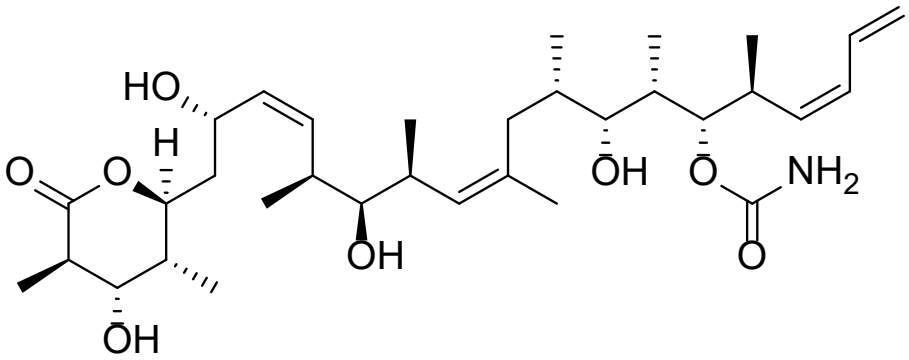
Total synthesis of Discodermolide

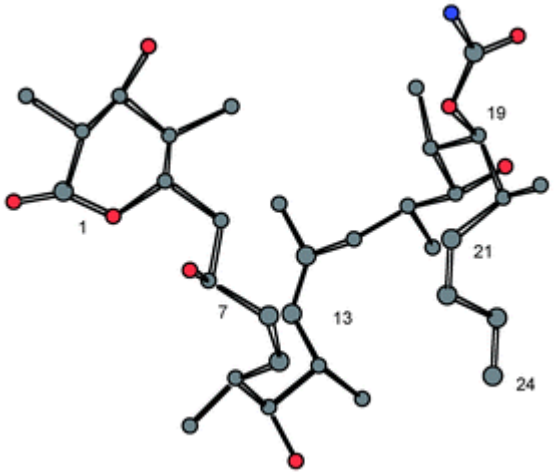
ORG. PROC. RES. DEV. **2004**, *8*, 92-130

PRODUCTION OF 60G OF DISCODERMOLIDE

NOVARTIS

Structure and properties





- Linear polypropionate containing 13 stereocenters
- Tetrasubstituted δ-lactone
- Alkenes of defined geometry
- U-shaped conformation

Natural source

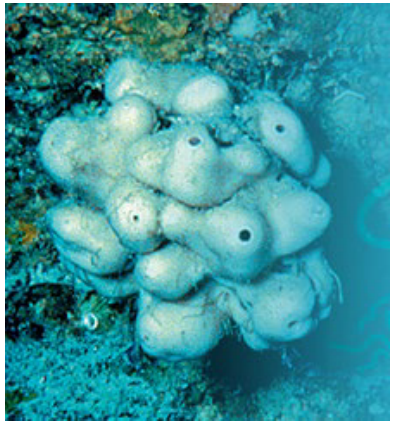
Caribbean deep-sea sponge

Isolated at the Harbor Branch Oceanographic Institution in 1990

0.002% w/w isolation yield from frozen sponge

Potent immunosuppressive agent

Potent cytotoxicity (microtubule stabilizing agent)



Historical overview

1990

Isolation / Harbor Branch Oceanographic Institution
J. Org. Chem. **1990**, *55*, 4912-4915
J. Org. Chem. **1991**, *56*, 1346 (correction)

1993

First Total Synthesis; S. Schreiber
J. Am. Chem. Soc. **1993**, *115*, 12621-12622

1998

Licensed by Novartis for development as a new-generation anticancer drug

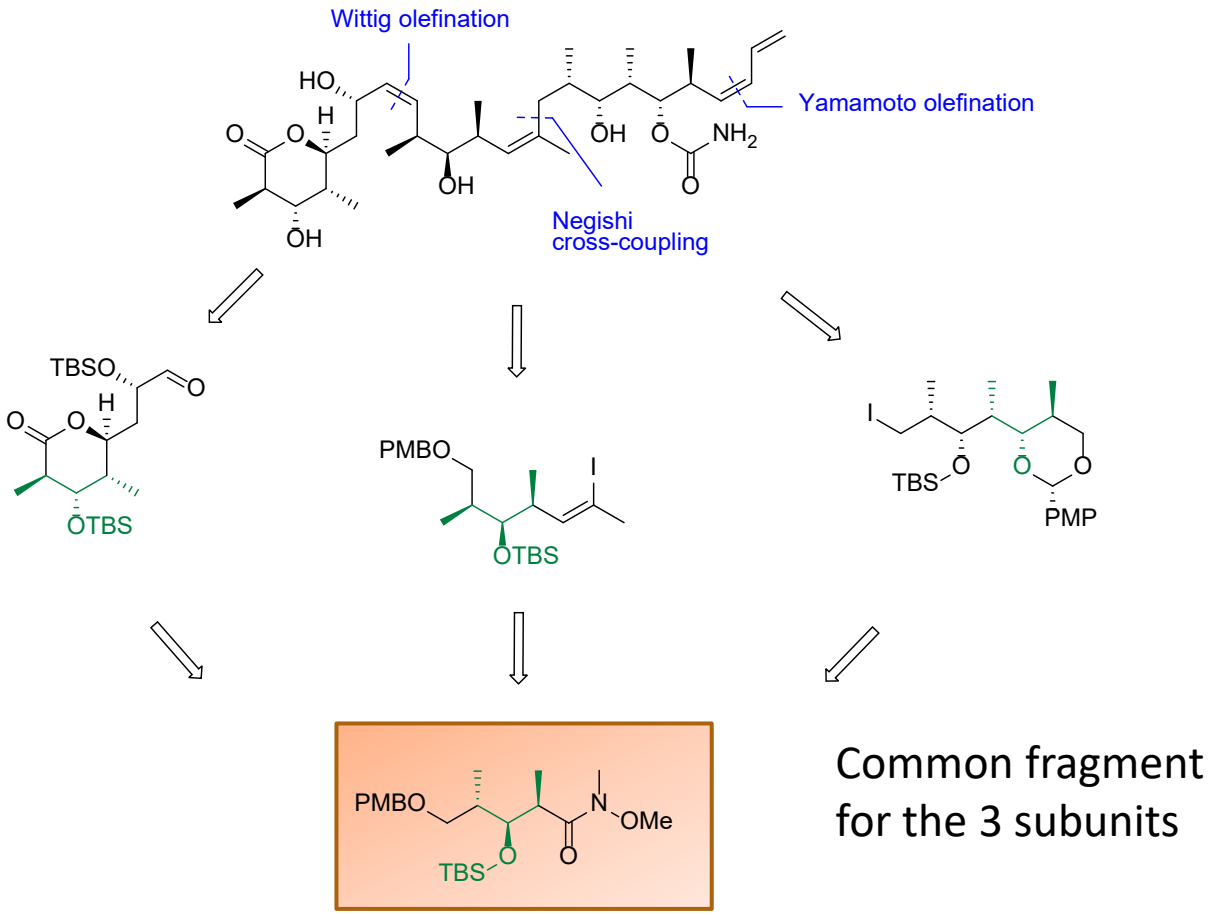
1999

First gram scale synthesis; A. B. Smith
Org. Lett. **1999**, *1*, 1823-1826

2004

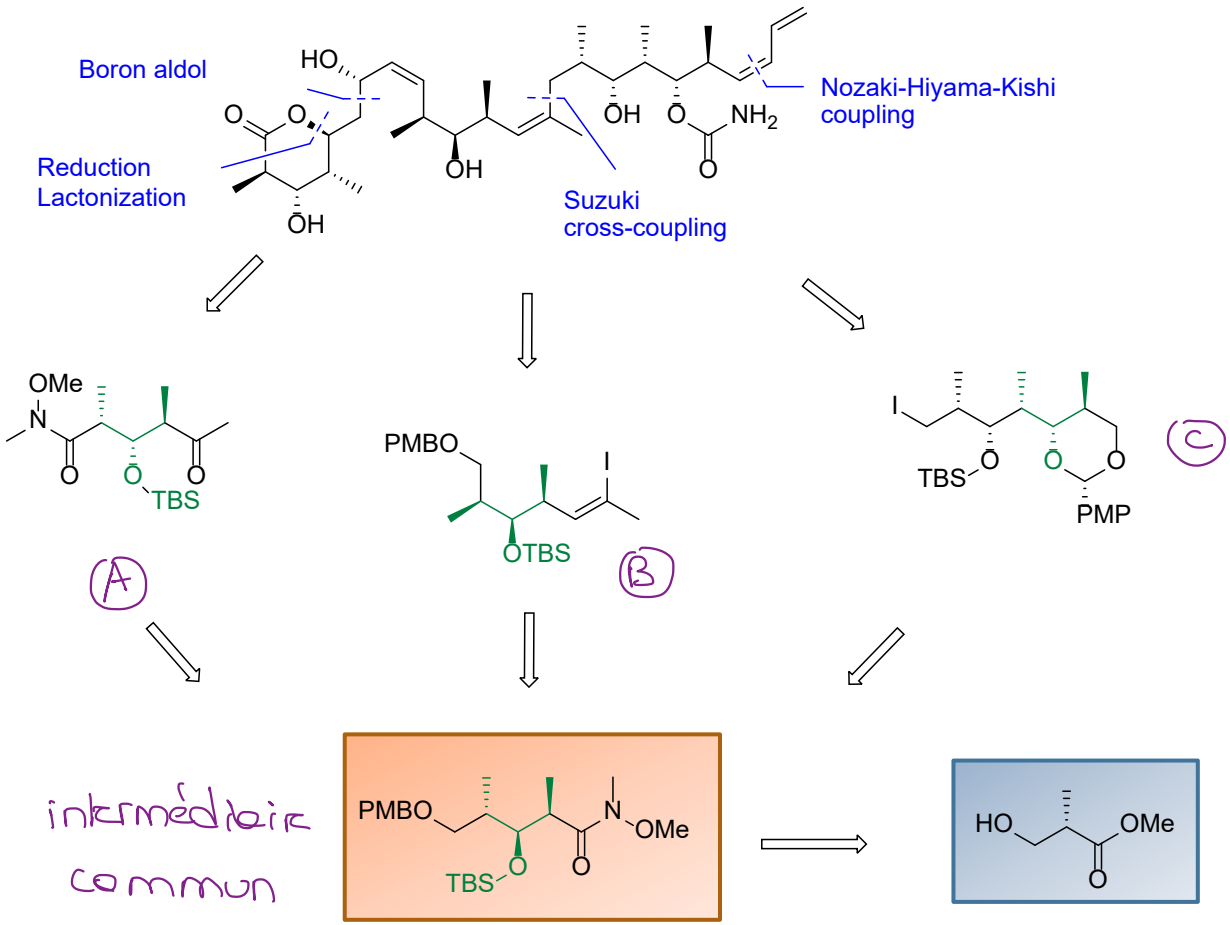
60 g scale synthesis; Novartis Process Group
Org. Res. Proc. Dev. **2004**, *8*, 92-130

Strategy of A. B. Smith, III



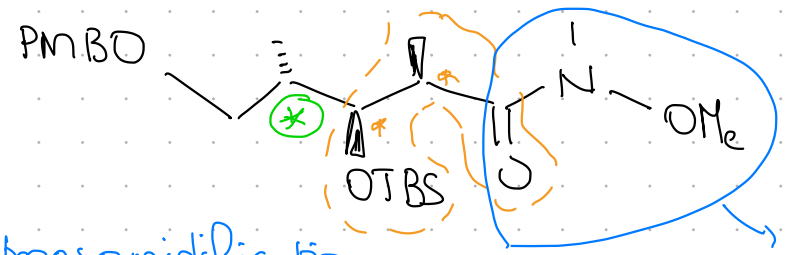
Common fragment for the 3 subunits

Strategy by Novartis



I- Synthèse de l'intermédiaire commun

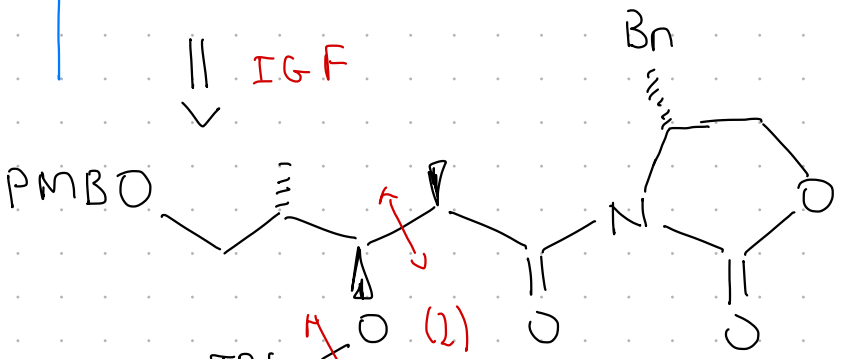
. Aldolisation diastéréosélective



transamidification

aldol

amide de Weinreb

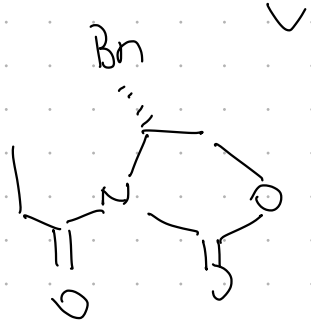


O-Si

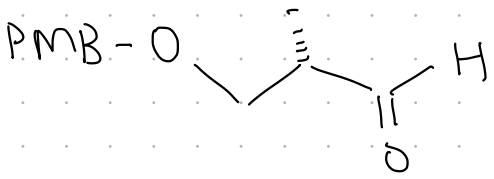
C-C

aldolisation

protection

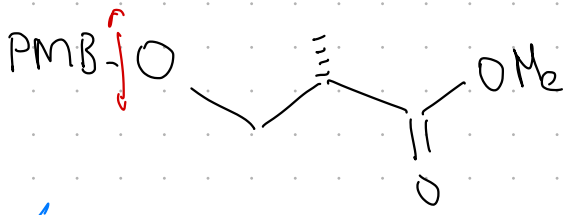


+



IGF

réduction [ox]

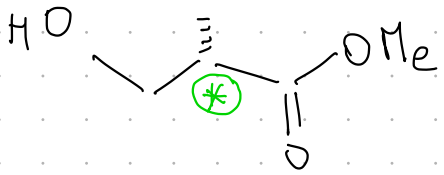


protection

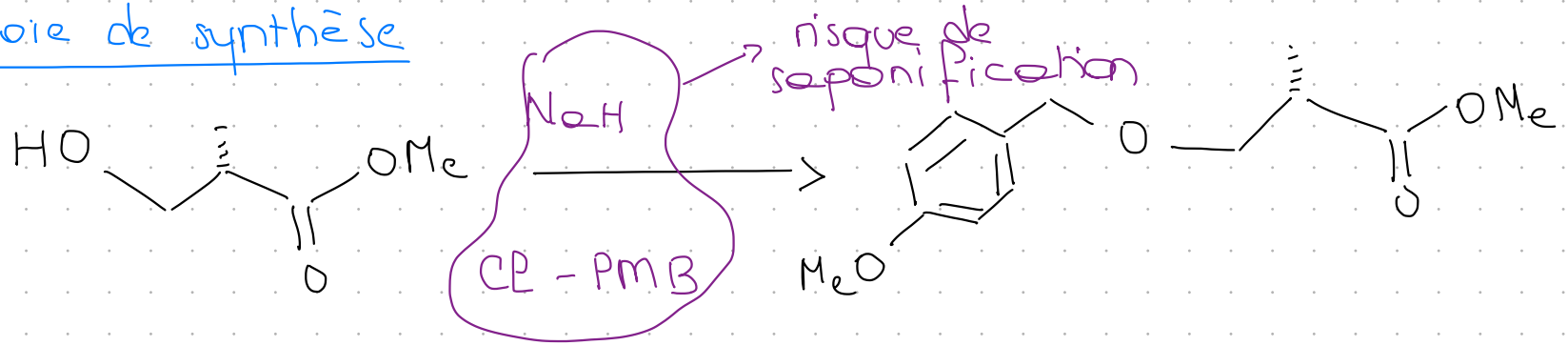
C-O

complète

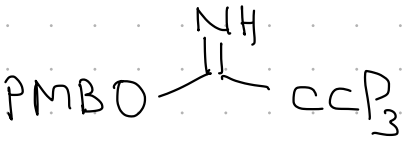
produit de départ



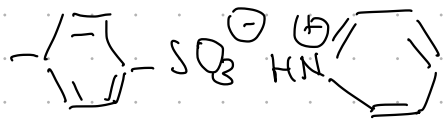
Voie de synthèse



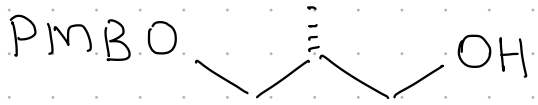
conditions réelles



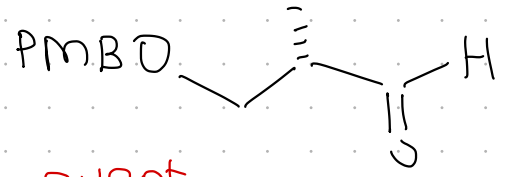
PPTS

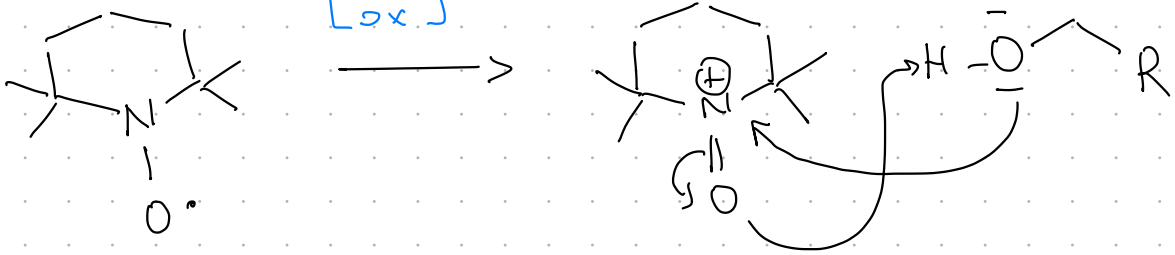
PPTS :  quant.

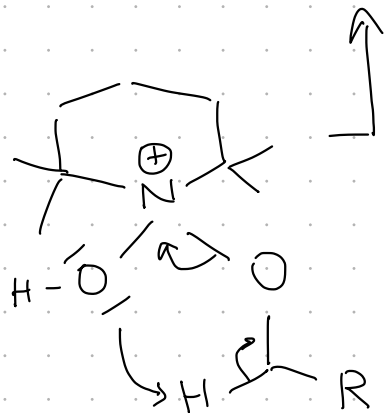
LiAlH4 ou LiBH4 → quant.

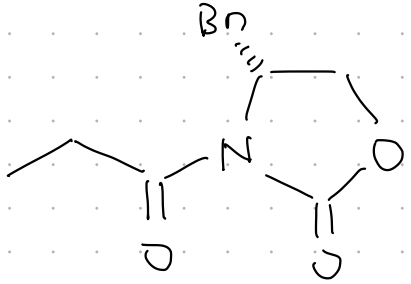


Swern ou TEMPO NaOCl → quant.

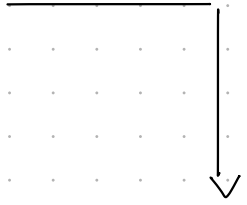


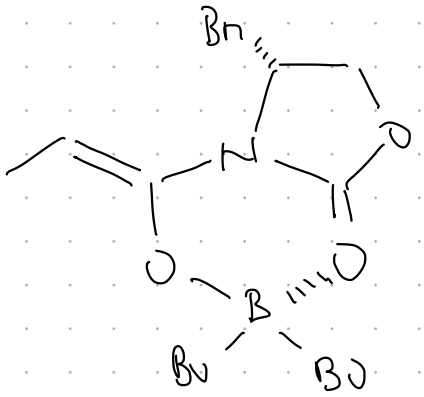




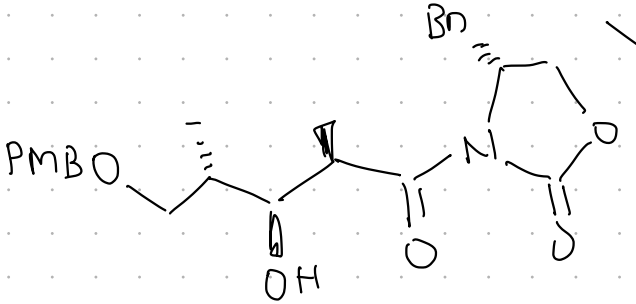


Bu_2BOTf, NEt_3

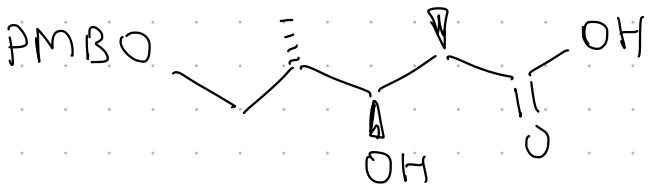




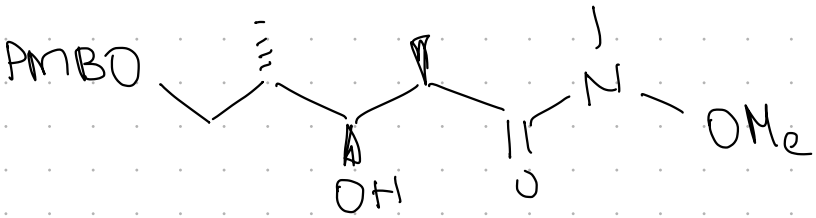
75 - 80 °C



LiOOH

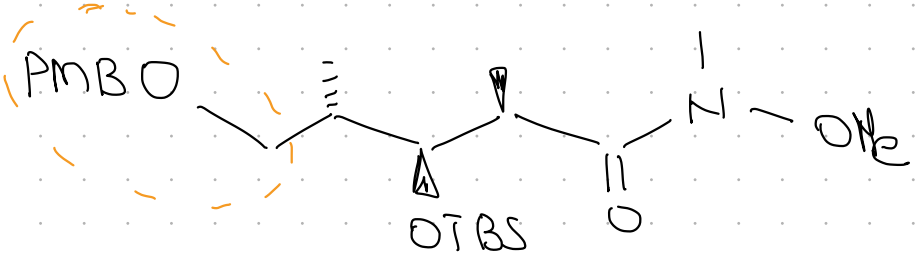


MeONHMe



TBSOTf

2,6-lutidine



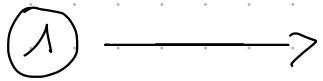
intermédiair commun

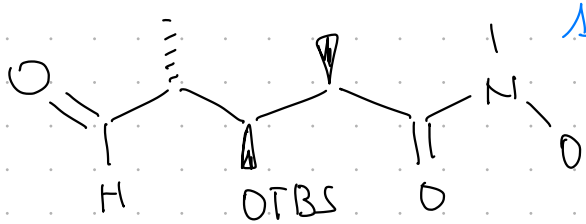
(1)

II - Synthèse du fragment (A)

