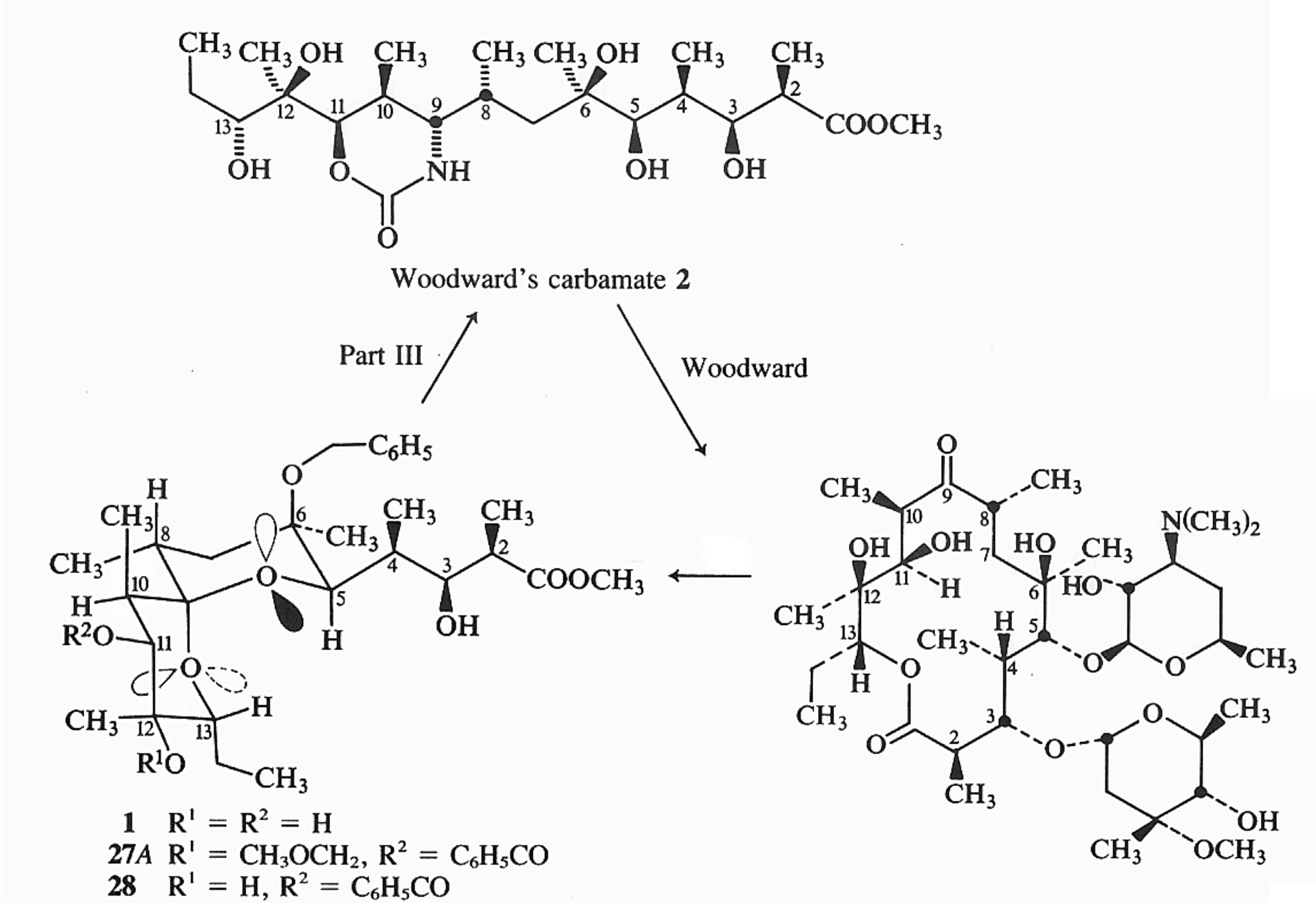
SECTION 12

« POT-POURRI » in Organic Synthesis

(2018)

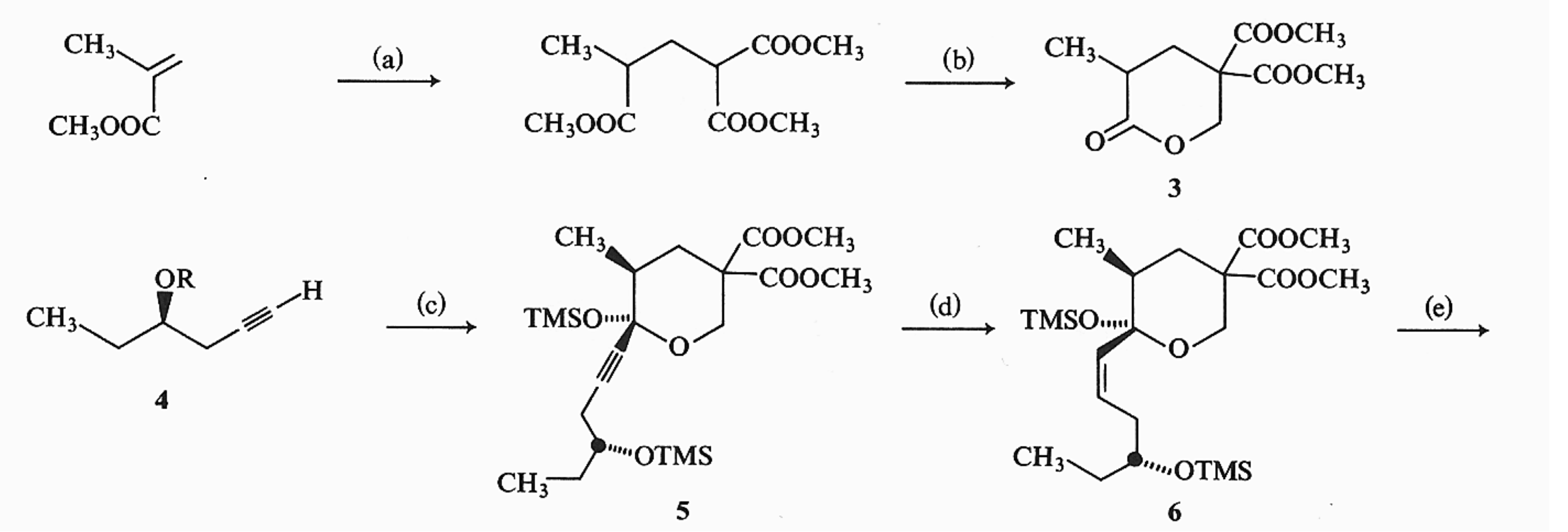
Total Synthesis of Erythromycin A via a Spiroketal



ERYTHROMYCIN A

DESLONGCHAMPS *et al.* Can. J. Chem. 1985, *63*, 2810-2820.

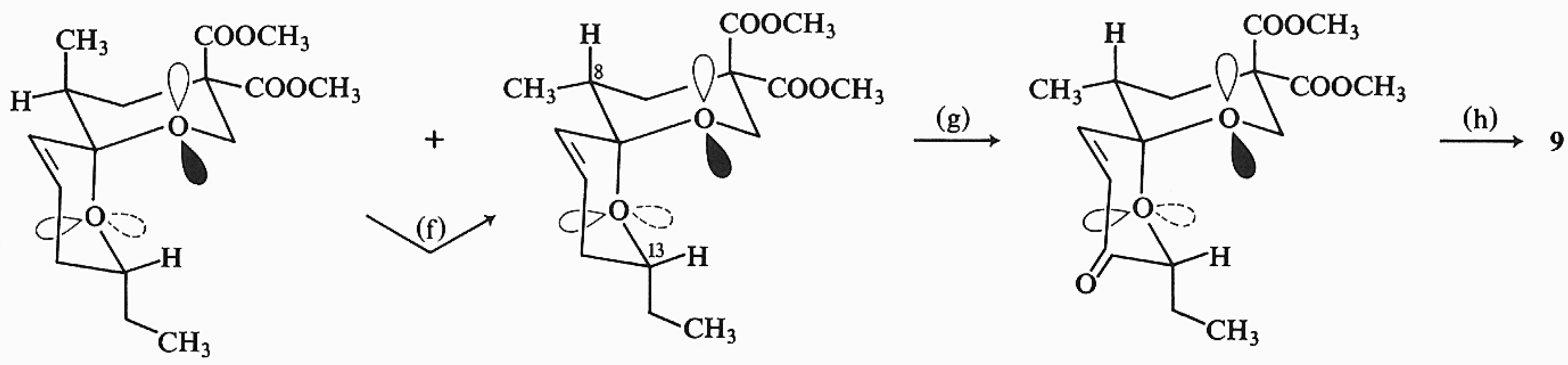
Tetrahydropyran Derivative as Starting Material



(a) $CH_2(COOCH_3)_2$, CH_3ONa, CH_3OH, reflux, 9 h, 76%
(b) NaH, benzene, $(CH_2O)_3$, r.t., 3 h, 62%
(c) *n*-BuLi, compound **3**, TMSCl, THF, −78°C → 0°C, 4 h, 80%, ref. 7
(d) Lindlar catalyst, H_2, cyclohexane, 15°C, 30 h, ~100%
(e) $(CH_3)_3SiOSO_2CF_3$, CH_2Cl_2, −78°C, 5 h, 84%, ref. 9

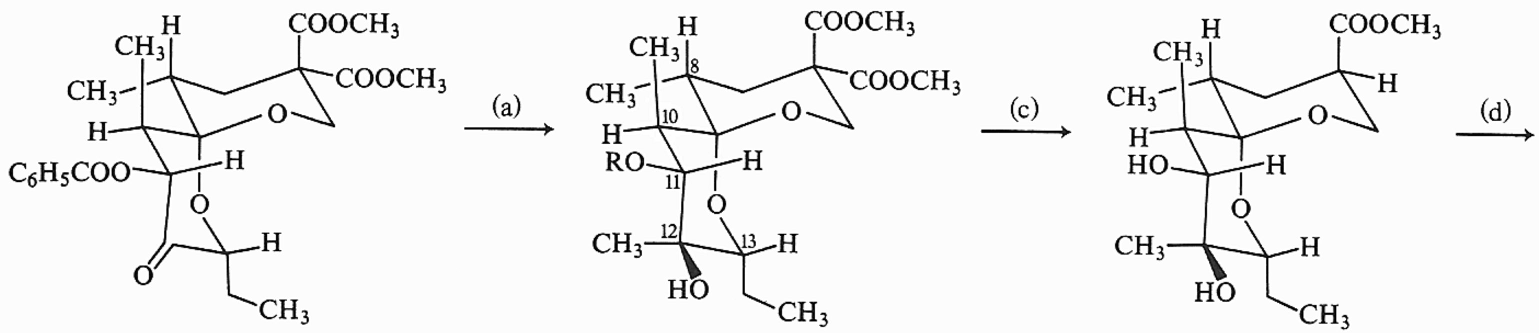
DESLONGCHAMPS *et al.* Can. J. Chem. 1985, *63*, 2810-2820.

Spiroketal Controlling Introduction of Stereogenic Centers – PART I



7A **7B** **8**

(f) Pyridinium *p*-toluenesulfonate, CH_2Cl_2, reflux, 40 h, 84%, ref. 10
(g) SeO_2 (2 equiv.), pyridine (4 equiv.), xylene, 140°C, 5 h; PCC, molecular sieve 3 Å, CH_2Cl_2, 25°C, 60% yield, ref. 11
(h) CuBr, CH_3Li, ether, 0−5°C, 15 min, ref. 12; $(C_6H_5CO_2)_2$, −78°C → 25°C, 30 min, 75%, ref. 13.



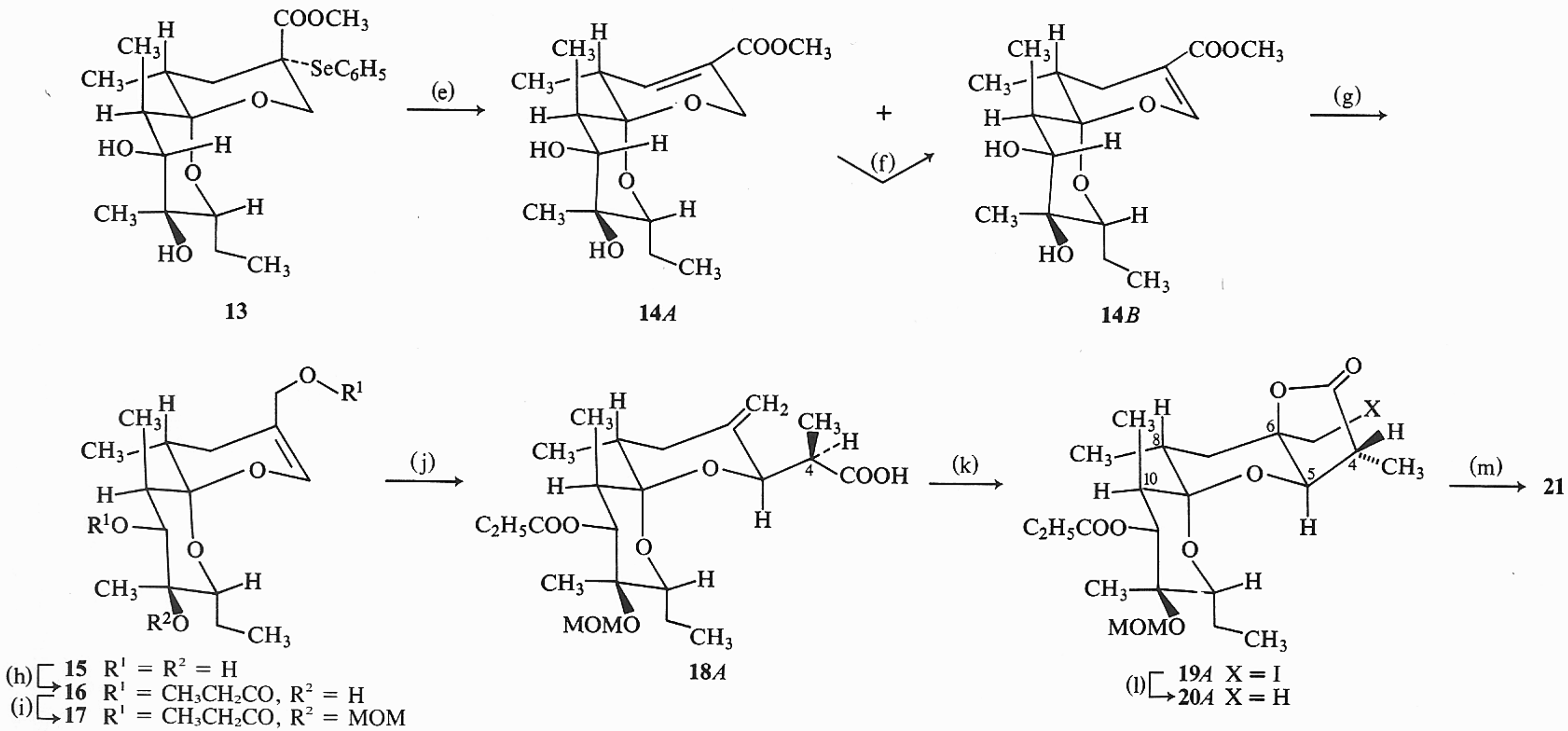
9

(b) **10** R = C_6H_5CO; **11** R = H

12A

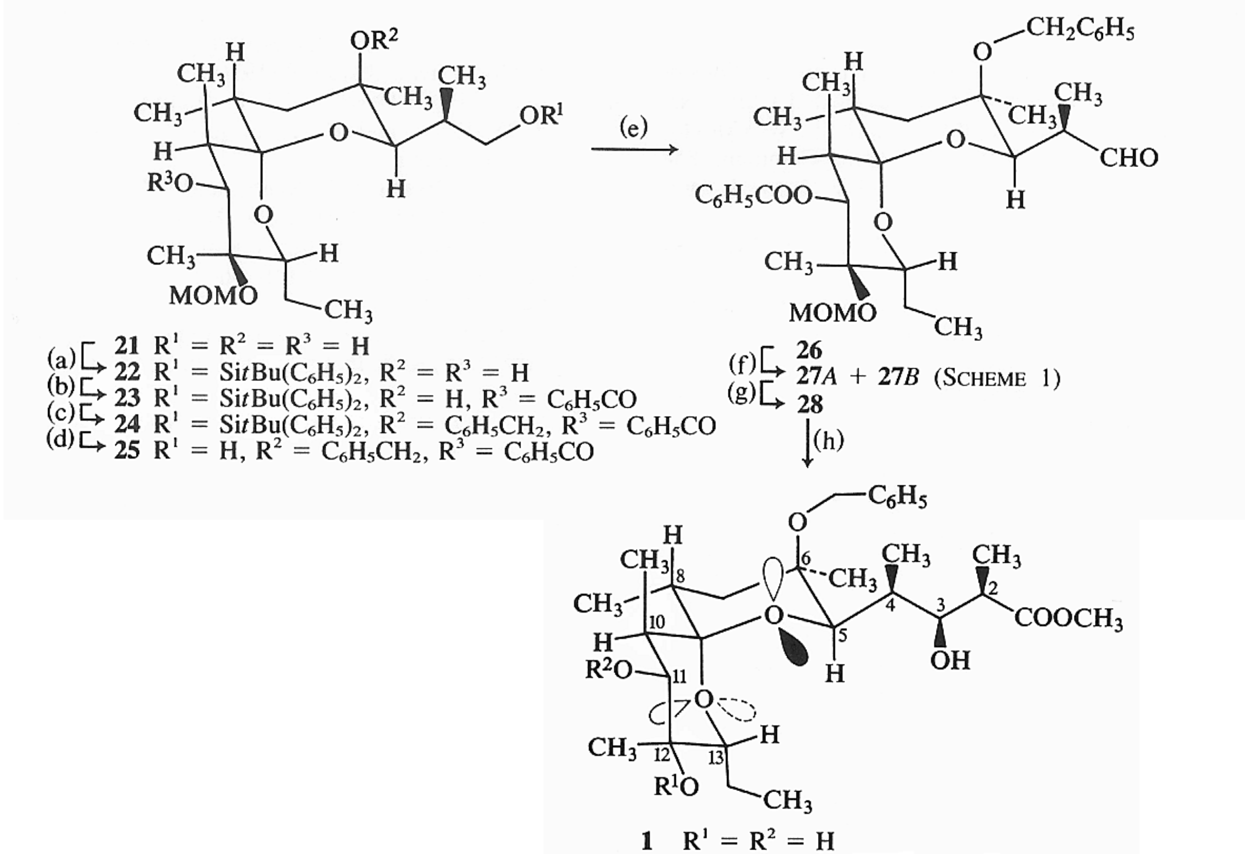
(a) CH_3MgBr, ether, −78°C, 1 h, 63%, ref. 14
(b) K_2CO_3, CH_3OH, 25°C, 1 h, 94%
(c) LiCl, DMSO−H_2O, 165−170°C, 70 min, 83%, ref. 15
(d) Lithium isopropylcyclohexylamide (LiCA), C_6H_5SeBr, DME, −78°C, 90 min, 89%, ref. 16

