Stereoselective Transannular Reactions

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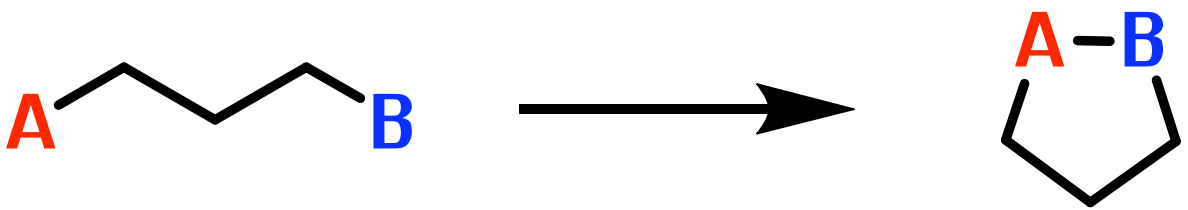
Outline

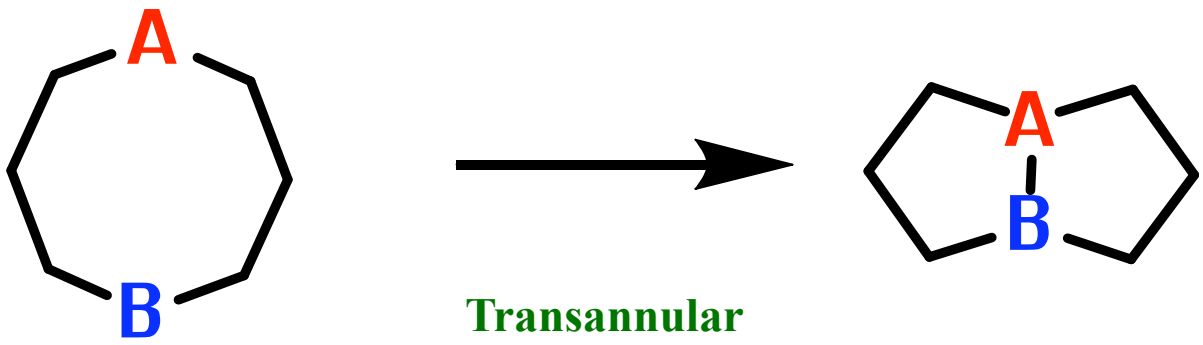
- Macrocycle Tutorial
  - Conformational analysis of C8-C10 rings
  - Energetics of transannular reaction
- Conformation Directed Stereoselective Transannular Reactions
  - Spirocyclic Systems
  - Bicyclic Systems
  - Tricyclic Systems
  - Polycyclic Systems
- Catalytic Systems
  - Enantioselective Catalytic Transannular Aldol Reactions
  - Enantioselective Catalytic Transannular Diels-Alder Reactions
- Conclusion

Comparison of Chemical Reactions

Intermolecular



Intramolecular



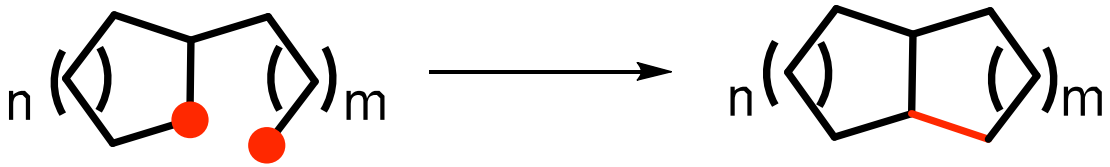
Transannular

"Transannular" Etymology

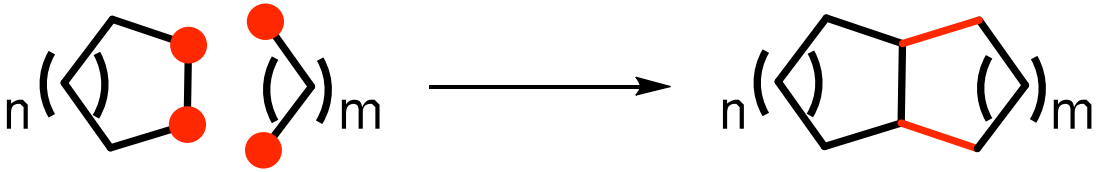
- Latin prefix ***TRANS*** - across or through
- Latin root ***ANNO*** – year
- Year is a circuit of the Sun, cycle

Cyclization Approaches

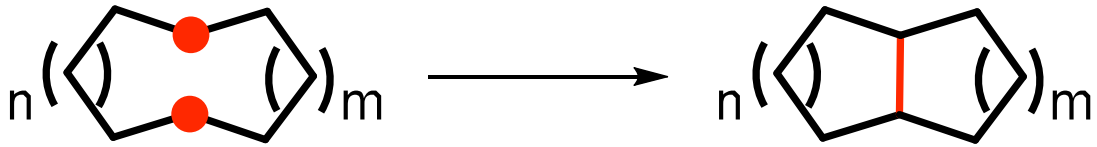
Annulation of Pendant Side-chain



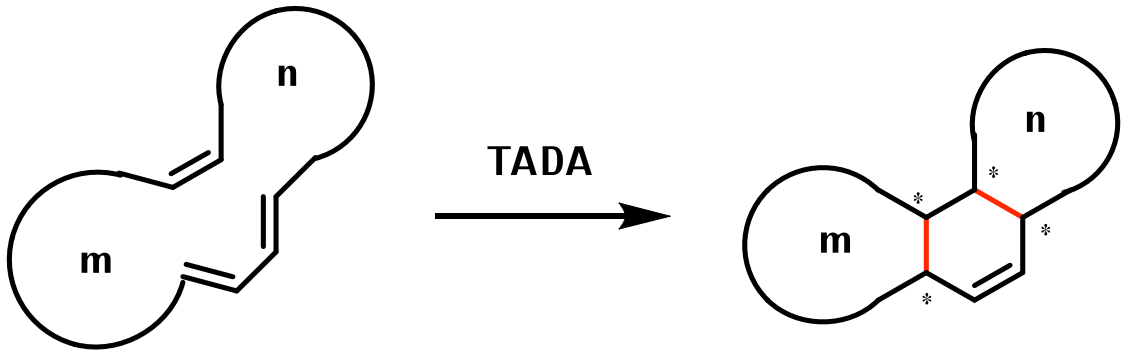
Cycloaddition Reaction



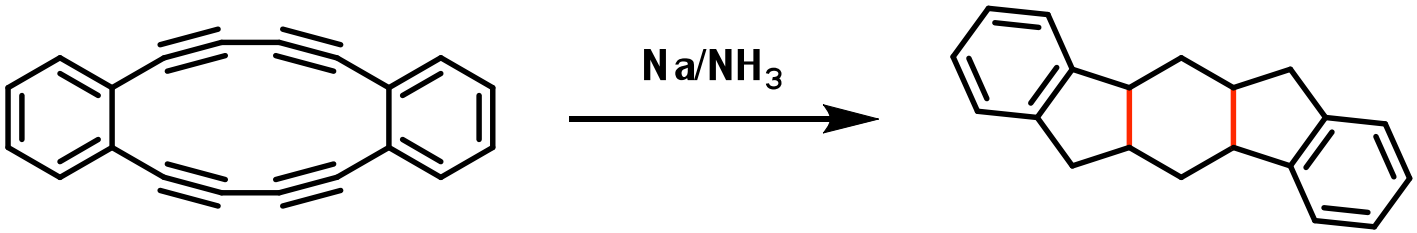
Transannular Reaction



Examples of Transannular Reaction

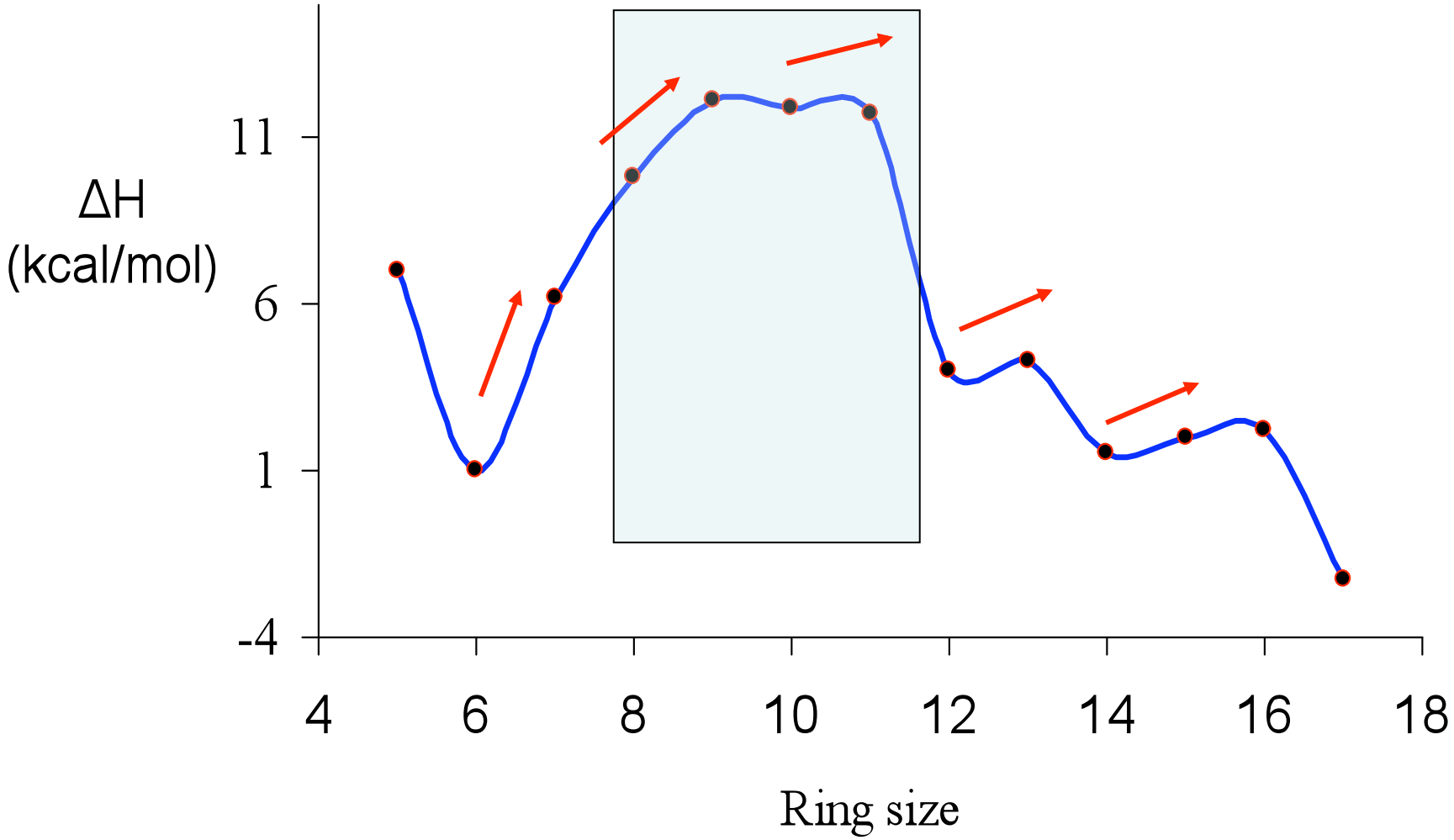


Deslongchamps, P. *Pure & Appl. Chem.* **1992**, *64*, 1831



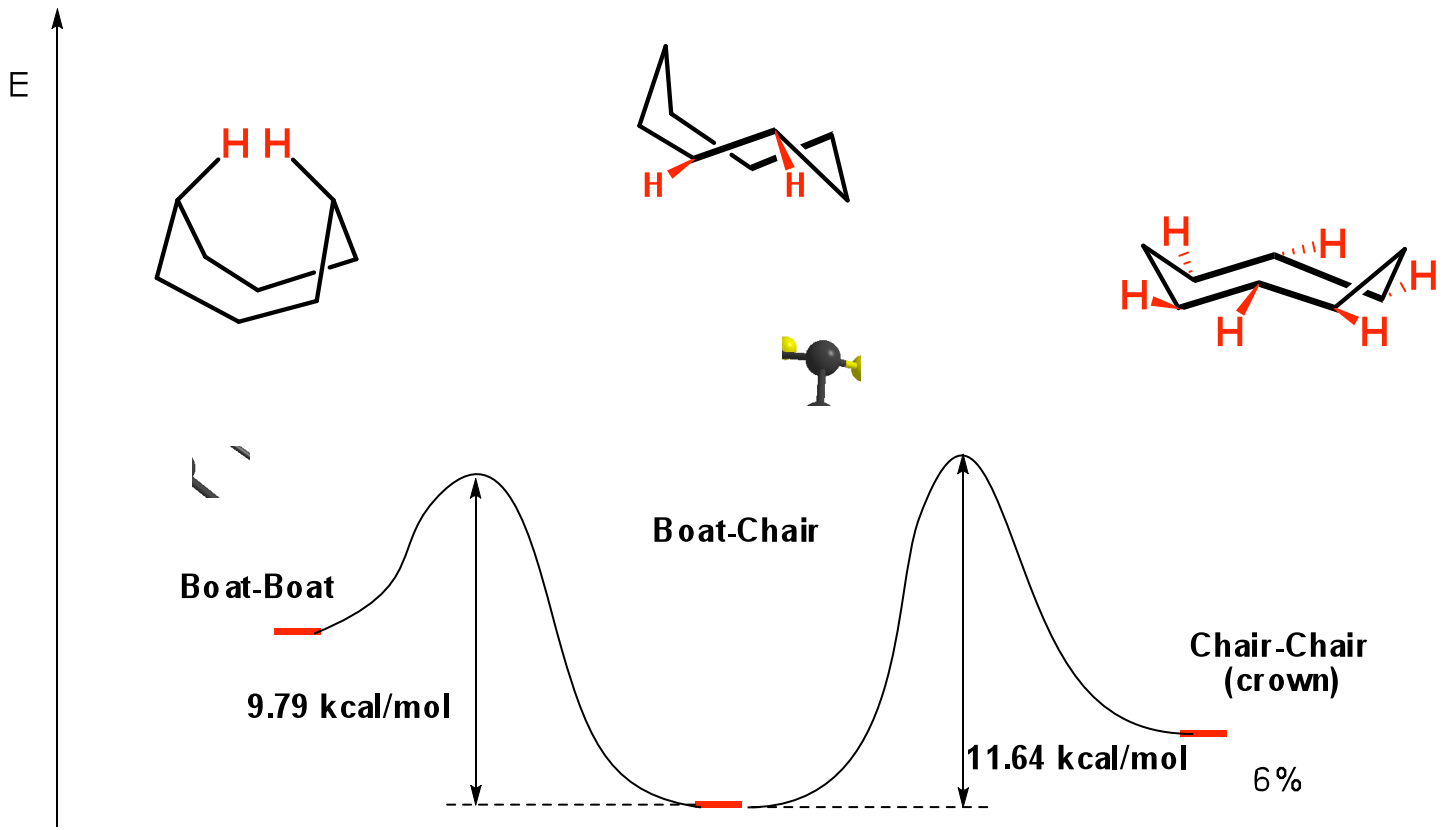
Schmidt, E. M.; Gleiter, R.; Rominger, F. *Chem. Eur. J.* **2003**, *9*, 1814

Enthalpy of Cycloalkanes



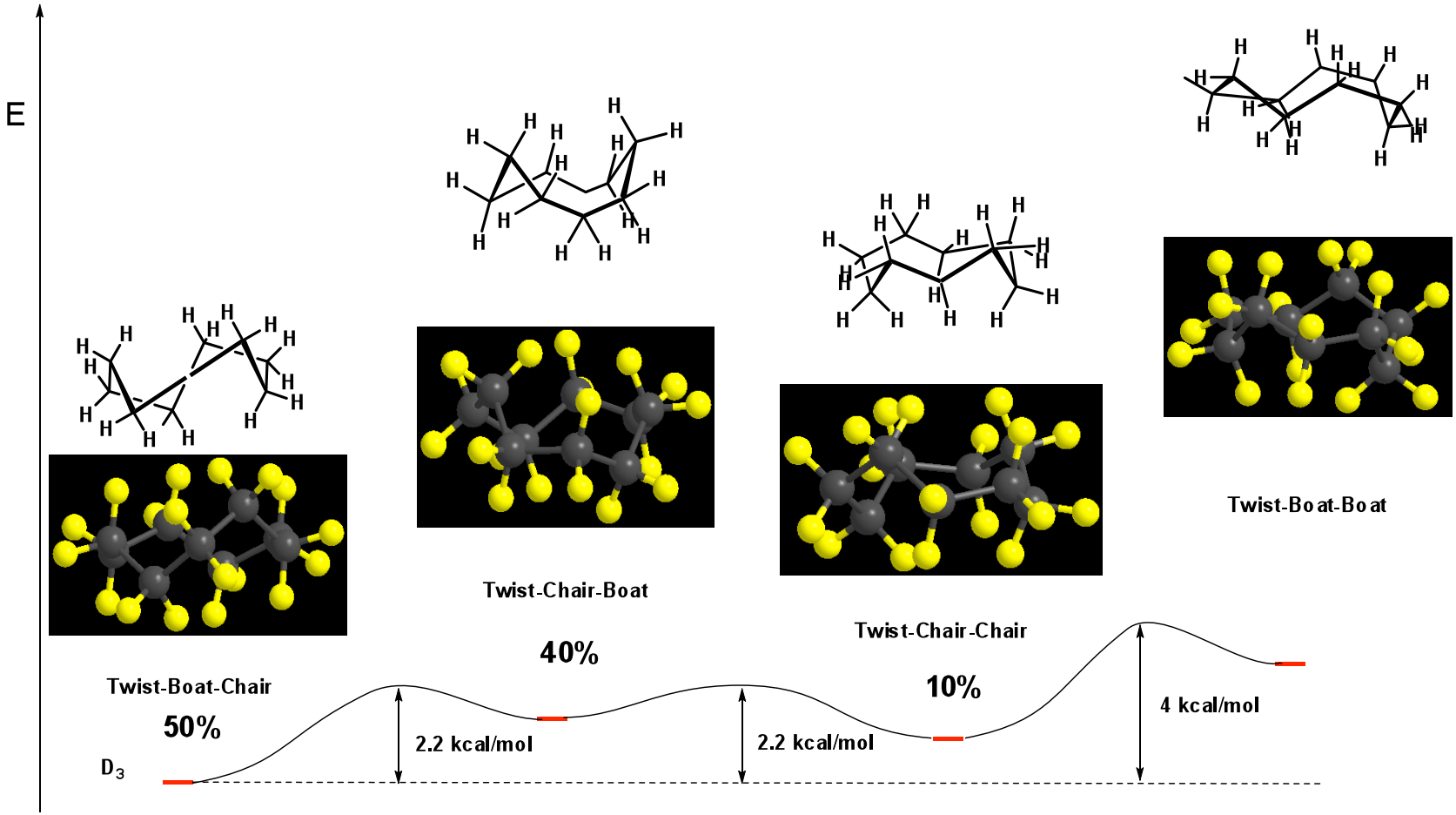
Dunitz, J.D.; Prelog, V.P. *Angew. Chem.* **1960**, *72*, 896

Conformations of Cyclooctane



Rocha, W. R.; Pleigo, J. R.; De Almeida, W. B. *J. Comp. Chem*. **1998**, *19*, 524

Conformations of Cyclononane



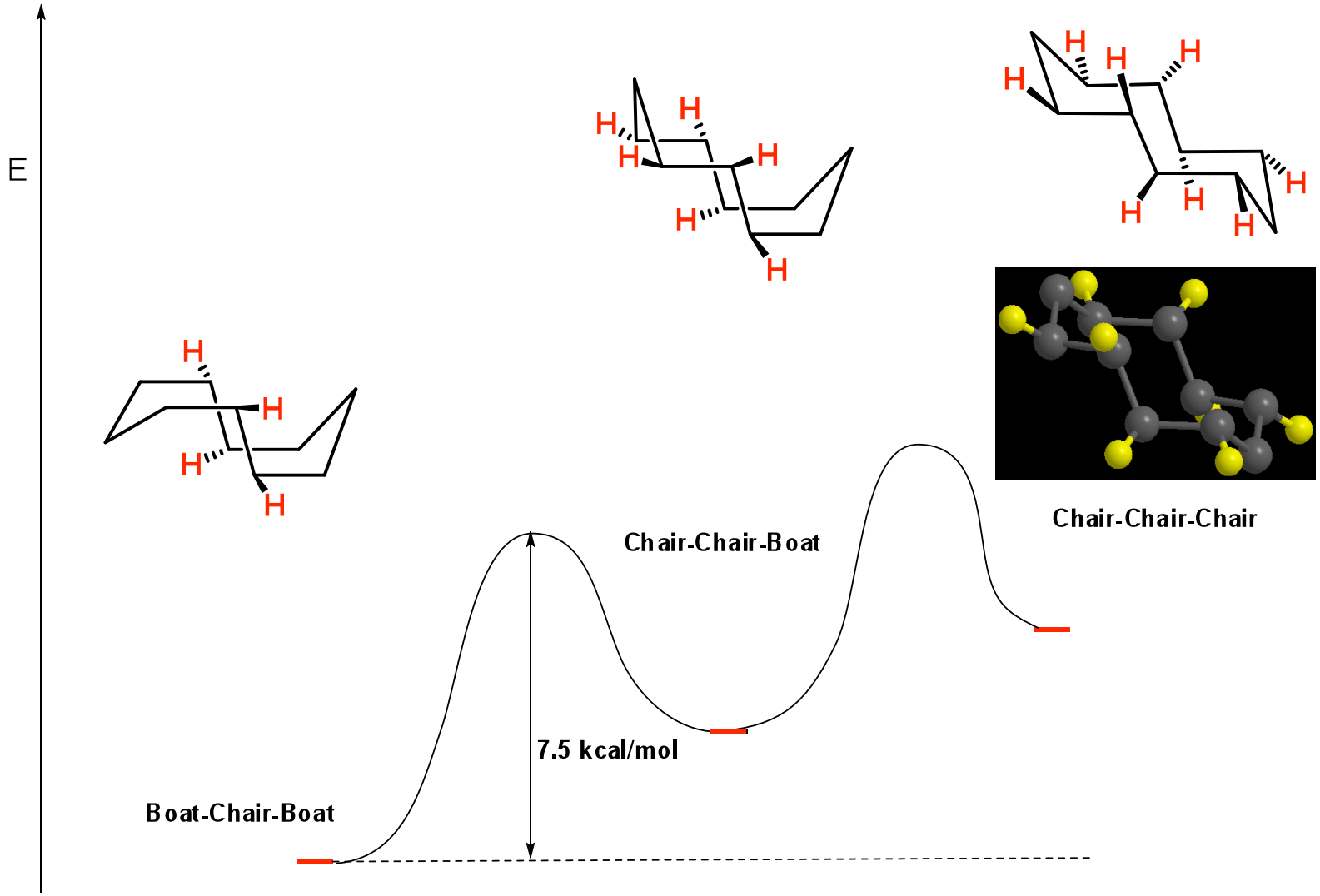
Hendrickson, J.B. *J. Am. Chem. Soc.* **1964**, *86*, 4854

Dale, J. *Acta, Chem. Scand.*, **1973**, *27*, 1115

Ferguson, D.M.; Glauser, W. A.; Raber, D. J. *J. Comp. Chem.* **1989**, *10*, 903