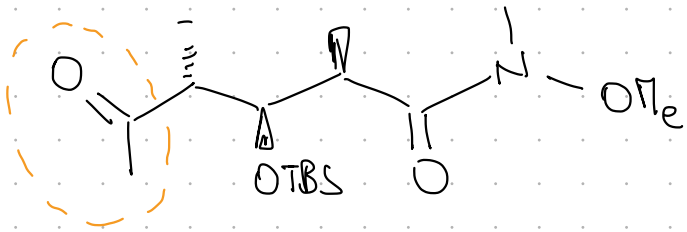
66% rdt global
2-3 kg

1. H_2 ; Pd/C cat.
2. TEMPO
$PhI(OAc)_2$





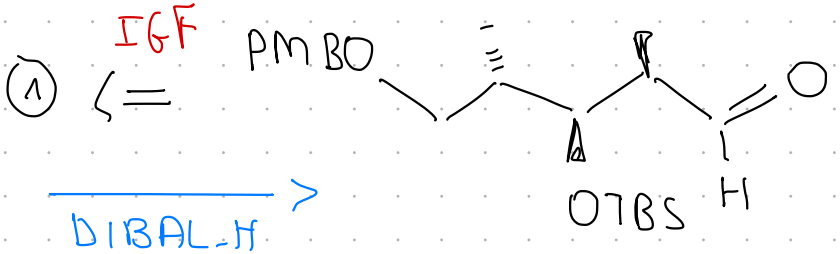
1. MeMgBr
2. SO_3 Pyr



(A)

III - Synthèse du fragment (B)

Z/E = 15/1

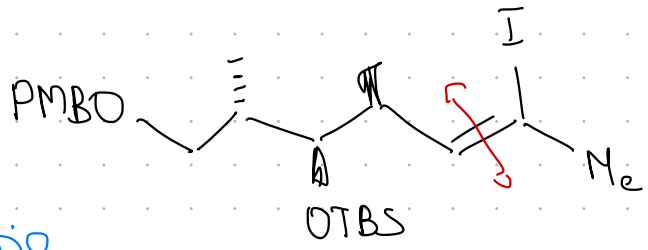


IGF

DIBAL-H
ou
Red-Al

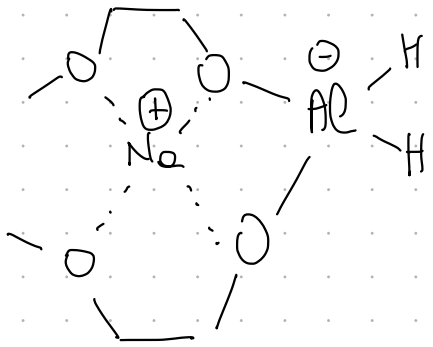
C-C

oléfination de Wittig

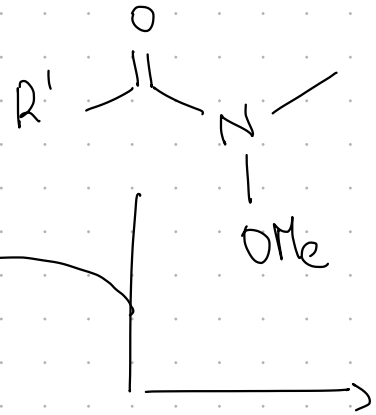


PPh_3P(I)(Me) ; NaHMDS

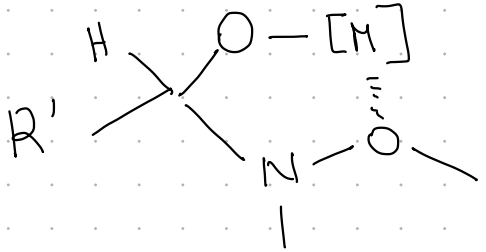
Red-Al



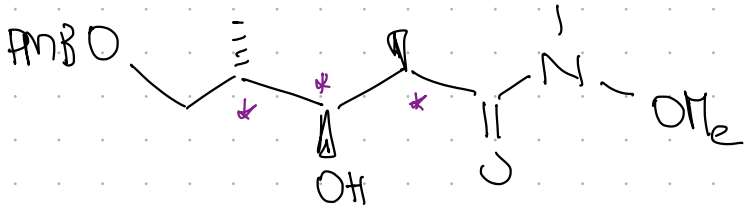
≡ [M]-H

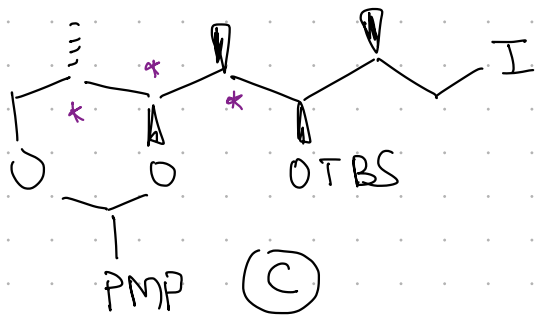


intermédiaire chélaté stable



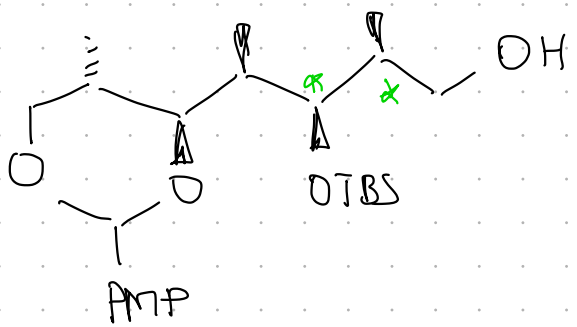
IV - Synthèse du fragment C



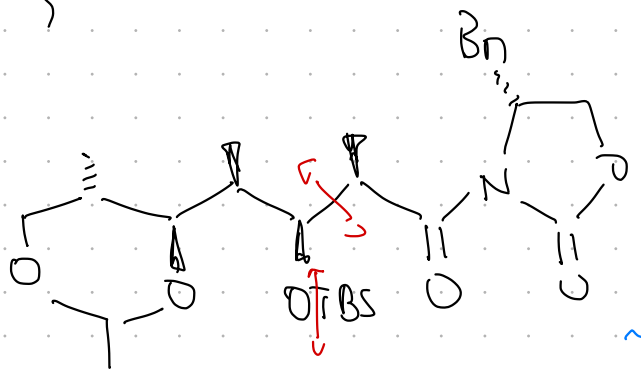


PMP : MeO

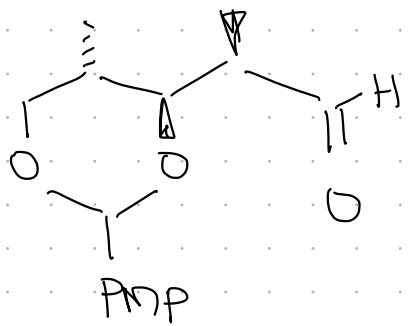
I_2, PPh_3, imidazole ⟵ IGF

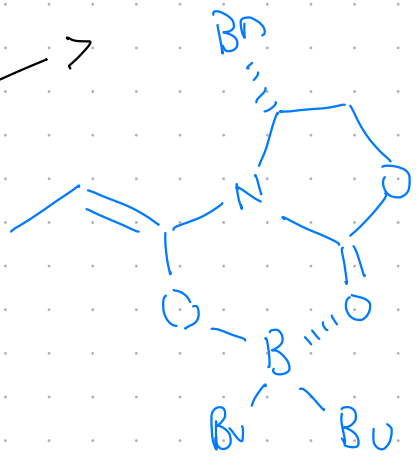


IGF ⟵ $LiBH_4$



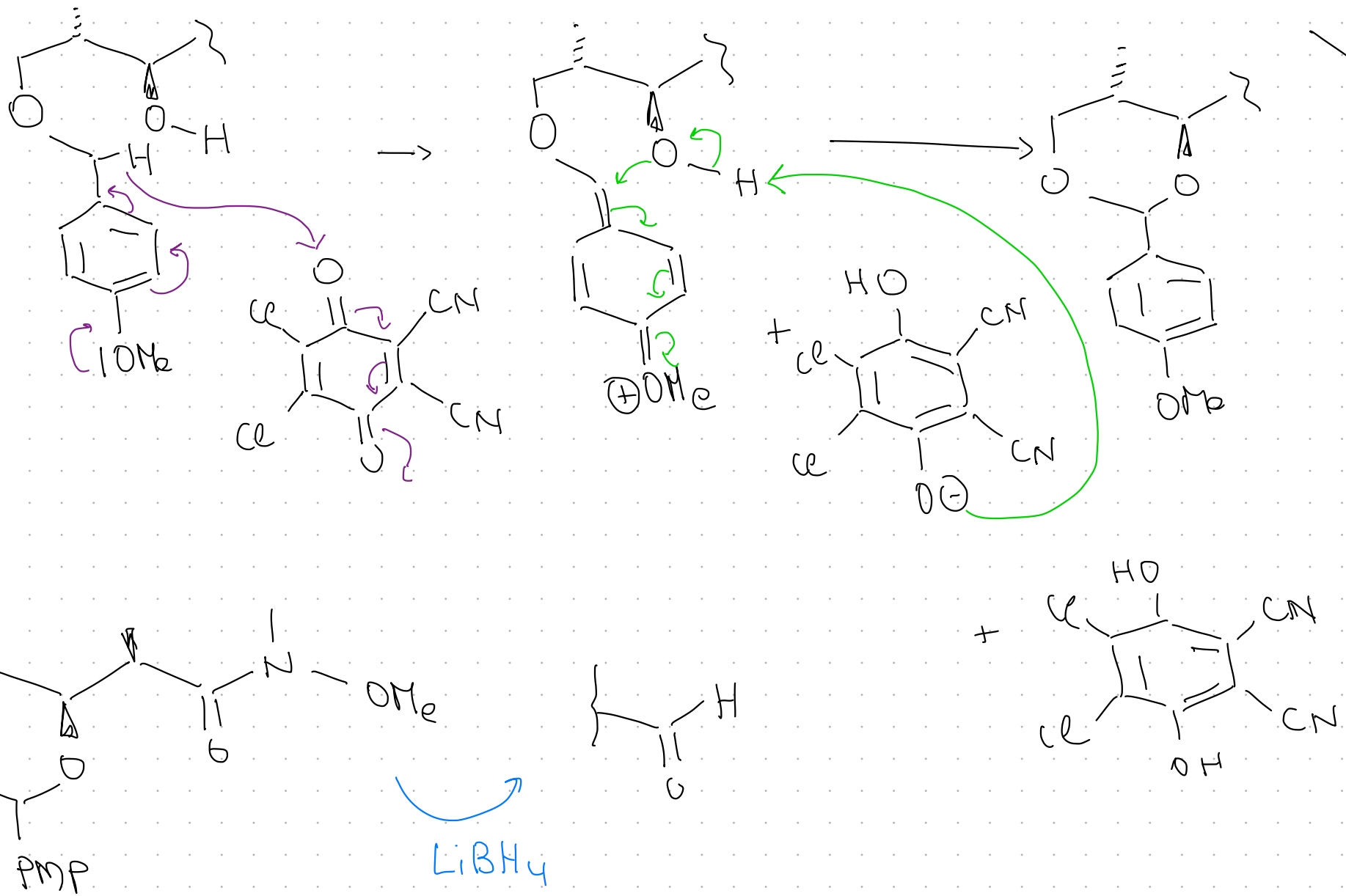
O-Si, C-C ⟸



1. 

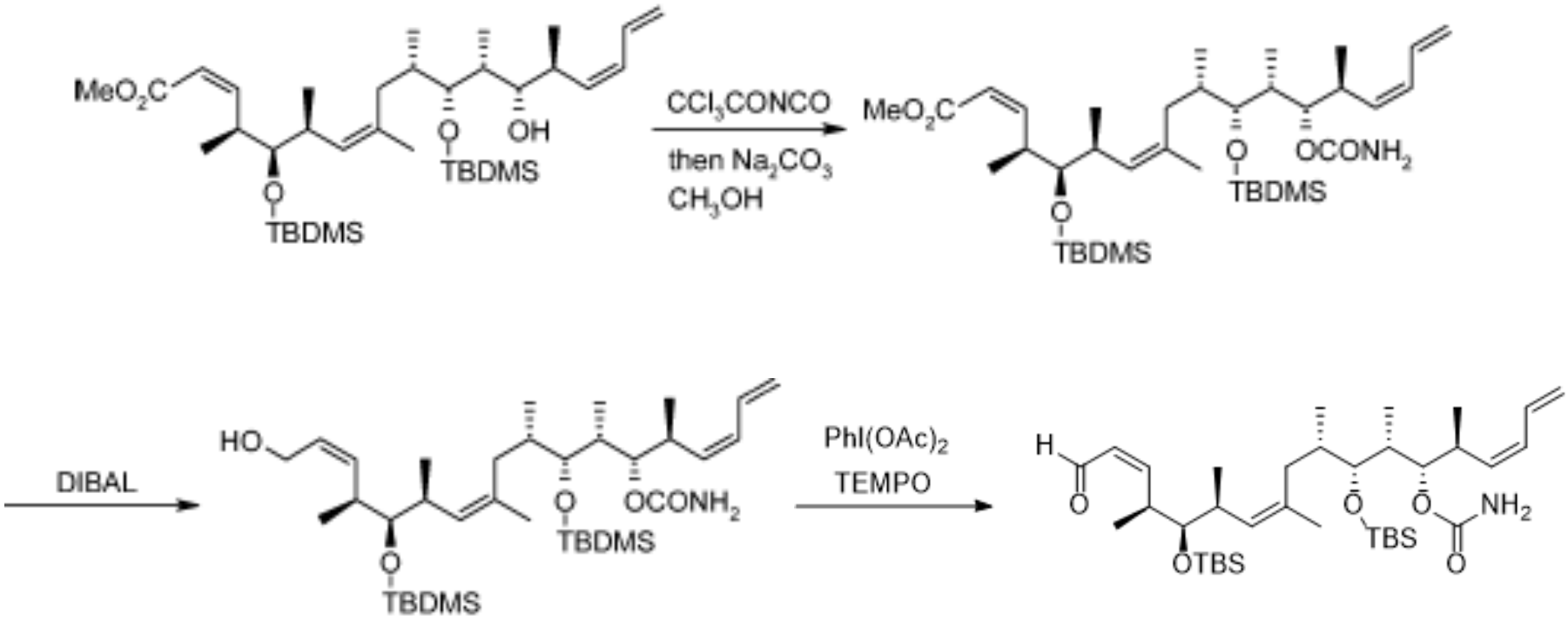
aldolisation stéréosélective

2. TBSOTf, 2,6-lutidine


OMe
CN
Cl
CN
Cl
OMe
HO
CN
Cl
CN
Cl
O
OMe
HO
CN
Cl
CN
Cl
OH

N
OMe
O
O
O
PMP
LiBH4
H
O

Final assembly



Final assembly