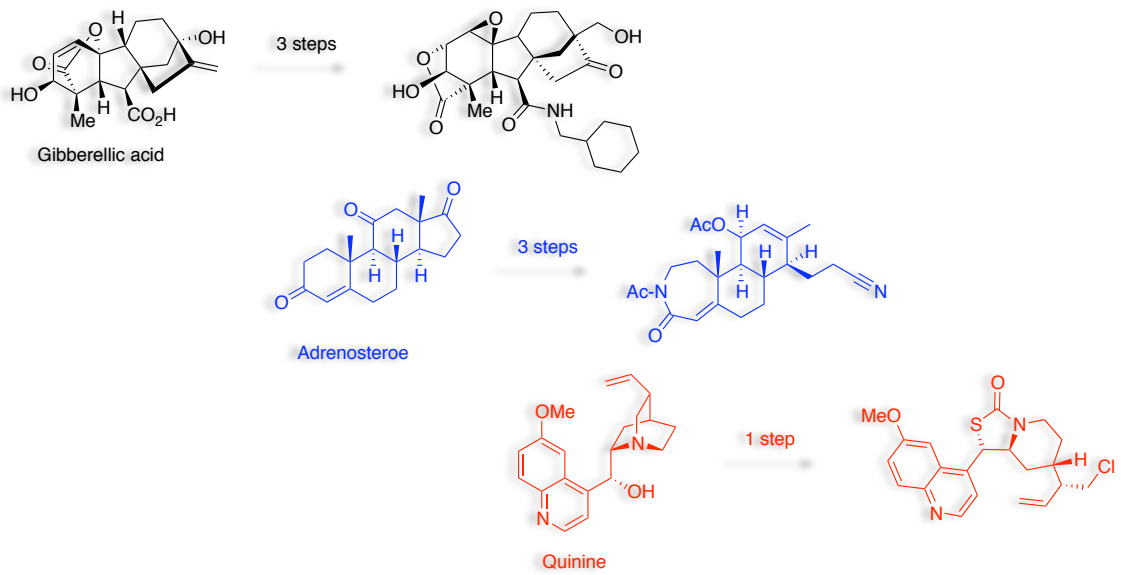
A ring-distortion strategy to construct stereochemically complex and structurally diverse compounds from natural products

R. W. Huigens III, K. C. Morrison, R. W. Hicklin, T. A. Flood Jr, M. F. Richter, and P. J. Hergenrother, *Nature Chemistry*, **2013**, *5*, 195-202

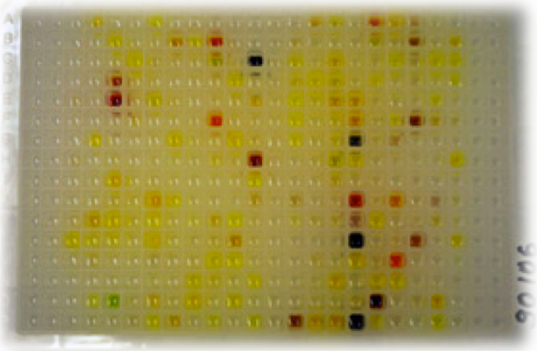
"…complexity to diversity"



Raffaele Colombo – 3/23/2013

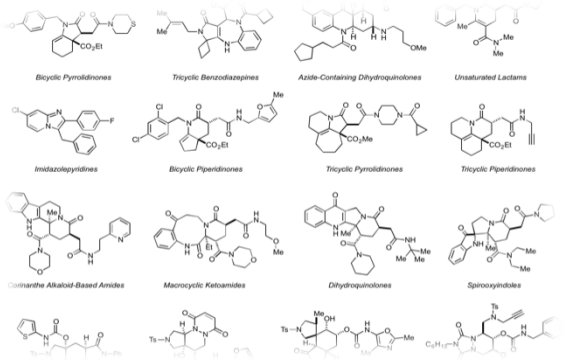
Lead identification

High-throughput screening



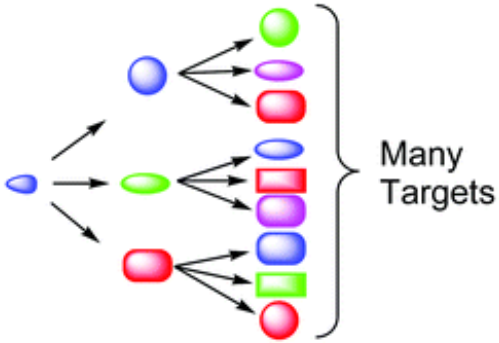
Collection of small molecules

Diversity libraries



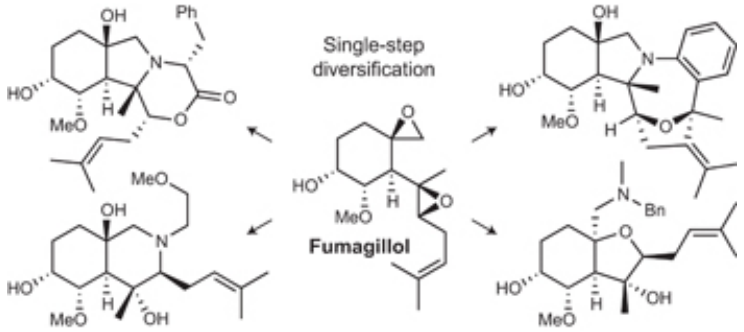
Previous approaches

Diversity oriented synthesis



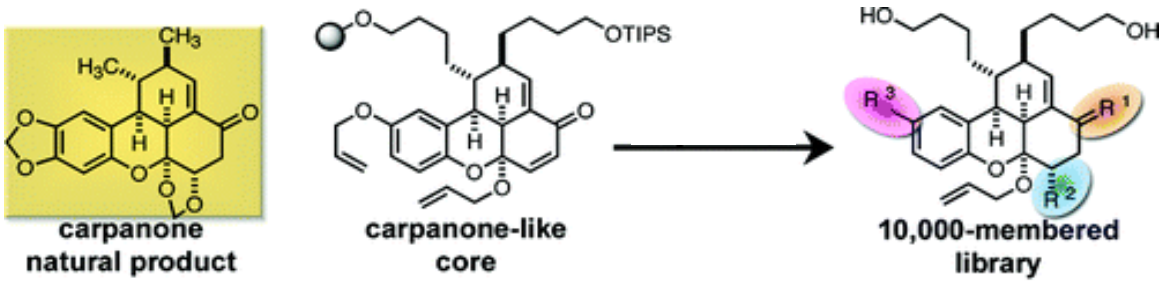
Schreiber, S. L. *Science*, **2000**, *287*, 1964-1969

Skeletal diversifications



Balthaser, B. R., Maloney, M. C., Beeler, A. B., Porco, J. A. & Snyder, J. K. *Nature Chem.* **2011**, *3*, 969–973

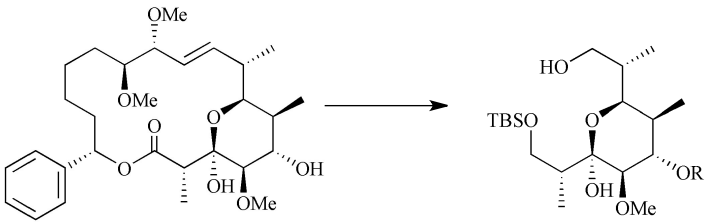
Decoration of scaffolds inspire by natural products



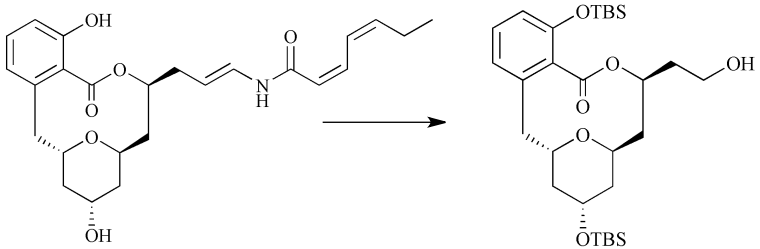
Goess, B. C., Hannoush, R. N., Chan, L. K., Kirchhausen, T. & Shair, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 5391–5403.

