

Denmark Group Meeting

June 26, 2001

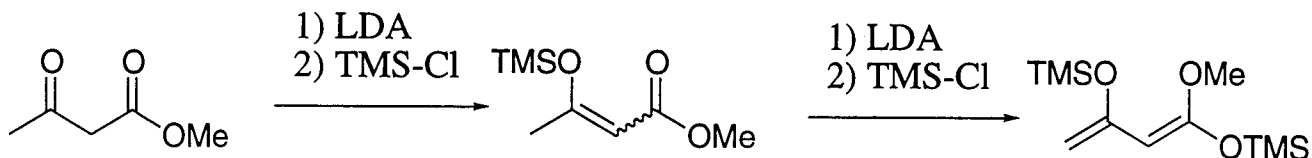
Tyson A. Miller

The Chan Reaction



Chan Diene: Dianion Equivalent of Methyl Acetoacetate

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Keck, G.E., Yu, T. *OL* (1999) 1 289.
Reports that Chan diene gives
"no synthetically useful results" when
used with $\text{Ti}(\text{O-}i\text{-Pr})_4$ and (*S*)-BINOL,
yet ...

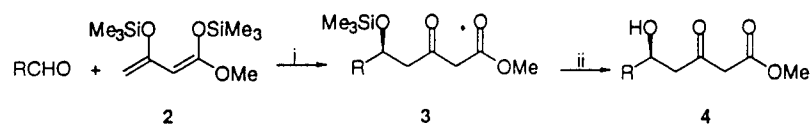


Table 1
Asymmetric aldol reaction promoted by $\text{Ti}(\text{IV})/(\text{S})\text{-BINOL}$ complex

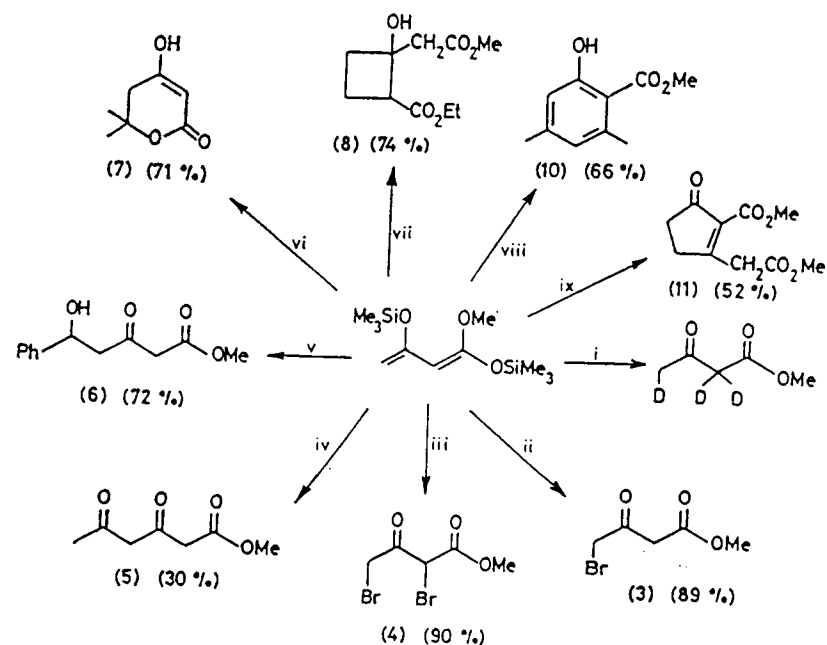
Entry	R	Product	Yield(%) ^a	Ee(%) ^b	$[\alpha]_D$
a	3-Furyl	4a	48	83	-36
b	C_6H_5	4b ^c	19	99	-46
		4b ^d	33	95	-45
c	<i>p</i> -NO ₂ C ₆ H ₄	4c	86	90	-39
d	<i>p</i> -CH ₃ OC ₆ H ₄	4d	54	93	-45
e	<i>n</i> -C ₉ H ₁₉	4e	50	87	-22

a) All the yields refer to isolated chromatographically pure compounds, whose structure were confirmed by ¹H-NMR and ¹³C analysis.¹⁶

b) E.e.s have been determined by HPLC analysis.

c) Yield refers to pure aldol 4b isolated directly after aldol reaction.

d) Yield refers to pure aldol 4b isolated after desilylation procedure.



Reagents: i, D₂O; ii, 1 mol Br₂; iii, 2 mol Br₂; iv, AcCl, ether, -78 °C; v, PhCHO, TiCl₄; vi, acetone, TiCl₄; vii, CH₂=CHCO₂Et, TiCl₄; viii, MeC(OSiMe₃)=CHCOMe, TiCl₄; ix, 2 mol TiCl₄.

Chan, T.-H., Brownbridge, P. *JCS CC* (1979) 578.

Soriente, A.; et al. *Tet. Asym.* (2000) 11 2255.

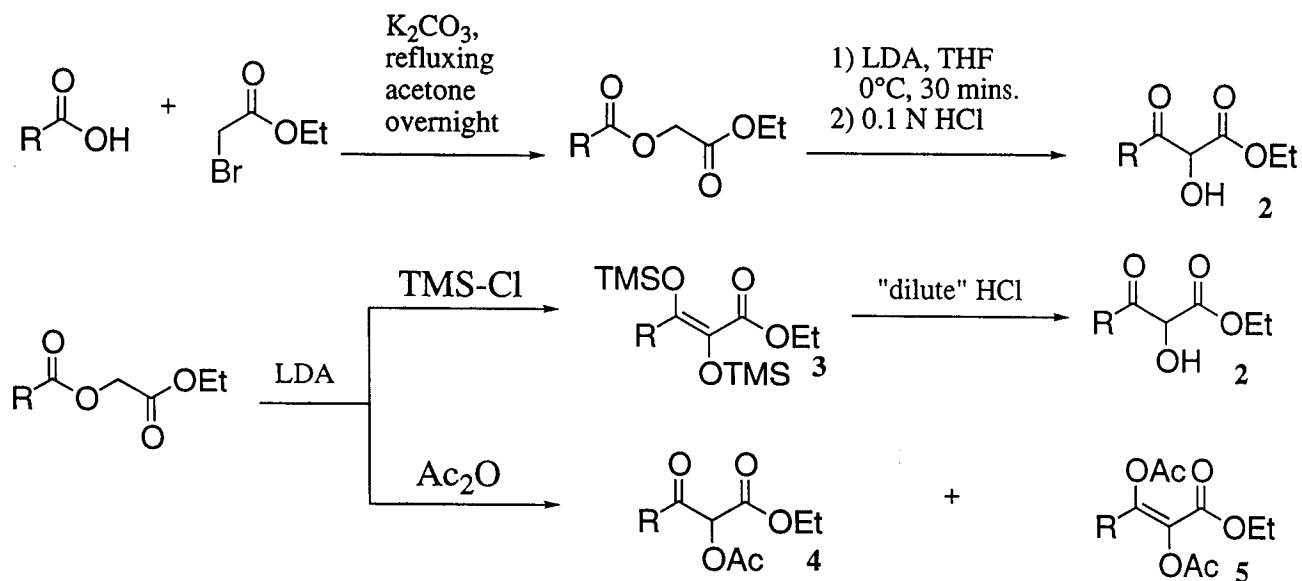
Scheme 1. Synthesis of δ -hydroxy- β -ketoesters 4; reagents:

(i) $\text{Ti}(\text{O-}i\text{-Pr})_4$, THF, *S*-(-)-BINOL, CH₂Cl₂, -78°C, m.s.;

(ii) H⁺/THF, 0°C

The Chan Reaction

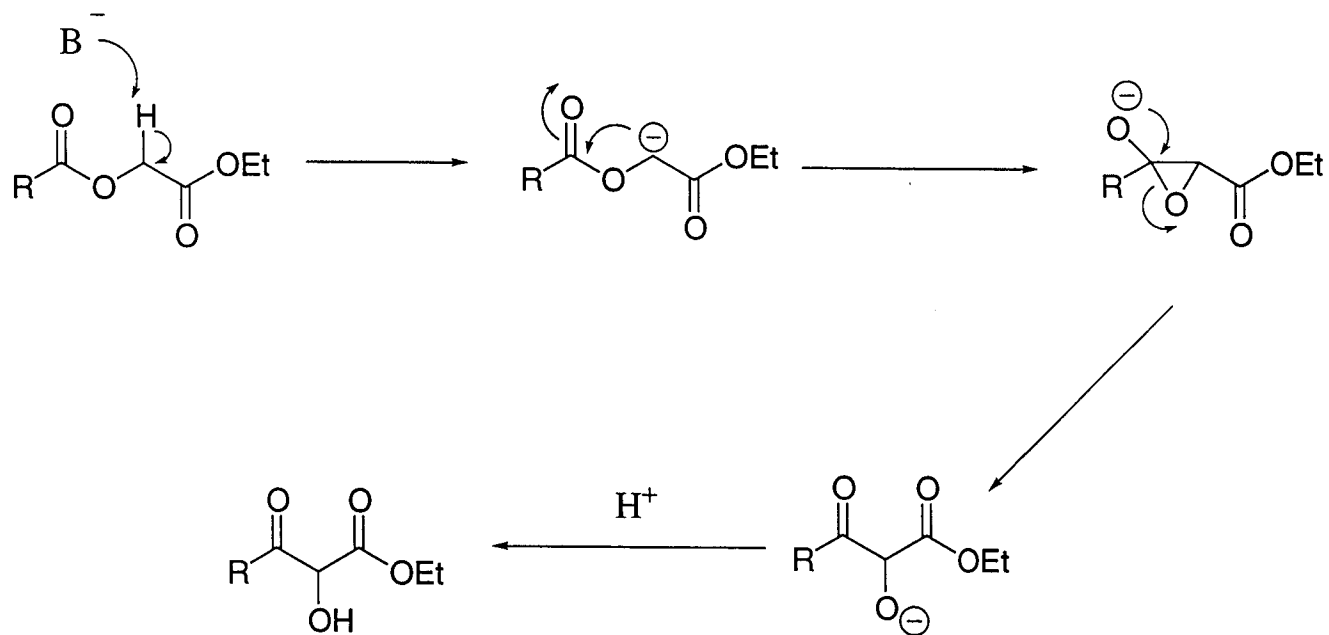
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α -Acyloxyacetate	Rxn Cond.	Product	% Yield Isolated
R = Ethyl	LDA, 0°C, H+	2a	57%
	LDA, 0°C, TMSCl	3a	87%
	LDA, 0°C, 1 eq Ac ₂ O	4a	35%
R = n-Pentyl	LDA, 0°C, H+	2b	52%
	LDA, 0°C, TMSCl	3b	65%
	LDA, 0°C, 1 eq Ac ₂ O	4b	45%
R = Cyclohexyl	LDA, 0°C, H+	2c	65%
	LDA, 0°C, TMSCl	3c	50%
	LDA, 0°C, 1 eq Ac ₂ O	4c	67%
	LDA, 0°C, 2 eq Ac ₂ O	5c	59%
R = sec-Pentyl	LDA, 0°C, H+	2d	65%
	LDA, 0°C, TMSCl	3d	62%
	LDA, 0°C, 1 eq Ac ₂ O	4d	65%
	LDA, 0°C, 2 eq Ac ₂ O	5d	62%
R = Phenyl	LHMDS, 0°C, 2 eq Ac ₂ O	5e	63%

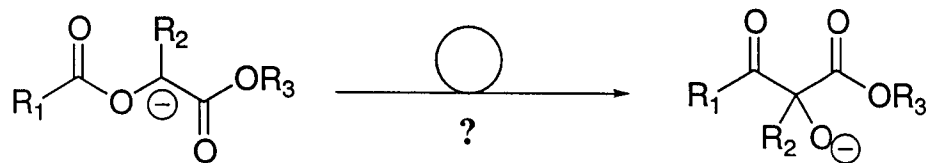
Proposed Mechanism

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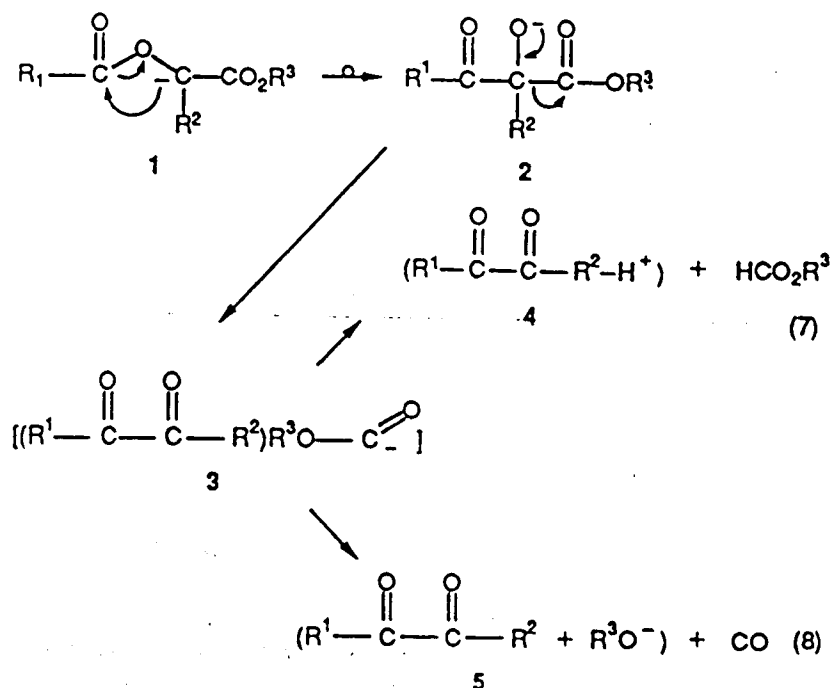


Gas Phase MS/MS of 1,2-Anionic Rearrangements

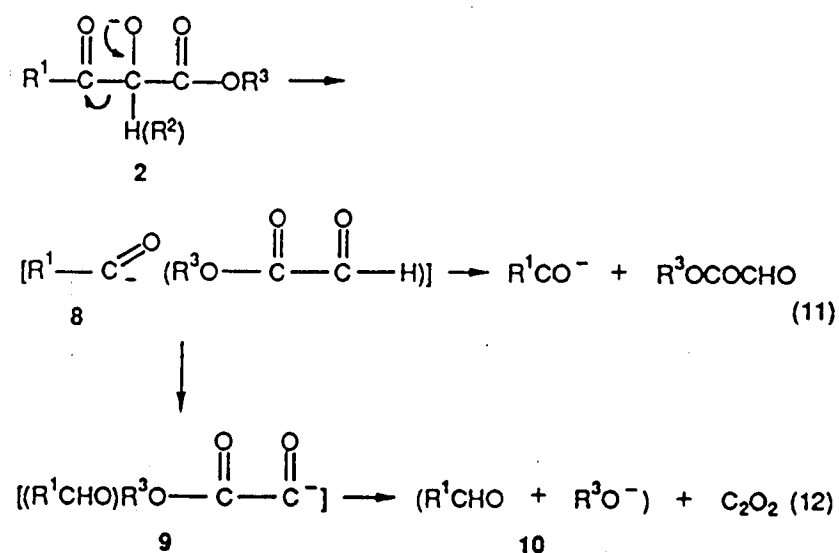
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Scheme II



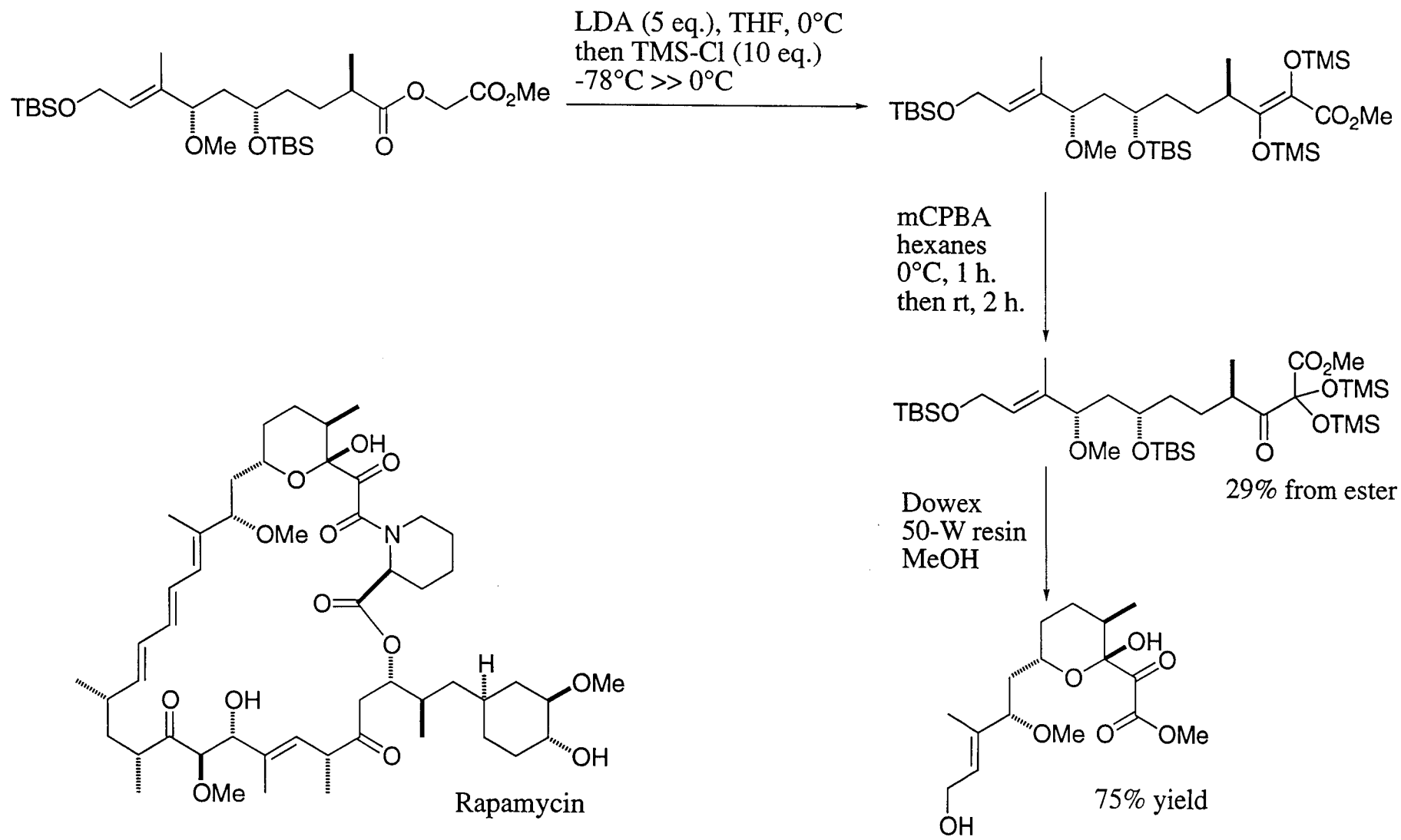
Scheme III



Study supports gas-phase 1,2-anionic rearrangement (also for α -(acyloxy)acetonitriles)

Tricarbonyl Subunit of Rapamycin

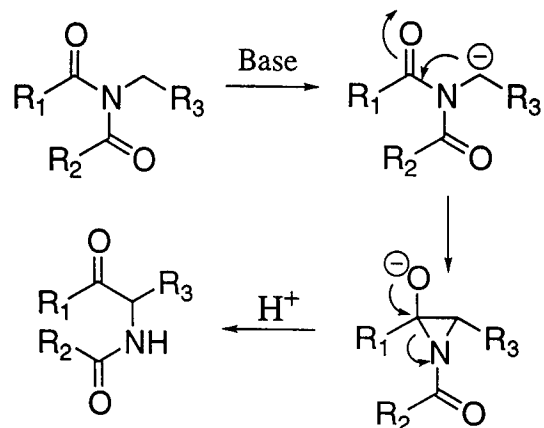
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White, J.D.; Jeffrey, S.C. JOC (1996) 61 2600.

N to C Acyl Migration Reaction of Imides: α -Aminoketones

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Proceeds with retention of configuration . . .

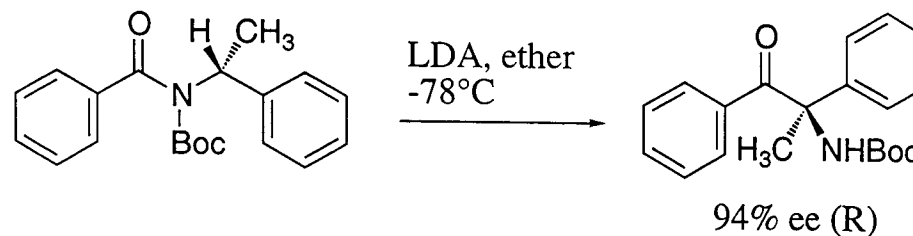
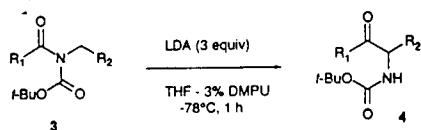


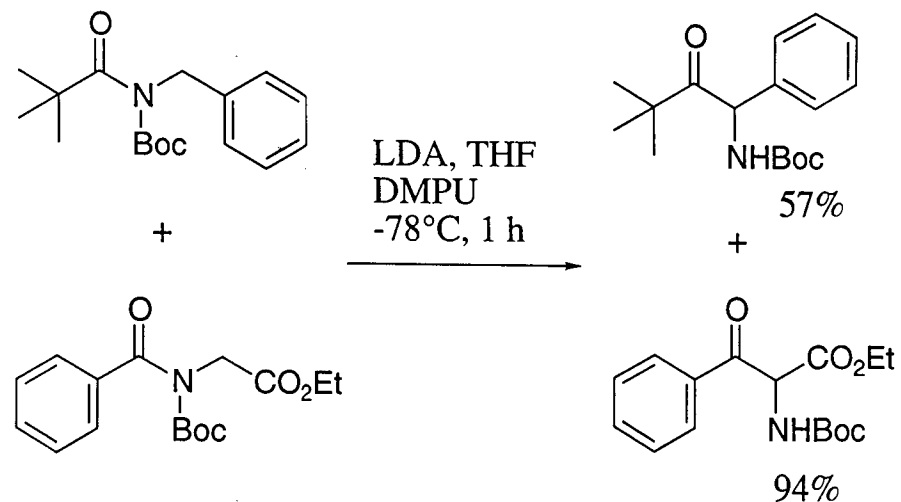
Table 1. N–C Acyl Migration Reaction of Imides.



run	R ₁	R ₂	yield (%) ^a
1	Ph-	-Ph	81
2	Ph-		89
3	Ph-	2-furyl	70
4	Ph-	CO ₂ Et	91
5	Ph-	CO ₂ t-Bu	82
6	Ph-		81 ^b
7	Ph-		71
8	Ph-		81
9	Ph-		80
10	MeO-	-Ph	55
11	t-Bu-	-Ph	98 ^c (58) ^d
12	PhCH ₂ CH ₂ -	CO ₂ Et	53 ^c (57) ^d

a) Isolated yields. b) Yield of the isomerized α,β -unsaturated ketone 5. c) Yields based on the consumed starting materials. d) Yields of the recovered starting material.

Crossover experiment shows no intermolecular migration . . .

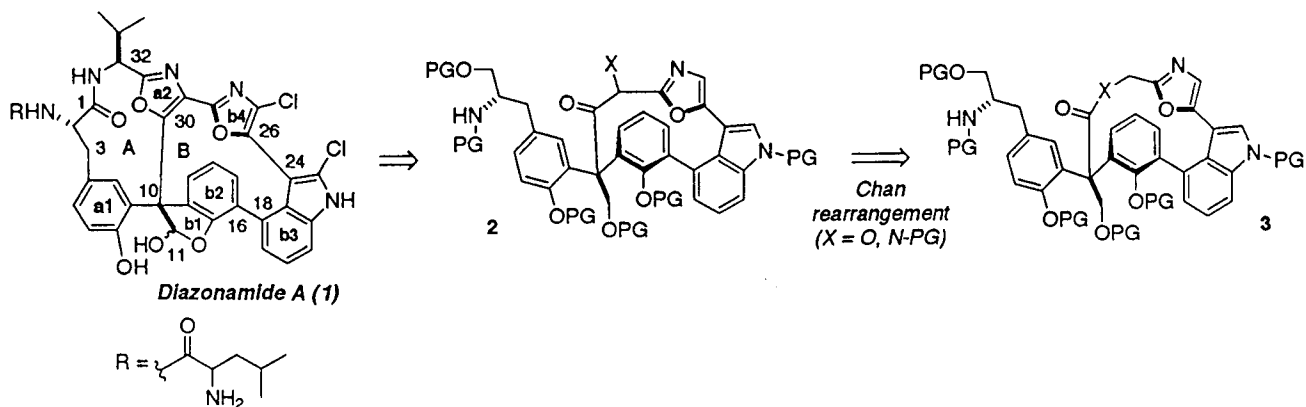


In addition, KH, KHMDS, and s-BuLi with sparteine showed no acyl migrated product.

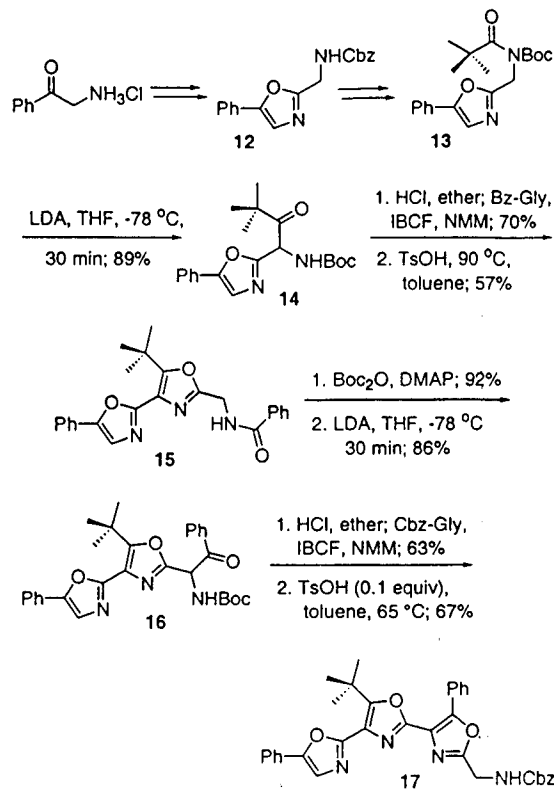
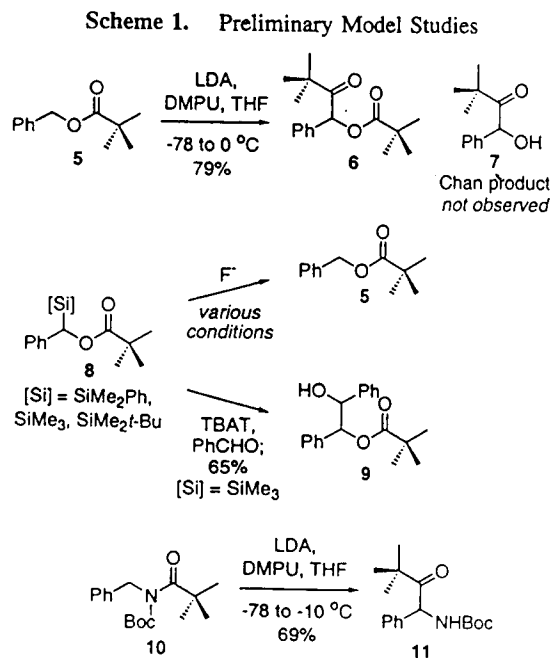
Hara, O.; Ito, M.; Hamada, Y. TL (1998) 39 5537.

Polyoxazole Synthesis Towards Diazonamide A

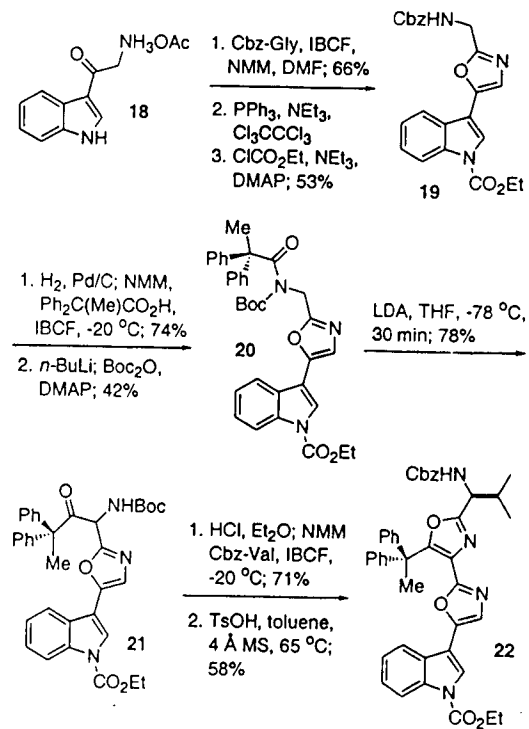
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Scheme 2. Polyoxazoles via Sequential Chan Reactions

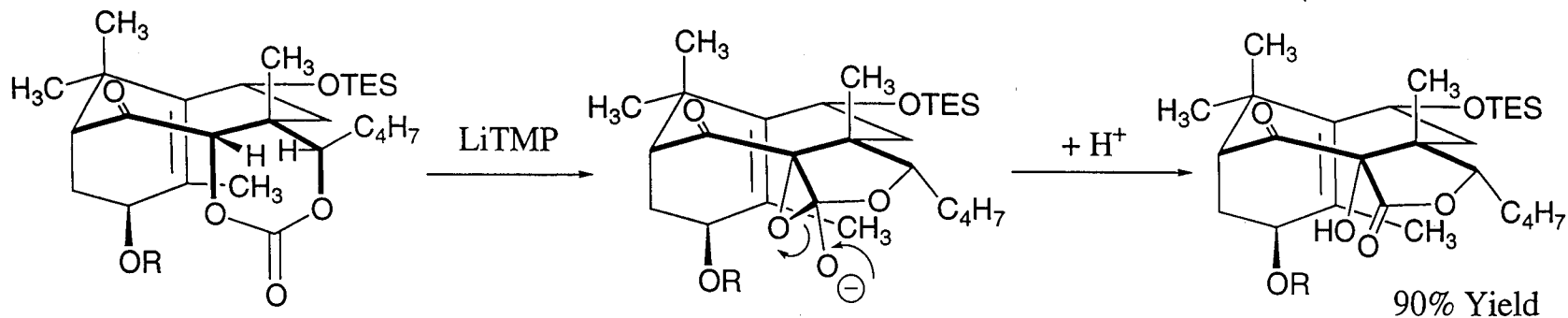
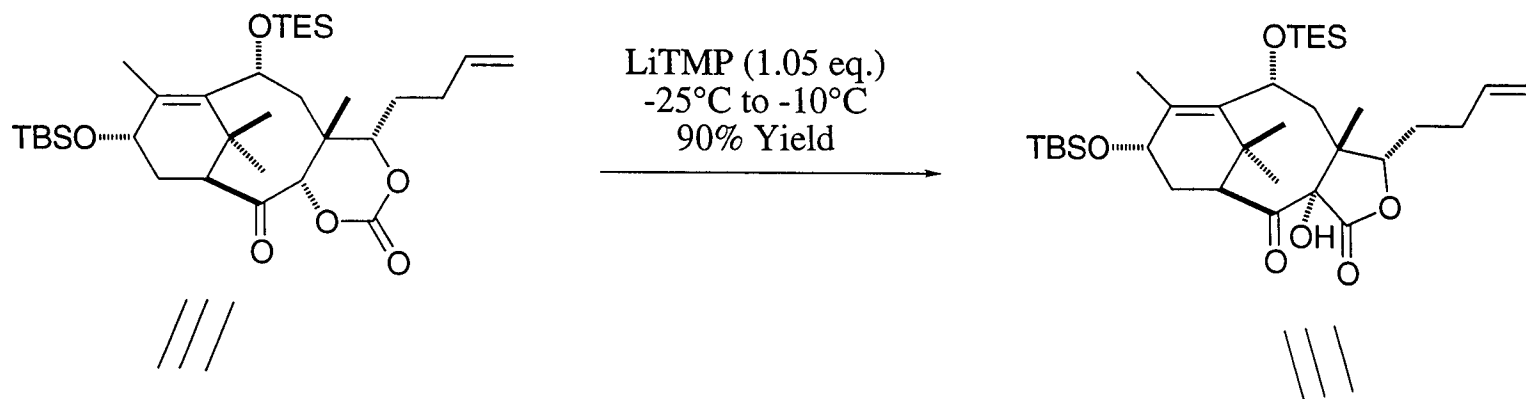
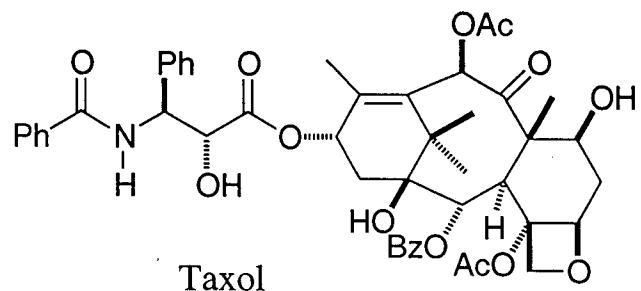


Scheme 3. Synthesis of the Indolyl Bisoxazole Fragment of Diazonamide A



Ring Reduction in Functionalization of Taxol B Ring

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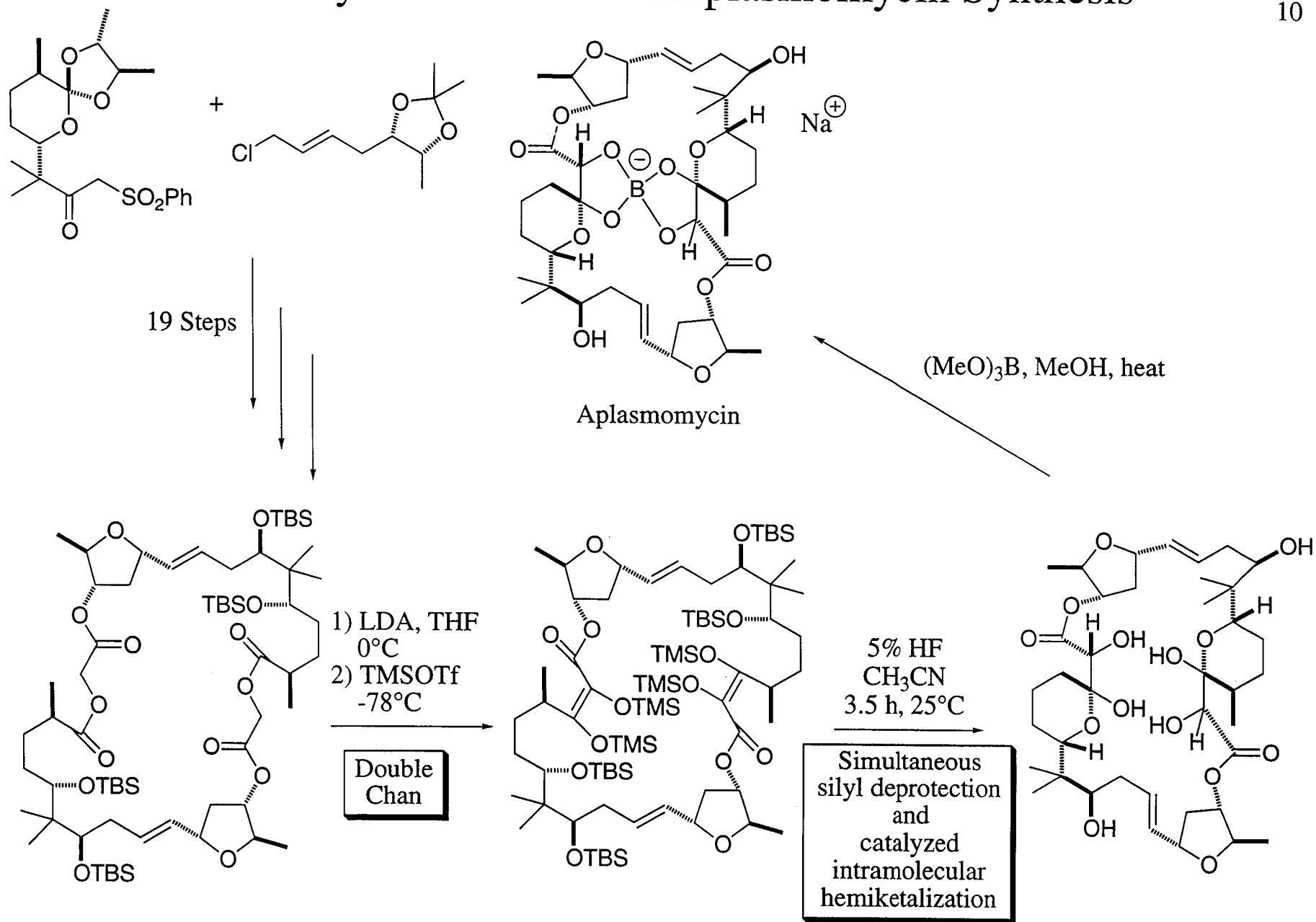


First example of cyclic system and stereoselective!

Holton, R.A.; et al. JACS (1994) 116 1597.

Macrocycle Reduction in Aplasmomycin Synthesis

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~~Holton, R.A.; et al. JACS (1994) 116 1597.~~

JD white 1994 JACS

Conclusion

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- 1) The Chan reaction was discovered in 1984, but has been used in a very limited number of cases.
- 2) There is evidence for an epoxide formation mechanism, which was substantiated by gas phase studies. In addition, other reaction analogs appear to follow the same mechanistic pathway.
- 3) The reaction has been featured in only a few syntheses (aplastomycin, boromycin, taxol, rapamycin, diazonamide A).
- 4) The Chan rearrangement has shown to proceed with retention of stereochemistry and with decent enantiomeric excesses, in cases where stereocenters are involved. (taxol subunit, acyclic imides)
- 5) Chan rearrangement products can yield useful synthetic intermediates, including tricarbonyl equivalents, α -hydroxy- β -ketoesters, polyoxazoles, and β -aminoketones.

References

Chan diene work

- Chan, T.H.; Brownridge, P. *JCS CC* (1979) 578.
Soriente, A.; DeRosa, M.; Villano, R.; Scettri, A. *Tet. Asym.* (2000) 11 2255.
Keck, G.E.; Yu, T. *OL* (1999) 1 289.
Brownridge, P.; Chan, T.H.; Brook, M.A.; Kang, G.J. *Can. J. Chem.* (1983) 61 688.

Original Chan Reaction

- Lee, S.D.; Chan, T.H.; Kwon, K.S. *TL* (1984) 25 3399.

Gas Phase MS of 1,2-Anionic Rearrangements

- Eichinger, P.C.H.; Hayes, R.N.; Bowie, J.H. *JACS* (1991) 113 1949.

N to C Acyl Migration with Imides

- Hara, O.; Ito, M.; Hamada, Y. *TL* (1998) 39 5537.

Chan Reaction used toward synthesis

- Rapamycin: White, J.D.; Jeffrey, S.C. *JOC* (1996) 61 2600.
Diazonamide A: Wipf, P.; Methot, J.-L. *OL* (2001) 3 1261.
Taxol: Holton, R.A.; et al (17 others). *JACS* (1994) 116 1597.
Aplasmomycin: White, J.D.; Vedananda, T.R.; Kang, M.; Choudhry, S.C. *JACS* (1986) 108 8105.
Boromycin: White, J.D.; et al (7 others). *JACS* (1989) 111 790.

Chan Reaction used for other reasons

- Fadnavis, N.W.; Vadivel, S.K.; Sharfuddin, M. *Tet. Asym.* (1999) 10 3675.

Other Ways to Make α -Hydroxy- β -Ketoesters

- Murahashi, S.; et al. (6 others). *JOC* (1993) 58 2929.
Araneo, S.; Clerici, A.; Porta, O. *TL* (1994) 35 2213.
Clerici, A.; Clerici, L.; Porta, O. *Tetrahedron* (1996) 52 11037.

Equilibria of Anions of α -Hydroxy- β -Diketones and α -Ketol Esters

- Rubin, M.B.; Inbar, S. *JOC* (1988) 53 3355.