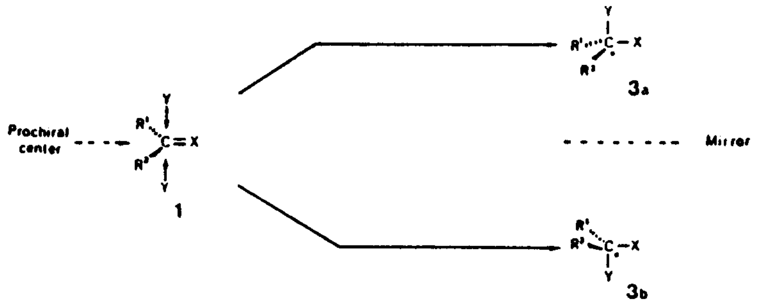
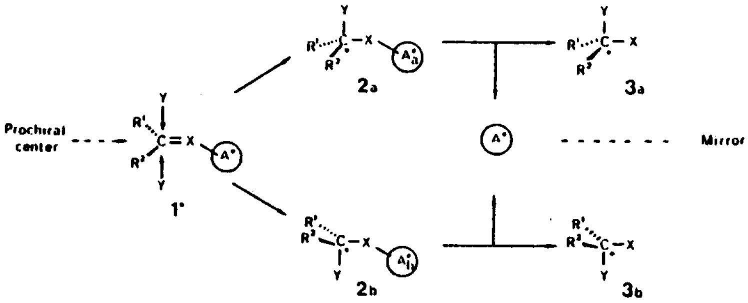
π - FACE STEREODIFFERENTIATION



π - FACE STEREODIFFERENTIATION

1 → 2 : Diastereoselection
1 → 3 : Enantioselection



CRITERIA FOR CHIRAL AUXILIARY GROUP A*:

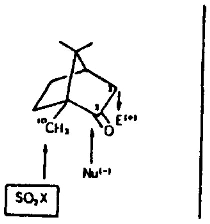
(1) Key Step 1 → 2
- a) Compatibility with a large range of substituents R^1, R^2 etc.
- b) High chemical yield
- c) High and predictable π-face-differentiation
- d) High diastereoselection (e.g. endo-selectivity in Diels-Alder reactions)
- e) Facile purification of the major product 2

(2) Easy availibility of both enantiomers A^*_a and A^*_b

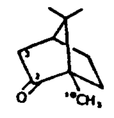
(3) Efficient attachment and non-destructive removal of A* with complete stereochemical retention

(4) Crystallinity of intermediates and products

CAMPHOR A CONFORMATIONALLY RIGID CHIRAL VEHICLE IN ORGANIC SYNTHESIS

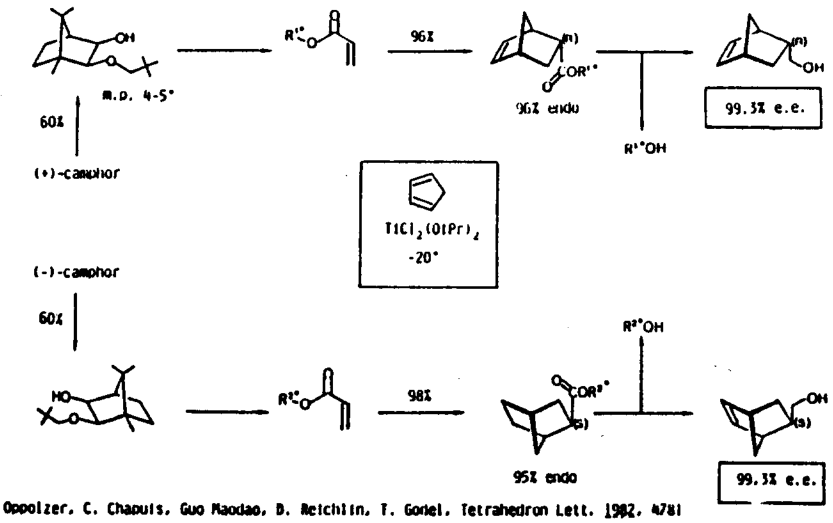


(+) - Camphor



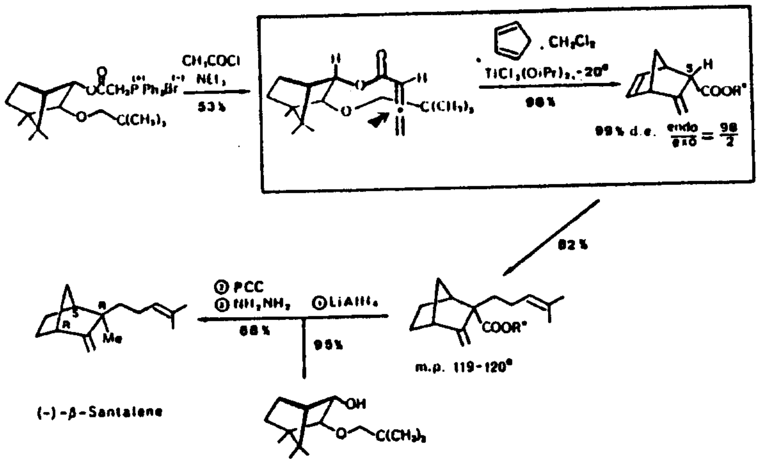
(-) - Camphor

ASYMMETRIC DIELS-ALDER ADDITIONS OF CYCLOPENTADIENE
TO CIS-NEOPENTYLOXYISOBORNYL ACRYLATES



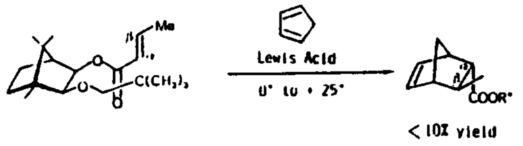
W. Oppolzer, C. Chapuis, Guo Maodao, D. Reichlin, T. Godel, Tetrahedron Lett. 1982, 4781

