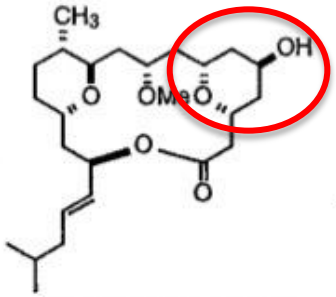
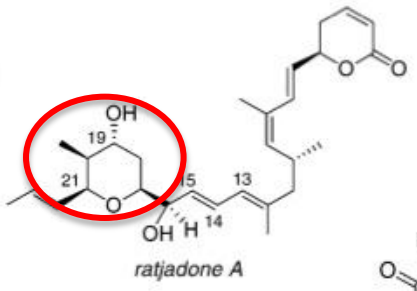
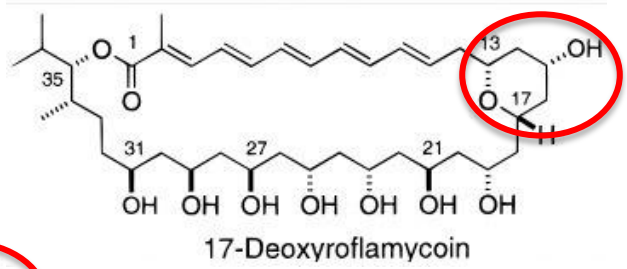
Prins reactions and Applications



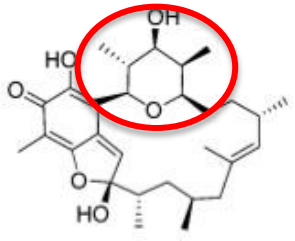
Leucascandrolide A
macrolide



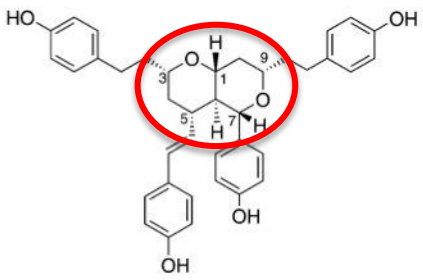
ratjadone A



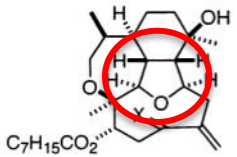
17-Deoxyroflamycoin



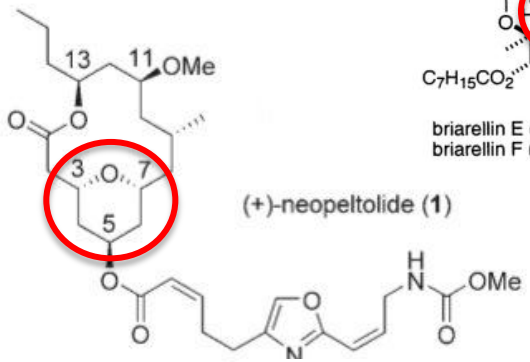
kendomycin



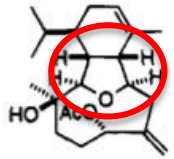
blepharocalyxin D.



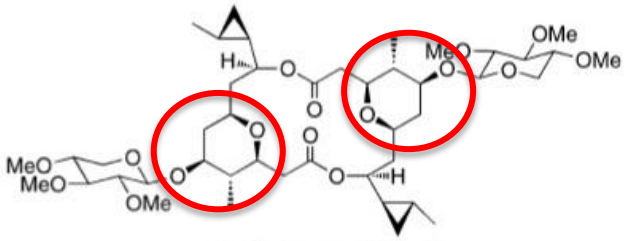
briarellin E (**4**): X = α-OH, β-H
briarellin F (**5**): X = O



(+)-neopeltolide (**1**)



(−)-7-deacetoxyalcyonin acetate (**2**)



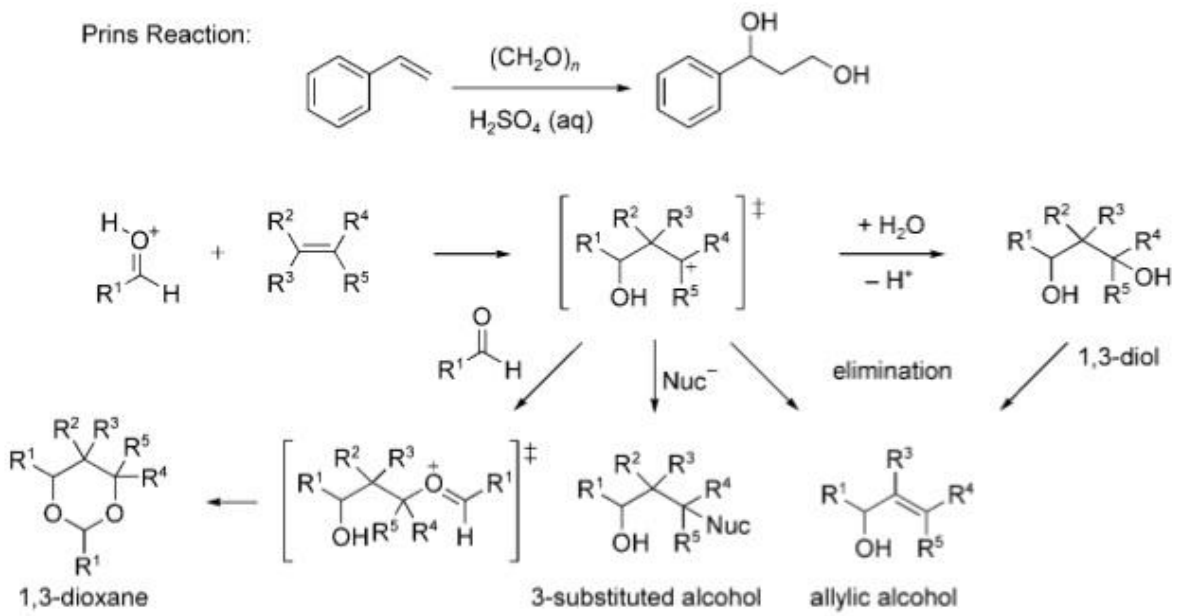
(−)-clavosolide A.

2012. 11.28
Haye Min Ko

Contents

1. Background

Another internationally well-known Delft student, with almost the same Christian names as Van ‘t Hoff, was Hendrik Jacobus Prins, who discovered two new organic reactions, both nowadays carrying the name Prins reaction. The first one, the addition of polyhalogen compounds to olefins, was found during the doctoral research (1911-1912) of Prins, the second one, on the acid-catalyzed addition of aldehydes to olefinic compounds, became of much industrial relevance. New examples of this Prins reaction are still regularly reported.

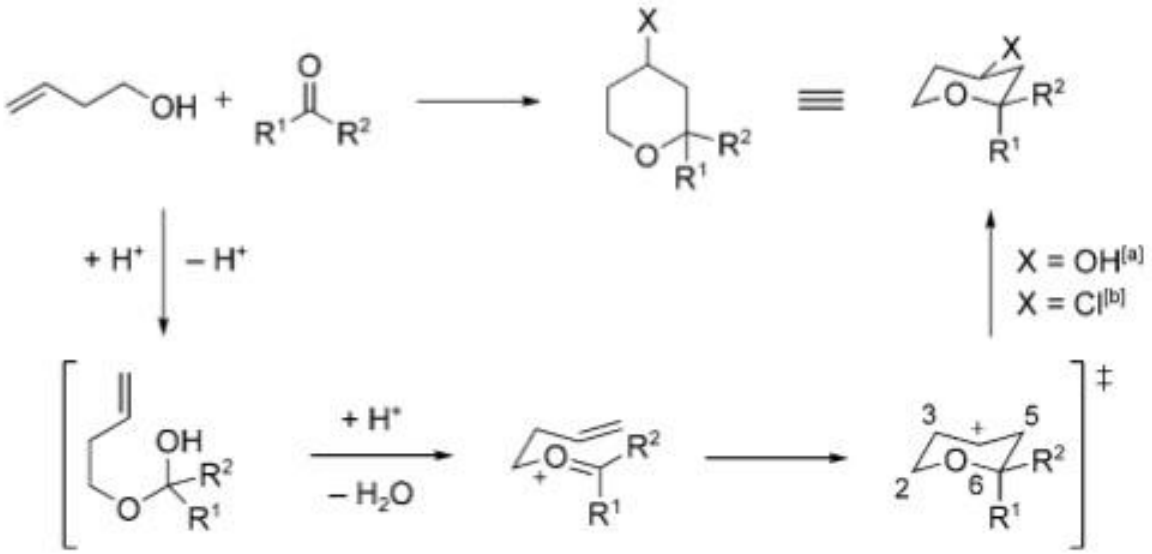


. The Prins reaction mechanism and possible reaction pathways. Nuc = nucleophile.

P. C. Bloys van Treslong Prins, *Chem. Weekbl*. **1919**, 1510.
P. C. Bloys van Treslong Prins, *Chem. Weekbl*. **1919**, 1072.

Synthesis of Tetrahydropyran Rings

In 1955, Hanschke was the first to report the selective synthesis of tetrahydropyran (THP) rings through a Prins reaction by combining 3-buten-1-ol with a variety of aldehydes or ketones in the presence of acid

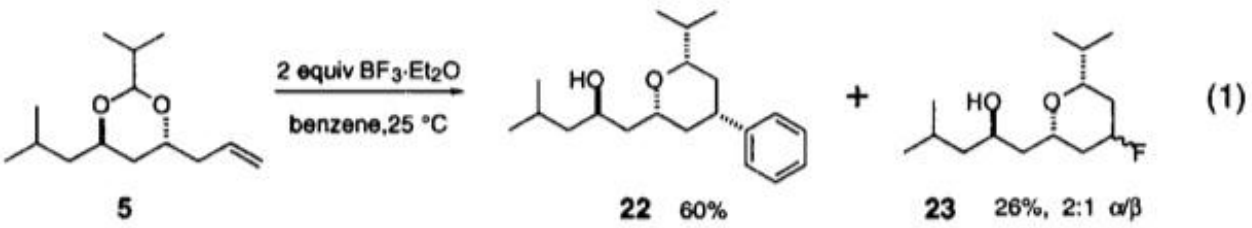


Scheme 3. The first report and mechanism of the synthesis of THP rings by the Prins reaction. [a] When H_2SO_4 was used. [b] When HCl was used.

