Synthesis of the entire carbon framework of the keracidin chromophore aglycon

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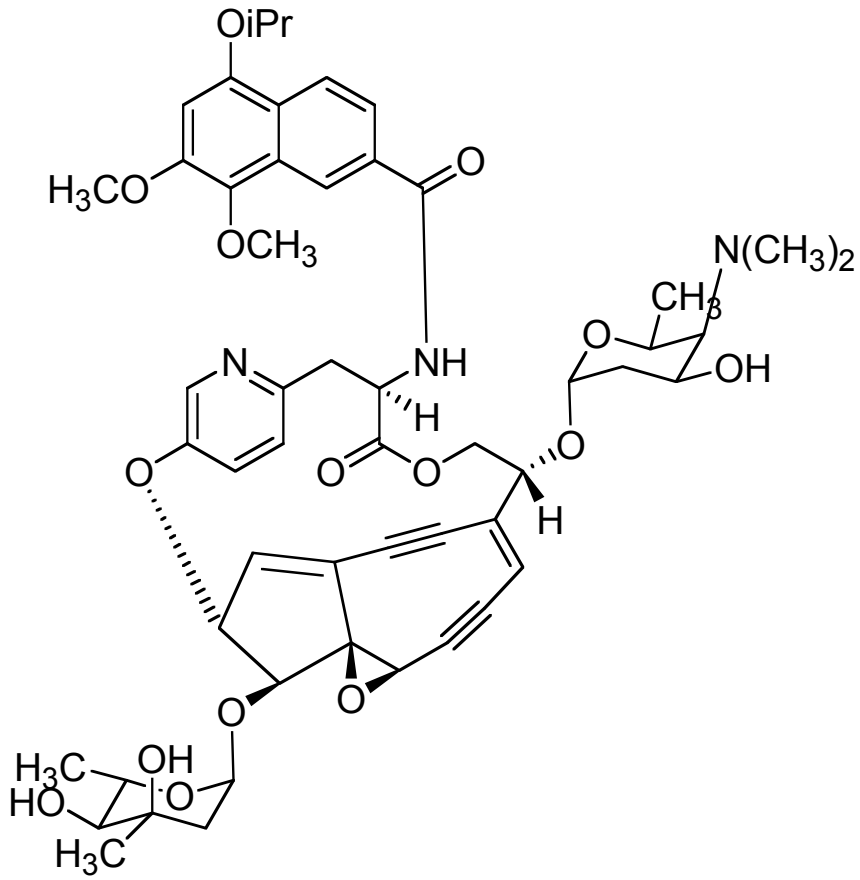
Kedarcidin

- Kedarcidin was isolated from fermentations of an actinomycete strain obtained Indian soil in 1991.
- Kedarcidin antitumour antibiotic, cytotoxic 9 membered enediyne chromophore
  - also shows activity against Gram-positive bacteria.
- The chromophore component determined by BMS in 1992 based on extensive spectroscopic analysis and degradation studies, complicated by low natural abundance and its high reactivity

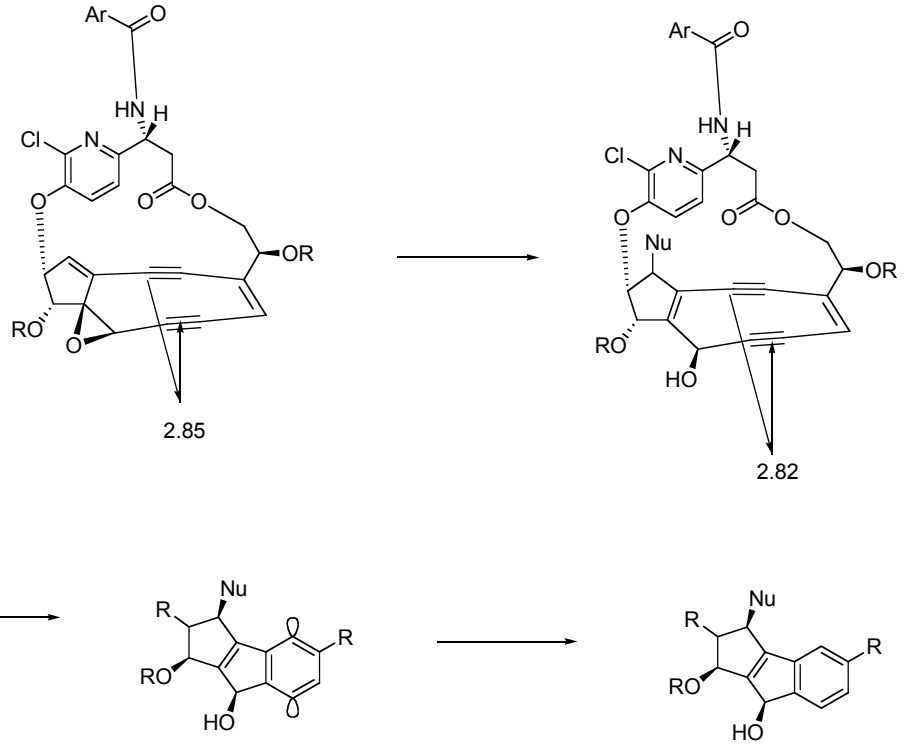
- Kedarcidin is composed of an acidic single chain polypeptide (114 residues) and a highly labile enediyne-containing chromophore

  - ASAAVSVSPA TGLADGATVT VSASGFATST SATALQCAIL ADGRGACNVA EFHDFSLSGG EGTTSVVVRR SFTGYVMPDG PEVGAVDCDT APGGCEIVVG GNTEEYENAA ISFE

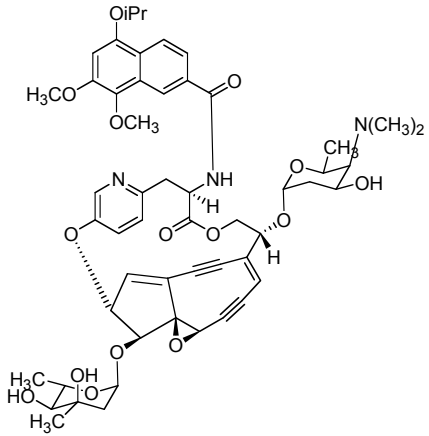


In-vitro Mechanism of action of Kerdacidin (BMS)

