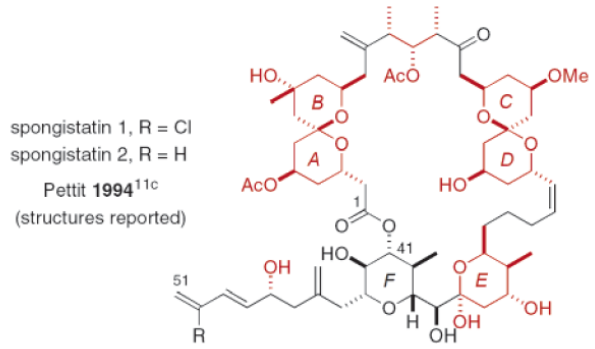
Total synthesis of Spongistatin

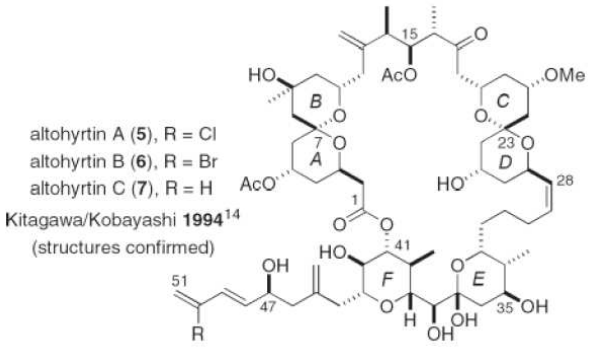
1. Introduction:

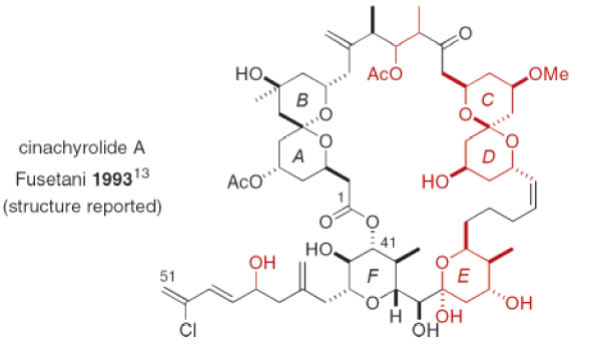
Isolation: Pettit et al. *J. Org. Chem*. **1993**, *58*, 1302.
Kitagawa et al. *Tetrahedron Lett*. **1993**, *34*, 1993.
Fusetani et al. *JACS*. **1993**, *115*, 3977.

The **antitumor activity** of Spongistatin family has been described as "probably the best to date in the NCI ' s evaluation programs."

Small natural supply:
(400 kg of sponge provided 13.8mg of spongistatin 1)







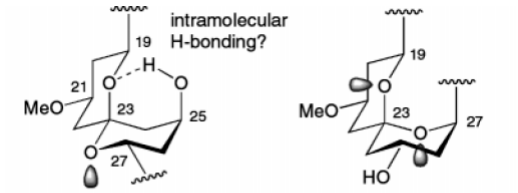
Total synthesis of spongistatins/Altohytins

Review: *Chem. Rev.* **2005**, *105*, 4237

1. **Evans** synthesis of spongistatin 2/Altohytin C
   Angew. Chem., Int. Ed. **1997**, *36*, 2738.
   Angew. Chem., Int. Ed. **1997**, *36*, 2741.
   Angew. Chem., Int. Ed. **1997**, *36*, 2744.
   Tetrahedron **1999**, *55*, 8671.
2. **Kishi** synthesis of spongistatin 1/Altohytin A
3. **Smith** synthesis of spongistatin 2/Altohytin A
4. **Paterson** synthesis of spongistatin 1/Altohytin A
5. **Crimmins** synthesis of spongistatin 1, 2/Altohytin A, C
6. **Heathcock** synthesis of spongistatin 2/Altohytin C
   JACS. **2003**, *115*, 12844.
   JACS. **2003**, *115*, 12836.
   J. Org. Chem. **2000**, *65*, 4145.
7. **Smith** synthesis of spongistatin 1/Altohytin A

Structural features:

1. 24 stereocenters together with a 42-membered macrolactone ring
2. Two spiroacetal units (AB and CD)



CD-1
desired CD-ring conformer
(axial-equatorial)
single anomeric effect

CD-2
undesired CD-ring conformer
(axial-axial)
double anomeric effect

3. Densely substituted tetrahydropyran rings (E and F)

Contents:

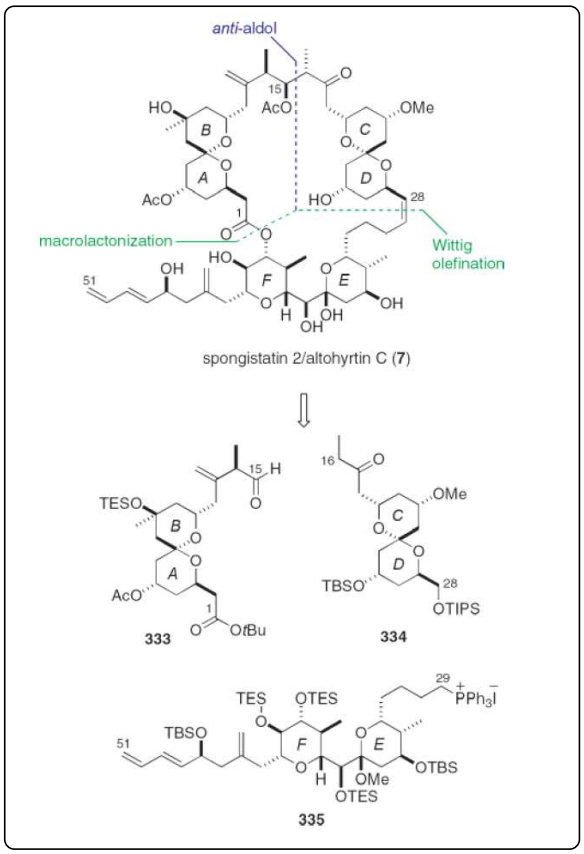
1. Heathcock synthesis of spongistatin 2/Altohytin C: (A highly convergent synthetic route)

Point of Heathcock synthesis of AB-ring, CD-ring segment:

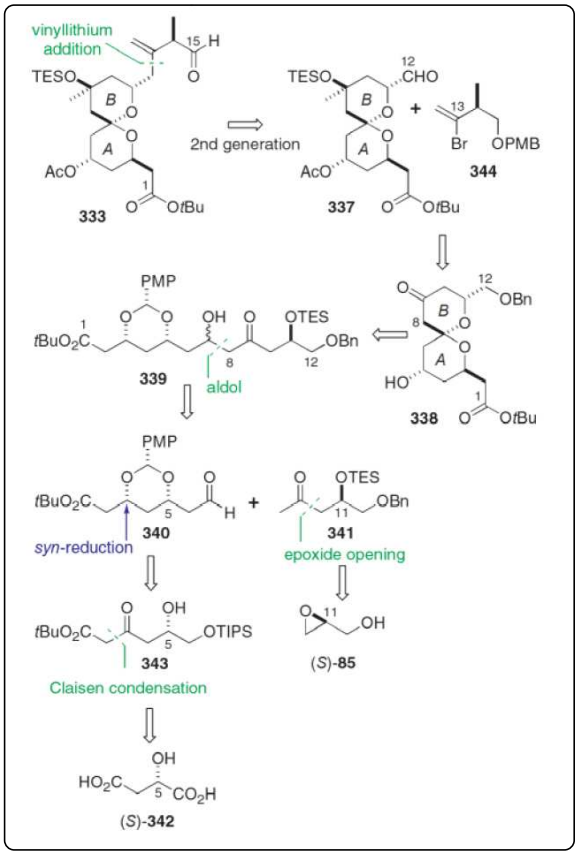
1. **Similar approaches to the AB and CD spiroketal subunits.**
2. **Stereocontrolled kinetic spirocyclization**
3. **Prepared 9.6g AB-ring, CD-ring segment (a total of 62 step, with a longest linear sequence of 35 steps.)**

Retrosynthetic analysis:

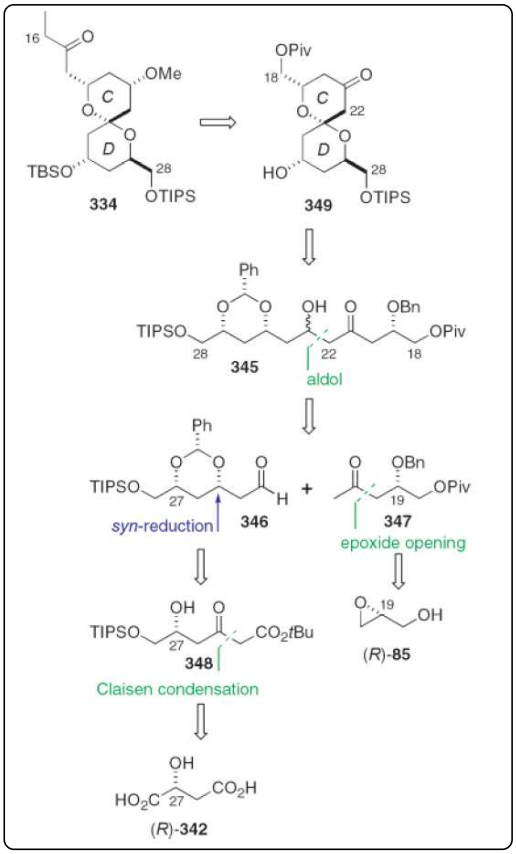
Scheme 1. Heathcock synthesis of spongistatin 2/Altohytin C



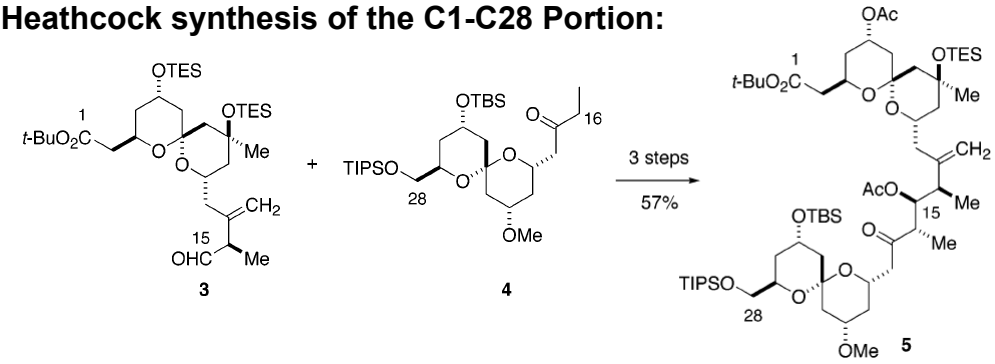
Scheme 2. Retro-synthesis of the AB-ring segment



