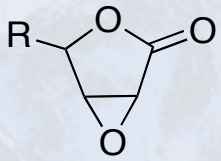
Topic Review:

The Chemistry of Robert K. Boeckman, Jr.

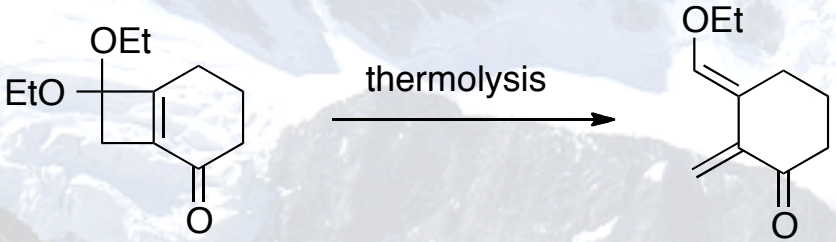
Topic Review
Berne, 18.07.2013

Index

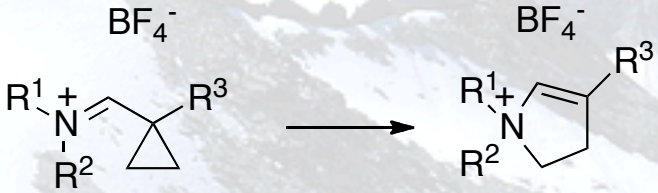
- Introduction – About Robert K. Boeckman, Jr.
- General Method to α,β-epoxy-γ-butyrolactones:



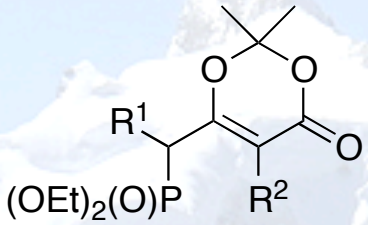
- Diels-Alder cycloaddition of Juglone derivatives: thermolysis of cyclobutanes to dienes



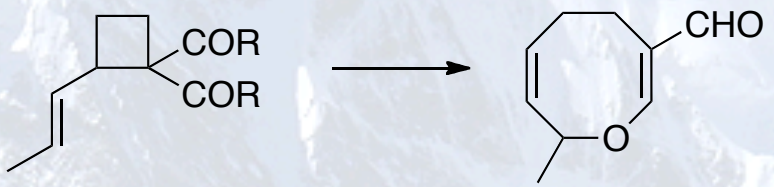
- Cyclopropyl iminium ion rearrangement:

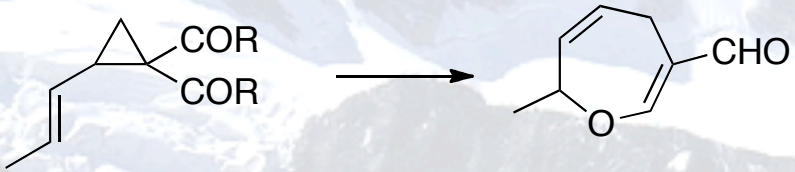


- thermally labile highly substituted dioxinone phosphonates:

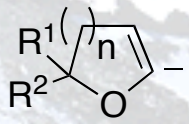


- retro-Claisen Rearrangement: method to 7- or 8-membered ring ethers:



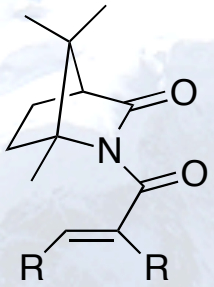


- cyclic vinyl ether carbanions:

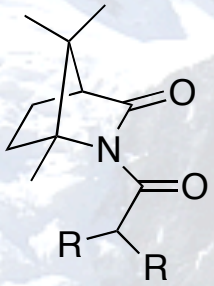


n = 1 or 2

- camphor-derived lacatams
  - chiral auxiliary in Diels-Alder cycloadditions:



  - chiral auxiliary in aldol reactions:



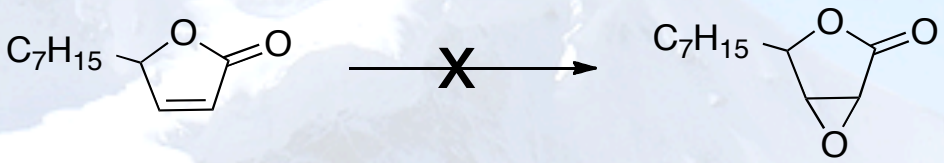
- Other Syntheses

About Robert K. Boeckman, Jr.:

- B.S., Carnegie Institute of Technology – 1966
- Ph.D., Brandeis University – 1970 (Prof. James B. Hendrickson)
- Post Doctoral Appointments 1970-1972 - NIH Fellowship, Columbia University
- Professor at University of Rochester
- Since 2003 Chair of Chemistry at University of Rochester
- Associated Editor for the Journal of Organic Synthesis

http://www.chem.rochester.edu/faculty/faculty.php?name=boeckman

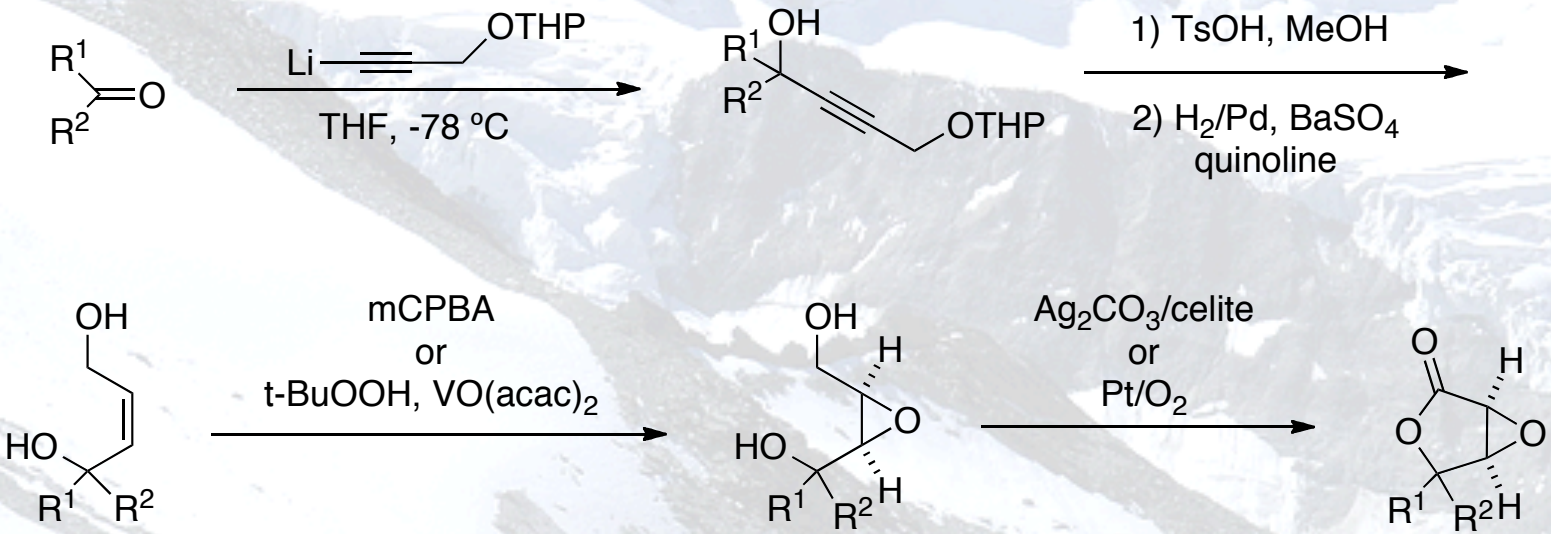
General Method to α,β-epoxy-γ-butyrolactones



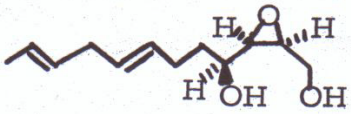
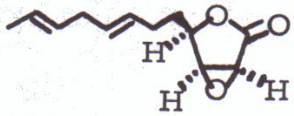
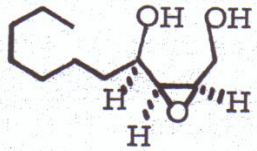
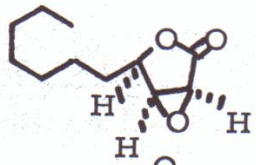
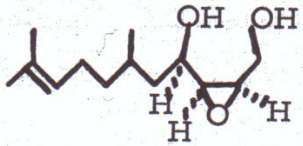
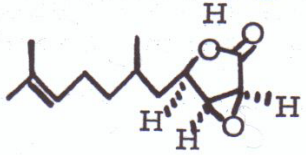
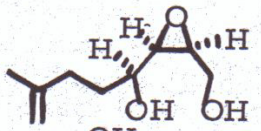
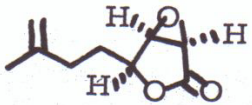
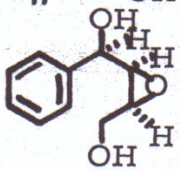
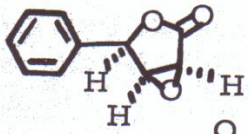
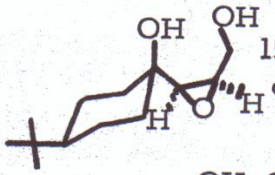
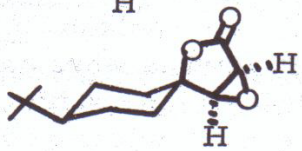
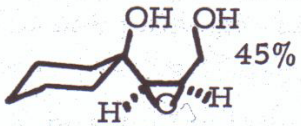
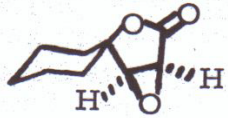
Problem:

Lactones are inert to all common peracids and weakly basic reagents. Use of strongly basic hydrogen peroxide result in isomerization to the γ ketoacid

Solution:



R. K. Boeckman Jr., E. W. Thomas, *Tet. Lett.* **1976**, 4045.

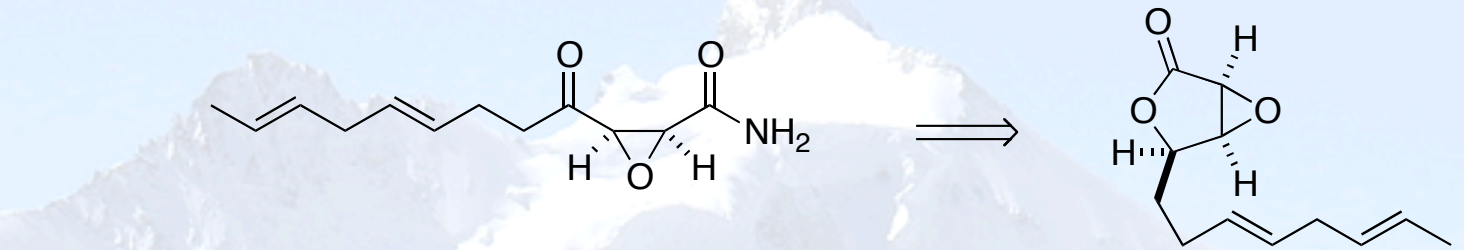
epoxy diol[1]	yield	method of epoxidation	epoxy lactone	Ag_2CO_3/ celite (yield)[2,3,4]	PtO_2 (yield)[2,3]
	45%	B		40-60%	20%
	45%	A		60%	70%
	45%	B		50%	30%
	45%	B		20%	--
	55%	A		trace	50%
	15% of one diastereomer	A		80%	90%
	45%	A		70%	40%

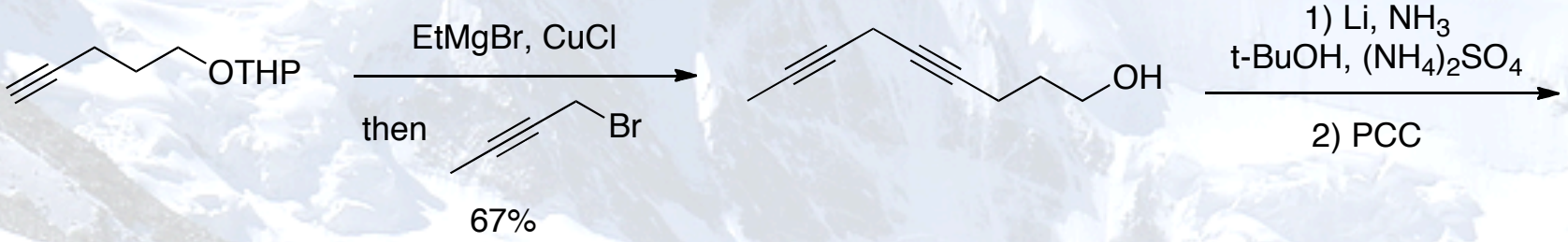
A = mCPBA
B = $tBuOOH/VO(acac)_2$

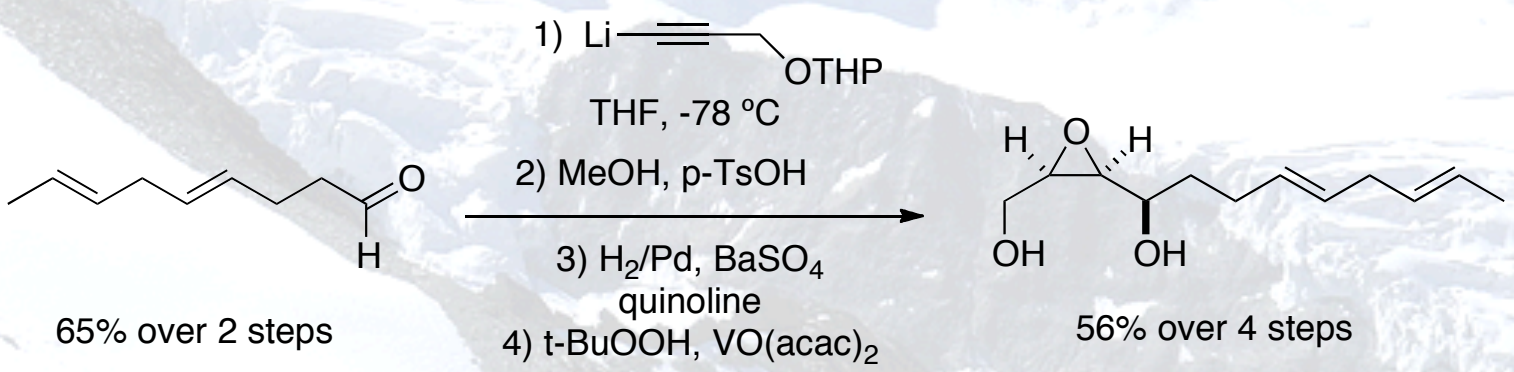
1) Stereochemistry of the major diastereomer present to the extent of ~7:1 in the crude diol epoxides.
2) Isolated yields purified by chromatography on SiO_2.
3) Characterized by IR, NMR, MS (High and Low Resolution) and elemental analysis (where appropriate).
4) The remainder of the material isolated was the corresponding keto alcohol in 1°, 2° cases.

R. K. Boeckman Jr., E. W. Thomas, *Tet. Lett.* **1976**, 4045.

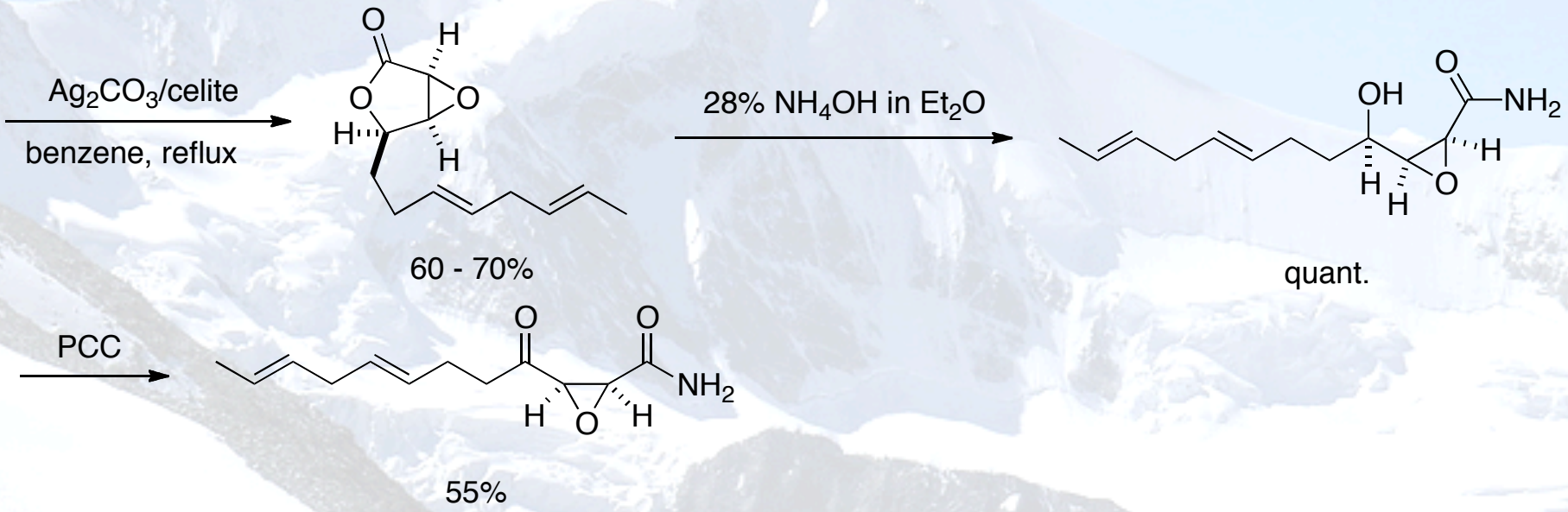
Application to the total synthesis of *dl*-Cerulenin:







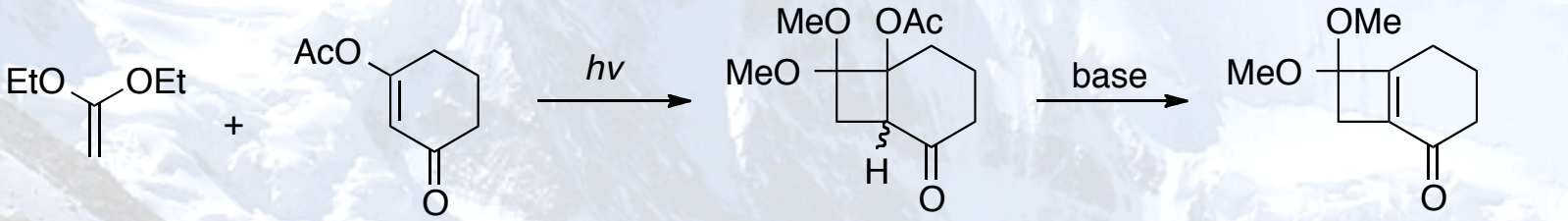
R. K. Boeckman Jr., E. W. Thomas, *J. Am. Chem. Soc.* **1977**, 2805.
R. K. Boeckman Jr., E. W. Thomas, *J. Am. Chem. Soc.* **1979**, 987.

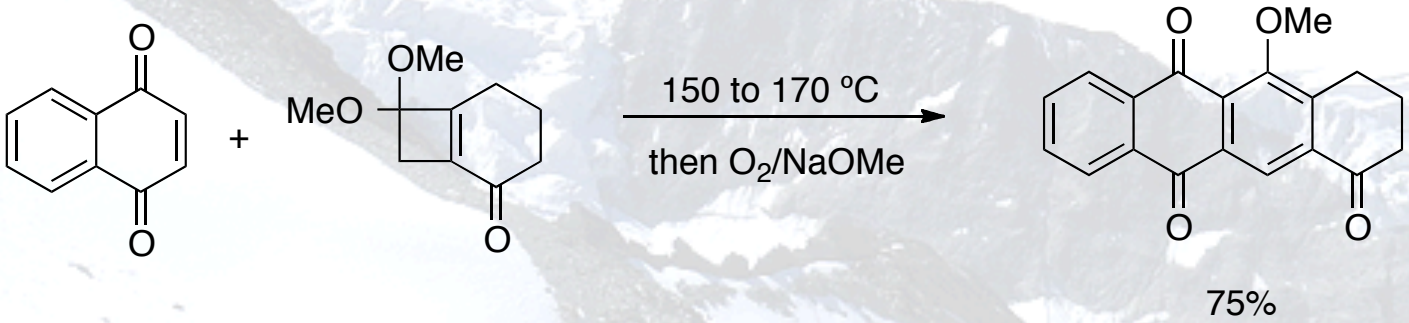


R. K. Boeckman Jr., E. W. Thomas, *J. Am. Chem. Soc.* **1977**, 2805.
R. K. Boeckman Jr., E. W. Thomas, *J. Am. Chem. Soc.* **1979**, 987.

