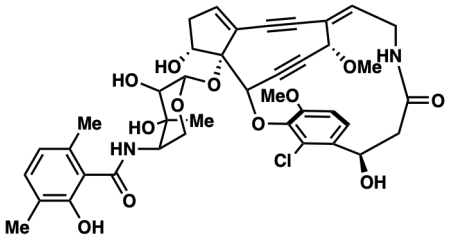
What is a glycosylated natural product?

- Secondary metabolites that serve as signal and defense chemicals
- Two parts:
  1. Glycon – the carbohydrate part, either monomers or oligomers
     - In nature, stepwise glycosylation occurs with various glycosyltransferases after synthesis of the aglycon
  2. Aglycon – non-carbohydrate part, covalently bound by O (most common, hydroxyl group on aglycon is glycosylation site), N, S, or C (only one not hydrolyzed by acid, can usually be added on early in the synthesis)



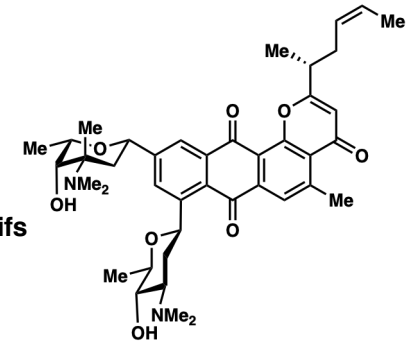
(-)-maduropeptin chromophore revised structure

Why do we care about them?

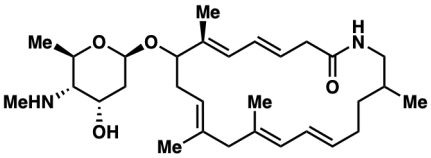
- Pharmacological activity: antitumor, antiinfective, immunomodulatory,
- Glycon has role in pharmacokindetic / pharmacodynamic properties
  - Can also be a part of pharmacophore

Common challenges in their total syntheses:

- Aglycone, often published as a synthesis in its own right
- Saccharide, different classes of glycosides have their own common sugar motifs
- Condensation/selective glycosylation of the two parts
- Necessity for several protecting group modifications



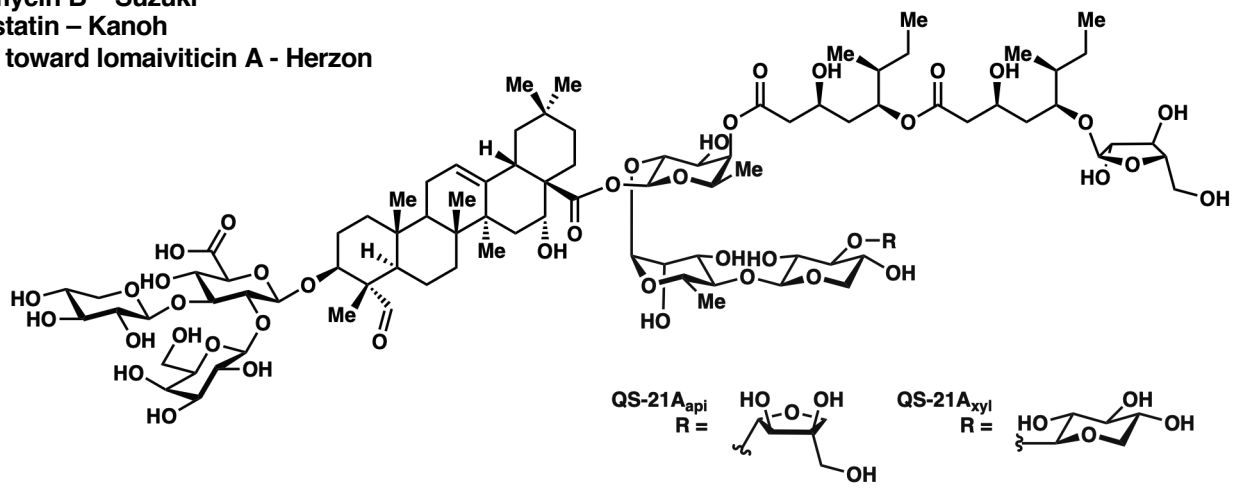
saptomycin B

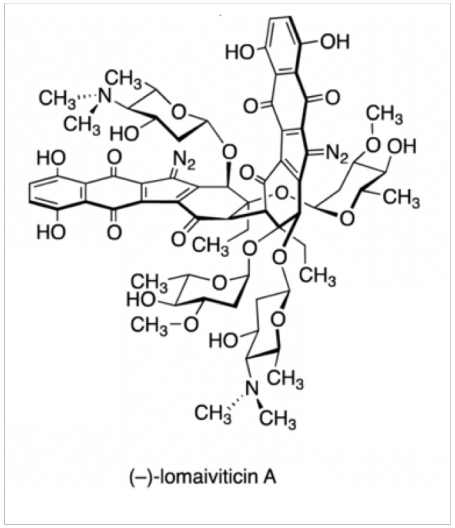


vicenistatin

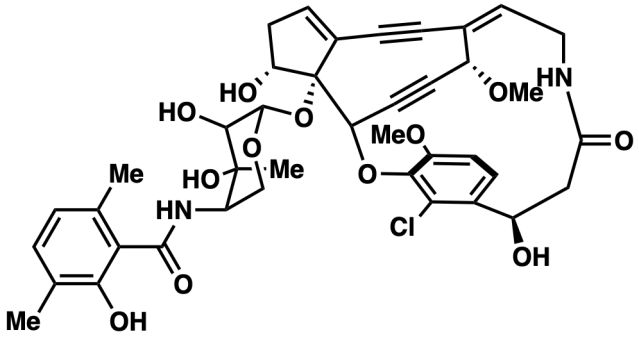
Talk Outline:

1. (-)-maduropeptin chromophore
2. QS-21A – Gin
3. Saptomycin B – Suzuki
4. Vicenistatin – Kanoh
5. Efforts toward Iomaiviticin A - Herzon



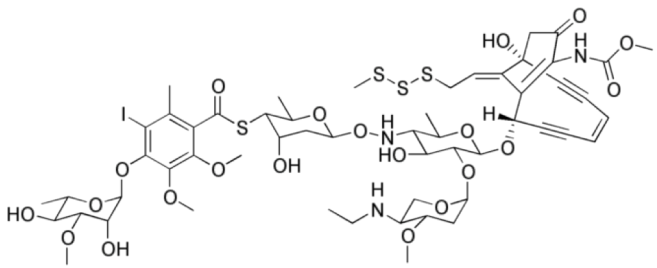


(–)-Iomaiviticin A



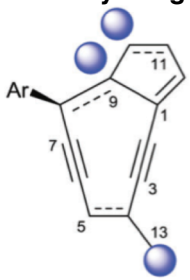
(-)-maduropeptin chromophore revised structure

- Class: enediyne (9 and 10)
- Isolated from Actinomadura madurae in 1992 as a 1:1 mixture of protein and ligand
- Potent antitumor and antibacterial activities, proposed to be because of site selective DNA cleavage
- Proposed as the MeOH adduct of unknown chromophore (see DNA cleavage mechanism)

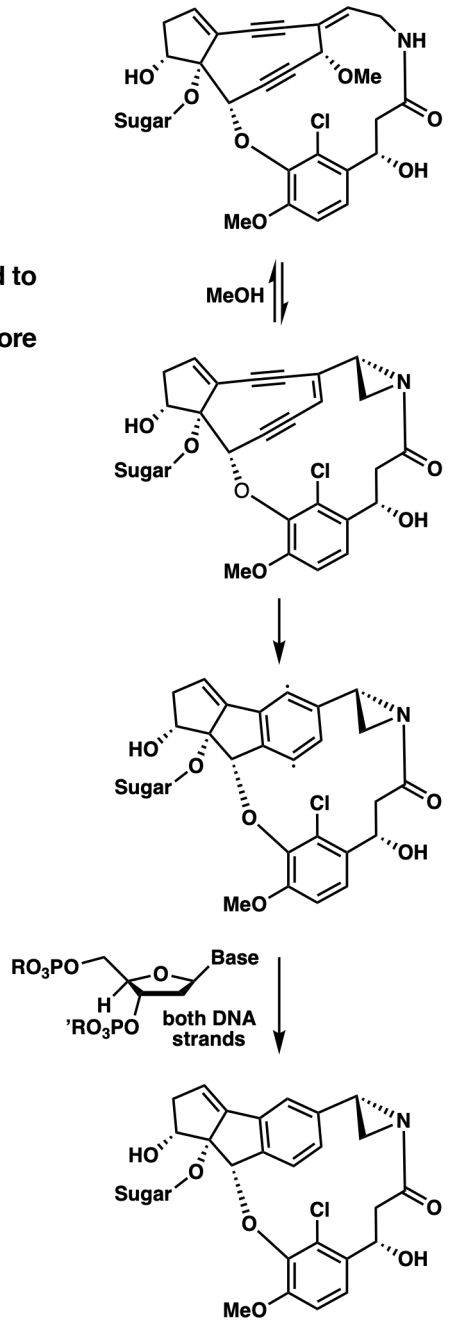


Calicheamycin – a 10-enediyne
A "Classic" Total Synthesis by Nicolaou (1992)