Spiroketal Controlling Introduction of Stereogenic Centers – PART II



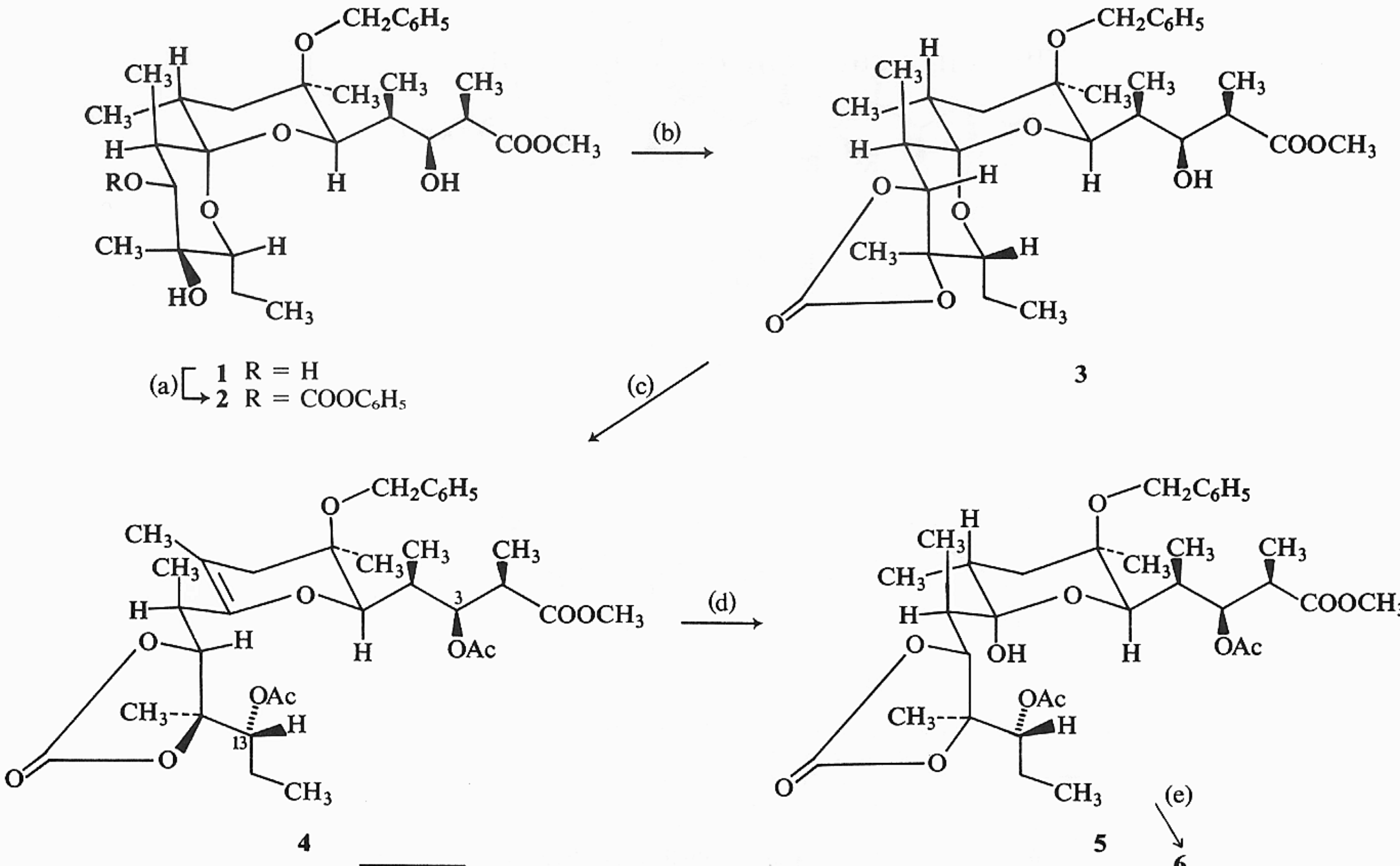
(e) H_2O_2, pyridine, CH_2Cl_2, 25°C (30 min) and 45°C (30 min), 86%
(f) Pd/C—10%, H_2, xylene, 138°C, 2 h, ~100%
(g) LAH, THF, 0°C → 25°C, 2 h, 90%
(h) $(C_2H_5)_3N$, $(CH_3CH_2CO)_2O$, DMAP, 25°C, 1 h, 99%
(i) Diisopropylethylamine, CH_3OCH_2Cl, CH_2Cl_2, 50°C, 4 h, 90%, ref. 17
(j) LDA, *tert*-butyldimethylsilyl chloride (TBSCl), THF, HMPA (10%), −78°C, 145 min, ref. 18
(k) $KHCO_3$, KI, I_2, H_2O-CH_3OH, 0°C (30 min) and 25°C (15 h), 65% yield from **17**, ref. 19
(l) Ra−Ni, $NaHCO_3$, H_2 (50 psi), C_2H_5OH, 25°C, 24 h, 85% yield of **20***A* and **20***B* (ratio 70:30)
(m) LAH, THF, 0°C (5 min) and 25°C (1 h), 90%

Spiroketal Controlling Introduction of Stereogenic Centers – PART III



(a) TBDPSCl, imidazole, DMF, 25°C, 60 min, 95%, ref. 20
(b) C_6H_5COCl, pyridine, 70°C, 24 h, 78%
(c) $((CH_3)_3Si)_2NK$, $C_6H_5CH_2Br$, THF, 0°C → 25°C, 20 min, 92%
(d) $(n\text{-}Bu)_4NF$, THF, 65–70°C, 2 h, 95%
(e) PCC, molecular sieve 3 Å, AcONa, CH_2Cl_2, 30 min, 85%, ref. 11
(f) Methyl propionate, zirconocene dichloride, LDA, THF, −78°C (40 min), −78°C → 25°C (30 min), and −50°C (1 h), 60% yield of **27***A* and **27***B* (96:4), ref. 21
(g) HCl 1 *N*, CH_3OH, 25°C, 8 h, 93%
(h) K_2CO_3, CH_3OH, 25°C, 2 h, 95%

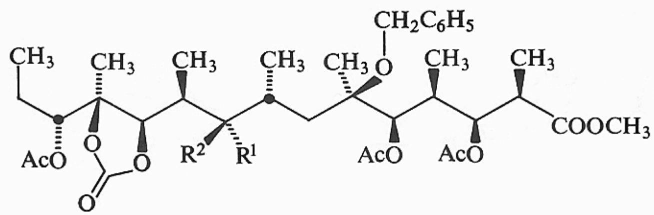
Cyclic Carbonate Useful to Open Spiroketal System



(a) C_6H_5OCOCl, pyridine, CH_2Cl_2, 0°C, 30 min, 82%
(b) Imidazole, xylene, 95°C → 100°C, 40 min, 98%
(c) PTSOH, CH_3COOH, $(CH_3CO)_2O$, 60°C → 70°C, 30 min, 81%
(d) HCl (30%), acetone, 25°C, 24 h, 68%
(e) $(CH_3CO)_2O$, $(C_2H_5)_3N$, DMAP, CH_2Cl_2, 25°C, 20 h, 74%

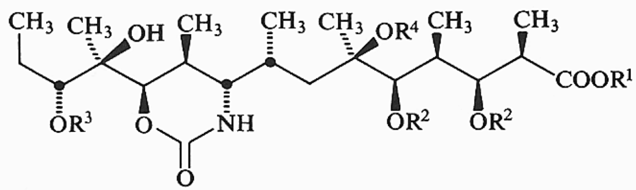
DESLONGCHAMPS *et al.* Can. J. Chem. 1985, *63*, 2810-2820.

Synthesis of Woodward Carbamate Key Intermediate



(a) **6** $R^1, R^2 = O$
7A $R^1 = H, R^2 = OH$
(b) **8** $R^1 = H, R^2 = CH_3SO_2$
(c) **9** $R^1 = N_3, R^2 = H$
(d) **10** $R^1 = NH_2, R^2 = H$

↓ (e)



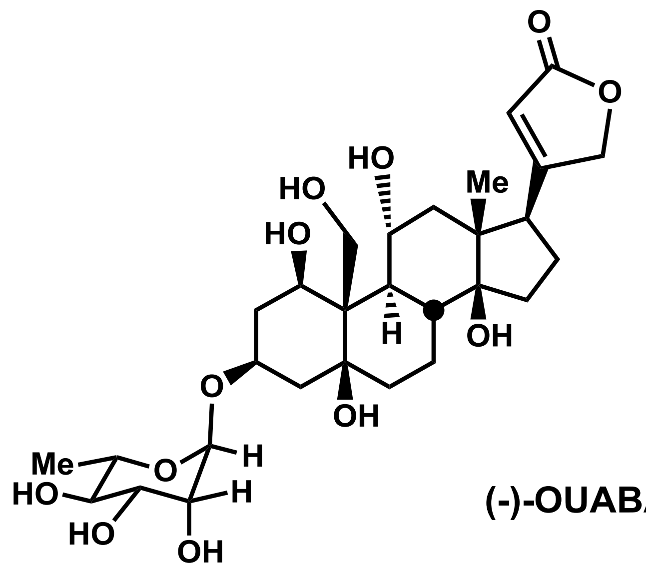
(f) **11** $R^1 = CH_3, R^2 = R^3 = Ac, R^4 = C_6H_5CH_2$
12 $R^1 = H, R^2 = R^3 = Ac, R^4 = C_6H_5CH_2$
(g) **13** $R^1 = R^2 = R^3 = H, R^4 = C_6H_5CH_2$
(h) **14** $R^1 = CH_3, R^2 = R^3 = H, R^4 = C_6H_5CH_2$
(i) **15** $R^1 = CH_3, R^2 = R^3 = R^4 = H$
(j) **16** $R^1 = CH_3$, R^2 = 2,4,6-trimethylbenzaldehyde acetal, $R^3 = R^4 = H$

(a) $NaBH_4$, THF, CH_3OH, 25°C, 90 min, 72% yield of **7***A* and **7***B* (ratio 66:34)
(b) CH_3SO_2Cl, pyridine, 0°C, 20 h, 100%
(c) LiN_3, HMPA, 60°C, 1 h, 91%, ref. 3
(d) PtO_2, H_2, THF, 25°C, 3h, 100%
(e) Benzene, reflux, 120 h, 76%
(f) LiI, pyridine, reflux, 122 h, ref. 4
(g) NaOH 1 *N*, CH_3OH, 25°C, 70 h
(h) CH_2N_2, $CHCl_3$–ether, 25°C, 10 min, 60% yield from **11**
(i) Pd/C (10%), H_2, $CH_3COOC_2H_5$, 25°C, 11 h, 30 min, 85%
(j) Dimethyl acetal of mesitaldehyde, CF_3COOH (cat.), CH_2Cl_2, 0°C, 116 h, 40%, ref. 1

DESLONGCHAMPS *et al.* Can. J. Chem. 1985, *63*, 2810-2820.

La première synthèse totale de la OUABAÏNE,

un stéroïde cardioactif



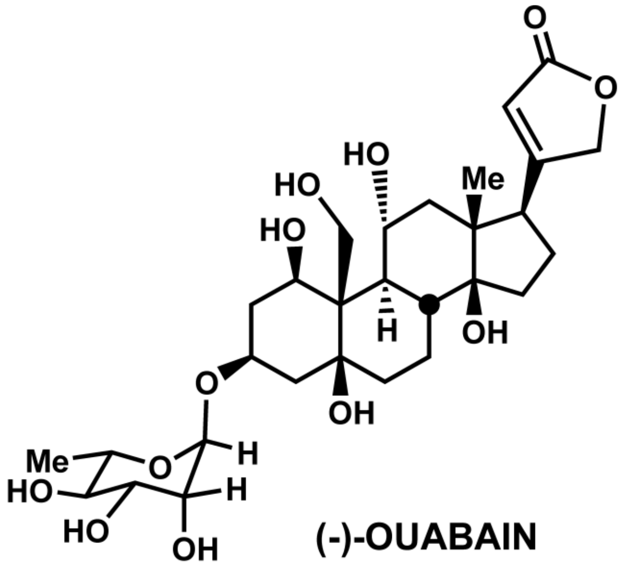
(-)-OUABAÏNE

Hongxing ZHANG, Maddi SRIDHAR Reddy, Serge POENIX, Pierre DESLONGCHAMPS.

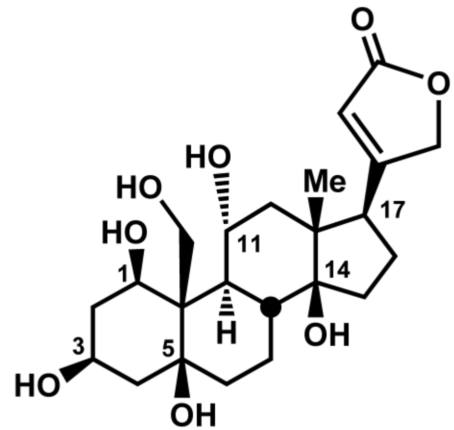
<u>Angew.</u> <u>Chem.</u> <u>Int.</u> <u>Ed</u>. *47,* 1272-1275 (2008).

<u>Chem.</u> <u>Asian</u> <u>J.</u> *4,* 725-741 (2009).

OUABAIN, a cardioactive steroid



(-)-OUABAIN



(+)-OUABAGENIN

(1) Isolated from plants in 1888 (M. Arnaud. *Compt. Rend. Acad. 107,* 1011).

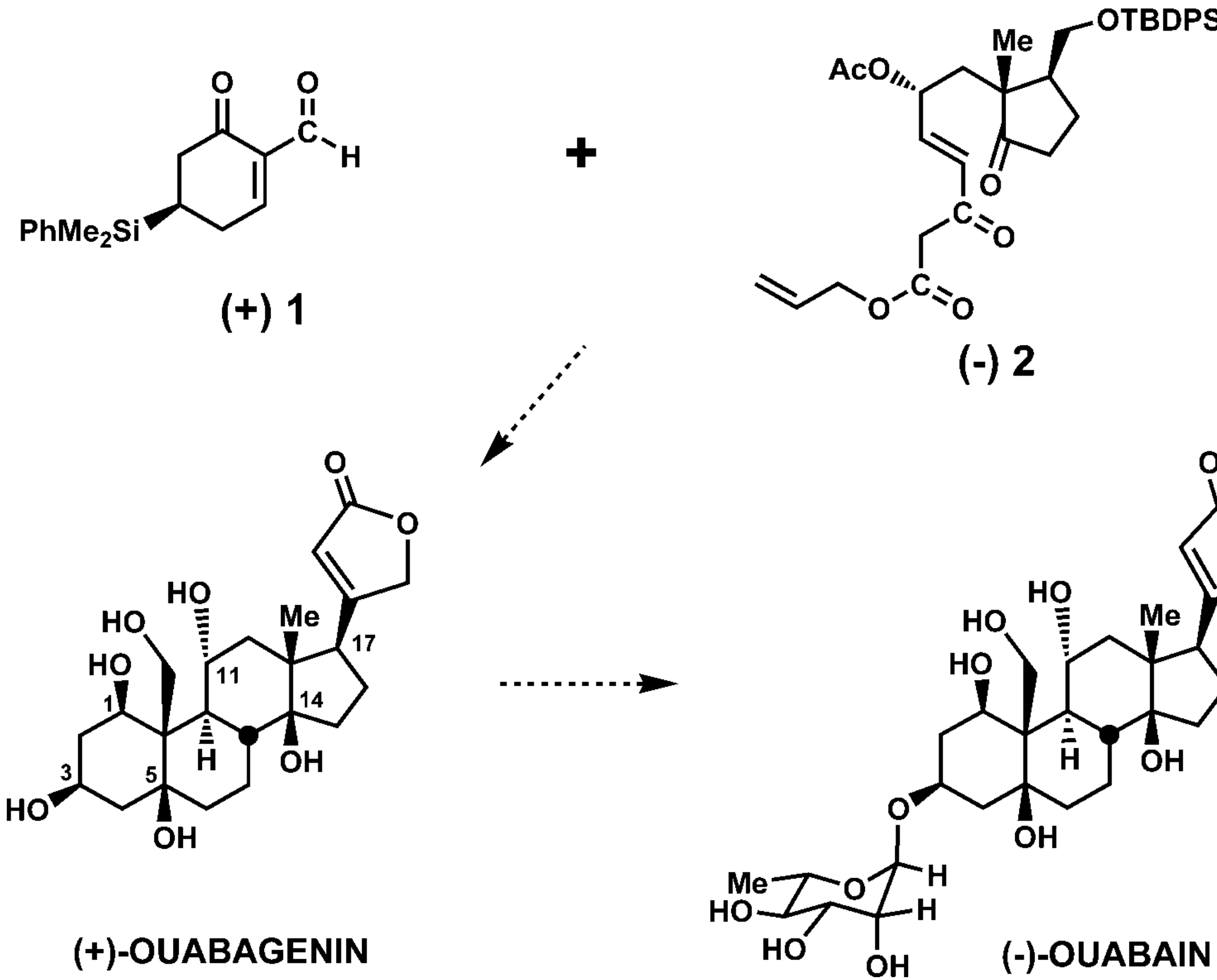
(2) Structure elucidation: C. Mannich, G. Siewert. *Ber.* (1942), *75,* 737 and K. Florey, M. Ehrenstein. *J. Org. Chem.* (1954), *19,* 1174.

(3) Suggestion of an ouabain-like compound in mammals. A. Szent-Gyorgi (1953).

