ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

pubs.acs.org/OPRD

Article

Synthesis of the C1−C13 Fragment of Eribulin on a Kilogram Scale

Seong Taek Kim, Yongseo Park, Namhyeon Kim, Jaeun Gu, Wongyoung Son, Jisu Hur, KangHee Lee, Areum Baek, Ju Young Song, U Bin Kim, Kee-Young Lee, Chang-Young Oh, Seokhwi Park, and Hyunik Shin*

Cite This: *Org. Process Res. Dev.* 2022, 26, 123−128

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: An improved kilogram-scale synthesis of the C1−C13 fragment of eribulin is disclosed. Rh-mediated *6-endo-tet* cyclization of a vinyl epoxide provides a crystalline tetrahydropyran intermediate, which was transformed to a lactol intermediate having the bicyclic motif of the C3−C12 fragment. This intermediate was further elaborated into the C1−C13 fragment of eribulin following the precedent sequence of reactions.

KEYWORDS: *eribulin, C1−C13 eribulin fragment, π-allyl rhodium complexes, 6-endo cyclization, tetrahydropyran synthesis, catalyst poisoning*

INTRODUCTION

Eribulin mesylate (**1**) is a microtubule dynamics inhibitor, indicated for treatment of patients with late-stage metastatic breast cancer[1−3] or with inoperable liposarcoma.[4] Its mode of action is distinct from that of paclitaxel (Taxol), involving high affinity binding to microtubule plus ends, leading to mitotic arrest and cell death.[5] Structurally, eribulin is one of the most complex nonpeptide drugs currently on the market, with its macrocyclic carbon skeleton bristling with 19 stereocenters (Figure 1). Eribulin was inspired by natural product halichondrin B (**2**)[6] and represents its truncated form, largely retaining the right hemisphere of the molecule. The discovery, chemical synthesis, and therapeutic utilization of eribulin by the team of Eisai and Kishi *et al.* of Harvard University can be considered as one of the era-defining achievements in medicinal and process development chemistry enabled by state-of-the-art organic synthesis.[7,8]

Due to the inherently complicated molecular structure of eribulin, synthetic innovations which streamline and endow efficiency in its chemical synthesis are an important and ongoing topic of research.[9−11] In this regard, the successful commercial process by Eisai showcases a representative example by combining two key fragments, C1−C13 (**3**)[12] and C14−C35 (**4**)[13] subunits, for the production of **1** (Scheme 1).

Previously, we have disclosed our route toward the C1−C13 fragment of eribulin, utilizing intramolecular ring-closing metathesis of **5** as the key step to forge the bicyclic ring motif (Scheme 2, top).[14] This route, however, suffered from a significant drawback due to the inherent disadvantages associated with cross-metathesis reactions. Namely, the reaction was hindered by self-dimerization and other side products when executed without considerable dilution, presenting a significant challenge for scale-up and further process development. Rectifying this shortcoming, we herein report an alternative approach to the C1−C13 fragment, whereupon successful utilization of Rh-mediated *6-endo* cyclization of vinyl epoxide **6** and subsequent intramolecular lactol formation enabled an effective and vastly more scalable route toward the bicyclic ring system (Scheme 2, bottom). Our improved approach represents a scale-up of what was a limited, centigram synthetic process to one defined by kilograms, allowing us to continue to maneuver toward an effective process development of **1**.

RESULTS AND DISCUSSION

Our synthesis starts from chiral aldehyde **7**, which is accessible from **8** in eight steps and was described previously. Lautens have previously disclosed Rh-mediated ring opening of vinyl epoxides,[15] resulting in 1,2-addition of the nucleophile, likely through a π-allyl rhodium intermediate. Building upon this work, Ha and co-workers reported an intramolecular variant of the Rh-mediated ring-opening reaction of vinyl epoxides, exclusively affording *6-endo-tet* cyclization to give tetrahydropyrans.[16] It should be noted that *6-endo-tet* cyclizations are technically disfavored by Baldwin's rules,[17] and our desired product was to be accessed by an "anti-Baldwin cyclization". Inspired by an aforementioned report by Ha, we thought to rapidly access the vinyl epoxide cyclization precursor from our previously attained synthetic intermediate. We therefore reacted aldehyde **7** with triethyl phosphonoacetate in a Horner−Wadsworth−Emmons (HWE) reaction to furnish vinyl ester **6** in good yield (Scheme 3).

