Pierre Deslongchamps

Steven Crossley

Pierre Deslongchamps (1938 - present; 75 years old)

Education
B.Sc., University of Montreal, 1959
Ph.D. (Z. Valenta), University of New Brunswick, 1964
Post Doc. (R.B. Woodward), Harvard University, 1965

Independent Career
Assistant Professor, University of Montreal, 1966
Assistant Professor, University of Sherbrooke, 1967
Professor, University of Sherbrooke, 1972
Professor Emeritus, University of Sherbrooke, 2006

Notable Accomplishments
- author in over 270 publications and 9 patents
- author of "*Stereoelectronic Effects in Organic Chemistry*" (1983)
- over 500 invited lectures
- Executive Scientific Advisor at Omega Chem
- founder of Neokimia, Inc.
- President of the Canadian Society for Chemistry (1989-1990)
- elected Fellow of the Canadian Royal Society, the Royal Society of London and the French Academy of Sciences

Selected Awards
Canada Gold Medal for Science and Engineering, Guggenheim Fellowship for Natural Sciences, Izaac Walton Killam Memorial Scholarship, Merck Sharpe and Dohme Award, National Order of Quebec, Prix Marie-Victorin, Sloan Fellowship, Steacie Prize and Fellowship

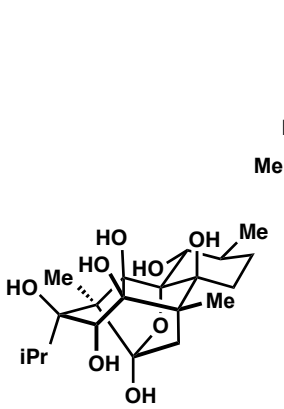
Students in Academia (of whom I am aware)
Dennis Hall (University of Alberta), Louis Barriault (University of Ottowa), Gislain Deslongchamps (University of New Brunswick; son), Guillaume Belanger (University of Sherbrooke)

Noteworthy Points:
- PhD work involved structural elucidation of *Ormosia* and *Lycopodium* alkaloids *via* degradation and synthesis studies
- post-doctoral work was on the Woodward/Eschenmoser vitamin B_{12} synthesis

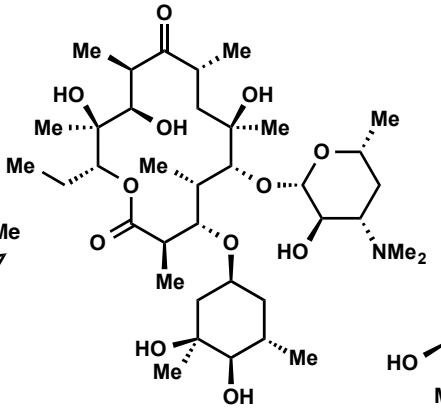
Research Focus
A) Organic synthesis of natural and unnatural molecules of the family of terpenes, steroids, alkaloids and lipids
Specifically, a) development of a general strategy for the synthesis of polycyclic natural and unnatural molecules related to steriods and terpenes
b) study of transannular and Diels-Alder reactions; anionic polycyclizations
c) combinatorial solid phase synthesis of macrocyclic compounds
B) Stereoelectronic effects in organic chemistry
Specifically, a) in the Michael and Diels-Alder reactions
b) study of the reactivity (hydrolysis) of acetals, esters, amides and related functional groups

Discussed here:
- selected sytheses (Triquinacene, Ryanodol, Erythromycin, Oubagenin, Cassaine) with a focus on transannular reactions and to a lesser degree, stereoelectronic effects

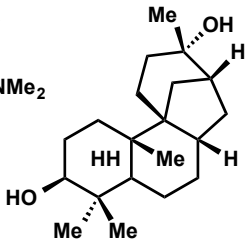
Not discussed here:
- combinatorial solid phase sythesis of macrocyclic compounds
- in depth: stereoelectronic effects
- miscellaneous work on reagent development