E. Hanschke, *Chem. Ber*. **1955**, *88*, 1053 – 1061.

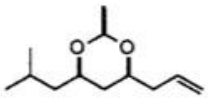
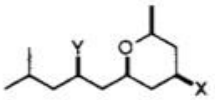
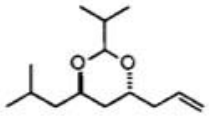
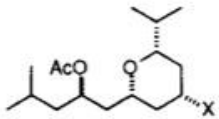
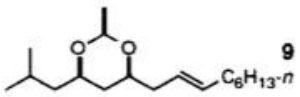
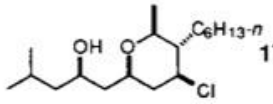
2. The Prins Reaction

Cyclization of acetals



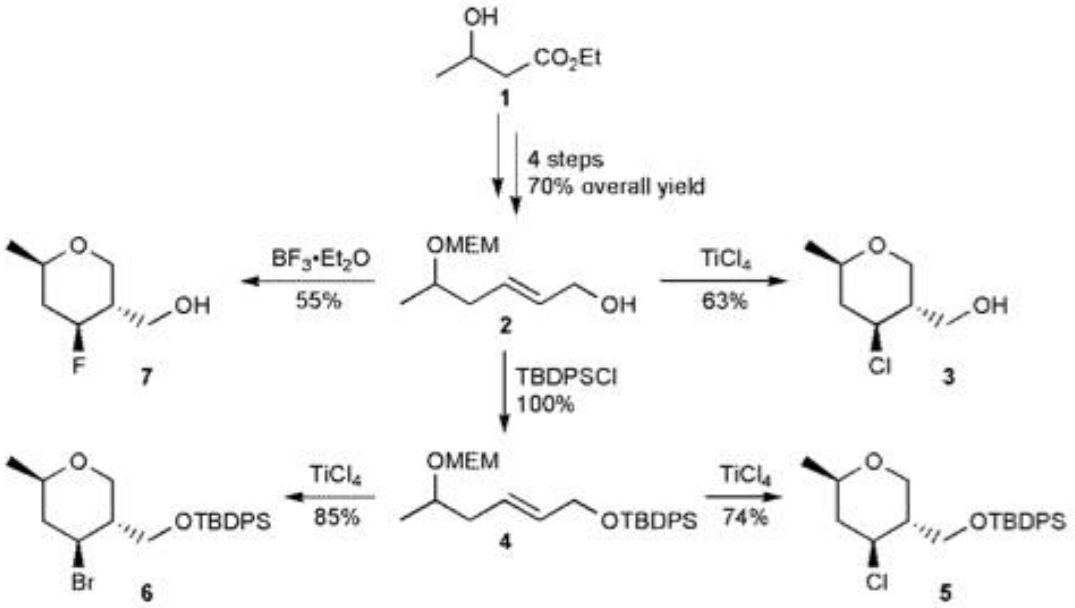
5 **22** 60% + **23** 26%, 2:1 α/β (1)

Table 1. Prins Cyclization of 4-Allyl-1,3-Dioxanes Promoted by Lewis Acids.

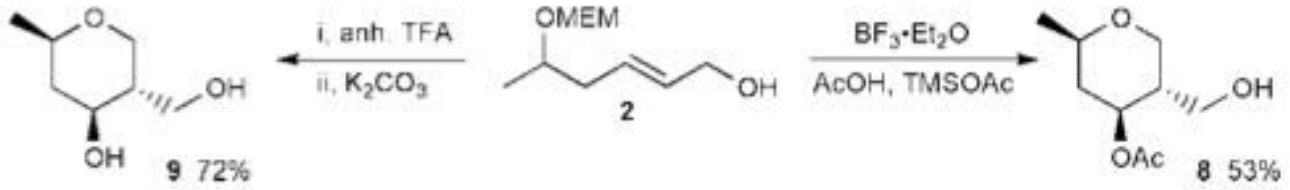
Entry #	SM		Conditions[a]	Yield	Product		Selectivity[b]
1		**7**	A	81% (X = Cl, Y = OH)		**15**	93:7
2			B	86% (X, Y = OAc)			91:7:2
3		**5**	C	84% (X = OAc)		**16**	94:6
4			D	54% (X = OAc) 33% (X = F)			
5		**9**	A	71%		**17**	98:2

(a) Conditions. **A**: 2 equiv. $TiCl_4$, CH_2Cl_2, -78 °C, 2 h. **B**: i. 4 equiv. $BF_3{\cdot}OEt_2$, 10equiv. HOAc, cyclohexane, 25 °C; ii. Ac_2O, Et_3N, DMAP. **C**: i. 4 equiv. $BF_3{\cdot}OEt_2$, 10 equiv. HOAc, 2 equiv. TMSOAc, cyclohexane, 25 °C; ii. Ac_2O, Et_3N, DMAP. **D**: i. 2 equiv. $BF_3{\cdot}2AcOH$, CH_2Cl_2, -10–0° C; ii. Ac_2O, Et_3N,DMAP. **E**: i. 10 equiv. $BF_3{\cdot}OEt_2$, 10 equiv. HOAc, cyclohexane, 25°C; ii. Ac_2O,Et_3N, DMAP. **F**: 2 equiv. $TiCl_4$, CH_2Cl_2, -98 °C, 2 h.
(b) The major isomer is shown andthe second isomer results from axialtrapping at the 4-position of the tetrahydropyran ring. The configurations of other minor isomers were not determined.

Cyclization of homoallylic acetals



Scheme 1

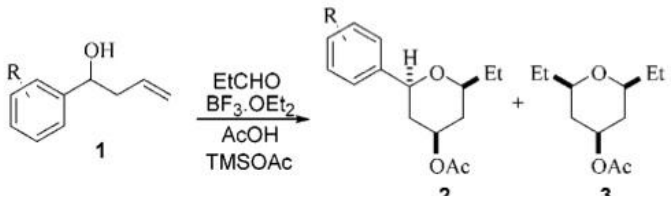


Scheme 2

Y. Hu, D. J. Skalitzky, S. D. Rychnovsky, *Tetrahedron Letters,* **1996**, *37(48)*, 8679-8682.

E. H. Al-Mutairi, S. R. Crosby, J. Darzi, J. R. Harding, R. A. Hughes, C. D. King, T. J. Simpson, R. W. Smith, C. L. Willis, *Chem. Commun*., **2001**, 835–836.

Cyclization of homoallylic alcohols



entry	R =	2 (%)	3 (%)	4 (%)	5 (%)	1 (%)
i	**1a**; 3,4-OCH_2O	20	21	26	17	
ii	**1b**; 4-OMe	15	21	21	18	
iii	**1c**; H	54	24		23	
iv	**1d**; 3-F	46	9		9	23
v	**1e**; 2-Cl	57				36
vi	**1f**; 4-NO_2[a]	36				43
vii	**1g**; 3,4,-diOAc	67				

[a] 7% of the 4-F analogue was isolated due to extended reaction time (16 h).

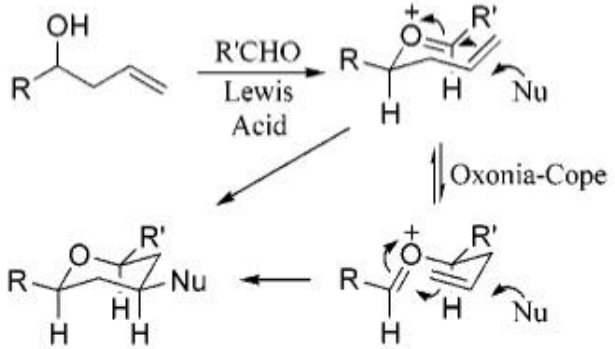
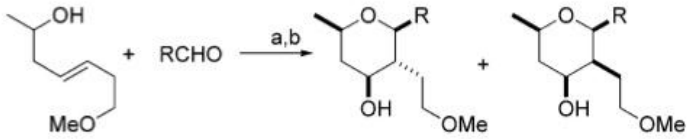


Figure 1. Oxonia-Cope rearrangement.

Table 1. Reaction of Homoallylic Alcohol **10** with a Range of Aldehydes[a]

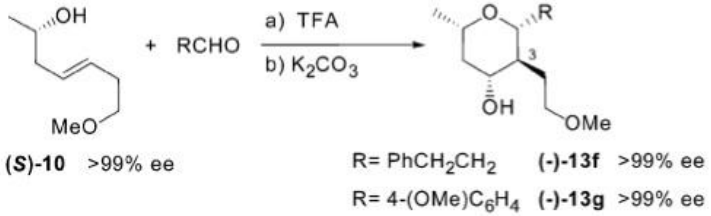


10 9 : 1 *E* : *Z* **13** **14** *ca.* 93 : 7

(a) TFA, CH_2Cl_2; (b) K_2CO_3, MeOH

entry		R	yields **13** + **14** (%)
i	**13a**	$H_2C{=}CHCH_2CH_2$	97
ii	**13b**	$CH_3CH{=}CH$	47
iii	**13c**	$H_2C{=}CH$	65
iv	**13d**	Ph	63
v	**13e**	2-BrC_6H_4	65
vi	**13f**	4-$(OMe)C_6H_4$	39[b]
vii	**13g**	$PhCH_2CH_2$	84
viii	**13h**		73

Scheme 6. Cyclization of Enantioenriched Homoallylic Alcohols



(*S*)-10 >99% ee

R= $PhCH_2CH_2$ **(-)-13f** >99% ee

R= 4-$(OMe)C_6H_4$ **(-)-13g** >99% ee

S. R. Crosby, J. R. Harding, C. D. King, G. D. Parker, C. L. Willis, *Org, Lett,* **2002**, *4*, 577-580.

C. St. J. Barry, S. R. Crosby, J. R. Harding, R. A. Hughes, C. D. King, G. D. Parker, C. L. Willis *Org, Lett,* **2003**, *5*, 2429-2432.

Axial-Selective Prins Cyclizations

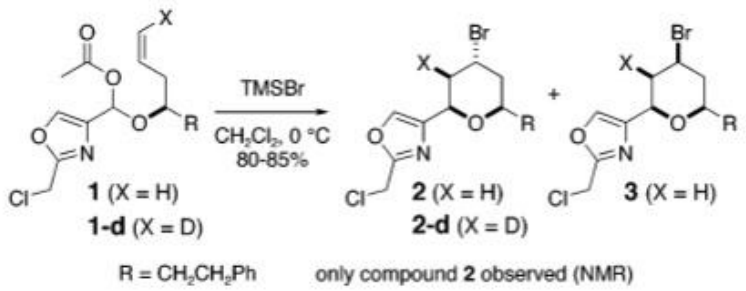
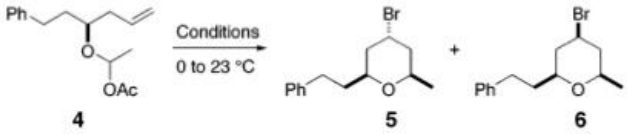


Table 1. Prins Cyclizations of α-Acetoxy Ether **4** Lead to Axial or Equatorial Products



entry[a]	Lewis acid	additive	solvent	yield **5** (%)	yield **6** (%)
1	$SnBr_4$	lutidine	CH_2Cl_2	9	79
2[c]	TMSBr	none	CH_2Cl_2	71	7
3[d]	TMSBr	lutidine	CH_2Cl_2	98	0
4	TMSBr	lutidine	hexanes	0	0
5[b]	HBr	none	CH_2Cl_2	60	27
6	AcBr	lutidine	CH_2Cl_2	96	0

[a] Reactions used 100 mg of **4**, 0.2 equiv of lutidine (when present), 2.5 equiv of Lewis acid in 2 mL of solvent, and were run at 0 °C (1 h) to 23 °C. Isolated yields are reported. [b] Excess HBr was used in the reaction. [c] GC analysis of the crude reaction mixture showed a 13:1 mixture of **5** and **6**. [d] GC analysis of the crude reaction mixture showed a 41:1 mixture of **5** and **6**.

