Ischia Advanced School of Organic Chemistry 2016

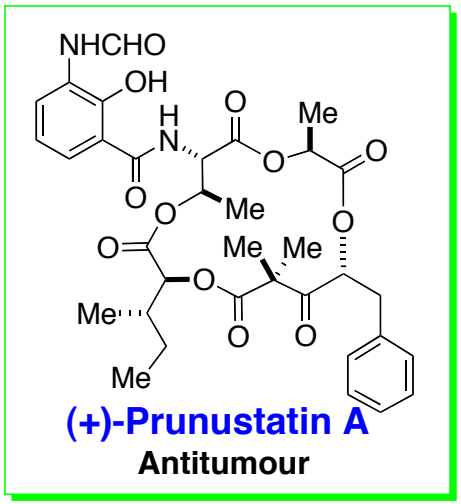
Thursday 29th September, 2016

Total Synthesis of the Naturally-Occurring GRP78 Modulators (+)-Prunustatin A and (+)-Brefeldin A, and Immunosuppressant (+)-SW-163A

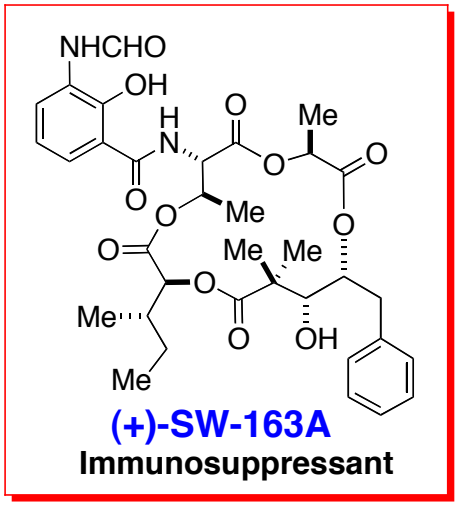
Karl J Hale

The School of Chemistry & Chemical Engineering

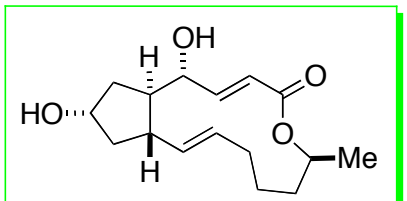
Queen's University Belfast



(+)-Prunustatin A
Antitumour



(+)-SW-163A
Immunosuppressant



(+)-Brefeldin A
Antitumour

Research Interests of the Hale Group

- Total Synthesis of Pharmacologically-Active, Complex, Natural Products of Potential Value to Human Medicine
- Chemical Biology and Medicinal Chemistry
- New Reaction Development
- Physical Organic Chemistry, and the Elucidation of Complex Reaction Mechanisms Through the Use of Novel Small Molecule Reporter Probes
- Methods for Linking Small Molecules to Proteins

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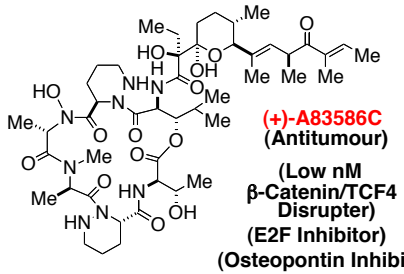
Research Interests of the Hale Group

Total Synthesis of Pharmacologically-Active, Complex, Natural Products of Value to Human Medicine

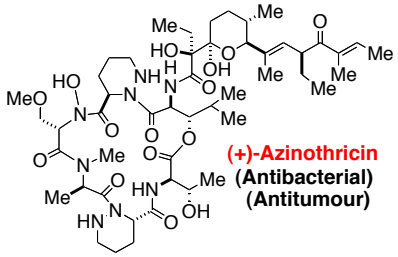
Some of the Complex Bioactive Natural Products Synthesised By The Hale Group Over The Past Decade



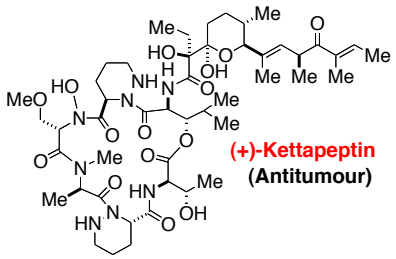
(+)-A83586C
(Antitumour)

(Low nM β-Catenin/TCF4 Disrupter)
(E2F Inhibitor)
(Osteopontin Inhibitor)

QUB (2nd Generation Synthesis)
Hale, Manaviazar et al. *Org. Lett.* **2009,** *11*, 733.
UCL (1st Generation Synthesis)
Hale and Cai *Chem. Comm.* **1997,** 2319.

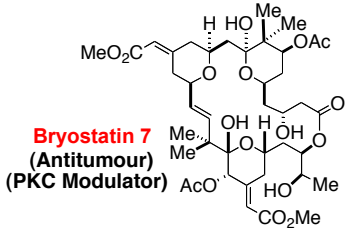


(+)-Azinothricin
(Antibacterial)
(Antitumour)



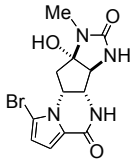
(+)-Kettapeptin
(Antitumour)

Hale, Manaviazar et al. *Org. Lett.* **2009,** *11*, 733.
Hale, Manaviazar et al. *Chem. Comm.* **2010,** *46*, 4021.



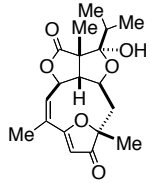
Bryostatin 7
(Antitumour)
(PKC Modulator)

Formal Total Synthesis
Hale, Manaviazar et al.
Org. Lett. **2006,** *8*, 4477.
Hale, Frigerio, Manaviazar
Org. Lett. **2003,** *5*, 503.
Hale, Hummersone, Bhatia
Org. Lett. **2000,** *2*, 2189.
Hale, Manaviazar et al.
Tetrahedron Lett.
1995, *36*, 1359.



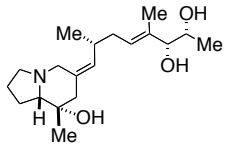
(-)-Agelastatin A
(Antitumour)
(nM β-Catenin Downregulator)
(Osteopontin Inhibitor)

Hale, Domostoj et al.
Org. Lett. **2004,** *6*, 2615.
Hale, Domostoj et al.
Strategy and Tactics in Organic Synthesis, **2005** *6*, 352.
Hale, Domostoj, El-Tanani et al.
Mol. Cancer. Therapeutics **2008**, *7*, 548.



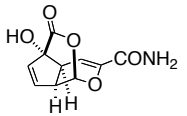
(+)-Eremantholide A
(Antitumour)

Hale and Li
Org. Lett. **2007,** *9*, 1267.
Hale and Li
Strategy and Tactics in Organic Synthesis, **2012** *8*, 127.



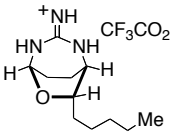
(+)-Pumiliotoxin B
(Cardiotonic)

Formal Total Synthesis
Hale, Manaviazar et al.
Tetrahedron Lett.
2011, *52*, 2080.



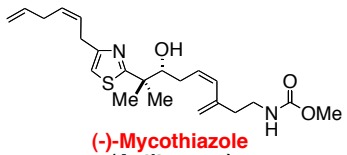
(-)-Echinosporin
(Antitumour)

Formal Total Synthesis
Hale and Flasz *Org. Lett.*
2012, *14*, 3024.



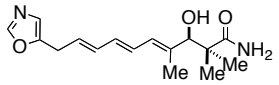
(+)-Monanchorin
(Mast Cell Inhibitor)

Hale and Wang
Org. Lett. **2014,** *16*, 2154.



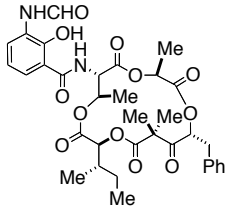
(-)-Mycothiazole
(Antitumour)
(HIF-1 Inhibitor)

Hale and Wang
Org. Lett. **2015,** *17*, 4200.



(-)-(3*R*)-Inthomycin C
(Antitumour)

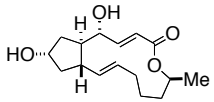
Hale, Grabski, Manaviazar et al.
Org Lett. **2014,** *16*, 1164.
Hale, Manaviazar, Hatakeyama et al.
Org Lett. **2014,** *16*, 3536.



(+)-Prunustatin A

(Antitumour)
(GRP78 Inhibitor)

Hale, Manaviazar, Nockemann
Org. Lett. **2016,** *18*, 2902.



(+)-Brefeldin A
(Antitumour)
(Golgi Complex Disrupter)

Hale and Xiong
Org. Lett. **2016,** *18*, 4254.

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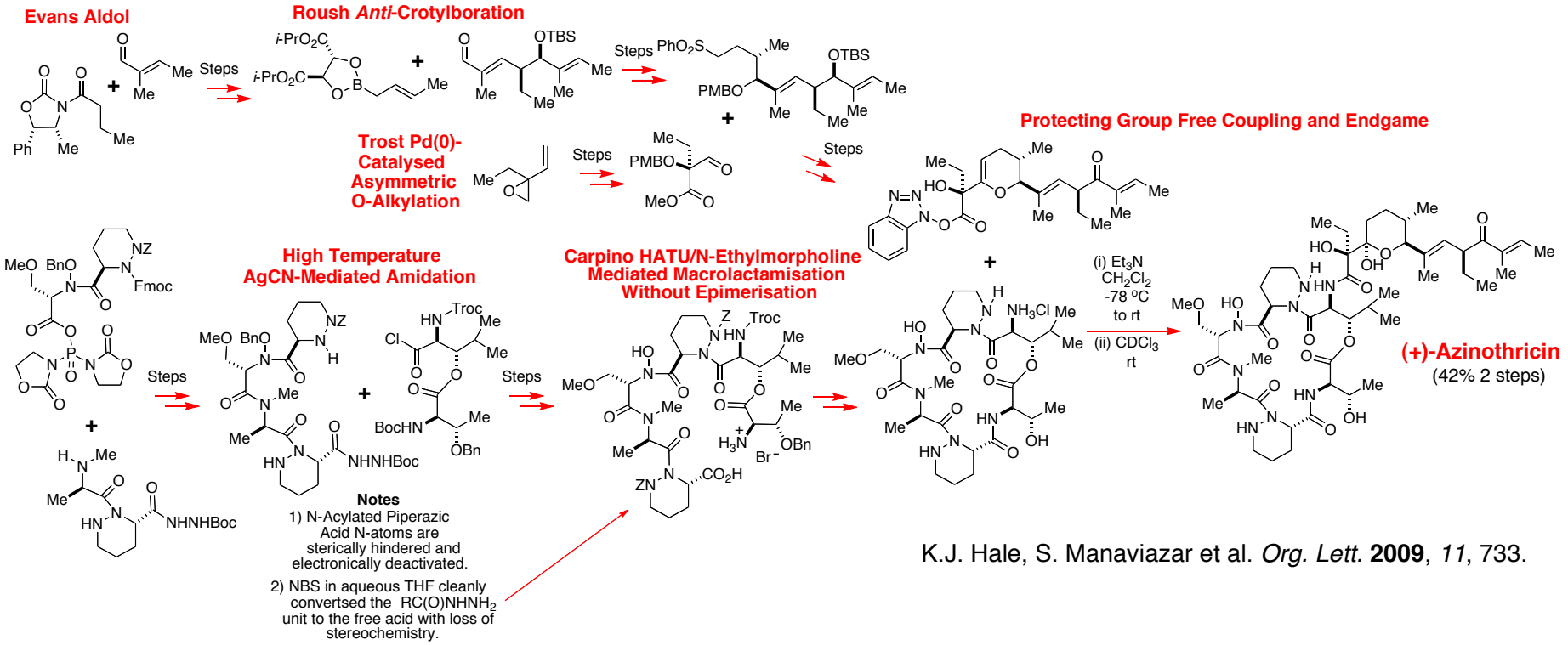
Research Interests of the Hale Group

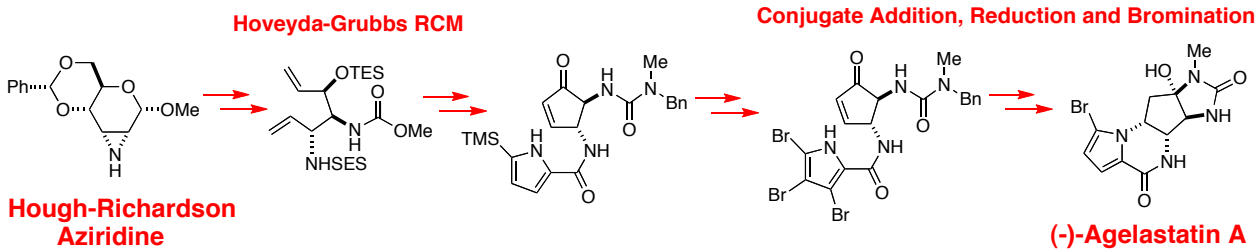
Total Synthesis of Pharmacologically-Active, Complex, Natural Products of Value to Human Medicine

First Asymmetric Total Synthesis of the Antitumour Natural Product, (+)-Azinothricin



K.J. Hale, S. Manaviazar et al. *Org. Lett.* **2009**, *11*, 733.

Enantiospecific Total Synthesis of the Antitumour Alkaloid (-)-Agelastatin A



M. Domostoj, K.J. Hale, et al. *Org. Lett.* **2004**, *6*, 2615.
M. Domostoj, K.J. Hale, et al. *Org. Lett.* **2003**, *5*, 2927.