The C11-OTES-protecting group of **6** was to be deprotected with the aim of providing the internal hydroxy nucleophile

Received: July 22, 2021
Published: December 14, 2021

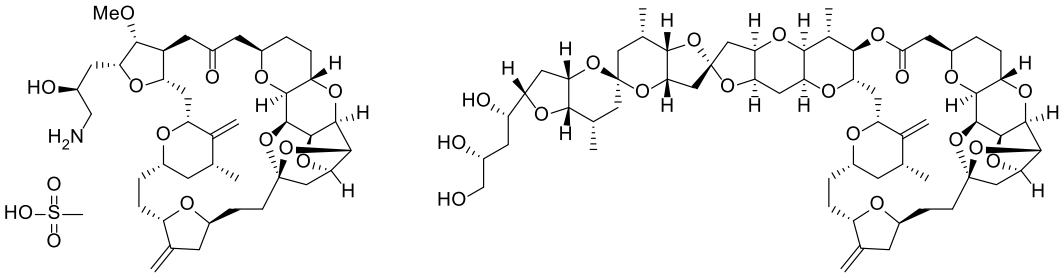
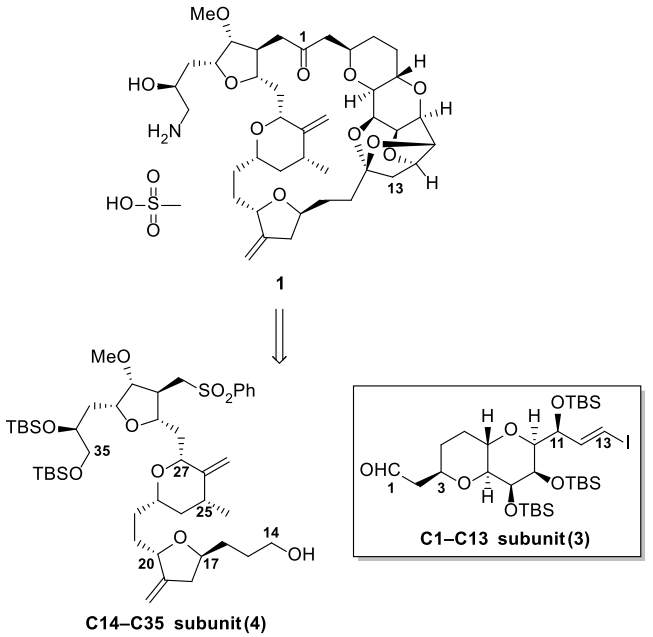


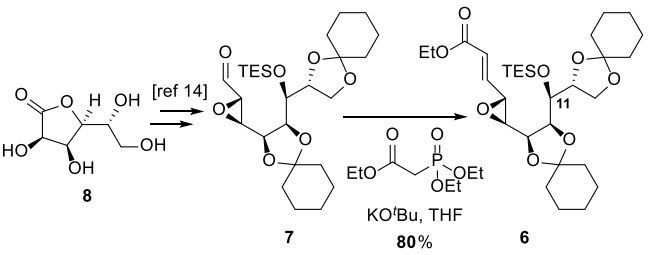
Figure 1. Structures of eribulin mesylate and halichondrin B.

Scheme 1. Commercial Synthesis of 1



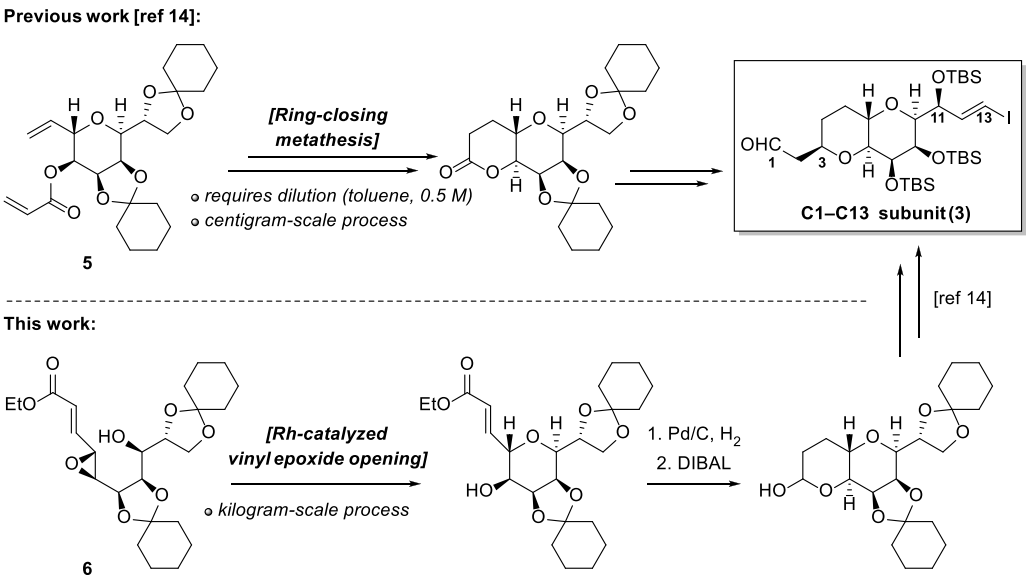
needed for the cyclization reaction. Due to the basic character of TBAF, its treatment on silyl ether **6** afforded the desired deprotected product **9** alongside significant formation of 5-*exo*-cyclized, tetrahydrofuran side product **10** (Table 1, entry 1). Attempts of utilizing HF·pyridine also gave unsatisfactory results (entry 2). Propitiously, it was discovered that treatment of **6** with TBAF buffered by imidazole·HCl yields deprotected free alcohol **9** in high yield after column chromatography (entry 3).