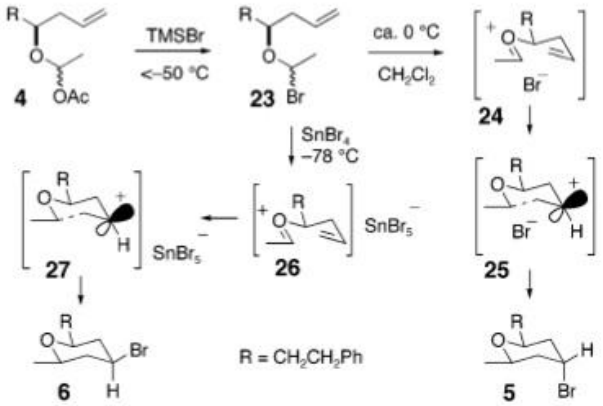
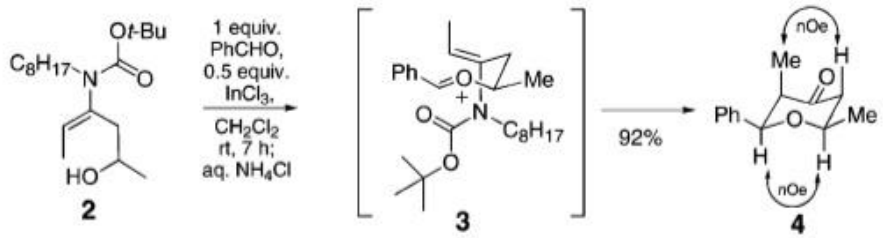


Figure 2. Mechanism for the formation of axial bromide **5** with TMSBr and the equatorial bromide **6** with $SnBr_4$ catalysis.

R. Jasti, J. Vitale, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2004**, *126*, 9904-9905.

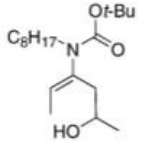
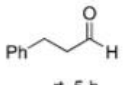
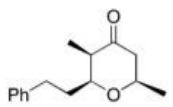
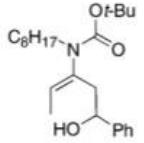
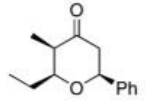
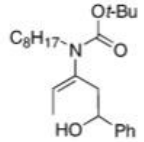
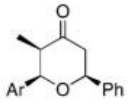
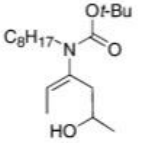
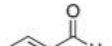
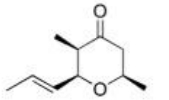
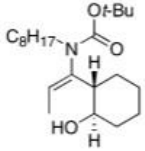
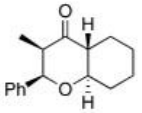
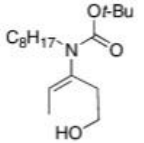
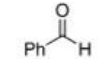
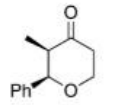
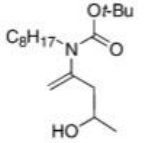
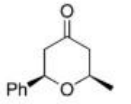
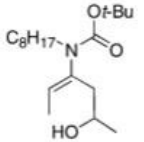
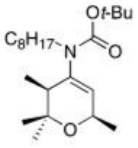
Prins Cyclizations of Enecarbamates

Scheme 2



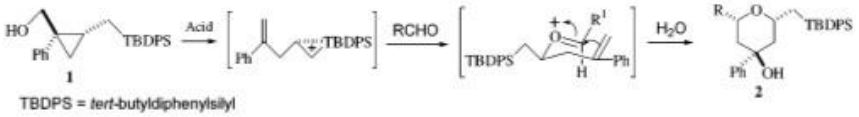
K. N. Cossey, R. L. Funk,
J. Am. Chem. Soc. **2004**, *126*, 12216-12217.

Table 1. Prins Cyclizations of Enecarbamates

entry	enamide	aldehyde (2 equiv.) temperature, time	product[a]	yield
1		 rt, 5 h		80%
2		 0 °C to rt, 13 h		70%
3		 0 °C to rt, 2.5 h Ar = *p*-tolyl		74%
4		 0 °C to rt, 4.5 h		91%
5		 rt, 2 h		84%
6		 0 °C to rt, 5 h		83%
7		 1. TMSCl, rt, 21 h 2. TMSOTf, CH_3CN -78°C, 40 min		60%
8		 (10 equiv.) rt, 24 h		49%

Prins Cyclizations of Cyclopropyl Carbinols

Scheme 1



TBDPS = *tert*-butyldiphenylsilyl

Table 1. Prins Cyclization of **1** with Aldehydes

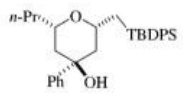
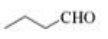
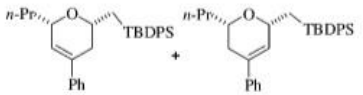
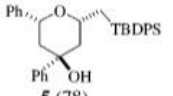
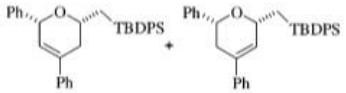
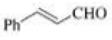
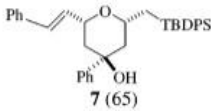
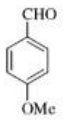
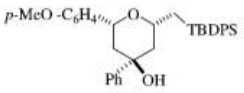
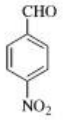
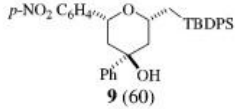
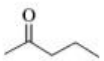
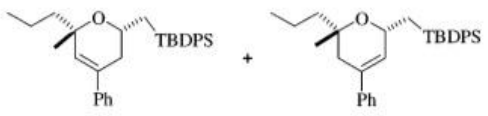
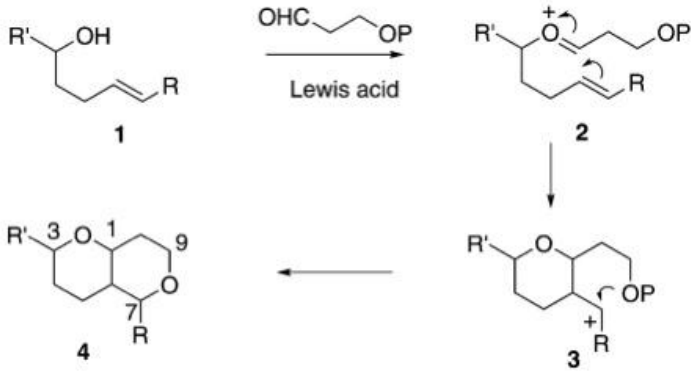
Entry	Acid	Aldehyde	Product (Yield %)
1	TFA		 **3** (72)
2	BF_3•OEt_2		 **4a** (52) + **4b** (26)
3	TFA		 **5** (78)
4	BF_3•OEt_2		 **6a** (48) + **6b** (32)
5	TFA		 **7** (65)
6	TFA		 **8** (61)
7	TFA		 **9** (60)

Table 2. Reaction of **1** with Ketones in the Presence of BF_3·OEt_2

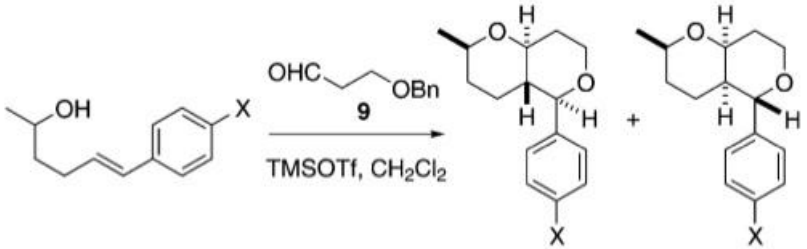
Entry	Ketone	Products (yield)
1		 **10 a** (38) + **10 b** (27)
2		 **11 a** (45) + **11 b** (30)
3		 **12 a** (36) + **12 b** (24)

V. K. Yadav, N. V. Kumar, *J. Am. Chem. Soc.* **2004**, *126*, 8652-8653.

Prins Cyclizations of γ, δ-*Unsaturated Alcohols*



Scheme 2. Proposed cyclization of γ,δ-unsaturated alcohol **1**. P = protecting group

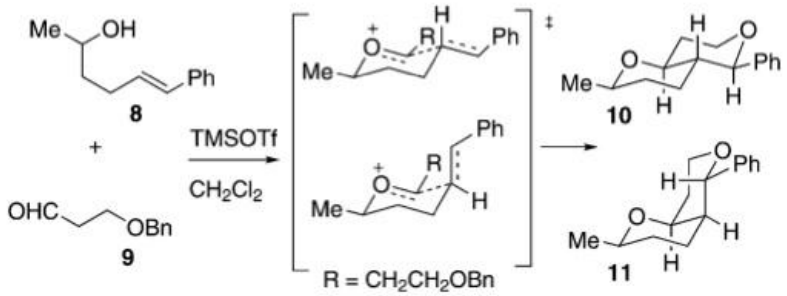


8 X = H
12 X = Cl
15 X = Br
17 X = OMe (Decomposition)
18 X = OSO_2Ph
20 X = CF_3

10 X = H, 77%
13 X = Cl, 75%
16 X = Br , 78%
19 X = OSO_2Ph, 83%
21 X = CF_3, 73%

11 X = H,
14 X = Cl,

Scheme 4. Reaction of alkenols with 3-benzyloxypropanal. Bn = benzyl



Scheme 5. Formation of the two diastereomers **10** and **11**.

A. J. Bunt, C. D. Bailey, B. D. Cons, S. J. Edwards, J. D. Elsworth, T. Pheko, C. L. Willis, *Angew. Chem. Int. Ed*. **2012**, *51*, 3901 –3904.

Cascada Reaction using Prins Cyclizations

Mukaiyama Aldol-Prins Cyclization

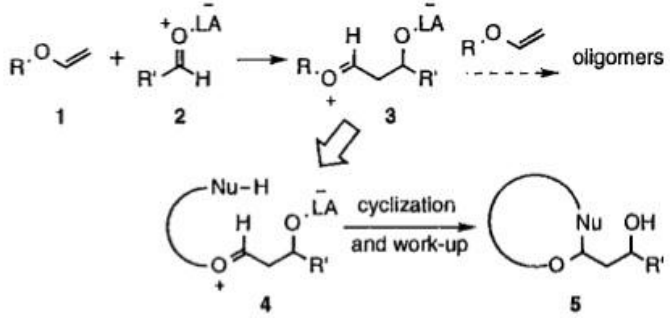


Figure 1. Conceptualization of the aldol–Prins reaction to avoid oligomerization in the reaction of electrophiles with alkyl enol ethers.

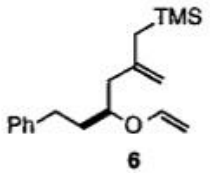
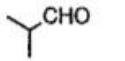
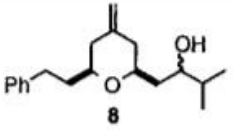
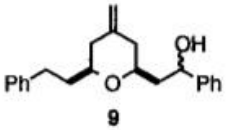
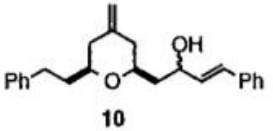
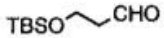
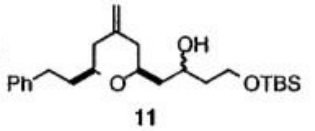
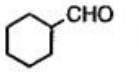
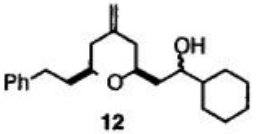
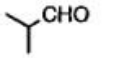
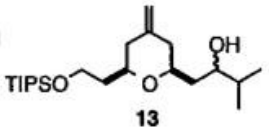


Table 1. Aldol–Prins Cyclizations with Simple Aldehydes[a]

Enol	Aldehyde	Yield[b]	Epimer Ratio[c]	Product
6		98%	1:1	 **8**
6	PhCHO	84%	1.2:1	 **9**
6		87%	1.4:1	 **10**
6		87%	1.8:1	 **11**
6		72%	1.7:1	 **12**
21[d]		72%	1.1:1	 **13**

[a] Aldol-Prins cyclizations were run using 2.5 equiv of $BF_3 \cdot OEt_2$, 2.5 equiv of aldehyde and 1.5 equiv of 2,6-di-*tert*-butylpyridine. [b] Product yields are after chromatography. [c] Diastereomeric ratios were based on isolated yields or ^1H NMR analysis. [d] 2.0 equiv of $BF_3 \cdot OEt_2$, 1.2 equiv of isobutyraldehyde and 1.2 equiv of 2,6-di-*tert*-butylpyridine were used.