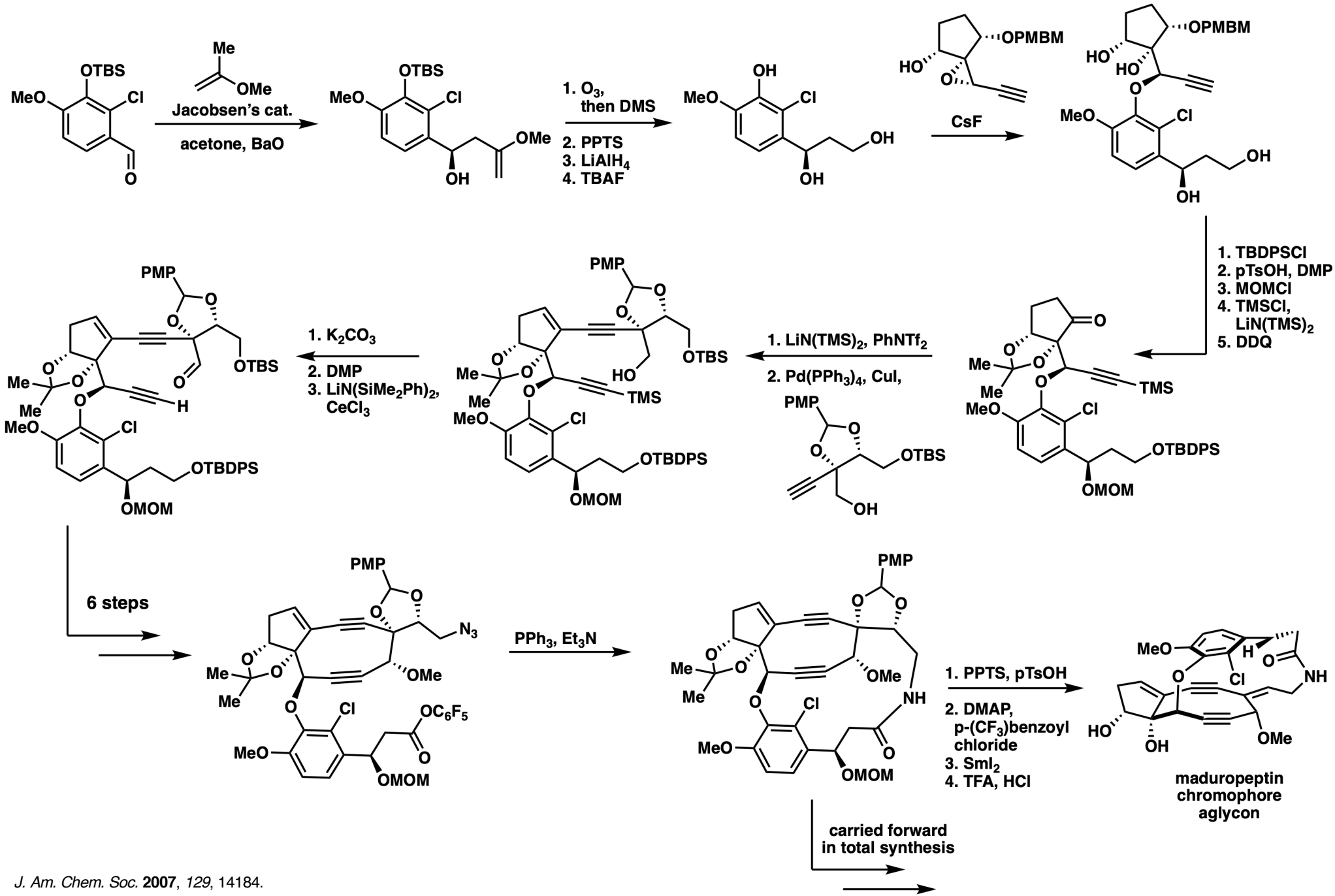
9-Enediyne Aglycon Motif



C-1027 (C-9, **87**; **i**)
neocarzinostatins (C-10, **88**; **ii**, **ii**
maduropeptin (C-9, **89**; **iv**)
kedarcidin (C-10, **90**; C-13, **91**; **v**

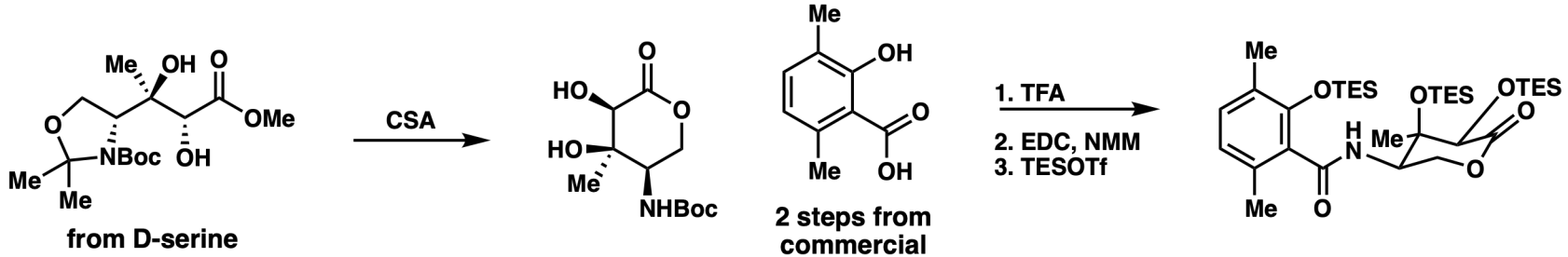


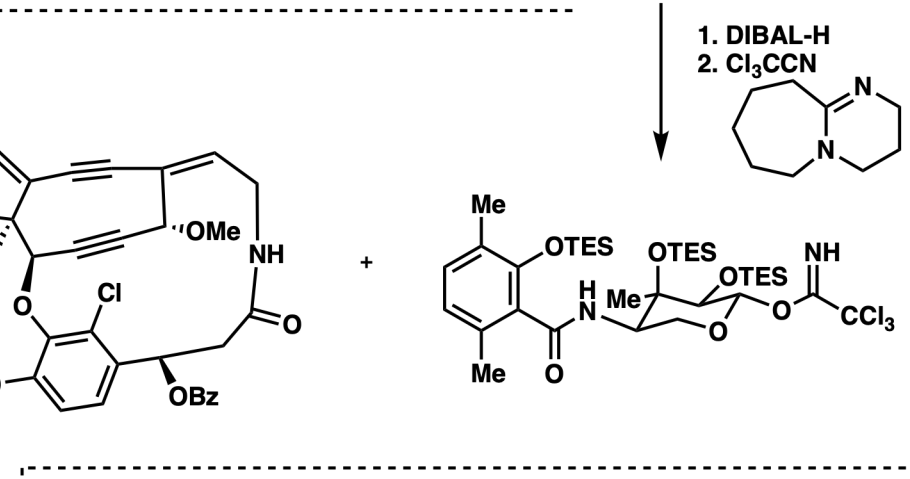
J. Am. Chem. Soc. **2007**, *129*, 14184.
J. Am. Chem. Soc. **2009**, *131*, 12072.

