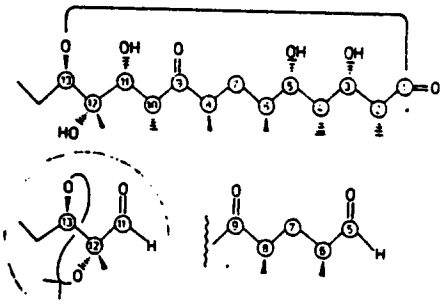
AS IT HAPPENED

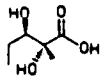
IN THE LABORATORIES OF
Reinhard W. Hoffmann
Philipps-Universität Marburg

EN ROUTE TO THE "LEFT HAND" PORTION
OF MACROLIDE-ANTIBIOTICS

6-Desoxy-
Erythronolid A



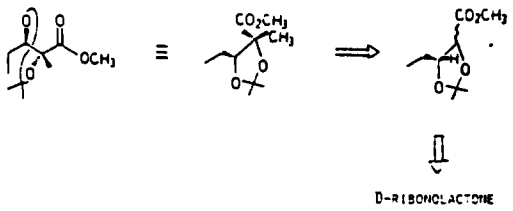
PREVIOUS APPROACHES



Bergelson's acid	resolved
S. Masamune	1979
M. Yamaguchi	1979
J.D. White	1979

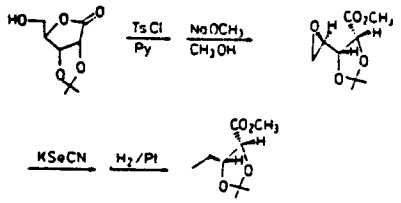
racemic	
P.A. Grieco	1979
E.J. Corey	1979
C. Santelli-Rouvier	1982

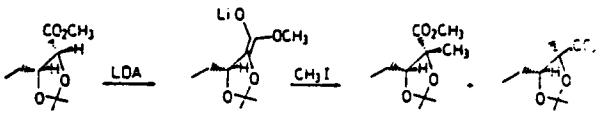
THE CONCEPT:



D-RIBONOLACTONE

THE REALIZATION:



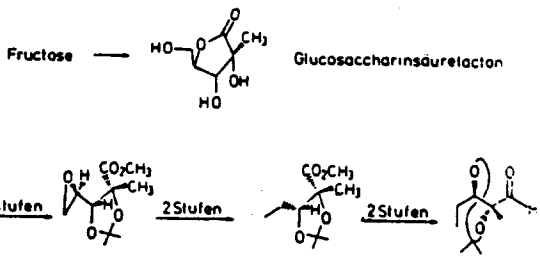


HERE IT HAPPENED:

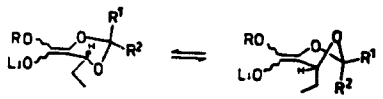
W. LADNER

EXPECTED	90	: 10
FOUND	13	: 87

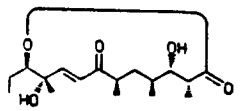
PROVEN BY INDEPENDENT SYNTHESIS



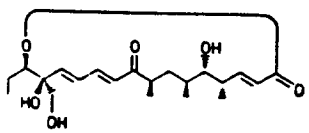
A POSSIBLE CAUSE?



IF YOU CAN'T CHANGE THE REACTION
CHANGE YOUR TARGET!