D. J. Kopecky, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2001**, *123*, 8420-8421.

Oxonia-Cope Prins Cyclization

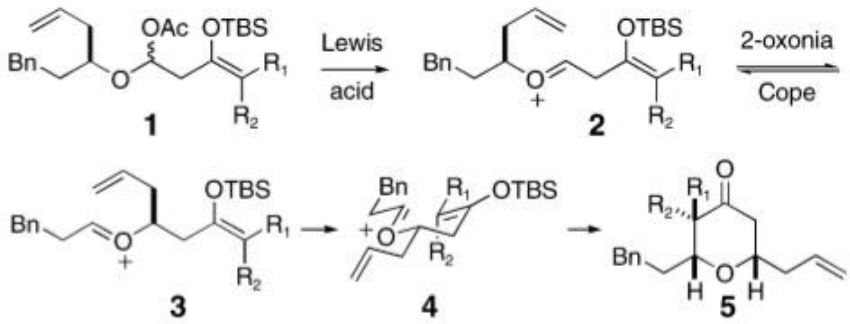
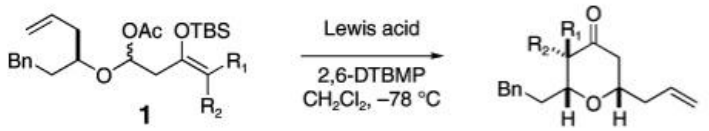


Figure 1. 2-Oxonia-Cope rearrangement of the oxocarbenium ion **2** sets up the intramolecular cyclization reaction of **4**.

Table 2. Oxonia-Cope Prins Cyclization of Silyl Enol Ether Substrates

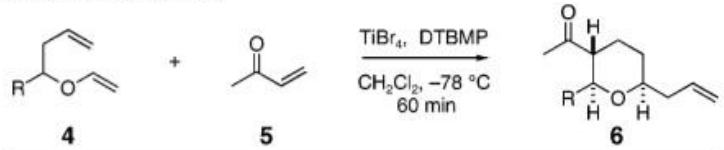


Entry	R_1	R_2	Lewis acid (product ratio)	Product	Yield (%)
1	H	H	TMSOTf	**17**	99
2	Et	H	TMSOTf (1.6:1 eq/ax)	**18**	99
3[a]	CH_2=CH	H	TMSOTf (2.1:1 eq/ax)	**19**	84
4	Me	Me	TMSOTf	**20**	92
5	$(CH_2)_5$		TMSOTf	**21**	93
6	Ph	Me	TMSOTf	**22**	88
7[b]	CH_2O-TBDPS	Me	TMSOTf (1.2:1)	**23**	77

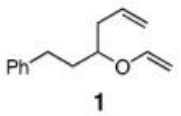
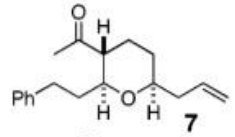
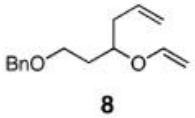
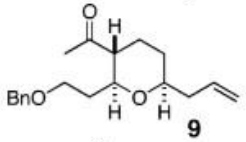
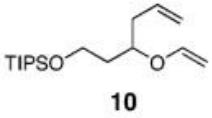
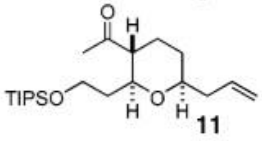
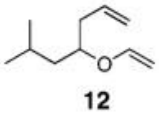
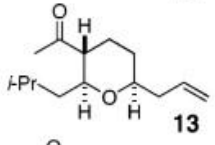
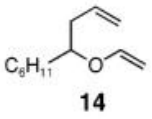
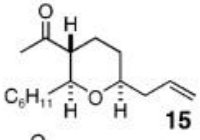
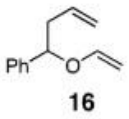
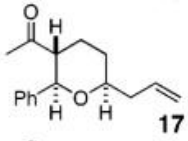
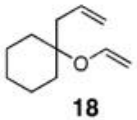
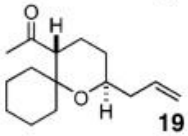
J. E. Dalgard, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2004**, *126*, 15662-15663.

Mukaiyama-Michael Cascade Reaction

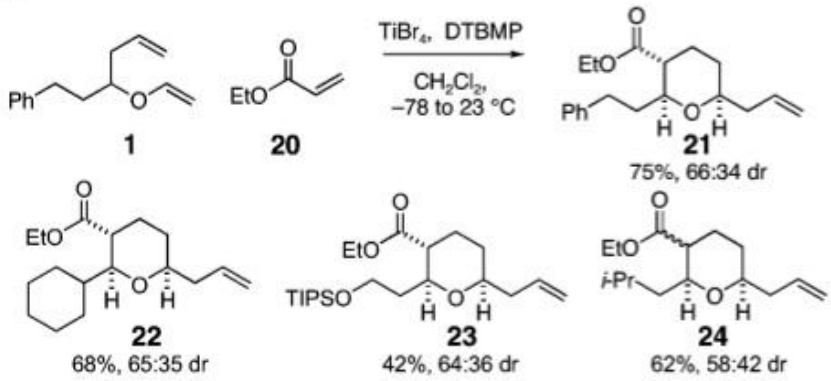
Table 1. Mukaiyama−Michael Cascade Reaction with 3-Butene-2-one (MVK)



4 + 5 → 6

Entry[a]	Enol Ether	Product[b]	Yield (%)
1	 1	 7	74
2	 8	 9	72
3	 10	 11	63
4	 12	 13	72
5	 14	 15	74
6[c]	 16	 17	65
7	 18	 19	74

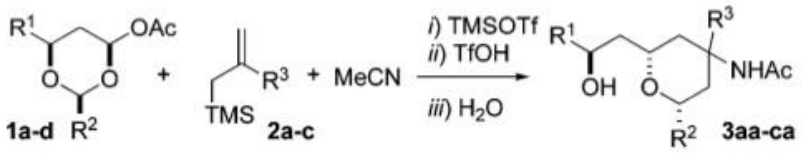
Scheme 1. Mukaiyama−Michael Cascade Reaction with Ethyl Acrylate



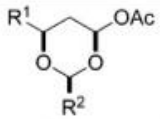
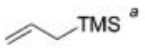
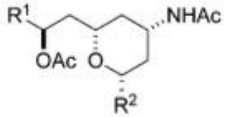
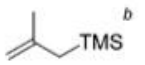
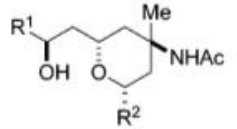
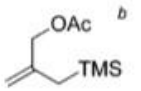
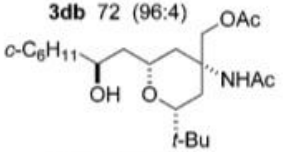
M. L. Bolla, B. Patterson, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2005**, *127*, 16044-16045.

Sakurai-Prins-Ritter multicomponent Reaction

Table 1. Sequential Sakurai−Prins−Ritter Reactions

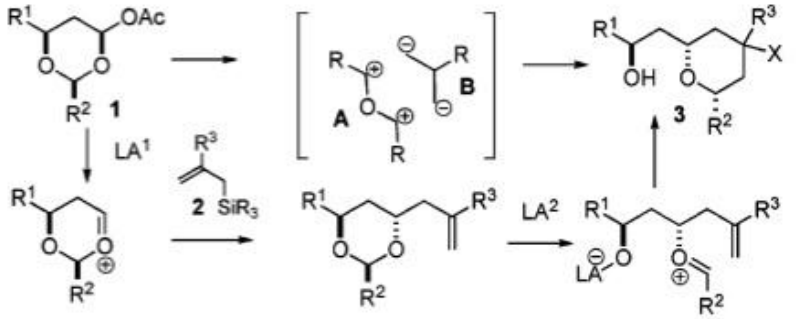


1a-d **2a-c** **3aa-ca**

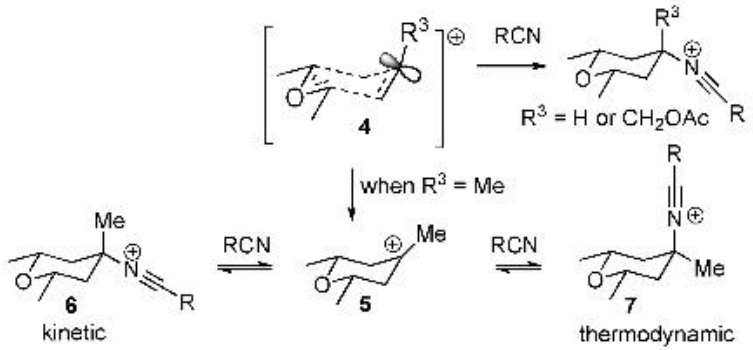
Entry	1,3-Dioxane	Allyl silane	Product, yield (%) (dr)
		 [a]	
		2a	
1	**1a**: R^1= *c*-C_6H_{11}; R^2=*t*-Bu		**3aa** 79 (97:3)
2	**1b**: R^1= *c*-C_6H_{11}; R^2=*n*-Pr		**3ba** 80 (97:3)
3	**1c**: R^1= $Ph(CH_2)_2$; R^2=*t*-Bu		**3ca** 77 (97:3)
4	**1d**: R^1= $Ph(CH_2)_2$; R^2=*n*-Pr		**3da** 75 (98:2)
5	**1e**: R^1= $PivO(CH_2)_2$; R^2=$(CH_2)_3Cl$		**3ea** 59 (90:10)
		 [b]	
		2b	
6	**1a**		**3ab** 88 (97:3)
7	**1b**		**3bb** 71 (97:3)
8	**1c**		**3cb** 80 (96:4)
9	**1d**		**3db** 72 (96:4)
		 [b]	
		2c	
10	**1a**		**3ac** 61 (99:1)[c]

[a] Procedure A: (i) TMSOTf (1 equiv), −45 °C; (ii) TfOH (2 equiv), −45 to −15 °C; (iii) Ac_2O, −15 to 0 °C, CH_2Cl_2/MeCN (1:1). [b] Procedure B: (i) TMSOTf (1 equiv), −45 °C; (ii) TfOH (2 equiv), −45 to 0 °C;(iii) $NaHCO_3$, MeCN; see Supporting Information for details. [c] Tertiary alcohol

