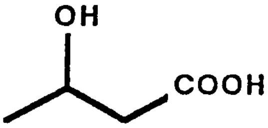
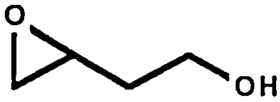
L39

KNOWN C-4 POLYOXYGENATED UNITS

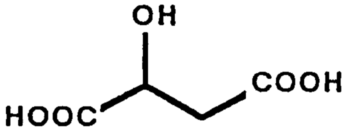
(METHODS OF PREPARATION)



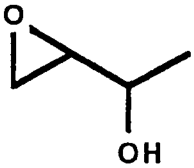
(ENZYMES NATURAL)



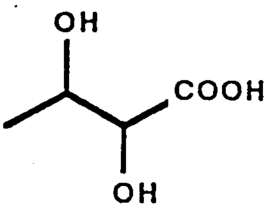
(SYNTHETIC ENZYMES)



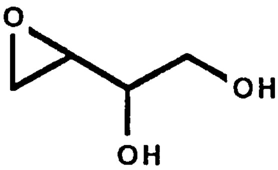
(ENZYMES NATURAL)



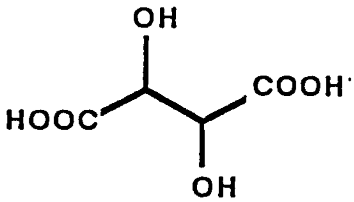
(SYNTHETIC)



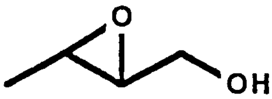
(ENZYMES SYNTHETIC)



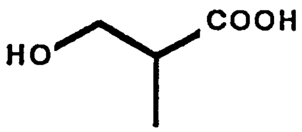
(SYNTHETIC)



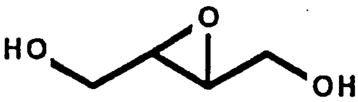
(NATURAL)



(ENZYMES SYNTHETIC)

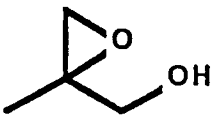


(ENZYMES)



(ENZYMES SYNTHETIC)

(SYNTHETIC)



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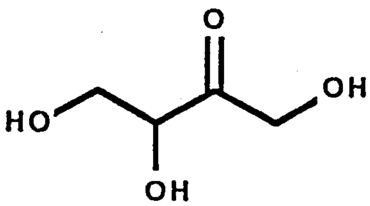

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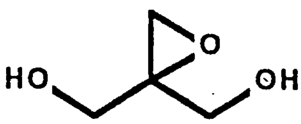

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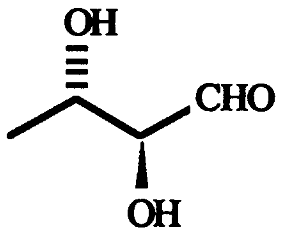

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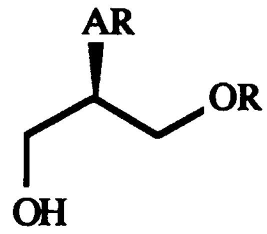
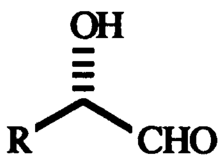


3

4



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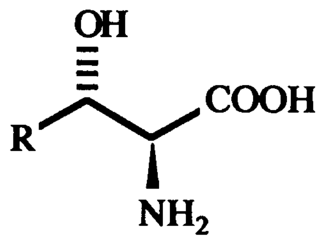

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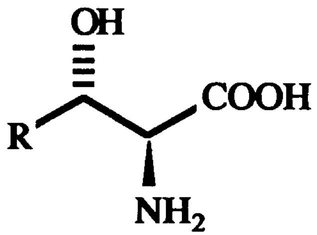

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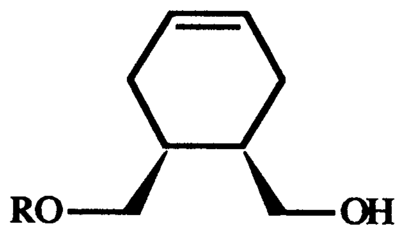

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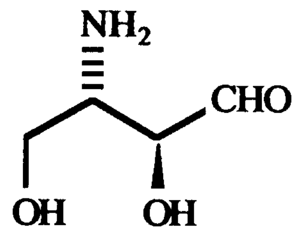


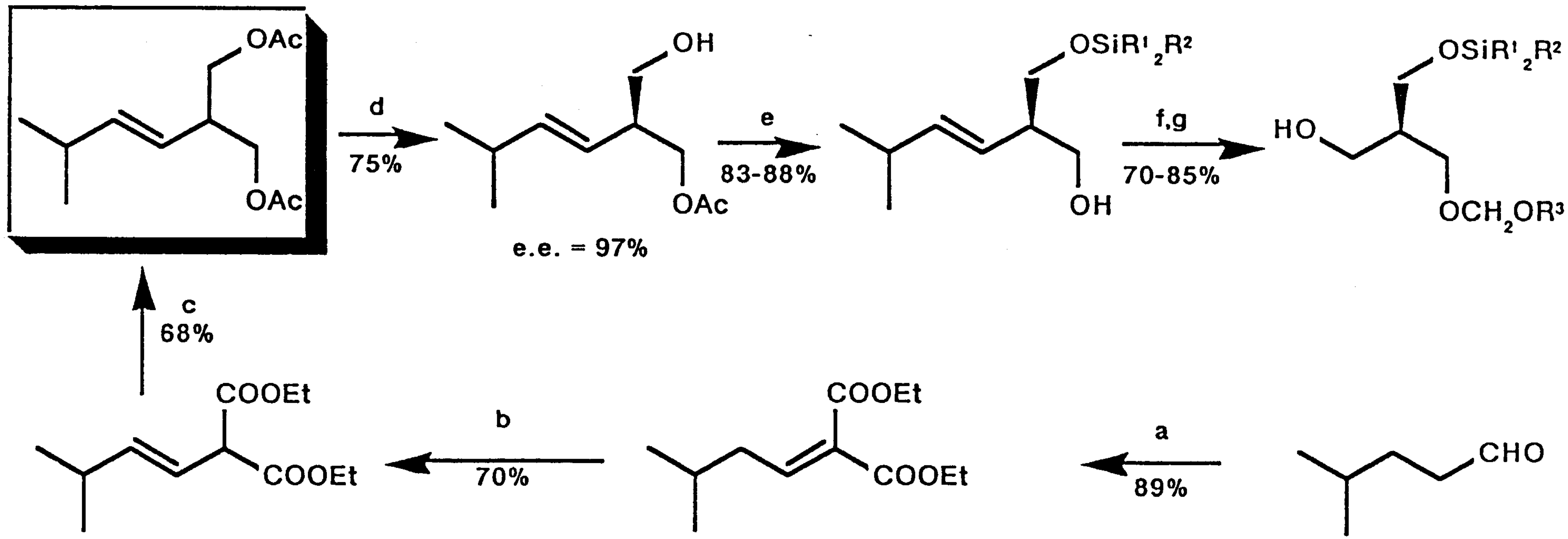
6

G. Guanti, L. Banfi, and E. Narisano

1 *Tetrahedron Lett.*, 3547 (1986)
2 *JCS Perkin 1, 2369 (1988)*
3 *Tetrahedron*, 7081 (1990)
4 *Chem. Lett.*, 1683 (1988)
5 *Tetrahedron*, 5553 (1988)
6 *Tetrahedron Lett.*, 5507 (1989)
7 *Tetrahedron Lett.*, 4639 (1986)
8 *Tetrahedron Lett.*, 5507 (1989)

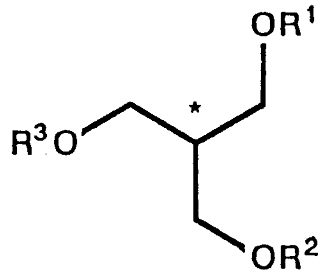
L133

RECOMMENDED SUBSTRATE OF CHOICE AS SYNTHETIC EQUIVALENT OF THYM*



a) Diethyl malonate, piperidinium acetate, benzene, reflux; b) NaH, THF, 40°C, then H^+; c) $LiAlH_4$, Et_2O; then Ac_2O, pyridine; d) Enzymatic procedure (see ahead); e) R2R12SiCl, imidazole, DMF, or $R^2R^1{}_2Si$-OTf, 2,6-lutidine, CH_2Cl_2; then KOH, MeOH; f) R_3OCH_2Cl, EtN(i Pr)$_2$, CH_2Cl_2; g) O_3, CH_2Cl_2; then $NaBH_4$, MeOH.

L34



THYM*

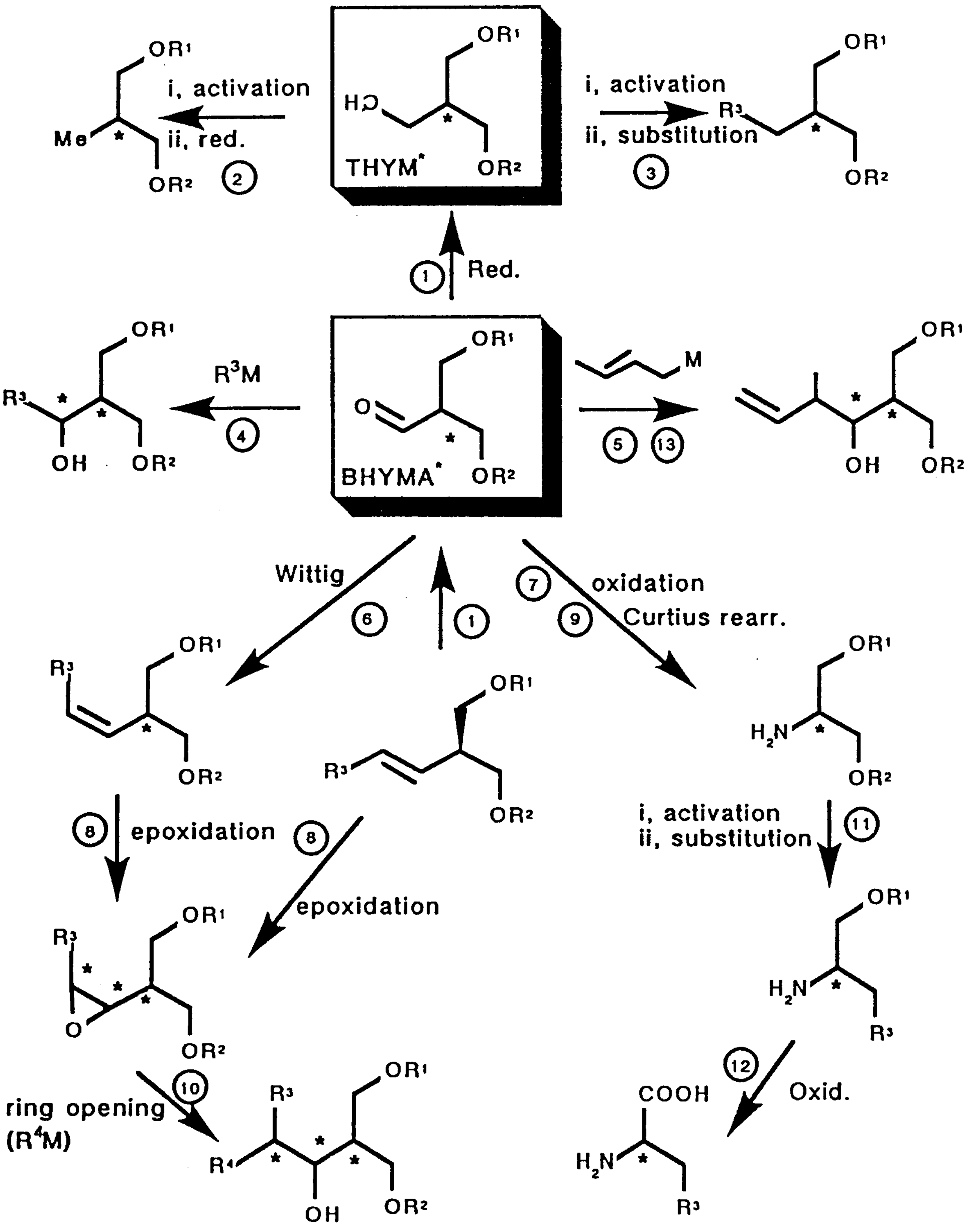
ASYMMETRIZED *TRIS* (HYDROXYMETHYL)METHANE

PROPERTIES:

