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Practical Stereoselective Synthesis of Eribulin Fragment toward Building a Hybrid Macrocyclic Toolbox

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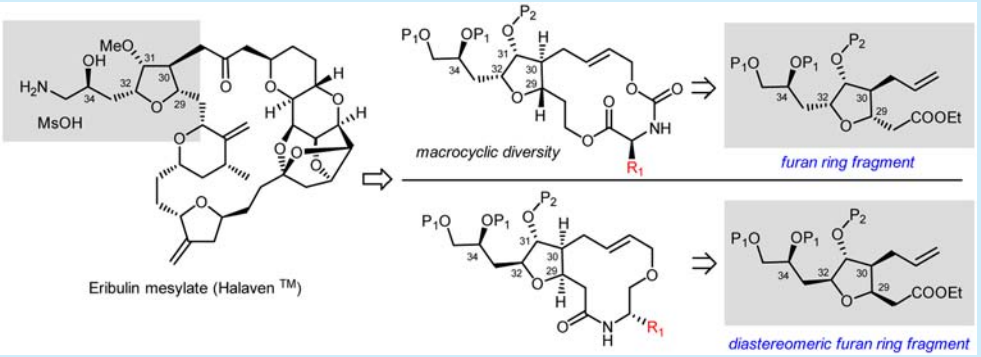
Supporting Information



ABSTRACT: A practical stereoselective synthesis to obtain the substituted furan ring as the substructure of eribulin is developed. An asymmetric *syn*-aldol and intramolecular oxy-Michael were two key steps in our approach. The functionalized furan derivatives were then utilized further to build the 14- and 12-membered macrocyclic diversity as *trans*- and *cis*-fused (C-29 and C-30) compounds. This is the first report of building a chemical toolbox with macrocyclic small molecules having *trans*- or *cis*-fused 14- or 12-membered rings containing the substructure of eribulin and its diastereomer.

Eribulin mesylate (Halaven, **F1.1**) is a nontaxane, first-in-class, microtubule dynamics inhibitor approved by the FDA for use in patients who previously received at least two prior chemotherapeutic regiments for metastatic breast cancer.[1] Eribulin is a synthetic analogue of halichondrin B (structure not shown) marine natural product.[1a,2] The novel mechanism of action of eribulin differs from other known classes of tubulin-targeted agents, such as taxane (paclitaxel and docetaxel), vinca alkaloids (vinorelbine and vinblastine), and epothilones (ixabepilone), that bind to an interdimer interface or β-tubulin subunit alone and inhibit the microtubular growth phase of microtubular dynamics instability in interphase cells without causing any change in the shortening.[3] They also promote the centromere spindle relaxation without affecting the rate of stretching of microtubules.

In eribulin-treated human lymphoma and prostate cancer cells, several correlations of apoptosis are seen, like cytochrome c release from mitochondria, activation of caspase-3 and 9, and the cleavage of PARP, including phosphorylation of Bcl-2.[4] These results clearly demonstrate that eribulin has a broad spectrum of antitumor activity against a wide variety of human cancer types.

The fascinating architecture of eribulin can serve as an excellent starting point in developing a diversity synthesis program utilizing one of the key fragments building a chemical toolbox to hunt for small molecule modulators of protein−protein interactions[5] and in selected signaling pathways.[6] As part of our continuous interest in building a toolbox having compounds with different types of natural product-inspired macrocyclic rings,[7] we initiated studies that started with the stereodefined furan moiety as highlighted in **1.1** (Scheme 1). Our generic structure to explore the additional macrocyclic chemical space is shown as **1.2**. In addition to this, we also plan to develop the synthesis of a diastereomeric furan moiety (see **1.3**) for further stereochemical diversity in the macrocyclic chemical space.

Our specific diversity-based synthesis targets (**1.4** and **1.6**) are shown in Scheme 1. There are several attractive features in **1.4**. The functionalized stereodefined furan moiety is preserved as the substructure of eribulin. The incorporation of *trans*-fused (C-29 and C-30) 14-membered ring with an embedded amino acid moiety can allow the synthesis of analogues with variation in the chiral side chain. The synthesis of **1.4** can be achieved from the functionalized furan derivative **1.5**. Along similar lines, and using the diastereomeric furan moiety **1.7** (*cis* relationship between functional groups at C-29 and C-30 and *trans* between C-31 and C-32), we plan to develop the 12-membered ring based diversity synthesis. One of the key objectives in our approach is to develop an efficient and practical stereoselective synthesis of both stereodefined, enantiomerically pure furan moieties **1.5** and **1.7**.