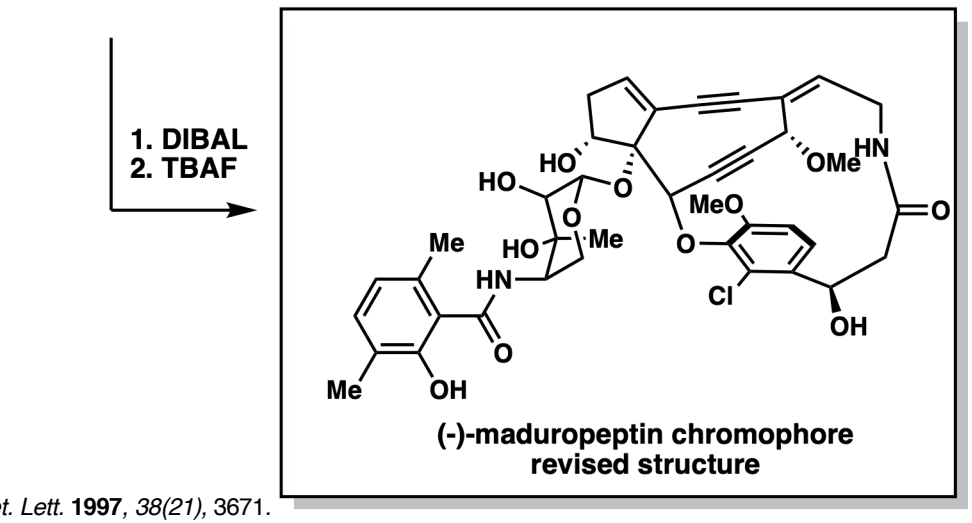


J. Am. Chem. Soc. **2007**, *129*, 14184.

Nicolaou - Synthesis of Maduropeptin Aryl Amide

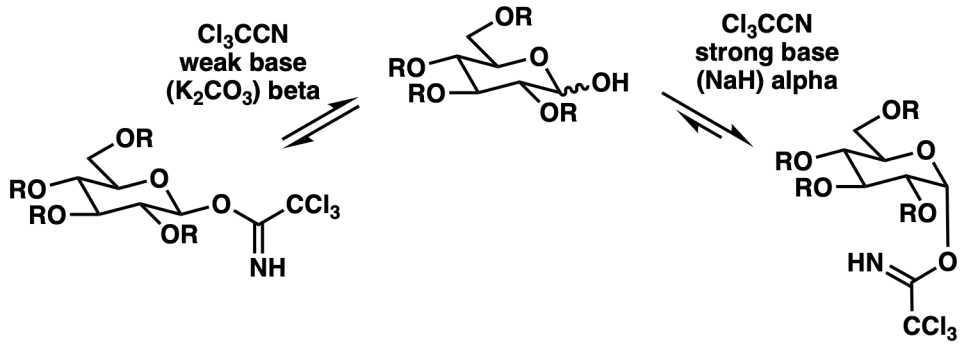






The Schmidt Donor - A Popular Glycosyl Donor in Synthesis

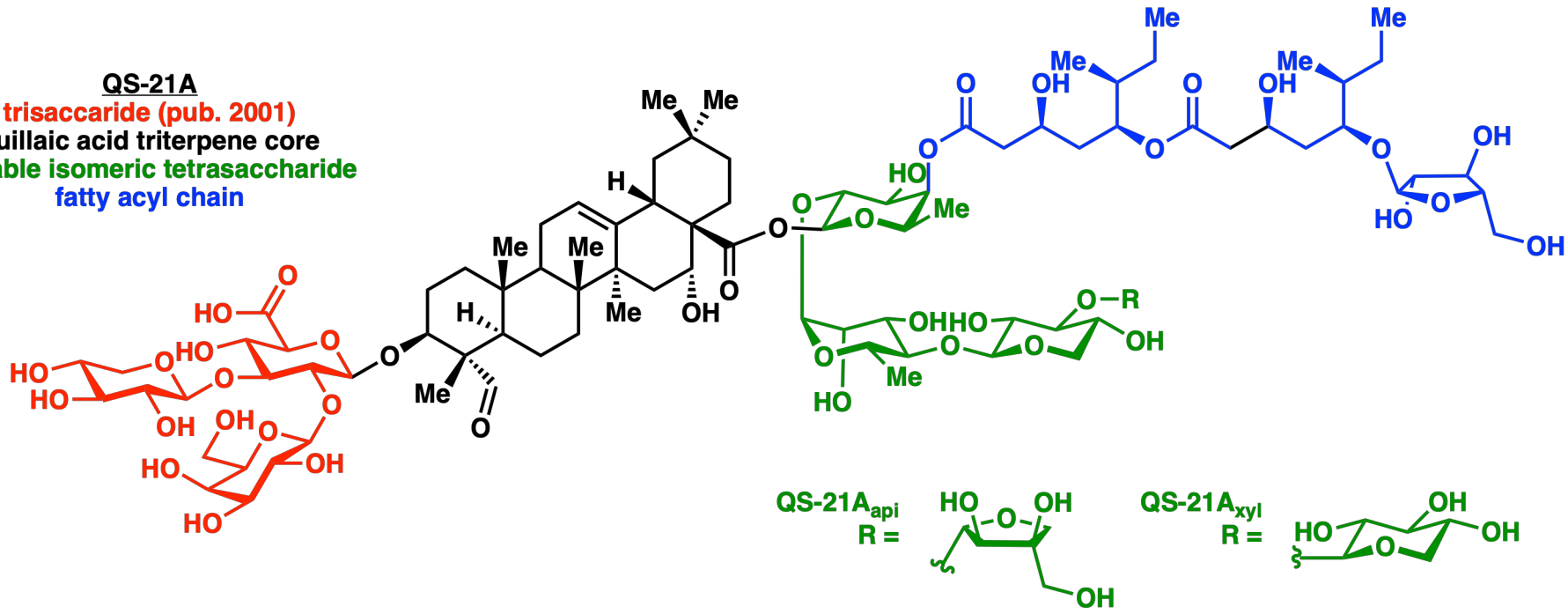
- easy to make and stereoselective, just change base
- mild glycoslyation conditions (cat. Lewis acid e.g. TMSOTf, $BF_3{\cdot}OEt_2$)
- released trichloroacetamide is not acidic, and can be transformed back to Cl_3CCN (atom economic)



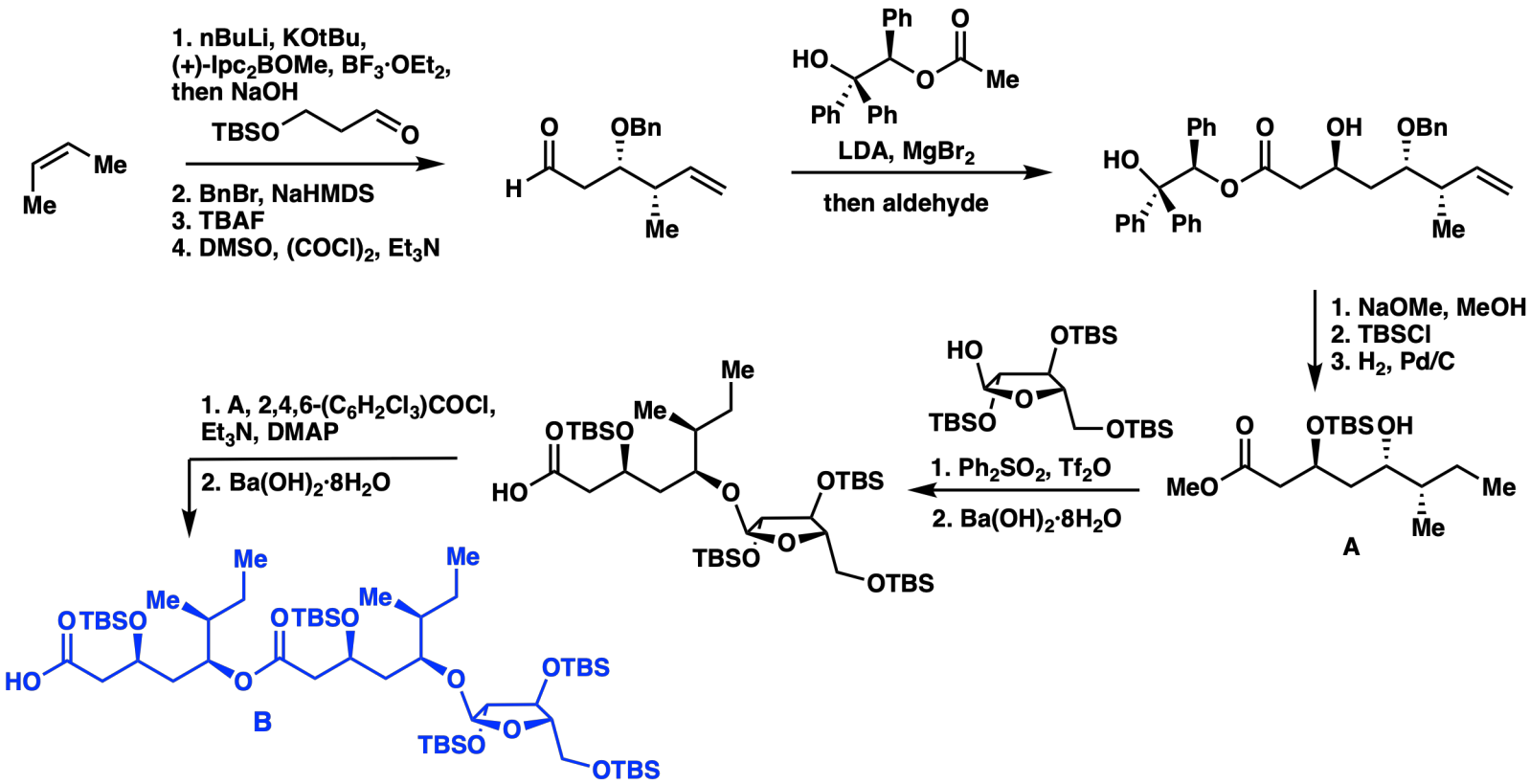
Tet. Lett. **1997**, *38(21)*, 3671.
J. Am. Chem. Soc. **2009**, *131*, 12072.
Glycoscience, Chapter 3.2, **2008**, 452.

- *Quillaja saponaria* Molina tree (soapbark tree)
  - Tree is currently regulated as isolation destroys the plant
- indiginous to South America
- Used by the Andean people as an expectrant
- Now: adjuvant for vaccines; enhances cellular immune responses
  - Over 80 vaccine studies include: melanoma, various cancers, malaria, HIV-1
- QS-21 is 65% apiose, 35% xylose

QS-21A
trisaccaride (pub. 2001)
quillaic acid triterpene core
variable isomeric tetrasaccharide
fatty acyl chain



Org. Lett. **2001,** *3(12)*, 1801.
J. Am. Chem. Soc. **2005,** *127*, 3256.