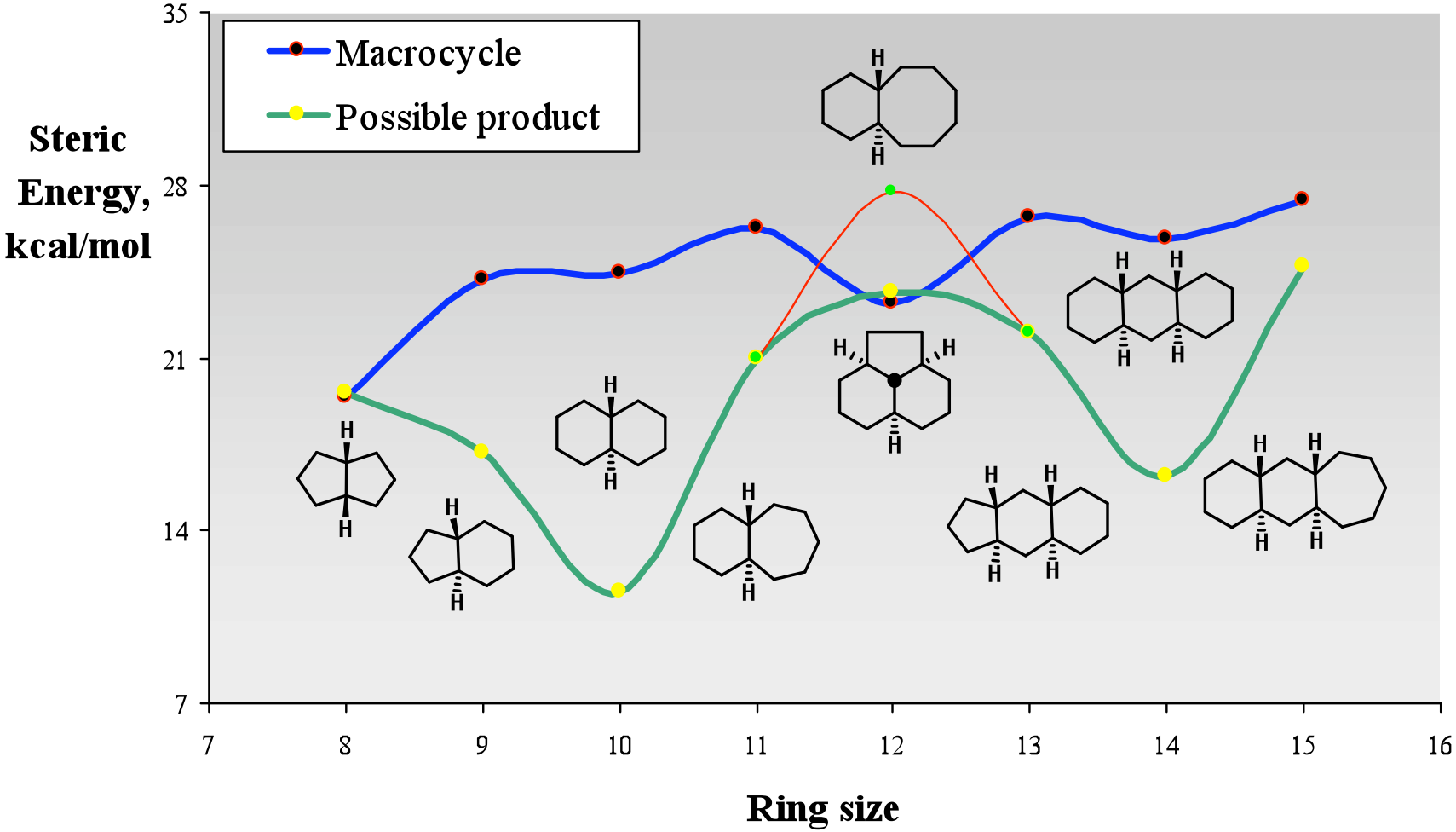
Kolossviry, I.; Guida, W.C. *J. Am. Chem. Soc.* **1993,** *115***,** 2107

Conformations of Cyclodecane



Kolossviry, I.; Guida, W.C. *J. Am. Chem. Soc.* **1993,** *115,* 2107
Pawar, D. M.; Smith, S. V.; Odom, R. M.;Noe, E. A. *J. Am. Chem. Soc.* **1998,** *120,* 10715

Connection of a Macrocycle and its Possible Product



Facts for Macrocycles

- Macrocycles tend to decrease their strain
- Reactive sites are in close proximity
- Even-membered macrocycles are more symmetrical, have higher interconversion barrier
- Odd-membered cycles are less symmetrical, have smaller interconversion barrier

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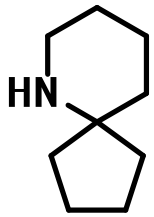
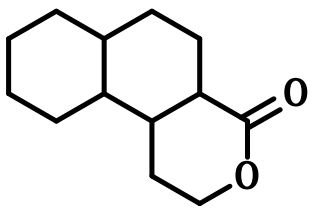
- Conclusion

Types of Cycles via Transannular Reactions

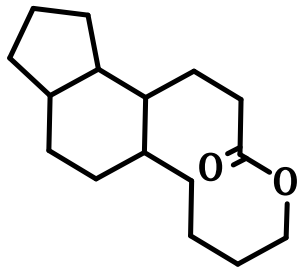


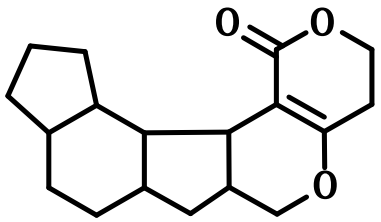
spirocycle

fused bicycles



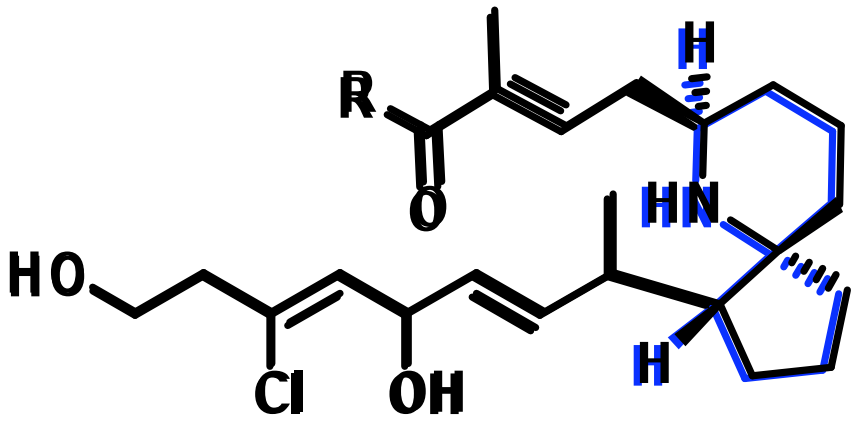
tricycle





pentacycle

Pinnaic and Tauropinnaic acid

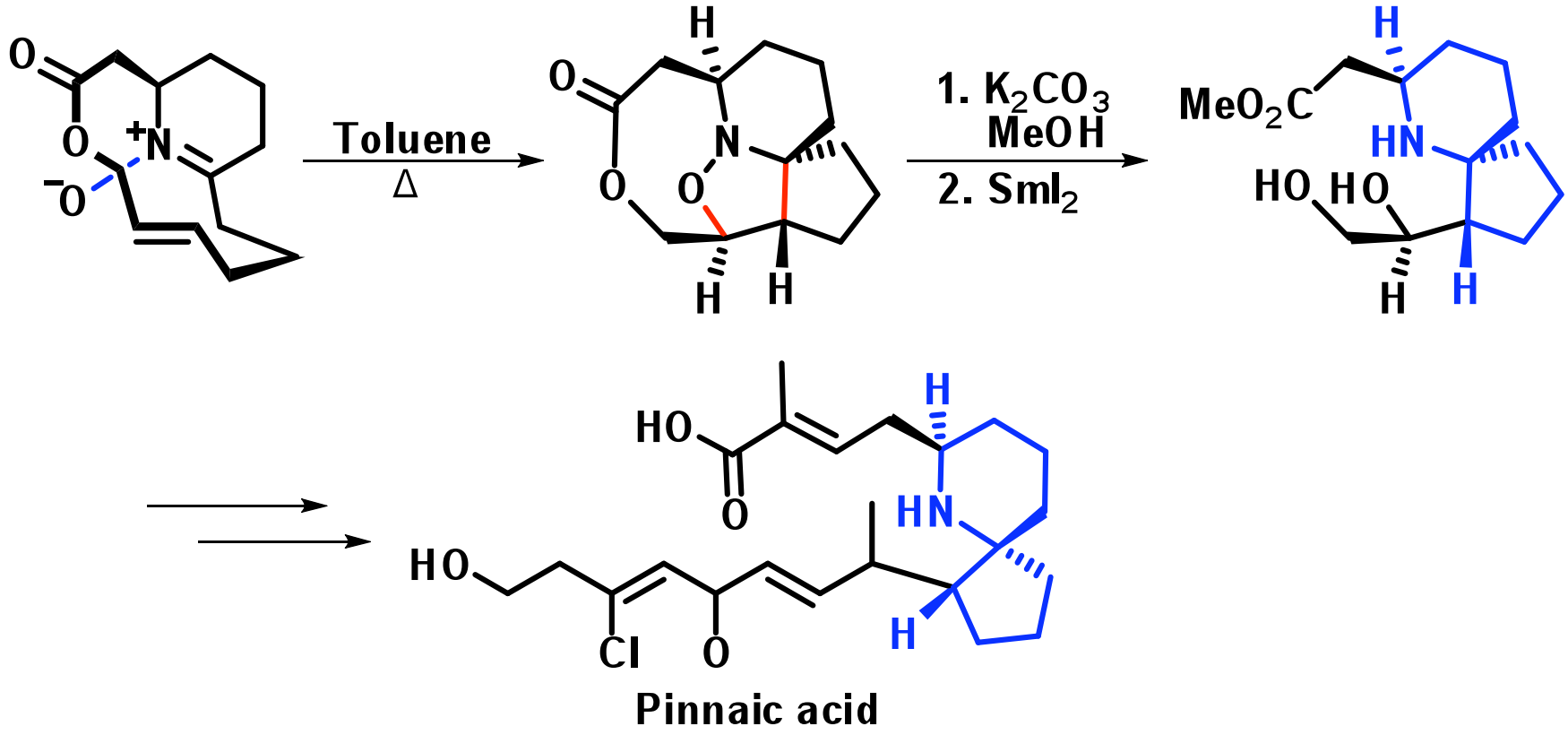


Pinnaic acid R = OH
Tauropinnaic acid R = $NH(CH_2)_2SO_3H$

Isolated in 1996
17 syntheses are published

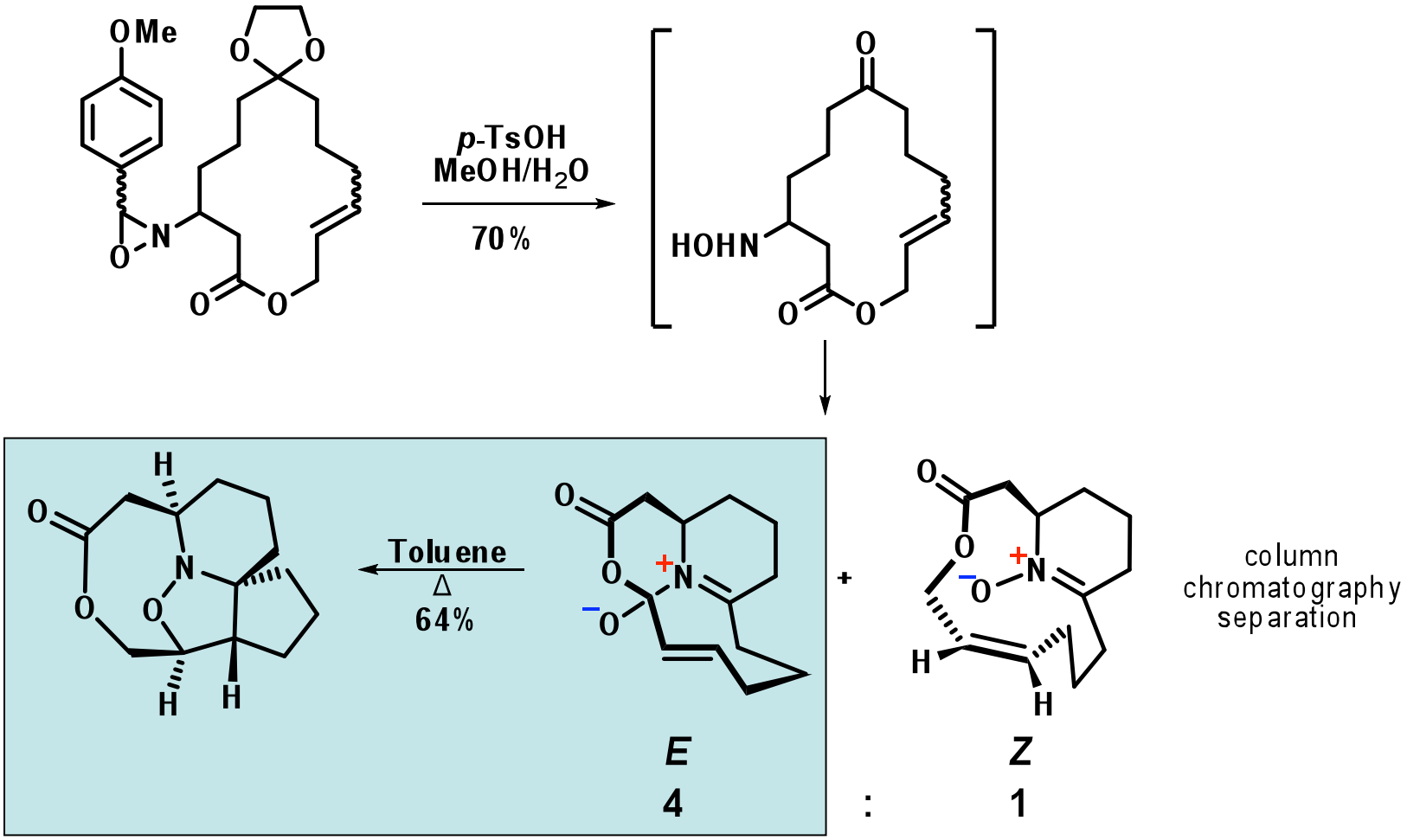
Clive, D. L. J.; Yu, M.; Wang, J.; Yeh, V. S. C.; Kang, S. *Chem. Rev.* **2005**, *105*, 4483

Transannular Nitrone Cycloaddition Towards Pinnaic Acid



White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 413

Stereoselectivity Controlled by Ring Size



White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 413

Fused Bicycles by Transannular Reactions

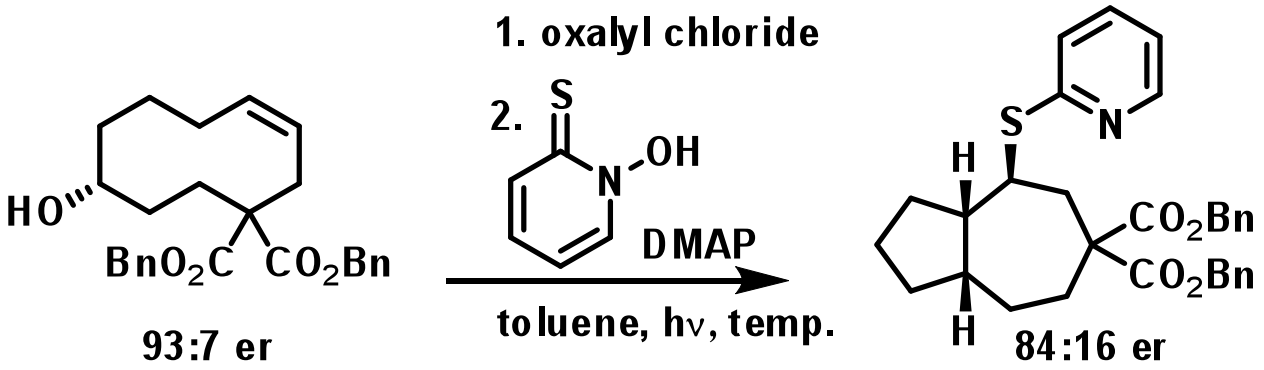
spirocycle

fused bicycles

tricycle

pentacycle

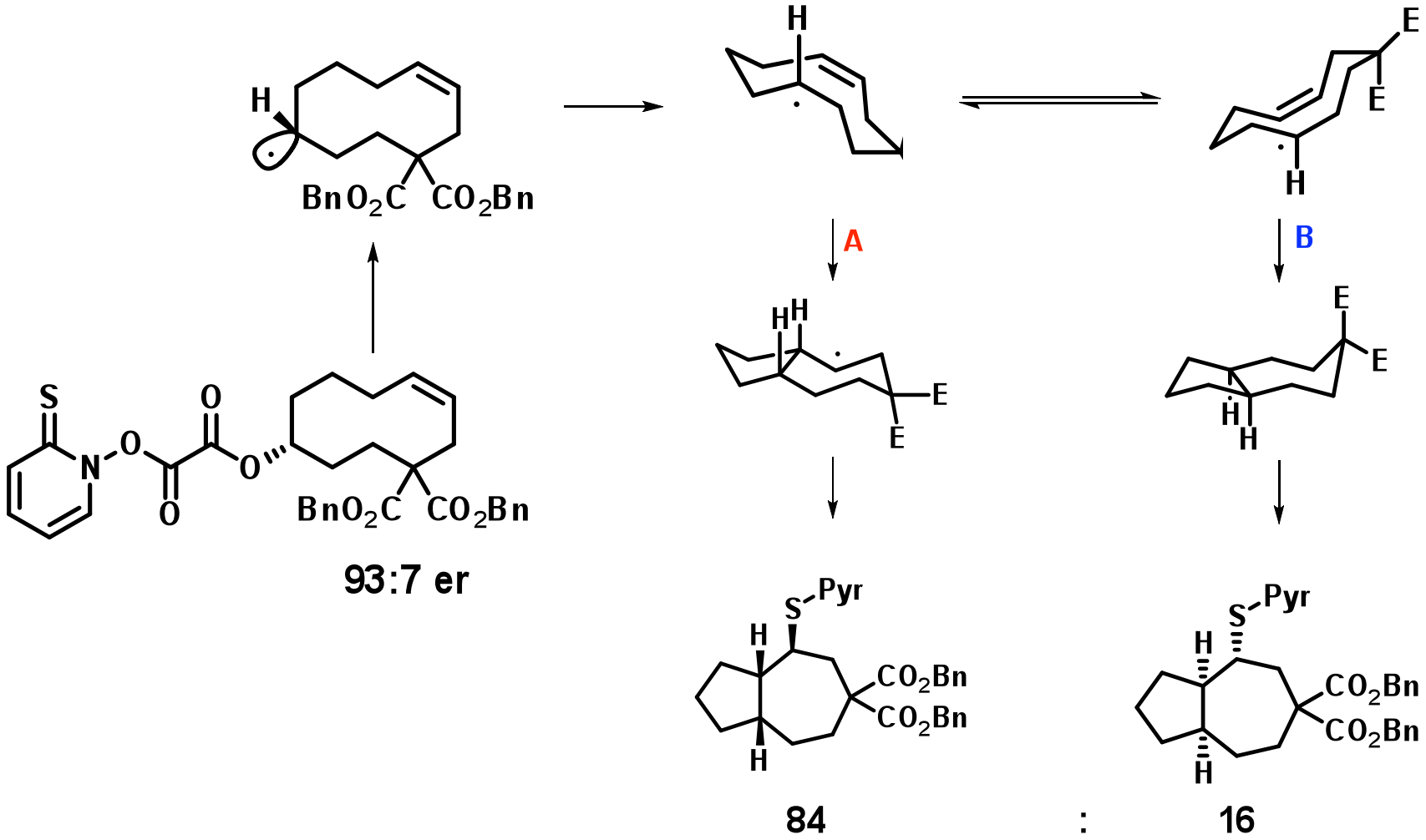
Memory of Chirality in Transannular Cyclization



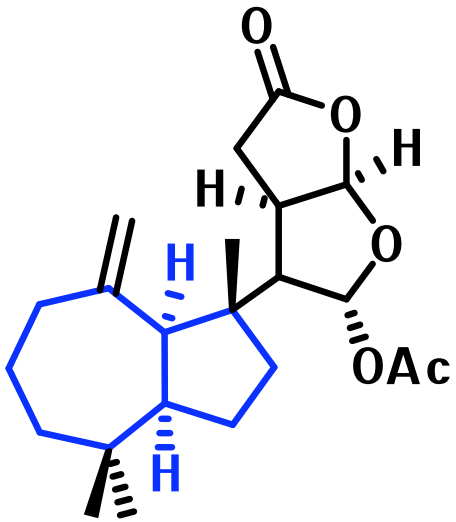
entry	temp (°C)	yield (%)	er
1	23	88	63 : 37
2	0	67	79 : 21
3	-15	51	84 : 16
4	-35	43	84 : 16

Dalgard, J. E.; Rychnovsky, S. D. *Org. Lett.* **2004**, *6*, 2713

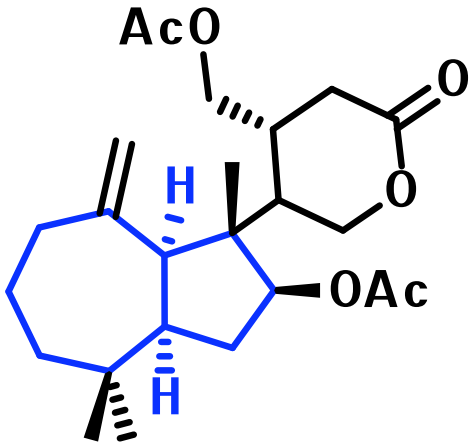
Radical Stereoselective Transannular Cyclization



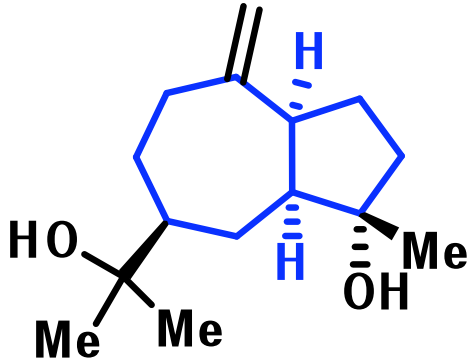
Natural Products with 5,7-Fused Ring



Dendrilolide A



Shahamin K

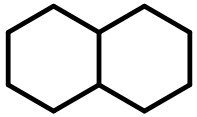


Pleocarpene

Clardy, J.; Cun-Leng, H.;.; Molinski, T. F.; Van Duyne, G. D. *J. Org. Chem.* **1986**, *51*, 4564
Andersen, R. J.; Desilva, E. D.; Dumdei, E.; Morris, S. A. *J. Nat. Prod*. **1991**, *54*, 993