Shown in Scheme 2 is our synthetic plan to access the furan derivative **1.5**. We envisioned an asymmetric intramolecular

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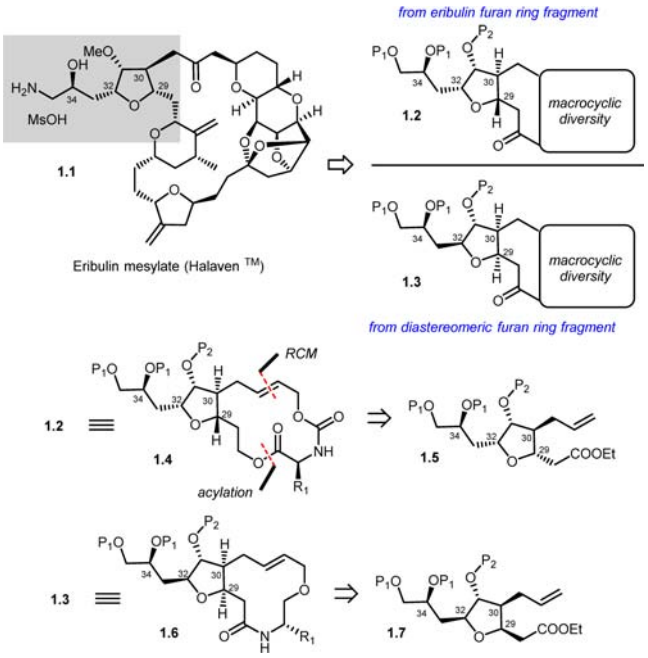
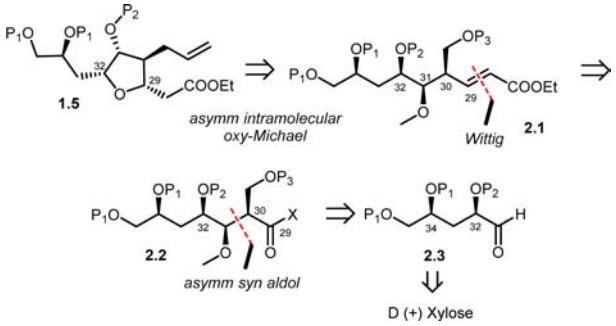
Scheme 1. Eribulin Fragment-Derived Hybrid Macrocycles Having 14- and 12-Membered Rings, 1.4 and 1.6, from the Corresponding Furan Moieties 1.5 and 1.7



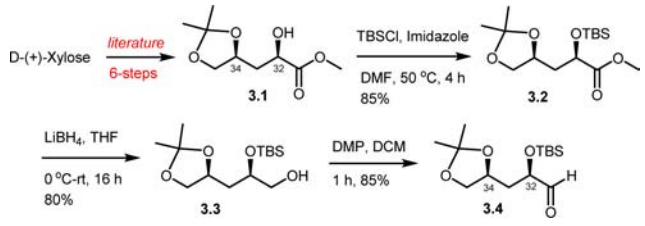
Scheme 2. Our Retrosynthetic Analysis of 1.5



oxy-Michael reaction giving **1.5** as the key ring-forming step from an acyclic precursor **2.1**. Based on the stereochemical outcome of this reaction, we can obtain either C-29 and C-32 *cis*- or *trans*-oriented functional groups. Compound **2.1** can be easily obtained from **2.2** via a two-carbon extension. In our synthetic planning for the target **2.2**, we decided to rely upon an asymmetric *syn* aldol reaction using a chiral auxiliary approach. The key aldehyde needed for the aldol reaction can easily be obtained from D-(+)-xylose in a simple series of steps. To the best of our knowledge, this approach has not been developed in the past for obtaining the stereodefined functionalized furan moiety of eribulin.[8]

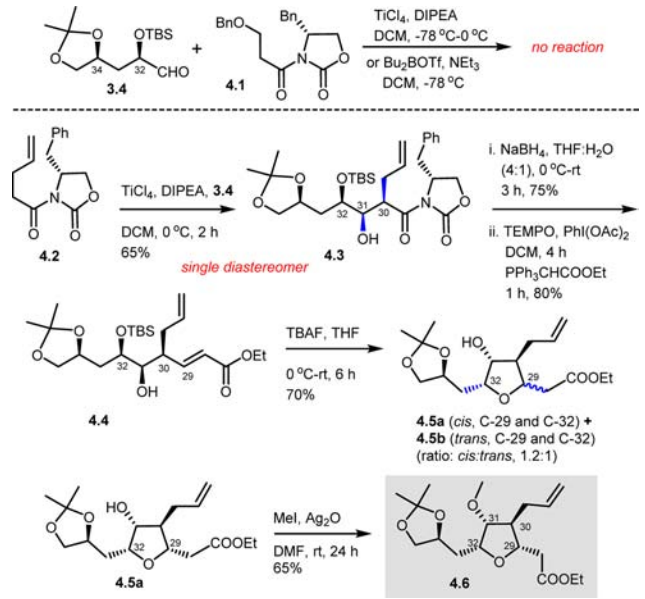
Following the synthesis plan as outlined in Scheme 2, our first goal is to develop a practical synthesis of **1.5** from **3.4** as an aldehyde needed for the aldol reaction. The synthetic steps to achieve this objective are shown in Scheme 3. Compound **3.1** was easily prepared from D-(+)-xylose following the literature procedure.[9] This β-OH carboxyl ester was then subjected to silyl protection (**3.2**) and subsequent reduction to give **3.3** as an alcohol moiety. The DMP oxidation led to obtaining the corresponding aldehyde **3.4**.

Scheme 3. Synthesis of Key Aldehyde 3.4 from D-(+)-Xylose



Our attempts to carry out the *syn*-aldol reaction are shown in Scheme 4. To our surprise, the first attempt using a keto

Scheme 4. Asymmetric *syn*-Aldol Approach Followed by Stereoselective Intramolecular Oxy-Michael Reaction to Obtain a Stereodefined Furan Derivative, 4.6



derivative **4.1** with aldehyde **3.4** did not result in successful aldol preparation under Lewis acid catalyzed reaction conditions (note: the synthesis details are provided in the Supporting Information). We then switched to **4.2** as the keto moiety having Evans' chiral auxiliary.[10] An advantage with this approach is that, if successful, this would directly allow us to add an allyl group at the C-30 site with the correct stereochemistry. This aldol (conditions: $TiCl_4$, DIPEA, DCM, 0 °C) worked well and produced **4.3** as a *single diastereomer*. The stereochemistry was assigned following the key intramolecular oxy-Michael reaction. Thus, **4.3** was subjected to a series of transformations and a two-carbon extension reaction giving **4.4**, a precursor to an intramolecular oxy-Michael reaction. When subjected to desilylation conditions (TBAF, THF), this directly produced the furans **4.5a** (*cis*) and **4.5b** (*trans*) at C-29 and C-32 as the separable diastereomeric mixture with 1.2:1 (*cis*:*trans*) ratio. The clean *cis* product obtained was then thoroughly subjected to NOE studies for the structural assignments (see the Supporting Information). In one case, **4.5a** (*cis*, C-29 and C-32) was further derivatized using MeI/Ag_2O conditions, giving **4.6**, a desired material needed to complete the 14-membered macrocyclic synthesis.

Having access to furan moiety **4.6** with the correct stereochemistry at various chiral centers, we then developed our plan for the 14-membered macrocyclic synthesis.

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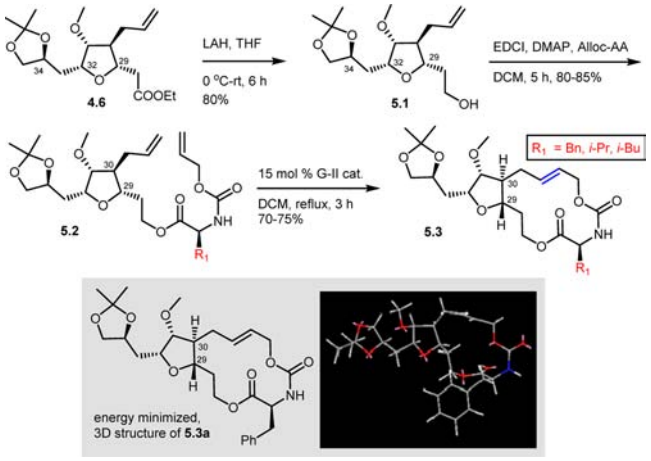
Compound **5.1** (Scheme 5) was easily obtained from **4.6** and the primary −OH group was then acylated (EDCI, DMAP)

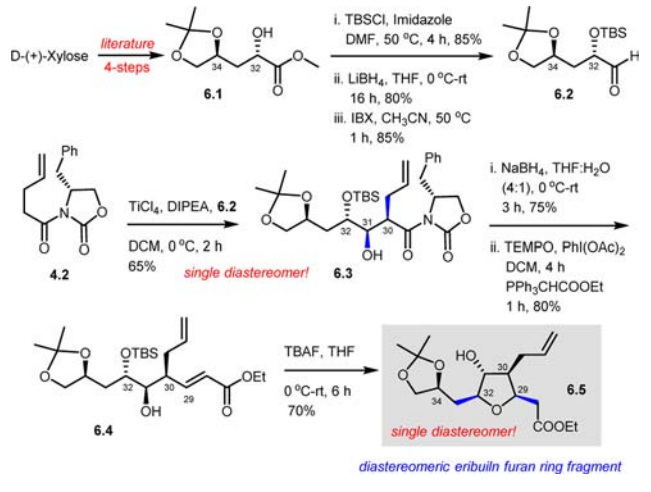
Scheme 5. Diversity-Based Synthesis of 14-Membered Macrocyclic Ring *Trans* Fused (C-29 and C-30) to the Stereodefined Furan Moiety