ENANTIOSELECTIVE SYNTHESIS OF (-)-β-SANTALENE



W. Oppolzer & C. Chapuis. Tetrahedron Lett. 24 (43), 4665 (1983).

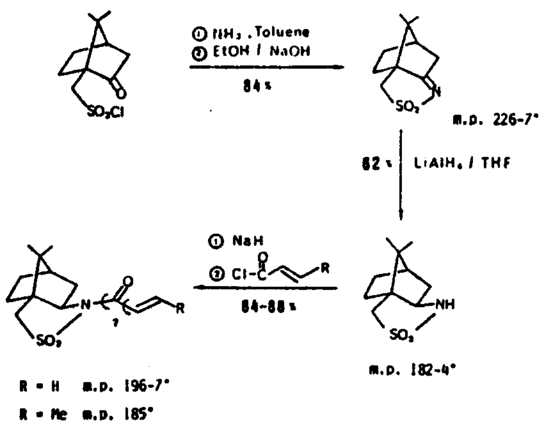
ATTEMPTED DIELS-ALDER ADDITION OF CYCLOPENTADIENE TO NEOPENTYLETHER SHIELDED CROTONATE.



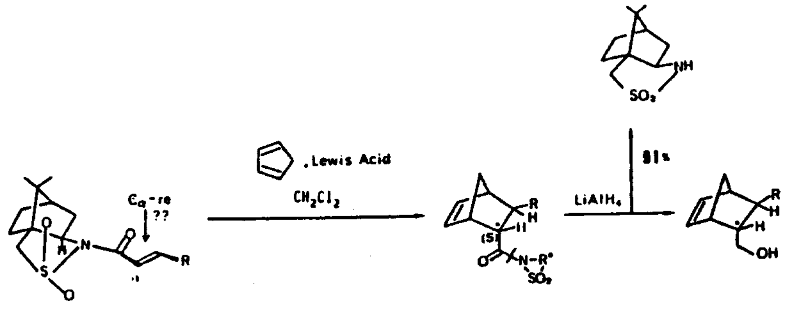
< 10% yield

∴ Steric hindrance of C_α, C_β-tetragonalizations.

CAMPHOR-DERIVED N-ACYL SULTAMS: PREPARATION



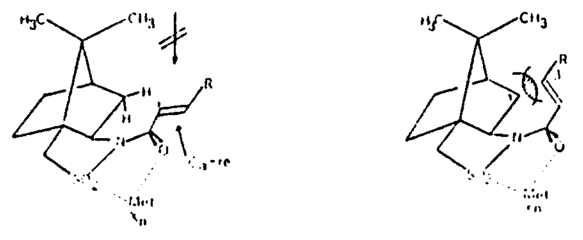
HIGHLY ACCELERATED ASYMMETRIC DIELS-ALDER ADDITIONS TO N-ACRYLOYL AND N-CROTONOYL SULTANS



R	Lewis Acid(eq)	Reaction Temp.	Endo% (C=0)	d.e.% crude	d.e.% cryst.	m.p.°C cryst.	Yield cryst.
H	none	+ 25°	89	66			
Me	none	+ 25°	78	53			
H	$EtAlCl_2$ (1.5)	-130°	99.5	95	99	185.5-7	84
Me	$TiCl_4$ (0.5)	- 78°	99	93	99	184-5	83

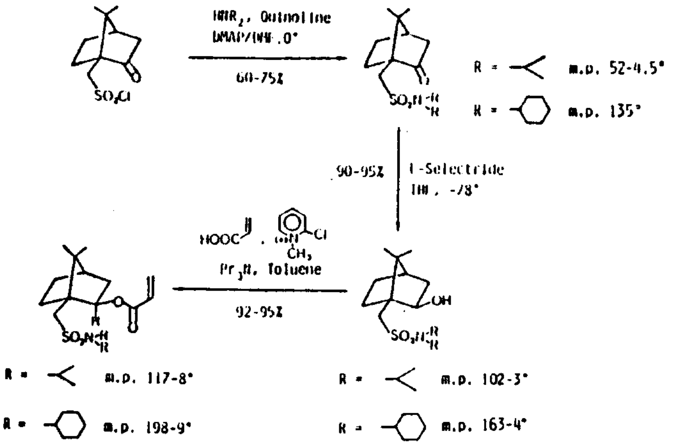
W. Oppolzer, Ch. Chapuis, G. Bernardinelli, Helv. Chim. Acta 67, 1397 (1984)

ASYMMETRIC DIELS-ALDER ADDITIONS TO CAMPHOR-DERIVED N-ACYL SULTAMS: TENTATIVE RATIONALIZATION.