Previous approaches

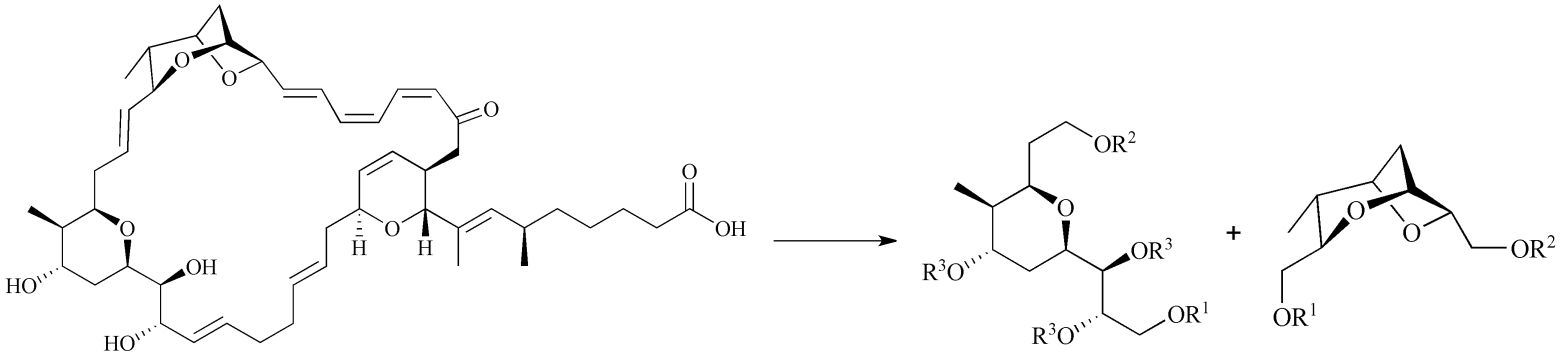
Building blocks from natuaral products



Soraphen

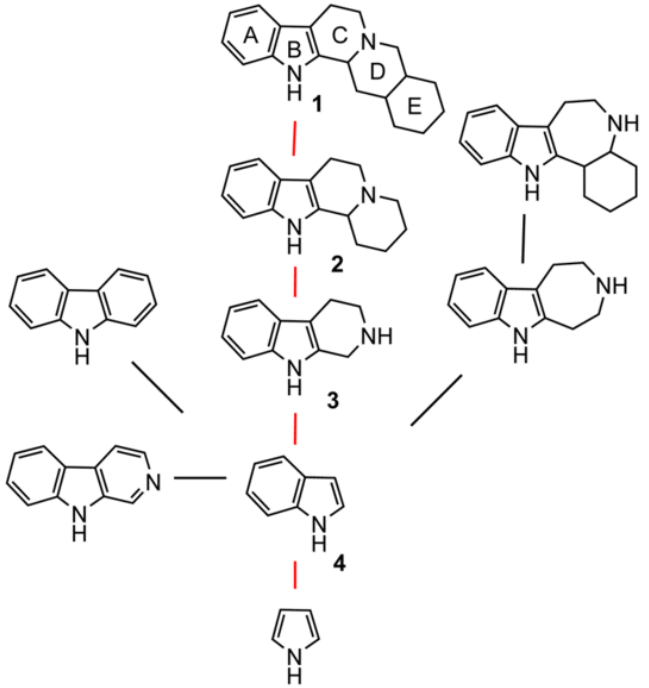


Apicularen

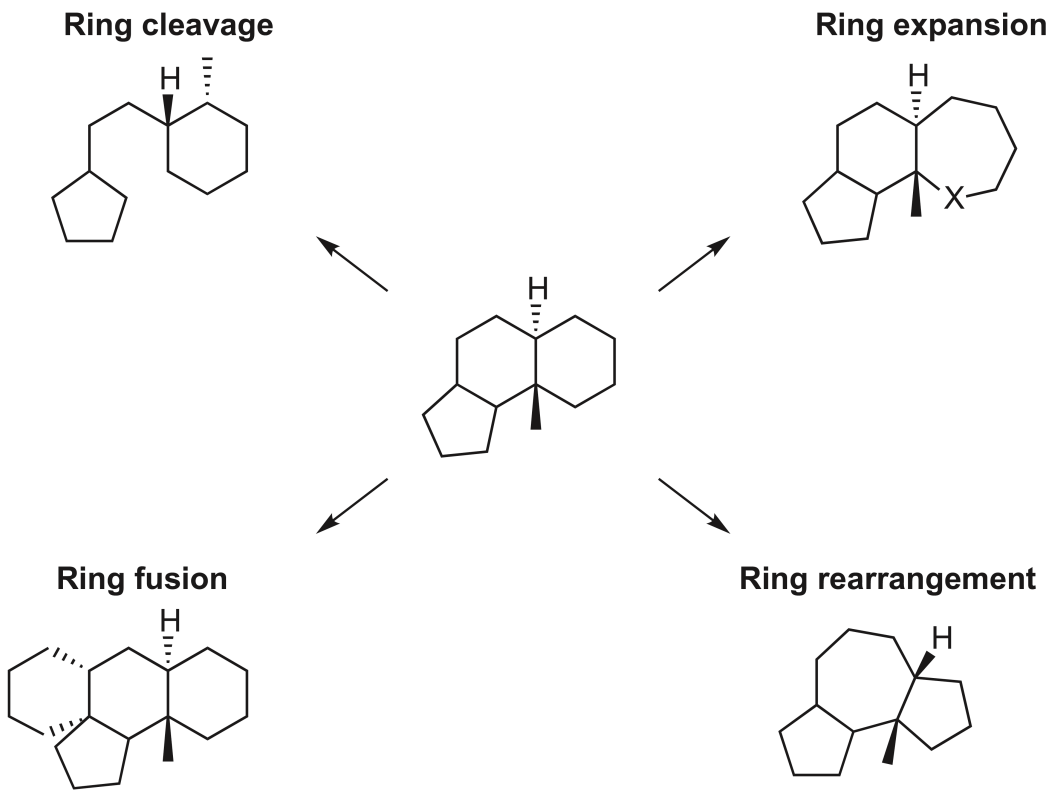


Sorangicin

Biology oriented synthesis



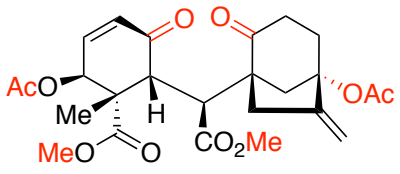
CtD: ring distorsion



From natural product to complex and diverse scaffold

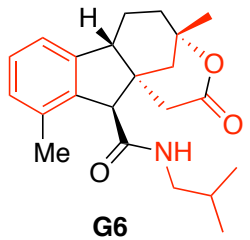
Gibberellic acid

Plant hormone isolated from Gibberella fujikuroi and produced industrially on the tonne scale
Price: 100-300 $/kg



