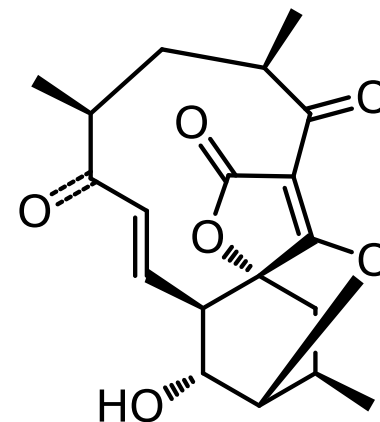


# **Totalsynthese von (–)-atrop-Abyssomicin C nach Filip Bihelevic & Radomir N. Saicic**



Patrick Größer, Diego Jahn, Susanne Nowotni, Paul Plate,  
Richard Weichert

Dresden, 13.12.2012



- 1 Einleitung
- 2 Retrosynthese
- 3 Synthese der Edukte und Reagenzien
- 4 Syntheseschritte
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  - 4.2 Versuche zur Etablierung der Spirotetronateinheit
  - 4.3 Schluss des Elfrings und finale Schritte
- 5 Zusammenfassung
- 6 Abkürzungsverzeichnis

# 1. Einleitung

- Suche nach alternativen Antibiotika zur Bekämpfung von Bakterien wie z. B.: *Staphylococcus aureus*
- 2002: A. Bermingham & J. P. Derrick: Möglichkeit, die *p*-Aminobenzoessäure- (*p*-ABA-) Biosynthese von Mikroorganismen zu unterbinden
- *p*-ABA wird für die Synthese von Tetrahydrofolsäure benötigt
- 2004: erster Bericht und Strukturaufklärung von atrop-Abyssomicin C aus dem Actinomycetengat Bakterienstamm (*Verrucosispora*-Bakterium)
- erster, natürlich vorkommender Inhibitor der *p*-ABA-Synthese aus einer Sedimentprobe im Japanischen Meer

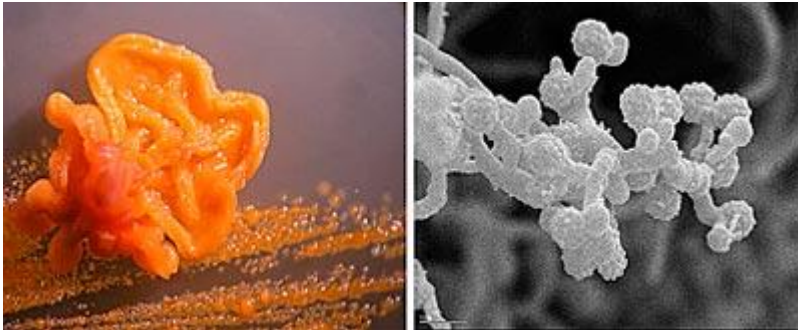


Abbildung 1: *Verrucosispora*-Bakterium  
([http://www.hpfiender-group.de/metabolites.php?metabolite\\_id=1](http://www.hpfiender-group.de/metabolites.php?metabolite_id=1))

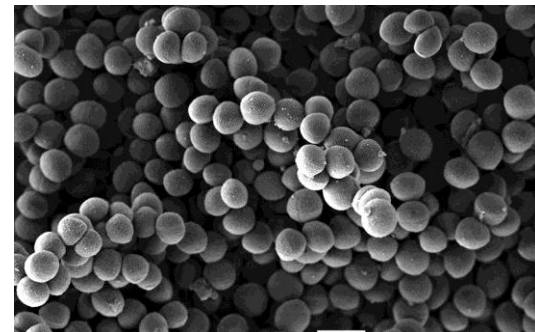


Abbildung 2: *Staphylococcus aureus*  
([http://www.rki.de/SharedDocs/Bilder/InfAZ/Staphylokokken/EM\\_Tab\\_Staphylokokken.html](http://www.rki.de/SharedDocs/Bilder/InfAZ/Staphylokokken/EM_Tab_Staphylokokken.html).)

Bermingham, J. P. Derrick, *BioEssays* **2002**, 24, 637–648; R. D. Süßmuth, *Angew. Chem.* **2004**, 116, 2628–2630.

# 1. Einleitung

- nur atrop-Abyssomicin C weist eine antibiotische Aktivität auf
- *Abyssos* (griechisch): der Abgrund, die Tiefe
- „atrop“: von Atropisomerie
- Spezialfall der axialen Chiralität<sup>[3]</sup>
- Rotation um  $\sigma$ -Bindung sterisch gehindert
- hier aufgrund der Ringspannung

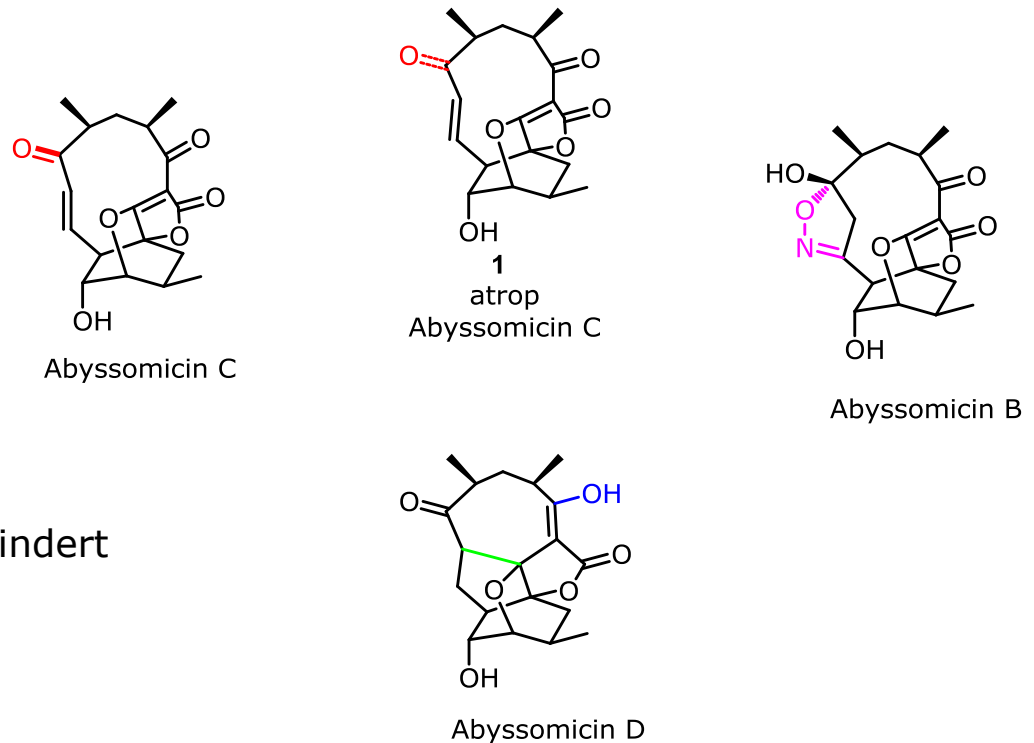


Abbildung 3: Übersicht einiger Varianten aus der Familie der Abyssomicine <sup>[2]. [4]</sup>

## 2. Retrosynthese

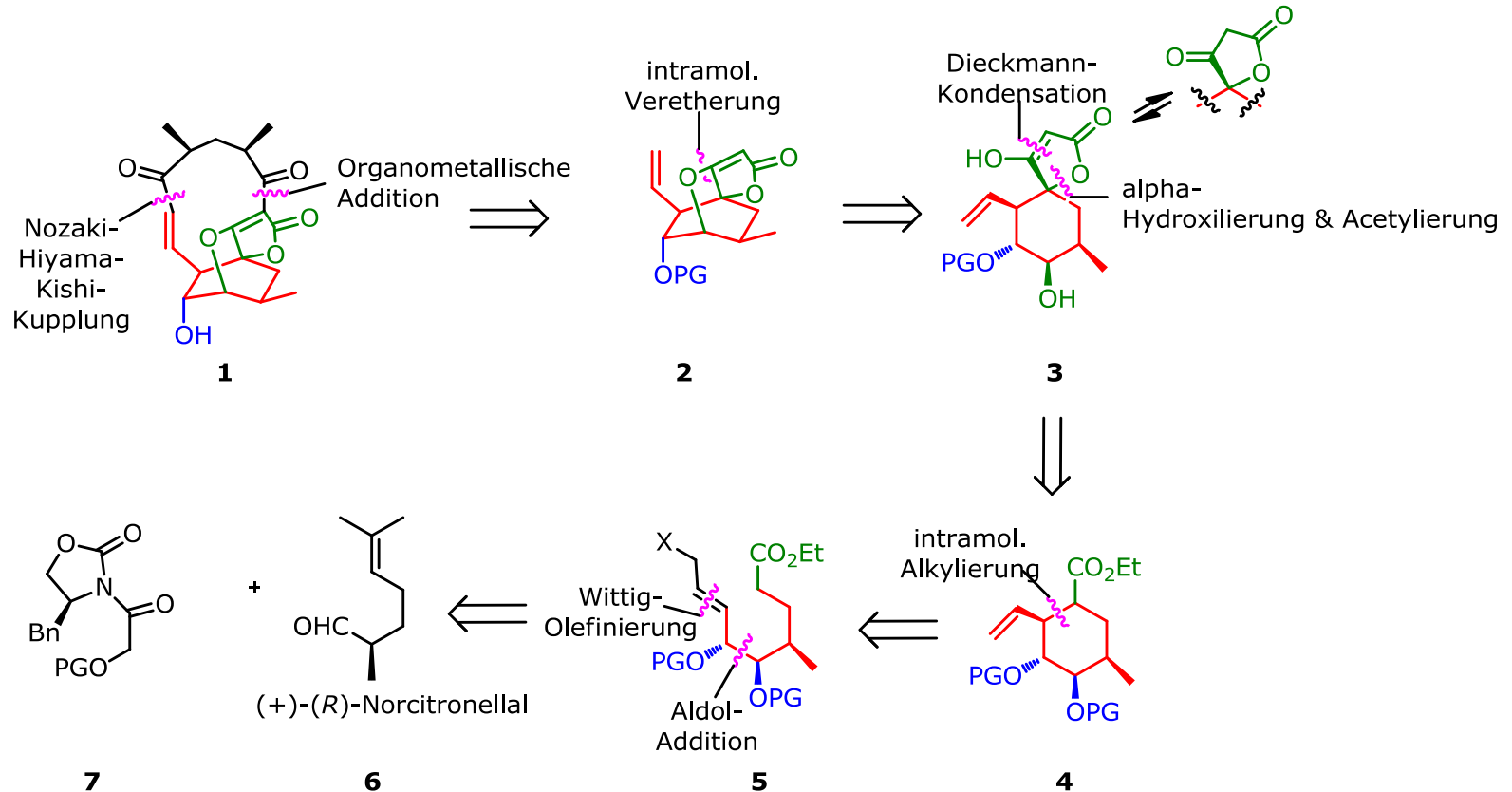
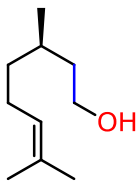
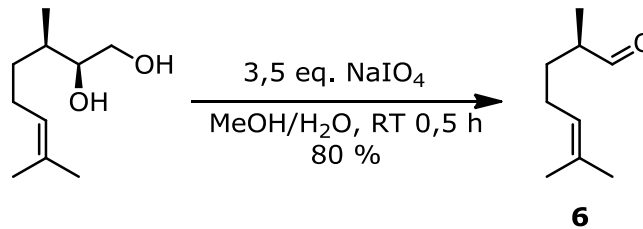


Abbildung 4: Retrosynthese von Abyssomicin C

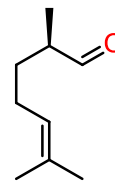
F. Bihelovic, R. N. Saicic, *Angew. Chem.* **2012**, *124*, 5785-5789.

