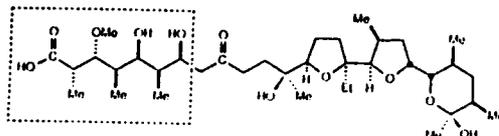
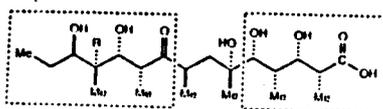
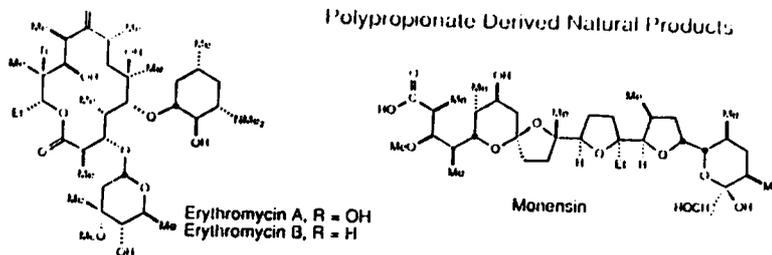
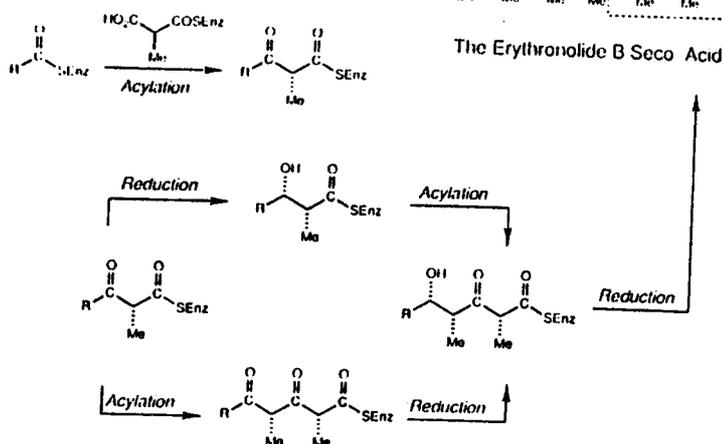


Polypropionate Derived Natural Products



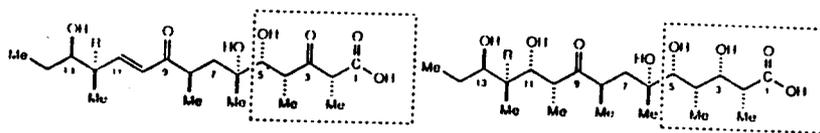
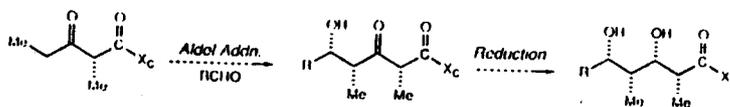
Polyketide Biosynthesis

Acylation-Reduction Permutations



Chiral Dipropionyl Synthons

Projected Applications in Macrolide Synthesis

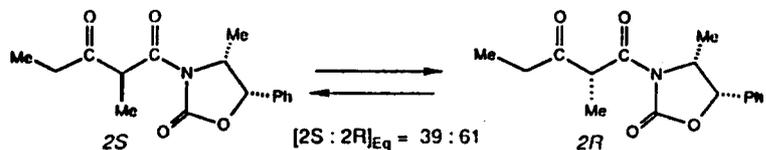
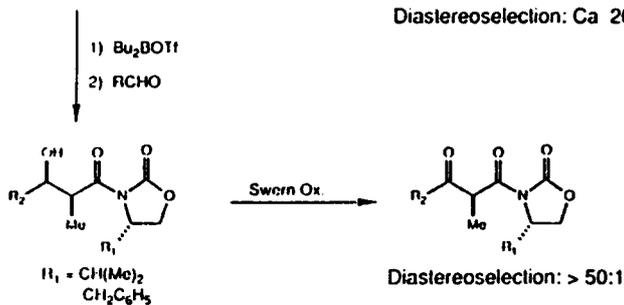
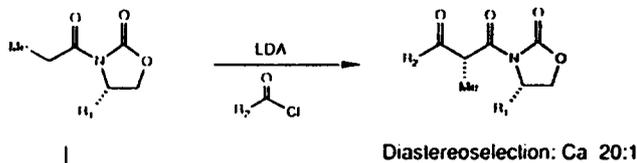


The Picromycin Seco Acid, R = OH
The Narbomycin Seco Acid, R = H

The Erythromycin Seco Acids
R = H, OH.

Epimerization Studies

Chiral 1,3-Dicarbonyl Synthons



Basic Conditions

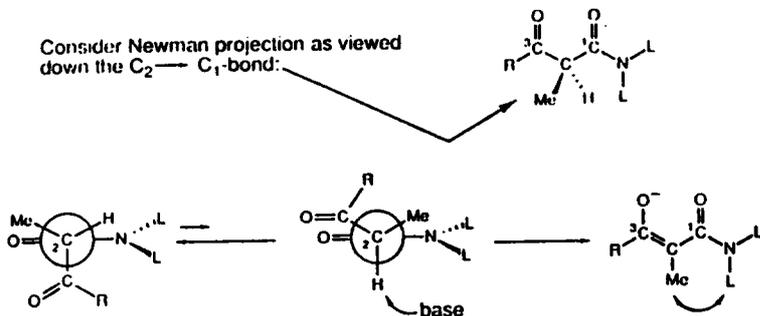
- 1) Et_3N (3 equiv), 25°C.....total equilibration, 18 hours
- 2) $\text{EtN}(\text{C}_2\text{H}_5)_2$, 25°C.....no equilibration, 3 hours
- 3) Pyridine, CD_3OD , 25°C.....no exchange after, 3 days

Acidic Conditions

- 1) Acetic Acid, 25°C.....no equilibration, 24 hours
- 2) $\text{HCl} \cdot \text{CHCl}_3$, 25°C.....no equilibration, 24 hours

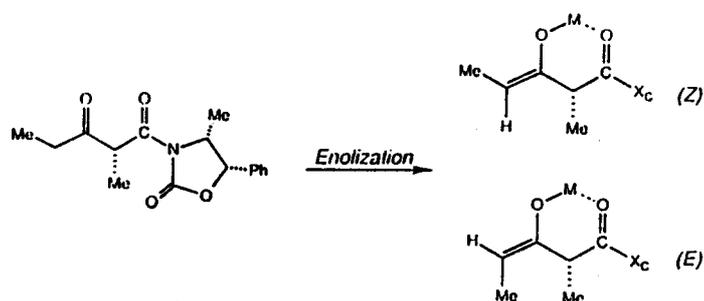
Steric Inhibition to $\text{C}_2\text{H} \cdots \text{C}=\text{O}$ Overlap

Consider Newman projection as viewed down the $\text{C}_2 \rightarrow \text{C}_1$ bond:



The attenuated kinetic acidity is projected to be due to developing A(1,3) interaction between nitrogen ligand and the C_2 -substituent during the enolization process.

Regioselective Enolization



Conditions

Bu_2BOTf , R_3N

$\text{Sn}(\text{OTf})_2$, R_3N

LiNR_2 , TMSCl

Metal

BL_2

SnOTf

SiMe_3

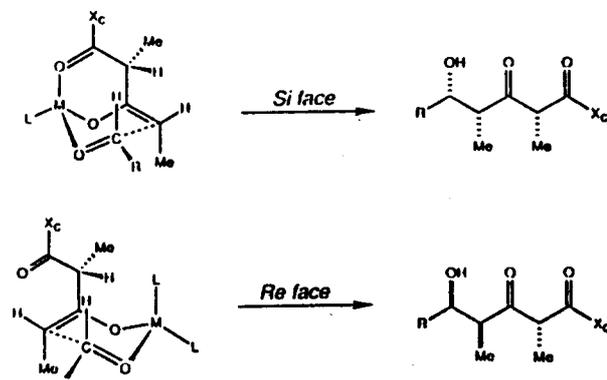
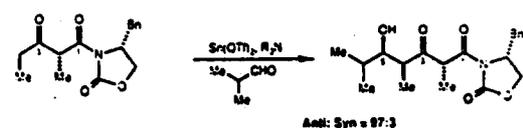
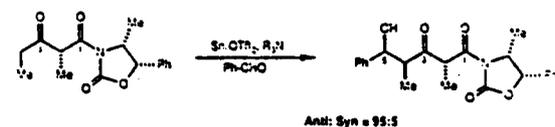
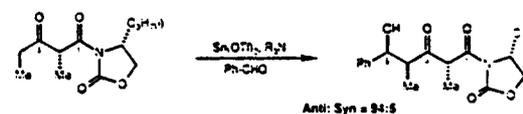
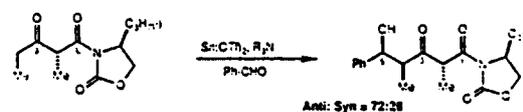
(Z):(E) Ratio

>95 : 5

>95 : 5

67 : 33

Diastereoselective Aldol Addition Options

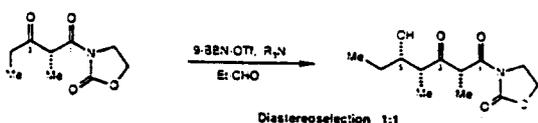
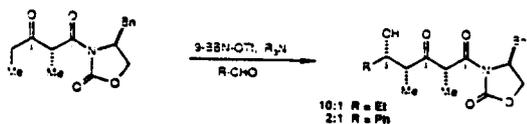
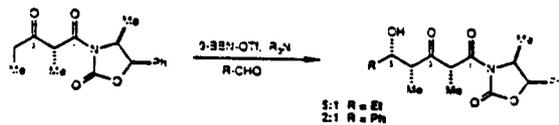
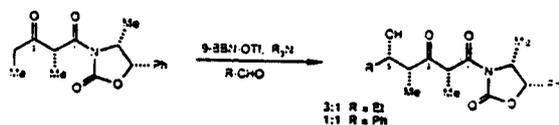
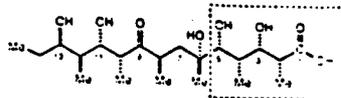
The C_{12} - C_{13} Aldol Rxn.
Syn-Anti
Diastereoselection

Questions:

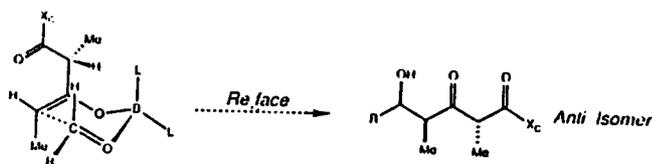
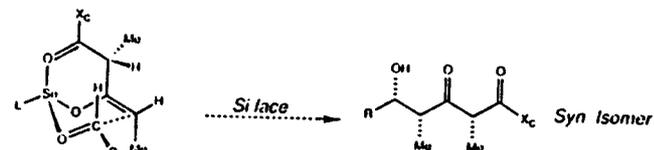
Can one hope to select for either transition state?

