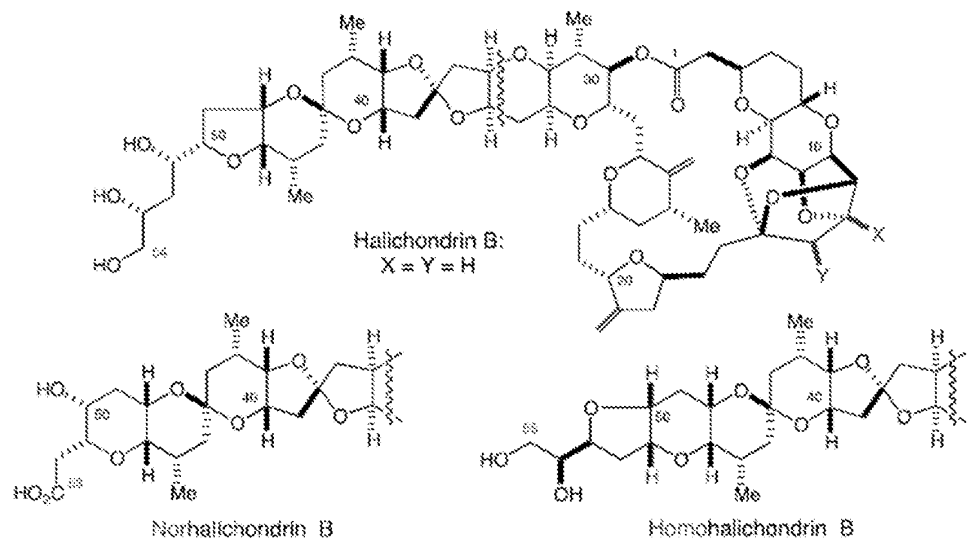




	A series (X = Y = OH)	B series (X = Y = H)	C series (X = OH; Y = H)
Halichondrin	Note-1	known	known
Norhalichondrin	known	known	known
Homohalichondrin	known	known	known

Figure 1

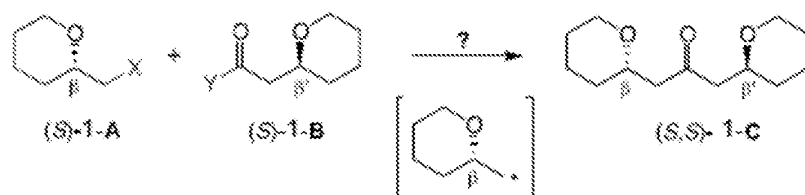


Figure 2A

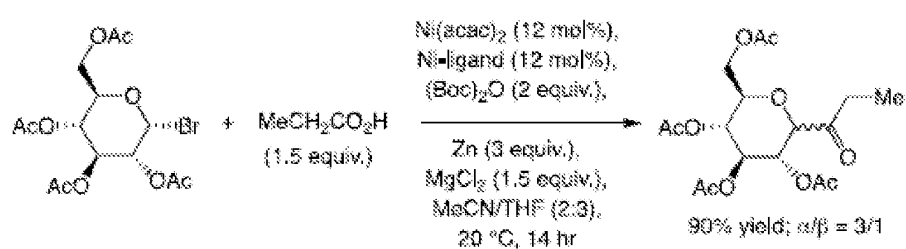
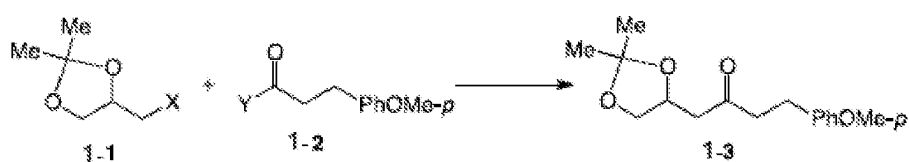


