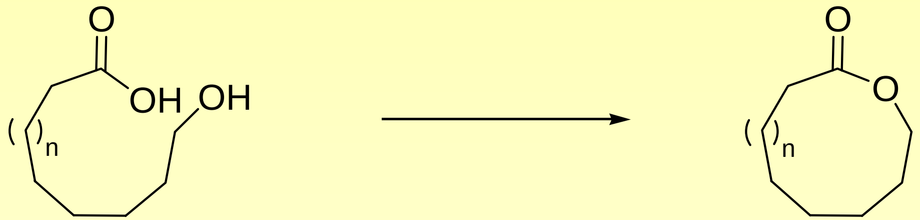
Macrolactonization in the Total Synthesis of Natural Products



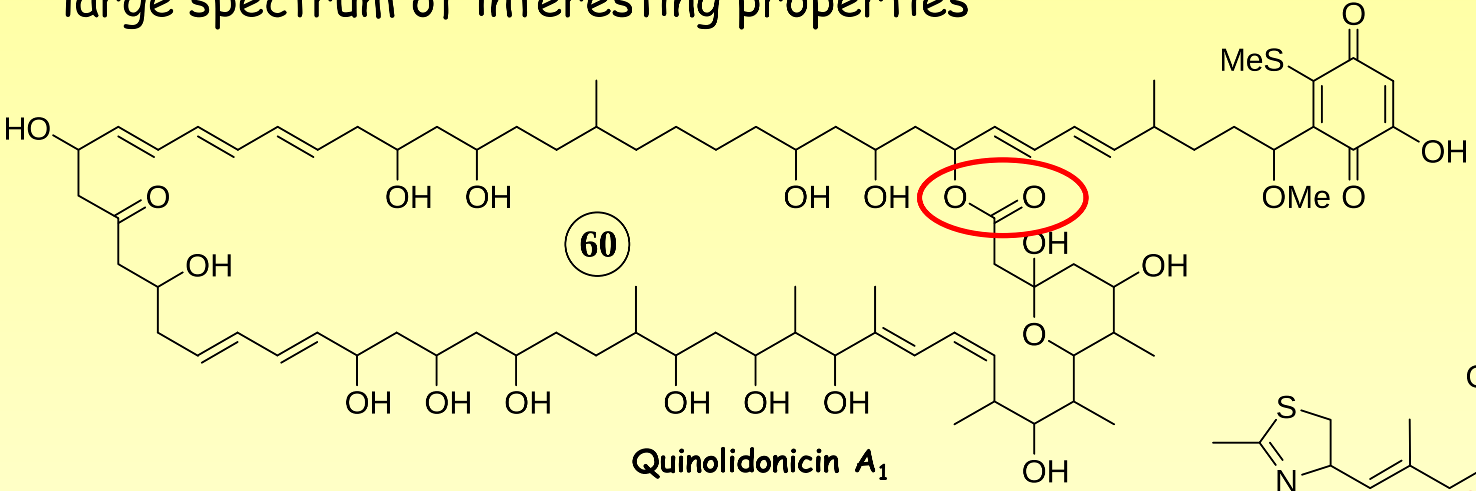
Thomas Boddaert

Le 15 Novembre 2007

Introduction

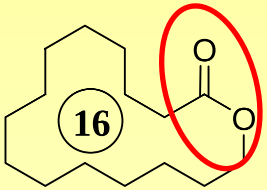
Exemples of natural macrocyclic lactones

Many natural products have a macrocyclic lactone motif, and present a large spectrum of interesting properties



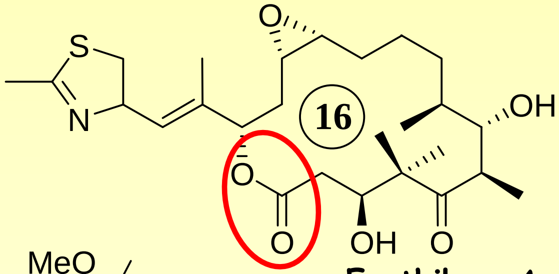
Quinolidonicin A_1

cytotoxic



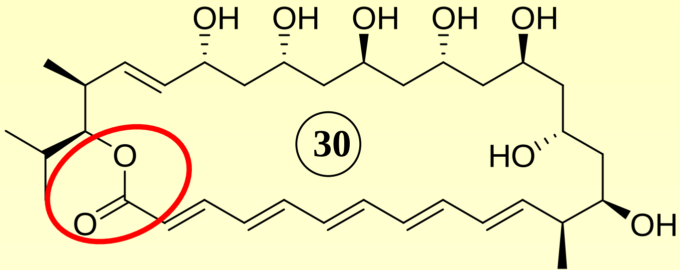
Exaltolide^R

Perfumery



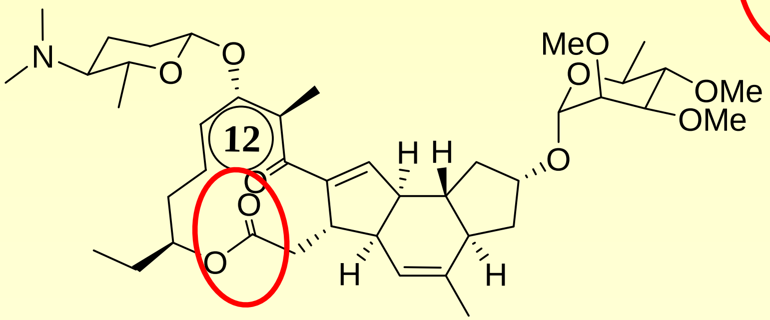
Epothilone A

Anti-cancer



Roxaticine

Antibiotic



Spinosyn A (R=H) and D (R=Me)

insecticidal

Introduction

Enthalpic against Entropic factors

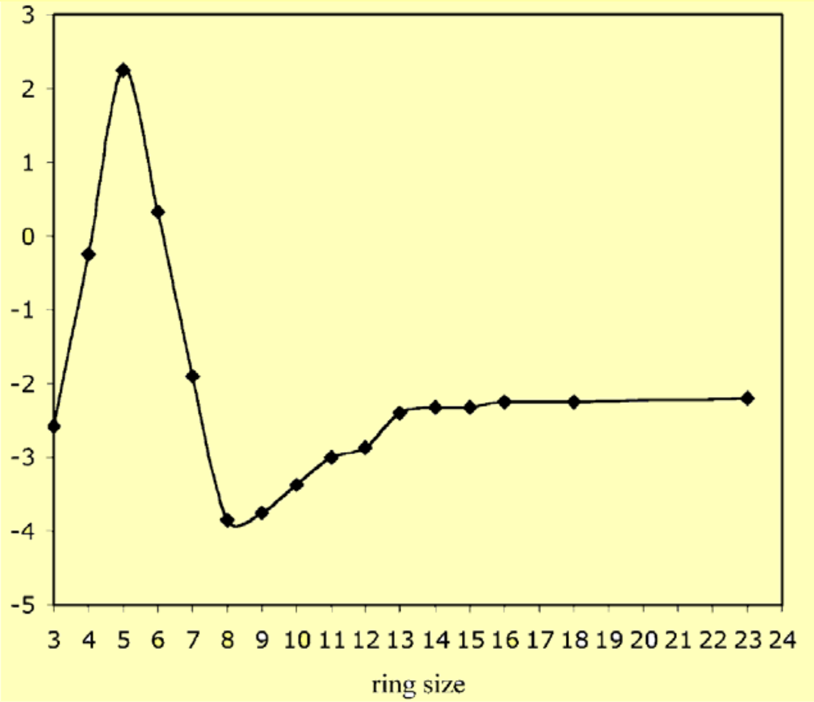
Studies by Illuminati et al. and by Stoll et al. were carried out about the lactonization of ω bromo or hydroxyl alkanoic acid.

They showed that dependence of two types of energies:

- the enthalpy
- the entropy

For medium ring: entropy < enthalpy

For large ring : entropy > enthalpy



⇒ The most difficult cases appear to be n = 8 to 11.

Illuminiati, G.; Mandolini, L. *Acc. Chem. Res.* **1981** ,*14*, 95.

Stoll, M.; Rouvé, A. *Helv. Chim. Acta* **1935**, *18*, 1087.

Galli, C.; Giovannelli, G.; Illuminati, G.; Mandolini, L. *J. Org.Chem.* **1979**, *44*, 1258.

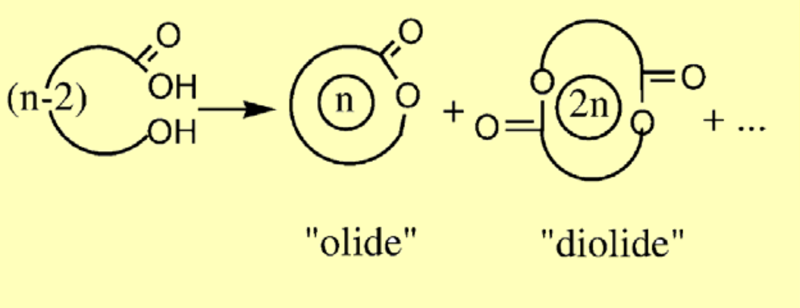
Introduction

Intramolecular against Intermolecular lactonization

The macrolactonization is in the competition with the inter-molecular reaction.

To avoid this problem two classical technics had been developed:

- the high dilution
- the slow addition



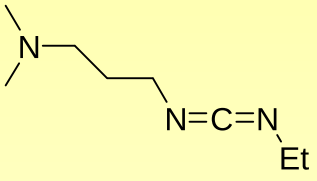
But recently, others alternatives have been carried out to avoid high dilution.

This method results by the immobilisation of the seco-acid by using: microemulsions, zeolites, inverse micelles, solid-liquide phase transfer catalysis…

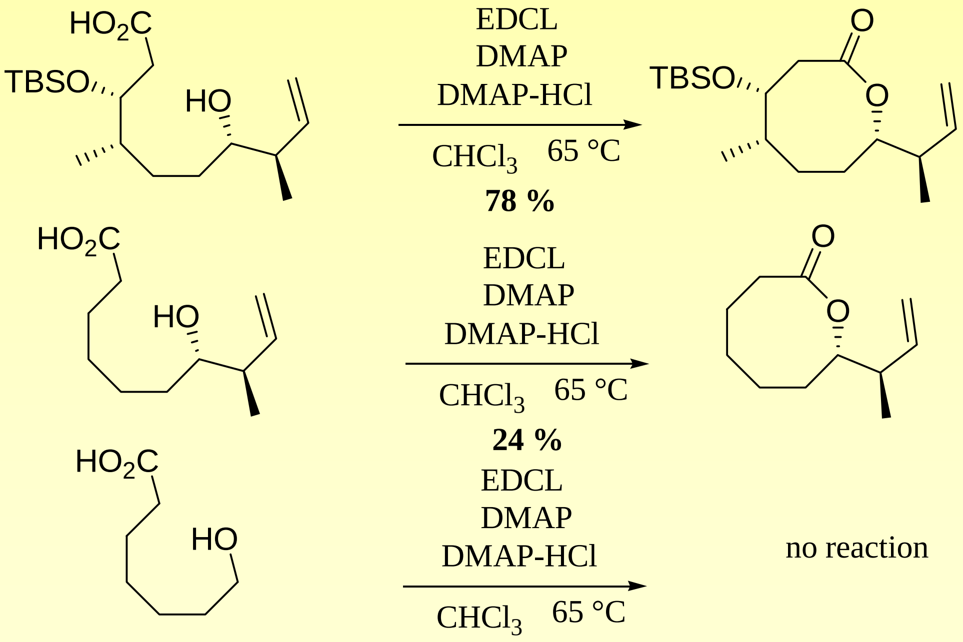
Introduction

Influence of the Conformation

Many studies showed the impact of the substituents and the conformation of the seco-acid.



EDCI



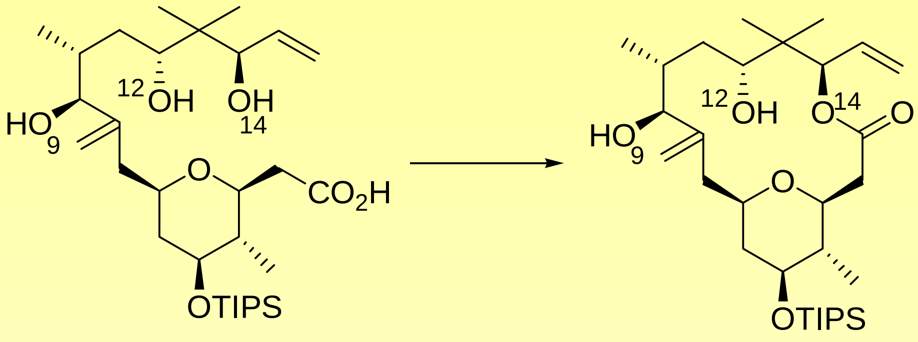
Octalatin derivatives

Andrus, M. B.; Argade, A. B. *Tetrahedron Lett.* **1996**, *37*, 5049.
Buszek, K. R.; Jeong, Y.; Sato, N.; Still, P. C.; Muino, P. L.; Ghosh, I. *Synth. Commun.* **2001**, *31*, 1781.

