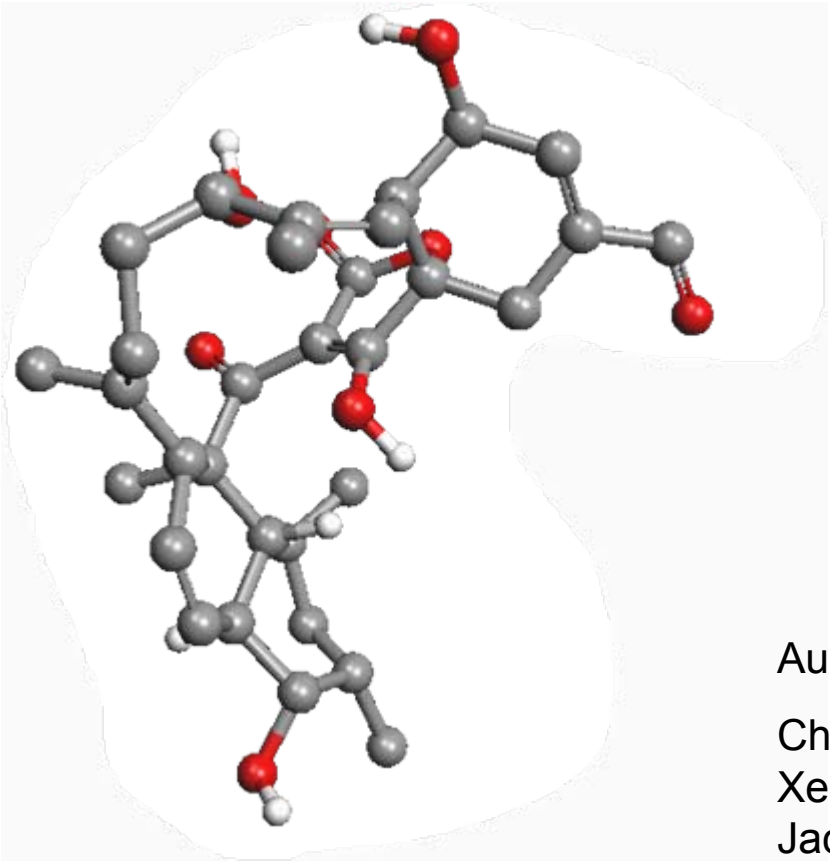
Totalsynthese von (+)-Tetronolid



R. K. Boeckman, Jr., P. Shao, S. T. Wrobleski, D. J. Boehmler, G. R. Heintzelman, A. J. Barbosa

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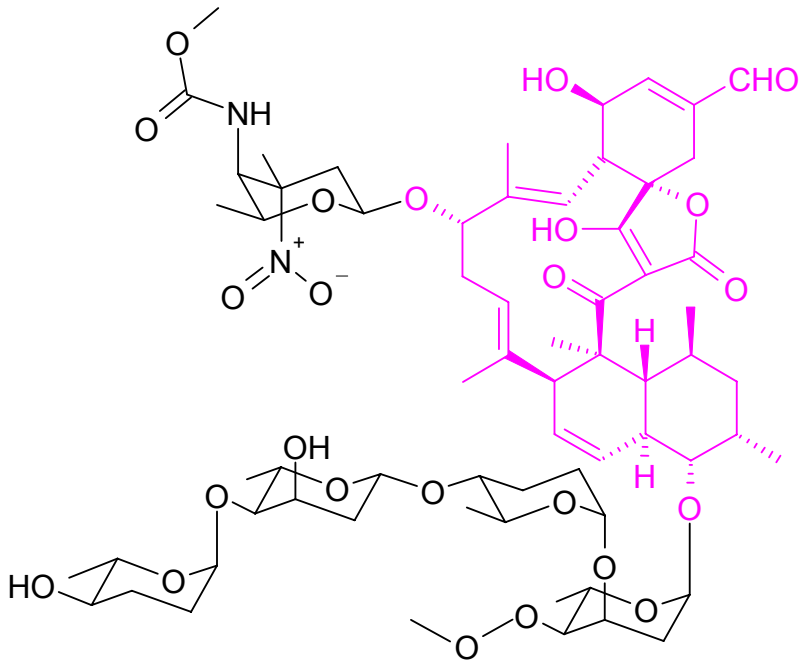
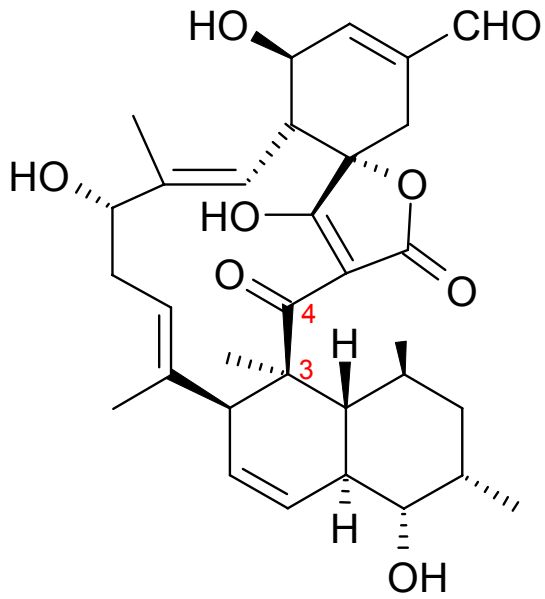
Ausgearbeitet von:

Christina Dreher, Franziska Höfner, Markus Klose, Xenia Lojewski, Julia Maurer, Andreas Meier, Jacqueline Menzel, Isabelle Vogt



- Tetronolid ist Aglyconeinheit des Tetrocarcins A
- Tetrocarcin A isoliert aus Bakterien (Aktinomyzeten)

Quelle: www.pubmed.gov

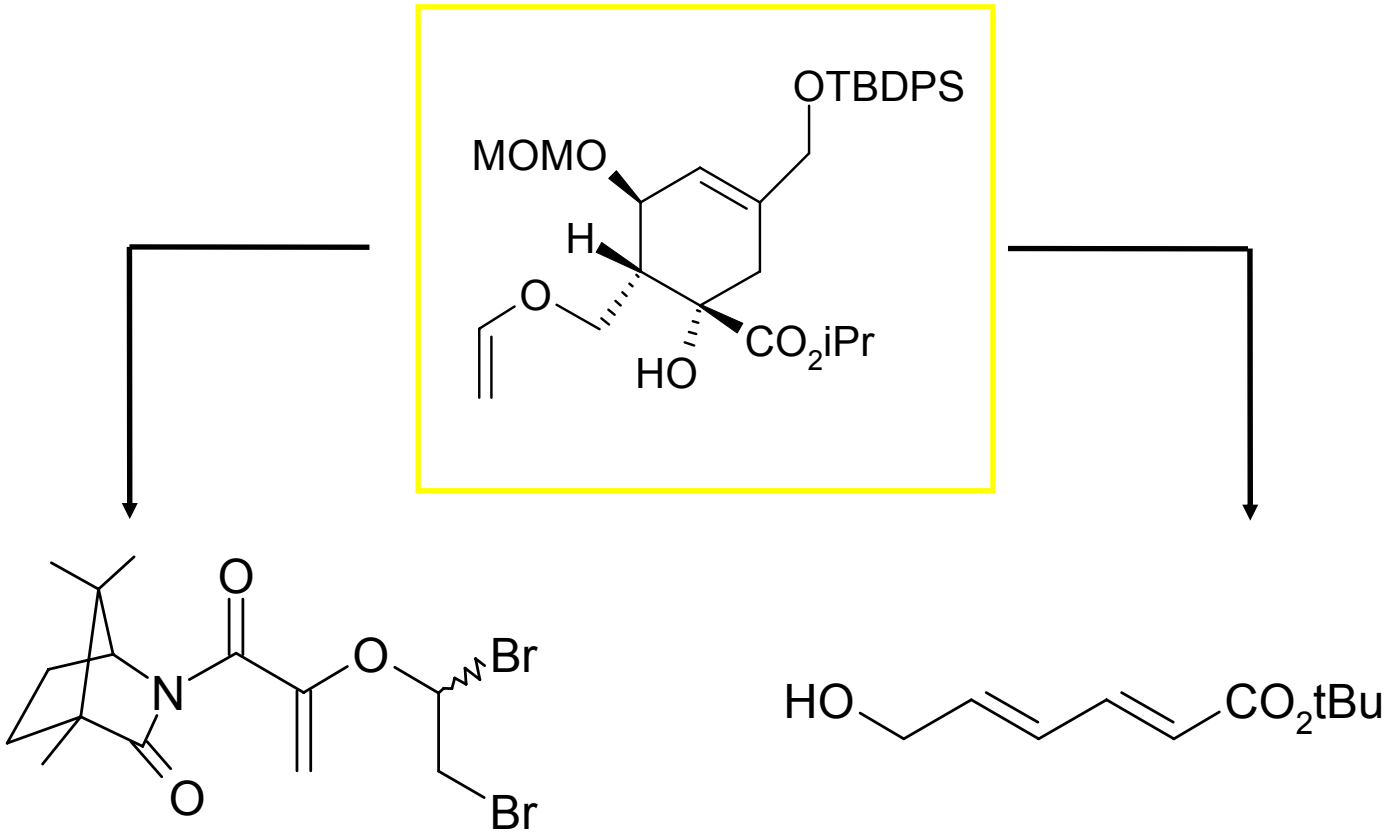


- Tetrocarcin A ist ein Antitumor Medikament, es wirkt gegen einige Sarkome, Melanome und Leukämie
- Enzym Caspase kann den programmierten Zelltod auslösen
- normalerweise wird es von Bcl-2 (einem Proto-Onkogen) vernichtet, so dass Zelle überlebt
- Tetrocarcin A greift Bcl-2 an, somit kann Caspase die Zelle über endoplasmatisches Reticulum bzw. Mitochondrien zerstören
- es wird weiter an Tetrocarcinen als Krebsmedikament geforscht

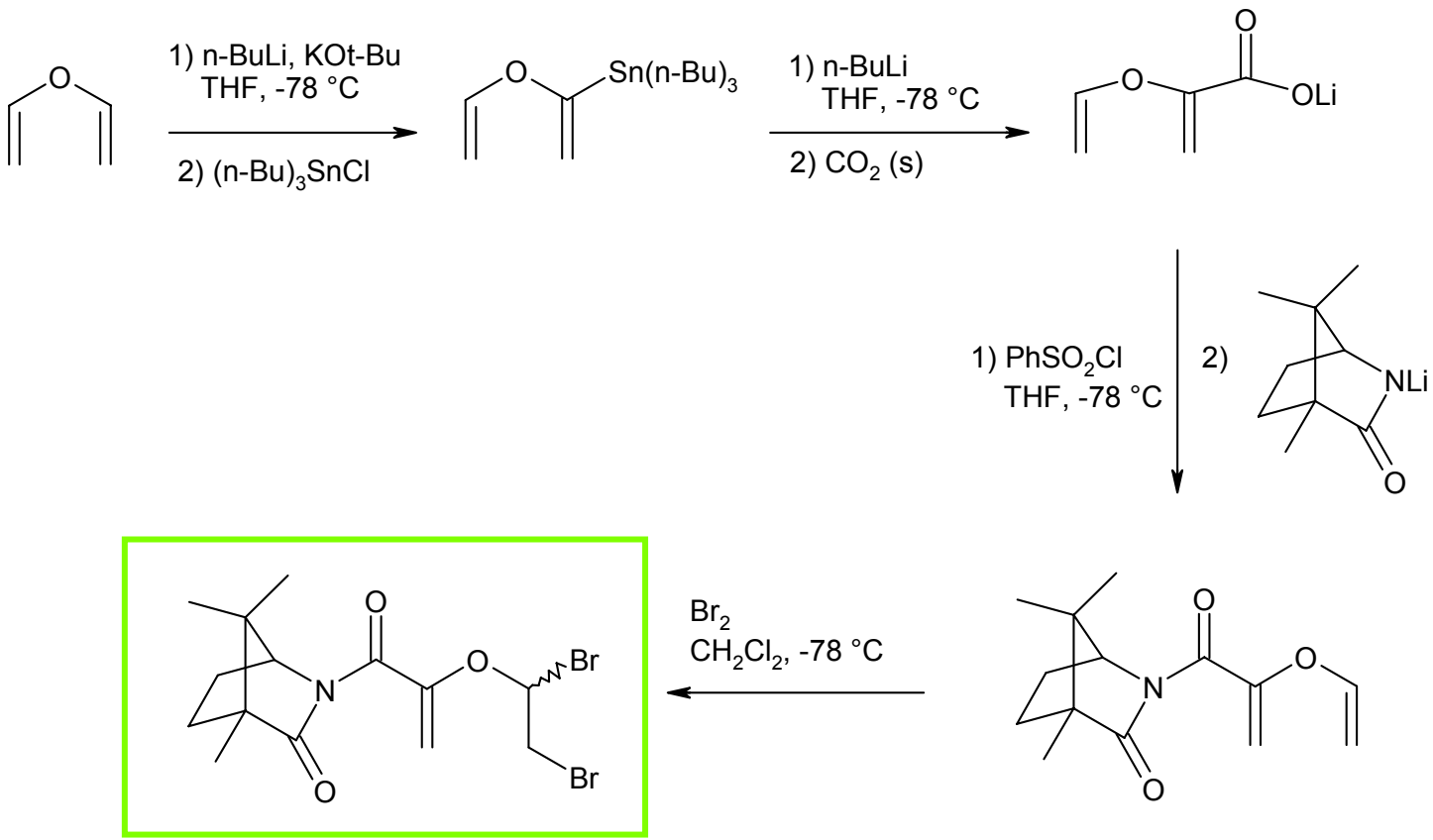
Literatur: B. Adler, H. Ziesmer (Hrsg.); Chemische Karzinogenese, deutscher Verlag für Grundstoffindustrie Stuttgart, **1996**

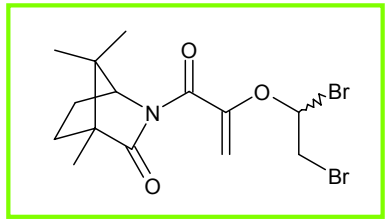
W. Pschyrembel, Pschyrembel – Klinisches Wörterbuch, 258. Auflage, Berlin, New York, W. de Gruyter, **1998**

Darstellung des oberen Fragments

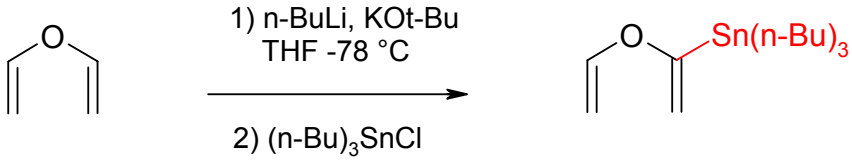


I.1. Synthese der Untereinheit 1





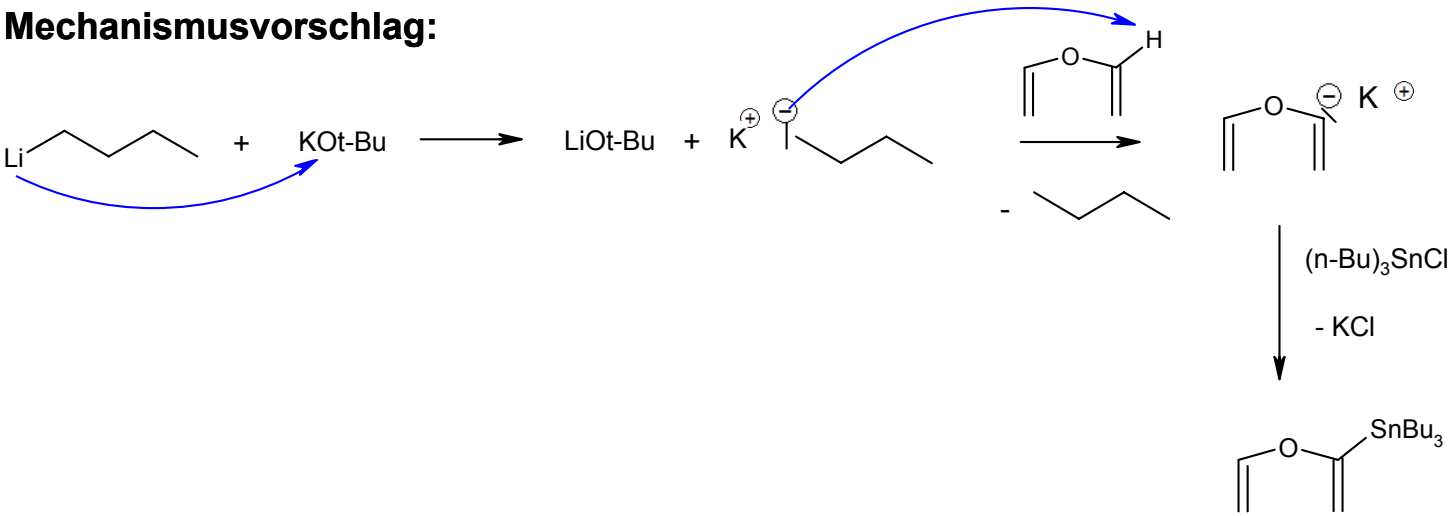
I.1.1. Herstellung des α-stannylierten Ethenyloxyethens

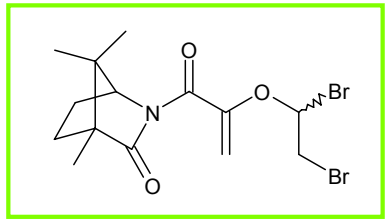


98%

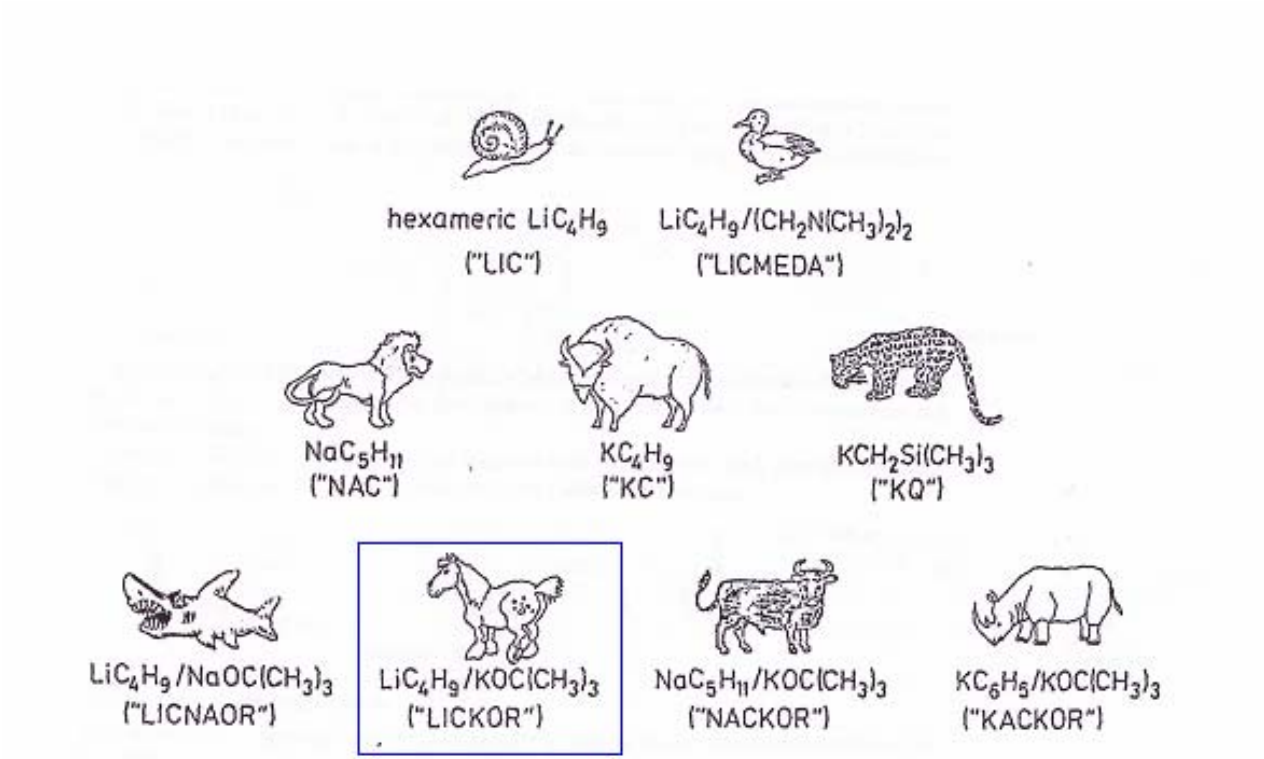
KOt-Bu / n-BuLi = Schlosser-Base (LICKOR)

Mechanismusvorschlag:





Basenstärken



Literatur: M. Schlosser *Modern Synthetic Methods* **1992**, *6*, 239

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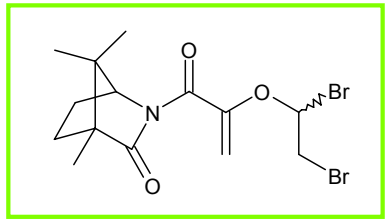
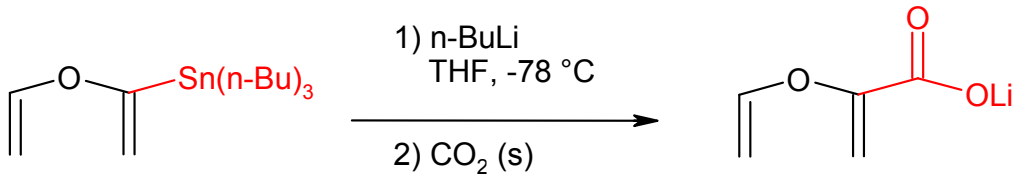
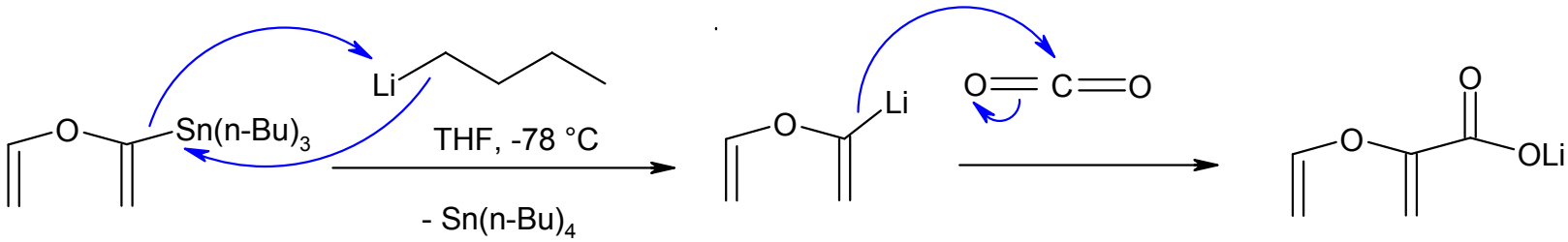


I.1.2. Herstellung des Lithium-Carboxylats

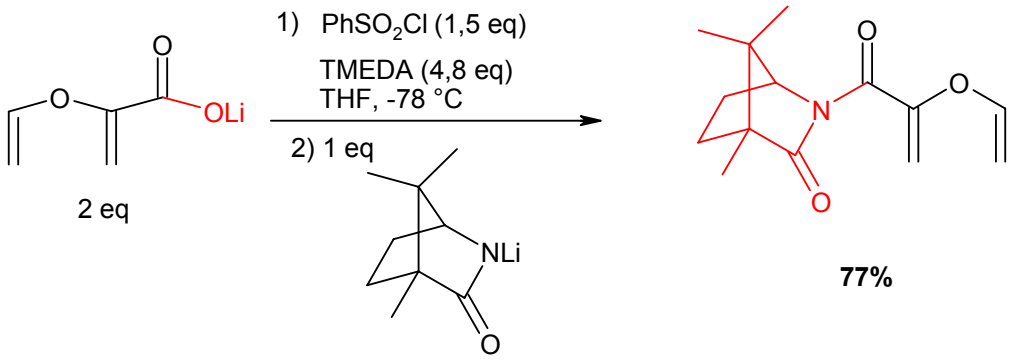


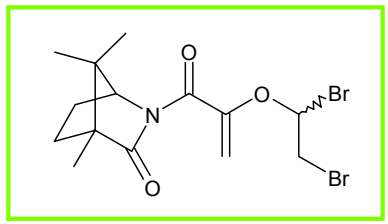
89%

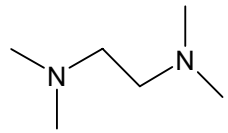
Mechanismusvorschlag:



I.1.3. Einführung des Lactamderivats





TMEDA = 

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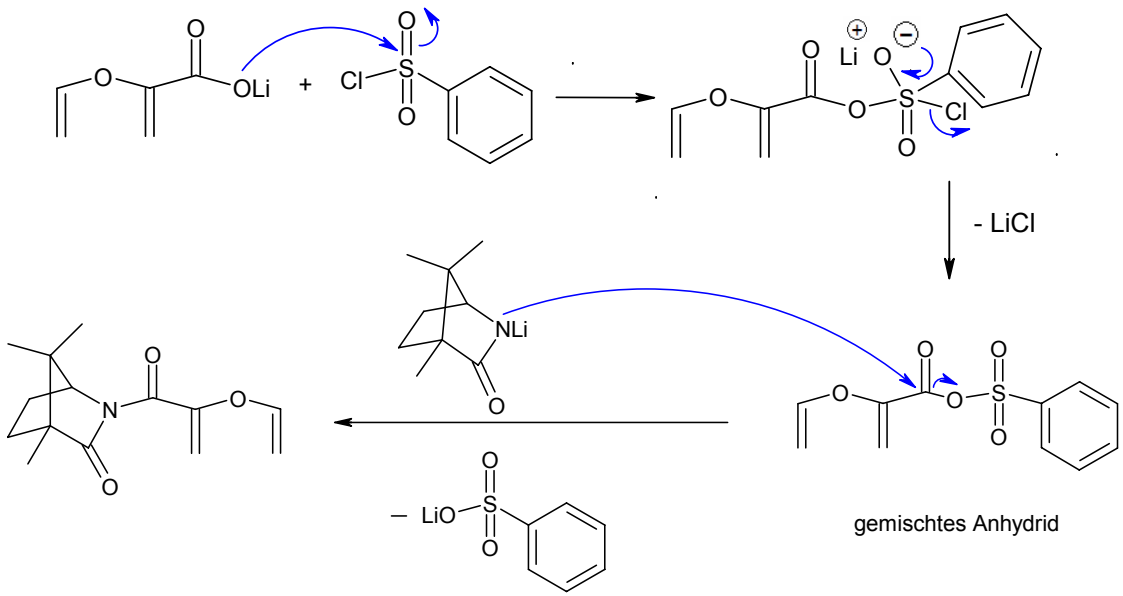
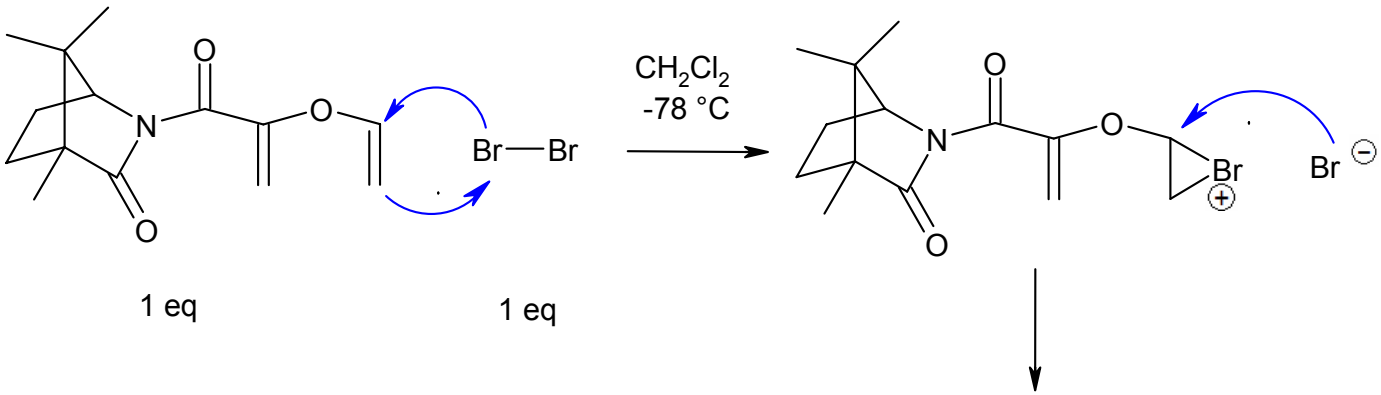


I.1.4. Bromierung der Doppelbindung

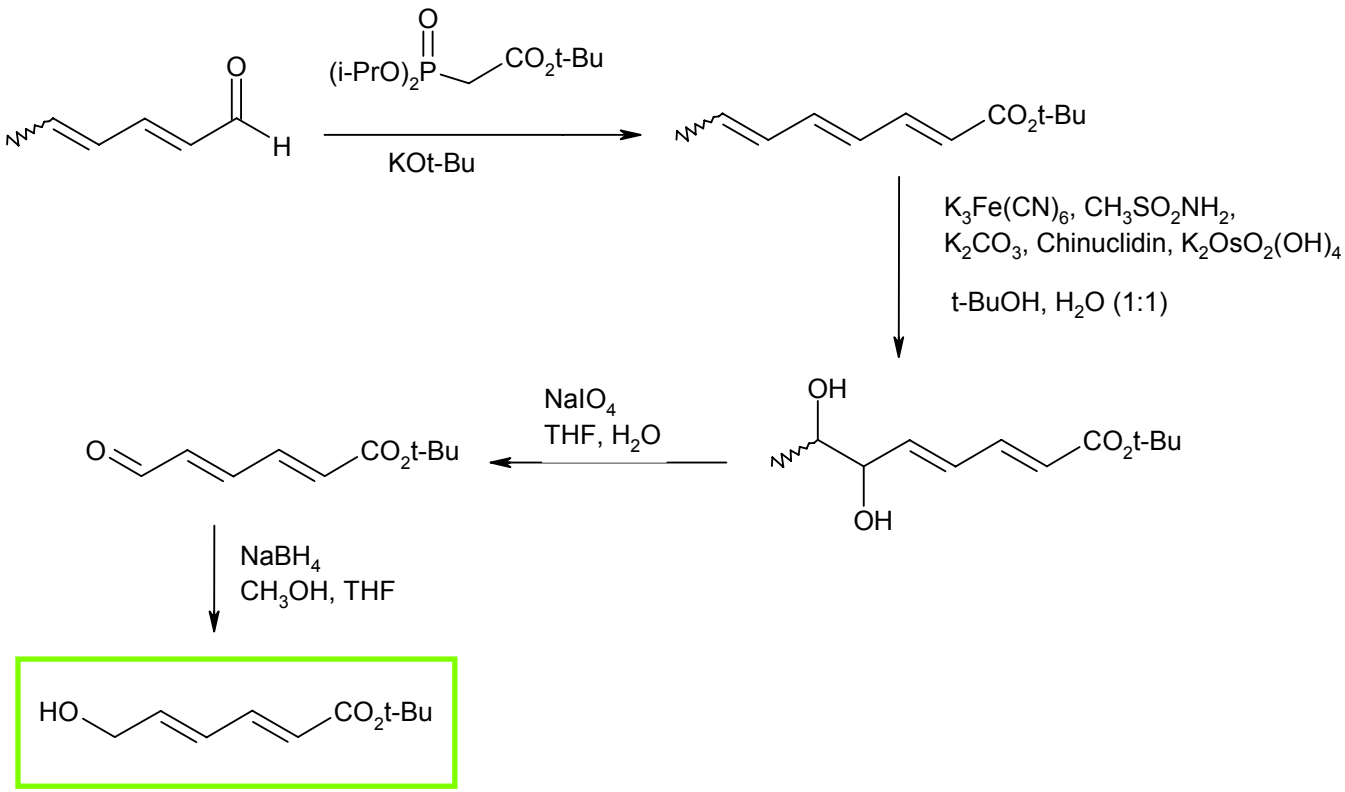


1 eq

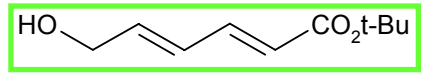
1 eq

~100%

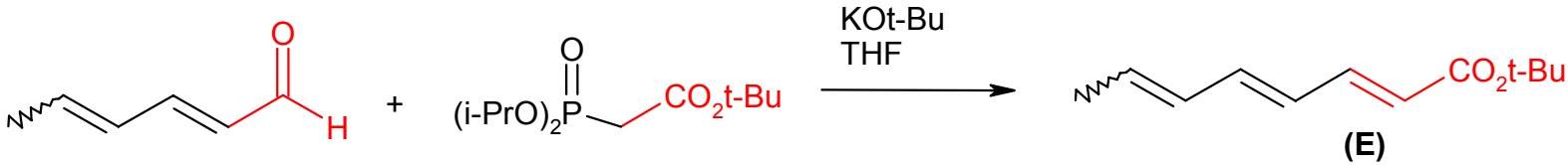
I.2. Synthese der Untereinheit 2



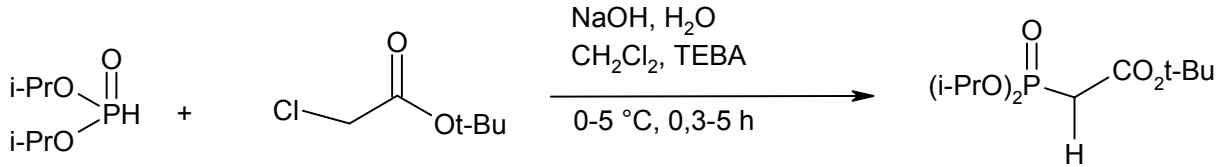
I.2.1. Herstellung des Triens

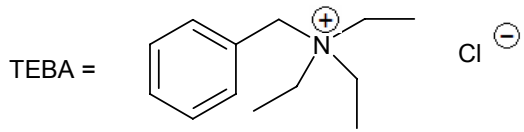


(Horner-Wadsworth-Emmons-Reaktion)

