IASOC XVII

The Consilience of Logic, Chance and the Unforseen in Organic Synthesis

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Lecture outline

- Selected vignettes of concept-based ideas
- Selected vignettes of logic and knowledge-based ideas
- Selected vignettes of chance-based outcomes
- Selected vignettes exploring the third dimension
- Lessons from nature and natural products

Selected Vignettes of Concept-based Ideas

(Somewhat dated but of lasting impact)

Stereo- and regiochemical Control in Bond Formation

APPLICATION AND EXPLORATION OF NOTIONS OR CONCEPTS

↓

DESIGN OF REAGENTS, CATALYSTS, REACTIONS, ETC.

↓

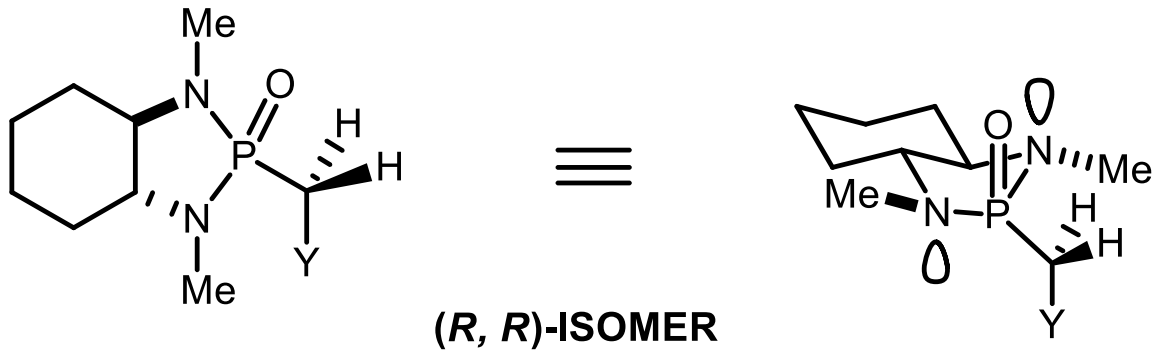
INNOVATION AND Discovery

EXPLOITATION OF « EFFECTS »

INHERENT / IMPOSED

- TOPOLOGY
- STEREOELECTRONIC
- SYMMETRY / ASYMMETRY
- STERIC BIAS
- CONFORMATION
- COORDINATION / CHELATION
- PROXIMITY / AFFINITY
- KINETIC / THERMODYNAMIC

Combining metal coordination, conformational bias topology, stereoelectronics, and C_2 symmetry in one reagent