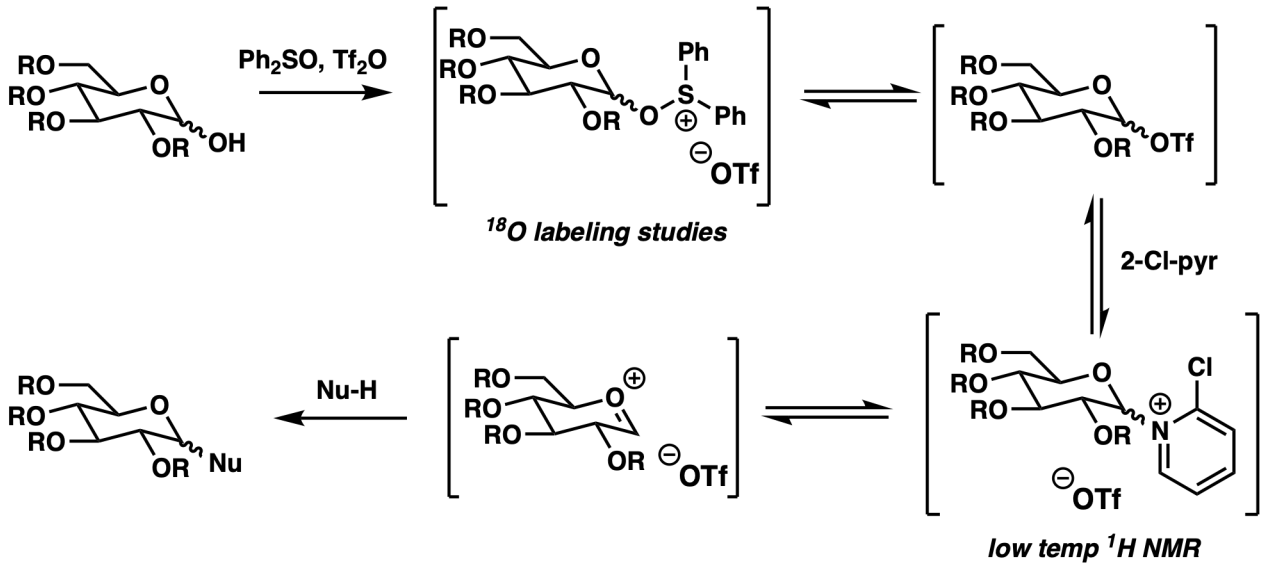


Dehydrative Glycosylation with Activated Diphenyl Sulfonium Reagents

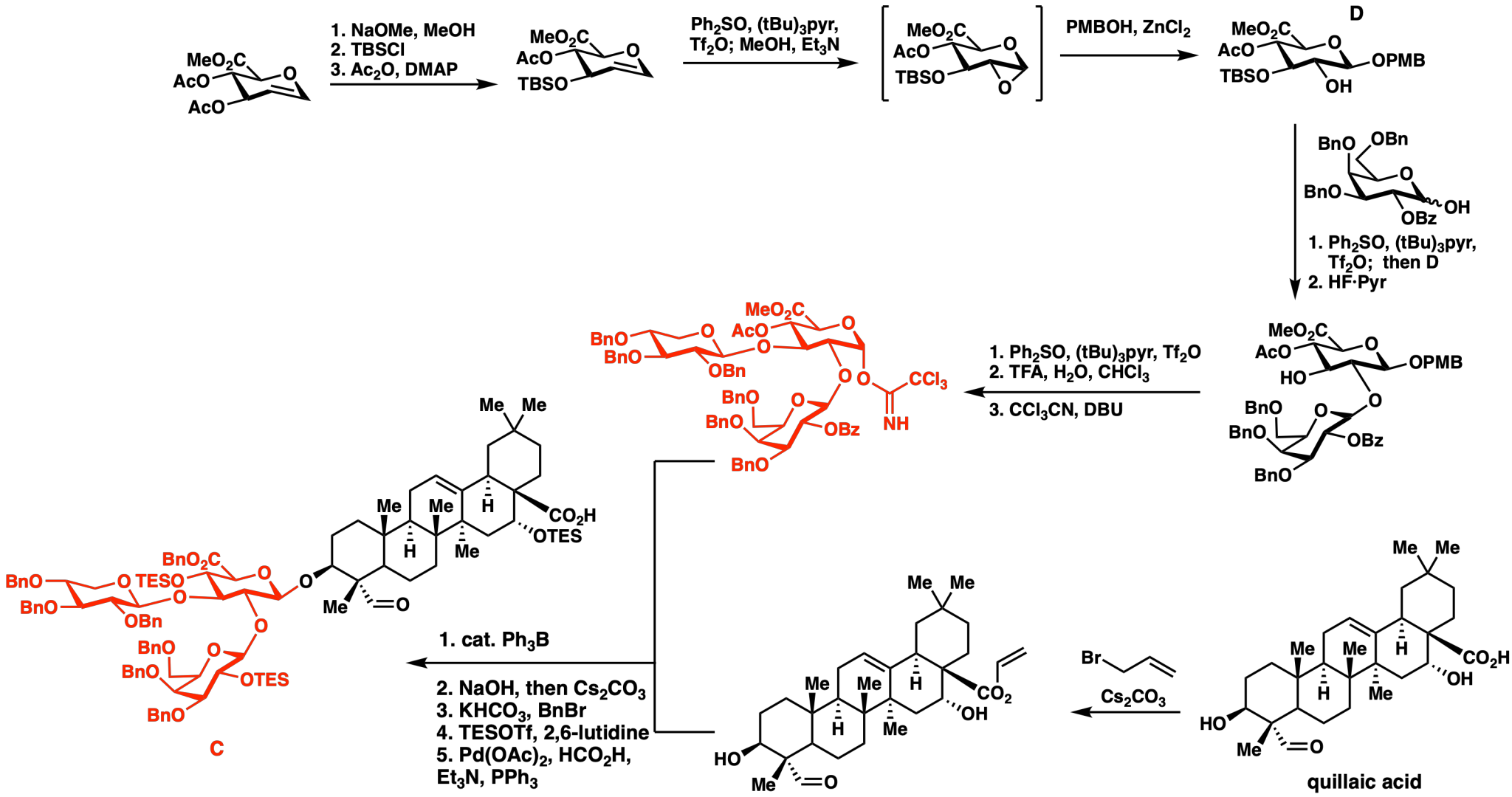
- no need for LG at anomeric carbon
- previous methods focused on development of new LGs
- can use OH group as direct glycosyl donor

One pot anomeric derivatization, activation, and derivitization!

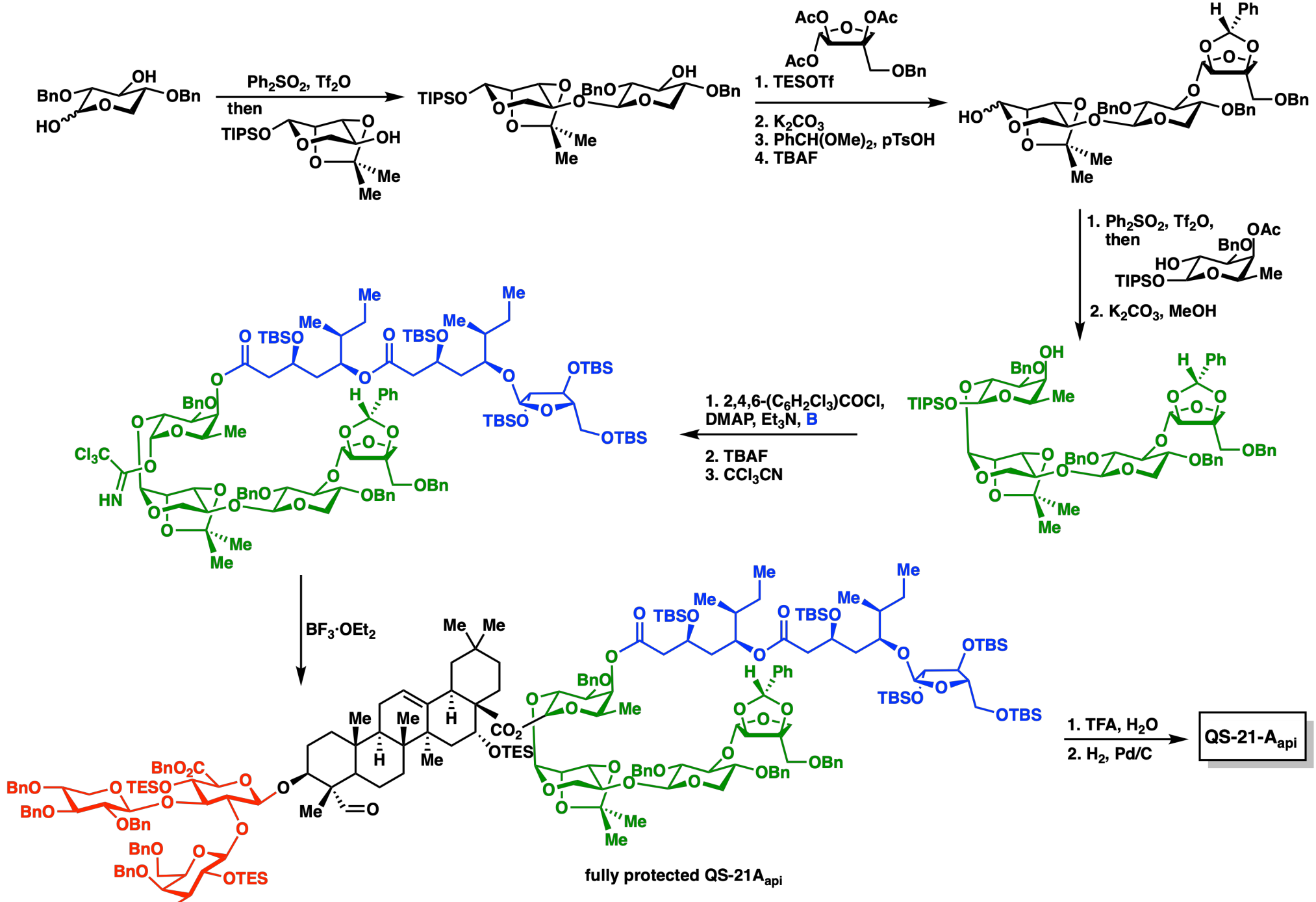
Anomeric ratios of products are kinetically derived.



J. Am. Chem. Soc. **1986,** *108*, 5919.
J. Am. Chem. Soc. **2000,** *122*, 4269.
J. Am. Chem. Soc. **2005,** *127*, 3256.

