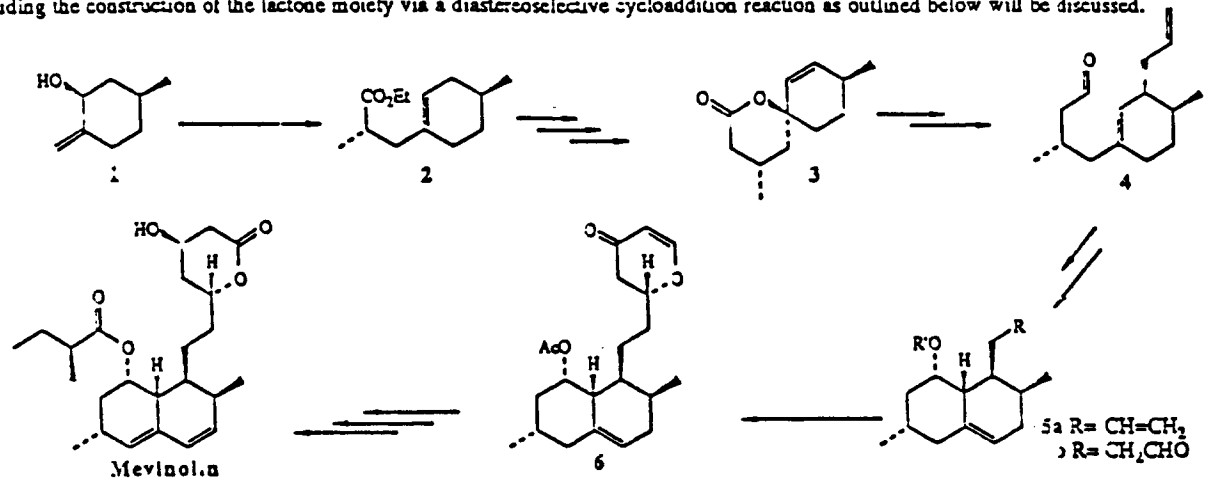
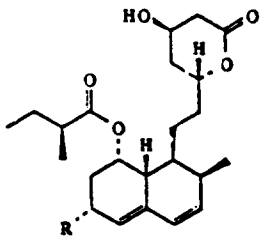
ASYMMETRIC TOTAL SYNTHESIS OF MEVINOLIN

P. M. Wovkulich, P. C. Tang, N. K. Chadha, J. C. Barrish and M. R. Uskokovic

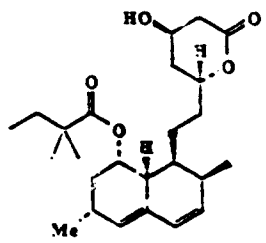
Natural Products Chemistry Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Details of the asymmetric total synthesis of mevinolin via a route employing several stereoselective sequences to introduce the chiral centers including the construction of the lactone moiety via a diastereoselective cycloaddition reaction as outlined below will be discussed.

