STEREOCHEMICAL CONTROL IN BOND FORMATION

APPLICATION AND EXPLORATION OF NOTIONS OR CONCEPTS

↓

DESIGN OF REAGENTS, CATALYSTS, REACTIONS, ETC.

↓

INNOVATION

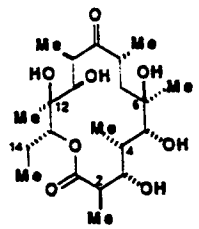
EXPLOITATION OF "EFFECTS"

INHERENT / IMPOSED

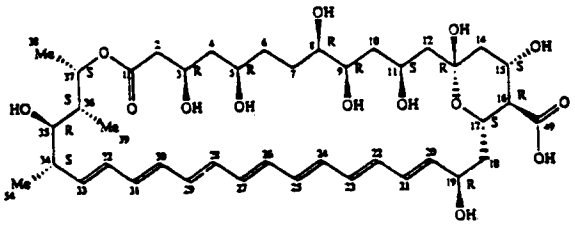
- TOPOLOGY
- STEREOELECTRONIC
- SYMMETRY / ASYMMETRY
- STERIC BIAS
- CONFORMATION
- COORDINATION / CHELATION
- PROXIMITY / AFFINITY
- KINETIC / THERMODYNAMIC

Figure 2

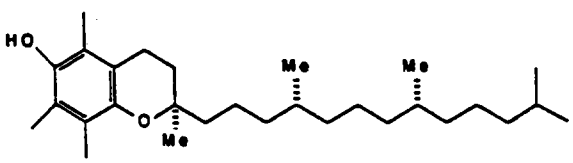
NATURE'S GIFTS



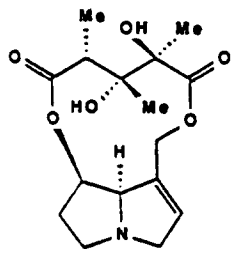
ERYTHRONOLIDE A



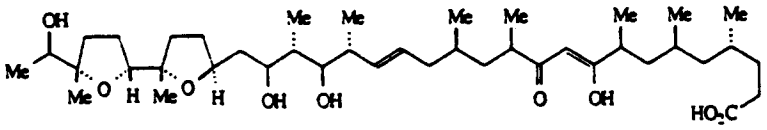
Amphotericin B Aglycone



VITAMIN E

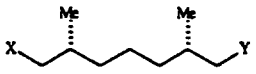


MONOCROTALINE

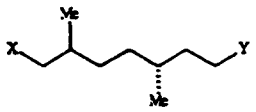


IONOMYCIN

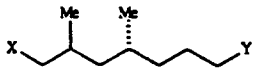
HOW TO CONTROL THE STEREOCHEMISTRY OF VICINAL, ALTERNATING OR REMOTE CARBON ATOMS ?



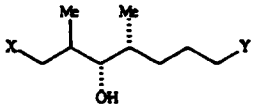
1,5 –
(ISOPRENOID)



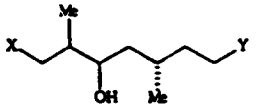
1,4 –
(ACETATE. PROPIONATE)



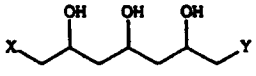
1,3 –
(DEOXYPROPIONATE)



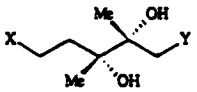
1,2,3 –
(PROPIONATE)



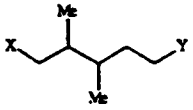
1,2,4 –
(ACETATE. PROPIONATE)



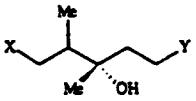
1,3,5 –
(POLYKETIDE)



1,2 –



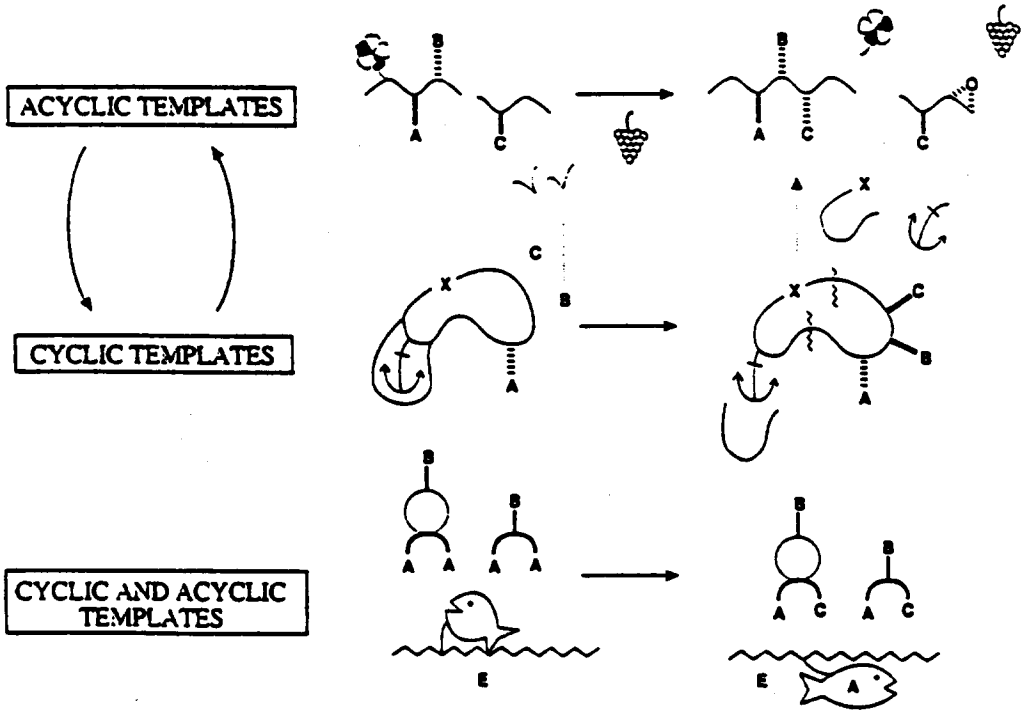
1,2 –
(AMINO ACID PRECURSOR ?)



1,2 –

STRATEGIES FOR STEREOCHEMICAL CONTROL

HOMOCHIRAL, RACEMIC AND ACHIRAL SUBSTRATES



ACCESS TO POLYPROPIONATE-TYPE AND RELATED 3-CARBON SUBUNITS

CHEMICAL METHODS

ACYCLIC TEMPLATES

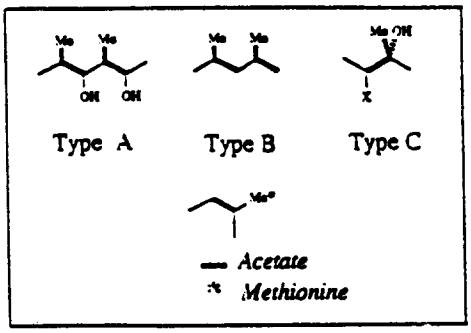
- ALDOL
- EPOXYALCOHOL - CUPRATE
- ALLYLIC ALCOHOL - HYDROBORATION
- ASYMMETRIC HYDROGENATION
- OTHER METHODS

CYCLIC TEMPLATES

- CARBOHYDRATES
- CARBOCYCLES
- DITHIADECALIN SYSTEMS
- DIOXASPIROACETALS
- HETERO DIELS - ALDER
- OTHER METHODS

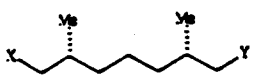
CHEMOENZYMATIC METHODS

- ESTERASES, LIPASES, etc. (MESO DIESTERS, etc.)
- BAKER'S YEAST
- OTHER

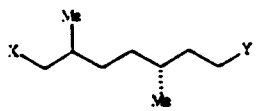


VICINAL, ALTERNATING AND REMOTE SUBSTITUTION

TOWARD A GENERAL STRATEGY FROM A SINGLE CHIRAL PROGENITOR ...

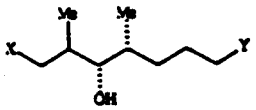


1,5 – (ISOPRENOID)

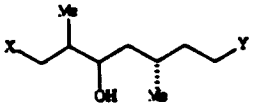


1,4 – (ACETATE, PROPIONATE)

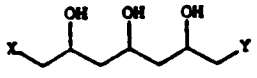
1,3 – (DEOXYPROPIONATE)



1,2,3 – (PROPIONATE)

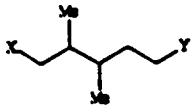


1,2,4 – (ACETATE, PROPIONATE)

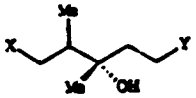


1,3,5 – (POLYKETIDE)

1,2 –

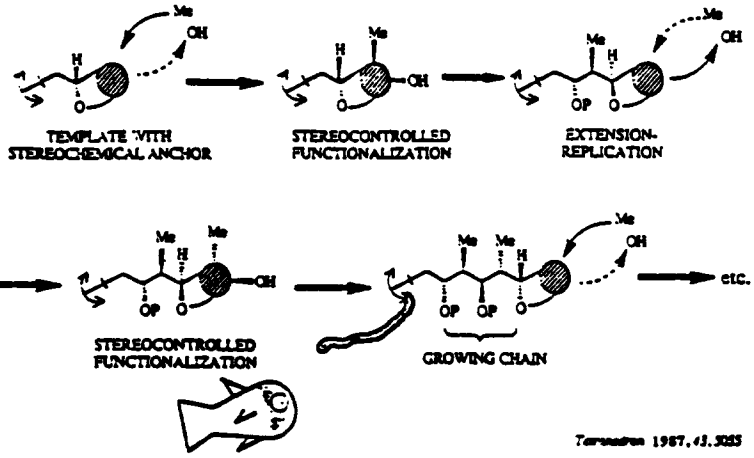


1,2 – (AMINO ACID PRECURSOR ?)