Scheme 3.Retro-synthesis of CD-ring segment:



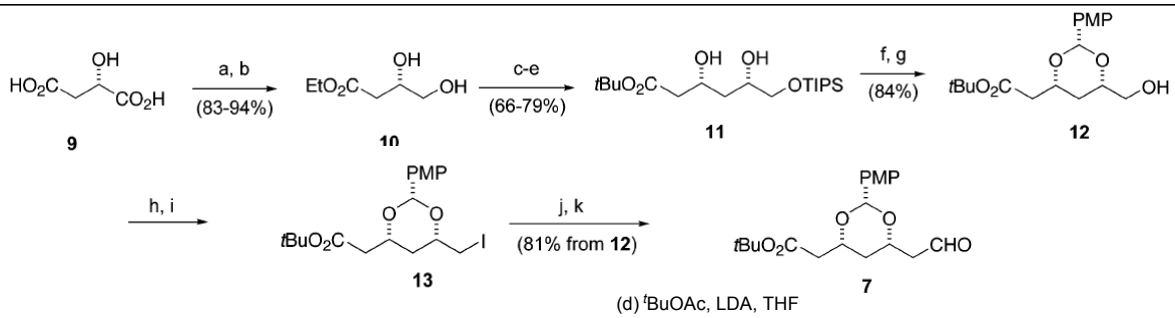
Heathcock synthesis of the C1-C28 Portion:



Target compound

1. Synthesis of the AB-ring segment

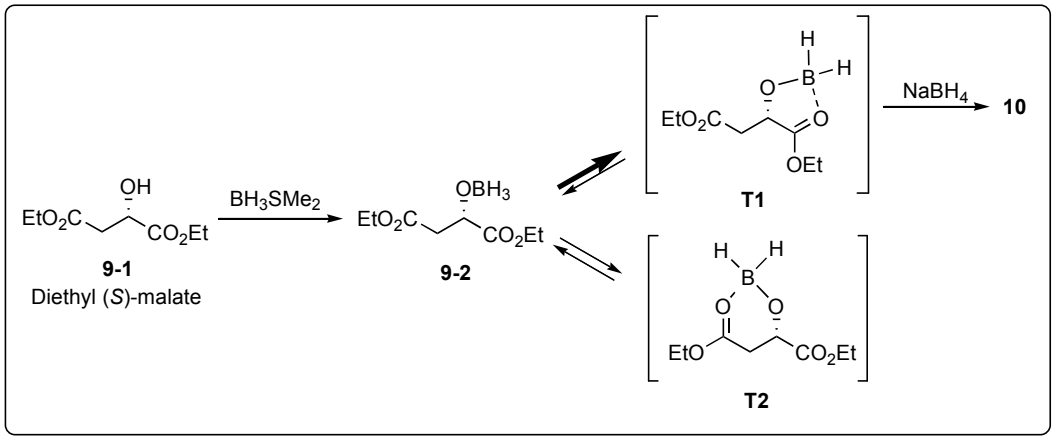
Scheme 4. Synthesis of the AB-ring segment



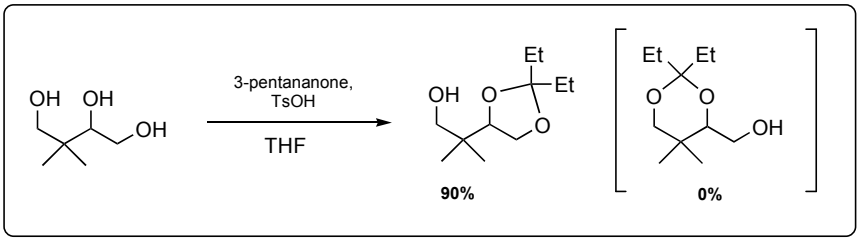
(d) ^{t}BuOAc, LDA, THF

[a] (a) EtOH, $SOCl_2$; (b) BMS, $NaBH_4$, THF; (c) TIPSCl, imidazole, DMF; (d) *tert*-butylthio acetate, THF; (e) Et_2BOMe, $NaBH_4$, THF, MeOH; (f) 4-MeOPhCH(OMe)$_2$, PPTS, CH_2Cl_2; (g) TBAF, THF; (h) 4-ClPhSO$_2$Cl, Et_3N CH_2Cl_2; (i) NaI, $NaHCO_3$, Na_2SO_3, MEK; (j) vinylmagnesium bromide, Li_2CuCl_4, THF; (k) O_3, MeOH, CH_2Cl_2, Bu_3P.

9 ⟶ **10** (ref: *Tetrahedron* **1992**, *48*, 4067.)

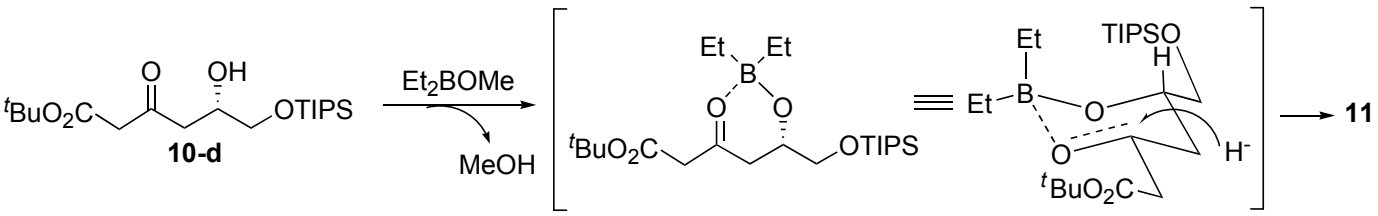


Relative reation: Diol protection



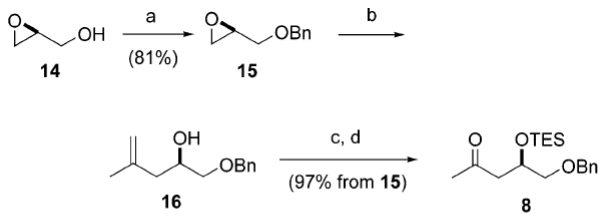
Carbohydr. Res., **1978**, *65*, 229

10 ⟶ **11** (ref: *Tetrahedron Lett* **1987**, *28*, 155.)



10-d

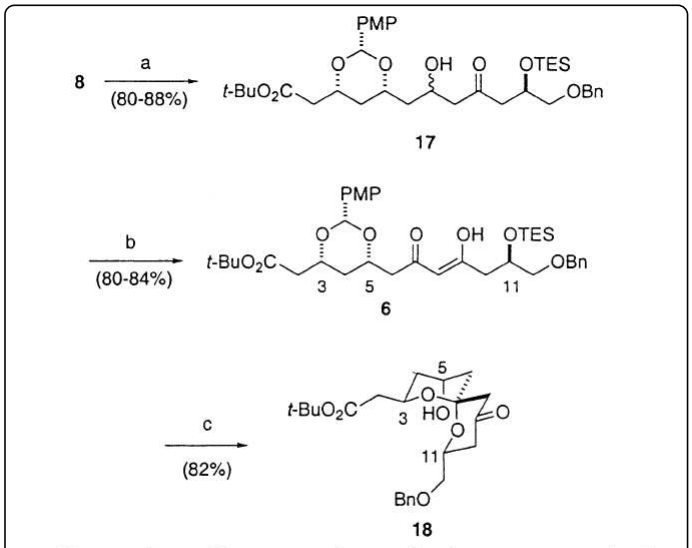
Scheme 5. Synthesis of the AB-ring segment



14 **15** **16** **8**

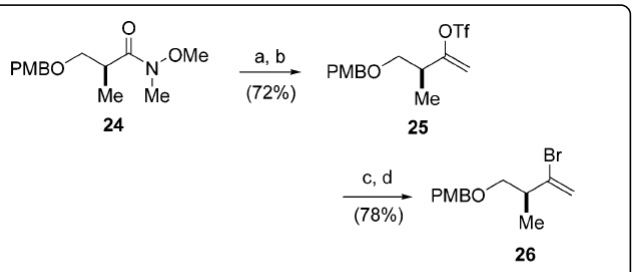
[a] (a) NaH, BnBr, DMF; (b) isopropenylmagnesium bromide, Li_2CuCl_4, THF; (c) TESCl, imidazole, DMF; (d) (i) O_3, $NaHCO_3$, MeOH, CH_2Cl_2; (ii) DMS.

Scheme 6. Synthesis of the AB-ring segment



[a] (a) LDA, then **7**; (b) Dess–Martin, 1 equiv of H_2O, THF, CH_2Cl_2; (c) 10:10:1 THF:CH_3CN:12 N HCl.

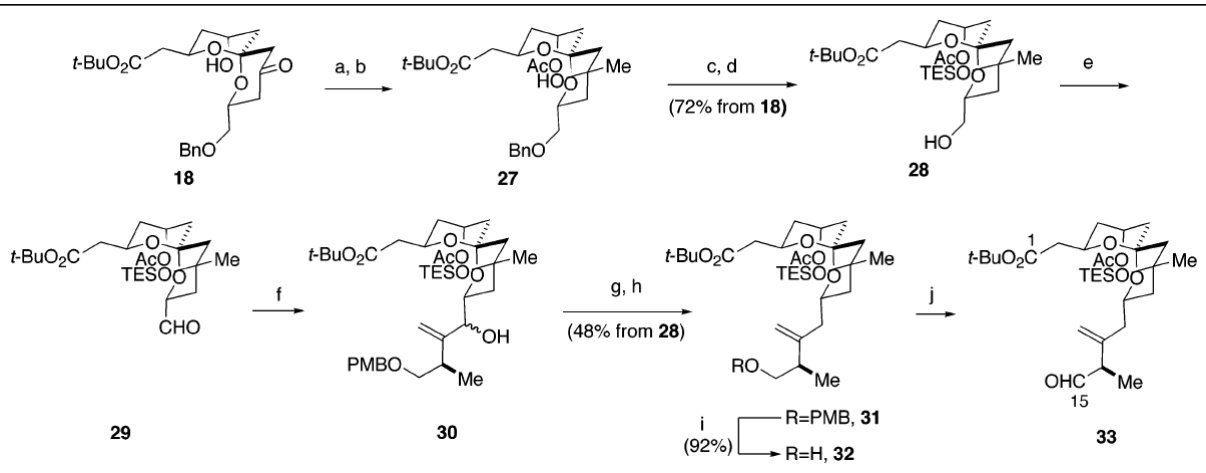
Scheme 7. Synthesis of the AB-ring segment



24 **25** **26**

[a] (a) MeLi, Et_2O; (b) LiHMDS, 4-chloro-2-aminopyridyl triflimide, THF; (c) Bu_3SnH, LDA, CuCN, THF; (d) NBS, CH_2Cl_2.

