Ciara M. Ordner

Enolate Alkylation of Epoxides

June 5, 2020

Enolates :
- well established nucleophiles
- some consider one of the "backbones of organic synthesis"

Epoxides:
- well established electrophiles (polar, strained ring)
- many ways to make enantioselectively (Sharpless, Shi, Jacobsen, etc.)

And yet…

> ***"In spite of their intrinsic synthetic potential, addition reactions of metal enolates of non-stabilized esters, amides, and ketones to epoxides are not widely used in the synthesis of complex molecules."***
>
> ***- Paolo Crotti and Mauro Pineschi***
> ***Aziridines and Epoxides in Organic Synthesis***

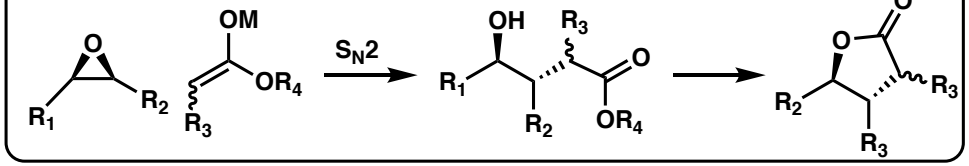
Things to keep in mind:

- Ketone and ester enolate alkylations of epoxides often require various additives, whereas standard amide enolates (more stable, more nucleophilic) and malonic enolates tend to readily undergo alkylation.

- Ketone enolates can equilibrate, and ester enolates can fragment to ketenes/alkoxides.

- Stable enolate = good alkylation

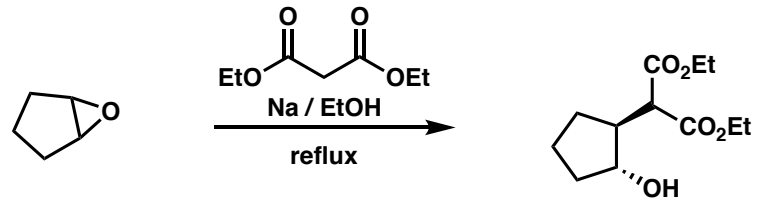
General Scheme



Some good reviews:
Tetrahedron, 2000, 56, 9, 1149-1163.
Aziridines and Epoxides in Organic Synthesis
edited by Andrei K. Yudin

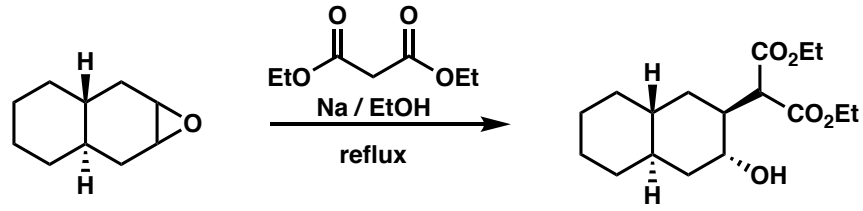
Malonate

Oldest reported enolate alkylation of epoxides:



70-75% yield

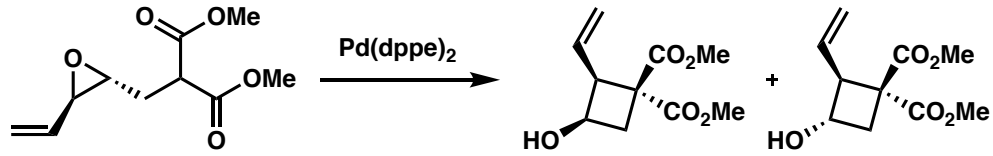
J. Am. Chem. Soc. 1942, 64, 11, 2606–2610



94% yield

J. Am. Chem. Soc. 1961, 83, 3, 606–614

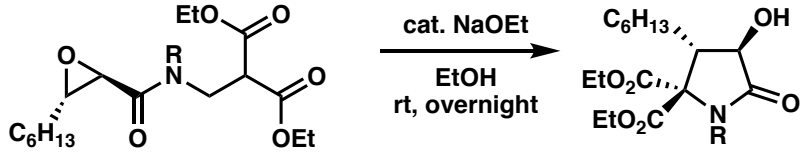
Cyclobutane formation:



4:1 syn:anti
70% yield

Tet. Lett. 1995, 36, 14, 2487–2490

Lactam formation:



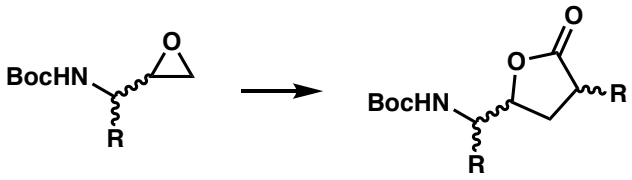
R = H 78% yield
R = Me 93% yield

Tetrahedron 1996, 52, 29, 9909–9924

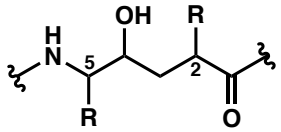
See also: Chem. Lett. 1983, 169-172
Bul. Chem. Soc. Jap. 1984, 57, 8, 2135-2139.

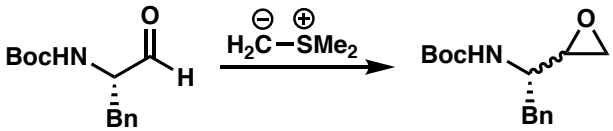
Enolate Alkylation of Epoxides

Industry Adventures with Malonates



Peptide analog synthesis:
- can access all 8 stereoisomers
- facile R group variability



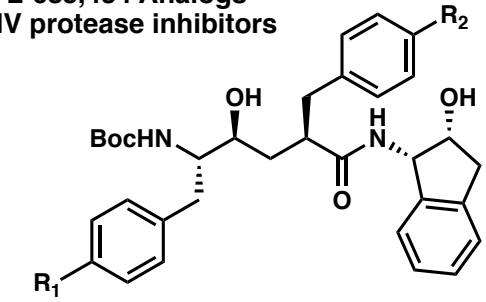


Epoxide Synthesis
- retention of stereo.
-separable diast.