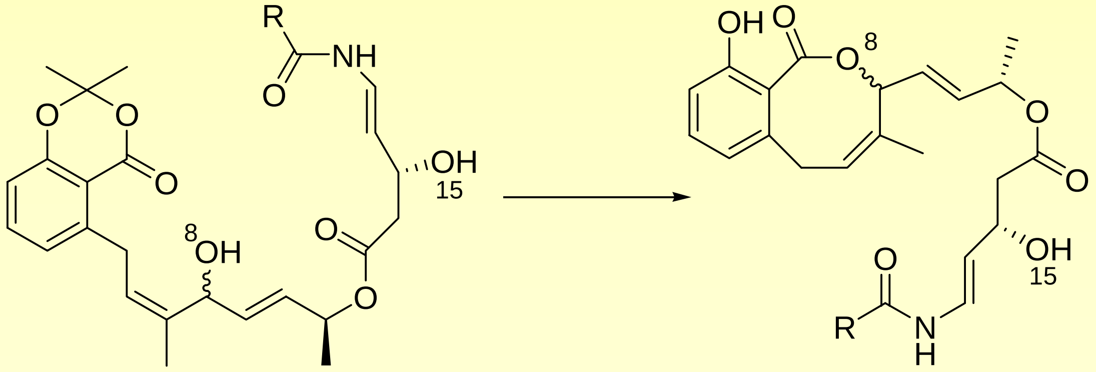
Introduction

Influence of the Conformation

The space-conformation of the molecule is even important. Several groups have described selective macrolactonization (14) were three nonprotected hydroxyl groups (12 or 9) due to the conformation of the molecule.



Polycavernoside



Lobatamide C

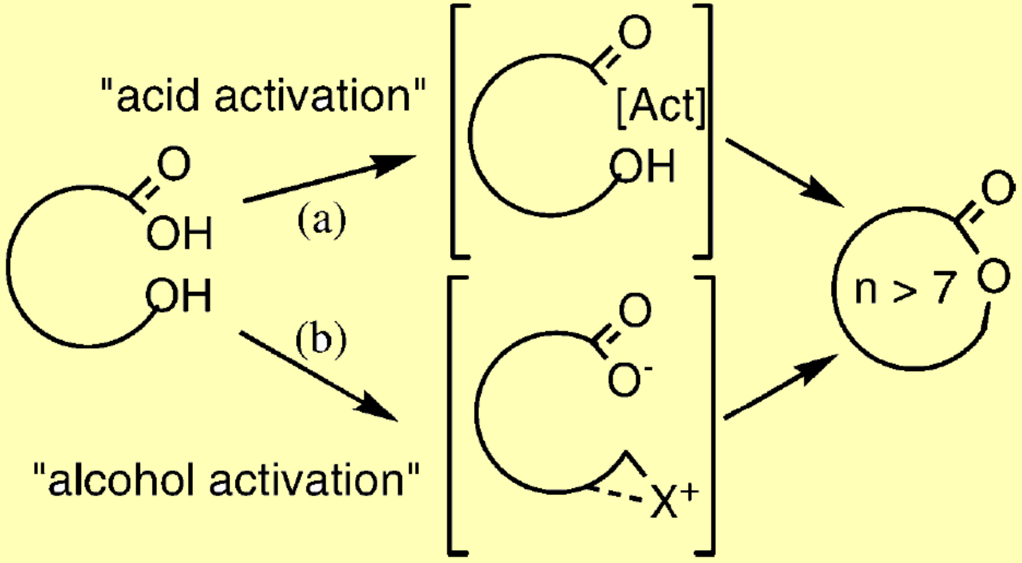
The 8- rather than the 15- membered lactone was selectively obtained in a Boeckman type macrolactonization

White, J. D.; Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 8593.
Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889.

Introduction

Two methods are frequency use to realise the macrolaconization:

- The « acid » activation
- The « alcohol » activation



« Acid » Activation

Through thioester

Cyanuric chloride (CC)

Mukaiyama's Salt

Mixed anhydrides and basic activation

Mixed anhydrides under lewis acid activation

Phosphorus-based reagents

Carbodiimides

Chloroimidasolinium and chloroformamidinium chlorides

Tin-Based reagents

Boeckman's method

« Activated » ester: transesterification and translactonization methods

Photochemistry

Carbonylative macrolactonizations

Parenty, A.; Moreau, X.; Campagne, J.-M.; *Chem. Rev.* **2006**, *106*, 911.

« Acid » Activation

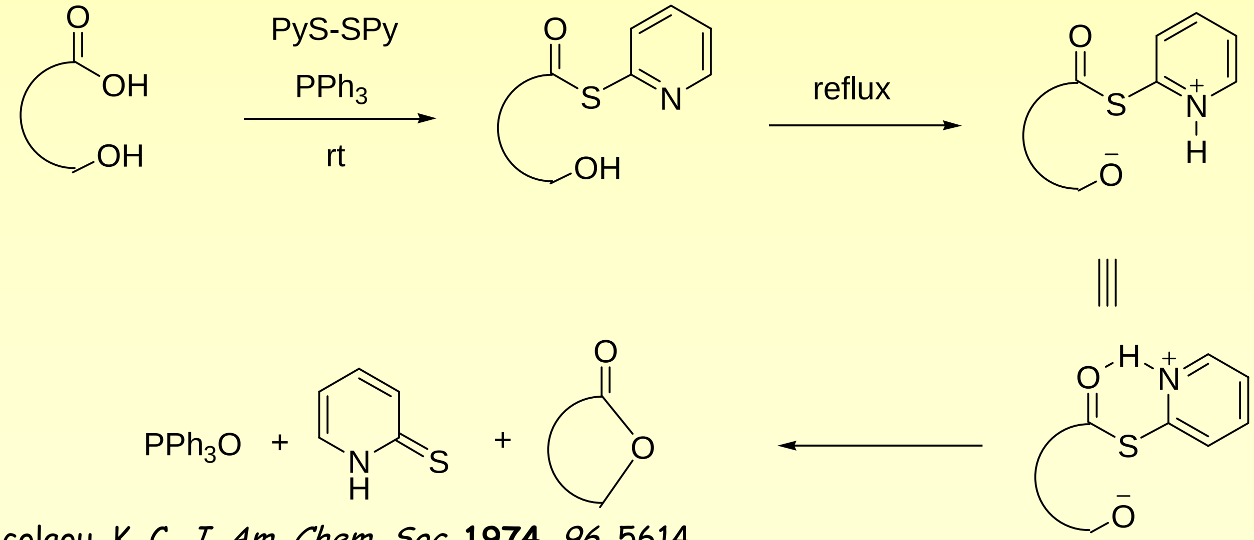
Through Thioester

1. Corey (Nicolaou, Brunelle) and Gerlach Reactions

One of the most popular macrolactonization.

This « double activation » method was discribed by Corey and Nicolaou in 1974

One pot, two-step reaction: the synthesis of the thioester at room temperature and the lactonisation under reflux.



Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.

Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707.

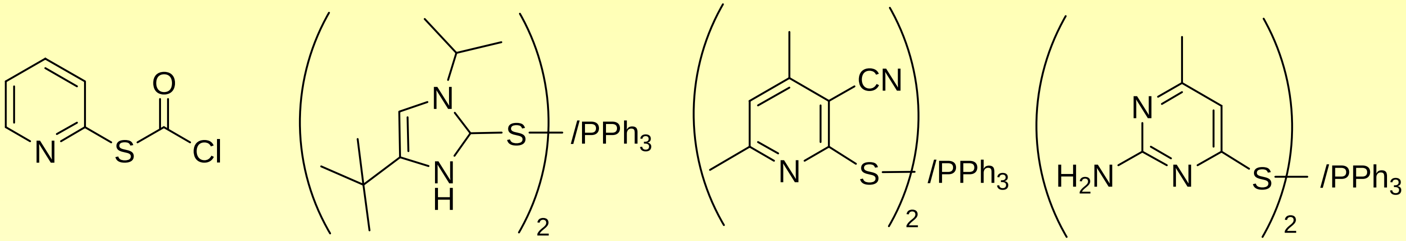
« Acid » Activation

Through Thioester

1. Corey (Nicolaou, Brunelle) and Gerlach Reactions

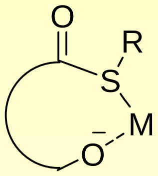
Many variants of this reaction were developed to increase the yields or to do reaction under milder conditions :

- The formation of other thioester.



- The utilisation of metal (Ag, Cu or Hg), to create a chelation between the sulfur atom and the alcoholate.

Gerlach's modification is the most popular one. It uses silver salts (AgClO4, AgBF4, AgOTf) and allows some reaction to be carry out at room temperature.

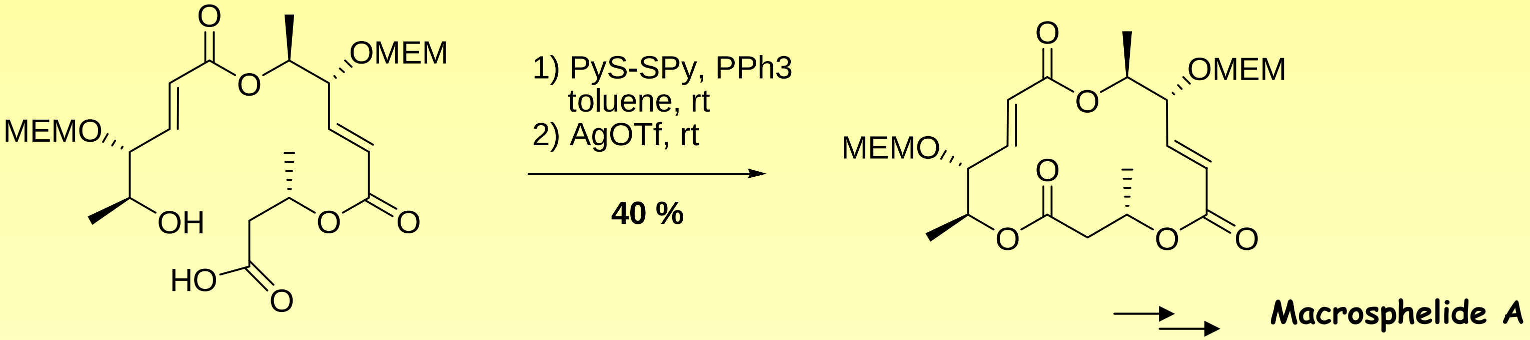


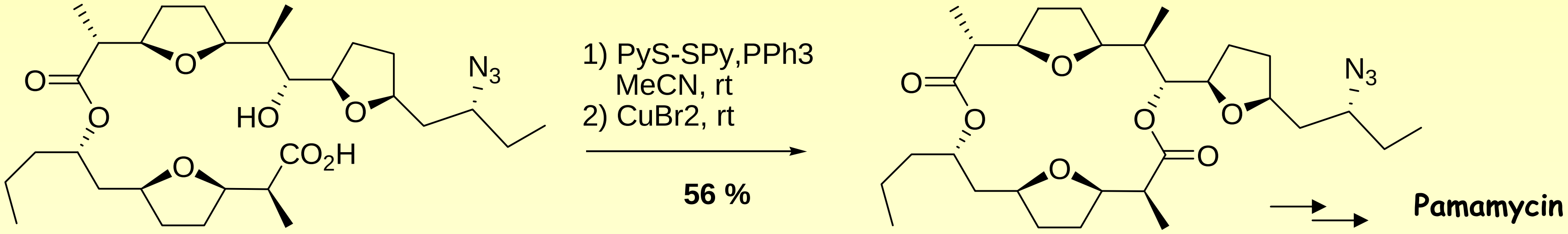
Schmidt, U.; Heermann, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 308.
Nimitz, J. S.; Wollenberg, R. H. *Tetrahedron Lett.* **1978**, *19*, 3523.
Corey, E. J.; Clark, D. A. *Tetrahedron Lett.* **1979**, 2875.
Hillis, L. R.; Ronald, R. C. *J. Org. Chem.* **1985**, *50*, 470. Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1974**, *57*, 2661.

« Acid » Activation

Through Thioester

1. Corey (Nicolaou, Brunelle) and Gerlach Reactions





⇒ The Gerlach conditions is the most universal method, but the macrolactonization is still substrate-dependant.

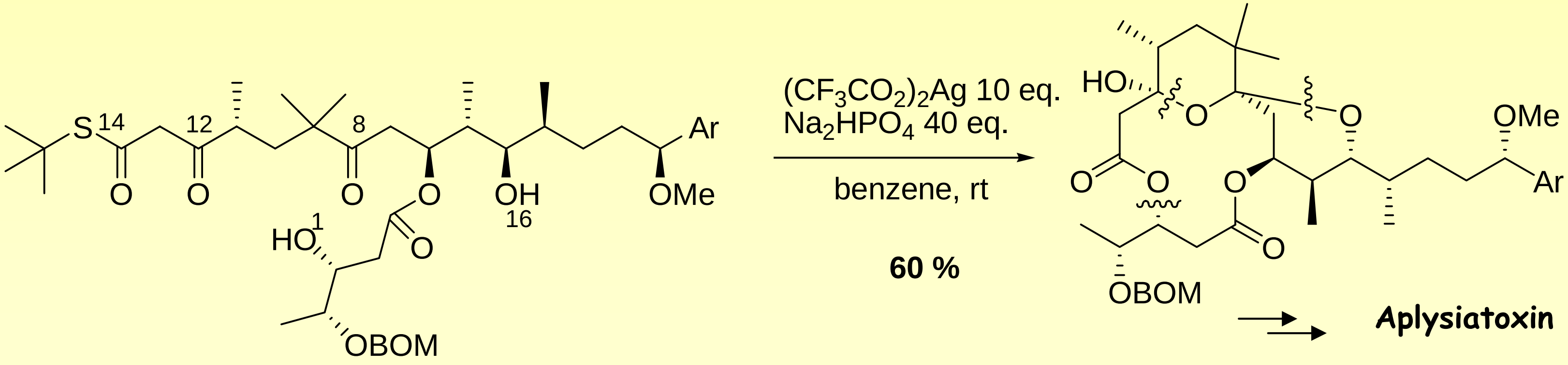
Kusaka, S.-i.; Dohi, S.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **2003**, *44*, 8857.
Kang, S. H.; Jeong, J. W.; Hwang, Y. S.; Lee, S. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1392.

« Acid » Activation

Through Thioester

2. Masamune Reaction

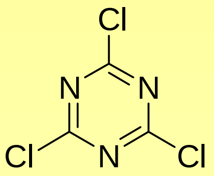
In this method, a benzyl or *tert*-butyl thioester is prepared and isolated. And in a second step a thiophilic metal salt is added [$Ag(CO_2CF_3)_2$, CuOTf, $Hg(CO_2CF_3)_2$].



Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed.Engl.* **1977**, *16*, 585.
Park, P. U.; Broka, C. A.; Johnson, B. F.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 6205.

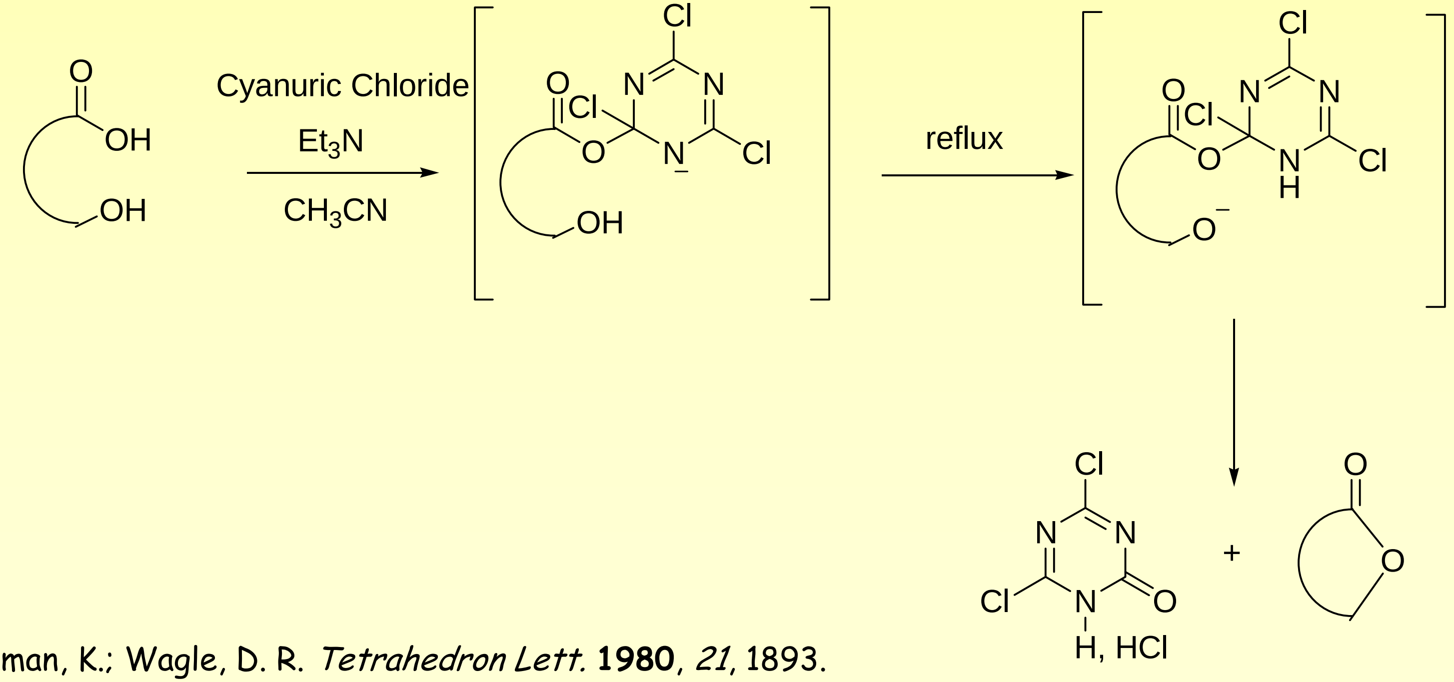
« Acid » Activation

Cyanuric Chloride (CC)



Cyanuric Chloride

Vantakaraman introduced this reaction in 1980, the mechanism is not far from the Corey and Nicolaou lactonization , involves a « double activation ».

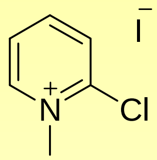


Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett.* **1980**, *21*, 1893.
Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett.* **1979**, *20*, 3037.

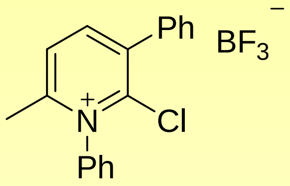
« Acid » Activation

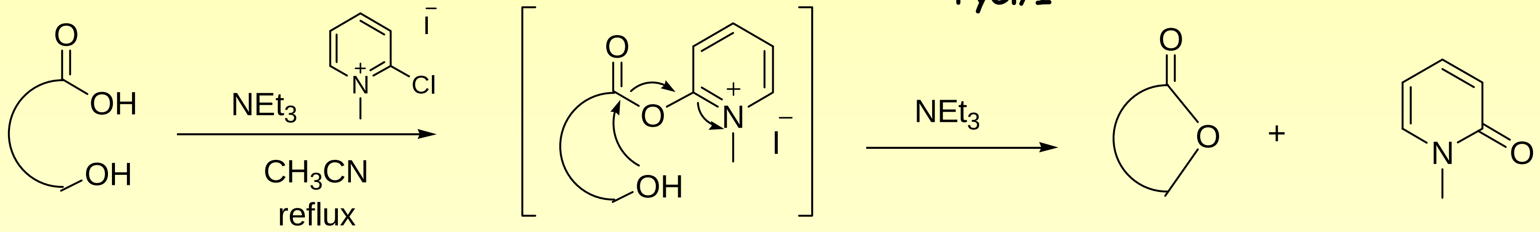
Mukaiyama's Salt

The macrolactonization by the utilisation of the 1-methyl-2-chloropyridinium iodide was introduced by Mukaiyama in 1974. Two years later, a second catalyst was use with 2,6-lutidine to avoid the decomposition of the pyridium salt by the triethylamine.



PyCl/I

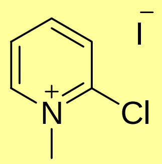




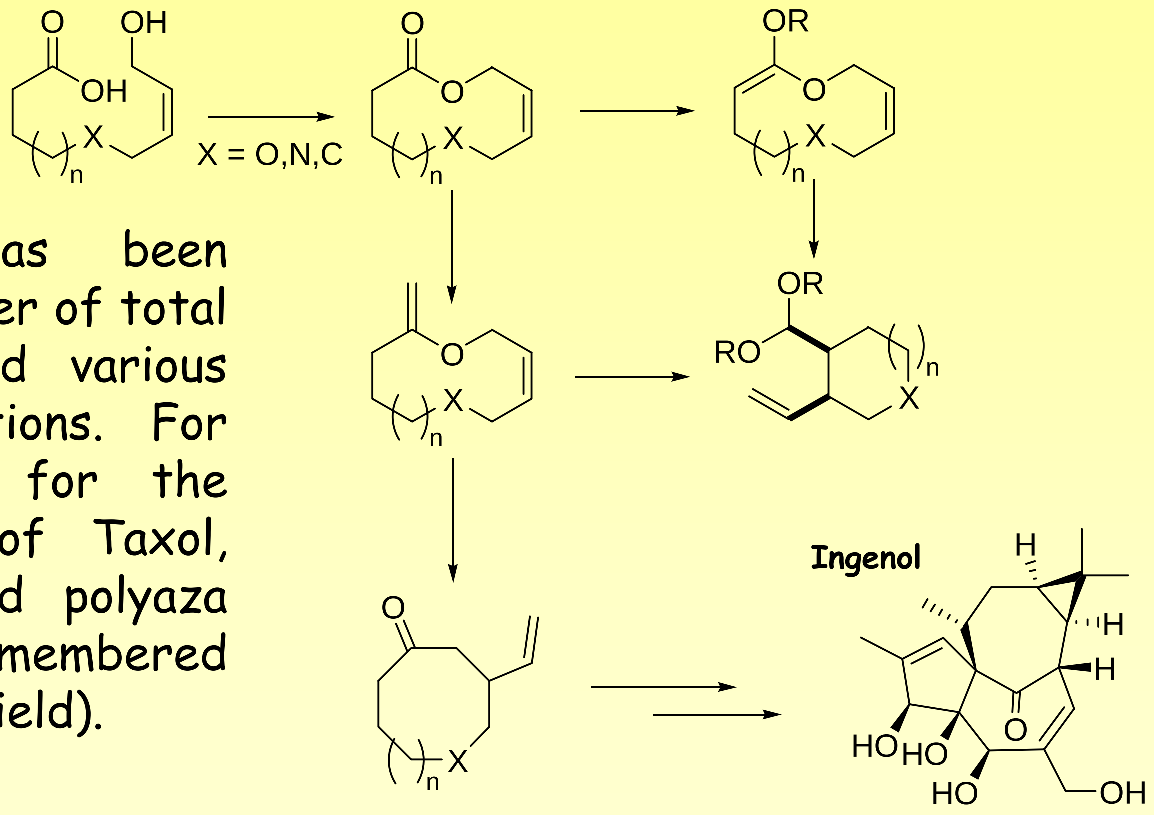
The Mukaiyama macrolactonization is usually carried out under high dilution conditions (c = 10^{-3} M) with the slow addition of the hydroxy acid into refluxing acetonitrile. But very recently, a PS-supported reagent was developed by Tye.

Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.
Narasaka, K.; Maruyama, K.; Mukaiyama, T. *Chem. Lett.* **1978**, 885.
Convers, E.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2004**, *45*, 3401.

« Acid » Activation



Mukaiyama's Salt



This methodology has been successfully used in a number of total and formal syntheses and various other synthethic applications. For exemples, it was used for the syntheses of analogues of Taxol, prostaglandin F2α-1,15 and polyaza macrocyclic lactones (98 membered ring in an impressive 48 % yield).

This macrolactonization, followed by a Claisen rearrangement has proved to be particularly useful in many total syntheses, like analogues of ingenol.

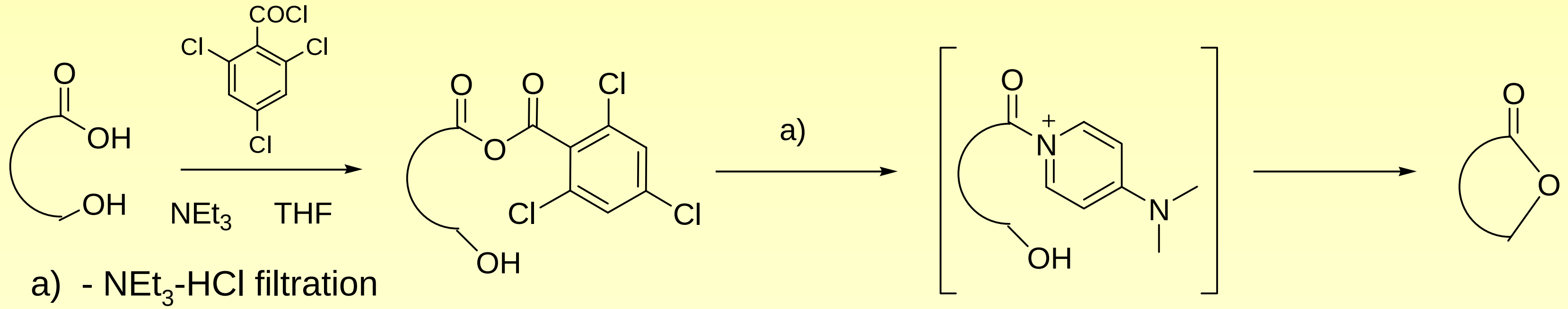
Yuan, H.; Kingston, D. G. I.; Sackett, D. L.; Hamel, E. *Tetrahedron* **1999**, *55*, 9707.
Funk, L.; Olmstead, T. A.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298.
Garcia-Rubio, S.; Meinwald, J. *J. Org. Chem.* **2001** , *66*, 1082.

« Acid » Activation

Mixed Anhydrides and Basic Activation

1. Yamaguchi-Yonemitsu Conditions

The Yamaguchi reagent, 2,4,6-trichlorobenzoyl chloride, discovered in 1979, is probably the most popular method for performing macrolactonizations. The Yamaguchi protocol and variations have been used in more than 200 synthetic applications.



a) - NEt_3-HCl filtration
- Evaporation and dilution in toluene
- slow addition anhydride to a refluxing solution of DMAP (cat) in toluene

Generally filtration of the NEt_3-HCl salt is not crucial. A PS-supported DMAP reagent has been reported.

Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
Storer, R. I.; Takemoto, T.; Jackson, P. S.; Brown, D. S.; Baxendale, I. R.; Ley, S. V. *Chem. Eur. J.* **2004**, *10*, 2529.

« Acid » Activation

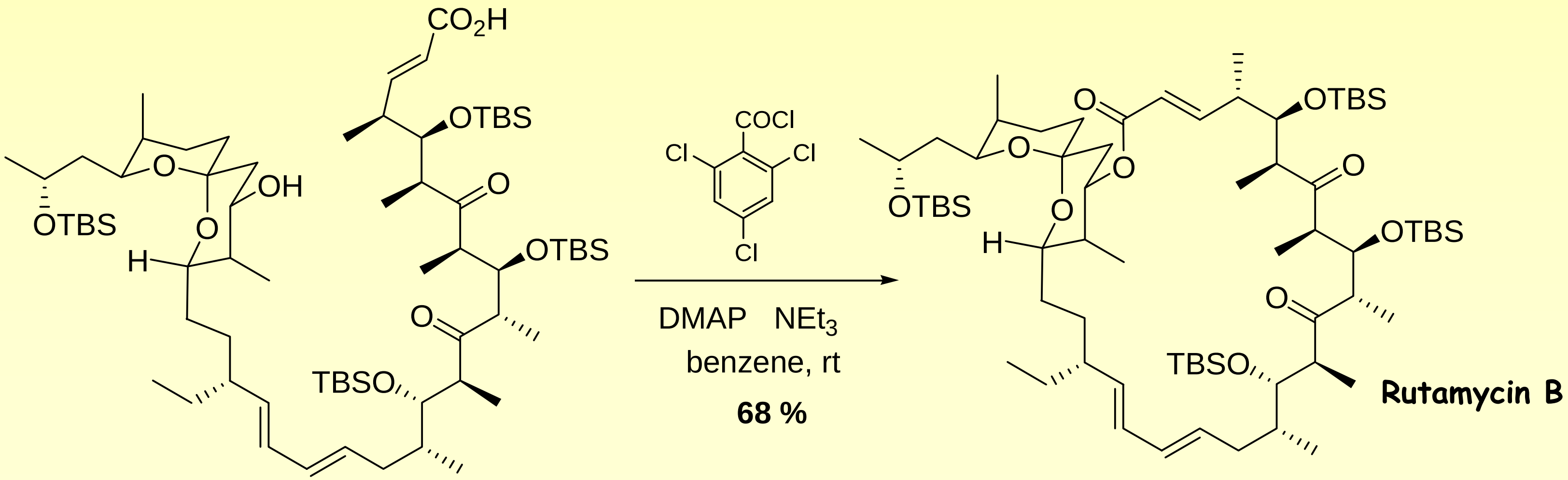
Mixed Anhydrides and Basic Activation

1. Yamaguchi-Yonemitsu Conditions

Two major modifications have been developed by Yonemitsu:

- « modified Yamaguchi conditions » : the direct addition of a large amount of DMAP to the anhydride at room temperature.