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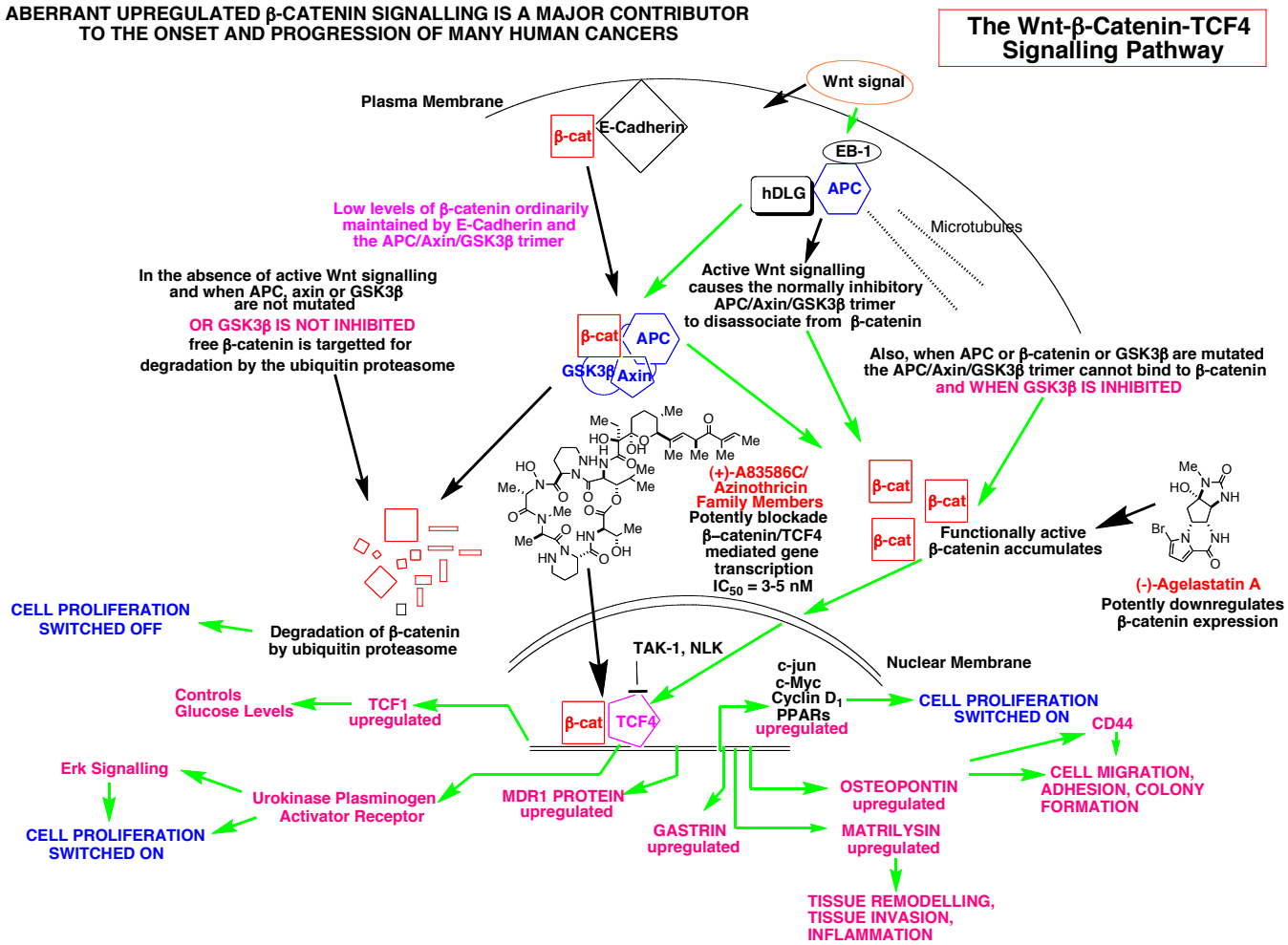
Research Interests of the Hale Group
Chemical Biology and Medicinal Chemistry



For our elucidation of the mechanisms of antitumour action of the A83586C/Azinothricin/Citropeptin Class of antitumour macrolides, see: Hale, Manaviazar, Wood, Chen, and El-Tanani et al. *Org. Lett*. **2009**, *11*, 737.

For a detailed account of our chemical biology and med chem efforts on A83586C and its congeners see: Hale, Manaviazar, and George *Chem. Comm*. **2010**, *46*, 4021.

For our elucidation of the β-catenin downregulatory antitumour mechanism of (-)-agelastatin A, see: El-Tanani, Hale, Domostoj, and Manaviazar et al. *Mol. Cancer Ther.* **2008**, *7*, 548.

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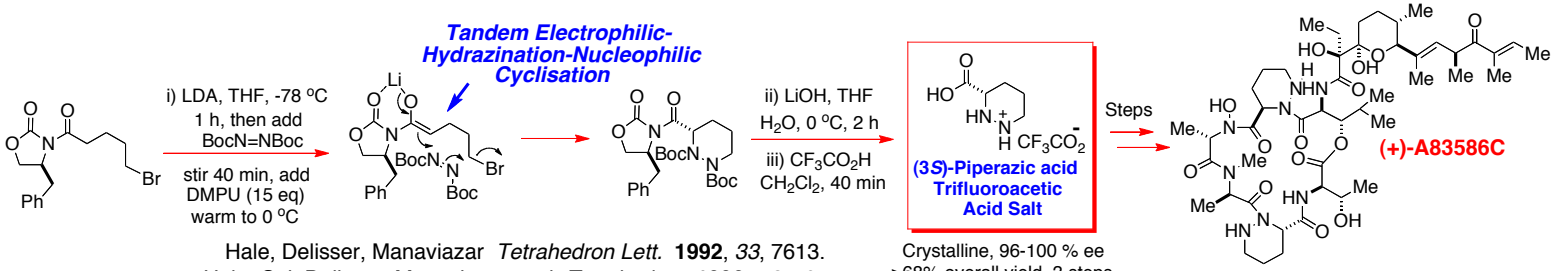
Research Interests of the Hale Group

New Reaction Development

The Tandem Electrophilic Hydrazination-Nucleophilic Cyclisation Method for Piperazic Acid Assembly

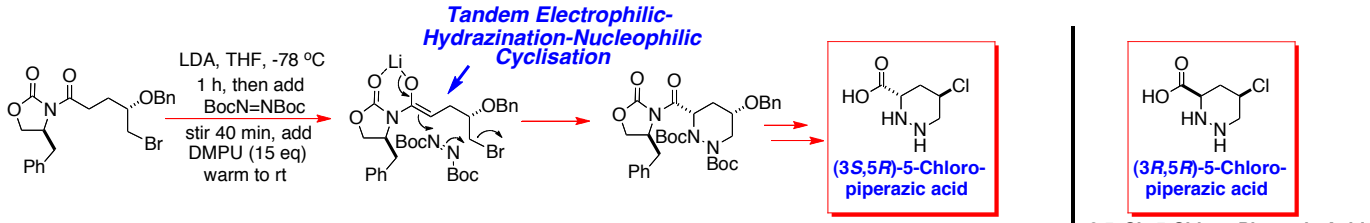
How The (+)-A83586C Venture Spurred Development of The Tandem Electrophilic Hydrazination-Nucleophilic Cyclisation Method



Hale, Delisser, Manaviazar *Tetrahedron Lett.* **1992**, *33*, 7613.
Hale, Cai, Delisser, Manaviazar et al. *Tetrahedron* **1996**, *52*, 1047.

Crystalline, 96-100 % ee
>68% overall yield, 3 steps
No chromatography required

Total Synthesis of (+)-A83586C:
Hale and Cai
JCS Chem Comm. **1997**, 2319.

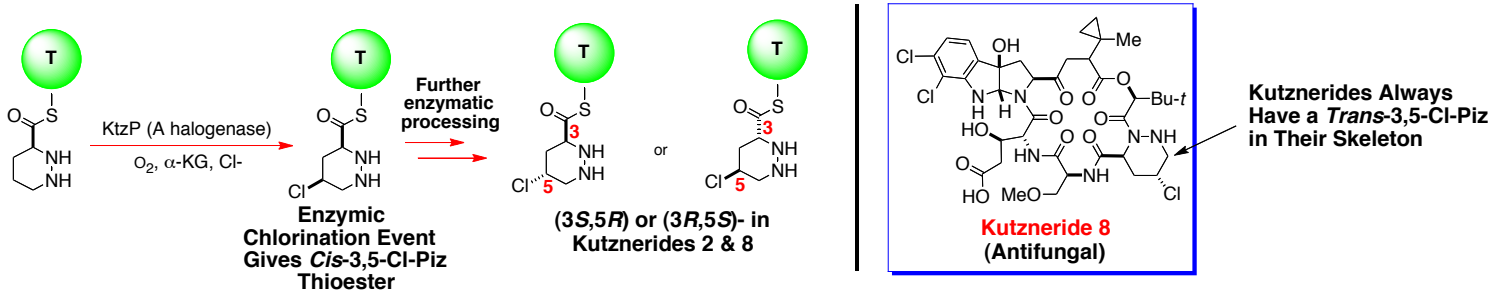


3,5-*Trans*-5-Chloro-Piperazic Acid | **3,5-*Cis*-5-Chloro-Piperazic Acid**

Hale, Manaviazar and Jogiya, *Tetrahedron Lett.* **1998**, *39*, 7163.
Hale, Manaviazar, Chumnongsaksarp et al. *Pure & Appl. Chem.* **2000**, *72*, 1659.
Hale, Manaviazar, Stevenson *Tetrahedron Lett.* **2015**, *56*, 3662.

How Our Tandem Asymmetric Electrophilic Hydrazination-Nucleophilic Cyclisation Helped Provide New Insights Into Kutzneride Biosynthesis

The above strategy was used to prepare the *cis*- and *trans*-5-Cl-Piz reference standards needed to deduce the stereochemistry of KtzP halogenase mediated piperazic acid chlorination during kutzneride biosynthesis.



Enzymic Chlorination Event Gives *Cis*-3,5-Cl-Piz Thioester

(3*S*,5*R*) or (3*R*,5*S*)- in Kutzneride 2 & 8

Kutzneride 8 (Antifungal)

Kutzneride Always Have a *Trans*-3,5-Cl-Piz in Their Skeleton

Following thioesterase release, NMR correlation of the resulting free 5-Cl-Piz with our synthetic 3,5-*trans*-5-chloro-piperazic acid revealed that the kutzneride P halogenase initially installs a *cis*-3,5-chloropiperazic acid into the kutzneride, and that this then undergoes further enzymatic processing to give the 3,5-*trans*-5-chloropiperazic acid residues found in the actual natural products themselves.

Walsh, Hale, Manaviazar, Schroeder et al. *Biochemistry,* **2011**, *50*, 6063.

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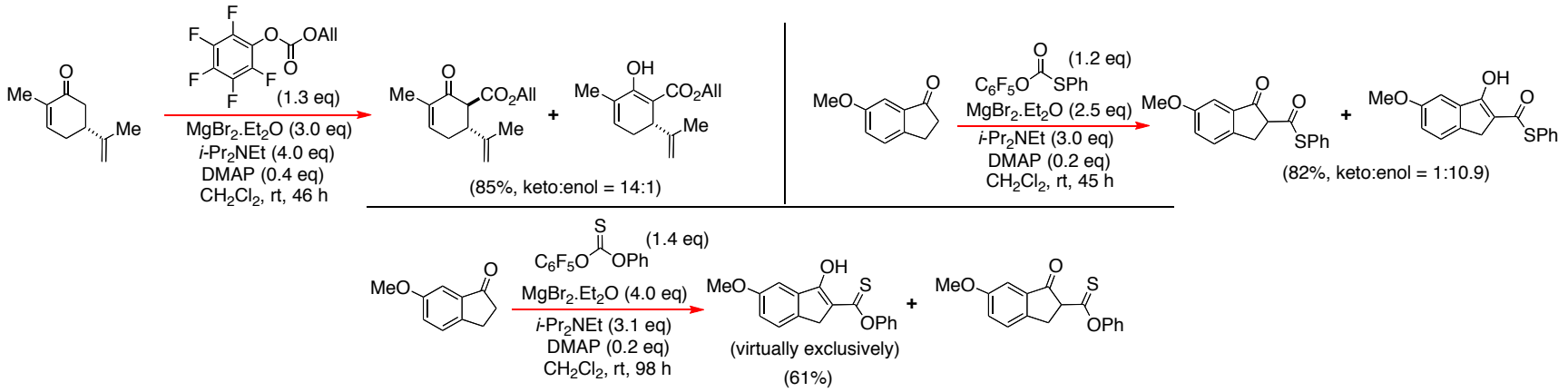
Research Interests of the Hale Group

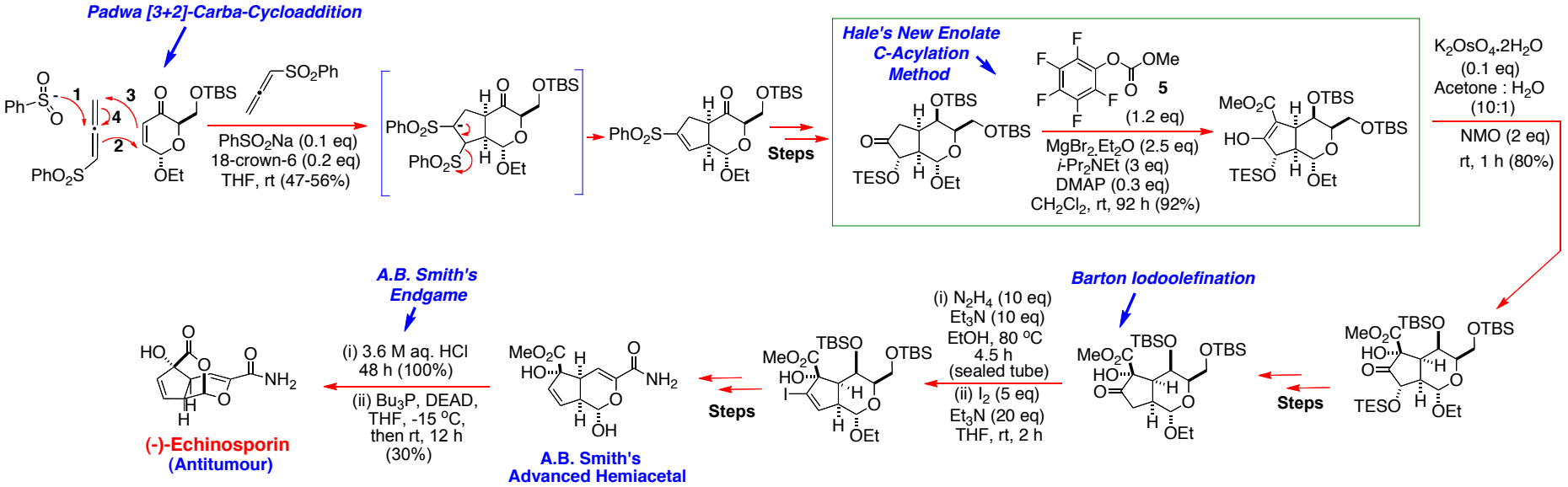
New Reaction Development

A New Mild Method For Ketone Enolate C-Acylation



New Ketone Enolate C-Acylation Method: K.J. Hale, M. Grabski and J.T. Flasz *Org. Lett.* **2013**, *15*, 370.

Use of the Ketone Enolate C-Acylation Method with Pentafluorophenyl Carbonates In the Formal Total Synthesis of (-)-Echinosporin



(-)-Echinosporin Formal Synthesis: J. T. Flasz and K.J. Hale *Org. Lett.* **2012**, *14*, 3024.