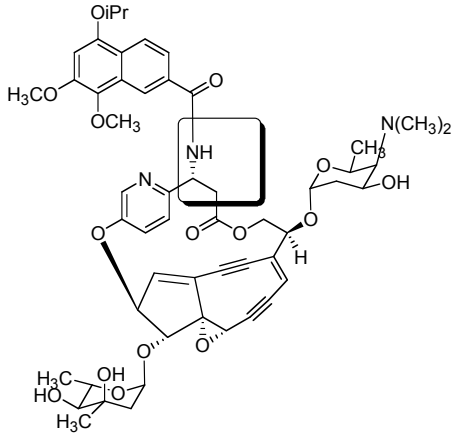
- Bonding between acetylenic carbons (2&7) is 2.85 A
  - Cycloaromatisation not possible as epoxide causes [3.3.0]-type TS
  - too strained
- Epoxide opening by attack at C-12 (2.82 A) allows the cycloaromatosation to now be energetically favourable
  - resulting in diradical
- Diradicals responsible for DNA damage



Questions arising synthesis – revision of structure

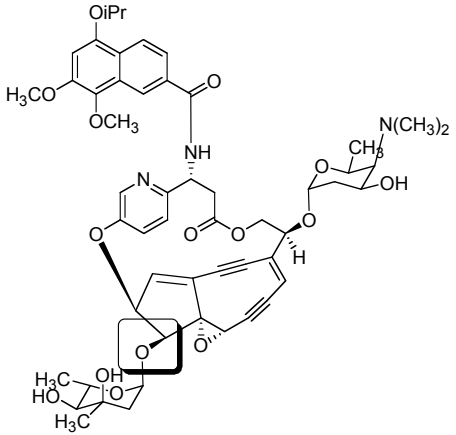


Original Structure



Hirama's revised structure (1997)

- Reversed handness of molecule
-α azatyrosyl residue of ansa bridge to β amino acid
-(based on degradation study of core moiety after synthesis)

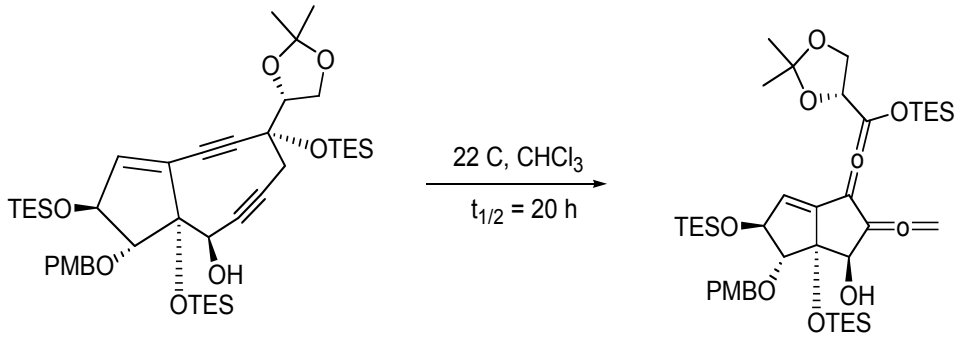


Myers's revised structure (2007)

- Stereochem of C10 (based on spectroscopic data of total synthesis)

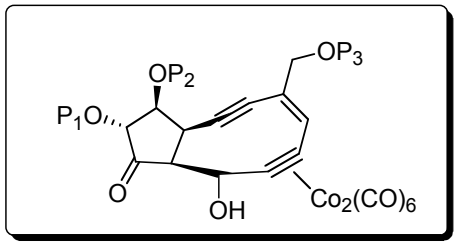
Synthetic Considerations

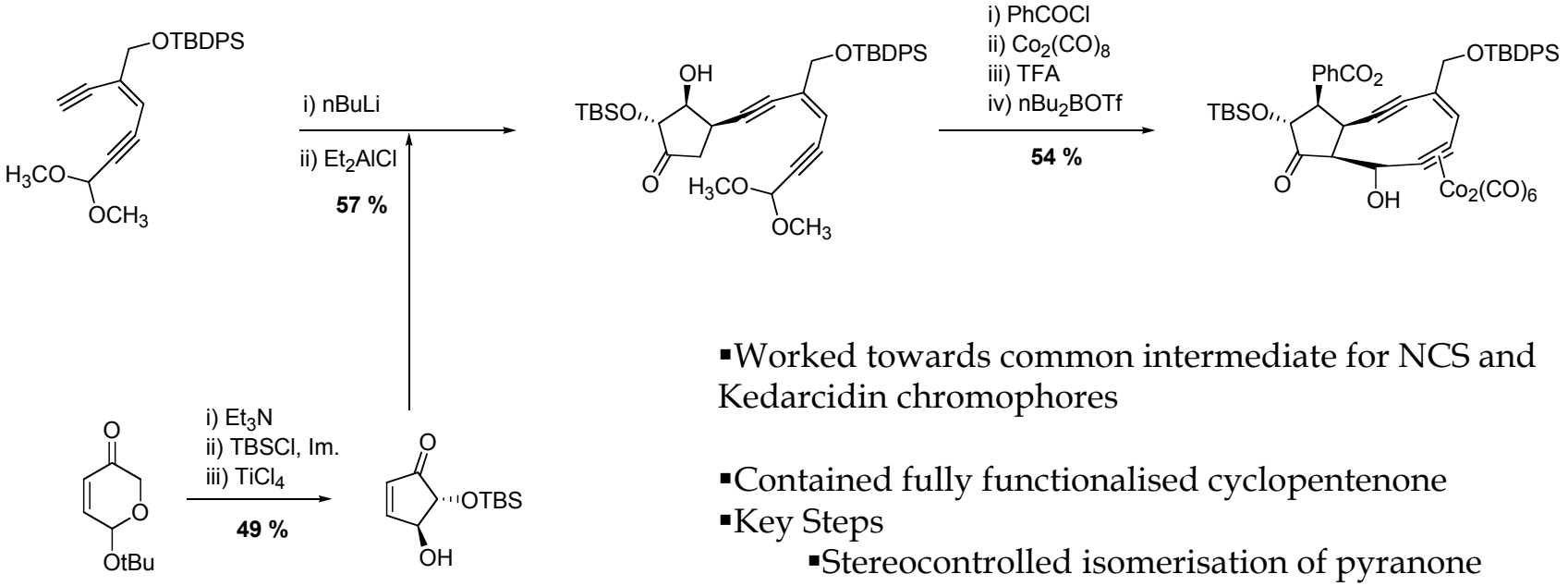
- High enthalpic and entropic barriers during construction of 9 membered bicyclic core
- Short bench life of strained diyne products (bond angles approx 160 ^{o})
- Can undergo spontaneous Bergmann cycloaromatisation or Cope rearrangements at room temps



- Require late stage installation of 9 membered ring
- Limited number of groups working towards total synthesis (Myers, Hirama, Magnus and Caddick)

Stereoselective Synthesis of Bicyclic Core - Caddick



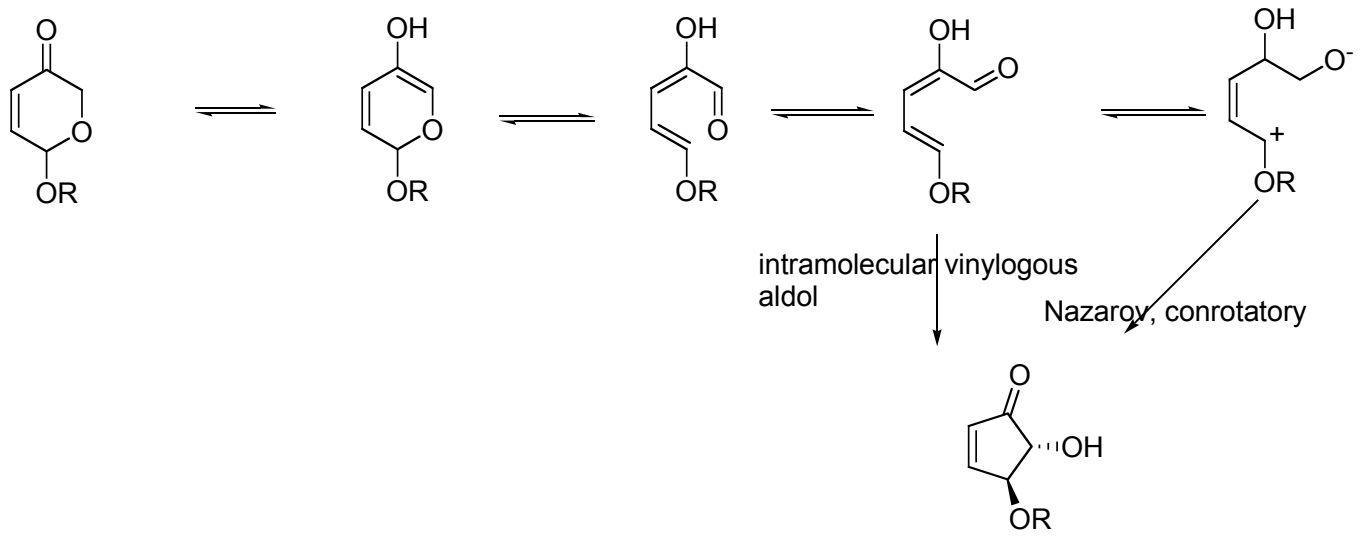


- Worked towards common intermediate for NCS and Kedarcidin chromophores

- Contained fully functionalised cyclopentenone
- Key Steps
  - Stereocontrolled isomerisation of pyranone
  - Regioselective alkyne complexation
  - Stereoselective intramolecular Aldol

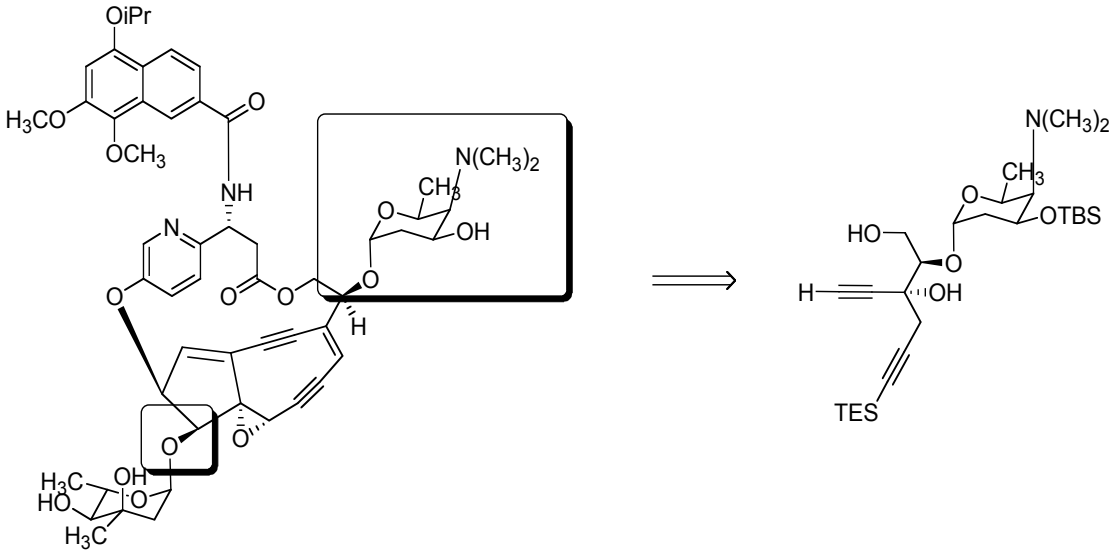
- Magnus *et al* use similar strategy to access core

Ring Contraction Mechanism

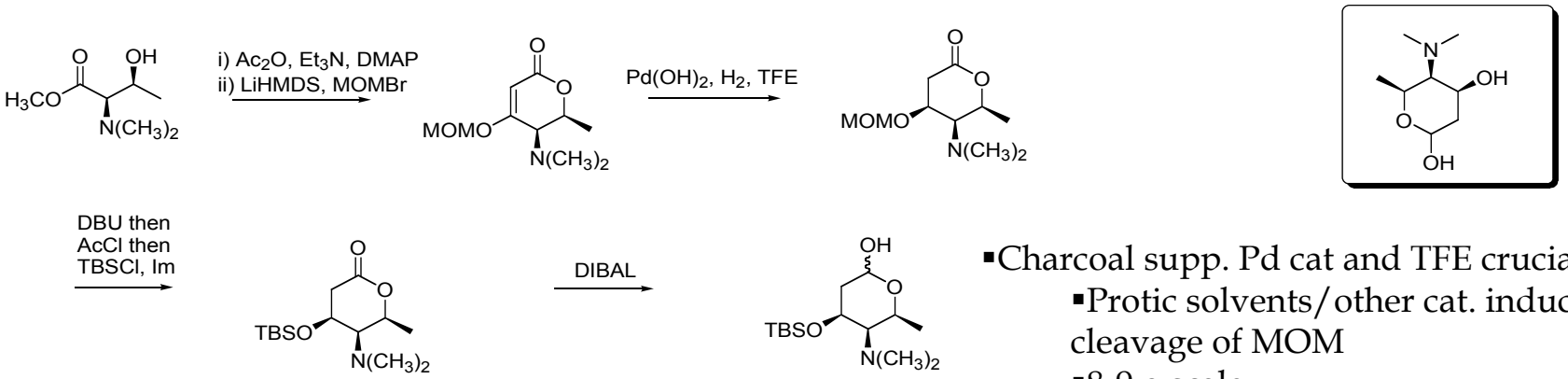


Total Synthesis - Myers

- Marcocyclic Transannulation
- Retrosynthetic analysis identified advanced precursor
  - Rare amino sugar –L-kedarosamine
  - Chromophore precursor
- Gram quantity synthesis of advanced intermediate