Can both reactions be rendered diastereoselective?

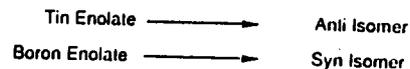
The C₂-C₅ Aldol Rxn.
Syn-Anti
Diastereoselection



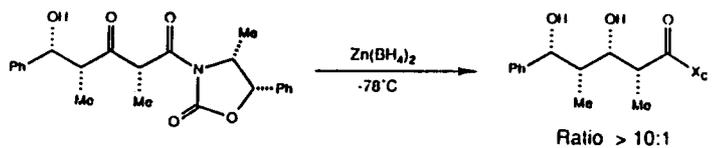
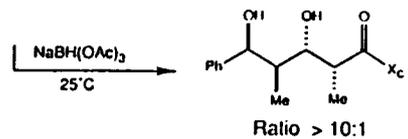
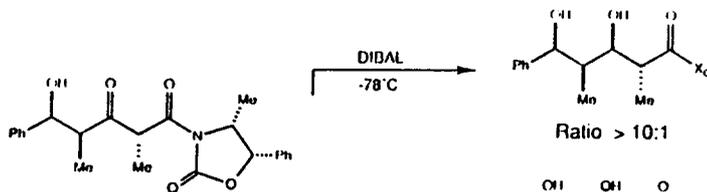
The Prediction:



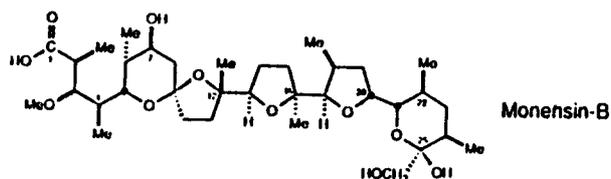
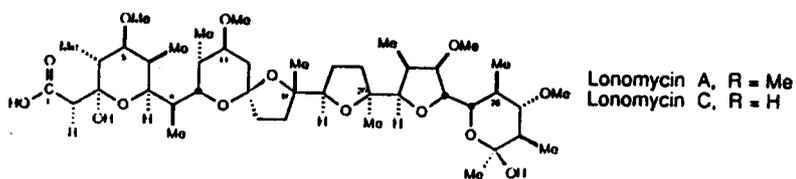
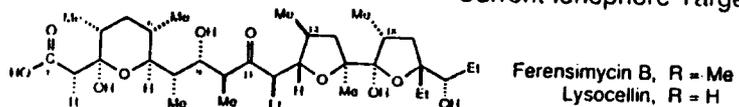
The Observations:



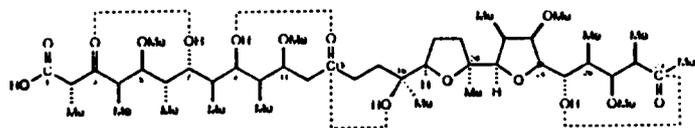
Stereoselective Reductions



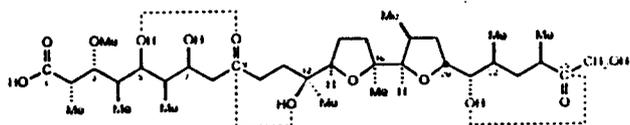
Current Ionophore Targets



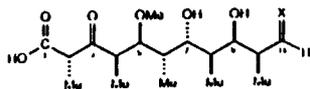
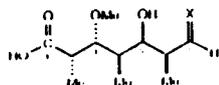
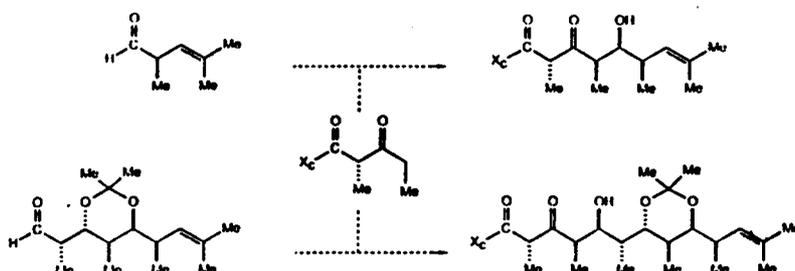
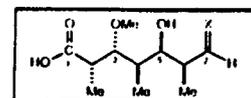
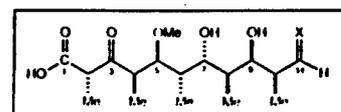
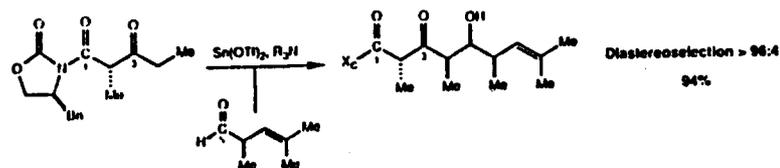
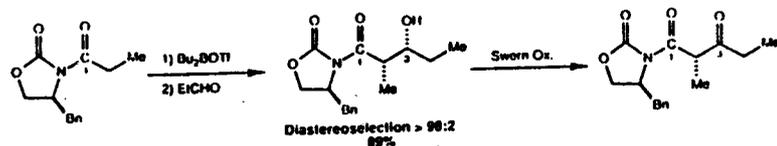
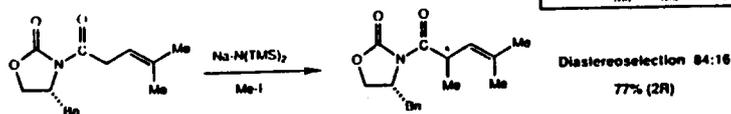
Polypropionate Synthons



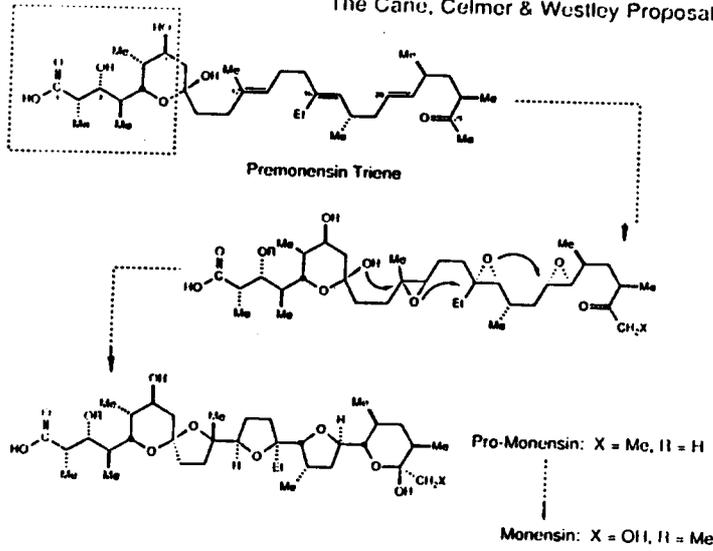
Lonomycin-A



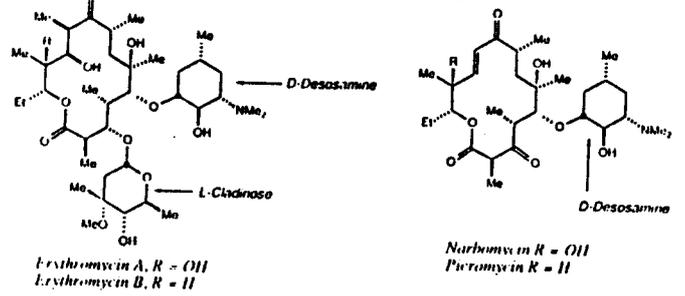
Monensin-B

Lonomycin-A:
C₁-C₁₁ SynthonsMonensin B:
C₁-C₇ SynthonsMonensin-B:
C₁-C₇ SynthonsLonomycin-A:
C₁-C₁₁ SynthonsMonensin C₁-C₇ Synthons

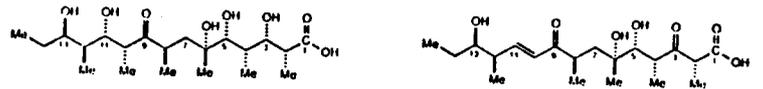
The Cane, Celmer & Westley Proposal



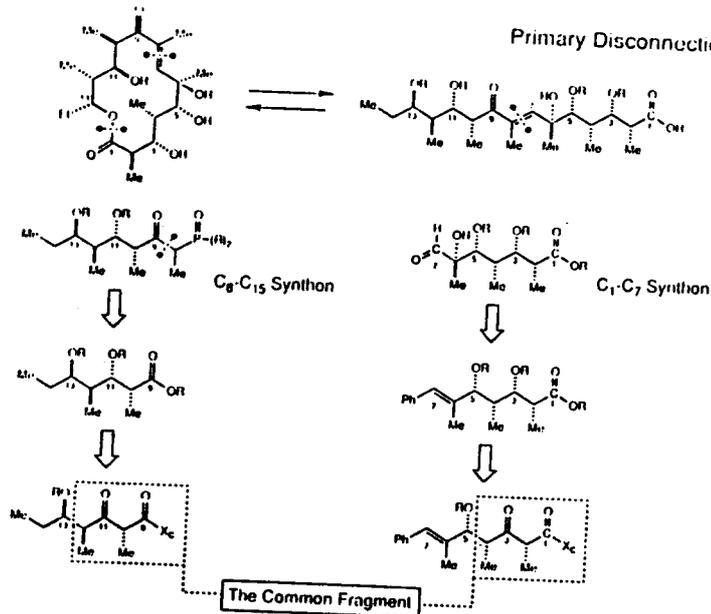
The 14-Membered Macrolides



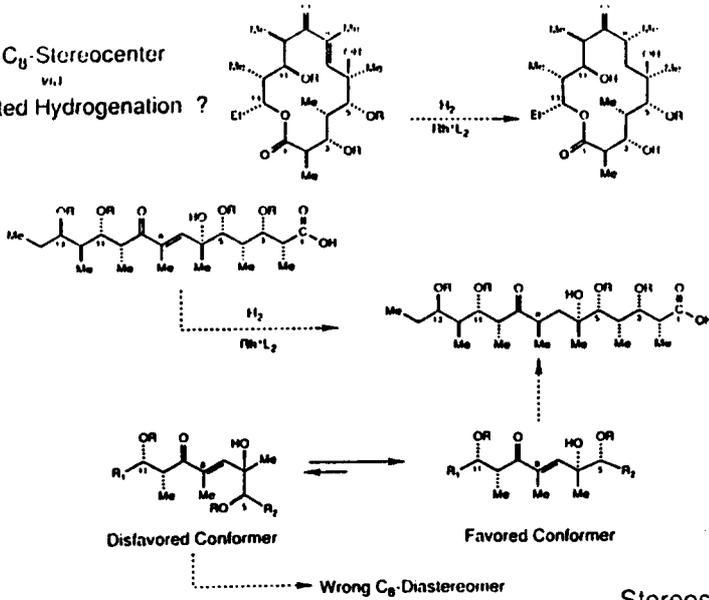
The Seco Acids



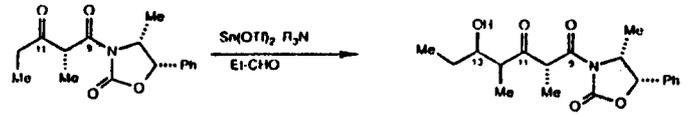
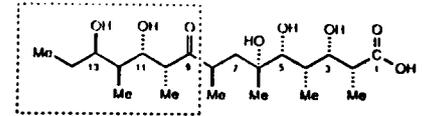
Primary Disconnections



