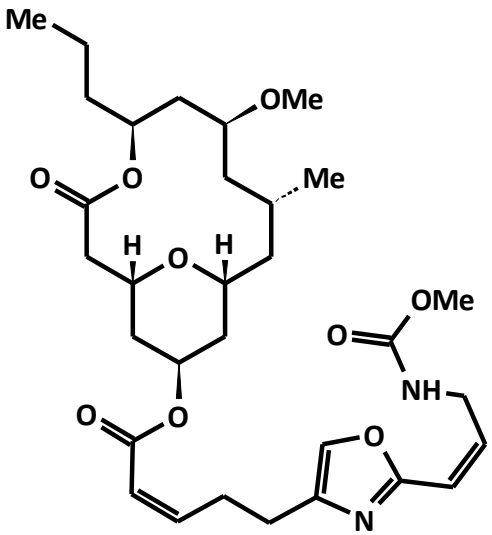
TECHNISCHE UNIVERSITÄT DRESDEN

Totalsynthese von (+)-Neopeltolid

nach Sasaki et al.



S. Freitag, A. Wolf, P. Strubel,
K. Schnaars, R. Zimmermann

H. Fuwa, A.Saito, M. Sasaki, Angew. Chemie 2010, 122, 3105-3108

1. Allgemeines

Entdeckung

- 2007 Amy E. Wright…Entnahme zweier Proben eines Schwammes der Gattung Daedalopelta an Nordwestküste Jamaicas in Meerestiefe von 400 m
- über Vakuum-Säulen-Chromatografie konnte Neopeltolid als farbloses Öl gewonnen werden
- Struktur der unbekannten Substanz konnte mittels spektroskopischer Untersuchungen aufgeklärt werden

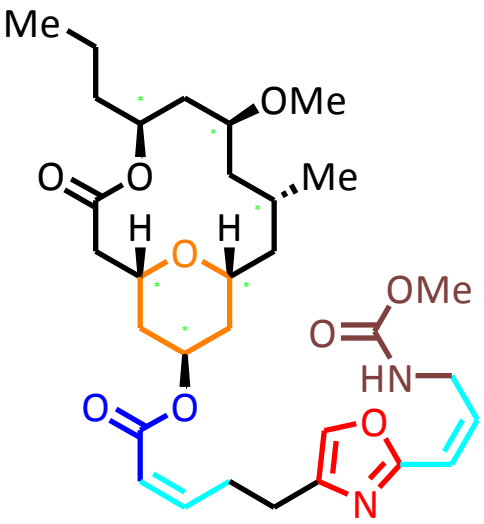
Verwendung

- Neopeltolid inhibiert A-549 Lungen-Adenokarzinom (IC_{50}=1,2 nM)
- Inhibition der mitochondrialen ATP-Synthese

A. E. Wright, *J. Nat. Prod.* 2007, 70, 412-416

1.1 Strukturmerkmale

- **14-gliedriges Makrolacton**
- **dreifach substituierte 2,6-cis-Tetrahydropyran-Untereinheit**
- **sechs stereogene Zentren**
- **C_5 acylierte mit oxazol-und carbamathaltige Seitenkette**
- **Z-Konfigurierte Doppelbindungen**

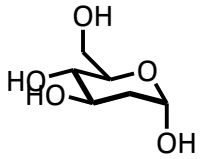


Viktor V. Vintonyak, Martin E. Mayer, *Org. Let.* 2008, 10, 1239-1242

1.2 Blockierung der ATP-Synthese

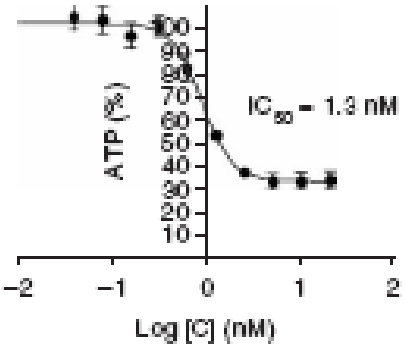
- **zunächst konnte effektive Zellwachstumsblockierung in Hefe durch Verbindung mit Galactose oder Glycerin festestellt werden**
- **gentechnische Analysen…Schlussfolgerung: evtl. Blockierung der ATP-Synthese**
- **vier Komplexe in der Atmungskette konnten beteiligt sein, Auswertungen wiesen auf Cytochrom bc1-Komplex als zelluläres Target**

2-Desoxy-D-glucose (2-DG):

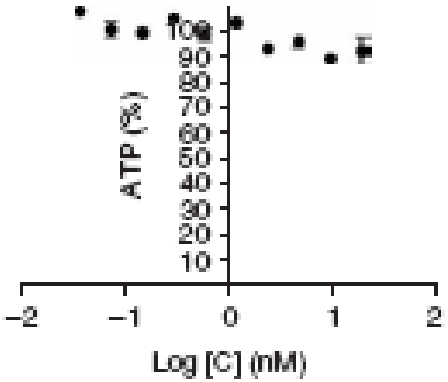


Inhibition von A549-Zelllinie

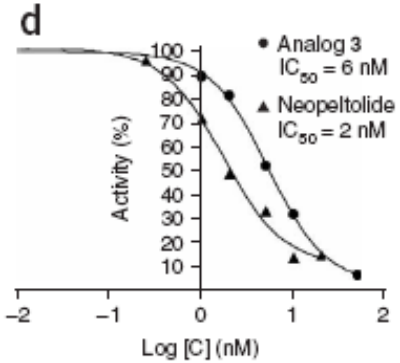
- in Gegenwart von 2-DG



- in Abwesenheit von 2-DG



Enzymatische Aktivität des bc1-Komplexes



S. A. Kozmin, *nat. chem. bio.* 2008, 4, 418

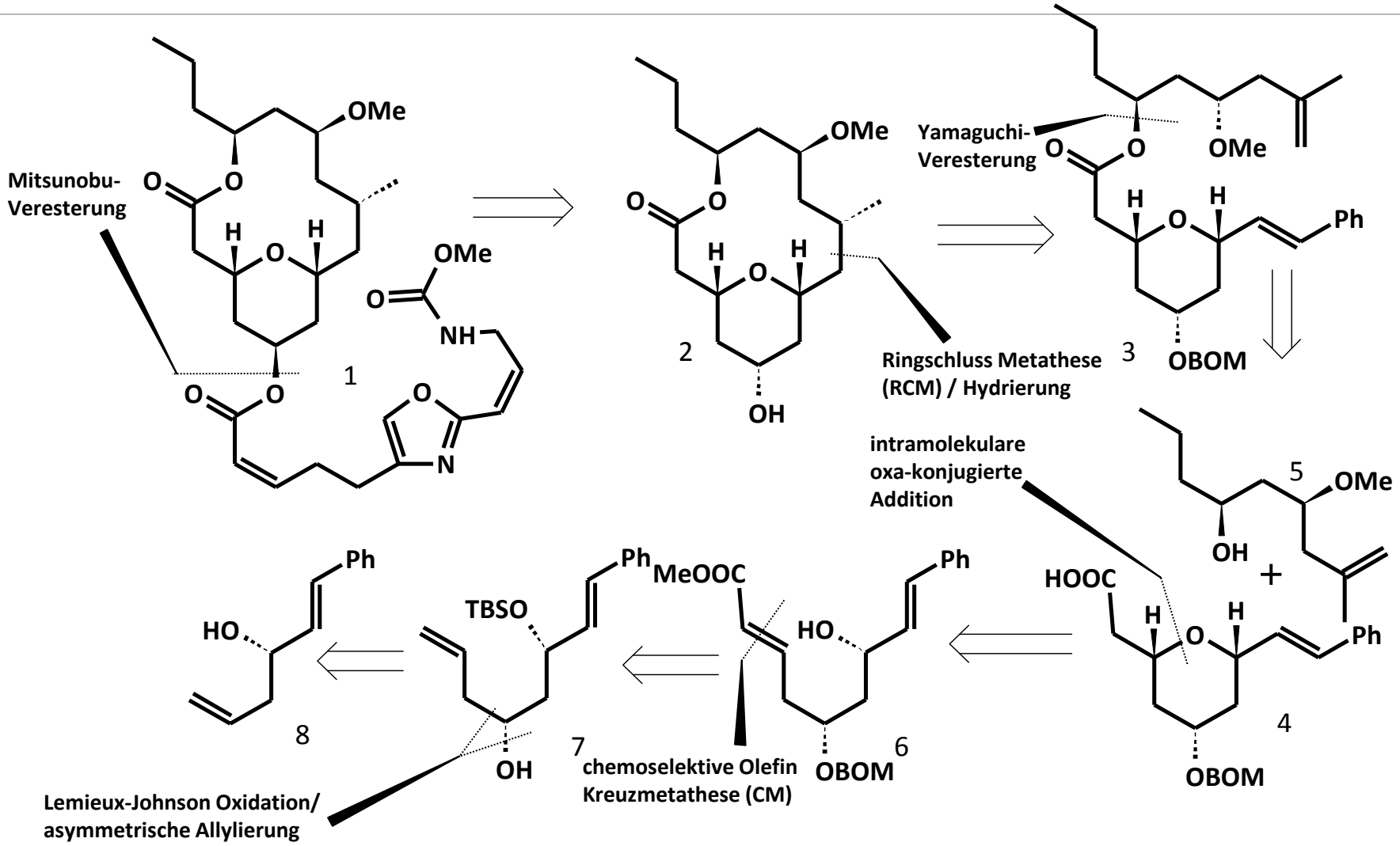
1.3 Stoffgruppe Makrolacton

- **enthalten intramolekulare Estergruppe**
- **entstehen aus Hydroxycarbonsäuren unter Wasserabspaltung**
- **in der Regel spricht man ab 13 Ringgliedern von einem Macrolacton**
- **Makrocyclen mit Lactonfunktion sind wegen möglicher biologischer oder pharmazeutischer Wirkung bedeutende Zielstrukturen**
- **traditionelle Cyclisierungen: Yamaguchi-Reaktion, Mitsunobu-Reaktion**

Reinhard Brückner, *Reaktionsmechanismen*, 3. Auflage, S. 297

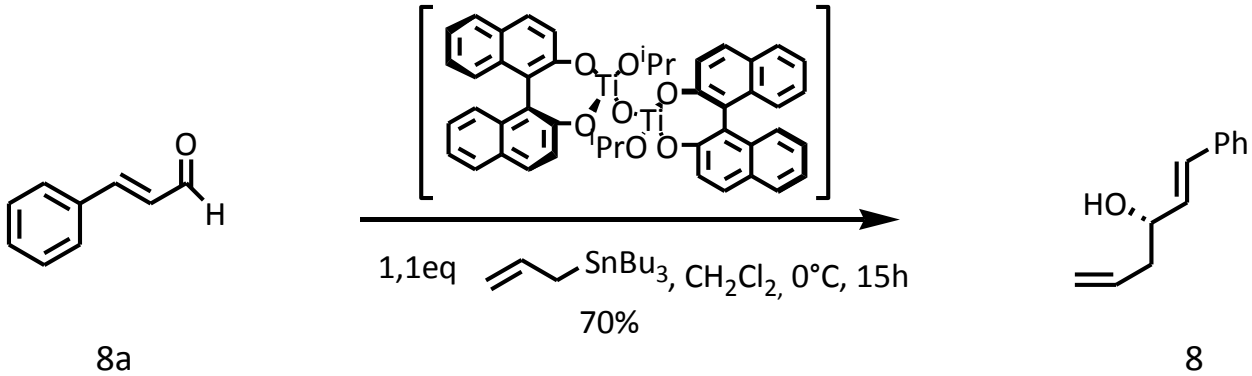
E. A. Crane, K. A. Scheidt, *Angew. Chem.* 2010, 122, 8494

Retrosynthese



H. Fuwa, A. Saito, M. Sasaki, Angewandte Chemie International Edition 2010, 49, 3041-3044

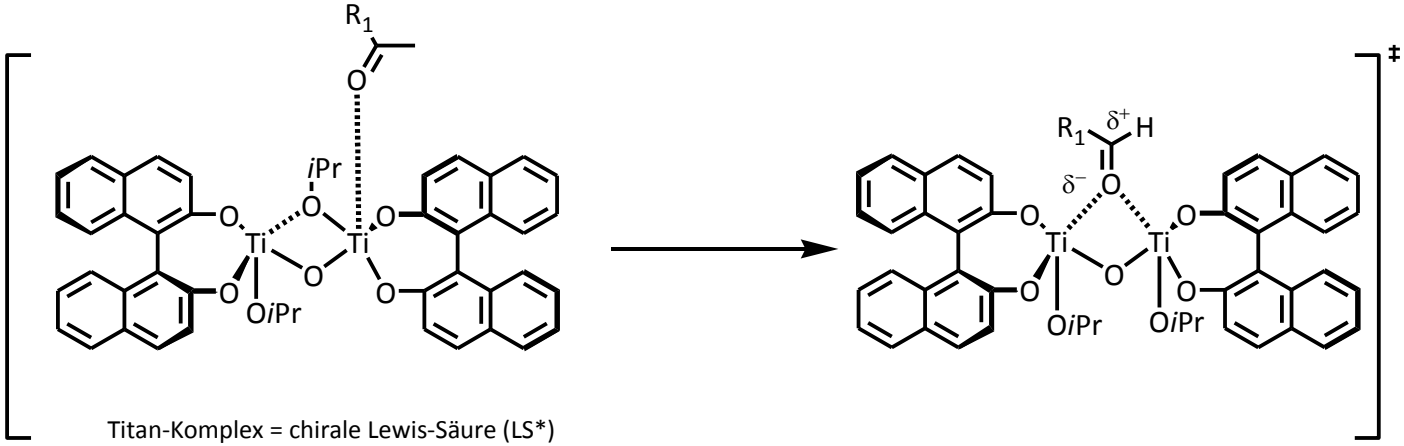
Katalytische asymmetrische Allylierung



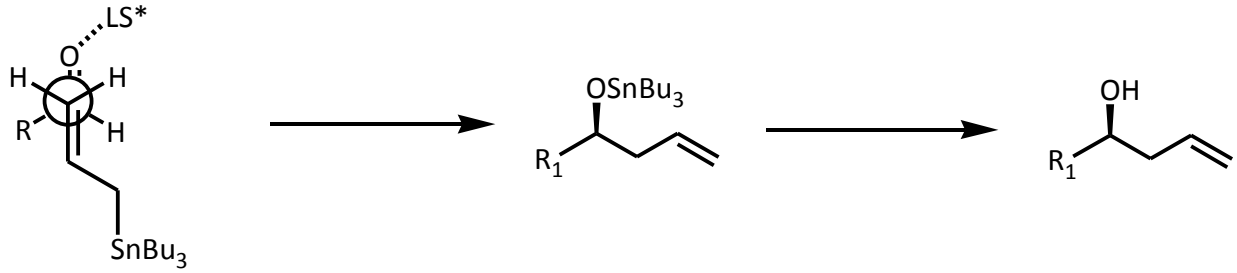
H.Hanawa, K. Maruoka, *Chem. Eur. J.* 2003, 9, 4405-4413
K.Maruoka, *Pure Appl. Chem.* 2002, 74, 123-128
S. E. Denmark, J. R. Heemstra, *Angew. Chem.* 2005, 117, 4760-4777

Katalytische asymmetrische Allylierung

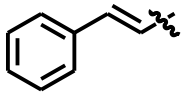
Mechanismusvorschlag:



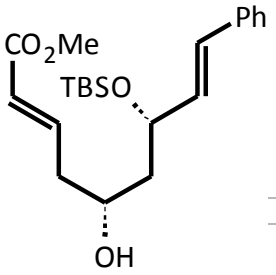
offener Übergangszustand



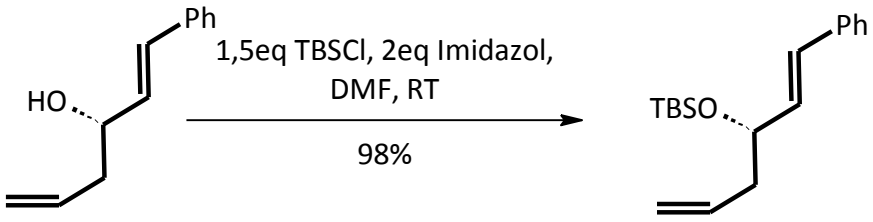
R_1 =



(2E,5R,7S,8E)-5,7- Dihydroxy-9-phenylnona-2,8-diensäure



Einführung einer Silyletherschutgruppe



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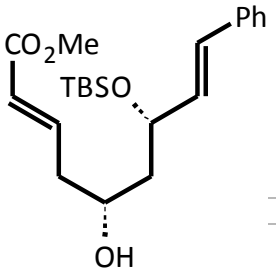
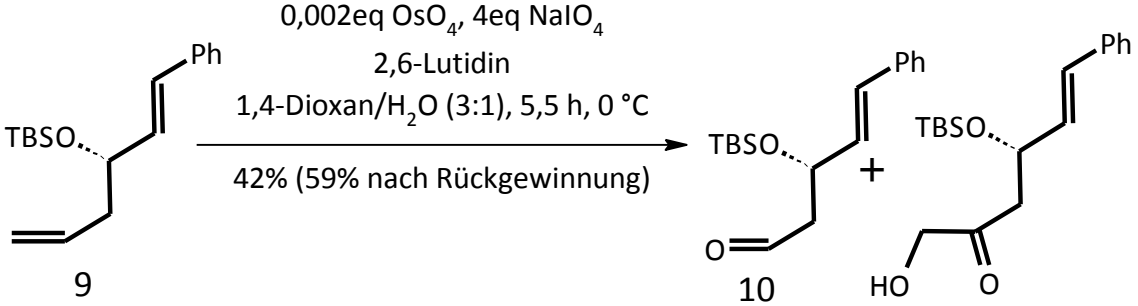
- **Einführung einer sterisch großen Silylether-Schutzgruppe**
- **Verhindert Eliminierung**
- **Doppelbindung angrenzend zur Phenylgruppe wird sterisch abgeschirmt**

J. Robertson, Protecting Group Chemistry, 1. Auflage, Oxford Univ. Press, 2002, 74ff.
A. Barthel, D. Bauer, H. Brinkmann, P. Forster, S. Gebke, P. Gotze, „Schutzgruppen“, OCIII, Vortrag gehalten am 04.11.2010

(2E,5R,7S,8E)-5,7- Dihydroxy-9-phenylnona-2,8-diensäure

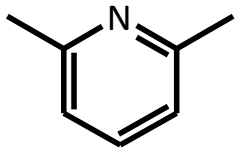


Chemoselektive und oxidative Spaltung von Olefinen



Nebenprodukt (ca. 29%)

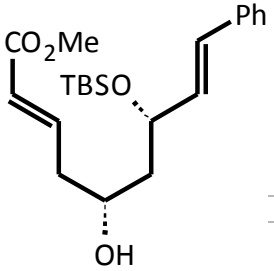
- **chemoselektive Spaltung der endständigen Doppelbindung**
  - **erst Dihydroxylierung**
  - **anschließend oxidative Spaltung**
- **Rückgewinnung von 29 % Edukt**
- **verbesserte Methode zur klassischen** *Lemieux-Johnson*-**Oxidation nach** *Wensheng Yu, Yan Mei, Ying Kang, Zhengmao Hua, and Zhendong Jin*
  - **Unterdrückung von Nebenprodukten**
  - **höhere Ausbeute**
- **2,6-Lutidin fungiert als schwache Base**
  - **Ligandenbeschleunigung durch Adduktbildung mit OsO_4**



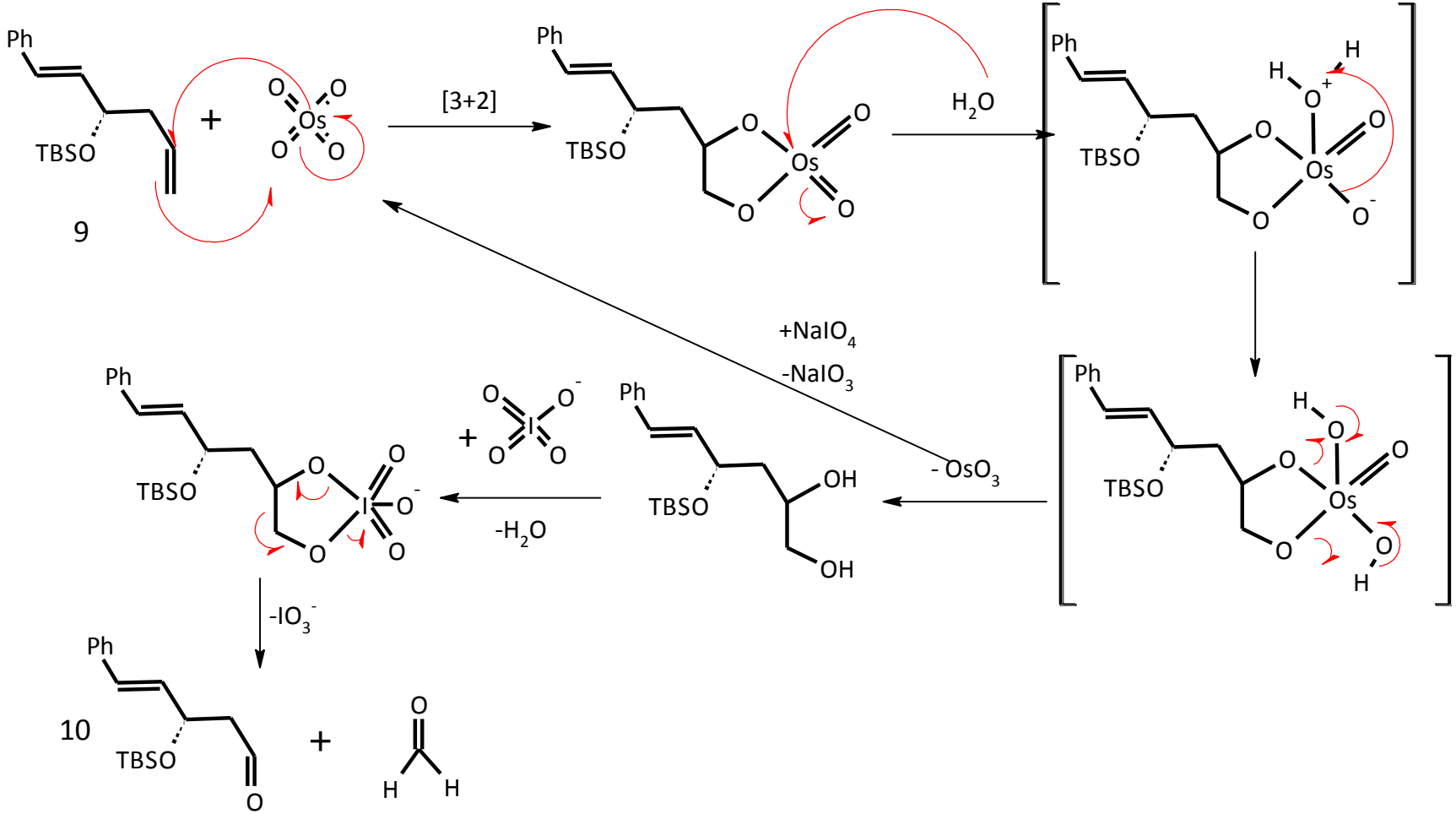
2,6-Lutidin

R. Brückner, Reaktionsmechanismen, 3. Auflage, Spektrum Akademischer Verlag, 2009, S.760f.
W. Yu, Y. Mei, Y. Kang, Z. Hua, ORGANIC LETTERS, 2004, Vol. 6, No. 19, 3217-3219

(2E,5R,7S,8E)-5,7- Dihydroxy-9-phenylnona-2,8-diensäure



Mechanismusvorschlag:



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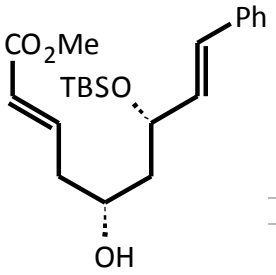
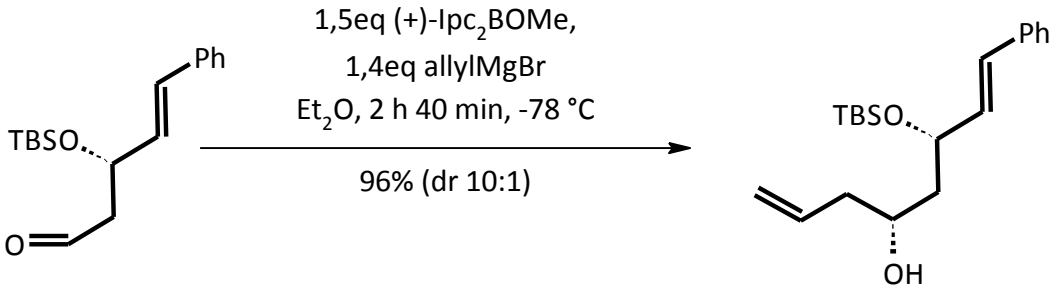


Asymmetrische Allylierung

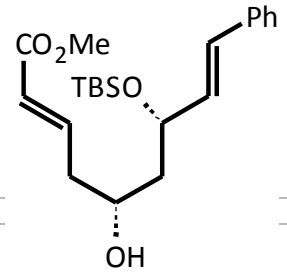


10 11

- **stereoselektive Allylierung am Aldehyd nach** *Brown und Jadhav*
- **stereogene Information erzeugt duch die Isopinocampheol-Liganden**
- **Erzeugung der reaktiven Komponente in situ**
- **Reaktion über einen sechsgliedrigen Übergangszustand**

H. C. Brown, P. K. Jadhav, J . Am. Chem. Soc., 1983, 105, 2092-2093

(2E,5R,7S,8E)-5,7- Dihydroxy-9-phenylnona-2,8-diensäure



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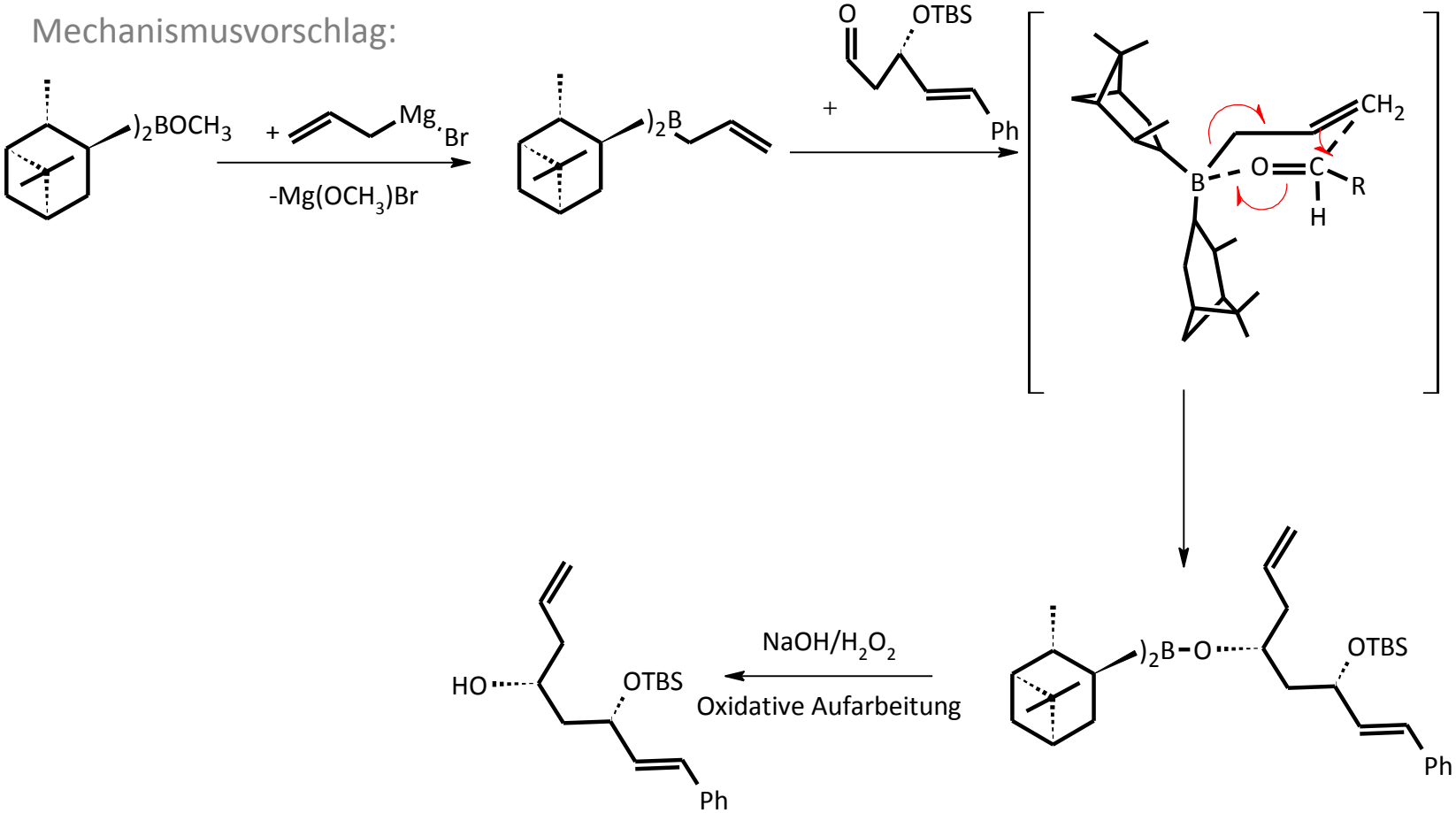

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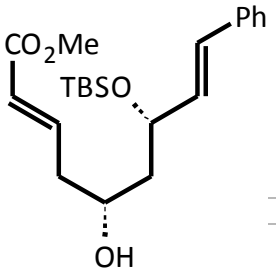
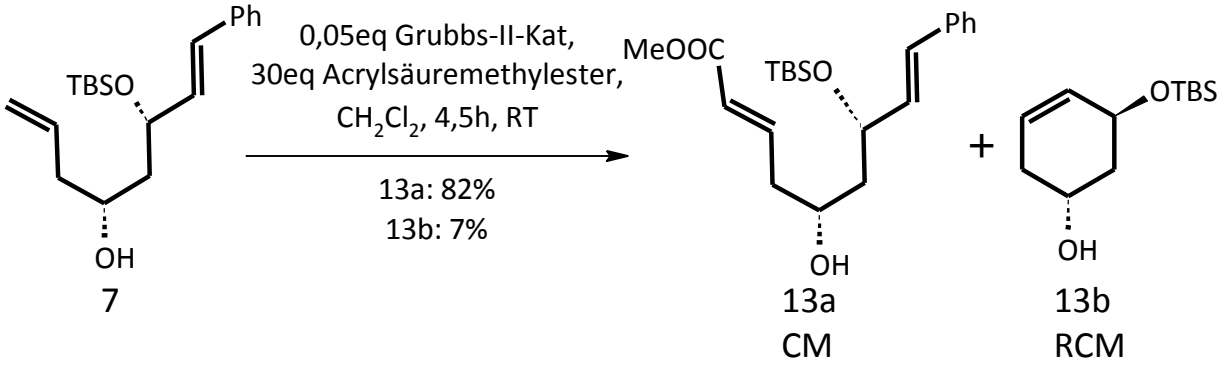


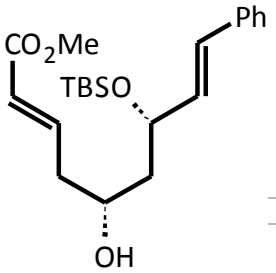
Chemoselektive Olefin-Kreuzmetathese



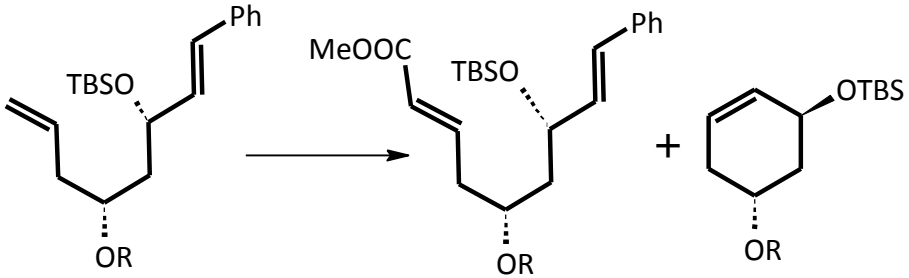
- **E-selektive Olefin-Kreuzmetathese an der endständigen, elektronenreichen Doppelbindung mit einem elektronenarmen Acrylsäure-Derivat**
- **Ziel: Unterdrückung der Konkurrenzreaktion, der Ringschlusskreuzmetathese**
- **Untersuchungen zur Wahl des richtigen Katalysators**
  - ***Grubbs*- Katalysator der 2. Generation oder *Hoveyda-Blechert*- Katalysator der 2. Generation**
- **Variierung der Reaktionsparameter**
  - **Entdeckung einer dirigierenden Wirkung der Hydroxygruppe**
  - **30-facher Überschuss an Acrylsäuremethylester**

H. Fuwa, A. Saito, M. Sasaki, Angew. Chem. 2010, 122, 3105
C. Keßler, F. Borrmann, C. Eckholdt, D. Gieseler, P. Jehnichen, I. Beyer, „Olefinmetathese“, OCIII, Vortrag gehalten am 18.11.2010

(2E,5R,7S,8E)-5,7- Dihydroxy-9-phenylnona-2,8-diensäure



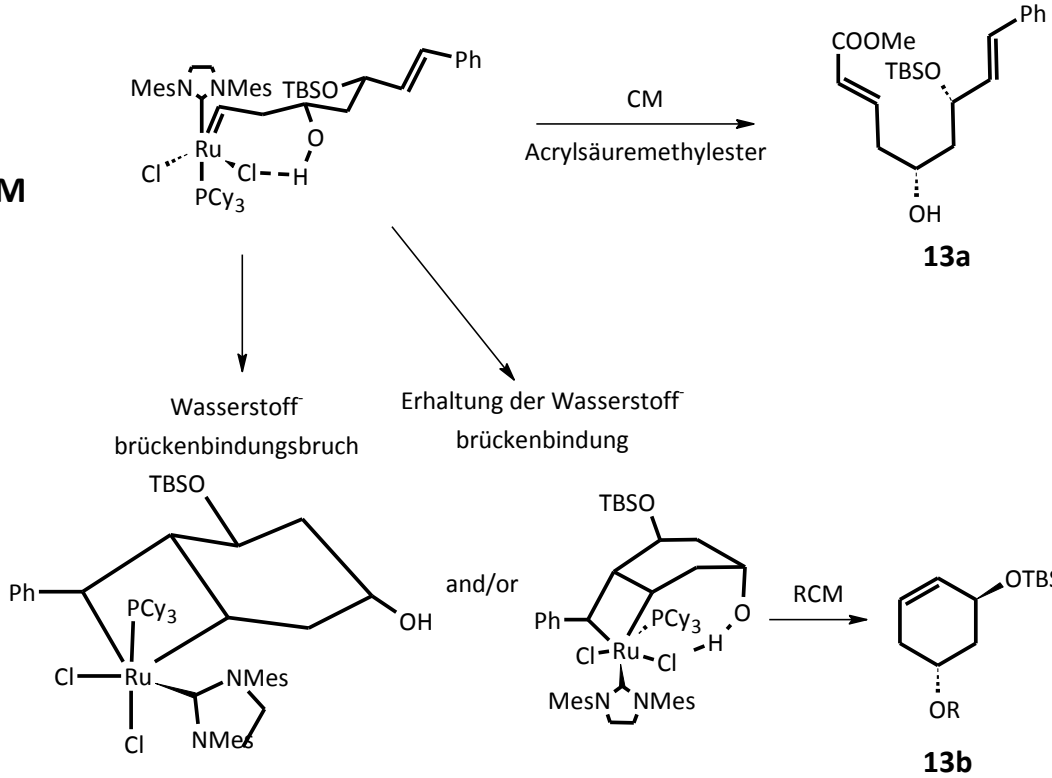
- Variierung der Reaktionsparameter



11: R= BOM **12a: R= BOM** **12b:R= BOM**
7: R= H **13a: R= H** **13b:R= H**

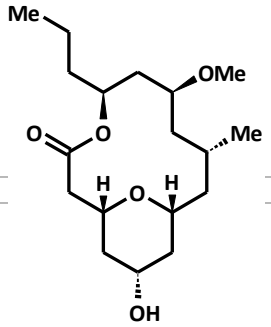
Substrat	Reaktions Parameter	Ausbeute	
11	20 eq Acrylsäure-methylester, CH_2Cl_2	12a, 25%	12b, 71%
11	Acrylsäuremethyl-ester, Toluol (1:1)	12a, 51%	12b, 46%
7	Acrylsäuremethyl-ester, CH_2Cl_2 (1:1)	13a, 77%	13b, 7%
7	30 eq Acrylsäure-methylester, CH_2Cl_2	13a, 82%	13b, 7%

- Zwischenprodukt während der Kreuzmetathese

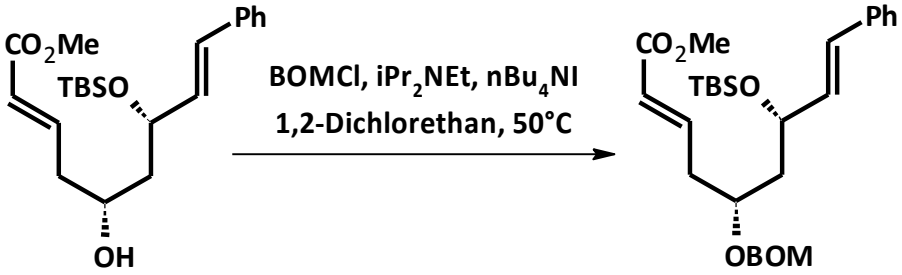


H. Fuwa, A. Saito, M. Sasaki, Angew. Chem. 2010, 122, 3105

Synthese des Macrocyclus 2

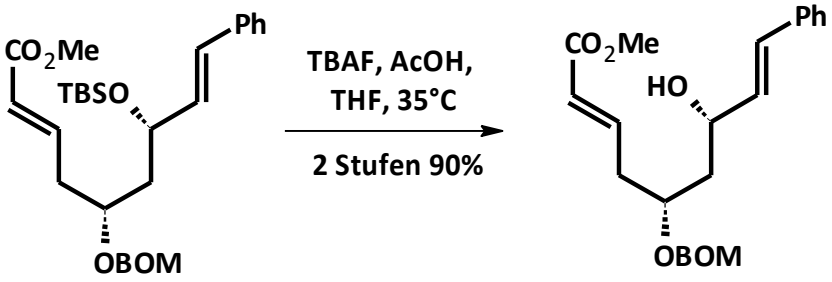


Schutz des Alkohols



13a 12a

Desilylierung



12a 6

H. Fuwa, A. Saito, M. Sasaki, *Angew. Chemie* 2010, 122, 3105-3108

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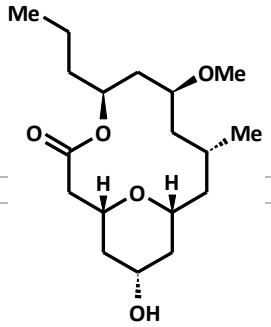
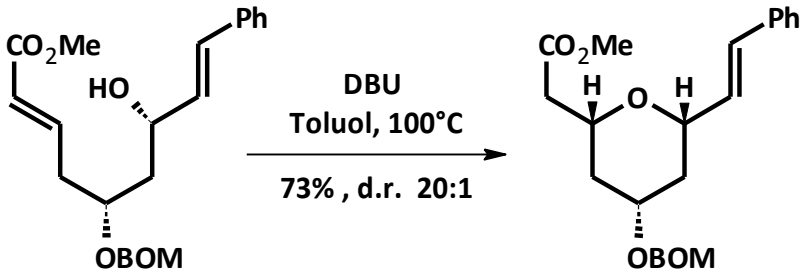


intramolekulare oxakonjugierte Addition



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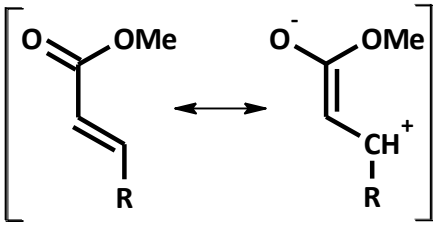
mesomere Greenzformel:



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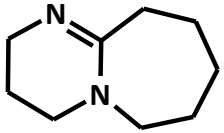
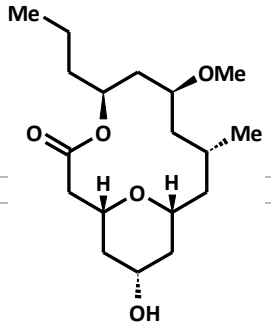
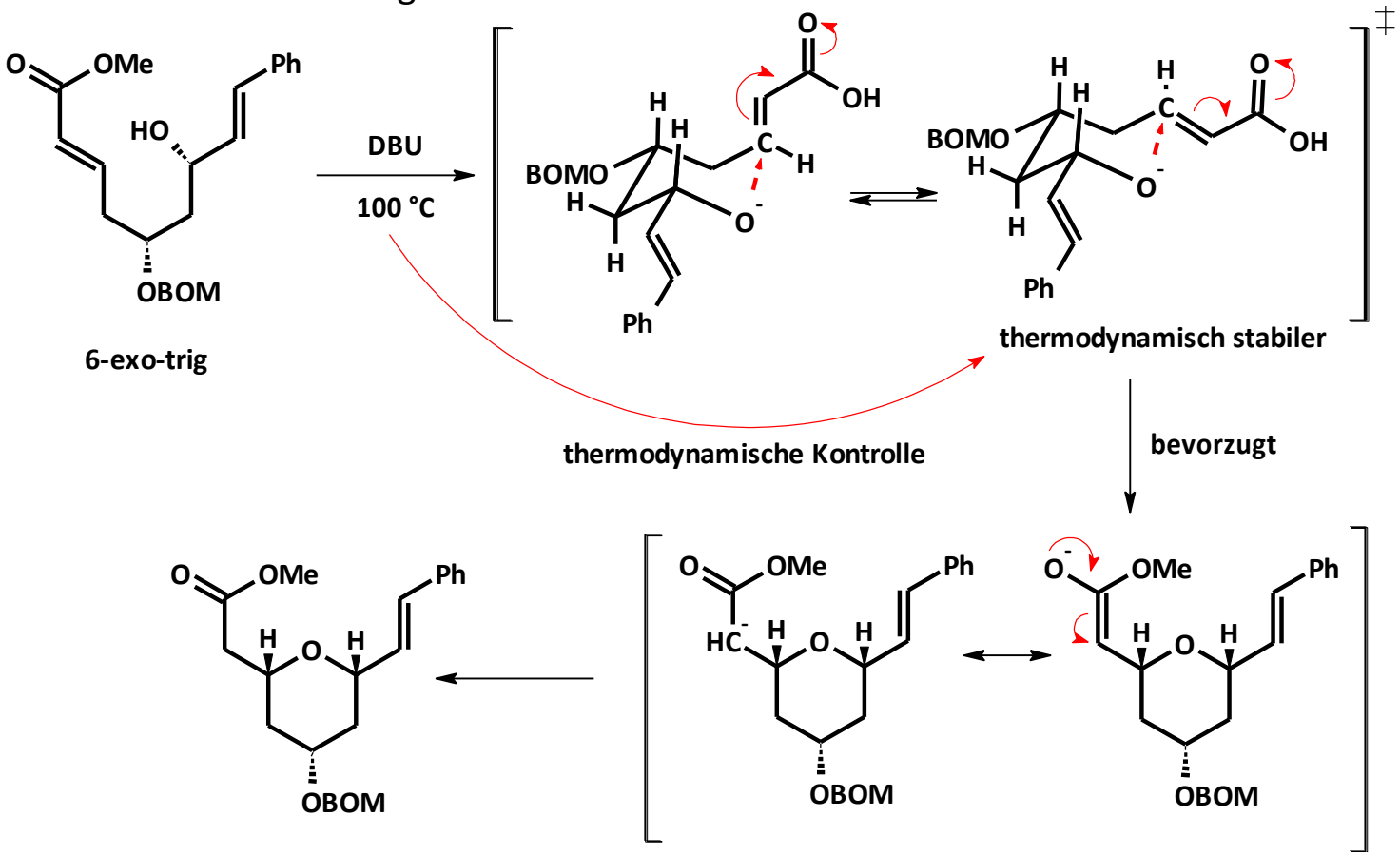


H. Fuwa, A. Saito, M. Sasaki, *Angew. Chemie* 2010, 122, 3105-3108

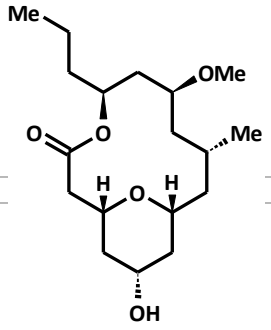
Synthese des Macrocyclus 2



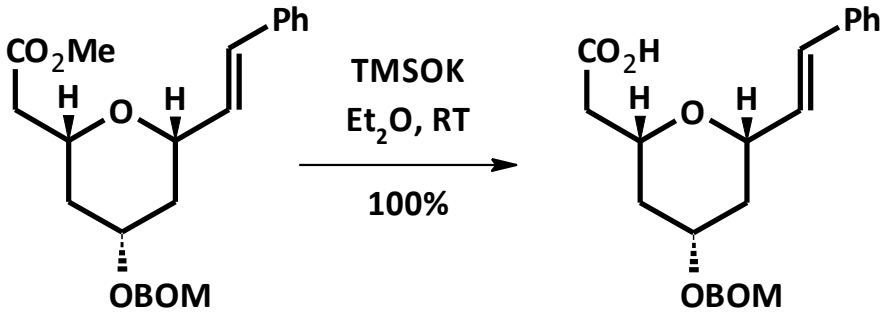
Mechanismusvorschlag:



Synthese des Macrocyclus 2



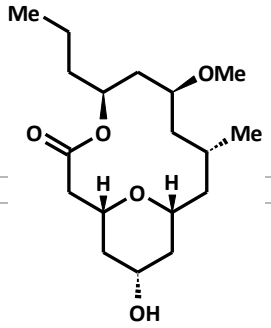
Hydrolyse des Esters



14 4

H. Fuwa, A. Saito, M. Sasaki, *Angew. Chemie* 2010, 122, 3105-3108
E. D. Laganis, B. L. Chenard, *Tetrahedron Lett*. 1984, 25, 583.

Synthese des Macrocyclus 2



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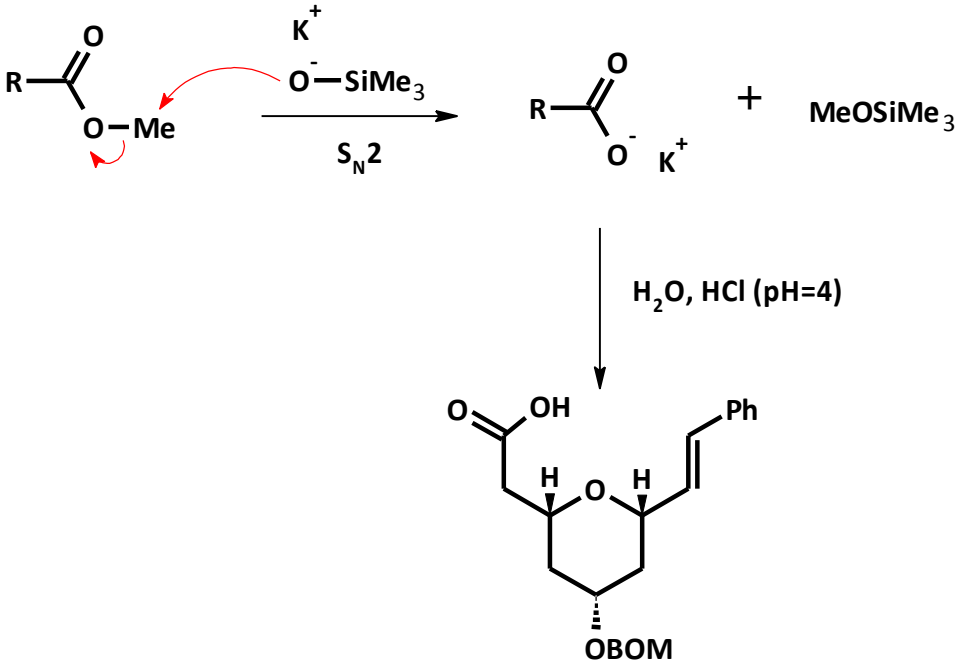

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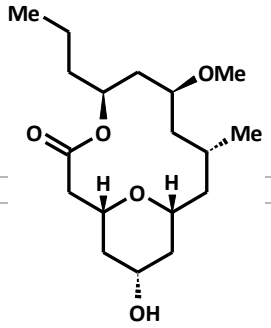
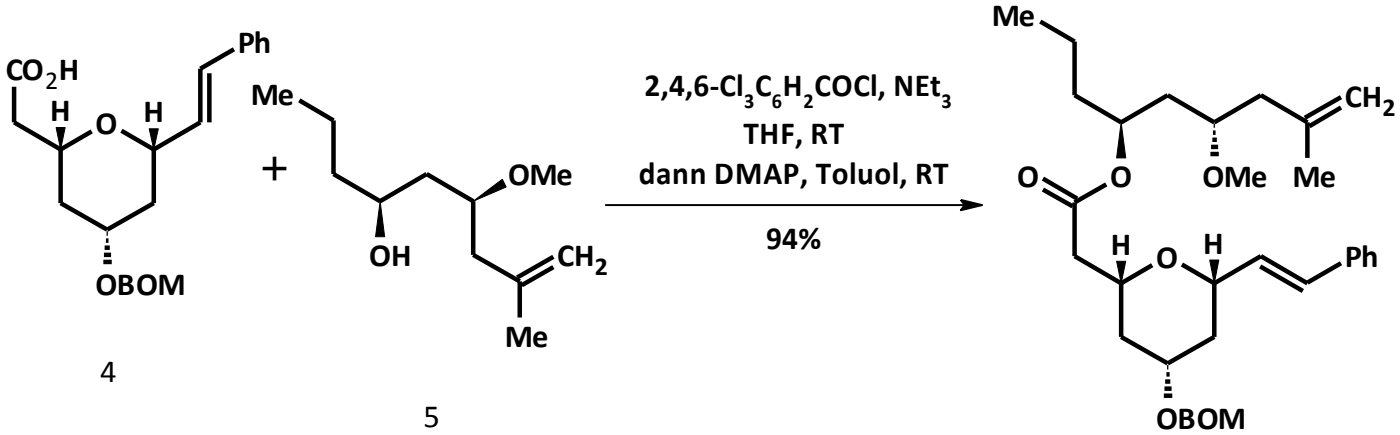
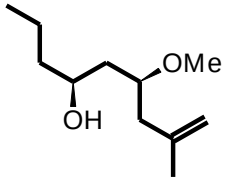


Veresterung nach Yamaguchi

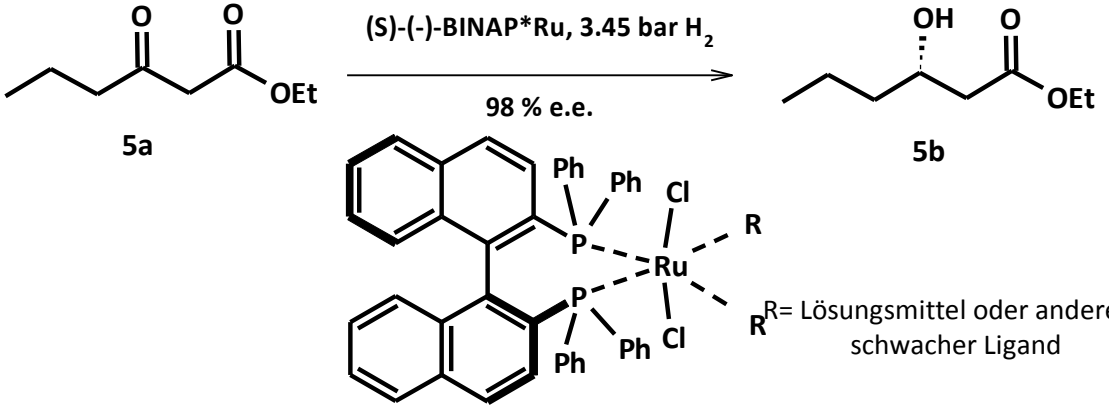


H. Fuwa, A. Saito, M. Sasaki, *Angew. Chemie* 2010, 122, 3105-3108
J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn*. 1979, 52, 1989 – 1993.

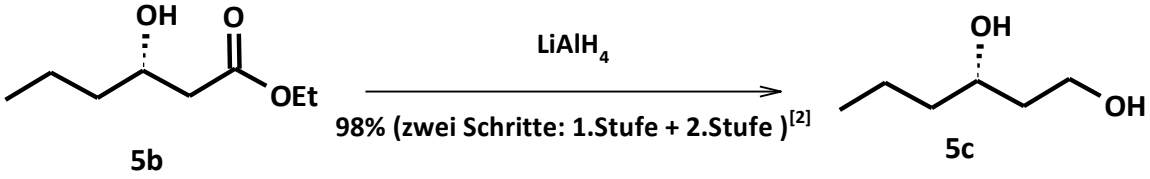
Synthese von Edukt 5



1. Stufe: Asymmetrische Hydrierung funktionalisierter Ketone[1]

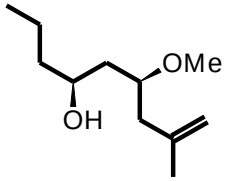


2. Stufe: Reduktion mit $LiAlH_4$ [1]

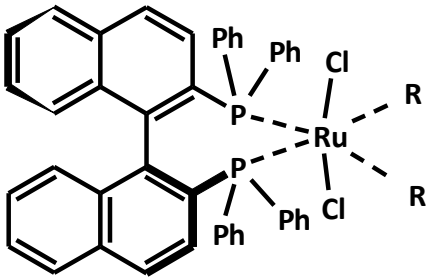


[1] J.Org. Chem. 1992, 57, 5990-5994, Douglass F. Taber, P.Bruce Deker, and Lee J. Silverberg
[2] H. Fuwa, A. Saito, M. Sasaki, Chem. Eur. J., 2009, 15, 12807-12818

Synthese von Edukt 5

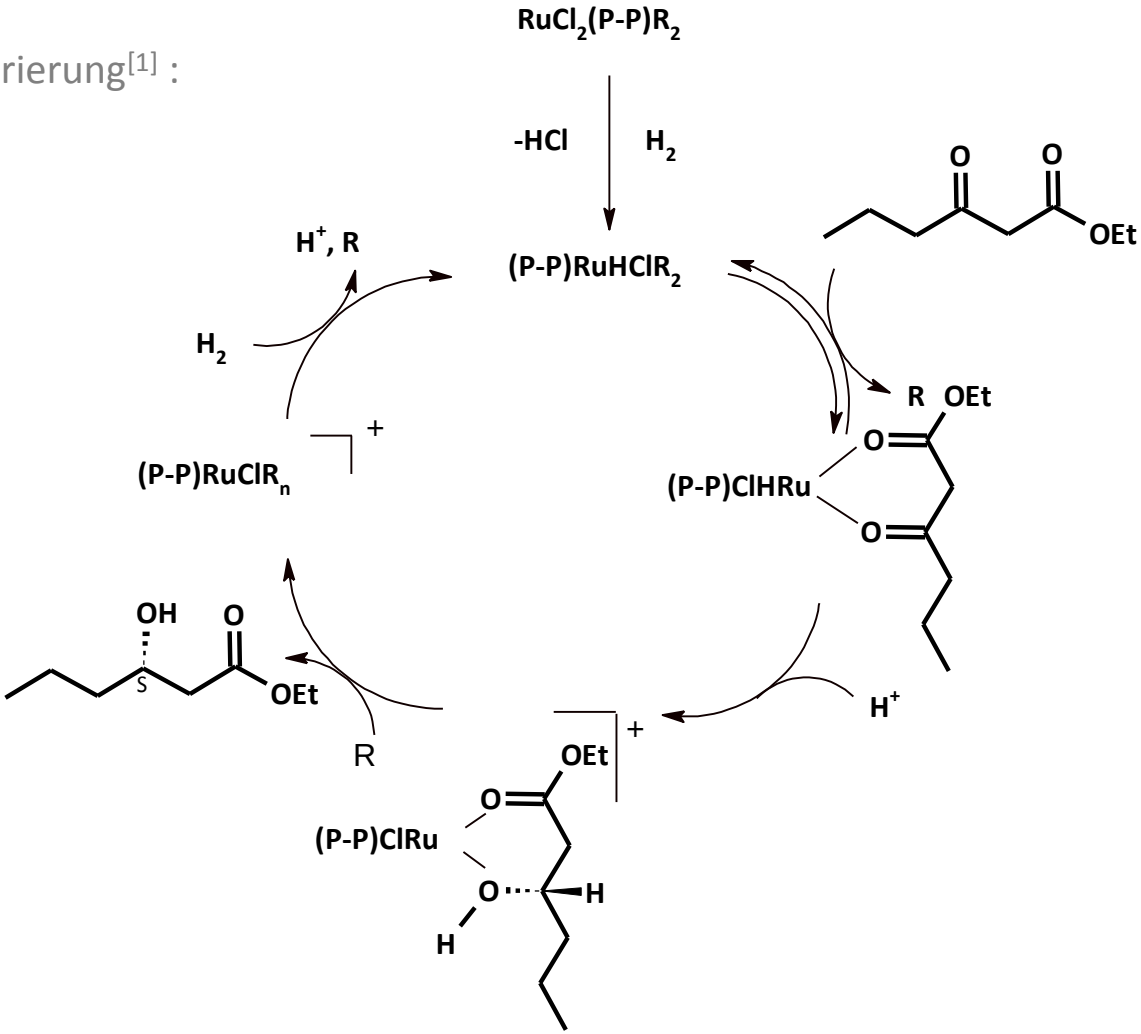


1.1 Modell Asymmetrische Hydrierung[1] :

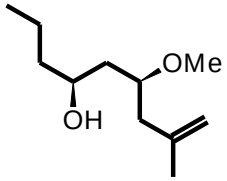


R= Lösungsmittel oder anderer schwacher Ligand

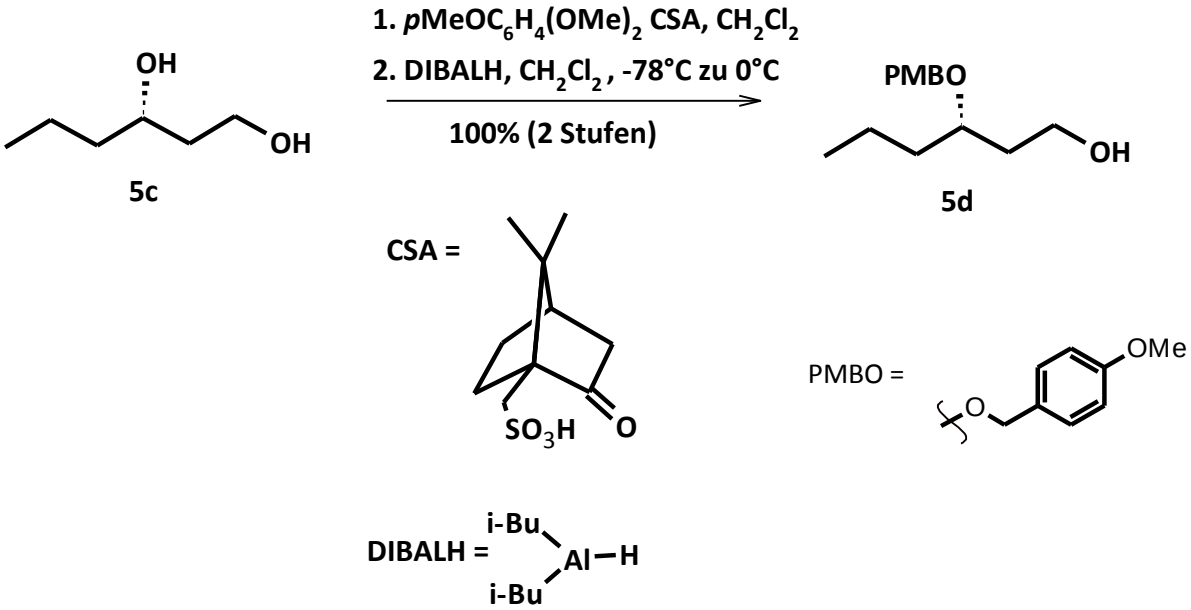
(P-P) = (S)-BINAP



[1] R. Noyori, M. Kitamura, T. Ohkuma, PNAS 2004, 101, 5356-5362

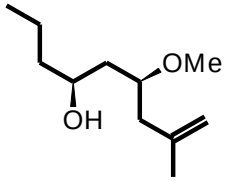


3. Stufe: selektive Einführung der PMB-Schutzgruppe (Acetalisierung/Reduktion zum Alkohol)[1]

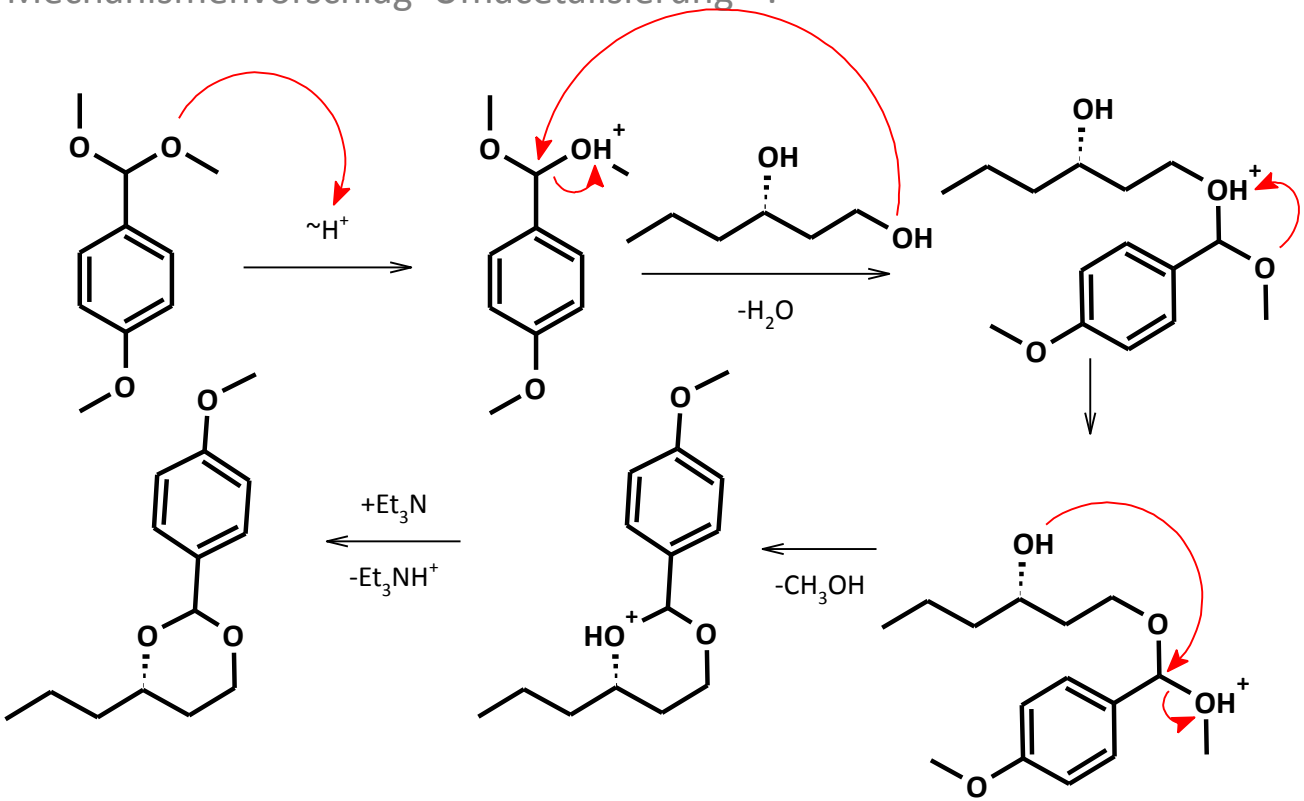


[1] Supporting information zu H. Fuwa, A. Saito, M. Sasaki, Chem. Eur. J., 2009, 15, 12807-12818

Synthese von Edukt 5

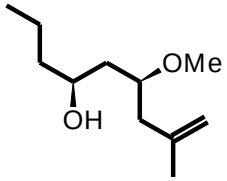


3.1 Mechanismenvorschlag Umacetalisierung[1]:

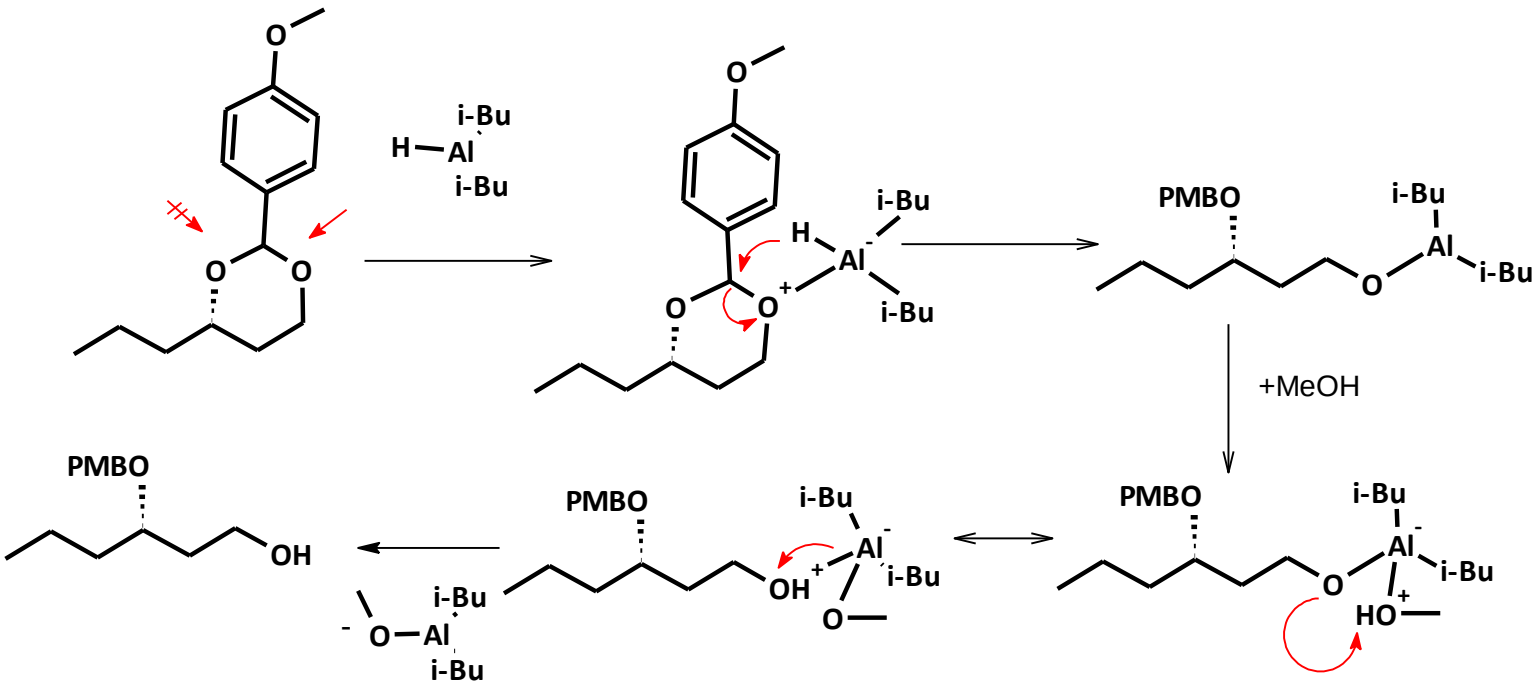


[1]OCII Übung, 6.Seminar, Aufgabe 6.2.4

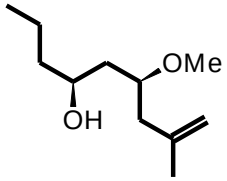
Synthese von Edukt 5



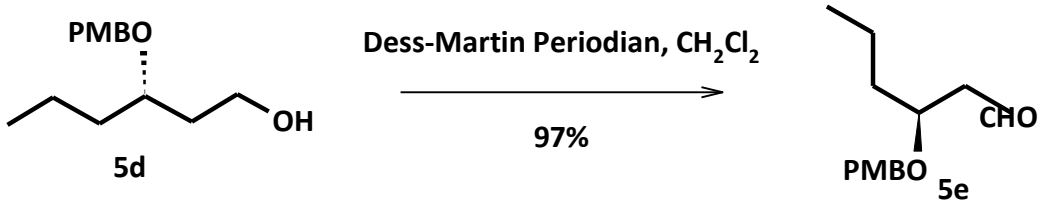
3.2 Mechanismenvorschlag selektive Reduktion zum Alkohol:



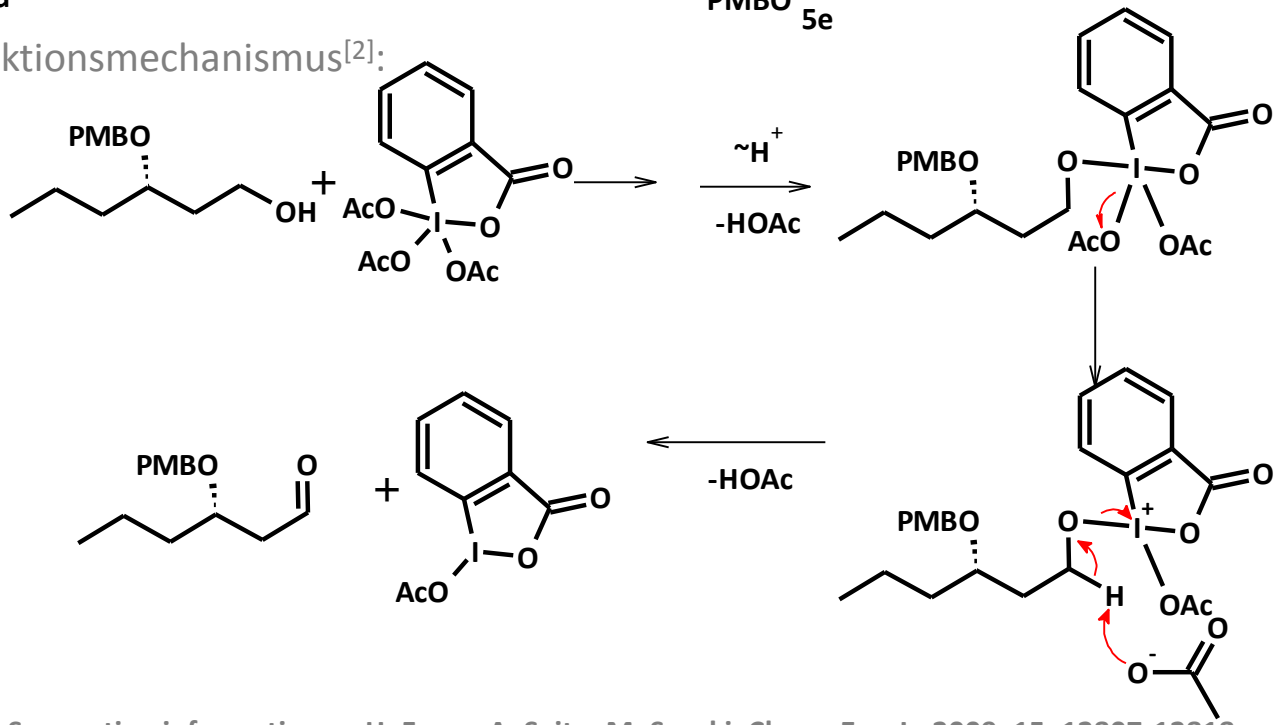
[1]OCII Übung, 8.Seminar



4.Stufe: Oxidation mit Dess-Martin Periodinan[1]

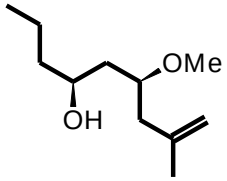


4.1 .Reaktionsmechanismus[2]:

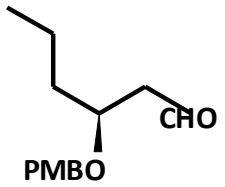


[1] Supporting information zu H. Fuwa, A. Saito, M. Sasaki, Chem. Eur. J., 2009, 15, 12807-12818
[2] Reaktionsmechanismen, 3.Auflage, Reinhardt Brückner, S.746

Synthese von Edukt 5



5.Stufe: Asymmetrische Allylborierung[1]

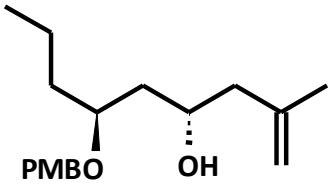


5e

(-)-Ipc_2BOMe
(2-Methylprop-2-en-1-yl)lithium Et_2O, -78 °C

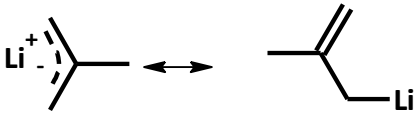
dann 10% aq NaOH
30% aq H_2O_2, RT

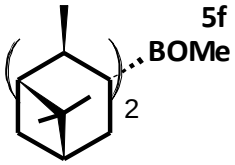
97% (dr 17:1)



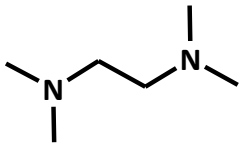
5f

(2-Methylprop-2-en-1-yl)lithium=

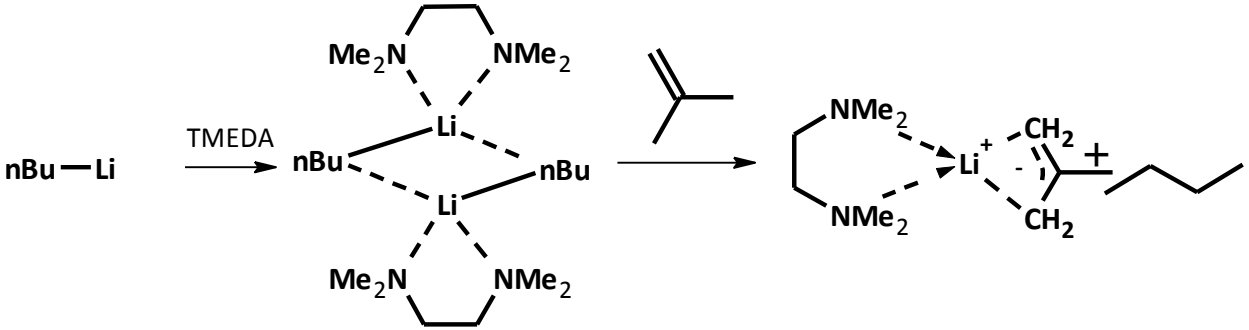




TMEDA =

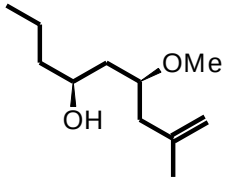


5.1 .Synthese des (2-Methylprop-2-en-1-yl)lithium[2,3,4] :

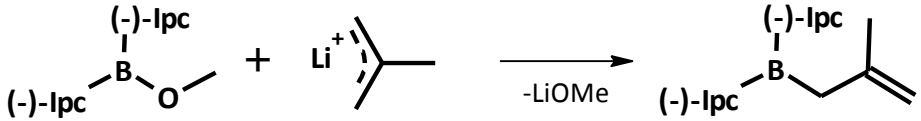


[1] Supporting information zu H. Fuwa, A. Saito, M. Sasaki, Angewandte Chemie International Edition 2010, 49, 3041-3044
[2] J.Org. Chem., Vol. 51, No.4, 1986 S.434 Jadhav et al.
[3] Reaktionsmechanismen, 3.Auflage, Reinhardt Brückner, S.399
[4]Tetrahedron Letters No. 42, pp 4115-4118, 1973, S. Akiyama, John Hooz

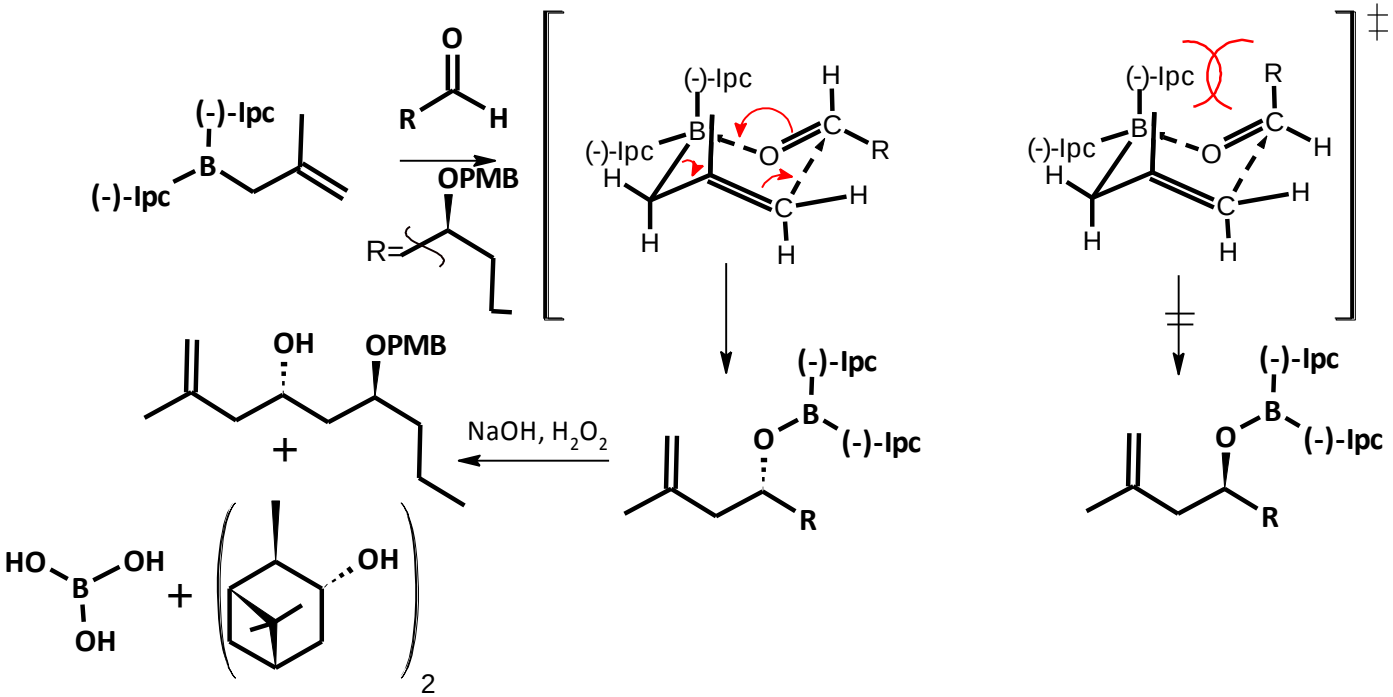
Synthese von Edukt 5



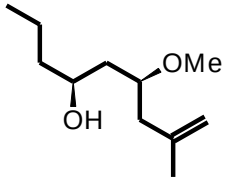
5.2. Synthese des Methallyldiisopinocamphenylboran[1]:



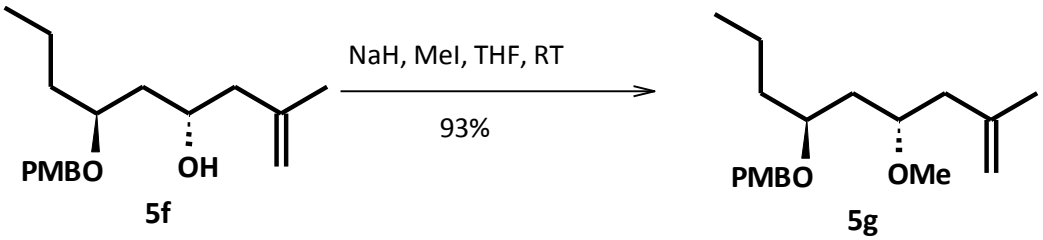
5.3. Mechanismenvorschlag (Asymmetrische Allylborierung)[2]:



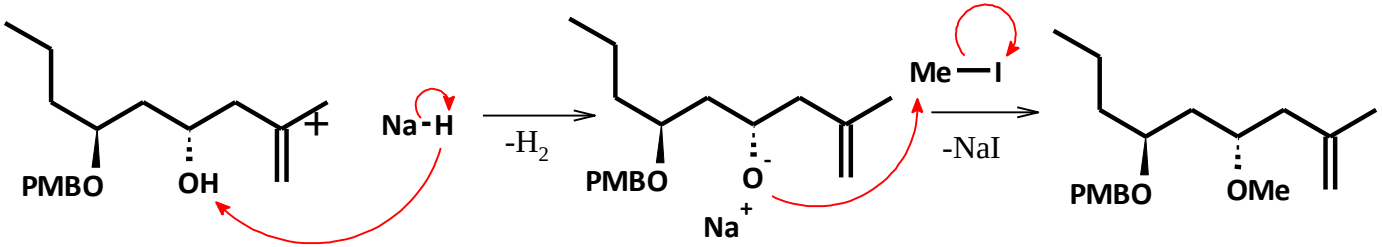
[1] J.Org. Chem., Vol. 51, No.4, 1986 S.434 Jadhav et al.
[2]ARKIVOC 2007 (ii) 121-144, ISSN 1424-6376, J. Subash Chandra, M.Venkat Ram Reddy, S.122



6.Stufe: Methylierung des homoallylischen Alkohols[1]

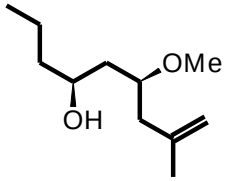


6.1 .Mechanismusvorschlag:

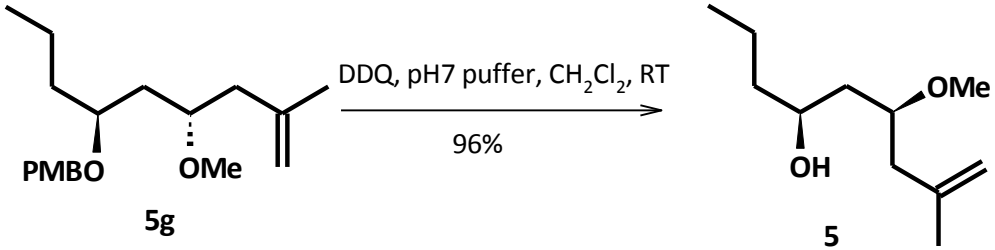


[1] Supporting information zu H. Fuwa, A. Saito, M. Sasaki, Angewandte Chemie International Edition 2010, 49, 3041-3044

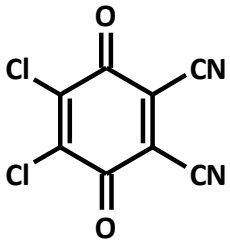
Synthese von Edukt 5



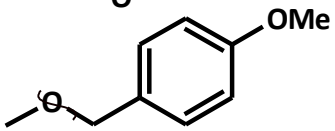
7.Stufe: Entfernung der p-Methoxybenzyl-Schutzgruppe[1]



DDQ =

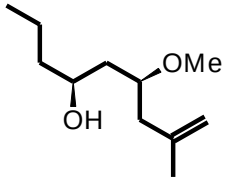


PMBO =

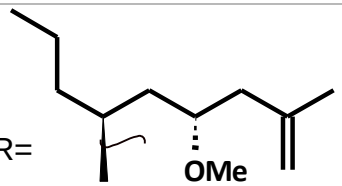


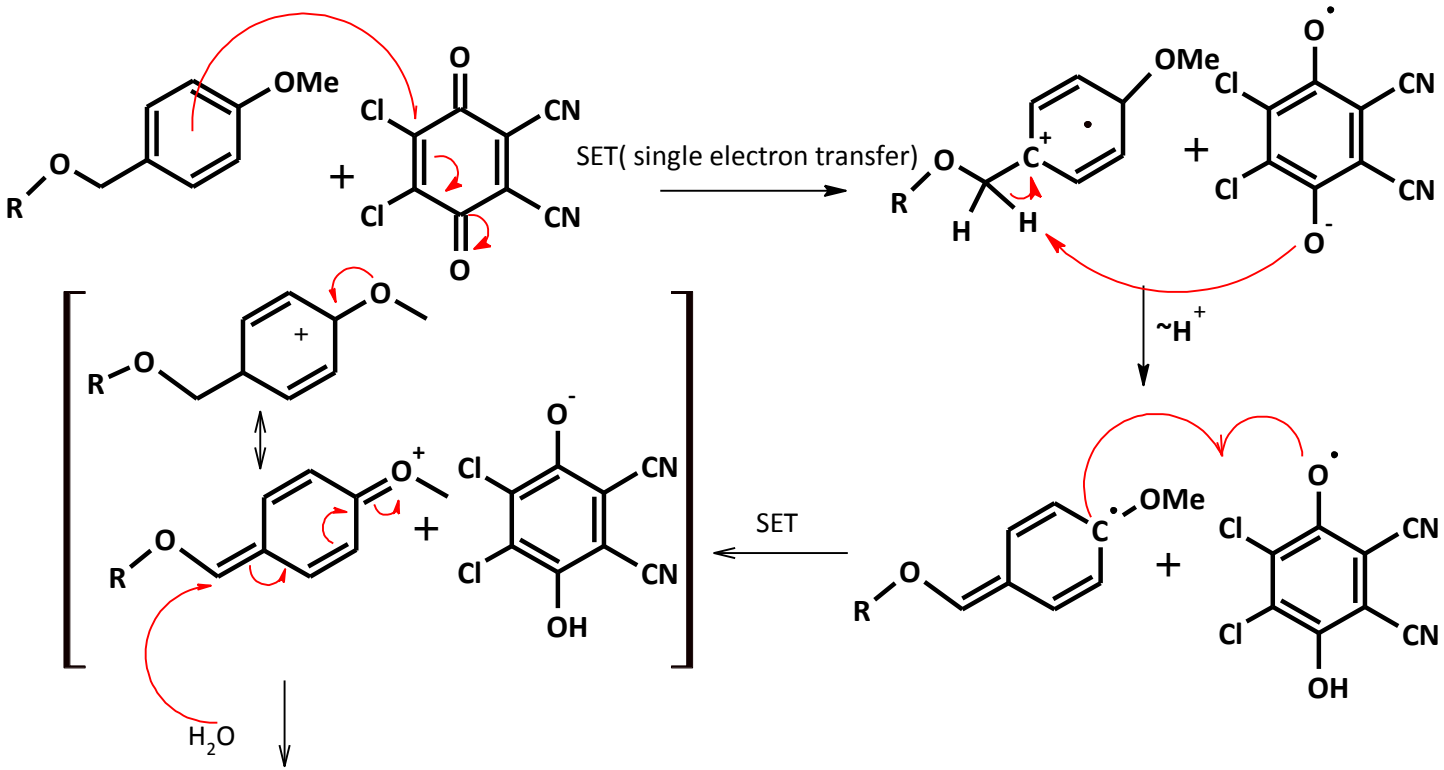
[1] Supporting information zu H. Fuwa, A. Saito, M. Sasaki, Angewandte Chemie International Edition 2010, 49, 3041-3044

Synthese von Edukt 5



7.1(a) Reaktionsmechanismus[1]:

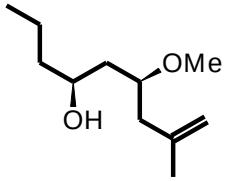




(siehe nächste Folie)

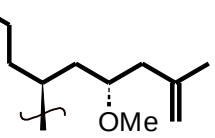
[1]OCII Übung, 5.Seminar, Aufgabe 5.4.1

Synthese von Edukt 5

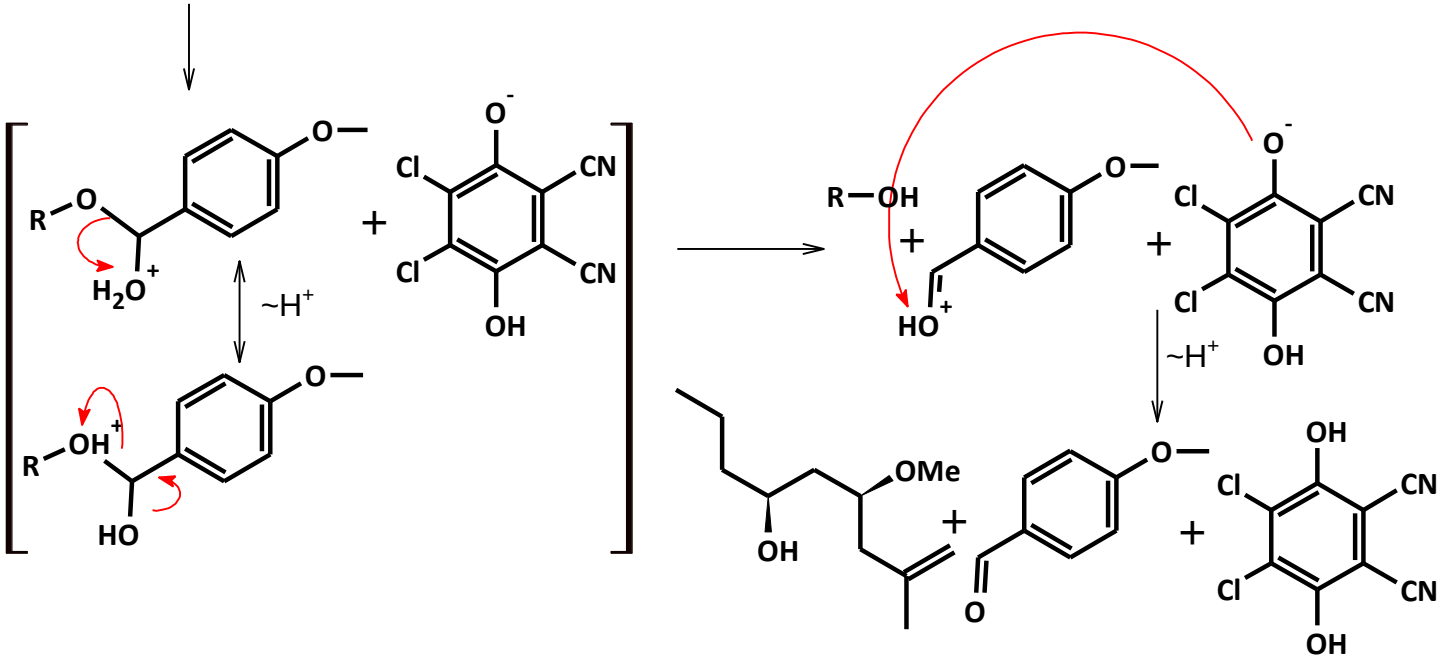


7.1(b) Reaktionsmechanismus[1]:

R=

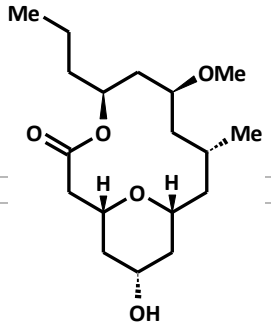


(Fortsetzung 7.1(a))

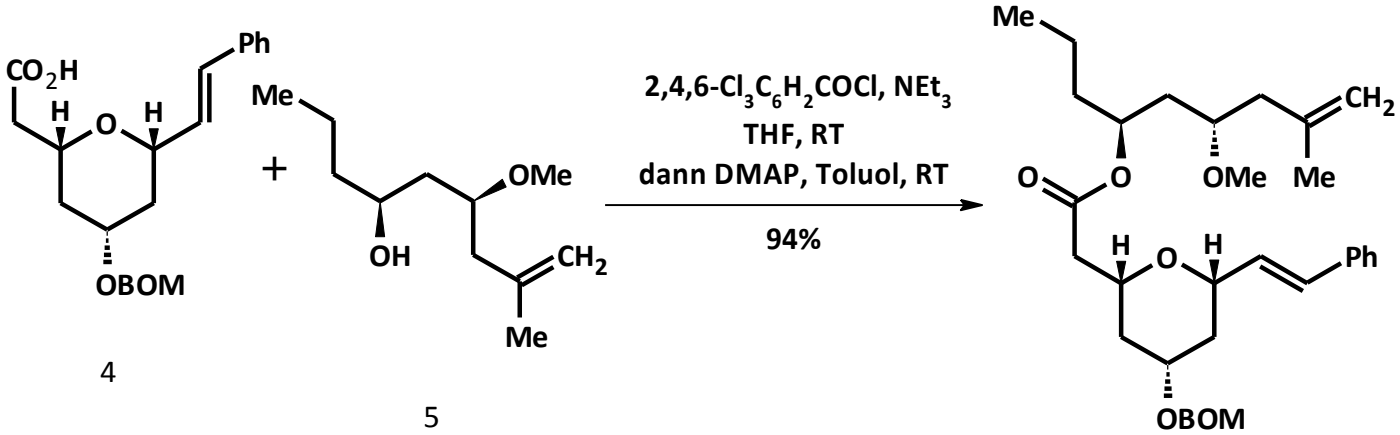


[1]OCII Übung, 5.Seminar, Aufgabe 5.4.1

Synthese des Macrocyclus 2

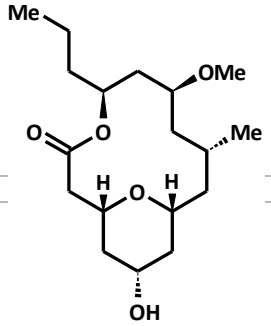


Veresterung nach Yamaguchi

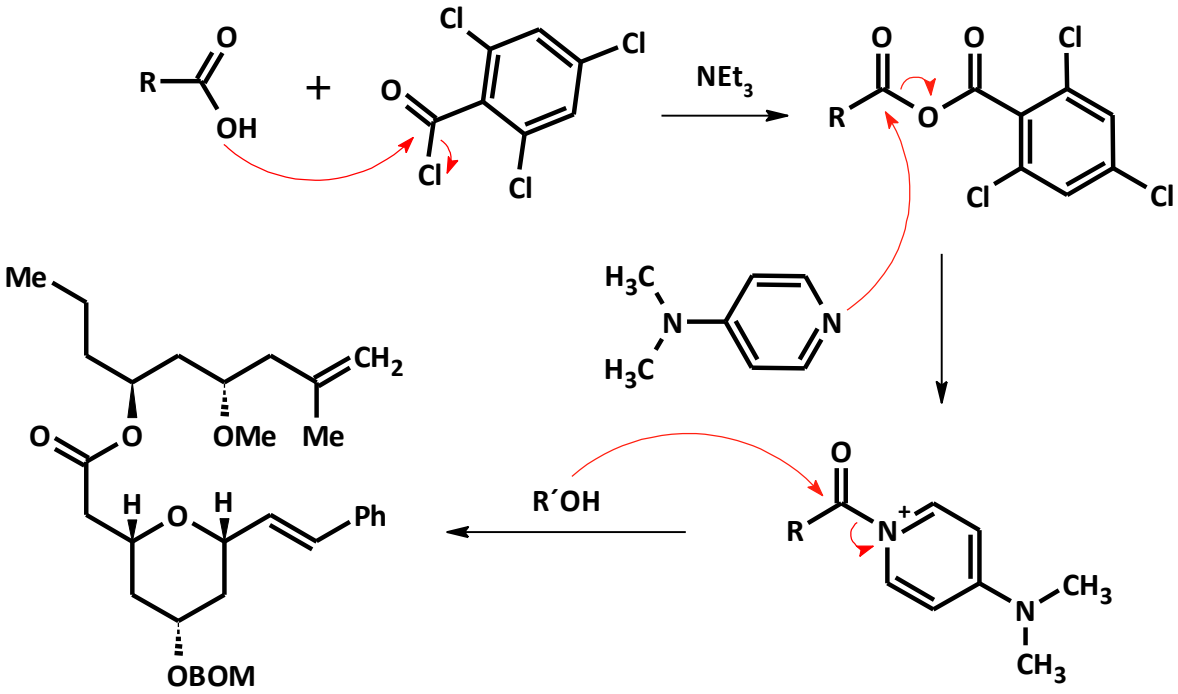


H. Fuwa, A. Saito, M. Sasaki, *Angew. Chemie* 2010, 122, 3105-3108
J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn*. 1979, 52, 1989 – 1993.

Synthese des Macrocyclus 2

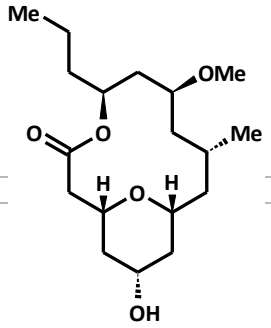


Mechanismusvorschlag:

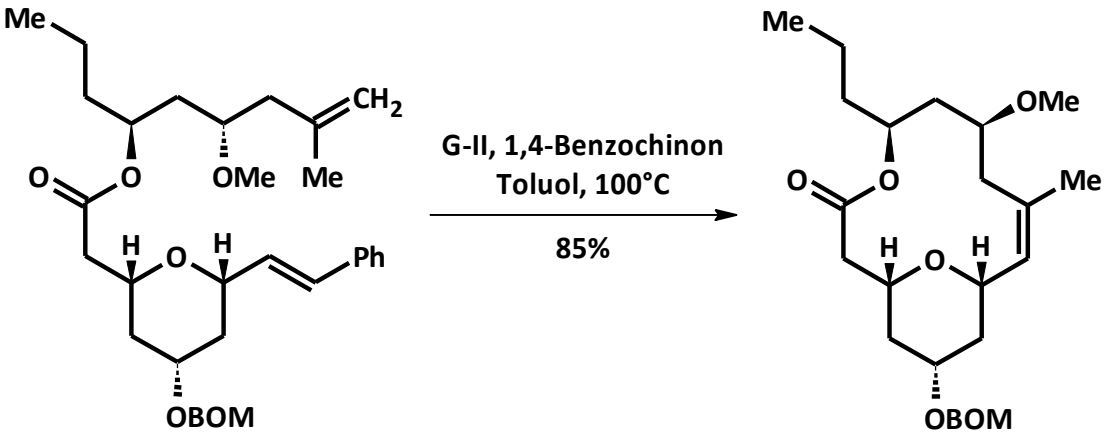


3

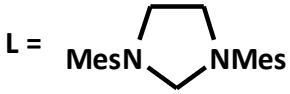
Synthese des Macrocyclus 2

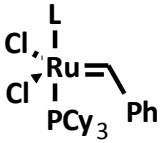


Olefinmetathese



3 15

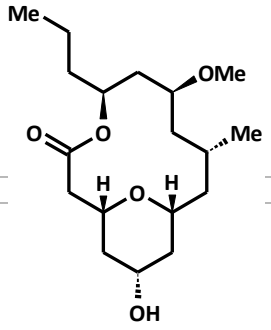




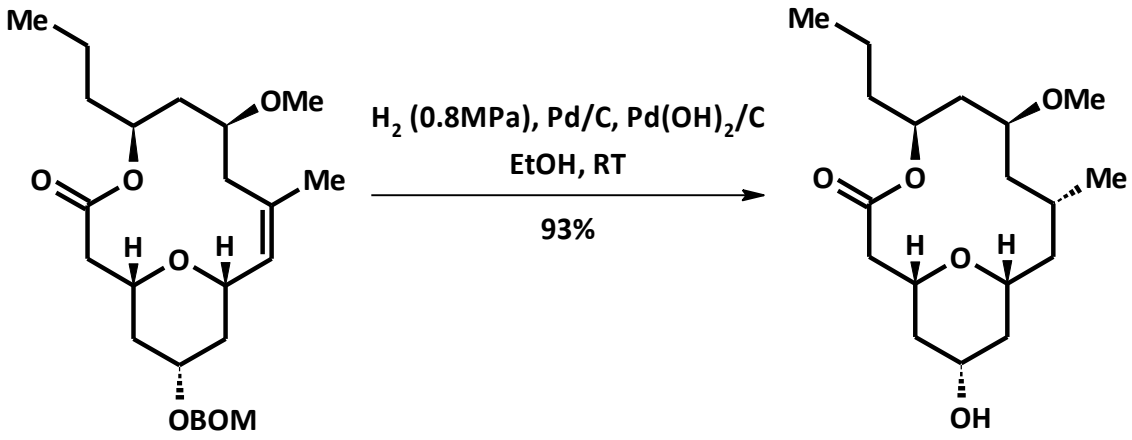
G-II

H. Fuwa, A. Saito, M. Sasaki, *Angew. Chemie* 2010, 122, 3105-3108
S. H. Hong, H. P. Sanders, C. W. Lee, R. H. Grubbs, *J. Am. Chem. Soc*. 2005, 127, 17160 – 17161.

Synthese des Macrocyclus 2



Katalytische Hydrierung

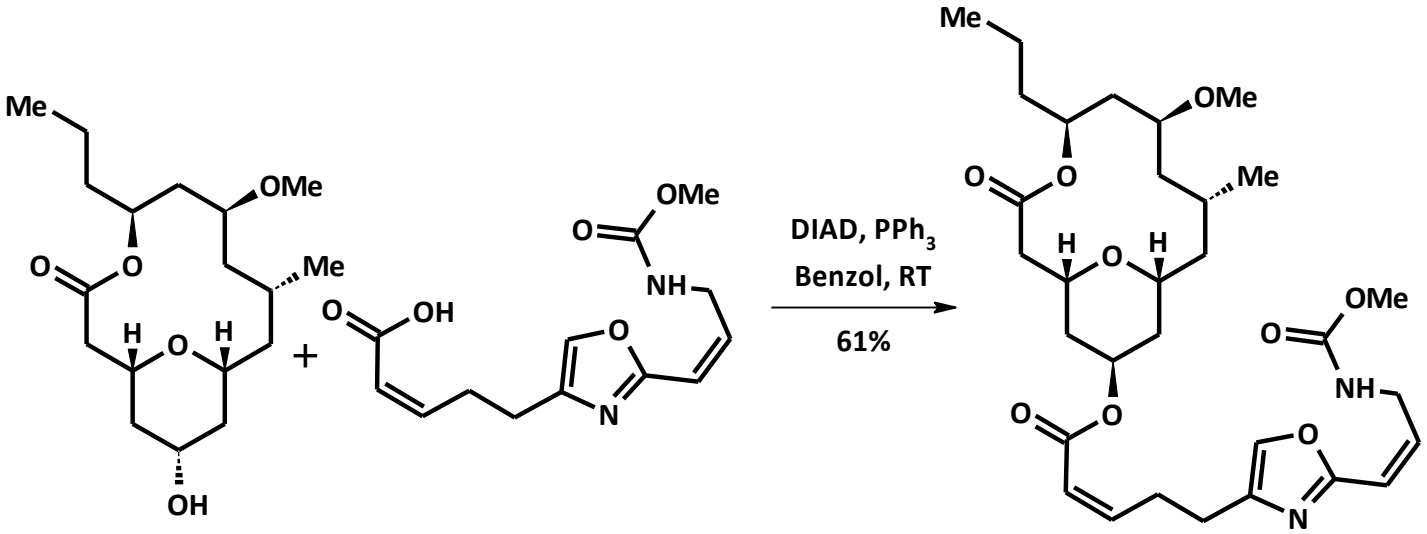


15 2

H. Fuwa, A. Saito, M. Sasaki, *Angew. Chemie* 2010, 122, 3105-3108

Darstellung von (+)-Neopeltolid 1

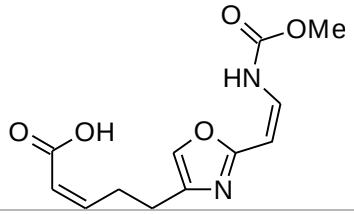
Mitsunobu-Reaktion



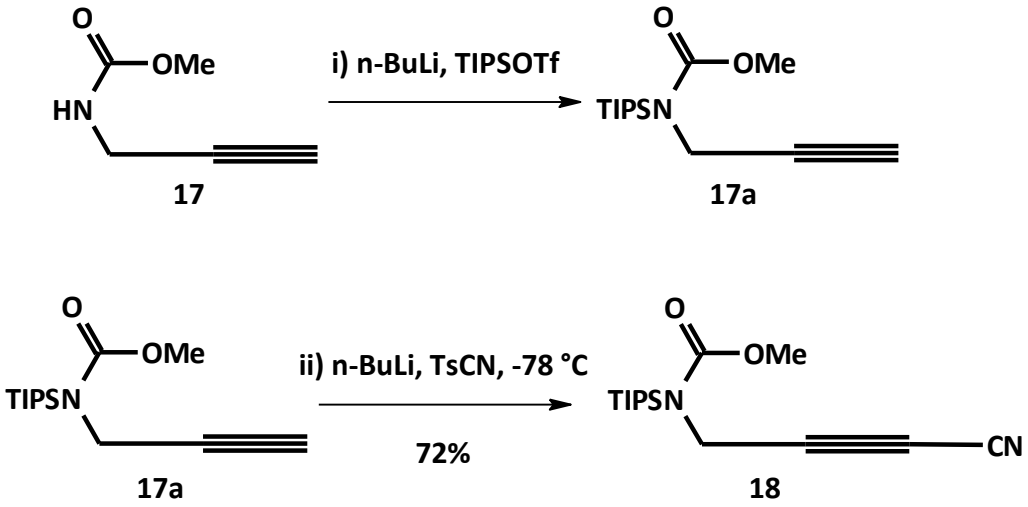
2 16 1

H. Fuwa, A. Saito, M. Sasaki, *Angew. Chemie* 2010, 122, 3105-3108
H. Fuwa, S. Naito, T. Goto, M. Sasaki, *Angew. Chem*. 2008, 120, 4815 – 4817.

Synthese von Edukt 16[1]

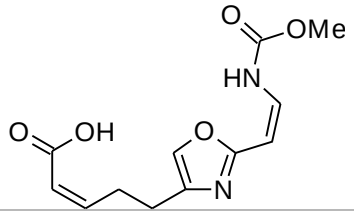


1. Stufe: Einführung der Schutzgruppe und Cyanierung



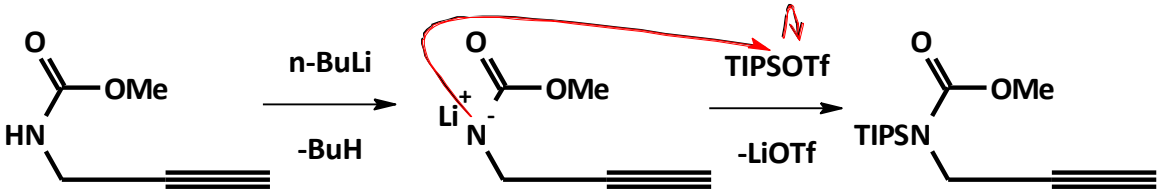
[1]Y. Wang, J. Janjic, S. A. Kozmin, J. Am. Chem. Soc. 2002, 124, 13670
D. Kahne, D. B. Collum, *Tetrahedron Lett. 1981, 22, 5011*

Synthese von Edukt 16

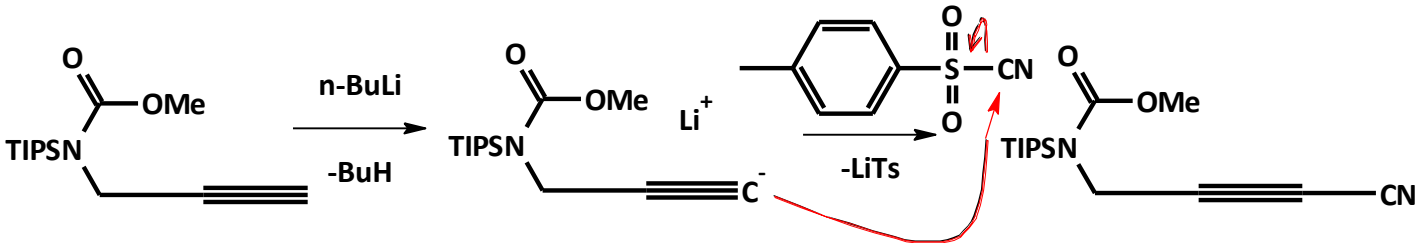


Mechanismusvorschläge:

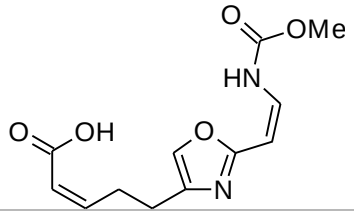
Einführung der Schutzgruppe



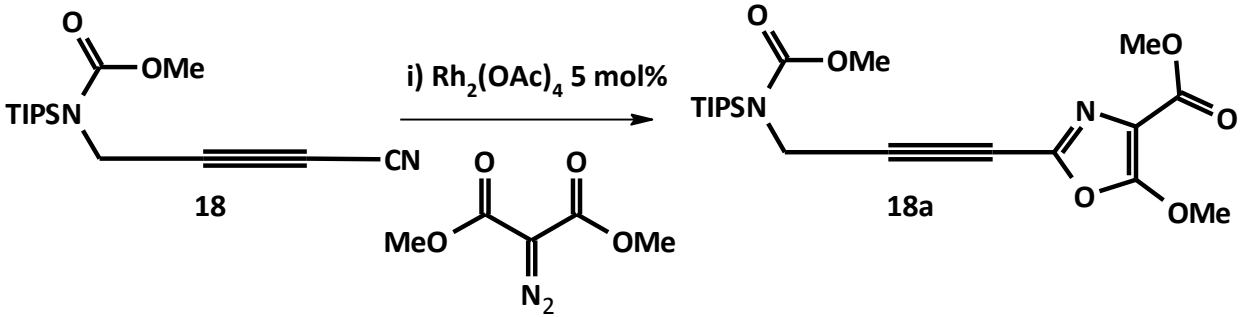
Cyanierung

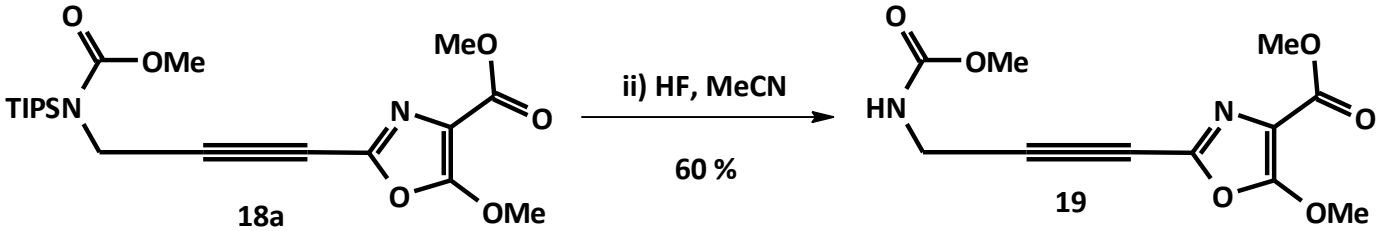


Synthese von Edukt 16



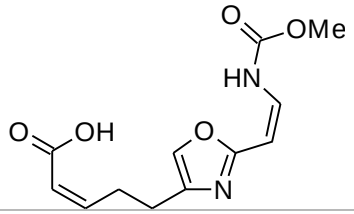
2. Stufe: Bildung des Oxazols und Entfernung der Schutzgruppe





R. D. Connell, F. Scavo, P. Helquist, B. Åkermark, *Tetrahedron Lett. 1986, 27, 5559*

Synthese von Edukt 16



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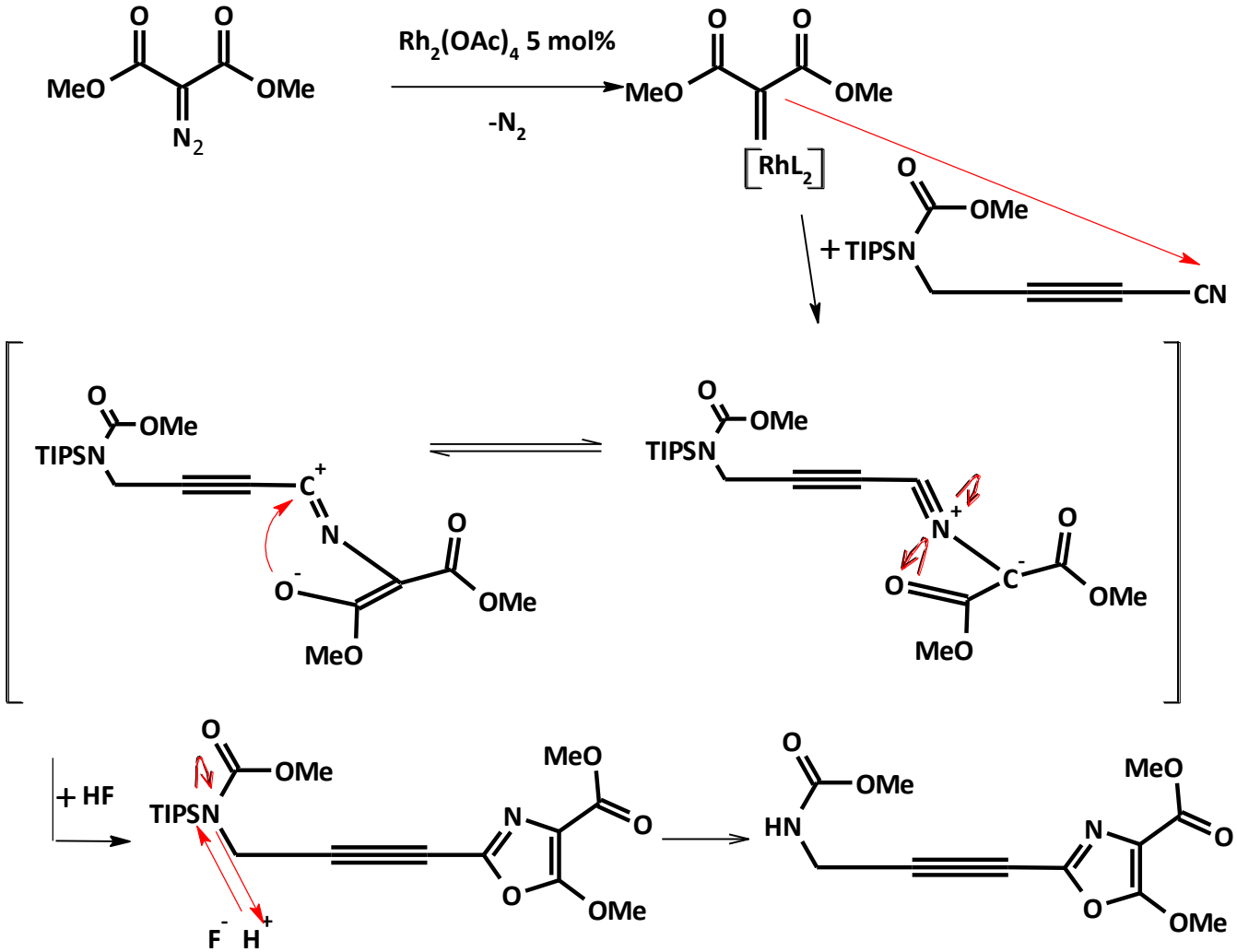

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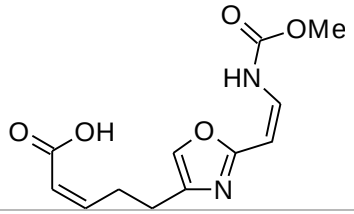
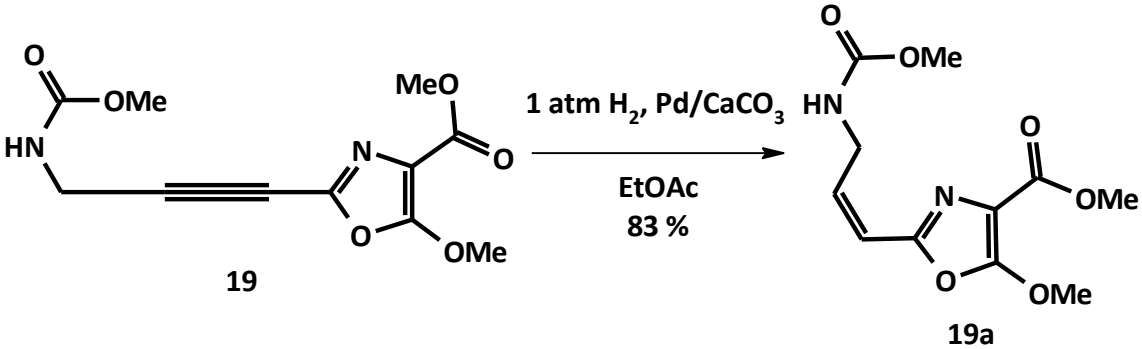
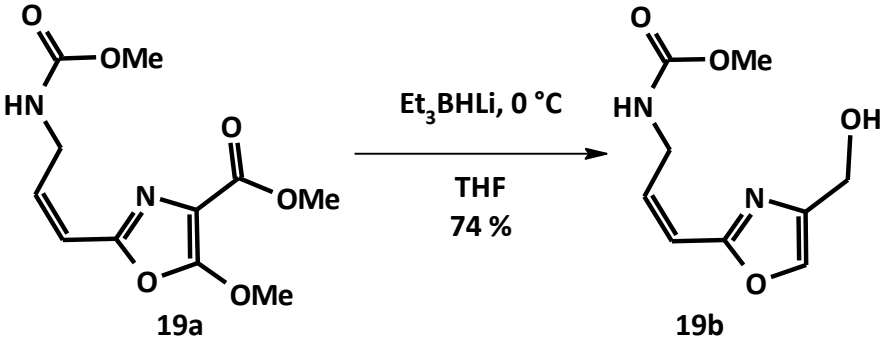


3. Stufe: Hydrierung mit Lindlar-Katalysator

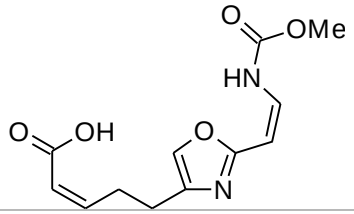


4. Stufe: Reduktion mit Super-Hydrid®

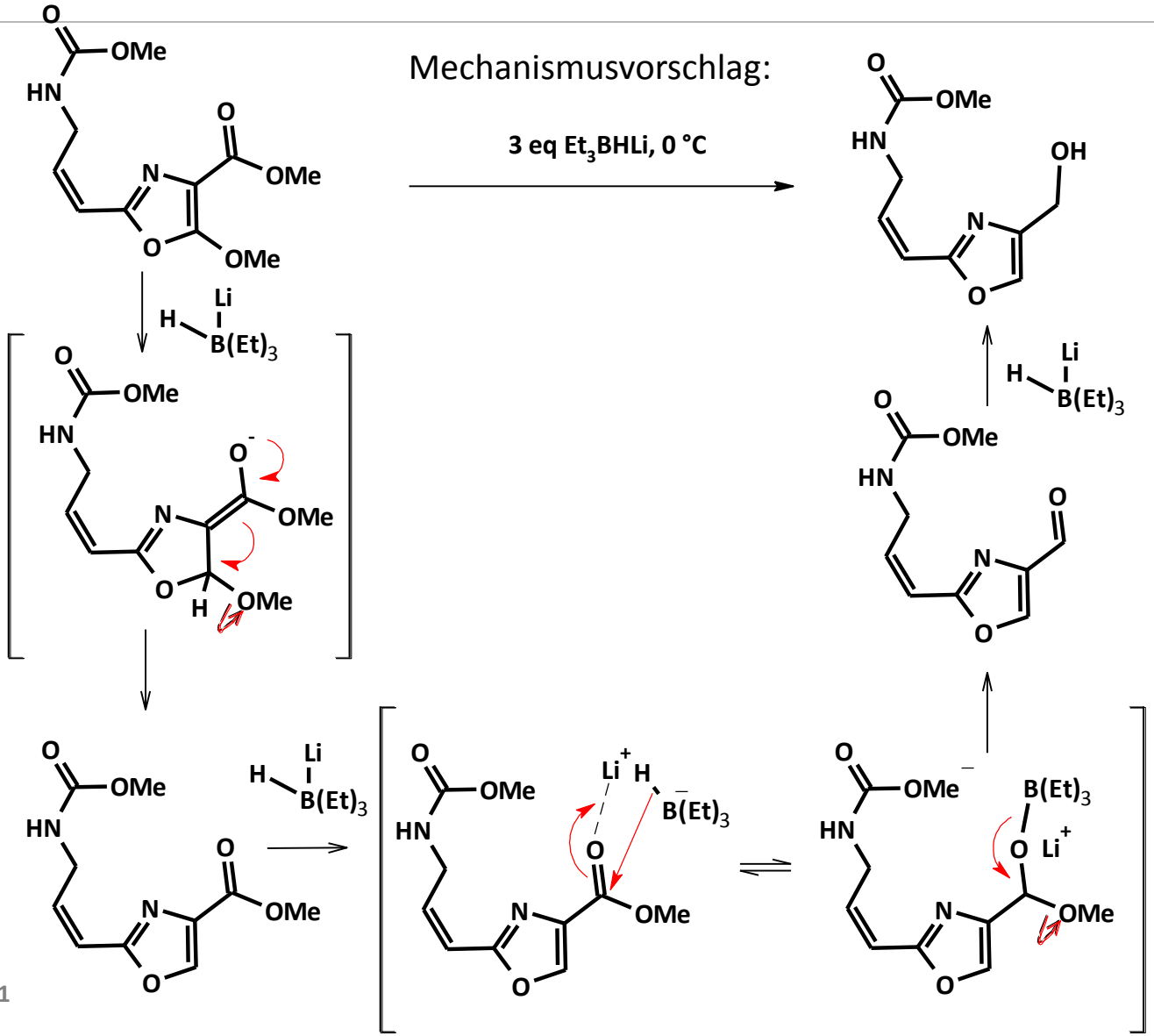


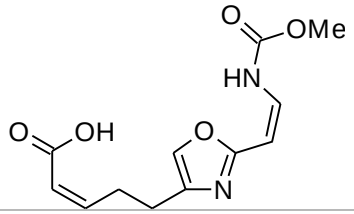
R. D. Connell, F. Scavo, P. Helquist, B. Åkermark, *Tetrahedron Lett. 1986, 27, 5559*

Synthese von Edukt 16

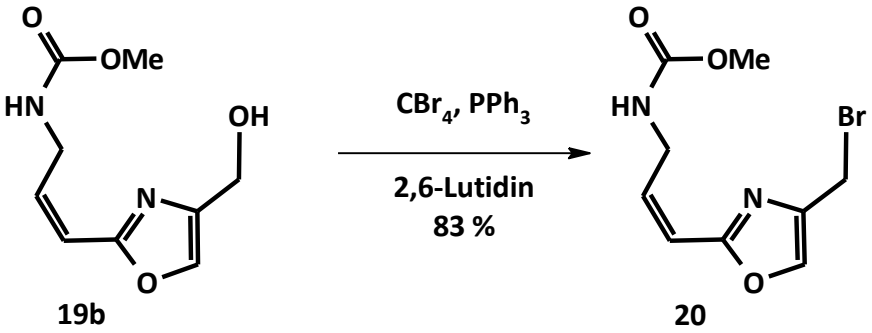


Mechanismusvorschlag:

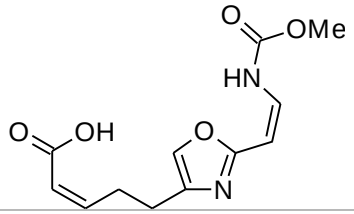




5. Stufe: Mukaiyama-Redoxkondensation



Synthese von Edukt 16



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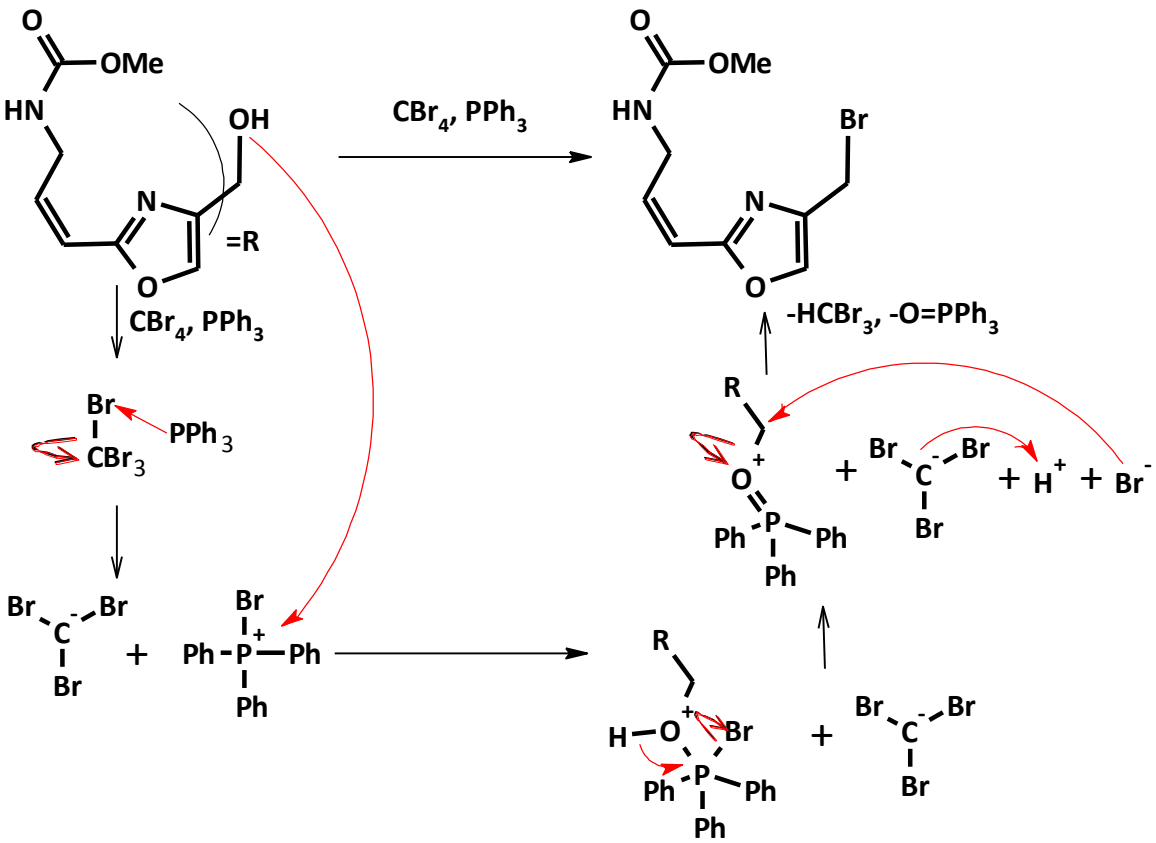
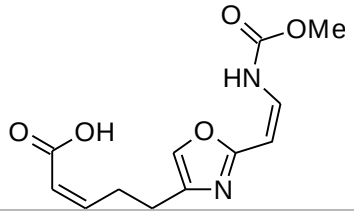
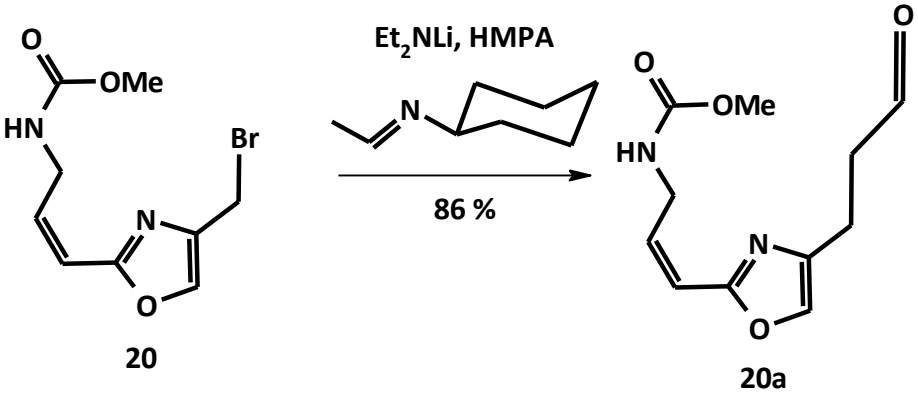


R. Brückner, *Reaktionsmechanismen*, 3. Auflage, Spektrum Verlag, S. 99f.



6. Stufe: Alkylierung



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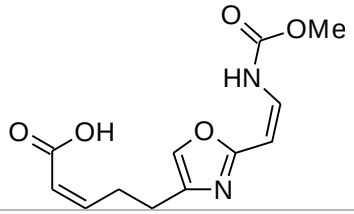

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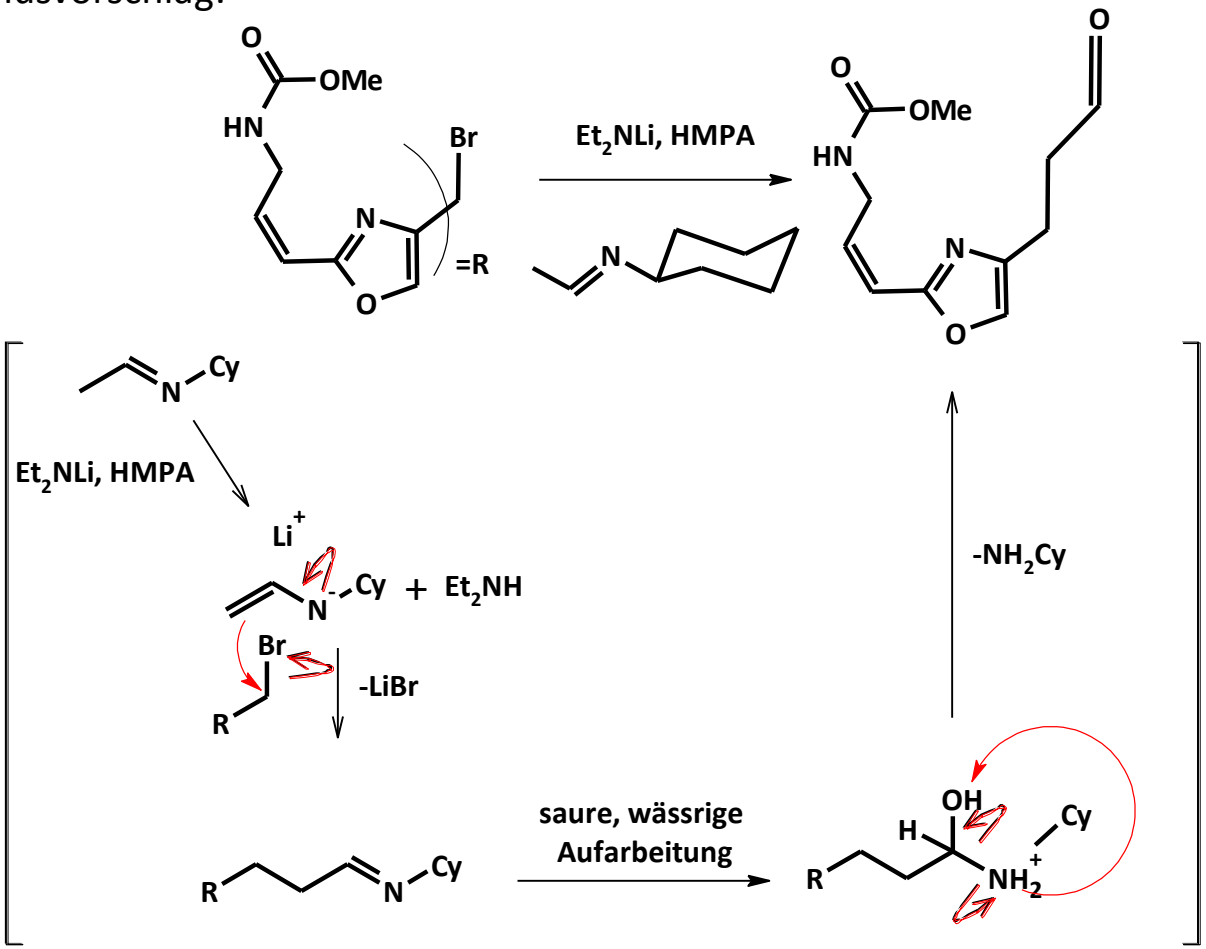
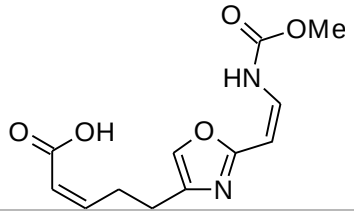
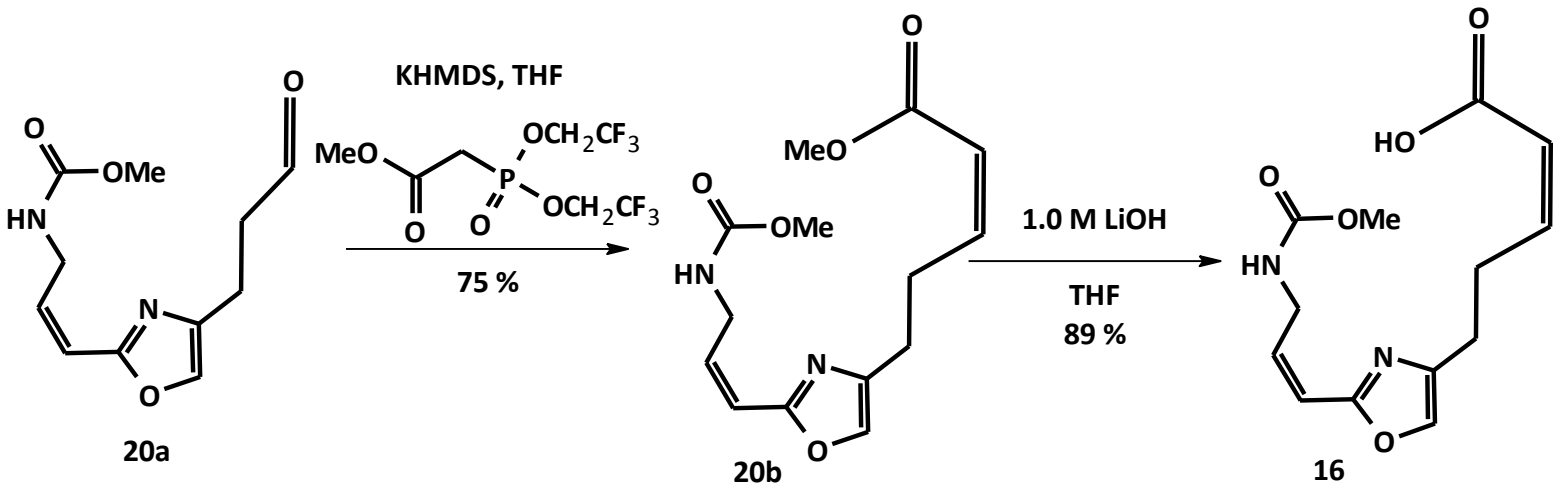


R. Brückner, *Reaktionsmechanismen*, 3. Auflage, Spektrum Verlag, S. 543f.

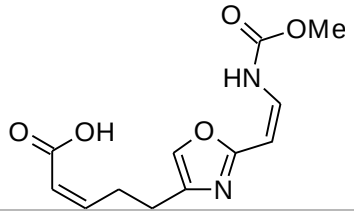


7./8. Stufe: Still-Gennari-Variante der HWE-Reaktion und Verseifung des Esters



W. C. Still, C. Gennari, Tetrahedron Lett. 1983, 24, 4405

Synthese von Edukt 16



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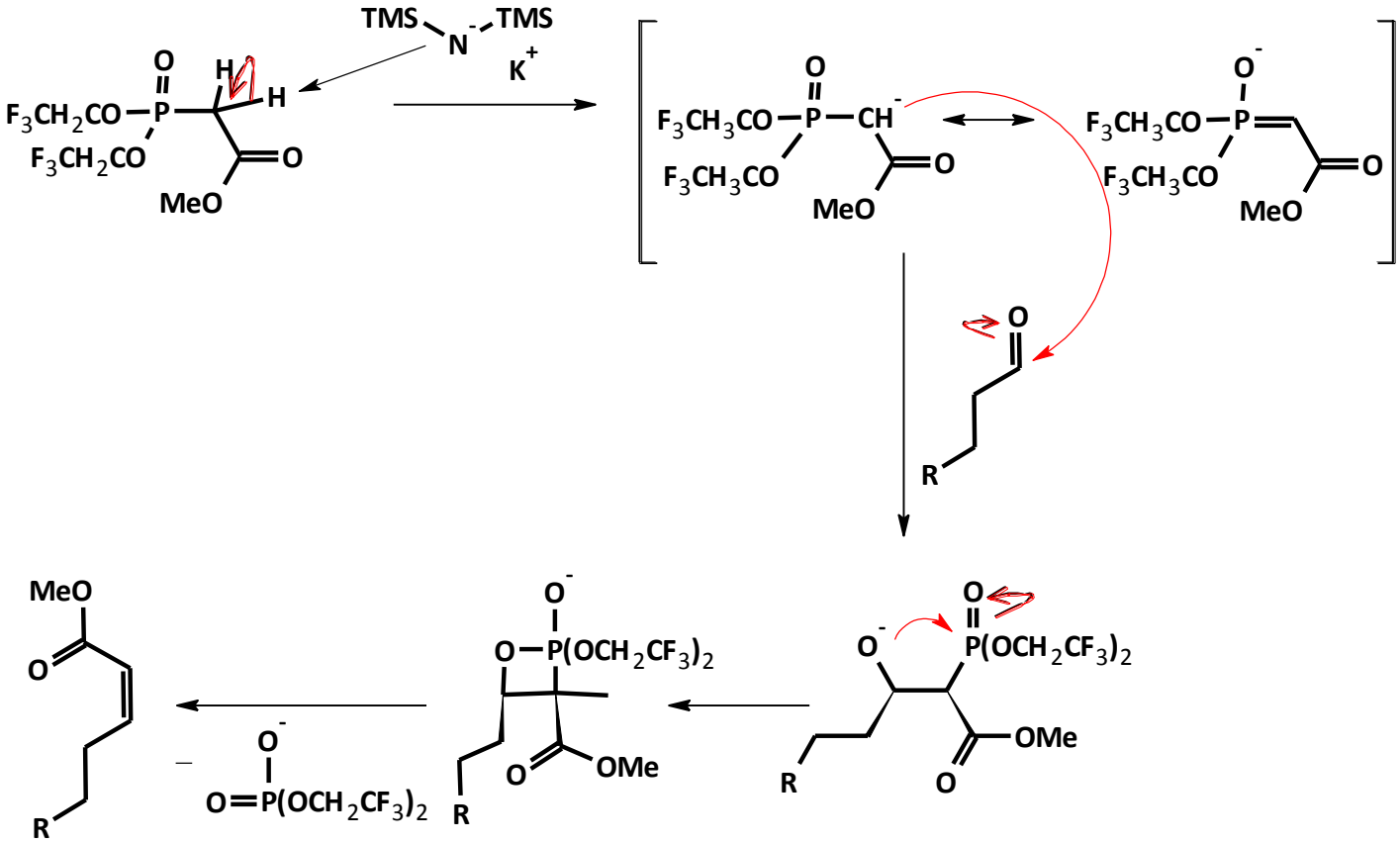
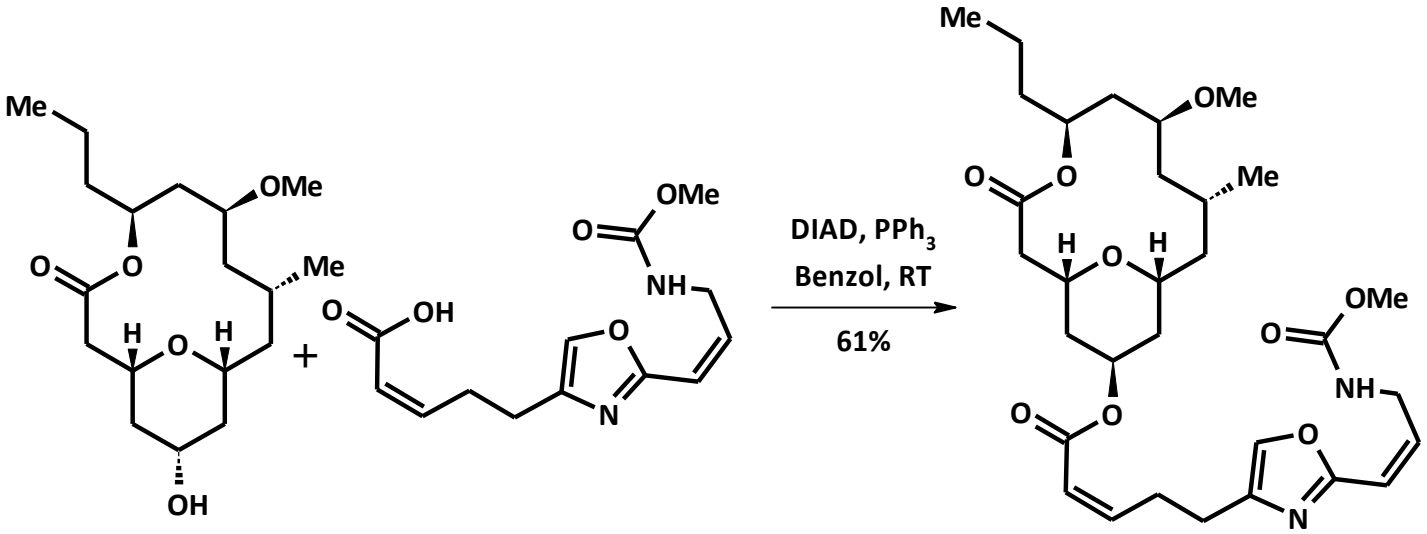


W. C. Still, C. Gennari, Tetrahedron Lett. 1983, 24, 4405
R. Brückner, *Reaktionsmechanismen*, 3. Auflage, Spektrum Verlag, S. 472 ff

Darstellung von (+)-Neopeltolid 1

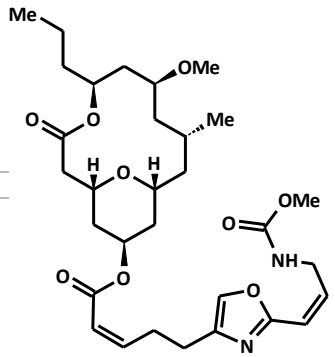
Mitsunobu-Reaktion



2 16 1

H. Fuwa, A. Saito, M. Sasaki, *Angew. Chemie* 2010, 122, 3105-3108
H. Fuwa, S. Naito, T. Goto, M. Sasaki, *Angew. Chem*. 2008, 120, 4815 – 4817.

Darstellung von (+)-Neopeltolid 1



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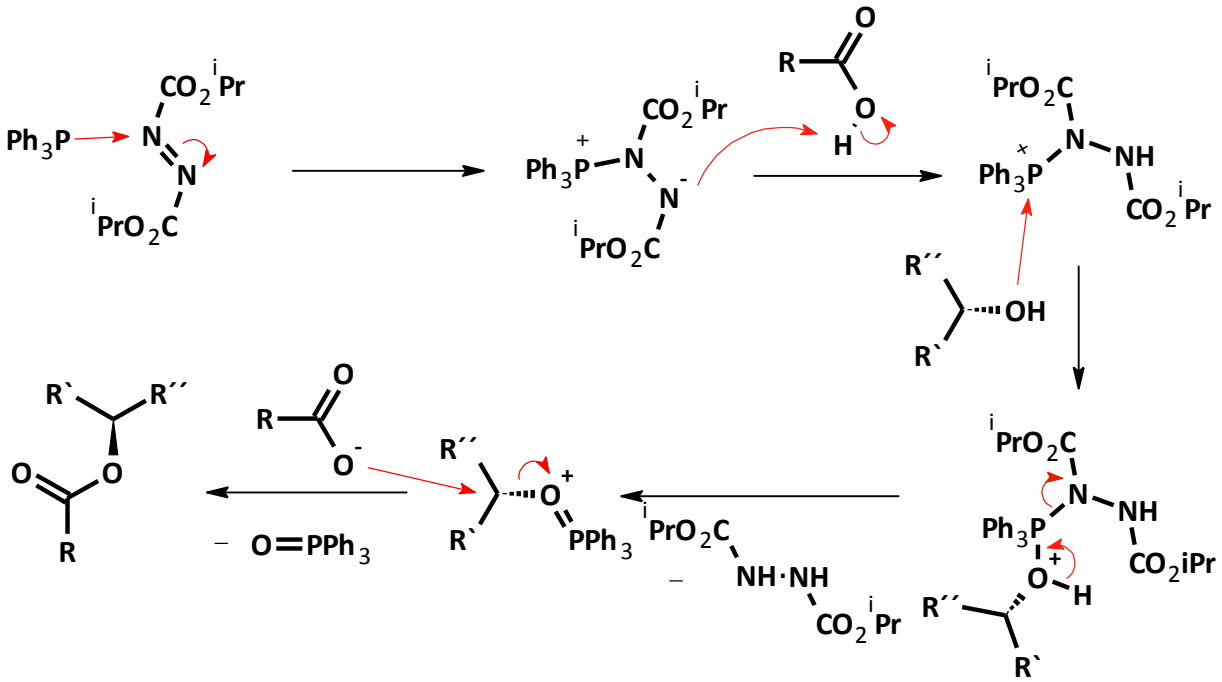

R. Brückner, *Reaktionsmechanismen*, 3. Auflage, Spektrum Verlag, 97f.

Vergleich der Vollsynthesen

Arbeitsgruppe	Jahr	Ausbeute	Stufen
Sasaki	2010	11,9%	13
Roulland	2009	6,2%	16
Scheidt	2008	2,3%	17
Sasaki	2008	8,3%	25
Kozmin	2008	8,9%	15
Maier	2008	23,0%	17 (bis Verb. 2)
Panek	2007	1,3%	19

H. Fuwa, A.Saito, M. Sasaki, Angew. Chemie 2010, 122, 3105-3108
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H. Fuwa, S. Naito, M. Sasaki, Angew. Chemie 2008, 120, 4815-4817
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V. V. Vintonyak, M. E. Maier, Org. Letters 2008, Vol. 10, No. 6, 1239-1242
W. Youngsaye, J. T. Lowe, J. S. Panek, Angew. Chemie 2007, 46, 9211-9214

Abkürzungsverzeichnis

Ac	**Acetat**
BINAP	**(2,2´–Bis(diphenylphosphino)–1,1´–binaphthyl)**
BOM	**Benzyloxymethyl**
Bu	**Butyl**
(R)CM	**(Ring-)Kreuzmethathese**
CSA	**Camphersulfonsäure**
Cy	**Cyclohexyl**
DBU	**1,8-Diazabicyclo[5.4.0]undec-7-en**
DDQ	**2,3-Dichloro-5,6-dicyano-1,4-benzochinon**
DIAD	**Diisopropylazodicarboxylat**
DIBALH	**Diisobutylaluminiumhydrid**
DMAP	**4-Dimethylaminopyridin**
DMF	**Dimethylformamid**
Et	**Ethyl**
HMPA	**Hexamethylphosphoramid**
^{i}Pr	***iso*-Propyl**
(+) – Ipc_2BOMe	**Diisopinocampheolmethoxyboran**
KHMDS	**Kaliumhexamethyldisilazan**
Me	**Methyl**
Mes	**Mesytilen**
OMe	**Methoxy**
Ph	**Phenyl**
PMBO	***para*-Methoxybenzyloxy**
TBAF	**Tetrabutylammoniumfluorid**
TBS	***tert*-Butyldimethylsilyl**
THF	**Tetrahydrofuran**
TIPOTf	**Triisopropyltriflat**
TMS	**Trimethylsilyl**
TsCN	**Tosylcyanid**