

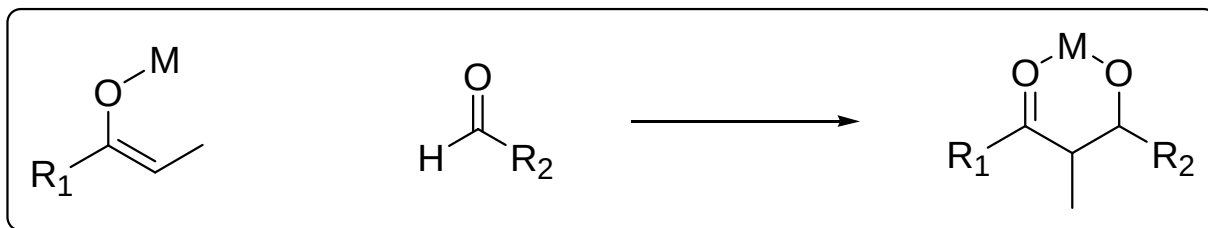
Stereoselektive Aldol-Addition

AK Prof. Schreiner - Vortragsseminar

12.01.2007

Christian Kleiner

Institut für Organische Chemie, Justus-Liebig-Universität Gießen

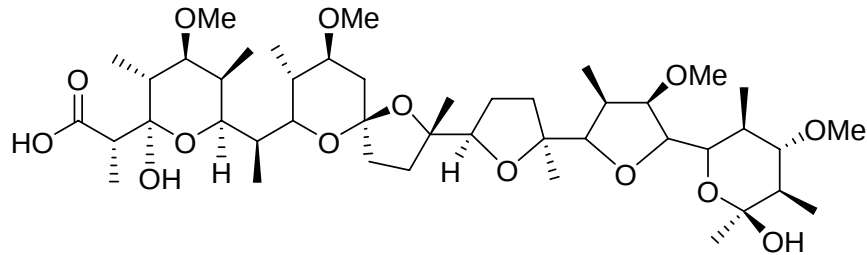




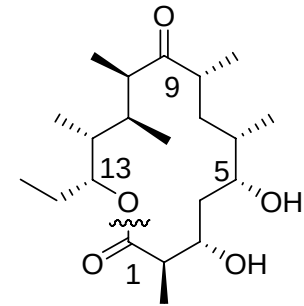
1. Einleitung
 - Polyketide Naturstoffe
 - Aufbau polyketidischer Naturstoffe
 - Stereochemische Herausforderungen
2. Aldol-Reaktion – Stereokontrolle in C-C-Verknüpfungsschritt
 - “Einfache” Diastereoselektivität
 - “Substrat-kontrollierte” Stereoselektivität (Cram/anti-Cram; Felkin-Anh)
 - “Reagenz-kontrollierte” Stereoselektivität
3. Syn-Aldol-Reaktionen
4. Anti-Aldol-Reaktionen
5. Dipropionyl-Synthon zum Aufbau von Stereotriaden:
Acylierung-Aldol-Reduktion-Sequenz
6. Organokatalytische Aldol Reaktionen
7. Anwendung der stereoselektiven Aldol-Reaktion:
Synthese komplexer Polyketide & anderer Polyhydroxyeinheiten-enthaltender Naturstoffe
 - Lonomycin
 - 6-Deoxyerythronolid B
 - Sanglifehrin A

I. Einleitung

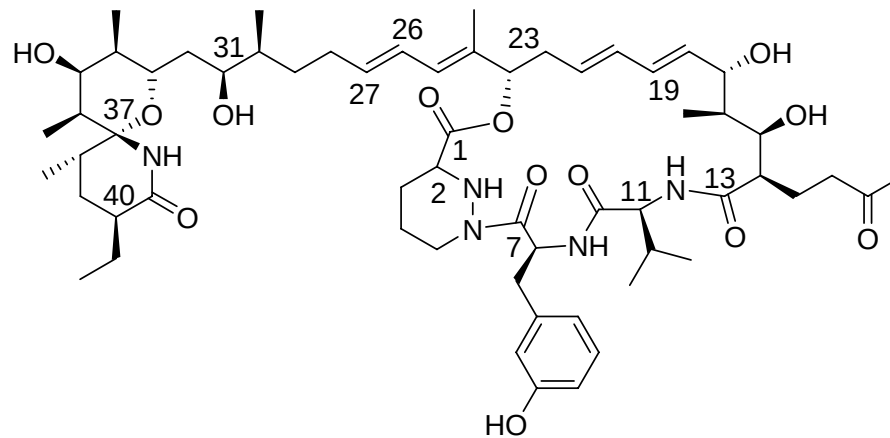
I.1. Polyketide Naturstoffe



Lonomycin

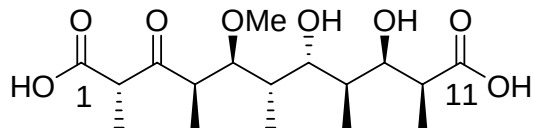


6-Deoxyerythronolid B

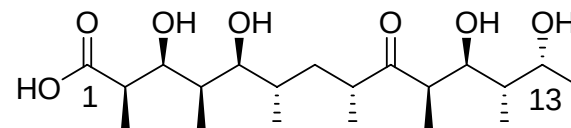


Sanglifehrin A

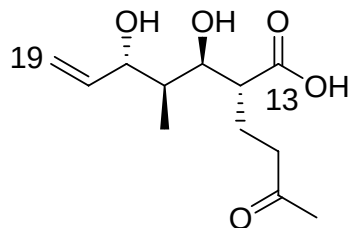
“Secosäuren” polyketider Naturstoffe



C₁-C₁₁-Fragment von Lonomycin

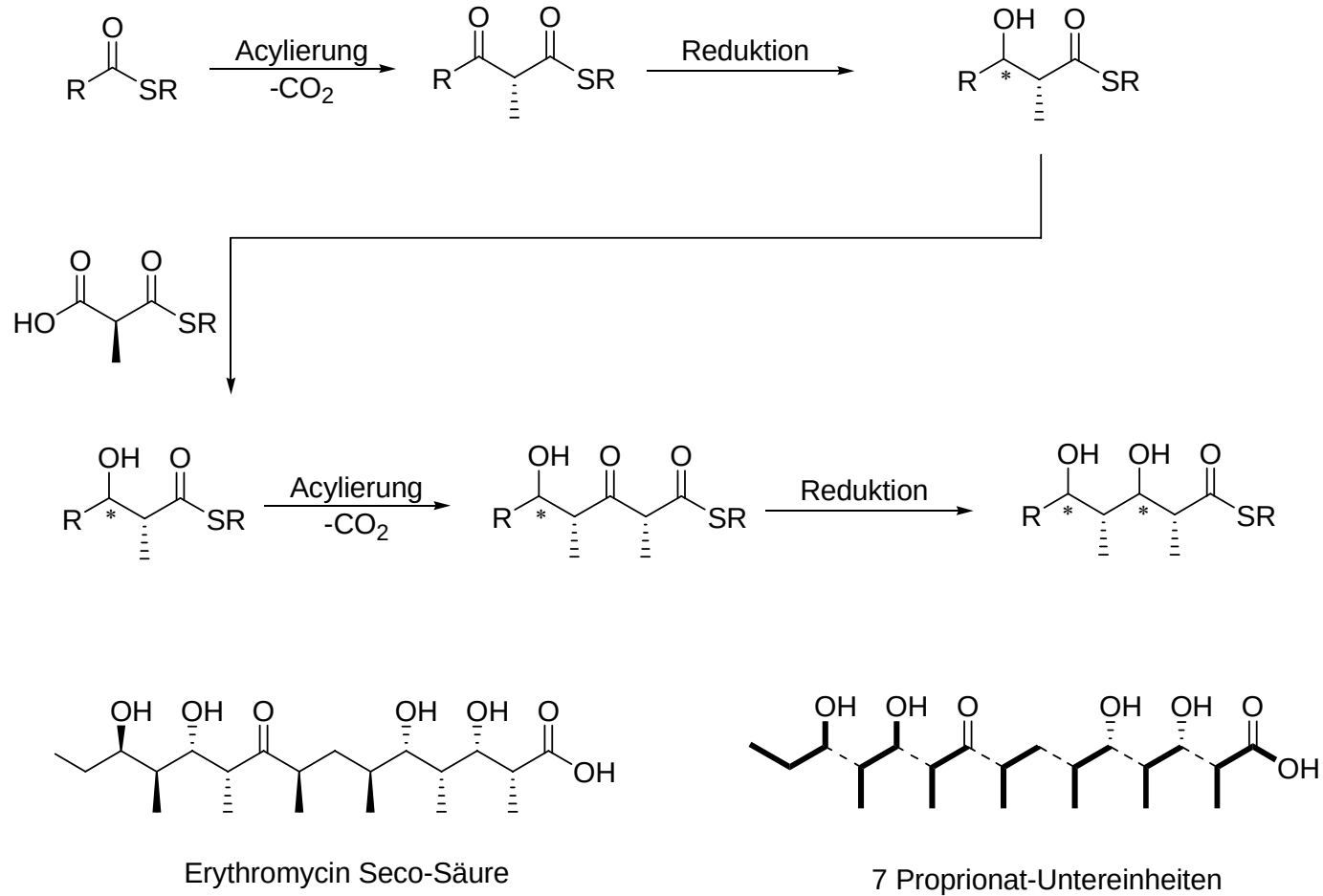


C₁-C₁₃-Fragment von 6-Deoxyerythronolid B



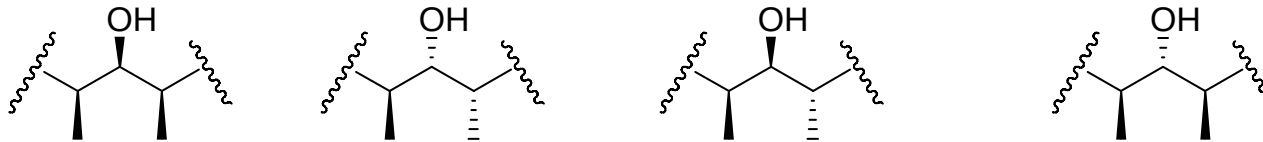
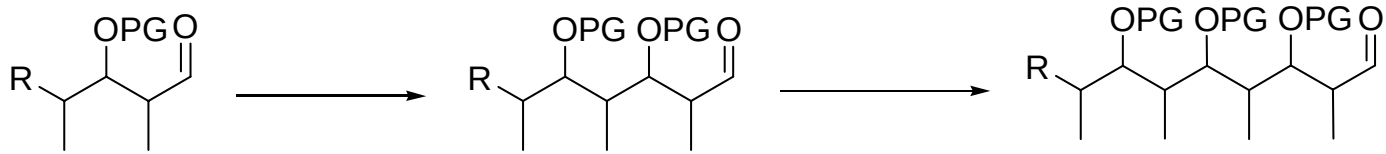
C₁₃-C₁₉-Fragment von Sanglifehrin A

1.2 Polypropionat Biosynthese – Elementare Schritte: Acylierung, Reduktion

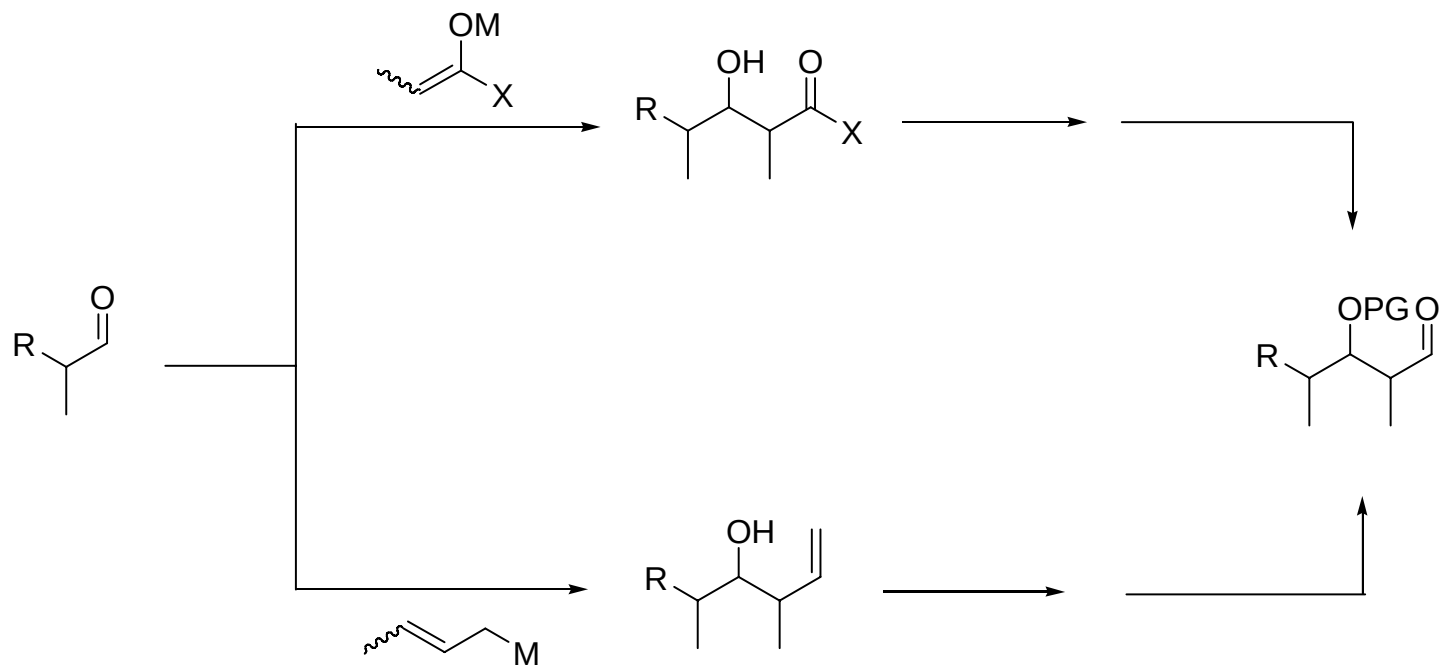


I.3 Aufbau polyketider Naturstoffe

I.3.1 Prinzip der iterativen Kettenverlängerung zur Synthese von Stereotriaden

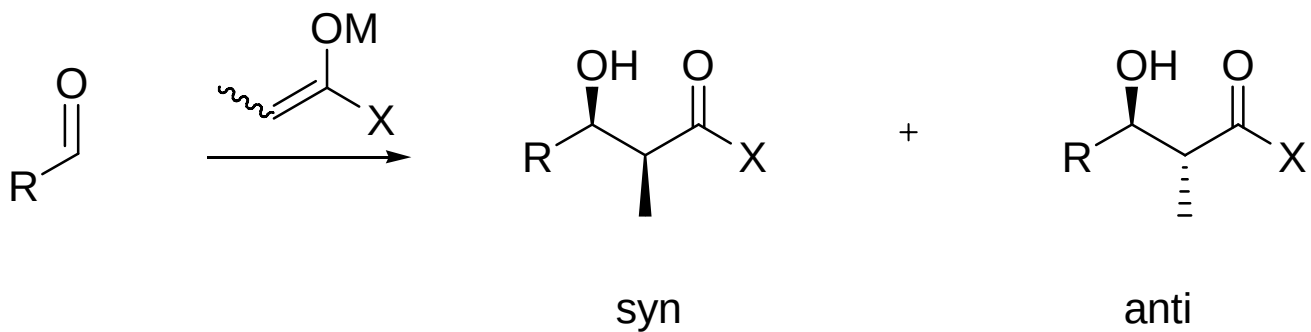


Aldoladdition & analoge C-C-Verknüpfungsreaktionen zum Aufbau von Stereotriaden



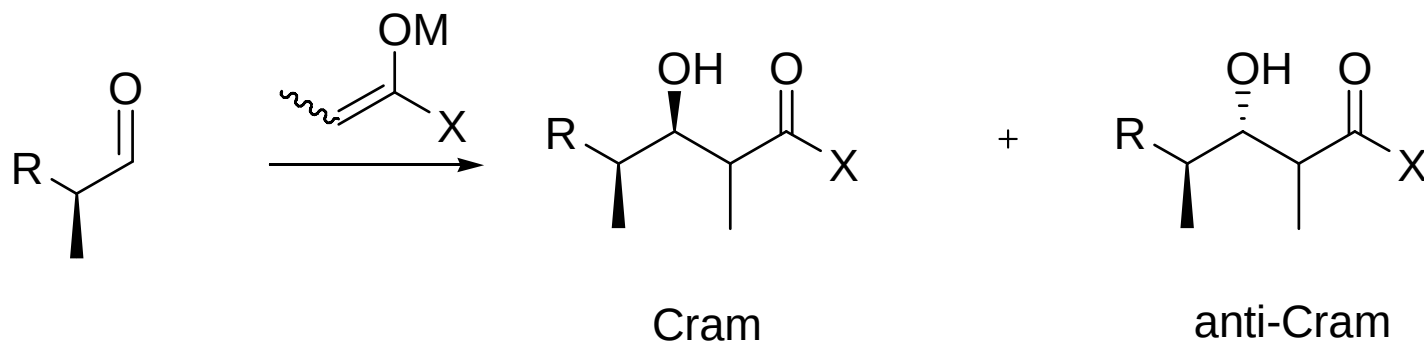
Stereochemische Herausforderungen

Einfache Diastereoselektivität

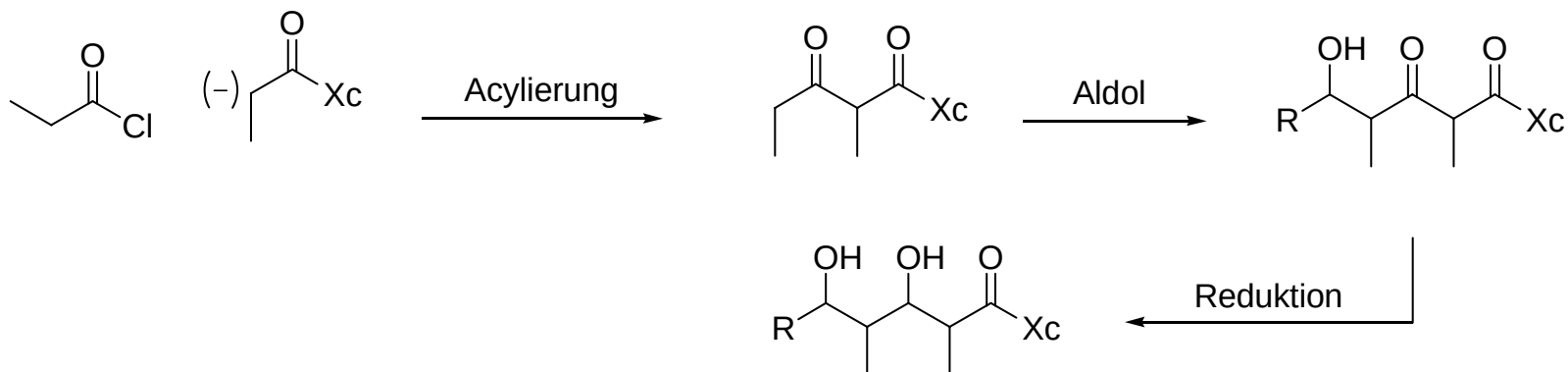


Stereochemische Herausforderungen

Substrat – kontrollierte Stereoselektivität



I.3.2 Alternative zum iterativen Ansatz: *Acylierungs-Aldol-Reduktions-Sequenz*

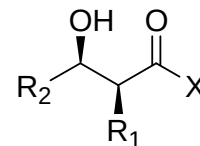
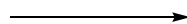
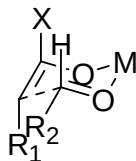