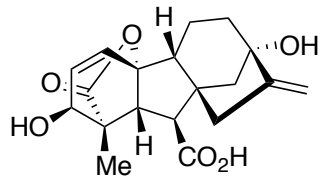
G1

5 steps



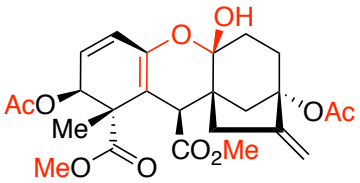
G6

3 steps



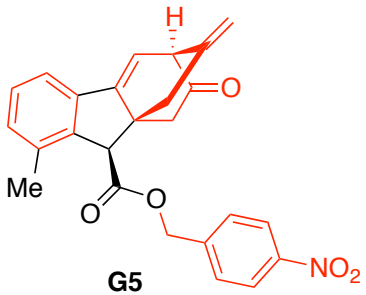
Gibberellic acid

5 steps



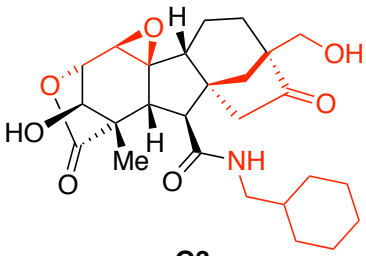
G2

3 steps

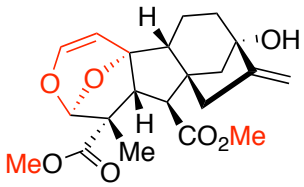


G5

3 steps

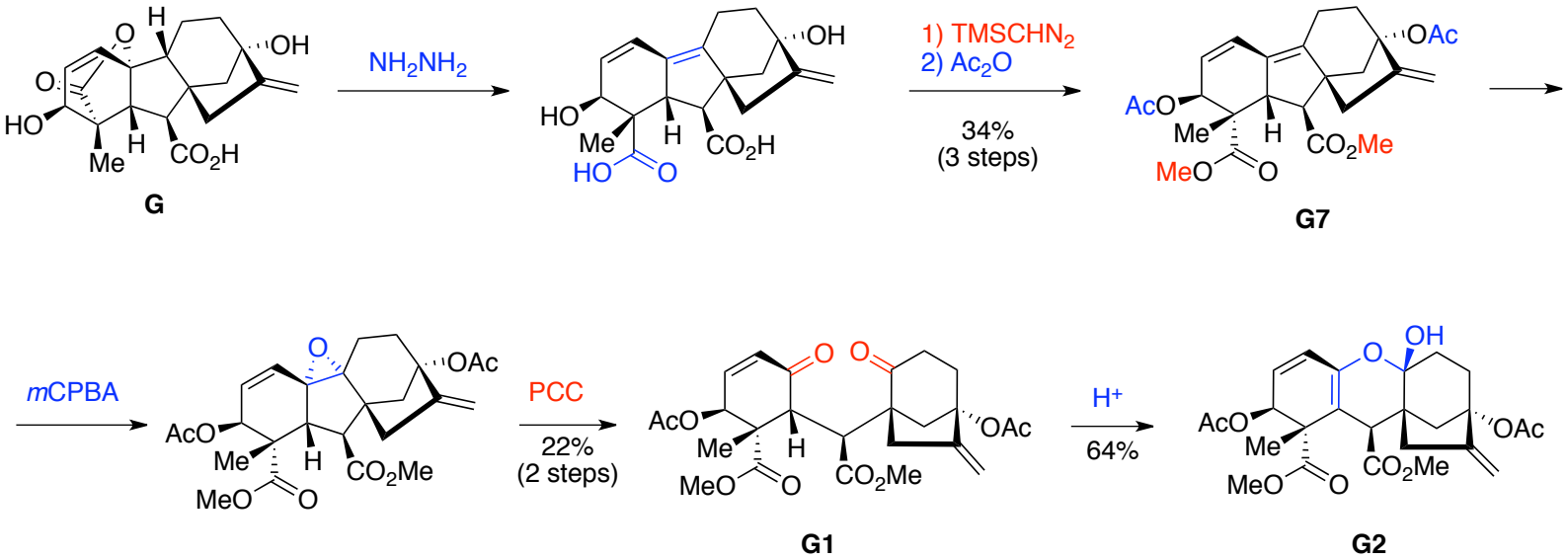


G3



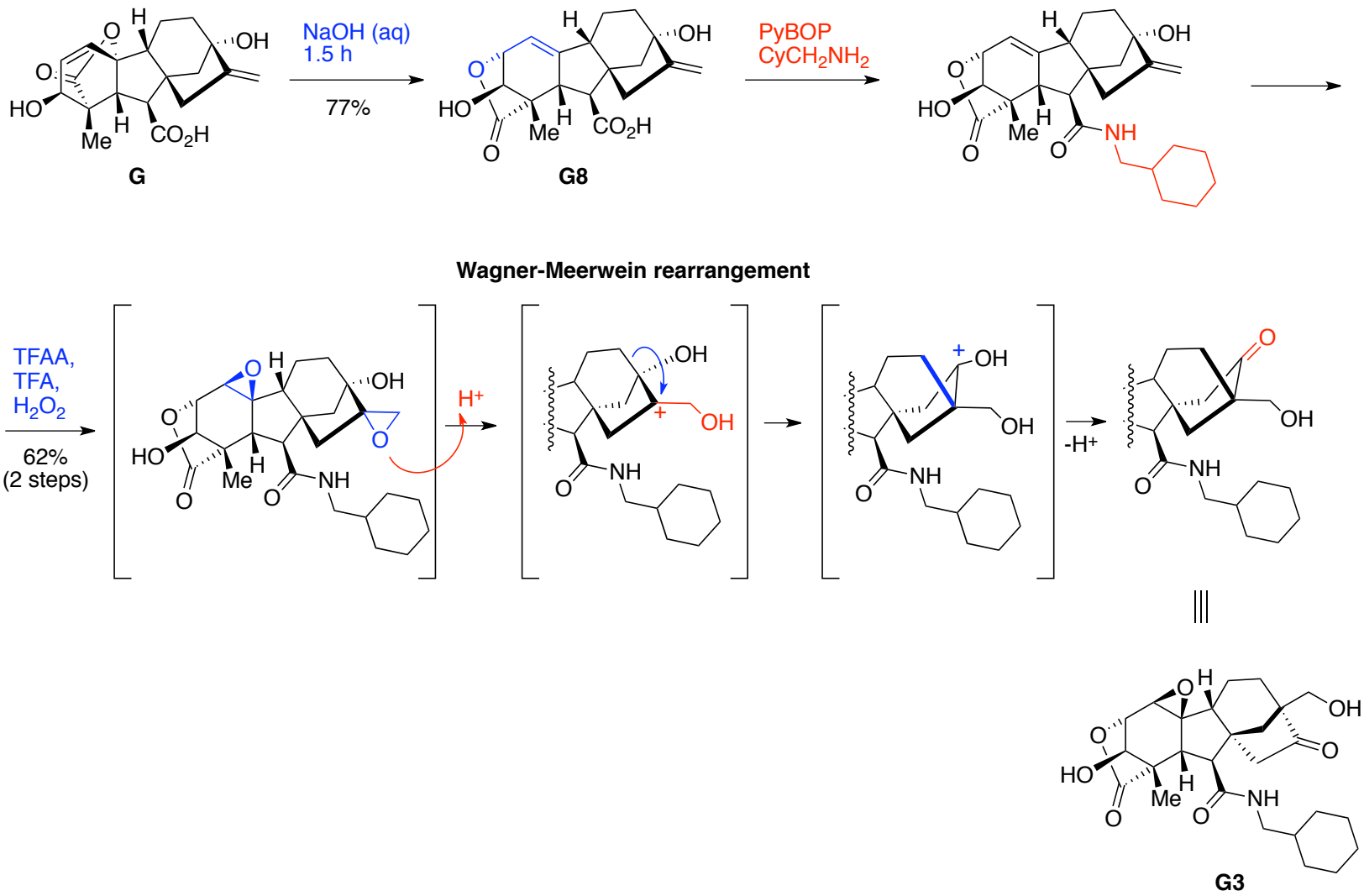
G4

Synthesis of G1 and G2



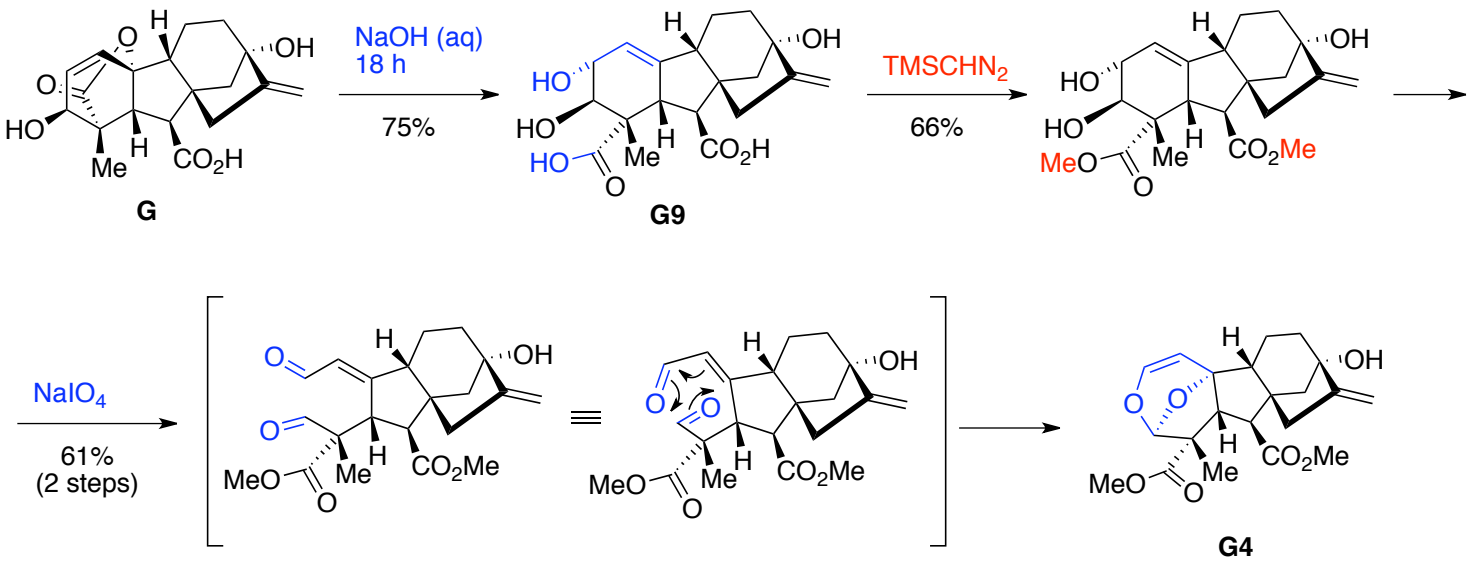
For the hydrazine-promoted elimination see: Grove, J. F.; Mulholland, T. P. C. Gibberellic acid. Part 12. The stereochemistry of allogibberic acid. *J. Chem. Soc.* **1960**, 3007–3022

Synthesis of G3



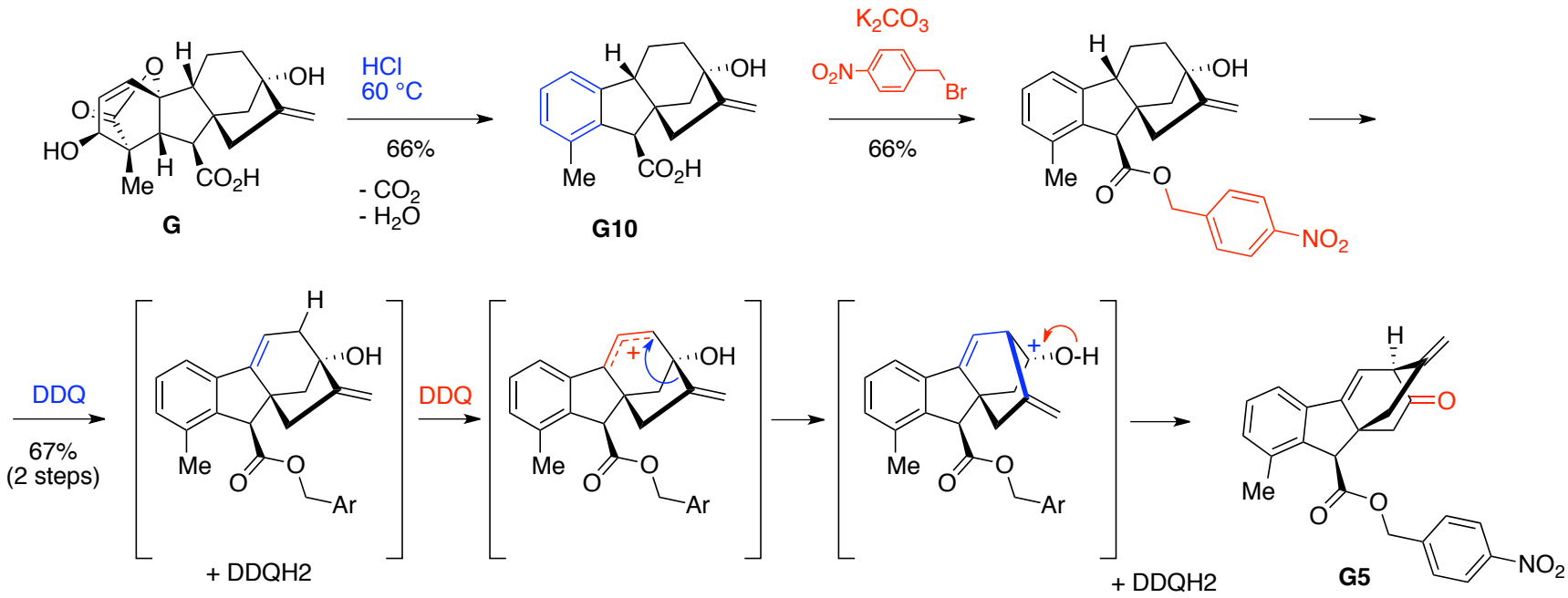
For the lactone rearrangment see: Henderson, J. H.; Graham, H. D. A possible mechanism for biological and chemical activity of gibberellic acid. *Nature*, **1962**, *193*, 1055–1056.

Synthesis of G4



For the lactone cleavage see: Cross, B. E., Grove, J. F. & Morrison, A. Gibberellic acid. 18. Some rearrangements of ring A. *J. Chem. Soc.* **1961**, 2498–2515.

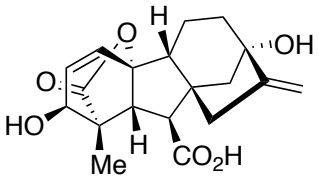
Synthesis of G5



For the aromatization of ring A see: Cross, B. E. Gibberellic acid. Part I. *J. Chem. Soc*. **1954**, 4670–4676.

For the DDQ rearrangment see: Cross, B. E.; Markwell, R. E. Rearrangements of the gibbane skeleton during reactions with 2,3-dichloro-5,6-dicyanobenzoquinone. *J. Chem. Soc. Perkin Trans. I*, **1973**, 1476–1487

Synthesis of G6

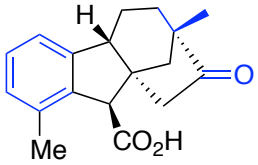


G

HCl
reflux

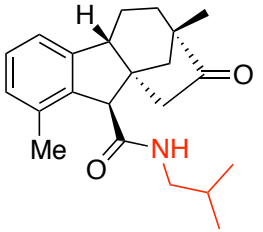
32 %

- CO_2
- H_2O
W-M rearr.



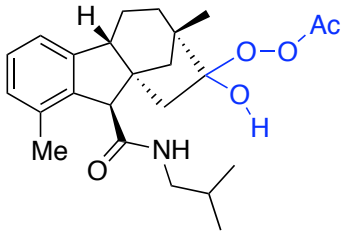
G11

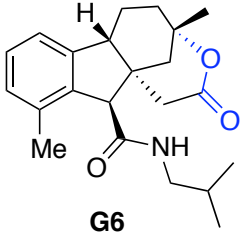
$SOCl_2$
i-$BuNH_2$



AcOOH

18%
(2 steps)