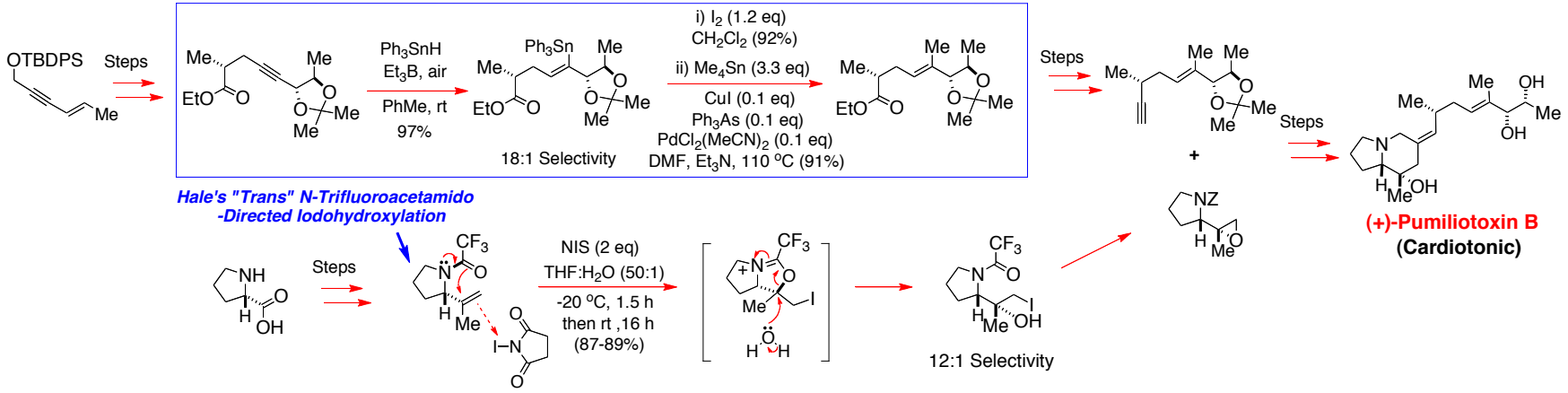
(-)-Echinosporin Total Synthesis: A. B. Smith III, G. Sulikowski. K. Fujimoto et al. *J. Am. Chem. Soc.* **1992**, *114*, 2567.

Research Interests of the Hale Group

New Reaction Development

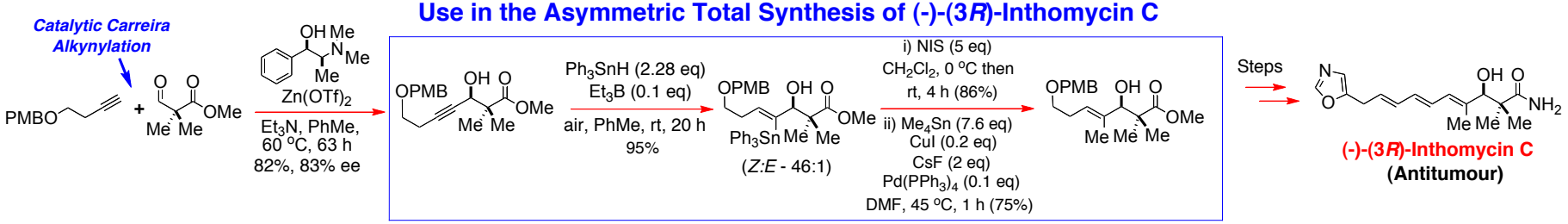
The O-Directed Free Radical Hydrostannation Reaction Of Alkylacetylenes With Ph_3SnH/cat. Et_3B/O_2 in PhMe

Use in a Formal Total Synthesis of (+)-Pumiliotoxin B



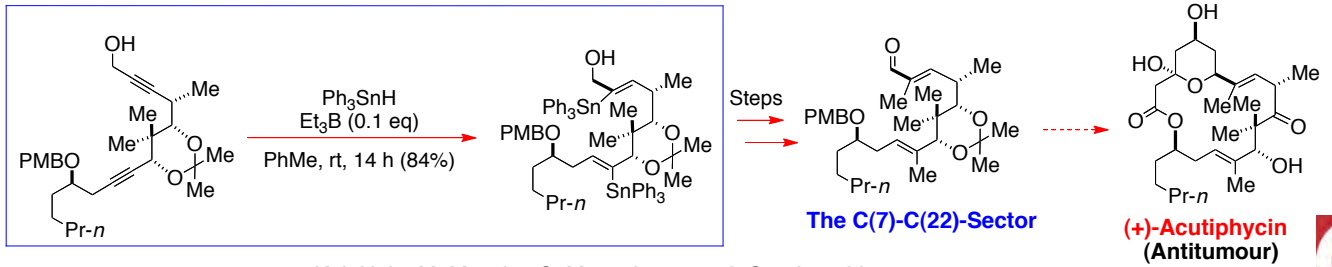
S. Manaviazar, K.J. Hale, A. LeFranc *Tetrahedron Lett.* **2011**, *52*, 2080.

Use in the Asymmetric Total Synthesis of (-)-(3*R*)-Inthomycin C



K.J. Hale, M. Grabski, S. Manaviazar *et al. Org. Lett.* **2014**, *16*, 1164.

Deployment of a New "Double O-Directed Free Radical Hydrostannation" in a Synthesis of the C(7)-C(22)-Sector of (+)-Acutiphycin



K.J. Hale, M. Maczka, S. Manaviazar *et al. Org. Lett.* **2014**, *16*, 1168.

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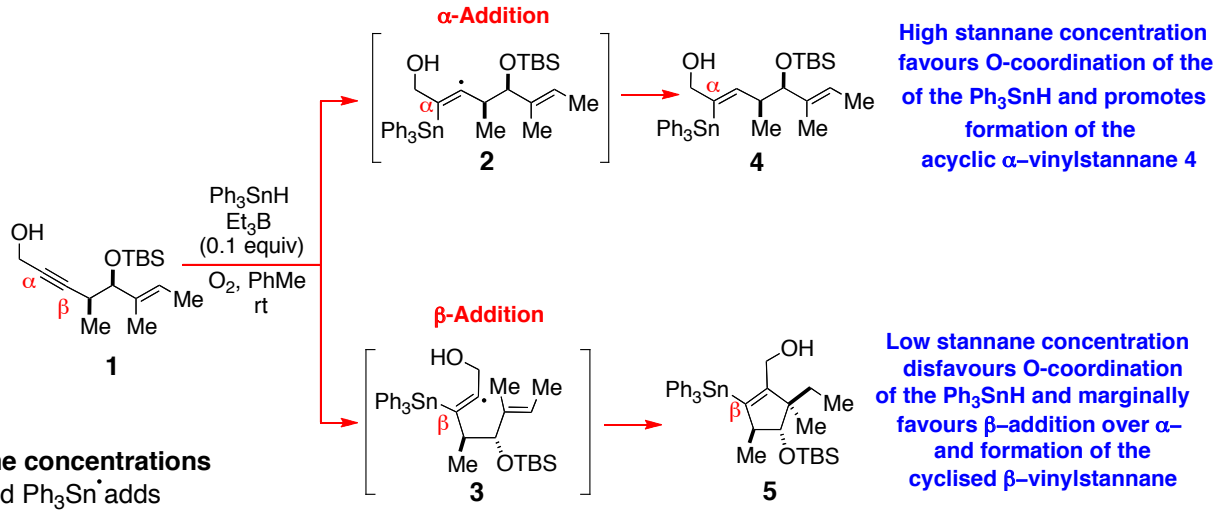
Research Interests of the Hale Group

Physical Organic Chemistry and Elucidating Complex Reaction Mechanisms With Small Molecule Probes

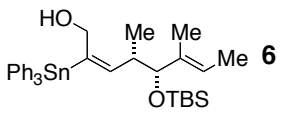
The Definitive Probe Experiment Which Proved That Propargyloxy O-Coordination to the Ph_3SnH Was Responsible for the α-Stannylated Products Preferentially Arising In the O-Directed Free Radical Hydrostannation of Propargylically-Oxygenated Alkylacetylenes



At low stannane concentrations uncoordinated $Ph_3Sn^{\bullet}$ adds to the acetylene and electronic control is dominant; minimal coordination occurs between the stannane and the propargylic OH

Alkynol *c* in PhMe	Ph_3SnH (equiv)	Time	Main Products	Ratio α : β Addition	% Yield
0.01 M	3 equiv	24 h	**4** : **5**	1 : 1.7	56
0.1 M	1.5 equiv	16 h	**4** : **5**	3.5 : 1	67
0.1 M	4 equiv	5.5 h	**4** : **5**	4.5 : 1	79
0.1 M	6 equiv	5.5 h	**4** : **5**	11.1 : 1	78

At high stannane concentrations coordination between the Ph_3SnH the propargylic OH readily occurs and O-coordinative control becomes dominant. It is now the O-coordinated $Ph_3Sn^{\bullet}$ that preferentially adds because it is formed faster and it has greater longevity in solution.



6

A barely detectable quantity of **6** was also formed in all these reactions.The structure of **6** is thus only tentatively assigned.

If electronic effects were primarily responsible for determining the regiochemistry of stannyl radical addition, then one would not see the ratio of α : β addition products changing to any significant degree as the concentration of stannane increased. However. it does change very dramatically, as one can see. The only rational explanation of this behaviour is O-coordinative control overriding the inherent electronic preferences of uncoordinated stannyl radical addition.

K.J. Hale, S. Manaviazar, P. Dimpoulos *et al. Org. Lett.* **2005**, *7,* 5377.

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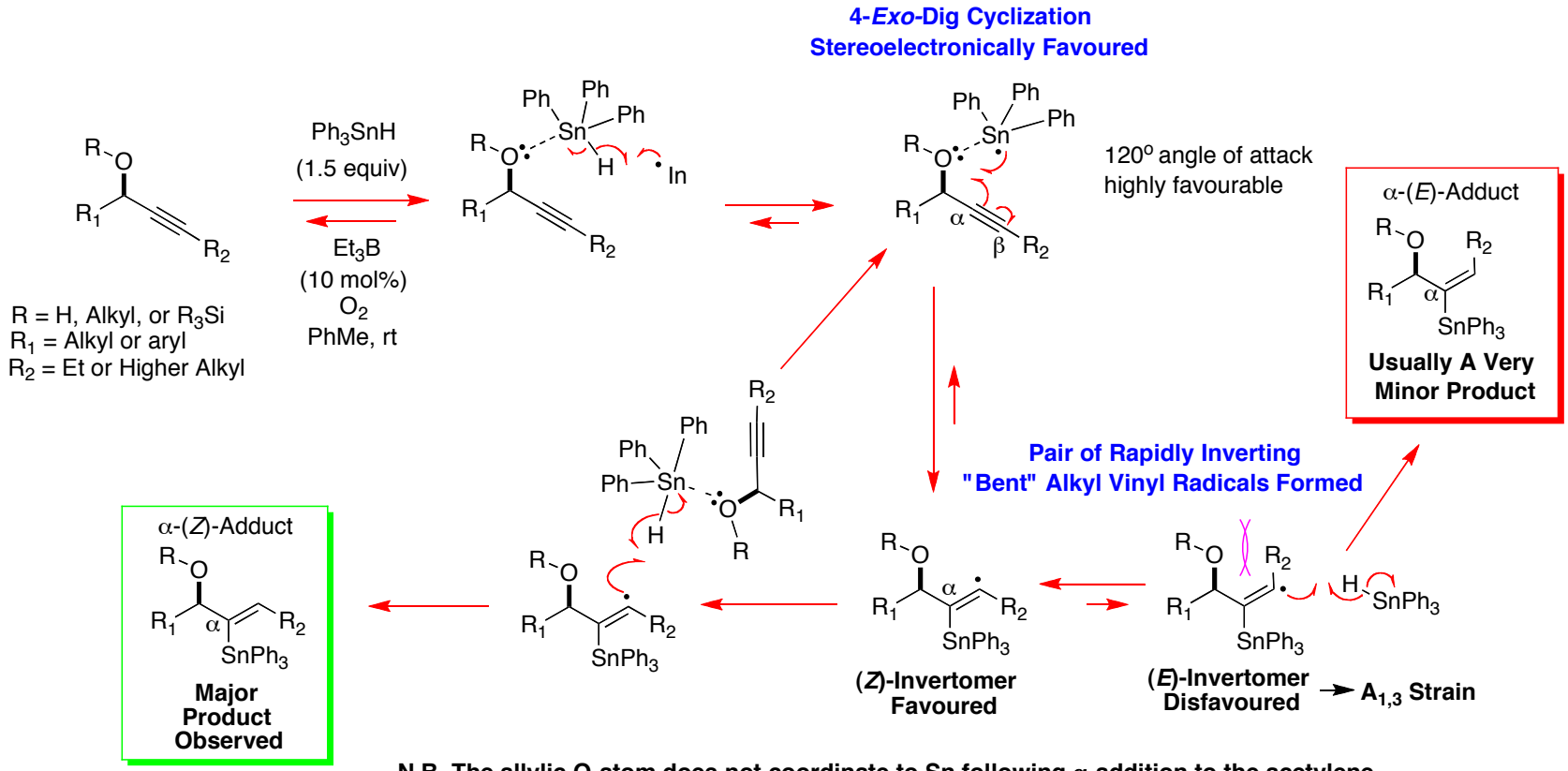
Research Interests of the Hale Group

Physical Organic Chemistry and Elucidating Complex Reaction Mechanisms With Small Molecule Probes

The Mechanism of the O-Directed Hydrostannation of Alkylacetylenes with Ph_3SnH/cat. Et_3B



N.B. The allylic O-atom does not coordinate to Sn following α-addition to the acetylene.

X-ray crystallography confirms that no such coordination occurs in the α-(Z)-adducts.

This lack of internal O-coordination in the fully developed α-stannylvinyl radical makes the reverse elimination less favourable, and helps promote formation of the α-(Z)-adduct.

Internal 1,5-H-Atom Abstraction by the Vinyl Radicals Can Also Occur.

