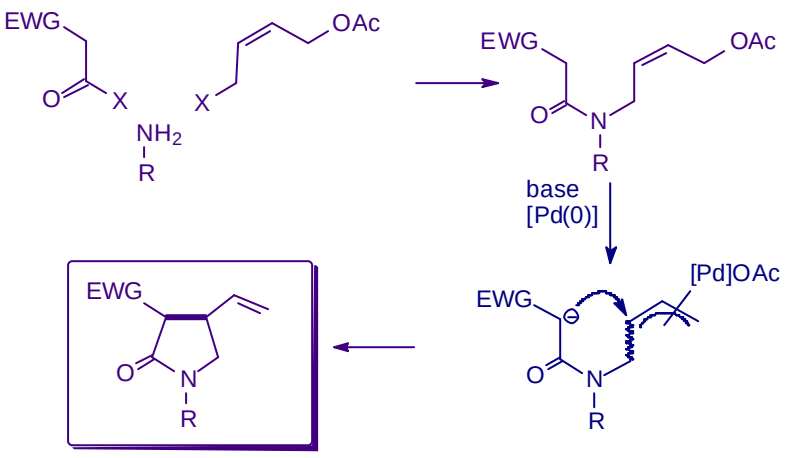
ISCHIA ADVANCED SCHOOL OF ORGANIC CHEMISTRY

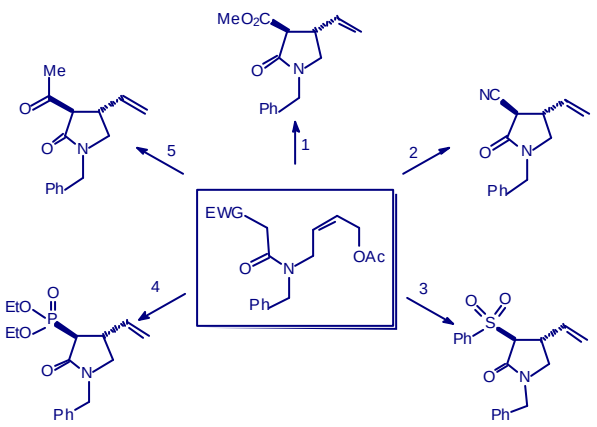
New Aspects of Multistep Palladium-Catalyzed Processes

September 24 2002

The Targets: Pyrrolidones



The First Results

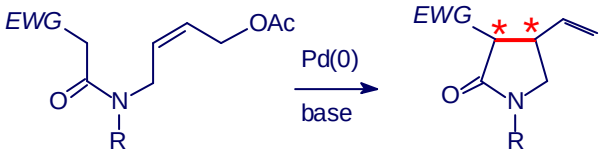


Entry	EWG	Yield %
1	CO_2Me	70
2	CN	70
3	COMe	77
4	SO_2Ph	80

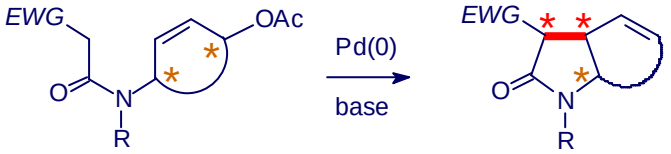
$Pd(dba)_2$, PPh_3, BSA, AcOK cat., THF, 70°C, 15h

Giambastiani, G.; Pacini, B.; Porcelloni, M.; Poli, G. *J.Org.Chem.* **1998**, *63*, 804-807

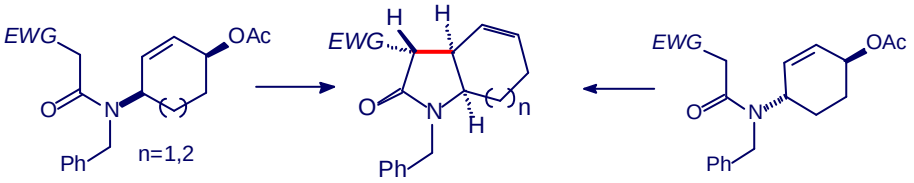
From internal…



…to facial diastereoselection



Cyclization of the cis and trans precursors



EWG=MeO_2C, PhO_2S

i: $Pd(OAc)_2$ / dppe, NaH, DMF, 100°C

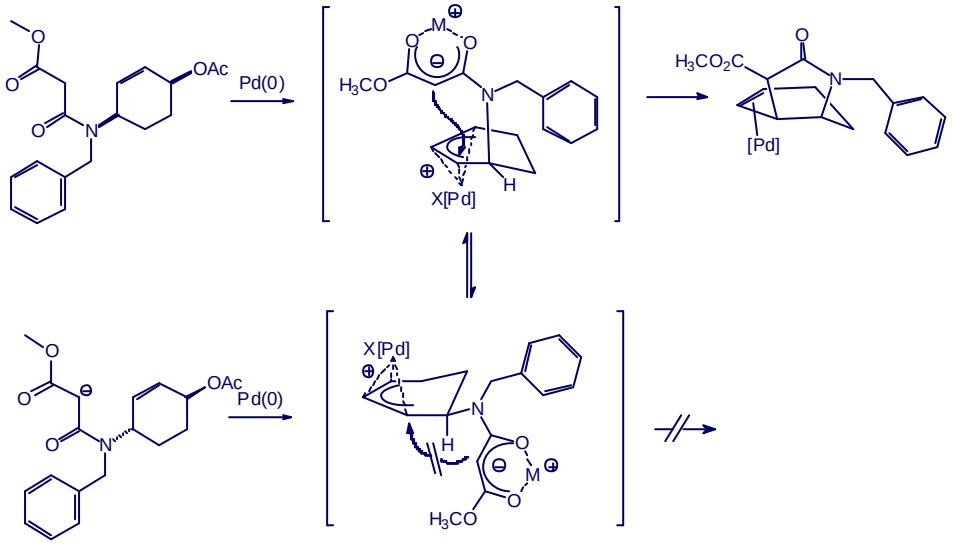
EWG=MeO_2C

90% (n=1; *EWG* =MeO_2C,PhO_2S)
87% (n=2; *EWG* =MeO_2C)

73% (*EWG* =MeO_2C)

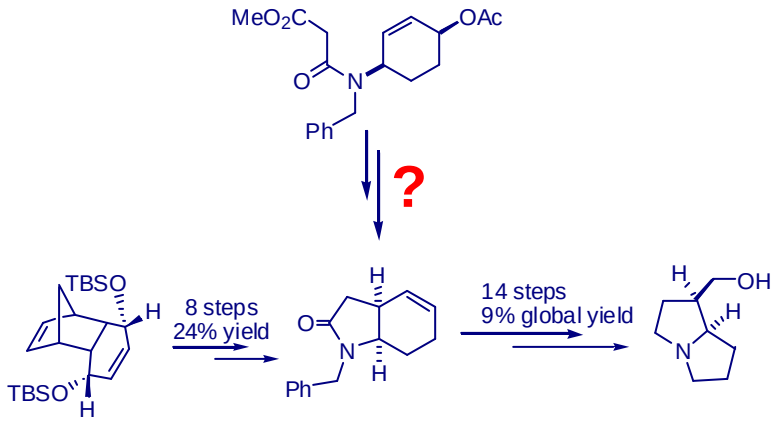
The reactions is stereoconvergent

Mechanistic Rationale



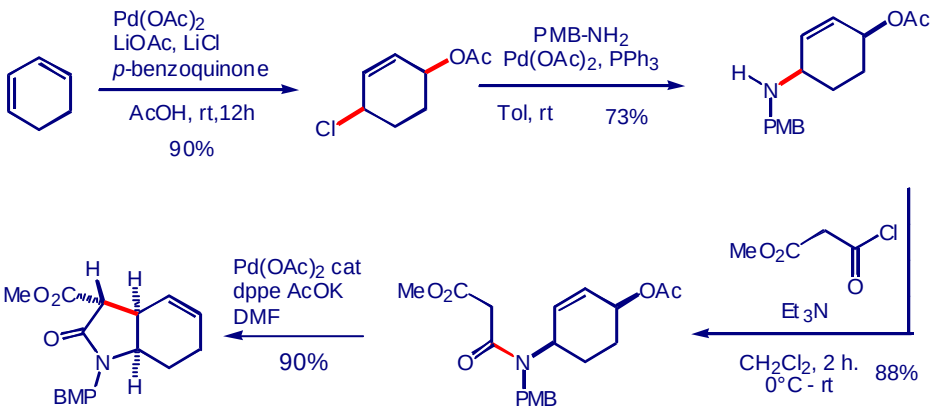
Isoretronecanol (1)

A New Synthetic Application

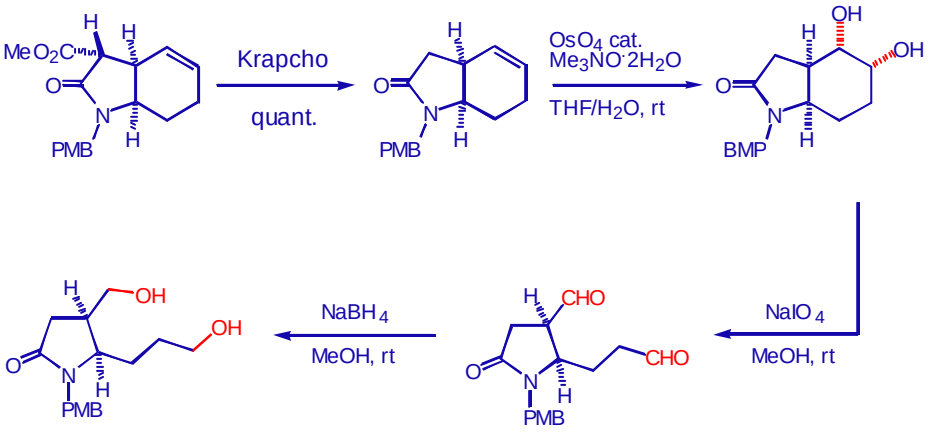


K. Ogasawara, N. Konno, M. Kishi, K. Hiroya, *Heterocycles* , **1998,** *49*, 33-37

Isoretronecanol (2)

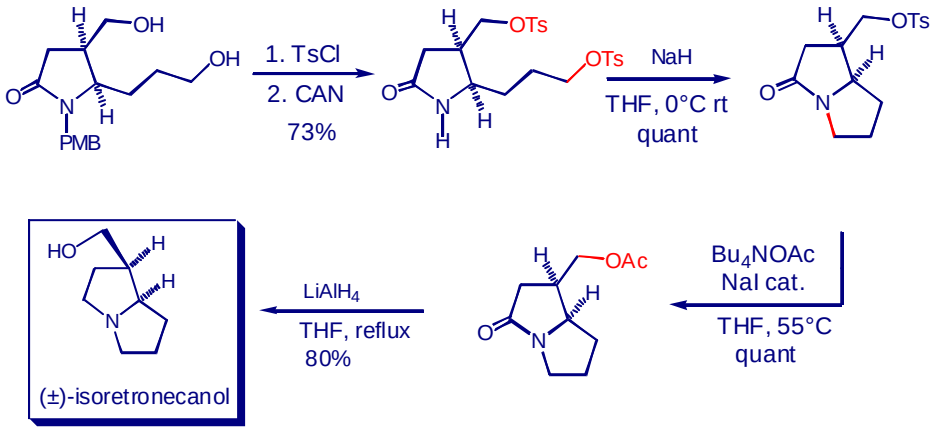


Isoretronecanol (3)



95% yield, 3 steps

Isoretronecanol (3)

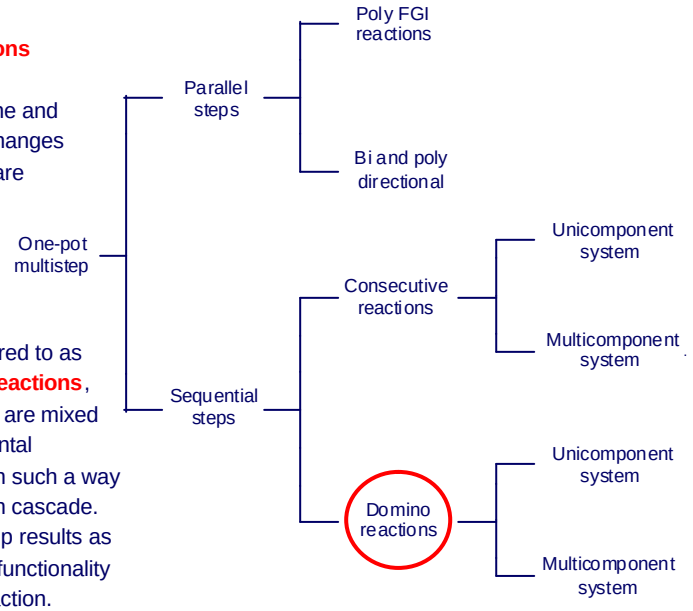


12 steps
29% global yield

One-pot Multistep Sequences

In **consecutive reactions** the first step does not promote the second one and external reagents or changes in reaction conditions are required to favor propagation.

In **domino** (often referred to as **tandem** or **cascade**) **reactions**, reagents and catalysts are mixed together and experimental conditions are set up in such a way to promote the reaction cascade. Each bond-forming step results as a consequence of the functionality left by the previous reaction.

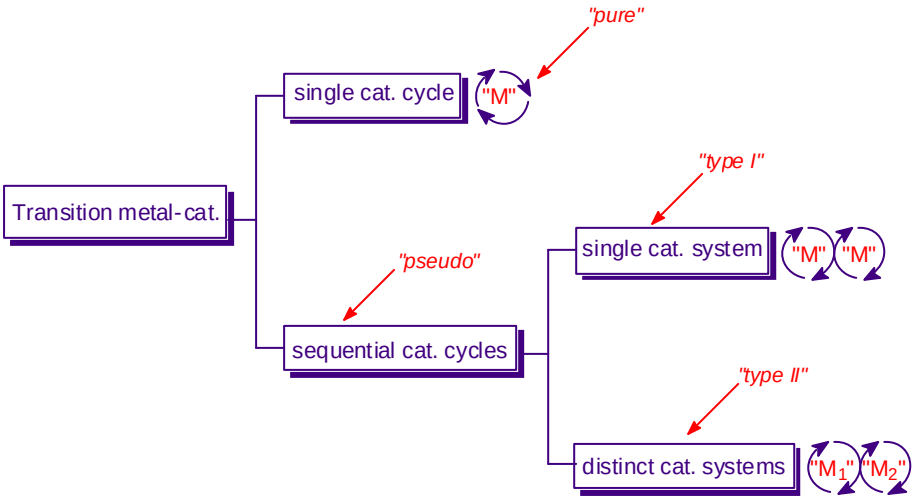


Domino Processes

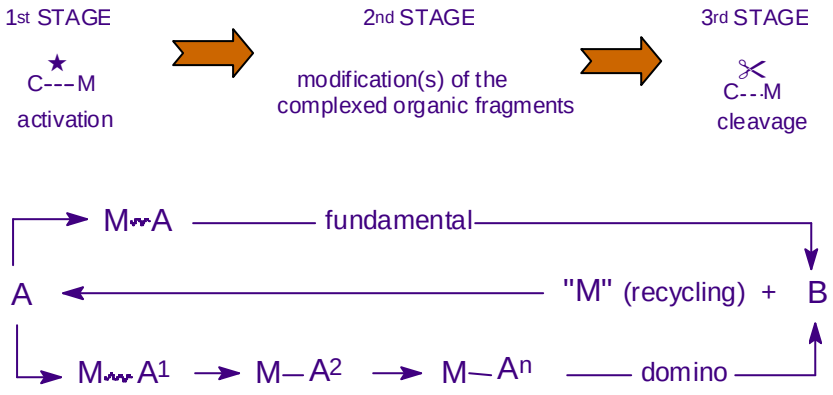
"*…a domino reaction is a process involving two or more bond-forming transformations which take place under the same reaction conditions without additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step".*

Tietze, L. F. *Chem. Rev.*, **1996**, *96*, 115-136

Transition Metal-Catalyzed Domino Processes

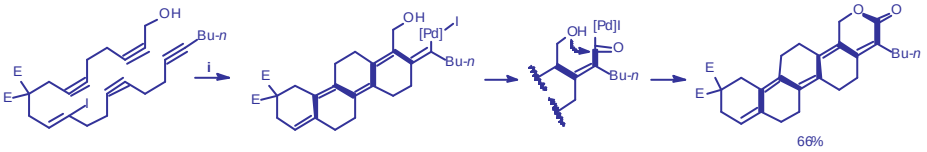


A Metal-Catalyzed "Pure" Domino Process



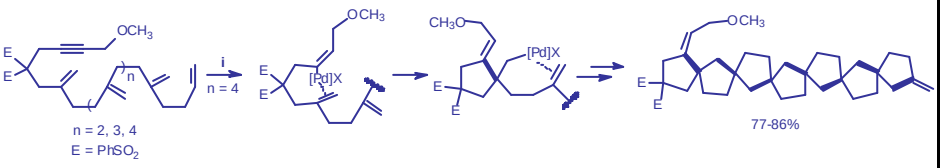
Poli, G.; Giambastiani, G. Heumann, A. *Tetrahedron* **2000**, *56*, 5959-5989

Examples of Pd-catalyzed Domino Processes



i : CO (1.1atm.), 5 mol% $Cl_2Pd(PPh_3)_4$, NEt_3 (2 eq.), CO (1.1atm.), MeOH, 70° C, 1d; E = CO_2Et

Negishi, E.; Copéret, C.; Sugihara, T.; Shimoyama, I.; Zhang, Y.; Wu, G.; Tour, J.M. *Tetrahedron*, **1994**, *50*, 425.

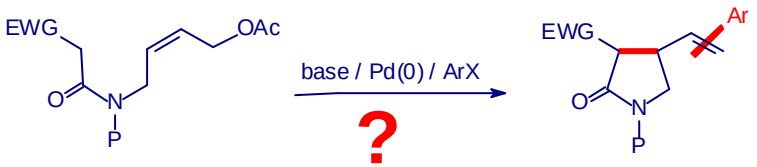


i : 2.5% $(dba)_3Pd_2CHCl_3$, 10% Ph_3Sb, AcOH, PhH, 50-65° C

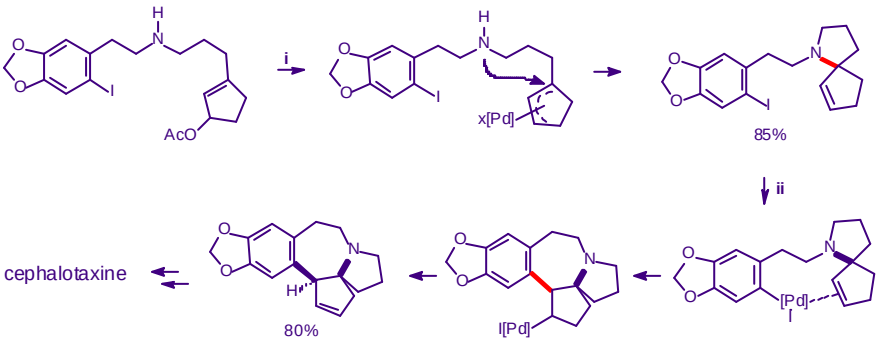
Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.*, **1991**, *113*, 701.

Inventing a *type I* TM-cat. Domino process

Is such a transformation possible in a *pseudo*-domino fashion ?



Tietze's Synthesis of Cephalotaxine

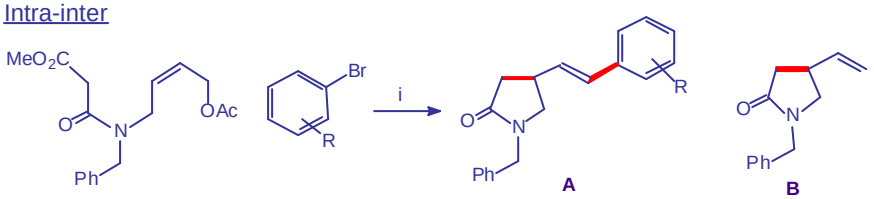


i : 8 mol% $Pd(PPh_3)_4$, NEt_3 (1.7 eq.), CH_3CN, 50° C, 10h
ii : 6 mol% Herrmann cat., nBu_4NOAc (2.2 eq.), CH_3CN / DMF / H_2O (5/5/1)

Tietze, L. F.; Schirok, H. *Angew. Chem. Int. Ed. Engl.,* **1997**, 1124. Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264.

Pseudo-domino Allylic alkylation / Heck

Intra-inter

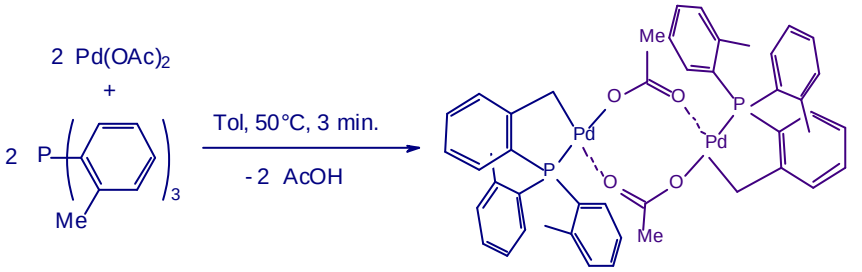


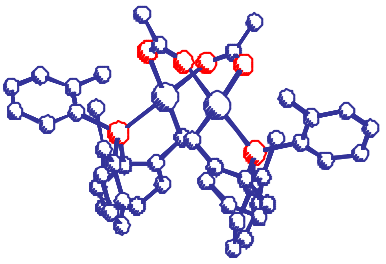
i: NaH (1.2 eq.), ArBr (1.4 eq.), AcONa (1.1 eq.), H.B. cat (0.05 eq.), DMAc, 140°C, 47h

Entry	ArX	time (h)	A (%)	B (%)
1	3-MeO	47	58	36
2	4-MeO	50	38	42
3	H	31	54	30
4	3-MeCO	22	59	-
5	4-MeCO	22	60	-

Poli, G.; Giambastiani, G.; Pacini, B. *Tetrahedron Lett.,* **2001**, *42, 5179-5182*

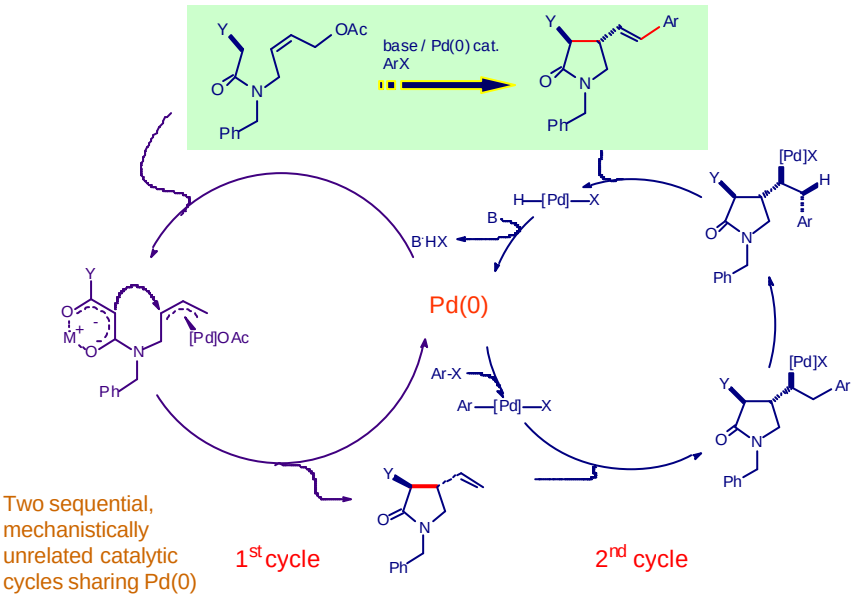
Herrmann-Beller Phosphapalladacycle





Herrmann, W.A.; Brossmer, C.; Ofele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.*, **1995**, *34*, 1844

A"*Type I*" Pd-cat. Pseudo-Domino Process

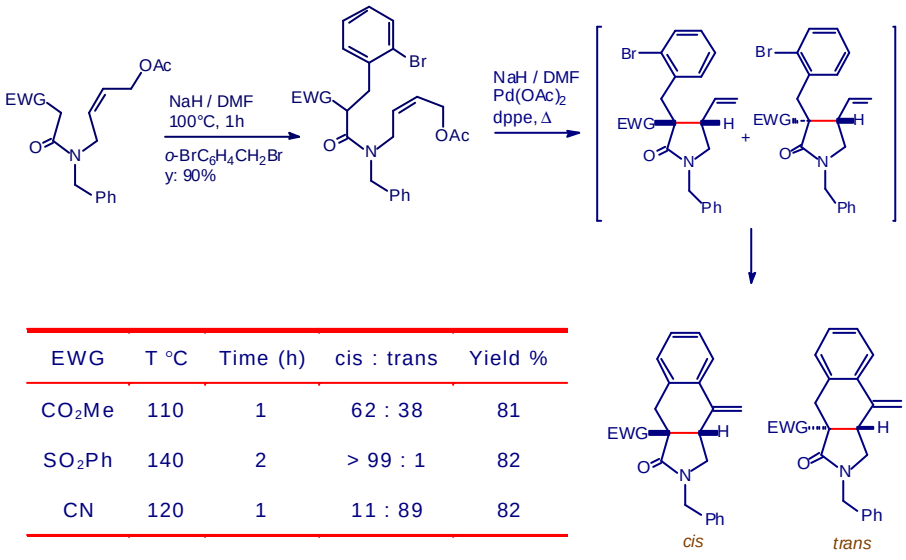


Two sequential, mechanistically unrelated catalytic cycles sharing Pd(0)

1st cycle

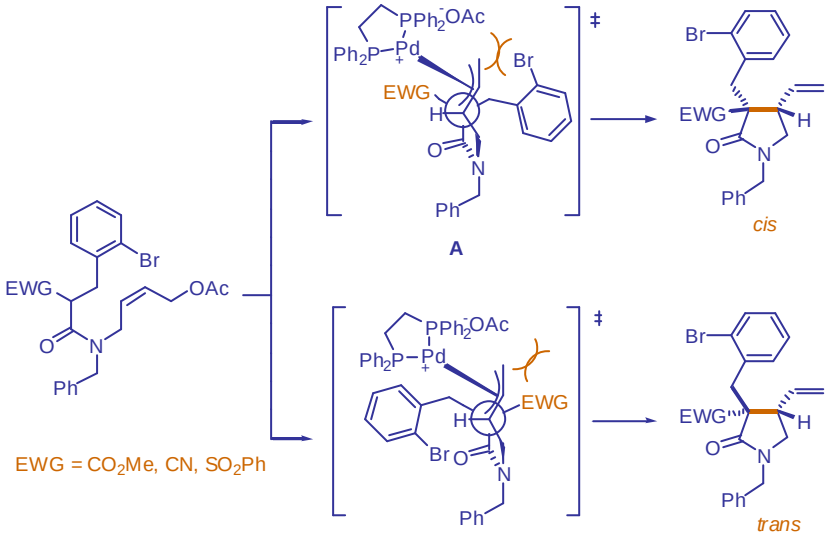
2nd cycle

Intra-intra Allylic alkylation / Heck

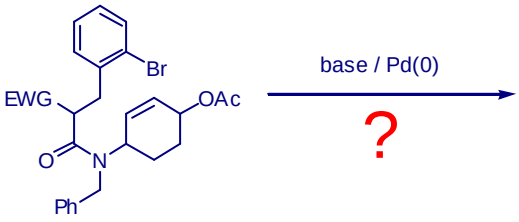


EWG	T °C	Time (h)	cis : trans	Yield %
CO_2Me	110	1	62 : 38	81
SO_2Ph	140	2	> 99 : 1	82
CN	120	1	11 : 89	82

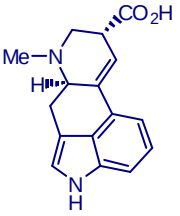
Stereochemical Rationalization



More Complex Pseudo-Domino Processes

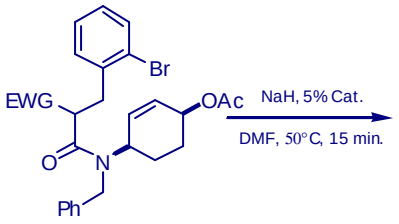


EWG : CO_2Me, SO_2Ph, CN

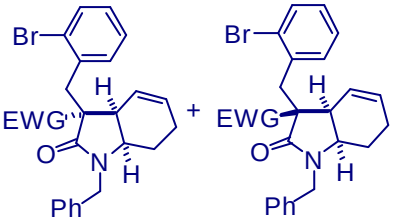


lysergic acid

Simple Allylic Alkylation on the Benzylated Precursor



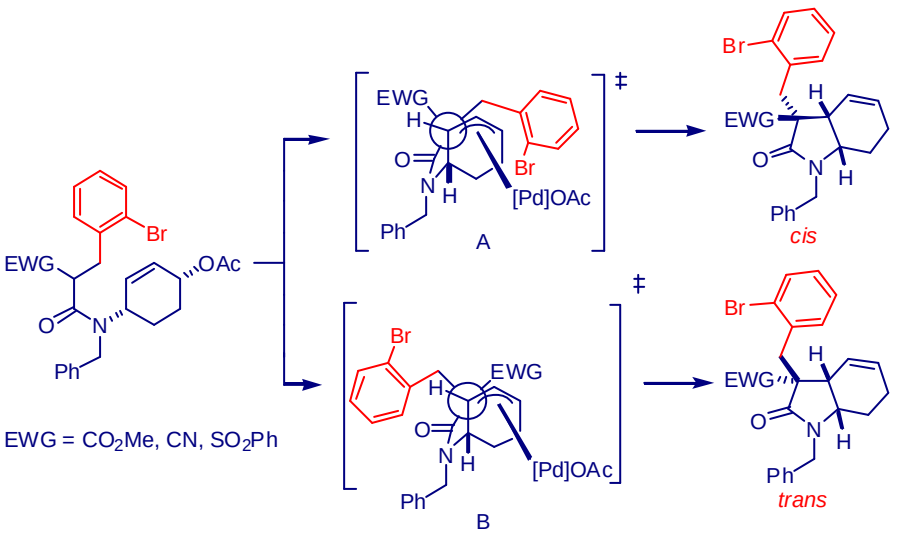
EWG = CO_2Me, CN, SO_2Ph



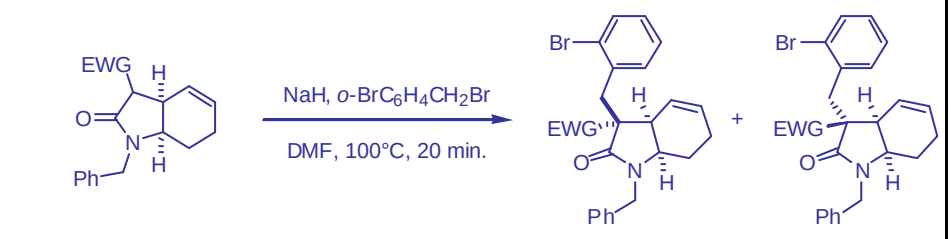
cis *trans*

EWG	Cat.	cis : trans	Yield %
CO_2Me	$Pd(OAc)_2$ / dppe	90 : 10	80
	HB cat	90 : 10	80
CN	$Pd(OAc)_2$ / dppe	> 1 : 99	75
	HB cat	80 : 20	85
SO_2Ph	$Pd(OAc)_2$ / dppe	> 99 : 1	75
	HB cat	> 99 : 1	75

A working model



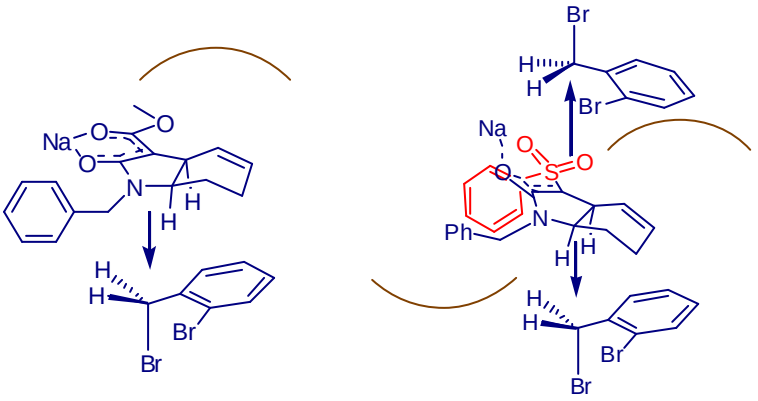
Benzylation of the Cyclized Material



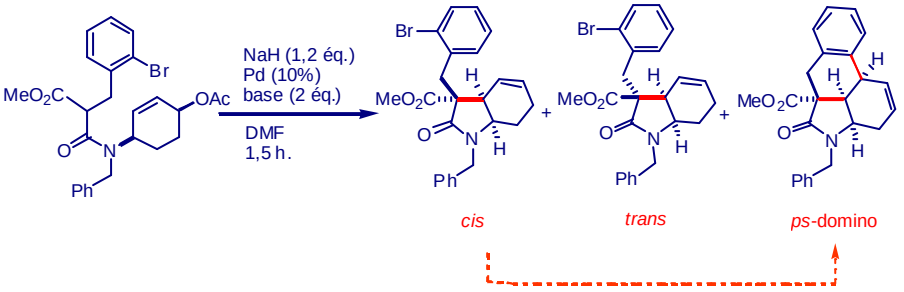
EWG = CO_2Me, SO_2Ph, CN (6:4)

EWG	cis : trans	Rdt %
CO_2Me	0 : 100	95
SO_2Ph	25 : 75	95
CN	0 : 100	95

The Role of the Carbanion Activating Group

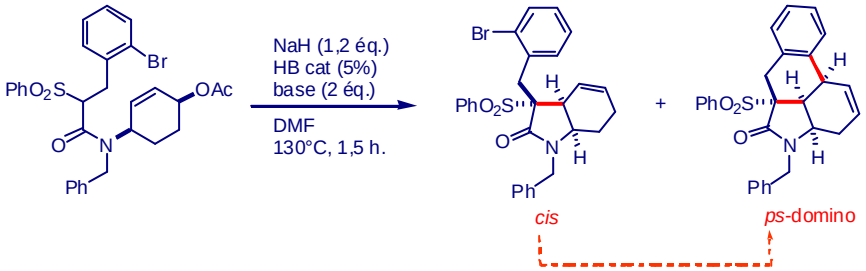


The *Pseudo*-Domino Process (CO_2Me)



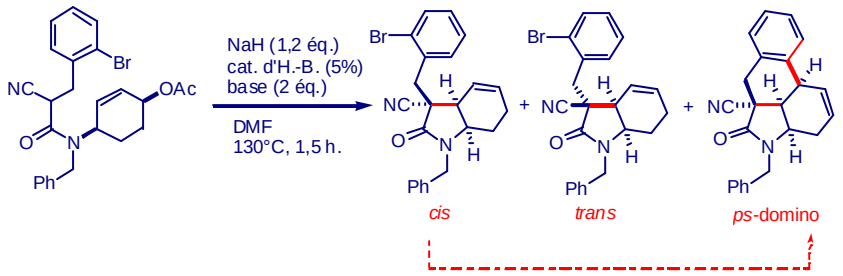
Pd source	T °C	Base	*cis* : *trans* : *ps-domino*	yield%	*ps*-domino %
$Pd(OAc)_2$/dppe	rt to 130	-	90 : 10 : 0	80	0
$Pd(OAc)_2$/dppe	rt to130	AcONa	90 : 10 : 0	80	0
$Pd(OAc)_2$/dppe	rt to 130	AcOK	-	75	0-60
HB cat	rt to 130	AcOK	66 : 10: 24	85	20
HB cat	130	AcOK	48 : 8 : 44	85	40
HB cat	130	*n*-Bu_4NOAc	20 : 10 : 70	85	60

The *Pseudo*-domino Process (SO_2Ph)



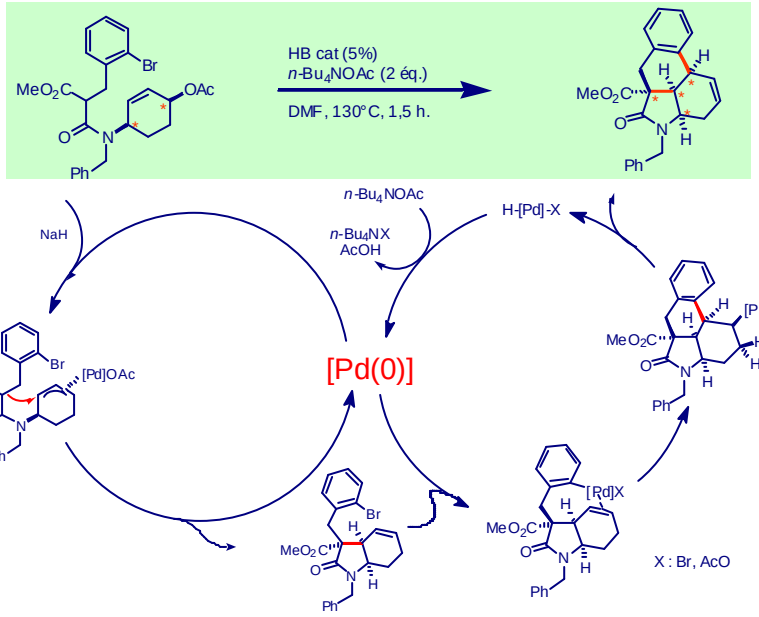
Pd	T °C	Base	*cis* : *ps*-domino	yield %	*ps*-domino
HB cat	130	AcOK	100 : 0	35%	0%
HB cat	130	*n*-Bu_4NOAc	30: 70	30%	21%

The *Pseudo*-domino Process (CN)

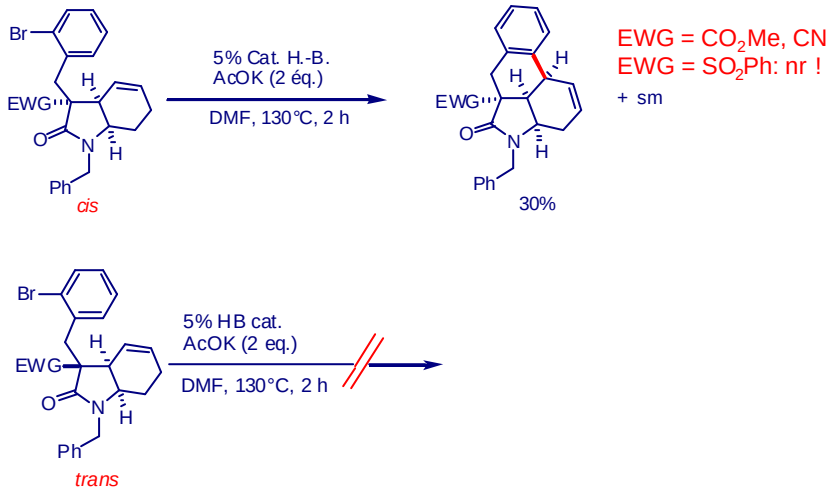


Pd	T °C	Base	*cis* : *trans*: *ps*-domino	Yield	*ps*-domino
HB cat	130	AcOK	35 : 15 : 50	89%	45%
HB cat	130	*n*-Bu_4NOAc	6 : 19 : 75	87%	65%

The Catalytic Cycle

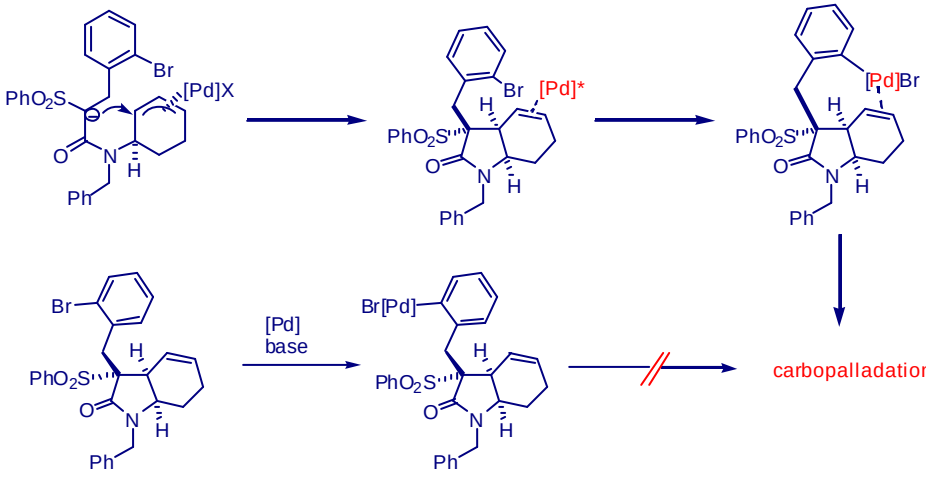


Heck from the Already Cyclized Precursor



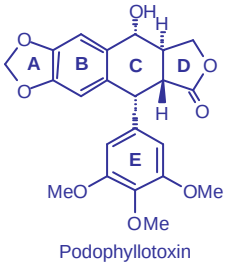
A Tempting Hypothesis

Intramolecular extra-activation



Target: an Aza-analog of Podophyllotoxin

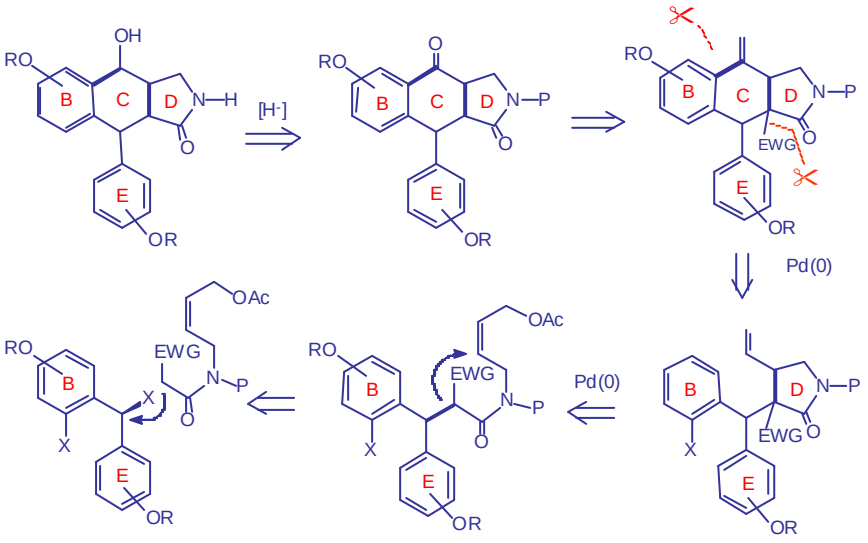
Podophyllum peltatum
(North America)



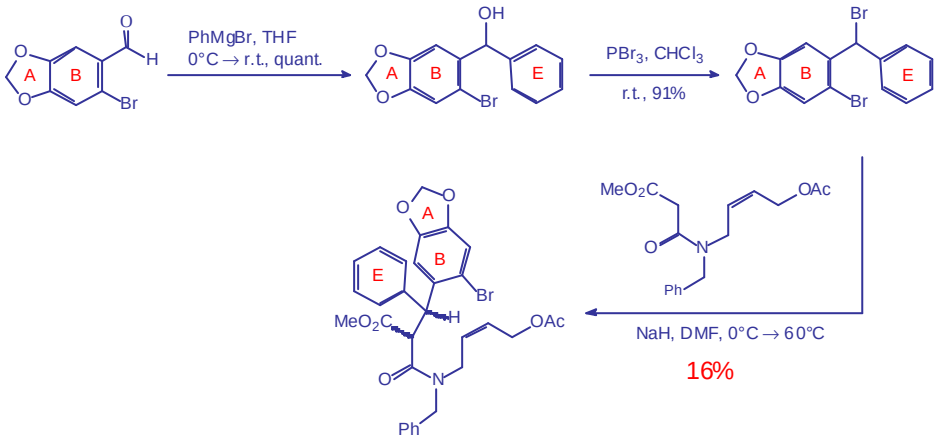
Podophyllotoxin

Podophyllum emodi
(Indian subcontinent)

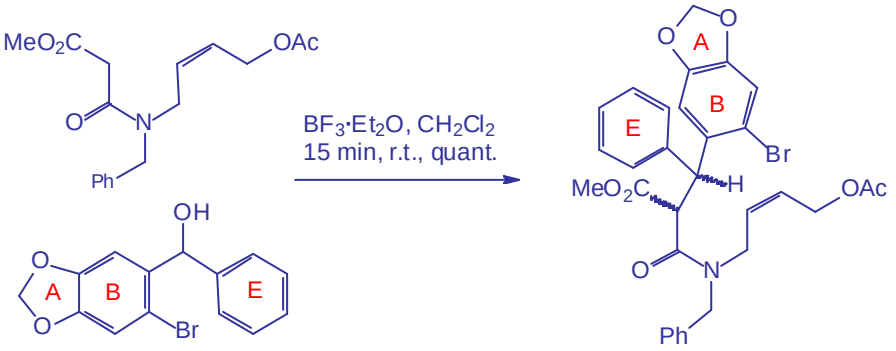
Aza-Podophyllotoxin: Retrosynthetic Analysis



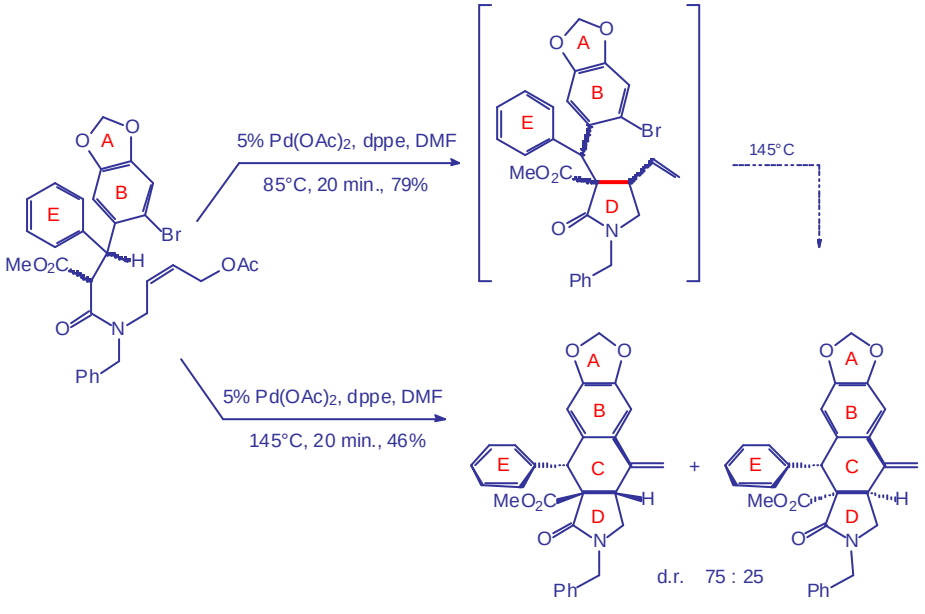
Synthesis of the Cyclization Precursor (1)



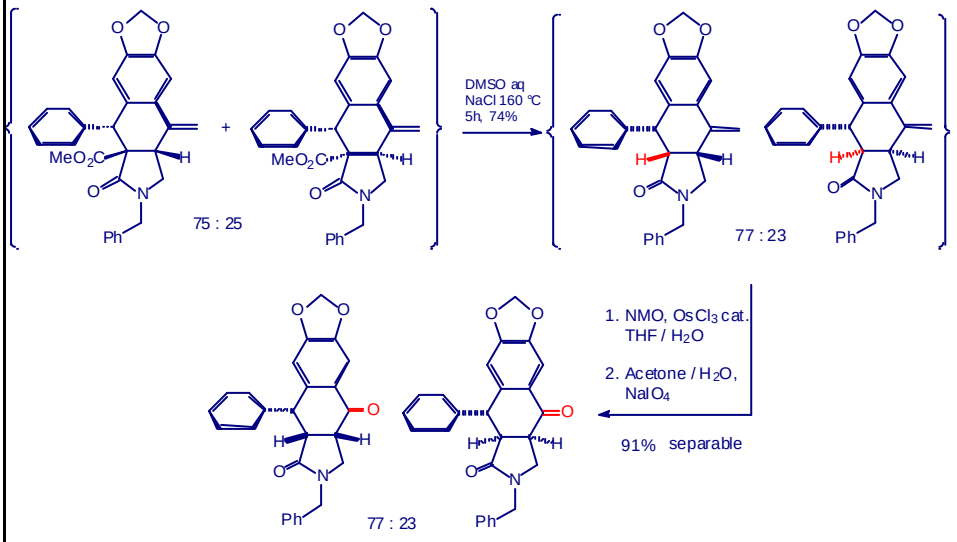
Synthesis of the Cyclization Precursor (2)



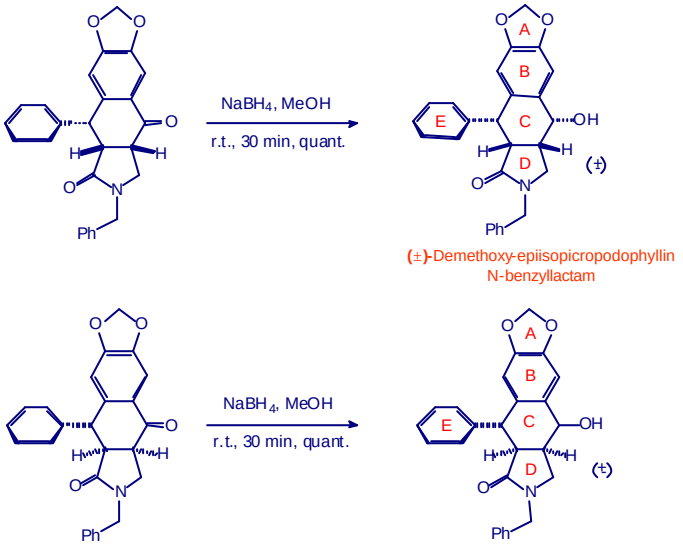
The Cyclization at Work



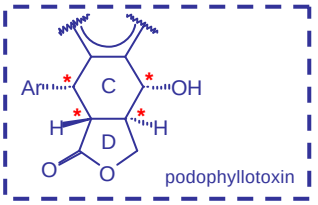
Decarboxylation and Oxidative Cleavage

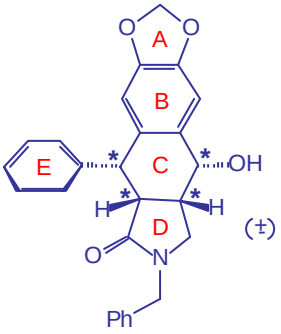


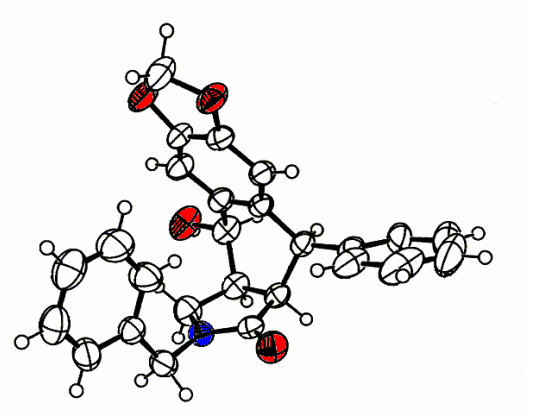
Reduction of the Carbonyl Function



The X-ray Crystal Structure

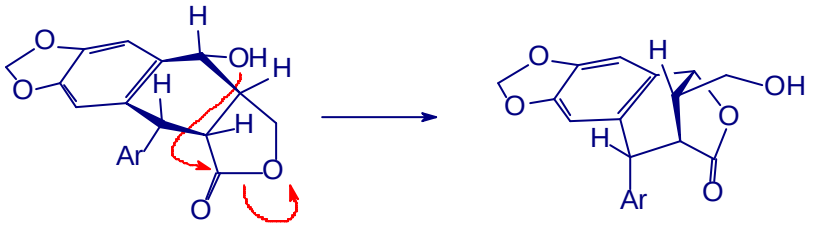






(±)-DEMETHOXY-EPIISOPICROPODOPHYLLIN N-BENZYL

The Epiisopicropodophyllin Motif



Forsey, S.P.; Rajapaksa, D.; Taylor, N.J.; Rodrigo, R. *J. Org. Chem.*, **1989**, *54*, 4280

Acknowledgements

Guillaume Prestat
David Madec

Sébastien Lemaire
Maxime Vitale

Prof. Per-Ola Norrby

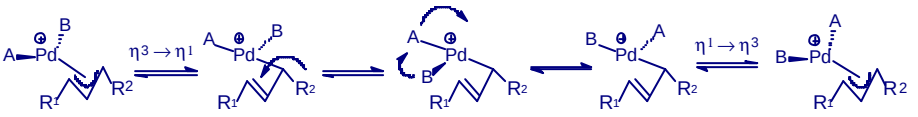
UPMC + CNRS

Giuliano Giambastiani
Barbara Pacini
Simona Pampana

MURST + CNR

Facial exchange in the π-allyl complex

apparent allyl rotation



Pd(0) resubstitution pathway