Diels-Alder cycloaddition of Juglone derivatives: thermolysis of cyclobutanes to dienes

a general route to substances which might serve as stable, thermal precursors of alkoxy-substituted butadienes by in situ conrotatory opening of a cyclobutene

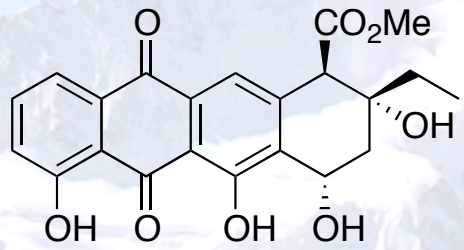




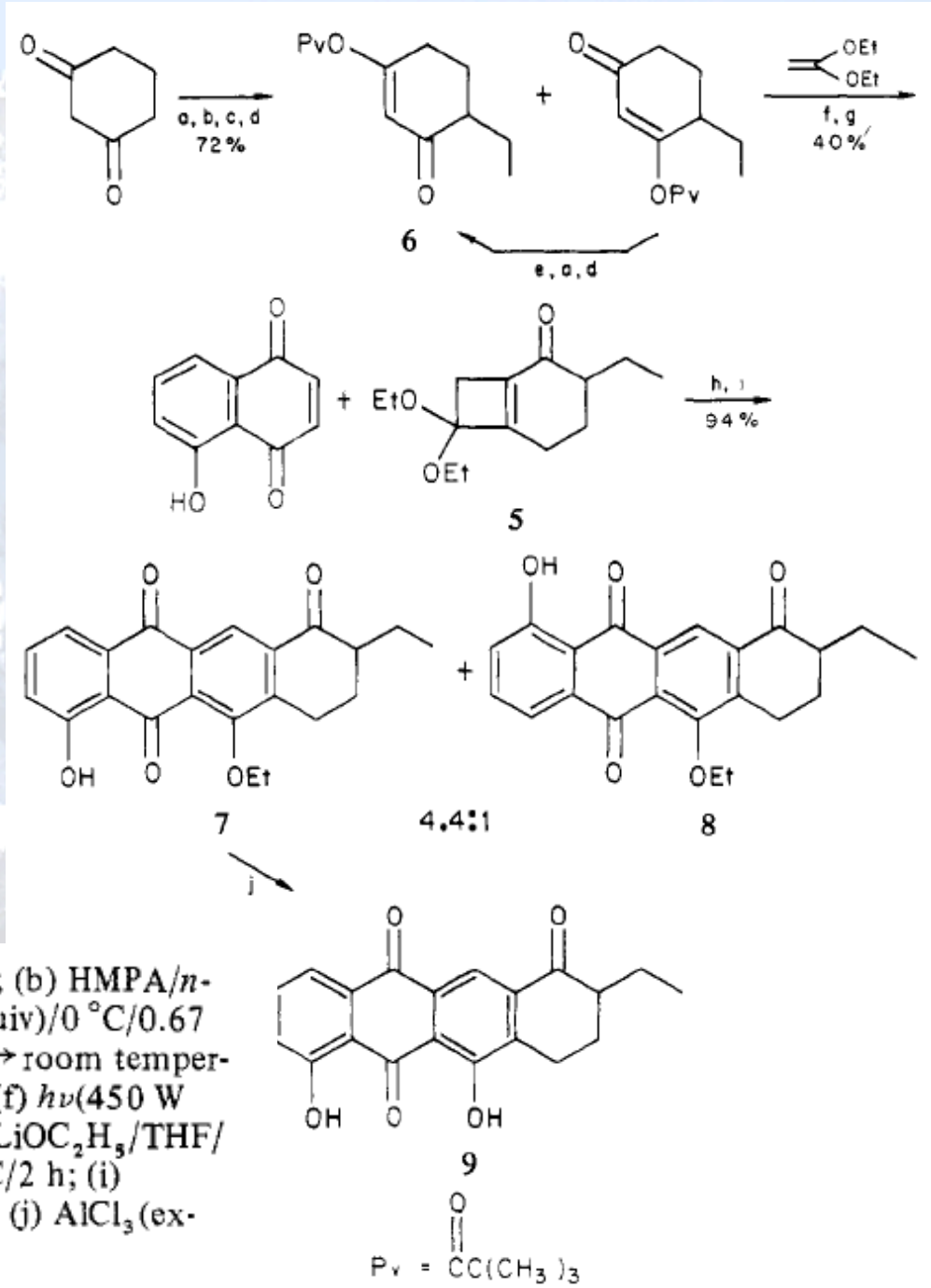
=> facile entry into these anthraquinone systems

R. K. Boeckman, M. H. Dalton, T. Nagasaka, T. Watanabe, *J. Org. Chem.* **1977**, 2946.

Application: Synthesis of Aklavinone



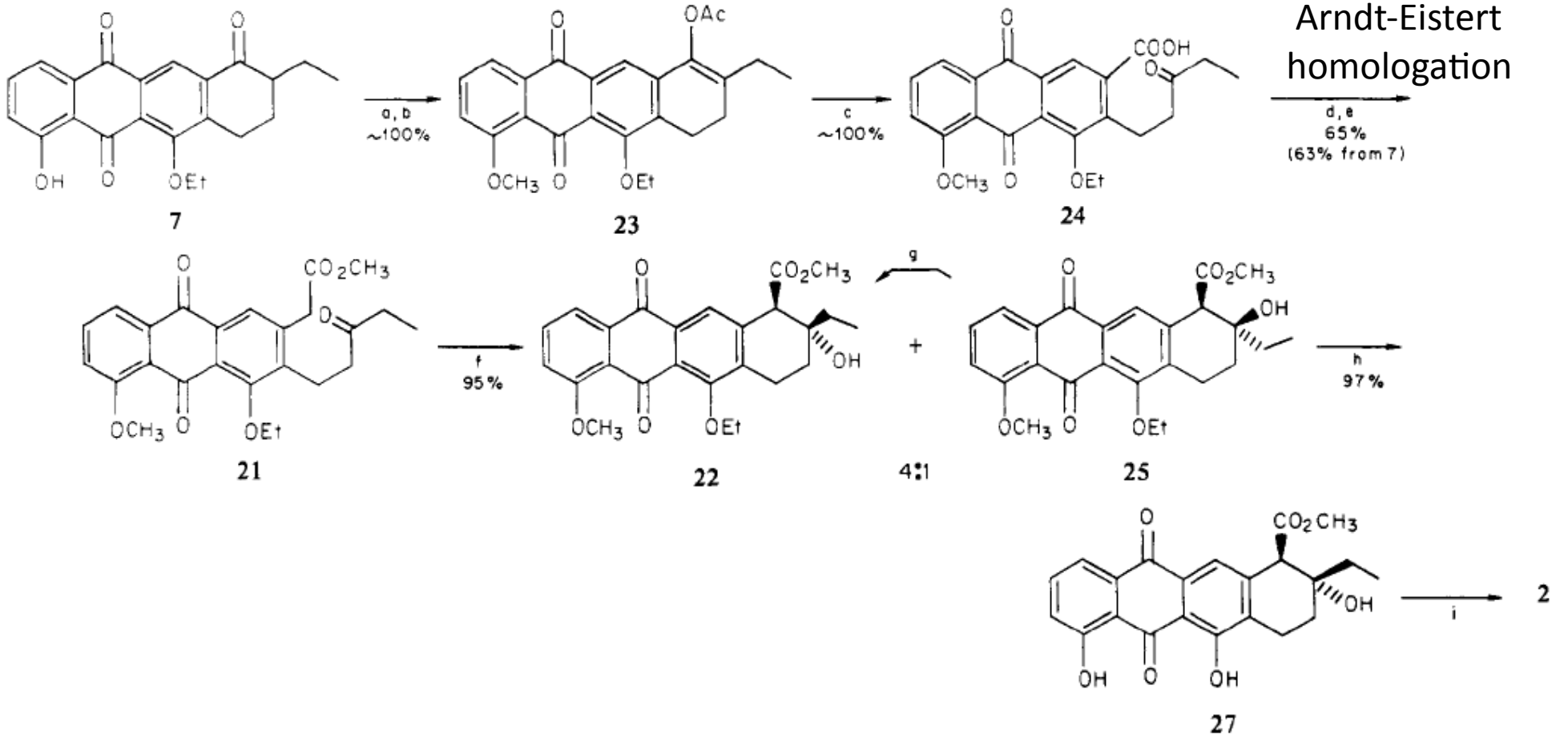
(+)-Aklavinone



[a] Reagents: (a) NaH (1.1 equiv)/THF/0 °C/0.5 h; (b) HMPA/*n*-BuLi (1.1 equiv)/0 °C/0.75 h; (c) CH_3CH_2I (1.1 equiv)/0 °C/0.67 h; (d) $[(CH_3)_3CCO]_2O$ (1.5 equiv)/−78 °C (1.5 h) → room temperature (12 h); (e) KOH/CH_3OH/room temperature; (f) *hν*(450 W Hg/corex filter)/ether/room temperature/40 h; (g) $LiOC_2H_5$/THF/room temperature/14 h; (h) mesitylene/175–180 °C/2 h; (i) $NaOCH_3$(cat)/O_2/CH_3OH/room temperature/0.5 h; (j) $AlCl_3$(excess)/PhH/room temperature/6 h.

R. K. Boeckman, F.-W. Sum, *J. Am. Chem. Soc.* **1982**, 4604.

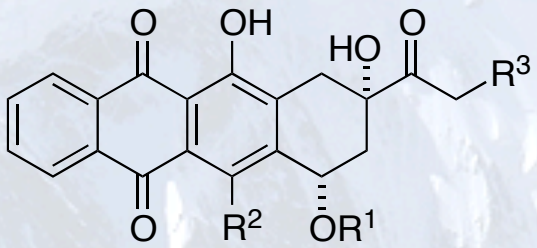
Arndt-Eistert homologation



[a] Reagents: (a) $CH_3I/Ag_2O/CH_2Cl_2/\Delta/40$ h; (b) $Ac_2O/HClO_4$(cat)/CH_2Cl_2/room temperature/3.5 h; (c) $O_3/CH_2Cl_2/-78$ °C/1 h; $CH_3SCH_3/-78$ °C → room temperature; aqueous NaOH extraction; (d) $SOCl_2$/Py (cat)/CH_2Cl_2/room temperature/4 h; CH_2N_2/Et_2O–THF/0 °C (0.5 h) → room temperature (0.5 h); (e) $Ag_2O/CH_3OH/\Delta/2$ h; (f) Triton $B(OH^-)$/anhydrous CH_3OH–CH_2Cl_2 (2:1)/−20 °C/2 h; (g) Et_3N/CH_2Cl_2/room temperature/12 h; (h) $AlCl_3$ (excess)/CH_2Cl_2/room temperature/40 h; (i) Br_2/CCl_4/AIBN/Δ/1 h; THF–H_2O (1:1).

R. K. Boeckman, F.-W. Sum, *J. Am. Chem. Soc.* **1982**, 4604.

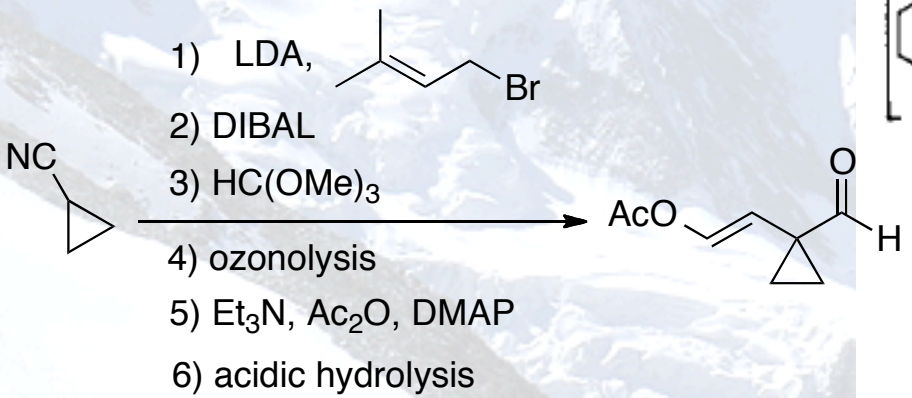
Application: Synthesis of Daunomycinone and Adriamycinone

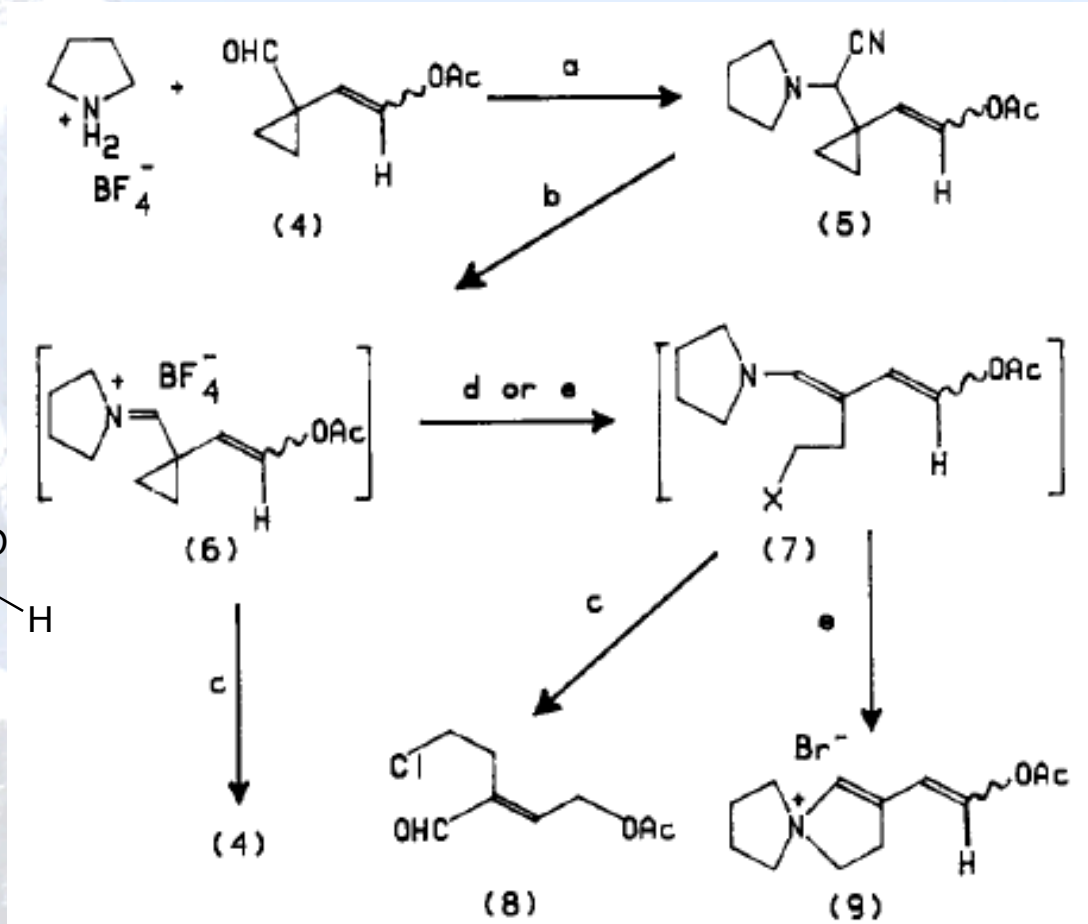


Daunomycinone (1): $R^3 = R^1 = H$, $R^2 = OH$
Adriamycinone (2): $R^3 = R^2 = OH$, $R^1 = H$

R. K. Boeckman Jr., S. H. Cheon, *J. Am. Chem. Soc.* **1983**, 4112.

Cyclopropyl iminium ion rearrangement

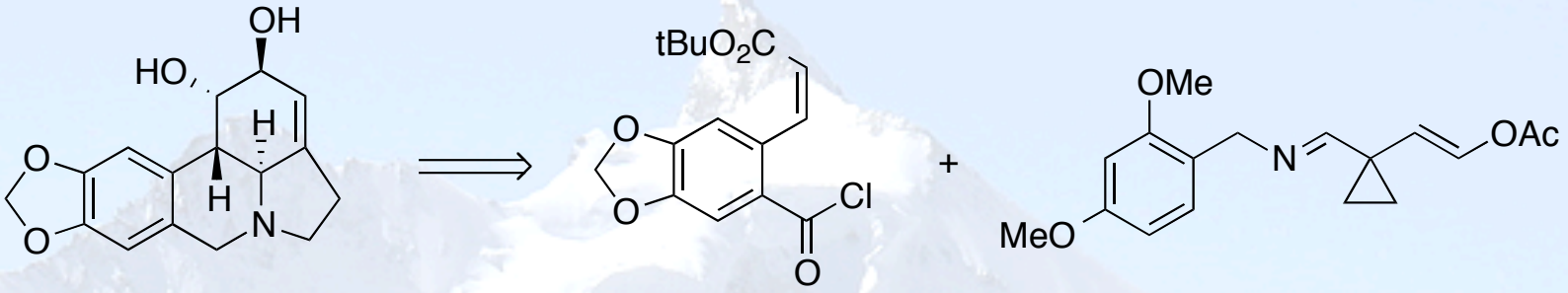


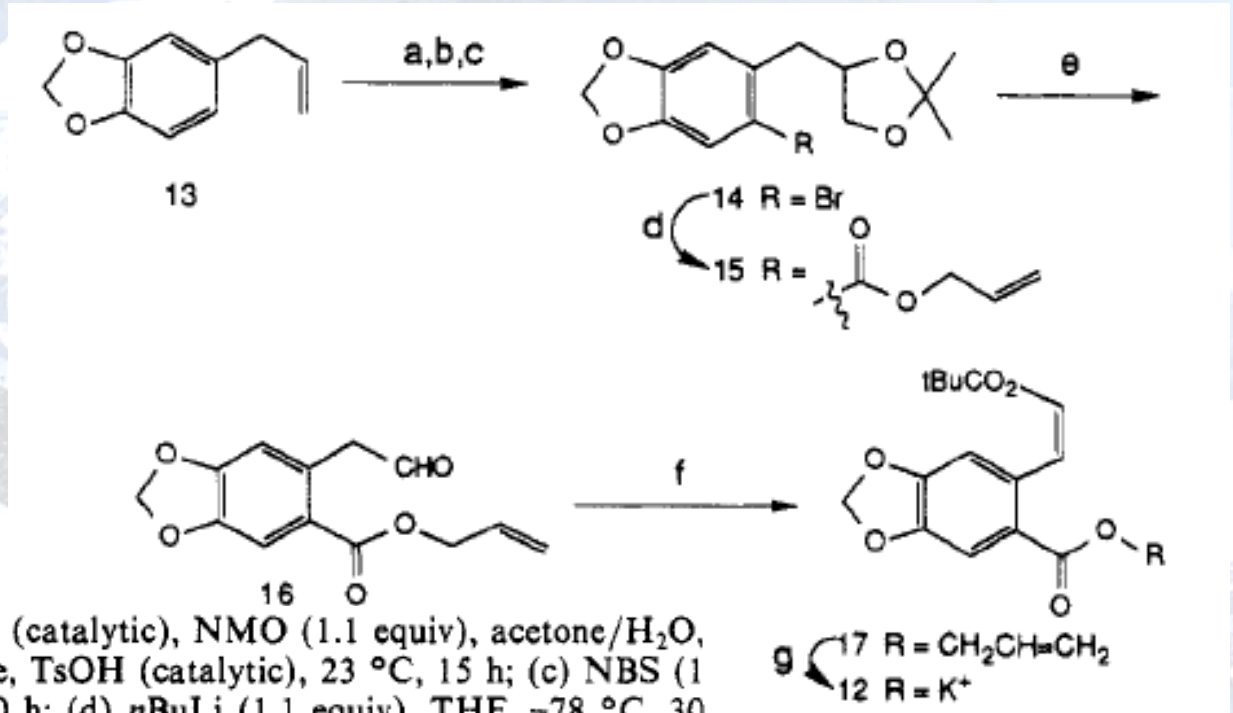


[a] Reagents: (a) KCN, $MgSO_4$/THF/40 °C/36 h; (b) $AgBF_4$ (1.5 equiv)/DME/room temperature; (c) H_2O; (d) LiCl (1.5 equiv)/DME/room temperature (1.5 h) then 82 °C/1 h; (e) LiBr (1.5 equiv)/CH_3CN/room temperature (4 h).