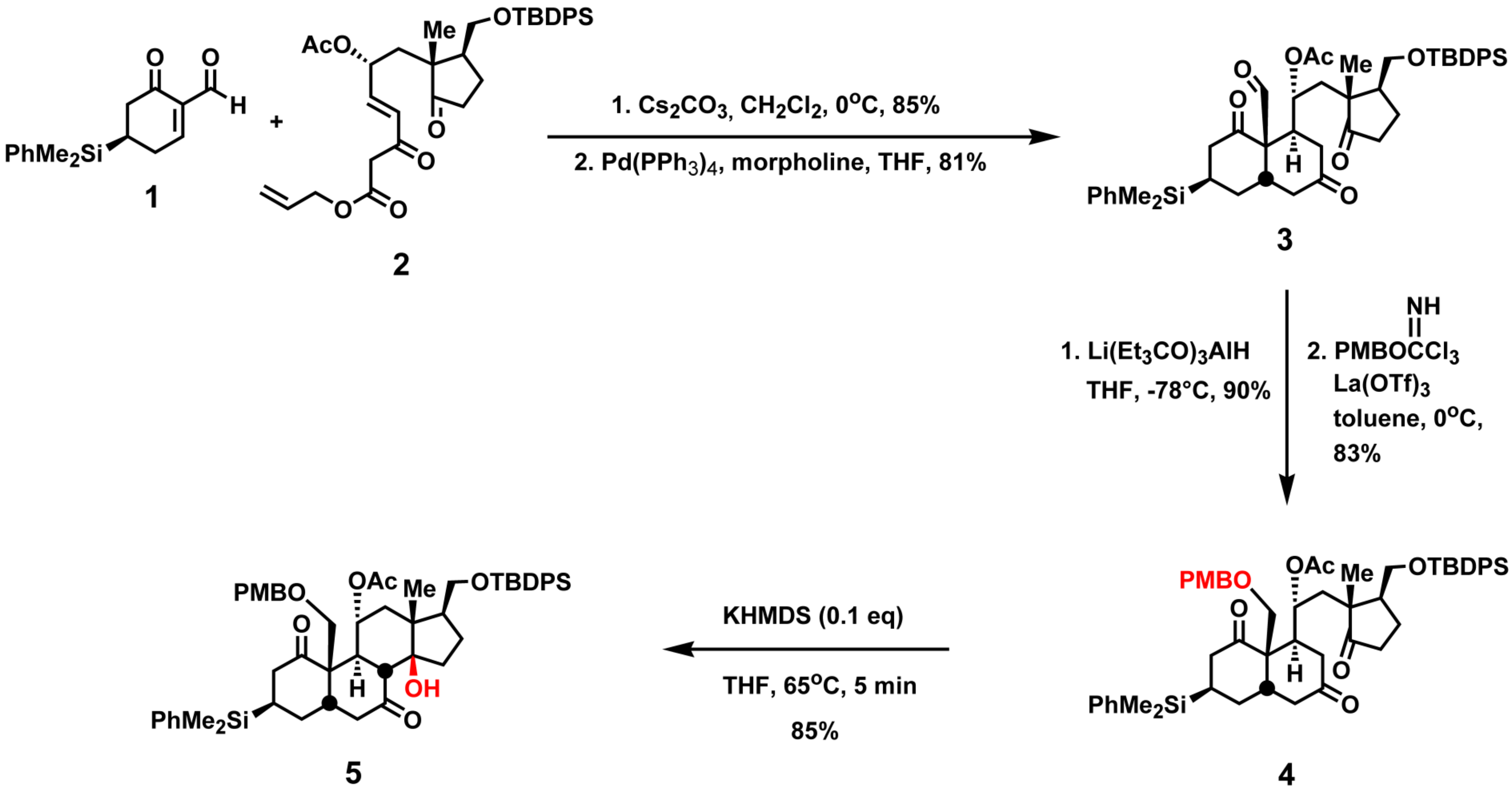
(4) Observed in human blood. S.M. Hamlyn *et al.* *Proc. Natl. Acad. Sci. USA* (1991), *88,* 6259.

(5) "Endogenous ouabain in mammals is identical with ouabain from plant origin.
A. Kawamura, J. Guo, F. Maggioli, N. Berooa, and K. Nakanishi.
Pure and Appl. Chem. (1999), *71,* 1643.

SELECTED UNICHIRAL BUILDING BLOCKS



Key Tetracyclic OUABAIN Intermediate



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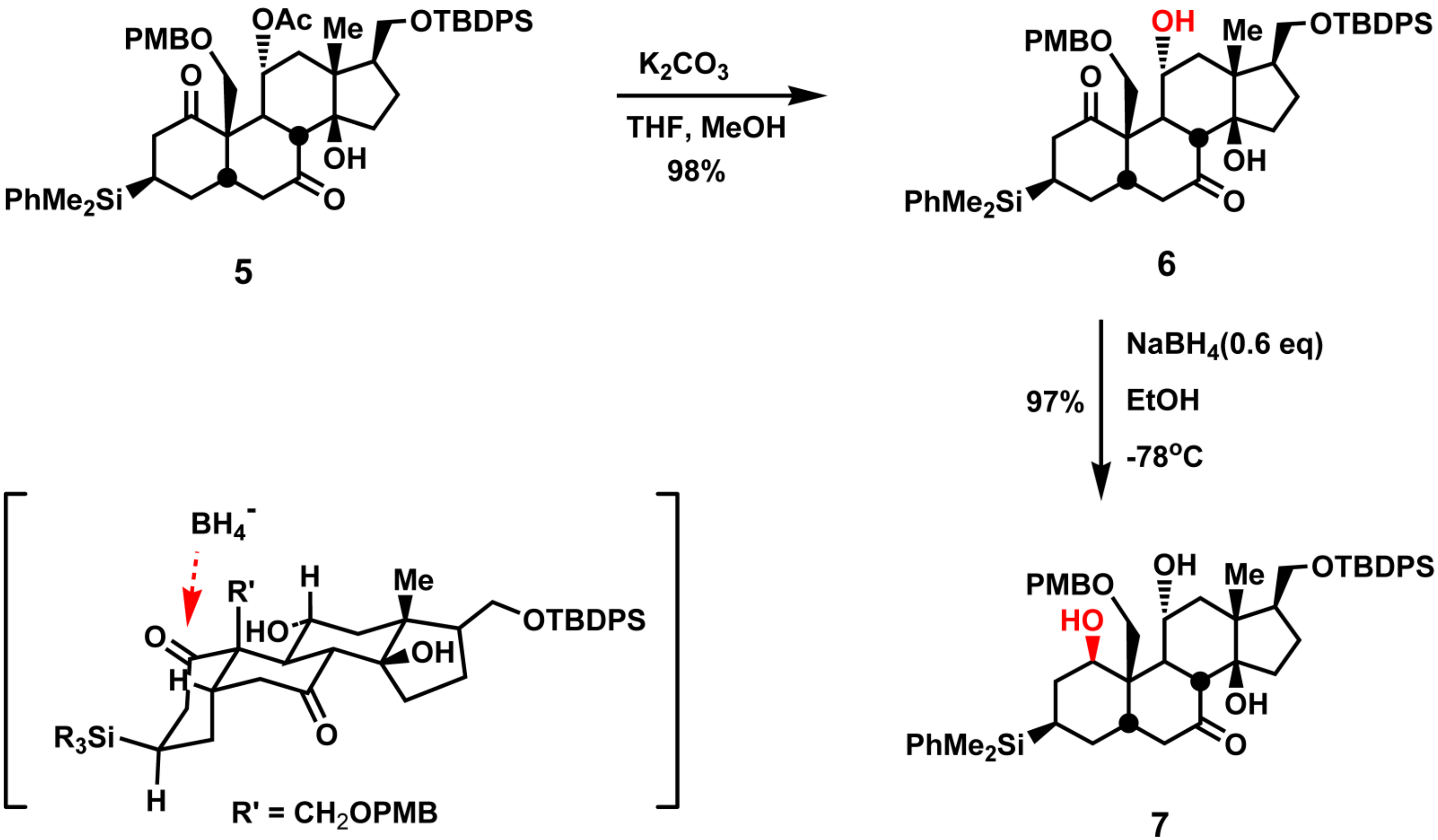
Serge PHOENIX

SELECTIVE REDUCTION AT C1



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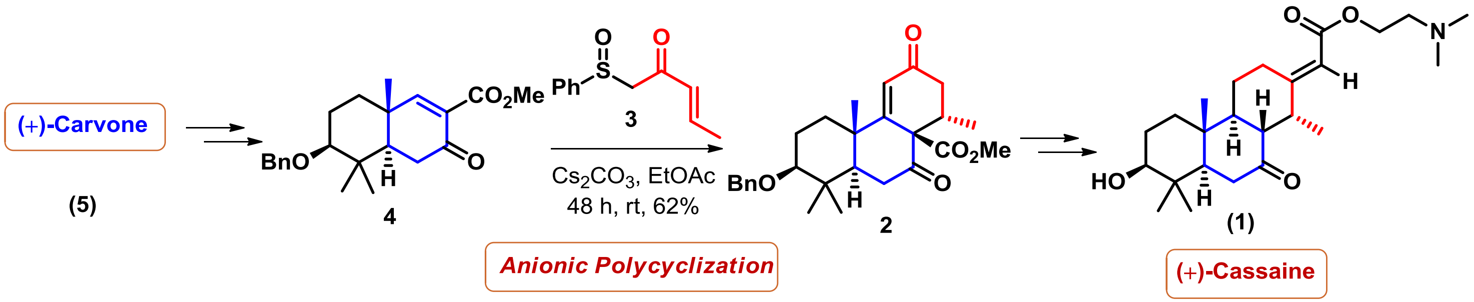
Total Synthesis of (+)-Cassaine Utilizing an Anionic Polycyclization Strategy

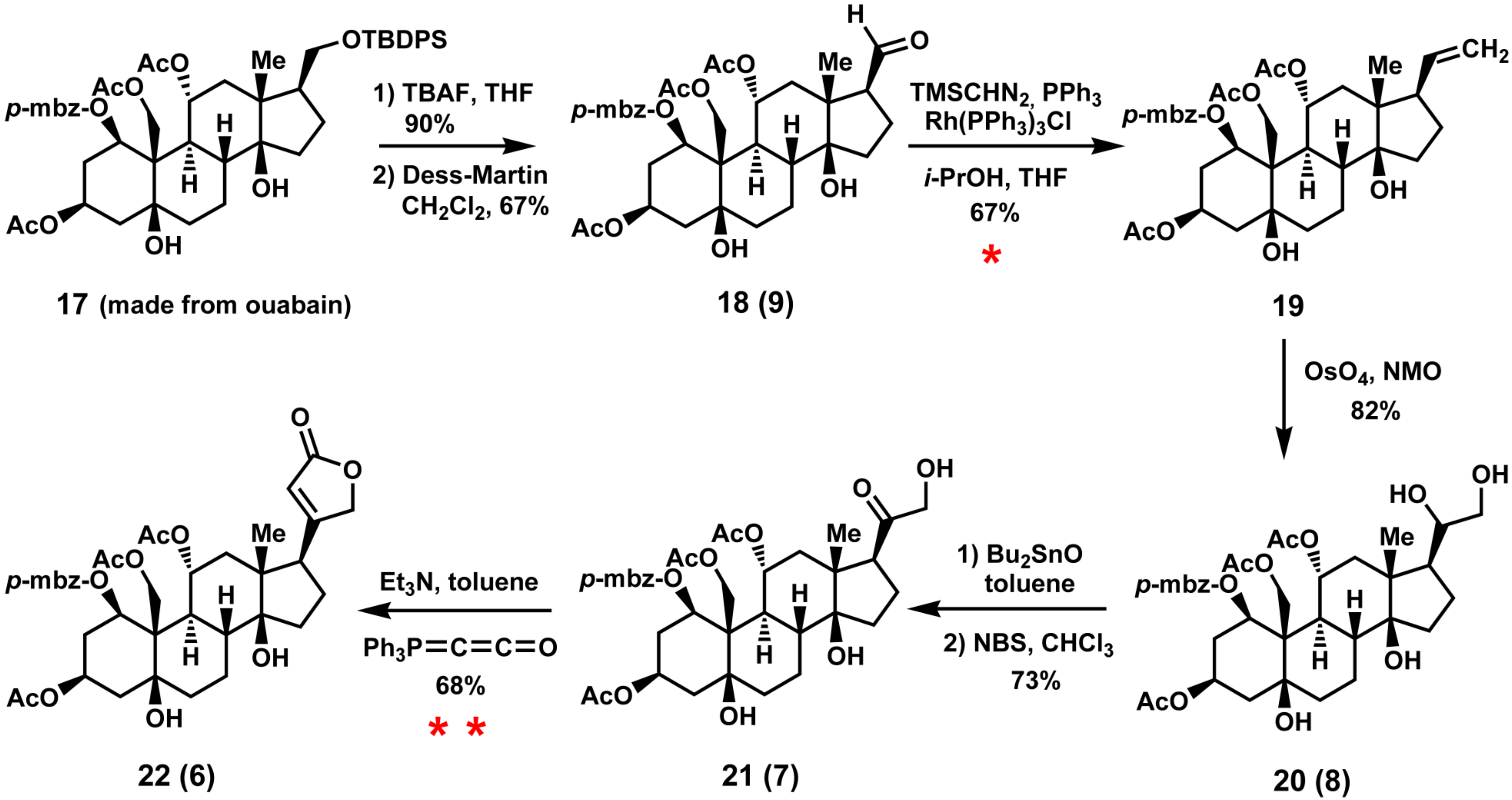
K. Ravindar, P.-Y. Caron, P. Deslongchamps

Org. Lett. **2013**, *15*, 6270-6273.
J. Org. Chem. **2014**. In Press.



FIN

SYNTHESIS OF OUABAGENIN TETRAESTER



* H. Lebel and V. Paquet. JACS (2004), *126,* 320

* * H.J. Bestman and D. Sandmeier. Chem. Ber. (1980), *113,* 2038

G. Stork *et al.* JACS (1996), *118,* 10660

SRIDHAR R. MADDI
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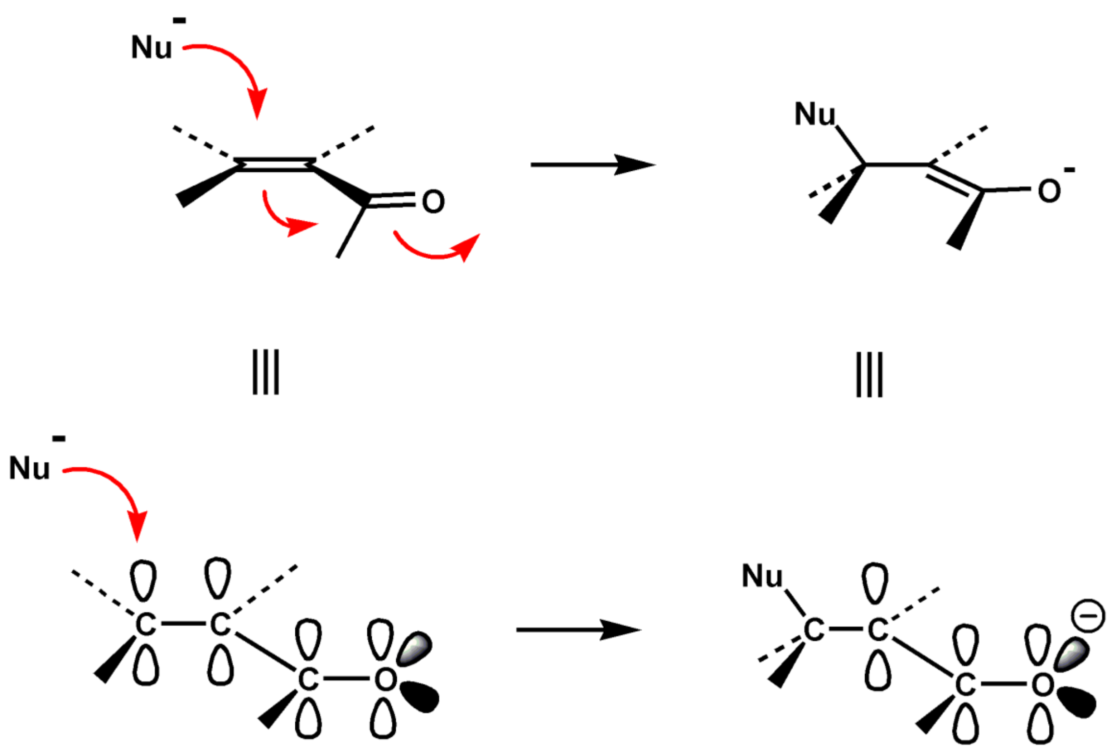
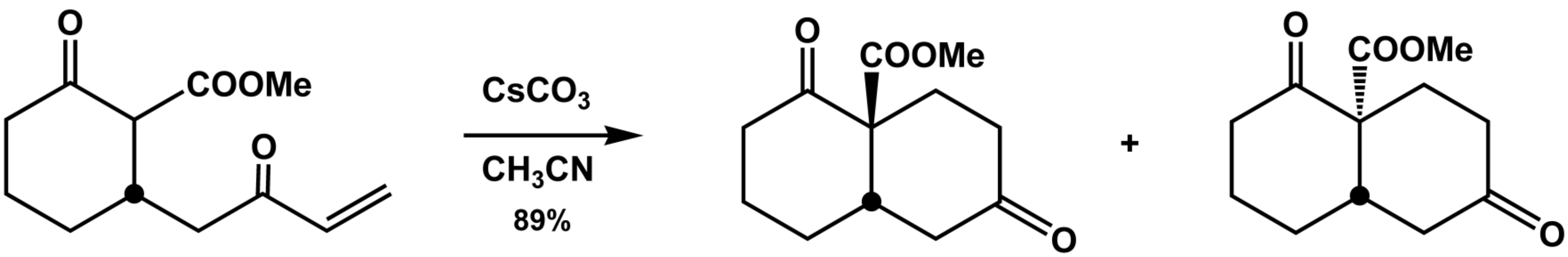
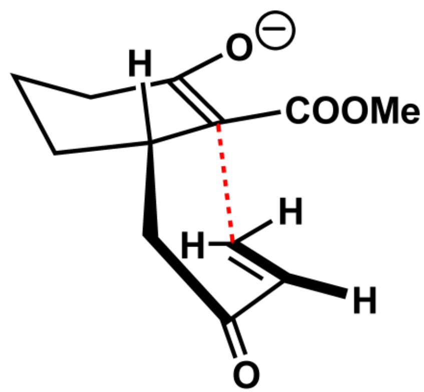
Michael addition on enone (Stereoelectronic parameter)