- « Yonemitsu conditions » : the DMAP is directly introduced at room temperature from the beginning.



DMAP NEt_3
benzene, rt
68 %

Rutamycin B

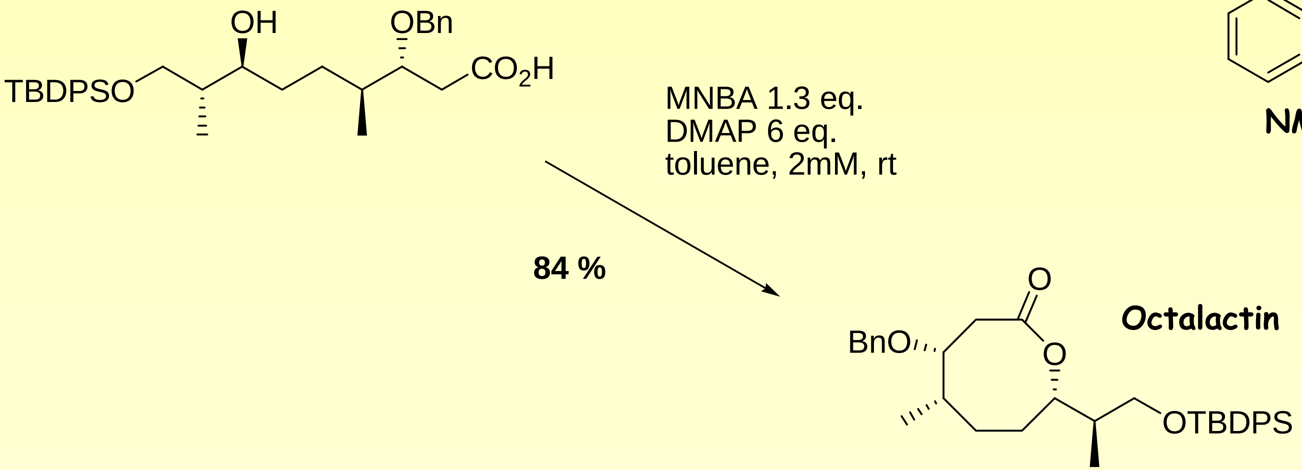
Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446.
Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7.
Tone, H.; Nishi, T.; Oikawa, Y.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *28*, 4569.

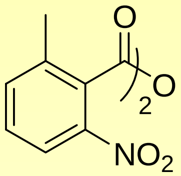
« Acid » Activation

Mixed Anhydrides and Basic Activation

2. NMBA (2-methyl-6-nitrobenzoique anhydride)

The use of 2-nitro-6-nitrobenzoic anhydride has been described recently in 2002 by Shiina. This reaction can be carried out at room temperature in DCM in presence of an excess of DMAP or with triethylamine and 20 % of (dimethylamino)-pyridine oxide.





NMBA

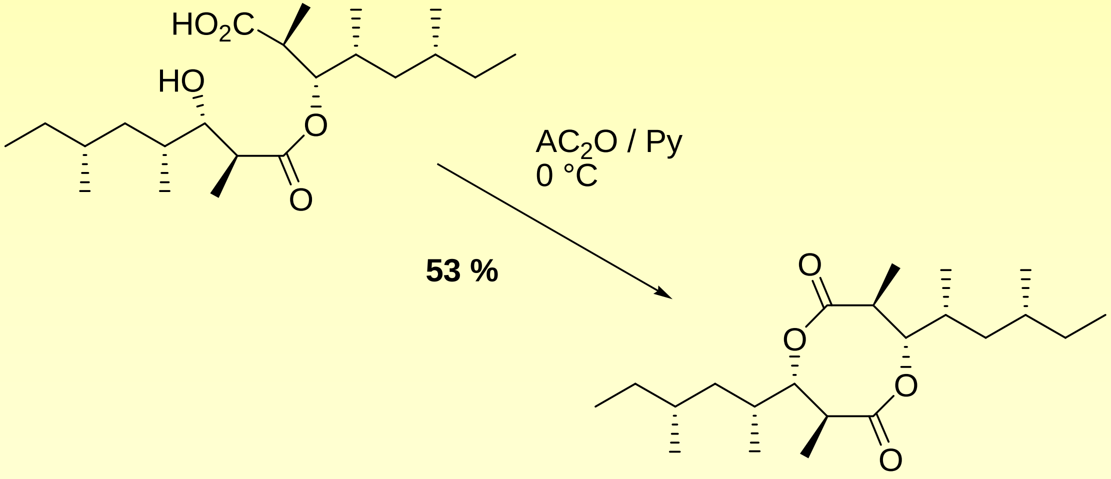
Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535.
Shiina, I.; Oshiumi, H.; Hashizume, M.; Yamai, Y.-s.; Ibuka, R. *Tetrahedron Lett.* **2004**, *45*, 543.
Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822.

« Acid » Activation

Mixed Anhydrides and Basic Activation

3. Miscellaneous Mixed Anhydrides

Several others mixed anhydrides, obtained from pivaloyl chloride, trifluoroacetic anhydride, acetic anhydride and Boc$_2$O have been described.



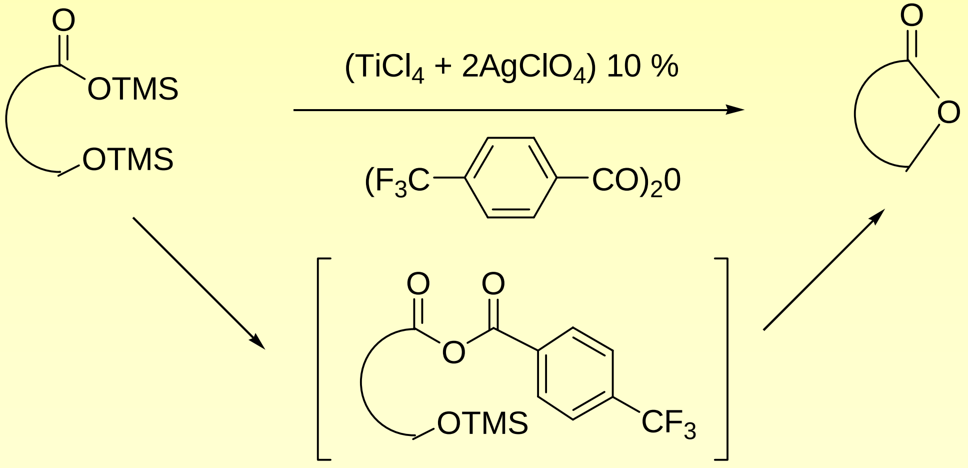
White, J. D.; Johnson, A. T. *J. Org. Chem.* **1994**, *59*, 3347.

« Acid » Activation

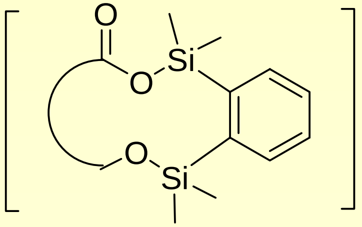
Mixed Anhydrides under Lewis Acid Activation

1. Mukaiyama-Shiina Catalysts

In 1993, Mukaiyama and Shiina described the macrolactonization of silyl ω-siloxycarboxylates at room temperature. This reaction is done in the presence of *p*-trifluoromethylbenzoic anhydride (TFBA) and 0.1 equiv Of Ti(IV) catalyst.



In 1997, Mukaiyama and Shiina have developed an alternative strategy based on the Rh-catalyzed formation of a cyclic silyl siloxycarboxylate intermediate.



Mukaiyama, T.; Izumi, J.; Miyashita, M.; Shiina, I. *Chem. Lett.* **1993**, 907.
Mukaiyama, T.; Izumi, J.; Shiina, I. *Chem. Lett.* **1997**, 187.

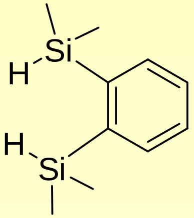
« Acid » Activation

Mixed Anhydrides under Lewis Acid Activation

2. Yamamoto Catalysts

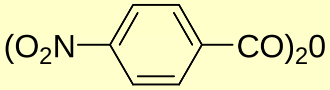
Yamamoto investigated independently the macrolactonization of mixed anhydrides using a catalytic amount of $Sc(OTf)_3$. The anhydride used for this method is the *p*-nitrofluoromethylbenzoic anhydride.

Mukaiyama-Shiina



n = 8, 85 % (diolide 4 %)
n = 9, 87 % (diolide 8 %)
n = 10, 88 % (diolide 8 %)
n = 11, 83 % (diolide 10 %)

Yamamoto



n = 6, 71 % (diolide <1 %)
n = 7, 52 % (diolide 3 %)
n = 8, 87 % (diolide <1 %)
n = 10, 99 % (diolide <1 %)

Even if the particulary impressive results for medium ring lactones (n = 8-10), this methodology has not been widely used yet in total synthesis.

Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560.

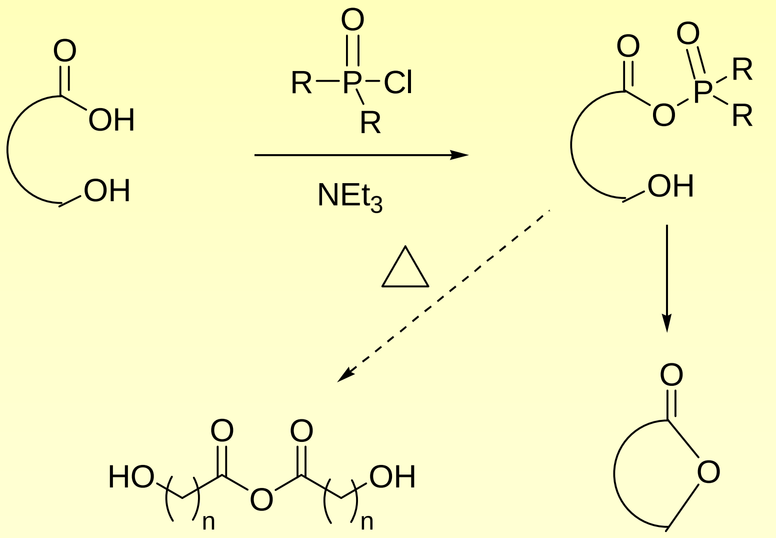
« Acid » Activation

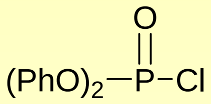
Phosphorus-Based Reagents

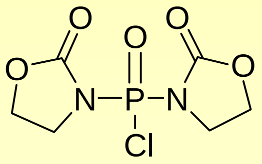
This reaction is widely used in the synthesis of peptides, but has also found some applications in macrolactonizations.

Masamune and Corey were the first in 1982, to recongnize the potential of mixed carbon-phosphorus anhydrides.

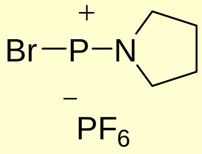
Masamune showed the need to perform the reaction at a temperature below 80 °C, to avoid the formation of symmetric anhydrides.



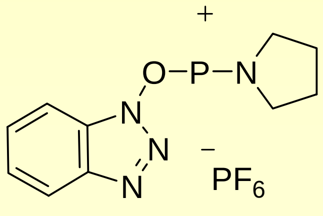

$(PhO)_2P(O)Cl$



BOP-Cl



pyBrOP-Cl

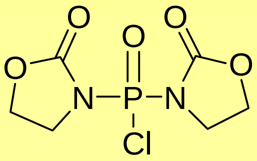


pyBOP-Cl

Coste, J.; Frerot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1991**, *32*, 1967.

Kaiho, T.; Masamune, S.; Toyoda, T. *J. Org. Chem.* **1982**, *47*, 1612.

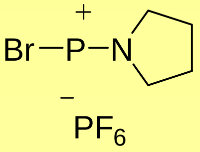
Corey, E. J.; Hua, D. H.; Pan, B. C.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 6818.