Scheme 1. [3+3] Cyclocondensation Strategy



Scheme 2. Stereochemical Rationale Based on Alder's Model



O. L. Epstein, T. Rovis, *J. Am. Chem. Soc.* **2006**, *128*, 16480-16481.

2-2. Synthesis of Tetrahydrofurans via Prins Cyclizations

Scheme 1

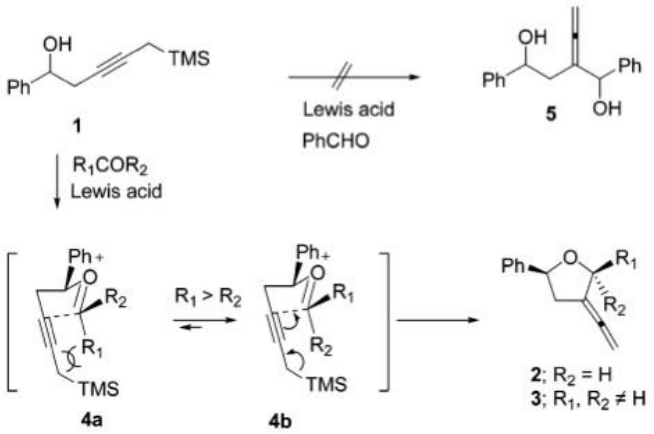
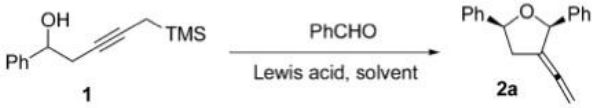


Table 1. Prins-Type Cyclization of Substrate **1** and Benzaldehyde under Various Conditions[a]

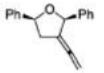
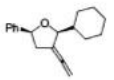
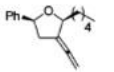
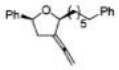
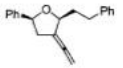
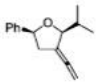
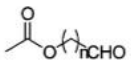
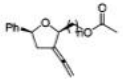
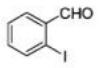
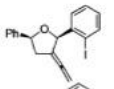
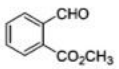
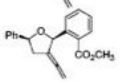
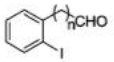
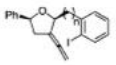
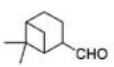
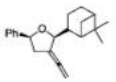


entry	Lewis acid	solvent	time (h)	yield **2a** (%)[b]	*cis/trans*[c]
1	$InCl_3$	CH_2Cl_2	17	22	40:1
2	$BF_3.Et_3O$	CH_2Cl_2	17	69	8:1
3	$SnCl_4$	CH_2Cl_2	17	80	40:1
4	$SnCl_4$	Et_2O	15	80	40:1
5	TMSOTf	CH_2Cl_2	4	33	3:1
6	TMSOTf	Et_2O	4	91	40:1

[a] All reactions were carried out on a 0.35 mmol scale at −78 °C to room temperature in the presence of 1.1 equiv of Lewis acid. [b] Isolated yields. [c] Ratio based on ^1H NMR spectra.

C. Shin, S. N. Chavre, A. N. Pae, J. H. Cha, H. Y. Koh, M. H. Chang, J. H. Choi, Y. S. Cho, *Org. Lett.* **2005**, *7*, 3283-3285.

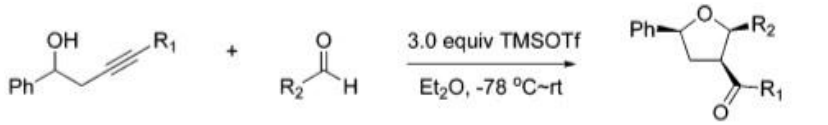
Table 2. Prins-Type Cyclization of Substrate **1** and Various Aldehydes[a]

entry	aldehyde	product	No	yield[b]	cis/trans[c]
1	Ph-CHO		**2a**	91	40:1
2			**2b**	86	cis only
3	$CH_3(CH_2)_4CHO$		**2c**	71	cis only
4	$Ph(CH_2)_5CHO$		**2d**	63	cis only
5	$Ph(CH_2)_2CHO$		**2e**	73	cis only
6	$(CH_3)_2CHCHO$		**2f**	83	cis only
7			**2g** **2h** **2i**	82 (n=3) 86 (n=4) 98 (n=5)	cis only cis only cis only
8			**2j**	93	cis only
9			**2k** **2l**	58 82 (n=1)	cis only cis only
10			**2m** **2n**	78 (n=2) 77 (n=3)	cis only cis only
11			**2o**	85	cis only

[a] All reactions were carried out on a 0.35−0.55 mmol scale. [b] Isolated yields. [c] Ratio based on ^1H NMR spectra.

2-2. Synthesis of Tetrahydrofurans via Prins Cyclizations

Scheme 1. Synthesis of 2,3,5-Trisubstituted Tetrahydrofurans

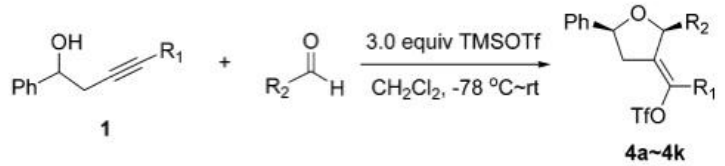


1a R_1 = phenyl
1b R_1 = CH_3

2a R_2 = 4-nitrophenyl
2b R_2 = phenyl
2c R_2 = methyl
2d R_2 = isopropyl

3a R_1 = phenyl, R_2 = 4-nitrophenyl (35%)
3b R_1 = methyl, R_2 = 4-nitrophenyl (41%)
3c R_1 = methyl, R_2 = phenyl (38%)
3d R_1 = methyl, R_2 = methyl (30%)
3e R_1 = methyl, R_2 = isopropyl (18%)

Table 1. Synthesis of 3-Furanylidene Derivatives



entry	R_1	R_2	no.	yield[a] (%)
1	methyl	4-nitrophenyl	**4a**	77
2	methyl	phenyl	**4b**	68
3	methyl	2-naphthyl	**4c**	68
4	methyl	4-chlorophenyl	**4d**	76[b]
5	methyl	2-nitrophenyl	**4e**	35
6	methyl	methyl	**4f**	68
7	methyl	ethyl	**4g**	69[c]
8	methyl	isopropyl	**4h**	60
9	methyl	*n*-pentyl	**4i**	65
10	methyl	2-phenylethyl	**4j**	61[c]
11	phenyl	4-nitrophenyl	**4k**	64

[a] Isolated yields. Two stereoisomers (cis/trans) were obtained in ratios of 8:1[b] and 5:1,[c] respectively, which were determined by ^{1}H NMR spectroscopy.

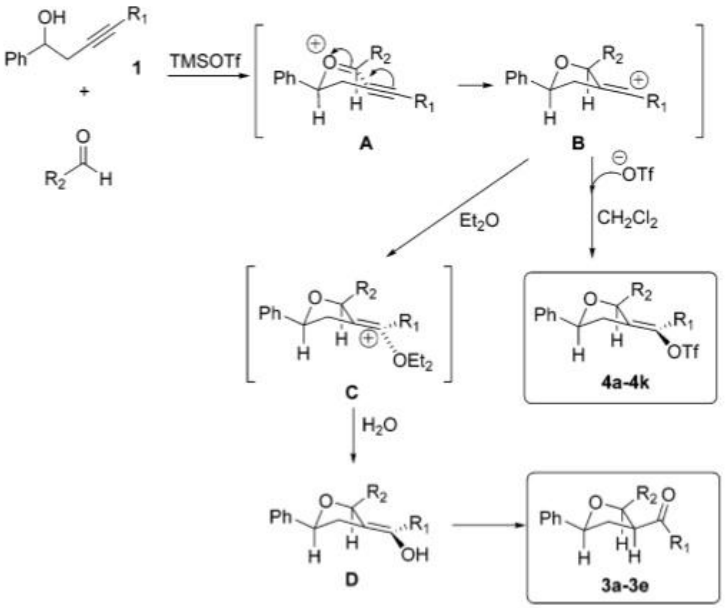
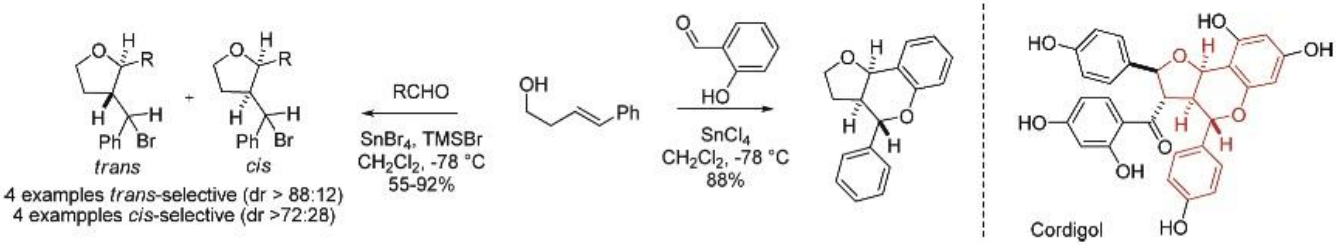


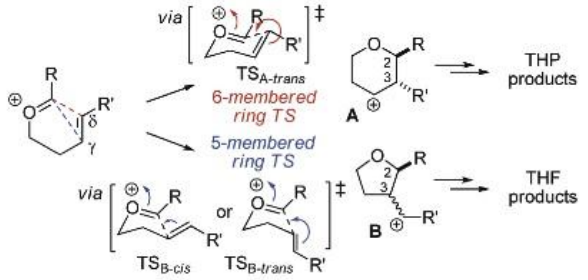
Figure 1. Proposed mechanism for the two different solvent systems.

S. N. Chavre, H. Choo, J. H. Cha, A. N. Pae, K. I. Choi, Y. S. Cho, *Org. Lett.* **2006**, *8*, 3617-3619.

2-2. Synthesis of Tetrahydrofurans via Prins Cyclizations



Scheme 1. Type III γ,δ-Unsaturated Oxonium-Prins Cyclizations



Scheme 4. Molecular Structure of **10** and a Probably Pathway for Its Formation

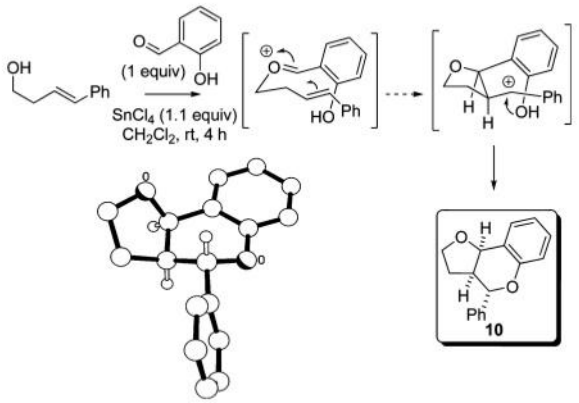
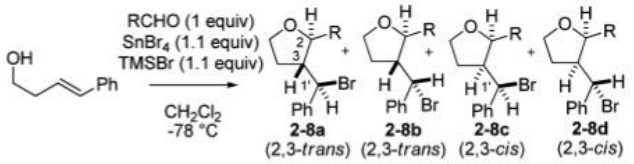


Table 2. Oxonium Prins Cyclizations: Exploration of the Scope with Respect to the Aldehyde Component



entry	R	prod.	time (h)	yield[a] (%)	dr (**a/b/c/d**[b])
1	Me	**2**	1.5	55	0:0:60:40
2	*i*-Pr	**3**	3	92	8:0:80:12
3	Ph	**4**	1.5	60	77:12:11:0
4	*o*-BrC_6H_4	**5**	2	71[c]	28:0:72:0
5	*o*-$NO_2C_6H_4$	**6**	2.5	83	0:0:100:0
6	*o*-$MeOC_6H_4$	**7**	4	58[d]	87:13:0:0
7	*p*-BrC_6H_4	**8**	2	55	68:20:12:0

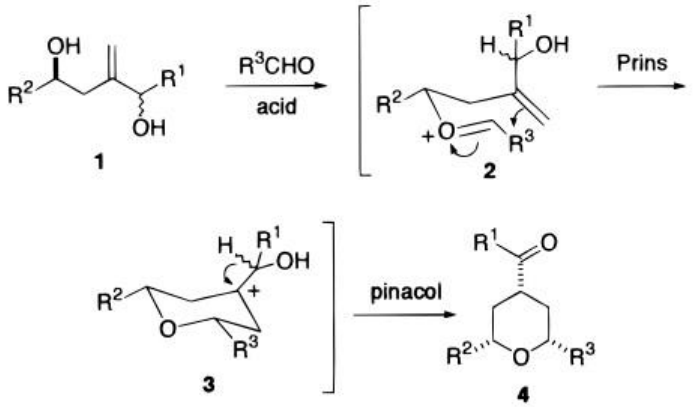
[a] The yield is that of the inseparable mixture of isomers unless otherwise indicated. [b] Ratios by integration of ^1H NMRs of the crude reaction mixtures; assignment of 2,3-stereochemistry is via NOESY (see the Supporting Information); the configuration at C1′ in the major 2,3-*trans* and 2,3-*cis* isomers is assumed to be that of **a/c** by analogy with that determined by X-ray for **6c** (Scheme 2). [c] **5c** 44%, **5d** 27%, separable. [d] **5a** 58%, **5b** not isolated, separable.