P. Dimopoulos, K.J. Hale, S. Manaviazar *et al. Org. Lett.* **2005**, *7,* 5377.

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Research Interests of the Hale Group

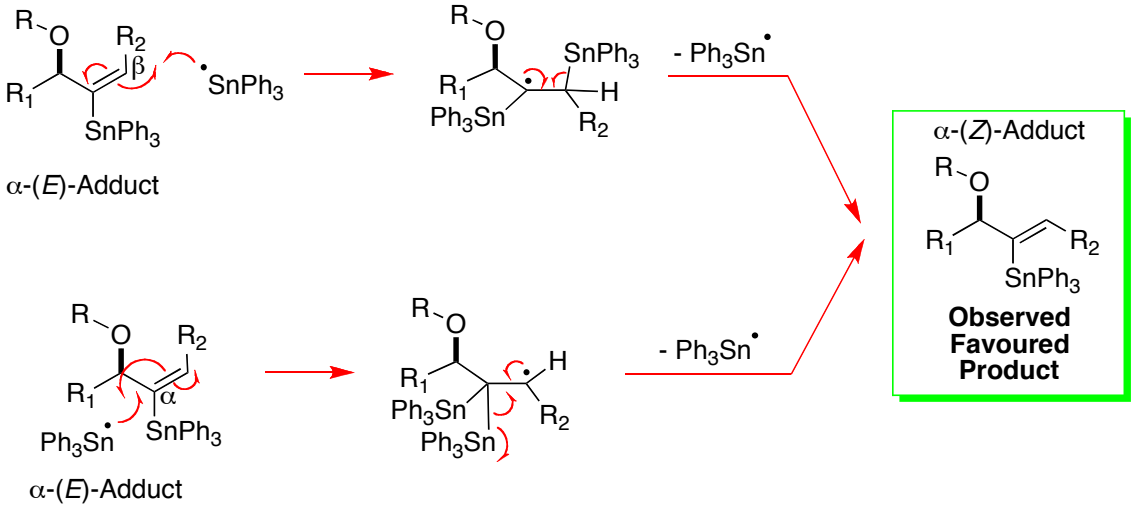
Physical Organic Chemistry and Elucidating Complex Reaction Mechanisms With Small Molecule Probes

The Mechanism of the O-Directed Hydrostannation of Alkylacetylenes with Ph_3SnH/cat. Et_3B

The Disfavoured (*E*)-α–Vinylstannane Geometric Isomer Isomerises Under the Reaction Conditions

Two Main Mechanisms By Which It Does This:

β-Stannyl Radical-Addition with C-C Bond Rotation and Elimination



α-Stannyl Radical-Addition with C-C Bond Rotation and Elimination

P. Dimopoulos, K.J. Hale, S. Manaviazar *et al. Org. Lett.* **2005**, *7,* 5377.

Queen's University Belfast

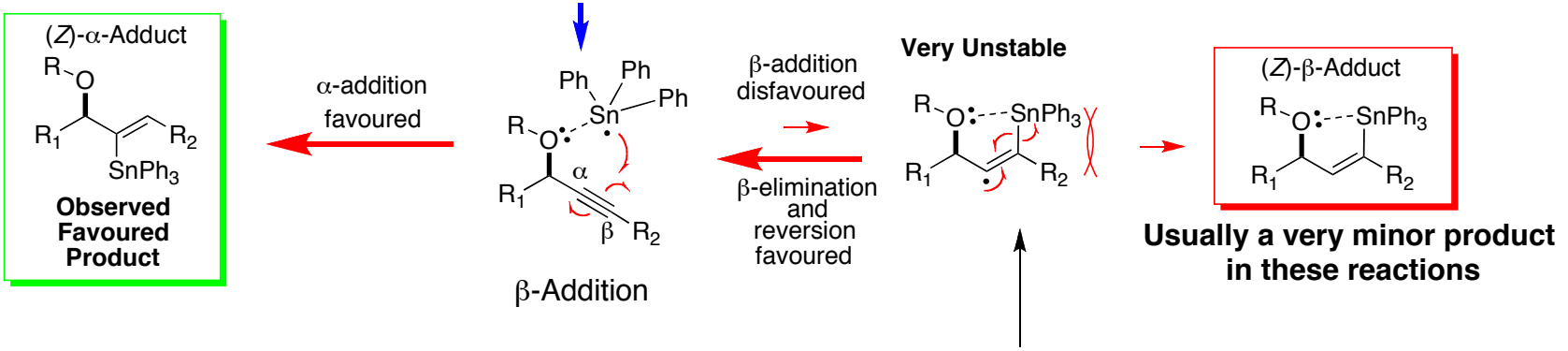
Research Interests of the Hale Group

Physical Organic Chemistry and Elucidating Complex Reaction Mechanisms With Small Molecule Probes

The Mechanism of the O-Directed Hydrostannation of Alkylacetylenes with Ph_3SnH/cat. Et_3B

O-Directed β-C-Addition is Not Favoured Due to Coordinative Elimination of the Intermediary β-Stannyl(alkyl)vinyl Radicals

The O-Directed β-Additive 5-*Endo*-Dig Cyclization is Less Favoured Stereoelectronically



Strong internal O-coordination in the β-stannylvinyl radical adducts weakens the C-Sn bond and this, along with the geminal repulsion indicated, almost certainly favours the reverse retro-stannation reaction:
i.e. β-elimination of the intermediary vinylstannyl radical to its O-coordinated stannyl radical acetylene precursor.

P. Dimopoulos, K.J. Hale, S. Manaviazar *et al. Org. Lett.* **2005**, *7,* 5377.

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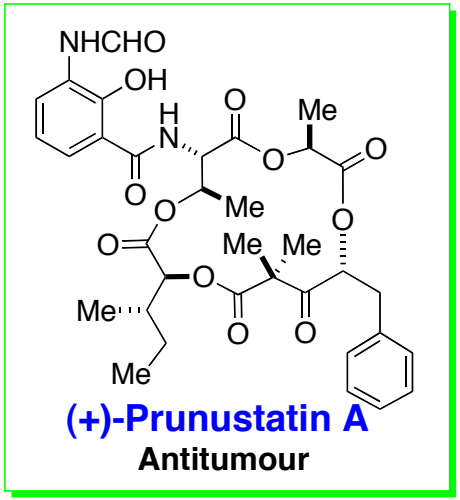
(+)-Prunustatin A



(+)-Prunustatin A
Antitumour

- Isolated from fermentation broths of *Streptomyces violaceoniger* (4521-SVS3) by Shin-ya et al. [1,2]

- *Streptomyces violaceoniger* (4521-SVS3) is indigenous to soil of the Okinawan island of Kumejima.[1,2]

- (+)-Prunustatin A is a very powerful downregulator of GRP78 expression in stressed (glucose-deprived) HT1080 human fibrosarcoma cells at very low drug concentrations (IC_{50} = 11.5 nM) and, at the 100 nM level, it causes full cancer cell apoptosis.[1]

- GRP78 (78 kDa glucose-regulated protein) is an endoplasmic reticulum (ER) protein that is produced in response to cell stress and hostile environments.

- It is massively upregulated in untreatable, drug-resistant, hypoxic solid tumours.

- High GRP78 levels switch on the unfolded protein response within tumours, which renders them recalcitrant to treatment with drugs and radiotherapy.

- As a result of this profile, (+)-prunustatin A might be of potential value for treating currently incurable hypoxic solid human tumours.

- (+)-Prunustatin A has recently been synthesised by the groups of Kawanishi and Usuki.[3,4]

[1] **Isolation and Biological Activity:** (a) K. Shin-ya *et al. J. Antibiot.* **2005**, *58*, 206.
[2] **Structure Determination**: K. Shinya *et al. Org. Lett.* **2007**, *9*, 4239.
[3] **First Total Synthesis**: S. Yamakoshi and E. Kawanishi *Tetrahedron Lett.* **2014**, *55*, 1175.
[4] **Second Total Synthesis**: Y. Usuki *et al. Asian JOC* **2015**, *4*, 737.

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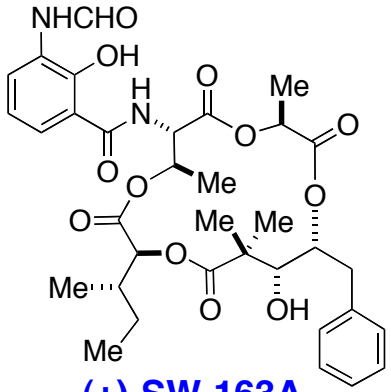
(+)-SW-163A



(+)-SW-163A

Immunosuppressant

- (+)-SW-163A was first isolated by Takahashi *et al.* in 2001 from culture broths of *Streptomyces sp.* SNA15896, a soil microbe from the Yuuki region of Japan.[1,2]

- (+)-SW-163A inhibits the immune response of murine splenic lymphocytes with an IC_{50} value of 62 nM.[1]

- (+)-SW-163A also inhibits lymphocyte blastogenesis with an IC_{50} value of 48 nM.[1]

- Unlike, (-)-FK506 and cyclosporin A, which both suppress the immune response by blocking T-cell function, (+)-SW-163A prevents T-cells and B-cells from simultaneously becoming primed and activated.

- As such, (+)-SW-163A is of considerable pharmaceutical interest, since (-)-FK506 and cyclosporin A are both extremely toxic.

- The introduction of (+)-SW-163A could potentially herald a new safe era for human transplant surgery and improve many patient outcomes, since (+)-SW-163 is non-cytotoxic towards unstressed eukaryotic cells.

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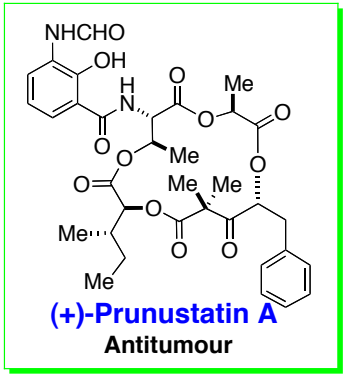
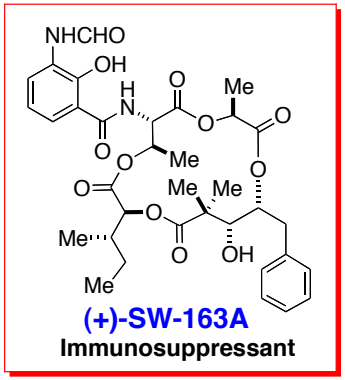
[1] **Isolation and Biological Activity:** K. Takahashi *et al. J. Antibiot.* **2001**, *54*, 867.
[2] **Structure Determination**: K. Shinya *et al. Org. Lett*. **2007**, *9*, 4239.

Objectives of the Present Research Programme



(+)-Prunustatin A
Antitumour



(+)-SW-163A
Immunosuppressant

Background

➢ (+)-Prunustatin A and (+)-SW-163A are both in extremely short supply and presently inaccessible to the wider scientific community and the pharmaceutical industry.

➢ The producing organisms are also not generally accessible and closely guarded by the owners.

➢ To enter human clinical development, new, easily executed, total syntheses of both agents urgently need to be developed.

➢ The two recent total syntheses of (+)-prunustatin A by Kawanishi[1] and Usuki[2] are tricky to carry out and, in the case of the 2014 Kawanishi synthesis, no experimental details of the route have ever been reported, making its repetition extremely difficult.

Objectives of Present Research Programme

➢ To develop a practical, easy to execute, new total synthesis of both compounds to help expedite their future clinical evaluation and allow future med chem refinement.

➢ To use these new synthetic routes to prepare novel probes and analogues that could allow the biological targets of these agents to be isolated and identified.

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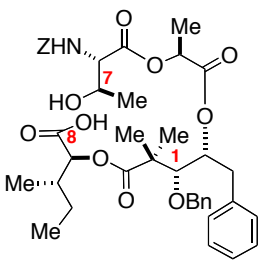
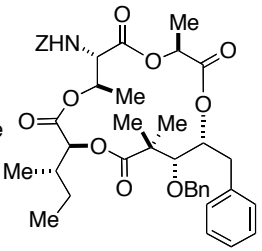
[1] **First Total Synthesis**: S. Yamakoshi and E. Kawanishi *Tetrahedron Lett.* **2014**, *55*, 1175.
[2] **Second Total Synthesis**: Y. Usuki *et al. Asian JOC* **2015**, *4*, 737.

Early Defeats! These Outcomes Revealed The Nature of the Problem That We Were Confronting!

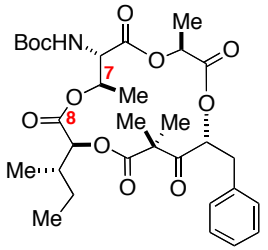


0.75 g

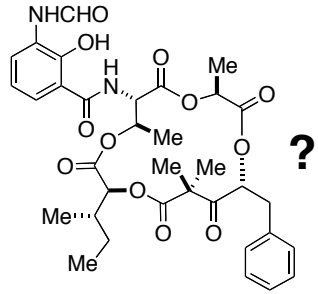
2,4,6-Trichlorobenzoyl chloride (10 equiv)
Et_3N (2 equiv), C_6H_6
rt, 15 h then dilute with C_6H_6 and add dropwise to DMAP (7 equiv) in C_6H_6 at 2-4 °C over 6 h; then stir at rt 7 d
74%



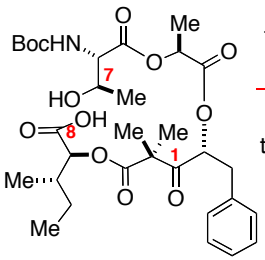
0.54 g
Single product formed!



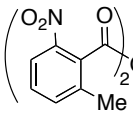
Single product formed!
However, the products from either route were both different !!



(+)-Prunustatin A
Not produced by either route!
Rather, diastereoisomers of prunustatin A were synthesized instead!