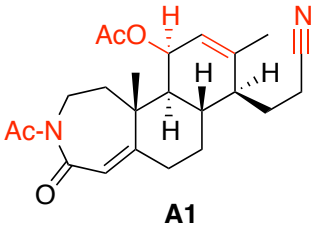




G6

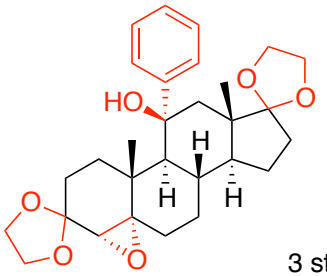
Adrenosterone

Steroid hormne produced in the adrenal cortex of mamals
Price: 100-300 $/kg



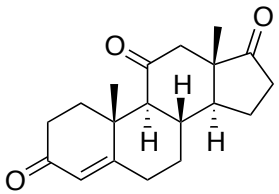
A1

3 steps



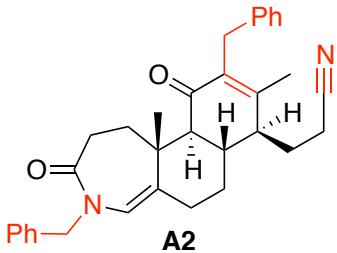
A5

3 steps



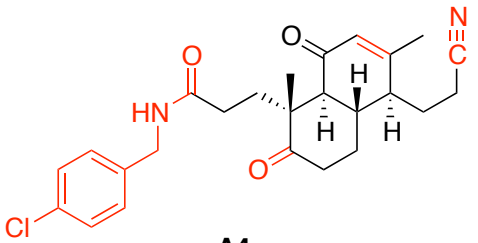
Andrenosterone

2 steps



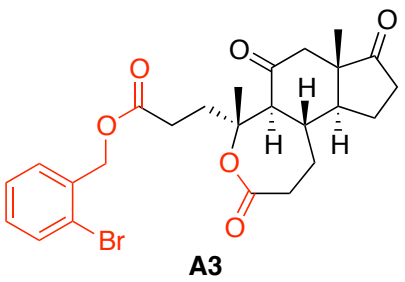
A2

3 steps



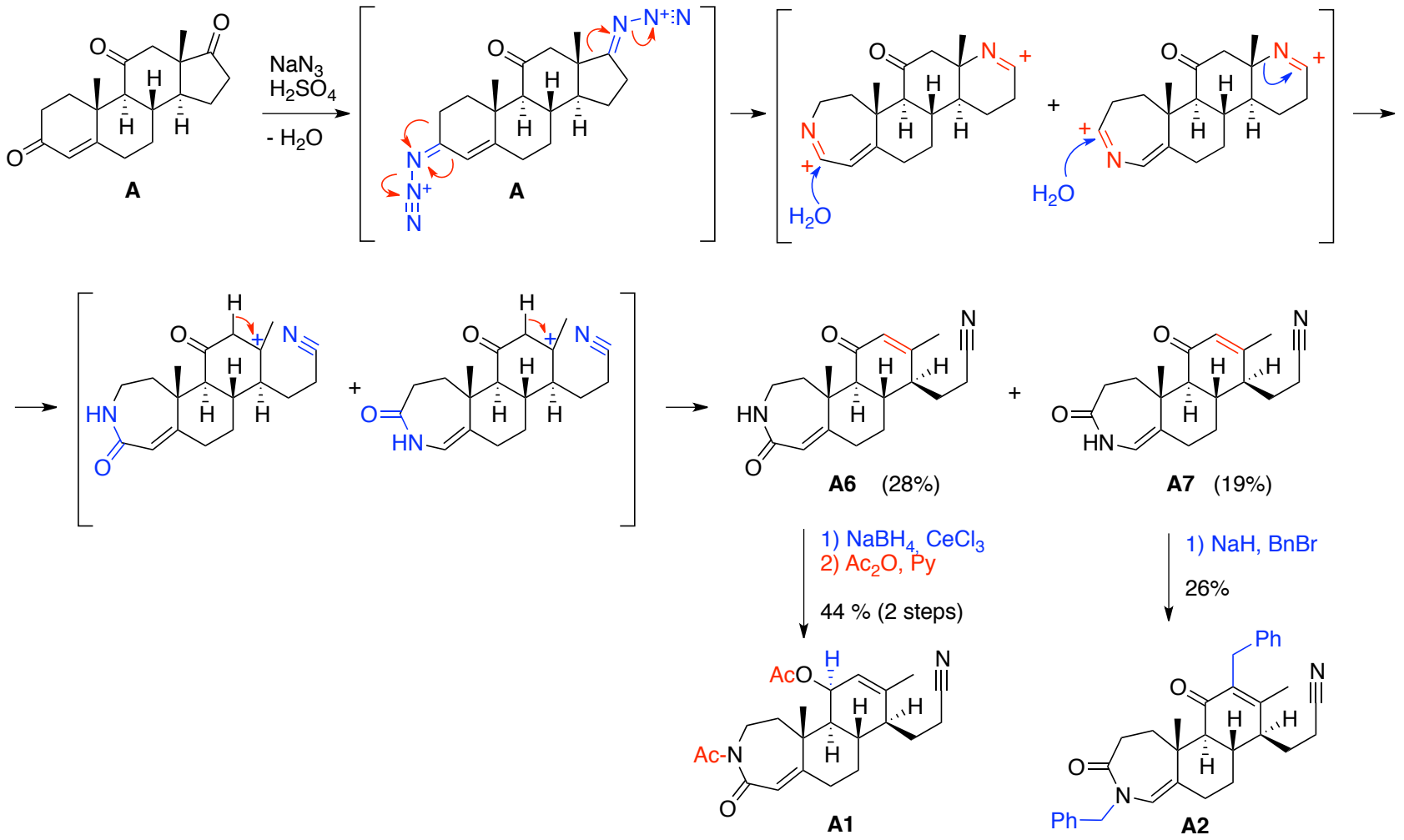
A4

3 steps



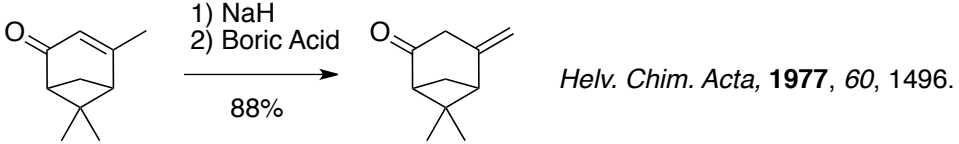
A3

Synthesis of A1 and A2

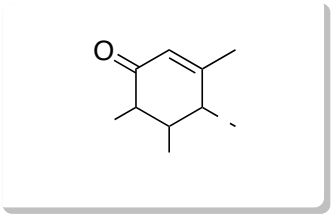


3-methyl-α,β-unsaturated ketones

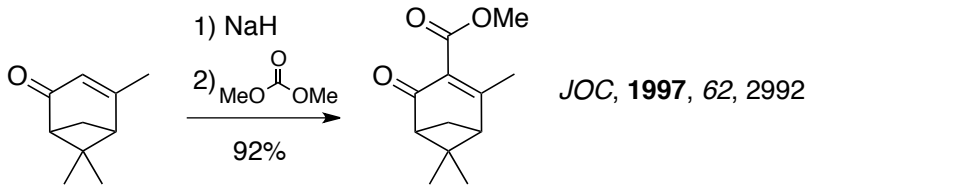
Verbenone



Helv. Chim. Acta, **1977**, *60*, 1496.

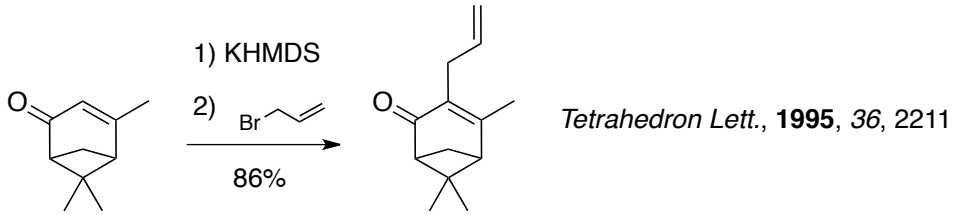


NaH



JOC, **1997**, *62*, 2992

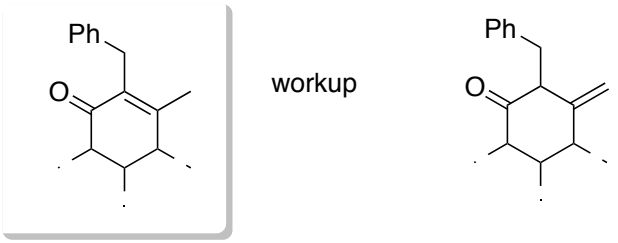
BnBr



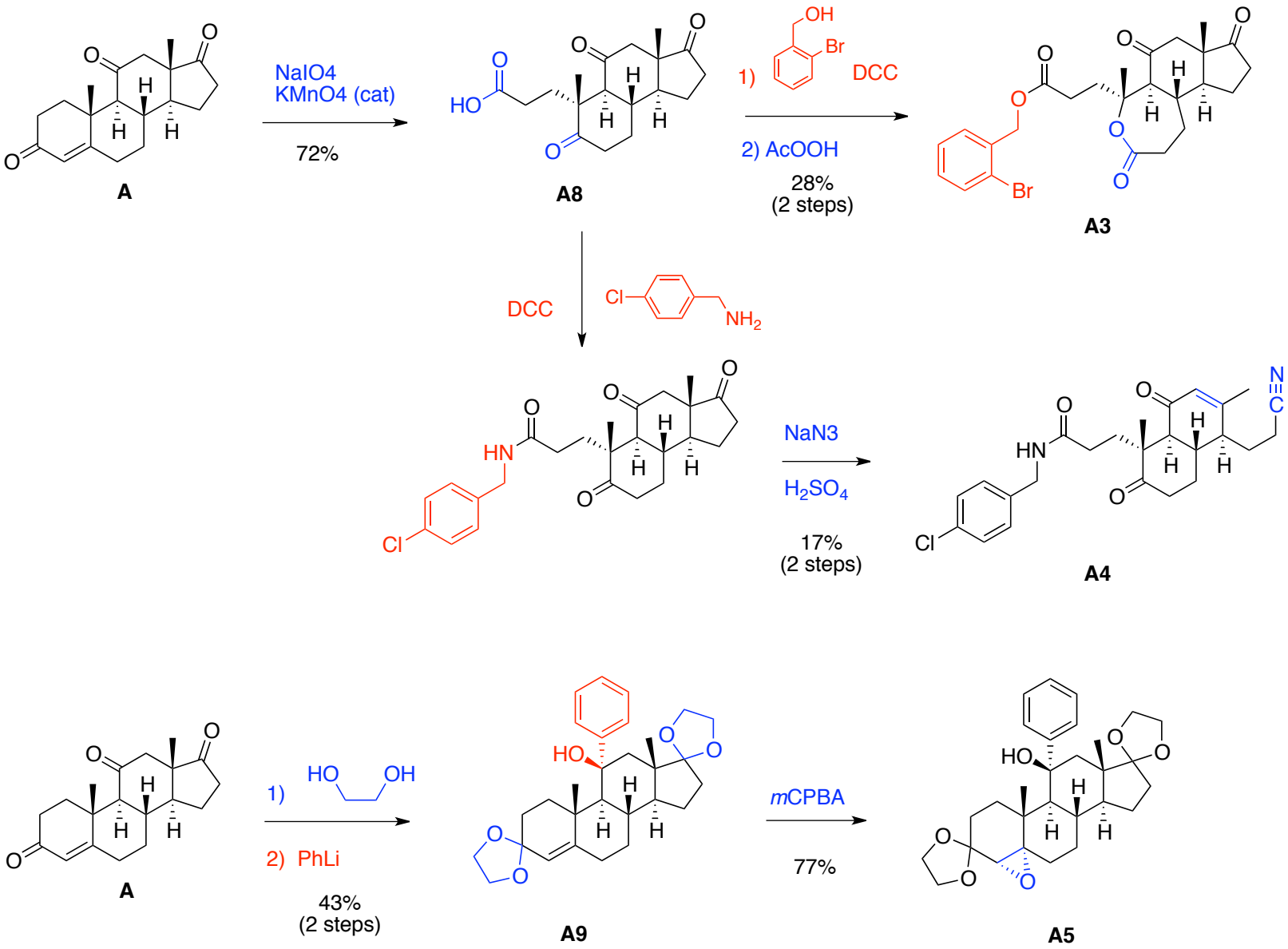
Tetrahedron Lett., **1995**, *36*, 2211

Isophorone derivative

EJMC, **2006**, *41*, 905



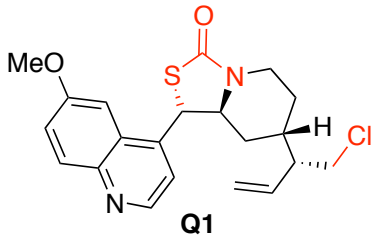
Synthesis of A3, A4 and A5



Quinine

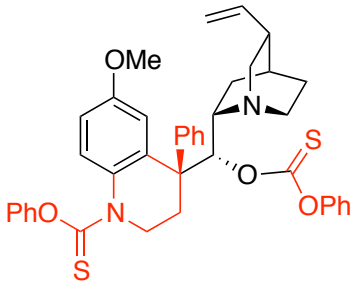
Alkaloid isolated from the bark of the genus *Cinchona*, used as food additive, antimalarial therapeutic and catalyst scaffold.

