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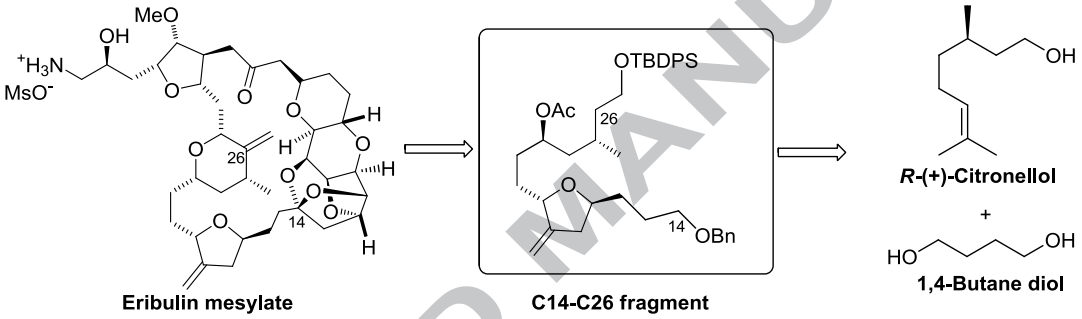

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A practical synthesis of C14-C26 fragment of anticancer drug, eribulin mesylate

Nadella Lavanya, Nayani Kiranmai, Prathama S. Mainkar and Srivari Chandrasekhar *

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

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ABSTRACT

High yielding synthesis of C14-C26 fragment of Eribulin is achieved from commercially available *R*-(+)-citronellol and 1,4-butane diol utilizing the chirality of citronellol 'methyl' centre as C25, organocatalytic epoxidation to install C23 chirality and Sharpless asymmetric dihydroxylation to install chirality at C20 and C17.

Eribulin mesylate (**1**) (Halaven®) has attracted global attention as the last line of chemotherapeutic agent in the cure of metastatic cancer for patients who have already undergone chemotherapy with other drugs and not responded. Also, this drug has become a reference drug in the text books as pruned version of Halichondrin B.[1] Eribulin (**1**) induces apoptotic mechanism on cancer cells with minimal neurotoxic effects on patients.[2] The seminal contributions in discovering this drug through total synthesis by Kishi *et al.*[3] inspired several research groups globally to develop new synthetic strategies.[3-6] Sticking to the basic retrosynthetic plan, a good number of improved strategies have been designed. More recently, an industrially viable synthesis of eribulin is reported by researchers from Eisai Company, Japan.[7] Despite all these efforts, treatment regimen costs an average of ~4,000 USD per cycle.[8] Thus more efficient, scalable and cost effective approaches are welcome. Recently, we have reported a synthesis of C14-C26 fragment as our initial effort[9] towards the gigantic target (Figure 1).

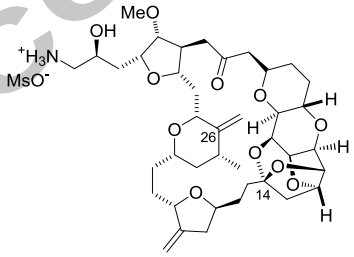
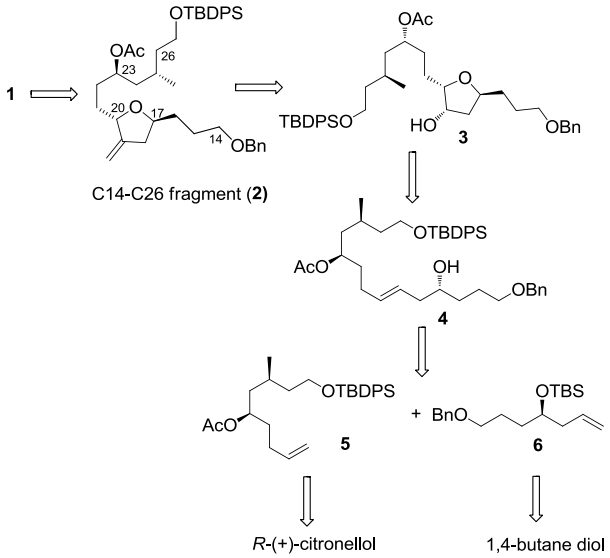


Figure 1. Structure of eribulin mesylate (**1**)

Our continuous efforts have now resulted in achieving C1-C13 (see the preceeding paper)[10a] and C28-C35 fragments (see the following paper)[10b] very efficiently. Herein, we report a short and practical synthesis of C14-C26 fragment **2** of eribulin, starting from commercially available *R*-(+)-citronellol and 1,4-butane diol.

The retrosynthetic delineation is shown in scheme 1. We have planned to construct the tetrahydrofuran ring of **3** from alcohol **4** through Sharpless asymmetric dihydroxylation followed by an *insitu* S_N2-cyclization. The alcohol **4** could be synthesized by cross-metathesis reaction between **5** and **6**, which inturn could be obtained from *R*-(+)-citronellol and 1,4-butane diol, respectively.