Scheme 3. Synthesis of Vinyl Epoxide 6



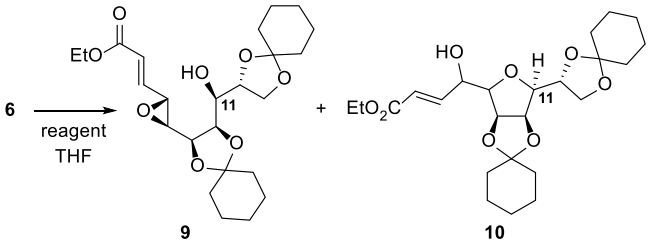
Having **9** in hand, we first attempted to use well-described acid-mediated catalysis to affect the 6-*endo* cyclization in order to access the required tetrahydropyran.[18] Treatment of **6** with PPTS (Table 2, entry 1) and CSA (entry 2), however, afforded significant amounts of 5-*exo*-cyclized tetrahydrofuran **10**, in which selectivity for **11** became marginally preferred over **10** from an initial ratio of **11**/**10** = 1:3 to 3:2 as the acidity of the catalysts decreased. Although disappointing, this could be anticipated by us, given the similar literature precedent,[19] as the presence of the strongly electron-withdrawing *α*,*β*-

Scheme 2. Previous Work and Current Approach to 3



https://doi.org/10.1021/acs.oprd.1c00295
Org. Process Res. Dev. 2022, 26, 123−128

Table 1. Deprotection of Silyl Ether 6



entry	reagents	yield, **9** (%)	yield, **10** (%)
1	TBAF	65	16
2	HF·pyridine	61	24
3	TBAF, imidazole·HCl	77	0

unsaturated ester would be counterproductive in fully activating the C−O bond of the epoxide directly adjacent to the alkene. We therefore applied Ha's Rh-catalyzed cyclization strategy,[16] which smoothly furnished desired **11** in high yield *via* the Rh-catalyzed 6-*endo* cyclization,[20] at 2 mol % catalyst loading (entry 3). In cyclization, complete inversion of the stereochemistry at the C6 position was observed, with the desired *trans*-cyclized **11** being the only isolated product. We rationalize this stereochemical outcome by considering that the formation of the intermediary π-allyl rhodium complex is affected with retention of stereochemistry with respect to the leaving group per mechanistic model proposed by Lautens,[21] followed by subsequent inversion during the intramolecular hydroxyl group attack onto the π-allyl rhodium complex, resulting in net inversion. Due to the high cost of the rhodium catalyst, we thought to reduce the catalyst loading (entries 4−6) and found that 0.05 mol % of the catalyst was enough to enable the transformation to be run in a high yield (entry 5). Further optimization of the reaction temperature allowed the reaction to give consistently high yields at multigram scales with considerably shorter reaction times (entry 7).

During a thorough investigation into the TES deprotection step, a seemingly peculiar problem was discovered as the scale increases to multi-decagram quantities. First, the TBAF/imidazole·HCl-mediated deprotection of **6** showed clean conversion, but in the course of chromatography, varying amount of the tetrahydrofuran side product **10** was formed. As this could be attributed to the slightly acidic nature of the silica gel interacting with increased residence time as the purification scale increases, we moved to remove the need for chromatographic purification following the TES deprotection in the later larger scale-up campaign. However, subjecting the crude, unpurified **9** in Rh-catalyzed 6-*endo* cyclization gave inconsistent yields and conversion, irrespective of our optimization efforts as shown in Table 2, entry 7. Eventually, we deduced that when pushing crude **9** through the cyclization step, the presence of residual chloride and fluoride ions was poisoning the Rh catalyst which is deployed in very minute quantities, retarding the cyclization event. In this regard, we tested for the presence of halide ions in each aqueous washing in the extractive work-up process of TBAF/imidazole·HCl-mediated deprotection step of **9** by the addition of $AgNO_3$ to the aqueous wash and inspecting for precipitation.[22]

After the third aqueous wash, no precipitation was formed in this test, indicating the removal of residual halide ions. With the material now free of halides, subjecting it under Rh-mediated cyclization afforded **11** as a crystalline solid in high and consistent yields, as shown in Table 2, entry 8. In our process, no chromatographic steps are performed from **7** to **11**.