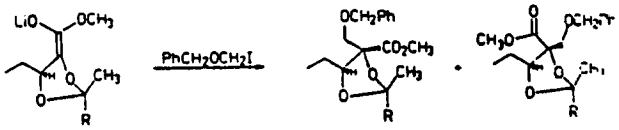


Methynolid

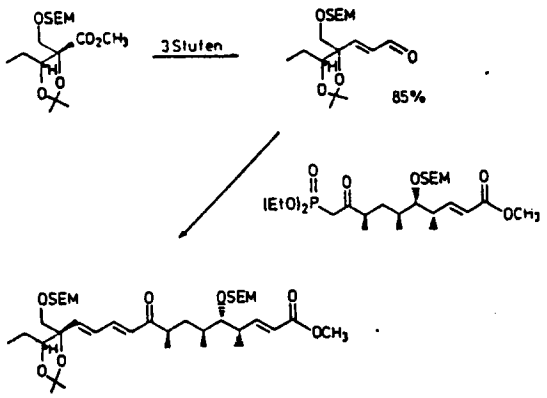


Mycinolid V

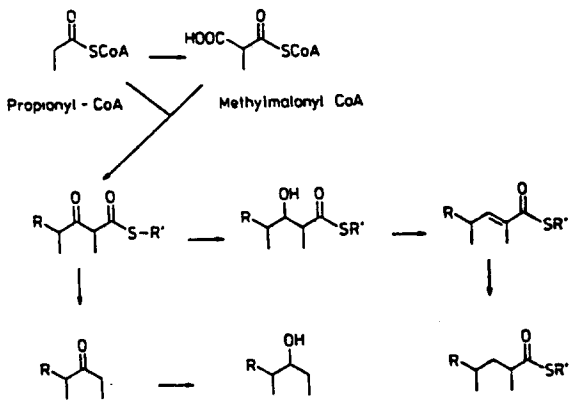
K: DITRICH'S WAY TO MYCINOLIDE V



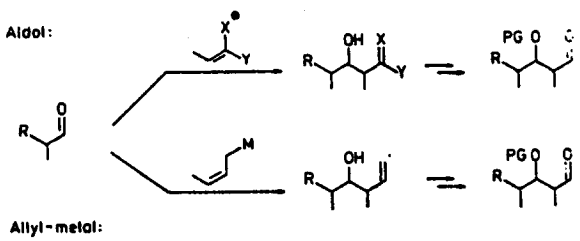
R=CH_3	95%	75 : 25
R=$(CH_3)_3C$	57%	>95 : <5



HOW NATURE DOES IT:



HOW THE CHEMIST COULD DO IT:

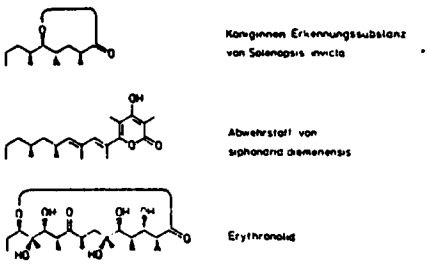


ALLYLBORONATES

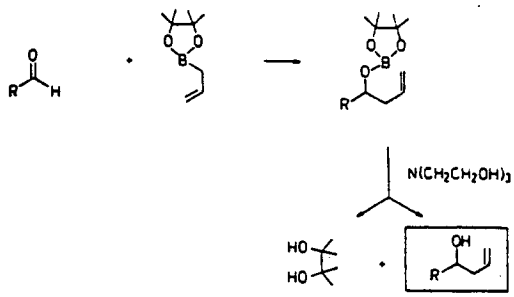
DEFINED ORGANOMETALLIC REAGENTS FOR DEFINED STEREOSELECTION

Reinhard W. Hoffmann
Fachbereich Chemie der
Philipps-Universität Marburg

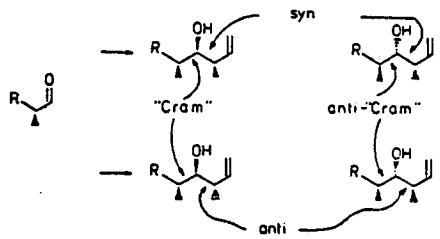
Propionate-derived Natural Products
Target Molecules for Stereoselective Synthesis



OUR WAY TO DO IT:

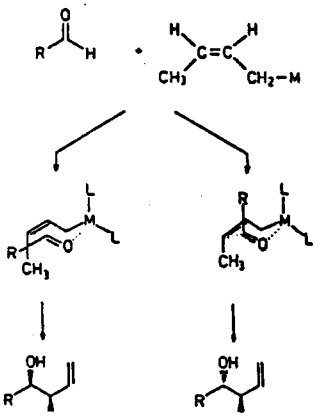


PARAMOUNT, THE PROBLEM OF CREATING EACH OF THE STEREOCHEMICAL TRIPLETS SELECTIVELY !

