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Graphical Abstract

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Synthesis of C1-C11 Eribulin Fragment and its Diastereomeric Analogues

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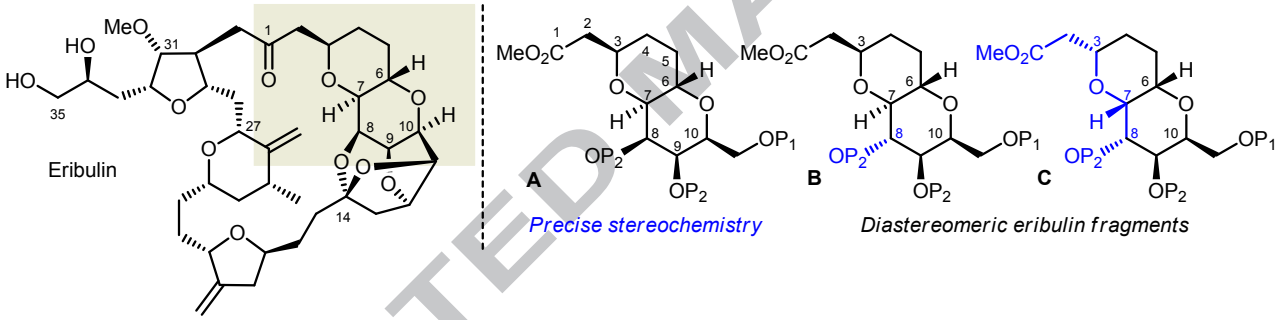

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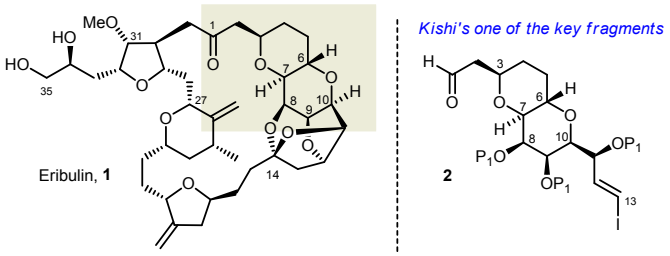
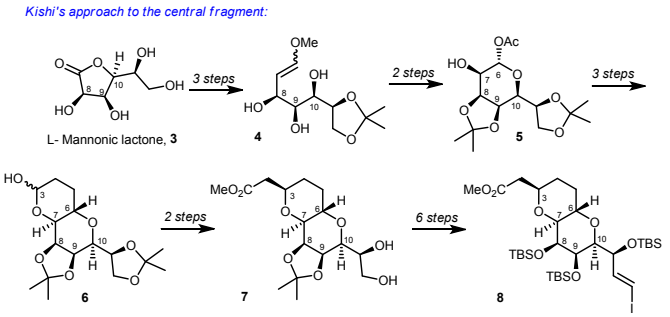
ABSTRACT

A practical stereoselective synthesis of the central C1-C10 fragment of eribulin and its two diastereomeric analogs is developed. Our approach relied on the use of L-ascorbic acid as the starting material which allowed accessing a key intermediate with a syn diol moiety (C9 and C10 of eribulin) and a carboxylic ester group. A functionalized six membered lactone having several required hydroxyl groups was then obtained. In a number of steps, the lactone was converted to an intermediate for our key *oxa*-Michael reaction. A regio- and stereocontrolled intramolecular oxa-Michael reaction completed the synthesis of the C1-11 fragment having a trans-fused tetrahydropyrans with the exact stereochemistry of various hydroxyl groups, as in eribulin.

