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Scalable synthesis of the C14–C23 fragment of Eribulin and Halichondrin B

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Abstract

A novel, scalable approach to the C14–C23 fragment of eribulin mesylate is disclosed. Key 2,3-Wittig rearrangement is strategically effected via [Rh] mediated decomposition of 1,2,3-triazole intermediate to derive the 2,5-*trans*-tetrahydrofuran motif, enabling multi-kilogram access to the desired C14–C23 fragment.

KEYWORDS
carbene, eribulin, Halichondrin B, rhodium (II) catalysis, stereoselectivity, Wittig rearrangement

Marine natural products have been used as a drug by itself or as a lead structure for further refined drug candidate.[1] Among the latter case, eribulin mesylate (**1**) occupies a prominent position as a chemotherapeutic anticancer agent,[2] which itself is a truncated/modified structure of the natural product halichondrin B (**2**, Figure 1).[3] Its chemical complexity comprising of 19 stereogenic centers represent a formidable challenge in terms of its chemical synthesis; and more so in controlling its quality when developed as an active pharmaceutical ingredient (API). Recently, utility of eribulin has been further extended as a payload in antibody drug conjugate.[4]

Despite the considerable complexity involved in the task of commercial drug manufacture, Eisai Ltd. in collaboration with Prof. Kishi group successfully completed its commercial production, which stands as a monumental achievement in synthetic chemistry.[5] The commercial process of Eisai features extensive use of the Nozaki-Hiyama-Kishi (NHK) reaction in critical C–C bond formations, showcasing this important reaction featuring excellent stereoselectivity and high functional group tolerance (Scheme 1). The retrosynthetic analysis allows eribulin to be constructed from simpler building-blocks, including a key fragment which is inclusive of the C14–C23 moiety (**3**).

As a generic API developer, we became intrigued in realizing the commercial production of eribulin, drawn largely to its challenging synthesis and its commercial success as a chemotherapeutic agent. Along this endeavor, we have published our efforts on the synthesis of the C1–C13 intermediate using olefin metathesis[6] and Rh-mediated 6-*endo* cyclization as key steps.[7] Herein, we disclose a scalable synthesis of the C14–C23 intermediate **4** (Scheme 2d), which features a 2,5-*trans* disubstituted tetrahydrofuran framework.

In the literature, fragments of eribulin which are inclusive of the C14–C23 backbone have been prepared using enantio- and diastereoselective NHK reaction in good selectivity of ca. 95:5 ratio (Scheme 2a).[8] Later a chiral pool approach starting from 1,2-5,6-diisopropylidene glucose has been disclosed (Scheme 2b).[9] Recently, a radical-induced ring closure approach to Halichondrin B's C14–C23 fragment has been disclosed, although the precursor's C20 epimer had to be separated by chromatography (Scheme 2c).[10] Our own approach toward this fragment utilizes the 2,3-Wittig rearrangement, which is substrate derived from [Rh] mediated decomposition of triazole **5** as the key strategic reaction for the construction of the 2,5-*trans*-tetrahydrofuran motif (Scheme 2d).[11]

In general, the use of 2,3-Wittig rearrangement through carbonyl ylide intermediate is well precedented.[12] The ylide is usually formed by the reaction of stabilized carbene with the lone pair of oxygen, where the stereochemistry is governed by 1,2-*trans* preference of substituents in the 5-memeberred ring followed by *cis*-fused transition state

