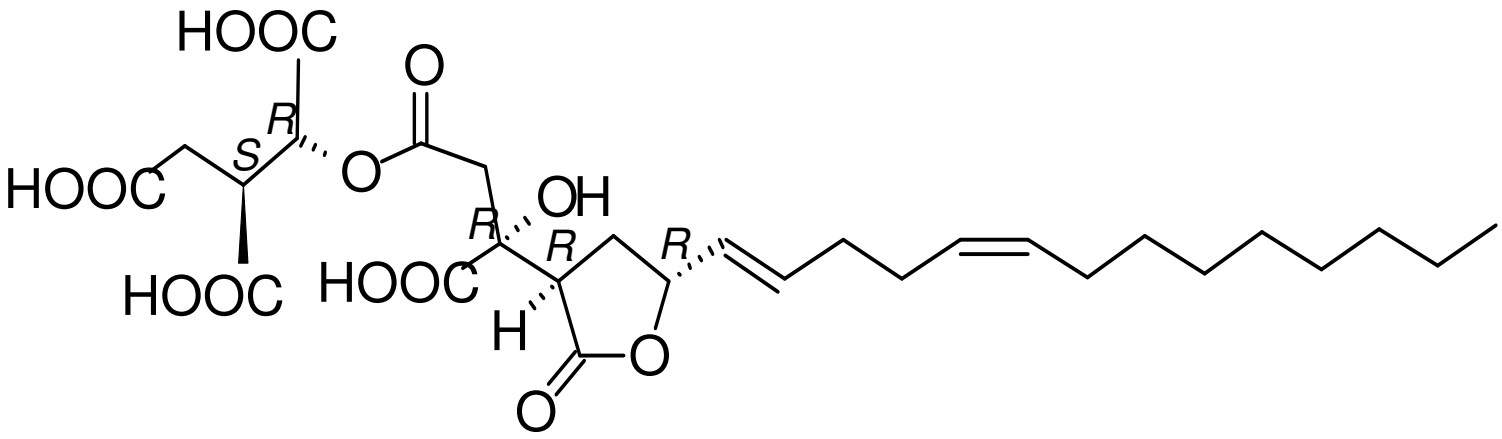
TECHNISCHE UNIVERSITÄT DRESDEN

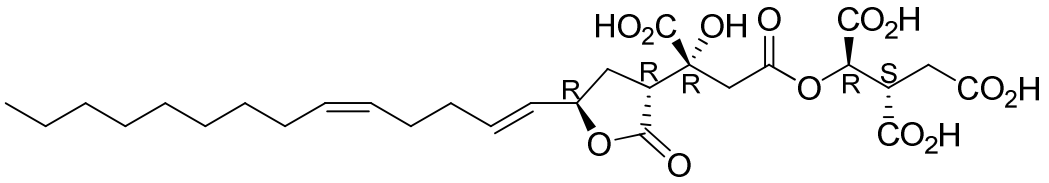
Totalsynthese von Citrafungin A



Fanny Epperlein, Michael Hans, Anja Hartmann, René Jatzke, Marco Kunaschk,
Christian Pätzold, Anne-Kathrin Weniger

Inhaltsverzeichnis

1. Einführung

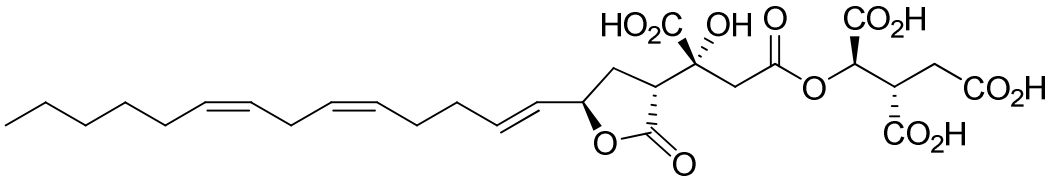


Citrafungin A

- Molmasse M = 585 g/mol
- Natürlich vorkommendes Fungizid, einsetzbar in der Landwirtschaft
- 2004 von Singh et. al. aus Rinderdung extrahiert und als „Citrafungin“ benannt
- 2006 erste Totalsynthese von Citrafungin A durch Hatekayama et. al. vorgestellt
- Mittlere inhibitorische Konzentration IC_{50} 2,5-15µM
- Minimale Hemm-Konzentration MIC 0,44-55µM

Schlüsselreaktionen:

- asymmetrische Aldol-Reaktion eines chiralen Oxazolidinons
- Seebach Alkylierung (Selbstreproduktion eines Stereozentrums (SRS))
- Hydrozirkonierung mit anschließender Kupplung eines Aldehyds zu einem Lacton



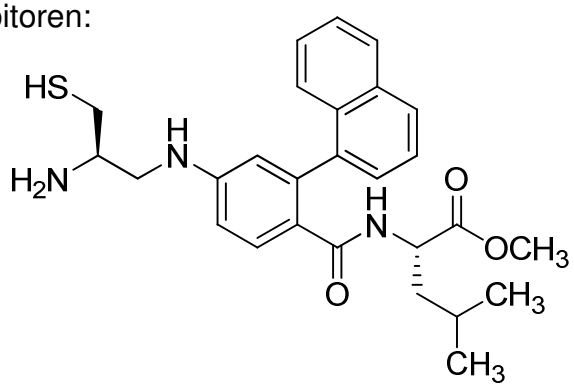
Citrafungin B

Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9697

2. Biochemische Wirkungsweise

- Hemmung der Produktion und Aktivierung von Geranylgeranyltransferase I (GGTase I)
- GGTase I entscheidender Bestandteil beim Aufbau von Zellwänden (von Pilzen)
- Citrafungin A spezifisch für die Hemmung fungaler GGTase I

Humane GGTase-Inhibitoren:



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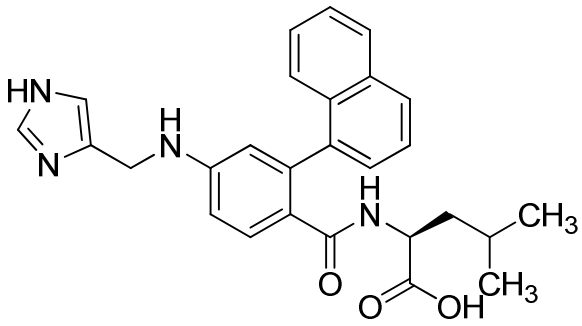
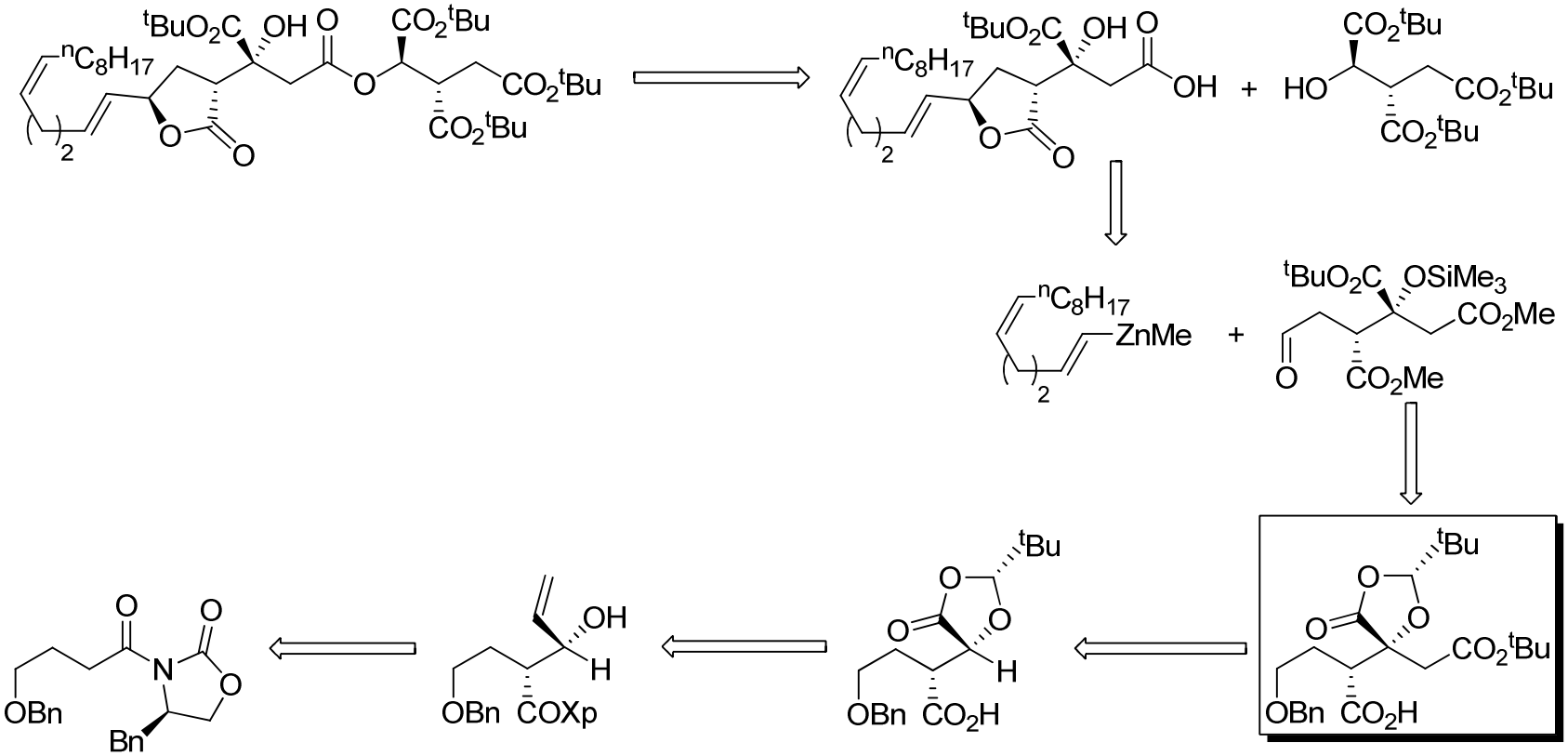


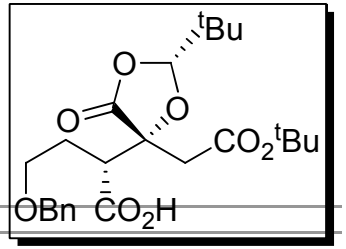
GGTI-2133

Singh, Zink, Doss, Polishook, Ruby, Register, Kelly, Bonfiglio, Williamson, Kelly, *Org. Lett.* **2006**, 6, 337-340
Bilder: Merck4Biosciences (03.12.09)

3. Retrosynthese

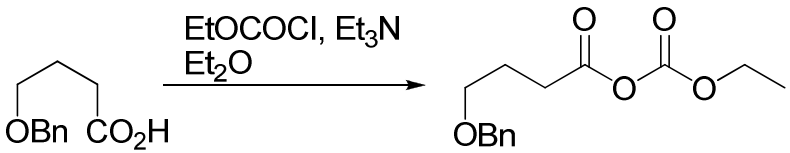


Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9697

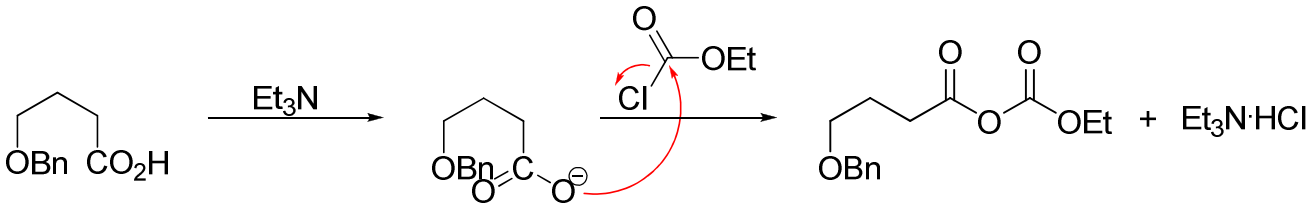


4. Synthese des Dioxolanon

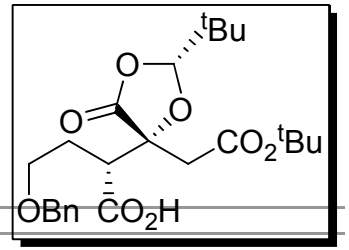
Carbonsäureaktivierung



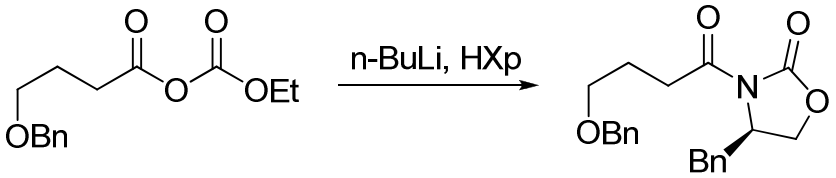
Mechanismus

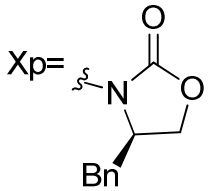


Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9698
Brückner, „*Reaktionsmechanismen*“, 3.Auflage, Spektrum Akademischer Verlag, **2004**, S.279f



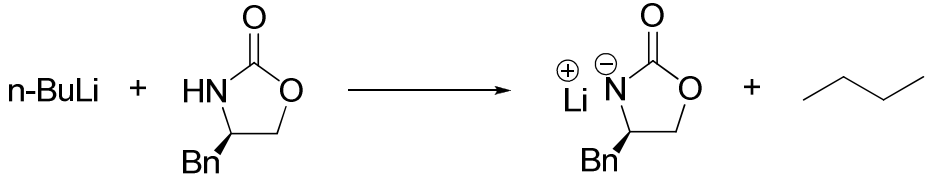
Einführung des Evans-Auxiliars

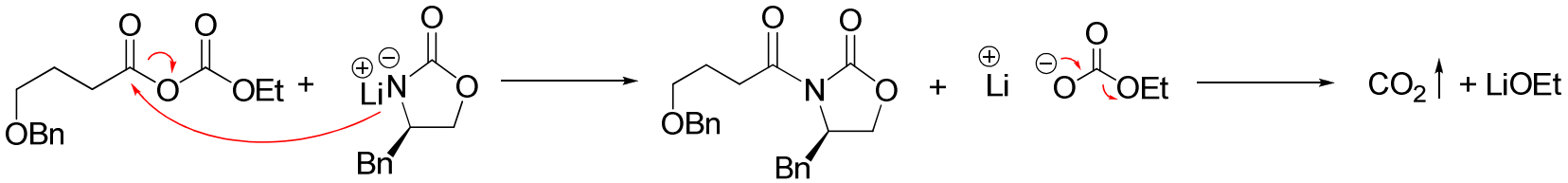




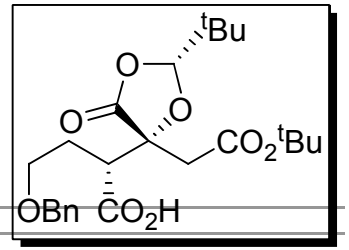
85% Ausbeute Carbonsäureaktivierung + Einführung des Evans-Auxiliars

Mechanismus

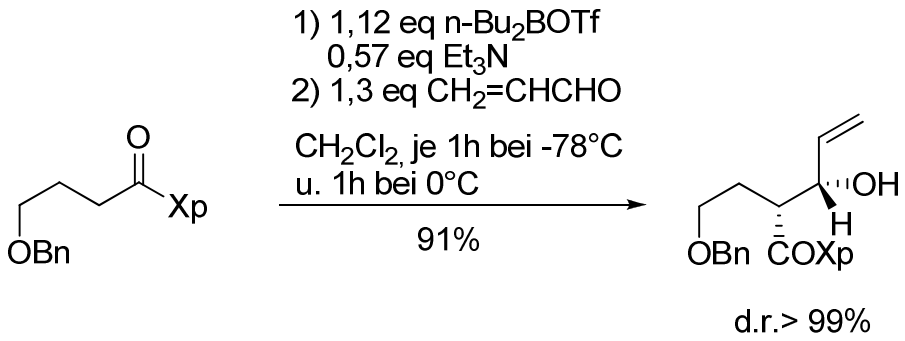




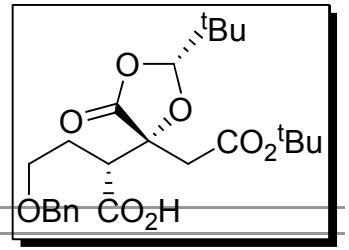
Calo, Richardson, Barrett, *J. Org. Chem.,* **2008**, 73, 9692-9698
Brückner, „*Reaktionsmechanismen“,* 3.Auflage, Spektrum Akademischer Verlag, **2004**, 297ff, 343



Evans-Aldol-Reaktion



d.r.> 99%



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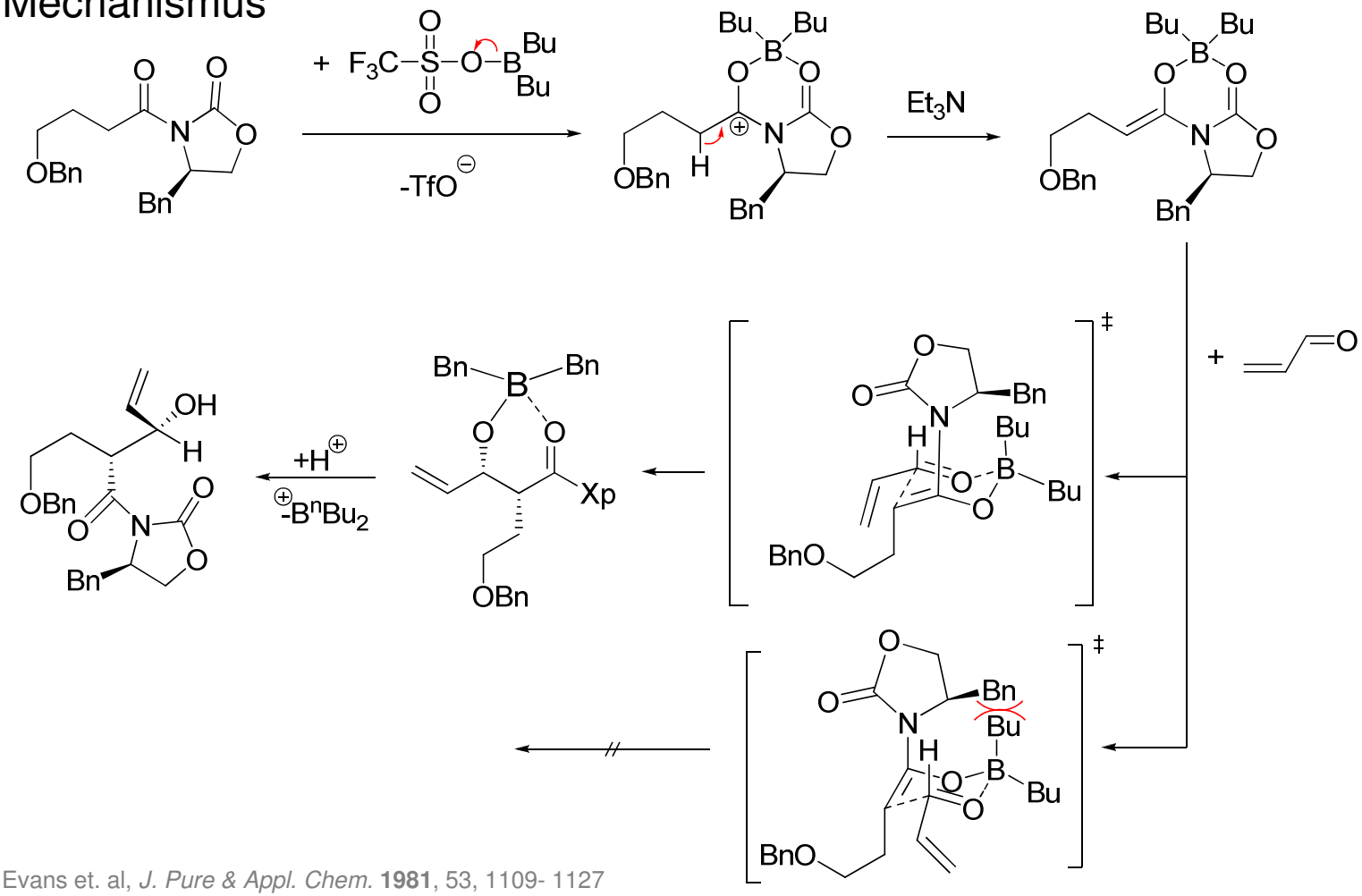
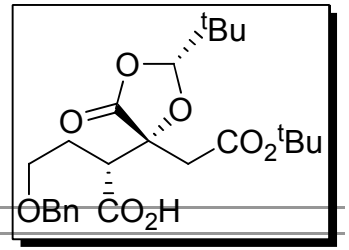
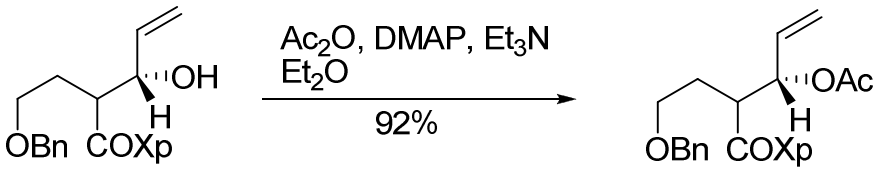


Evans et. al, *J. Pure & Appl. Chem.* **1981**, 53, 1109- 1127



Acetylierung



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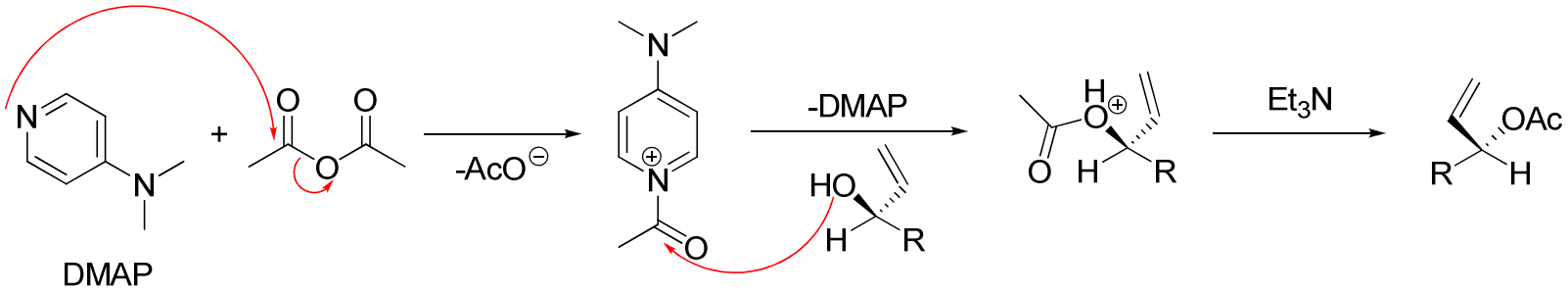
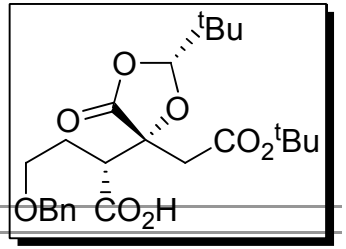
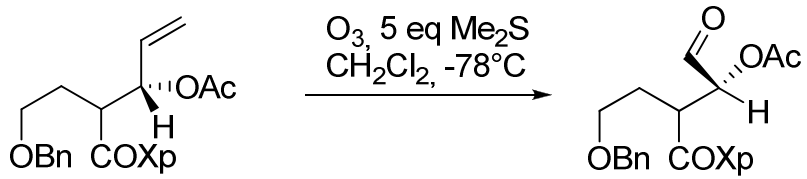


Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9698
Carey, Sundberg, *„Organische Chemie“*, 1.Auflage, VCH Weinheim, **1995**, 892



Ozonolyse



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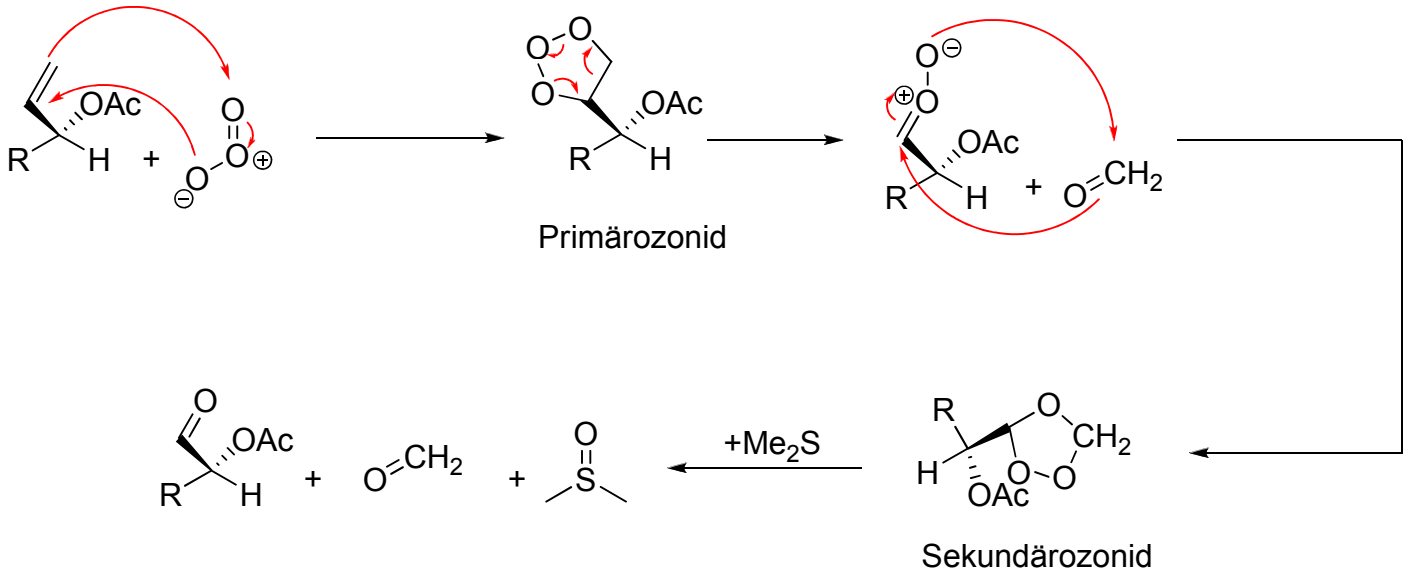

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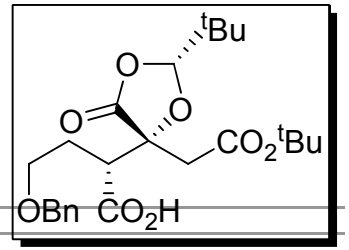
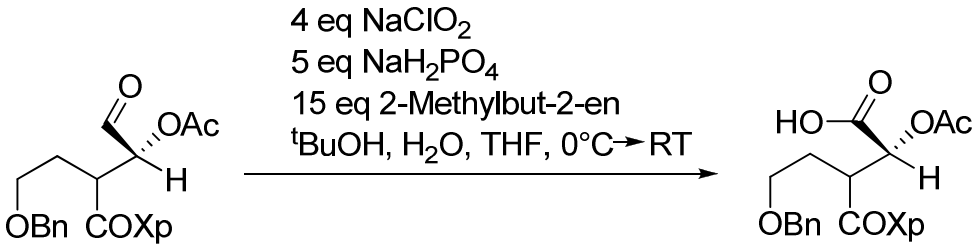
Brückner, „*Reaktionsmechanismen“,* 3.Auflage, Spektrum Akademischer Verlag, **2004**, 675ff, 761f



Pinnick-Oxidation



85% Ausbeute Ozonolyse + Pinnick-Oxidation

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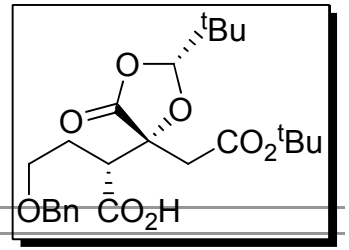
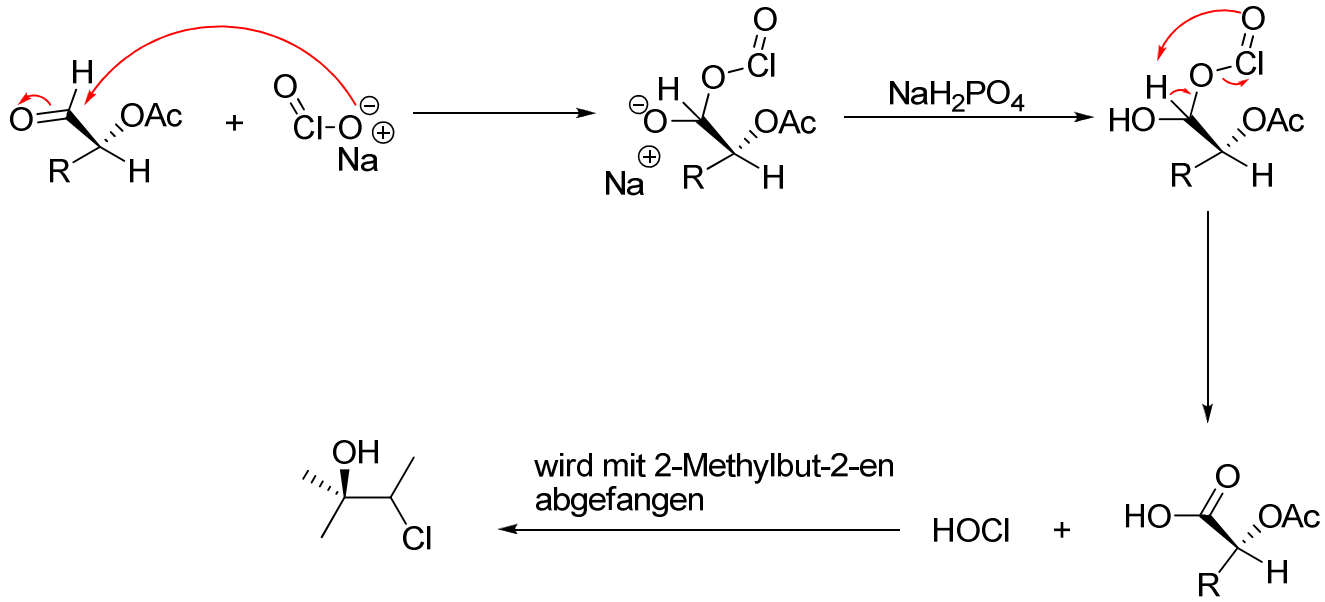
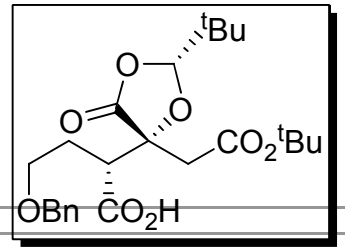
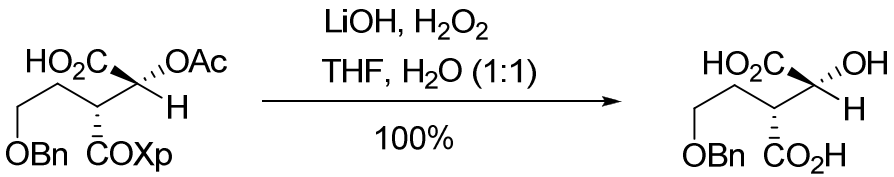


Mechanismusvorschlag





Dualhydrolyse



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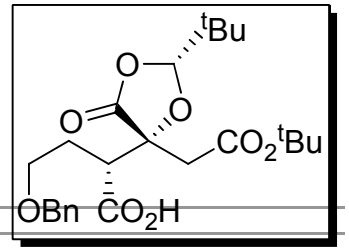
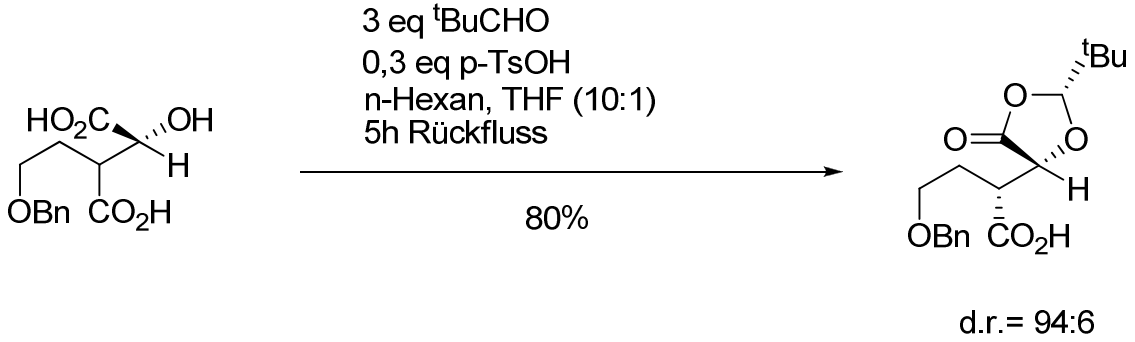
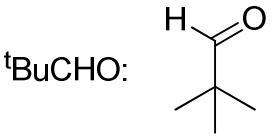
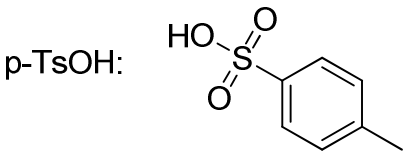


SRS-Reaktion: I.) Acetalisierung



d.r.= 94:6





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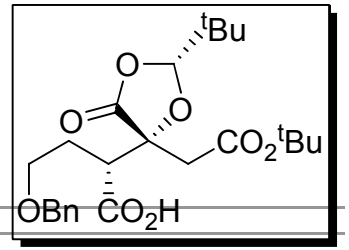
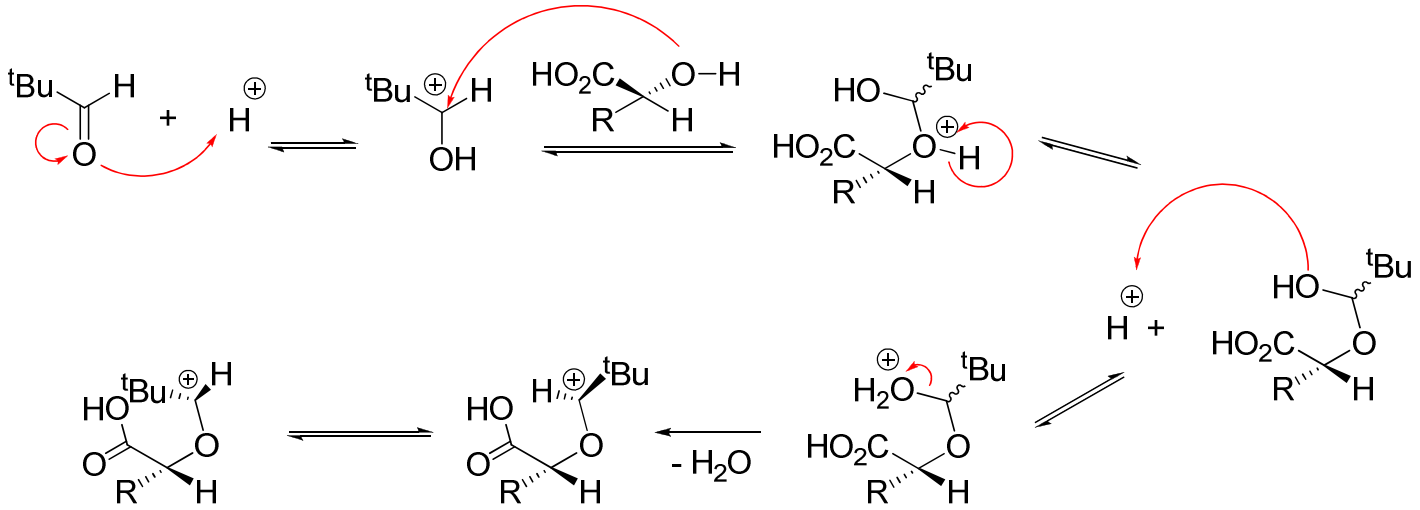
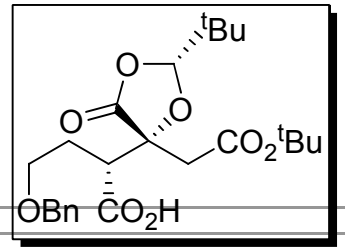


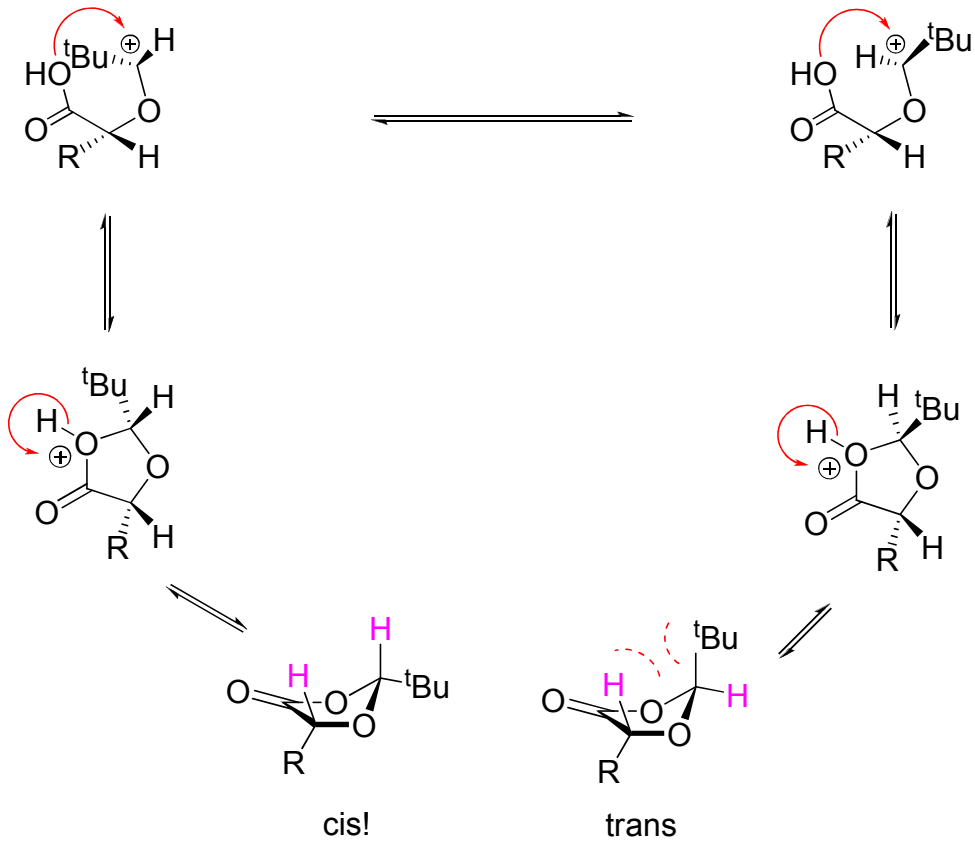
Mechanismus (Teil 1)



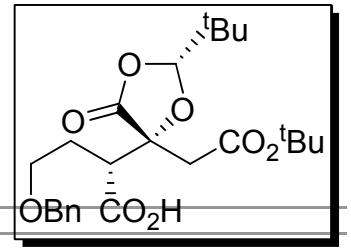
Seebach, Sting, Hoffmann, *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 2708–2748



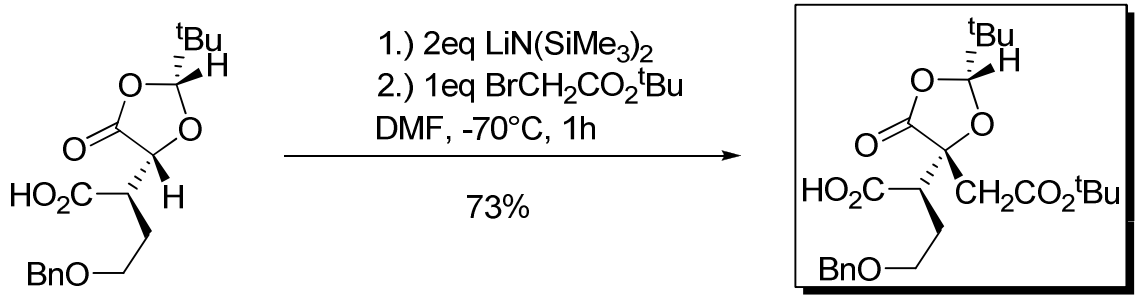
Mechanismus (Teil 2)

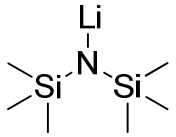


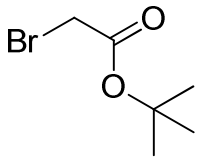
Seebach, Sting, Hoffmann, *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 2708–2748

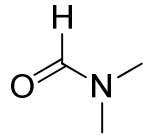


SRS-Reaktion: II.) Alkylierung



LiN(SiMe$_3$)$_2$: 

BrCH$_2$CO$_2$^{t}Bu: 

DMF: 

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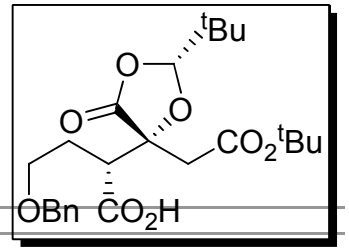
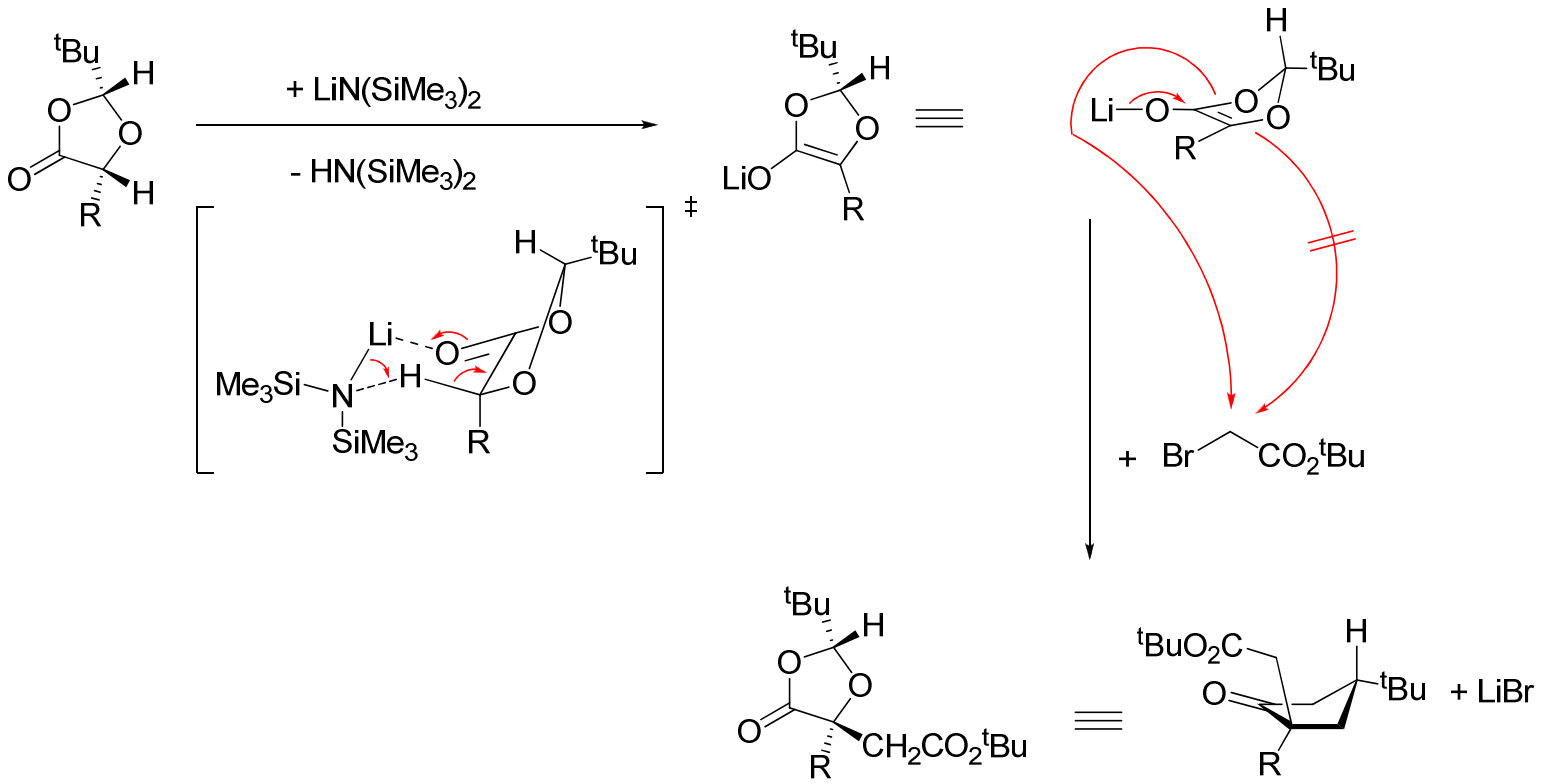
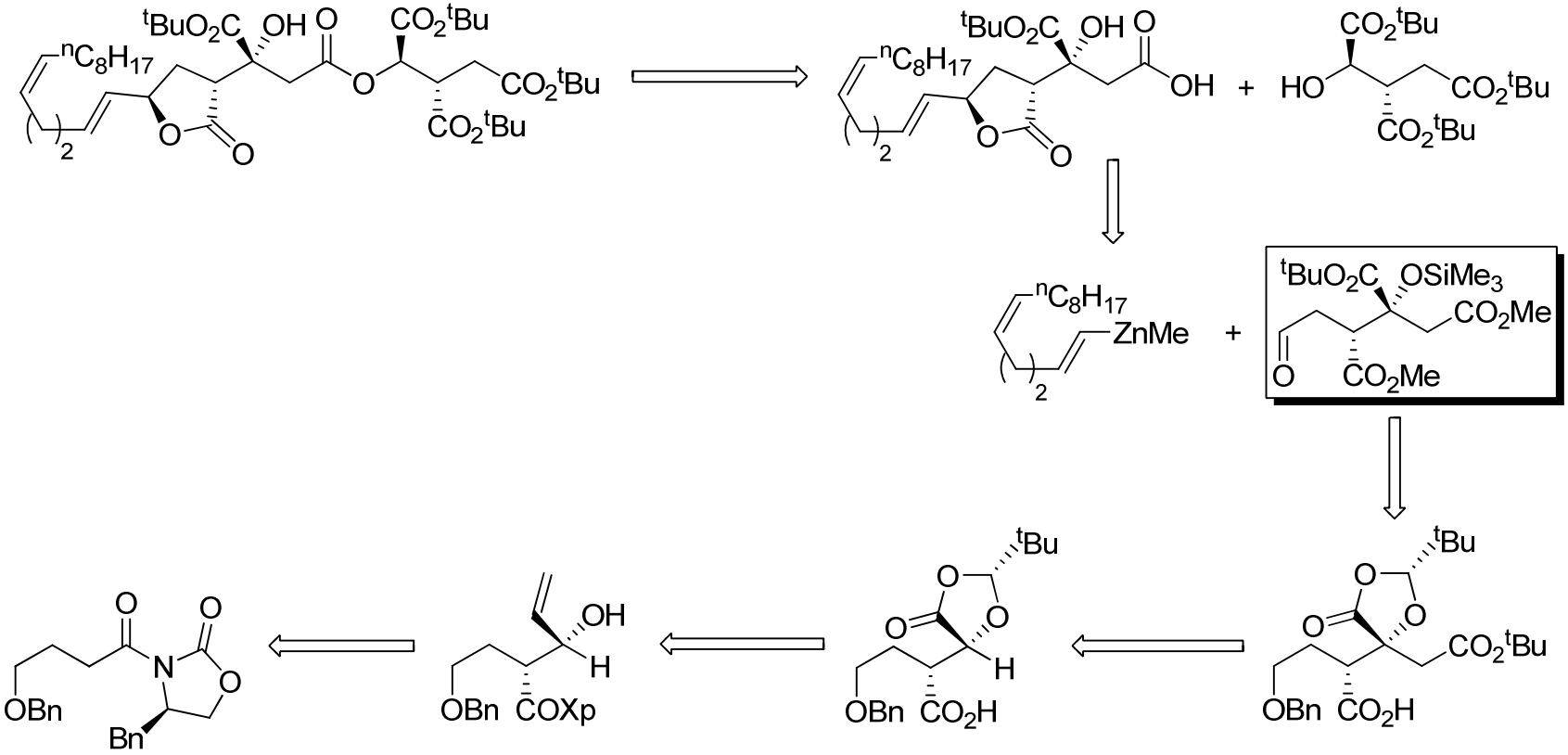


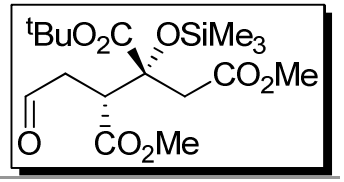
Mechanismus



Seebach, Sting, Hoffmann, *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 2708–2748

5. Synthese des Aldehyds





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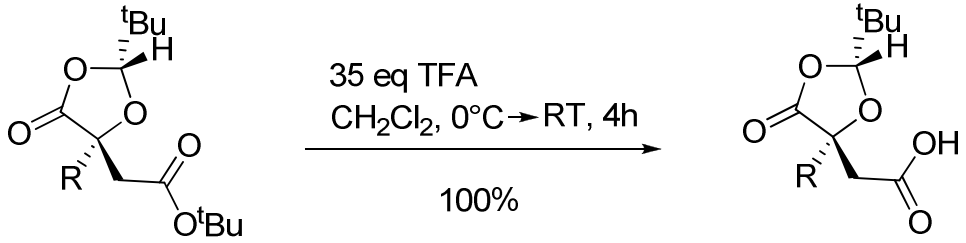
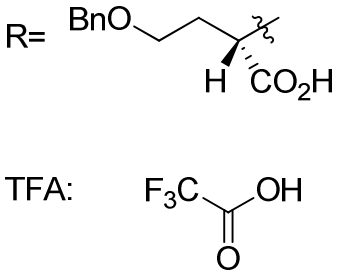
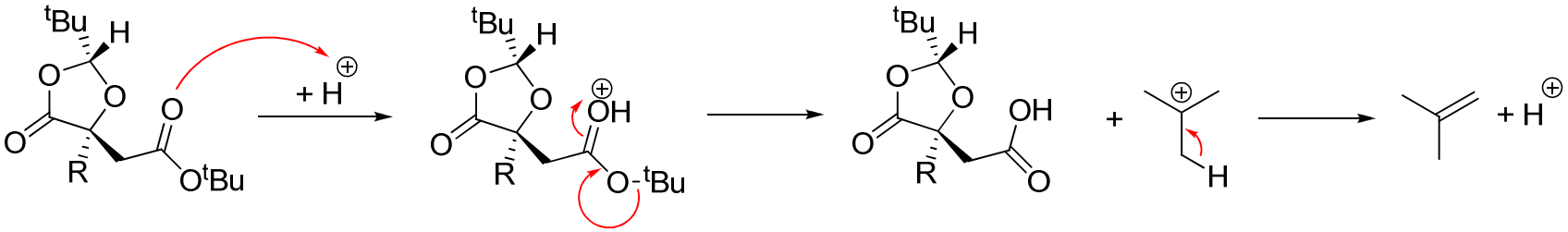
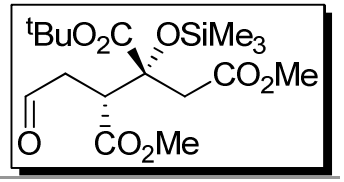




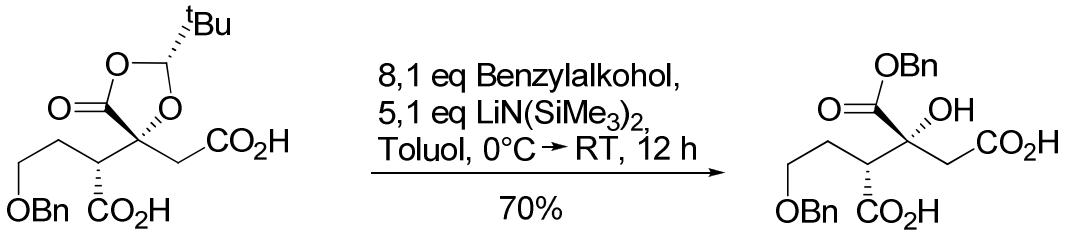
Mechanismus

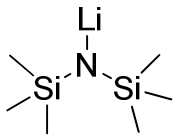


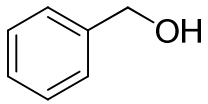
Calo, Richardson, Barrett, *J. Org. Chem.,* **2008**, 73, 9692-9698
Brückner, *„Reaktionsmechanismen“*, 3. Auflage Spektrum Akademischer Verlag, **2004**, 191
Kocienski, *„Protecting Groups“,* Thieme, **2005**



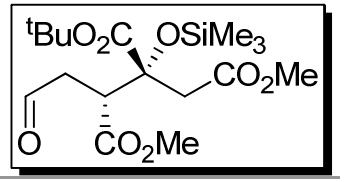
Öffnung des Dioxolanons



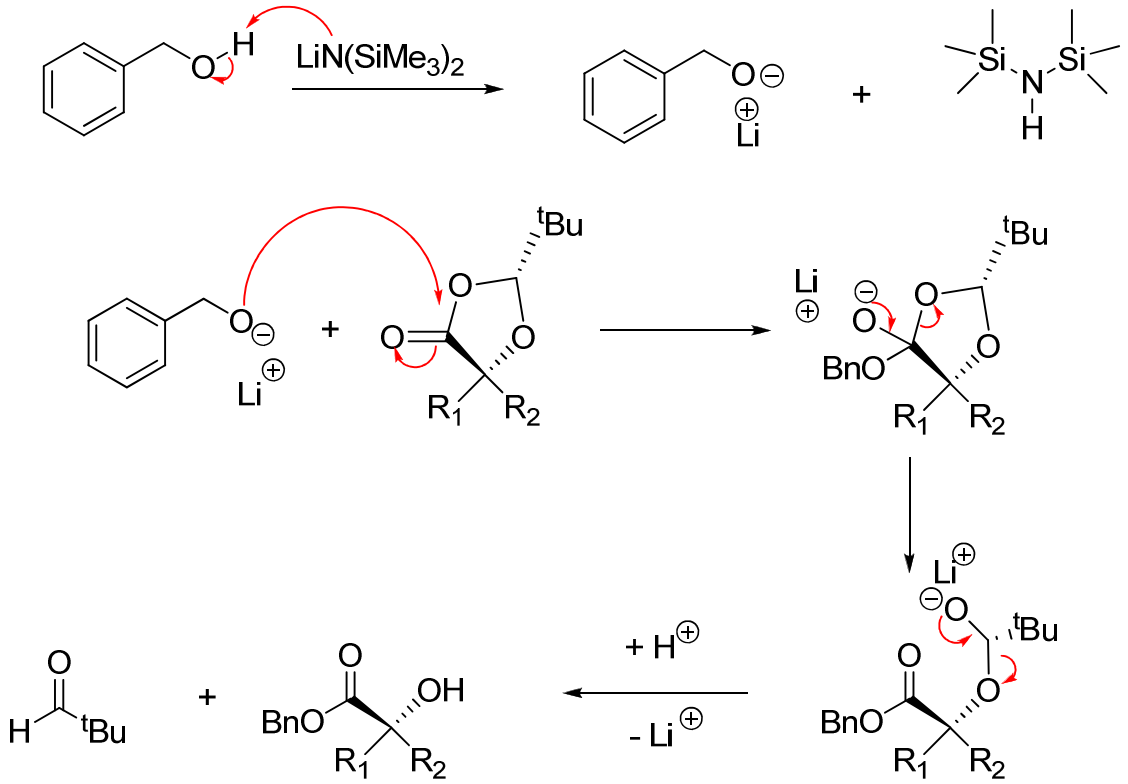
LiN(SiMe$_3$)$_2$: 

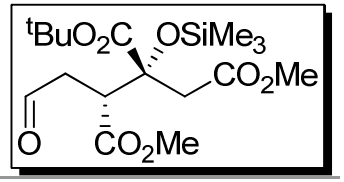
Benzylalkohol: 

Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9698

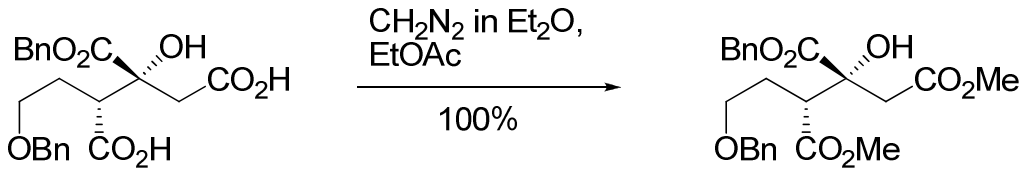


Mechanismusvorschlag

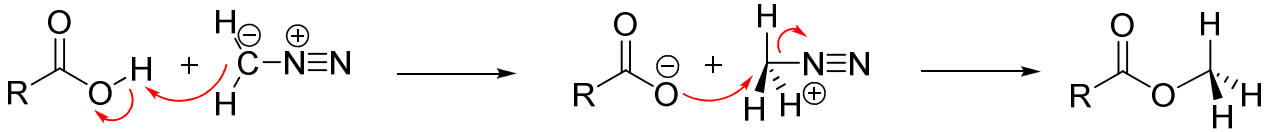




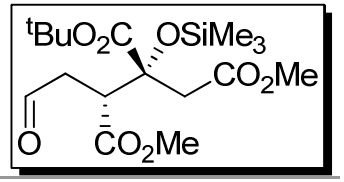
Alkylierung nach S_N2



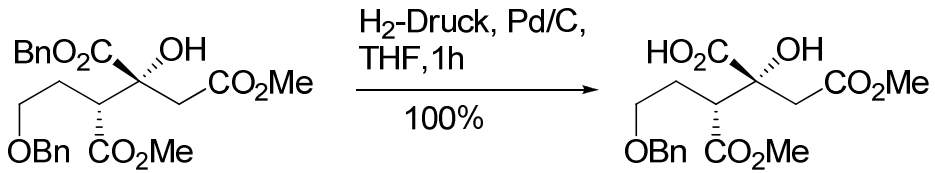
Mechanismus



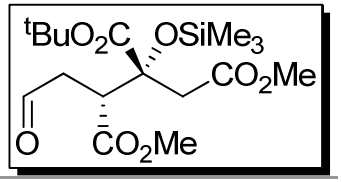
Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9698
Brückner, *„Reaktionsmechanismen“*, 3..Auflage, Spektrum Akademischer Verlag, **2004**, 97



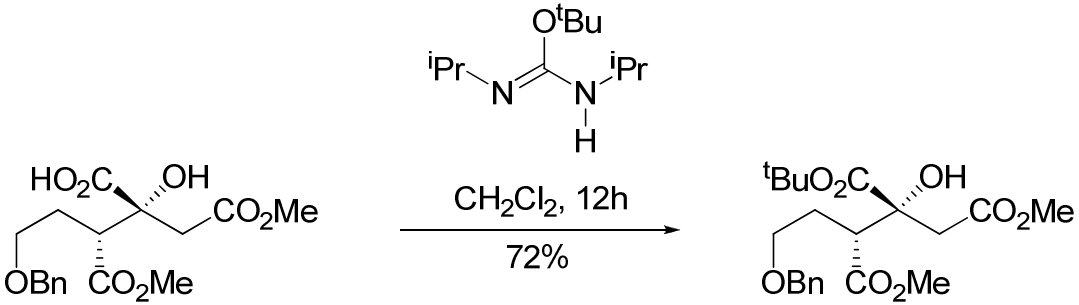
Selektive Hydrogenolyse des Benzylesters



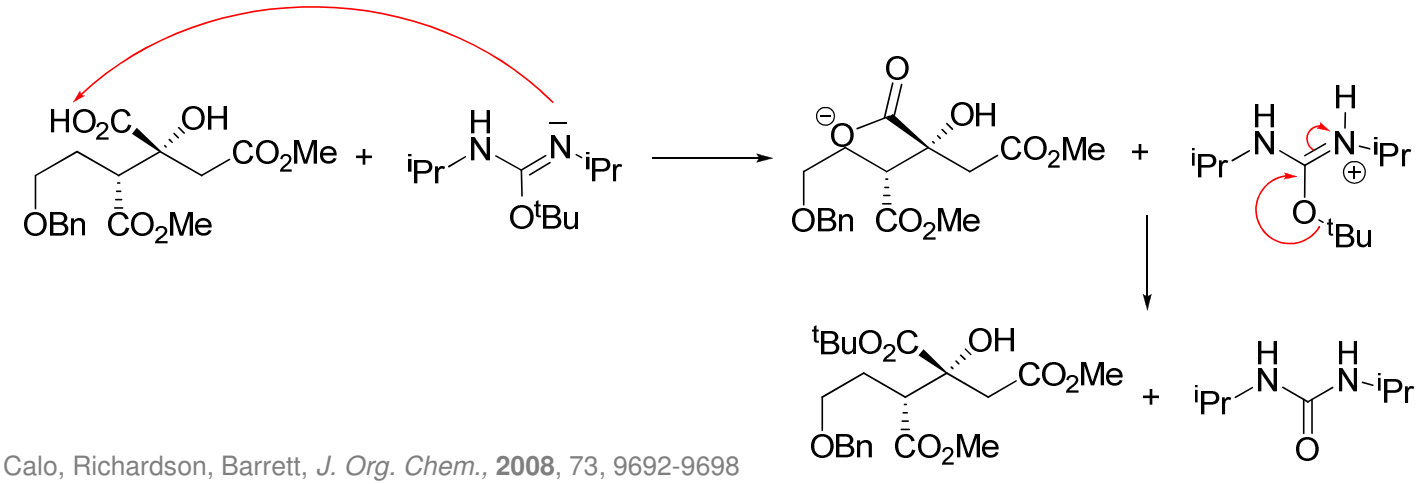
Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9698



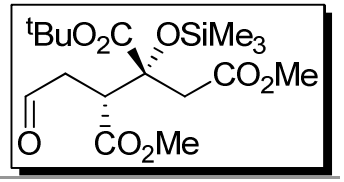
Schützen der freien Säure



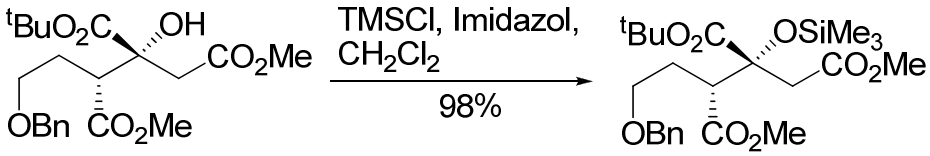
Mechanismusvorschlag



Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9698



Schützen des Alkohols



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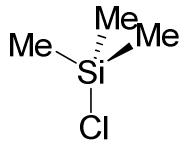

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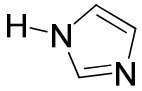

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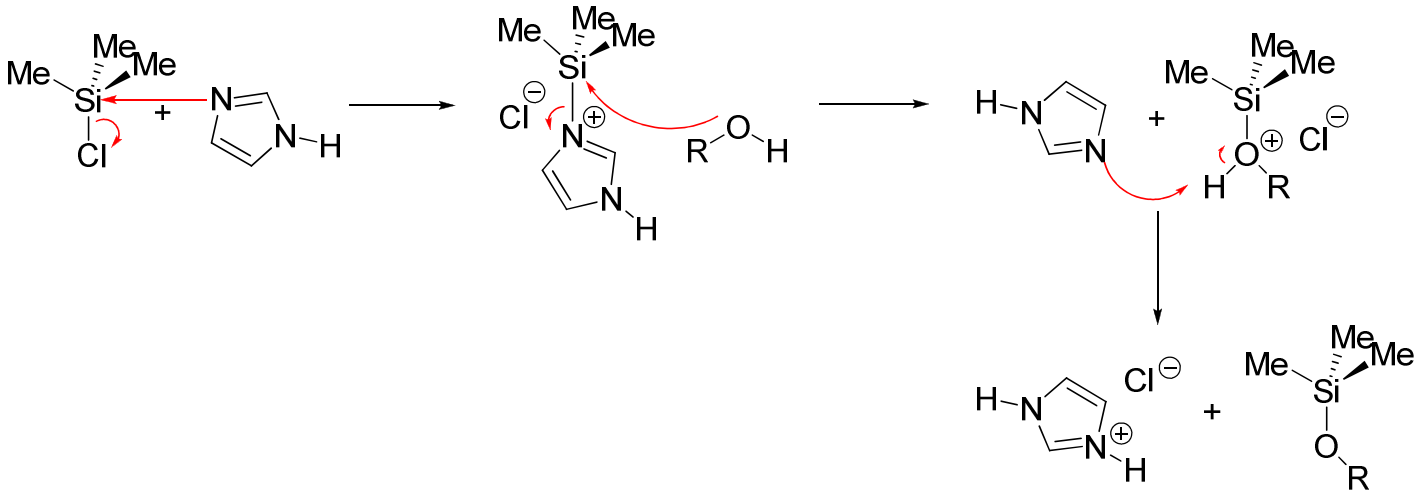
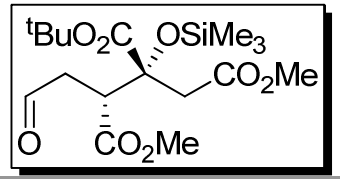
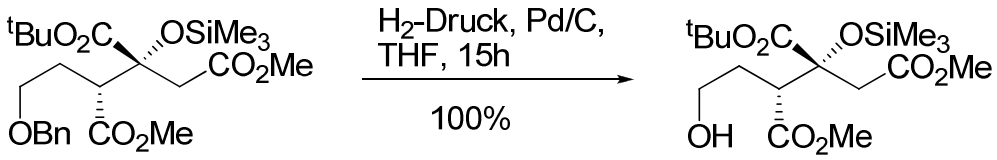


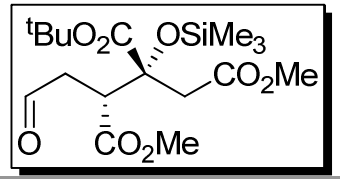
Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9698



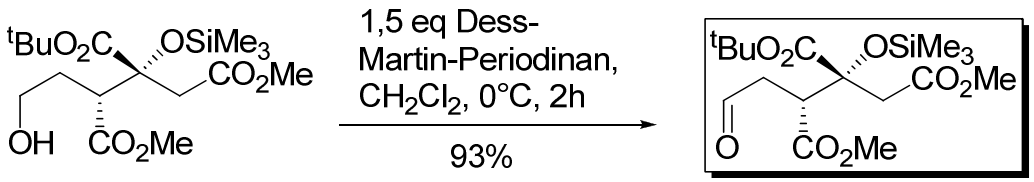
Selektive Hydrogenolyse des Benzylethers



Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9698



Dess-Martin-Oxidation



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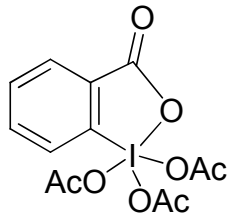
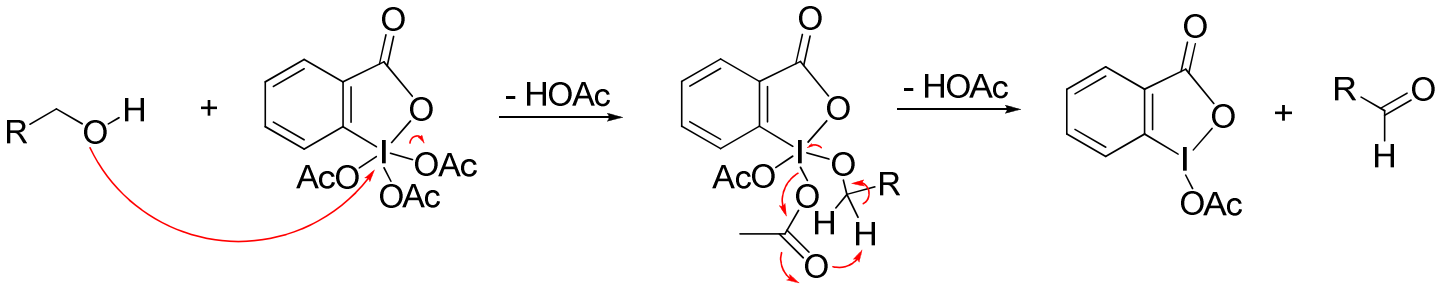


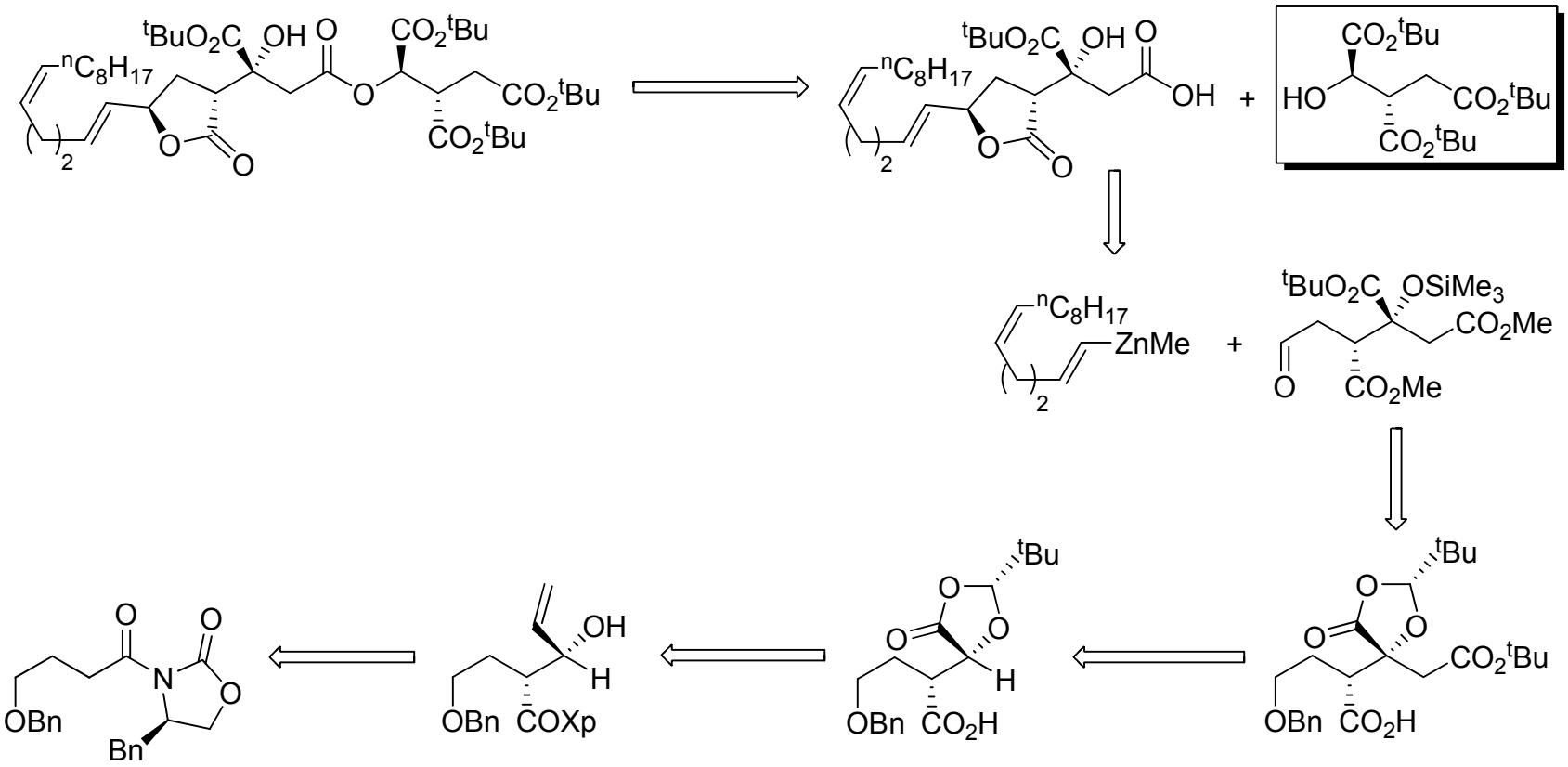
Mechanismus

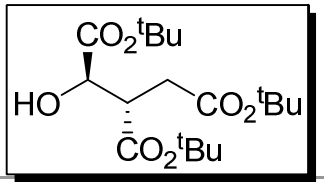


Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9698

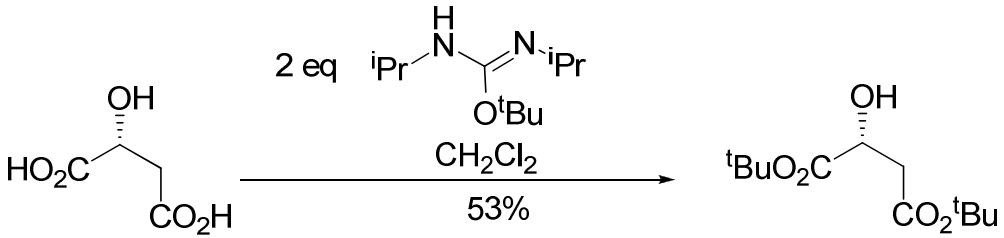
Brückner, *„Reaktionsmechanismen“,* 3..Auflage, Spektrum Akademischer Verlag, **2004**, 746

6. Synthese des Alkohols

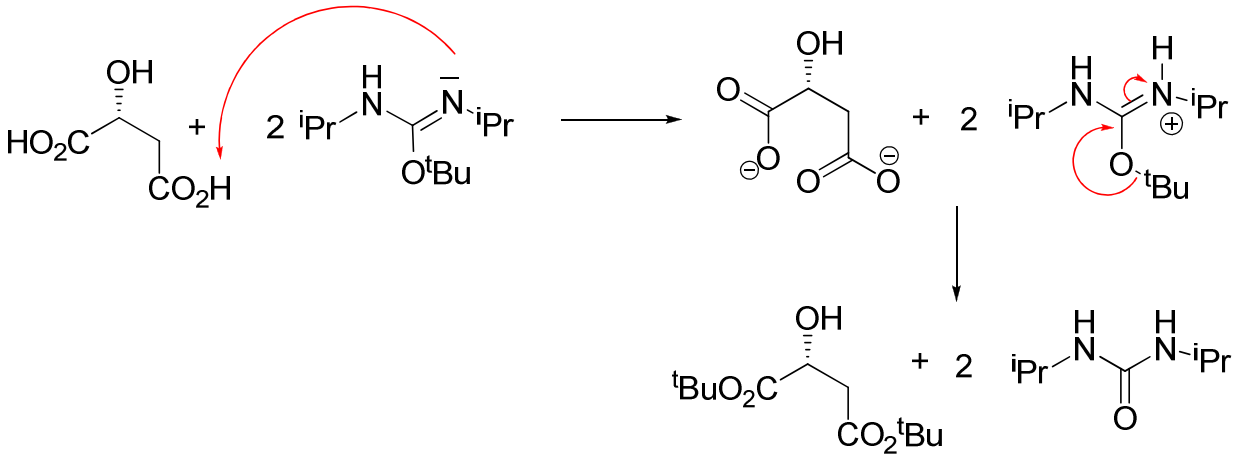




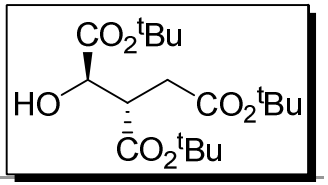
Schützen der freien Säuren



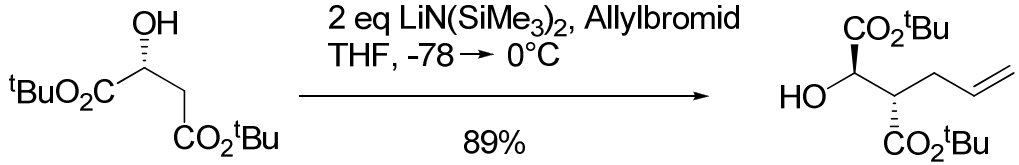
Mechanismusvorschlag



Amer, Takahashi, Ishihara, Hatakeyama, *Heterocycles* **2007**, 72,181-185



Fráter-Alkylierung



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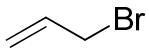
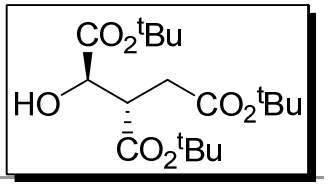
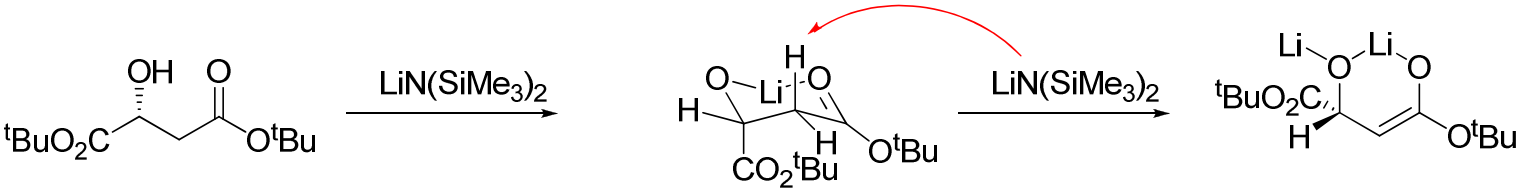
Allylbromid 

Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9698

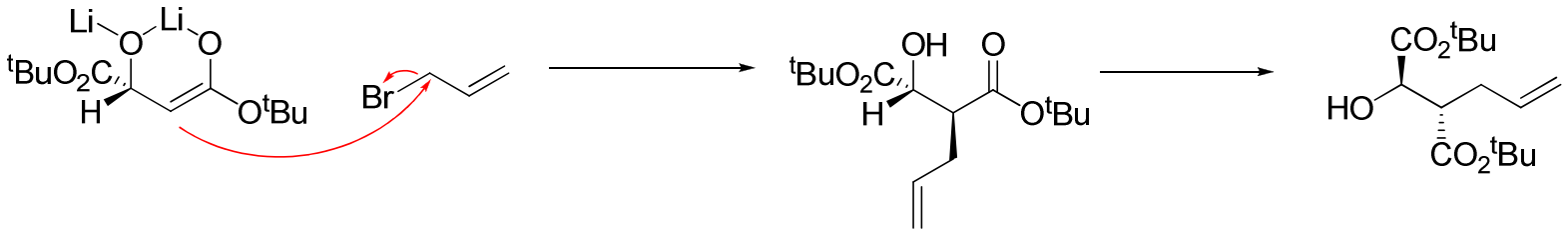


Mechanismus

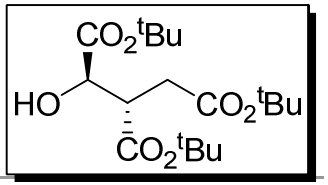
Doppeldeprotonierung



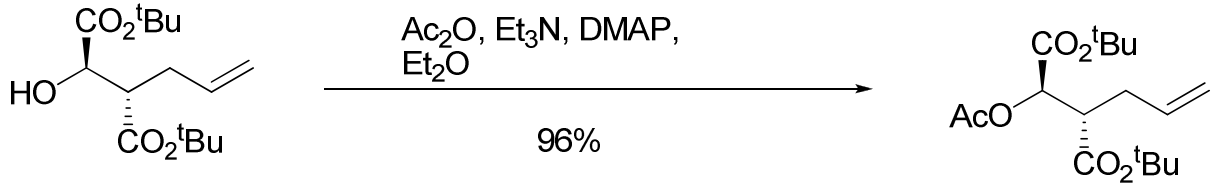
Alkylierung



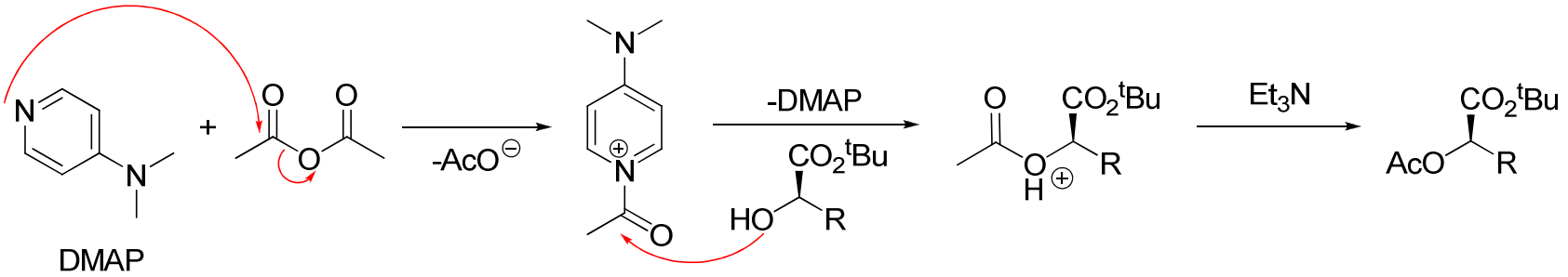
Fráter, *Helv. Chim. Acta,* **1979**, 62, 2825-2828



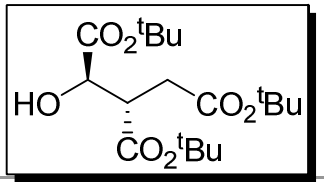
Acetylierung



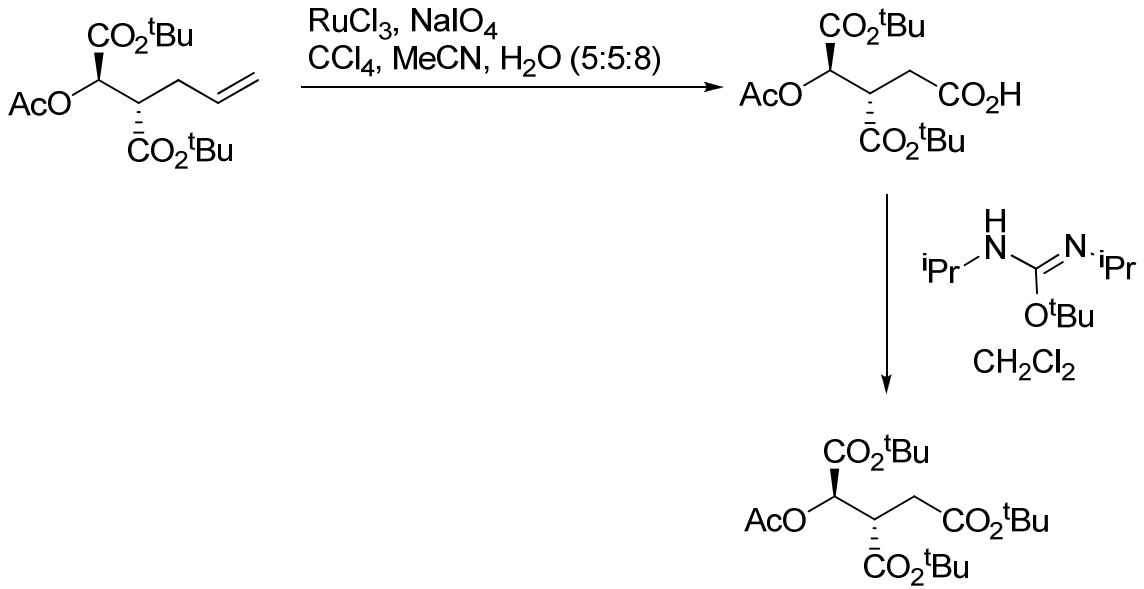
Mechanismus



Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9698
Carey, Sundberg, *„Organische Chemie“*, 1.Auflage, VCH Weinheim, **1995**, 892

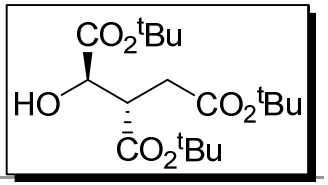


Lemieux-von Rudloff-Oxidation

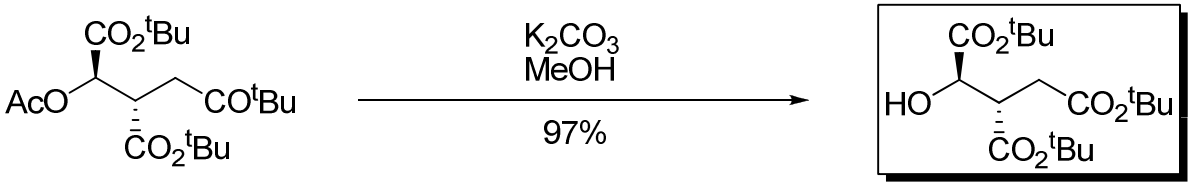


Ausbeute für beide Reaktionen: 75%

Calo, Richardson, Barrett, *J.Org.Chem.* **2008**, 73, 9692
Carlsen, Katsuki, Martin, Sharpless, *J. Org.Chem.* **1981**, 46, 3936-3938

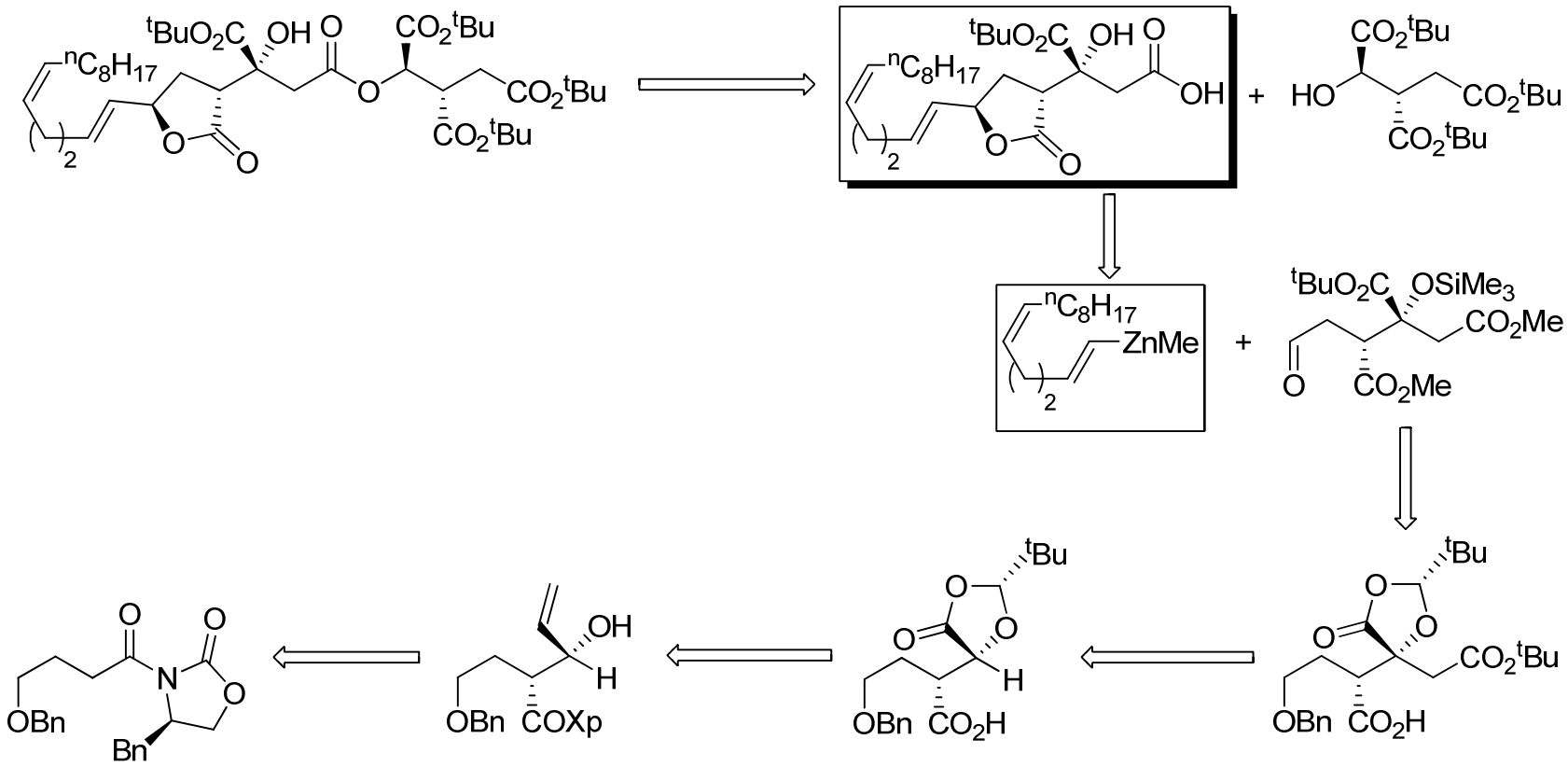


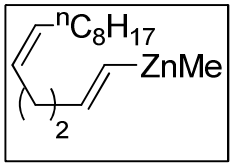
Hydrolyse



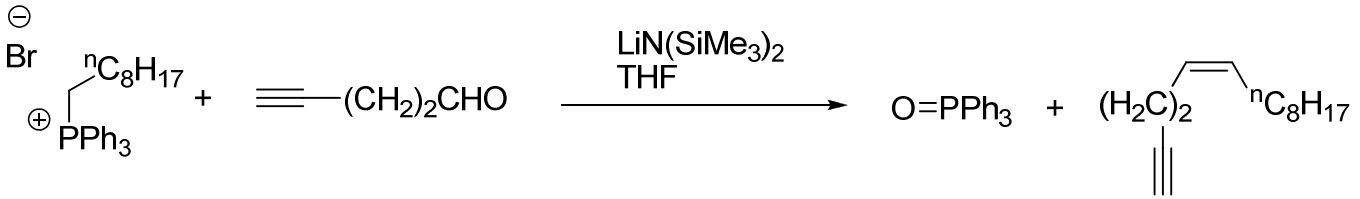
Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9698

7. Synthese der Säure

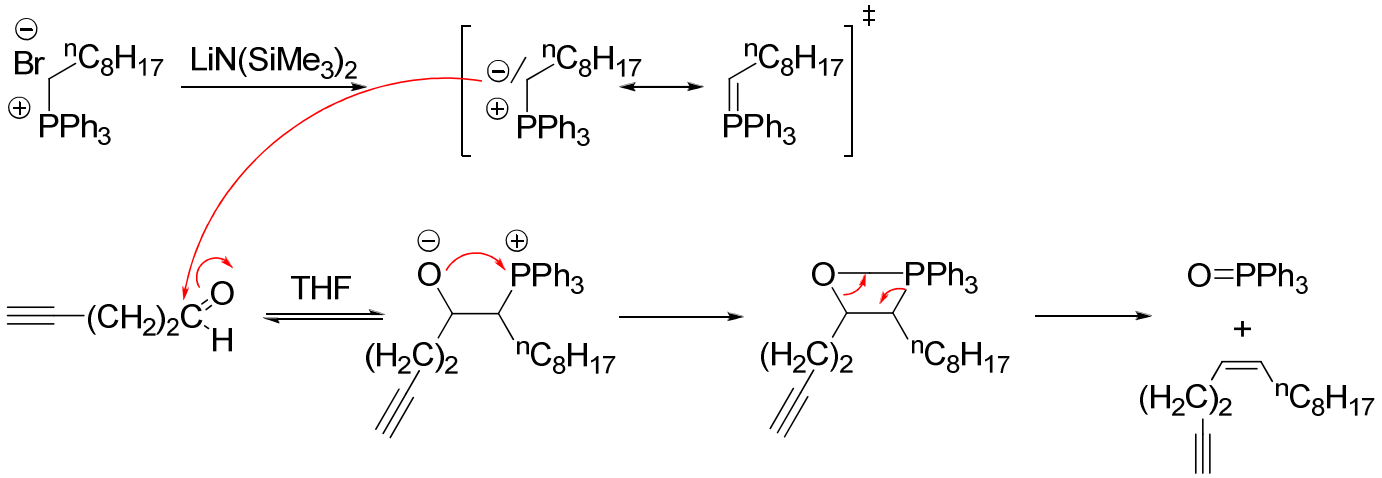




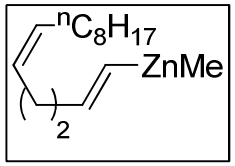
Wittig-Reaktion



Mechanismus



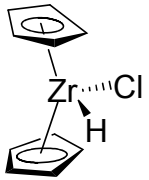
Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9698



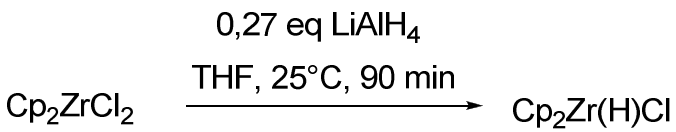
Hydrozirkonierung

Allgemeines

- regio- und stereoselektiv, d.h. Reaktion erfolgt an Doppelbindung bzw. Dreifachbindung und ergibt hauptsächlich das trans-Produkt
- Wird mit Hilfe des *Schwartz*-Reagenzes (Abbildung rechts) durchgeführt
- Ermöglicht die schnelle Addition von Aldehyden, Epoxiden und Isocyanaten

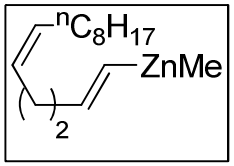


Herstellung des *Schwartz*-Reagenzes:

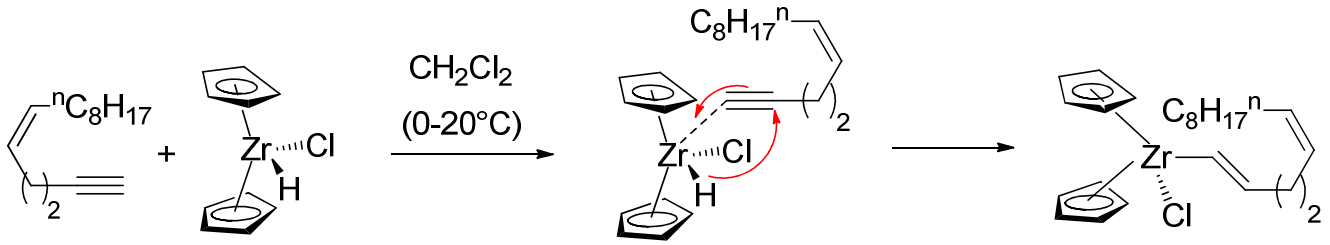


Cp = Cyclopentadienyl

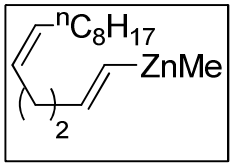
Murakami, Hirono, Furusawa, *Tetrahedron* **2005**, 61, 9233-9241
Hart, Schwartz, *J. Am. Chem. Soc.* **1974**, 96, 8115-8116



Mechanismusvorschlag



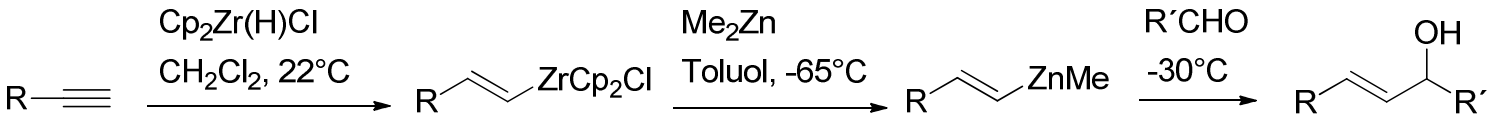
Calo, Richardson, Barrett, *J. Org. Chem.*, **2008**, 73, 9692-9698



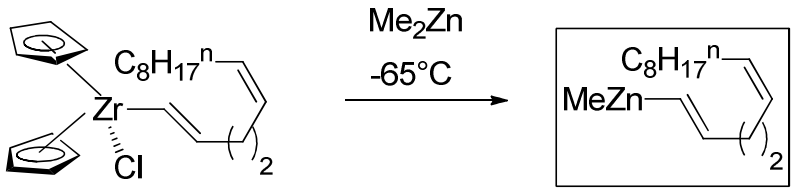
Transmetallierung

- Ergibt selektiv das trans-Produkt
- Erfolgt oft nach Hydrozirkonierung
- Organischer Rest wird von einem Metall auf das Andere übertragen

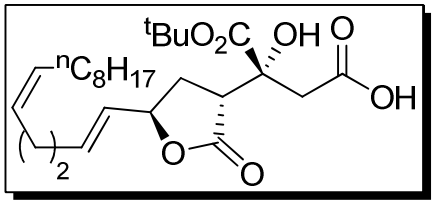
Allgemeines Beispiel:



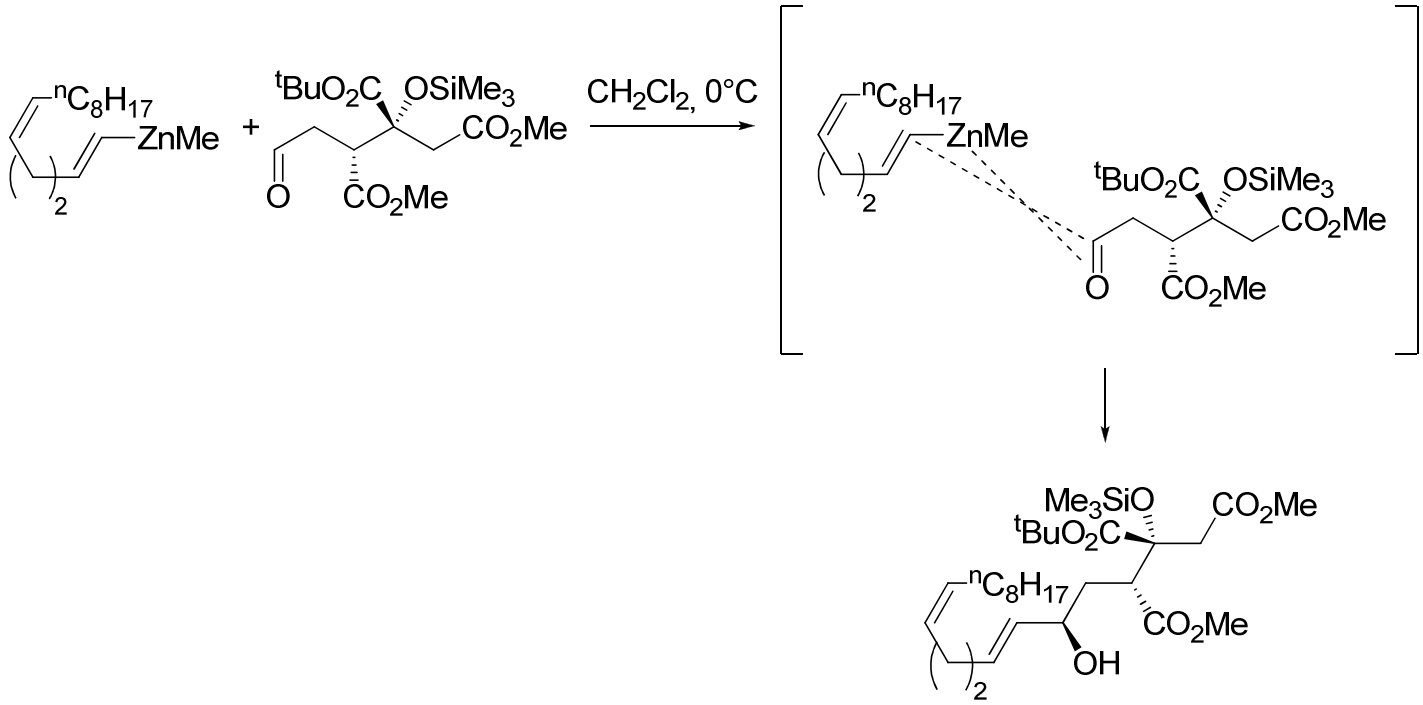
In Citrafungin A - Totalsynthese:



Wipf, Ribe, *J. Org. Chem.* **1998**, 63, 6454-6455
Calo, Richardson, Barrett, *J. Org. Chem.,* **2008**, 73, 9692-9698



Selektive Addition



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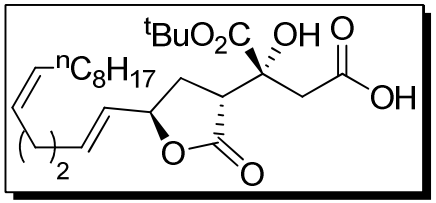

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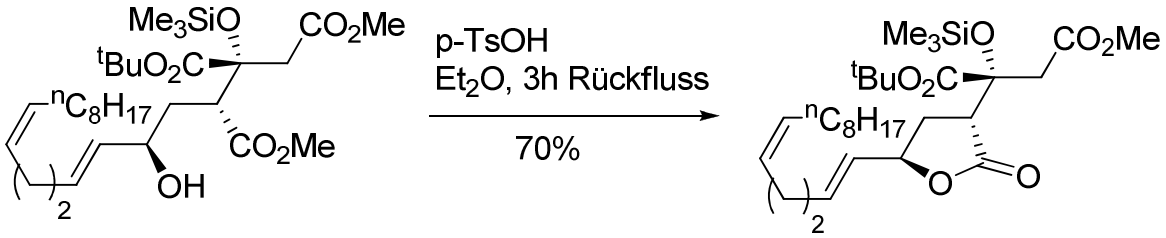

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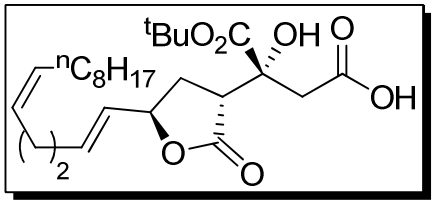
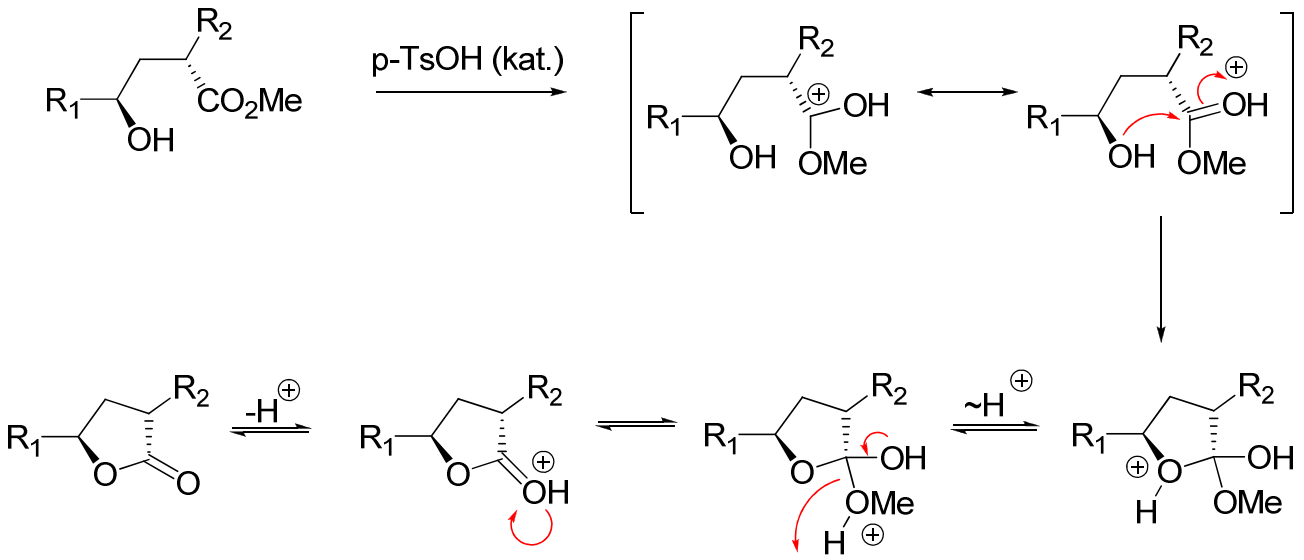
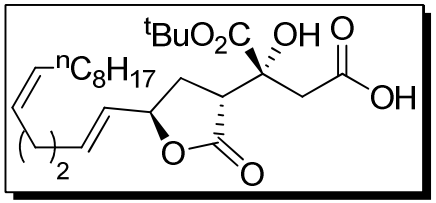
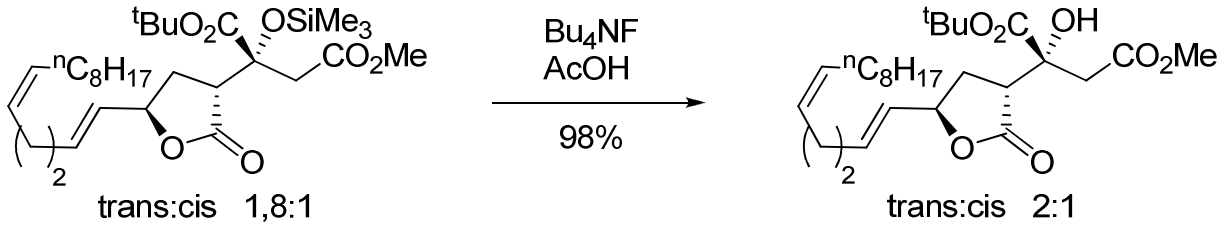


Mechanismus





Spaltung des Silylethers



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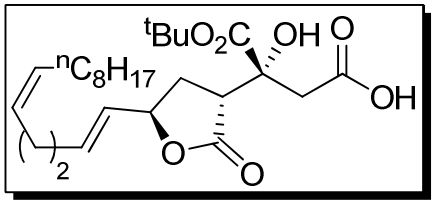

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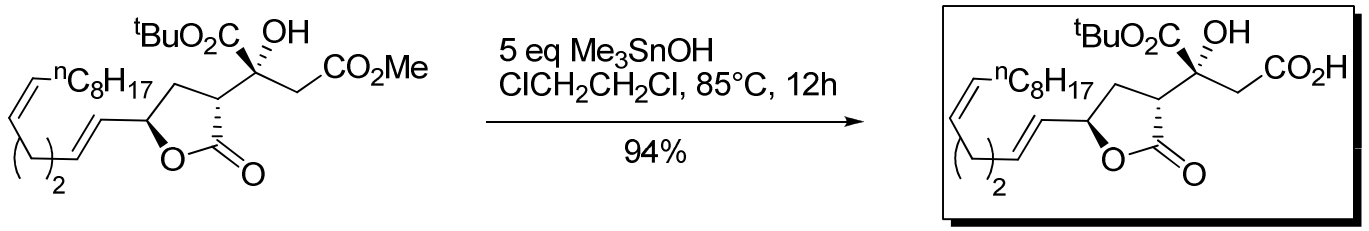

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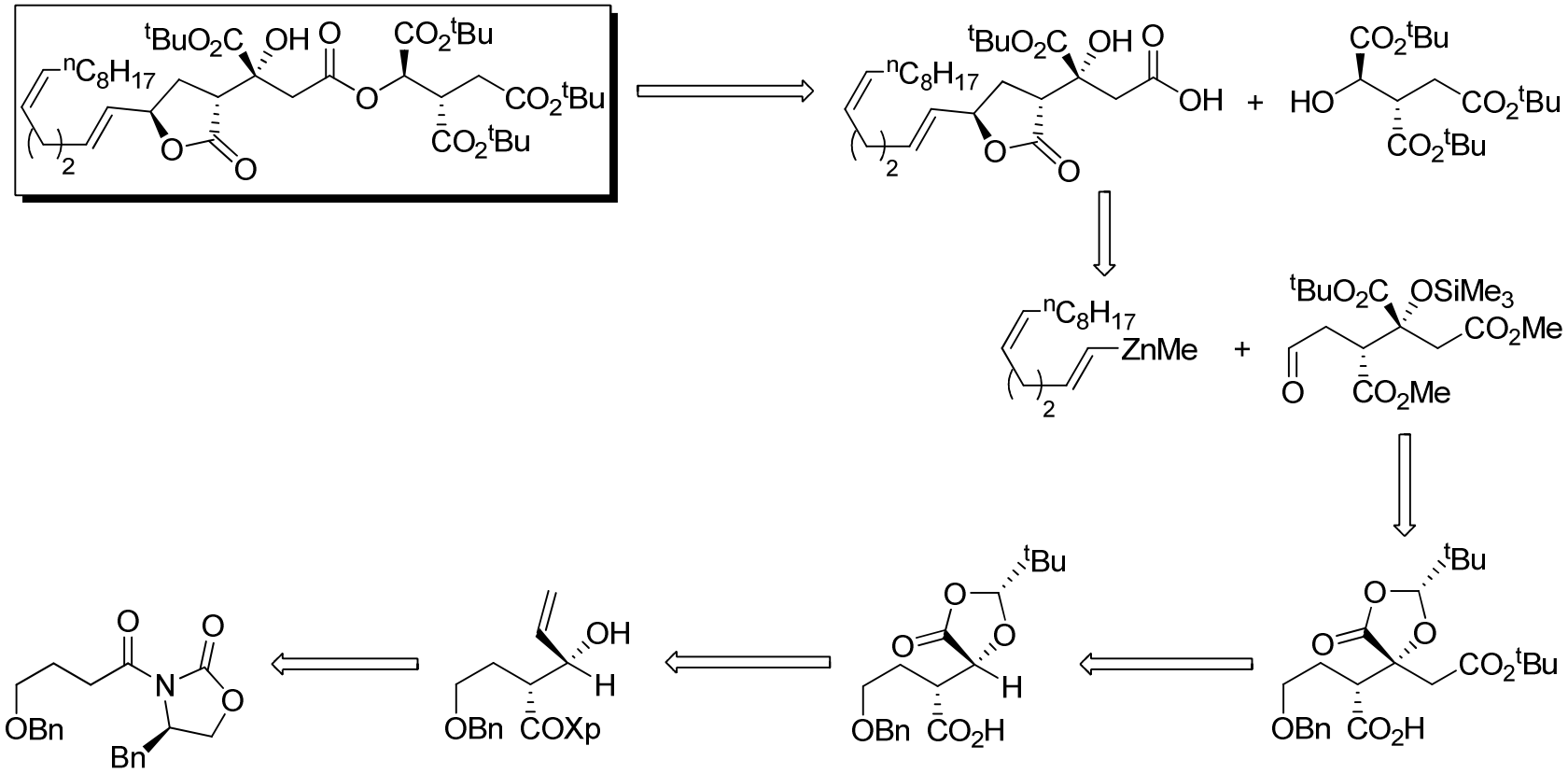
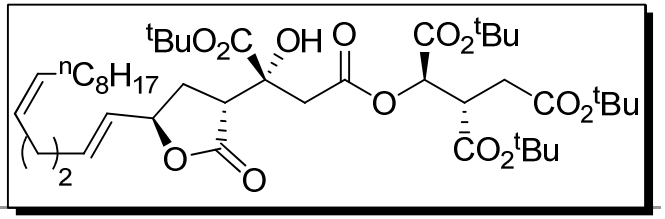
8. Synthese von Citrafungin A





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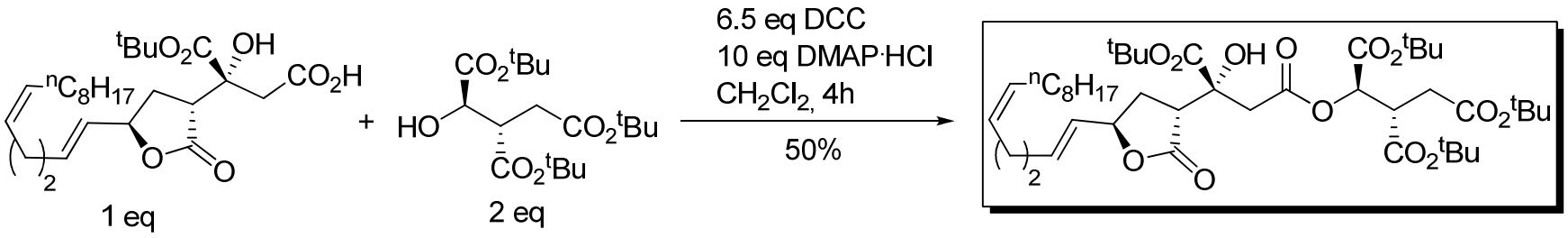

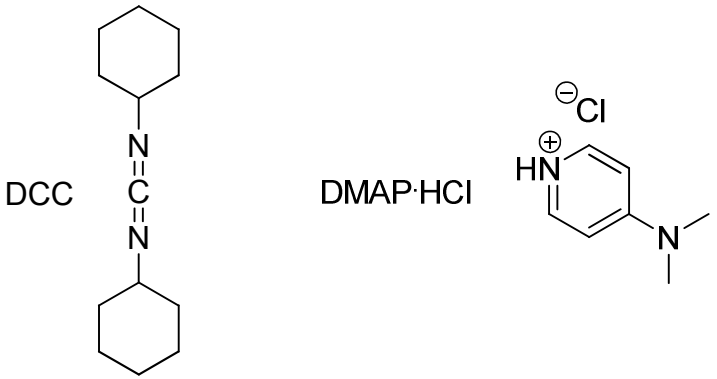

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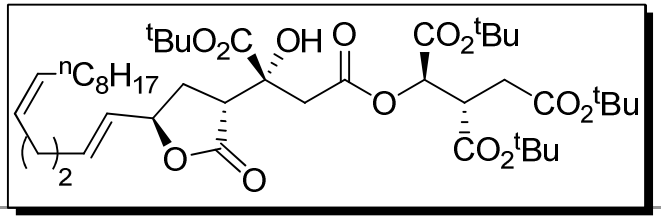
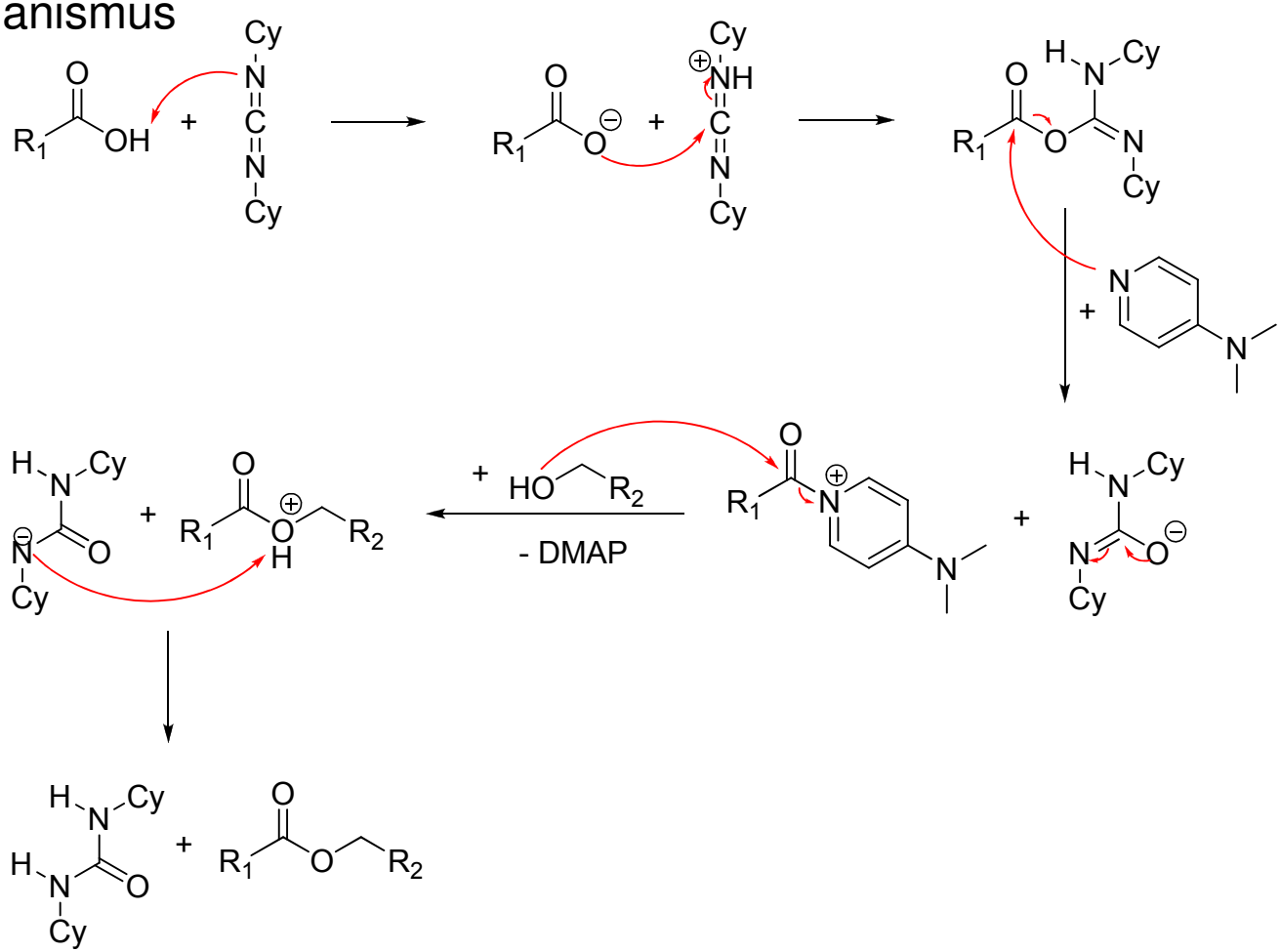
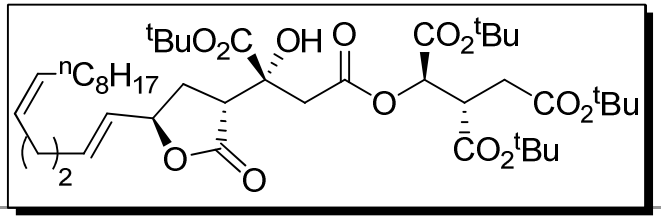


Mechanismus



Brückner, „*Reaktionsmechanismen*“, 3. Auflage, Spektrum Akademischer Verlag, **2004** , 313-314



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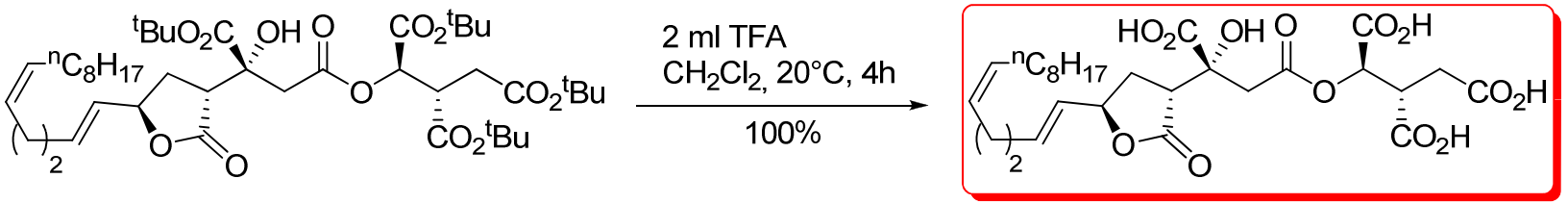

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10. Abkürzungsverzeichnis

°C	Grad Celsius	h	Stunde(n)
Ac	Acetat	IC	Mittl. Inhibitorische Konzentration
Bn	Benzyl	kat.	katalytisch
^{t}Bu	tert-Butyl	TMSCl	Trimethylsilylchlorid
Bu	Butyl	Min	Minuten
Tf	Trifyl	Me	Methyl
Cp	Cyclopentadienyl	MIC	Minimale Hemm-Konzentration
Cy	Cyclohexyl	p-TsOH	para-Toluensulfonsäure
DCC	N,N'-Dicyclohexylcarbodiimid	^{i}Pr	iso-Propyl
DMAP	4-(Dimethylamino)-pyridin	R	Rest
DMF	N,N-Dimethylformamid	RT	Raumtemperatur
eq.	Äquivalente	TFA	Trifluorethansäure
Et	Ethyl	THF	Tetrahydrofuran
GGTase	GeranylgeranylTransferase	Xp	(R)-4-Benzyl-2-oxazolidinon