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A unified strategy for the total syntheses of eribulin and a macrolactam analogue of halichondrin B

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A unified synthetic route for the total syntheses of eribulin and a macrolactam analog of halichondrin B is described. The key to the success of the current synthetic approach includes the employment of our reverse approach for the construction of cyclic ether structural motifs and a modified intramolecular cyclization reaction between alkyl iodide and aldehyde functionalities to establish the all-carbon macrocyclic framework of eribulin. These syntheses, together with our previous work on the total syntheses of halichondrin B and norhalichondrin B, demonstrate and validate the powerful reverse approach in the construction of cyclic ether structural motifs. On the other hand, the unified synthetic strategy for the synthesis of the related macrolactam analog provides inspiration and opportunities in the halichondrin field and related polycyclic ether areas.

asymmetric synthesis | cyclization | Nicholas etherification | total synthesis

Significance

More than 20 years have passed since the first total synthesis of eribulin was reported, and numerous attempts thereafter failed to reach the final target; a unified strategy for the total syntheses of eribulin and its macrolactam analogue is reported. These syntheses feature a reverse approach for the construction of cyclic ether structural motifs and an alkyl iodide–aldehyde macrocyclization.

The halichondrins, as a family of potent antitumor natural products (1–3), have attracted considerable attention from synthetic organic chemists in academia (4–10) and the pharmaceutical industry (11–15). The pioneering work of Kishi and coworkers (4), combined with the endeavors from Eisai Co., Ltd. (16–20), led to the discovery and development of eribulin (its clinically used mesylate salt is marketed under the trade name Halaven), an analog inspired by the structure and biological properties of halichondrin B, as a successful clinical drug against metastatic breast cancer and liposarcoma (21–24). Following our recent total syntheses of halichondrin B (**1**) (Fig. 1) (25) and norhalichondrin B (**2**) (Fig. 1) (26), through our reverse approach to cyclic ether structural motifs (forming the C–O bond first followed by C–C bond construction) and employing convergent synthetic strategies, we now report efficient total syntheses of eribulin (**3**) (Fig. 1) and the related macrolactam analog **4** (Fig. 1) of halichondrin B (**1**).

The so far reported syntheses of eribulin and other analogs of halichondrin B (**1**) by Eisai Co., Ltd. through two alternative synthetic sequences are highlighted in Fig. 2*A* (14). Further medicinal chemistry (structure–activity relationships) studies (16–20) with halichondrin B (**1**) analogs pointed to fragment *A′* of eribulin and fragment *ABCDEFG* of halichondrin B as critical structural motifs of these molecules for structural modifications directed toward optimization of their biological and pharmacological properties. Thus, from the medicinal chemistry point of view, a late-stage installation of fragment *A′* (e.g., **7a** and **7b**) (Fig. 3) could improve the synthetic efficiency for the preparation of related designed analogs. With these considerations and our previously developed synthetic methods in mind, we envisioned a unified synthetic strategy for the total synthesis of eribulin (all-carbon macrocycle) and other related macrolactone and macrolactam analogs of the halichondrins, as outlined in Fig. 2*B*. Such a strategy may facilitate the synthesis of multiple designed analogs, including all-carbon macrocycle-based structures and featuring similar isosteric substitutions, thus providing an opportunity for the discovery and optimization of next generation anticancer lead compounds in the area, as shown in Fig. 2*B*.

Thus, based on the above reasoning and prospects for further advances in this area, the retrosynthetic analysis (Fig. 3) of eribulin, a macrocarbocycle, and related macrolactone and macrolactam analogs of the halichondrins led, first, to advanced open-chain, intermediate **6** through the appropriate crucial macrocycle disconnections and necessary functional group interconversions. Further disconnection of ring *H* of precursor **6** via retro-Nozaki–Hiyama–Kishi coupling and cycloetherification led to fragment *A′* (**7a** or **7b**) and fragment *IJKLMN* (**8**) (25) as required building blocks for the projected total syntheses of eribulin (**3**) and related analogs (e.g., **5**), as shown in Fig. 3.

Results and Discussion

Improved Synthesis of Fragment *MN* (17) and Further Optimization of Its Conversion to Fragment *IJKLMN* (8). Scheme 1 summarizes the synthesis of required fragment *MN* (**17**) starting with our previously reported building blocks **9** and **10** through the intermediacy

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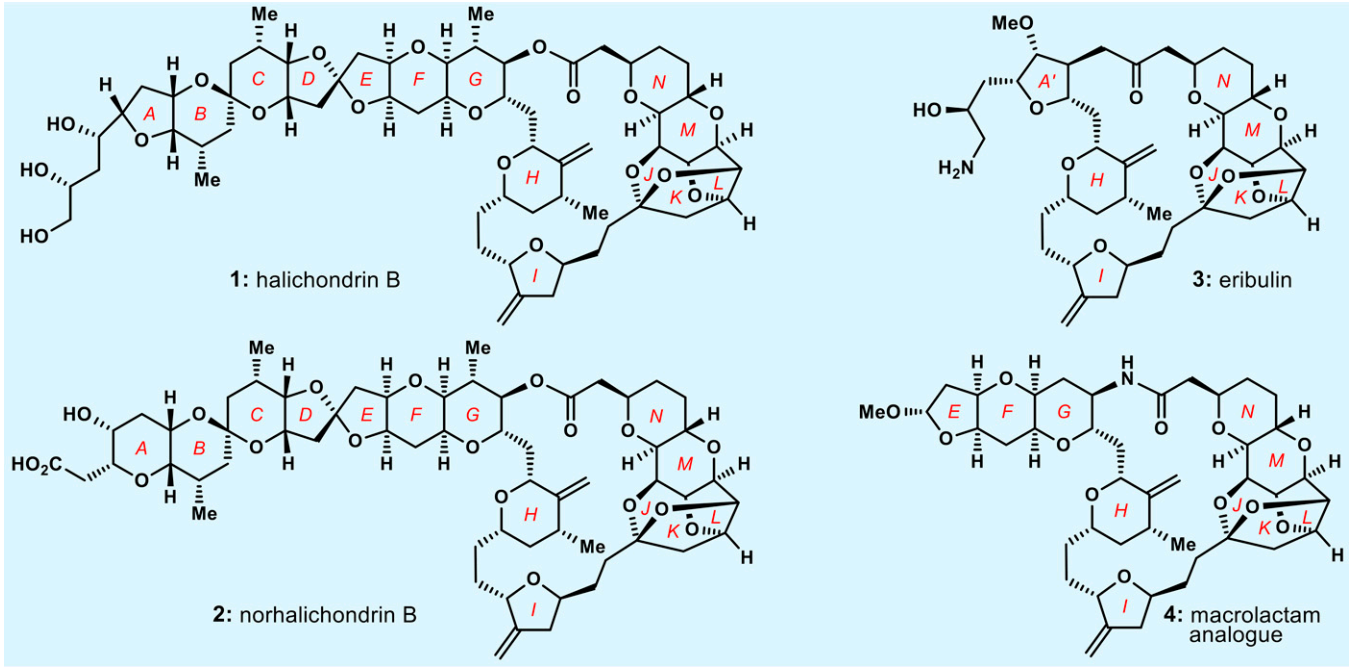


Fig. 1. Molecular structures of halichondrin B (**1**), norhalichondrin B (**2**), eribulin (**3**), and macrolactam analog **4**.

of aldehyde **11** (25). Instead of our previously used tin-mediated radical cyclization (25), a nickel-catalyzed ynal reductive cyclization (27, 28) was employed to construct the bicyclic ring system with improved yield. Thus, aldehyde **11** was subjected to $Ni(cod)_2$/*n*-Bu_3P/Et_3SiH conditions (29), leading to transient intermediate **12**, which was selectively deprotected (0.5 M aq. HCl) to afford allylic alcohol **13** in 83% yield (as compared with 53% yield with tin reductive conditions) (25). The excellent diastereoselectivity at C8 (>15:1) in forming bicyclic intermediate **13** indicated that the nickel-catalyzed ynal reductive cyclization may proceed through a preferred chair transition state **12a**, as shown in Scheme 1. It should be noted that other conditions, such as SmI_2, Cp_2TiCl (30), $Cp_2Ti(PMe_3)_2$ (31), $PtCl_2$/$P(p\text{-}CF_3C_6H_4)_3$ (32), and $VCl_3(THF)_3$/Zn (33), either led to low yield or failed to produce the desired product (**13**).

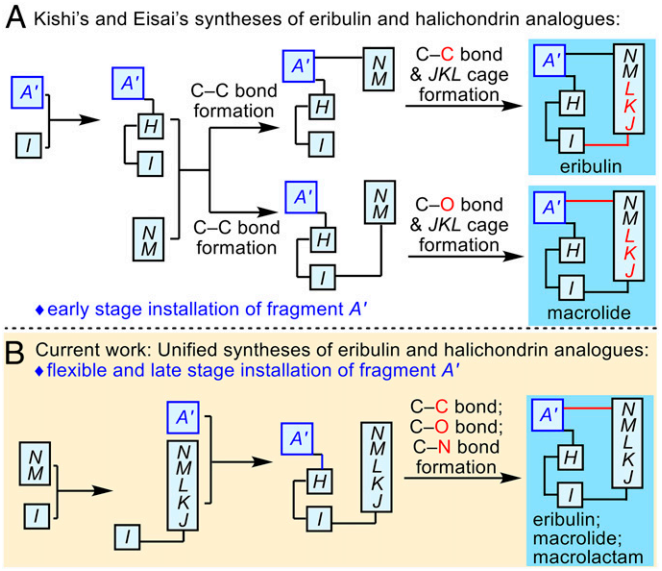


Fig. 2. Syntheses of eribulin and related analogs. (*A*) Outline of Kishi's and Eisai's syntheses of eribulin (**3**) and other halichondrin analogs. (*B*) Outline of our unified synthesis of eribulin (**3**) and other halichondrin analogs.