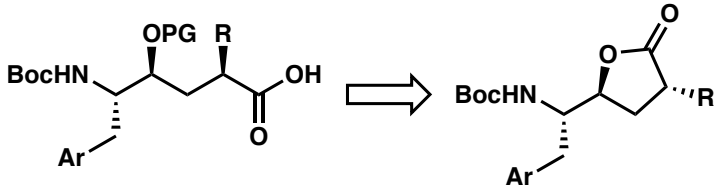
Merck: J. Org. Chem. 1985, 50, 23, 4615–4625

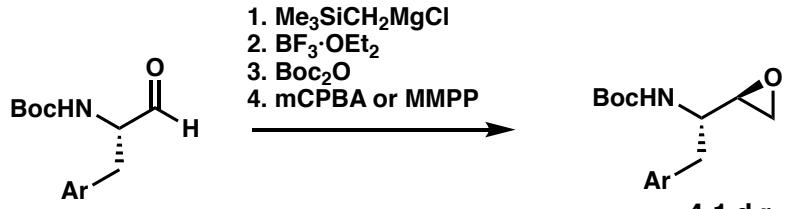
Merck

L-685,434 Analogs
HIV protease inhibitors

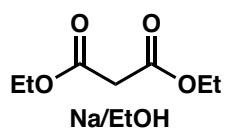


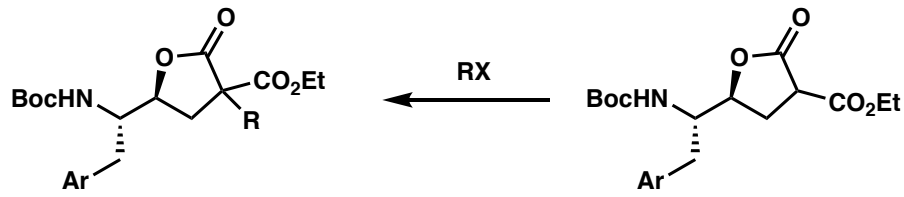
L-685,434 Analogs

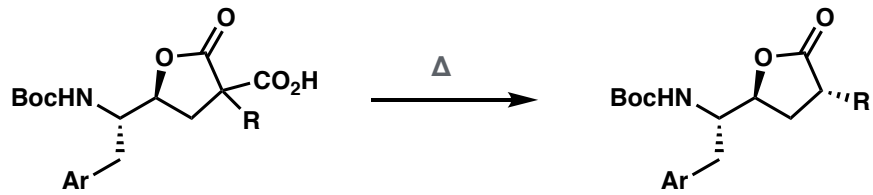




4:1 d.r.







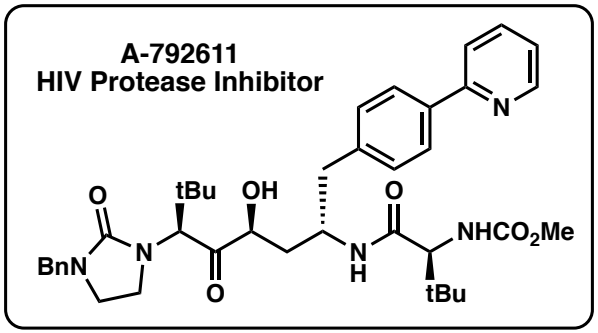
can equilibrate undesired diastereomer with base

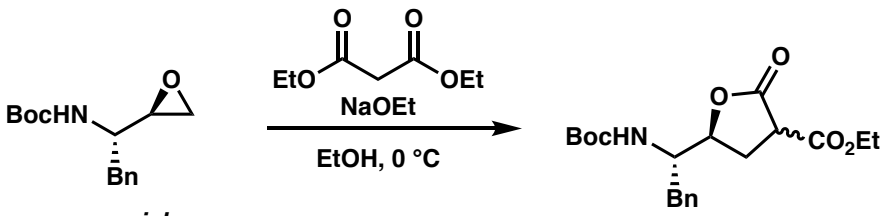
J. Med. Chem. 1992, 35, 10, 1685–1701
J. Med. Chem. 1992, 35, 10, 1702–1709

Enolate Alkylation of Epoxides

Abbott

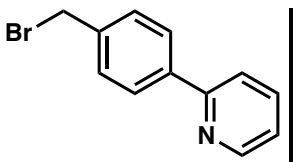
A-792611
HIV Protease Inhibitor



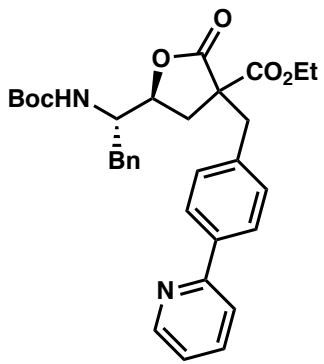


commercial enantiopure

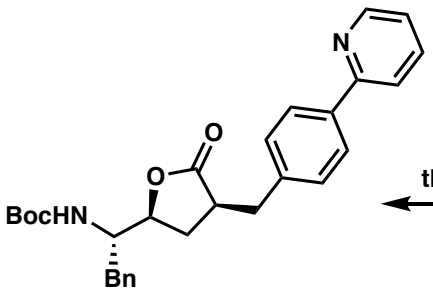
78% yield
1:1 d.r.



NaOEt
EtOH, 0 °C



LiOH,
then AcOH



82% yield
over 2 steps
5:1 d.r.

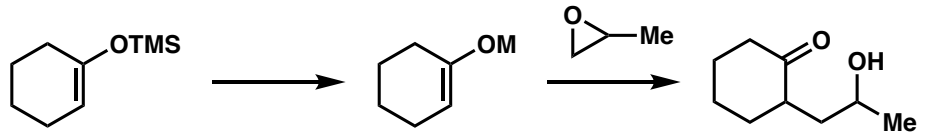
recrystallization

97:3 d.r.

