Accepted Manuscript

Synthesis of the C1–C13 fragment of eribulin mesylate

Hyosun Lee, Yongseo Park, Heesun Jung, Sung Tak Kim, Seunghee Sin, Eunjung Ko, In-Soo Myeong, Hyungwook Moon, Changhun Seol, Yunkyung Jung, Eunim Jung, Junkyu Lee, Keeyoung Lee, Changyoung Oh, Juyoung Song, Suhwan Yoon, Wonjae Kang, Jaehun Jung, Hyunik Shin

PII: S0040-4020(19)30722-7

DOI: https://doi.org/10.1016/j.tet.2019.06.050

Reference: TET 30442

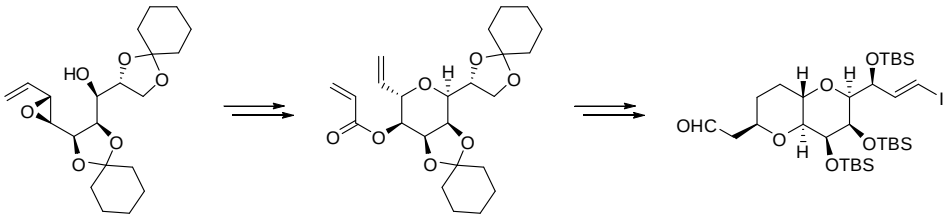
To appear in: *Tetrahedron*

Received Date: 15 May 2019

Revised Date: 21 June 2019

Accepted Date: 28 June 2019

Please cite this article as: Lee H, Park Y, Jung H, Kim ST, Sin S, Ko E, Myeong I-S, Moon H, Seol C, Jung Y, Jung E, Lee J, Lee K, Oh C, Song J, Yoon S, Kang W, Jung J, Shin H, Synthesis of the C1–C13 fragment of eribulin mesylate, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.06.050.



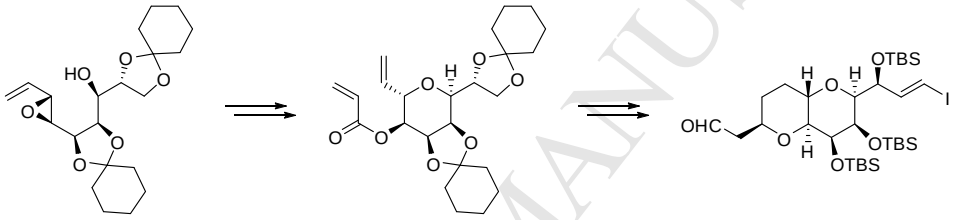
Synthesis of the C1-C13 Fragment of Eribulin Mesylate

Hyosun Lee,[a] Yongseo Park,[a] Heesun Jung,[a] Sung Tak Kim,[a] Seunghee Sin,[a] Eunjung Ko,[a] In-Soo Myeong,[b] Hyungwook Moon,[a] Changhun Seol,[a] Yunkyung Jung,[a] Eunim Jung,[a] Junkyu Lee,[a] Keeyoung Lee,[a] Changyoung Oh,[a] Juyoung Song,[a] Suhwan Yoon,[a] Wonjae Kang,[a] Jaehun Jung,[a] Hyunik Shin*[a]

hishin@yonsungchem.co.kr

[a] R&D Center, Yonsung Fine Chemicals Co. Ltd. Innoplex-2-dong, 306 Sinwon-ro, Youngtong-gu, Suwon-si, Kyeonggi-do 16675, Republic of Korea
[b] School of Pharmacy, Sungkyunkwan University, Seobu-ro 2066, Suwon-si, Gyeonggi-do 16419, Republic of Korea

ABSTRACT



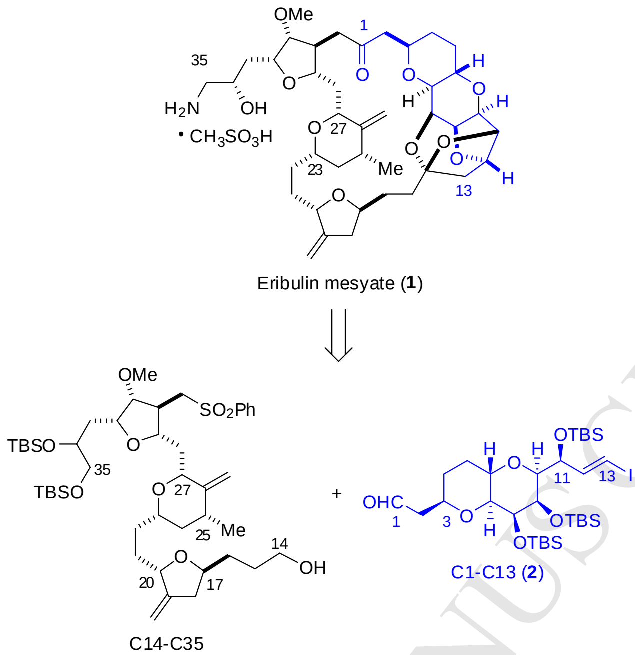
Synthesis of the C1-C13 fragment of eribulin mesylate has been accomplished. It features a highly stereoselective construction of a trans-dihydropyran framework using three key reactions: (1) Sharpless epoxidation, (2) regioselective ring opening, and (3) olefin metathesis.

1. Introduction

Influencing the tubulin dynamic is an important tool for the control of cell cycle arrest. In this context, various anticancer therapeutics incorporating tubulin dynamic stabilization have been developed, and their use effectively induces cell cycle arrest of cancerous cells. In particular, paclitaxel is the most popular regimen,[1] following which ixabepilone[2] and eribulin mesylate[3] have been added to this armamentarium for combatting refractory cancer cases.

Halavan® (the commercial name of eribulin mesylate **1**)[4] is a modified (truncated) marine natural product of halichondrin B[5] and was launched in the United States in 2010 for the treatment of recurring breast cancer after first-line anthracycline/capecitabine action. Although it has proved to be successful as a new chemotherapeutic treatment option, its complex structure presents a significant challenge to its commercial production. Despite its considerable complexity, derived from 19 chiral centers, eribulin mesylate has been successfully commercialized by Eisai pharmaceutical Company using NHK reactions as a key C-C bond-forming tool. In its commercial synthesis, eribulin has been assembled[4d] from two fragments: C1-C13,[4e] and C14-C35[4f] subunits (Scheme 1). Furthermore, the synthesis has continuously evolved and is now much greener and more efficient in terms of the purification operations used in the generation of rigid intermediates, making it possible to

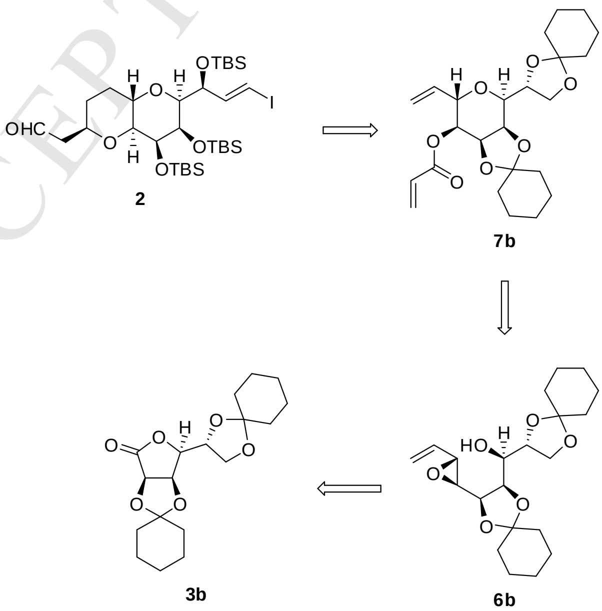
eliminate chromatography processes, particularly in the synthesis of C14-C26 fragment.[4i]



Scheme 1. Commercial synthesis of Eribulin mesylate (**1**).

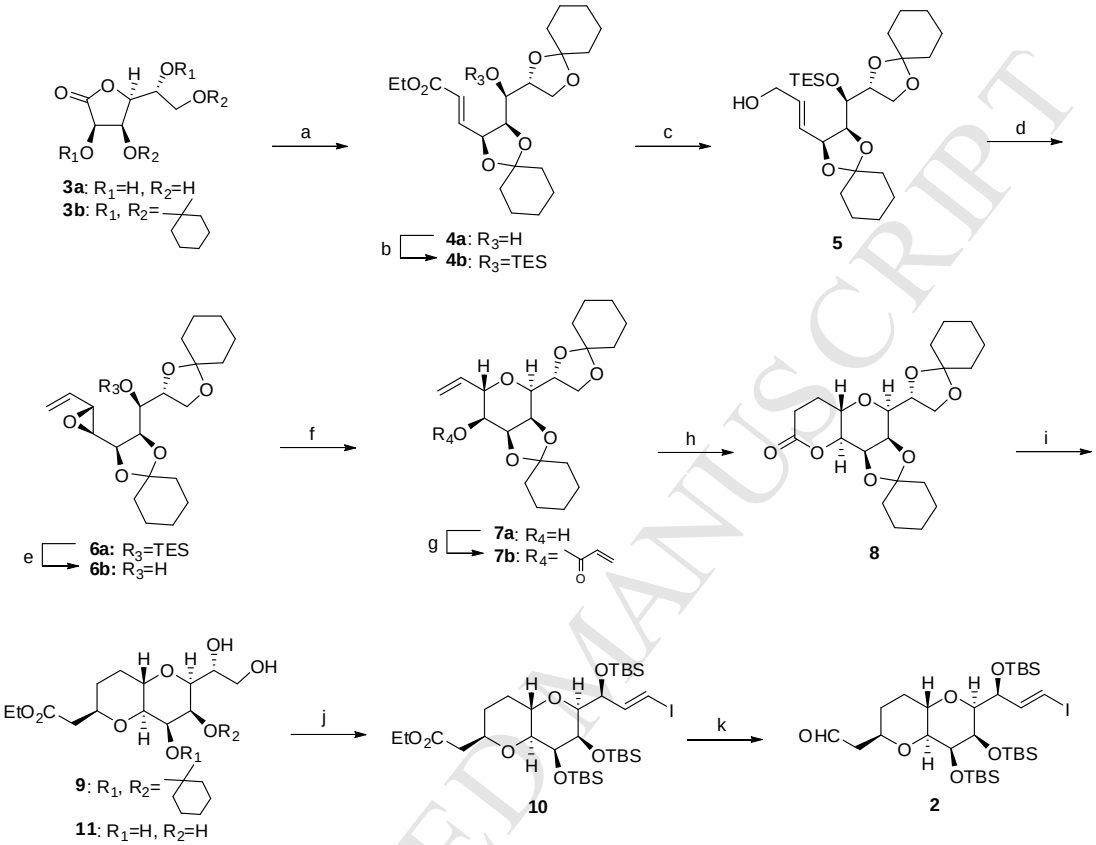
2. Results and discussion

Taking this background into account, a synthesis of the C1-C13 fragment (**2**) of eribulin mesylate (**1**) was devised using two key reactions: (1) the regioselective vinyl epoxide ring opening to form the *trans* dihydropyran framework and (2) subsequent intramolecular olefin metathesis reaction to complete the bicyclic structure of the C1-C13 motif (**Scheme 2**).



Scheme 2. Synthetic strategy of C1-C13 fragment (**2**).

The synthesis started from the known intermediate **3b**, prepared in a single step from readily available D-(-)-gulono-1,4-lactone (**3a**, Scheme 3) in a 66% yield.[6] DIBAL reduction of **3b** to lactol and its Wittig olefination provided α,β–unsaturated ester **4a**.[7]

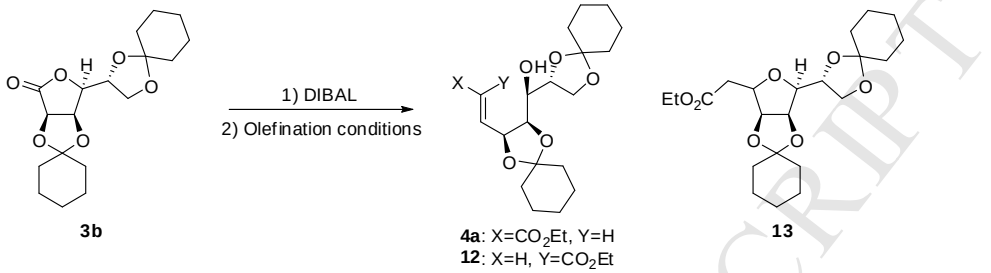


Scheme 3. Synthesis of **2**. *Reagents and conditions*: (a) i. DIBAL, THF/toluene, −10°C, 15 h; ii. $Ph_3P{=}CHCO_2Et$, benzoic acid, CH_2Cl_2, 50°C, 24 h, 64% (for two steps); (b) i. TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 1 h, quant.; ii. 5 mol% PBu_3, THF, 50°C, 24 h, 78%; (c) DIBAL, CH_2Cl_2, −20°C, 88%; (d) i. (−)-DET, Ti(O*i*Pr)$_4$, CH_2Cl_2, 0°C, 15 h, 62%; ii. DMP, CH_2Cl_2, 0°C, 1.5 h, 97%; iii. $MePPh_3Br$, NaHMDS, THF, 0°C, 1 h, 71%; (e) TBAF, THF, 0°C, 1 h, 82%; (f) PPTS, CH_2Cl_2, 0°C, 7 h, 93%; (g) acrylic acid, DIC, DMAP, CH_2Cl_2, rt, 5 h, 80%; (h) i. Grubbs' 2nd cat., toluene, reflux, 24 h, 88%; ii. Pd/C, H_2, EtOAc, 6 h, 99%; (i) i. DIBAL, THF/toluene, −10°C, 15 h; ii. triethyl phosphonoacetate, t-BuOK, THF, 60°C, 20 h, 80% (for two steps); iii. AcOH, 40°C, 5 h, 91%; (j) using ref. 4e conditions: i. $NaIO_4$, EtOAc, 15°C, quant.; ii. $CrCl_2$, $NiCl_2$, 1-bromo-2-trimethylsilylethene, DMSO, MeCN, 30°C, 64%; iii. AcOH, H_2O, 95°C, crystallization, 66%; iv. TBSOTf, 2,6-lutidine, MTBE, 30°C, crystallization, 97%; v. NIS, MeCN, toluene, TBSCl, 35°C, 89%; and (k) DIBAL, BHT, toluene, −65°C, 1 h, 92%.

At this olefination stage, a significant undesired reaction was encountered after methylene chloride reflux, where the tetrahydrofuranyl side product was formed as a major product via the oxa-Michael addition of the secondary hydroxyl group to α,β–unsaturated ester (Entry 1, Table 1).[8] This problem could be resolved by the addition of benzoic acid[9] with moderate E/Z stereoselectivity in a ratio of 5:1 (Entry 2). Horner–Wadsworth–Emmons reaction conditions were used, but only oxa-Michael reaction adduct **13** was afforded (Entries 3-5). The lowered stereoselectivity could be improved marginally to 6:1 in toluene (Entries 6 and 7) and to 7:1

in THF at 50℃ (Entries 8 and 9). Next, the secondary alcohol of **4a** was protected as a TES group to provide **4b**. At this point, the moderate E/Z stereoselectivity of **4a** could be enhanced under thermodynamically controlled conditions — when **4b** was heated at 50℃ for 24 h in the presence of 5 mol% of tributylphosphine, the E/Z ratio was better than 30:1.[10]

Table 1. Olefination of **3b**.



3b

4a: X=CO_2Et, Y=H
12: X=H, Y=CO_2Et

13

Entry	Reagents and additive	Solvent	Temp.	Time	Ratio (**4a**:**12**:**13**)[a]	Yield (%)[b]
1	Ph_3P=$CHCO_2Et$	DCM	reflux	48 h	**13** only	75
2	Ph_3P=$CHCO_2Et$, benzoic acid	DCM	reflux	48 h	5:1:0	70
3	Triethyl phosphonoacetate, KHMDS	THF	rt	4 h	**13** only	63
4	Triethyl phosphonoacetate, LiHMDS	THF	rt	4 h	**13** only	57
5	Triethyl phosphonoacetate, LiCl, DIPEA	THF	rt	4 h	**13** only	62
6	Ph_3P=$CHCO_2Et$, benzoic acid	toluene	90 ℃	4 h	6:1:2	51
7	Ph_3P=$CHCO_2Et$, benzoic acid	toluene	50 ℃	24 h	6:1:0	61
8	Ph_3P=$CHCO_2Et$, benzoic acid	THF	50 ℃	48 h	7:1:0	73
9	Ph_3P=$CHCO_2Et$, benzoic acid	THF	60 ℃	48 h	7:1:3	66

[a] Ratios were determined by ^{1}H NMR analysis.
[b] Yields refer to two-step yields of mixed products.

Reduction of the ester group of **4b** afforded the allylic alcohol **5**. For the introduction of the epoxide group, mCPBA epoxidation was performed, which resulted in low stereoselectivity in a ratio of 2:1 by ^{1}H NMR analysis. Next, diastereoselective Sharpless epoxidation[11] at 0℃ using (−)-diethyltartarate, *t*-BuOOH, and titanium isopropoxide provided the epoxide intermediate in a high diastereoselectivity of 30:1. Initially, *t*-BuOOH was used as an oxidant, which was changed to cumyl hydroperoxide considering its ready availability on a large scale and at low cost with the same outcome. To guide the regioselectivity of cyclization, the vinyl group was introduced via oxidation-Wittig olefination to provide **6a**. Subsequent deprotection of the TES group by TBAF afforded **6b**. As was well demonstrated in Nicolau's research,[12] the cyclization under mild acid catalysis of PPTS induced 6-endo cyclization exclusively to provide the pyran intermediate, the secondary alcohol group of which was condensed with acrylic acid in the presence of DIC and a catalytic amount of DMAP to afford **7b**. Next, the intramolecular metathesis reaction[13] of **7b** in the presence of Grubb's second-generation catalyst in toluene at 80°C was attempted, and it provided α,β-unsaturated lactone in an excellent yield of 88%. Hydrogenation using palladium as a catalyst provided the lactone **8**.

Reduction of **8** by DIBAL afforded a lactol intermediate. Its Horner–Wadsworth–Emmons

reaction[14] provided a transient α,β-unsaturated ester intermediate, which underwent cyclization by the oxa-Michael addition of the hydroxyl group to the double bond to form compound **9**. At this step, it is critical to run the reaction for at least 20 h to enrich the thermodynamically more stable **9** in which the carboxymethyl substituent occupies the equatorial position via a Michael–retro-Michael reaction sequence. At an early stage of the reaction, the axial and equatorial diastereomers were observed in a 1:1 ratio, which slowly merged to **9** in a 98:2 ratio after 20 h. In the course of selective deprotection of the cyclohexylidene groups, a small portion of fully deprotected tetraol compound **11** was purified, which forms a good crystal for singe-crystal X-ray analysis in which the ethoxycarbonyl methyl group exists in the disordered form (Figure 1). This provided unambiguous structural information, particularly for the induced stereogenic centers.

Although methyl ester of **9** is known in the literature, ethyl ester **9** has not been reported. In this regard, in the present study, **9** was transformed to **10** following conversion conditions used with the methyl ester of **9** to provide **10** with comparable results.[4e] Final reduction of the ester group of **10** provided **2**, whose properties showed good agreement with the reported data.[4d] The full details about synthesis from **9** to **10** are in the Supporting Information.

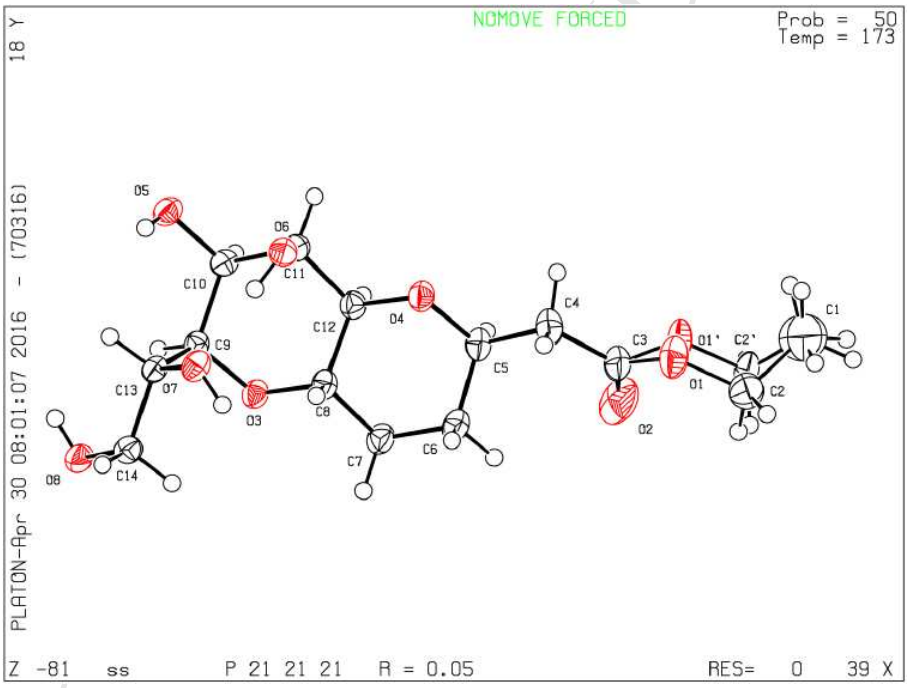


Figure 1. X-ray crystal structure of **11**.

3. Conclusion

In conclusion, a synthetic route to the C1-C13 fragment of eribulin mesylate was devised. This synthesis used the regioselective ring opening of the vinyl epoxide of **6** and intramolecular olefin metathesis reaction as key steps in high regioselectivity and stereoselectivity.

4. Experimental section

4.1. General methods

Optical rotations were measured with a polarimeter in the solvent specified. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopic data were recorded with a Fourier transform NMR (FT-NMR) spectrometer at 75 or 300 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.

4.2. (*E*)-ethyl 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)acrylate (**4a**)

To a solution of **3b** (30 kg, 89 mol) in THF (110 L) and toluene (75 L) was added DIBAL (89 L, 11 mol) at −10℃. The reaction mixture was stirred at −10℃ for 0.5 h and quenched with an aqueous KNa tartrate·$4H_2O$ (120 L) solution. The layers were separated, and the aqueous layer was extracted with MTBE (30 L). The mixture was filtered through a pad of Celite and concentrated *in vacuo*. The resulting substance was immediately used without further purification. To a solution of the above resulting substance (37 g, 110 mmol) in CH_2Cl_2 (370 mL) were added $Ph_3P{=}CHCO_2Et$ (1.6 kg, 220 mmol) and benzoic acid (1.3 g, 11 mmol) at 50℃. The reaction mixture was stirred at 50℃ for 24 h, after which time thin-layer chromatography (TLC) analysis indicated a complete reaction. The reaction mixture was filtered and washed with MTBE/heptane (1:10, 90 mL X 3). The solvent was removed *in vacuo*. Purification by silica gel chromatography (hexanes:ethyl acetate = 5:1) gave the product **4a** (29 kg, 70.0 mol, 64%, two steps) as a colorless oil; $[\alpha]_D^{20}$ +1.8 (*c* 0.5, $CHCl_3$); IR (neat) ν_{max} 3447, 2936, 2861, 1719, 1449, 1367, 1280, 1164, 1100, 1136, 930, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.47 (s, 1H), 4.67-4.70 (m, 1H), 4.62 (d, *J* = 6.0 Hz, 1H), 4.10-4.40 (m, 4H), 3.70-3.75 (m, 1H), 1.38-1.66 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 113.7, 110.4, 101.7, 85.2, 82.8, 79.6, 75.4, 65.7, 36.3, 35.7, 35.0, 34.4, 25.1, 25.0, 24.0, 24.0, 23.8, 23.8; HRMS (ESI+) [$(M+Na)^+$] *m/z* calcd. for $C_{22}H_{34}O_7+Na^+$ 433.2197; found 433.2197.

4.3. (E)-ethyl 3-((2S,3S)-3-((S)-((R)-1,4-dioxaspiro[4.5]decan-2-yl)(triethylsilyloxy)methyl)-1,4-dioxaspiro[4.5]decan-2-yl)acrylate (**4b**)

To a solution of **4a** (87 g, 210 mmol) in CH_2Cl_2 (440 mL) was added 2,6-lutidine (32 mL, 270 mmol) and TESOTf (53 mL, 230 mmol) at 0℃. The reaction mixture was stirred at 0℃ for 1 h and quenched with aqueous 20% NH_4Cl (0.4 L) solution. The layers were separated, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel chromatography (hexanes:ethyl acetate = 10:1) gave the product **4b** (87 g, 170 mmol, 78%) as a colorless oil; $[\alpha]_D^{20}$ +155.6 (*c* 0.5, $CHCl_3$); IR (neat) ν_{max} 2936, 2875, 1715, 1448, 1415, 1366, 1232, 1194,

1166, 1108, 1033, 935, 827, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.02 (dd, *J* = 15.0, 6.0 Hz, 1H), 6.05 (dd, *J* = 15.0, 3.0 Hz, 1H), 4.67-4.79 (m, 1H), 4.09-4.31 (m, 2H), 3.89-4.00 (m, 1H), 3.76-3.86 (m, 2H), 1.39-1.77 (m, 20H), 0.93-0.98 (m, 9H), 0.55-0.69 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0, 144.6, 123.4, 109.8, 78.6, 76.5, 76.1, 71.3, 65.4, 60.5, 37.3, 35.9, 34.8, 25.2, 25.1, 24.0, 24.0, 23.8, 23.8, 14.2, 6.9, 5.2; HRMS (ESI+) [$(M+Na)^+$] *m/z* calcd. for $C_{28}H_{48}O_7Si+Na^+$ 547.3062; found 547.3060.

4.4. (*E*)-3-((2*S*,3*S*)-3-((*S*)-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)(triethylsilyloxy)methyl)-1,4-dioxaspiro[4.5]decan-2-yl)prop-2-en-1-ol (**5**)

To a solution of **4b** (12 kg, 22 mol) in CH_2Cl_2 (58 L) was added DIBAL (45 L, 53 mol) at −20℃. The reaction mixture was stirred at −10℃ for 0.5 h and quenched with KNa tartrate·$4H_2O$ (24 kg) and water (70 kg). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (24 L). The mixture was filtered through a pad of Celite and concentrated *in vacuo*. Purification by silica gel chromatography (hexanes:ethyl acetate = 10:1) gave the product **5** (9.5 kg, 20 mol, 88%) as a colorless oil; $[\alpha]_D^{20}$ −12.5 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3422, 2936, 2874, 1448, 1365, 1281, 1232, 1164, 1105, 1006, 936, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 5.79-5.95 (m, 2H), 4.58-4.62 (m, 1H), 4.09-4.19 (m, 4H), 3.93-3.98 (m, 1H), 3.80-3.86 (m, 1H), 3.72-3.76 (m, 1H), 1.32-1.75 (m, 20H), 0.94-1.00 (m, 9H), 0.65-0.70 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.9, 128.1, 109.9, 109.3, 78.6, 77.8, 76.1, 71.3, 65.4, 62.9, 37.6, 35.8, 35.2, 35.0, 25.2, 25.2, 24.0, 23.9, 23.9, 23.8, 7.0, 5.3; HRMS (ESI+) [$(M+Na)^+$] *m/z* calcd. for $C_{26}H_{46}O_6Si+Na^+$ 505.2956; found 505.2951.

4.5. (1*S*)-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)((2*R*,3*S*)-3-((2*S*,3*R*)-3-vinyloxiran-2-yl)-1,4-dioxaspiro[4.5]decan-2-yl)methanol (**6b**)

To a solution of (−)-DET (2.1 mL, 12 mmol) with 3 Å MS in CH_2Cl_2 (110 mL) was added Ti(*i*-PrO)$_4$ (1.8 mL, 6.2 mmol) and 80% cumene hydroperoxide (17 mL, 93 mmol) at −10℃. Compound **5** (30 g, 62 mol) in CH_2Cl_2 (110 mL) solution was added to a solution of the above mixture. The reaction mixture was stirred for 15 h and quenched with NaOH solution (160 mL). The mixture was filtered through a pad of Celite and concentrated *in vacuo*. Purification by silica gel chromatography (hexanes:ethyl acetate = 5:1) gave the epoxide (19 g, 39 mmol, 62%). To a solution of epoxide (19 g, 39 mmol) in CH_2Cl_2 (86 mL) was added DMP (33 g, 77 mmol) at 0℃. The reaction mixture was stirred at room temperature for 1.5 h and quenched with 20% $Na_2S_2O_3$ (170 mL) and 5% $NaHCO_3$ (170 mL). The layers were separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting aldehyde was immediately used without further purification. To a solution of $MePPh_3Br$ (18 g, 50 mmol) in THF (76 mL) was added 2 M NaHMDS (24 mL, 48 mmol) at 0℃. The resulting aldehyde (19 g, 39 mmol) in THF (38 mL) solution was added to a solution of the above mixture. The reaction mixture was stirred for 3 h and quenched with sat. NH_4Cl solution (76 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel chromatography (hexanes:ethyl acetate = 15:1) gave **6a** (14 g, 28 mmol, 71%). To a solution of **6a** (10 g, 20 mmol) in THF (100 mL) was added TBAF (26 mL, 27 mmol) at 0℃. The reaction mixture was stirred for 1 h and quenched with sat. NH_4Cl (42 mL). The layers were separated, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel

chromatography (hexanes:ethyl acetate = 1:1) gave **6b** (6.3 g, 16 mmol, 82%); $[\alpha]_D^{20}$ −11.3 (*c* 0.5, $CHCl_3$); IR (neat) ν_{max} 3446, 2929, 2855, 1457, 1365, 1100, 930, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.48-5.65 (m, 2H), 5.30-5.34 (m, 1H), 4.22-4.31 (m, 2H), 4.06-4.16 (m, 2H), 3.89-3.94 (m, 2H), 3.74-3.79 (m, 1H), 3.29-3.32 (m, 1H), 3.20 (dd, *J* = 8.1, 2.1 Hz, 1-H), 2.48 (d, *J* = 7.6 Hz, 1H), 1.40-1.75 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.3, 120.2, 110.2, 110.2, 77.8, 77.2, 76.1, 69.2, 65.6, 58.3, 57.5, 37.0, 36.1, 34.9, 34.4, 25.2, 25.1, 24.0, 23.8, 23.7; HRMS (ESI+) [$(M+Na)^+$] *m/z* calcd. for $C_{21}H_{32}O_6+Na^+$ 403.2191; found 403.2085.

4.6. (3a*R*,4*S*,6*S*,7*S*,7a*S*)-4-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)-6-vinyltetrahydro-3a*H*-spiro[[1,3]dioxolo[4,5-c]pyran-2,1'-cyclohexan]-7-ol (**7a**)

To a **6b** (6.3 g, 16 mmol) in CH_2Cl_2 (31 mL) was added PPTS (2.1 g, 8.3 mmol) at 0℃. The reaction mixture was stirred for 7 h. TEA (2.3 mL) was added to the reaction mixture. The solvent was removed *in vacuo*. Purification by silica gel chromatography (hexanes:ethyl acetate = 3:1) gave the **7a** (5.8 g, 15 mmol, 93%); $[\alpha]_D^{20}$ −19.8 (*c* 0.3, $CHCl_3$); IR (neat) ν_{max} 3423, 2931, 2855, 1449, 1366,1281, 1165, 1100, 932, 848, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.95-6.06 (m, 1H), 5.51-5.58 (m, 1H), 5.23-5.27 (m, 1), 4.51-4.55 (m, 1H), 4.27-4.38 (m, 2H), 4.21-4.24 (m, 1H), 4.09-4.14 (m, 1H), 3.77-3.82 (m, 1H), 3.53-3.64 (m, 2H), 1.30-1.82 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 116.1, 111.5, 110.1, 75.8, 74.7, 73.7, 73.5, 72.5, 68.9, 65.3, 36.5, 35.7, 35.1, 34.7, 25.2, 25.1, 24.0, 24.0, 23.8; HRMS (ESI+) [$(M+Na)^+$] *m/z* calcd. for $C_{21}H_{32}O_6+Na^+$ 403.2091; found 403.2097.

4.7. (3a*R*,4*S*,6*S*,7*S*,7a*R*)-4-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)-6-vinyltetrahydro-3a*H*-spiro[[1,3]dioxolo[4,5-c]pyran-2,1'-cyclohexane]-7-yl acrylate (**7b**)

To a solution of **7a** (5 g, 13 mmol) in CH_2Cl_2 (75 mL) was added acrylic acid (3.6 mL, 53 mmol), DIC (8.3 mL, 53 mmol), and DMAP (0.32 g, 2.7 mmol) at 0℃. The reaction mixture was stirred at room temperature for 5 h until TLC showed complete reaction. Diethyl ether (83 mL) was added to the reaction mixture. The reaction mixture was filtered, and the solvent was removed *in vacuo*. Purification by silica gel chromatography (hexanes:ethyl acetate = 1:1) gave **7b** (4.6 g, 11 mmol, 80%) as a colorless oil; $[\alpha]_D^{20}$ −55.6 (*c* 0.5, $CHCl_3$); IR (neat) ν_{max} 2934, 2858, 1731, 1449, 1407, 1366, 1277, 1186, 1104, 937, 848 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.46-6.52 (m, 1H), 6.16-6.25 (m, 1H), 5.77-5.92 (m, 2H), 5.54-5.61 (m, 2H), 5.18-5.23 (m, 2H), 4.56-5.01 (m, 1H), 4.31-4.38 (m, 1H), 4.24 (dd, *J* = 7.7, 1.8 Hz, 1H), 4.15 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.77 (dd, *J* = 8.4, 6.9 Hz, 1H), 3.56 (dd, *J* = 8.1, 1.8 Hz, 1H), 1.22-1.88 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 134.7, 132.1, 127.8, 116.1, 112.0, 110.2, 75.7, 74.4, 73.8, 72.2, 71.5, 70.1, 65.3, 36.5, 35.6, 35.1, 35.1, 25.1, 25.1, 24.0, 23.9, 23.8; HRMS (ESI+) [$(M+Na)^+$] *m/z* calcd. for $C_{24}H_{34}O_7+Na^+$ 457.2197; found 457.2199.

4.8. Ethyl 2-[1'*S*,2'*S*,6'*S*,7'*S*,9'*S*,12'*R*]-7'-[(2*R*)-1,4-dioxaspiro[4,5]decan-2-yl]-3',5',8',13'-tetraoxaspiro[cyclohexane-1,4'-tricyclo[7.4.0.$0^{2,6}$]tridecane]-12'-yl]acetate (**9**)

To a solution of **7b** (5 g, 12 mmol) in toluene (250 mL) was added a second Grubbs catalyst (0.4 g, 0.5 mmol). The reaction mixture was stirred at reflux for 24 h. The solvent was removed *in vacuo*. Purification by silica gel chromatography (hexanes:ethyl acetate = 1:1) gave a bicyclic product (4.1 g, 10 mmol, 88%). To a solution of bicyclic product (4.1 g, 10

mmol) in EtOAc (20 mL) was added 10% Pd/C (0.41 g). The reaction mixture was stirred under H_2 for 6 h. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The resulting substance **8** (4.1 g, 10.0 mmol, 99%) was immediately used without further purification. To a solution of **8** (4.1 g, 10.0 mmol) in THF (10 mL) and toluene (7 mL) was added DIBAL (8.4 mL, 12 mmol) at −10℃. The reaction mixture was stirred at −10℃ for 0.5 h and quenched with aqueous KNa tartrate·$4H_2O$ (10 mL) solution. The layers were separated, and the aqueous layer was extracted with MTBE (10 mL). The combined organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting substance was immediately used without further purification. To a solution of triethyl phosphonoacetate (3.4 g, 15 mmol) in THF (38 mL) was added *t*-BuOK (1.7 g, 15 mmol). The resulting substance (4.1 g, 10 mmol) was added to a solution of reaction mixture. The reaction mixture was stirred at 60℃ for 20 h and quenched with sat. NH_4Cl solution (21 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (8.4 mL). The combined organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica gel chromatography (hexanes:ethyl acetate = 3:1) gave an ester compound (4.6 g, 9.7 mol, 96%). To the ester compound (4.6 g, 9.7 mmol) was added AcOH (75 mL) and water (18 mL). The reaction mixture was stirred at 40℃ for 5 h. Toluene (90 mL) was added to the reaction mixture. The solvent was removed *in vacuo*. Purification by silica gel chromatography (dichloromethane:methanol = 20:1) gave **9** (3.6 g, 8.9 mmol, 91%) as a colorless oil; $[\alpha]_D^{20}$ −40.8 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3447, 2936, 2863, 1733, 1448, 1371, 1339, 1285, 1196, 1164, 1102, 1033, 952, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.56 (dd, *J*=8.3, 2.8 Hz, 1H), 4.45 (dd, *J*=8.4, 1.5 Hz, 1H), 4.13 (q, *J*=7.1 Hz, 2H), 3.72-3.97 (m, 6H), 3.51 (dd, *J*=10.3, 2.9 Hz, 1H), 2.70 (dd, *J*=16.0, 6.8 Hz, 1H), 2.41 (dd, *J*=16.0, 6.1 Hz, 1H), 2.05-2.17 (m, 1H), 1.33-1.84 (m, 13H), 1.20-1.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 111.1, 110.1, 76.3, 75.2, 74.2, 71.8, 71.4, 66.1, 65.5, 60.5, 40.5, 36.3, 35.6, 35.3, 33.5, 30.0, 25.1, 24.0, 23.8, 23.7, 14.2; HRMS (ESI+) [$(M+Na)^+$] *m/z* calcd. for $C_{20}H_{32}O_8+Na^+$ 423.1989; found 423.1987.

4.9. Ethyl 2-((2R,4aS,6S,7R,8S,8aS)-7,8-bis(tert-butyldimethylsilyloxy)-6-((S,E)-1-(tert-butyldimethylsilyloxy)-3-iodoallyl)octahydropyrano[3,2-b]pyran-2-yl)acetate (**10**)

Colorless oil; $[\alpha]_D^{20}$ −32.2 (*c* 0.4, $CHCl_3$); IR (neat) ν_{max} 2953, 2930, 2857, 1740, 1472, 1254, 1080, 835, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 6.86 (dd, *J* = 14.6, 7.8 Hz, 1H), 6.28 (dd, *J* = 14.6, 0.7 Hz, 1H), 4.88-4.92 (m, 1H), 4.07-4.21 (m, 3H), 3.77-3.90 (m, 3H), 3.42-3.51 (m, 1H), 2.93 (dd, *J* = 9.6, 2.2 Hz, 1H), 2.53 (dd, *J* = 15.4, 8.1 Hz, 1H), 2.36 (dd, *J* = 15.4, 5.1 Hz, 1H), 1.92-1.97 (m, 1H), 1.70-1.82 (m, 1H), 1.23-1.28 (m, 3H), 0.94 (s, 9H), 0.92 (s, 9H), 0.86 (s, 9H), 0.02-0.11 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 146.7, 81.3, 78.8, 77.6, 74.1, 73.6, 72.7, 70.7, 64.3, 60.5, 40.9, 30.6, 28.8, 26.7, 26.3, 26.1, 19.1, 18.7, 18.2, 14.2, −3.4, −3.8, −3.9, −-4.3, −4.5, −4.7 ; HRMS (ESI+) [$(M+Na)^+$] *m/z* calcd. for $C_{33}H_{65}IO_7Si_3+Na^+$ 807.1989; found 807.1987.

4.10. 2-((2*R*,4a*S*,6*S*,7*R*,8*S*,8a*S*)-7,8-bis(*tert*-butyldimethylsilyloxy)-6-((*S*,*E*)-1-(tert-butyldimethylsilyloxy)-3-iodoallyl)octahydropyrano[3,2-*b*]pyran-2-yl)acetaldehyde (**2**)

To a solution of **10** (120 g, 160 mmol) and BHT (0.8 g, 3 mmol) in toluene (1.6 L) was added

DIBAL (16 mL, 190 mmol) at −65℃. The reaction mixture was stirred at −65℃ for 1 h and quenched with an aqueous 1 N HCl (1.3 L) solution. The layers were separated, and the aqueous layer was extracted with MTBE (1 L) and washed with 5% $NaHCO_3$ (1.2 L) and 10% NaCl (1.2 L). The mixture was filtered through a pad of Celite and concentrated *in vacuo*. Purification by silica gel chromatography (hexanes:ethyl acetate = 10:1) gave **2** (110 g, 140 mol, 92%) as a colorless oil; $[\alpha]_D^{20}$ −38.6 (*c* 0.5, $CHCl_3$); IR (neat) ν_{max} 2953, 2929, 2857, 2360, 1732, 1472, 1361, 1254, 1082, 835, 777, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 9.78-9.79 (m, 1H), 6.85 (dd, *J* = 14.6, 7.9 Hz, 1H), 6.29 (dd, *J* = 14.6, 0.7 Hz, 1H), 4.88-4.92 (m, 1H), 4.08-4.11 (m, 1H), 3.81-3.93 (m, 3H), 3.45-3.53 (m, 1H), 2.95 (dd, *J* = 9.6, 2.3 Hz, 1H), 2.63 (ddd, *J* = 16.5, 8.5, 2.6 Hz, 1H), 2.44 (ddd, *J* = 16.4, 4.4, 1.7 Hz, 1H), 1.95-1.98 (m, 1H), 1.74-1.79 (m, 1H), 1.32-1.46 (m, 2H), 0.94 (s, 9H), 0.93 (s, 9H), 0.86 (s, 9H), 0.02-0.11 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.8, 146.7, 81.3, 79.0, 77.7, 73.6, 72.8, 72.6, 70.7, 64.2, 30.9, 28.8, 26.7, 26.3, 26.1, 19.1, 18.8, 18.2, −3.4, −3.8, −3.9, −4.4, −4.6; HRMS (ESI+) $[(M+Na)^+]$ *m/z* calcd. for $C_{31}H_{61}IO_6SI_3+Na^+$ 763.2713; found 763.2705.

5. Acknowledgments

This work was supported by the Advanced Technology Center (ATC) Program (No.10048257) funded by the Ministry of Trade, industry & Energy (MI, Korea). We thank Prof. Ok-Sang Jung at Pusan National University for X-ray crystal structural analysis of **11** and Prof. James D. White at Oregon State University for his insightful comments.

6. References

1. Rowinsky, E. K.; Donehower, R. C. *N. Engl. J. Med.* **1995,** *332*, 1004-1014.
2. (a) Wartmann, M.; Altmann, K. *Curr. Med. Chem. – Anti-Cancer Agents* **2002,** *2*, 123-148; (b) Low, J. A.; Wedam, S. B.; Lee, J. J.; Berman, A. W.; Brufsky, A.; Yang, S. X.; Poruchynsky, M. S.; Steinberg, S. M.; Mannan, N.; Fojo, T. *J. Clin. Oncol.* **2005,** *23*, 2726-2734; (c) Thomas, E. S.; Gomez, H. L.; Li, R. K.; Chung, H.-C.; Fein, L. E.; Chan, V. F.; Jassem, J.; Pivot, X. B.; Klimovsky, J. V.; De Mendoza, F. H. *J. Clin. Oncol.* **2007,** *25*, 5210-5217; (d) Perez, E. A.; Lerzo, G.; Pivot, X.; Thomas, E.; Vahdat, L.; Bosserman, L.; Viens, P.; Cai, C.; Mullaney, B.; Peck, R. *J. Clin. Oncol.* **2007,** *25*, 3407-3414; (e) Thomas, E.; Tabernero, J.; Fornier, M.; Conté, P.; Fumoleau, P.; Lluch, A.; Vahdat, L. T.; Bunnell, C. A.; Burris, H. A.; Viens, P. *J. Clin. Oncol.* **2007,** *25*, 3399-3406.
3. (a) Towle, M. J.; Salvato, K. A.; Budrow, J.; Wels, B. F.; Kuznetsov, G.; Aalfs, K. K.; Welsh, S.; Zheng, W.; Seletsky, B. M.; Palme, M. H. *Cancer Res.* **2001,** *61*, 1013-1021; (b) Zheng, W.; Seletsky, B. M.; Palme, M. H.; Lydon, P. J.; Singer, L. A.; Chase, C. E.; Lemelin, C. A.; Shen, Y.; Davis, H.; Tremblay, L. *Bioorganic Med. Chem. Lett.* **2004,** *14*, 5551-5554; (c) Newman, S. *Curr. Opini. Invest. Drugs* **2007,** *8*, 1057-1066; (d) Vahdat, L. T.; Pruitt, B.; Fabian, C. J.; Rivera, R. R.; Smith, D. A.; Tan-Chiu, E.; Wright, J.; Tan, A. R.; DaCosta, N. A.; Chuang, E. *J. Clin. Oncol.* **2009,** *27*, 2954-2961; (e) Cragg, G. M.; Kingston, D. G.; Newman, D. J. *Anticancer agents from natural products*; CRC press, 2011.
4. (a) Yang, Y.-R.; Kim, D.-S.; Kishi, Y. *Org. Lett.* **2009,** *11*, 4516-4519; (b) Shan, M.; Kishi, Y. *Org. Lett.* **2012,** *14*, 660-663; (c) Murthy, A. S.; Mahipal, B.; Chandrasekhar,

S. *Eur. J. Org. Chem.* **2012,** *2012*, 6959-6966; (d) Austad, B. C.; Calkins, T. L.; Chase, C. E.; Fang, F. G.; Horstmann, T. E.; Hu, Y.; Lewis, B. M.; Niu, X.; Noland, T. A.; Orr, J. D. *Synlett* **2013,** *24*, 333-337; (e) Chase, C. E.; Fang, F. G.; Lewis, B. M.; Wilkie, G. D.; Schnaderbeck, M. J.; Zhu, X. *Synlett* **2013,** *24*, 323-326; (f) Austad, B. C.; Benayoud, F.; Calkins, T. L.; Campagna, S.; Chase, C. E.; Choi, H.-w.; Christ, W.; Costanzo, R.; Cutter, J.; Endo, A. *Synlett* **2013,** *24*, 327-332; (g) Rudolph, A.; Alberico, D.; Jordan, R.; Pan, M.; Souza, F. E.; Gorin, B. *Tetrahedron Lett.* **2013,** *54*, 7059-7061; (h) Melvin, J. Y.; Zheng, W.; Seletsky, B. M. *Nat. Prod. Rep.* **2013,** *30*, 1158-1164; (i) Belanger, F.; Chase, C. E.; Endo, A.; Fang, F. G.; Li, J.; Mathieu, S. R.; Wilcoxen, A. Z.; Zhang, H. *Angew. Chem.* **2015,** *127*, 5197-5200; (j) Jimmidi, R.; Guduru, S. K. R.; Arya, P. *Org. Lett.* **2015,** *17*, 468-471; (k) Murthy, A. S.; Chandrasekhar, S. *Tetrahedron Lett.* **2015,** *56*, 4280-4282; (l) Lavanya, N.; Kiranmai, N.; Mainkar, P. S.; Chandrasekhar, S. *Tetrahedron Lett.* **2015,** *56*, 4283-4285; (m) Chavan, L. N.; Chegondi, R.; Chandrasekhar, S. *Tetrahedron Lett.* **2015,** *56*, 4286-4288; (n) Fukuyama, T.; Chiba, H.; Takigawa, T.; Komatsu, Y.; Kayano, A.; Tagami, K. *Org. Process Res. Dev.* **2015,** *20*, 100-104; (o) Fukuyama, T.; Chiba, H.; Kuroda, H.; Takigawa, T.; Kayano, A.; Tagami, K. *Org. Process Res. Dev.* **2015,** *20*, 503-509; (p) Lee, J. H.; Li, Z.; Osawa, A.; Kishi, Y. *J. Am. Chem. Soc.* **2016,** *138*, 16248-16251; (q) Konda, S.; Khatravath, M.; Mallurwar, N. K.; Rao, P.; Sripelly, S.; Iqbal, J.; Arya, P. *Synthesis* **2016,** *48*, 1663-1683; (r) Gaddam, V.; Nadella, L.; Sukumar, G.; Mainkar, P. S.; Chandrasekhar, S. *Synthesis* **2018,** *50*, 1901-1906.

5. (a) Jackson, K. L.; Henderson, J. A.; Phillips, A. J. *Chem. Rev.* **2009,** *109*, 3044-3079; (b) Ueda, A.; Yamamoto, A.; Kato, D.; Kishi, Y. *J. Am. Chem. Soc.* **2014,** *136*, 5171-5176; (c) Yan, W.; Li, Z.; Kishi, Y. *J. Am. Chem. Soc.* **2015,** *137*, 6219-6225; (d) Li, J.; Yan, W.; Kishi, Y. *J. Am. Chem. Soc.* **2015,** *137*, 6226-6231; (e) Yahata, K.; Ye, N.; Ai, Y.; Iso, K.; Kishi, Y. *Angew. Chem. Int. Ed.* **2017,** *56*, 10796-10800; (f) Yahata, K.; Ye, N.; Iso, K.; Ai, Y.; Lee, J.; Kishi, Y. *J. Org. Chem.* **2017,** *82*, 8808-8830; (g) Yahata, K.; Ye, N.; Iso, K.; Naini, S. R.; Yamashita, S.; Ai, Y.; Kishi, Y. *J. Org. Chem.* **2017,** *82*, 8792-8807.
6. Austad, B.; Chase, C. E.; Fang, F. G. WO2005118565, 2005.
7. (a) Ichiyanagi, T.; Fukunaga, M.; Tagashira, R.; Hayashi, S.; Nanjo, M.; Yamasaki, R. *Tetrahedron* **2011,** *67*, 5964-5971; (b) Martinková, M.; Pomikalová, K.; Gonda, J.; Vilková, M. *Tetrahedron* **2013,** *69*, 8228-8244.
8. (a) Ohrui, H.; Jones, G. H.; Moffatt, J. G.; Maddox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975,** *97*, 4602-4613; (b) Collins, P. M.; Overend, W. G.; Shing, T. S. *J. Chem. Soc., Chem. Commun.* **1982**, 297-298.
9. (a) Mulzer, J.; Kappert, M. *Angew. Chem. Int. Ed. Engl.* **1983,** *22*, 63-64; (b) Buchanan, J. G.; Edgar, A. R.; Power, M. J.; Theaker, P. D. *Carbohydr. Res.* **1974,** *38*, C22-C24; (c) Corey, E.; Goto, G. *Tetrahedron Lett.* **1980,** *21*, 3463-3466; (d) Marriott, D.; Bantick, J. *Tetrahedron Lett.* **1981,** *22*, 3657-3658.
10. Han, S. B.; Kong, J. R.; Krische, M. J. *Org. Lett.* **2008,** *10*, 4133-4135.
11. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980,** *102*, 5974-5976.
12. Nicolaou, K.; Prasad, C.; Somers, P.; Hwang, C. *J. Am. Chem. Soc.* **1989,** *111*, 5330-5334.
13. Yu, M.; Lou, S.; Gonzalez-Bobes, F. *Org. Process Res. Dev.* **2018,** *22*, 918-946.
14. (a) Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958,** *91*, 61-63; (b) Horner, L.; Hoffmann, H.; Wippel, H.; Klahre, G. *Chem. Ber.* **1959,** *92*, 2499-2505; (c) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961,** *83*, 1733-1738; (d)

Wadsworth, D.; Schupp III, O.; Seus, E.; Ford Jr, J. *J. Org. Chem.* **1965,** *30*, 680-685.