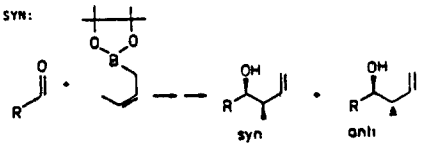


A SIMPLER PROBLEM, STEREOCHMICAL DUBLETS, SYN/ANTI

Diastereomere Übergangszustände

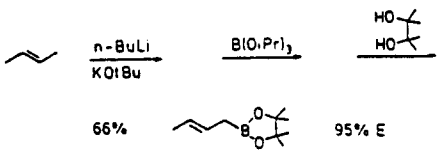


Z GIVES SYN:



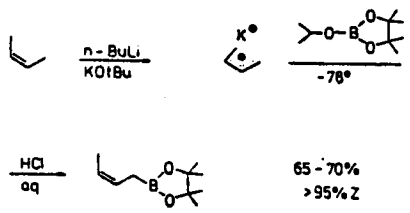
	syn	anti
R = CH_3-	> 96	< 4
Ø -	> 96	< 4
$(CH_3)_2CH$-	94	6

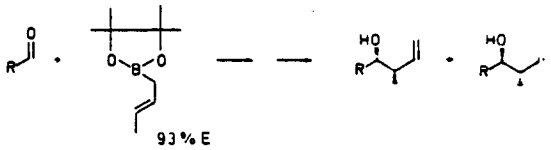
AND E GIVES ANTI:



66% 95% E

REQUIRES STEREOHOMEGENEOUS CROTYLBORONATES:

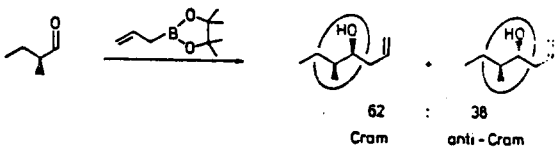




93 % E

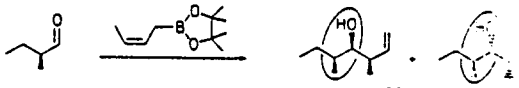
R = CH_3-	7	93
C_6H_5 -	6	94
$(CH_3)_2CH$ -	4	96

THE OTHER STEREOCHMICAL DUBLET:
CRAM-/ANTI-CRAM-SELECTIVITY

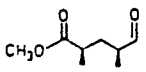


62 : 38
Cram anti-Cram

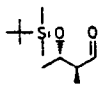
REVERSED SELECTIVITY WITH Z-CROTYLBORONATES



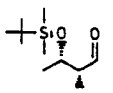
syn 30 70 anti



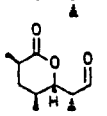
40 60



9 91



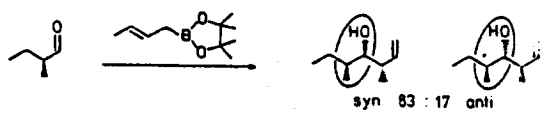
40 60



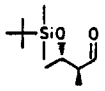
30 70

INCREASED SELECTIVITY WITH E-CROTYLBORONATES:

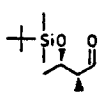
1,2 - Asymmetric Induction with E-Crotyl



syn 83 : 17 anti

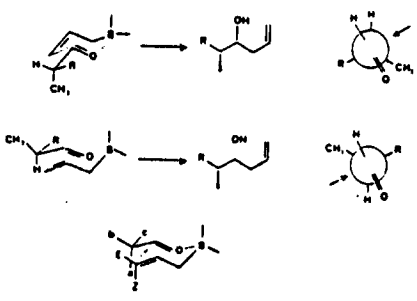


95 : 5

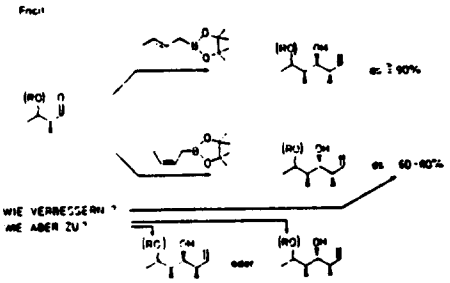


(98 : 2)