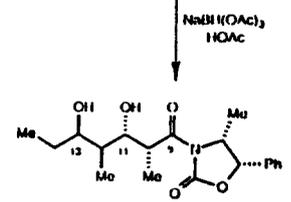
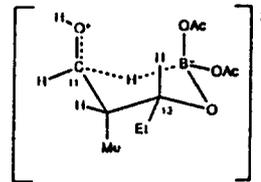
The C₉-Stereocenter
Directed Hydrogenation ?



Stereoselective Construction
of the C₉-C₁₅ Synthons

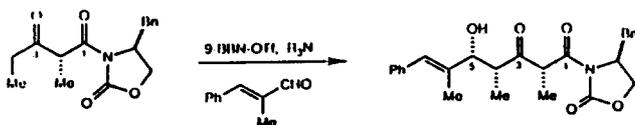
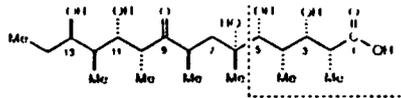


Diastereoselection 10:1 (86%)

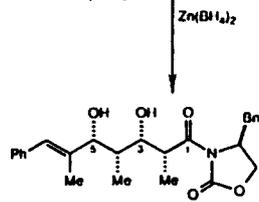
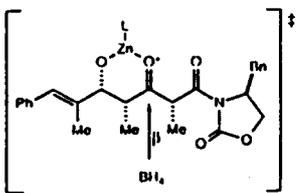


Diastereoselection > 20:1 (95%)

Stereoselective Construction
of the C₁-C₅ Synthons

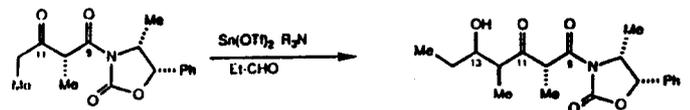


Diastereoselection 2:1 (50%)

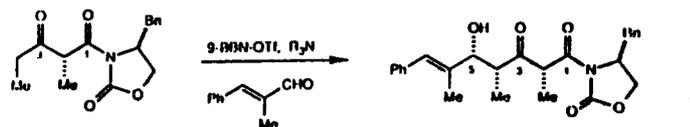


Diastereoselection > 20:1 (70%)

Asymmetric Aldol
Bond Constructions

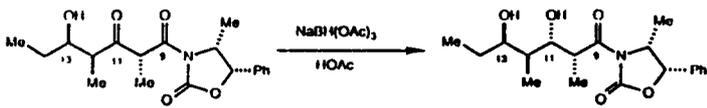
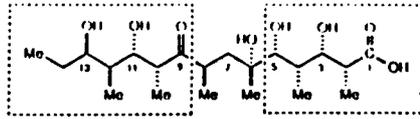


Diastereoselection 10:1 (88%)

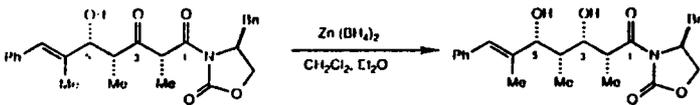


Diastereoselection 2:1 (50%)

Stereoselective Reductions C₃ & C₁₁



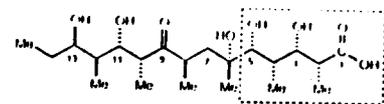
Diastereoselection > 10:1 (82%)



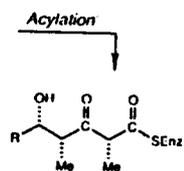
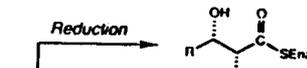
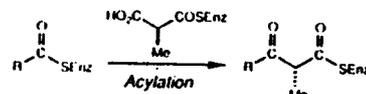
Diastereoselection > 20:1 (70%)

Polyketide Biosynthesis

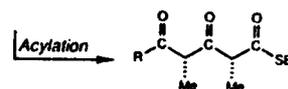
Acylation-Reduction Permutations



The Erythronolide B Seco Acid



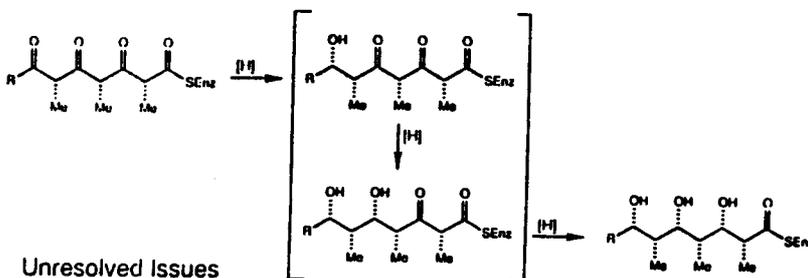
Reduction



Reduction

Assume that Polyacylation
precedes reduction.

Polyketide Biosynthesis



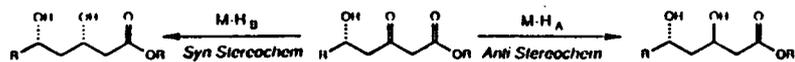
A) If a polycarbonyl substrate is generated what is the sequence of carbonyl reduction events ?

B) Are the stereochemical relationships at the methyl-bearing centers established at the time of C-C bond construction or in conjunction with carbonyl reduction ?

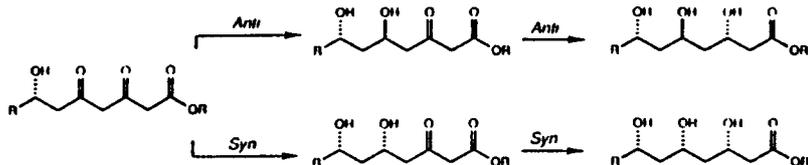
How can we simulate enzymatically regulated reductions of the type illustrated below?



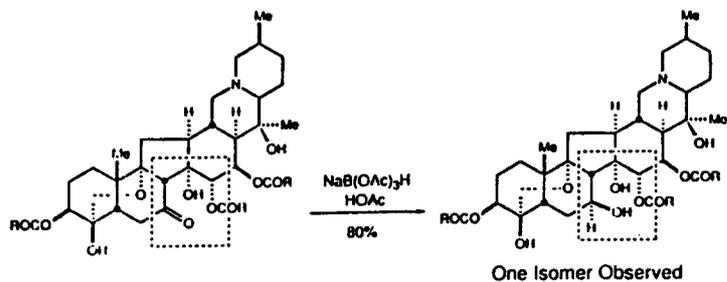
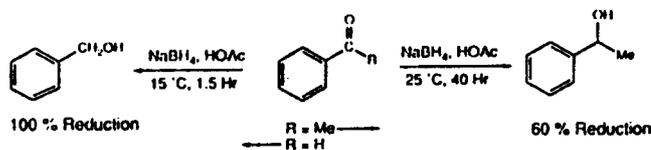
Design a "hydroxyl-directed carbonyl reduction"



If the reductions proceed strictly via hydroxyl direction then.....

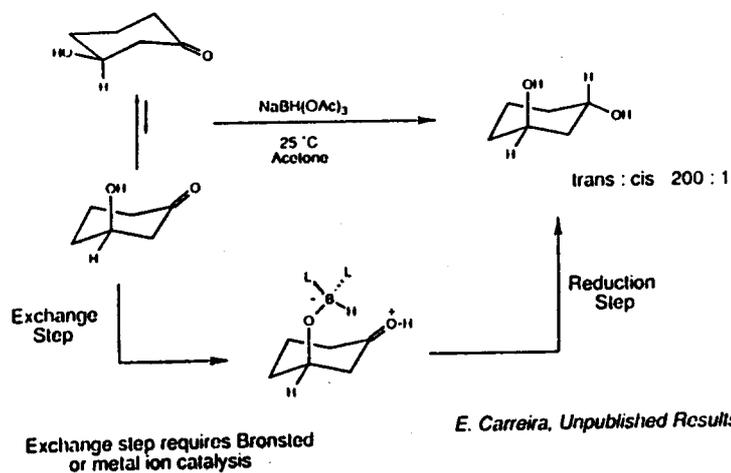


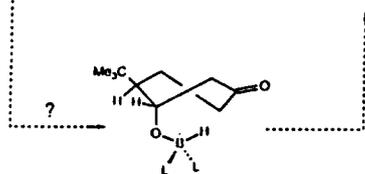
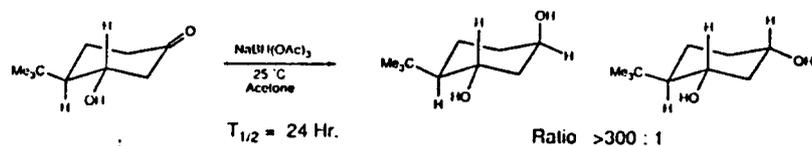
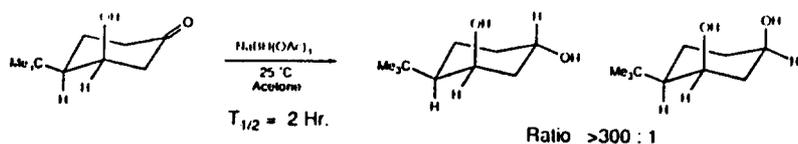
Stereoselective Reduction of Hydroxy-ketones with $\text{NaBH}(\text{OAc})_3$