Eribulin (**1**) is a non-taxane drug and first-in-class microtubule dynamics inhibitor which was approved by FDA in 2010 for use in patients who previously received at least two prior chemotherapeutic regiments for the metastatic breast cancer.[1-5] The birth of eribulin originated from the Kishi group while working on the total synthesis of halichondrin and its various analogues to search for a better microtubule binding agent.[6-18] Eribulin seems to have a different binding site compared to other known classes of tubulin-targeted agents such as taxane (paclitaxel and docetaxel), vinca alkaloids (vinorelbine and vinblastine), and epothilones (ixabepilone).[19,20] Eribulin binds to an inter-dimer interface or β-tubulin subunit alone and inhibits the microtubular growth phase of microtubular dynamics instability in interphase cells without affecting on the shortening of microtubule.[19,20] It is also known to promote the centromere spindle relaxation without affecting the rate of stretching.[5] Shown in Scheme **1** is a key central fragment having trans-fused pyrans and densely populated functional groups, **2**.[17] Over the years, Kishi[8] and others[21-23] have reported several approaches to the total synthesis of this key central fragment. One of the plans of the Kishi's synthesis is shown in Scheme **2**. In their approach, L-mannonic lactone, **3** was converted to **4** in three steps and this produced the six membered derivative **5** easily. *C*-Alkylation strategy then led to producing **6** which was converted to scaffold, **7** by an intramolecular oxa-Michael reaction.[36] Further, chemical transformations completed the total synthesis of the central fragment, **8**. Shown in Scheme 3 are our three targets that are based on the central C1-C11 fragment of eribulin. The bicyclic compound **9** has the precise stereochemistry of several functional groups as in eribulin. For example, it has a similar trans-fused pyran moiety, two secondary hydroxyl groups at C9 and C11, one primary hydroxyl group at C11 and a chiral side chain with the carboxyl ester moiety at C3. The second target (**10**) has an epimeric hydroxyl group at C8 and the rest is the same as in **9**. Compound **11** as the third target has a cis-fused pyran moiety, the reversal of the stereochemistry of hydroxyl group at C8 and the chiral side chain at C3 compared to **9**. Our first objective was to develop a practical and scalable stereoselective synthesis of all the three compounds, i.e. **9**, **10** and **11**, and preferably, to use a cheap chiral starting material to make it scalable and attractive. In continuation of our ongoing efforts to building a macrocyclic compound collection having the key fragments of bioactive natural products and related compounds,[24-26] we plan evaluating them in several challenging biological targets related to protein-protein interactions[27,28] and pathways in cytoskeleton-based targets.[29-33]

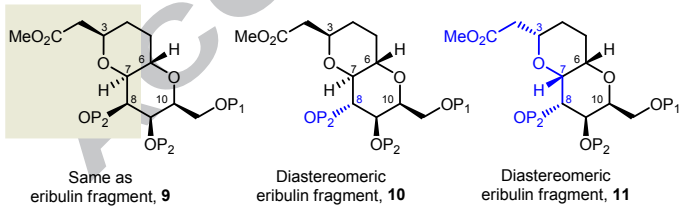


Scheme 1. Eribulin (**1**) and a central key fragment having trans-fused pyrans with several other functional groups, **2**.

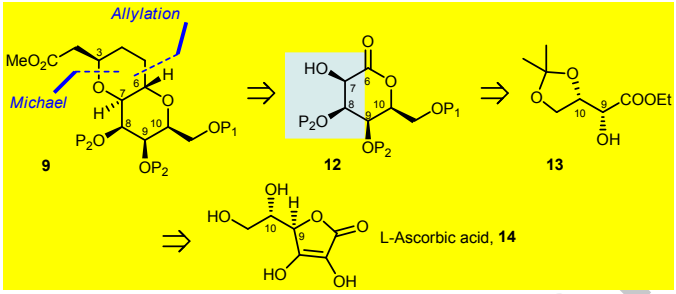


Scheme 2. Kishi's approach to the synthesis of the central fragment.

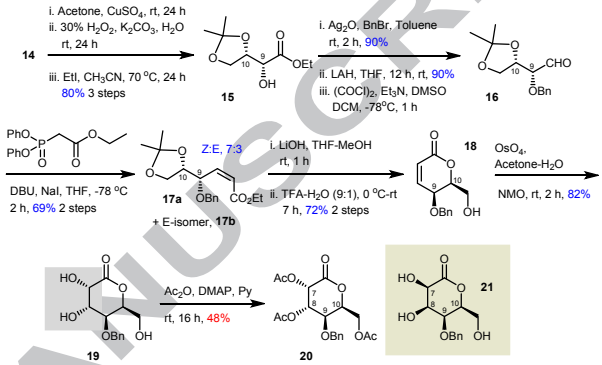
Our plan to obtain **9** (Scheme **4**) starts with L-ascorbic acid (**14**) [34] which is a cheap source to produce **13** in large amounts. This can then lead to producing the lactone (**12**) needed for our next key steps. Following the literature procedure,[34] L-ascorbic acid (**14**) gave **16** (Scheme **5**) via **15**. It was then subjected to Wittig olefination to obtain the cis-product (**17a**) as the major isomer which led to producing a lactone **18**[35] easily. When subjected to cis hydroxylation conditions (OsO_4), it gave **19** which was fully characterized following acetylation (**20**). The details of the stereochemical assignments are provided in the supporting material. Failing to reach compound **21** by this approach, we then developed an alternate path which is shown in Scheme **6**. For obtaining an easy to access to both compounds **21** and **19**, we then tried Sharpless facial selective dihydroxylation on **17a** and this approach produced **22** and **23** (Scheme **6**) as two separable diastereomers in a 7:3 ratio (note: the stereochemistry was assigned after cyclization). Upon subjection to acidic conditions, **22** produced **21** and **23** gave **19** respectively in high yields (Scheme **6**).