# 3. Synthese der Edukte und Reagenzien

# Synthese von (+)-(R)-Norcitronellal



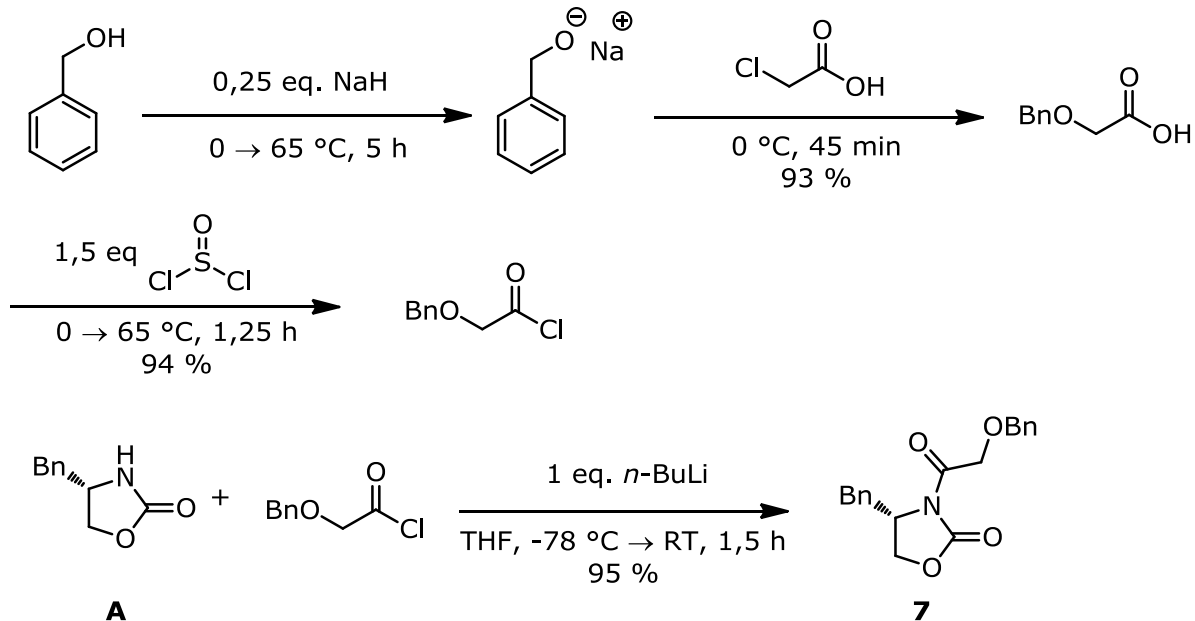
Citronellool



Norcitronellal

- Nor ein Kohlenstoffatom weniger
- al Aldehyd
- ol Alkohol

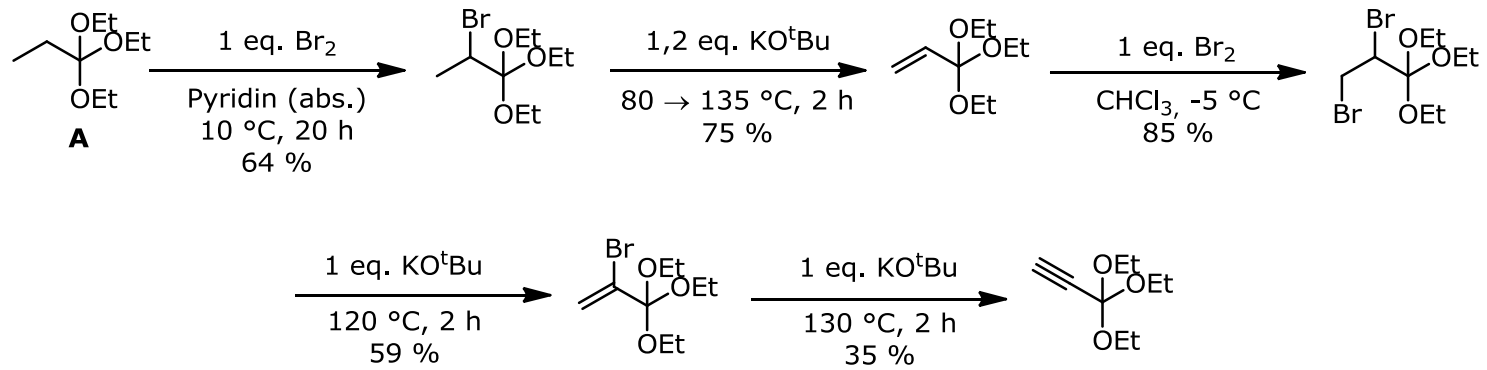
## Synthese des Auxiliars



- Kosten für **A**: 5 g 94,30 \$ (Sigma Aldrich)

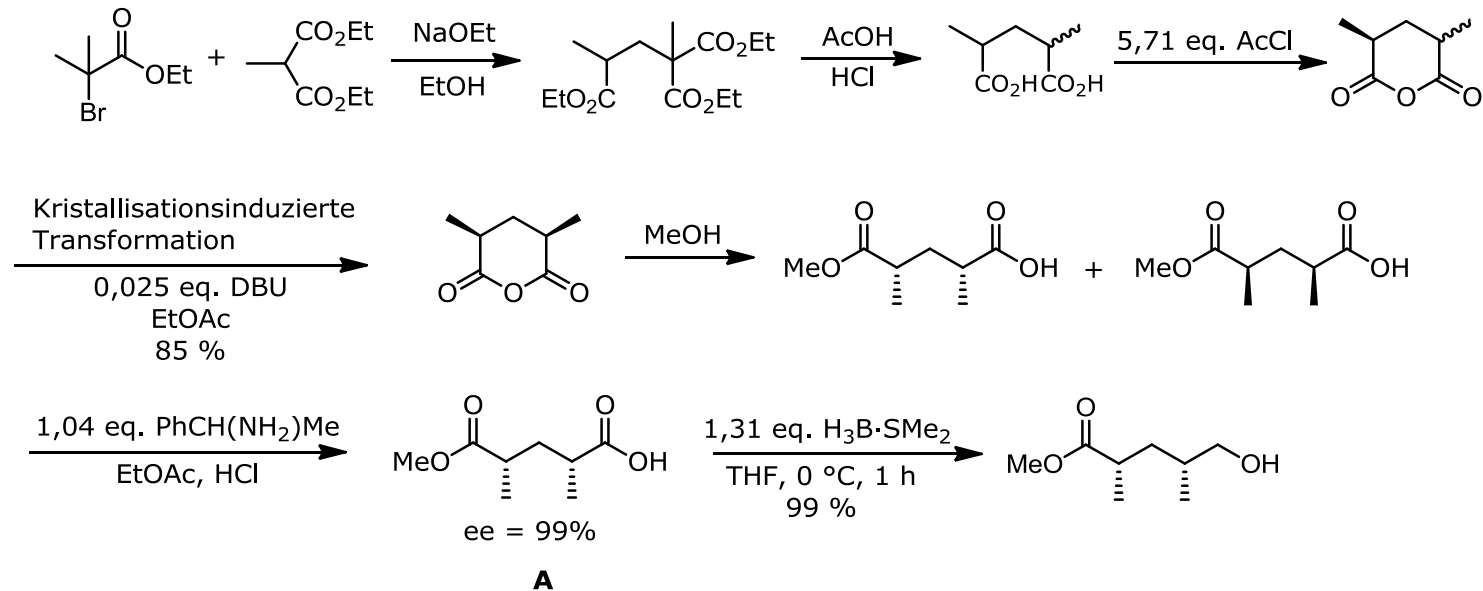


# Synthese des Propinorthoesters



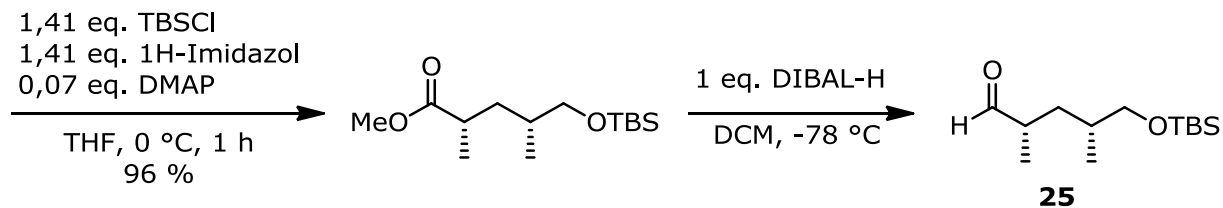
- Kosten für **A**: 100 ml 40,70 \$ (Sigma Aldrich)

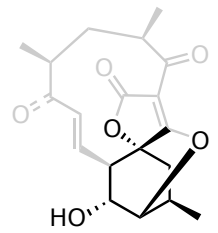
# Synthese des Aldehyds



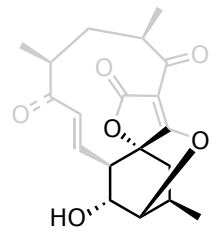
- um **A** zu erhalten, wurde das (-)-(S)-Salz weiter verwendet

## Synthese des Aldehyds

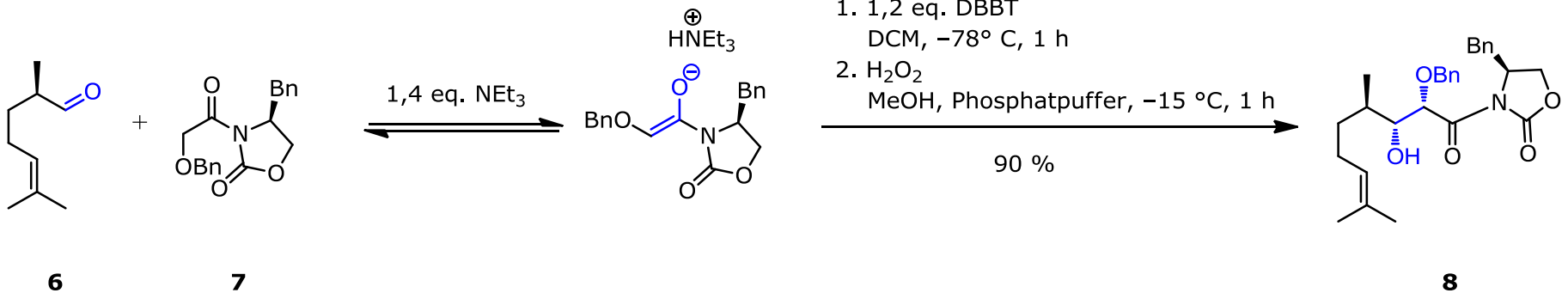


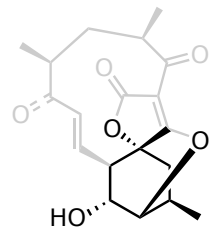


# 4.1 Aufbau des Cyclohexanrings

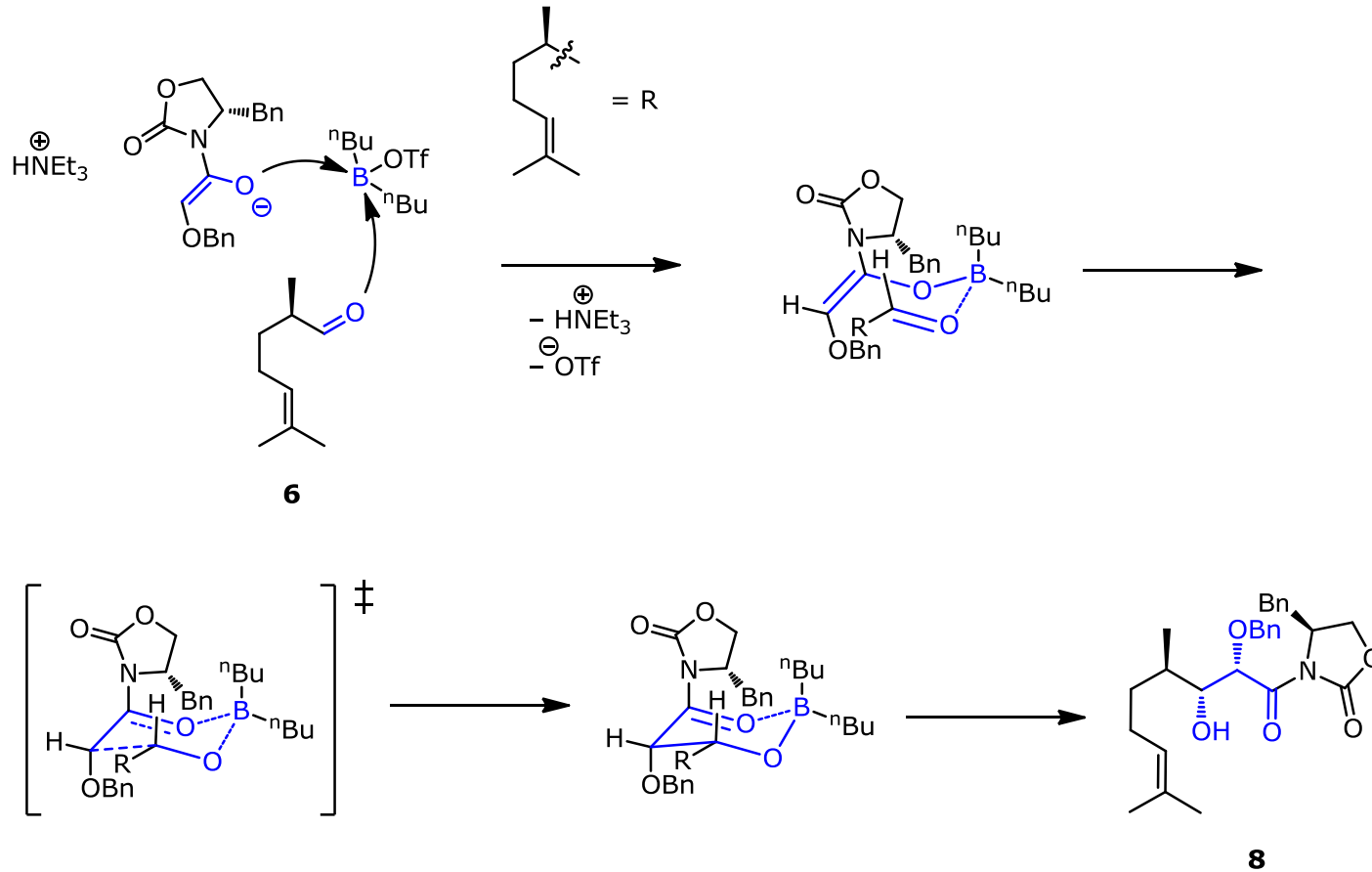


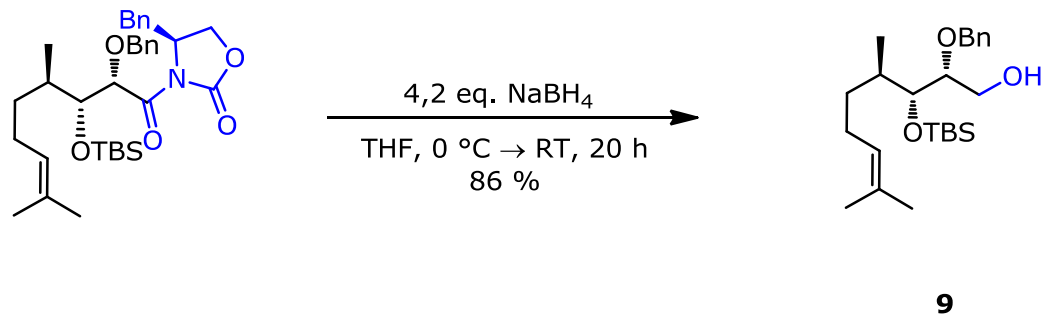
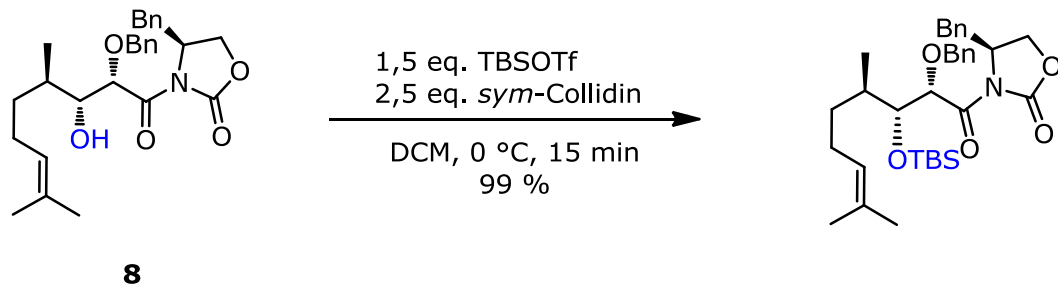
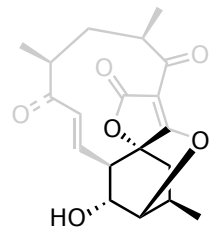
- Substratinduziert (auxiliarinduziert)
- Bildung des kinetischen Enolats

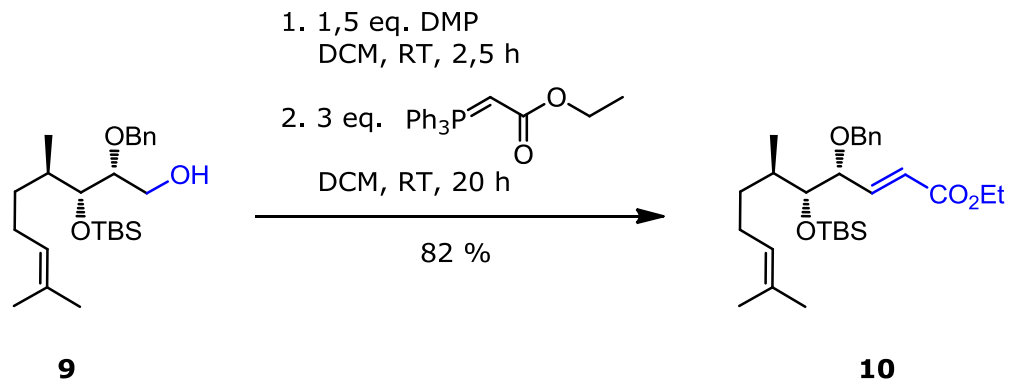
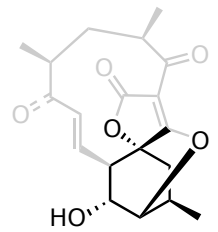




- Zimmerman-Traxler-Modell

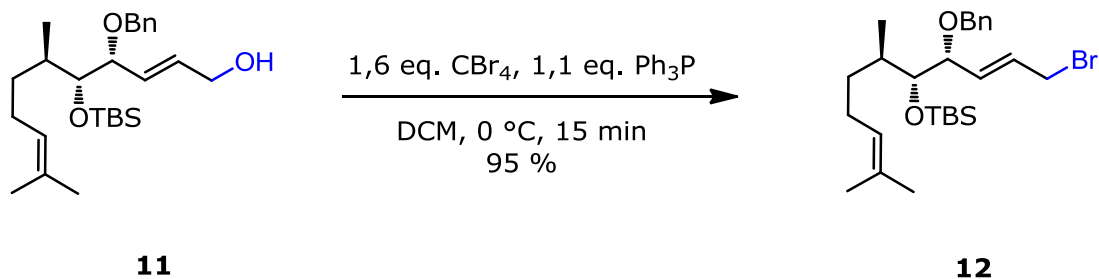
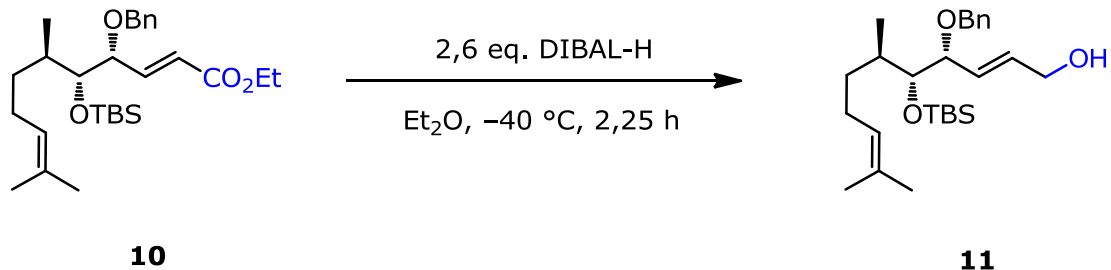
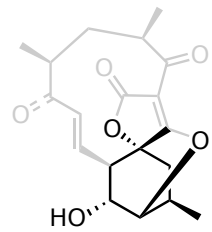


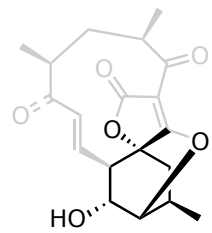




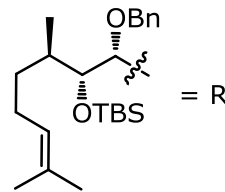
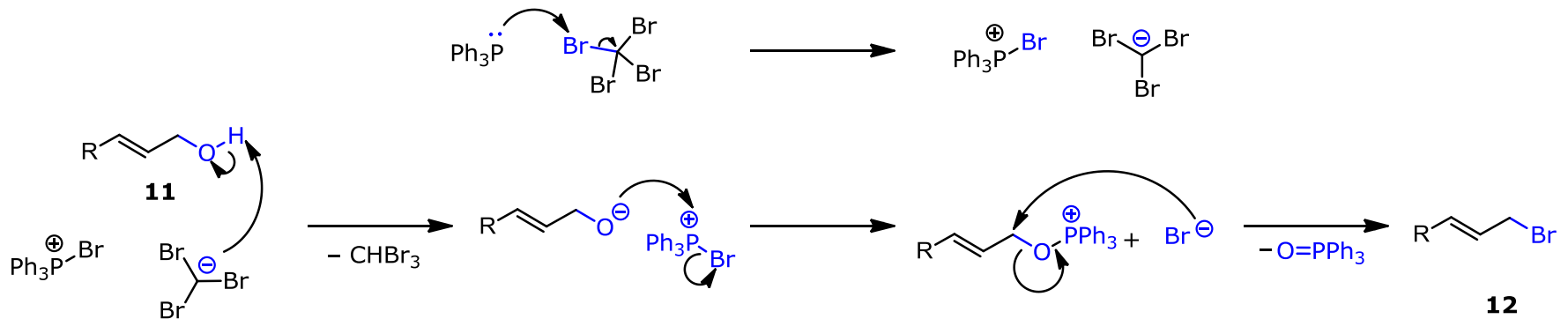
A. G. M. Barrett, D. Hamprecht, M. Ohkubo, *J. Org. Chem.* **1997**, 62, 9376–9378.

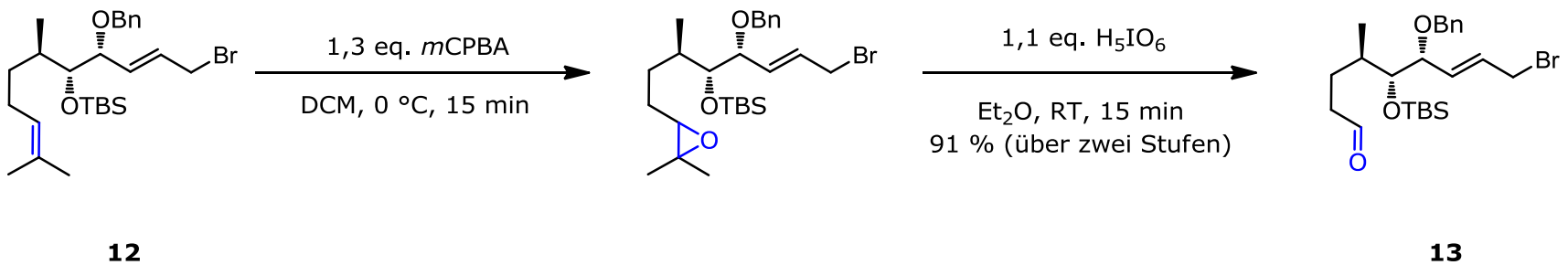
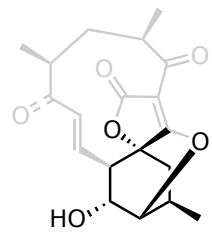


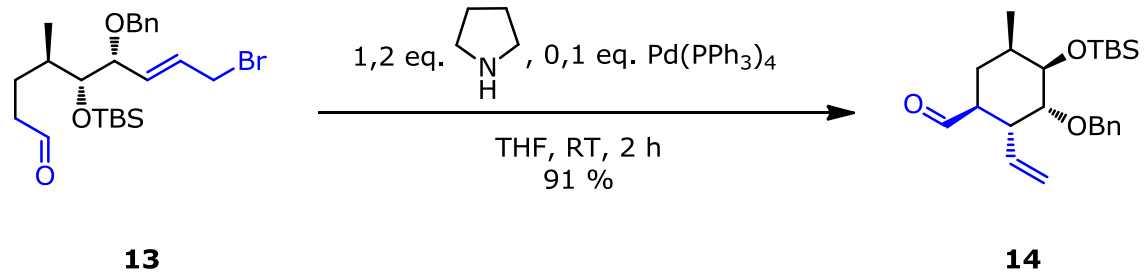
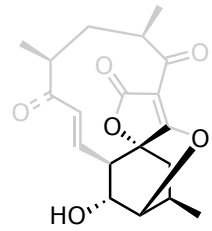




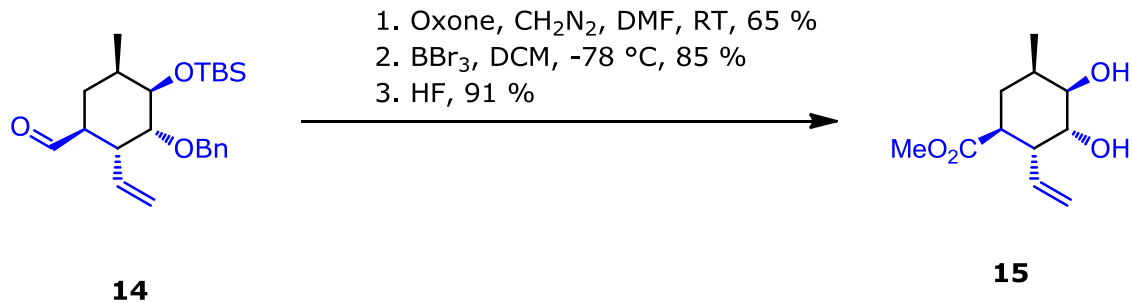
- Appel-Reaktion:
  - Triebkraft: Bildung der P-O-Bindung
  - S<sub>N</sub>2-Mechanismus: Inversion der Konfiguration und trigonal-bipyramidaler ÜZ

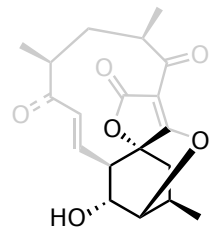




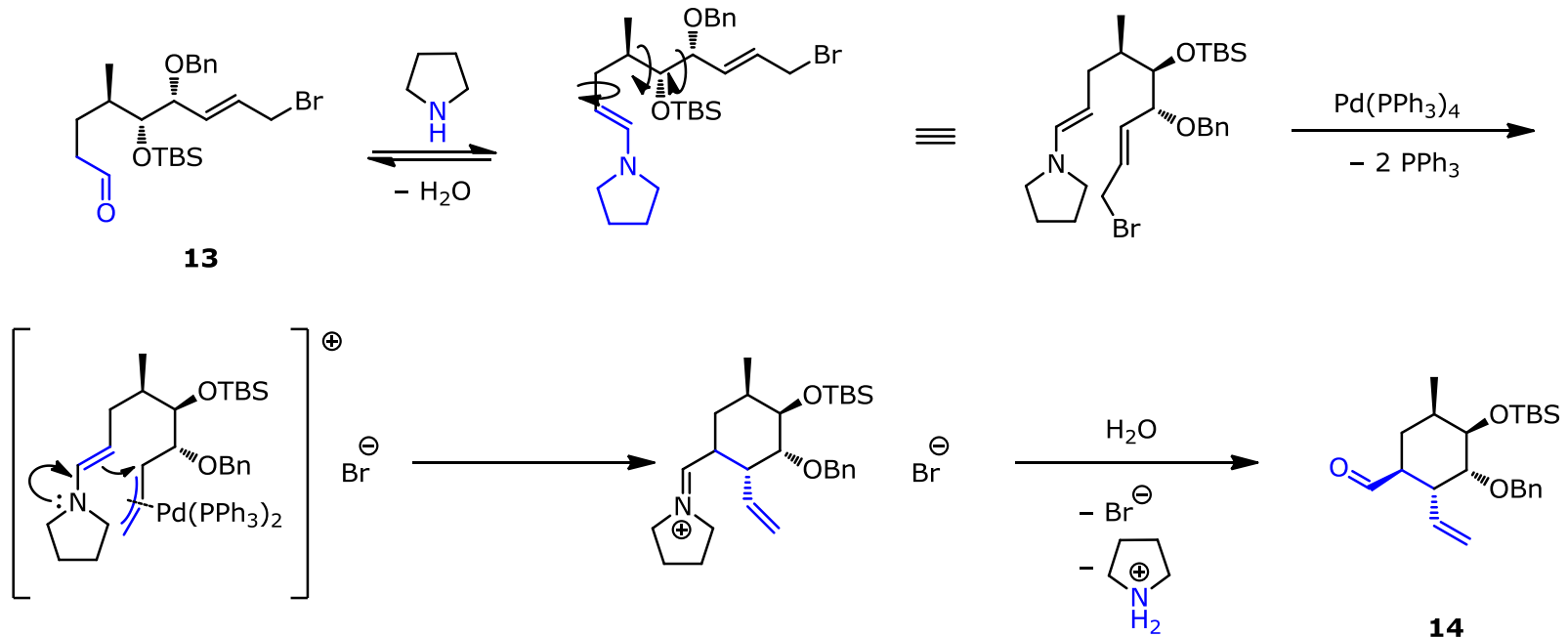


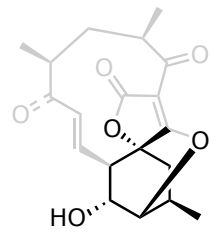
- Überführung in Methyl ester für Kristallstrukturanalyse



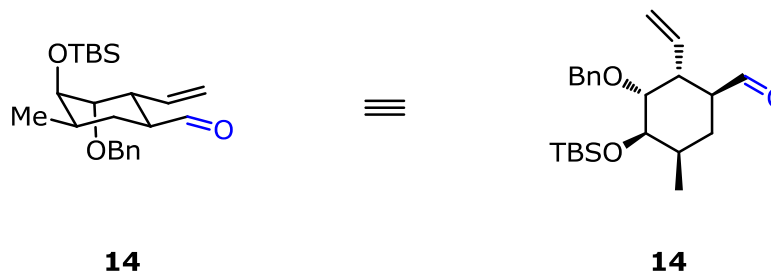
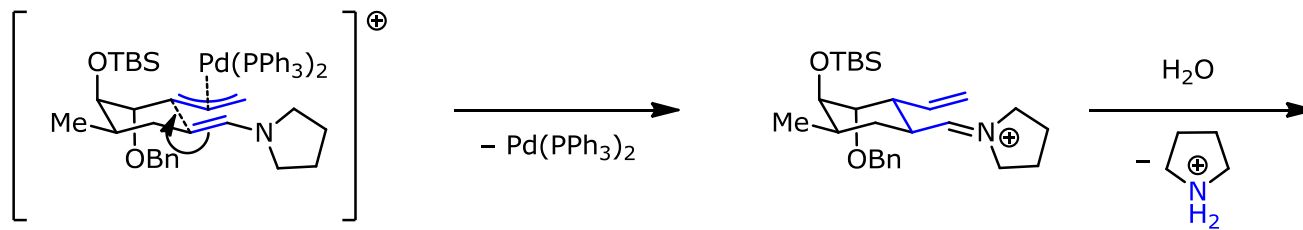


- Enaminkatalyse verbessert Ausbeute und Reaktionsbedingungen
- reaktive Palladium-Spezies wird *in situ* generiert
- Pd-Komplex aktiviert allylisches Ende für nucleophilen Angriff

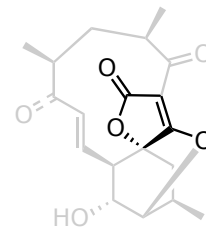




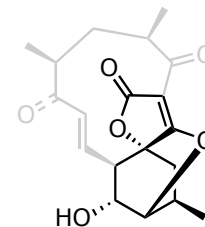
- Tsuji-Trost-Reaktion



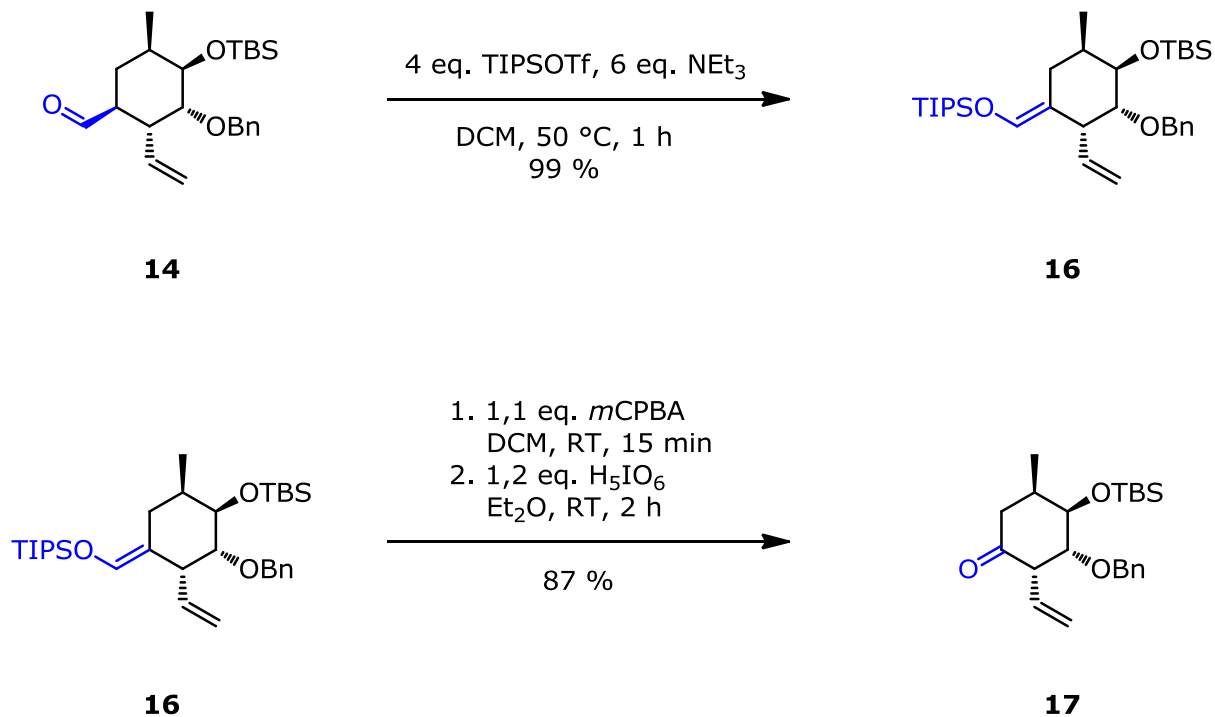
B. List, *Asymmetric Organocatalysis*, Springer-Verlag, Berlin Heidelberg, **2010**, S. 29–40.



## 4.2 Versuche zur Etablierung der Spirotetronateinheit

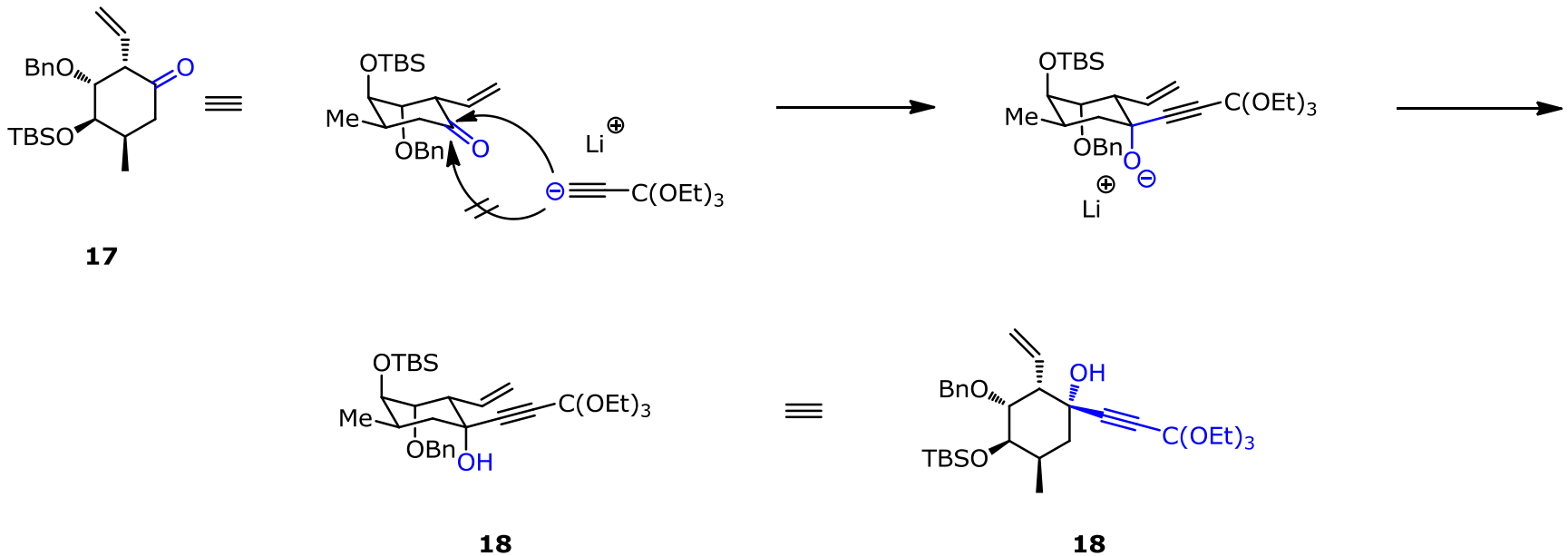
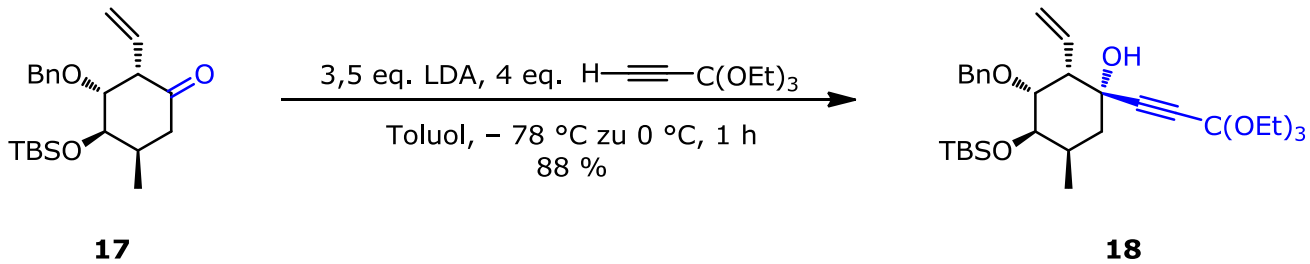
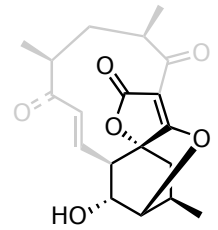


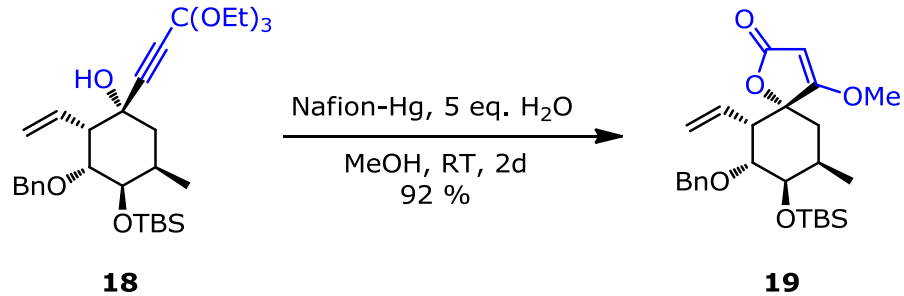
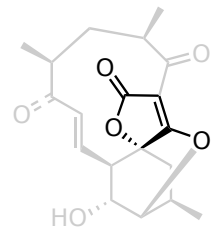
- Geplanter Syntheseweg über  $\alpha$ -Hydroxylierung am Aldehyd  
→ keine Stereoselektivität
- Alternative Synthese



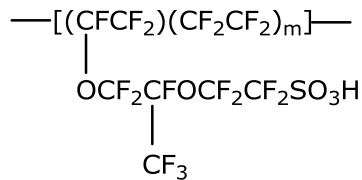


# Reaktion mit Triethoxypropin Mechanismusvorschlag

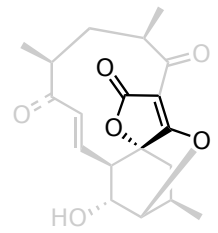




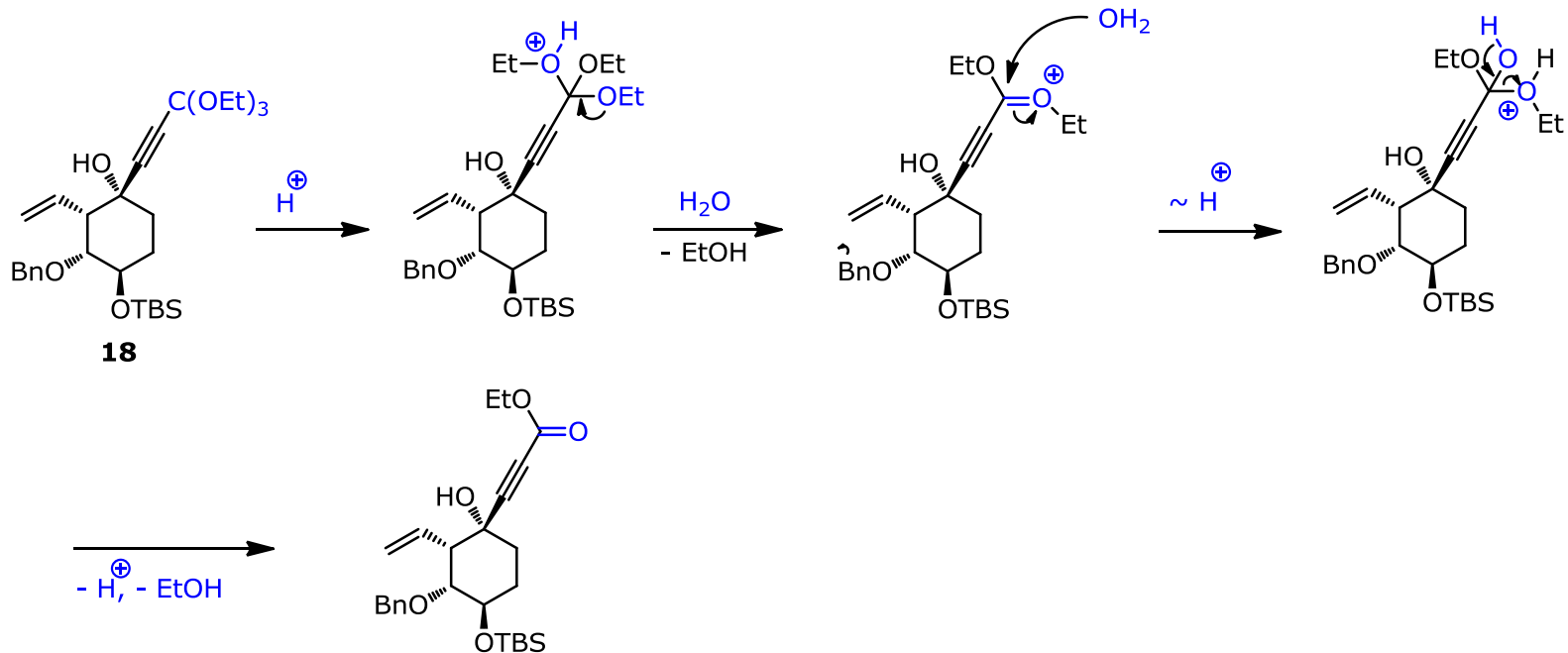
- Nafion: sulfoniertes Copolymer aus fluoriertem Vinylether mit Tetrafluorethylen

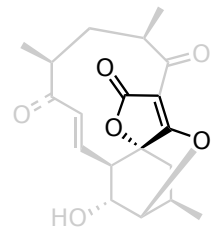


- komplexiert Hg
- fungiert als Brønsted- und Lewis-Säure

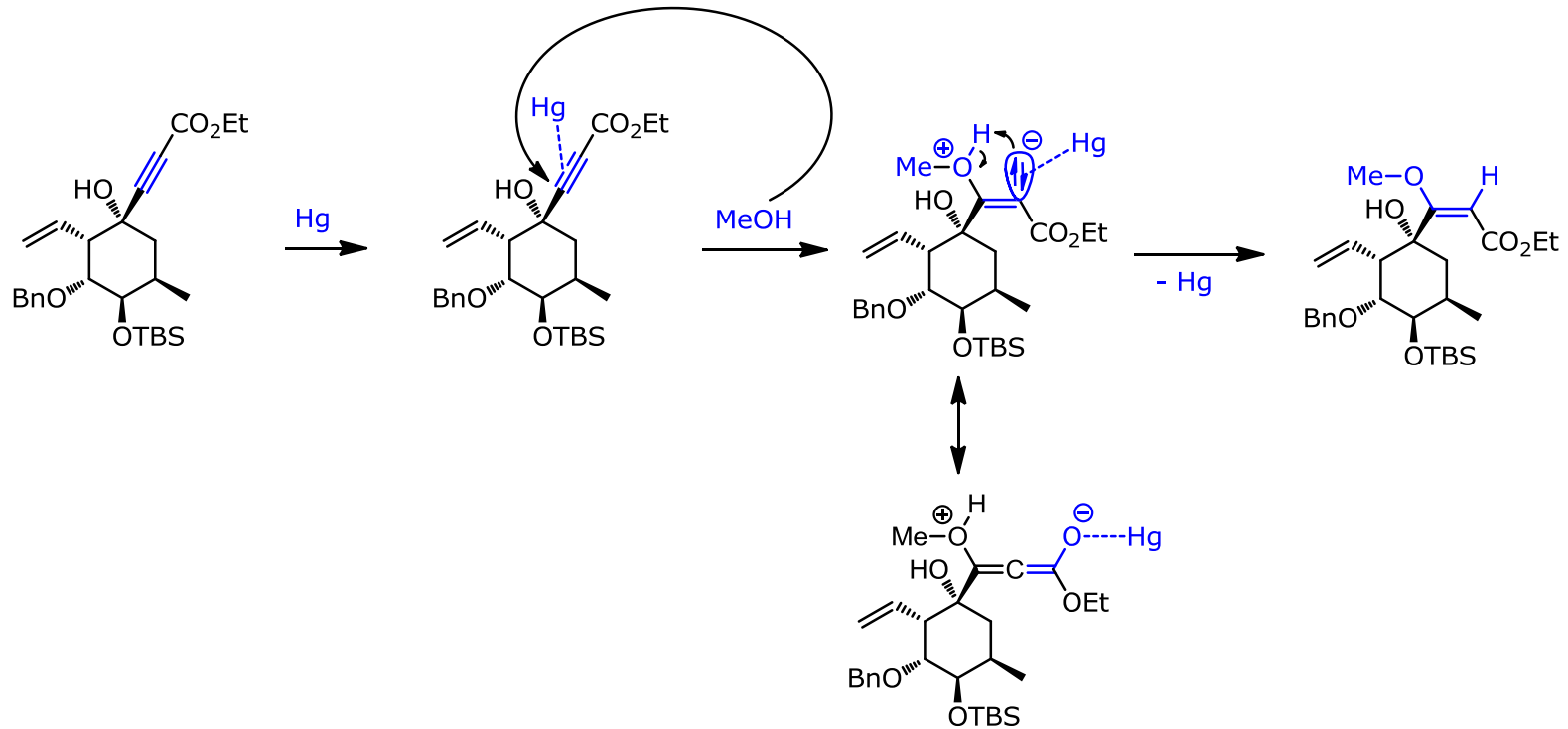


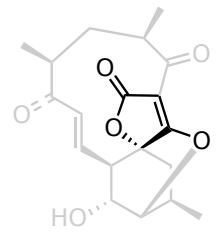
- Orthoester-Hydrolyse



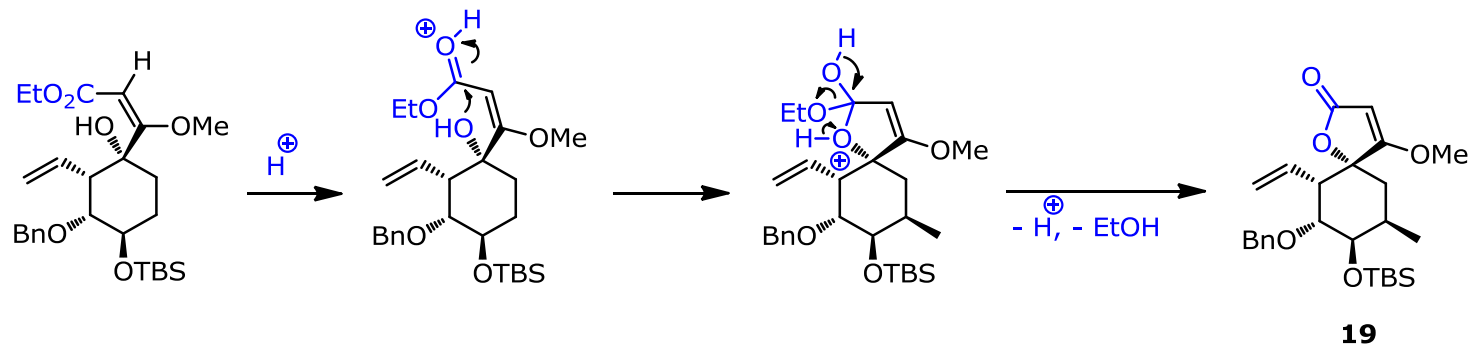


- *trans*-Addition des Methanols

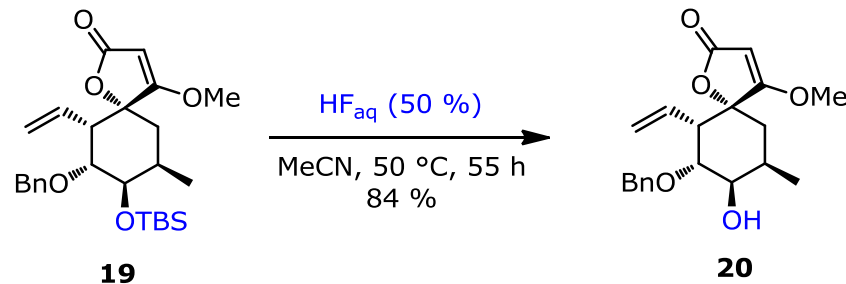


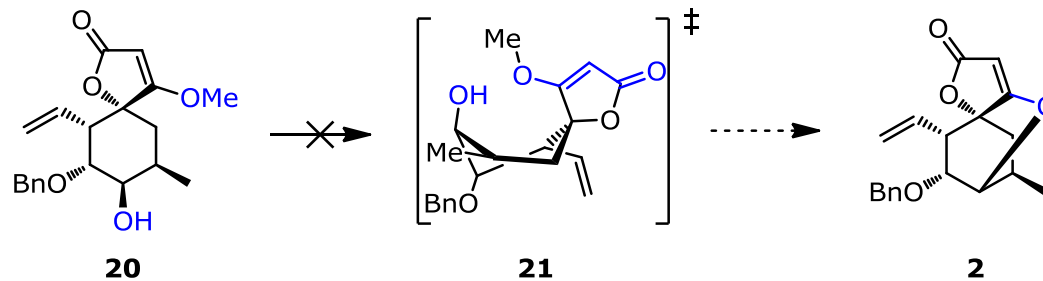
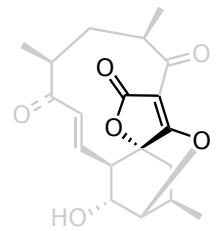


- Lactonisierung

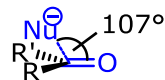
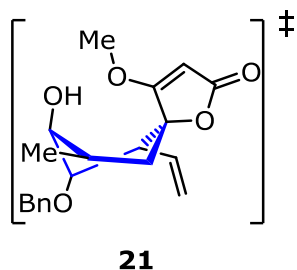
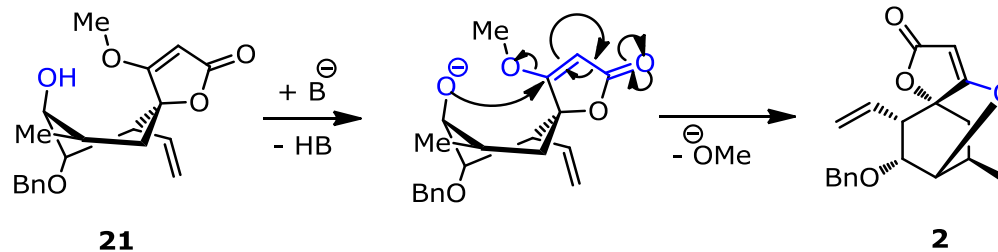


## TBS-Abspaltung



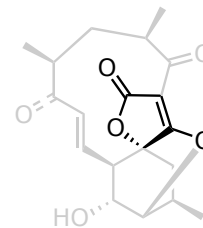


- Theoretischer mechanistischer Verlauf:



- ungünstige Wannenkonformation
- kein Angriff im Bürgi-Dunitz-Winkel möglich

→ Änderung des Syntheseweges hin zu einem flexibleren Alkin-Derivat



## Allgemeines

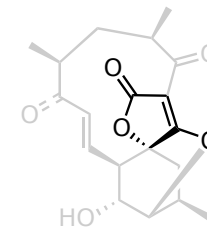
Aktivierung von C-C-Mehrfach- sowie Carbonylbindungen  
→ vereinfachter Angriff von Nucleophilen

## Typische Reaktionen

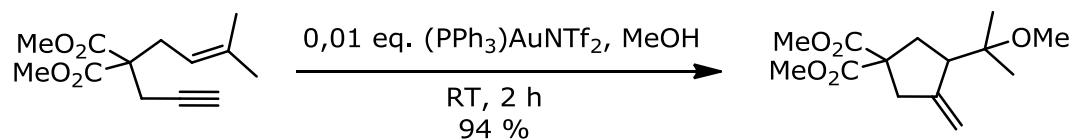
- Cyclisierungen
- Selektive Oxidation
- Nucleophile Additionen an  $\pi$ -Systeme

## Gagosz-Gold-Katalysator:

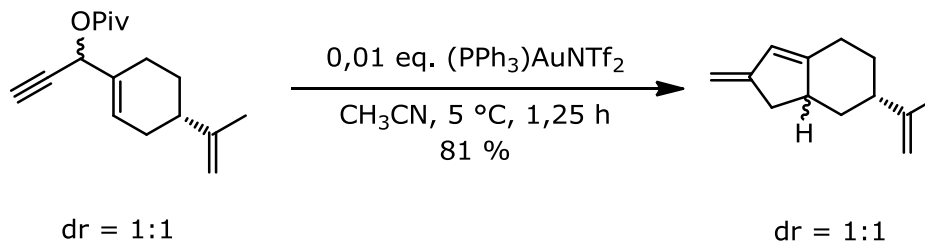
- $(PPh_3)_3AuNTf_2$  (Triphenylphosphingold(I)-bis(trifluormethansulfonyl)imidat)
- luftstabil
- Cycloisomerisierung von Eninen



- Methoxycyclisierung

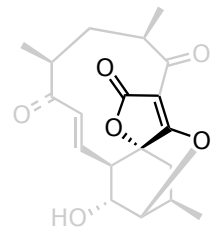


- Rautenstrauch-Umlagerung

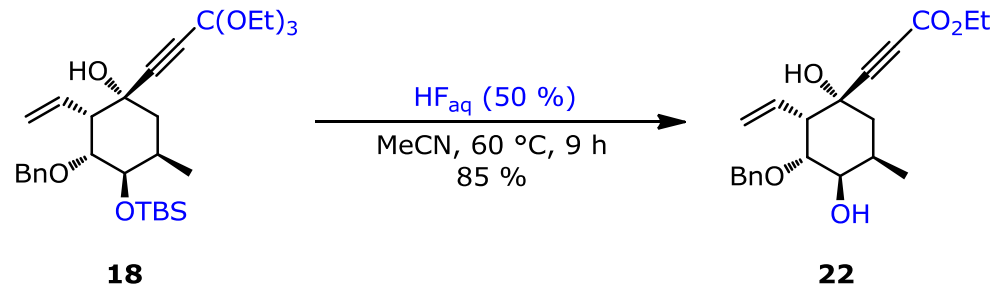


N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, 7, 4133–4136.

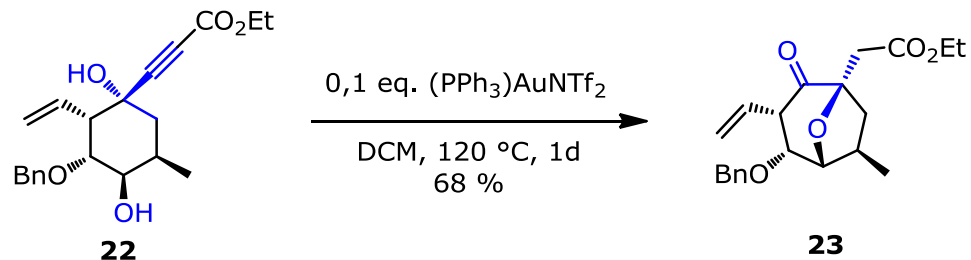


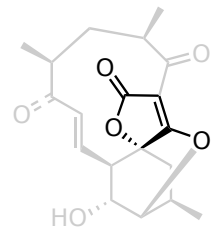


- Orthoester-Hydrolyse und Entschützung

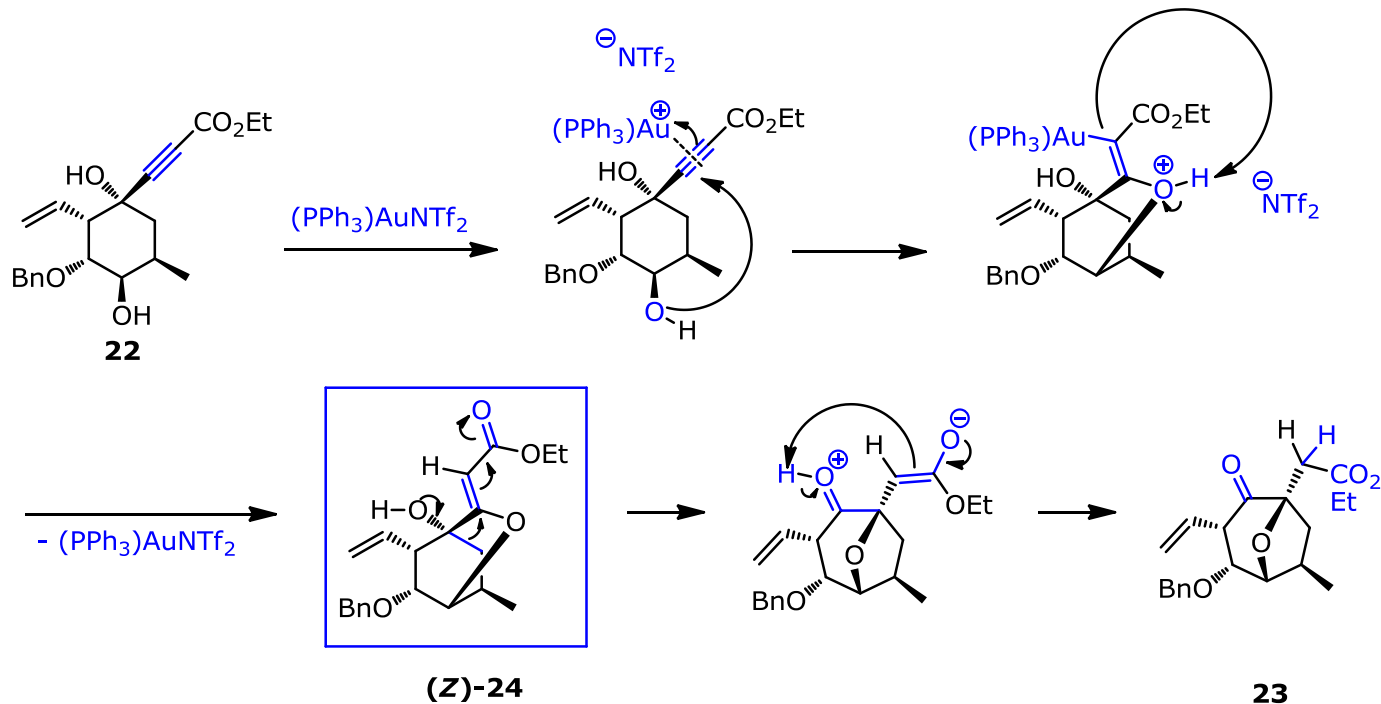


- Cycloisomerisierung

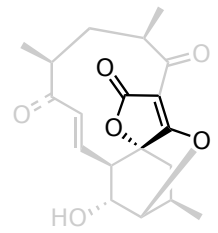




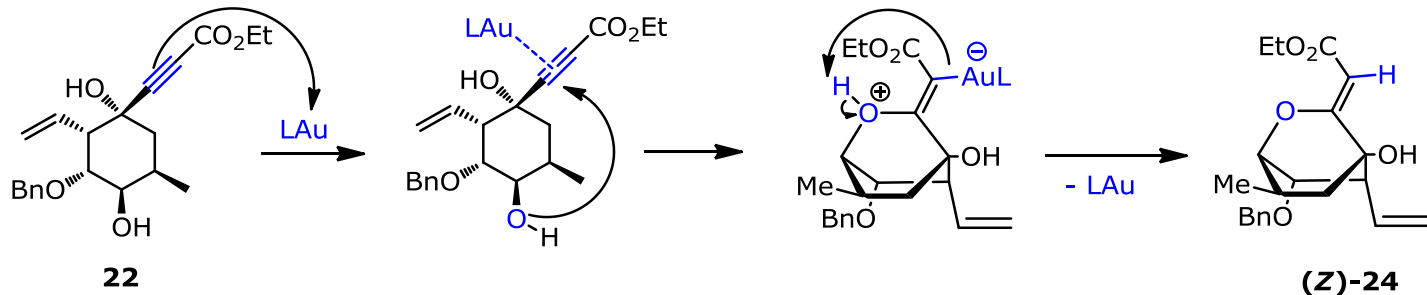
- vermeintlicher Mechanismus



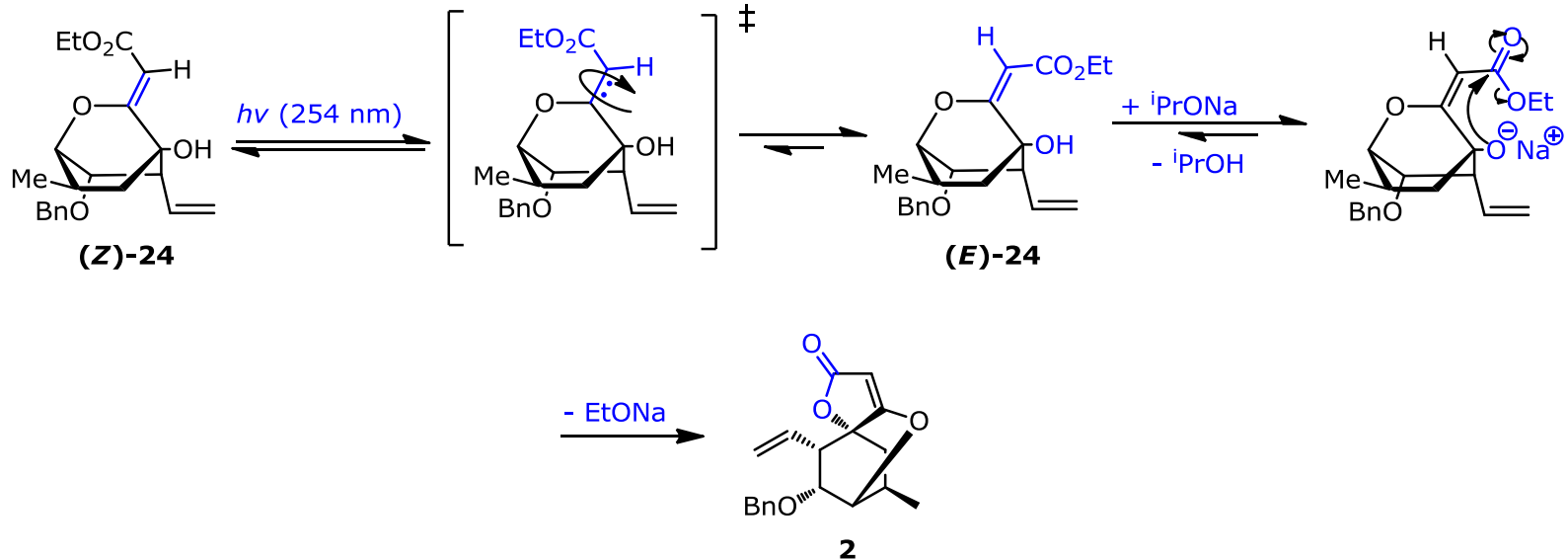
→ erhofftes Intermediat muss nach der Protodeaurierung zwischenzeitlich entstanden sein; 7-Ring-Bildung begünstigt durch hohe Temperatur



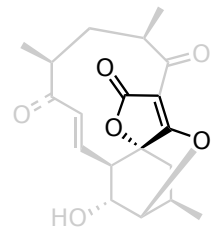
- Verbesserung der Cycloisomerisation: Isopropanol (Lösungsmittel), 70 °C



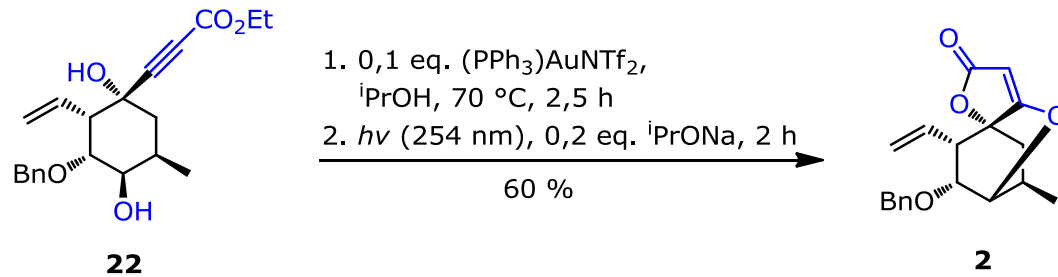
- *Z-E*-Isomerisierung durch UV-Bestrahlung und basische Lactonisierung

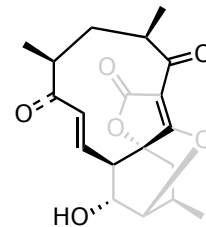


M. B. Smith, J. March, *March's Advanced Organic Chemistry*, 6. Aufl., 2007, S. 346



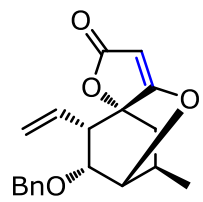
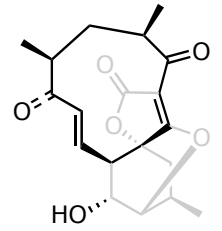
- Zusammenfassung der drei Syntheseschritte im Eintopf-Verfahren





## 4.3 Schluss des Elfrings und finale Schritte

# 1,2-Addition am Aldehyd



**2**

1. 1,3 eq. *t*-BuLi, THF, -78 °C, 45 min

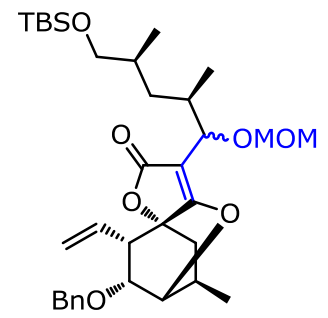
2. 1,5 eq. TBSO-CH<sub>2</sub>-CH(CH<sub>3</sub>)-CH<sub>2</sub>-CH(CH<sub>3</sub>)-CHO  
**25**

-78 °C, 10 min → -40 °C, 40 min

3. 1,5 eq. MOMBr, -40 °C → -25 °C, 1 h

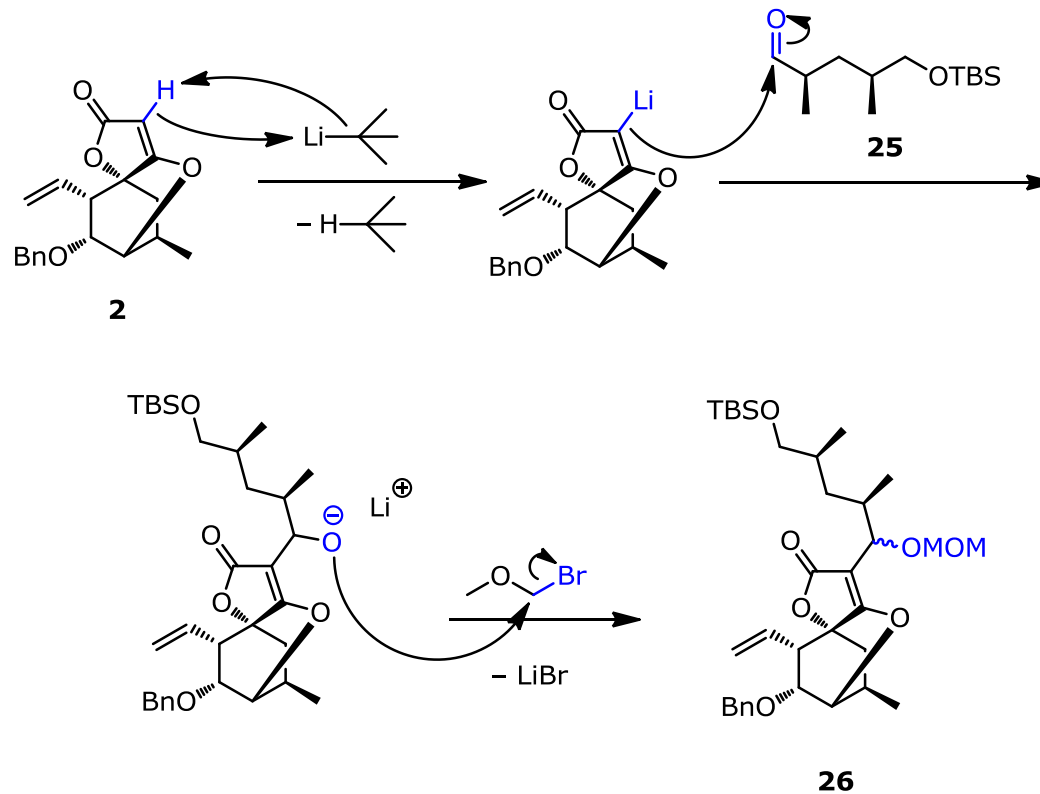
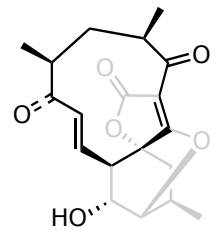


44 % (79 % brsm.)

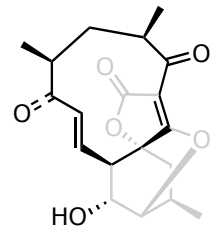


**26**

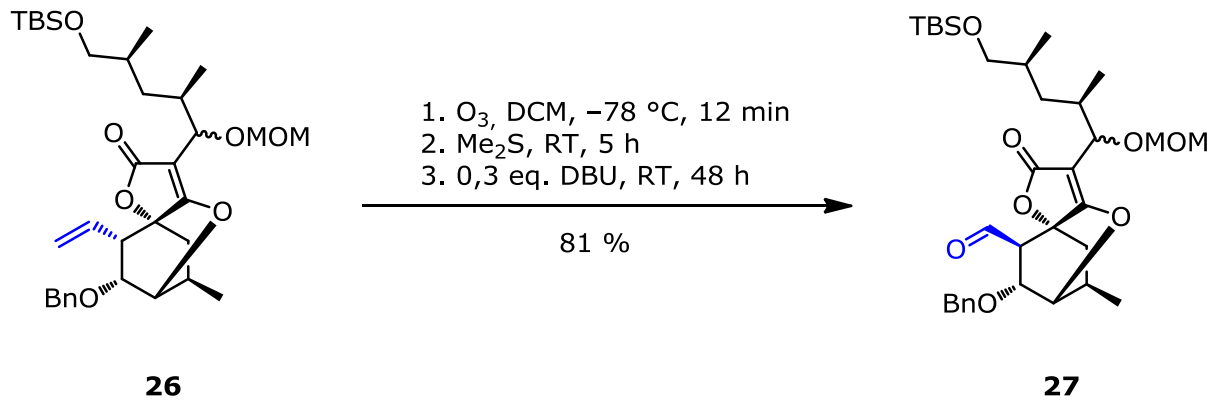
# 1,2-Addition am Aldehyd Mechanismus



J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, New York, 1. Aufl., **2001**, S. 214–215.

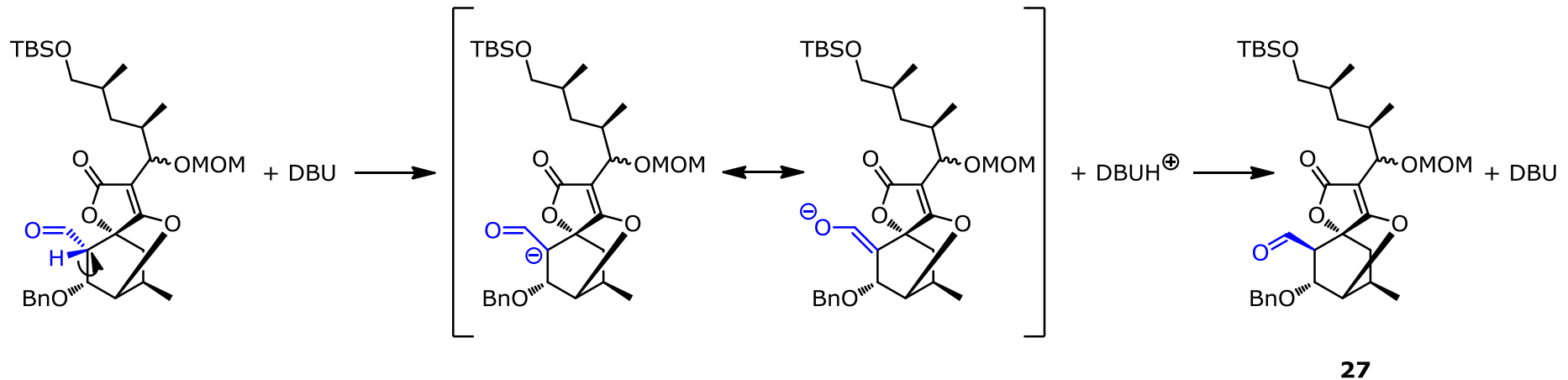
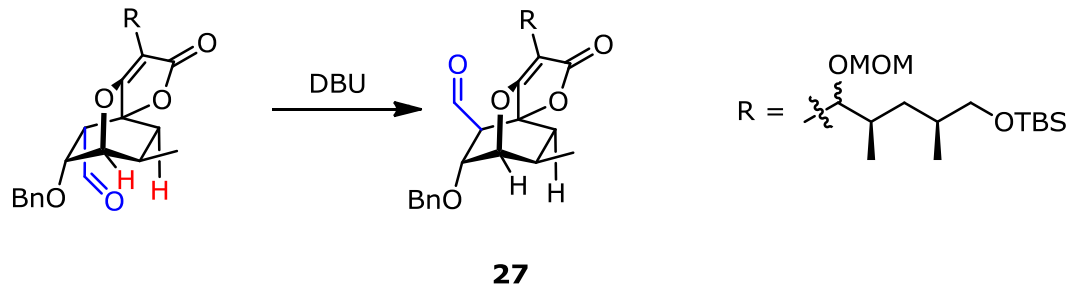
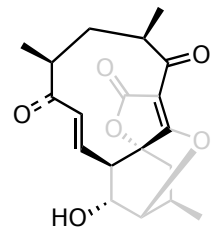


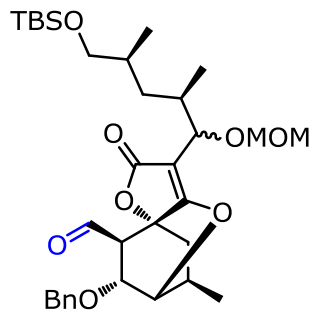
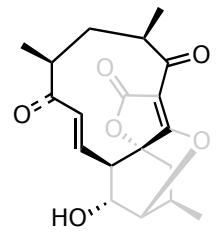
- Ozonolyse
- Anschließende Epimerisierung



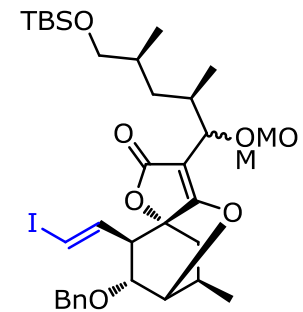
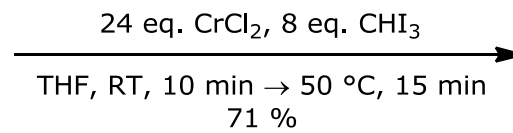


# Basische Epimerisierung mit DBU



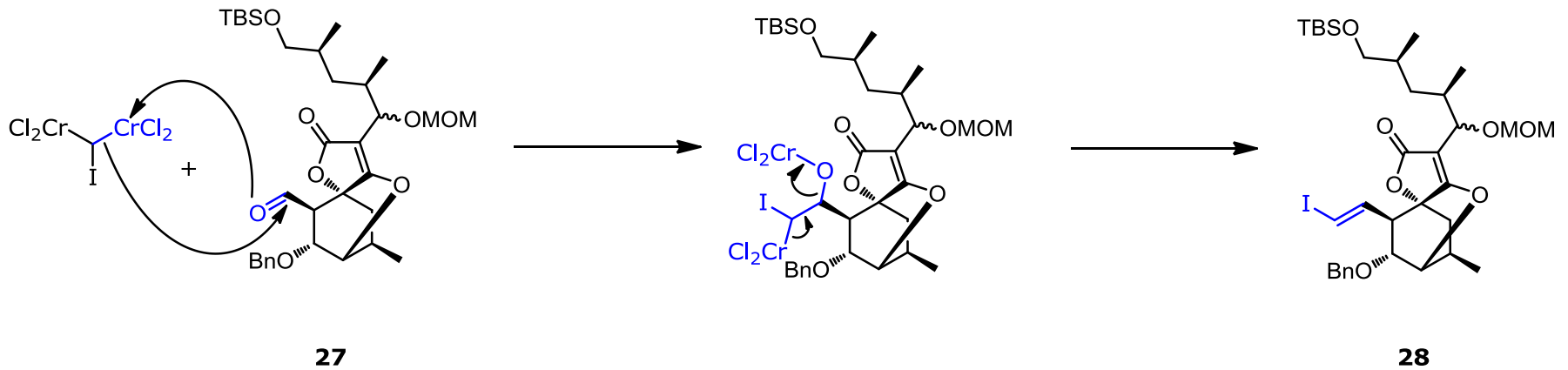
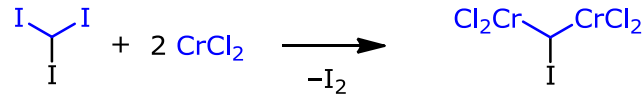
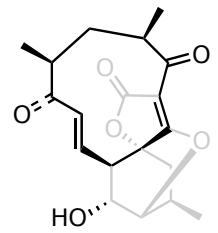


**27**

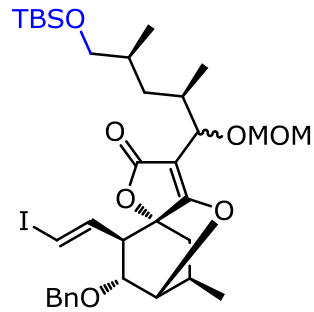
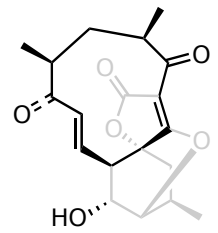


**28**

# Takai-Olefinierung Mechanismusvorschlag

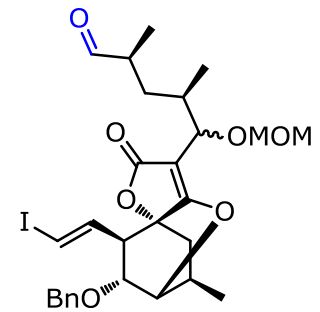


K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.

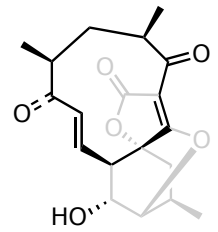


**28**

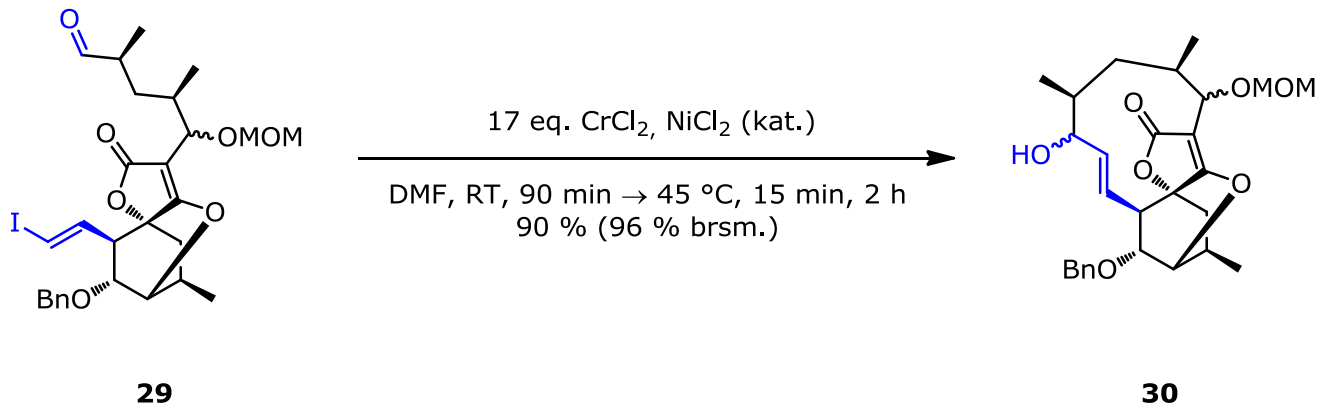
1. 1 M HCl (kat.), MeOH, RT, 1 h, 94 %  
 2. 2 eq. DMP, DCM, RT, 15 min, 88 %

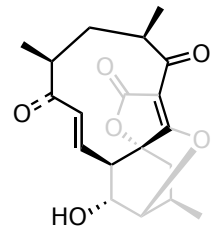


**29**

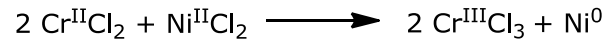


- Kupplungsreaktion mit Nickel(0)-Katalysator und Chrom(III)

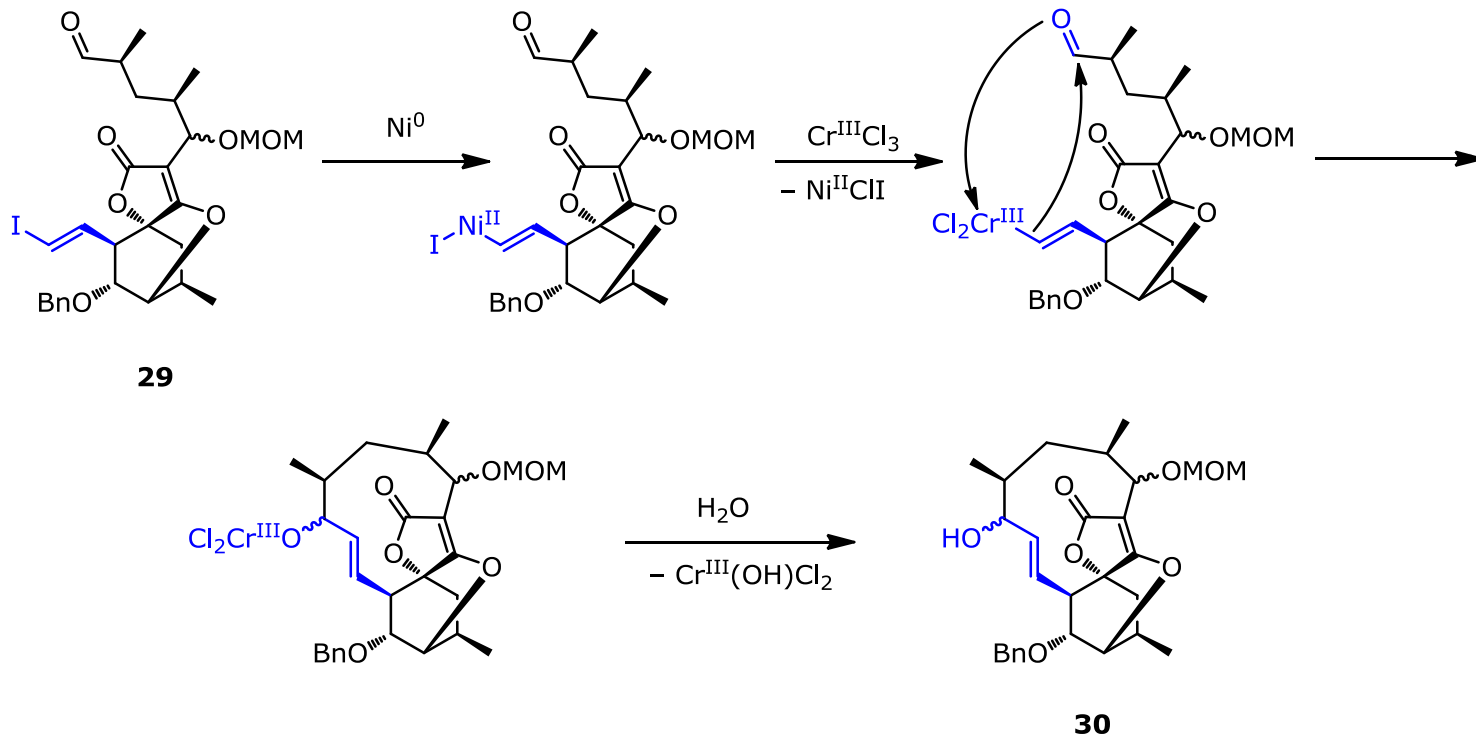


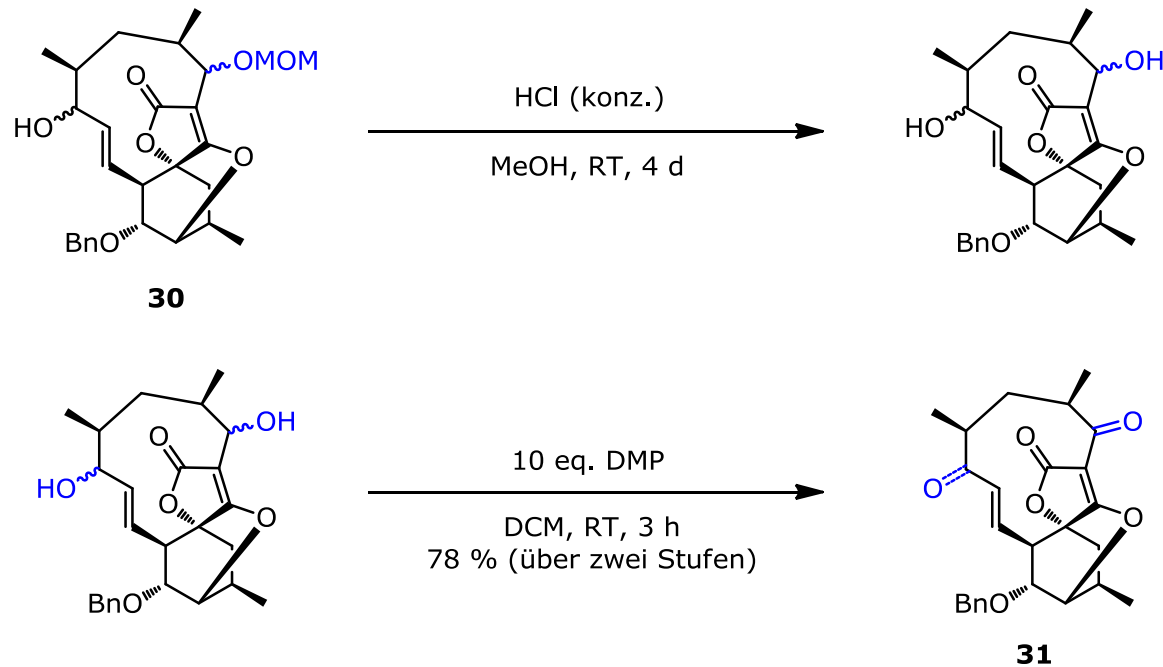
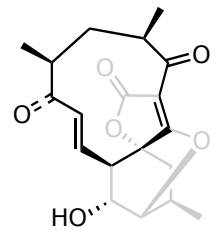


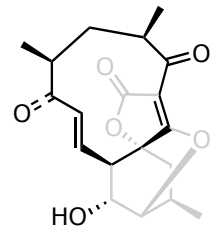
- Aktivierung des Katalysators



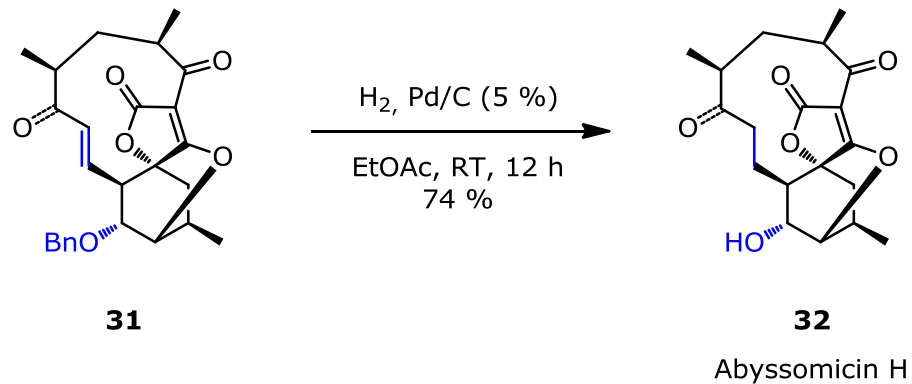
- Oxidative Addition von Nickel(0)
- Transmetallierung durch Chrom(III)







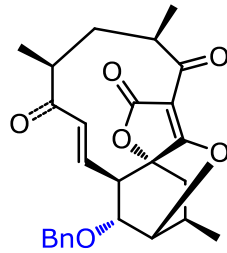
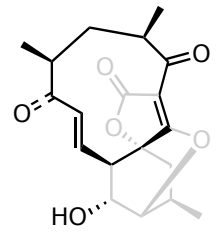
- Nebenreaktion: Hydrierung einer Doppelbindung



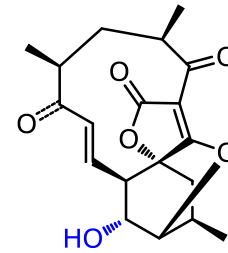
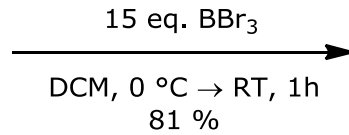




# Entschützung zum atrop-Abyssomicin C



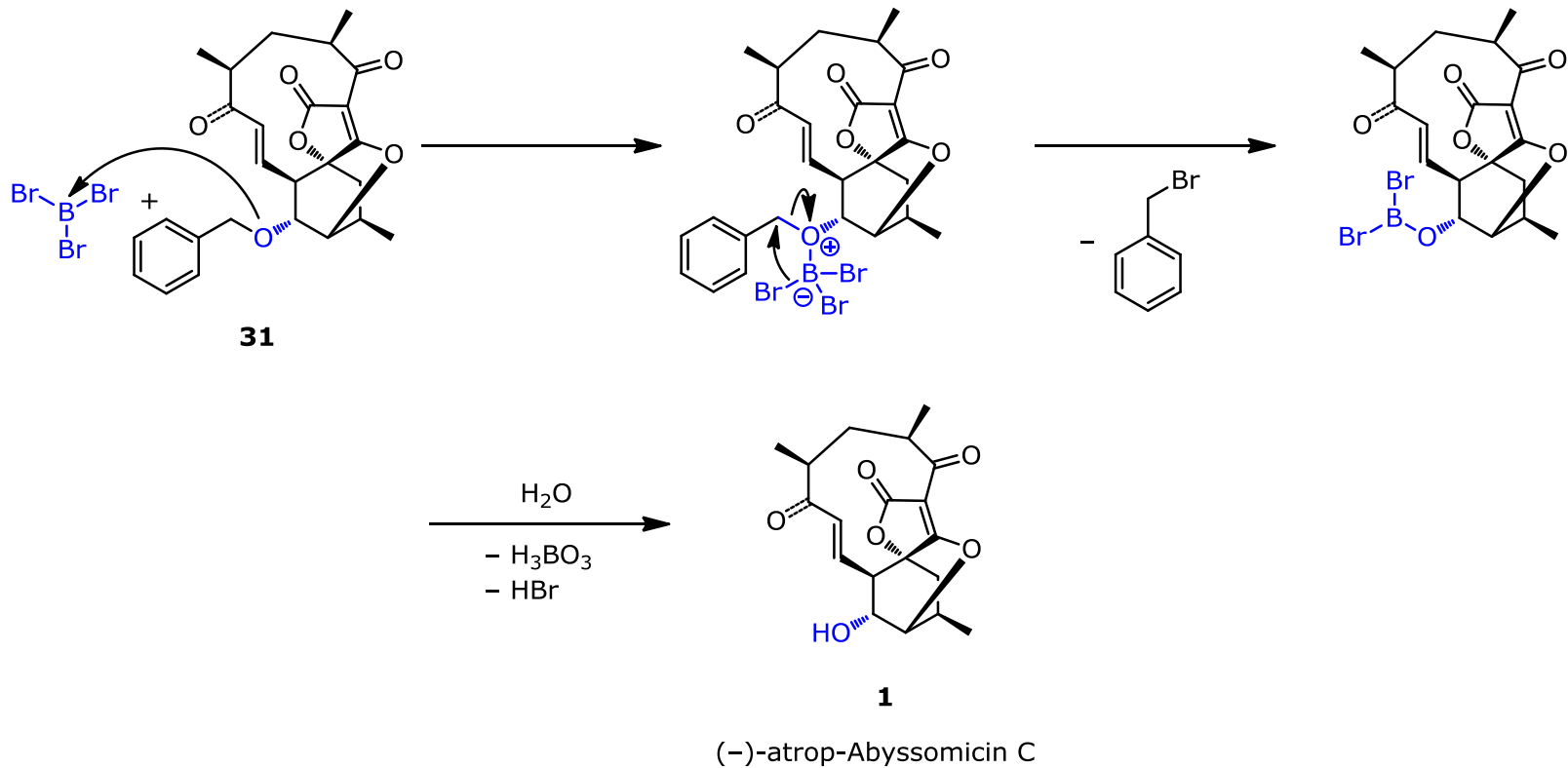
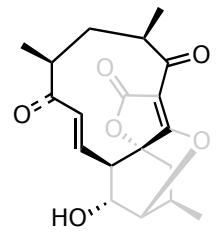
**31**



**1**

(-)-atrop-Abyssomicin C

# Entschützung zum atrop-Abyssomicin C Mechanismus



J. McOmie, M. Watts, D. West, *Tetrahedron* **1968**, 24, 2289–2292.

# 5. Zusammenfassung

Wichtige Schritte:

- Auxiliarinduzierte Aldoladdition
- Duale Katalyse
- Goldkatalyse
- Epimerisierung
- Nozaki-Hiyama-Kishi-Reaktion (Ringschluss)

Gesamtausbeute: 1,37 %

Anzahl der Schritte: 22

## 6. Abkürzungsverzeichnis

ABA	Aminobenzoessäure	RT	Raumtemperatur
Ac	Acetyl	<i>t</i>	<i>tert</i>
Bn	Benzyl	TBS	<i>tert</i> -Butyldimethylsilyl
Bu	Butyl	Tf	Triflat
brsm.	Based on recovered starting material (umsatzbezogene Ausbeute)	TIPS	Triisopropylsilyl
DBBT	Di- <i>n</i> -butylbortrifluoromethansulfonat	THF	Tetrahydrofuran
DBU	1,8-Diazabicyclo[5.4.0]undec-7-en	ÜZ	Übergangszustand
DCM	Dichlormethan		
DIBAL-H	Diisobutylaluminiumhydrid		
DMF	<i>N,N</i> -Dimethylformamid		
DMP	Dess-Martin-Periodinan		
Et	Ethyl		
eq.	Äquivalente		
kat.	katalytisch		
konz.	konzentriert		
LDA	Lithiumdiisopropylamid		
<i>m</i> CPBA	<i>meta</i> -Chlorperbenzoessäure		
Me	Methyl		
<i>p</i>	<i>para</i>		
PG	Protection group (Schutzgruppe)		
Piv	Pivaloyl		



**»Wissen schafft Brücken.«**