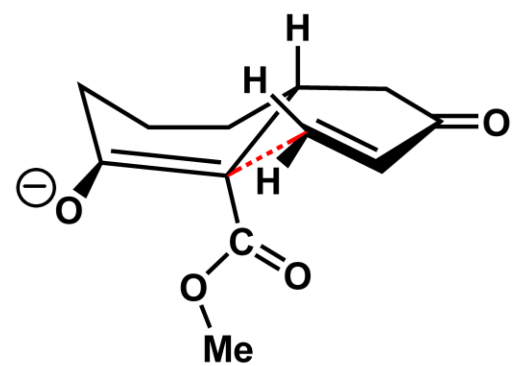
INTRAMOLECULAR MICHAEL ADDITION OF A CYCLIC β-KETOESTER



cis (100%) *trans* (0%)



cis TS

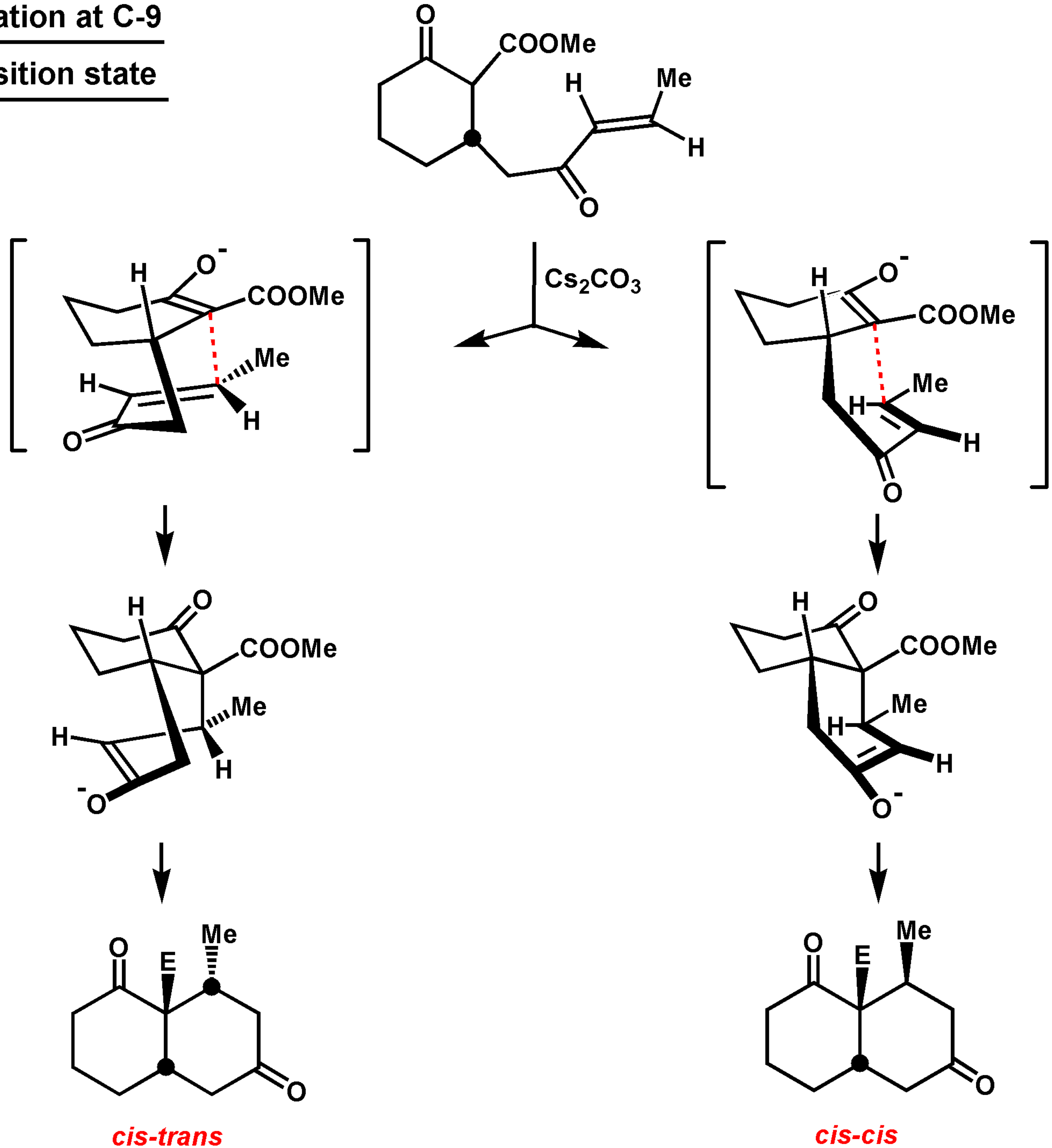


trans TS

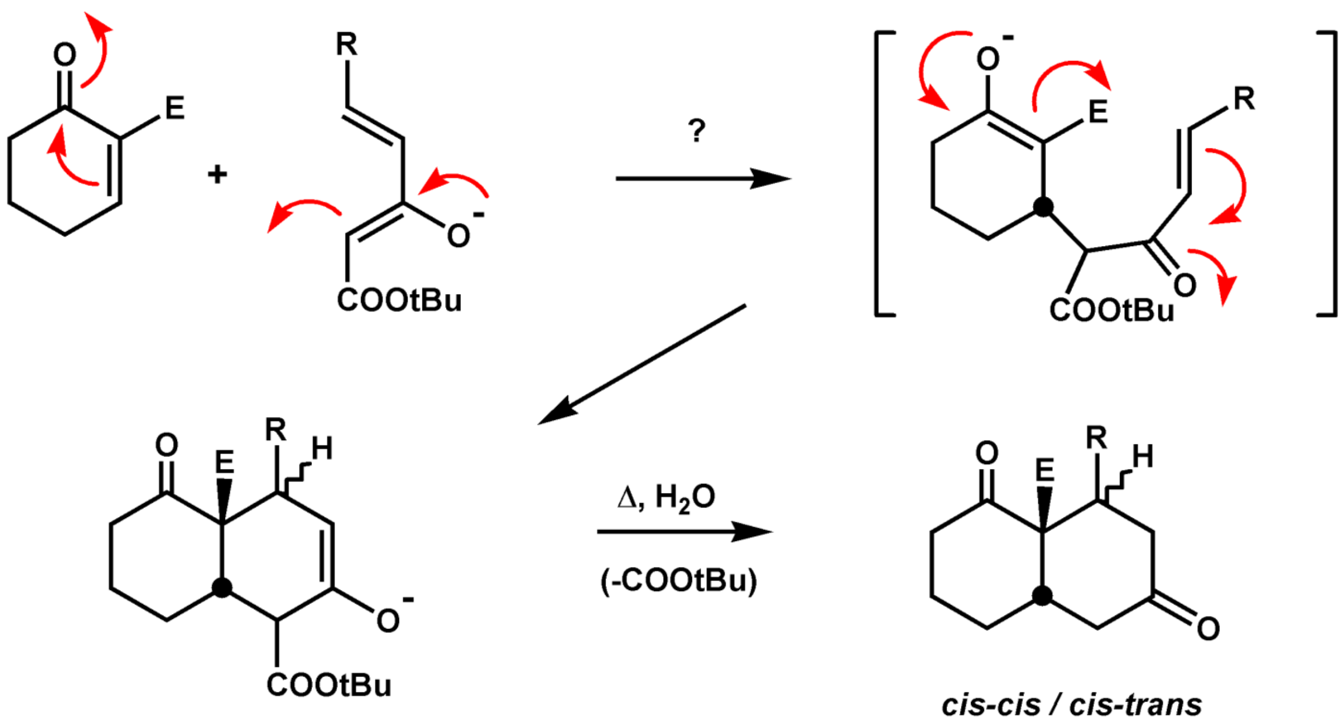
poor orbital alignment

G. Berthiaume, J.-F. Lavallée, P. Deslongchamps.
Tetrahedron Lett. (1986), *27,* 5451.

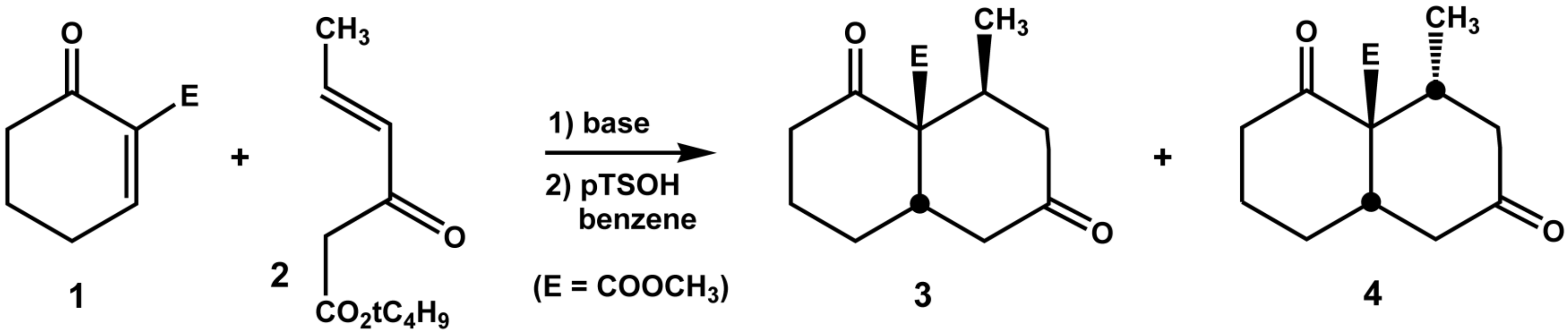
Configuration at C-9 and transition state



How about an intermolecular situation?



STEREOSELECTIVE INTERMOLECULAR ANIONIC CYCLIZATION

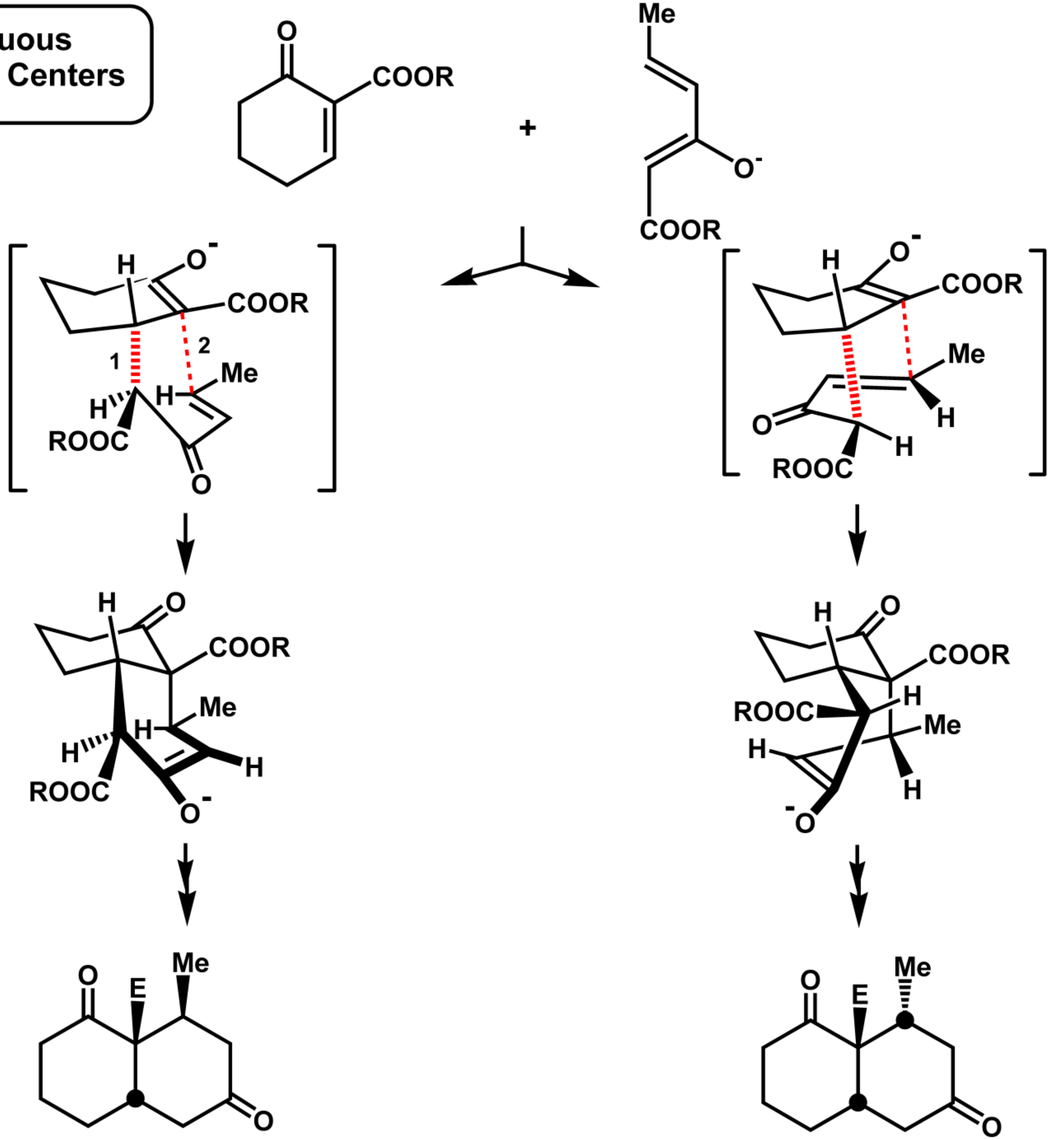


Entry	Base/Solvent	Ratio
		3 : 4
1	Cs_2CO_3 / DMF	54 : 46
2	KH / CH_3CN	50 : 50
3	Cs_2CO_3 / CH_3CN	75 : 25
4	Cs_2CO_3 / C_6H_6	95 : 5
5	Cs_2CO_3 / $CHCl_3$	>99 : 1

J.-F. LAVALLÉE, P. DESLONGCHAMPS.

Tetrahedron Lett. *29*, 5117 (1988).

3 Contiguous Stereogenic Centers

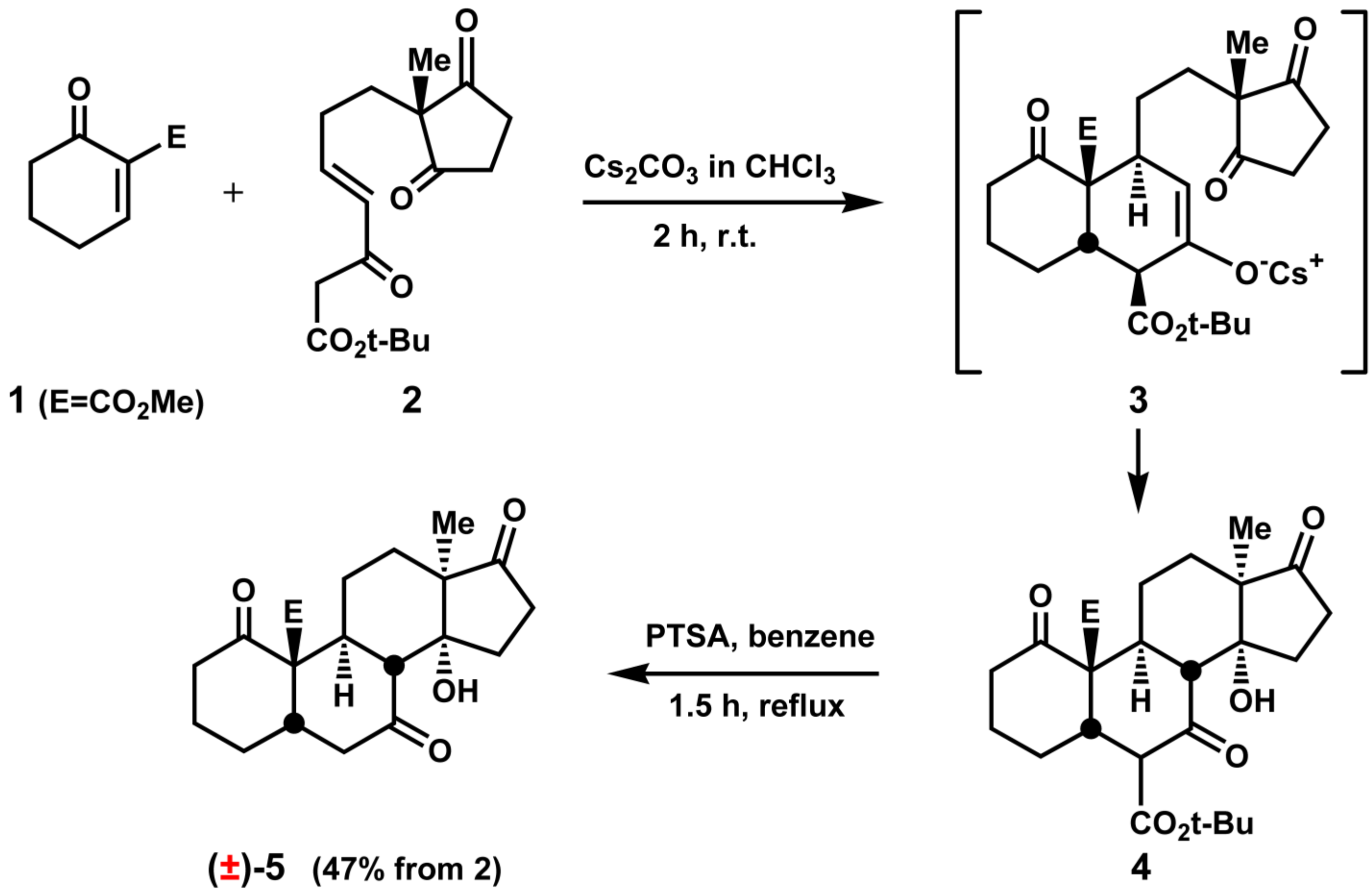


cis-cis (major isomer)

(E = COOMe)