Scheme 3. Eribulin central fragment-based three targets and derived macrocyclic compounds.

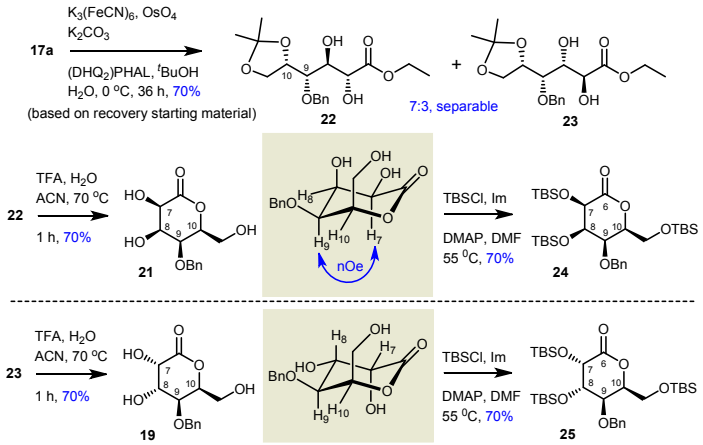


Scheme 4. Our synthetic planning for **9.**

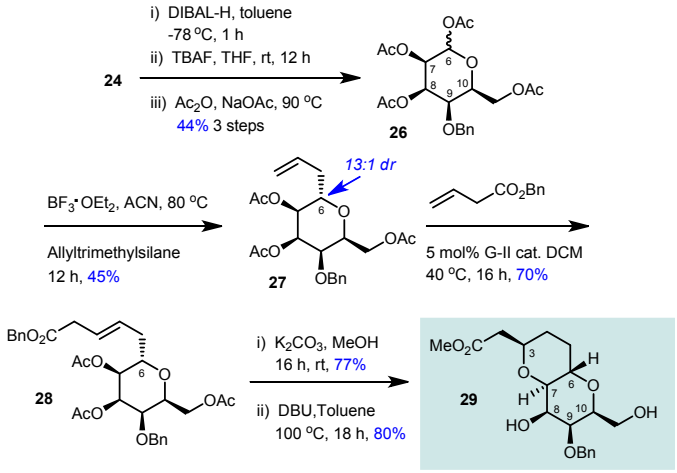


Scheme 5. Synthesis of a diastereomeric lactone, **20** from L-ascorbic acid, **14.**

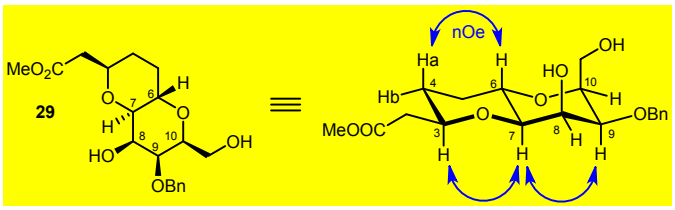
Both of them were thoroughly assigned by 1D and 2D NMR and MS. Compound **21** was simply transformed to **24**. As shown in Scheme **7**, **24** was then converted to **26** in an easy transformation. In two steps that utilized the Lewis acid catalyzed *C*-allylation[37] at C-6 and further cross metathesis produced **28**, a key precursor to try an intramolecular oxa-Michael reaction. When **28** was subjected to deacetylation under basic conditions in methanol, it produced the triol derivative with the trans-esterified product. This material on exposure to DBU in refluxing toluene gave the expected Michael product (**29,** scheme **7)** as the thermodynamically stable isomer (via double bond isomerisation) having the *trans*-fused pyran moiety. This product was thoroughly assigned by 2D NMR (see Scheme **8**).



