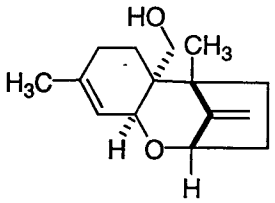
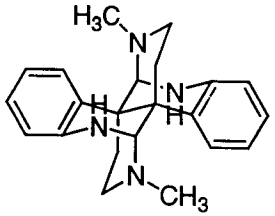
Approaches to the Simultaneous Generation of Vicinal Quaternary Stereocenters

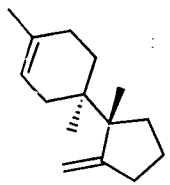
Michael Ober 07/24/01



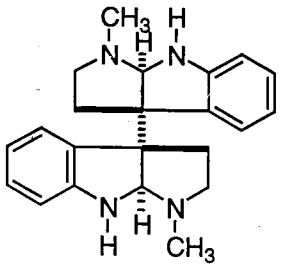
(+)-15-hydroxytrichothec-9,12-diene



meso-calycanthine

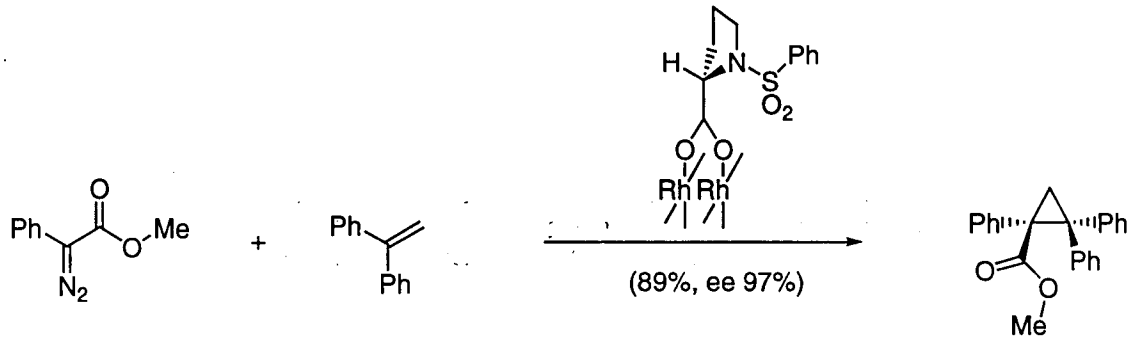


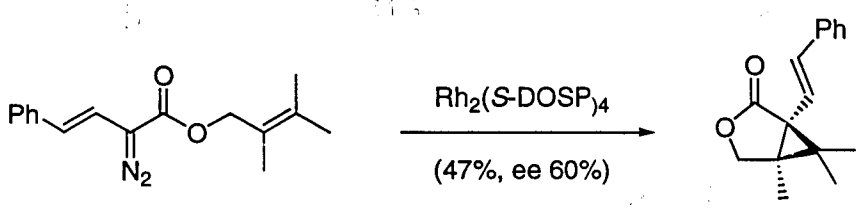
(-)-trichodiene



(+)-chimonanthine

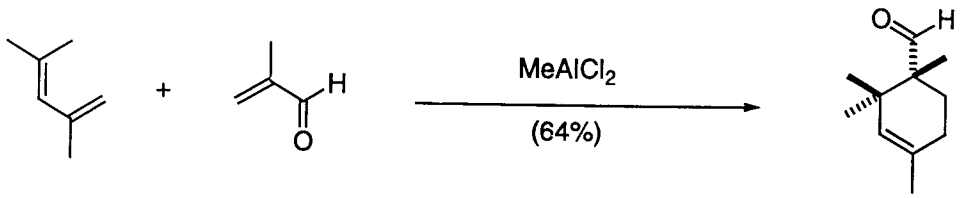
Cyclopropanation of Polysubstituted Olefins

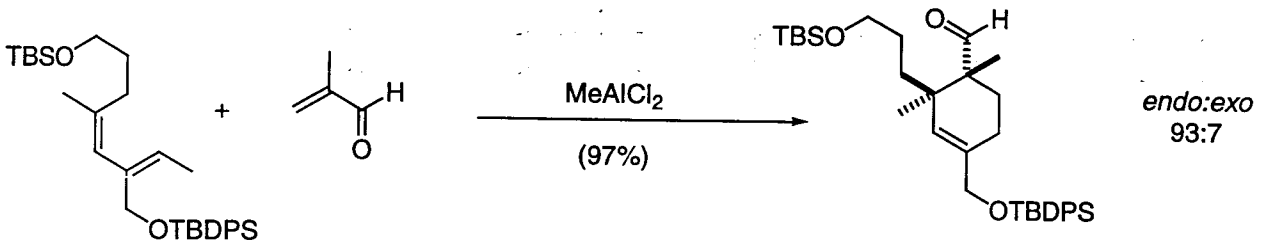


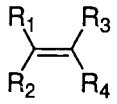


Doyle MP *et al Tetrahedron Lett.* **1996**, *37*, 4129
Doyle MP *et al J. Org. Chem.* **1999**, *64*, 8501

Diels-Alder Reaction



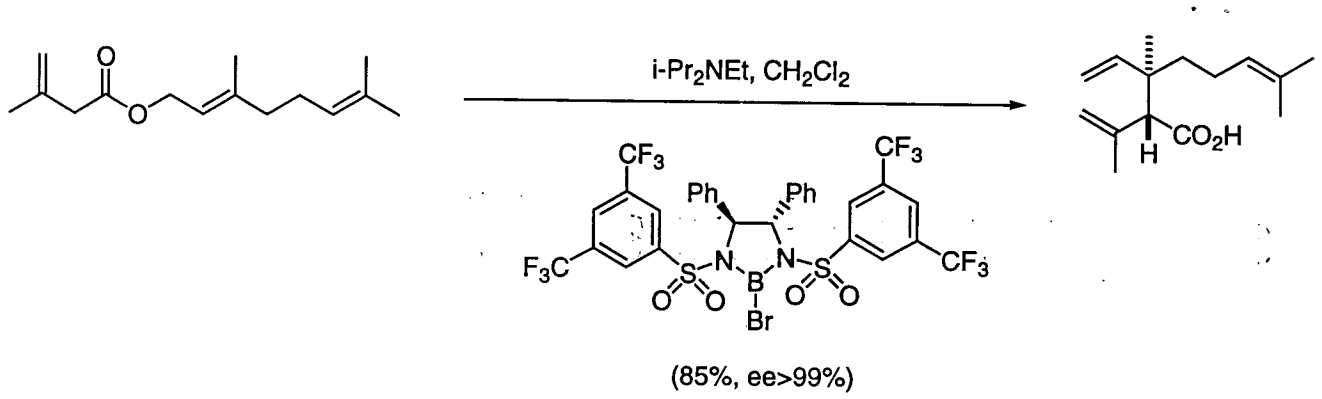




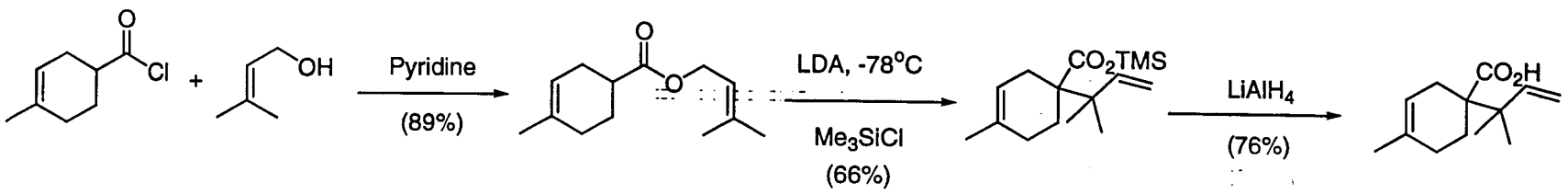
Diels-Alder reactions on tetra-substituted olefins is poor at best due to steric conjestion and poor reactivity

Roush WR *et al J. Am. Chem. Soc.* **1997**, *119*, 7402

[3,3] Sigmatromic Rearrangements

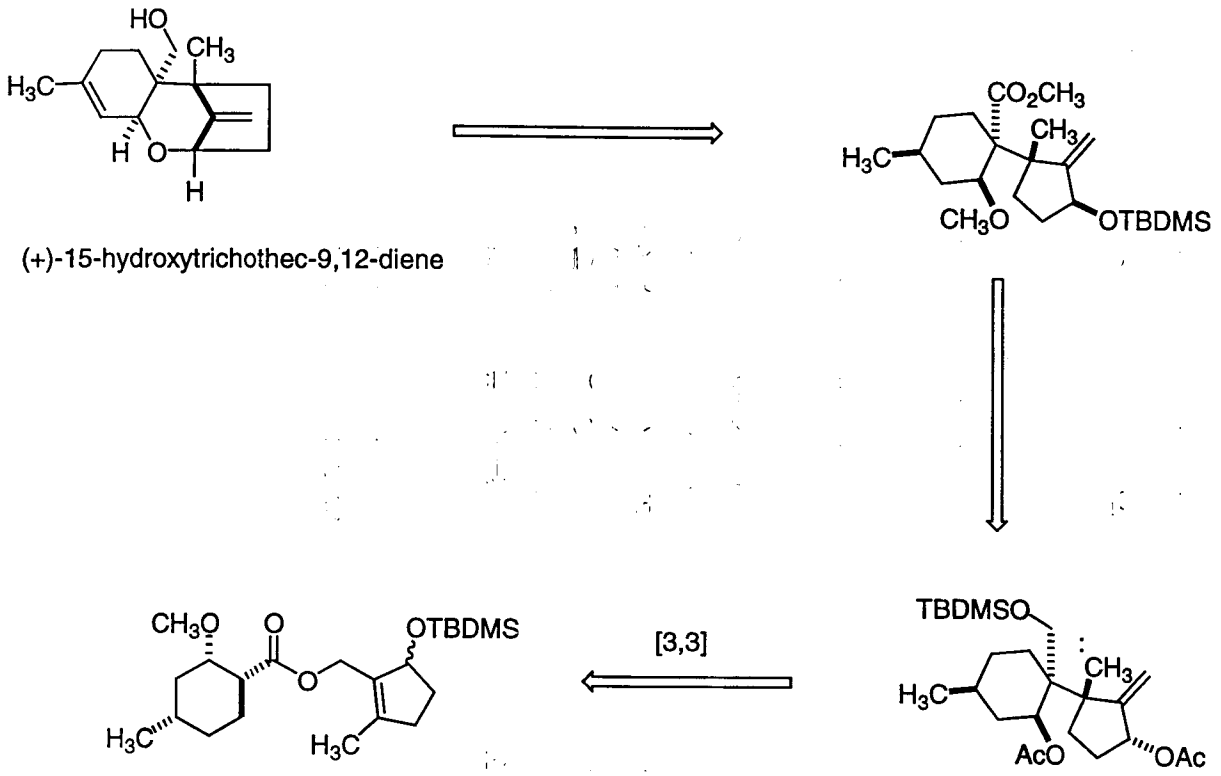


(85%, ee>99%)



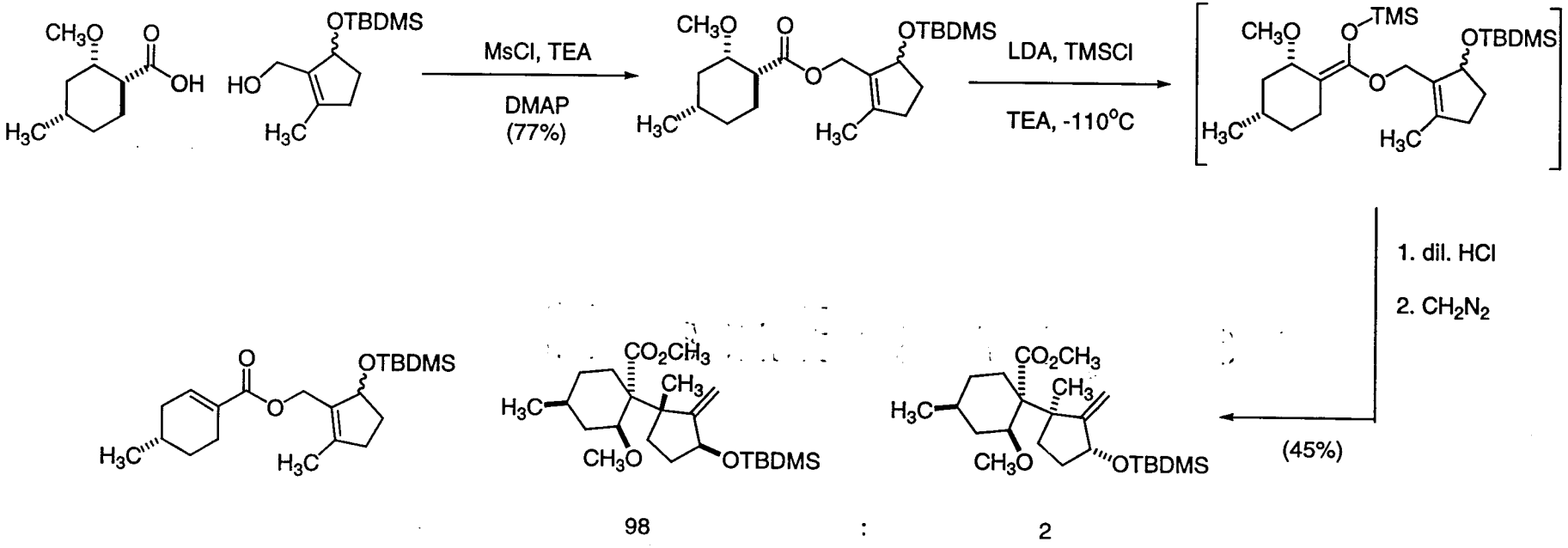
Corey EJ *et al J. Am. Chem. Soc.* **1995**, *117*, 193
Gilbert JC *et al J. Org. Chem.* **1986**, *51*, 4485

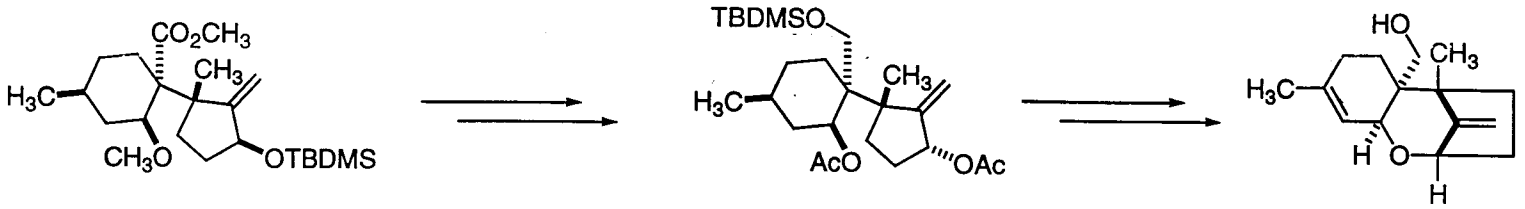
Ireland-Claisen Rearrangement



Gilbert JC *et al Tetrahedron* **1994**, *50*, 1651

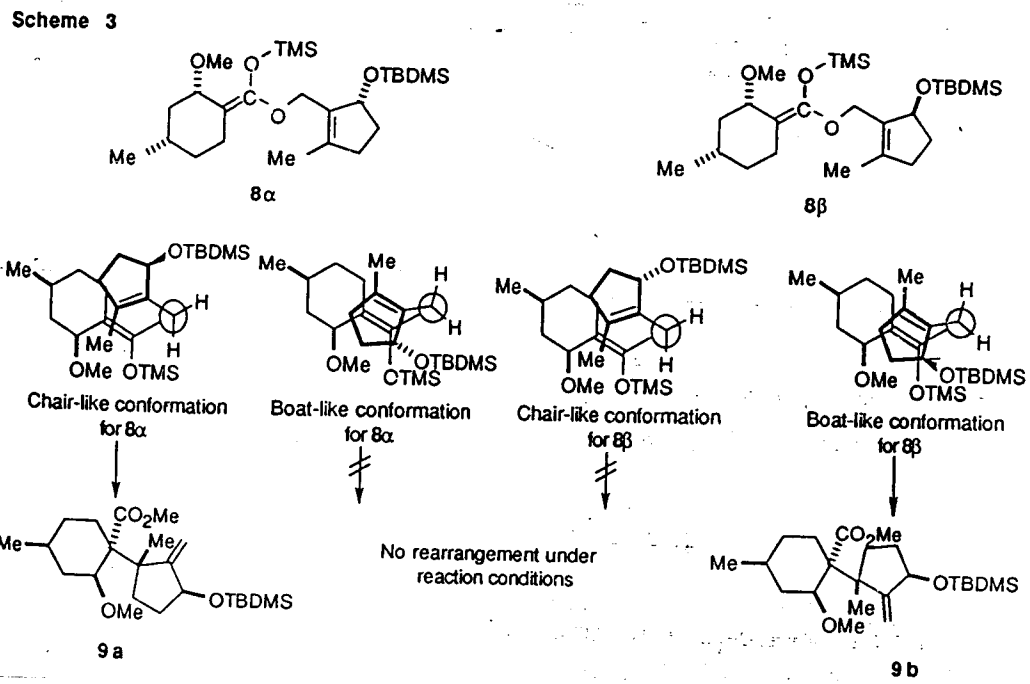
(+)-15-Hydroxytrichothec-9,12-diene





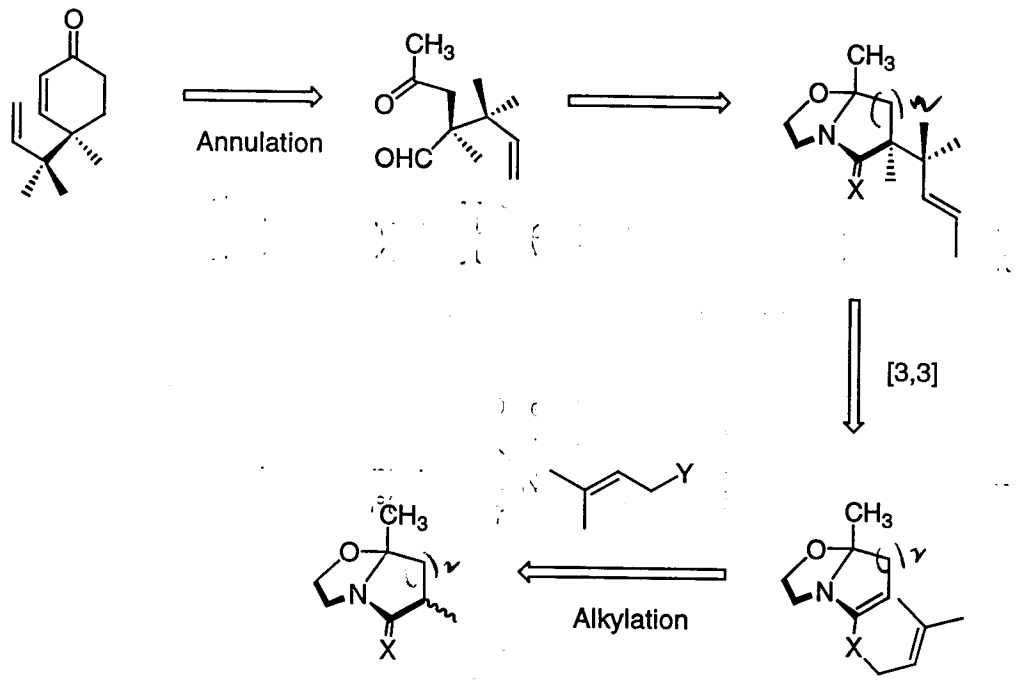
Gilbert JC *et al Tetrahedron* **1994**, *50*, 1651

Ireland-Claisen Rearrangement



Gilbert JC *et al Tetrahedron* **1994**, *50*, 1651

Thio-Claisen Rearrangement



Meyers AI *et al J. Am. Chem. Soc.* **1994**, *116*, 2633

Thio-Claisen Rearrangement

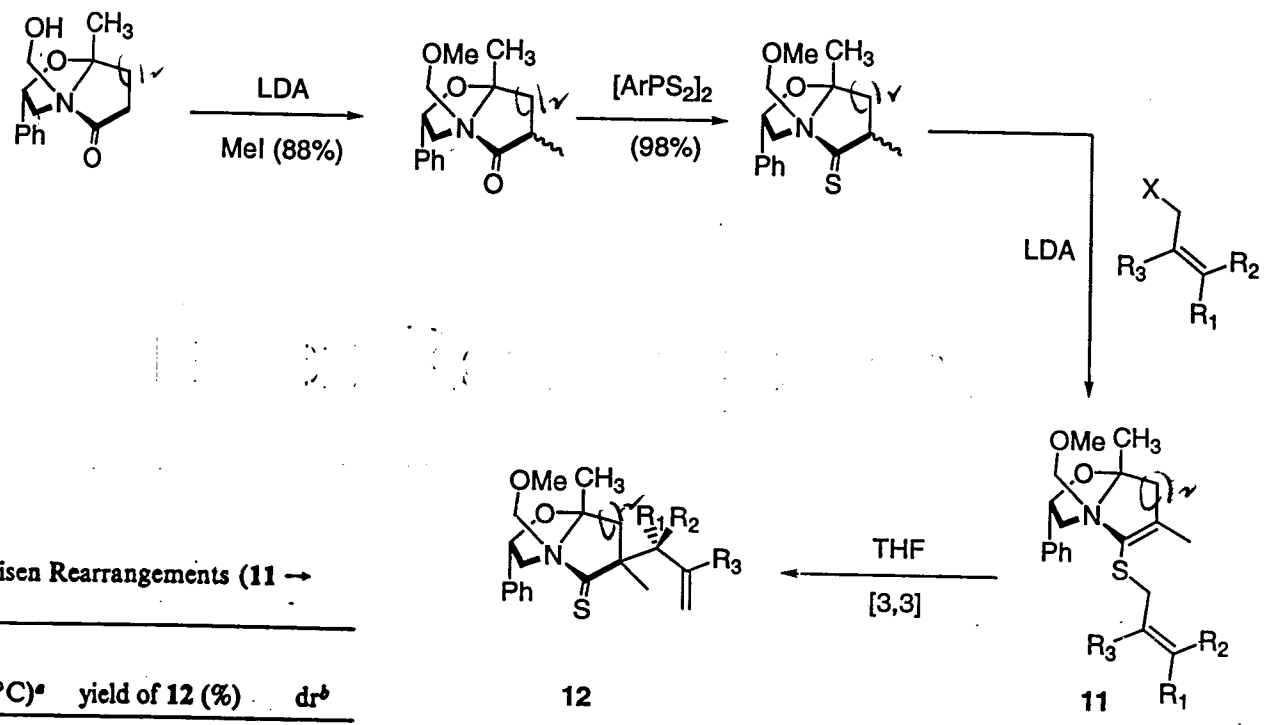


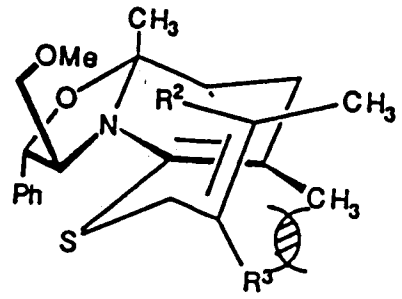
Table 1. Diastereoselective Thio-Claisen Rearrangements (**11** → **12**)

	allyl halide						
entry	R^1	R^2	R^3	X	T (°C)[a]	yield of **12** (%)	dr[b]
a	H	H	Me	Cl	25	71	3:1
b	Me	H	H	Br	25	79	91:9
c	Ph	H	H	Br	140	48	>99:1
d	Me	Me	H	Br	140	68	>99:1

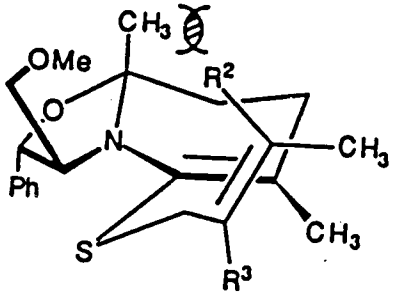
[a] Rearrangements at room temperature were carried out in THF; at 140 °C, xylene was the solvent employed. [b] Diastereomeric ratios determined by capillary GLC and 300-MHz NMR integration of the benzylic proton in the oxazolidine ring.

Meyers AI *et al J. Am. Chem. Soc.* **1994**, *116*, 2633

Thio-Claisen Rearrangement

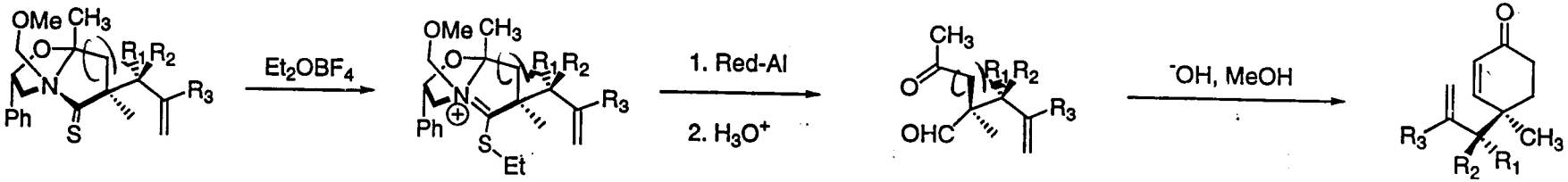


A, R^3 = alkyl; R^2 = H



B, R^3 = H, R^2 = alkyl

Figure 1.



Meyers AI *et al J. Am. Chem. Soc.* **1994**, *116*, 2633

(-)-Trichodiene

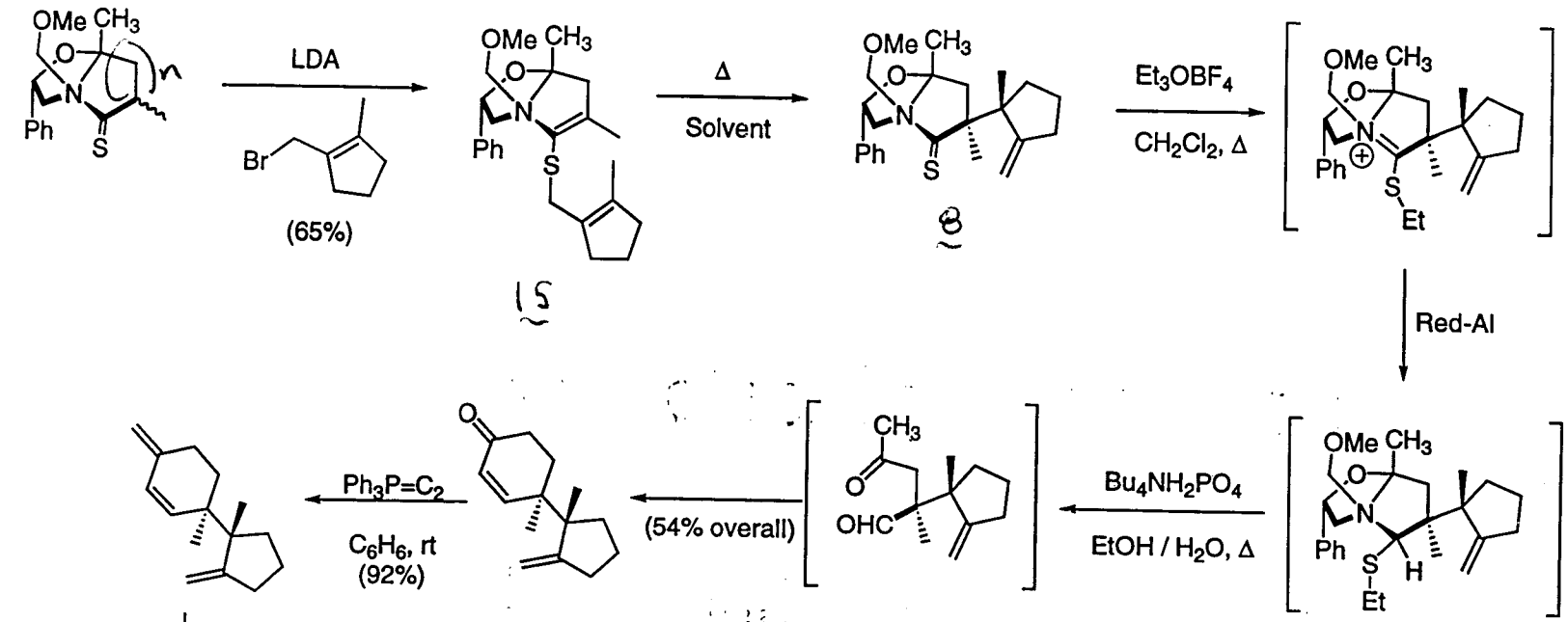


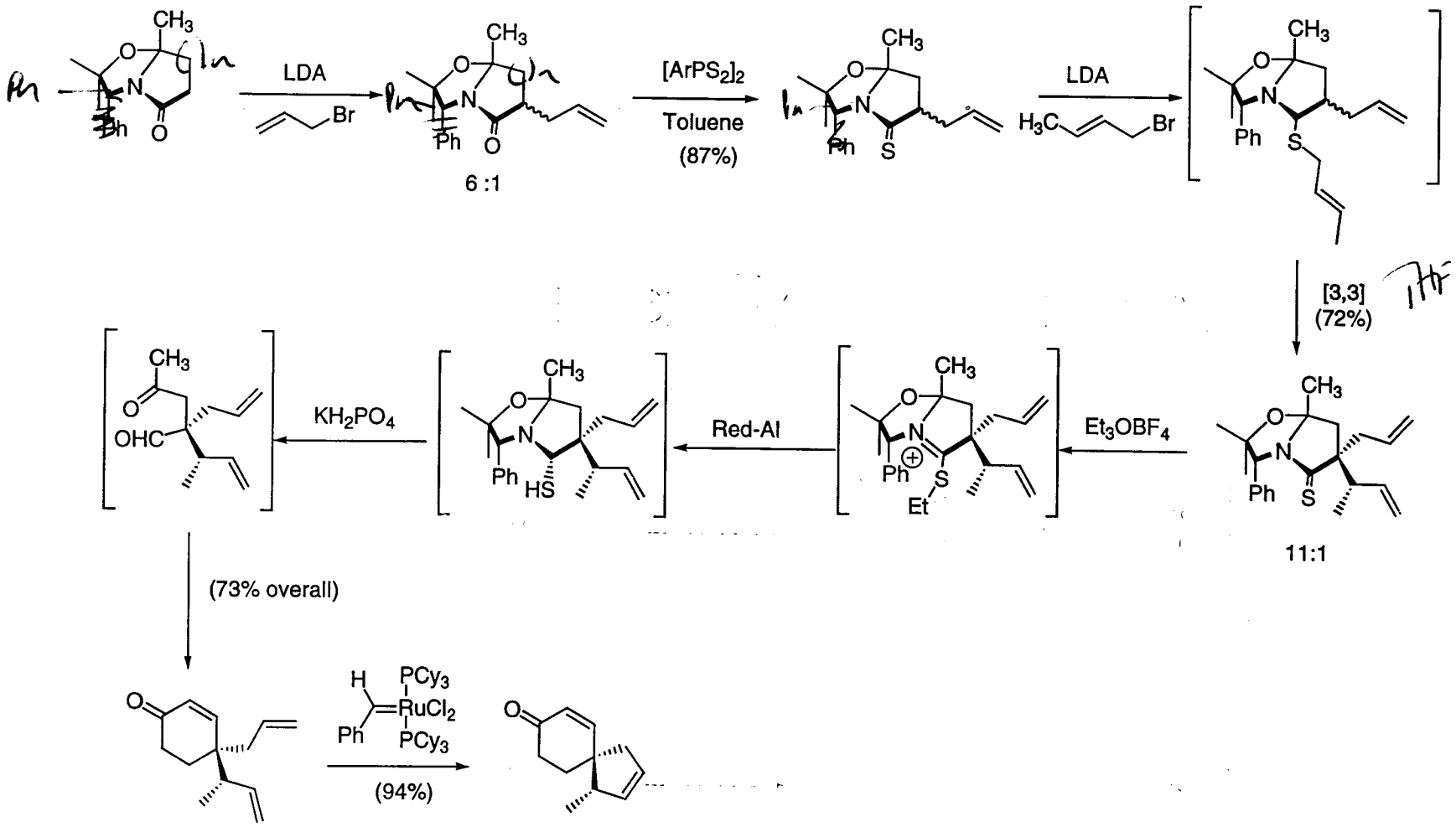
Table 1. Effect of Solvents and Temperature on the Equilibrium of 15, 8

entry	solvent	T (°C)	ratio 15:8[a]
1	xylenes	140	100:0
2	MeCN	80	65:35
3	DME	83	60:40
4	dioxane	101	60:40
5	Bu_2O	140	60:40
6	HMPA	100	48:52
7	DMF	90	36:64
8	DMSO	80	dec[b]
9	H_2O:MeOH (3:1)	90	dec
10	EtOH	78	dec

[a] Ratio determined via integration of the benzylic protons of **15** and **8** in the ^1H NMR spectrum of the crude reaction mixture. [b] dec = decomposition.

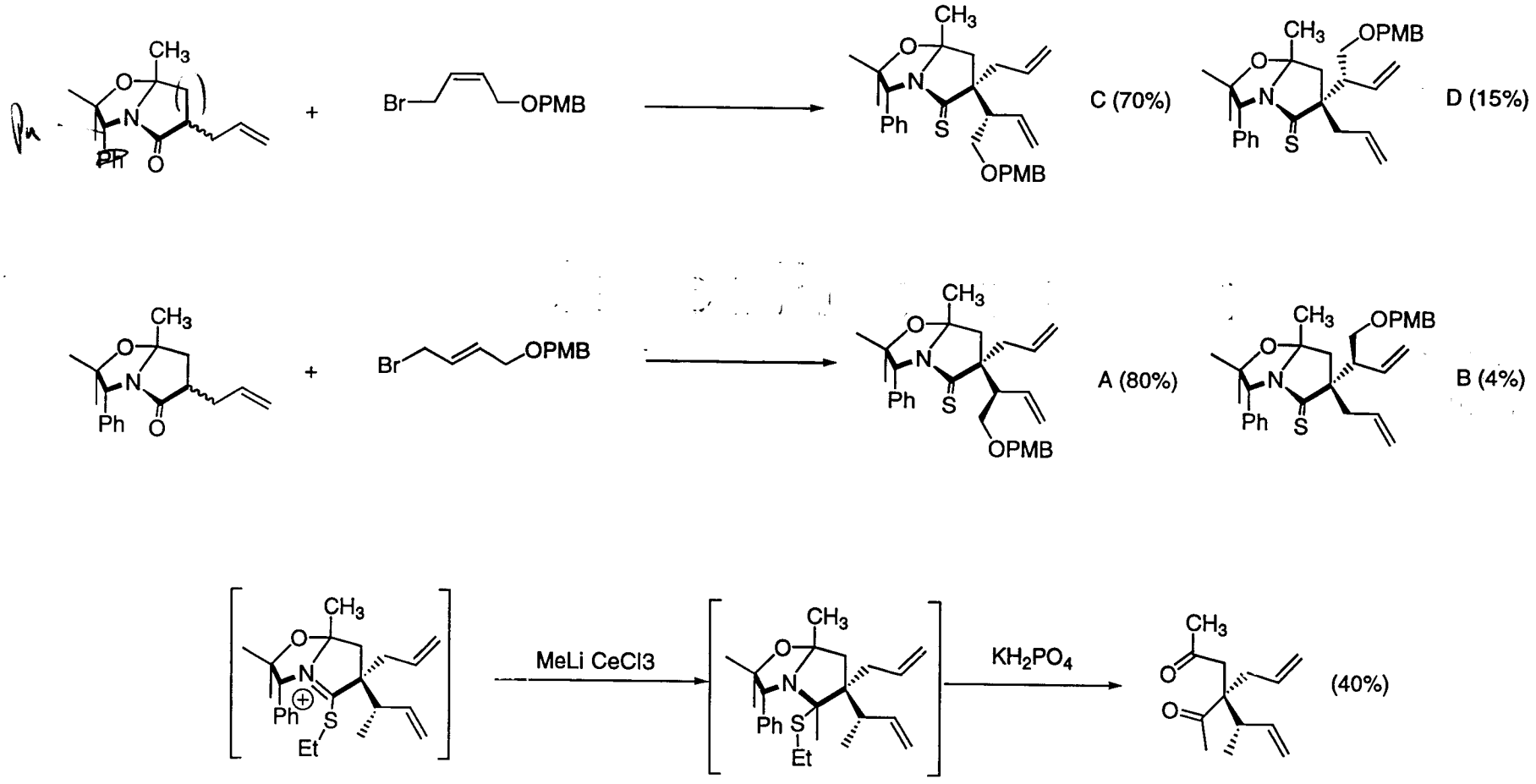
Meyers AI *et al J. Am. Chem. Soc.* **1998**, *120*, 5453

Spiro-Connected Cyclopentenes



Meyers AI *et al J. Org. Chem.* **1999**, *64*, 3585

Thio-Claisen Rearrangement



Meyers AI *et al J. Org. Chem.* **1999**, *64*, 3585

Thio-Claisen Rearrangement

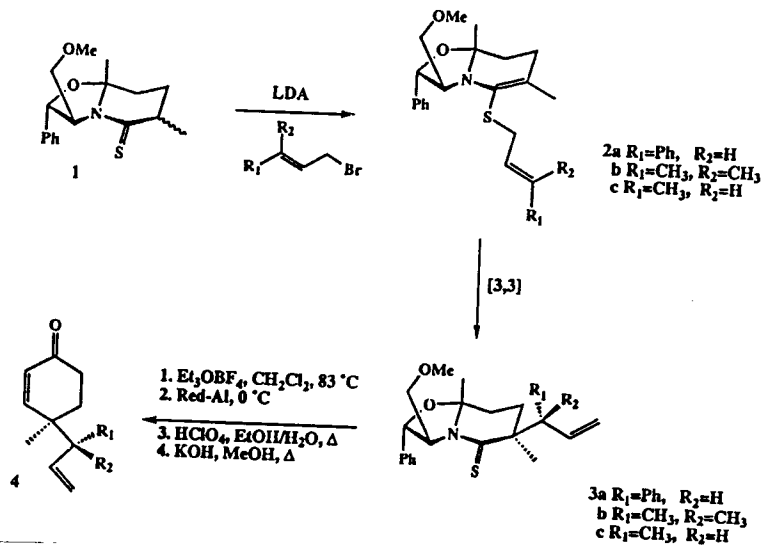


Table 2
Thio-Claisen rearrangement of *N,S*-ketene acetal **2b** to thiolactam **3b** with palladium and nickel catalysts

Entry	Catalyst (10 mol %)	Temp (°C)	Time (h)	d.r.[a] (*exo:endo*) 3b	Yield[b] of 3b (%)
1	no catalyst	140		>99:1[c]	68
2	$PdCl_2(MeCN)_2$	65	36	>20:1	65
3	$PdCl_2(dppf)$	65	48	>20:1	66
4	$Pd_2(dba)_3$	65	36	>20:1	50
5	$NiCl_2(Ph_3P)_2$	65	37	>20:1	62
6	$Ni(Ph_3P)_4/LiCl$	65	24	2.2:1	40
7	$Ni(Ph_3P)_4/ZnCl_2$	65	24	3:1	63
8	$Ni(COD)_2$	65	44	>20:1	70

[a]Ratio determined by ^1H NMR, [b]Isolated yield of major *exo* diastereomer, [c]Ratio determined by GC.

Meyers AI *et al Tetrahedron Lett.* **2000**, *41*, 1361

Thio-Claisen Rearrangement

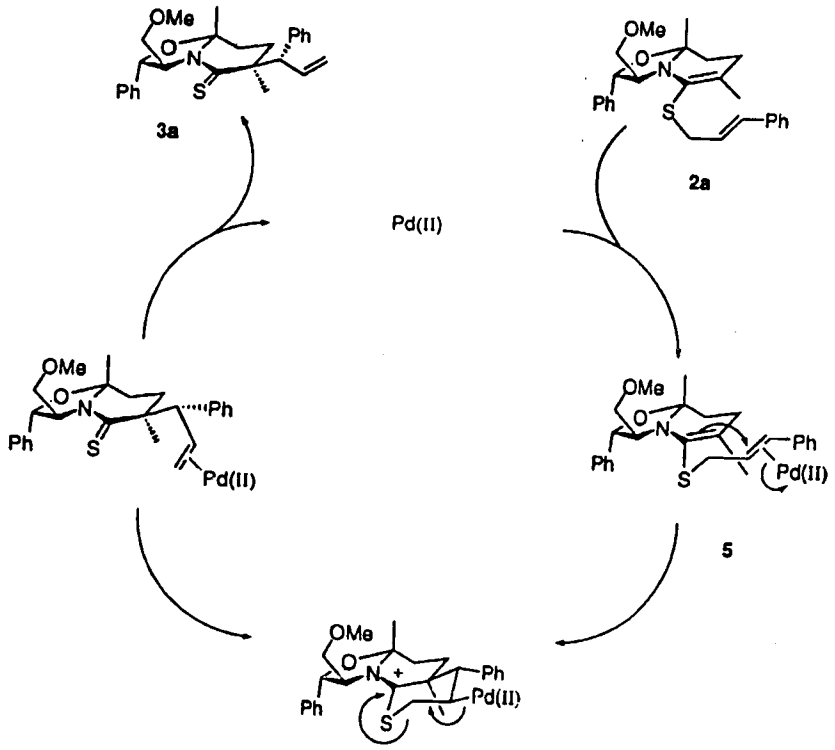


Fig. 1.

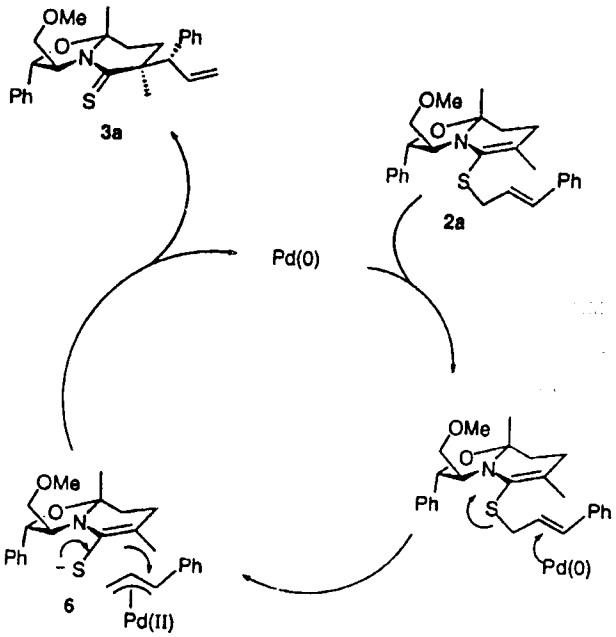
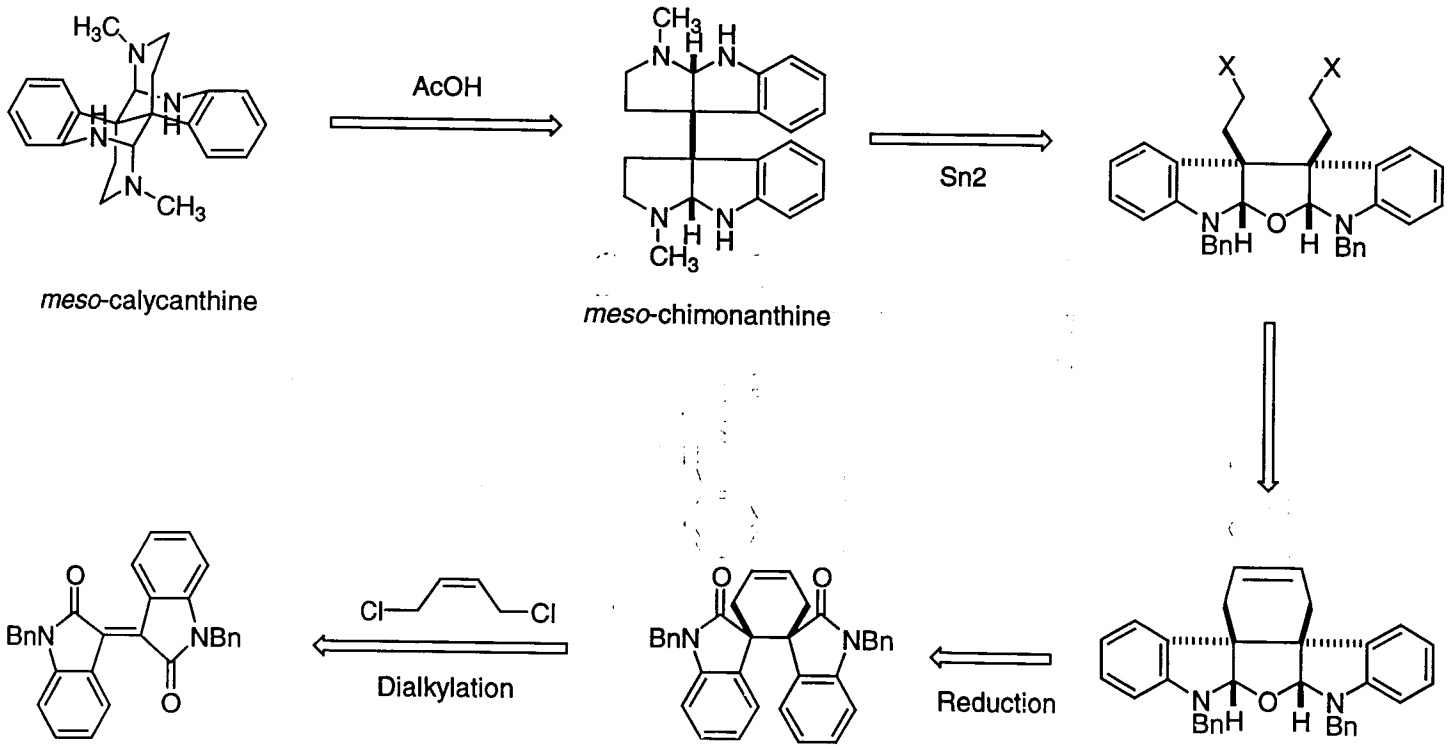


Fig. 2.

Meyers AI *et al Tetrahedron Lett.* **2000**, *41*, 1361

Stereoselective Dialkylation

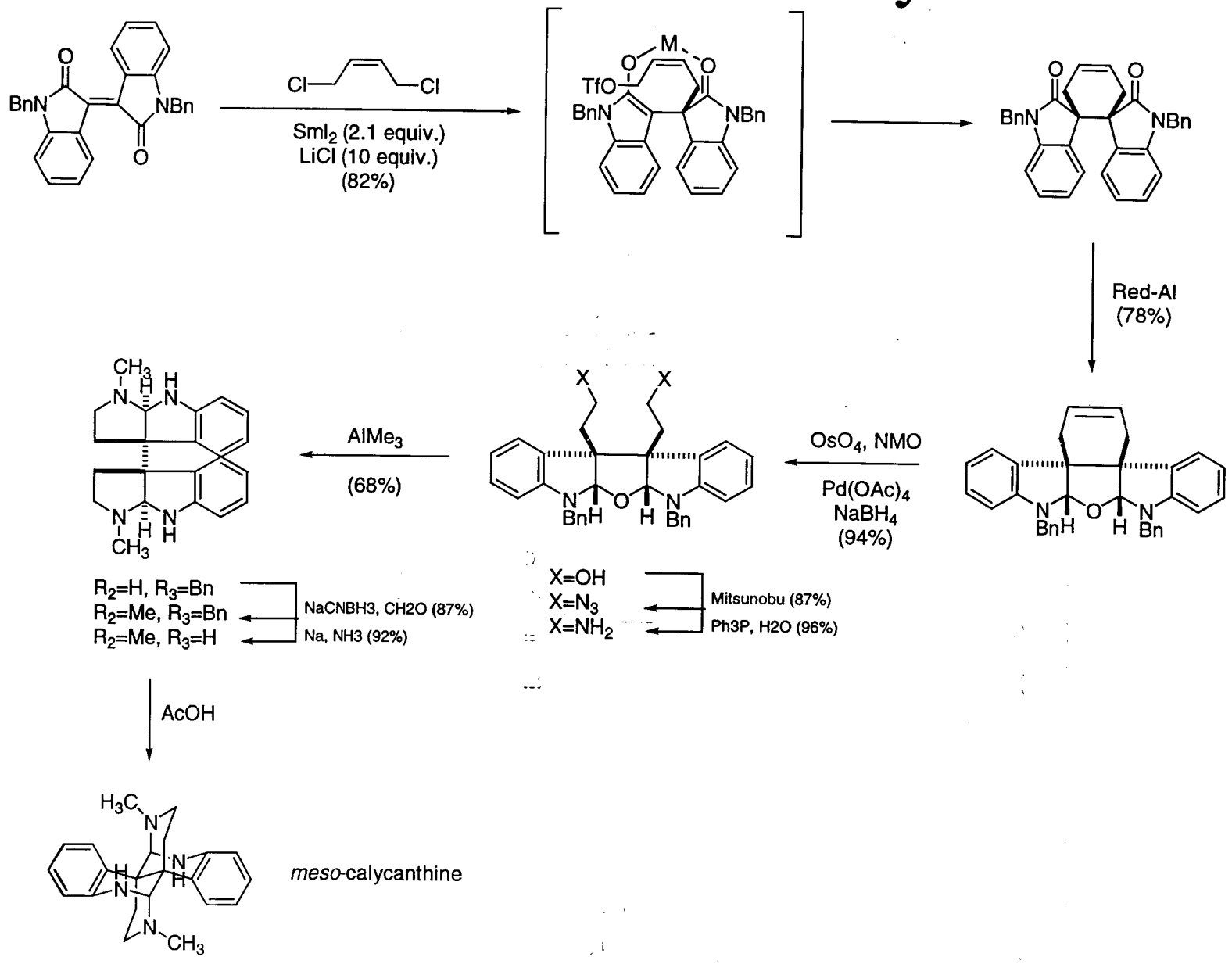


meso-calycanthine

meso-chimonanthine

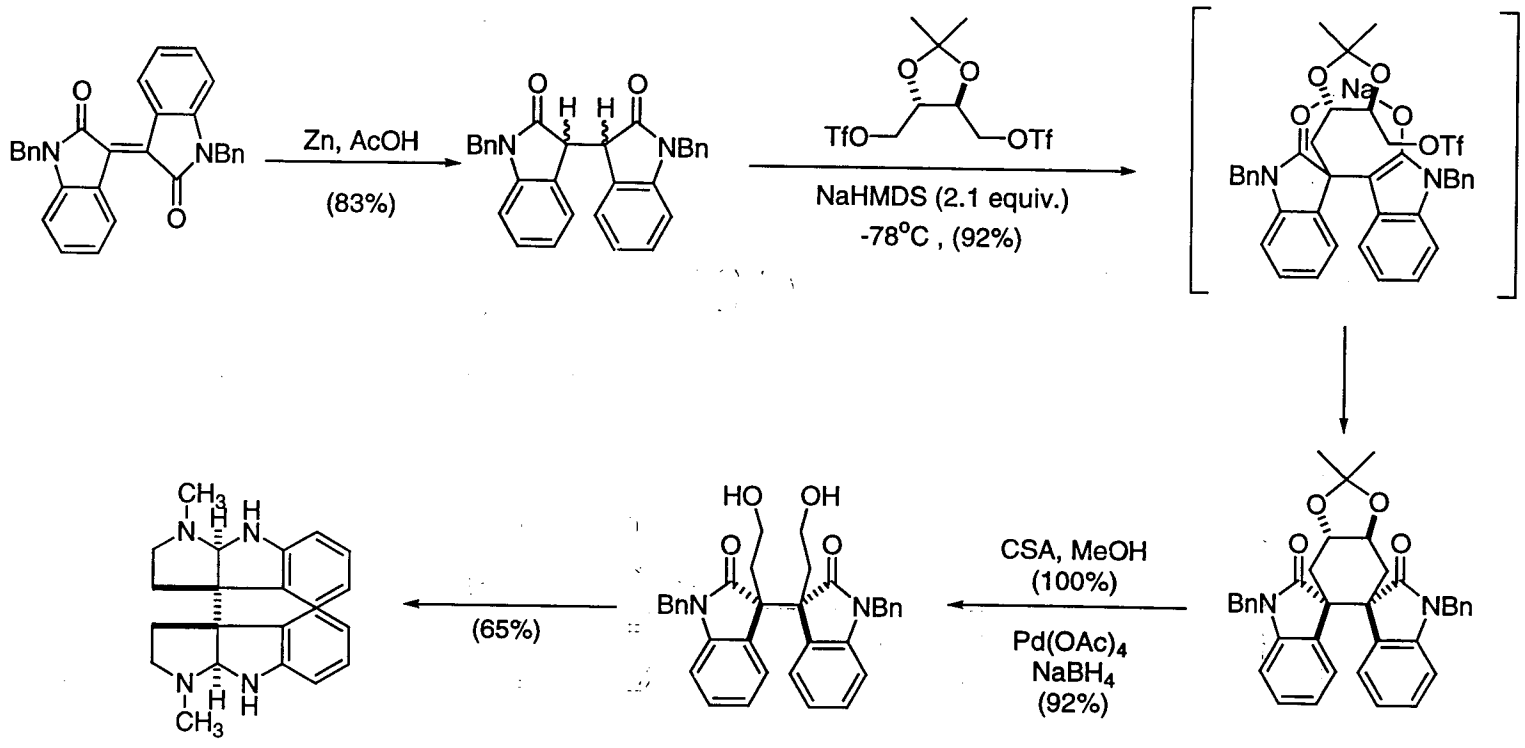
Overman LE *et al J. Am. Chem. Soc.* **1996**, *118*, 8166

Meso-Chrimnanthine / -Calycanthine



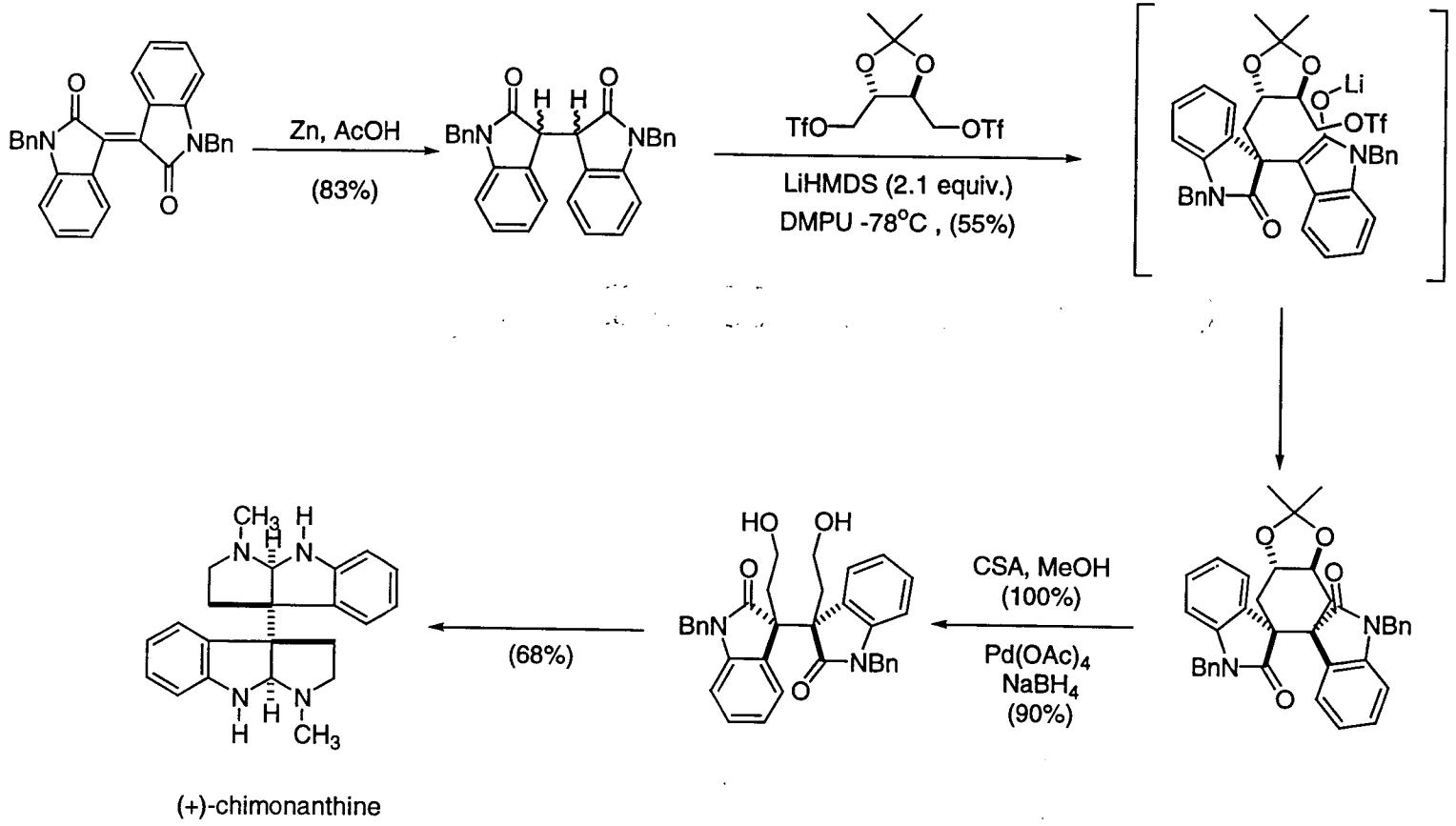
Overman LE *et al J. Am. Chem. Soc.* **1996**, *118*, 8166

Meso-Chrimonanthine



Overman LE *et al Angew. Chem. Int. Ed.* **2000**, *39*, 213

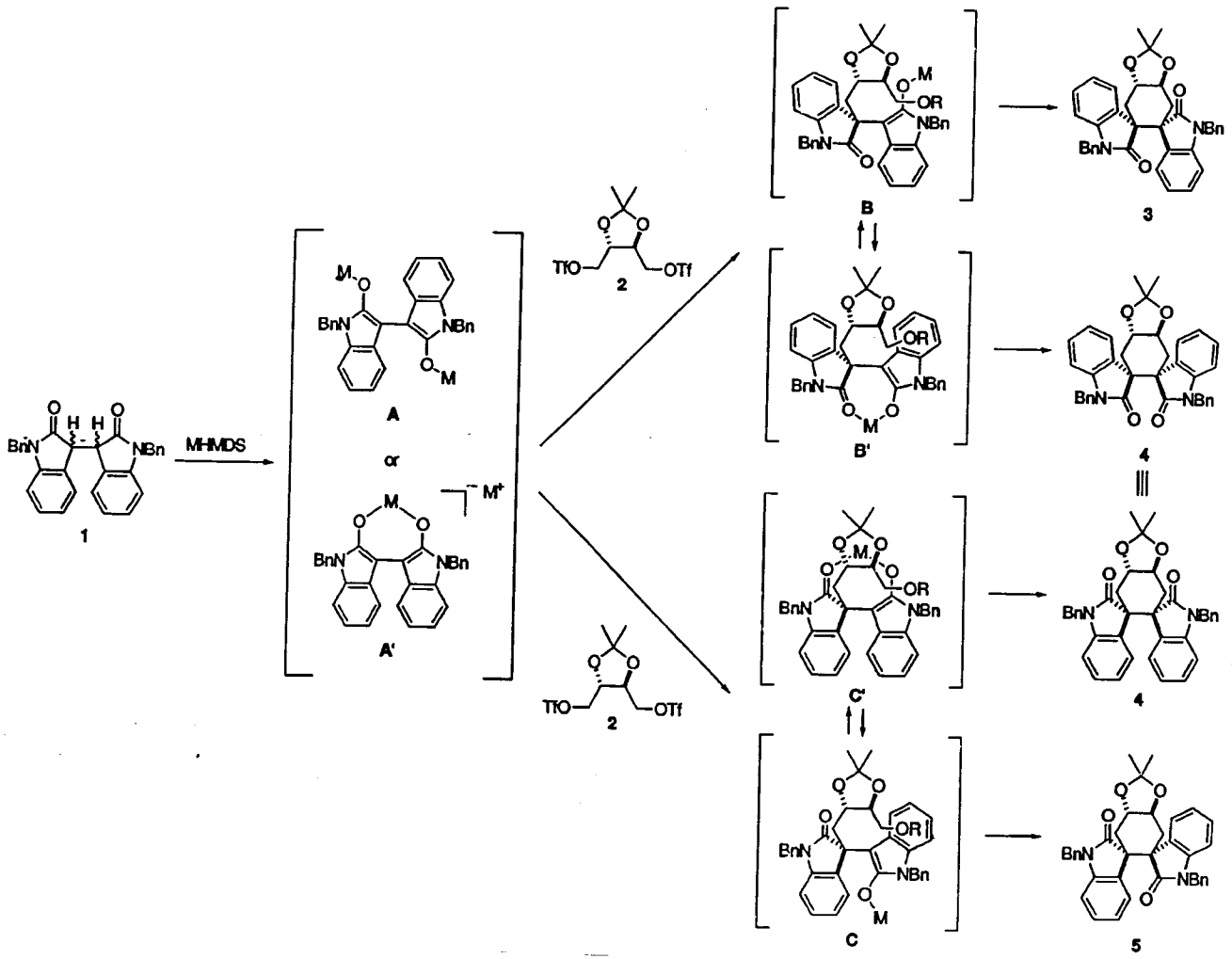
(+)-Chimonanthine



Overman LE *et al Angew. Chem. Int. Ed.* **2000**, *39*, 213

Investigations of the Reaction

Scheme 1. Stereoselective Dialkylation Reactions



Overman LE *et al Org. Lett.* **2000**, *2*, 3241

Investigations of the Reaction

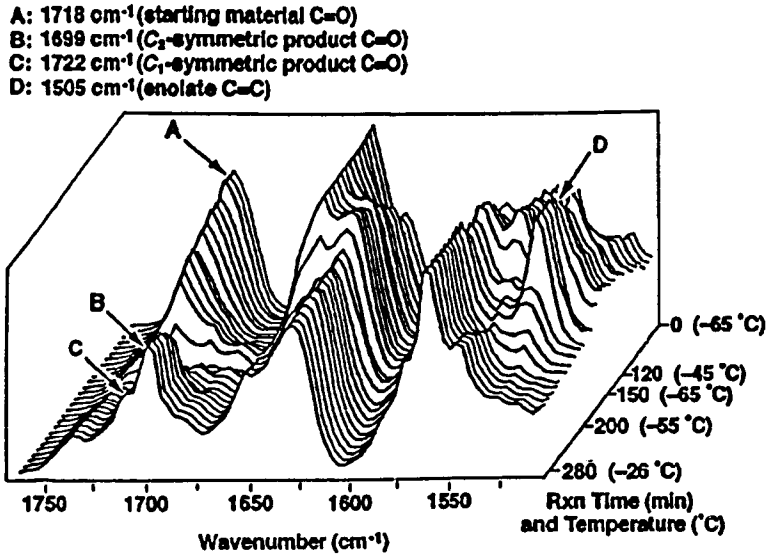


Figure 1. IR data from the LHMDS-mediated dialkylation. LHMDS was added at −65 °C and the reaction was wafmed to −45 °C over 2 h. The reaction was then recooled to −65 °C, ditriflate **2** was added, and the reaction was slowly warmed to −26 °C.

Table 1. In Situ IR Spectroscopic Analysis of Reaction of **1** and **2**[a]

entry	base	concn, M	dienolate formation, °C	alkylation, °C
1	LHMDS	0.13	−17	not detected
2	LHMDS	0.31	−45	−55
3	NaHMDS	0.31	−76	−52
4	KHMDS	0.31	−71	−60

[a] Reactions conducted in 9:1 THF−DMPU using 2.2 equiv of base and 1.2 equiv of **2**.

Investigations of the Reaction

Table 2. Effect of Cosolvent on Stereoselectivity in the LHMDS-Promoted Reaction of **1** and **2**[a]

entry	solvent	3:4:5[b]	3:5
1	THF	6:10:1	6:1
2	9:1 THF–DMPU	41:28:1	41:1
3	8:2 THF–DMPU	47:24:1	47:1
4	7:3 THF–DMPU	53:18:1	53:1
5	1:1 THF–DMPU	22:8:1	22:1
6[c]	DMPU	5:2:1	5:1
7[d]	8:2 THF–HMPA	100:19:nd[e]	100:nd
8[d]	7:3 THF–HMPA	100:12:1	100:1
9	1:1 THF–HMPA	11:1.4:1	11:1
10[f]	HMPA	5:1:1	5:1

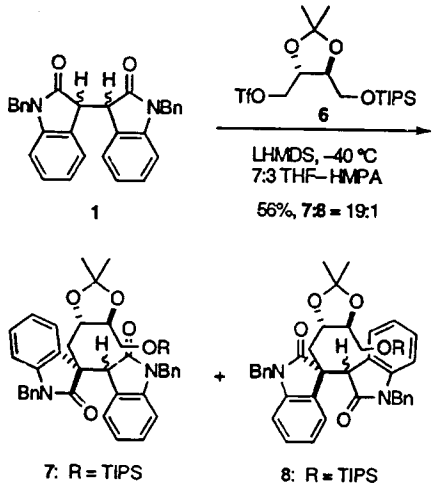
[a] Reactions conducted at −40 °C, 0.3 M in **1** except as noted. [b] Determined by HPLC. [c] At 0 °C. [d] Mean product ratio reported. [e] None detected. [f] At room temperature.

Table 3. Effects of Crown Ethers on Stereoselectivity in the Reaction of **1** and **2**[a]

entry	base	conditions	4:3[b]
1	KHMDS	THF	44:1
2	KHMDS	THF, 3 equiv of 18-C-6	4:1
3	KHMDS	THF, 5 equiv of 18-C-6	3:1
4	NaHMDS	THF	56:1
5	NaHMDS	THF, 3 equiv of 15-C-5	16:1
6	NaHMDS	THF, 5 equiv of 15-C-5	11:1
7	LHMDS	7:3 THF–HMPA	1:8
8	LHMDS	7:3 THF–HMPA, 5 equiv of 12-C-4	1:9

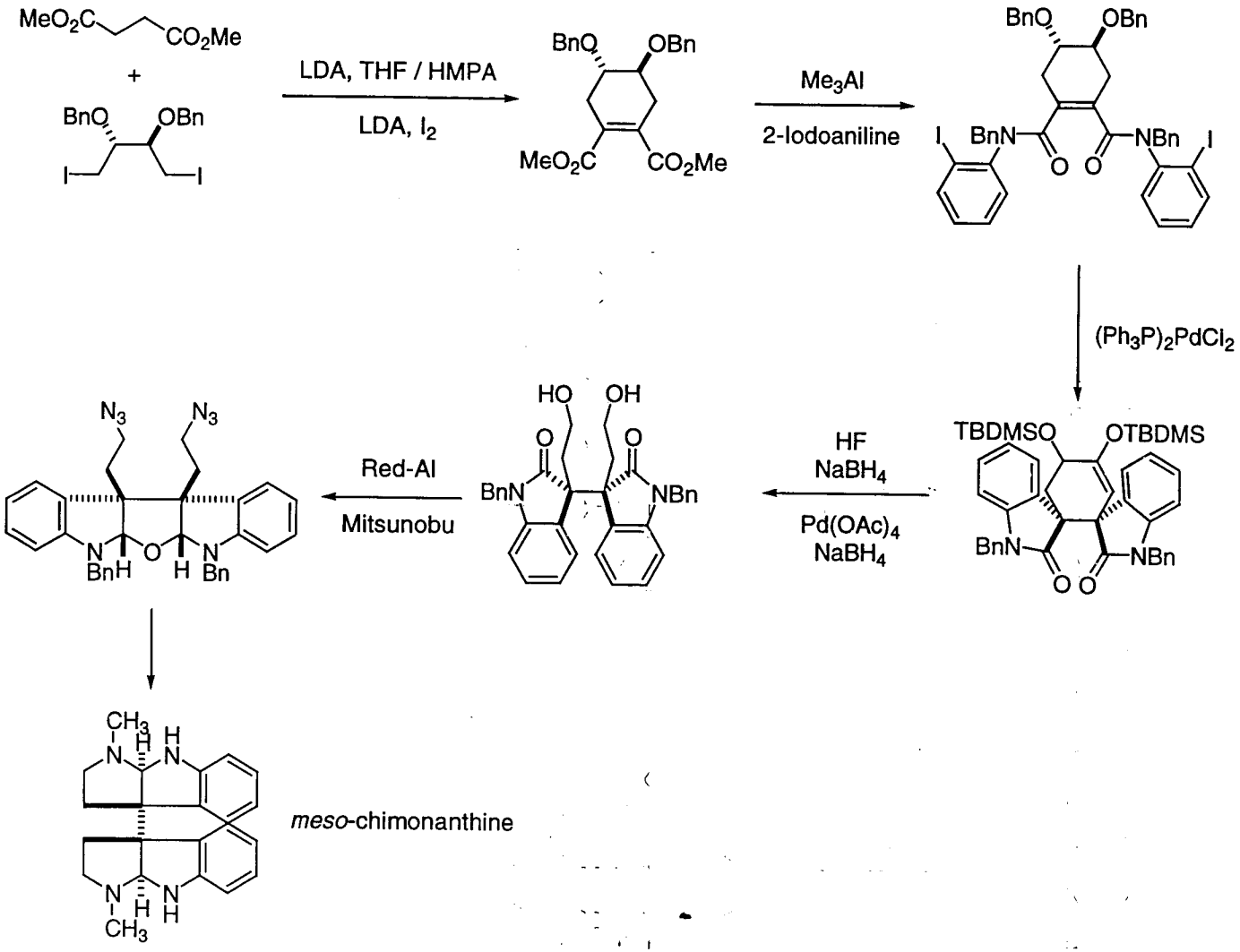
[a] Reactions conducted at −40 °C, 0.3 M in **1**. [b] By HPLC analysis. In each case, C_2-symmetric product **5** was detected as a minor component.

Scheme 2. Estimating Stereoselection in the First Alkylation Step



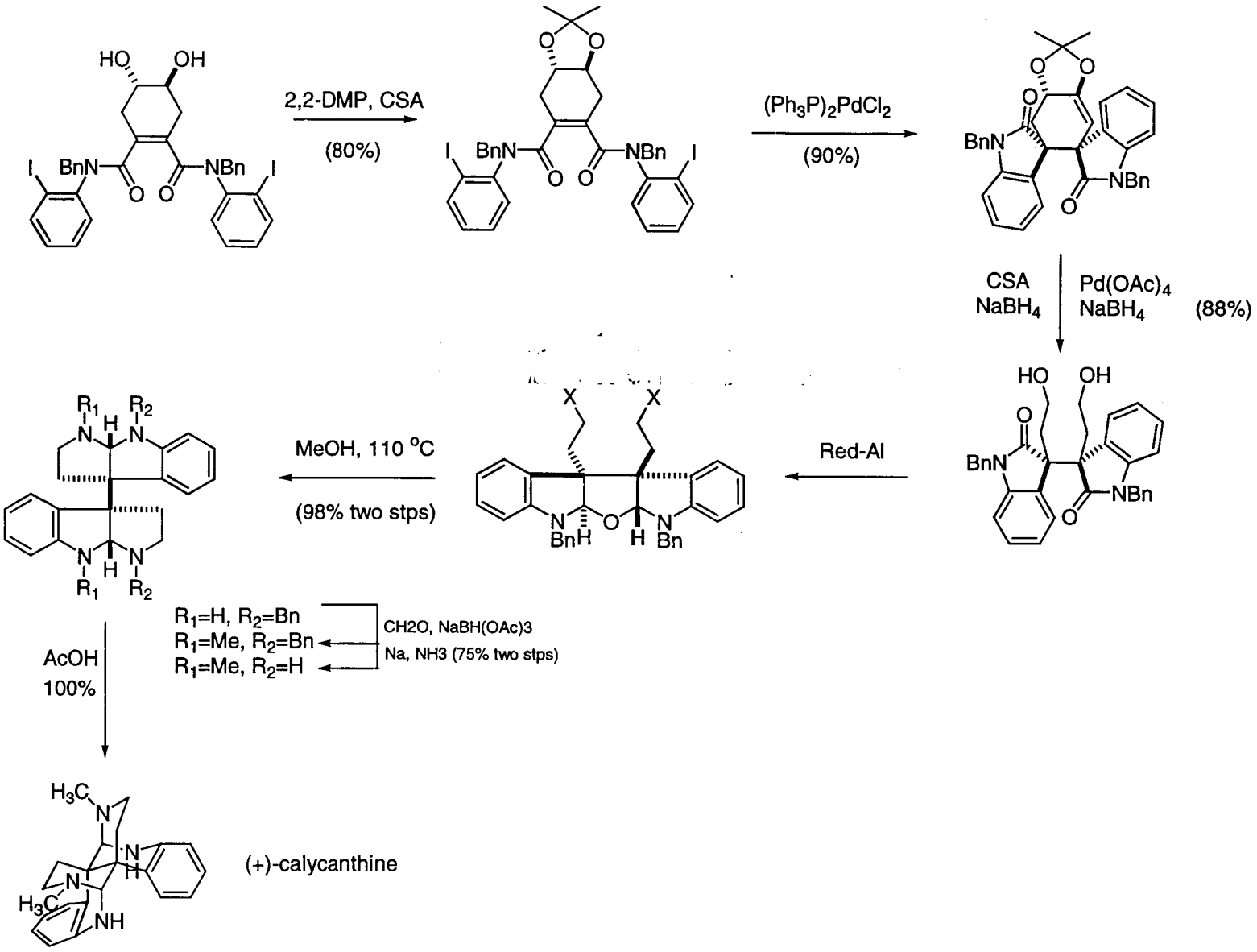
Overman LE *et al Org. Lett.* **2000**, *2*, 3241

Meso-Chrimonanthine



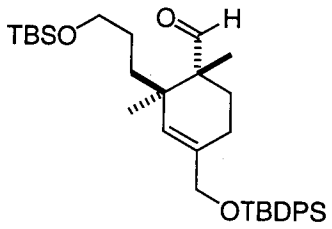
Overman LE *et al J. Am. Chem. Soc.* **1999**, *121*, 7702

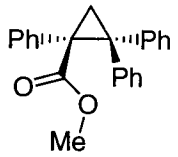
(-)-Chimonanthine / (+)-Calycanthine

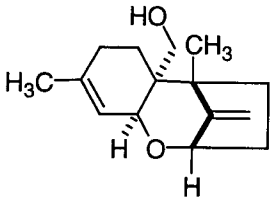


Overman LE *et al J. Am. Chem. Soc.* **1999**, *121*, 7702

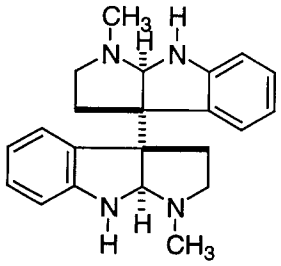
Conclusions



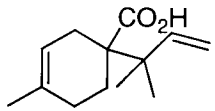


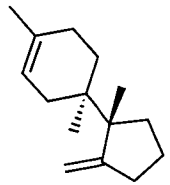


(+)-15-hydroxytrichothec-9,12-diene

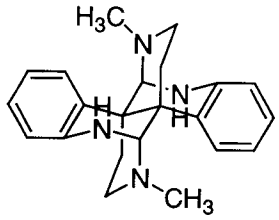


(+)-chimonanthine





(-)-trichodiene



meso-calycanthine

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