Treatment of alcohol **13** with Dess–Martin reagent afforded enone **14**, whose olefinic bond was oxidatively cleaved (O_3, MeOH; then, $NaBH_4$) to furnish, directly and stereoselectively (34, 35), diol **15** in 65% overall yield for the two steps, as shown in Scheme 1. One-pot acetonide formation and desilylation of the latter [12 M aqueous (aq.) HCl, acetone:MeOH, 77% yield] followed by Dess–Martin oxidation [Dess–Martin periodinane (DMP), 82% yield] of the resulting primary alcohol led to the desired fragment *MN* (**17**). The current eight-step sequence to **17** in 14% overall yield from building block **10** represents a significant improvement from our previous nine-step sequence (6.3% overall yield) (25).

Having improved the synthetic route to fragment *MN* (**17**), we turned our attention to optimizing the benzyl cleavage from diol **19**, which was achieved in two steps and 78% overall yield (25), as shown in Scheme 2. After extensive experimentation, a continuous flow process (*SI Appendix* includes details) was developed to achieve the sought-after improvement. Thus, exposure of a mixture of **19** [2:1 diastereomeric ratio (*dr*) at C12], 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ), and 2,6-di-*tert*-butyl-4-methylphenol (BHT) to light-emitting diode (LED) light (λ = 390 nm) (36, 37) using a continuous flow process resulted in clean and efficient cleavage of the benzyl protecting group, affording the corresponding triol intermediate as a mixture of C12 epimers (**20** and C12-*epi*-**20**, 2:1 *dr*). The latter mixture was then exposed to intramolecular ketalization conditions (*p*-TsOH·H_2O), affording cage compound **21** (70% yield from **19**) and leaving behind C12-*epi*-**20** (67% from C12-*epi*-**19**), which was isolated and recycled through epimerization at C12 (NaOMe) to **20** (90% yield, 2.2:1 *dr*), thus further enriching the material supply of **21**. Finally, the desired mesylate **8** (fragment *IJKLMN*) was prepared from **21** (MsCl, Et_3N, 95% yield) as previously reported (25) and shown in Scheme 2.

First Generation Synthesis of Fragment *A′* (33) and Efforts toward Eribulin (3). Our first attempt to synthesize eribulin (**3**) required, in addition to fragment *IJKLMN* (**8**), *p*-tolylsulfone aldehyde fragment *A′* (**33**) (Scheme 3) (ref. 14; the synthesis of a related fragment *A*/*A′* is in refs. 38–40). The synthesis of

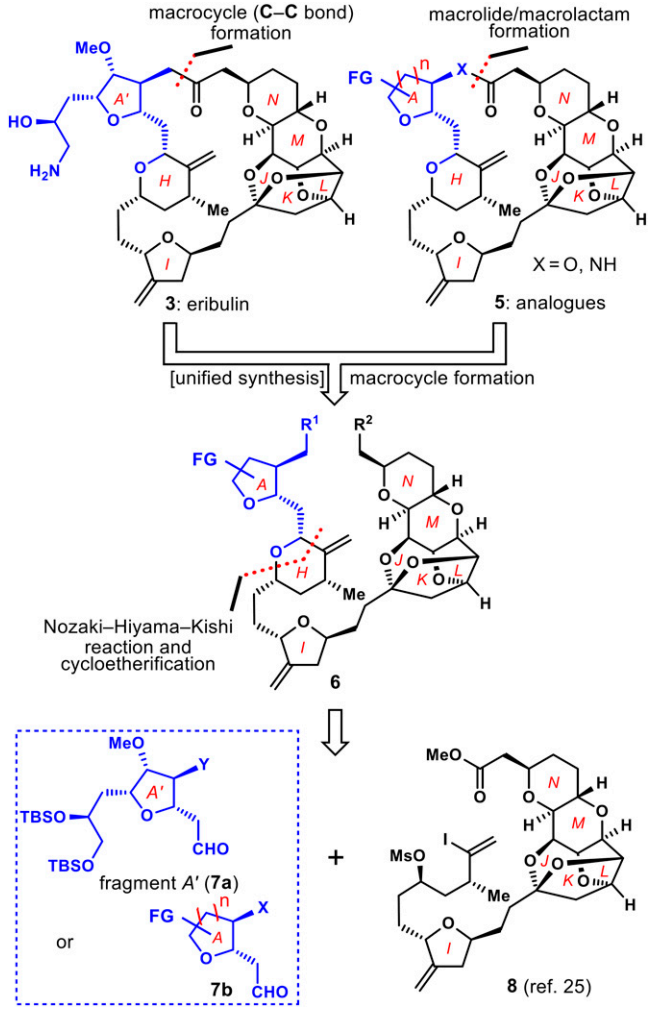
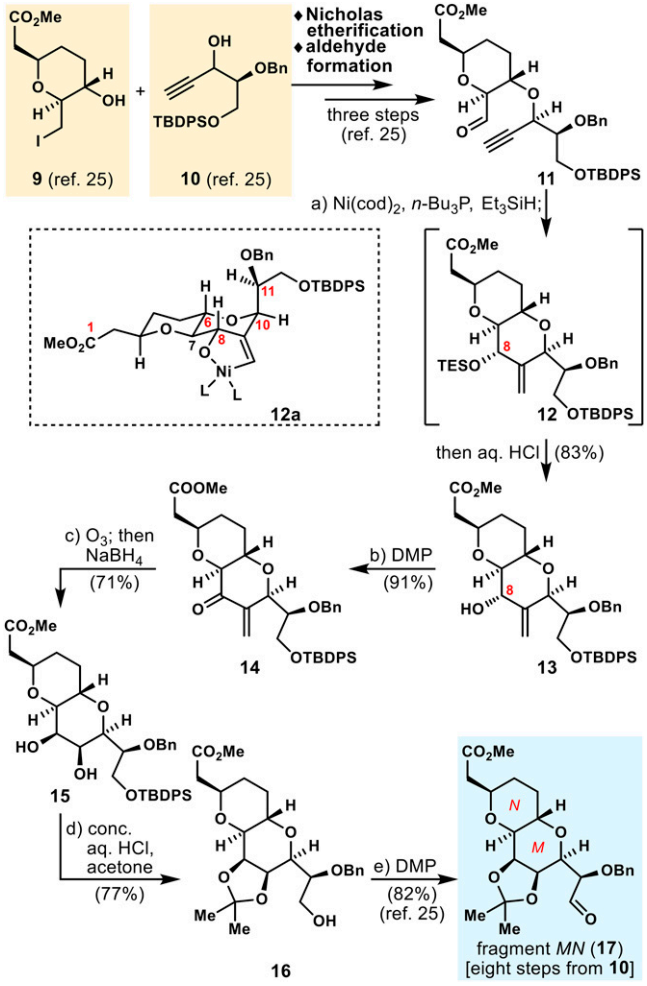


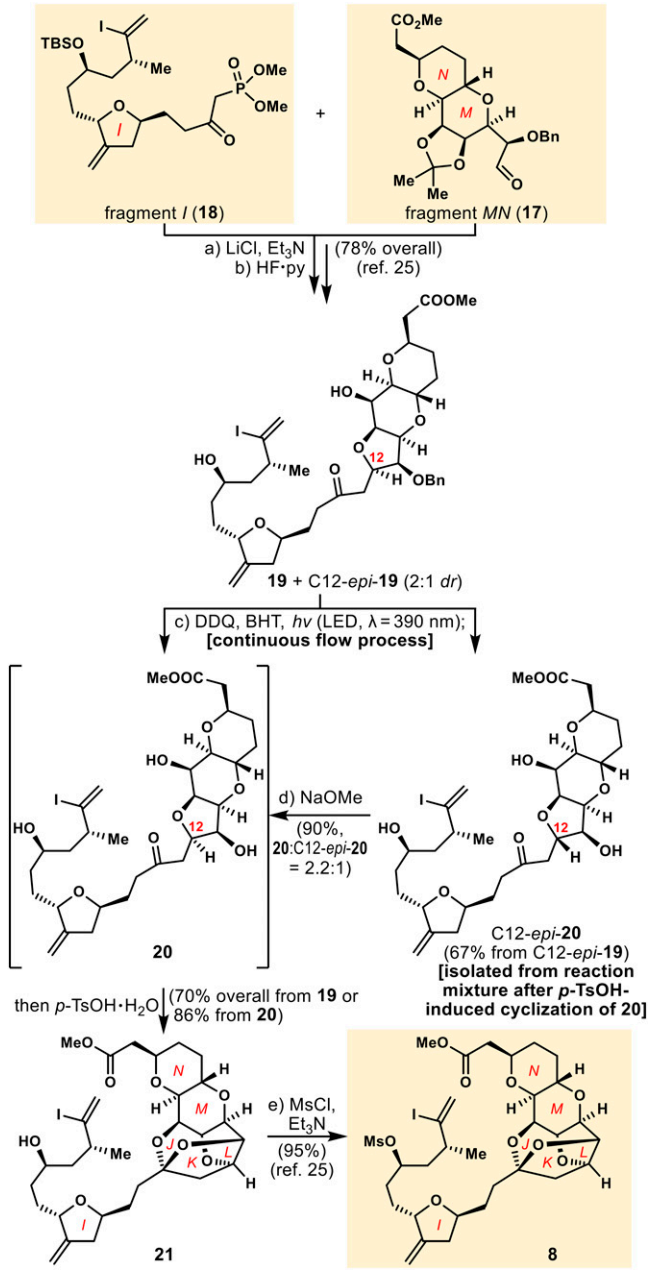
Fig. 3. Unified retrosynthetic analysis of eribulin (**3**) and related analogs (**5**).

