Seminar Synthetic methods

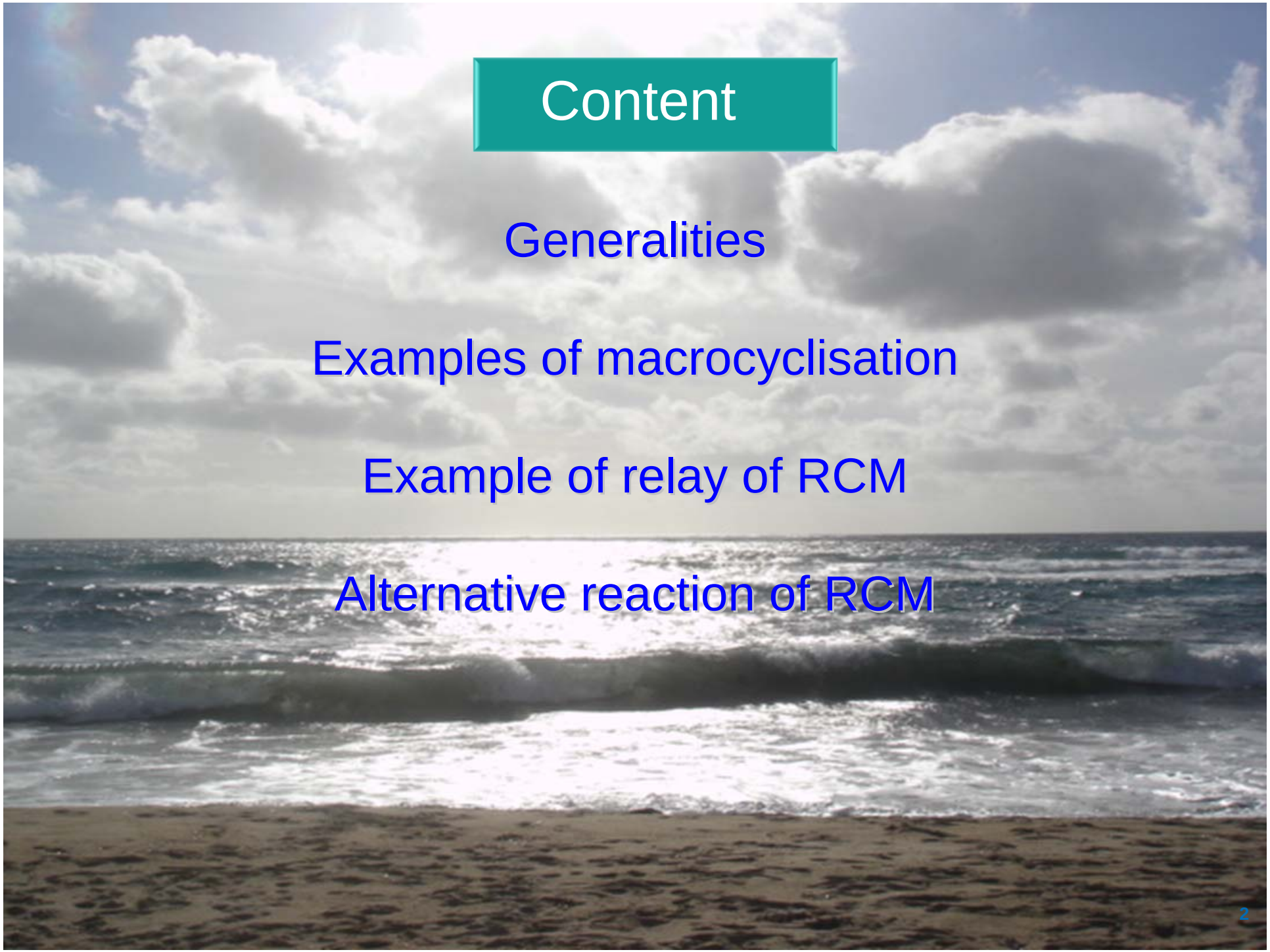
Thursday 3 december 2009

Macrocyclisation

By Ring-closing Metathesis

(RCM)

Romain BLANC



Content

Generalities

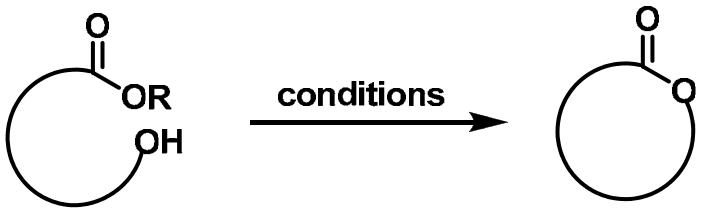
Examples of macrocyclisation

Example of relay of RCM

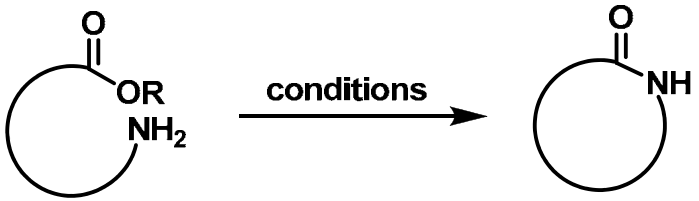
Alternative reaction of RCM

How create a macrocycle in total synthesis today?

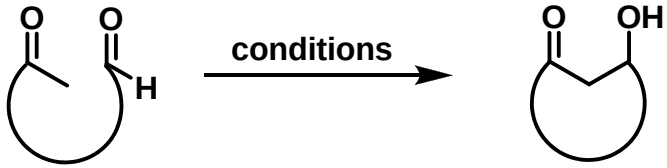
- Macrolactonisation



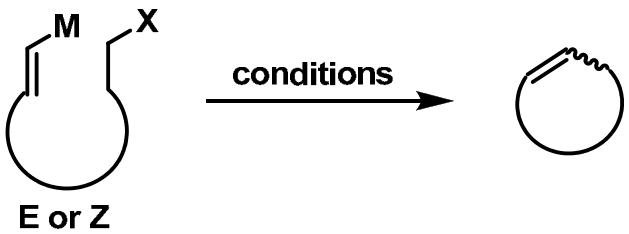
- Macrolactamisaton:



- Macroaldolisation:



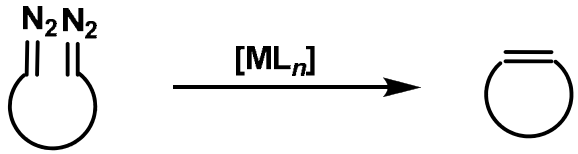
- Organometallic reactions:



M = transition metal
X = halogen or leaving group

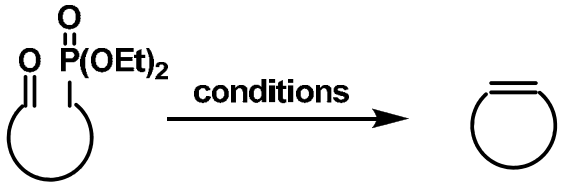
How create a macrocycle in total synthesis today?

- a carbene dimer reaction:

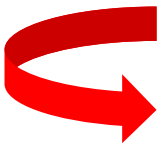


- The McMurry reaction:

- Horner-Wadsworth-Emmons:



- Ring-closing metathesis:



Used as key step in total synthesis

History of Metathese:

- the alkene metathesis was discovered around 1960.
- The first mechanism was proposed by Chauvin[1] in 1970.
- approuved and valided by Casey,[2] Katz[3] and Grubbs[4] group

Nobel prize in 2005

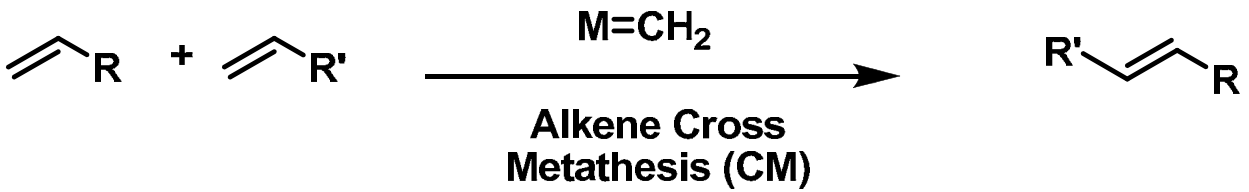
Yves Chauvin
France,
Institut francais du pétrole

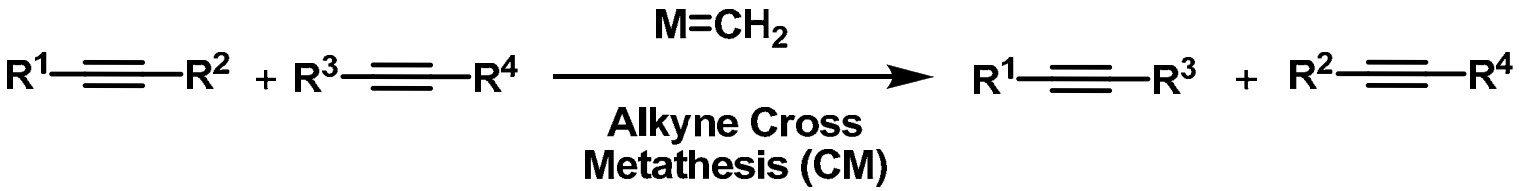
Robert H. Grubbs
Caltech, USA
South Weast

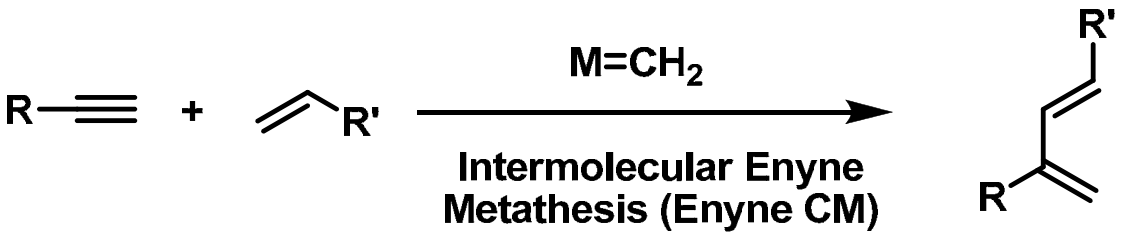
Richard R. Schrock
(MIT) USA
North East

[1] J.-L. Hérisson, Y. Chauvin, *Makromol. Chem.* **1971**, *141*, 161–176. [2] C. P. Casey, T. J. Burkhardt, *J. Am. Chem. Soc.* **1974**, *96,* 7808–7809. [3] T. J. Katz, J. McGinnis, *J. Am. Chem. Soc.* **1975**, *97*, 1592–1594. [4] a) R. H. Grubbs, P. L. Burk, D. D. Carr, *J. Am. Chem. Soc.* **1975**, *97*, 3265 – 3267; b) R. H. Grubbs, D. D. Carr, C. Hoppin, P. L.Burk, *J. Am. Chem. Soc.* **1976**, *98*, 3478–3483.

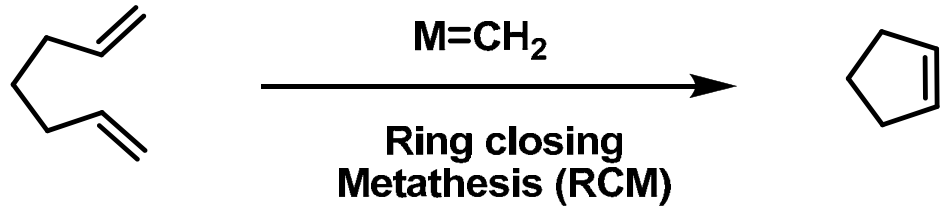
Distinct modes of metathesis:

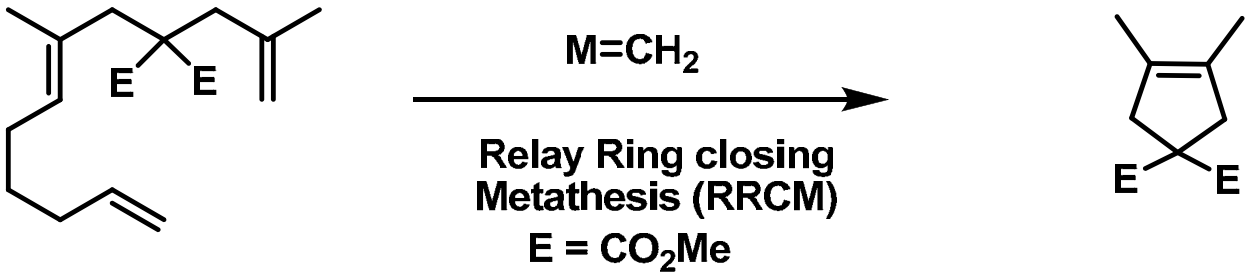


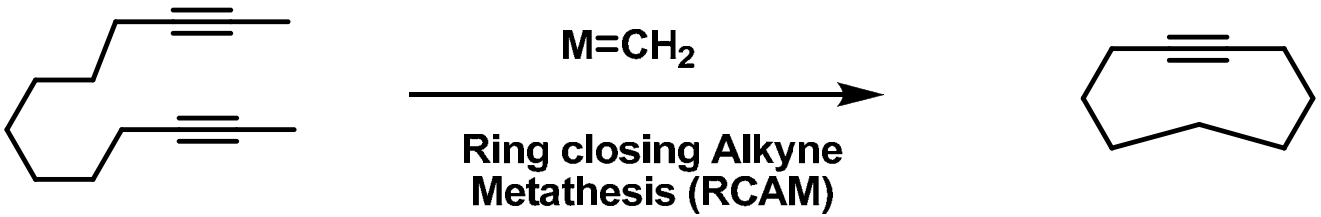




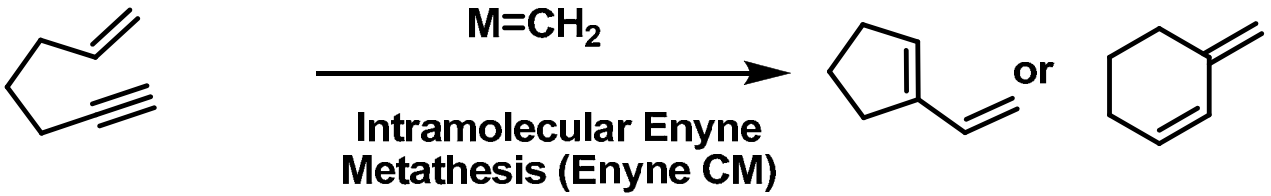
Distinct modes of metathesis:

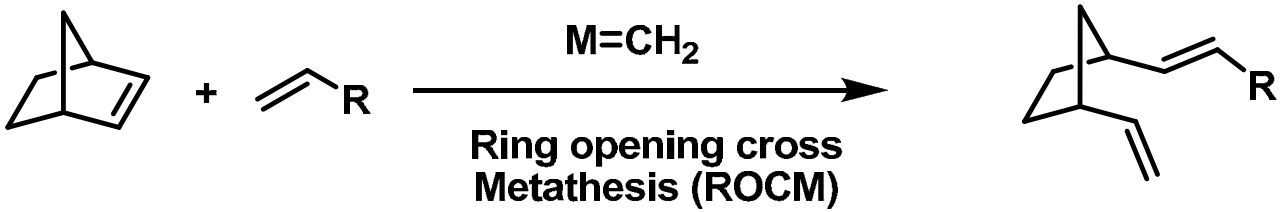


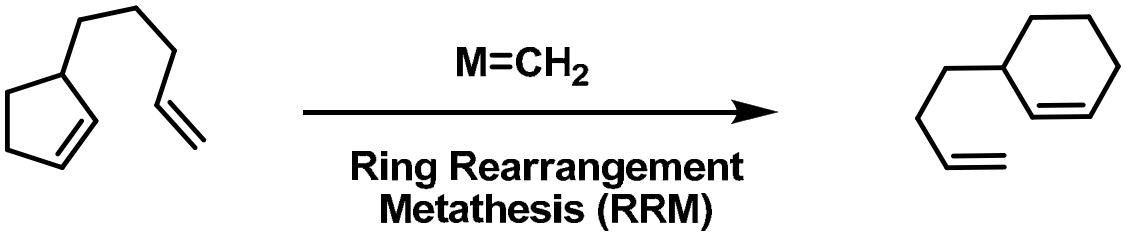




Distinct modes of metathesis:







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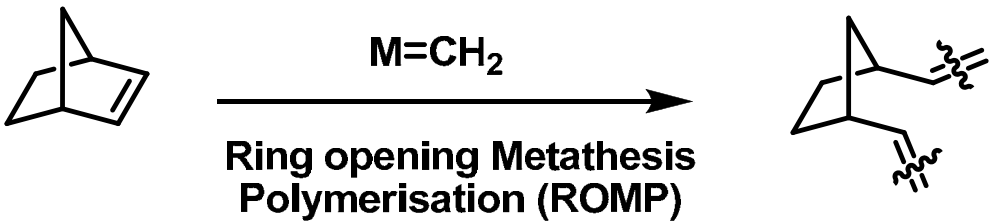
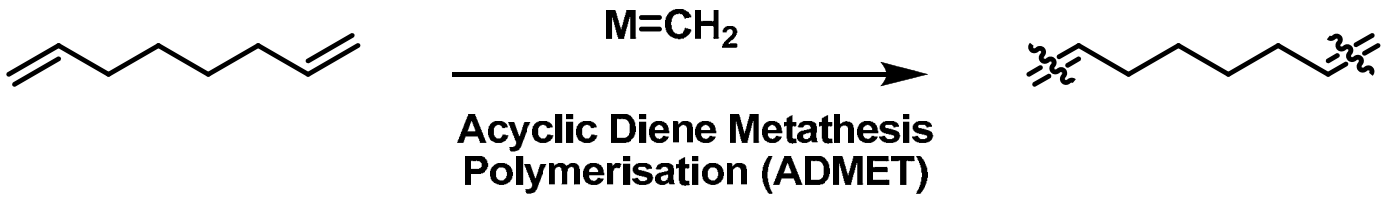




Ring-closing metathesis (RCM)

Advantages:

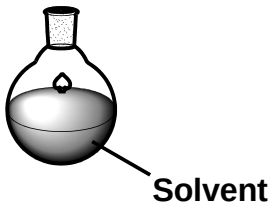
- compatible with more fonctionnal groups
- double bond can be transformed into others fonctionnal groups
- not affected into further stages

Disadvantages:

- control over stereochemistry of the double bond
- competition of intra / inter molecular process
- conditions of the reaction

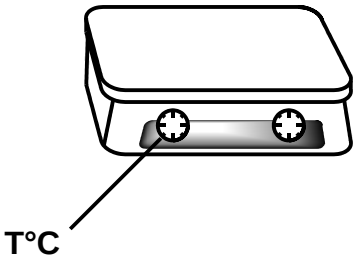
Reaction conditions for RCM:

Solvents:



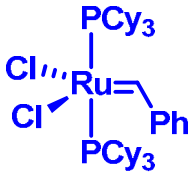
- Favored in the nonpolar solvent
- Toluene and dichloromethane were prefered

Others parametters:

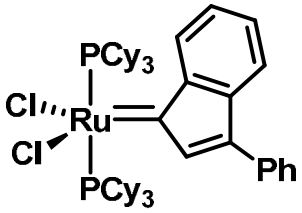


- 1 to 25 mol% of catalyst
- 0.25 to 8 mM of concentration
- presence of N is not tolerated due to the electron pair
- stability of the final product (thermodynamic control)
- Temperature have effect of the isomer formation (*E*/*Z*)

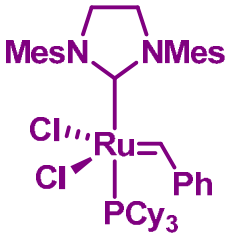
Catalyst:



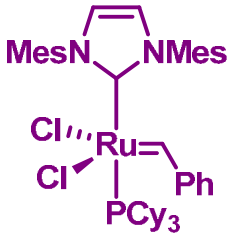
A



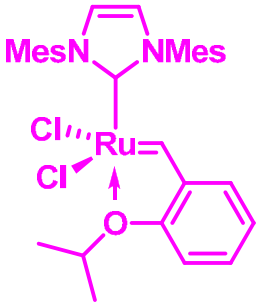
B



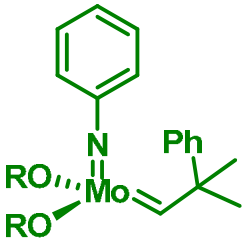
C



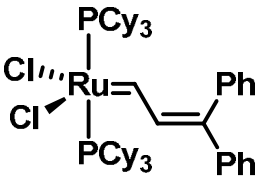
D



E



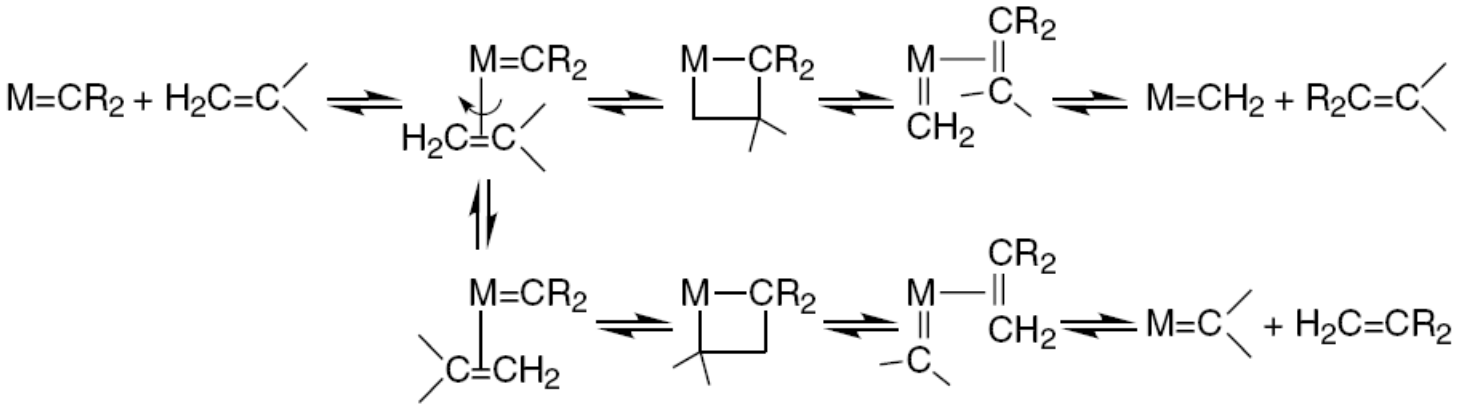
F



G

- **A** (*Grubbs I*) is the cheapest, thermally unstable and fails to react with subtitued olefins
- **B** derivatives of **A** improve the kinetics of the initial reaction
- **C** and **D** (*Grubbs II*) given better results with substitued olefins and are most air-stable
- **E** (*Hoveyda-Grubbs*) and derivatives on aromatic groupment given the *third* generation catalyst
- **F** (*Schrock*) is highly reactive but sensitive to water, oxygen and to several functional groups

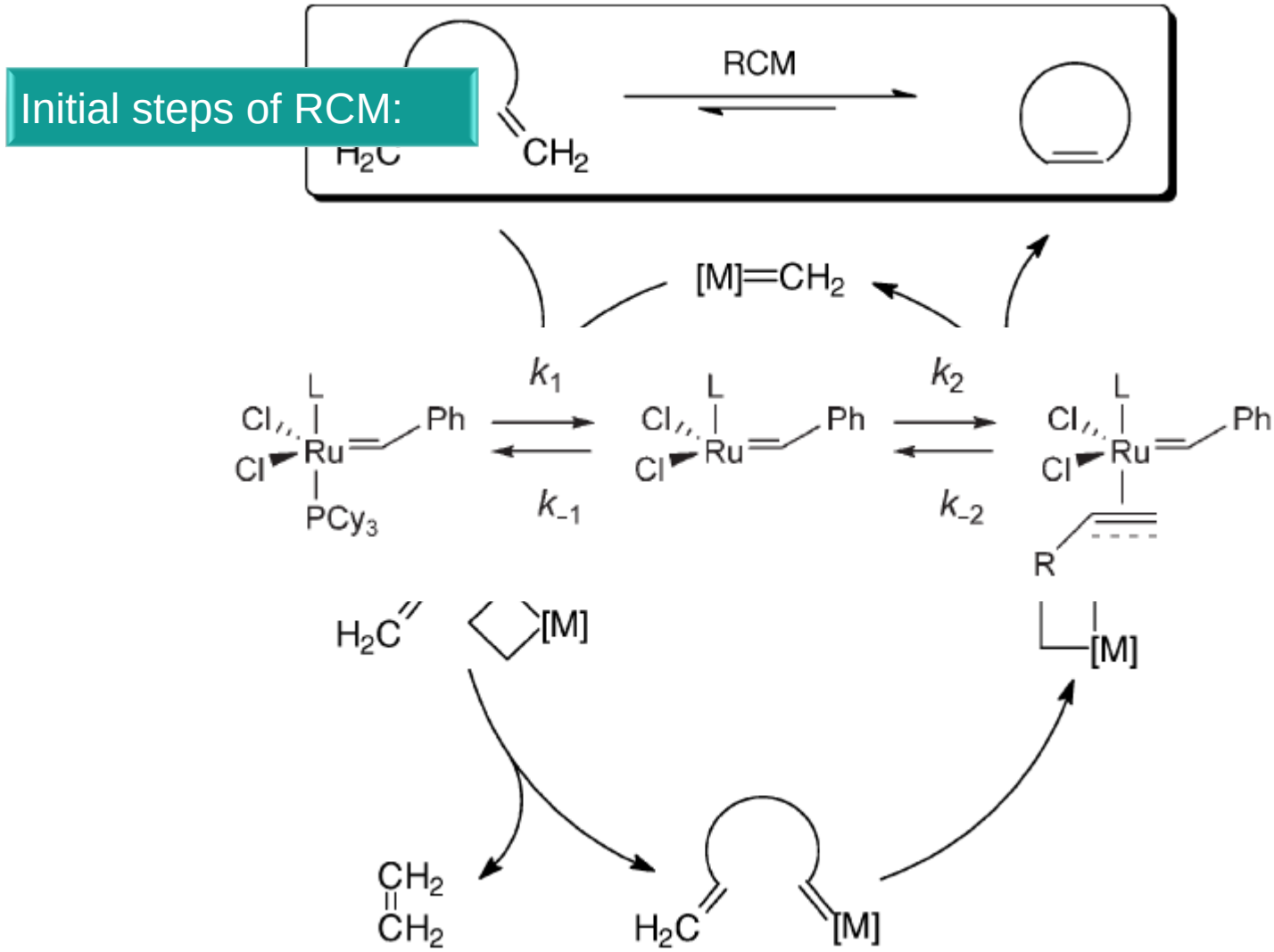
Mechanism of Alkene:



Chauvin's mechanism for alkene metathesis

Mechanism of RCM:

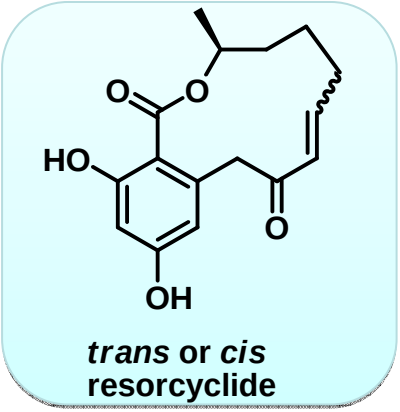
Initial steps of RCM:



Macrocyclic lactones:

Macrocyclic structures with one or more ester linkages referred as macrolides

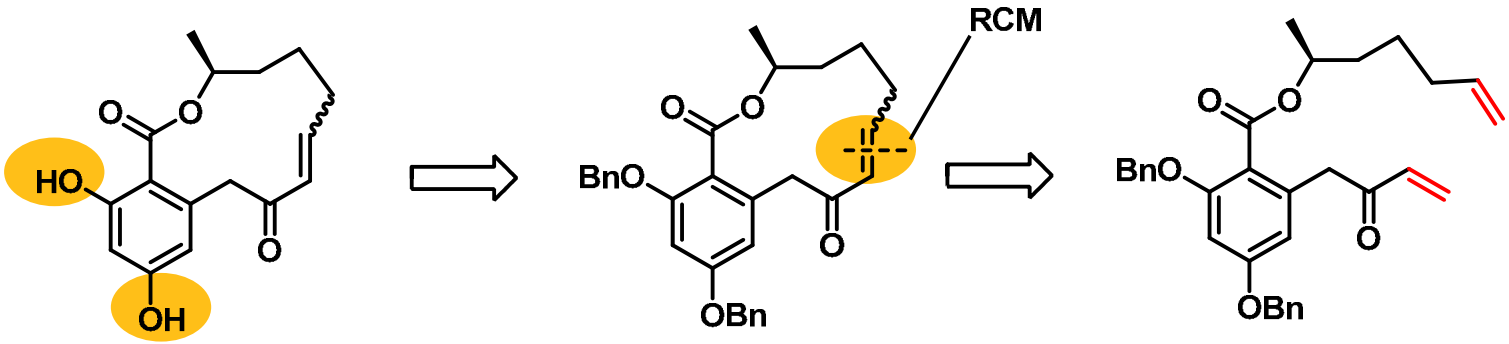
Generally, macrolides are very importante target due to their medicinal and biological activity.



***trans* or *cis* resorcyclide**

- isolated from different *Penicillium* species
- possess biological activities

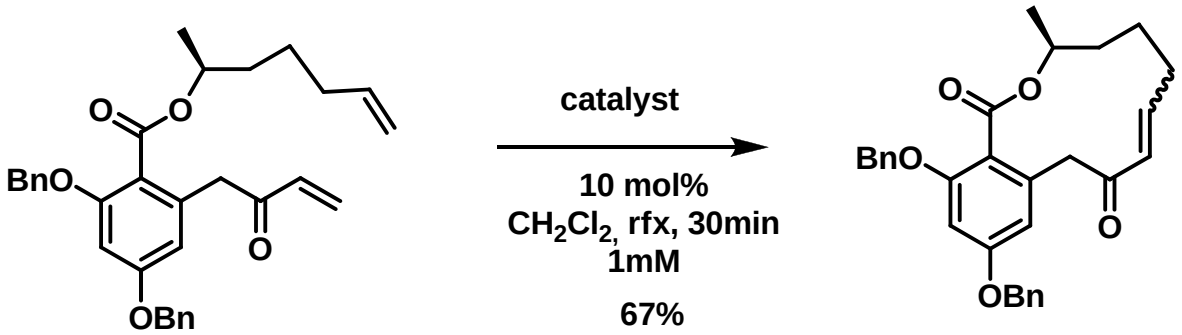
Retrosynthetic Scheme:

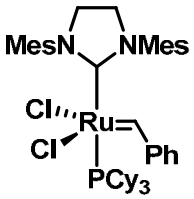


E. A. Couladouros et *al*, *Org. Lett*. **2004**, *6*, 977-980

Macrocyclic lactones:

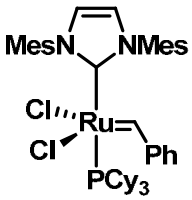
Synthesis Scheme:





C

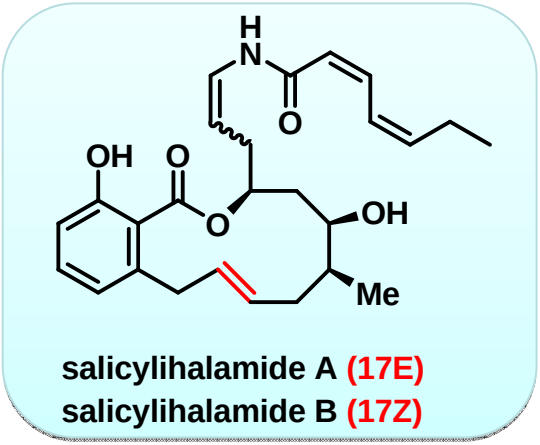
Conditions	Catalyst, yield
toluene, 110 °C, 10 min, 0.2 mM	**C** (5–10 mol%), 60%
CH_2Cl_2, Δ*T*	**D** (5 mol%), 85% (*E*)
toluene, 80 °C, 15 h	**D** (6 mol%), 69% (*E*)
toluene, 80 °C, 4 h	**D** (5 mol%), 91% (*E*)
CH_2Cl_2, Δ*T*, 30 min, 1 mM	**C** (10 mol%), 67%
CH_2Cl_2, Δ*T*, 1 h, 0.5 mM	**C** (2 mol%), 40%
CH_2Cl_2, Δ*T*, 10 h.	**C** (25 mol%), 38%
toluene, 120 °C, 10 min, 2 mM	**C** (5 mol%), 87%



D

E. A. Couladouros et *al*, *Org. Lett*. **2004**, *6*, 977-980

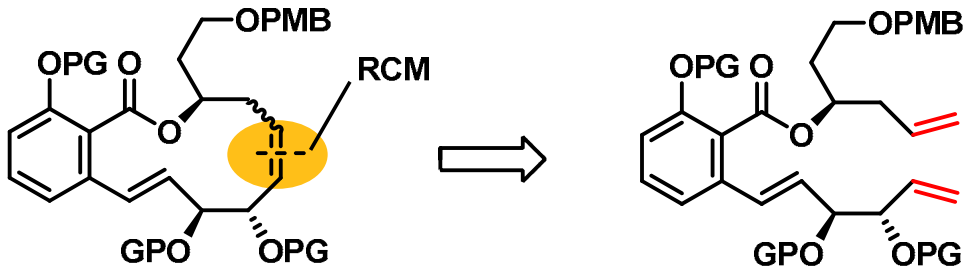
RCM to modele of salicylic macrolide



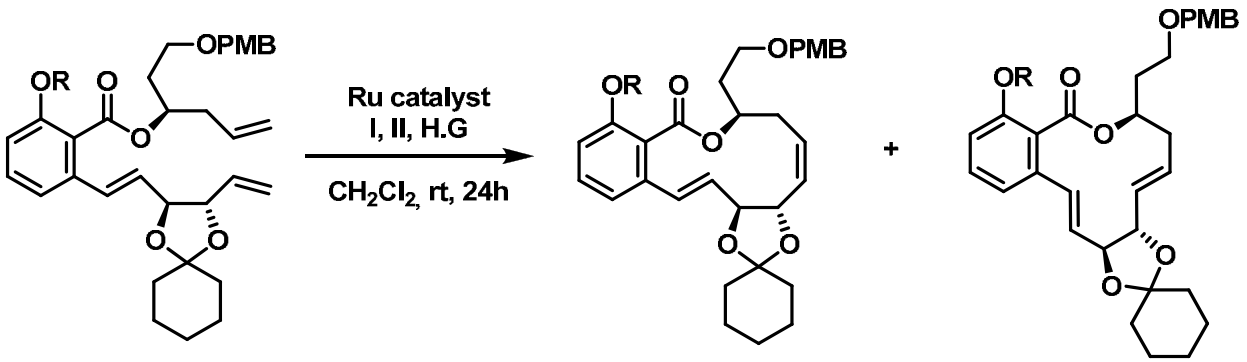
salicylihalamide A (17E)
salicylihalamide B (17Z)

- exibited potent cytotoxic activity against various human cancer cell lines
- possess a labile enamide side chain, 12-menbered lactone and oxidation states
- many studies rely on a RCM strategy for constructing the lactone

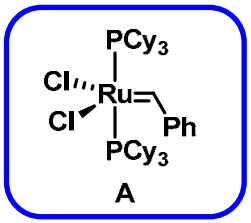
Retrosynthetic Scheme:



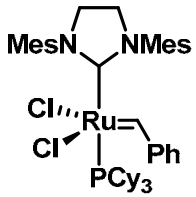
H. Nemoto et *al. Chem. Eur. J*, **2008**, *14*, 5275-5281



Entry	OR	Cat (mol%)	Yield of *E*	Yield of *Z*
1	H	A (5)	64	0
2		A (10)	72	0
3		A (20)	78	0
4		B (5)	21	16
5		C (5)	10	11
6		C (5)	44	39
7	TBS	A (5)	47	0
8		B (5)	35	6
9		C (5)	30	6
10	Me	A (5)	38	0
11		B (5)	51	24
12	MOM	A (5)	77	0
13		B (5)	51	29



A



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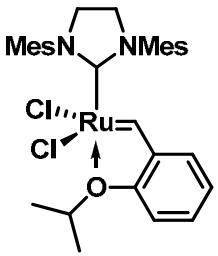
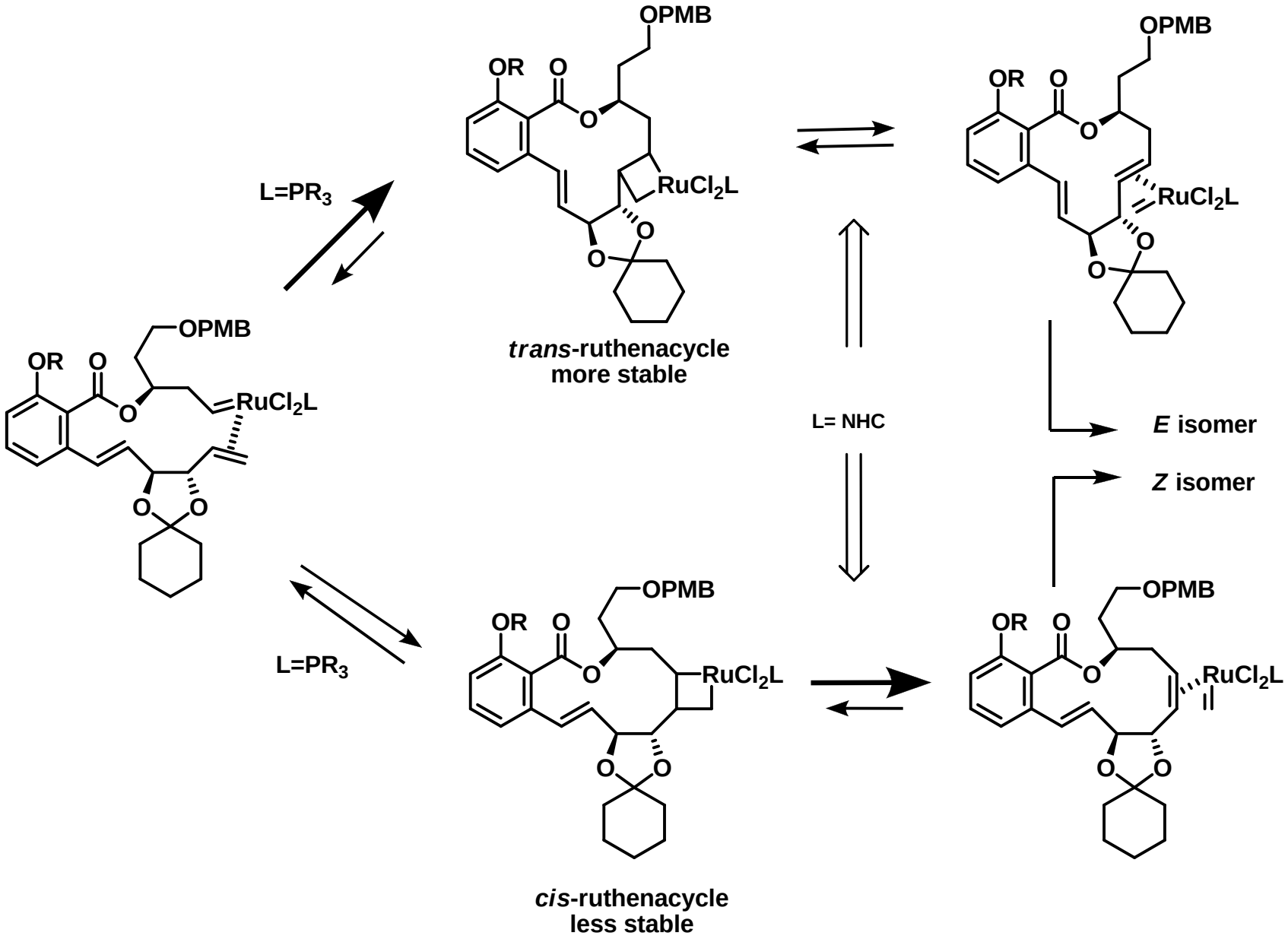


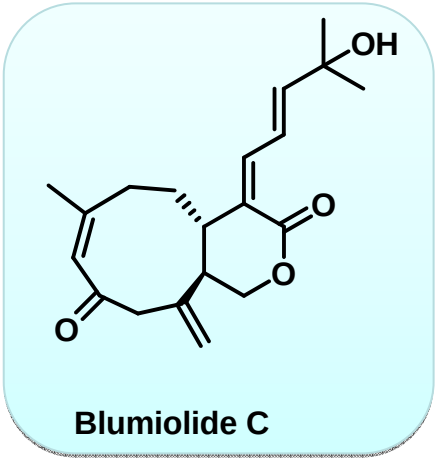
C

H. Nemoto et *al. Chem. Eur. J*, **2008**, *14*, 5275-5281



H. Nemoto et *al. Chem. Eur. J*, **2008**, *14*, 5275-5281

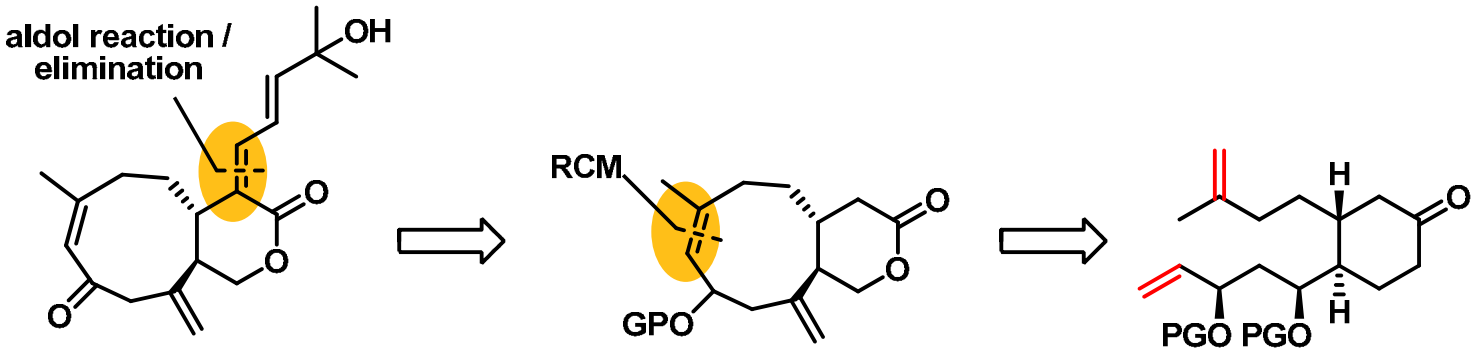
RCM for Blumiolide C:



Blumiolide C

- isolated in 2005 by El-Gamal et *al.* from the soft coral *Xenia blumi*
- have biological activies as antiproliferative, antiangiogenic, antibacterial effects.
- nine-menbered carbocyclic ring with *Z* double bond was the difficulties.
- used a ring closing metathesis as key steps

Retrosynthetic Scheme:

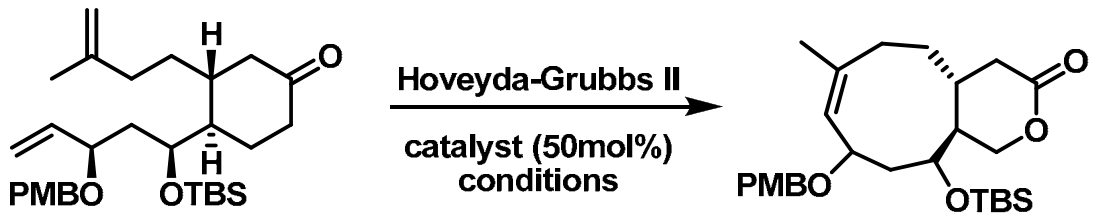


Blumiolide C

K. H. Altmann et *al*. *Angew. Chem. Int. Ed*. **2008**, *47*, 10081-10085

RCM for Blumiolide C:

Synthesis Scheme:



only *Z* isomere!!!

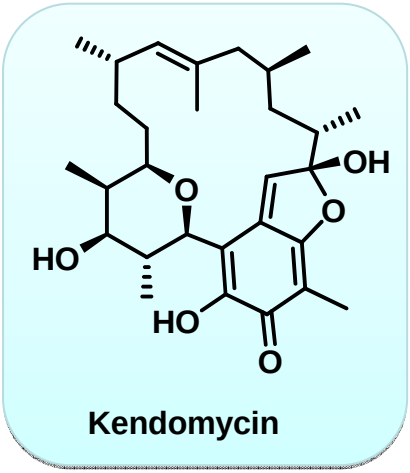
Optimisation of reaction conditions for the RCM-based cyclisation:

T°C	T	Solvent	Additive	Yield (%)
60	2d	Toluene	BQ	0
90	3d	Toluene	BQ	66
90	3d	Toluene	-	66
160	1.5h	Toluene	-	60
190	1h	*o*-$Cl_2C_6H_4$	-	28
160	30min	*o*-$Cl_2C_6H_4$	-	0

Blumiolide was synthetised in a total of 27 steps with 1% overall yield

K. H. Altmann et *al*; *Angew. Chem. Int. Ed*. **2008**, *47*, 10081-10085

RCM for Kendomycin:



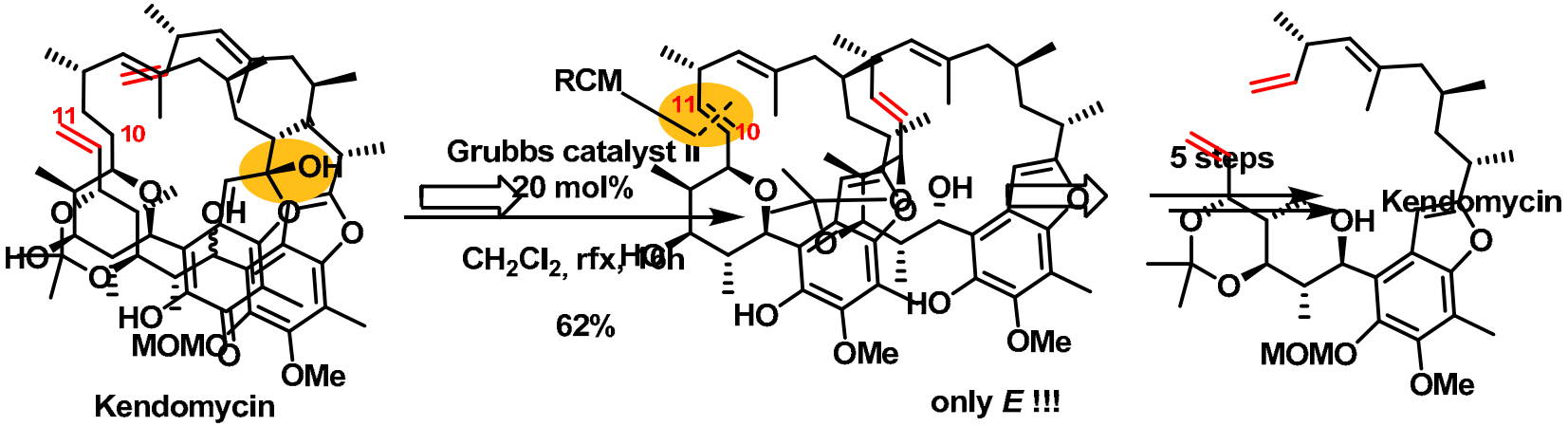
Kendomycin

- isolated from *Streptomyces* species
- have a potent endothelin receptor antagonist, antiosteoperotic compound, antibacterial and cytostatic activity.
- three total synthesis and one formal synthesis was descripted in literature
- The formation of the strained macrocyclic *ansa*-ring was the difficulty.
- used a ring closing metathesis as key steps

J. Mulzer et *al*; *Angew. Chem. Int . Ed*. **2009**, *48*, 6032-6036

RCM for Kendomycin:

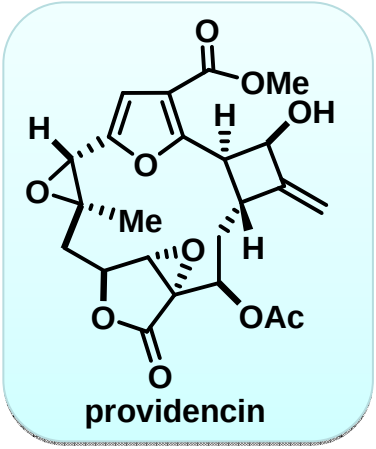
Synthesis Scheme: e:



Kendomycin was synthetised in a total 23 linear steps with 1.3% overall yield

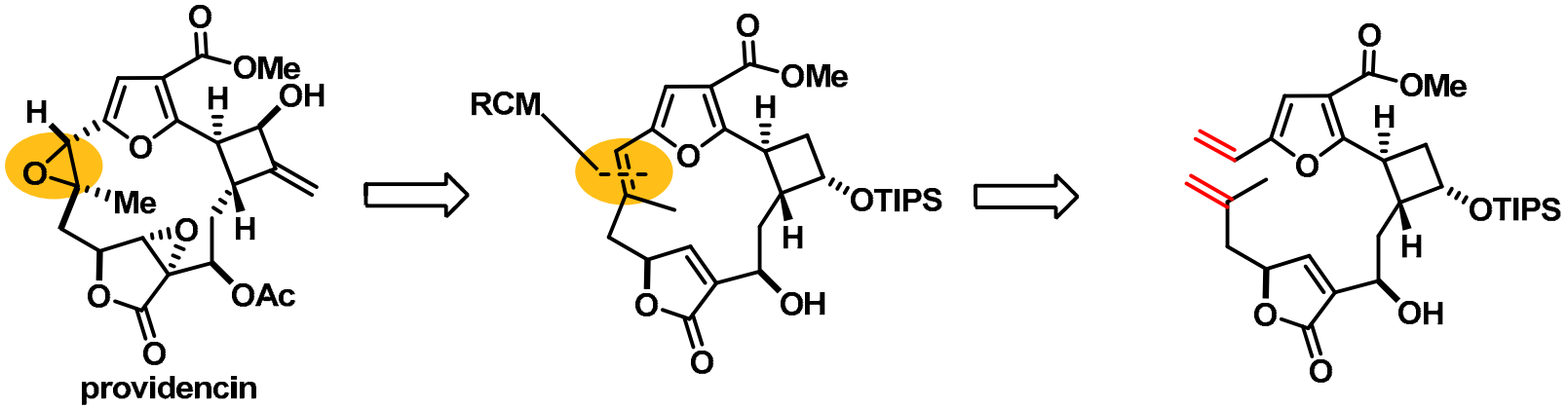
J. Mulzer et *al*; *Angew. Chem. Int . Ed*. **2009**, *48*, 6032-6036

RCM for Providencin:



- isolated in 1918 by Rodriguez group from the sea plume *Pseudopterogorgia Kallos*
- exhibits moderate antibacterial activity
- have the ring strain and the high density of oxygenated as synthetic difficulties

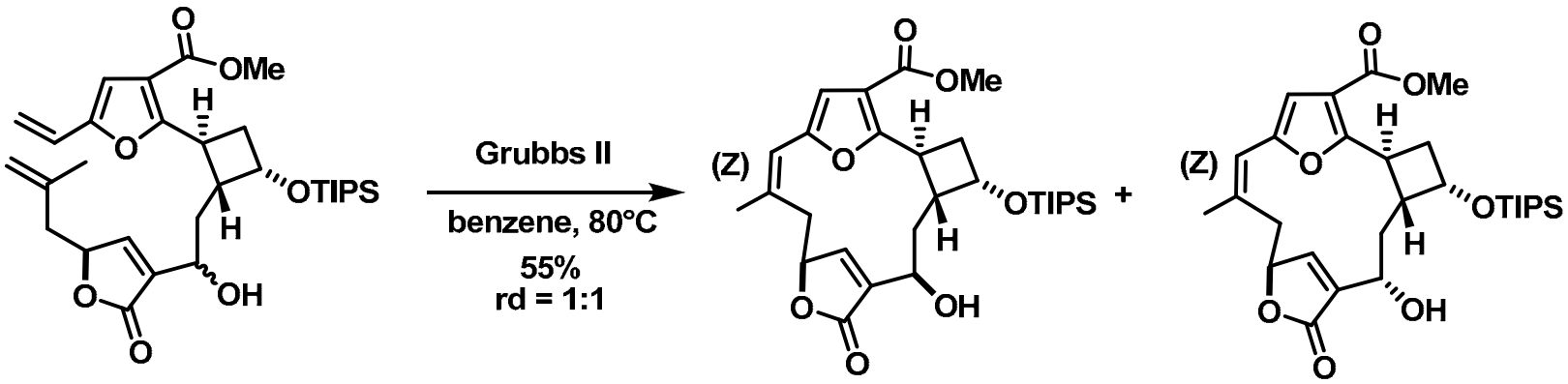
Retrosynthetic Scheme:



J. Mulzer. et *al*. *Synlett*, **2009**, *9*, 1357-1366

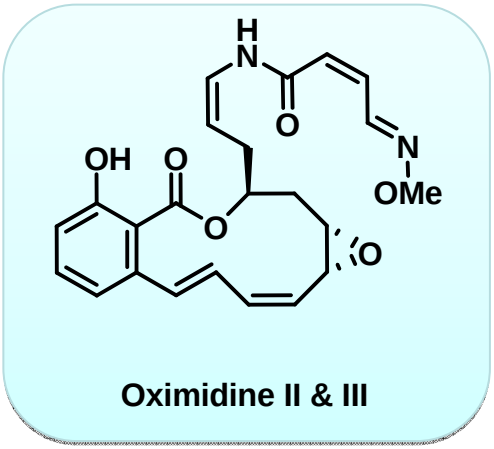
RCM for Providencin:

Synthesis Scheme:



J. Mulzer. et *al*. *Synlett*, **2009**, *9*, 1357-1366

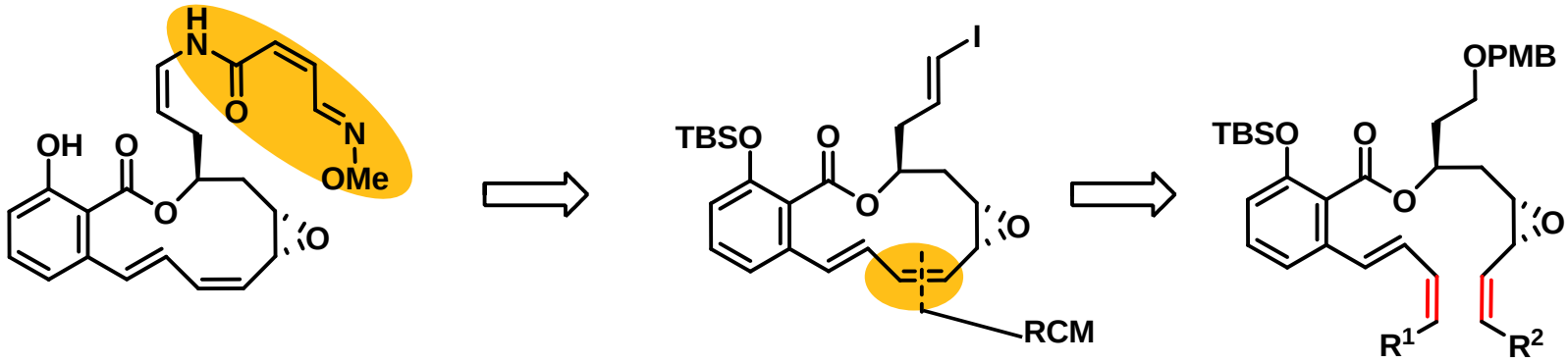
RCM for Oximidine:



Oximidine II & III

- isolated from *Pseudomonas species* Q52002
- exhibits antitumor activity
- have a macrolactone, an epoxide and a diene *E*,*Z*

Retrosynthetic Scheme:



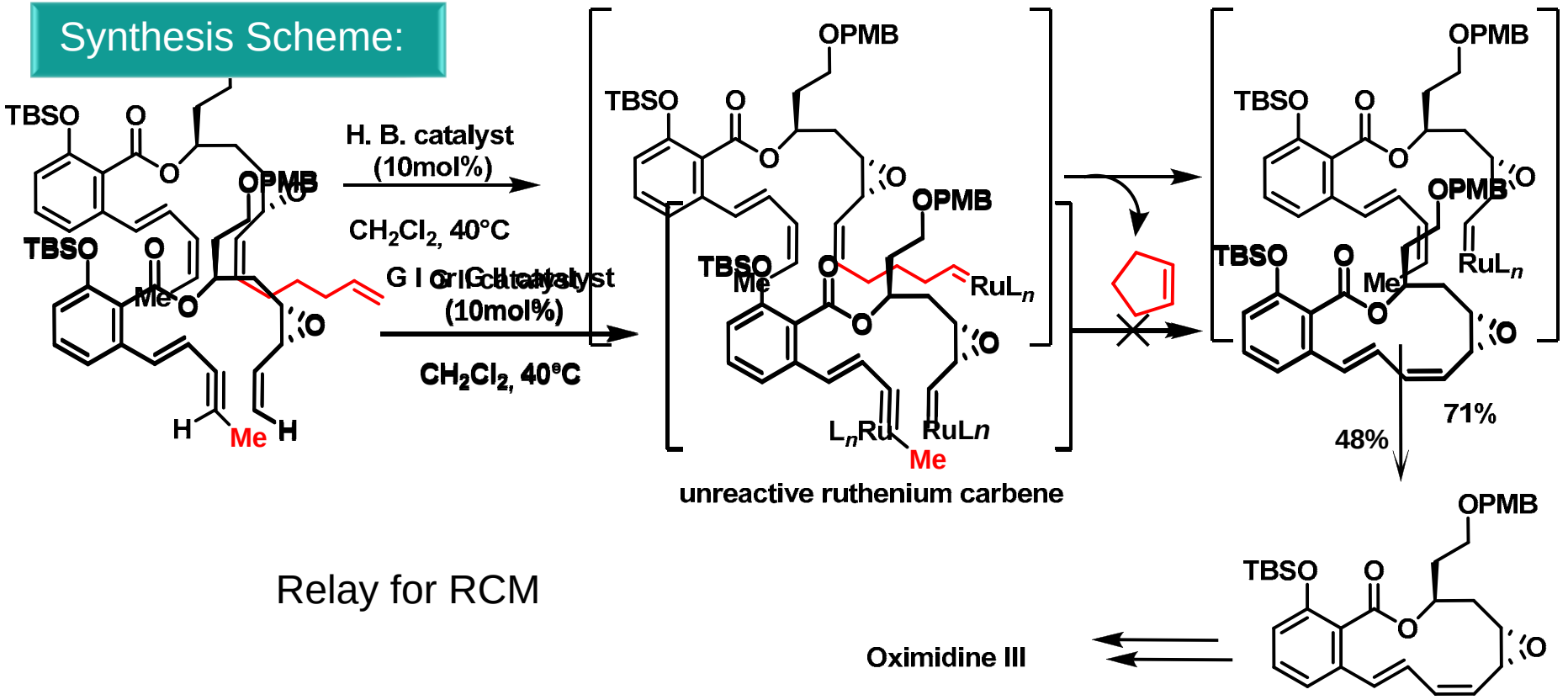
Oximidine II & III

J. A Porco et *al. J. Am. Chem. Soc.* **2003**, *125*, 6040 –6041

RCM for Oximidine:

Synthesis Scheme:

Synthesis Scheme:

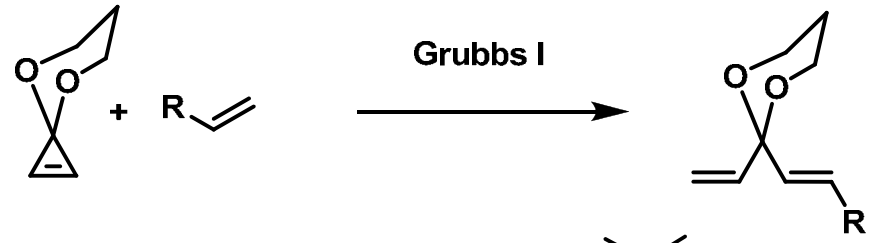


Relay for RCM

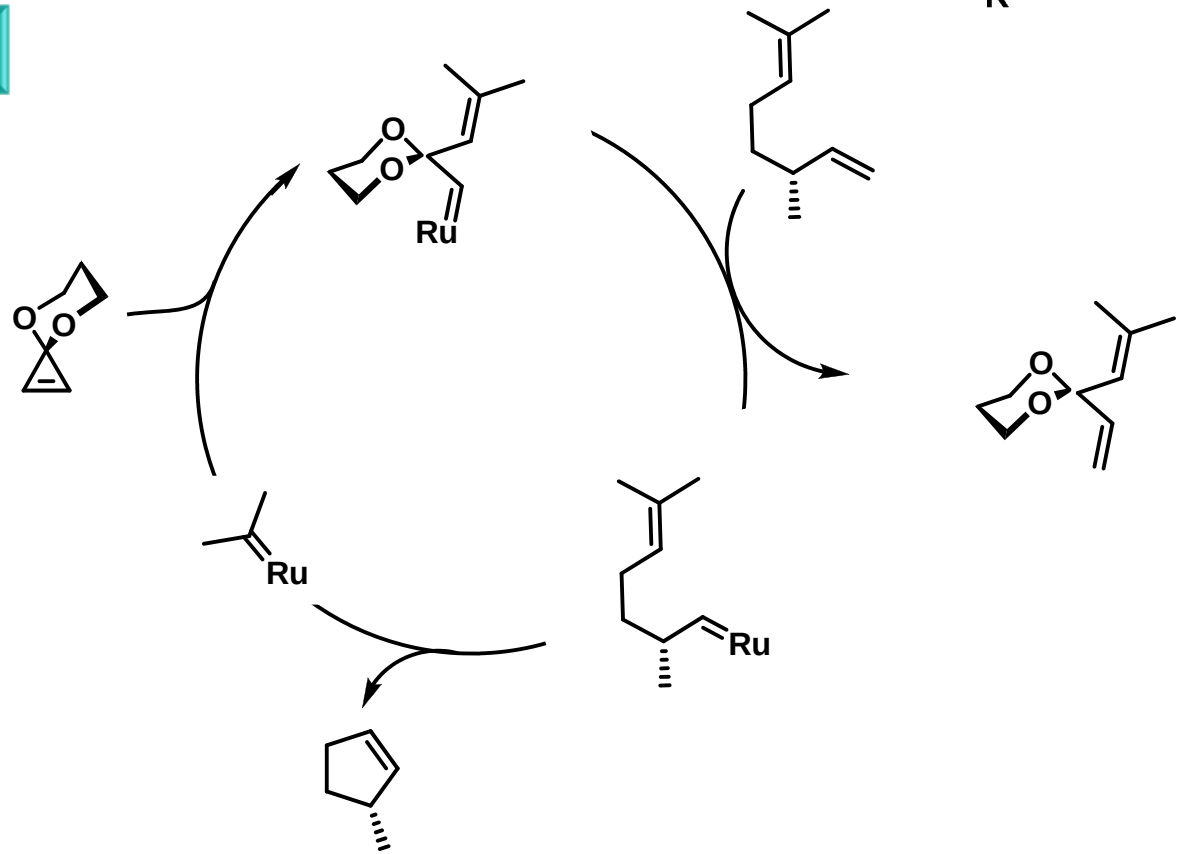
D. J. Wallace, *Angew. Chem. Int. Ed.* **2005**, *44*, 1912 –1915

Relay for metathesis

The concept was first introduced by J. L Parrain

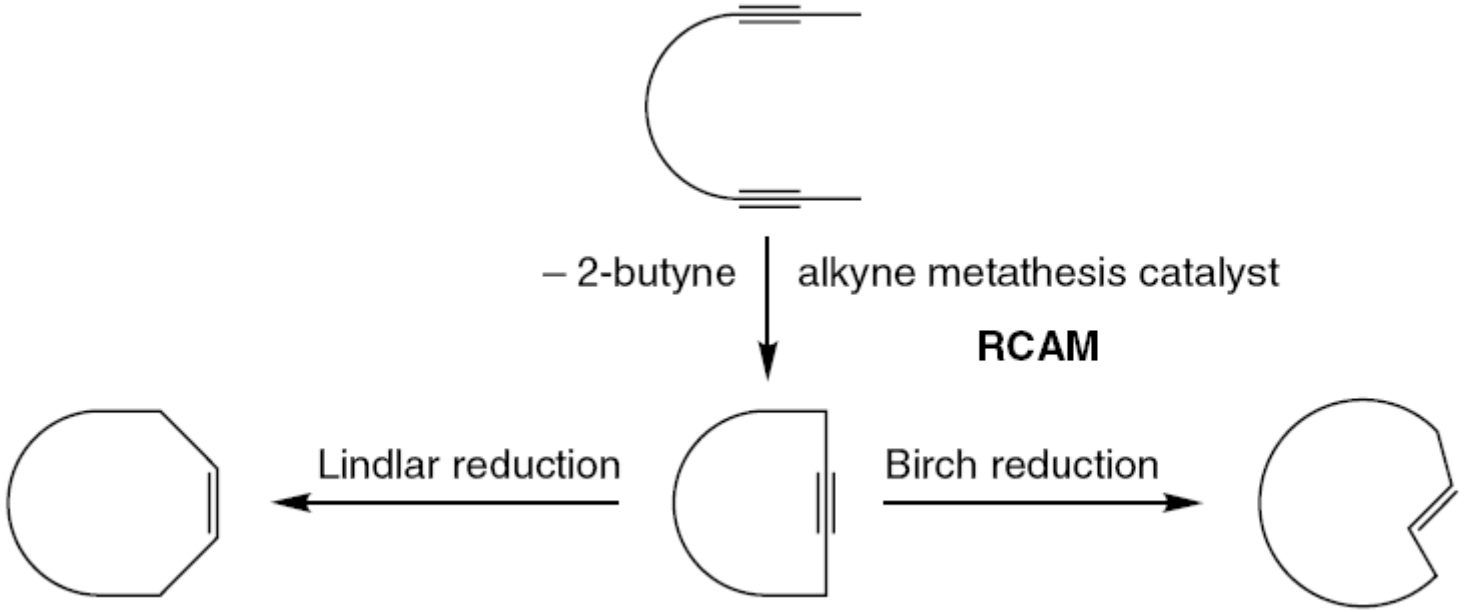


Mechanism:

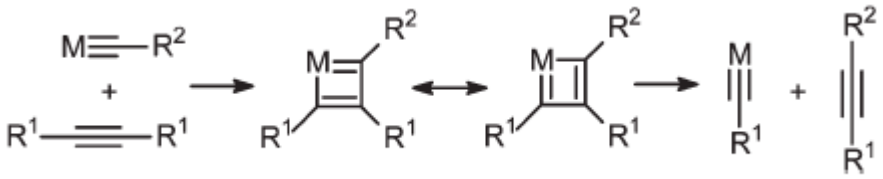


J. L. Parrain et *al, Chem. Comm.* **1998**, 2567-2568

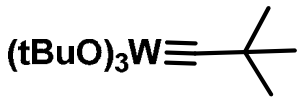
RCAM used in Macrolactonisation:

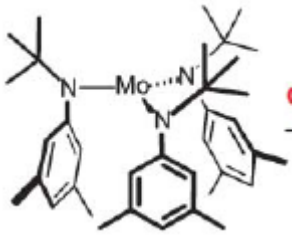


Mechanism:



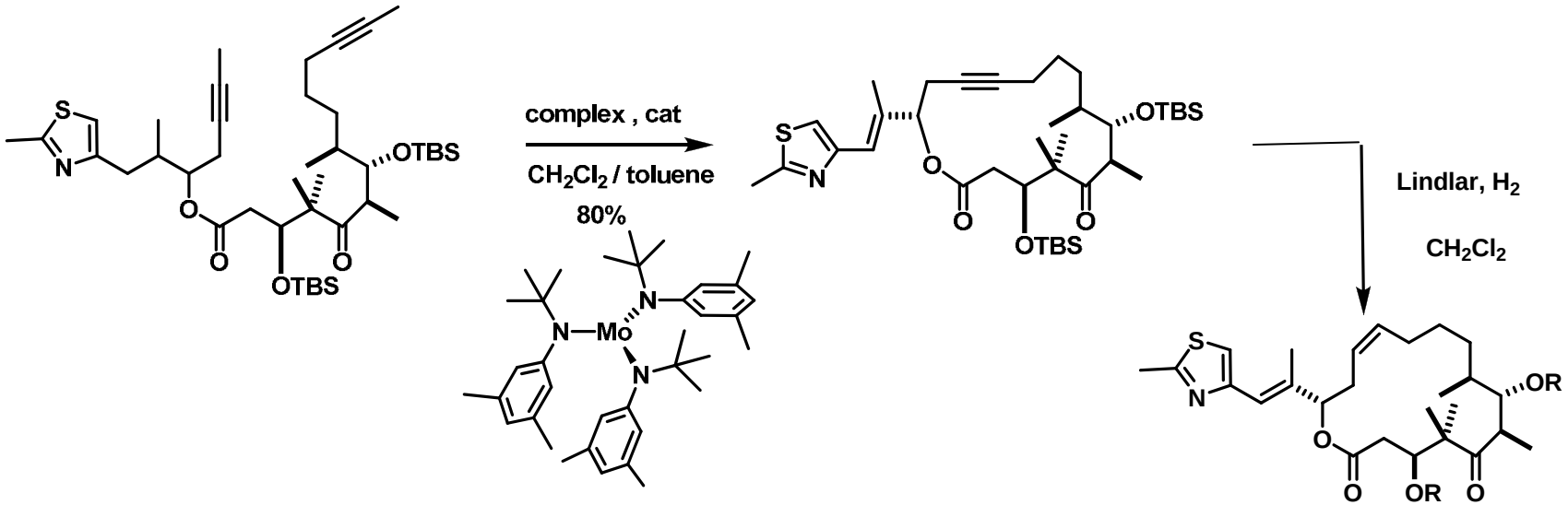
Catalyst:



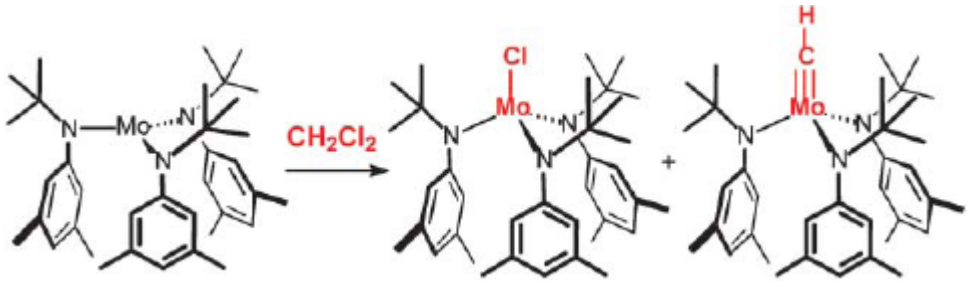


RCAM for the Epothilone:

Preparation of *Z* cycloalkenes:



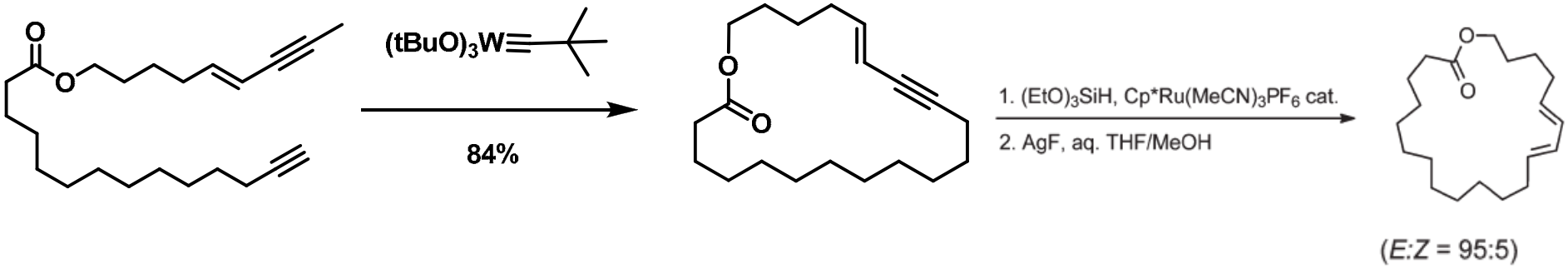
Activation of Molybdene complex :



A. Furstner, *Chem. Comm.* **2005**, 2307 – 2320

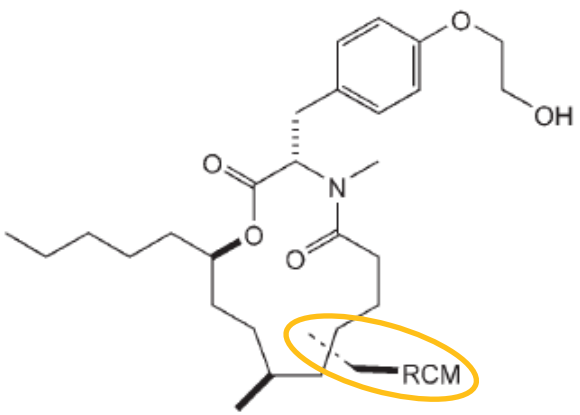
RCAM for the Epothilone:

Preparation of *E* cycloalkenes:

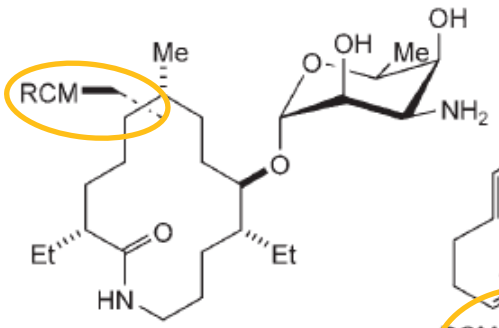


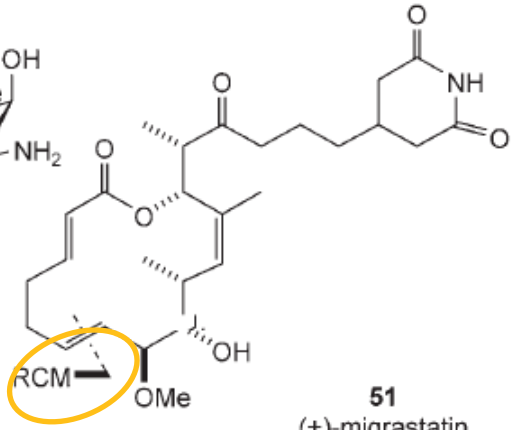
A. Furstner, *Chem. Comm.* **2005**, 2307 – 2320

Examples of macrolyde antibiotics formed by RCM



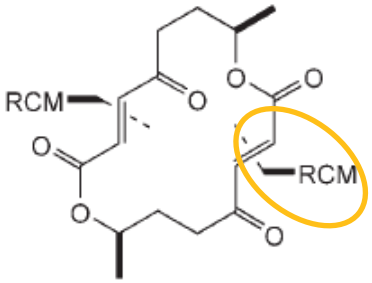
48
PF1163B



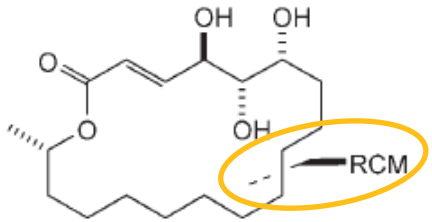


50
Sch38516 (fluvirucin B1)

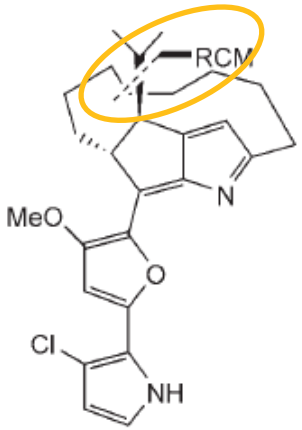
51
(+)-migrastatin



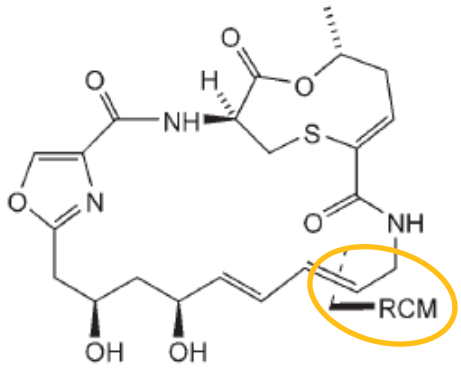
52
(–)-pyrenophorin



53
(+)-aspicilin

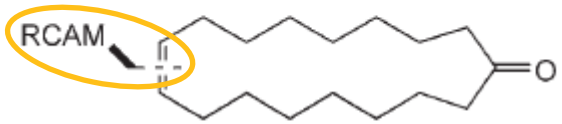


49
roseophilin

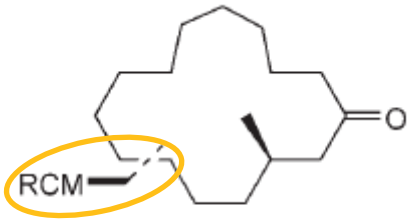


54
(–)-griseoviridin

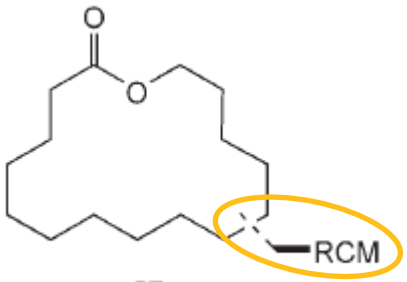
Conditions for RCM to give musk macrolides:



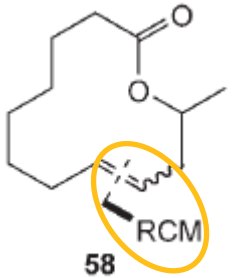
56
civetone



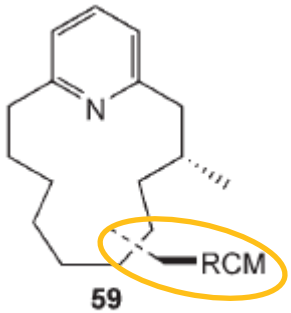
55
(–)-muscone



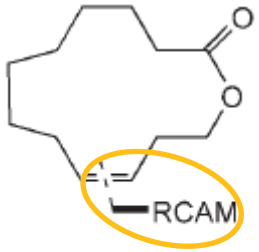
57
exaltolide



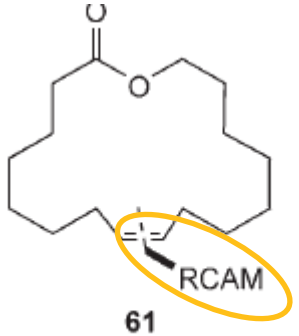
58
recifeiolide



59
(+)-muscopyridine



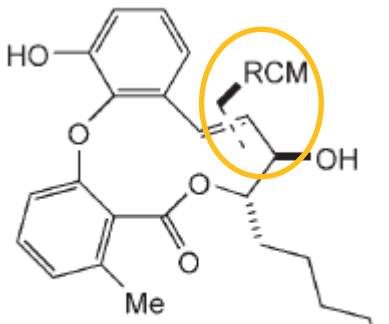
60
yuzu lactone



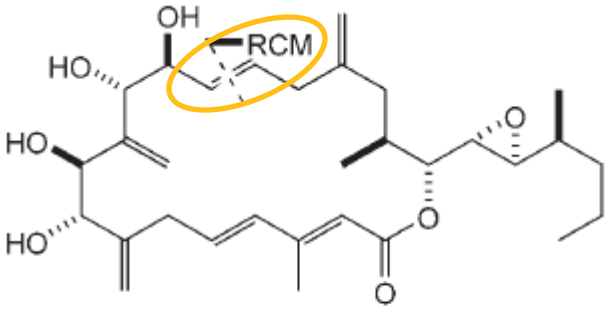
61
ambretolide

A. Gradillas, J. Pérez-Castells, *Angew. Chem. Int. Ed.* **2006**, *45*, 6086 – 6101

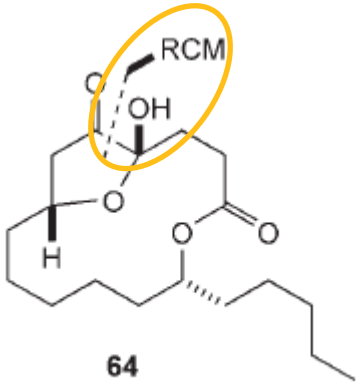
Conditions for RCM to give 11-to 20 macrolides:



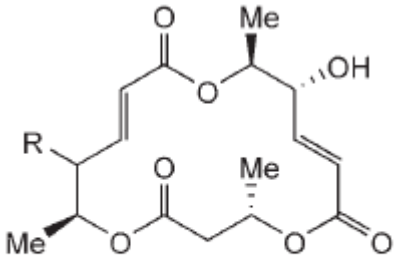
62
(+)-aspercylide C



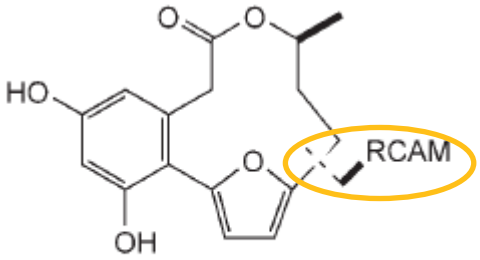
73
amphidinolide A



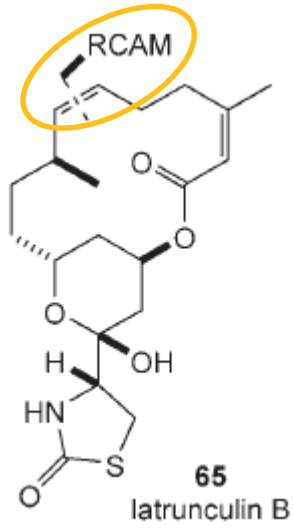
64
(–)-gloeosporone



R = COH; macrosphelide A
R = C=O; macrosphelide B



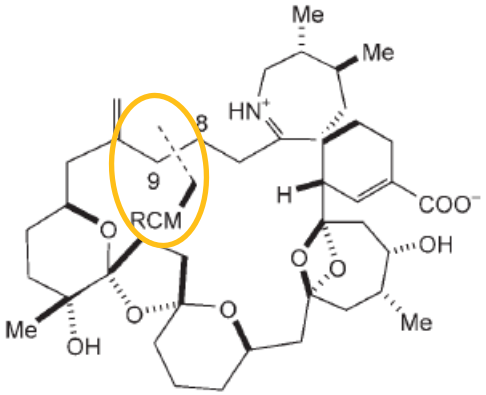
63
citreofuran



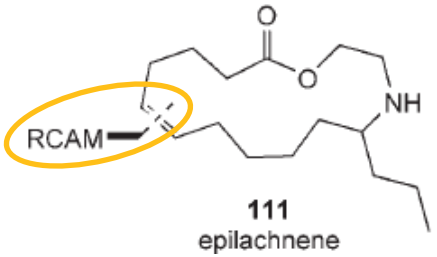
65
latrunculin B

A. Gradillas, J. Pérez-Castells, *Angew. Chem. Int. Ed.* **2006**, *45*, 6086 – 6101

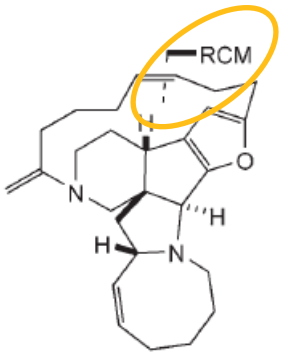
Conditions for RCM to give alkaloids:



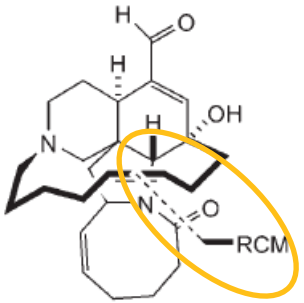
110
pinnatoxin A



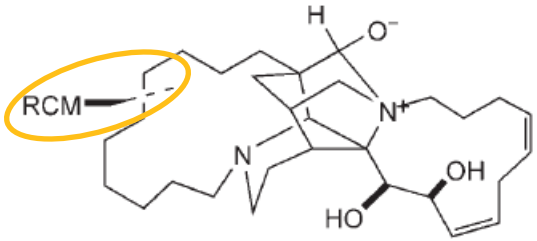
111
epilachnene



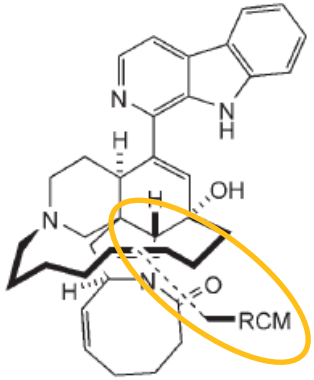
112
(+)-nakadomarin



114
ircinal



115
sarain A



113
manzamine A

A. Gradillas, J. Pérez-Castells, *Angew. Chem. Int. Ed.* **2006**, *45*, 6086 – 6101

Conclusion

- very efficient method for macrocyclisation reactions
- use for numerous synthesis of natural product
- cannot be to control the stereoselectivity