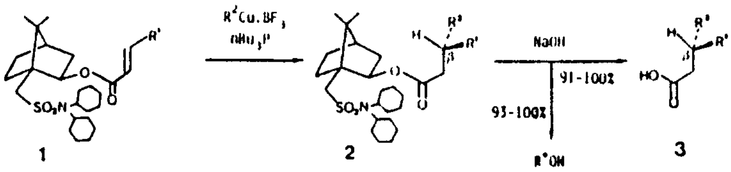
PRACTICAL ASYMMETRIC DIELS-ALDER ADDITION:

PREPARATION OF 10-SULFONAMIDO-ISOBORNYL ACRYLATES



W. Oppolzer, Ch. Chapuis, G. Bernardinelli, Tetrahedron Lett., 25, 5885 (1984)

ASYMMETRIC 1,4-ADDITIONS OF ORGANOCOPPER REAGENTS TO SULFONAMIDE-SHIELDED ISOBORNYL-ENOATES

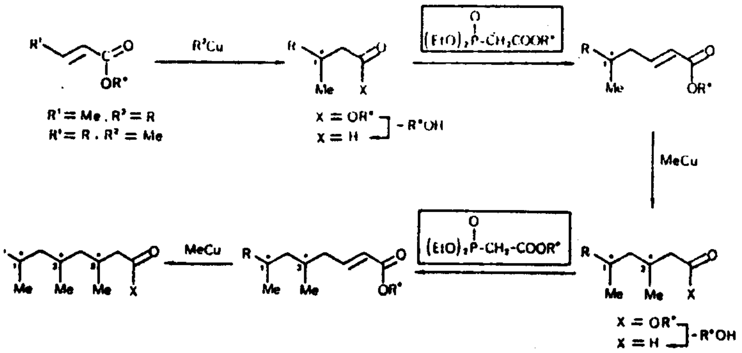


R^1	R^2	Molequiv. R^2Cu	Yield% of 2	e.e.% of 3
Me	nPr	2	98	95 (97)$^{a)}$
Me	nBu	2	89	97
Me	vinyl	10	80	98
Me	2-propenyl	10	84	94
nPr	Me	10	65	93
nBu	Me	10	93	97

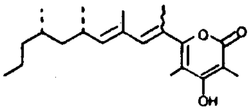
a) after crystallization

W. Oppolzer, Ph. Dudfield, Th. Stevenson, Th. Godel, Helv. Chim. Acta 68, 212 (1985)

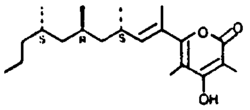
THE PHOSPHONATE - CHIRON APPROACH TO "DESOXY-POLYPROPIONATE" CHAINS.



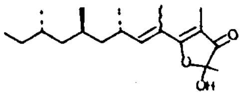
"DESOXY-POLYPROPIONATE" METABOLITES OF PULMONATES

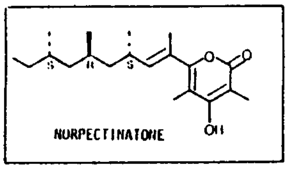


(E): DIEMENSIN-A
(Z): DIEMENSIN-B
D.J. Faulkner et al.
Tetrahedron Lett. 1983, 1917.



PECTINATONE
C. Ireland et al.
Tetrahedron Lett. 1983, 3055.

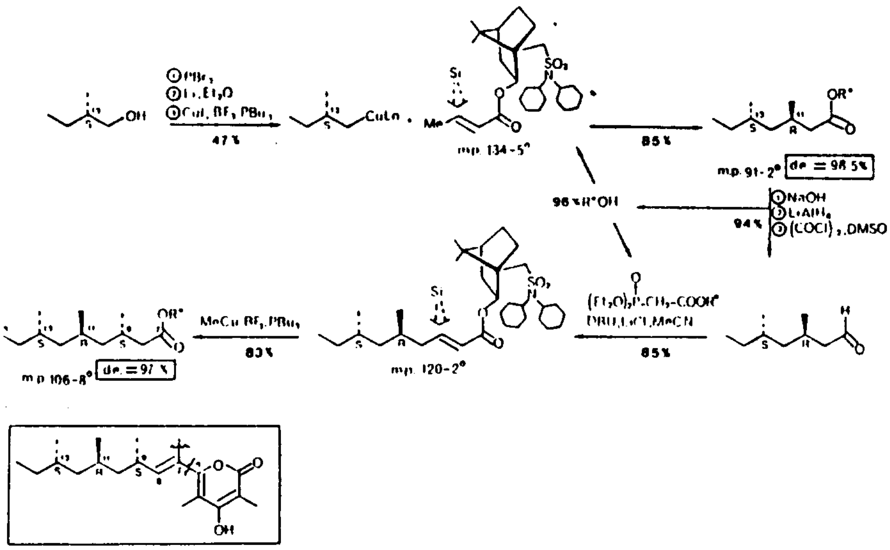




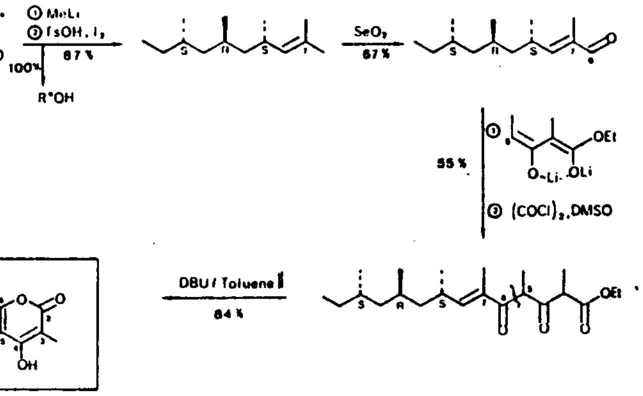
NORPECTINATONE

D.J. Faulkner et al. J. Org. Chem. 49, 2506 (1984).

ENANTIOSELECTIVE SYNTHESIS OF "NORPECTINATONE": ASSEMBLY OF C-7/C-15 - CHAIN.



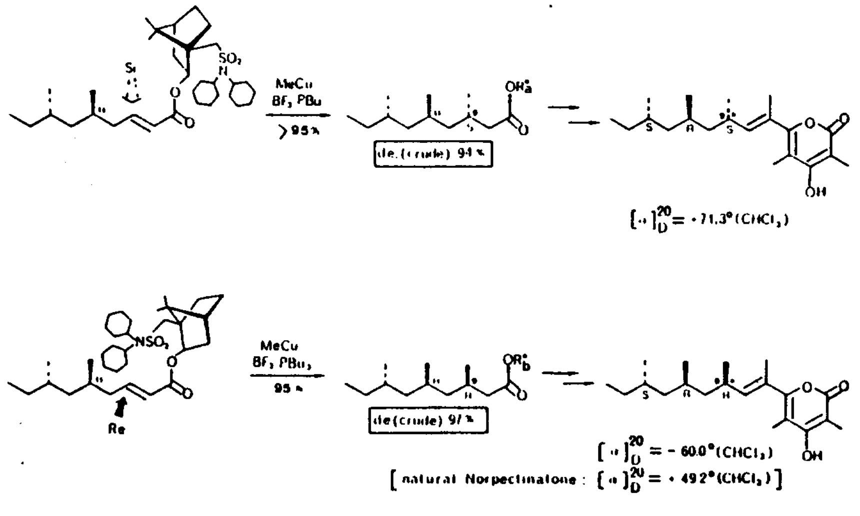
ENANTIOSELECTIVE SYNTHESIS OF "NORPECTINATONE": THE (E)-C-7/C-8-CONJUGATED 4-HYDROXY-α-PYRONE UNIT.



Natural: oil ; [α]$_D$ +49.2°(c=2.5,CHCl$_3$); UV(EtOH): 300 nm (ε 7600), 232 nm (ε 13100).

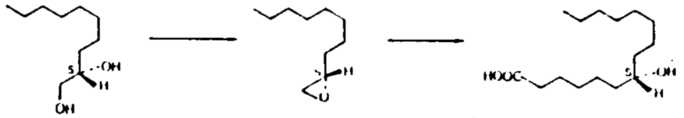
Synth.:m.p. 101-6°, [α]$_D$ +71.3°(c=1.1,CHCl$_3$); UV(EtOH): 300nm (ε 10450), 231.9 nm (ε 19430)

ENANTIOSELECTIVE SYNTHESIS OF "NORPECTINATONE": AUXILIARY-DIRECTED GENERATION OF C-9-EPIMERS.



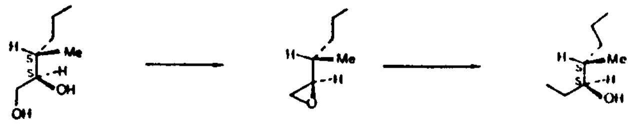
∴ Auxiliary overrides influence of 3-positioned center C-11.

SYNTHESES OF CHIRAL NATURAL PRODUCTS FROM 1,2-DIOLS



Spore germination inhibitor
in Lygodium japonicum

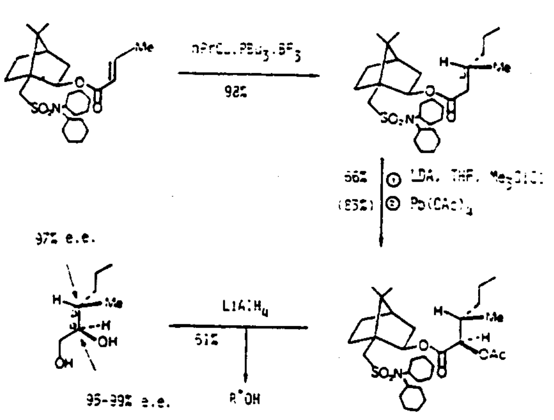
Y. Masaoka, M. Sakakibara, K. Mori, Agric. Biol. Chem. 46, 2319 (1982)



Pheromone of Elm Bark Beetle

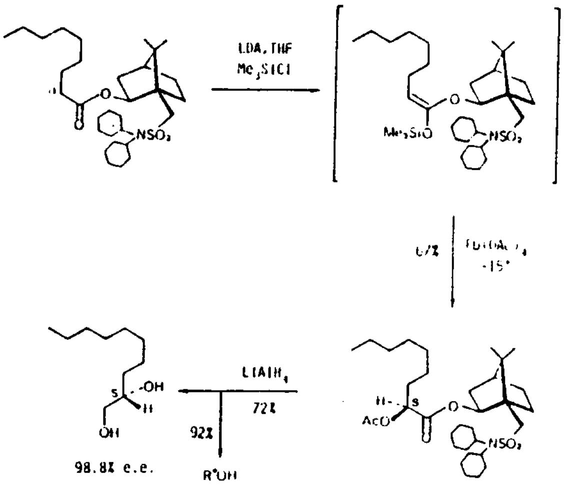
K. Mori, H. Iwasawa, Tetrahedron 36, 2209 (1980)

ASYMMETRIC SYNTHESIS OF (2R,3S)-3-METHYL-HEXAN-1,2-DIOL BY α- AND β-FUNCTIONALIZATION OF A CROTONATE

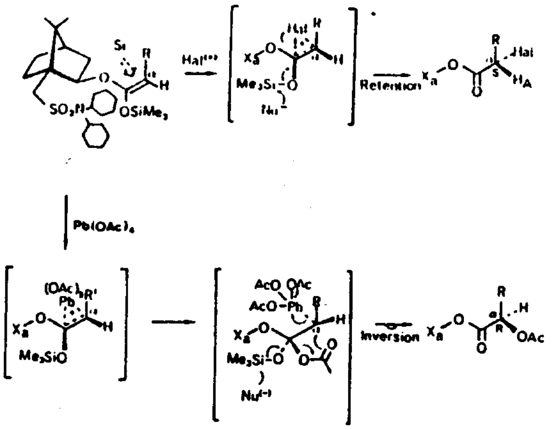


W. Oppolzer, Ph. Dudfield, Helv. Chim. Acta 68, 216 (1985)

ASYMMETRIC ACETOXYLATION OF SULFONAMIDE-SHIELDED O SILYLKETENE ACETALS. APPLICATION



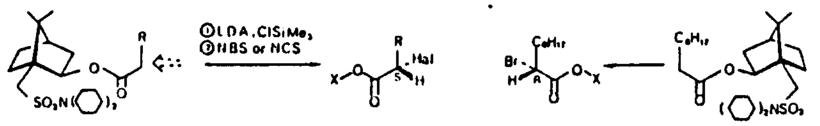
ASYMMETRIC HALOGENATION: ANALOGY TO ACETOXYLATION

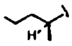


① C_α -Si- Attack by Hal^+

② Opposite Face-Differentiation of C.Hal versus C.O - Bond Formation

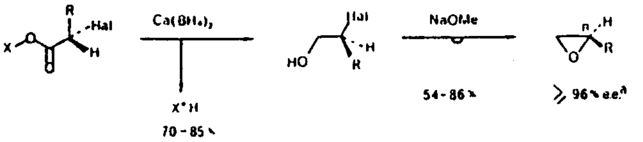
ASYMMETRIC HALOGENATION OF CARBOXYLIC ACID - ESTERS.



R	Hal	yield % cryst.	d.e % cryst. [a]	d.e % [a] cryst.	yield % cryst.
nC_8H_{17}	Cl	62	>99	>96	68
CH_3	Cl	77	98		
nC_4H_9	Br	68	>96		
nC_4H_9	Cl	67	>96		
C_6H_5	Cl	54	>96		
	Br	66	>96		
 H'	Br	59	>96		

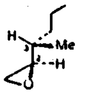
a) ^{1}H-NMR and HPLC

CONVERSION OF α-HALOESTERS TO ENANTIOMERICALLY PURE HALOHYDRINS AND EPOXIDES.



a) Complexation Capillary GC
(CHIRA METAL NI-R-CAM/SE 54, V. Schurig et al)

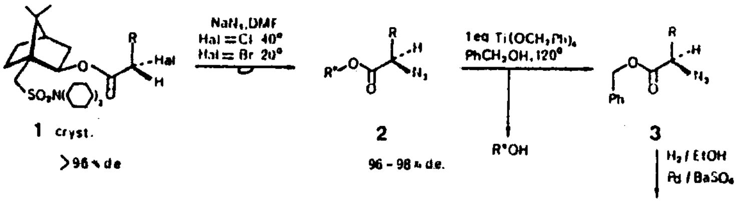
e.g.



> 98 % e e a (2R,3R)

W. Oppolzer, Ph. Dudfield, Tetrahedron Lett. 26, 5037 (1985)

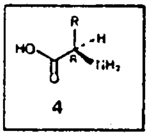
ASYMMETRIC SYNTHESIS OF α-AMINO ACIDS:



1 cryst.
>98 % de

2
96 - 98 % de.

3



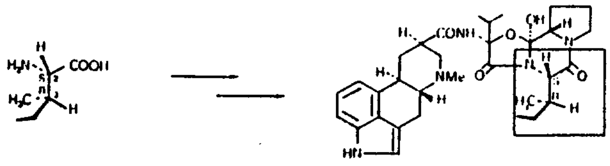
4

R	Overall Yield 1 4	Purification of 2	d.e. %[a] of 2	e.e. %[b] of 4
nC_4H_9	63	cryst.	96.0	94.4
$(CH_3)_2CHCH_2$	70	cryst.	98.0	96.4
nC_6H_{13}	70	flash chrom.	100.0	98.0
CH_2Ph	57	cryst.	95.0	94.7
C_2H_5	63	cryst.		94.0
n-C_3H_7	81	cryst.	97.0	95.7

a) HPLC

b) Capillary GC Chirasil Val of N-trifluoroacetyl propionates

EPICRIPTINE Ⓢ : ALLOISOLEUCINE-DERIVED PSYCHOTROPIC ERGOT PEPTIDE.

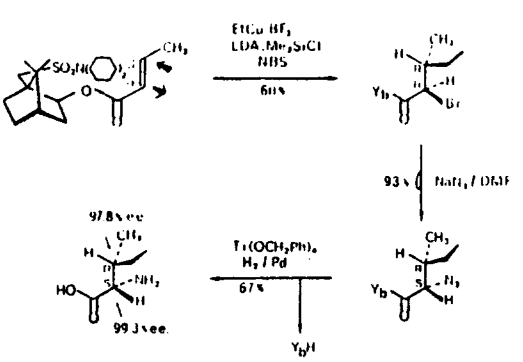


L-Alloisoleucine

Epicriptine

R.K.A. Giger, Sandoz Ltd., Offenlegungsschrift DE 33 03 616 A 1 (1983)
R.K.A. Giger, J.M. Rigouret, "International Congress of Gerontology", New York, July 1985.

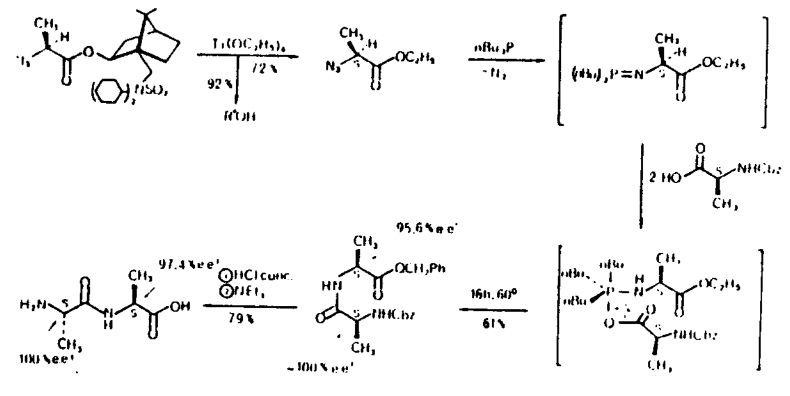
ENANTIOSELECTIVE SYNTHESIS OF L-ALLOISOLEUCINE BY FACE-SELECTIVE 1,4-BIFUNCTIONALIZATION OF A CHIRAL CROTONATE



L-Alloisoleucine

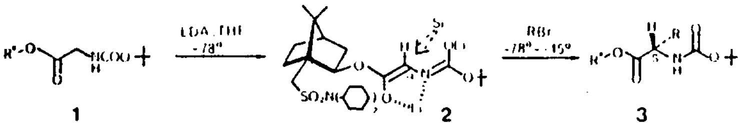
W. Oppolzer, R. Pedrosa, R. Moretti, Tetrahedron Lett., 27, 831 (1986)

PEPTIDE COUPLING OF ENANTIOMERICALLY PURE α-AZIDOESTERS

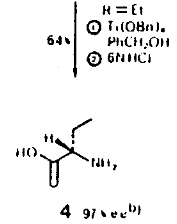


1) GC, Chirasil-Val: N. Oi et al., J. Chrom. 1980, 202, 302
Triphenyl-iminophosphoranes: J. Vilarrasa et al., Tetrahedron Lett. 1984, 4881

AMINO ACIDS BY ASYMMETRIC ALKYLATION OF GLYCINATES



1 2 3

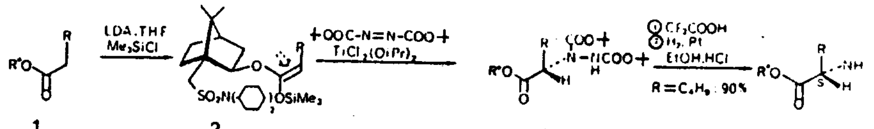


4 97% ee^b)

	yield % crude 3	d.e.%^a) crude 3	yield % cryst 3	d.e.%^a) cryst 3
CH_3CH_2	58	92	42	>99
$CH_3(CH_2)_3Br$	56	89	41	96.4
$PhCH_2Br$	64	44	31	>99

a) HPLC; b) GC (Chirasil-Val)

AMINO ACIDS BY ASYMMETRIC 1,4-ADDITION OF O-SILYLKETENE ACETALS TO DI-t-BUTYL AZODICARBOXYLATE

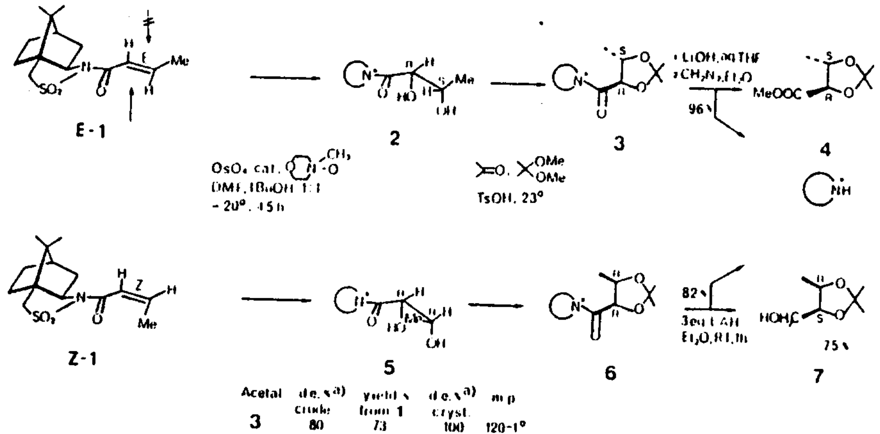


1 2 3 4

R	d.e. %^a) crude 3	d.e. %^a) chrom. 3	yield % chrom. 3
nC_4H_9	93	100	85
CH_3	94	100	81

a) by HPLC

ASYMMETRIC BISHYDROXYLATION.

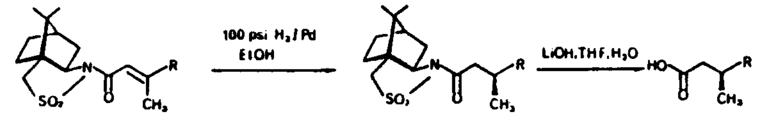


Acetal	d.e. %^a) crude	yield % from 1	d.e. %^a) cryst.	m.p.
3	80	73	100	120-1°
6	82	76	99	126-7°

a) capillary GC

ASYMMETRIC HYDROGENATION OF CONJUGATED CAMPHORSULFONIMIDES : HYPOTHESIS

'ASYMMETRIC HYDROGENATION OF VARIOUS (E)-3-METHYL-3-ALKYL-2-EN-IMIDES.

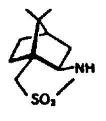


E/Z = 98/2

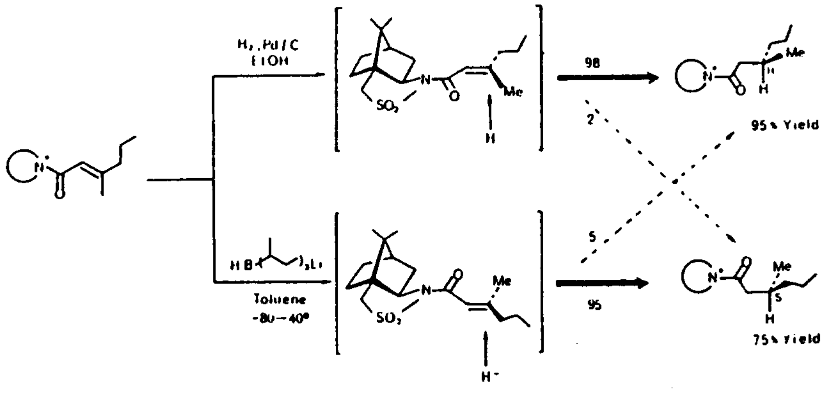
$$\boxed{\frac{E-Z}{E+Z} \times 100 = 96}$$

R	yield % crude	d.e. %[a)] crude
C_2H_5	99	>93
nC_3H_7	95	95
iC_3H_7	97	91
nC_4H_9	94	90
nC_6H_{13}	99	92
nC_8H_{17}	93	92.4

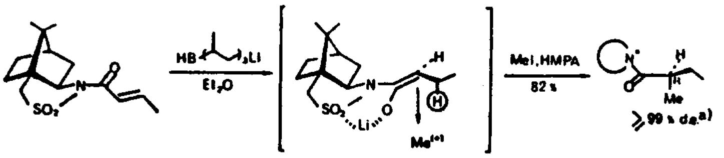
a) by capillary - GC



α,β-OLEFINIC SULTAM IMIDES : OPPOSITE β-STEREODIFFERENTIATION ON ADDITION OF HYDROGEN VERSUS HYDRIDE

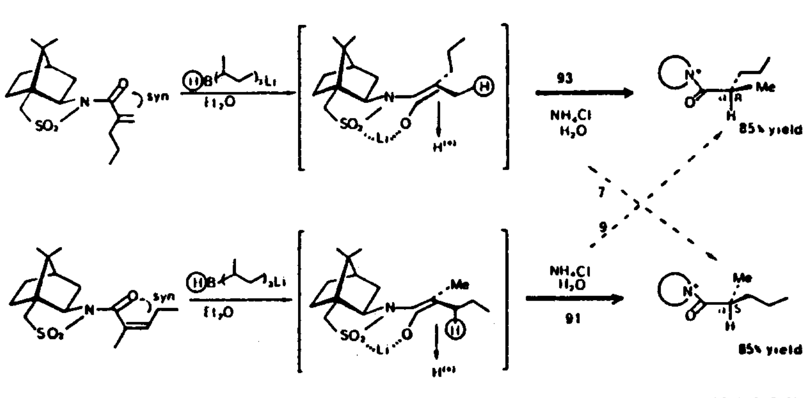


α,β-OLEFINIC SULTAM IMIDES : α-STEREODIFFERENTIATION ON 1,4-HYDRIDE ADDITION/ENOLATE ALKYLATION



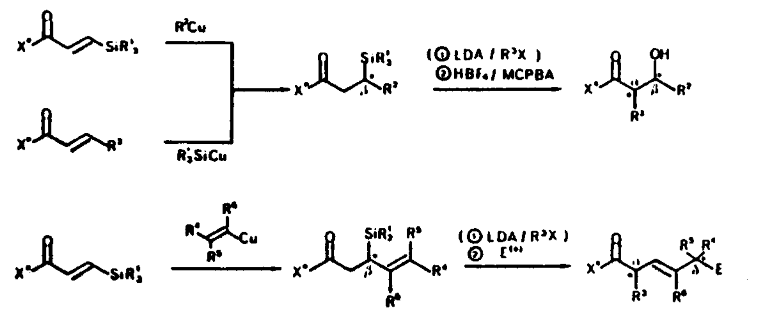
a) by ^{1}H-NMR (360 MHz)

α,β-OLEFINIC SULTAM IMIDES : α-STEREODIFFERENTIATION ON 1,4-HYDRIDE ADDITION / ENOLATE PROTONATION

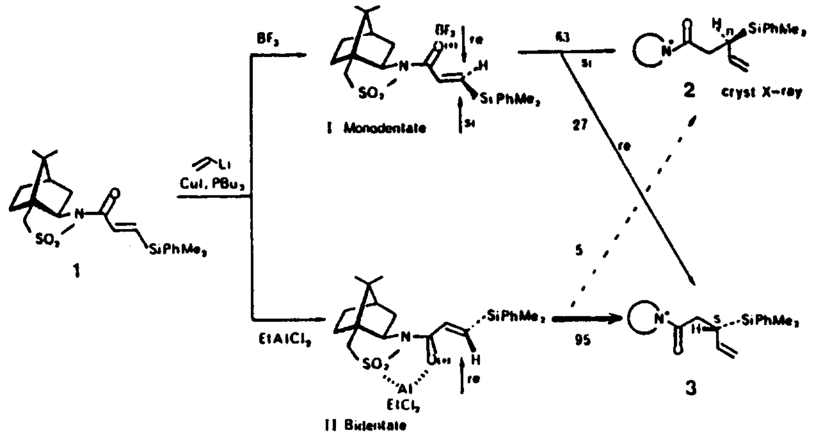


Postulate : enolate geometry dictated by location of the olefinic bond

PROPOSAL : PREPARATION AND FUNCTIONALIZATION OF ENANTIOMERICALLY PURE β-SILYLCARBOXYL DERIVATIVES



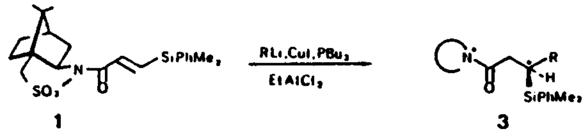
1,4-ADDITION OF VINYLCOPPER TO β-SILYLENOYL IMIDE : LEWIS-ACID DEPENDENT DIASTEREOTOPICITY



∴ $EtAlCl_2$ chelates stronger than BF_3

3 formed selectively via the bidentate complex II

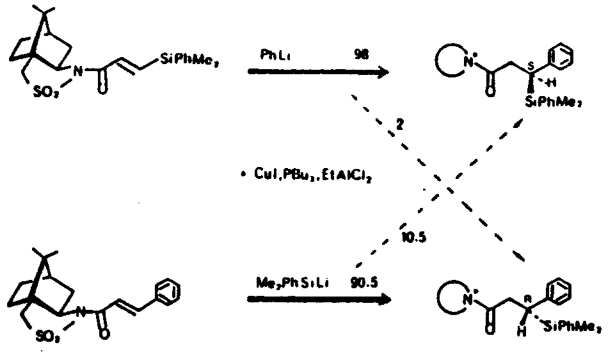
π -FACE-SELECTIVE 1,4-ADDITION OF ORGANOCOPPER REAGENTS TO β-SILYLENOYL SULTAM-IMIDE



R	d.e. %[a)] 3 crude	d.e. %[a)] 3 cryst.	Yield % 3 cryst.
Vinyl	90	96	57
Me	86	93.5	61
Et	86	92	62
nPr	88	96	57
iPr	86	94	64
nBu	91.5	97	61
Ph	95.5	~100	86

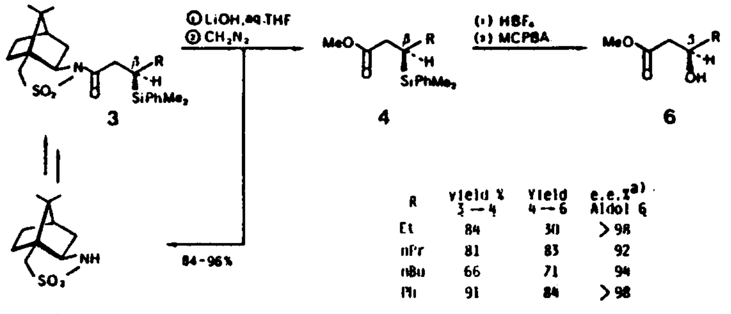
a) determined by GC

REVERSED ASYMMETRIC INDUCTION ON 1,4-ADDITION BY CHOICE OF $SiPhMe_2$ AS RESIDENTIAL OR TRANSFERRED GROUP.



∴ virtually unchanged diastereotopicity

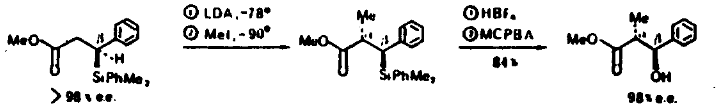
CONVERSION OF β-SILYL CARBOXYLIMIDES TO ENANTIOMERICALLY PURE "ACETATE-ALDOLS"



R	yield % 3 → 4	Yield 4 → 6	e.e.%[a)] Aldol 6
Et	84	30	> 98
nPr	81	83	92
nBu	66	71	94
Ph	91	84	> 98

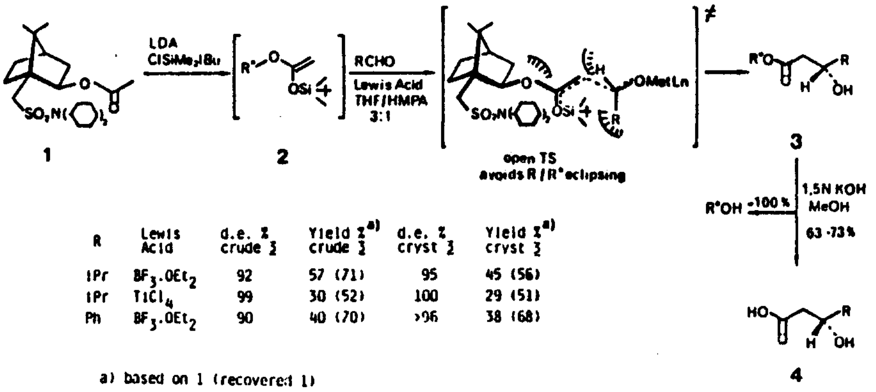
a) by Eu (HFC)$_3$-^{1}H-NMR

CONVERSION OF A β-SILYLCARBOXYL IMIDE TO AN ENANTIOMERICALLY PURE ANTI-"PROPIONATE-ALDOL"



anti/syn crude	anti/syn chrom	yield % chrom
97:3	100	72

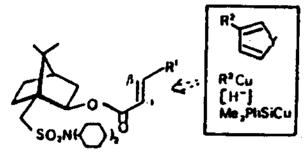
ENANTIOMERICALLY PURE "ACETATE ALDOLS" BY ASYMMETRIC "MUKAIYAMA - ALDOLISATION"

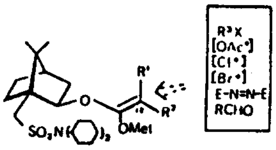


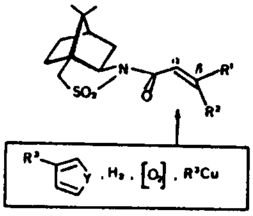
R	Lewis Acid	d.e. % crude %	Yield %$^{a)}$ crude %	d.e. % cryst %	Yield %$^{a)}$ cryst %
iPr	$BF_3.OEt_2$	92	57 (71)	95	45 (56)
iPr	$TiCl_4$	99	30 (52)	100	29 (51)
Ph	$BF_3.OEt_2$	90	40 (70)	>96	38 (68)

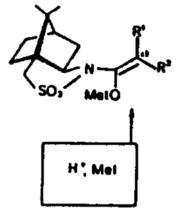
a) based on 1 (recovered 1)

CAMPHOR SULFONIC ACID AUXILIARIES : CHAMELEONS IN ASYMMETRIC SYNTHESIS









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