Scheme 6. Synthesis of the required lactones, **24** and **25**.

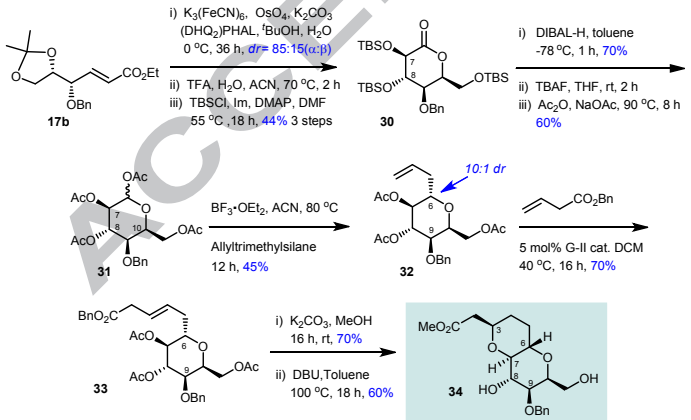


Scheme 7. Synthesis of eribulin central fragment.



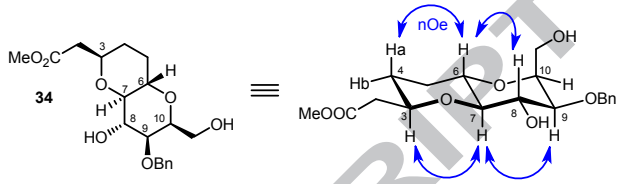
Scheme 8. Assignment of **29** by nOe.

In another study for developing the synthesis of **34** (Scheme **9**) having an epimeric group at C8, the *trans* isomer of the Wittig product, **17b** was used as the starting material. The Sharpless selective dihydroxylation on **17b** produced (α-face attack) diol in 85:15 (α:β) diastereomeric ratio. This led to producing the lactone **30** in two steps having a 1,2-*trans* relationship between two hydroxyl groups at C7 and C8. This upon subjection to DIBAL-H reduction followed by the stereoselective alkylation led the synthesis of the required intermediate, **32** via compound **31**. When subjected to similar conditions, as in the previous example, compound **32** produced **33**, a key material to try our key intramolecular oxa-Michael reaction.

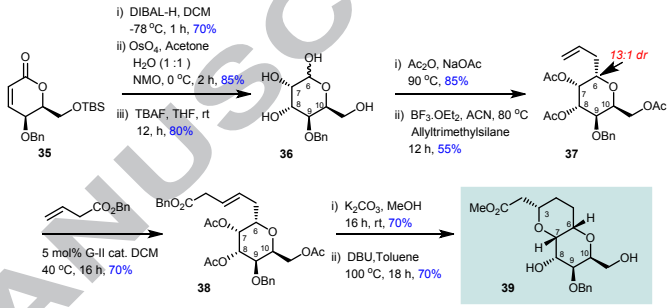


Scheme 9. Synthesis of **34** having 1,2-trans fused pyrans and an epimeric hydroxyl group at C-8.

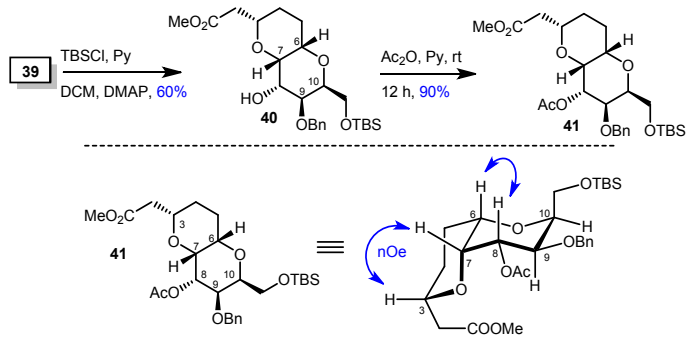
This upon basic conditions gave the expected Michael product **34** in high yields. Once again, as before, the product was well-characterized by MS, 1D and 2D NMR studies and the key nOe sites are shown in Scheme **10**. Our synthesis for the third target **39** having 1,2-cis fused pyran moiety is shown in **Scheme 11**. **35**, a lactone derivative was obtained from **18** easily, and this produced **36** in a simple 3 step transformation. This was then subjected to C-allylation conditions which gave **37**, and finally, the cross metathesis led to producing the desired key starting material, **38** to try our Michael approach. As with two previous examples, this also produced the expected Michael product, **39** as a single diastereomer that resulted from the regio- and stereoselective reaction. As we have done before, **41** (Scheme **12**) was thoroughly subjected to nOe studies for the stereochemical assignment.