Scheme 8. Synthesis of the AB-ring segment



18 **27** **28** **29** **30** **33**

[a] (a) MeLi, $CeCl_3$, THF; (b) Ac_2O, DMAP, CH_2Cl_2; (c) TESOTf, 2,6-lutidine, CH_2Cl_2; (d) H_2, $Pd(OH)_2$, THF; (e) Moffat–Swern; (f) bromide **26** plus 2 equiv of *t*-BuLi, Et_2O, then **29**; (g) *N*-formylbenzotriazole, DMAP, CH_2Cl_2; (h) $Pd_2(dba)_3$, Bu_3P, NH_4CO_2H, cyclohexane; (i) DDQ, CH_2Cl_2, H_2O; (j) Dess–Martin, CH_2Cl_2.

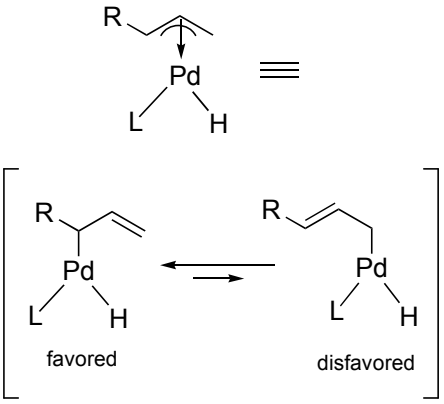
30 ⟶ **31** (ref: *Chem. Lett* **1984**, 1017.)

Scheme 9. Mechanism

Table 1. Ligand effect

SM	Ligand	Ratio of product

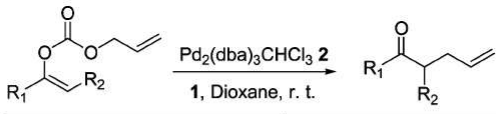
Scheme 10. Ligand effect

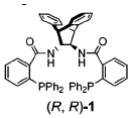


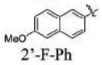
Recent report of Pd-catalyzed asymmetric allylic alkylation:

Trost et al. *JACS*. **2005**, *127*, 17180.

Table 2. Reaction of various allyl enol carbonates of acylic ketones

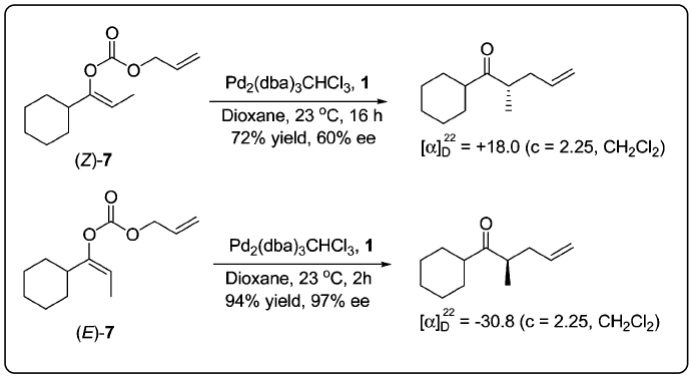




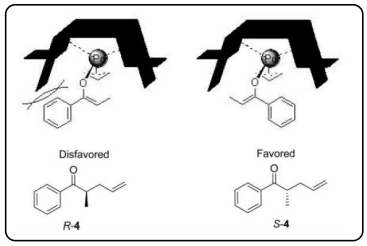
	R_1	R_2	Z/E^b	time	yield	ee
1	Ph	Me	>98/2	2 h	94%	94%
2	Ph	Et	>98/2	2 h	94%	94%
3	Ph	C_5H_{11}	>98/2	16 h	93%	92%[c]
4	Ph	*i*-Pr	>98/2	24 h	30%	32%[c]
5	Ph	CH_2Ph	>98/2	1 h	75%	88%
6		Me	>98/2	1 h	90%	95%
7	2'-F-Ph	Me	>98/2	1 h	80%	94%
8	3'-Cl-Ph	Me	>98/2	1 h	97%	93%
9	4'-Br-Ph	Me	>98/2	1 h	94%	93%
10	2'-OMe-Ph	Me	>98/2	16 h	99%	98%[c]
11	Pyridyl	Me	>98/2	1 h	95%	73%[c]
12	3'-NO_2-Ph	Me	>98/2	1 h	83%	82%
13	Furyl	Me	>98/2	4 h	89%	88%
14	2'-CF_3-Ph	Me	>98/2	2 h	94%	92%
15	Mesityl	Me	5/95	6 h	99%	96%[c]
16	Mesityl	Me	96/4	16 h	trace	NA
17		Me	>98/2	5 h	94%	88%
18		Me	25/1	0.3h	93%	91%

[a] Unless otherwise indicated, all reactions were performed on a 0.3 mmol scale at 0.1 M in 1,4-dioxane at 23 °C using 2.5% **2** and 5.5% ligand **1**; the yields were isolated yields, and enantiomeric excess values were determined by chiral HPLC. [b] *Z/E* ratio was determined by ^{1}H NMR. [c] The enantiomeric excess values were determined by analysis of the derivative described in Supporting Information.

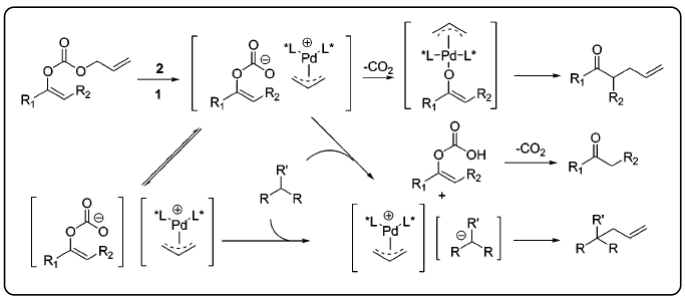
Scheme 11. Double bond geometry controls the configuration and enantiomeric excess of product



Scheme 12. Model for the enantioselectivity

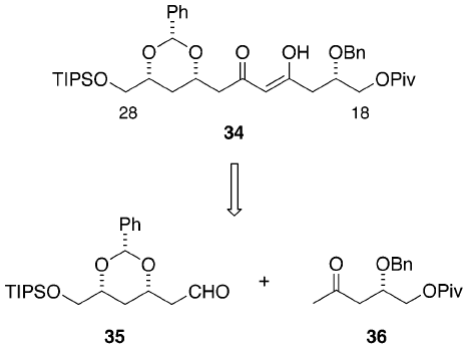


Scheme 13. Proposed mechanism

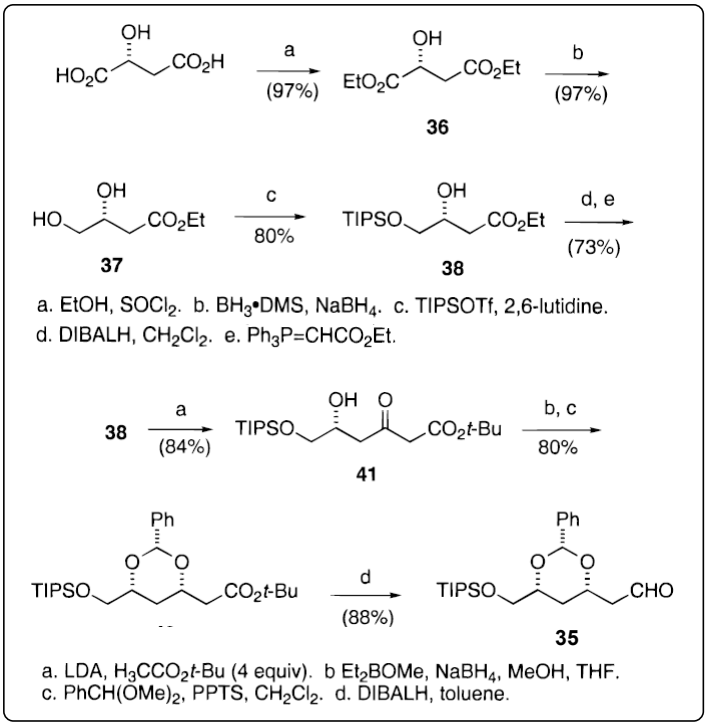


2. Synthesis of the CD-ring segment:

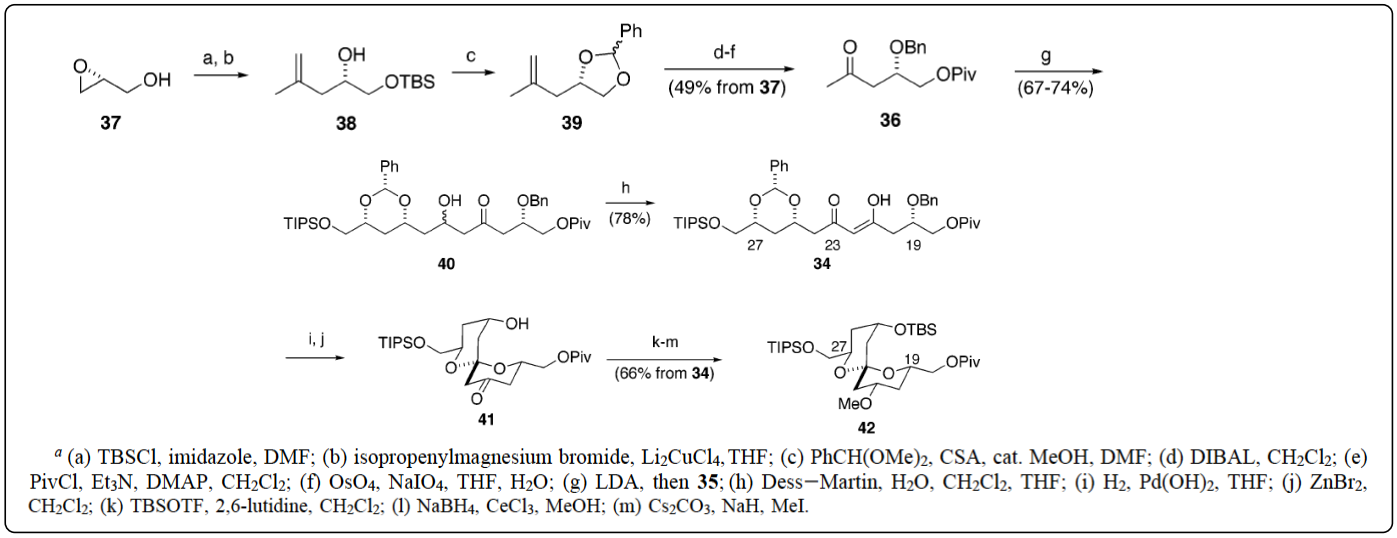
Target compounds



Scheme 14. Synthesis of **35**



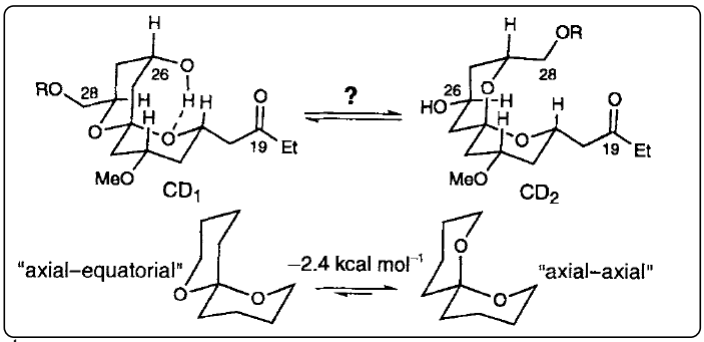
Scheme 15. Synthesis of the CD-ring segment



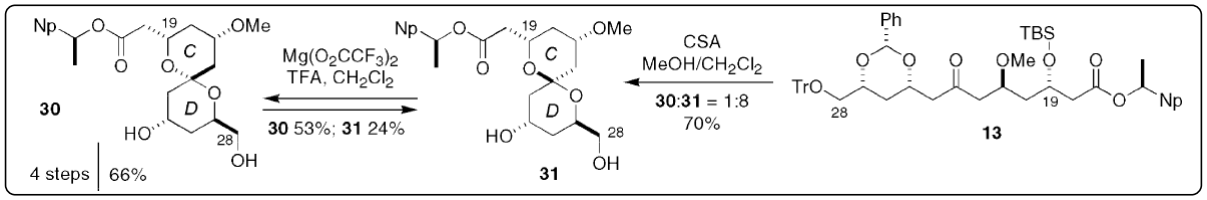
[a] (a) TBSCl, imidazole, DMF; (b) isopropenylmagnesium bromide, Li_2CuCl_4, THF; (c) $PhCH(OMe)_2$, CSA, cat. MeOH, DMF; (d) DIBAL, CH_2Cl_2; (e) PivCl, Et_3N, DMAP, CH_2Cl_2; (f) OsO_4, $NaIO_4$, THF, H_2O; (g) LDA, then **35**; (h) Dess–Martin, H_2O, CH_2Cl_2, THF; (i) H_2, $Pd(OH)_2$, THF; (j) $ZnBr_2$, CH_2Cl_2; (k) TBSOTF, 2,6-lutidine, CH_2Cl_2; (l) $NaBH_4$, $CeCl_3$, MeOH; (m) Cs_2CO_3, NaH, MeI.

34 ⟶ 41 (stereocontrolled kinetic spirocyclization reaction)

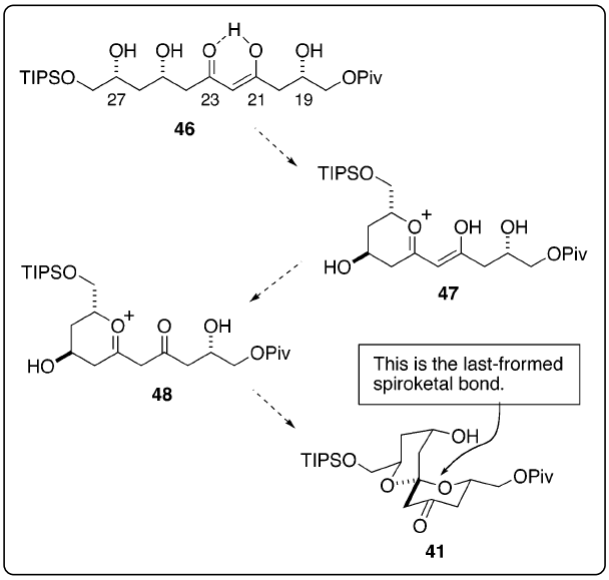
Scheme 16. Conformations of CD-ring
(Single anomeric effect)



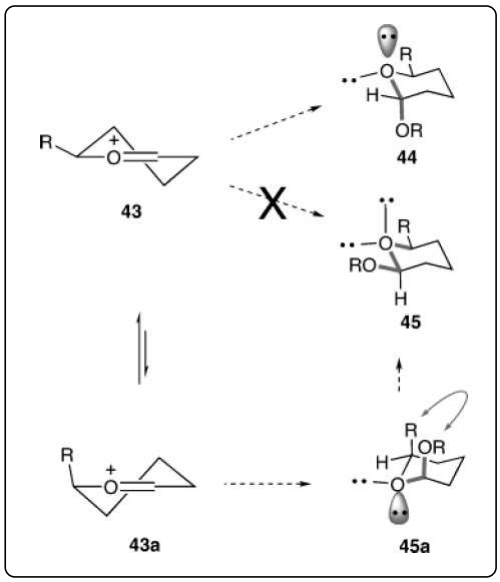
Scheme 17. Evans synthesis of CD-ring segment



Scheme 18. Mechanism of spirocyclization



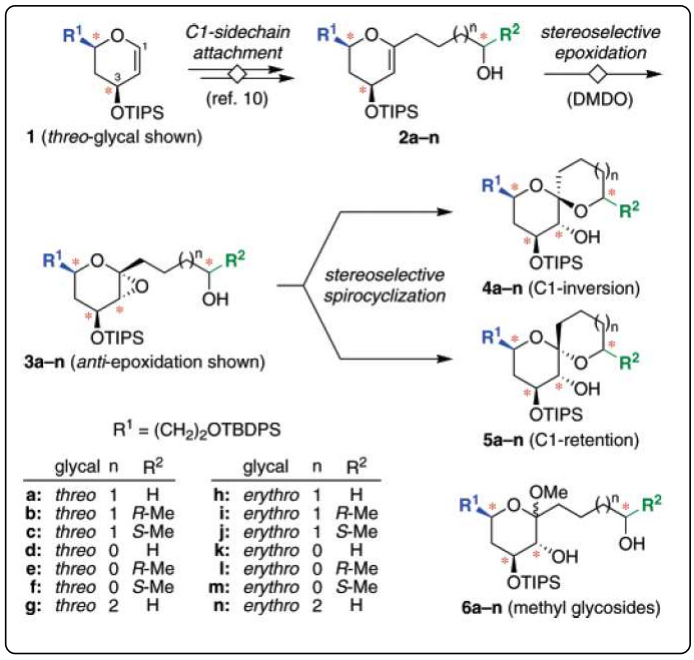
Scheme 19. A kinetic result



Recent report of stereocontrolled kinetic spirocyclization reaction:

Tan D. S. et al. *JACS*. **2005**, *127*, 13796.

Scheme 20. Epoxide-based approach to the synthesis of spiroketals



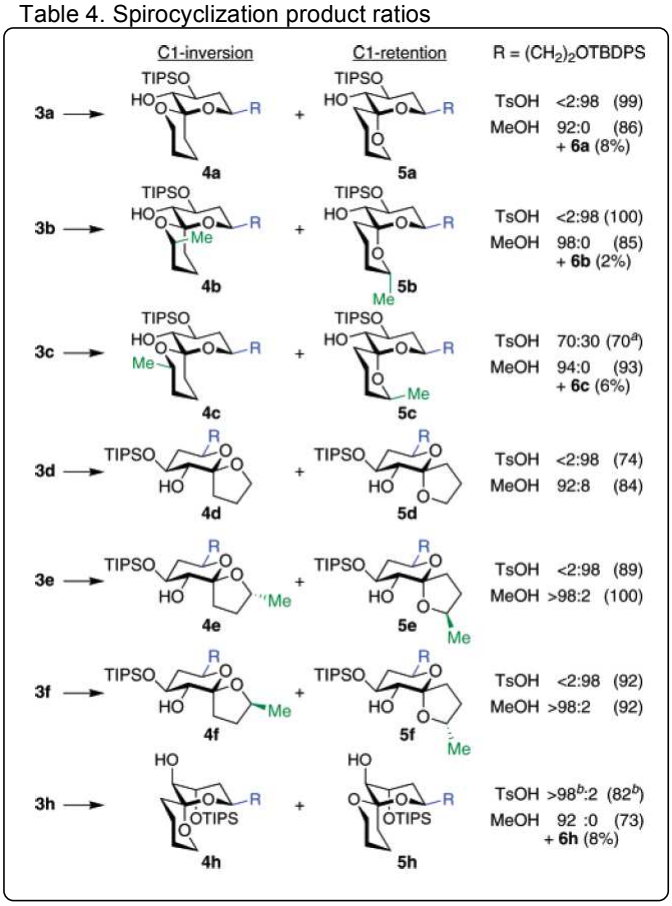
	glycal	n	R^2		glycal	n	R^2
a:	*threo*	1	H	**h:**	*erythro*	1	H
b:	*threo*	1	*R*-Me	**i:**	*erythro*	1	*R*-Me
c:	*threo*	1	*S*-Me	**j:**	*erythro*	1	*S*-Me
d:	*threo*	0	H	**k:**	*erythro*	0	H
e:	*threo*	0	*R*-Me	**l:**	*erythro*	0	*R*-Me
f:	*threo*	0	*S*-Me	**m:**	*erythro*	0	*S*-Me
g:	*threo*	2	H	**n:**	*erythro*	2	H

Table 3. Alcohol-induced spirocyclizations

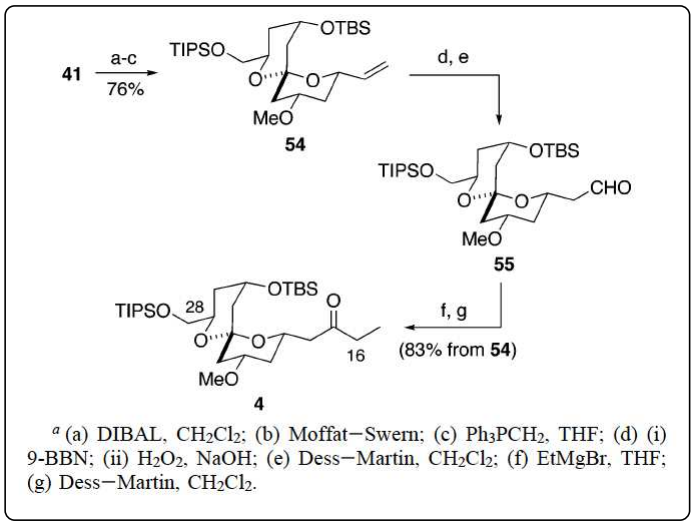
entry	ROH	vol[b]	temp (°C)	time (h)	4a (%)	5a (%)	6a[c] (%)
1	MeOH	5	−78	1	80	0	20
2	MeOH	5	−63	1	92	0	8
3	MeOH	5	−44	1	92	3	5
4	MeOH	5	0	1	71	21	8
5	CH_3OD	5	−63	1	87	0	13
6	EtOH	5	−63	2	77	0	23
7	*i*-PrOH	5	−63	2	72	4	24
8	MeOH	0.5	−63	1	50	8	42
9	EtOH	0.5	−63	2	59	6	35
10	*i*-PrOH	0.5	−63	2	69	8	23
11	CF_3CH_2OH	0.5	−63	2	70	14	16
12	$(CF_3)_2CHOH$	0.5	−63	2	70	30	0

[a] Product ratios determined by NMR. [b] Volume of alcohol added to **3a** relative to the initial volume of 1:1 acetone/CH_2Cl_2 used in the preceding epoxidation reaction. [c] Formed as a ≈1:1 mixture of α- and β-anomers.