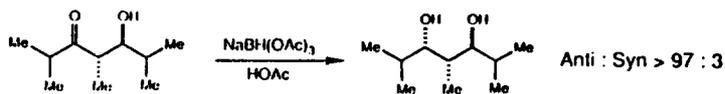
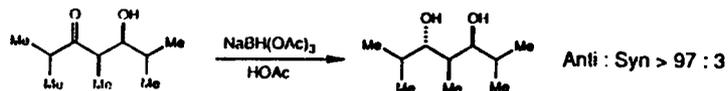
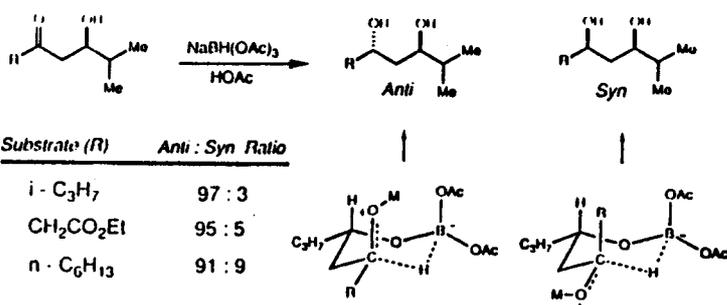
A. K. Saksena, P. Mangiaracina. (1983)

Stereoselective Reduction of Hydroxy-ketones with $\text{NaBH}(\text{OAc})_3$





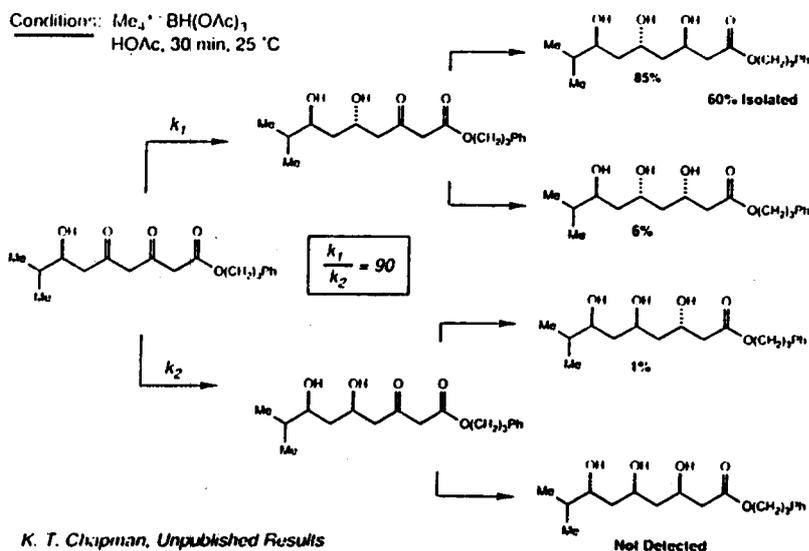
E. Carreira, Unpublished Results.



K. Chapman, Unpublished Results

Propagating Carbonyl Reductions

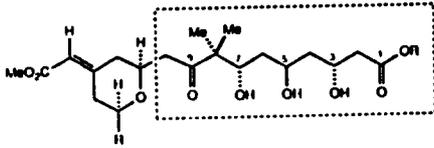
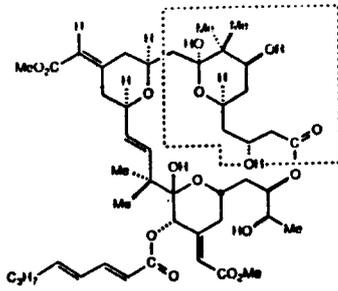
Condition: Me₃BH(OAc)₃
HOAc, 30 min, 25 °C



K. T. Chapman, Unpublished Results

Bryostatin I, $R = \text{CO-CH}_3$
 Bryostatin II, $R = \text{H}$

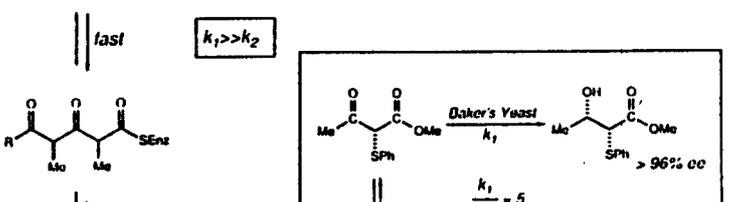
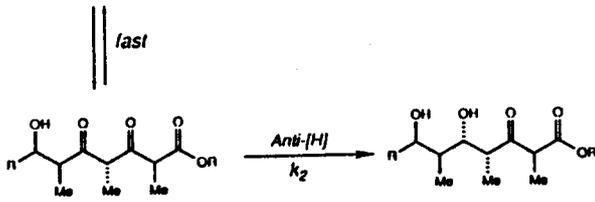
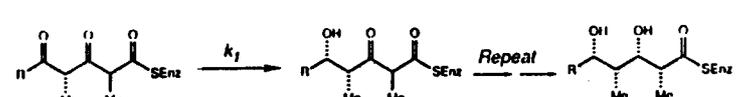
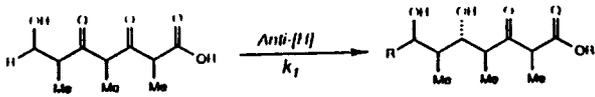
G.R.Petit & Co-workers, 1982



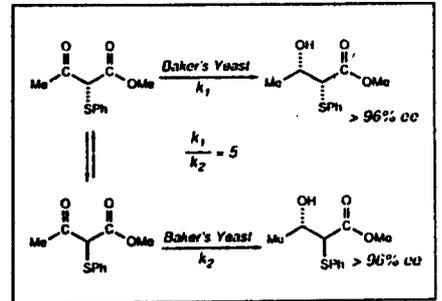
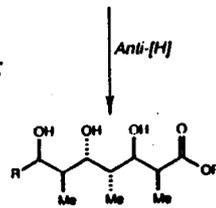
Propagating Carbonyl Reductions

Assume that the methyl-bearing stereocenters are set in conjunction with C=O reduction.

Polyketide Biosynthesis

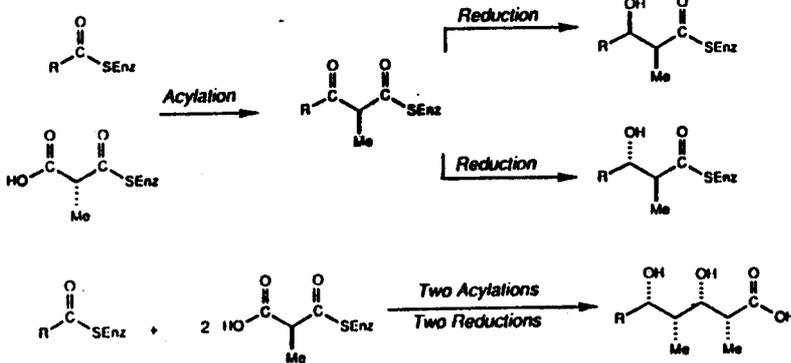


Assume $k_2 \gg k_1$Now repeat:



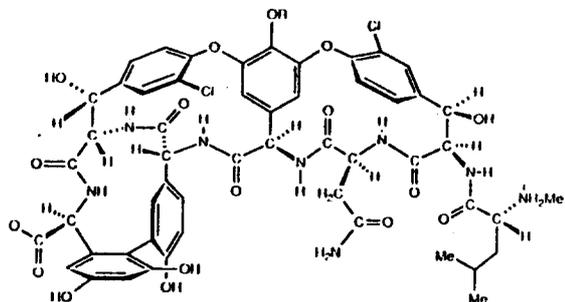
Polyketide Biosynthesis
 1,3-Dioxygen Relationships

The Erythronolide B Seco Acid



The sequencing of Acylation & Reduction Events Currently Unknown.

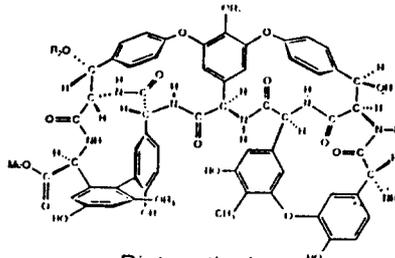
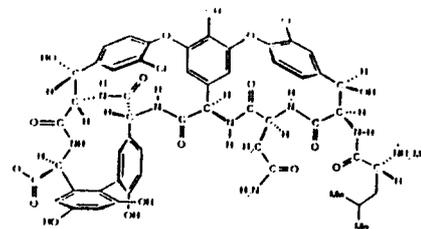
Vancomycin



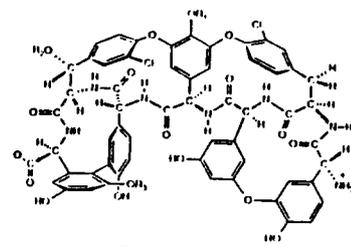
ISOLATED FROM *STREPTOMYCES ORIENTALIS*

PATENTED 1962, ELI LILLY & Co.