R. K. Boeckman Jr., P. F. Jackson, J. P. Sabatucci, *J. Am. Chem. Soc.* **1985**, 2191.

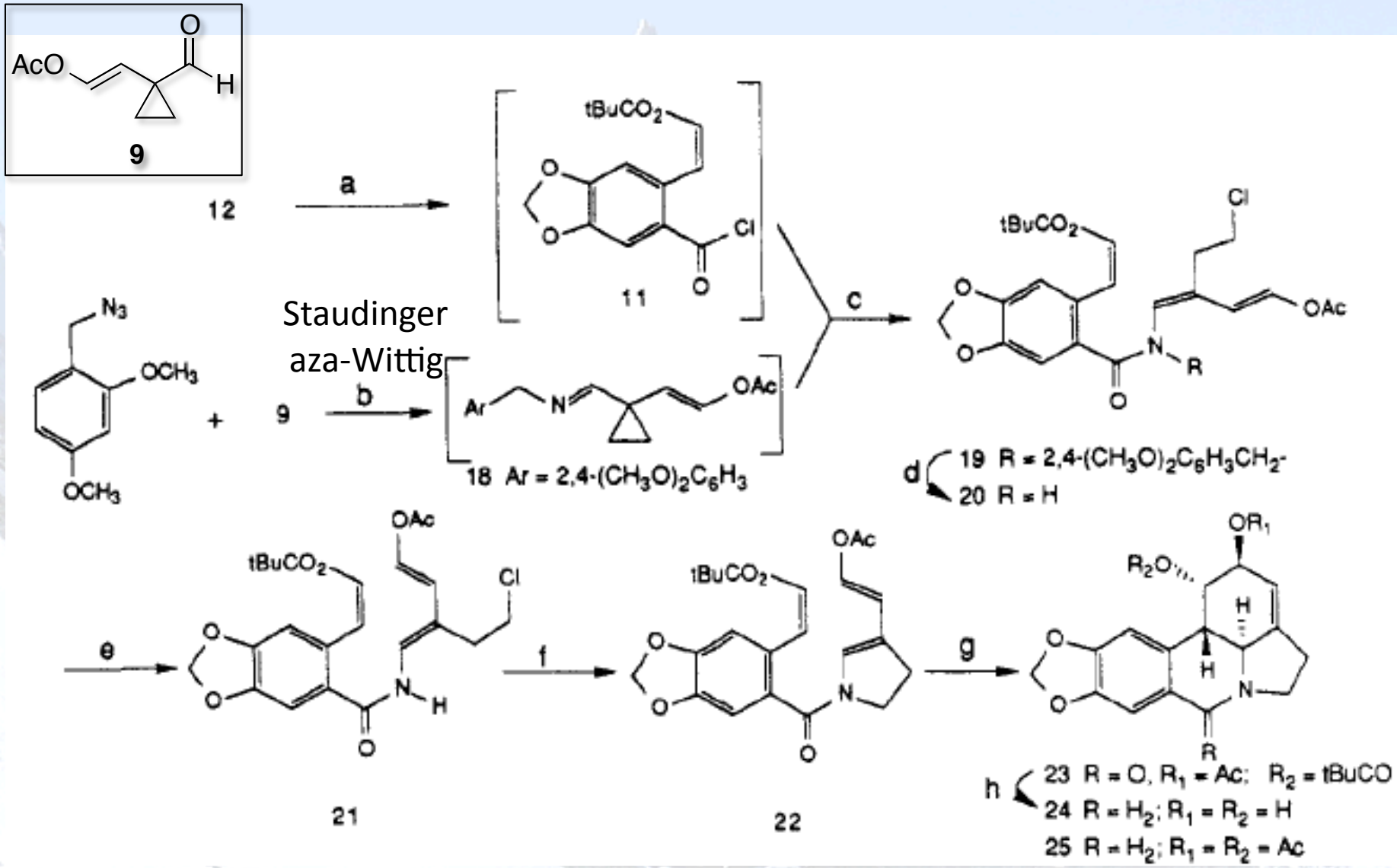
Application: Synthesis of (±)-Lycorine





[a] Reagents: (a) OsO_4 (catalytic), NMO (1.1 equiv), acetone/H_2O, 23 °C, 15 h; (b) acetone, TsOH (catalytic), 23 °C, 15 h; (c) NBS (1 equiv), DMF, 23 °C, 20 h; (d) *n*BuLi (1.1 equiv), THF, −78 °C, 30 min, then $ClCO_2CH_2CH{=}CH_2$ (1.1 equiv), THF, −78 °C (1 h) → 23 °C (1 h); (e) H_5IO_6 (1.2 equiv), 1 N HCl/THF (1:1), 23 °C, 3.5 h; (f) $((CH_3)_3CCO)_2O$ (1.1 equiv), Et_3N (1.3 equiv), DMF, 23 °C, 15 h; (g) $Pd(C_6H_5)_3P)_4$ (catalytic), $C_5H_{11}C(C_2H_5)CO_2K$, EtOAc/CH_2Cl_2 (1:1), 23 °C, 15 h.

R. K. Boeckman Jr., S. W. Goldstein, M. A. Walters, *J. Am. Chem. Soc.* **1988**, 8250.

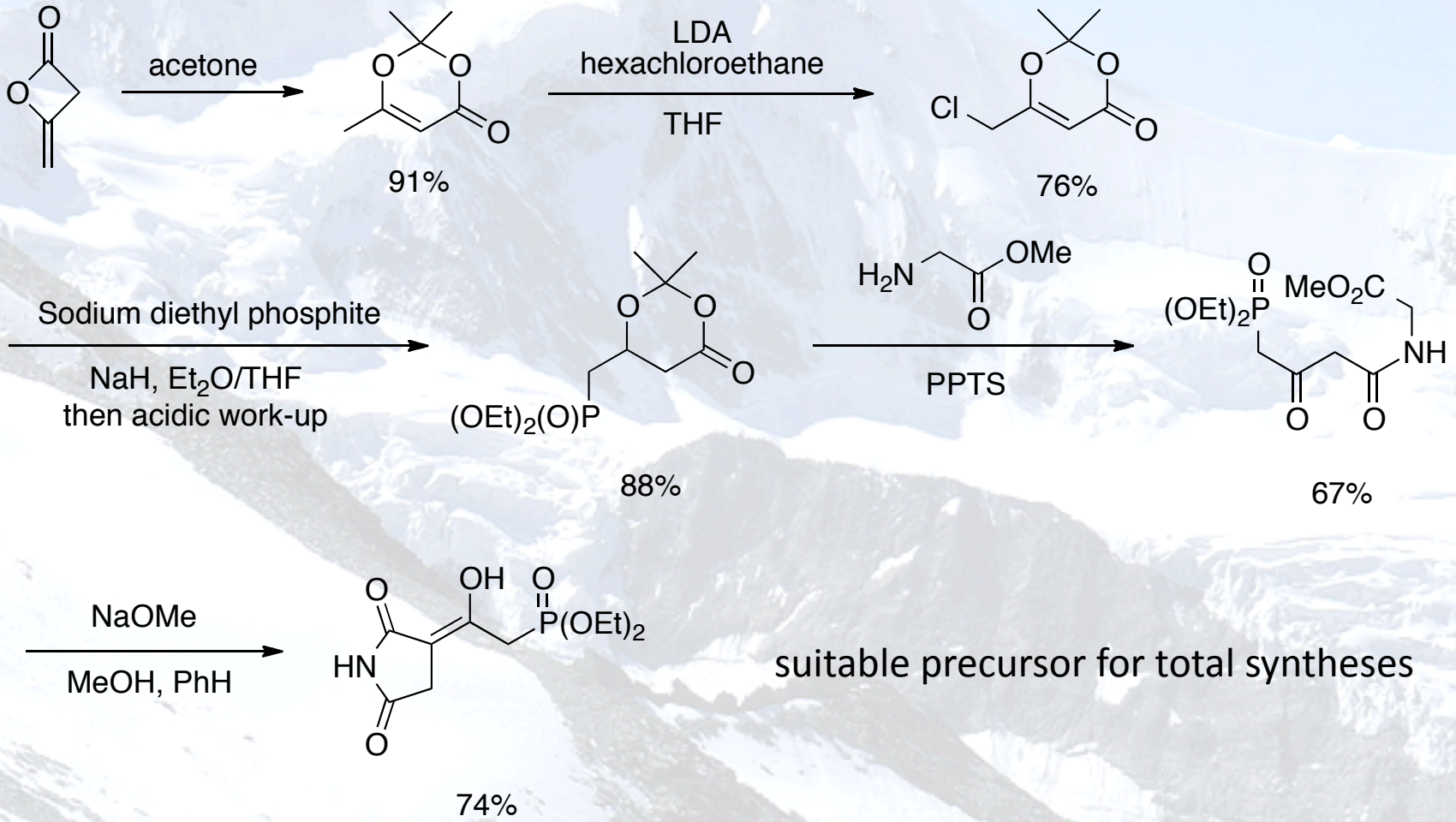


[a] Reagents: (a) $(COCl)_2$ (3 equiv), PhH, Δ, 12 h; (b) Ph_3P (1.0 equiv), Et_2O, 23 °C, 4 h; (c) CH_3CN, 23 °C, 15 h; (d) 40% TFA/CH_2Cl_2 (0.25 M), 23 °C, 40 min; (e) $Pd(CH_3CN)_2Cl_2$ (0.25 equiv), $PhCH_3$, (0.1 M), 23 °C, 5 h; (f) DBU (1 equiv), $CHCl_3$, 23 °C, 2 h; (g) 2-$ClPhCH_3$, Δ, 56 h; (h) LAH (xs), THF, Δ, 2 h.

R. K. Boeckman Jr., S. W. Goldstein, M. A. Walters, *J. Am. Chem. Soc.* **1988**, 8250.

Thermally labile highly substituted dioxinone phosphonates

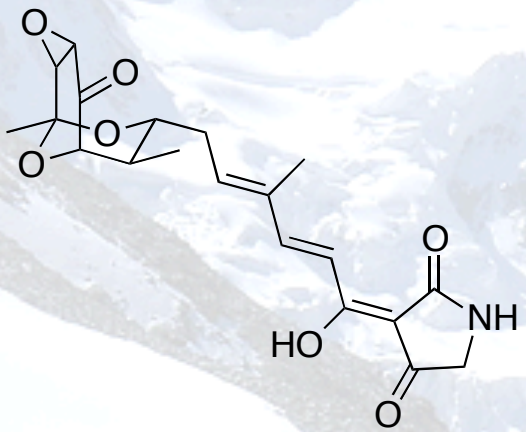
development of a general method for construction of unsaturated 3-acyl-tetramic acids

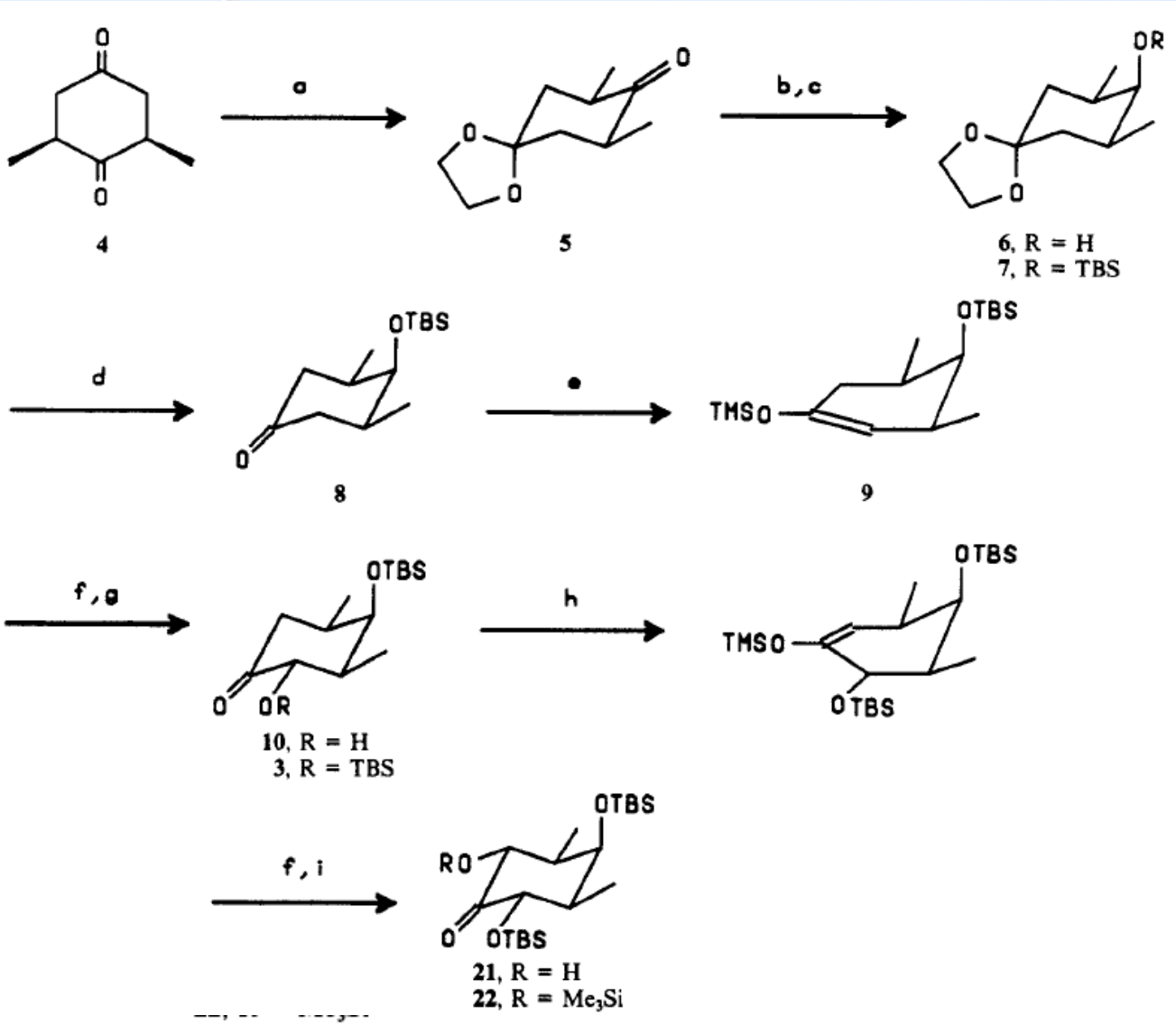


suitable precursor for total syntheses

R. K. Boeckman, A. J. Thomas, *J. Org. Chem.* **1982**, 2823.

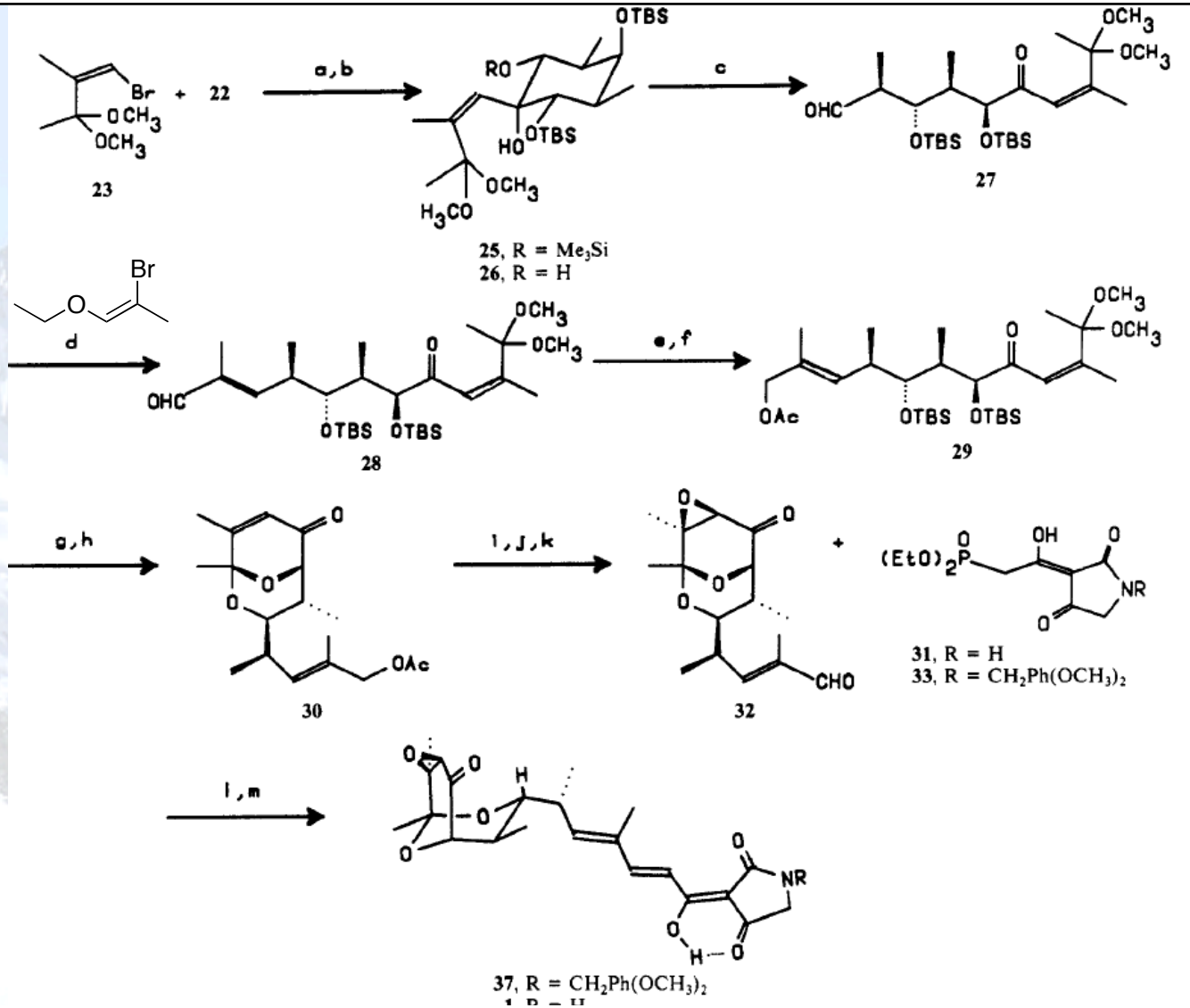
Application: Synthesis of (±)-Tirandamycin A





[a] Reagents: (a) $HOCH_2CH_2OH$ (0.95 equiv), *p*-TsOH (catalytic), PhH, reflux 24 h; (b) L-Selectride (1.25 Me_3SiCl equiv), THF, −78 °C, 5 h; (c) *t*-Bu$(CH_3)_2$SiOTf (1.2 equiv), 2,6-lutidine (2 equiv), CH_2Cl_2, 0 °C, 1 h; (d) *p*-TsOH (catalytic), acetone, reflux, ~48 h; (e) LDA (1.3 equiv), THF, −78 °C, 1 h, Me_3SiCl (2 equiv), −78 °C, 1.5 h; (f) OsO_4 (catalytic), *N*-methylmorpholine *N*-oxide (2 equiv), THF–H_2O (3:1), room temperature ~12 h; (g) *t*-Bu$(CH_3)_2$SiCl (3 equiv), imidazole (6 equiv), DMF, ~12 h; (h) LDA (3 equiv), THF, −30 °C, 1 h and then Me_3SiCl (4 equiv), −30 °C, 1.5 h; (i) Me_3SiCl (5 equiv), anhydrous Et_3N (5.3 equiv), room temperature, ~2.4 h, nonaqueous workup.

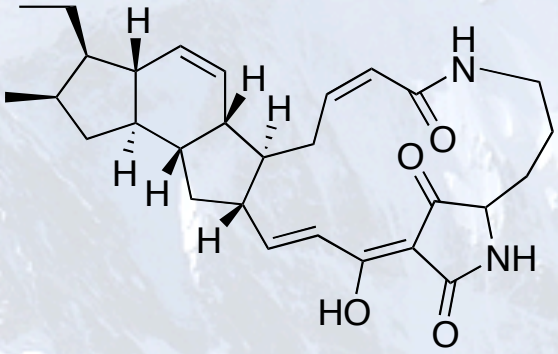
R. K. Boeckman Jr., J. E. Starrett Jr., D. G. Nickell, P.-E. Sum, *J. Am. Chem. Soc.* **1986**, 5549.



[a] Reagents: (a) Bromide **23** (1.1 equiv), *t*-BuLi (2 equiv), Et_2O, −78 °C → room temperature, 1.5 h; ketone **22** (1 equiv), Et_2O, −78 °C, 0.25 h; (b) Et_3N–HF (excess), CH_2Cl_2, room temperature, 3 h; (c) $Pb(OAc)_4$ (1.5 equiv), THF , 0 °C, 5 min; (d) (*Z*)-2-bromo-1-ethoxy-1-propene (1.5 equiv), *sec*-BuLi (1.5 equiv), Et_2O, −78 °C, 0.33 h; aldehyde **27** (1 equiv), −78 °C, 0.25 h; *p*-nitrobenzoyl chloride (2 equiv), −78 °C → room temperature,3 h; Et_3N–HF, aqueous acetonitrile, 60 °C, 4 h; (e) $NaBH_4$ (1 equiv), EtOH, 0 °C, 1 h; (f) CH_3COCl, pyridine, DMAR, CH_2Cl_2, room temperature, 0.25 h; (g) *n*-Bu_4NF (0.5 M in THF, 6 equiv), THF, room temperature, 1.5 h; (h) BF_3–Et_2O (excess), CH_2Cl_2, −78 °C, 0.25 h; (i) DBU (6 equiv), *t*-BuOOH (6 equiv), THF, 60 °C, 12 h; (j) K_2CO_3 (excess), methanol, room temperature, 0.5 h; (k) PDC (1.5 equiv), CH_2Cl_2, room temperature, 1 h; (l) tetramic acid **33** (2 equiv), KO-*t*-Bu (2.1 equiv), THF (0.4 M in **33**), 0 °C, 1 h, and then **31** (1 equiv), 0 °C, 12 h, quenched with 5% HCl; (m) CF_3COOH (anhydrous), neat (0.1 M in **33**), room temperature, 0.33 h.