Fused Bicycles by Transannular Reactions

spirocycle

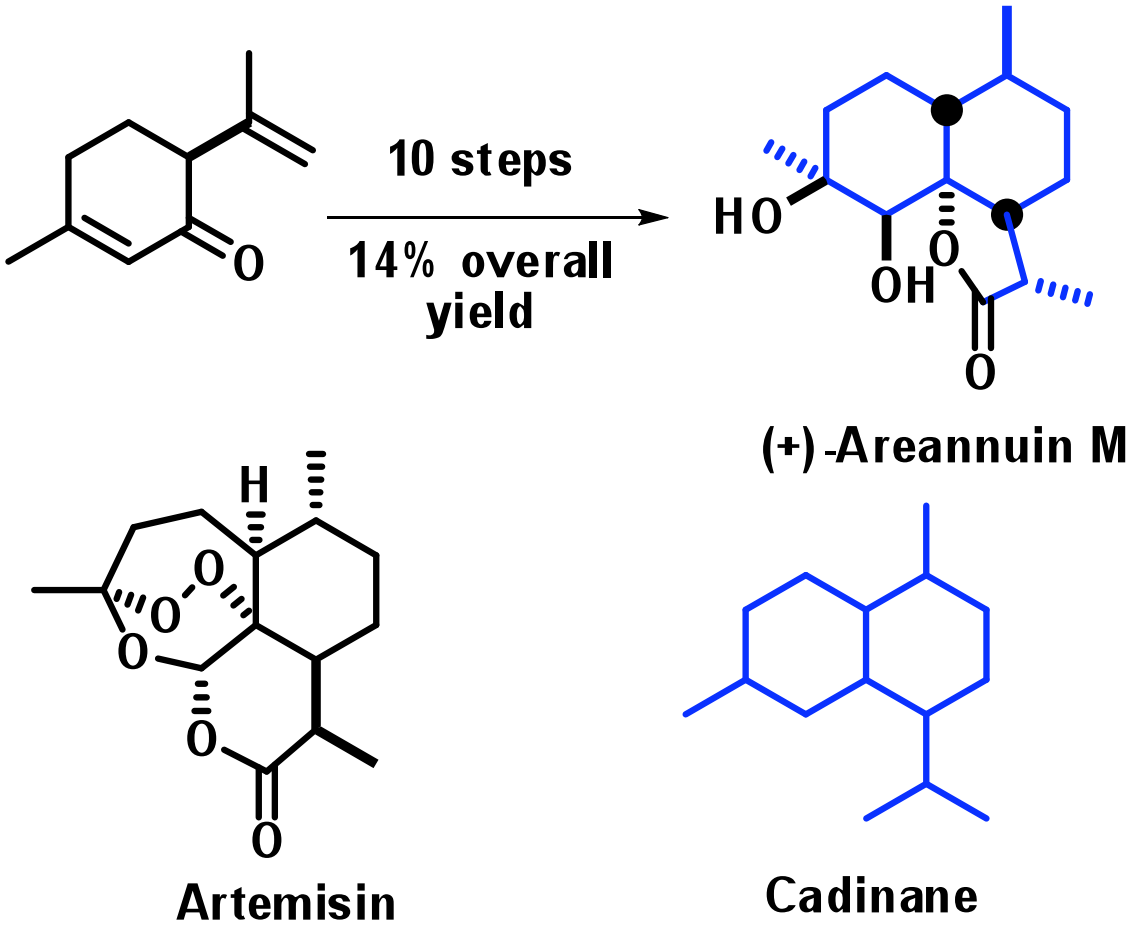


bicycles

Tricycle

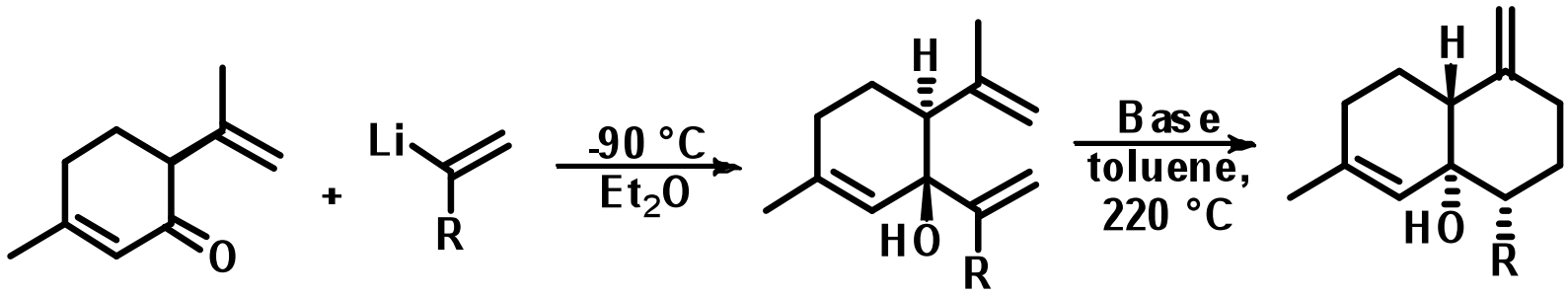
pentacycle

Cadinane Frame in Natural Products



Barriault, L.; Deon, D. H. *Org. Lett.* **2001**, *3*,1925

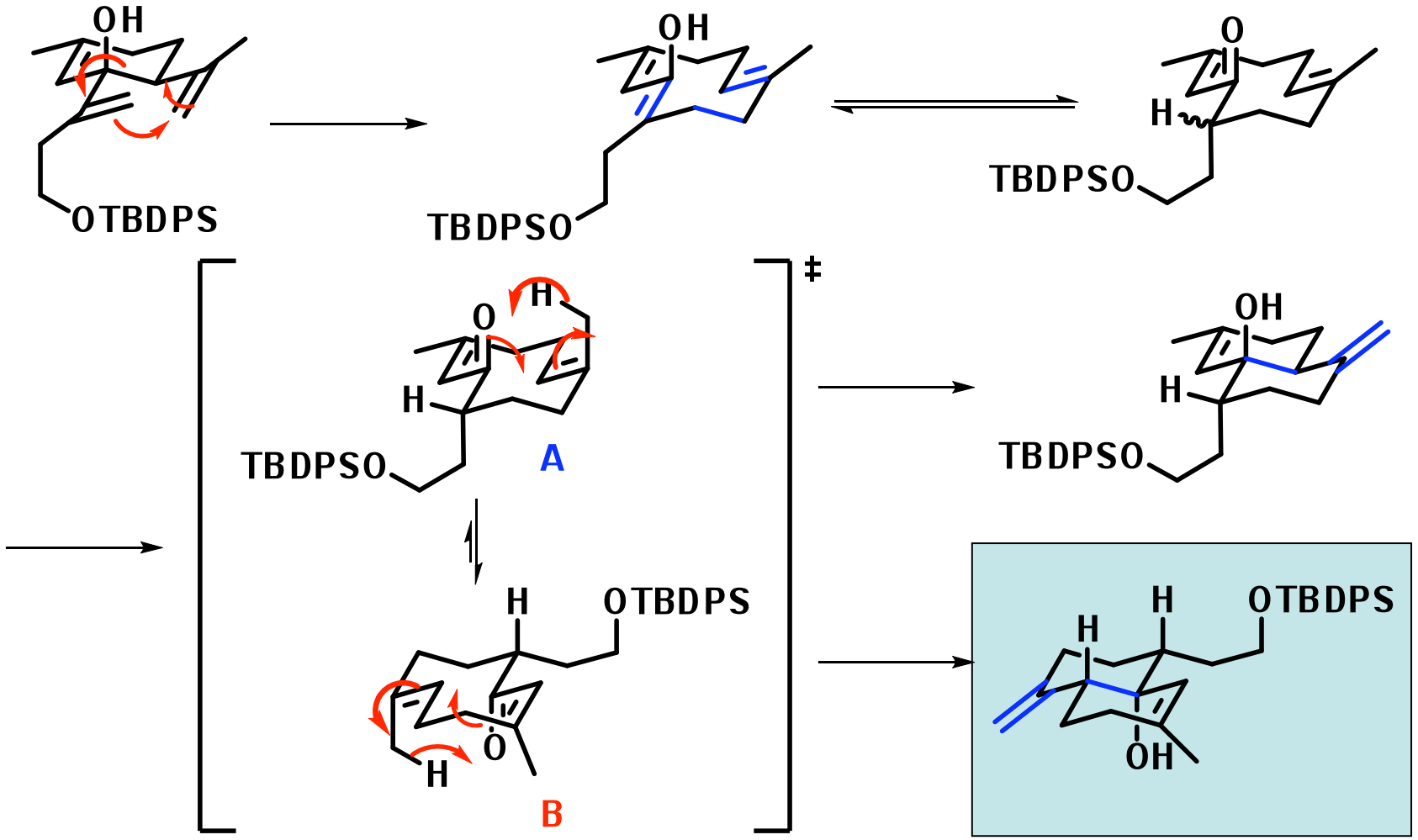
Oxy-Cope/Ene Cascade towards Cadinane Frame



Entry	R	yield (%)	ee(%)	dr
1	CF_3	17	70	8.5 : 1
2	OEt	26	74	1 : 2.5
3	$(CH_2)_2OTBDPS$	66	82	25 : 1
4	2-naphthyl	76	84	25 : 1

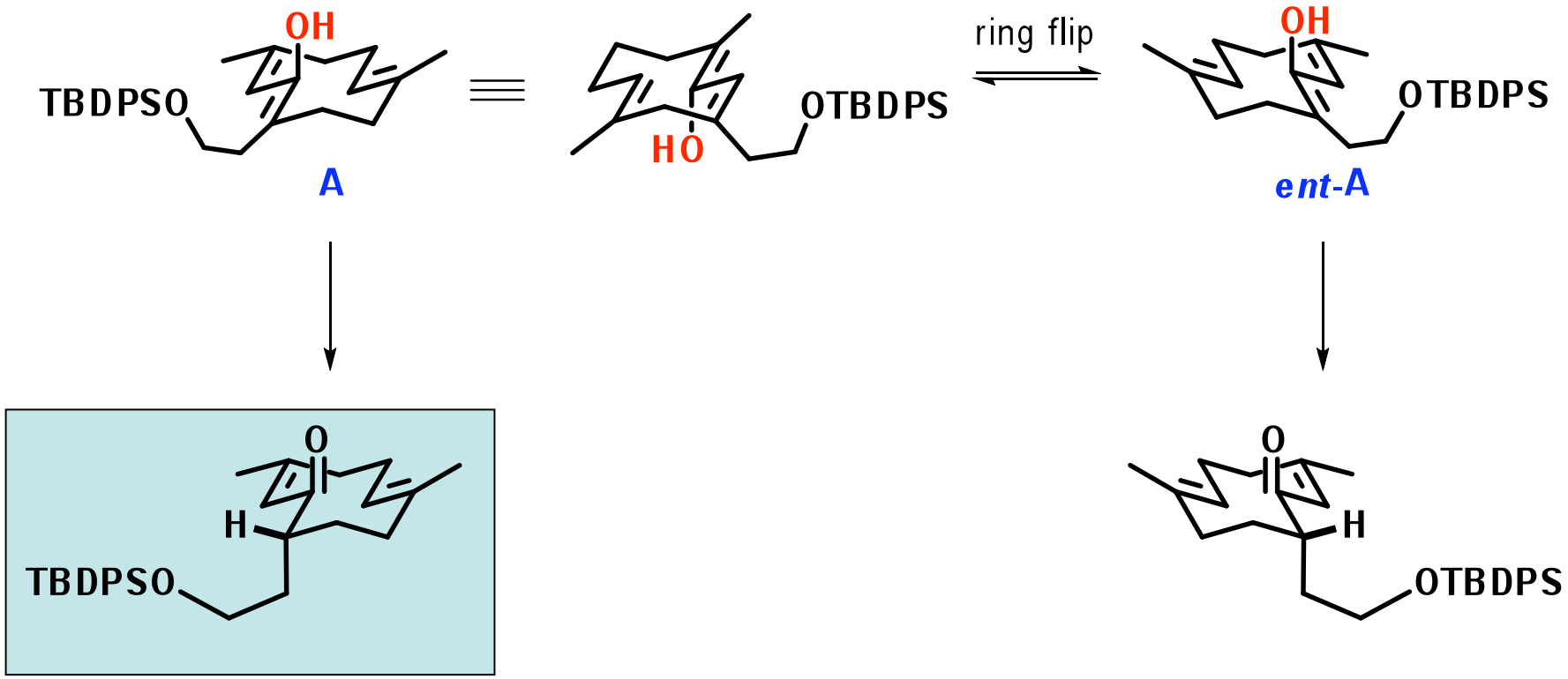
Gauvreau, D.; Barriault, L. *J. Org. Chem.,* **2005**, *70*, 1382

Stereoselective Cascade Oxy-Cope/Ene Reaction



Gauvreau, D.; Barriault, L. *J. Org. Chem.* **2005**, *70*, 1382

Chirality Transfer in Tandem Process

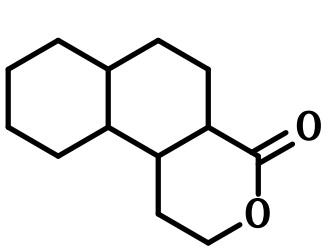


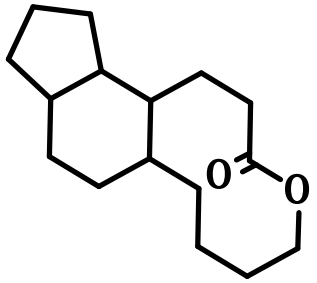
Gauvreau, D.; Barriault, L. *J. Org. Chem.* **2005**, *70*, 1382

Tricycles by Transannular Reactions

spirocycle

bicycles

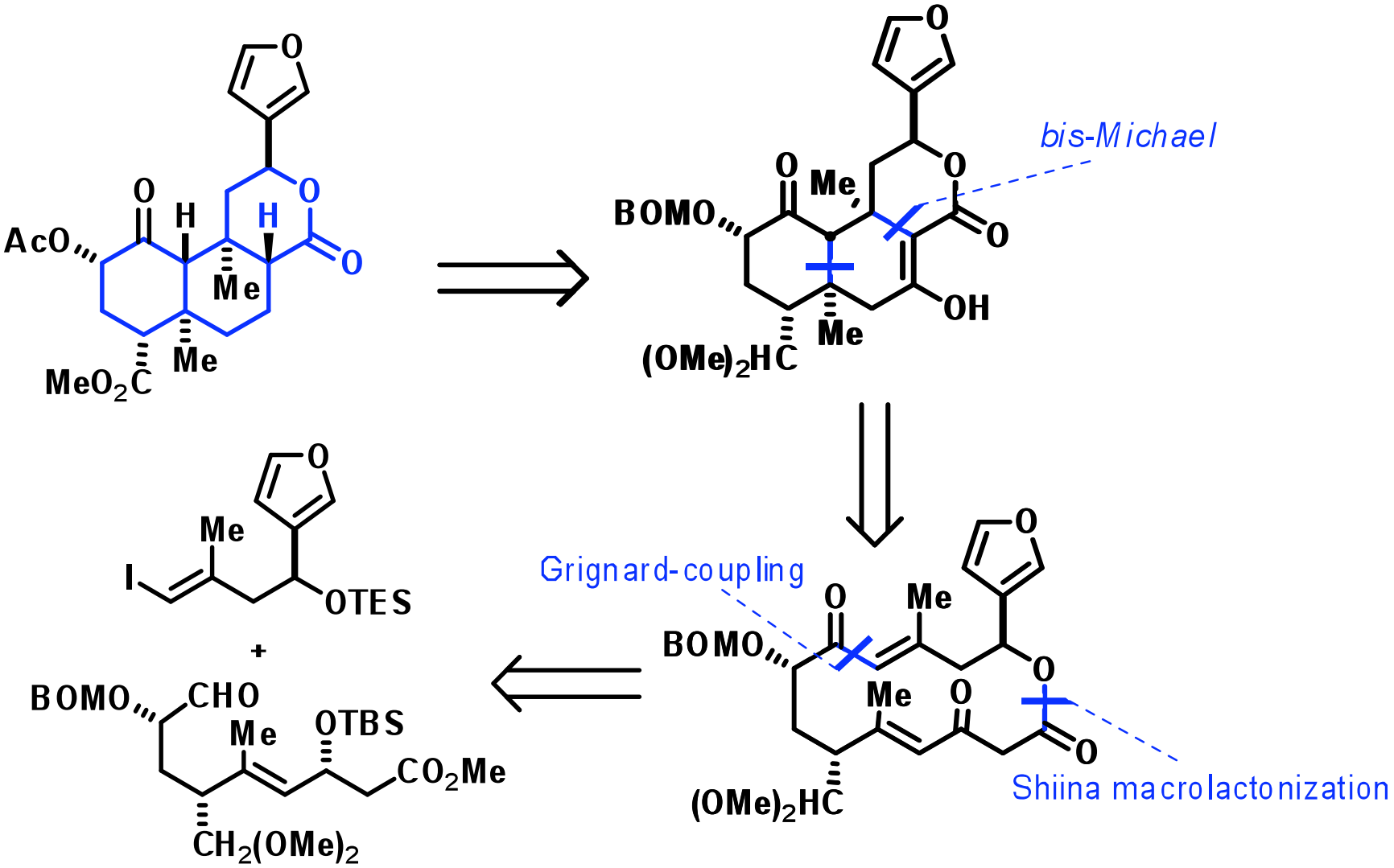




Tricycle

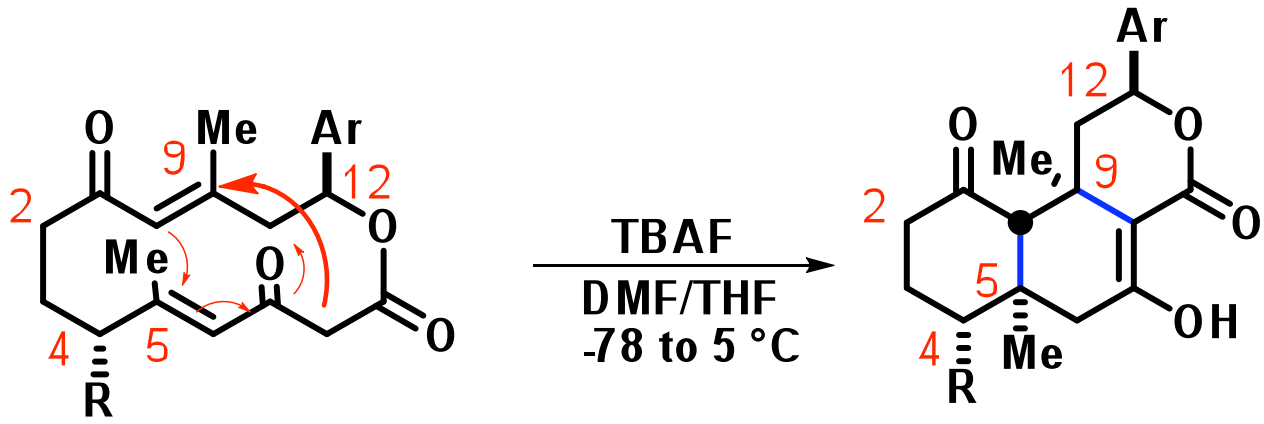
pentacycle

Salvinorin A



Scheerer, J. R.; Lawrence, J. F.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968

Bis-Michael Reaction Cascade

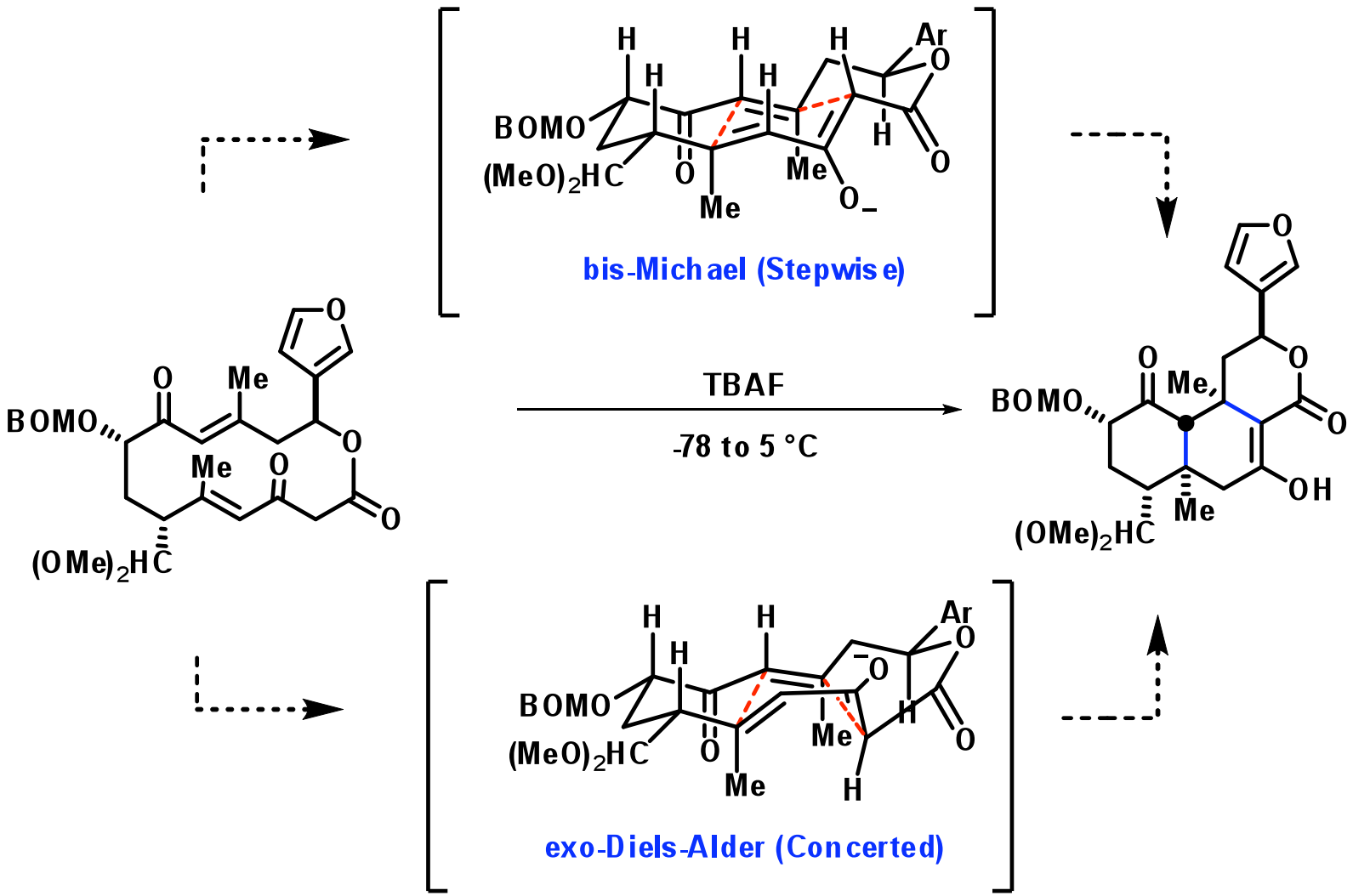


Ar= 2-furyl

entry	R	yield(%)	dr
1	H	95	95:5
2	$CH(OMe)_2$	95	>95:5

Scheerer, J.R.; Lawrence, J.F.; Evans, D.A. *J. Am. Chem. Soc.* **2007**, *129*, 8968

Transannular Cyclization Analysis

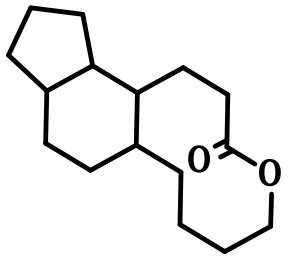


Scheerer, J. R.; Lawrence, J. F.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968