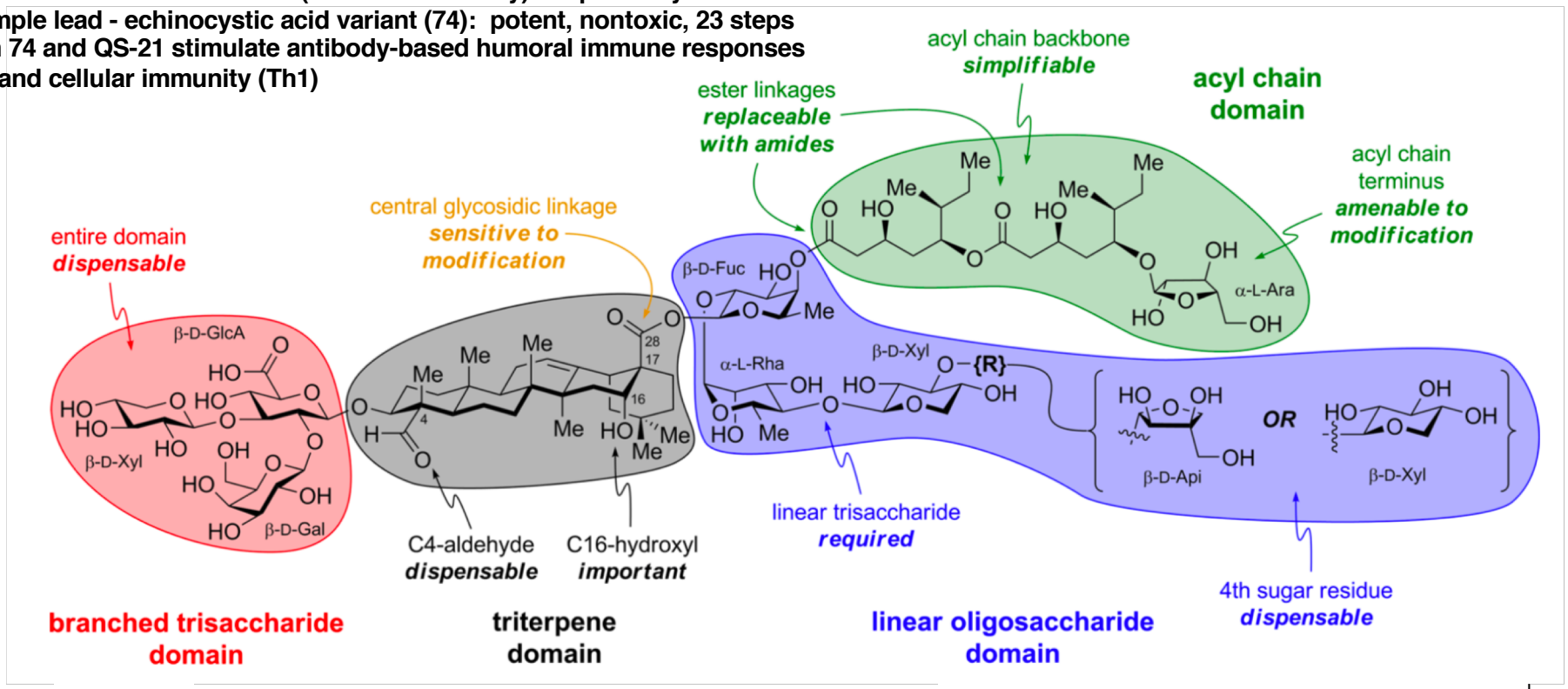


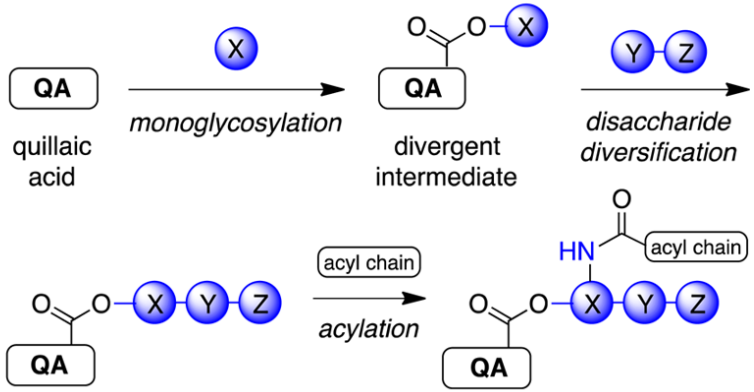
Org. Lett. **2001,** *3(12)*, 1801.
J. Am. Chem. Soc. **2005,** *127*, 3256.

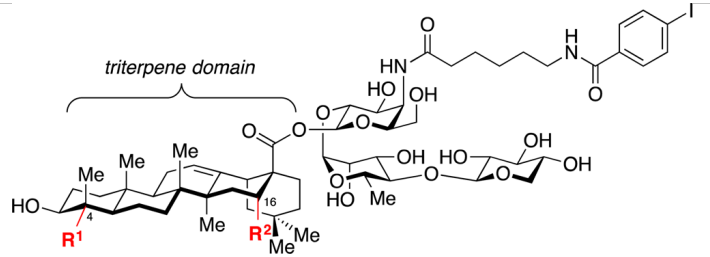


J. Am. Chem. Soc. **2005,** *127*, 3256.

- **Nearly 50 analogs prepared!**
- **SAR: can delete trisaccharide (decreases toxicity) simplifies synthesis**
- **Example lead - echinocystic acid variant (74): potent, nontoxic, 23 steps**
- **Both 74 and QS-21 stimulate antibody-based humoral immune responses (Th2) and cellular immunity (Th1)**

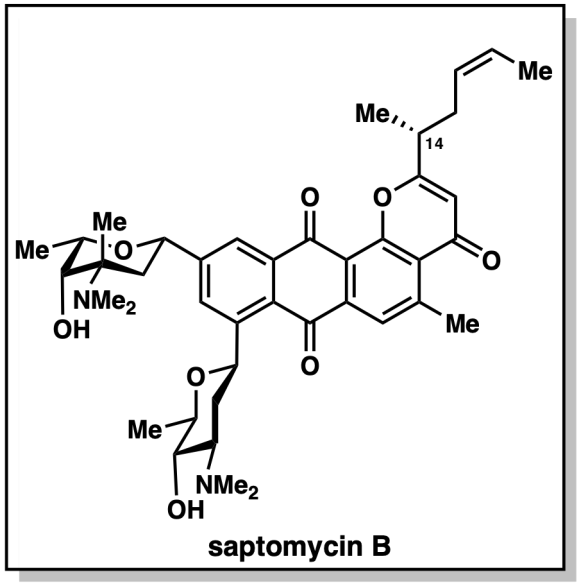






QS saponin	R^1	R^2	triterpene
72 (SQS-1-0-5-18)	CHO	OH	quillaic acid
73 (SQS-1-11-5-18)	CH_2OH	OH	caullophylogenin
74 (SQS-1-8-5-18)	Me	OH	echinocystic acid
75 (SQS-1-9-5-18)	CHO	H	gypsogenin
76 (SQS-1-10-5-18)	CH_2OH	H	hederagenin
77 (SQS-1-7-5-18)	Me	H	oleanolic acid

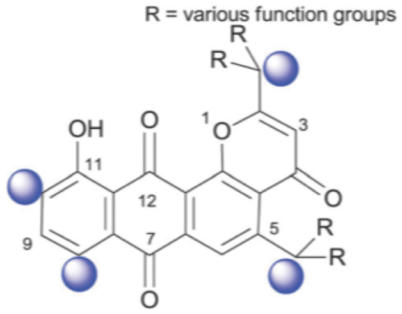
Acc. Chem. Res. **2016,** *49*, 1741.



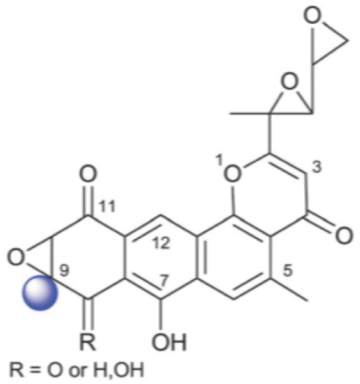
saptomycin B

- Class: pluramycin
- Isolated in 1993 from soil in Japan by Sapporo Breweries researchers
- Antitumor antibiotic produced by Streptomyces (both in humans and in rodents)
- Pluramycins have N-alkyl amino sugars – critical for cytotoxicity
- C-glycoside linkage
- First total synthesis, defined stereochemistry at C14

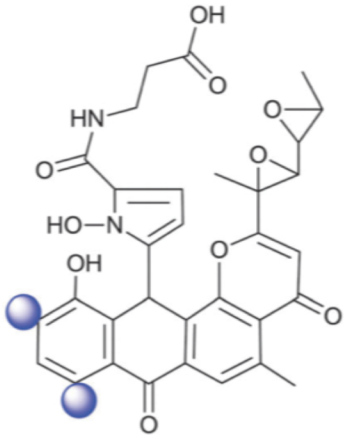
Pluramycin Aglycon Motifs



hedamycin, kidamycins, rubiflavins, altromycins, DC-92B, DC-92D, saptomycins, pluraflavins, HP-530 series, PD 121222, SS 21020B, SS 21020C, A51493A