Vancomycin

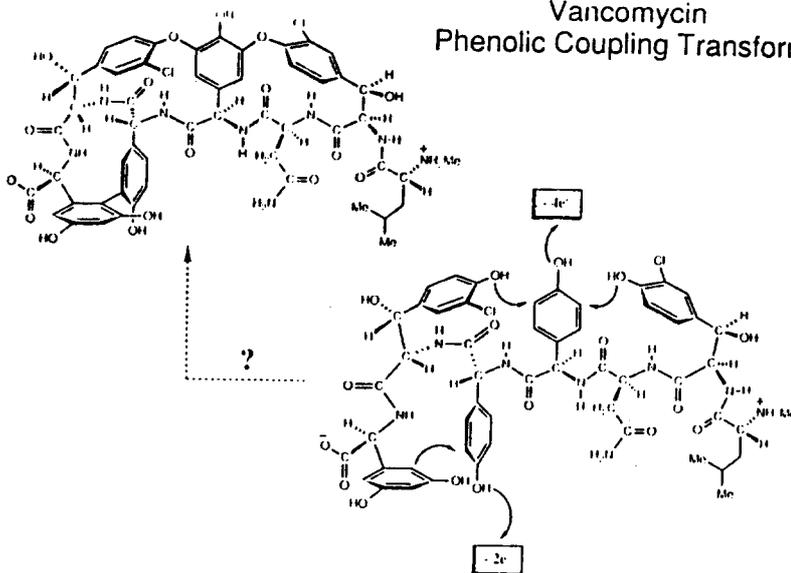


Ristocetin A

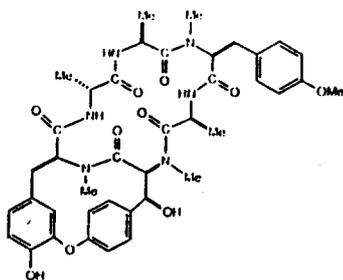


Teicoplanin

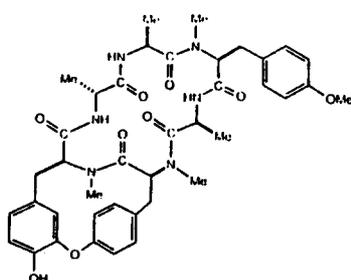
Vancomycin Phenolic Coupling Transform



Antineoplastic Hexapeptides



Bouvardin

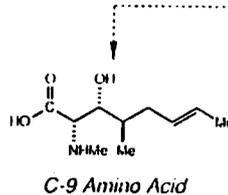
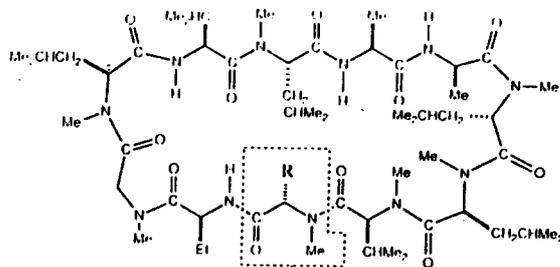


Deoxybouvardin

R. B. Bates & Co-workers
J. Am. Chem. Soc. 99, 8040, (1977)

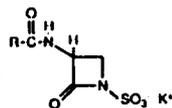
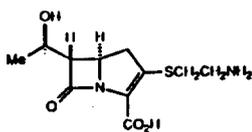
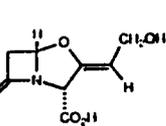
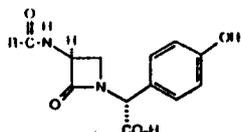
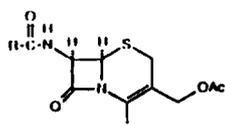
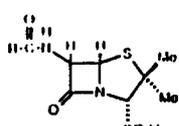
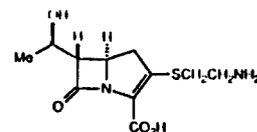
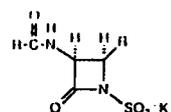
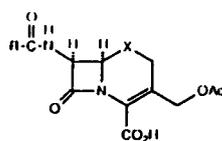
Isolated from *Bouvardia ternifolia*

Cyclosporine A



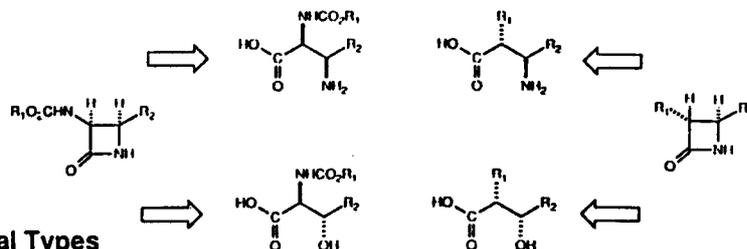
C-9 Amino Acid

- Isolation: 1970
- Immunosuppressive Properties: 1972
- Structure: 1975
- Clinical Trials: 1978
- First Synthesis: 1983

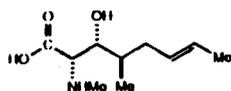
β -Lactam Antibiotics β -Lactam Antibiotics: Acyclic Precursors

Target Structure

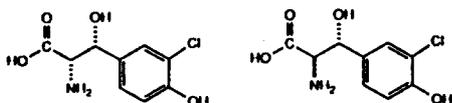
Required Amino Acid Structural Types



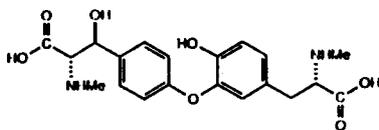
Cyclosporin A

 β -Lactam Antibiotics

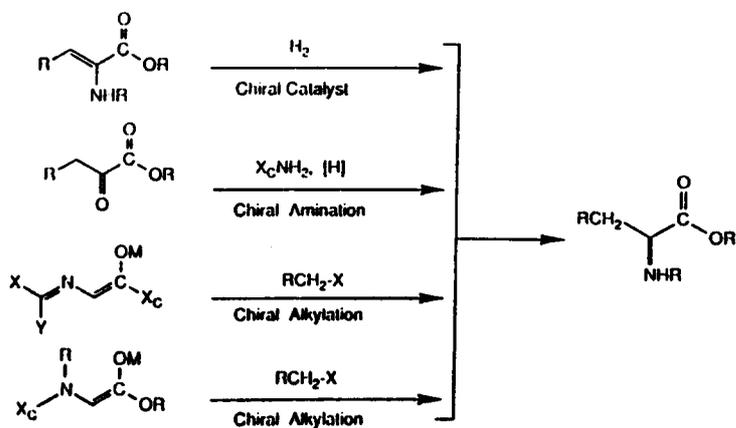
Vancomycin



Bouvardin

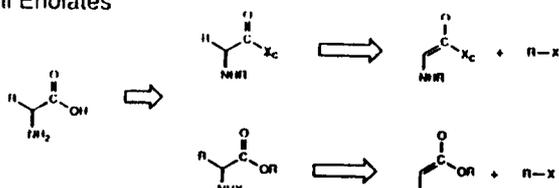


Enantioselective Amino Acid Synthesis

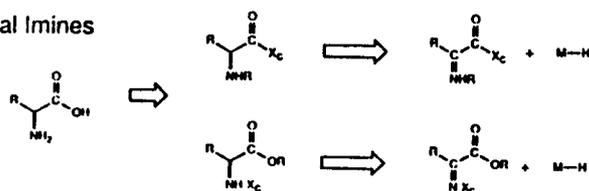


The Stereodifferentiating Event

A. Chiral Enolates



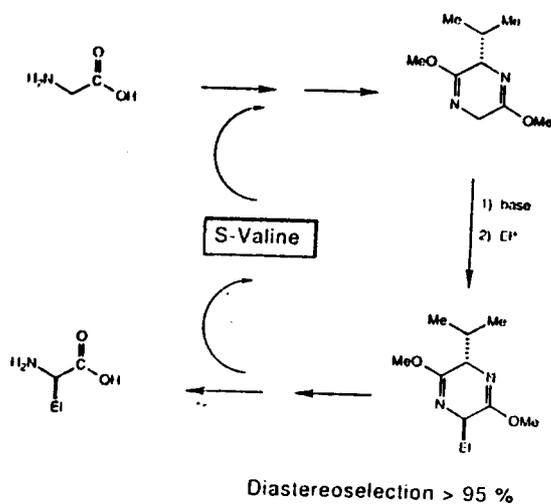
B. Chiral Imines



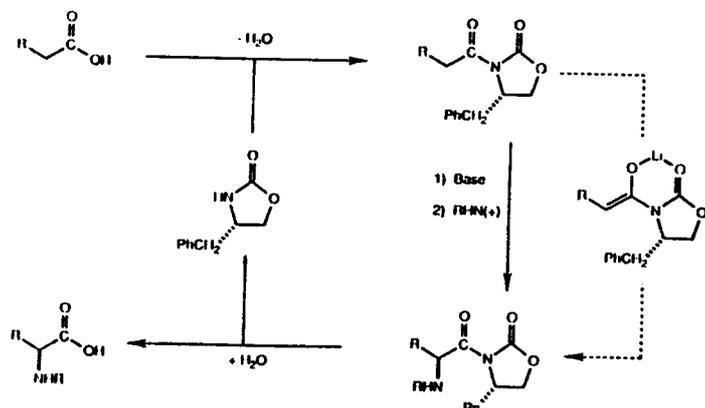
Case A: Rate of reaction strongly dependent upon structure of R-X.

Case B: Rate of reaction not strongly influenced by substrate structural changes.

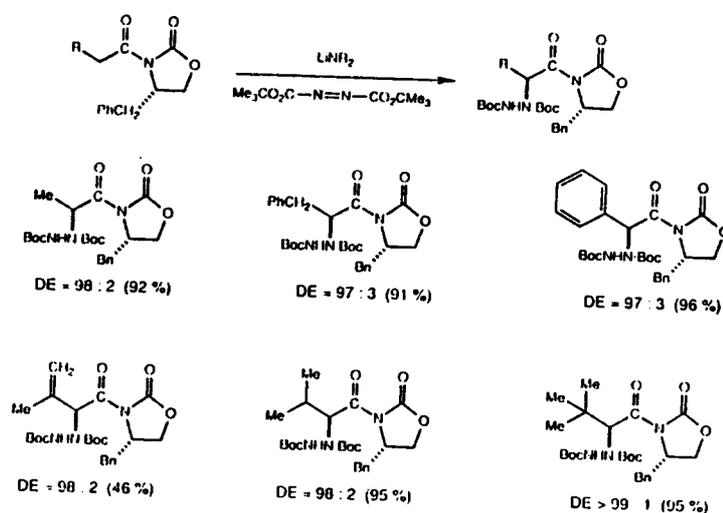
The Schollkopf Chiral Enolate System



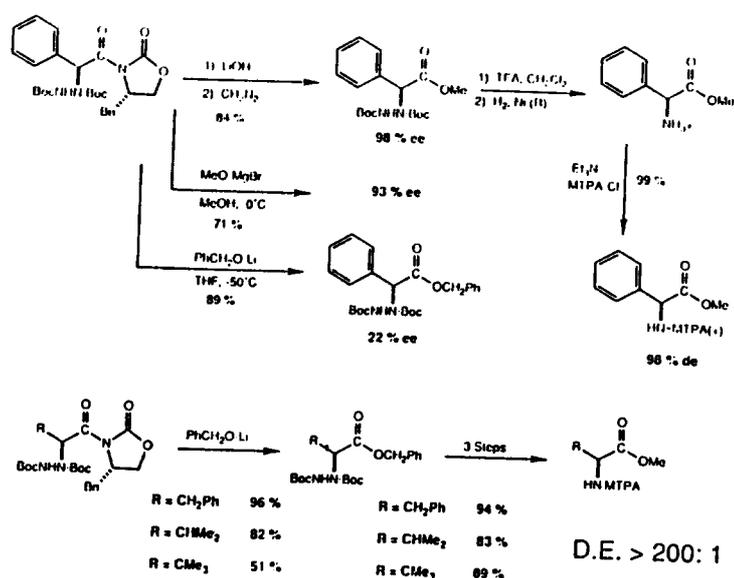
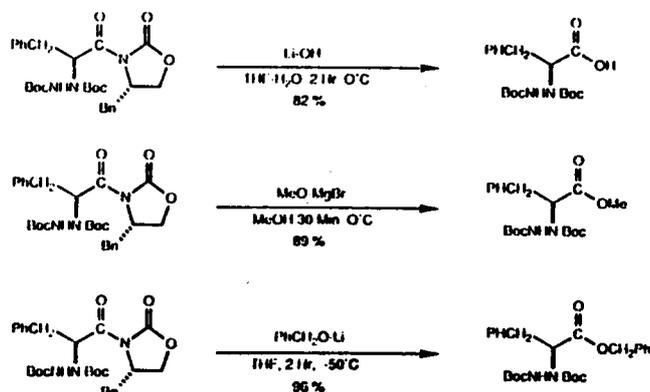
Asymmetric Enolate Amination