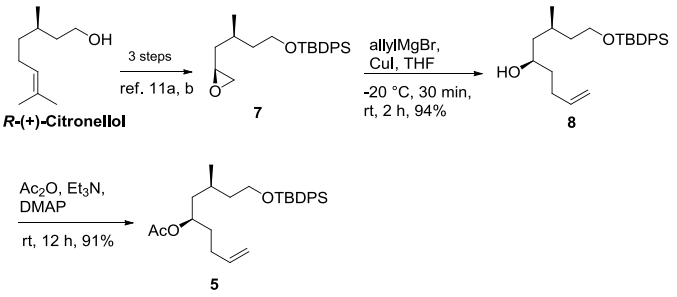


Scheme 1: Retrosynthetic analysis for C14-C26 fragment of Eribulin

The primary hydroxyl group of commercially available *R*-(+)-citronellol was protected as *tert*-butyldiphenylsilyl ether, ozonolysis of the olefinic bond yielded aldehyde[11a] which was converted to epoxy silyl ether **7** using organocatalytic reaction conditions,[11b,12,13] in multiples of grams. CuI catalyzed regioselective opening[14] of epoxide **7** was achieved with allylmagnesium bromide to get alcohol **8** in 94% yield. The liberated secondary hydroxyl group has been protected as acetate **5** by reacting with Ac_2O/Et_3N/DMAP in CH_2Cl_2 at rt for 12 h in 91% yield (Scheme 2).

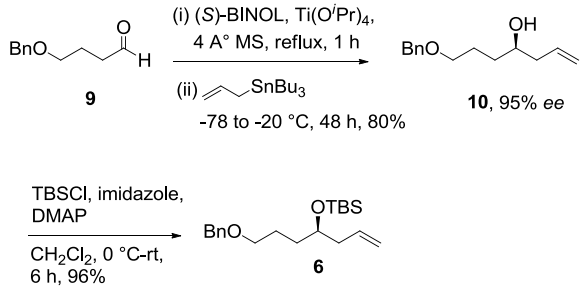
*Corresponding author. Tel.: +91 40 27193210; fax: +91 40 27160512.
E-mail address: srivaric@iict.res.in (S. Chandrasekhar).

Dedicated to Dr. M. Lakshmi Kantam on her 60th birthday.



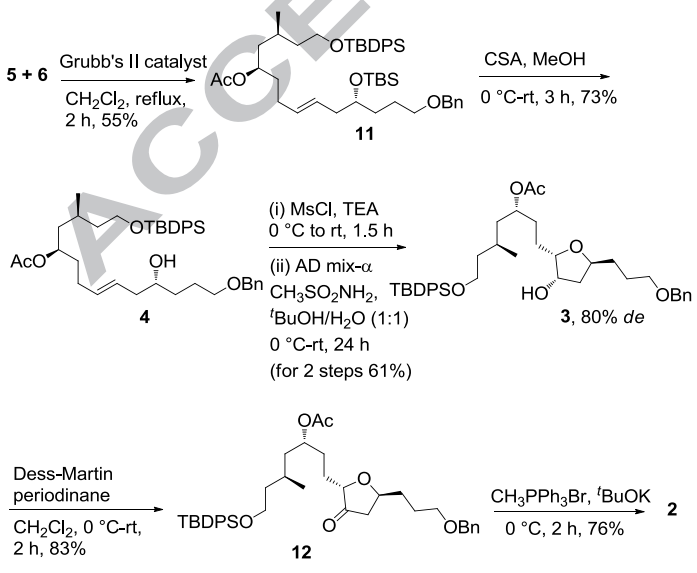
Scheme 2: Preparation of acetate **5**

The homoallyl alcohol **10** was synthesized on gram scale from aldehyde **9** (obtained from 1,4-butane diol).[15] The asymmetric Keck allylation[16] on 4-benzyloxybutyraldehyde **9** catalysed by (*S*)-BINOL gave homoallyl alcohol **10** in 80% yield with 95% *ee* (determined by chiral HPLC).[17] The secondary alcohol **10** was silylated to **6** using TBSCl and imidazole in 96% yield (Scheme 3).



Scheme 3: Preparation of silylether **6**

The utilization of Grubbs' 2nd generation catalyst[18] allowed us to stitch **5** and **6** to realize **11** in 55% yield with differentially protected tetrol functionality and the C14-C26 carbon framework (Scheme 4). Selective deprotection of secondary silyl ether with camphorsulfonic acid in methanol gave secondary alcohol **4** in 73% yield. A well adapted strategy was chosen to construct the furan ring, wherein the hydroxyl group was converted to mesylate ester which on exposure to Sharpless asymmetric dihydroxylation conditions using AD mix-α and methanesulfonamide in ^{t}BuOH/H_2O (1:1) allowed a smooth dihydroxylation followed by



Scheme 4: Preparation of C14-C26 fragment **2**

insitu S_N2 cyclization[9,19] to provide hydroxytetrahydrofuran derivative **3** in 61% yield with 80% *de*. The free hydroxyl group of **3** was oxidized with Dess-Martin periodinane in CH_2Cl_2 to keto derivative **12** in 83% yield, which upon Wittig reaction provided the target exomethylene tetrahydrofuran **2** in 76% yield.

In conclusion, a practical and high yielding synthesis of C14-C26 fragment of Eribulin is achieved having all the required functionalities to elaborate the total synthesis.

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Supporting Information

Supplementary data associated with this article, experimental and characterization data, can be found in the online version.