Tricycles by Transannular Reactions

spirocycle

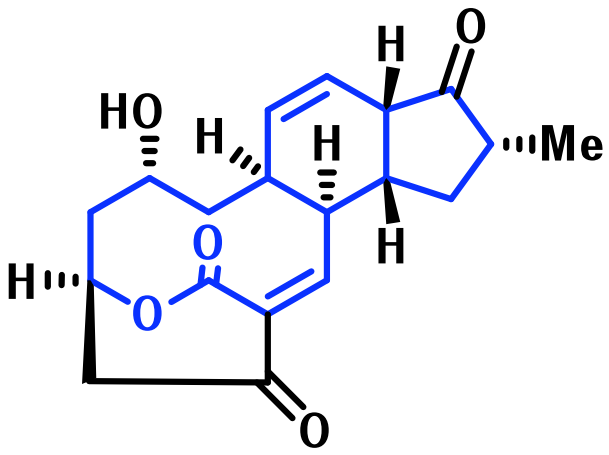
bicycles



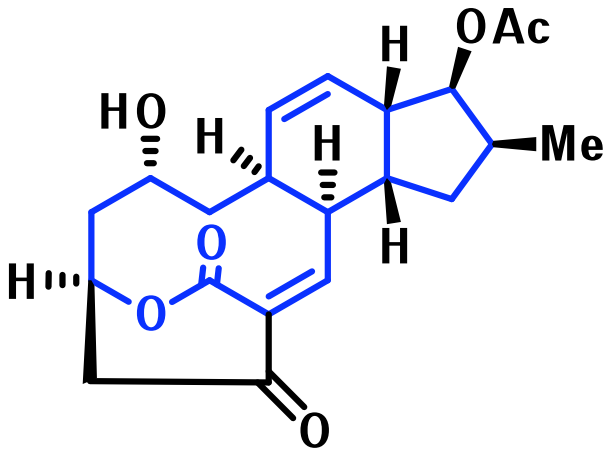
Tricycle

pentacycle

Macquarimicin A and Cohleamycin A



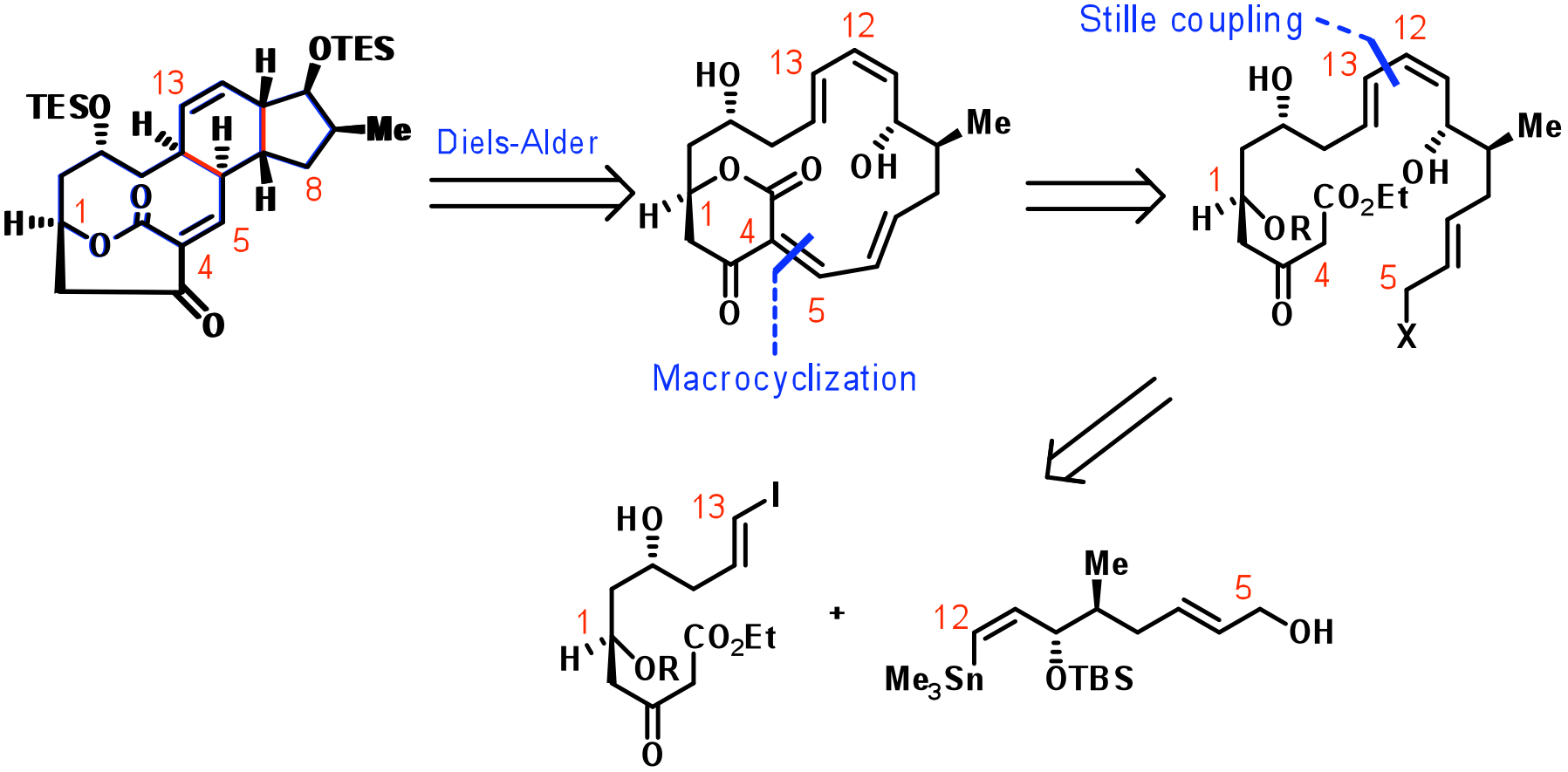
Macquarimicin A



Cohleamycin A

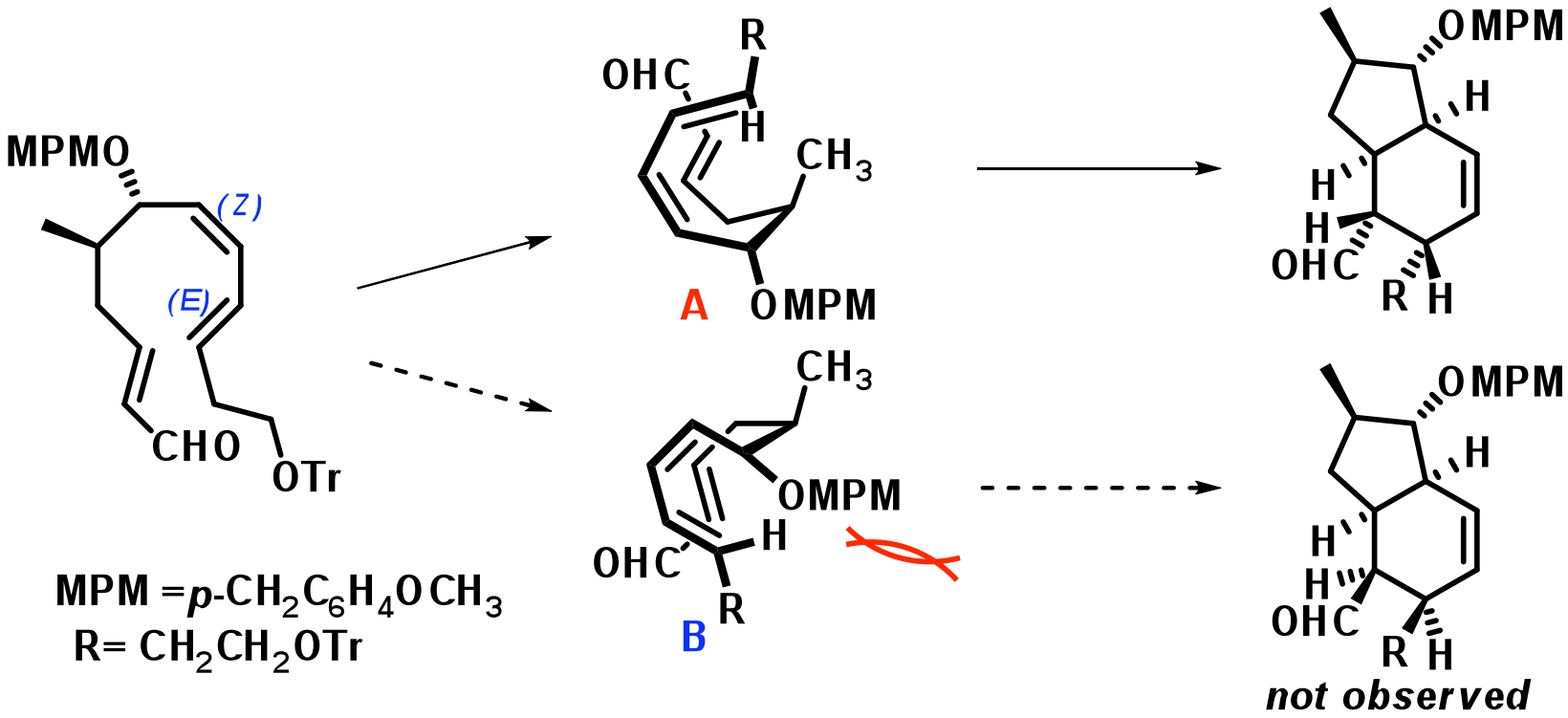
Munakata, R.; Katakai, H.; Ueki, T.; Tadano, K. *J. Am. Chem. Soc.* **2003**, *125*, 14723
Dineen, T. A.; Rousch, W. *Org. Lett.* **2004**, *6*, 2043

Retrosynthetic Analysis of Cochleamycin A



Dineen, T. A.; Rousch, W. *Org. Lett.* **2004**, *6*, 2043

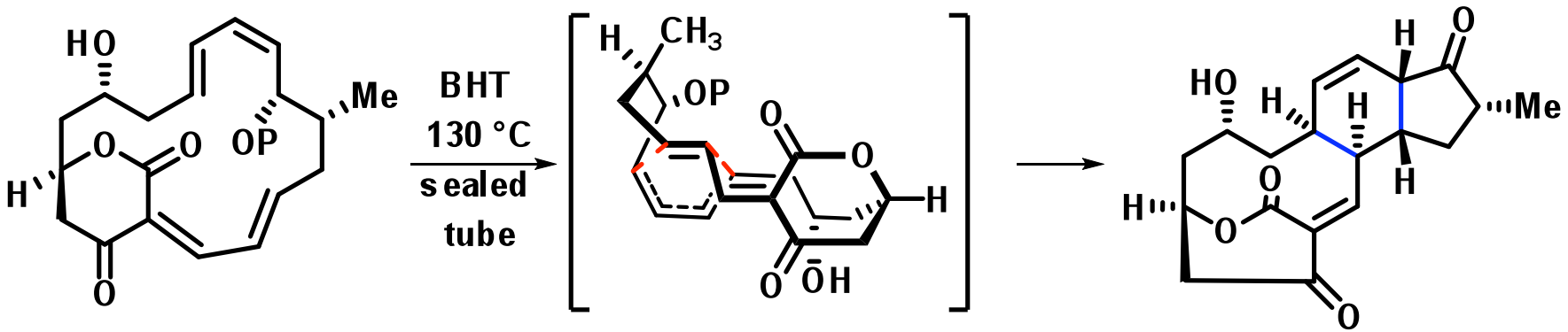
Diastereoselectivity Model Study of IMDA



Munakata, R.; Katakai, H.; Ueki, T.; Tadano, K. *J. Am. Chem. Soc.* **2003**, *125*, 14722

Munakata, R.; Ueki, T.; Katakai, H.; Tadano, K. W. *Org. Lett.* **2001**, *3*, 3029

Role of Lactone in TADA

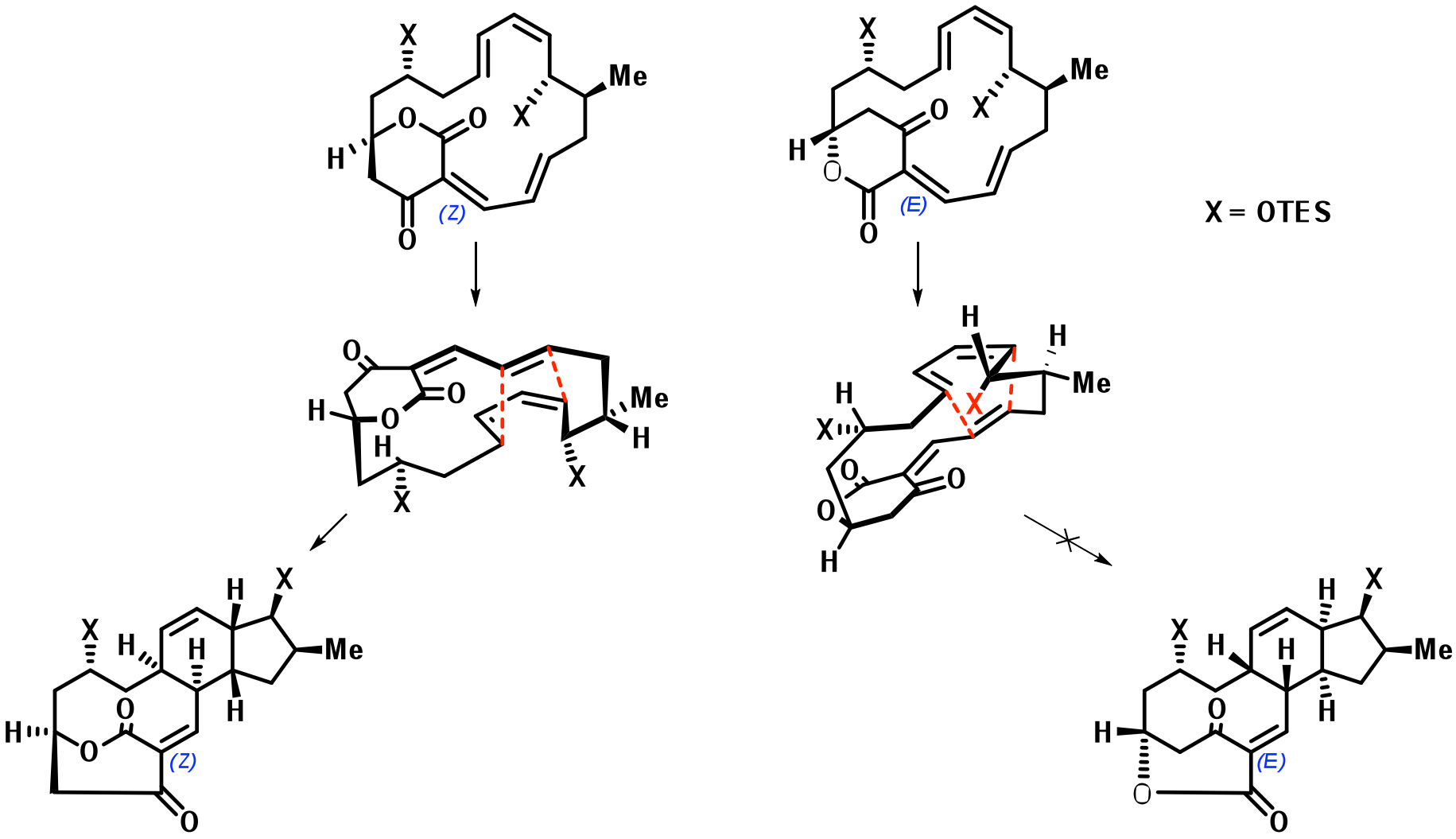


BHT = 2,6-*tert*-butylhydroxytoluene

Munakata, R.; Katakai, H.; Ueki, T.; Tadano, K. *J. Am. Chem. Soc.* **2003**, *125*, 14722

Munakata, R.; Ueki, T.; Katakai, H.; Tadano, K. W. *Org. Lett.* **2001**, *3*, 3029

Influence of Olefin in TDA Transition States



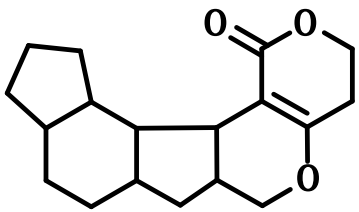
Dineen, T. A.; Rousch, W. *Org. Lett.* **2004**, *6*, 2043

Pentacycles by Transannular Reactions

spirocycle

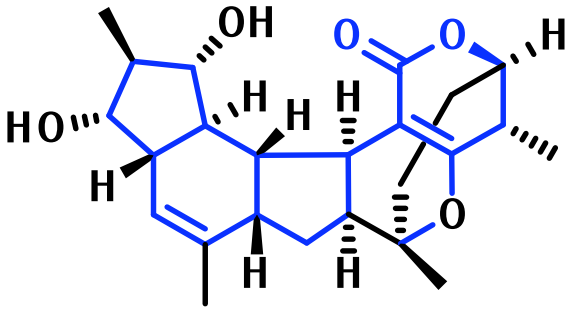
bicycles

Tricycle

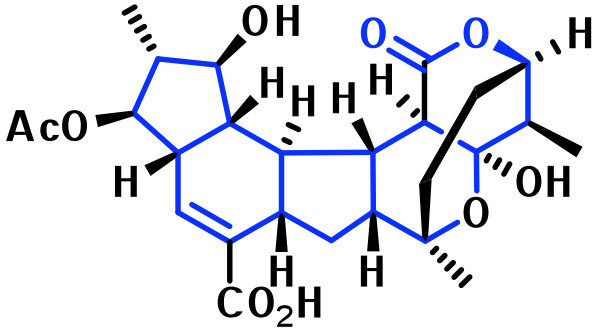


pentacycle

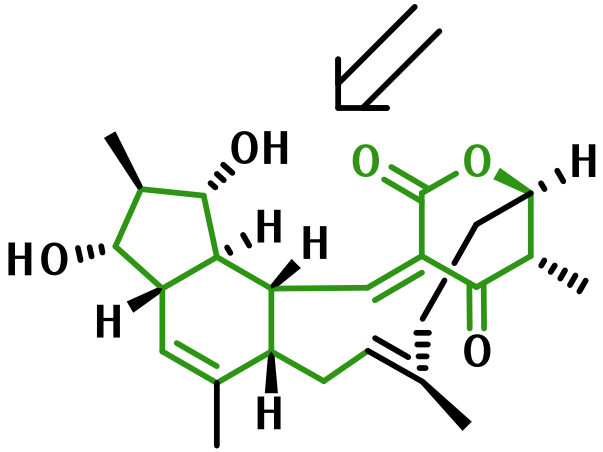
(-)-FR182877 and Hexacyclinic Acid and Connection with Cohleamicin A

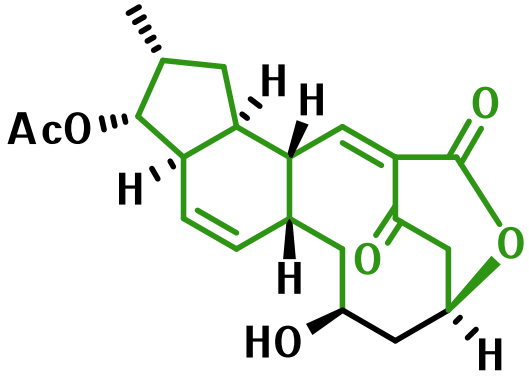


(+)-FR182877 (WS9885B)

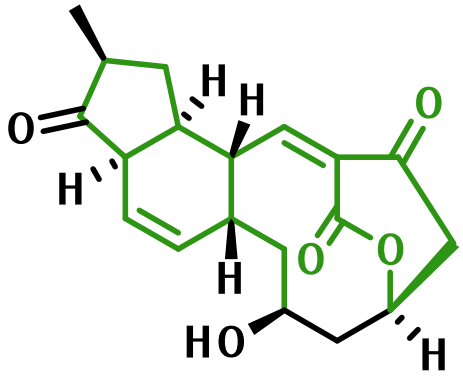


Hexacyclinic Acid





Cohleamycin A



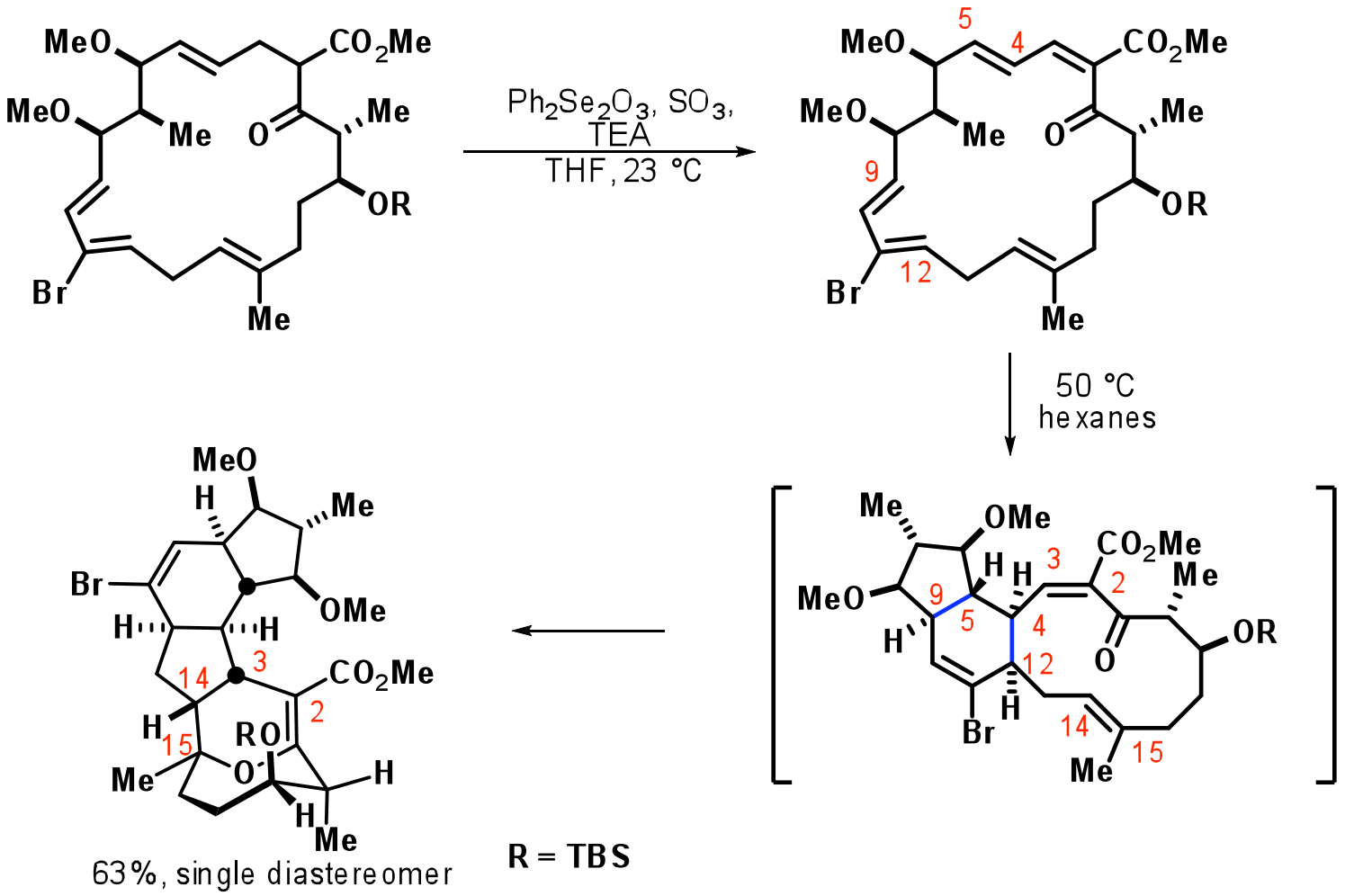
Macquarimicin A

Evans, D.A.; Starr, J.T. *Angew. Chem. Int. Ed.* **2002**, 41, 1787

Evans, D.A.; Starr, J.T. *J. Am. Chem. Soc.* **2003**, *125*, 13531

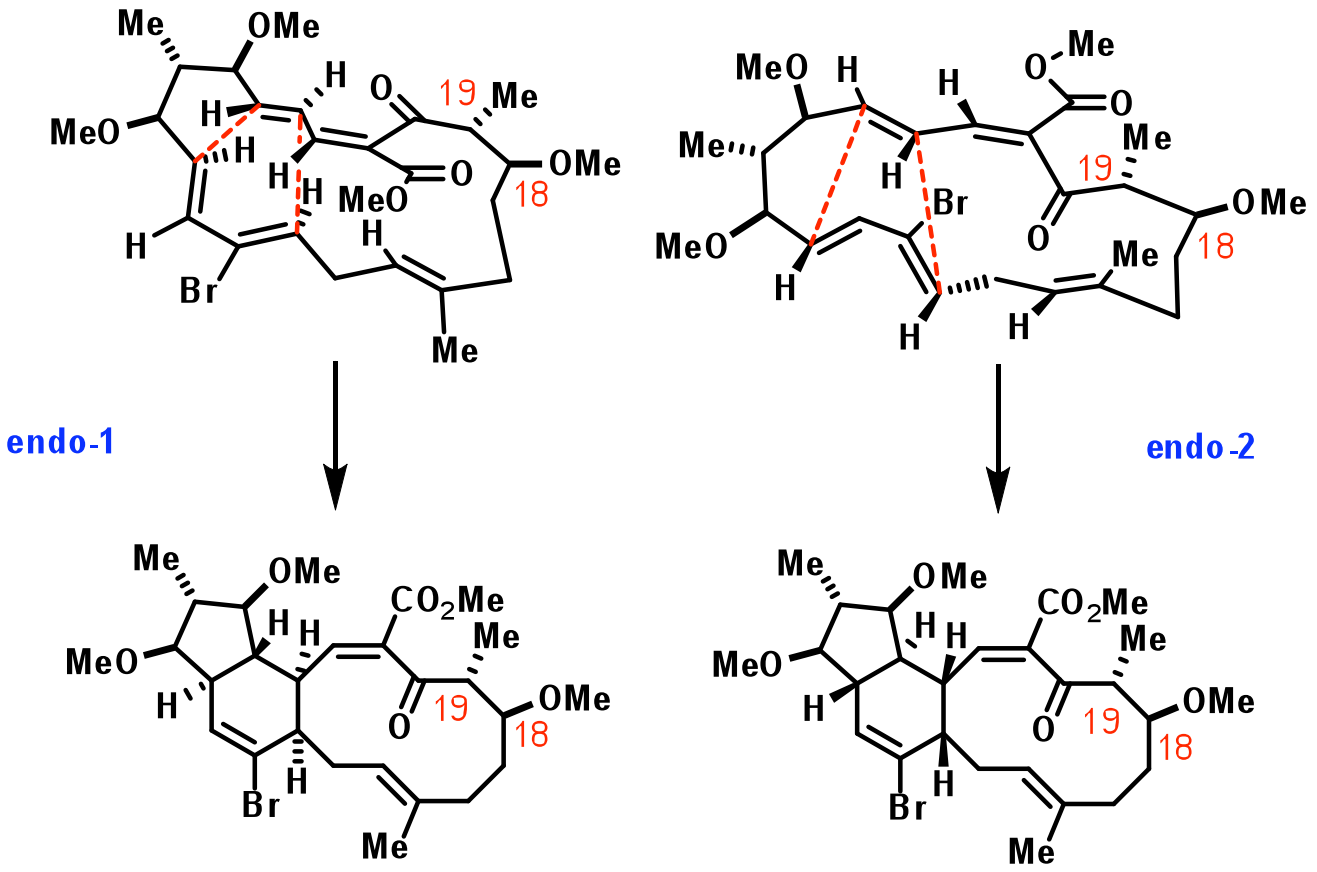
Vosburg, D.A.; Vanderwal, C.D.; Sorensen, E.J. *J. Am. Chem. Soc.* **2002**, *124*, 4552

Cascade Transannular Cycloadditions in the Synthesis of FR-182877



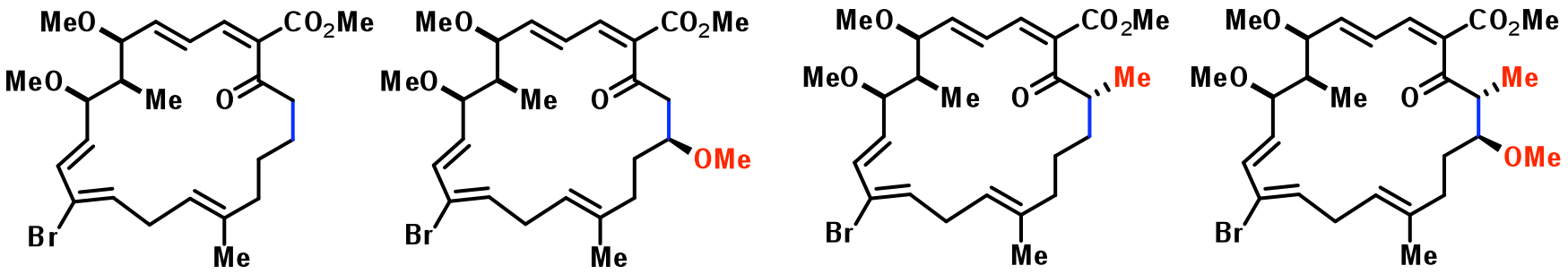
Evans, D.A.; Starr, J.T. *J. Am. Chem. Soc.* **2003**, *125*, 13531

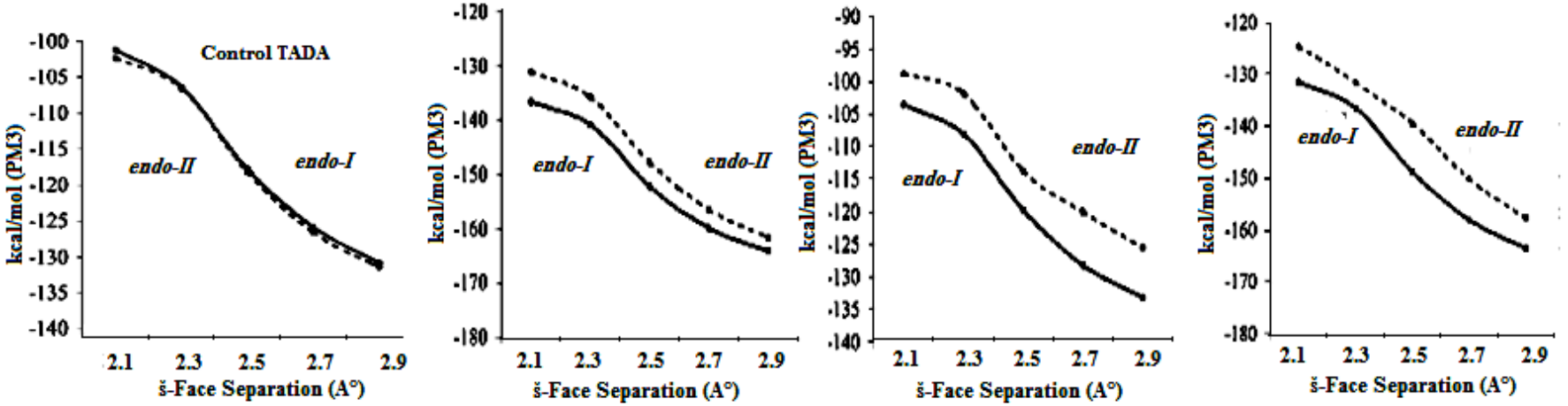
System Design for Semiempirical Calculations for First Cycloaddition



Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531

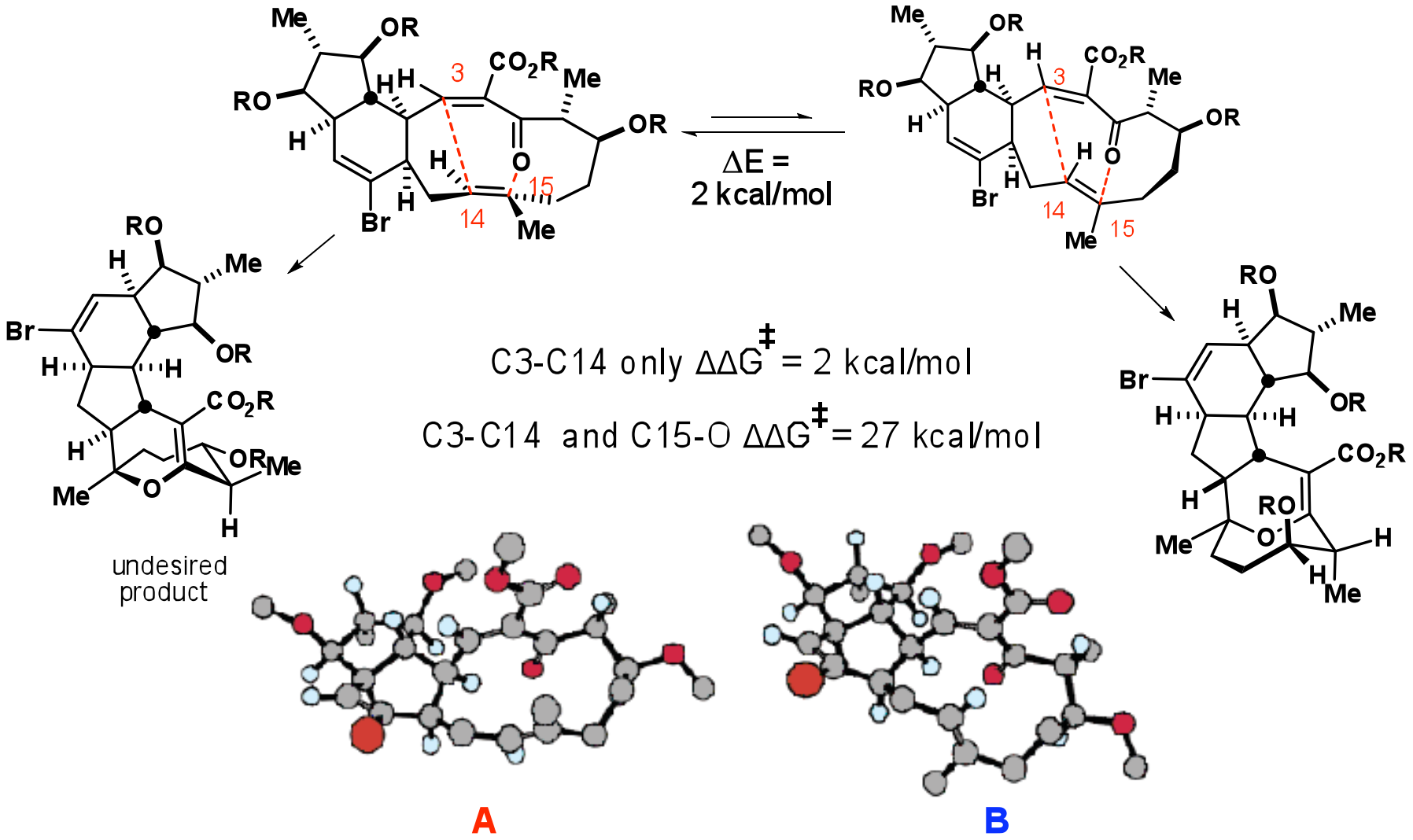
Screening of Substituted Macrocycles





Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531

Ananlysis of Hetero Diels-Alder Cycloaddition

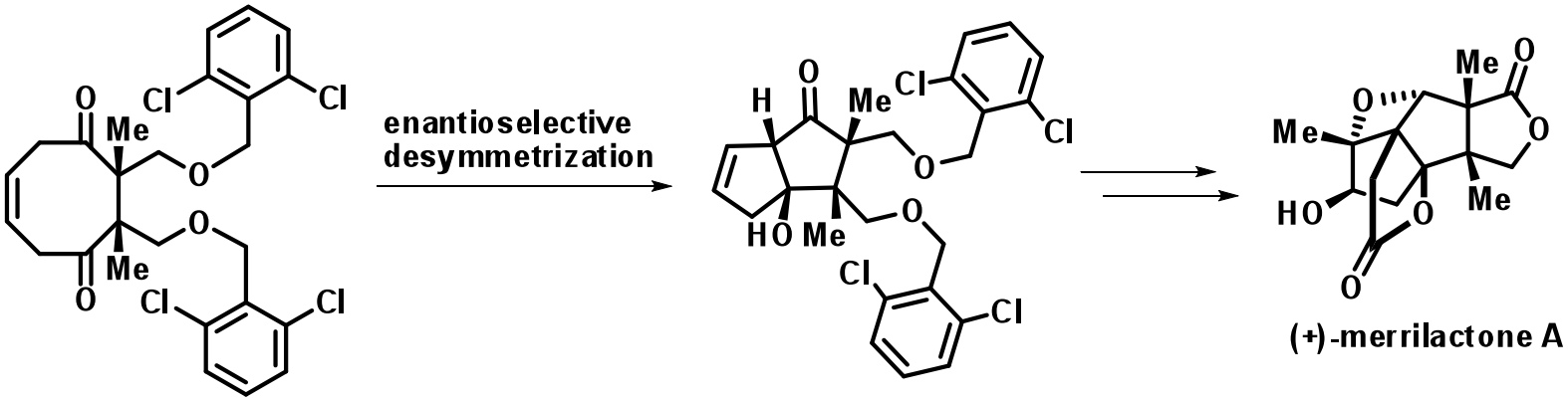


Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531

Outline

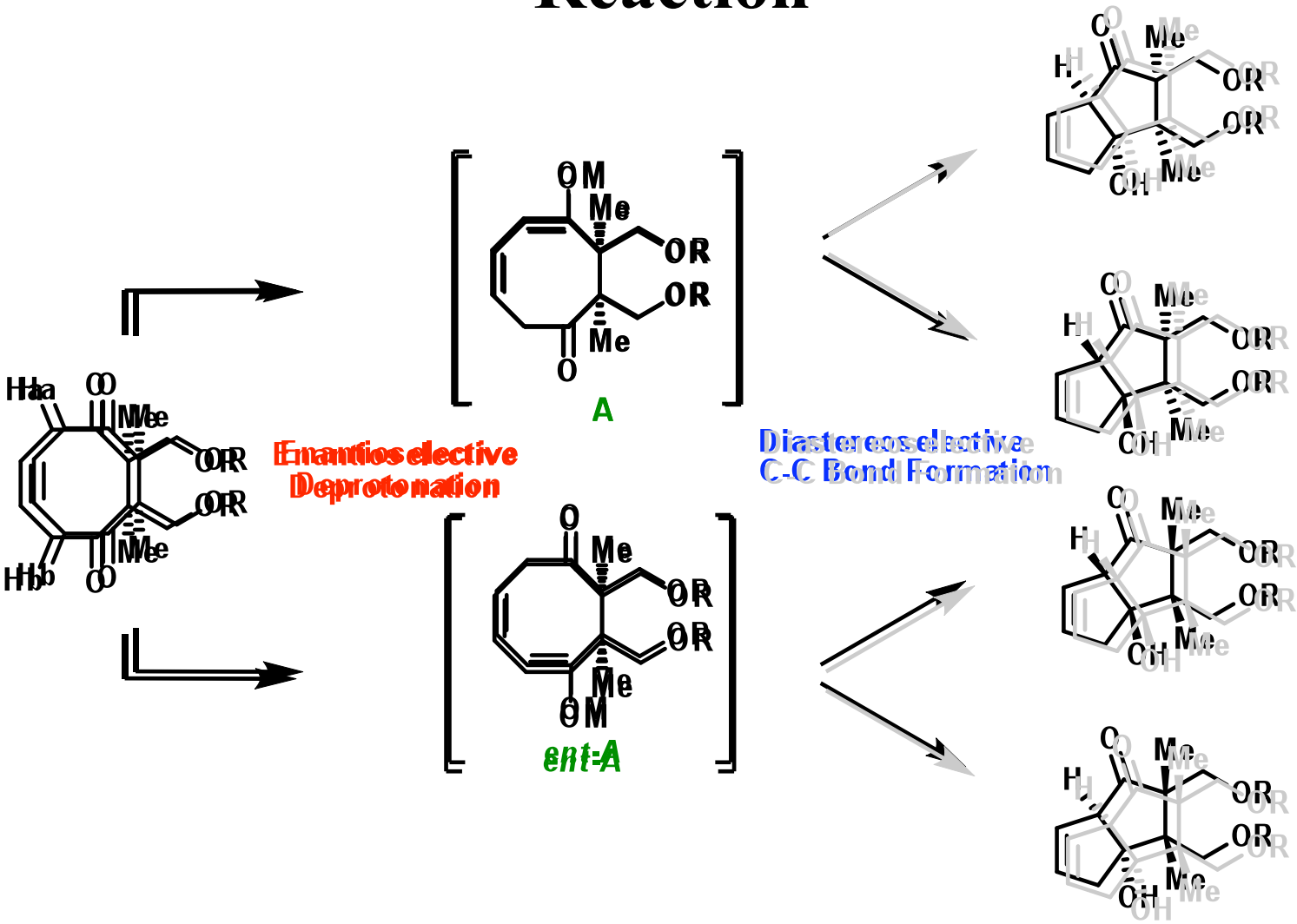
- Macrocycle Tutorial
  - Conformational analysis of C8-C10 rings
  - Energetics of transannular reaction
- Conformation Directed Stereoselective Transannular Reactions
  - Spirocyclic Systems
  - Bicyclic Systems
  - Tricyclic Systems
  - Polycyclic Systems
- Catalytic Systems
  - **Enantioselective Catalytic Transannular Aldol Reactions**
  - **Enantioselective Catalytic Transannular Diels-Alder Reactions**
- Conclusion

Transannular Catalytic Aldol Reaction in Synthesis of (+)-Merrilactone A



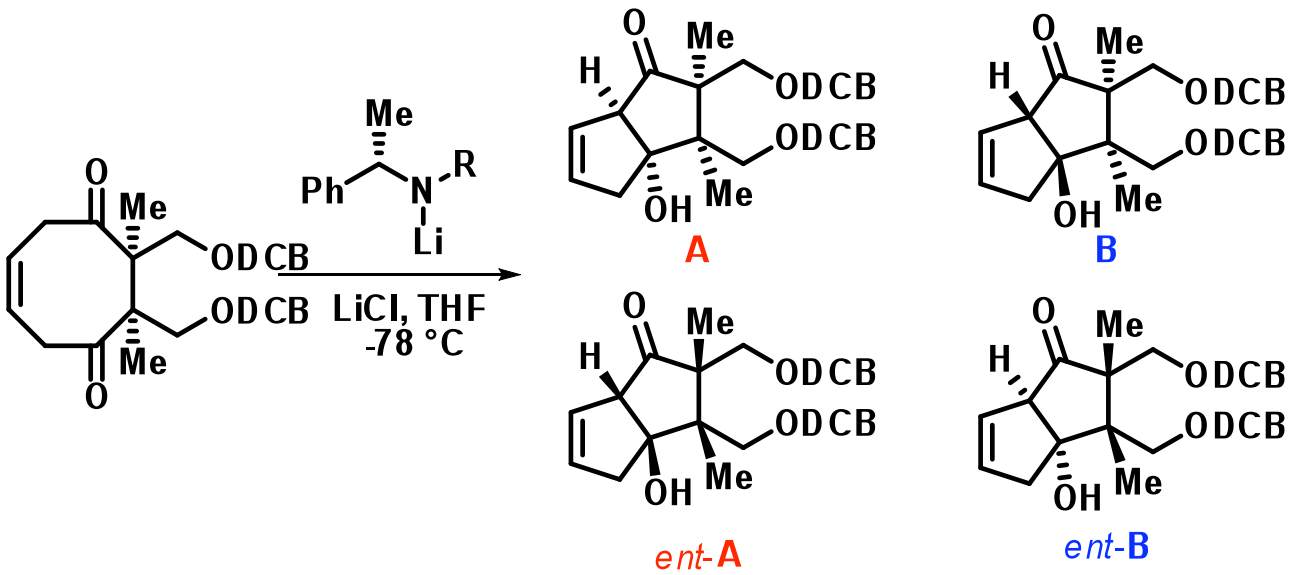
Inoue, M.; Sato, T.; Hirama; M. *Angew. Chem. Int. Ed.* **2006**, *45*, 4848

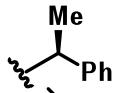
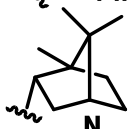
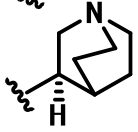
Two Distinct Steps in Transannular Aldol Reaction



Inoue, M.; Lee, N.; Kasuya, S.; Sato, T.; Hirama; M, *J. Org. Chem.* **2007**, *72*, 3065

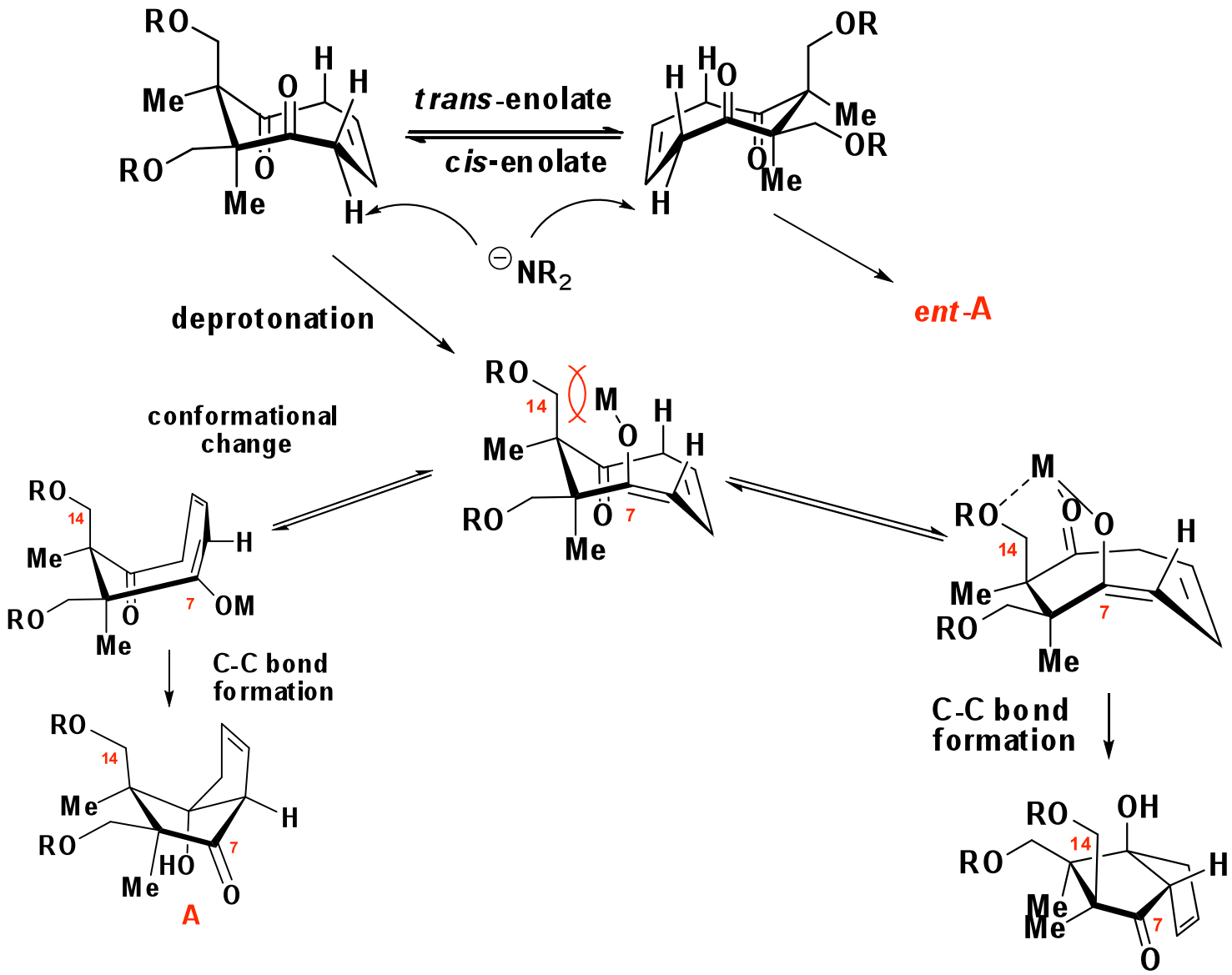
Enantioselective Transannular Aldol Reaction



entry	R	dr	er (A:*ent*-A)	Yield,%
1	-*p*-ClC$_6$H$_4$	19:1	1:2.4	87
2	-TBS	15:1	1:1.3	73
3		6:1	1:1	100
4		3:1	2.7:1	94
5		6:1	4.7:1	90