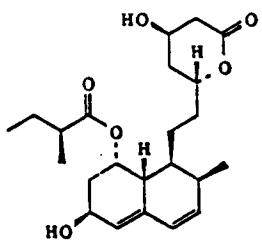




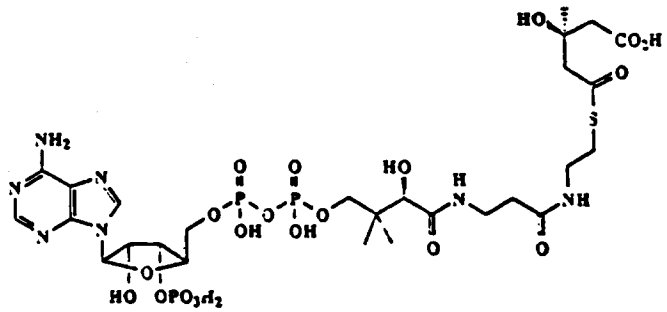
Mevinolin R = Me
Compactin R = H



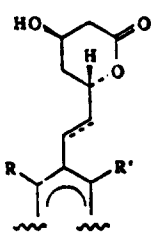
Simvastatin



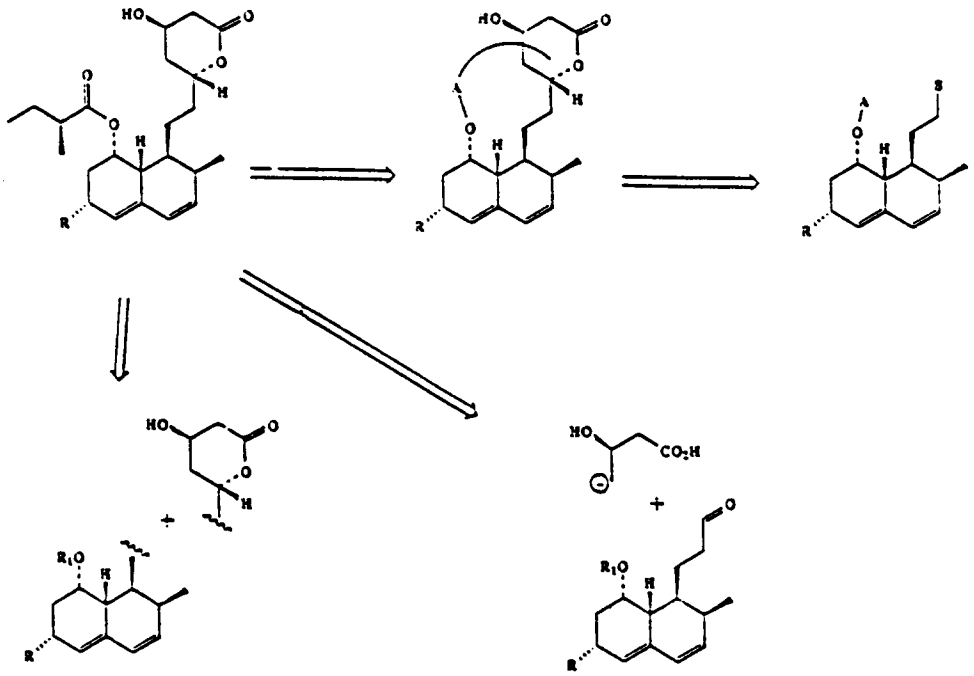
Pravastatin

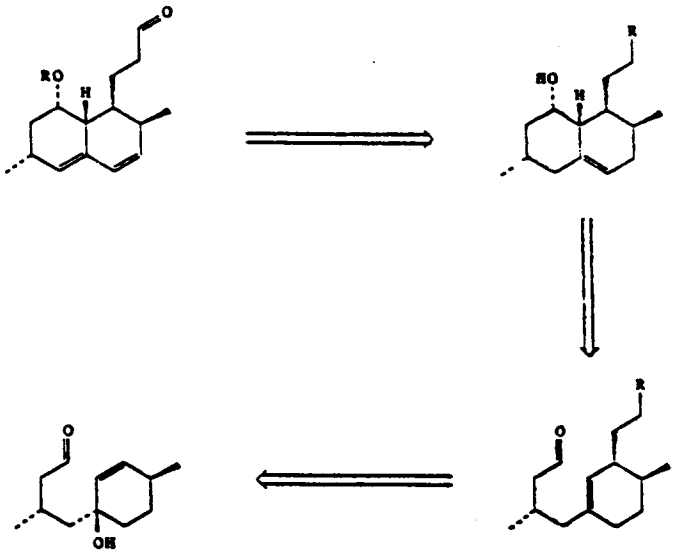


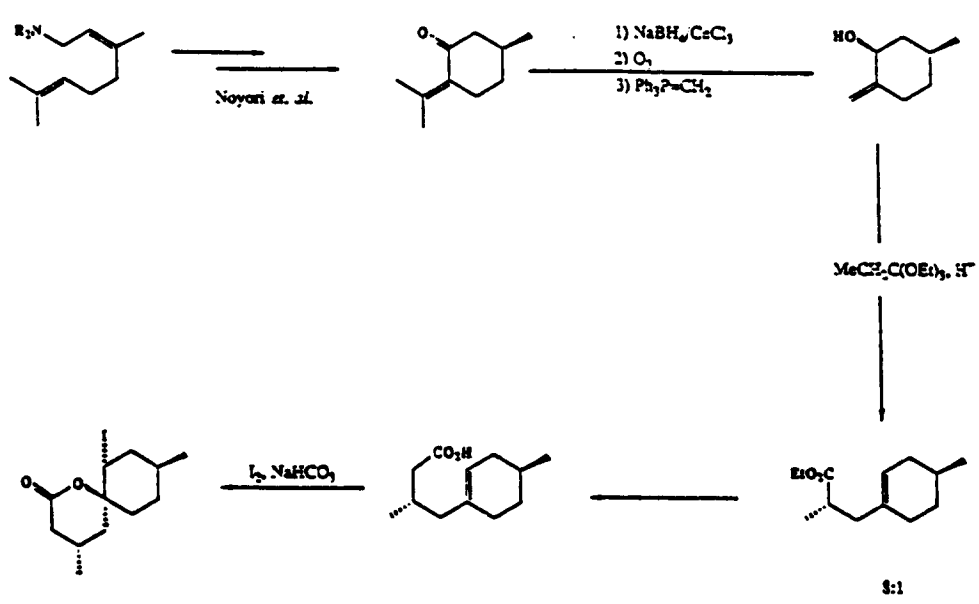
Hydroxymethylglutaryl Co A