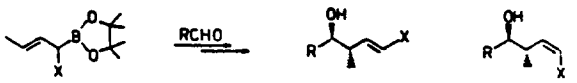
ALLOWS FIRST EXPERIMENTAL INVESTIGATION INTO THE ORIGIN OF 1,2-ASYMMETRIC INDUCTION:



WHERE ARE WE WITH RESPECT TO THE SYNTHESIS OF THE STEREOCHMICAL TRIPLETS?



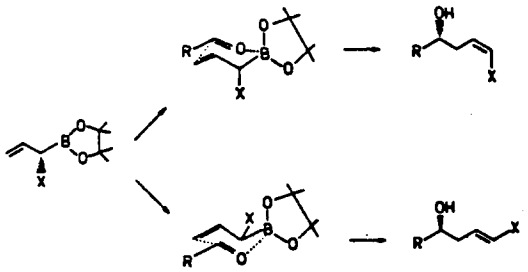
ASYMMETRIC INDUCTION FROM α-CHIRAL CROTYLBORONATES CAN BE EVALUATED IN THE RACEMIC SERIES:



X = CH_3	R = Pr	28	:	72	
X = $Si(CH_3)_3$	R = Ph	13	:	87	(D.S.Matteson)
X = Cl	R = Ph, Pr	3	:	97	

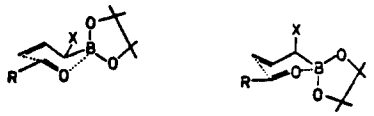
REQUIRES CHIRAL REAGENTS OF HIGH ASYMMETRIC INDUCTION
- REAGENT CONTROL OF STEREOSELECTIVITY -

α -CHIRAL ALLYLBORONATES :



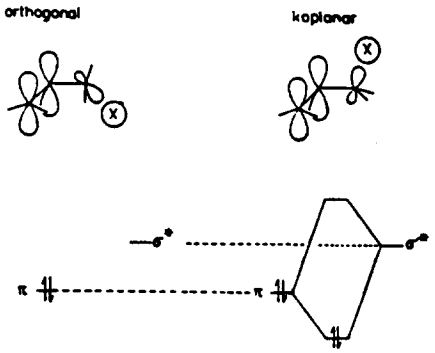
THE MORE POLAR C-X, THE MORE PRODUCT WITH Z-CONFIGURATION OF THE DOUBLE BOND

= PREFERENCE FOR AXIAL DISPOSITION OF THE C-X-BOND IN THE TRANSITION STATE!



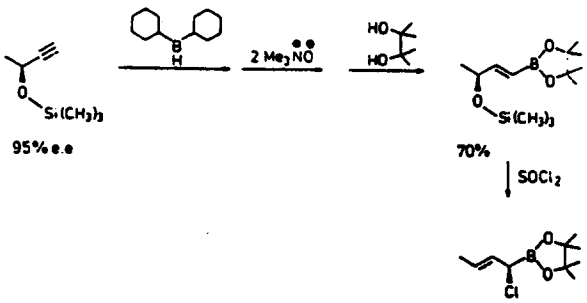
π →σ*- Wechselwirkung in Allylsystemen

A POSSIBLE EXPLANATION:

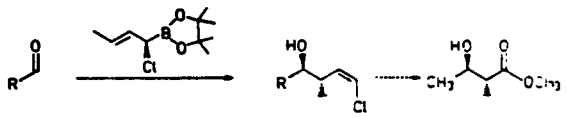


S.Schreiber (1983), K.Houk (1984), S.Danishefsky (1985)

α -CHLORO-CROTYLBORONATES OF HIGH e.e.

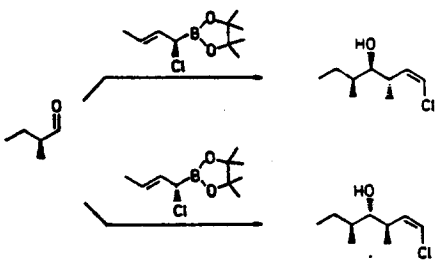


ASYMMETRIC INDUCTION ON ADDITION TO ACHIRAL ALDEHYDES

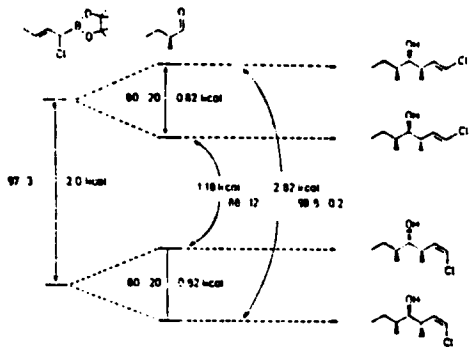


R = CH_3-	92% ee
= CH_3-CH_2-	96% ee
= $(CH_3)_2$CH-	95% ee
= C_6H_5-	96% ee

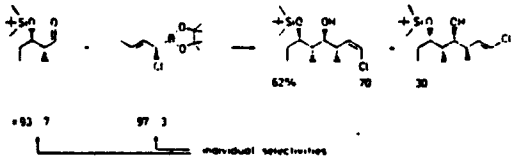
DOUBLE STEREODIFFERENTIATION AND REAGENT CONTROL OF STEREOSELECTIVITY ON ADDITION TO CHIRAL ALDEHYDES



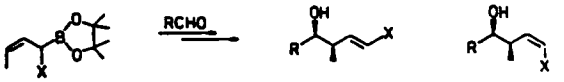
NUMERICAL EVALUATION OF COMPETING TRANSITION STATES REVEALS WHERE THE CRUCIAL PROBLEM IS:



AND WHERE THE PRESENT LIMITATIONS OF OUR METHOD ARE

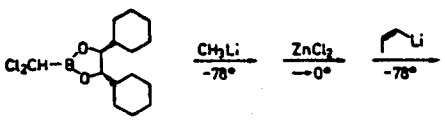


WHAT ARE THE CHANCES FOR α-CHIRAL-Z-CROTYLBORONATES?

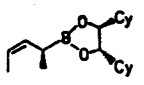


X = $Si(CH_3)_3$	R = Ph	90	: 10	(D.S.Matteson)
X = Cl	R = Pr	90	: 10	
X = CH_3	R = Pr	>95	: <5	

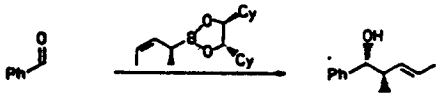
SYNTHESIS



75%

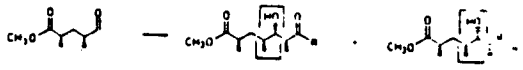


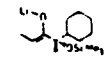
AND PERFORMANCE

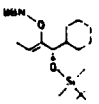


99.5% e.e.

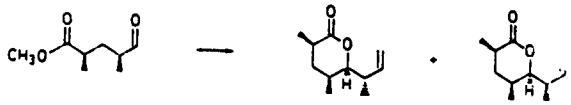
ANOTHER STEREOCHEMICAL TRIPLET:
EARLIER SOLUTIONS BY ALDOL-ADDITION

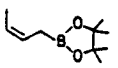


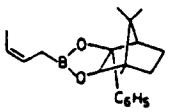


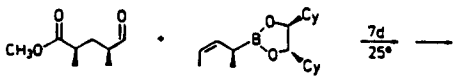


BY ALLYL-METAL-ADDITION









85% ds >95%

THE MAN WHO DID IT:

CH_3-CH=CH-CH_2-B(OR)$_2$	H.J.ZEIß
CH_3-CH=CH-CHX-B(OR)$_2$	S.DRESELY, G.KÖSTER, H.J.LANZ, K.STÜRMER, K.DITRICH
CRAM-/ANTI-CRAM	U.WEIDMANN

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