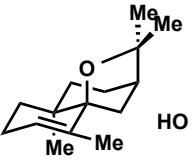
(+)-Ryanodol



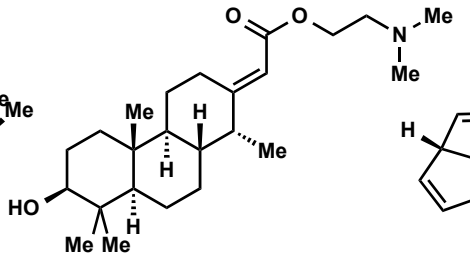
(−)-Erythromycin A



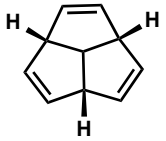
Maritimol



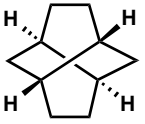
α-Agarofuran



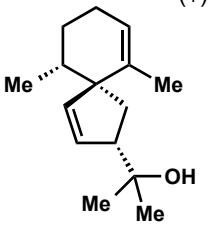
(+)-Cassaine



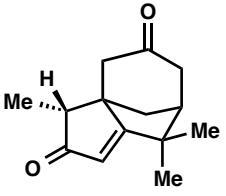
Triquinacene



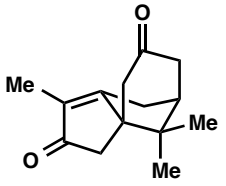
Twistane



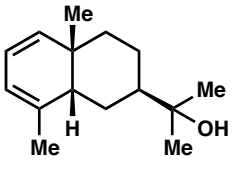
Agarospirol



α-patchoulene core



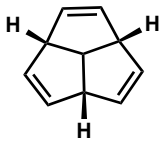
β-cedrene core



(+)-Occidentalol

Triquinacene

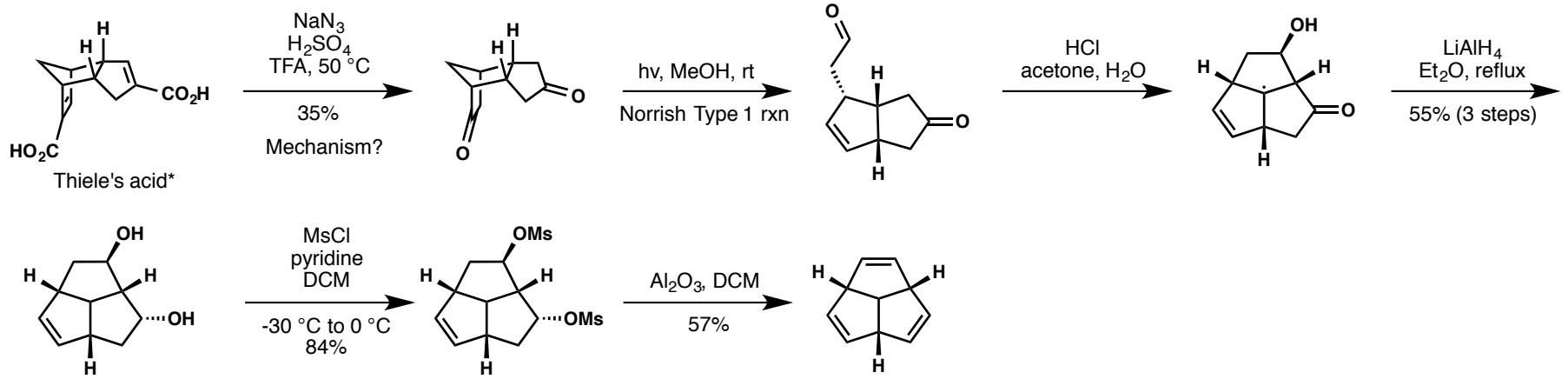
Steven Crossley



Triquinacene

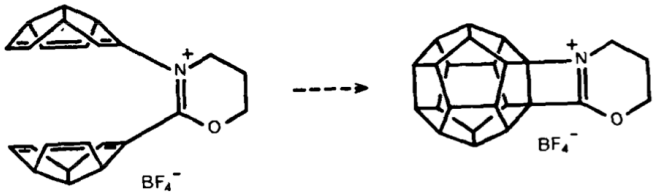
- first made by Woodward and coworkers in 1964
- targeted with dodecahedrane in mind, but the final dimerization was never realized

Can. J. Chem. **1978**, *56*, 1687
Also: Can. J. Chem. **1971**, *49*, 531; *Syn. Commun.* **1973**, *3*, 161; *Tetrahedron* **1981**, *37*, 4385



Thiele's acid*

Idea: to induce dimerization via thermal, photochemical, electrochemical or chemical means in order to access the dodecahedrane core



*"At the turn of the century, Thiele reported that carbonation of cyclopentadienylpotassium results in formation of a dimeric material, $C_{14}H_{16}O_4$, mp 210 °C, which subsequently became known as “Thiele’s acid" - *Tetrahedron* **1993**, *49*, 2613; *J. Chem. Ber.* **1900**, *33*, 666; **1901**, *34*, 68

Stereoelectronic Effects in Acetals

Steven Crossley

"The first condition to be fulfilled by men of science, applying themselves to the investigation of natural phenomena, is to maintain absolute freedom of mind, based on philosophical doubt. Yet we must not be in the least sceptical; we must believe in science, i.e., in determinism; we must believe in a complete and necessary relation between things, among the phenomena proper to living things as well as in others; but at the same time we must be thoroughly convinced that we know this relation only in a more or less approximate way, and that the theories we hold are far from embodying changeless truths. When we propound a general theory in our sciences we are sure only that, literally speaking, all such theories are false. They are only partial and provisional truths which are necessary to us, as steps on which we rest, so as to go on with investigation; they embody only the present state of our knowledge, and consequently they must change with the growth of science, and all the more often when sciences are less advanced in their evolution."

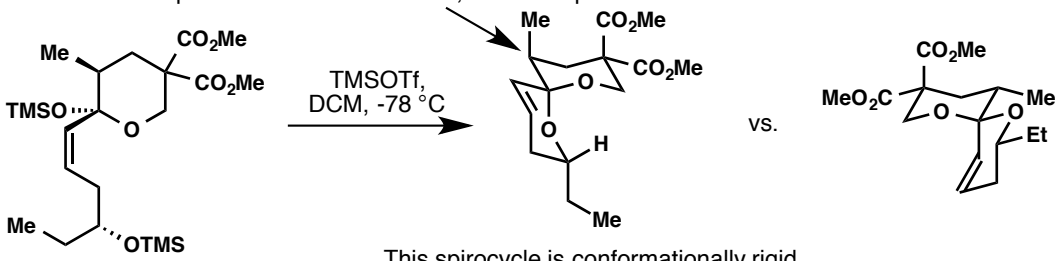
(from Claude Bernard, 1865) in Deslongchamps, P. "Stereoelectronic Effects in Organic Synthesis", Baldwin, J., Ed.; Pergamon Press: Toronto, **1983**

"Deslongchamps...has made seminal contributions to stereoelectronic theory" - Prof. Sir Jack E. Baldwin

This discussion is restricted to Deslongchamp's work on stereoelectronic effects in the conformational preferences of acetals. However, he also examined stereoelectronic effects in the reactivity and on the conformational preferences of esters, amides, and multiple other heteroatom containing systems, as well in Diels-Alder reactions, Michael additions and similar unsaturated systems in great detail. The sampling below was chosen to convey the nature and capacity of Deslongchamp's analyses, while the interested reader is directed to the primary literature for further readingon the scope of Deslongchamp's work.

Consider this transformation which was planned in Deslongchamp's formal synthesis of Erythromycin A:

1:1 mixture of epimers at this stereocenter, which is epimerizable under acidic conditions



This spirocycle is conformationally rigid
Can you explain why?