A. C. Spivey, L. Laraia, A. R. Bayly, H. S. Rzepa, A. J. P. White, *Org. Lett.* **2010**, *12*, 900-903.

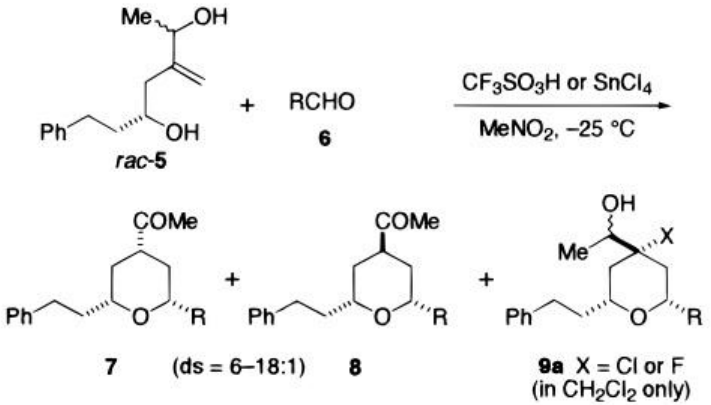
2-3. Prins-pinacol reaction

Synthesis of Tetrahydropyrans

Scheme 1



Scheme 2



a R = CH_2CH_2Ph; **b** R = Me; **c** R = CH_2Ph; **d** R = *i*-Pr;
e R = *t*-Bu; **f** R = (*E*)-CH=CHPh; **g** R = Ph

Table 1. Synthesis of all-*cis*-4-Acetyl-2,6-disubstituted Tetrahydropyrans **7**[a]

cmpd	RCHO	acid	stereosel[b]	Yield of **7**[c] (%)
7a	$PhCH_2CH_2CHO$	TfOH	18:1	81[d]
		$SnCl_4$	10:1	65
7b	MeCHO	TfOH	11:1	73[d]
		$SnCl_4$	10:1	66[d]
7c	$PhCH_2CHO$	TfOH[e]	6:1	61
		$SnCl_4$	8:1	56
7d	*i*-PrCHO	TfOH[e]	14:1	65
		$SnCl_4$	12:1	68
7e	*t*-BuCHO	TfOH	9:1	76[f]
		$SnCl_4$	10:1	50
7f	(*E*)-PhCH=CHCHO	TfOH	6:1	68[g]
		$SnCl_4$	8:1	59[g]
7g	PhCHO	TfOH[e]	8:1	61
		$SnCl_4$	6:1	76[f]

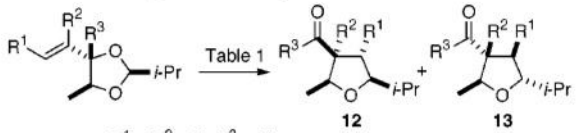
[a] Reactions were conducted in $MeNO_2$ and employed 75 or 150 mg of *rac*-**5** (0.25 M), and unless otherwise noted, 0.50 equiv of acid. All products are racemic. [b] Ratio of **7**:**8** in the crude reaction product by capillary GLC analysis. [c] Yield of stereoisomerically pure **7** after silica gel chromatography. [d] Stereoisomers **7** and **8** were not separated, and the yield refers to this mixture. [e] 0.25 equiv of TfOH was employed. [f] This product contained a trace of the minor diastereomer **8**. [g] This product contained a small amount of an acetal impurity.

M. J. Cloninger, L. E. Overman, *J. Am. Chem. Soc.* **1999**, *121*, 1092-1093.

2-3. Prins-pinacol reaction

Synthesis of Tetrahydrofurans

Table 1. Rearrangements of Syn Acetals **6s−10s**[a]

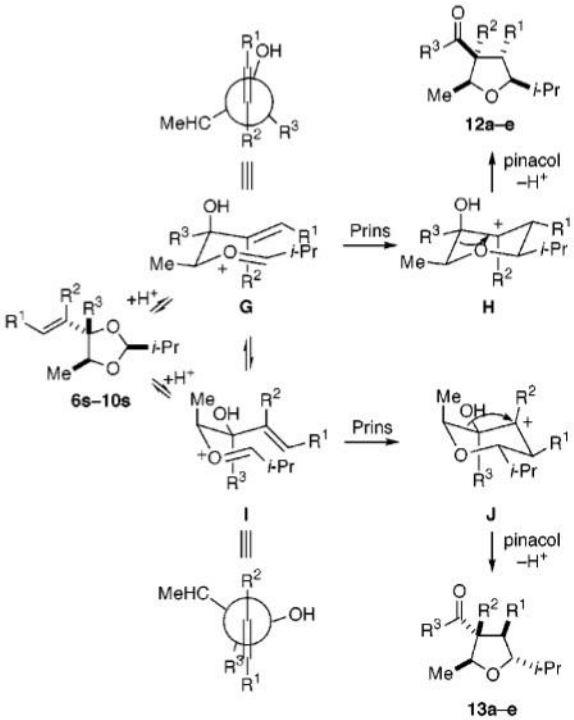


		12	13
6s	$R^1 = R^2 = H$, $R^3 = Me$	**a**	**a**
7s	$R^1 = H$, $R^2 = R^3 = Me$	**b**	**b**
8s	$R^1–R^2 = (CH_2)_3$, $R^3 = Me$	**c**	**c**
9s	$R^1 = R^2 = H$, $R^3 = i\text{-Pr}$	**d**	**d**
10s	$R^1–R^2 = (CH_2)_3$, $R^3 = i\text{-Pr}$	**e**	**e**

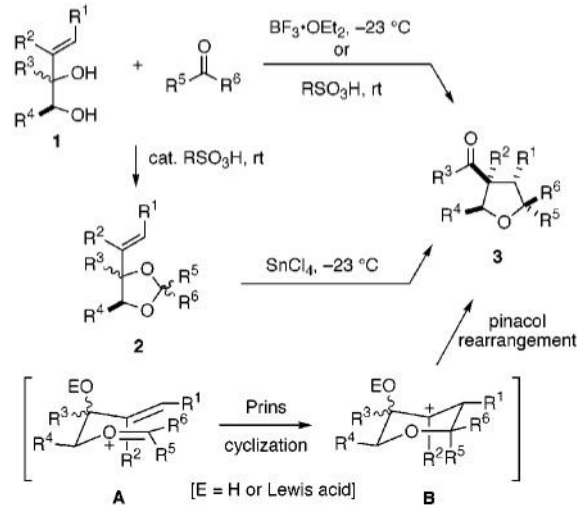
entry	acetal	acid	time, h	% conv	12:13[b]
1	**6s**	$SnCl_4$	14	31[c]	>99:1
2	**6s**	TfOH	14	90[d]	>99:1
3	**7s**	$SnCl_4$	14	94	97:3
4	**7s**	TfOH	14	88	97:3
5	**8s**	$SnCl_4$	6	80	>99:1
6	**9s**	$SnCl_4$	17	67[e]	>99:1
7	**9s**	TfOH	16	98	96:4
8	**10s**	TfOH	14	82[d]	90:10

[a] Reactions were conducted in CH_2Cl_2 at −78 °C in the presence of 1.1 equiv of $SnCl_4$ or 3 equiv of TfOH with acetals of >97% diastereomeric purity. The acetal concentration was 0.01 M. [b] Product ratios were determined by capillary GLC analysis. [c] **6s** was recovered in 65% yield. [d] Isolated yield. [e] **9s** was recovered in 28% yield.

Scheme 3. Model for Stereoselection in the Syn Diol Series



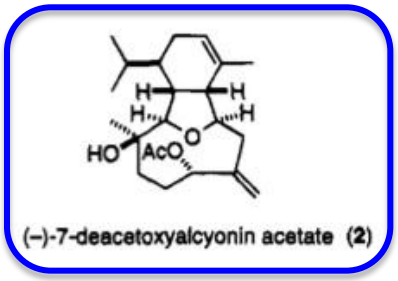
Scheme 1



F. Cohen, D. W. C. MacMillan, A. Romero, L. E. Overman, *Org. Lett.* **2001**, *3*, 1225-1228.

2-3. Prins-pinacol reaction

Application – Total synthesis of (-)-7-Deacetoxyalcynonin Acetate



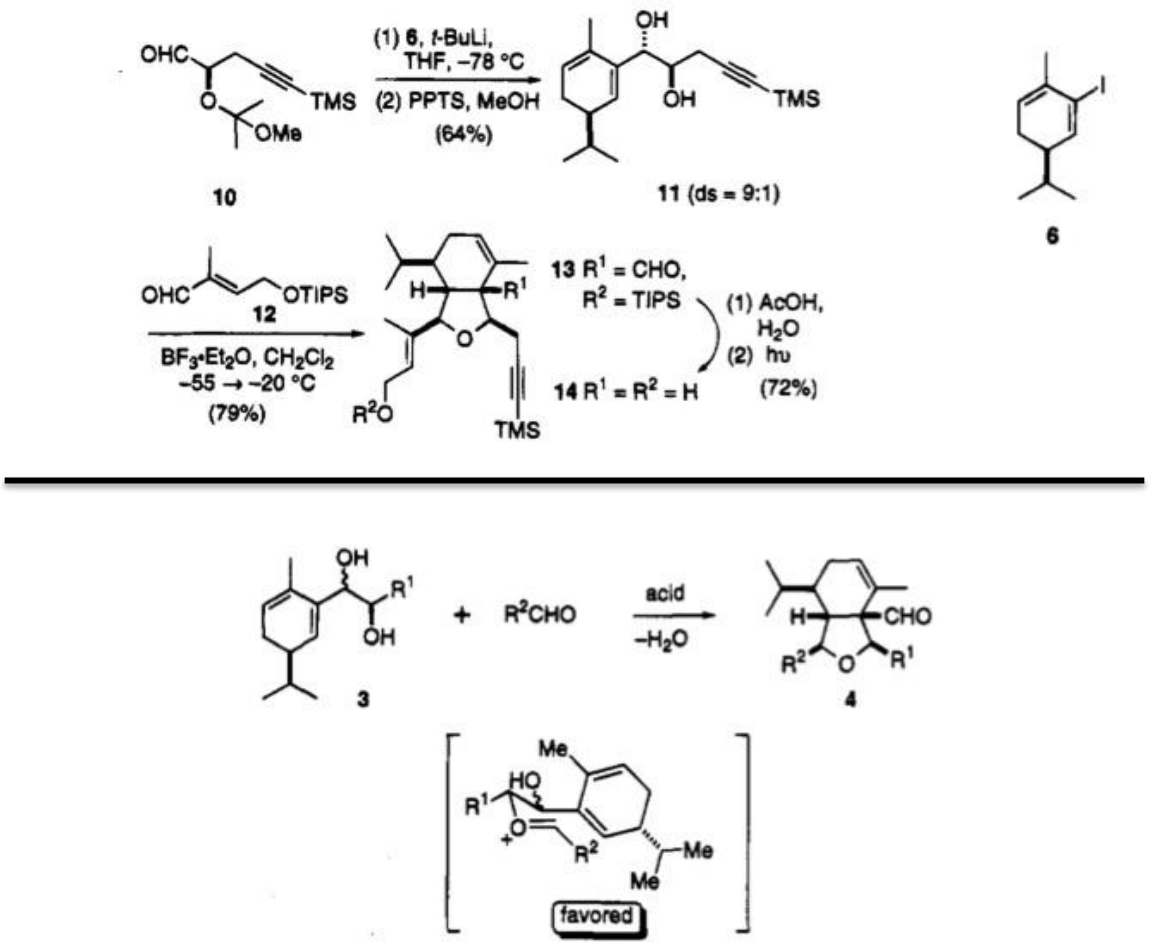
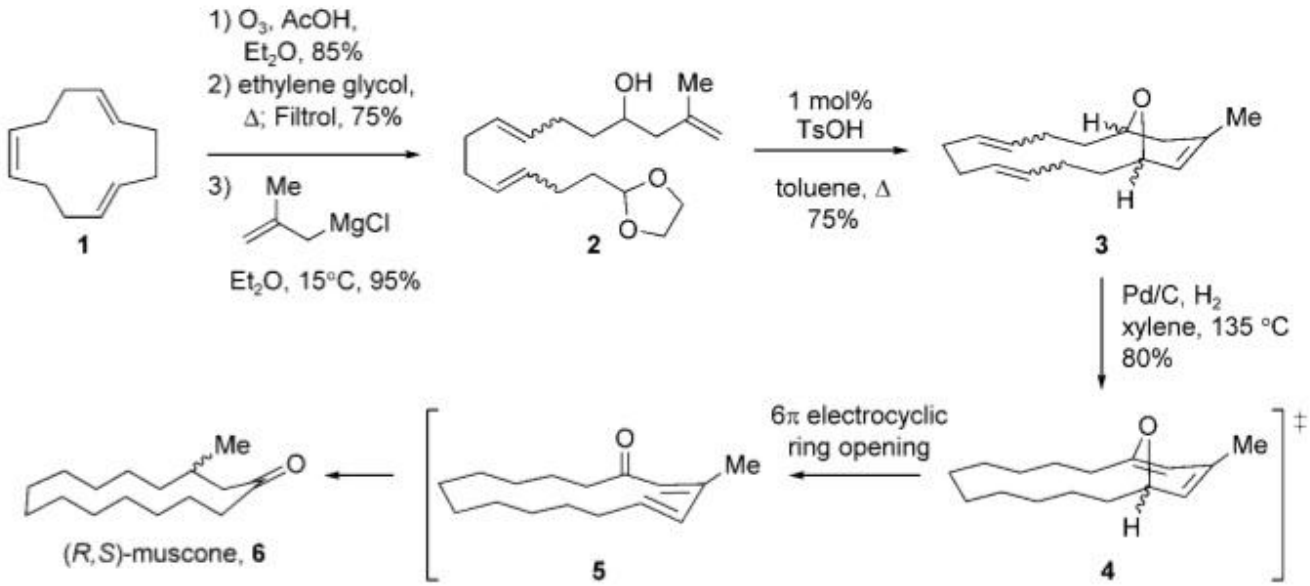


Figure 1. Stereochemical analysis of the Prins-pinacol reaction.

D. W. C. MacMillan, L. E. Overman, *J. Am. Chem. Soc.* **1995**, *117*, 10391-10392.

3. Prins-Type Macrocyclizations

3-1. Early Prins Macrocyclizations

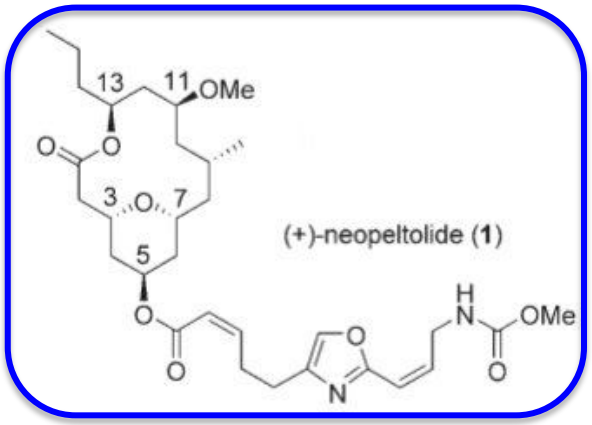


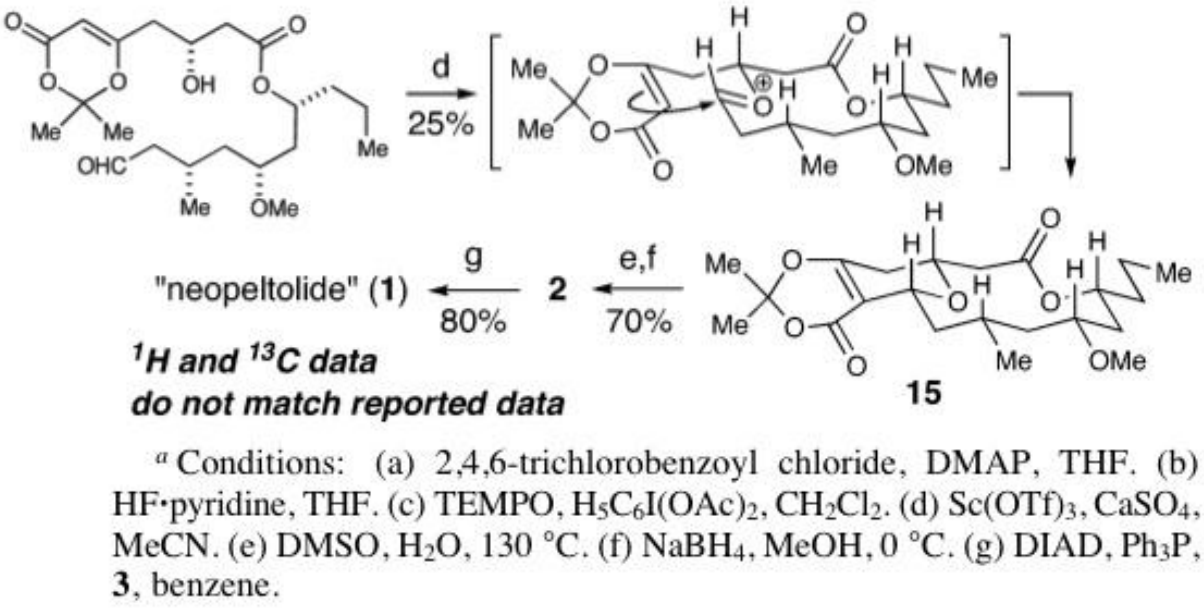
Scheme 5. Formal synthesis of (*R*,*S*)-muscone by Schulte-Elte et al. TsOH = *p*-toluenesulfonic acid.

K. H. Schulte-Elte, A. Hauser, G. Ohloff, *Helv. Chim. Acta* **1979**, *62*, 2673 – 2680.
E. A. Crane, K. A. Scheidt, *Angew. Chem. Int. Ed*. **2010**, *49*, 8316 – 8326.

3-2. Application in Natural Product Synthesis

The Scheidt Group approach





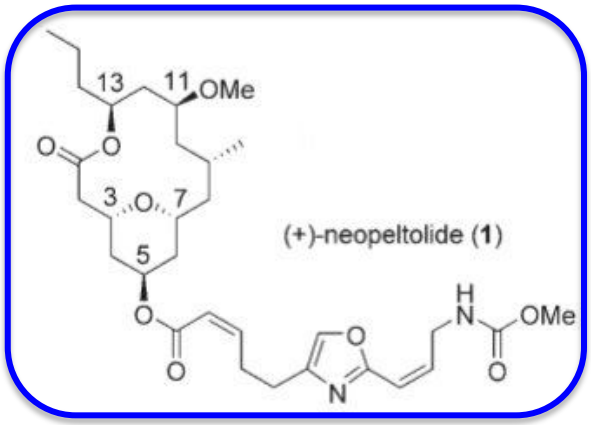
[a] Conditions: (a) 2,4,6-trichlorobenzoyl chloride, DMAP, THF. (b) HF·pyridine, THF. (c) TEMPO, $H_5C_6I(OAc)_2$, CH_2Cl_2. (d) $Sc(OTf)_3$, $CaSO_4$, MeCN. (e) DMSO, H_2O, 130 °C. (f) $NaBH_4$, MeOH, 0 °C. (g) DIAD, Ph_3P, **3**, benzene.

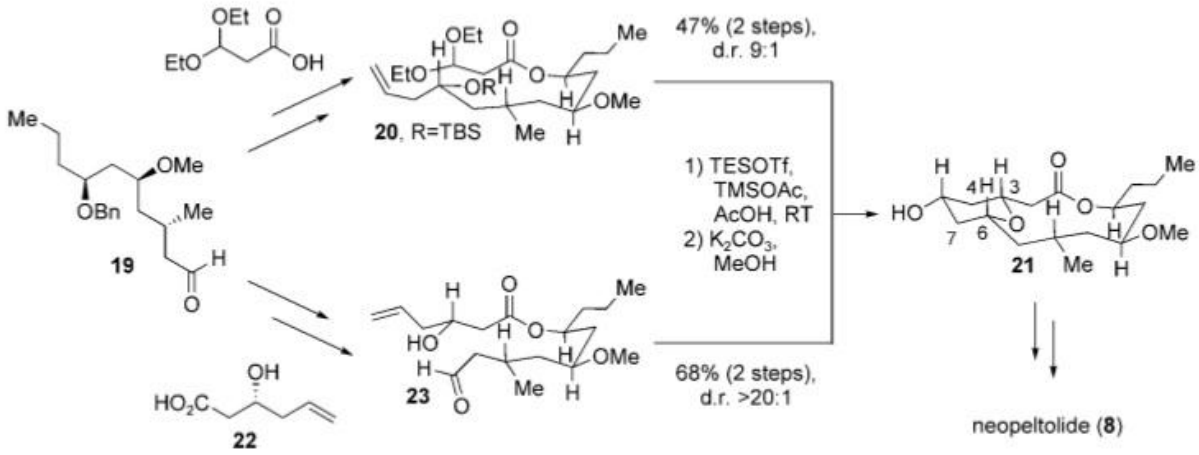
D. W. Custar, T. P. Zabawa, K. A. Scheidt, *J. Am. Chem. Soc*. **2008**, *130*, 804 – 805..

E. A. Crane, K. A. Scheidt, *Angew. Chem. Int. Ed*. **2010**, *49*, 8316 – 8326.

3-2. Application in Natural Product Synthesis

The Lee Group approach





Scheme 9. Synthetic strategies toward neopeltolide by Lee et al. Bn = benzyl, TMS = trimethylsilyl.

S. K. Woo, M. S. Kwon, E. Lee, *Angew. Chem. Int. Ed*. **2008**, *47*, 3242 – 3244.
E. A. Crane, K. A. Scheidt, *Angew. Chem. Int. Ed*. **2010**, *49*, 8316 – 8326.

3-2. Application in Natural Product Synthesis

Studies towards Clavosolide A by The Rychnovsky Group

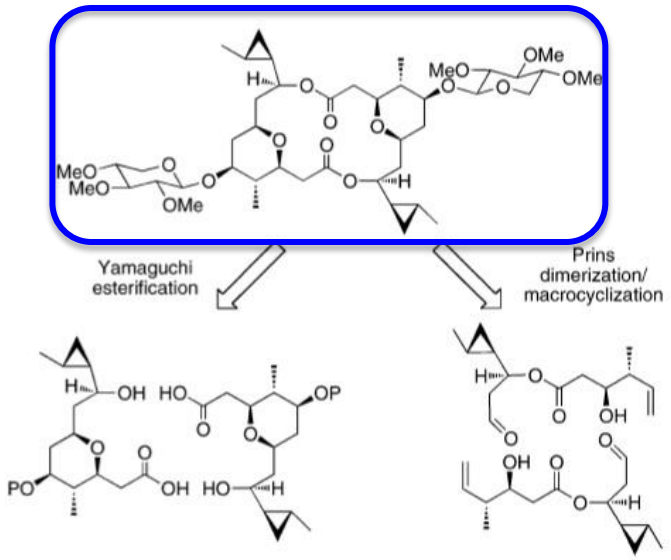
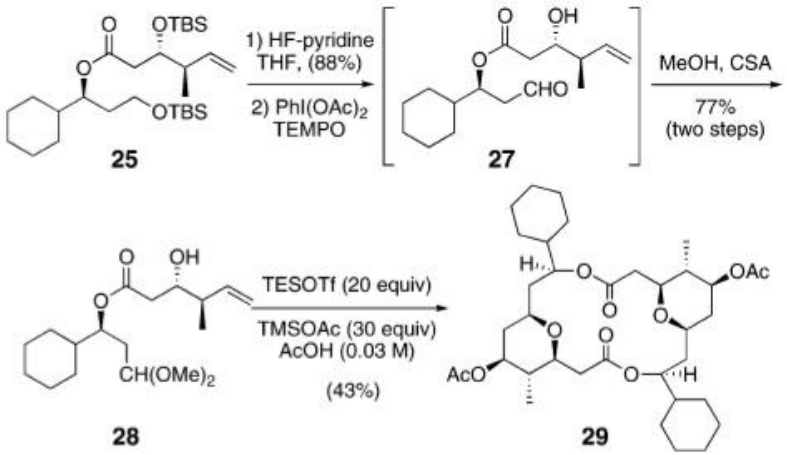


Figure 2. Two alternative strategies for the dimerization and cyclization of (−)-clavosolide A.

Scheme 5. Prins Dimerization and Macrocyclization

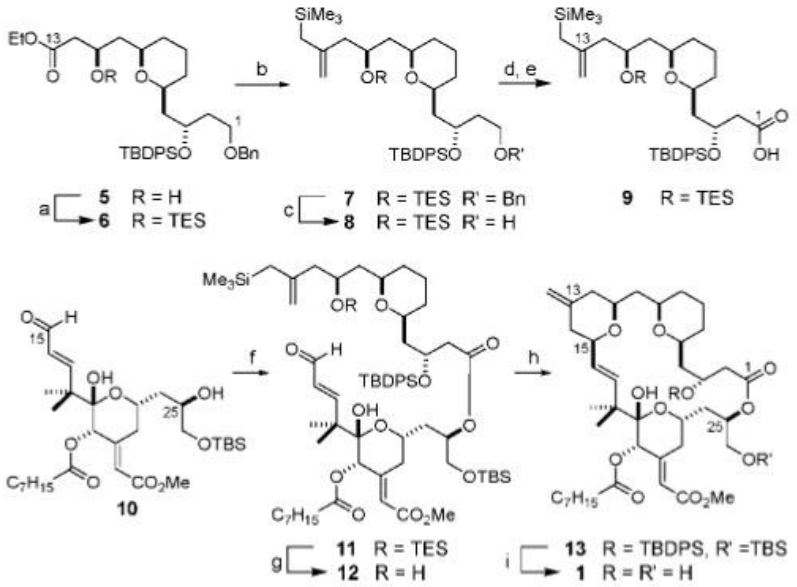


M. R. Gesinski, K. Tadpetch, S. D. Rychnovsky, *Org. Lett*. **2009**, *11*, 5342 – 5345.
E. A. Crane, K. A. Scheidt, *Angew. Chem. Int. Ed*. **2010**, *49*, 8316 – 8326.

3-2. Application in Natural Product Synthesis

The Wender Group approach

Scheme 1. Synthesis of Bryostatin Analogue **1**[a]



[a] Reagents and conditions: (a) TES-Cl, imidazole, CH_2Cl_2, rt, 97%; (b) (i) $CeCl_3$, $TMSCH_2MgCl$, THF, −78 °C → rt, 12 h, (ii) SiO_2, CH_2Cl_2, rt, 69%; (c) Li^0, naphthalene, THF, −25 °C, 93%; (d) TPAP (10 mol %), NMO (3 equiv), powdered 4Å MS, CH_2Cl_2, rt; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, 2:1 *t*-BuOH:H_2O, 0 °C, 89% from **8**; (f) **9**, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, then **10**, DMAP, rt; (g) PPTS (30 mol %), 1:4 H_2O:THF, rt, 71% from **9**; (h) TMS-OTf, Et_2O, −78 → 0 °C, 93%; (i) HF•py, THF, rt, 77%.

P. A. Wender, B. A. DeChristopher, A. J. Schrier, *J. Am. Chem. Soc*. **2008**, *130*, 6658 – 6659.
E. A. Crane, K. A. Scheidt, *Angew. Chem. Int. Ed*. **2010**, *49*, 8316 – 8326.

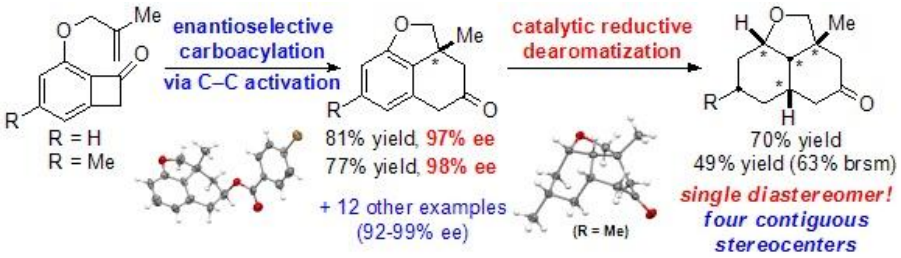
4. Conclusion

1. The Prins reaction has emerged as a powerful merged C-O and C-C bond-forming technique in the synthesis of tetrahydropyran ring with various substitution.

2. The application of the Prins macrocyclization in the past two years reflects the capacity of this approach to construct a tetrahydropyran ring simultaneously with a macrocycle in a convergent, selective and high-yielding manner.

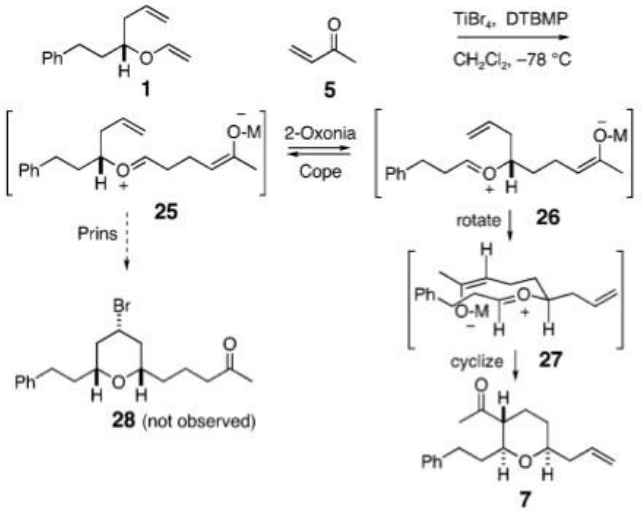
3. The application of this strategy toward the synthesis of bioactive macrocycles will continue, thereby firmly establishing it as a powerful method to form these important small molecules.

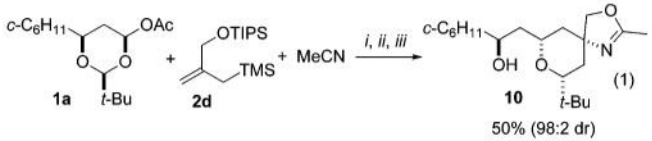
Thank you



Congratulation !!!

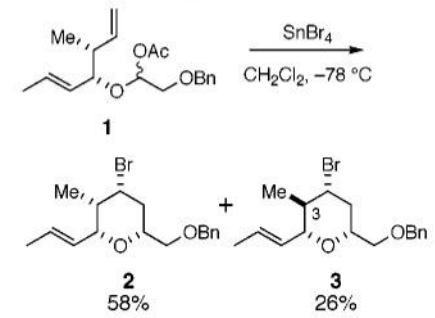
Quiz !





i) TMSOTf, CH_2Cl_2, -78 °C; *ii*) MeCN, TfOH, -45 to 0 °C; *iii*) $NaHCO_3$

Scheme 1. Unexpected C3 Epimerization in a Prins Cyclization



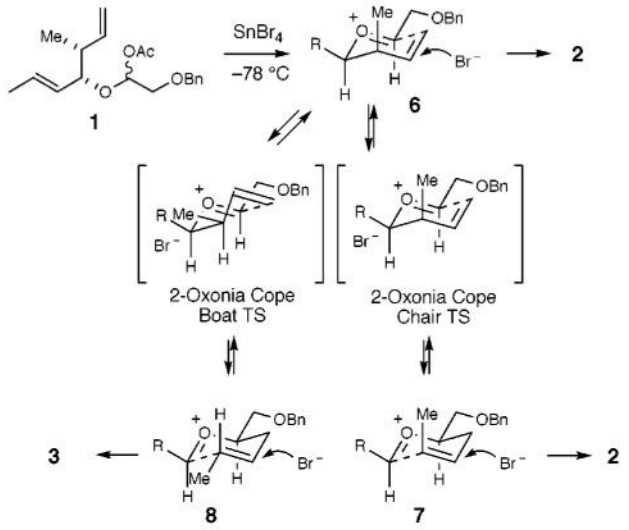


Figure 1. The chair and boat 2-oxonia Cope rearrangements that lead to tetrahydropyran **2** and its C3 epimer **3**.