R. K. Boeckman Jr., J. E. Starrett Jr., D. G. Nickell, P.-E. Sum, *J. Am. Chem. Soc.* **1986**, 5549.

Application: Synthesis of (+)-Ikarugamycin



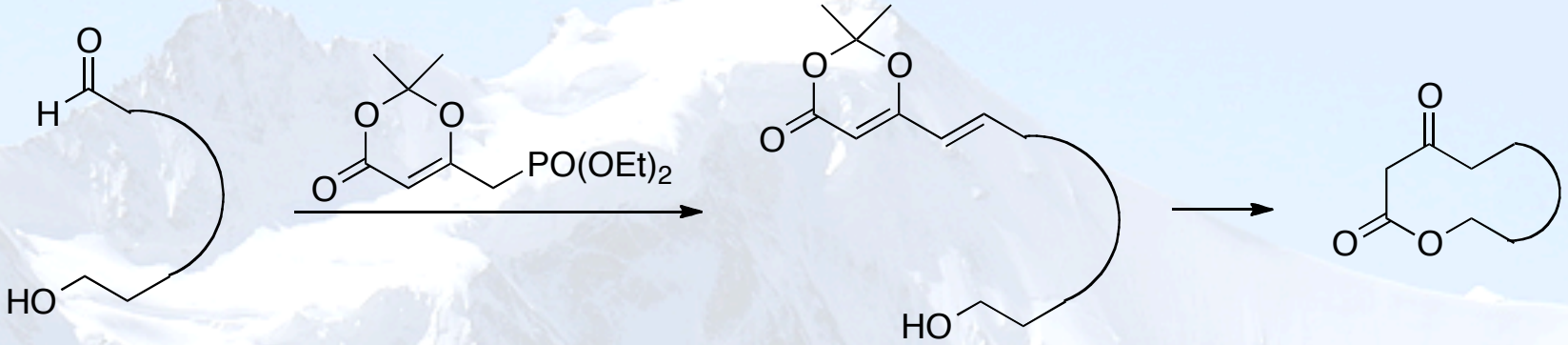
Idea:

• preparation of a tetracyclic intermediate by stereocontrolled intramolecular Diels-Alder reaction

• introduction of the tetramic acid and cyclization by dioxinone phosphonate

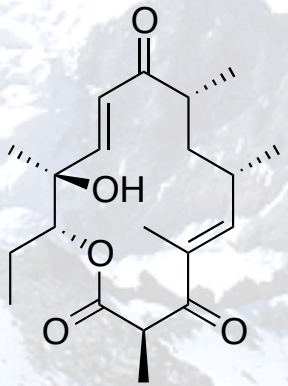
R. K. Boeckman Jr., C. H. Weidner, R. B. Perni, J. J. Napier, *J. Am. Chem. Soc.* **1989**, 8036

Highly efficient, selective methodology for formation of medium-ring and macrocyclic lactones via intramolecular ketene trapping

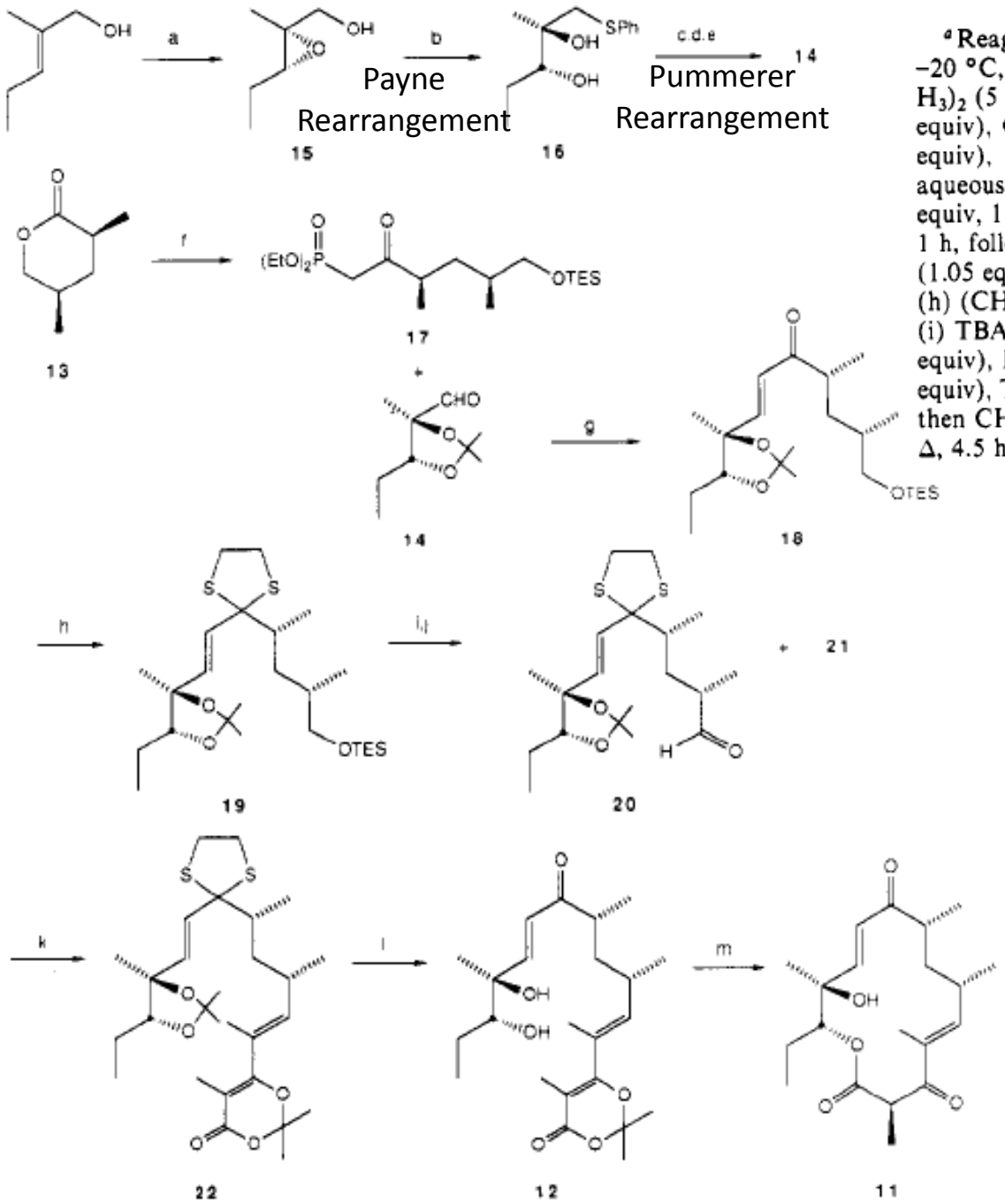


mild neutral conditions => just heating

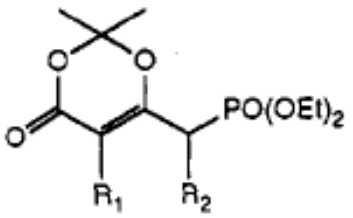
Application: Synthesis of (-)-Kromycin



R. K. Boeckman Jr., J. R. Pruitt, *J. Am. Chem. Soc.* **1989**, 8286.



[a] Reagents: (a) (−)-DMT, $Ti(OiPr)_4$, 3-Å molecular sieves, CH_2Cl_2, −20 °C, 24 h; (b) PhS^-K^+, KOH, H_2O, 25 °C, 8 h; (c) $(CH_3)_2C(OCH_3)_2$ (5 equiv), Amberlyst-15 (catalytic), 25 °C, 12 h; (d) MCPBA (1 equiv), CH_2Cl_2, 0 °C, 3 h; (e) $(CF_3CO)_2O$ (1 equiv), 2,6-lutidine (1 equiv), CH_3CN, 0 °C, 1 h, then $HgCl_2$ (excess), $CaCO_3$ (excess), aqueous THF, 25 °C, 4 h; (f) $CH_3P(O)(OEt)_2$ (1.5 equiv), nBuLi (1.5 equiv, 1.6 M in hexanes), THF, 0 °C, 2 h, then **13** (1 equiv), −78 °C, 1 h, followed by TESCl (3 equiv), −78 °C → 25 °C, 6 h; (g) *t*-BuOK (1.05 equiv), THF, 0 °C, 1 h, then **14** (1 equiv), −78 °C → 25 °C, 3h; (h) $(CH_2SSi(CH_3)_3)_2$ (1 equiv), ZnI_2 (catalytic) 0 °C → 25 °C, 12 h; (i) TBAF, THF, 0 °C, 10 min; (j) $(COCl)_2$ (1.5 equiv), DMSO (1.5 equiv), Et_3N (3 equiv), −78 °C, 1 h; (k) **21** (1.3 equiv), *t*-BuOK (1.3 equiv), THF, −78 °C → 25 °C, 5 h; (l) $TlNO_3$, CH_3OH, 25 °C, 5 min, then CH_3OH–H_2O (98:2, v/v), 25 °C, 1 h; (m) **12** (10^{-4} M), $PhCH_3$, Δ, 4.5 h.

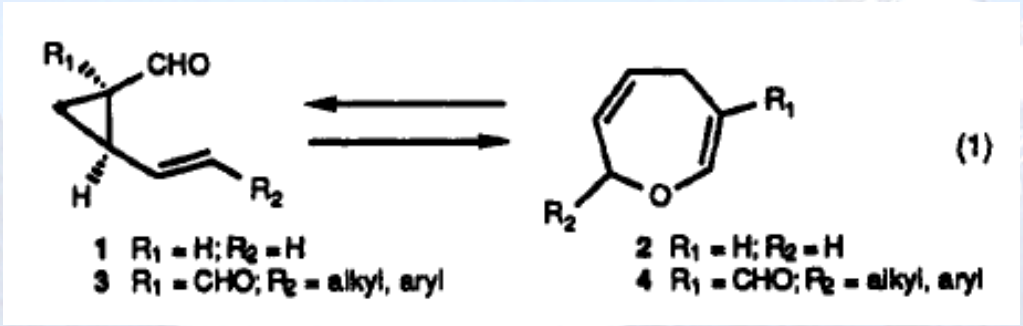


2 $R_1=R_2=H$

21 $R_1=R_2=CH_3$

R. K. Boeckman Jr., J. R. Pruitt, *J. Am. Chem. Soc.* **1989**, 8286.

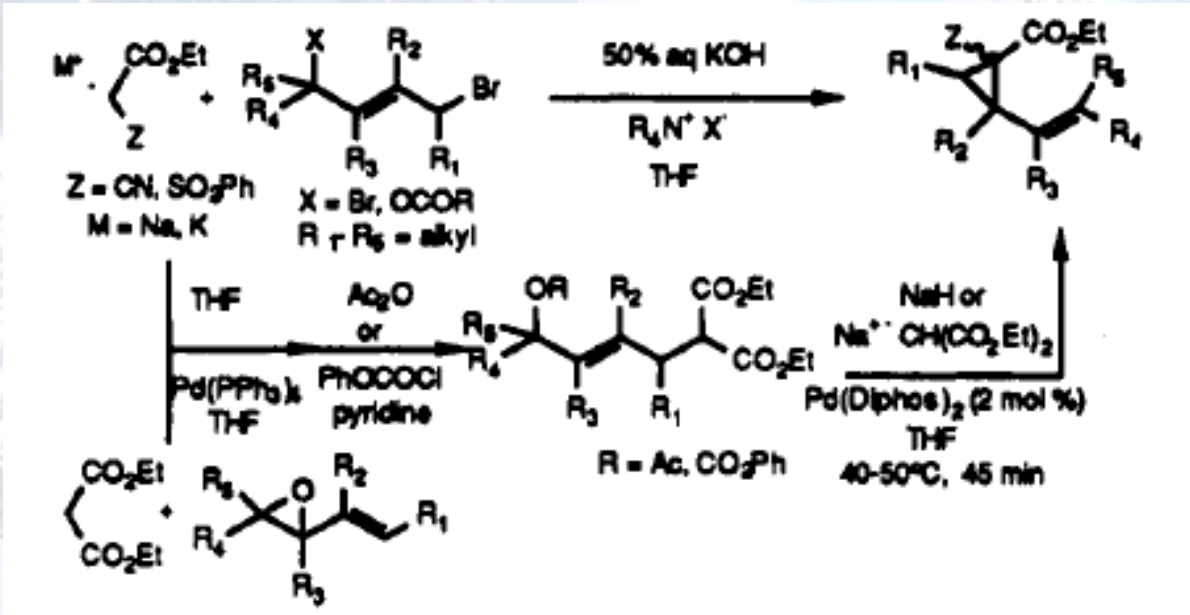
retro-Claisen Rearrangement: method to 7- or 8-membered ring ethers



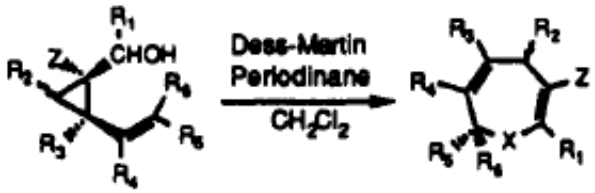
manipulation of the equilibrium to favor the medium-ring heterocycle using a suitable π-conjugating stabilizing group

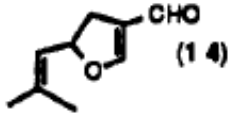
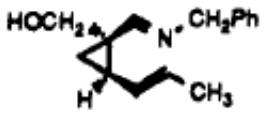
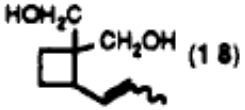
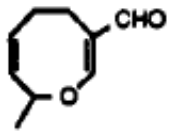
Two routes to cyclopropyl substrates:

1) Dialkylation of malonate or equivalent bifunctional electrophiles
2) Intramolecular Pd-catalyzed cyclization of malonyl allyl acetates or carbonates prepared by alkylation of malonate with differentiated bifunctional electrohpiles or by Pd-catalyzed alkylation of vinyl epoxides



R. K. Boeckman Jr., M. D. Shair, J. R. Vargas, L. A. Stolz, *J. Org. Chem.* **1993**, 1295.

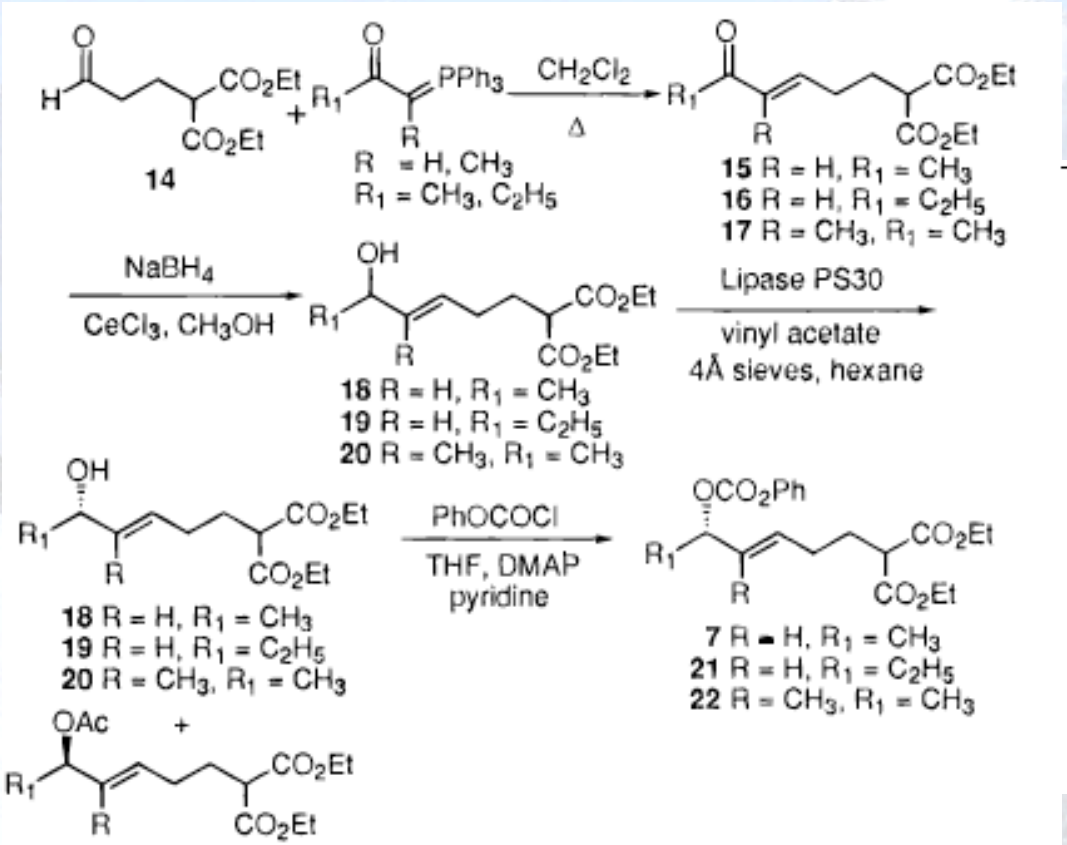


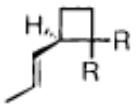
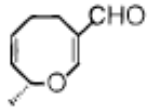
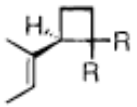
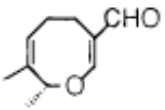
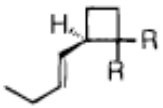
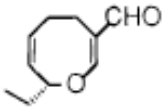
substrate[a,b]	prepn[c]	product[d]	yield[e] (%)
R_5 or R_6 = CH_3 (6)	A, B	R_5 or R_6 = CH_3 (8)	85
R_4 = CH_3	A	R_4 = CH_3	95
R_3 = CH_3	A	R_3 = CH_3	95
R_2, R_5 = CH_3	A	R_2, R_5 = CH_3	91
R_4 = CH_3; R_5 = C_2H_5[f]	B, C	R_4 = CH_3; R_5 = C_2H_5[g]	90
R_5 = R_6 = CH_3 (13)	D	 (14)	95
R_4 = OAc; $R_5(R_6)$ = CH_3,C_2H_5 (15,16)	D	R_4 = OAc; $R_5(R_6)$ = CH_3,C_2H_5 (17)	57
Z = SO_2Ph	A	Z = SO_2Ph	97
Z = CN[h]	A	Z = CN[i]	90[j]
R_6 = CH_2Ph	B	R_6 = CH_2Ph (20)	68
R_1 = CH_3; R_5 = CH_2Ph (23)	E	R_1 = CH_3; R_5 = CH_2Ph (24)	83
R_1 = CH_2-2,4-$(CH_3O)_2Ph$; R_5 = CH_3	E	R_1 = CH_2-2,4-$(CH_3O)_2Ph$; R_5 = CH_3	70
	E	R_5 = CH_3; X = NCH_2Ph (27)	95
 (18)	F	 (19)	88

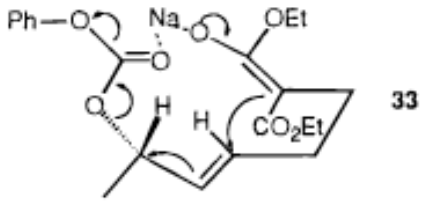
[a] R_n = H, Z = CH_2OH unless otherwise specified. [b] All reactions employed 2.5–3 equiv of oxidant and 9 equiv of pyridine at 25 °C for 30 min unless otherwise specified. [c] (A) alkylation of diethyl malonate with the appropriate dibromide; (B) Pd^0-catalyzed cyclization of monoalkylation product; (C) Pd^0-catalyzed alkylation of a vinyl epoxide then B; (D) reduction of formyl oxepin or oxacene then addition of an alkyllithium; (E) Pd^0-catalyzed alkylation of an allylic cyclic carbonate, then B; (F) 1,4 addition of vinyl Grignard reagent then acylation and reduction. [d] R_n = H, X = O, Z = CHO unless otherwise specified. [e] Yields of isolated chromatographically pure material. [f] A 2:1 mixture (*E*/*Z*) of diastereomers (95% ee) oxidized at 0 °C for 30 min. [g] oxepin exhibited 95% ee (determined by conversion to the SAMP hydrazone). [h] ~1:1 mixture of cyano alcohols rearranged. [i] Only *cis*-cyano aldehyde rearranged, trans was recovered unchanged. [j] Yield based on conversion of *cis*-cyano aldehyde.