"Stereoelectronic Effects in Organic Synthesis", Baldwin, J., Ed.; Pergamon Press: Toronto, **1983**; *Can. J. Chem.* **1981**,*59*, 1105; 1132

Stereoelectronic Effects in Acetals

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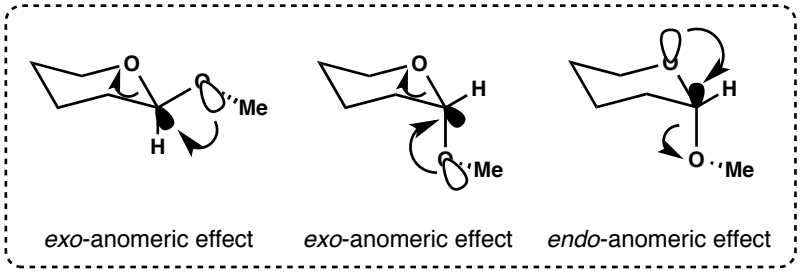
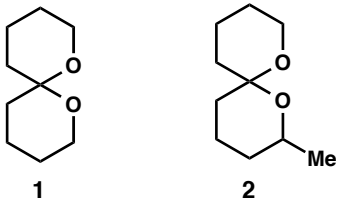
Key Idea: The answer to this question "can be rationalized by taking into account the anomeric and *exo*-anomeric effects and the usual steric interactions" - P. Deslongchamps



exo-anomeric effect *exo*-anomeric effect *endo*-anomeric effect

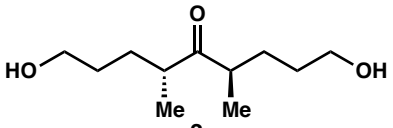
In the anomeric effect, there is a preference for a substituent on the anomeric carbon to be in the synclinal (gauche) position over the anti-periplanar (anti) position.

Which of their possible conformations do the following acetals/ketals adopt?



1

2



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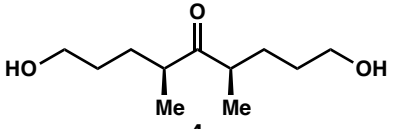

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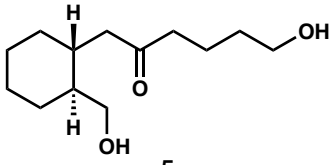

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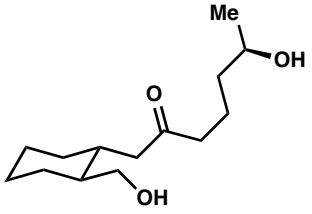

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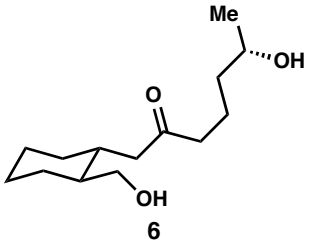

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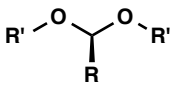
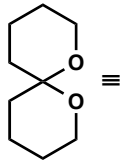


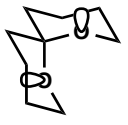
8

Note: Only the oxygen sp^3 orbitals which are anti-periplanar to an adjacent C-O sp^{3*} antibonding orbitals are shown

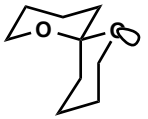
Consider a 1,7-dioxaspiro[5.5]undecane **1** and its three possible conformations:



1



1A



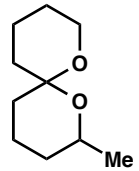
1B

1C

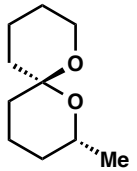
Relative Energies (kcal/mol):			
from Stereoelectronic effects	0	1.4	2.8
from Steric considerations	1.6	2.6	3.6
Net ΔE	**0**	**2.4**	**4.8**

Low temperature (148 K) ^{13}C NMR experiments showed that 1,7-dioxaspiro[5.5]undecane **1** exists in conformation **1A** only.

Consider the methyl substituted spiro system **2**, which exists as two isomers, **3** and **4**, both of which are able to adopt four different conformations:



2



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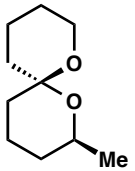
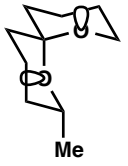
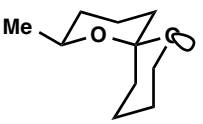


10

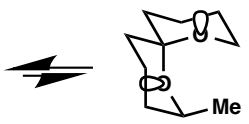
Evaluation of anomeric and steric effects indicates that conformation **3A** is lowest in energy for spirocycle **9**, while spirocycle **10** should exist as a mixture of major **10A** and minor **10B** conformers:



9A



10A



10B

Relative ΔE (kcal/mol):	**0**	**2.4**	**2.9**

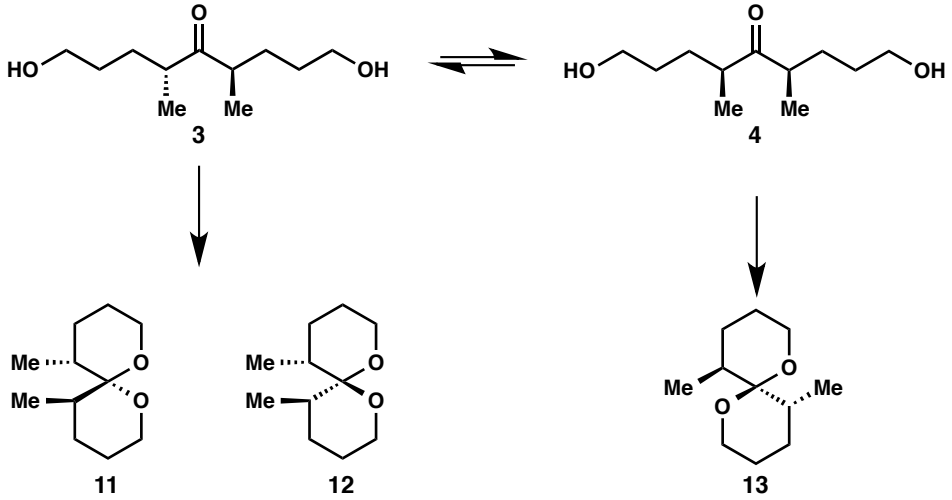
Conformer **9A** is most stable. Moreoever, since isomer **9** and **10** are interconvertible under thermodynamically controlled conditions (isomer **10** becomes the enantiomer of **9**), we expect to see conformer **9A** exclusively under these conditions. This conclusion was confirmed experimentally.