with three different amino acid moieties giving **5.2**. This set the stage to attempt our crucial ring-closing metathesis as the stitching reaction. In all three cases, 14-membered macrocycle was formed cleanly with a *trans* olefin moiety using 15 mol % of Grubbs' catalyst. Although not reported here, **5.3** can further be utilized to add more diversity sites through the utilization of both primary and secondary −OH groups following the deprotection. Combination of a novel stereoselective approach for obtaining the stereodefined furan moiety and its further utilization in the synthesis of *trans*-fused (C-29 and C-30) 14-membered ring led us to produce a new family of eribulin fragment-based hybrid macrocycles.

Finally, our synthetic plan for obtaining a stereodefined furan derivative, **6.5**, which is one of the diastereomers of **4.6**, is shown in Scheme 6. Using the literature procedure,[9] **6.1** was obtained from D-(+)-xylose in four steps. An α-OH aldehyde **6.2** was obtained from **6.1** in three steps in high yield. Using Evans' chiral auxiliary-based keto derivative, **4.2** was then

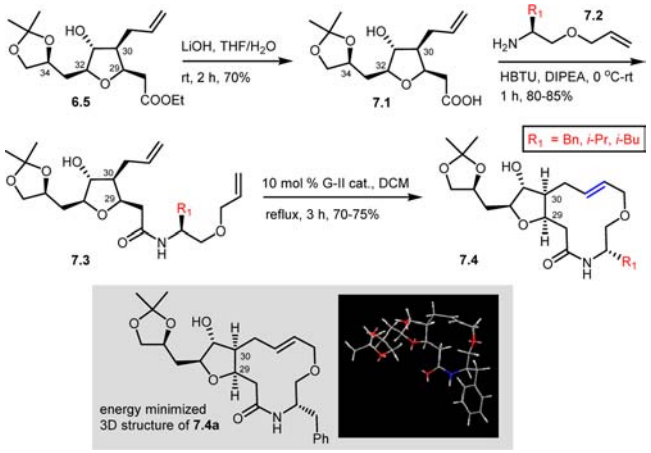
Scheme 6. Asymmetric *syn*-Aldol Followed by an Intramolecular Oxy-Michael Approach to the Synthesis of 6.5



reacted with aldehyde **6.2** under Lewis acid catalyzed aldol reaction ($TiCl_4$, DIPEA, DCM, 0 °C).[10] As in the previous aldol study, this reaction also worked very well, and the aldol product **6.3** as a *single diastereomer* having three contiguous stereocenters (C-30, 31 and 32) was obtained. Once again, the stereochemistry was thoroughly assigned after an intramolecular oxy-Michael reaction. To achieve this, **6.4** was obtained from **6.3** and upon desilylation (TBAF, THF) conditions gave the desired cyclic product **6.5**. In this series, the reaction was clean, and **6.5** was obtained as a *single diastereomer* (see the Supporting Information for the structural assignments). It differs from **4.6** in that it has *cis* (C-29 and C-30) and *trans* (C-31 and C-32) functional groups.

The synthesis of *cis*-fused (C-29 and C-30) macrocycle with an embedded amino alcohol moiety to the furan ring is shown in Scheme 7. Compound **7.1** with a free −COOH group was

Scheme 7. Synthesis of 12-Membered Ring *Cis* Fused (C-29 and C-30) to the Furan Moiety



obtained from **6.5**, and this was then coupled (HBTU, DIPEA) with three different amino alcohols **7.2** to obtain **7.3** as a precursor for the ring-closing metathesis-stitching reaction. As we observed in the previous 14-membered macrocyclic ring formation, this approach worked well, and in all three cases, a 12-membered ring with a *trans* olefin (**7.4**) was obtained in high yields. The full characterization is provided in the Supporting Information.

To summarize, we report a practical and short stereoselective synthesis of two isomeric, stereodefined furan derivatives, **4.6** and **6.5**, respectively. Both of these compounds were then utilized further to incorporate diversity-based 14- and 12-membered rings, respectively. These compounds represent a new family of hybrid macrocyclic natural products having the substructure and the diastereomeric furan fragment of eribulin. The biological evaluation of all these compounds is ongoing, and, these studies will be reported as they become available.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental section and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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