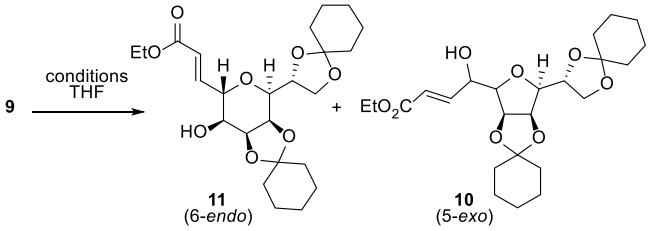
With **11** in hand, we moved to affect the second cyclization to construct the bicyclic motif of **3** (Scheme 4). Reduction of the double bond of **11** *via* hydrogen gas in the presence of Pd/C gave aliphatic ester **12**, and treatment of **12** with DIBAL smoothly afforded lactol **13**, which intercepted our previously disclosed synthetic pathway *en route* to **3**. By use of the synthetic pathway described here, kilogram quantities of **3** were accessed.[11]

In conclusion, a scalable synthetic route toward key intermediate **3** for eribulin is disclosed. Key features include the removal of residual halides acting as catalyst poison in the crude reaction mixture of **9** and its intramolecular Rh-catalyzed 6-*endo* cyclization. Further effort toward eribulin with the scale-up of **3** is ongoing and will be disclosed in due course.

EXPERIMENTAL SECTION

General Methods. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopic data were recorded with a Fourier

Table 2. Rh-Mediated Cyclization of 9

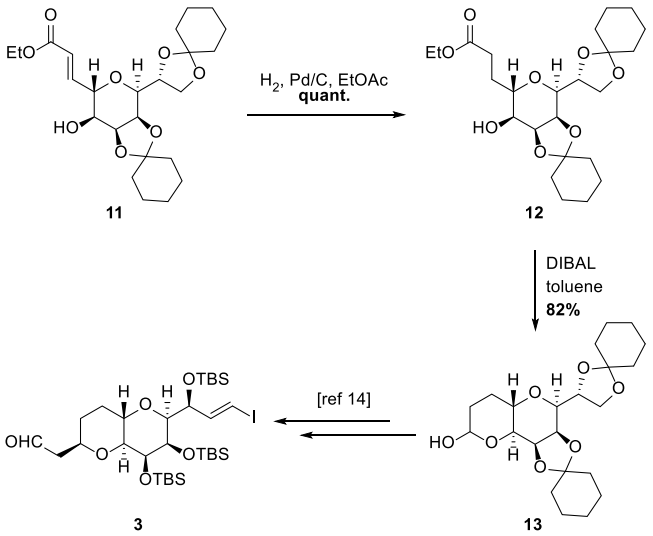


entry	S.M. (g)	catalyst	temp.	time (h)	ratio, **11**/**10**[a]	yield, **11** (%)
1	1	PPTS	20−35 °C	24	3:2	n.d.[b]
2	1	CSA	−40 °C	18	1:3	n.d.[b]
3	1	$[Rh(CO_2)Cl]_2$ 2 mol %	rt	24	>99:1	77
4	1	$[Rh(CO_2)Cl]_2$ 1 mol %	rt	24	>99:1	93
5	1	$[Rh(CO_2)Cl]_2$ 0.5 mol %	rt	24	>99:1	90
6	1	$[Rh(CO_2)Cl]_2$ 0.2 mol %	rt	24	>99:1	26
7	6.4	$[Rh(CO_2)Cl]_2$ 0.5 mol %	70	2.5	>99:1	87
8	3370	$[Rh(CO_2)Cl]_2$ 0.5 mol %	60	4	>99:1	95

[a]Ratios were determined by NMR intensities. [b]n.d.= not determined.

https://doi.org/10.1021/acs.oprd.1c00295
Org. Process Res. Dev. 2022, 26, 123−128

Scheme 4. Synthesis of 3



transform NMR (FT-NMR) spectrometer at 300 or 75 MHz. Chemical shift values are reported in parts per million (ppm) relative to TMS or $CDCl_3$ as the internal standard, and coupling constants are reported in hertz. Infrared (IR) spectra were measured with a Fourier transform IR (FT-IR) spectrometer. Mass spectroscopic data were obtained with a Jeol JMS 700 high-resolution mass spectrometer equipped with a magnetic-sector electric-sector double-focusing analyzer. Flash chromatography was performed using mixtures of ethyl acetate and hexane as eluents. Unless otherwise stated, all the nonaqueous reactions were carried out under an argon atmosphere with commercial-grade reagents and solvents. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. Dichloromethane was distilled from calcium hydride.

Ethyl (*E*)-3-((2*R*,3*S*)-3-((2*S*,3*S*)-3-((*S*)-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl) ((triethylsilyl)oxy)methyl)-1,4-dioxaspiro[4.5]decan-2-yl)oxiran-2-yl)acrylate (6). To a chilled solution of KO^{t}Bu (0.95 kg, 8.47 mol, 1.75 equiv) in THF (21.6 L) at 15 °C was dropwise added triethyl phosphonoacetate (1.97 kg, 8.78 mol, 1.82 equiv) and the reaction mixture was stirred for 1 h. A solution of aldehyde **7** (2.4 kg, 4.83 mol) in THF (2.4 L) was then added to the reaction mixture dropwise and the reaction mixture was stirred for further 2 h. [In-process check; TLC (Hex/EtOAc = 4:1)]. NH_4Cl (12 L, 10%, aq.) was then added dropwise followed by EtOAc (12 L) and the reaction mixture was further stirred for 30 min. The layers were separated, and the aqueous layer was extracted further with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford the crude product **6** as brown oil (2.71 kg, 80%) and taken to the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.66 (dd, J = 15.7, 7.2 Hz, 1H), 6.17 (dd, J = 15.7, 0.5 Hz, 1H), 4.30−4.17 (m, 4H), 4.04−3.99 (m, 2H), 3.93−3.88 (m, 1H), 3.79 (dd, J = 7.7, 5.5 Hz, 1H), 3.43 (dd, J = 7.1, 1.5 Hz, 1H), 3.10 (dd, J = 7.7, 2.0 Hz, 1H), 1.67−1.37 (m, 23H), 1.00−0.93 (m, 9H), 0.61−0.77 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.53, 143.30, 124.59, 110.03, 109.66, 78.38, 77.21, 77.13, 76.10, 70.60, 65.37, 60.68, 58.44, 55.60, 37.70, 35.74, 35.17, 34.63, 25.21, 25.04, 23.96, 23.91, 23.63, 14.19, 6.95, 5.28.

Ethyl (*E*)-3-((2*R*,3*S*)-3-((2*S*,3*R*)-3-((*S*)-hydroxy((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)methyl)-1,4-dioxaspiro[4.5]-decan-2-yl)oxiran-2-yl)acrylate (9). To a solution of **6** (6.04 kg, 10.7 mol) in THF (60 L) was added imidazole-HCl (0.78 kg, 7.46 mol, 0.7 equiv) and the reaction mixture was cooled to 5 °C. TBAF (3.9 kg, 14.9 mol, 1.0 M in THF, 1.4 equiv) was then added dropwise and the reaction mixture was warmed to room temperature and stirred for 2 h. [In-process check; TLC (Hex/EtOAc = 4:1)]. Upon completion of the reaction, the reaction mixture was chilled to 5 °C and H_2O (30 L) was added followed by EtOAc (30 L) and the mixture was stirred for further 30 min. Layers were then separated, and the aqueous layer was extracted with EtOAc. The combined organic fractions were washed with H_2O three times to completely remove the residual fluoride ion. The presence of fluoride was tested by taking an aliquot of the aqueous washings, adding $AgNO_3$, and observing for precipitation. If precipitation was observed, the organic layer was washed again with H_2O. [In-process check; visual inspection of the $AgNO_3$ treated aq. Layer, see the Supporting Information.]. Upon confirmation of no presence of residual halide ions derived in the aqueous wash, combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford the desired crude product **9** as yellow oil (3.73 kg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): 6.68 (dd, J = 15.7, 7.1 Hz, 1H), 6.17 (dd, J = 15.7, 0.6 Hz, 1H), 4.06−4.29 (m, 5H), 3.78−3.94 (m, 3H), 3.43 (dd, J = 7.0, 1.4 Hz, 1H), 3.27 (dd, J = 7.8, 1.9 Hz, 1H), 2.49 (d, J = 7.6 Hz, 1 H), 1.24−1.73 (m, 23H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.49, 143.09, 124.64, 110.38, 110.28, 77.22, 76.13, 69.12, 65.58, 60.67, 58.50, 55.80, 36.93, 36.08, 34.86, 34.38, 25.14, 25.03, 24.00, 23.82, 23.65, 14.19, 1.74, −0.01.