"Stereoelectronic Effects in Organic Synthesis", Baldwin, J., Ed.; Pergamon Press: Toronto, **1983**; *Can. J. Chem.* **1981**,*59*, 1105; 1132

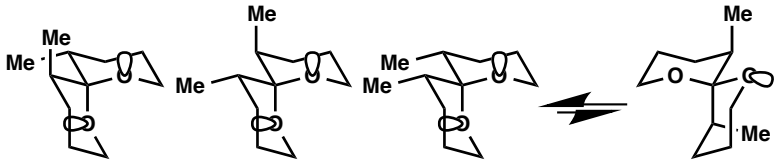
Stereoelectronic Effects in Acetals

Steven Crossley

Consider the dimethyl substituted systems **3** and **4**. Upon cyclization, compound **3** has two possible isomers, **11** and **12**, while meso compound **4** has one, **13**:



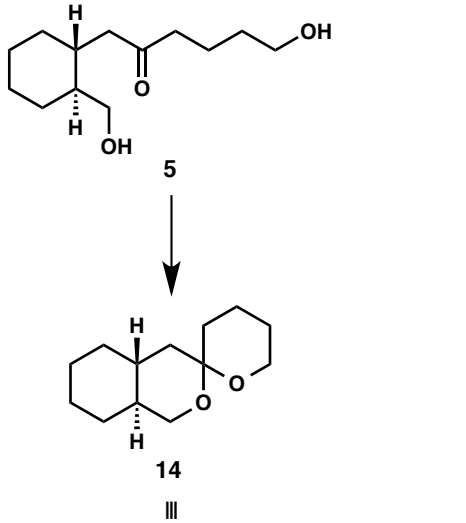
Conformational analysis with consideration of anomeric and steric considerations indicate isomers **11** and **12** each exist in primarily one conformation, **11A** and **12A** respectively, (of a possible three different conformations each), while **13** exists as a mixture of major **13A** and minor **13B** conformers (of a possible four conformers):



Rel. ΔE (kcal/mol):	**0**	**1.8**	**3.1**	**3.7**

Under acidic conditions which are sufficient to promote epimerization of the stereocenters of diastereomers **3** and **4**, compounds **3**, **4**, **11**, **12** and **13** are interconvertible. Under acidic equilibrating conditions, a ~ 97:3 mixture of **11A**:**12A** was indeed observed by low temperature ^{13}C NMR. This result is consistent with the analysis above.

Compound **5** cyclizes to form a tricycle **14**, which has two isomers, **15** and **16**. These in turn can exist in two possible conformations, of which the more stable are denoted **15A** and **16A**:



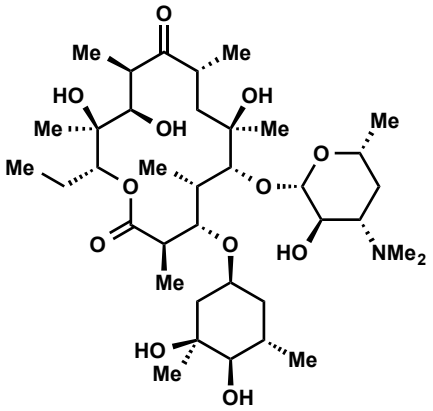
Relative ΔE (kcal/mol):	**0**	**2.4**

Only compound **15A** is observed under mildly acidic conditions in low temperature NMR experiments.

"Stereoelectronic Effects in Organic Synthesis", Baldwin, J., Ed.; Pergamon Press: Toronto, **1983**; *Can. J. Chem.* **1981**,*59*, 1105; 1132

Erythromycin A

Steven Crossley

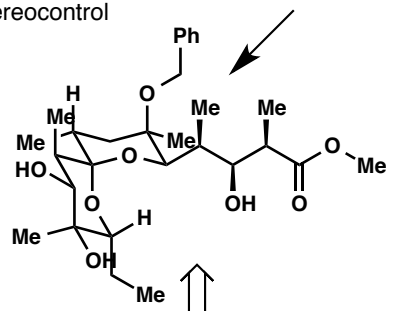


(–)-Erythromycin A

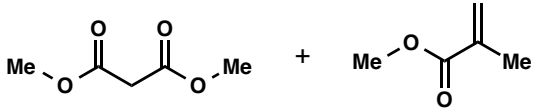
Can. J. Chem. **1985**, *63*, 2810, 2814, 2818;
Can. J. Chem. **1984**, *62*, 2929

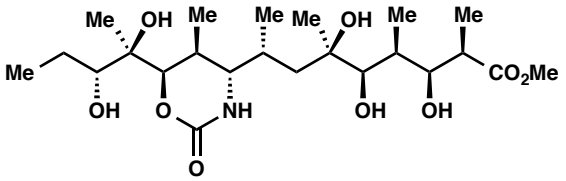
- Deslongchamp's formal synthesis, 56 linear steps
- cf. Woodward *et. al. J. Am. Chem. Soc.* **1981**, *103*, 3210, 3213, 3215 (50 linear steps)
- The purpose of this synthesis was to showcase insight gained from studying stereoelectronic effects in acetal chemistry
  As a result, the synthesis works by functionalizing a conformational rigid dioxaspirocycle, which is later unravelled to reveal Woodward's carbamate

Key idea: stereoelectronic effects control the formation of the 1,7-dioxaspiro[5.5]undecane system, intermediate to Woodward's carbamate, facilitating high stereocontrol



- conformationally rigid (2 anomeric effects) spirocycle which can be built with high stereocontrol and then elaborated to Woodward's carbamate
- found to be identical to an erythronolide degradation product





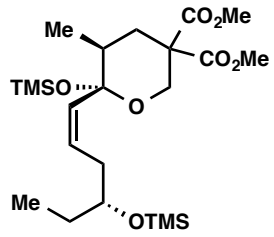
Woodward's carbamate

14 steps, 1.1%
see Woodward's papers

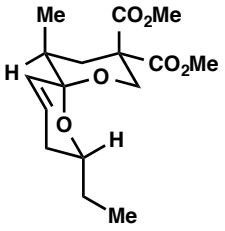
(–)-Erythromycin A

4 steps

(Michael addition, formaldeyde addition then lactonization, alkynylation then silylation, Lindlar hydrogenation)

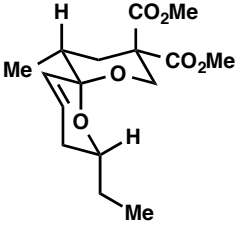


TMSOTf, DCM, -78 °C
1:1 mixture

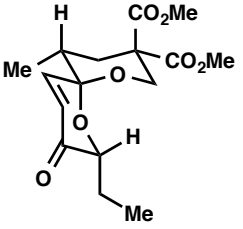


conformationally rigid

pyr, pTsOH
DCM, reflux



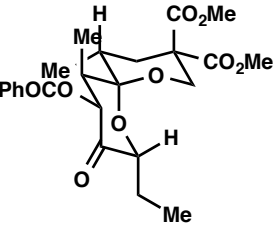
SeO_2, pyr., xylenes,140 °C;
PCC, 3 Å MS, DCM, 60% (2 steps)



CuBr, MeLi, Et_2O, 0 - 5 °C;
$(PhCO_2)_2$, -78 °C to 25 °C, 75%

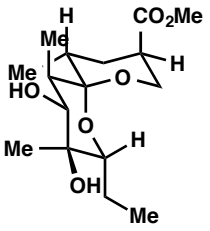
Erythromycin A

Steven Crossley



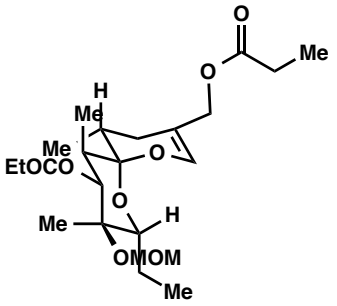
3 steps

(MeMgBr addition;
hydrolysis;
Krapcho decarboxylation)



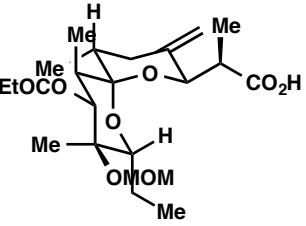
6 steps

(selenation, oxidation,
then elimination,
Pd/C isomerization,
LAH reduction,
ethyl ester formation,
MOM protection)

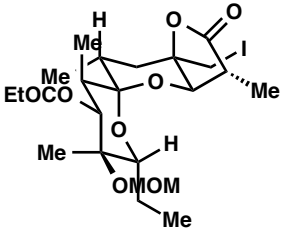


LDA, TBSCl,
DCM, 50 °C

4:1 d.r.
Claisen rearrangment

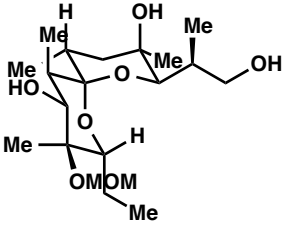


$KHCO_3$, KI, I_2,
H_2O-MeOH



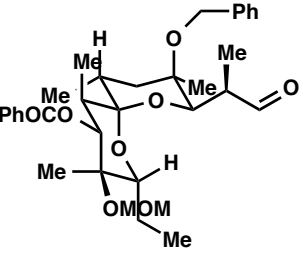
2 steps

(Ra-Ni reduction,
LAH reduction)



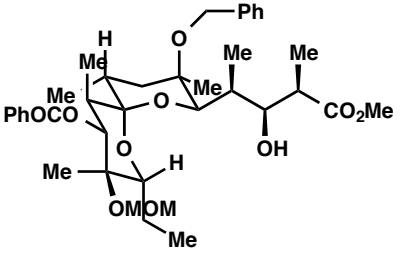
5 steps

(1° ROH protection;
3° ROH protection;
2° ROH protection;
1° ROH
deprotection;
PCC oxidation)



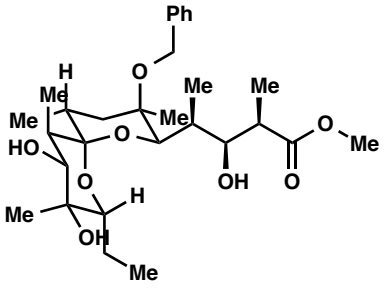
methyl propionate,
Cp_2ZrCl_2, LDA,
THF, -78 °C to r.t.,
then down to -50 °C

96:4 d.r.



1 N HCl, MeOH;

K_2CO_3, MeOH



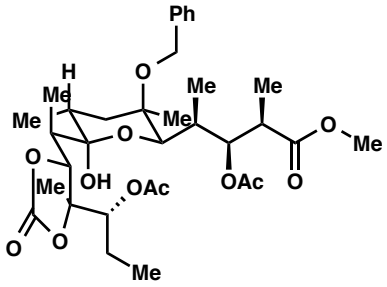
1,7-dioxaspiro[5.5]undecane system

4 steps

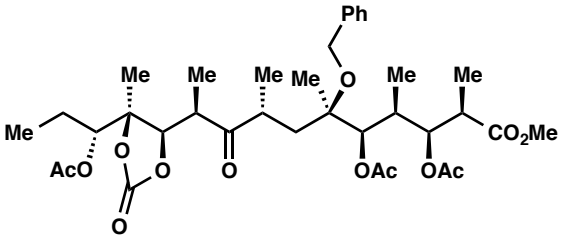
(carbonate formation,
acid catalyzed ring opening,
acetate protection
Markovnikov hydration)

Erythromycin A

Steven Crossley

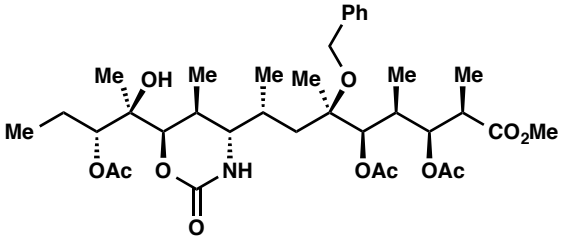


$(MeCO)_2O$
pyr, DMAP,
DCM, 74%



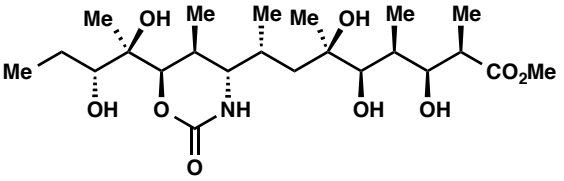
5 steps

($NaBH_4$ reduction (2:1 mix),
mesylation,
azidination,
PtO_2 hydrogenolysis,
carbamate formation)



4 steps

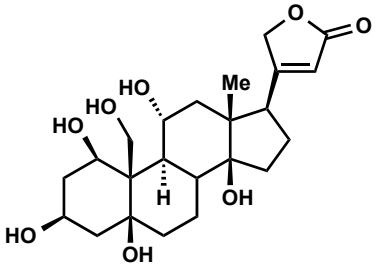
(ester hydrolysis,
global acetate hydrolysis,
methyl ester formation,
hydrogenolysis



Woodward's carbamate

Oubagenin

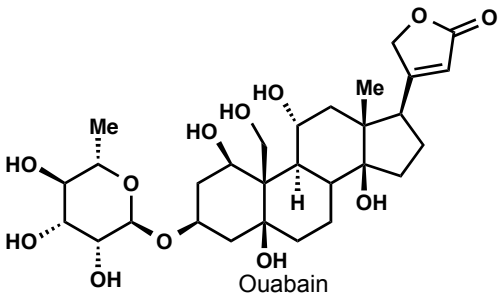
Steven Crossley



Ouabagenin

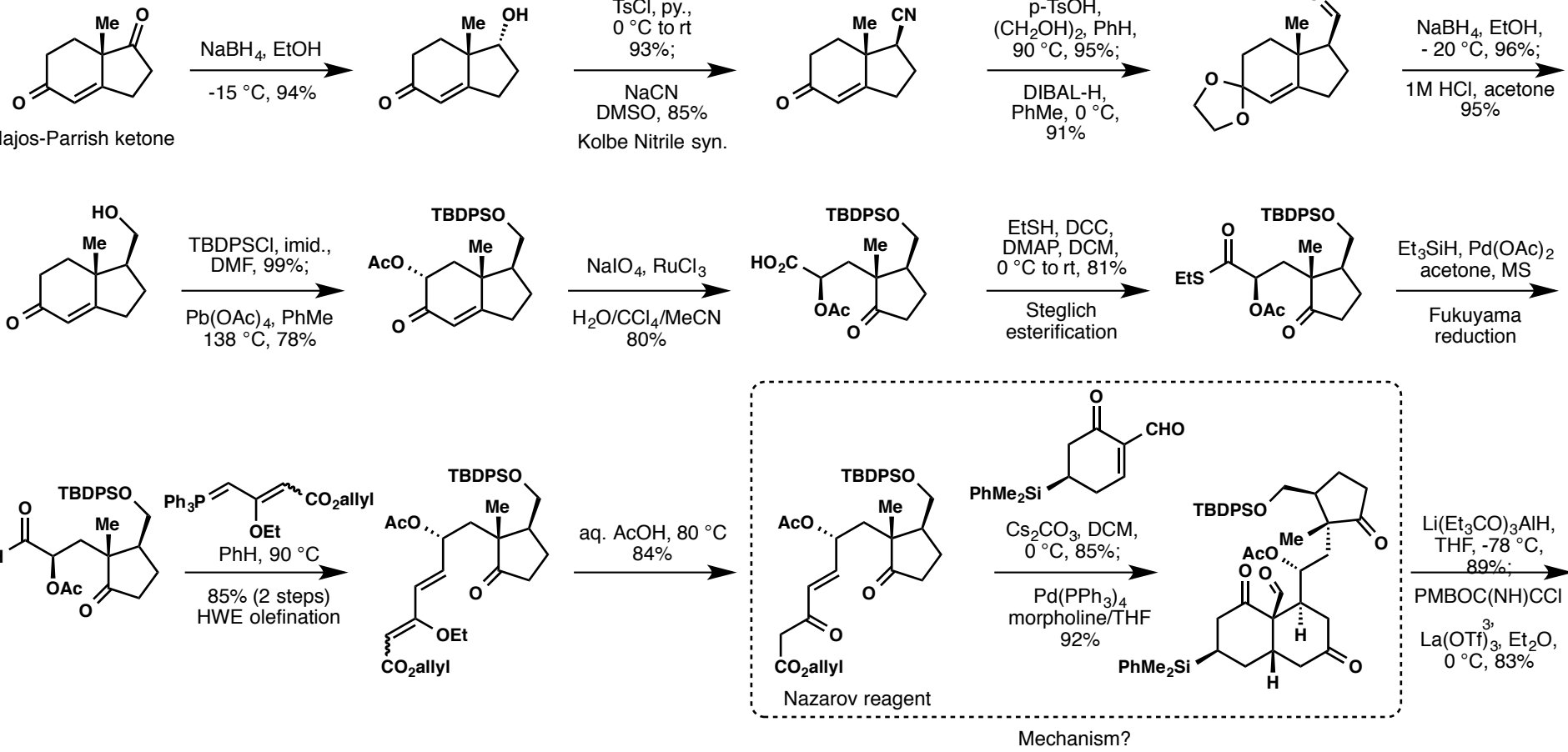
- 1st total synthesis
- 41 steps for longest linear sequence
- a cardioactive steroid

features a **polyanionic cyclization strategy**
aka. a double Michael addition followed by an aldol condensation