0.3 g

Add hydroxy acid in THF: CH_2Cl_2, (1:1) dropwise over 9 h
to

(1.3 equiv)
MNBA
and DMAP (2 equiv) in THF, rt. Stir 48 h
49%

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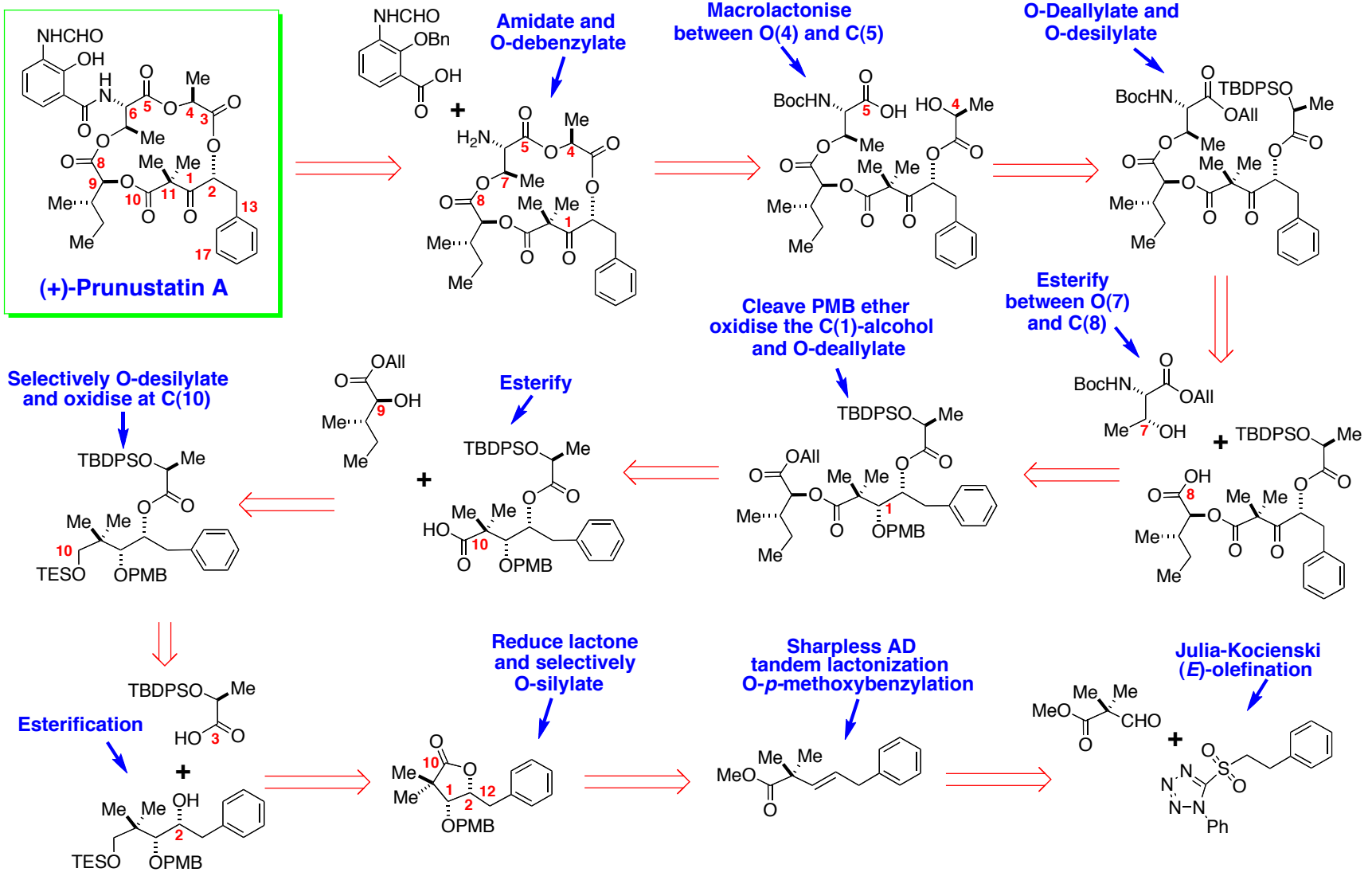
Our Revised Retrosynthetic Planning for (+)-Prunustatin A



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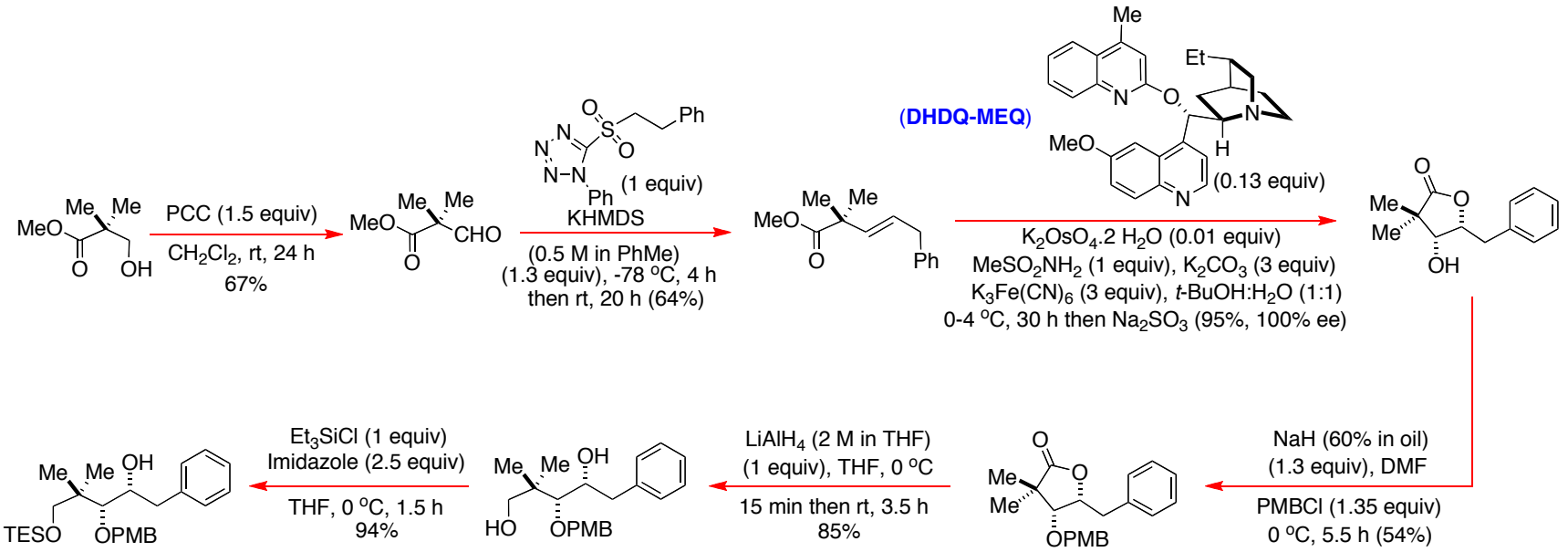
Our New Synthetic Route (+)-Prunustatin A



DHQD-MEQ Ligand: K.B. Sharpless et al. *J. Org. Chem.* **1991**, *56*, 4585.

This is best for ADs in sterically-hindered systems such as this alkene here.

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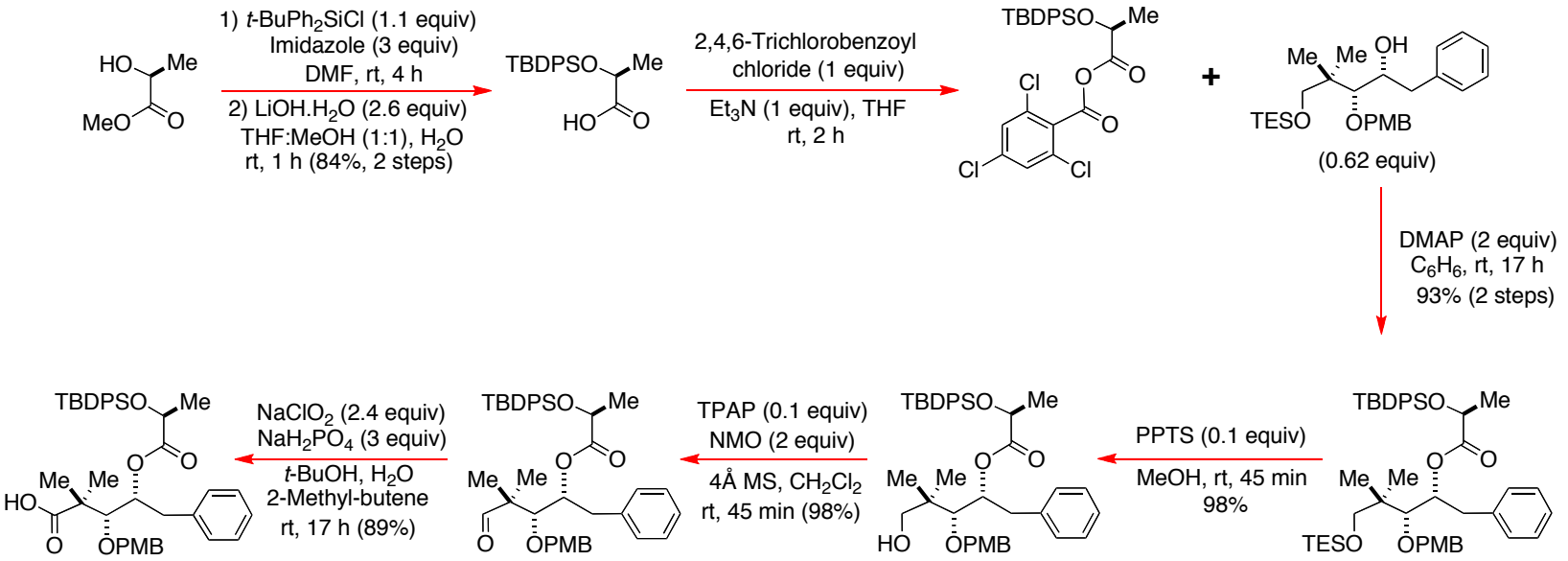
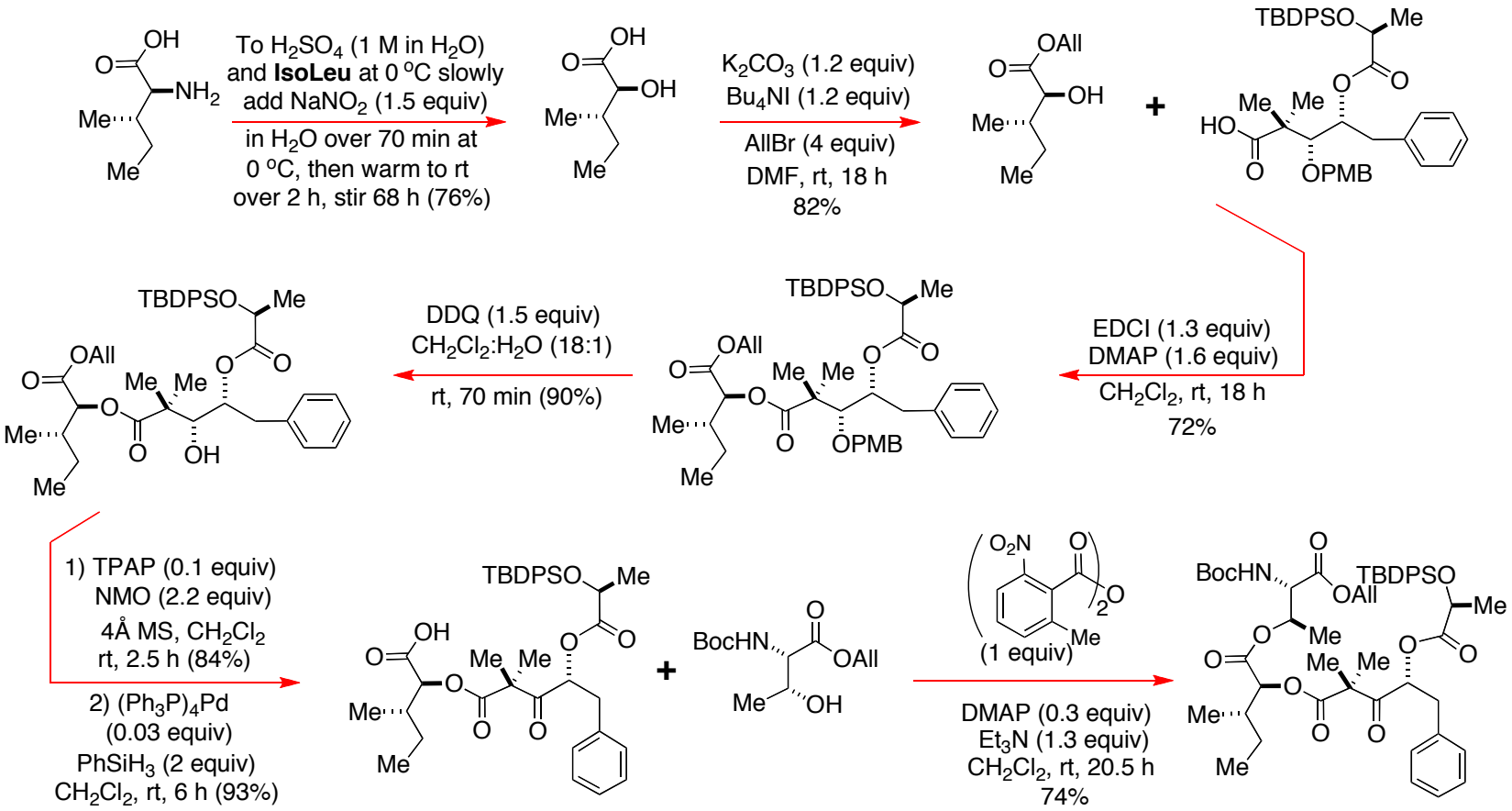
Our New Synthetic Route (+)-Prunustatin A