- New C-4 chiral building block useful for any C-branched molecule
- "Chiral methyne" bonded to three CH_2OH that can be manipulated indipendently one at a time
- Precursor of many natural products
- System with "latent C_{3v} symmetry"
- Double stereodivergency: Enantiodivergency and Diastereo-divergency [it is possible to obtain both the enantiomers and both the diastereoisomers (in the creation of a new chiral centre) with just <u>one</u> control of stereoselection (protection-deprotection trick)].

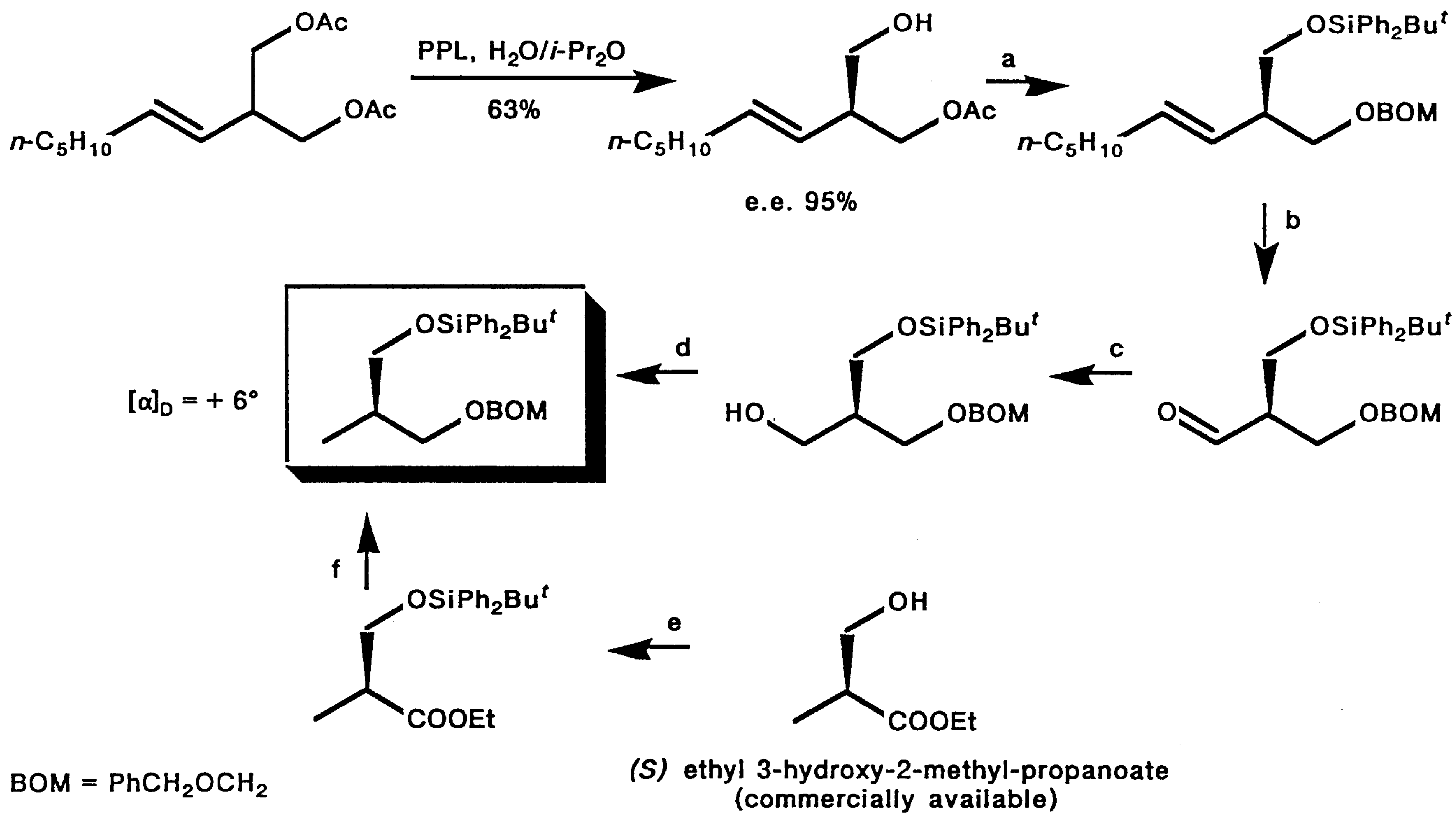
G. Guanti *et. al.*, *Tetr. Lett.*, 1989, *30*, 2697; *Tetr.: Asymm.*, 1990, *1*, 721; *J.O.C.*, 1992, 57, 1540; *Tetr. Lett.*, 1990, *31*, 6421; 1991, *32*, 267, 6939, 6943.

SURVEY OF POSSIBLE ELABORATIONS OF THYM* AND RELATED SYSTEMS



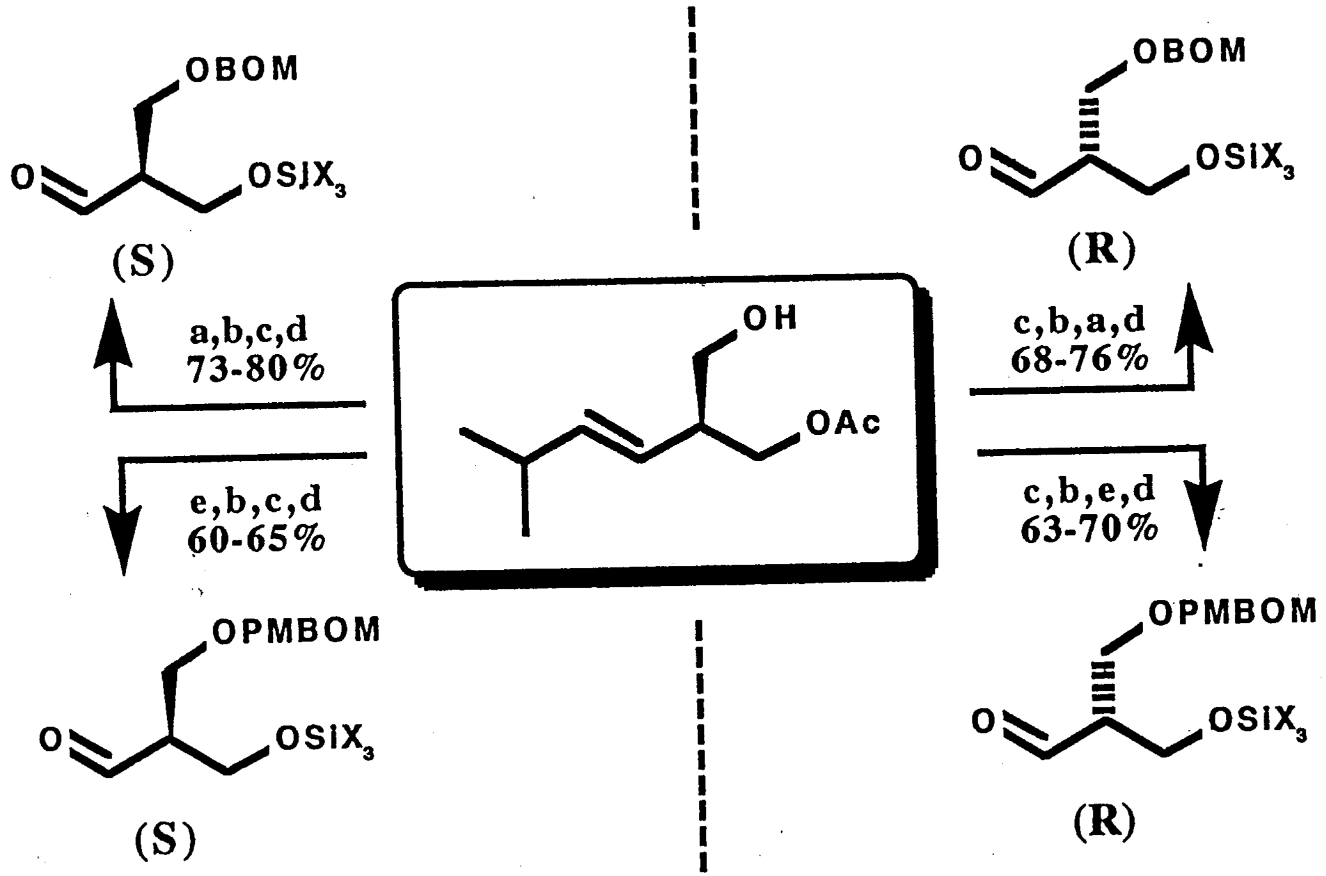
1, 2 G. Guanti *et. al.*, *Tetr. Lett.*, 1989, *30*, 2697; *Tetr.: Asymm.*, 1990, *1*, 721; *J.O.C.*, 1992, 1540. 4 *Tetr. Lett.*, 1990, *31*, 6421; 1991, *32*, 267. 5 *Tetr. Lett.*, 1991, *32*, 6939. 6, 8 *Tetr. Lett.*, 1991, *32*, 6943. 3,7, 9, 10, 11, 12,13 Under investigation

DETERMINATION OF ABSOLUTE CONFIGURATION



a) i, *t*-$BuPh_2SiCl$, DMF, imidazole; ii, KOH, MeOH; iii, BOM-Cl, *i*-Pr_2NEt, CH_2Cl_2. b) O_3, Me_2S. c) $NaBH_4$. d) i, TsCl Et_3N, DMAP; ii, $NaBH_4$, DMSO. e) *t*-$BuPh_2SiCl$, DMF, imidazole. f) i, $LiAlH_4$; ii, BOM-Cl, *i*-Pr_2NEt, CH_2Cl_2.

L61

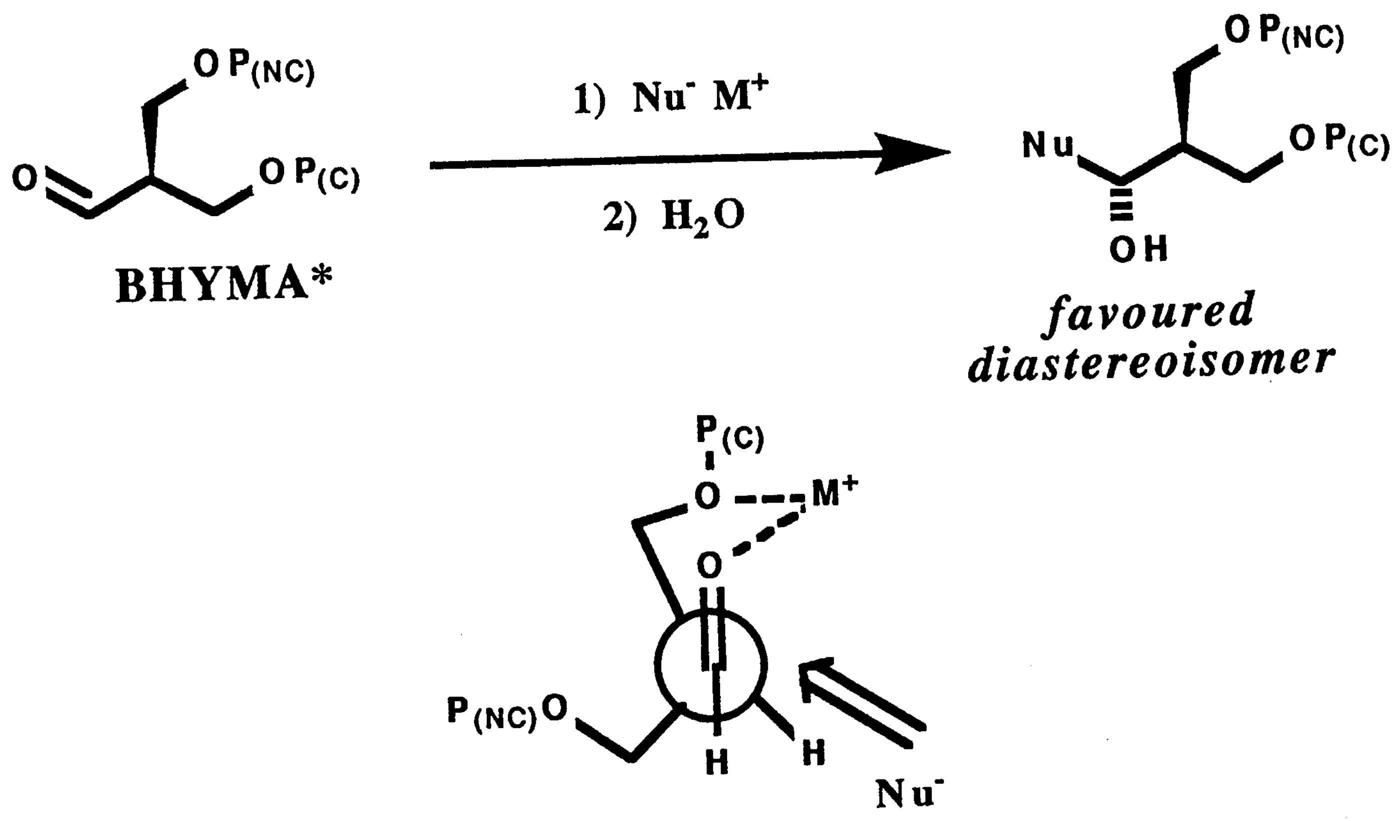


BOM= $PhCH_2OCH_2$
PMBOM= 4-MeO-$C_6H_4CH_2OCH_2$

SiX_3 = Me_2t BuSi
SiX_3 = Ph_2t BuSi
SiX_3 = $(i\ Pr)_3Si$

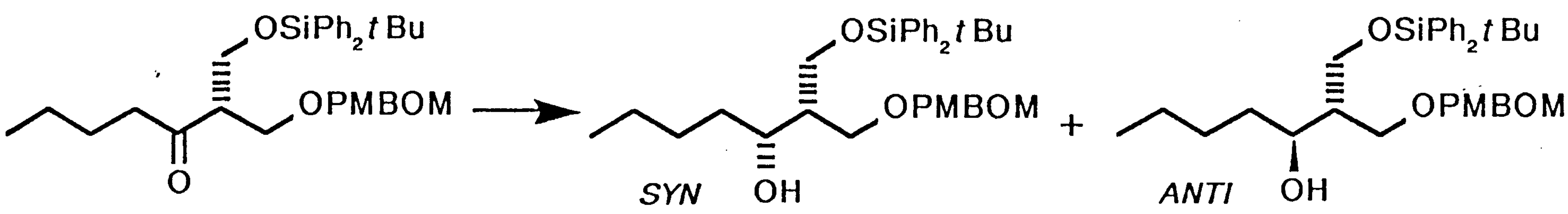
a) BOM-Cl, EtN(*i* Pr)$_2$, CH_2Cl_2; b) KOH, MeOH; c) Me_2t BuSiCl, DMF, imidazole, or Ph_2t BuSiCl, DMF, imidazole, or $(i\ Pr)_3SiOTf$, 2,6-lutidine, CH_2Cl_2; d) O_3, MeOH-CH_2Cl_2, then Me_2S. e) PMBOM-Cl, EtN(*i* Pr)$_2$, CH_2Cl_2;

L67


O P(NC)
O P(C)
O
BHYMA*
1) Nu⁻ M⁺
2) H2O
Nu
OH
favoured
diastereoisomer
P(C)
O
M+
O
P(NC)O
H
H
Nu-

L132

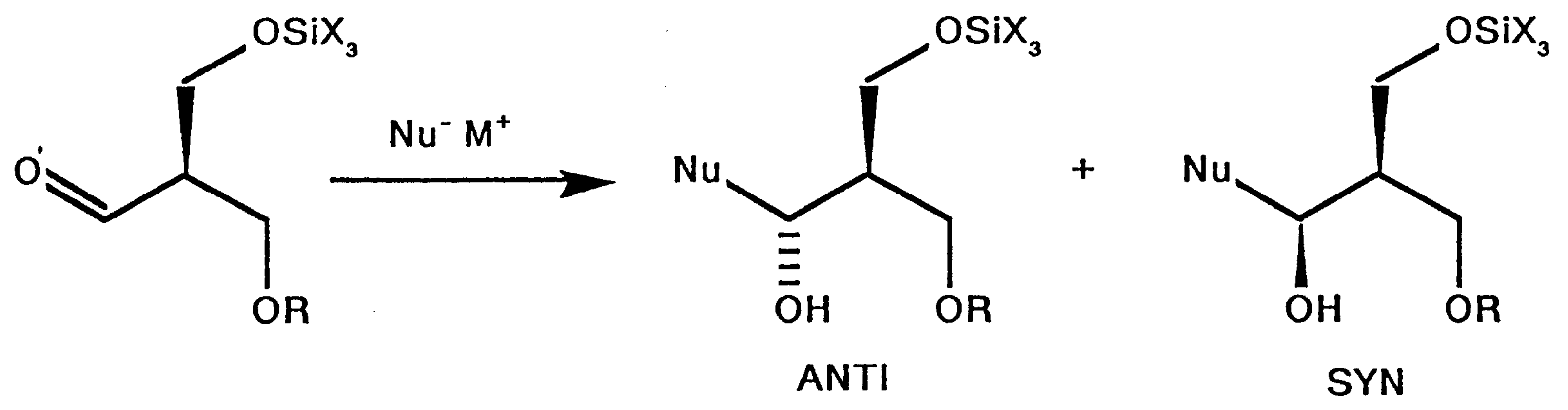
STEREOSELECTIVE KETONE REDUCTIONS



Effect of Lewis acid in reductions with DIBALH

Entry	Lewis acid	Temperature	*syn* : *anti*	Yield
1	none	-78°C	51 : 49	74%
2	$Ti(OiPr)_4$	-78°C → r.t.	47 : 53	65%
3	$Ti(OiPr)_3Cl$	-78°C → r.t.	52 : 48	79%
4	Et_2AlCl	-78°C	54 : 46	82%
5	CdI_2	-78°C → r.t.	60 : 40	79%
6	$CdCl_2$	-78°C	60 : 40	88%
7	$Mg(CF_3COO)_2$	-78°C → r.t.	52 : 48	70%
8	ZnI_2	-78°C	67 : 33	50%
9	$MgBr_2$	-78°C	88 : 12	94%

Reactions performed in Et_2O with 5 eq. of Lewis acid and 2 eq. of reducing agent (with the exception of entries 2, 5, 7 and 8 where an excess. of DIBALH were required to bring reaction to completion)

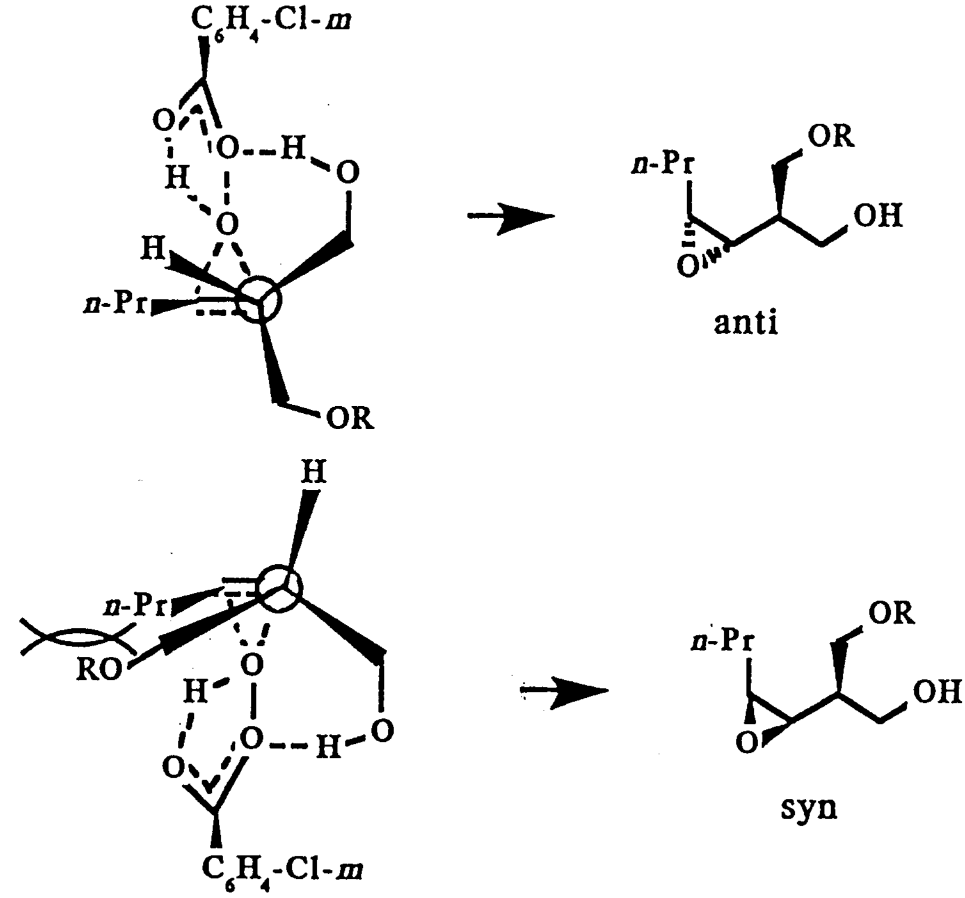


Chelation-controlled addition of C-nucleophiles to BHYMA*				
R	X_3Si	$Nu^- M^+$	Yield[a]	Diast. ratio[b]
BOM	$Me_2 t BuSi$	Me_2CuLi	74%	95 : 5
PMBOM	$Me_2 t BuSi$	Me_2CuLi	84%	95 : 5
BOM	$Me_2 t BuSi$	Et_2CuLi	87%	93 : 7
BOM	$Me_2 t BuSi$	$n Bu_2CuLi$	93%	87 : 13
BOM	$Me_2 t BuSi$	allyl-Sn(nBu)$_3$- $MgBr_2$[c]	70%	83 : 17
PMBOM	$Me_2 t BuSi$	allyl-Sn(nBu)$_3$- $MgBr_2$[c]	70%	86 : 14
BOM	$Ph_2 t BuSi$	allyl-Sn(nBu)$_3$- $MgBr_2$[c]	92%	87 : 13
PMBOM	$Ph_2 t BuSi$	allyl-Sn(nBu)$_3$- $MgBr_2$[c]	84%	87 : 13
PMBOM	(iPr)$_3$Si	allyl-Sn(nBu)$_3$- $MgBr_2$[c]	76%	85:15

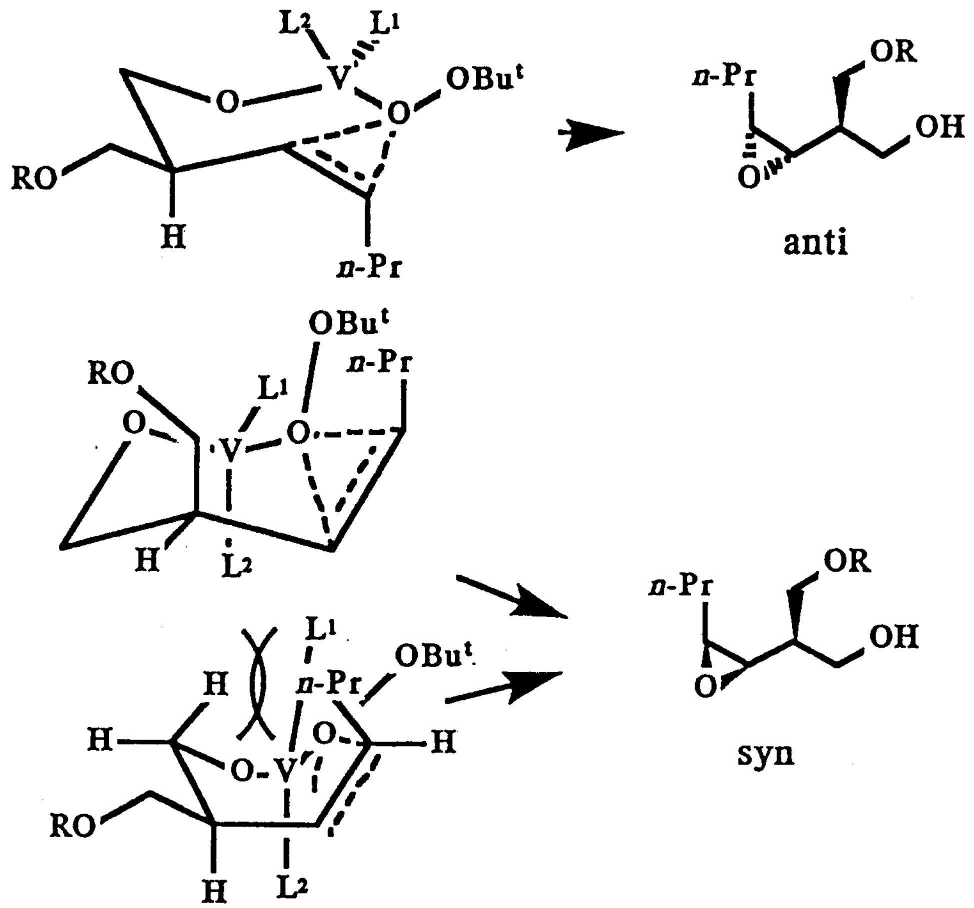
a) Yields of two steps: ozonolysis and condensation. b) The major isomer has always the relative configuration *anti*. c 2 eq. of $MgBr_2$, direct addition.

MODELS FOR EPOXYDATION OF *Z* SUBSTRATES

MCPBA

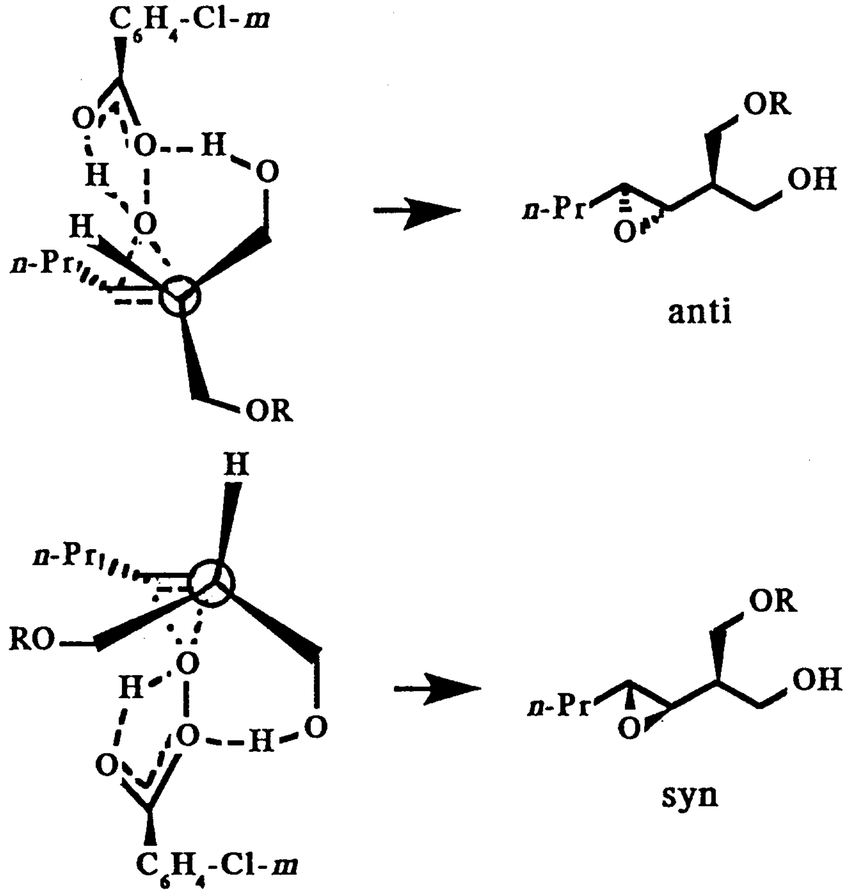


TBHP/V^{5+}

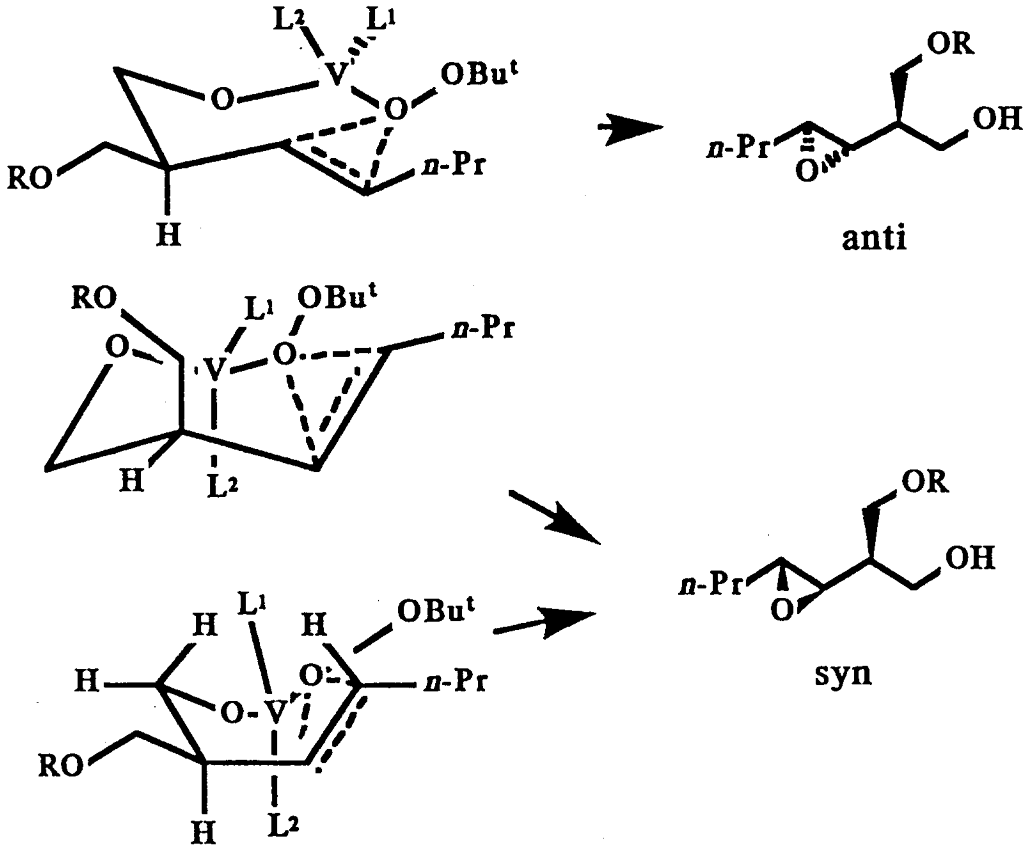


MODELS FOR EPOXYDATION OF *E* SUBSTRATES

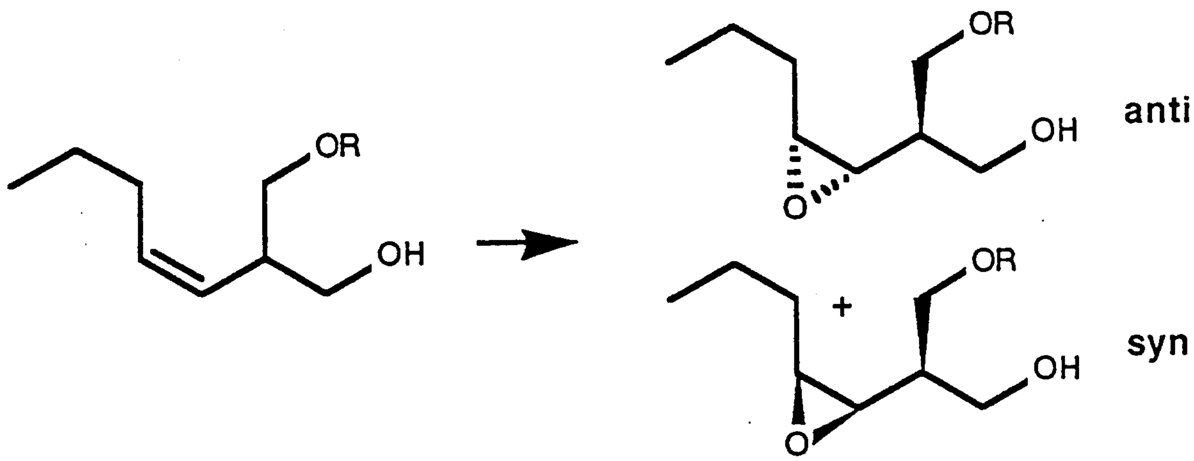
MCPBA



TBHP/V^{5+}



EPOXIDATION OF *Z*-MONOPROTECTED HOMOALLYLIC DIOLS

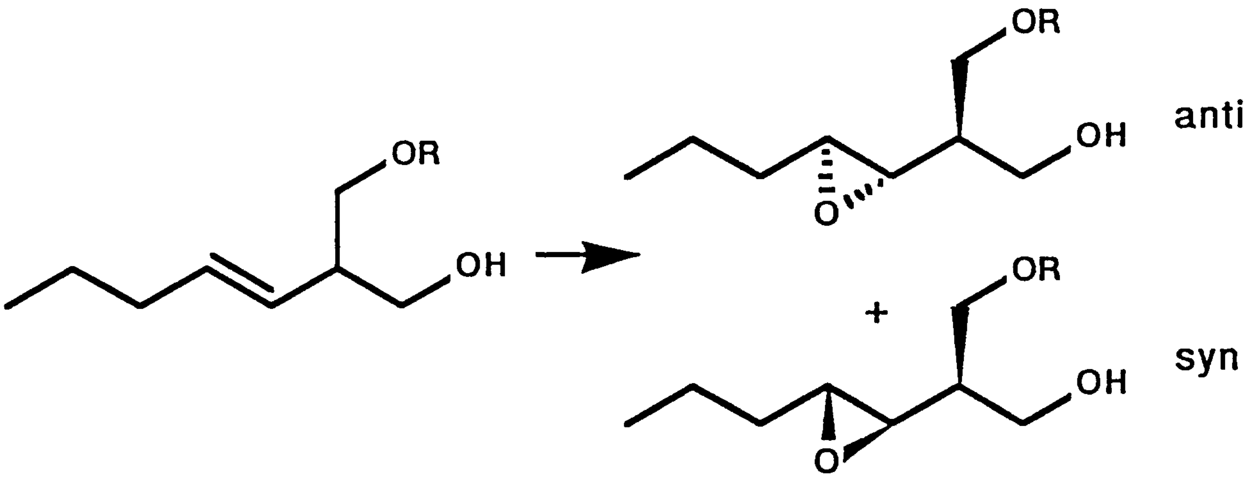


R (Abs. Config.)	Method	Yield	anti : syn
Ac *(S)*	MCPBA	82%	63 : 37
Bn *(S)*	MCPBA	71%	79 : 21
TBDMS *(R)*	MCPBA	79%	70 : 30
TBDPS *(R)*	MCPBA	72%	85 : 15
Tr *(R)*	MCPBA	95%	79 : 21
Ac *(S)*	TBHP / V^{5+}	38%	72 : 28
Bn *(S)*	TBHP / V^{5+}	56%	> 95 : 5
PMB *(R)*	TBHP / V^{5+}	74%	> 95 : 5
TBDMS *(R)*	TBHP / V^{5+}	63%	> 95 : 5
TBDPS *(R)*	TBHP / V^{5+}	57%	> 95 : 5
Tr *(R)*	TBHP / V^{5+}	90%	> 95 : 5
TIPS *(R)*	TBHP / V^{5+}	95%	> 95 : 5

Enantiomeric purity of substrates and products was checked by synthesis of Mosher's esters and ^{1}H n.m.r. analysis.

MCPBA: 3-ClC_6H_4COOOH, dry CH_2Cl_2, r.t.
TBHP / V^{5+}: Me_3COOH, $VO(acac)_2$, dry CH_2Cl_2, r.t.

EPOXIDATION OF *E*-MONOPROTECTED HOMOALLYLIC DIOLS



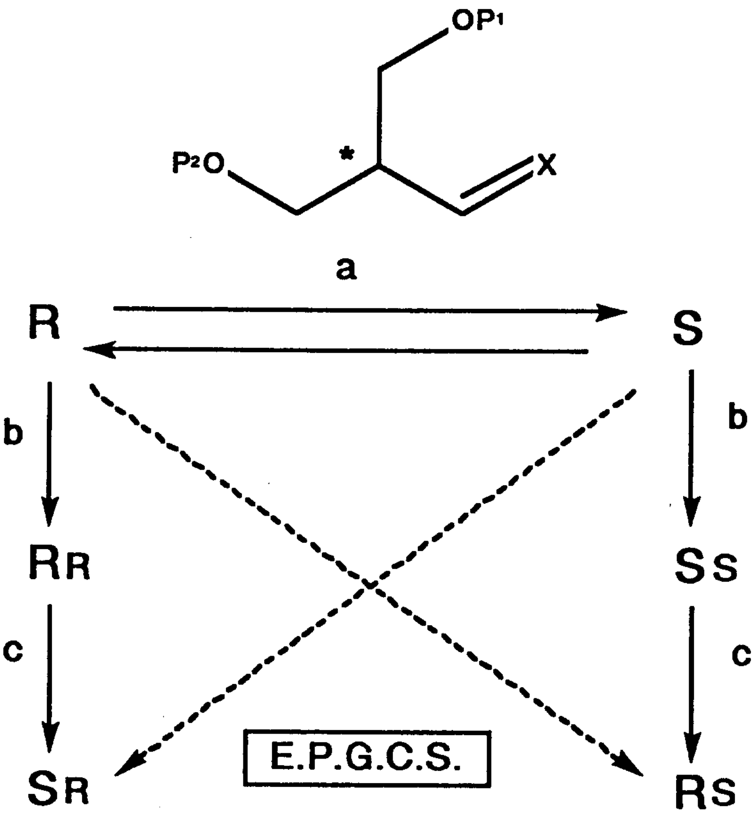
R (Abs. Config.)	Method	Yield	anti : syn
Ac *(S)*	MCPBA	84%	54 : 46
Bn *(S)*	MCPBA	86%	51 : 49
TBDMS *(R)*	MCPBA	77%	57 : 43
Ac *(S)*	TBHP / V^{5+}	58%	≅ 50 : 50
TBDMS *(R)*	TBHP / V^{5+}	96%	68 : 32

Enantiomeric purity of substrates and products was checked by synthesis of Mosher's esters and ^{1}H n.m.r. analysis.

MCPBA: 3-ClC_6H_4COOOH, dry CH_2Cl_2, r.t.

TBHP / V^{5+}: Me_3COOH, $VO(acac)_2$, dry CH_2Cl_2, r.t.

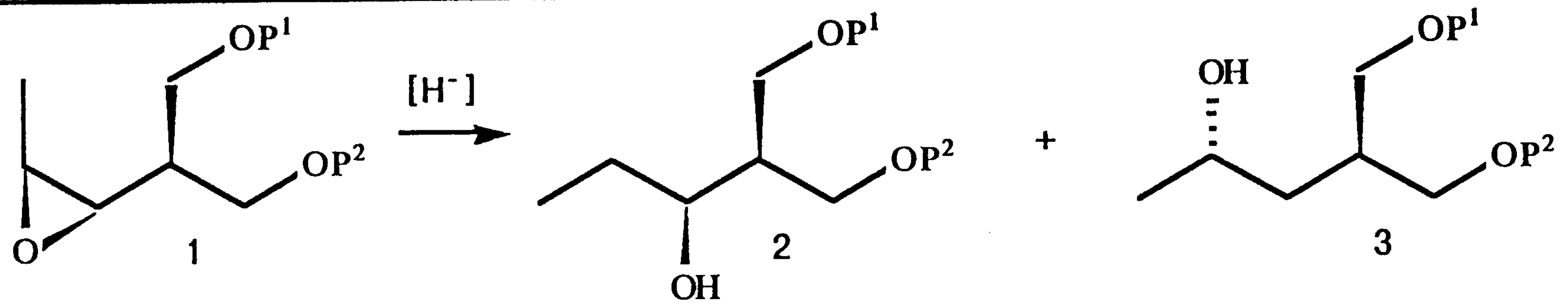
DOUBLE STEREODIVERGENCY SYSTEM



a) PROTECTION-DEPROTECTION TRICK-
(ENANTIODIVERGENCY)

b) DIASTEREOCONTROL

c) PROTECTION-DEPROTECTION TRICK-
DIASTEREODIVERGENCY

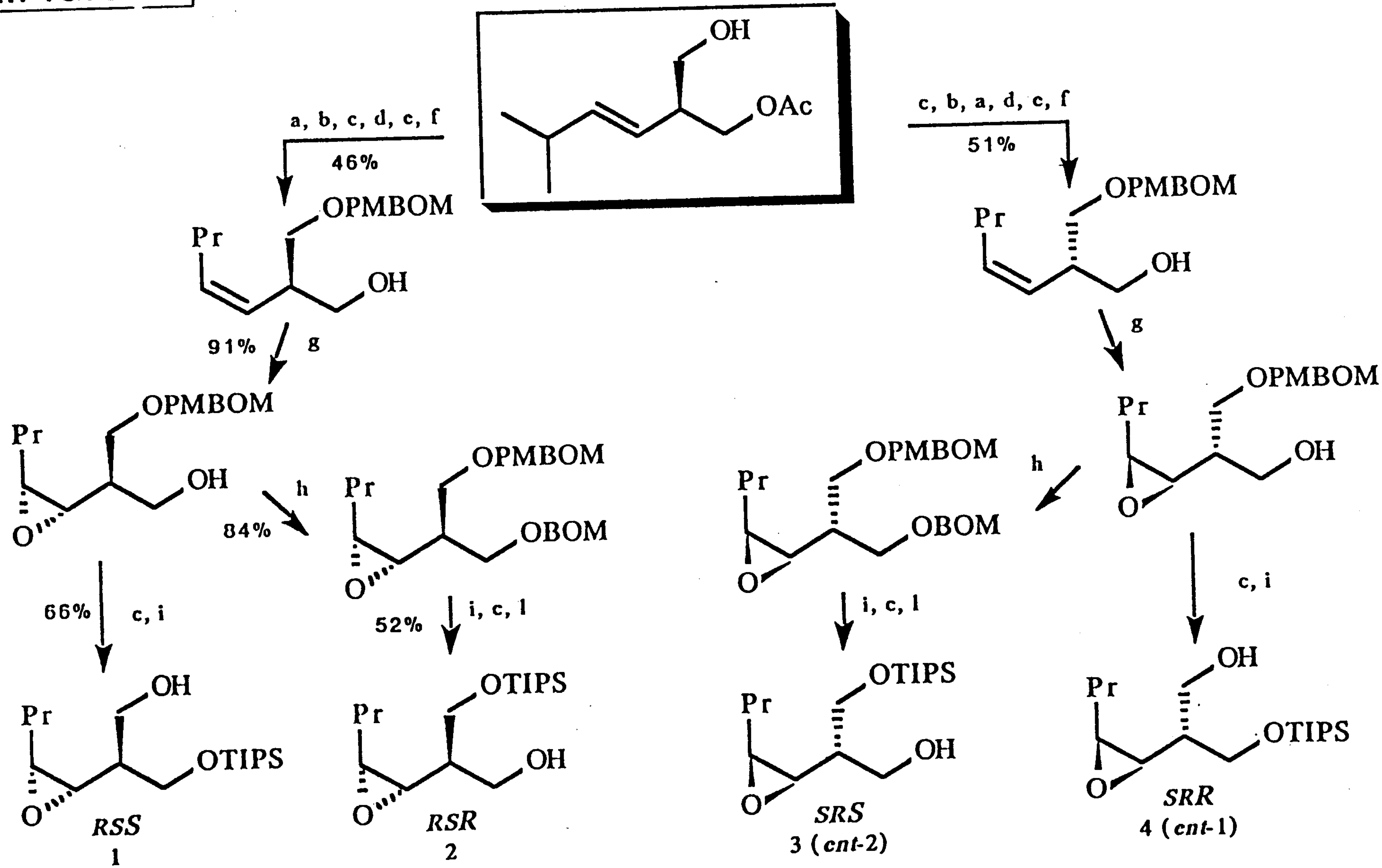


Hydride donor	Lewis acid[a]	Experimental conditions: other reagents, solvent, T, t	P^1, P^2	Yield[b] (%)	Regioisomer ratio 2 : 3
$LiAlH_4$	-	THF, r.t., 2 h	H, TIPS	36[c]	69 : 31
$LiAlH_4$	-	THF, reflux, 20 h	PMP, TIPS	n.r.[d]	-
$LiBH_4$	-	PhH, reflux, 20 h	H, TIPS	83 (92)	68 : 32
$LiBH_4$	$Ti(i\text{-PrO})_4$	PhH, r.t. → 50°C, 10 h	H, TIPS	68	82 : 18
$Zn(BH_4)_2$	-	THF, reflux, 15 h	H, TIPS	56 (83)	62 : 38
$Zn(BH_4)_2$	SiO_2	THF, r.t. → reflux, 6 h	H, TIPS	70 (79)	80 : 20
$Zn(BH_4)_2$	SiO_2	THF, r.t. → reflux, 15 h	PMP, TIPS	24 (37)	> 99 : 1
n-Bu_3SnH	MgI_2	AIBN, PhMe, -40°C → 110°C, 1 h	PMP, TIPS	60	> 99 :1
DIBAH	-	PhMe, reflux, 124 h	H, TIPS	-[d]	-
DIBAH	-	PhH, reflux, 20 h	PMP, TIPS	traces	-
DIBAH	$BF_3{\cdot}Et_2O$	CH_2Cl_2, -78°C, 3.5 h	PMP, TIPS	75 (97)	95 : 5

[a] Order of mixing: substrate + Lewis acid + hydride donor. [b] Isolated yield; figures reported in paranthesis refer to yield based on unrecovered substrate. [c] Partial deblocking of protection was observed. [d] No reaction was observed.

PMP = *p*-methoxyphenyl TIPS = triisopropylsilyl

E.P.G.C.S.

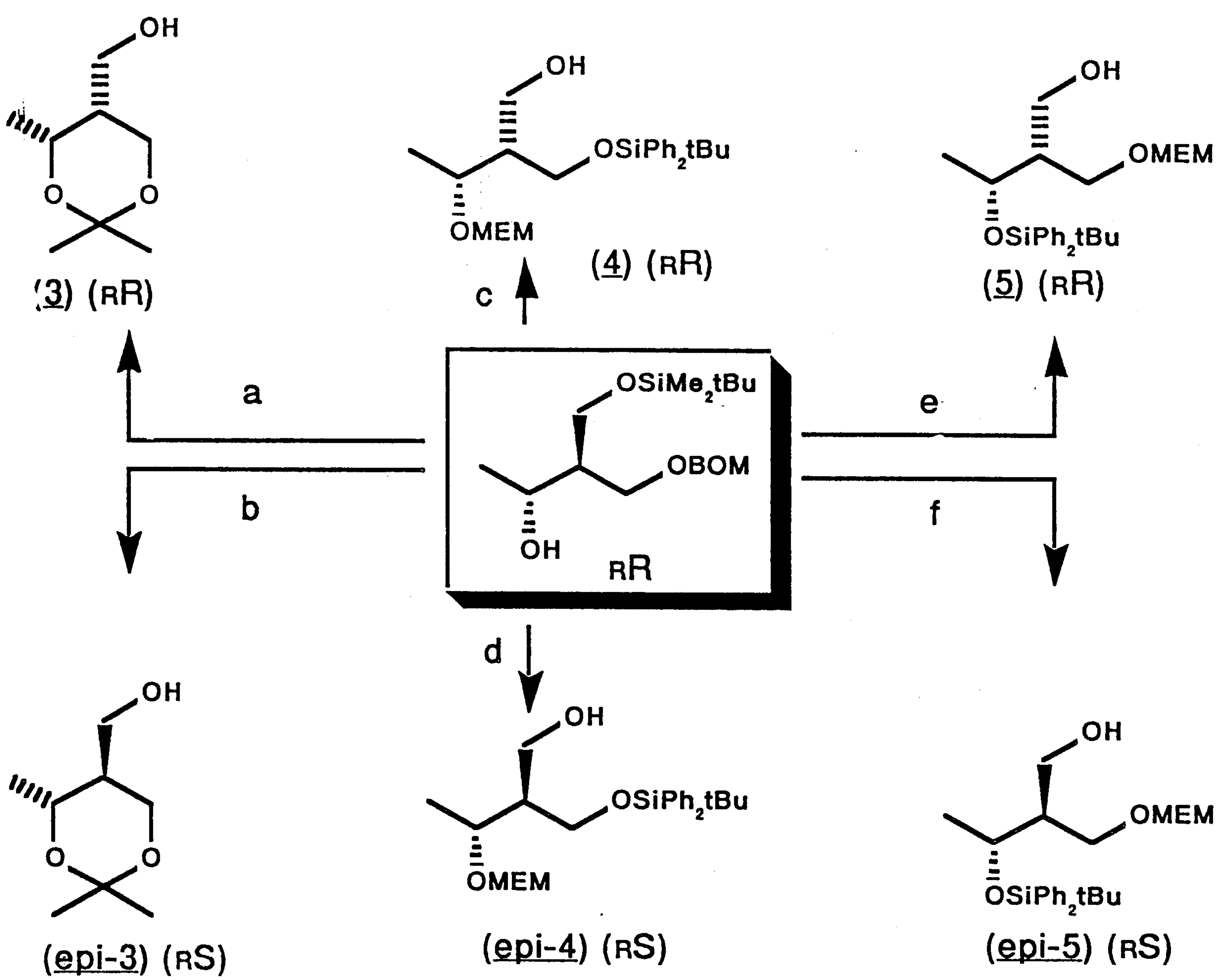


a) PMBOM-Cl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2. b) NaOH, H_2O-THF-MeOH. c) TIPS-Cl, imidazole, DMF. d) O_3, MeOH-CH_2Cl_2, -78°C. e) $Ph_3P{=}CHCH_2CH_2Me$, THF, -78°C → r.t.. f) $(n\text{-}Bu)_4NF \cdot 3H_2O$, THF. g) *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2. h) BOM-Cl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2. i) DDQ, pH 7 buffer, *t*-BuOH, CH_2Cl_2. l) H_2, 10% Pd/C, $CaCO_3$, MeOH.