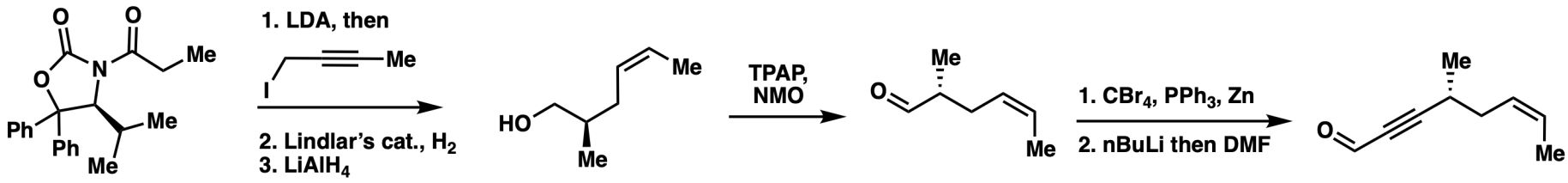


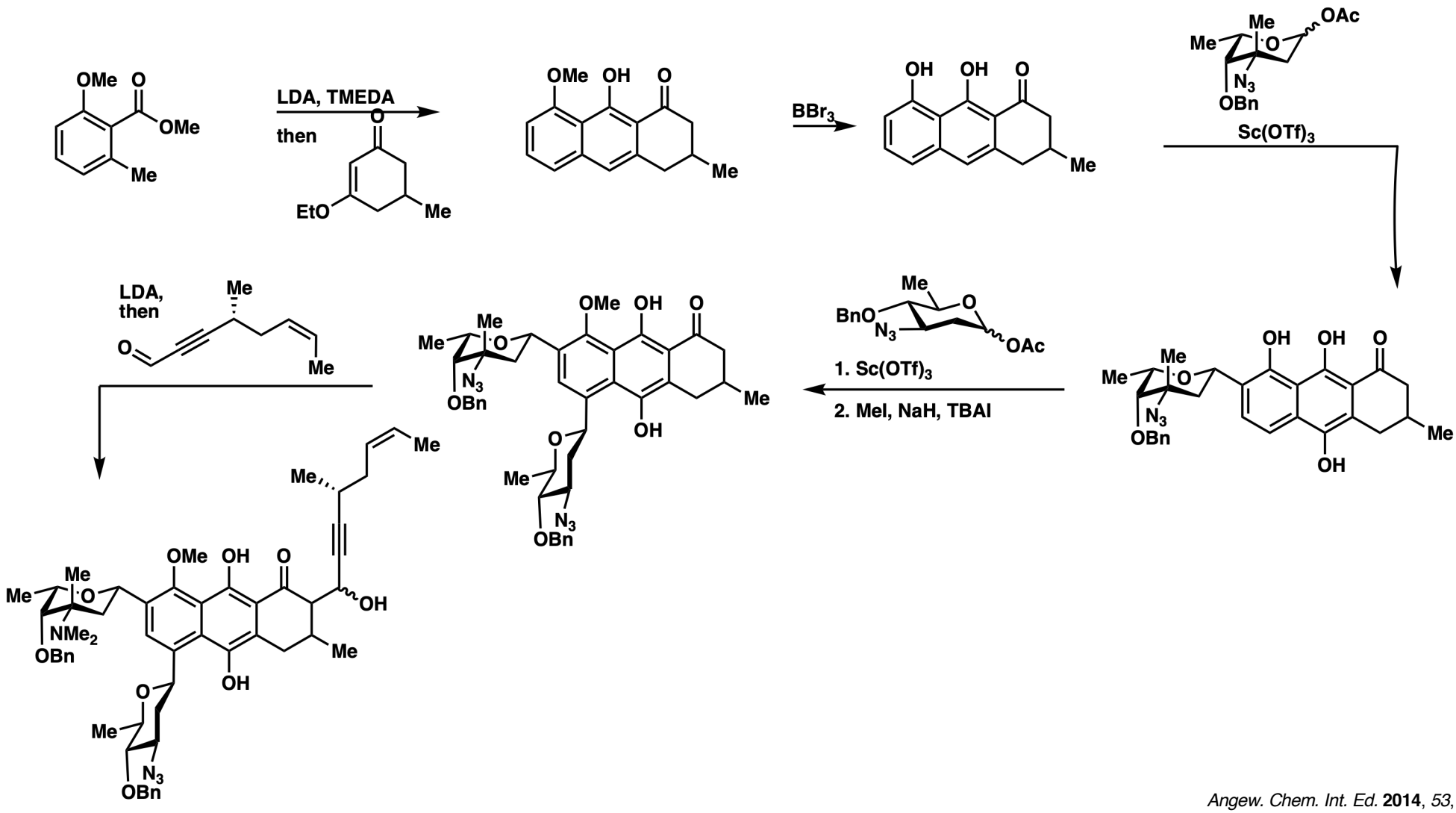
clecarmycins A1 and C



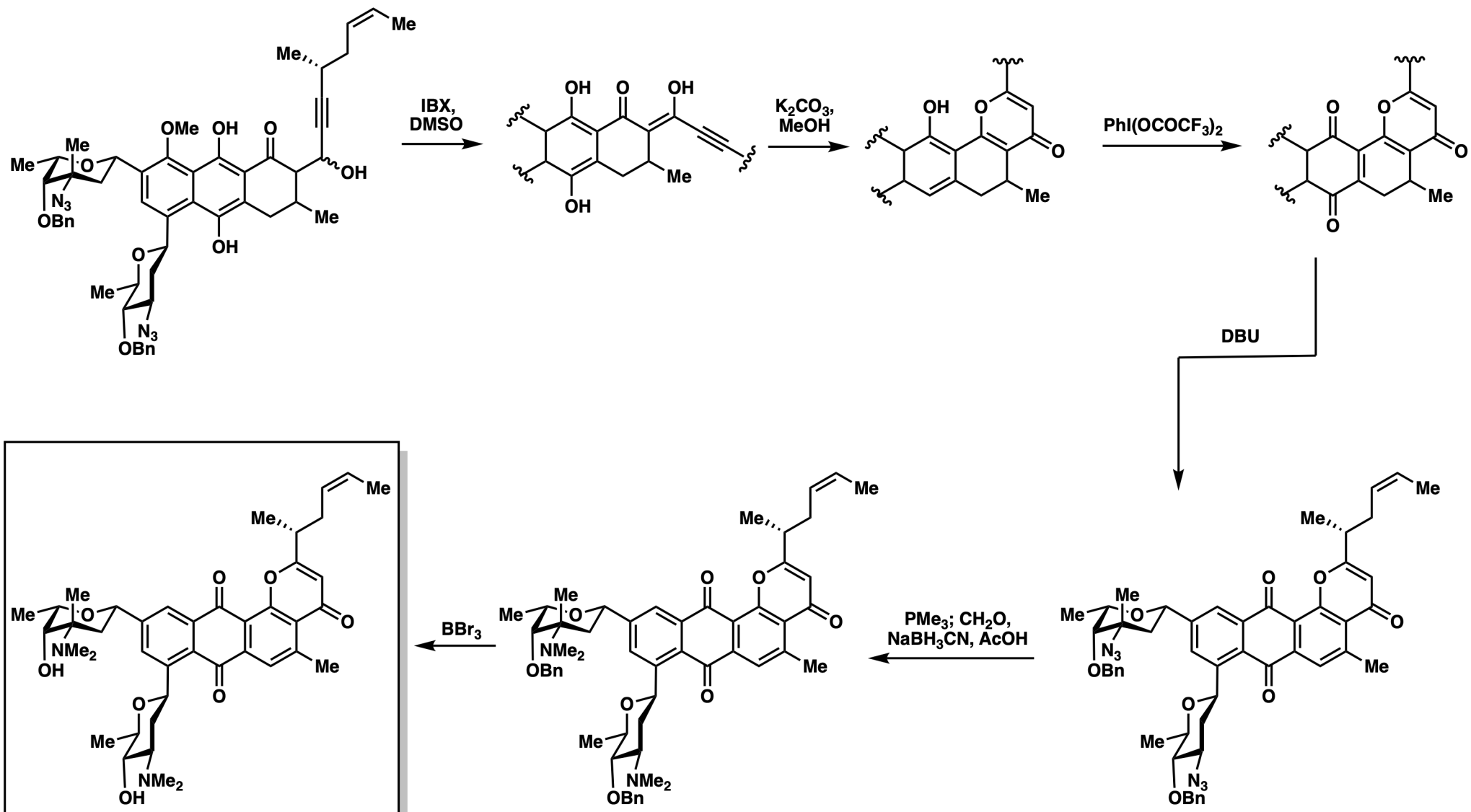
chromoxymycin

Angew. Chem. Int. Ed. **2014**, *53*, 1262.
Chem. Soc. Rev., **2015**, *44*, 7591.

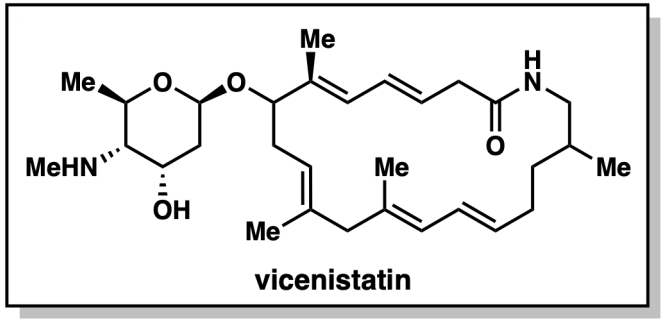




Angew. Chem. Int. Ed. **2014**, *53*, 1262.



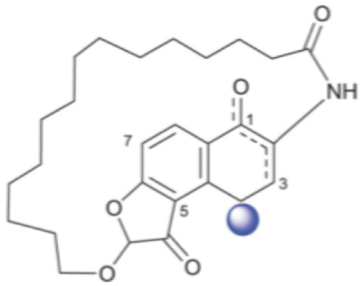
Angew. Chem. Int. Ed. **2014**, *53*, 1262.



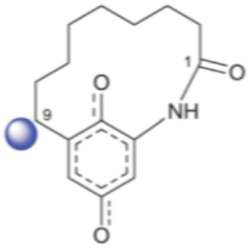
vicenistatin

- **Class: macrolactam**
- **Isolated from Streptomyces**
- **Synthesized previously by Kekinuma in 2002**
- **Antitumor antibiotic, also active against leukaemia, colon carcinoma**
- **Glycoside (amino sugar - vicenisamine) critical to antitumor activity**
- **Kanoh employs the use of a glycosyl fluoride**

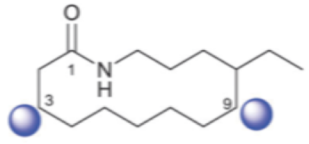
Macrolactam Aglycon Motifs



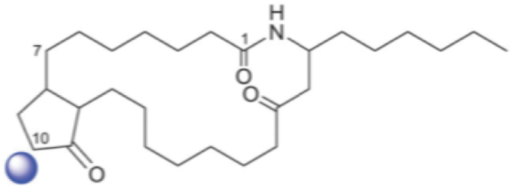
tolypomycin-R (C-4, **203a**)
tolypomycin-Y (C-4, **203b**)



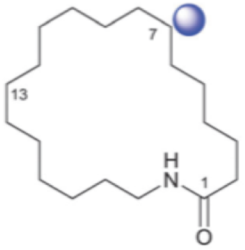
Q-1047 (C-9, **205**)



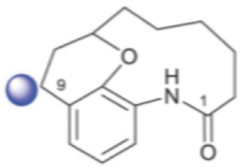
fluvirucins A1, A2 (C-3, **73**)
fluvirucins B1, B3, B5, B0,
SCH 39185, SCH 38516 (C-9, **73**)
fluviricins B2, B4, Sch-38511 (C-9, **207**)
SCH 42729 (C-9, **II**)
SCH 42282 (C-9, **III**)



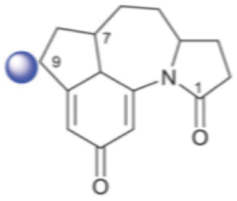
cremimycin (C-10, **131**)



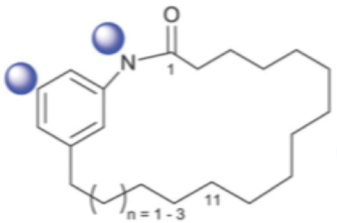
vicenistatins (C-7, **212**)
vincenistatin M (C-7, **64**)
3'-*epi*-vicenistatin (C-7, **213**)



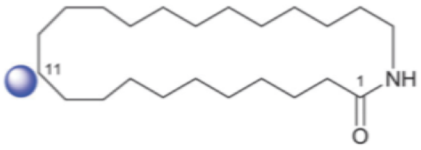
ansaetherone (C-7, **56**)



tetrapetalones (C-9, **56**)