tetrahydrofuran aldehyde fragment *A′* (**33**) started from readily available building blocks α-hydroxy ester **22** (41) and hydroxy acetylene **23** (25) as summarized in Scheme 3. Thus, Nicholas etherification of **22** and **23** [$Co_2(CO_8)$; then, $BF_3{\cdot}Et_2O$; then, $(NH_4)_2Ce(NO_3)_6$] furnished linear ethers **24a** (31% yield) and **24b** (46% yield) as a chromatographically separable mixture of diastereoisomers. The major and desired diastereoisomer **24b** (whose correct configuration was confirmed at a later stage [i.e., **26**] after a number of steps; see below) was then converted to cyclization precursor **25** through sequential reductions of its alkyne (Lindlar catalyst, H_2) and ester [diisobutylaluminum hydride (DIBAL-H)] functionalities, respectively, in 88% overall yield, as shown in Scheme 3. Exposure of the latter to hydroxylamine hydrochloride followed by oxidation (NaOCl) of the resulting oxime furnished the corresponding nitrile oxide leading to spontaneous 1,3-dipolar cycloaddition (a mechanistic rationale is in the dashed central box in Scheme 3), affording isoxazoline **26** (62% overall yield). The stereochemical configuration of **26** was confirmed by nuclear Overhauser effect (NOE) spectroscopic studies (*SI Appendix*), which also confirmed the configurations of its precursors **24b** and **25**. Reductive N–O bond cleavage within isoxazoline **26** [$Mo(CO)_6$, MeCN, 72% yield] followed by stereoselective reduction [$Me_4NBH(OAc)_3$, 95% yield] of the so-formed ketone **27** afforded diol **28** in 68% overall yield from **26**. The latter diol was transformed to sulfone **30**, in 81% overall yield, through a three-step sequence via intermediate **29** involving selective sulfurization (*p*-tolyl disulfide, *n*-Bu_3P, 90% yield) of the primary alcohol, methylation (NaH, MeI) of the secondary hydroxyl group, and oxidation (Oxone, 90% overall yield) of the resulting organosulfur derivative, as depicted in Scheme 3. Sulfone **30** was then subjected to desilylation [hydrogen fluoride-pyridine complex (HF·py)], and the resulting primary alcohol was reprotected with a pivaloyl group [pivaloyl chloride (PivCl), py] to afford olefin **31** (94% overall yield). Sharpless dihydroxylation [asymmetric dihydroxylation (AD)-mix-α, $MeSO_2NH_2$] of the latter led to the diastereoselective formation of the corresponding diol intermediate, which was silylated to form intermediate **32** in 70% overall yield as shown in Scheme 3. Selective cleavage of the pivaloyl protecting group of **32** (NaOMe), followed by Dess–Martin oxidation of the resulting primary alcohol, furnished the coveted sulfone–aldehyde fragment *A′* (**33**) in 81% overall yield, as shown in Scheme 3.

With both fragments *A′* (**33**) and *IJKLMN* (**8**) readily available, the stage was set for their coupling and further elaboration toward the targeted eribulin (**3**). Thus and as shown in Scheme 4, the Nozaki–Hiyama–Kishi (NHK) reaction (4) between **33** and **8** ($NiCl_2/CrCl_2$, 47% yield, unoptimized conditions) followed by cycloetherification [1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)] afforded sulfone methyl ester **35** (via transient intermediate **34**),



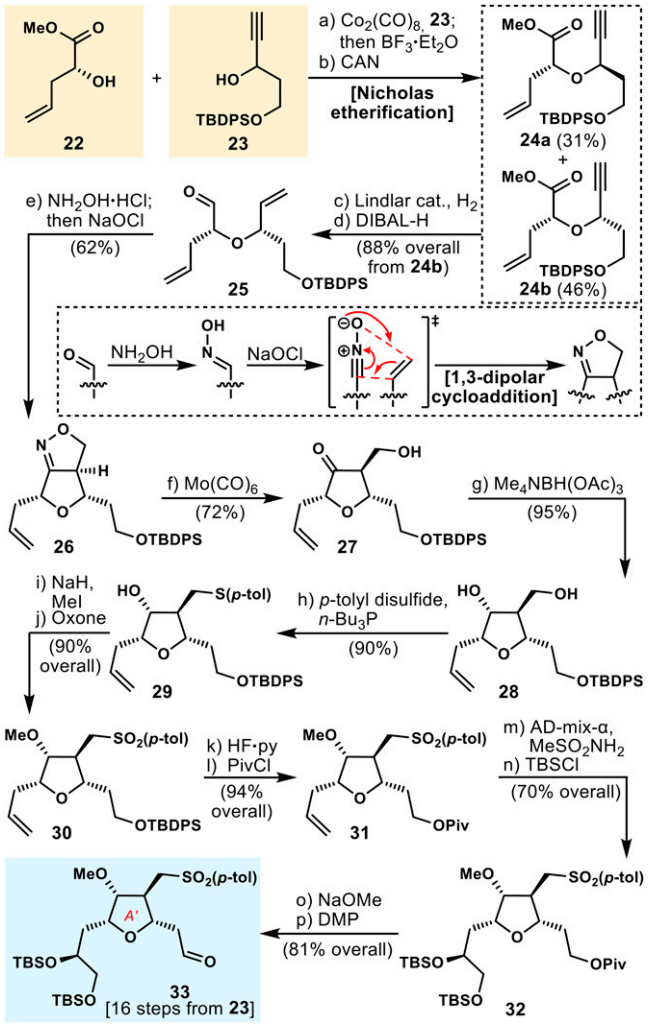
Scheme 1. Improved synthesis of fragment *MN* (**17**). Reagents and conditions. (a) $Ni(cod)_2$ (0.15 eq), *n*-Bu_3P (0.30 eq), Et_3SiH (7.0 eq), THF, 23 °C, 5 h; then, aq. HCl (0.5 M), 23 °C, 3 h, 83% yield. (b) DMP (2.5 eq), CH_2Cl_2, 0 → 23 °C, 1.5 h, 91%. (c) O_3 (excess), MeOH, −78 °C; then, $NaBH_4$ (5.0 eq), −78 → 23 °C, 1.5 h; 71%. (d) Aq. HCl (12 M), acetone:MeOH (4:1, *vol/vol*), 0 → 23 °C, 10 h, 77%. DMP, 3-oxo-1λ^5,2-benziodoxole-1,1,1(3*H*)-triyl triacetate; $Ni(cod)_2$, bis(cyclooctadiene)nickel(0).



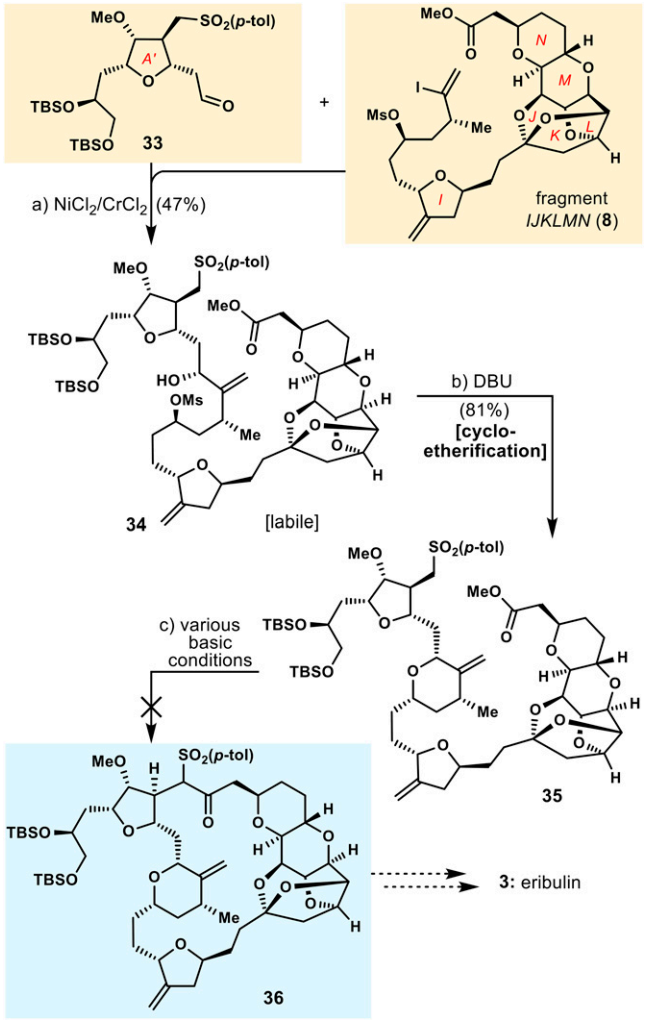
Scheme 2. Further optimization to fragment *IJKLMN* (**8**). Reagents and conditions. (c) DDQ (2.8 eq), BHT (0.2 eq), MeCN, *hν* (LED, λ = 390 nm), continuous flow process (*SI Appendix*), 23 °C; then, *p*-TsOH·H_2O (0.3 eq), 5 min, 23 °C for **21**: 70% from **19**, for C12-*epi*-**20**, 67% from C12-*epi*-**19**. (d) NaOMe (excess), MeOH, 23 °C, 7 h, 90% (**20**: C12-*epi*-**20** = 2.2:1 *dr*). BHT, 2,6-di-*tert*-butyl-4-methylphenol; DDQ, 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile; *p*-TsOH·H_2O, *p*-toluenesulfonic acid.

