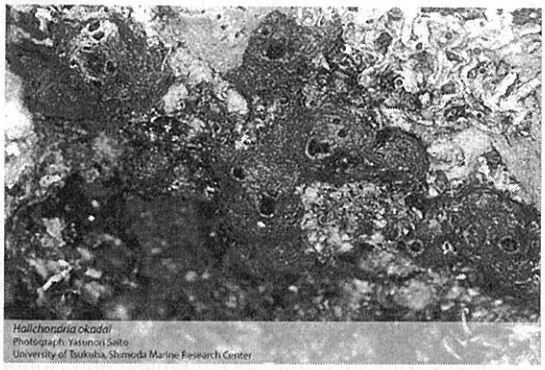
Success Story

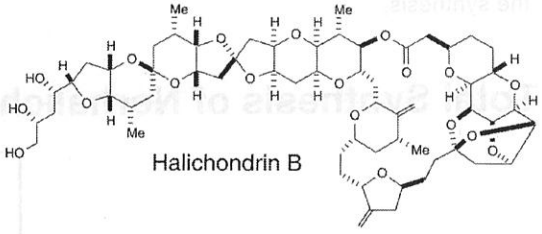
The Halichondrin and E 7389

Literature seminar 03/02/10
Sachiyo Nakanowatari (B4)

1986 Halichondrin B is a macrocyclic polyether initially isolated from the sponge Halichondria okadai received in 1986.



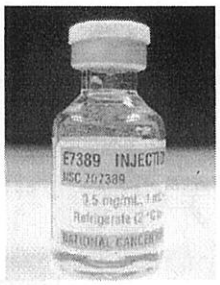
1992 It was accepted for preclinical development by NCI in 1992 after it was found to be highly cytotoxic in murine leukemia cells. Difficulty in collecting sufficient material for developmental studies slowed the progress of this interesting material.

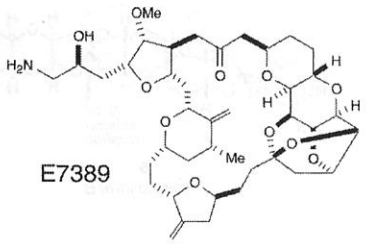


1998 The drug received a new lease on life with the development of a complete synthetic method in 1998 by Dr. Yoshito Kishi of Harvard University and the discovery that its activity resides in the macrocyclic lactone C1-C38 moiety. The way was now open for development of a simplified synthetic analog. Researchers at Eisai Research Institute, who licensed the synthetic technology from Harvard, accomplished the synthesis of the resulting drug, E7389. E7389 was presented to the DDG for preclinical development in 1998.
E7389, like its parent natural compound, is classified as a tubulin depolymerizer, and it shows activity at least equal to the naturally occurring chemical. It acts to disrupt the polymerization of the microtubules necessary in mitosis. This general characteristic places E7389 in the group of drugs that includes Vinca alkaloids, dolastatins, cryptophycin, and so forth, but its tubulin interactions appear to be unique, and it was found to have greater activity against lung and breast tumors in animal studies than either the parent halichondrin B or paclitaxel.

NATIONAL CANCER INSTITUTE

Dr.Yoshito Kishi





2002 E7389 entered phase I clinical trials in 2009 global phase III study results show E7389 meets primary endpoint of overall survival. E7389 is now in their final stage to be approved shortly.

(This text was cited from NCI homepage;
http://dtp.nci.nih.gov/timeline/noflash/success_stories/S4_halichondrinB.htm)

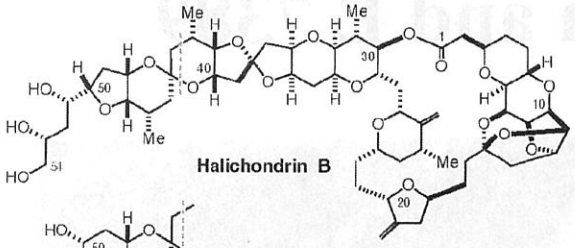
Eisai hhc human health care

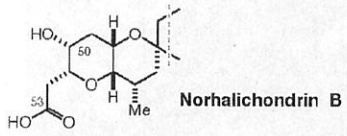
Contents

eribulin
(eribulin mesylate)

eribulin; E7389's generic name

1. Introduction





-Isolated from the sponges *Halichondria okadai* (Hirata and Uemura, 1986), *Axinella* species (Pettit et al., 1991), and *Lissodendoryx* species (Litaudon et al., 1997)

-posesess an unusual steucture;
2,6,9-trioxatricyclo[3.3.2.0]decane ring system, as well as a 22-membered macrolactone ring, two exocyclic olefins, and an array of polyoxygenated pyran and furan rings

- Only 12.5mg of Halichondrin B was isolated from 600kg of wet sponge

- showed the impressive biological activity;
IC_{50} of 0.093 ng /ml against B-16 melanoma cells

- noncompetitive inhibitors of vinca alkaloids that occupy the vinca- binding domain on tubulin, suppress the growth of microtubules, and inhibit polymerization, thereby inducing cell cycle arrest and apoptosis

- Synthesized by Kishi and co-workers first in 1992, second by Phillips and co-workers in 2009. Synthetic work by Burke, byYonemitsu and Horita, and by Salmon but none of them have yet to report the completition of the synthesis.

2. Total Synthesis of Norhalichondrin B by Kishi and Co-workers

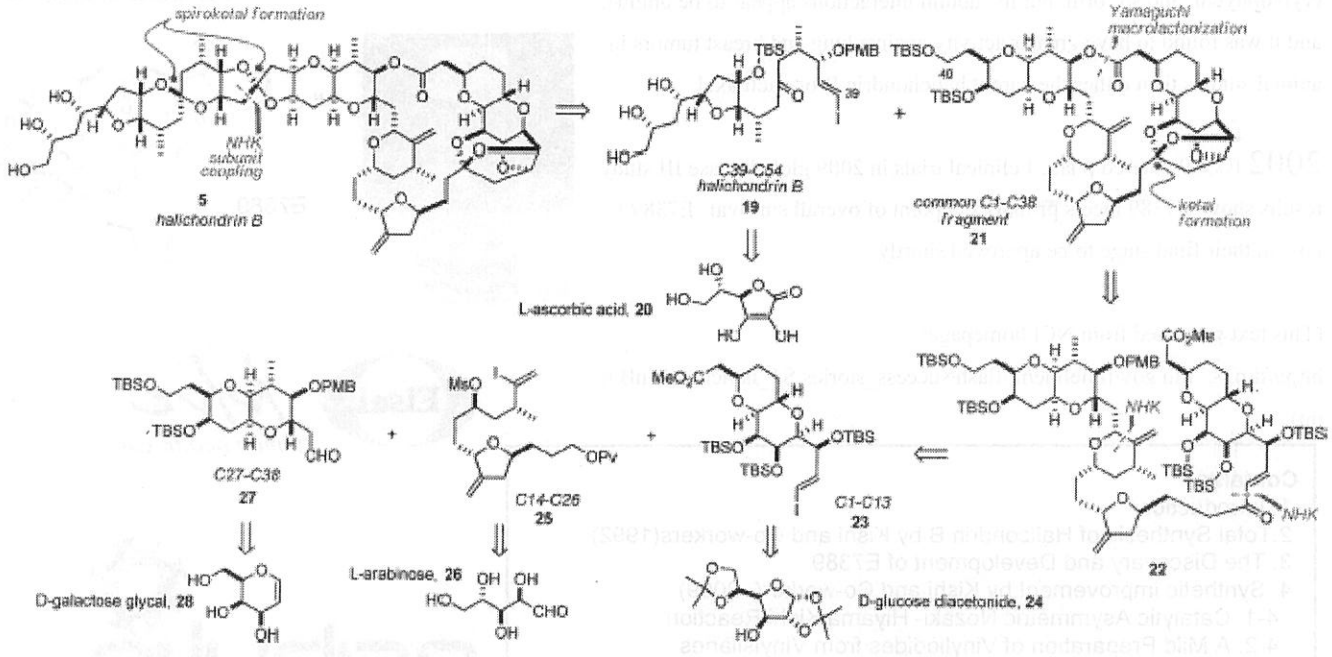
A Ground-Breaking Piece of Work

Total Synthesis of Halichondrin B and Norhalichondrin B

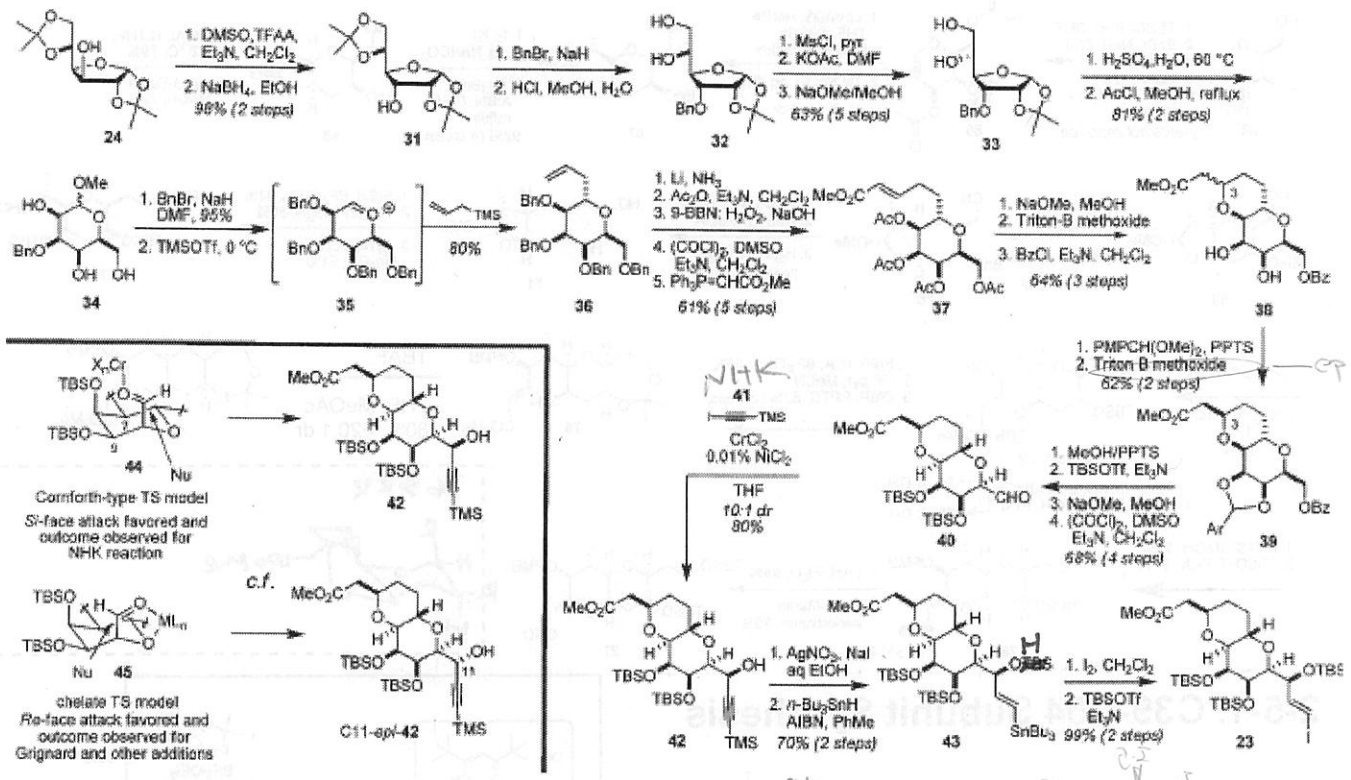
Thomas D. Aicher, Keith R. Buszek, Francis G. Fang, Craig J. Forsyth, Sun Ho Jung, Yoshito Kishi,* Michael C. Matelich, Paul M. Scola, Denice M. Spero, and Suk Kyoon Yoon