II. Aldol-Reaktion – Stereokontrolle im C-C-Verknüpfungsschritt

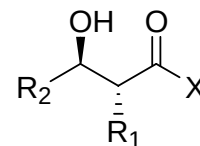
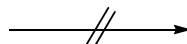
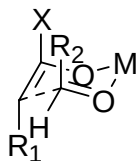
II.1. Einfache Diastereoselektivität: Sesselkonformation im Übergangszustand



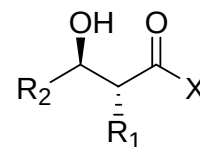
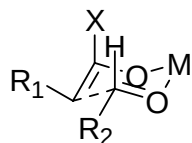
Z-Enolat



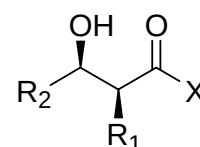
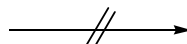
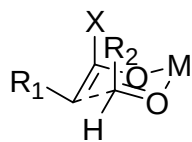
syn



E-Enolat

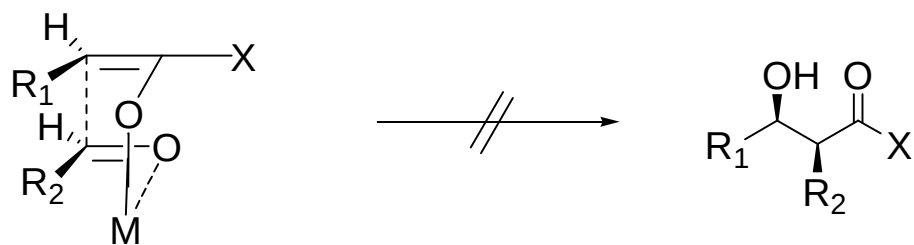
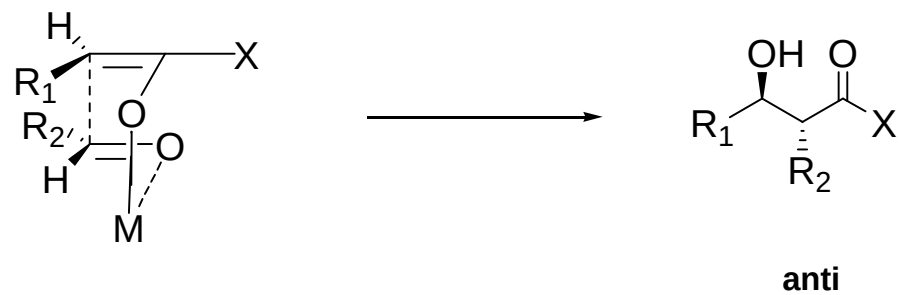


anti

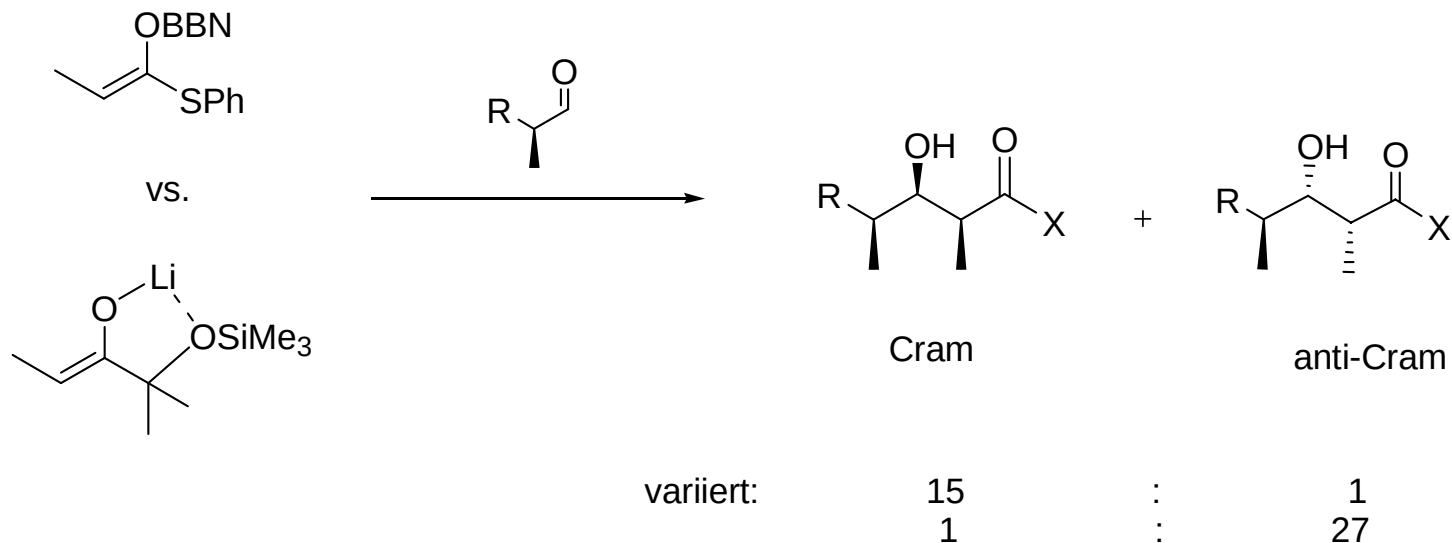




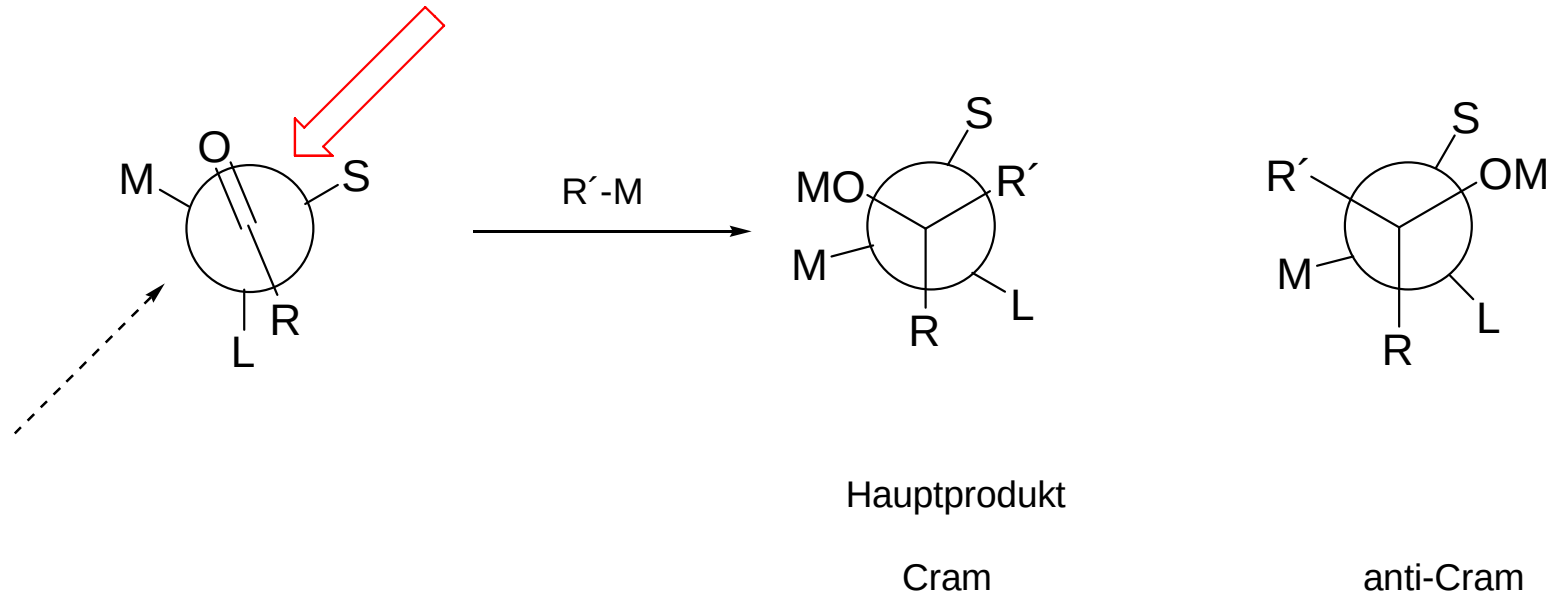
Z-Enolat

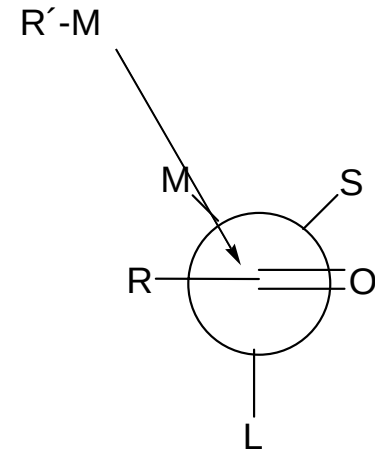
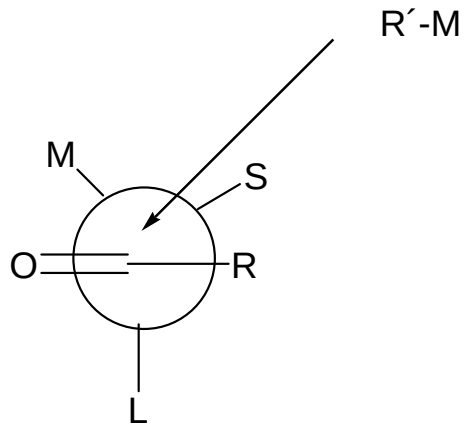


II.2 Substrat-kontrollierte Stereoselektivität – Cram / anti-Cram

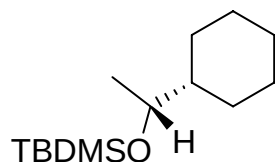


Cram – Berücksichtigung von sterischen Wechselwirkungen

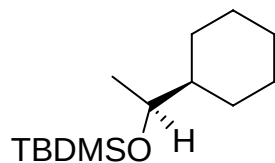




Sterische Kompression "R'M-S-R" geringer als "R'M-M-R"

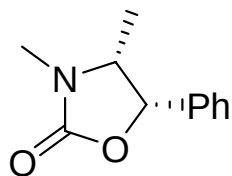
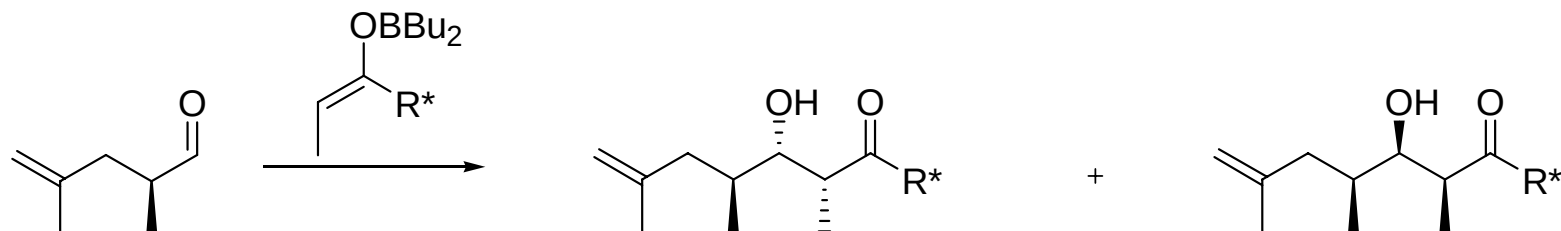


•

$$R^* =$$


S. Masamune et al., *Angew. Chem.* **1985**, 98, 1.

Reagens-kontrollierte Stereoselektivität – Syn-Aldole über Evans-Enolate

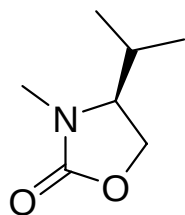


660

:

1

R* =

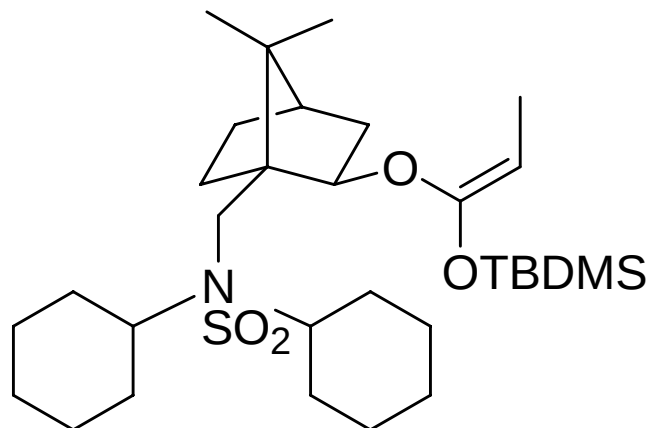
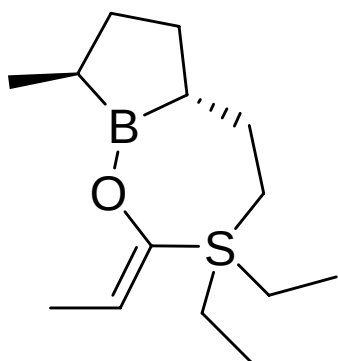


1

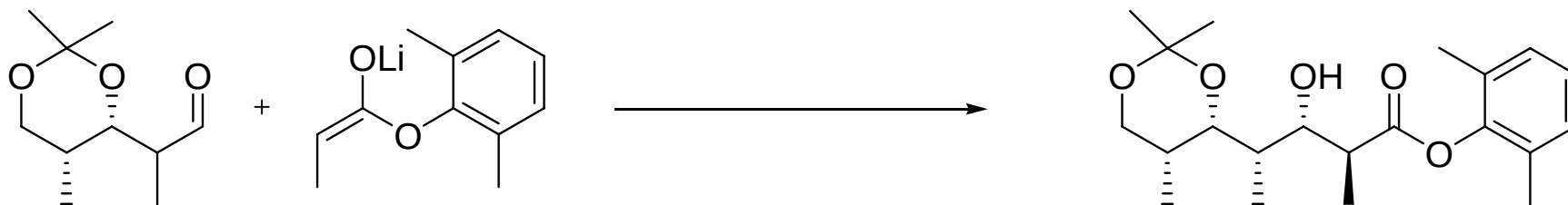
:

400

Reagens-kontrollierte Stereoselektivität – Anti-selektive Enol-Derivate

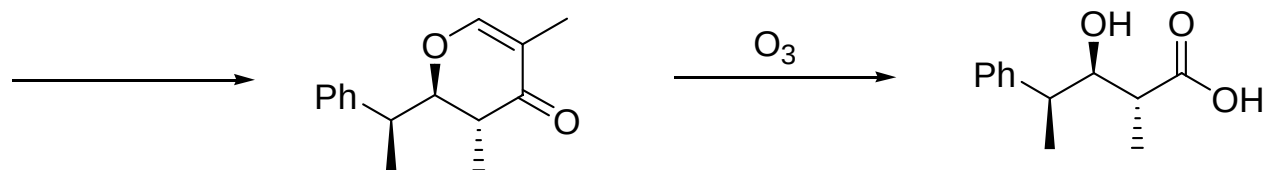
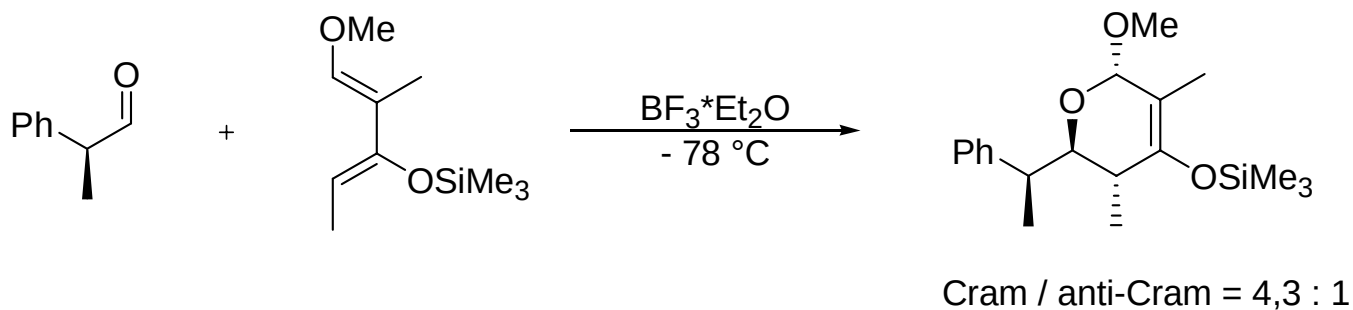