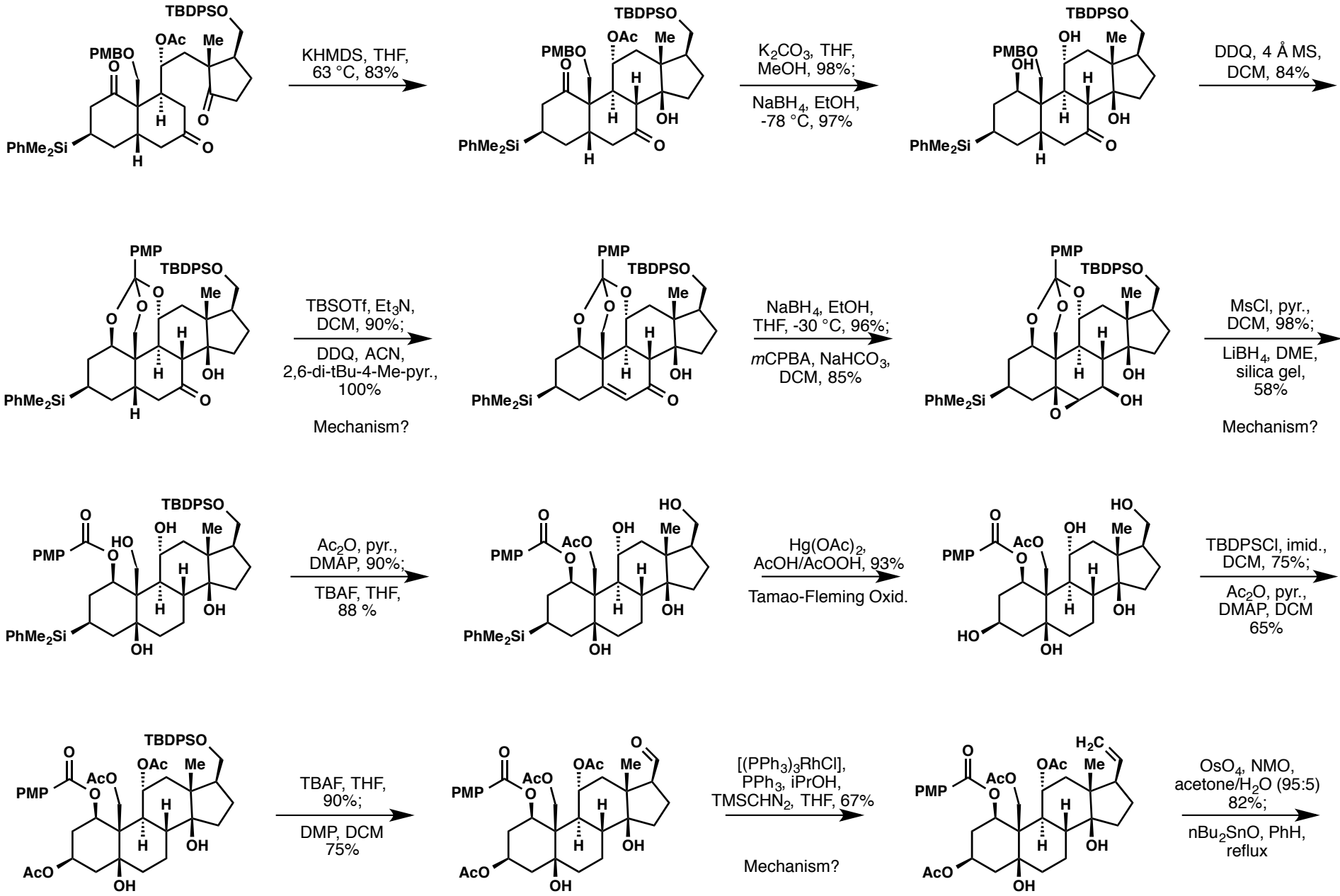
Ouabain

Angew. Chem. Int. Ed. **2008**, *47*, 1272; C*hem. Asian J.* **2009**, *4*, 725
Initial Studies: *Tet. Lett.* **1988**, *29*, 6033; **1990**, *31*, 2961; *Can. J. Chem.* **1992**, *70*, 1939; **2005**, *83*, 728; *Org. Lett.* **2002**, *4*, 4693
Polyanionic cyclization: *Tet. Lett.* **1988**, *29*, 6033; **1990**, *31*, 3969;, *Syn. Lett.* **1990**, *9*, 516; *Tetrahedron* **2002**, *58*, 6555; *Org. Lett.* **2002**, 4, 4693; **2010**, *12*, 508; *Helv. Chem. Acta* **2003**, *86*, 3730; *J. Org. Chem.* **2006**, *71*, 614; **2003**, *68*, 2183; 6140, **2004**, *69*, 832