Asymmetric Enolate Amination



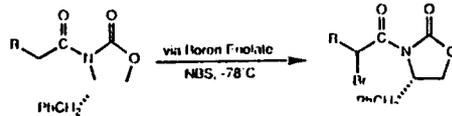
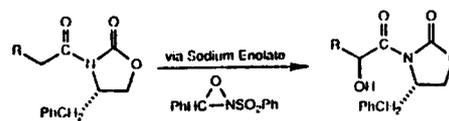
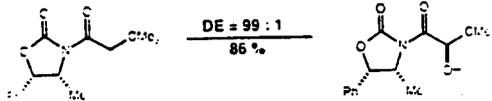
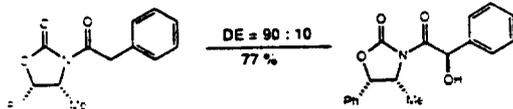
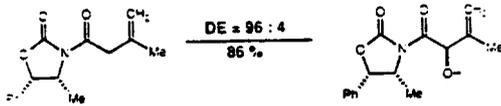
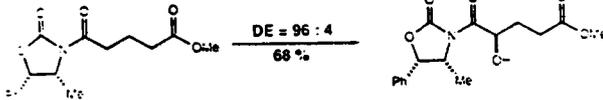
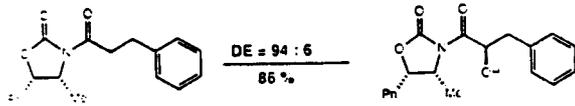
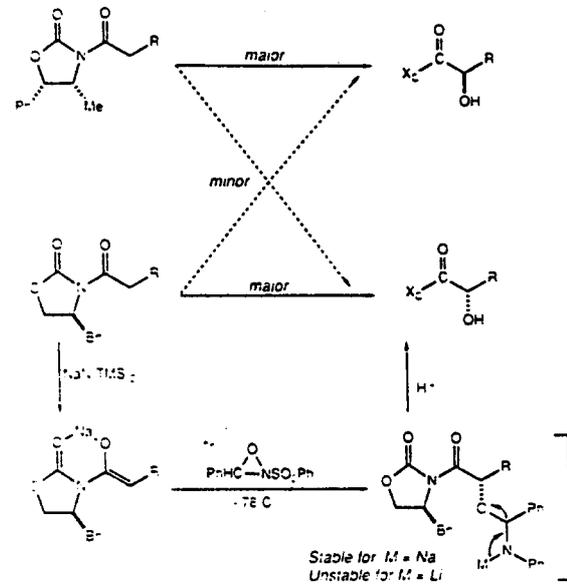
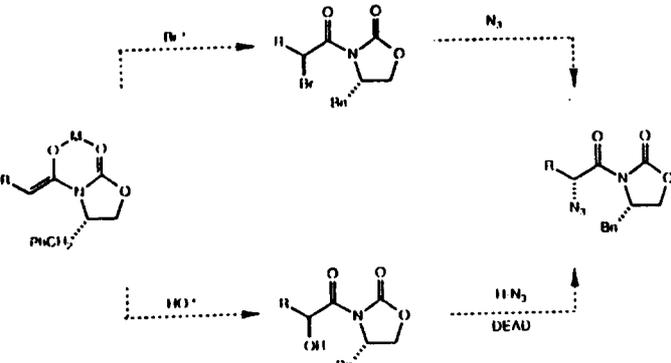
Stereoselective Transesterification & Hydrolysis



Enantiomeric purity was found to be greater than 99.5% in all cases.

Enolate Amination Alternatives

Asymmetric Enolate Hydroxylation

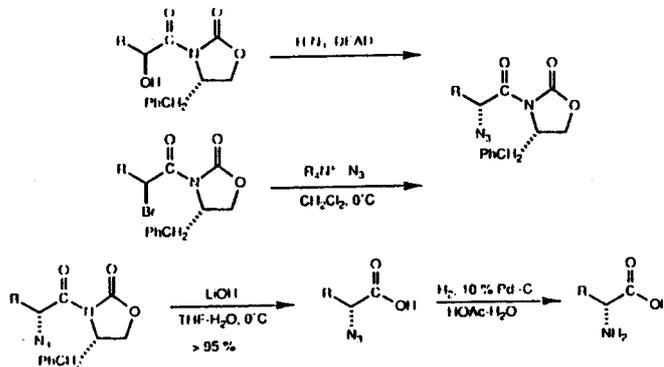


M = Li, Na
M = BR₂

M-NR₂
R₂BOTf, R₃N

R = Ph 90 : 10 77 %
R = CH₂Ph 95 : 5 86 %
R = CHMe₂ 99 : 1 86 %
R = CMe₃ 99 : 1 94 %

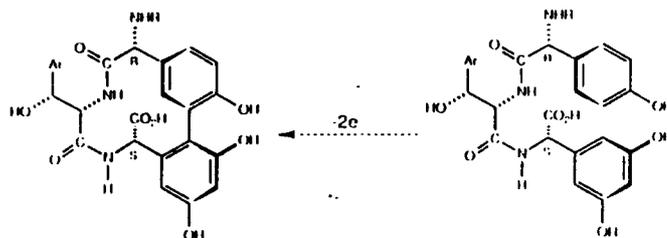
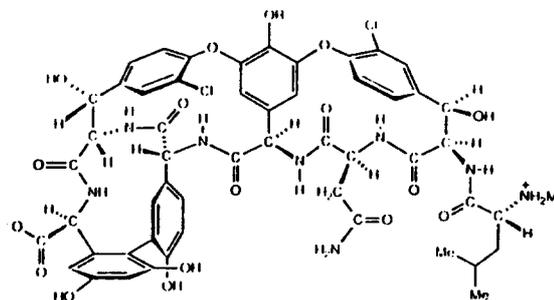
R = Ph 78 : 22 67 %
R = CH₂Ph 95 : 5 83 %
R = CH₂CHMe₂ 95 : 5 86 %
R = CHMe₂ 96 : 4 80 %

Overall Yield of
Optically Pure Acid

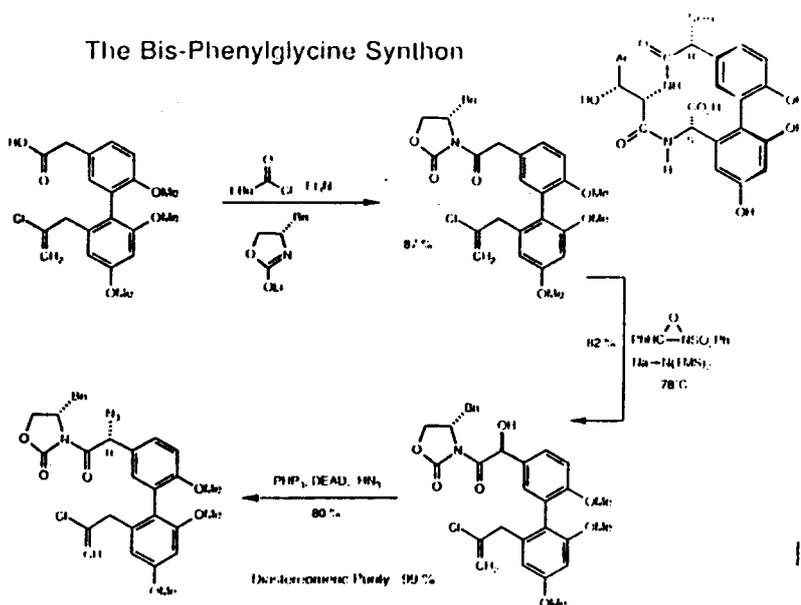
R = Ph 94 %
R = CH₂Ph 95 %
R = CH₂CHMe₂ 88 %
R = CHMe₂ 87 %