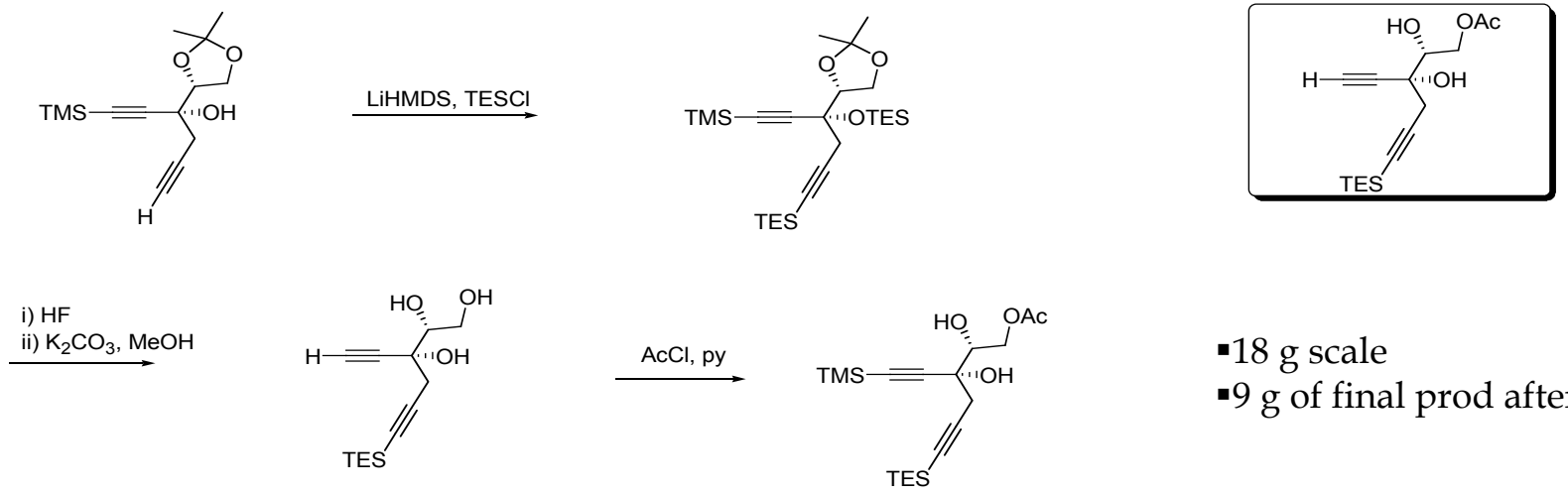


Synthesis of L-Kedarosamine



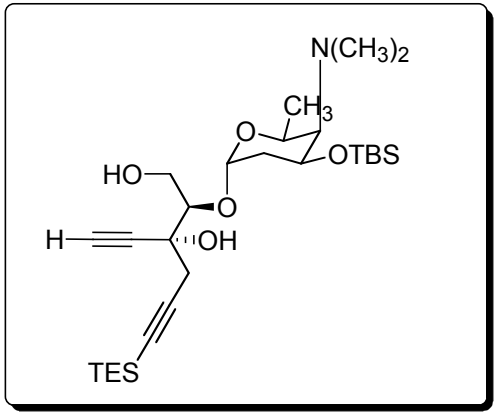
- Charcoal supp. Pd cat and TFE crucial
  - Protic solvents/other cat. induced reductive cleavage of MOM
  - 8-9 g scale

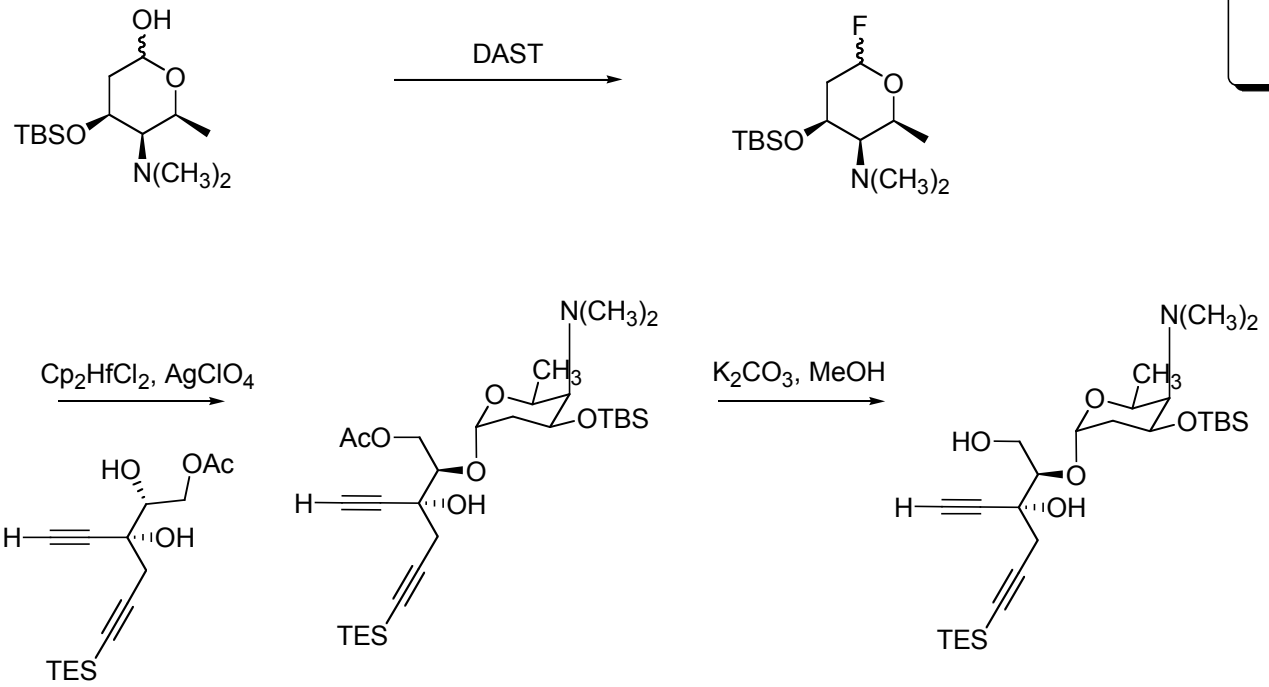
Synthesis of Dialkynyl Diol



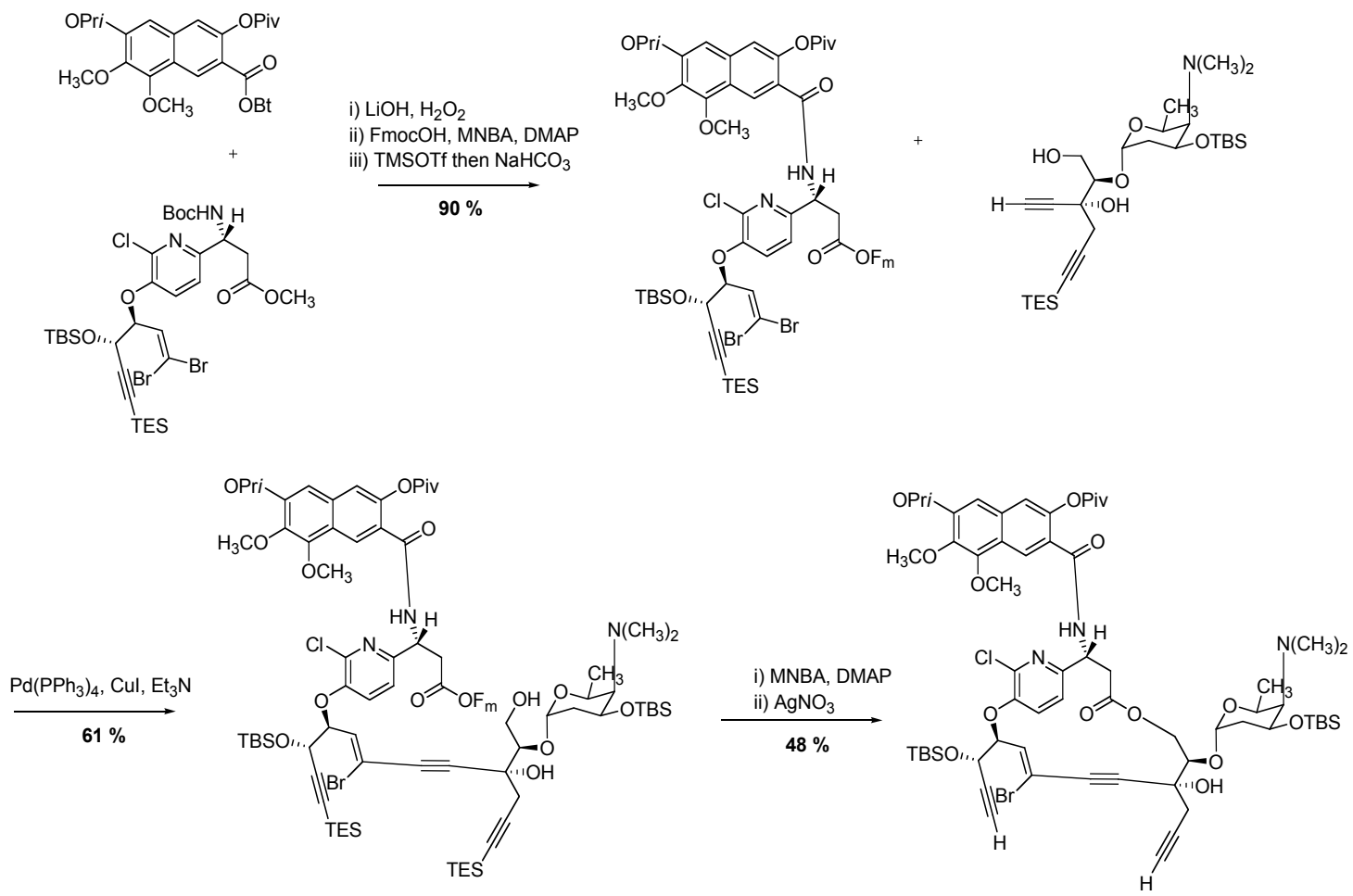
- 18 g scale
- 9 g of final prod after chrom.

Synthesis of Kedarcidin Chromophore Precursor

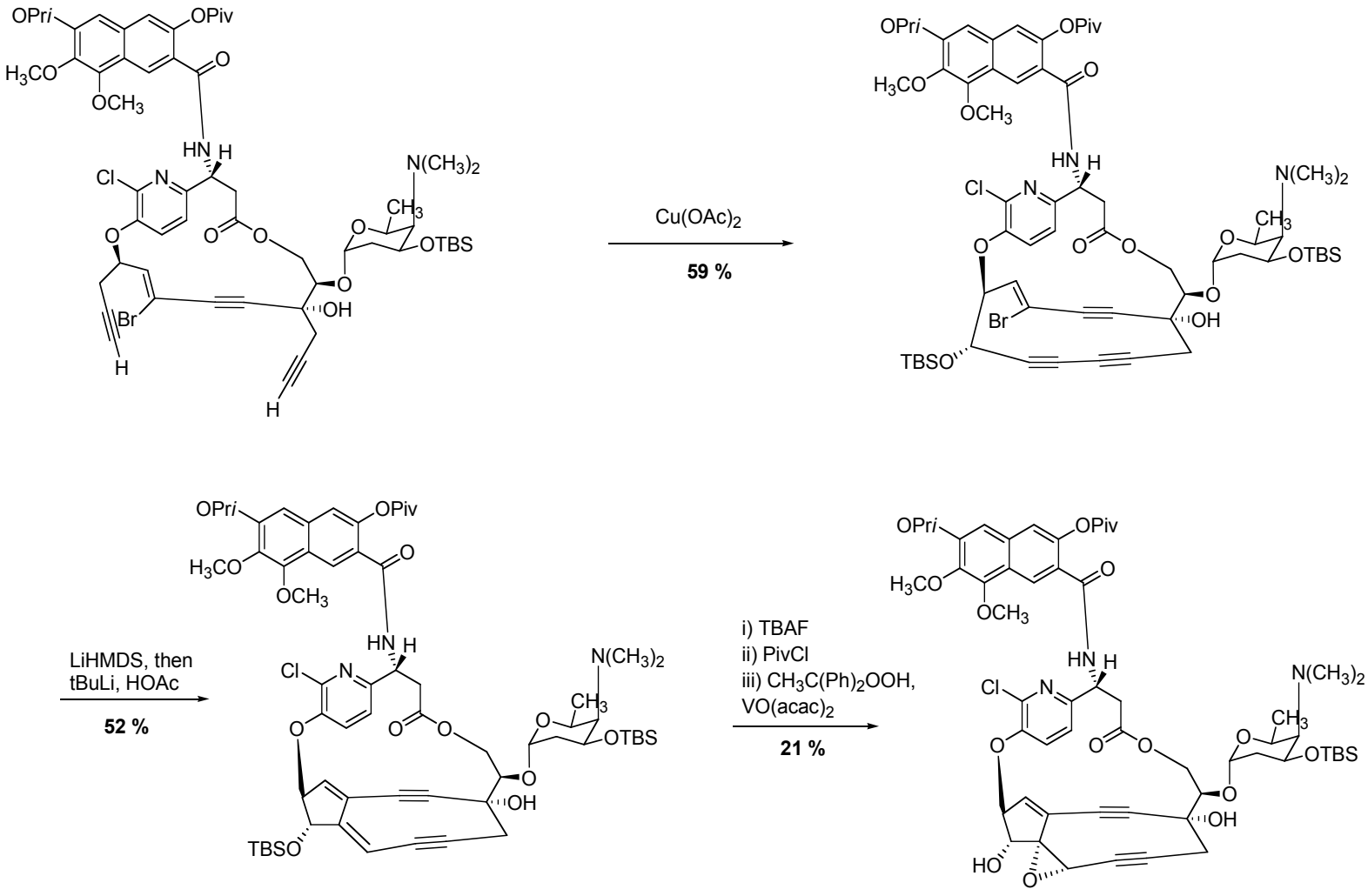




- Alpha selective glycosidic coupling – glycosyl fluoride most effective
  - Not stable to chromatography (used crude)
  - 60 % over 3 steps on 1.2 g scale

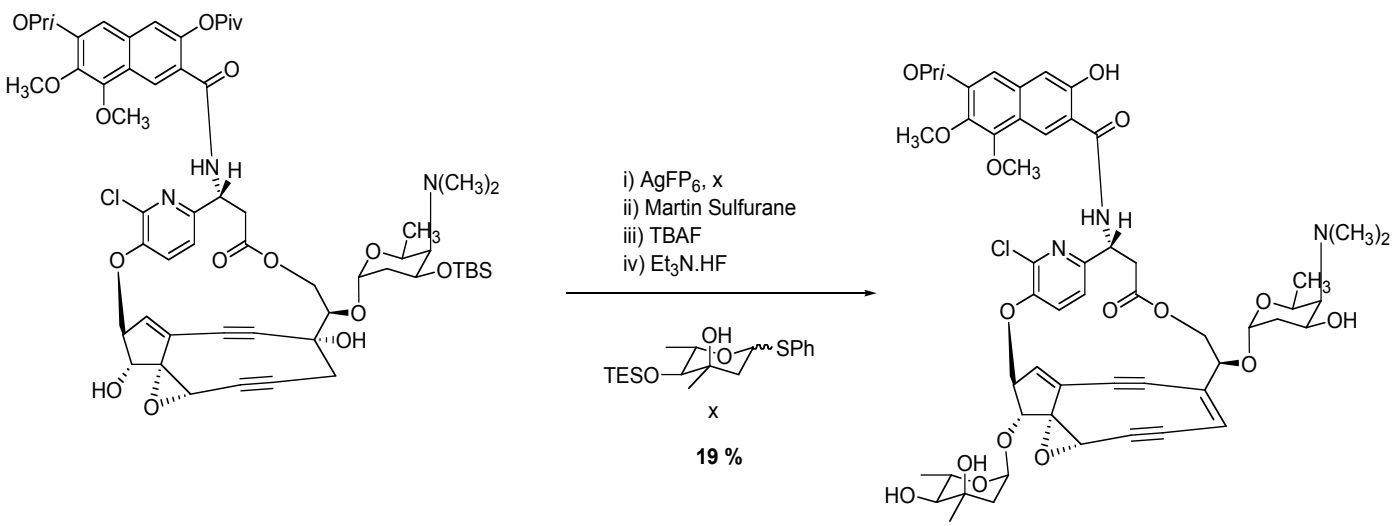


- Piv group selected to allow mild, fluoride-based deprotection
- Shiina macrolactonisation – preformed on gram scale



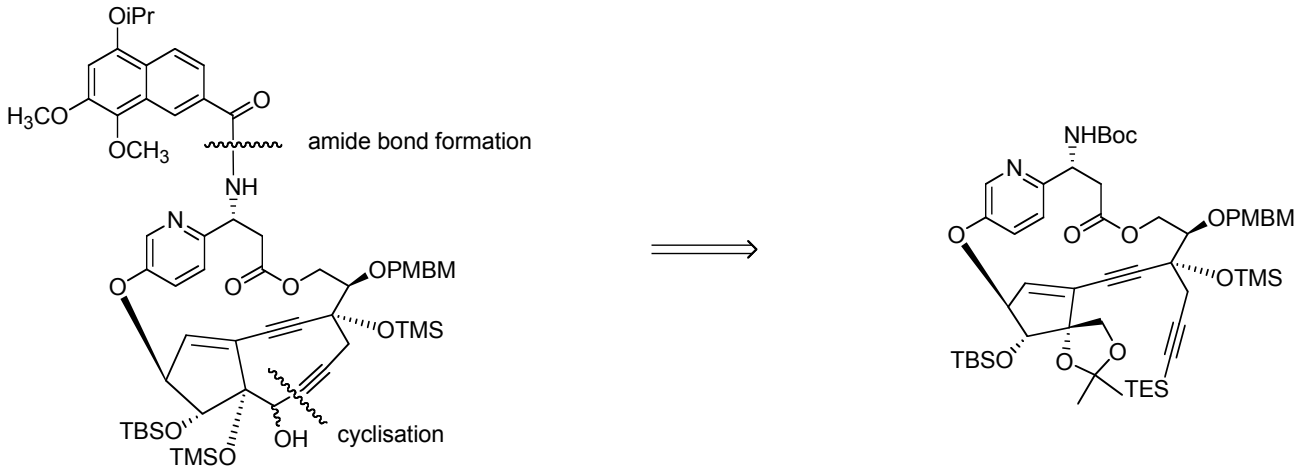
- Macrocyclisation – modified Eglinton cond.
  - Product extremely unstable – directly subjected to transannular cyclisation

- V directed epoxidation only successful with hindered oxygen source
  - Confirmed by nOe expt.

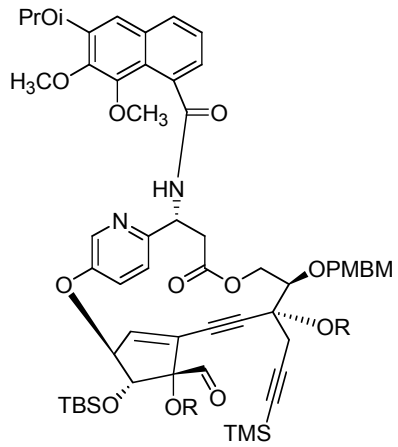


- First total synthesis
  - Intramolecular Songashira coupling (61 %)
  - Two macrolactonisation reactions (66 % and 59 %)
- Corrected overall structure

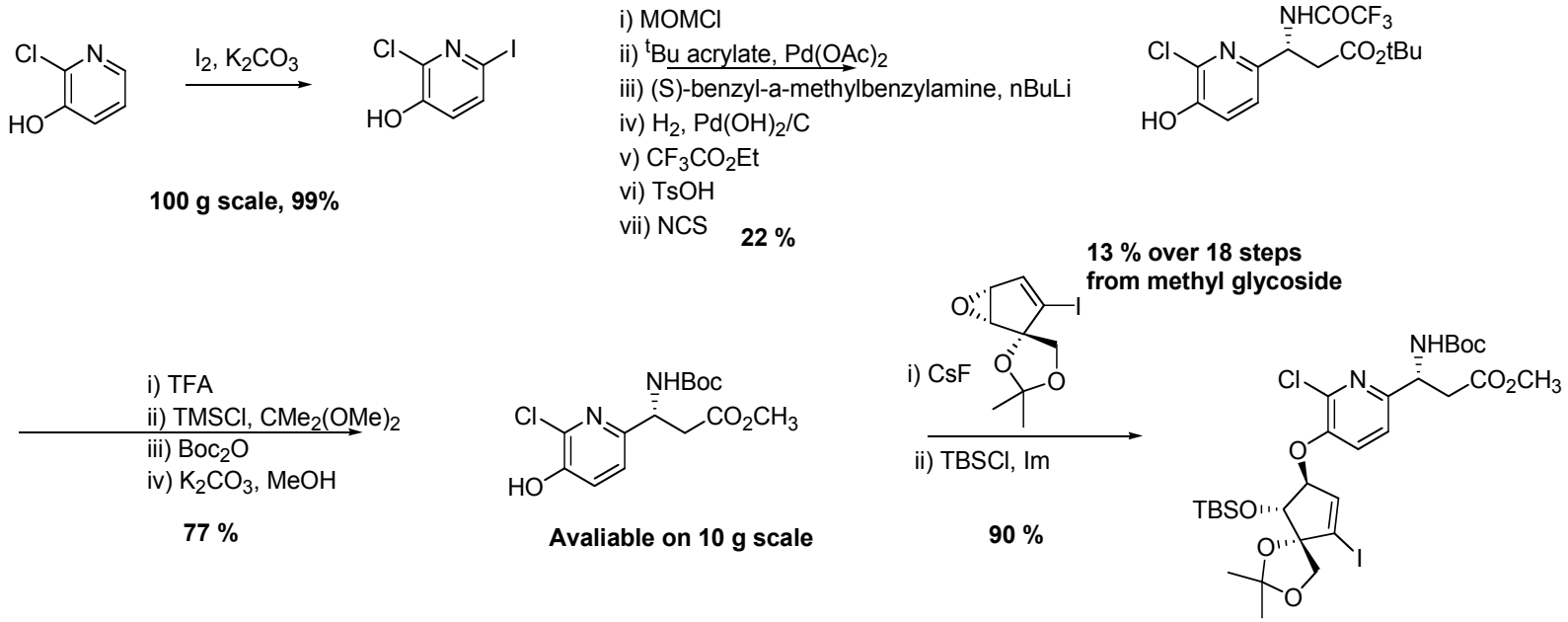
Title Paper - Retrosynthesis



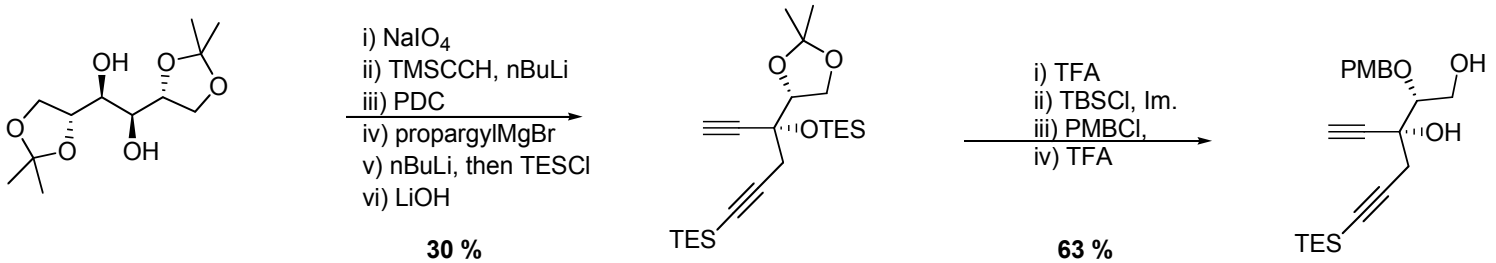
- $CeCl_3/LiN(TMS)_2$ mediated cyclisation protocol between C7-C8 to form nine membered diyne core
- Require gram quantities of aldehyde (cyclisation precursor)

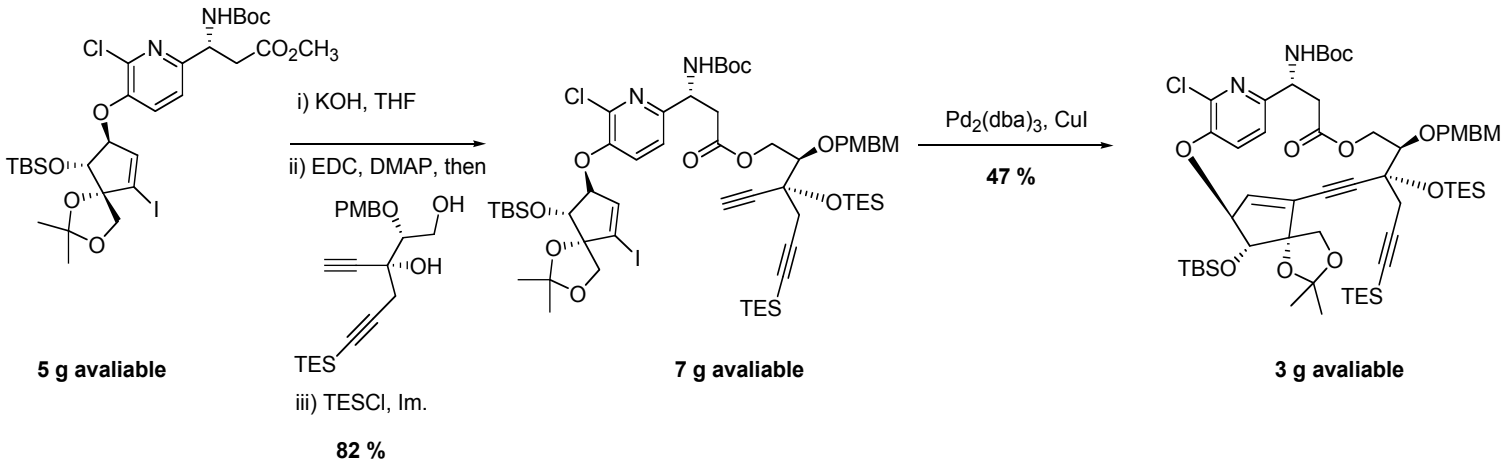


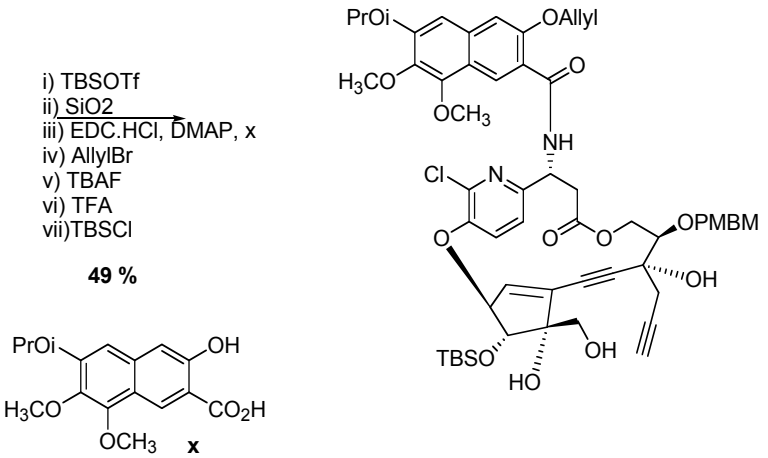
Scale up of cyclisation precursor



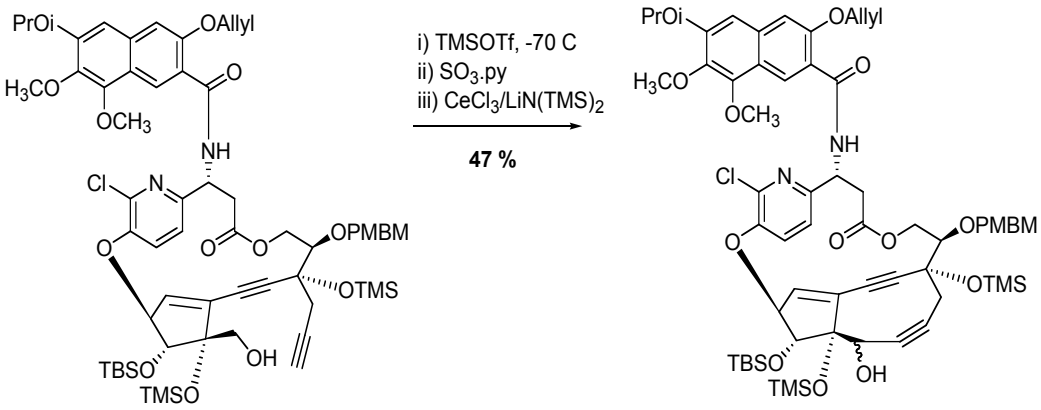
- Large scale production of required fragments







- Boc removal by conversion to o-silylcarbamate
- Intermediate stubborn to selective deprotection
- Global desilylation, then hydrolysis of acetonide to give tetraol
- Treatment with TBSCl gave triol – selectively protected 2Y C10 OH
  - Transannular steric replusion from ansamacrocyclic bridge during protection of C8 1Y OH



3:1
α-OH at C8
β-OH at C8

- Dess-Martin or Swern ox – complex mixtures
  - Oxidative cleavage or chlorination of electron rich naphthol unit
  - IBX or SO_3.py reliable methods

- C8 stereochem confirmed by nOe study of corresponding mesylate

- Can also utilise $YbCl_3$ as an alternative to $CeCl_3$ to initiate the anionic formation of unstable nine membered cores

Nine membered cyclisation study results

Entry	Additive	Temp	Time (h)	Yield (%)	4a/4b
1	$CeCl_3$	-25 to rt	1	<7	2/1
2	$CeCl_3$	-15	18	26	3/1
3	**$CeCl_3$**	**-25**	**25**	**47**	**3/1**
4	$CeCl_3$	-50	69	12	3/1
5	None	-25	36	0	-
6	$YbCl_3$	-25	36	22	2/3

Outcomes of synthesis

- α stereoselectivity due to repulsion of the ansamacrolide framework
- α isomer not stable at rt ($t_{1/2}$ = 13 h), can be stored in benzene matrix at -30 ^{o}C without deterioration

Conclusions

- Constructed multicyclic diyne anasmacrolide possessing the entire framework of kedarcidin
  - Through $CeCl_3$ mediated anionic formation of unstable 9 membered cores