J. Org. Chem. 2006, 71, 5369-5372

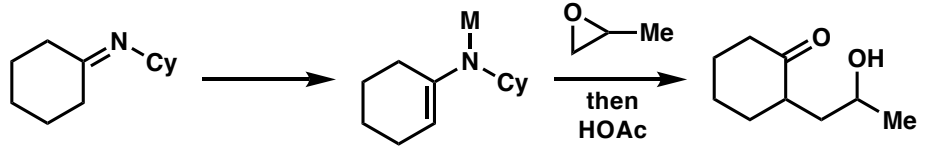
Ketones

Early work: imine salt workaround



M = Li, MgBr

"low to moderate yields"

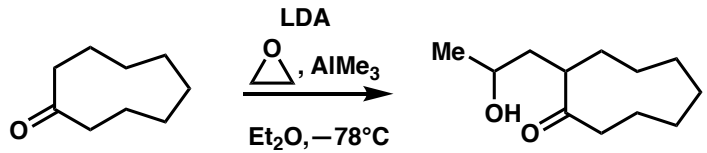


M = Li, MgBr

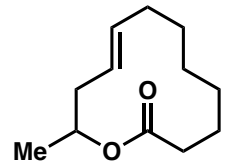
75% yield

J. Org. Chem. 1975, 40, 20, 2963–2965

Seminal report: Schreiber's total synthesis of (±)-recifeiolide



80% yield
96% brsm

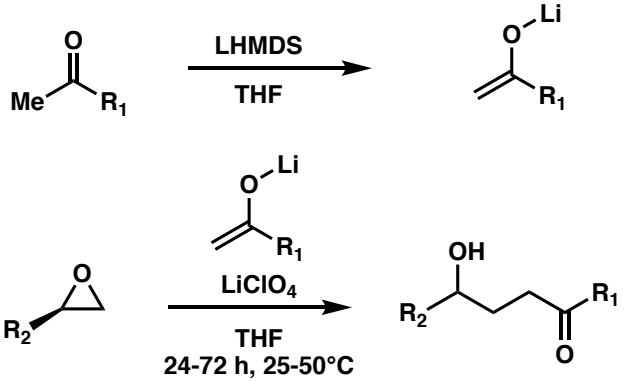


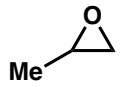
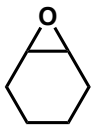
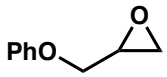
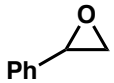
(±)-recifeiolide

J. Am. Chem. Soc. 1980, 102, 6163-6165

Enolate Alkylation of Epoxides

First published method: Paolo Crotti's time to shine



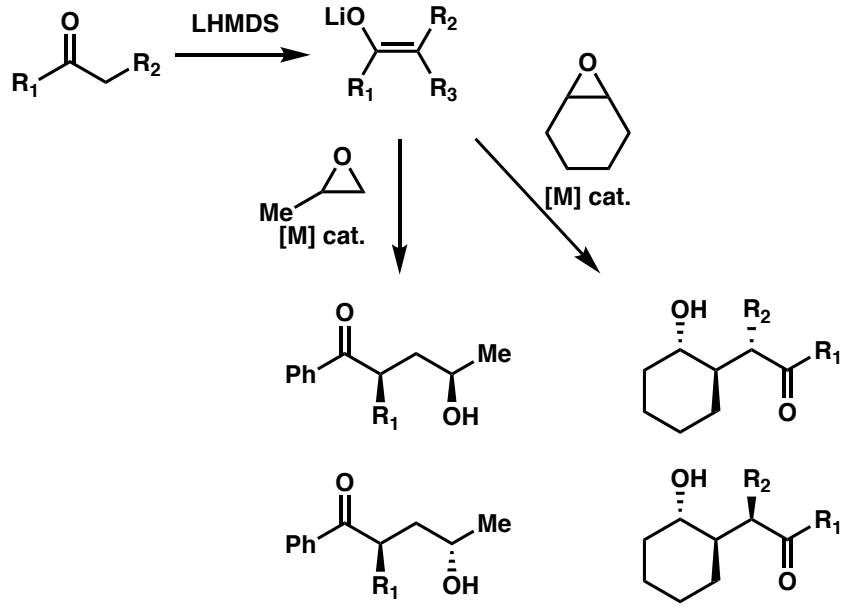
Epoxide	R_1	Additive	α attack %	β attack %	Yield %
	tBu	$LiClO_4$	<1	>99	98
	Ph	$LiClO_4$	<1	>99	86
	tBu	$LiClO_4$			80
	tBu	—			17
	Ph	$LiClO_4$			95
	Ph	—			12
	tBu	$LiClO_4$	<1	>99	90
	tBu	—	<1	>99	30
	Ph	$LiClO_4$	<1	>99	76
	Ph	—	<1	>99	15
	tBu	$LiClO_4$	9	91	95
	tBu	—	9	91	30
	Ph	$LiClO_4$	12	88	80
	Ph	—			0

Tet. Lett. 1991, 32, 51, 7583-7586

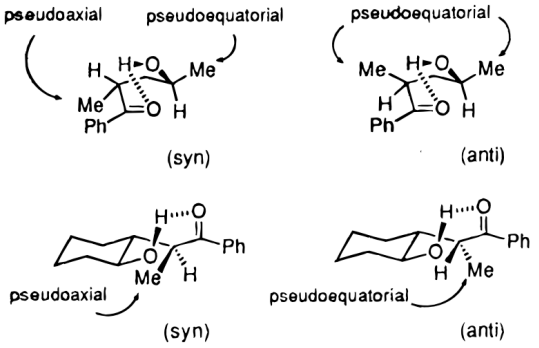
Crotti later discovers that $Y(OTf)_3$ promotes reaction in almost quantitative yields with milder, shorter reaction conditions (0°C - r.t., 18 hr).
- Same substrate scope has yields (80-99%),
**** Worse α:β selectivity observed w/ styrene oxide***
R_1 = tBu - 40:60, R_1 = Ph - 85:15

Tet. Lett. 1994, 35, 29, 6537-6540

"But wait - there's more!" -Crotti, probably



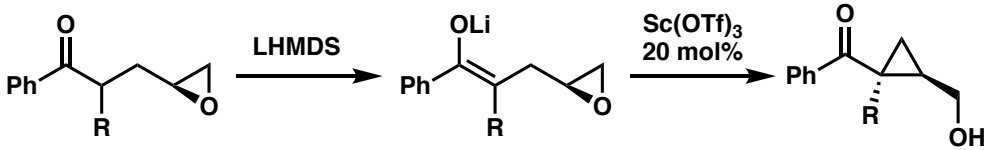
Superier catalyst was determined to be 10 mol % $Sc(OTf)_3$ (78-95% yield).
Unfortunately, method has poor diastereoselectivity.
Slight *syn* preference - best *syn:anti* w/ $Y(OTf)_3$ 60:40.
Other catalysts screened:
$Y(OTf)_3$, $Ti(Cp_2)(OTf)_2$, $Zr(Cp)_2(OTf)_2$, Ph_4SbOTf, $Yb(camph)_3$
Moral of the story:
Lewis acids allow for milder epoxide enolate alkylation conditions.



J. Org. Chem. 1996, 61, 9548-9552

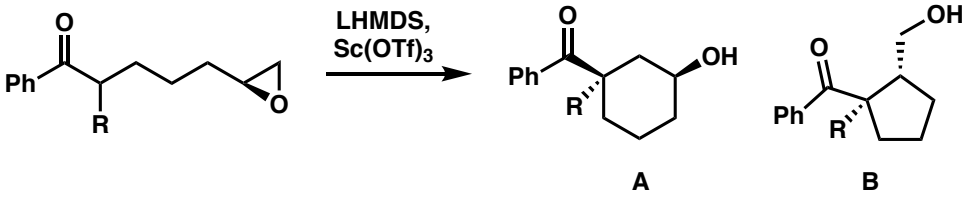
Intramolecular Ketone Enolate Alkylation

4,5-epoxy ketone



R	Yield
H	94%
Me	86%

6,7-epoxy ketone

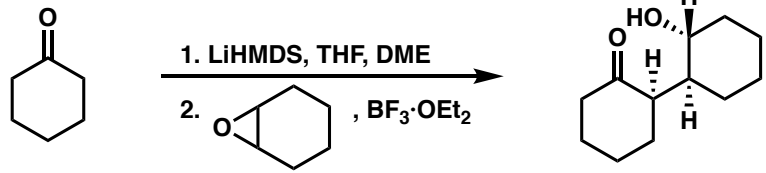


with 5,6 epoxy ketones, reaction described as "unexpectedly inefficient" yielding only a complex mixture of products

R	Yield	A:B
H	98%	84:12
Me	92%	80:0

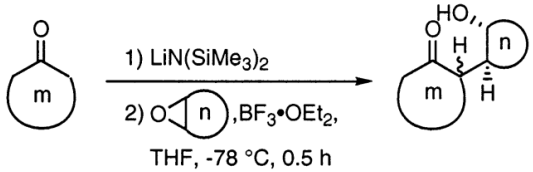
Tetrahedron. 1999, 55, 18, 5853-5866

A modern building block



Tet. Lett. 2000, 41, 49, 9655-9659

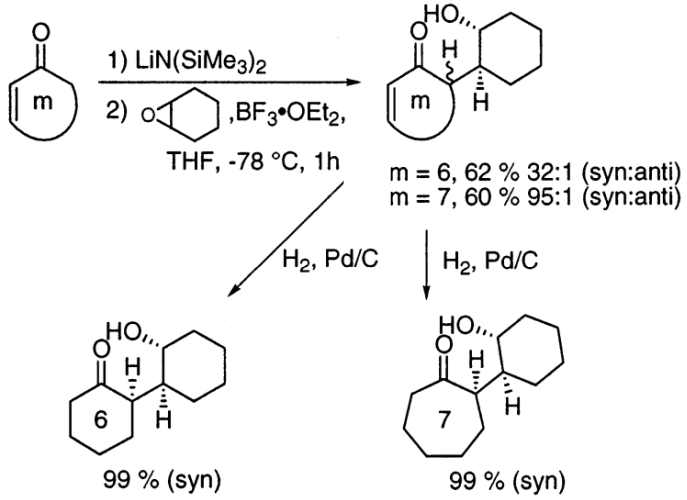
Stereochemical studies:



m	n	product	% yield	dr (*syn*:*anti*) (H/H)
5	6	**1**	70	6:1
6	5	**2**	57	5:1
6	6	**3**	76	8:1
7	5	**4**	75	4:1
7	6	**5**	73	8:1

Syn diastereomer = kinetic product.
Equilibrating pure syn or anti product with KOH at r.t. for 2 days gives 2:3 ratio of syn:anti diastereomers.
Use of NaHMDS instead of LHMDS increases yield but severely diminishes diastereoselectivity.

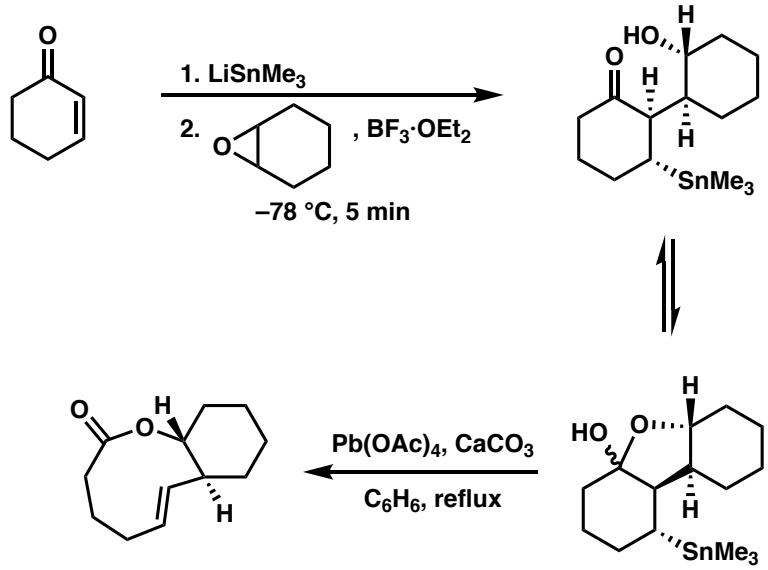
Use of enones over ketones improves stereoselectivity.



