Total Syntheses of Disorazoles A_1 and B_1 and Full Structural Elucidation of Disorazole B_1

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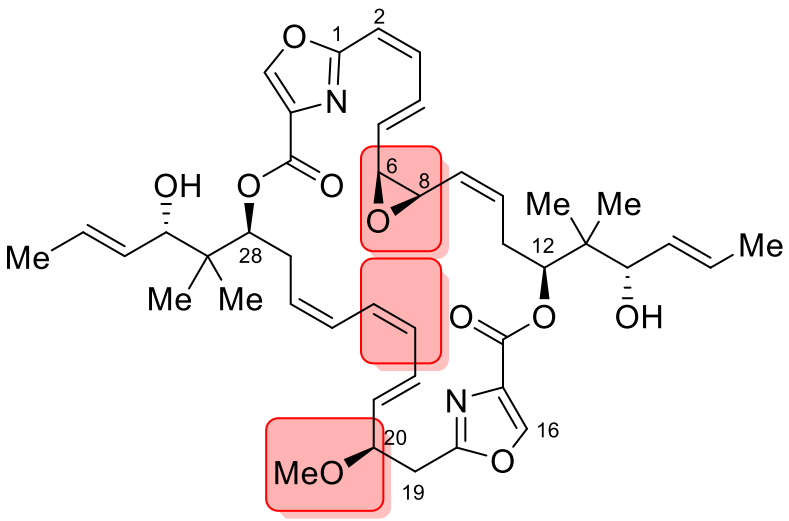
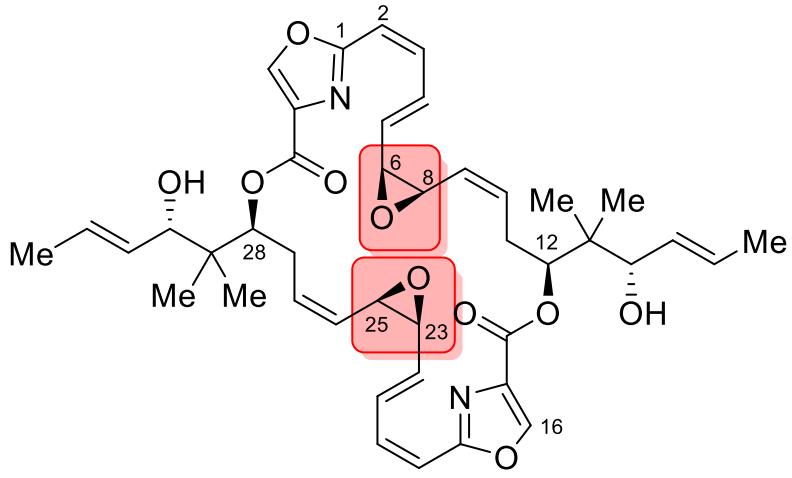
Prof. Wipf Research Group
University of Pittsburgh
Literature Seminar, Nov 18, 2017

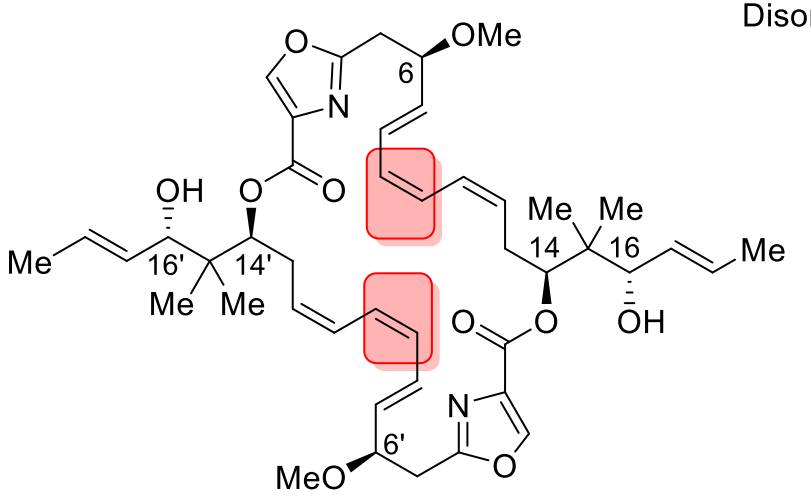
Disorazoles A_1, B_1 and C_1



Disorazole A_1 (**1**)



Disorazole B_1 (**2**)



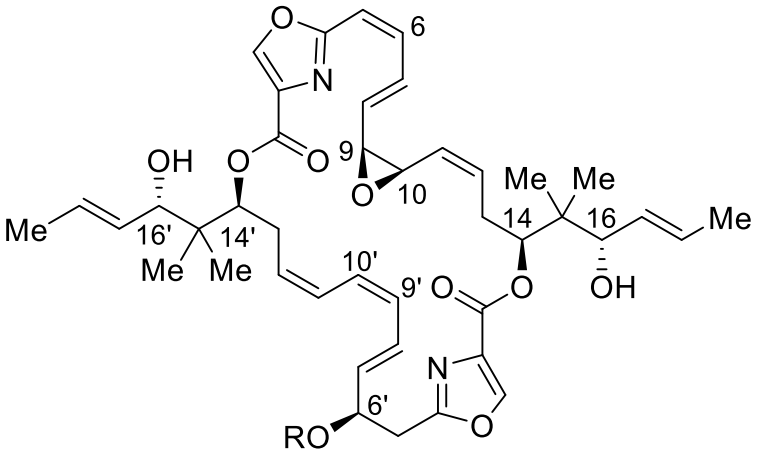
Disorazole C_1 (**3**)

Nicolaou, K. C. et al. *J. Am. Chem*. Soc. **2017**, *139*, 15636-15639.

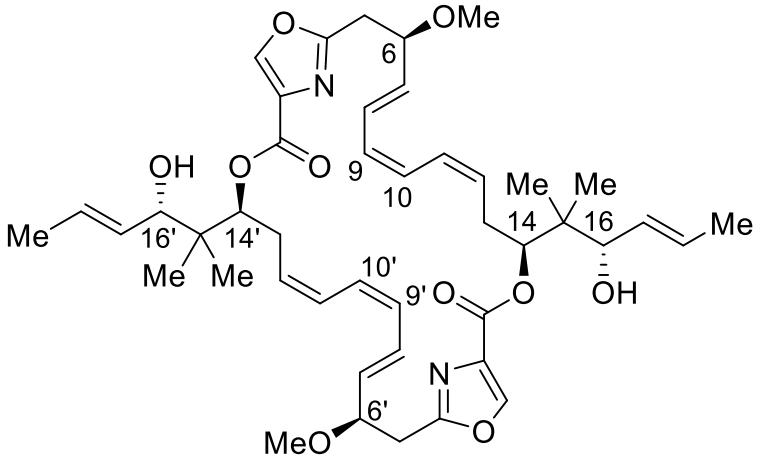
Wipf, P. et al. *J. Am. Chem*. Soc. **2004**, *126*, 15346-15347.

- Family of 29 related macrocyclic polyketides
- Isolated in 1994 from fermentation broth of the gliding myxobacterium *Sorangium cellulosum*
- Disorazole A_1 was the major component
- Disorazole A_1, E and C_1 showed exceptional biological activities
- Disruption of microtubule polymerization

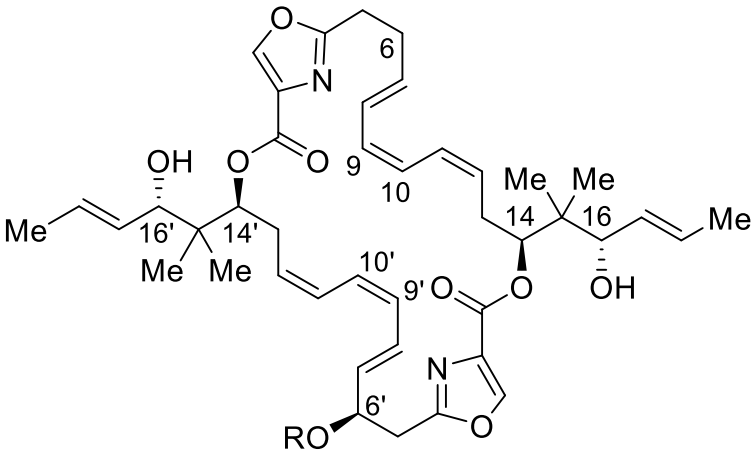
Jansen, R et al. *Liebigs Ann. Chem*. **1994**, 759−773.
Wipf, P. et al. *Nat. Prod. Rep*. **2009**, *26*, 585−601.



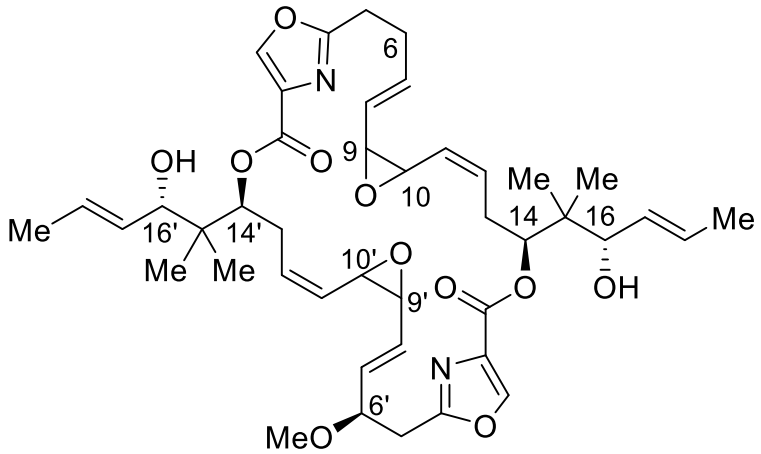
Disorazole A_1 (**1**) 69.8%, (R = Me)
Disorazole A_2 (**4**) 0.9%, (R = H)
Disorazole A_4 (**5**) 2.1%, (R = Me, 11' *E*)
Disorazole A_5 (**6**) 2.7%, (R = Me, 9', 11' *E*)
Disorazole A_7 (**7**) 1.6%, (R = Me, *trans-epoxide*)
Disorazole D_1 (**8**) 1.4%, (R = Me, 9', 10' diol)



Disorazole C_1 (**3**) 0.3%



Disorazole F_1 (**9**) 3.7%, (R = Me)
Disorazole F_2 (**10**) 0.5%, (R = H)
Disorazole F_3 (**11**) 0.4%, (R = Me, 9, 11 *E*)



Disorazole E_1 (**12**) 8.7%
Disorazole E_2 (**13**) <0.1%, (*trans*-9,10-epoxide)
Disorazole E_3 (**14**) 0.1%, (7(*Z*)*trans*-9,10-epoxide)

Wipf, P. et al. *Nat. Prod. Rep*. **2009**, *26*, 585−601.

Antiproliferative activity of Disorazole A_1

		IC_{50} in (nM)		
Cell Line	**Origin**	**Disorazole A_1**	**Epothilone B**	**Vinblastine**
A549	*Human lung carcinoma*	0.0023 ± 0.0005	0.26 ± 0.14	5.9 ± 0.5
PC-3	*Human prostate adenocarcinoma*	0.0071 ± 0.0012	2.0 ± 0.3	0.82 ± 0.06
SK-OV-3	*Human ovary adenocarcinoma*	0.0049 ± 0.0001	0.64 ± 0.07	1.4 ± 0.1
A-498	*Human kidney carcinoma*	0.016 ± 0.004	4.3 ± 3.6	46 ± 12
U-937	*Human histiocytic lymphoma*	0.002 ± 0.001	0.09 ± 0.01	0.43 ± 0.13
K-562	*Human myelogenous leukemia*	0.006 ± 0.001	0.69 ± 0.03	8.7 ± 1.8
KB-3.1	*Human cervix carcinoma*	0.0025 ± 0.0003	1.6 ± 0.6	8.6 ± 0.3
KB-V1	*Human cervix carcinoma (multi-drug resistant)*	0.042 ± 0.008	0.57 ± 0.03	114 ± 31
L929	*Mouse fibroblasts*	0.0038 ± 0.0002	1.3 ± 0.6	28 ± 7

5

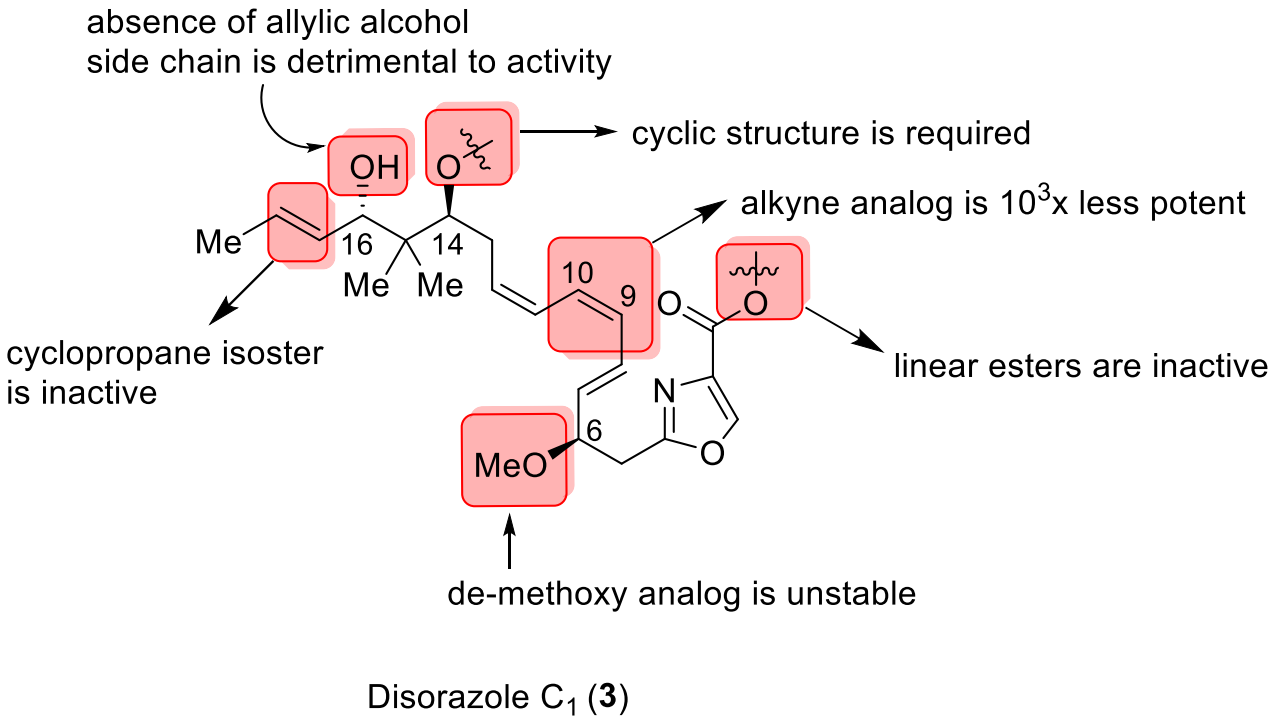
Wipf, P. et al. *Nat. Prod. Rep*. **2009**, *26*, 585−601.

Antiproliferative activity of Disorazole C_1

		IC_{50} in (nM)		
Cell Line	**Origin**	**Disorazole C_1**	**Vincristine**	**Vinblastine**
A549	*Human lung carcinoma*	2.21 ± 0.23	21.62 ± 2.68	1.52 ± 0.09
PC-3	*Human prostate adenocarcinoma*	1.57 ± 0.10	4.68 ± 0.29	0.86 ± 0.08
MDA-MB-231	*Human breast epithelial adenocarcinoma*	3.53 ± 0.19	7.16 ± 0.37	1.34 ± 0.21
2008	*Human ovarian carcinoma*	1.91 ± 0.23	21.81 ± 2.92	2.24 ± 0.16
Quiescent WI-38	*Normal lung fibroblast*	>100	N/D	>100
HCT-116 WT	*Human colorectal carcinoma*	1.09± 0.41	5.62 ± 0.33	1.40 ± 0.07
HCT-116 p53 -/-	*Human colorectal carcinoma*	2.25 ± 0.71	5.42 ± 0.47	2.17 ± 0.35
DC3F WT	*Chinese hamster lung cancer fibroblasts*	5.55	17.53	
VCRD-5L	*Chinese hamster lung cancer fibroblasts (multi-drug-resistant)*	6.77	N/A	

Wipf, P. et al. *Nat. Prod. Rep*. **2009**, *26*, 585−601.

Disorazole C_1 SAR studies

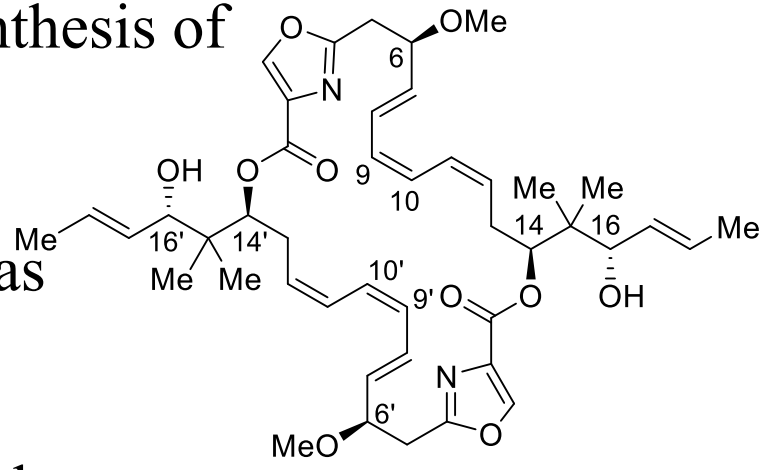


Disorazole C_1 (**3**)

Wipf, P. et al. *Nat. Prod. Rep*. **2009**, *26*, 585−601.

Enantioselective total synthesis of Disorazole C_1

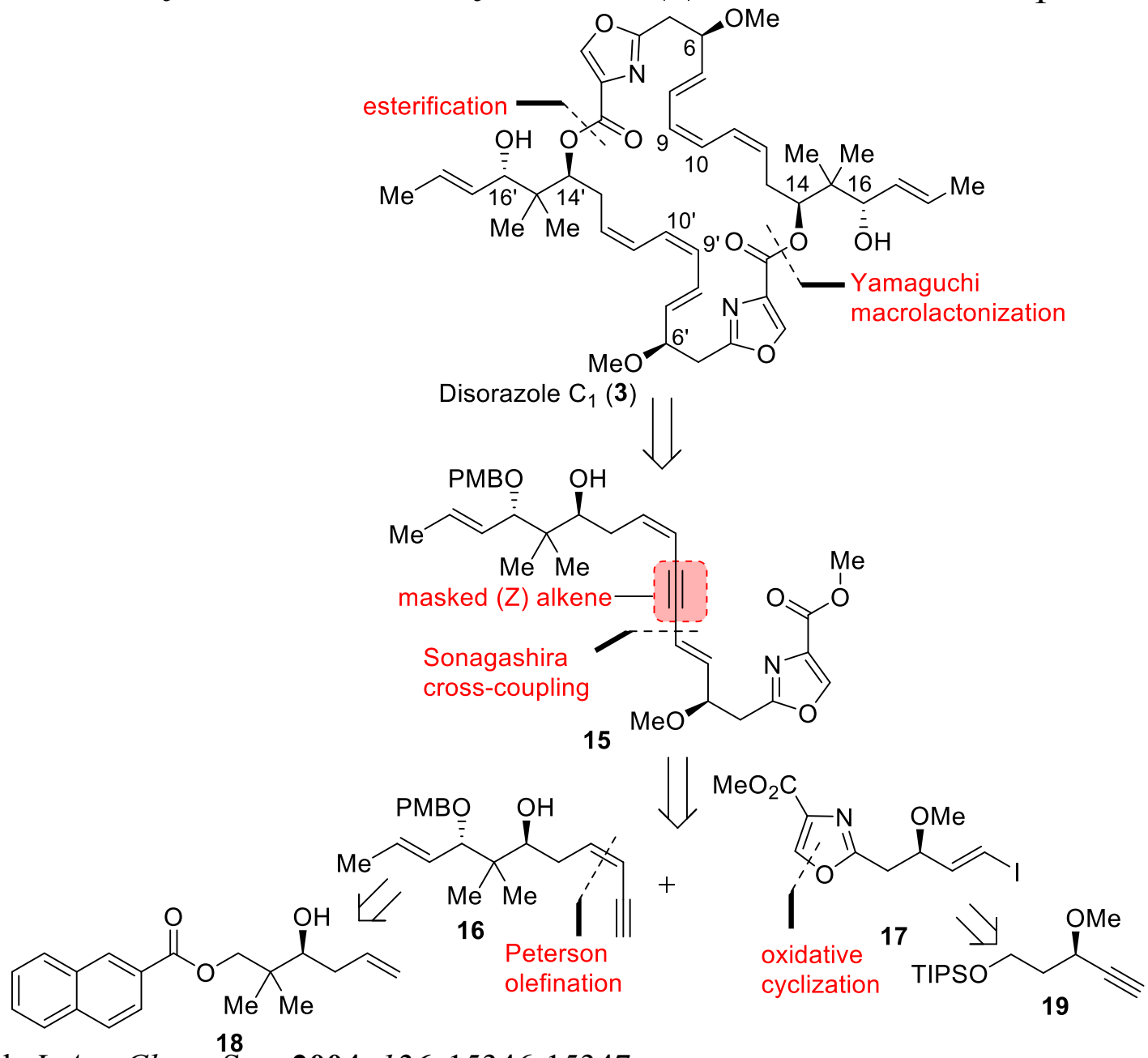
- Meyer's group partially synthesized in 2000
- Hoffmann's group first reported the synthesis of a masked fragment of (3) in 2002
- First successful total synthesis of (3) was achieved by Wipf group in 2004
- In 20 linear steps and 1.5% overall yield
- Hoffmann group also synthesized northern hemisphere of disorazole A_1 and D_1



Disorazole C_1 (**3**)

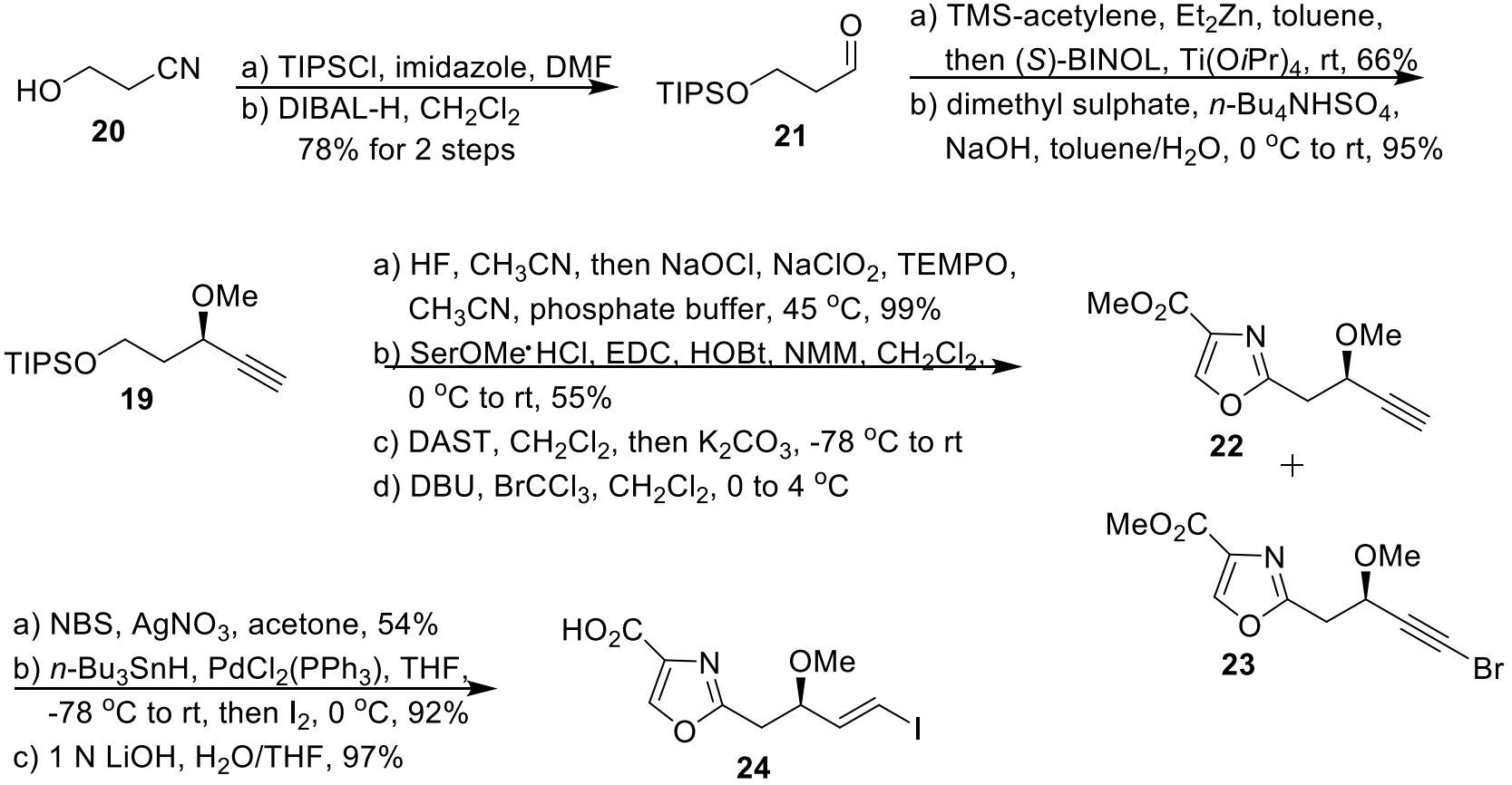
Wipf, P. et al. *Nat. Prod. Rep*. **2009**, *26*, 585−601.

Wipf's retrosynthetic analysis of (-)-disorazole C_1



Wipf, P. et al. *J. Am. Chem.* Soc. **2004**, *126*, 15346-15347.

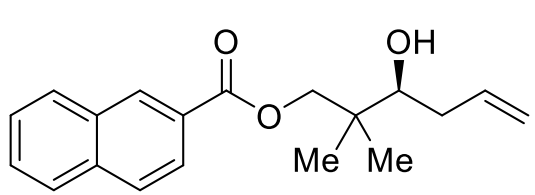
Wipf's oxazole fragment synthesis



Wipf, P. et al. *J. Am. Chem*. Soc. **2004**, *126*, 15346-15347.

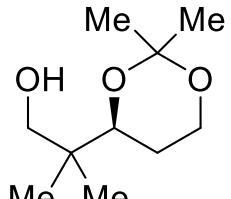
Wipf, P. et al. *Nat. Prod. Rep*. **2009**, *26*, 585−601.

Wipf's enyne fragment synthesis



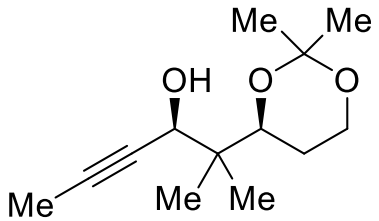
18

a) O_3/O_2, Sudan III, MeOH/CH_2Cl_2,
- 78 °C, then $NaBH_4$, - 78 °C to rt, 88%
b) 2,2-dimethoxypropane, PPTS, THF,
0 °C to rt, 97%
c) 1 N LiOH, THF/MeOH, 0 °C to rt, 82%



25

a) oxalyl chloride, DMSO, Et_3N, -78 °C
b) propyne, *n*-BuLi, THF, - 78 °C to 0 °C,



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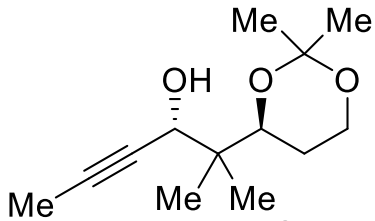
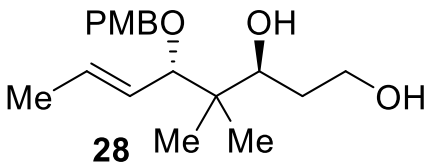


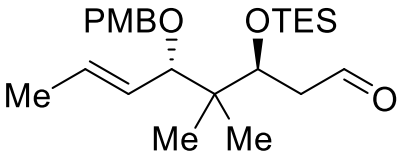
27

a) Red-Al, THF, 83%
b) PMBBr, Et_3N, KHMDS, THF, - 78 °C to rt,
c) AcOH/THF/H_2O (4:1:1), 60 °C , 84% for 2 steps



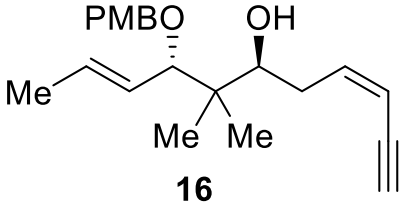
28

a) TESOTf, 2,6-lutidine,
CH_2Cl_2, 0 °C
b) oxalyl chloride, DMSO,
Et_3N, CH_2Cl_2, -78 °C,
75% for 2 steps



29

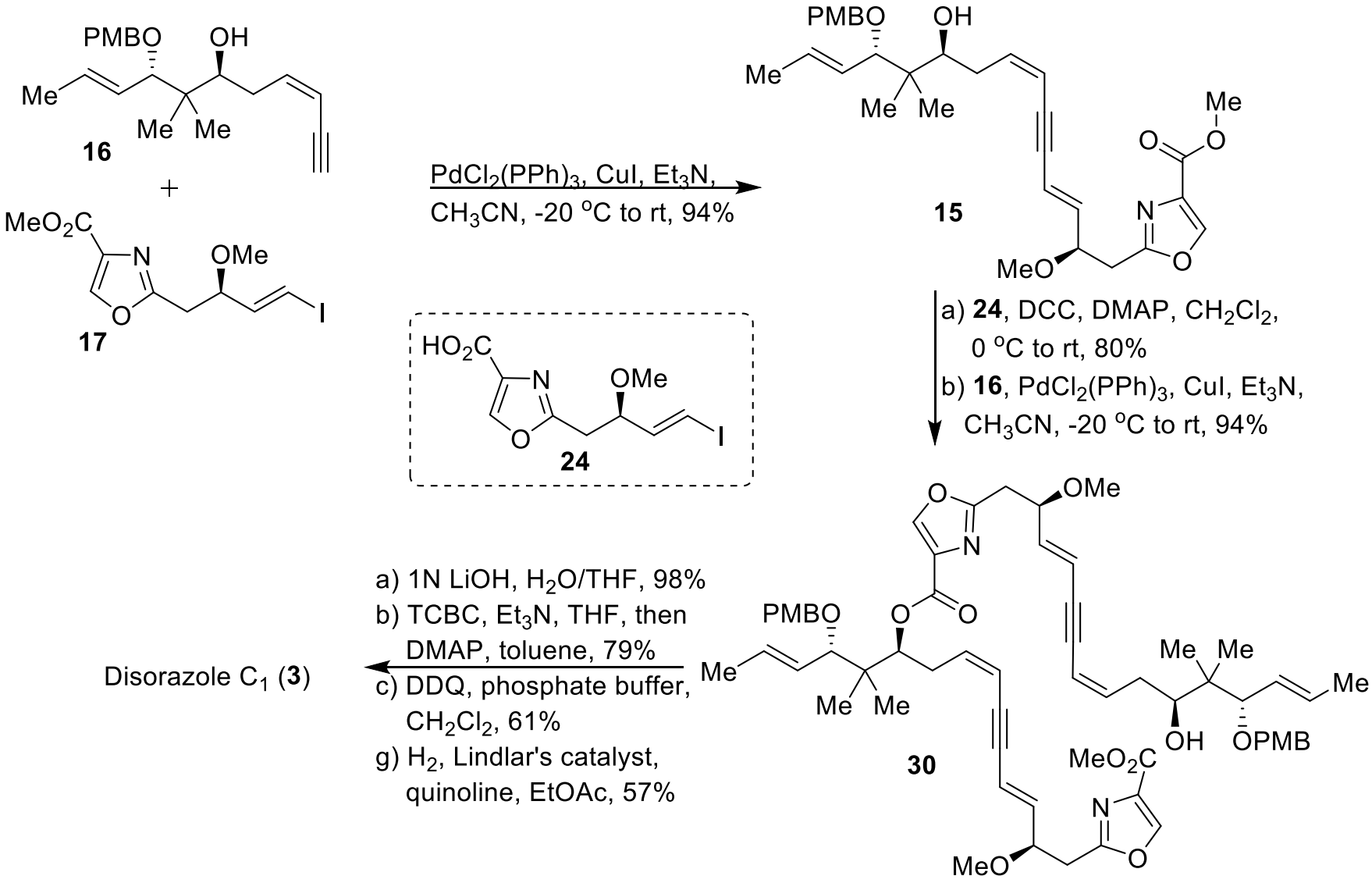
a) 1,3-*bis*(TIPS)propyne, *n*-BuLi, THF, - 78 °C
b) chloroacetic acid, MeOH/CH_2Cl_2
c) TBAF, THF, 0 °C to rt, 94%



16

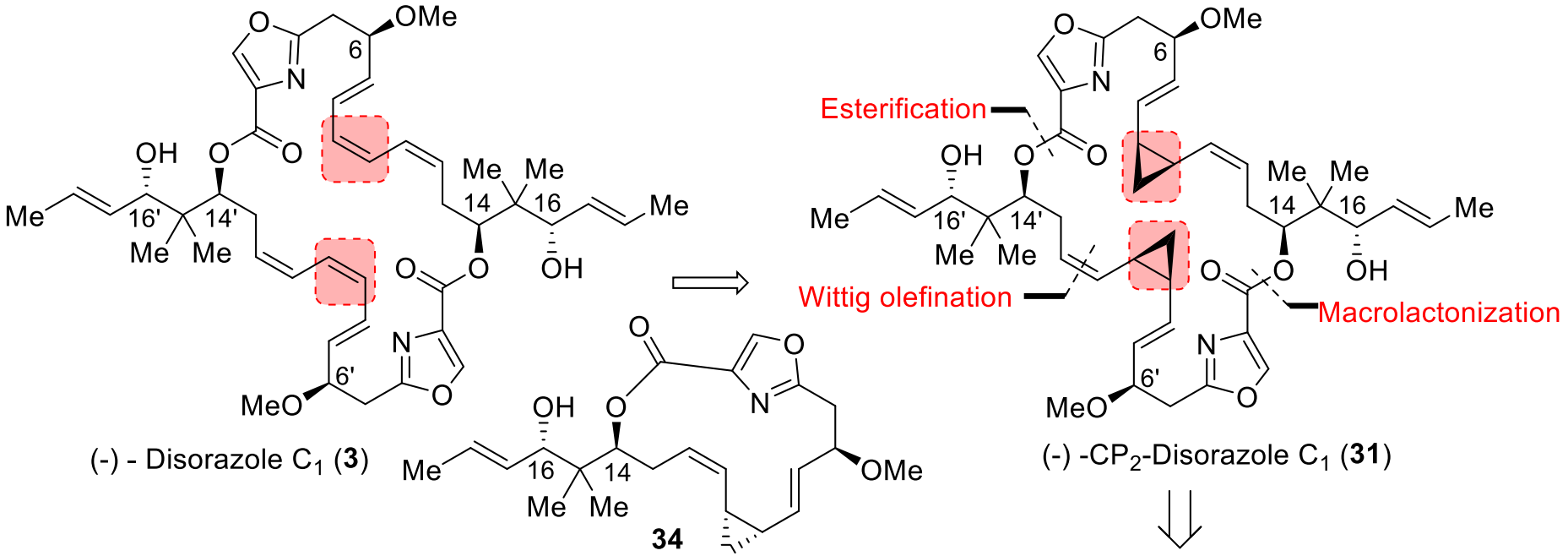
Wipf, P. et al. *J. Am. Chem*. Soc. **2004**, *126*, 15346-15347.
Wipf, P. et al. *Nat. Prod. Rep*. **2009**, *26*, 585−601.

Wipf's total synthesis of disorazole C_1

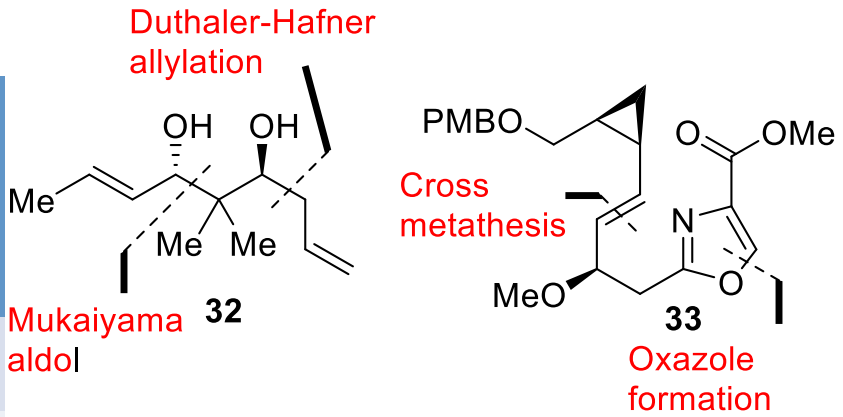


Wipf, P. et al. *J. Am. Chem.* Soc. **2004**, *126*, 15346-15347.

Wipf's retrosynthetic analysis of (-)-CP$_2$-disorazole C$_1$ (**31**)



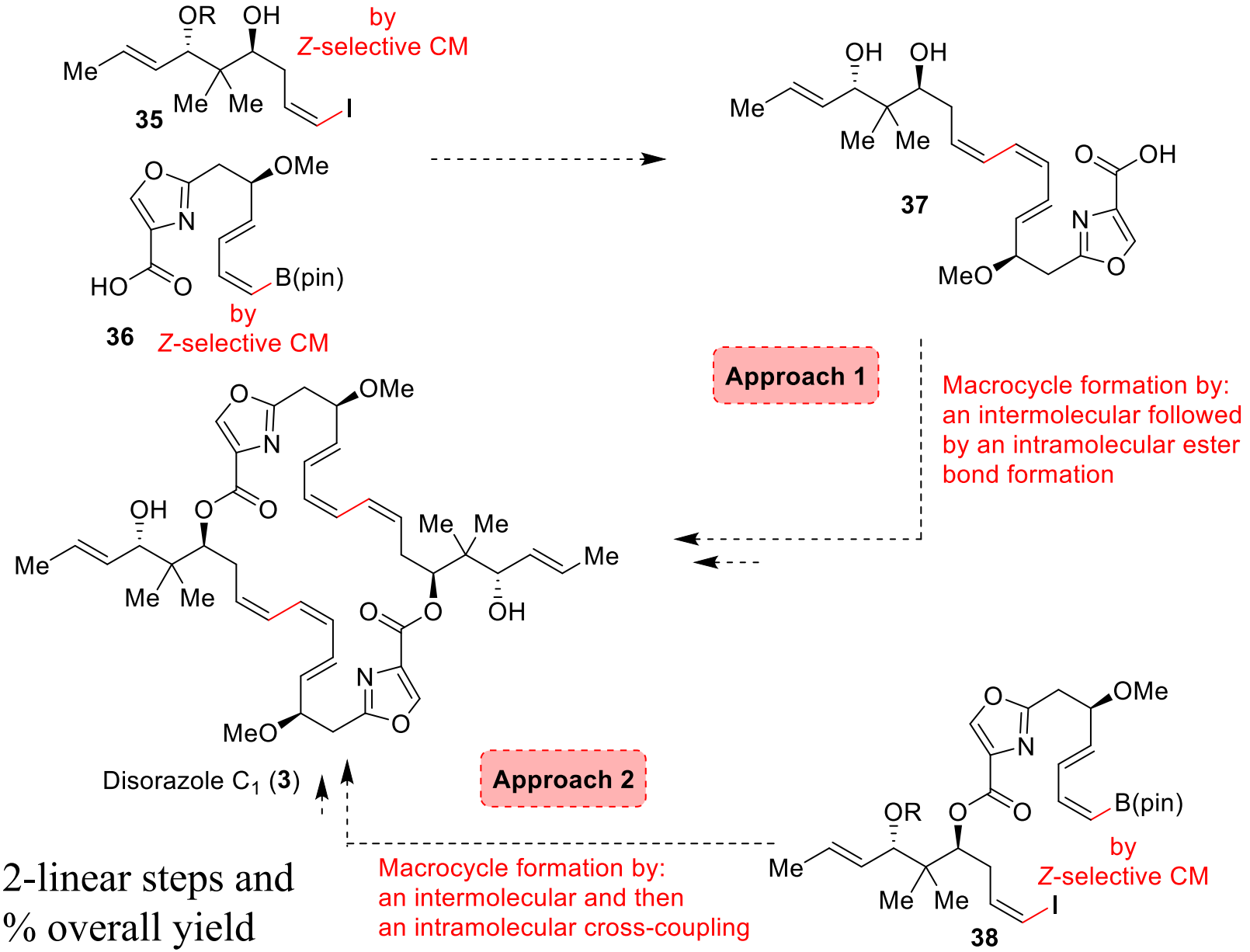
cell line	31 IC$_{50}$ [nm]	34 IC$_{50}$ [nm]	vincristine IC$_{50}$ [nm]
RKO	28.0 ± 9.2	>50	18.6 ± 7.6
HCT116	28.3 ± 11.6	>50	35.2 ± 11.9
H630	49.5 ± 25.0	>50	68.0 ± 16.3



- 23-linear steps and 1.1% overall yield

Wipf, P. et al. *Org. Lett.* **2011**, *13*, 4088-4091

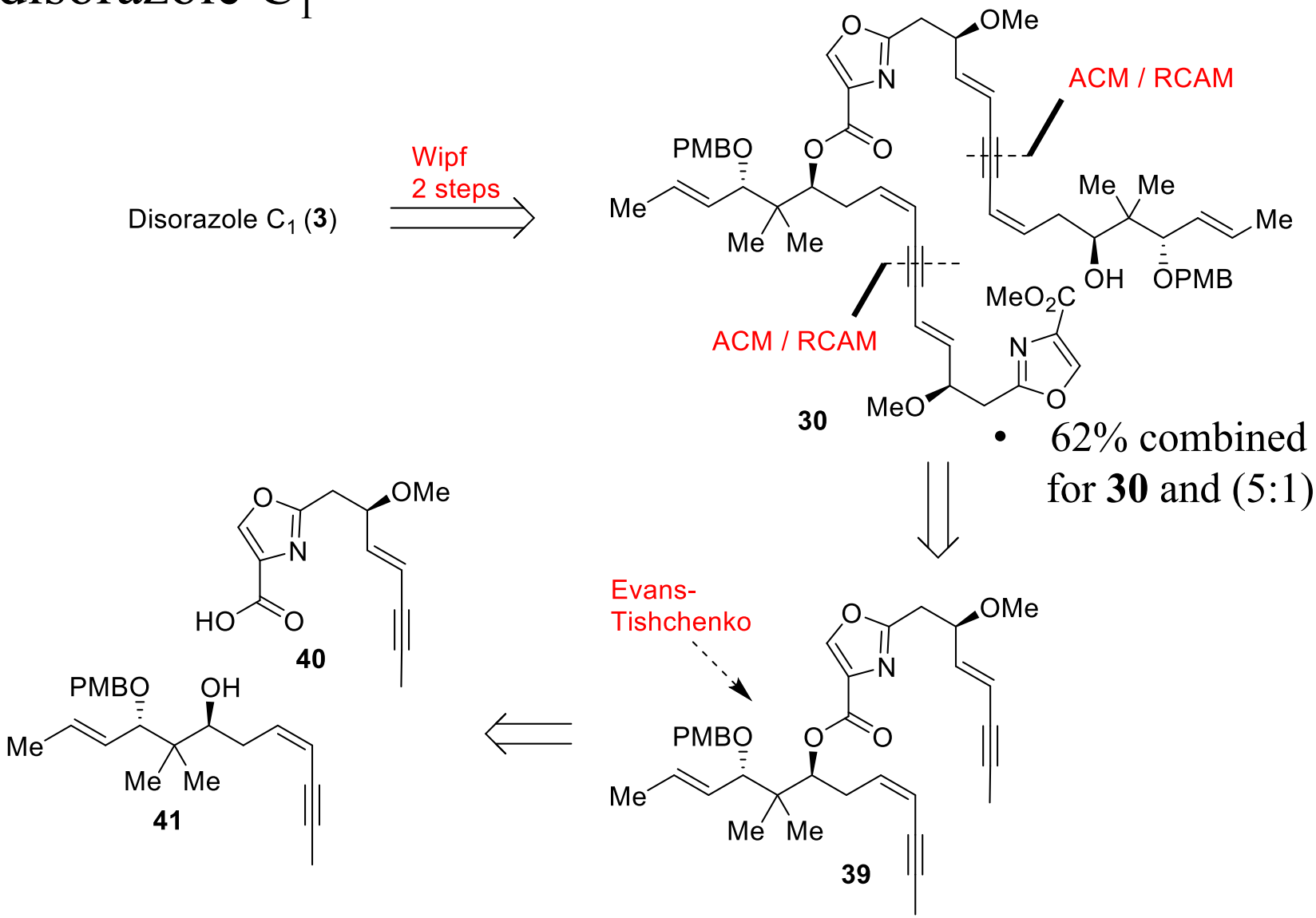
Hoveyda's approach for the total synthesis of disorazole C_1



- 12-linear steps and 8% overall yield

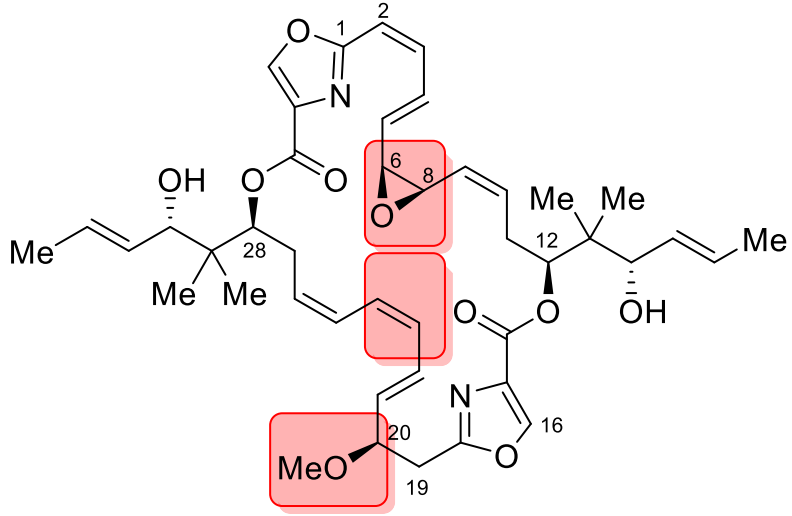
Hoveyda, A. H et al. *J. Am. Chem.* Soc. **2014**, *136*, 16136-16139.

Hulme's alkyne metathesis strategy for the total synthesis of disorazole C_1

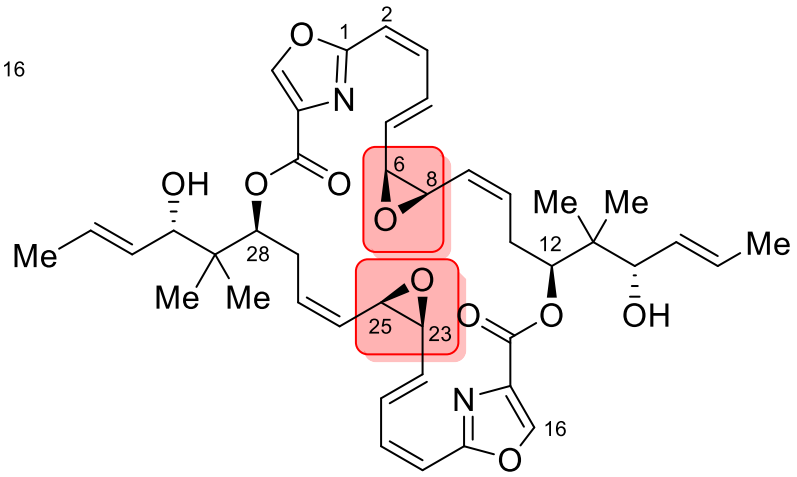


Hulme, A. N. et al. *Angew. Chem. Int. Ed.* **2015**, 54, 7086-7090.

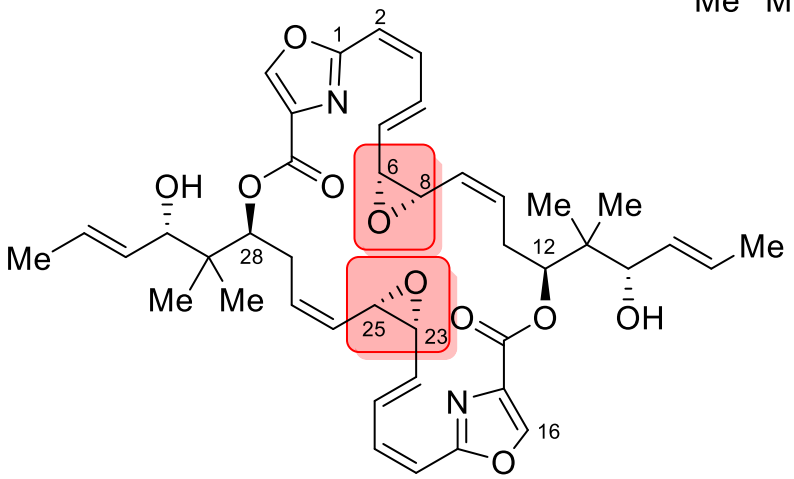
Total synthesis of disorazole A_1 and B_1 and full structural elucidation of disorazole B1



Disorazole A_1 (**1**)



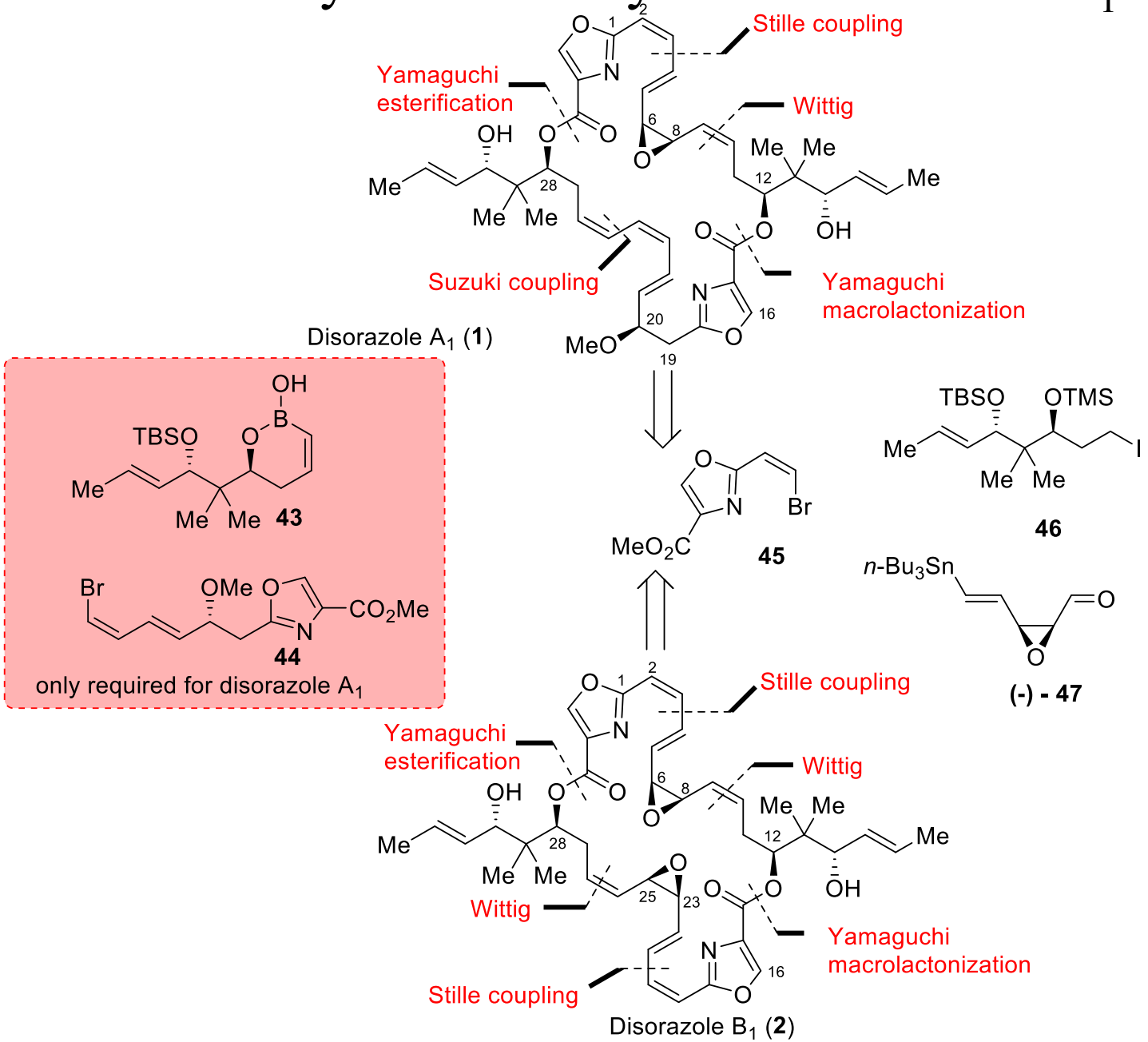
Disorazole B_1 (**2**)



6,8,23,25-tetra-*epi*-disorazole B_1 (**42**)

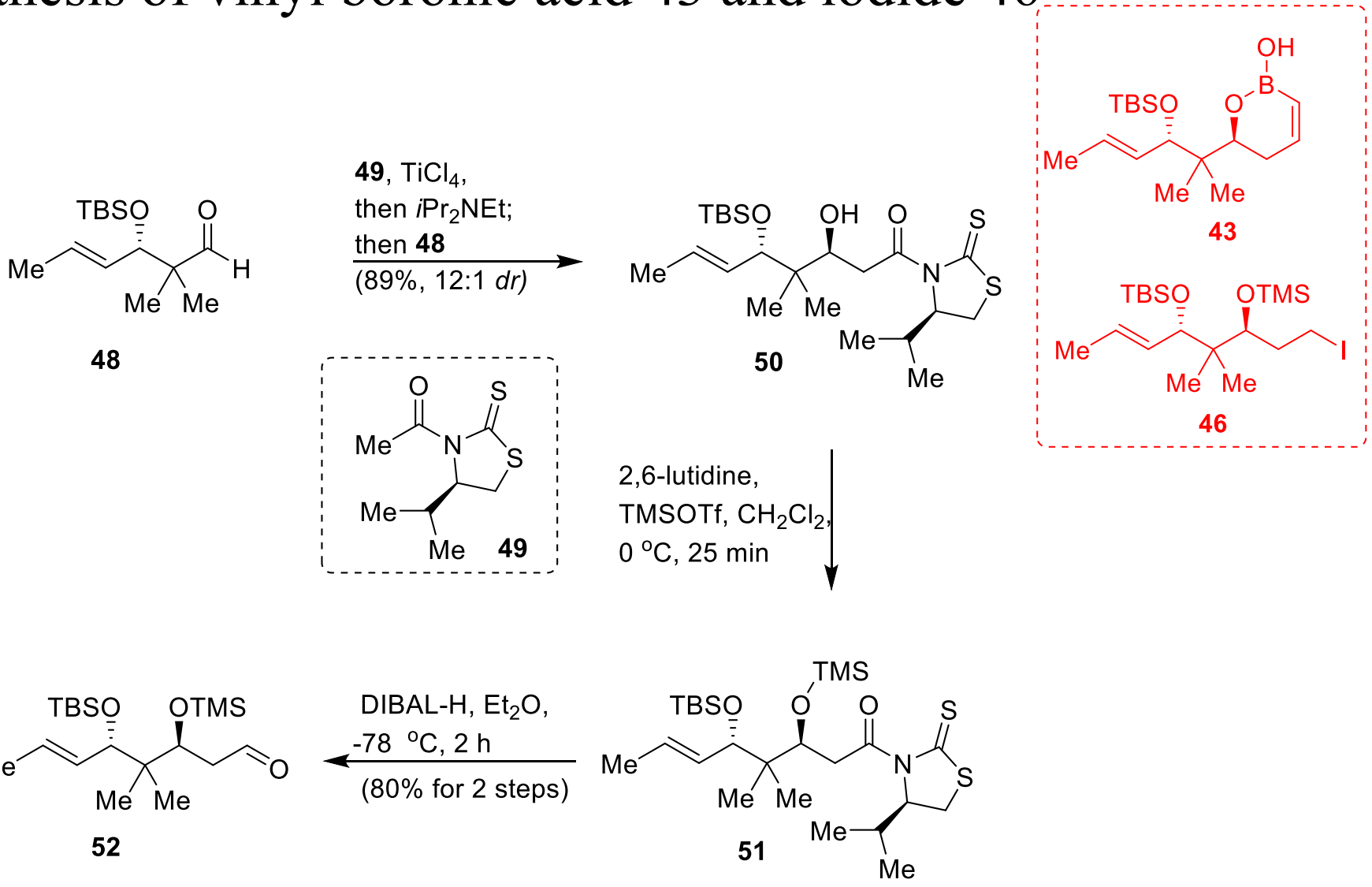
Nicolaou, K. C. et al. *J. Am. Chem.* Soc. **2017**, *139*, 15636-15639.

Nicolaou's retrosynthetic analysis of disorazole A_1 and B_1



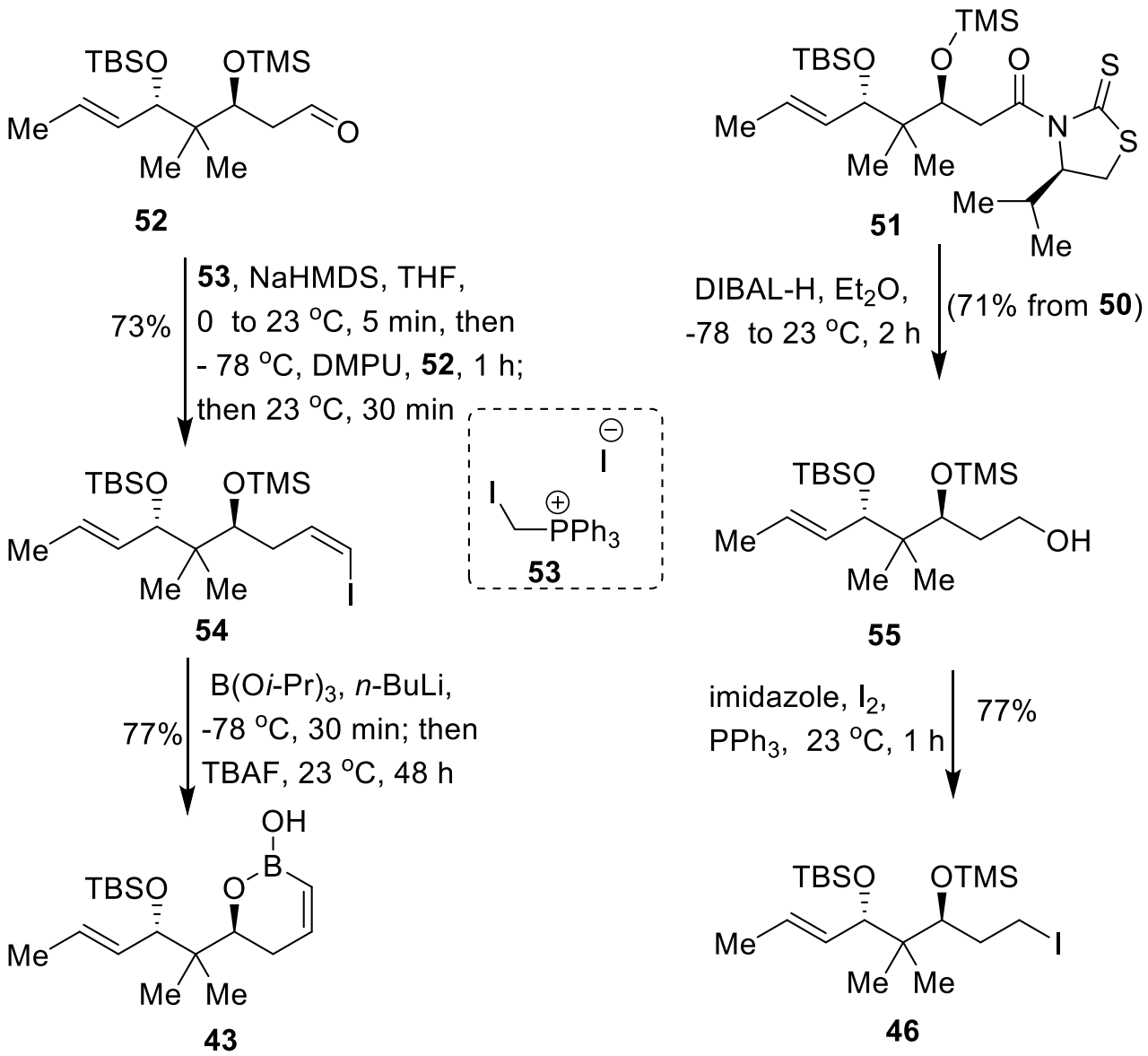
Nicolaou, K. C. et al. *J. Am. Chem.* Soc. **2017**, *139*, 15636-15639.

Synthesis of vinyl boronic acid 43 and iodide 46



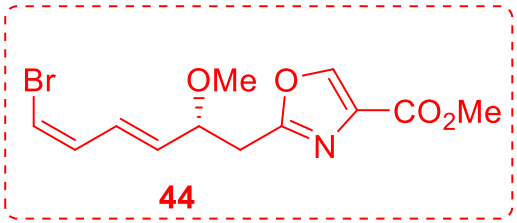
Nicolaou, K. C. et al. *J. Am. Chem.* Soc. **2017**, *139*, 15636-15639.

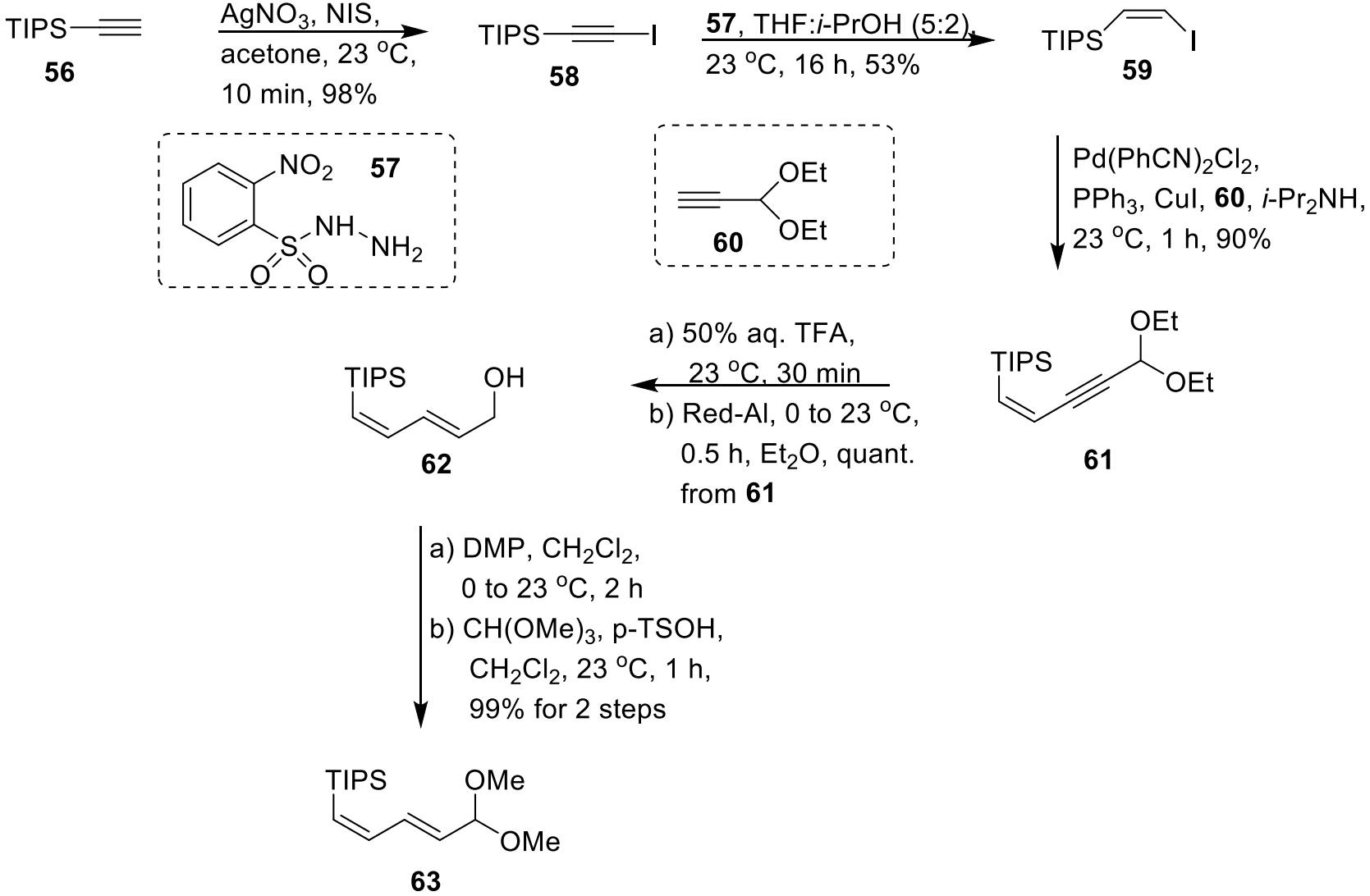
Synthesis of vinyl boronic acid 43 and iodide 46 cont'd



Nicolaou, K. C. et al. *J. Am. Chem*. Soc. **2017**, *139*, 15636-15639.

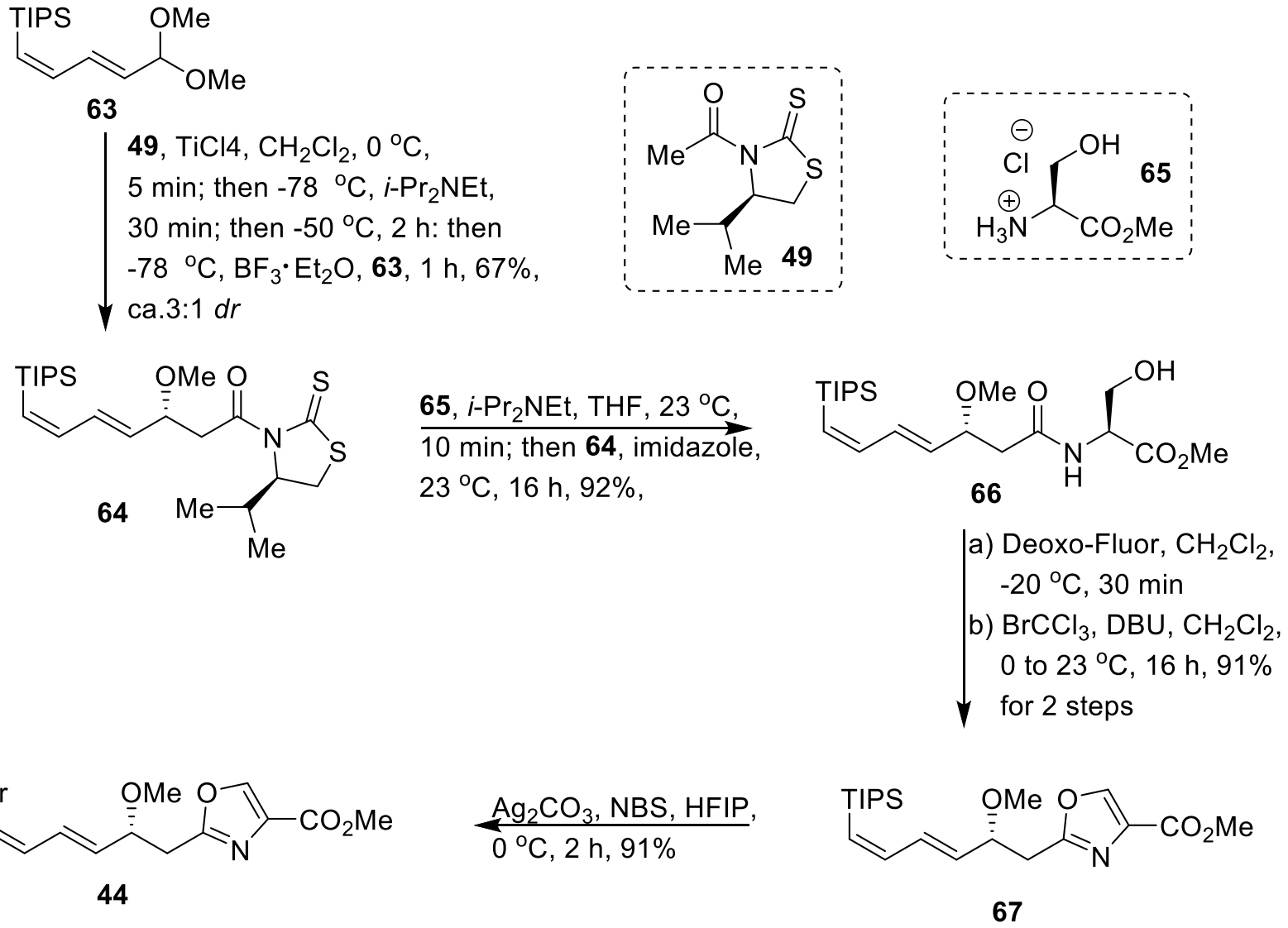
Synthesis of vinyl bromide fragment 44





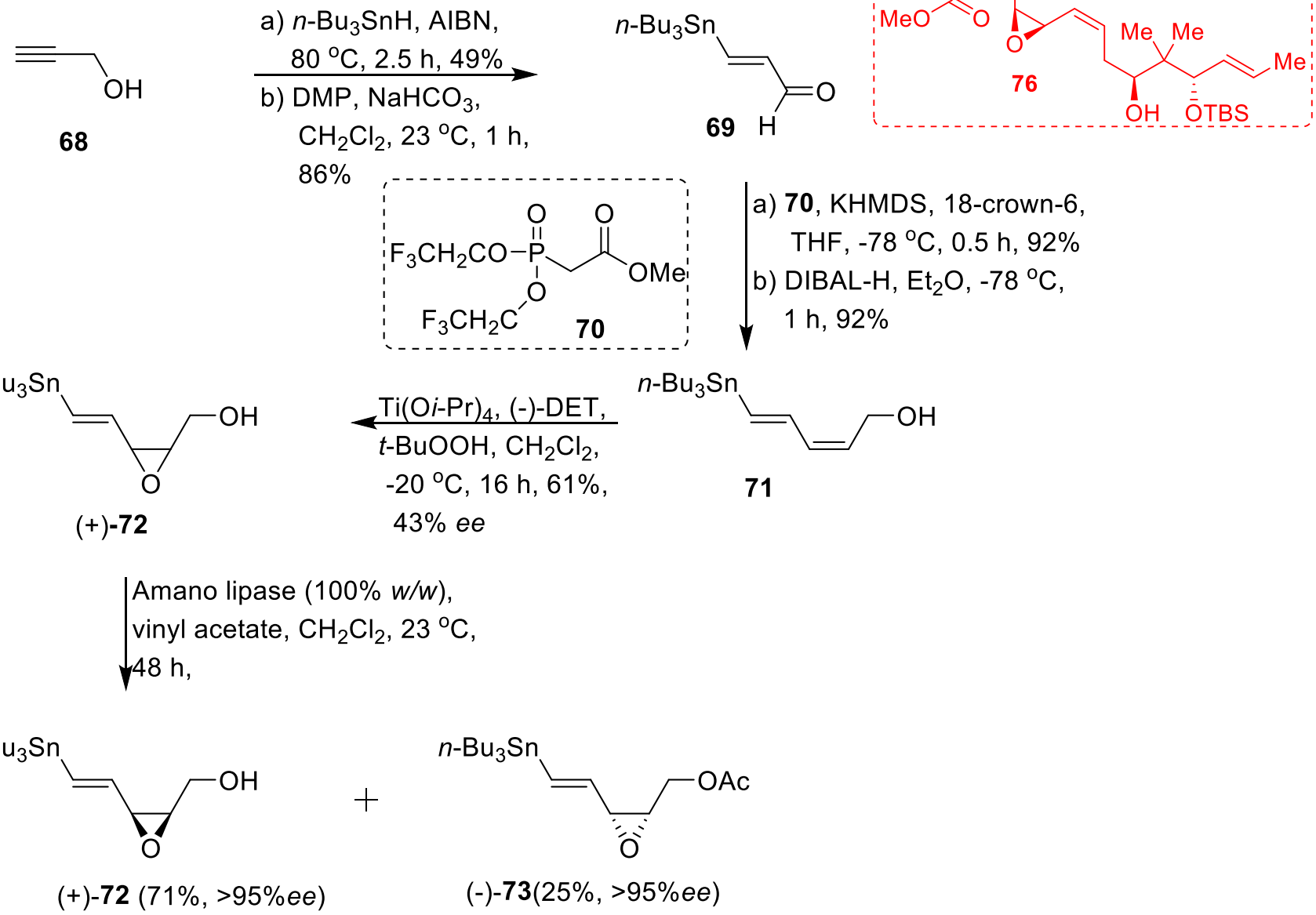
Nicolaou, K. C. et al. *J. Am. Chem.* Soc. **2017**, *139*, 15636-15639.

Synthesis of vinyl bromide fragment 44 cont'd



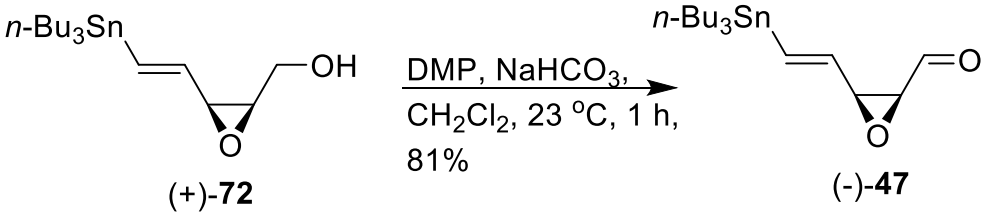
Wipf, P. et al. *Org. Lett*. **2000**, *2*, 1165-1168.
Nicolaou, K. C. et al. *J. Am. Chem*. Soc. **2017**, *139*, 15636-15639.

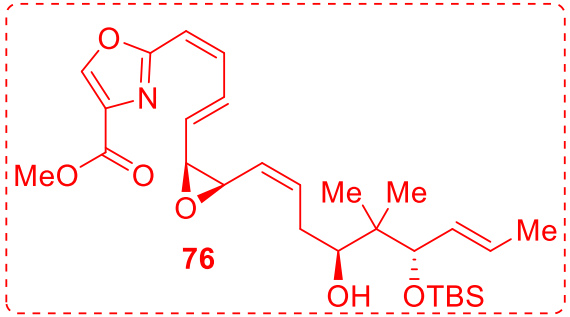
Synthesis of epoxide fragment 76

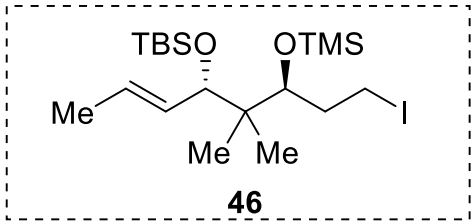


Nicolaou, K. C. et al. *J. Am. Chem.* Soc. **2017**, *139*, 15636-15639.

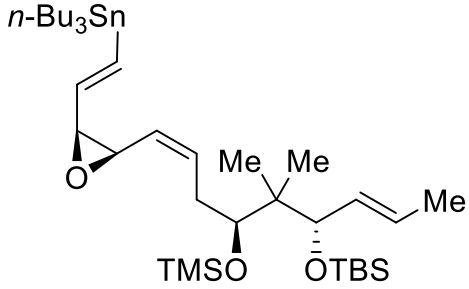
Synthesis of epoxide fragment 76 cont'd

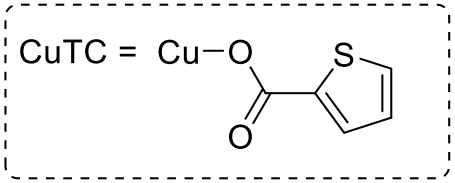




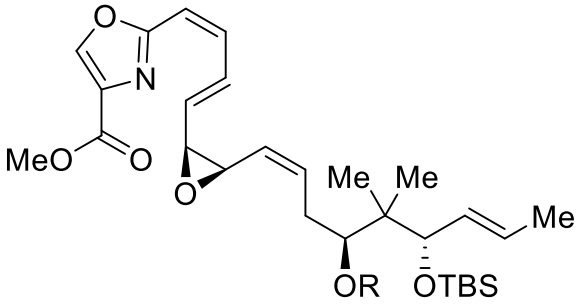


46, PPh_3, *i*-Pr_2NEt,
90 °C, 16 h; then -78 °C,
LiHMDS, DMPU, (-)-**47**,
THF, 15 min; then 23 °C,
1 h, 76%





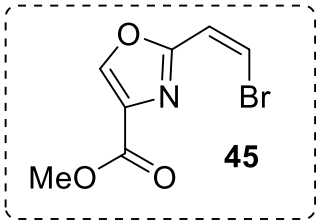
45, CuTC, NMP,
23 °C, 1 h, 74%

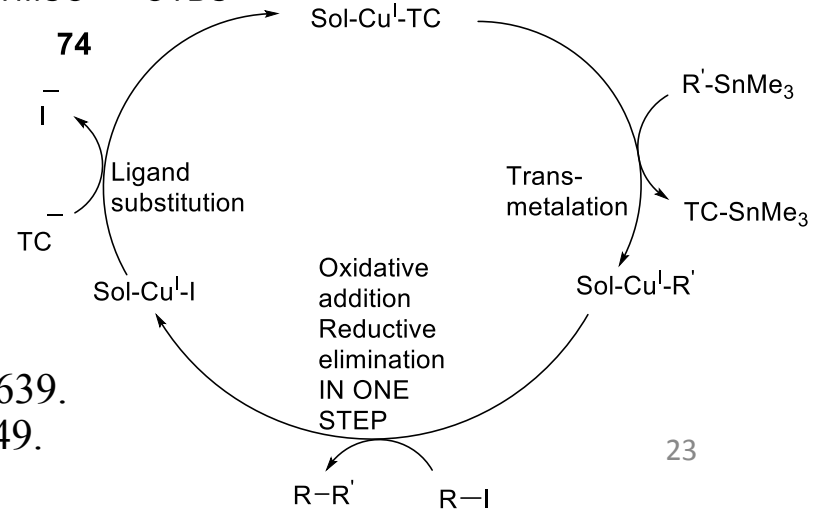


$Et_3N{\cdot}3HF$, THF,
23 °C, 1 h, 76%

75, R= TMS

76, R= H





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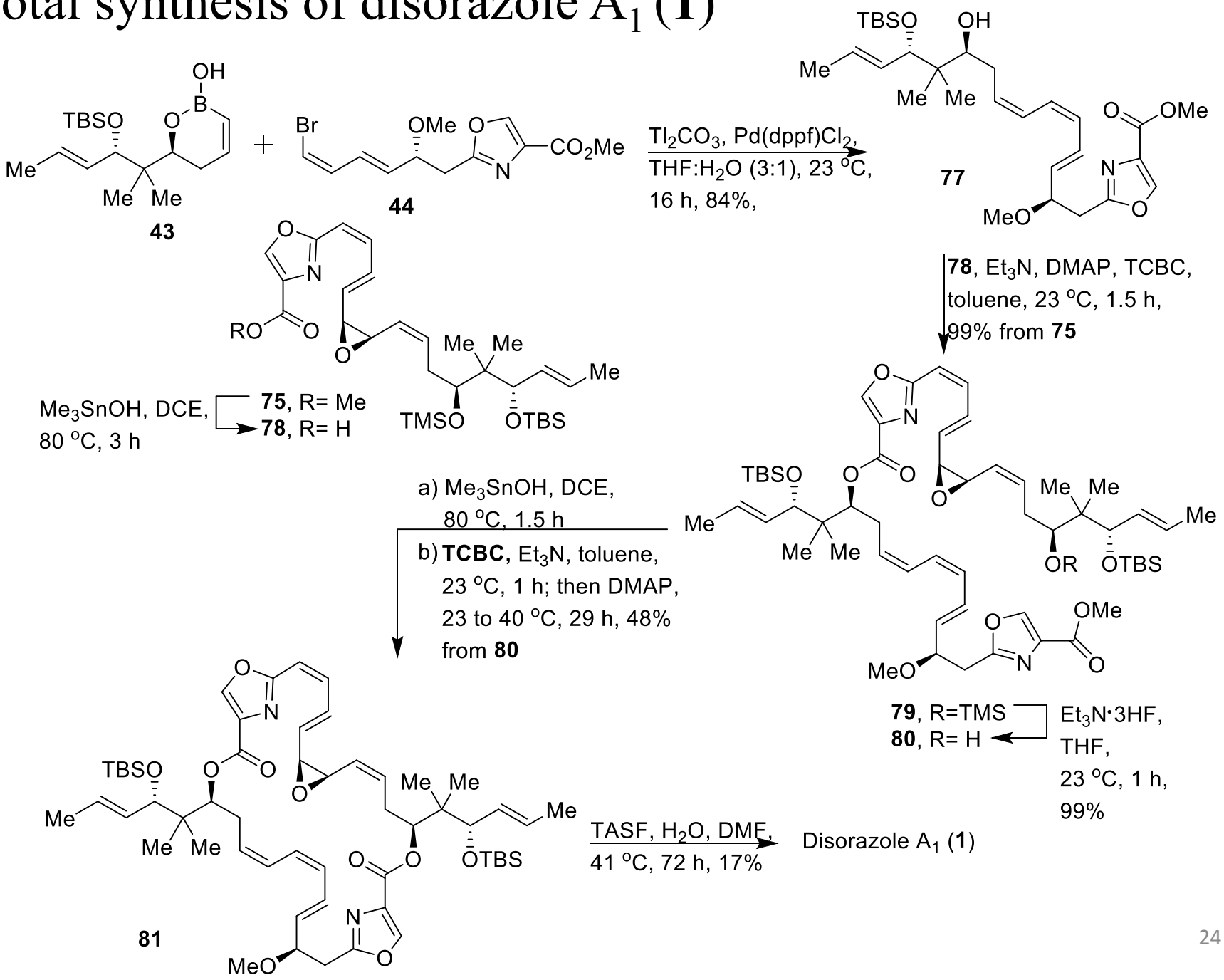
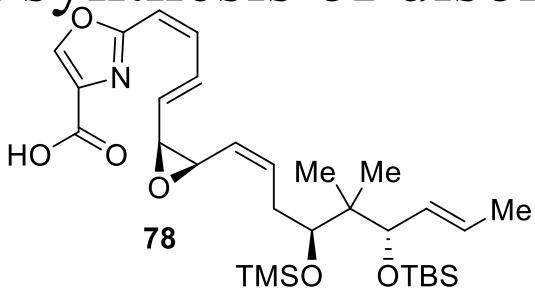
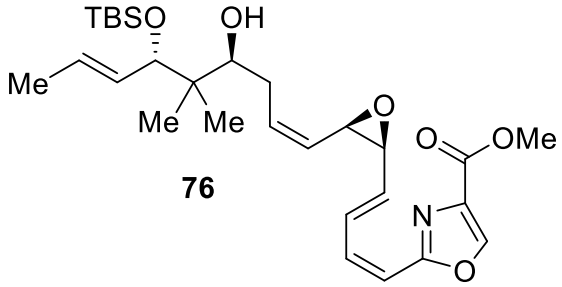
Total synthesis of disorazole A_1 (**1**)



Total synthesis of disorazole B_1 (**2**)

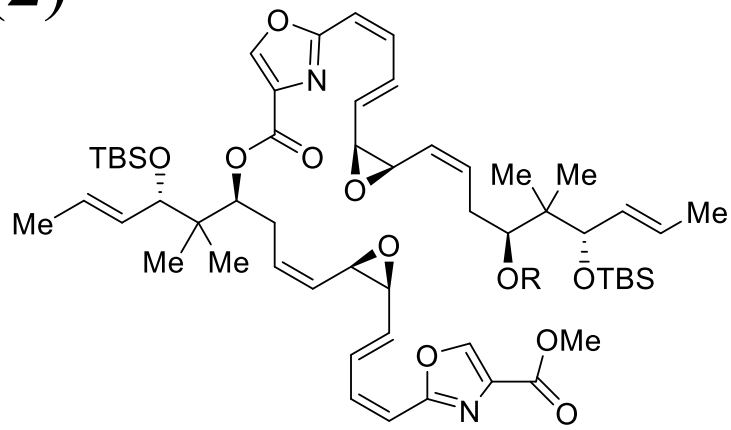


78



76

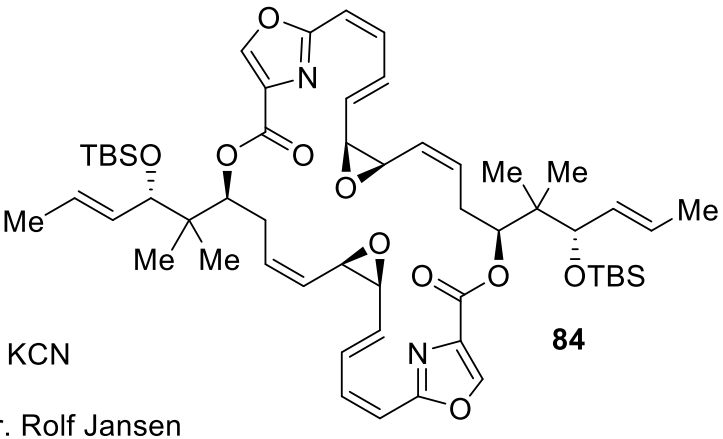
Et_3N, DMAP, TCBC,
toluene, 23 °C, 1 h,
98%



82, R=TMS
83, R= H

$Et_3N{\cdot}3HF$, THF,
23 °C, 1 h, 91%

a) Me_3SnOH, DCE,
80 °C, 1.5 h
b) TCBC, Et_3N, toluene,
23 °C, 1 h; then DMAP,
23 to 40 °C, 29 h, 48%
for 2 steps



84

TASF, H_2O, DMF,
40 to 45 °C, 72 h,
64%

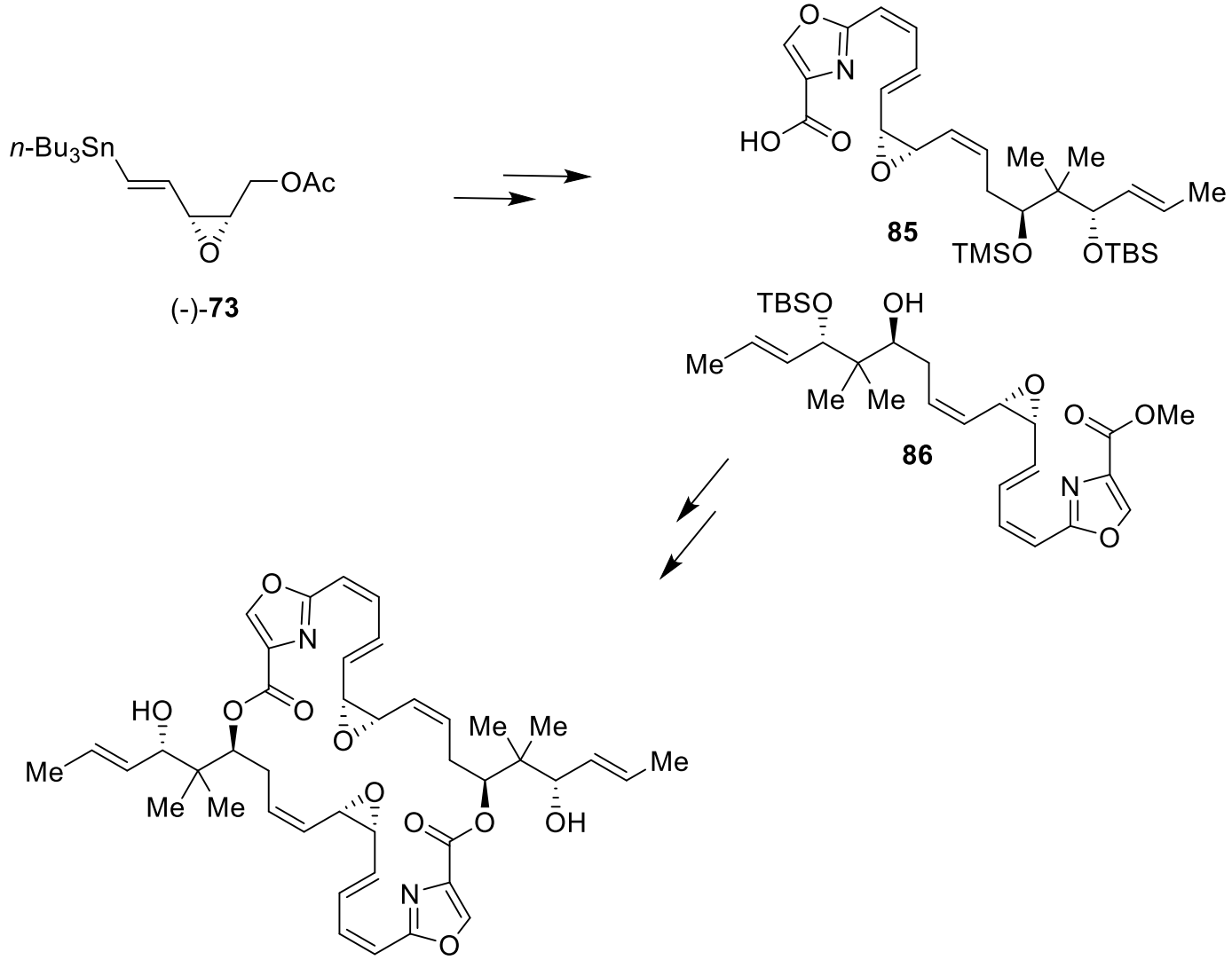
Disorazole B_1 (**2**)

$[\alpha]_D^{25} = -59$ (*c* 0.61, MeOH:CH_2Cl_2 1:1, *v*/*v*)) synthesis by Prof. KCN

$[\alpha]_D^{22} = -65$ (*c* 0.5, MeOH:CH_2Cl_2 1:1, *v*/*v*)) clarification from Dr. Rolf Jansen

$[\alpha]_D^{22} = +64.7$ (*c* 0.5, MeOH:CH_2Cl_2 1:1, *v*/*v*)) isolation by Dr.Rolf Jansen

Total synthesis of 6,8,23,25-tetra-*epi*-disorazole B_1 (**42**)



6,8,23,25-tetra-*epi*-disorazole B_1 (**42**)

$[\alpha]_D^{25} = -147$ (*c* 0.5, MeOH:CH_2Cl_2 1:1, *v*/*v*)

Nicolaou, K. C. et al. *J. Am. Chem*. Soc. **2017**, *139*, 15636-15639.

Conclusion

- First total syntheses of disorazoles A_1 and B_1
- Full structural assignment of disorazole B_1
- Sharpless epoxidation / enzymatic kinetic resolution
- Series of coupling reactions

Thank you
Prof. Peter Wipf

Thanks to Prof. Wipf Research Group