Table 4. Spirocyclization product ratios

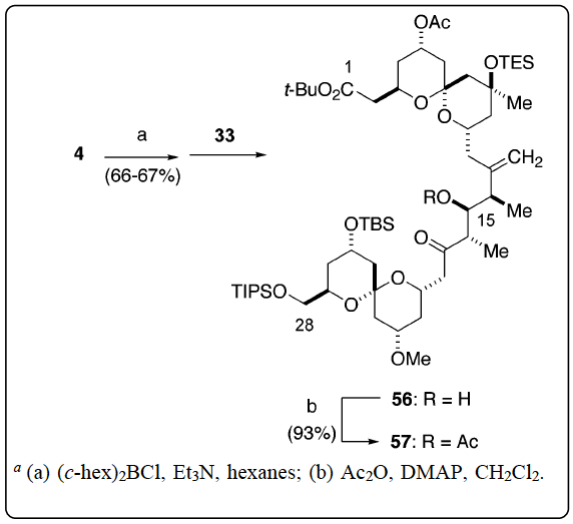


Scheme 21. Synthesis of the CD-ring segment

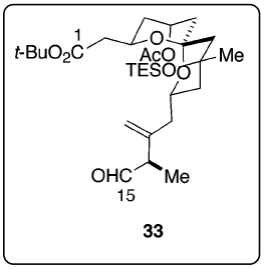


[a] (a) DIBAL, CH_2Cl_2; (b) Moffat–Swern; (c) Ph_3PCH_2, THF; (d) (i) 9-BBN; (ii) H_2O_2, NaOH; (e) Dess–Martin, CH_2Cl_2; (f) EtMgBr, THF; (g) Dess–Martin, CH_2Cl_2.

Scheme 22. Connection of AB-ring segment with CD-ring segment.

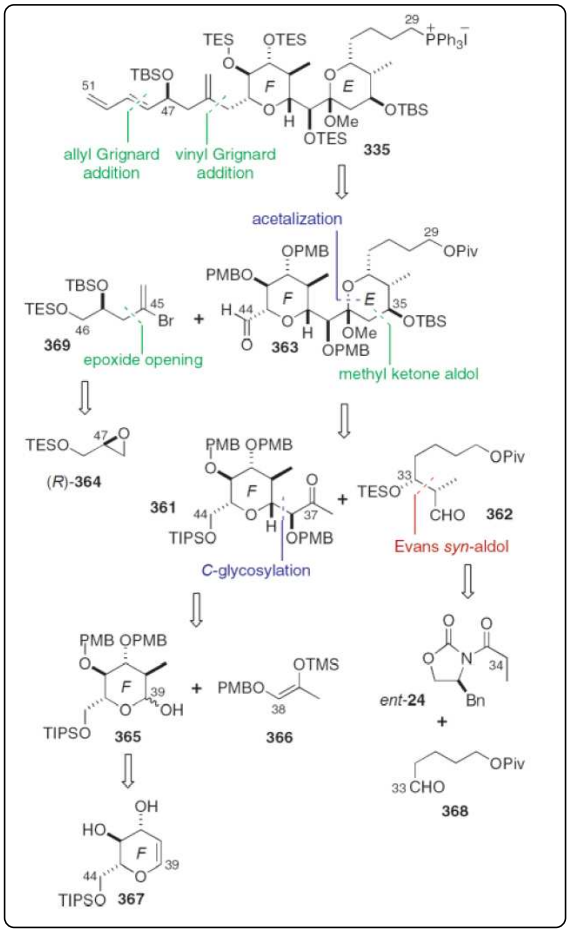


[a] (a) (*c*-hex)$_2$BCl, Et_3N, hexanes; (b) Ac_2O, DMAP, CH_2Cl_2.



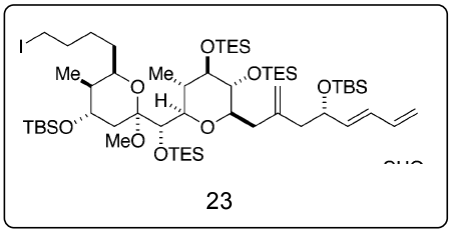
3.0. Synthesis of E,F-ring segment:

Scheme 23. Heathcock retro-synthesis of E,F-ring segment(C29-C51)



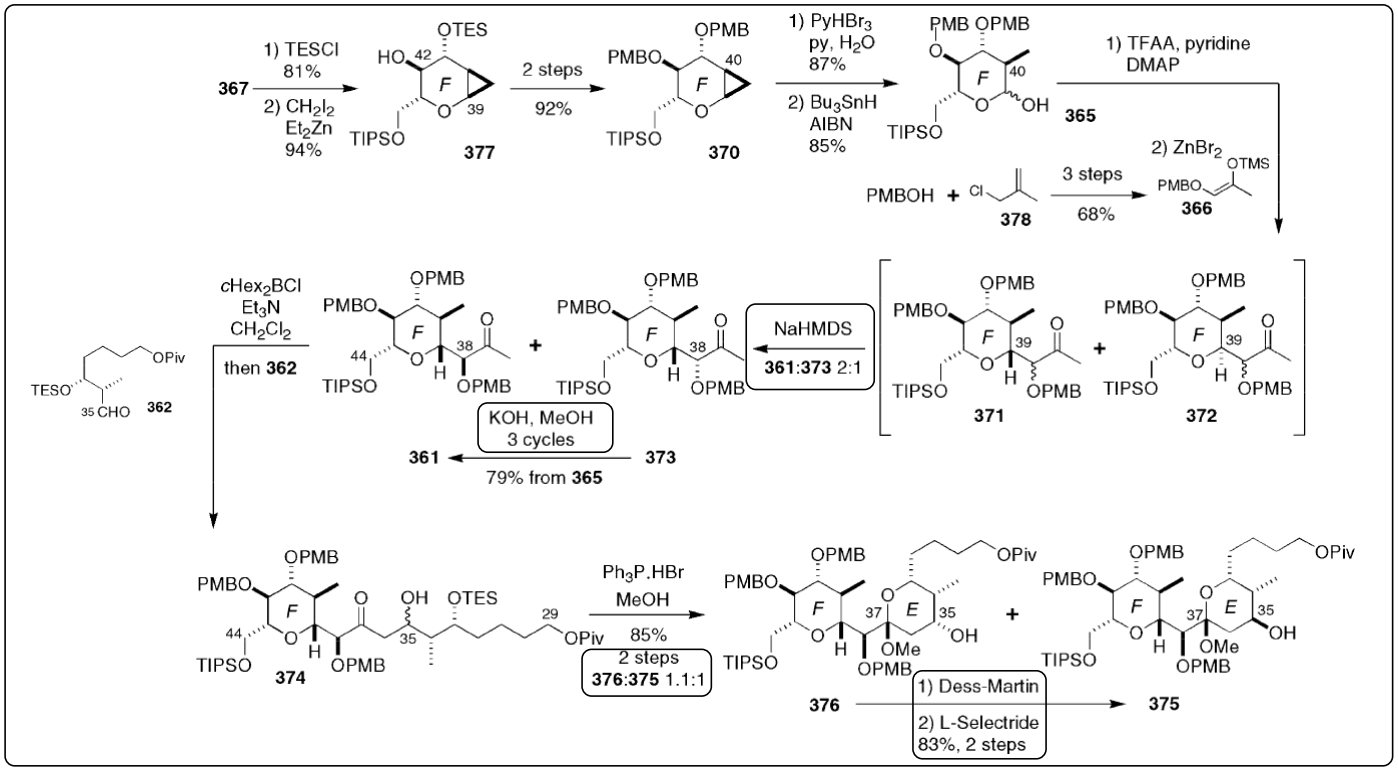
C29-C51 iodide required 44 steps with a longest linear sequence of 33 steps.

The overall yield was 6.8%, and 2 g of the iodide 23 was prepared.