which underwent smoothly the expected intramolecular displacement at the mesylate position under the basic conditions employed (81% yield), as shown in Scheme 4. Unfortunately, however, attempts to induce the macrocyclization of *p*-tolylsulfone methyl ester **35** under various basic conditions [e.g., lithium diisopropylamide (LDA) (42), sodium hexamethyldisilazide (NaHMDS) (43), potassium hexamethyldisilazide (KHMDS) (44), potassium *tert*-butoxide (KO*t*-Bu) (45)] failed to form the desired eribulin precursor **36**, leading us to search for an alternative approach.

Second and Successful Attempt toward Eribulin (3) from Building Block 28 and Fragment *IJKLMN*. Having failed to complete the synthesis of eribulin (**3**) from building block **28** via fragment *A*′ (**33**) (Scheme 4), we adopted an approach to reach the target molecule (i.e., **3**) by employing a version of fragment *A* (i.e., *A*″; **38**) and fragment *IJKLMN* (**8**), as shown in Scheme 5. Our strategy envisioned an iodoaldehyde substrate **44** (Scheme 5) as a precursor to eribulin's macrocyclic structural motif through an intramolecular C–C bond formation. To this end, the desired fragment *A*″ (**38**) (Scheme 5) was synthesized from readily available building block **28** (for its synthesis) (Scheme 3), as



Scheme 3. First synthesis of fragment *A*′ (**33**) of eribulin via Nicholas reaction. Reagents and conditions. (a) $Co_2(CO)_8$ (1.2 eq), CH_2Cl_2, 23 °C, 20 min; then, $BF_3{\cdot}Et_2O$ (2.0 eq), 0 °C, 0.5 h. (b) CAN (5.0 eq), acetone, 0 → 23 °C, 1 h, 31% for **24a** and 46% for **24b**. (c) Lindlar catalyst (10% *wt*/*wt*), quinoline (1.1 eq), EtOAc, 23 °C, 0.5 h, 95%. (d) DIBAL-H (1.0 M in toluene, 1.2 eq), CH_2Cl_2, −78 °C, 0.5 h, 93%. (e) $NH_2OH{\cdot}HCl$ (2.2 eq), py:EtOH (5:1, *vol*/*vol*), 23 °C, 0.5 h; then, NaOCl (8.0 eq), CH_2Cl_2, 23 °C, 3 h, 62% overall. (f) $Mo(CO)_6$ (2.0 eq), MeCN:H_2O (4:1, *vol*/*vol*), 80 °C, 2 h, 72%. (g) $Me_4NBH(OAc)_3$ (1.5 eq), MeOH, 0 °C, 0.5 h, 95%. (h) *p*-tolyl disulfide (3.0 eq), *n*-Bu_3P (3.0 eq), py, 23 °C, 3 h, 90%. (i) NaH (4.0 eq), MeI (6.0 eq), THF:DMF (1:1, *vol*/*vol*), 0 → 23 °C, 0.5 h. (j) Oxone (3.0 eq), THF:H_2O (1:1, *vol*/*vol*), 23 °C, 2 h, 90% overall. (k) HF·py (100 eq), THF, 0 → 23 °C, 2 h. (l) PivCl (1.5 eq), py:CH_2Cl_2 (1:1, *vol*/*vol*), −20 °C, 1.5 h, 94% overall. (m) AD-mix-α (1.60 g/mmol), $MeSO_2NH_2$ (100 mg/mmol), *t*-BuOH:H_2O (1:1, *vol*/*vol*), −5 °C, 36 h. (n) TBSCl (3.0 eq), imidazole (4.8 eq), DMAP (0.3 eq), CH_2Cl_2, 0 → 23 °C, 48 h, 70% overall (C2-*epi*-**32** 14% overall yield). (o) NaOMe (0.5 M in MeOH, 5.0 eq), MeOH, 0 → 23 °C, 2 h, 88%. (p) DMP (2.5 eq), CH_2Cl_2, 0 → 23 °C, 0.5 h, 92%. AD-mix-α, mixture of $K_3Fe(CN)_6$ (49.88 mol %), K_2CO_3 (49.88 mol %), (9*S*)-(9″*S*)-9,9″-[1,4-phthalazinediylbis(oxy)]bis[10,11-dihydro-6′-methoxycinchonan] (0.16 mol %), and $K_2OsO_2(OH)_4$ (0.07 mol %); CAN, diammonium cerium(IV) nitrate; DIBAL-H, diisobutyl aluminum hydride; DMAP, *N*,*N*-dimethylpyridin-4-amine; DMF, *N*,*N*-dimethylformamide; Oxone, potassium peroxymonosulfate; PivCl, pivaloyl chloride; py, pyridine; TBSCl, chloro(1,1-dimethylethyl)dimethyl silane.

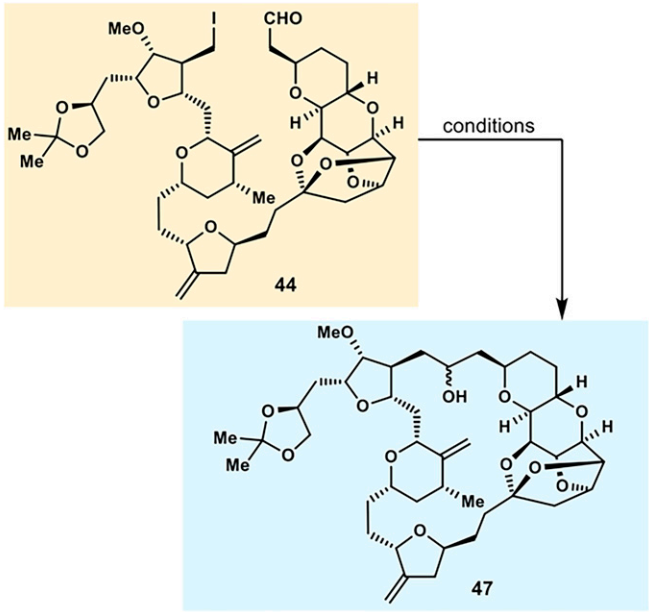


Scheme 4. First synthetic attempt toward eribulin. Reagents and conditions. (a) **33** (3.0 eq), **8** (1.0 eq), 2% $NiCl_2/CrCl_2$ (10.0 eq), THF:DMF (4:1, *vol/vol*), 23 °C, 24 h, 47%. (b) DBU (84 eq), toluene, 110 °C, 1 h, 81%. (c) For example, LDA, NaHMDS, KHMDS, and KO*t*-Bu. DBU, 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine; KHMDS, potassium 1,1,1-trimethyl-*N*-(trimethylsilyl)silanaminide; KO*t*-Bu, potassium *tert*-butoxide; LDA, lithium *N*-(propan-2-yl)propan-2-aminide; NaHMDS, sodium 1,1,1-trimethyl-*N*-(trimethylsilyl)silanaminide.

summarized in Scheme 5. Thus, **28** was first converted to fully protected acetonide tetrahydrofuran **37** through a four-step sequence involving 1) selective *p*-methoxybenzyl (PMB) protection of its primary alcohol [PMB-trichloroacetimidate (PMB-TCAI)]; 2) methylation of its secondary alcohol [NaH, methyl iodide (MeI)]; 3) diastereoselective dihydroxylation (AD-mix-α, $MeSO_2NH_2$); and 4) acetonide protection [*p*-TsOH·H_2O, 2,2-dimethoxypropane (2,2-DMP)] of the so-generated diol in 45% overall yield for the four steps as depicted in Scheme 5. Desilylation of **37** [*N*,*N*,*N*-tributylbutan-1-aminium fluoride (TBAF)] followed by Dess–Martin oxidation (DMP) of the resulting primary alcohol furnished coveted aldehyde fragment *A″* (**38**) in 88% overall yield (13 steps from **23** as opposed to 16 steps for fragment *A′* [**33**] from the same building block **23**) (Scheme 3). Coupling of fragment *A″* (**38**) with fragment *IJKLMN* (**8**) by Nozaki–Hiyama–Kishi reaction (25, 26, 46, 47) [$NiCl_2/CrCl_2$/ligand (−)-**39**, optimized conditions] followed by cycloetherification (DBU) afforded PMB-protected ester **40** in 56% overall yield. Oxidative cleavage (DDQ, 71% yield) of the PMB protective group within **40** furnished precursor **41** for further advancement to the targeted eribulin molecule (**3**) (Scheme 3).

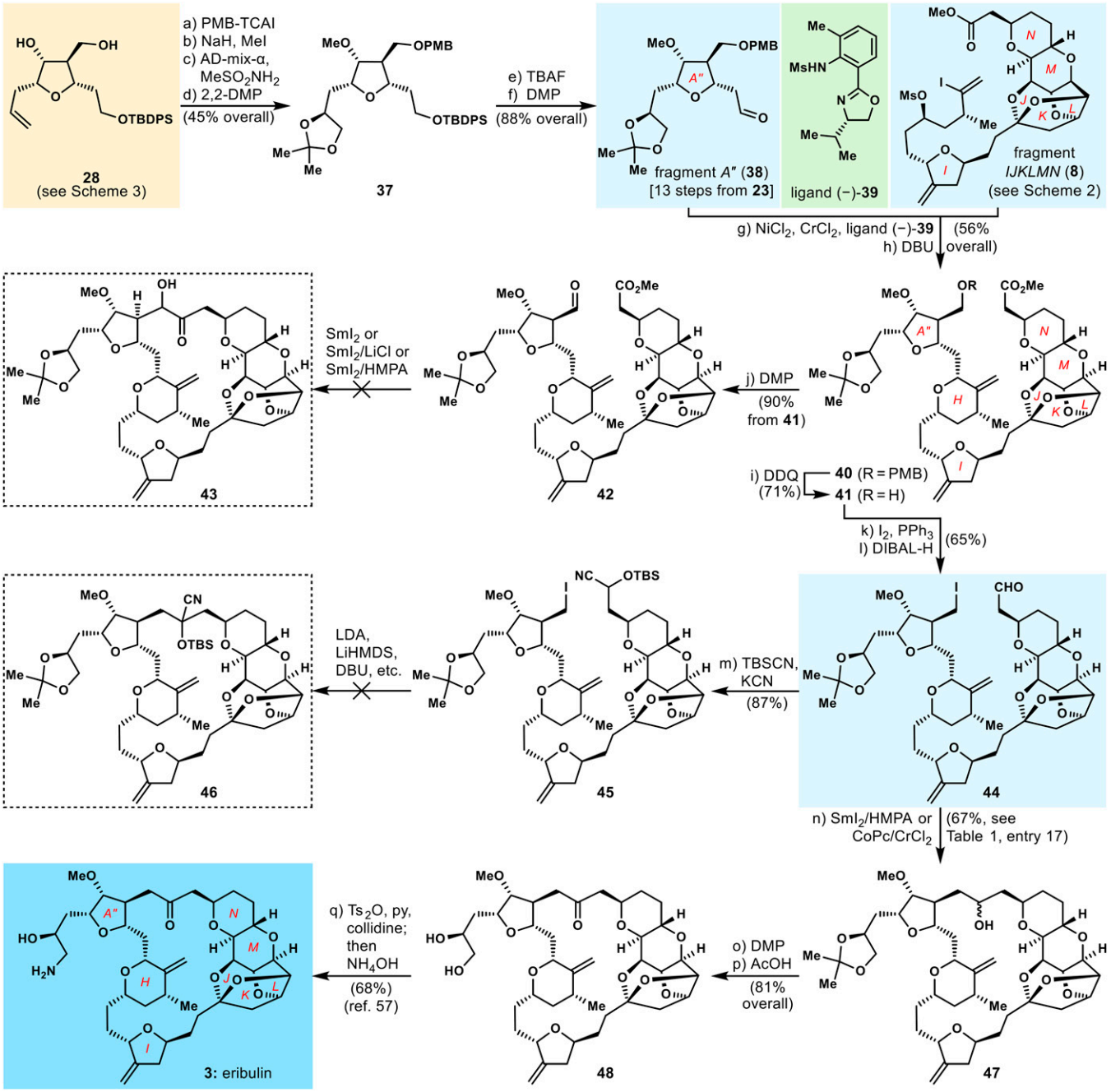
Forming the eribulin macrocycle through the remaining C–C bond was a challenge given the limited number of methods available for constructing such an all-carbon ring (48, 49). In the halichondrin and eribulin field, Kishi and Eisai scientists employed an intramolecular Nozaki–Hiyama–Kishi reaction (vinyl iodide–aldehyde coupling), ring-closing metathesis, and Horner–Wadsworth–Emmons olefination to form the related macrocycle within their target molecules (50). In our case and

Table 1. Screening and optimization of the macrocyclization reaction of 44



entry	reagent(s)	additive	solvent	ϑ / °C	yield (47)
1	SmI_2	—	THF	−78→23	n.d.[a]
2	SmI_2	HMPA	THF	−78→23	<15%[a]
3	*t*-BuLi	—	THF	−78	n.d.[b]
4	AIBN/*n*-Bu_3SnH	—	toluene	90	n.d.[c]
5	$NiCl_2/CrCl_2$	—	DMF or DMSO	23	n.d.
6	$NiCl_2/CrCl_2$	(−)-**39**	THF	23	n.d.
7	CoPc/$CrCl_2$	(−)-**39**	MeCN or DME	23	<20%
8	CoPc/$CrCl_2$	—	DMF	23	41%
9	$VB_{12}/CrCl_2$	—	DMF	23	42%[d]
10	CoPc/$CrCl_2$	—	DMF	40	37%
11	CoPc/$CrCl_2$	—	DMF	80	43%
12	CoPc/$CrCl_2$	—	DMF	23	33%[e]
13	CoPc/$CrCl_2$	—	DMF	23	43%[f]
14	CoPc/$CrCl_2$	—	DMF	23	47%[g]
15	CoPc/$CrCl_2$	4 Å MS	DMF	23	27%
16	CoPc/$CrCl_2$	KI	DMF	23	53%
17	CoPc/$CrCl_2$	KI	DMF	23	67%[h]

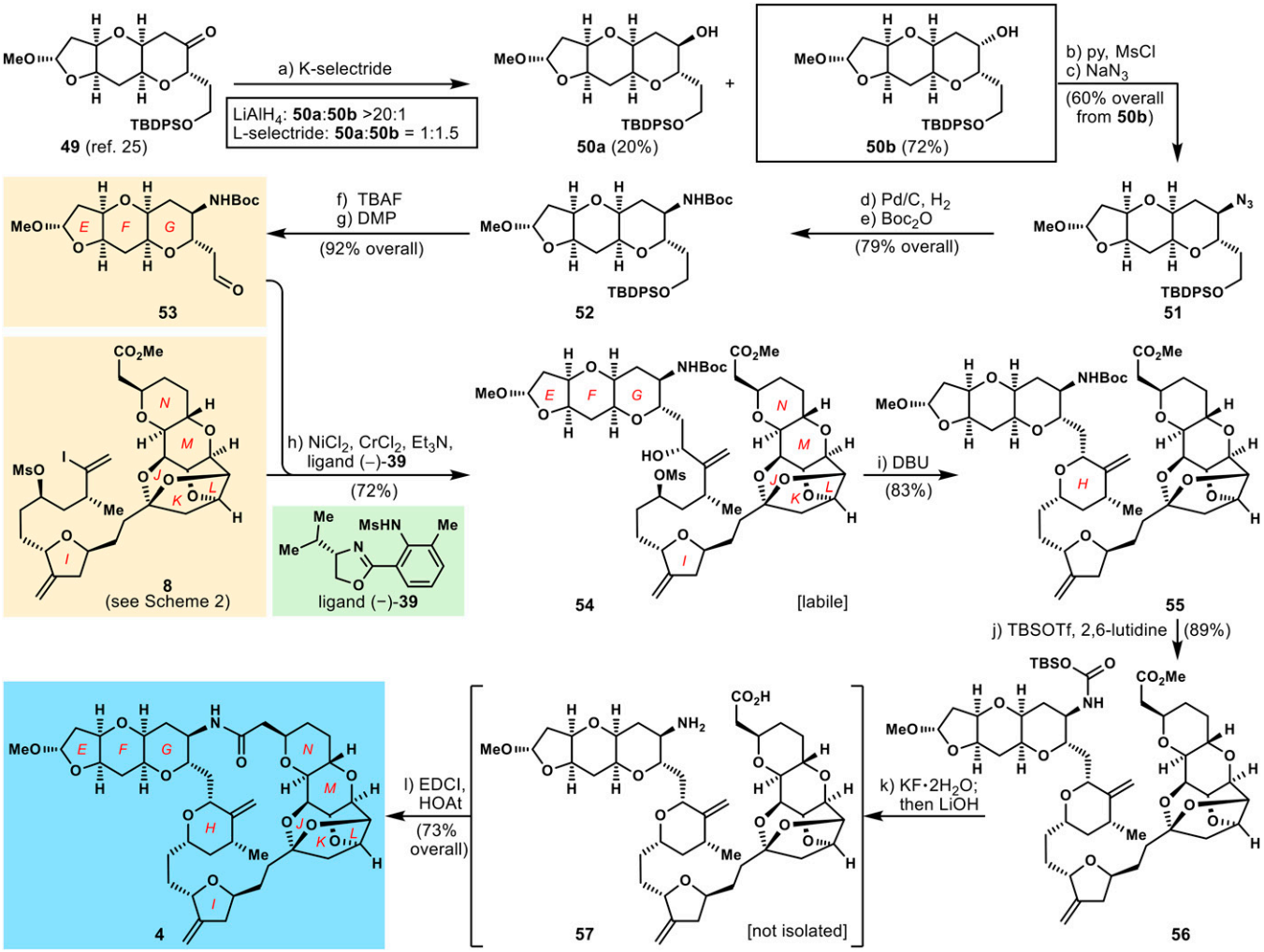
Conditions: all reactions were carried out with **44** (1.0 mg, 1.1 μmol, 1.0 eq), solvent (2.0 mL), 23 °C to 80 °C, 48 h; for entries **5** to **17**, $NiCl_2$ (2.0 eq) or CoPc (1.0 eq), $CrCl_2$ (50 eq), additive (20 eq), isolated yields. AIBN, 2,2′-(1,2-diazenediyl)bis[2-methylpropanenitrile]; CoPc, (*SP*-4-1)-[29*H*,31*H*-phthalocyaninato(2−)-κN^{29},κN^{30},κN^{31},κN^{32}]cobalt; DME, 1,2-dimethoxyethane; DMF, *N*,*N*-dimethylformamide; DMSO, (methanesulfinyl)methane; HMPA, hexamethylphosphoric triamide; MeCN, acetonitrile; MS, molecular sieve; n.d., not detected; THF, oxolane; VB_{12}, vitamin B_{12}.
[a]SmI_2 (90 eq).
[b]*t*-BuLi (2.0 to 5.0 eq).
[c]AIBN (1.0 eq), *n*-Bu_3SnH (5.0 eq).
[d]VB_{12} (0.1 eq).
[e]CoPc (0.2 eq).
[f]CoPc (3.0 eq).
[g]$CrCl_2$ (150 eq).
[h]12-mg scale, $CrCl_2$ (100 eq).



Scheme 5. Second and successful attempt for the synthesis of eribulin (**3**) from building block **28** and fragment *IJKLMN*. Reagents and conditions. (a) PMB-TCAI (1.0 eq), (±)-CSA (0.1 eq), CH_2Cl_2:*n*-hexane (4:1, *vol/vol*), 0 → 23 °C, 4 h, 65%. (b) NaH (6.0 eq), MeI (5.0 eq), THF:DMF (4:1, *vol/vol*), 0 → 23 °C, 1 h, 92%. (c) AD-mix-α (1.60 g/mmol), $MeSO_2NH_2$ (100 mg/mmol), *t*-BuOH:H_2O (1:1, *vol/vol*), −5 °C, 36 h. (d) 2,2-DMP (5.0 eq), *p*-TsOH·H_2O (0.2 eq), acetone, 23 °C, 20 min, 75% for the two steps. (e) TBAF (1 M in THF, 2.2 eq), THF, 23 °C, 2 h, 95%. (f) DMP (2.5 eq), CH_2Cl_2, 0 → 23 °C, 1 h, 93%. (g) $CrCl_2$ (3.0 eq), $NiCl_2$ (0.2 eq), ligand (−)-**39** (2.5 eq), Et_3N (5.0 eq), THF, 23 °C, 10 h, 69%. (h) DBU (63 eq), toluene, 110 °C, 1 h, 81%. (i) DDQ (10.0 eq), CH_2Cl_2:pH 7 buffer (10:1, *vol/vol*), 23 °C, 3 h, 71%. (j) DMP (2.5 eq), CH_2Cl_2, 23 °C, 1 h, 90%. (k) imidazole (5.0 eq), PPh_3 (3.0 eq), I_2 (2.5 eq), THF, 0 → 23 °C, 1 h, 92%. (l) DIBAL-H (1.0 M in toluene, 2.0 eq), CH_2Cl_2, −78 °C, 1 h, 71%. (m) KCN (1.0 eq), 18-crown-6 (1.0 eq), TBSCN (5.0 eq), THF, 23 °C, 2 h, 87%. (n) CoPc (1.0 eq), KI (20 eq), $CrCl_2$ (100 eq), DMF, 23 °C, 48 h, 67%. (o) DMP (5.0 eq), CH_2Cl_2, 23 °C, 0.5 h, 90%. (p) AcOH:H_2O (2:1, *vol/vol*), 50 °C, 1 h, 90%. (q) Ts_2O (1.1 eq), 2,4,6-collidine (4.0 eq), pyridine (0.1 eq), CH_2Cl_2, −10 → 0 °C, 2 h; then, NH_4OH:*i*-PrOH (excess, 1:1, *vol/vol*), 0 → 30 °C, 20 h, 68%. 18-crown-6, 1,4,7,10,13,16-hexaoxacyclooctadecane; (±)-CSA, (±)-(7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonic acid; 2,2-DMP, 2,2-dimethoxypropane; LiHMDS, lithium 1,1,1-trimethyl-*N*-(trimethylsilyl)silanamidide; PMB-TCAI, 2,2,2-trichloroethanimidic acid (4-methoxyphenyl)methyl ester; TBAF, *N*,*N*,*N*-tributylbutan-1-aminium fluoride; Ts_2O, *p*-toluenesulfonic anhydride.

in order to enrich the tool box for constructing such challenging all carbon ring macrocycles, we opted to search for an alternative method to achieve such macrocyclizations. To this end, we converted key advanced intermediate **41** to various potential precursors (i.e., **42**, **44**, and **45**) for casting the required C–C bond of the targeted macrocycle, as shown in Scheme 5. Thus, Dess–Martin oxidation of the primary hydroxyl group within **41** led to aldehyde methyl ester **42** in 90% yield, whereas iodination (I_2, PPh_3) of **41** at the hydroxyl site, followed by DIBAL-H–induced selective reduction of the so-formed iodomethyl ester, furnished iodoaldehyde **44** in 65% overall yield, as shown in Scheme 5.

Attempts to induce macrocyclization of aldehyde methyl ester **42** employing SmI_2 (51–53) [or SmI_2/LiCl or SmI_2/



Scheme 6. Synthesis of halichondrin B macrolactam analog **4**. Reagents and conditions. (a) K-selectride (1.5 eq), THF, 0 °C, 20 min, 20% for **50a**, 72% for **50b**. (b) MsCl (1.5 eq), pyridine, 0 → 23 °C, 2 h. (c) NaN_3 (8.0 eq), DMF, 23 → 100 °C, 5 h, 60% for the two steps. (d) Pd/C (30 wt % Pd/C, 20% loading of **51**), H_2 (1 bar), MeOH, 23 °C, 2 h. (e) Boc_2O (2.0 eq), Et_3N (2.0 eq), THF, 0 → 23 °C, 1 h, 79% for the two steps. (f) TBAF (3.0 eq), THF, 23 °C, 3 h. (g) DMP (2.5 eq), CH_2Cl_2, 23 °C, 1 h, 85% for the two steps. (h) $CrCl_2$ (3.0 eq), $NiCl_2$ (0.2 eq), ligand (−)-**39** (2.5 eq), Et_3N (5.0 eq), THF, 23 °C, 15 h, 72%. (i) DBU (98 eq), toluene, 110 °C, 1 h, 83%. (j) 2,6-lutidine (10.0 eq), TBSOTf (5.0 eq), 0 → 23 °C, 2 h, 89%. (k) KF·$2H_2O$ (5.0 eq), THF:H_2O (10:1, *vol/vol*), 20 min; then, aq. LiOH (0.2 M), 23 °C, 3 h. (l) **57** (0.17 mM), EDCI (20 eq), HOAt (20 eq), CH_2Cl_2:DMF (5:1, *vol/vol*), 23 °C, 8 h, 73% for the two steps. EDCI, 3-{[(ethylimino)methylidene]amino}-*N*,*N*-dimethylpropan-1-amine; HOAt, 3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-ol; K-selectride, potassium tri*sec*-butyl(hydrido)borate(1−).

hexamethylphosphoric triamide (HMPA)] unfortunately failed to produce the expected macrocycle **43** as depicted in Scheme 5. Iodoaldehyde **44** was then converted to its *tert*-butyldimethylsilyl (TBS)-protected cyanohydrin derivative **45**, through the action of *tert*-butyldimethylsilyl cyanide (TBSCN) and KCN (87% yield), as a potential precursor of the expected macrocyclic TBS-protected hydroxynitrile derivative **46**, as shown in Scheme 5. However, several attempts to facilitate the intramolecular C–C bond formation required to form macrocycle **46** (Scheme 5) under basic conditions [e.g., LDA, lithium hexamethyldisilazide (LiHMDS), DBU, etc.] proved fruitless, leading us to attempt the SmI_2/HMPA and other protocols including CoPc/$CrCl_2$ conditions with alkyl iodoaldehyde **44**, as the precursor (Table 1, entries **1** to **9**). Our early screening studies revealed the Takai conditions (ref. 54; for examples of the intermolecular application of Takai's NHK-like coupling conditions employing alkyl halides in total synthesis, see refs. 55–57) (CoPc/$CrCl_2$ and VB_{12}/$CrCl_2$) (Table 1, entries **8** and **9**, highlighted beige) to be the most promising for further optimization and with the CoPc/$CrCl_2$ chosen as the simplest and more convenient combination of reagents for our purpose. As shown in Table 1, the use of the CoPc/$CrCl_2$ combination of reagents produced the desired macrocyclic product **47** in moderate to good yields (Table 1, entries **10** to **16**, highlighted blue), with 67% yield obtained by employing potassium iodide (KI) as an additive and adjusting the equivalents of $CrCl_2$ (Table 1, entry **17**, highlighted green). Whereas previous work in the halichondrin, eribulin, and other carbocyclic systems employed the Nozaki–Hiyama–Kishi reaction (58–61) (e.g., utilizing a vinyl halide–aldehyde and alkynyl halide–aldehyde coupling) to cast the relevant macrocycles, the present macrocyclization features an intramolecular coupling between an alkyl halide and an aldehyde functionality, thus representing an innovative paradigm for the construction of such challenging structural motifs, although the intermolecular version of this reaction was initially demonstrated by Takai et al. (54).

With the macrocycle construction problem solved, eribulin (**3**) was in reach, with only a three-step sequence remaining to complete its total synthesis. Thus, as shown in Scheme 5, hydroxy–acetonide **47** was treated with Dess–Martin reagent to achieve the pending oxidation of the hydroxyl group to its ketone counterpart followed by cleavage of the acetonide moiety from the latter precursor (AcOH) to furnish diol **48** in 81%

overall yield for the two steps. Finally, diol **48** was converted to eribulin (**3**) through selective tosylation (Ts_2O), followed by amination (62) (NH_4OH), in 68% overall yield, as depicted in Scheme 5.

Synthesis of Halichondrin B Macrolactam Analog 4. In an effort to further expand the scope of our synthetic strategy beyond eribulin and into the realm of analogs of the halichondrins, the synthesis of macrolactam **4** was undertaken and accomplished using the developed synthetic technologies and following our unified strategy, as summarized in Scheme 6. Thus, stereoselective reduction of tricyclic ketone **49** (25) with K-selectride led to diastereomeric and chromatographically separable alcohols **50a** (20% yield) and **50b** (72% yield). Mesylation (MsCl, py) of the major and desired isomer **50b** followed by azide formation (NaN_3), accompanied by stereochemical inversion, led to azide **51** in 60% overall yield. Reduction of the latter (Pd/C, H_2) followed by Boc protection of the resulting amine (Boc_2O, Et_3N) furnished TBDPS,Boc-bis–protected derivative **52** (79% overall yield), whose desilylation (TBAF) and oxidation of the resulting primary alcohol (DMP) led to aldehyde **53** (fragment *EFG*) in 92% overall yield for the two steps, as depicted in Scheme 6. Coupling of fragment *EFG* (**53**; equipped with a protected primary amine) and *IJKLMN* fragment (**8**) (Scheme 2 has the preparation) through Nozaki–Hiyama–Kishi reaction [$NiCl_2/CrCl_2$, Et_3N, ligand (−)-**39**, 72% yield] furnished coupling product **54**. The latter transient intermediate was subjected to cycloetherification to cast ring *H* in the growing molecule (DBU, 83% yield), affording advanced intermediate **55**. The latter was then transformed to its silyl carbamate counterpart (**56**) by exposure to *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine (63), in 89% yield, as shown in Scheme 6. Finally, precursor **56** was transformed to the coveted macrolactam halichondrin B analog **4**, in 73% overall yield, through transient amino acid **57** first by exposure to $KF{\cdot}2H_2O$ and LiOH (liberation of the amino and carboxyl groups, respectively) and thence, to 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and 1-hydroxy-7-azabenzotriazole (HOAt) (macrolactam formation).

Conclusion

The described herein total synthesis of eribulin (**3**) and halichondrin B macrolactam analog **4** by a unified synthetic strategy adds further applications to our recently reported (25, 26) reverse approach (forming the C–O bonds first followed by C–C bond formation) for the construction of cyclic ether structural motifs for the total synthesis of halichondrin-type natural products and analogs thereof. Together, their emergence and rich harvest of shorter routes than prior existing total syntheses of members of the halichondrin family of natural products and related analogs validate our approach and provide inspiration for further improvements and applications of this paradigm in designing and executing efficient synthetic strategies toward polycyclic ether component fragments of such target molecules for total synthesis endeavors. Furthermore, our development of the alkyl halide (i.e., iodide)–aldehyde intramolecular macrocycle formation through C–C bond formation described in this research report, utilizing Takai's conditions, adds significantly to the tool box of organic synthesis, particularly for challenging macrocyclic structural motifs. To the best of our knowledge, although the intermolecular version of the Takai conditions (54) was reported previously, its intramolecular version reported herein has not been used before for the construction of macrocyclic systems. Finally, the present synthetic strategies provide a flexible and late-stage installation of fragment *A′* (or *A″*) into the growing molecule toward eribulin-like molecules, a tactic that could potentially facilitate the synthesis and exploration of designed halichondrin and eribulin analogs as demonstrated in this research report with the syntheses of eribulin (**3**) and the halichondrin B macrolactam analog (**4**). Such studies, including biological evaluation of the synthesized molecules, are currently in progress.

Data Availability. All study data are included in the article and/or *SI Appendix*.

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1. D. Uemura *et al.*, Norhalichondrin A: An antitumor polyether macrolide from a marine sponge. *J. Am. Chem. Soc.* **107**, 4796–4798 (1985).
2. Y. Hirata, D. Uemura, Halichondrins–antitumor polyether macrolides from a marine sponge. *Pure Appl. Chem.* **58**, 701–710 (1986).
3. M. Litaudon *et al.*, Antitumor polyether macrolides: New and hemisynthetic halichondrins from the New Zealand deep-water sponge *Lissodendoryx* sp. *J. Org. Chem.* **62**, 1868–1871 (1997).
4. T. D. Aicher *et al.*, Total synthesis of halichondrin B and norhalichondrin B. *J. Am. Chem. Soc.* **114**, 3162–3164 (1992).
5. K. L. Jackson, J. A. Henderson, H. Motoyoshi, A. J. Phillips, A total synthesis of norhalichondrin B. *Angew. Chem. Int. Ed.* **48**, 2346–2350 (2009).
6. K. L. Jackson, J. A. Henderson, A. J. Phillips, The halichondrins and E7389. *Chem. Rev.* **109**, 3044–3079 (2009).
7. A. Yamamoto, A. Ueda, P. Brémond, P. S. Tiseni, Y. Kishi, Total synthesis of halichondrin C. *J. Am. Chem. Soc.* **134**, 893–896 (2012).
8. A. Ueda, A. Yamamoto, D. Kato, Y. Kishi, Total synthesis of halichondrin A, the missing member in the halichondrin class of natural products. *J. Am. Chem. Soc.* **136**, 5171–5176 (2014).
9. K. Yahata, N. Ye, Y. Ai, K. Iso, Y. Kishi, Unified, efficient, and scalable synthesis of halichondrins: Zirconium/nickel-mediated one-pot ketone synthesis as the final coupling reaction. *Angew. Chem. Int. Ed.* **56**, 10796–10800 (2017).
10. V. Praveen Kumar, Y. Kishi, Total synthesis of halistatins 1 and 2. *J. Am. Chem. Soc.* **142**, 14743–14749 (2020).
11. M. J. Towle *et al.*, *In vitro* and *in vivo* anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B. *Cancer Res.* **61**, 1013–1021 (2001).
12. D. A. Dabydeen *et al.*, Comparison of the activities of the truncated halichondrin B analog NSC 707389 (E7389) with those of the parent compound and a proposed binding site on tubulin. *Mol. Pharmacol.* **70**, 1866–1875 (2006).
13. M. J. Yu, W. Zheng, B. M. Seletsky, From micrograms to grams: Scale-up synthesis of eribulin mesylate. *Nat. Prod. Rep.* **30**, 1158–1164 (2013).
14. A. Bauer, *Story of Eribulin Mesylate: Development of the Longest Drug Synthesis* (Springer International Publishing, Cham, Switzerland, 2016), pp. 209–270.
15. S. Kawano *et al.*, A landmark in drug discovery based on complex natural product synthesis. *Sci. Rep.* **9**, 8656 (2019).
16. Y. Wang *et al.*, Structure-activity relationships of halichondrin B analogues: Modifications at C.30–C.38. *Bioorg. Med. Chem. Lett.* **10**, 1029–1032 (2000).
17. B. M. Seletsky *et al.*, Structurally simplified macrolactone analogues of halichondrin B. *Bioorg. Med. Chem. Lett.* **14**, 5547–5550 (2004).
18. W. Zheng *et al.*, Macrocyclic ketone analogues of halichondrin B. *Bioorg. Med. Chem. Lett.* **14**, 5551–5554 (2004).
19. S. Narayan *et al.*, Novel second generation analogs of eribulin. Part II. Orally available and active against resistant tumors in vivo. *Bioorg. Med. Chem. Lett.* **21**, 1634–1638 (2011).
20. S. Narayan *et al.*, Novel second generation analogs of eribulin. Part I. Compounds containing a lipophilic C32 side chain overcome P-glycoprotein susceptibility. *Bioorg. Med. Chem. Lett.* **21**, 1630–1633 (2011).
21. J. Cortes *et al.*; EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) investigators, Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): A phase 3 open-label randomised study. *Lancet* **377**, 914–923 (2011).
22. A. McBride, S. K. Butler, Eribulin mesylate: A novel halichondrin B analogue for the treatment of metastatic breast cancer. *Am. J. Health Syst. Pharm.* **69**, 745–755 (2012).
23. C. L. Osgood *et al.*, FDA approval summary: Eribulin for patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen. *Clin. Cancer Res.* **23**, 6384–6389 (2017).
24. I. Chabot, Q. Zhao, Y. Su, Systematic review of Real-World effectiveness of eribulin for locally advanced or metastatic breast cancer. *Curr. Med. Res. Opin.* **36**, 2025–2036 (2020).
25. K. C. Nicolaou *et al.*, A reverse approach to the total synthesis of halichondrin B. *J. Am. Chem. Soc.* **143**, 9267–9276 (2021).
26. K. C. Nicolaou *et al.*, A highly convergent total synthesis of norhalichondrin B. *J. Am. Chem. Soc.* **143**, 20970–20979 (2021).
27. G. M. Mahandru, G. Liu, J. Montgomery, Ligand-dependent scope and divergent mechanistic behavior in nickel-catalyzed reductive couplings of aldehydes and alkynes. *J. Am. Chem. Soc.* **126**, 3698–3699 (2004).
28. R. D. Baxter, J. Montgomery, Mechanistic study of nickel-catalyzed ynal reductive cyclizations through kinetic analysis. *J. Am. Chem. Soc.* **133**, 5728–5731 (2011).