R. K. Boeckman Jr., M. D. Shair, J. R. Vargas, L. A. Stolz, *J. Org. Chem.* **1993**, 1295.

Highly enantioselecitve rout to cyclobutane diesters:



vinylcyclobutane	$[\alpha]_D^{25}$	dihydrooxacene	$[\alpha]_D^{25}$	yield (%)
				
23 R = $CO_2C_2H_5$	136.0	**2**	31.7	70
28 R = CH_2OH	20.3			
				
26 R = $CO_2C_2H_5$	101.0	**31**	25.3	85
29 R = CH_2OH	15.1			
				
27 R = $CO_2C_2H_5$	68.4	**32**	21.6	82
30 R = CH_2OH	6.4			

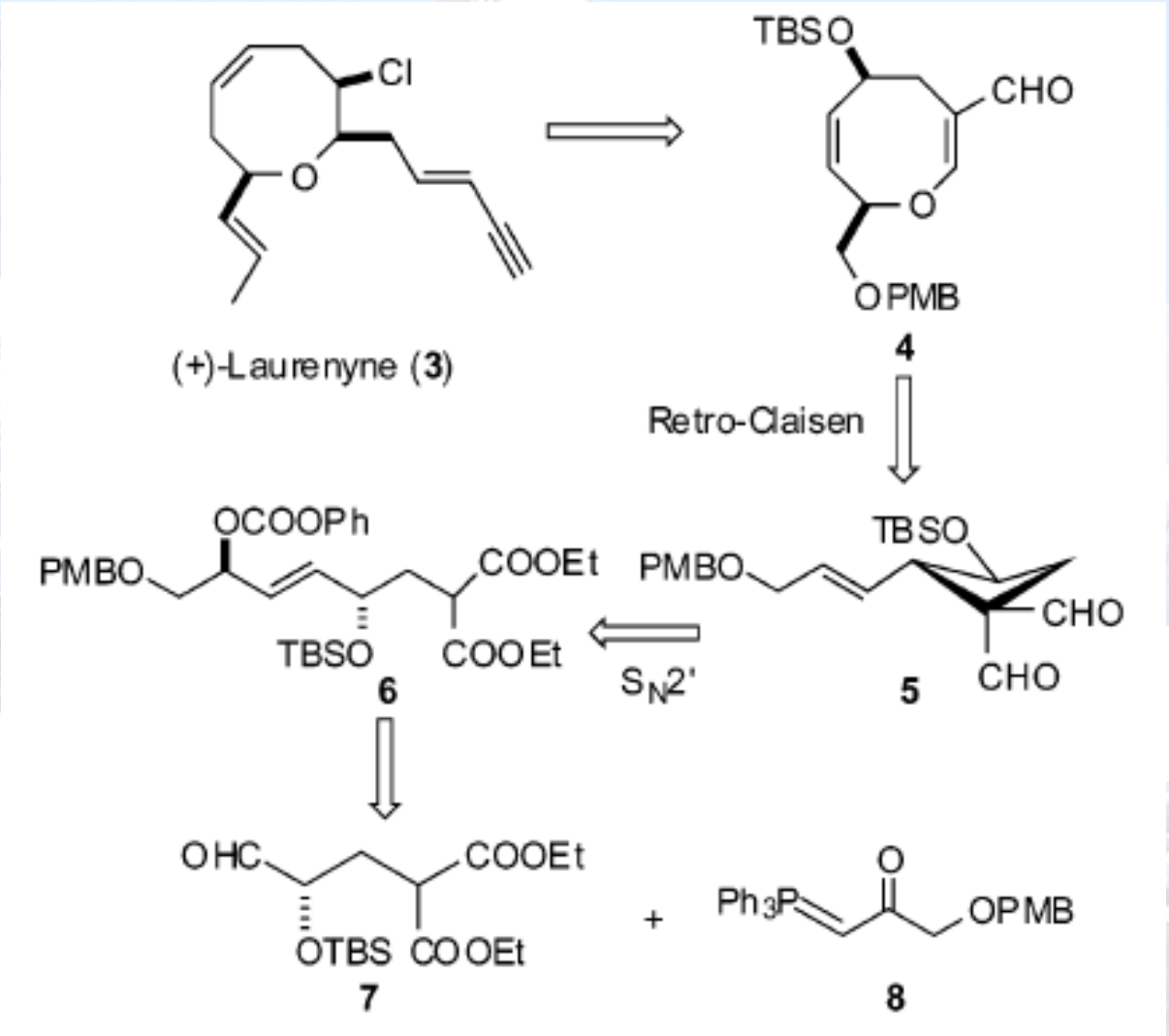


33

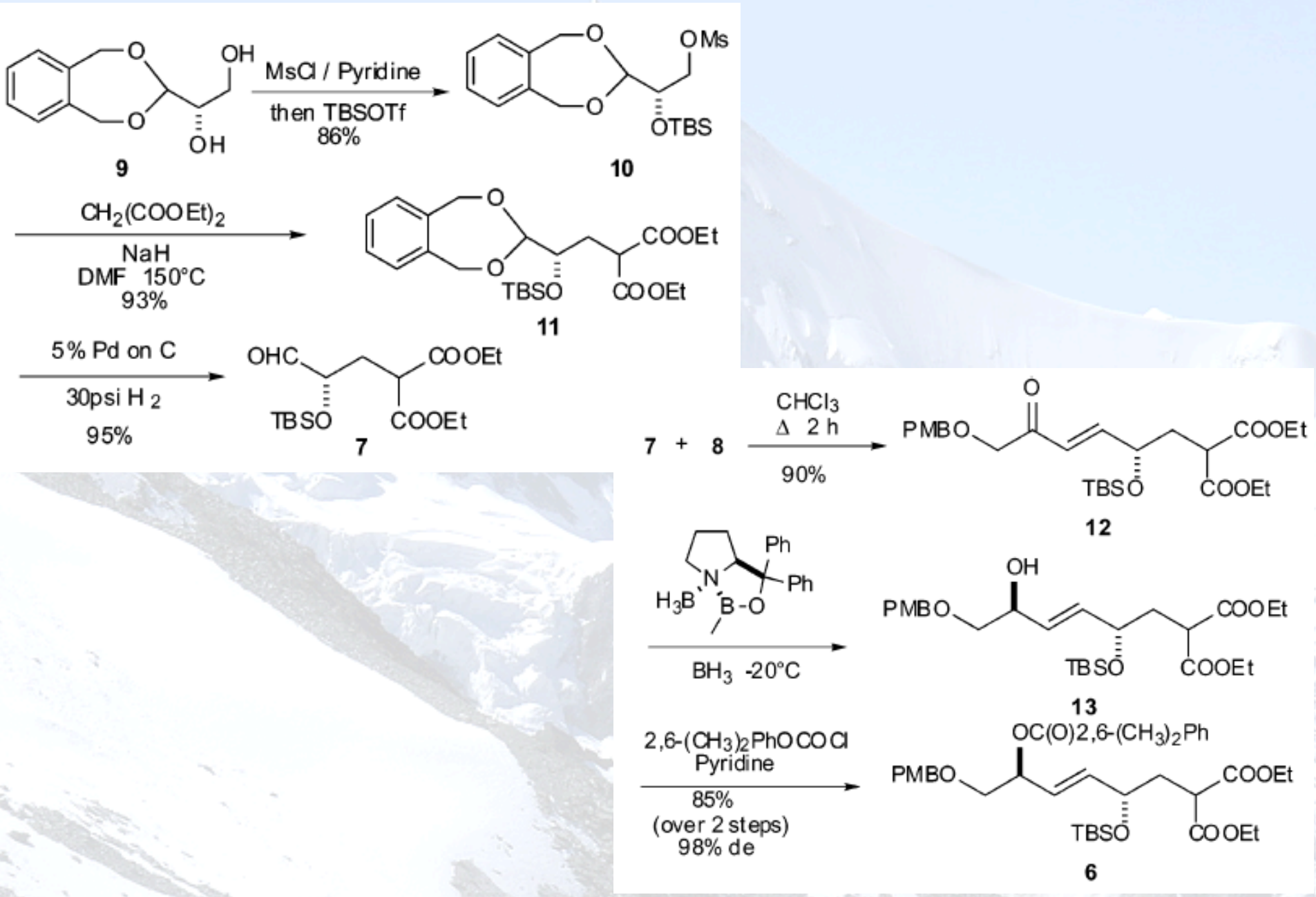
Preorganized complex is geometrically constrained to afford only *syn* substitution

R. K. Boeckman Jr., M. R. Reeder, *J. Org. Chem.* **1997**, 6456.

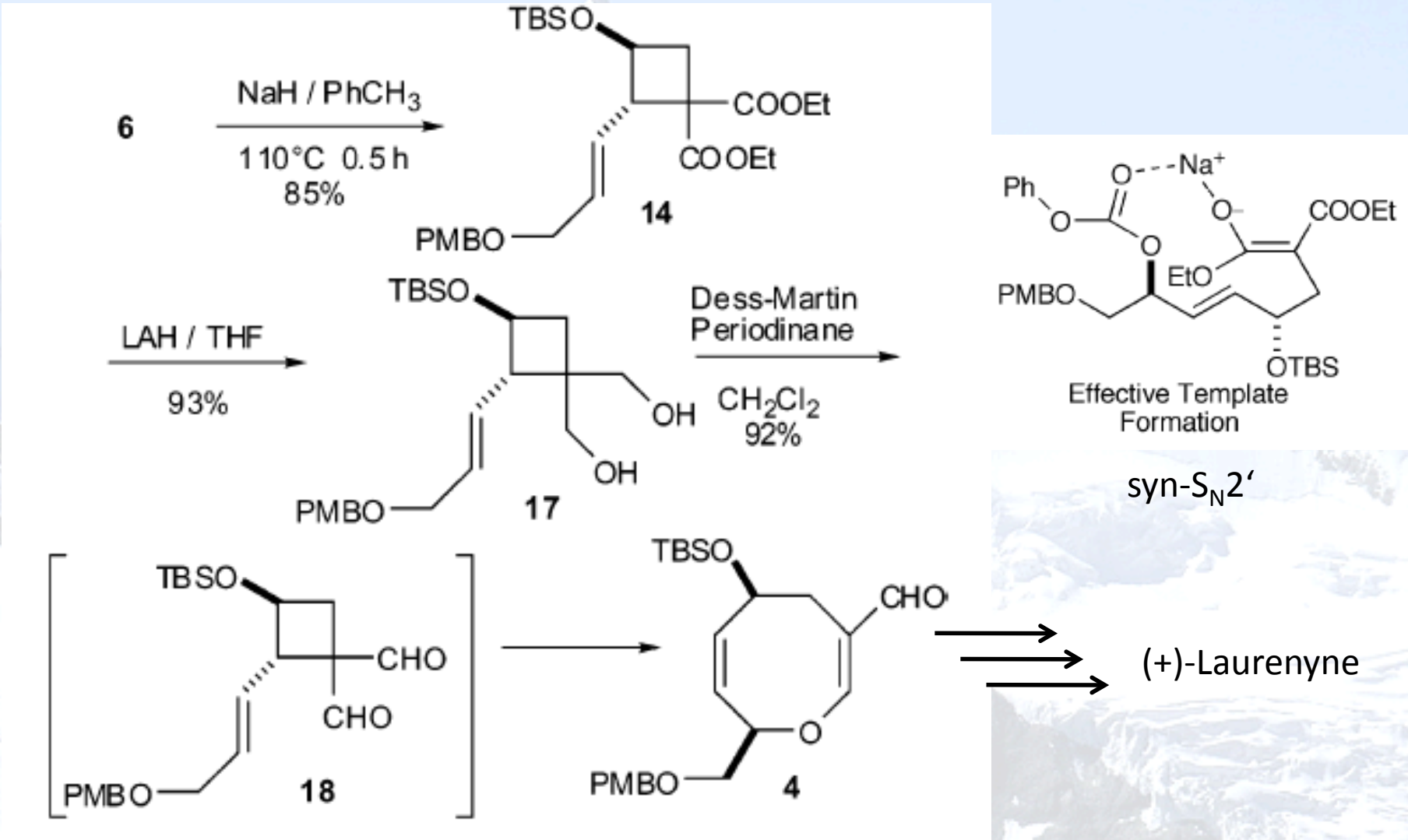
Application: Synthesis of (+)-Laurenyne



R. K. Boeckman Jr., J. Zhang, M. R. Reeder, *Org. Lett.* **2002**, 3891.



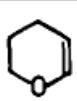
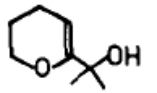
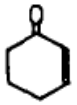
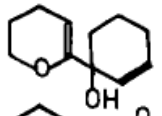
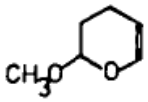
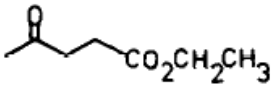
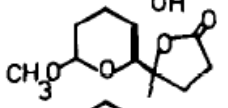
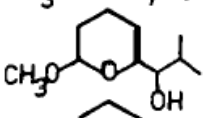
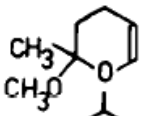
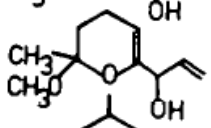
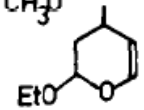
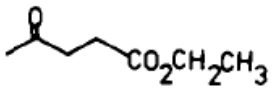
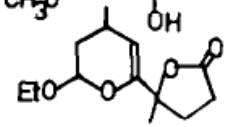
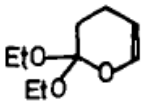
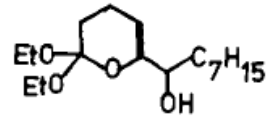
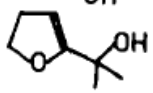
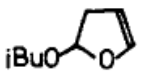
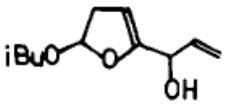
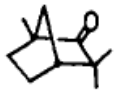
R. K. Boeckman Jr., J. Zhang, M. R. Reeder, *Org. Lett.* **2002**, 3891.



R. K. Boeckman Jr., J. Zhang, M. R. Reeder, *Org. Lett.* **2002**, 3891.

cyclic vinyl ether carbanions

t-BuLi: successfull for the formation of the lithium derivatives

Case	Reactant[a]	Carbonyl Component	Product	Yield[b]
1				86%
2	"			68%
3				86%
4	"	$(CH_3)_2CHCHO$		66%
5		$CH_2{=}CHCHO$		50%
6				47%
7		$C_7H_{15}CHO$		65%[c] 30%
8				78%
9		$CH_2{=}CHCHO$		68%[d]
10			—	N.R.

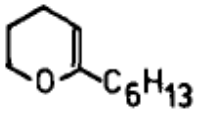
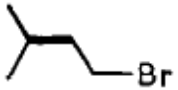
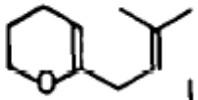
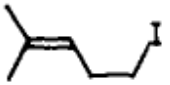
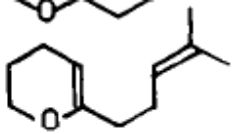
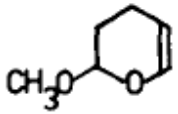
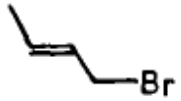
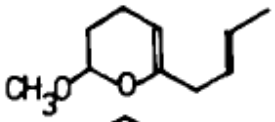
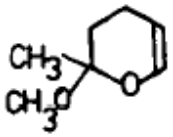
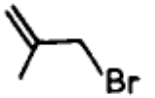
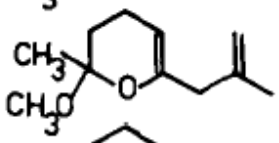
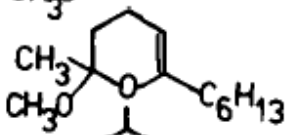
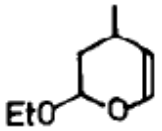
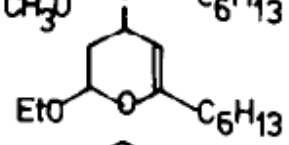
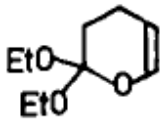
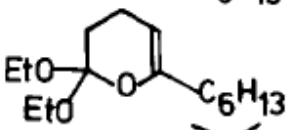
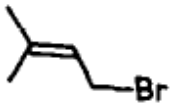
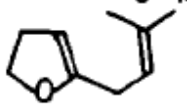
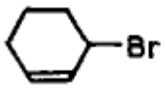
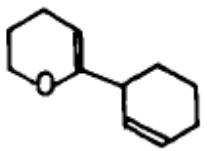
a) Typical procedure involves reaction of the derived anion (1 eq.) with the carbonyl compound (1 eq.) at -78°C in THF.

b) Isolated yields of purified products. Crude yields of reasonably pure products much higher in some cases.

c) Yield determined by NMR

d) Yield based upon recovered starting material

R. K. Boeckman Jr., K. J. Bruza, *Tetrahedron Lett.* **1977**, 4187
R. K. Boeckman Jr., K. J. Bruza, *Tetrahedron* **1981**, 3997.

Case	Vinyl Ether	Alkyl Halide	Product	Yield[a]
1		$C_5H_{11}CH_2I$		55%
2	"			53%
3	"			52%
4				61%
5				33% (70%)[b]
6	"	$C_5H_{11}CH_2I$		63%[b]
7		"		74%[b]
8		"		80%[b]
9				67%
10				60%

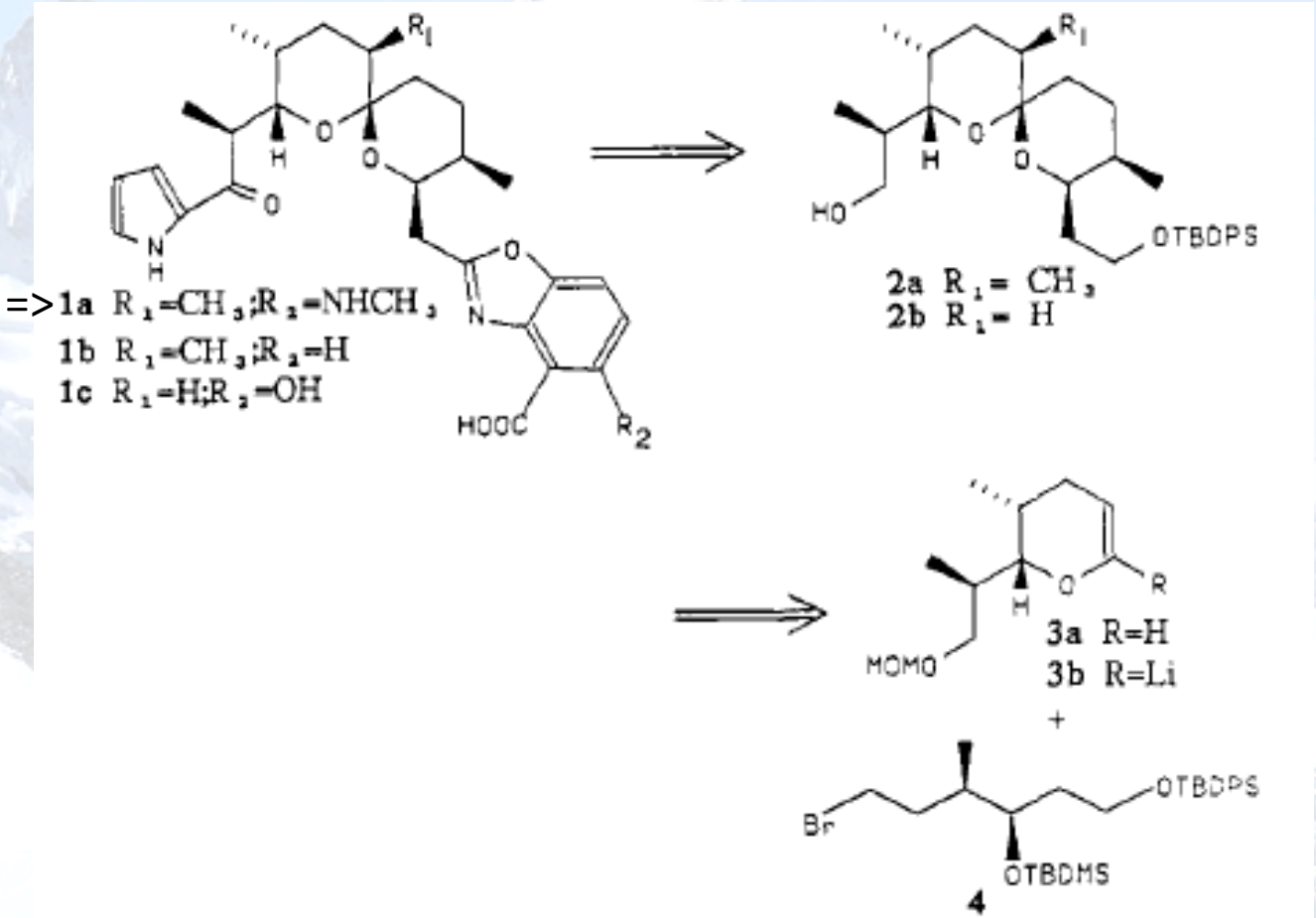
a) Isolated yields of chromatographically purified or distilled product.

b) Yield determined by NMR based upon recovered starting material.

R. K. Boeckman Jr., K. J. Bruza, *Tetrahedron Lett.* **1977**, 4187

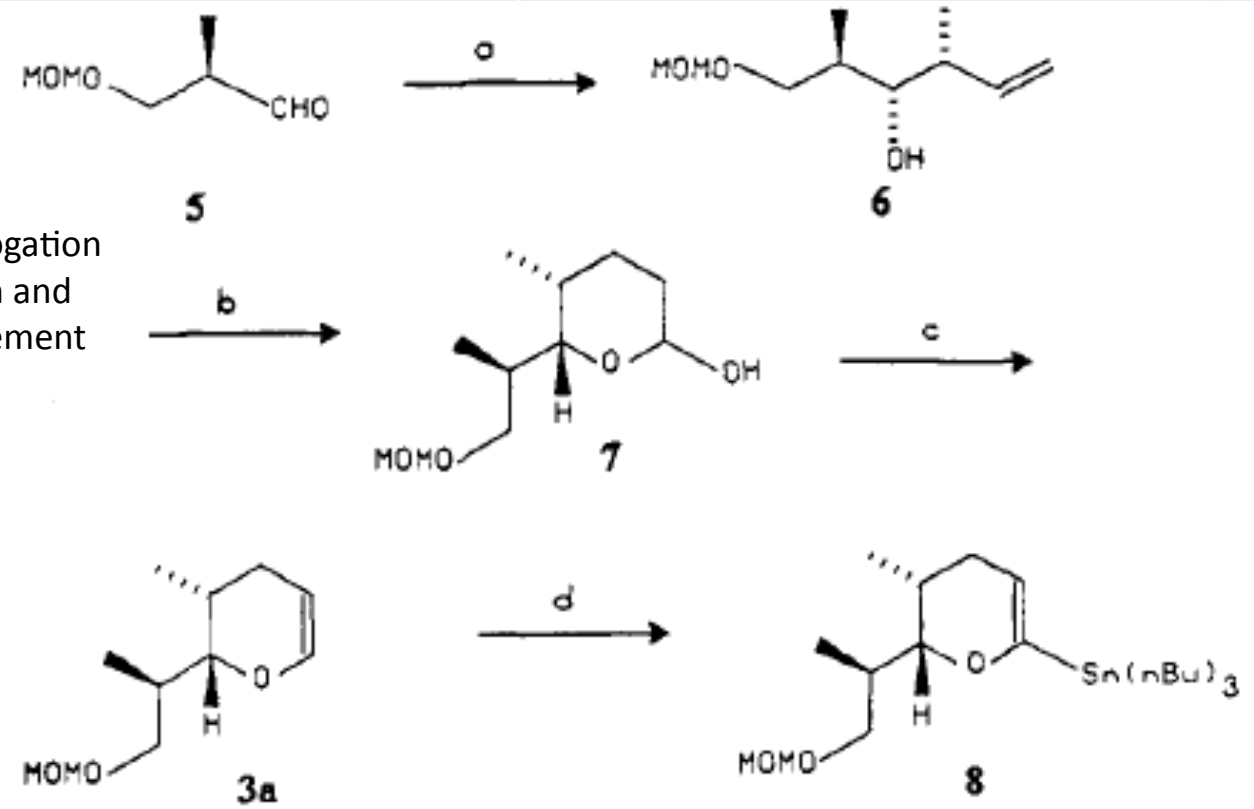
R. K. Boeckman Jr., K. J. Bruza, *Tetrahedron* **1981**, 3997.