II.4 Chirale Anti-Aldole über Substratkontrolle – Anti-selektive Enolate



> 500 : < 1

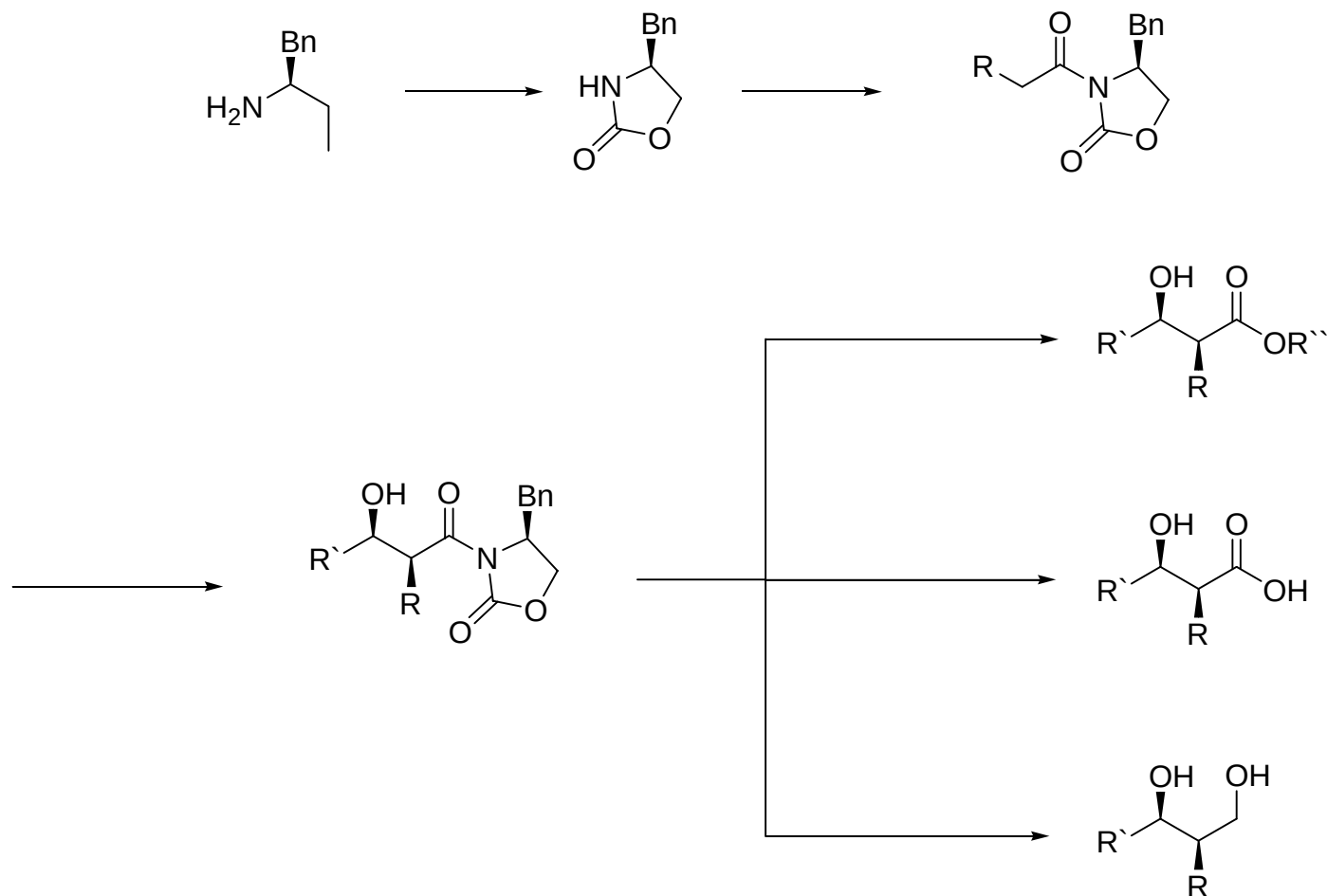
Cycloaddition von Danishefsky-Dienen (formale Aldol-Addition)



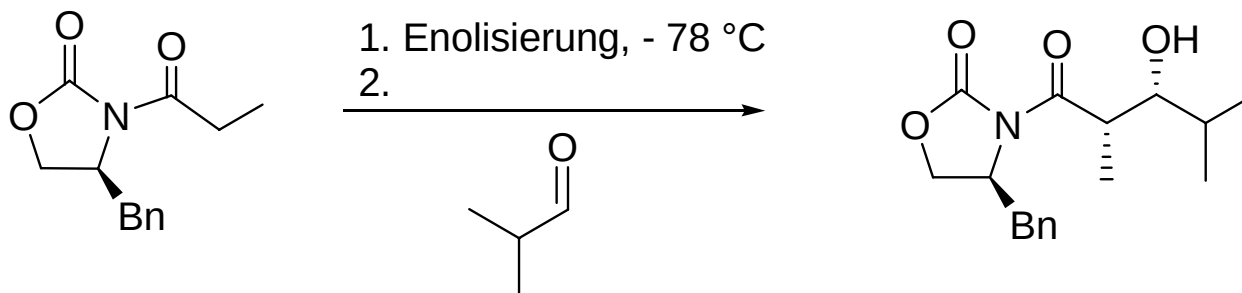
Mit ZnCl_2 : führt zu anti-Cram (1:10 via pericyclischen Übergangszustand)

III. Syn-Aldol Reaktion:

III.1. Chirale *N*-Acyloxazolidinone



Chirale N-Acyloxazolidinone: Bor- und Titan-Enolate zum Aufbau von Syn-Aldolen



TiCl₄, ⁱPr₂NEt, CH₂Cl₂:

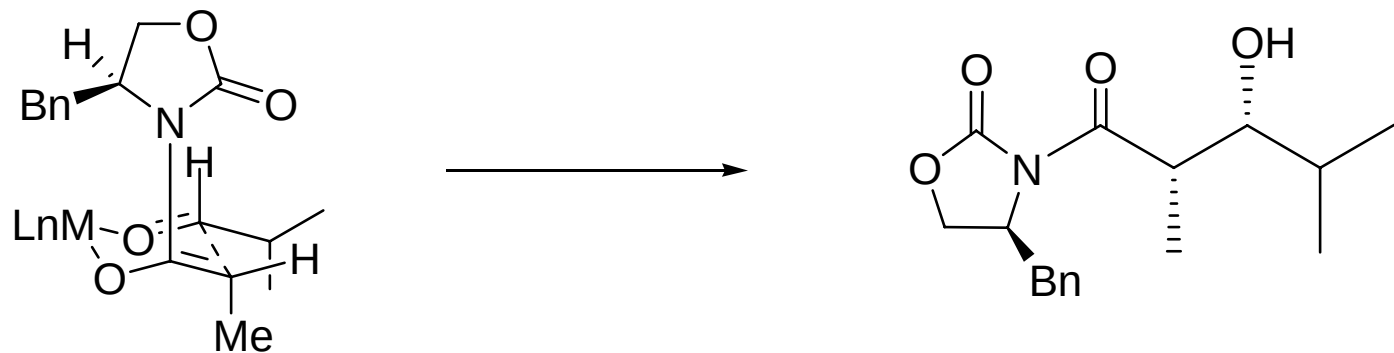
94 : 6 (87%)

TiCl₄, TMEDA, CH₂Cl₂:

98 : 2 (84%)

ⁿBu₂BOTf, Et₃N, CH₂Cl₂:

> 99 : 1 (83%)



relative Stereochemie (Syn-Anordnung): Z-Enolat Geometrie

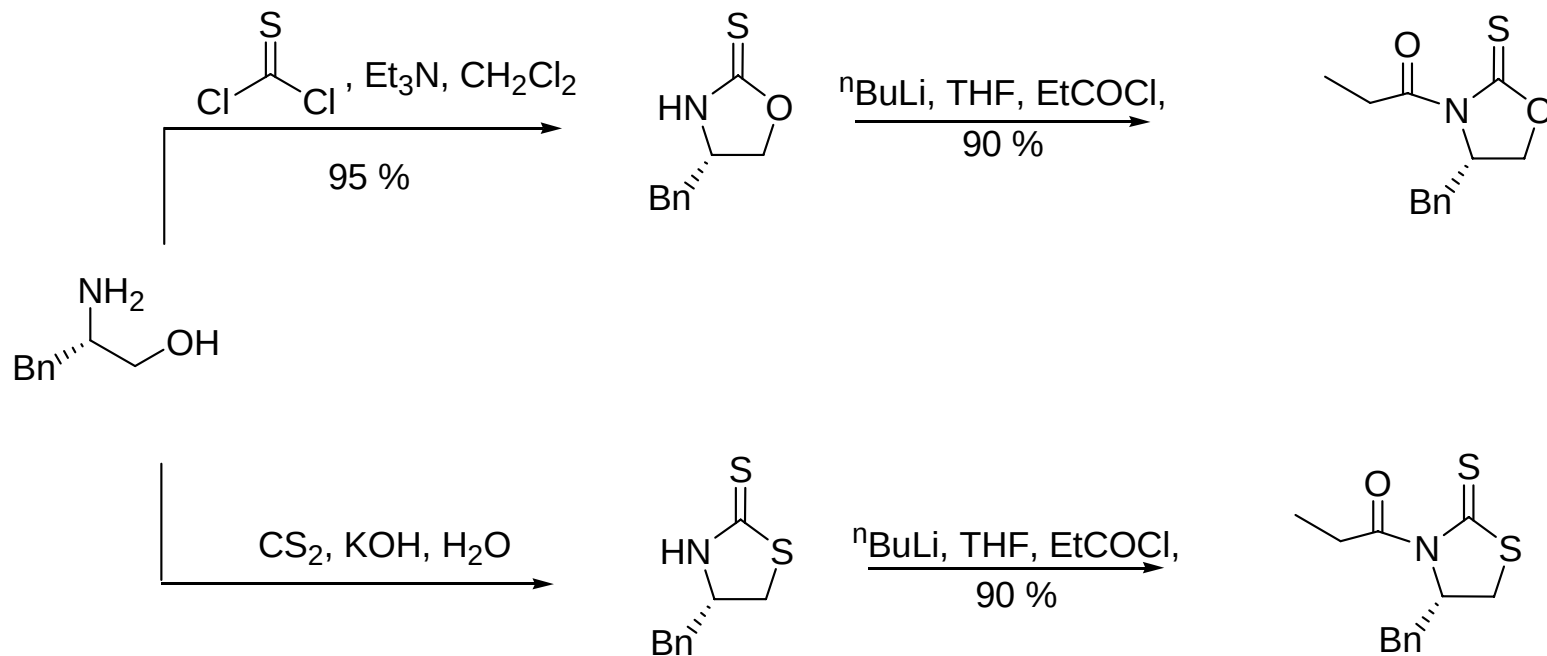
absolute Stereochemie:

Stereozentrum am Oxazolidinon

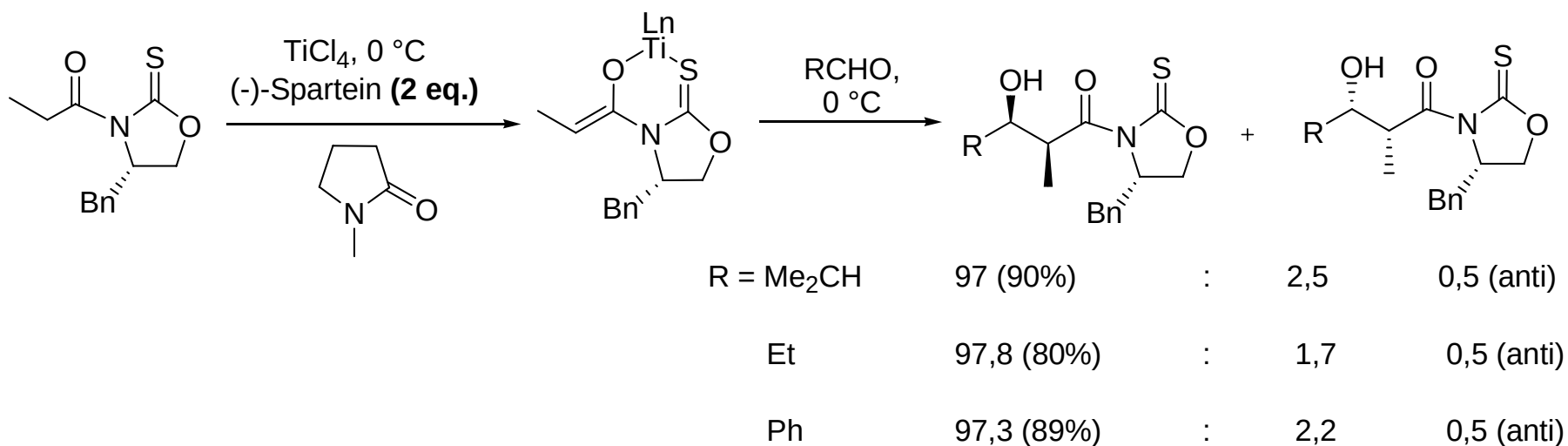
d_{B-O} : 1,36 - 1,47 Å

d_{Ti-O} : 1,62 Å

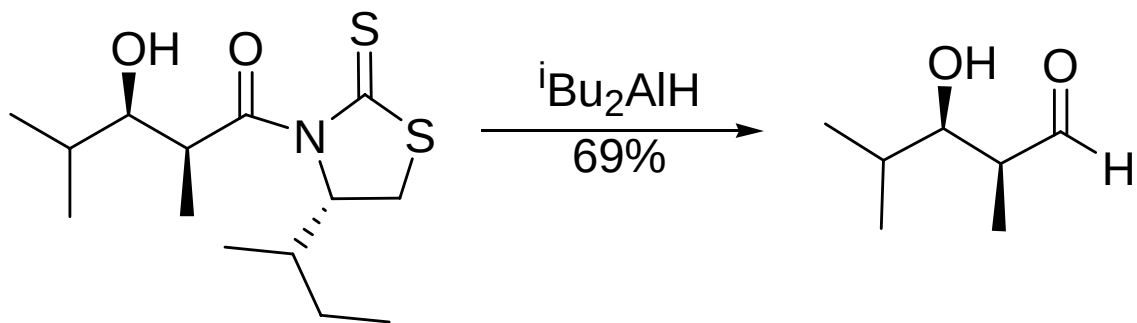
III.2 Chirale N-Acylthiazolidinthione und N-Acyloxazolidinthione



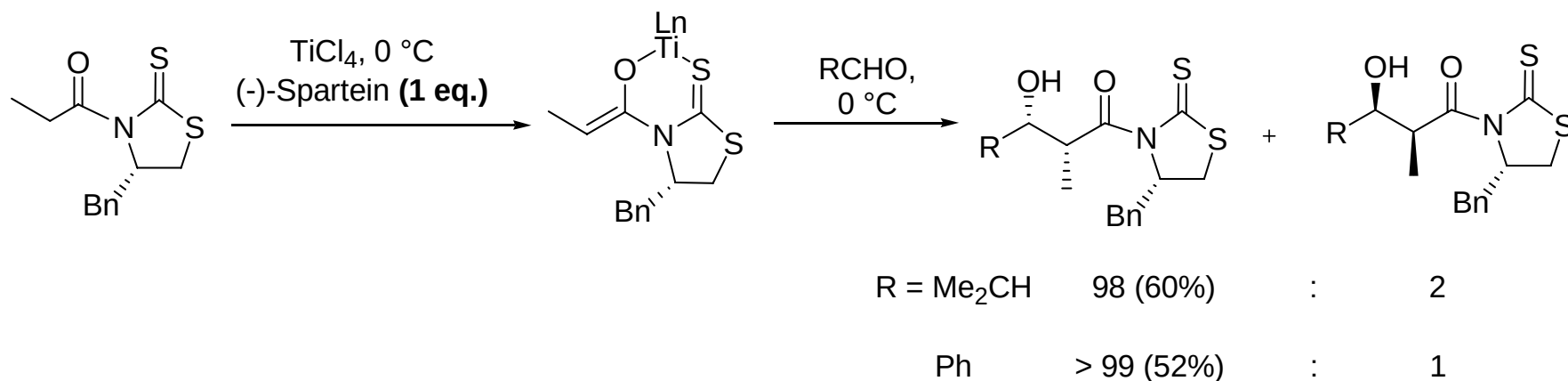
Chirale N-Acyloxazolidinthione (2 eq. Amin): “Evans” Syn-Aldole



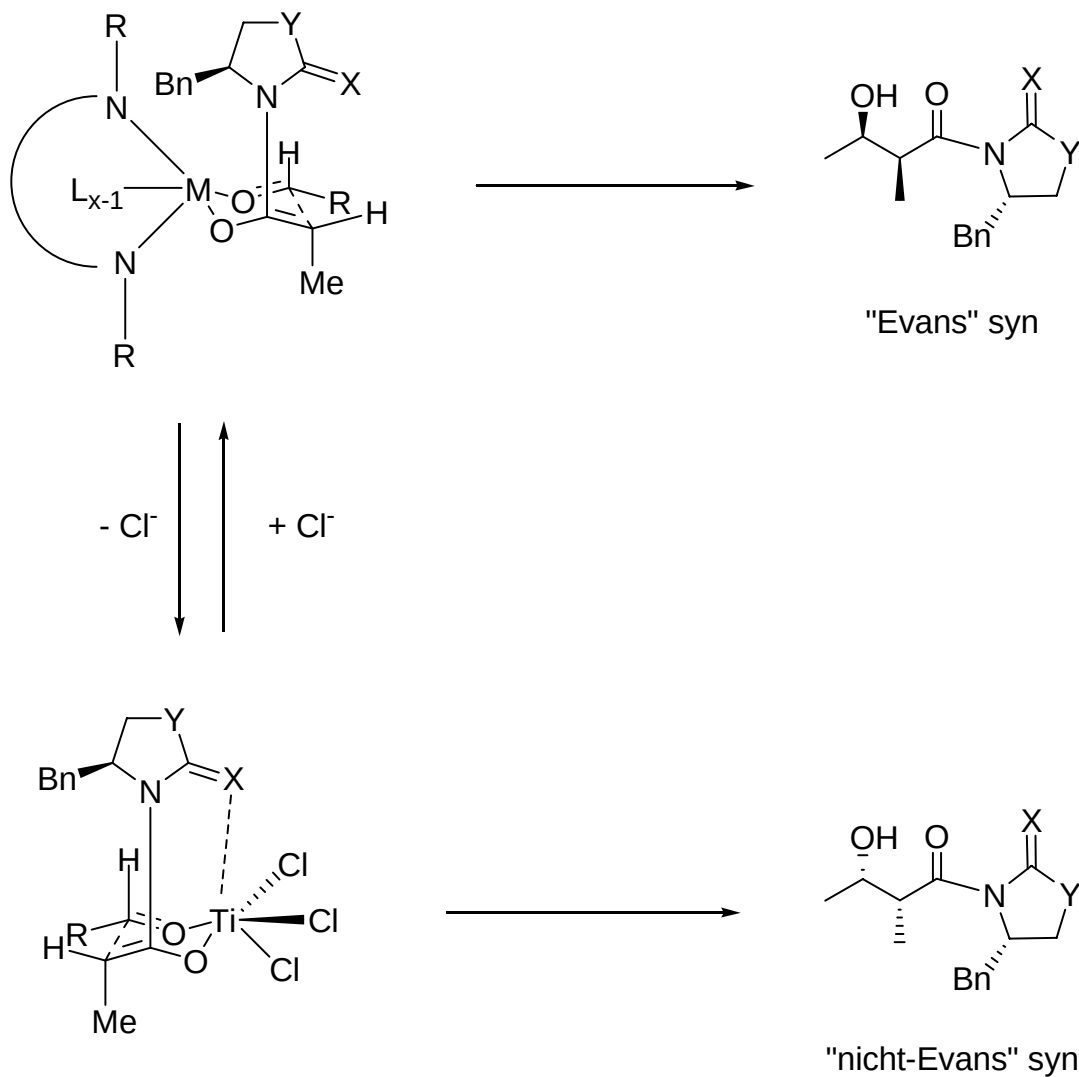
Direkte Umwandlung der N-Acylthiazolidinthione in Aldehyde