Price: 10-300 $/kg



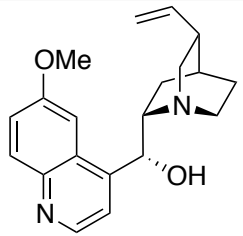
Q1

3 steps



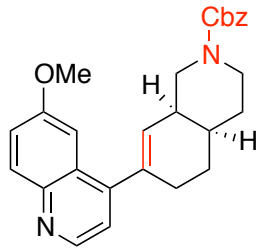
Q5

3 steps



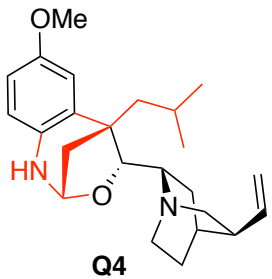
Quinine

2 steps



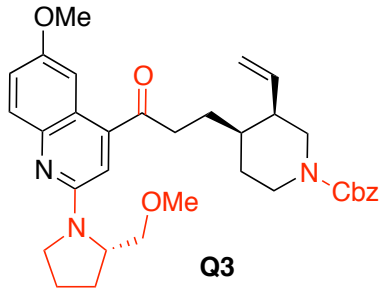
Q2

3 steps



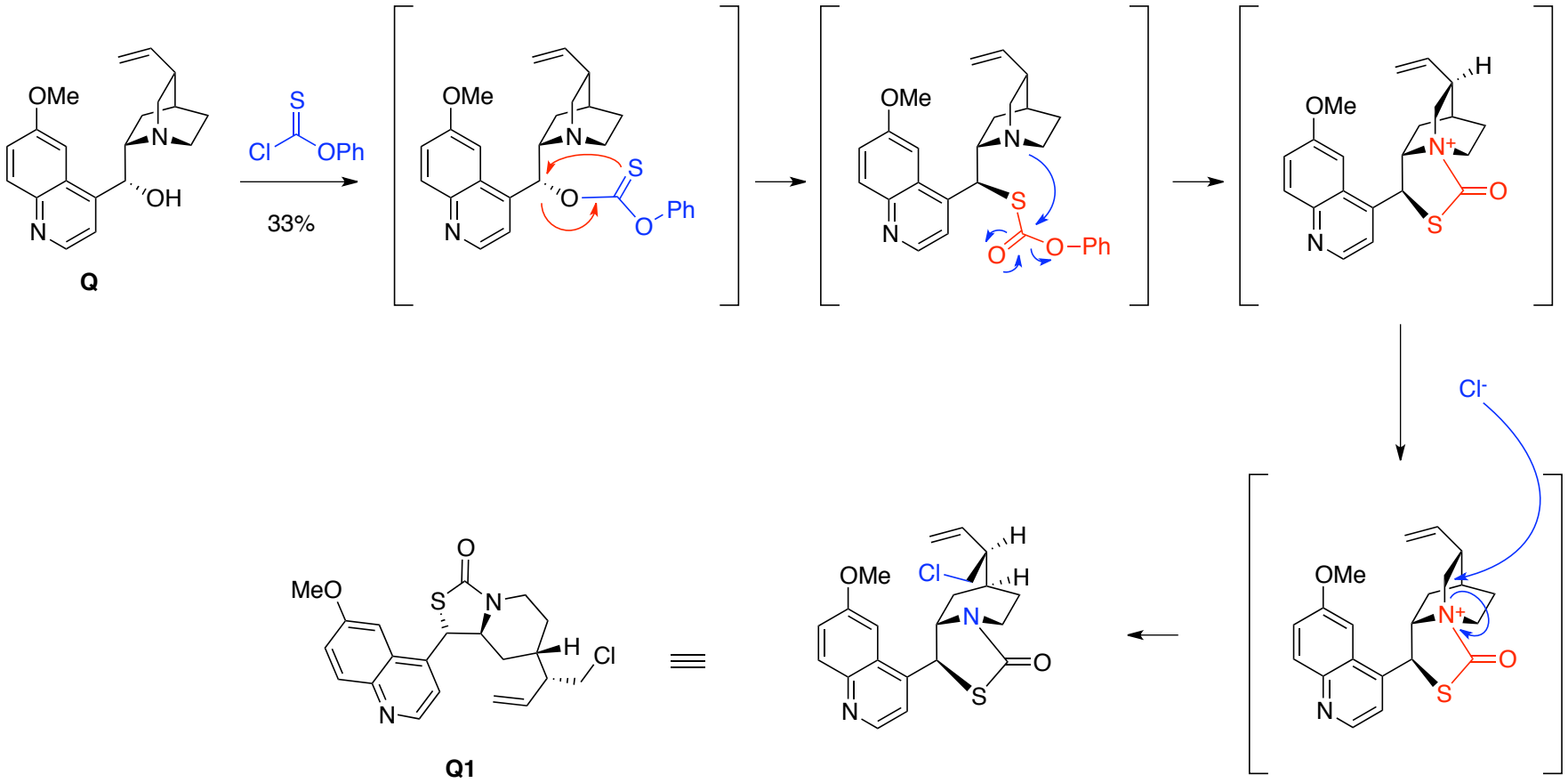
Q4

3 steps

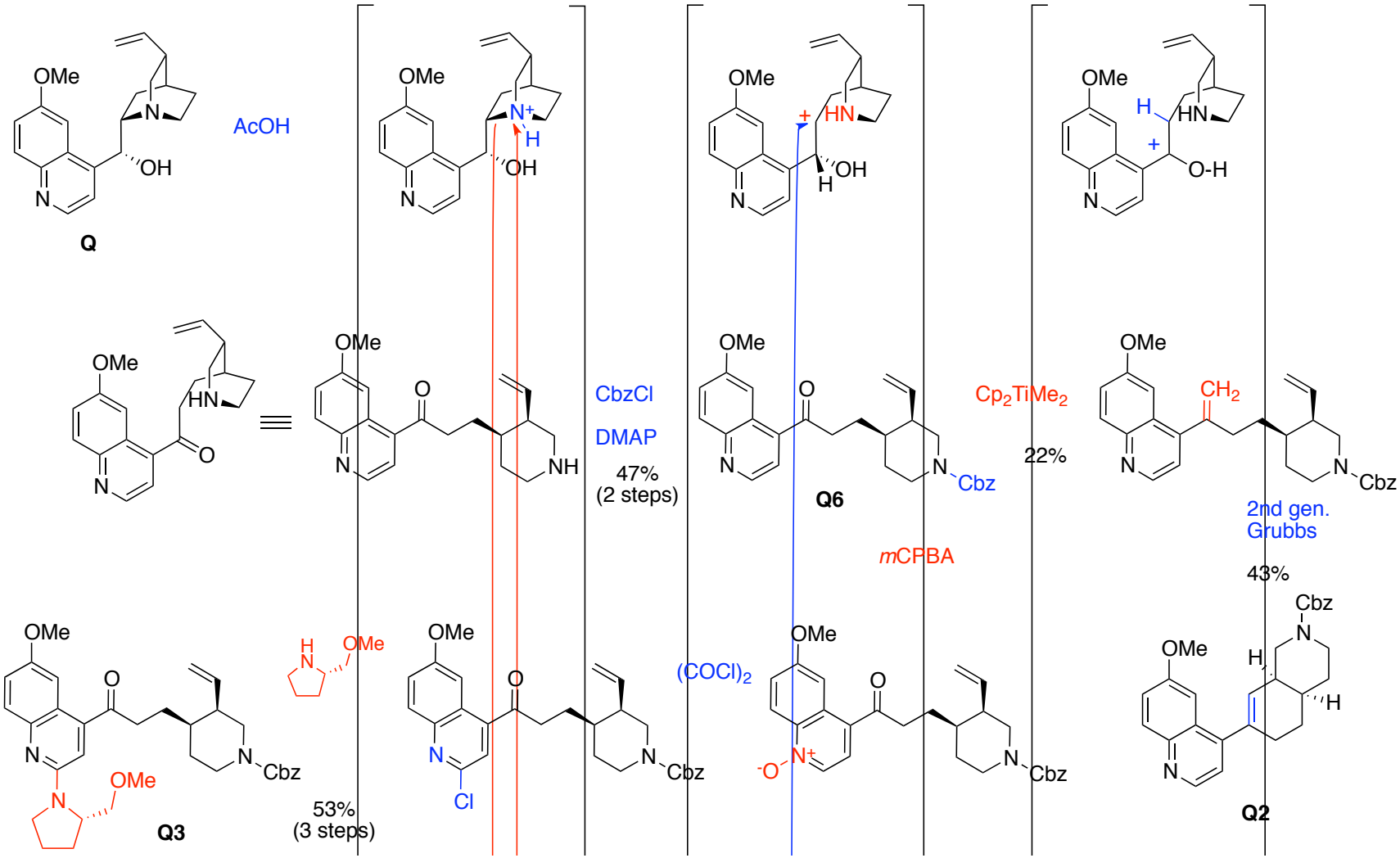


Q3

Synthesis of Q1

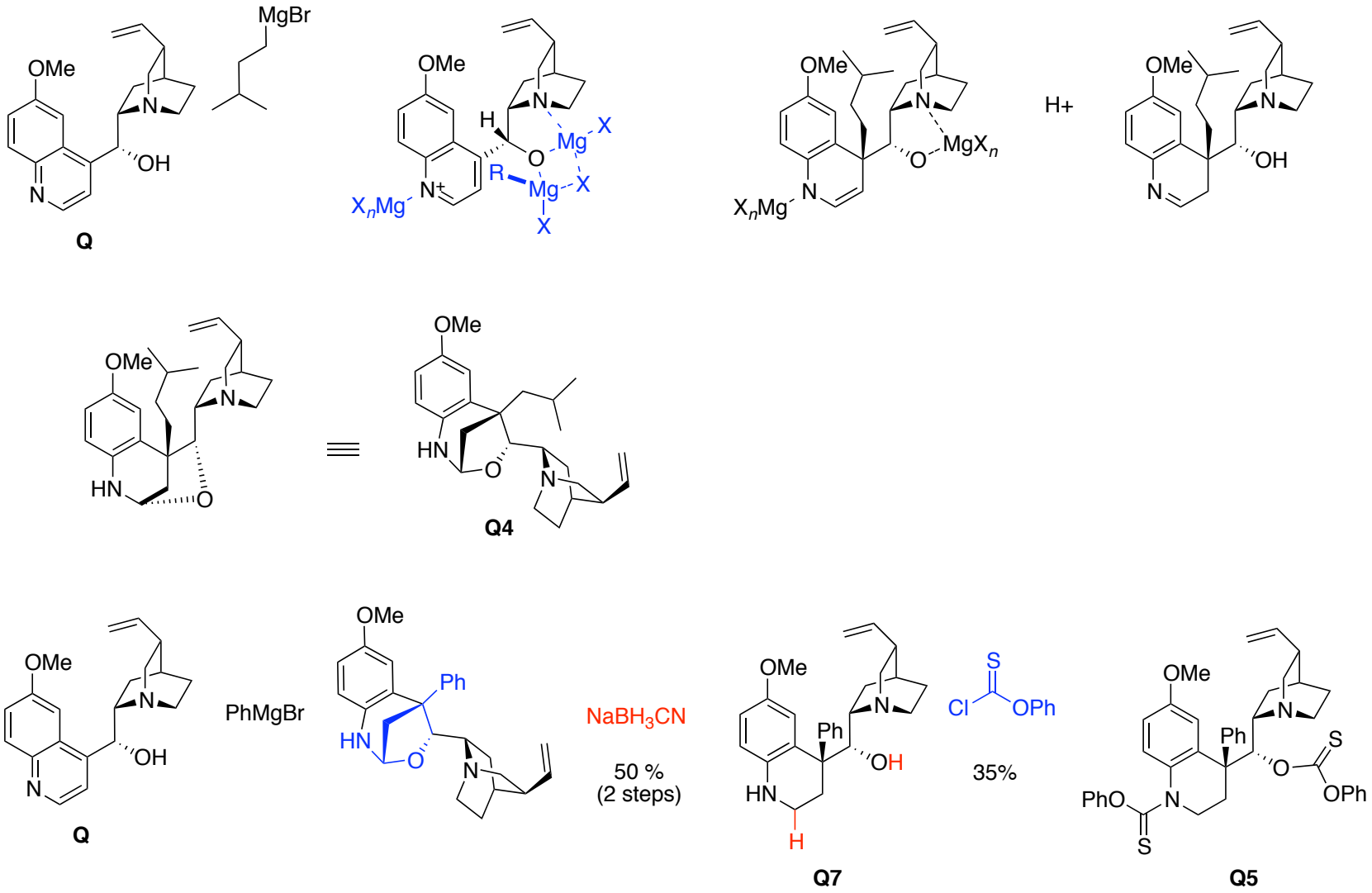


Synthesis of Q2 and Q3



For the acid-promoted ring cleavage see: Smith, A. C. & Williams, R. M. Rabe rest in peace: confirmation of