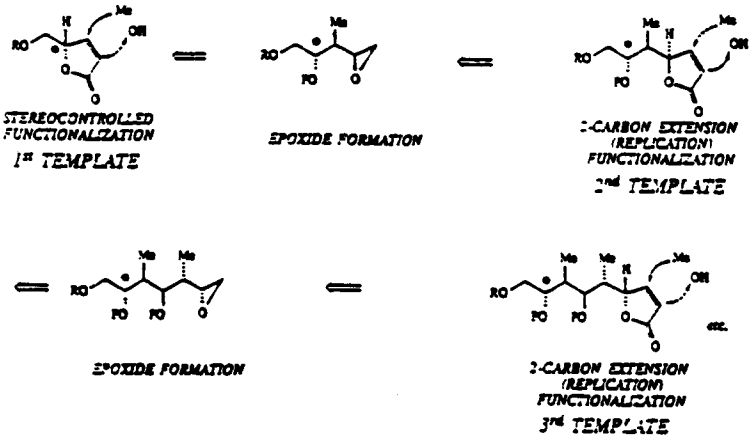
1,2 –

PROPIONATE AND DEOXYPROPIONATE DERIVED SUBUNITS



Tetrahedron 1987, 43, 3055

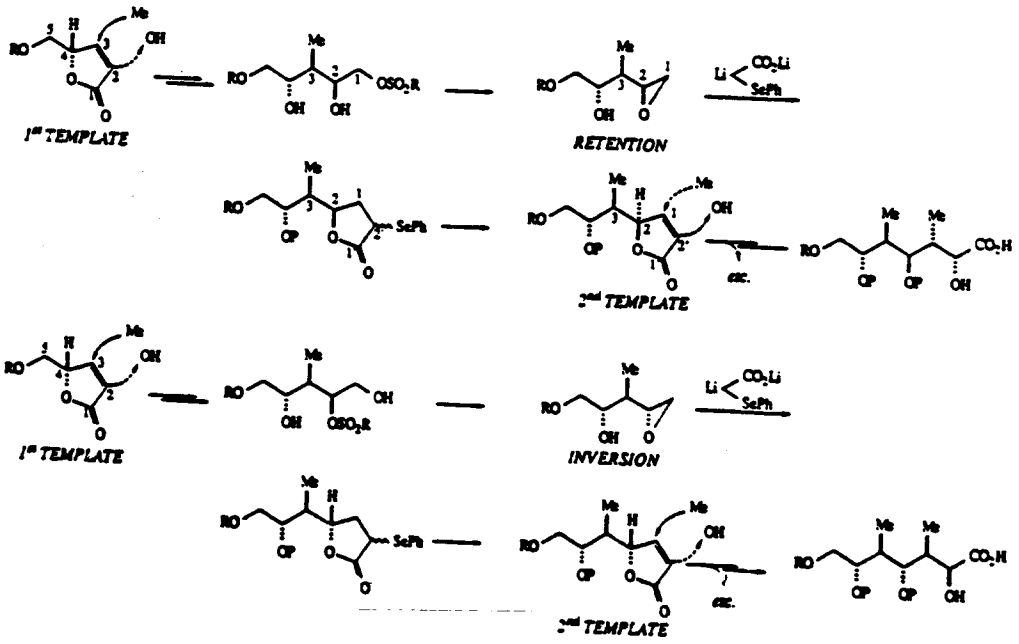
BUTENOLIDE REPLICATION STRATEGY



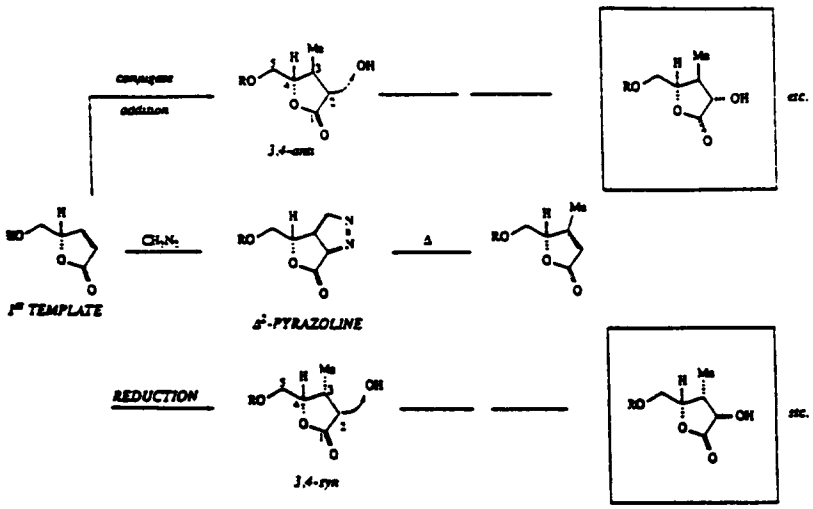
DURING EACH CYCLE CONJUGATE ADDITION (Me) AND ELECTROPHILE TRAPPING (OH) ARE CONTROLLED BY "ANTI" APPROACH TO NEIGHBORING "DOMINANT" GROUP

STEREOCHEMICAL VERSATILITY

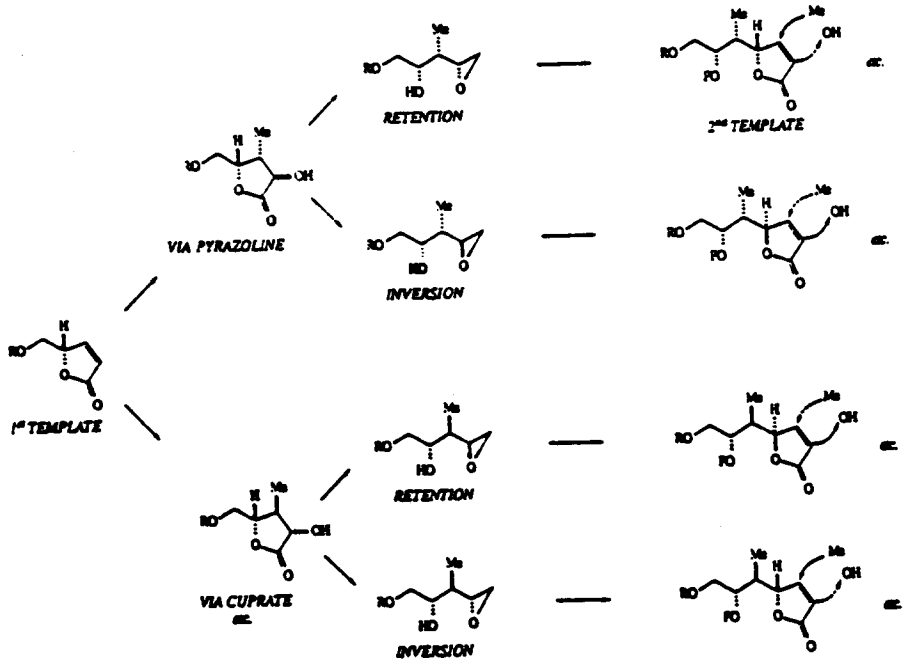
← LINEARITY →



CHOICE OF ANTI OR SYN-ORIENTATION VIA CHEMICAL MANIPULATION



TUNABLE STEREOCHEMISTRY

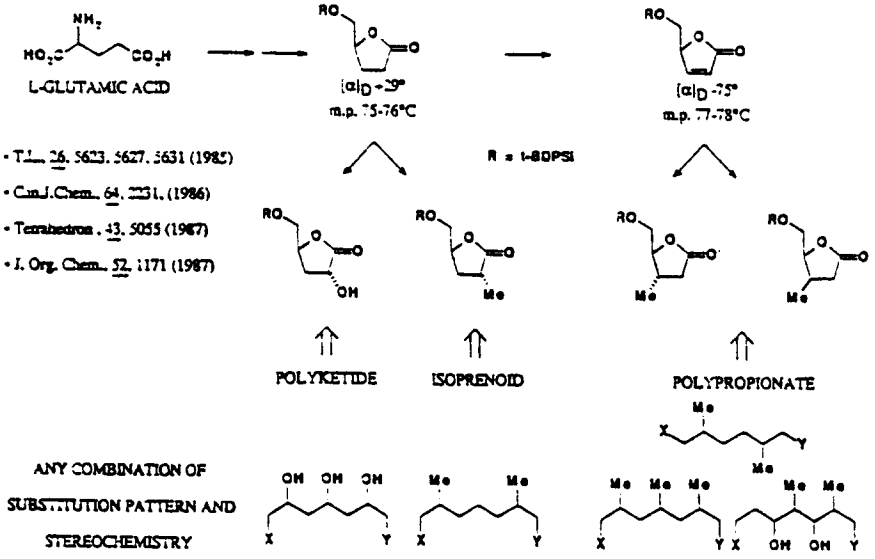


DURING EACH CYCLE CONJUGATE ADDITION (Me) AND ELECTROPHILE TRAPPING (OH) ARE CONTROLLED BY "ANTI" APPROACH TO NEIGHBORING "DOMINANT" GROUP

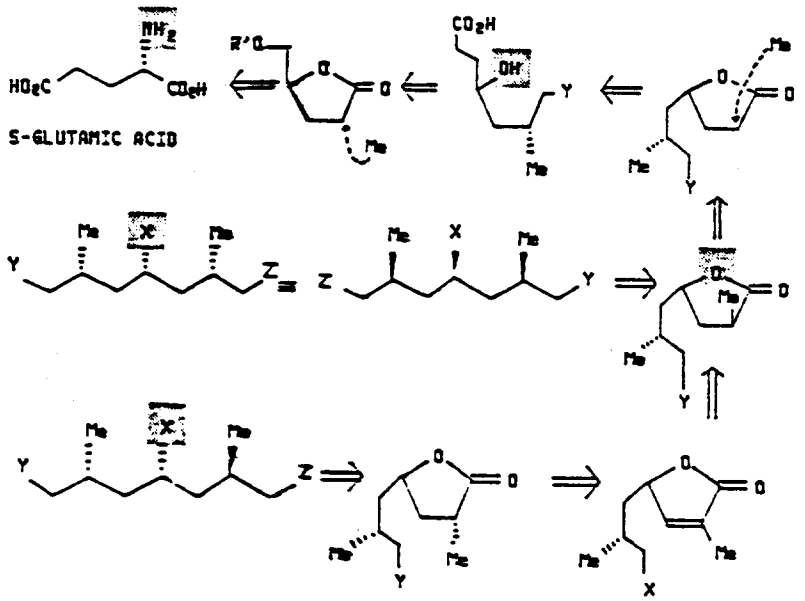
REPLICATING BUTENOLIDE (CHIRON) STRATEGY FOR POLYPROPIONATES

- GENERAL APPROACH FOR ANY COMBINATION OF SUBUNITS
- STEREOCHEMICAL FLEXIBILITY
- FUNCTIONAL DIVERSITY
- LINEARITY OR CONVERGENCE OF OPERATION
- HIGH PREDICTIVE POWER
- SINGLE CHIRAL PROGENITOR

REPLICATING LACTONE STRATEGY

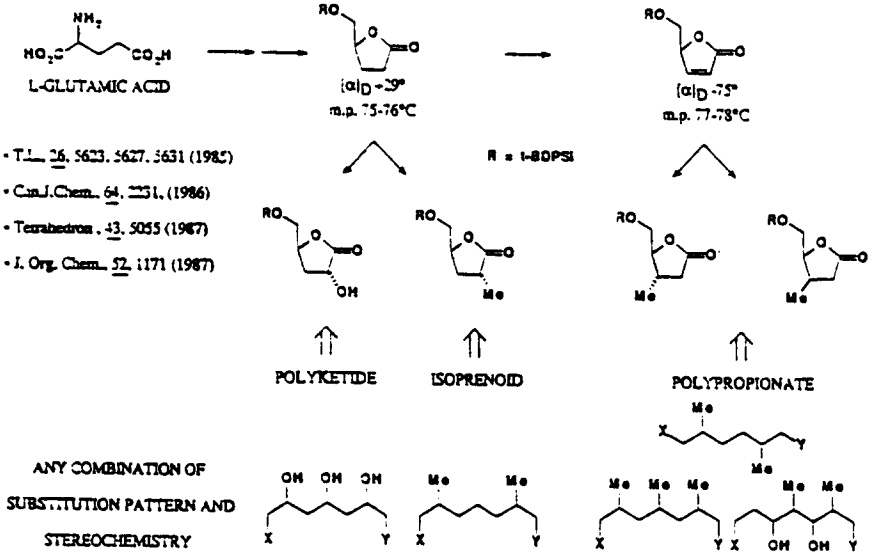


1,5-STEREOSELECTION VIA A REPLICATING TEMPLATE



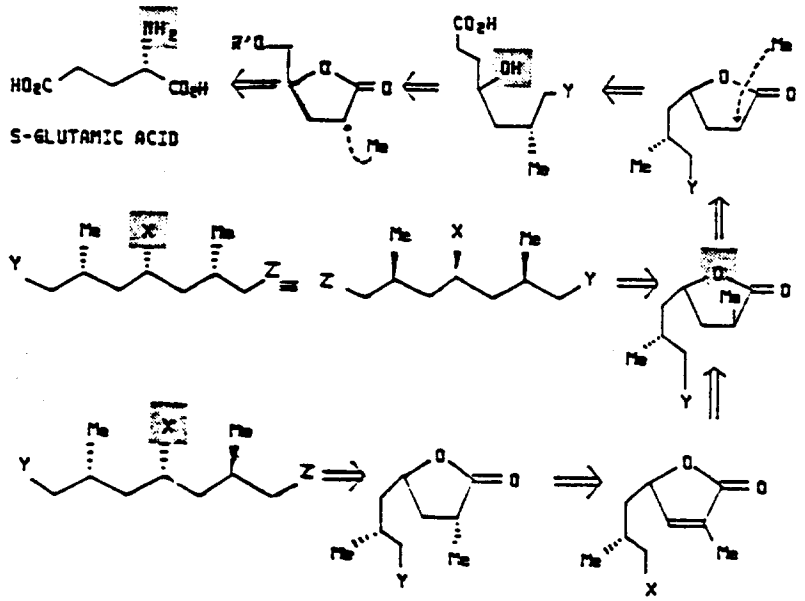
Tetrahedron Lett., 26, 3621 (1985)

REPLICATING LACTONE STRATEGY



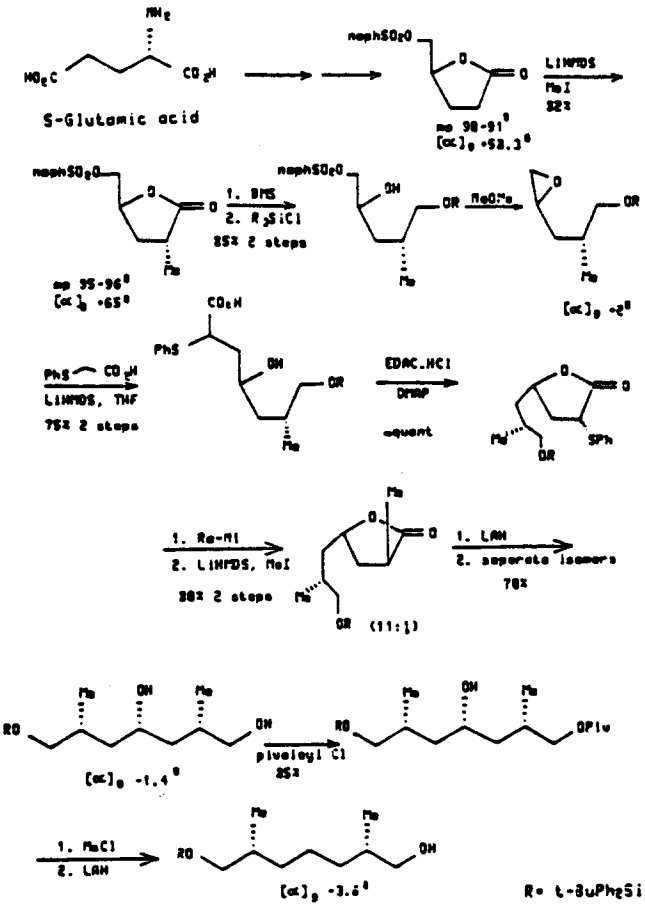
- T.L., 26, 5623, 5627, 5631 (1985)
- Can.J.Chem., 64, 2251, (1986)
- Tetrahedron, 43, 5055 (1987)
- J. Org. Chem., 52, 1171 (1987)

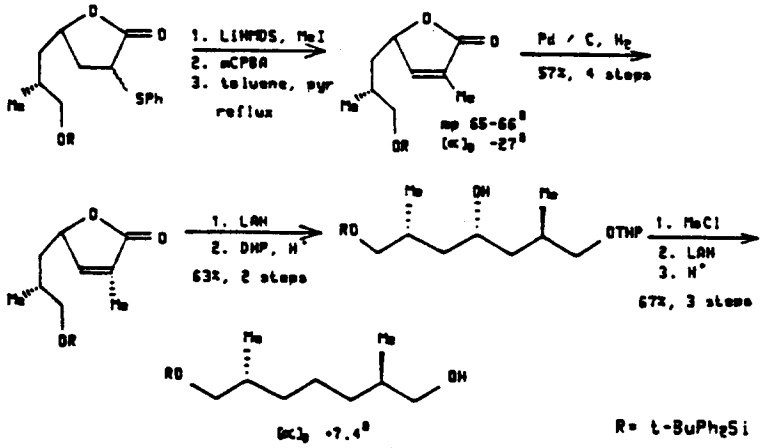
1,5-STEREOSELECTION VIA A REPLICATING TEMPLATE



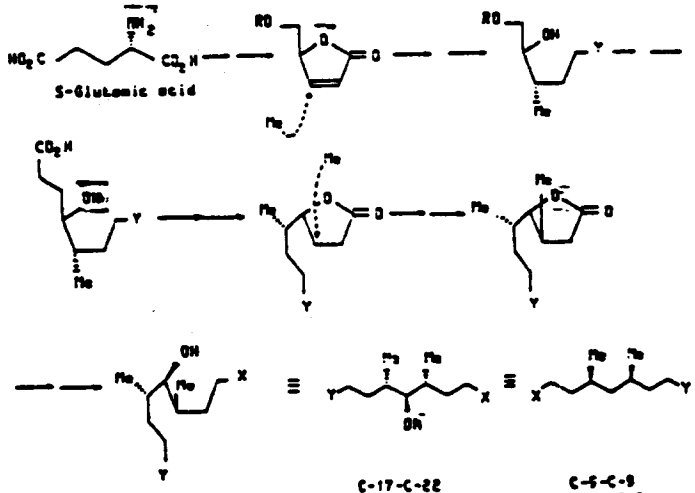
Tetrahedron Lett., 26, 56[illegible] (1985)

1,5-STEREOSELECTION





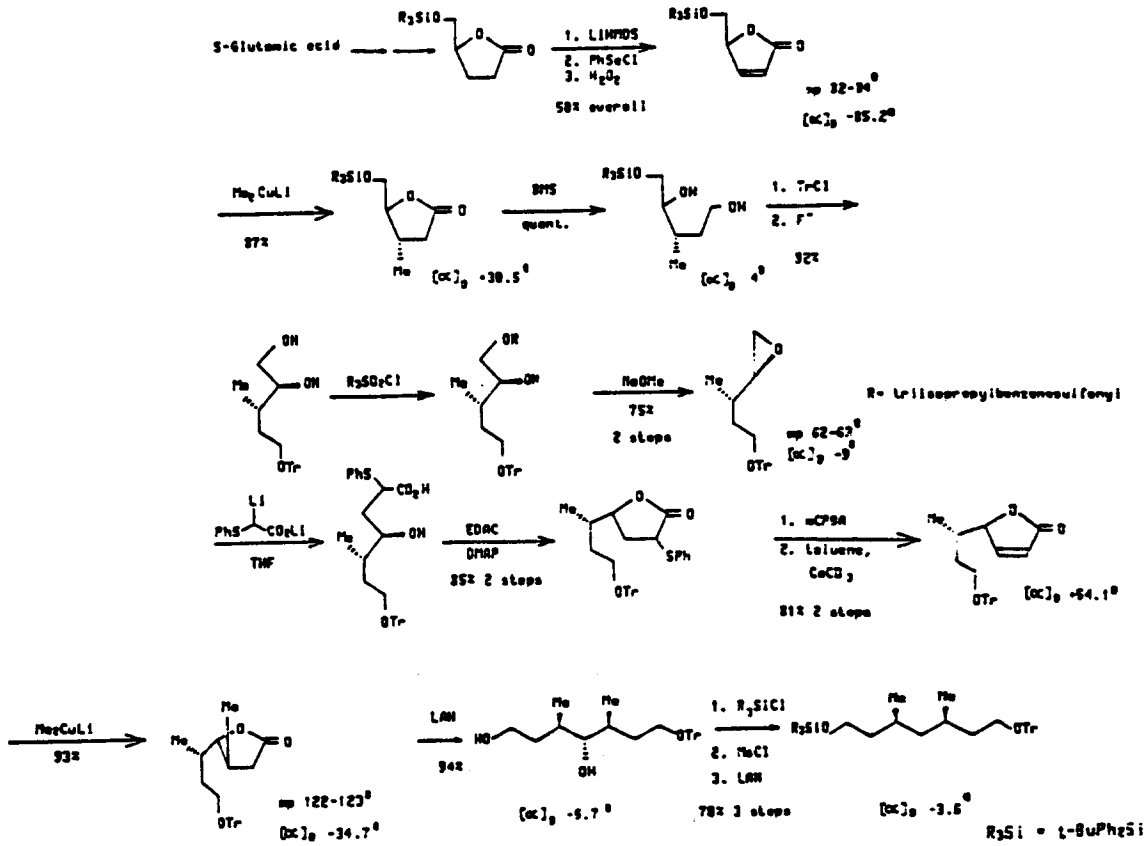
REMOTE STEREOSELECTION VIA A REPLICATING TEMPLATE



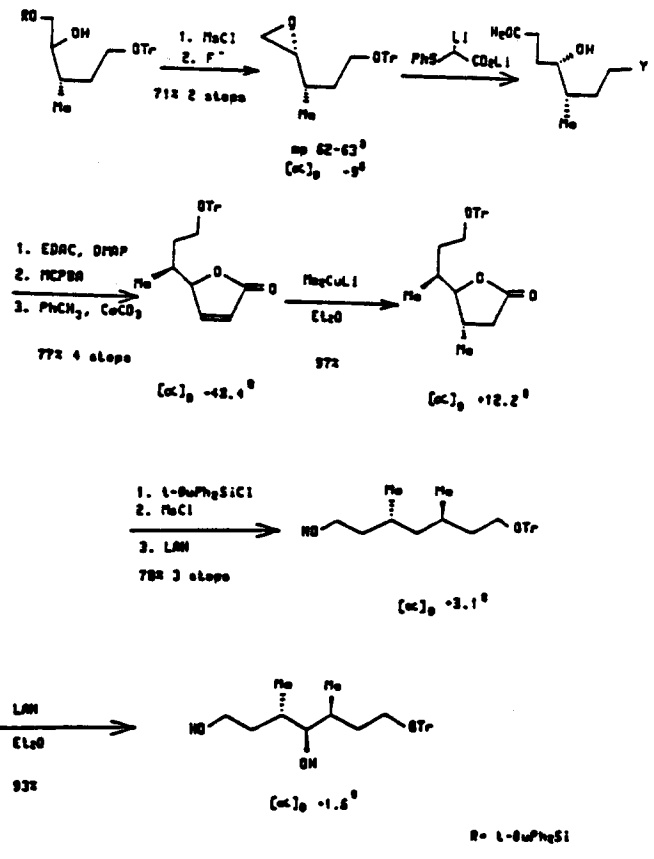
Tetrahedron Lett., 26, 2627 (1985)

Figure 18

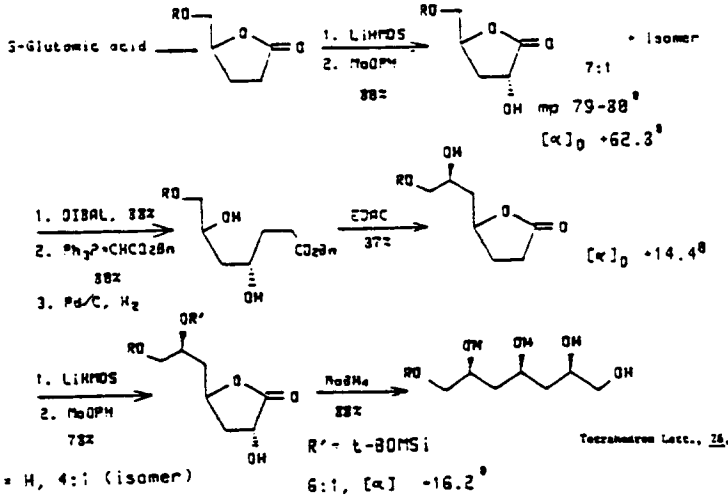
1,3 STEREOSELECTION (SYN)



1,3-STEREOSELECTION (ANTI)

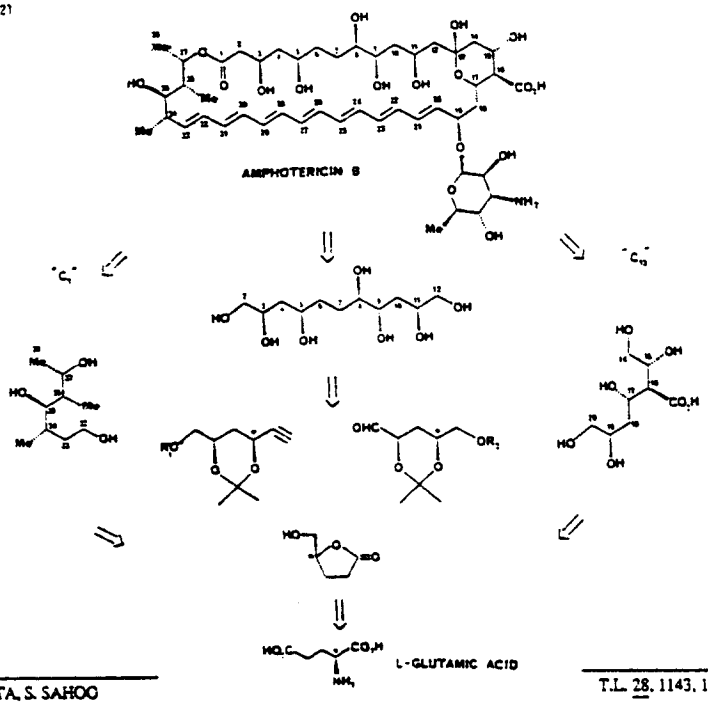


SYN, SYN -1,3,5 POLYOL



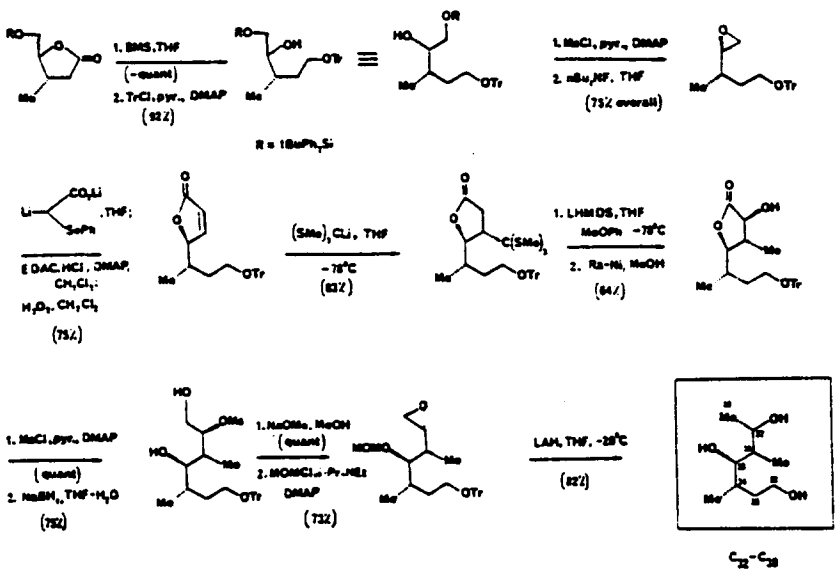
Tetrahedron Lett., 26, 3631 (1985)

Figure 21

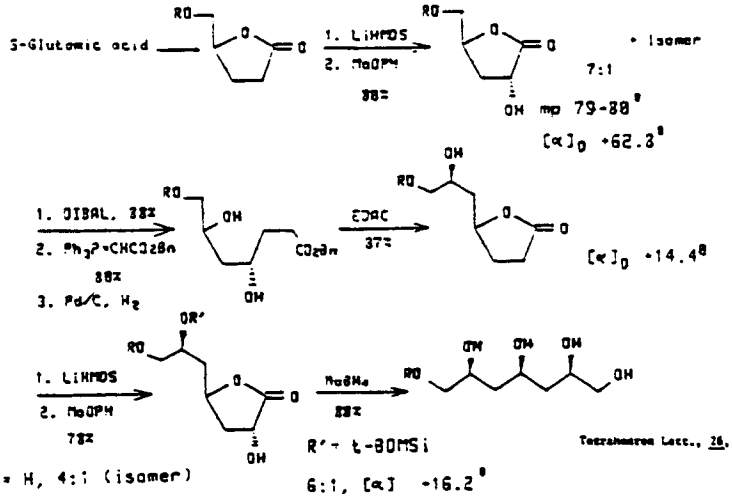


M. BOTTA, S. SAHOO

T.L. 28, 1143, 1147, 1151 (1987)

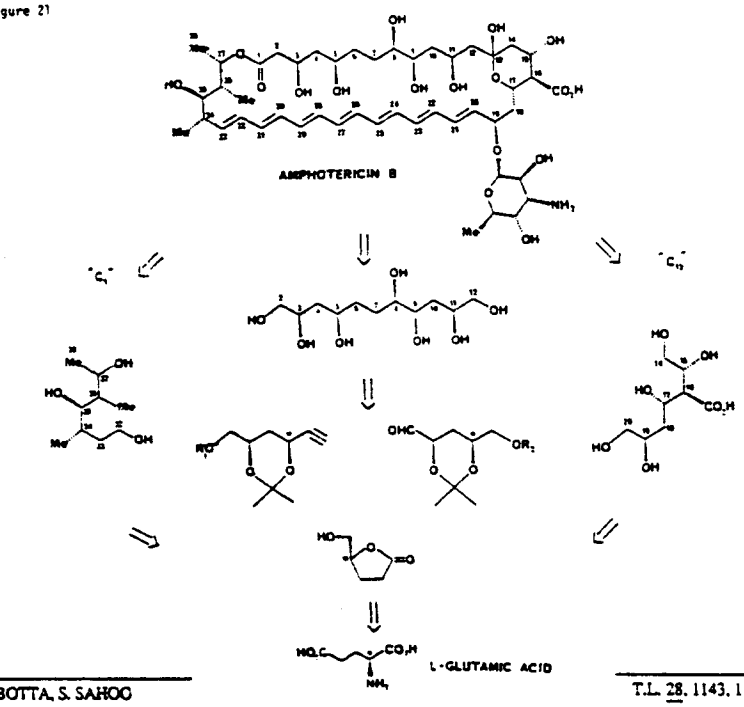


SYN, SYN -1,3,5 POLYOL



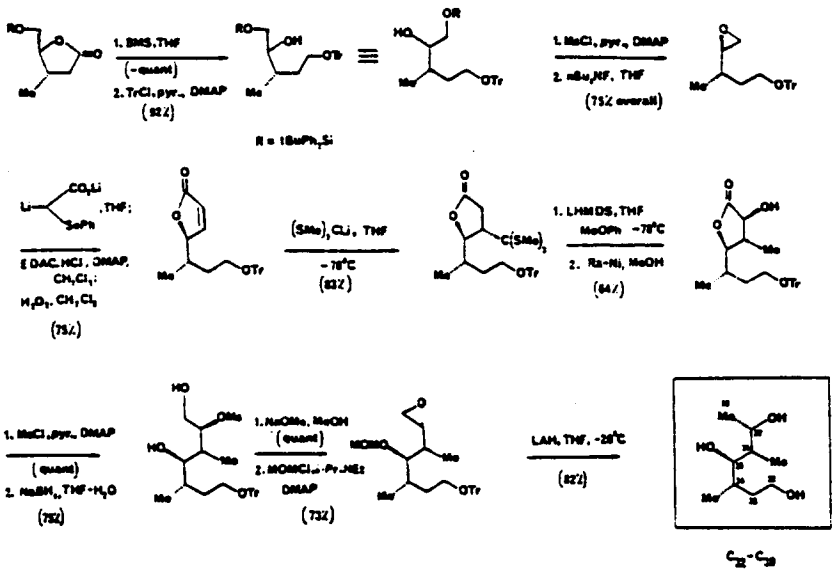
Tetrahedron Lett., 26, 3631 (1985)

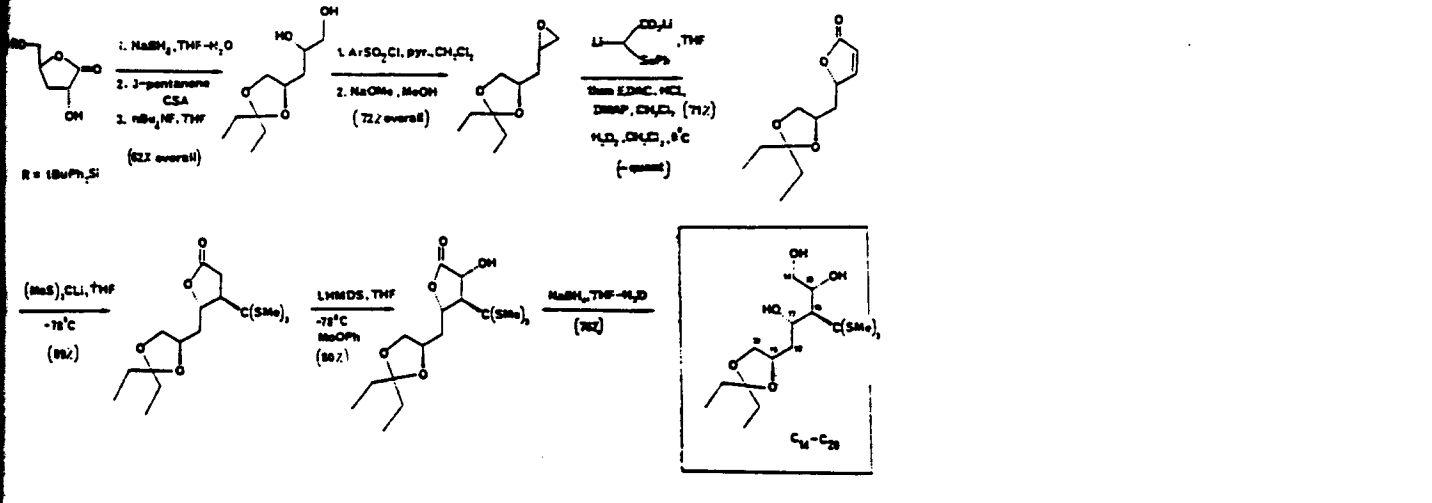
Figure 21

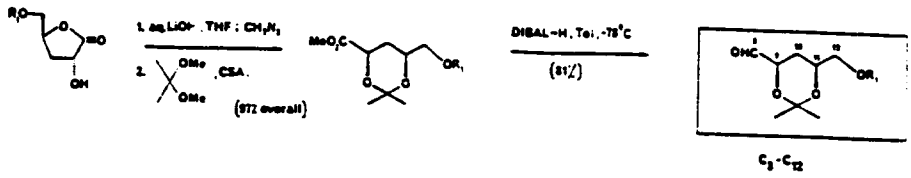


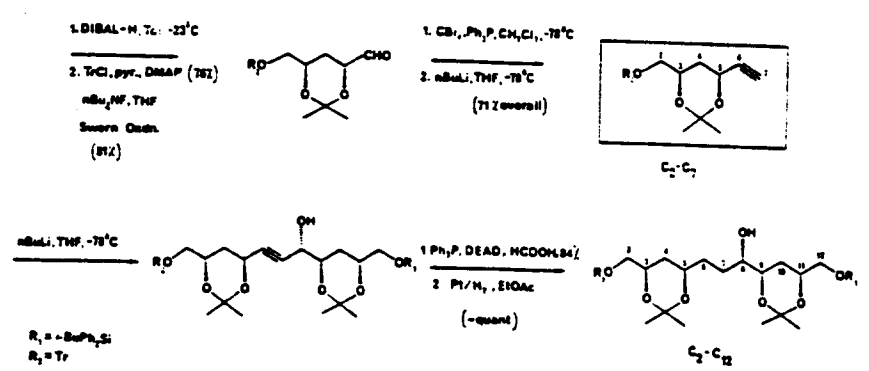
M. BOTTA, S. SAHOO

T.L. 28, 1143, 1147, 1151 (1987)

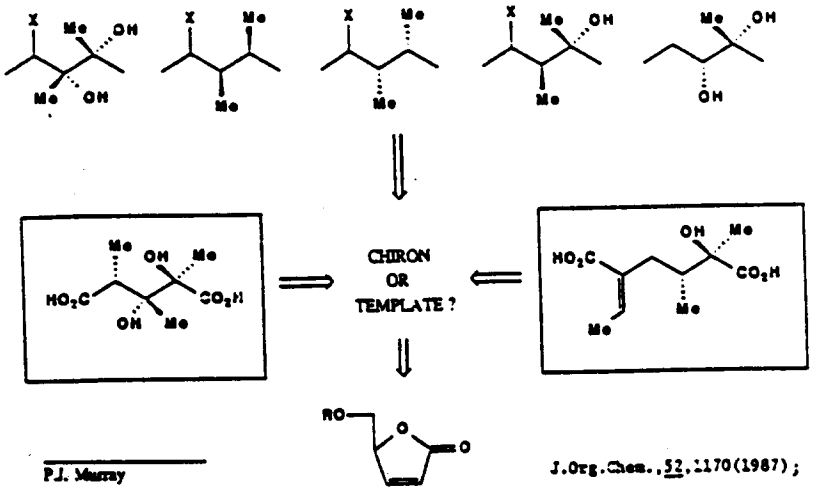








VICINAL SUBSTITUTION

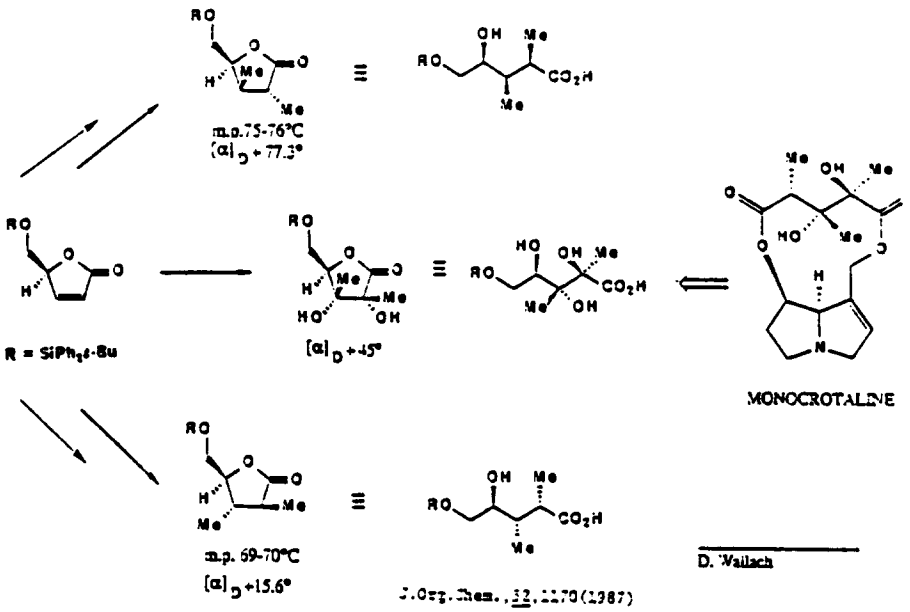


P.J. Murray

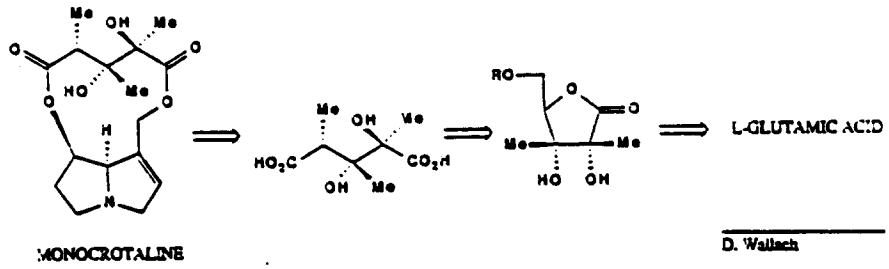
J.Org.Chem., 52, 1170(1987);

Figure 25

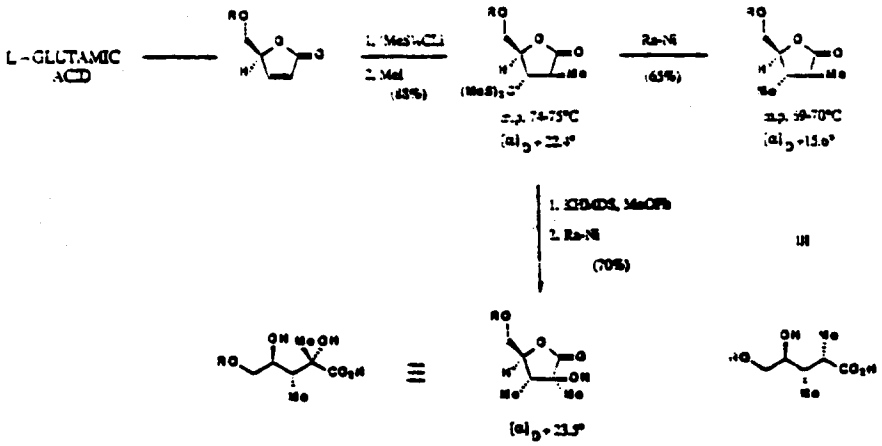
VICINAL SUBSTITUTION



D. Wallach



D. Wallach



P.J. Murray

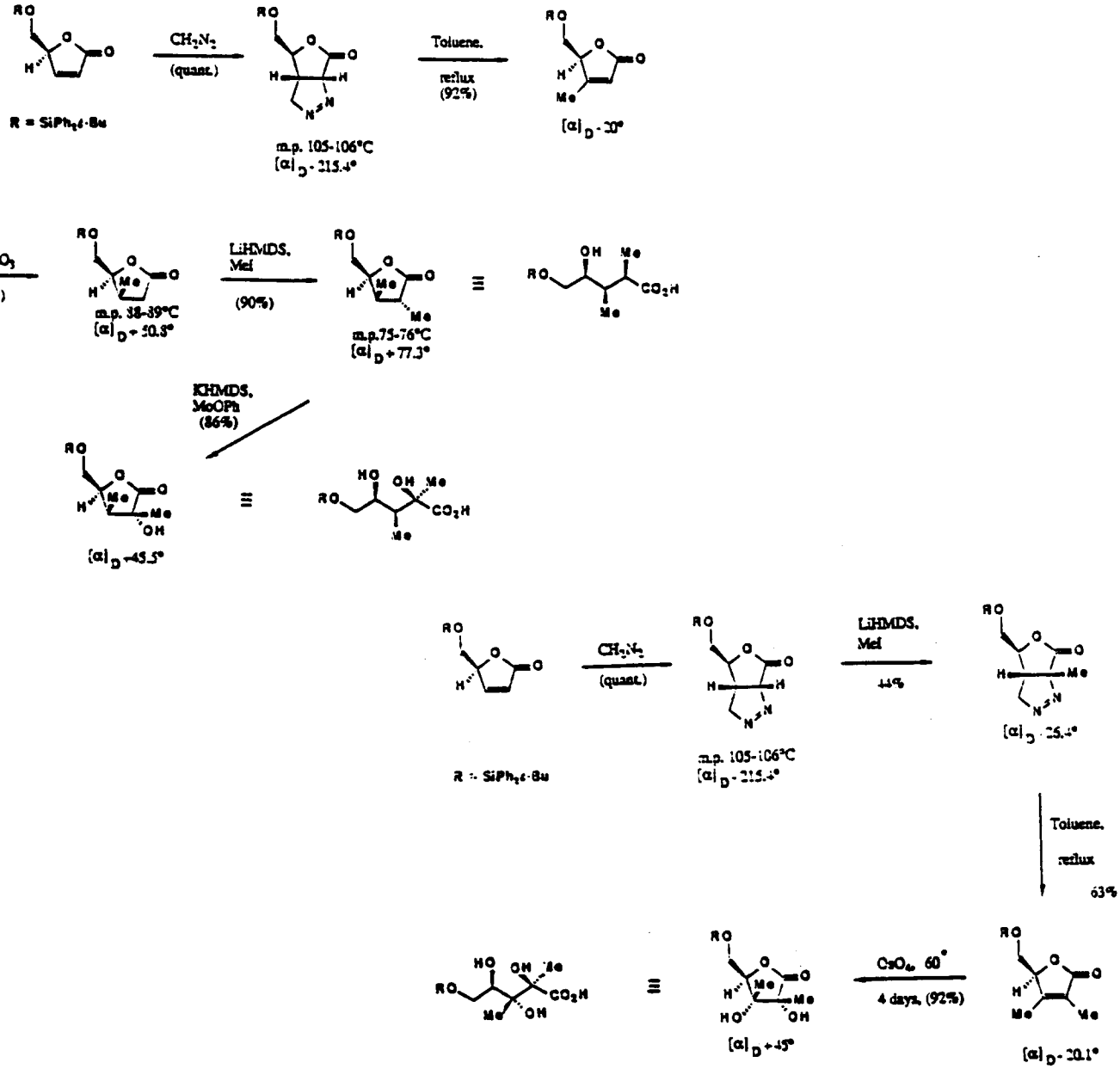

RO
CH_2N_2
(quant.)
Toluene,
reflux
(92%)
R = $SiPh_2t$-Bu
m.p. 105-106°C
$[\alpha]_D$ -215.4°
$[\alpha]_D$ -20°
Rh / Al_2O_3
(quant.)
m.p. 38-39°C
$[\alpha]_D$ +50.8°
LiHMDS,
MeI
(90%)
m.p.75-76°C
$[\alpha]_D$ +77.3°
KHMDS,
MoOPh
(86%)
$[\alpha]_D$ +45.5°
LiHMDS,
MeI
44%
$[\alpha]_D$ -25.4°
Toluene,
reflux
63%
CsO_4, 60°
4 days, (92%)
$[\alpha]_D$ +45°
$[\alpha]_D$ -20.1°

Figure 31

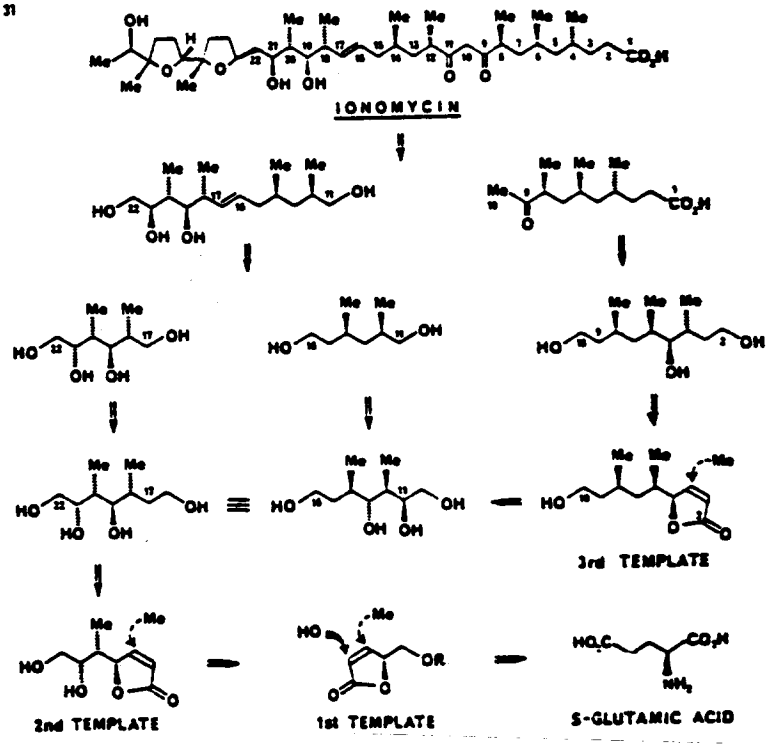
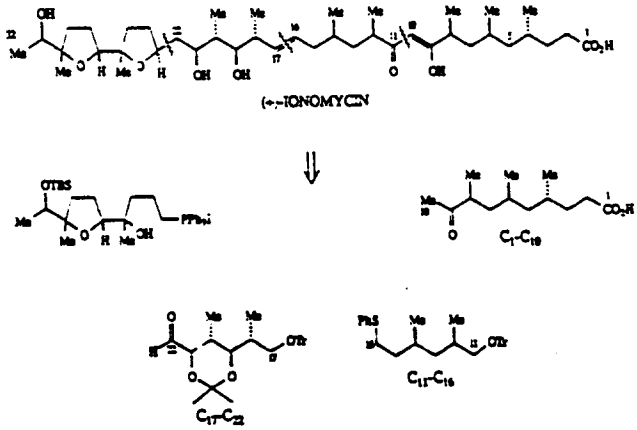
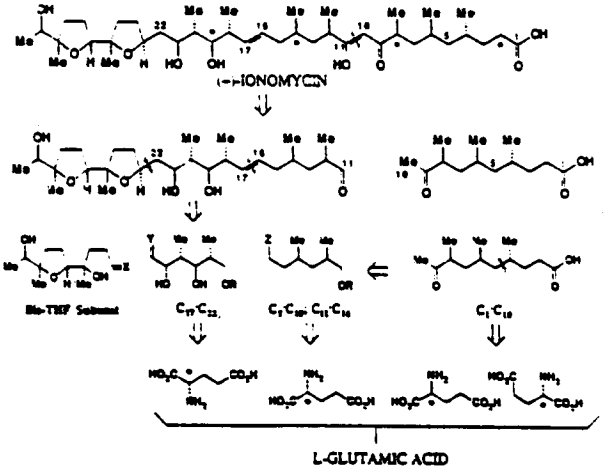

IONOMYCIN
3rd TEMPLATE
2nd TEMPLATE
1st TEMPLATE
S-GLUTAMIC ACID

Figure 2

SUBTARGETS AND CHIRONS

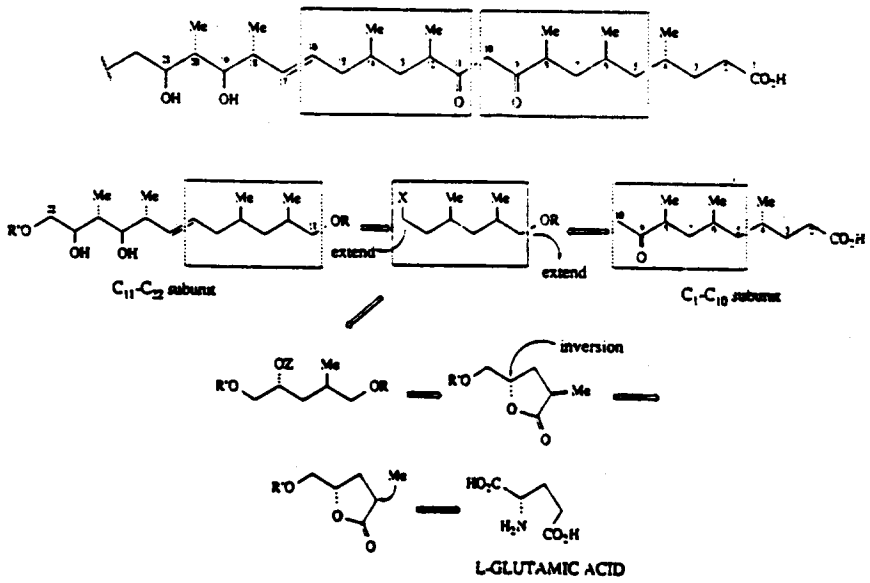


STEREOCHEMICAL DECODING-ANATOMY OF IONOMYCIN

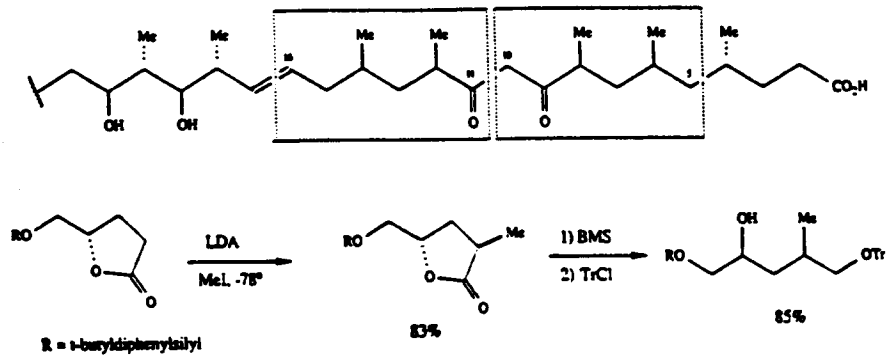


DESIGN AND STRATEGY

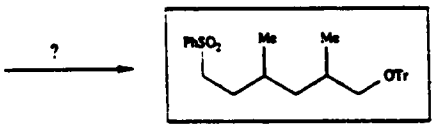
DISCOVERY OF COMMON SUBUNITS



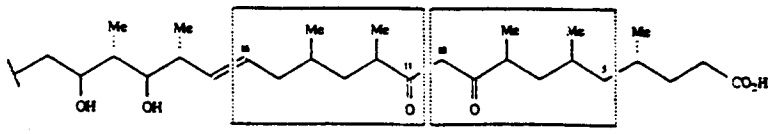
THE C_5-C_{10} AND C_{11}-C_{16} SUBUNITS - AN EXPEDITIOUS APPROACH

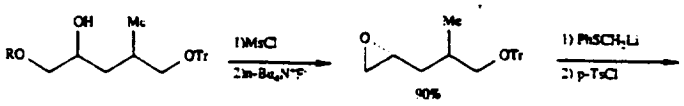


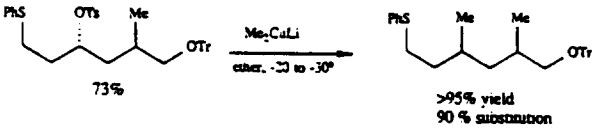
Tetrahedron Lett. 1985.26.5623

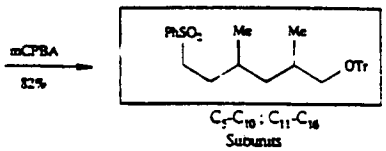


HOW TO REPLACE A SECONDARY HYDROXYL GROUP BY A METHYL ?





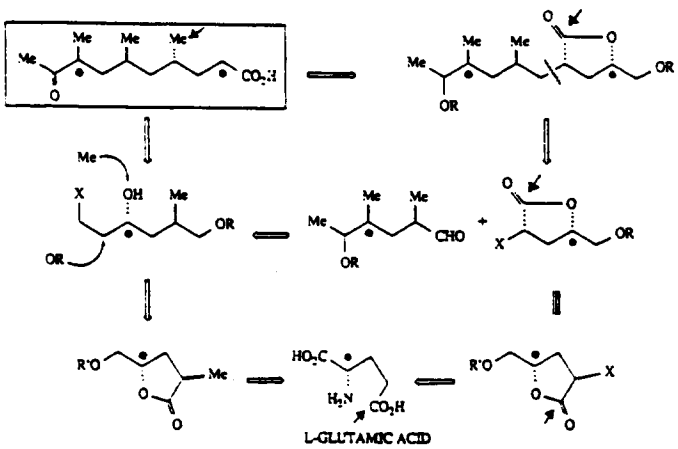




C_5-C_{10} ; C_{11}-C_{16}
Subunits

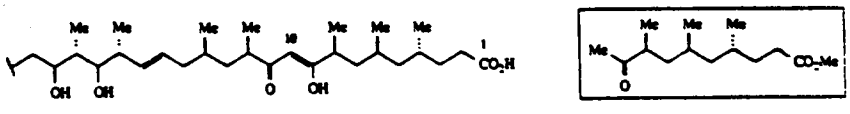
B. DeHoff

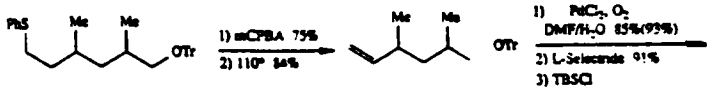
THE C_1 - C_{10} SUBUNIT

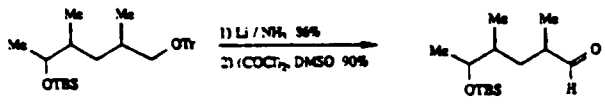


L-GLUTAMIC ACID

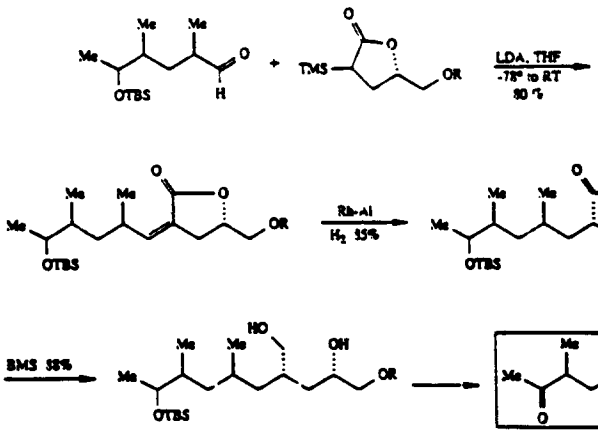
THE C_1 - C_{16} SUBUNIT

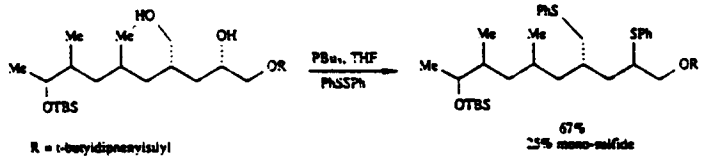




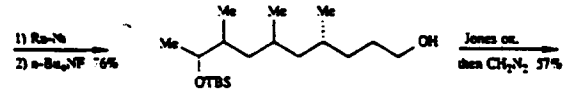


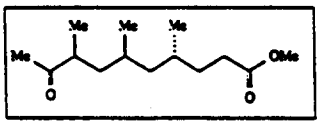
THE C_1-C_{10} SUBUNIT...





R = t-butyldiphenylsilyl

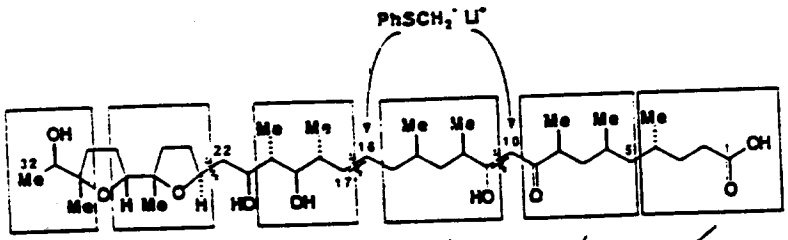


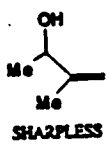


C_1-C_{10} Subunit

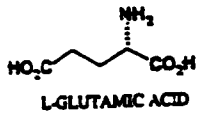
B. DeHoff

MEMORIES...

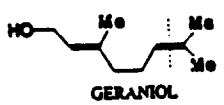




SHARPLESS



L-GLUTAMIC ACID



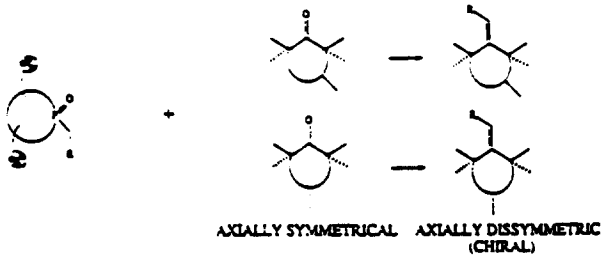
GERANIOL

B. DEHOFF
N. COOKE
P.J. MURRAY

DESIGN AND REACTIVITY OF AN ASYMMETRIC OLEFINATION REAGENT

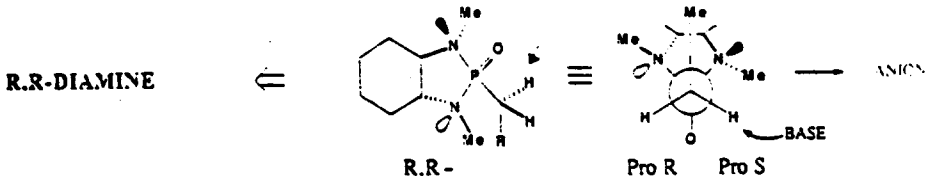
CONCEPT: ENANTIOTOPOS DIFFERENTIATION OF UNOCCUPIED ENANTIOTOPIC SPACES IN AN AXIALLY SYMMETRICAL (ACHIRAL) MOLECULE.

THE EFFECT: STRUCTURE, INHERENT CHIRALITY (BUILT-IN), TOPOLOGY, STEREOELECTRONIC EFFECT, CHELATION.



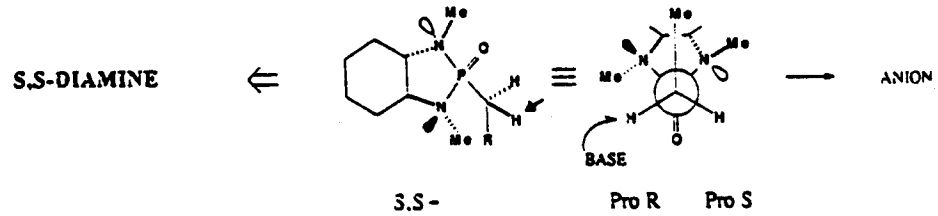
AXIALLY SYMMETRICAL — AXIALLY DISSYMMETRIC (CHIRAL)

TOPOLOGICALLY UNIQUE CHIRAL PHOSPHONAMIDES

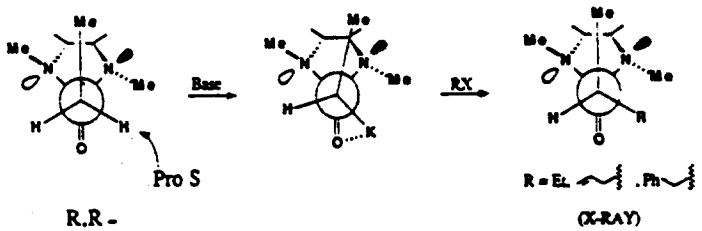


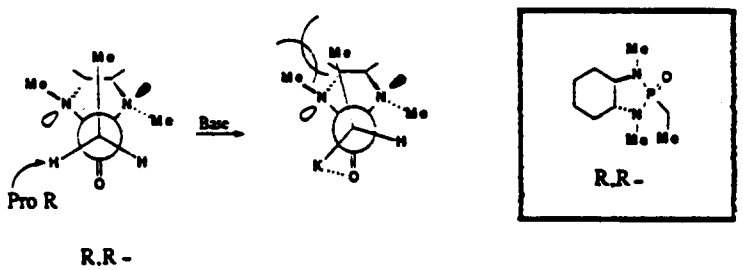
C2 SYMMETRY !

DIASTEREOFACIAL BIAS ?



STRUCTURE, INHERENT CHIRALITY (BUILT-IN), TOPOLOGY, STEREOELECTRONIC EFFECTS, COORDINATION / CHELATION, SYMMETRY

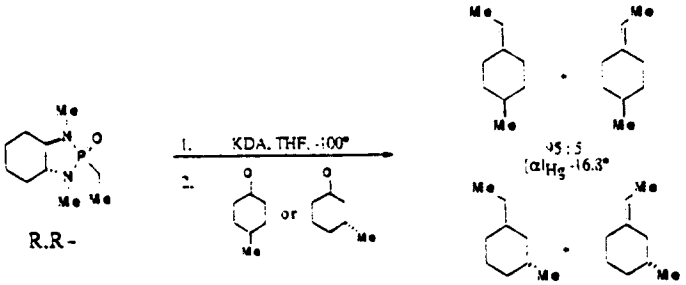




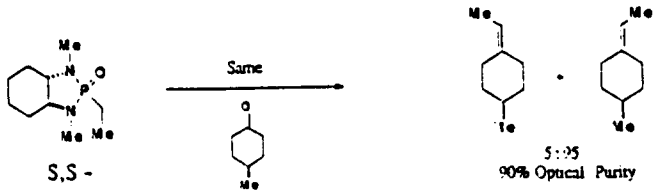
DELORME, D.

Figure -5

ASYMMETRIC OLEFINATION

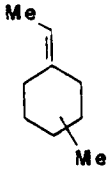


JACS, 106, 5754 (1984)
Proc. Nobel Symposium (1984)
Chim. Scripta, 25, 5 (1985)

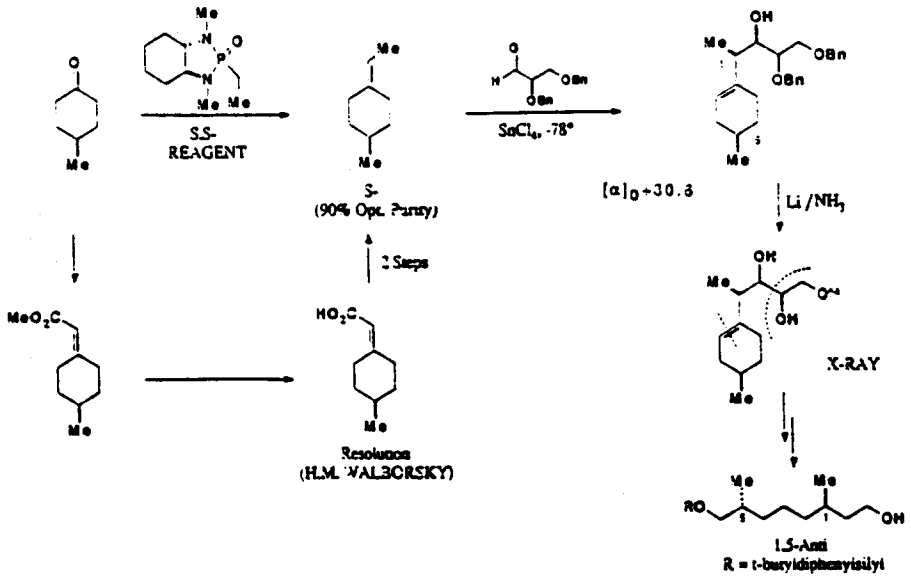


DELCRME, D.

BEAUDOIN, S.

WHAT TO DO WITH  ?

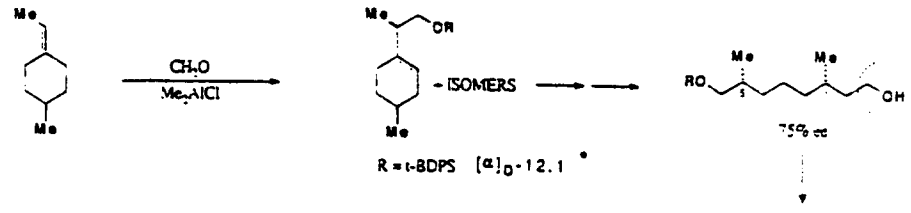
1,5-STEREOSELECTION VIA SEQUENTIAL ASYMMETRIC OLEFINATION AND ENE REACTIONS



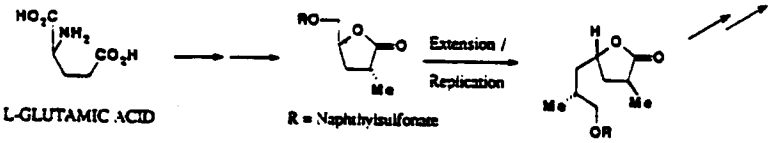
S. BEAUDOIN

1,5- STEREOSELECTION

VIA ENE REACTION :



VIA L-GLUTAMIC ACID – BUTYROLACTONE REPLICATION :

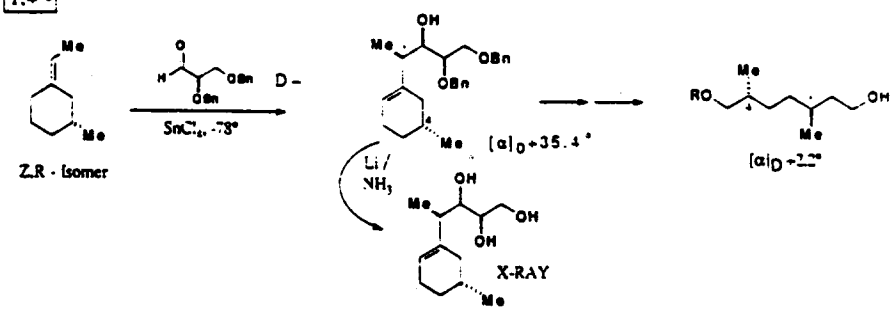


Tetrahedron Lett., 26, 5627 (1985)
P. J. MURRAY, S. P. SAHOO

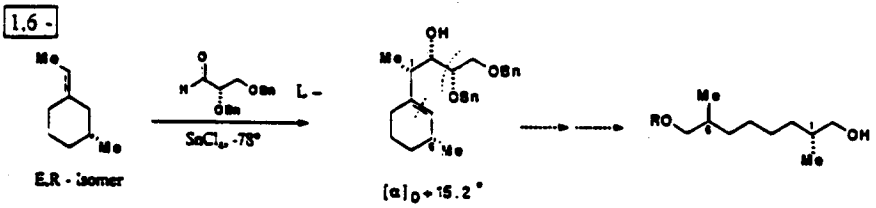
S. BEAUDOIN

1,4- or 1,6- STEREOSELECTION

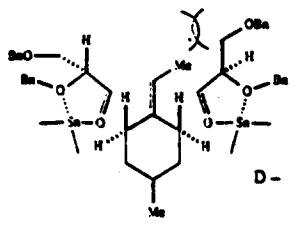
1,4 -



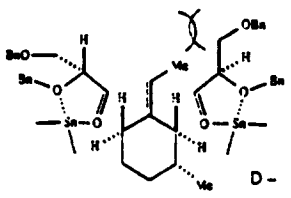
1,6 -



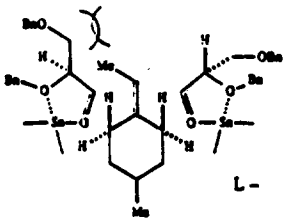
STEREOMATING OF MATCHED PAIRS



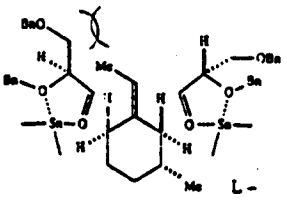
S - AND D -
ARE MATCHED FOR MATING



Z,R - AND D -
ARE MATCHED FOR MATING



R - AND L -
ARE MATCHED FOR MATING



E,R - AND L -
ARE MATCHED FOR MATING