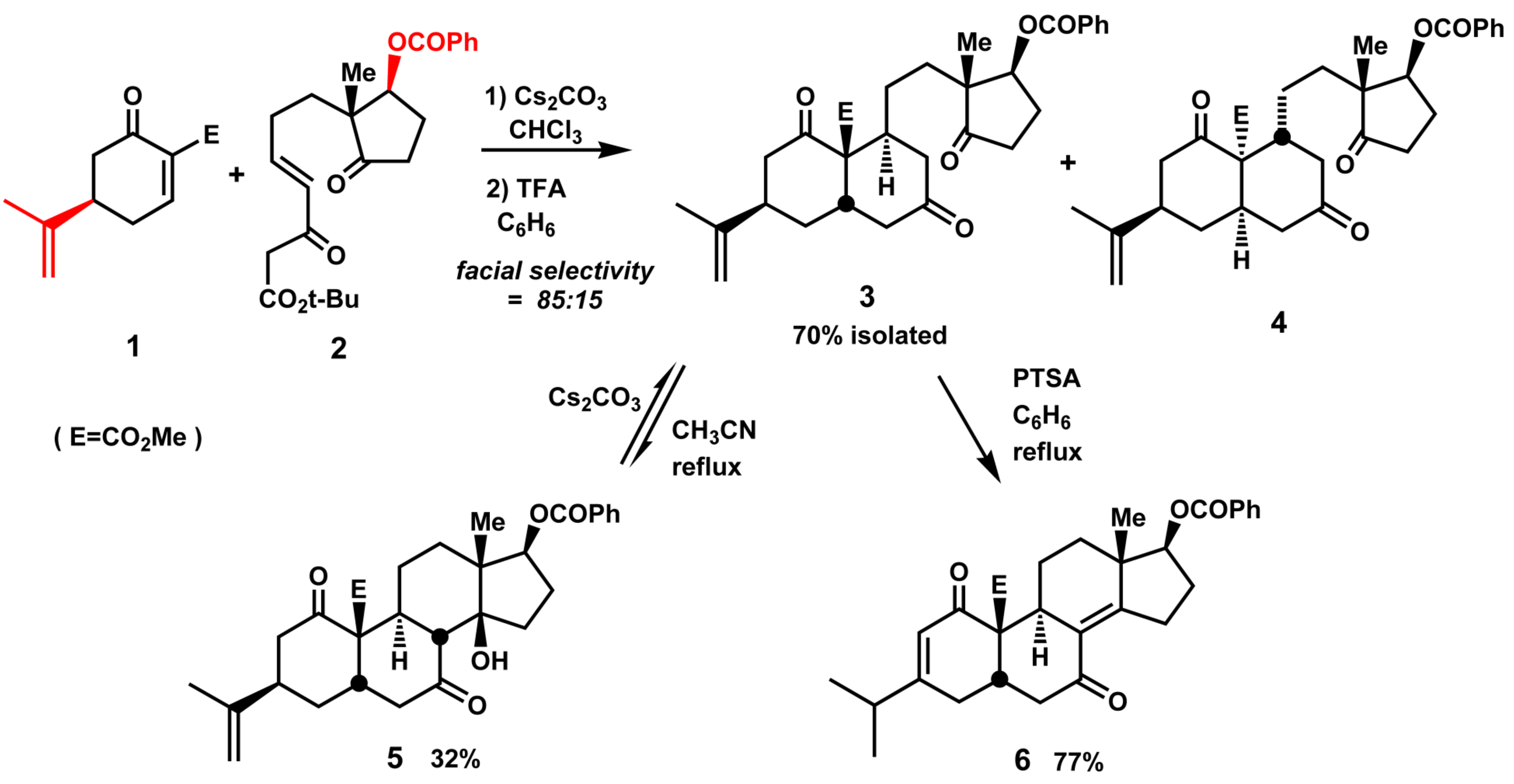
cis-trans

Generation of 6 Contiguous Stereogenic Centers



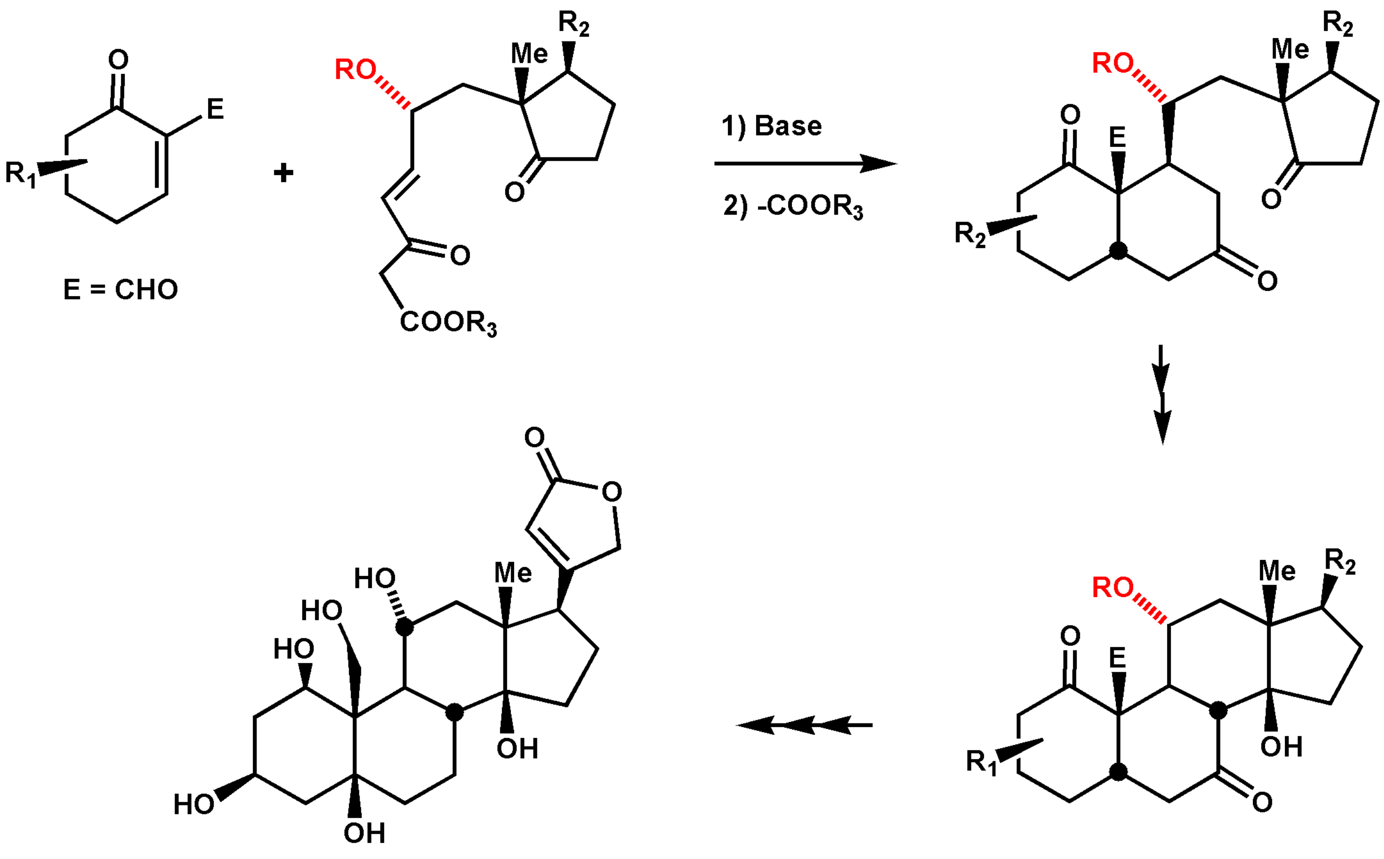
J.-F. LAVALLÉE, P. DESLONGCHAMPS.
Tetrahedron 29, 6033 (1988).

CONTROL OF FACIAL SELECTIVITY AND ALDOL REACTION



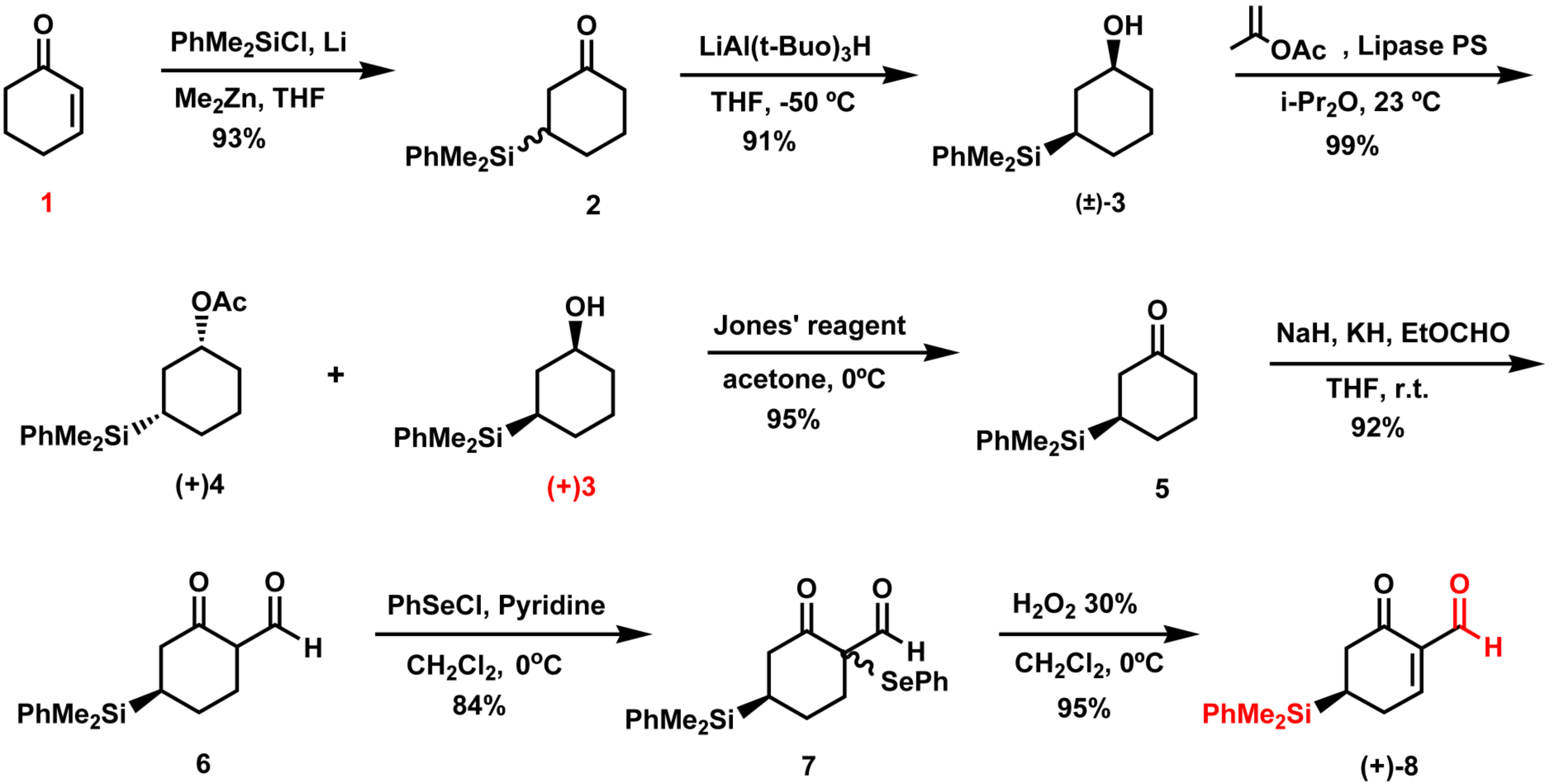
R. RUEL, P. DESLONGCHAMPS.
Tetrahedron 31, 3961 (1990).

Retrosynthetic Analysis (II)



ouabagenin

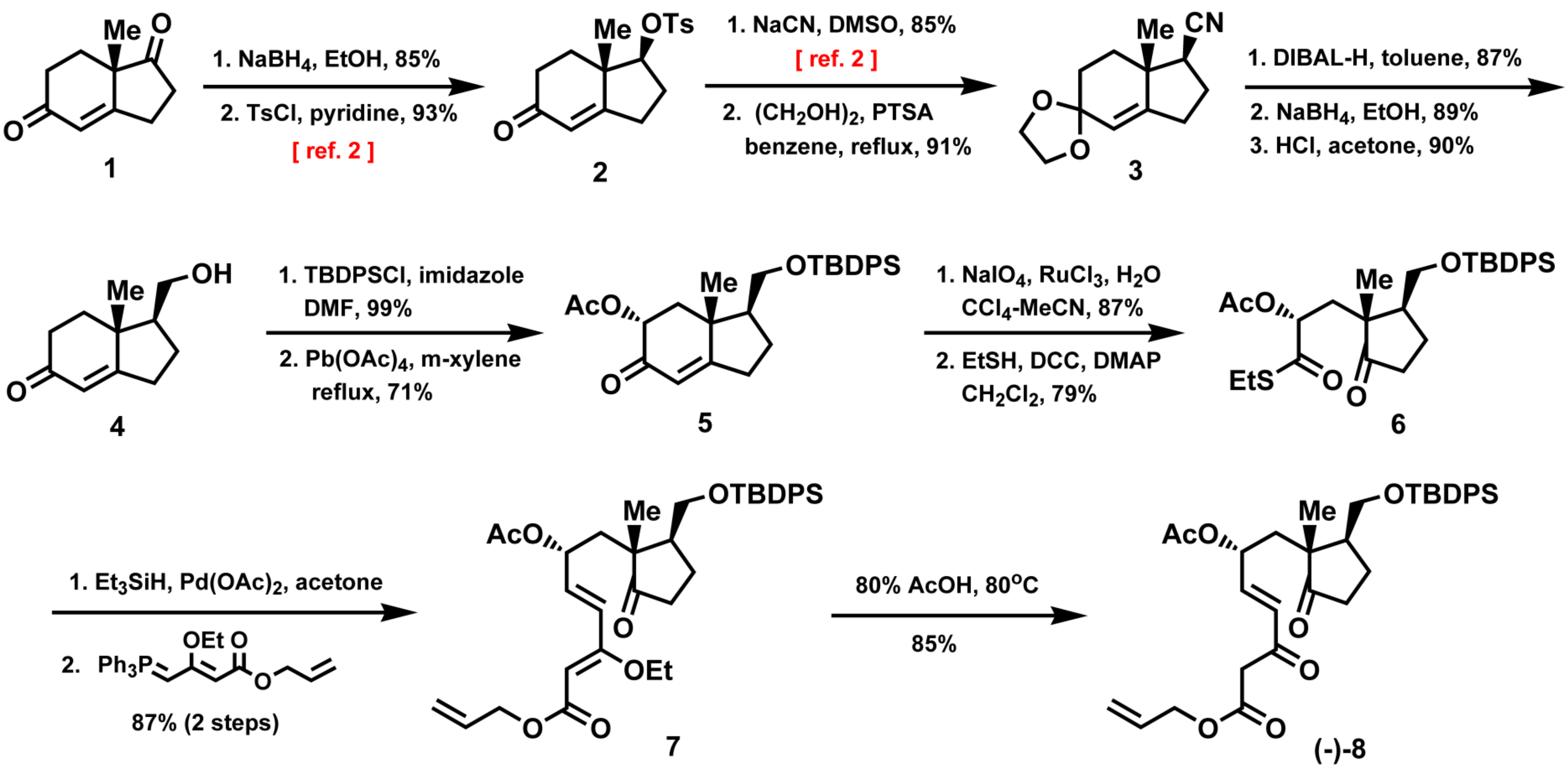
SYNTHESIS OF UNICHIRAL RING A



[1 to (+)3]: Sarakinos, G.; Corey, E.J. *Org. Lett. 1,* 811 (1999).
Trudeau, S.; Deslongchamps, P. *J. Org. Chem. 69,* 832 (2004).

Hongxing ZHANG
Stéphane TRUDEAU

SYNTHESIS OF UNICHIRAL RING D



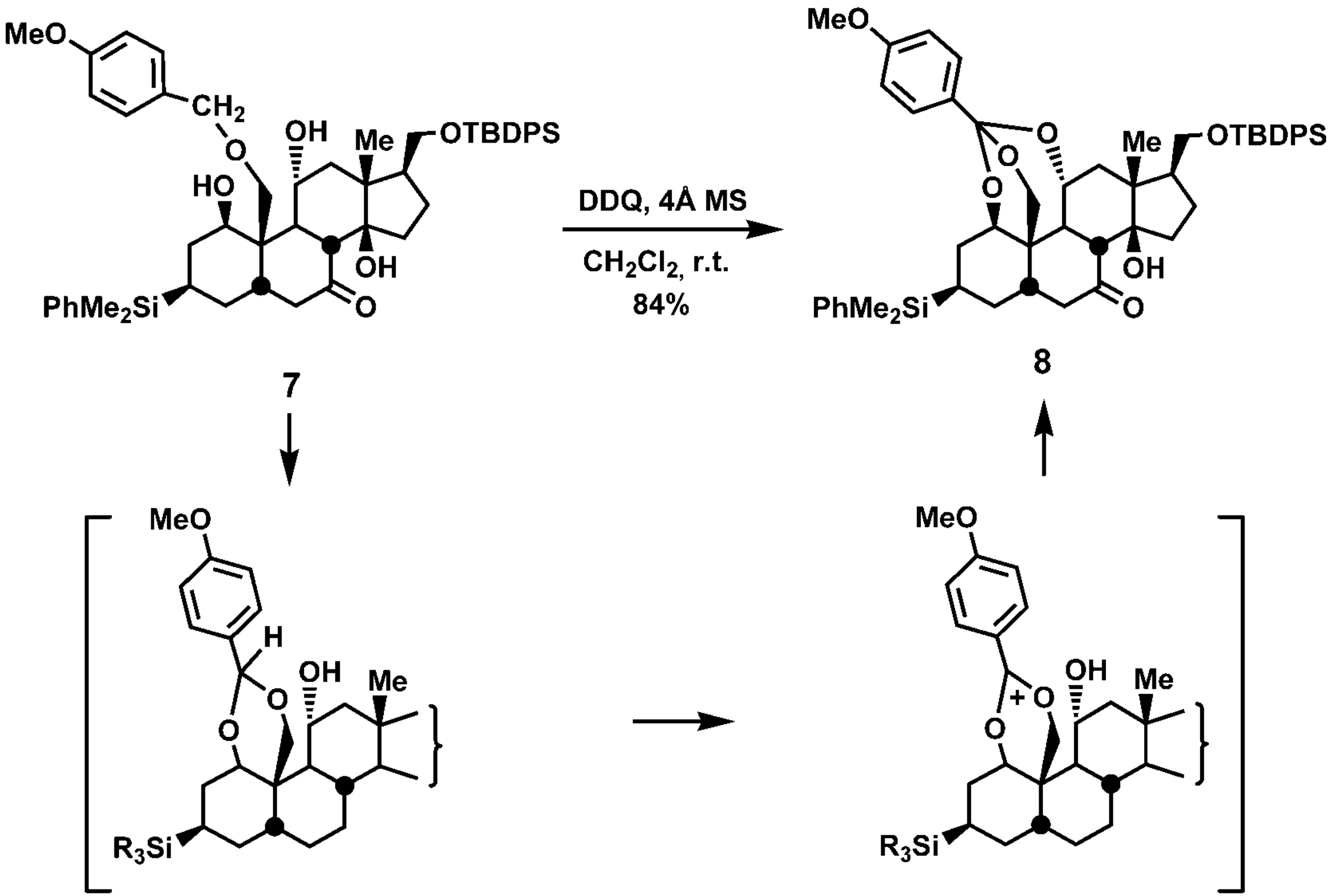
[1] Hajos, Z.G.; Parrish, D.R. Org. Synth. *63,* 26 (1985).