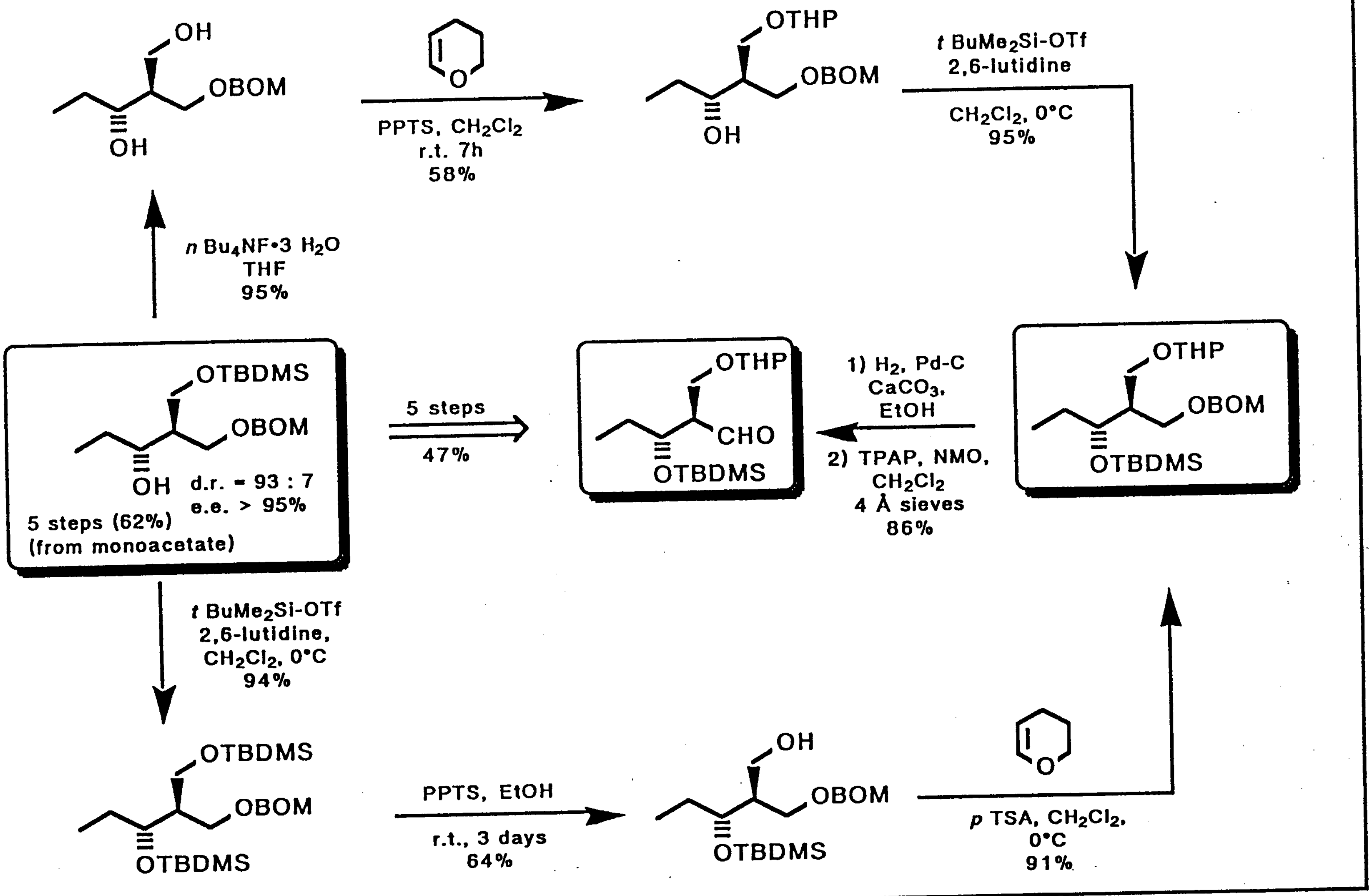
E-71

L29

DIASTEREODIVERGENCY

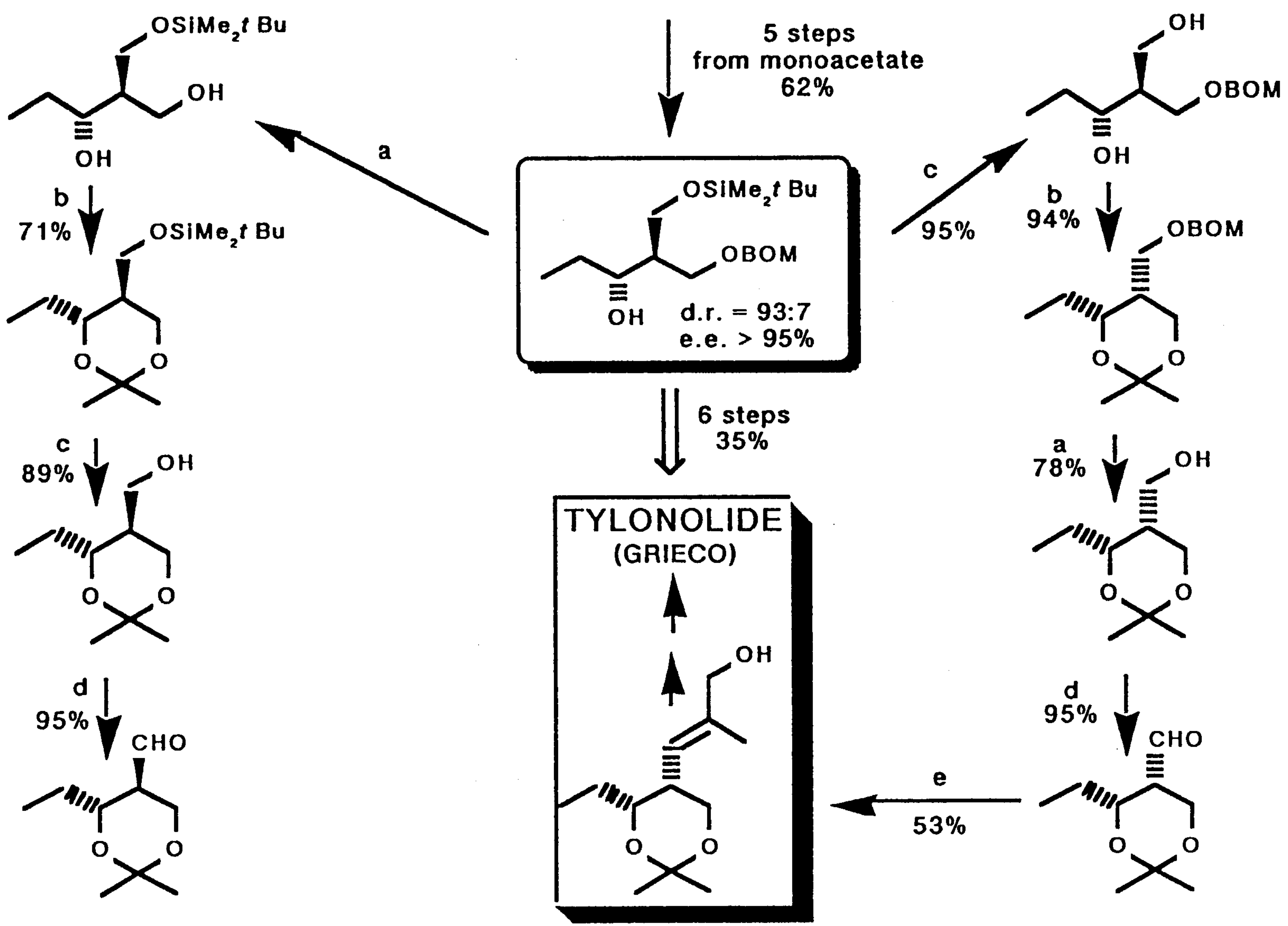


L125



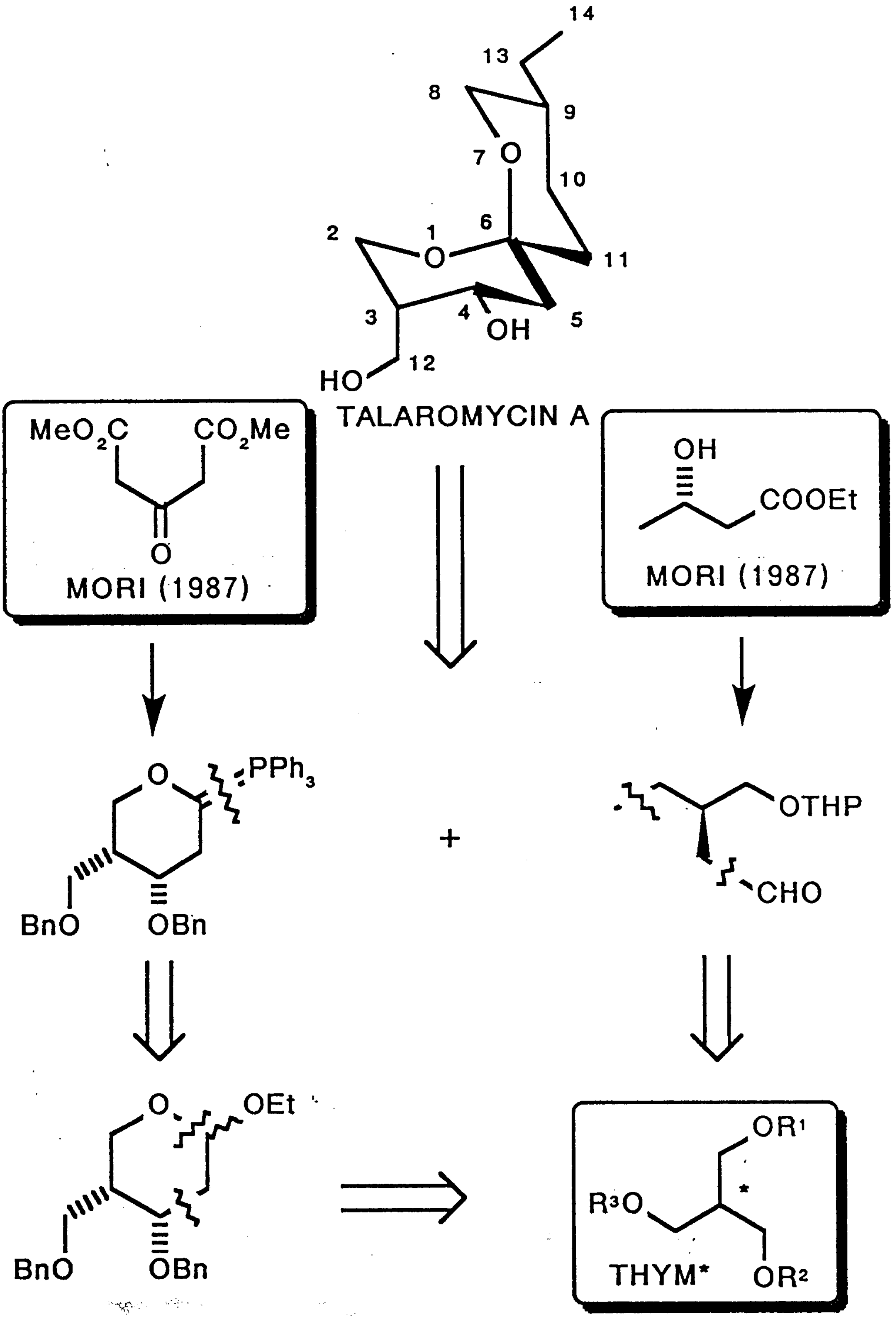
OH
OBOM
OH
PPTS, CH2Cl2
r.t. 7h
58%
OTHP
OBOM
OH
t BuMe2Si-OTf
2,6-lutidine
CH2Cl2, 0°C
95%
n Bu4NF•3 H2O
THF
95%
OTBDMS
OBOM
OH
d.r. = 93 : 7
e.e. > 95%
5 steps (62%)
(from monoacetate)
5 steps
47%
OTHP
CHO
OTBDMS
1) H2, Pd-C
CaCO3,
EtOH
2) TPAP, NMO,
CH2Cl2
4 Å sieves
86%
OTHP
OBOM
OTBDMS
t BuMe2Si-OTf
2,6-lutidine,
CH2Cl2, 0°C
94%
OTBDMS
OBOM
OTBDMS
PPTS, EtOH
r.t., 3 days
64%
OH
OBOM
OTBDMS
p TSA, CH2Cl2,
0°C
91%

L126



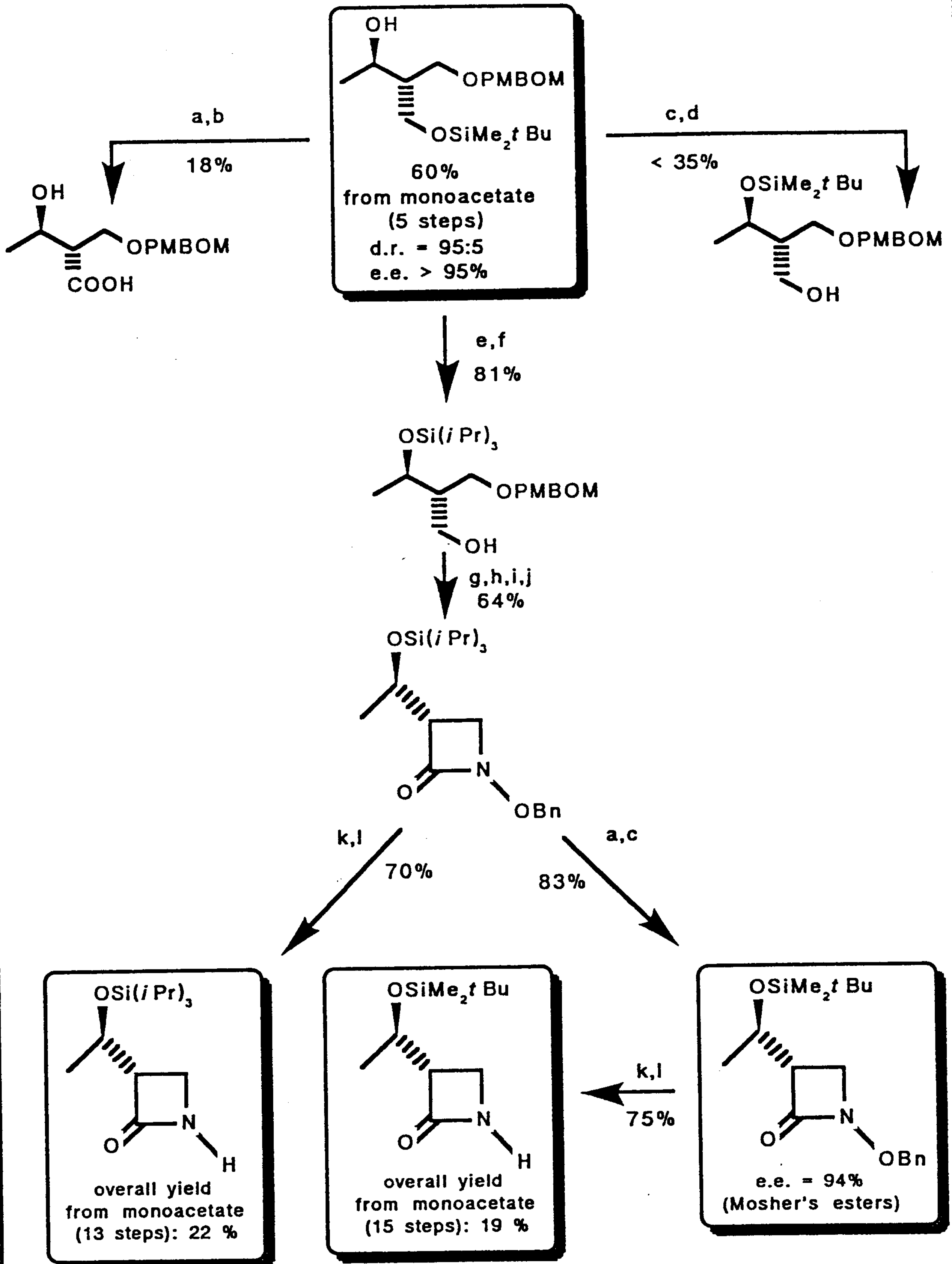
a) H_2, Pd-C, $CaCO_3$, EtOH; b) $H_2C{=}C(Me)$-OMe, *p* TSA, CH_2Cl_2, 0°C; c) *n* $Bu_4NF \cdot 3\ H_2O$, THF; d) TPAP, NMO, 4 Å sieves, CH_2Cl_2; e) 1. $Ph_3P{=}C(Me)$-COOEt, toluene, reflux; 2. DIBAH, CH_2Cl_2, -78°C.

L127

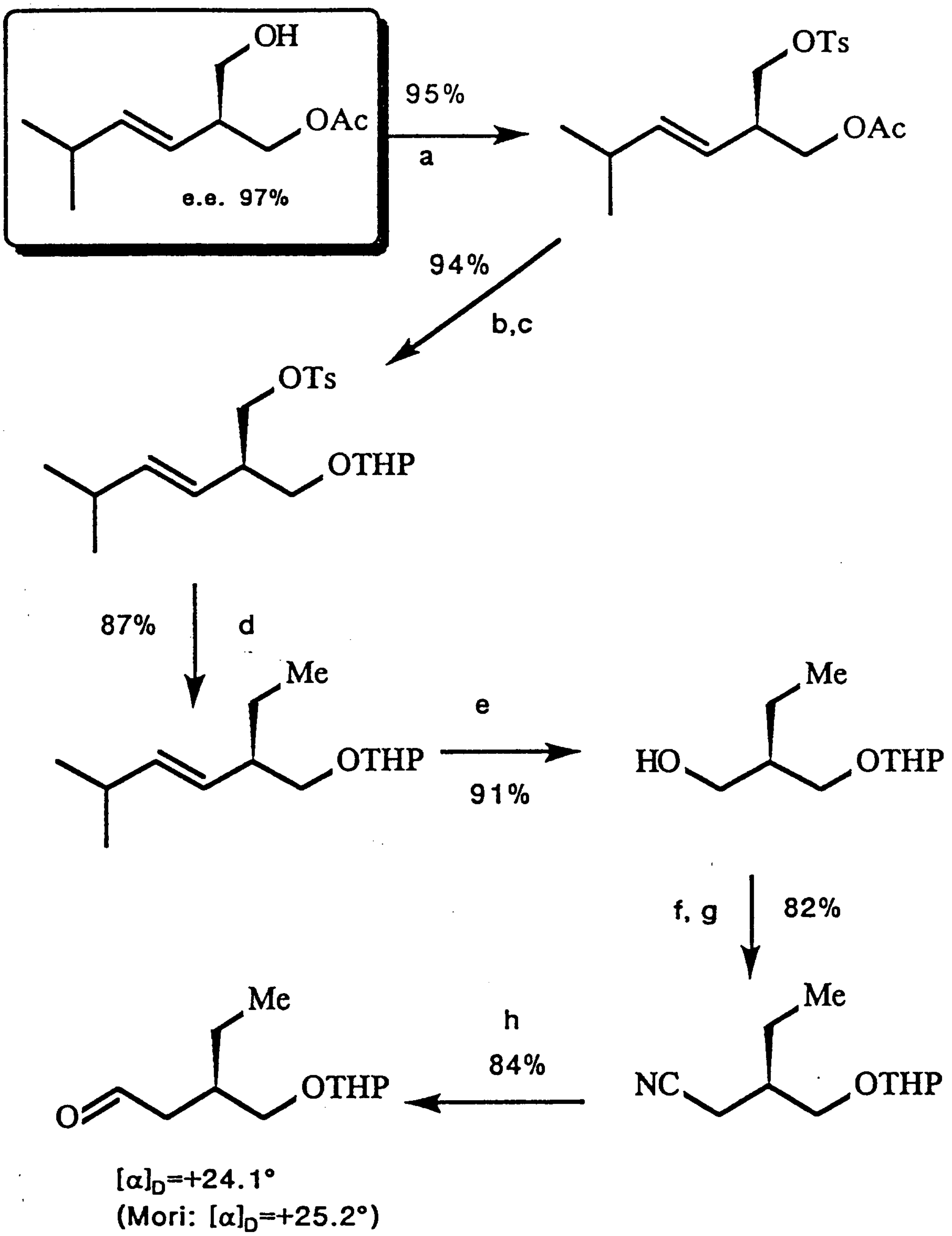


14
13
8
9
7 O
10
2
1
6
O
11
3
4
OH
5
HO
12
TALAROMYCIN A
MeO2C
CO2Me
O
MORI (1987)
OH
COOEt
MORI (1987)
PPh3
O
BnO
OBn
+
OTHP
CHO
O
OEt
BnO
OBn
OR1
R3O
*
THYM*
OR2

L95



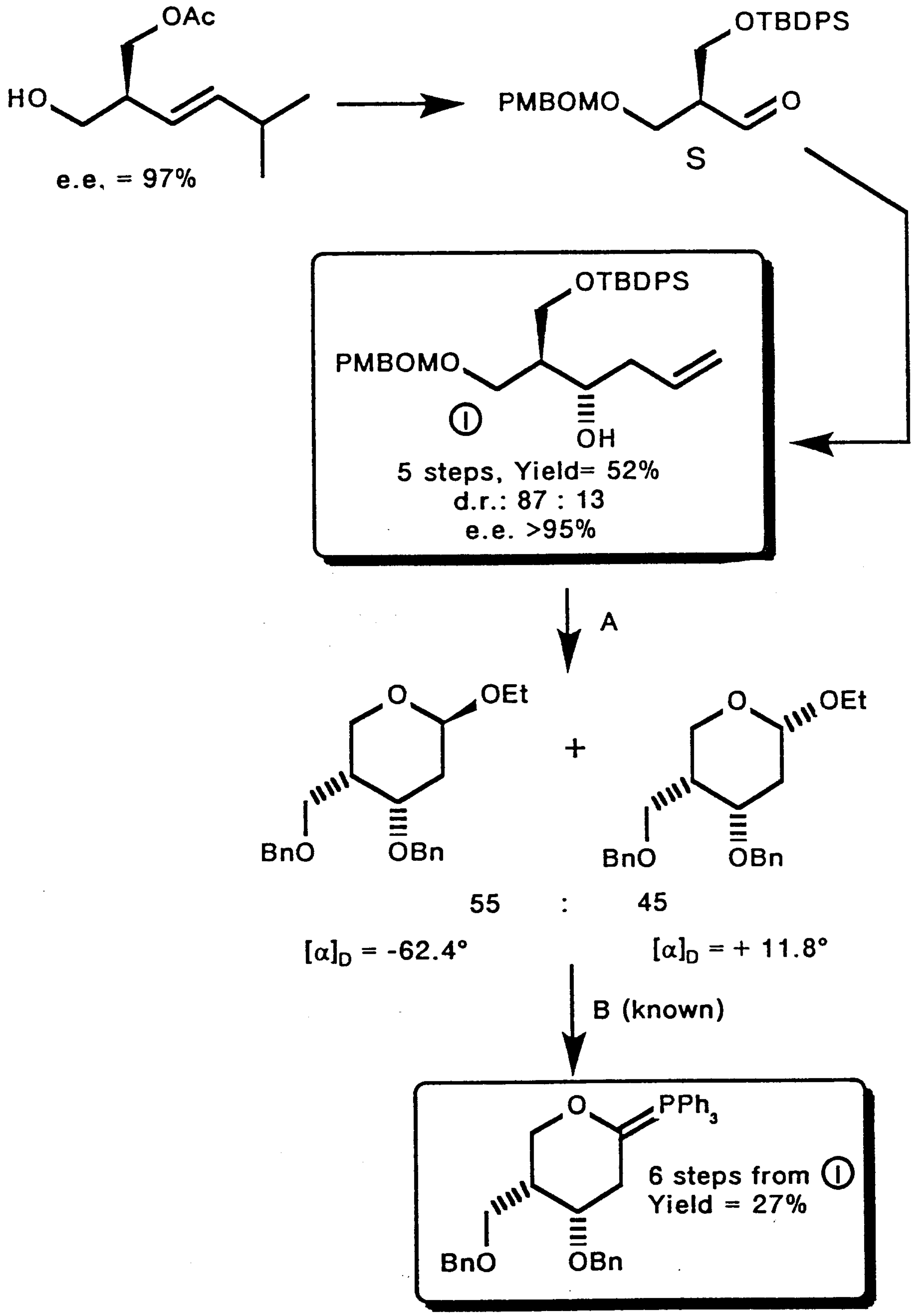
a) (nBu$_4$)NF•3H_2O; b) Pt, O_2; c) Me$_2$$t$BuSi-OTf, 2,6-lutidine, CH_2Cl_2; d) PPTS, EtOH; e) (iPr)$_3$Si-OTf; f) pTSA, iPrOH, 4Å sieves; g) Jones reagent; h) BnONH$_2$, DCC, N-hydroxybenzotriazole; i) DDQ; j) Ph$_3$P, DEAD; k) H_2, Pd-C; l) TiCl$_3$, pH 7, H_2O-MeOH.



8 steps
y. 49%
e.e. 95%

a) Ts-Cl, CH_2Cl_2, Et_3N, r. t. ; b) LiOH, THF-H_2O; c) dihydropyran, CH_2Cl_2, *p* TSA; d) Me_2CuLi, Et_2O, r. t. ; e) O_3 -78°C, then Me_2S, then $NaBH_4$; f) MsCl, Et_3N,CH_2Cl_2, -30°C ; g) NaCN, Bu_4NI, DMSO, 70°C; h) DIBAH, Et_2O, -35°C.

L128



A: 1) DDQ; 2) O_3, MeOH, CH_2Cl_2; Me_2S; 3) *p* TSA, EtOH; 4) *n* Bu_4NF, THF; 5) BnBr, NaH, DMF

B: $Ph_3PH^+BF_4^-$, MeCN