U. Bin Kim and Srinivas Samala contributed equally to the manuscript.

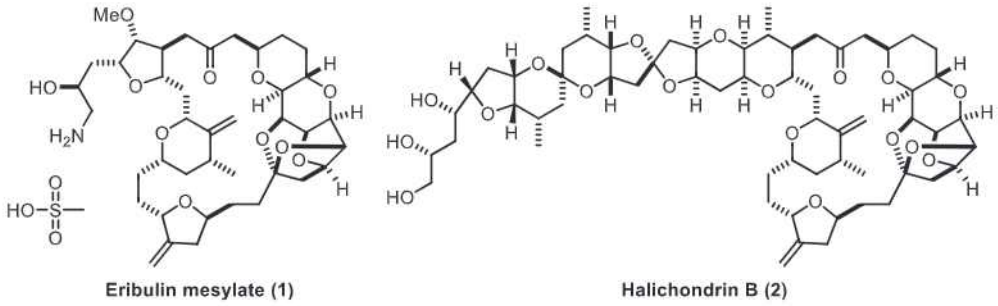
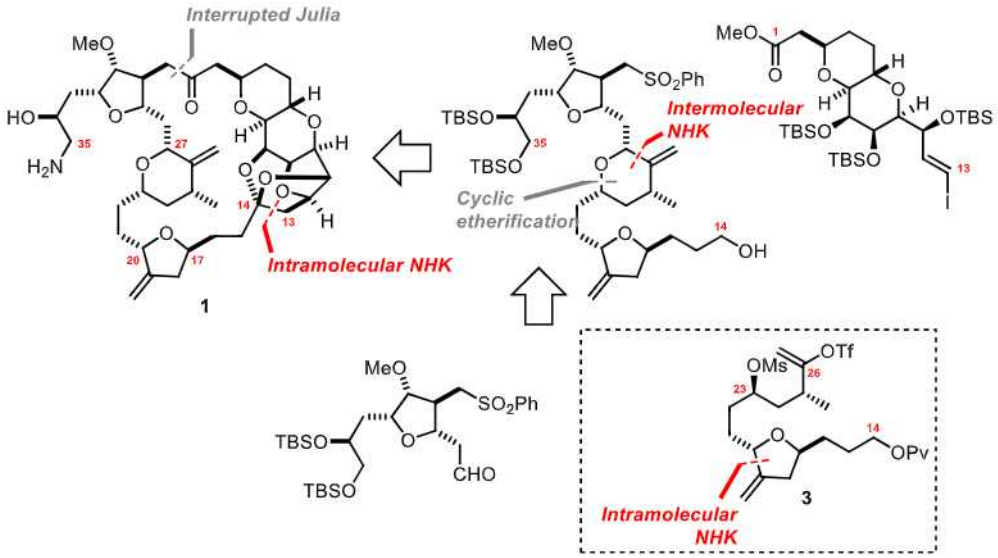


FIGURE 1 The structures of eribulin mesylate (**1**) and Halichondrin B (**2**)



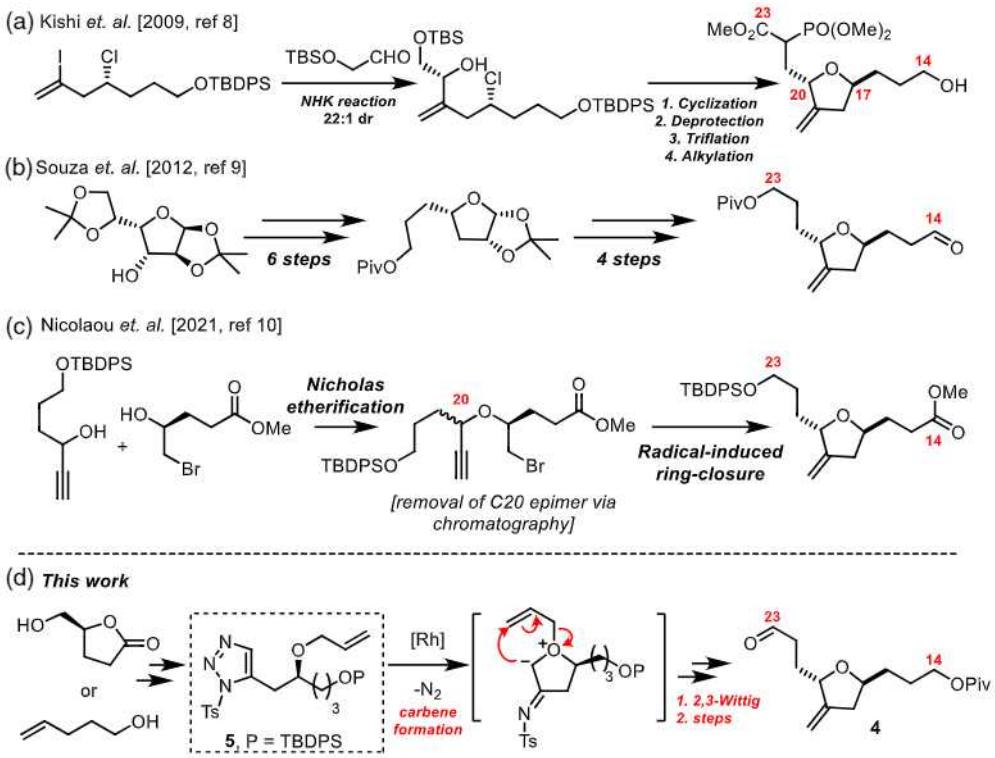
SCHEME 1 The commercial synthesis of **1**; key NHK disconnections highlighted in red.

of [3.3.0]-ring system. Although this reaction sequence provides 2,5-*trans* tetrahydrofuranone skeleton stereoselectively, the precursor α-diazocarbonyl derivatives in general are prepared by the reaction of acyl chloride with diazomethane,[13] which limits the routine use of this reaction, particularly during larger scale operation. As there are known reports of [Rh] mediated carbene-generation and ring formation reactions in the literature[14] and as we had multi-kilogram scale preparations in mind, we were determined to utilize triazole **5** as an alternative precursor of α-diazocarbonyl derivatives[11] in a large-scale campaign toward C14–C23 fragment **4**.

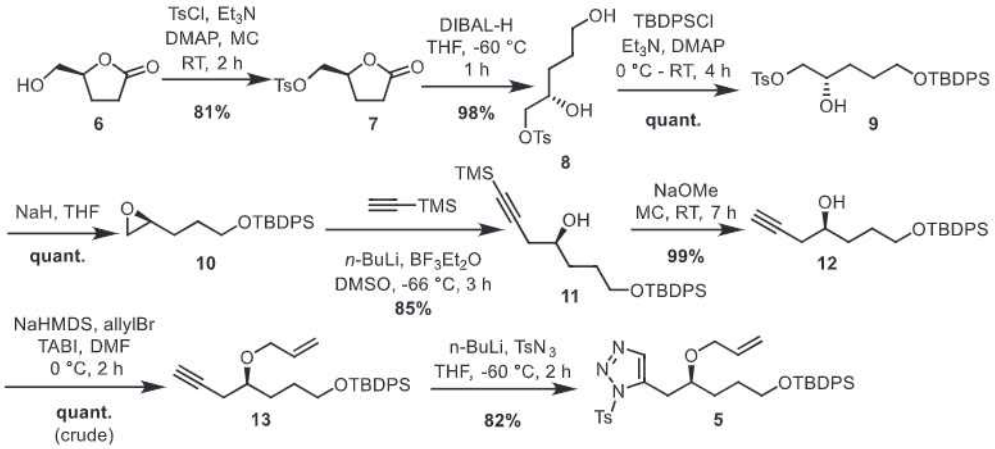
At the early state of maneuver, we first used lactone **6** as a starting material to derive the required triazole precursor **5** (Scheme 3).

The following reaction sequence was smoothly affected; first, tosylation of the primary alcohol of **6** was achieved in 81% yield to afford **7**, which was reduced using DIBAL-H at −60°C to afford diol **8**. Selective protection of the primary hydroxyl group furnished **9**, and subsequent base mediated epoxide formation afforded compound **10**. Ring opening of the epoxide by TMS acetylide under the Lewis acid catalysis at cryogenic conditions provided homopropargyl alcohol **11** and deprotection of the TMS group gave **12**, which was followed by allylation of the secondary alcohol to furnish **13**. Conditions described by Boyer[11] then effected the required cycloaddition reaction with tosyl azide to finally furnish triazole **5** in a regioselective manner in good yield.

For its thermal profile, DSC analysis indicates that **5** is thermally stable below ca. 150°C, with the significant exothermic event climaxing at 208°C (Figure 2, left). Accompanying TGA analysis shows gradual loss of mass beginning ca. 150°C followed by significant loss of mass at ca. 202.07°C. This stability gave us a clue for scale up of the reaction itself and the next Wittig rearrangement as well. With the triazole **5** in hand and its thermal stability deduced, we set to effect the [Rh] mediated carbene formation followed by sequential 2,3-Wittig rearrangement (Scheme 4). For controlling the exothermic heat of the reaction, triazole was added portion-wise to the solution of Rh catalyst at 60°C, then slowly raised to 90°C. In this manner, we could control the heat of the reaction in dose dependent manner. The reaction proceeded well to provide trans 2,5-disubstituted tetrahydrofuranone **14** in 71% yield with 20:1 diastereoselectivity ratio, where the



SCHEME 2 Previous (a–c) and our (d) approach toward C14–C23 fragment (**4**) of eribulin



SCHEME 3 Synthesis of triazole **5**.

transient imine intermediate was hydrolyzed to ketone under acidic work-up conditions.

Next, C19 carbonyl group of **14** was transformed to *exo*-vinyl group of **15** under various conditions. The Wittig reaction furnished desired product in excellent yield (Table 1, entry 1) and modified Julia-Kocienski reaction (entries 3 and 4) provided comparable results at RT and −63°C temperatures respectively with similar degree of epimerization at the C20 stereocenter. Although we attempted olefination with the Nysted reagent expecting minimal epimerization, we observed no conversion (entry 2). Therefore, considering the ease of operation in large plant-scale, we moved forward to prepare **15** utilizing Wittig conditions (Table 1, entry 1).

We next explored conditions to selectively install the hydroxyl functionality at the C23 position, aiming for chemoselective hydroboration-oxidation of 1-substituted olefin over 1,2-disubstitued olefin via the use of bulky borane reagents (Table 2). This task however proved not to be straightforward: use of 9-BBN (entry 1) and thexylborane (entry 3) showed no chemoselectivity and furnished undesired diol. Although use of disiamylborane showed good chemoselectivity (entry 2), a large excess of reagent up to 16 equiv. was required for the completion

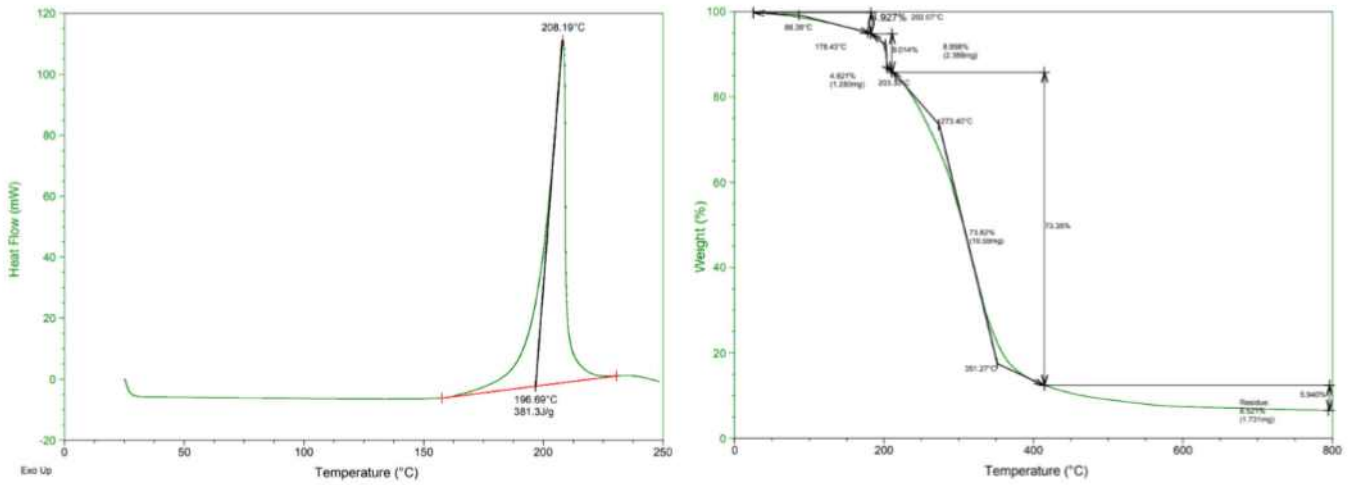
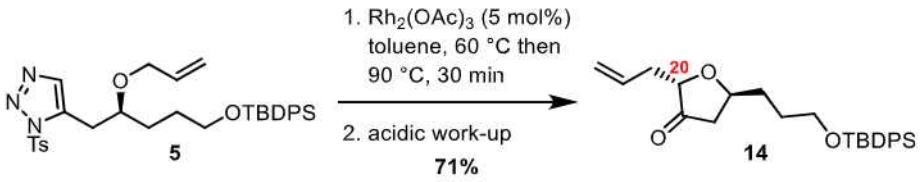
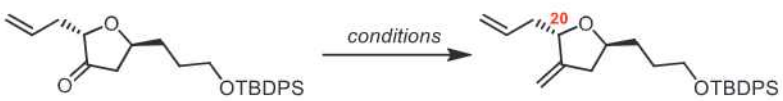