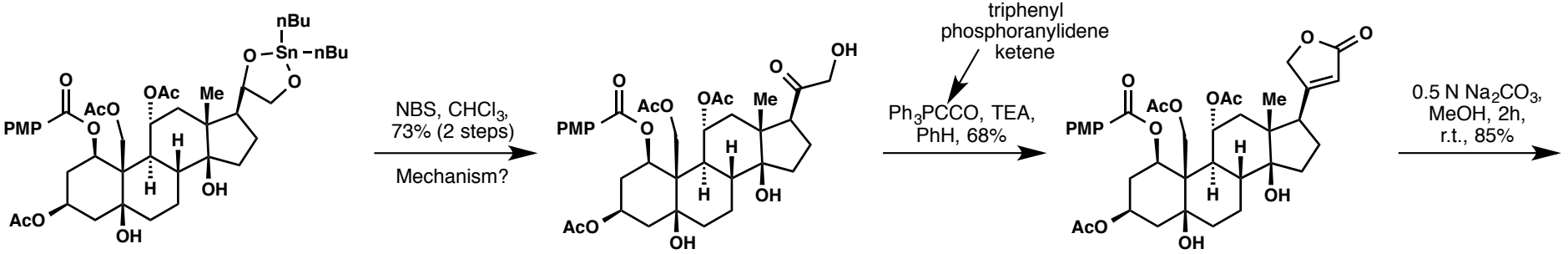
Oubagenin

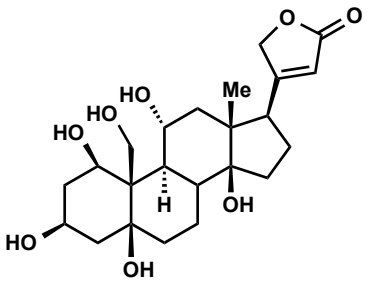
Steven Crossley



Oubagenin

Steven Crossley

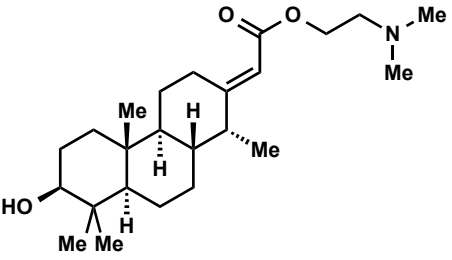




Oubagenin

(+)-Cassaine

Steven Crossley



(+)-Cassaine

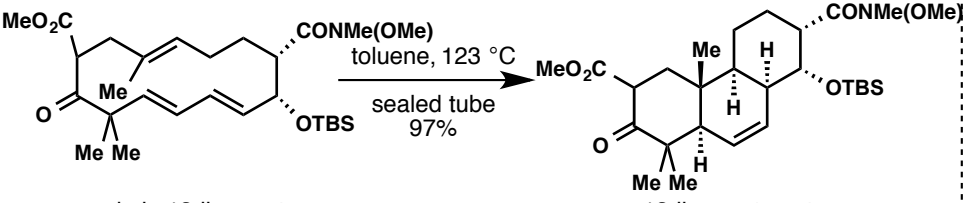
transannular Diels-Alder (TADA) strategy

- a nonsteroidal inhibitor of Na^+, K^+-ATPase
- features a trans-anti-trans tricyclic system; 6 stereocenters; an *exo*-α,β-unsaturated ester

Key Idea: stereocontrolled construction of trans-anti-cis tricycle through TADA reaction on trans-trans-trans macrocyclic triene

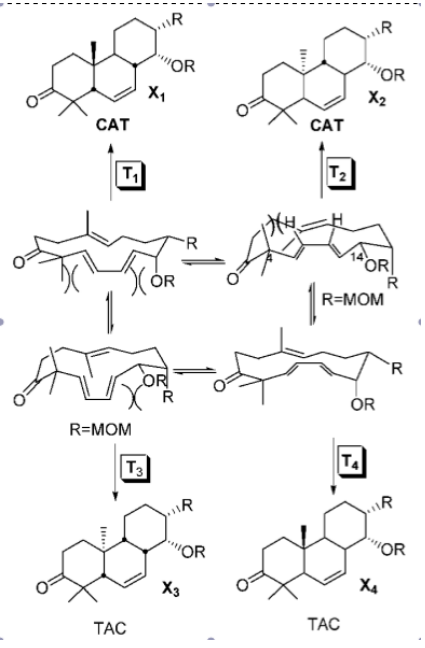
J. Am. Chem. Soc. **2008**, *130*, 13989

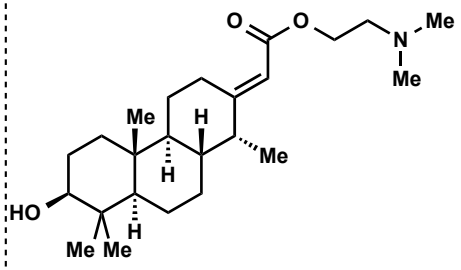
for TADA development, see: *J. Org. Chem.* **2006**, *71*, 7370; **2003**, *68*, 9983; **2003**, *68*, 6847; **2002**, *67*, 5269; *J. Am. Chem. Soc.* **2000**, *122*, 4526; *Tet. Lett.* **1988**, *29*, 1641; *Org. Lett.*, **2000**, *2*, 4149



made in 13 linear steps
(for larger fragment)

13 linear steps to
(+)-Cassaine





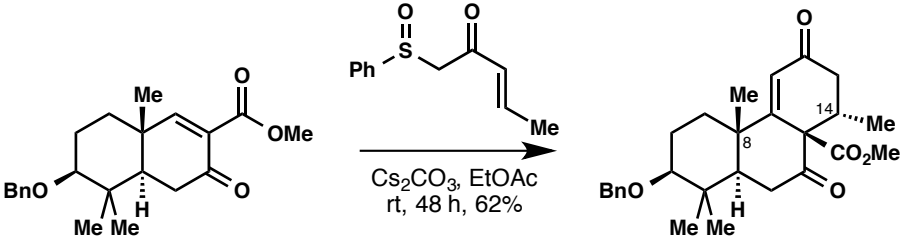
(+)-Cassaine

anionic polycyclization strategy

- reaction between a Nazarov reagent with an α,β–unsaturated EWG
- initially believed to be a cycloaddition, but that view was later amended. Now considered to be a double Michael addition
- C-14 Me group is axial, which is difficult to achieve otherwise
- C-10 Me group forces the Nazarov reagent to approach from the α-face in an *endo* manner

Org. Lett. **2013**, *15*, 6270; **2011**, *12*, 508

see also: *Tet. Lett.* **1988**, *29*, 6033; **1990**, *31*, 3969;, *Syn. Lett.* **1990**, *9*, 516; *Tetrahedron* **2002**, *58*, 6555; *Org. Lett.* **2002**, 4, 4693; **2010**, *12*, 508; *Helv. Chem. Acta* **2003**, *86*, 3730; *J. Org. Chem.* **2006**, *71*, 614; **2003**, *68*, 2183; 6140, **2004**, *69*, 832



from (+)-Carvone

- diastereomerically pure