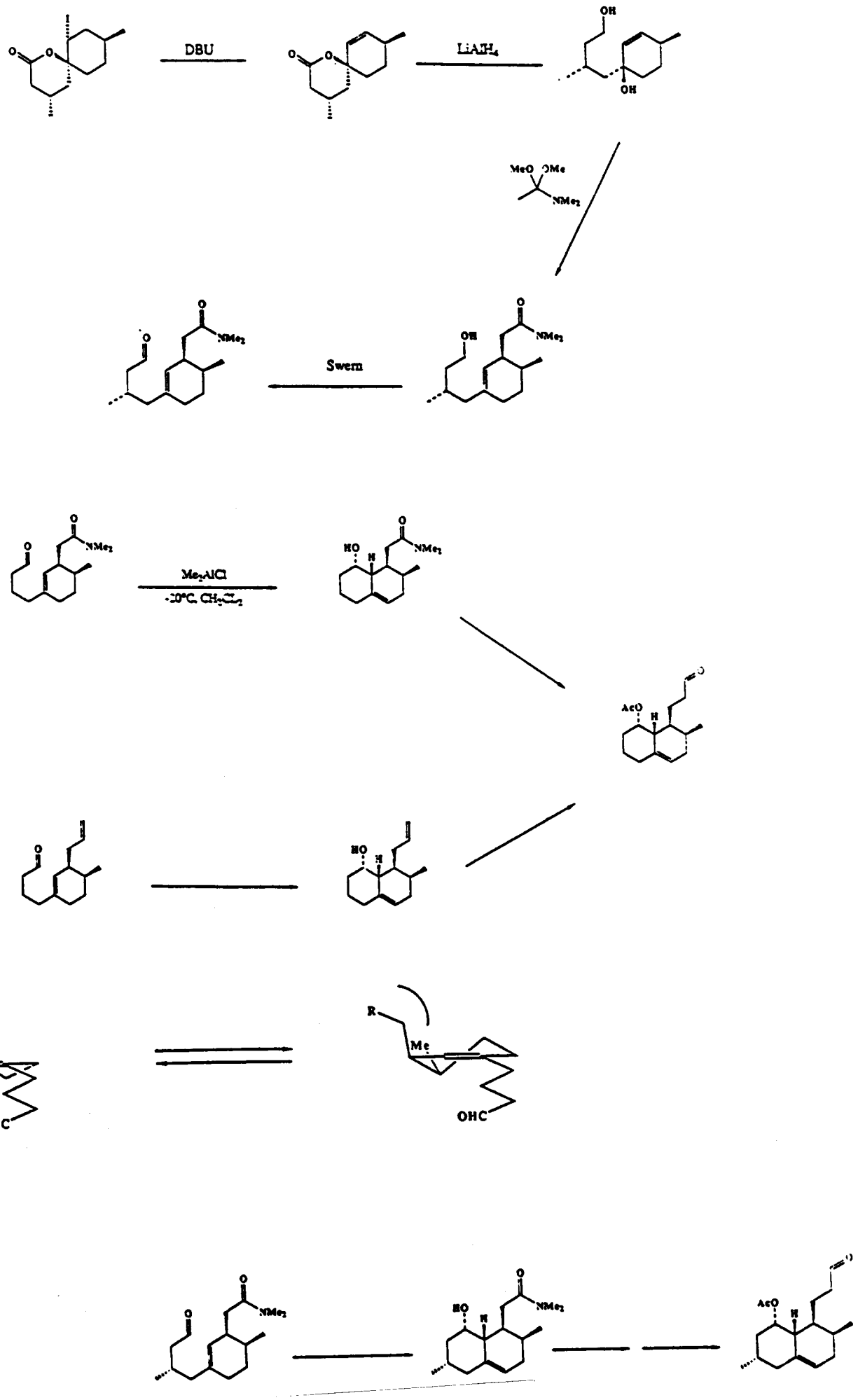


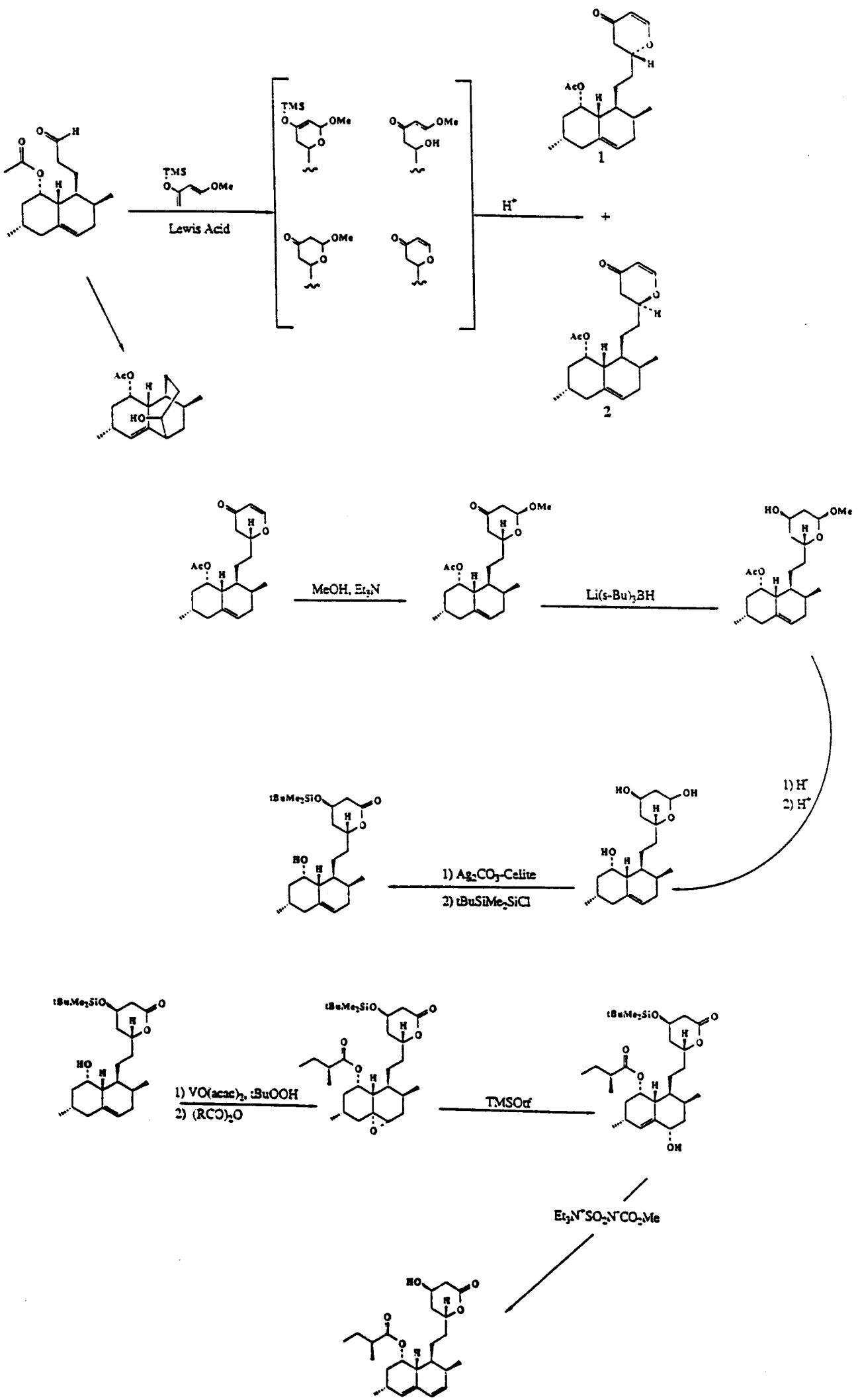
Aromatic Analogs






Noyori et. al.
1) NaBH4/CeCl3
2) O3
3) Ph3P=CH2
MeCH2C(OEt)3, H+
I2, NaHCO3
9:1

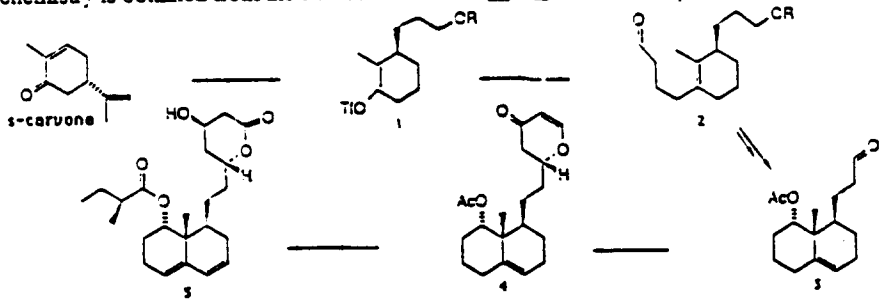

DBU
LiAlH4
Swern
Me2AlCl
-20°C, CH2Cl2

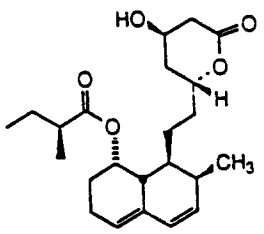

TMS
OMe
Lewis Acid
H+
AcO
HO
1
2
MeOH, Et3N
Li(s-Bu)3BH
tBuMe2SiO
1) Ag2CO3-Celite
2) tBuSiMe2SiCl
1) H+
2) H+
1) VO(acac)2, tBuOOH
2) (RCO)2O
TMSOtf
Et3N+SO2N-CO2Me

TOTAL SYNTHESIS OF THE ANGULAR METHYL REGIOISOMER OF COMPACTIN.

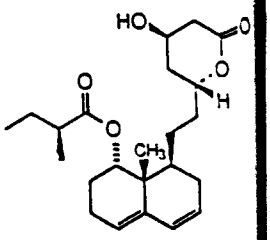
P.C. TANG, N.K. Chadha, P.M. Wovkulich, and M.R.Uskokovic,
Natural Products Chemistry Department, Hoffmann-La Roche Inc., Nutley, NJ 07110.

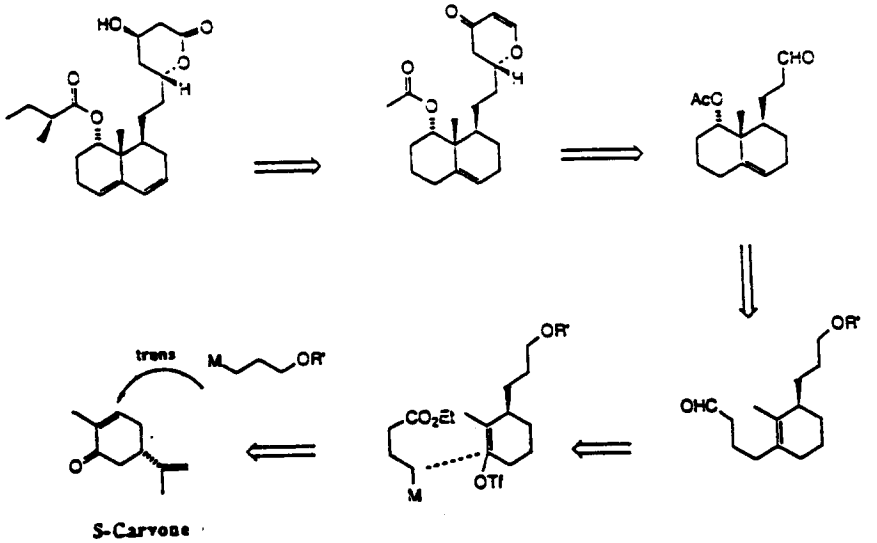
Total synthesis of the angular methyl regioisomer 5 of compactin from s-carvone will be described. Control of stereochemistry is obtained from the stereoselective ene (2 to 3) and hetero Diels-Alder (3 to 4) reactions.



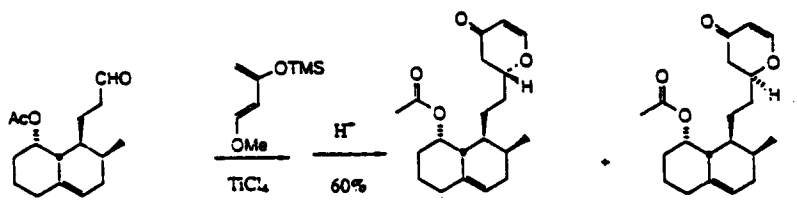


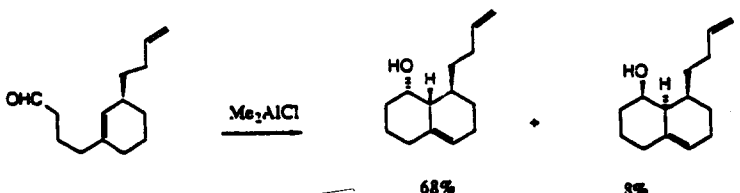
Compactin

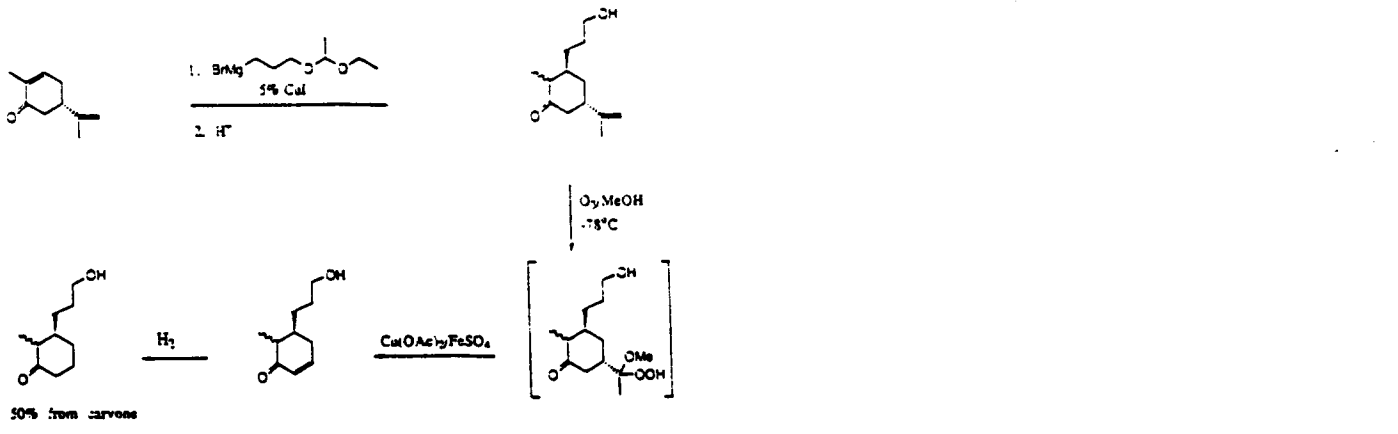


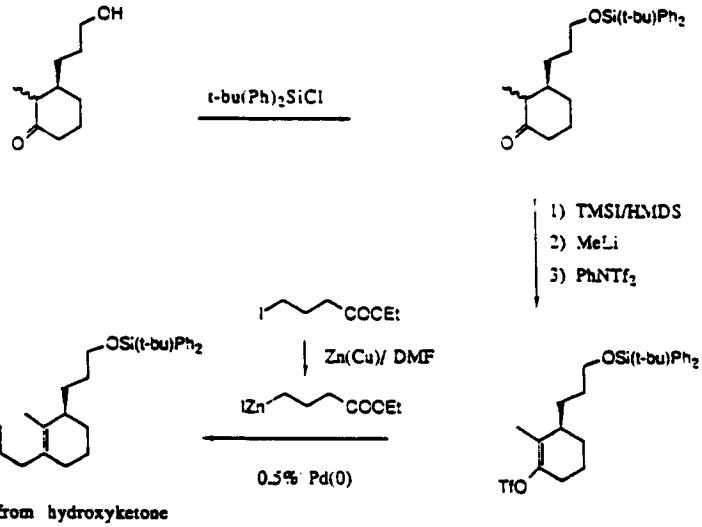


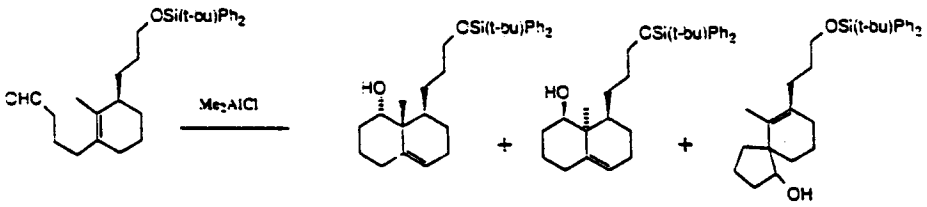
S-Carvone

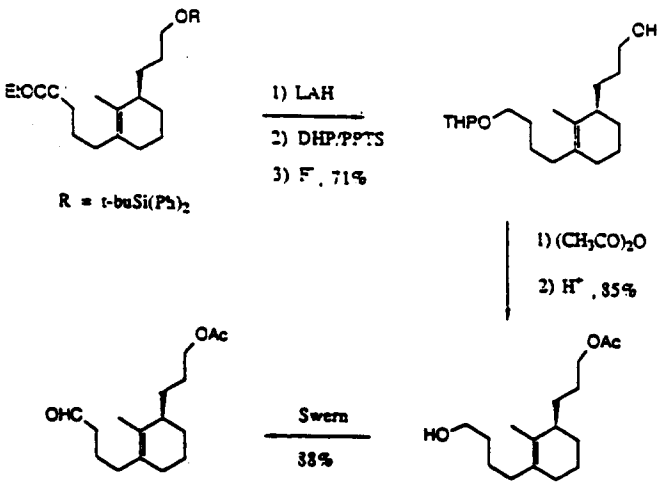


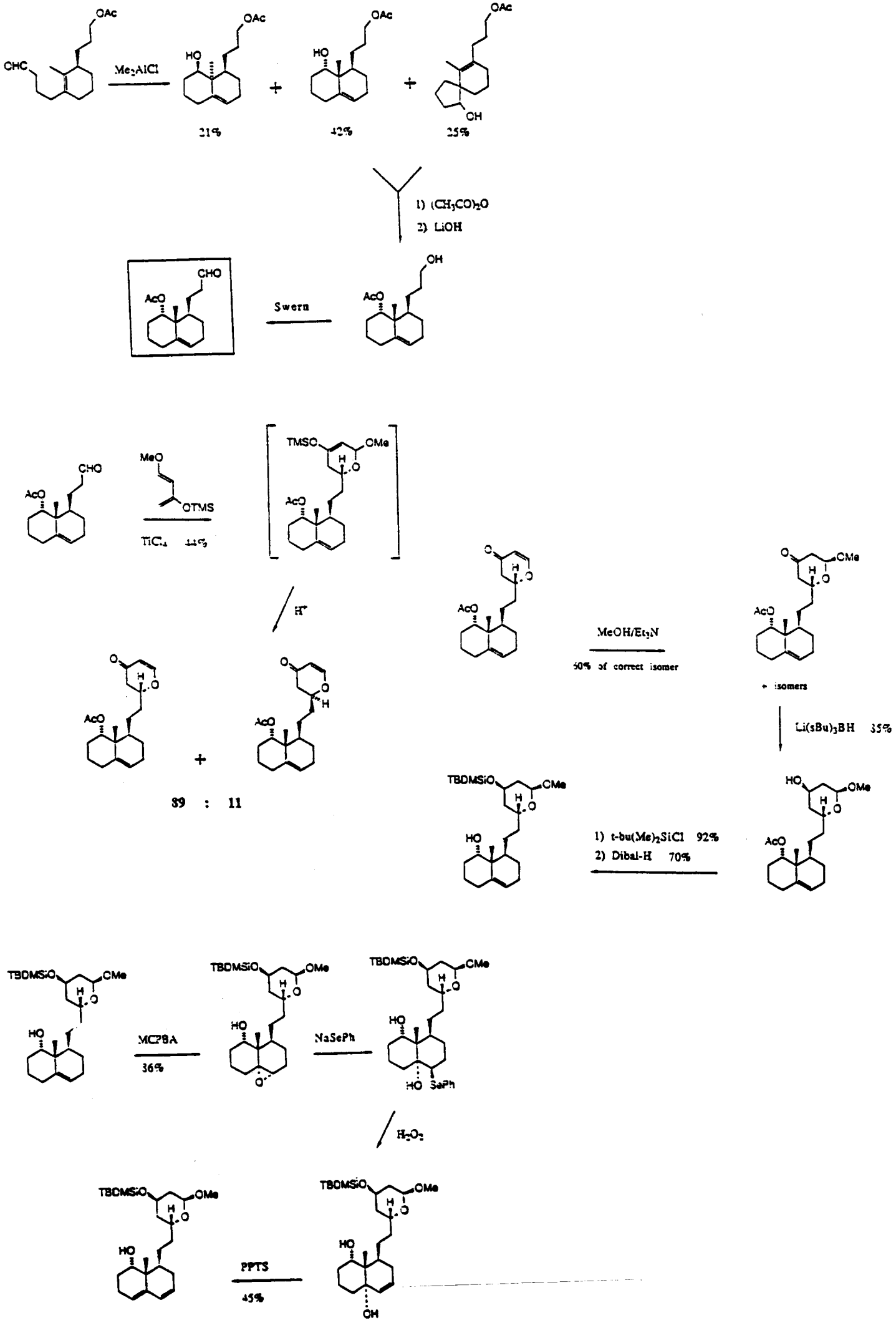