29. X.-Q. Tang, J. Montgomery, Nickel catalysis in the stereoselective preparation of quinolizidine, pyrrolizidine, and indolizidine alkaloids: Total synthesis of (+)-allopumiliotoxin 267A. *J. Am. Chem. Soc.* **121**, 6098–6099 (1999).
30. S. Jana, S. C. Roy, Radical promoted cyclizations of aromatic carbonyl compounds to benzopyrans using titanocene(III) chloride. *Tetrahedron Lett.* **47**, 5949–5951 (2006).
31. W. E. Crowe, M. J. Rachita, Titanium-catalyzed reductive cyclization of δ,ε-unsaturated ketones and aldehydes. *J. Am. Chem. Soc.* **117**, 6787–6788 (1995).
32. M. P. Shinde, X. Wang, E. J. Kang, H.-Y. Jang, Platinum-catalyzed hydrogenative cyclization of yne-enones, yne-aldehydes, and yne-dienes. *Eur. J. Org. Chem.*6091–6094 (2009).
33. T. Inokuchi, H. Kawafuchi, S. Torii, Vanadium(II)-promoted cyclization of 5,6-enals or 5,6-ynals. A stereoselective approach to *trans*-2-alkyl- or *trans*-2-alkylidenecyclopentanols. *J. Org. Chem.* **56**, 4983–4985 (1991).
34. D. Herlem, J. Kervagoret, D. Yu, F. Khuong-Huu, A. S. Kende, Studies toward the total synthesis of polyoxygenated labdanes: Preliminary approaches. *Tetrahedron* **49**, 607–618 (1993).
35. D. Herlem, F. Khuong-Huu, A. S. Kende, Studies toward the total synthesis of diterpenes in the labdane series. III. Synthesis of two epimeric 6,7,8-trihydroxylabdadienes. *Tetrahedron* **50**, 2055–2070 (1994).
36. M. A. Rahim, S. Matsumura, K. Toshima, Deprotection of benzyl ethers using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) under photoirradiation. *Tetrahedron Lett.* **46**, 7307–7309 (2005).
37. C. Cavedon *et al.*, Visible-light-mediated oxidative debenzylation enables the use of benzyl ethers as temporary protecting groups. *Org. Lett.* **23**, 514–518 (2021).
38. Y.-R. Yang, D.-S. Kim, Y. Kishi, Second generation synthesis of C27—C35 building block of E7389, a synthetic halichondrin analogue. *Org. Lett.* **11**, 4516–4519 (2009).
39. R. Jimmidi, S. K. R. Guduru, P. Arya, Practical stereoselective synthesis of eribulin fragment toward building a hybrid macrocyclic toolbox. *Org. Lett.* **17**, 468–471 (2015).
40. L. N. Chavan, R. Chegondi, S. Chandrasekhar, Tandem organocatalytic approach to C28–C35 fragment of eribulin mesylate. *Tetrahedron Lett.* **56**, 4286–4288 (2015).
41. K. Mikami, T. Kasuga, K. Fujimoto, T. Nakai, Asymmetric [2,3]Wittig rearrangement involving chiral potassium azaenolates. The dramatic influence of the potassium counterion and its complexation with 18-crown-6. *Tetrahedron Lett.* **27**, 4185–4188 (1986).
42. Y. Ohtsuka, T. Oishi, An effective synthesis of medium-ring ketones. *Tetrahedron Lett.* **20**, 4487–4490 (1979).
43. J. Sim *et al.*, Stereoselective synthesis of 1,4,5-tri-*cis*-guaiane sesquiterpene: First total synthesis of (−)-dendroside C aglycon. *Org. Lett.* **20**, 586–589 (2018).
44. A. M. P. Koskinen, A. J. Pihko, Synthesis of DEFG ring system of cneorins. *ARKIVOC (Gainesville, Fl, USA)* **2008**, 20–35 (2009).
45. M. Corbet, "Applications de la chimie radicalaire des xanthates: Synthèse d'alcaloïdes d'origine marine; Synthèse de thiéno[2,3-*b*]thiopyranones; Synthèse de thioéthers aryliques; Approche à la synthèse totale du (+)-maritimol," PhD dissertation, École polytechnique X, Paris, France (2009).
46. B. Austad, C. E. Chase, F. G. Fang, "Intermediates for the preparation of analogs of halichondrin B." US Patent US 7982060 B2 (2004).
47. Z. Zhang, J. Huang, B. Ma, Y. Kishi, Further improvement on sulfonamide-based ligand for catalytic asymmetric 2-haloallylation and allylation. *Org. Lett.* **10**, 3073–3076 (2008).
48. V. Martí-Centelles, M. D. Pandey, M. I. Burguete, S. V. Luis, Macrocyclization reactions: The importance of conformational, configurational, and template-induced preorganization. *Chem. Rev.* **115**, 8736–8834 (2015).
49. K. T. Mortensen, T. J. Osberger, T. A. King, H. F. Sore, D. R. Spring, Strategies for the diversity-oriented synthesis of macrocycles. *Chem. Rev.* **119**, 10288–10317 (2019).
50. F. G. Fang, D.-S. Kim, H.-W. Choi, C. E. Chase, "Macrocyclization reactions and intermediates and other fragments useful in the synthesis of halichondrin macrolides." US Patent US 10913749 B2 (2019).
51. K. C. Nicolaou, S. P. Ellery, J. S. Chen, Samarium diiodide mediated reactions in total synthesis. *Angew. Chem. Int. Ed.* **48**, 7140–7165 (2009).
52. J. T. S. Yeoman, V. W. Mak, S. E. Reisman, A unified strategy to *ent*-kauranoid natural products: Total syntheses of (−)-trichorabdal A and (−)-longikaurin E. *J. Am. Chem. Soc.* **135**, 11764–11767 (2013).
53. J. Ao, C. Sun, B. Chen, N. Yu, G. Liang, Total synthesis of isorosthin L and isoadenolin I. *Angew. Chem. Int. Ed.* **61**, e202114489 (2022).
54. K. Takai, K. Nitta, O. Fujimura, K. Utimoto, Preparation of alkylchromium reagents by reduction of alkyl halides with chromium(II) chloride under cobalt catalysis. *J. Org. Chem.* **54**, 4732–4734 (1989).
55. G. Pattenden, N. J. Ashweek, C. A. G. Baker-Glenn, G. M. Walker, J. G. K. Yee, Total synthesis of (−)-ulapualide A: The danger of overdependence on NMR spectroscopy in assignment of stereochemistry. *Angew. Chem. Int. Ed.* **46**, 4359–4363 (2007).
56. F.-A. Kang, N. Jain, Z. Sui, Enantioselective synthesis of (8*S*,13*S*,14*R*)-7-oxa-estra-4,9-diene-3,17-dione. *Tetrahedron Lett.* **48**, 193–197 (2007).
57. G. Pattenden *et al.*, Total synthesis of (−)-ulapualide A, a novel tris-oxazole macrolide from marine nudibranchs, based on some biosynthesis speculation. *Org. Biomol. Chem.* **6**, 1478–1497 (2008).
58. A. Fürstner, Carbon–carbon bond formations involving organochromium(III) reagents. *Chem. Rev.* **99**, 991–1046 (1999).
59. L. A. Wessjohann, G. Scheid, Recent advances in chromium(II)- and chromium(III)-mediated organic synthesis. *Synthesis* **1999**, 1–36 (1999).
60. K. Takai, Addition of organochromium reagents to carbonyl compounds. *Org. React.* **64**, 253–612 (2004).
61. A. Gil, F. Albericio, M. Álvarez, Role of the Nozaki–Hiyama–Takai–Kishi reaction in the synthesis of natural products. *Chem. Rev.* **117**, 8420–8446 (2017).
62. B. C. Austad *et al.*, Commercial manufacture of Halaven: Chemoselective transformations en route to structurally complex macrocyclic ketones. *Synlett* **24**, 333–337 (2013).
63. M. Sakaitani, Y. Ohfune, Syntheses and reactions of silyl carbamates. 1. Chemoselective transformation of amino protecting groups via *tert*-butyldimethylsilyl carbamates. *J. Org. Chem.* **55**, 870–876 (1990).