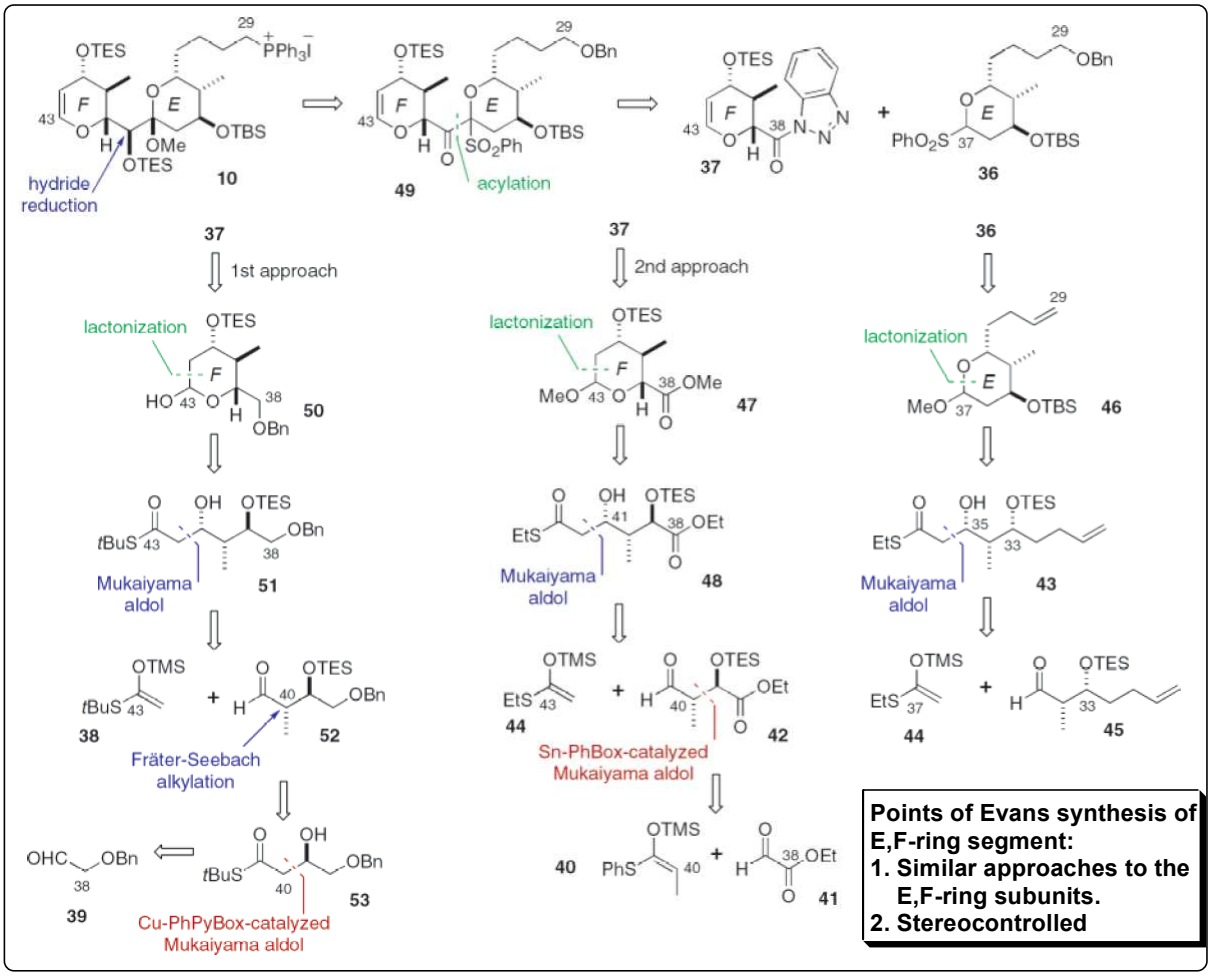
But, not excellent stereocontrol!

Scheme 24. Heathcock of synthesis of E,F-ring segment:

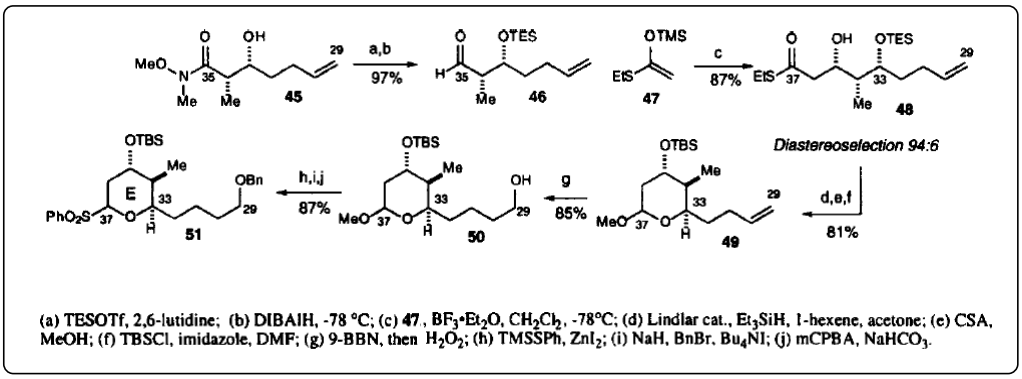


3. Evans synthesis of E,F-ring segment

Scheme 25. Evans retro-synthesis of E,F-ring segment



Scheme 26. Synthesis of E-ring segment



(a) TESOTf, 2,6-lutidine; (b) DIBAlH, -78 °C; (c) **47**, BF_3•Et_2O, CH_2Cl_2, -78°C; (d) Lindlar cat., Et_3SiH, 1-hexene, acetone; (e) CSA, MeOH; (f) TBSCl, imidazole, DMF; (g) 9-BBN, then H_2O_2; (h) TMSSPh, ZnI_2; (i) NaH, BnBr, Bu_4NI; (j) mCPBA, $NaHCO_3$.

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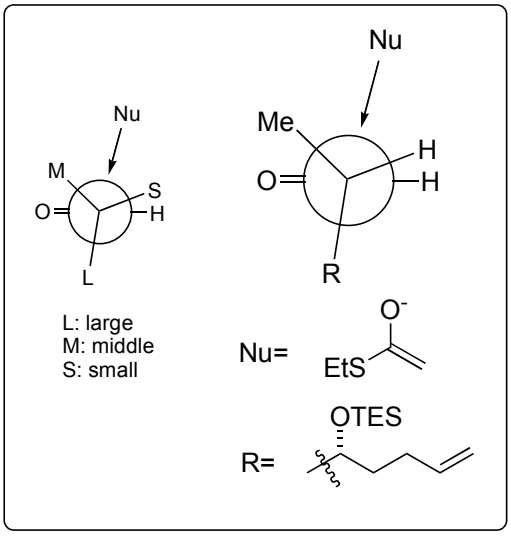
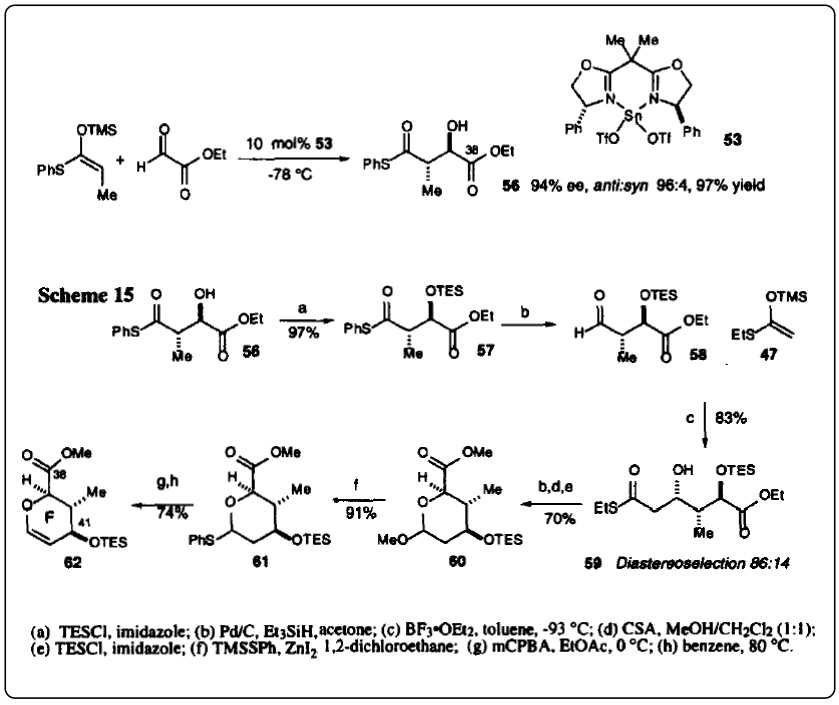
Felkin selective addition of silyl ketene acetal:



Scheme 27. Evans synthesis of F-ring segment:



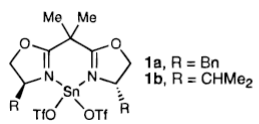
(a) TESCl, imidazole; (b) Pd/C, Et_3SiH, acetone; (c) BF_3•OEt_2, toluene, -93 °C; (d) CSA, MeOH/CH_2Cl_2 (1:1); (e) TESCl, imidazole; (f) TMSSPh, ZnI_2 1,2-dichloroethane; (g) mCPBA, EtOAc, 0 °C; (h) benzene, 80 °C.

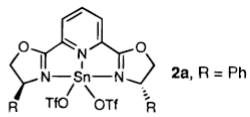
Catalytic asymmetric anti-aldol reaction:

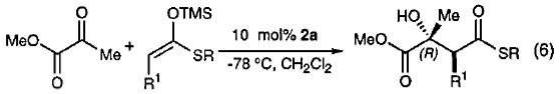
a. Catalytic enantioselective anti-aldol reaction using Tin(II) complex.

Evans et al. *JACS*. **1997**, *119*, 10859.
JACS. **1997**, *119*, 7893.

Table 4. enantioselective anti-aldol reaction between methyl pyruvate and silyl ketene acetals



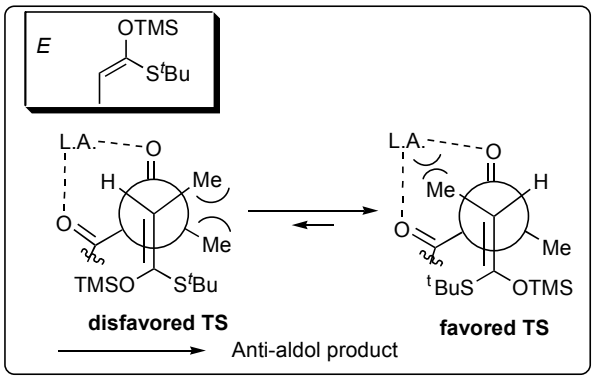


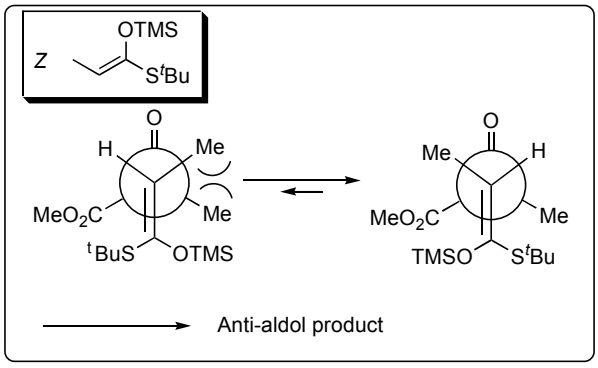


entry	SR	R^1	enolsilane geometry[a]	*anti:syn*	% ee[b,c]	% yield
1	S^{t}Bu	Me	(Z)	99:1	99	94
2	S^{t}Bu	Me	(*E*)	99:1	96	84
3	S^{t}Bu	Et	(Z)	98:2	97	84[d]
4	S^{t}Bu	^{i}Bu	(Z)	99:1	99	81[d]
5	SEt	Me	(Z)	95:5	92	91
6	SEt	Et	(Z)	99:1	97	94[d]
7	SEt	^{i}Bu	(Z)	99:1	97	76[d]

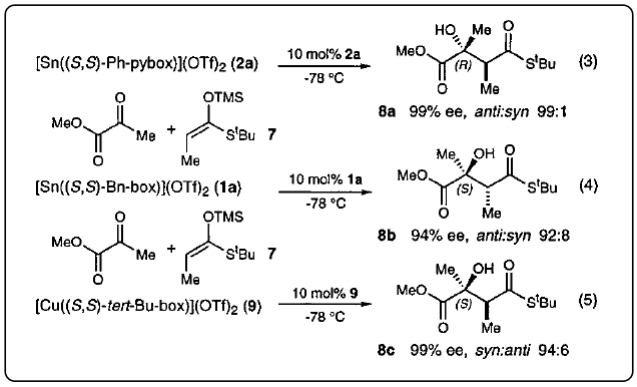
[a] Enolsilane isomeric purity ≥95%. [b] Product ratios determined by HPLC using a Chiralcel OD-H column after hydrolysis of the product TMS ether (ref 10). [c] Relative and absolute stereochemical assignments determined by independent synthesis (see Supporting Information). [d] Product configuration assigned by analogy.

Scheme 28. Anti-selectivity

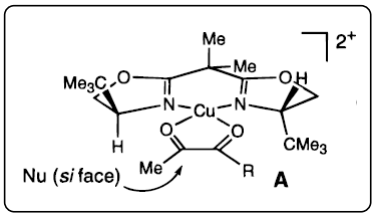




Scheme 29. Anti and syn control.



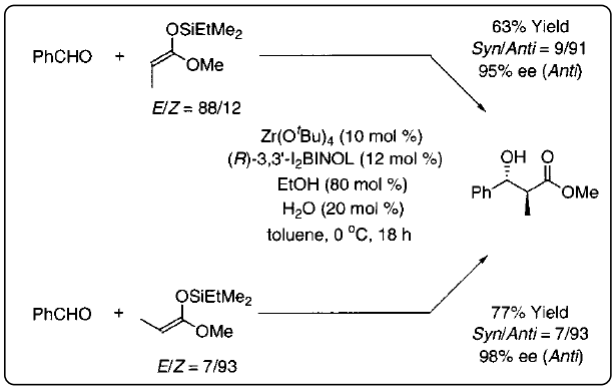
Scheme 30. Enantioselective formation of (5)



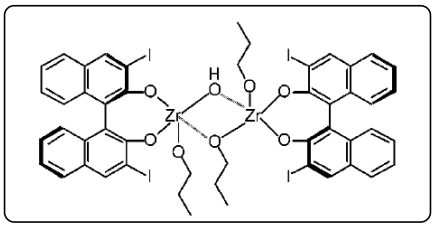
b. Anti-selective asymmetric aldol reaction using zirconium complex

Kobayashi et al. *JACS*. **2002**, *124*, 3292.

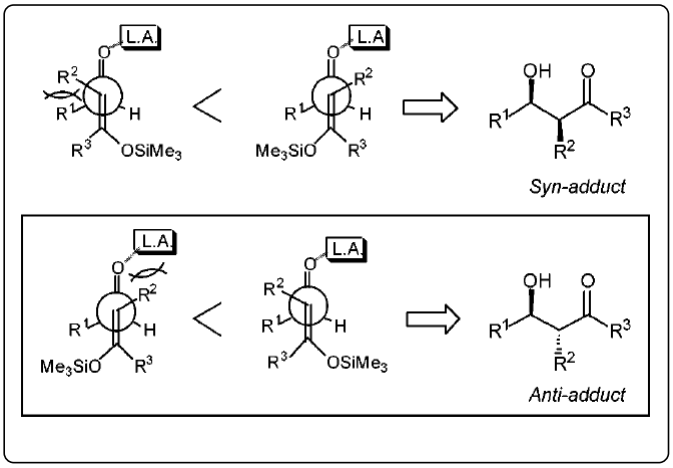
Scheme 31. Effect of geometry of the silyl enolates



Scheme 32. Assumed catalyst structure



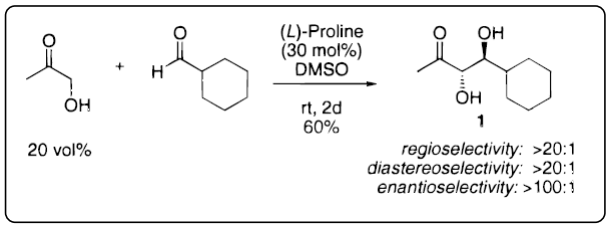
Scheme 33. Assumed transition states



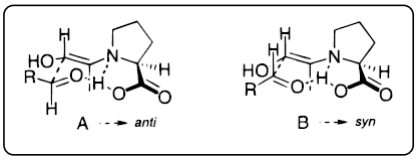
c. Catalytic asymmetric synthesis of anti-1,2-diols using organocatalysis

List et al. *JACS*. **2000**, *122*, 7386.

Scheme 34. Anti-aldol



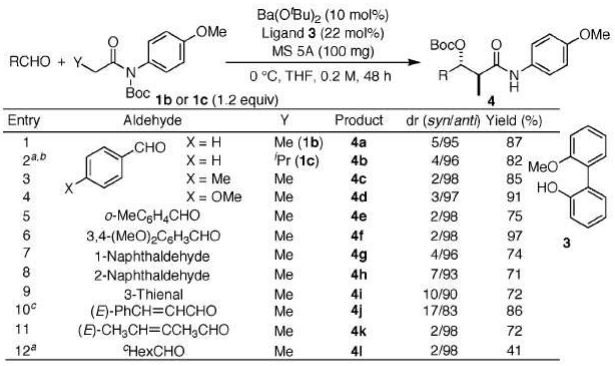
Scheme 35. Potential transition states



d. Anti-selective catalytic aldol reactions of amides with aldehydes

Kobayashi et al. *JACS*. **2006**, *128*, 8704.

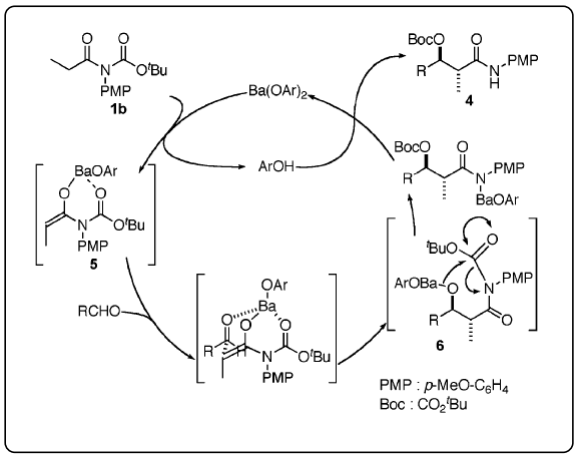
Table 5. Various aldehydes



Entry	Aldehyde	Y	Product	dr (*syn*/*anti*)	Yield (%)
1		X = H, Me (**1b**)	**4a**	5/95	87
2[a,b]		X = H, ^{i}Pr (**1c**)	**4b**	4/96	82
3		X = Me	**4c**	2/98	85
4		X = OMe	**4d**	3/97	91
5	*o*-MeC$_6$H$_4$CHO	Me	**4e**	2/98	75
6	3,4-(MeO)$_2$C$_6$H$_3$CHO	Me	**4f**	2/98	97
7	1-Naphthaldehyde	Me	**4g**	4/96	74
8	2-Naphthaldehyde	Me	**4h**	7/93	71
9	3-Thienal	Me	**4i**	10/90	72
10[c]	(*E*)-PhCH=CHCHO	Me	**4j**	17/83	86
11	(*E*)-CH$_3$CH=CCH$_3$CHO	Me	**4k**	2/98	72
12[a]	^{c}HexCHO	Me	**4l**	2/98	41

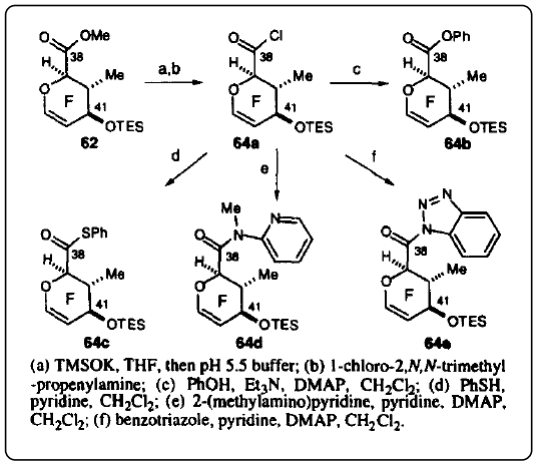
[a] Room temperature in DME. [b] Relative configuration was assigned by analogy. [c] 2,6-Dimethylphenol was used instead of ligand **3**.

Scheme 36. Assumed catalytic cycle



Synthesis of E,F-ring segment (continued):

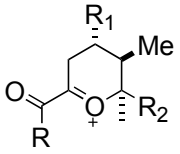
Scheme 37. Evans synthesis of F-ring segment



(a) TMSOK, THF, then pH 5.5 buffer; (b) 1-chloro-2,*N*,*N*-trimethyl-propenylamine; (c) PhOH, Et$_3$N, DMAP, CH_2Cl_2; (d) PhSH, pyridine, CH_2Cl_2; (e) 2-(methylamino)pyridine, pyridine, DMAP, CH_2Cl_2; (f) benzotriazole, pyridine, DMAP, CH_2Cl_2.

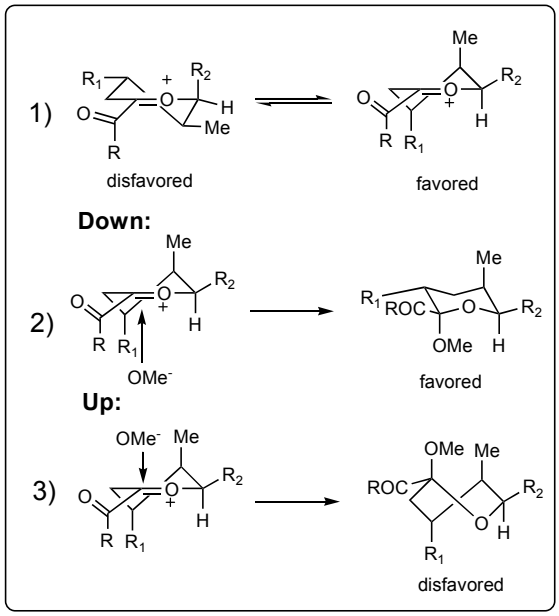
Scheme 39.