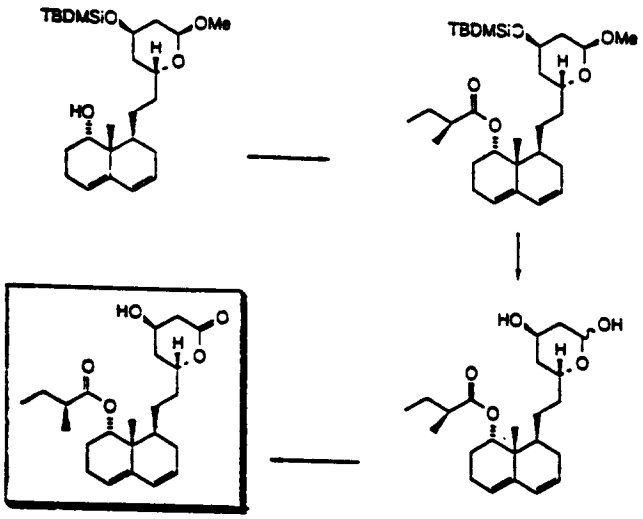

1. BrMg
5% CuI
2. H+
O2, MeOH
-78°C
H2
Cu(OAc)2/FeSO4
OMe
OOH
50% from carvone

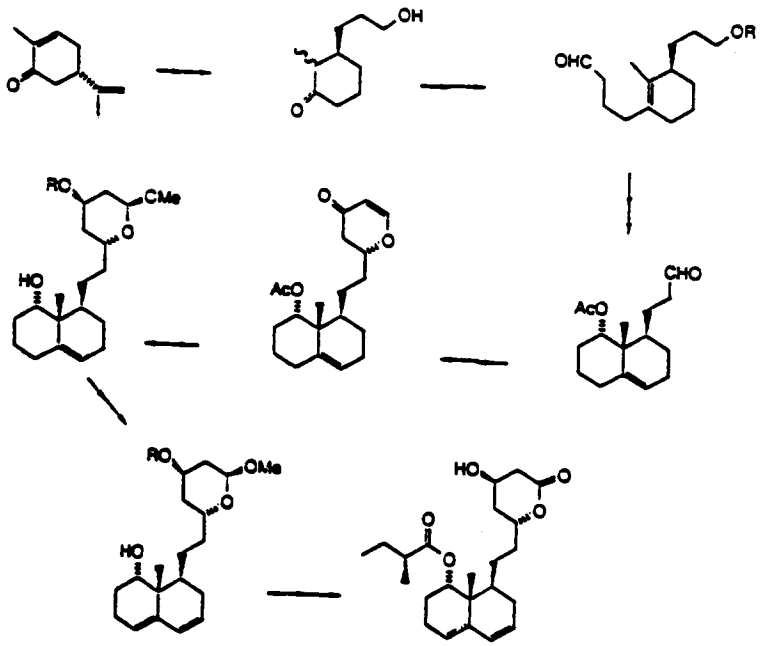

t-bu(Ph)2SiCl
1) TMSI/HMDS
2) MeLi
3) PhNTf2
Zn(Cu)/ DMF
0.5% Pd(0)
72% from hydroxyketone


Me2AlCl
1.3
1.0
3.5


R = t-buSi(Ph)2
1) LAH
2) DHP/PPTS
3) F-, 71%
1) (CH3CO)2O
2) H+, 85%
Swern
38%


Me2AlCl
21%
42%
25%
1) (CH3CO)2O
2) LiOH
Swern
TiCl4
H+
89 : 11
MeOH/Et3N
50% of correct isomer
+ isomers
Li(sBu)3BH 35%
1) t-bu(Me)2SiCl 92%
2) Dibal-H 70%
MCPBA
36%
NaSePh
H2O2
PPTS
45%


TBDMSiO
OMe
HO
TBDMSiO
OMe
HO
HO
OH


OH
OHC
OR
RO
CMe
HO
AcO
AcO
CHO
RO
OMe
HO
HO