Our New Synthetic Route (+)-Prunustatin A



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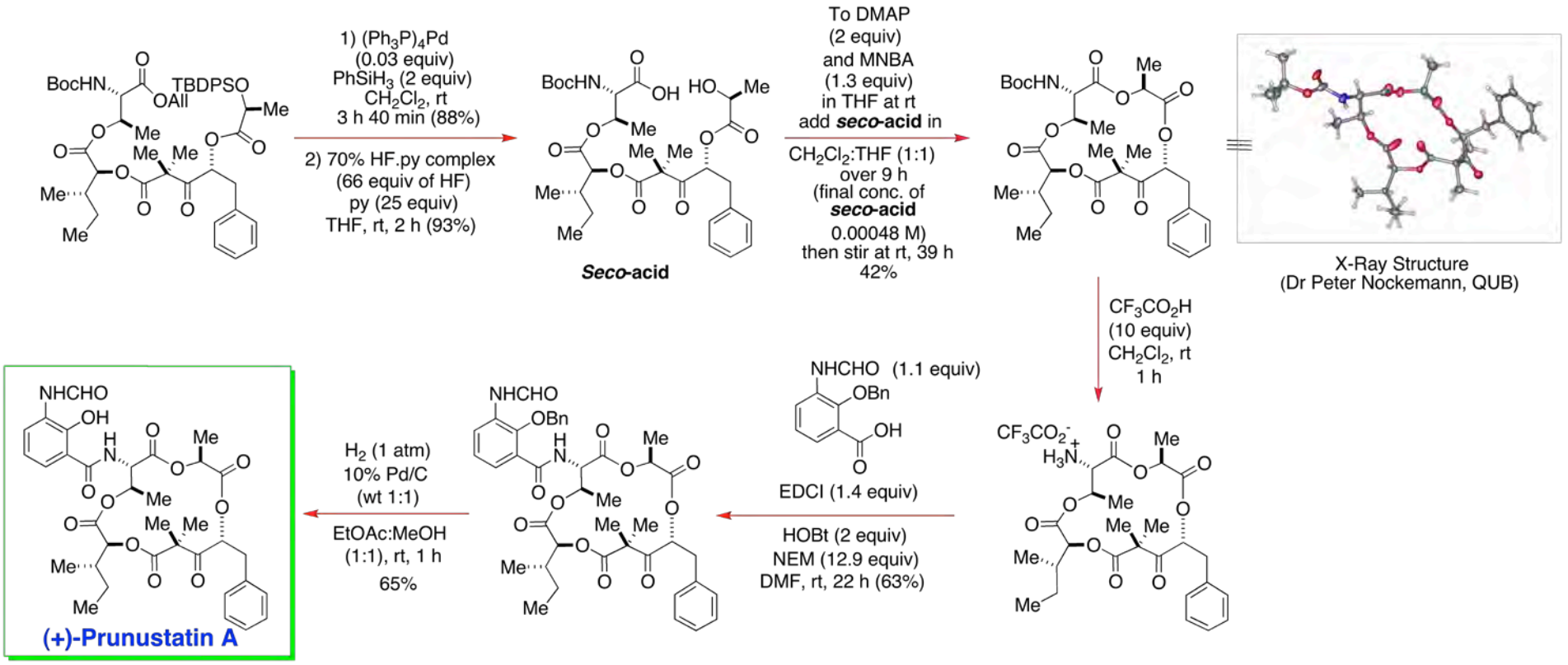
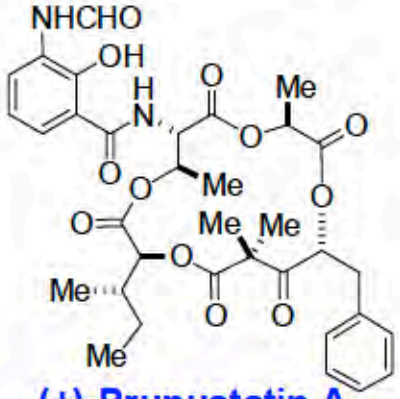
Completion of Our New Total Synthesis of (+)-Prunustatin A



Soraya Manaviazar

SM-19-87
PROTON
Ref: 0.00 ppm (CDCl3-TMS)



(+)-Prunustatin A


```
Current Data Parameters
NAME                  SM-19-87
EXPNO                       20
PROCNO                       1

F2 - Acquisition Parameters
Date_               20151119
Time                   15.51
INSTRUM                spect
PROBHD    5 mm PABBO BB/
PULPROG                 zg30
TD                    131072
SOLVENT                CDCl3
NS                         16
DS                          0
SWH               12019.230 Hz
FIDRES             0.091699 Hz
AQ                5.4526453 sec
RG                        161
DW                   41.600 usec
DE                   10.66 usec
TE                   301.6 K
D1               0.10000000 sec
TD0                         1

======== CHANNEL f1 ========
SFO1            399.9024695 MHz
NUC1                      1H
P1                   11.00 usec

F2 - Processing parameters
SI                    131072
SF              399.9000097 MHz
WDW                       EM
SSB                        0
LB                    0.10 Hz
GB                         0
PC                      1.00
```

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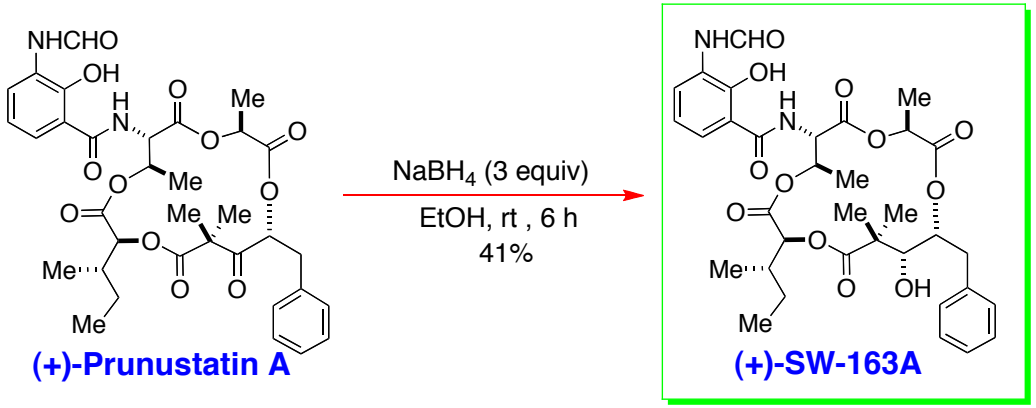
Completion of The First Total Synthesis of (+)-SW-163A



(+)-Prunustatin A

(+)-SW-163A

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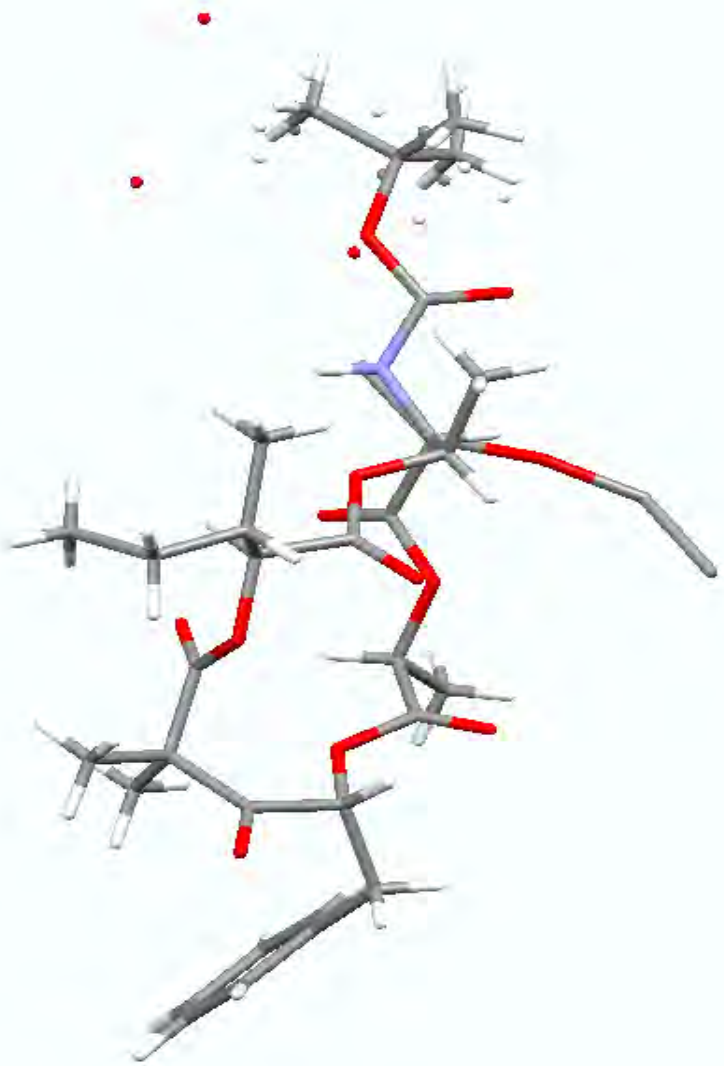
Origin of the Stereoselectivity of Reduction In the Total Synthesis of (+)-SW-163A



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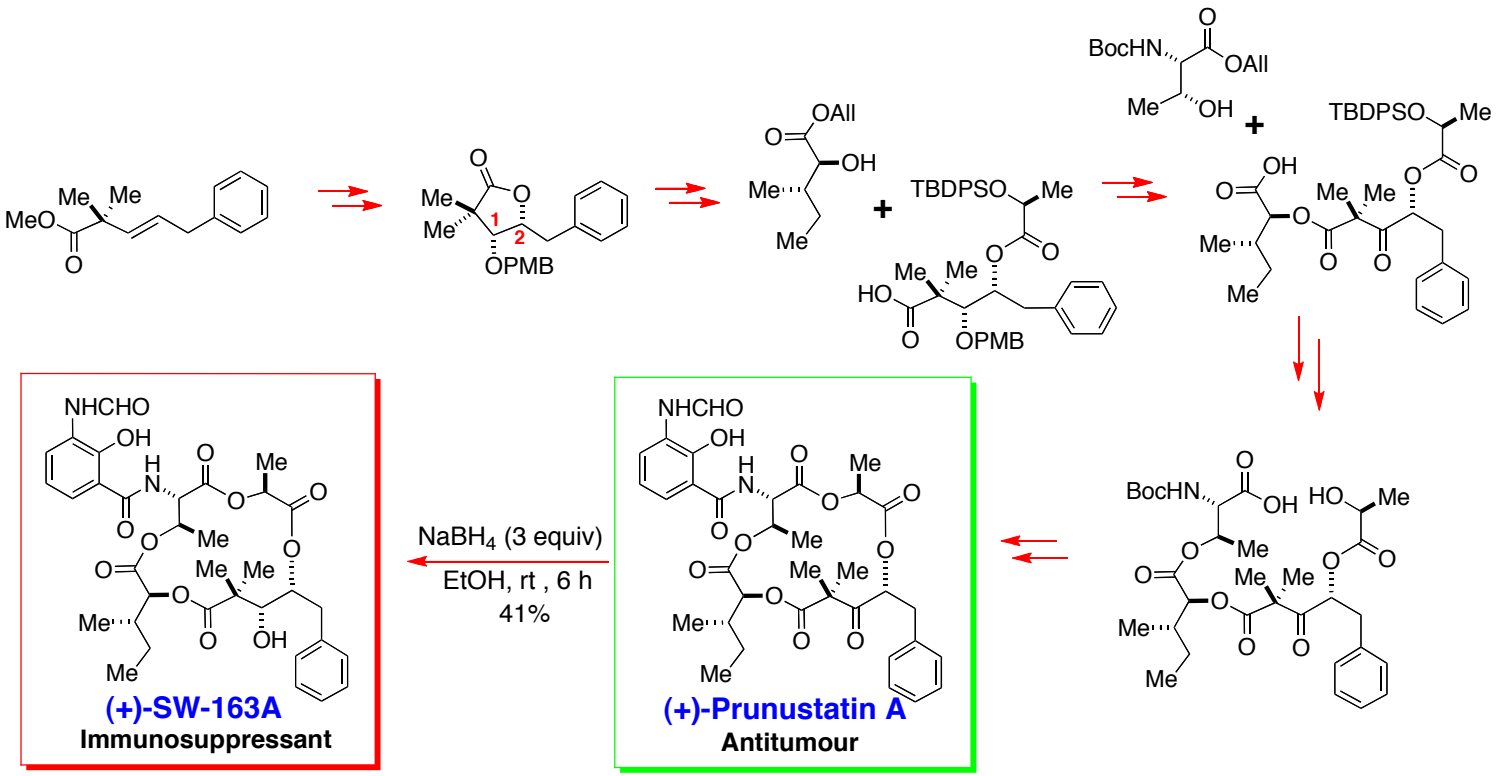
Summary
Of Our New Total Synthesis
(+)-Prunustatin A and (+)-SW-163A



For our recent published total synthesis of (+)-prunustatin A and (+)-SW-163A, see:

S. Manaviazar, P. Nockemann, and K.J. Hale *Org. Lett*. **2016**, *18*, 2902.

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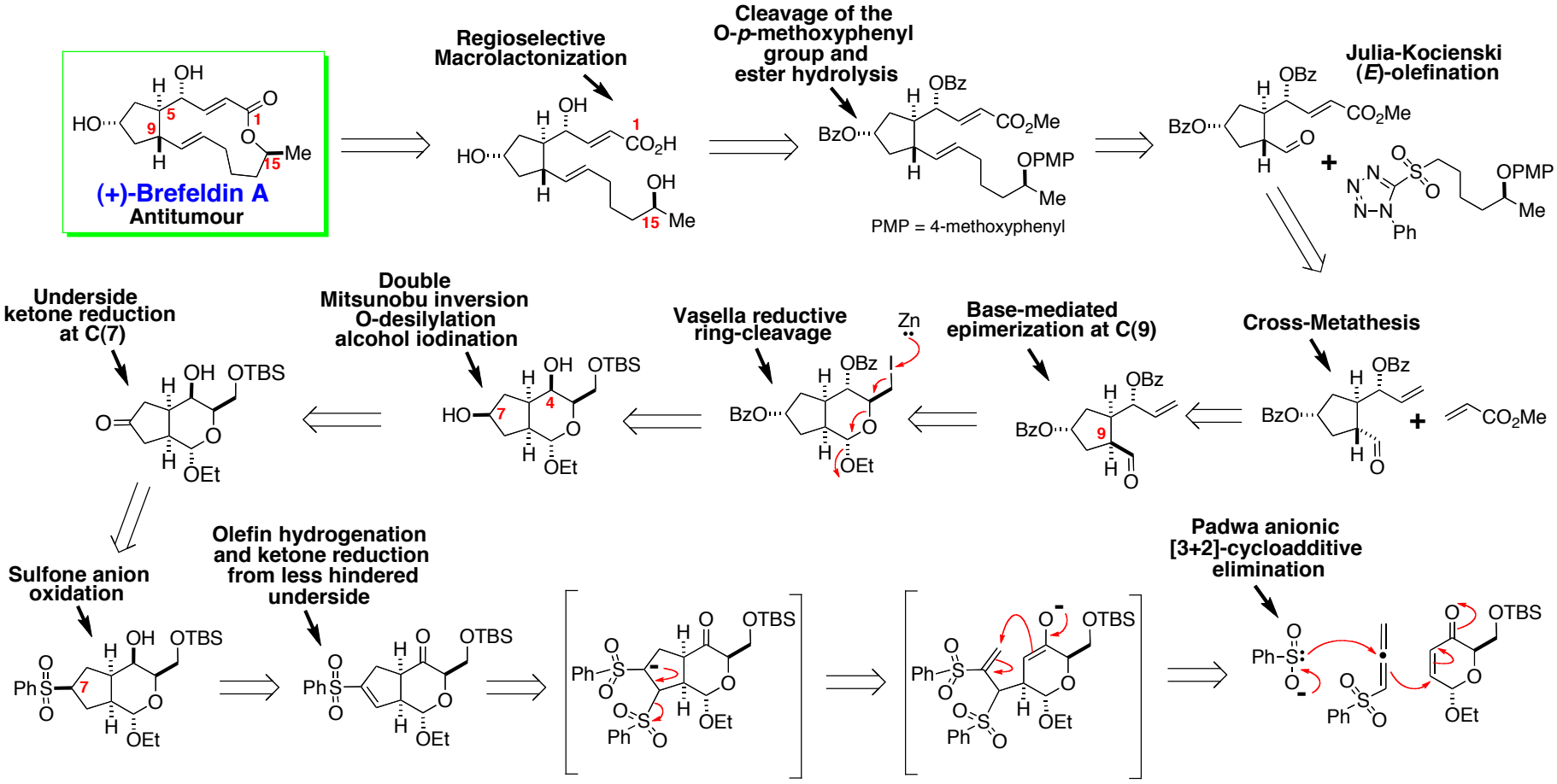
Retrosynthetic Analysis of (+)-Brefeldin A