[2] Caine, D.; Kotian, P.L.G. J. Org. Chem. *57,* 6587 (1992);
see also Overman, L.E. *et al.* J. Org. Chem. *61,* 6760 (1996).

[3] Yang, Z.; Shannon, D.; Truong, V.-L.; Deslongchamps, P. Org. Lett. *4,* 4693 (2002).

Vouy-Linh TRUONG
Hongxing ZHANG

ORTHOESTER FORMATION AT C1, C11, AND C19



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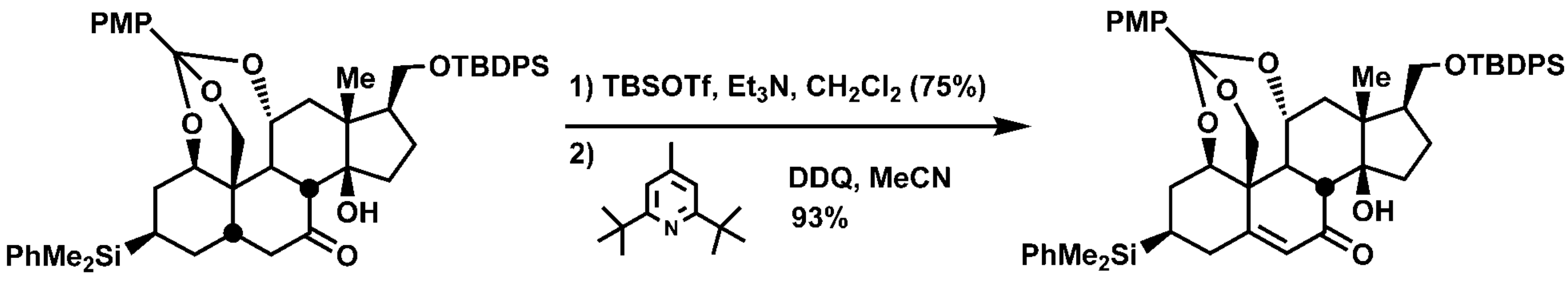
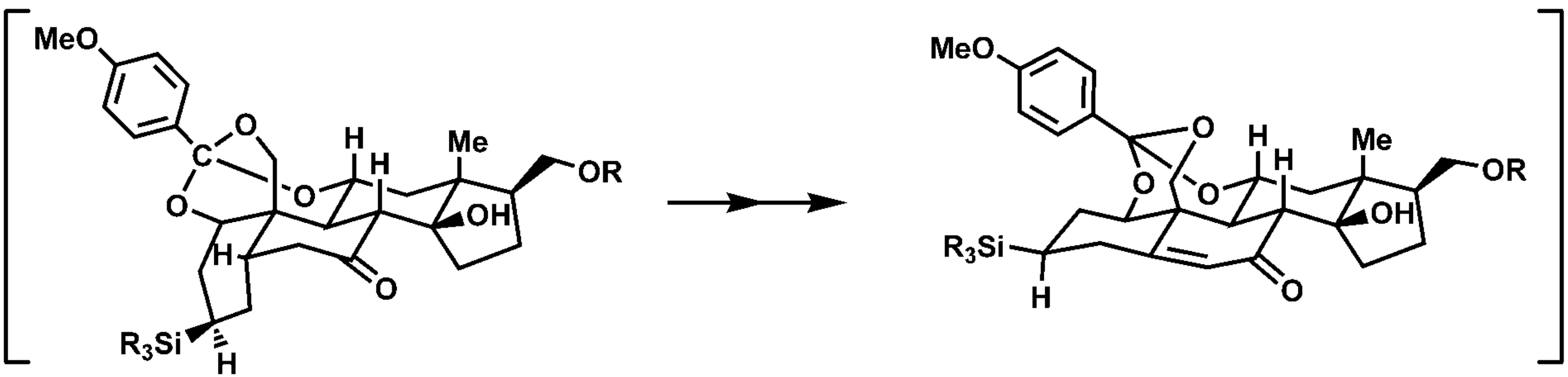
GENERATION OF UNSATURATION AT C5-C6



8 PMP = *p*-methoxyphenyl 10



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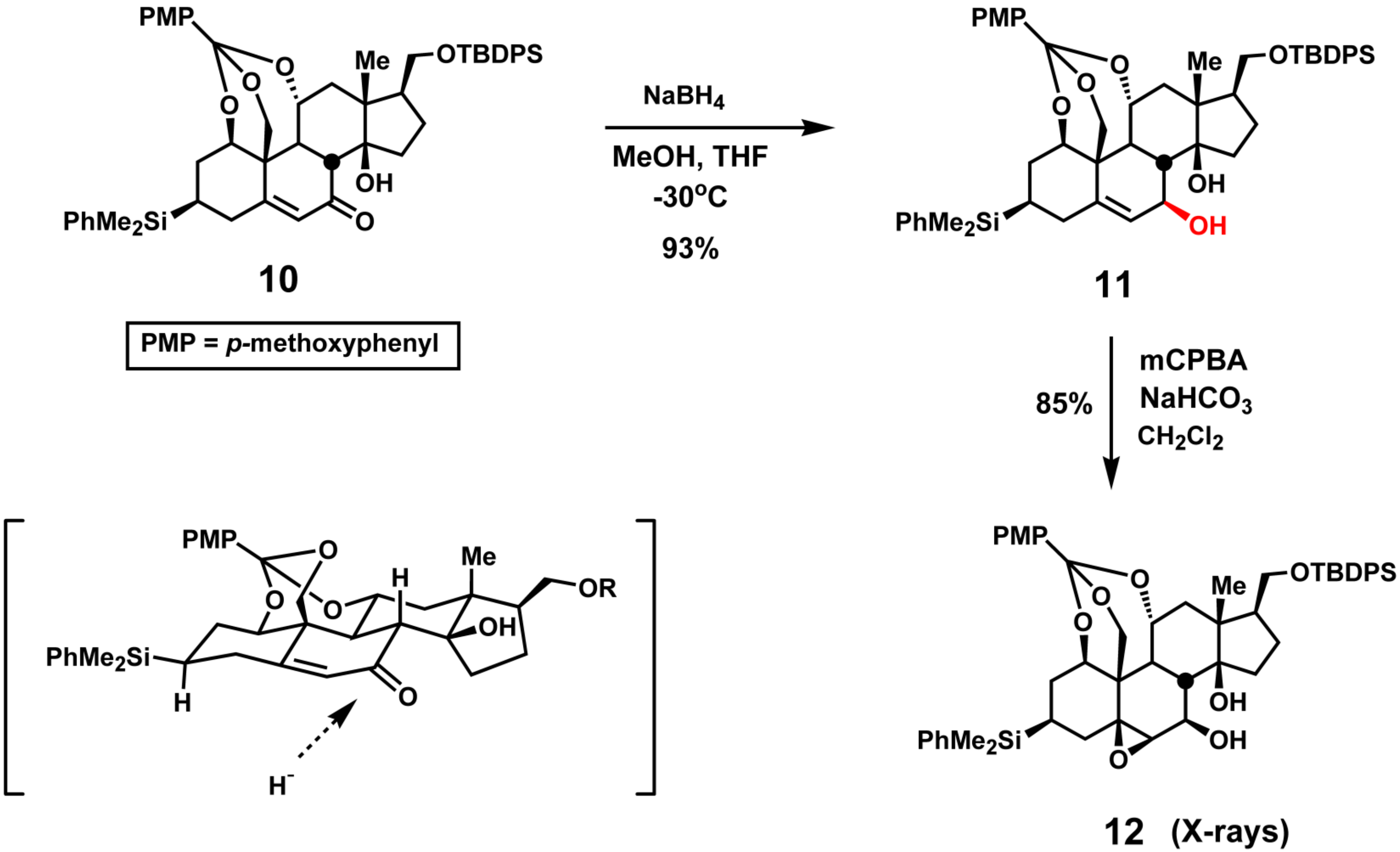
FORMATION OF C5-C6 EPOXIDE AND β-OH AT C7



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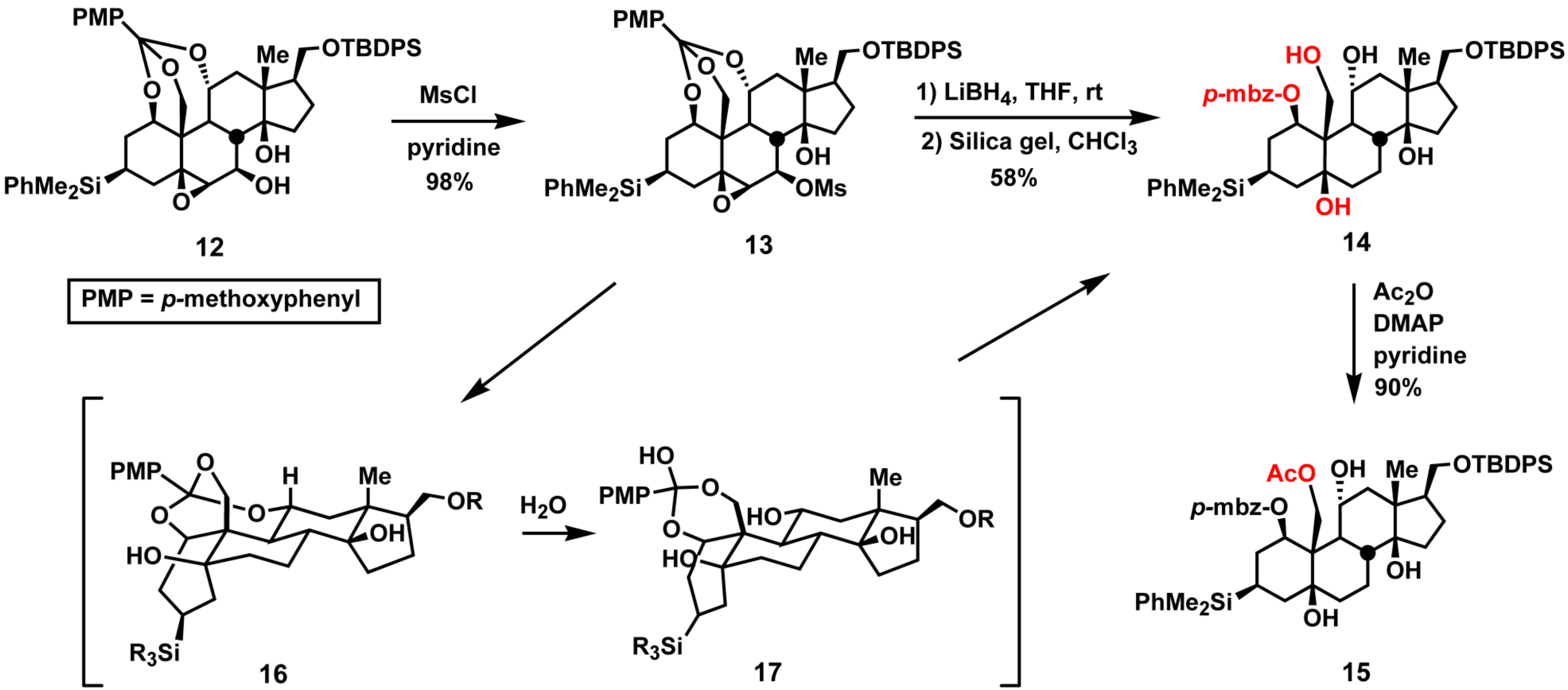
INTRODUCTION OF β-OH GROUP AT C5



PMP = *p*-methoxyphenyl

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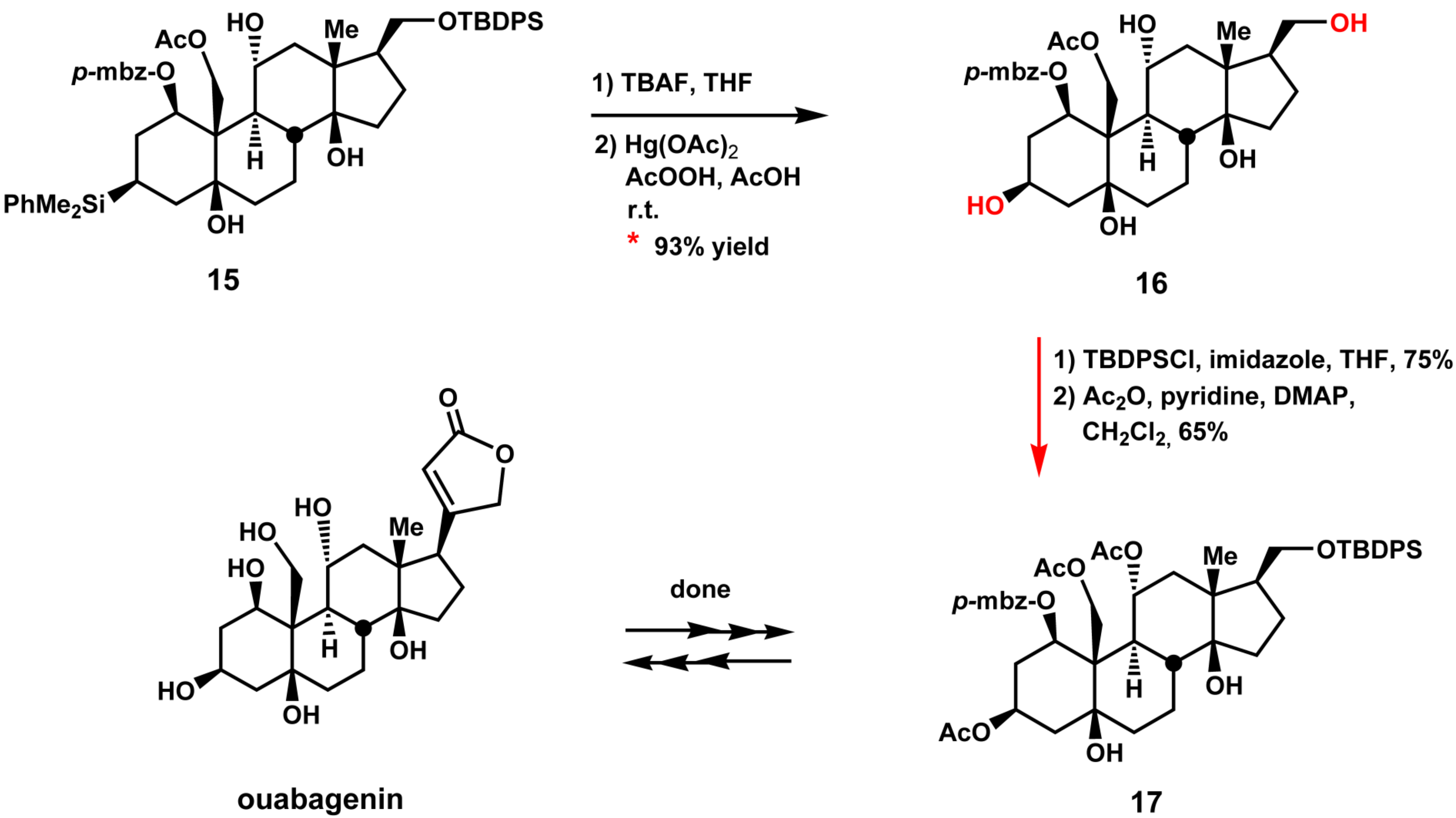
INTRODUCTION OF β-OH AT C3