Scheme 10. Assignment of **34** by nOe.



Scheme 11. Synthesis of **39** having 1,2-*cis* fused pyrans and isomeric functional groups at C-8 and C-3.



Scheme 12. Assignment of **41**.

To summarize, a simple and practical synthesis to obtain eribulin central C1-C11 fragment and its two diastereomeric analogues is developed. The key steps involved in the synthesis are lewis acid catalyzed *C*-glycoside allylation; crass metathesis; alkene isomerisation and intra molecular oxa-Michael additions. The key scaffolds (**9**, **10**, **11** Scheme 3) were further utilized in obtaining a diverse set of 17-membered macrocyclic compounds. The biological evaluation of all the compounds generated from this program is ongoing and these studies will be published in a due course**.**

Conflicts of interest

There are no conflicts to declare.

Acknowledgment

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Supplementary data

Supplementary data (Detailed experimental procedures, characterization data and copies of NMR spectra for all the new compounds are provided.) associated with this article can be found, in the online version, at

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Graphical Abstract

- Synthesized precise C1-C11 eribulin fragment from L-ascorbic acid.
- Synthesized two diastereomeric analogs of precise eribulin fragment.
- Dihydroxylation; *C*-allylation; crass metathesis and oxa-Michael are key reactions.
- All the synthesized compounds are fully characterized by 1D and 2D NMR techniques.

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Synthesis of C1-C11 Eribulin Fragment and its Analogs for Building A Diverse Set of Macrocycles

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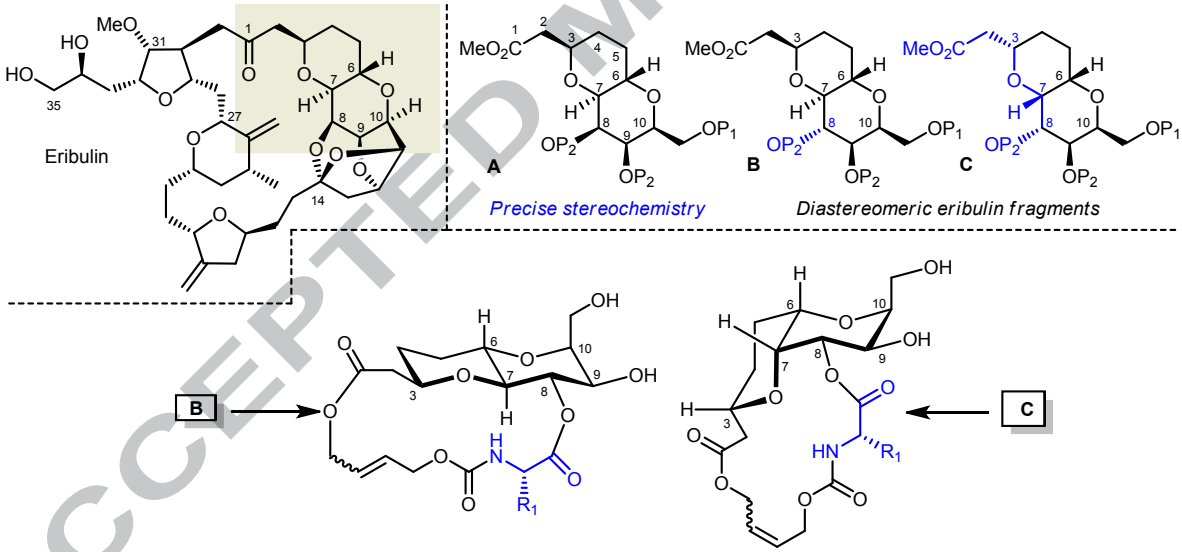

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