the rabekindler conversion of D-quinotoxine into quinine: experimental affirmation of theWoodward–Doering formal total synthesis of quinine. *Angew. Chem. Int. Ed*. **2008** *47*, 1736–1740.

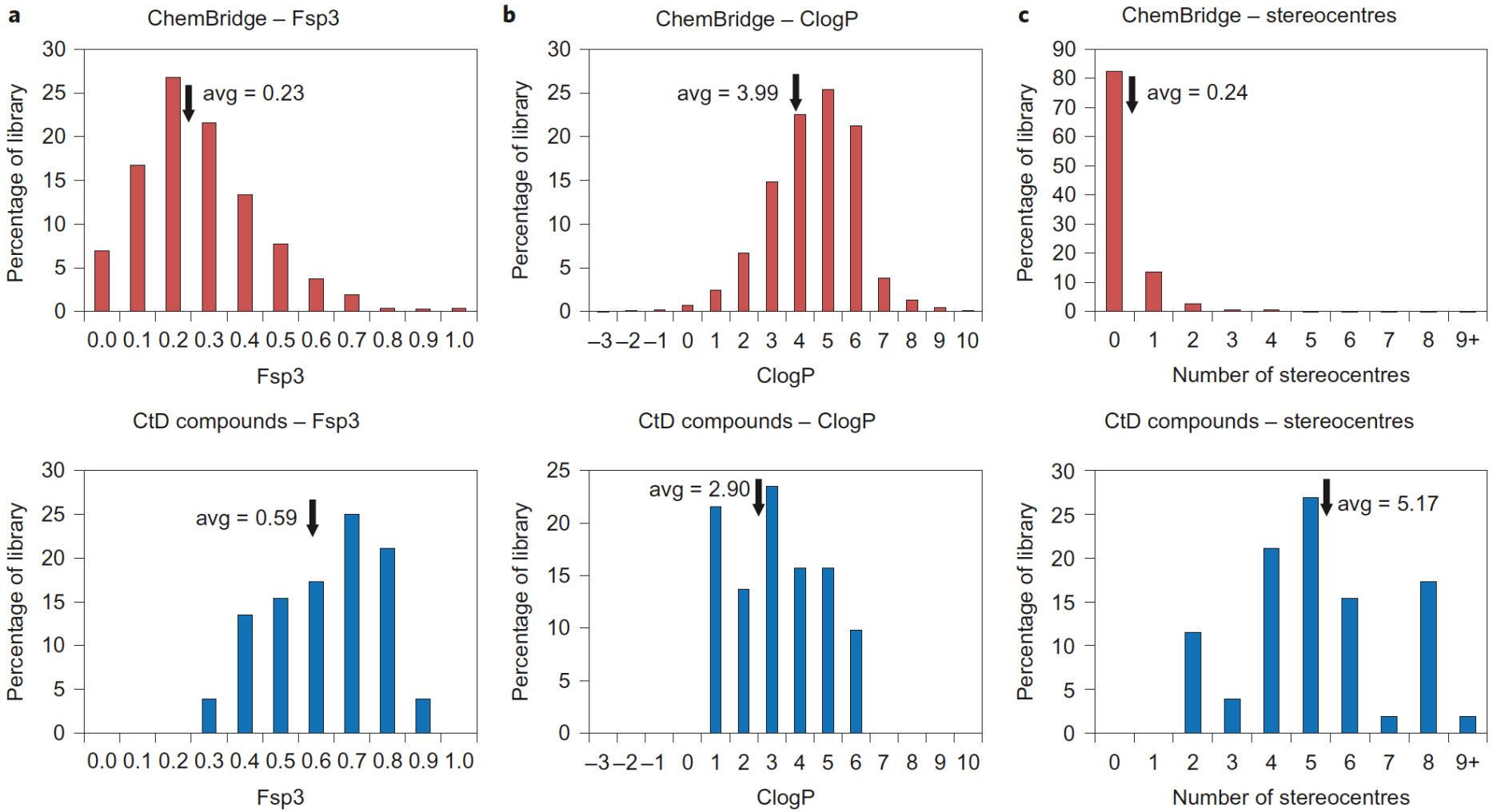
Synthesis of Q4 and Q5



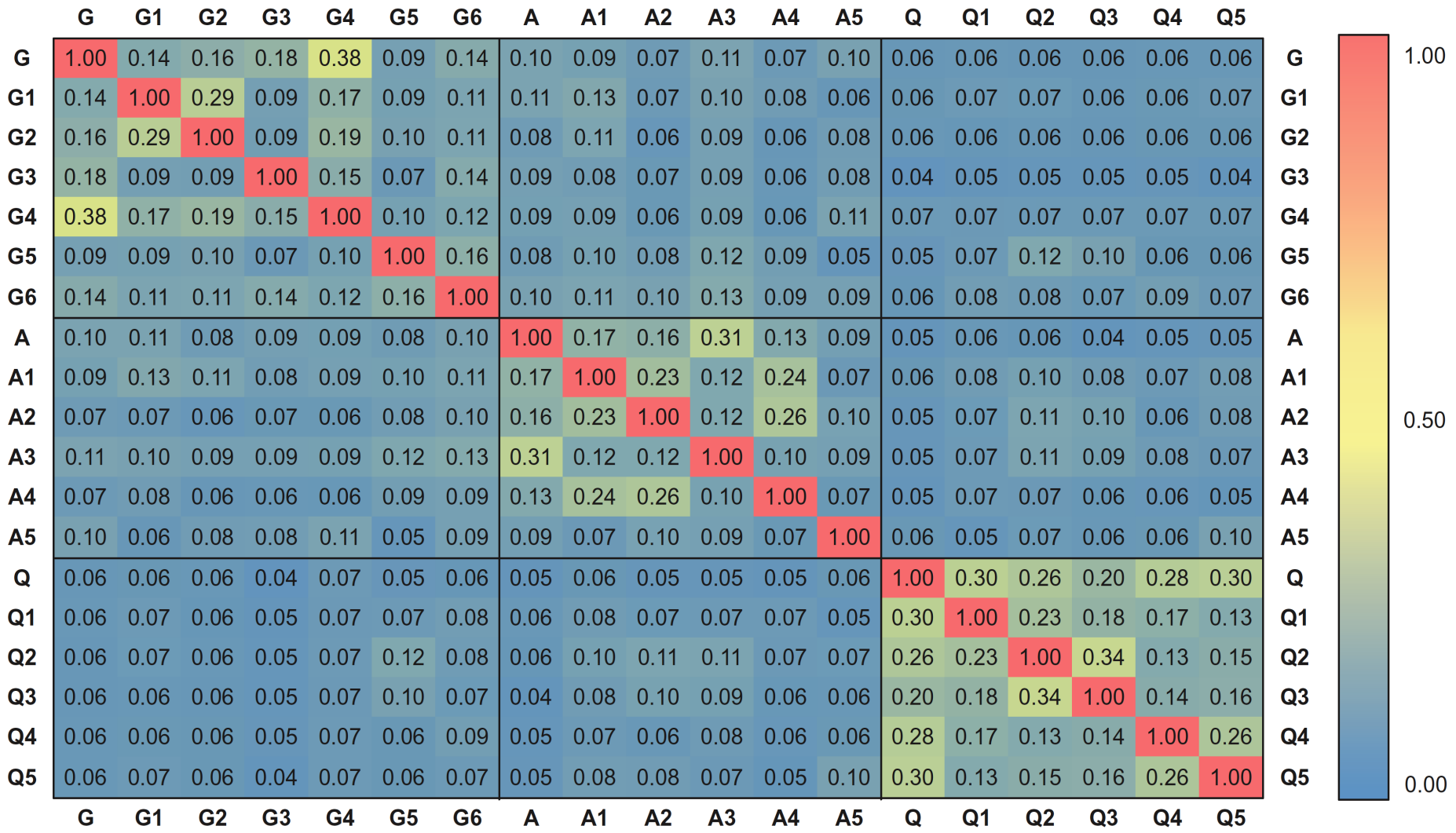
For the Grignard addition to Quinine see: Hintermann, L., Schmitz, M. & Englert, U. Nucleophilic addition of organometallic reagents to cinchona alkaloids: simple access to diverse architectures. *Angew. Chem. Int. Ed.* **2007,** *46*, 5164–5167.