Ethyl (*E*)-3-((3a′*R*,4′*S*,6′*S*,7′*S*,7a′*S*)-7′-hydroxy-4′-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)tetrahydro-4′*H*-spiro-[cyclohexane-1,2′-[1,3]dioxolo[4,5-*c*]pyran]-6′-yl)-acrylate (11). A solution of vinyl ester **9** (3.37 kg, 7.45 mol) in THF (34 L) was degassed for 2 h bubbling dry Ar gas through the reaction mixture. $[Rh(CO)_2Cl]_2$ (14.5 g, 0.037 mol, 0.5 mol %) was added, the reaction temperature was then elevated to 60 °C, and the reaction mixture was stirred for 4 h [In-process check; TLC (Hex/EtOAc = 3:1)]. The reaction mixture was then cooled from 60 °C to room temperature and concentrated *in vacuo*. The residue was then diluted with CH_2Cl_2 and filtered through a pad of silica and concentrated *in vacuo*. To the residue was added a minimal amount of CH_2Cl_2 to dissolve the residue, and heptane (7 vol) was added and stirred very slowly overnight. The desired product precipitated out, which was filtered and collected to yield pure **11** (3.2 kg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (dd, J = 15.7, 3.2 Hz, 1H), 6.42 (dd, J = 15.7, 2.0 Hz, 1H), 4.58−4.54 (m, 1H), 4.45−4.41 (m, 1H), 4.37−4.31 (m, 1H), 4.26−4.10 (m, 4H), 3.82−3.77 (m, 1H), 3.66−3.58 (m, 1H), 3.44 (dd, J = 7.9, 1.4 Hz, 1H), 2.20 (d, J = 10.3 Hz, 1 H), 1.78−1.41 (m, 20H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.71, 146.01, 121.09, 111.82, 110.32, 75.48, 74.13, 73.96, 73.56, 73.40, 68.42, 65.12, 60.34, 36.50, 35.69, 34.88, 34.77, 25.14, 25.02, 23.95, 23.76, 23.73, 14.18.

Ethyl 3-((3a′*R*,4′*S*,6′*S*,7′*S*,7a′*S*)-7′-hydroxy-4′-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)tetrahydro-4′*H*-spiro-[cyclohexane-1,2′-[1,3]dioxolo[4,5-*c*]pyran]-6′-yl)-propanoate (12). To a solution of **11** (3.2 kg, 7.07 mol) in EtOAc (6.0 L) was added dry Pd/C (10%) slurried with EtOAc (0.32 kg in 400 mL, 0.1 wt %) and H_2 gas was bubbled

https://doi.org/10.1021/acs.oprd.1c00295
Org. Process Res. Dev. 2022, 26, 123−128

through the reaction mixture for 1 h. The reaction mixture was then stirred under an atmosphere of H_2 overnight [in-process check; TLC (Hex/EtOAc = 3:1)]. The reaction mixture was then filtered through a pad of Celite and washed with EtOAc (care was taken to ensure that the filtered Pd/C is never filtered to dryness and a minimum liquid layer of EtOAc solvent was always present. After the product was undetectable by EtOAc washings, the filtered Pd/C and Celite were deactivated by the addition of H_2O) and concentrated *in vacuo* to afford crude **12** (3.23 kg, quant.), which was put to the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.52−4.45 (m, 1H), 4.35−4.21 (m, 2H), 4.18−4.03 (m, 3H), 3.88−3.76 (m, 2H), 3.59−3.48 (m, 2H), 2.67−2.40 (m, 2H), 2.24 (d, J = 10.6 Hz, 1H), 2.14−2.01 (m, 2H), 1.93−1.78 (m, 1H), 1.78−1.69 (m, 2H), 1.68−1.46 (m, 16H), 1.45−1.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.88, 111.12, 109.98, 75.59, 73.35, 73.24, 72.77, 71.59, 68.82, 65.38, 60.33, 36.56, 35.74, 35.07, 34.28, 29.86, 27.21, 25.16, 25.07, 24.03, 23.98, 23.78, 23.71, 14.23.

(3a′*R*,4′*S*,5a′*S*,9a′*S*,9b′*S*)-4′-((*R*)-1,4-Dioxaspiro[4.5]-decan-2-yl)octahydrospiro[cyclohexane-1,2′-[1,3]-dioxolo[4,5-*d*]pyrano[3,2-*b*]pyran]-8′-ol (13). To a chilled solution of **12** (3.23 kg, 7.13 mol) in toluene (32.3 L) at −65 °C was dropwise added DIBAL (5.5 kg, 7.6 mol, 1.2 M in toluene, 1.07 equiv) and the reaction mixture was stirred for 30 min. DIBAL (2.25 kg, 3.55 mol, 1.2 M in toluene, 0.5 equiv) was added and the reaction mixture was further stirred for 30 min. DIBAL (2.25 kg, 3.55 mol, 1.2 M in toluene, 0.5 equiv) was added once again and the reaction mixture was again stirred for 30 min. [In-process check; TLC (Hex/EtOAc = 1:1)]. The reaction mixture was cooled to 10 °C and a solution of 2 N KNa tartrate·4H_2O (8 kg) and H_2O (24 L) was added dropwise and the reaction mixture was further stirred for 15 h at room temperature. Layers were separated, and the aqueous layer was extracted with toluene. Combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford desired **13** (2.4 kg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.35 (br s, 1H), 4.45 (dd, J = 8.3, 3.2 Hz, 1H), 4.37−4.24 (m, 2H), 4.13−4.06 (m, 2H), 3.98−3.72 (m, 3H), 2.47−2.46 (m, 1H), 2.04−1.23 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.92, 110.13, 91.66, 76.25, 74.06, 71.60, 71.48, 67.38, 66.26, 65.50, 36.31, 35.65, 35.23, 33.40, 31.82, 28.85, 25.12, 24.70, 23.98, 23.95, 23.77, 23.58; HRMS m/z: (ESI+) found $[M + Na]^+$ 433.2212, $C_{22}H_{34}NaO_7^+$ requires 433.2197.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00295.

Detailed experimental procedure for synthesis of **9**; experimental procedures describing synthesis of **13** to **3**; and copies of ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Hyunik Shin − *R&D Center, Yonsung Fine Chemicals Company Limited, Suwon-si 16675, Republic of Korea;* orcid.org/0000-0002-0222-8418; Email: hishin@yonsungchem.co.kr

Authors

Seong Taek Kim − *R&D Center, Yonsung Fine Chemicals Company Limited, Suwon-si 16675, Republic of Korea*

Yongseo Park − *R&D Center, Yonsung Fine Chemicals Company Limited, Suwon-si 16675, Republic of Korea*

Namhyeon Kim − *R&D Center, Yonsung Fine Chemicals Company Limited, Suwon-si 16675, Republic of Korea*

Jaeun Gu − *R&D Center, Yonsung Fine Chemicals Company Limited, Suwon-si 16675, Republic of Korea*

Wongyoung Son − *R&D Center, Yonsung Fine Chemicals Company Limited, Suwon-si 16675, Republic of Korea*

Jisu Hur − *R&D Center, Yonsung Fine Chemicals Company Limited, Suwon-si 16675, Republic of Korea*

KangHee Lee − *R&D Center, Yonsung Fine Chemicals Company Limited, Suwon-si 16675, Republic of Korea*

Areum Baek − *R&D Center, Yonsung Fine Chemicals Company Limited, Suwon-si 16675, Republic of Korea*

Ju Young Song − *R&D Center, Yonsung Fine Chemicals Company Limited, Suwon-si 16675, Republic of Korea*

U Bin Kim − *R&D Center, Yonsung Fine Chemicals Company Limited, Suwon-si 16675, Republic of Korea*

Kee-Young Lee − *R&D Center, Yonsung Fine Chemicals Company Limited, Suwon-si 16675, Republic of Korea*

Chang-Young Oh − *R&D Center, Yonsung Fine Chemicals Company Limited, Suwon-si 16675, Republic of Korea*

Seokhwi Park − *R&D Center, Yonsung Fine Chemicals Company Limited, Suwon-si 16675, Republic of Korea;* orcid.org/0000-0003-3982-5264

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.oprd.1c00295

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is supported by the Advanced Technology Center (ATC) Program (no. 10048257) funded by the Ministry of Trade, Industry, and Energy of Korea.

■ REFERENCES

(1) Cortes, J.; O'Shaughnessy, J.; Loesch, D.; Blum, J. L.; Vahdat, L. T.; Petrakova, K.; Chollet, P.; Manikas, A.; Diéras, V.; Delozier, T.; Vladimirov, V.; Cardoso, F.; Koh, H.; Bougnoux, P.; Dutcus, C. E.; Seegobin, S.; Mir, D.; Meneses, N.; Wanders, J.; Twelves, C. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *The Lancet* **2011**, *377*, 914−923.

(2) McBride, A.; Butler, S. K. Eribulin mesylate: A novel halichondrin B analogue for the treatment of metastatic breast cancer. *Am. J. Health-Syst. Pharm.* **2012**, *69*, 745−755.

(3) Chabot, I.; Zhao, Q.; Su, Y. Systematic review of Real-World effectiveness of eribulin for locally advanced or metastatic breast cancer. *Curr. Med. Res. Opin.* **2020**, *36*, 2025−2036.

(4) Osgood, C. L.; Chuk, M. K.; Theoret, M. R.; Huang, L.; He, K.; Her, L.; Keegan, P.; Pazdur, R. FDA Approval Summary: Eribulin for Patients with Unresectable or Metastatic Liposarcoma Who Have Received a Prior Anthracycline-Containing Regimen. *Clin. Cancer Res.* **2017**, *23*, 6384−6389.

(5) O'Shaughnessy, J.; Kaklamani, V.; Kalinsky, K. Perspectives on the mechanism of action and clinical application of eribulin for metastatic breast cancer. *Future Oncol.* **2019**, *15*, 1641−1653.

(6) Hirata, Y.; Uemura, D. Halichondrins - antitumor polyether macrolides from a marine sponge. *Pure Appl. Chem.* **1986**, *58*, 701−710.