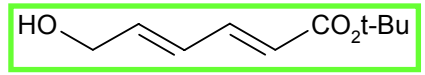


Herstellung des Phosphonsäurediisopropylesters über Phasentransferkatalyse:





Literatur (Phasentransferkatalyse): W. Ye, X. Liao *Synthesis* **1985**, 986



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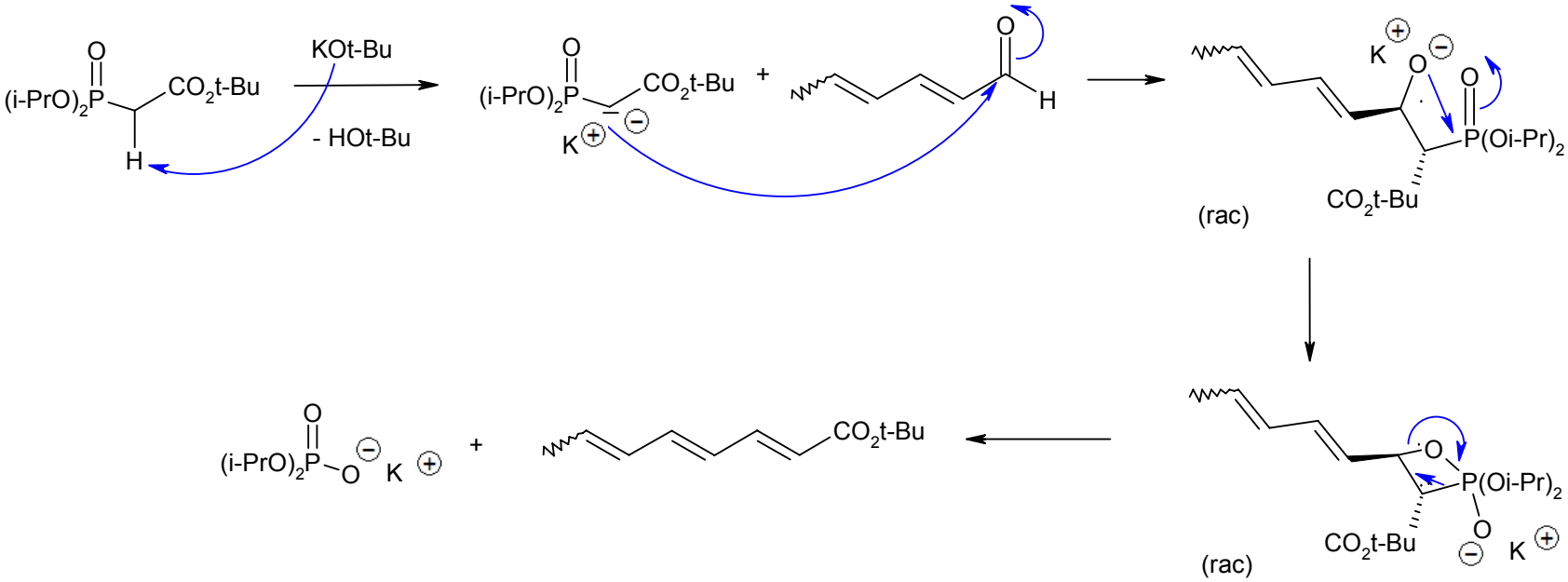
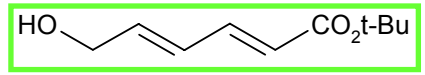
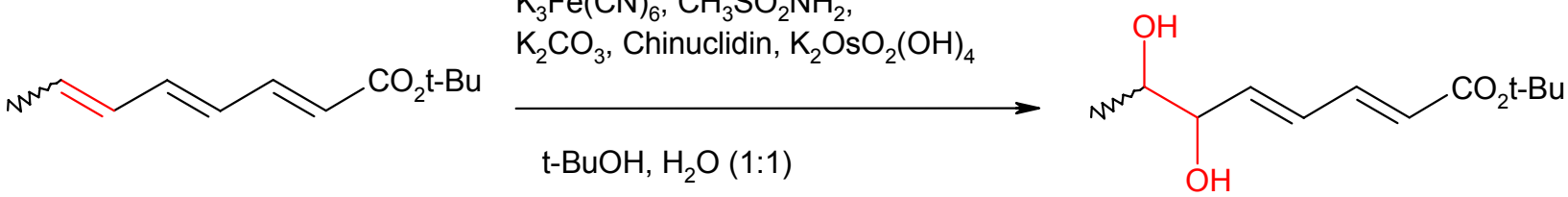
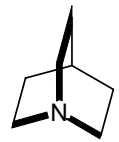




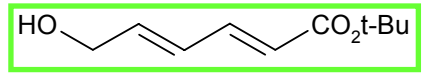
I.2.2. Sharpless- Dihydroxylierung



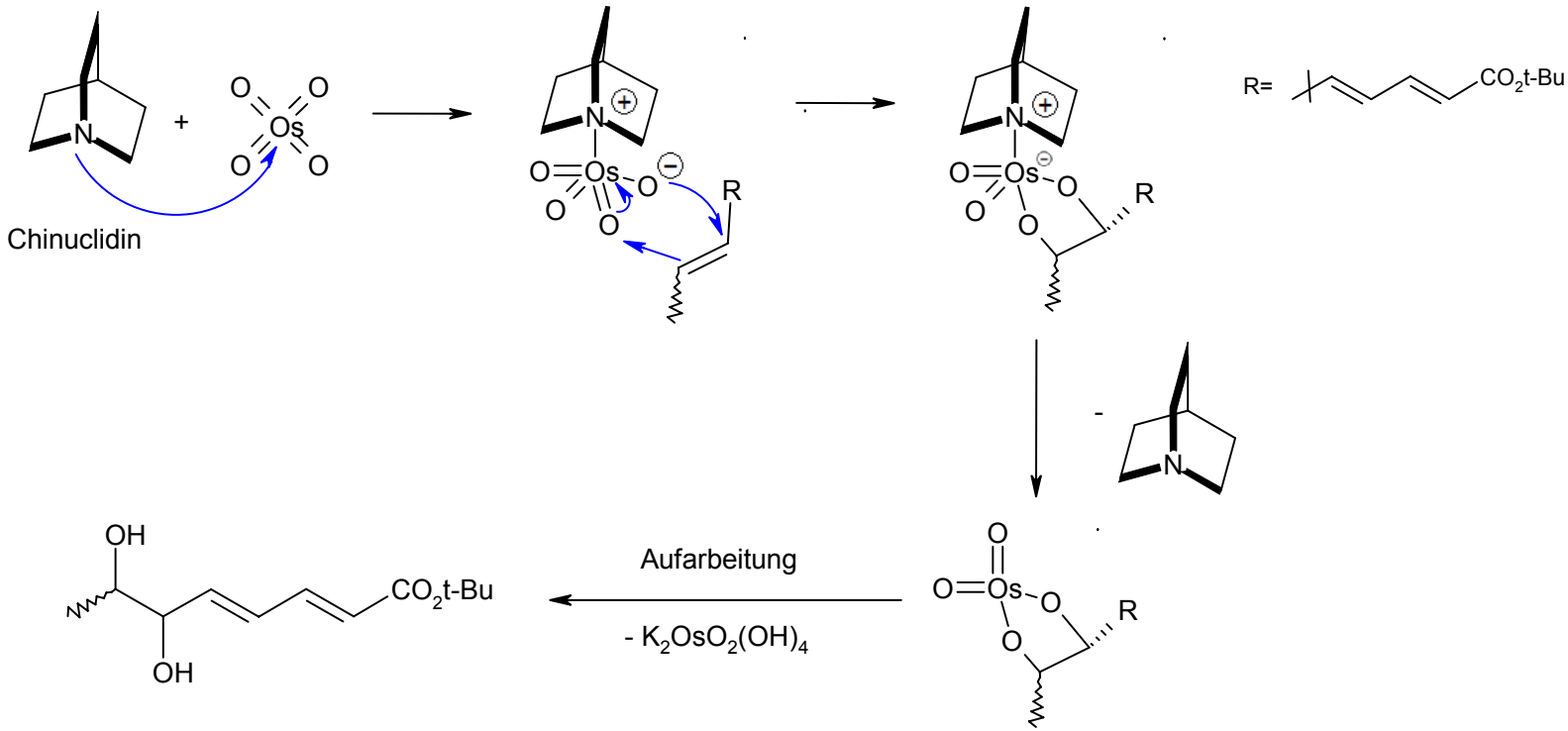
Chinuclidin:



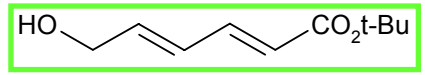
- Einsatz der Osmium(VI)-Spezies ($K_2OsO_2(OH)_4$) erfolgt katalytisch, wird durch Kaliumhexacyanoferrat(III) zu Osmiumtetroxid(VIII) oxidiert
- ermöglicht eine cis-vicinale Dihydroxylierung an der Doppelbindung



Mechanismusvorschlag:

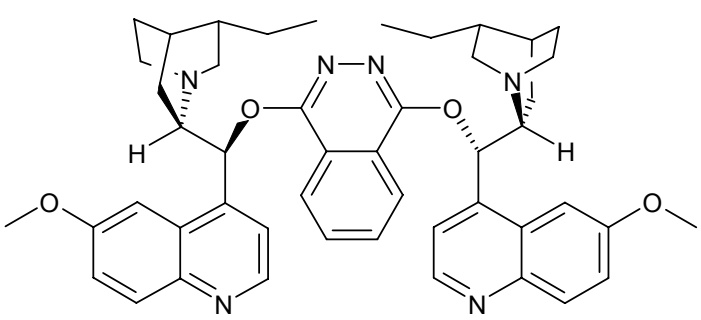


Sharpless- Dihydroxylierung - allgemein

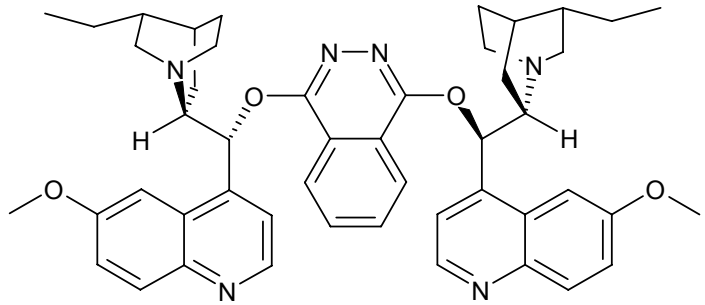


- Sharpless- Dihydroxylierung = Asymmetrische Dihydroxylierung (AD)
- ermöglicht die enantioselektive Darstellung von 1,2-Diolen
- Enantioselektivität wird durch Zugabe von chiralen Liganden z.B. $(DHQD)_2PHAL$, $(DHQ)_2PHAL$ erreicht
- Ligand beschleunigt die Reaktion und trägt die chirale Information
- Kontrolle der Stereoselektivität über zugesetztes Reagenz, wird als **Additivkontrolle der Stereoselektivität** bezeichnet

Beispiele für chirale Liganden:

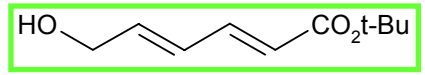


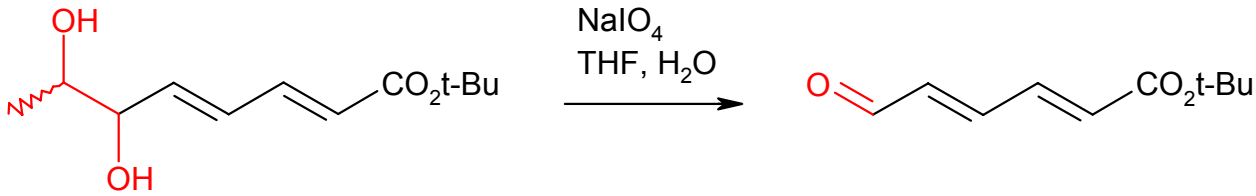
$(DHQD)_2PHAL$



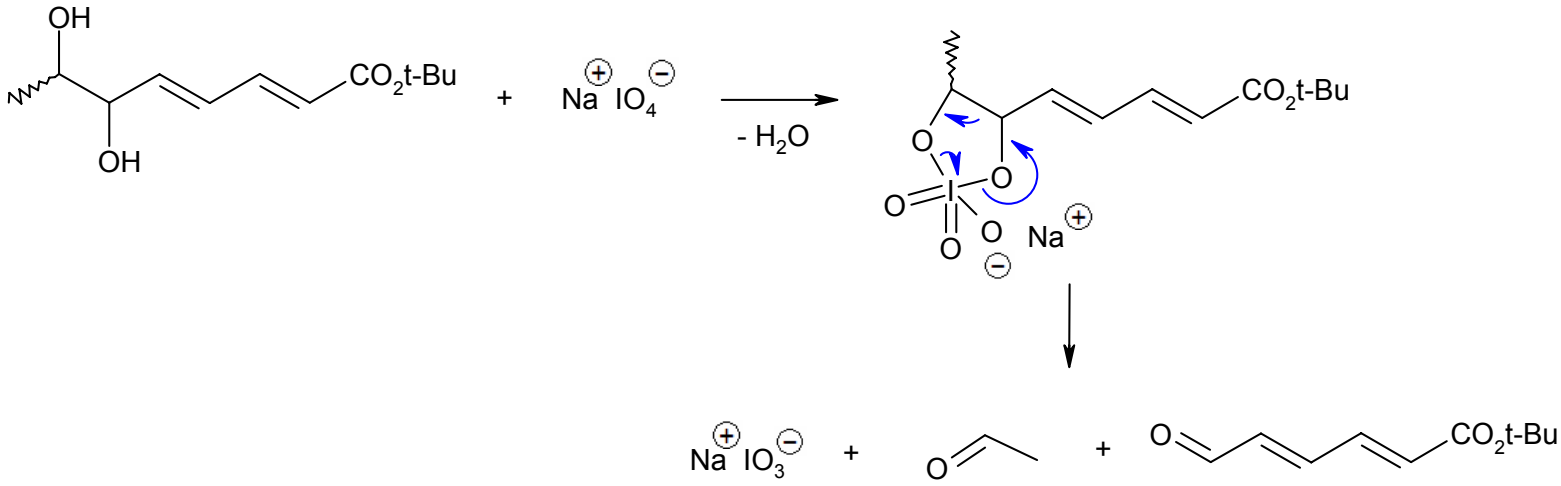
$(DHQ)_2PHAL$

I.2.3. Oxidative Spaltung des vicinalen Diols

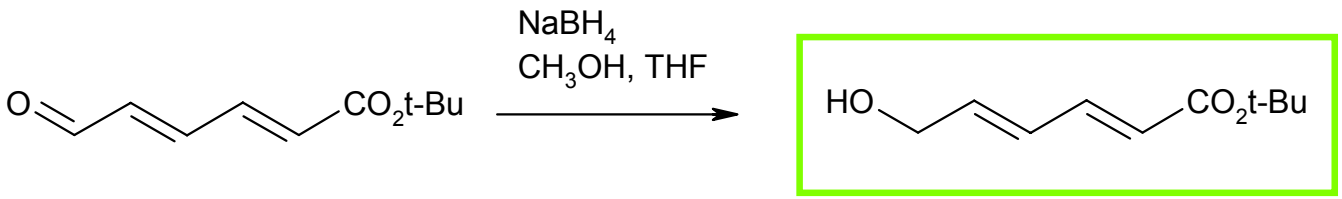




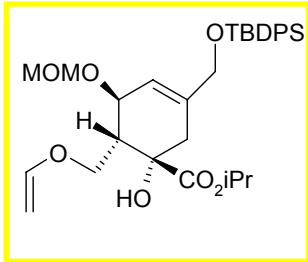
Mechanismusvorschlag:



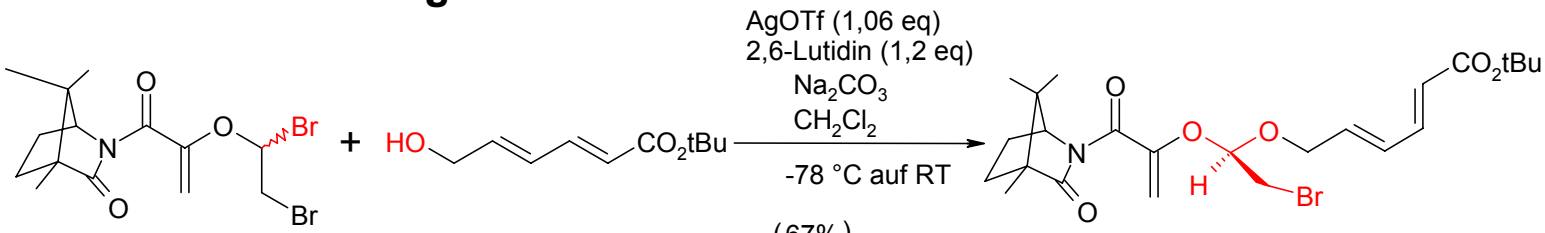
I.2.4. Reduktion mit Natriumborhydrid



I.3. Zusammenfügen der Untereinheiten

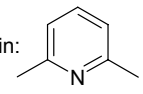


I.3.1. Acetalbildung

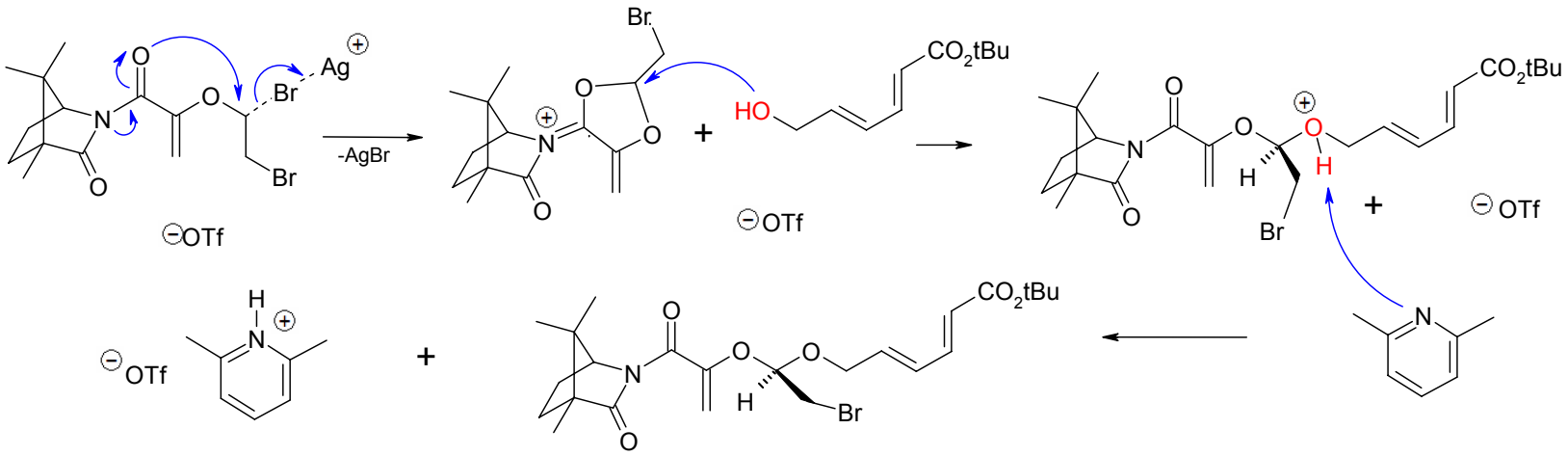


96:4 dr

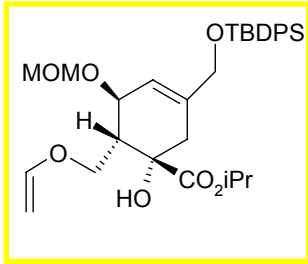
2,6-Lutidin:

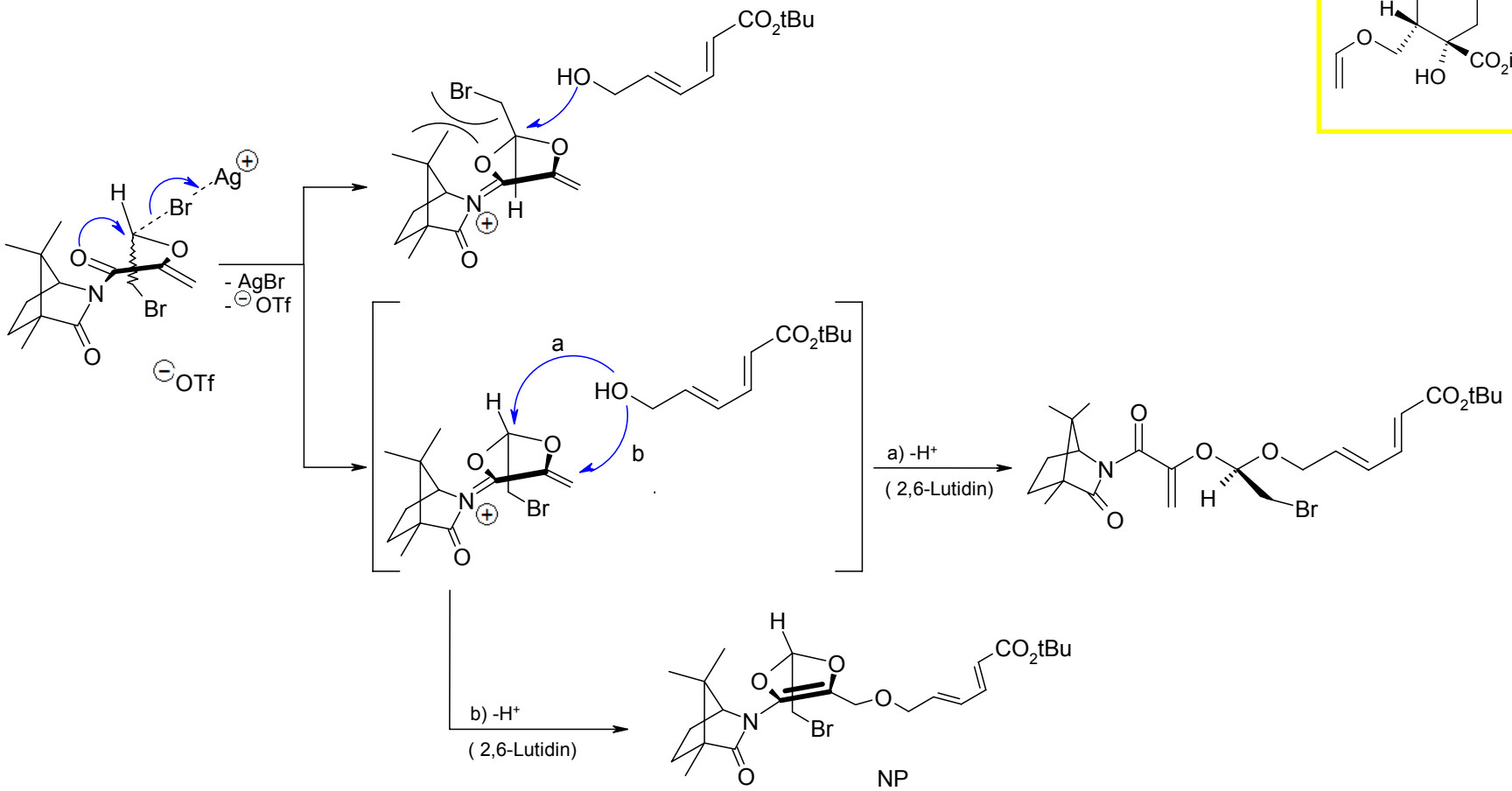


Mechanismusvorschlag:

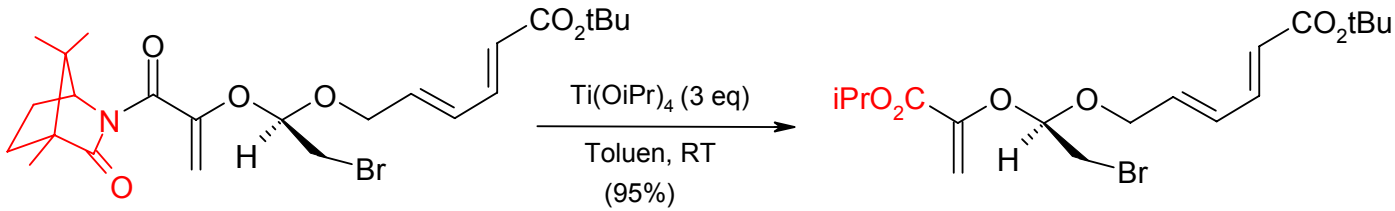


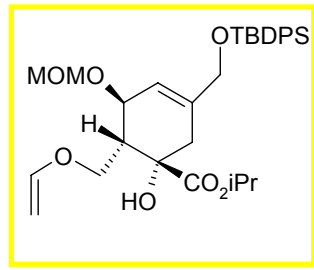
Stereochemie:



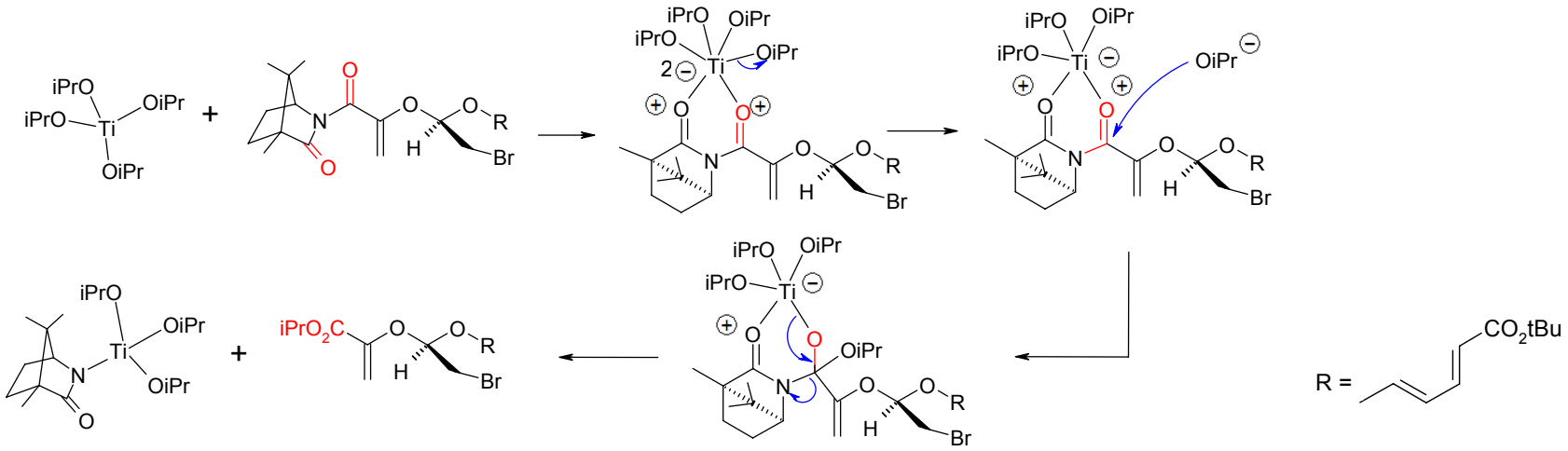


I.3.2. Ligandenaustausch





Mechanismusvorschlag:



nach R.K. Boeckman; P. Shao; S.T. Wrobleski; D.J. Boehmler; G.R. Heintzelman; A.J. Barbosa

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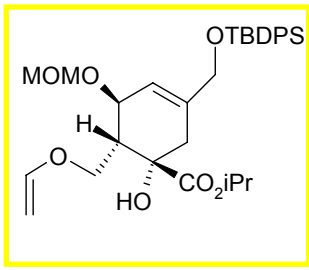
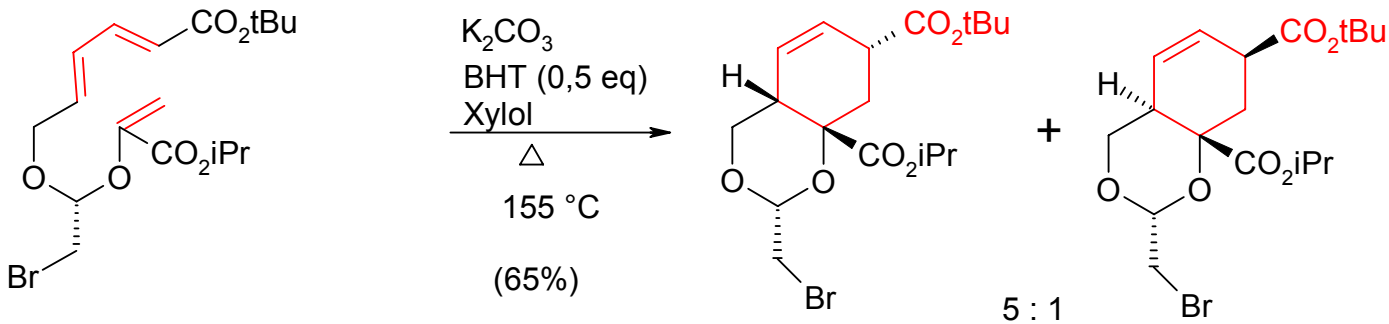


I.3.3. Intramolekulare Diels-Alder Reaktion



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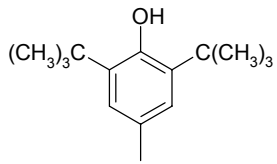

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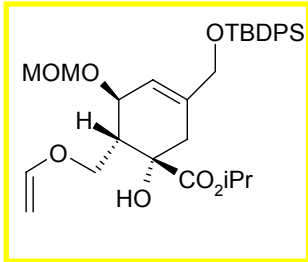
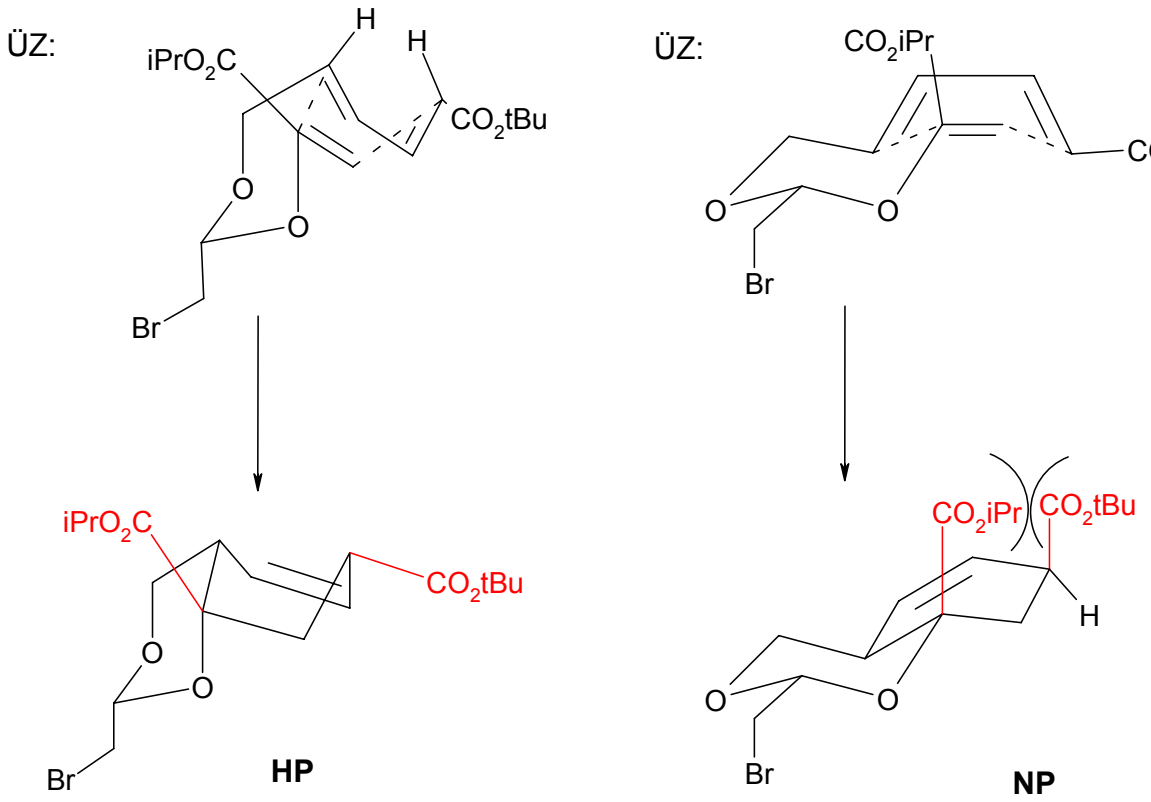
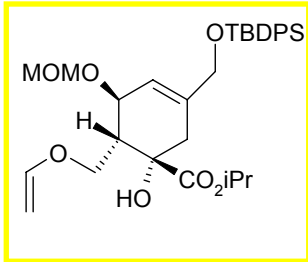
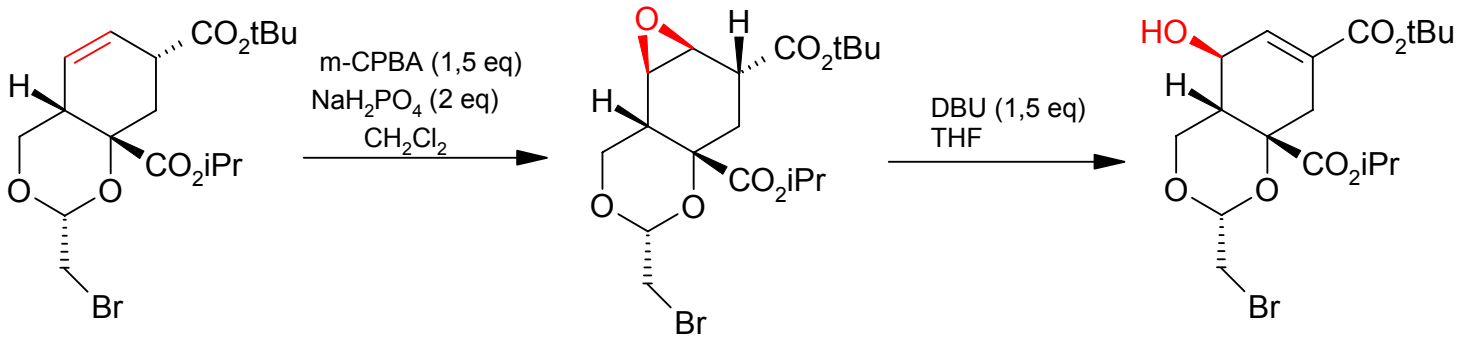


Stereochemie:

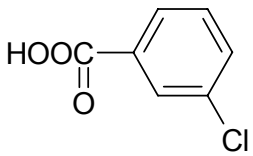




I.3.4. Epoxidierung und Eliminierung zum Alkohol



m-CPBA:



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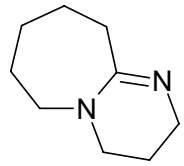
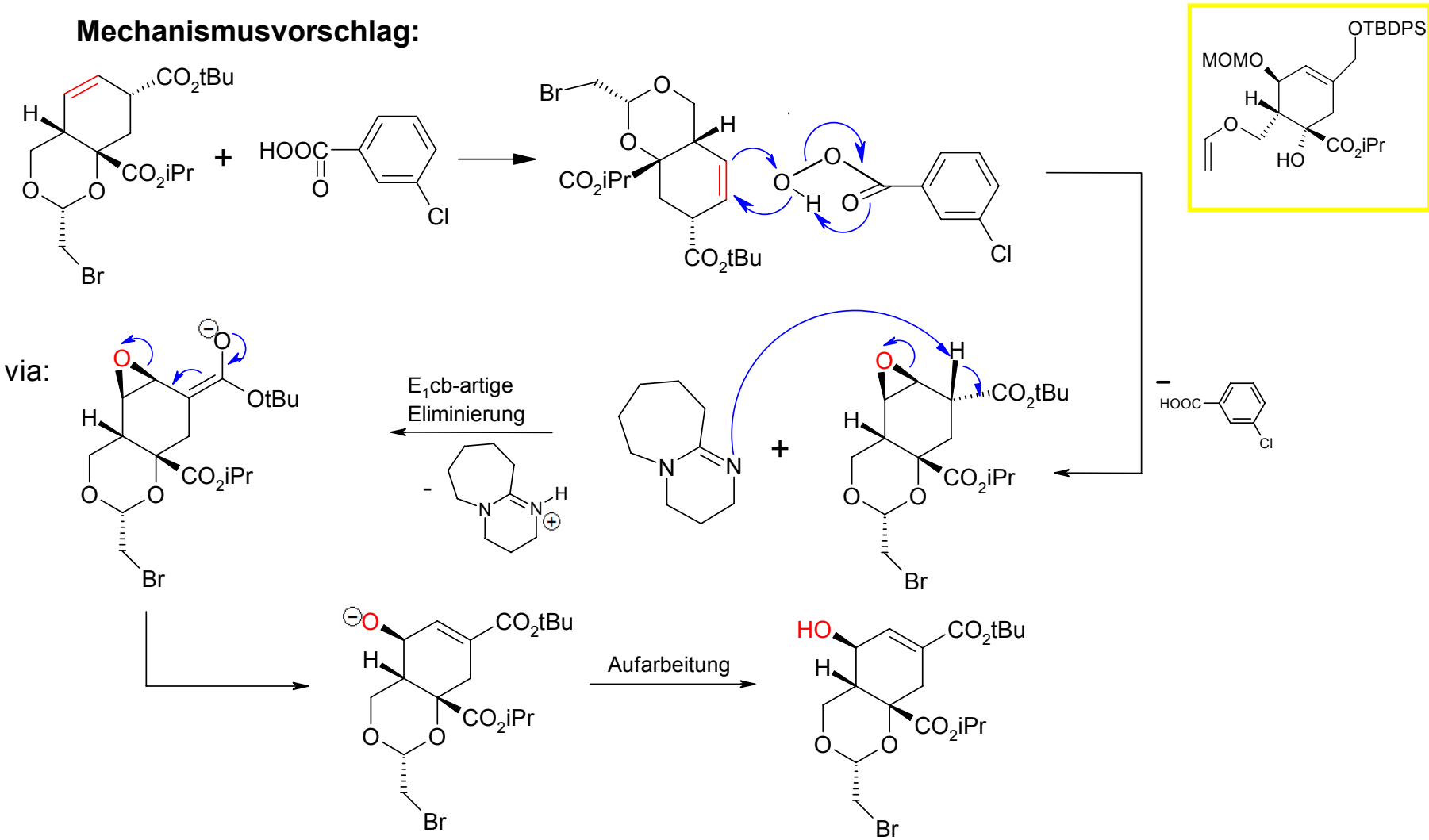
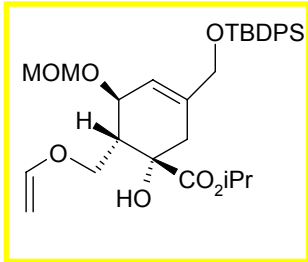


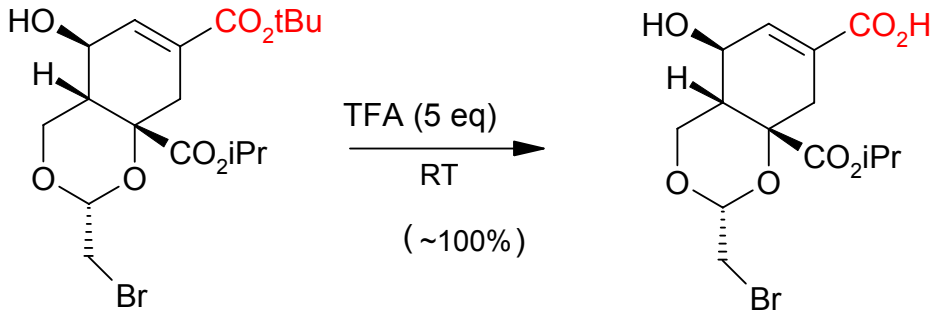
Mechanismusvorschlag:

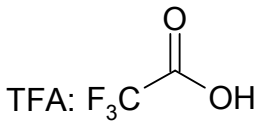


Literatur: R. Brückner, Reaktionsmechanismen; Spektrum Akademischer Verlag, 3. Auflage, **2004**, S. 116ff

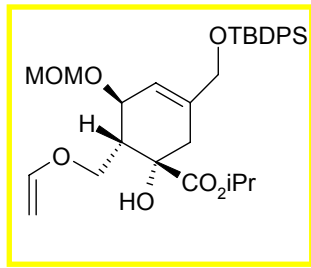


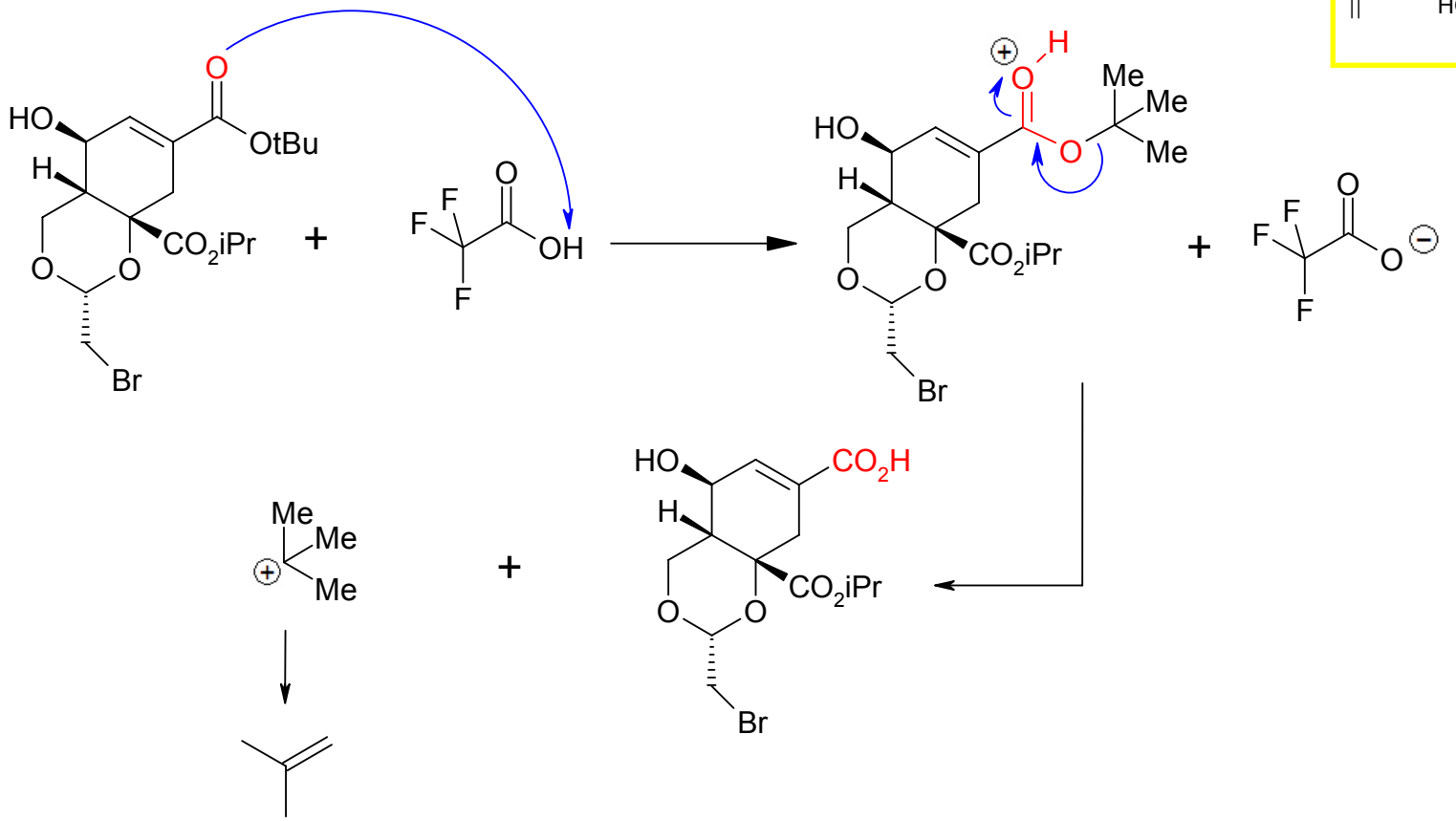
I.3.5. Verseifung:

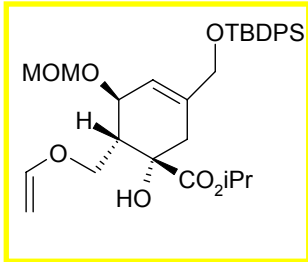




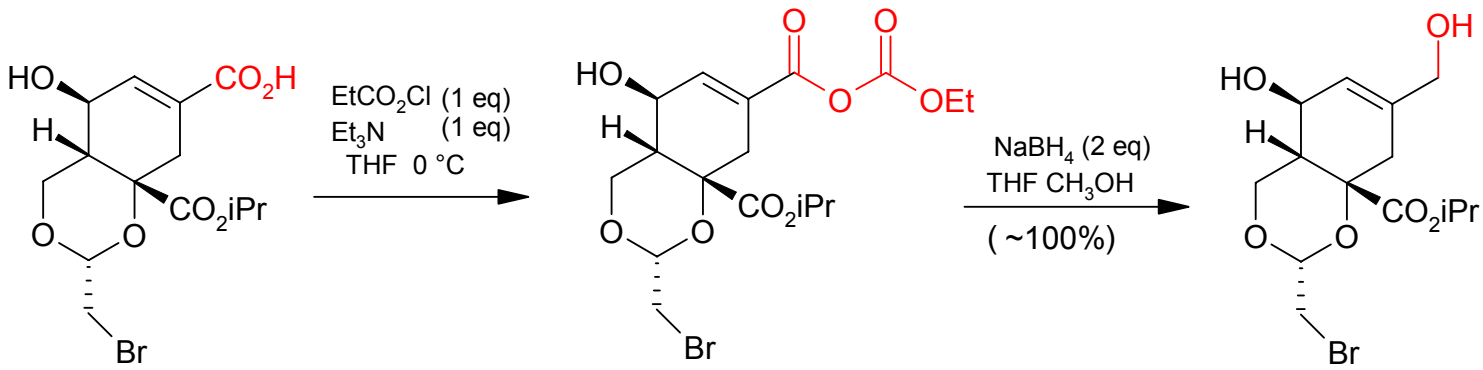
Mechanismusvorschlag:







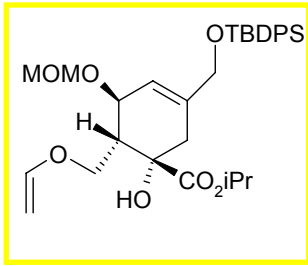
I.3.6. Bildung eines gemischten Anhydrids und anschließende Reduktion zum Alkohol

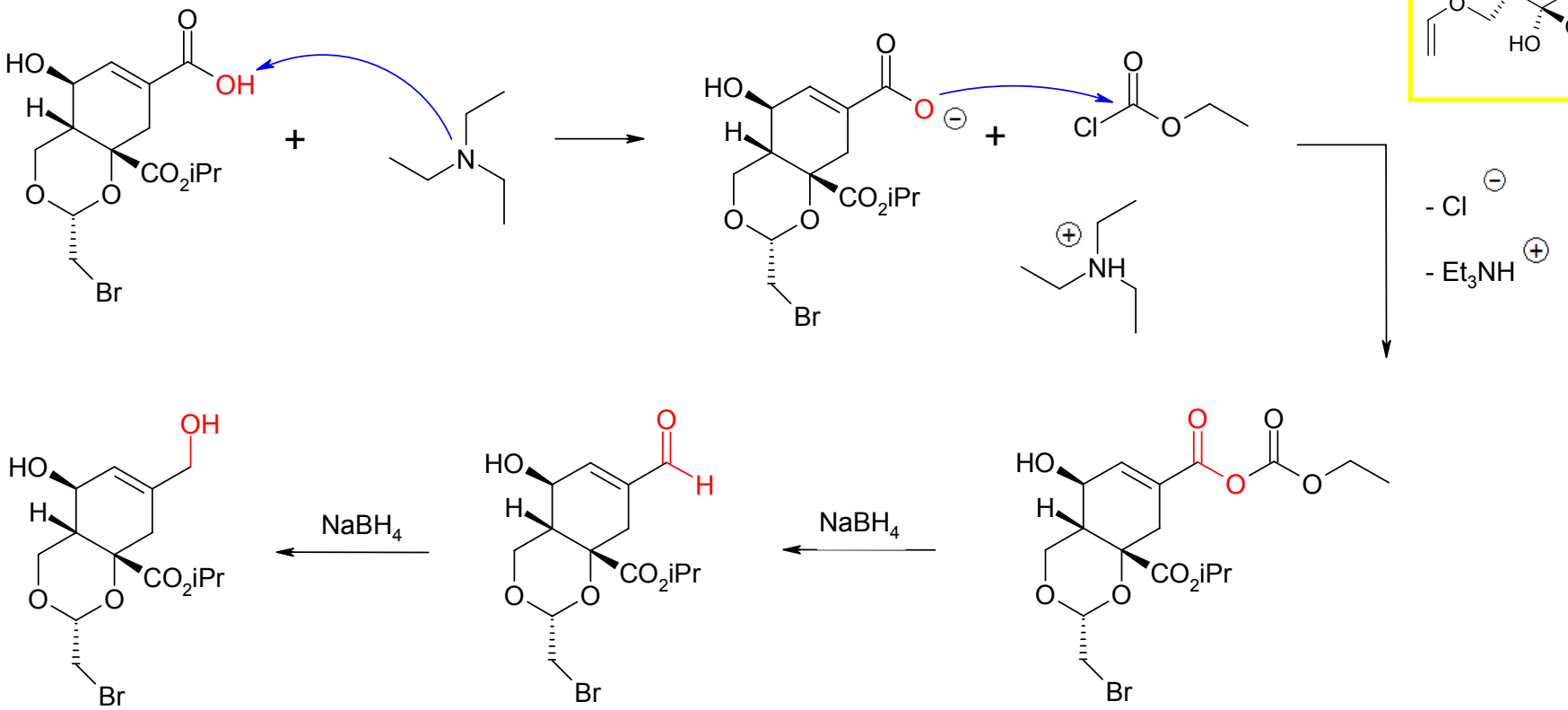


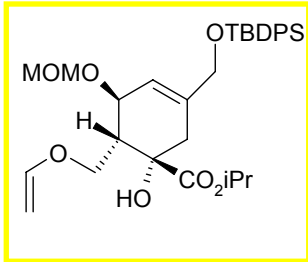
nach R.K. Boeckman; P. Shao; S.T. Wrobleski; D.J. Boehmler; G.R. Heintzelman; A.J. Barbosa

J. Am. Chem. Soc. **2006**, *128*, 10572

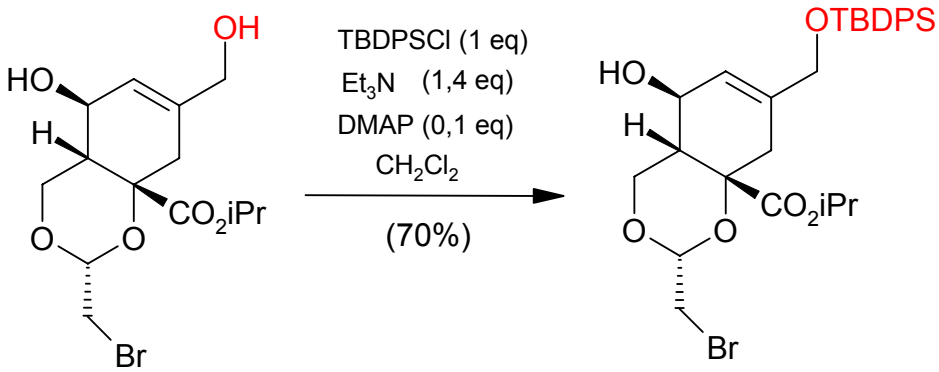
Mechanismusvorschlag:

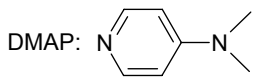


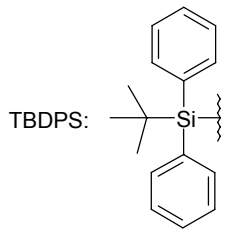


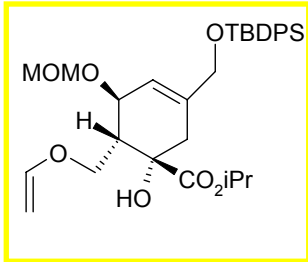


I.3.7. Einführung der Schutzgruppe

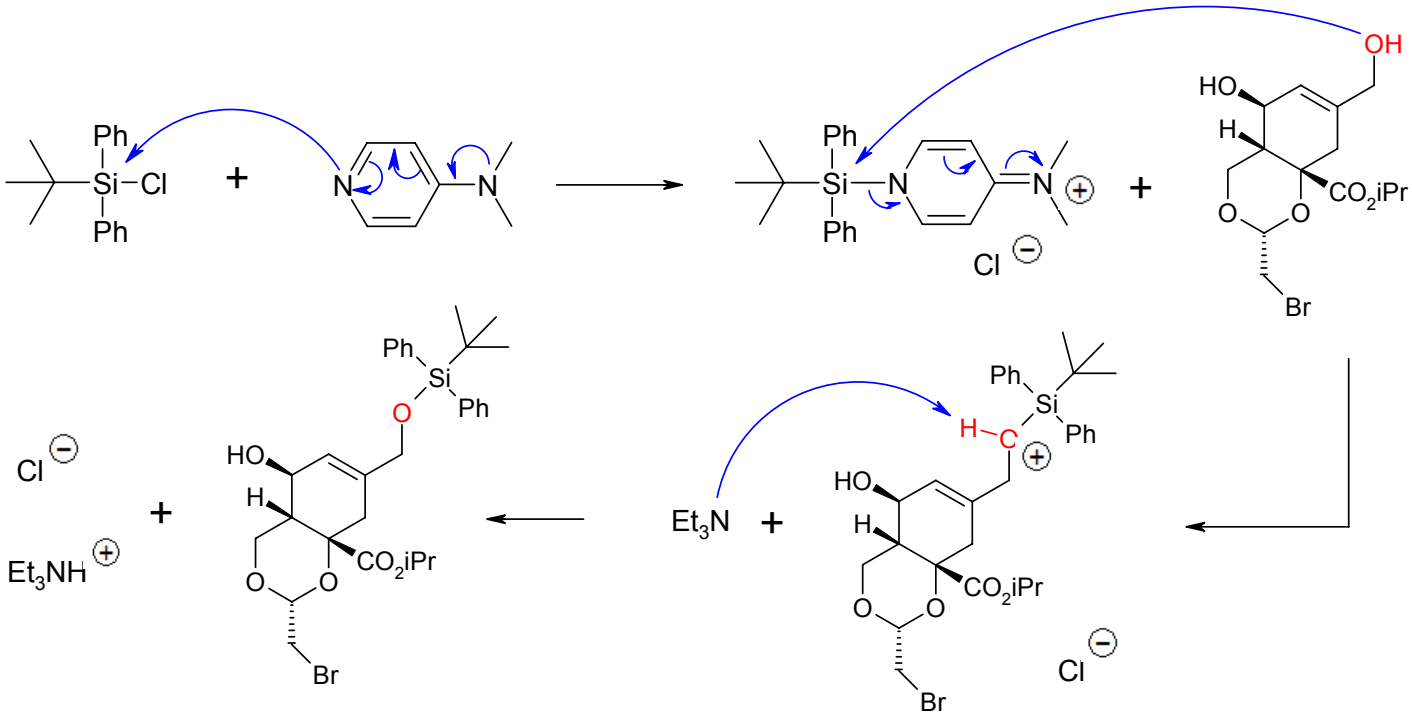


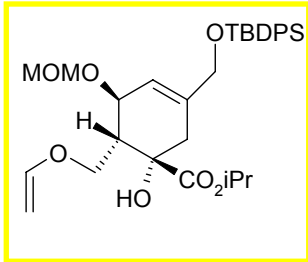




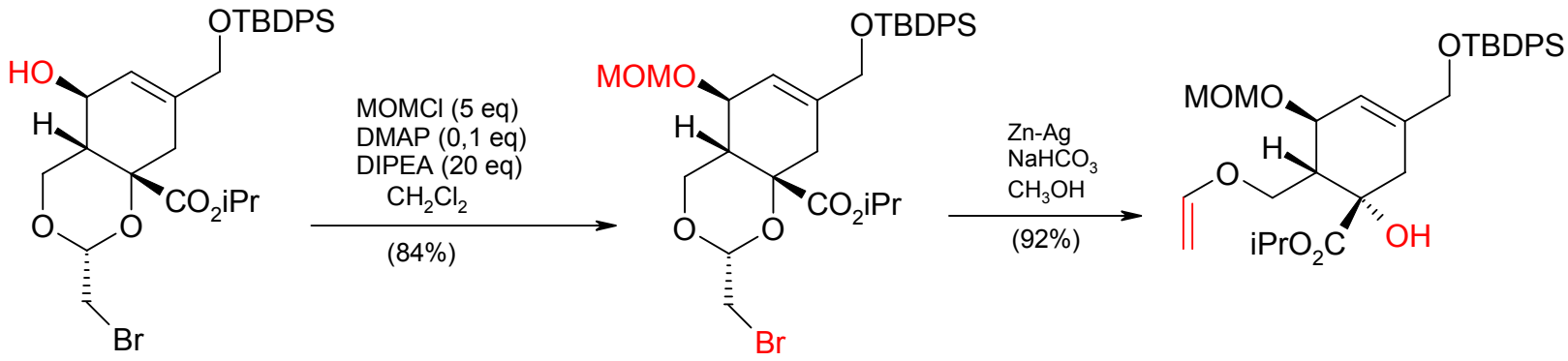


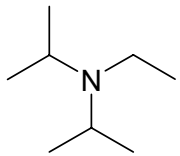
Mechanismusvorschlag:

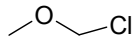


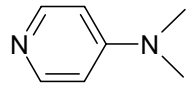


I.3.8. Einführung der Schutzgruppe MOM und Acetalspaltung

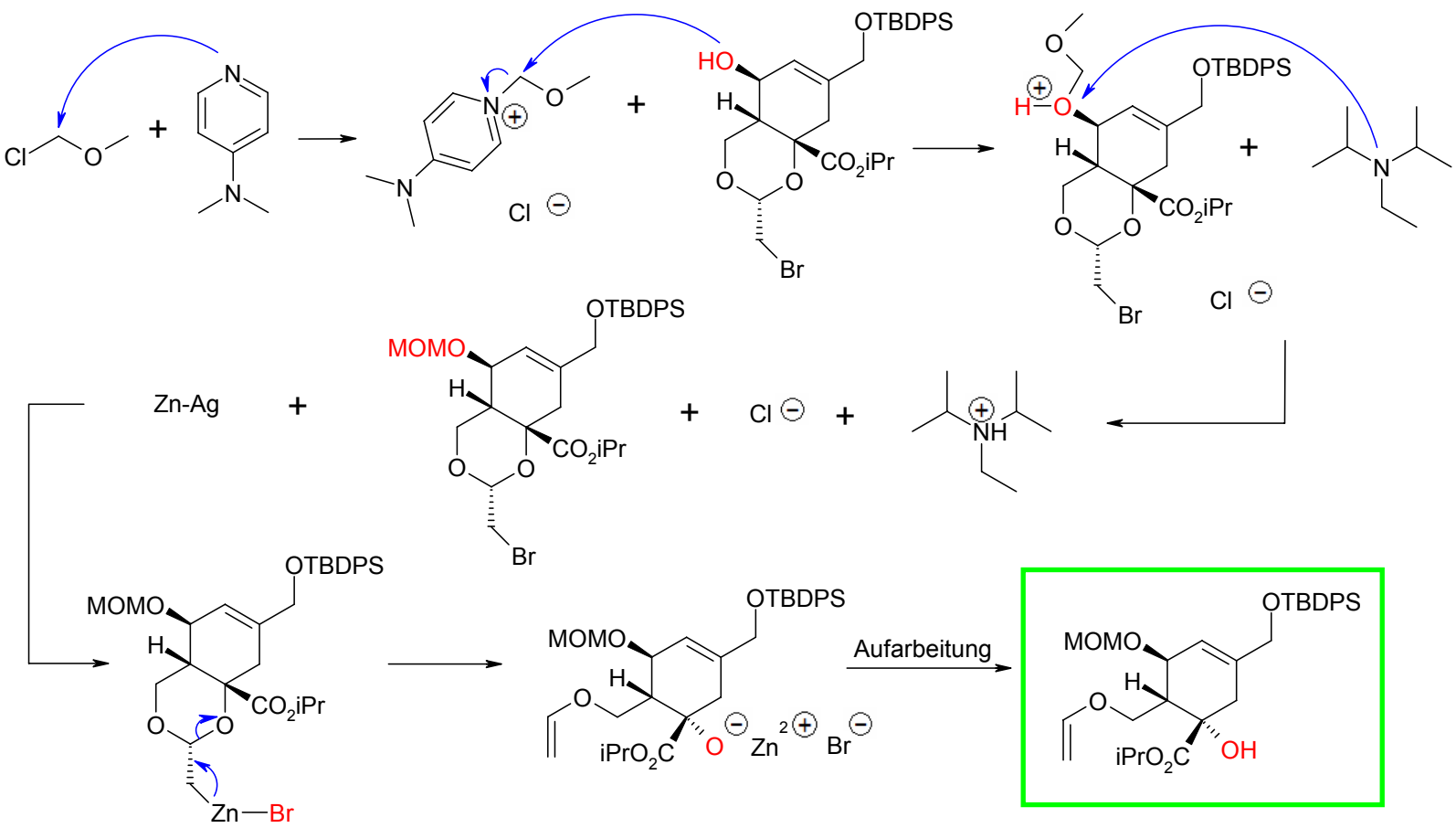


DIPEA: 

MOMCl: 

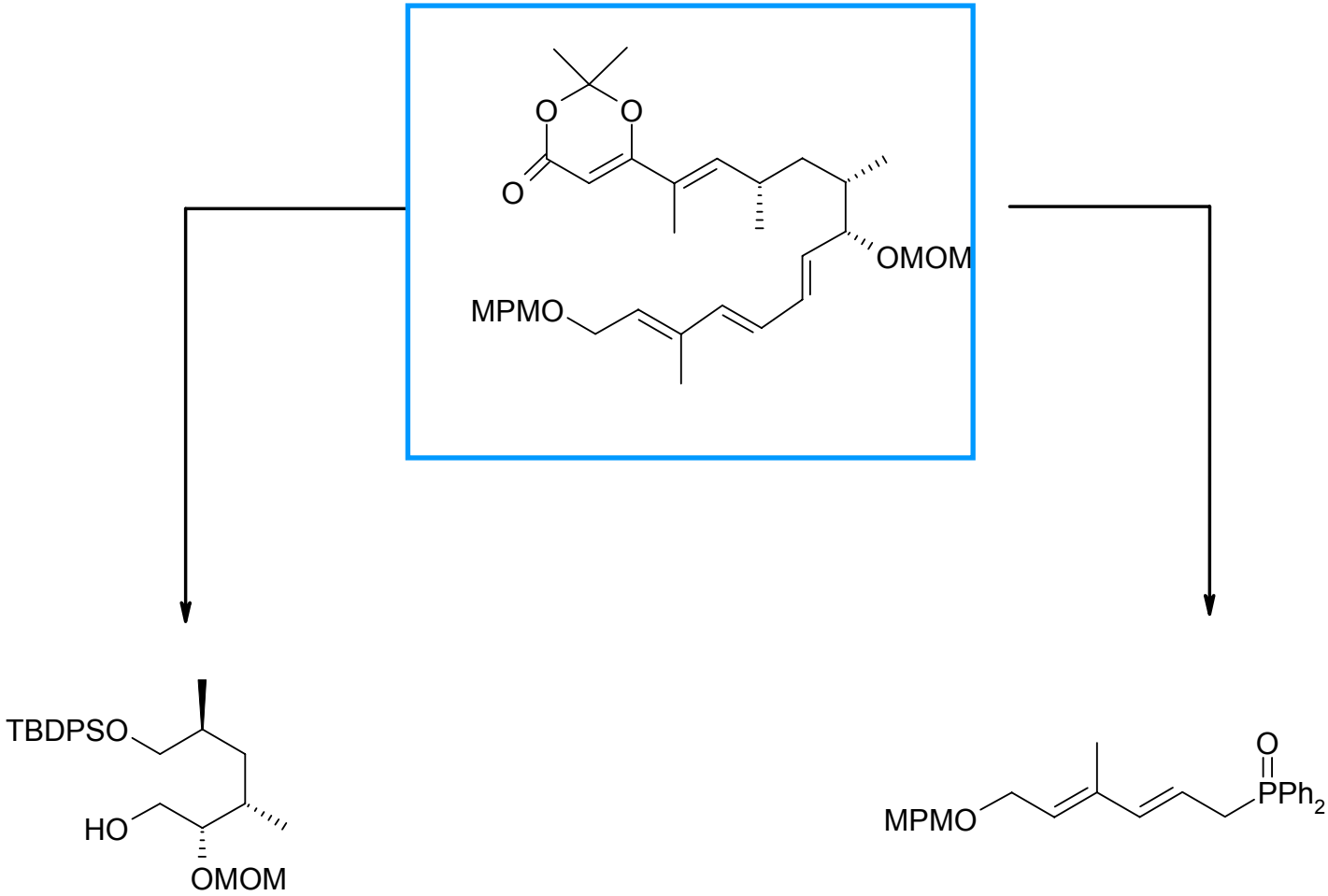
DMAP: 

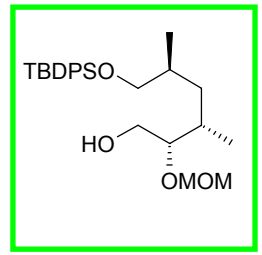
Mechanismusvorschlag:



Quelle: www.uni-leipzig.de/~organik/giannis/d/OCF/Schutzgruppen_2.pdf

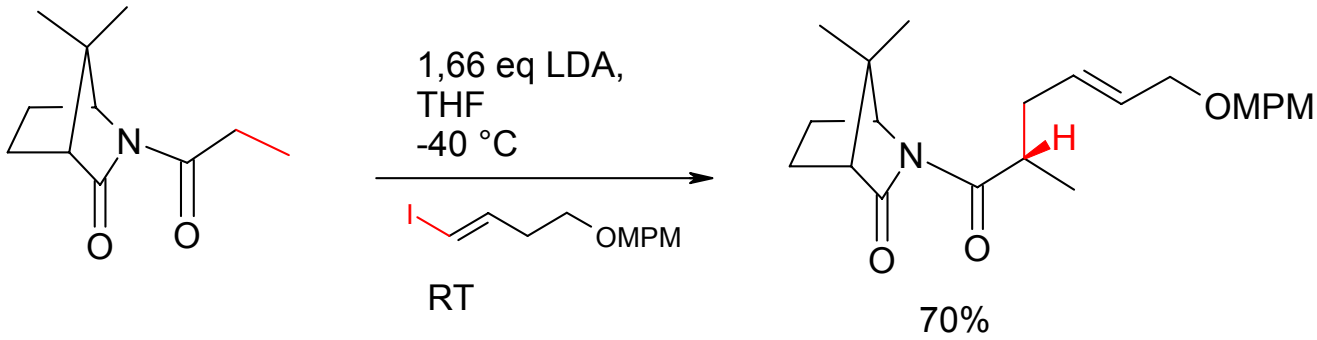
Darstellung des unteren Fragments

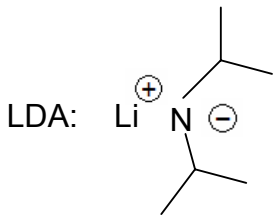


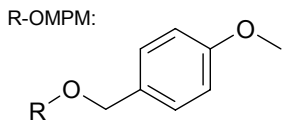


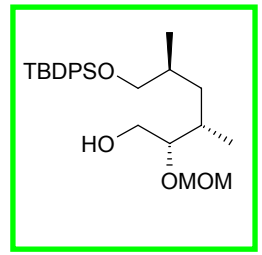
II.1. Synthese erstes Fragment

II.1.1. Diastereoselektive Alkylierung des Lithiumenolates



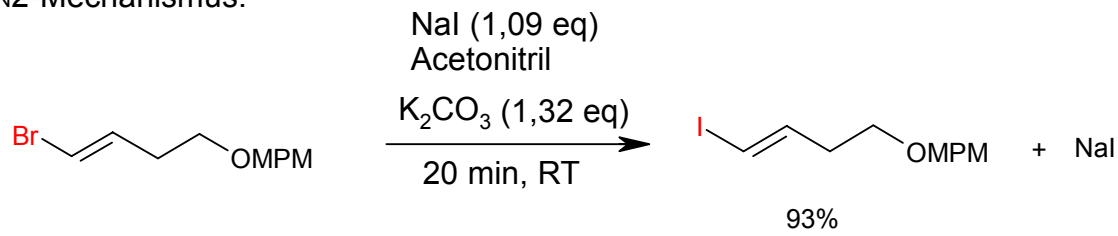






Herstellung des Alkylierungsreagenzes:

S_N2-Mechanismus:



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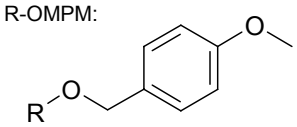
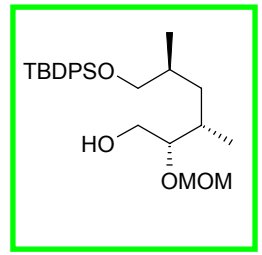
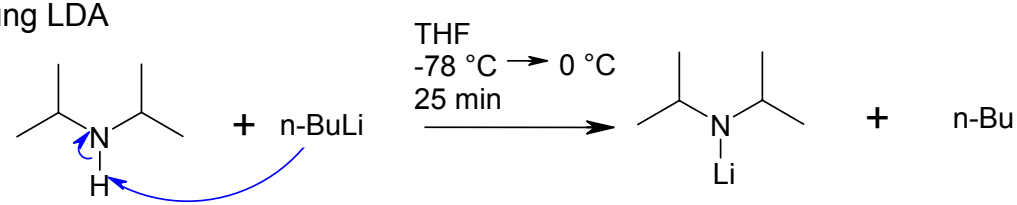


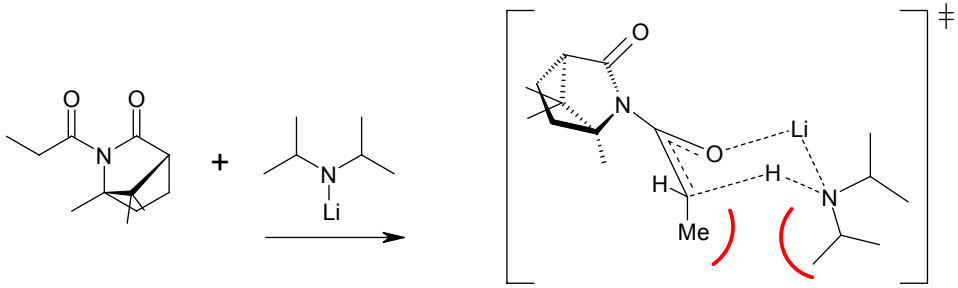


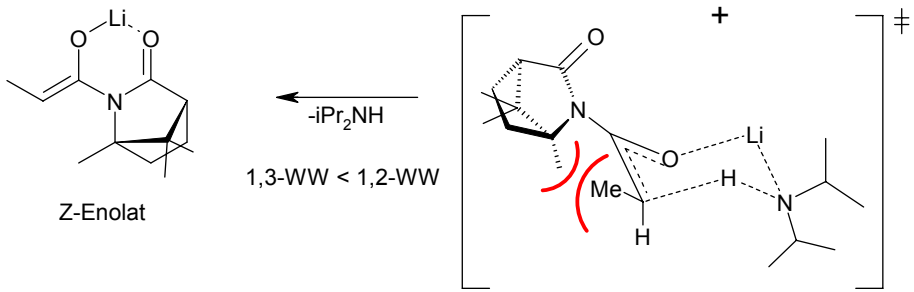
Mechanismus:

1. Bildung LDA

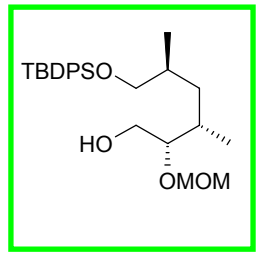


2. Z-Enolatbildung am Auxiliar

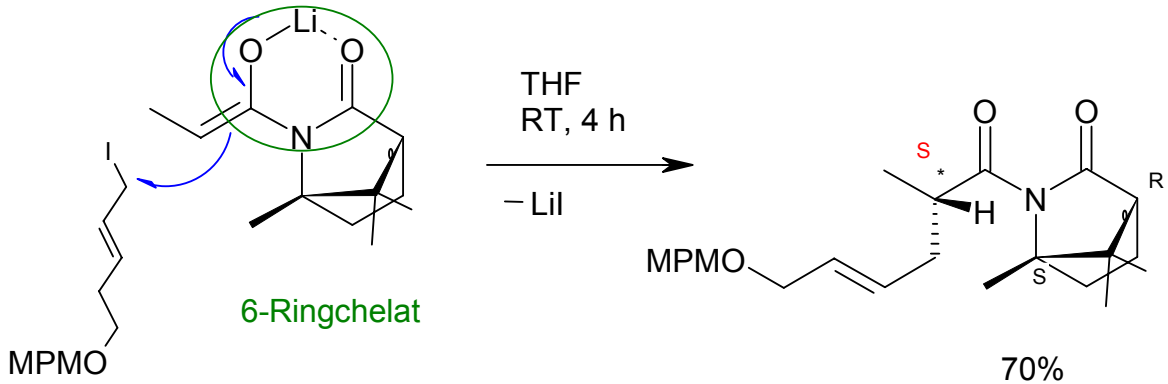




Literatur: R. Brückner, Reaktionsmechanismen; Spektrum Akademischer Verlag, 3. Auflage, **2004**, S. 533

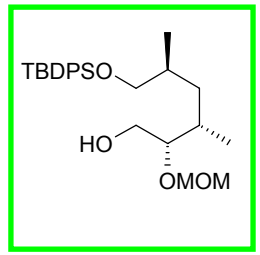


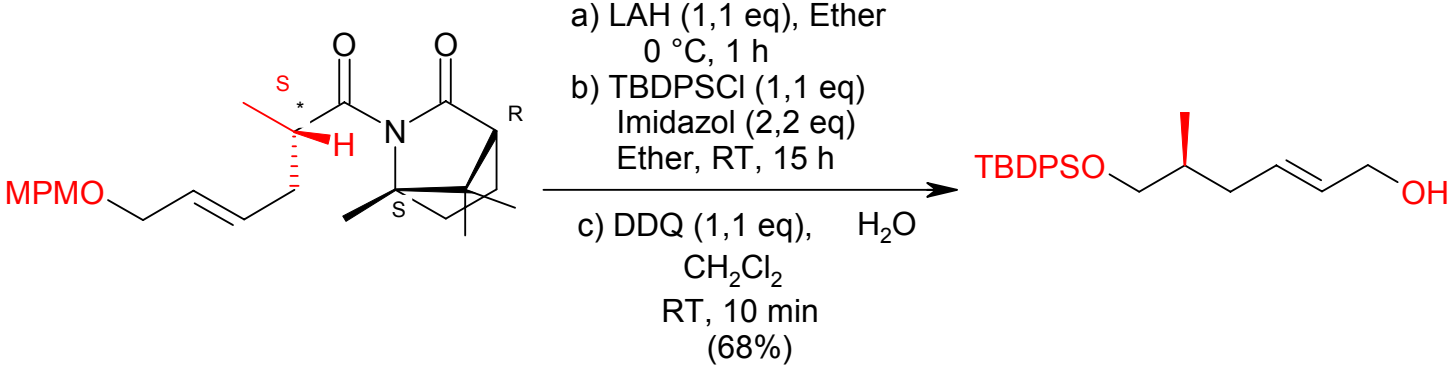
3. S_N2 Reaktion



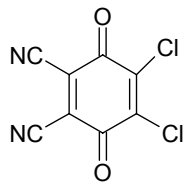
Rückseitenangriff

II.1.2. Syntheseschritte zum Alkohol unter Abspaltung vom Auxiliar

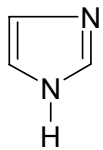




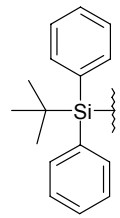
DDQ:



Imidazol:

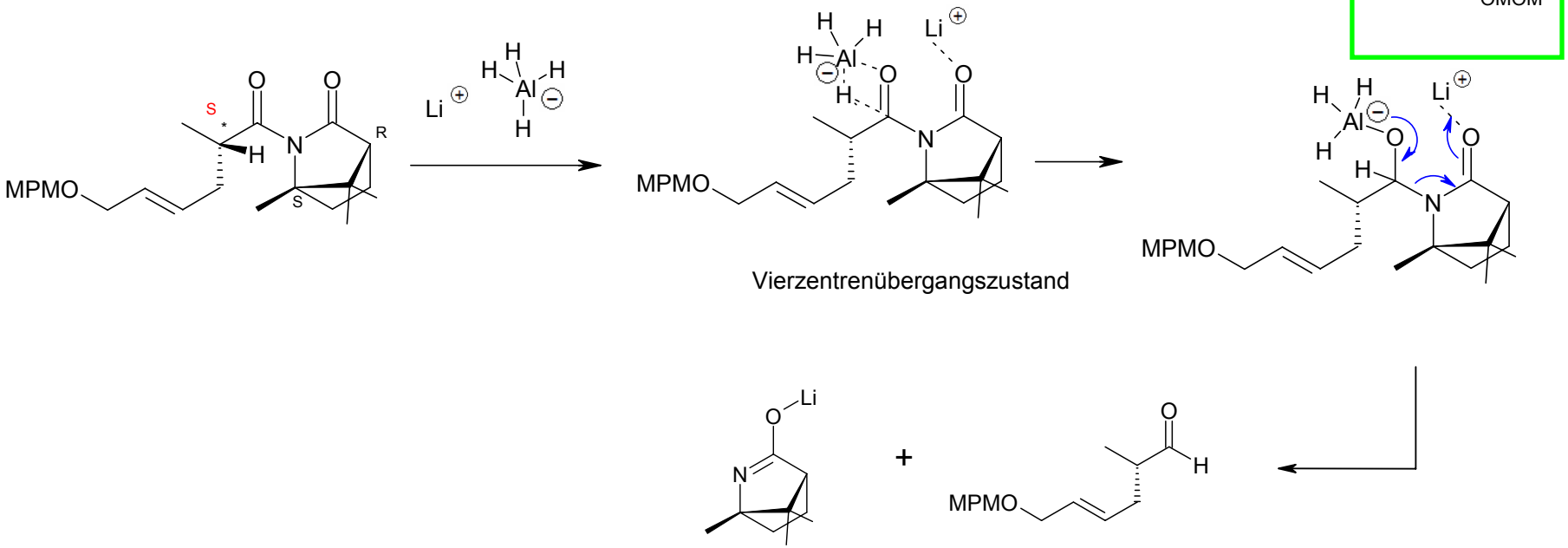


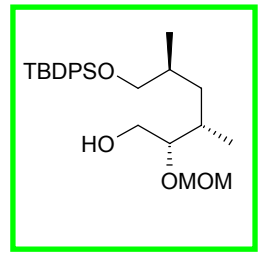
TBDPS:



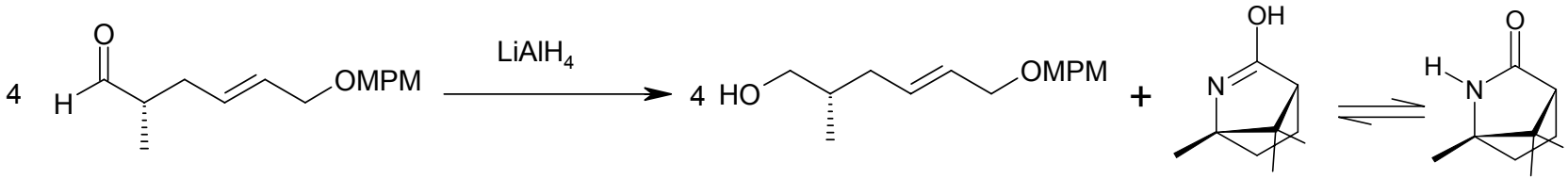
Mechanismusvorschlag

1. Spaltung zum Aldehyd:





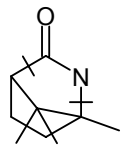
2. Reduktion mit LAH zum Alkohol:



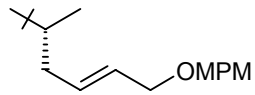
90%
>95% ee

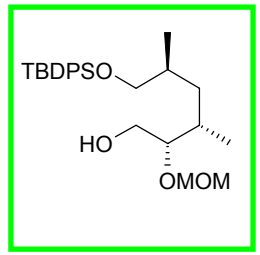
94%

^{2}R:



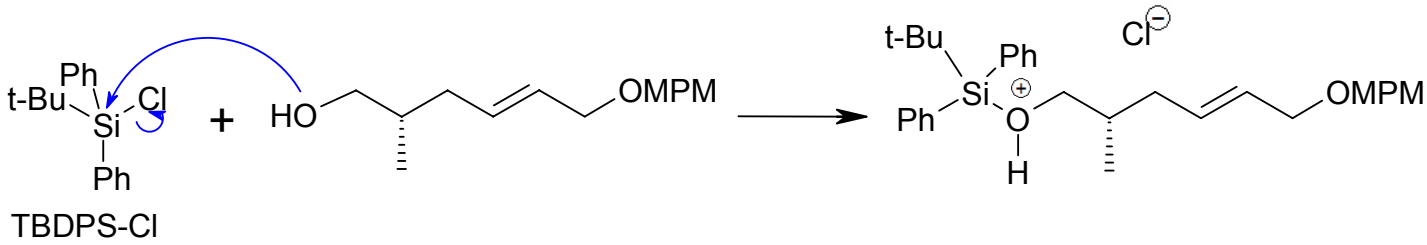
^{1}R:



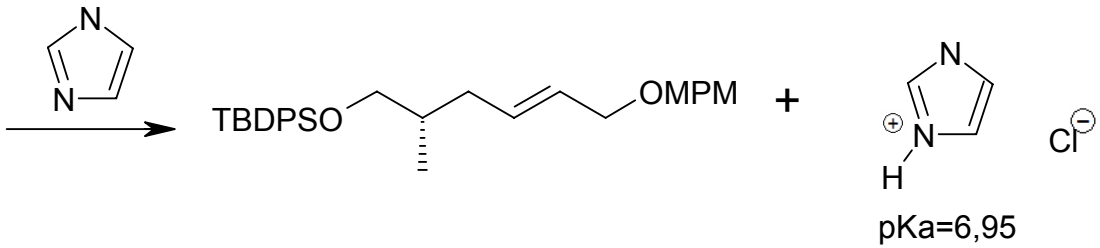


Einbau der TBDPS-Schutzgruppe, Mechanismusvorschlag:

nucleophiler Angriff:

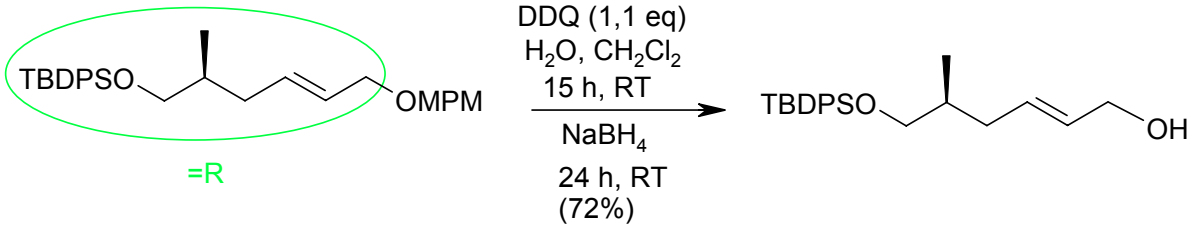


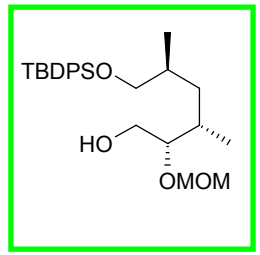
Deprotonierung



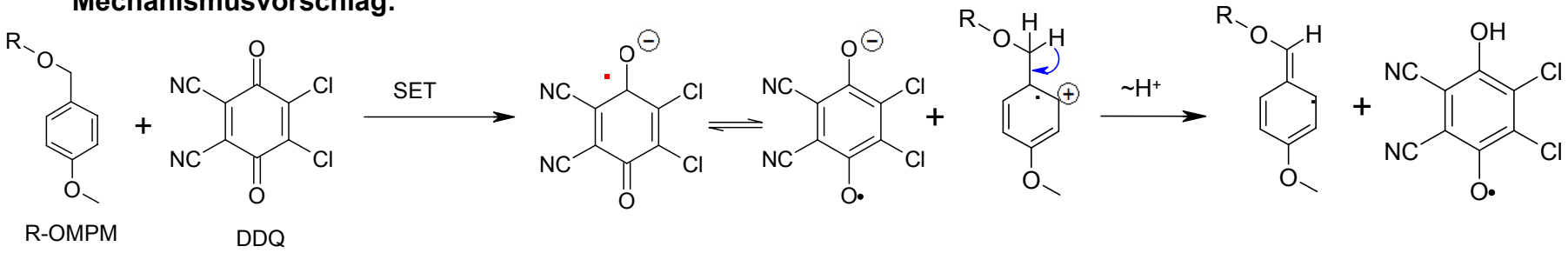
pKa=6,95

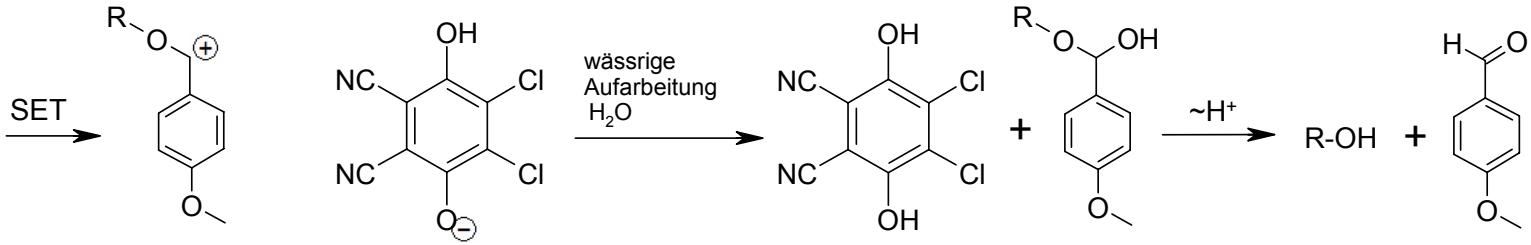
3. Entschützen der PMB-Schutzgruppe mittels DDQ:





Mechanismusvorschlag:



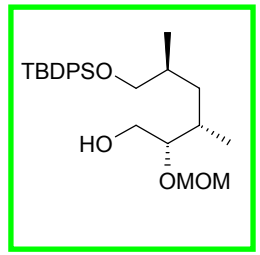


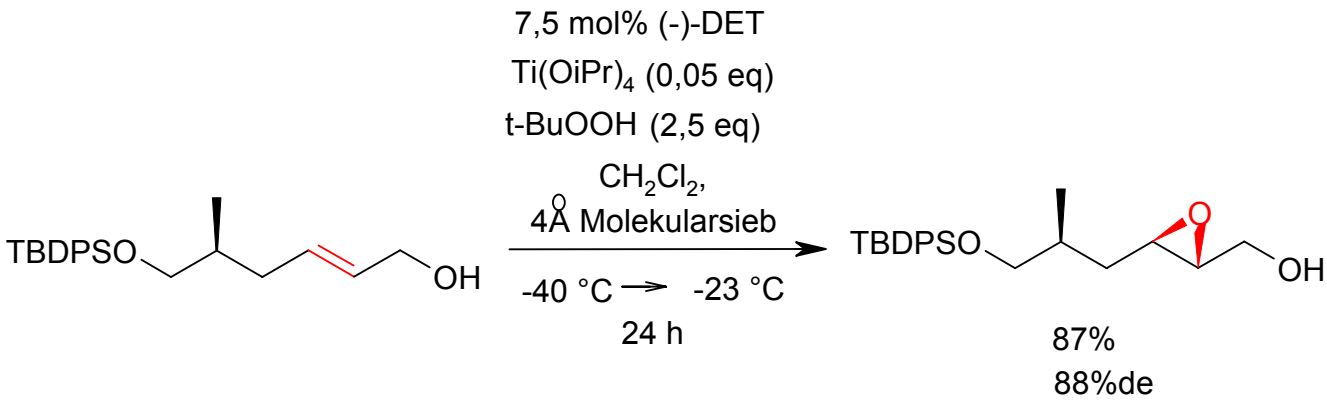
Zusatz von $NaBH_4$ zur Verhinderung der Teiloxidation des entstandenen Alkohols zum ungesättigten Aldehyd während des Entschützens mit DDQ

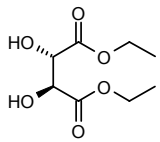
nach R.K. Boeckman; P. Shao; S.T. Wrobleski; D.J. Boehmler; G.R. Heintzelman; A.J. Barbosa

J. Am. Chem. Soc. **2006**, *128*, 10572

II.1.3. Sharpless Epoxidierung von Allylalkoholen





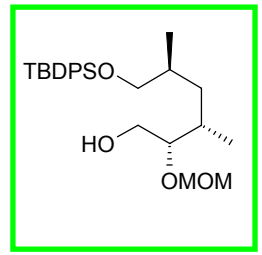
(-)-DET: 

(+)-Tetronolid

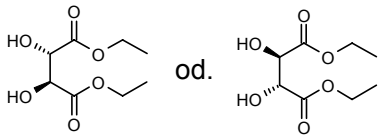
nach R.K. Boeckman; P. Shao; S.T. Wrobleski; D.J. Boehmler; G.R. Heintzelman; A.J. Barbosa

J. Am. Chem. Soc. **2006**, *128*, 10572

Allgemein:

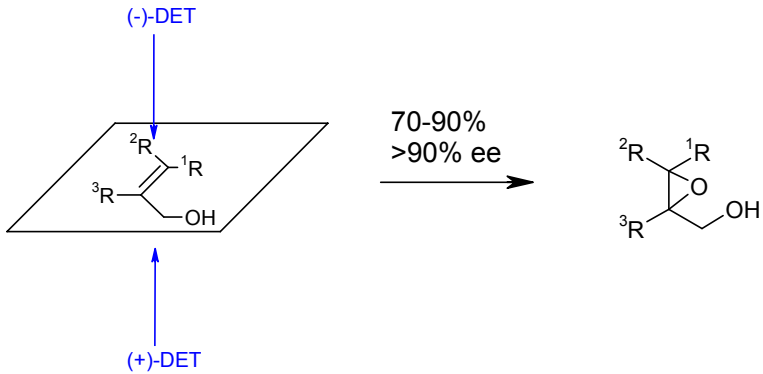


(-)-DET (L-Weinsäurediethylester): od. (+)-DET (D-Weinsäurediethylester):



+ $Ti(OiPr)_4$ + t-BuOOH —*in situ*→ "Additivkontrolle der Stereoselektivität" aktivierter Komplex

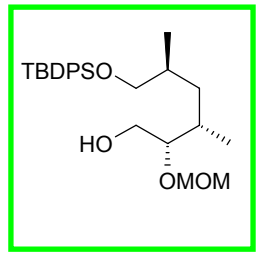
chirales Additiv | achirales Reagenz | Oxidationsmittel



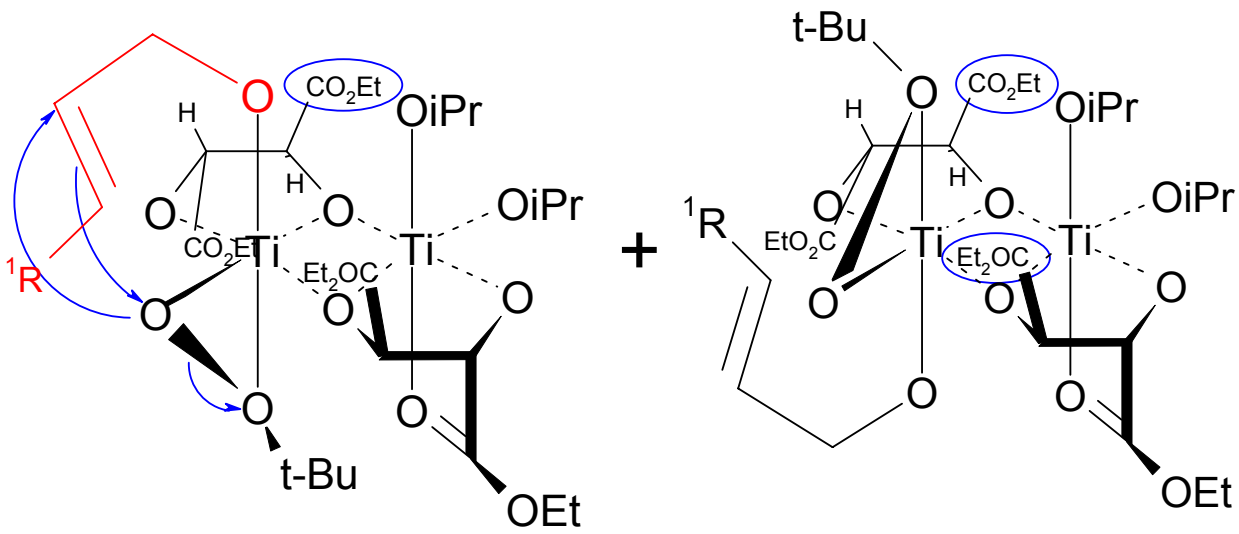
70-90%
>90% ee

Vorteile:
- Unkompliziertheit : alle Reagenzien sind preiswert käuflich erweblich und einfach zurückgewinnbar
- Zuverlässigkeit: auf nahezu alle Allylalkohole anwendbar, aber unsensitiv gegenüber anderen Substratstrukturen
- hohe optische Reinheit: generell >90% ee
- vorhersehbare Stereochemie (Additivkontrolle)
- Vielseitigkeit als Intermediat: synthetischer Zugang zu enantiomerenreinen Zielmolekülen

Katalytisch wirksames Reagenz der Sharpless-Epoxidierung:



Sauerstoffübertragende Zwischenstufe



stärker sterisch gehindertes Diastereomer

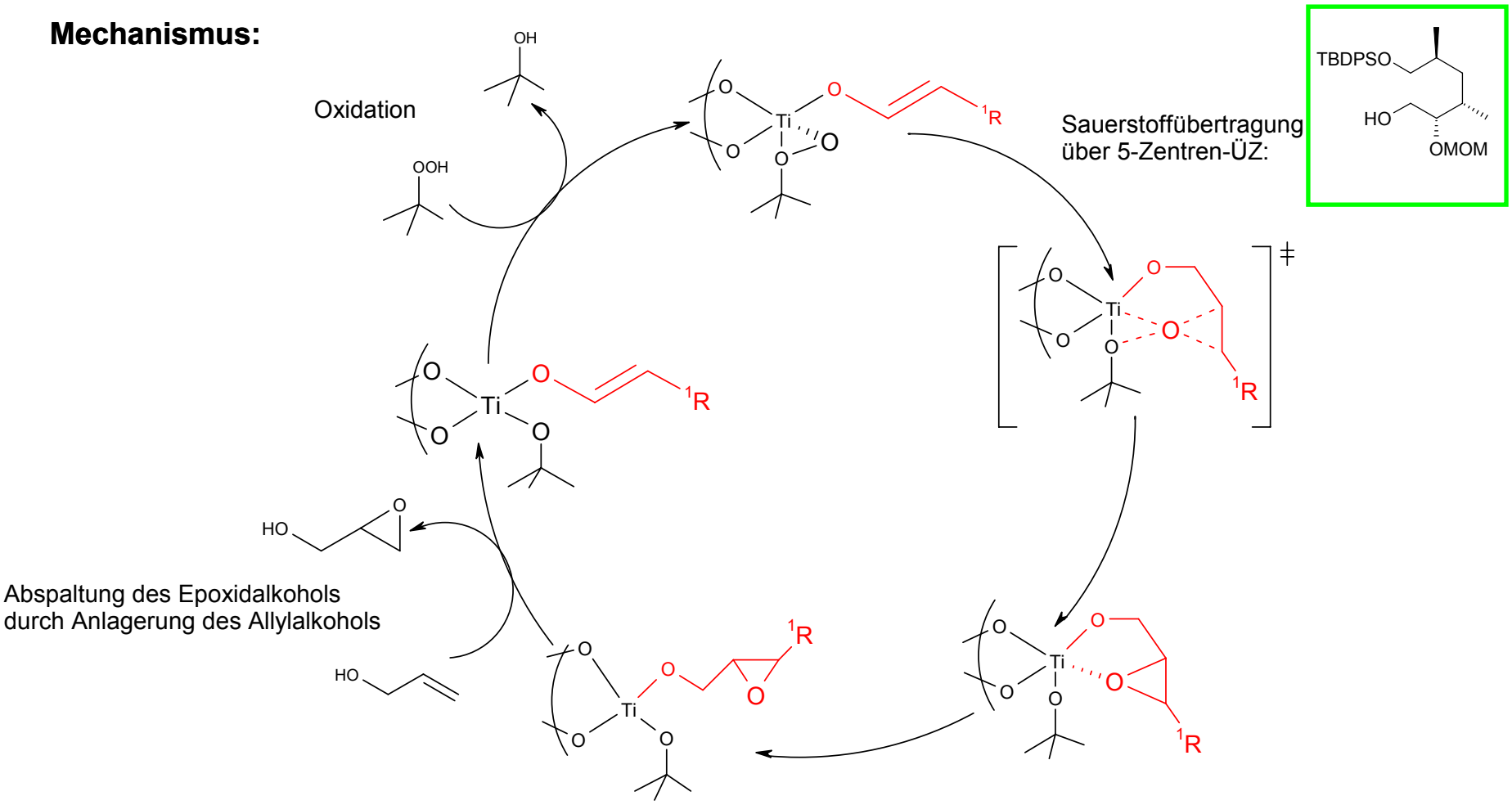
- die tert-Bu-O-Ti-Substruktur befindet sich auf derjenigen Seite der Fünfring/Vierring/Fünfring-Mittelebene, die nur eine β-ständige CO_2Et-Gruppe enthält

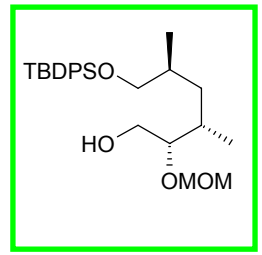
(+)-Tetronolid

nach R.K. Boeckman; P. Shao; S.T. Wrobleski; D.J. Boehmler; G.R. Heintzelman; A.J. Barbosa

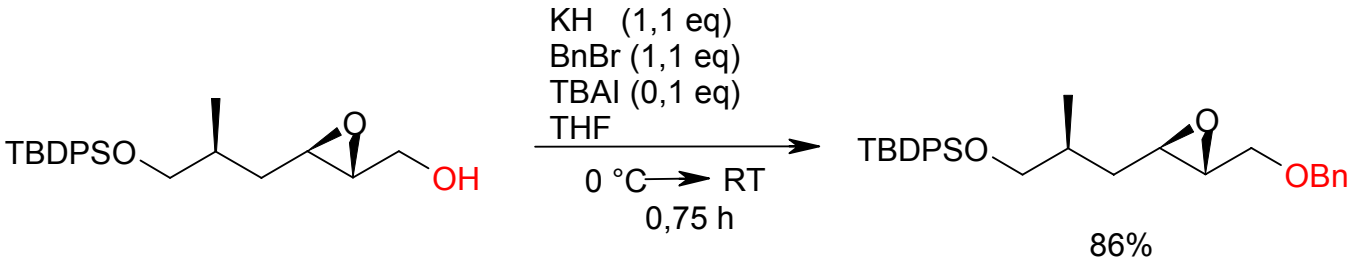
J. Am. Chem. Soc. **2006**, *128*, 10572

Mechanismus:

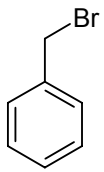




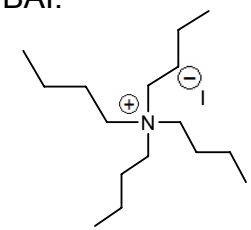
II.1.4. Darstellung des Epoxidethers durch Williamson-Ethersynthese

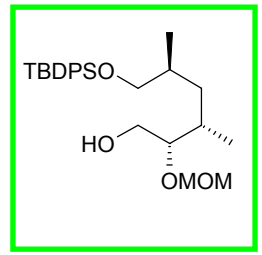


BnBr:



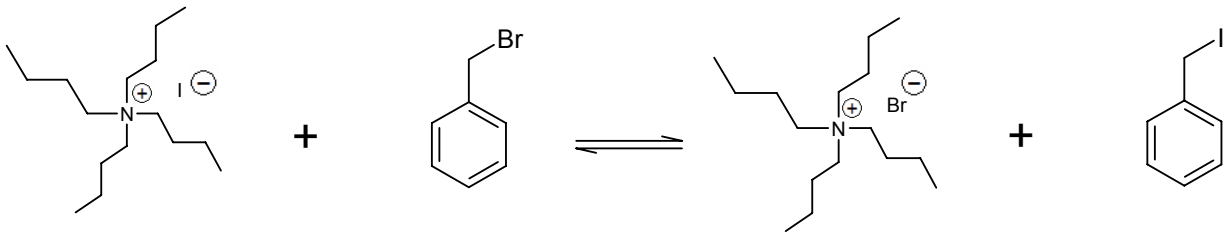
TBAI:





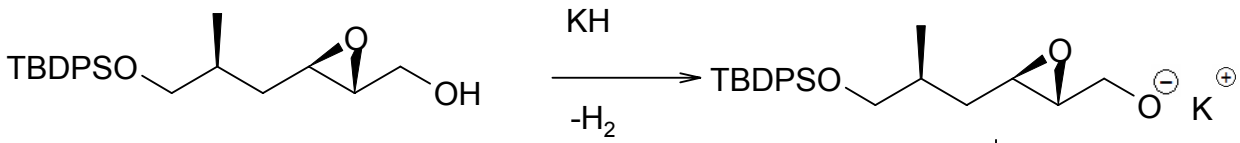
Mechanismusvorschlag:

Halogenaustausch über Finkelstein-Reaktion



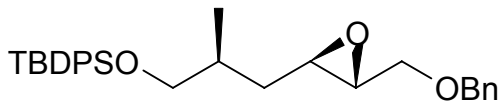
BnBr

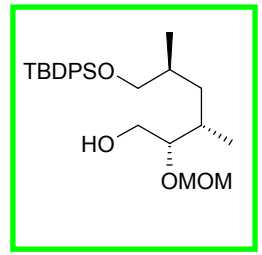
Deprotonierung



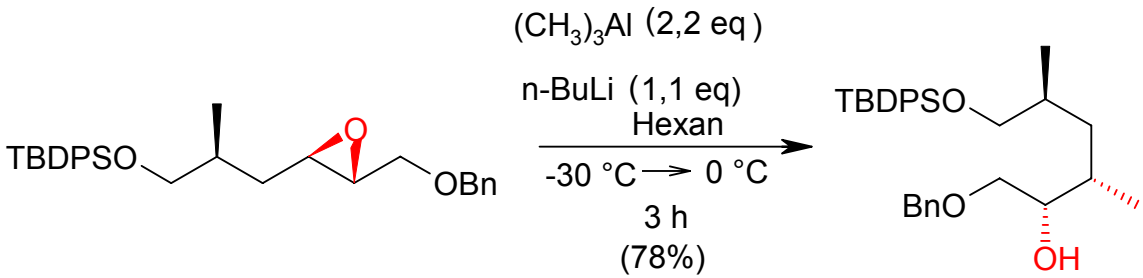
+ BnI
- KBr

SN2-Mechanismus

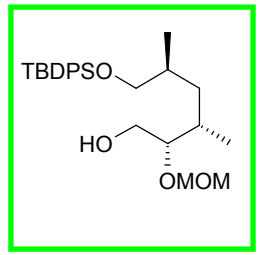




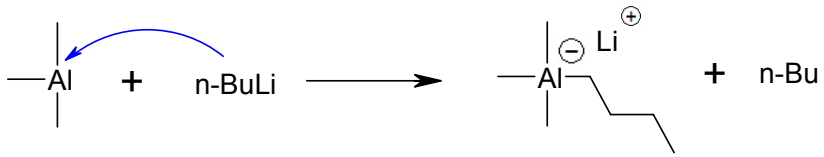
II.1.5. Selektive Ringöffnung des 2,3 – Epoxyalkohols mittels Aluminium- Komplex



Mechanismusvorschlag:

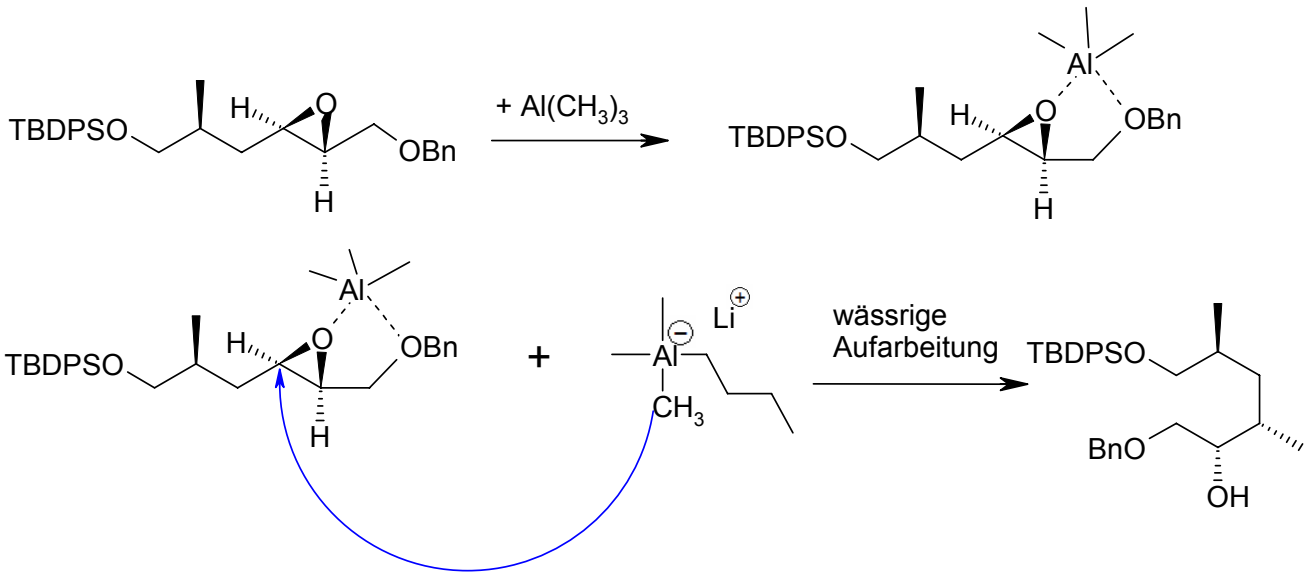


Bildung des Aluminium-Komplexes



Addition und nucleophile Ringöffnung:

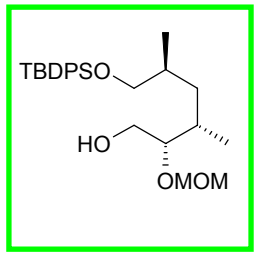
Mechanismusvorschlag:

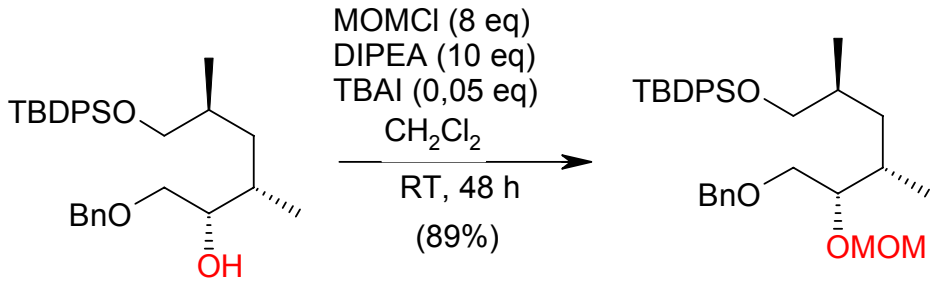


regioselektiver Angriff an C3

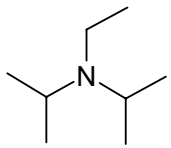
Lit.: G. Lin, Y. Li, A. Chan, Principles and Applications of Asymmetric Synthesis, Wiley-Interscience, 1. Auflage, S. 209f

II.1.6. Schützen des Alkohols mittels MOM-Cl

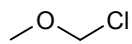




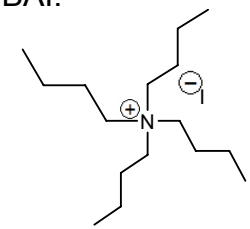
DIPEA:



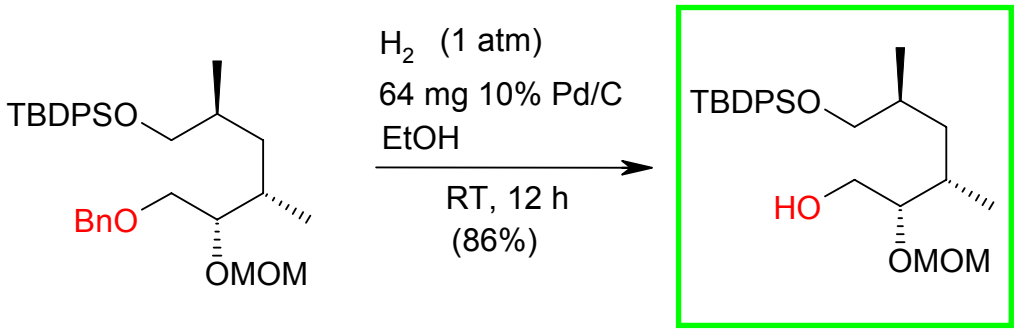
MOM-Cl:



TBAI:



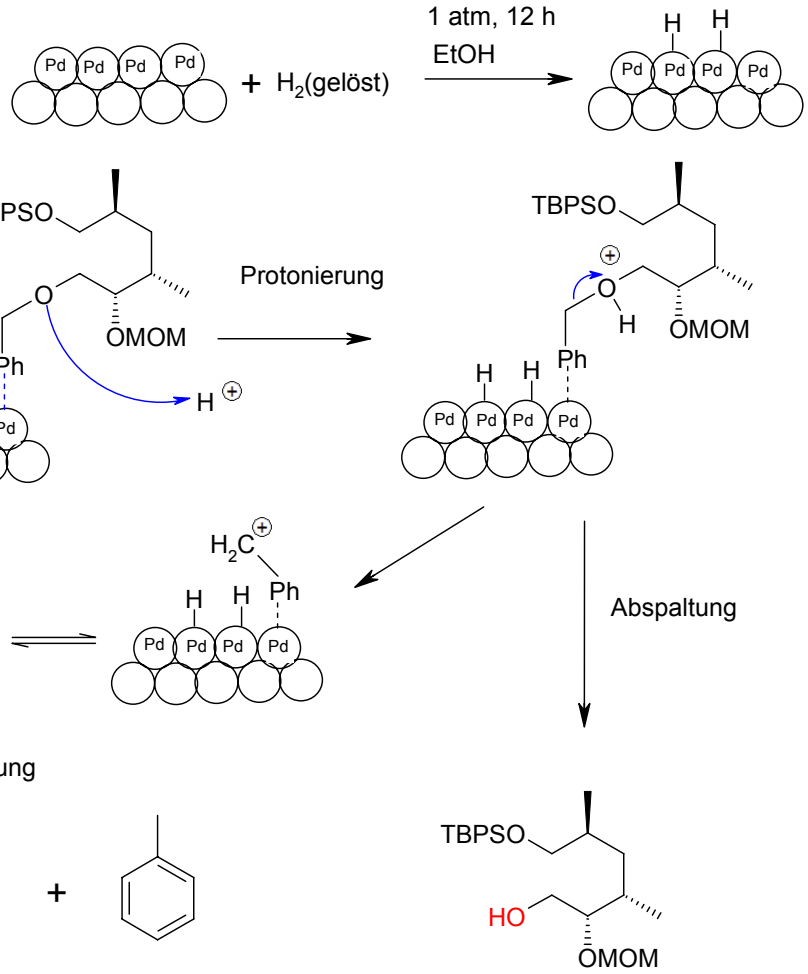
II.1.7. Hydrierung am Pd/C-Katalysator

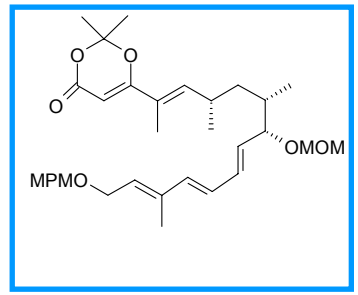


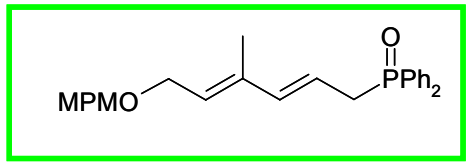
Mechanismusvorschlag:

Heterogen katalysierte Hydrierung

Adsorption des H_2 an der Katalysatoroberfläche:

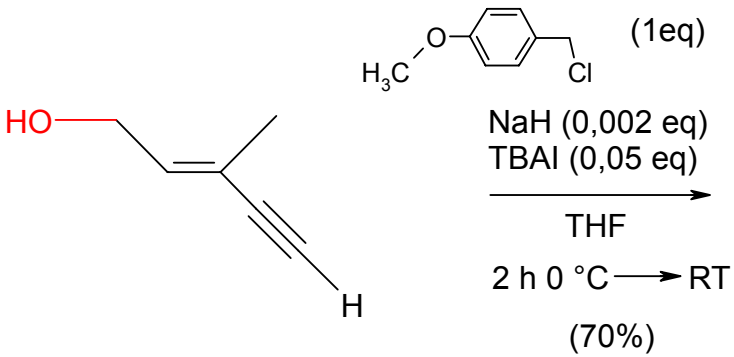






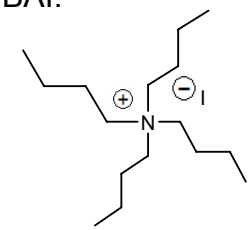
II.2. Synthese zweites Fragment

II.2.1. Schützen der Hydroxygruppe mittels MPMCl

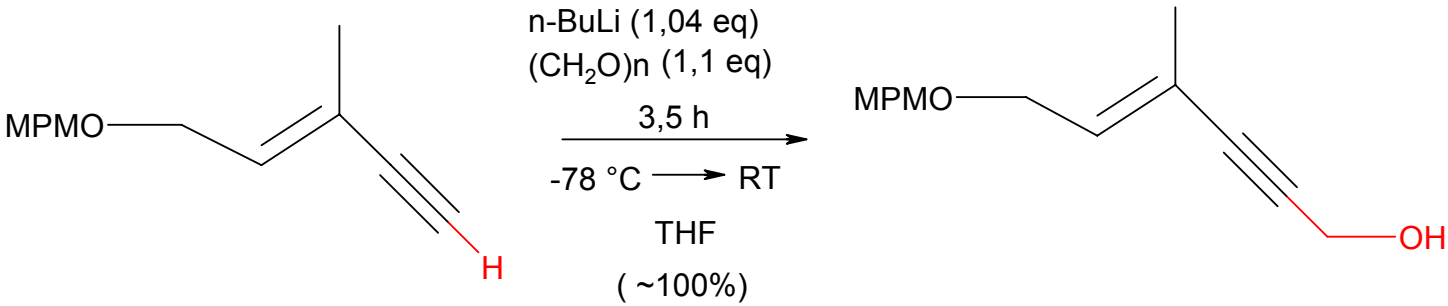


• Williamson-Ethersynthese

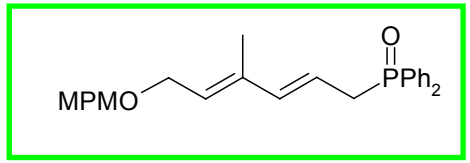
TBAI:



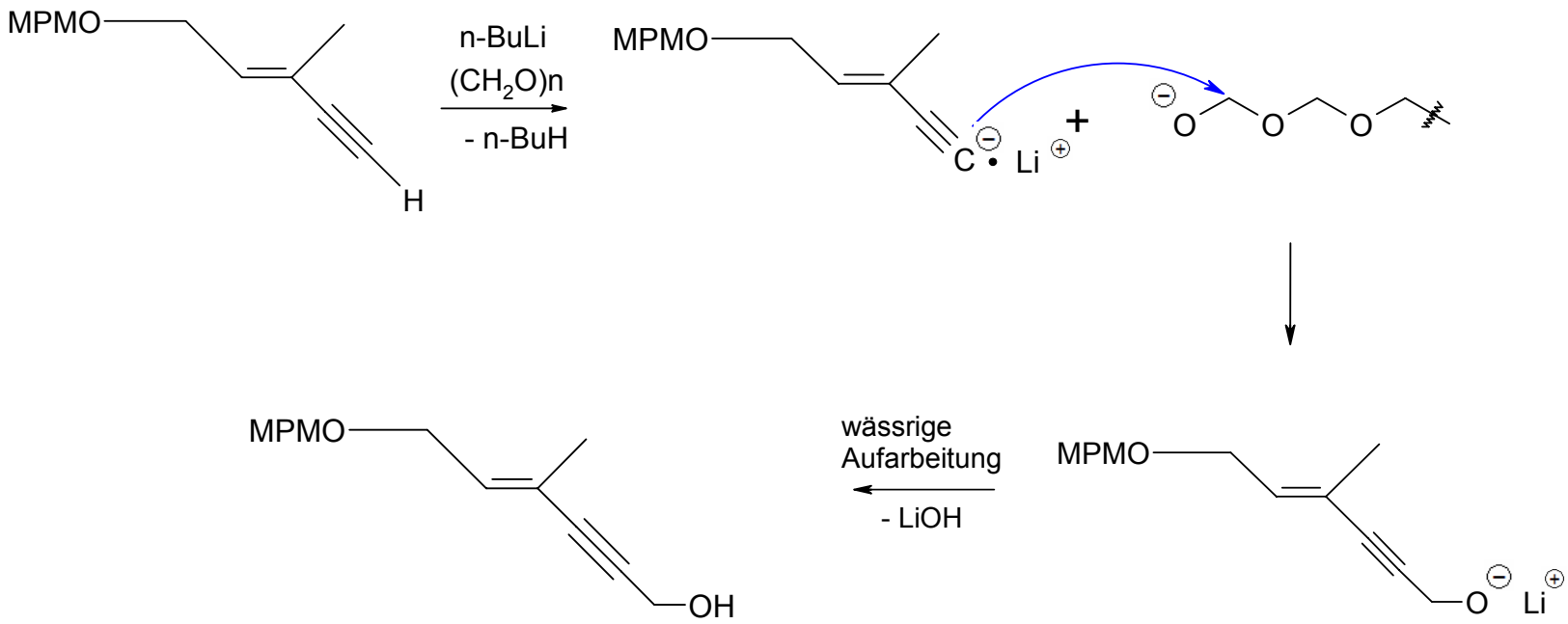
II.2.2. Einführen einer zweiten Hydroxygruppe

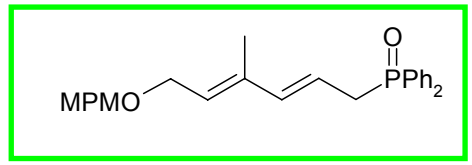


Mechanismusvorschlag:

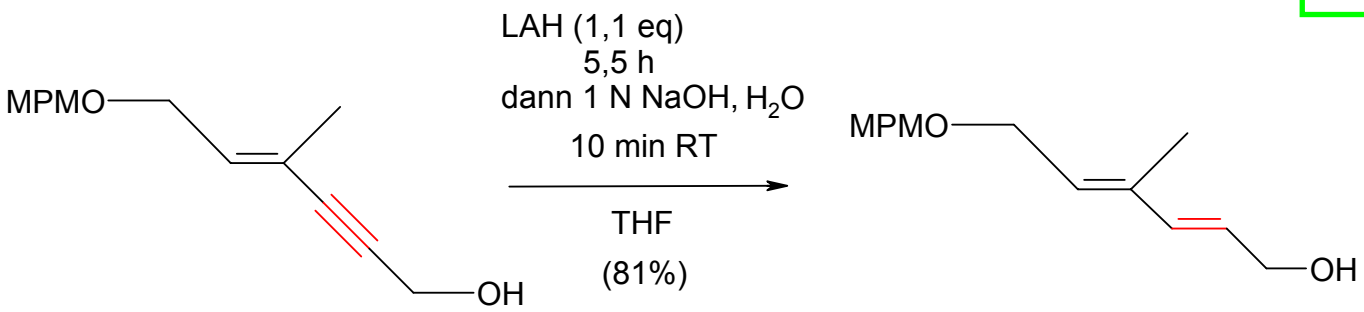


• Hydroxymethylierung

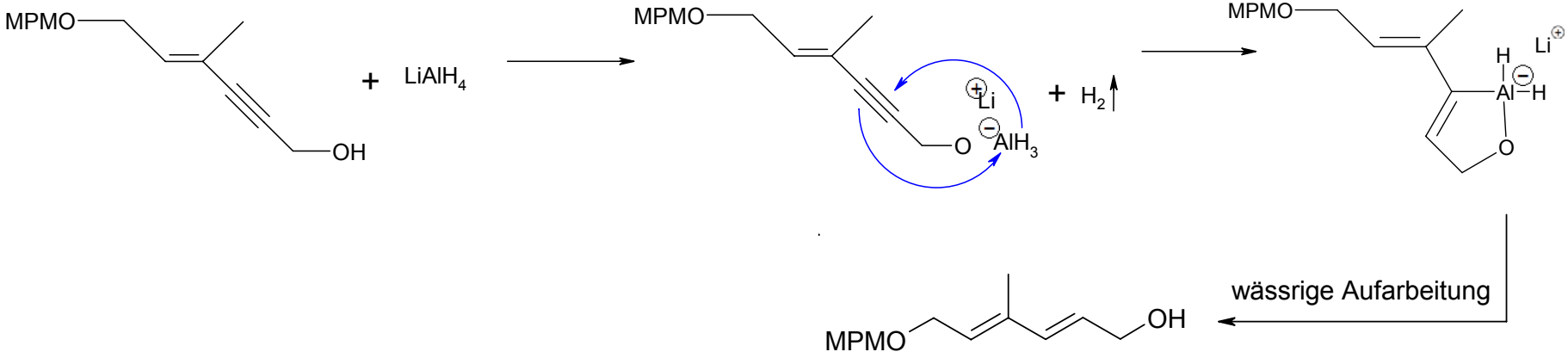


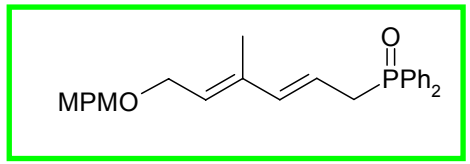


II.2.3. Hydrierung der Dreifachbindung

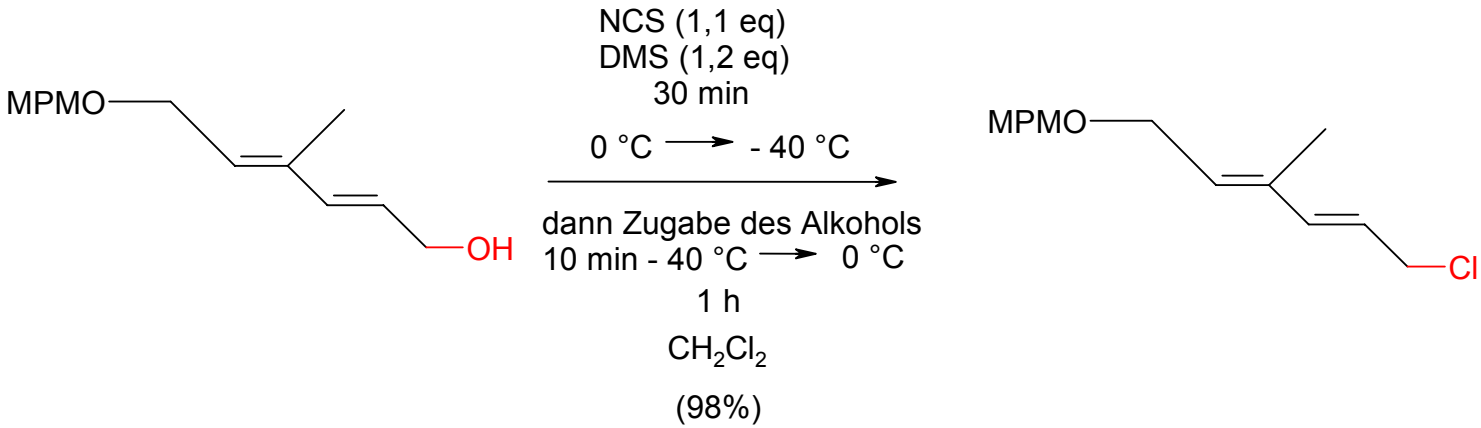


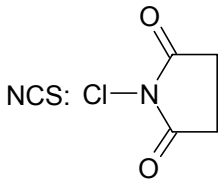
Mechanismusvorschlag:

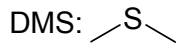




II.2.4. Chlorierung







nach R.K. Boeckman; P. Shao; S.T. Wrobleski; D.J. Boehmler; G.R. Heintzelman; A.J. Barbosa

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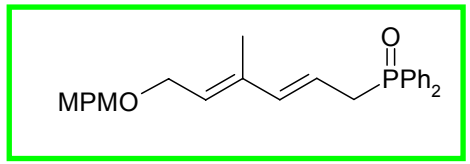
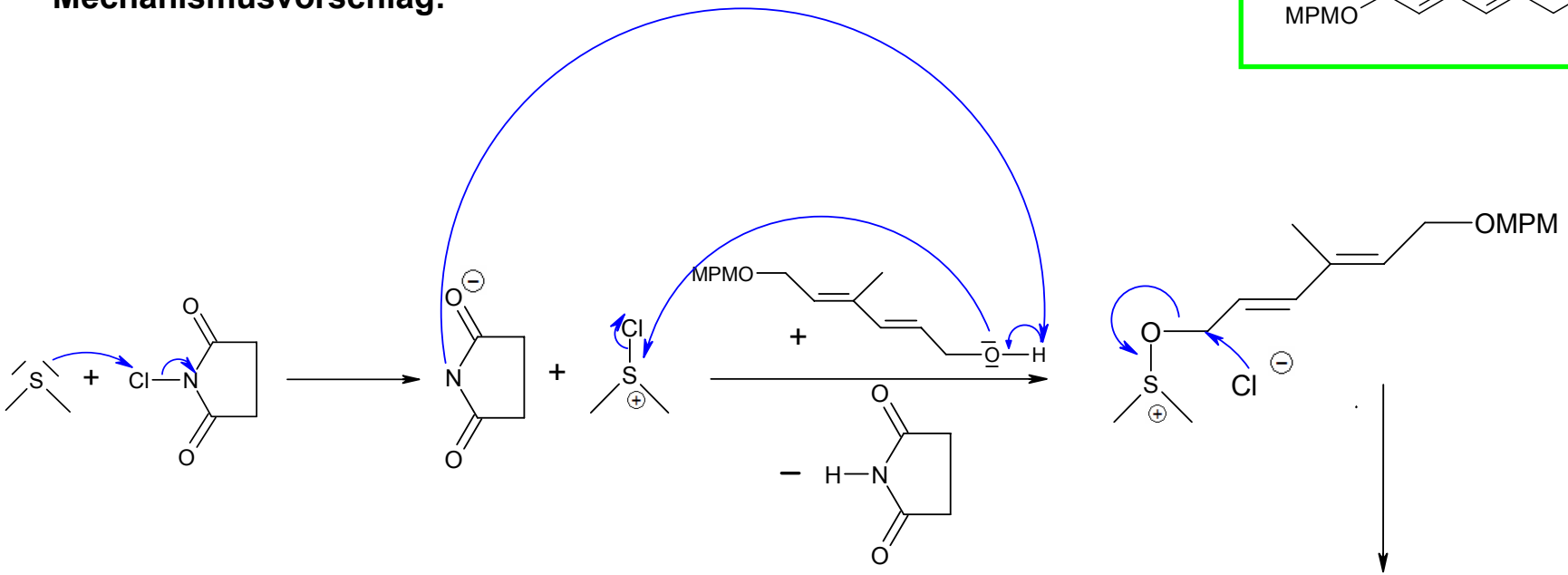
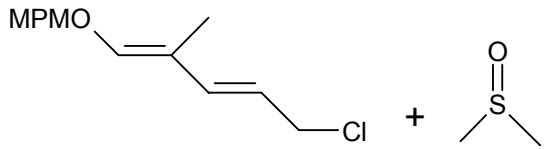


Mechanismusvorschlag:

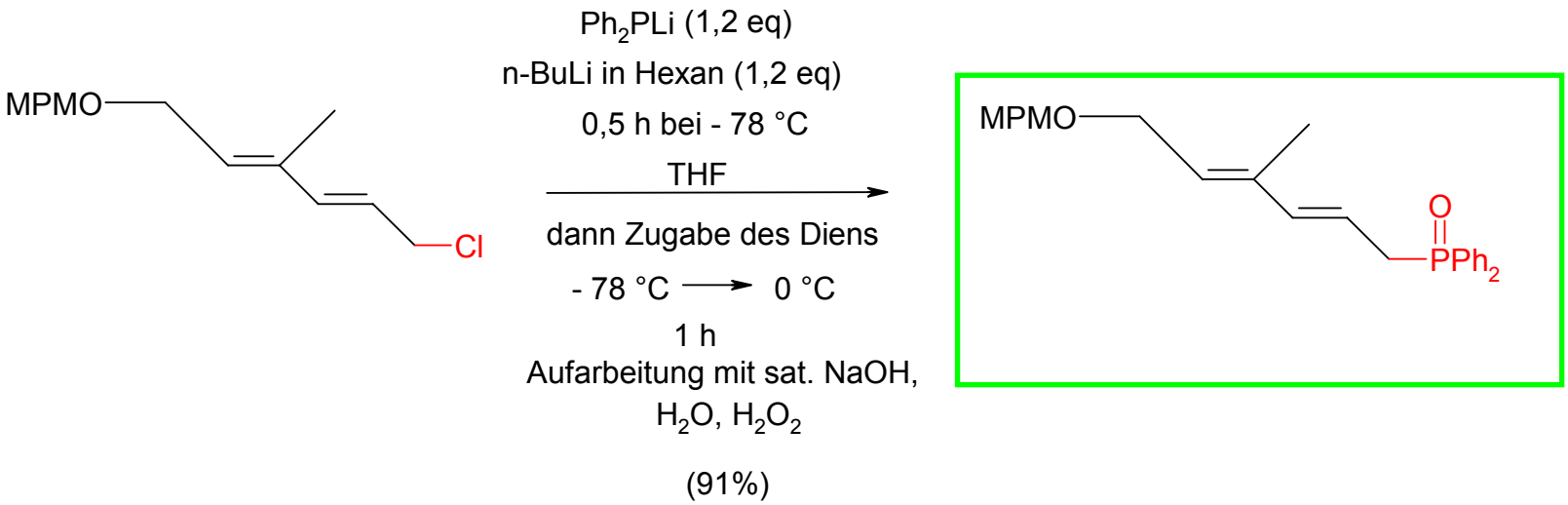


- Sulfoxoniumintermediat ist sehr instabil
- da Bildung und Zerfall des Intermediates in Dichlormethan ohne Triethylamin ablaufen, wird sofort das Chlorid gebildet

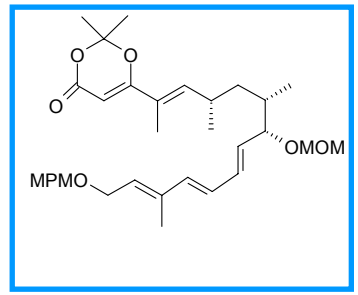


Literatur: E.J. Corey, C.U. Kim, M. Takeda *Tetrahedron Lett.* **1972**, *42*, 4339

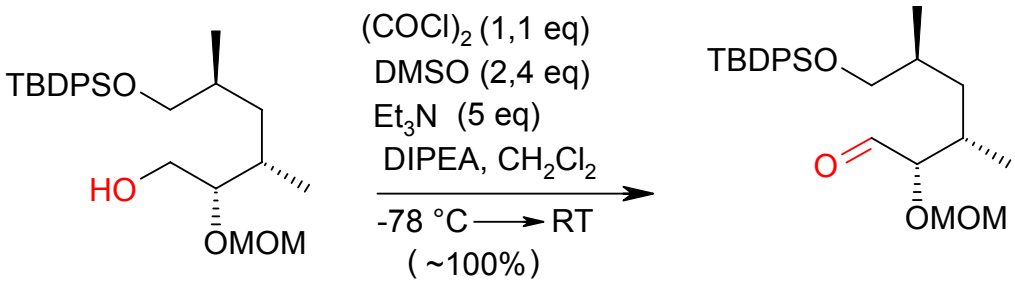
II.2.5. Darstellung des Phosphins



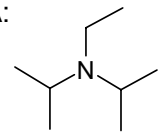
II.3. Vereinen der Fragmente



II.3.1. Oxidation des Alkohols nach Swern

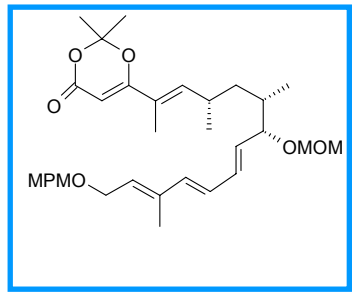


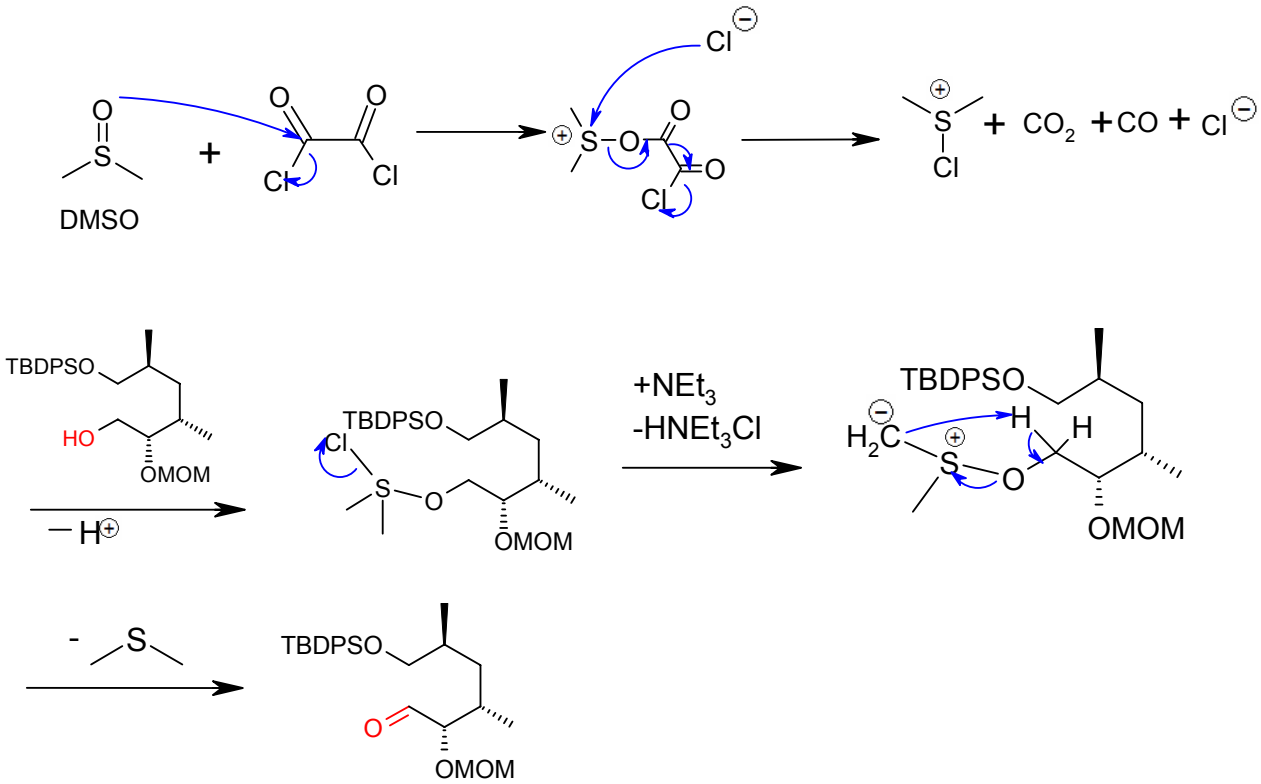
DIPEA:



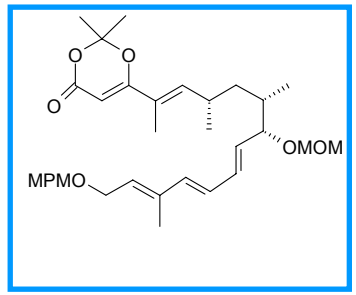
DMSO:

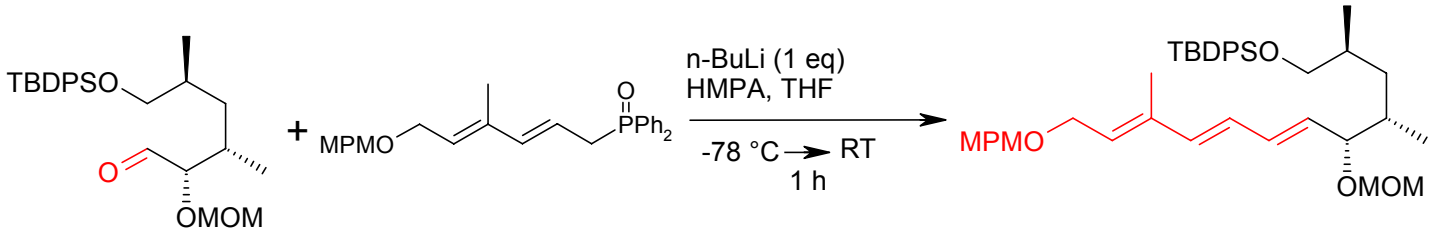
Mechanismus:



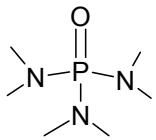


II.3.2. Horner-Wadsworth-Emmons-Reaktion

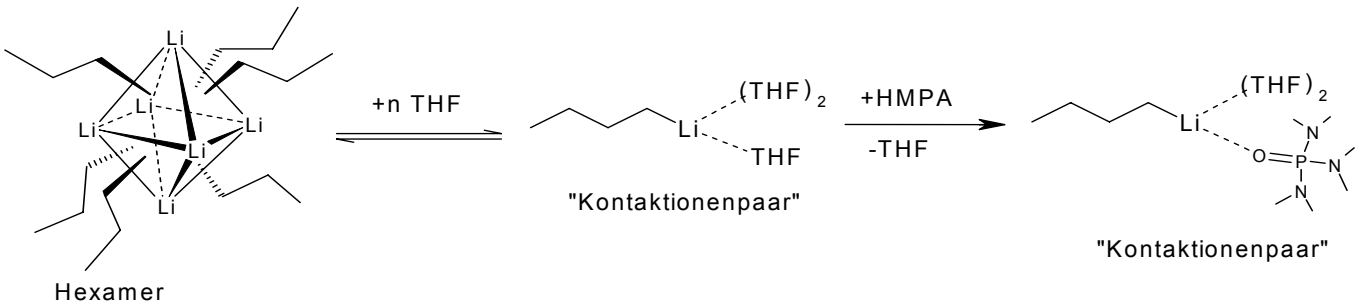




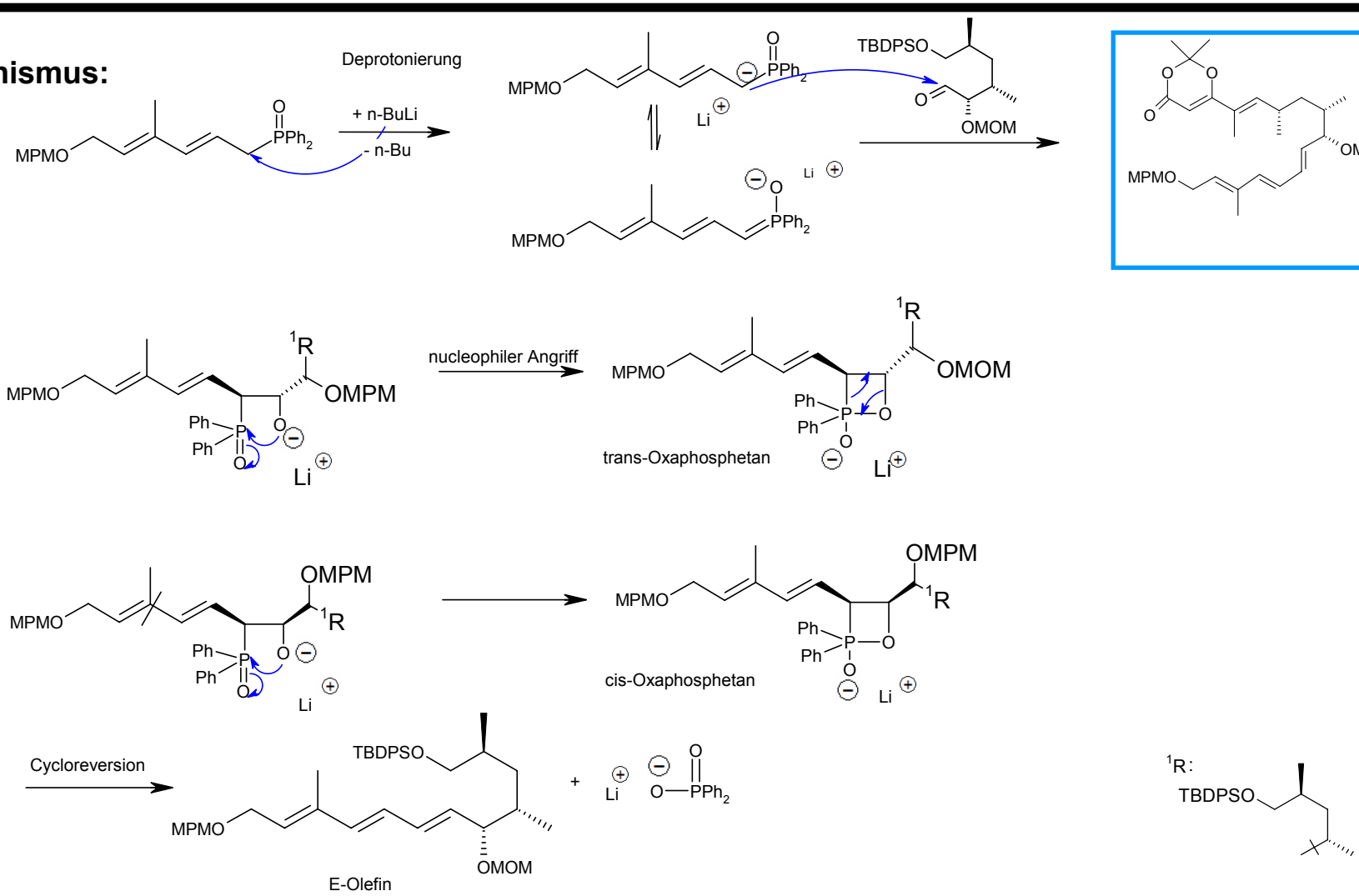
Zusatz von HMPA:



Zusatz zum Aufbrechen von n-BuLi-Hexameren
koordiniert stark zum Lithiumkation

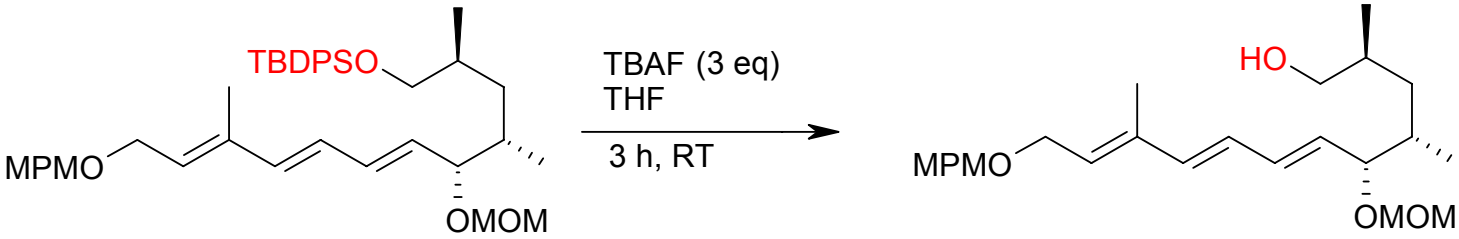


Mechanismus:

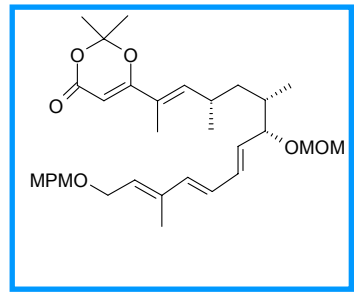


Literatur: R. Brückner; Reaktionsmechanismen, Spektrum Akademischer Verlag; 3. Auflage, **2004**; S. 185f

II.3.3. Entschützen der TBDPS-Gruppe



99%

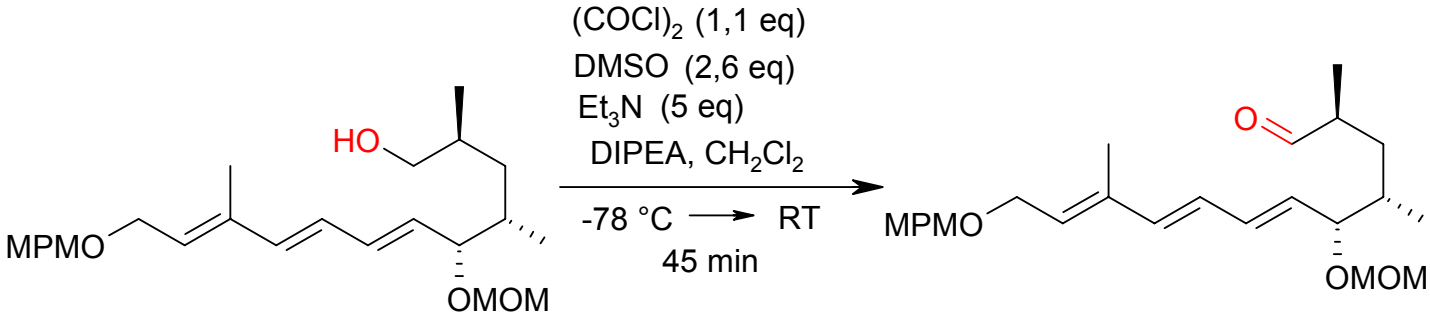


TBAF: $Bu_4N^{\oplus}F^{\ominus}$

Desylierungsreagenz

TBDPS-OR: $tBuPh_2Si$-OR

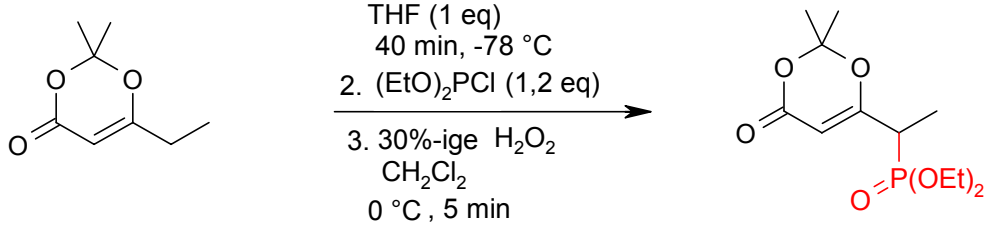
II.3.4. Swern-Oxidation



~100%

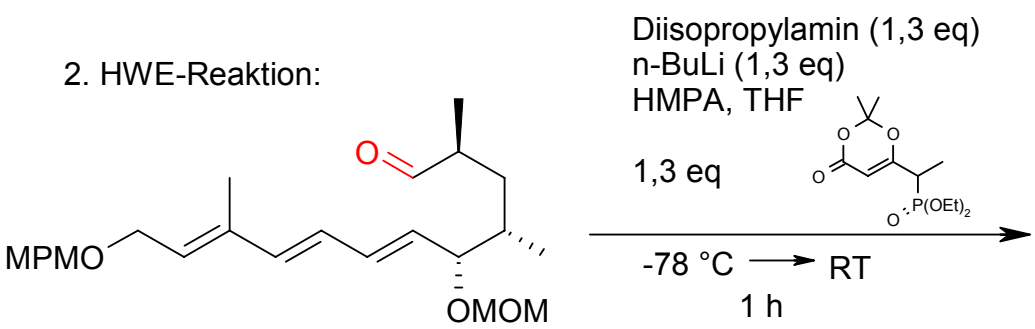
II.3.5. Abschließende HWE-Reaktion

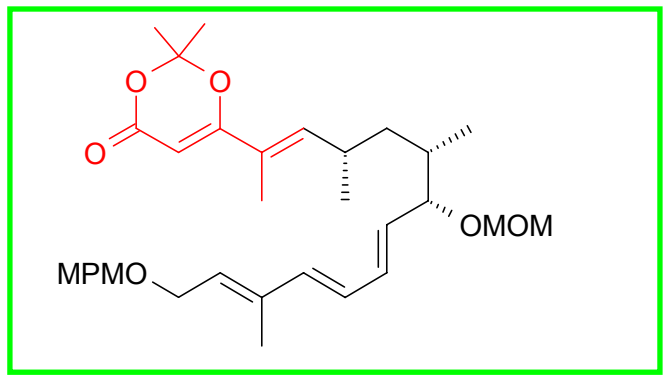
Herstellung des Phosphinoxids für die HWE-Reaktion durch Deprotonierung, weiter über nucleophile Substitution und anschließende Oxidation



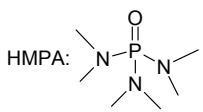
74%

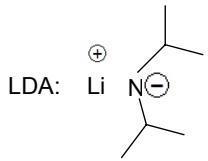
2. HWE-Reaktion:



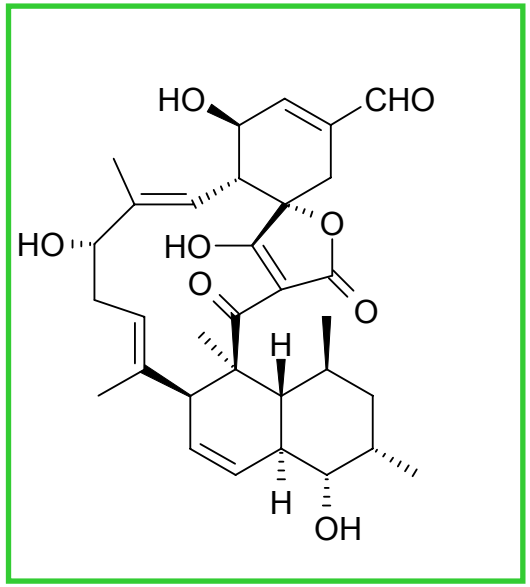


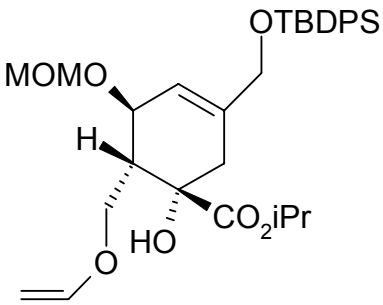
78%

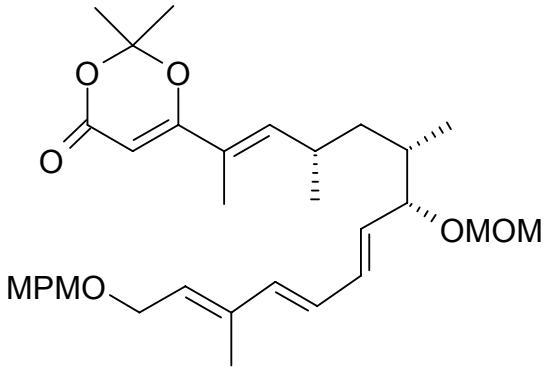




(+) - Tetronolid







nach R.K. Boeckman; P. Shao; S.T. Wrobleski; D.J. Boehmler; G.R. Heintzelman; A.J. Barbosa

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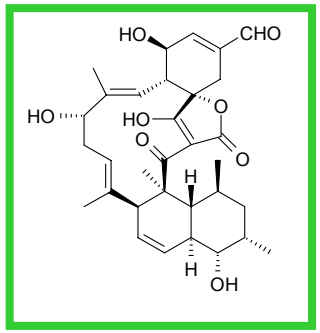
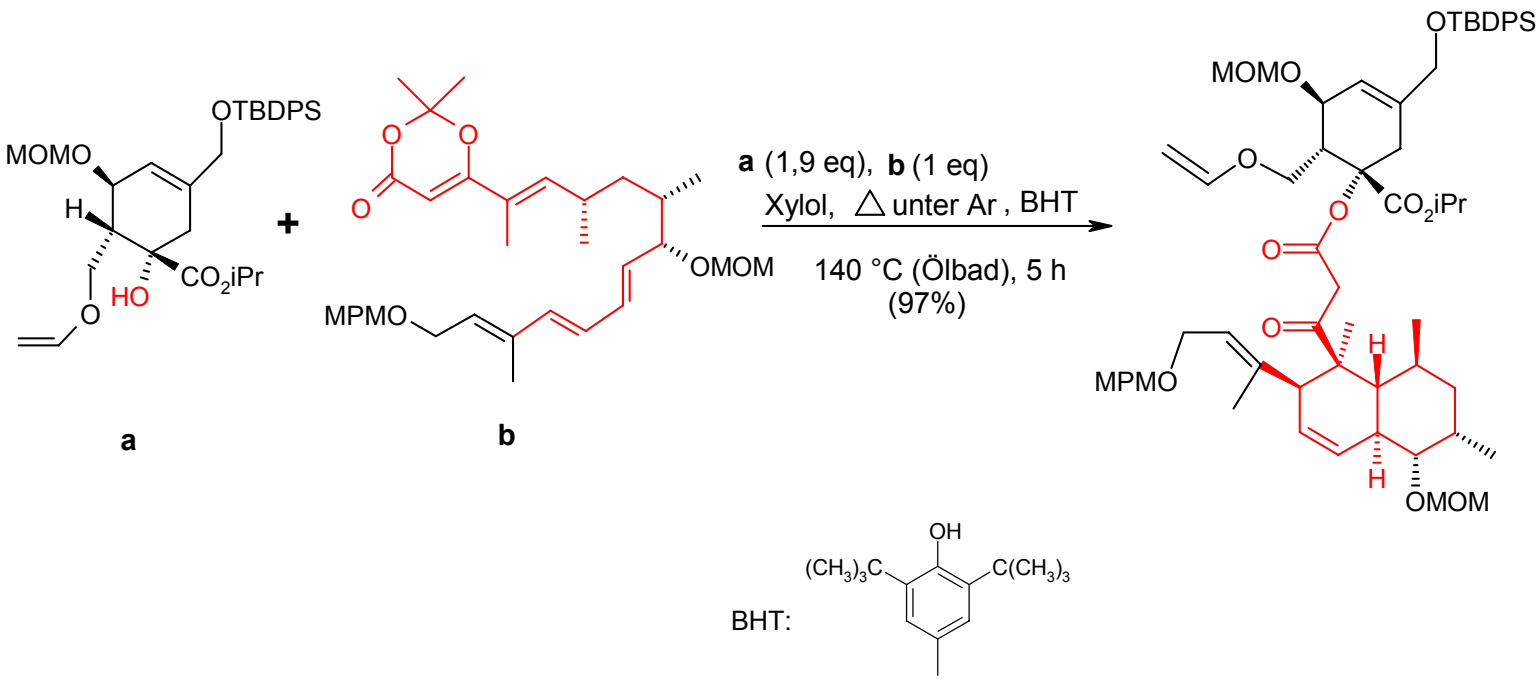


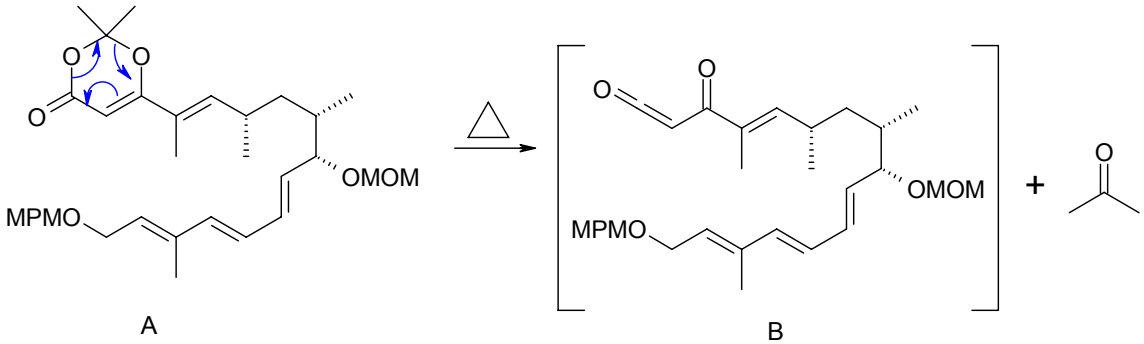
III.1. Zusammenfügen der Untereinheiten

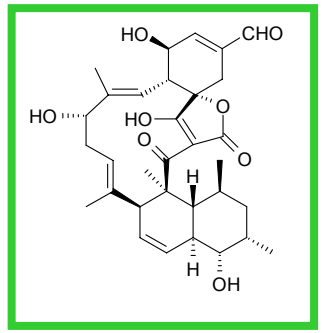
III.1.1. Tandem Keten-Trapping/[4+2]Cycloaddition



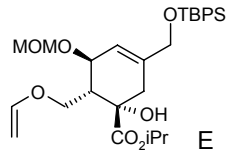
Mechanismus:

Stufe 1: Retro-Hetero-Diels-Alder



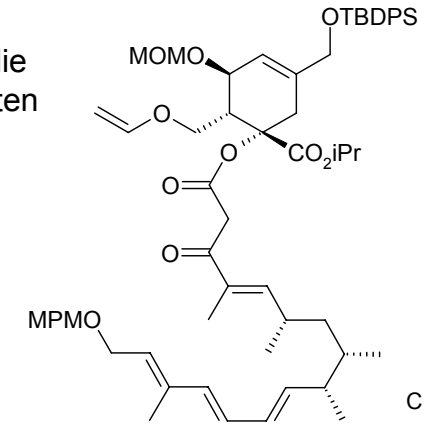


Stufe 2: Nucleophile Addition



E

- Retro-Diels-Alder-Reaktion
- durch Erwärmen erhöht sich die Ringspannung in A, die Bindungen brechen und klappen um, es entsteht ein Keten
- danach erfolgt nucleophiler Angriff der OH-Gruppe auf Keten-Kohlenstoff unter Ausbildung eines β-Ketoesters



C

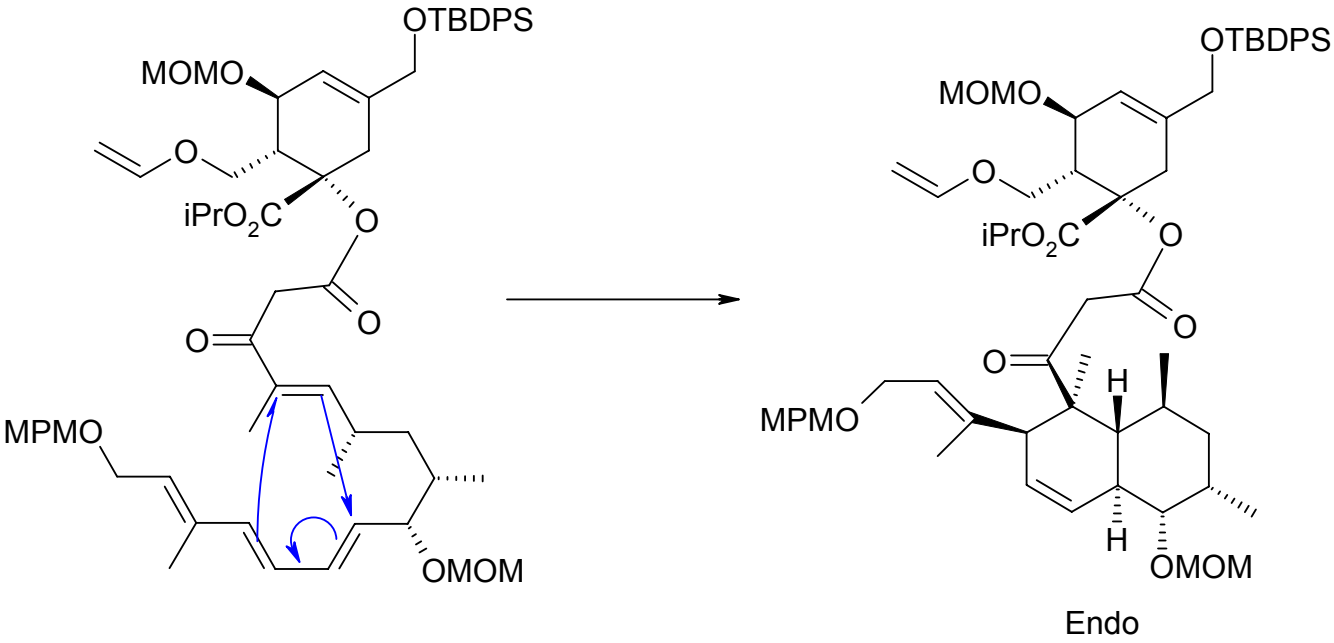
Literatur: R. Brückner, Reaktionsmechanismen, Spektrum Akademischer Verlag; 3. Auflage, **2004**, S. 293

R. Boeckman *Tetrahedron Lett.* **1991**, *33*, 4091

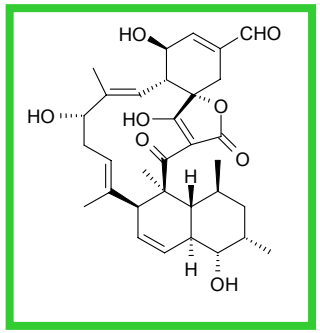
nach R.K. Boeckman; P. Shao; S.T. Wrobleski; D.J. Boehmler; G.R. Heintzelman; A.J. Barbosa

J. Am. Chem. Soc. **2006**, *128*, 10572

Diels-Alder-Reaktion:

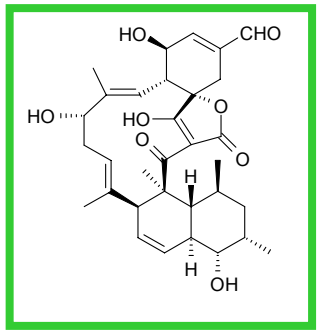


Endo

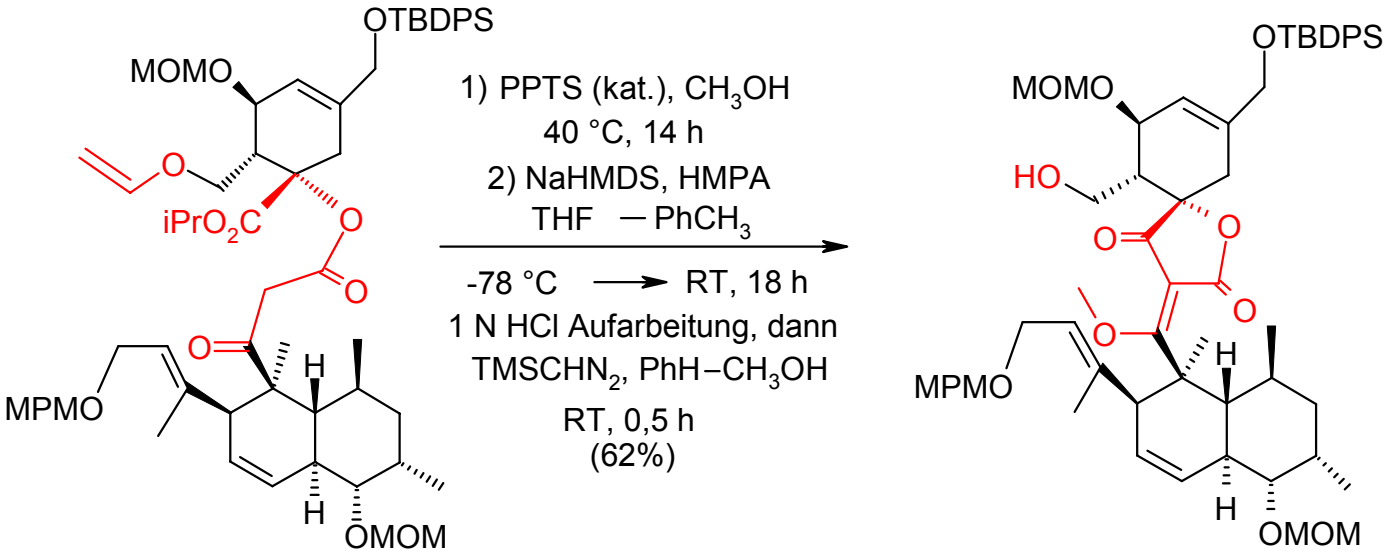


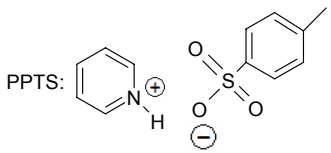
- Reaktion läuft in einem Schritt ab: die beiden neuen C-C-Bindungen und die neue Doppelbindung werden gleichzeitig mit dem Brechen der drei Doppelbindungen gebildet
- auf Grund anziehender Wechselwirkungen zwischen π-System des Diens und π-System des ungesättigten Substituenten am Dienophil wird Endo-Produkt gebildet

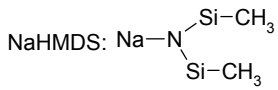
Literatur: R. Boeckman *Tetrahedron Lett.* **1991**, *33*, 4091

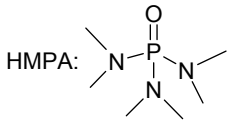


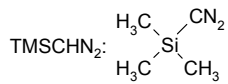
III.1.2. Ringschluss zur Spirotetronsäure



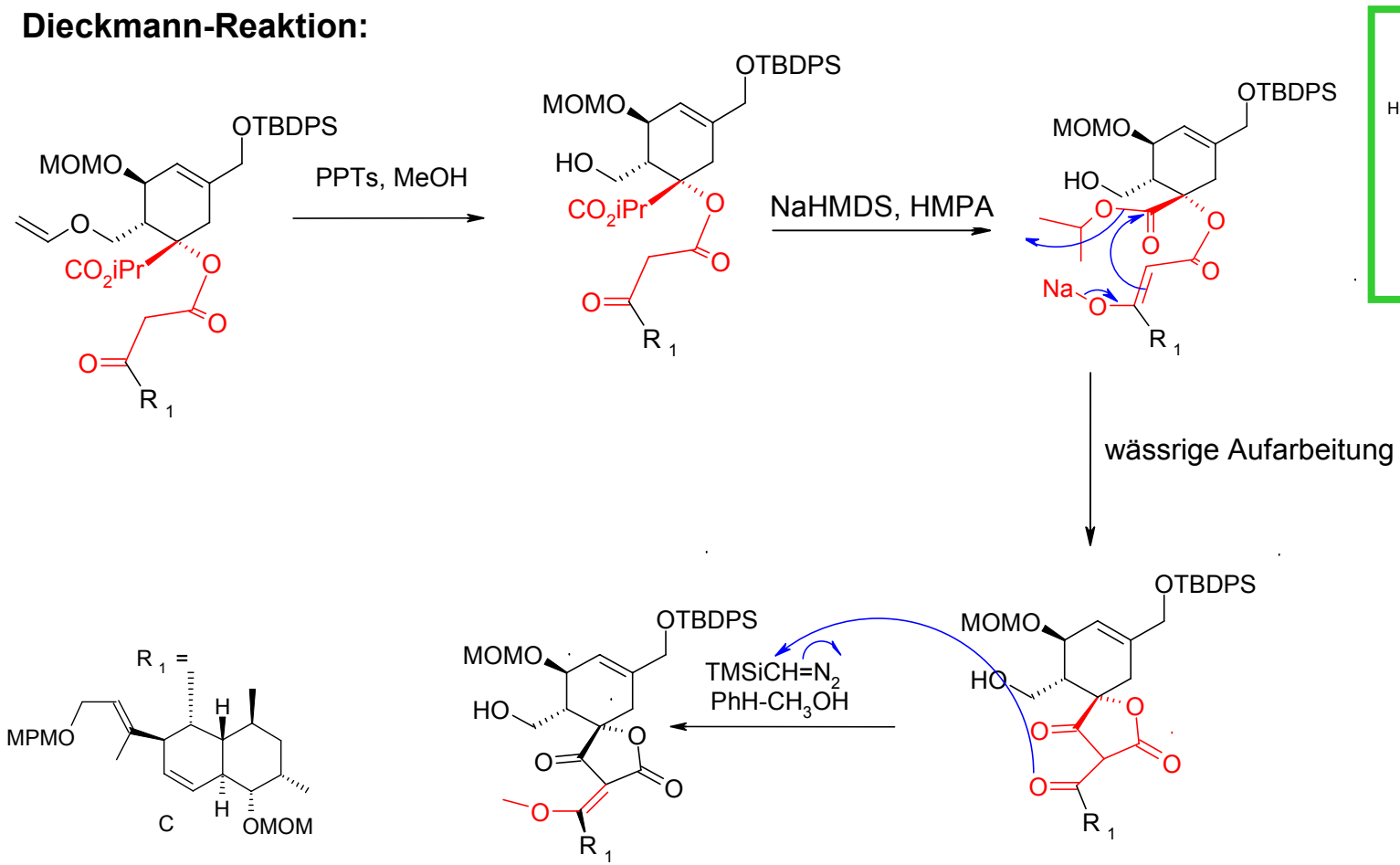






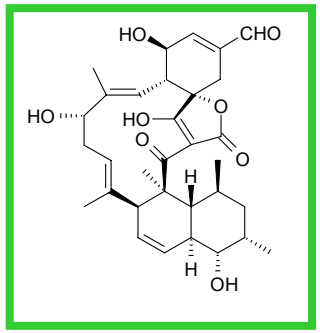


Dieckmann-Reaktion:

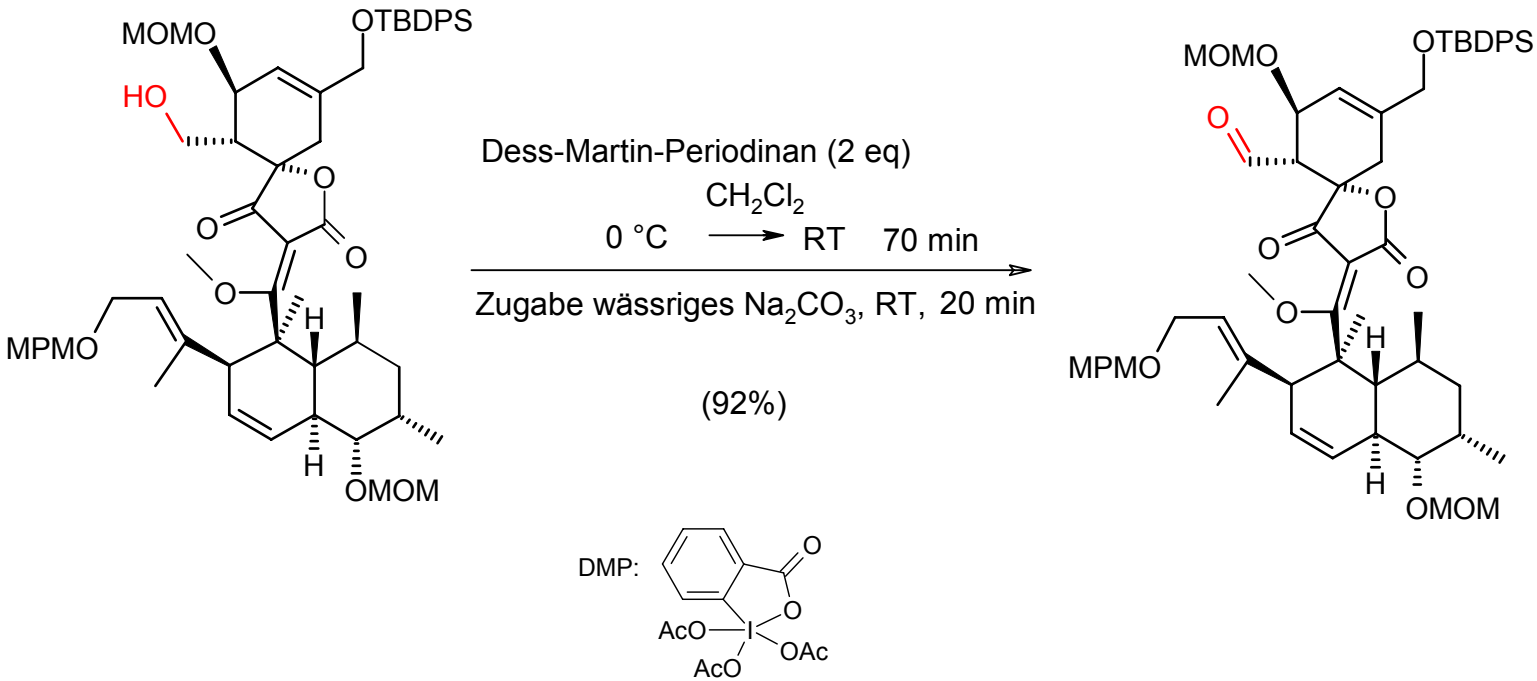


Literatur: R. Lacey *J. Chem. Soc*. **1954**, 832

III.2. Erarbeitung des Intermediates, das den makrozyklischen Ringschluss ermöglicht



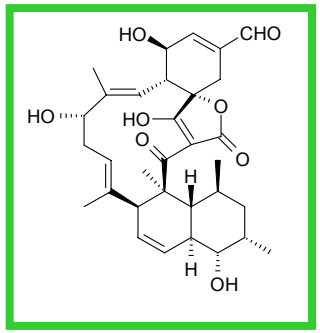
III.2.1. Oxidation des primären Alkohols zum Aldehyd mittels DMP

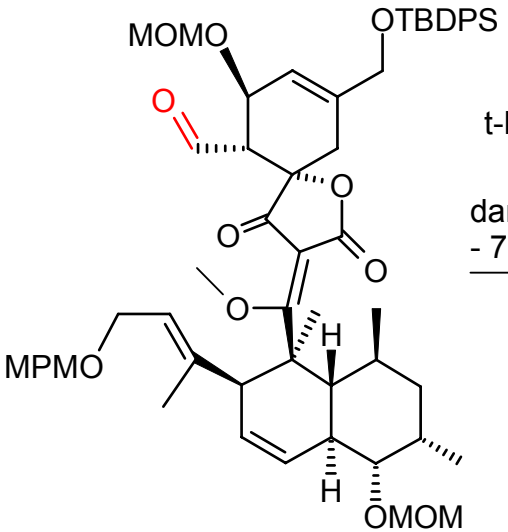


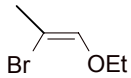
nach R.K. Boeckman; P. Shao; S.T. Wrobleski; D.J. Boehmler; G.R. Heintzelman; A.J. Barbosa

J. Am. Chem. Soc. **2006**, *128*, 10572

III.2.2. Grignard-Reaktion zur Gewinnung des (E)-Enals







(5,6 eq)

t-BuLi (9,7 eq), $MgBr_2 \cdot Et_2O$ (1,07 eq)

THF/ Et_2O, -78 °C, 55 min

dann Zugabe des Eduktes

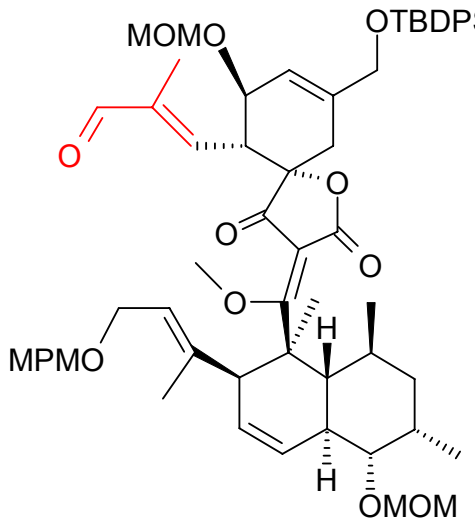
- 78 °C (10 min) ⟶ - 20 °C (über 20 min)

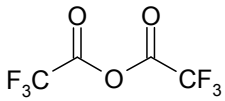
wässrige Aufarbeitung gefolgt von TFAA (12,5 eq), TFA (23 eq)

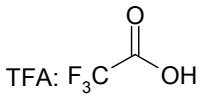
CH_2Cl_2

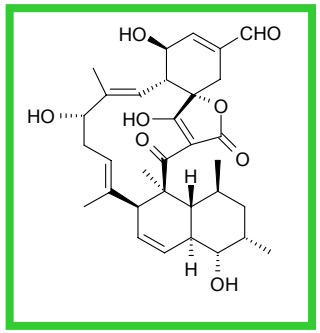
0 °C, 15 min

(85%)



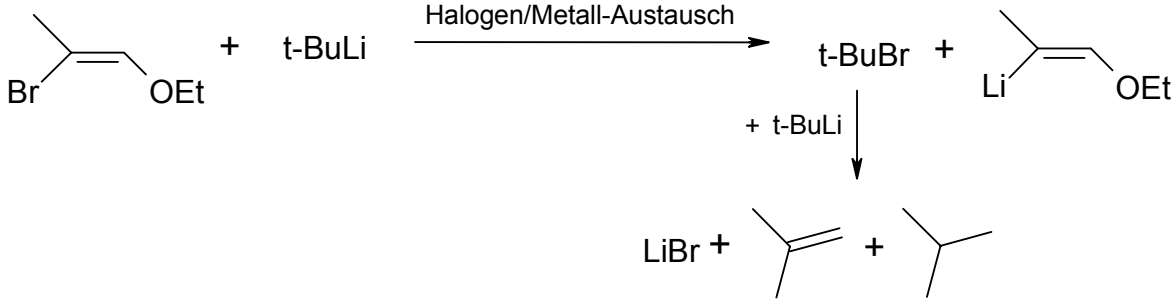
TFAA: 

TFA: 

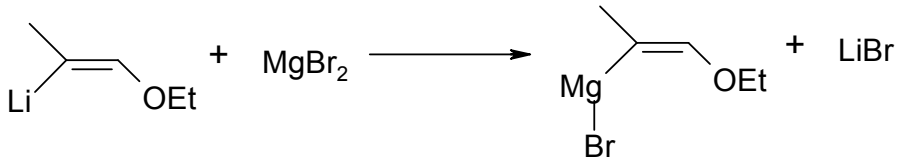


Mechanismusvorschlag:

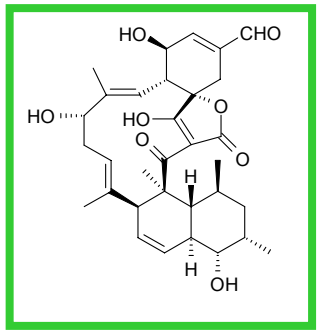
- Intoleranz des Grignard-Reagenzes gegenüber Brom
- Lithium hingegen reagiert rasch unter Halogen/Metall-Austausch



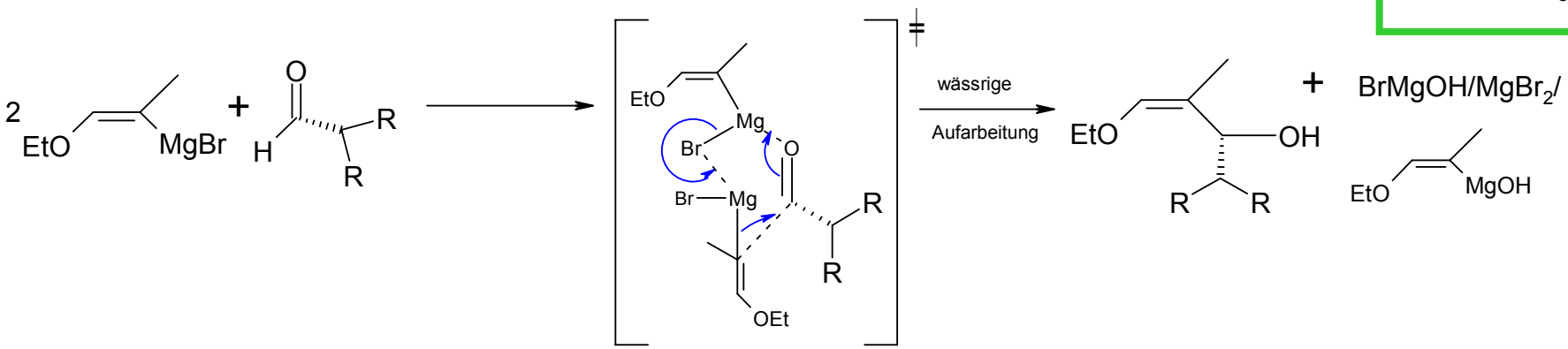
- Austausch von Lithium gegen Magnesium erfolgt nun schnell, da Lithium elektropositiver als Magnesium ist
- LiBr-Bildung trägt wesentlich zur Triebkraft der Reaktion bei



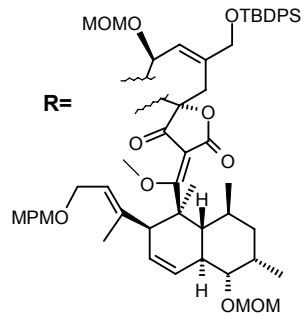
- um Stereoisomerisierung von E nach Z zu verhindern, wird bei tiefer Temperatur gearbeitet



Grignard-Übergangszustand:



- 6-gliedriger ÜZ, wobei die Stereochemie bezüglich der eingeführten OH-Gruppe egal ist, da diese im Folgeschritt entfernt wird
- vollständige Retention der Doppelbindungskonfiguration



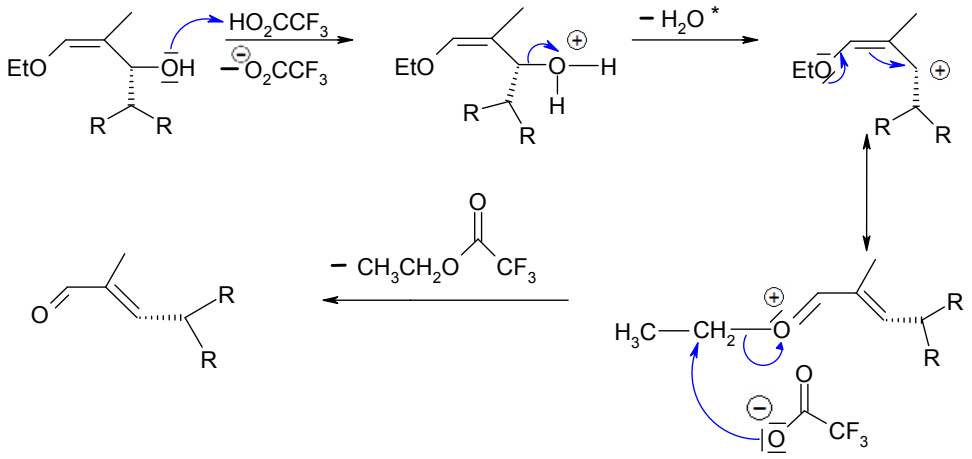
Literatur: F.A. Carey; R.J. Sundberg; Advanced Organic Chemistry, Part B, Springerverlag, 4.Auflage; **2001**, S. 446ff

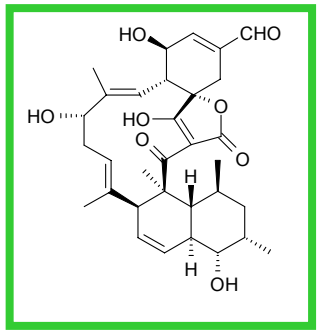
(+)-Tetronolid

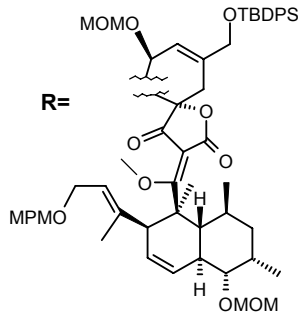
nach R.K. Boeckman; P. Shao; S.T. Wrobleski; D.J. Boehmler; G.R. Heintzelman; A.J. Barbosa

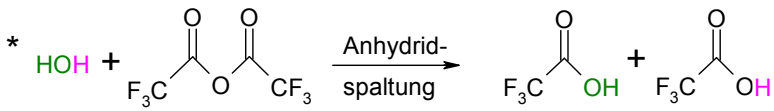
J. Am. Chem. Soc. **2006**, *128*, 10572

Mechanismusvorschlag für die Darstellung des α-β-ungesättigten Aldehyd mittels TFA:





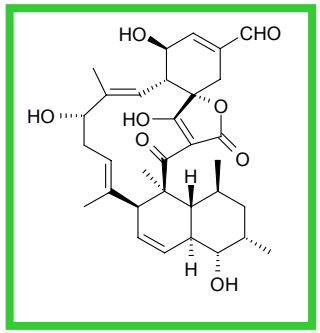


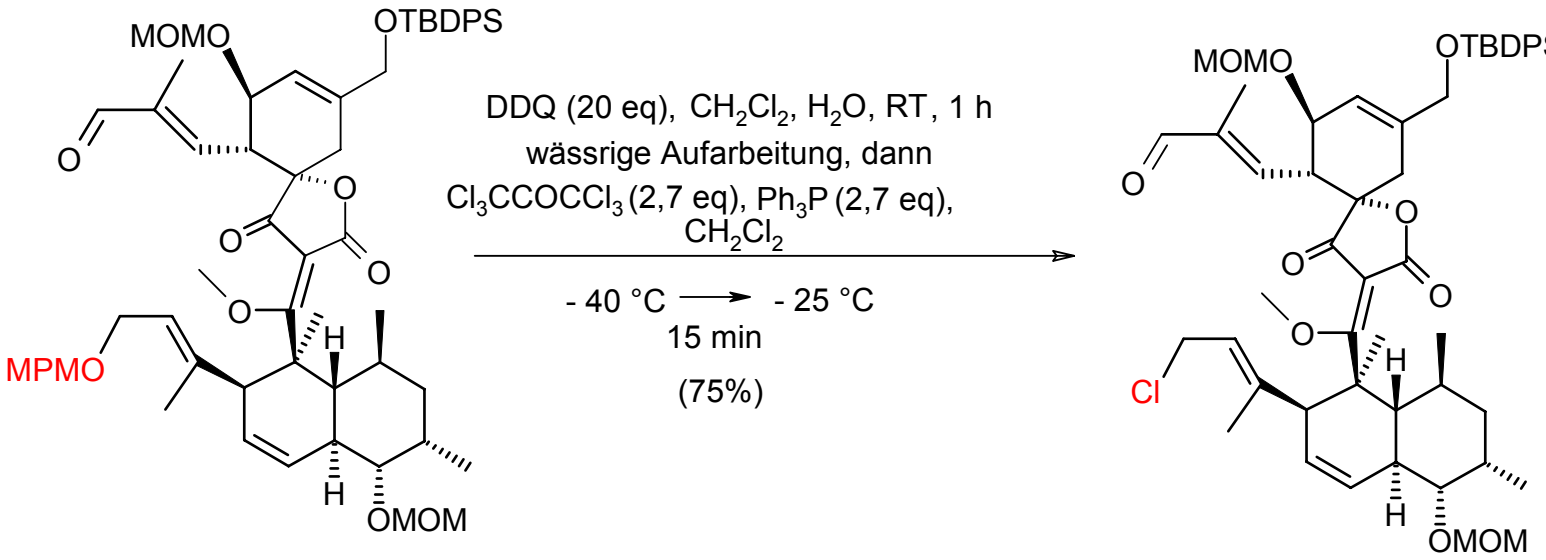


- das entstandene Wasser wird durch TFAA aus dem Reaktionsgemisch entfernt

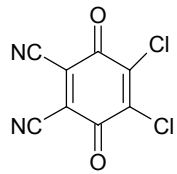
Literatur: R. Brückner; Reaktionsmechanismen, Spektrum Akademischer Verlag; 3. Auflage, **2004**; S. 185f

III.2.3. Darstellung des Allylchlorids

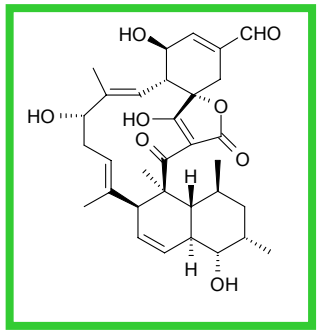


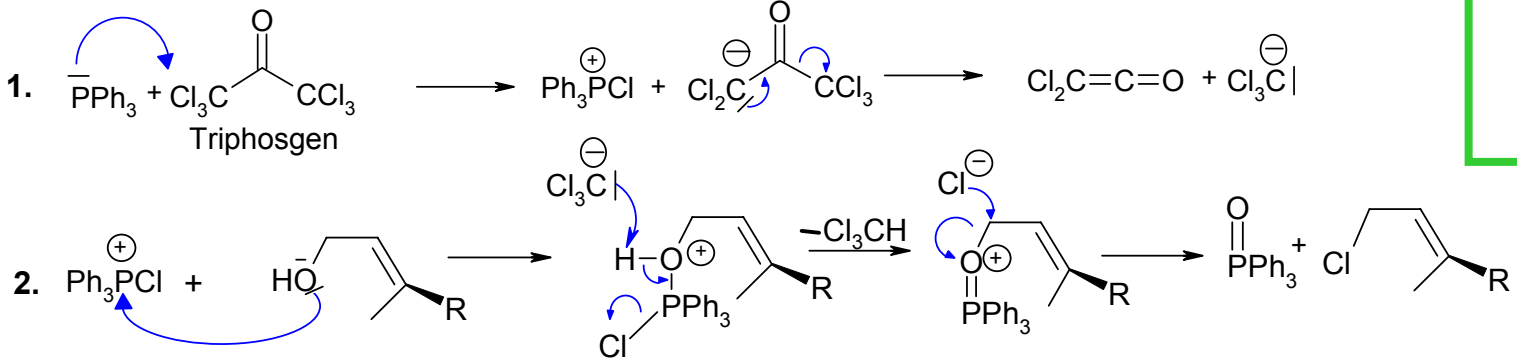


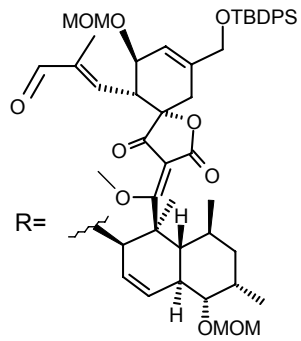
DDQ:



Mechanismusvorschlag der Chlorierung (Mukaiyama-Redoxkondensation):



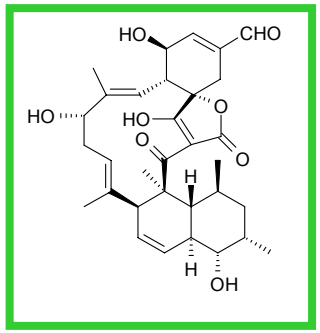




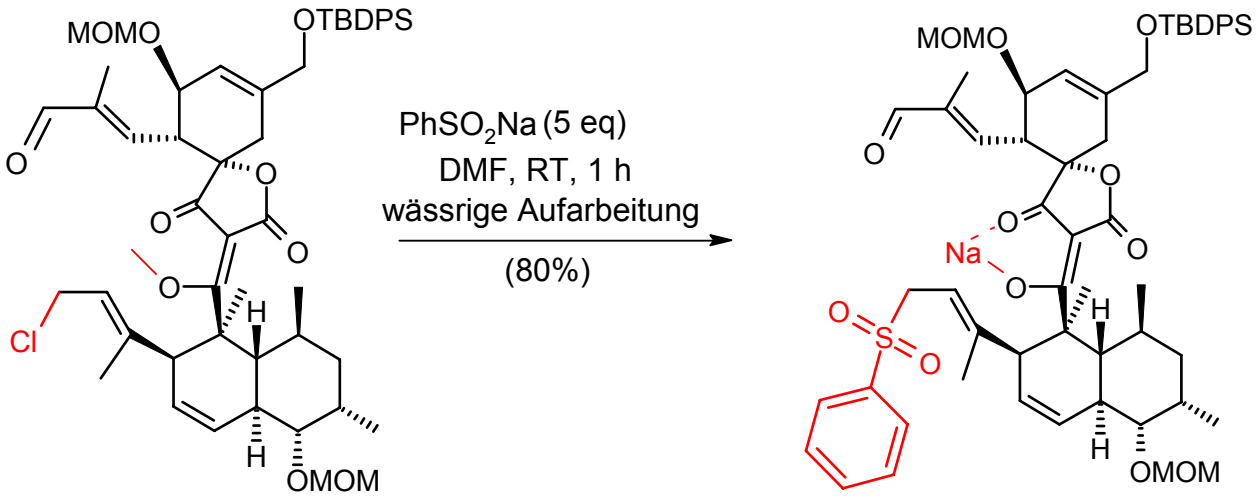
- Chlorierung darf nicht an Doppelbindung stattfinden
- bei Aufarbeitung darf es zu keiner Umlagerung bzw. Eliminierung kommen
- Hexachloraceton ist weniger flüchtig als Tetrachlormethan und hat die bessere Abgangsgruppe

→ milde Reaktionsbedingungen, hohe Regio- und Stereoselektivität, leichte Aufarbeitung

Literatur: R.M. Magid, O.S. Fruchey, W.L. Johnson, T.G. Allen *J. Org. Chem.* **1979**, *44*, 359

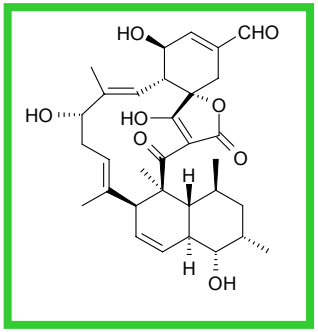


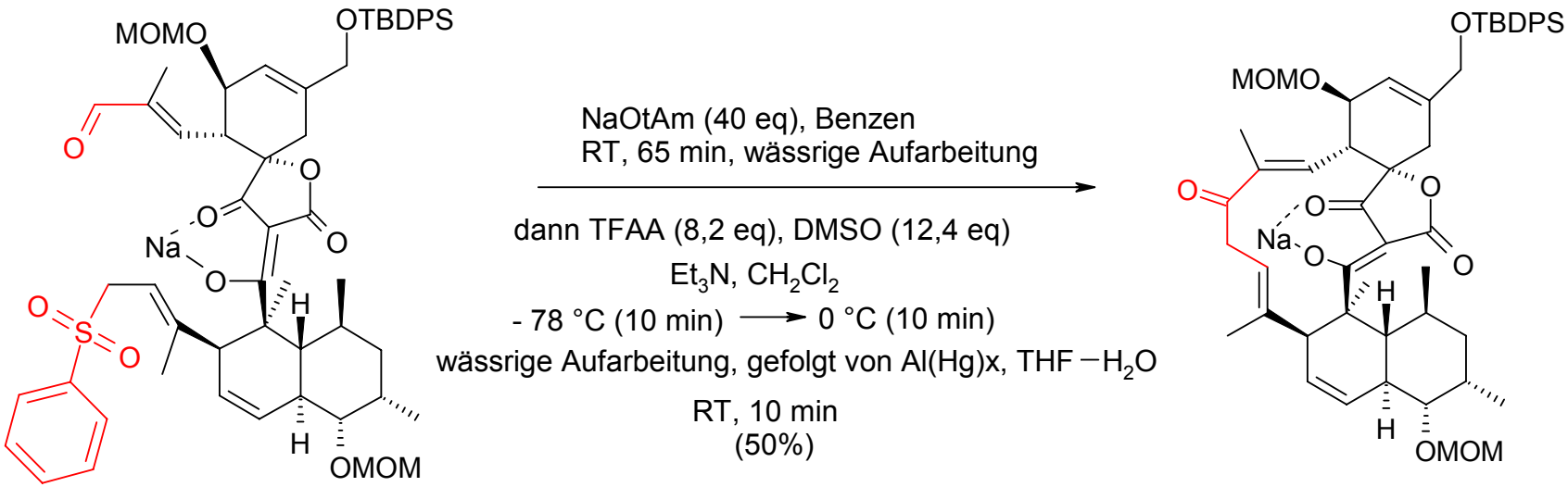
III.2.4. Darstellung des Allylsulfons

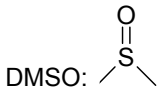


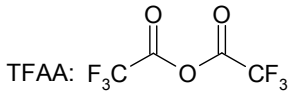
- SN2-Reaktion mit dem Ziel das Allylsulfon zu erhalten
- Desalkylierung des O-Methyltetronates durch Natrium war eigentlich nicht vorgesehen
- Salz war jedoch viel leichter zu handhaben und nur in Abwesenheit der Methylgruppe konnte die folgende Makrozyklisierung erfolgen
- Grund: leichte Drehbarkeit um die C3-C4-Bindung ohne Methylgruppe
- Natrium spielt bei der Makrozyklisierung die Rolle eines „Vermittlers“, indem es am Sulfonat und am Sauerstoffatom des Aldehyden im Übergangszustand koordiniert

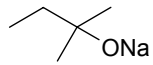
III.3. Makrozyklischer Ringschluss



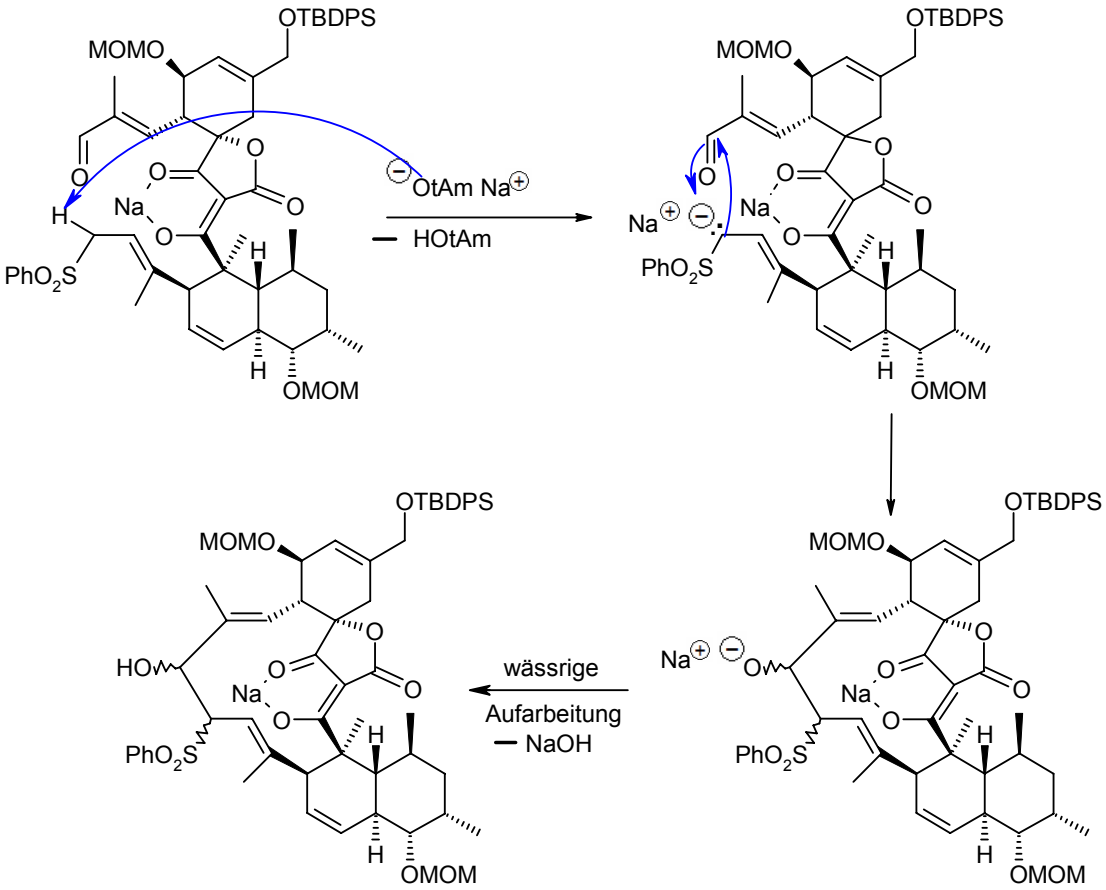


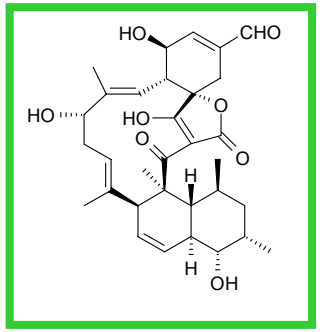
DMSO: 

TFAA: 

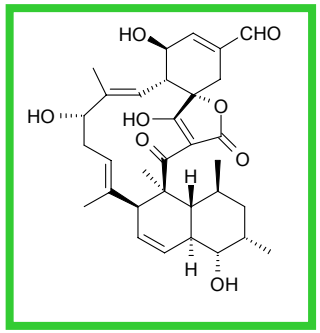
NaOtAm: 

Mechanismusvorschlag für die Makrozyklisierung:

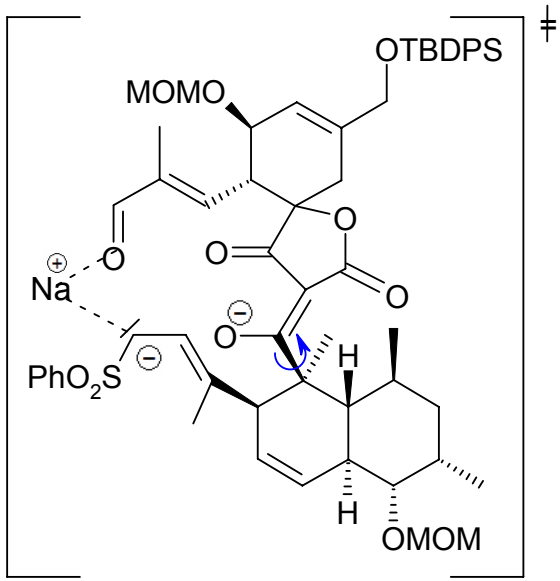




- basenkatalysierte intramolekulare Kondensation des α-Sulfonyl - ω-Aldehyd
- es entstehen dabei 4 Diastereomere

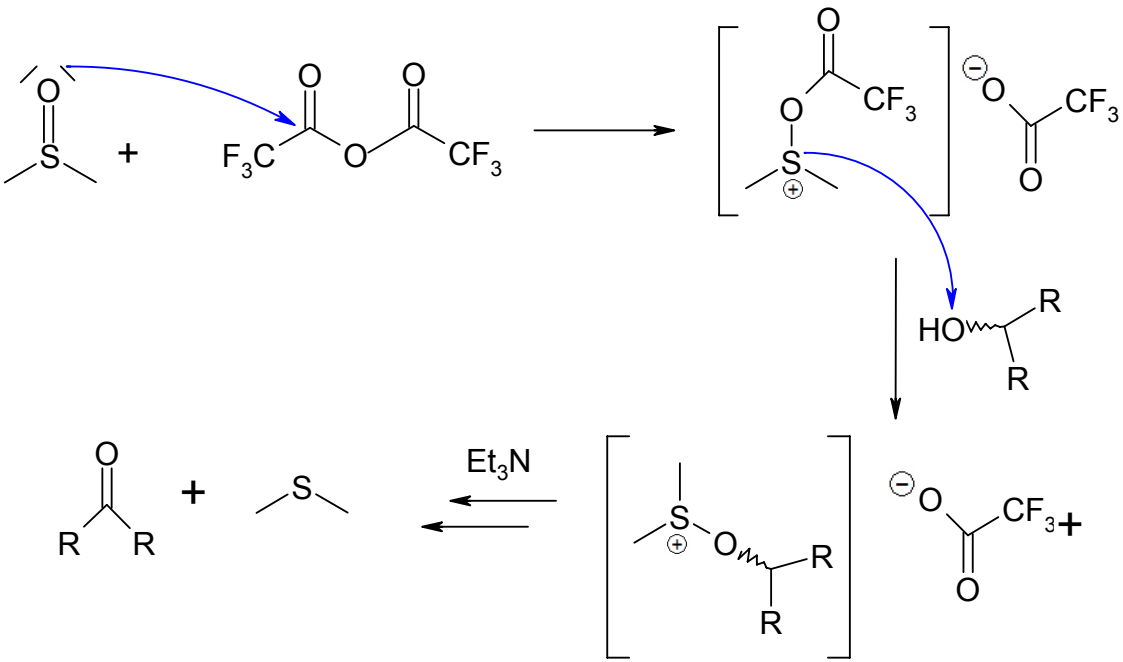


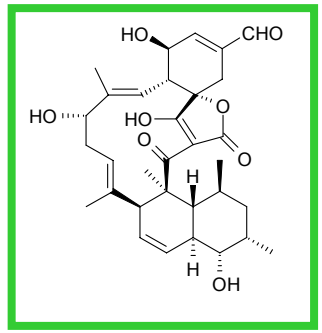
- es wird dabei folgender Natriumvermittelter Übergangszustand angenommen:



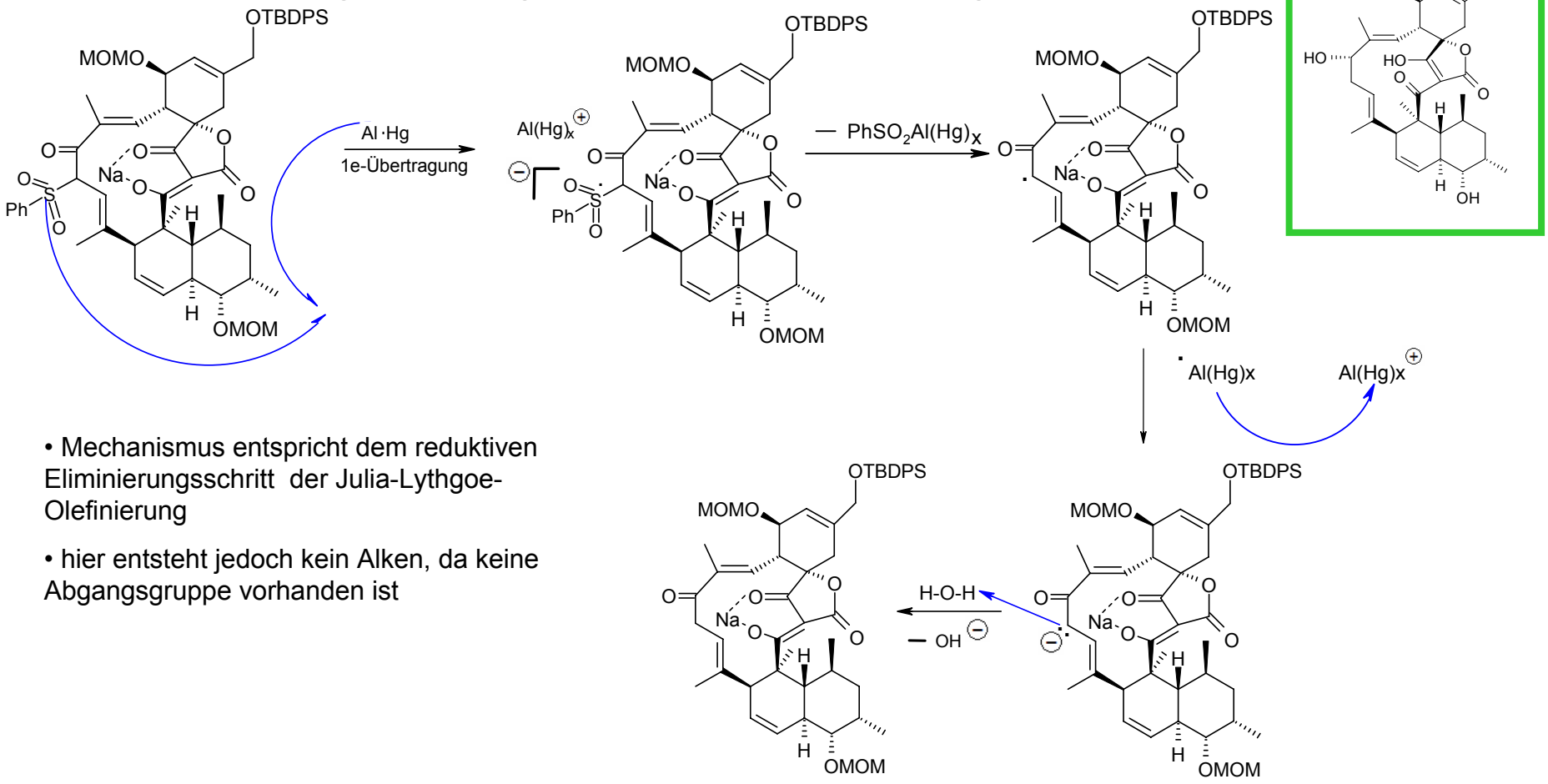
- Na koordiniert am Sulfonatcarbanion und am Aldehydsauerstoff
- einfache Drehung um die C3-C4-Bindung ermöglicht leichten Ringschluss

Mechanismus der Swern-Oxidation mit TFAA:



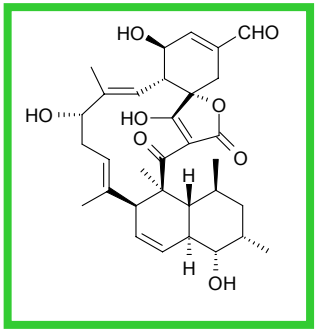


Reduktive Entfernung der Sulfongruppe mittels Aluminiumamalgam:

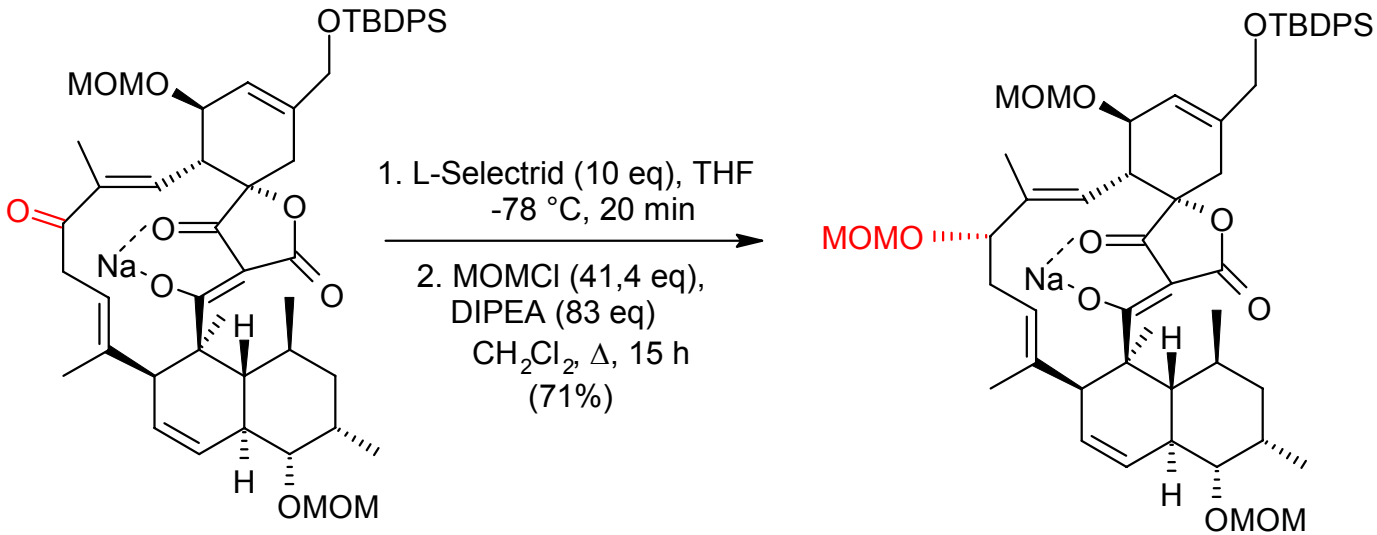


- Mechanismus entspricht dem reduktiven Eliminierungsschritt der Julia-Lythgoe-Olefinierung
- hier entsteht jedoch kein Alken, da keine Abgangsgruppe vorhanden ist

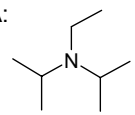
III.4. Letzte Schritte zum (+)-Tetronolid



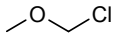
III.4.1. Schützen der Spirotetronateinheit



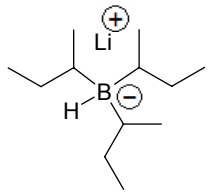
DIPEA:

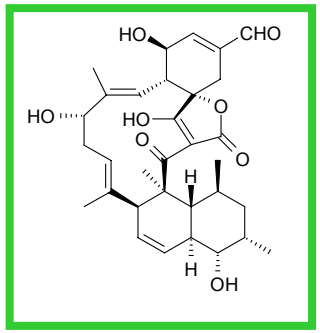


MOM-Cl:

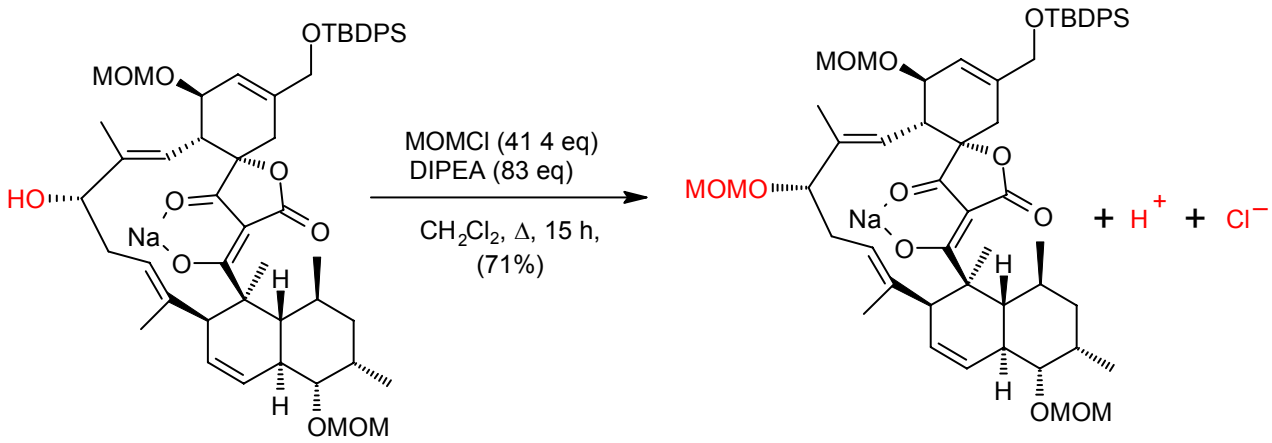


L-Selectrid:



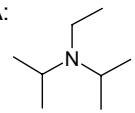


Schützen der Hydroxyfunktion:

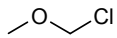


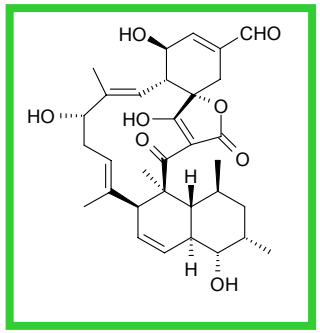
- Schützen der gebildeten Hydroxygruppe durch den Einsatz von MOMCl und DIPEA (milde Base), wodurch vollkommen geschütztes Spirotetronat entsteht

DIPEA:

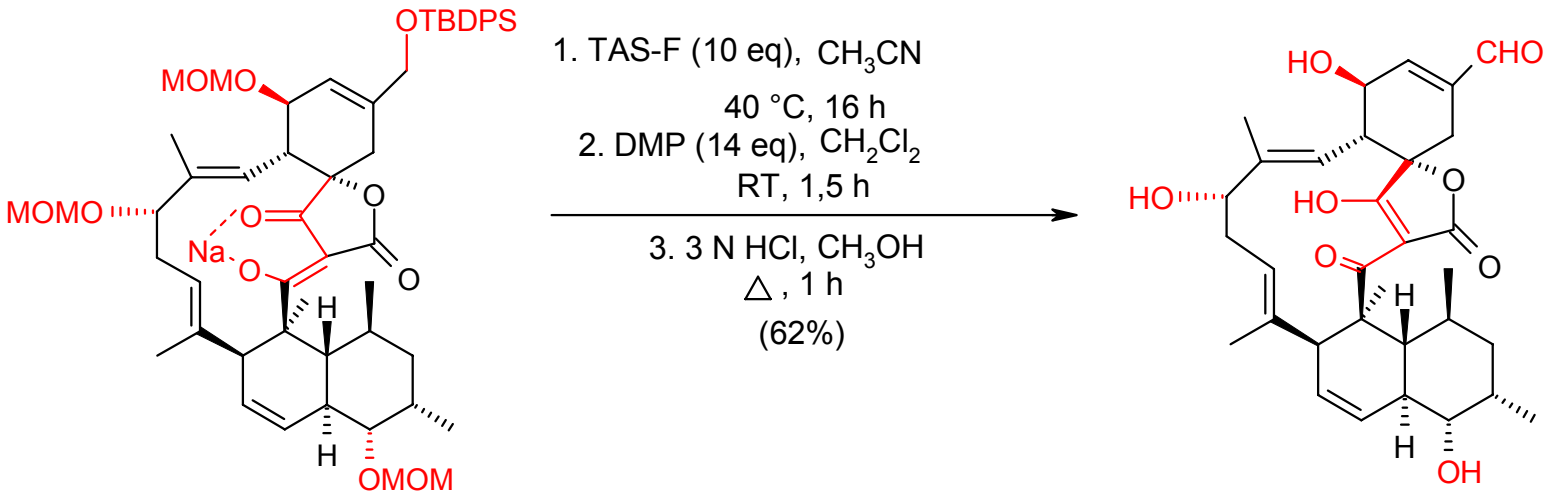


MOM-Cl:



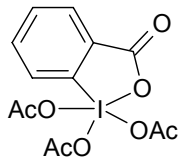


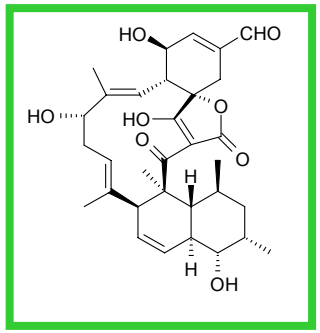
III.4.2. Entfernung aller Schutzgruppen



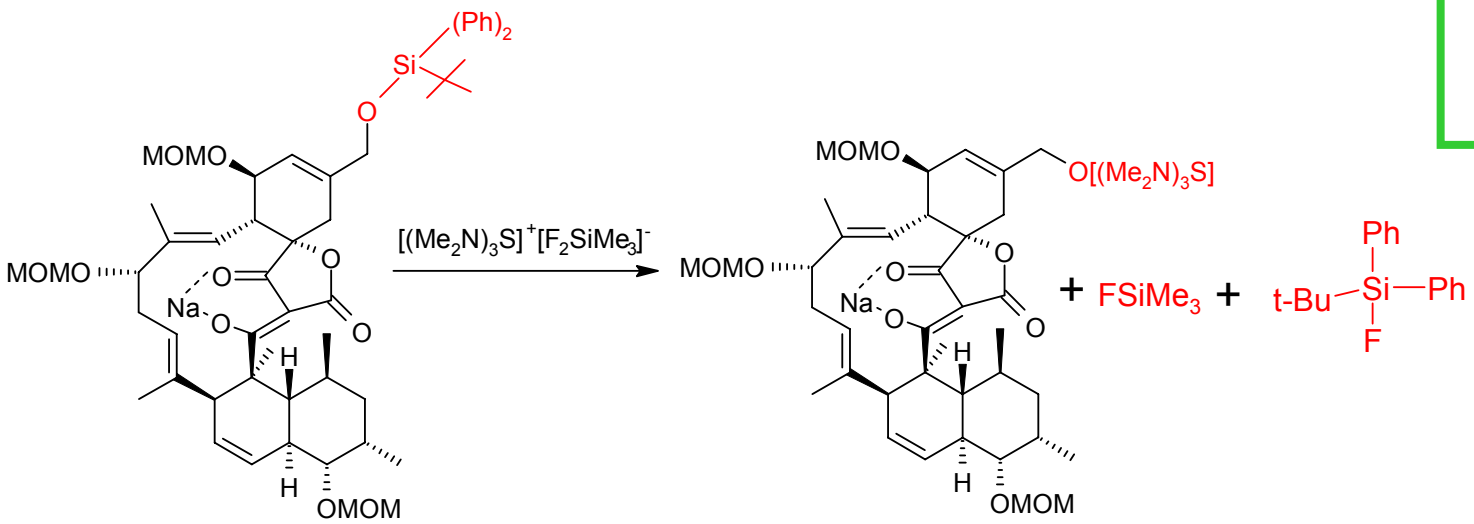
TAS-F: $[(Me_2N_3)S]^+[F_2SiMe_3]^-$

DMP:





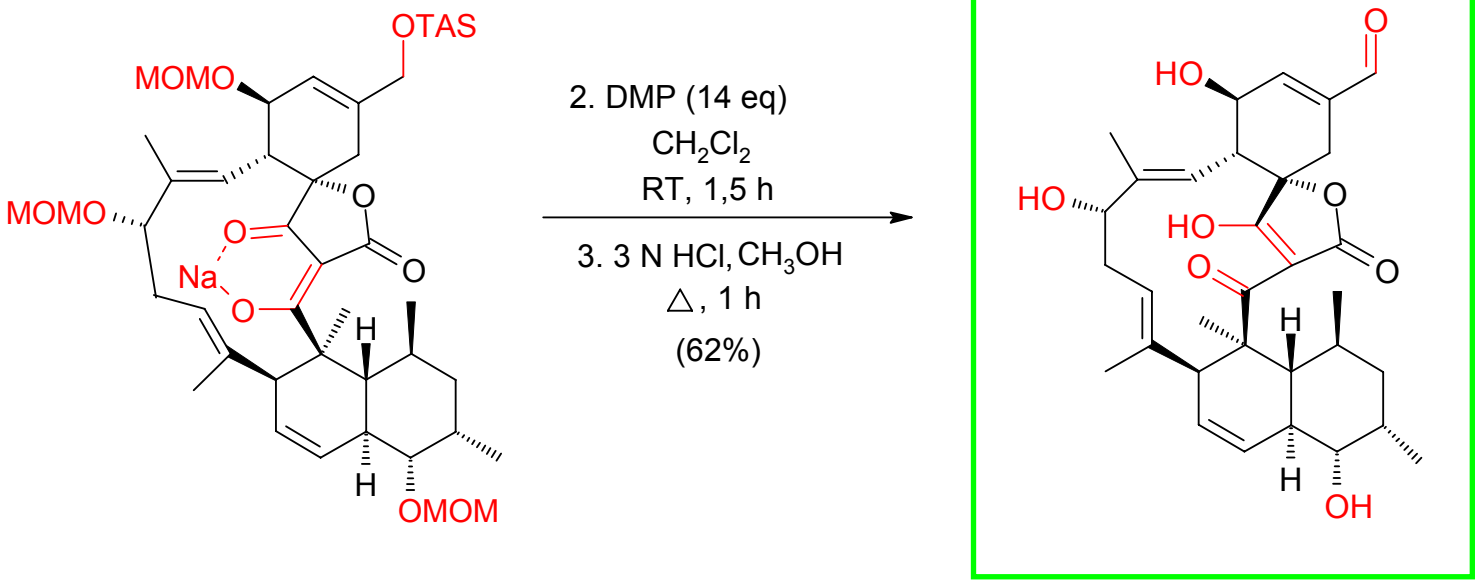
Zuerst erfolgt Spaltung der Silylethergruppe mit dem sehr milden Reagenz TAS-F:



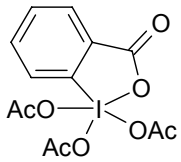
Literatur: K. A. Scheidt, H. Chen, B. C. Follows, S. R. Chemler, D. S. Coffey, W. R. Roush *J. Org. Chem.* **1998**, *63*, 6436

R. Noyori, I. Nishida, J. Sakata, M. Nishizawa J. *Am. Chem. Soc*. **1980**, *102*, 1223

Schutzgruppenspaltung:



DMP:



(+) - Tetronolid

- mittels DMP wird das Alkoholat oxidiert
- danach werden sämtliche Schutzgruppen sauer entfernt

IV Reaktionsübersicht

V Verwendete Abkürzungen/Trivialnamen

BHT	2-(1,1-Dimethylethyl)-4-methoxyphenol
Bn	Benzyl
Bu	Butyl
Chinuclidin	1-Azabicyclo[2.2.2]octan
DBU	Diazabicycloundecen
DDQ	2,3-Dichlor-5,6-dicyano-benzochinon
DET	(+) oder (-)Diethyltartrat
DIPEA	N,N-Diisopropylethylamin
DMAP	Dimethylaminopyridin
DMF	Dimethylformamid
DMP	Dess-Martin-Periodinan
DMS	Dimethylsulfid
DMSO	Dimethylsulfoxid
Et	Ethyl
HMPA	Hexamethylphosphorsäuretriamid
i-Pr	Iso-Propyl
LAH	Lithiumaluminiumhydrid
LDA	Lithiumdiisopropylamid
L-Selectrid	Lithium-(tri-sek-butyl)borhydrid
2,6-Lutidin	2,6-Dimethylpyridin
m-CPBA	meta-Chlorperbenzoesäure
MOM	Methoxymethyl
MPM	Methoxyphenylmethyl
NaOtAm	Natrium tert-amyloxid
NaHMDS	Natriumhexamethyldisilazan
NCS	N-Chlorsuccinimid
Ph	Phenyl
PPTS	Pyridinium-para-toluensulfonat
p-Ts	para-Toluensulfonat
RT	Raumtemperatur
SET	Single Electron Transfer
TAS-F	Tris(dimethylamino)sulfoniumdifluorotrimethylsilikat
TBAF	Tert-Butyl-Ammonium-Fluorid
TBAI	Tetrabutylammoniumiodid
TBDPS	tert-Butyldiphenylsilyl
t-Bu	Tert-Butyl
TEBA	Triethylbenzylammoniumchlorid
Tf	Triflat
TFA	Trifluoracetatsäure
TFAA	Trifluoracetanhydrid
THF	Tetrahydrofuran
TMEDA	N, N, N‘, N‘ - Tetramethylethylendiamin
TMS	Trimethylsilyl