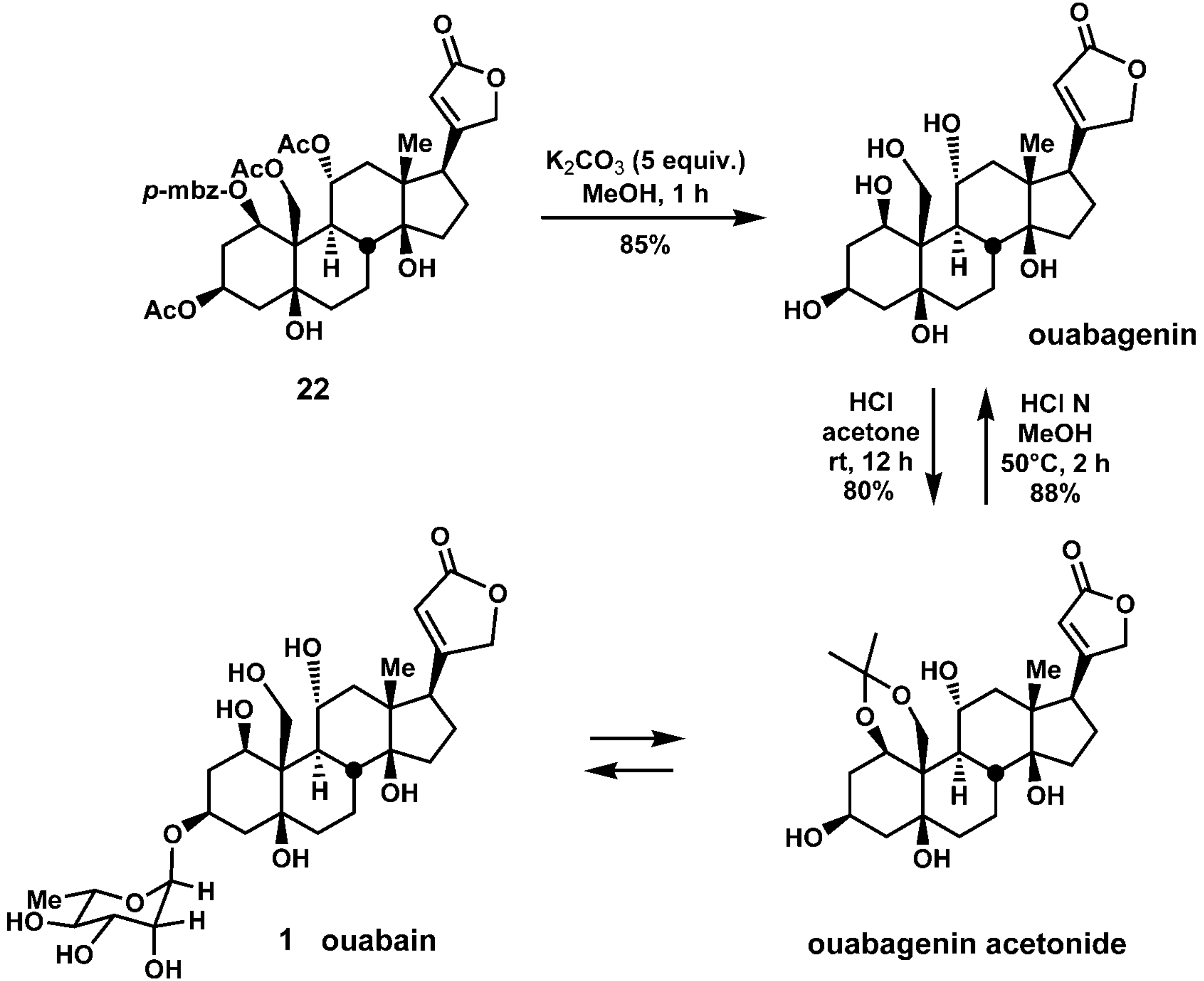


SERGE PHOENIX
SRIDHAR R. MADDI

* K. Tamao *et al.* Organometallics *2,* 1694 (1983)

I. Fleming, P.E.J. Sanderson. Tetrahedron Lett. *28,* 4229-32 (1987)

SYNTHESIS OF OUABAGENIN ACETONIDE



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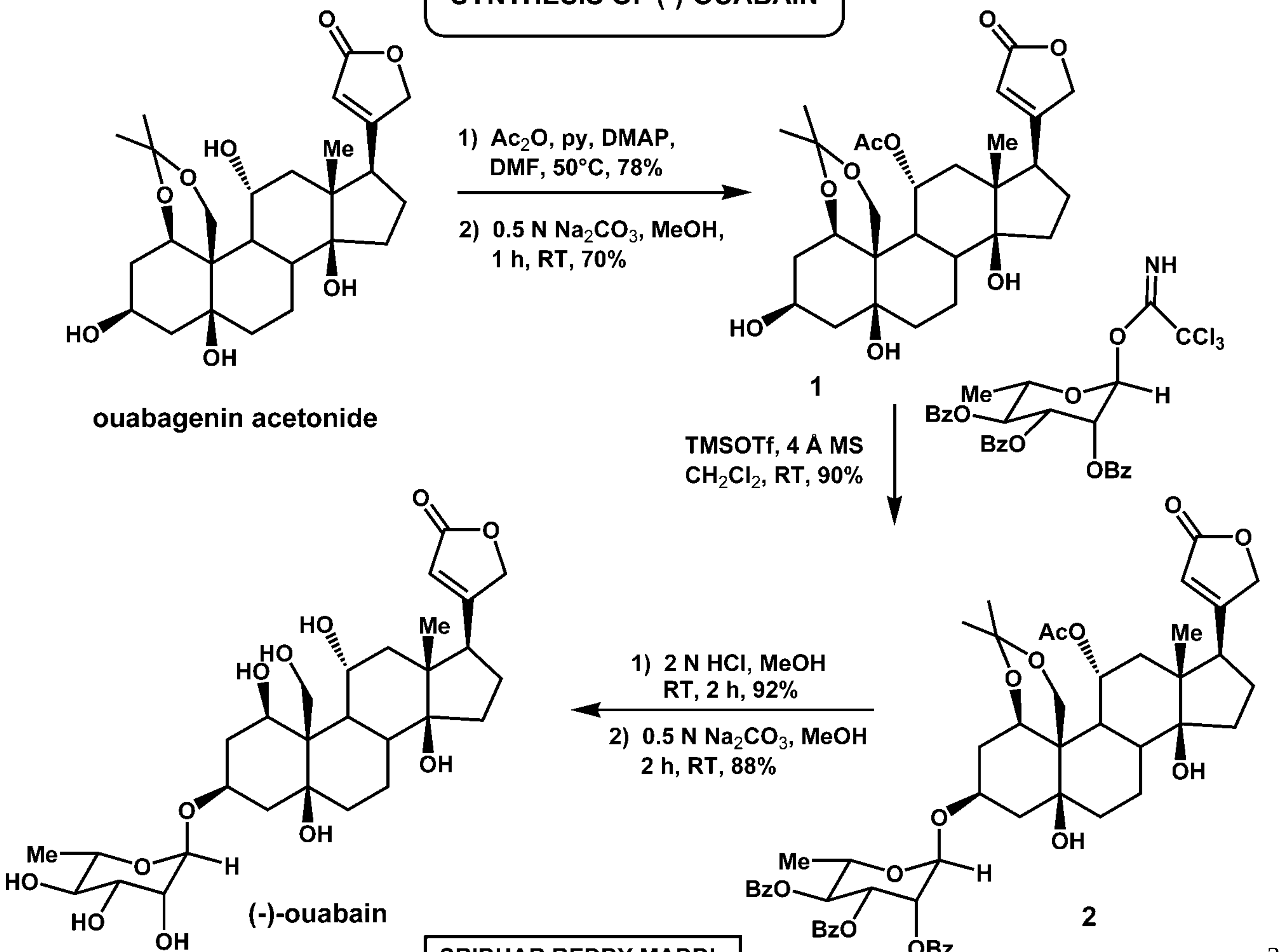
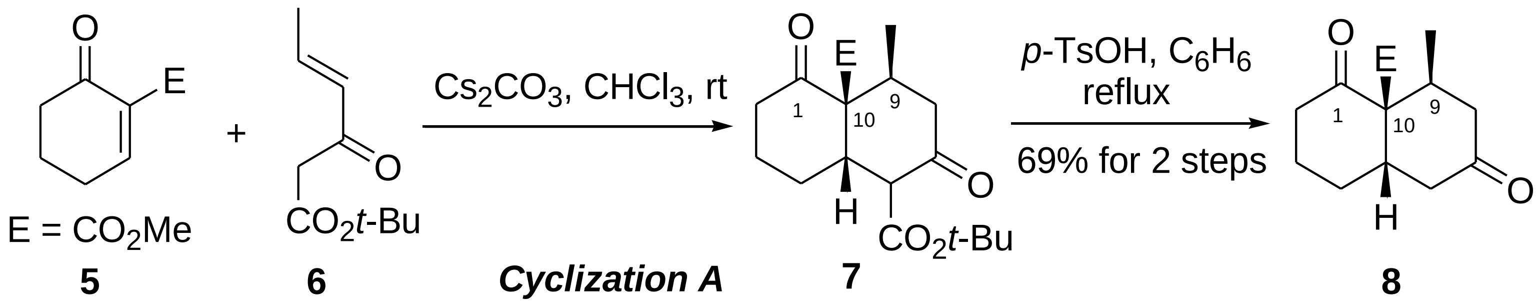
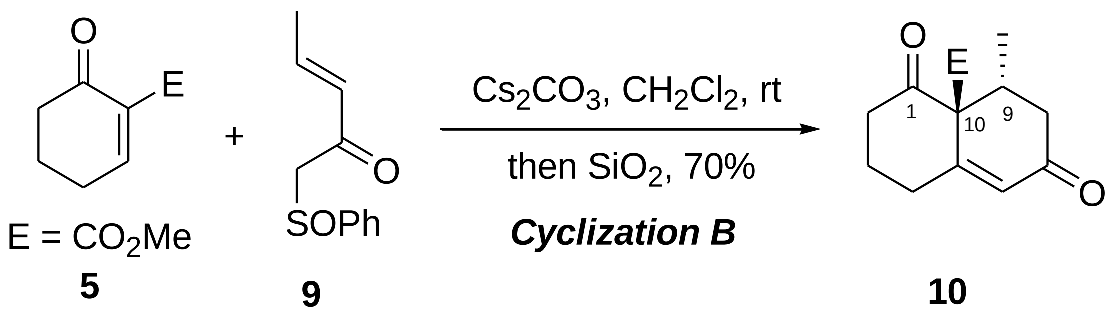
SYNTHESIS OF (-)-OUABAIN



SRIDHAR REDDY MADDI

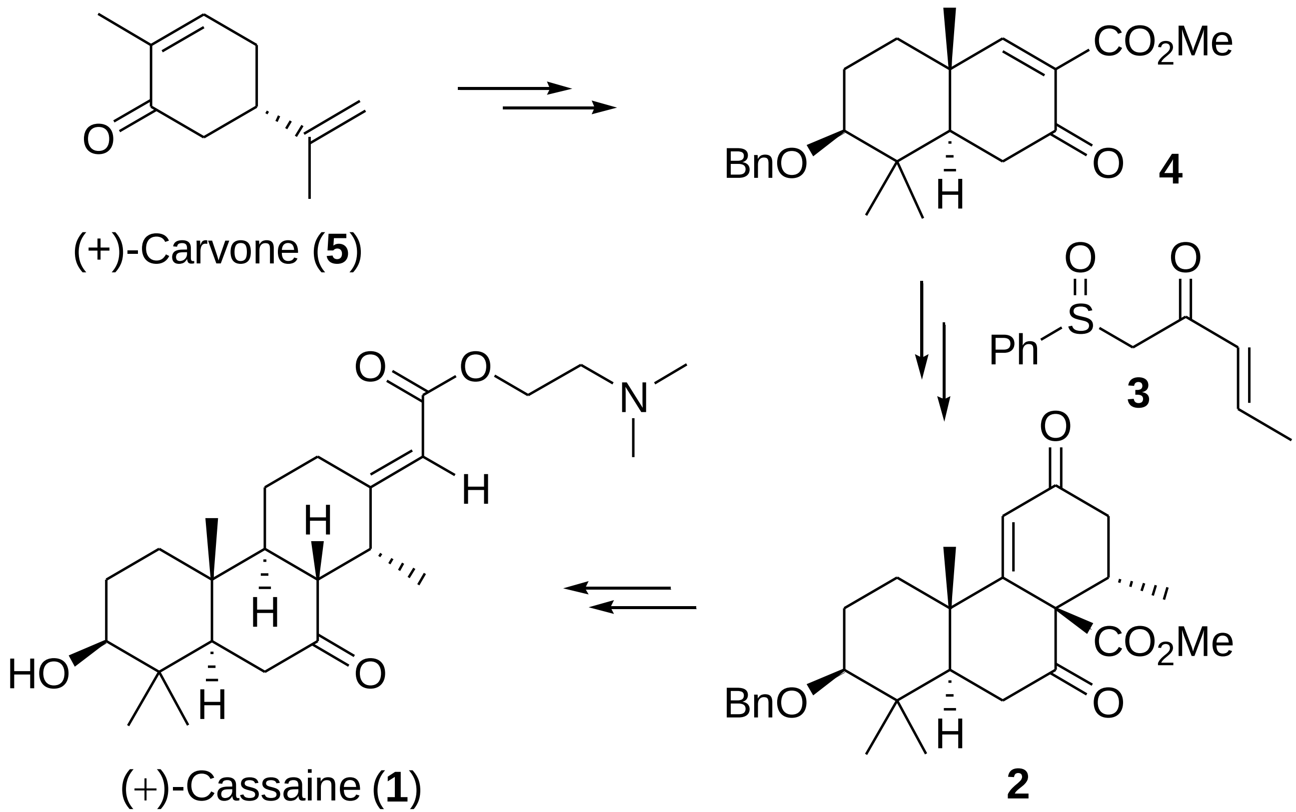
Representative Examples of Anionic Polycyclization



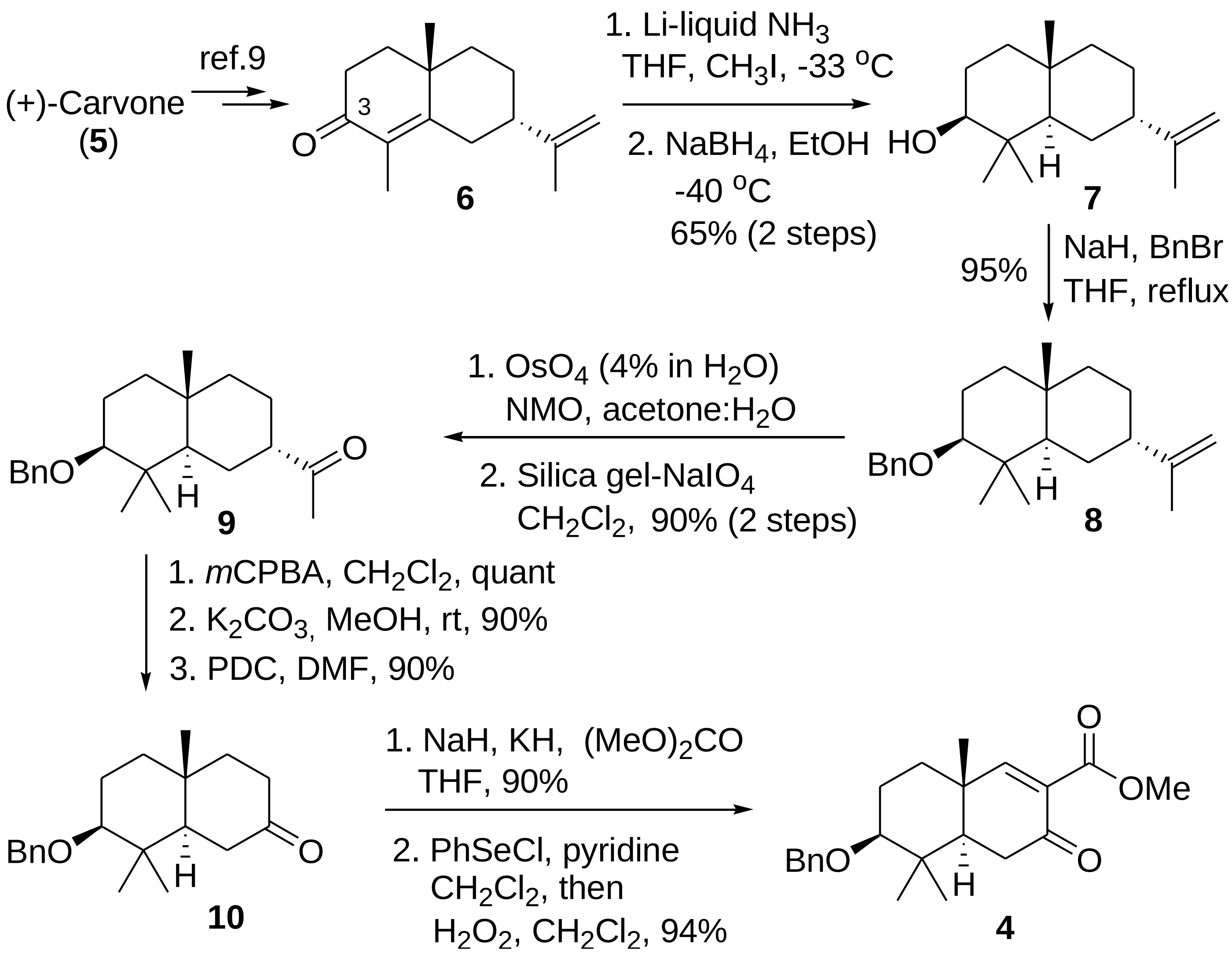


(a) Lavallée, J.-F.; Deslongchamps, P. Tetrahedron Lett. *1988*, *29*, 6033.
(b) Spino, C.; Deslongchamps, P. Tetrahedron Lett. **1990**, *31*, 3969.

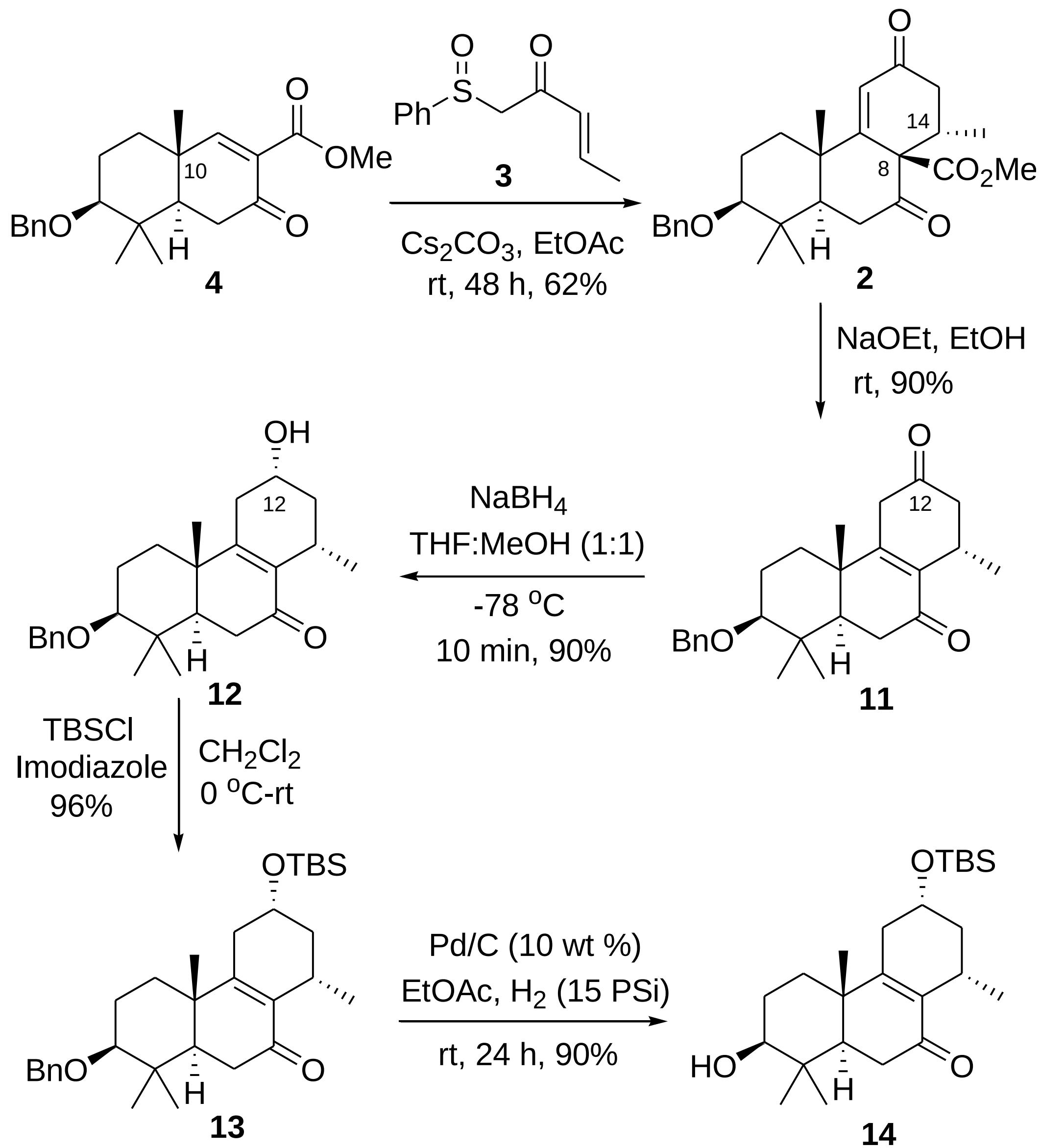
Synthetic Analysis of (+)-Cassaine (1)



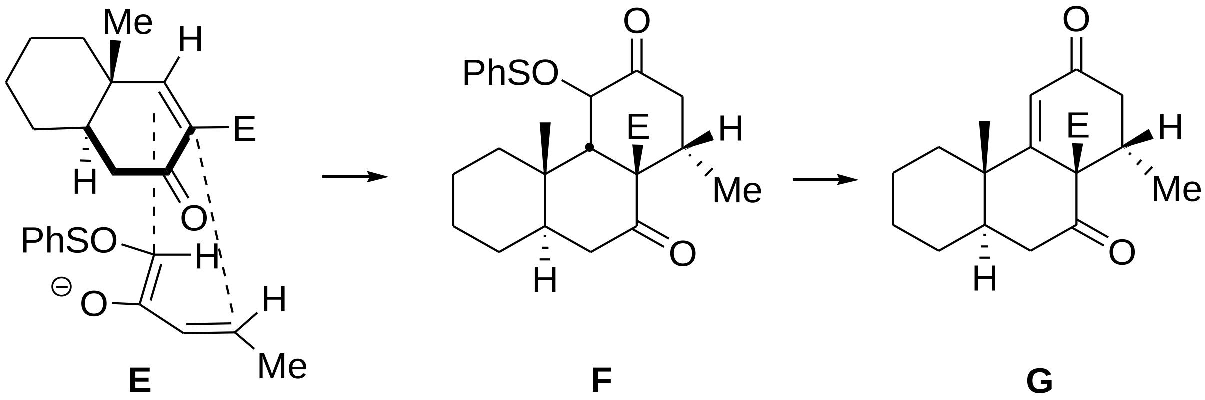
Synthesis of β-Keto Ester 4

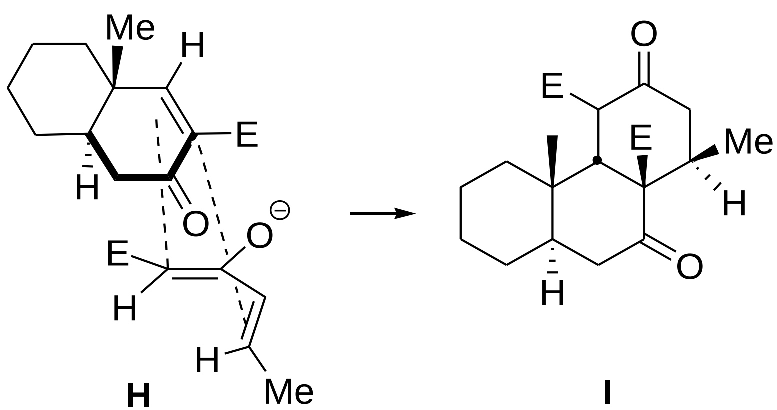


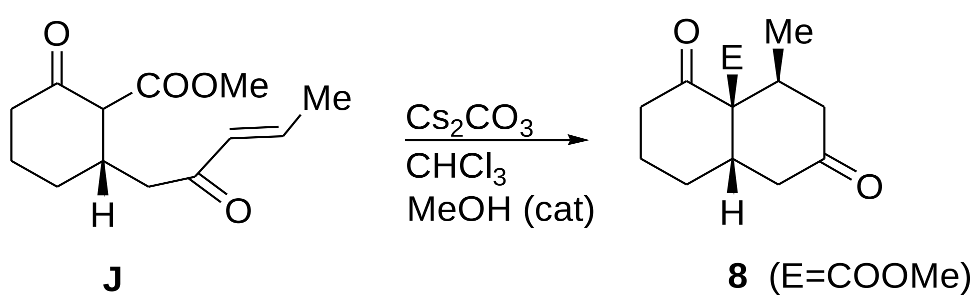
Synthesis of Tricycle 14



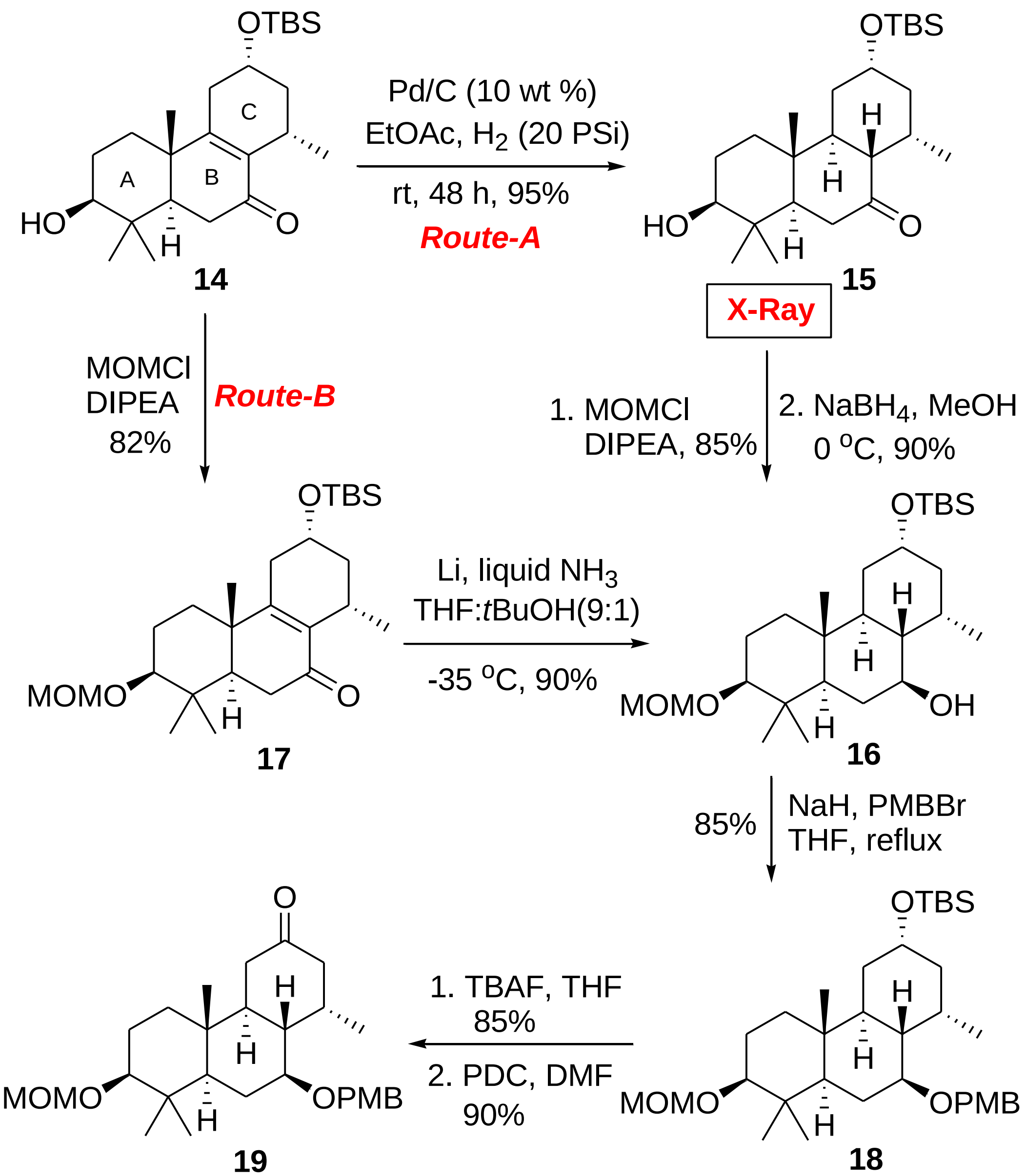
Plausible Mechanism for the Synthesis of *cis-cis* decalin Systems



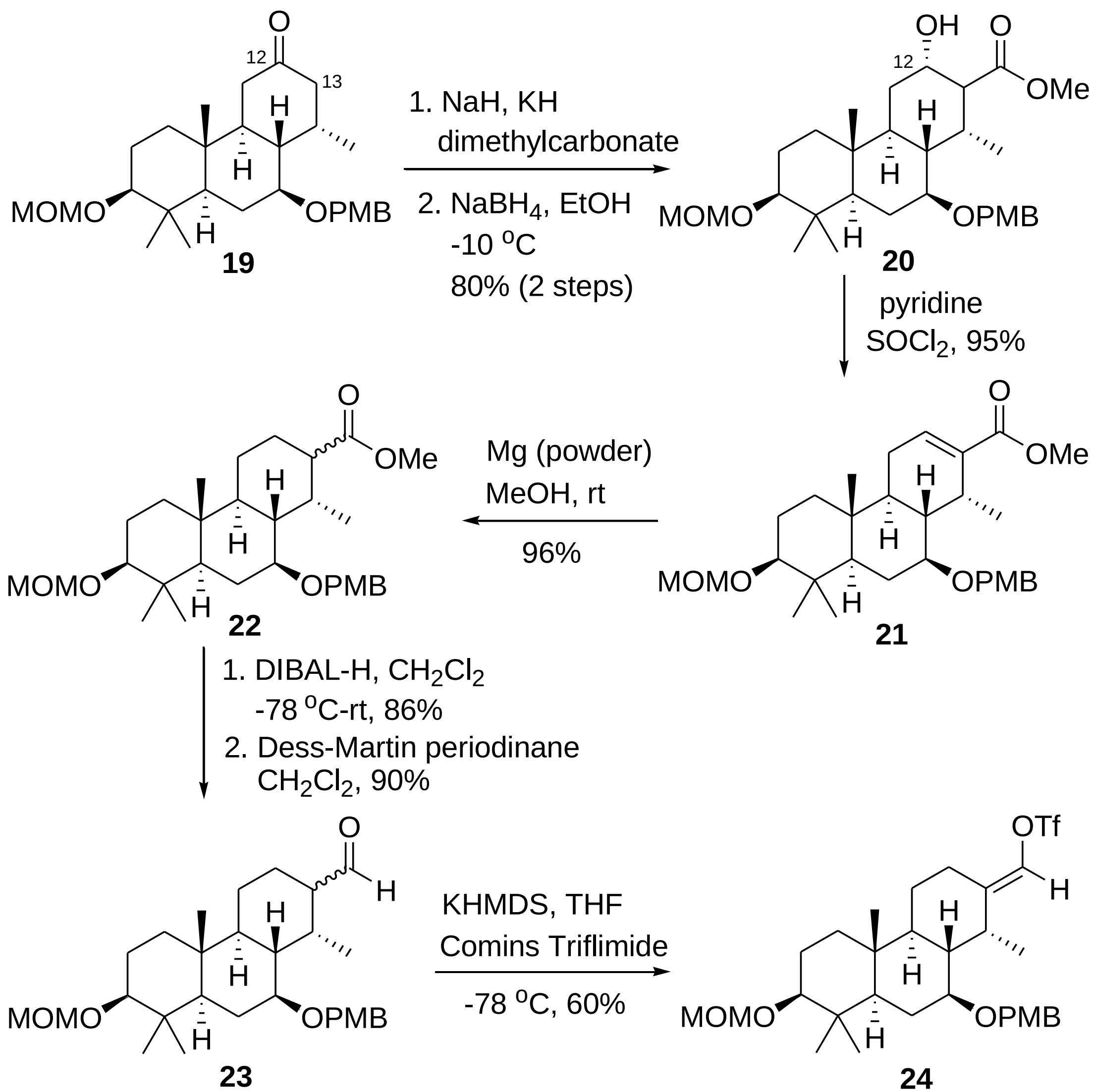




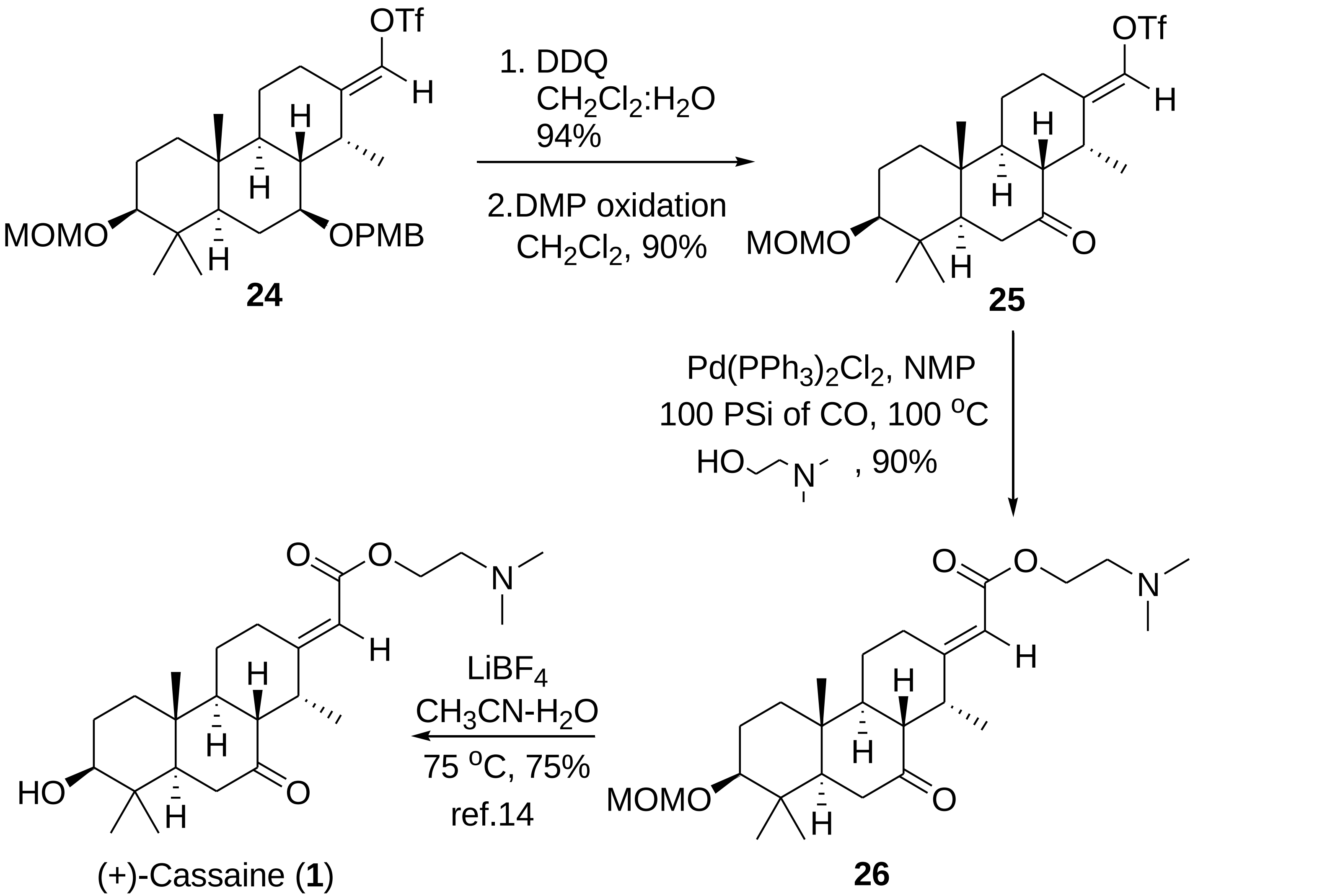
Synthesis of Ketone Intermediate 19



Synthesis of Vinyl Triflate 24



Synthesis of (+)-Cassaine (1)



STRATEGY IS A PLAN

usually starts with small molecules containing minimum functional groups and stereochemistry

A GOOD PLAN:

- **MAXIMUM bond formation within a chemical step**
- **MINIMUM functional group**
  - **transformation**
  - **activation *(in situ)***
  - **protection**
  - **deprotection**

A GOOD YIELD:

- **high chemo-, regio-, and stereoselectivity**

OTHER ELEMENTS:

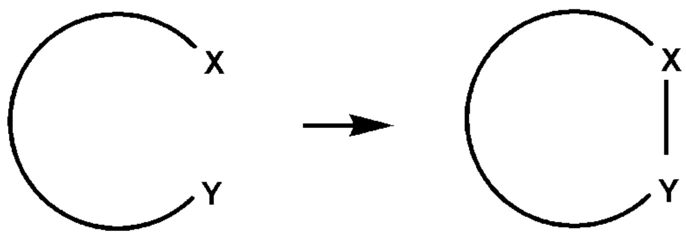
1) **convergence**
2) **chronology of appearance of desired functional groups**

CHEMISTS HAVE THREE DIFFERENT TACTICS TO RESTRICT THE APPROACH OF A REAGENT TOWARD A SUBSTRATE

1. intermolecular process (highly disymmetrical)

X + Y ⟶ X—Y

2. intramolecular process



3. transannular process