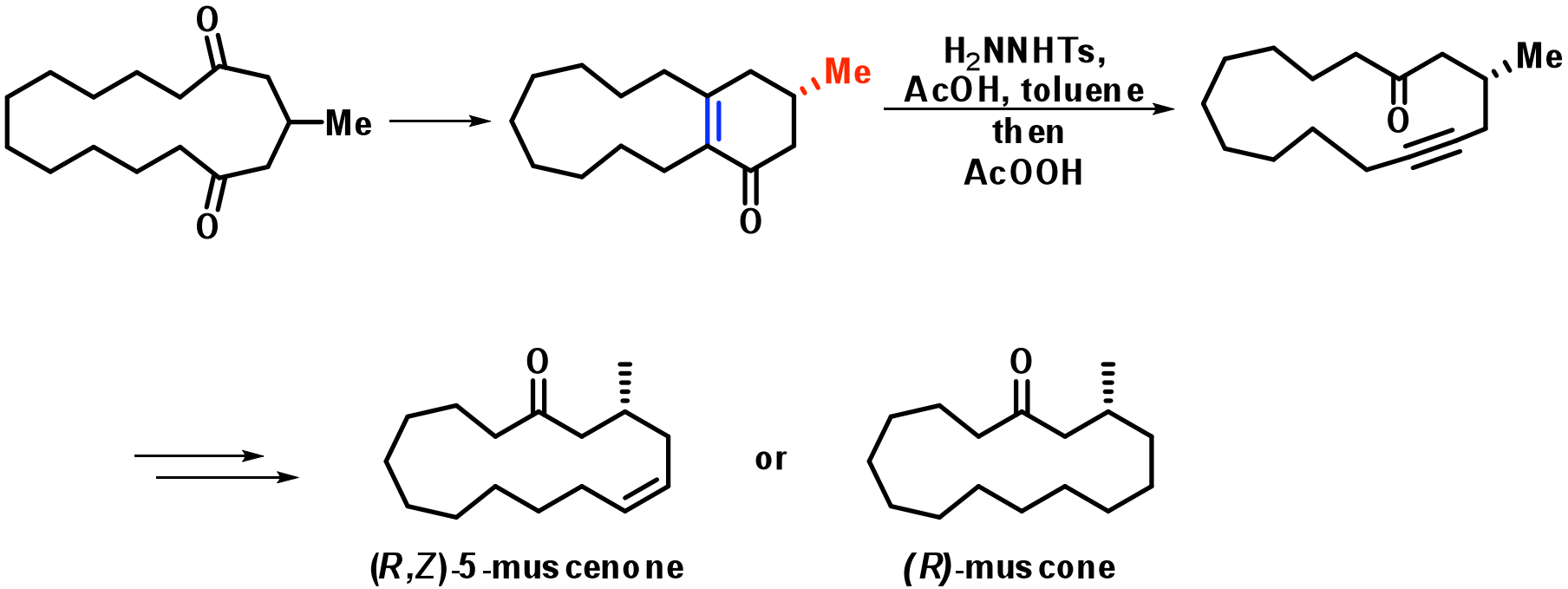
Inoue, M.; Lee, N.; Kasuya, S.; Sato, T.; Hirama; M, *J. Org. Chem.* **2007**, *72*, 3065

Mechanistic Consideration of Aldol Reaction



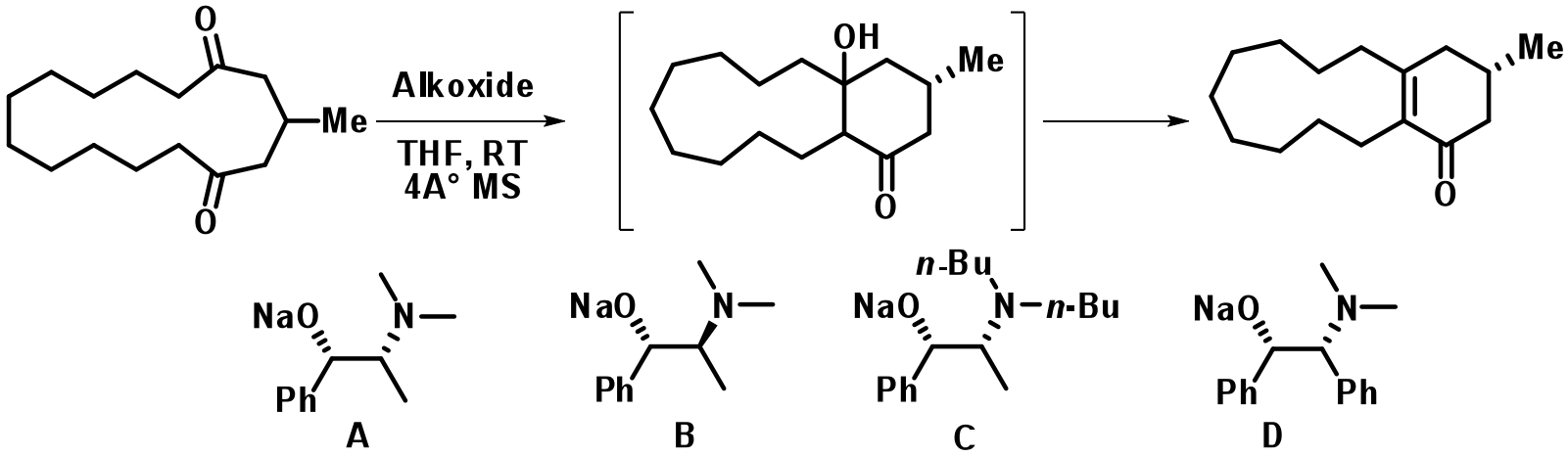
Inoue, M.; Sato, T.; Hirama; M. *Angew. Chem. Int. Ed.* **2006**, *45*, 4848

Enantioselective Intramolecular Aldol Addition/Dehydration of Macrocyclic Diketone



Knopff, O.; Kuhne, J.; Fehr, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 1307

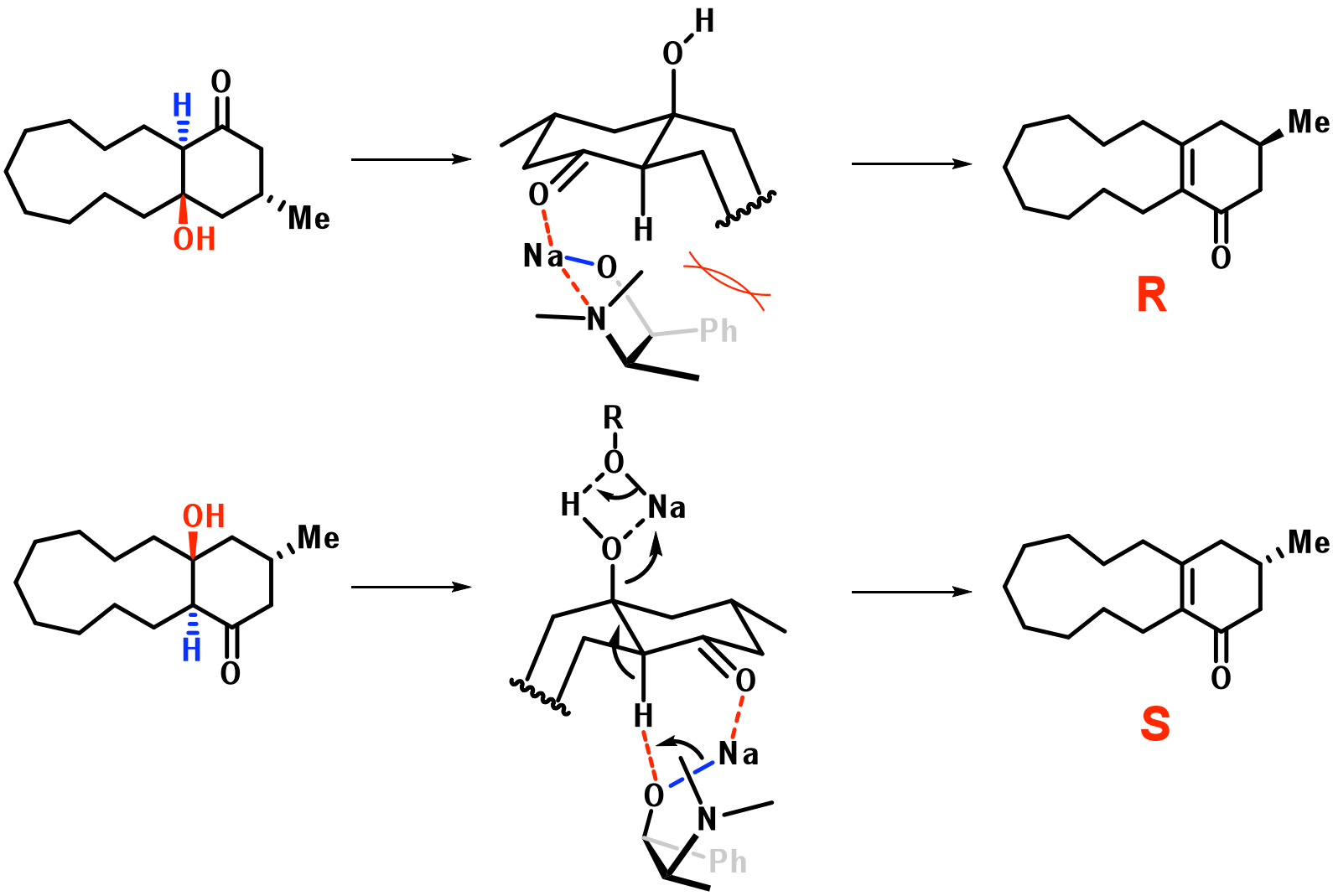
Effect of Base on Formation of Aldol Product



Entry	Alkoxide	yield, (%)	ee, (%)
1	4 eq. A	88	53
2	4 eq. B	85	36
3	4 eq. C	49	25
4	4 eq. D	56	50
5	8 eq. A	90	76

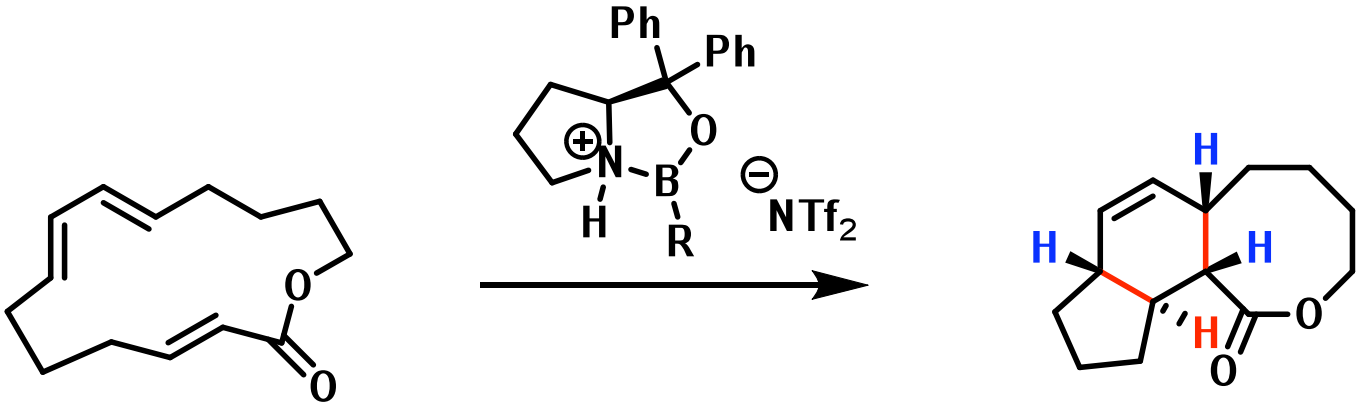
Knopff, O.; Kuhne, J.; Fehr, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 1307

Enantiomer-Differentiating Aldol Dehydration



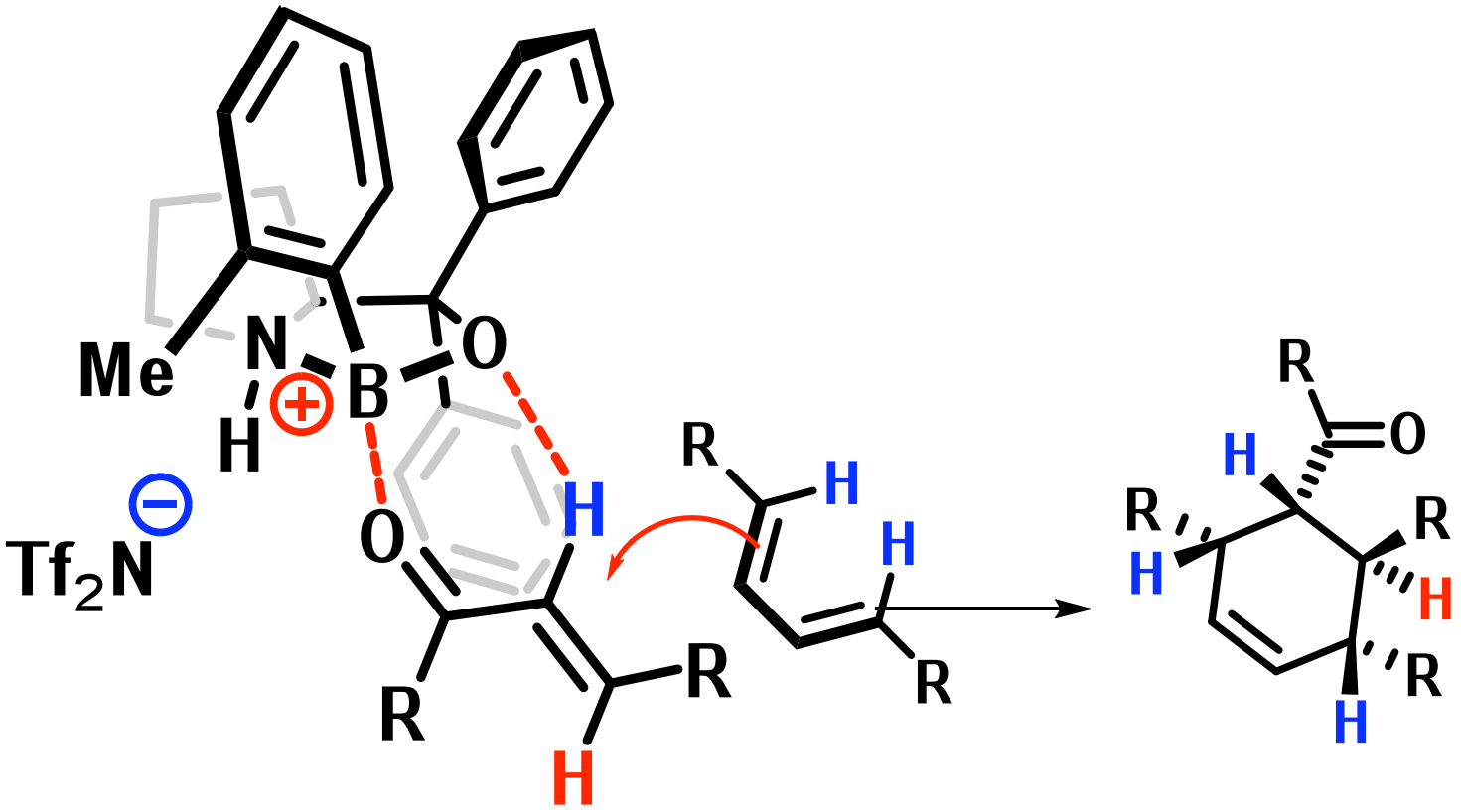
Knopff, O.; Kuhne, J.; Fehr, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 1307

Asymmetric Catalysis of Transannular Diels-Alder Reaction



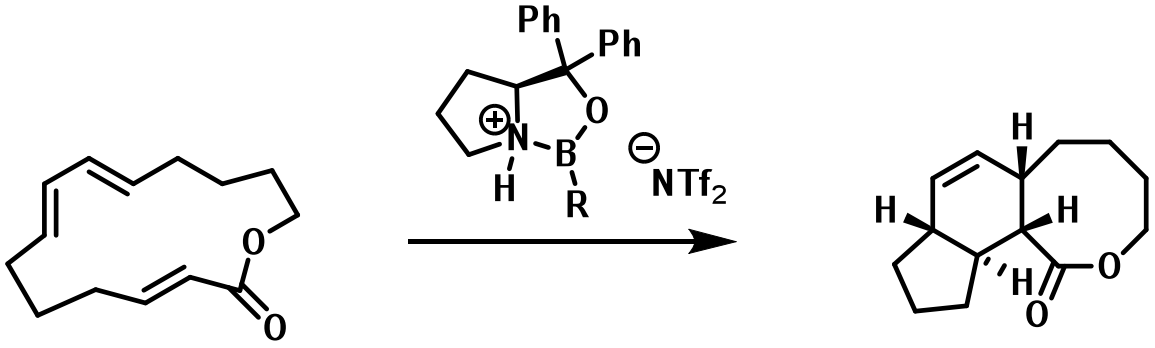
Balskus, E. P.; Jacobsen, E. N. *Science* **2007**, *317*, 1736

The Role of Oxazaborolidinine



Zhou, G.; Hu, Q.-Y.; Corey, E.J. *Org. Lett.* **2003**, *5*, 3979
Ryu, D.H.; Corey, E.J. *J. Am. Chem. Soc.* **2003**, *125*, 6388

Oxazaboralidine Catalyst Screening



Entry	R	%, Conversion	% ee
1	CH_3	85	10
2	C_6H_5	66	80
3	2-$CH_3C_6H_4$	11	49
4	3-$CH_3C_6H_4$	10	48
5	4-$CH_3C_6H_4$	32	71
6	3-FC_6H_4	63	82
7	4-FC_6H_4	95	82
8	2-FC_6H_4	>95	90

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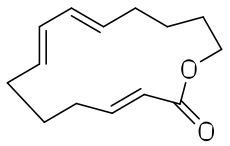
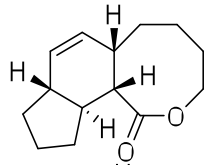
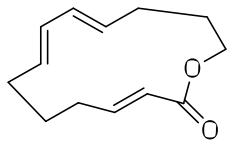
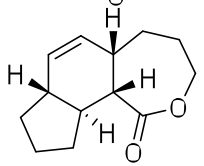
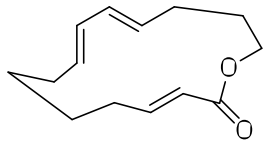
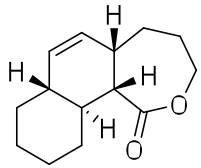
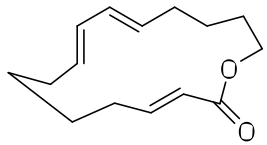
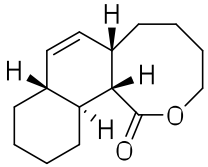
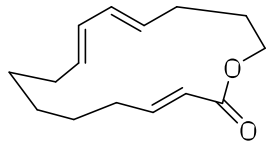
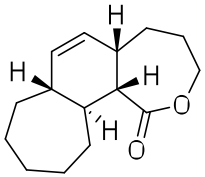
Substrate Scope of Asymmetric Catalytic TADA

Entry	Macrocycle	product	yield, %	ee, %	dr
1			69	90	>19:1
2			80	92	>19:1
3			78	90	5.9:1
4			62	88	8.8:1
5			15	85	5:1

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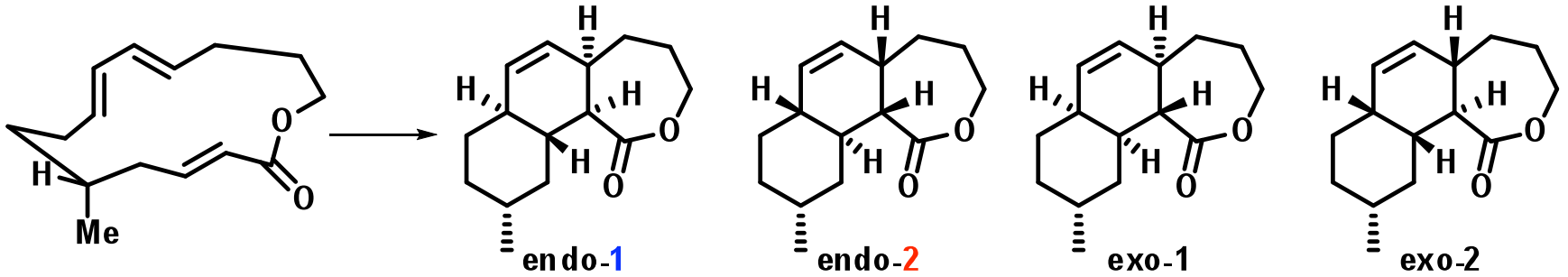
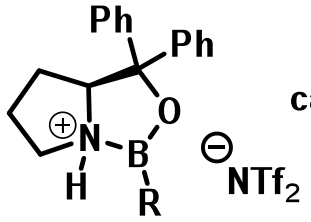
Catalyst Controled Diastereoselective TADA, Biased Macrocycle



Conditions				
$MeAlCl_2$, DCM, -78 °C to rt, 1h	93.7	3.5	2.8	0.0
toluene, 120 °C, 12h	73.3	6.4	18.9	1.4
20 mol% cat., toluene, rt, 20h	57.3	29.8	8.1	4.7



catalyst, R = 2-FC_6H_4

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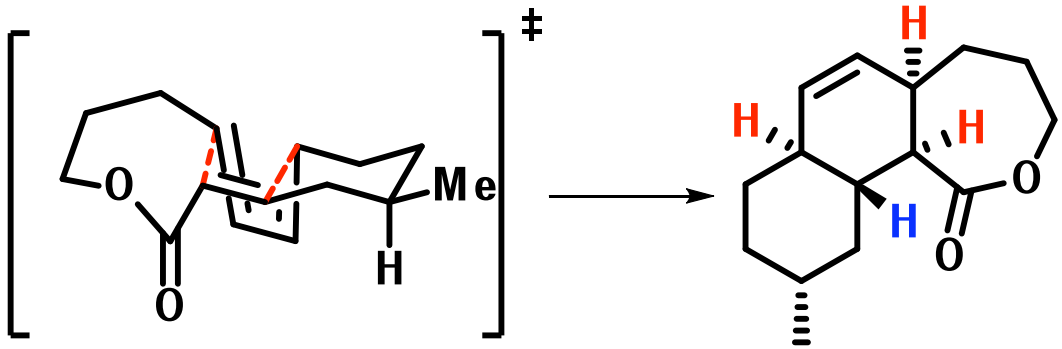
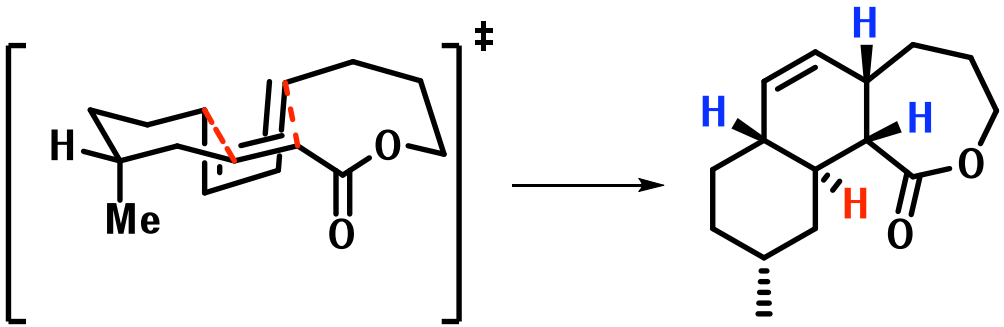
Intrinsic Prerequisite for Diastereoselectivity



endo-1

Favored by substrate control



endo-2

Disfavored by substrate control

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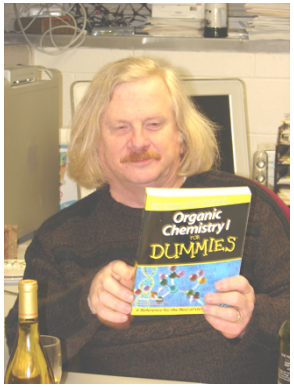
Conclusion

- Rapid increase in complexity
- Transannular reactions are powerful tool for construction of polycyclic systems
- Different reactions can be used
- Selectivity can be controlled by conformation or by catalyst

Acknowledgment

Dr. Wulff



Dr. Borhan

Dr. Jackson

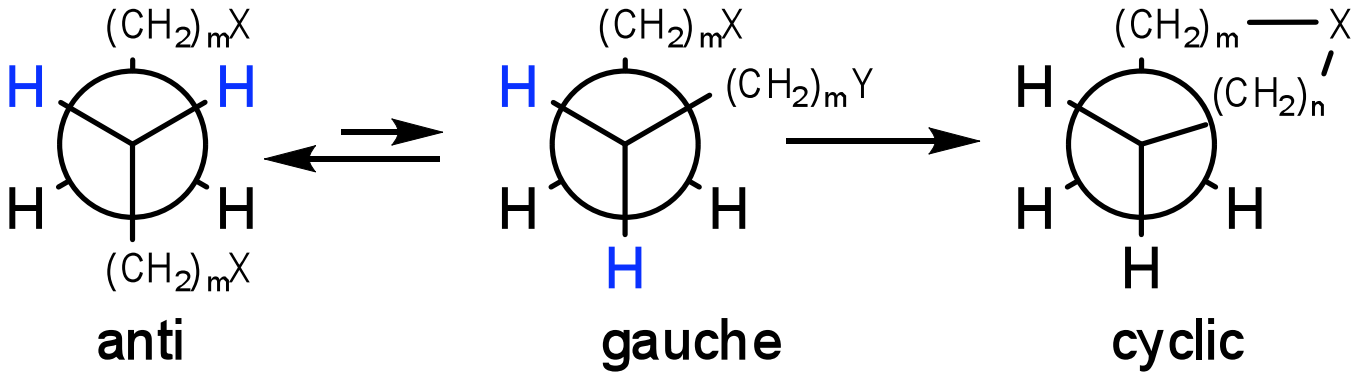
Aman, Anil, Li, Young, Munmun, Nilanjana, Zhenzhie, Ding, Victor, Alex, Kostas, Mercy, Roosbeh

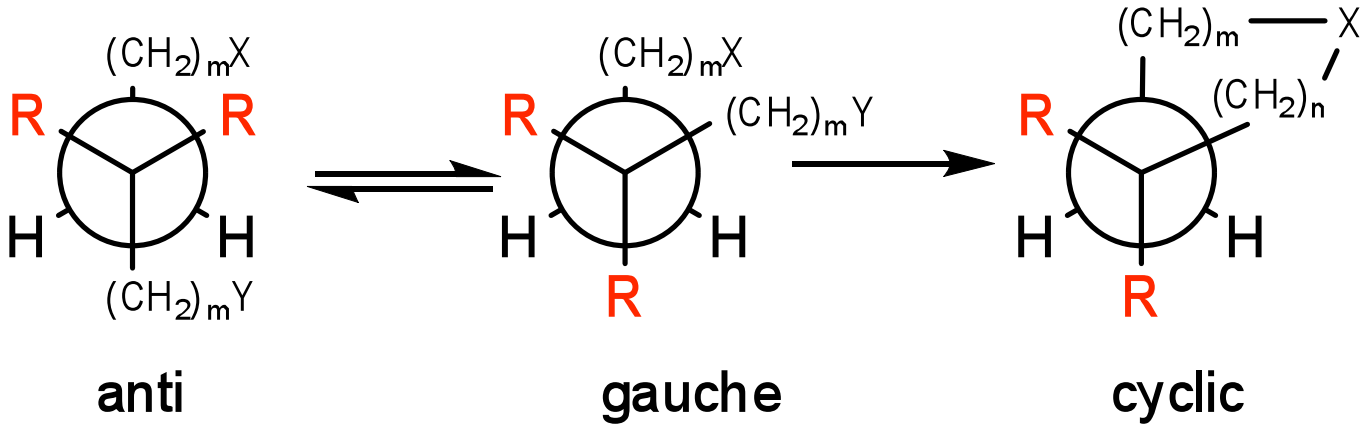
Happy Halloween!!!

Happy Halloween!!!

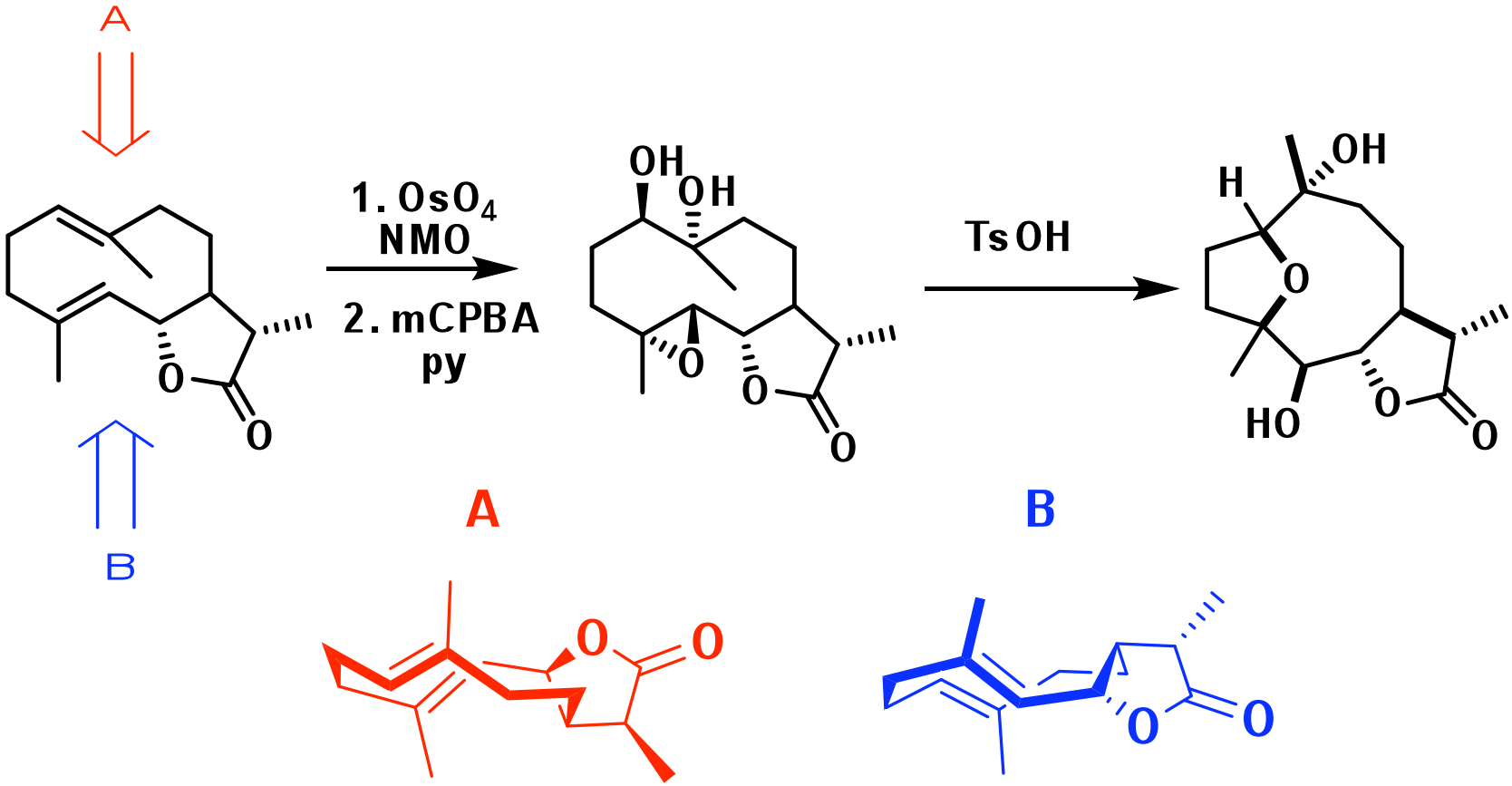
Happy Halloween!!!

Gem-Dialkyl Effect. Rotamer effect



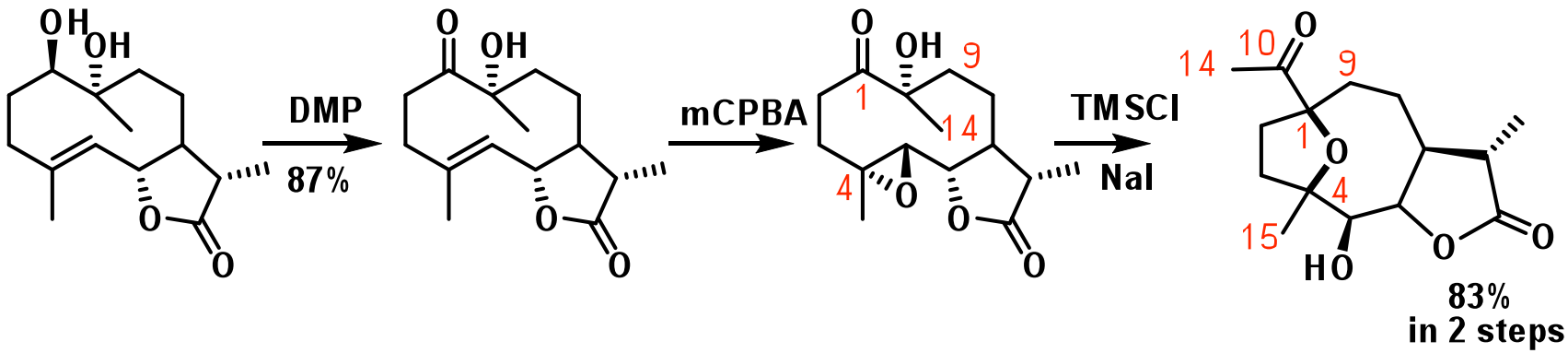


Diversity Oriented Synthesis

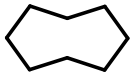
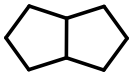
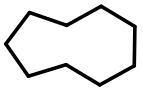
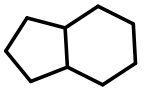
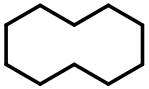
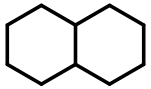
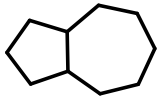
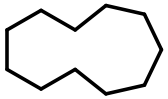
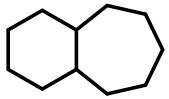
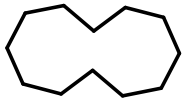
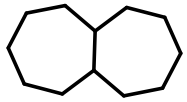
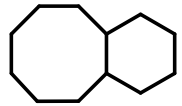
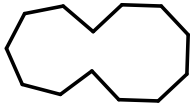
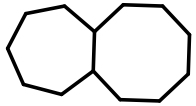
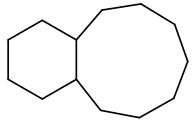


A. Rosales, R. E. Estevez, J.M. Cuerva. J. E. Oltra
B. Angew. Chem. Int. Ed **2005**, 44, 319

DOS.


OH
OH
O
O
DMP
87%
O
OH
O
O
mCPBA
O
OH
9
1
14
4
O
O
O
TMSCl
NaI
14
10
O
9
1
O
4
15
HO
O
O
83%
in 2 steps

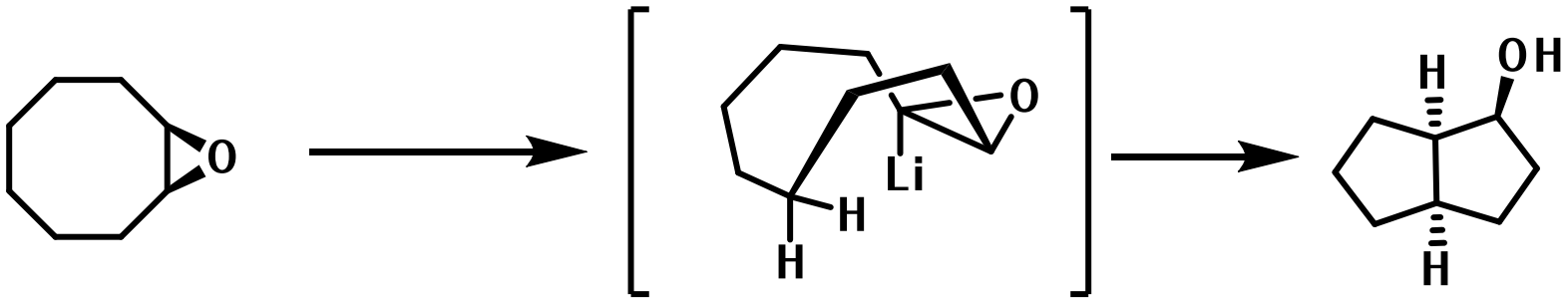
Potential for Transannulation

Cycloalkane	Steric Energy, kcal/mol	Strain Energy, kcal/mol[a]	Product	Steric Energy, kcal/mol	Strain Energy, kcal/mol[a]		
8 	19.37	11.9		cis: 19.61 trans: 26.66	cis: 12.0 trans: 18.4		
9 	24.14	15.5		cis: 18.31 trans: 17.14	cis: 8.9 trans: 7.9		
10 	25.61	16.4		cis: 20.01 trans: 17.15	cis: 4.1 trans: 1.0		cis 13.4 trans13.1
11 	26.26	11.8		cis: 24.2 trans: 20.97			
12 	28.32	-		cis 32.91 trans: 36.85			cis: 35.35 trans: 29.18
13 	26.65	-		cis: 36.70 trans: 38.91			cis:43.91 trans:31.32

Steric Energy calculated by MM2 model ***endo*-Išš**

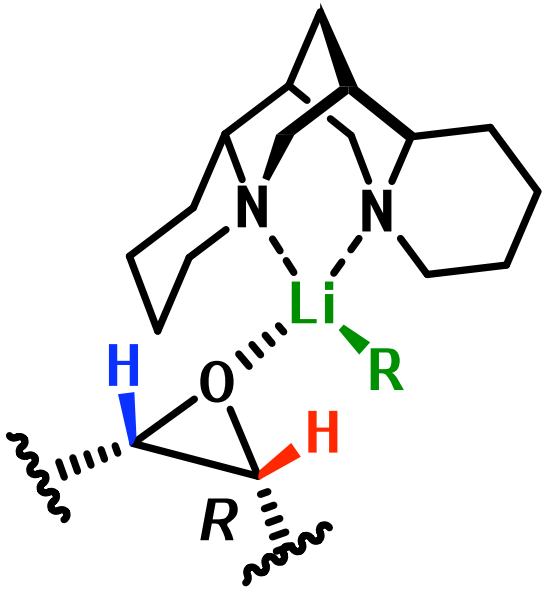
a: E.M. Engler, J.D. Andose, P.v. R. Schleyer, J. Am. Chem. Soc. 1973, 95, 8005
S.Chang, D.McNally, M.J. Hickney, R.H. Boyd, J. Am. Chem. Soc. 1970, 92, 3109

Bicyclic Alcohol via Enantioselective α-Deprotonation

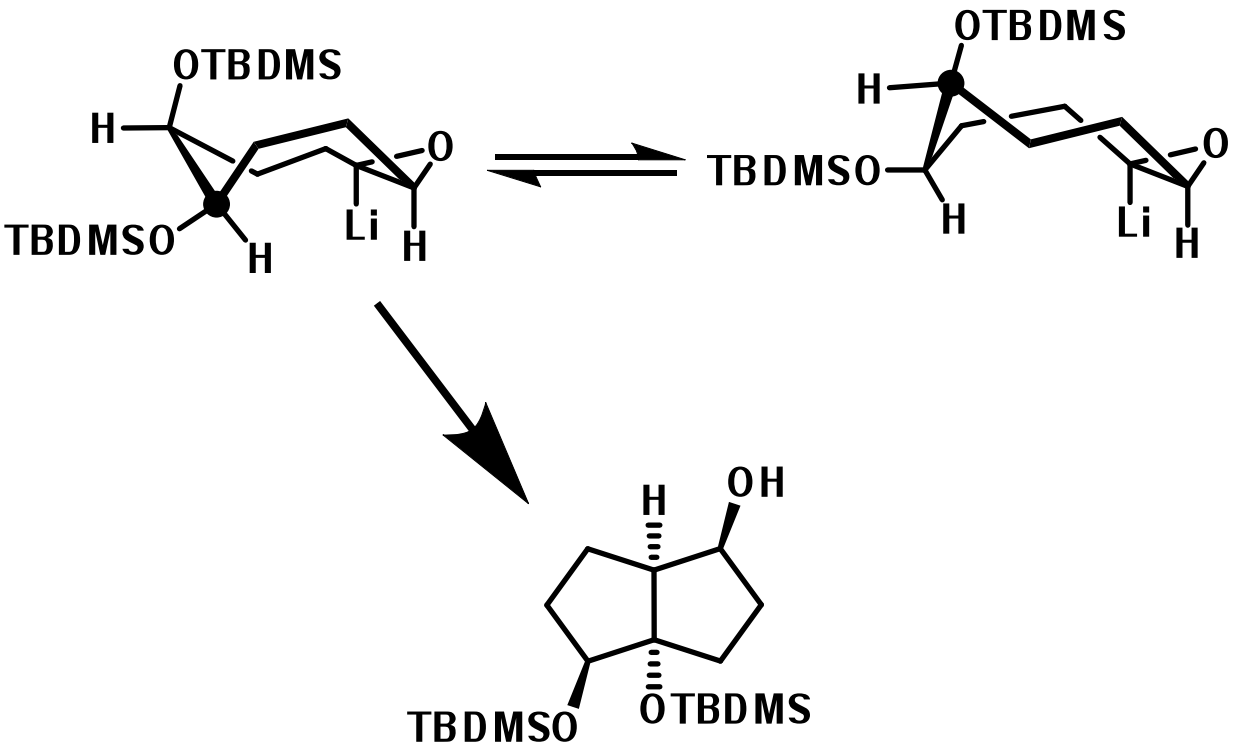


D. M. Hodgson, et al *J. Chem. Soc., Perkin Trans. 1* **1998**, 2151

(-) Sparteine as Directing Ligand

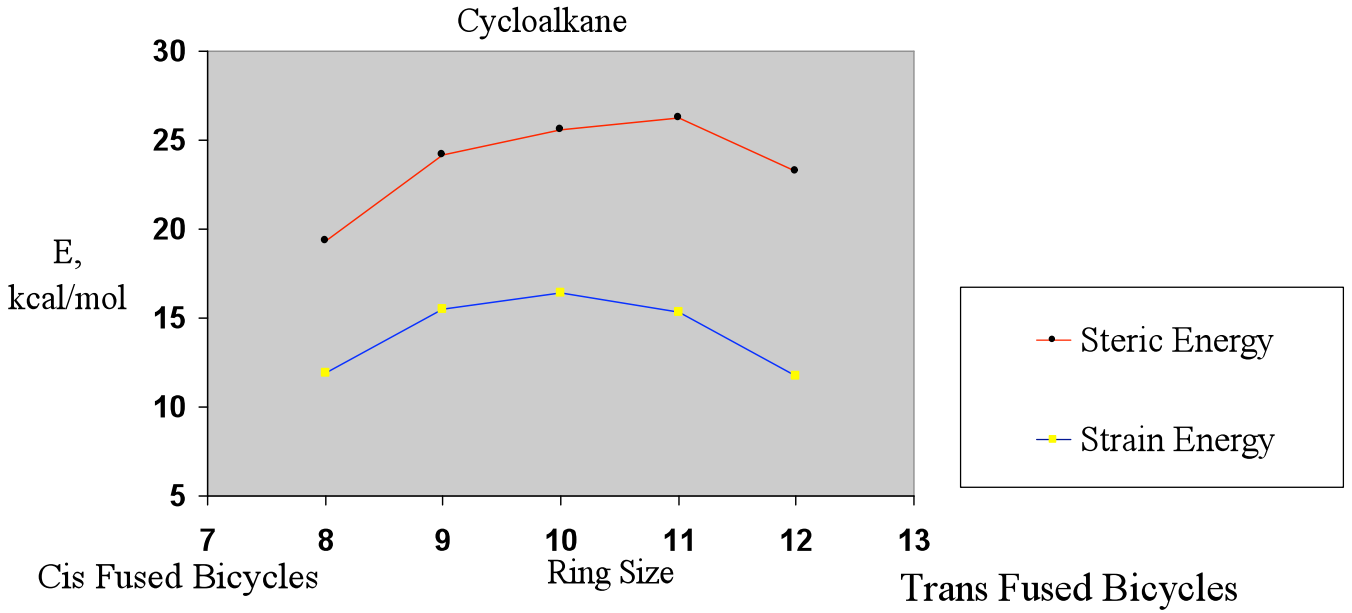


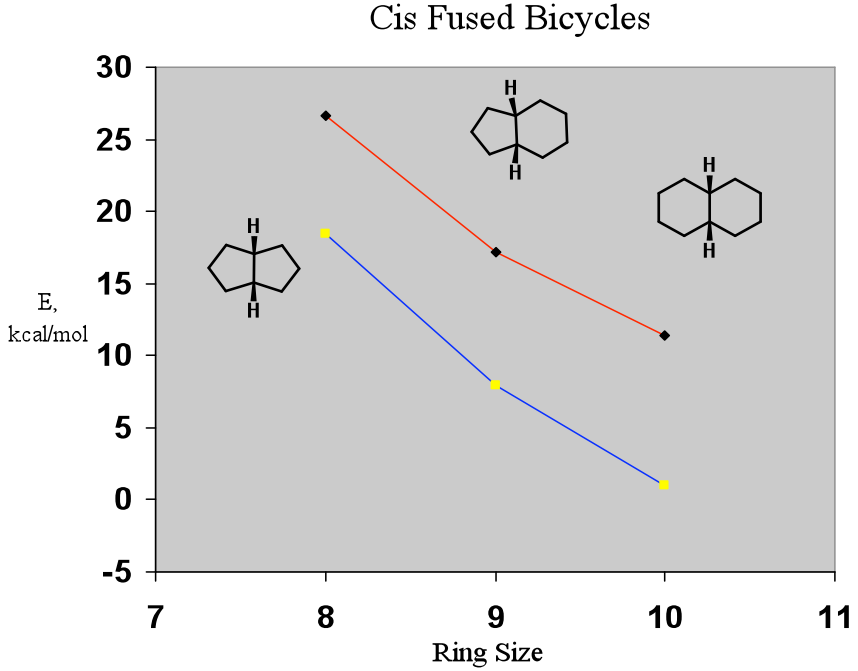
Conformational interconversion

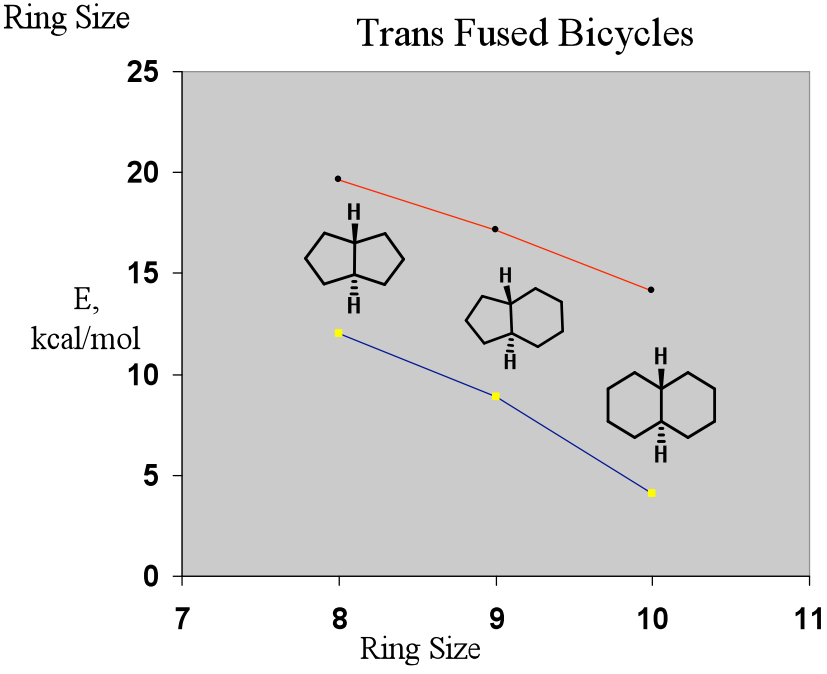


D. M. Hodgson, et al *J. Chem. Soc., Perkin Trans. 1* **2001**, 2161
D. M. Hodgson, I. D. Cameron, *Org. Lett.* **2001**, *3*, 441

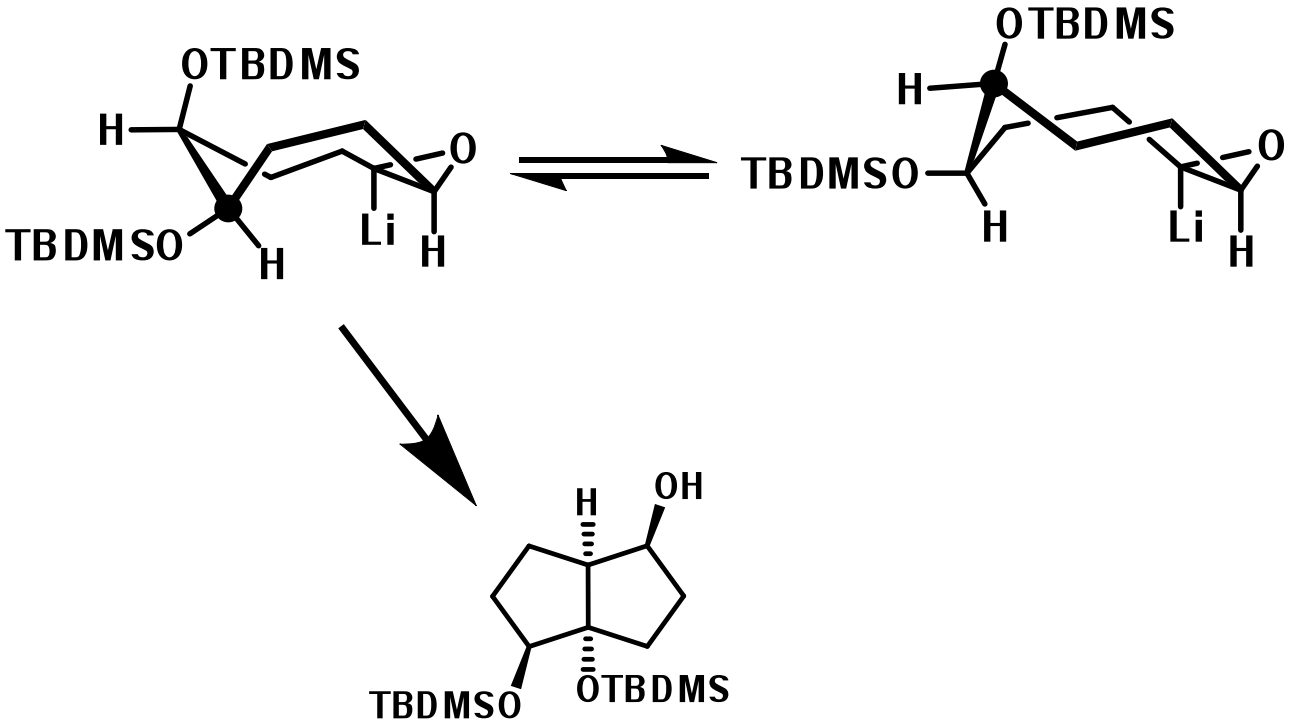
Correlation of Steric and Strain Energy







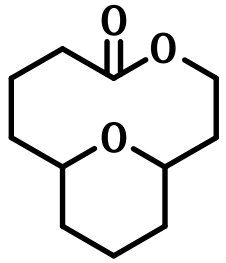
Conformational interconversion



D. M. Hodgson, et al *J. Chem. Soc., Perkin Trans. 1* **2001**, 2161
D. M. Hodgson, I. D. Cameron, *Org. Lett.* **2001**, *3*, 441

Bridged Bicycle via Transannular Reaction

spirocycle



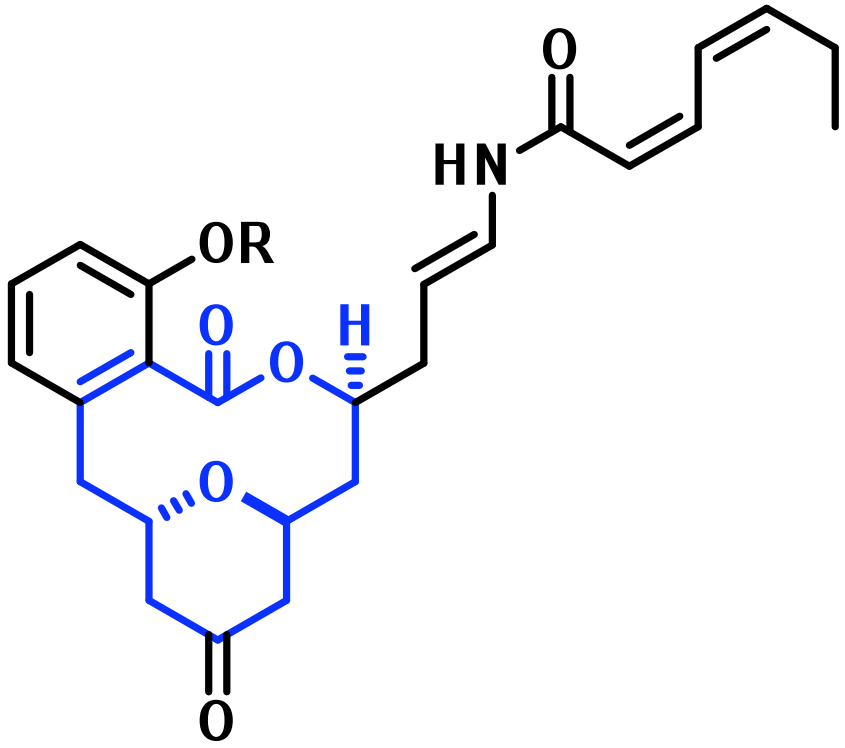
bridged bicycle

fused bicycles

tricycle

pentacycle

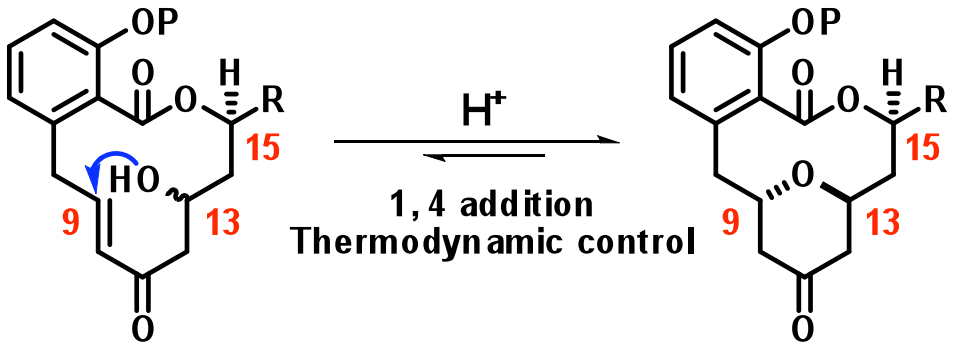
Apicularens

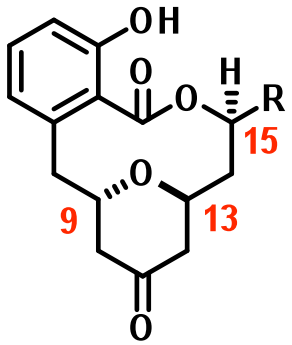


Apicularen A: R = H
Apicularen B: R = *N*-acetyl-β-glucosamine

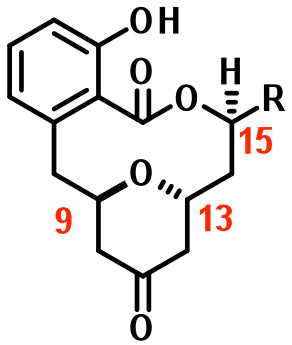
Petri, A. F.; Bayer, A.; Maier, M. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 5821
Li,M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087
Hilli, F.; White, J. M.; Rizzacasa, M. *Org. Lett.* **2004**, *6*, 1289

Energy Difference in Apicularen-type Ring

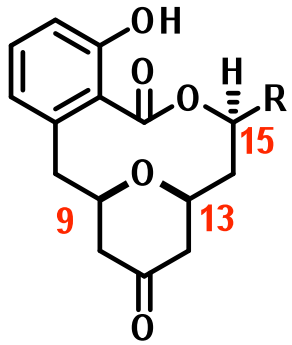




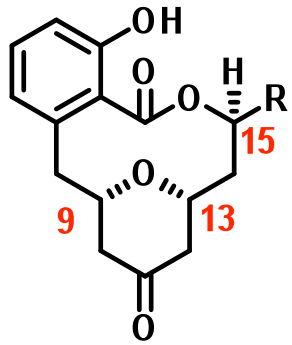
Twist boat
9,13-*Trans*-13,15-*Syn*
160 KJmol^{-1}



Twist boat
9,13-*Trans*-13,15-*Anti*
173 KJmol^{-1}



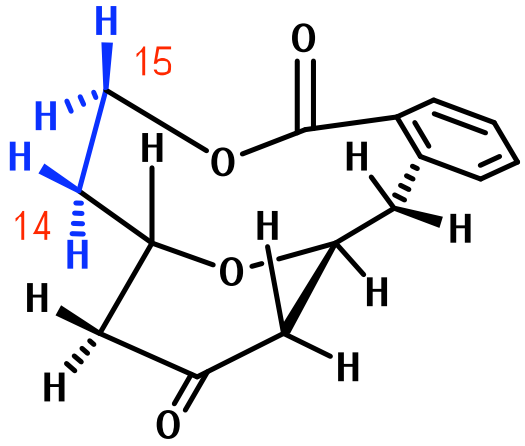
Chair
9,13-*Cis*-13,15-*Syn*
171 KJmol^{-1}



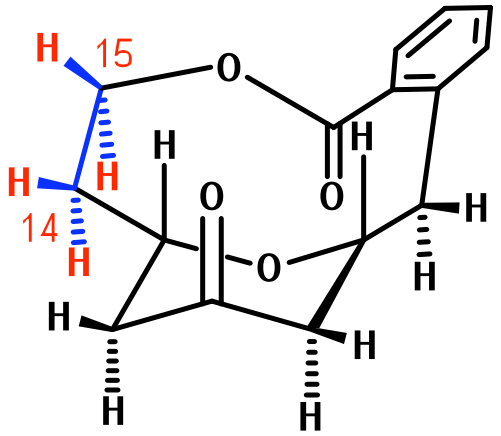
Chair
9,13-*Cis*-13,15-*Anti*
171 KJmol^{-1}

Hilli, F.; White, J. M.; Rizzacasa, M. *Org. Lett.* **2004**, *6*, 1289

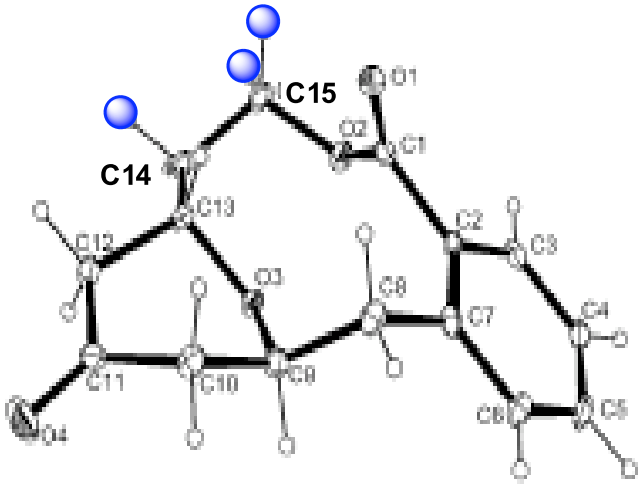
Core Conformations of Apicularen

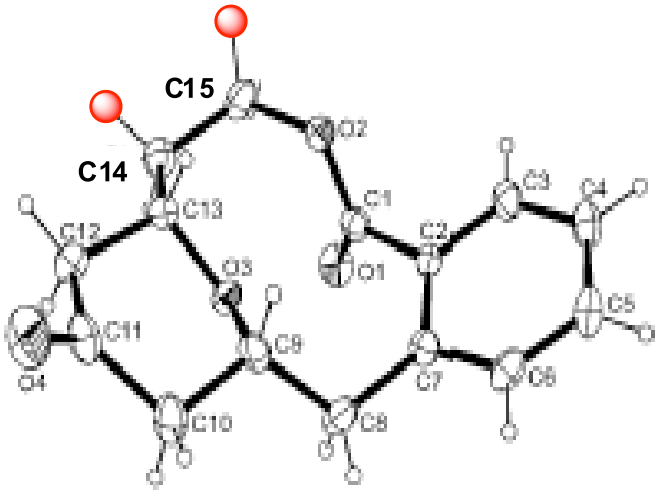


Twist Boat



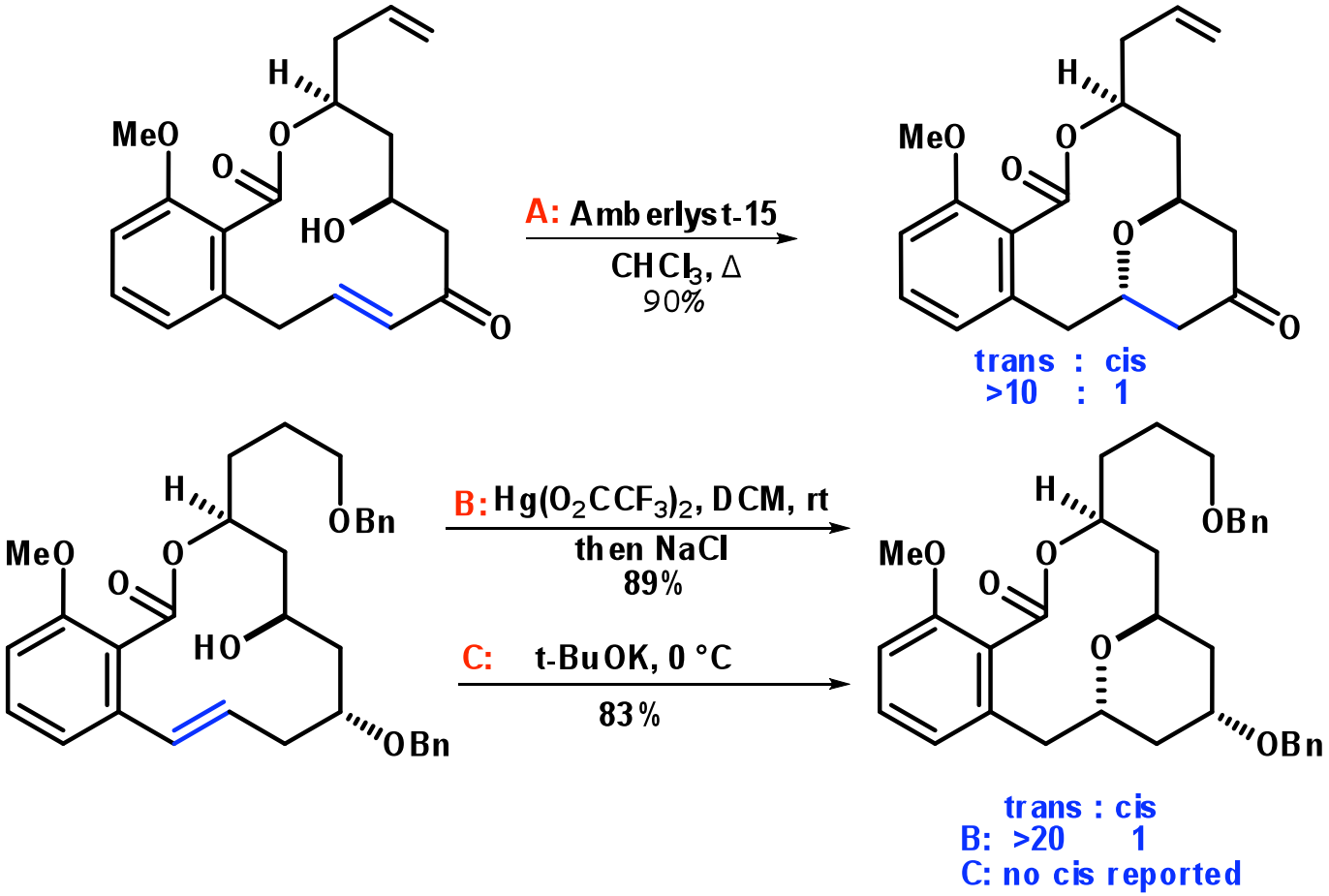
Chair





Hilli, F.; White, J. M.; Rizzacasa, M. *Tetrahedron Lett.* **2002**, *43*, 8507

Synthetic Approaches Towards Apicularen A



A. Hilli, F. ;White, J. M.; Rizzacasa, M. *Org. Lett.* **2004**, *6*, 1289

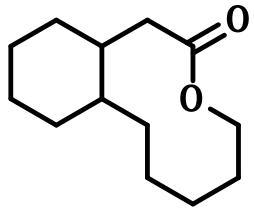
B. Petri, A. F.; Bayer, A.; Maier, M. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 5821,

C. Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087

Fused Bicycles by Transannular Reactions

spirocycle

bridged bicycle

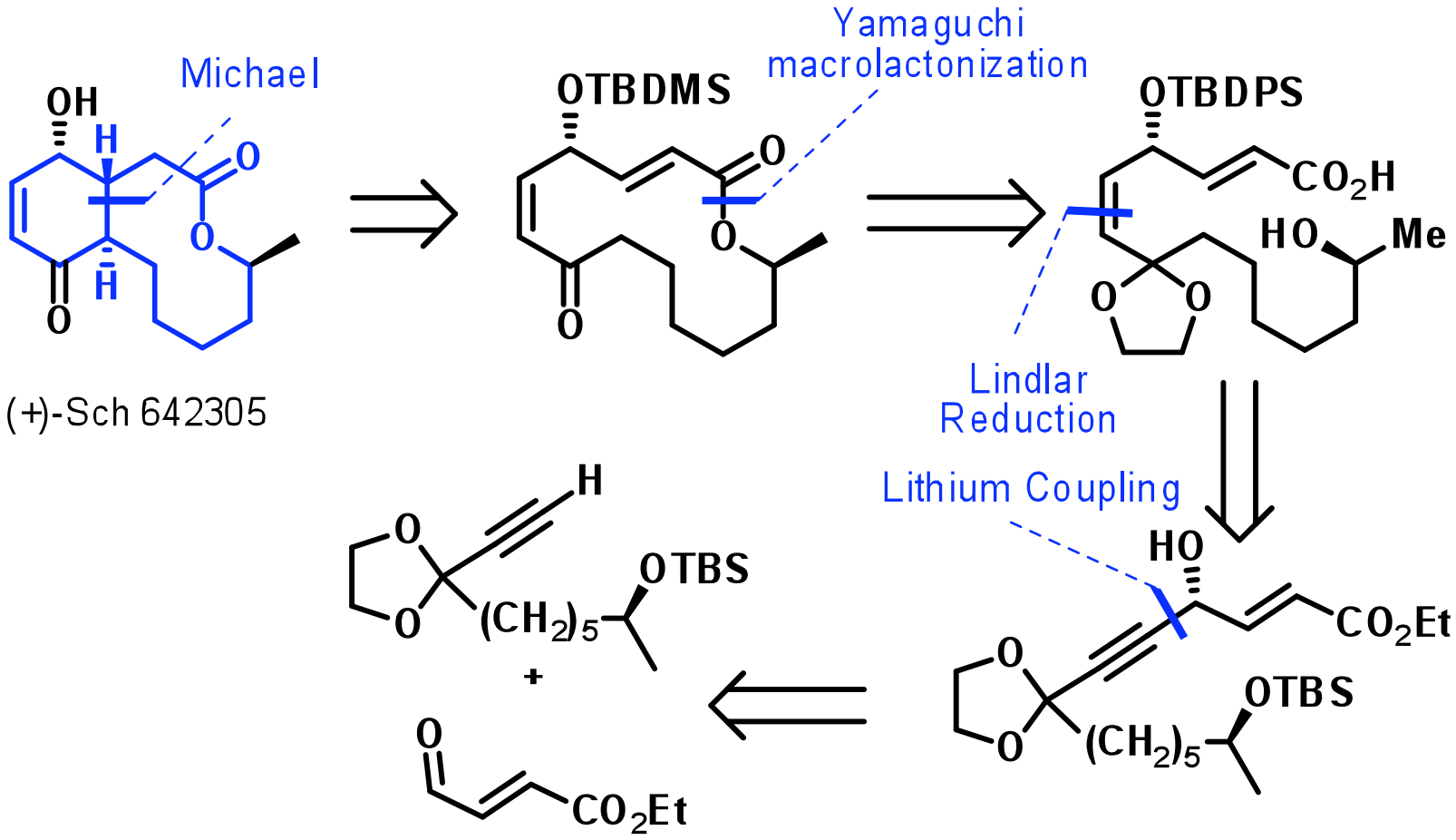


fused bicycles

tricycle

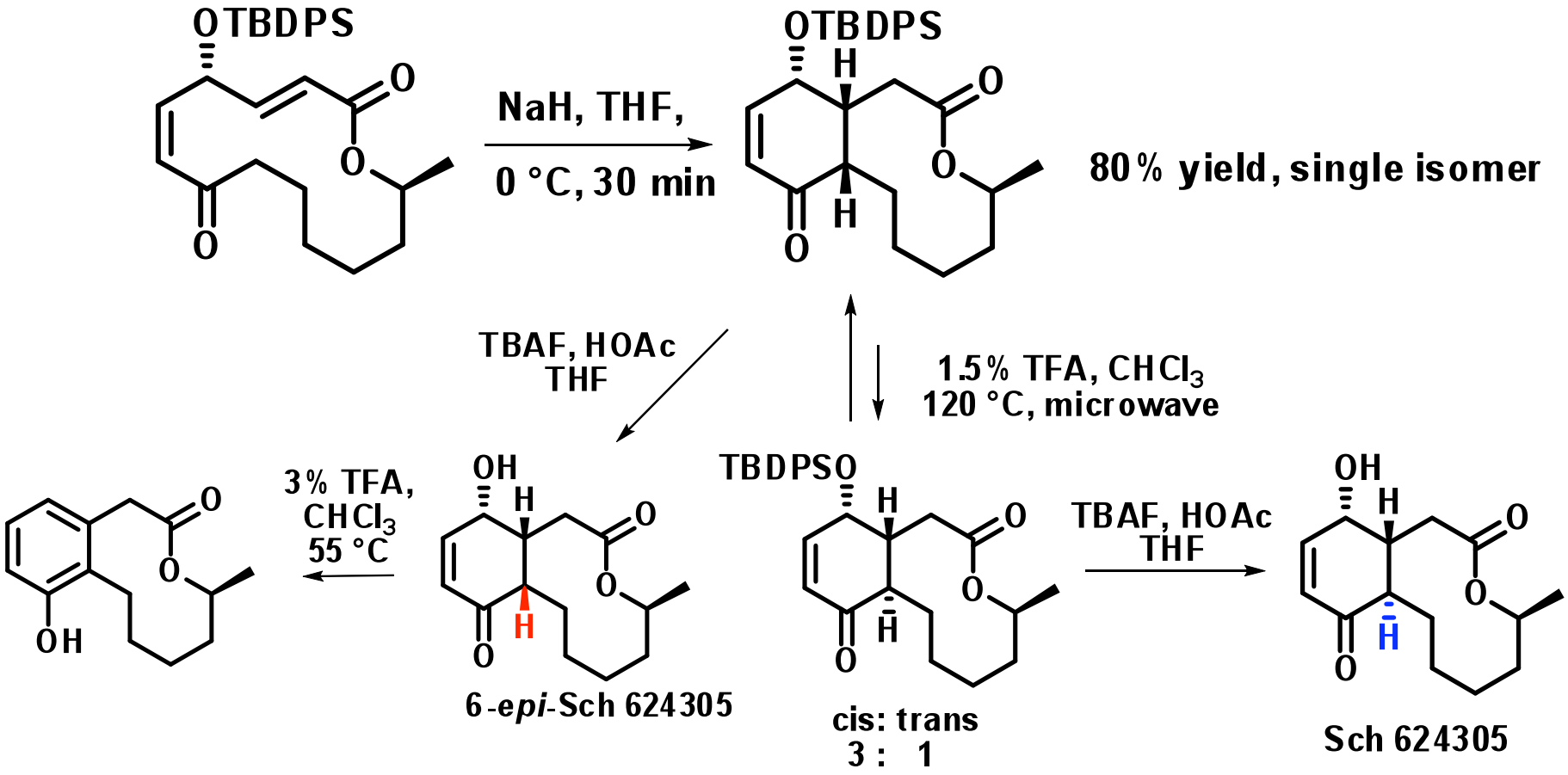
pentacycle

Retrosynthetic Analysis of (+)-Sch-642305



Snider, B. B.; Zhou, J. *Org. Lett.* **2006**, *8*, 1283

Transannular Michael Reaction



Snider, B. B.; Zhou, J. *Org. Lett.* **2006**, *8*, 1283

Rational for Observed Selectivity