group of **9** was protected as its benzyl ether (**15**). Stereoselective ring opening of the epoxide (**15**) with acetone in the presence of $BF_3{\cdot}OEt_2$ at 0 °C afforded the pure acetonide **16** in 92% yield.[9e,14] Debenzylation of **16** under the Birch conditions[15] using liquid ammonia and lithium metal afforded the primary alcohol **8** in 90% yield as a colorless liquid. Swern oxidation of the primary alcohol **8** followed by C_2-Wittig reaction afforded the α,β-unsaturated ester **17** in 96% yield over two steps. Reduction of double bond of the ester **17** with $NaBH_4$ and $NiCl_2.6H_2O$ in MeOH[16] afforded the saturated ester, which was further reduced with $LiAlH_4$ in THF to give the saturated alcohol **18** in 96% yield in two steps. Swern oxidation of **18** followed by a two carbon Wittig reaction resulted in the formation of α,β-unsaturated ester **19** (exclusively *E*-isomer) in 91% yield over two steps. Cleavage of the isopropylidene acetal **19** with 80% aqueous acetic acid afforded the diol **20** in 96% yield. Selective silyl protection of the secondary alcohol of **20** with TBSOTf and 2,6-lutidine in CH_2Cl_2 at 0 °C afforded the silyl ester **21** in 93% yield. Reduction of the ester **21** with DIBAL-*H* furnished the primary allylic alcohol **22** in 90% yield (Scheme 2).



Scheme 2. Synthesis of precursor **22** for key intermediate **7a**.

The tetrahydrofuran moiety **7** was achieved by Sharpless asymmetric epoxidation protocol[17,18] using 1 equiv of L-DET, 1 equiv of Ti(O*i*Pr)$_4$ and 2.2 equiv of TBHP in CH_2Cl_2 at −20 °C to room temperature. The corresponding product was obtained as a mixture of *syn*-diol (major **7a**, 83% yield) along with a minor *anti*-diol (**7b**, 13% yield, Scheme 3). The formation of **7a** and **7b** could be explained by intramolecular stereoselective ring opening of the epoxide with hydroxyl function catalyzed by Ti(O*i*Pr)$_4$. Both products were easily separated by column chromatography and well characterized by NMR spectrum.



Scheme 3. Synthesis of key intermediate **7a**.

Selective sulfonylation of 1,2-diol[19] followed by treatment with NaH afforded the terminal epoxide **23** in 96% yield over two steps (Scheme 4). Regioselective opening of terminal epoxide **23** with