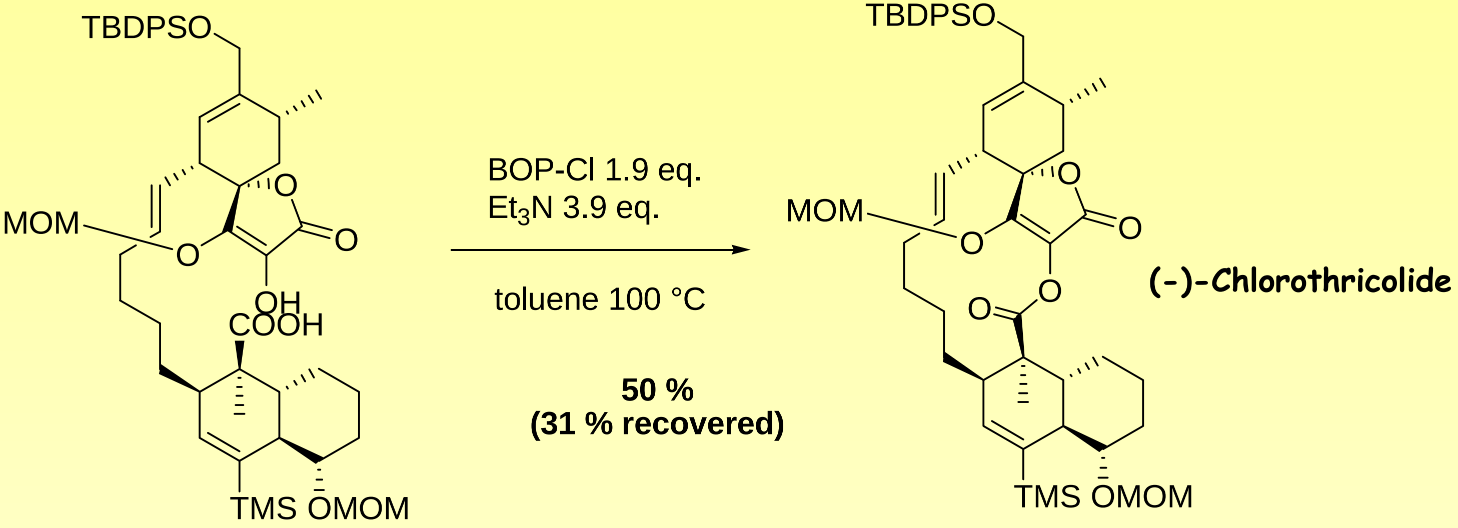
BOP-Cl

« Acid » Activation

Phosphorus-Based Reagents



pyBrOP-Cl



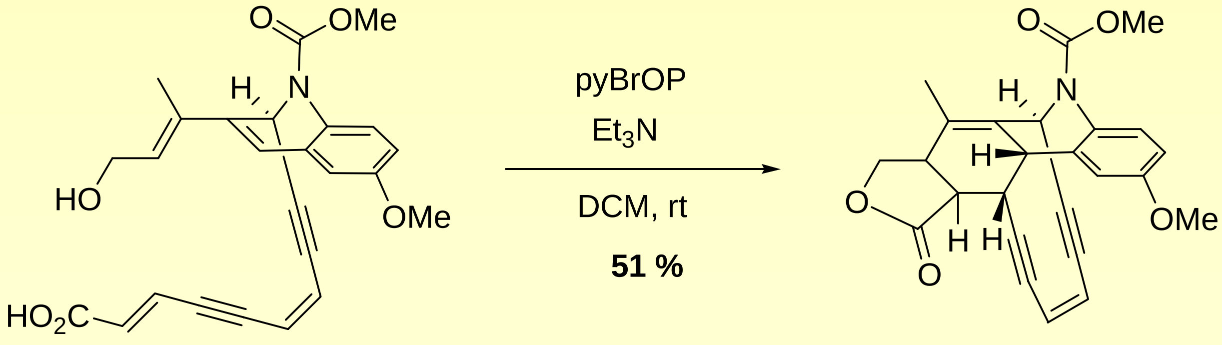
BOP-Cl 1.9 eq.
Et_3N 3.9 eq.

toluene 100 °C

50 %
(31 % recovered)

(-)-Chlorothricolide

Macrolactonization using pyBrOP reagent follows by a transannular Diels-Alder reaction at room temperature.



pyBrOP
Et_3N

DCM, rt

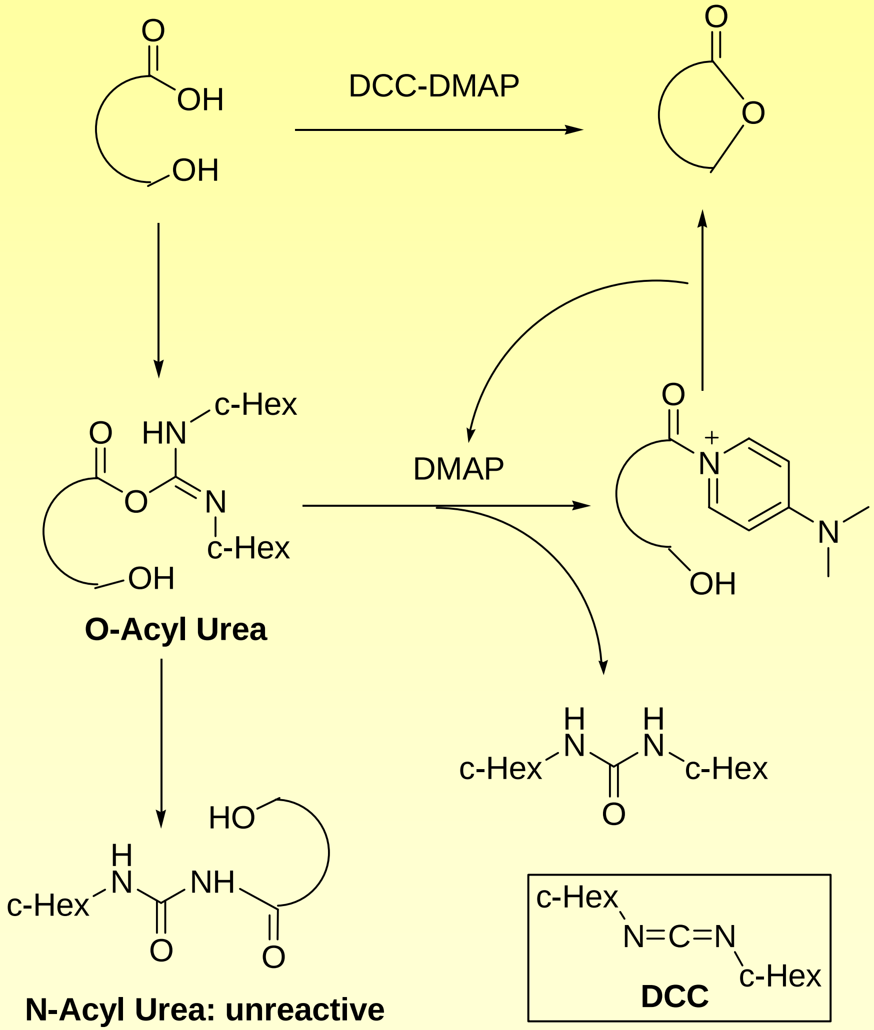
51 %

Dynemicin A

Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 7411.
Wood, J. L.; Porco, J. A., Jr.; Taunton, J.; Lee, A. Y.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5898.

« Acid » Activation

Carbodiimides



Dicyclohexylcarbodiimide (DCC) in the presence of pyridine was first used in a lactonization reaction by Woodward en route to reserpine in 1958.

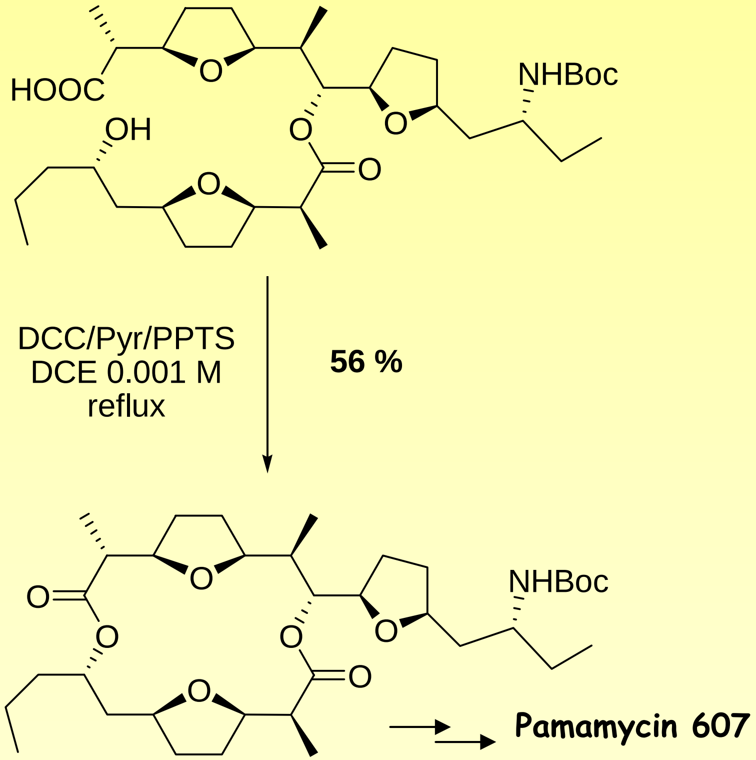
Steglich and Litivenko demonstrated the superior reactivity of DMAP-DCC in these reactions. Nevertheless, this methodology has been used rarely, because of an unreactive N-Acyl Urea byproduct.

Keck and Boden have shown the benefic effect of DMAP-HCl salt to avoid this undesirable byproduct. This method was rapidely recognized and used in a great number of total syntheses;

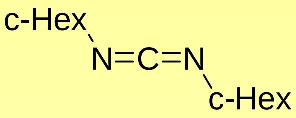
L.M. Litvinenko, A.I. Kirichenko,Dokl. Chem. 1967, 763 – 766; Dokl.Akad. Nauk SSSR Ser. Khim. 1967,176, 97 – 100.
W.Steglich, G.HQfle , Angew. Chem.1969, 81, 1001; Angew. Chem. Int. Ed. Engl. 1969, 8, 981.

« Acid » Activation

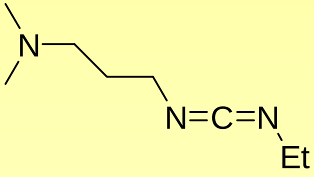
Carbodiimides



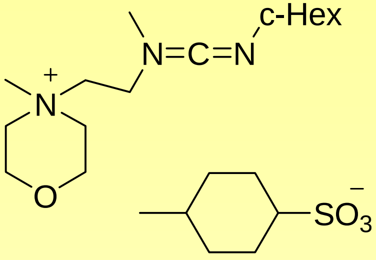
This protocole was the only one to give the macrolactones with good yiealds



DCC



EDCI



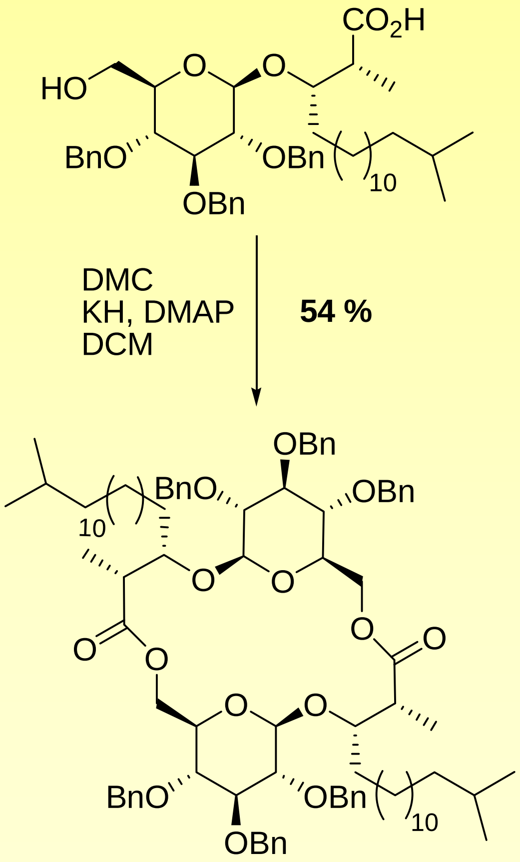
CMC

Several modifications have therefore appered:

- Proton sources: TFA, TsOH, CSA…
- Esterification reagents: soluble ureas (ex: CMC) or supported reagents.
- Base: Pyridine, PPTS, TEA.

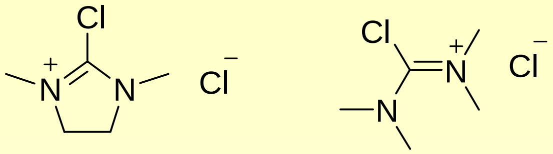
« Acid » Activation

Chloroimidasolinium and Chloroformamidinium Chlorides



DMC and tetramethylchloroformamidinium chloride were introduced by Sato in 1982. They are synthetized *in situ* by heating a DCE solution of the urea with oxalyl choride and then used after concentration.

DMC and an added metal allowed to obtain exclusively the macrodilactone.

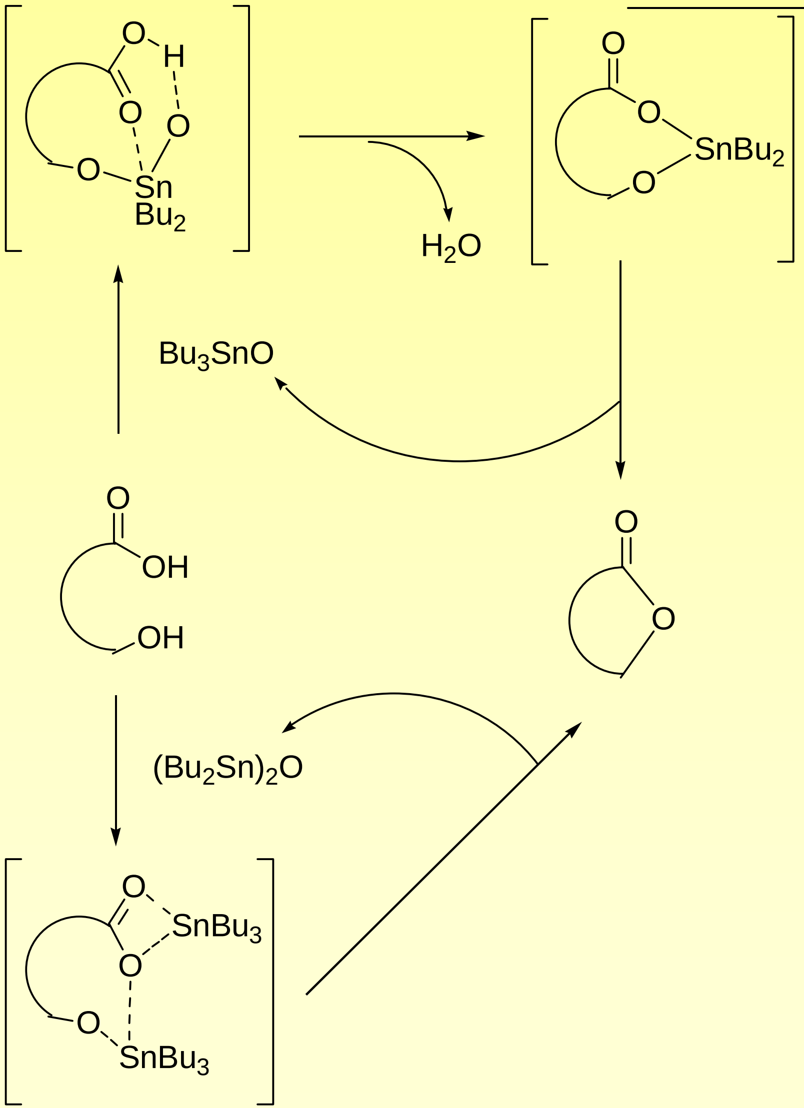


DMC

Fürstner, A.; Ruiz-Caro, J.; Prinz, H.; Waldmann, H. *J. Org. Chem.* 2004, *69*, 459.
Fujisawa, T.; Mori, T.; Fukumoto, K.; Sato, T. *Chem. Lett.* **1982**, 1891.

« Acid » Activation

Tin-Based Reagents



This reaction was born with the reactivity of tin oxides: cleavage of ester. Hanessian and Steliou showed in 1980s, the equilibrium of this reaction and developed this macrolactonization method by elimination of water.

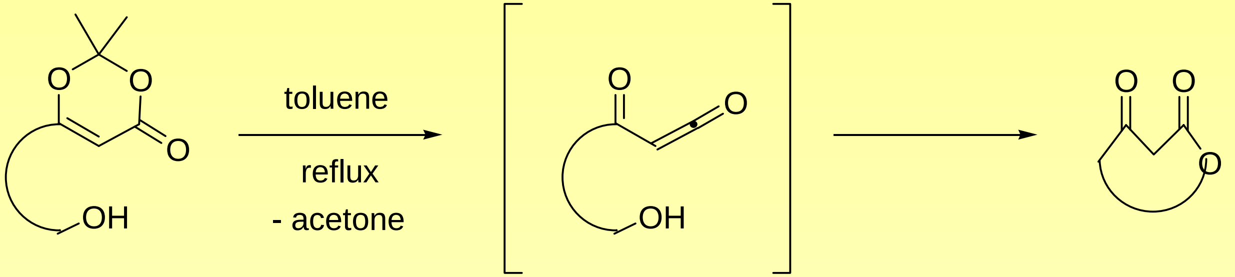
Two different pathways were described: one for Bu_3SnO and one for $(Bu_2Sn)_2O$.

Now new catalysts allow to do the reaction without Dean-Stark apparatus, because the new process is irreversible.

Steliou, K.; Szczygielska-Nowosielska, A.; Favre, A.; Poupart, M. A.; Hanessian, S. *J. Am. Chem. Soc.* **1980**, *102*, 7578.

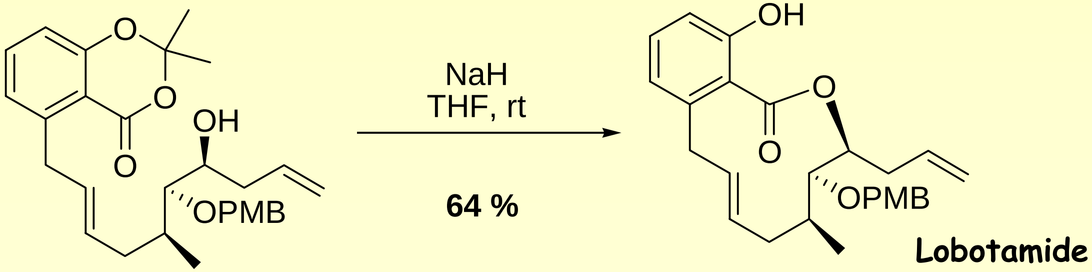
« Acid » Activation

Boeckman's Method



Dioxolenone thermolysis is a process for obtaining β-acetylketene derivatives. The ketene can be trapped intramoleculary by oxygen or nitrogen to give lactone or lactam.

This methodology has been used by Boeckman to develop an efficient macrolactonization method in 1989.



Lobotamide

Boeckman, R. K., Jr; Pruitt, J. R. *J. Am. Chem. Soc.* **1989**, *111*, 8286.

« Acid » Activation

« Activated » Ester: Transesterification and Translactonization Methods

1. Translactonizations

Corey and Nicolaou in 1977 made a study and showed that the translactonization proceed in high yields for n (number of increasing) = 1, 2 and 3. The interconversion rate usually decreases within increasing n because larger ring sizes are formed in the transition state.

In few total syntheses, macrolactones were obtained in good yields by translactonization of thiolactones.

In a number of total syntheses, the translactonization was not taking advantage of the size selectivity but only the thermodynamic preferences.

Translactonization have also been observed in several ring contractions of natural products.

⇒ Translatonization can be done under Basic or Acidic conditions.

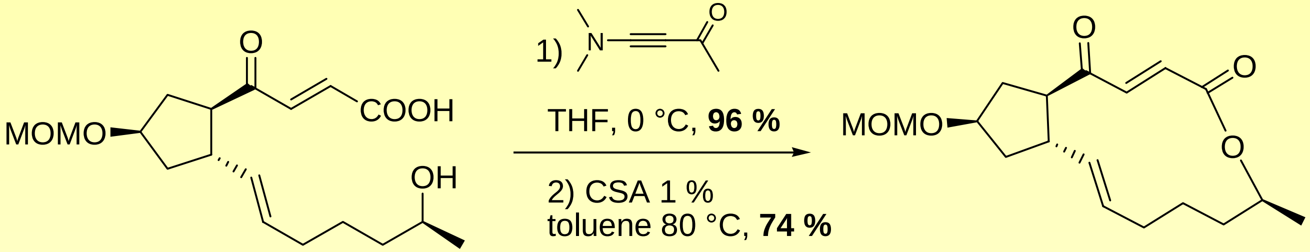
Corey, E. J.; Brunelle, D. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1977**, *99*, 7359.

« Acid » Activation

« Activated » Ester: Transesterification and Translactonization Methods

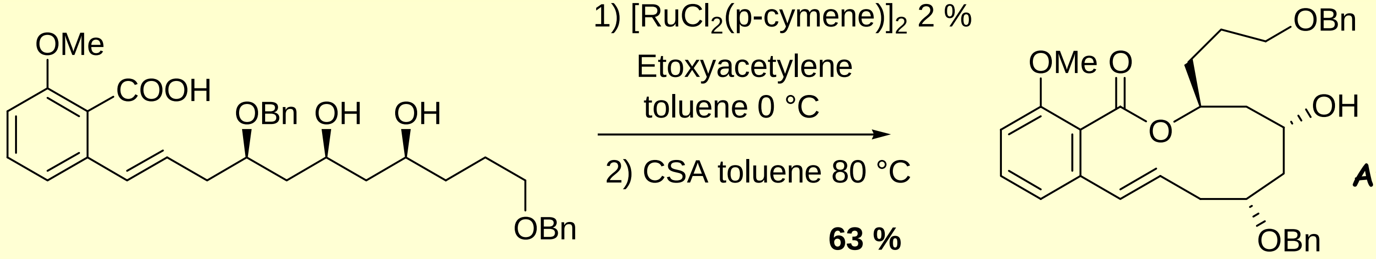
2. Through the Formation of a vinyl Ester

- In the Gais methodology the vinyl ester is formed by the reaction of the carboxylic acid and the 4-(dimethylamino)but-3-yn-2-one. The ester is treated in the presence of CSA to give the corresponding lactone.



Brefeldin A

- In the Trost methodology the vinyl ester is formed by the reaction of the acid function with the ethoxyacetylene, in the presence of Ruthenium-catalyst. The ester can be isolated and then it is treated in the presence of CSA too.



63 %

Apicularen A

Gais, H. J.; Lied, T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 145. Trost, B. M.; Chisholm, J. D. *Org. Lett.* **2002**, *4*, 3743.

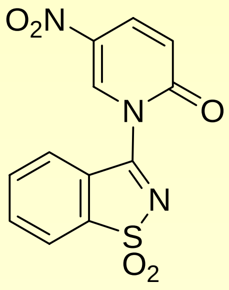
« Acid » Activation

« Activated » Ester: Transesterification and Translactonization Methods

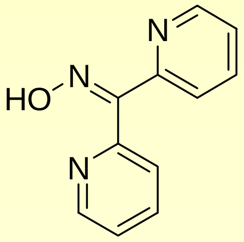
3. « Activated » Ester and Amide

« Unactivated » alkyl ester are rarely used in total syntheses. Severals groups have developed different « activated » amides and esters.

- Narasaka's Ester: (methylthio)methyl ester activated by oxidation with H_2O_2 and Mo(VI).
- Burke's Ester: trichloroethyl ester with potassium carbonate
- Palomo's Ester: di-2-pyridyl ketone oxime ester activated by copper salt.
- Kinoshita's Ester: BID-Npy in presence of TEA.
- Lactam: Alcoholysis of β-Lactam
- Activated Amides: carbodiimidazole
- Enzymatic Reactions: using lipase



Kinishita

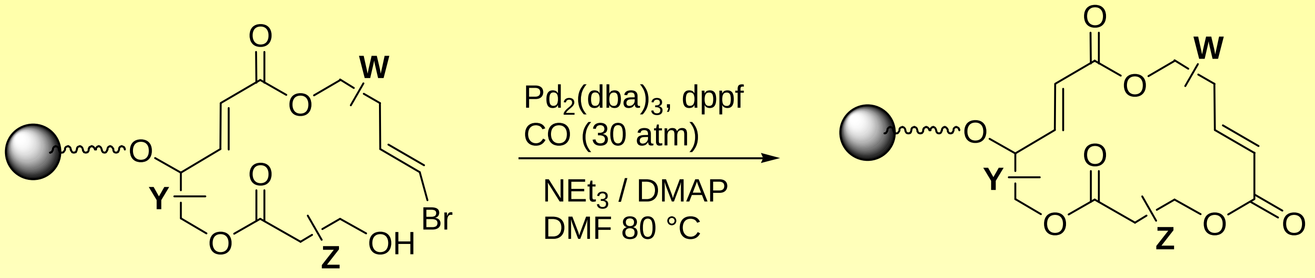


Palomo

« Acid » Activation

Carbonylative Macrolactonizations

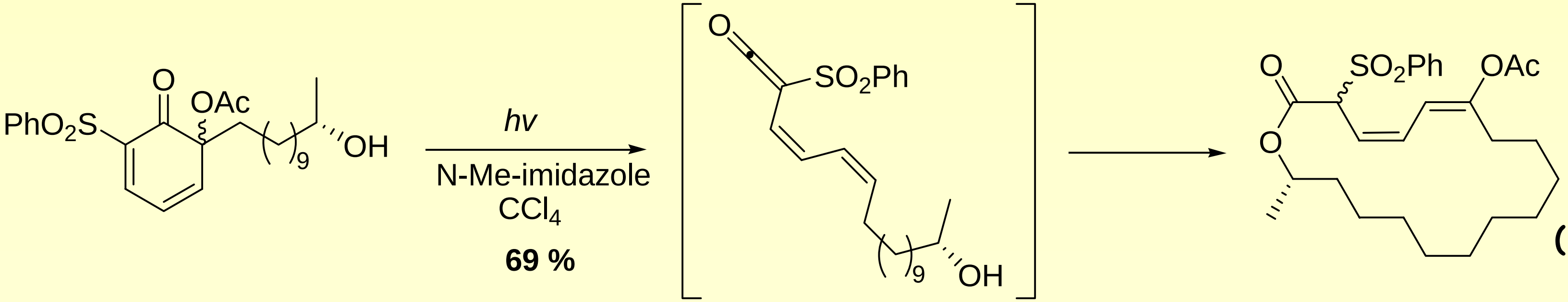
Palladium-catalyzed is extremely developed in organic chemistry, however it is rarely used for the macrolactonization.



a 122-member library

Photochemistry

Quinkert et al. Have described a photolactonization of *o*-quinol acetates.



(+)-Aspicilin

Quinkert, G.; Kueber, F.; Knauf, W.; Wacker, M.; Koch, U.; Becker,H.; Nestler, H. P.; Duerner, G.; Zimmermann, G.; et al. *Helv. Chim.Acta* **1991**, *74*, 1853.

Takahashi, T.; Kusaka, S.-i.; Doi, T.; Sunazuka, T.; Omura, S. *Angew.Chem., Int. Ed.* **2003**, *42*, 5230.

« Alcohol » Activation

Mitsunobu reactions

Eschenmoser reagent

Through alkylhalides and mesylates

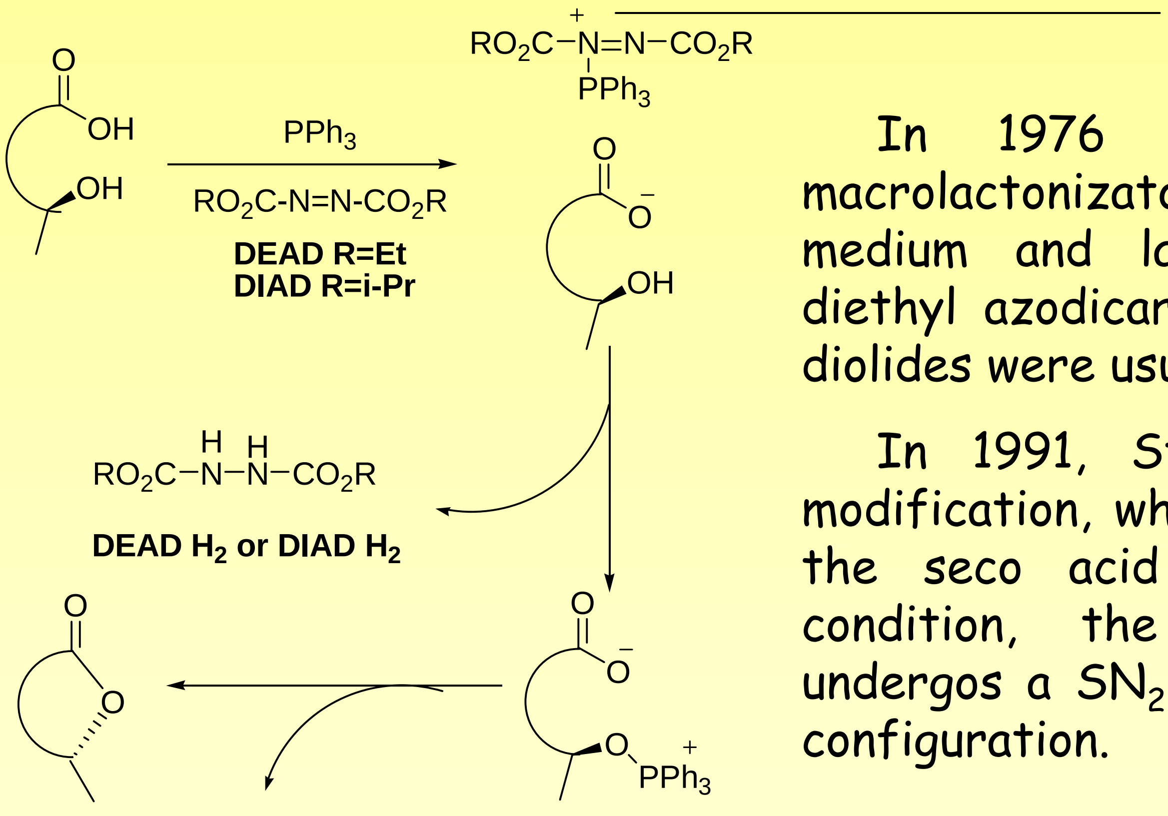
Iodo-lactonization

Epoxide ring-opening

Parenty, A.; Moreau, X.; Campagne, J.-M.; *Chem. Rev.* **2006**, *106*, 911.

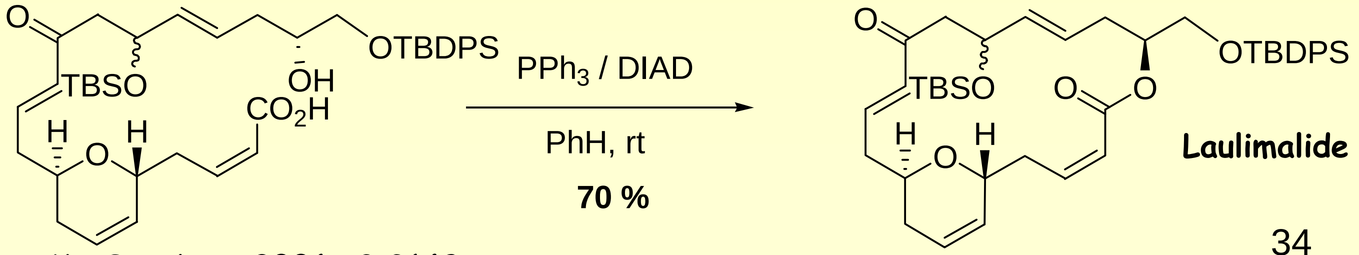
« Alcohol » Activation

Mitsunobu Reactions



In 1976 Mitsunobu described a macrolactonizaton protocol to obtain medium and large macrolactones. With diethyl azodicarboxylate (DEAD) and PPh$_3$ diolides were usually the major products.

In 1991, Steglich has introduced a modification, which is the slow addition of the seco acid to DEAD-PPh$_3$. In this condition, the alkoxyphosphonium salt undergos a SN$_2$ reaction with inversion of configuration.



Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149.
Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**,2455.

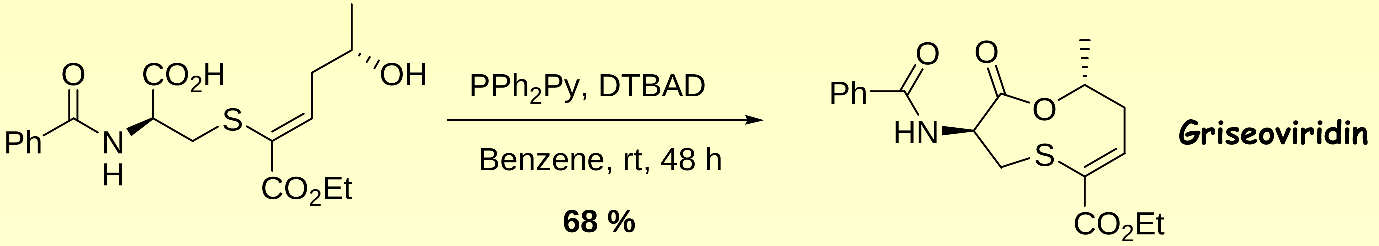
« Alcohol » Activation

Mitsunobu Reactions

In 1995 Evans used for the first time the DIAD at -10 °C in the Mitsunobu reaction.

To avoid the byproduct DIAD-H_2 or DEAD-H_2 and the PPh_3O, Marcantoni et al. used PPh_2Py (the oxide is water soluble) and *tert*-butyldiazodicarboxylate (DTBAD-H_2 decomposes into isoprene and CO_2).

The use of PS-supported reagents has also been described.



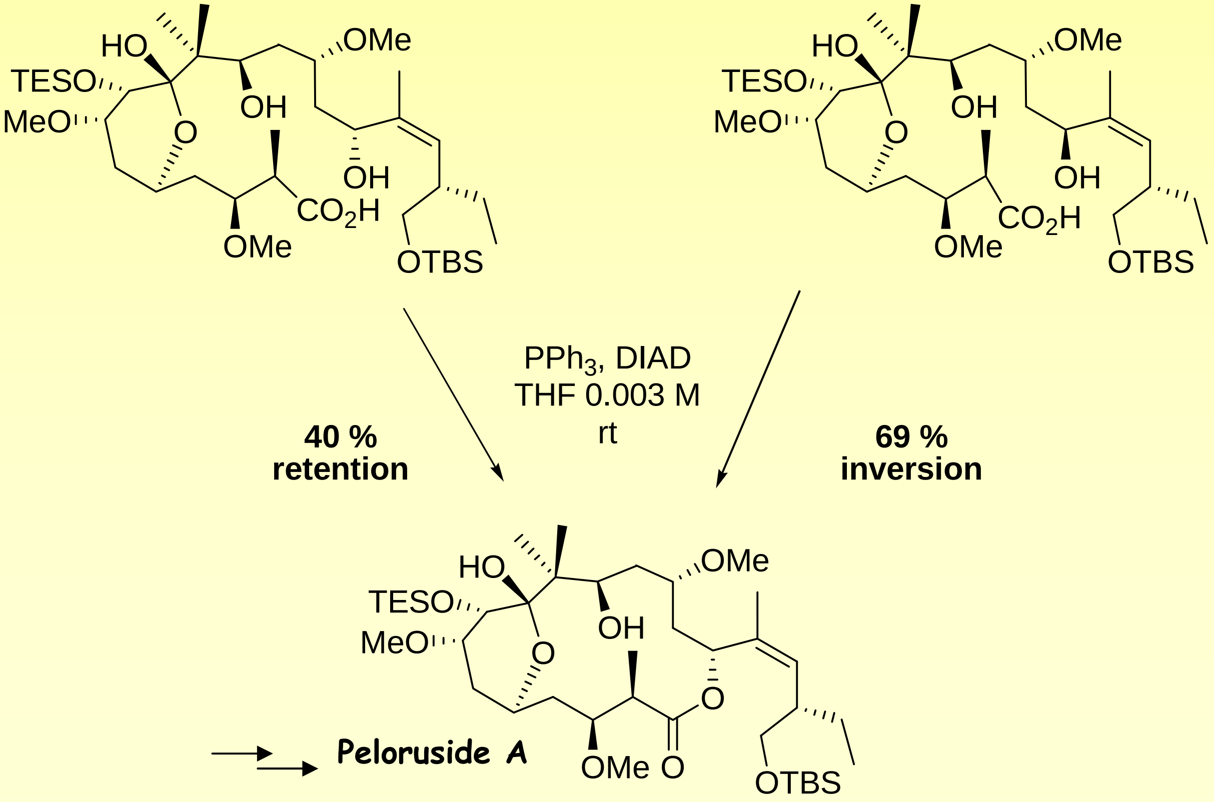
⇒ Many other phosphine/diazo pairs and solutions to purification problems have been used in intermolecular reactions.

Marcantoni, E.; Massaccesi, M.; Petrini, M.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2000**, *65*, 4553.

« Alcohol » Activation

Mitsunobu Reactions

In 2003 De Brabander obtained the same macrolactone from two epimers of a seco-acid. The retention of configuration can be explain by the formation of an acyloxyphosphonium derivative.


PPh_3, DIAD
THF 0.003 M
rt

40 %
retention

69 %
inversion

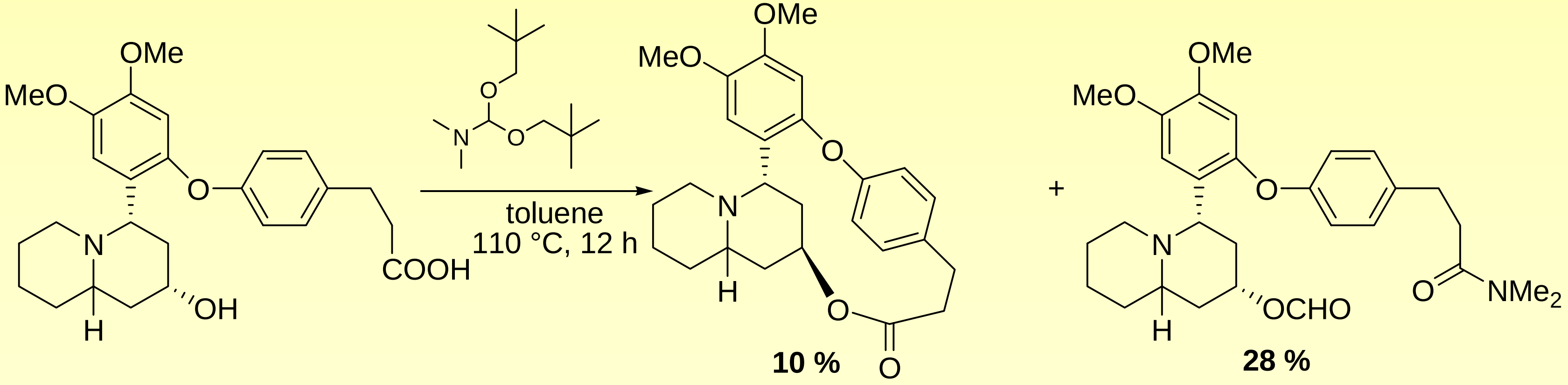
Peloruside A

Liao, X.; Wu, Y.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1648.

« Alcohol » Activation

Eschenmoser Reagent

The use of Eschenmoser esterification reagent has been described in the macrolactonization. But only one application in total synthesis of the quinolisidine gave low yield.



Quinolisidin

Vorbrueggen, H.; Krolikiewicz, K. *Angew. Chem., Int. Ed. Engl.* **1977**,*16*, 914.
Shishido, K.; Tanaka, K.; Fukumoto, K.; Kametani, T. *Chem. Pharm.Bull.* **1985**, *33*, 532.

« Alcohol » Activation

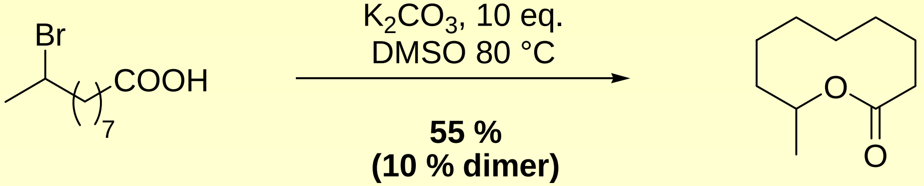
Through Alkylhalides and Mesylates

1. Alkylhalides

Macrolactonization of bromocarboxylic acid in the presence of potassium carbonate were first described in 1947 by Hunsdiecker and Erbach.

Later, iodo- and chloro- compounds and the influence of the base were also studied. This methodology has been applied to various syntheses.

Comparative studies have shown that this methodology is the most efficient to obtain 10-membered lactone model (55 %).



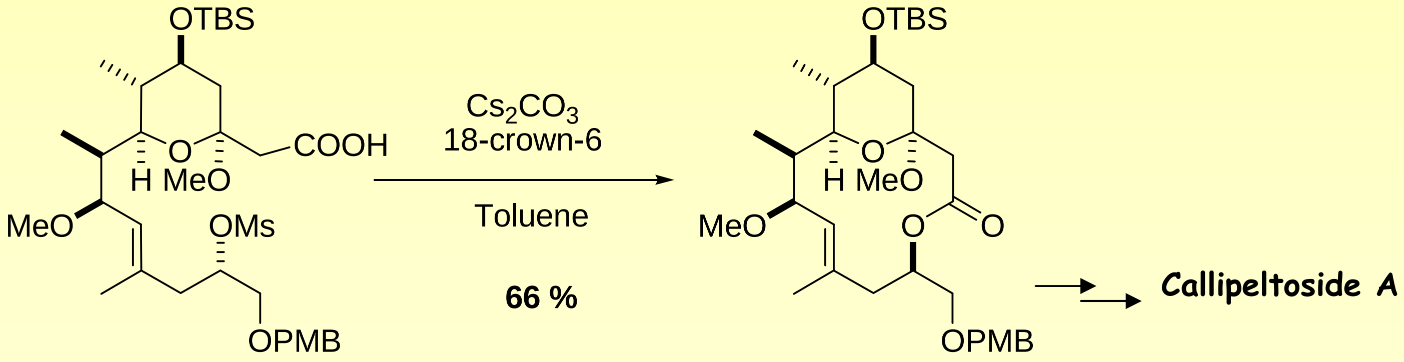
Bartra, M.; Vilarrasa, J. *J. Org. Chem.* 1991, *56*, 5132.

« Alcohol » Activation

Through Alkylhalides and Mesylates

2. Mesylates

Recently, Evans has published the total synthesis of callipeltoside A under alcohol activation by mesylate. In presence of Cs_2CO_3, the macrolactonization was carried out by a clean SN^2 inversion.

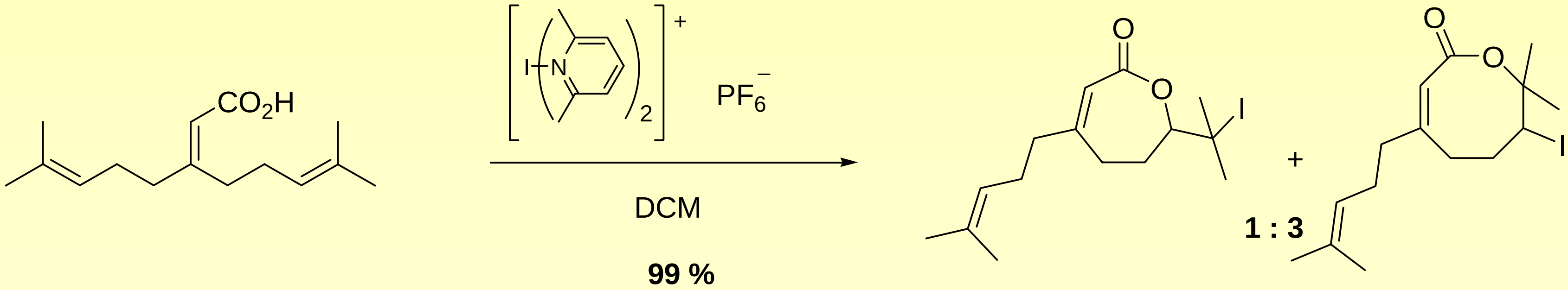


Evans, D. A.; Hu, E.; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, *124*, 5654.

« Alcohol » Activation

Iodo- Lactonization

The iodolactonization reactions are well-known process to obtain small rings. The lack of regioselectivity and slower reaction rates are the reasons why this methodology are less used for medium and large macrolactones.



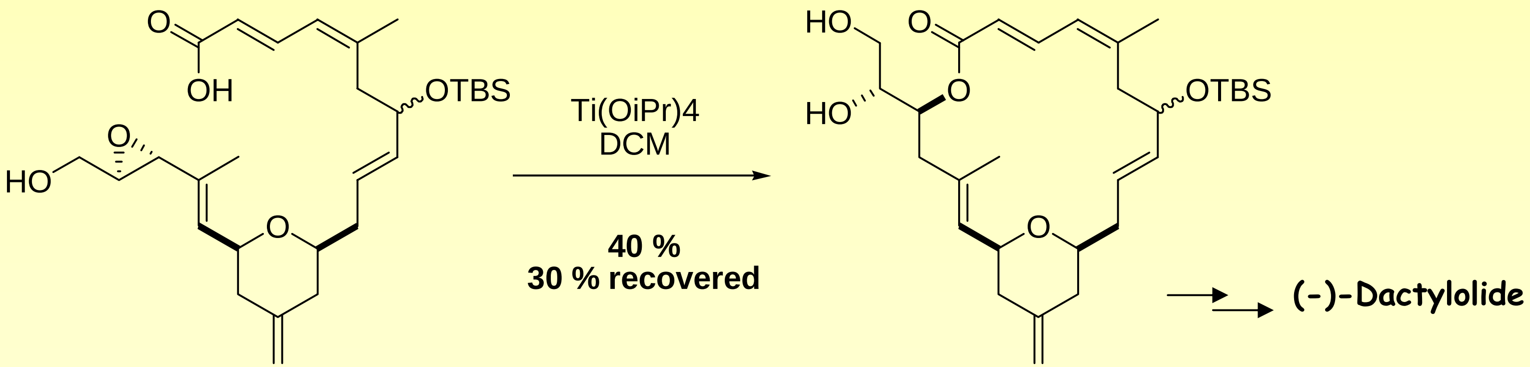
Bromolactonization using the corresponding bromide reagent have also been described with lower regioselectivities.

Rousseau, G.; Strzalko, T.; Roux, M.-C. *Tetrahedron Lett.* **2004**, *45*, 4503.

« Alcohol » Activation

Epoxide Ring-Opening

In 2003, Hoye used the Epoxide ring-opening method to finalize the total synthesis of the (-)-dactylolide.



Ti(OiPr)4
DCM

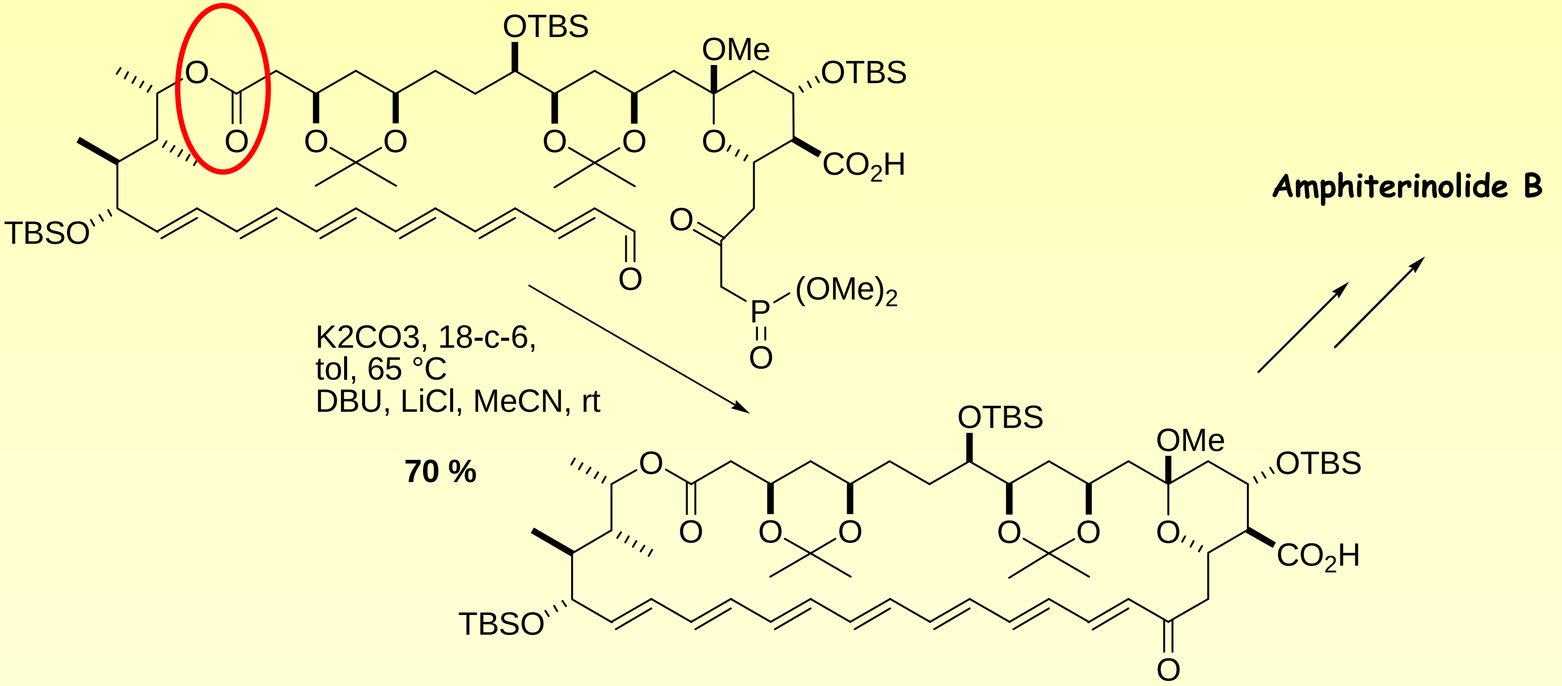
40 %
30 % recovered

(-)-Dactylolide

Hoye, T. R.; Hu, M. *J. Am. Chem. Soc.* **2003**, *125*, 9576.

Conclusion

Even through many other efficient macrocyclisation methods such as RCM, Intramolecular Cross-Coupling, Nozaki-Hiyama-Kishi, HWE methods have been developed over the years, the lactonization of seco-acids still appears to be one of the more frequently used approaches to obtain macrocyclic lactones.



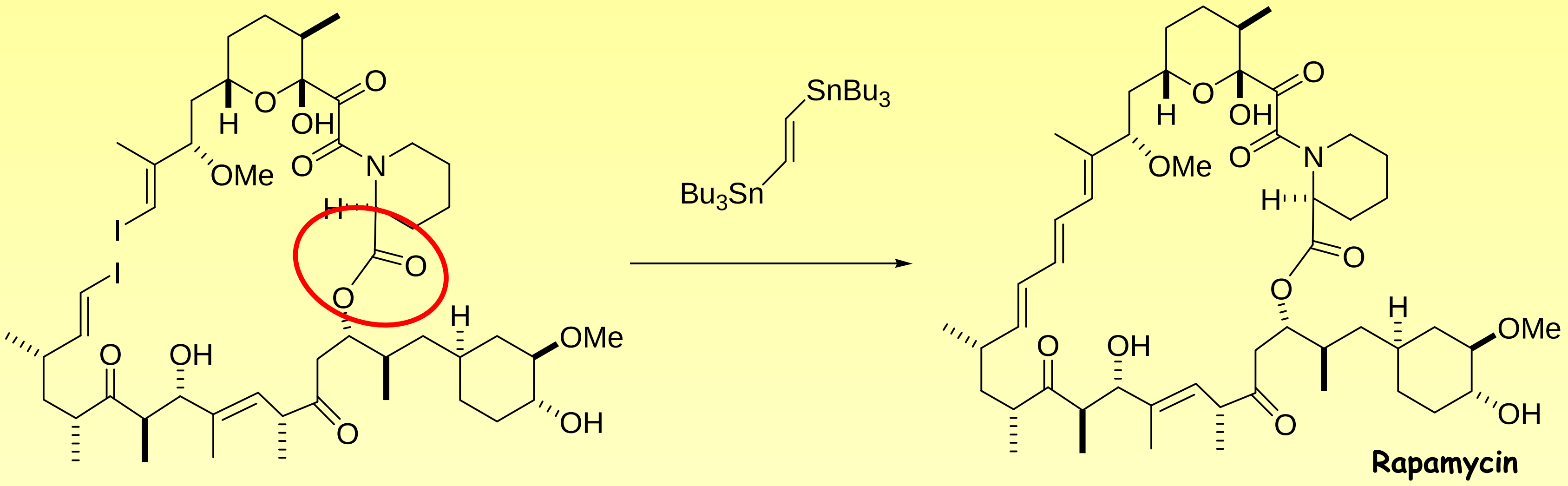
K2CO3, 18-c-6,
tol, 65 °C
DBU, LiCl, MeCN, rt

70 %

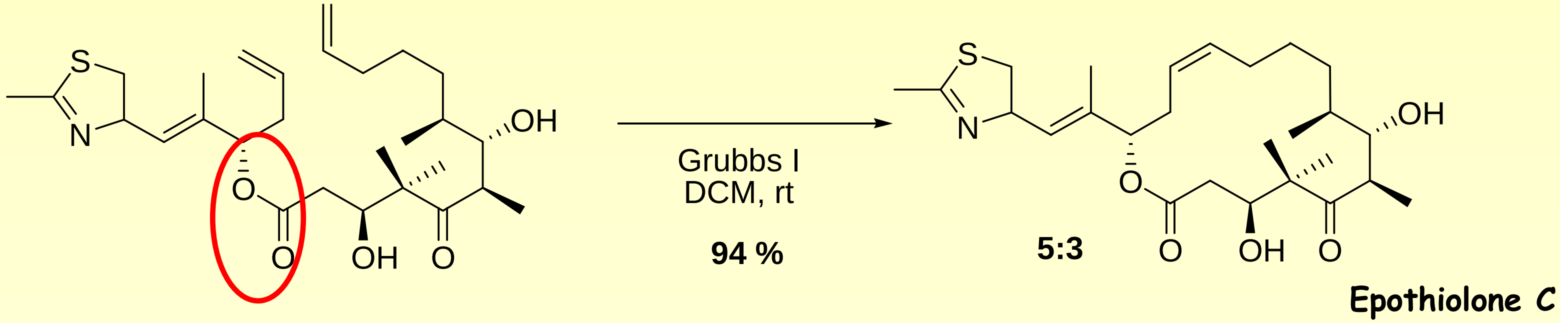
Amphiterinolide B

Nicolaou, K. C., Chakraborty, *Chem. Comm.* **1987**, 686.

Conclusion



Rapamycin



Epothilone C

Nicolaou, K. C., Chakraborty, T. K.; Piscopio, A.D. *J. Am. Chem. Soc.* **1993**, *115*, 4419.
Schinzer. *Angew. Chem., Int. Ed. Engl.* **1997**, 523.