65 ⟶ **66**

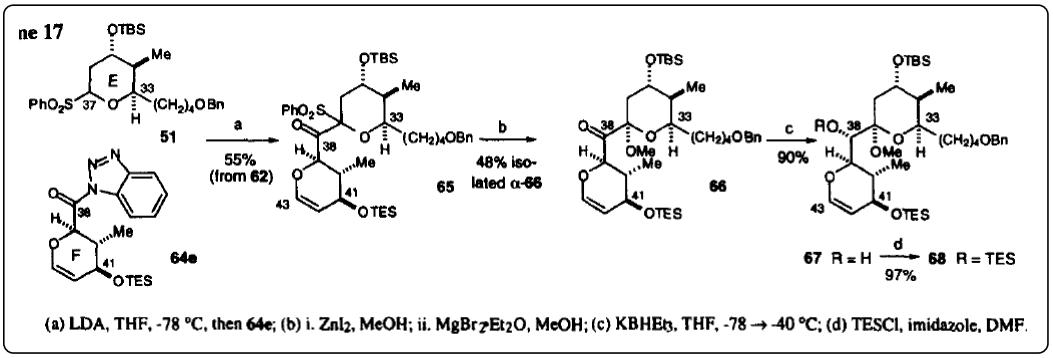


65a

R_1=OTBS
R_2=$(CH_2)_4$OBn
R=Ring F

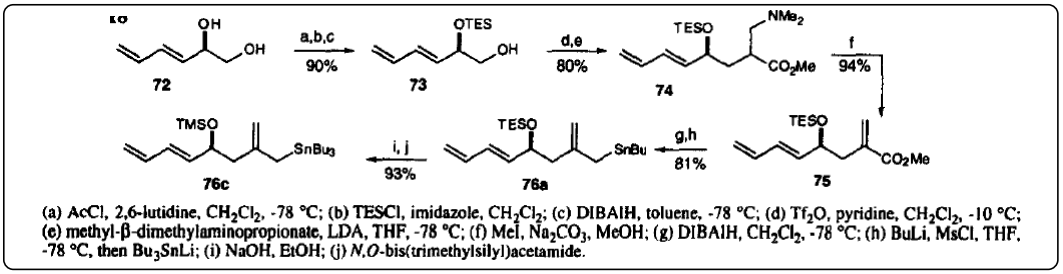


Scheme 38. Evans connection of E-ring and F-ring segment



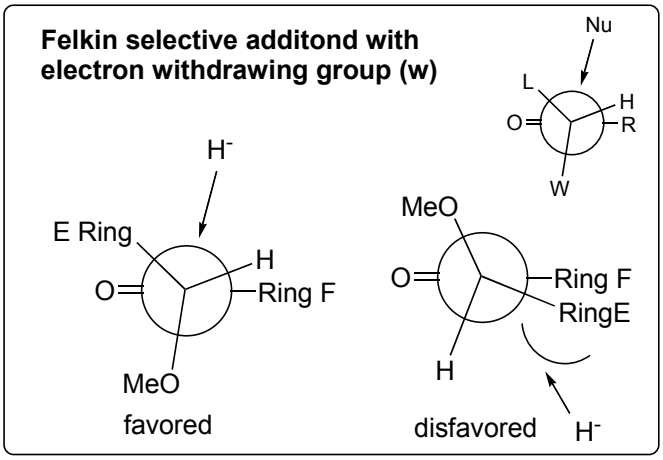
(a) LDA, THF, -78 °C, then **64e**; (b) i. ZnI$_2$, MeOH; ii. MgBr$_2$·Et$_2$O, MeOH; (c) KBHEt$_3$, THF, -78 → -40 °C; (d) TESCl, imidazole, DMF.

Scheme 41. Evans synthesis of E,F-ring segment

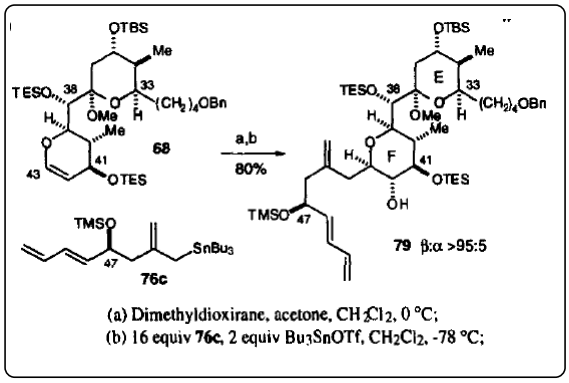


(a) AcCl, 2,6-lutidine, CH_2Cl_2, -78 °C; (b) TESCl, imidazole, CH_2Cl_2; (c) DIBAlH, toluene, -78 °C; (d) Tf_2O, pyridine, CH_2Cl_2, -10 °C; (e) methyl-β-dimethylaminopropionate, LDA, THF, -78 °C; (f) MeI, Na_2CO_3, MeOH; (g) DIBAlH, CH_2Cl_2, -78 °C; (h) BuLi, MsCl, THF, -78 °C, then Bu_3SnLi; (i) NaOH, EtOH; (j) *N*,*O*-bis(trimethylsilyl)acetamide.

Scheme 40. **65** ⟶ **66**

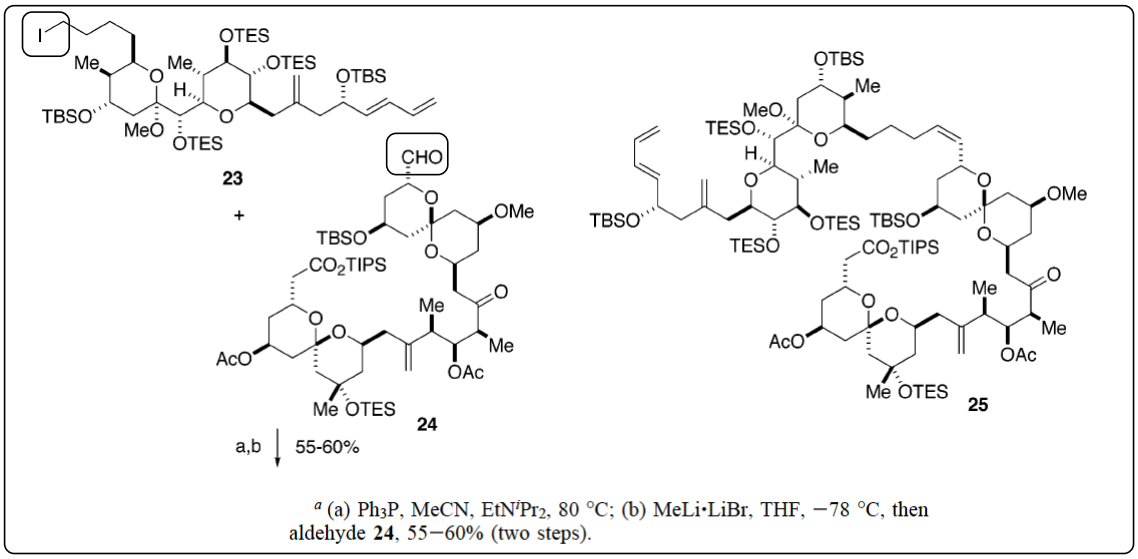


Scheme 42. Evans synthesis of E,F-ring segment

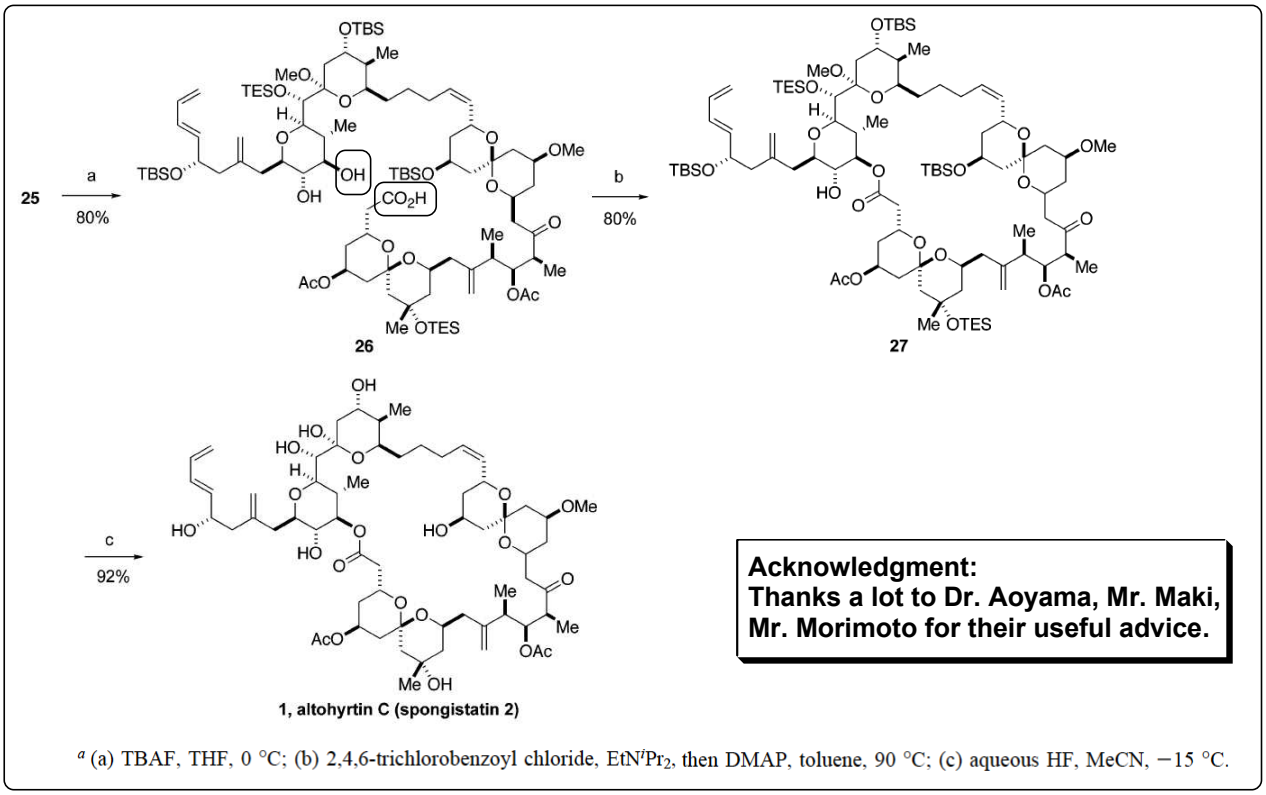


4. Heathcock connection of AB, CD, E, F-ring segment

Scheme 41.



Scheme 42.



Acknowledgment:
Thanks a lot to Dr. Aoyama, Mr. Maki, Mr. Morimoto for their useful advice.