Figure 2B



Welx System (X = I; Y = SPy): 39% yield

NiCl₂(dtbbpy), Mn, DMA, rt, 12 hr

Reisman System (X = I; Y = Cl): 21% yield

NiCl₂(dme), bis(oxazoline), Mn, 2,6-di-MePhCO₂H, DMA-THF, 20 °C, 24 hr

Gong System (X = Br; Y = OH): no desired product formation

(Boc)₂O, NiCl₂(dtbbpy), TBAI, MgCl₂, Zn, DMF-THF, 20 °C, 14 hr

Figure 2C

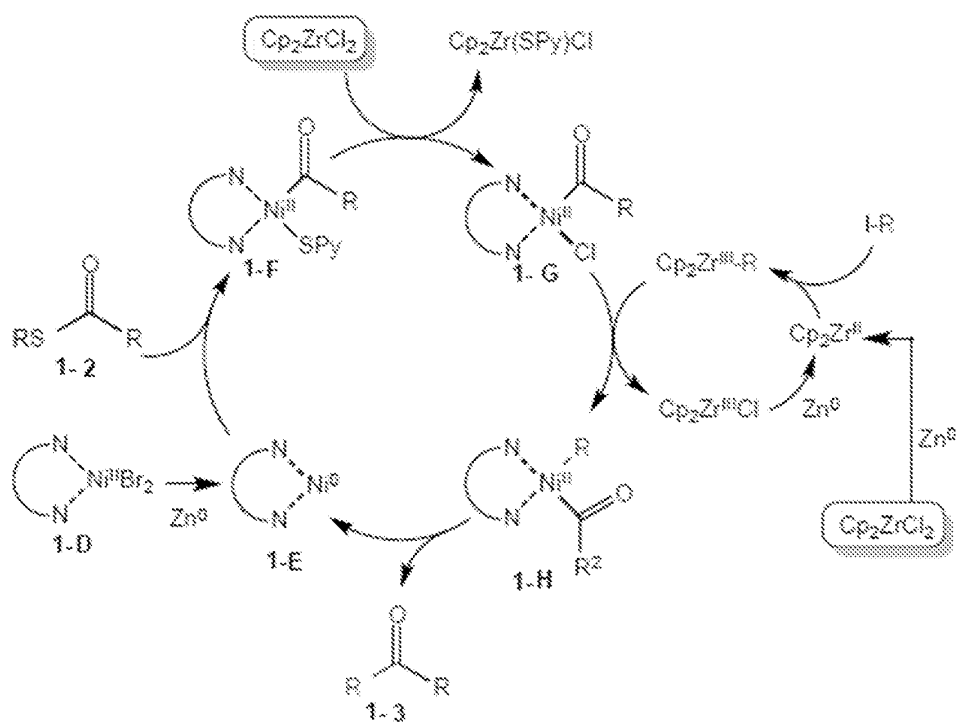


Figure 3A

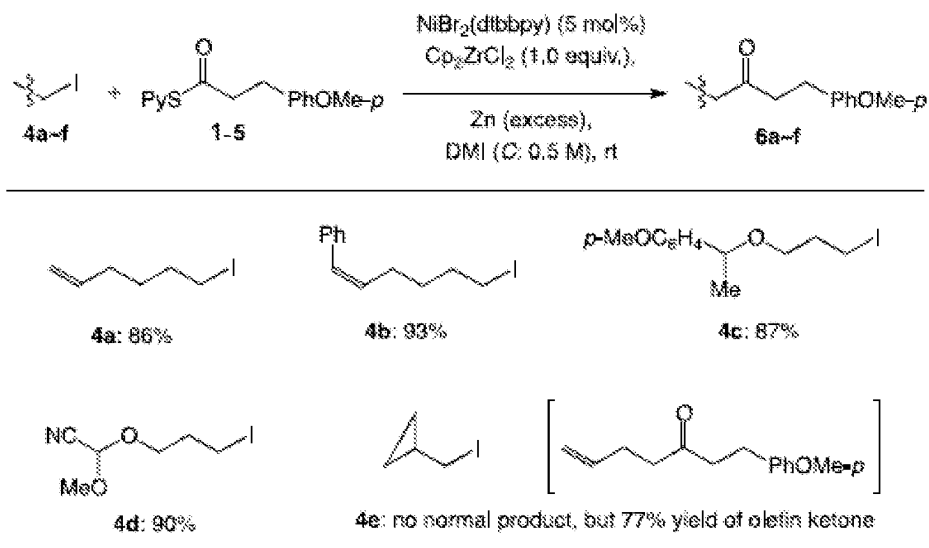


Figure 3B

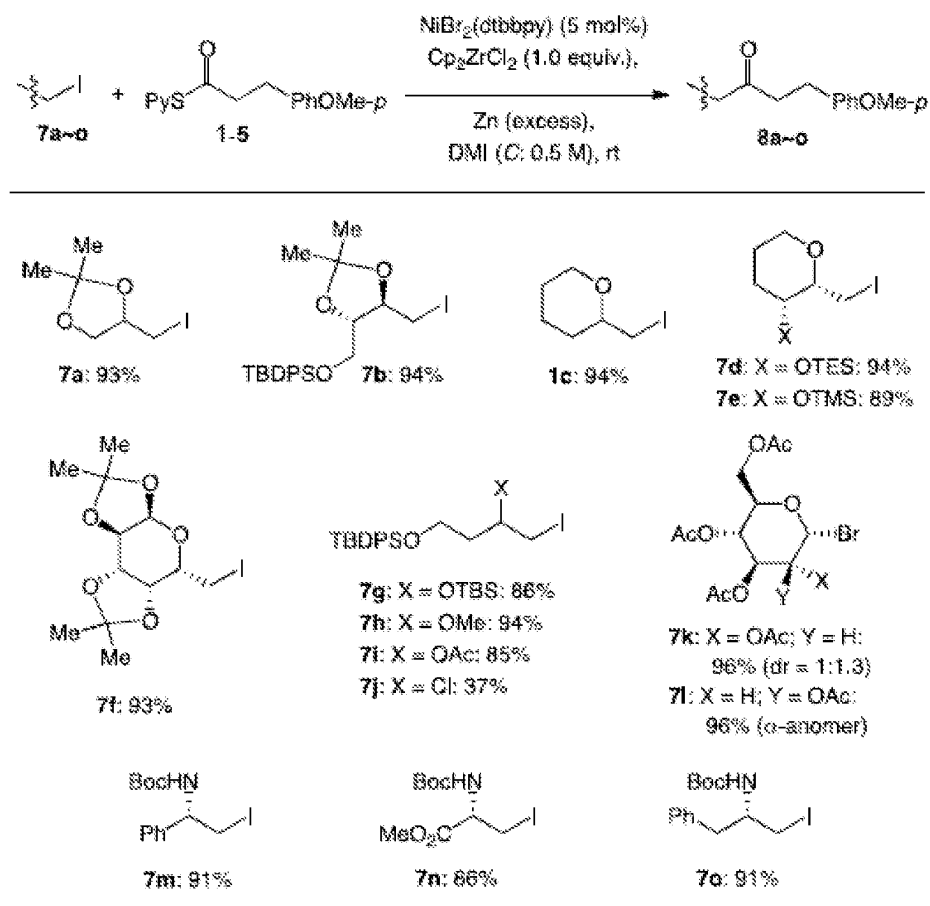


Figure 4

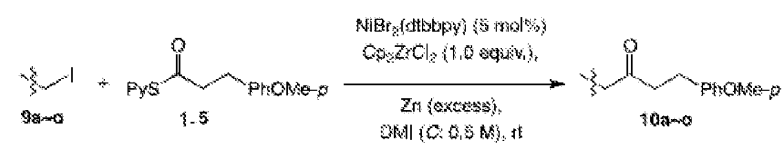
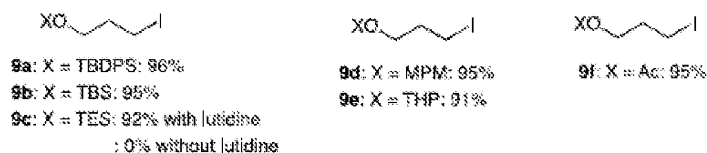
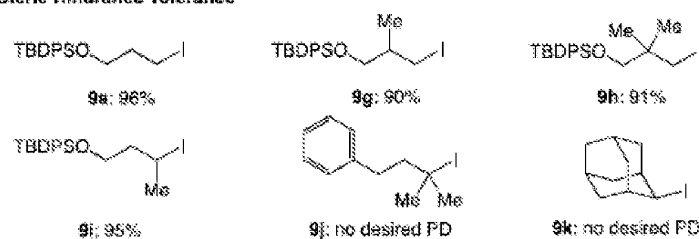
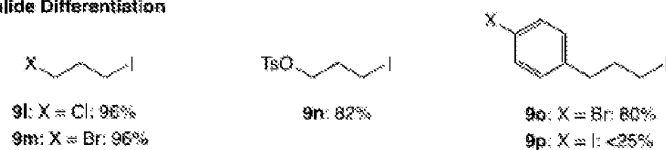
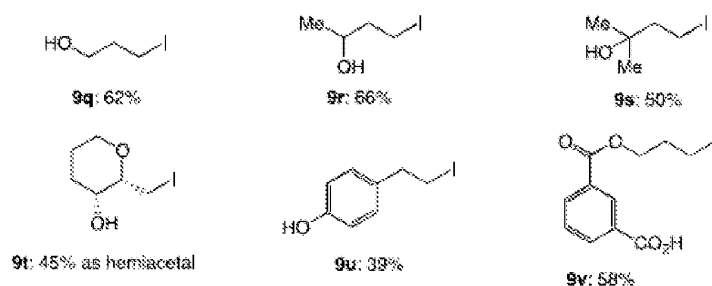
**a. Protecting Group Tolerance****b. Steric Hindrance Tolerance****c. Halide Differentiation****d. Substrates bearing Free Alcohol and Acid**

Figure 5A

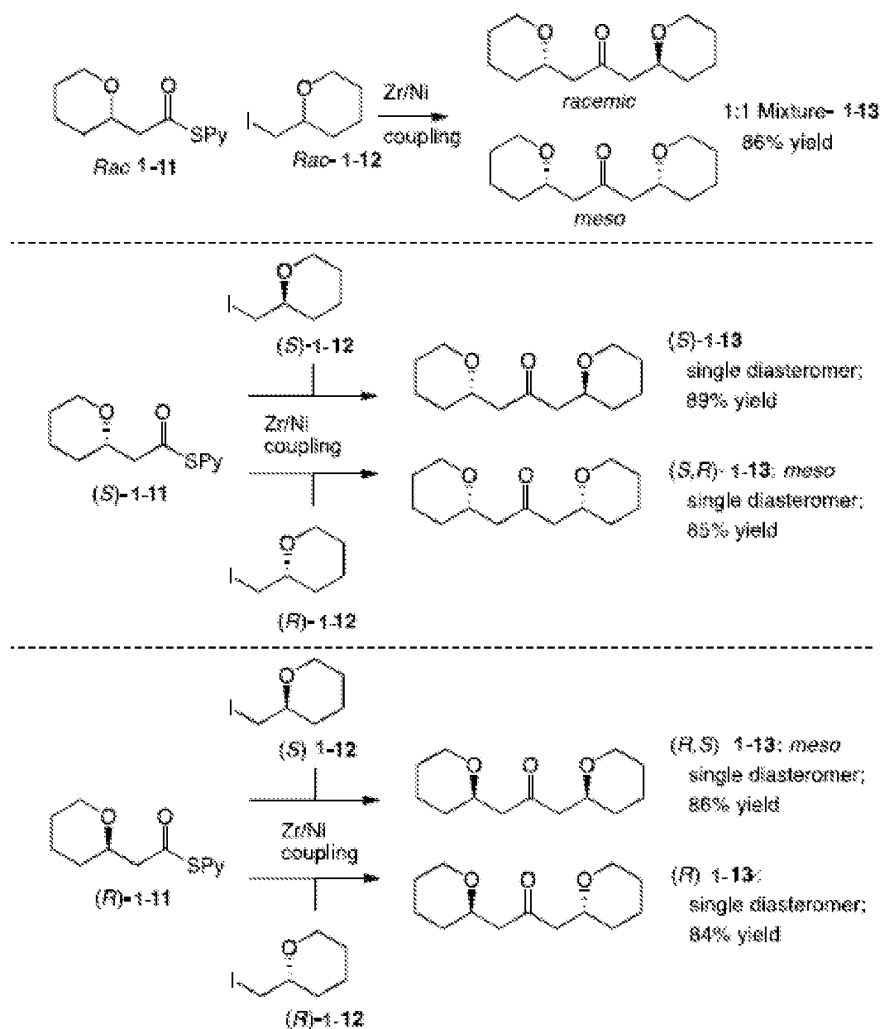


Figure 5B

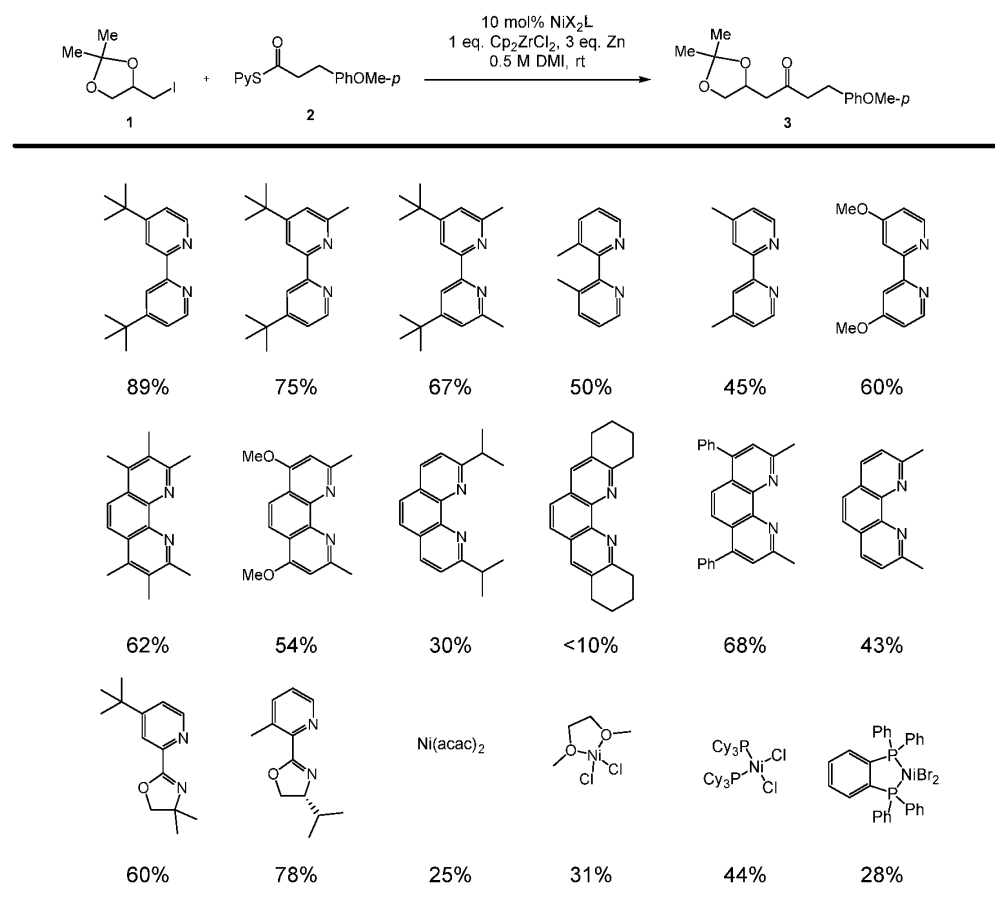
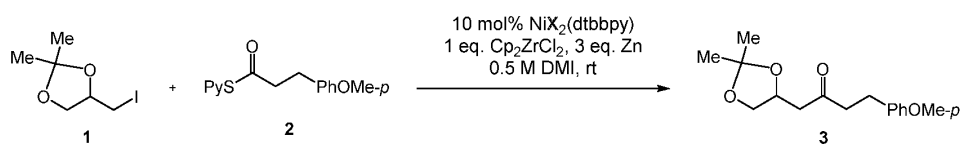
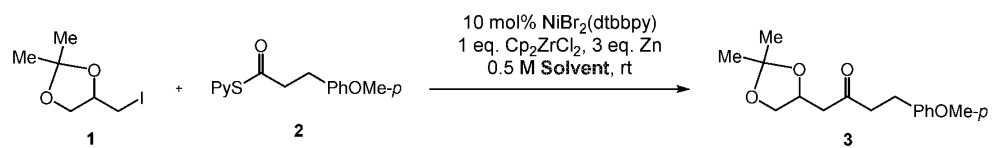