J. Org. Chem. 2003, 68, 8, 3049-3054

Enolate Alkylation of Epoxides

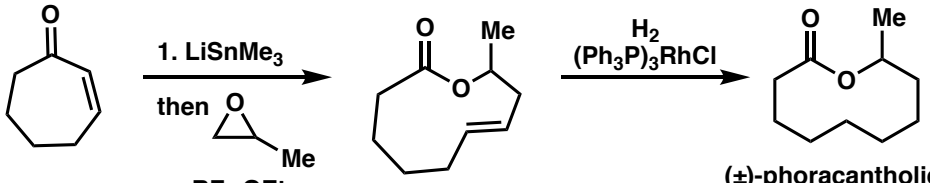
Enones



50% overall yield

Method works for both 1- and 1,2 substituted epoxides and 6- and 7-membered enones.
Substrate scope yields range from 31 to 51%.
Synthetic equivalent of n+3 homologous Baeyer–Villiger oxidation

Three Step Total Synthesis of (±)-Phoracantholide

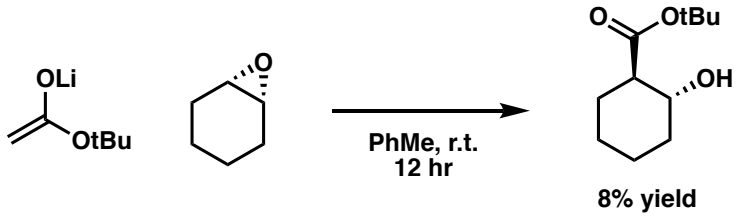


(±)-phoracantholide
45% yield

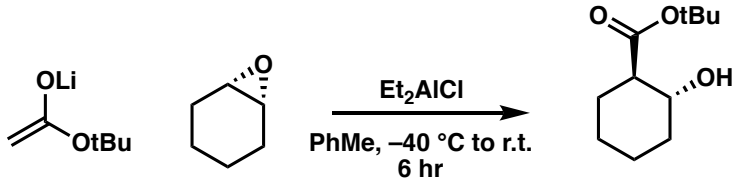
Tet. Lett. 2000, 41, 49, 9655-9659

Esters

Aluminum enolates enable this transformation.



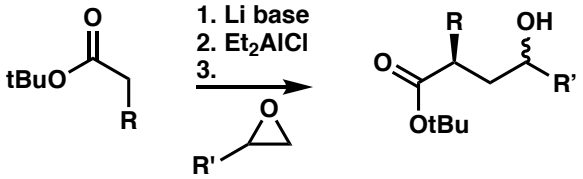
8% yield



68% yield

J. Org. Chem. 1976, 41, 9, 1669–1671

Monocyclic epoxides - Stephen Taylor



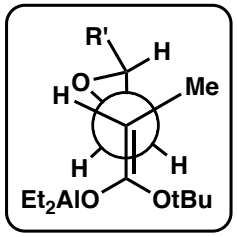
R	Base	R′	Yield[a]	*syn:anti*
H	LDA	Me	46	–
H	LDA	Et	52	–
H	LDA	*t*-Bu	49	
Me	LDA	Me	56 (70[b])	84:16
Me	LDA	Et	43	84:16
Me	LDA	*i*-Pr	56	88:12
Me	LDA	*t*-Bu	38	95:5
H	LHMDS	Me	58 (66[b])	–
H	LHMDS	Et	71	–
H	LHMDS	*t*-Bu	54	–
Me	LHMDS	Me	12	56:44
Me	LHMDS	Et	28	62:38

[a] Distilled yields.
[b] GC yields.

*<1% product w/o Et_2AlCl

Enolate Alkylation of Epoxides

Monocyclic epoxides cont.



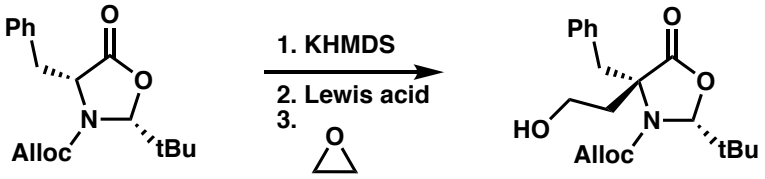
E enolate predominates syn preference

Other lessons learned:

- Low temp. minimizes Claisen condenation pdts
- Al NOT activating epoxide (no Markovnikov pdt)
- N of LHMDS coordinates less strongly to Al as LDA
- HMPA cosolvent presumed to coordinate with Al; does not improve selectivity with LHMDS
- α-substitution of ester has higher yields w/ LDA, but no α-substitution has higher yields w/ LHMDS

J. Org. Chem. 1989, 54, 2039-2040
J. Org. Chem. 1993,58, 7304-7307

Oxazolidinones

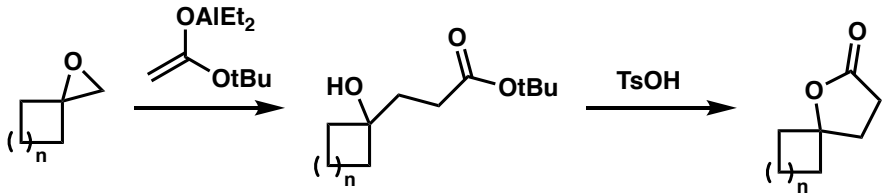


82% yield

Lewis Acid	Equiv	Yield
$TiCl_4$	3.3	0%
Bu_2BOTf	2.2	0%
$BF_3{\cdot}OEt_2$	2.2	29%
Me_3Al	2.1	46%
Et_2AlCl	1.1	36%
Et_2AlCl	2.1	69%
Et_2AlCl	3.1	49%

Tet. Lett. 1994, 35, 48, 8977-8980

Spirocyclic Lactone Synthesis



n = 1-4

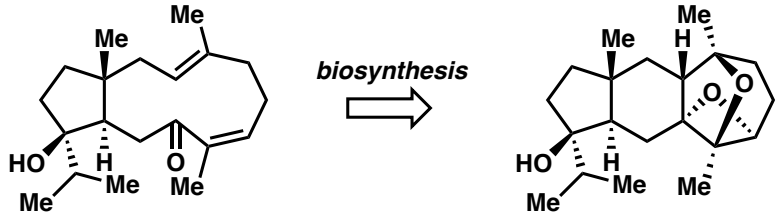
62-76% yield

81-99% yield

Synthesis 1988, 1009

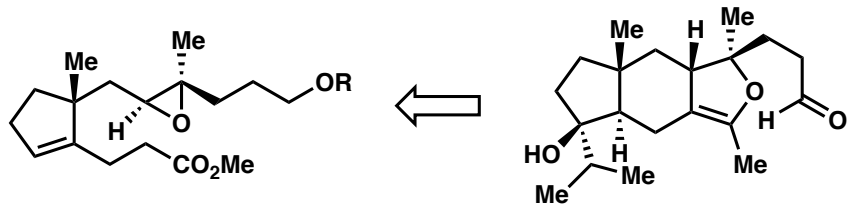
Failure of the ester-enolate alkylation:

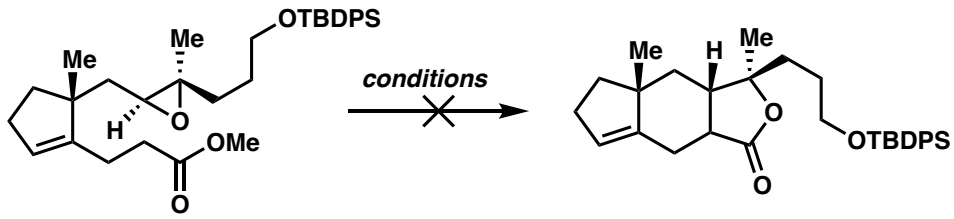
Total synthesis of marine diterpenoids (+)-dictyoxetane and (+)-dolabellane V



(+)-dolabellane V

(+)-dictyoxetane





Bases: LHMDS, KHMDS, LDA, NaH, KH,
Lewis Acids: TMSCl, $Ti(OiPr)_4$, Et_2AlCl, $AlCl_3$, $TiCl_4$

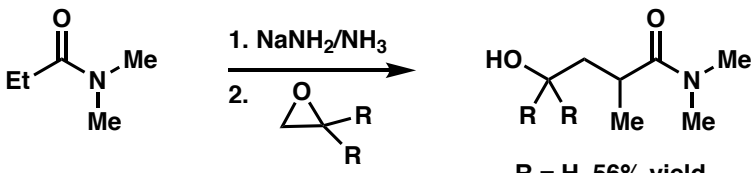
Only product (trace) was intermolecular Claisen condensation product. Halohydrin formation observed with $AlCl_3$ and $TiCl_4$.

Chem. Eur. J. 2016, 22, 15125-15136

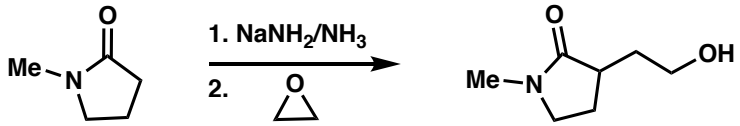
Enolate Alkylation of Epoxides

Amides

Early reports

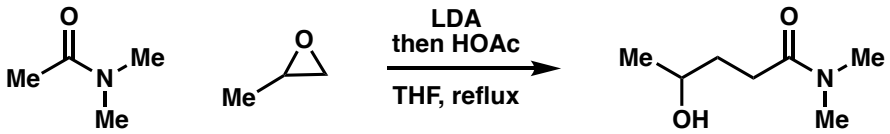


R = H, 56% yield
R = Me, 35% yield

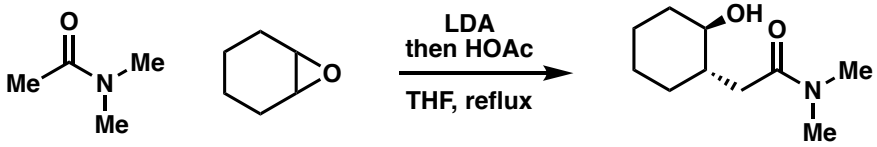


54% yield

Chem. Ber. 1972, 105, 1621-1633.



85% yield

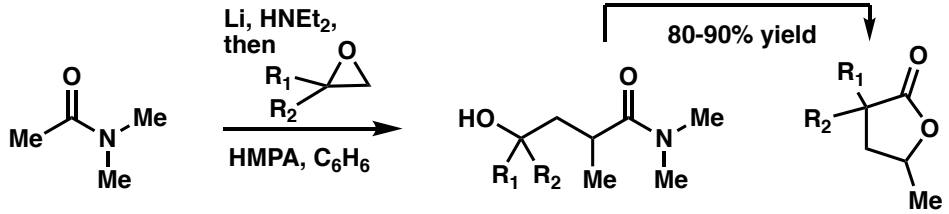


57% yield

J. Org. Chem. 1977, 42, 10, 1688–1690

Best yields observed with 1- and 1,1-substituted epoxides.

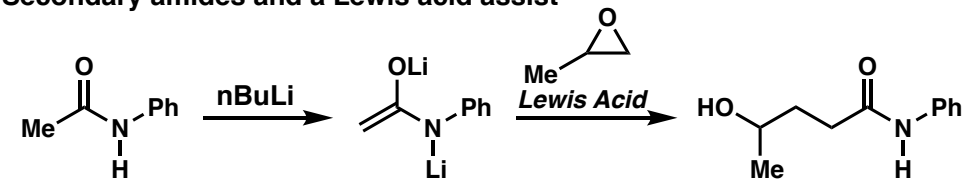
'Activated' amides with HMPA



R_1	R_2	Amide	Lactone
H	Me	72% yield	22% yield
Me	Me	51% yield	5% yield

Can. J. Chem. 1977, 55, 266-273

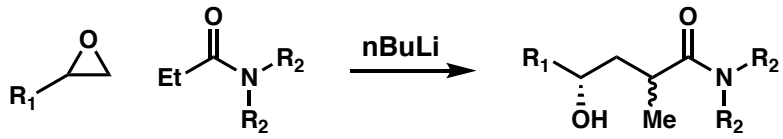
Secondary amides and a Lewis acid assist



Lewis Acid	$BF_3{\cdot}OEt_2$	$SnCl_4$	$TiCl_4$	Et_2AlCl	none
Yield	80%	64%	61%	53%	10%

Synth. Commun. 1988, 18, 1159-1165

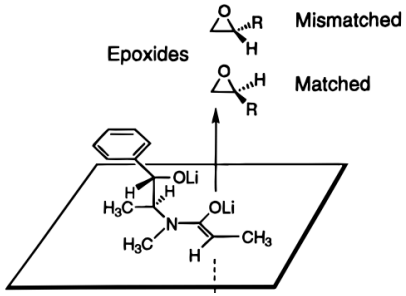
Diastereoselctivity improves with bulky epoxides and amides.
…and a very quick solvent "screen."

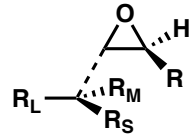


R_1	R_2	Solvent	*syn:anti*
Me	iPr	THF	63:37
Me	iPr	Et_2O	74:26
Ph	iPr	Et_2O	90:10

J. Org. Chem. 1981, 46, 2831-2833

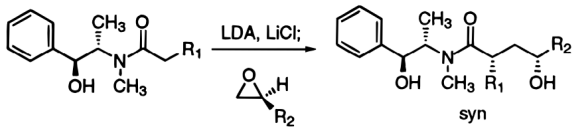
Myers: diastereoselectivity with pseudoephedrine amide enolates





"matched" case simplified

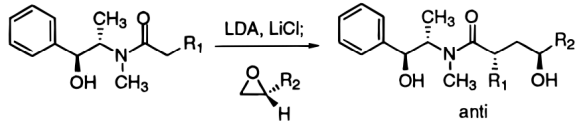
"Matched" Epoxides[a]



entry	R_1	R_2	temp (°C)	time (h)	isolated yield %	de %
1	CH_3	CH_3	−5	4	88	93
2	CH_3	C_6H_5	−5	7	82	90
3	CH_3	CH_2OTBS	−5	10	84	96
4	CH_3	CH_2OBn	−5	12	80	85
5	Bn	CH_3	−5	9	86	≥99
6	Bn	C_6H_5	−5	10	86	≥95
7	Bn	CH_2OTBS	−5	11	81	≥99
8	Bn	CH_2OBn	−5	12	87	≥95

[a] 2 equiv of epoxide was used in each experiment.

"Mismatched" Epoxides[a]



entry	R_1	R_2	temp (°C)	time (h)	isolated yield %	de %
1	CH_3	CH_3	−5	6	86	73
2	CH_3	C_6H_5	−5	10	73	25
3	CH_3	CH_2OTBS	0	21	78	12
4	CH_3	CH_2OBn	−5	13	78	38
5	Bn	CH_3	−5	10	79	45
6	Bn	C_6H_5	−5	15	72	46
7	Bn	CH_2OTBS	5	26	64	17
8	Bn	CH_2OBn	−5	12	80	36

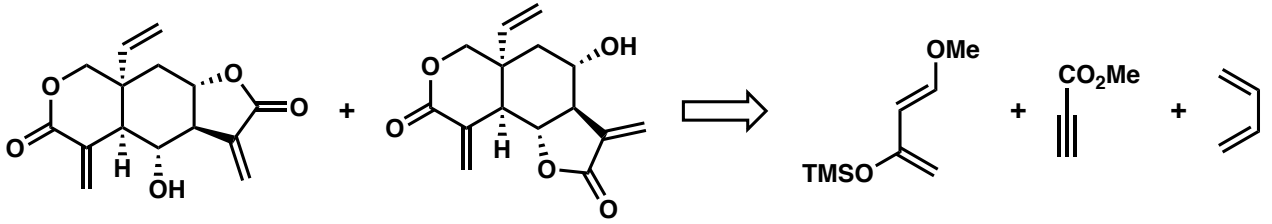
[a] 2 equiv of epoxide was used, except in entry 3, where 1.5 equiv was employed.

Syn product formation is highly selective, wheras anti product formation is not.

J. Org. Chem. 1996, 61, 2428-2440
Further reading on enolate facial selectivity:
Tet. Lett. 1988, 29, 4245
Tet. Lett. 1994, 35, 673

Carboxylic Acids

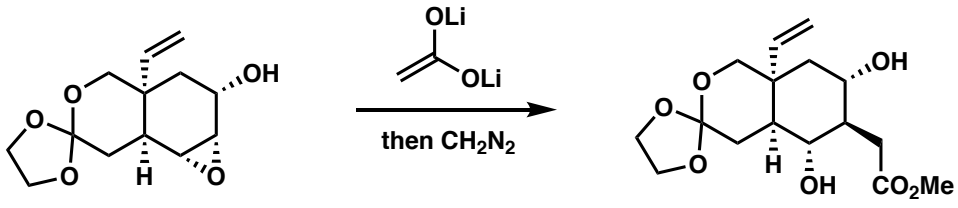
A Remarkable Epoxide Opening. An Expeditious Synthesis of Vernolepin and Vernomenin



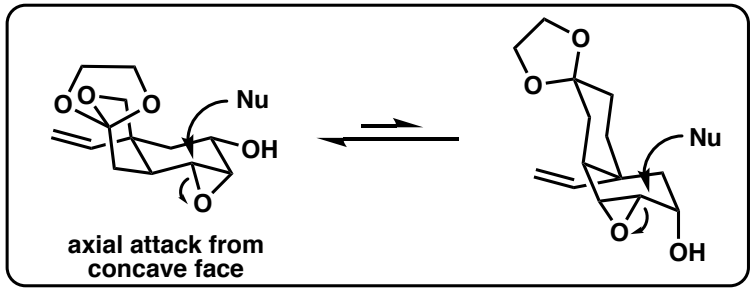
vernomenin

vernolepin

First time the 'Danishefsky diene' was used by the group.



56% yield

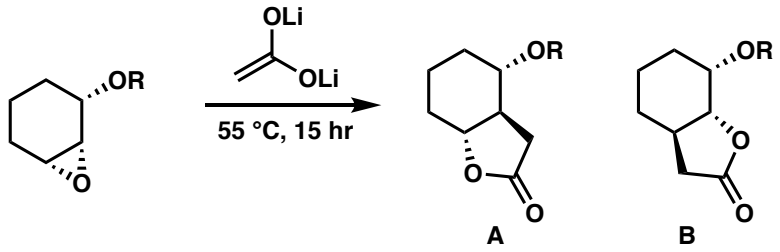


J. Am. Chem. Soc. 1976, 98, 10, 3028–3030
J. Am. Chem. Soc. 1977, 99, 18, 6066–6075

Enolate Alkylation of Epoxides

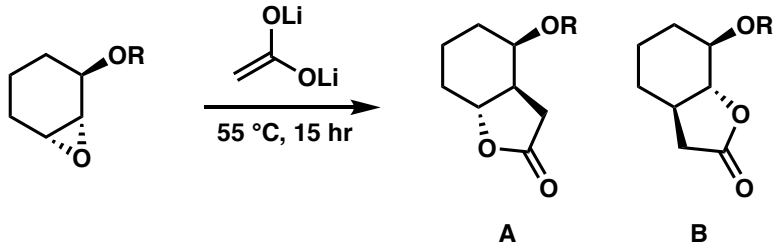
Danishefsky cont. - oxygen directing groups

Syn oxy-functionality



R	A : B
H	3 : 1
TMS	1 : 3.2

Anti oxy-functionality



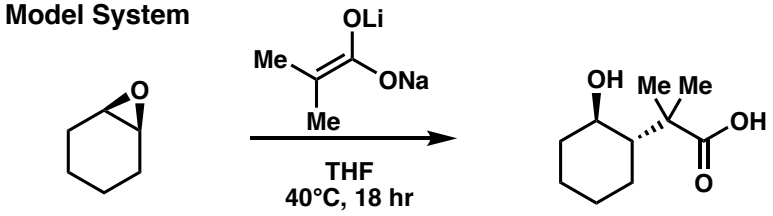
R	A : B
H	3.2 : 1
TMS	1 : 4.5

Dianion openings are affected by alpha-oxy-functionality, not by relative stereochemistry.

J. Org. Chem. 1977, 42, 2, 394–396

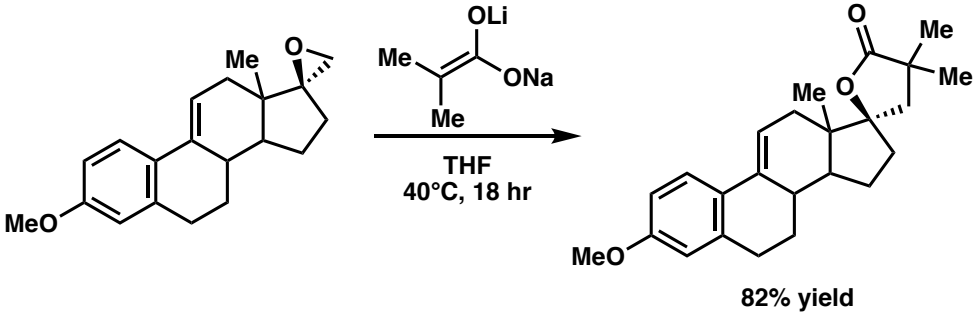
Spirocyclic lactone synthesis

Model System

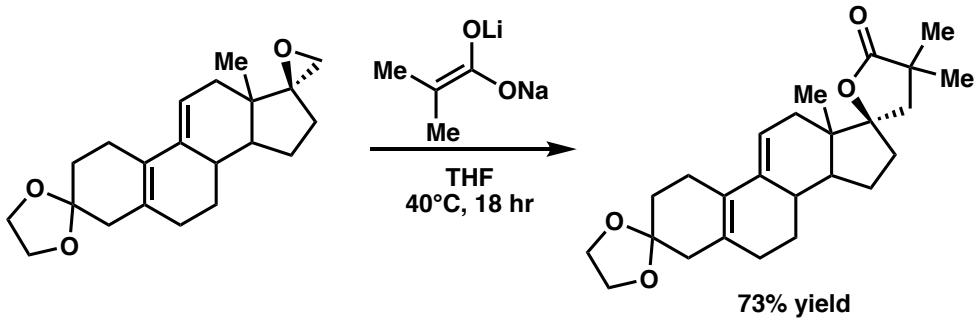


91% yield

- HMPA did not improve yields or reaction homogenatiy
- acidic workup yields lactone
- dianions can have solubility problems (large excess often used)



82% yield



73% yield