Fsp3, CLogP, stereocentres analysis

ChemBridge (150,000 compounds) vs. CtD (49 compounds)



Similarity metric analysis



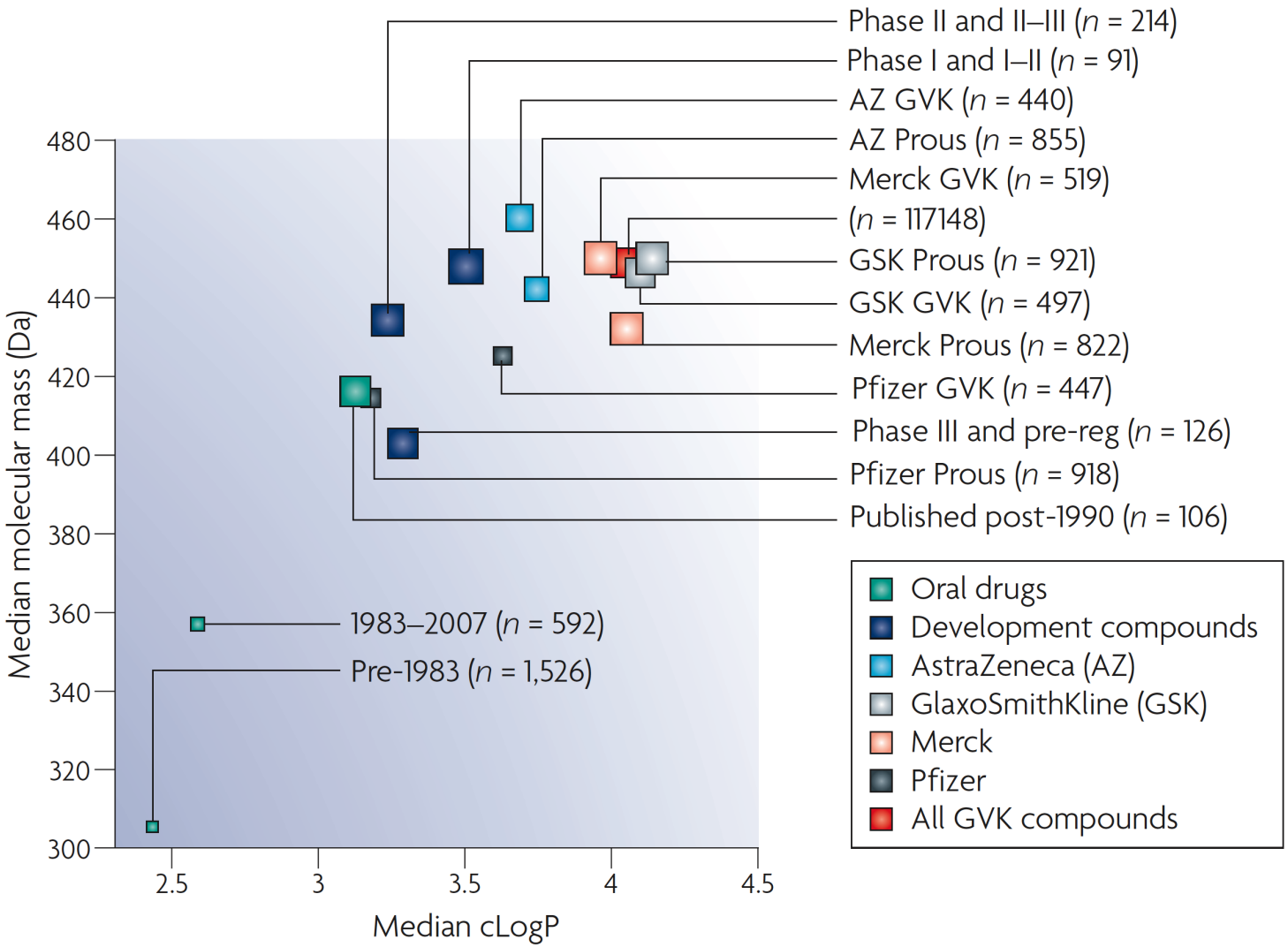
Based on: Rogers, D.; Hahn, M. Extended-connectivity fingerprints. *J. Chem. Inf. Model.* **2010**, *50*, 742–754.

Properties of molecules published in JMC between 1959 and 2009

	1959–1999	2000–2009
molecular wt	354.09	403.35
CLogP	2.61	2.98
TPSA	76.76	88.08
rotatable bonds	5.80	6.42
HB donors	1.58	1.80
HB acceptors	3.65	4.25
complexity	43.91	47.45
fraction sp^3	0.39	0.35

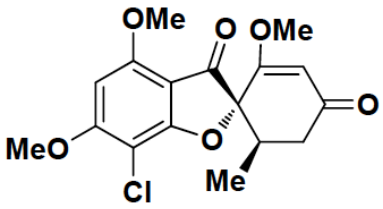
Walters, W. P., Green, J., Weiss, J. R. & Murcko, M. A. What do medicinal chemists actually make? A 50-year retrospective. *J. Med. Chem.* **2011**, *54*, 6405–6416.

Median cLog P and molecular mass

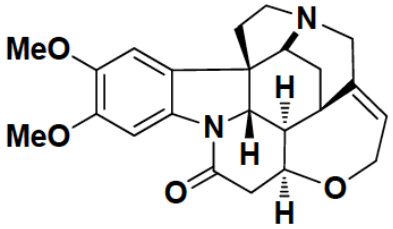


Leeson, P. D. & Springthorpe, B. The influence of drug-like concepts on decision-making in medicinal chemistry. *Nature Rev. Drug Discov.* **2007**, *6*, 881–890.

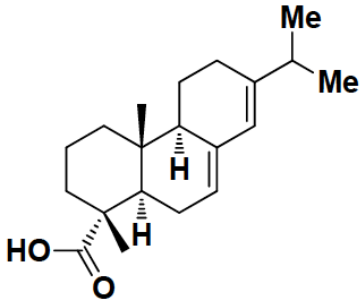
Possible NPs for CtD approch



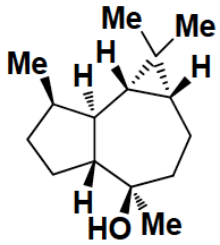
Griseofulvin



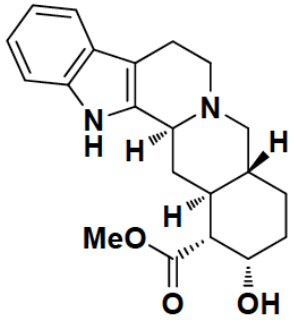
Brucine



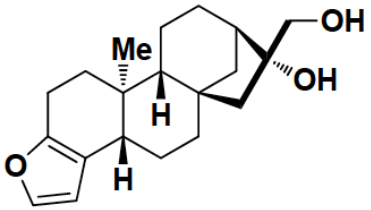
Abietic Acid



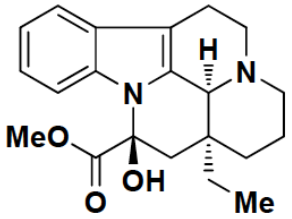
(-)-Globulol



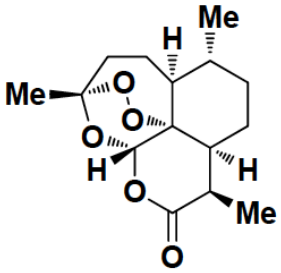
Yohimbine



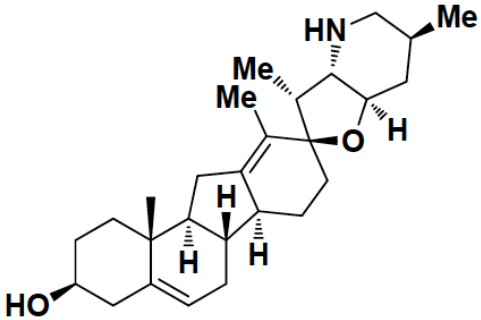
Cafestol



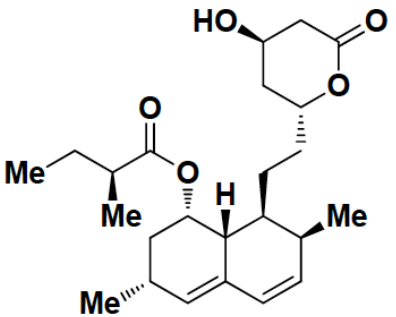
Vincamine



Artemisinin

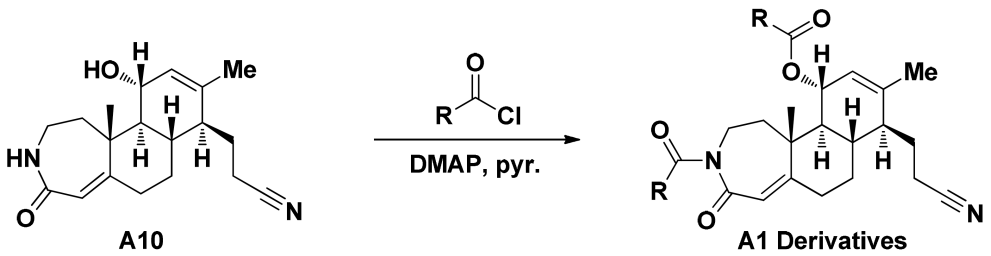


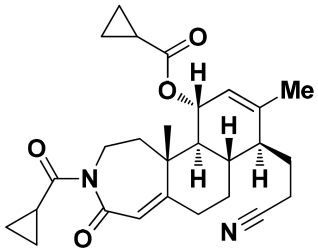
Cyclopamine



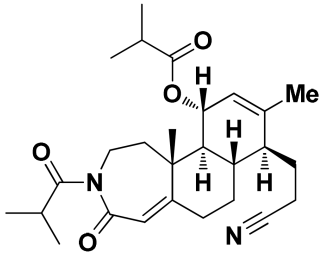
Lovastatin

“traditional” derivatization strategies – ex1

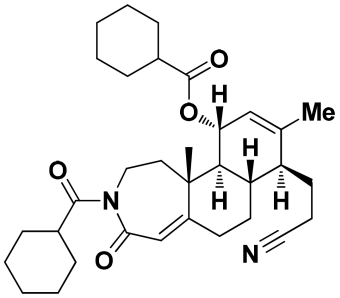




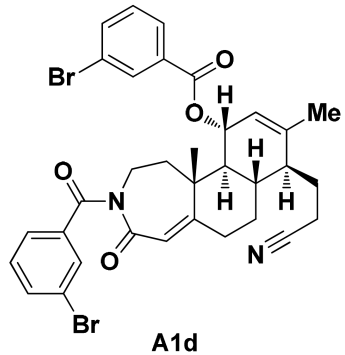
A1a
(35%)



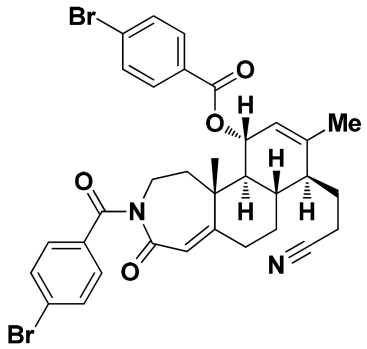
A1b
(52%)



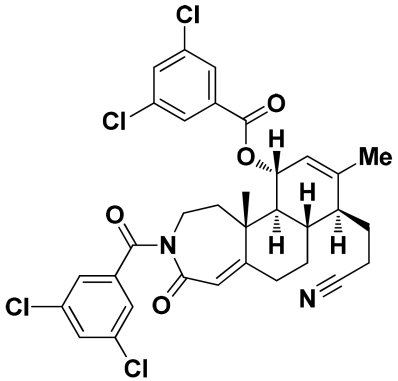
A1c
(76%)



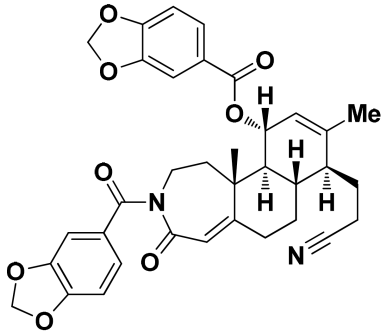
A1d
(39%)



A1e
(68%)

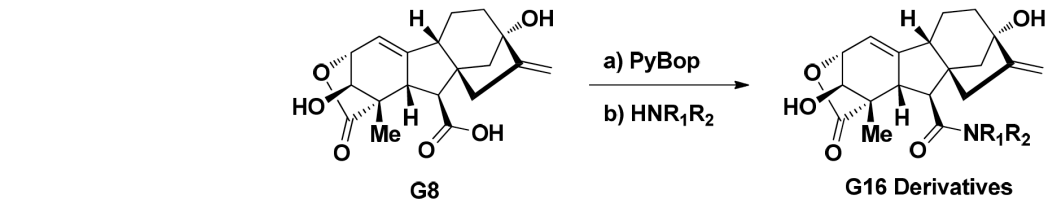


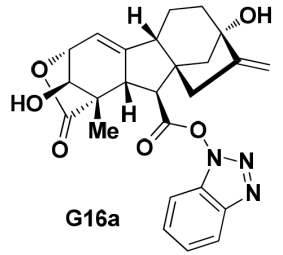
A1f
(55%)

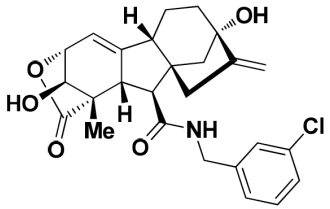


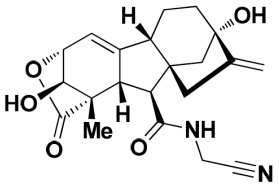
A1g
(39%)

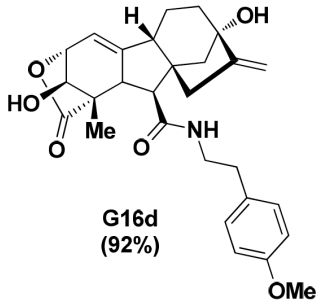
“traditional” derivatization strategies – ex2

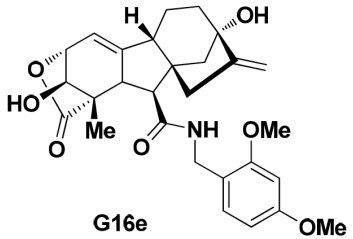


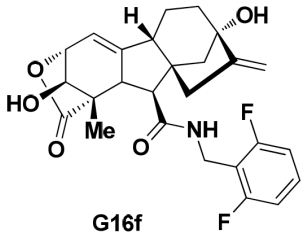

G16a

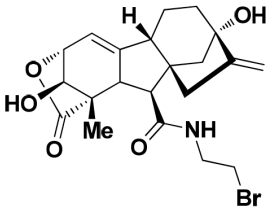

G16b
(91%)

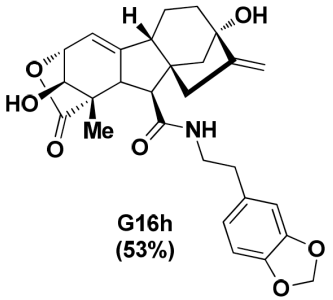

G16c
(63%)

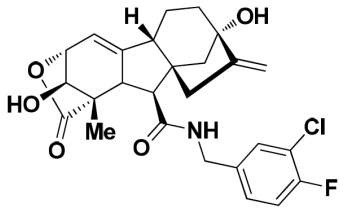

G16d
(92%)

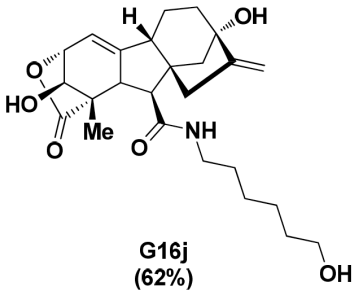

G16e
(99%)

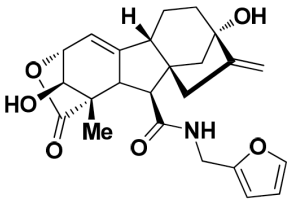

G16f
(57%)


G16g
(58%)

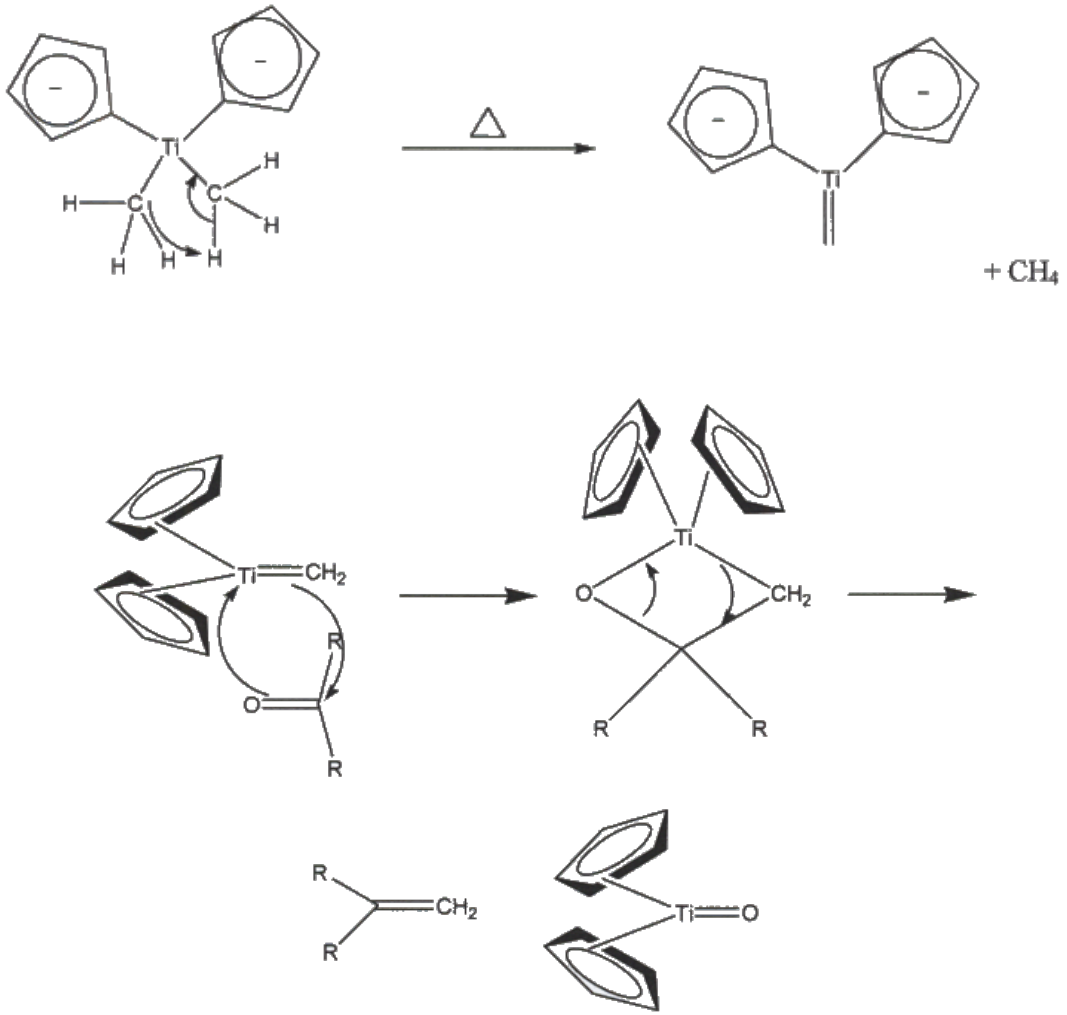

G16h
(53%)


G16i
(65%)

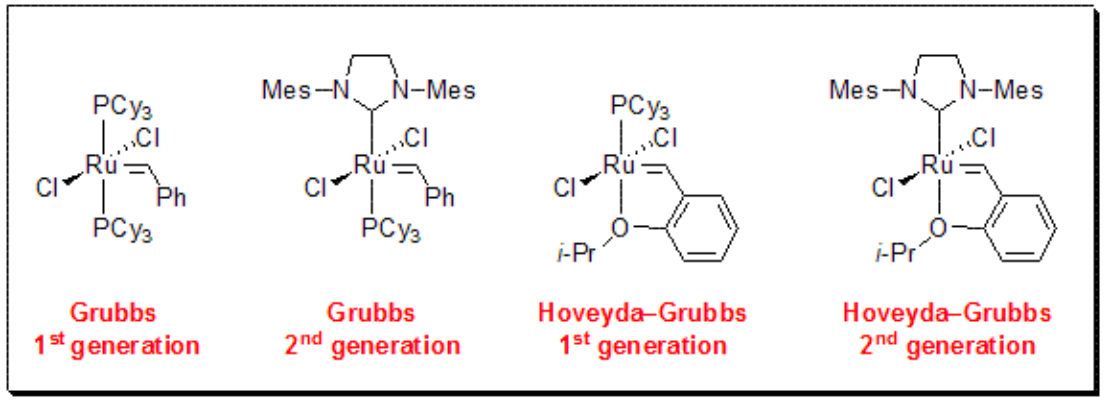

G16j
(62%)


G16k
(83%)

Pestasis Reagent

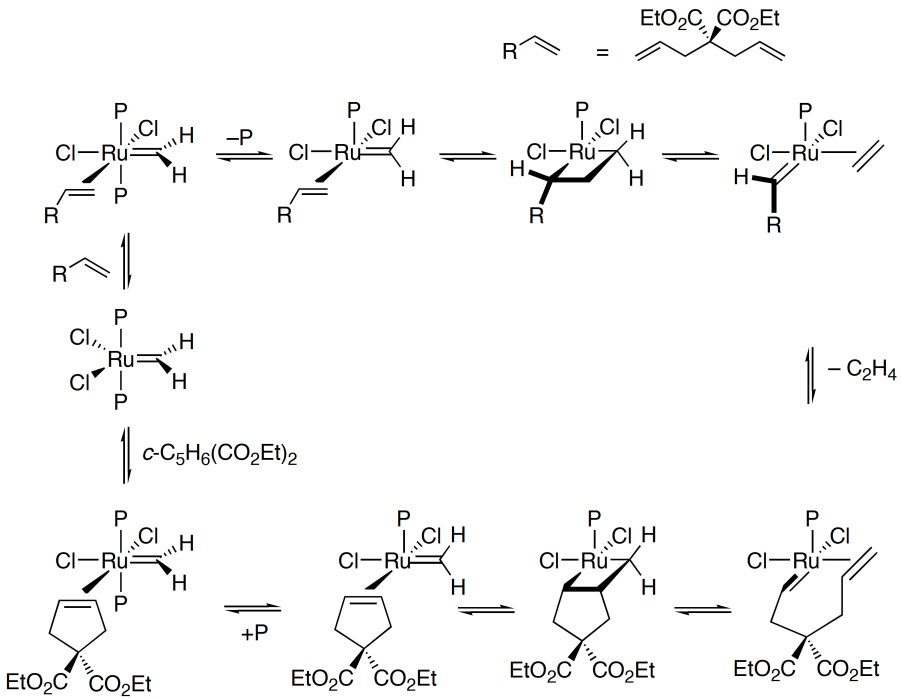


RCM catalysis



Dissociative:

P = P(*c*-Hex)$_3$



Associative: