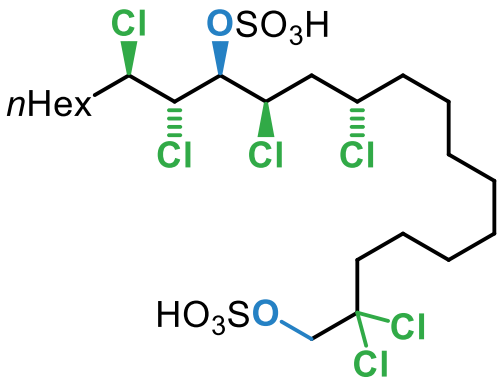
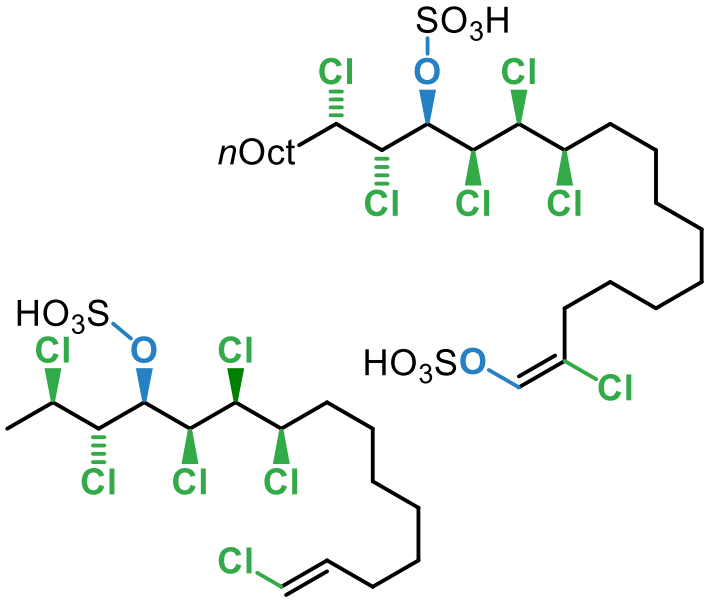
12.05.20

Wissenschaftlicher Vortrag
Im Rahmen des Habilitationsverfahrens





FCI
FONDS DER
CHEMISCHEN
INDUSTRIE

DFG

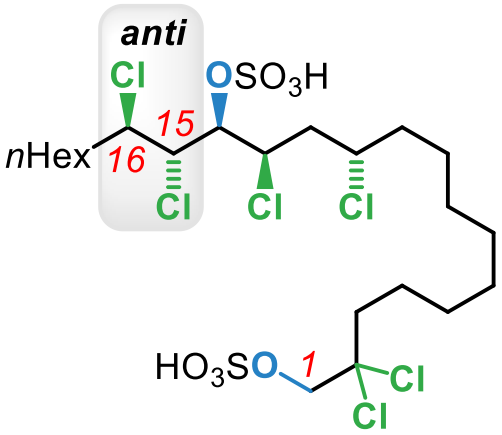
Sulfolipide – Polyhalogenierte toxische Naturstoff aus Algen

Universität des Saarlandes

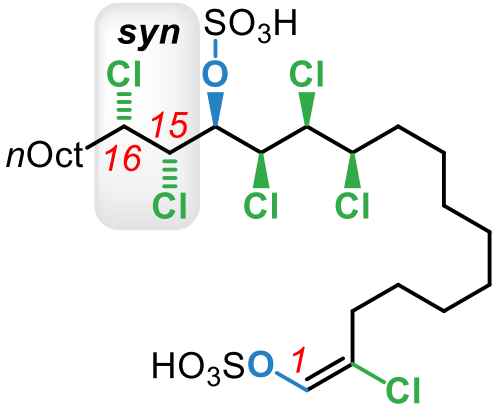
Peter Huy

Peterhuylab.de

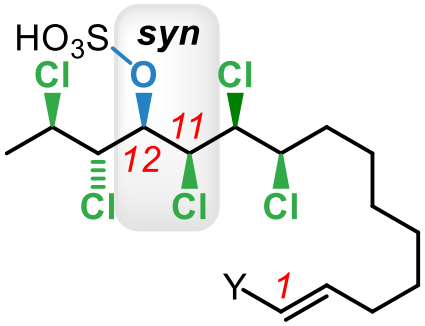
- Lipohil: Polychlorierte acylische Motive
- Hydrophil: Sulfonat-Gruppen



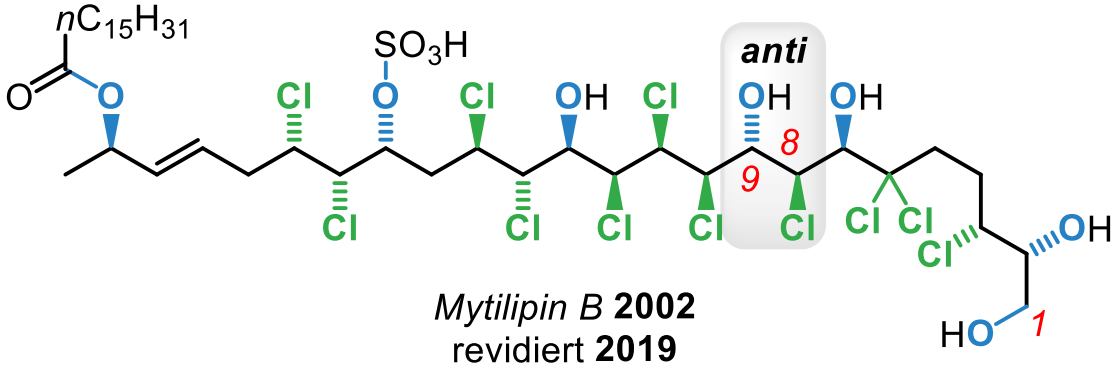
Danicalipin A
1969



Malhamensilipin A
1994



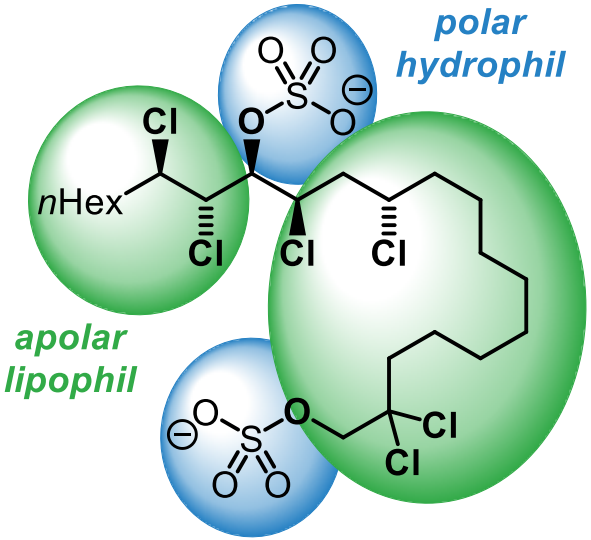
Mytilipin A **2001** (Y = Cl)
Deschloromytilipin A **2010** (Y = H)

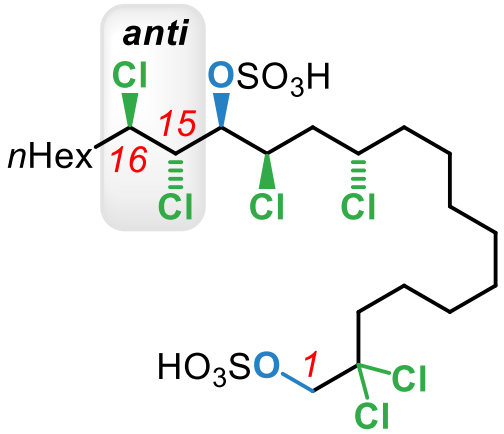


Mytilipin B **2002**
revidiert **2019**

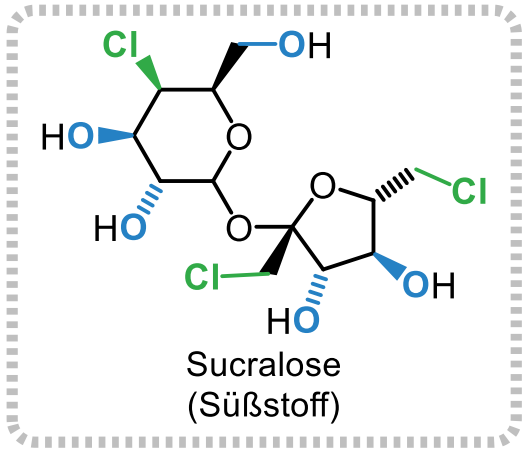
Übersichtsartikel: (a) Vanderwal *et al.*, *Nat. Prod. Rep.* **2011**, *28*, 15. (b) Carreira *et al.*, *Eur. J. Org. Chem.* **2012**, 1685. (c) Matsuda *et al.*, *Tetrahedron Lett.* **2014**, *55*, 3003. (d) Vanderwal *et al.*, *Acc. Chem. Res*. **2014**, *47*, 718. (e) Huy *et al.*, *Nachr. Chem.* **2019**, *67(9)*, 63.

- Lipohil: Polychlorierte acylische Motive
- Hydrophil: Sulfonat-Gruppen → **Chlorosulfolipide**
- Isoliert aus Süsswasseralgen und Muscheln

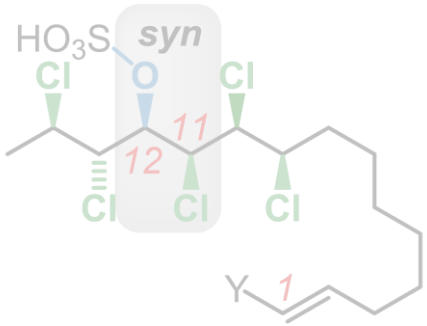




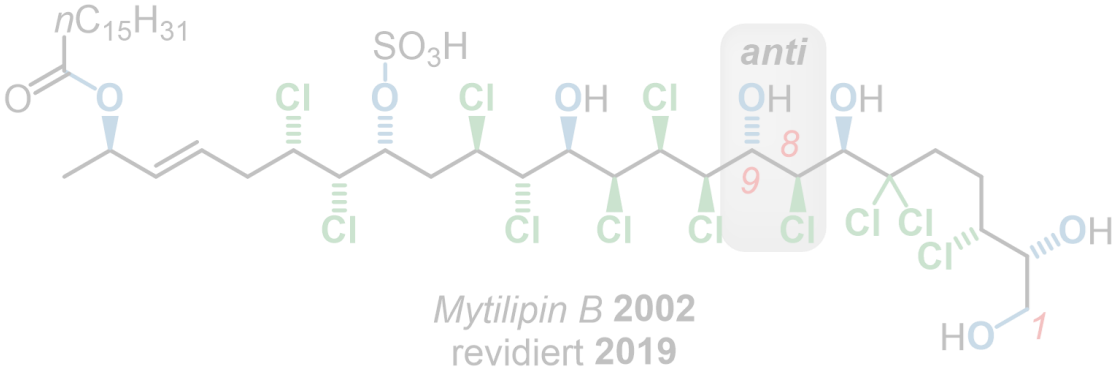
Danicalipin A
1969



Sucralose
(Süßstoff)



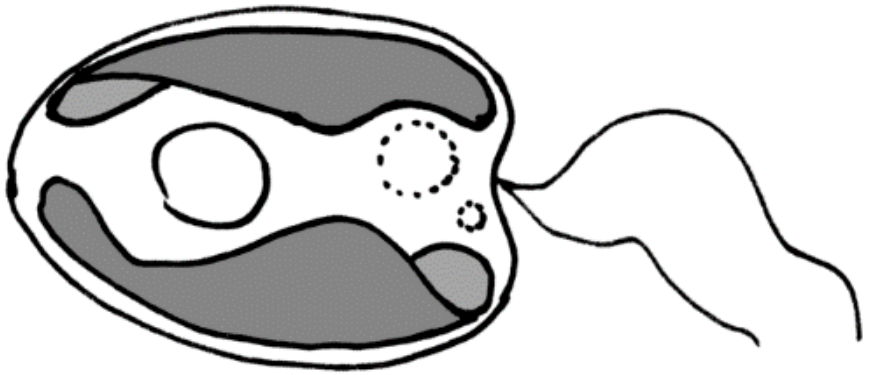
Mytilipin A **2001** (Y = Cl)
Deschloromytilipin A **2010** (Y = H)

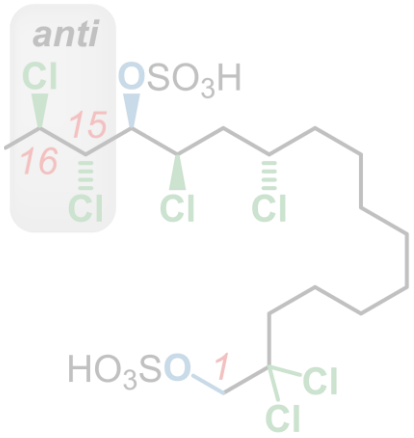


Mytilipin B **2002**
revidiert **2019**

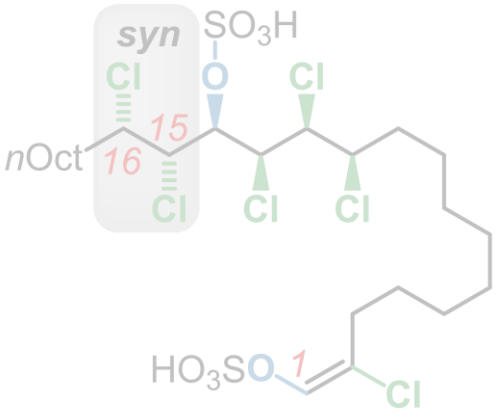
Übersichtsartikel: (a) Vanderwal *et al.*, *Nat. Prod. Rep.* **2011**, *28*, 15. (b) Carreira *et al.*, *Eur. J. Org. Chem.* **2012**, 1685. (c) Matsuda *et al.*, *Tetrahedron Lett.* **2014**, *55*, 3003. (d) Vanderwal *et al.*, *Acc. Chem. Res*. **2014**, *47*, 718. (e) P. H. Huy, P. Grewelinger, *Nachr. Chem.* **2019**, *67(9)*, 63.

- Hauptvorkommen goldbraunen Mikroalgen *Ochromonas danica* aus der Adriatischen See
- Hauptbestandteil der Flagellen zur Fortbewegung

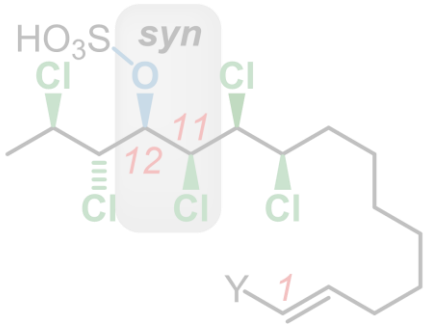




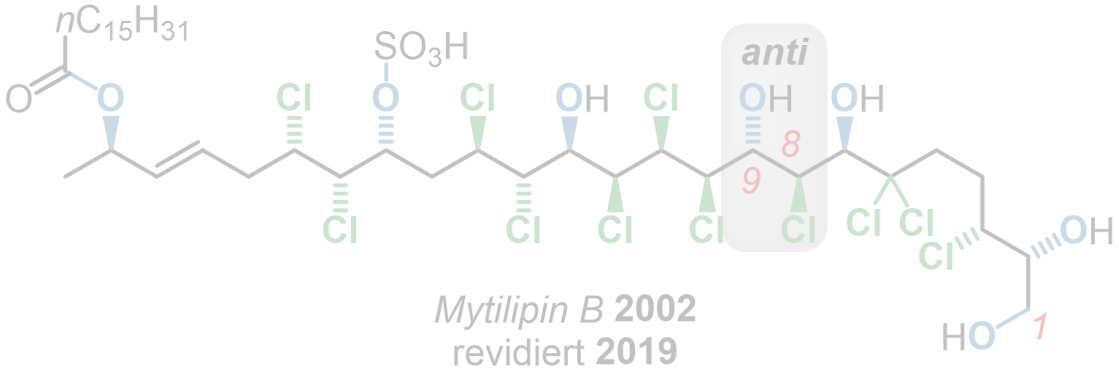
Danicalipin A **1969**



Malhamensilipin A **1994**



Mytilipin A **2001** (Y = Cl)
Deschloromytilipin A **2010** (Y = H)

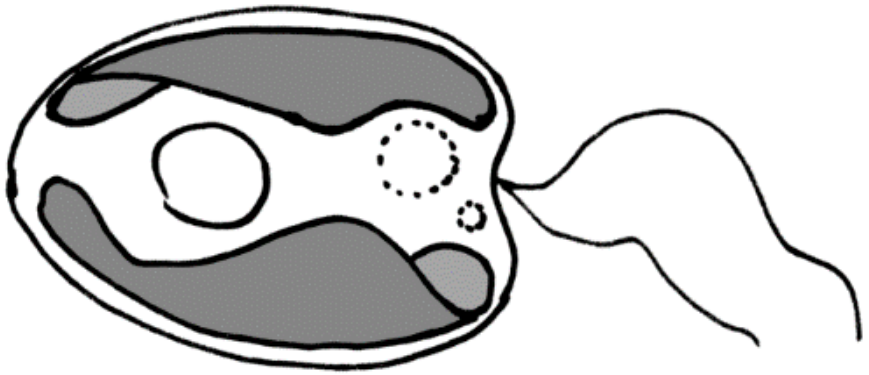


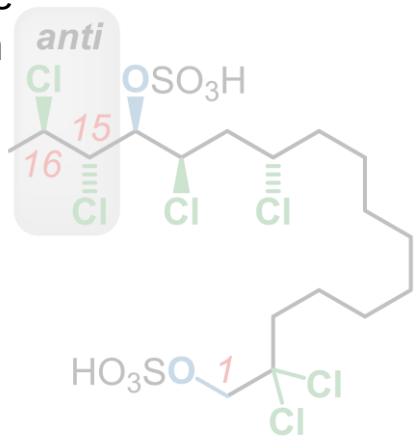
Mytilipin B **2002**
revidiert **2019**

Übersichtsartikel: (a) Vanderwal *et al.*, *Nat. Prod. Rep.* **2011**, *28*, 15. (b) Carreira *et al.*, *Eur. J. Org. Chem.* **2012**, 1685. (c) Matsuda *et al.*, *Tetrahedron Lett.* **2014**, *55*, 3003. (d) Vanderwal *et al.*, *Acc. Chem. Res*. **2014**, *47*, 718. (e) P. H. Huy, P. Grewelinger, *Nachr. Chem.* **2019**, *67(9)*, 63. picture from https://de.wikipedia.org/wiki/Ochromonas

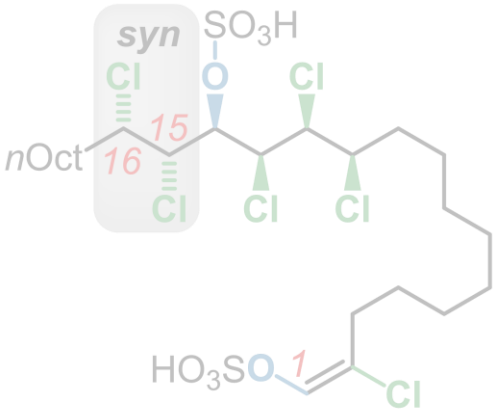
- Hauptvorkommen goldbraunen Mikroalgen *Ochromonas danica* aus der Adriatischen See
- Hauptbestandteil der Flagellen zur Fortbewegung

- Cytotoxisch, antimikrobiell und antiproliferative
- Lebensgefährliche Meeresfrüchtevergiftungen

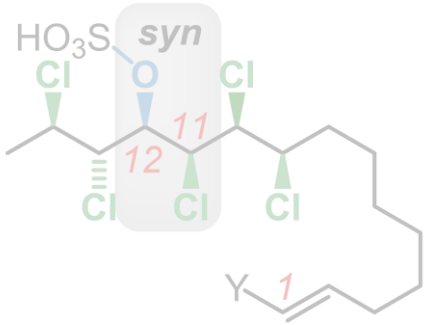




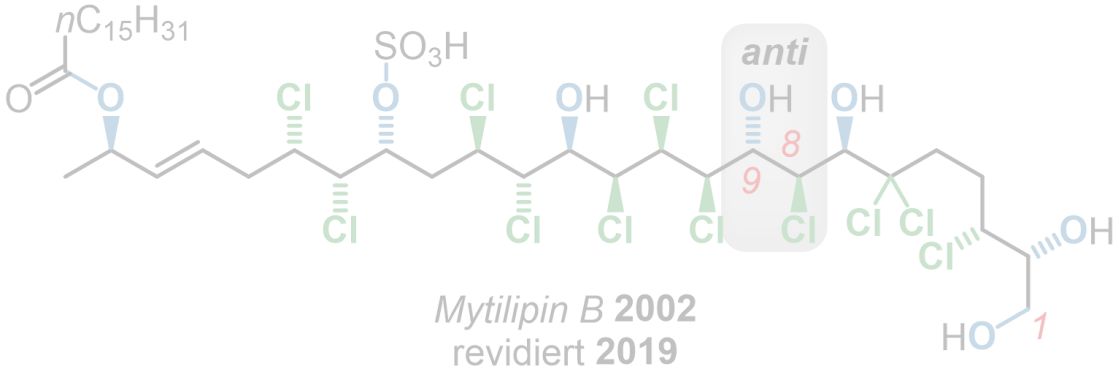
Danicalipin A
1969



Malhamensilipin A
1994



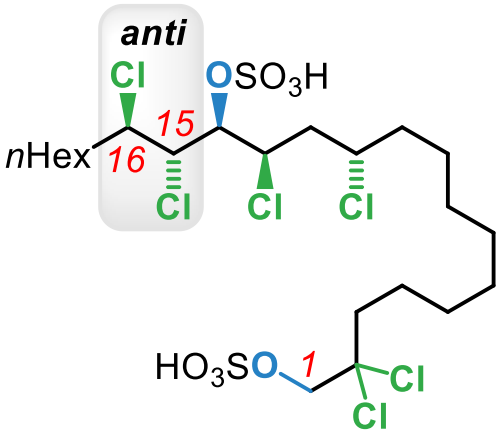
Mytilipin A **2001** (Y = Cl)
Deschloromytilipin A **2010** (Y = H)



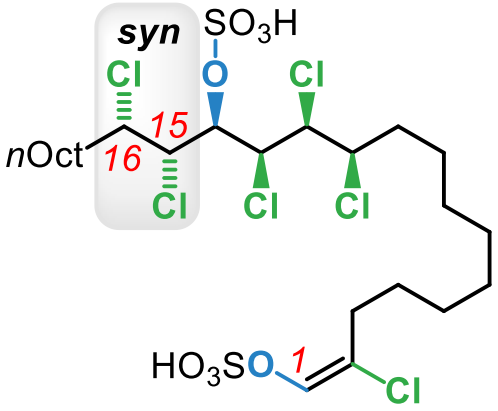
Mytilipin B **2002**
revidiert **2019**

Übersichtsartikel: (a) Vanderwal *et al.*, *Nat. Prod. Rep.* **2011**, *28*, 15. (b) Carreira *et al.*, *Eur. J. Org. Chem.* **2012**, 1685. (c) Matsuda *et al.*, *Tetrahedron Lett.* **2014**, *55*, 3003. (d) Vanderwal *et al.*, *Acc. Chem. Res*. **2014**, *47*, 718. (e) P. H. Huy, P. Grewelinger, *Nachr. Chem.* **2019**, *67(9)*, 63. picture from https://de.wikipedia.org/wiki/Ochromonas

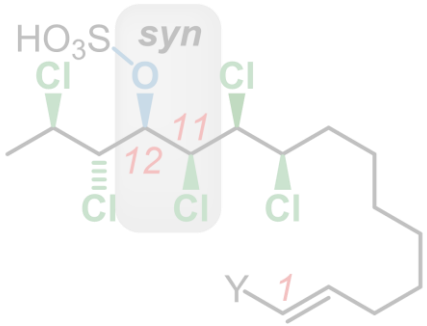
- Hohe Stereochemische Komplexität
- *anti*- und *syn*-1,2-Dichloride



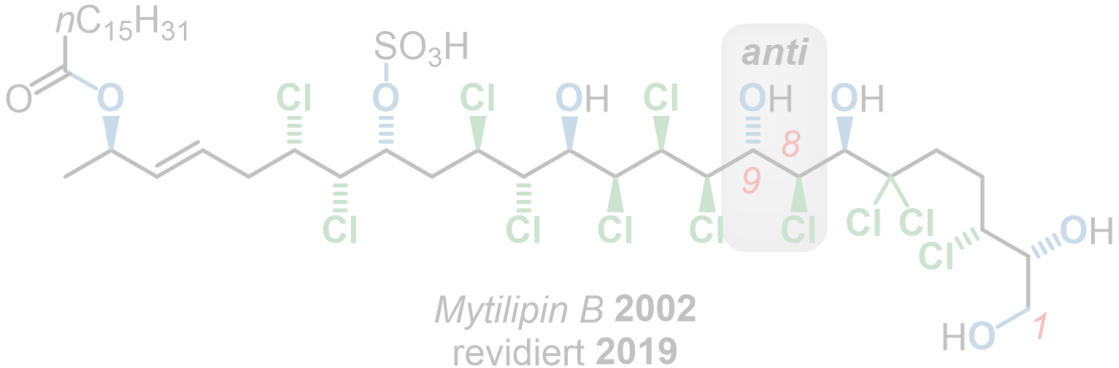
Danicalipin A
1969



Malhamensilipin A
1994



Mytilipin A **2001** (Y = Cl)
Deschloromytilipin A **2010** (Y = H)



Mytilipin B **2002**
revidiert **2019**

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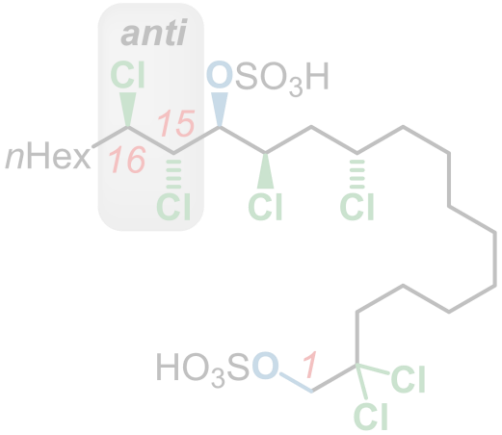
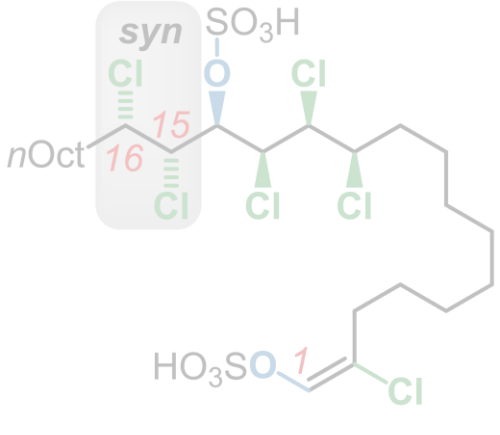
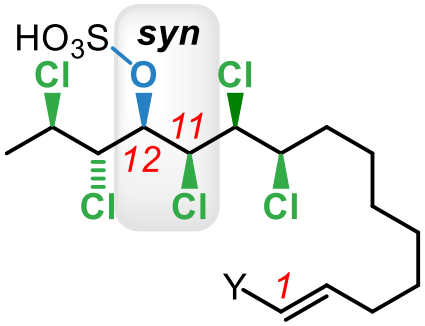
- Hohe Stereochemische Komplexität
- *anti*- und *syn*-1,2-Dichloride
- *anti*- und *syn*-Chlorhydrine
- Erste Isolation **1969**
- Erste Totalsynthese **2009**



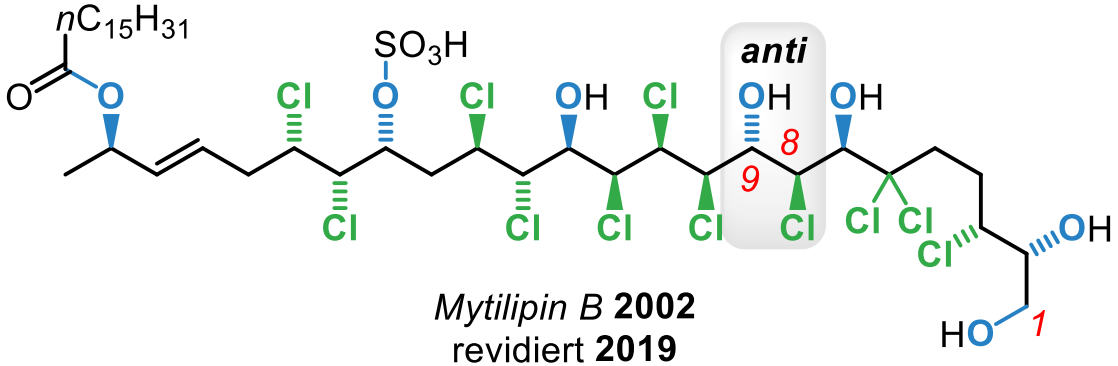
Danicalipin A
1969



Malhamensilipin A
1994

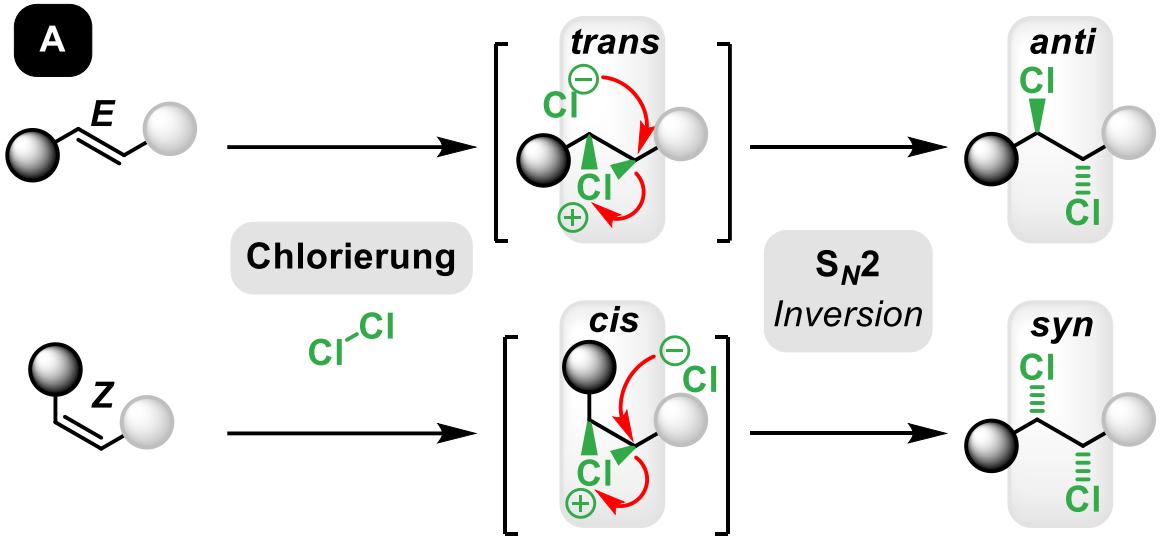


Mytilipin A **2001** (Y = Cl)
Deschloromytilipin A **2010** (Y = H)



Mytilipin B **2002**
revidiert **2019**

Übersichtsartikel: (a) Vanderwal *et al.*, *Nat. Prod. Rep.* **2011**, *28*, 15. (b) Carreira *et al.*, *Eur. J. Org. Chem.* **2012**, 1685. (c) Matsuda *et al.*, *Tetrahedron Lett.* **2014**, *55*, 3003. (d) Vanderwal *et al.*, *Acc. Chem. Res*. **2014**, *47*, 718. (e) P. H. Huy, P. Grewelinger, *Nachr. Chem.* **2019**, *67(9)*, 63.



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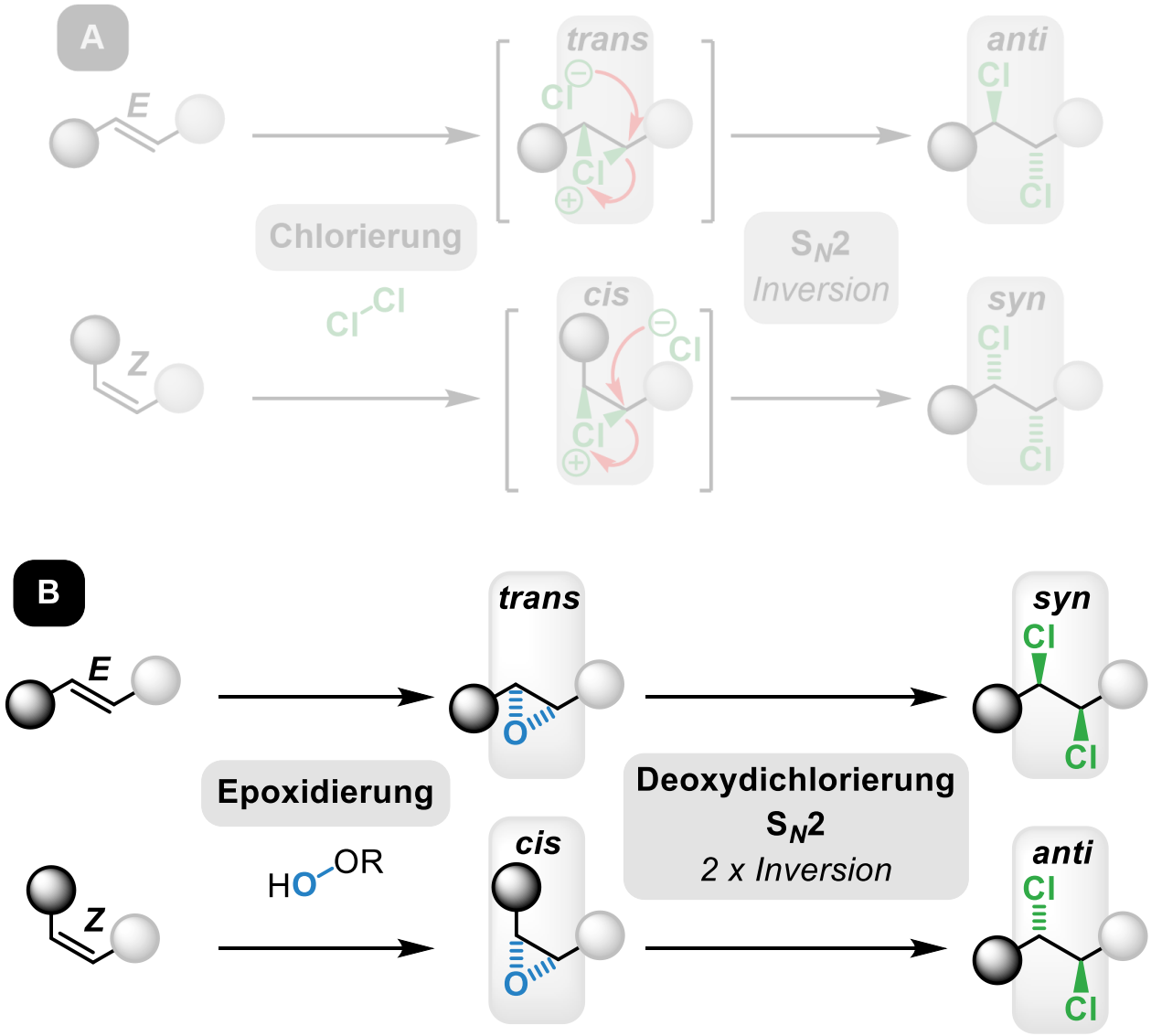
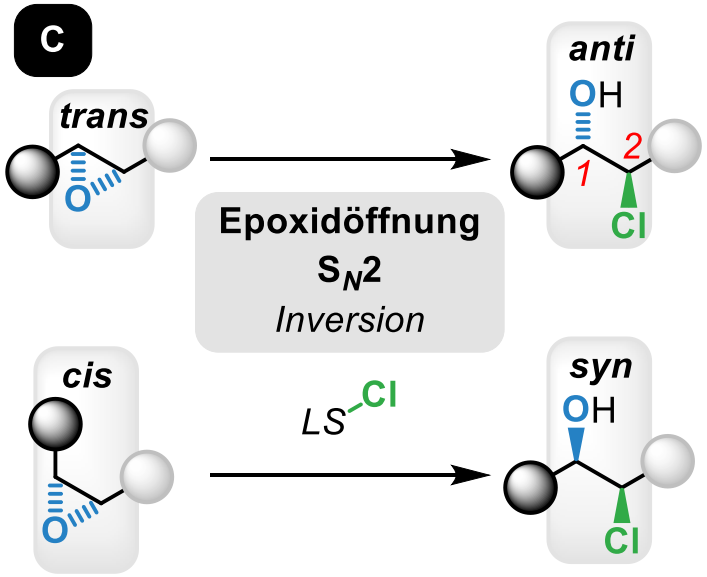


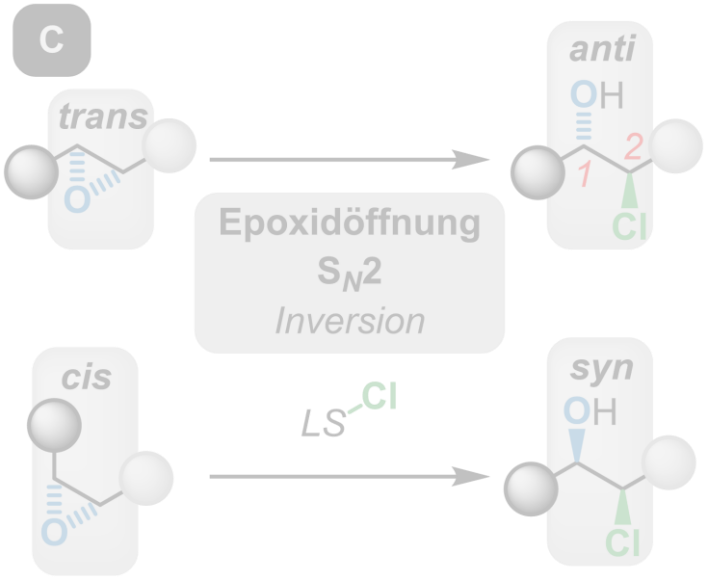
Übersichtsartikel: (a) Vanderwal *et al.*, *Nat. Prod. Rep.* **2011**, *28*, 15. (b) Carreira *et al.*, *Eur. J. Org. Chem.* **2012**, 1685. (c) Matsuda *et al.*, *Tetrahedron Lett.* **2014**, *55*, 3003. (d) Vanderwal *et al.*, *Acc. Chem. Res*. **2014**, *47*, 718. (e) P. H. Huy, P. Grewelinger, *Nachr. Chem.* **2019**, *67(9)*, 63.

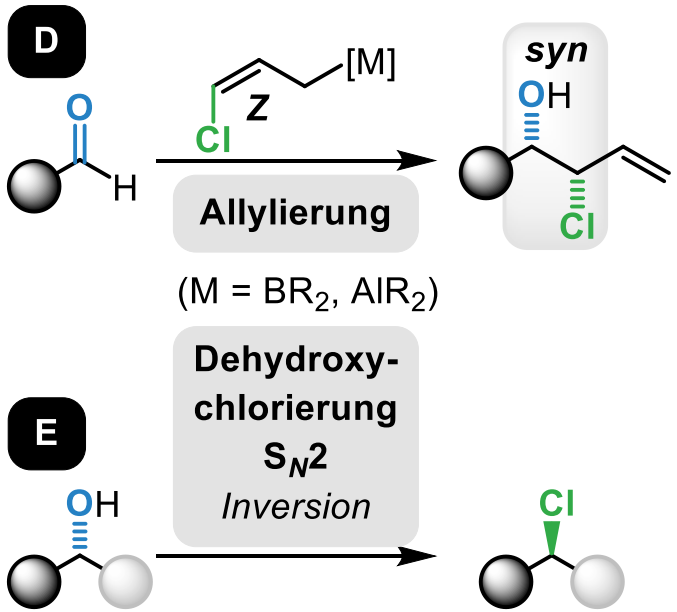


***Lewis*-Säuren** (*LS*)

- Ti(+*IV*), Zr(+*IV*), B(+*III*), Si(+*IV*)

Übersichtsartikel: (a) Vanderwal *et al.*, *Nat. Prod. Rep.* **2011**, *28*, 15. (b) Carreira *et al.*, *Eur. J. Org. Chem.* **2012**, 1685. (c) Matsuda *et al.*, *Tetrahedron Lett.* **2014**, *55*, 3003. (d) Vanderwal *et al.*, *Acc. Chem. Res*. **2014**, *47*, 718. (e) P. H. Huy, P. Grewelinger, *Nachr. Chem.* **2019**, *67(9)*, 63.

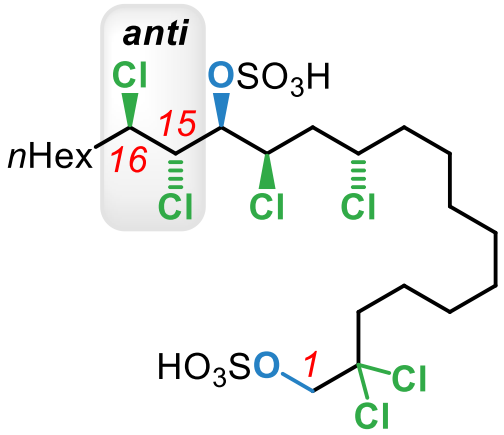




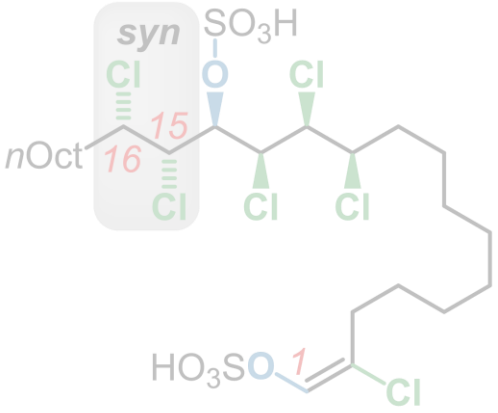
***Lewis*-Säuren** (*LS*)

- Ti(+*IV*), Zr(+*IV*), B(+*III*), Si(+*IV*)

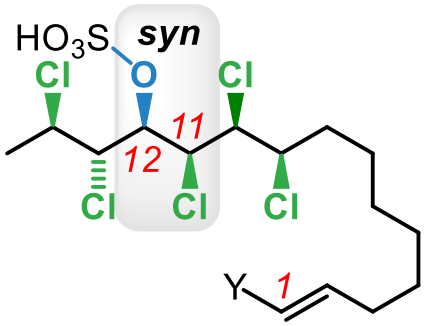
Übersichtsartikel: (a) Vanderwal *et al.*, *Nat. Prod. Rep.* **2011**, *28*, 15. (b) Carreira *et al.*, *Eur. J. Org. Chem.* **2012**, 1685. (c) Matsuda *et al.*, *Tetrahedron Lett.* **2014**, *55*, 3003. (d) Vanderwal *et al.*, *Acc. Chem. Res*. **2014**, *47*, 718. (e) P. H. Huy, P. Grewelinger, *Nachr. Chem.* **2019**, *67(9)*, 63.



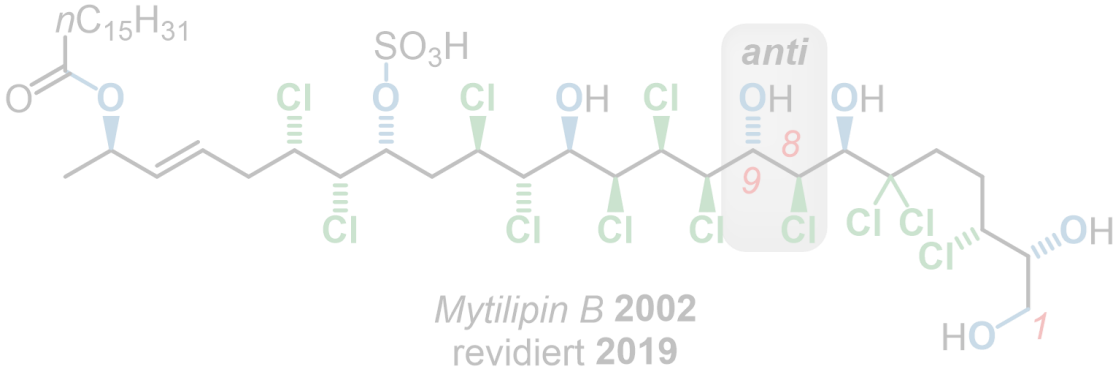
Danicalipin A
1969



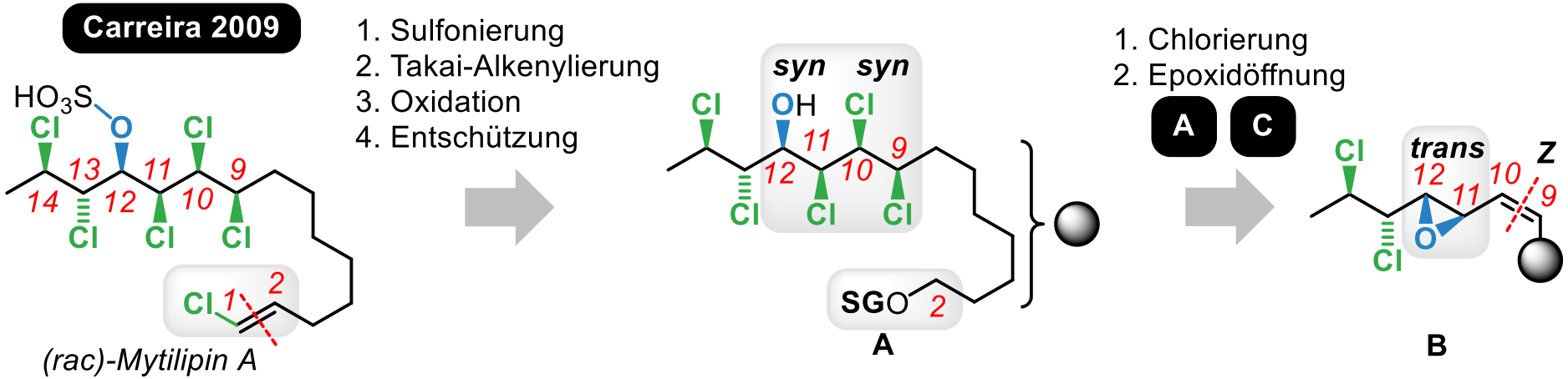
Malhamensilipin A
1994



Mytilipin A **2001** (Y = Cl)
Deschloromytilipin A **2010** (Y = H)

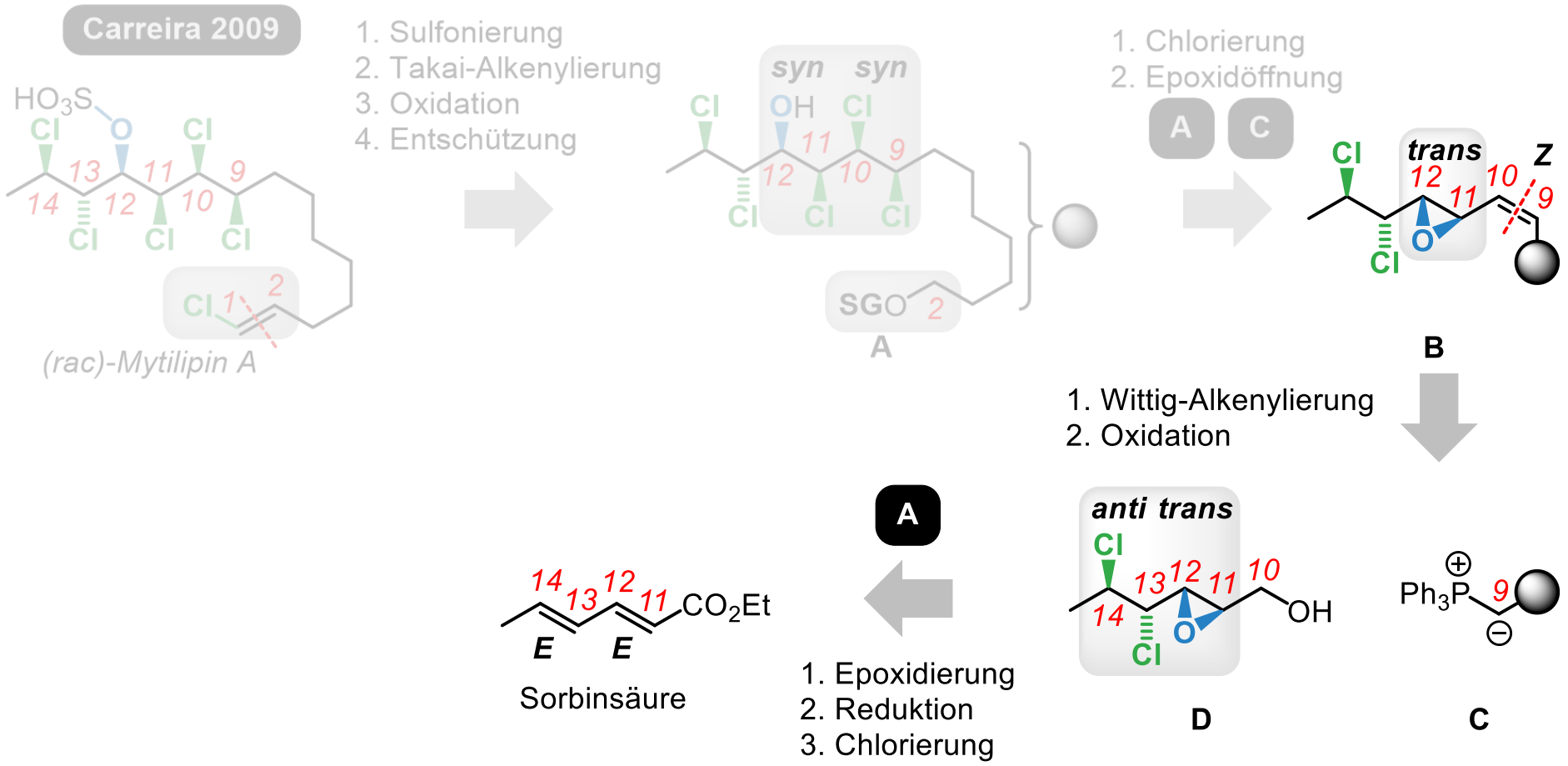


Mytilipin B **2002**
revidiert **2019**



- Isoliert von Muschel *Mytilus galloprovincialis*
- 6 Stereozentren
- 11 lineare Stufen

(a) Isolierung: Fattorusso *et al.*, *J. Org. Chem.* **2001**, *66*, 578. (b) Synthese: Carreira *et al.*, *Nature* **2009**, *457*, 573.



- Isoliert von Muschel *Mytilus galloprovincialis*
- 6 Stereozentren
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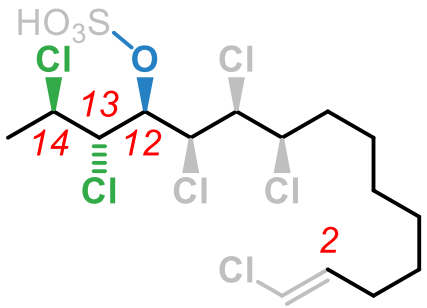
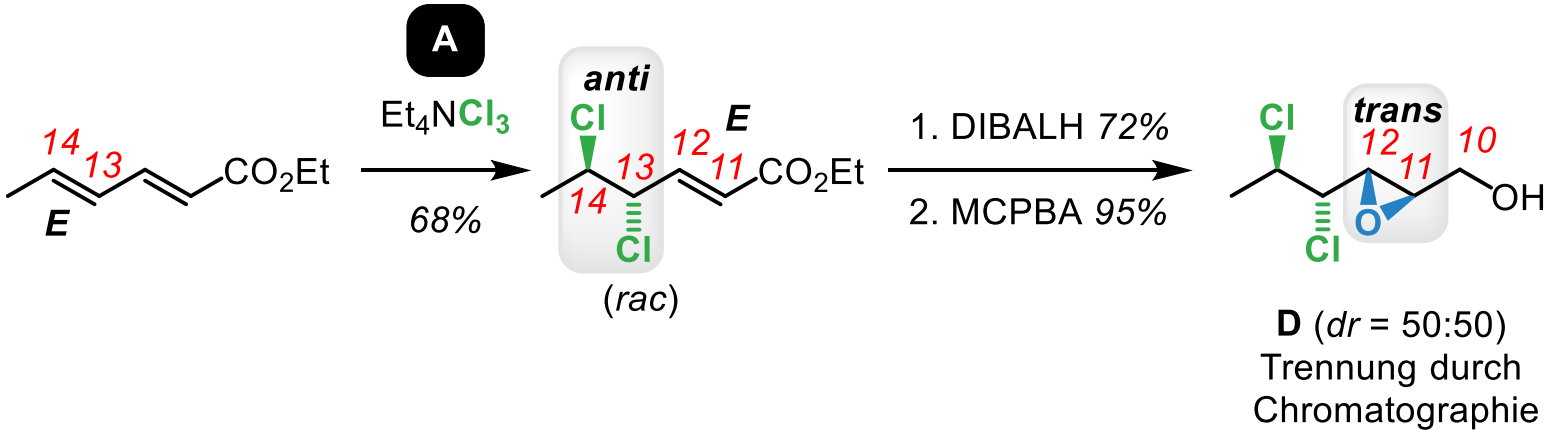
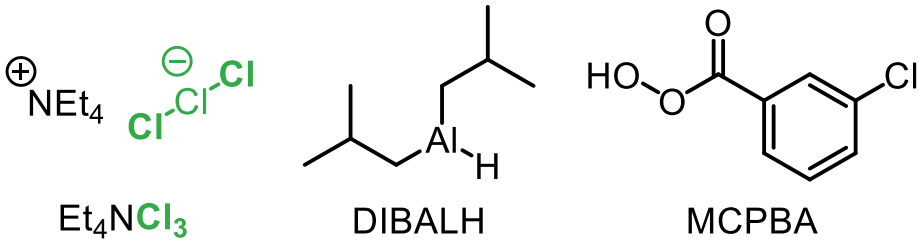
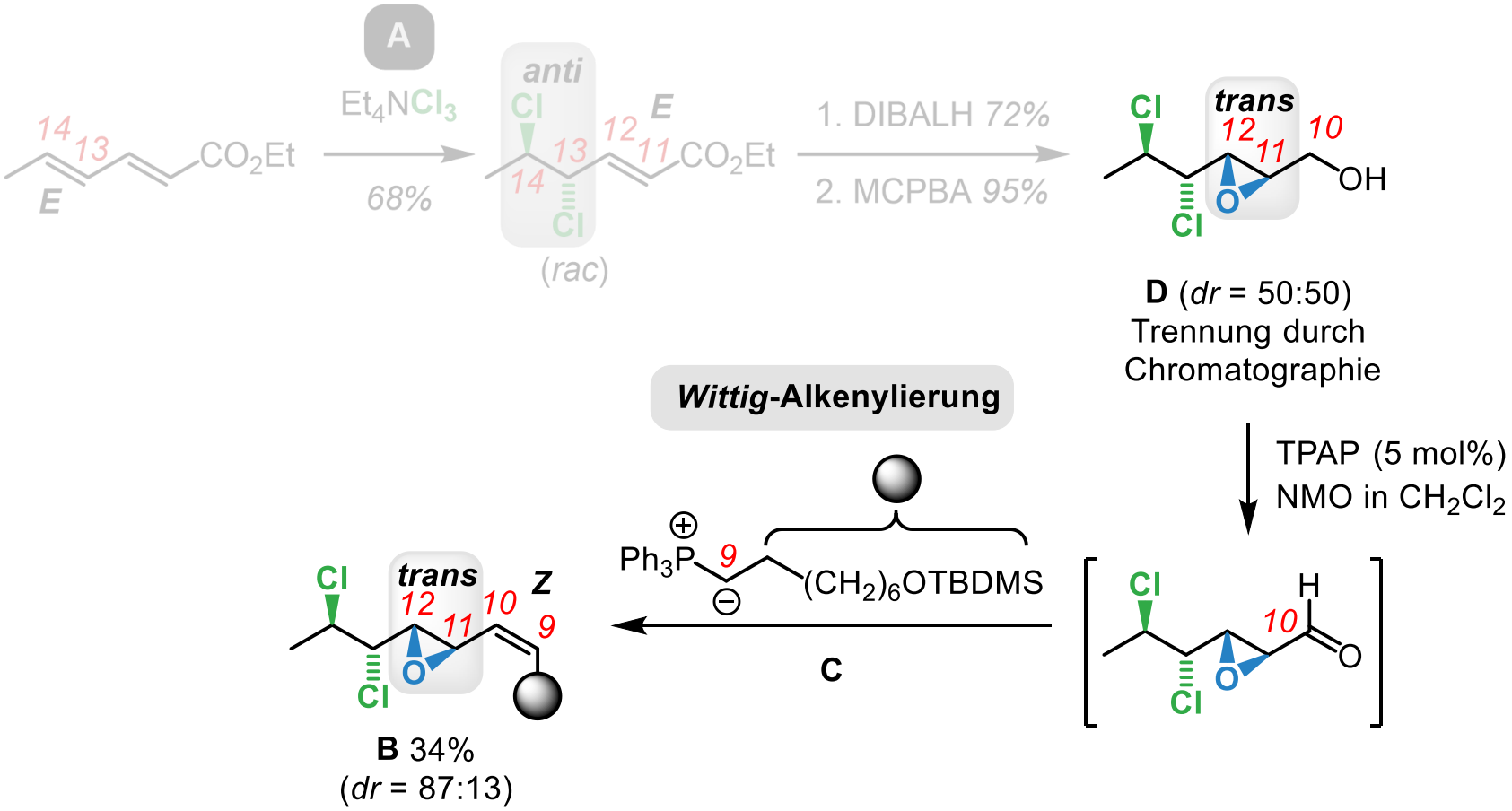
(a) Isolierung: Fattorusso *et al.*, *J. Org. Chem.* **2001**, *66*, 578. (b) Synthese: Carreira *et al.*, *Nature* **2009**, *457*, 573.

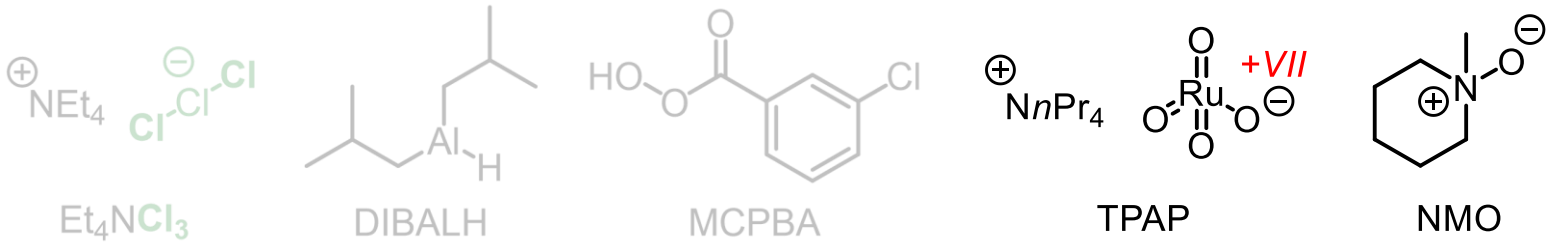


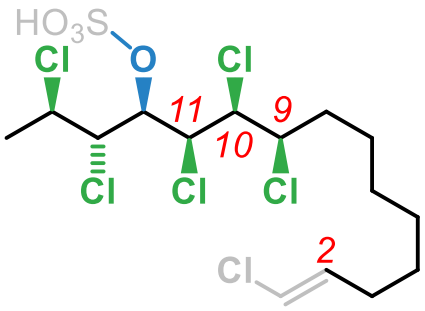
(rac)-Mytilipin A

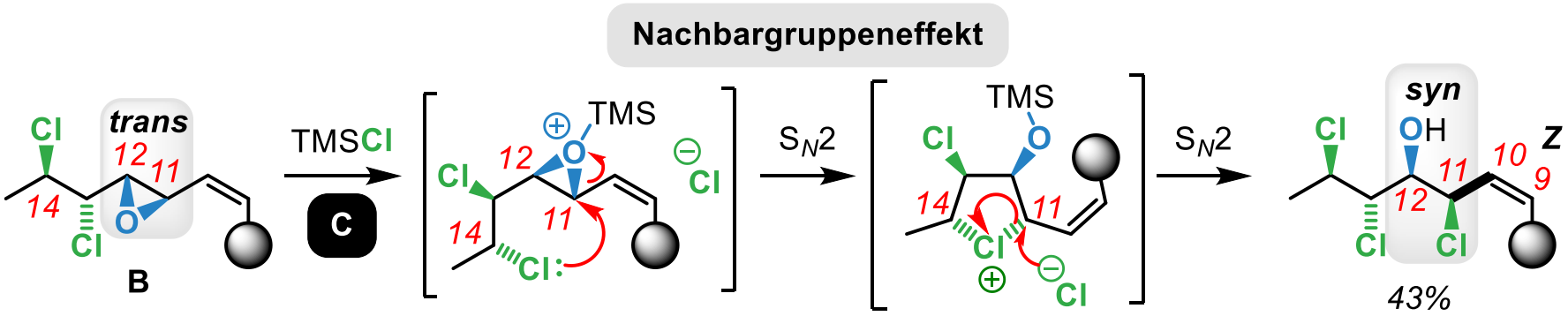

A
Et4NCl3
68%
anti
E
(rac)
1. DIBALH 72%
2. MCPBA 95%
trans
D (dr = 50:50)
Trennung durch
Chromatographie

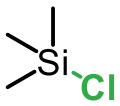

Et4NCl3
DIBALH
MCPBA


A
Et_4NCl_3
68%
anti
E
(rac)
1. DIBALH 72%
2. MCPBA 95%
trans
D (dr = 50:50)
Trennung durch
Chromatographie
TPAP (5 mol%)
NMO in CH_2Cl_2
Wittig-Alkenylierung
Ph_3P
$(CH_2)_6OTBDMS$
C
trans
Z
B 34%
(dr = 87:13)

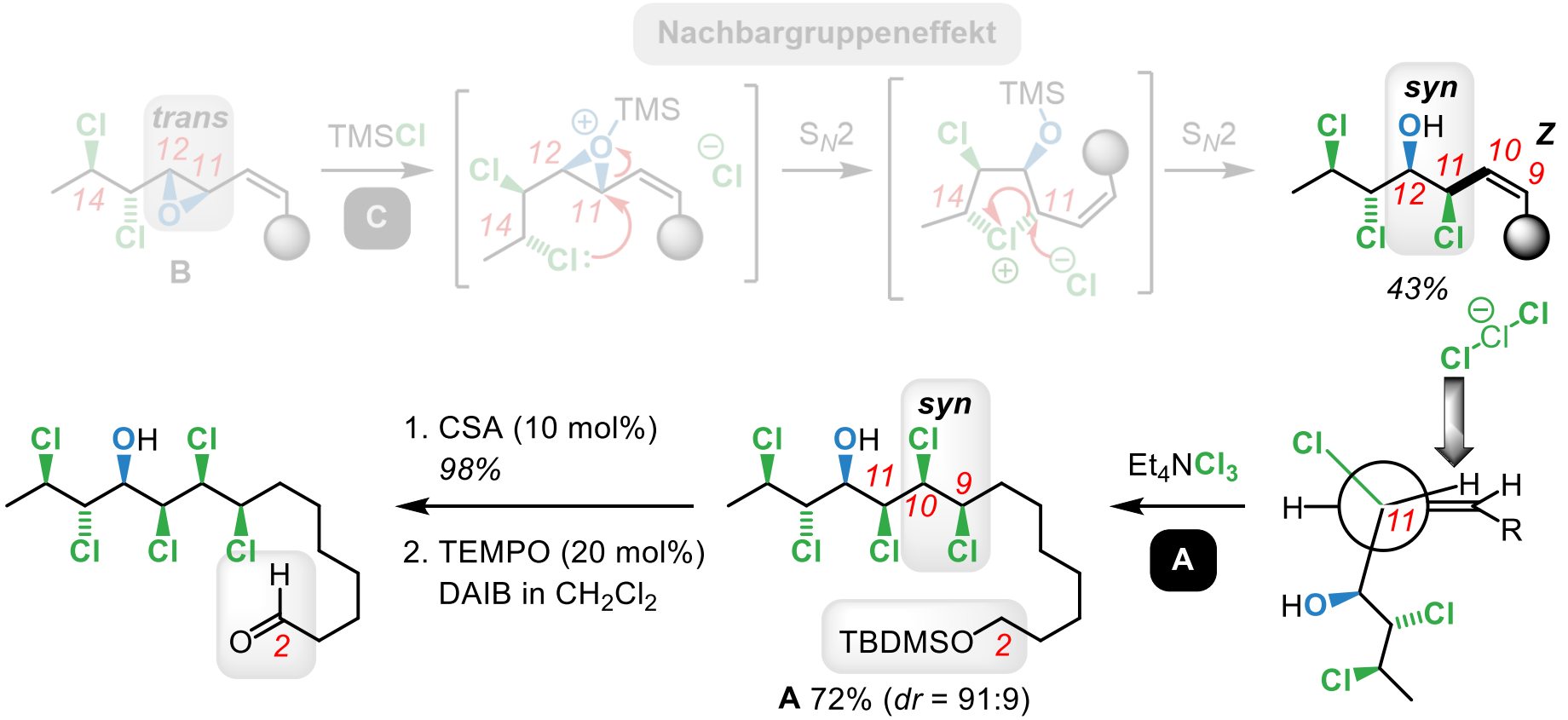

Et_4NCl_3
DIBALH
MCPBA
$NnPr_4$
+VII
TPAP
NMO

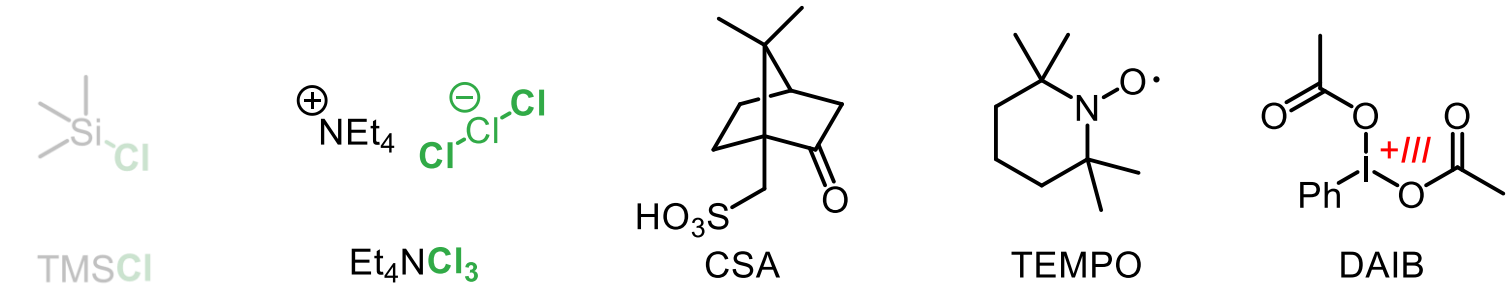

HO3S
Cl
O
Cl
11
9
10
Cl
Cl
Cl
Cl
2

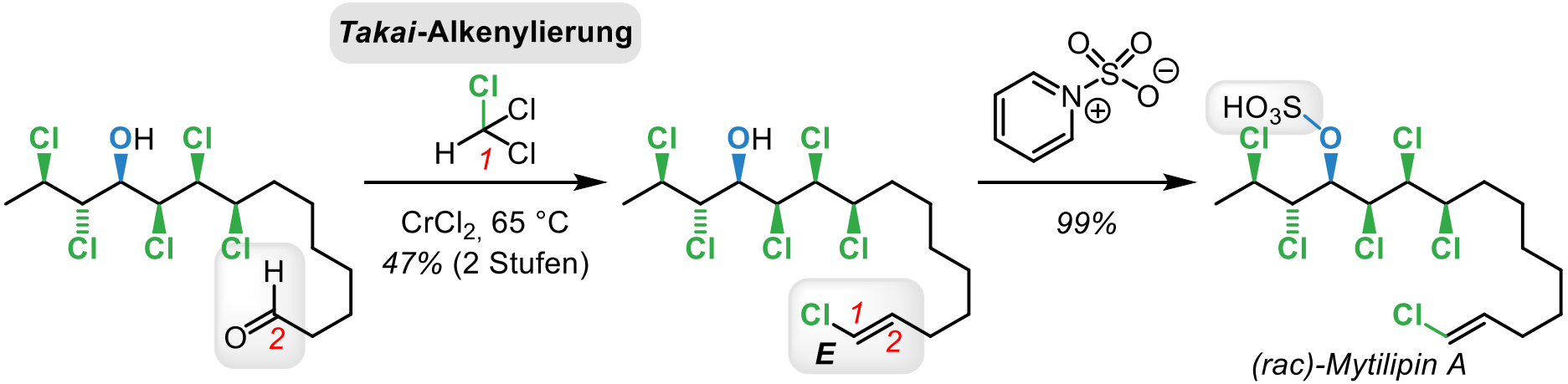

Nachbargruppeneffekt
trans
B
TMSCl
C
TMS
S_N2
S_N2
syn
OH
Z
43%


Si
Cl

TMSCl

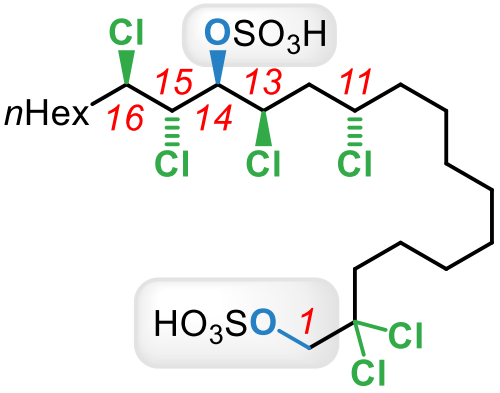

Nachbargruppeneffekt
trans
B
TMSCl
C
TMS
SN2
TMS
SN2
syn
Z
43%
1. CSA (10 mol%)
98%
2. TEMPO (20 mol%)
DAIB in CH2Cl2
syn
TBDMSO
A 72% (dr = 91:9)
Et4NCl3
A


TMSCl
Et4NCl3
CSA
TEMPO
DAIB



Takai *et al.* (a) *J. Am. Chem. Soc.* **1986**, *108*, 7408. (b) *J. Am. Chem. Soc.* **1987**, *109*, 951.

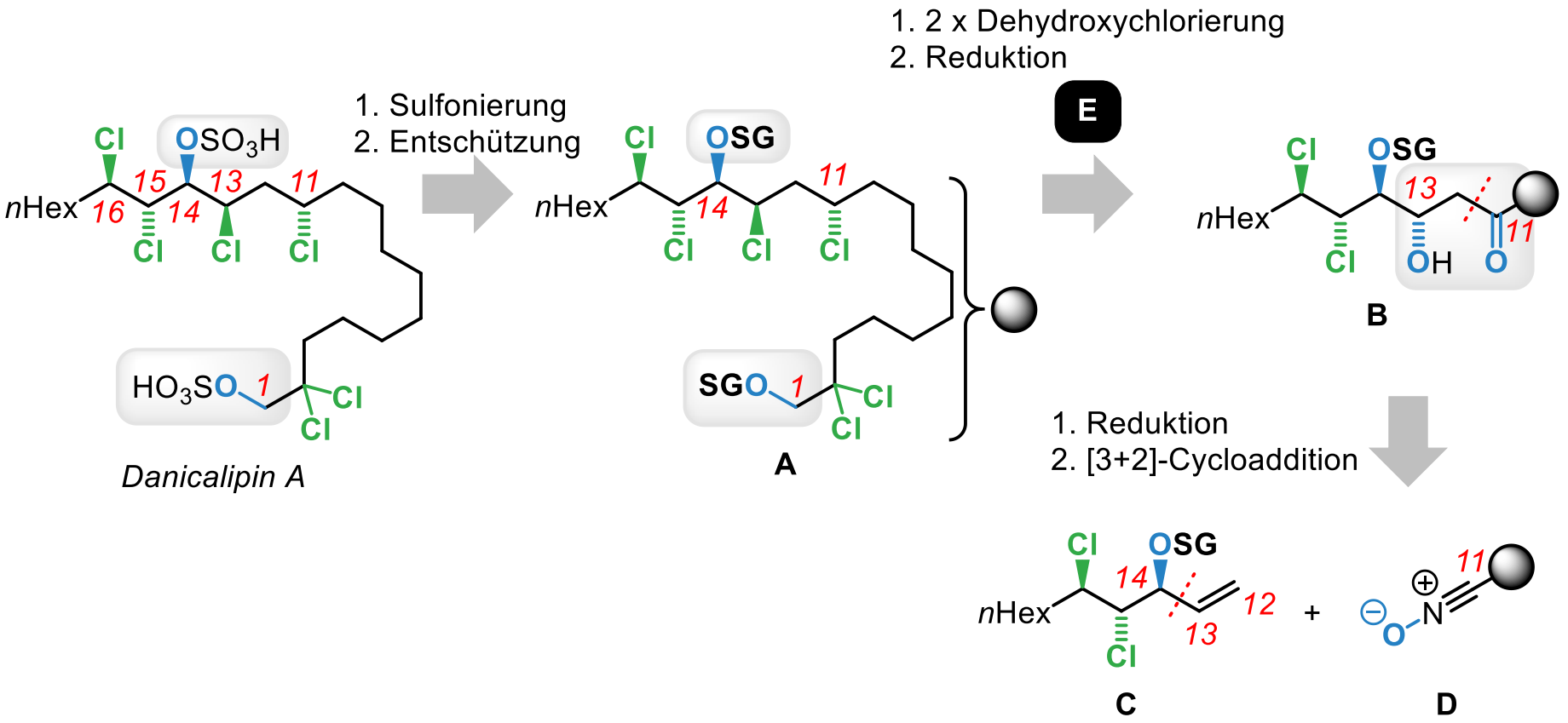
Yoshimitsu + Tanaka 2011



Danicalipin A

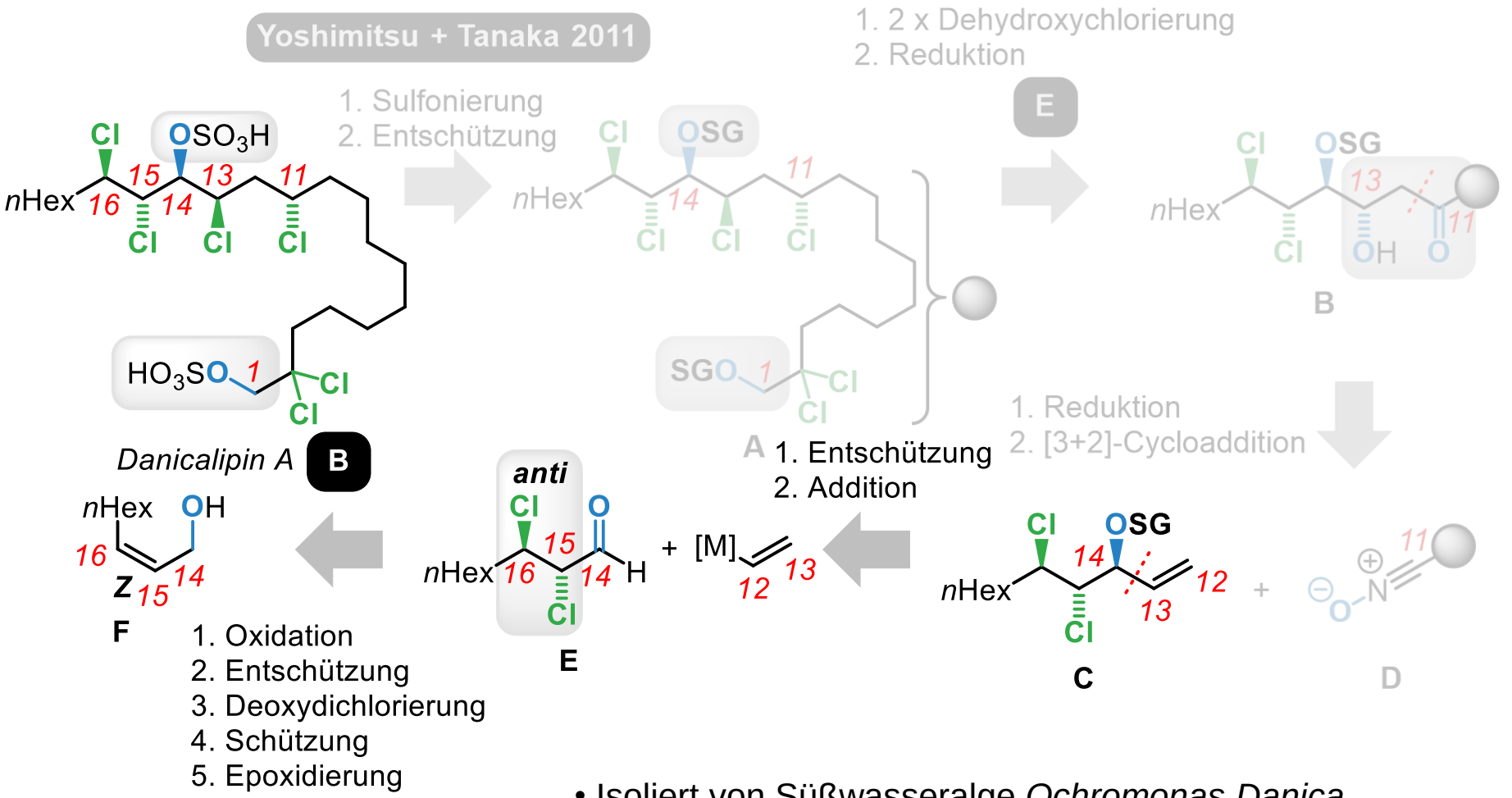
- Isoliert von Süßwasseralge *Ochromonas Danica*
- 5 Stereozentren
- 14 lineare Stufen

Isolierung: (a) Elovson, Vagelos, *Proc. Natl. Acad. Sci. U.S.A.* **1969**, *62*, 957. (b) Vanderwal *et al., J. Am. Chem. Soc*. **2009**, *131*, 7570. (b) Synthese: Yoshimitsu, Tanaka *et al.*, *Org. Lett.* **2011**, *13*, 908.



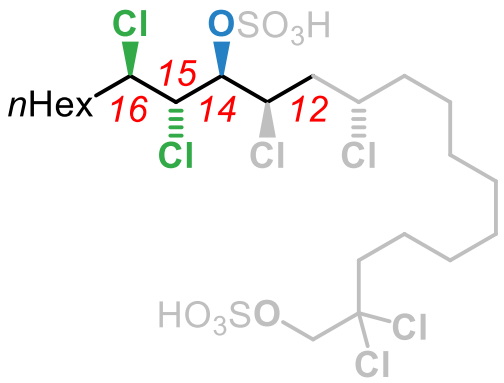
- Isoliert von Süßwasseralge *Ochromonas Danica*
- 5 Stereozentren
- 14 lineare Stufen

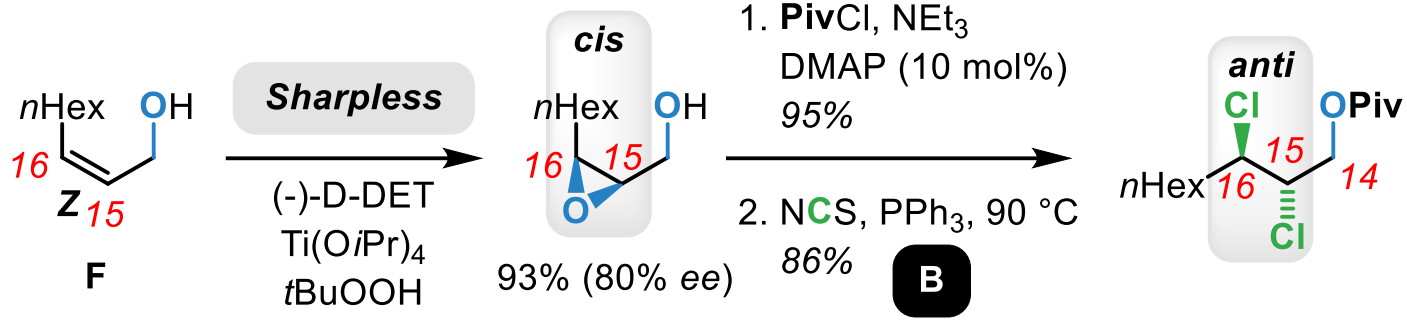
Isolierung: (a) Elovson, Vagelos, *Proc. Natl. Acad. Sci. U.S.A.* **1969**, *62*, 957. (b) Vanderwal *et al., J. Am. Chem. Soc*. **2009**, *131*, 7570. (b) Synthese: Yoshimitsu, Tanaka *et al.*, *Org. Lett.* **2011**, *13*, 908.

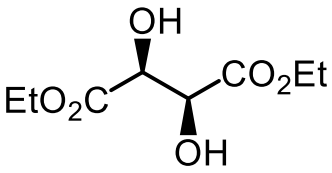


- Isoliert von Süßwasseralge *Ochromonas Danica*
- 5 Stereozentren
- 14 lineare Stufen

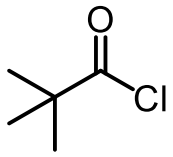
Isolierung: (a) Elovson, Vagelos, *Proc. Natl. Acad. Sci. U.S.A.* **1969**, *62*, 957. (b) Vanderwal *et al., J. Am. Chem. Soc*. **2009**, *131*, 7570. (b) Synthese: Yoshimitsu, Tanaka *et al.*, *Org. Lett.* **2011**, *13*, 908.


Cl
OSO3H
15
nHex
16
14
12
Cl
Cl
Cl
HO3SO
Cl
Cl

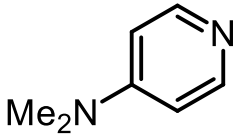




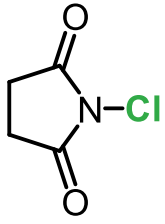
(-)-D-DET



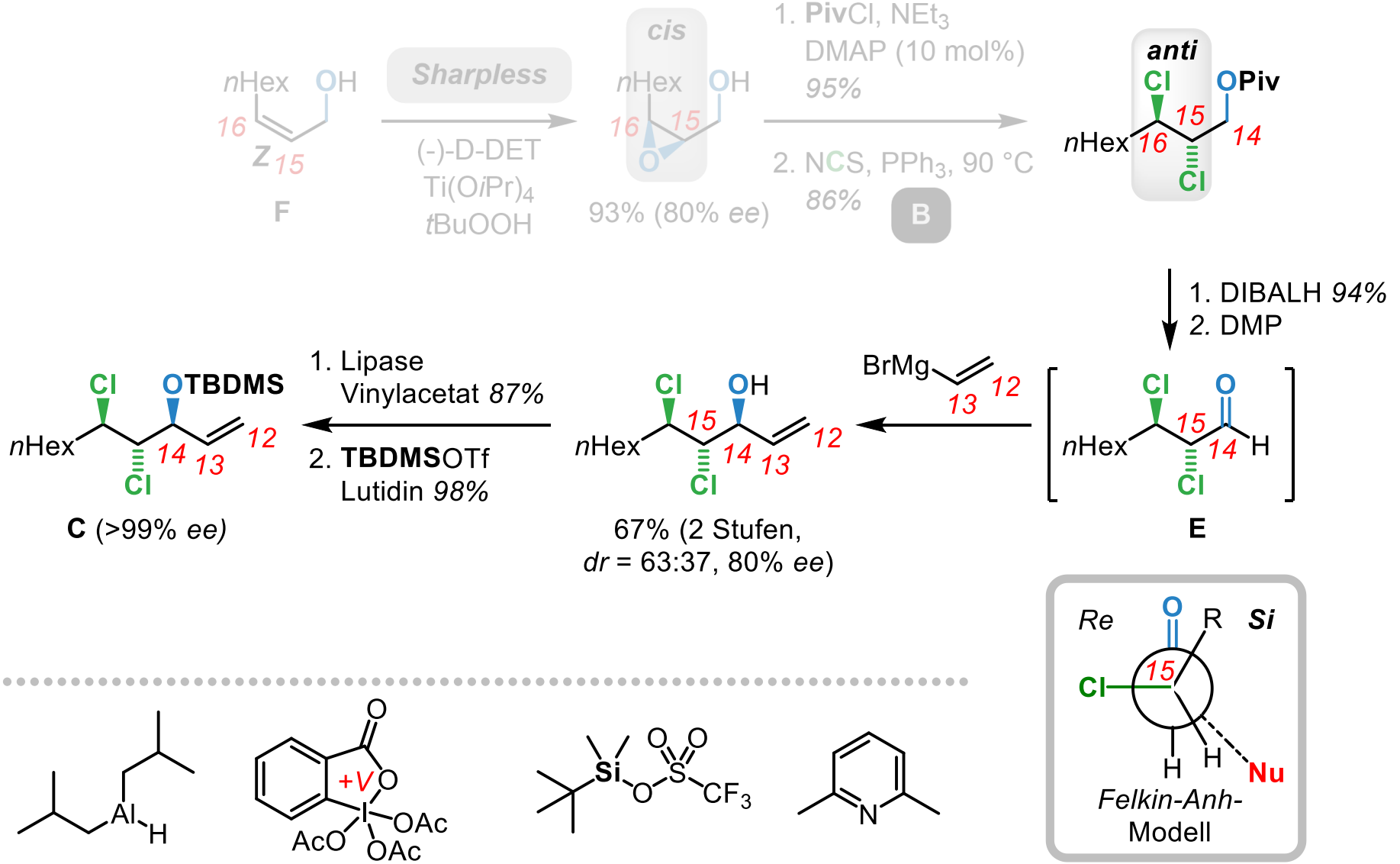
PivCl

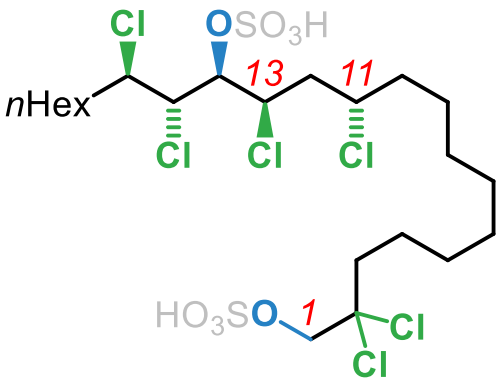


DMAP

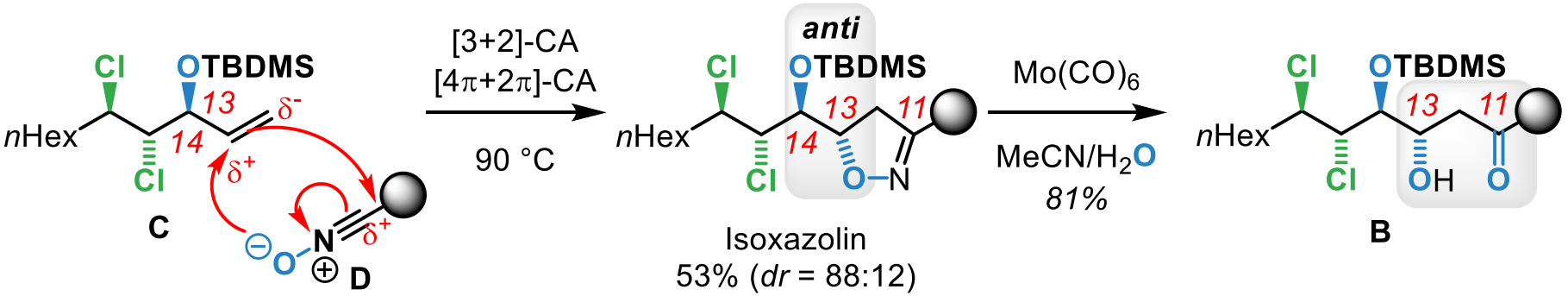


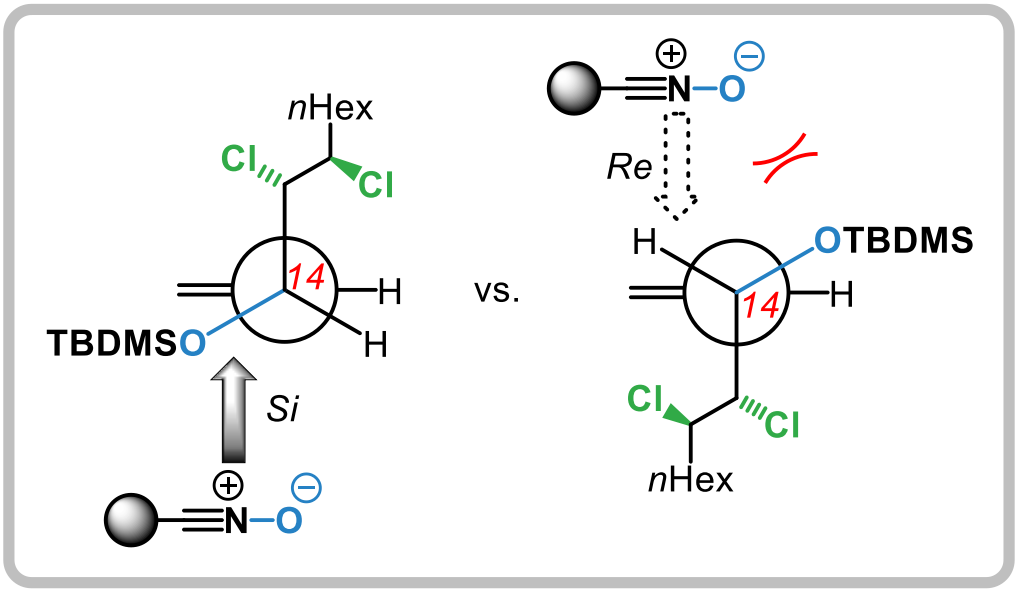
NCS


nHex
OH
16
Z 15
F
Sharpless
(-)-D-DET
Ti(OiPr)4
tBuOOH
cis
nHex
OH
16
15
O
93% (80% ee)
1. PivCl, NEt3
DMAP (10 mol%)
95%
2. NCS, PPh3, 90 °C
86%
B
anti
Cl
OPiv
15
nHex
16
14
Cl
1. DIBALH 94%
2. DMP
BrMg
13
12
Cl
O
15
nHex
14
H
Cl
E
1. Lipase
Vinylacetat 87%
2. TBDMSOTf
Lutidin 98%
Cl
OH
15
nHex
14
13
12
Cl
67% (2 Stufen,
dr = 63:37, 80% ee)
Cl
OTBDMS
nHex
14
13
12
Cl
C (>99% ee)
Re
O
R
Si
Cl
15
H
H
Nu
Felkin-Anh-
Modell
Al
H
DIBALH
+V
O
I
OAc
AcO
OAc
DMP
Si
O
O
S
O
CF3
TBDMSOTf
N
Lutidin

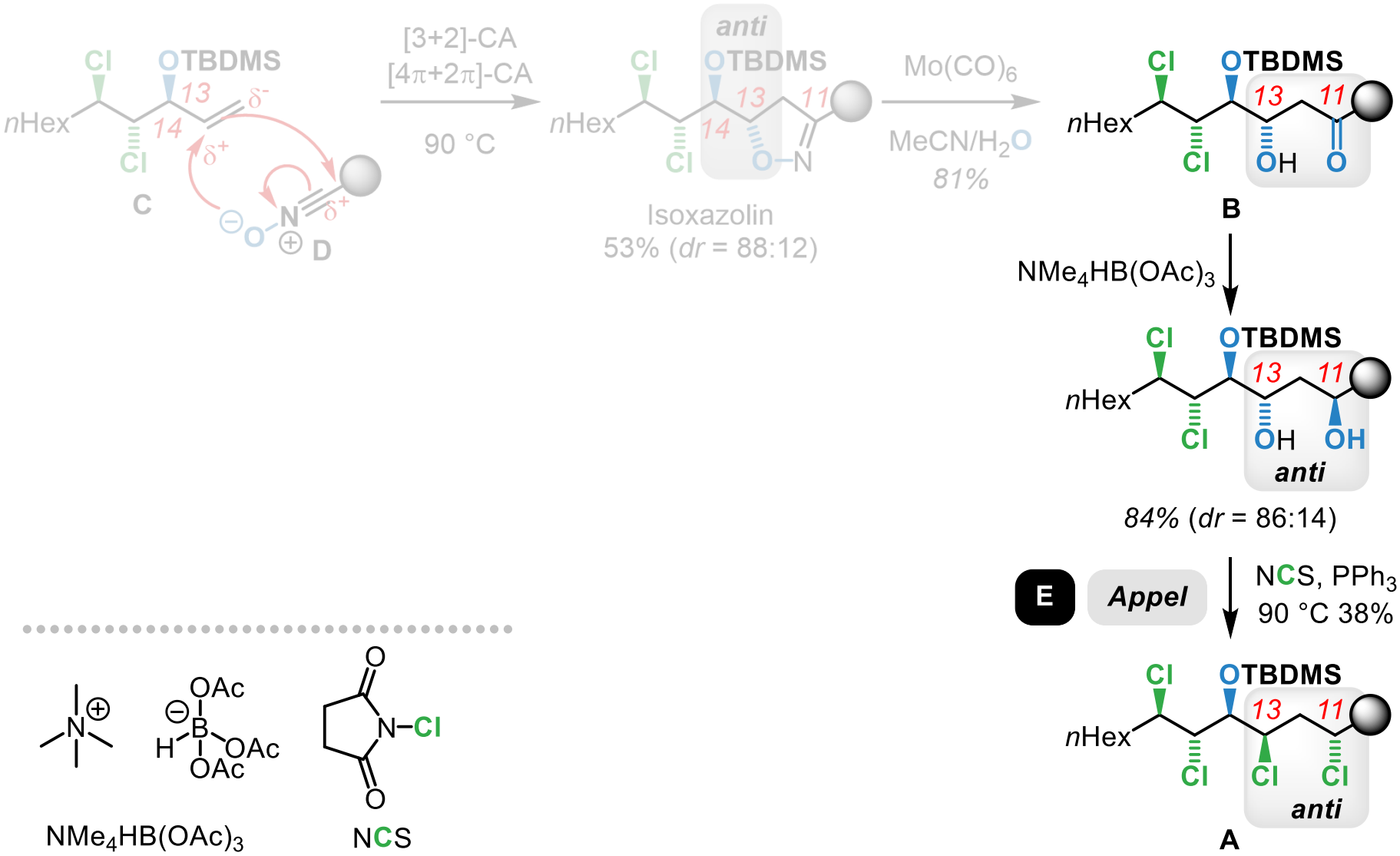


(a) Houk *et al., J. Am. Chem. Soc.* **1986**, *108*, 2755. (b) Kobayashi *et al., Chem. Soc. Perkin Trans. I* **1985**, 1401.
(c) Goti, Brandi *et al., Tetrahedron Lett.* **1990**, *31*, 3351. (d) Evans *et al., J. Am. Chem. Soc.* **1988**, *110*, 3560.

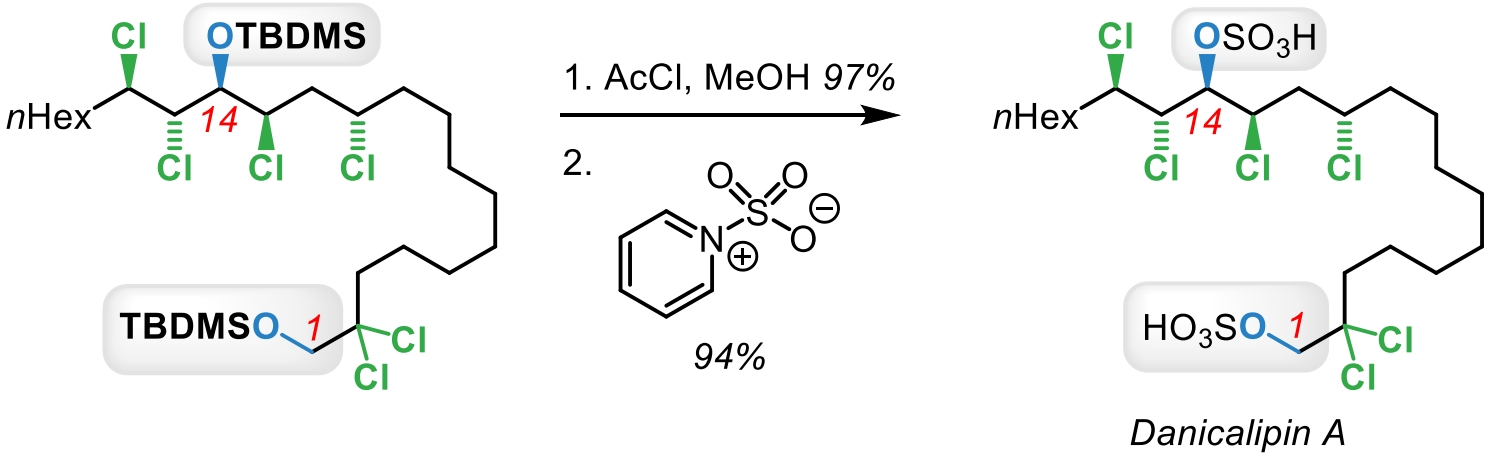




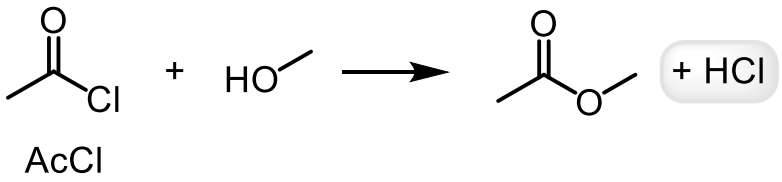
(a) Houk *et al., J. Am. Chem. Soc.* **1986**, *108*, 2755. (b) Kobayashi *et al., Chem. Soc. Perkin Trans. I* **1985**, 1401.
(c) Goti, Brandi *et al., Tetrahedron Lett.* **1990**, *31*, 3351. (d) Evans *et al., J. Am. Chem. Soc.* **1988**, *110*, 3560.



(a) Houk *et al., J. Am. Chem. Soc.* **1986**, *108*, 2755. (b) Kobayashi *et al., Chem. Soc. Perkin Trans. I* **1985**, 1401.
(c) Goti, Brandi *et al., Tetrahedron Lett.* **1990**, *31*, 3351. (d) Evans *et al., J. Am. Chem. Soc.* **1988**, *110*, 3560.

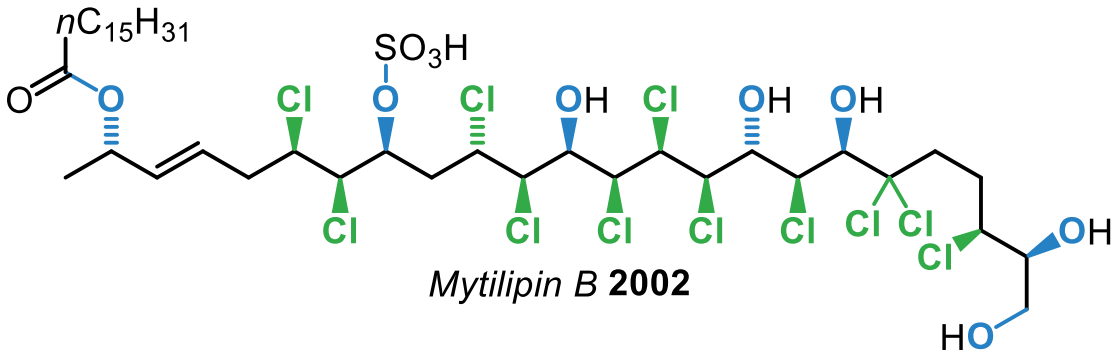


Danicalipin A



AcCl

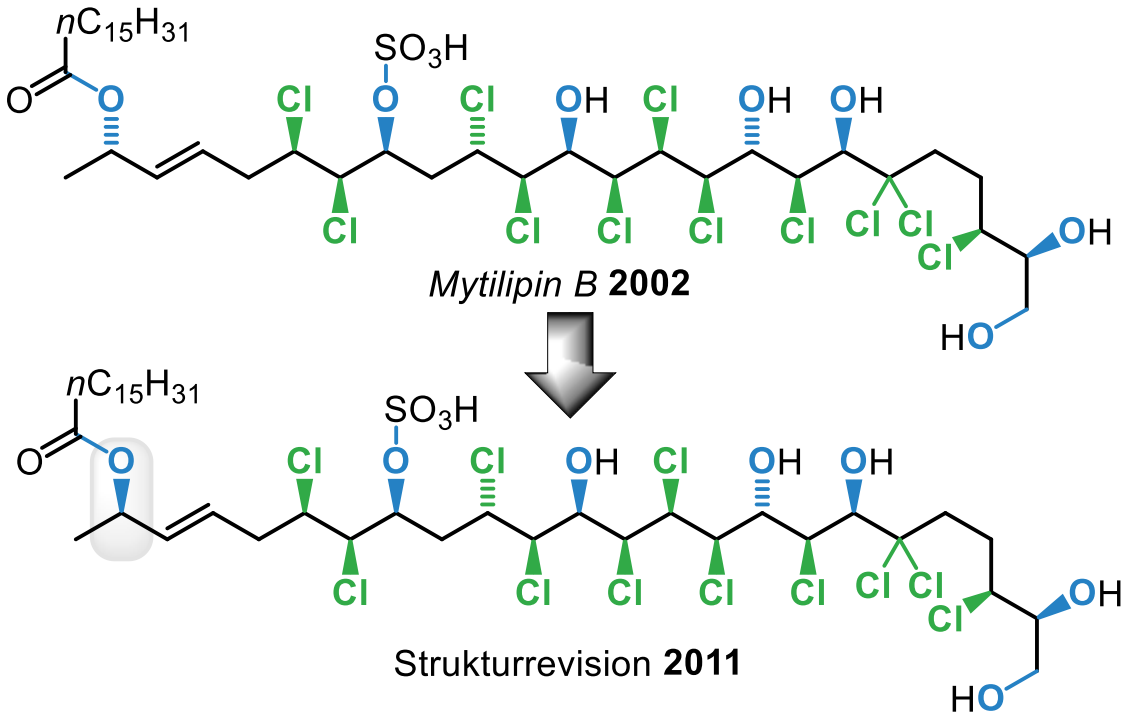
- Isoliert von Muschel *Mytilus galloprovincialis*
- 15 Stereozentren



Mytilipin B **2002**

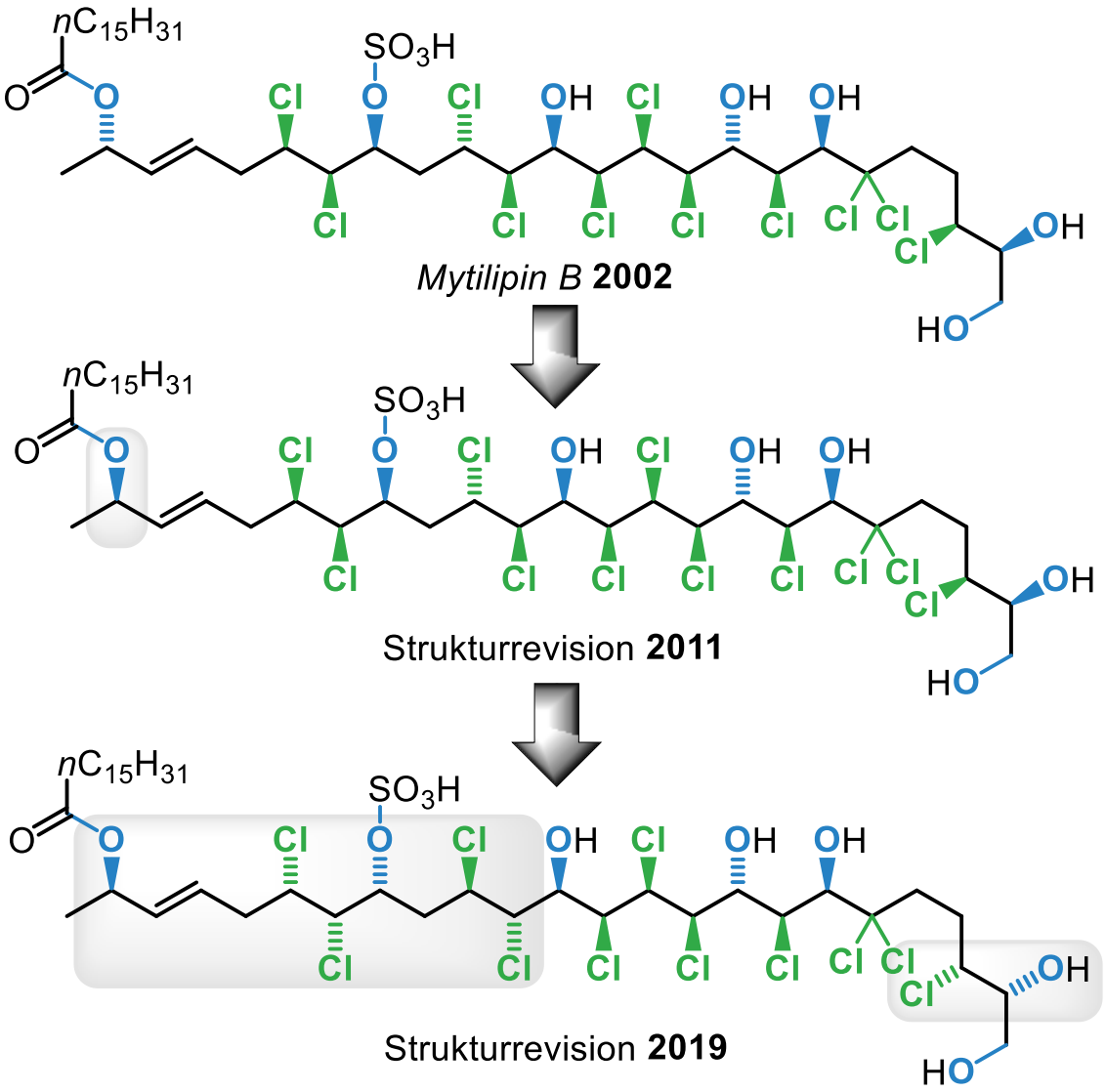
(a) Ciminiello, Fattorusso *et al., J. Am. Chem. Soc.* **2002**, *124*, 13114. (b) Carreira *et al., Angew. Chem. Int. Ed.* **2011**, *50*, 7940. (c) Carreira *et al., J. Am. Chem. Soc.* **2019**, *141*, 10510.

- Isoliert von Muschel *Mytilus galloprovincialis*
- 15 Stereozentren



(a) Ciminiello, Fattorusso *et al., J. Am. Chem. Soc.* **2002**, *124*, 13114. (b) Carreira *et al., Angew. Chem. Int. Ed.* **2011**, *50*, 7940. (c) Carreira *et al., J. Am. Chem. Soc.* **2019**, *141*, 10510.

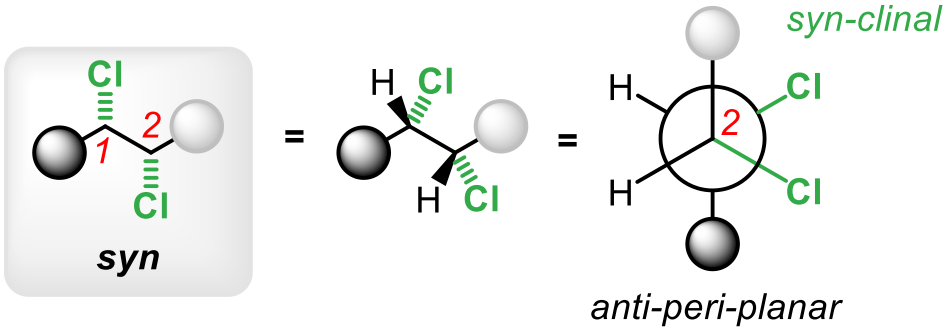
- Isoliert von Muschel *Mytilus galloprovincialis*
- 15 Stereozentren
- 31 lineare Stufen



(a) Ciminiello, Fattorusso *et al., J. Am. Chem. Soc.* **2002**, *124*, 13114. (b) Carreira *et al., Angew. Chem. Int. Ed.* **2011**, *50*, 7940. (c) Carreira *et al., J. Am. Chem. Soc.* **2019**, *141*, 10510.

- Rigide Konformation
- *Carreiras* Spektroskopische Datenbank

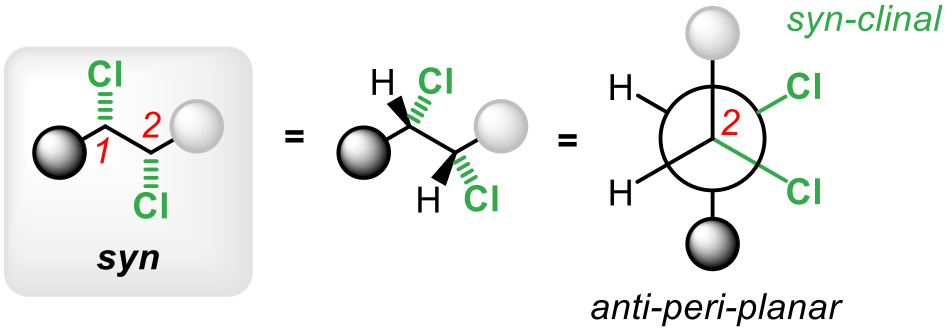
→ Bestimmung von Konfiguration durch NMR-Kopplungskonstanten

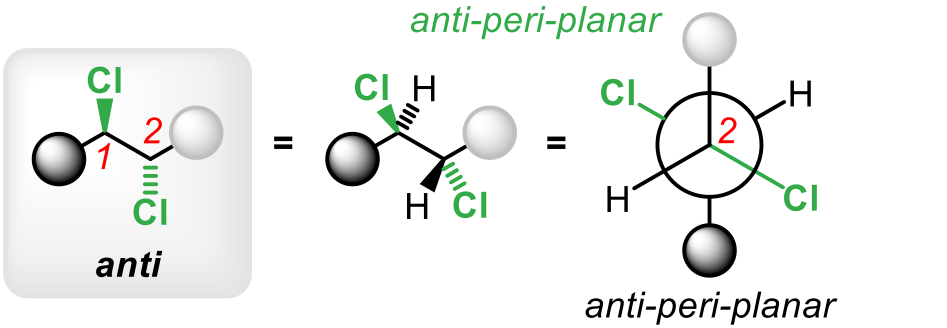


Carreira *et al. J. Am. Chem. Soc.* **2009**, *131*, 15866.

- Rigide Konformation
- *Carreiras* Spektroskopische Datenbank

→ Bestimmung von Konfiguration durch NMR-Kopplungskonstanten





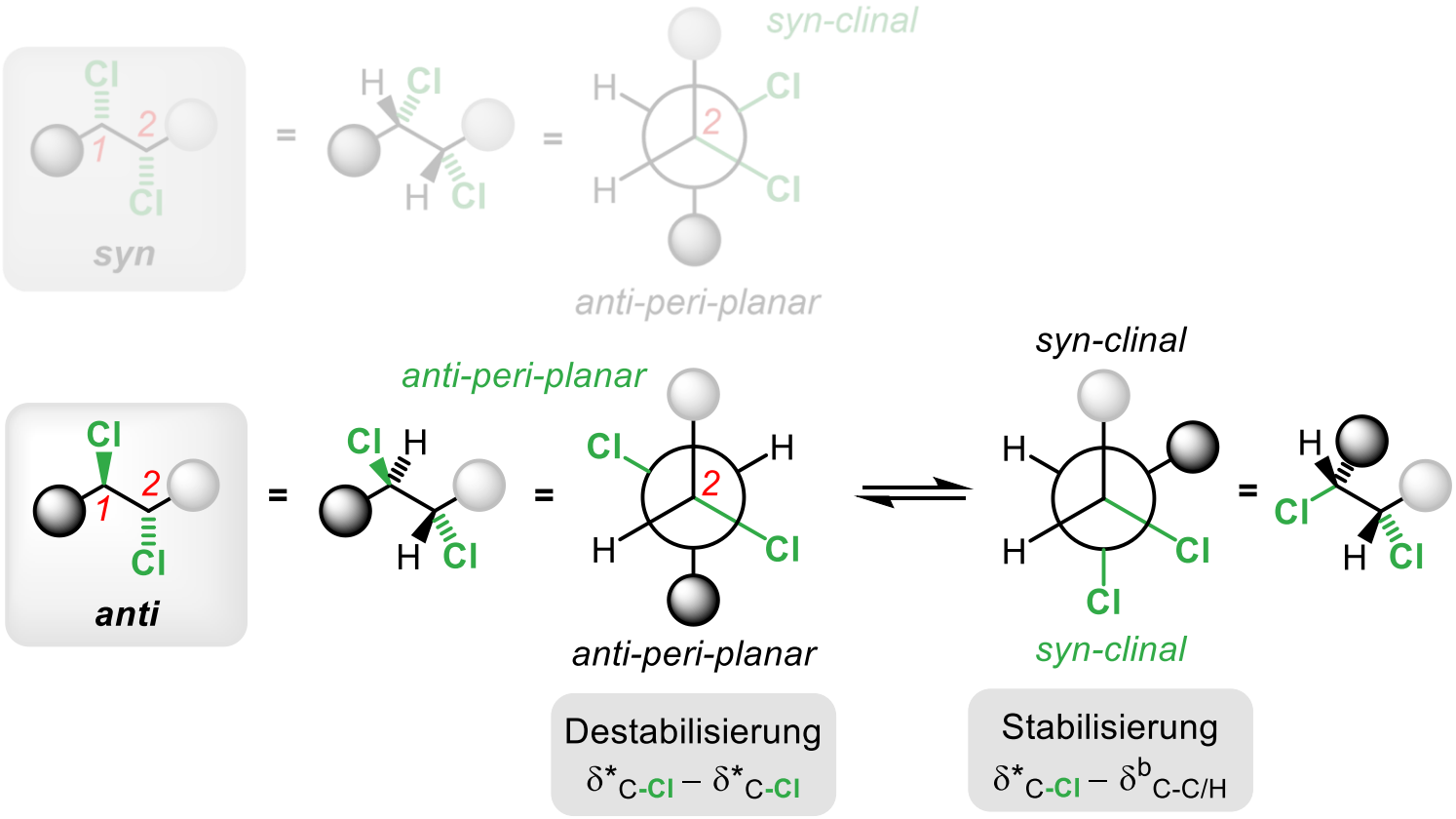
Destabilisierung

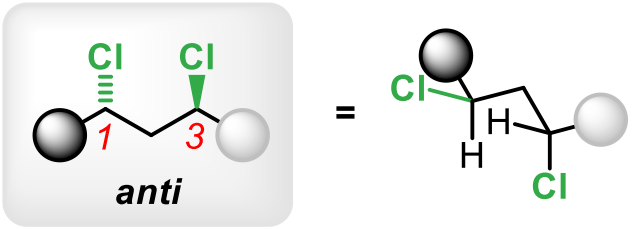
$\delta^*_{C\text{-}Cl} - \delta^*_{C\text{-}Cl}$

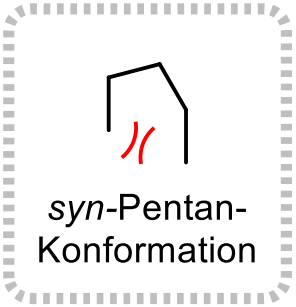
Carreira *et al. J. Am. Chem. Soc.* **2009**, *131*, 15866.

- Rigide Konformation
- *Carreiras* Spektroskopische Datenbank

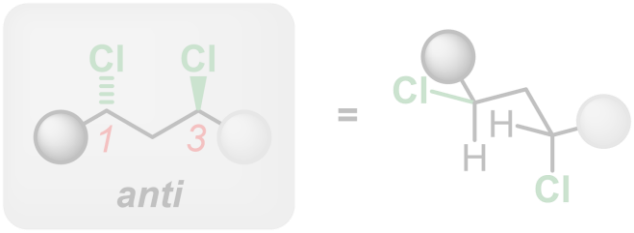
→ Bestimmung von Konfiguration durch NMR-Kopplungskonstanten



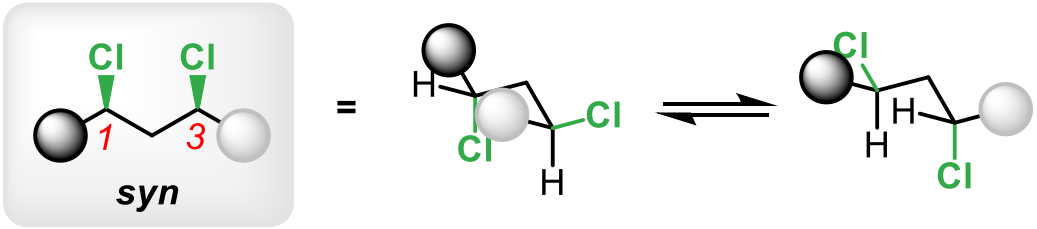




Carreira *et al. J. Am. Chem. Soc.* **2009**, *131*, 15866.

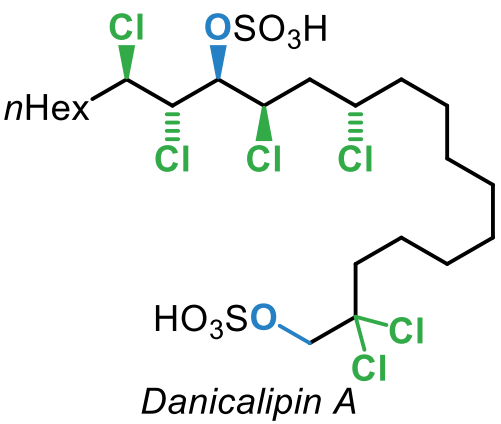


syn-Pentan-Konformation

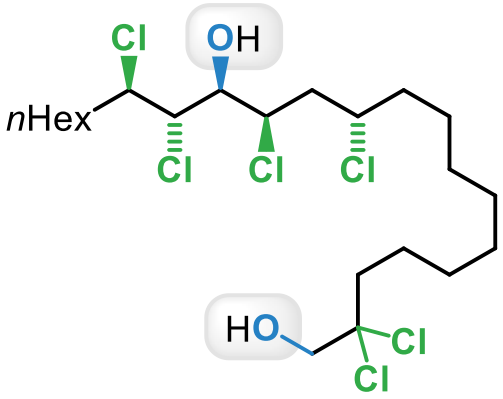


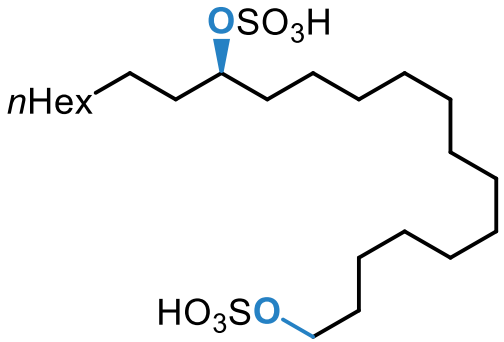
Carreira *et al. J. Am. Chem. Soc.* **2009**, *131*, 15866.

Toxizität
<30 μM
30-100 μM
>100 μM



Danicalipin A

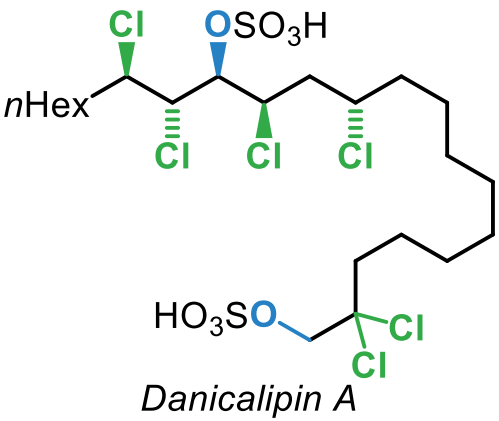




Salzwassergarnele **LC_{50}** [μM]	5.3	>141	63.8
A549 Zellen **EC_{50}** [μM]	26.5	41.4	69.3
HT-29 Zellen **EC_{50}** [μM]	15.5	>166	84.4
Hepa 1-6 Zellen **EC_{50}** [μM]	14.3	17.3	39.1

Carreira *et al.*, *Angew. Chem. Int. Ed.* **2016**, *55*, 639.

Toxizität
<30 μM
30-100 μM
>100 μM



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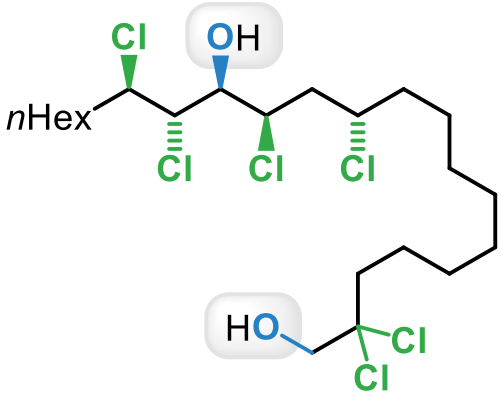
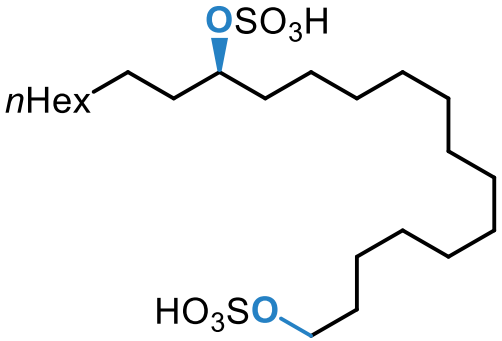
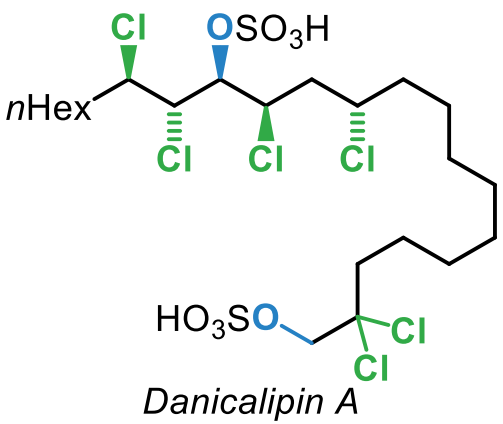




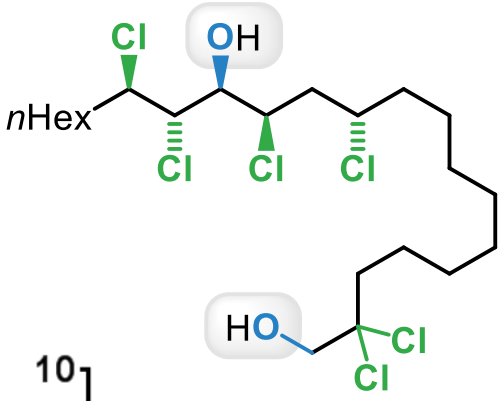
Salzwassergarnele **LC_{50}** [μM]	5.3	>141	63.8
A549 Zellen **EC_{50}** [μM]	26.5	41.4	69.3
HT-29 Zellen **EC_{50}** [μM]	15.5	>166	84.4
Hepa 1-6 Zellen **EC_{50}** [μM]	14.3	17.3	39.1

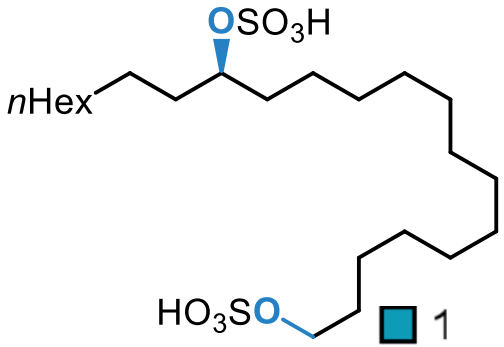
→ Toxizität : **Cl-Atom und Sulfonatgruppen essentiell**

Carreira *et al.*, *Angew. Chem. Int. Ed.* **2016**, *55*, 639.



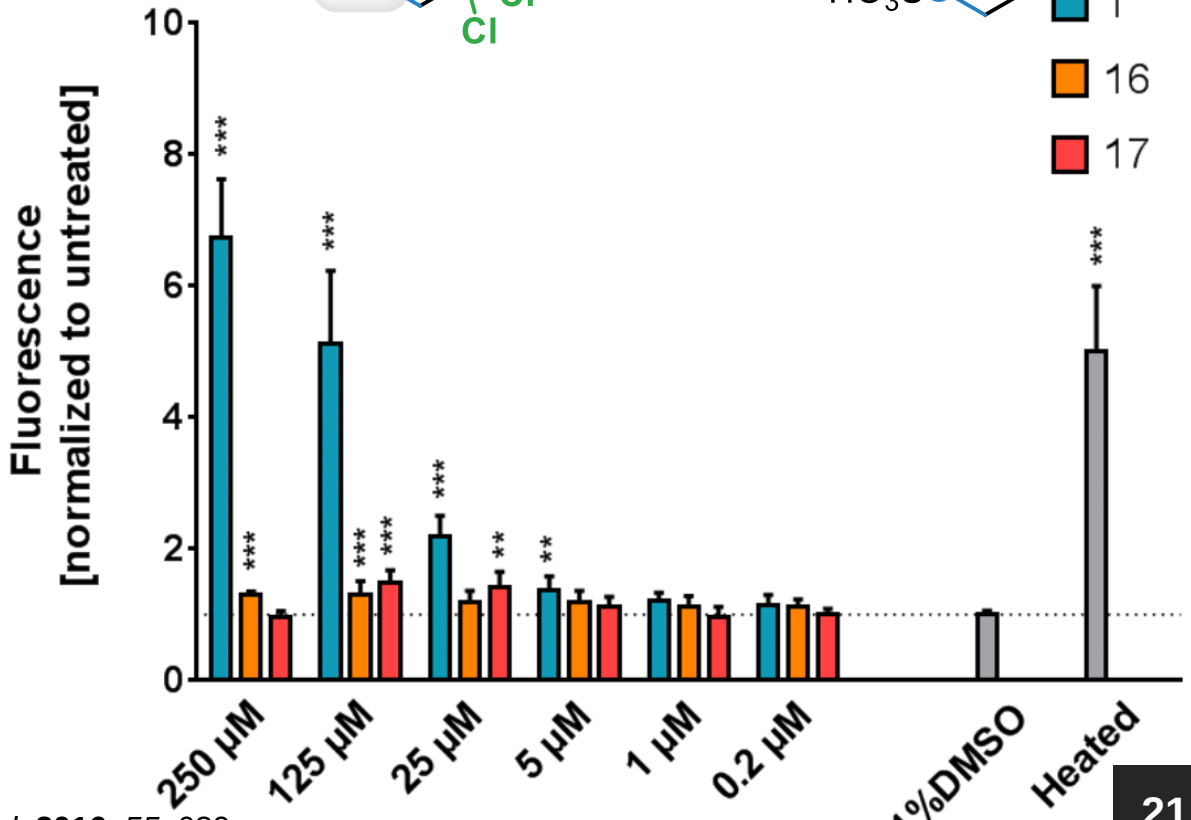
Danicalipin A





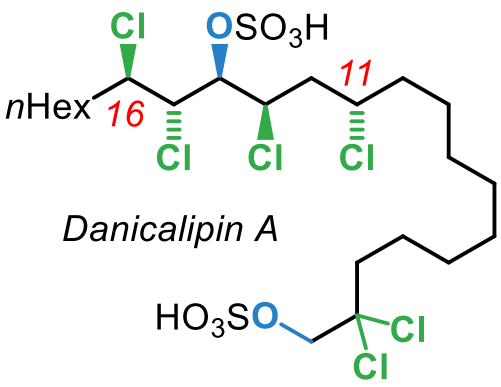
Permeabilität Zellmembran

Fluoreszenz von Gram-negativen E. *coli DH5α* Bakterien mittels Hoechst 33342

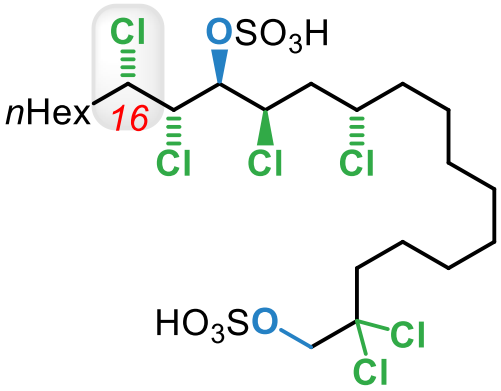


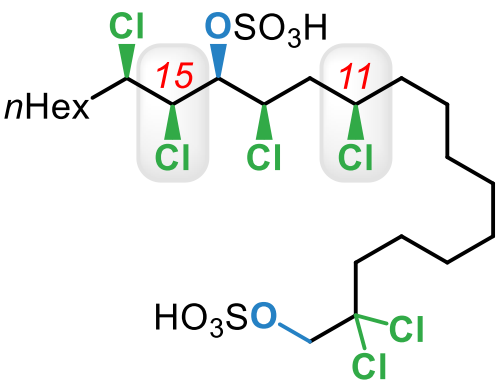
Picture from Carreira *et al.*, *Angew. Chem. Int. Ed.* **2016**, *55*, 639.

Toxizität
<5 μM
5-20 μM
>20 μM



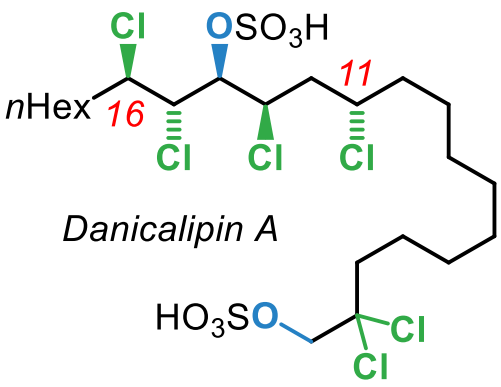
Danicalipin A





Carreira *et al.*, *Chem. Sci.* **2017**, *8*, 690.

Toxizität
<5 μM
5-20 μM
>20 μM



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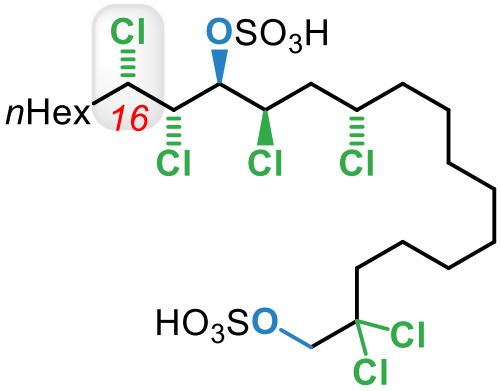
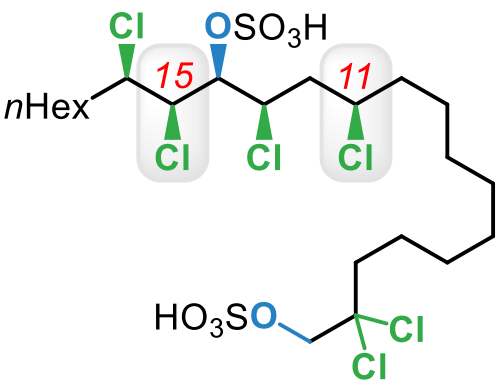
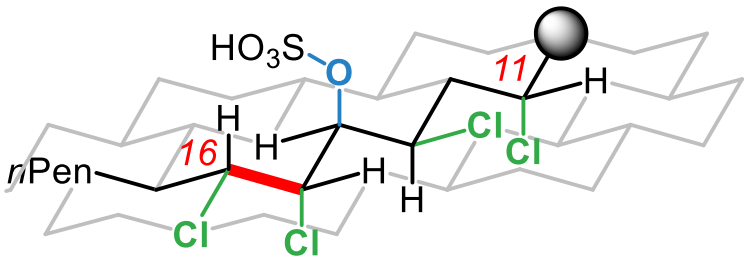
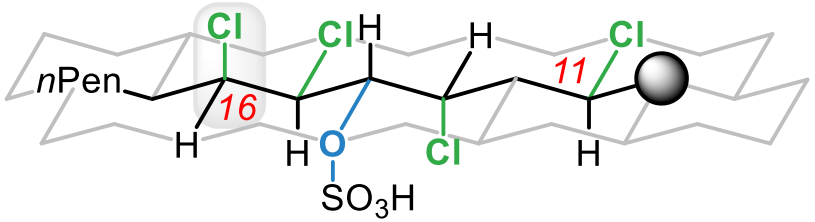




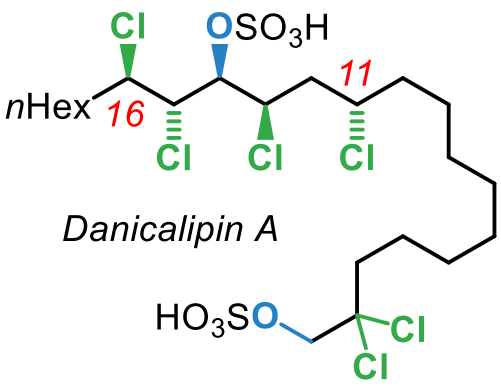
Änderung Vorzugsonformation



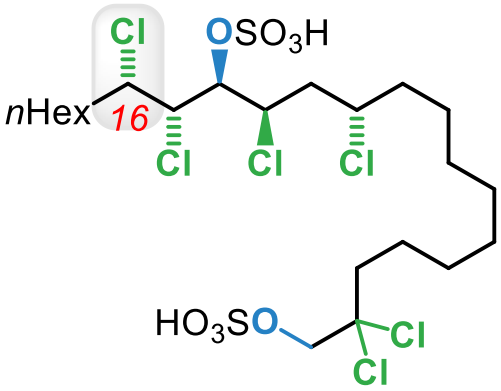


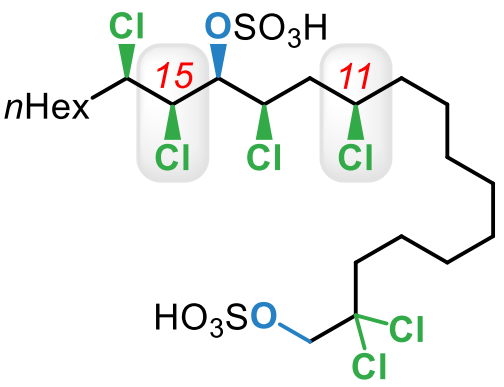
Carreira *et al.*, *Chem. Sci.* **2017**, *8*, 690.

Toxizität
<5 μM
5-20 μM
>20 μM



Danicalipin A

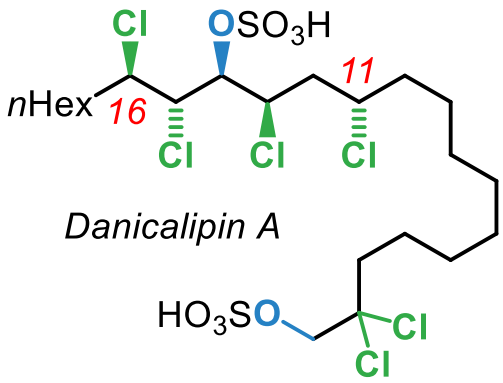


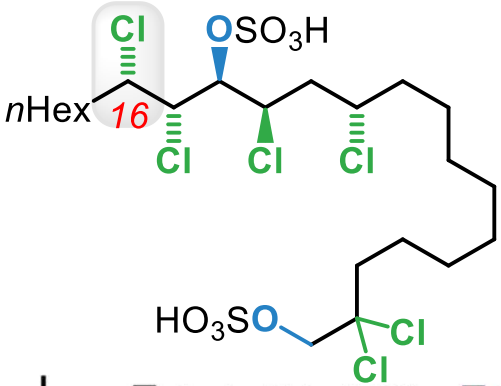


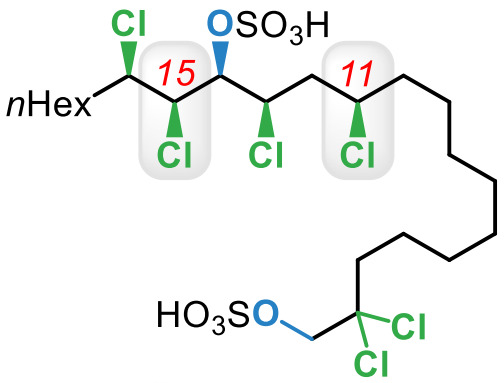
Salzwassergarnele **LC_{50}** [μM]	2.5	5.7	4.5
A549 Zellen **EC_{50}** [μM]	32.2	42.6	36.0
HT-29 Zellen **EC_{50}** [μM]	14.7	10.9	3.7
Hepa 1-6 Zellen **EC_{50}** [μM]	14.7	13.3	10.2

→ Toxizität: *Einfluss relative Konfiguration gering*

Carreira *et al.*, *Chem. Sci.* **2017**, *8*, 690.

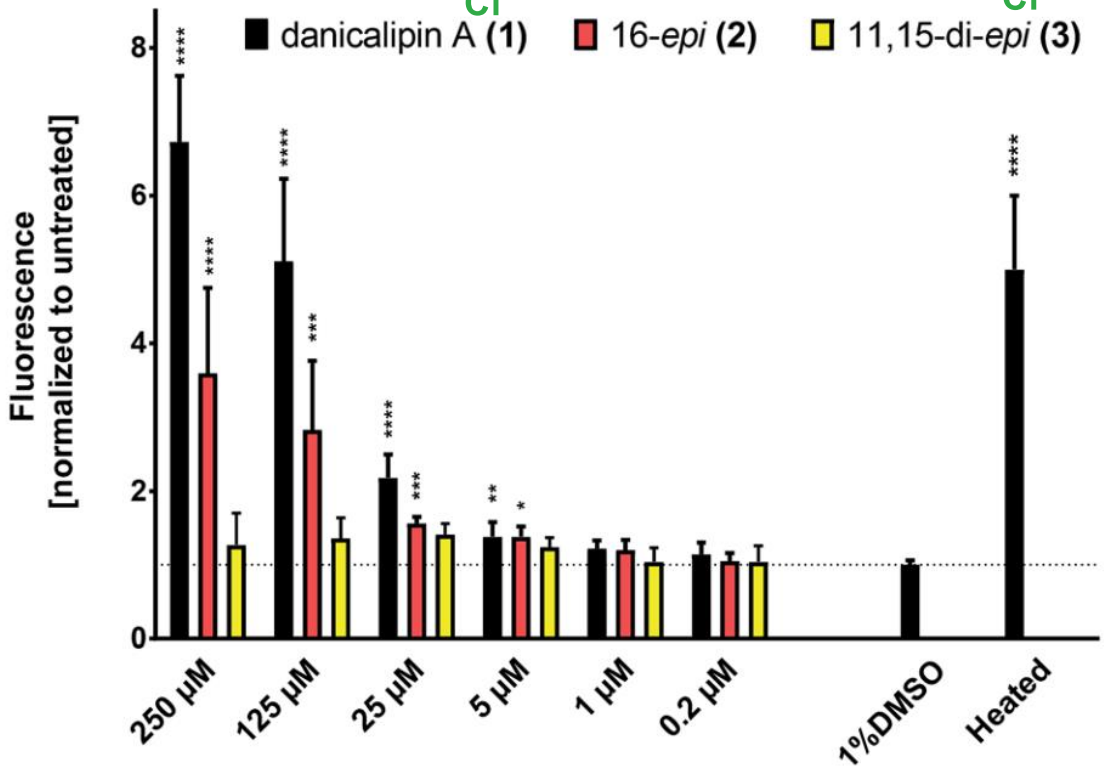






Permeabilität Zellmembran

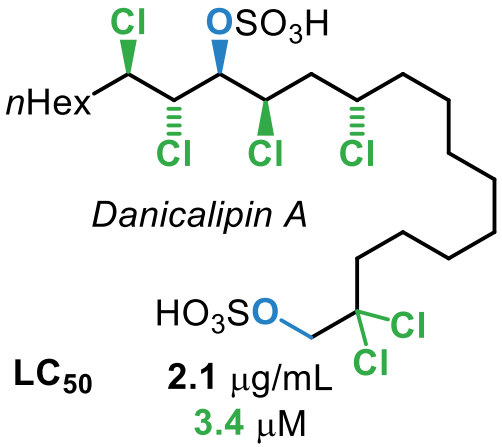
Fluoreszenz von Gram-negativen E. *coli DH5α* Bakterien mittels Hoechst 33342



→ Zellpermeabilität: **Relative Konfiguration essentiell**

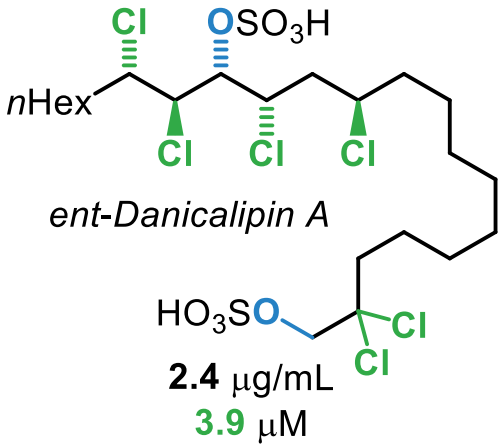
Picture from Carreira *et al.*, *Chem. Sci.* **2017**, *8*, 690.

Toxizität
<30 μM
30-100 μM
>100 μM



Danicalipin A

LC_{50} **2.1** μg/mL
3.4 μM



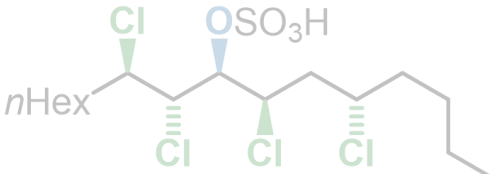
ent-Danicalipin A

2.4 μg/mL
3.9 μM

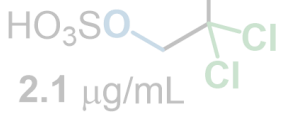
→ Toxizität Salzwassergarnelen: Absolute Konfiguration keinen Einfluss

(a) Umezawa,. Matsuda *et al.*, *Org. Lett.* **2011**, *13*, 904. (b) Carreira *et al.*, *Angew. Chem. Int. Ed.* **2016**, *55*, 2555

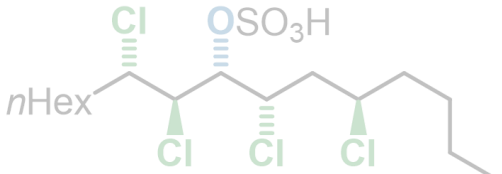
Toxizität
<30 μM
30-100 μM
>100 μM



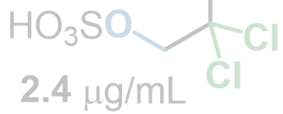
Danicalipin A



LC_{50} 2.1 μg/mL
3.4 μM

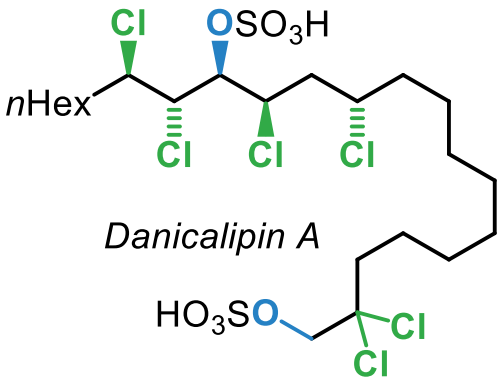


ent-Danicalipin A



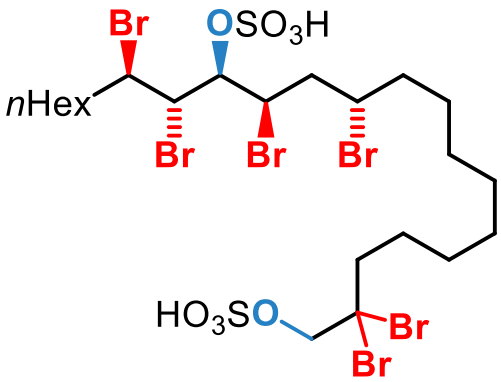
2.4 μg/mL
3.9 μM

→ Toxizität Salzwassergarnelen: Einfluss Absolute Konfiguration keinen

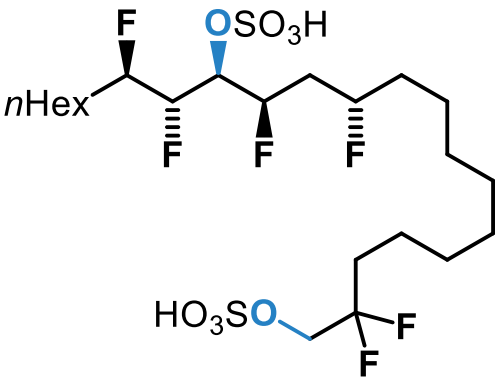


Danicalipin A

LC_{50} [μM] **5.3**



4.7

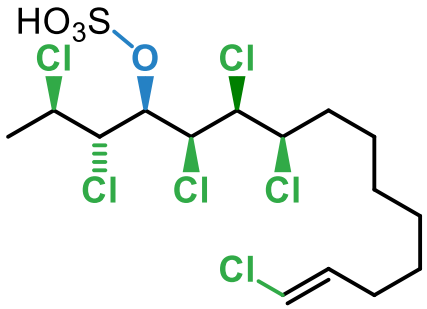


72.2

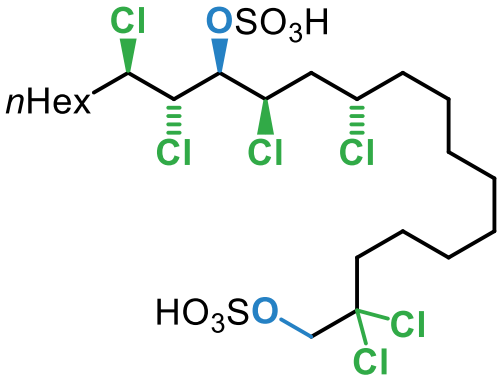
→ Toxizität Salzwassergarnelen: **Cl**/**Br**-Austausch kein Effekt
Cl/**F**-Austausch Verminderung Toxizität

(a) Umezawa,. Matsuda *et al.*, *Org. Lett.* **2011**, *13*, 904. (b) Carreira *et al.*, *Angew. Chem. Int. Ed.* **2016**, *55*, 2555

- Naturstoffklasse **Chlorsulfolipide**
- Synthesestrategien
- Beispiele Totalsynthesen

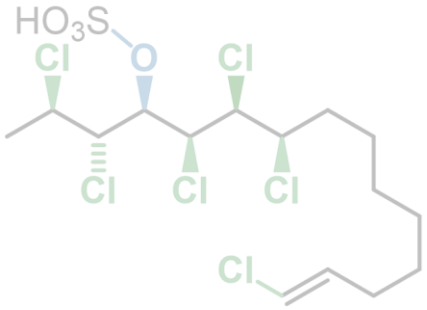


Mytilipin A

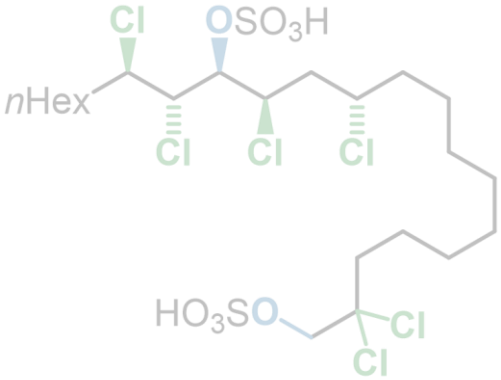


Danicalipin A

- Naturstoffklasse **Chlorsulfolipide**
- Synthesestrategien
- Beispiele Totalsynthesen

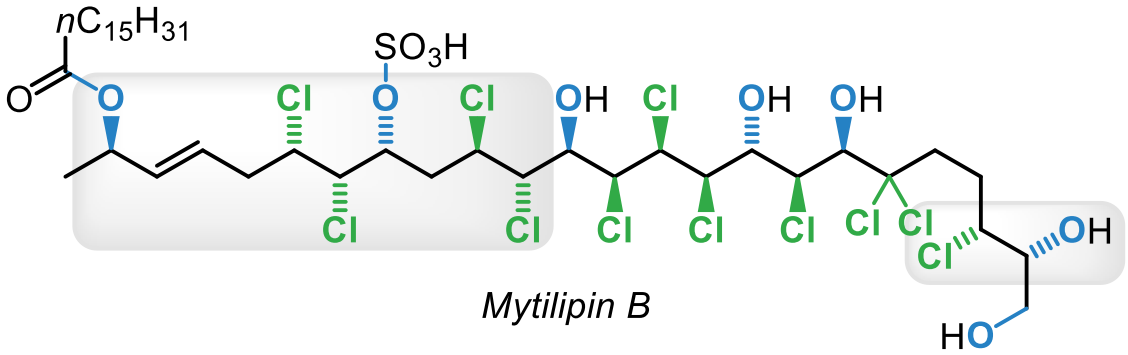


Mytilipin A



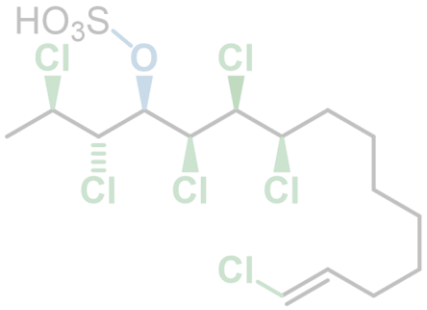
Danicalipin A

- Strukturrevision durch Totalsynthese

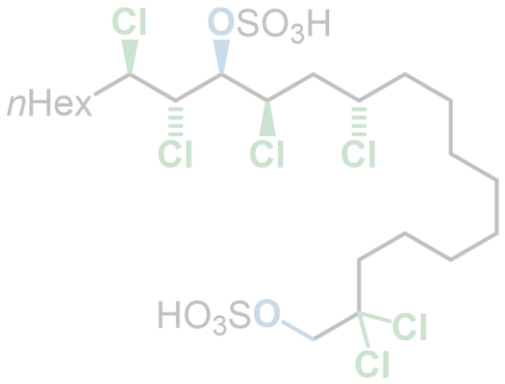


Mytilipin B

- Naturstoffklasse **Chlorsulfolipide**
- Synthesestrategien
- Beispiele Totalsynthesen

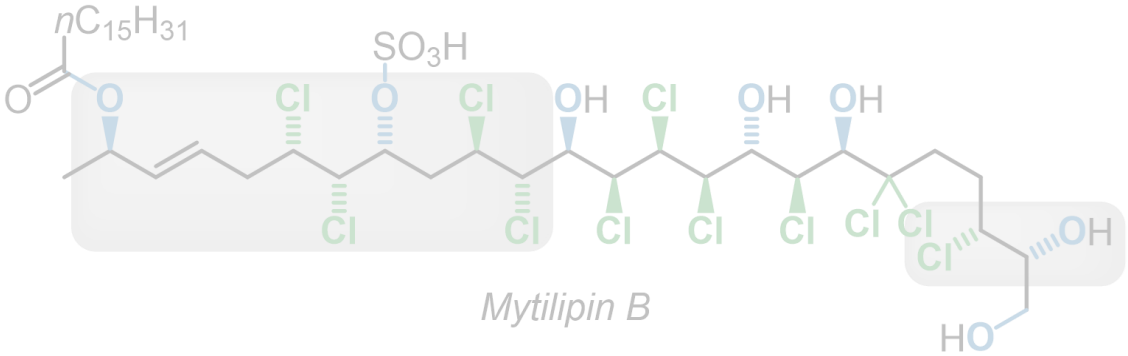


Mytilipin A

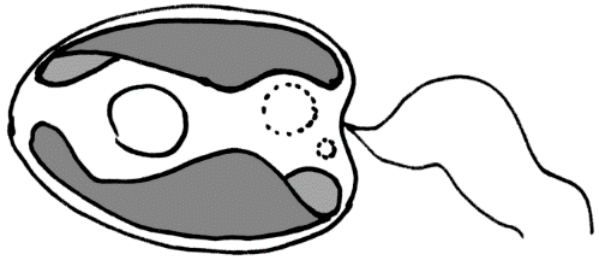


Danicalipin A

- Strukturrevision durch Totalsynthese



Mytilipin B



- Rigide Konformation → Bestimmung relative Konfiguration per NMR
- Struktur-Wirkungs-Beziehung:
  Sulfolipide erhöhen Flexibiltät der Zellmembran von einzelligen Mikroalgen
  → Essentiell für Fortbewegung

Carreira *et al.*, *Chem. Sci.* **2017**, *8*, 690. picture from https://de.wikipedia.org/wiki/Ochromonas

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- Philipp Grewelinger (BSc)
- Marc Scheider (MSc)
- Christelle Mbouhom (BSc)
- Isabel Filbrich (MSc)
- Julia Dräger (BSc)
- Sebastian Motsch (MSc)

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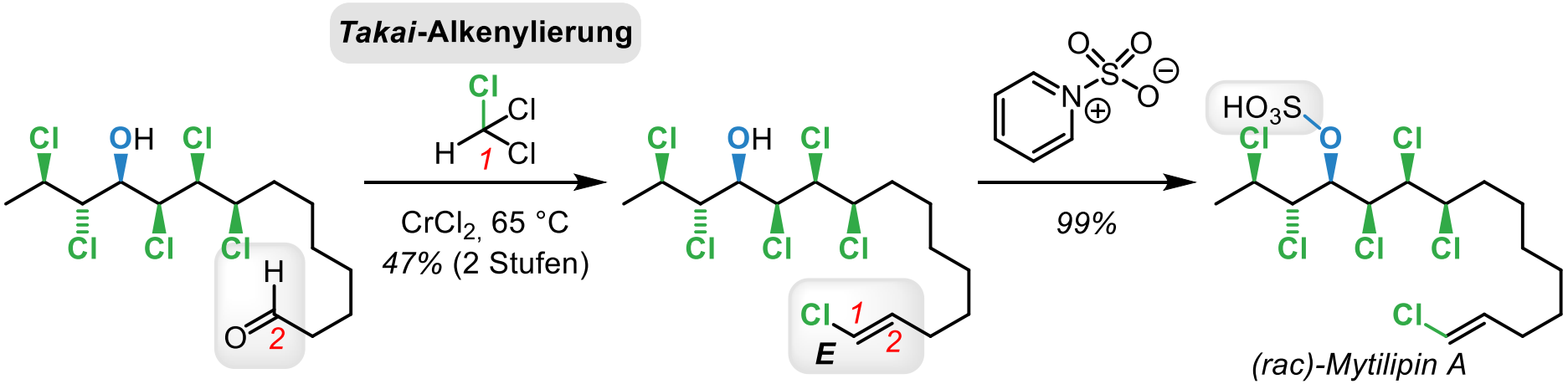
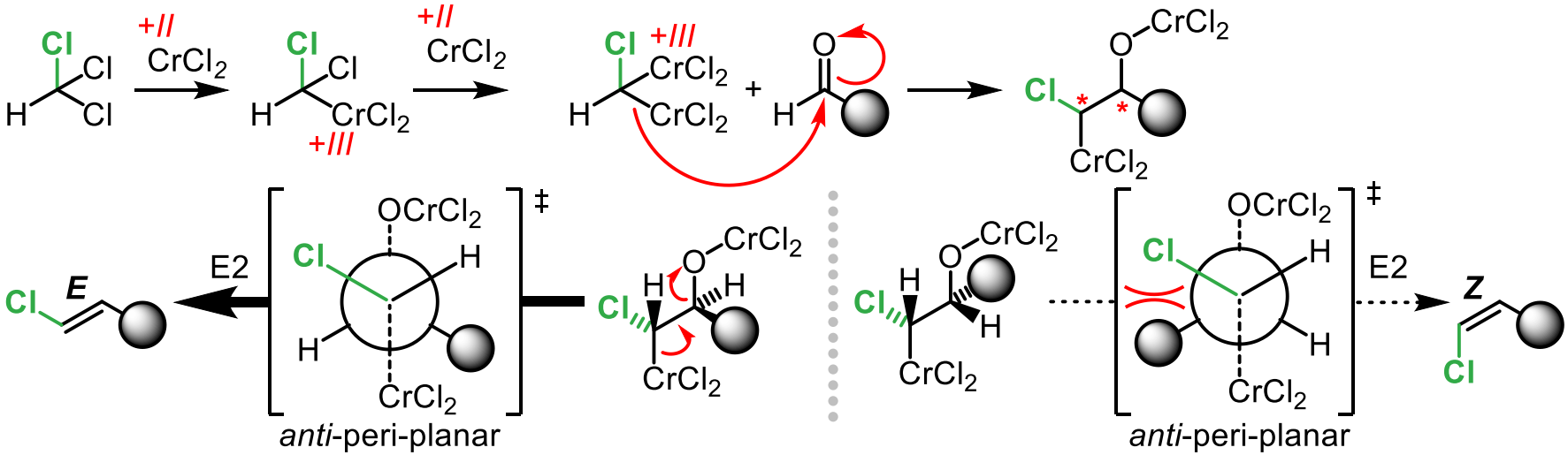
- G. Hilt
- S. Heiles

Funding

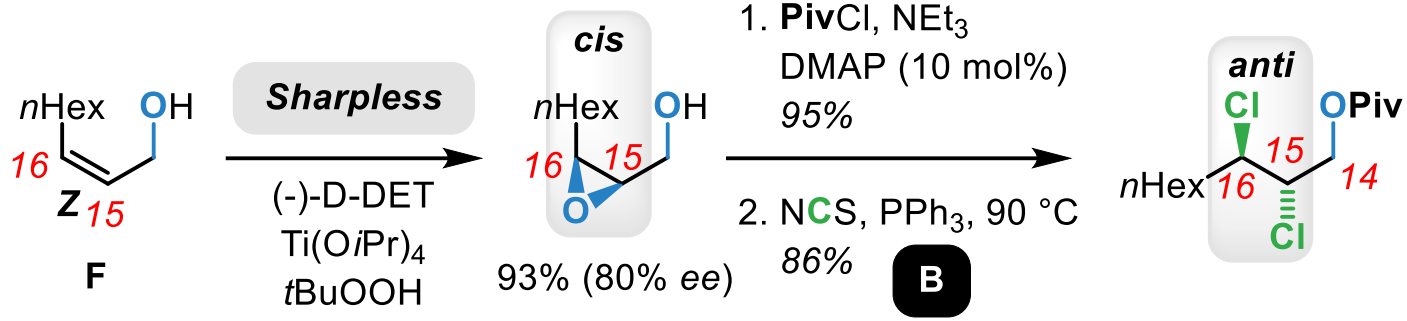
FCI
FONDS DER
CHEMISCHEN
INDUSTRIE

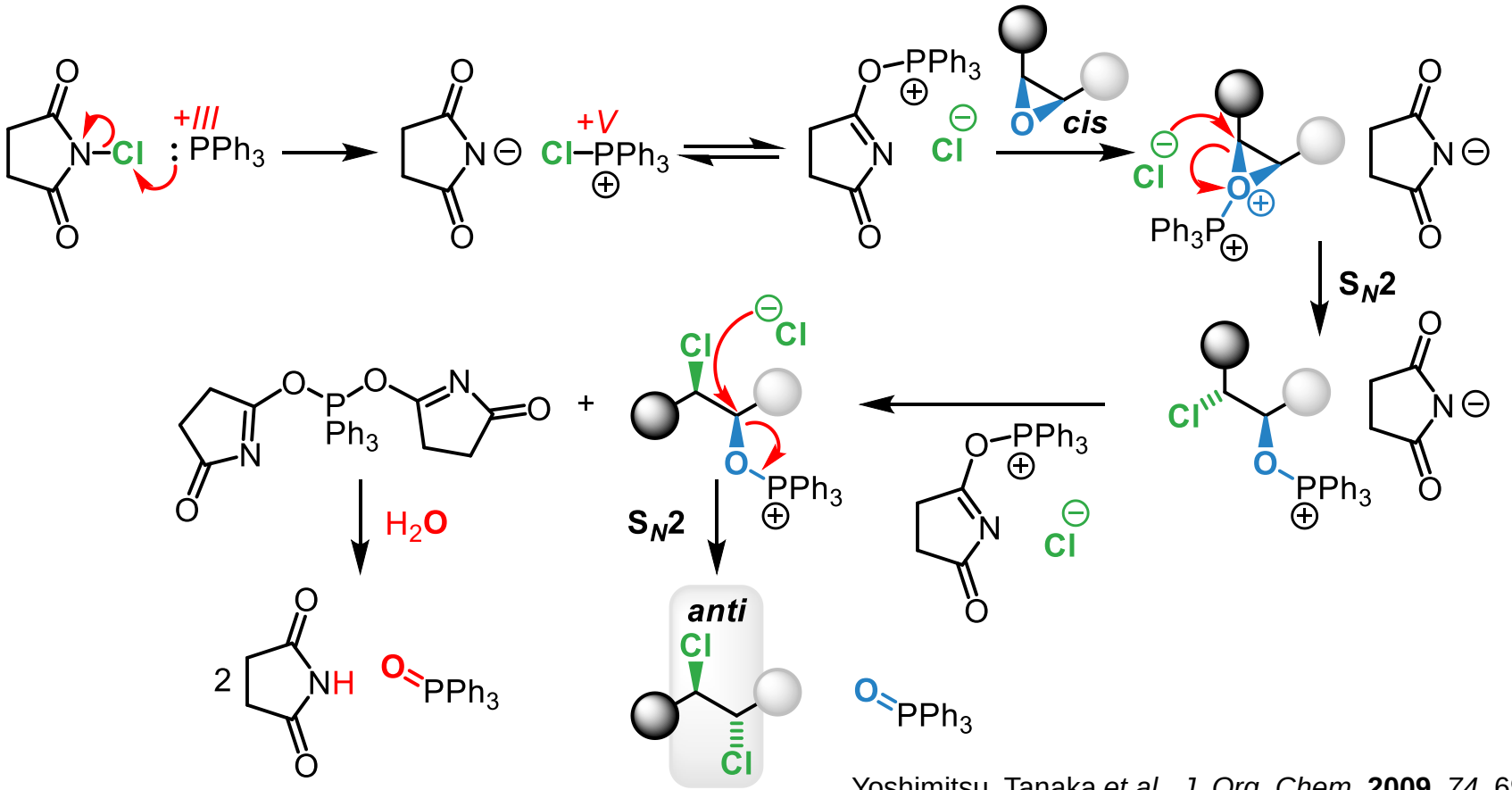
DFG



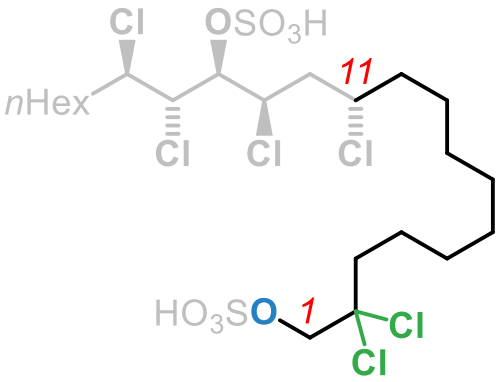


Takai *et al.* (a) *J. Am. Chem. Soc.* **1986**, *108*, 7408. (b) *J. Am. Chem. Soc.* **1987**, *109*, 951.

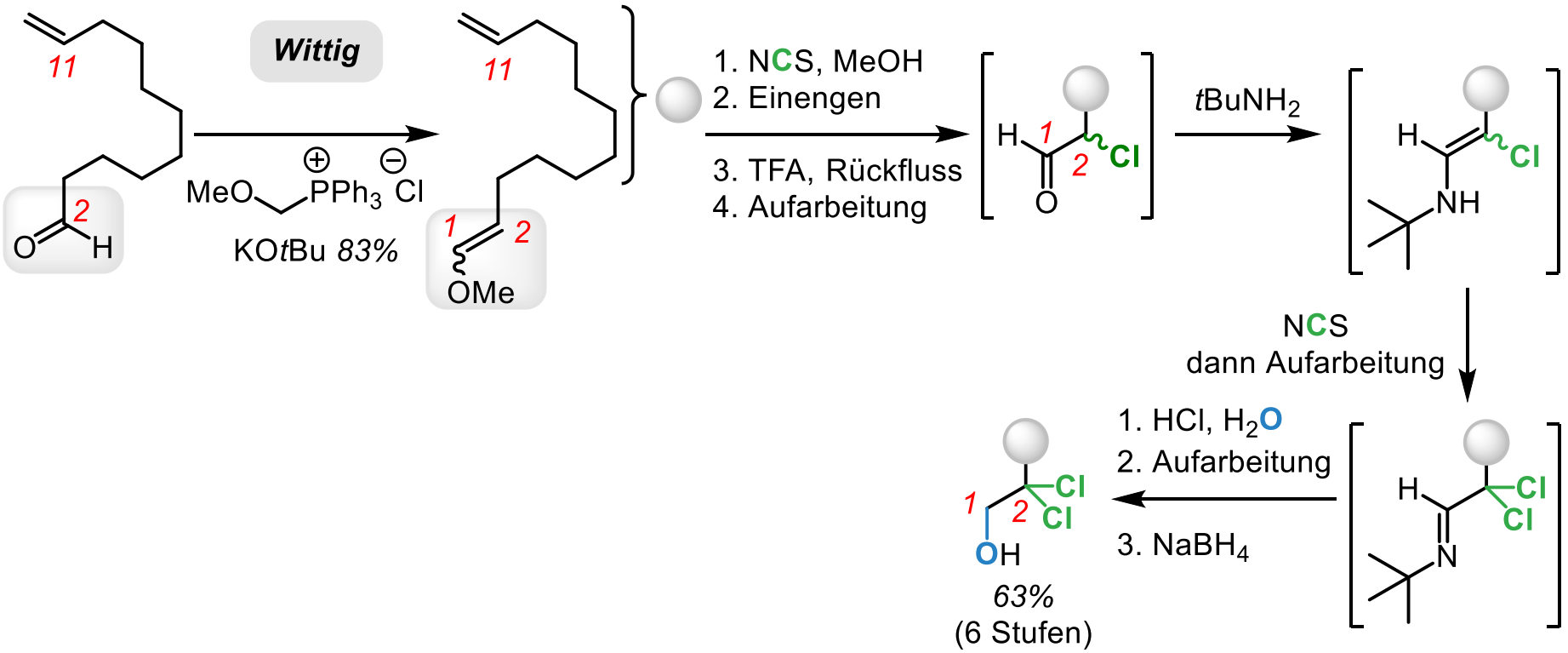


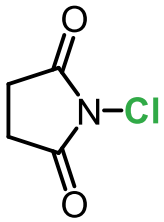


Yoshimitsu, Tanaka *et al.*, *J. Org. Chem.* **2009**, *74*, 696

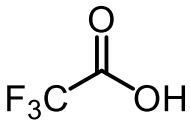


Kimpe *et al., Synthesis* **1975**, 455.



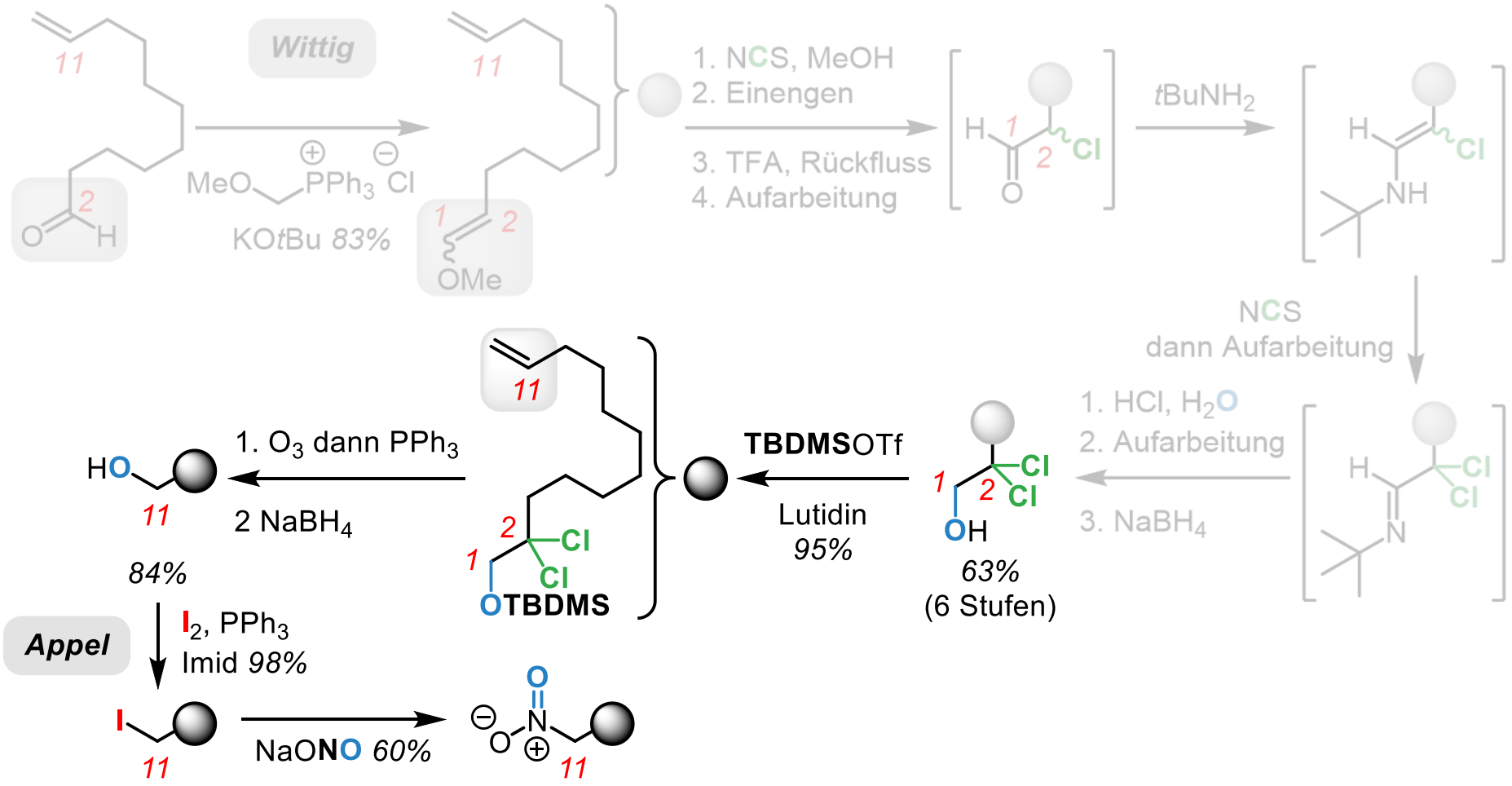


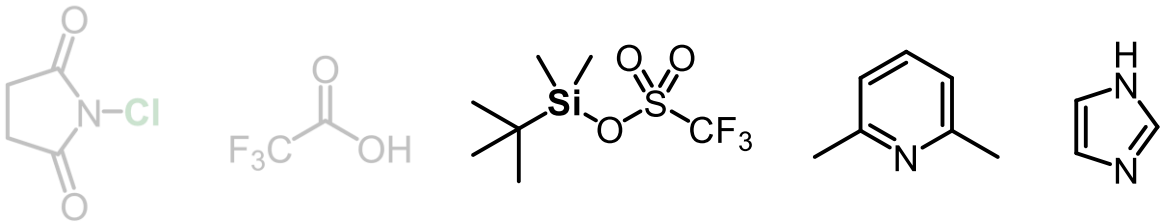
NCS



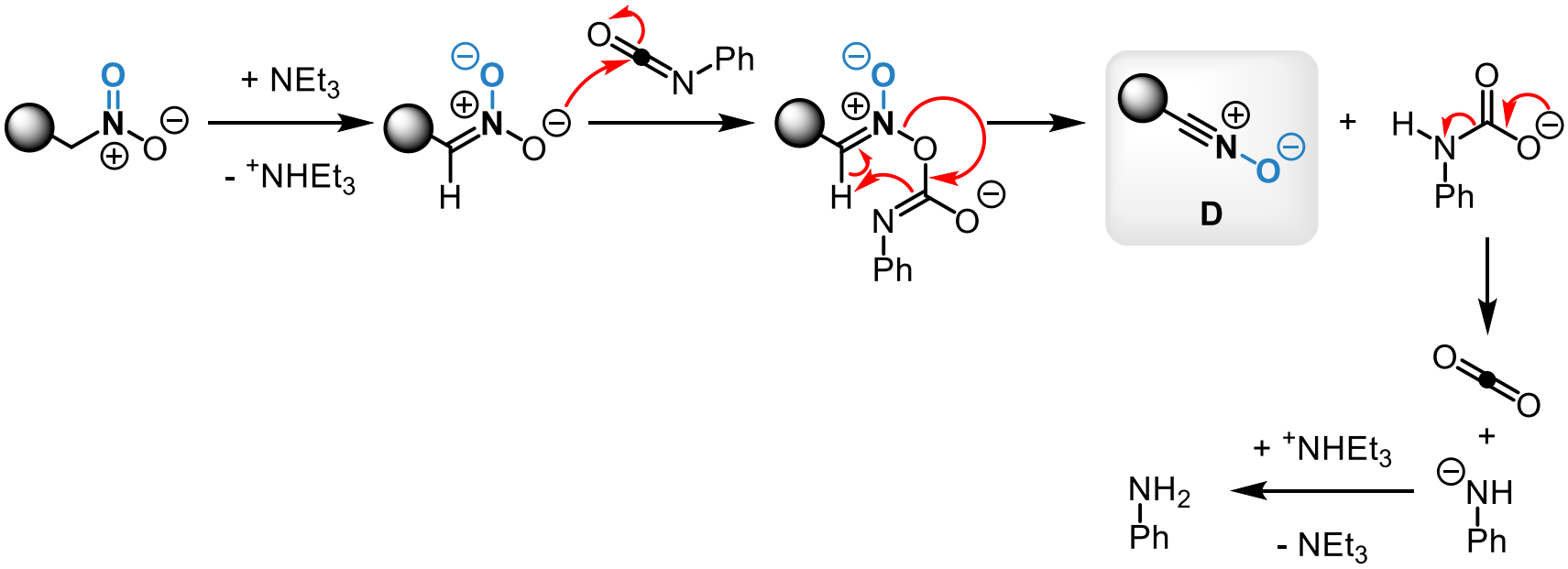
TFA

Kimpe *et al., Synthesis* **1975**, 455.





Kimpe *et al.*, *Synthesis* **1975**, 455.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- +NHEt3
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H
Ph
D
H
Ph
+
+ +NHEt3
- NEt3
NH2
Ph
NH
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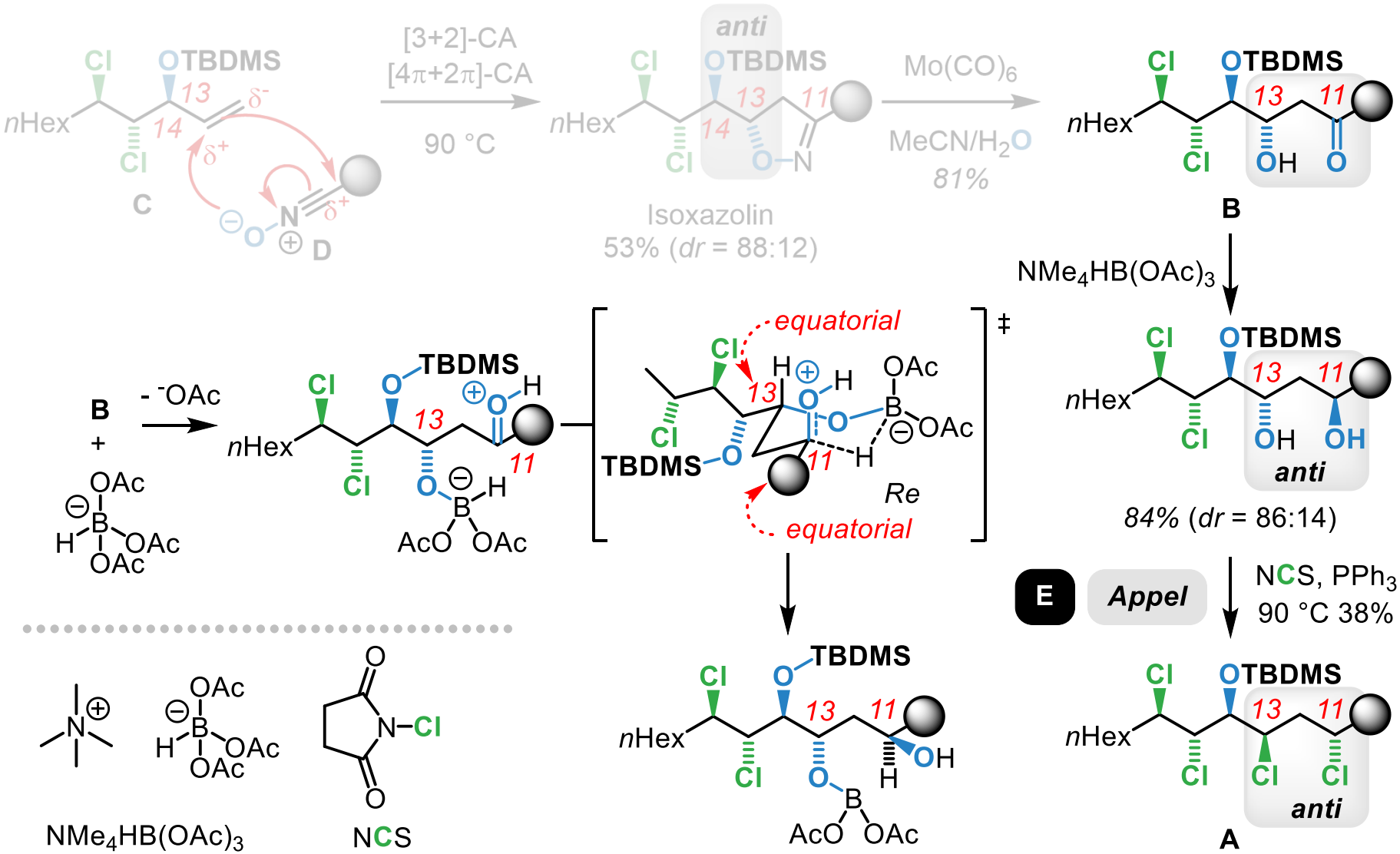

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(c) Goti, Brandi *et al., Tetrahedron Lett.* **1990**, *31*, 3351. (d) Evans *et al., J. Am. Chem. Soc.* **1988**, *110*, 3560.