Application: Synthesis of (-)-A-23187 (Calcimycin)



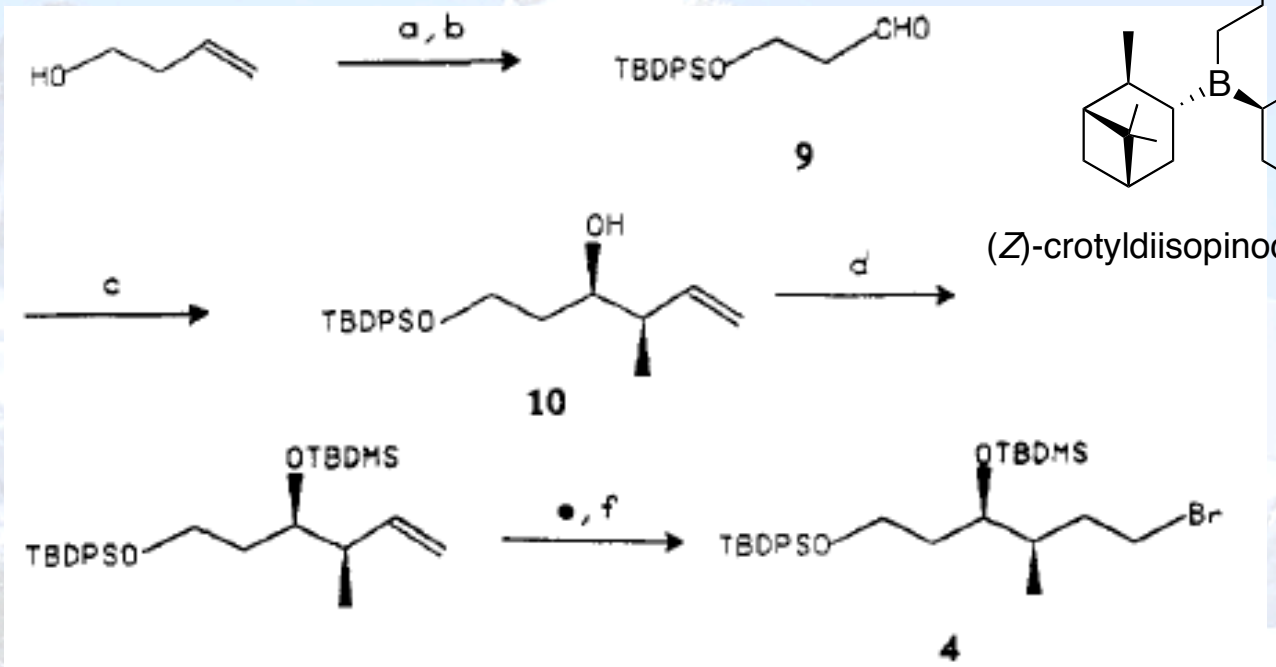
R. K. Boeckman Jr., A. B. Charette, T. Asberom, B. H. Johnston, *J. Am. Chem. Soc.* **1987**, 7553
R. K. Boeckman Jr., A. B. Charette, T. Asberom, B. H. Johnston, *J. Am. Chem. Soc.* **1991**, 5337

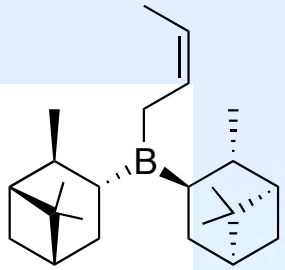
one carbon homologation via hydroboration and addition rearrangement



[a] Reagents: (a) crotyltributylstannane (1.4 equiv), $MgBr_2$–Et_2O (2 equiv), CH_2Cl_2, −23 °C, 3 h; (b) BH_3–THF (1 equiv), THF, room temperature, 12 h, then successive addition of CH_3OH (1 equiv), 0 °C → room temperature, 2 h, $LiCH(SPh)OCH_3$ (3 equiv) in THF, −40 °C → −10 °C, 2 h, $HgCl_2$ (3 equiv), −10 °C → room temperature, 3 h, and H_2O_2 (12 equiv), pH 7, room temperature, 3 h; (c) MsCl (1.5 equiv), Et_3N (3 equiv), CH_2Cl_2, 14 h; (d) KO-*t*-Bu (3 equiv), *n*-BuLi (3 equiv), THF, −78 °C, 1 h then Bu_3SnCl (3.2 equiv), −78 °C → room temperature, 45 min.

R. K. Boeckman Jr., A. B. Charette, T. Asberom, B. H. Johnston, *J. Am. Chem. Soc.* **1987**, 7553
R. K. Boeckman Jr., A. B. Charette, T. Asberom, B. H. Johnston, *J. Am. Chem. Soc.* **1991**, 5337

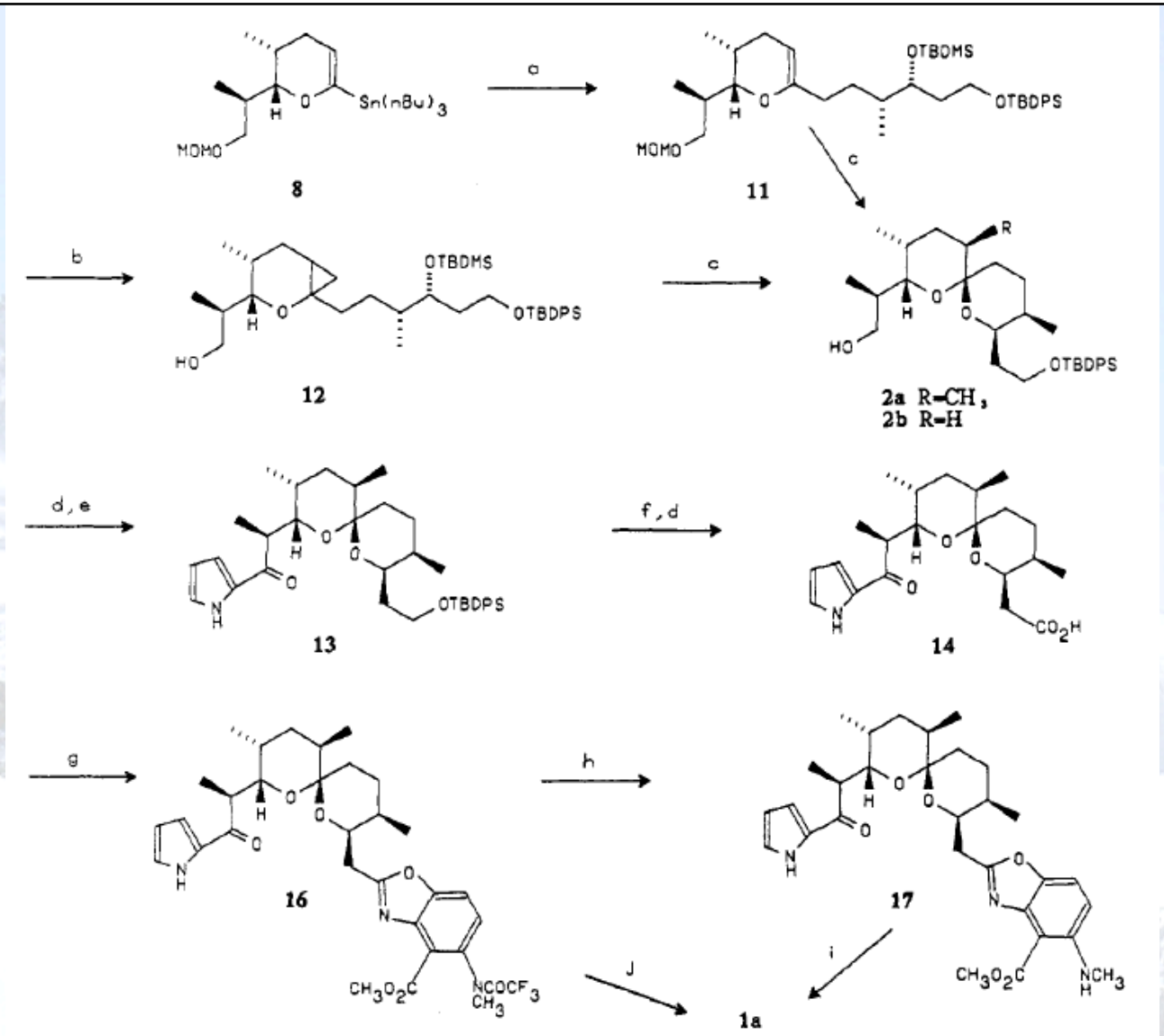


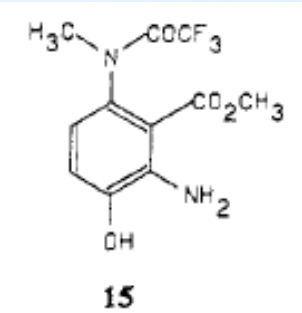


(*Z*)-crotyldiisopinocampheyl borane

[a] **Reagents:** (a) TBDPSCl (1.1 equiv), imidazole (2 equiv), DMF, room temperature, 6 h; (b) O_3, CH_2Cl_2–CH_3OH (7:3), –78 °C; DMS, –78 °C to room temperature, 6 h; (c) (*Z*)-crotyldiisopinocampheylborane (1 equiv), THF, –78 °C, 5 h; H_2O_2, NaOH; (d) TBDMSOTf (1.3 equiv), Et_3N (3 equiv), CH_2Cl_2, room temperature, 1 h; (e) $B-H_3$–THF (1.5 equiv); H_2O_2, NaOH; (f) Ph_3P (2 equiv), CBr_4 (2 equiv), Et_2O, room temperature, 6 h.

R. K. Boeckman Jr., A. B. Charette, T. Asberom, B. H. Johnston, *J. Am. Chem. Soc.* **1987**, 7553
R. K. Boeckman Jr., A. B. Charette, T. Asberom, B. H. Johnston, *J. Am. Chem. Soc.* **1991**, 5337





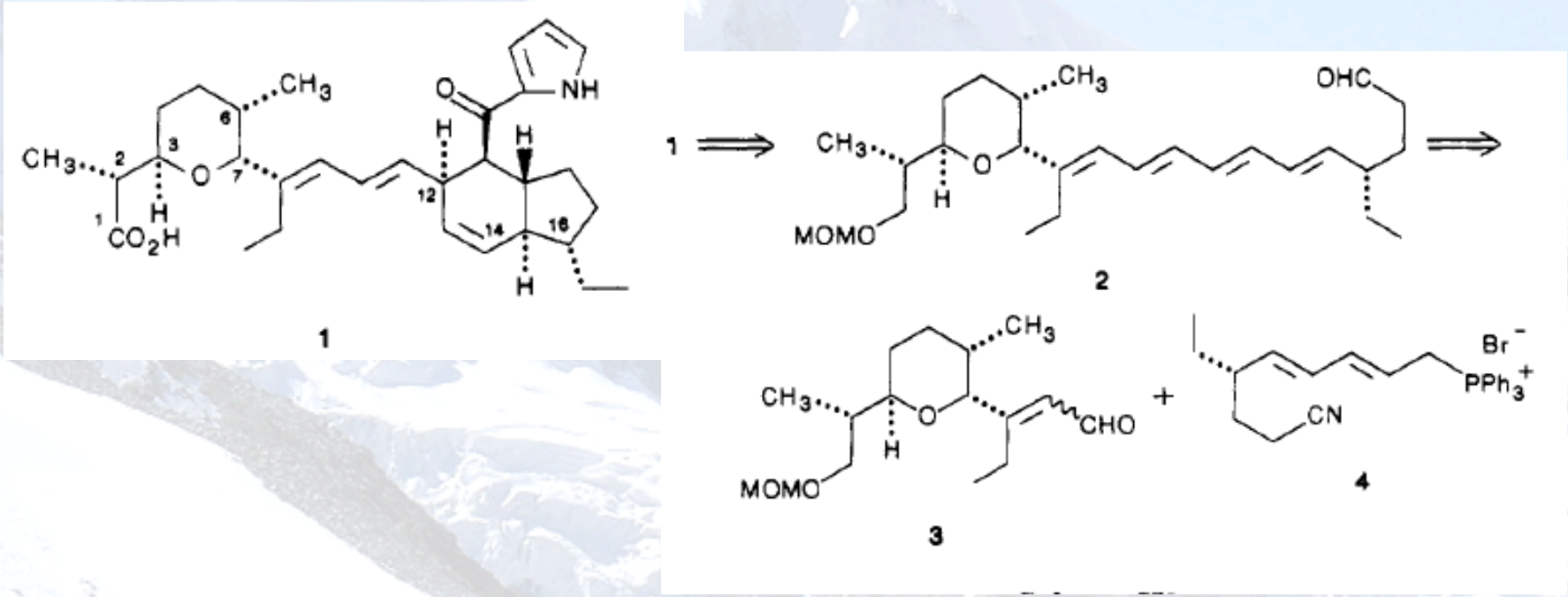
15

[a] Reagents: (a) *n*-BuLi (1.1 equiv), THF, −78 °C → 0 °C, 20 min; **4** (1.5 equiv), THF–HMPA, 0 °C → room temperature 16 h; (b) Et_2Zn (5 equiv, 1.0 M in hexanes), CH_2I_2 (10 equiv), ether, room temperature 5 h; (c) *p*-TsOH-H_2O (2 equiv), benzene, 55 °C, 5 h (3 h for **11**); (d) CrO_3, H_2SO_4, acetone, −20 °C → −5 °C, 1 h; (e) Ph_3P (4 equiv), 2,2′-dipyridyldisulfide (4 equiv), CH_2Cl_2, room temperature 16 h; pyrrole magnesium chloride (18 equiv), toluene, −78 °C, 295 h; (f) TBAF (2 equiv), THF, room temperature 2 h; (g) BOP (1 equiv), Et_3N (5 equiv), **15** (1 equiv), DMF, 65 °C, 18 h; PPTS (3 equiv), $ClCH_2CH_2Cl$, 4 A sieves, 80 °C, 24 h; (h) TBAF (2 equiv), THF, room temperature 3 h; (i) LiSPr (3 equiv), HMPA, room temperature 1 h; (j) LiSPr (10 equiv), HMPA, room temperature 3.5 h.

R. K. Boeckman Jr., A. B. Charette, T. Asberom, B. H. Johnston, *J. Am. Chem. Soc.* **1987**, 7553
R. K. Boeckman Jr., A. B. Charette, T. Asberom, B. H. Johnston, *J. Am. Chem. Soc.* **1991**, 5337

Application: Synthesis of (-)-X-14547A (Indamycin)

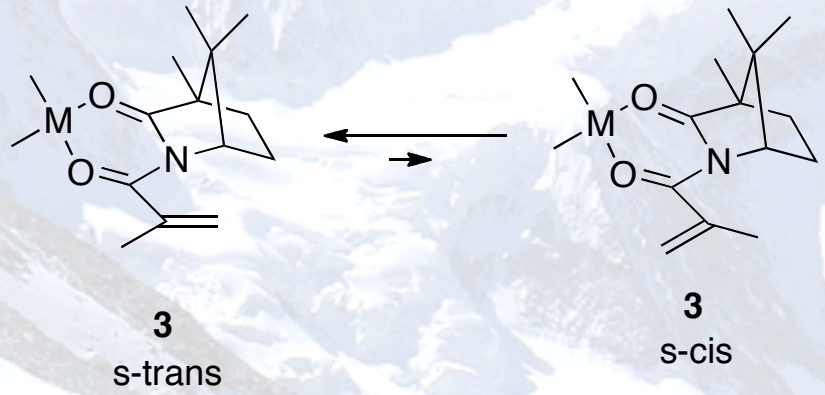
intramolecular [4+2] cycloaddition



R. K. Boeckman Jr., E. J. Enholm, D. M. Demko, A. B. Charette, *J. Org. Chem.* **1986**, 4743.

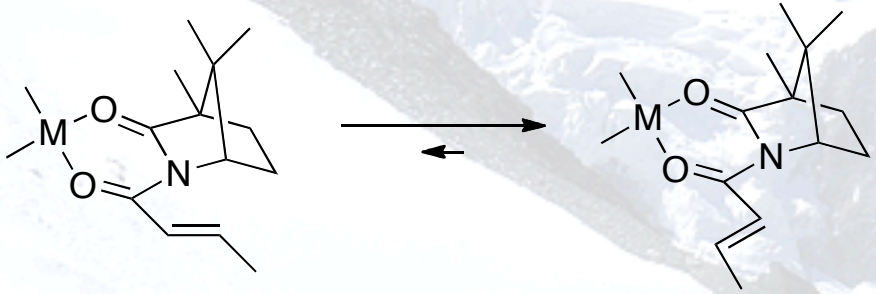
camphor-derived lacatams: chiral auxiliary in Diels-Alder cycloadditions

dienophiles



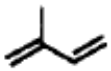
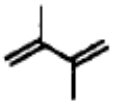
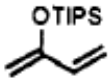
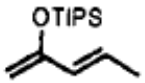
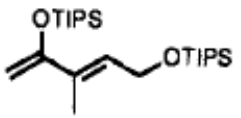
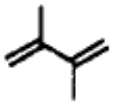
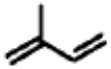
3
s-trans

3
s-cis



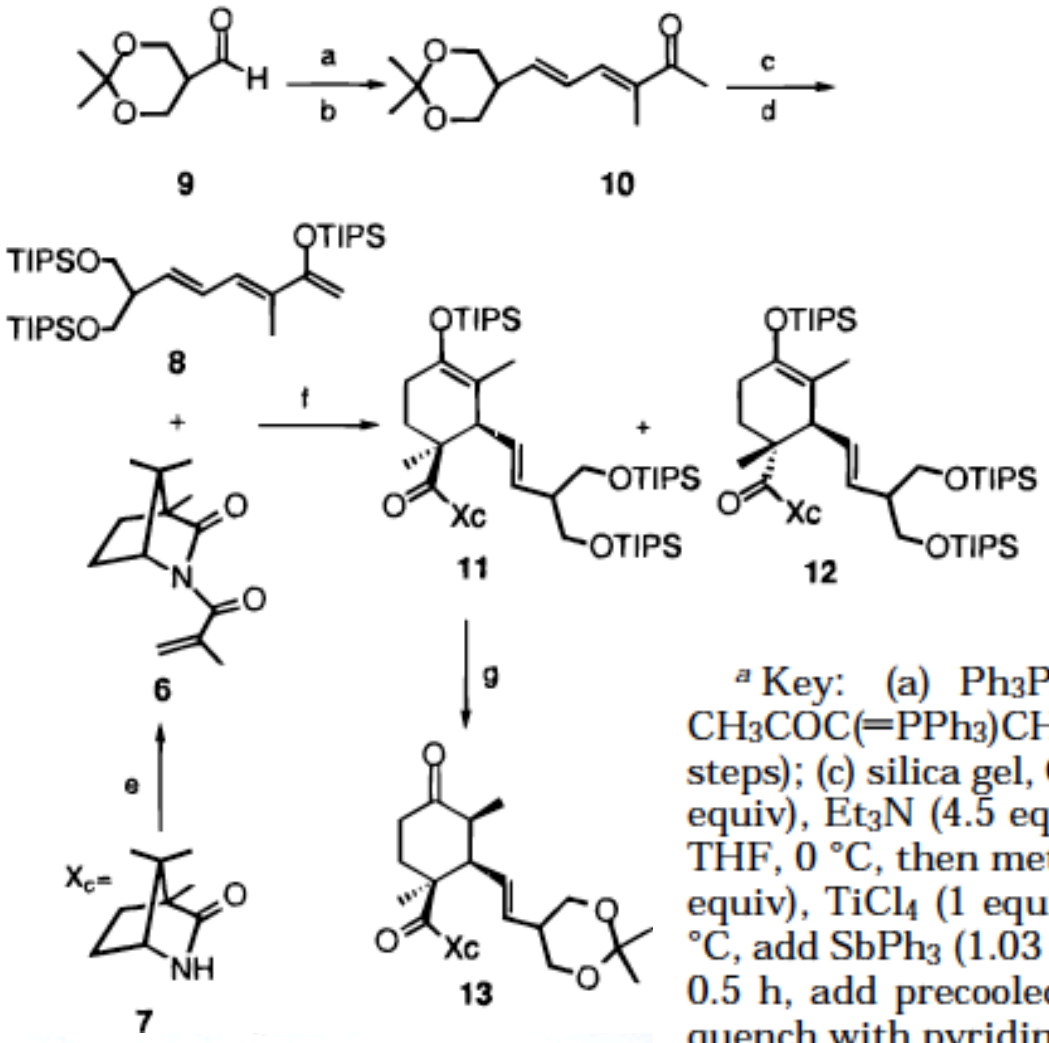
4
s-trans

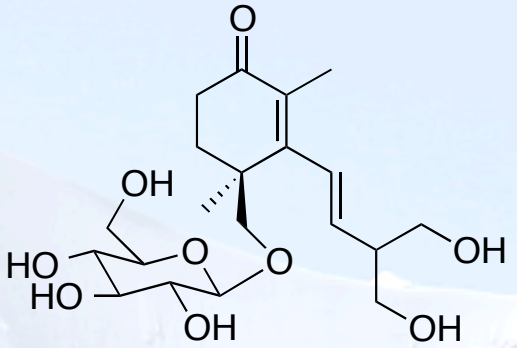
4
s-cis

dienophile	diene	π-facial selectivity	endo/exo	yield (%)
3		91:9[d]	90:10	93
3		85:15[e]		61
3		90:10		79
3		95:5		82
3		90:10	67:33	63
3		57:43[f]		89
3		50:50[f]	87:13	91
3[g]		88:12[h–j]	>98:2	95
4		95:5		82
4		~95:5	92:8	97
4		96:4		83