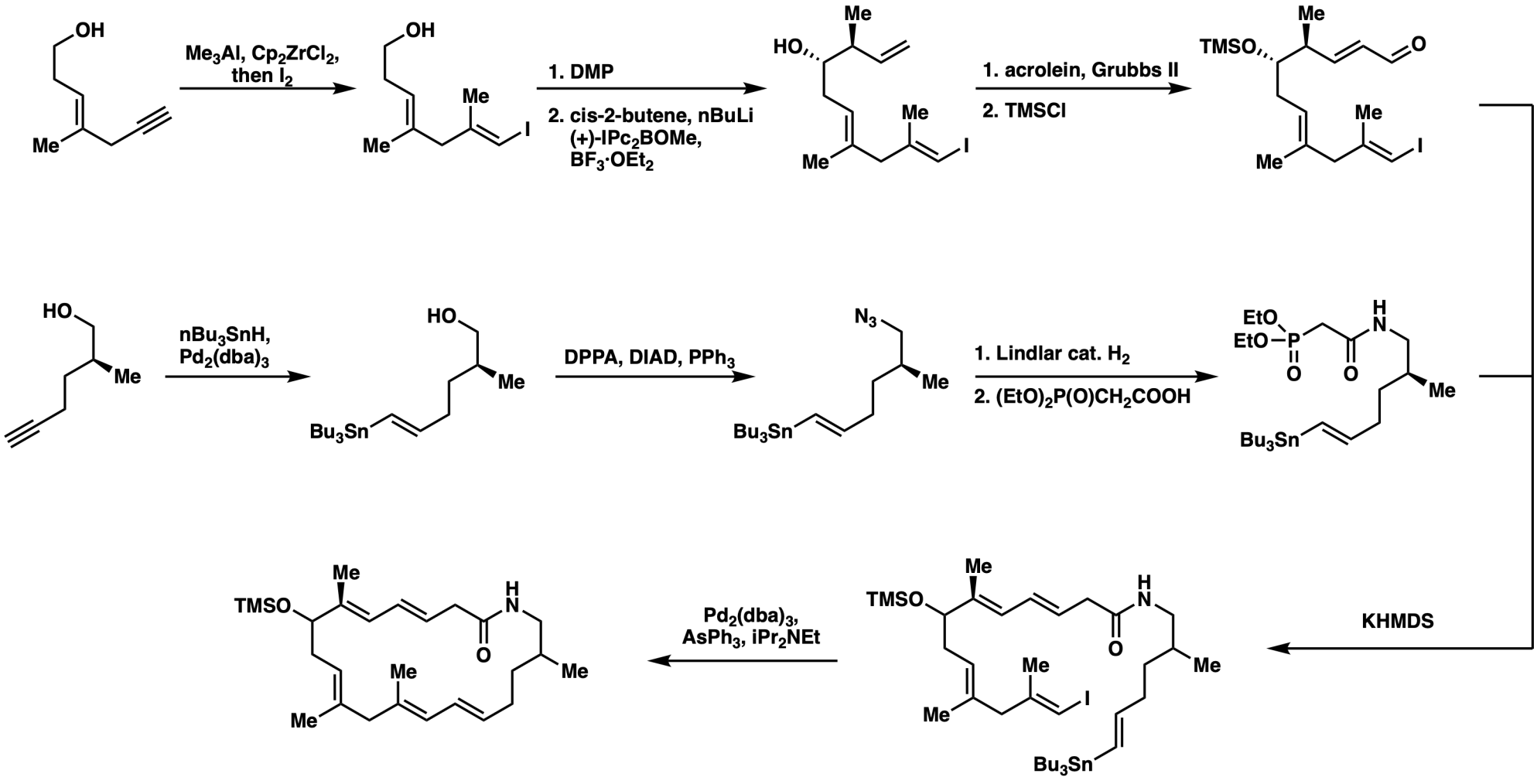
ansamitocinoside (*N*-, N-19, **104**)
ansacarbamitocins (*N*-, N-19, **104**)
mycotrienin II (C-22, **104**)



incednine (C-11, **IV**)

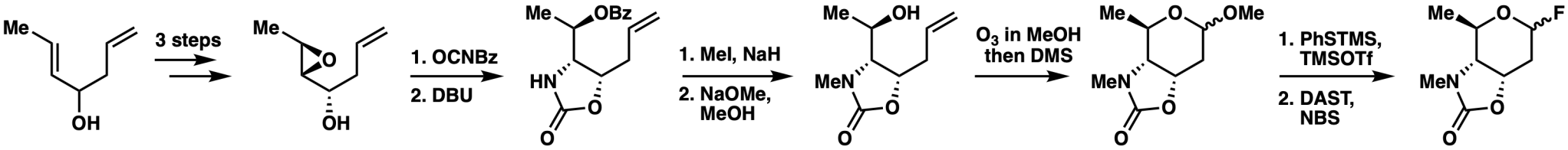
Syn. Lett. **2010**, *17*, 2589.
Chem. Soc. Rev., **2015**, *44*, 7591.

Synthesis of Macrocycle/Aglycon

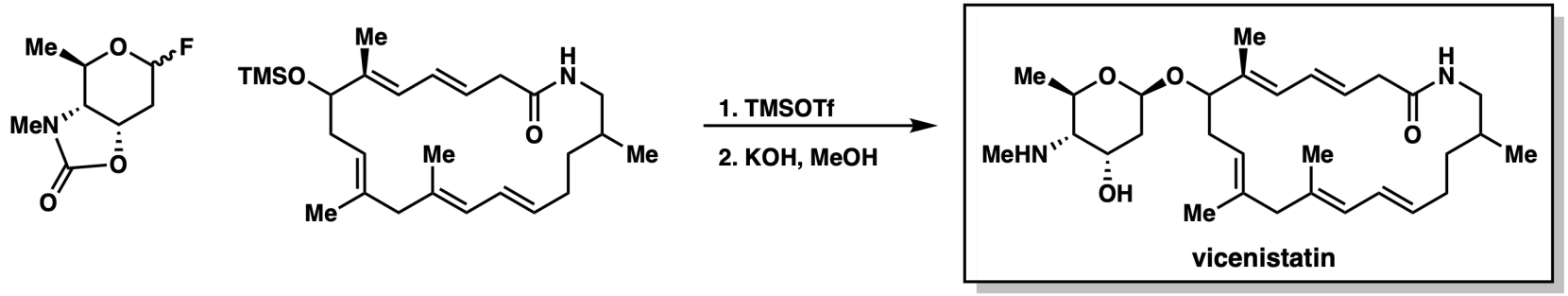


Syn. Lett. **2010**, *17*, 2589.

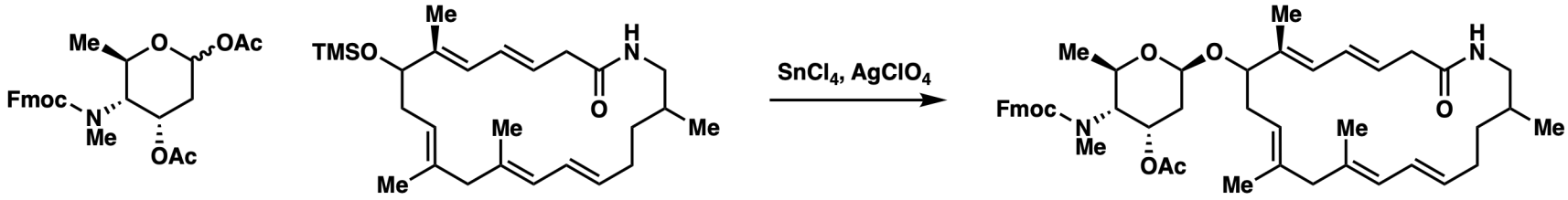
Synthesis of Glycon



Endgame



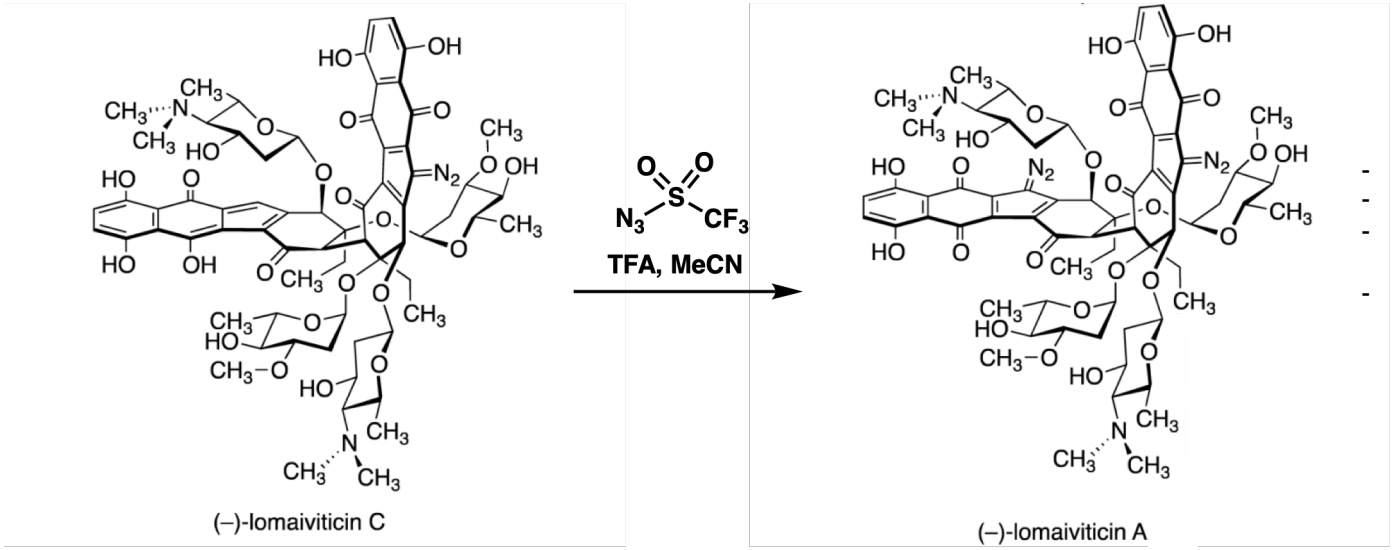
Kakinuma Glycoslyation to Vicenistatin



"Although Kakinuma et al. have accomplished this glycosylation using glycosyl acetate under the Mukaiyama conditions…the reaction could not be reproduced in our hands."