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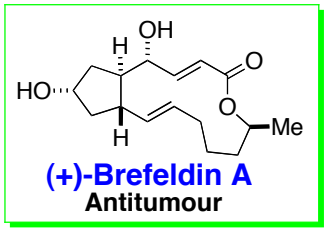
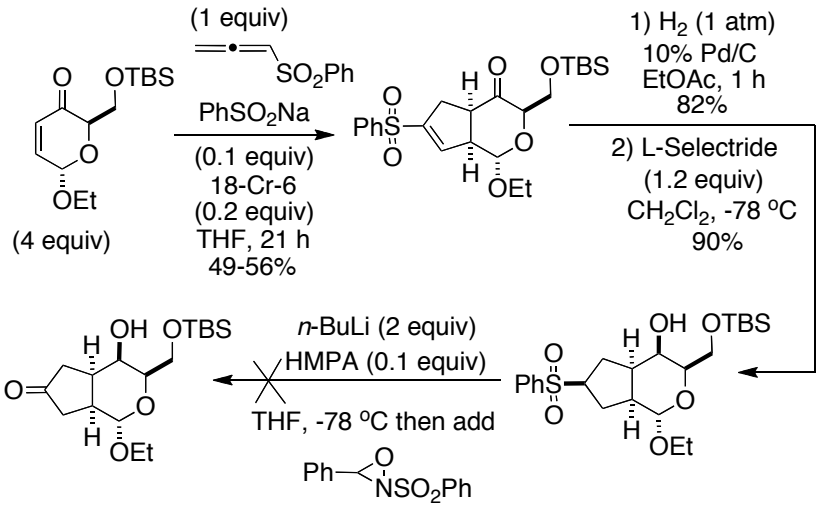
Our Initial Foray On (+)-Brefeldin A





For our (-)-echinosporin synthesis Padwa [3+2]-cycloadditive elimination, see:
J. T. Flasz and K.J. Hale *Org. Lett.* **2012**, *14*, 3024.

For Padwa's seminal publications on his allenylsulfone [3+2]-cycloadditive elimination, see:
A. Padwa and P. E. Yeske *J. Am. Chem. Soc.* **1988**, *110*, 1617.
A. Padwa and P. E. Yeske *J. Org. Chem.* **1988**, *56*, 6386.
A. Padwa, S. H. Wattterson, and Z. Ni *J. Org. Chem.* **1994**, *59*, 3256.

None of these Padwa publications attempted to apply the [3+2]-cycloadditive elimination on chiral substrates.

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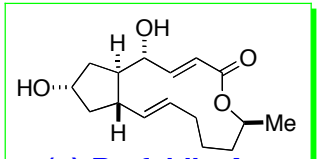
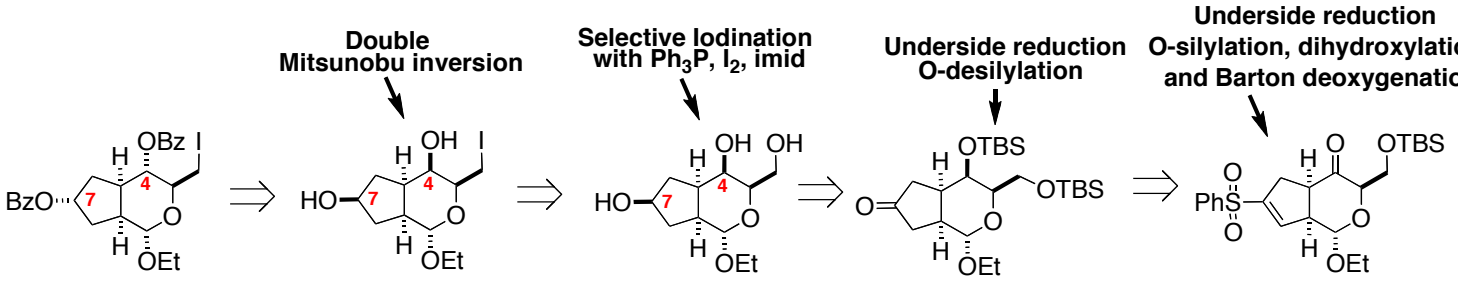
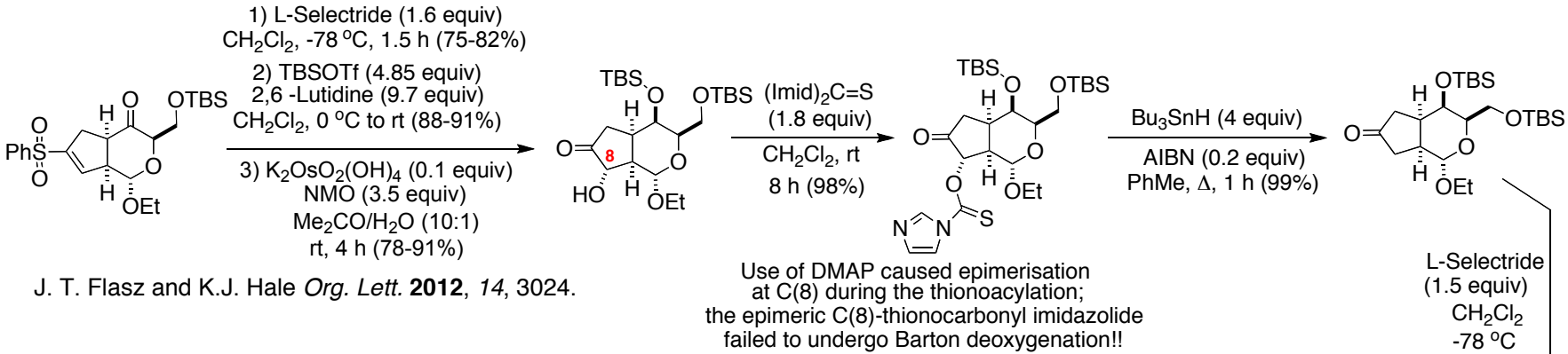
Revised Retrosynthetic Analysis of Advanced Iodide





Attempted Implementation and a Quick Evaluation of Double Mitsunobu Inversion Feasibility

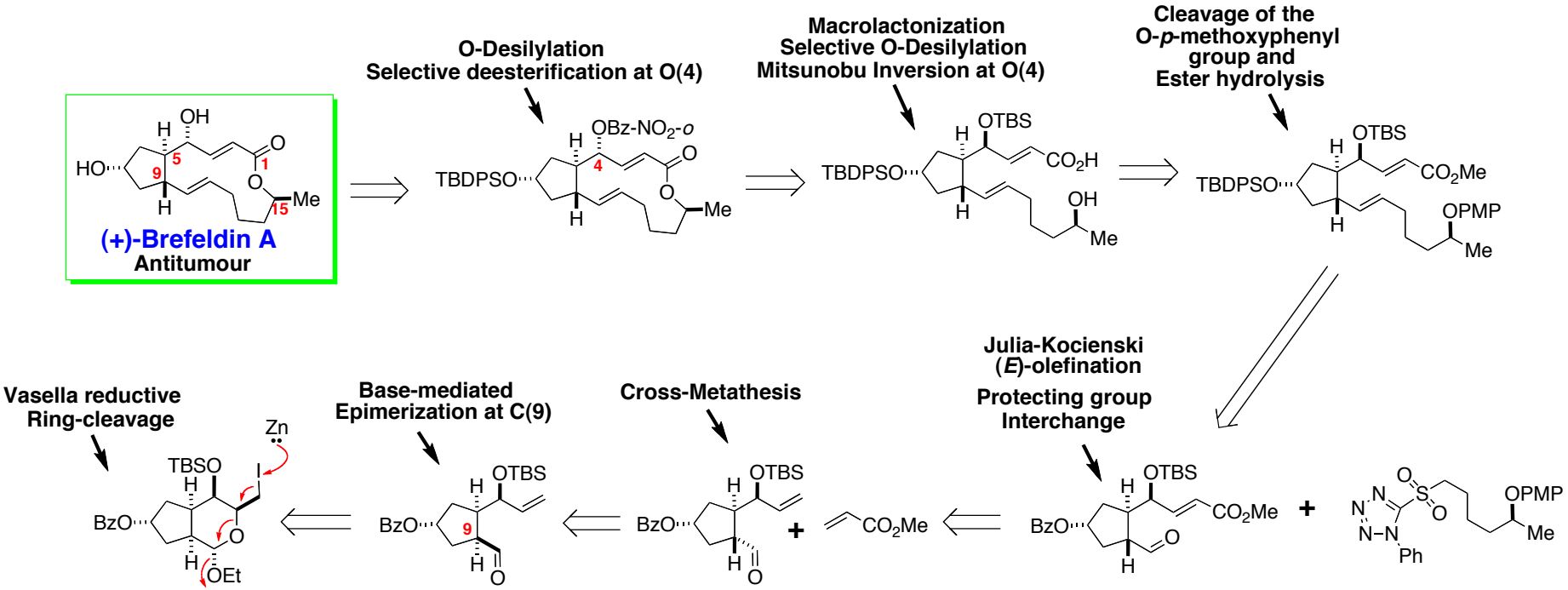


J. T. Flasz and K.J. Hale *Org. Lett.* **2012**, *14*, 3024.

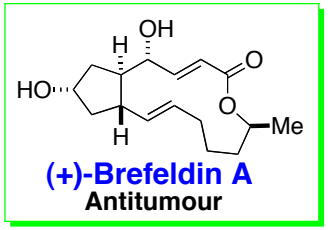
Use of DMAP caused epimerisation at C(8) during the thionoacylation; the epimeric C(8)-thionocarbonyl imidazolide failed to undergo Barton deoxygenation!!

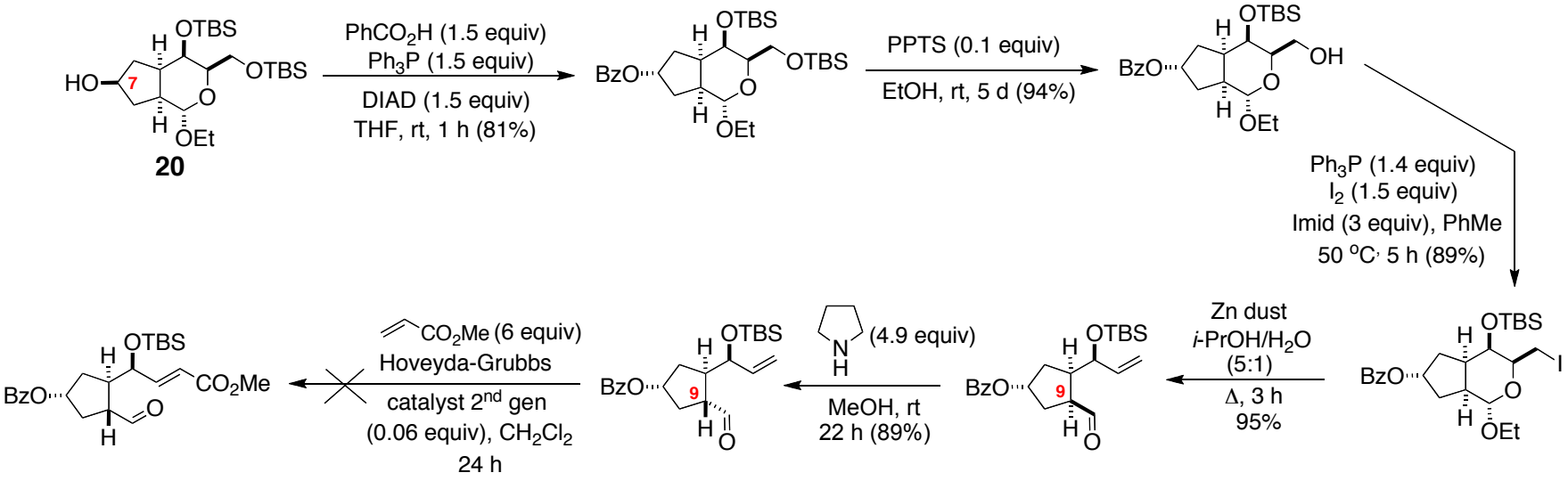
Clearly the C(4)-OH in the above di-O-benzoate is far too hindered to undergo Mitsunobu Inversion. C(4)-inversion would thus have to be postponed until after the pyranoside ring had been fragmented.