R. K. Boeckman Jr., S. G. Nelson, M. D. Gaul, *J. Am. Chem. Soc.* **1992**, 2258.

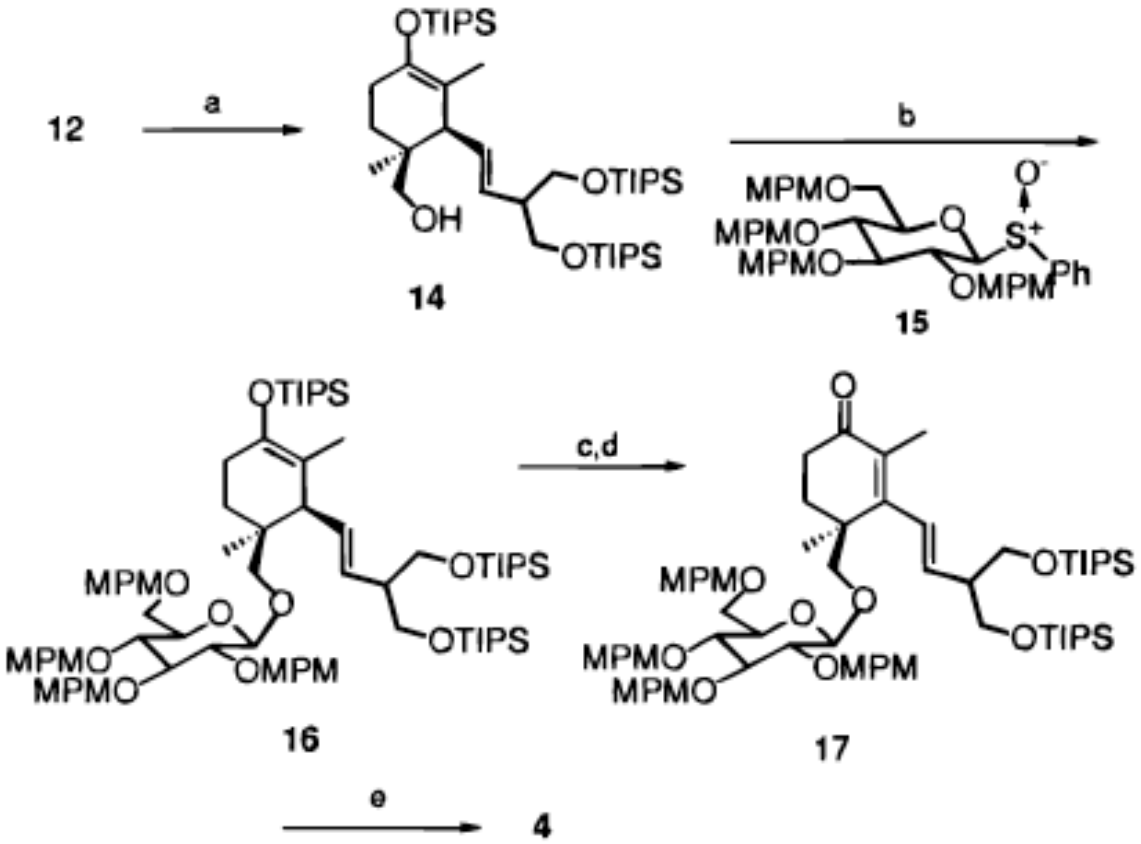
Application: Synthesis of (-)-Cassioside





[a] Key: (a) $Ph_3P{=}CHCHO$ (1 equiv), benzene, reflux; (b) $CH_3COC(=PPh_3)CH_3$ (0.76 equiv), benzene, reflux (60%, two steps); (c) silica gel, CH_2Cl_2/H_2O (9:1), rt (>99%); (d) TIPSOTf (3.2 equiv), Et_3N (4.5 equiv), CH_2Cl_2, rt (100%); (e) *n*-BuLi (1 equiv), THF, 0 °C, then methacryloyl chloride (1.1 equiv), rt, 2 h; (f) **6** (1 equiv), $TiCl_4$ (1 equiv), CH_2Cl_2, −20 °C, 0.25 h then cool to −78 °C, add $SbPh_3$ (1.03 equiv) and $(CH_3)_3Al$ in hexanes (1 equiv), stir 0.5 h, add precooled (−78 °C) **8** (2 equiv) in CH_2Cl_2, stir 48 h; quench with pyridine (89%); (g) **11** (1 equiv), TBAF (xs)/THF/−78 °C, 12 h, then $(CH_3)_2C(OCH_3)_2$ (xs)/H_2SO_4 (catalytic), acetone, rt, 18 h.

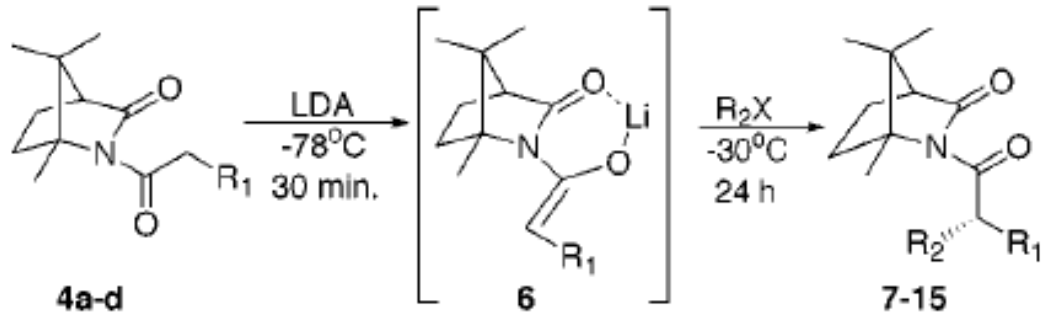
R. K. Boeckman Jr., Y. Liu, *J. Org. Chem.* **1996**, 7984



[a] Key: (a) $LiBH_4$ (xs), THF, rt, 48 h (72%); (b) Tf_2O (1.8 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (5.9 equiv), molecular sieves (4 Å), **15** (2.0 equiv), CH_2Cl_2, −90 °C (50%); (c) $Pd(OAc)_2$ (1.2 equiv), AgOTf (1.2 equiv), I_2 (1.0 equiv), **16** (1.0 equiv), CH_3CN−CH_2Cl_2 (1:9), rt; (d) Et_3N (xs), NaI (xs), acetone, rt (60% over two steps); (e) CAN (9.2 equiv), CH_3CN−H_2O (1:9) (80%).

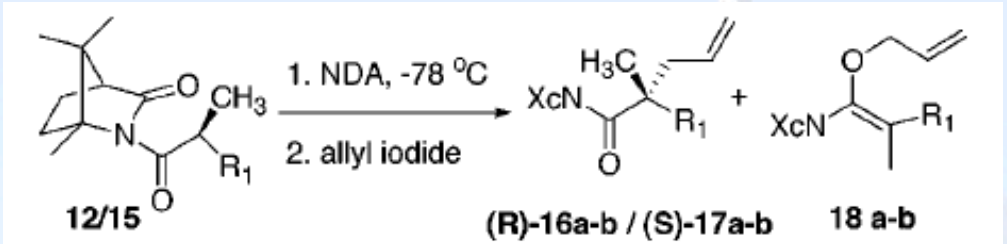
R. K. Boeckman Jr., Y. Liu, *J. Org. Chem.* **1996**, 7984

camphor-derived lacatams: chiral auxiliary in aldol reactions



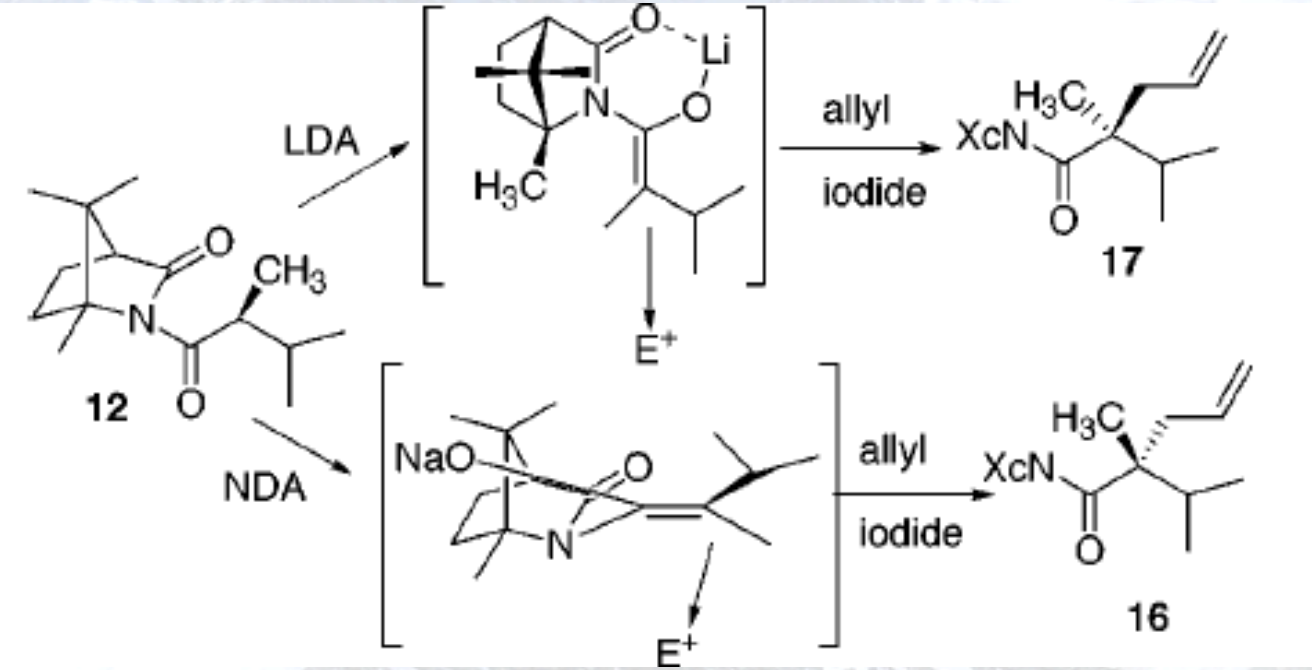
4 R_1	R_2X	dr[a]	yield (%)	product
a CH_3	$CH_2{=}CHCH_2Br$	49:1	90	**7**
a CH_3	$PhCH_2Br$	99:1	89[b]	**8**
a CH_3	$PMBOCH_2CH{=}CHCH_2I$	99:1	70	**9**
a CH_3	tBuCH=CHCH=$CHCH_2I$	99:1	85	**10**
b C_2H_5	CH_3I	99:1	50	**11**
c iC_3H_7	CH_3I	49:1	92[c]	**12**
d allyl	CH_3I	49:1	73[c]	**13**
a CH_3	PhCOCl	20:1	82	**14**
b C_2H_5	C_2H_5COCl	50:1	68[d,e]	**15**

R. K. Boeckman Jr., D. J. Boehmler, R. A. Musselman, *Org. Lett*. **2001**, 3777



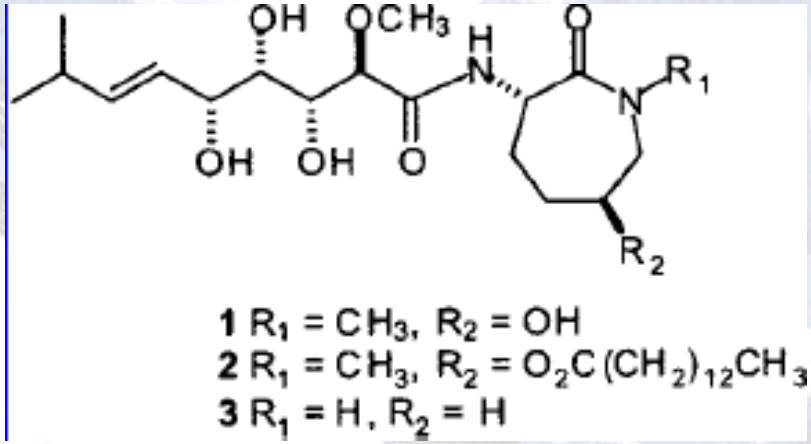
R_1	temp[a] (°C)	yield (conv) 16 + 17 (%)	16a,b:17a,b[b,c]	18 (%)
12 iPr	0	36 (65)	13.7:1	0
12 iPr	−30	60 (76)	20.5:1	10
15 C(O)Et	−40	67 (100)	99:1	0

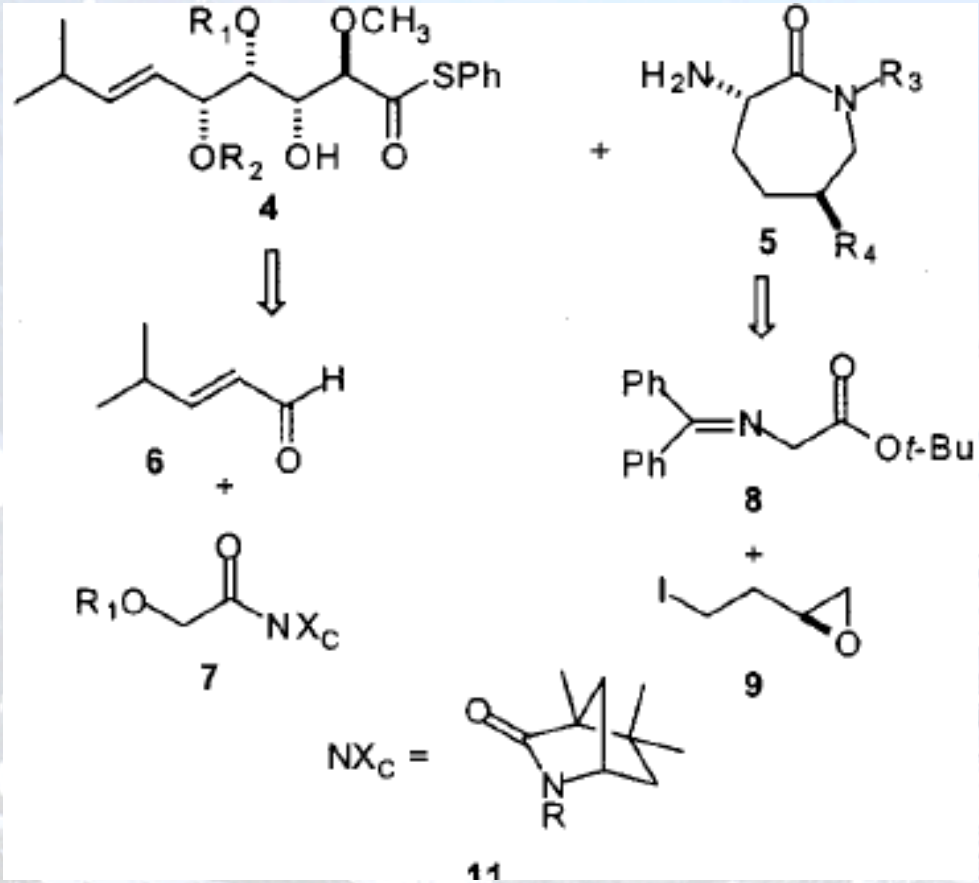
LDA gave low yields and poor dr selectivity => NDA



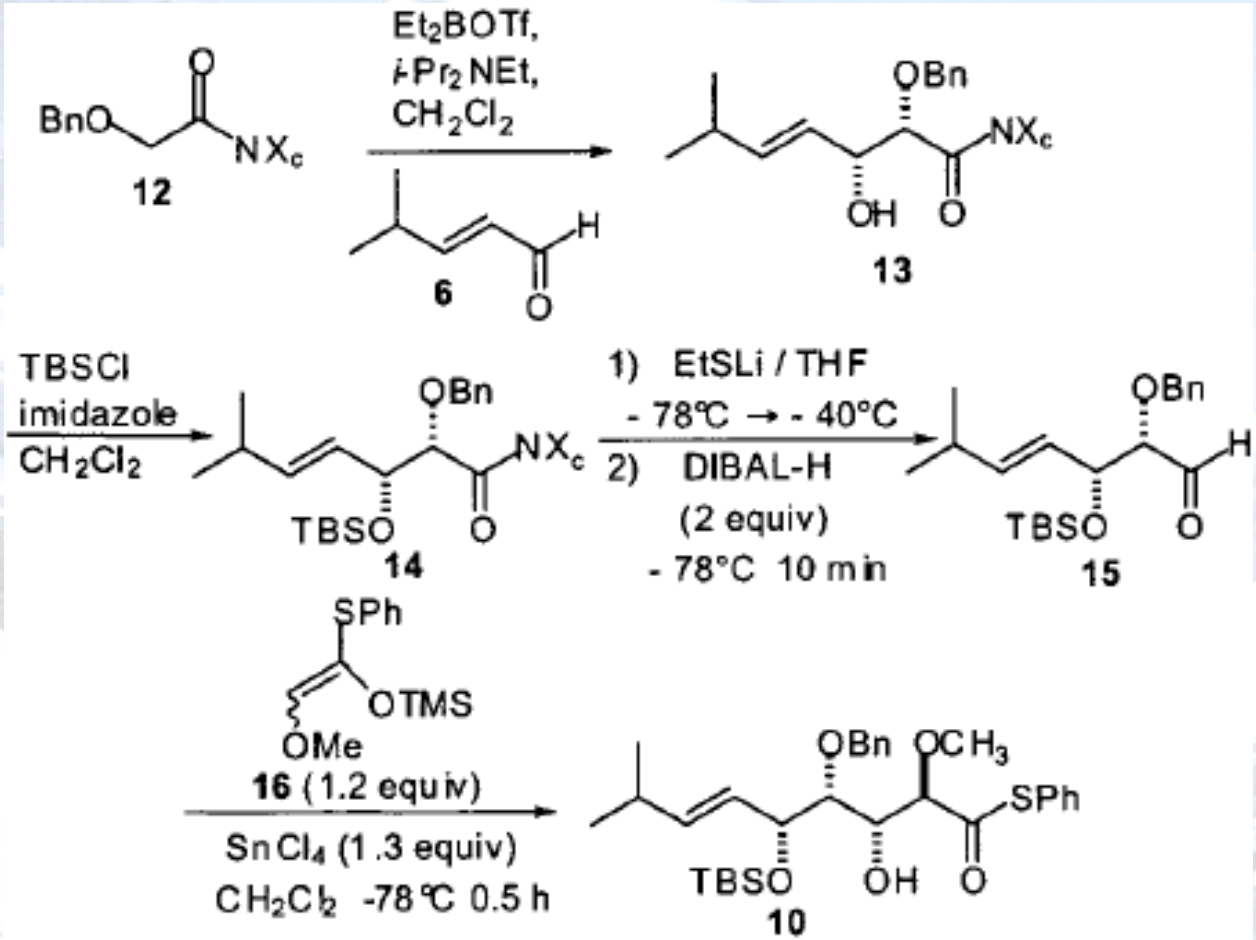
R. K. Boeckman Jr., D. J. Boehmler, R. A. Musselman, *Org. Lett*. **2001**, 3777

Application: Synthesis of Bengamides B, E and Z

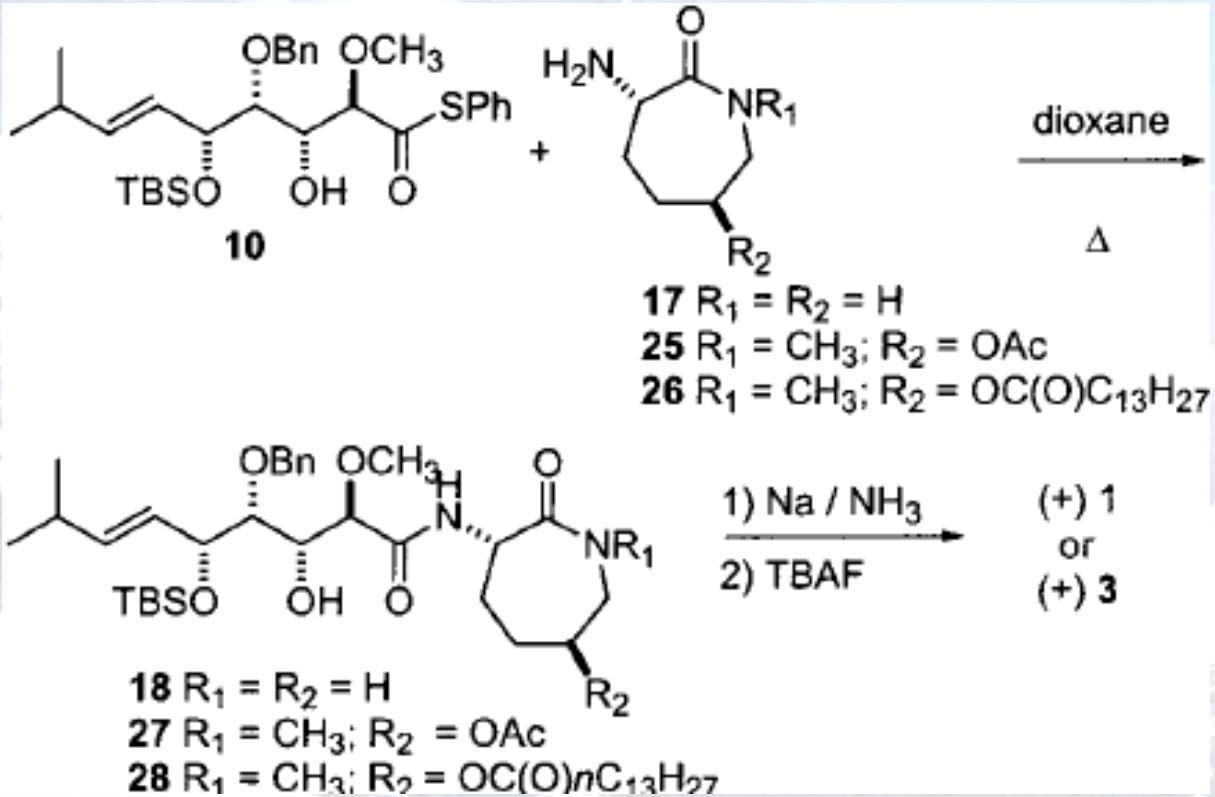




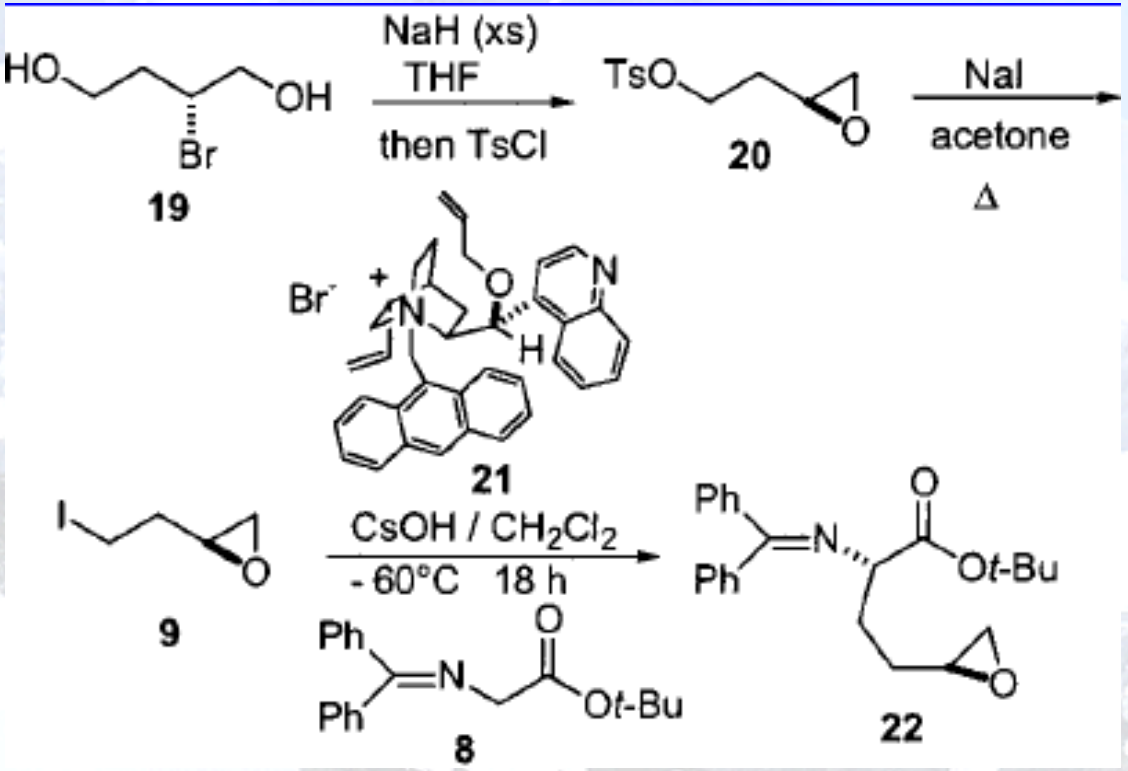
R. K. Boeckman Jr., T. J. Clark, B. C. Shook, *Org. Lett.* **2002**, 2109.



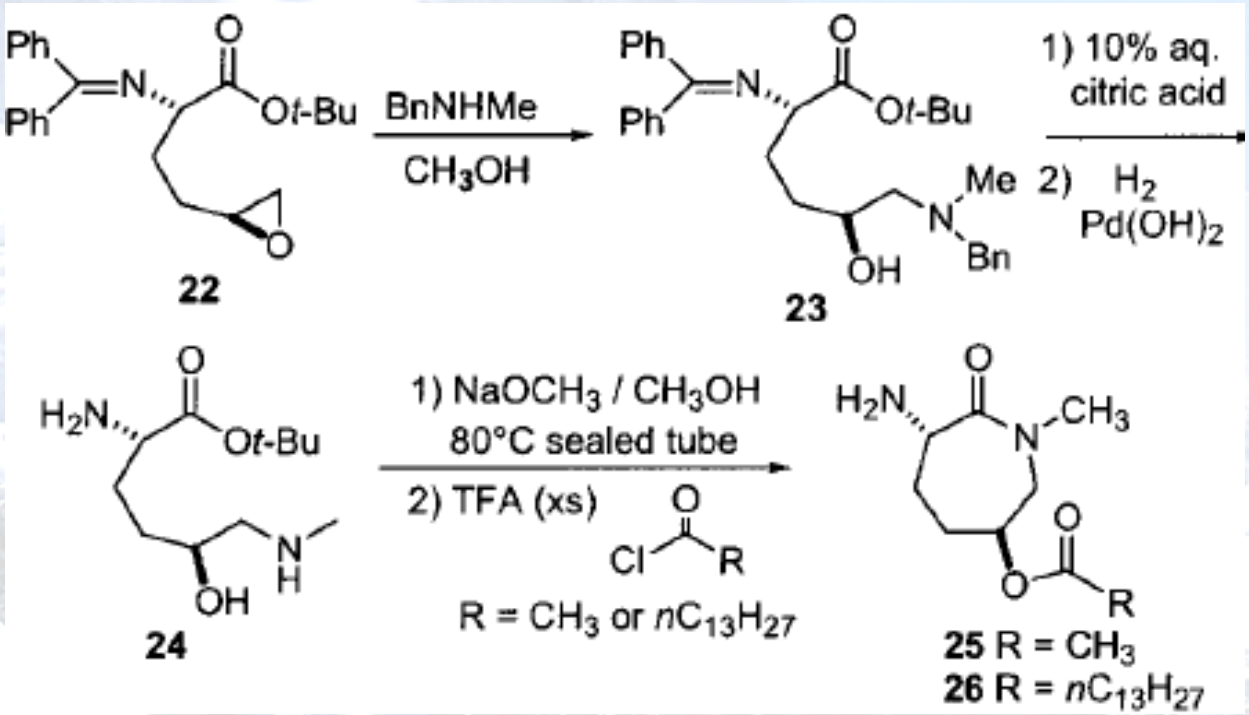
R. K. Boeckman Jr., T. J. Clark, B. C. Shook, *Org. Lett.* **2002**, 2109.



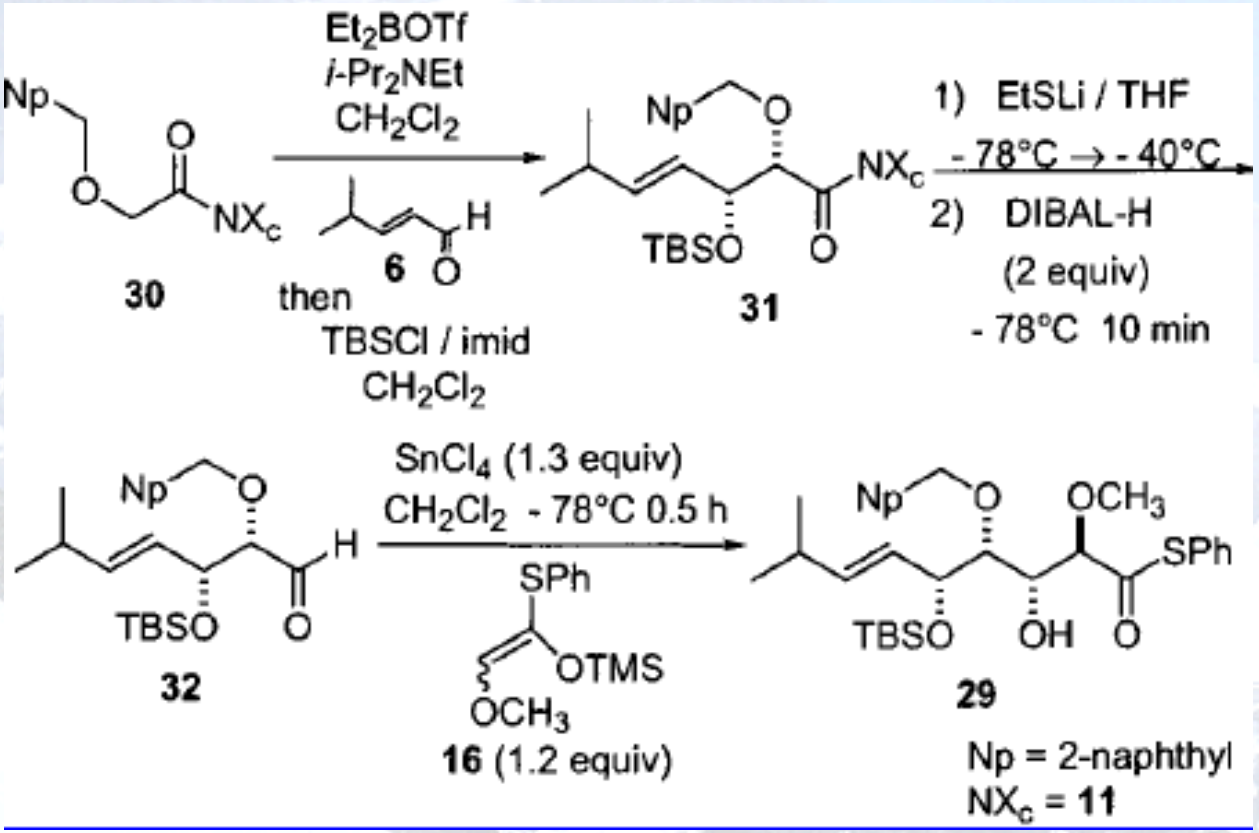
R. K. Boeckman Jr., T. J. Clark, B. C. Shook, *Org. Lett.* **2002**, 2109.



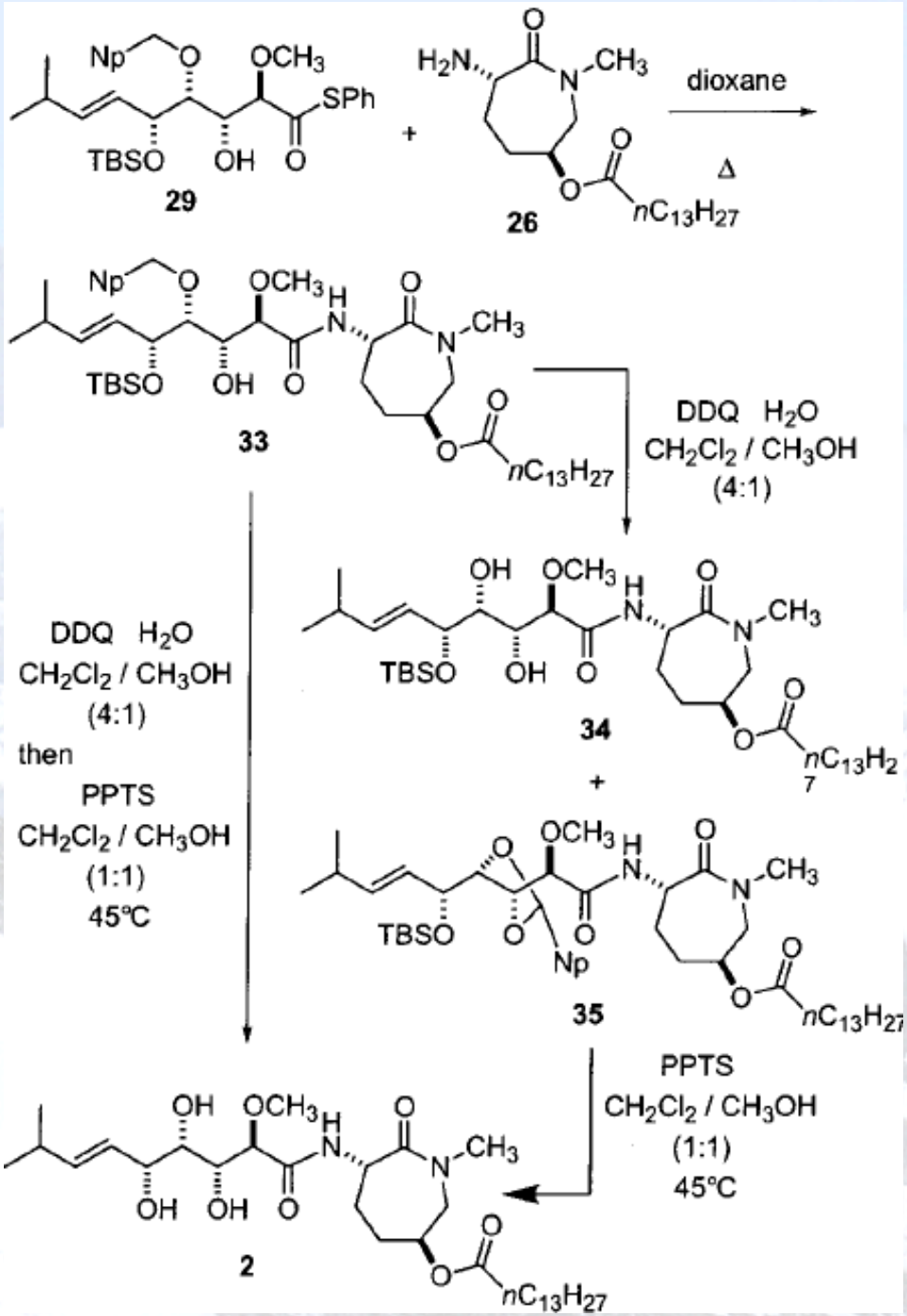
R. K. Boeckman Jr., T. J. Clark, B. C. Shook, *Org. Lett.* **2002**, 2109.



R. K. Boeckman Jr., T. J. Clark, B. C. Shook, *Org. Lett.* **2002**, 2109.

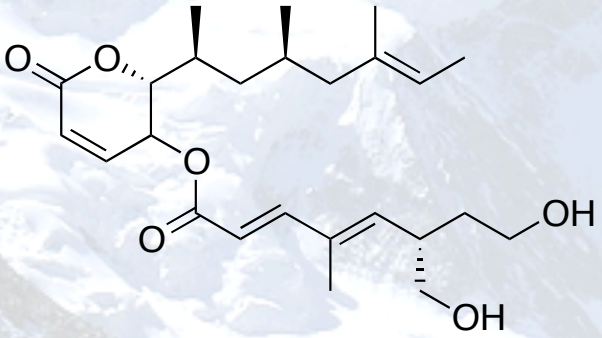


R. K. Boeckman Jr., T. J. Clark, B. C. Shook, *Org. Lett.* **2002**, 2109.



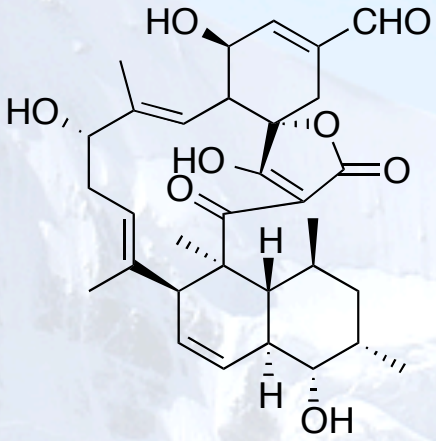
R. K. Boeckman Jr., T. J. Clark, B. C. Shook, *Org. Lett.* **2002**, 2109.

Application: Synthesis of (-)-Rasfonin and (+)-Tetronolide



(-)-Rasfonin

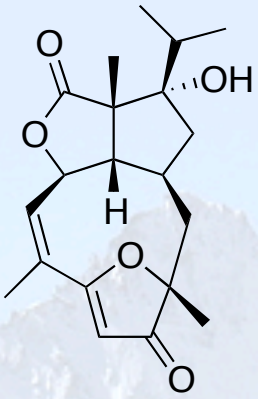
R. K. Boecklman Jr., J. E. Pero, D. J. Beohmler, *J. Am. Chem. Soc.*, **2006**, 11032



(+)-Tetranolide

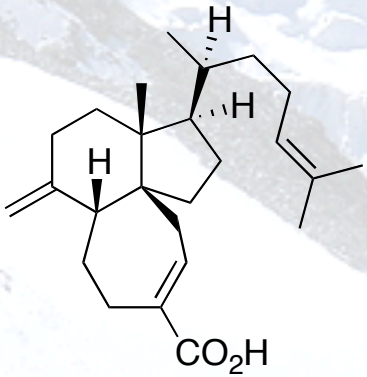
R. K. Boeckman, P. Shao, S. T. Wrobleski, D. J. Boehmler, G. R. Heintzelman, A. J. Barbosa, *J. Am. Chem. Soc.* **2006**, 10572

Other Syntheses



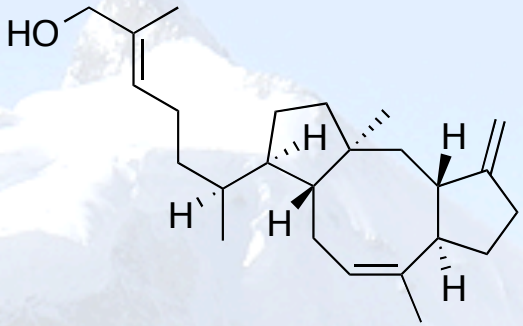
(+)-Erenmantholide A
Ramberg-Bäcklund Rearrangement

R. K. Boeckman Jr., S. K. Yoon, D. K. Heckendorn, *J. Am. Chem. Soc.* **1991**, 9682.



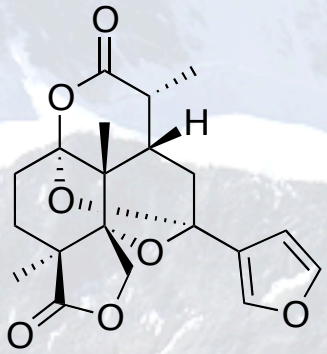
Gascardic Acid

R. K. Boeckman Jr., D. M. Blum, S. D. Arthur, *J. Am. Chem. Soc.* **1979**, 5060.



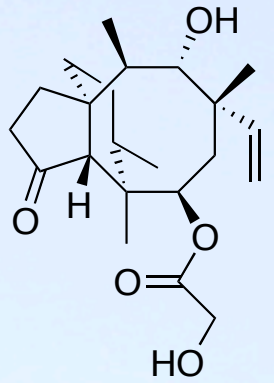
(±)-Ceroplastol I

R. K. Boeckman Jr., A. Arvanitis, M. E. Voss, *J. Am. Chem. Soc.* **1989**, 2737.



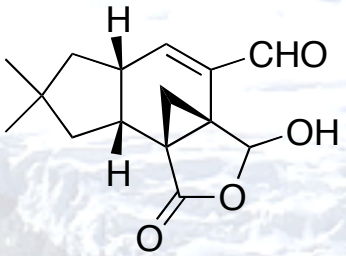
(+)- and (-)-Saudin

R. K. Boeckman Jr., M. d. R. Ferreira, L. H. Mitchell, P. Saho, *J. Am. Chem. Soc.* **2002**, 190.



(±)-Pleuromutilin
Oxy-Cope Rearrangement

R. K. Boeckman Jr., D. M. Springer, T. R. Alessi, *J. Am. Chem. Soc.* **1989**, 8284.



(±)-Marasmic Acid
Intramolecular Diels-Alder Cyclization

R. K. Boeckman Jr., S. S. Ko, *J. Am. Chem. Soc.* **1980**, 7149.


END