Syn. Lett. **2010**, *17*, 2589.
J. Chem. Soc., Perkin Trans. **2002**, *1*, 949.

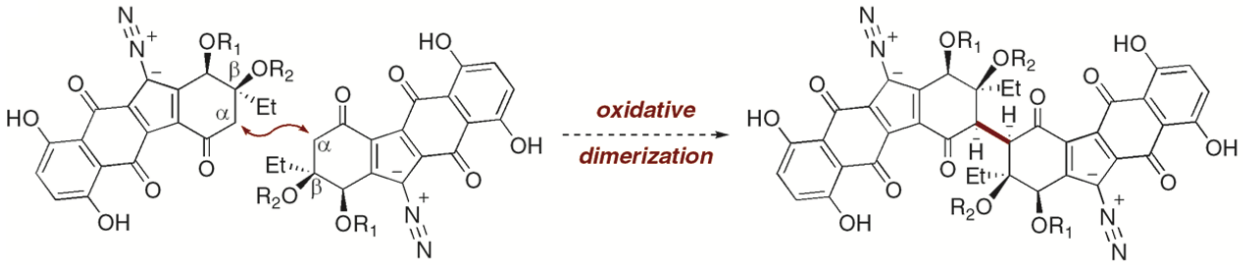
Semisynthesis to Lomaiviticin A



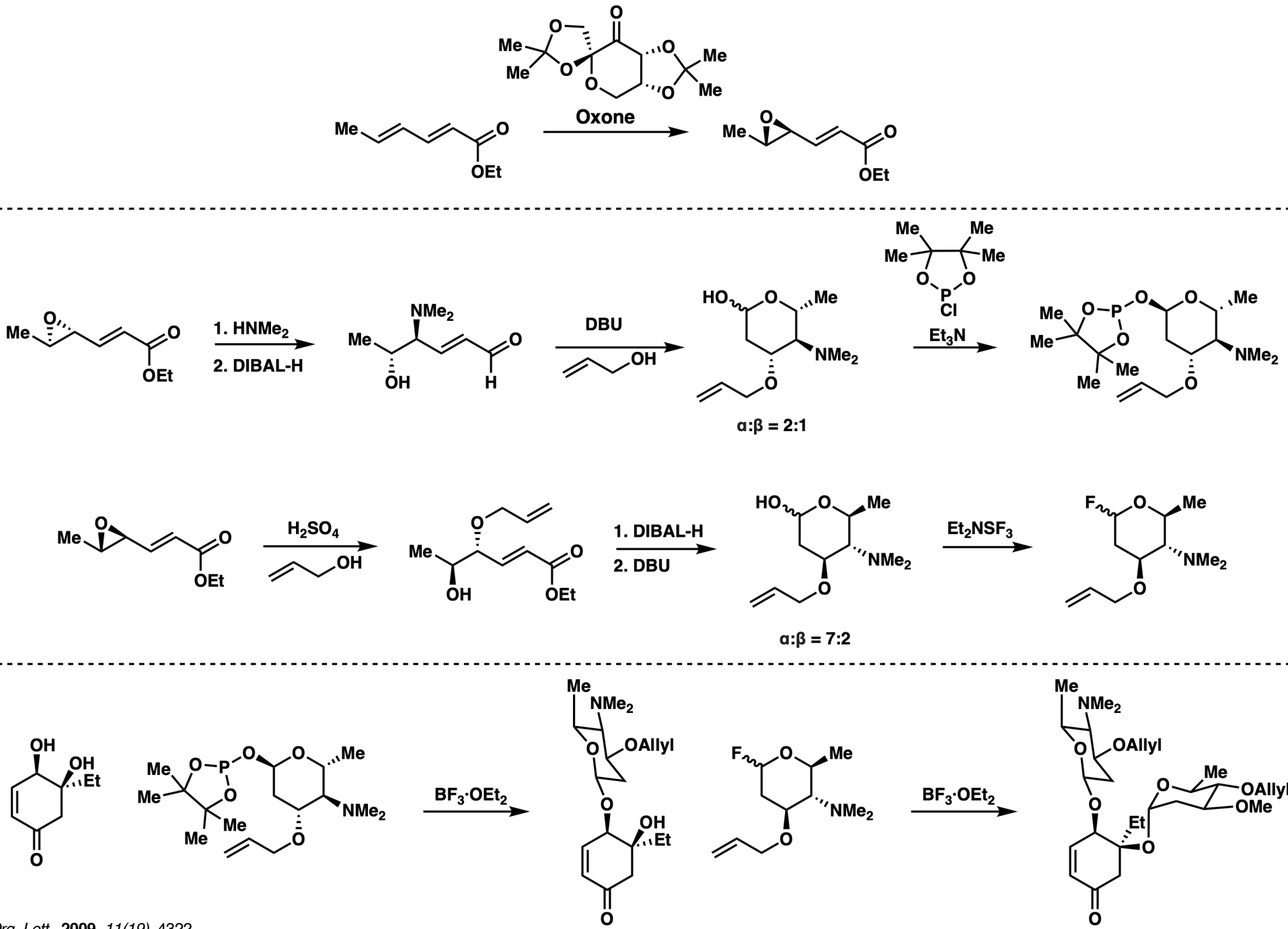
- **Class: kinamycins (diazo group)**
- **Bioactivity: antimicrobial, chemotherapeutic**
- **Proposed to form reactive intermediates under reducing conditions (unique to chemotherapeutics)**
- **Currently semisynthesis is their main source of the target for mechanism of action studies**

"Current efforts are focused on completion of the total synthesis of lomaiviticin A and elucidation of the mechanism of action of the natural product."
- Herzon Lab Website

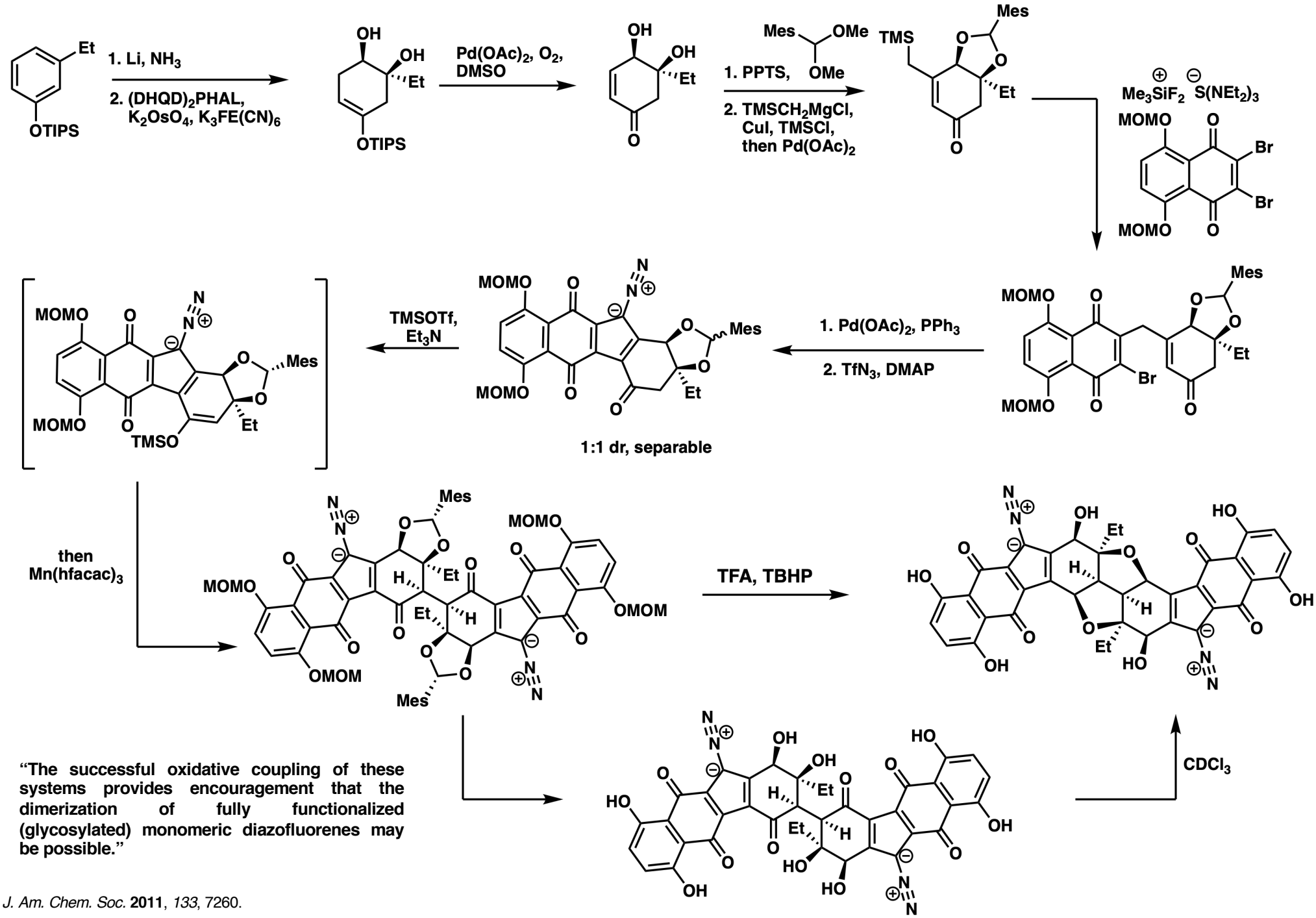
Guiding Biosynthesis Hypothesis



Org. Lett., **2009,** *11(19)*, 4322.
J. Am. Chem. Soc. **2011**, *133*, 7260.
J. Am. Chem. Soc. **2012**, *134(41)*, 17262.
J. Am. Chem. Soc. **2012**, *134*, 15285.



Org. Lett., **2009,** *11(19)*, 4322.



"The successful oxidative coupling of these systems provides encouragement that the dimerization of fully functionalized (glycosylated) monomeric diazofluorenes may be possible."

J. Am. Chem. Soc. **2011**, *133*, 7260.