Figure 5C



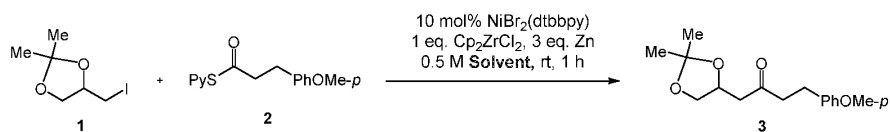
Entry	$\text{Ni}(\text{dtbbpy})\text{X}_2$	Reaction times (h)	Results (%)
1	Cl	1	89
2	Br	0.5	93
3	I	1	57

Figure 5D



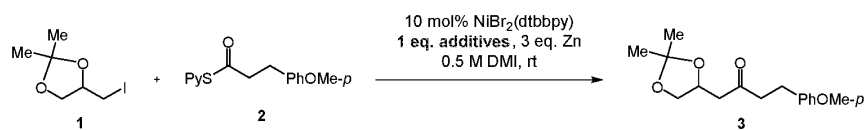
Entry	Solvent	Reaction times (h)	Results (%)
1	DMI	0.5	89
2	DMF	1	<10
3	DMA	1	75
4	DMPU	1	67
5	DMSO	1	60
6	HMPU	1	63
7	THF	4	57
8	Et ₂ O	6	40
9	MeCN	1	30
10	toluene	12	36
11	1,4-dioxane	2	56
12	CH ₂ Cl ₂	4	44
13	DME	2	50
14	NMP	1	70
15	HFIP	12	<10
16	EtOAc	12	<10

Figure 5E



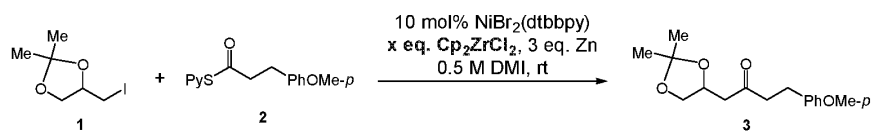
Entry	Co-Solvent	Results (%)
1	DMI-EtOAc (1:1)	78
2	DMI-MeCN (1:1)	45
3	DMI-THF (1:1)	55
4	DMI-DME (1:1)	20
5	DMI-PrCN (1:1)	20
6	DMA-EtOAc (1:1)	64
7	DMI-EtOAc (5:1)	88
8	DMI-EtOAc (3:1)	83
9	DMI-EtOAc (2:1)	78
10	DMI-EtOAc (1:1)	70
11	DMI-EtOAc (1:2)	40
12	DMI-EtOAc (1:4)	<10
13	DMI-EtOAc (1:20)	<10

Figure 5F



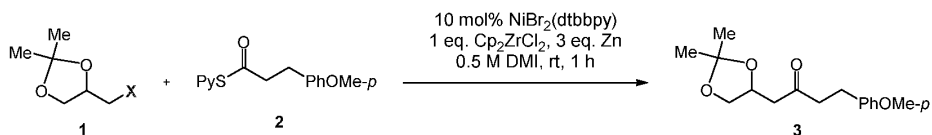
Entry	additive	Results (%)
1	none	50
2	Cp ₂ ZrCl ₂	92
3	TESCl	60
4	TMSCl	<10
5	CoPc (1 mol%)	30
6	CrCl ₂ (25 mol%)	46
7	Lil	51
8	MgCl ₂	34
9	<i>p</i> -F-styrene (10 mol%)	76
10	<i>p</i> -CF ₃ -styrene (10 mol%)	55

Figure 5G



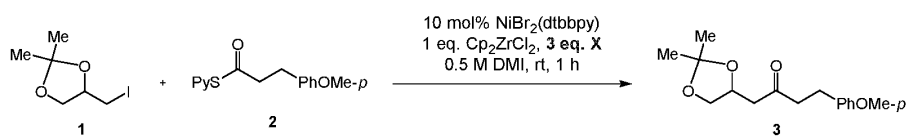
Entry	equiv. Cp ₂ ZrCl	Reaction times (h)	Results (%)
1	0	12	45
2	0.1	12	51
3	0.5	3	51
4	1.0	<1	94
5	2.0	<1	90

Figure 5H



Entry	X	Results (%)
1	I	90
2	Br	<10
3	Br+LiI	85

Figure 5I



Entry	Reductant	Results (%)
1	Zn	90
2	Mn	80
3	Mg	25
4	tetrakis(dimethylamino)ethylene	20

Figure 5J

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Entry	Concentration (M)	Time (h)	Results (%)
1	0.5	0.5	92
2	0.25	1	72
3	0.1	4	30
4	0.05	12	17
5	0.025	12	<10
6	0.001	12	<10
7	0.1 (3 eq. Cp ₂ ZrCl ₂ , 30 mol% Ni(dtbppy)Br ₂)	1.5	85
8	0.05 (3 eq. Cp ₂ ZrCl ₂ , 30 mol% Ni(dtbppy)Br ₂)	3	76
9	0.001 (5 eq. Cp ₂ ZrCl ₂ , 50 mol% Ni(dtbppy)Br ₂)	6	55

Figure 5K

Entry	ratio of 1 and 2	Results (%)
1	1.5:1.0	89
2	1.2:1.0	89
3	1.1:1.0	80
4	1.0:1.0	75
5	0.8:1.0	75

Figure 5L

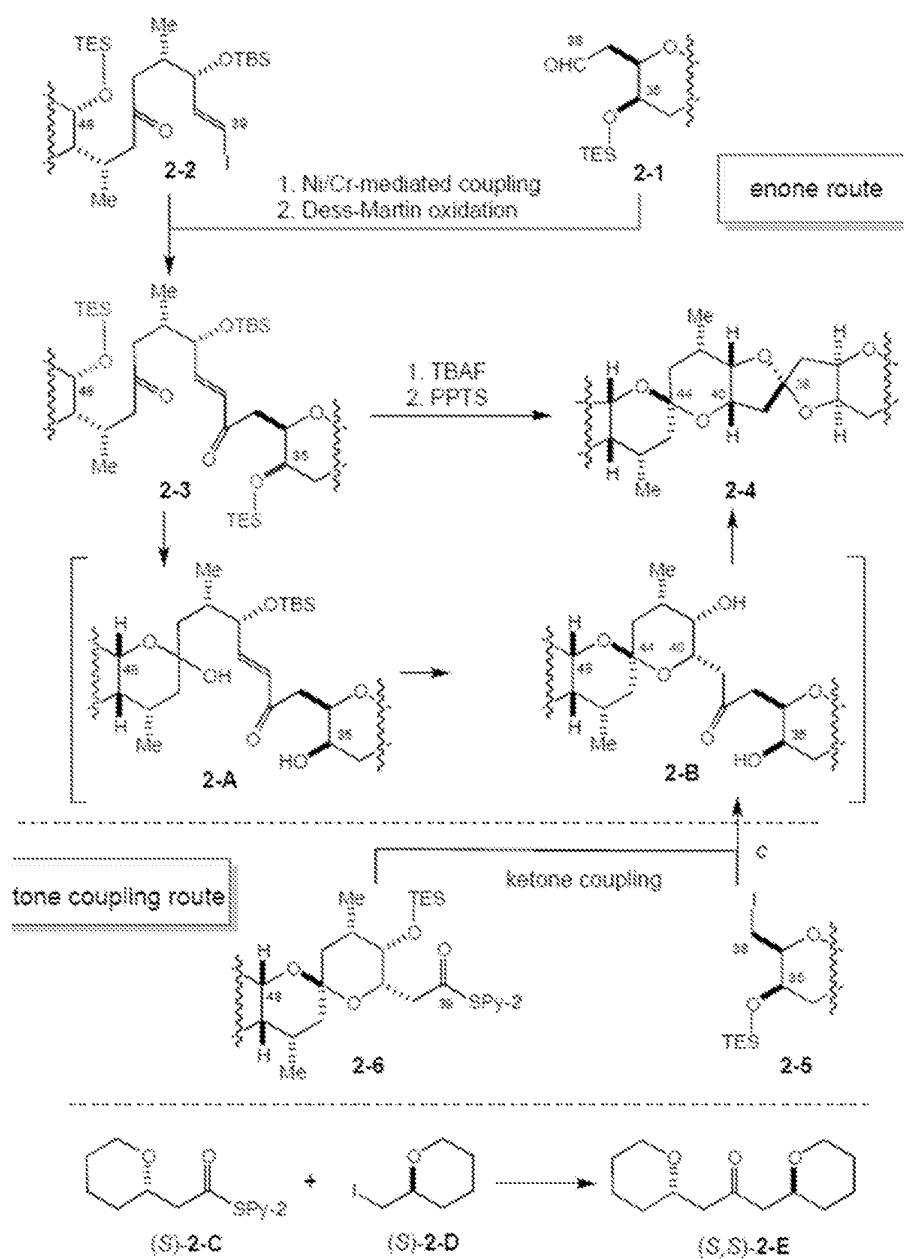


Figure 6

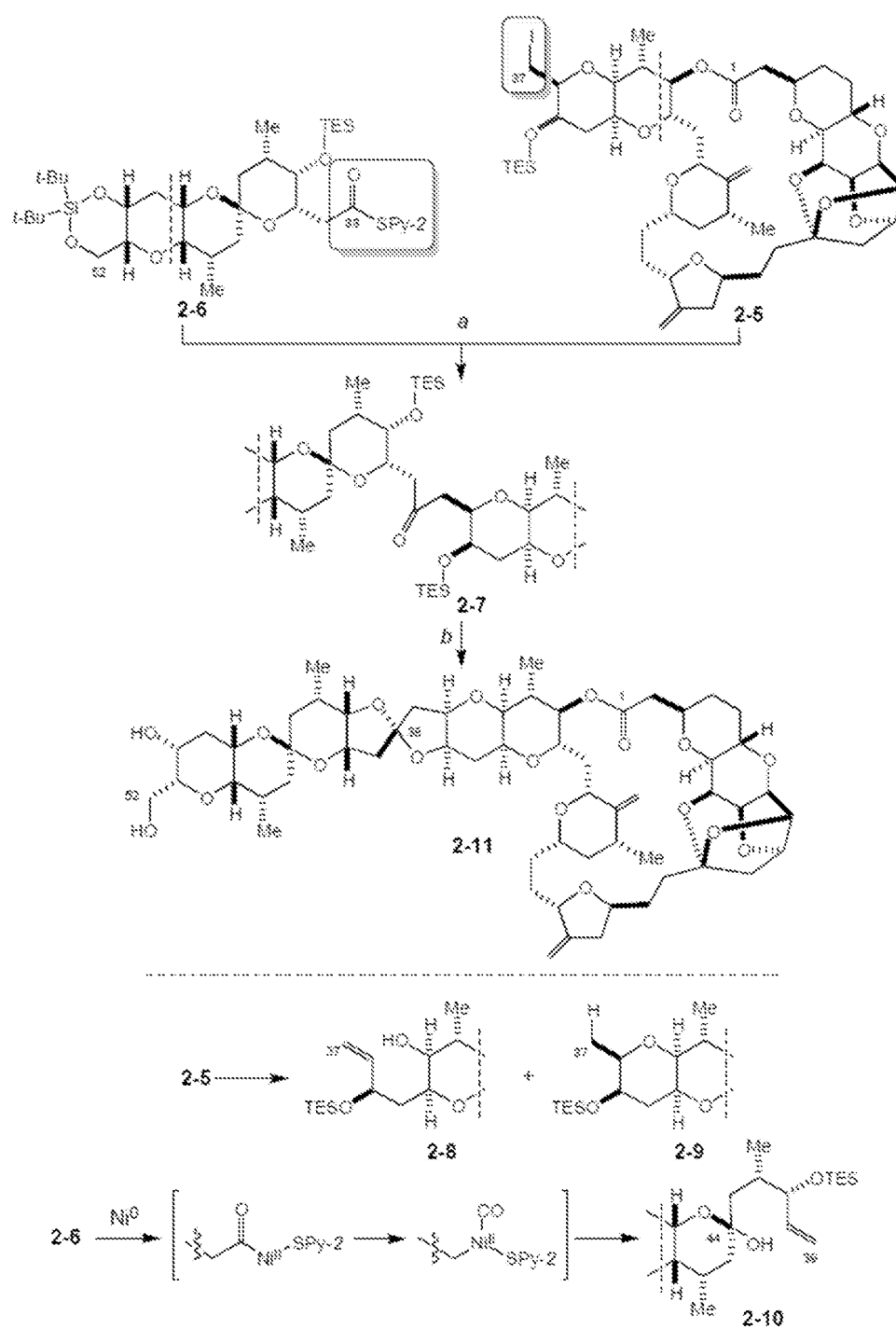


Figure 7

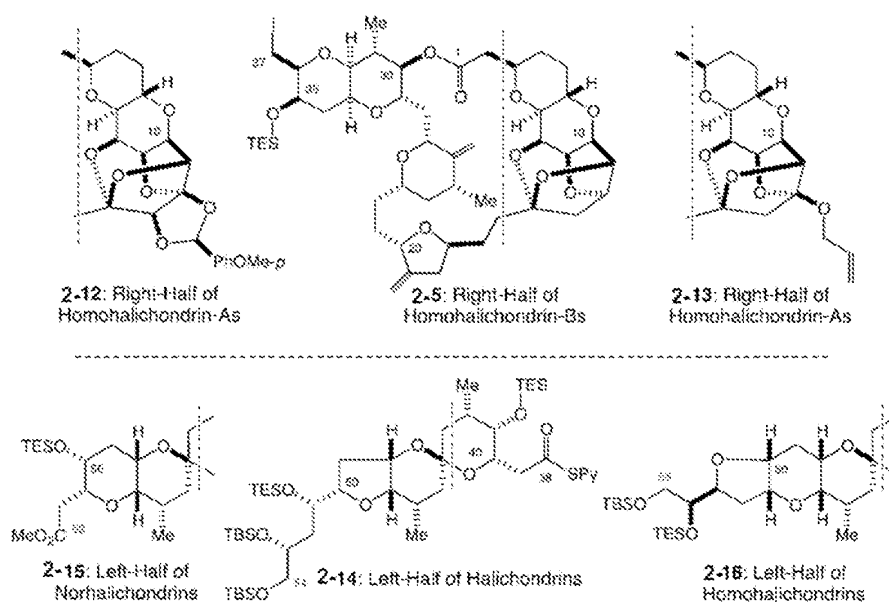


Figure 8A

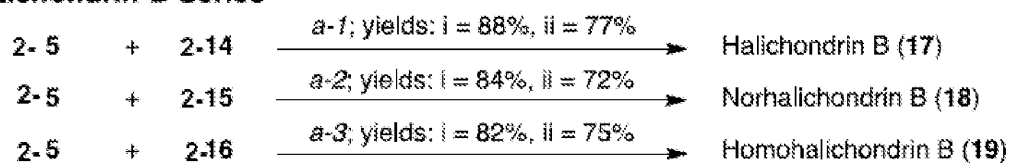
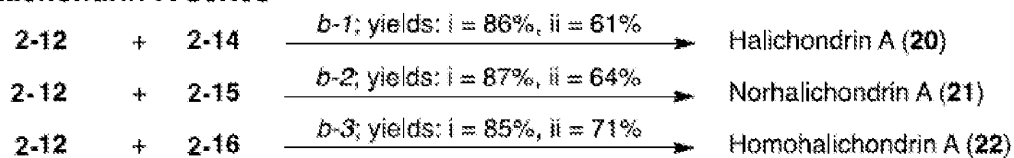
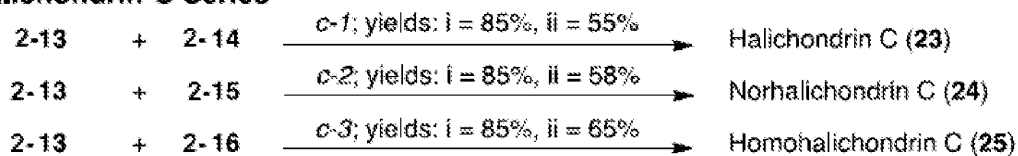
Halichondrin-B Series**Halichondrin-A Series****Halichondrin-C Series**

Figure 8B

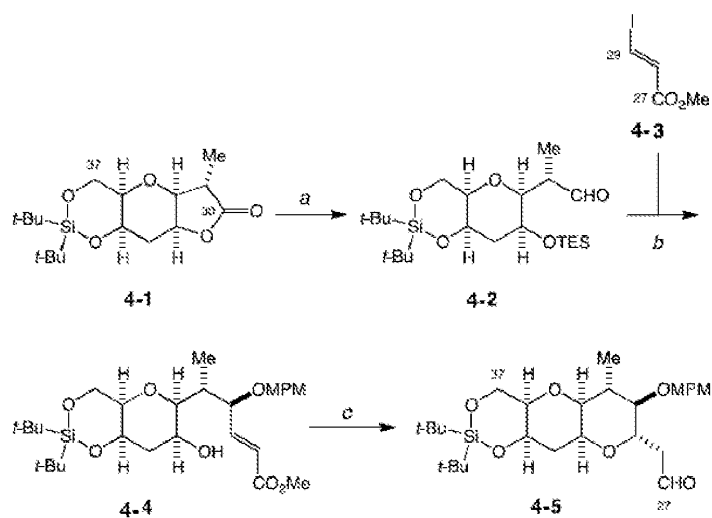


Figure 9A

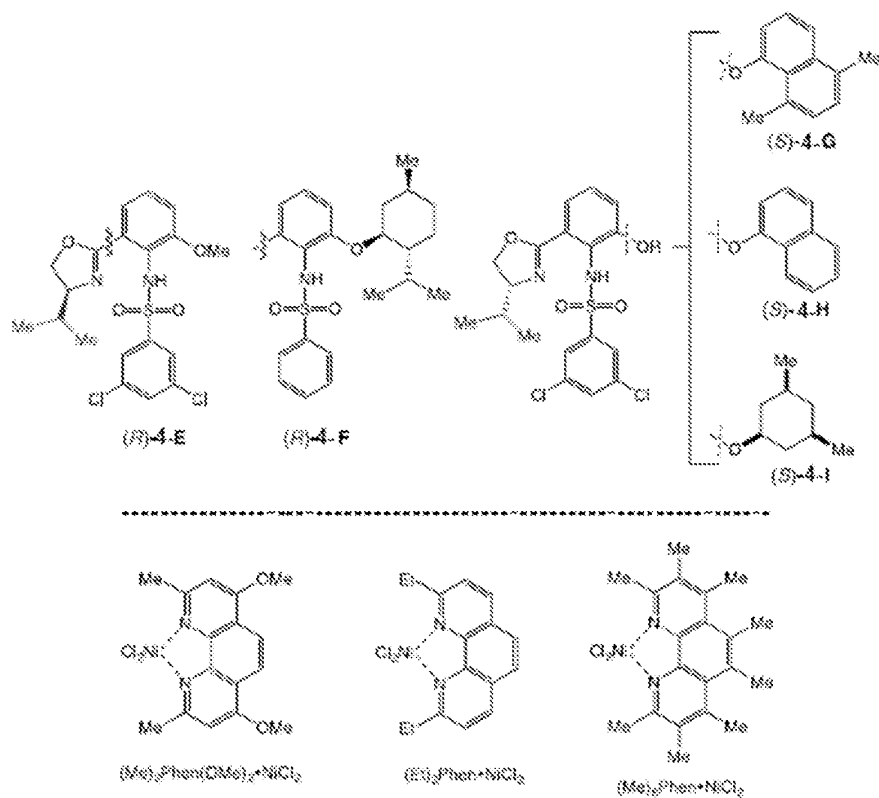


Figure 9B

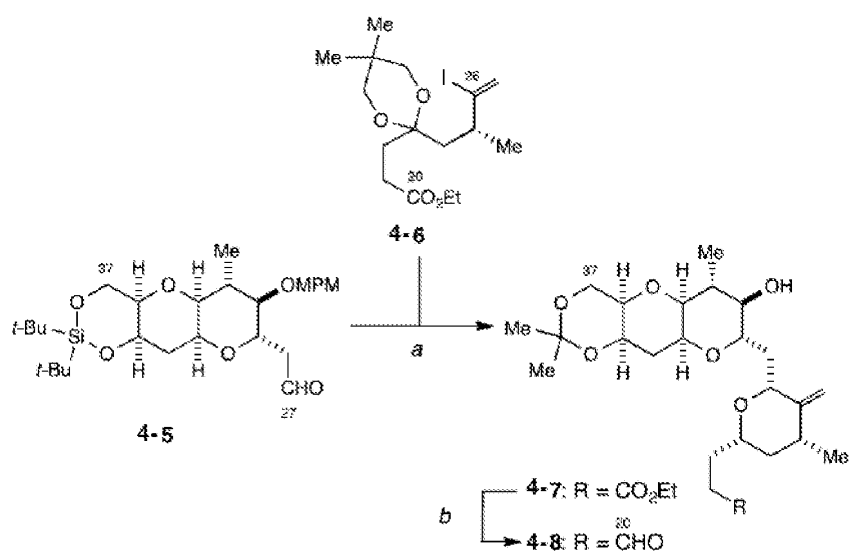


Figure 10A

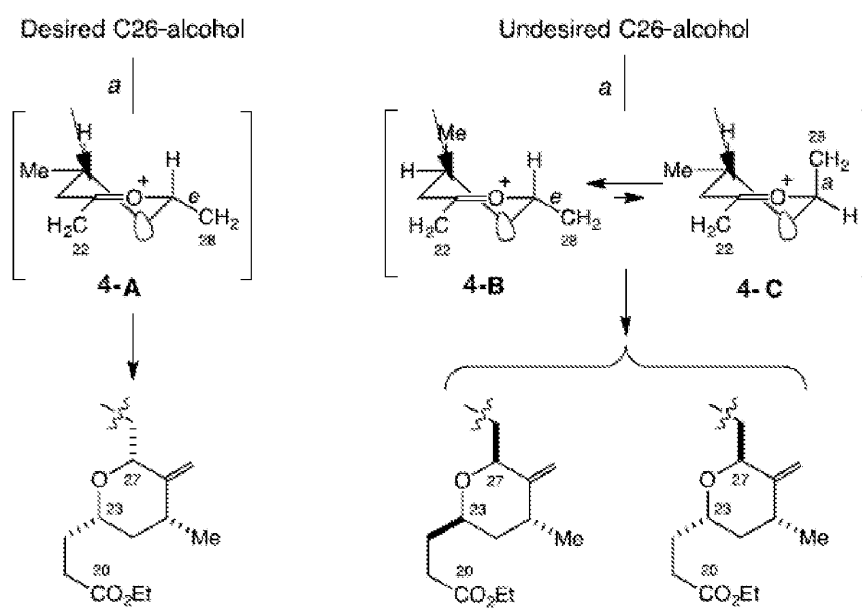


Figure 10B

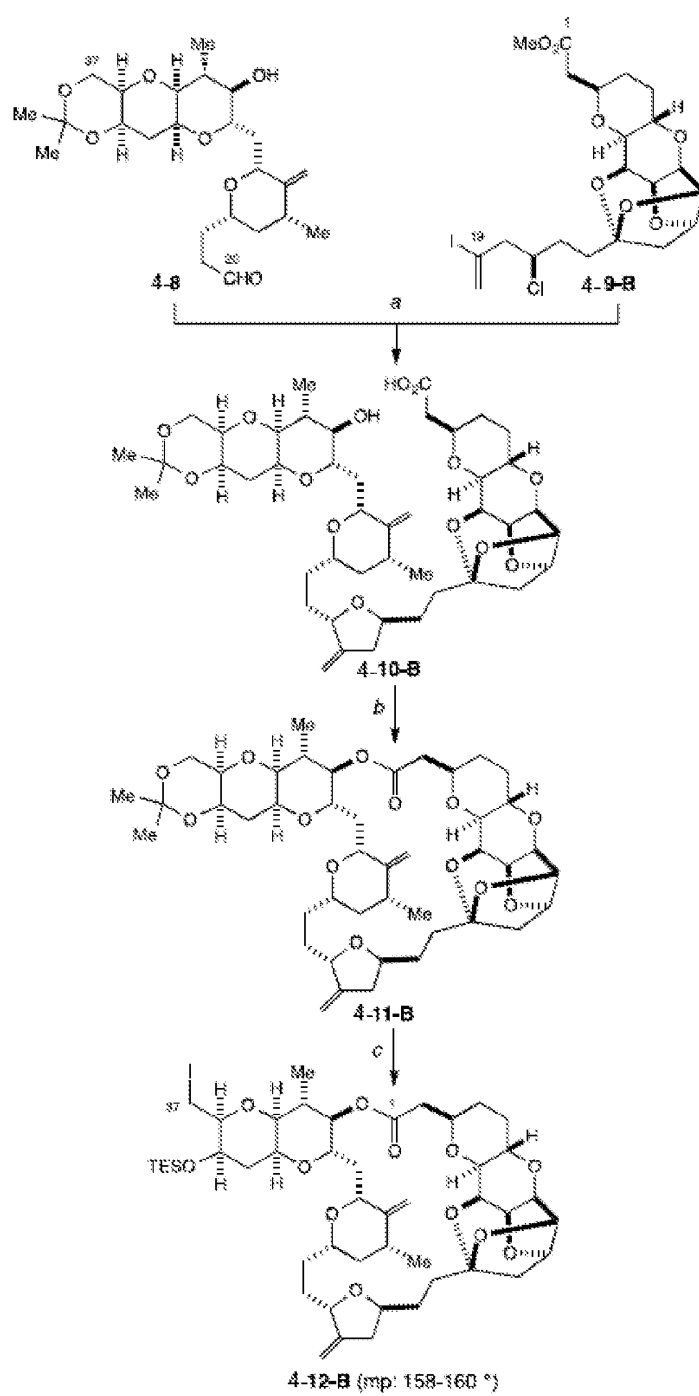


Figure 11

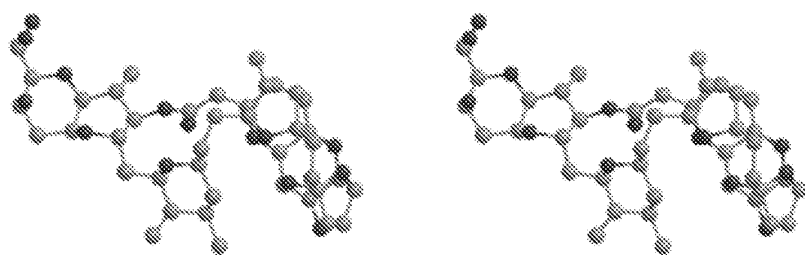


Figure 12

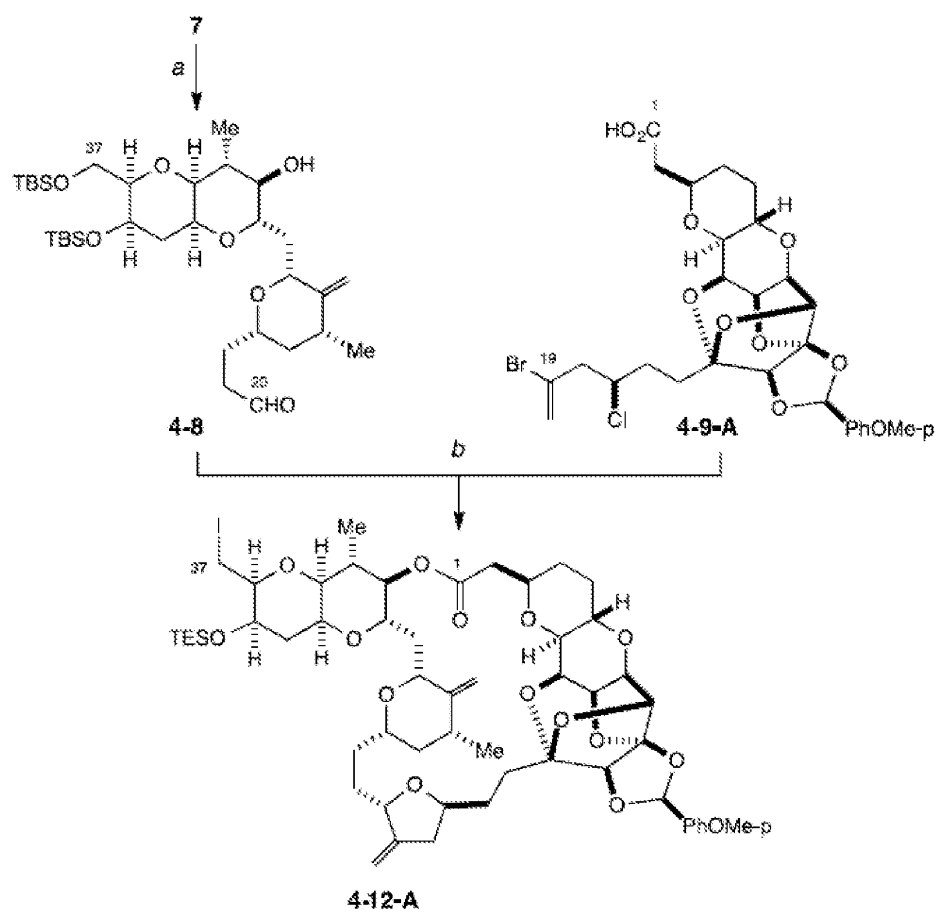


Figure 13

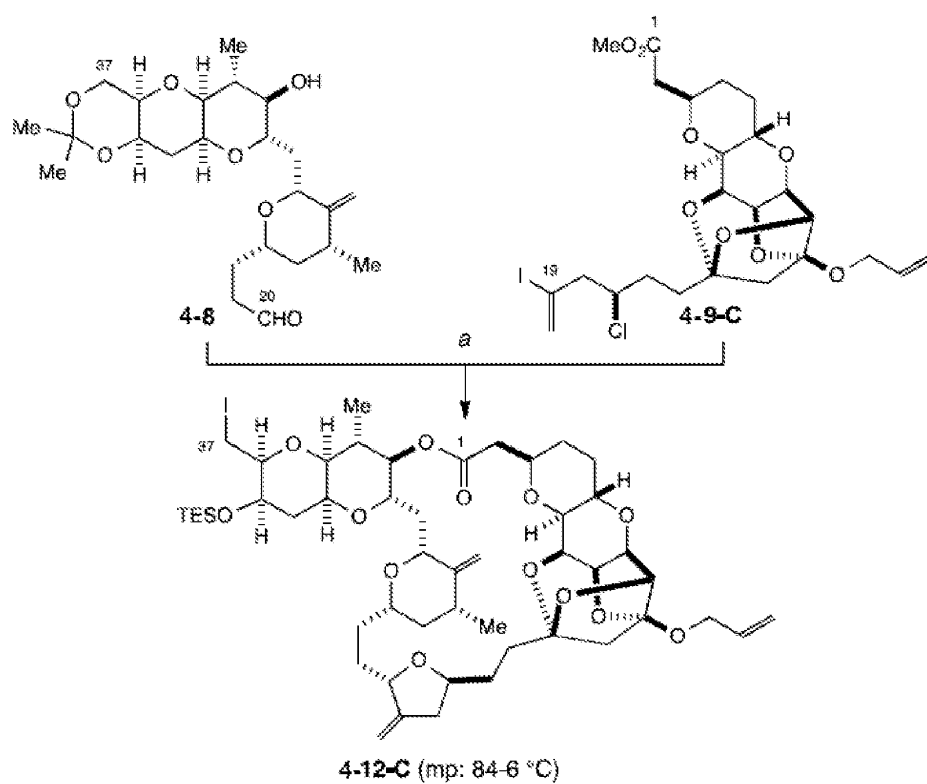


Figure 14A

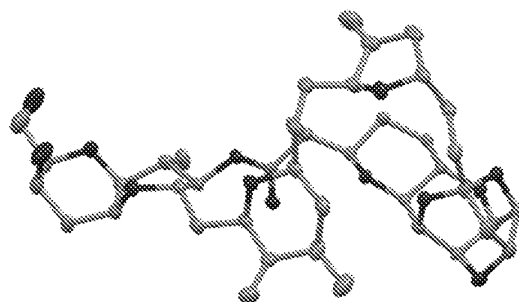
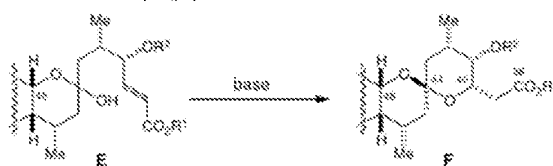
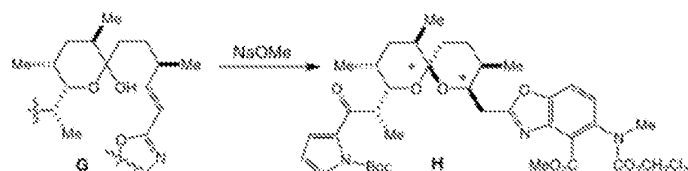


Figure 14B

Plan for construction of the [6.6]-spiroketal



Precedent 1



Precedent 2

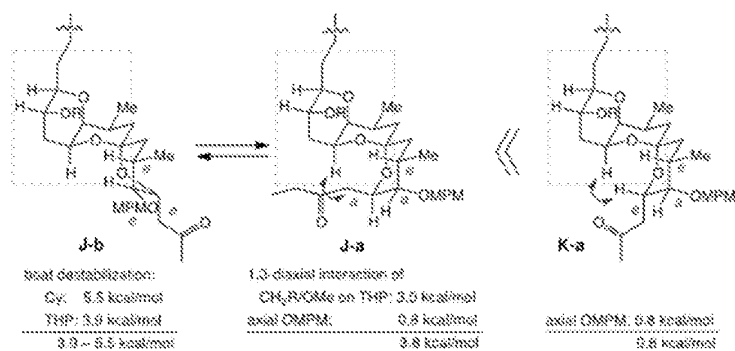
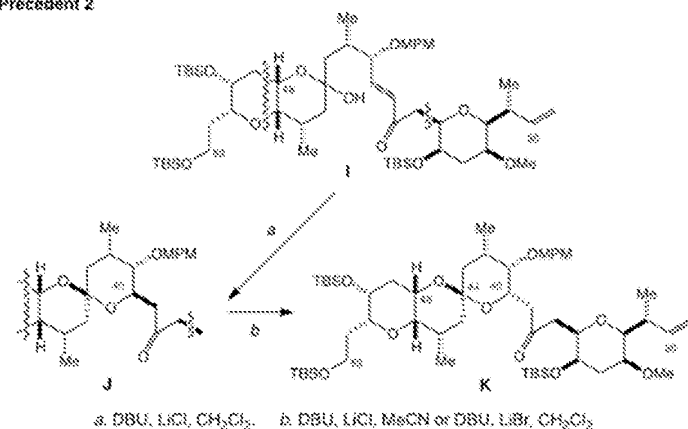


Figure 15

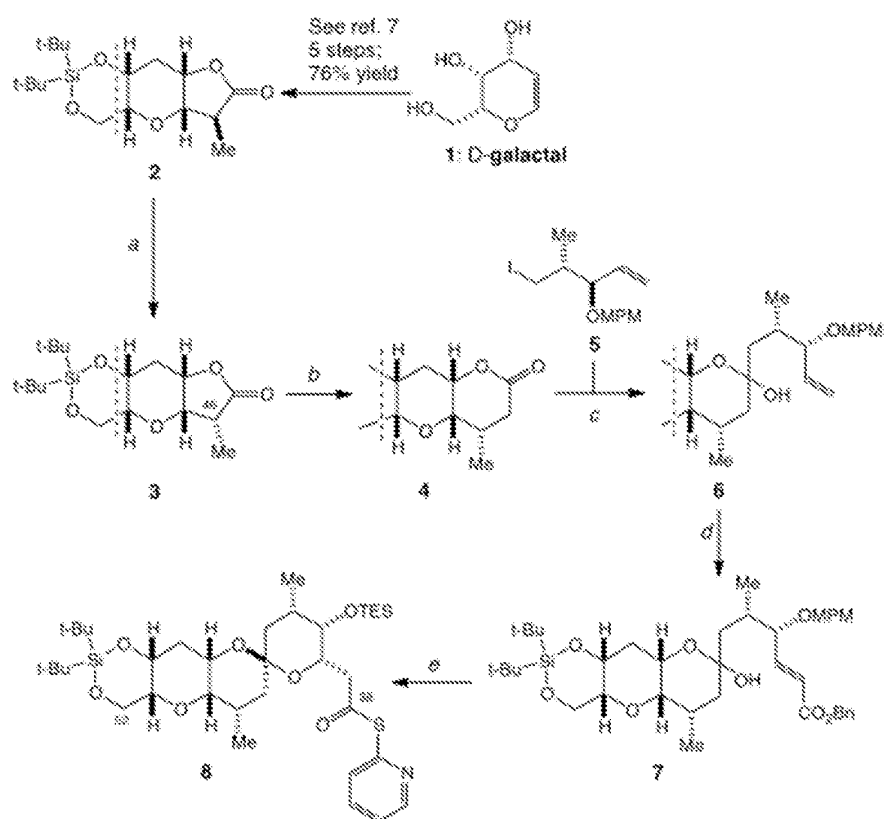


Figure 16

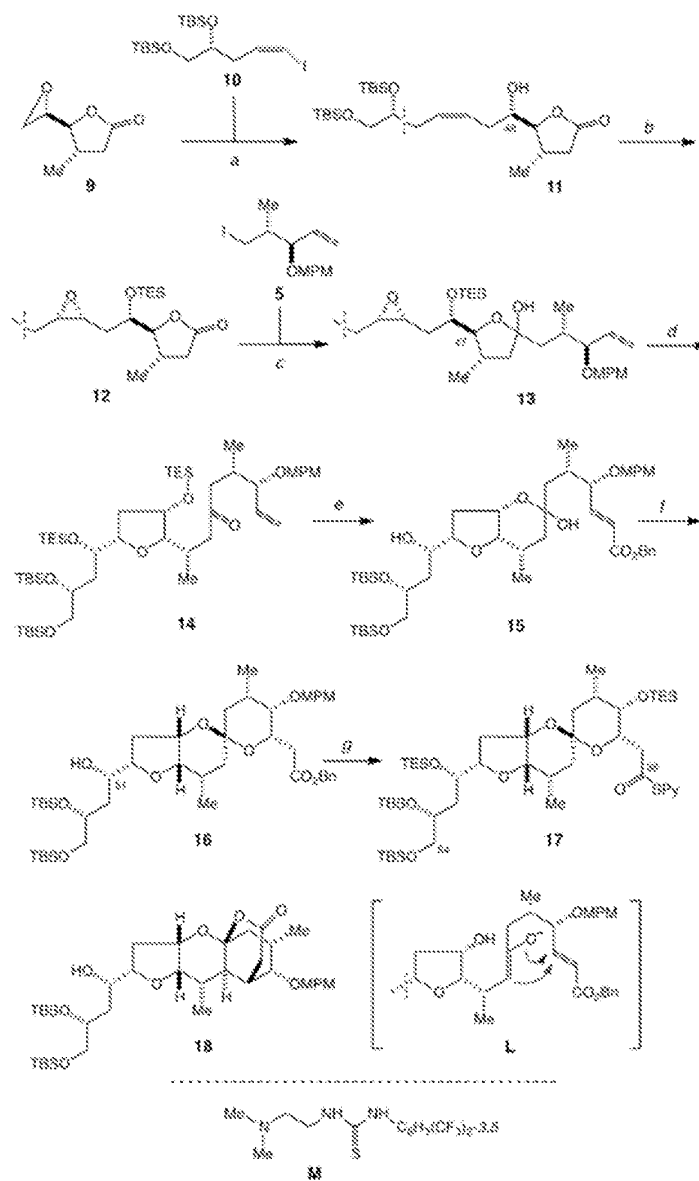


Figure 17

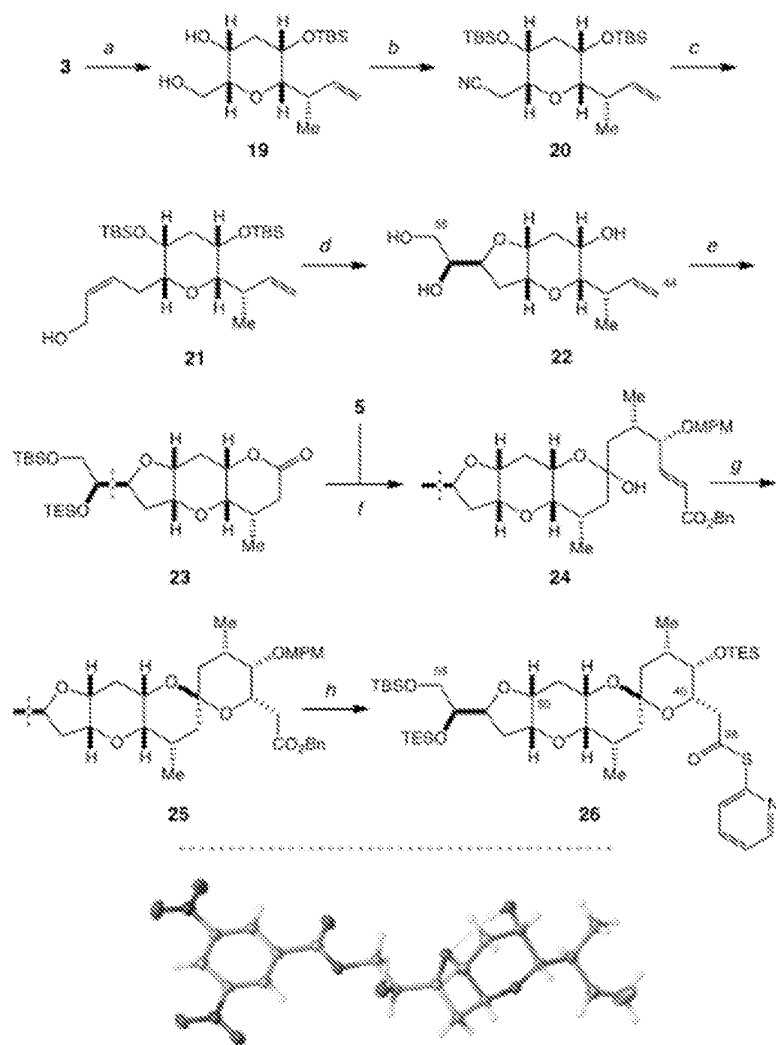


Figure 18

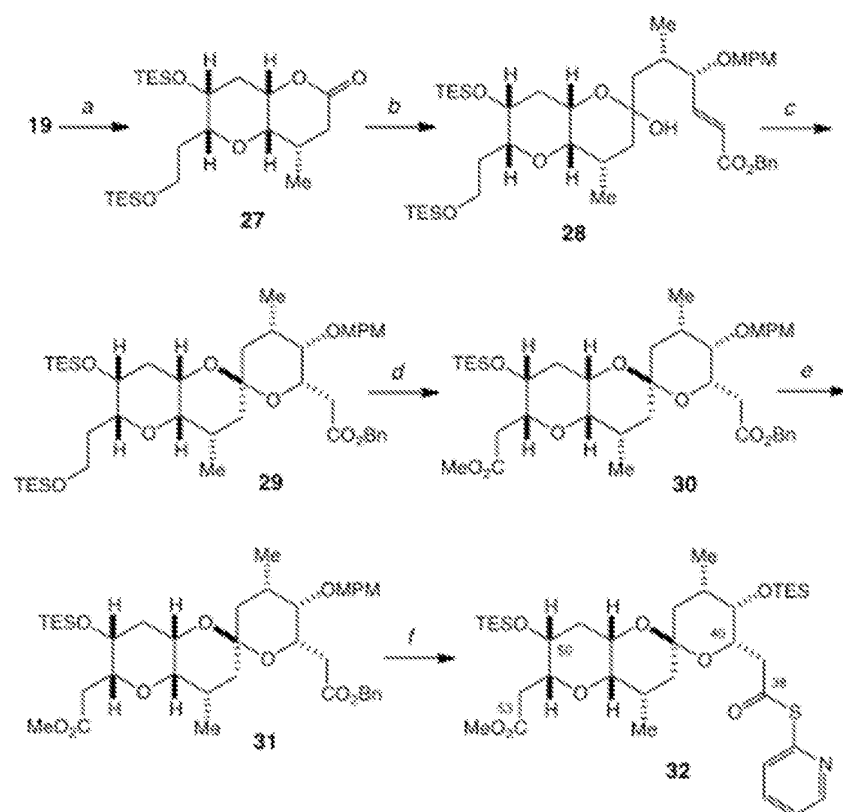
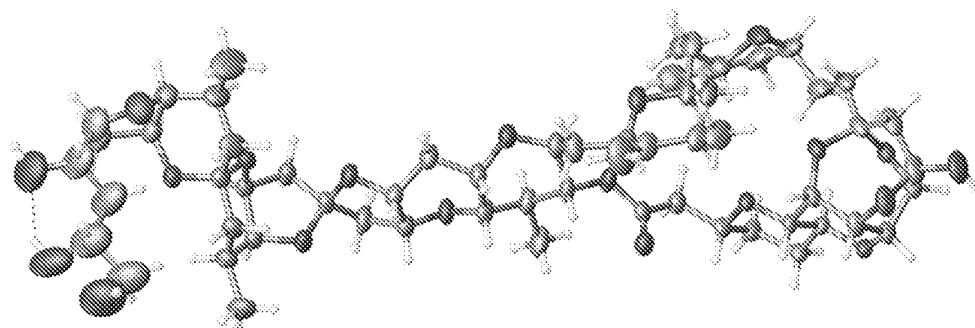


Figure 19

**Figure 20**

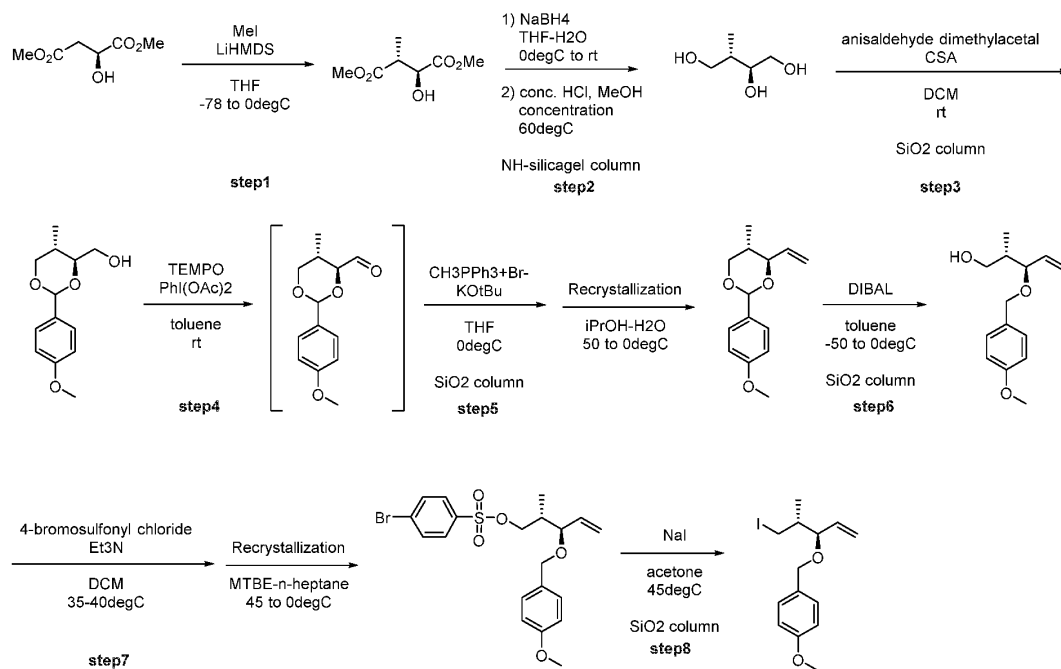


Figure 21

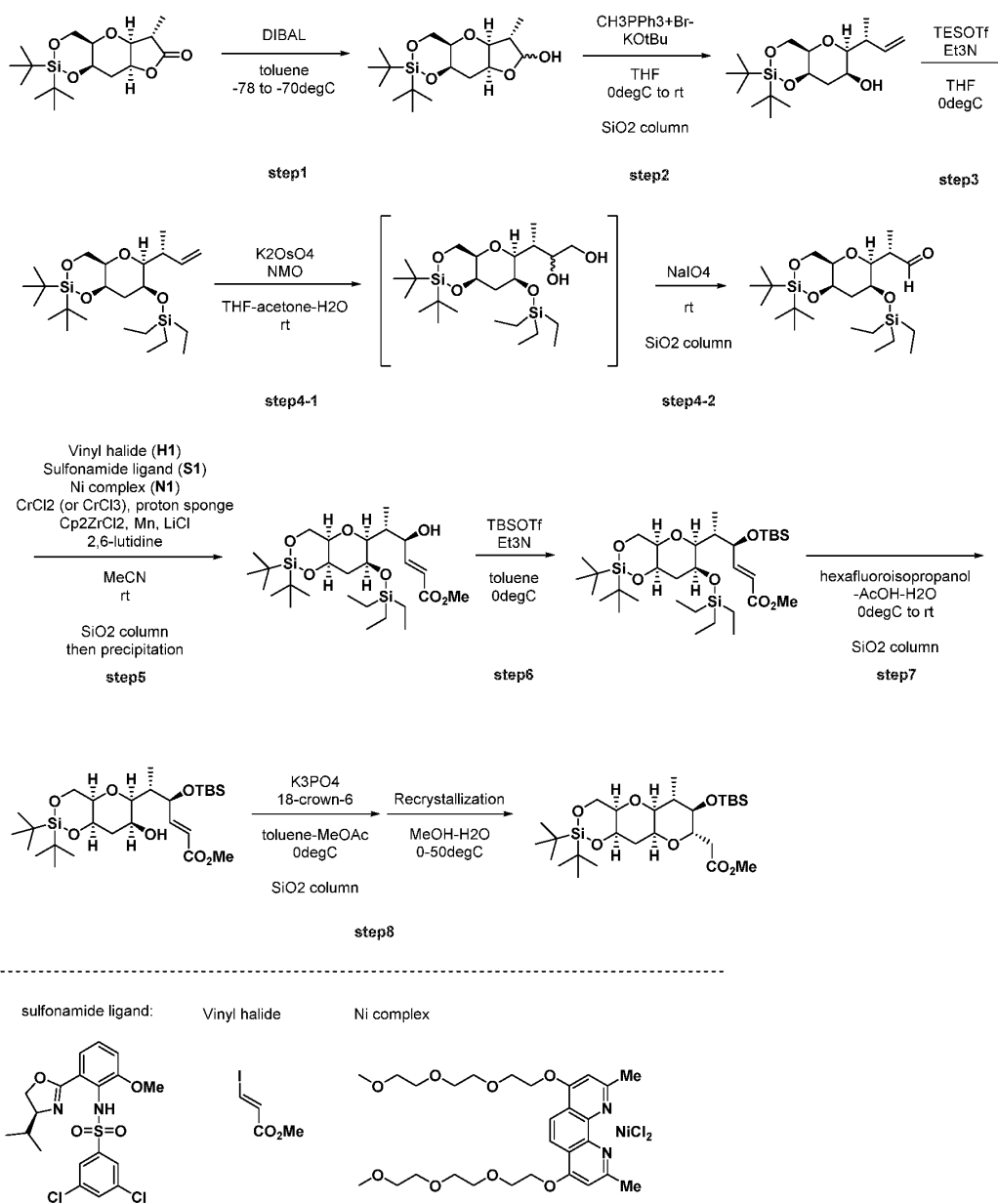


Figure 22

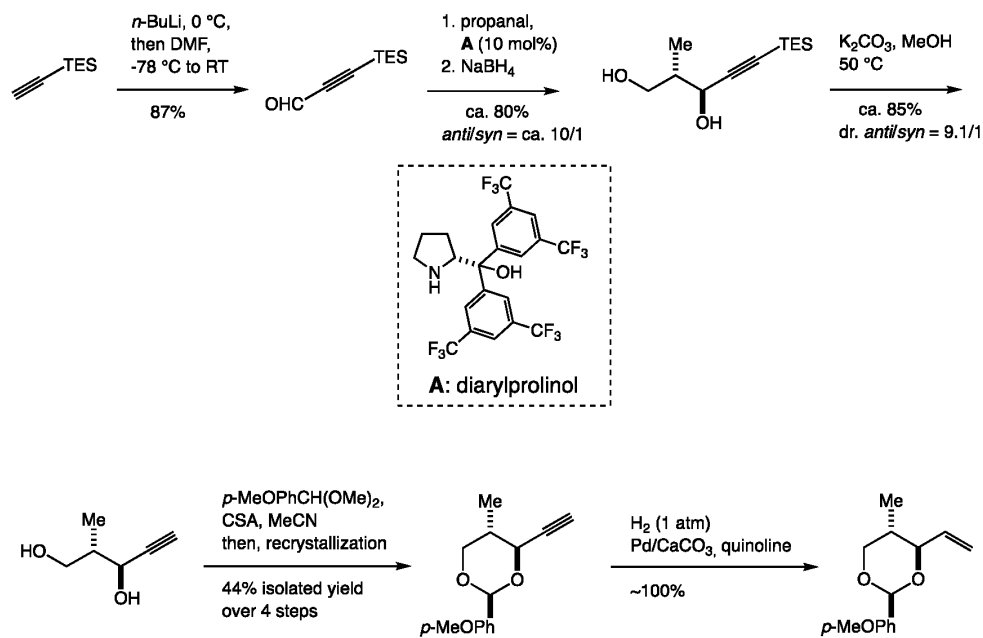


Figure 23