Chirale N-Acylthiazolidinthione (1 eq. Amin): “Nicht-Evans” Syn-Aldole



Chelatisierungseffekte als Erklärung für die Umkehr der enantiofacialen Selektivität (2 vs 1 eq. Amin)

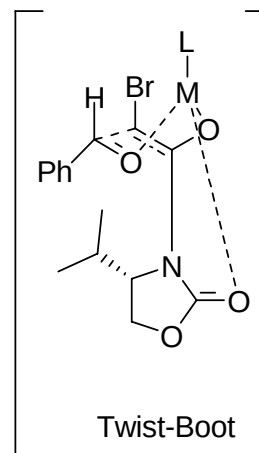
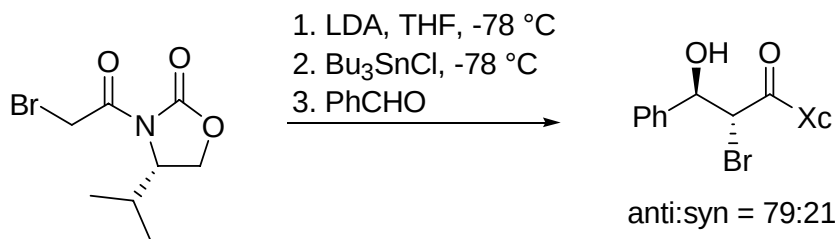


IV. Anti-Aldole

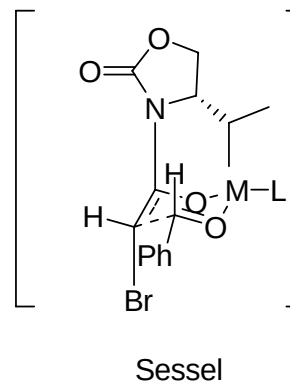
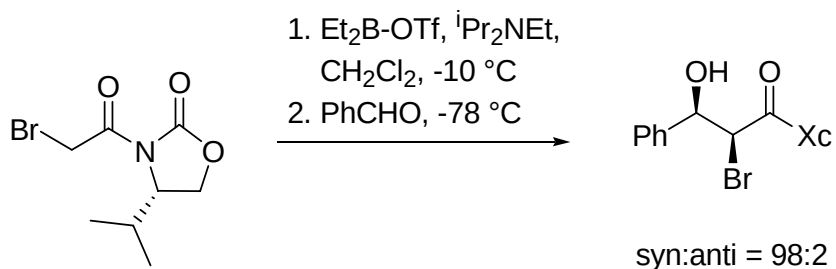
IV.1. via halogenierte Carboxamid-Enolate



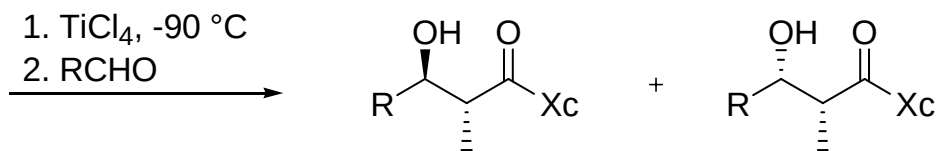
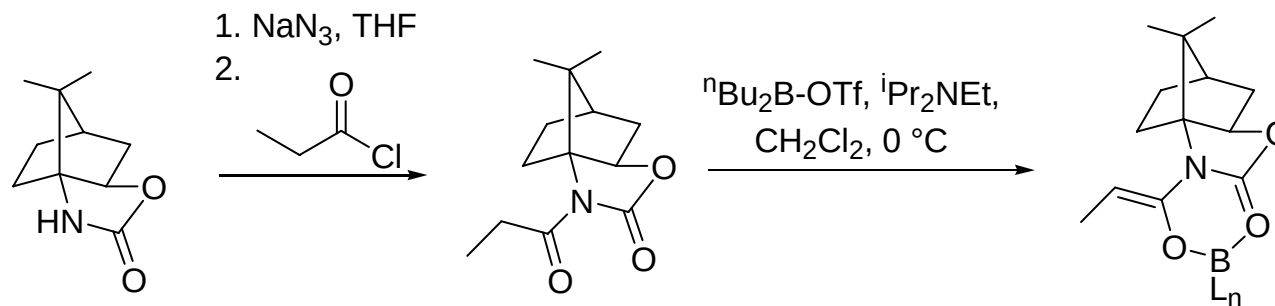
Chelat



Nicht-Chelat

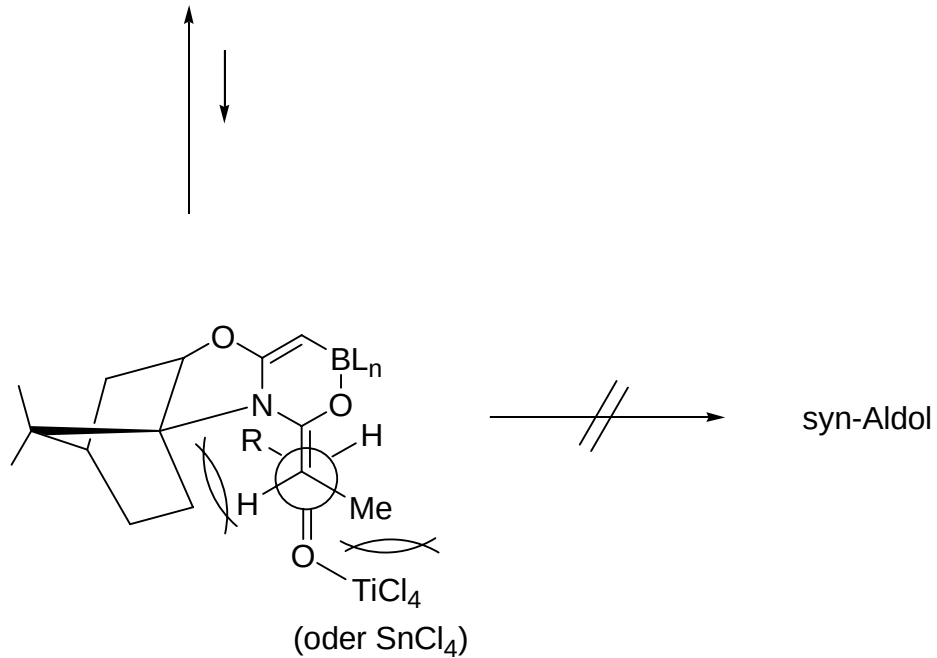
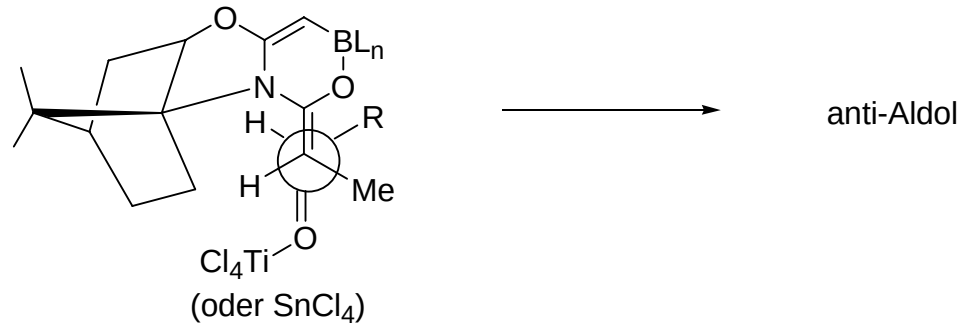


IV.2. Anti-Aldole via Z-Bor-Enolate – Zusatz von Co-Katalysatoren

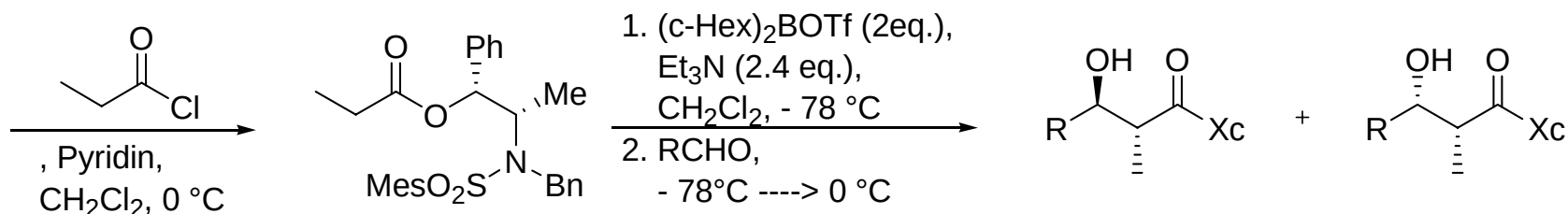
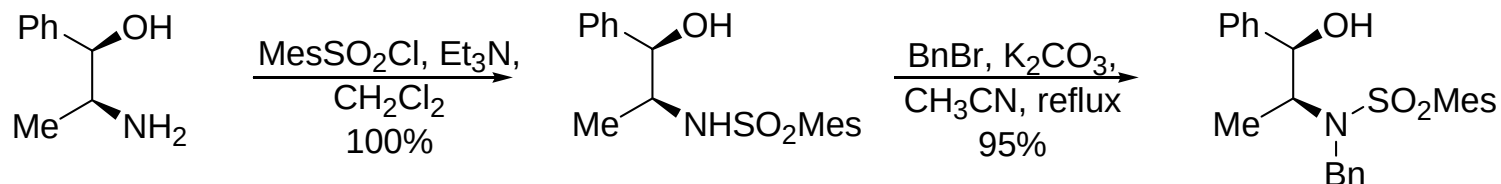


$\text{R} = i\text{Pr}$	99	:	1	(90%)
Et	99	:	1	(85%)
$n\text{Pr}$	99	:	1	(90%)
MeCH=CH	99	:	1	(91%)
Ph	78	:	22	(89%)

“Offener” Übergangszustand auf Grund von Co-Katalysator → Anti-Aldol Produkt



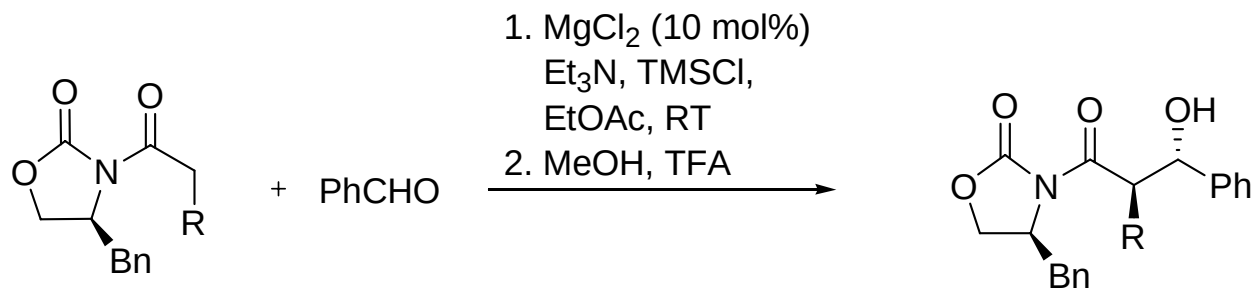
IV.3 Anti-Aldole via *E*-Bor-Enolate



R =	Et	> 98	:	2	(90%)
	Pr	> 98	:	2	(96%)
	<i>i</i> Pr	> 98	:	2	(98%)
	Ph	> 98	:	2	(93%)

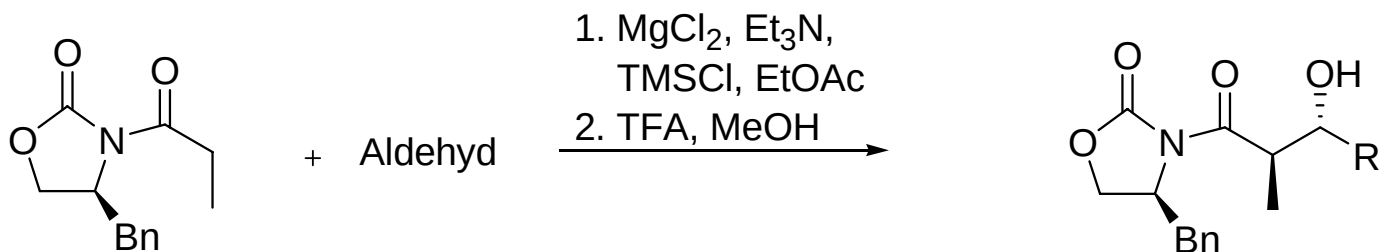
Diastereofaciale Selektivität für anti- Isomere: > 95:5

IV.4. Anti-Aldole via chirale N-Acyloxazolidinone: Einfluss von MgX_2 (katalyt.)



R	dr	Ausbeute (%)
CH_3	32:1	91
CH_2CH_3	32:1	88
CH_2Ph	26:1	94
CH_2CHMe_2	32:1	91
$\text{CH}_2\text{CH=CH}_2$	28:1	91
CHMe_2	3,5:1	36 % conv.

Universalität des Anti-Aldol Prozesses nach Evans

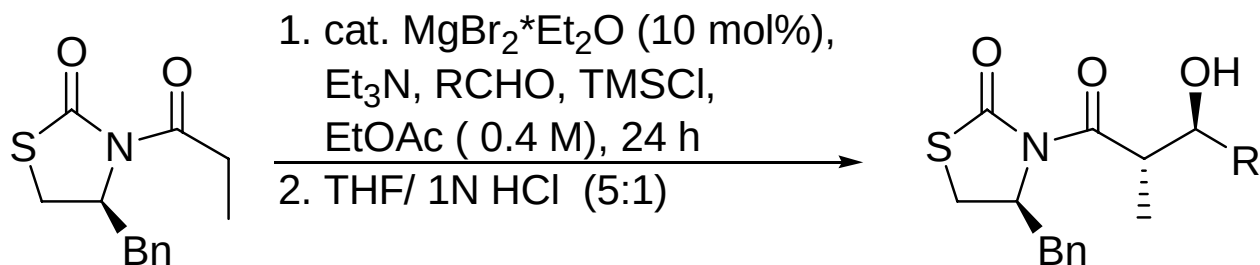


	Aldehyd	Variante	dr	Ausbeute (%)
	X = Me	A	24:1	--
	X = OMe	A	23:1	91
	X = NO ₂	B	7:1	71
	X = Ph, Y = H	B	21:1	92
	Y = Ph, Y = Me	A	28:1	92
	Y = H, Y = Me	B	16:1	77
		A	14:1	91
		B	6:1	80

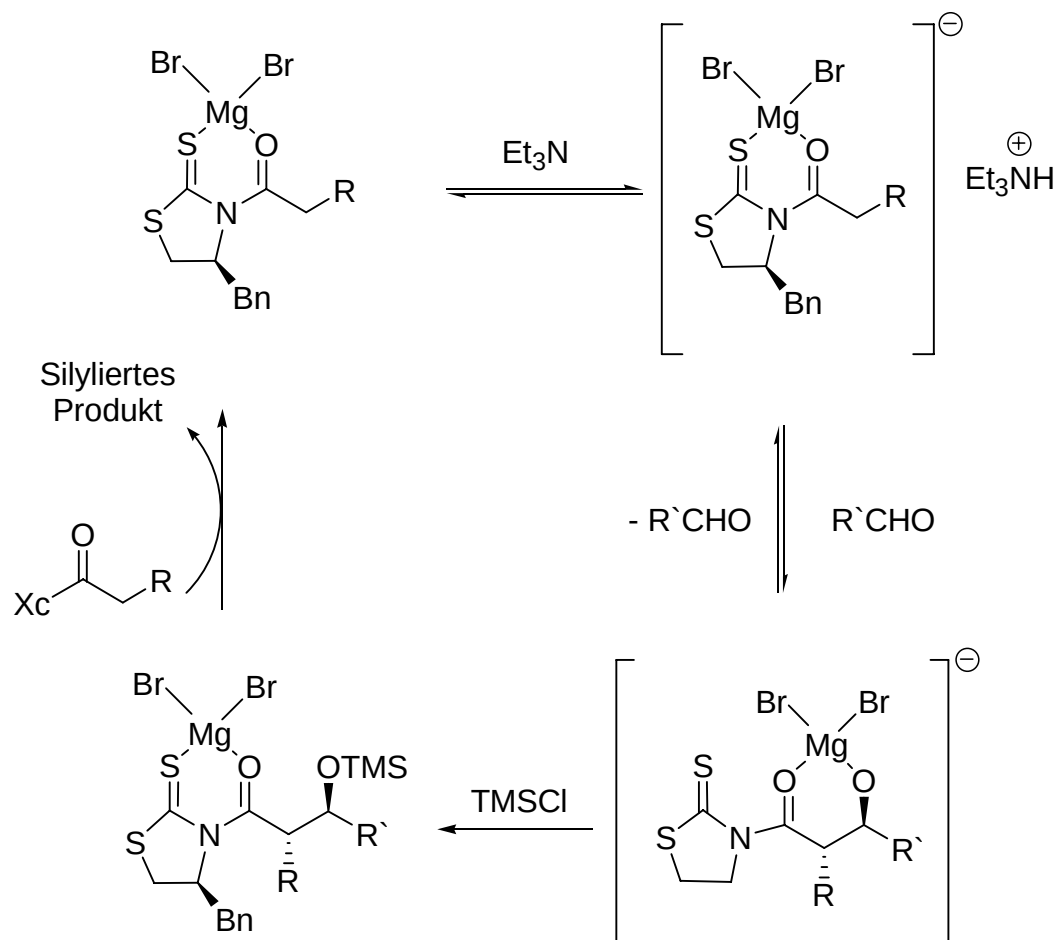
A = 1 eq *N*-Propionyloxazolidinon, 0.2 eq MgCl₂, 2 eq Et₃N, 1.5 eq TMSCl, 1.2 eq Aldehyd, 0.5 M in EtOAc, 24 h

B = wie A, aber 0.1 eq MgCl₂ & Zugabe von equiv. NaSbF₆ (0.2 M in EtOAc)

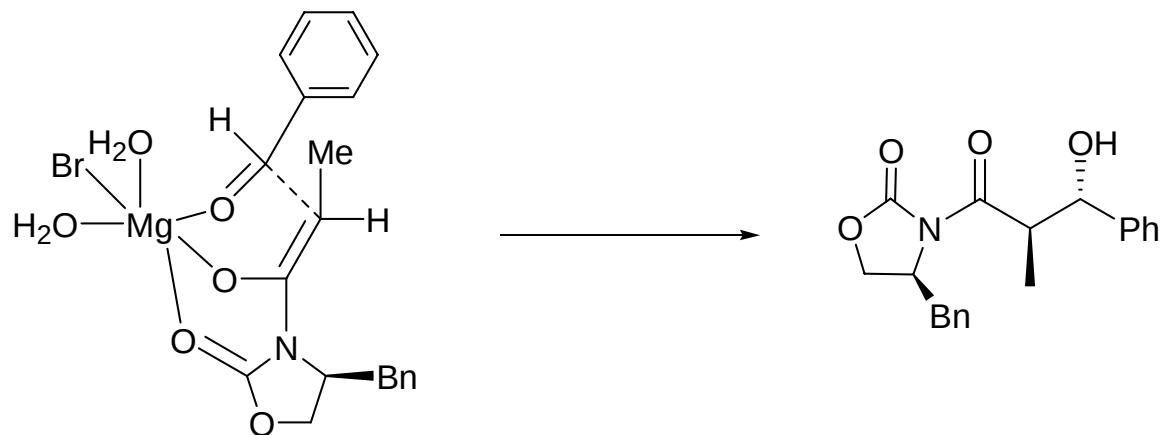
IV.5. Evans Anti-Aldol Prozess: Übertragung auf chirale *N*-Acylthiazolidinthione



R	dr	Ausbeute (%)
Ph	19:1	85
4-MeC ₆ H ₄	19:1	92
4-MeOC ₆ H ₄	19:1	91
CH=CHPh	10:1	87
C(CH ₃)=CHPh	19:1	90
2-Naphtyl	7:1	84
C(CH ₃)=CH ₂	7:1	56



PM3 Berechnungen: Twist-Bootkonformation ist bevorzugt



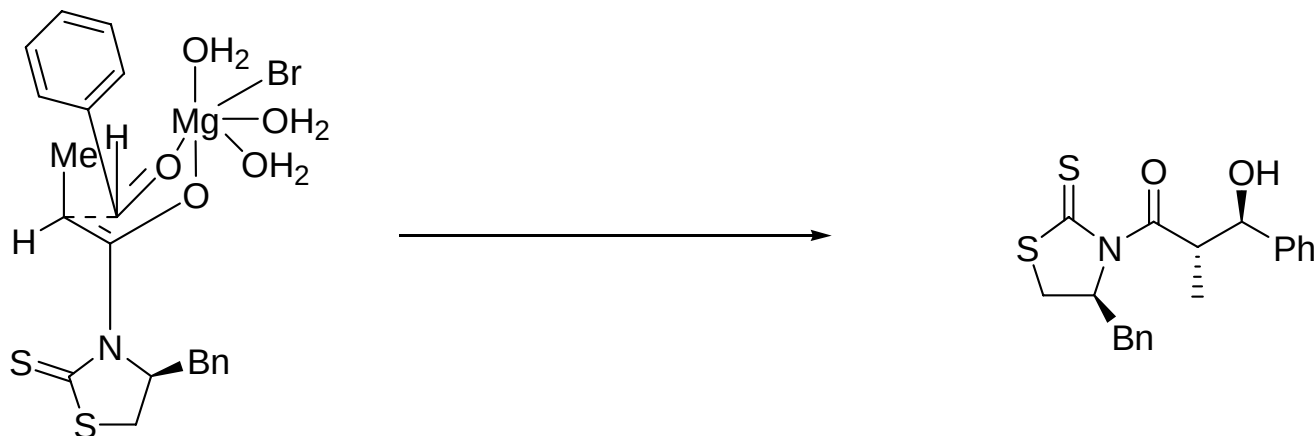
$\Delta E = -2.5$ kcal/mol (im Vgl. zum Sessel)

Chelat-Kontrolle

Vgl.: Alkylierung (D.A. Evans, JACS, 1982, 104, 1737.)

Michael-Addition (D.A. Evans, JACS, 1997, 119, 6452.)

PM3 Berechnungen: Twist-Bootkonformation ist bevorzugt

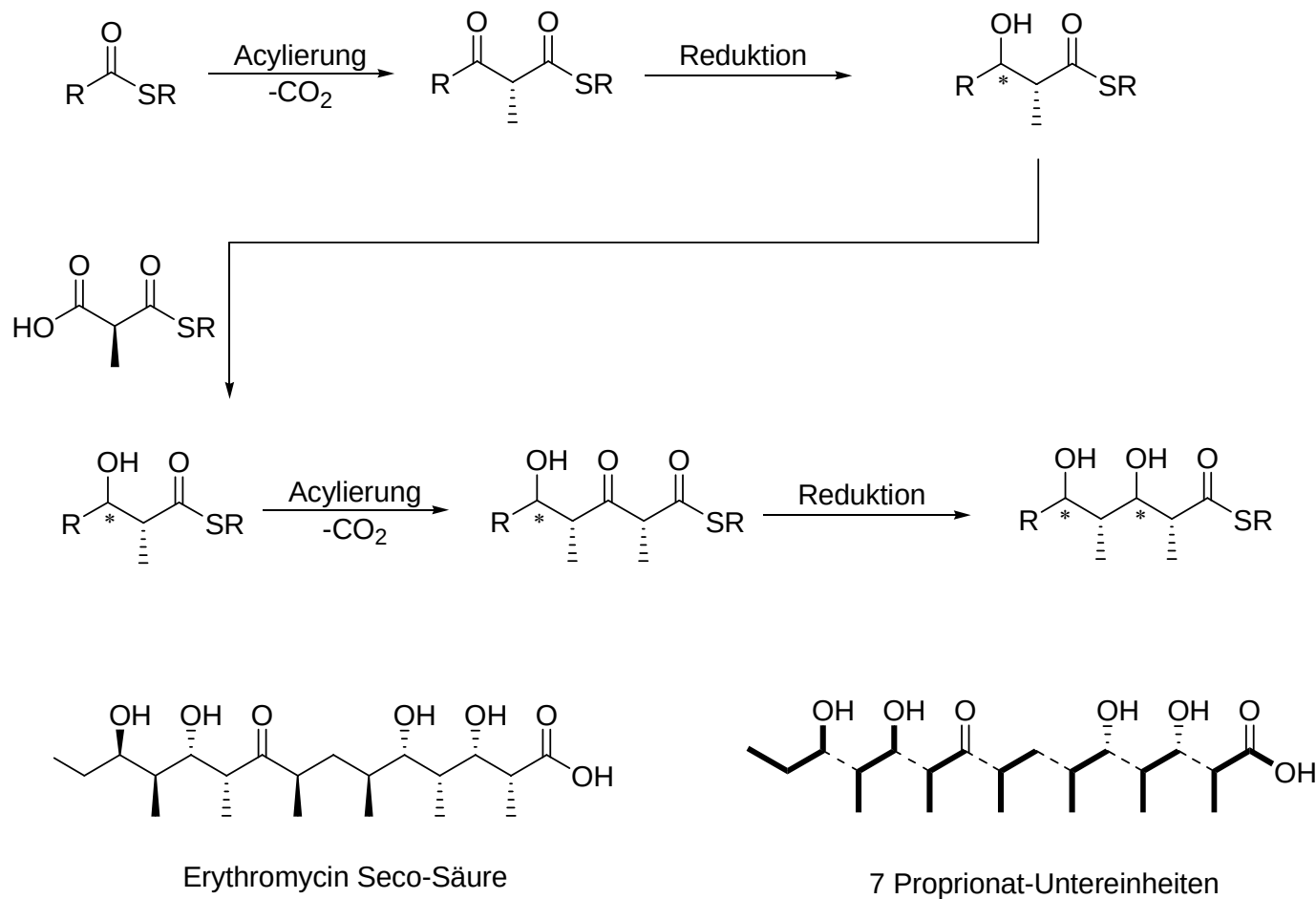


$\Delta E = -2.8 \text{ kcal/mol}$ (im Vgl. zum Sessel)

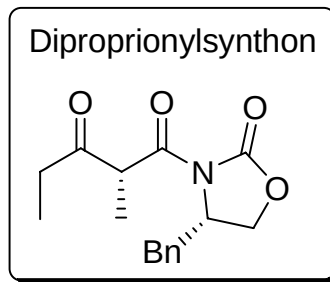
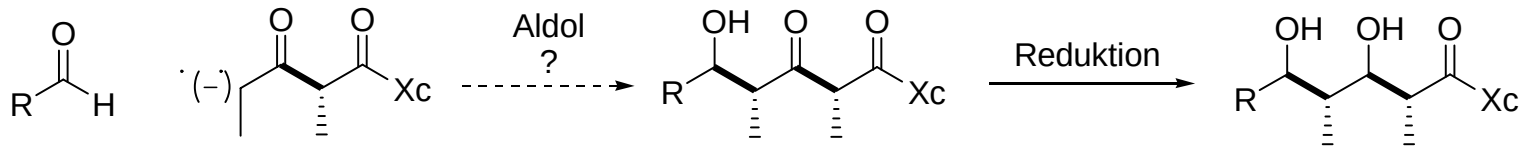
Minimierung der $\text{C}=\text{O} \longleftrightarrow \text{C}=\text{S}$ Dipol Interaktion

V. Dipropionyl-Synthon zum Aufbau von Stereotriaden

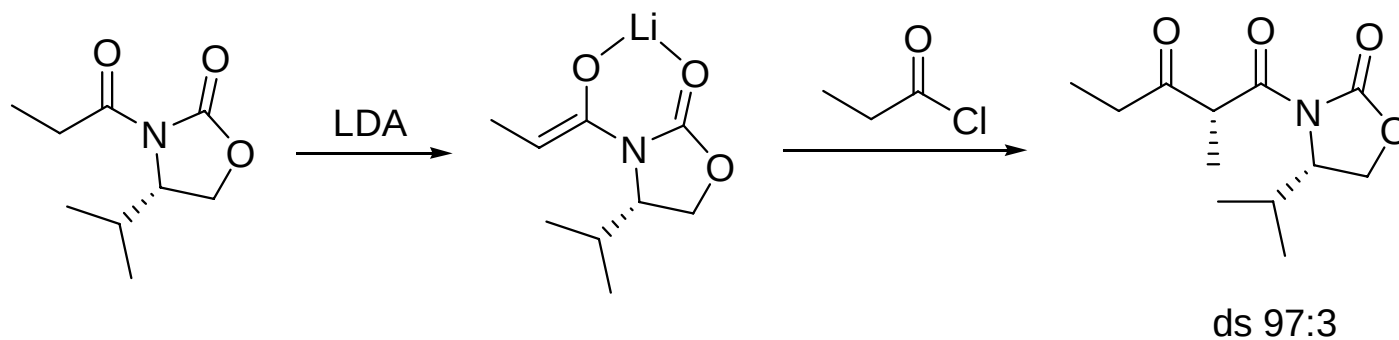
V.1. Polypropionat Biosynthese – Elementare Schritte: Acylierung, Reduktion



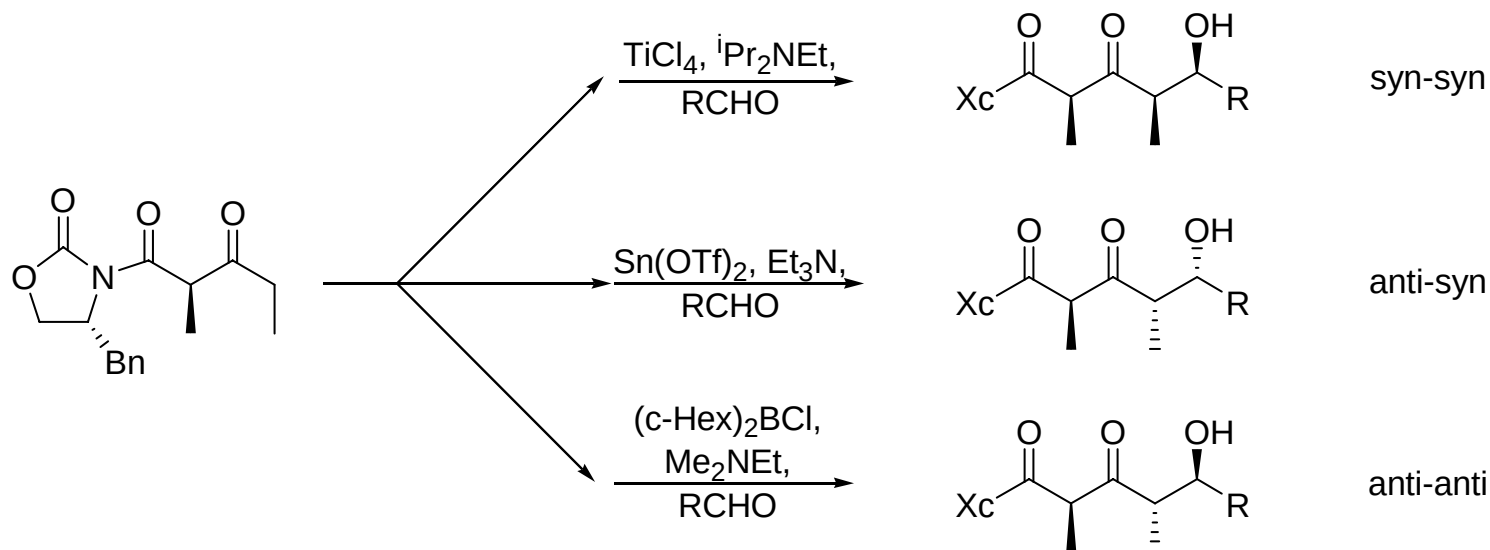
V.2 "Laboratory Mimic" der Polypropionat Biosynthese



Enolat Acylierung führt zu chiralen β -Ketoimiden



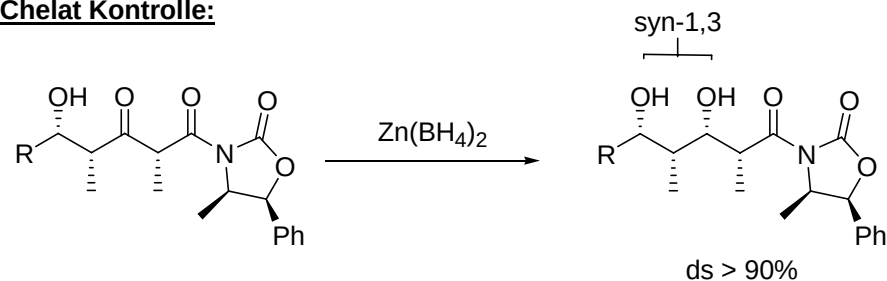
Aldol-Reaktion über β -Ketoimidenolate



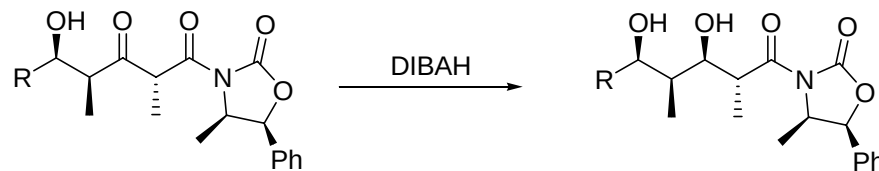
Stereoselektive Reduktion: Chelatkontrolle oder OH-gesteuerte 1,3-Induktion



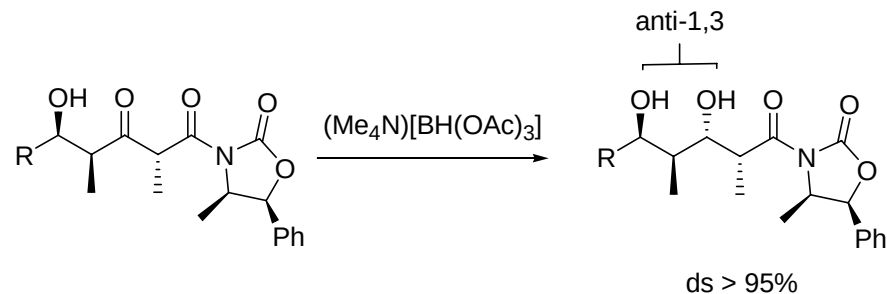
Chelat Kontrolle:



Steuerung erfolgt durch β -Chelatisierung (δ -OH-M- β -CO):



OH-gesteuerte 1,3-Induktion:

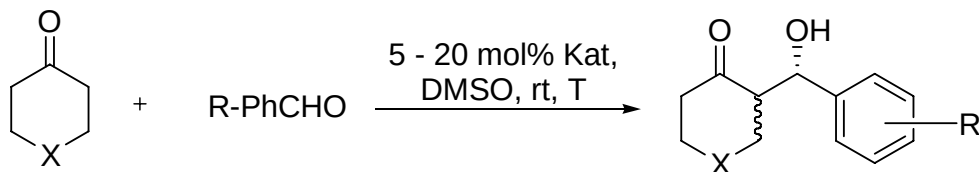




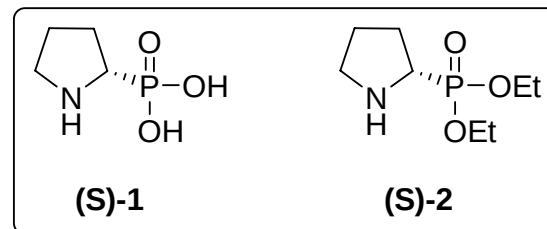
VI. Organokatalytische Aldol Reaktionen

VI.1. Aminophosphonate als Organokatalysatoren:

Versuche zur *syn* Selektivität in der Gegenwart von Lewis Säuren

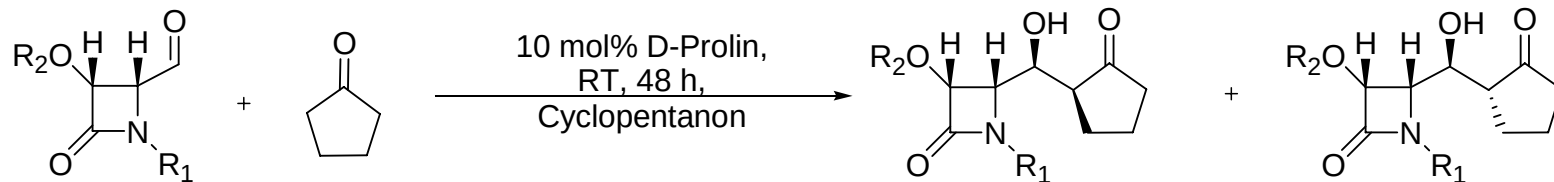


X = Heteroatom CH₂ R = 4-NO₂ 2-Cl T = 21 - 144 h

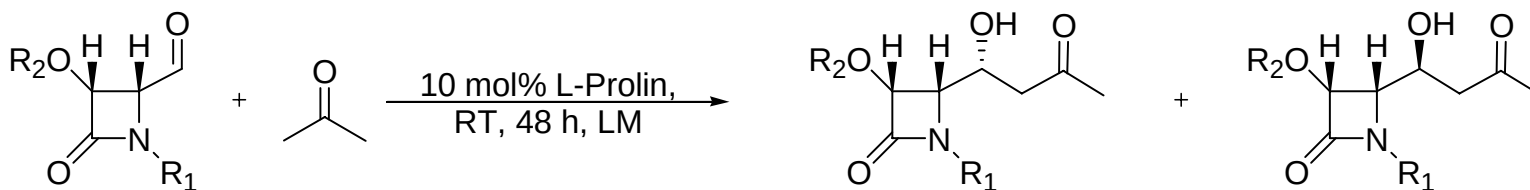


		Kat (mol%)	Ausbeute [%] (syn/anti)
X = --	Y = 4-NO ₂	1 (20)	51 (1:1)
X = --	Y = 4-NO ₂	2 (20)	51 (3:2)
X = CH ₂	Y = 4-NO ₂	1 (20)	47 (1:1)
X = CH ₂	Y = 4-NO ₂	2 (20)	91 (1:2)
X = O	Y = 4-NO ₂	2 (5)	79 (1:4)
X = S	Y = 4-NO ₂	2 (5)	36 (1:9)
X = CH ₂	Y = 2-Cl	2 (5)	68 (1:1)

VI.2. Unsubstituiertes Prolin als Organokatalysator

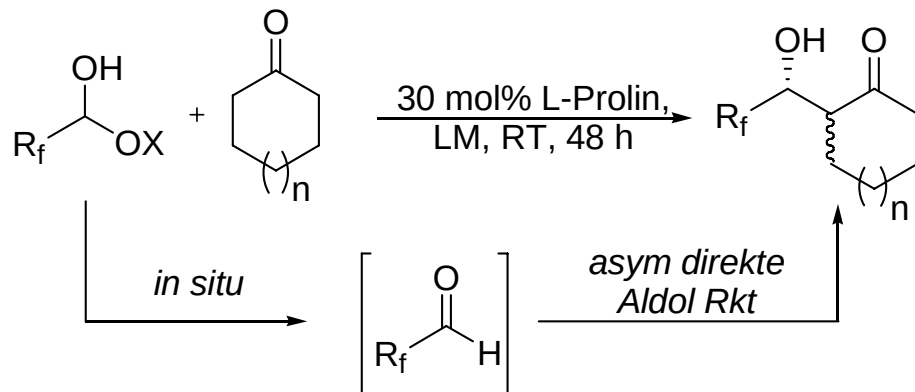


		Lösungsmittel	Ausbeute [%] (syn/anti)
R ₁ = Me	R ₂ = PMP	CP	80 (8:2)
R ₁ = Ph	R ₂ = PMP	CP	77 (85:15)
R ₁ = Ph	R ₂ = Allyl	CP	73 (8:2)



		Lösungsmittel	Ausbeute [%] (syn/anti)
R ₁ = Me	R ₂ = PMP	DMSO	85 (7:3)
R ₁ = Me	R ₂ = PMP	DMF	80 (8:2)
R ₁ = Me	R ₂ = PMP	Aceton	94 (100:0)
R ₁ = Ph	R ₂ = PMP	Aceton	90 (100:0)
R ₁ = Ph	R ₂ = Allyl	Aceton	100 (100:0)

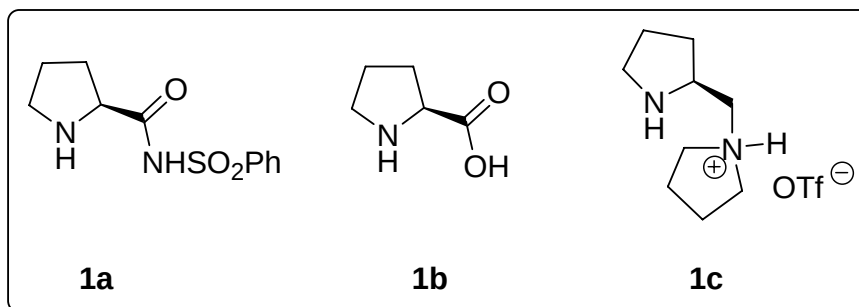
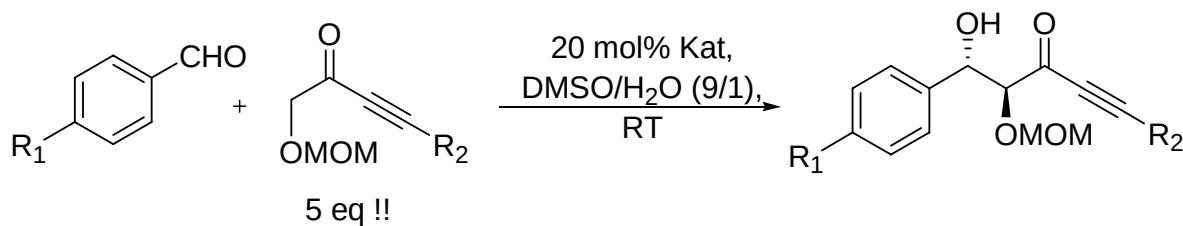
VI.2. Unsubstituiertes Prolin als Organokatalysator für die Aldol Reaktion von Trifluoracetaldehyd-ethyl-hemiacetal mit Ketonen



R_f	X	n	Ausbeute (%)	syn / anti
CF_3	Et	0	96	98:2
CF_3CF_2	H	0	77	94:6
CF_3	Et	1	68	4:96
CF_3CF_2	H	1	64	1:99

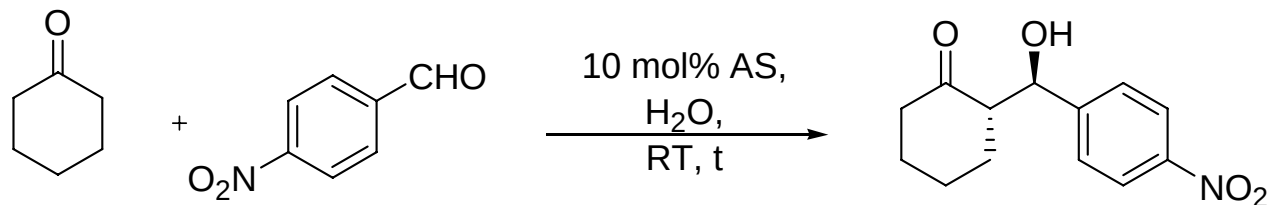
?

VI.3. Enantioselective, organokatalytische Aldol Reaktionen von Ynonen



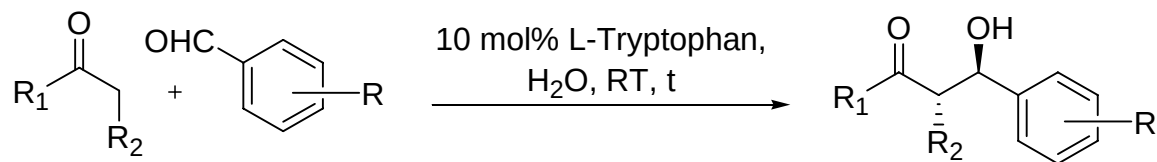
R ₁	R ₂	Kat	t (h)	Ausbeute (%)	syn/anti
NO ₂	Me	1a	48	52	1:9
NO ₂	Me	1b	48	15	?
NO ₂	Me	1c	48	38	1:3
NO ₂	Ph	1a	120	90	1:9
CF ₃	SiEt ₃	1a	120	75	1:3
H	Me	1a	120	26	1:13
Br	Ph	1a	120	65	1:9

VI.4. L- Aminosäuren als Katalysatoren: Asymmetrische Aldol Reaktion in Wasser



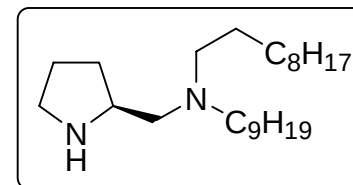
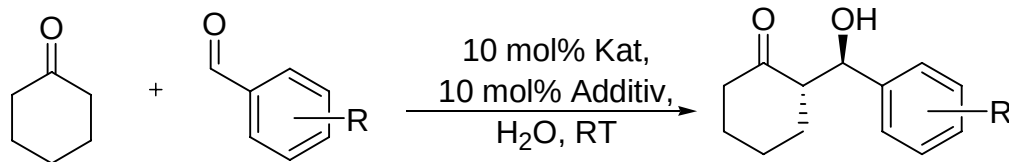
AS	t (h)	Ausbeute (%)	syn/anti
L-Alanin	109	32	1:12
L-Valin	144	84	1:4
L-Leucin	96	81	1:3
L-Tyrosin	28	< 5	--
L-Phenylalanin	48	75	1:4
L-Tryptophan	36	82	1:4

VI.4. L-Tryptophan - Asymmetrische Aldol Reaktion in Wasser



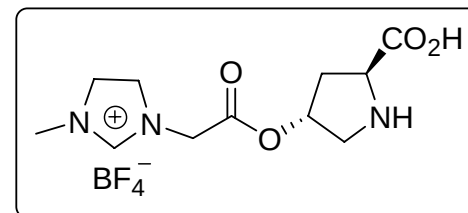
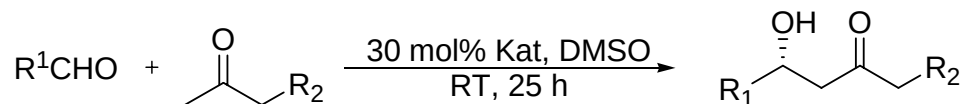
Produkt	T (h)	Ausbeute (%)	syn/anti
	24	77	1:52
	24	79	1:20
	24	78	1:6
	96	66	1:17
	72	49	1:5
	48	99	4:1
	20	94	1:1

VI.5. Organokatalytische Aldol Reaktionen in Wasser



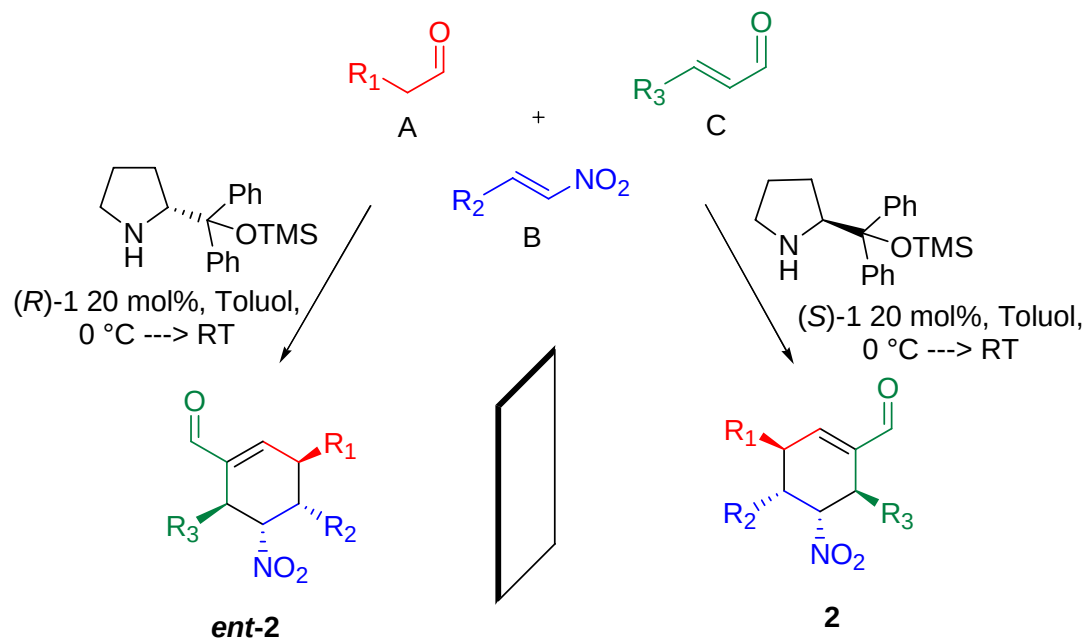
R	Additiv	t (h)	Ausbeute (%)	syn / anti
4-NO ₂	AcOH	24	81	40:60
4-NO ₂	(+)-CSA	24	99	32:68
4-NO ₂	Sc(OTf) ₃	24	94	16:84
4-CN	TFA	48	99	14:86
4-CO ₂ Me	TFA	48	89	10:90
4-Cl	TFA	72	74	12:88
4-OMe	TFA	72	5	14:86
2-NO ₂	TFA	24	98	11:89

VI.6. Ionische Flüssigkeit als Einheit an Prolin

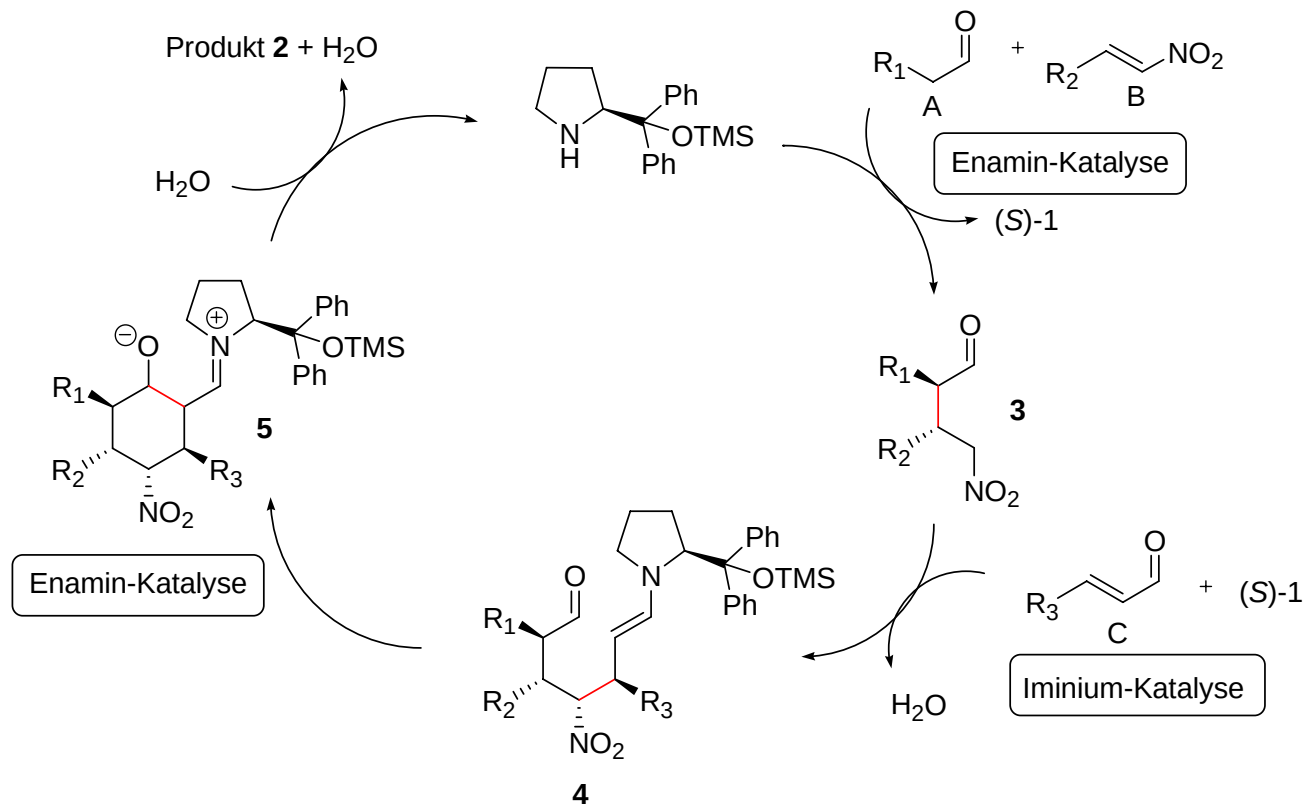


R ₁	R ₂	Ausbeute (%)	ee (%)
4-CNC ₆ H ₄	H	46	72
C ₆ H ₅	H	52	60
4-AcNHC ₆ H ₄	H	50	63
4-BrC ₆ H ₄	H	60	75
2-ClC ₆ H ₄	H	83	70
c-C ₆ H ₁₁	H	49	86
4-NO ₂ C ₆ H ₄	CH ₃	56	75
4-NO ₂ C ₆ H ₄	H	60	87

VI.7. Reaktionskaskaden: Michael/Michael/Aldol Kontrollierter Aufbau von 4 Stereozentren



VI.7. Katalysezyklus



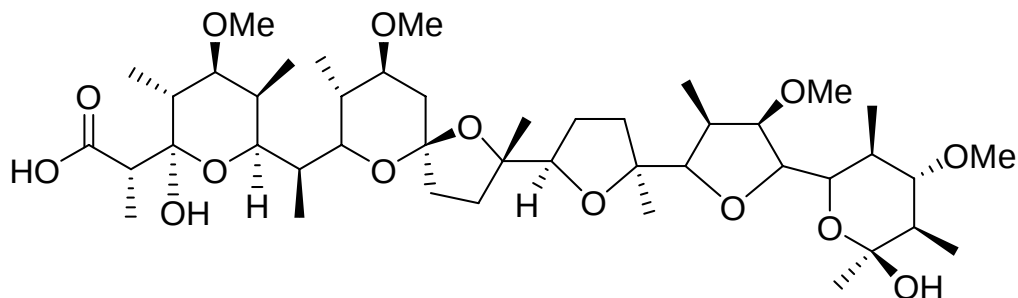


R ₁	R ₂	R ₃	Ausbeute (%)	d.r.	d.e, e.e. (%)
Me	Ph	Ph	40	78:22	> 99
Me	<i>o</i> -ClPh	Ph	51	84:16	> 99
Et	Ph	Ph	58	80:20	> 99
Bn	Ph	Ph	38	89:11	> 99
CH ₂ OTBS	Ph	Ph	54	99:1	99
Me	Ph	Me	25	68:32	> 99

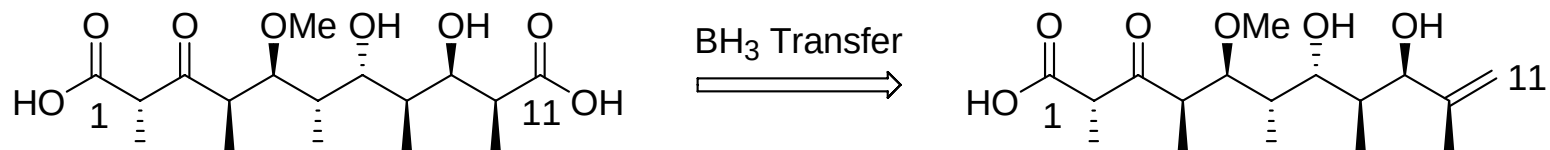


VII. Anwendung der Stereoselektiven Aldol-Reaktion

VII.1. Lonomycin-Synthese

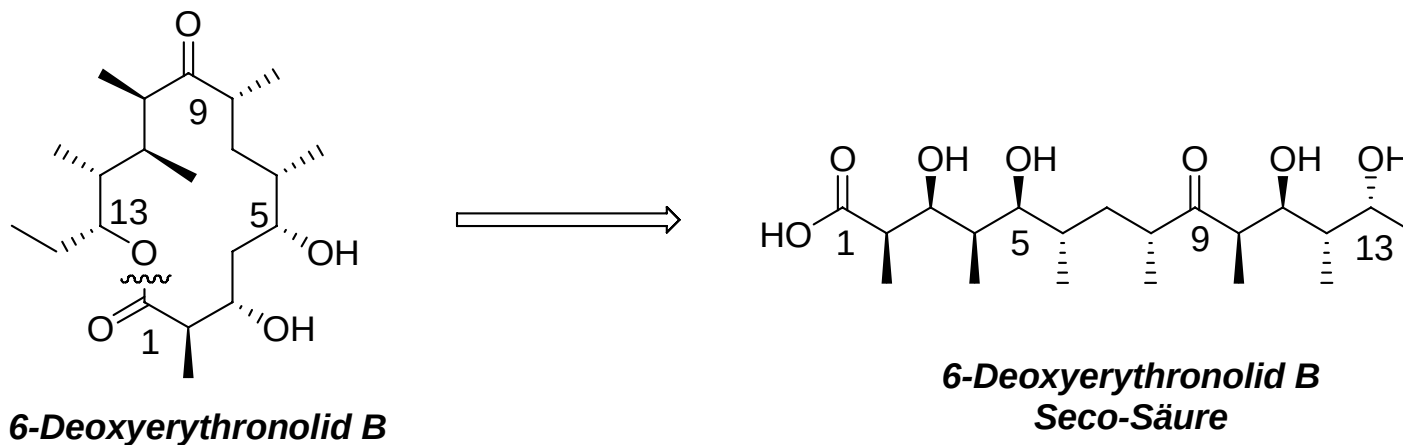


Lonomycin

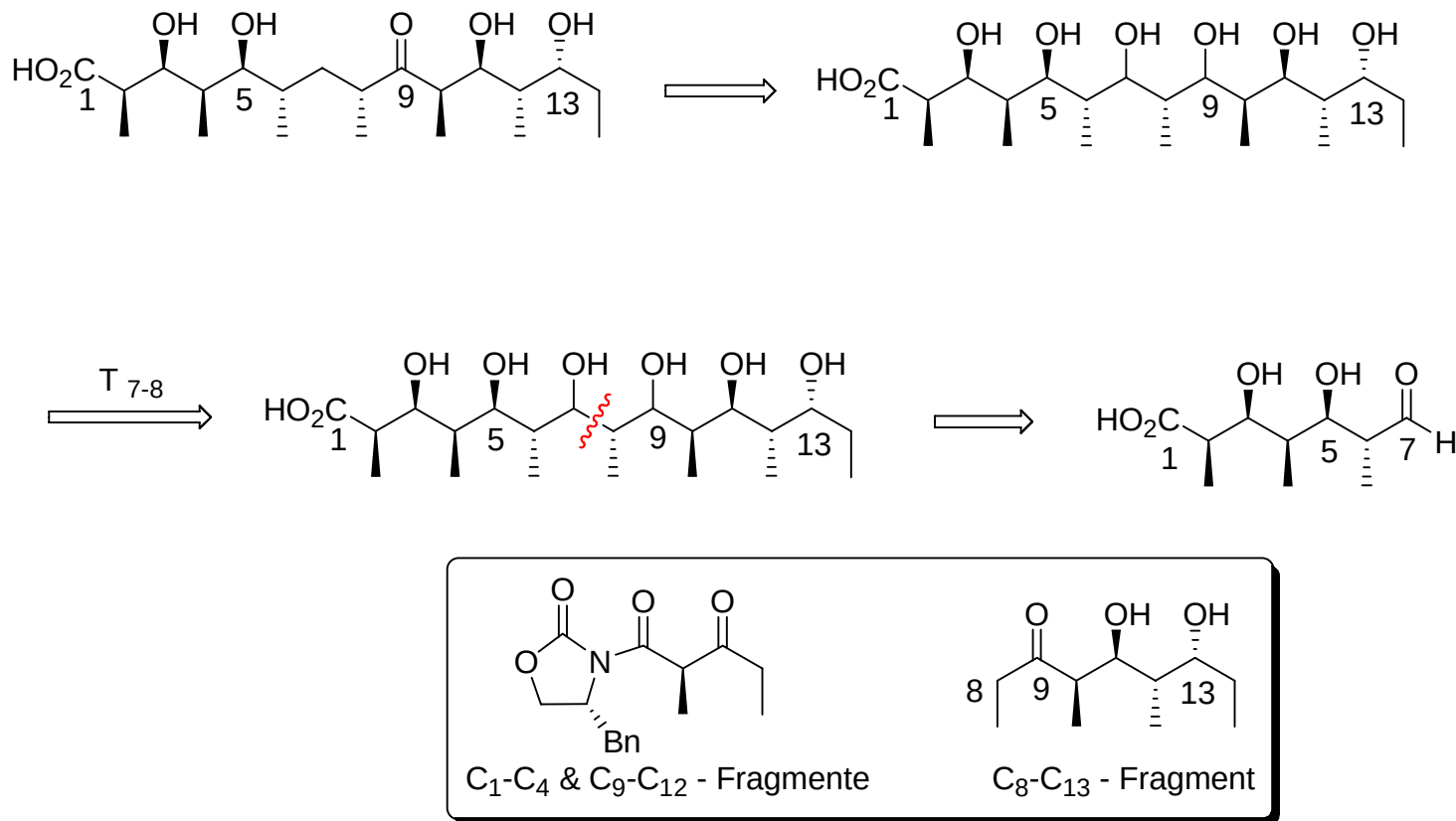




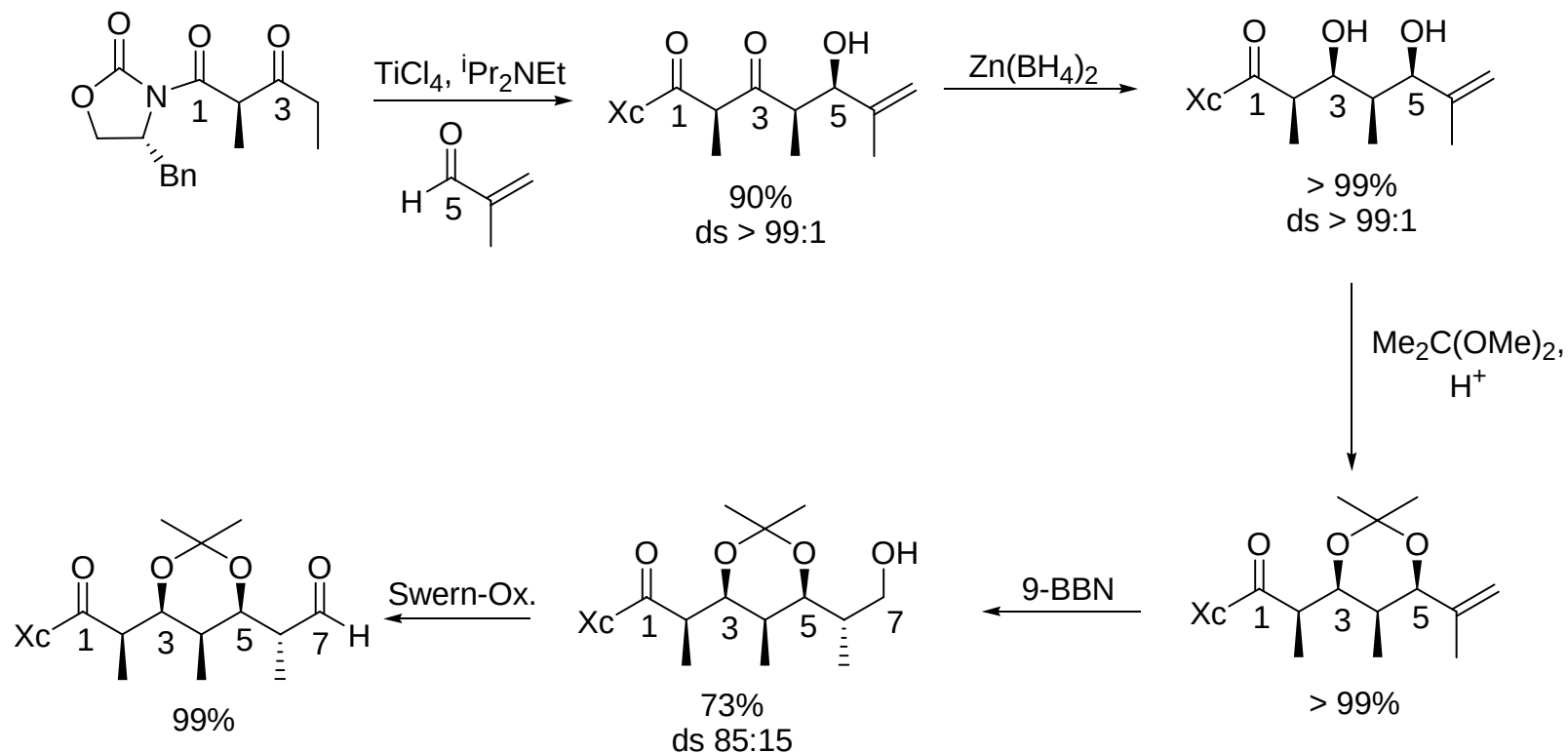
VII.2. 6-Deoxyerythronolid B und Öffnung zur Seco-Säure



Retrosynthese der 6-Deoxyerythronolid B Seco-Säure

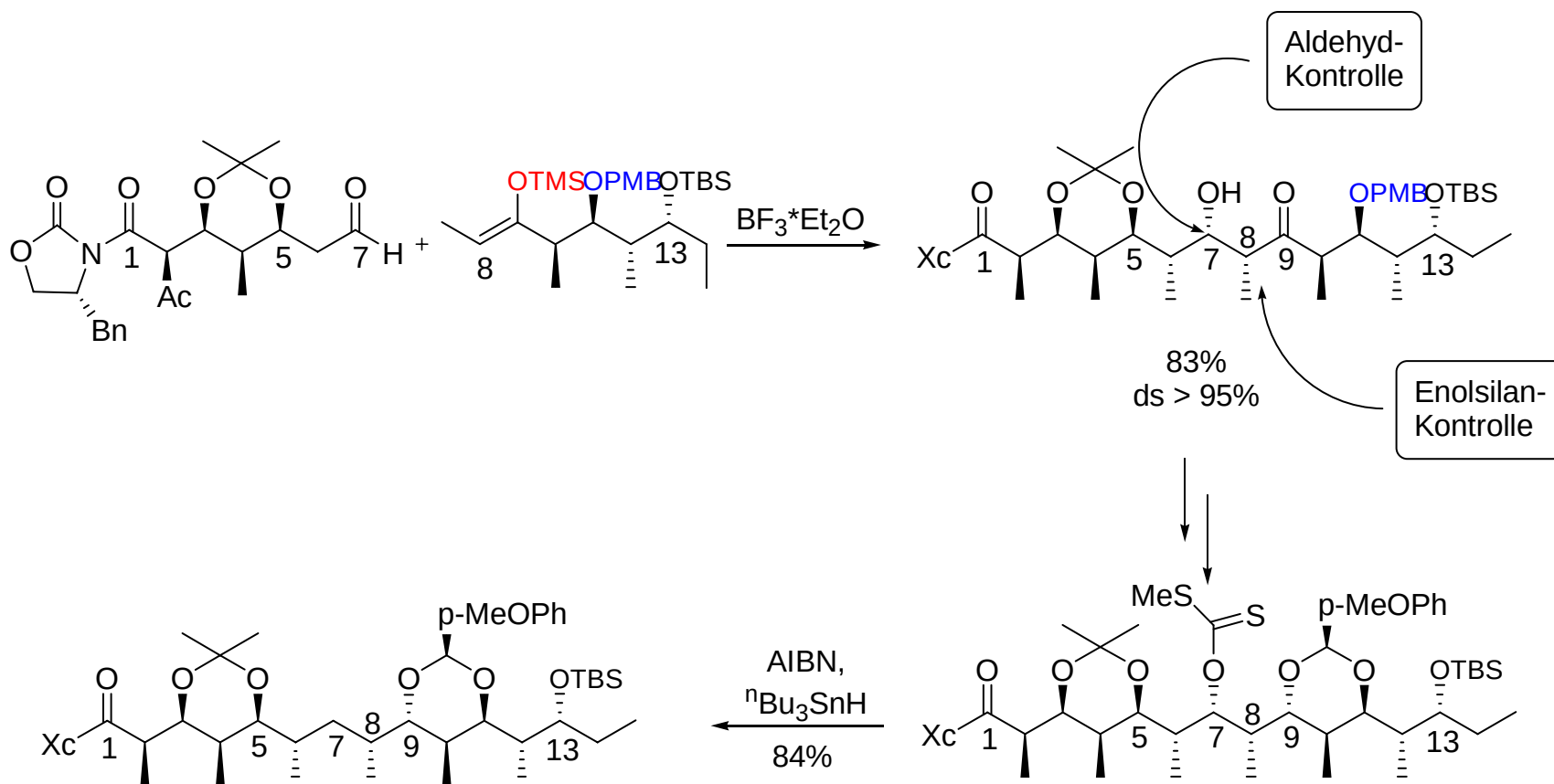


6-Deoxyerythronolid B: Synthese des C₁-C₇ Fragments / Ti-Enolat → Syn-Syn

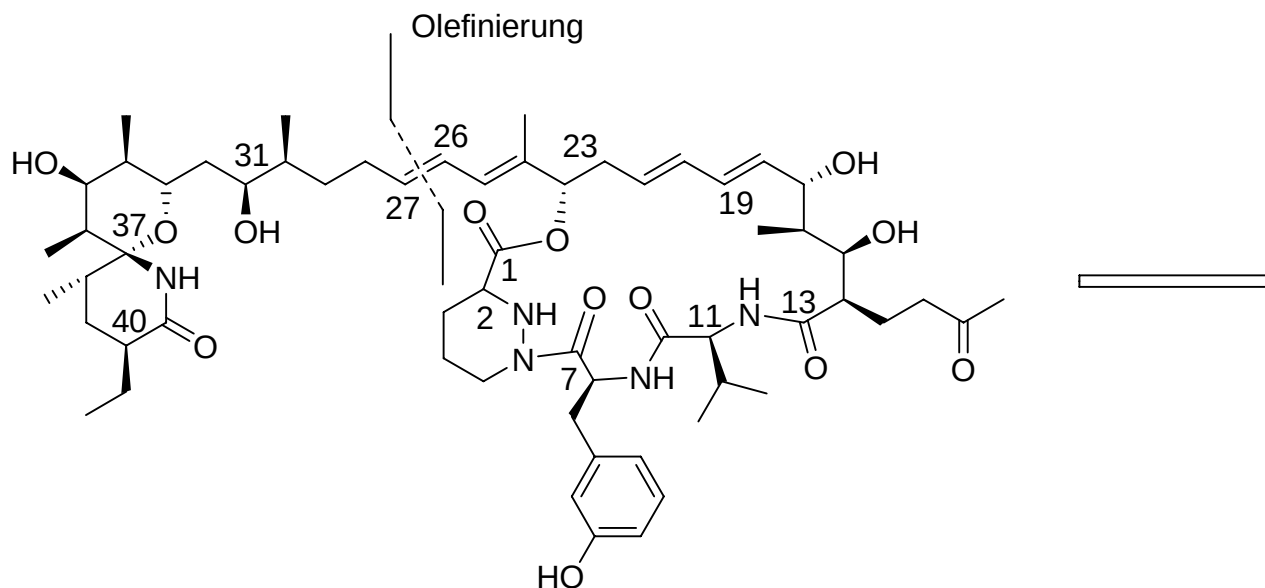




6-Deoxyerythronolid B: Aldol Fragment Kupplung, Reduktion & Deoxygenierung



VII.3. Sanglifehrin A: Spiroketal und Makrozyklus

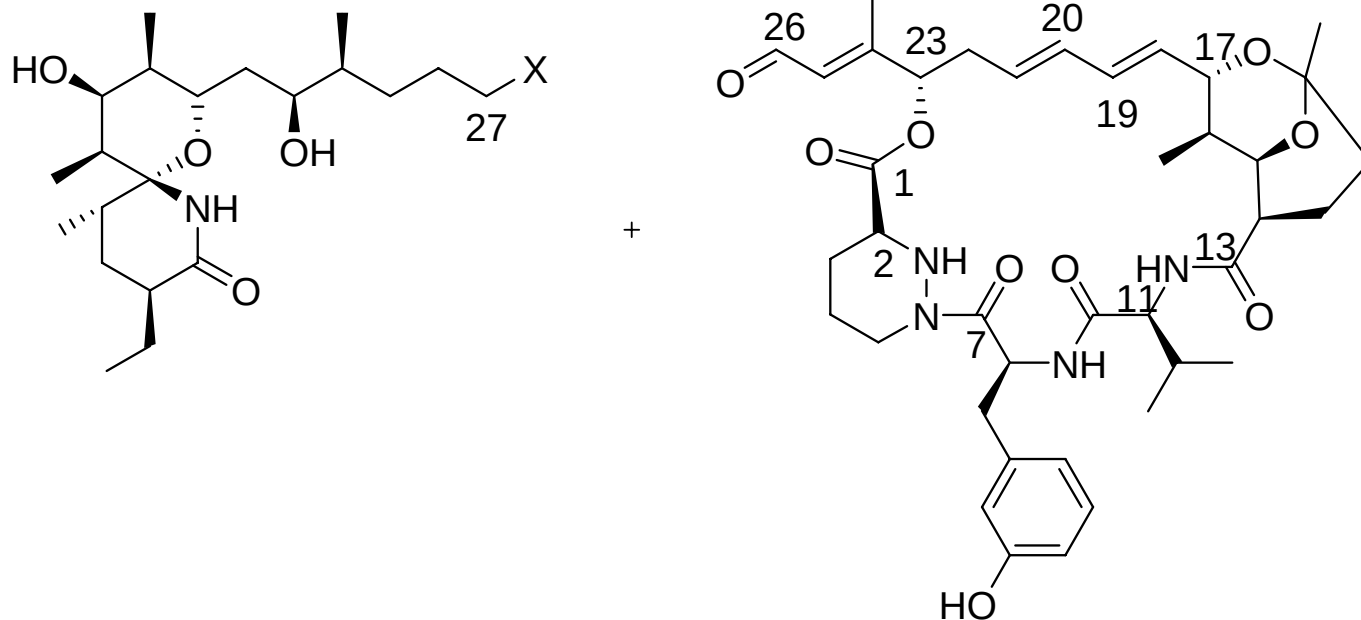


Sanglifehrin A

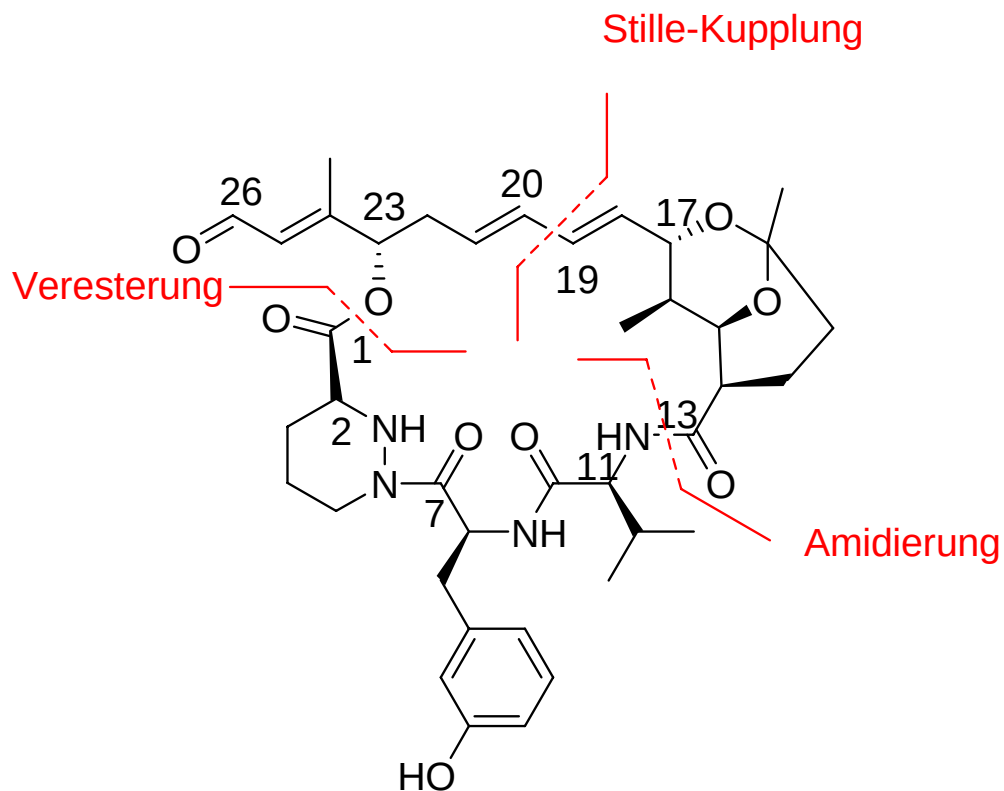
Totalsynthese: K.C. Nicolaou et al., *Angew. Chem., Int. Ed.* **1999**, 38, 2447.

Relaysynthese: R. Metternich et al., *J. Org. Chem.* **1999**, 64, 9632.

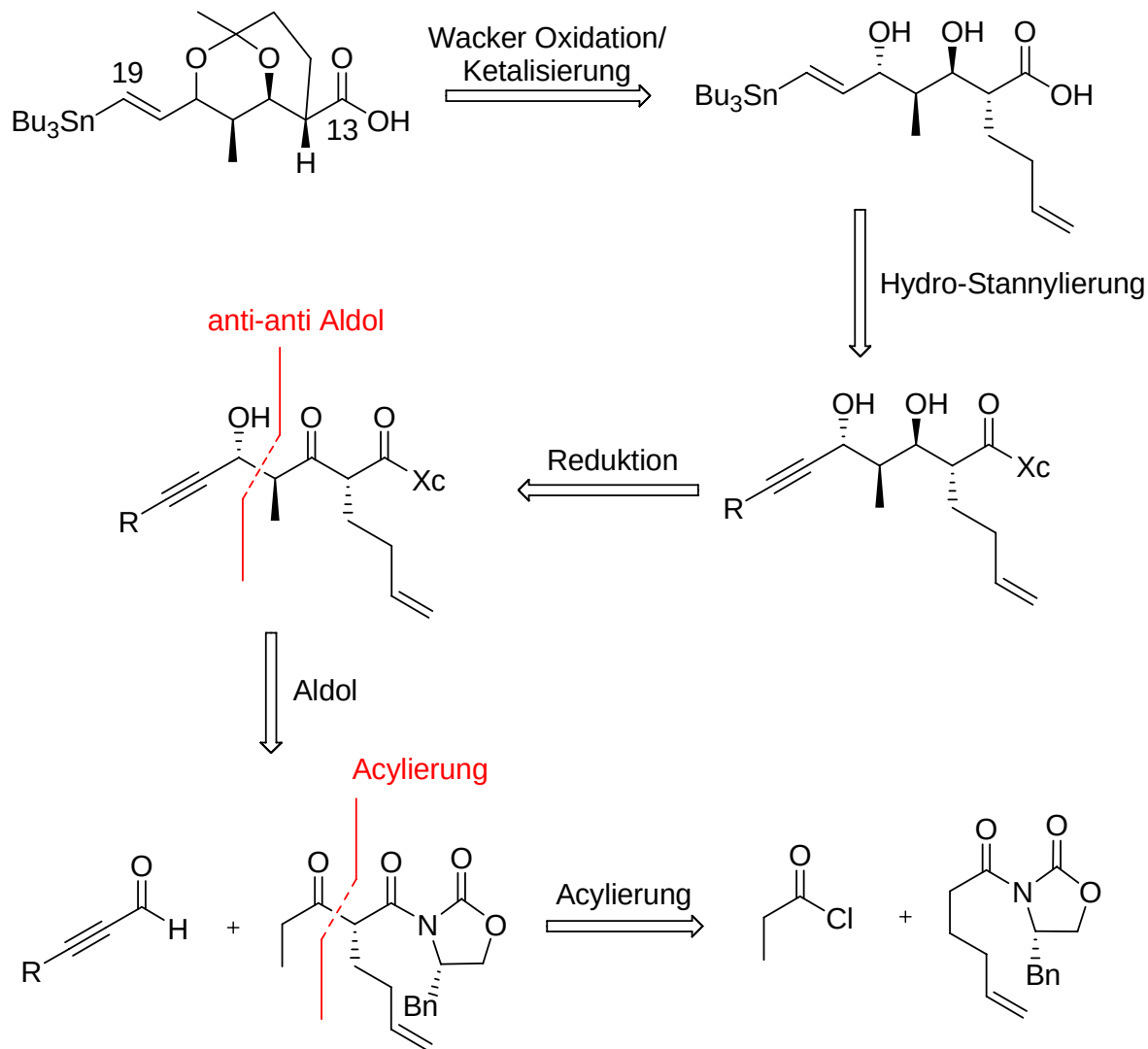
Sanglifehrin A: Spiroketal und Makrozyklus



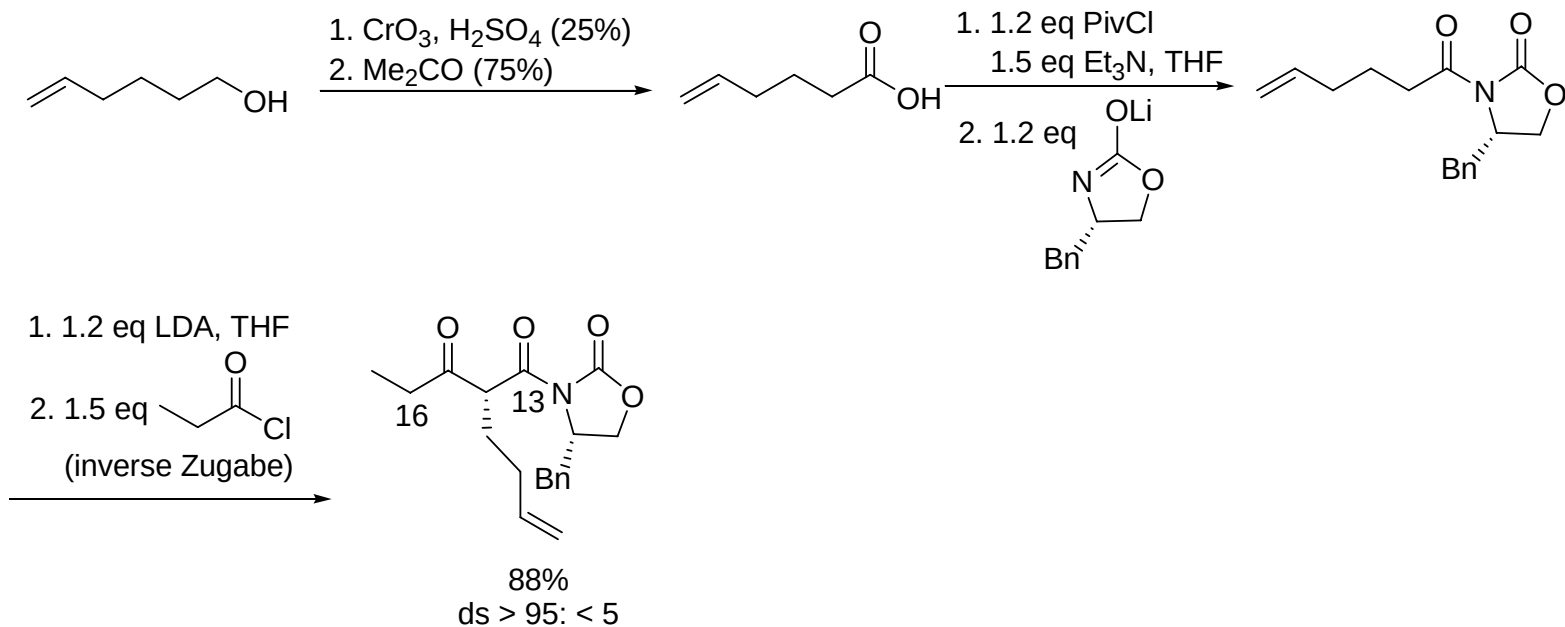
Sanglifehrin A: Retrosynthetische Analyse des C₁-C₂₆-Makrocyclus



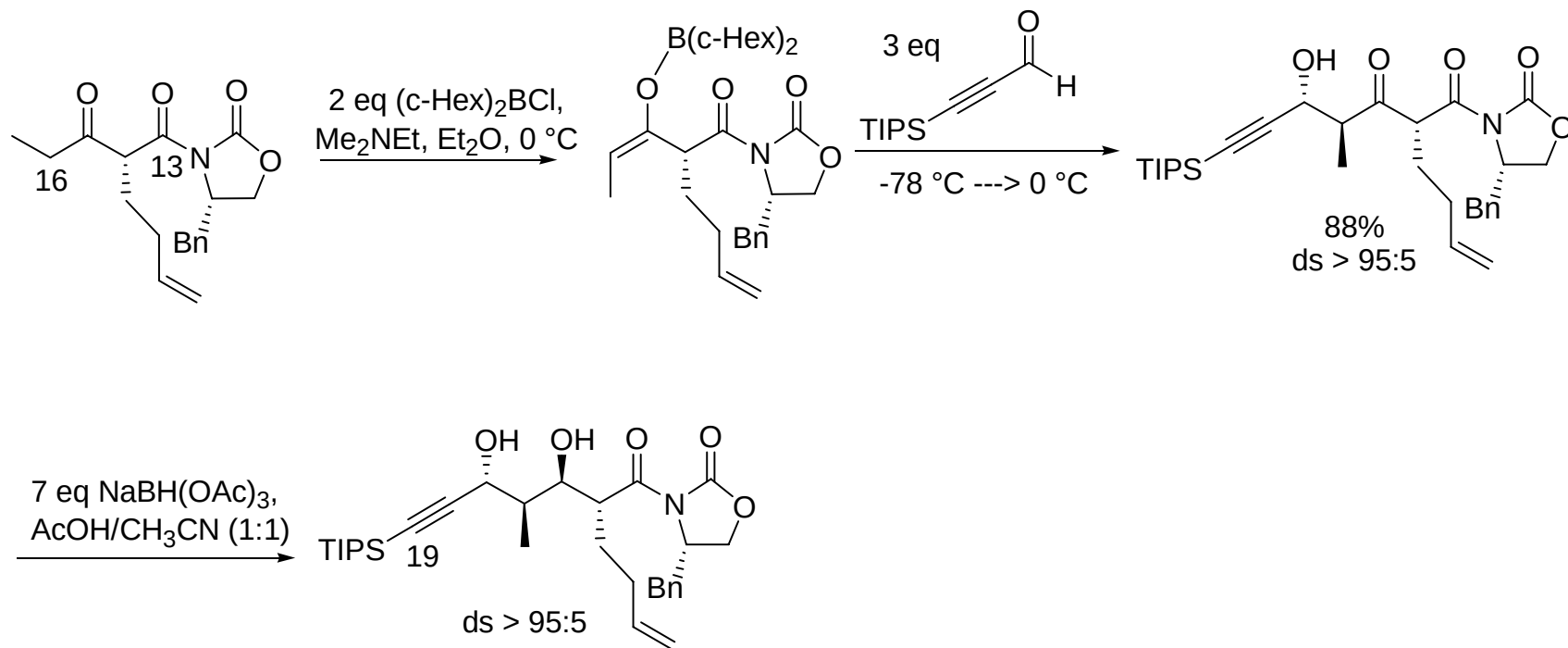
Retrosynthetische Analyse des C₁₃-C₁₉ Fragments



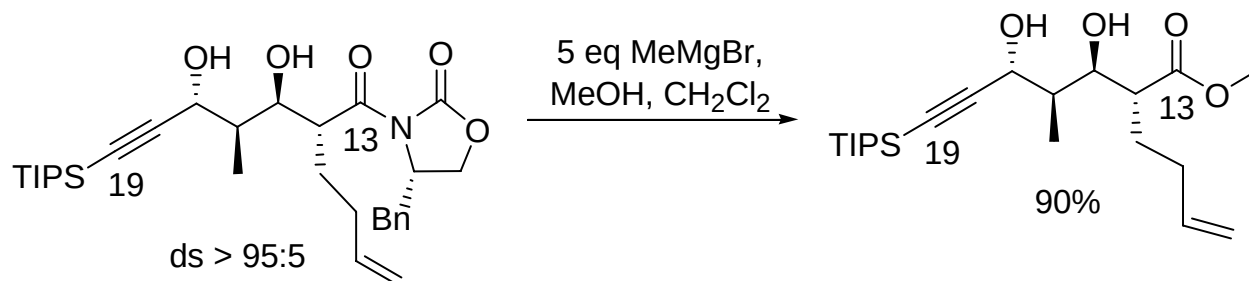
C₁₃-C₁₉ Fragment: Synthese des chiralen β -Ketoimids (C₁₃-C₁₆)



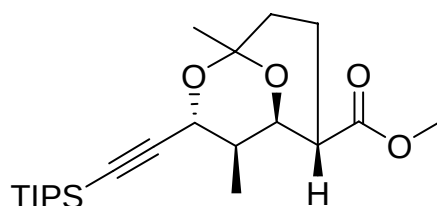
C₁₃-C₁₉ Fragment: anti-anti Aldol und diastereoselektive Reduktion



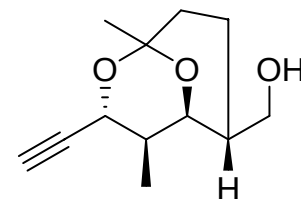
C₁₃-C₁₉ Fragment: Wacker Oxidation und Hydrostannylierung



1. 0.05 eq PdCl₂
0.01 eq Benzochinon
DMF-H₂O (78%)
2. HF-Pyridin, CH₃CN,
0 °C (78%)

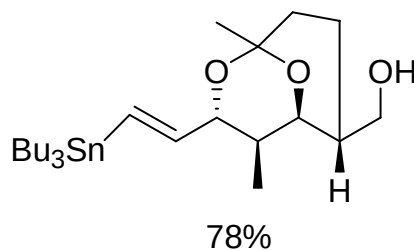


1. LiAlH₄, Et₂O (88%)
2. 1.4 eq TBAF, THF
(85%)

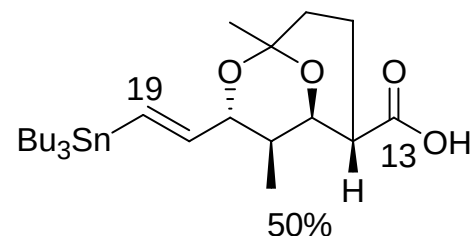


X-ray

2.2 eq (Bu₃Sn)BuCuCNLi,
THF, -78 °C



1. TPAP, NMO
2. NaClO₂





Danke für die Aufmerksamkeit &

Entschuldigung für die Überlänge !!!

Acknowledgment



Current group members (alphabetical)

Shadi Amiri
Dr. Ekaterina. D. Butova
Prof. Dr. Andrey A. Fokin
Dr. Natalya A. Fokina
Christian Kleiner
Mike Kotke
Volker Lutz
Anika Merz
Christian Müller
Adelina Nemirowski
Dr. H. Peter Reisenauer
Tatyana Rodionova
Dr. Parham Rooshenas
Prof. Dr. Peter R. Schreiner, PhD
Hartmut Schwertfeger
Dr. Boryslav Tkachenko
Steffen Wagner
Lukas Wanka
Torsten Weil
Derek Wolfe
Zhiguo Zhang



Sorry, kein neueres Photo verfügbar!!

Support

Deutsche Forschungsgemeinschaft | Fonds der Chemischen Industrie | DAAD | Chevron | BASF | Merz Pharma