Revised Retrosynthetic Plan

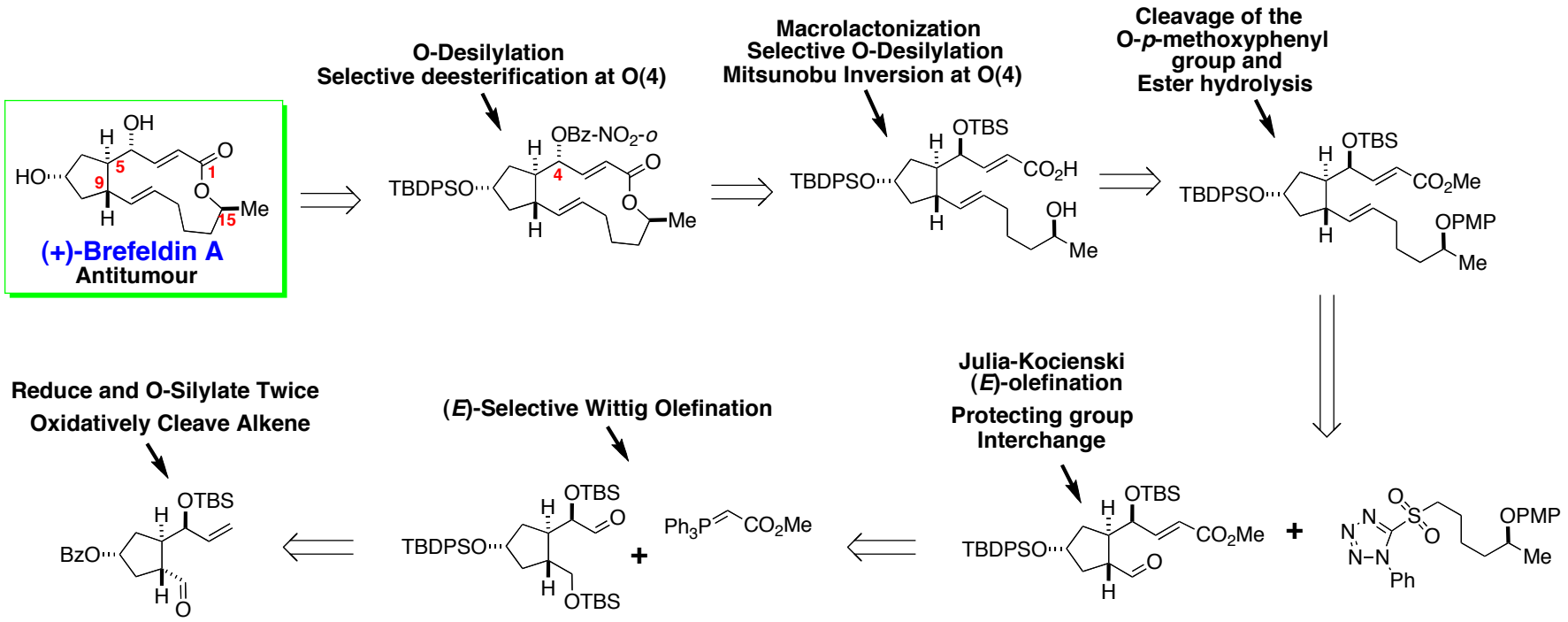


Attempted Implementation of the C(9)-Aldehyde Epimerisation and Olefin Cross-Metathesis Tactics

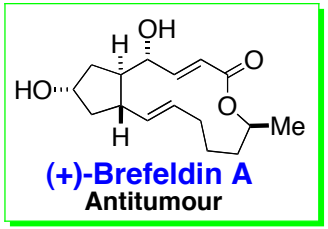


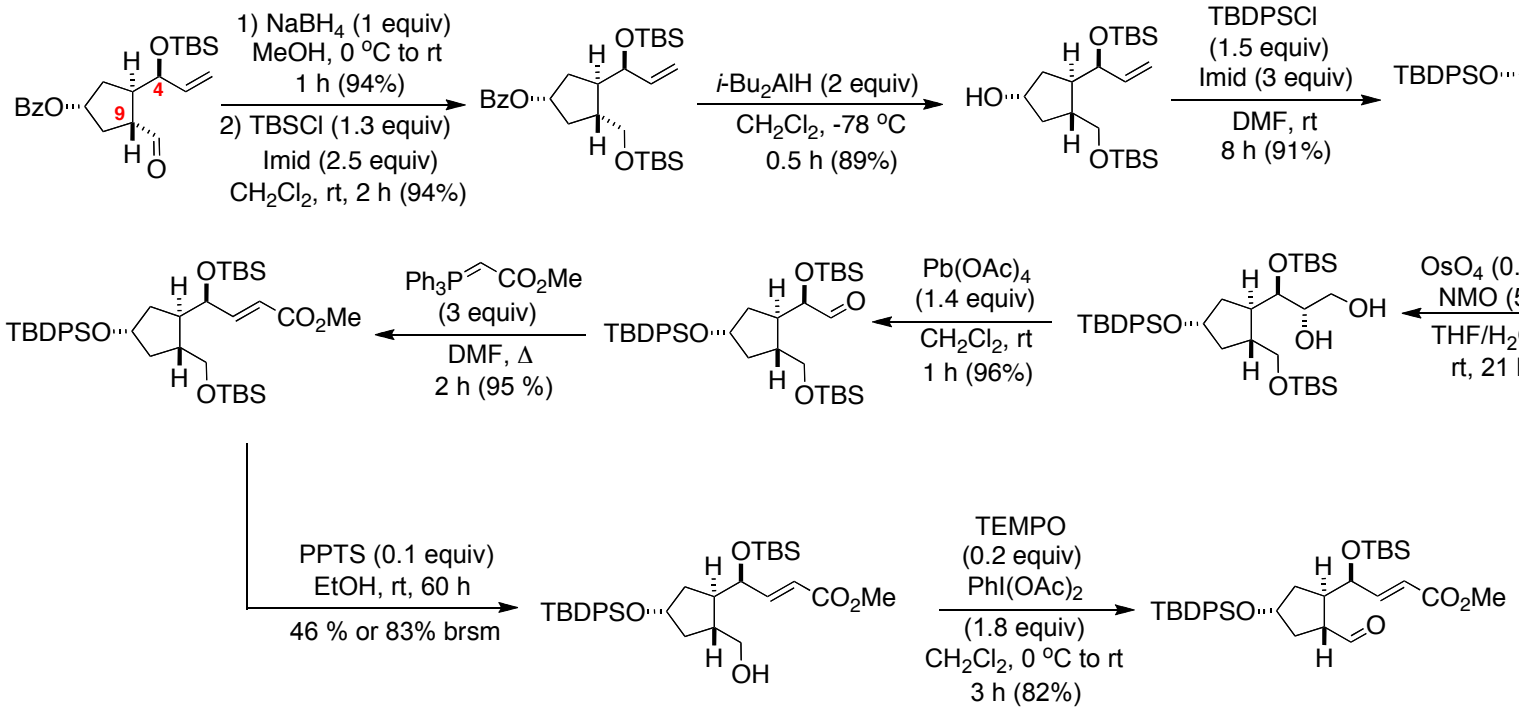


Further Revised Retrosynthetic Plan

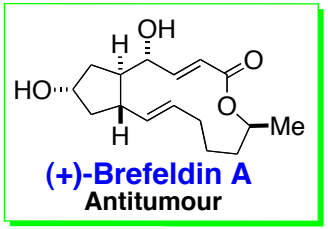


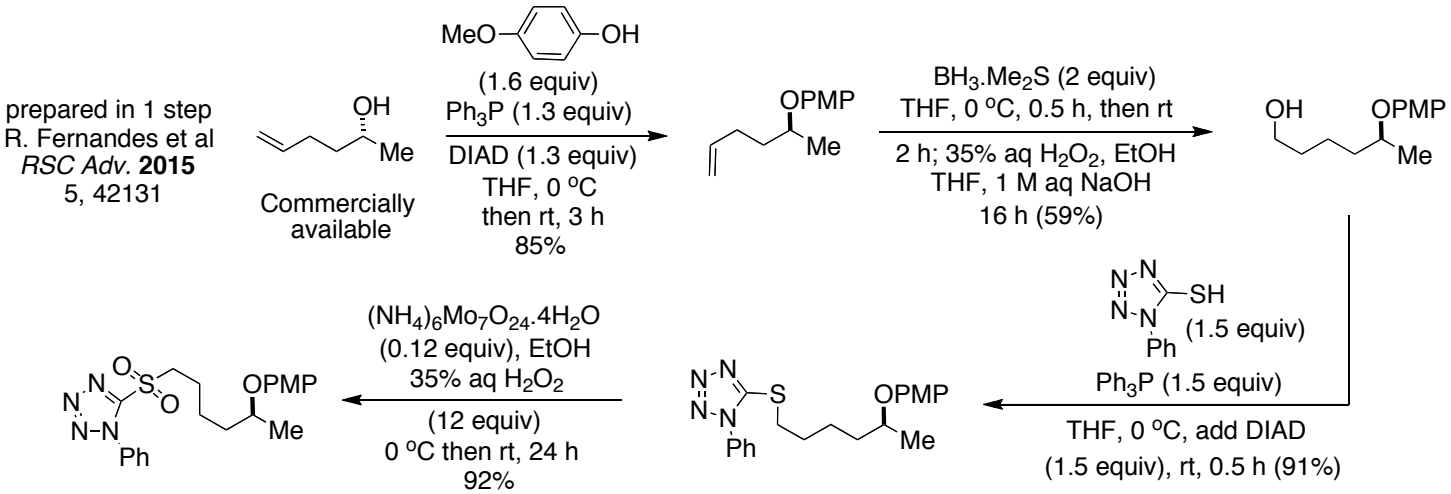
Success in the Stabilised Wittig Strategy for C(1)-C(3) Elaboration





A New Improved Synthesis of the N-Phenyltetrazolylsulfone





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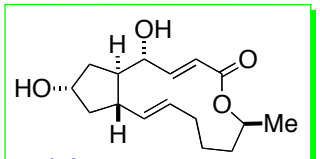
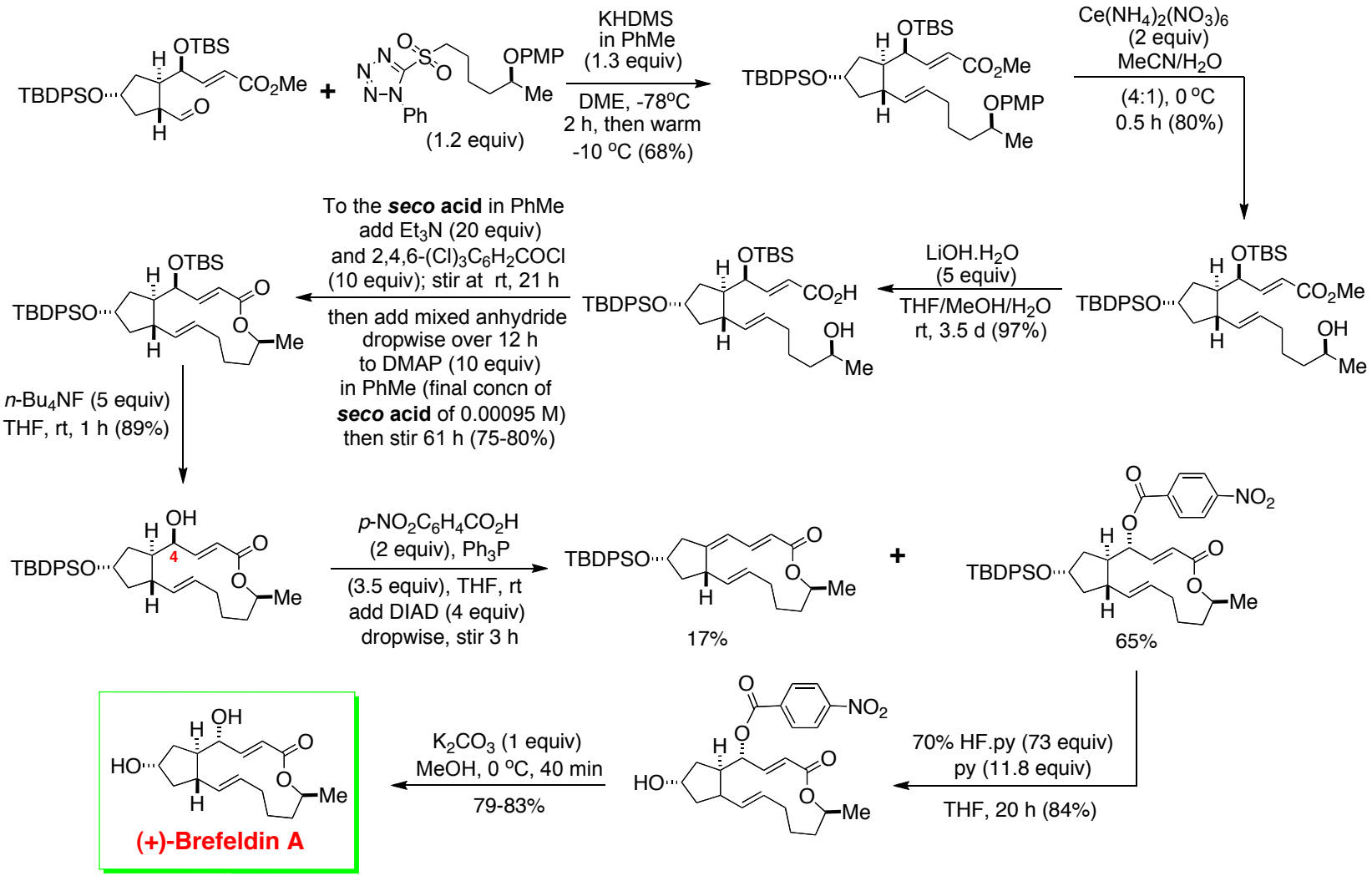
Completion of the Total Synthesis of (+)-Brefeldin A





For our recent report on the enantioselective total synthesis of (+)-brefeldin A, see:
Z. Xiong and K.J. Hale *Org. Lett.* **2016**, *18*, 4254.

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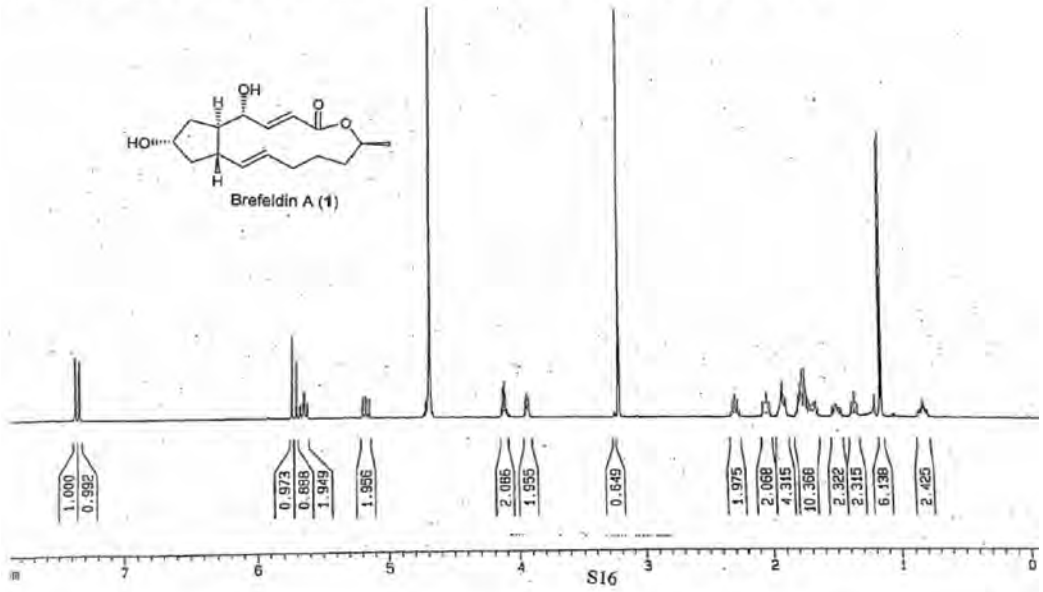
^{1}H NMR spectrum of Kim's synthetic (+)-brefeldin A (**1**) in CD_3OD at 500 MHz:



^{1}H NMR spectrum of our synthetic (+)-brefeldin A (**1**) in CD_3OD at 600 MHz: