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Article

Proprietary Synthesis of the C27−C35 Fragment of Eribulin and Its Elaboration toward the C14−C35 Subunit

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ABSTRACT: Successful kilogram-scale preparation of the C27−C35 sulfide fragment of Eribulin was presented, which was elaborated with the C14−C26 fragment to produce a proprietary C14−C35 sulfide intermediate. The sulfide group was then oxidized to yield the known C14−C35 sulfone intermediate of Eribulin.

KEYWORDS: *Eribulin, patent life cycle management, sulfide, NHK coupling, oxetanes, proprietary process development*

INTRODUCTION

The sophisticated structures of natural products, which have been optimized through extensive evolutionary processes, serve as blueprints or starting points for the design and generation of innovative pharmaceuticals.[1] Eribulin mesylate (**1**, Figure 1) exemplifies this approach as an FDA-approved anticancer agent, which is indicated for the treatment of metastatic breast cancer.[2] Eribulin (**1**) is a truncated structural analogue of halichondrin B (**2**), a natural product originally sourced from the marine sponge *Halichondria okadai*.[3] Structurally, Eribulin contains 19 stereocenters within its molecular framework comprising 40 carbons, posing a significant challenge to medicinal and process chemists.[4] In this context, the Eisai process development team, in laudable collaboration with the late Professor Yoshito Kishi from Harvard University, developed a scalable process for synthesizing and unifying C14−C26 fragment **3** and C27−C35 fragment **4** with C1−C13 fragment **5** to ultimately commercialize Eribulin, the process of which is described in a series of patents[5−7] and accompanying journal articles.[8−10]

As a commercial API manufacturer, we took special interest in the process development of Eribulin, as it arguably represents the pinnacle of process chemistry in terms of sheer complexity. Our overall strategy for the synthesis of Eribulin drew direct inspiration from the series of convergent C−C bond formation reactions disclosed by Eisai between the aforementioned three intermediates (**3**−**5**) (Scheme 1). Consequently, our aim was to devise a modified approach to the key segments that would both endow the route with advantages from a chemistry perspective and cautiously circumvent the intellectual property claimed by the originators.

Typically, it is of utmost importance for a generic API manufacturer to devise a proprietary approach to gain access to the market as soon as possible, preferably immediately following the expiration of the API substance patent. In the case of Eribulin, the patent US6214865[5] had covered the API substance and expired in 2023. However, as a typical patent life cycle management strategy, the Eisai team had filed additional patents protecting the intermediates of Eribulin and their chemical manufacturing processes, which hampered generic API developer's timely market entry. Most of these patents[11−15] are set to expire in 2025, with one exception of patent USRE46965,[16] which claims the C14−C35 intermediate with the expiration date of Jan. 2027.

In this context, we have previously disclosed our original approach to C1−C13 fragment **5**, utilizing olefin metathesis[17] and Rh-mediated 6-*endo* cyclization,[18] as well as a novel route to C14−C23 fragment, utilizing 2,3-Wittig rearrangements as key steps.[19] It was noted that Eisai's synthetic pathway for the C27−C35 sulfone fragment **4** has been disclosed previously, and as alluded to above, the elaborated C14−35 sulfone mesylate intermediate **8** is protected by Eisai patent USRE46965[16] until 2027 (Scheme 2, top).

With this in mind, we present our novel synthetic strategy for the kilogram-scale preparation of C27−C35 sulfide fragment **7** and its coupling with C14−C26 fragment in a telescoped process to momentarily access **9** en-route to **10**. Per careful patent analysis, this completely side-steps intermediate **8** which was claimed in USRE46965 by virtue of C27-sulfide functionality (highlighted blue, compound **9**, Scheme 2) and thereby achieves independence from Eisai's intermediate patent claims (Scheme 2, bottom). Cyclized sulfide **10** intercepts Eisai's C14−C35 intermediate **6** after a single oxidation step, making it available for future assembly with C1−C13 fragment **5** to produce Eribulin.

Upon analyzing the synthetic challenge with regard to the C27−C35 sulfone **4**, we noticed that in the Eisai's US8445701 patent, the required intermediate **11** is obtained through a six-step process starting from D-glucurono-3,6-lactone, which

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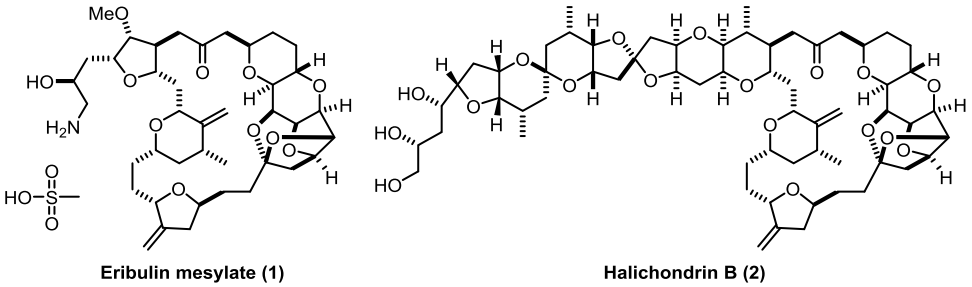
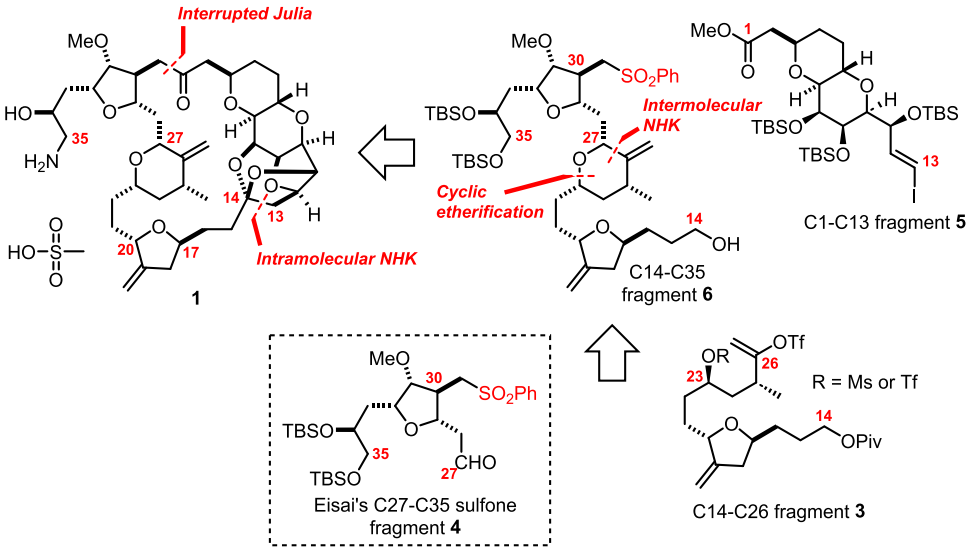
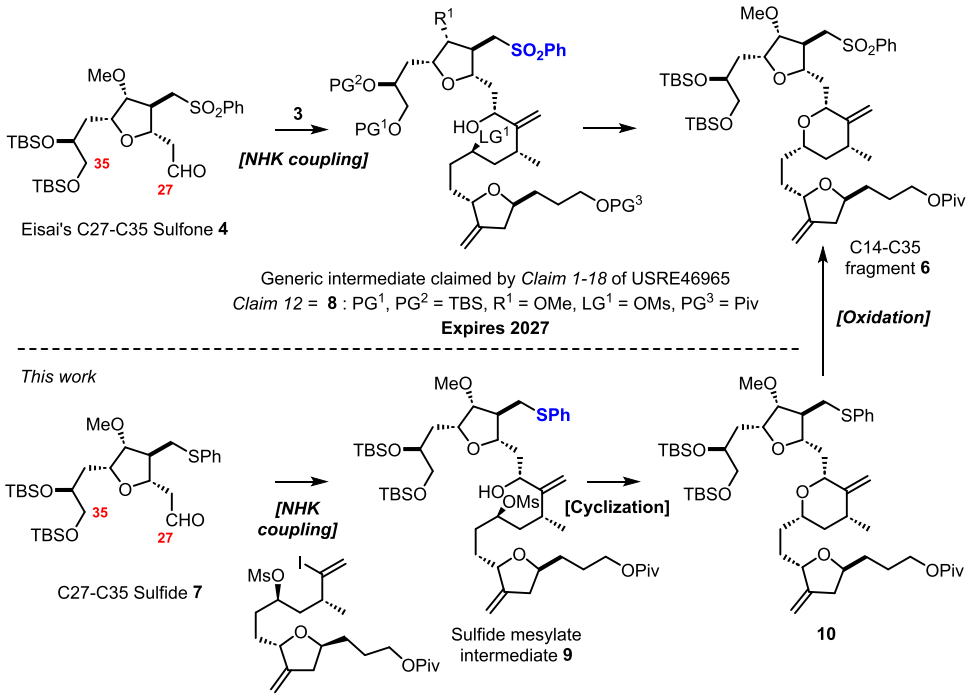


Figure 1. Eribulin mesylate (**1**) and Halichondrin B (**2**).

Scheme 1. Commercial (Eisai) Synthesis of Eribulin (1)



Scheme 2. Eisai Synthesis (Top) and This Work (Bottom) towards Eisai's Advanced C14−C35 Intermediate 6



includes the use of DIBAL under cryogenic conditions (Scheme 3, top).

To expedite the attainment of this intermediate, we proposed using an oxetane functionality that could be accessed through short elaboration from a xylose-derived starting

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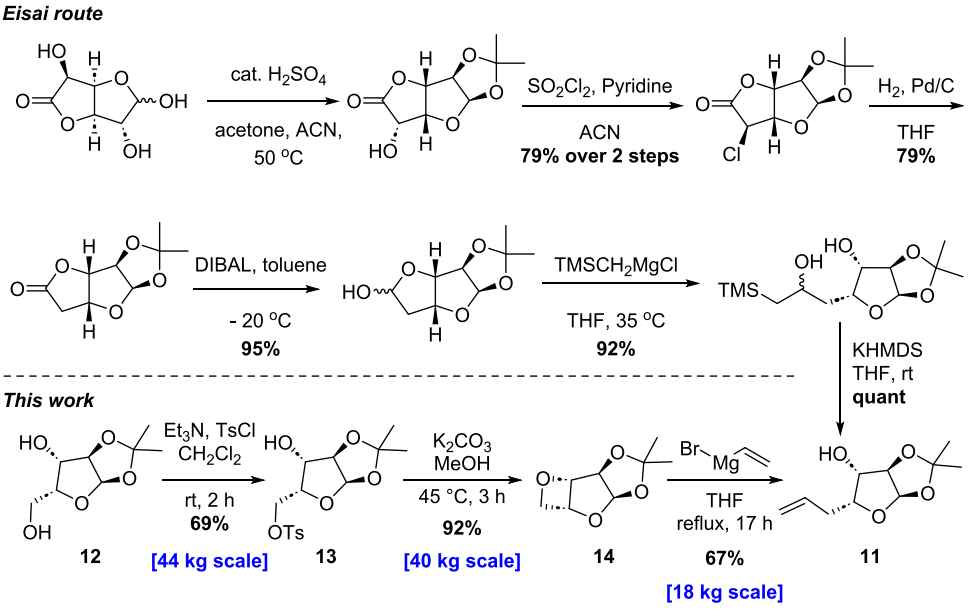
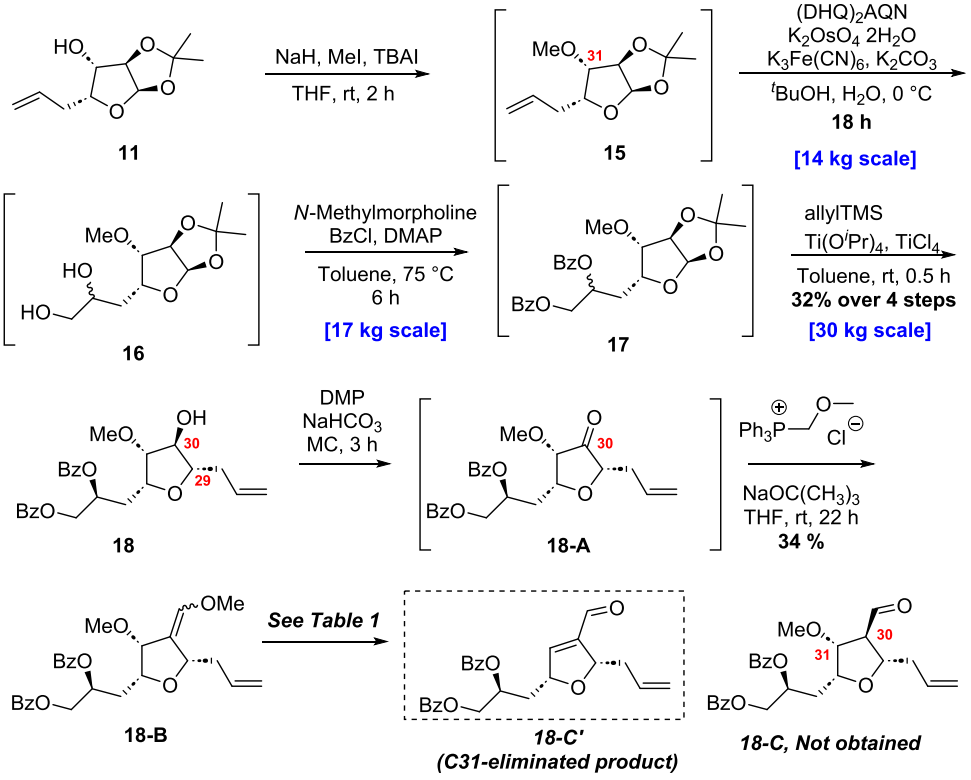
Scheme 3. Eisai Synthesis (Top) and This Work (Bottom) towards Intermediate 11



Scheme 4. Synthesis of 18



material (Scheme 3, bottom). With this modification, our synthetic approach rapidly intercepts Eisai's intermediate **11** before diverging once more in subsequent steps. Therefore, we started our work with commercially available xylose acetonide **12**, which underwent selective tosylation to provide **13** as a solid. Treatment of **13** with K_2CO_3 in MeOH induced smooth intramolecular etherification to give oxetane intermediate **14**, which was reacted with vinylmagnesium bromide in THF to intercept Eisai intermediate **11** in good yield, without the use of cryogenic reaction conditions.

As stated above, subsequent reactions once again diverge completely with one reported by Eisai (Scheme 4).[8−10] The C31 secondary hydroxyl group was methylated using MeI to generate **15**.[20] The Sharpless dihydroxylation of **15** yielded diol **16** diastereoselectively in a 3:1 ratio. Following this, the hydroxyl groups were protected as benzoates to obtain compound **17**. The acetonide ring was opened using allyltrimethylsilane in the presence of $Ti(O^iPr)_4$, producing **18**, which was purified by recrystallization to obtain the desired diastereomer. With **18** in hand, representing the elaborated carbon backbone of the C27−C35 fragment of Eribulin, which

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lacks only the C30-methyl sulfide, we schemed its development into the desired C27−C35 sulfide **7**. Initially, the secondary hydroxyl group of **18** was oxidized by Dess−Martin periodinane (DMP) to ketone **18-A** with the view of installing the required stereocenter at C30 via Wittig olefination with methoxymethyl-triphenylphosphonium chloride. We hypothesized that subsequent acid-induced hydrolysis would furnish the desired, thermodynamically stabilized aldehyde **18-C**. Although methyl vinyl ether could be accessed from crude **18-A** (unoptimized), to our surprise, it was found that exposing this moiety to various acids resulted in elimination of the C31 methoxy group (Table 1, entries 1−5) or it proved unreactive (entries 6−8), putting an end to this approach.

Table 1. Attempted Hydrolysis of 18-B

entry	reagents (equiv)	solvent	temp.	result
1	CF_3COOH (1−2)	CH_2Cl_2	0 °C-rt	**18-C′** (67%)[a]
2	1 M HCl (0.5)	THF/H_2O	rt	**18-C′**[b]
3	phosphoric acid (1)	CH_2Cl_2	rt	**18-C′**[b]
4	MSA (1)	CH_2Cl_2	rt	**18-C′**[b]
5	MSA (0.1)	$MeOH/H_2O$	rt	**18-C′**[b]
6	CH_3COOH (1)	CH_2Cl_2	rt	no conversion
7	benzoic acid (1)	CH_2Cl_2	rt	no conversion
8	PPTS (1)	$MeOH/H_2O$	rt	no conversion

[a]Isolated yield of **18-C′**. [b]Major product observed by crude NMR analysis, **18-C′** not isolated.

We recognized that methylenation of C30-ketone (such as **18-A**) followed by a hydroboration−oxidation sequence would also serve to introduce a hydroxyl functionality for eventual elaboration to the sulfide, although hydroboration will surely deliver the undesired diastereomer, necessitating an epimerization sequence. Furthermore, with respect to compound **18**, the C29 allyl moiety had to be functionalized first to enable hydroboration at the planned C30−30′ terminal olefin. Although superficially inelegant, we were hopeful that this slightly lengthy reaction sequence incorporating an epimerization step will be practical and amendable for our campaign. Starting again from **18** (Scheme 5), functionalization of the C29 allyl moiety ensured: (1) dihydroxylation, (2) cleavage of the vicinal diols by periodate, and (3) a final reduction step, which secured the primary alcohol **19**. Subsequent selective pivaloyl (Piv) protection furnished **20** smoothly. Further, DMP oxidation of **20** was uneventful,[21] furnishing C30-ketone **21** and setting the stage for the methylenation attempt.

The required methylenation of C30-ketone to form the hydroboration precursor required some optimization. Initially, Wittig olefination of **21** furnished the desired terminal olefin in very low conversion and unspecific decomposition of the bulk material (Table 2, entry 1). Employing Tebbe's reagent for methylenation was unsuccessful due to poor conversion (entry 2). Finally, the reaction with the Nysted reagent afforded selective methylenated product **22** in good yield without the aforementioned complications (entry 3).

With **22** in hand, its hydroboration using thexylborane followed by oxidation with sodium perborate successfully produced the primary alcohol **23** in 87% yield, which as expected, features inverted stereochemistry to the one desired (Scheme 6). Therefore, the planned epimerization process was executed: **23** was oxidized with DMP to furnish crude aldehyde **24**, which, when treated with triethylamine, installed the correct stereochemistry to furnish **25**. These reactions could gratifyingly be accomplished in multikilogram scales. Reduction of the aldehyde **25** with $NaBH_4$ furnished **26** and its transformation to mesylate afforded **27**. To prepare the sulfide, **27** was treated with sodium phenylthiolate to provide **28** in a good yield (92% over 2 steps). Next, the benzoate group was removed by $Mg(OMe)_2$ in MeOH to give **29**, and the generated hydroxyl groups were reprotected as TBS groups, affording **30** in good yield (71% in 2 steps). Treatment with DIBAL removed the pivaloate group to yield alcohol **31**, which was finally oxidized to the aldehyde using DMP, giving proprietary C27−C34 fragment **7**.

With a proprietary, kilogram-scale synthesis of the C27−C35 sulfide coupling partner **7** in hand,[22] we proceeded to investigate the coupling between **7** and the C14−C26 fragment **32**. The required vinyl iodide **32** was obtained through a two-step process from the previously disclosed C14−C23 fragment **33**[19] via known transformations (Scheme 7).[23,24] We were delighted to find that the NHK reaction between these fragments led to the formation of coupled sulfide intermediate **9**, circumventing the intermediate claims by Eisai. This intermediate was then cyclized under KHMDS conditions, yielding the advanced, novel sulfide fragment of C14−C35 subunit **10**. Finally, oxidation of the sulfide group using ammonium orthomolybdate afforded the known sulfone framework of **6**.

Scheme 5. Synthesis of 22

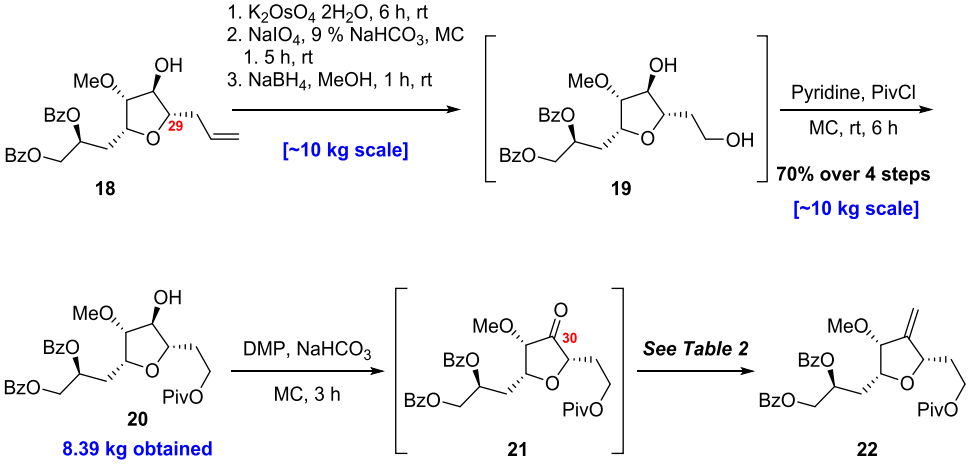

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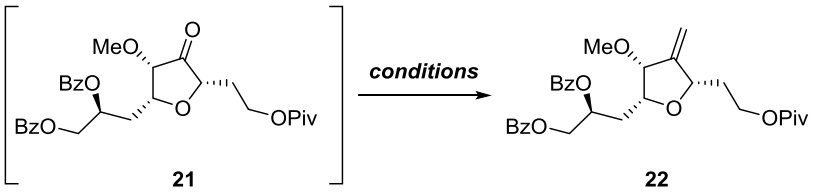
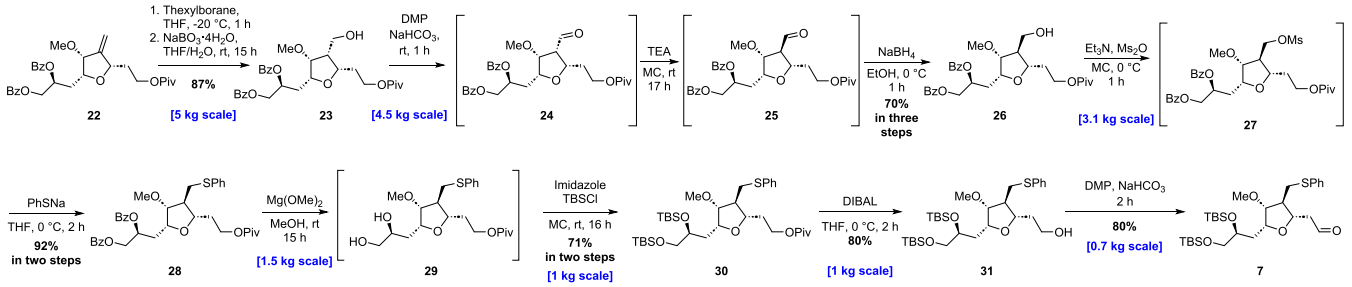
Table 2. Methylenation of 21

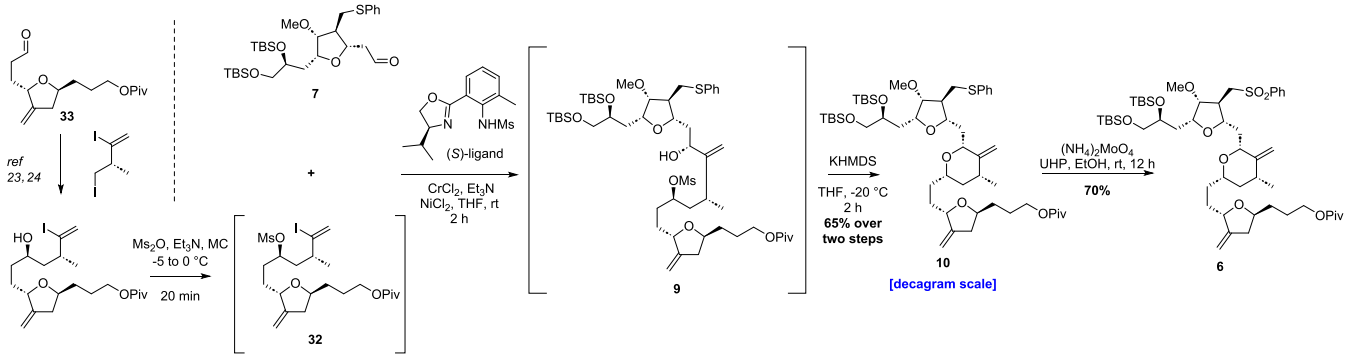


entry	reagents (equiv)	solvent	temp.	result
1	PPh_3CH_3Br (2), $NaOC(CH_3)_3$ (2)	THF	rt	unspecific decomposition
2	Tebbe reagent (0.5 M in toluene, 2)	THF	0 °C-rt	50% product conversion
3	Nysted reagent (20% in THF, 1), $TiCl_4$ (1.0 M in toluene, 1.1)	THF	5 °C-rt	63% over 2 steps

Scheme 6. Synthesis of 7



Scheme 7. Synthesis of 6



In summary, we have completed the synthesis of C27−C35 intermediate **7** and secured a proprietary route toward C14−C35 subunit of Eribulin. The employment of the oxetane moiety enables facile access to **11** without the necessity for column purification or cryogenic conditions, enhancing step efficiency, reducing energy consumption, and minimizing effluent production. While proprietary issues are not frequently discussed in the literature, it is crucial for a generic API developer to establish freedom of operation as early as possible. Careful patent analysis is needed, and constraints identified by such examinations can potentially lead to the development of inventive chemistry. To this end, we have utilized sulfide intermediate **7** in the union of C14−C26 fragment **32** to produce sulfide mesylate intermediate **9**, which is exempt from claims of Eisai's USRE46965. Cyclization and subsequent oxidation of this intermediate yield the known advanced C14−C35 sulfone intermediate **6**. Our laboratories are engaged in further work to convert **6** into eribulin mesylate (**1**).

EXPERIMENTAL SECTION

General Methods. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopic data were recorded with a Fourier transform NMR (FT-NMR) spectrometer at 300 or 75 MHz, using a Bruker Avance-III spectrometer. Chemical shift values are reported in parts per million (ppm) relative to tetramethylsilane (TMS) or $CDCl_3$ as the internal standard, and coupling constants are reported in hertz. 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 of the nonaqueous reactions were carried out under an argon atmosphere with commercial-grade reagents and solvents and used without further purification.

((3a*R*,5*R*,6*S*,6a*R*)-6-Hydroxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methyl 4-methylbenzenesulfonate (13). A 400 L reactor was charged with **12** (43.72 kg, 229 mol) and CH_2Cl_2 (330 L) and cooled to 0 °C. While maintaining the reaction temperature below 5 °C, triethylamine (27.8 kg, 275 mol, 1.2 equiv) was

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added over 0.5 h. To the reaction mixture was added *p*-toluenesulfonyl chloride (48.0 kg, 252 mol, 1.1 equiv) portionwise over 0.5 h. The reaction mixture was warmed to room-temperature (rt) and stirred for 2 h. Upon completion of the reaction (in process control: thin layer chromatography, TLC, hexane/ethyl acetate = 1:1), 15% NH_4Cl (aq, 165 L) was added and the reaction mixture was stirred for 15 min. Layers were separated, and the organic layer was washed with H_2O (165 L) and then concentrated *in vacuo*. To the concentrate was added toluene (66 L), and the reaction mixture was stirred at 40 °C for 15 min and then cooled to rt. Heptane (16.5 L) was added, and the reaction mixture was stirred for 1 h. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to afford the desired product **13** (54.2 kg, 157.3 mol, 68.7%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (2H, d, J = 8.3 Hz), 7.36 (2H, d, J = 8.1 Hz), 5.88 (1H, d, J = 3.5 Hz), 4.51 (1H, d, J = 3.5 Hz), 4.38−4.30 (3H, m), 4.18−4.10 (1H, m), 2.45 (3H, s), 2.41 (1H, bs), 1.46 (3H, s), 1.30 (3H, s). Data are in agreement with the literature.[25]

(2a*R*,3a*R*,6a*R*,6b*S*)-5,5-Dimethyltetrahydro-2*H*-oxeto-[2′,3′:4,5]furo[2,3-*d*][1,3]dioxole (14). A 200 L reactor was charged with **13** (40 kg, 116.2 mol), MeOH (320 L), and K_2CO_3 (24.08 kg, 174.2 mol, 1.5 equiv) and warmed to 45−50 °C and stirred for 3 h. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 1:1), the reaction mixture was cooled to rt and filtered. The filtrate was concentrated *in vacuo*, and to the residue was added H_2O (200 L), followed by CH_2Cl_2 (400 L), and the reaction mixture was stirred for 15 min. Layers were separated, and the organic layer was dried with Na_2SO_4 (500 g), filtered, and concentrated *in vacuo* to afford **14** (18.3 kg, 106.3 mol, 91.5%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.29 (1H, d, J = 3.6 Hz), 5.22 (1H, d, J = 3.9 Hz), 5.15−5.11 (1H, m), 4.78−4.74 (2H, m), 4.29−4.26 (1H, m), 1.43 (3H, s), 1.40 (3H, s). Data are in agreement with the literature.[26]

(3a*R*,5*R*,6*S*,6a*R*)-5-allyl-2,2-Dimethyltetrahydrofuro-[2,3-*d*][1,3]dioxol-6-ol (11). A 1000 L reactor was charged with **14** (18.3 kg, 106.3 mol) and THF (47.58 L) and cooled to 0 °C. Vinylmagnesium bromide was added over 1.5 h (1 M in THF, 212.6 L, 212.6 mol, 2 equiv), and the reaction mixture was warmed to 70 °C and stirred for 17 h. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 2:1), the reaction mixture was cooled to 0 °C and 15% NH_4Cl (aq, 183 L) was added, followed by EtOAc (183 L). The reaction mixture was stirred for 15 min, and then, layers were separated and the organic layer was concentrated *in vacuo*. To the concentrate were added toluene (36.6 L) and heptane (36.6 L), and the reaction mixture was stirred at 50 °C until complete dissolution of the concentrate. The reaction mixture was then cooled to 20 °C and stirred for 1 h to facilitate solidification. The solid was filtered, washed with a 5:1 mixture of toluene/heptane (36.6 L), and dried *in vacuo* to afford **11** (14.2 kg, 70.9 mol, 66.7%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.92−5.78 (2H, m), 5.22−5.08 (2H, m), 4.50 (1H, d, J = 3.8 Hz), 4.18 (1H, td, J = 2.5, 7.4 Hz), 4.08 (1H, bs), 2.57−2.36 (2H, m), 2.04 (1H, s), 1.49 (3H, s), 1.30 (3H, s). Data are in agreement with the literature.[27]

(3a*R*,5*R*,6*S*,6a*R*)-5-Allyl-6-methoxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (15).[20] To a chilled solution of **11** (1.0 g, 5 mmol) in THF (1.05 mL) at 0 °C were added NaH (0.156 g, 6.5 mmol, 1.3 equiv) and TBAI (0.092 g, 0.47 mmol, 0.05 equiv) and stirred for 1 min. To the reaction mixture was then added iodomethane (0.56 mL, 3.9 mmol, 1.8 equiv), and the reaction mixture was warmed to rt and stirred for 2 h. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 2:1), 15% NH_4Cl (aq, 1.05 mL) was added, followed by EtOAc (1.05 mL). Layers were separated, and the organic layer was washed with H_2O (1.05 mL) and concentrated *in vacuo* to afford **15** (0.877 g, 4 mmol, 82%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87 (1H, d, J = 3.8 Hz), 5.85−5.73 (1H, m), 5.18−5.05 (2H, m), 4.55 (1H, d, J = 3.9 Hz), 4.20−4.08 (1H, m), 3.56 (1H, d, J = 3.0 Hz) 3.40 (3H, s), 2.48−2.42 (2H, m), 1.49 (3H, s), 1.32 (3H, s). Data are in agreement with the literature.[27]

3-((3a*R*,5*R*,6*S*,6a*R*)-6-Methoxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)propane-1,2-diol (16). A 630 L reactor was charged with **15** (14.57 kg, 68 mol), ^{t}BuOH (189.4 L), H_2O (189.41 L), $(DHQ)_2AQN$ (291.4 g, 0.34 mol, 0.005 equiv), $K_3Fe(CN)_6$ (76.12 kg, 231.3 mol, 3.4 equiv), and K_2CO_3 (32 kg, 231.3 mol, 3.4 equiv), and the reaction mixture was cooled to −5 °C. To the reaction mixture was then added $K_2OsO_4{\cdot}2H_2O$ (75.2 g, 0.205 mol, 0.003 equiv), and the reaction mixture was stirred at 0 to −5 °C for 18 h. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 1:1), $Na_2S_2O_3$ (37.63 kg, 237.89 mol, 3.5 equiv) was added, and the reaction mixture was warmed to rt and stirred for 15 h. To the reaction mixture was added toluene (218.5 L), and the layers were separated. The organic layer was washed with 20% NaCl (aq, 145.7 L) and concentrated *in vacuo* to afford crude **16** (16.88 kg, 68 mol, ∼100%), which was used for the next step without further purification.

3-((3a*R*,5*R*,6*S*,6a*R*)-6-Methoxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)propane-1,2-diyl Dibenzoate (17). A 630 L reactor was charged with **16** (16.88 kg, 68 mol), toluene (168.8 L), *N*-methyl morpholine (22.34 L), and 4-dimethylaminopyridine (DMAP) (1.66 kg, 13.58 mol, 0.2 equiv) and cooled to 5 °C. Benzoyl chloride (23.7 L, 204.1 mol, 3 equiv) was then added dropwise while maintaining the temperature below 25 °C over 0.5 h. The reaction mixture was then warmed to 75 °C and stirred for 6 h. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 1:1), the reaction mixture was cooled to 0 °C, and then 1 N HCl aq (84.4 L) was added while maintaining the reaction temperature below 25 °C. The reaction mixture was warmed to rt and stirred for 15 min and left to stand for 15 min. Layers were separated, and the organic layer was washed sequentially with 20% NaCl (aq, 50.64 L), 5% $NaHCO_3$ (aq, 50.64 L), and H_2O (50.64 L). The separated organic layer was concentrated *in vacuo* to afford crude **17** (31.04 kg, 68 mmol, ∼100%) as a brown oil and taken to the next step without further purification.

(*S*)-3-((2*R*,3*R*,4*S*,5*S*)-5-Allyl-4-hydroxy-3-methoxytetrahydrofuran-2-yl)propane-1,2-diyl Dibenzoate (18). A 630 L reactor was charged with $TiCl_4$ (306 L, 306 mol, 1.0 M solution in toluene, 4.5 equiv) and toluene (93.12 L) and cooled to 0 °C. $Ti(O^iPr)_4$ (29.0 kg, 30.2 L, 102 mol, 1.5 equiv) was then added dropwise over 2 h while maintaining the temperature below 25 °C. The reaction mixture was then warmed to rt and stirred at 20−30 °C for 0.5 h. A separate 1000 L reactor was charged with crude **17** (31.04 kg, 68 mol), toluene (217.28 L), and allyltrimethylsilane (37.29 kg, 326.4 mol, 4.8 equiv) and stirred at rt for 30 min. The reaction

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mixture was cooled to below 0 °C and the $TiCl_4/Ti(O^iPr)_4$ solution prepared above was added dropwise over 3 h while maintaining the temperature below 25 °C. The reaction mixture was then stirred at rt for 1 h. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 2:1), the reaction mixture was cooled to below −5 °C, and 1 N HCl (aq, 186.24 L) was added and the reaction mixture was warmed to rt and stirred for 15 min. Layers were separated, and the organic layer was washed sequentially with 1 N HCl (aq, 93.12 L) and H_2O (93.12 L). The organic layer was then concentrated, and to the concentrate was added isopropanol (62.08 L) and the reaction mixture was again concentrated. To the concentrate was again added isopropanol (31.04 L) and then the mixture was warmed to 60 °C until the concentrate completely dissolved. The mixture was then cooled to 20 °C and stirred at this temperature for 1 h to facilitate solidification. Heptane (155.2 L) was charged and the solution was stirred at 20 °C for 1 h. The mixture was then filtered, solids were washed with heptane (31.04 L), and the resulting wet cake was vacuum-dried at 30 °C to obtain **18** (10.1 kg, 22.9 mol, 32.33% for 4 steps) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06−7.99 (4H, m), 7.58−7.51 (2H, m), 7.45−7.37 (4H, m), 5.89−5.75 (1H, m), 5.67−5.59 (1H, m), 5.16−5.04 (2H, m), 4.58−4.55 (2H, m), 4.19−4.13 (1H, m), 3.98−3.96 (1H, m), 3.67−3.61 (2H, m), 3.40 (3H, s), 2.48−2.24 (2H, m), 2.22 (2H, t, J = 6.6 Hz), 1.93 (s, bs); ^{13}C NMR (300 MHz, $CDCl_3$): δ 166.28, 166.16, 134.26, 133.11, 133.08, 130.04, 129.83, 129.75, 129.70, 128.39, 117.52, 87.90, 84.31, 79.09, 70.15, 65.85, 57.25, 37.99, 30.50; MS (ESI): 463.1756 $(M + Na)^+$.

(2*S*)-3-((2*R*,3*R*,4*S*,5*S*)-5-(2,3-Dihydroxypropyl)-4-hydroxy-3-methoxytetrahydrofuran-2-yl)propane-1,2-diyl Dibenzoate (Crude Diol). A 630 L reactor was charged with **18** (10.1 kg, 22.9 mol), acetonitrile (130 L), H_2O (130 L), $K_3Fe(CN)_6$ (26.4 kg, 80.2 mol, 3.5 equiv), K_2CO_3 (11.1 kg, 80.3 mol, 3.5 equiv), and K_2OsO_4-$2H_2O$ (84.0 g, 0.214 mol, 0.01 equiv) and stirred at rt for 18 h. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 1:1), $Na_2S_2O_3$ (12.7 kg, 80.3, 3.5 equiv) was added, and the reaction mixture was further stirred at rt for 6 h. EtOAc (100.0 L) was then added and layers were separated. The organic layer was concentrated *in vacuo* to afford **crude diol** (10.88, 22.9 mol, ∼100%), which was taken to the next step without further purification.

(*S*)-3-((2*R*,3*R*,4*S*,5*S*)-4-Hydroxy-3-methoxy-5-(2-oxoethyl)tetrahydrofuran-2-yl)propane-1,2-diyl Dibenzoate (Crude Aldehyde). A 500 L reactor was charged with **crude diol** (10.88 kg, 22.9 mol), CH_2Cl_2 (109 L), and 8% $NaHCO_3$ (aq, 5.44 L) and cooled to −5 °C. Sodium periodate (14.7 kg, 68.7 mol, 3.0 equiv) was added, and then the reaction temperature was warmed to rt and stirred for 1.5 h. Upon completion of the reaction (in process control: TLC, ethyl acetate/methanol = 15:1), the reaction mixture was filtered and to the filtrate was added 15% $Na_2S_2O_3$ (108.8 L, aq) and stirred for 15 min. The layers were separated, and the organic layer was dried with Na_2SO_4 (100 g) and filtered. Filtrate was concentrated *in vacuo* to afford **crude aldehyde** (10.6 kg, 23.8 mol, >100%), which was taken to the next step without further purification.

(*S*)-3-((2*R*,3*R*,4*S*,5*S*)-4-Hydroxy-5-(2-hydroxyethyl)-3-methoxytetrahydrofuran-2-yl)propane-1,2-diyl Dibenzoate (19). A 500 L reactor was charged with **crude aldehyde** (10.6 kg, 23.8 mol) and methanol (80.0 L) and cooled to −5 °C. Sodium borohydride (1.0 kg, 26.4 mol, 1.1 equiv) was then added in portions over 2 h, maintaining the temperature below 5 °C. The reaction mixture was then stirred at −5 °C for 1 h. Upon completion of the reaction (in process control: TLC, ethyl acetate/ methanol = 15:1), the reaction mixture was warmed to 0−5 °C and 15% NH_4Cl (aq, 106.0 L) was added. The reaction mixture was partially concentrated (ca. to 20% of original volume) and dichloromethane (DCM) (53.0 L) was then added and stirred for 15 min. Layers were separated, and the organic layer was concentrated *in vacuo* to obtain crude **19** (10.2 kg, 22.8 mol, ∼96%) as a pale yellow oil, which was taken to the next step without further purification.

(*S*)-3-((2*R*,3*R*,4*S*,5*S*)-4-Hydroxy-3-methoxy-5-(2-(pivaloyloxy)ethyl)tetrahydrofuran-2-yl)propane-1,2-diyl Dibenzoate (20). A 250 L reactor was charged with crude **19** (10.22 kg, 22.8 mol), dichloromethane (102.0 L), and pyridine (3.72 L, 46.05 mol, 2.0 equiv) and cooled to 0 to −5 °C. Pivaloyl chloride (4.24 L, 35.0 mol, 1.5 equiv) was added dropwise over 1 h, and the reaction mixture was stirred at 20−30 °C for 6 h. Upon completion of the reaction (In process control: TLC, hexane/ethyl acetate = 1:1), the reaction mixture was treated with 15% NH_4Cl (aq, 102 L) and stirred for 15 min. The layers were separated, and the organic layer was sequentially washed with 1 N HCl (51.0 L, aq) and H_2O (51.0 L). The organic layer was then concentrated *in vacuo* and purified via MPLC (hexane/ethyl acetate = 4:1 → hexane/ethyl acetate = 1:1) to yield **20** (8.39 kg, 15.8 mol, 69.2% in 4 steps) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06−7.98 (4H, m), 7.58−7.51 (2H, m), 7.45−7.38 (4H, m), 5.66−5.58 (1H, m), 4.60−4.51 (2H, m), 4.32−4.24 (1H, m), 4.18−4.03 (2H, m), 4.00−3.98 (1H, m), 3.67−3.61 (2H, m), 3.40 (3H, s), 2.21 (3H, t, J = 6.6 Hz), 2.00−1.86 (2H, m), 1.18 (9H, s); ^{13}C NMR (300 MHz, $CDCl_3$): δ 178.85, 166.25, 166.10, 133.10, 133.06, 133.04, 129.83, 129.73, 129.69, 128.38, 87.90, 82.56, 79.47, 70.13, 65.78, 61.38, 57.31, 38.77, 33.12, 30.42, 27.18; MS (ESI): 551.2281 $(M + Na)^+$.

(*S*)-3-((2*R*,3*S*,5*S*)-3-Methoxy-4-oxo-5-(2-(pivaloyloxy)-ethyl)tetrahydrofuran-2-yl)propane-1,2-diyl Dibenzoate (21). A 630 L reactor was charged with **20** (8.39 kg, 15.8 mol), dichloromethane (125.9 L), DMP (13.46 kg, 31.7 mol, 2.0 equiv), and $NaHCO_3$ (2.66 kg, 31.7 mol, 2.0 equiv), and the reaction mixture was stirred at rt for 3 h. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 3:1), the reaction mixture was treated with 10% $Na_2S_2O_3$ (83.9 L, aq) and 8% $NaHCO_3$ (83.9 L, aq) and further stirred for 15 min. Layers were separated and the organic layer was washed with 8% $NaHCO_3$ (83.9 L, aq), filtered, and the filtrate was concentrated *in vacuo* to yield crude **21** (8.36 kg, 15.9 mol, ∼100%) as a yellowish oil, which was taken to the next step without further purification.

(*S*)-3-((2*R*,3*R*,5*S*)-3-Methoxy-4-methylene-5-(2-(pivaloyloxy)ethyl)tetrahydrofuran-2-yl)propane-1,2-diyl Dibenzoate (22). A 630 L reactor was charged with Nysted reagent (36.2 kg of 20% solution in THF, 15.8 mol, 1 equiv) and THF (66.88 L), and the mixture was cooled to −10 °C. A solution of **21** (8.36 kg, 15.9 mol) in THF (16.72 L) was charged, followed by slow addition of $TiCl_4$ (17.46 L, 17.5 mol, 1.0 M solution in toluene, 1.1 equiv) via a diaphragm pump over 3 h while maintaining the temperature below 5 °C. The reaction mixture was then warmed to rt and stirred for 1.5 h. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 3:1), the reaction mixture was cooled

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to −10 °C, and 1 N HCl (83.6 L, aq) and EtOAc (83.6 L) were added. The mixture was then warmed to rt and stirred for 15 min. Layers were separated, and the organic layer was washed with H_2O (83.6 L × 3). The organic layer was concentrated *in vacuo*, and the crude product was purified via MPLC (hexane/ethyl acetate = 4:1) to furnish **22** (5.23 kg, 9.98 mol, 63% in 2 steps) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09−8.02 (4H, m), 7.60−7.53 (2H, m), 7.48−7.40 (4H, m), 5.70−5.63 (1H, m), 5.29 (1H, d, J = 2.1 Hz), 5.16 (1H, d, J = 1.2 Hz), 4.63−4.54 (2H, m), 4.41−4.37 (1H, m), 4.22−4.13 (2H, m), 4.02−3.95 (2H, m), 3.32 (3H, s), 2.34−2.27 (2H, m), 1.94 (2H, q, J = 6.6), 1.21 (9H, s); ^{13}C NMR (300 MHz, $CDCl_3$): 178.46, 166.23, 166.10, 149.06, 133.12, 133.07, 130.01, 129.83, 129.71, 129.70, 128.40, 128.38, 111.26, 81.93, 78.48, 70.06, 65.86, 61.18, 55.37, 38.71, 35.63, 30.33, 27.20; MS (ESI): 563.2053 $(M + K)^+$.

(*S*)-3-((2*R*,3*R*,4*R*,5*S*)-4-(Hydroxymethyl)-3-methoxy-5-(2-(pivaloyloxy)ethyl)tetrahydrofuran-2-yl)propane-1,2-diyl Dibenzoate (23). A 250 L reactor was charged with borane-tetrahydrofuran complex solution (21.6 L, 21.6 mol, 1.0 M solution in THF, 2.2 equiv) and cooled to −5 °C. A solution of 2,3-dimethyl-2-butene (1.82 kg, 21.6 mol, 2.2 equiv) in THF (19.03 L) was then added via a diaphragm pump over 2 h. The mixture was then stirred at 0 to −5 °C for 2 h to prepare the thexylborane solution. A separate 500 L reactor was charged with **22** (5.15 kg, 9.82 mol) and THF (51.5 L) and cooled to 0 to −5 °C. The above-prepared thexylborane solution in THF (43.2 L, 2.2 equiv) was slowly added via a diaphragm pump over 3 h while maintaining the temperature below 0 °C. The mixture was then warmed to rt and stirred for 1 h. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 3:1), the reaction mixture was cooled to below −10 °C and H_2O (51.5 L) was slowly added using a diaphragm pump while warming the mixture to 20−30 °C. Sodium perborate tetrahydrate (6.65 kg, 43.2 mol, 4.4 equiv) was then added to the reaction mixture, and the mixture was stirred at rt for 15 h. $NaBO_3{\cdot}4H_2O$ (1.51 kg, 9.82 mol, 1 equiv) was then added, and the reaction mixture was stirred at rt for 5 h. The reaction mixture was then filtered, and to the filtrate are added H_2O (25.75 L) and ethyl acetate (51.5 L), and the mixture was stirred for 15 min. Layers were then separated, and the organic layer was washed with 20% NaCl (25.75 L, aq) and concentrated *in vacuo* and the residue was purified via MPLC (hexane/ethyl acetate = 3:1) to **23** (4.62 kg, 8.51 mol, 86.7%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07−7.98 (4H, m), 7.58−7.51 (2H, m), 7.45−7.38 (4H, m), 5.69−5.61 (1H, m), 4.63−4.53 (2H, m), 4.22−4.04 (2H, m), 4.02−3.92 (3H, m), 3.90−3.75 (2H, m), 3.50 (3H, s), 2.56−2.48 (1H, m), 2.22−2.17 (2H, m), 2.06−2.02 (1H, m), 1.99−1.87 (1H, m), 1.80−1.69 (1H, m), 1.17 (9H, s); ^{13}C NMR (300 MHz, $CDCl_3$): δ 178.53, 166.27, 166.12, 133.13, 133.09, 130.01, 129.82, 129.73, 129.68, 128.41, 128.40, 83.65, 78.00, 75.73, 70.33, 65.76, 62.04, 60.70, 58.64, 53.44, 48.03, 38.70, 31.35, 31.05, 27.20; MS (ESI): 581.2157 $(M + K)^+$.

(*S*)-3-((2*R*,3*R*,4*R*,5*S*)-4-Formyl-3-methoxy-5-(2-(pivaloyloxy)ethyl)tetrahydrofuran-2-yl)propane-1,2-diyl Dibenzoate (24). A 250 L reactor was charged with **23** (4.56 kg, 8.40 mol) and dichloromethane (22.8 L) and cooled to 5−10 °C. A solution of DMP (7.13 kg, 16.8 mol, 2.0 equiv) in dichloromethane (45.6 L) was then slowly added via a diaphragm pump, followed by $NaHCO_3$ (1.41 kg, 16.8 mol, 2.0 equiv), and the reaction mixture was stirred for 1 h at rt. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 2:1), 10% $Na_2S_2O_3$ (45.6 L, aq) and 8% $NaHCO_3$ (45.6 L, aq) were slowly added via a diaphragm pump and stirred further for 30 min. The reaction mixture was then left to stand for 30 min, and the layers were separated. The organic layer was dried by addition of Na_2SO_4 (2.3 kg) and then filtered, and the filtrate was concentrated *in vacuo* to obtain crude **24** (4.54 kg, 8.40 mol, 100%), which was taken to the next step without further purification.

(*S*)-3-((2*R*,3*R*,4*S*,5*S*)-4-Formyl-3-methoxy-5-(2-(pivaloyloxy)ethyl)tetrahydrofuran-2-yl)propane-1,2-diyl Dibenzoate (25). A 250 L reactor was charged with **24** (4.54 kg, 8.40 mol), DCM (45.4 L), and triethylamine (1.3 L, 9.3 mol, 1.1 equiv), and the mixture was stirred for 17 h. H_2O (45.4 L) was then added, and the reaction mixture was stirred for 15 min. Layers were separated, and the organic layer was washed sequentially with 1 N HCl (45.4 L, aq) and water (45.4 L). The organic layer was concentrated *in vacuo* to afford crude **25** (4.56 kg, 8.43 mol, 100%) as a pale yellow oil, which was taken to the next step without further purification.

(*S*)-3-((2*R*,3*R*,4*S*,5*S*)-4-(Hydroxymethyl)-3-methoxy-5-(2-(pivaloyloxy)ethyl)tetrahydrofuran-2-yl)propane-1,2-diyl Dibenzoate (26). A 250 L reactor was charged with crude **25** (4.56 kg, 8.43 mol) and methanol (45.6 L) and cooled to −10 °C. Sodium borohydride (476 g, 12.6 mol, 1.5 equiv) was then charged in four portions while maintaining a temperature below 5 °C over 2 h. The reaction mixture was stirred further for 1 h at 0 °C. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 1:1), 15% NH_4Cl (45.6 L, aq) was added via a diaphragm pump, and the mixture was partially concentrated to leave behind 20% volume. Dichloromethane (45.6 L) was charged, and the reaction mixture was stirred for 30 min. Layers were separated, and the organic layer was concentrated *in vacuo* and then purified via MPLC (hexane/ethyl acetate = 3:1) to obtain **26** (3.16 kg, 5.82 mol, 69.3%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06−7.99 (4H, m), 7.57−7.51 (2H, m), 7.45−7.38 (4H, m), 5.66−5.58 (1H, m), 4.61−4.51 (2H, m), 4.21−4.04 (2H, m), 3.91−3.85 (1H, m), 3.70−3.66 (1H, m), 3.64−3.51 (3H, m), 3.33 (3H, s), 2.23 (2H, t, J = 6.6 Hz), 2.15−2.08 (1H, m), 1.97−1.91 (3H, m), 1.17 (9H, s); ^{13}C NMR (300 MHz, $CDCl_3$): δ 178.49, 166.26, 166.16, 133.10, 133.08, 130.07, 129.83, 129.72, 129.69, 128.40, 128.38, 84.62, 78.02, 77.62, 70.29, 65.82, 62.72, 61.61, 56.65, 52.68, 38.70, 34.83, 30.53, 27.18; MS (ESI): 581.2179 $(M + K)^+$.

(*S*)-3-((2*R*,3*R*,4*S*,5*S*)-3-Methoxy-4-(((methylsulfonyl)-oxy)methyl)-5-(2-(pivaloyloxy)ethyl)tetrahydrofuran-2-yl)propane-1,2-diyl Dibenzoate (27). A 100 L reactor was charged with **26** (3.16 kg, 5.82 mol), dichloromethane (32 L), and triethylamine (1.2 L, 0.88 kg, 8.73 mol, 1.5 equiv), and the reaction mixture was cooled to 0 to −5 °C. Methane sulfonic anhydride (1.32 kg, 7.57 mol, 1.3 equiv) was charged in 5 portions over 1 h while keeping the temperature below 5 °C. The reaction mixture was then stirred for 2.5 h at 0 °C. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 3:1), sat. $NaHCO_3$ (32 L, aq) was added to the reaction mixture and stirred for 15 min at rt. Layers were separated, and the organic layer was concentrated *in vacuo* to afford crude **27**, which was taken to the next step without further purification.

(*S*)-3-((2*R*,3*R*,4*S*,5*S*)-3-Methoxy-4-((phenylthio)-methyl)-5-(2-(pivaloyloxy)ethyl)tetrahydrofuran-2-yl)-propane-1,2-diyl Dibenzoate (28). A 200 L reactor was

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charged with a solution of crude **27** in THF (32 L) and cooled to 0 to −5 °C. Sodium thiophenolate (1.54 kg, 11.6 mol, 2 equiv) was slowly added over 1 h. The reaction was stirred at 0 °C for 16 h, and then 15% NH_4Cl (aq, 32 L) and ethyl acetate (32 L) were added and stirred for 15 min. Layers were separated, and the organic layer was concentrated *in vacuo* and purified via MPLC (hexane/ethyl acetate = 7:1 → hexane/ethyl acetate = 3:1) to furnish **28** (3.39 kg, 5.35 mol, 91.9% for 2 steps) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10−8.02 (4H, m), 7.61−7.53 (2H, m), 7.48−7.33 (4H, m), 7.32−7.28 (4H, m), 7.24−7.18 (1H, m), 5.67−5.60 (1H, m), 4.64−4.53 (2H, m), 4.19−4.03 (2H, m), 4.00−3.94 (1H, m), 3.73−3.67 (2H, m), 3.31 (3H, s), 2.95 (2H, d, J = 7.5 Hz), 2.25 (2H, t, J = 6.0 Hz), 2.21−2.14 (1H, m), 1.98−1.85 (2H, m), 1.21 (9H, s); ^{13}C NMR (300 MHz, $CDCl_3$): 178.36, 166.23, 166.09, 135.66, 133.11, 133.08, 130.07, 129.83, 129.74, 129.70, 129.28, 129.12, 128.41, 128.39, 126.42, 86.42, 80.51, 70.24, 65.78, 61.47, 56.79, 49.13, 38.71, 35.89, 34.85, 30.53, 27.23; MS (ESI): 673.2242 $(M + K)^+$.

2-((2*S*,3*S*,4*R*,5*R*)-5-((*S*)-2,3-Dihydroxypropyl)-4-methoxy-3-((phenylthio)methyl)tetrahydrofuran-2-yl)-ethyl Pivalate (29). A 200 L reactor was charged with **28** (1.59 kg, 2.50 mol), MeOH (12.66 kg), and magnesium methoxide (0.476 kg, 7−8% in methanol, 5.5 mol, 2.2 equiv) and stirred for 15 h at rt. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 1:1), 15% NH_4Cl solution (16.0 L, aq) was added and stirred for 15 min, and then partially concentrated *in vacuo* to remove MeOH. Dichloromethane (21.2 kg) was then added to the reaction mixture and for 15 min. Layers were separated, and the organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo* to obtain crude **29** (1.07 kg, 2.5 mol, ∼100%) as a pale yellow oil and taken to the next step without further purification.

2-((2*S*,3*S*,4*R*,5*R*)-5-((*S*)-2,3-Bis((*tert*-butyldimethylsilyl)oxy)propyl)-4-methoxy-3-((phenylthio)methyl)tetrahydrofuran-2-yl)ethyl Pivalate (30). A 200 L reactor was charged with crude **29** (1.07 kg, 2.5 mol), dichloromethane (14.58 kg), imidazole (0.854 kg, 12.6 mol, 5.0 equiv), and TBSCl (1.13 kg, 7.49 mol, 3.0 equiv), and the mixture was stirred for 16 h at rt. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 3:1) water (11.0 L) was added and stirred for 30 min. Layers were separated, and the organic layer was washed with water (11 L), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified via MPLC (hexane/ethyl acetate = 36:1 → hexane/ethyl acetate = 18:1→ hexane/ethyl acetate = 12:1) to obtain **30** (1.16 kg, 1.77 mol, 70.7% in 2 steps) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.29 (4H, m), 7.25−7.20 (1H, m), 4.24−4.10 (2H, m), 3.99−3.94 (1H, m), 3.82 (1H, qui, J = 5.1 Hz), 3.70−3.58 (3H, m), 3.54−3.49 (1H, m), 3.29 (3H, s), 3.05−2.88 (2H, m), 2.19−2.12 (1H, m), 2.02−1.87 (3H, m), 1.84−1.75 (1H, m), 1.22 (9H, s), 0.91 (9H, s), 0.90 (9H, s), 0.10 (6H, d, J = 3.6 Hz), 0.07 (6H, d, J = 1.7 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 178.41, 135.85, 129.19, 129.10, 126.34, 86.51, 80.05, 78.13, 71.36, 67.97, 67.87, 61.66, 56.80, 49.30, 38.72, 35.95, 34.93, 33.55, 27.23, 26.01, 25.93, 25.62, 18.41, 18.17, −4.09, −4.74, −5.31, −5.33; MS (ESI): 677.3707 $(M + Na)^+$.

2-((2*S*,3*S*,4*R*,5*R*)-5-((*S*)-2,3-Bis((*tert*-butyldimethylsilyl)oxy)propyl)-4-methoxy-3-((phenylthio)methyl)tetrahydrofuran-2-yl)ethan-1ol (31). A 200 L reactor was charged with **30** (1.16 kg, 1.77 mol) and THF (11.6 L) and cooled to −10 °C. Diisobutylaluminum hydride (1.2 M in toluene, 3.2 L, 3.84 mol, 2.17 equiv) was added dropwise to the reaction mixture at 5 °C over 3 h. The reaction was then stirred for 2 h at 0 to −5 °C. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 3:1), 1 N HCl (11.6 L, aq) was added dropwise to the reaction mixture at below 10 °C, followed by the addition of EtOAc (11.6 L) and stirred for 30 min. Layers were separated, and the organic layer was washed with water (11.6 L), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified via MPLC (hexane/ethyl acetate = 36:7) to yield **31** (799.88 g, 1.4 mol, 79.9%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.24 (4H, m), 7.24−7.19 (1H, m), 4.00−3.94 (1H, m), 3.83−3.75 (4H, m), 3.63−3.58 (2H, m), 3.53−3.48 (1H, m), 3.31 (3H, s), 3.04−2.90 (2H, m), 2.56 (1H, t, J = 5.7 Hz), 2.27−2.19 (1H, m), 2.04−1.90 (2H, m), 1.88−1.77 (2H, m), 0.92 (9H, s), 0.91 (9H, s), 0.10 (6H, d, J = 3.5 Hz), 0.08 (6H, d, J = 1.5 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 135.77, 129.18, 129.12, 129.04, 128.23, 126.39, 125.30, 86.49, 83.03, 71.26, 67.82, 60.94, 56.77, 49.25, 36.96, 35.96, 33.50, 26.00, 25.92, 21.47, 18.40, 18.17, −4.11, −4.75, −5.31, −5.32; MS (ESI): 593.3138 $(M + Na)^+$.

2-((2*S*,3*S*,4*R*,5*R*)-5-((*S*)-2,3-Bis((*tert*-butyldimethylsilyl)oxy)propyl)-4-methoxy-3-((phenylthio)methyl)tetrahydrofuran-2-yl)acetaldehyde (7). A 100 L reactor was charged with **31** (750 g, 1.3 mol) and dichloromethane (15 L) and cooled to 0 to −5 °C, followed by the addition of $NaHCO_3$ (221 g, 2.6 mol, 2.0 equiv). After stirring for 15 min, DMP (224 g, 521 mmol, 2.5 equiv) was charged portionwise over 10 min. The reaction was stirred for 2 h at 0 to −5 °C. Upon completion of the reaction (in process control: TLC, hexane/ethyl acetate = 3:1), 20% $Na_2S_2O_3$ (7.5 L, aq, 10 v/w) and 9% $NaHCO_3$ (7.5 L, aq, 10 v/w) were added via a diaphragm pump, and the reaction mixture was warmed to rt and stirred for 30 min. Layers were separated and the organic layer was washed with 9% $NaHCO_3$ (7.5 L, aq, 10 v/w) and filtered, and the filtrate was concentrated *in vacuo* to yield crude **7**. The crude residue was purified via MPLC (hexane/ethyl acetate = 12:1) to yield compound **7** as a yellowish oil (597 g, 1.04 mol, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.78 (1H, t, J = 1.7 Hz) 7.39−7.30 (4H, m), 7.26−7.20 (1H, m), 4.10−4.00 (2H, m), 3.84−3.76 (1H, m), 3.62−3.57 (2H, m), 3.52−3.47 (1H, m), 3.27 (3H, s), 3.16−3.10 (1H, m), 2.96−2.89 (1H, m), 2.84−2.67 (2H, m), 2.22−2.15 (1H, m), 2.02−1.94 (1H, m), 1.84−1.75 (1H, m), 0.91 (9H, s), 0.90 (9H, s), 0.09 (6H, d, J = 3.6 Hz), 0.06 (6H, d, J = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.40, 135.54, 129.40, 129.27, 126.58, 86.41, 78.58, 78.36, 71.38, 67.93, 56.92, 49.75, 49.50, 35.75, 33.65, 26.13, 26.06, 18.53, 18.30, −3.96, −4.62, −5.17, −5.20; MS (ESI): 591.2984 $(M + Na)^+$.

3-((2*S*,5*S*)-5-((3*R*,5*R*,7*R*)-8-((2*S*,3*S*,4*R*,5*R*)-5-((*S*)-2,3-Bis((*tert*-butyldimethylsilyl)oxy)propyl)-4-methoxy-3-((phenylthio)methyl)tetrahydrofuran-2-yl)-7-hydroxy-5-methyl-6-methylene-3-((methylsulfonyl)oxy)octyl)-4-methylenetetrahydrofuran-2-yl)propyl Pivalate (9). A 3 L five-neck round-bottom flask was equipped with a magnetic stir bar, oxygen detector inlet, outlet, thermometer, and capped with rubber septa. The round-bottom flask was charged with (*S*)-ligand (120 g, 4.65 equiv, 376.4 mmol) and THF (690 mL). Oxygen detector was turned on, and argon flow was maintained to sustain a level of oxygen below 200 ppm. To the reaction mixture was added $CrCl_2$ (46.7 g, 4.64 equiv, 377.6

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mmol) and cooled below 20 °C. Triethylamine (53.8 mL, 4.68 equiv, 378.2 mmol) was added in 2−3 portions and the reaction mixture was warmed to rt and stirred for 2 h. $NiCl_2$ (1.26 g, 0.12 equiv) was charged, followed by the addition of solution comprising **32** (46 g, 82.6 mmol, 1 equiv) and **7** (47 g, 82.6 mmol, 1 equiv) in THF (230 mL), and the reaction mixture was stirred at rt for overnight. The reaction mixture was then cooled to 0 to −5 °C, and ethylenediamine was added (72 mL, 1073 mmol, 13 equiv), then warmed to 10 °C, and stirred for 1 h. To the reaction mixture was added H_2O (470 mL) and *n*-heptane (940 mL) and stirred for 30 min. The reaction mixture was filtered through a pad of Celite and the filter cake was washed with *n*-heptane (470 mL) and MTBE (1.4 L). The combined filtrate was left to stand for 15 min and then layers were separated, and the organic layer was sequentially washed with 6% $NaHCO_3$ (940 mL, aq) and 10% NaCl (470 mL, aq), dried over Na_2SO_4, and concentrated *in vacuo* to afford the crude intermediate **9**, which was taken to the next step without further purification.

3-((2*S*,5*S*)-5-(2-((2*S*,4*R*,6*R*)-6-(((2*S*,3*S*,4*R*,5*R*)-5-((*S*)-2,3-Bis((*tert*-butyldimethylsilyl)oxy)propyl)-4-methoxy-3-((phenylthio)methyl)tetrahydrofuran-2-yl)methyl)-4-methyl-5-methylenetetrahydro-2*H*-pyran-2-yl)ethyl)-4-methylenetetrahydrofuran-2-yl)propyl Pivalate (10). A 20 L reactor was charged with crude intermediate **9** (86 g, 1.0 equiv, 86 mmol) and THF (4.8 L) and cooled to −20 °C. The reaction mixture was stirred at this temperature for 15 min, and then KHMDS (0.5 M in toluene, 481 mL, 240 mmol, 2.8 equiv) was added dropwise and stirred for 1.5 h. The reactor was warmed to 0 to −5 °C and 5% NH_4Cl (470 mL, aq) was added and stirred for 15 min. *n*-Heptane (470 mL) was then added, and the reaction mixture was warmed to rt and stirred for 30 min. Layers were separated and the aqueous layer was extracted with MTBE (470 mL). Combined organic extracts were washed with 2% NaCl (470 mL, aq) and dried over Na_2SO_4, filtered, and then concentrated *in vacuo* to afford crude compound **10**. The crude product was purified via MPLC (hexane/ethyl acetate = 10:1) to yield **10** (48.56 g, 53.7 mmol, 65% in two steps from **7**) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.29 (4H, m), 7.25−7.20 (1H, m), 4.99−4.98 (1H, m), 4.92 (1H, bs), 4.85−4.82 (1H, m), 4.81 (1H, d, J = 1.2 Hz). 4.41 (1H, d, J = 5.2 Hz), 4.10, 3.98 (3H, m). 3.95−3.90 (1H, m), 3.86−3.80 (2H, m), 3.71−3.67 (1H, m), 3.63−3.57 (2H, m), 3.52−3.49 (2H, m), 3.31 (3H, s), 3.07−3.01 (1H, m), 2.83−2.75 (1H, m), 2.71−2.64 (1H, m), 2.29−2.10 (4H, m), 2.03−1.95 (2H, m), 1.87−1.71 (3H, m), 1.67−1.62 (3H, m), 1.54−1.48 (2H, m), 1.29 (3H, bs), 1.21 (9H, s), 1.09 (3H, d, J = 6.4 Hz), 0.91 (9H, s), 0.90 (9H, s), 0.10 (6H, s), 0.07 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.57, 151.34, 150.97, 136.16, 129.50, 129.07, 126.36, 104.96, 104.68, 86.53, 80.67, 79.43, 77.85, 77.13, 76.78, 75.60, 71.51, 67.95, 64.28, 56.68, 49.28, 43.13, 38.86, 38.73, 37.85, 36.35, 35.83, 33.41, 31.89, 31.63, 31.45, 29.03, 27.22, 26.03, 25.95, 25.29, 22.70, 18.41, 18.19, 17.99, 14.12, −0.4.03, −4.72, −5.30; MS (ESI): 925.5437 $(M + Na)^+$.

3-((2*S*,5*S*)-5-(2-((2*S*,4*R*,6*R*)-6-(((2*S*,3*S*,4*R*,5*R*)-5-((*S*)-2,3-Bis((*tert*-butyldimethylsilyl)oxy)propyl)-4-methoxy-3-((phenylsulfonyl)methyl)tetrahydrofuran-2-yl)methyl)-4-methyl-5-methylenetetrahydro-2*H*-pyran-2-yl)ethyl)-4-methylenetetrahydrofuran-2-yl)propyl Pivalate (6). To a 5 L four-neck RBF was charged with **10** (95 g, 105 mmol, 1.0 equiv), EtOH (950 mL), $(NH_4)_2MoO_4$ (8.24 g, 42 mmol, 0.4 equiv) and cooled to −5 °C and stirred for 10 min. UHP (39.5 g, 420 mmol, 4.0 equiv) was then added portionwise. The reaction mixture was then warmed to rt and stirred for 12 h. The reaction mixture was then cooled to −5 °C, and 10% $NaHCO_3$ (1.8 L, aq), 10% $Na_2S_2O_3$ (1.8 L, aq), and EtOAc (1.8 L) were added. The reaction mixture was warmed to rt and stirred for 30 min. Layers were separated, and the organic layer was concentrated *in vacuo* to afford crude compound **11**. The crude product was purified via MPLC (hexane/ethyl acetate = 12:1) to yield **6** (68.8 g, 70%, 73.5 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99−7.95 (2H, m), 7.73−7.59 (3H, m), 4.93−4.92 (1H, m), 4.87 (1H, bs), 4.80 (1H, d, J = 1.2 Hz), 4.69 (1H, d, J = 1.8 Hz), 4.27 (1H, bs), 4.17−4.04 (3H, m). 4.02−3.94 (1H, m), 3.87−3.80 (3H, m), 3.73−3.66 (1H, m), 3.62−3.57 (2H, m), 3.53−3.47 (1H, m), 3.45−3.37 (4H, m), 3.06−3.03 (2H, m), 2.67−2.54 (2H, m), 2.27−2.18 (3H, m), 2.07−2.06 (1H, m), 2.04−1.99 (1H, m), 1.94−1.83 (2H, m), 1.80−1.73 (2H, m), 1.72−1.64 (1H, m), 1.60−1.37 (5H, m), 1.21 (9H, s), 1.09 (3H, d, J = 6.4 Hz), 0.91 (18H, s), 0.12 (6H, s), 0.07 (6H, s). Data are in agreement with the literature.[9]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.4c00150.

Experimental procedures and analytical data for novel compounds (^{1}H and ^{13}C NMR, MS) (PDF)

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Notes

The authors declare no competing financial interest.

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