FIGURE 2 DSC (left) and TGA (right) analysis of **5**



SCHEME 4 [Rh] mediated carbene-formation and subsequent 2,3-Wittig rearrangement.

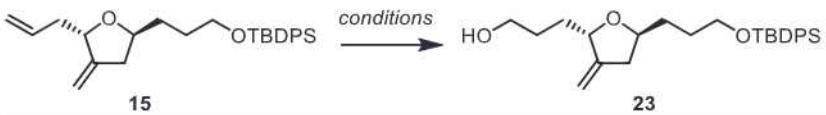
TABLE 1 Methylenation of **14**



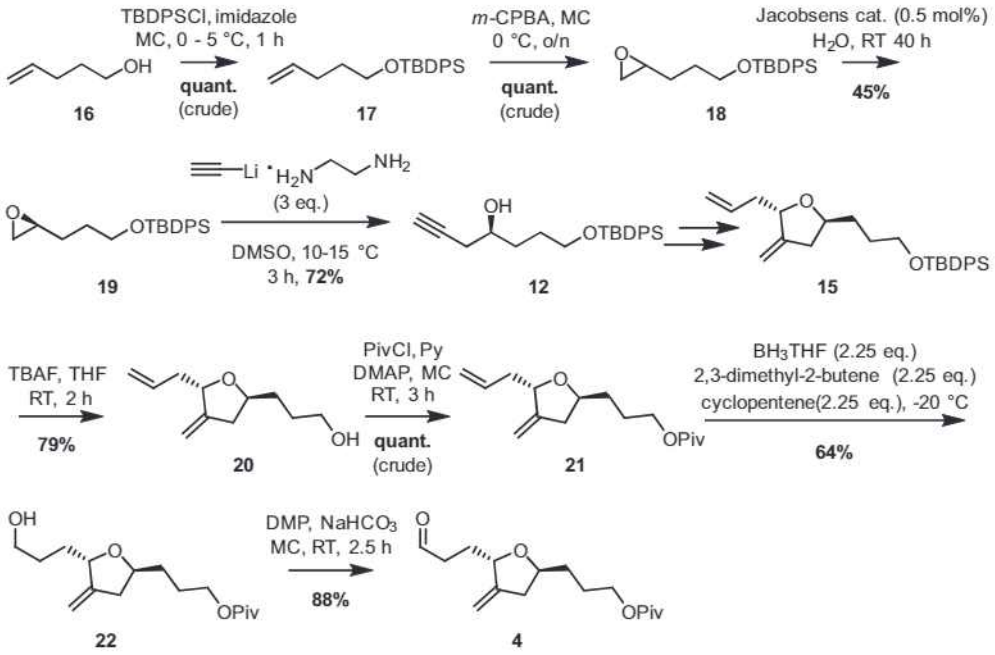
Entry	Reagents[a]	Temp. (°C)	Time (h)	Yield (%)
1	$MePh_3PBr$ (3.6 equiv.), *t*-BuOK (3.7 equiv.), THF	0	5	quant. (crude, ca. 92%) (C20 epimer 7.2%)
2	Nysted reagent (1.5 equiv.), $TiCl_4$ (1.5 equiv.), THF	−55	0.5	–
3	Benzoimidazolyl sulfone (1.2 equiv.), *t*-BuOK (1.2 equiv.), DMF	RT	8	40 (C20 epimer 5.4%)
4	Benzoimidazolyl sulfone (3.1 equiv.), NaHMDS (3 equiv.), THF	−63	7	68 (C20 epimer 6.4%)

[a]**14** contains 5% of C20 epimer.

TABLE 2 Chemoselective hydroboration–oxidation of **15**



Entry	Reagents (hydroboration)	Reagents (oxidation)	Temp. (°C)	Result/yield (%)
1	9-BBN (13 equiv.)	H_2O_2	0	Dihydroboration
2	BH_3·THF (16 equiv.), 2-methyl-2-butene (36 equiv.)	H_2O_2	−20	77
3	BH_3·THF (2.5 equiv.), 2,3-dimethyl-2-butene (5 equiv.)	$NaBO_3$	−20	Dihydroboration
4	BH_3·THF (2.5 equiv.), 2,3-dimethyl-2-butene (2.25 equiv.), cyclopentene (2.25 equiv.)	$NaBO_3$	−20	70



SCHEME 5 Modified synthesis of **4**.

of the reaction, which was impractical for a large-scale campaign. To overcome this issue, we finely tuned the steric bulk of thexylborane by adding a cyclopentane group. In the end, use of 2.25 equiv. of cyclopentylthexylborane followed by sodium perborate oxidation (entry 4) mediated the selective hydroboration-oxidation of C22–C23 olefin to furnish **23** in good yield.

Re-evaluating our synthesis described thus far, we considered that in the preparation of intermediate **12** from lactone **6**, a large amount of DIBAL under cryogenic conditions is required, which is not ideal for plant-scale implementation. Furthermore, to cleanly intercept intermediate **3** disclosed by Eisai and make our fragment amendable for further manipulation *en route* to eribulin, C14-OH protecting group needed to be changed from OTBDPS to OPiv. Under these considerations, we have modified the reaction route as shown in Scheme 5.

Starting from 4-pentene-1-ol (**16**), TBDPS protection afforded **17** and subsequent *m*-CPBA mediated epoxidation yielded epoxide **18**. Hydrolytic kinetic resolution (HKR) of epoxide **18** using Jacobsen's catalyst[15] worked well to provide epoxide **19** in 45% yield and >99% optical purity after thin film distillation of the crude mixture. The epoxide opening conditions was also modified, and lithium acetylide diethylamine complex was employed to render the reaction operable at ambient temperature,[16] and thereby intercepting intermediate **12** as described previously in Scheme 3. Intermediate **12** was taken forward to intermediate **15** as described above, whereupon TBAF deprotection of TBDPS alcohol furnished alcohol **20**. This was protected as a Piv group to yield **21**, and previously established chemoselective hydroboration-oxidation conditions were further optimized to afford **22** in good yield. Finally, multi-kilogram scale DMP oxidation furnished **4**, the desired C14–C23 fragment of eribulin.

To quantify the efficiency of two process described above, we have calculated process mass intensity (PMI)[17] value of the two routes up to the common intermediate **12**. The route described in Scheme 3 starting from lactone **6** to intermediate **12** has the PMI value of 236 while the route described in Scheme 5 starting from alcohol **16** to intermediate **12** has the PMI value of 191. More significantly, the latter route has the scalable advantage of avoiding the use of extreme cryogenic temperatures.

In summary, we have demonstrated that the use of triazole as a stabilized carbene precursor in the 2,3-Wittig rearrangement could be scaled up to multi-kilogram scale, which can further be manipulated into the C14–C23 fragment of eribulin (**4**). The route to the intermediate **12** using HKR reaction using Jacobsen's catalyst improved its greenness significantly. Although lithiumacetylide diethylamine complex is not used frequently in the synthetic community, its advantage in a large-scale production was clearly demonstrated in the epoxide opening of **19**. Fine tuning of the steric character of borane reagent by mixed ligand also reduced its mass intensity significantly without any loss in chemoselectivity. Further synthetic result toward eribulin will be disclosed in near future.

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