(7) Yu, M. J.; Zheng, W.; Seletsky, B. M. From micrograms to grams: scale-up synthesis of eribulin mesylate. *Nat. Prod. Rep.* **2013**, *30*, 1158−1164.
(8) Bauer, A. Story of Eribulin Mesylate: Development of the Longest Drug Synthesis. In *Synthesis of Heterocycles in Contemporary Medicinal Chemistry*; Časar, Z., Ed.; Springer International Publishing: Cham, 2016; pp 209−270.
(9) Jimmidi, R.; Guduru, S. K. R.; Arya, P. Practical Stereoselective Synthesis of Eribulin Fragment toward Building a Hybrid Macrocyclic Toolbox. *Org. Lett.* **2015**, *17*, 468−471.
(10) Khatravath, M.; Mallurwar, N. K.; Konda, S.; Gaddam, J.; Rao, P.; Iqbal, J.; Arya, P. Synthesis of C1C11 eribulin fragment and its diastereomeric analogues. *Tetrahedron Lett.* **2019**, *60*, 150915.
(11) Chavan, L. N.; Chegondi, R.; Chandrasekhar, S. Tandem organocatalytic approach to C28C35 fragment of eribulin mesylate. *Tetrahedron Lett.* **2015**, *56*, 4286−4288.
(12) Lewis, B.; Chase, C.; Fang, F.; Wilkie, G.; Schnaderbeck, M.; Zhu, X. Process Development of Halaven: Synthesis of the C1−C13 Fragment from D-(−)-Gulono-1,4-lactone. *Synlett* **2013**, *24*, 323−326.
(13) Chase, C.; Austad, B.; Benayoud, F.; Calkins, T.; Campagna, S.; Choi, H.-w.; Christ, W.; Costanzo, R.; Cutter, J.; Endo, A.; Fang, F.; Hu, Y.; Lewis, B.; Lewis, M.; McKenna, S.; Noland, T.; Orr, J.; Pesant, M.; Schnaderbeck, M.; Wilkie, G.; Abe, T.; Asai, N.; Asai, Y.; Kayano, A.; Kimoto, Y.; Komatsu, Y.; Kubota, M.; Kuroda, H.; Mizuno, M.; Nakamura, T.; Omae, T.; Ozeki, N.; Suzuki, T.; Takigawa, T.; Watanabe, T.; Yoshizawa, K. Process Development of Halaven: Synthesis of the C14−C35 Fragment via Iterative Nozaki−Hiyama−Kishi Reaction−Williamson Ether Cyclization. *Synlett* **2013**, *24*, 327−332.
(14) Lee, H.; Park, Y.; Jung, H.; Kim, S. T.; Sin, S.; Ko, E.; Myeong, I.-S.; Moon, H.; Suhl, C. H.; Jung, Y.; Jung, E.; Lee, J.; Lee, K.-Y.; Oh, C.-Y.; Song, J.; Yoon, S. H.; Kang, W.; Jung, J.; Shin, H. Synthesis of the C1C13 fragment of eribulin mesylate. *Tetrahedron* **2019**, *75*, 4570−4576.
(15) Fagnou, K.; Lautens, M. Rhodium-Catalyzed Ring Opening of Vinyl Epoxides with Alcohols and Aromatic Amines. *Org. Lett.* **2000**, *2*, 2319−2321.
(16) Ha, J. D.; Young Shin, E.; Kyu Kang, S.; Hee Ahn, J.; Choi, J.-K. Studies of rhodium-catalyzed ring opening of vinyl epoxides. *Tetrahedron Lett.* **2004**, *45*, 4193−4195.
(17) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. Rules for ring closure: ring formation by conjugate addition of oxygen nucleophiles. *J. Org. Chem.* **1977**, *42*, 3846−3852.
(18) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. Activation of 6-endo over 5-exo hydroxy epoxide openings. Stereoselective and ring selective synthesis of tetrahydrofuran and tetrahydropyran systems. *J. Am. Chem. Soc.* **1989**, *111*, 5330−5334.
(19) Armbrust, K. W.; Beaver, M. G.; Jamison, T. F. Rhodium-Catalyzed Endo-Selective Epoxide-Opening Cascades: Formal Synthesis of (−)-Brevisin. *J. Am. Chem. Soc.* **2015**, *137*, 6941−6946.
(20) Vilotijevic, I.; Jamison, T. Synthesis of Marine Polycyclic Polyethers via Endo-Selective Epoxide-Opening Cascades. *Mar. Drugs* **2010**, *8*, 763−809.
(21) Lautens, M.; Fagnou, K. Asymmetric Catalysis Special Feature Part I: Rhodium-catalyzed asymmetric ring opening reactions of oxabicyclic alkenes: Catalyst and substrate studies leading to a mechanistic working model. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5455−5460.
(22) $AgNO_3$ is routinely used to test for the presence of chlorides, bromides, and iodides. After the aqueous work-up, complete removal of residual halides in the successive aqueous washings is indicated by the lack of AgCl precipitation derived from imidazole·HCl, which, by proxy, also indicates complete removal of fluoride ions derived from TBAF. For details, please see the Supporting Information.

https://doi.org/10.1021/acs.oprd.1c00295
Org. Process Res. Dev. 2022, 26, 123−128