J. Am. Chem. Soc. **1992**, *114*, 3162–3164

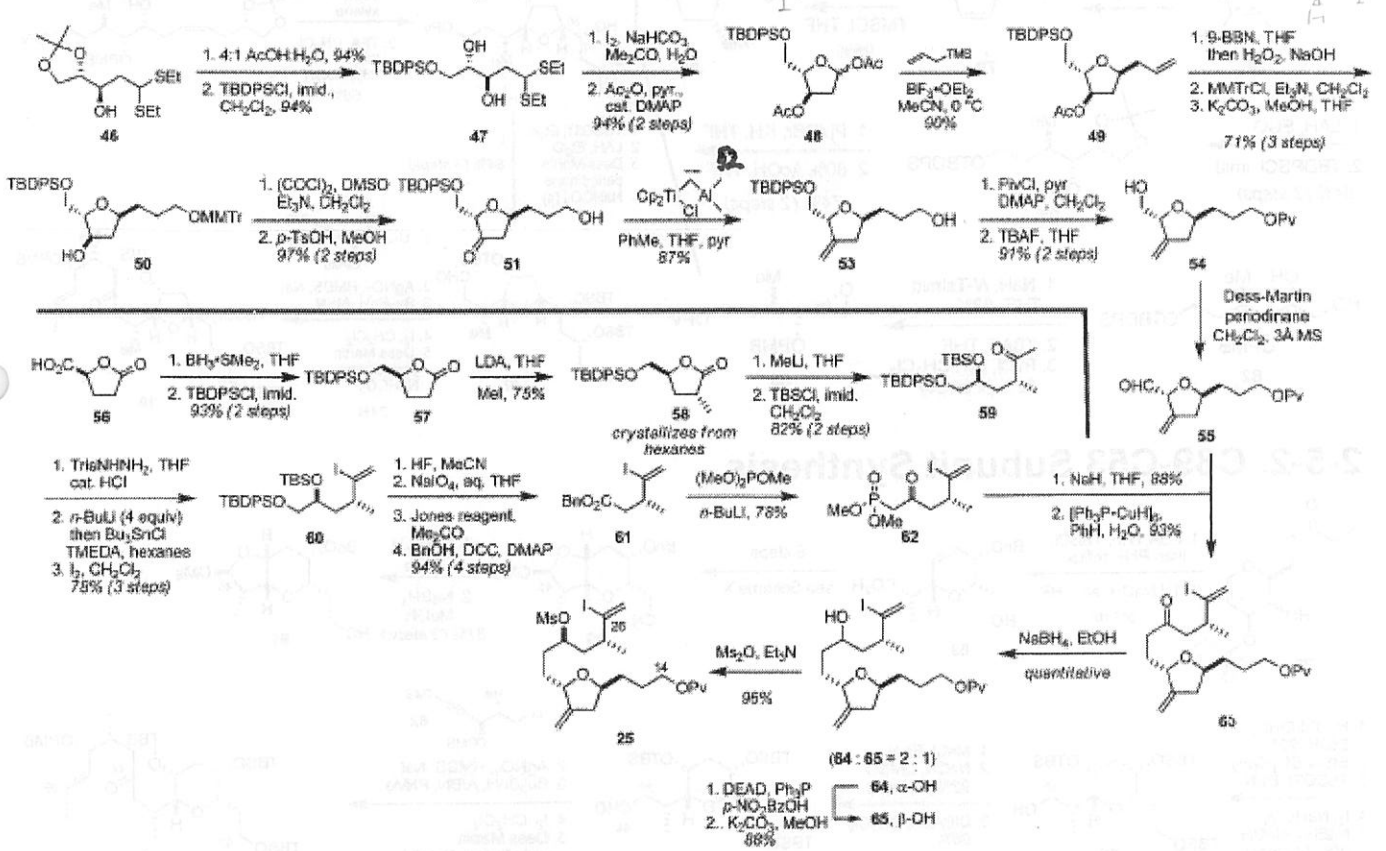
2-1. The Kishi's Strategy



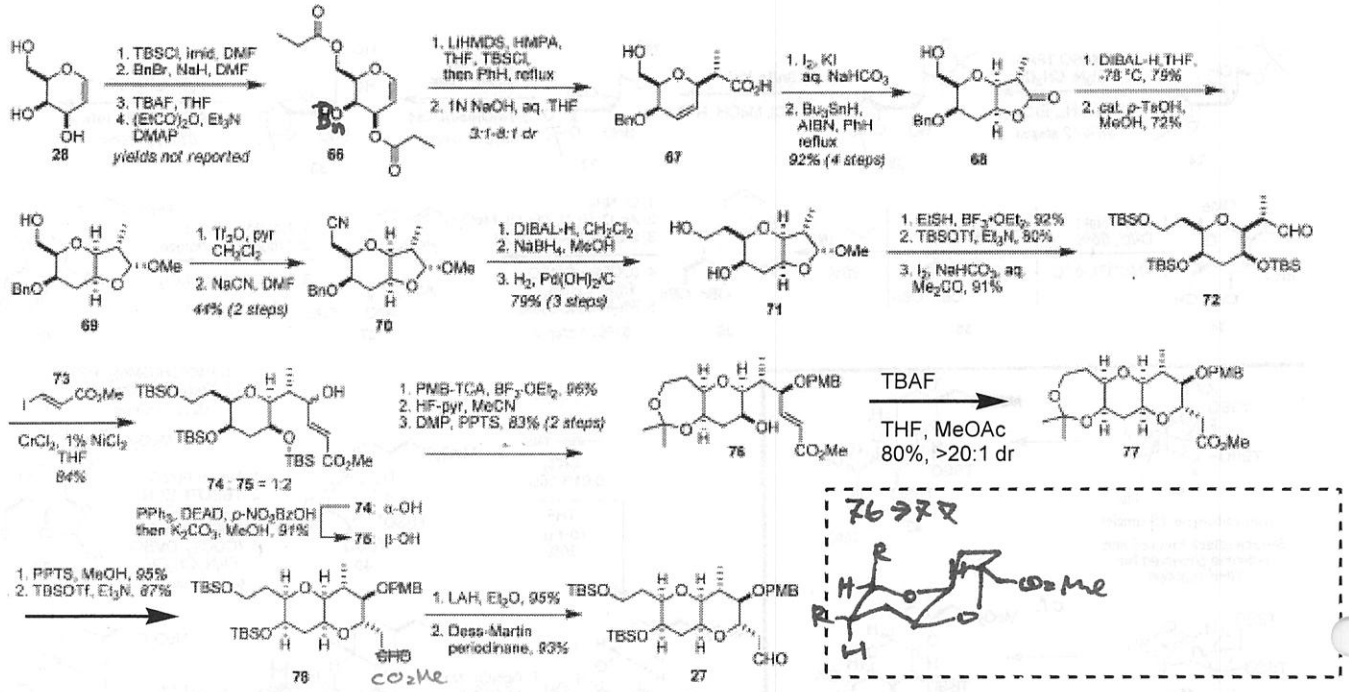
2-2. C1-C13 Subunit Synthesis



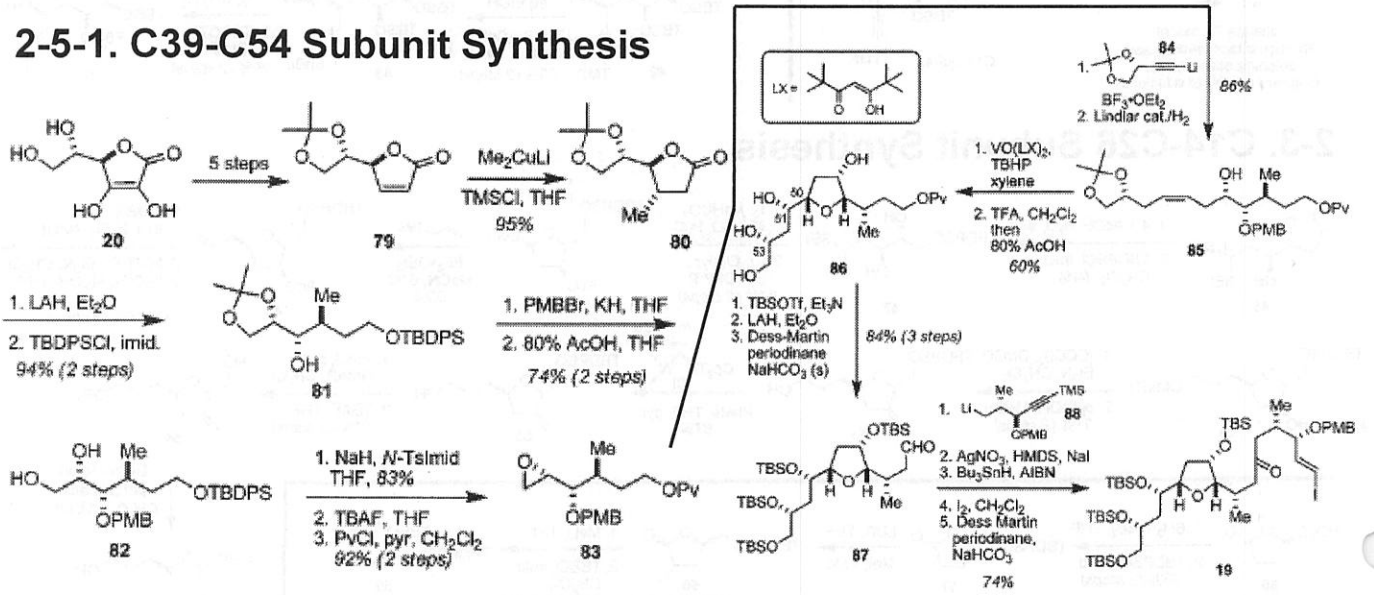
2-3. C14-C26 Subunit Synthesis



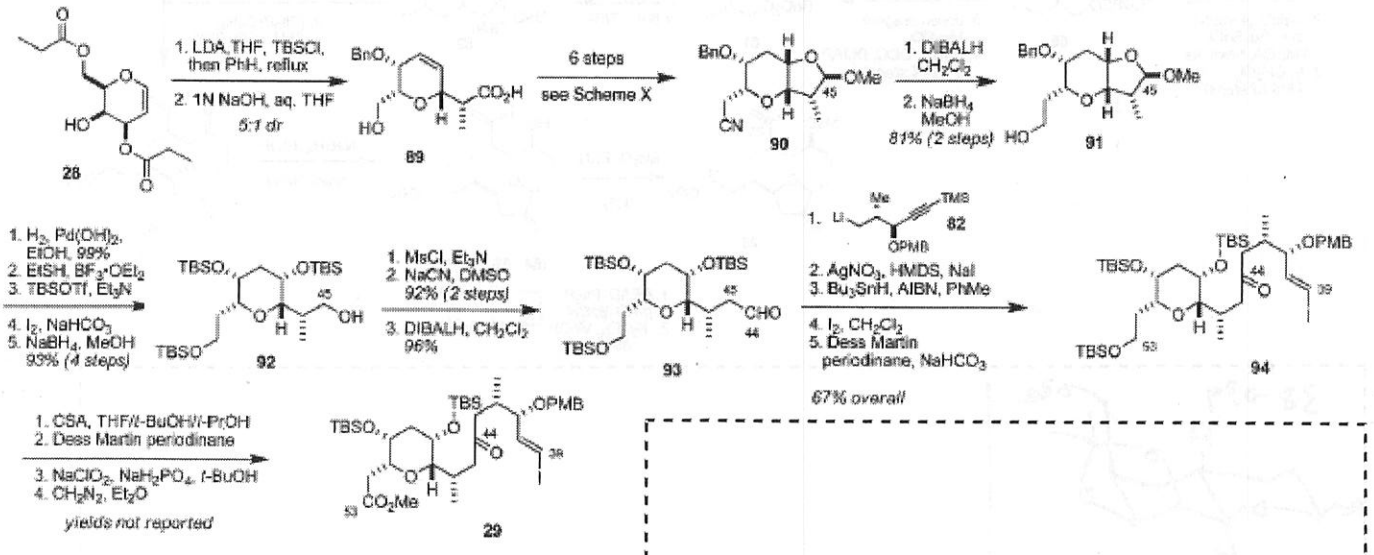
2-4. C27-C38 Subunit Synthesis



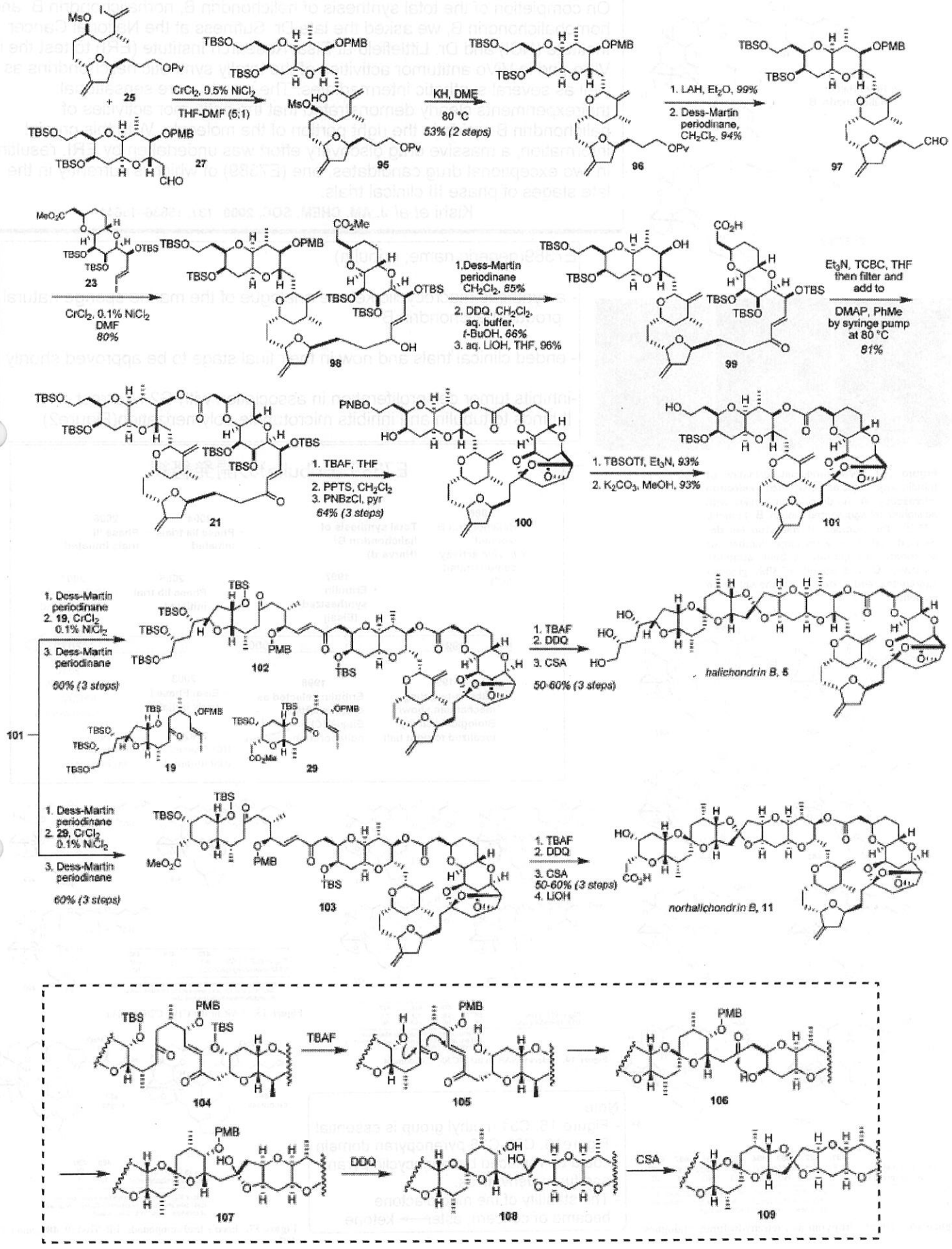
2-5-1. C39-C54 Subunit Synthesis



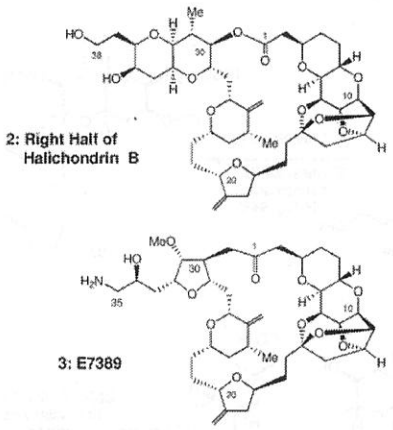
2-5-2. C39-C53 Subunit Synthesis



2-6. Subunit Couplings and Completionof the Synthesis



3. The Discovary and Development of E7389



On completion of the total synthesis of halichondrin B, norhalichondrin B, and homohalichondrin B, we asked the late Dr. Suffness at the National Cancer Institute (NCI) and Dr. Littlefield at Eisai Research Institute (ERI) to test the in Vitro and in ViVo antitumor activities of the totally synthetic halichondrins as well as several synthetic intermediates. The results were sensational: theirexperiments clearly demonstrated that the antitumor activities of halichondrin B reside in the right portion of the molecule. With this crucial information, a massive drug discovery effort was undertaken by ERI, resulting in two exceptional drug candidates, one (E7389) of which is currently in the late stages of phase III clinical trials.

Kishi *et al* **J. AM. CHEM. SOC. 2009**, *131*, 15636–15641

E7389(generic name; eribulin)

- a synthetic macrocyclic ketone analogue of the marine sponge natural product halichondrin B

- ended clinical trials and now in their final stage to be approved shortly

-inhibits tumor cell proliferation in association with G2-M arrest.
It binds to tubulin and inhibits microtubule polymerization(Figure2)

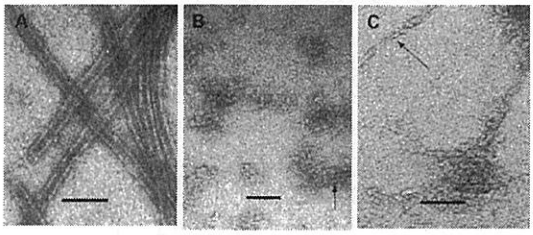
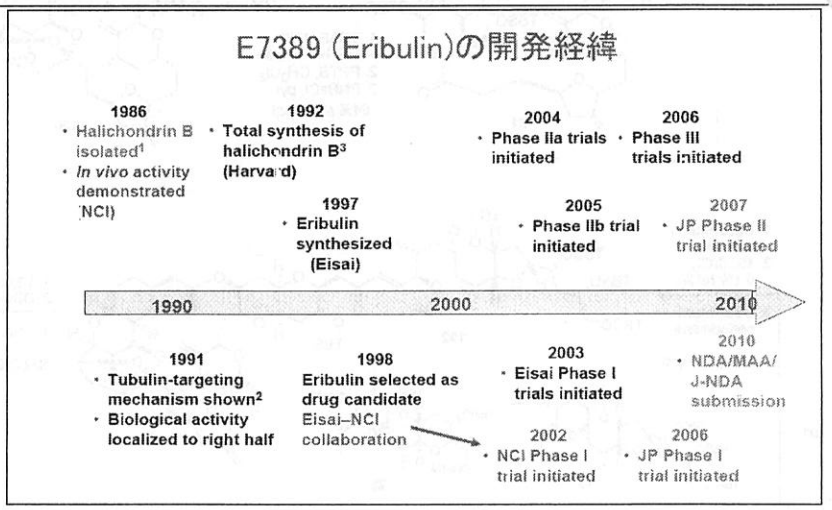
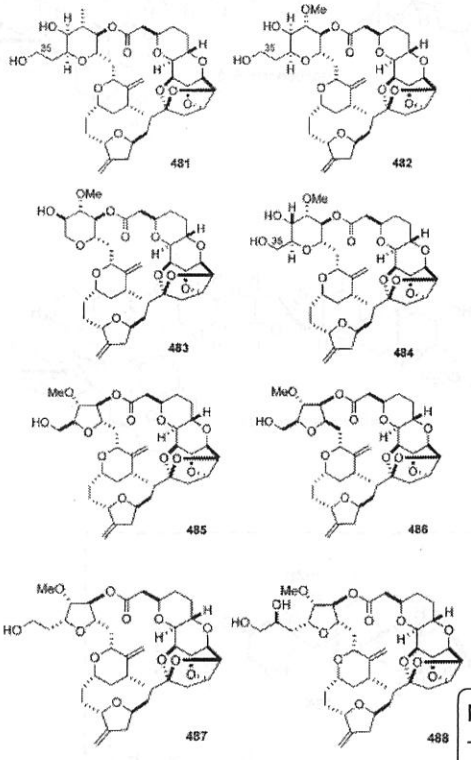


Figure 2. E7389-induced formation of tubulin aggregates as determined by electron microscopy. **A**, no drug, microtubules with no significant aggregated tubulin. **B**, 1 μmol/L E7389, the number of microtubules decreased and there were large numbers of aggregates of globular tubulin subunits (*arrows*). **C**, 3.3 μmol/L E7389, globular aggregates and sheets (not shown) were present.

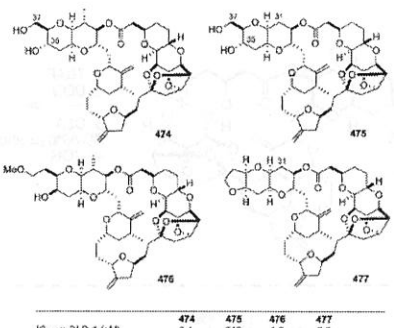




	481	482	483	484	485	486	487	488
IC_{50} vs DLD-1 (nM)	2.5	1.9	>1000	2.0	1	>1000	0.97	0.67
U937 reversibility ratio*	17	30	ND	22	33	ND	14	10

* ratio of IC_{50} for induction of complete mitotic block in U937 cells after 12h of treatment to IC_{50} for maintenance of complete mitotic block 10 hours later

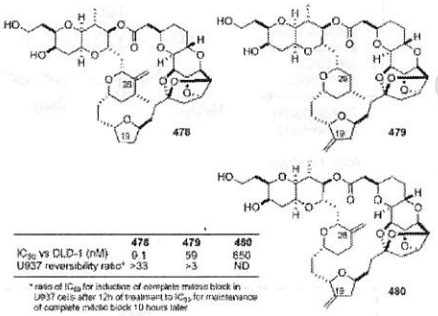
Figure 16. Tetrahydropyran and tetrahydrofuran analogues.



	474	475	476	477
IC_{50} vs DLD-1 (nM)	3.4	610	1.2	2.6
U937 reversibility ratio*	24	ND	>93	50

* ratio of IC_{50} for induction of complete mitotic block in U937 cells after 12h of treatment to IC_{50} for maintenance of complete mitotic block 10 hours later

Figure 14. Selected SAR in the ~C30–C38 domain.

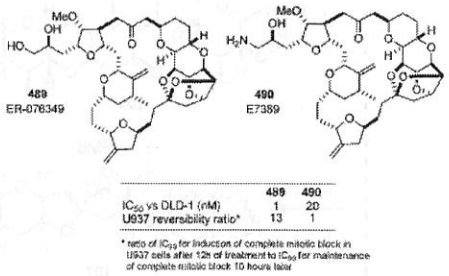


	478	479	480
IC_{50} vs DLD-1 (nM)	0.1	59	650
U937 reversibility ratio*	>33	>3	ND

* ratio of IC_{50} for induction of complete mitotic block in U937 cells after 12h of treatment to IC_{50} for maintenance of complete mitotic block 10 hours later

Figure 15. SAR in the C19–C26 domain.

Note
- Figure 15. C31 methyl group is essential
- Figure16. C29-C36 pyranopyran domain could be replaced by monocyclic pyran and furan derivatives.
- The stability of the macrolactone became of concern; ester⟶ ketone



	489	490
IC_{50} vs DLD-1 (nM)	1	20
U937 reversibility ratio*	13	1

* ratio of IC_{50} for induction of complete mitotic block in U937 cells after 12h of treatment to IC_{50} for maintenance of complete mitotic block 10 hours later

Figure 17. Eisai's lead compounds: ER-076439, **489**, and E7389, **490**.

4. Further Improvement by Kishi and Co-workers

Although Kishi and co-worker achieved total synthesis of Halicondrin B in 1991, they have continued to refine their chemistry toward Halichondrin and E7389. These improvements include;

5-1. Catalytic Asymmetric Nozaki- Hiyama Kishi Reaction
5-2. A Mild Preparation of Vinyliodides from Vinylsilanes
5-3. Effective Procedure for Slective Ammonolisis of Monosubstituted Oxiranes
5-4. Operationally Simple and Efficient Workup Procedure for TBAF-Mediated Desilylation
5-5. Refine Approach to a Number of Fragments

4-1. Catalytic Asymmetric Nozaki- Hiyama Kishi Reaction

ORGANIC LETTERS
2004
Vol. 6, No. 26
5031−5033

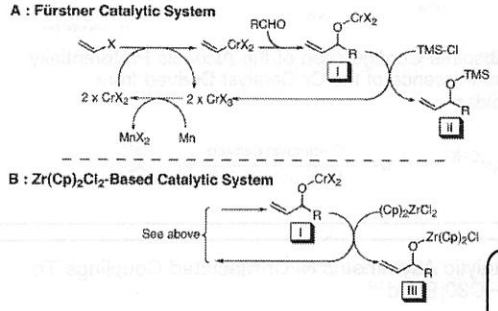
TMS-Cl as a dissociating agent(Cr-O)
Mn(0) as a reducing agent

Problem;
under TMS-Cl condition, with low catalyst-loading, asymmetric catalytic couplings smoothly progress only to a certain degree but not tocompletion.
This was due to the formation of TMS-enol ethers of aldehydes.

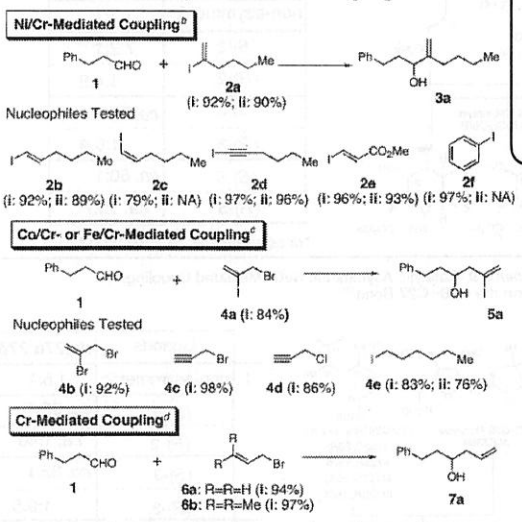
zirconocene indeed smoothly exchanges its chloride ligand(s) with an alkoxy group

- with small modifications, this catalytic process is effective for all three subgroups of Cr-mediated couplings
  i.e., (1) Ni/Cr-mediated alkenylation,
  (2) Co/Cr- and Fe/Cr-mediated 2-haloallylation alkylation
  (3) Cr-mediated allylation
- the catalyst loading can be lowered to 5 mol % without significant losses in chemical yields.
- Cp_2ZrCl_2 was found to be best
- manganese metal (powder) was best

Scheme 1



Scheme 2. Catalytic Cr-Mediated Coupling Reactions[a]



[a] **i** and **ii**: isolated yields with 10 and 5 mol % catalyst, respectively. [b] **1** (1.0 equiv), **2a**−**f** (2.0 equiv), sulfonamide (11 or 6 mol %), $CrCl_2$ (10 or 5 mol %), proton sponge or $(i\text{-Pr})_2(Et)N$ (11 or 6 mol %), $NiCl_2(dppp)$ (2 or 1 mol %), Cp_2ZrCl_2 (1.0 equiv), Mn (2.0 equiv), LiCl (2.0 equiv), MeCN (c = 0.2 M), rt. [c] **1** (1.0 equiv), **4a**−**e** (2.5 equiv), sulfonamide ligand (11 mol %), $CrBr_3$ (10 mol %), $(i\text{-Pr})_2(Et)N$ or $(Et)_3N$ (11 mol %), CoPc (0.2 mol %), Cp_2ZrCl_2 (1.0 equiv), Mn (3.0 equiv), 2,6-lutidine (11 mol %), THF (c = 0.2 M), 0 °C. [d] **1** (1.0 equiv), **6a,b** (2.0 equiv), $CrCl_3$−3THF (10 mol %), sulfonamide ligand (11 mol %), $(i\text{-Pr})_2(Et)N$ or $(Et)_3N$ (11 mol %), Mn (3.0 equiv), 2,6-lutidine (11 mol %), THF (c = 0.2 M), 0 °C.

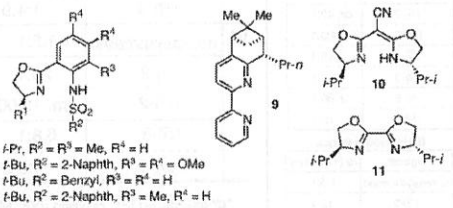
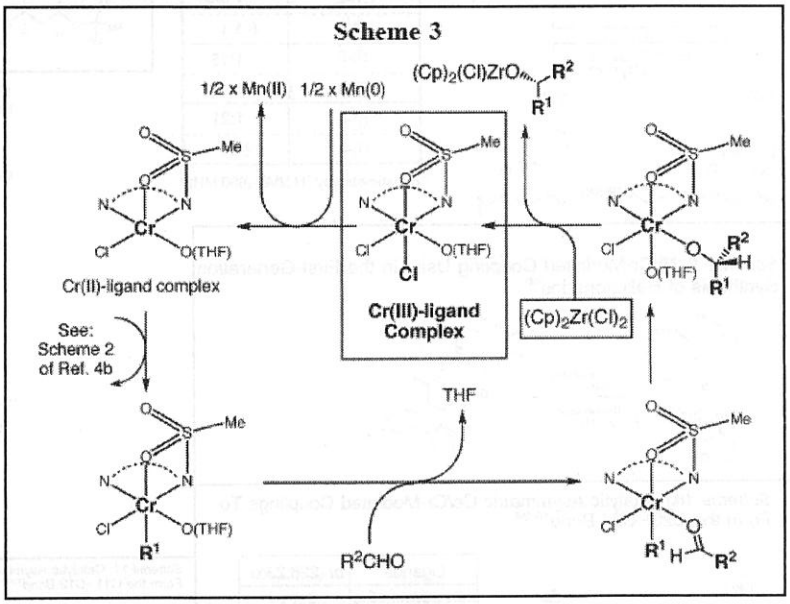


Figure 1. Chiral ligands for Ni/Cr-mediated couplings.

Scheme 3



Conclusion

$Zr(Cp)_2Cl_2$ is a more effective dissociating agent

The difference between TMS-Cl and $Zr(Cp)_2Cl_2$

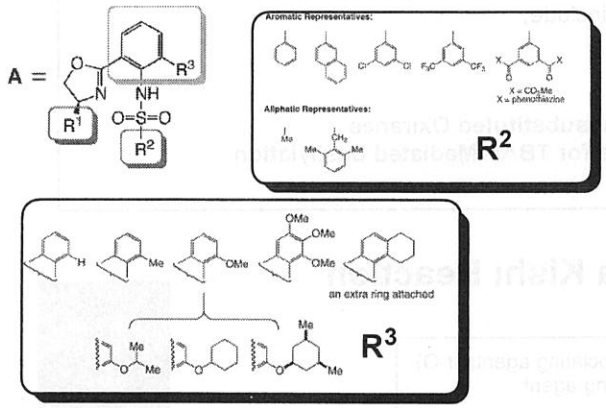
- the catalytic Cr-mediated coupling in the presence of TMS-Cl does not proceed to completion for enolizable aldehydes

- the coupling rate with $Zr(Cp)_2Cl_2$ is significantly faster than that with TMS-Cl ;effective for regenerating
  it is now possible to achieve the Cr-mediated coupling reactions in the presence of 1 mol % of the Cr catalyst

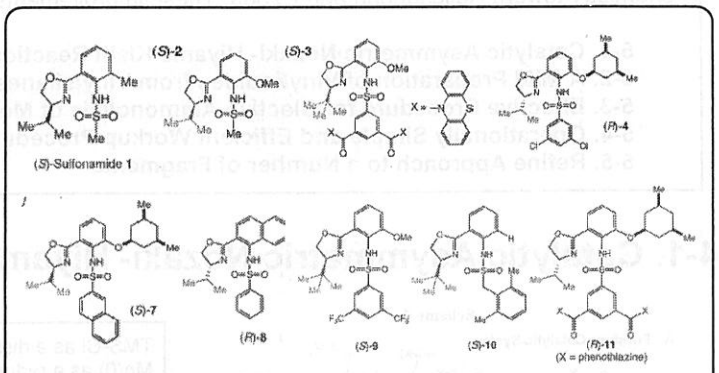
Toolbox Approach to the Search for Effective Ligands for Catalytic Asymmetric Cr-Mediated Coupling Reactions

development of a ligand-search strategy applicable to a broad range of substrates

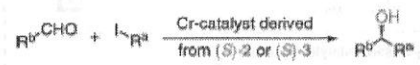
J. AM. CHEM. SOC. 2009, 131, 15387–15393



With three distinct sites (R^1, R^2, R^3) for structure modification, **A** (Figure above) provides us with access to structurally diverse chiral sulfonamides.

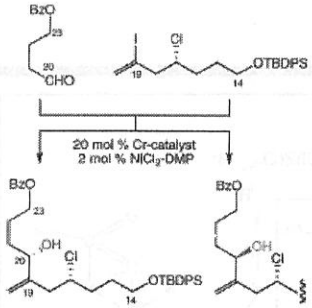


Scheme 5. Absolute Configuration of the Alcohols Preferentially Formed in the Presence of the Cr Catalyst Derived from (*S*)-Sulfonamides



Using the diverse C-C bond-forming cases selected from the halichondrin synthesis, we then demonstrate that a satisfactorychiral ligand can indeed be found from this pool.

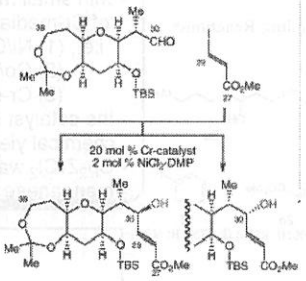
Scheme 6. Catalytic Asymmetric Ni/Cr-Mediated Couplings To Form the C19–C20 Bond[19]



Ligands	*dr* (20α:20β)*
non-asymmetric	1.2:1
(*S*)-2	1:8.0
(*R*)-2	8.1:1
(*S*)-3	1:15
(*R*)-3	16:1
(*S*)-4	1:21
(*R*)-4	24:1

*dr estimated by ^{1}H NMR (600 MHz)

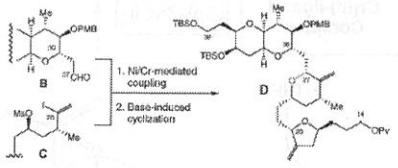
Scheme 7. Catalytic Asymmetric Ni/Cr-Mediated Couplings To Form the C29–C30 Bond[19]



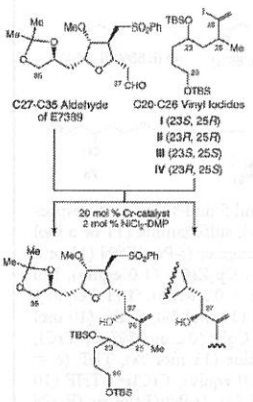
Ligands	*dr* (30β:30α)*
non-asymmetric	1.1:1
(*S*)-2	7.2:1
(*R*)-2	1:4.8
(*S*)-3	*ca.* 37:1
(*R*)-3	1:6.4
(*S*)-5	*ca.* 60:1
(*R*)-5	*ca.* 1:27

*dr estimated by ^{1}H NMR (600 MHz)

Scheme 8. Ni/Cr-Mediated Coupling Used in the First-Generation Synthesis of Halichondrins[6b]



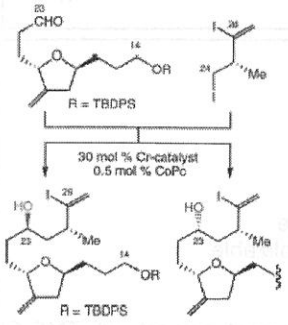
Scheme 9. Catalytic Asymmetric Ni/Cr-Mediated Couplings To Form the C26–C27 Bond[19]



	Ligands	*dr* (27α:27β)*
I	non-asymmetric	1.5:1
	(*S*)-2	*ca.* 36:1
	(*R*)-2	*ca.* 1:40
	(*S*)-3	*ca.* 32:1
	(*R*)-3	1:9.5
II	non-asymmetric	1.5:1
	(*S*)-2	14:1
	(*R*)-2	1:25
	(*S*)-6	*ca.* 47:1
	(*S*)-3	7.5:1
	(*R*)-3	1:11
III	non-asymmetric	1:1.7
	(*S*)-2	22:1
	(*R*)-2	*ca.* 1: 26
	(*S*)-3	5.0:1
	(*R*)-3	1:4.9
IV	non-asymmetric	1.5:1
	(*S*)-2	25:1
	(*R*)-2	*ca.* 1:100
	(*S*)-3	6.8:1
	(*R*)-3	1:5.2

*dr estimated by ^{1}H NMR (600 MHz)

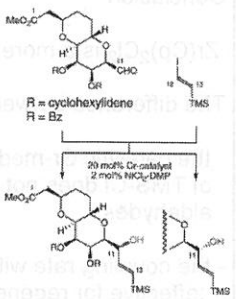
Scheme 10. Catalytic Asymmetric Co/Cr-Mediated Couplings To Form the C23–C24 Bond[19,24]



Ligands	*dr* (23β:23α)*
non-asymmetric	2.5:1
(*S*)-2	9.9:1
(*R*)-2	1:3.7
(*S*)-3	8.4:1
(*R*)-3	1:1.0
(*S*)-4	*ca.* 33:1
(*S*)-7	22:1
(*R*)-8	1:8.1

*dr estimated by ^{1}H NMR (600 MHz)

Scheme 11. Catalytic Asymmetric Ni/Cr-Mediated Couplings To Form the C11–C12 Bond[19]



Cyclohexylidene Series

Ligands	*dr* (11β:11α)*
non-asymmetric	2.0:1
(*S*)-2	*ca.* 42:1
(*R*)-2	4.6:1
(*S*)-3	6.8:1
(*R*)-3	1.5:1
(*S*)-9	*ca.* 80:1
(*R*)-9	10:1

Bisbenzoate Series

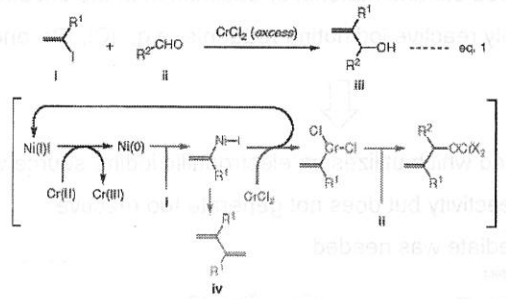
Ligands	*dr* (11β:11α)*
non-asymmetric	1.5:1
(*S*)-2	12:1
(*R*)-2	1:2.6
(*S*)-3	2.3:1
(*R*)-3	1:1.7
(*S*)-10	*ca.* 56:1
(*R*)-11	1:23

*dr estimated by ^{1}H NMR (600 MHz)

Dramatic Improvement in Catalyst Loadings and Molar Ratios of Coupling Partners for Ni/Cr-Mediated Coupling Reactions: Heterobimetallic Catalysts

J. AM. CHEM. SOC. ■ VOL. 131, NO. 46, 2009

Scheme 1. Ni/Cr-Mediated Coupling Reaction and Probable Reactive Intermediates

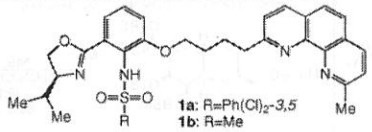


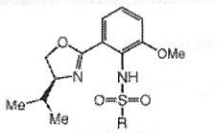
Problem;

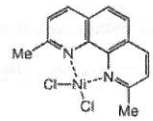
- the formation of dimer(byproduct); keep a low ratio of Ni to Cr salts
- a sligiht exess(typically 1.5 equiv) of an alkenyl halide is needed to ensure complete consumption of an aldehyde

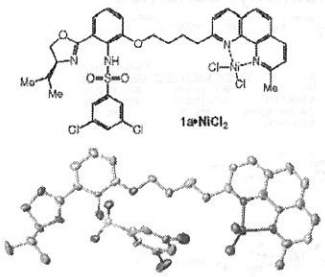
-----both problems are connected with the efficiency of the alkenyl-group transfer from nickel to chromium, i.e., reaction of alkenyl Ni(II) halide to give alkenyl Cr(III) halide rather than iv.

To enhance the transmetalation
- Place Ni and Cr metals in close proximity;
a ligand bearing two ligation sites, onecomplexed specifically to Cr and the other to Ni.



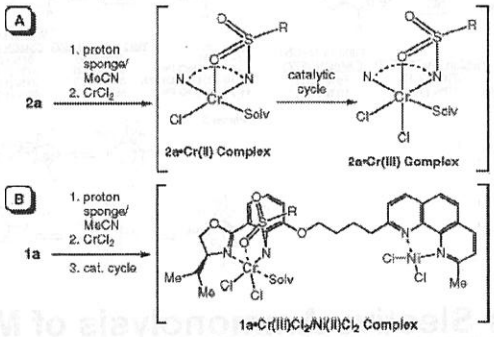






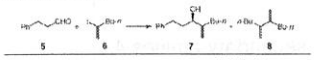
X-ray structure of 1a·$NiCl_2$.

Scheme 2. Proposed Structure of the Catalyst 1a·$CrCl_2$/$NiCl_2$[a]



[a] (A) Cr(II) and Cr(III) complexes derived from sulfonamide 2a (R = $PhCl_2$-3,5). (B) Cr(III) complex derived from tethered sulfonamide 1a (R = $PhCl_2$-3,5). Solv represents the fifth and sixth neutral ligands for the Cr(II) and Cr(III) complexes, respectively.

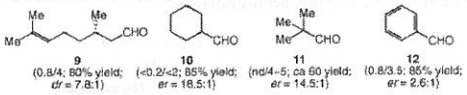
Table 1. Catalytic Asymmetric Ni/Cr-Mediated Coupling Reactions with 1a,b-$CrCl_2$/$NiCl_2$[a]



entry	cat.	Cr (%)[b]	5/6[c]	[C] (M)	t (h)[d]	Prod. dist. (%)[e] 7	8	5	8[f]
1	1a	1	1/1	0.4	1/20/28	>97	<3	~0	10.2:1
2	1a	1	1/1	0.8	1/20/24	>96	<4	~0	10.2:1
3	1a	1	1/1.1	0.8	1/14/20	>97	<3	~0	10.1:1
4	1a	2	1/1	0.8	1/4/6	>97	<3	~0	10.0:1
5	1a	2	1/1.1	0.8	0.5/1/1.5	~97	~3	~0	10.3:1
6	1b	1	1/1	0.8	1/14/20	>96	<4	~0	5.1:1
7	1b	1	1/1.1	0.8	1/14/18	>95	<5	~0	5.2:1
8[g]	2a/3	2/2	1/1.1	0.8	~5[h]	45	55	55	8.6:1
9[g]	2a/3	10/2	1/1.5	0.4	1/2/4	90	10	~0	9.8:1

[a] Coupling conditions employed for entries 1–7: catalyst/Mn (2 equiv)/ZnCl$_2$(py)$_2$ (1.2 equiv)/LiCl (0.5 or 2.0 equiv)/MeCN/rt. Couplings in entries 8 and 9 were conducted under the previously established conditions.[4b] Chromatographically homogeneous 7 was isolated in >90% yield for entries 1–7, 90% for entry 9, and 43% for entry 8. For details, see the Supporting Information. [b] Catalyst loading (mol %). [c] Molar ratio of 5 and 6. [d] Times for 50/90/100% conversion, as estimated by TLC. [e] Product distribution estimated from ^{1}H NMR spectra of crude products. [f] Enantiomeric ratio estimated from ^{1}H NMR spectra of Mosher esters derived from 7. [g] Because 3 was not completely soluble in MeCN at this concentration, a 5:1 mixture of MeCN and THF was used. [h] The product distribution was studied when 5 was completely consumed (~5 h). [i] Coupling was stopped when 5 was completely consumed (~4 h).

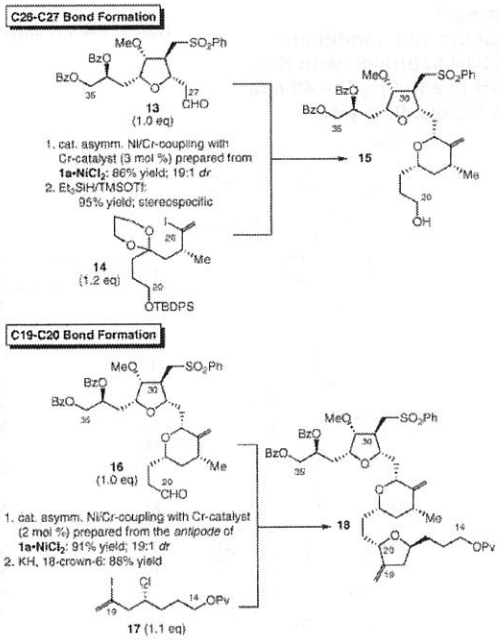
Table 2. Catalytic Asymmetric Ni/Cr-Mediated Couplings of 6 with Representative Aldehydes Using the Antipode of 1a·$CrCl_2$/$NiCl_2$[a]



9	10	11	12
(0.8/4; 80% yield; dr = 7.8:1)	(<0.2/<2; 85% yield; er = 16.5:1)	(nd/4–5; ca 60 yield; er = 14.5:1)	(0.8/3.5; 85% yield; er = 2.6:1)

[a] Coupling conditions: see Table 1. Numbers in parentheses indicate (1) ~50%/~100% conversion time (h) with 2 mol % catalyst loading, except for 10 (1 mol %), (2) isolated yield, and (3) stereoselectivity, respectively. Because of the high volatility of 11, it was technically difficult to estimate the ~50% conversion time and yield.

Scheme 3. C26–C27 and C19–C20 Bond Formations

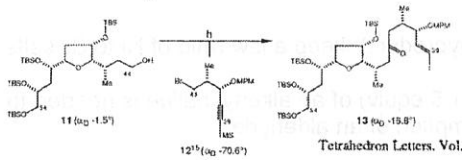


Delightful Results

- even with 1 mol % catalyst loading, the coupling progressed to completion in MeCN, furnishing the coupled product in >90% yield (entries 1-3)
- only a small amount of dimer 8 (e3%) was observed; thus, the coupling reached completion even with a 1:1 molar ratio of 5 and 6 (entries 1, 2, 4, and 6).
- the asymmetric induction by 1a,b- CrCl2/NiCl2 was practically identical with that by the corresponding previous Cr catalysts derived from (S)-sulfonamides 2a,b (entries 1-5 vs entry 9).
- the coupling rate was slightly higher at a substrate concentration of 0.8 M than at 0.4 M, but no significant difference was noticed in the coupling yields (entry 1 vs entry 2).

4-2. A Mild Preparation of Vinyliodides from Vinylsilanes

cf.their first synthesis of C1-C13 subunit synthesis



Tetrahedron Letters, Vol. 33, No. 12, pp. 1553-1556, 1992

(h) 1. Dess-Martin reagent[16]/CH_2Cl_2/RT. 2.

12[15]/*t*-BuLi/Et_2O/-78 °C, followed by treatment with the aldehyde at -78 °C. 3. $AgNO_3$ (6 equiv)/HMDS (7 equiv)/H_2O-EtOH (1:4)/RT. 4. *n*-Bu_3SnH/AIBN/toluene/80 °C. 5. I_2/CH_2Cl_2/RT. 6. same as step h.1.

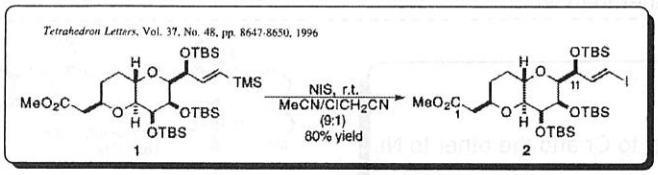
Problem;

recovered startind material or decimation of the substrate by highly reactive iodinating reagents, e.g., ICl, IBr, and IBF_4

⇩

a method which utilizes an electrophilic iodine source with highl reactivity but does not generate too reactive intermediate was needed.

A.



Tetrahedron Letters, Vol. 37, No. 48, pp. 8647-8650, 1996

NIS, r.t. MeCN/$ClCH_2CN$ (9:1) 80% yield

1 → 2

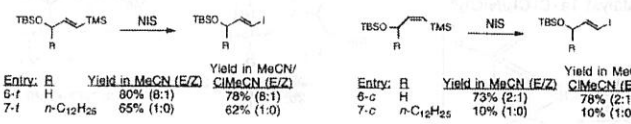
A: Aliphatic vinylsilanes

Entry	R	Yield in MeCN (E/Z)	Yield in MeCN/ClMeCN (E/Z)
1-*t*	*n*-hexyl	79% (2.8:1)	75% (2.8:1)
2-*t*	*i*-butyl	74% (1:0)	72% (1:0)
3-*t*	*t*-butyl	65% (1:0)	60% (1:0)
4-*t*	phenyl	95% (1:0)	95% (1:0)
5-*t*	4-formyl-phenyl	90% (1:0)	90% (1:0)

Entry	R	Yield in MeCN (E/Z)	Yield in MeCN/ClMeCN (E/Z)
1-*c*	*n*-hexyl	80% (1.2:1)	80% (1.2:1)
2-*c*	*i*-butyl	64% (1:12)	68% (1:12)
3-*c*	*t*-butyl	65% (0:1)	65% (0:1)
4-*c*	phenyl	95% (0:1)	95% (0:1)
5-*c*	4-formyl-phenyl	91% (0:1)	90% (0:1)

with bulkier allylic carbons, better overall retention of olefin geometry; scheme2

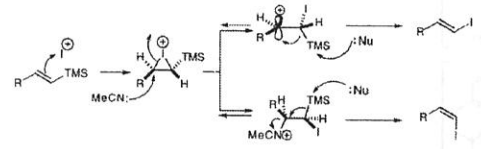
B: Silylated allylic alcohol-vinylsilanes



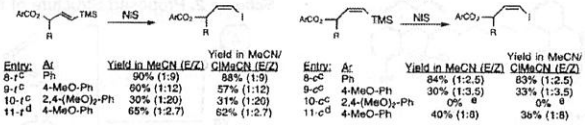
Entry	R	Yield in MeCN (E/Z)	Yield in MeCN/ClMeCN (E/Z)
6-*t*	H	80% (8:1)	78% (8:1)
7-*t*	n-$C_{12}H_{25}$	65% (1:0)	62% (1:0)

Entry	R	Yield in MeCN (E/Z)	Yield in MeCN/ClMeCN (E/Z)
6-*c*	H	73% (2:1)	78% (2:1)
7-*c*	n-$C_{12}H_{25}$	10% (1:0)	10% (1:0)

Scheme 2



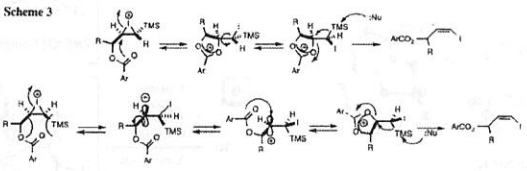
C: Acylated allylic alcohol-vinylsilanes *cis*-selectivity; scheme3



Entry	Ar	Yield in MeCN (E/Z)	Yield in MeCN/ClMeCN (E/Z)
8-*t*[c]	Ph	90% (1:9)	88% (1:9)
9-*t*[c]	4-MeO-Ph	60% (1:12)	57% (1:12)
10-*t*[c]	2,4-$(MeO)_2$-Ph	30% (1:20)	31% (1:20)
11-*t*[d]	4-MeO-Ph	65% (1:2.7)	62% (1:2.7)

Entry	Ar	Yield in MeCN (E/Z)	Yield in MeCN/ClMeCN (E/Z)
8-*c*[c]	Ph	84% (1:2.5)	83% (1:2.5)
9-*c*[c]	4-MeO-Ph	30% (1:3.5)	33% (1:3.5)
10-*c*[c]	2,4-$(MeO)_2$-Ph	0% [e]	0% [e]
11-*c*[d]	4-MeO-Ph	40% (1:0)	36% (1:8)

Scheme 3



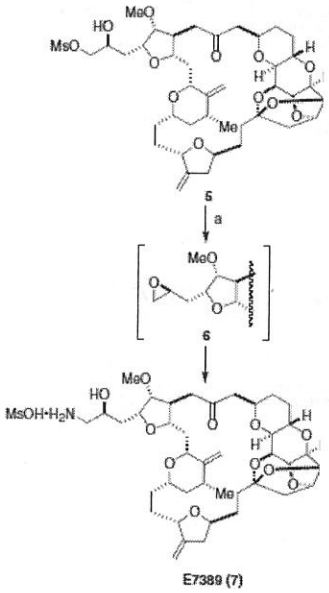
4-3. Effective Procedure for Slective Ammonolysis of Monosubstituted Oxiranes

Problem; - nucleophilic attack of ammonia can take place at the 1- or 2-position, that is, 1→2 versus 1→3

- the resultant 1,2-aminoalcohols 2 can react with the starting material 1, to yield the corresponding secondary amines 4.

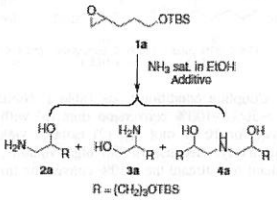
-slow conversion

Scheme 2
Reagents and conditions:
(a) EtOH saturated with NH_3, MsOH (5 equiv), [C] = 40 mM, rt, 3.5 days, 93% yield.



E7389 (7)

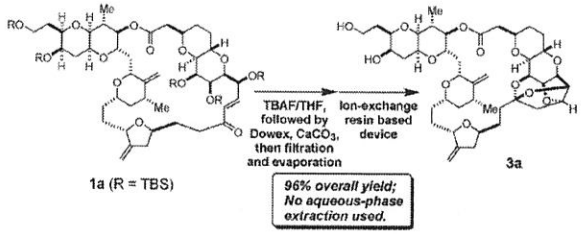
Table 1. Effect of additive and concentration on product distribution **A.Tetrahedron Letters 48 (2007) 8967–8971**



Entry	Additive	Concentration (mM)	Temperature[a]	Ratio 2a:4a
1	$Yb(OTf)_3{\cdot}nH_2O$ (0.1 equiv)	160	70	100:12
2	$Yb(OTf)_3{\cdot}nH_2O$ (0.1 equiv)	80	70	100:11
3a	$Yb(OTf)_3{\cdot}nH_2O$ (0.1 equiv)	40	70	100:3
3b			rt	100:8
4	$Yb(OTf)_3{\cdot}nH_2O$ (0.1 equiv)	20	70	100:2
5	$Sc(OTf)_3$ (0.1 equiv)	20	70	100:4
6a	MsOH (5 equiv)	80	70	100:8
6b			rt	100:9
7a	MsOH (5 equiv)	40	70	100:2
7b			rt	100:3
8a	MsOH (5 equiv)	20	70	100:1.5
8b			rt	100:2
9	MsOH (3 equiv)	40	rt	100:4.5
10	MsOH (1 equiv)	40	rt	100:5
11	NH_4Cl (5 equiv)	40	70	100:5
12	NH_4OAc (5 equiv)	40	70	100:6
13a	No additive	40	70	100:4
13b			rt	100:8

[a] Reaction time at 70 °C and at rt was 10 h and 82 h, respectively.

4-4. Operationally Simple and Efficient Workup Procedure for TBAF-Mediated Desilylation



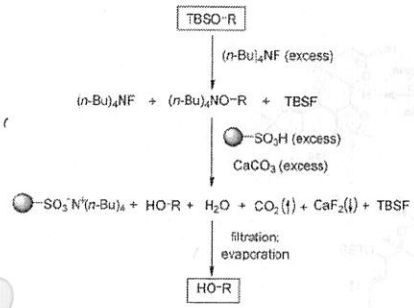
deprotected compound of 1a(tetra -ol) is highly water soluble

⇩

Aqueous-phase extraction is not ideal.

J. AM. CHEM. SOC. 2004, *126*, 7770−7771

Scheme 3. Overall Transformation



ORGANIC LETTERS
2007
Vol. 9, No. 4
723−726

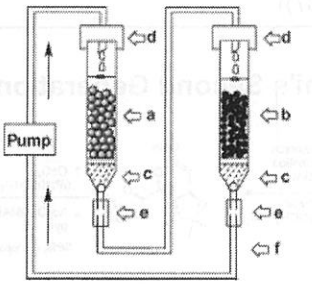
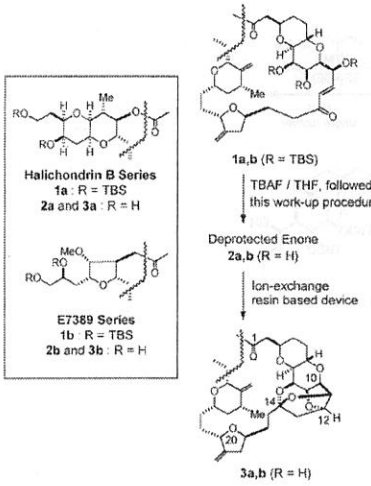


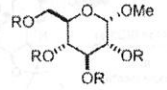
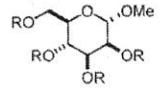
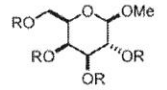
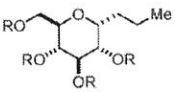
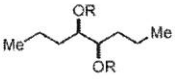
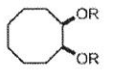
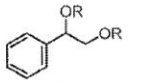
Figure 1. (a) Amberlite IRA 400 (OMe) column (diameter = 5 mm). (b) Rexyn 101 (H^+) column (diameter = 5 mm). (c) Basic Al_2O_3 (Baker) filter (diameter = 5 mm) with glass wool dividers. (d) Septum. (e) Teflon connector tube. (f) Teflon tubing. Pump: FMI QG50. For a 40 mg-scale experiment, approximately 0.4 cm^3 of Amberlite IRA 400, 0.4 cm^3 of Rexyn 101, and 0.1 cm^3 of alumina were placed in each column. The total volume of solvent was ca. 4 mL (c = ca. 0.01 M) and the flow-rate was ca. 2 mL per min.

Scheme 4. Application of This TBAF Workup Method to the Advanced Synthetic Stage in Both the Halichondrin B and E7389 Series



-xsTBAF; deprotection
-$CaCO_3$; HF scavenger(CaF is insoluble in THF)
-acidic ion-exchange resin; Michael adition and acetal formation
⟶ polycyclic ketal

Table 1. Substrates Used to Test the Feasibility and Efficiency of the TBAF Workup Protocol[a]

entry	substrate (R = TBS)/ product (R = H)	equiv of TBAF	crude yield (%)[b]	removed TBAF (%)[c]
1		8	111	99.3
2		8	110	99.5
3		8	107	99.5
4		8	106	99.5
5		4	95[d]	99.5
6		8	110	99.6
7		3	103	99.8

[a] Reaction conditions employed for desilylation: substrate (1 equiv), TBAF (3−8 equiv), THF, rt or heat, 4−28 h; $CaCO_3$, DOWEX 50WX8-400 (used as supplied), MeOH, rt, 1 h. [b]Based on the weight obtained after filtration and evaporation. [c]Estimated from ^1H NMR spectra of the crude compound. [d]Product was volatile.

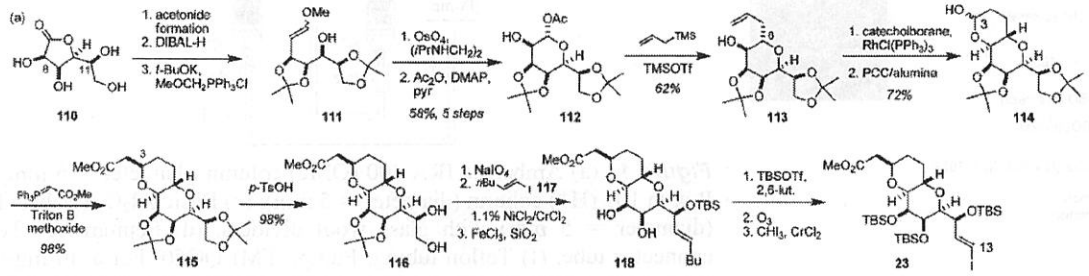
4-5. Refined Approach to a Number of Fragments

4--5-1. C1-C13 Subunit Synthesis

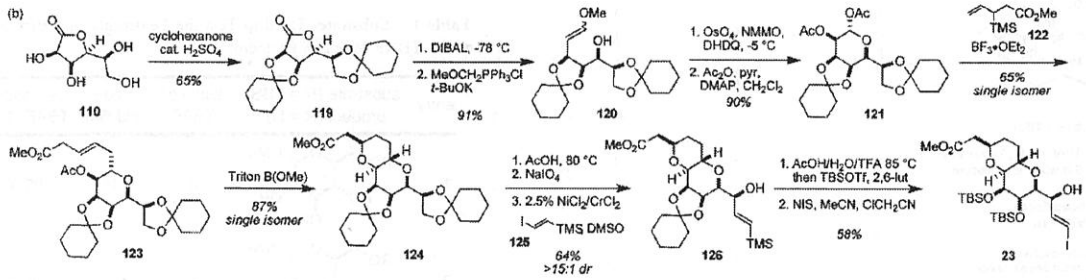
Kishi's C1-C13 Subunit Synthesis

2-2. First generation(1987); 31 steps, 4% overall yield(ref. (34))
5-1-1. Second generation(1992);16 steps(ref. (35))
5-1-2. Third generation(1996); 12 steps, 11% overall yield(ref. (37))

4-5-1-1. Kishi's Second Generation Approach to the C1-C13 Subunit

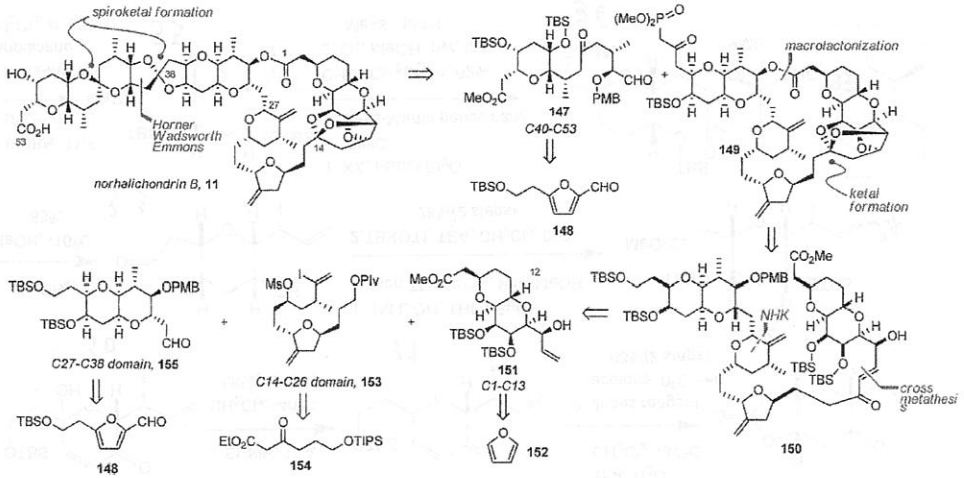


4-5-1-2. Kishi's Third Generation Approach to the C1-C13 Subunit

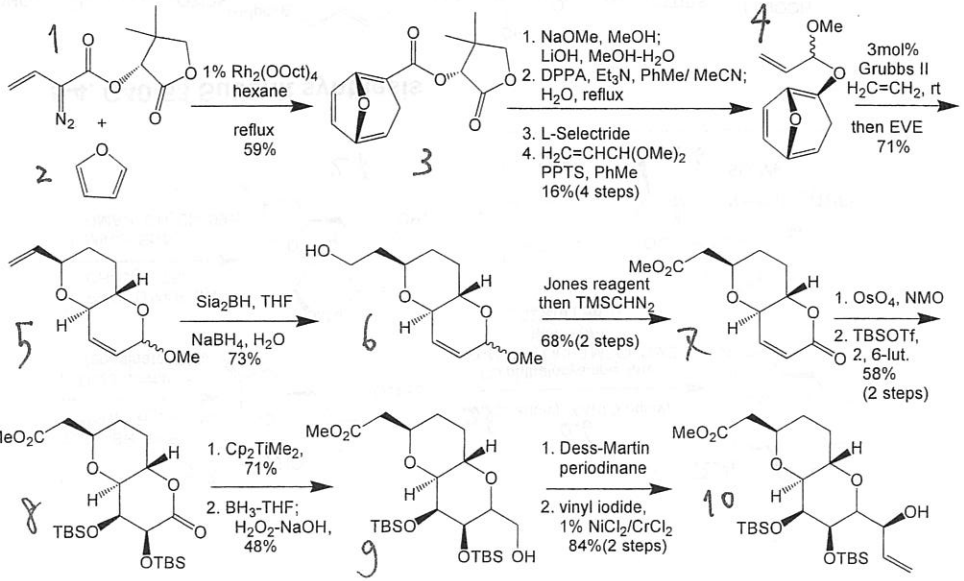


5. Total Synthesis of Norhalichondrin B by Phillips and Co-workers(2009)

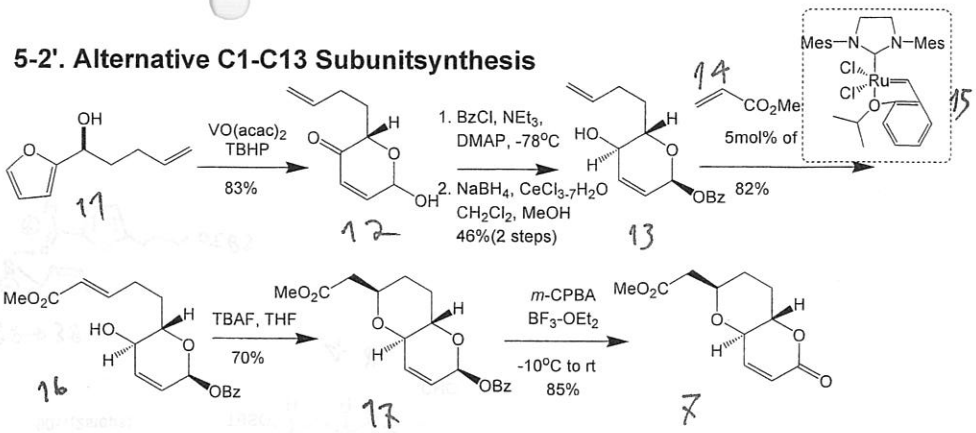
5-1. The Phillips strategy



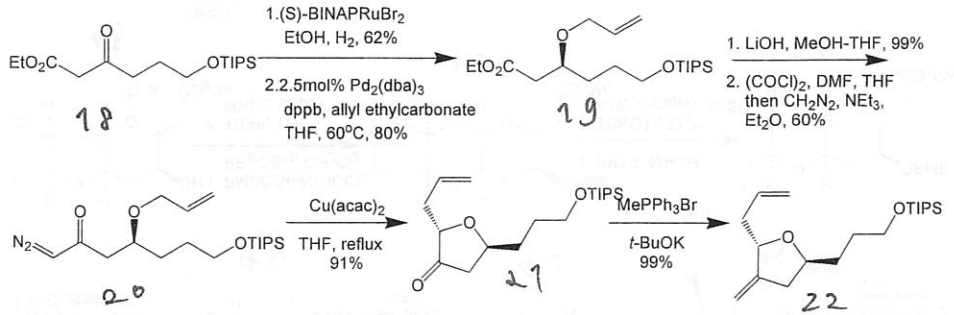
5-2. C1-C13 Subunit synthesis

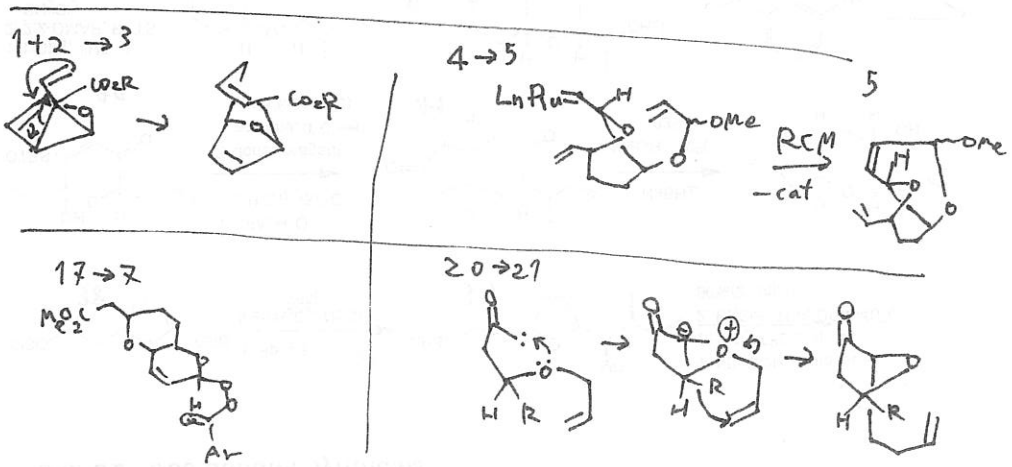


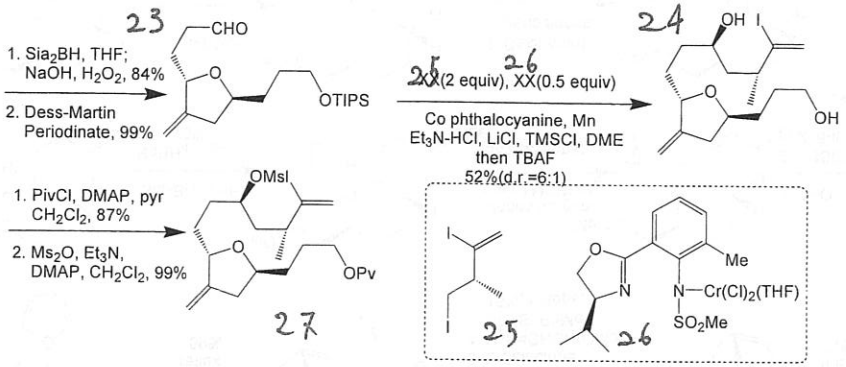
5-2'. Alternative C1-C13 Subunitsynthesis



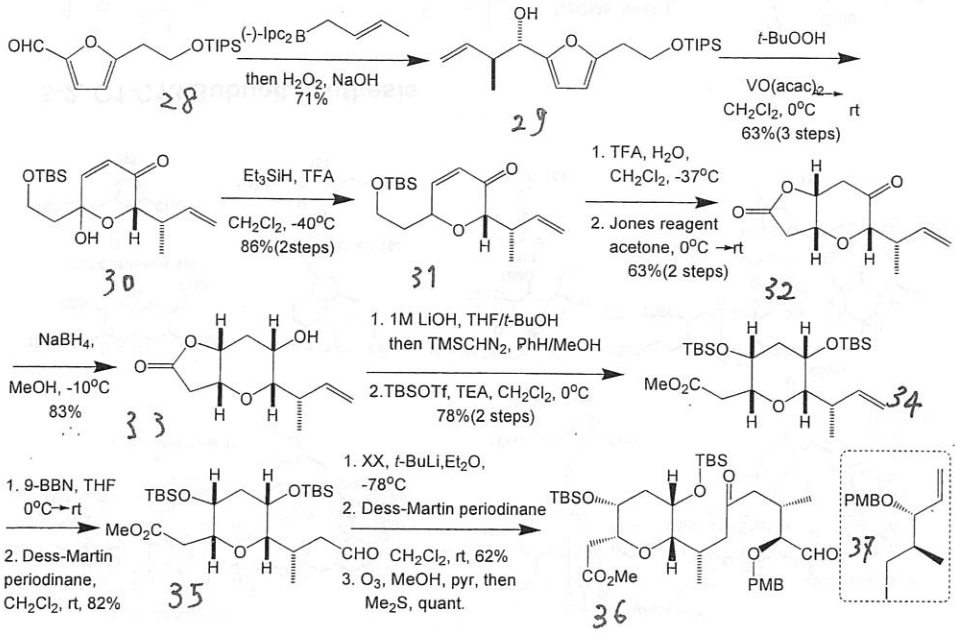
5-3. C14-C26 Subunit synthesis



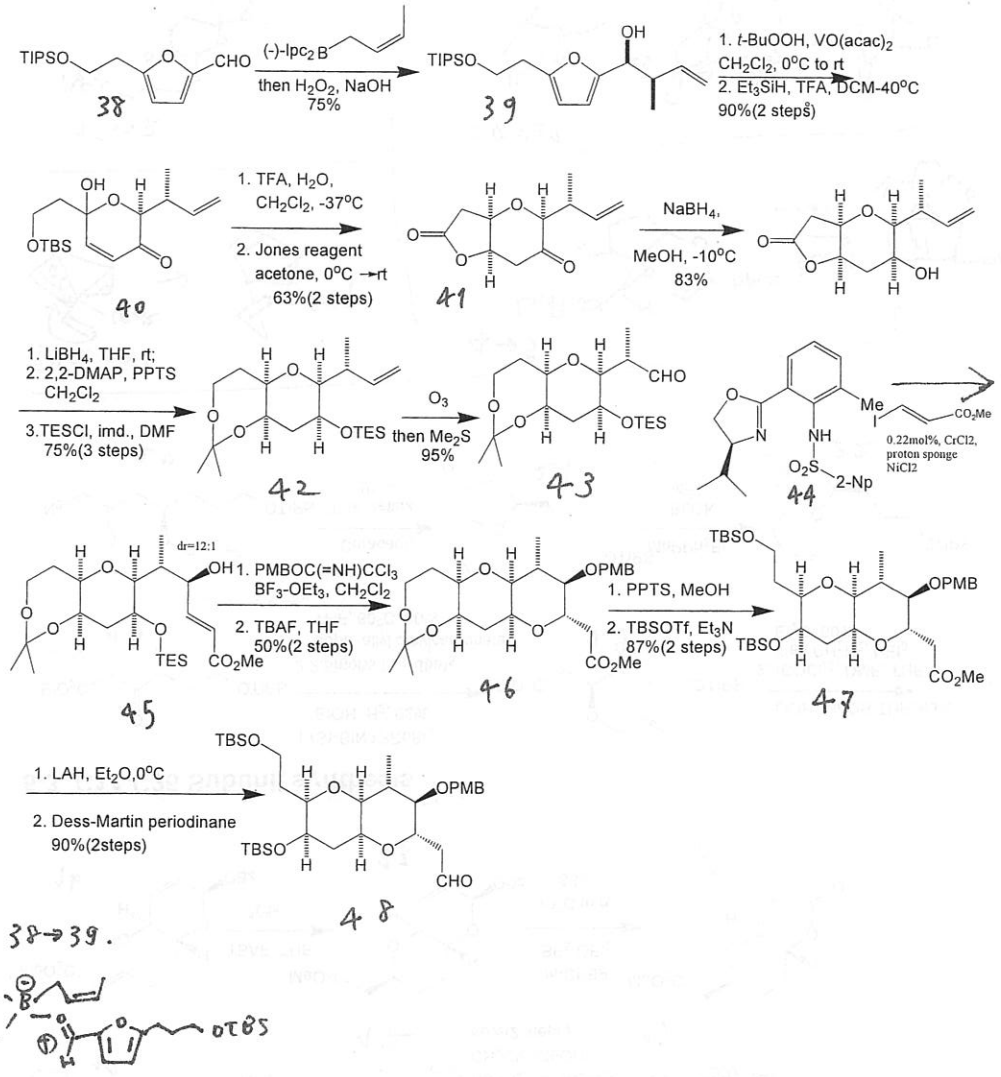




5-4. C40-53 Subunit synthesis

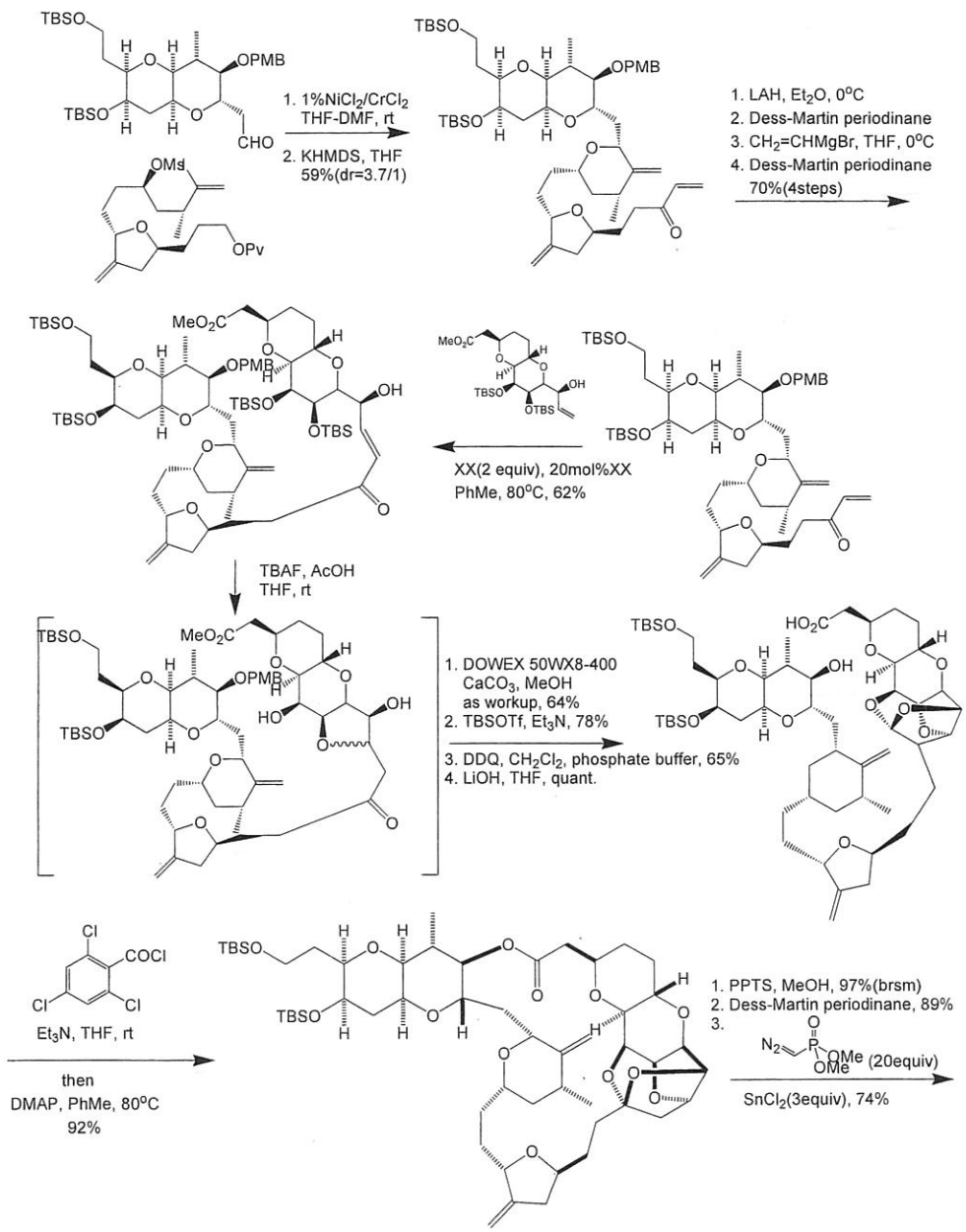


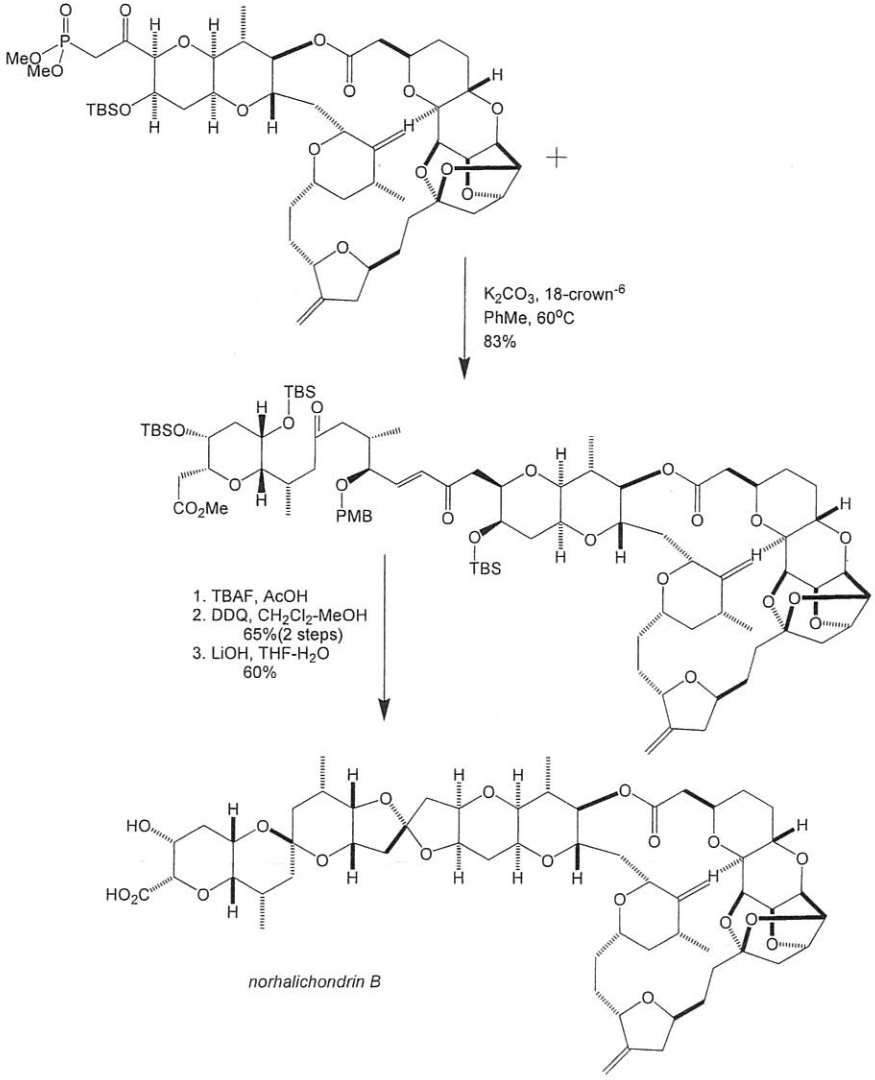
5-5. C27-C38 Subunit synthesis



38→39.

5-6. Subunit Couplings and Completion of the Synthesis





norhalichondrin B