63
Vancomycin

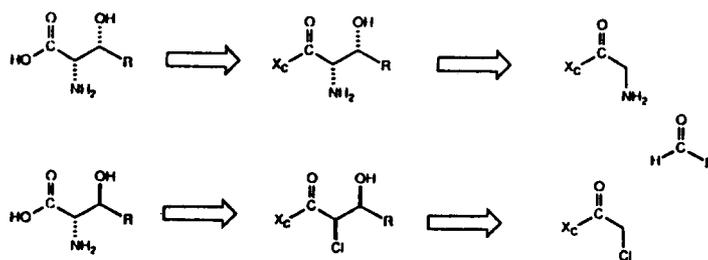
The BisPhenylglycine Synthase



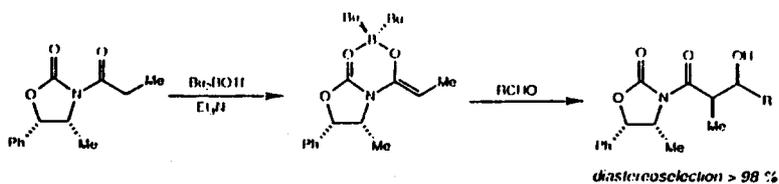
The Bis-Phenylglycine Synthase



β -Hydroxy α -Aminoacids: The Basic Plan



β -Hydroxy α -Aminoacids: Relevant Aldol Reactions

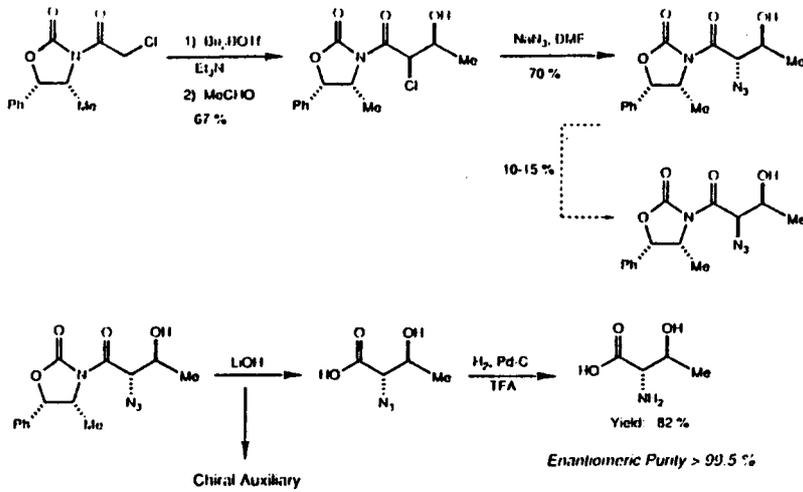


R	% DS	Yield
CH ₃	95	67 %
(CH ₃) ₂ CH-	96	75 %
C ₆ H ₅ -	97	79 %

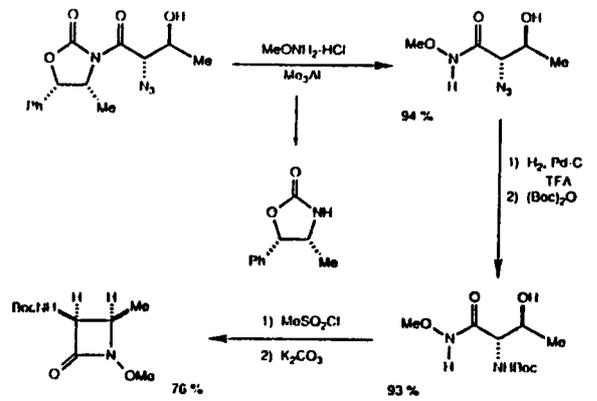
Observations:

- A. Starting chloroacetyl carboximide always recovered in 10-15 % yield.
- B. Reaction diastereoselection found to be time dependent

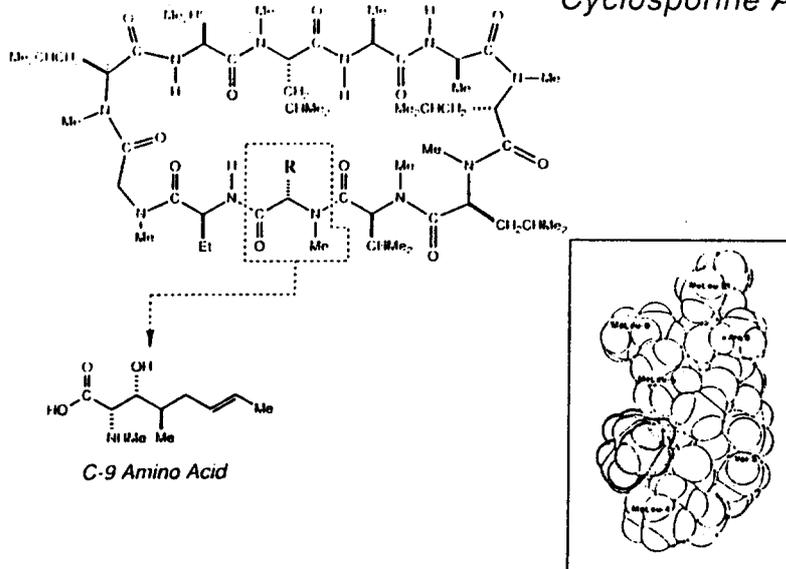
Allo-threonine Synthesis



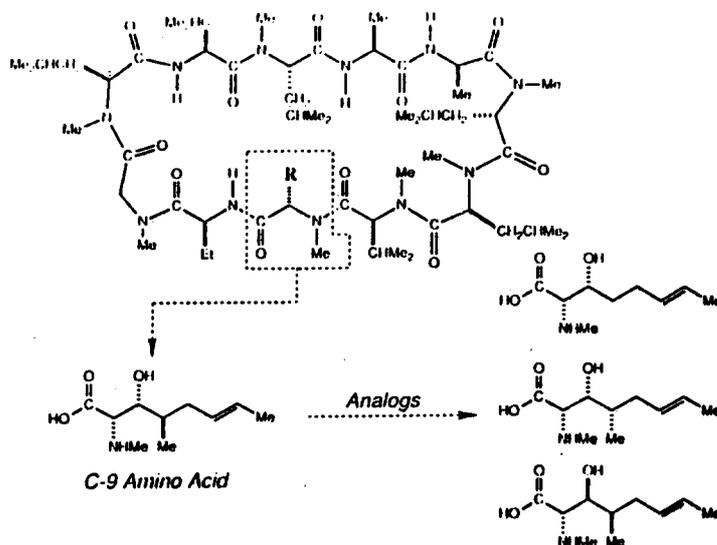
Monobactam Synthesis



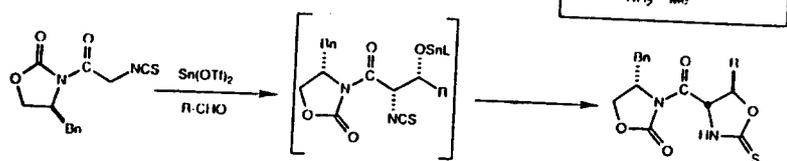
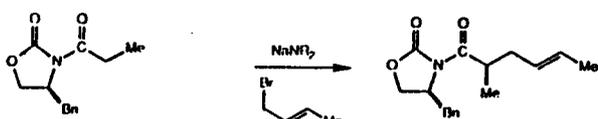
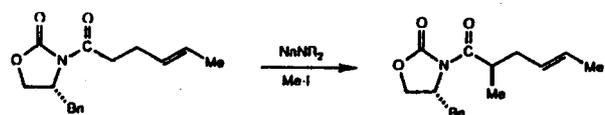
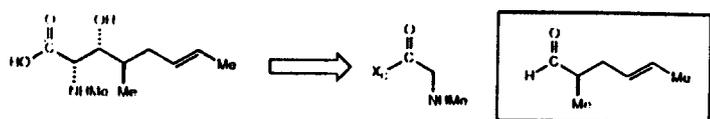
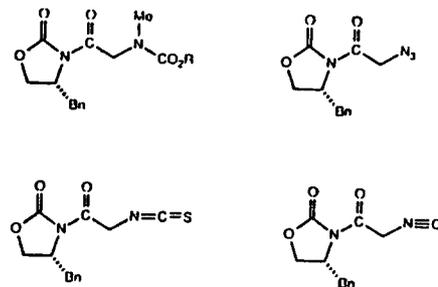
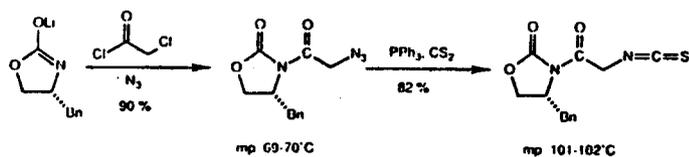
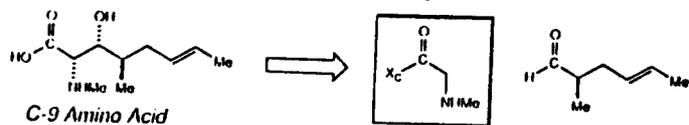
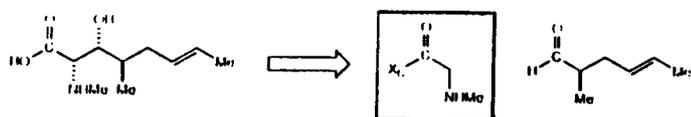
Cyclosporine A



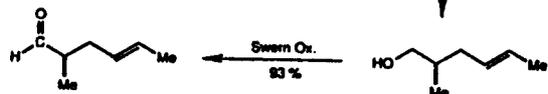
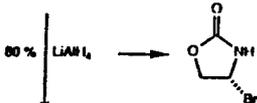
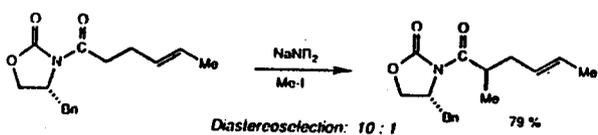
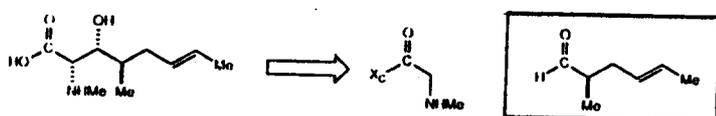
Cyclosporine A



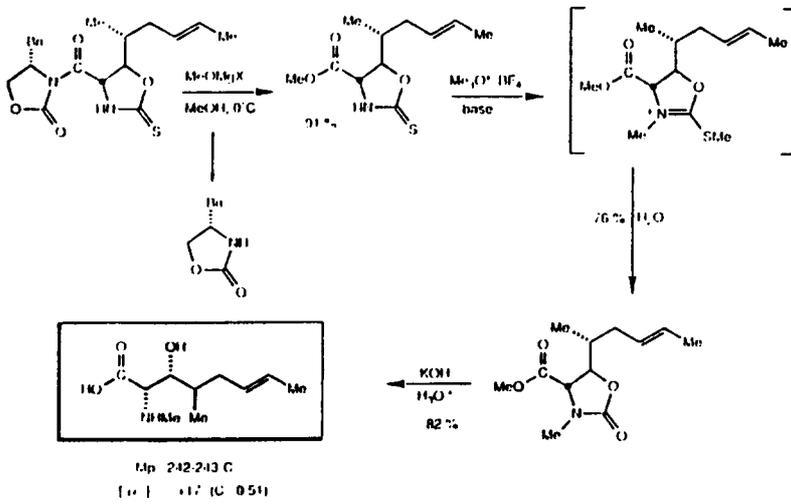
Chiral Glycine Enolate Synthons



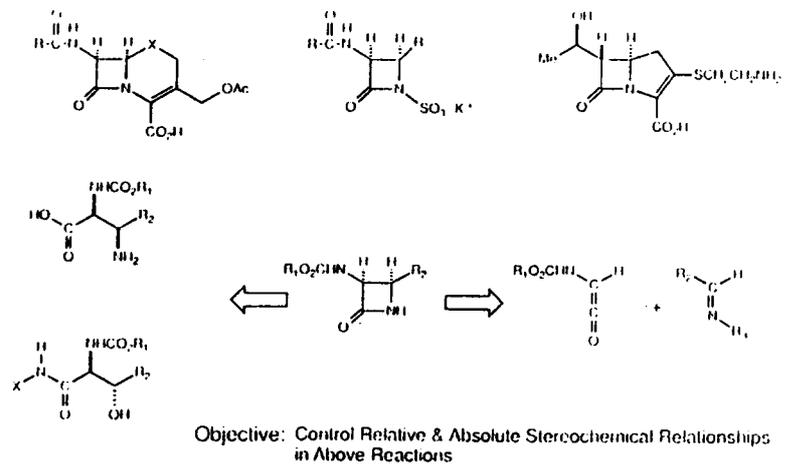
Structure	Diastereoselection	Yield
	94 : 6	73 %
	97 : 3	71 %
	93 : 7	81 %
	99 : 1	92 %



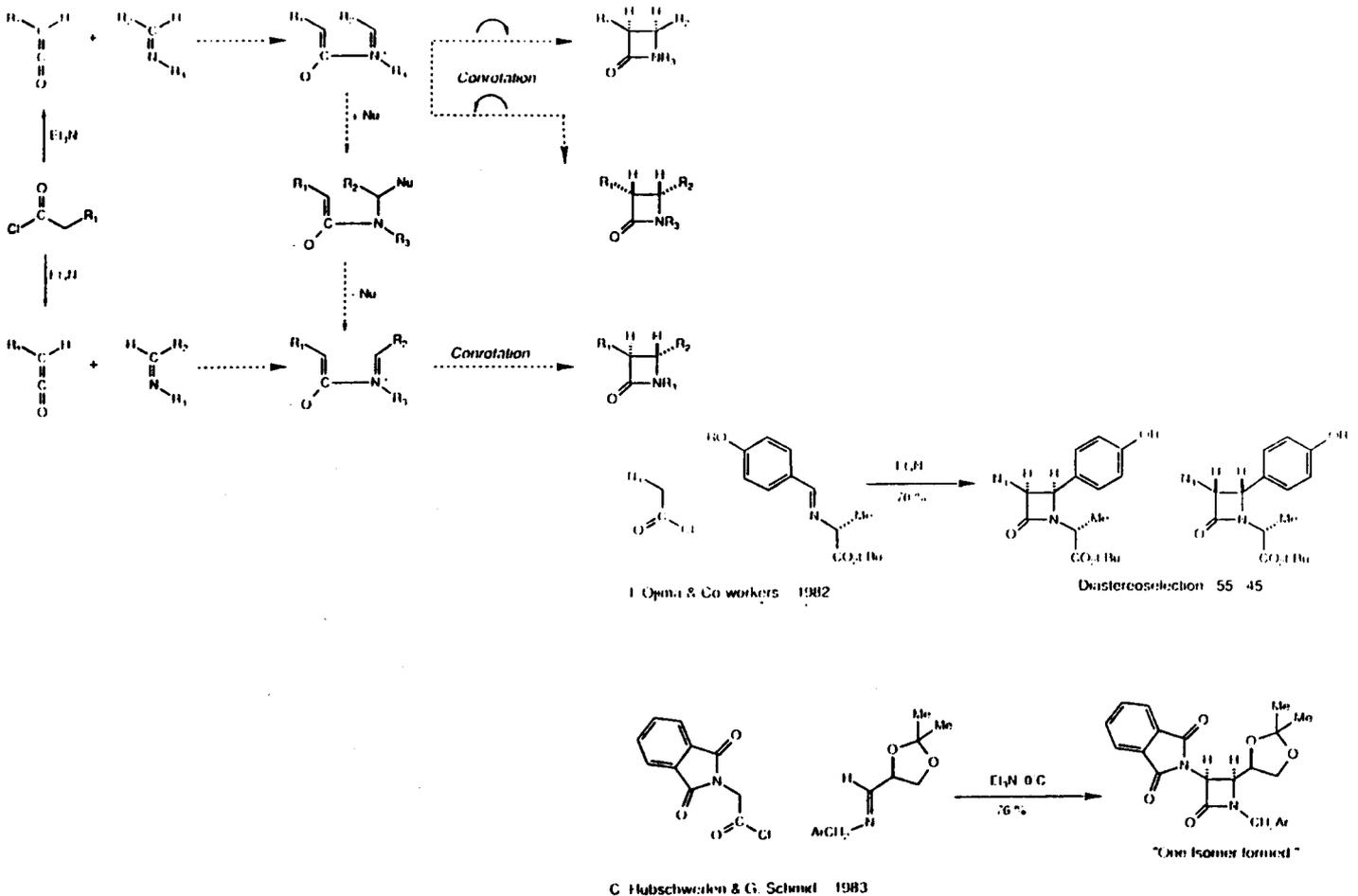
The Cyclosporin C-9 Amino Acid MeBmt



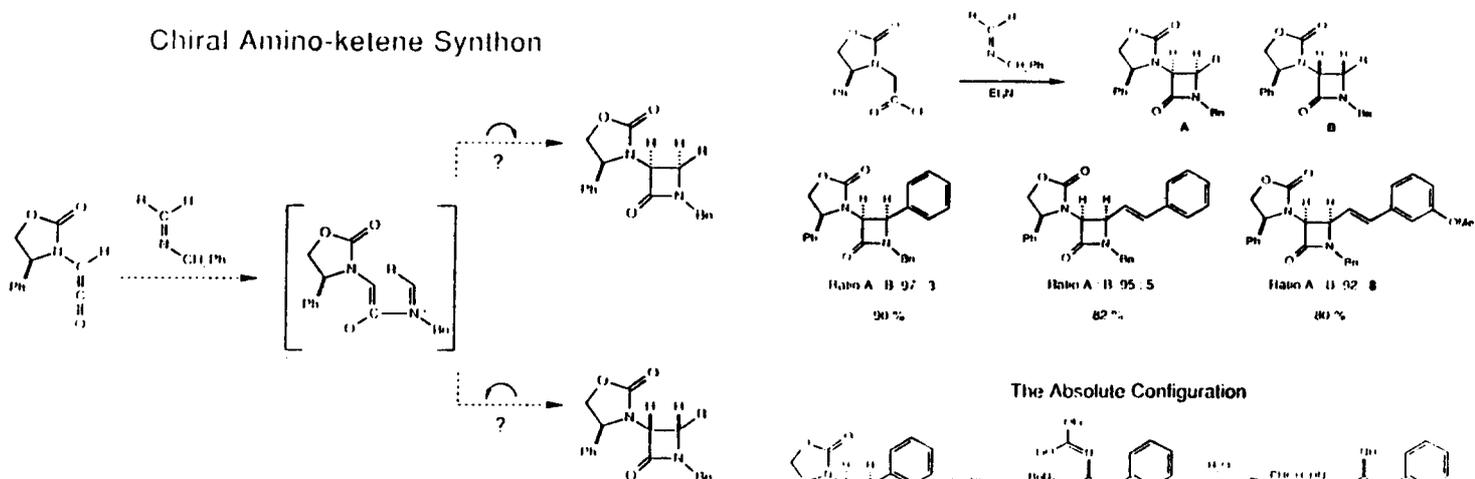
β -Lactam Antibiotics: Acyclic Precursors



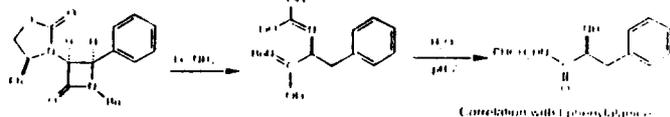
Kelene-Imine Cycloaddition: Internal Diastereoselection



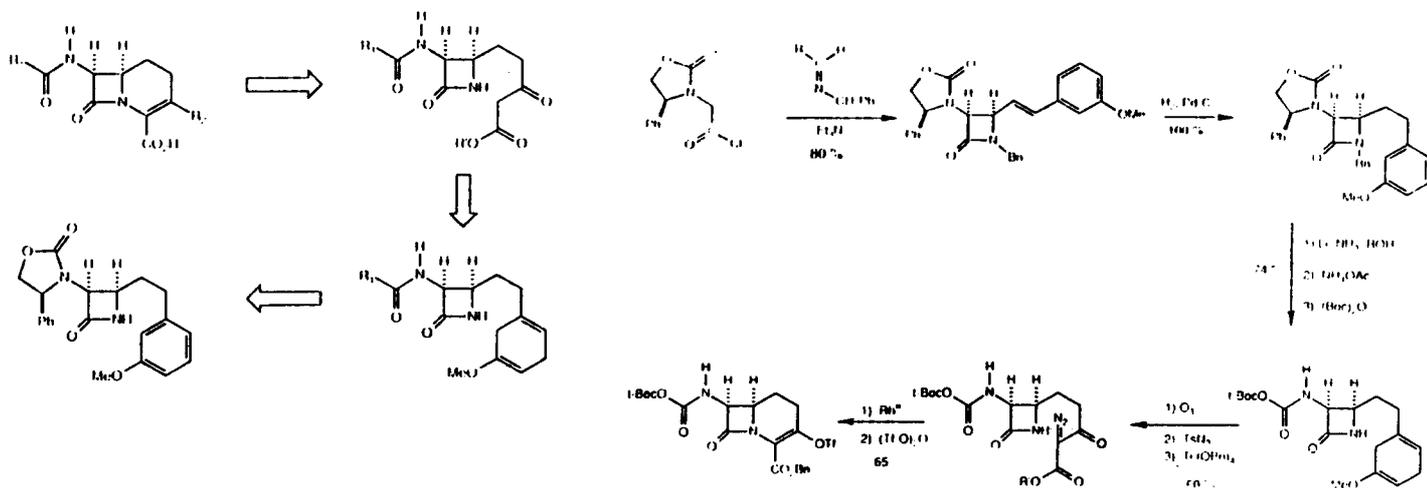
Chiral Amino-ketene Synthons



The Absolute Configuration



Carbacephalosporins: Retrosynthesis



Acknowledgments

The Aldol Studies: Dr. V. Novack & Dr. R. Metternich

The Erythronolide Project: Dr. R. Metternich

The Premonensin Project: M. Dimare

The Hydride Project: K. T. Chapman & E. Carrera

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Eli Lilly Company

National Institutes of Health

Merck Pharmaceuticals