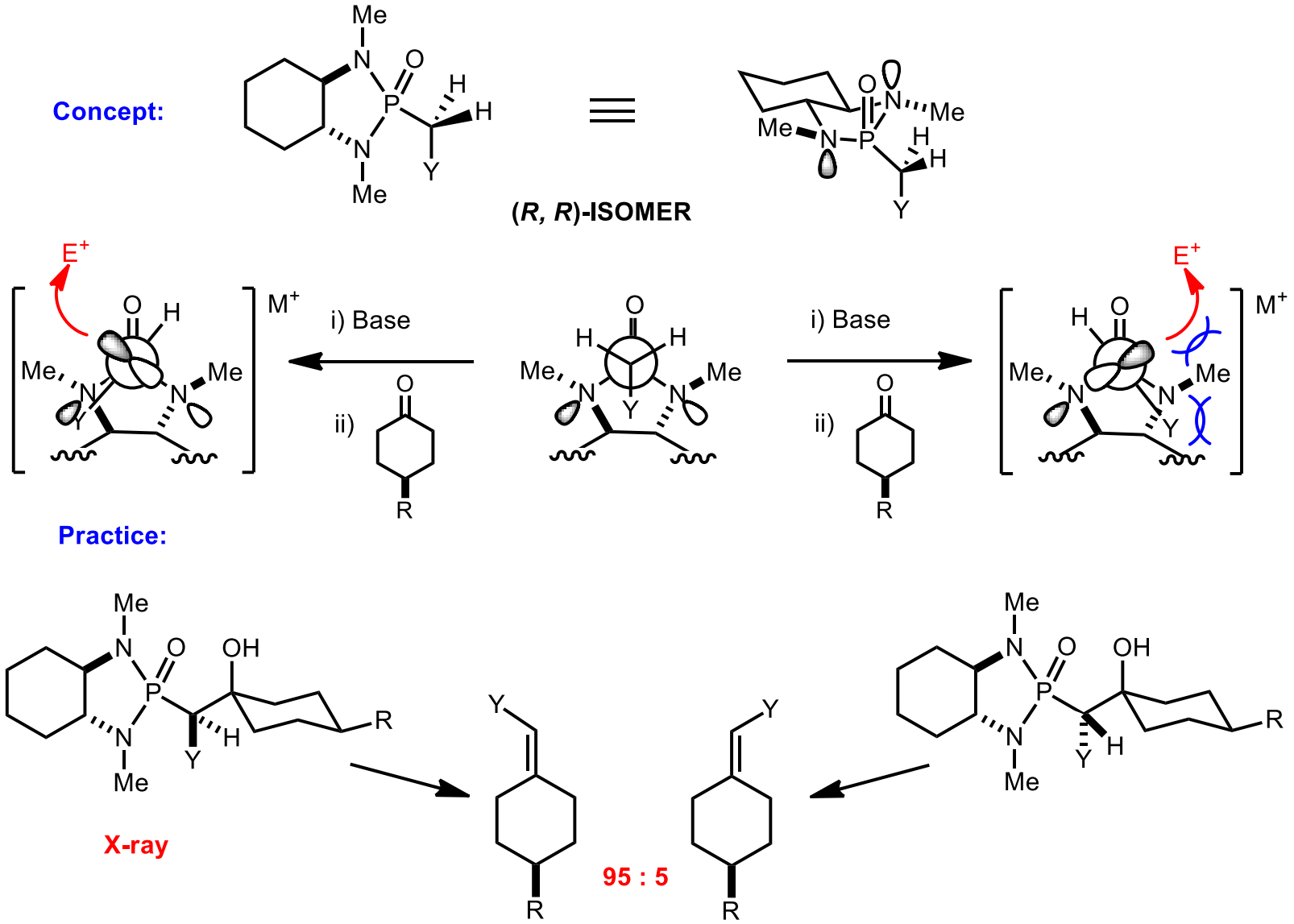
(*R*, *R*)-ISOMER

Earliest example of the use of 1,2-trans-diaminocyclohexane in asymmetric synthesis

with Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754

Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161;
Recent review: Focken, T.; Hanessian., S. *Beilstein J.Org.Chem*. **2014**, *110*, 1848

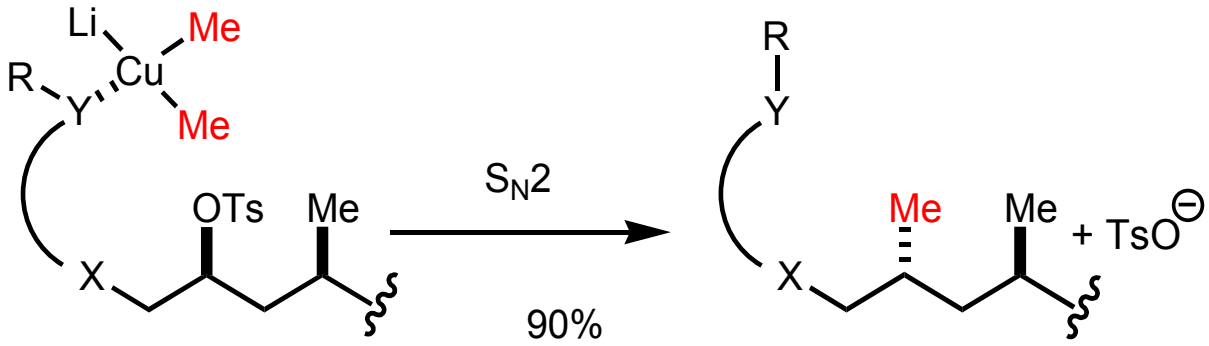
Design and reactivity of an asymmetric olefination reagent



with Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754; *with* Bennani, Y. L. *Chem. Rev.* **1997**, *97*, 3161

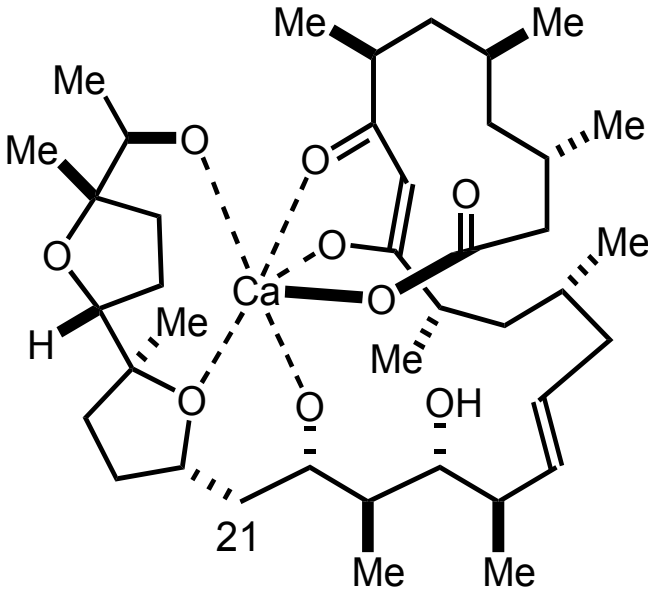
Internally Assisted "Carbon S_N2 Displacement"

Concept:



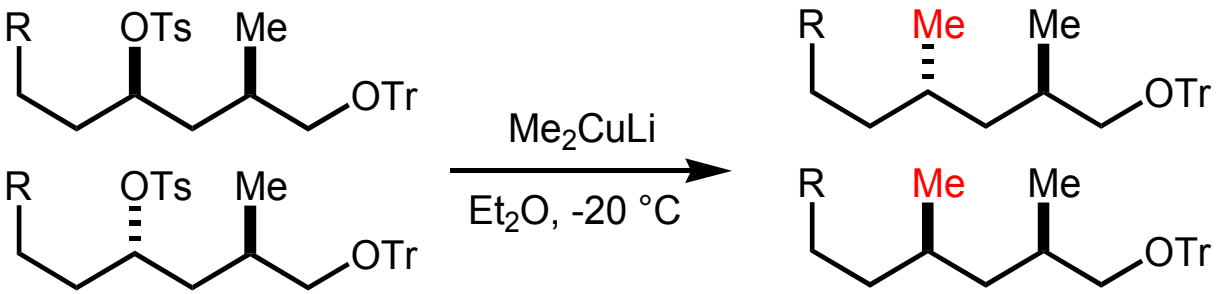
X = SPh
X = Y = OMOM, OMTM, etc...

Example of proximity assisted chelation



IONOMYCIN Ca salt

Practice:

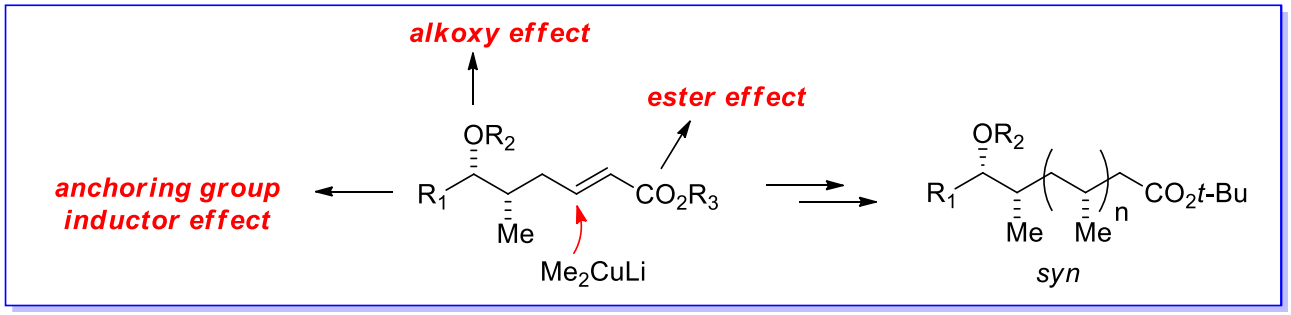


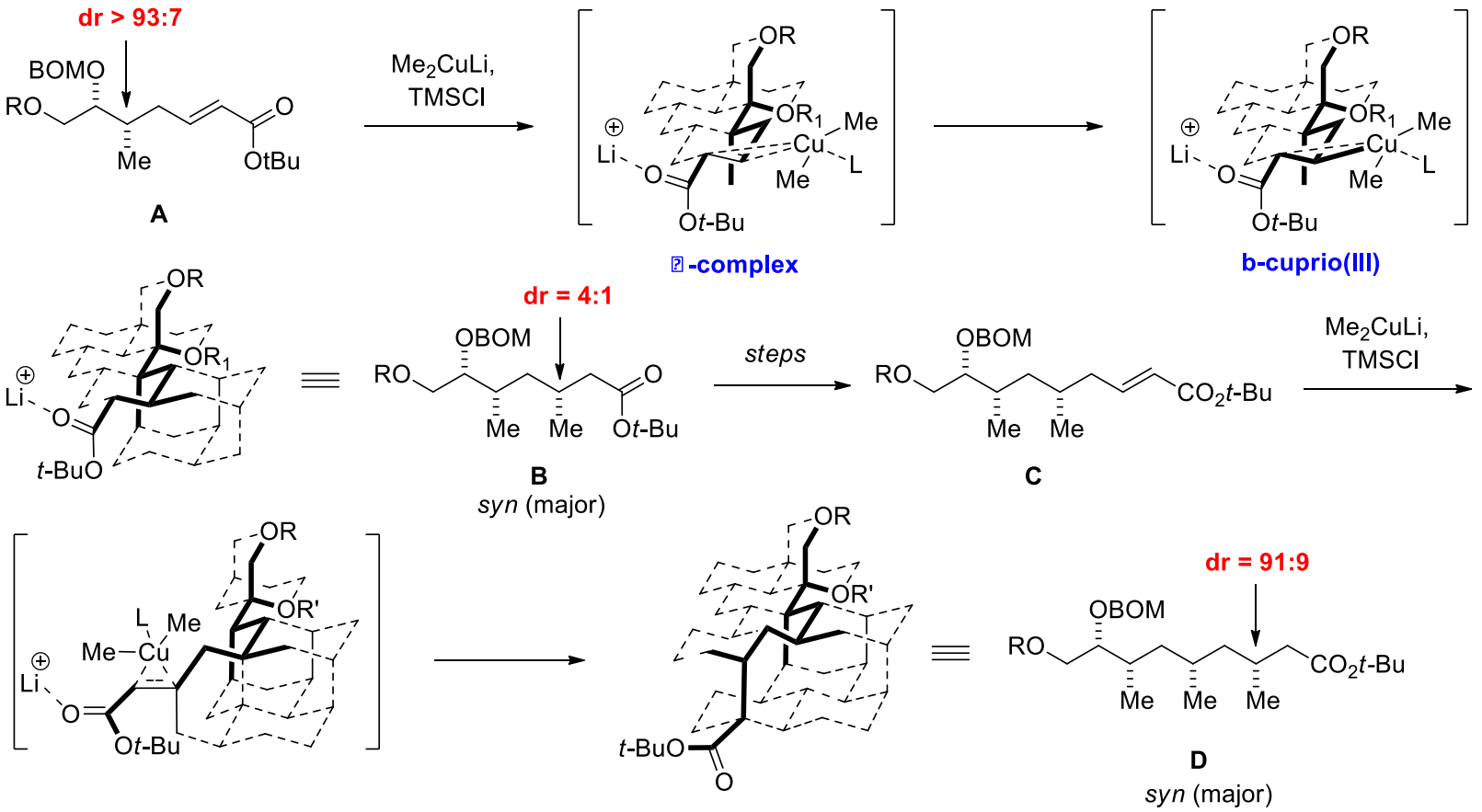
R = SPh, OMOM, MTM

Hanessian, S. et al. *J. Am. Chem. Soc.* **1990**, *112*, 5276
Hanessian, S. et al. *J. Org. Chem.* **1989**, *54*, 5831

Concept: Acyclic conformational control toward deoxypropionates: Iterative 1,2-and 1,3- induction via isotactic type folding

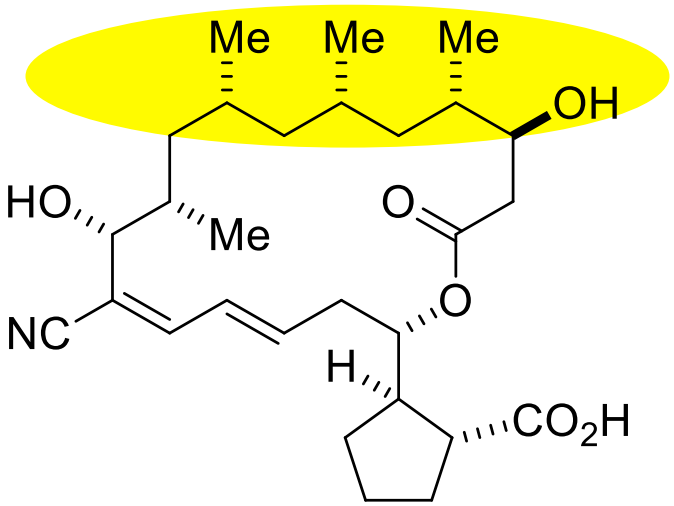
Avoiding Syn-pentane interactions



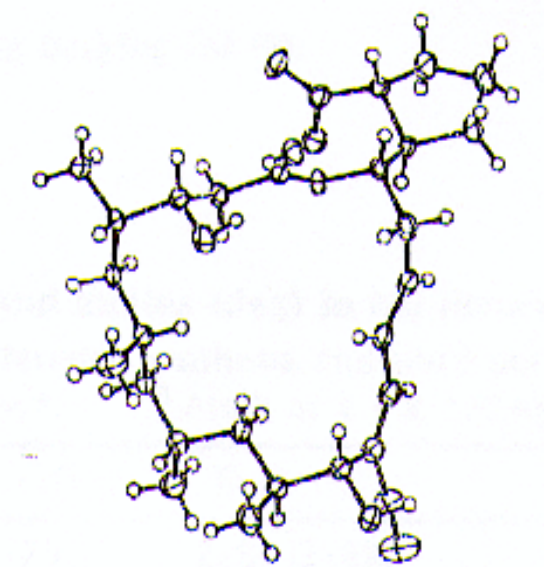


isotactic type folding is transmitted from adjacent resident stereocenters to the newly created triad

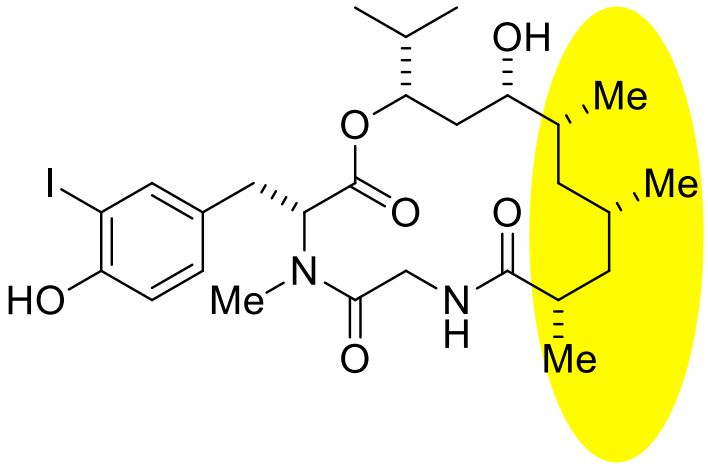
Extended deoxypropionates in natural products



Borrelidin



with Yang, Y.; Giroux, S.; Mascitti, V.; Ma, J.; Raeppel, F.J. *Am. Chem. Soc.* **2003**, *125*, 13784

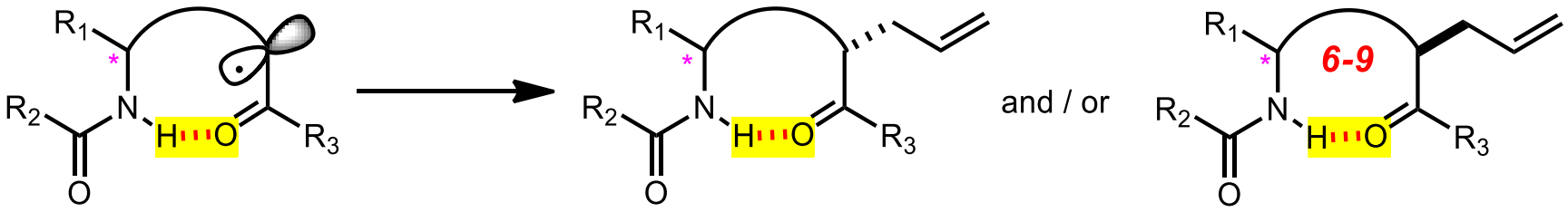


Doliculide

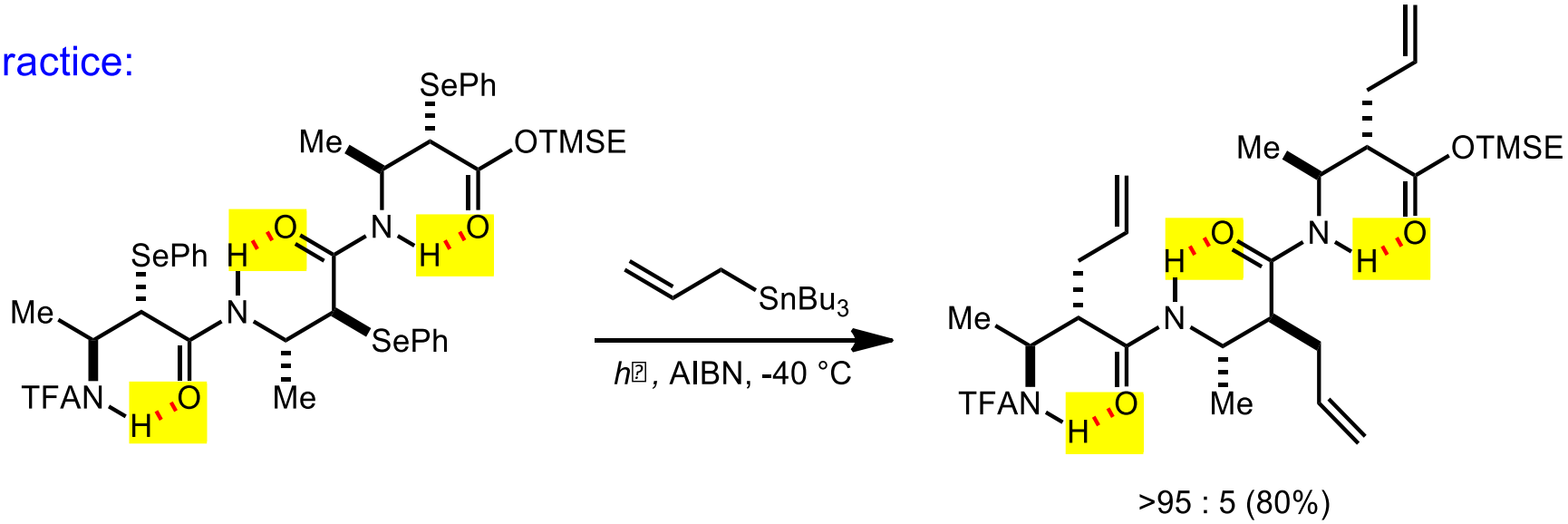
with Mascitti, V.; Giroux, S. *PNAS*, **2004**, *101*, 11996

H-Bonding as a stereocontrolling element in free radical allylations

Concept:



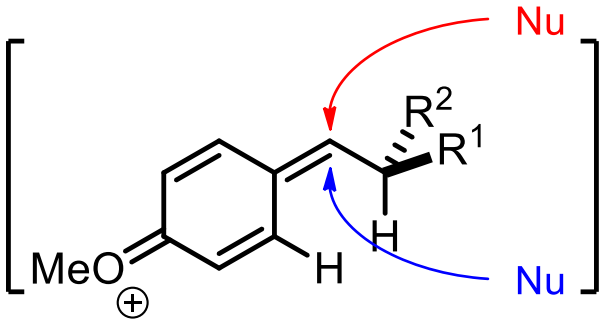
Practice:



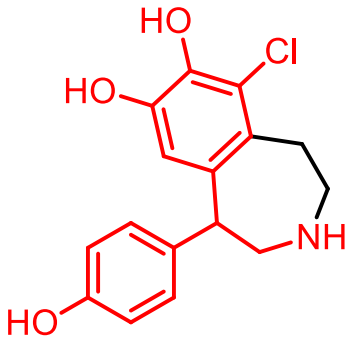
with Yang, H.; Schaum, R. *J. Am. Chem. Soc.* **1996**, *118*, 2507.

Catalytic Diastereoselective Friedel-Crafts Alkylation: Toward 1,1'-Diarylmethanes

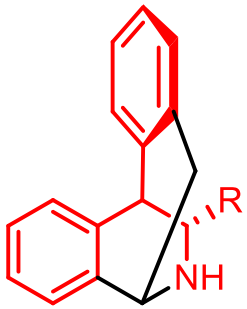
Basic concept:



Conformation avoids $A^{1,3}$ strain



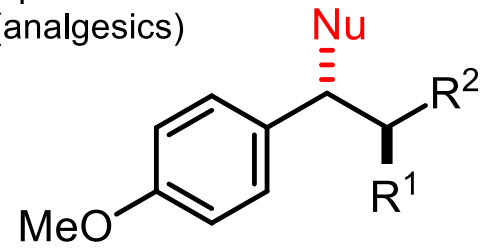
Fenoldopam (antihypertensive)

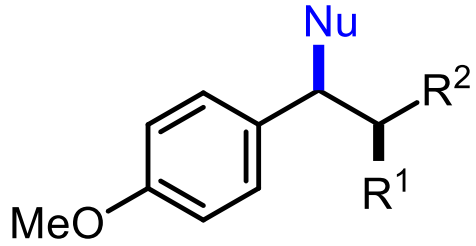


morphomimetics (analgesics)

Nu = electron rich aromatic or heteroaromatic

with Parthasarathy, M.; Mauduit, M.; Payza. K. *J.Med.Chem*. **2003**, *46*, 34



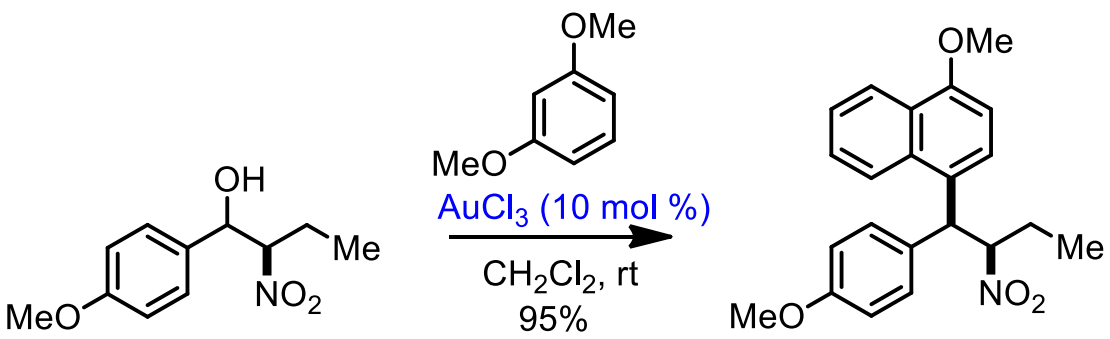


Major *syn*-diastereomer

with Chénard, E. *Org.Lett*. **2014**, *16*, 2668

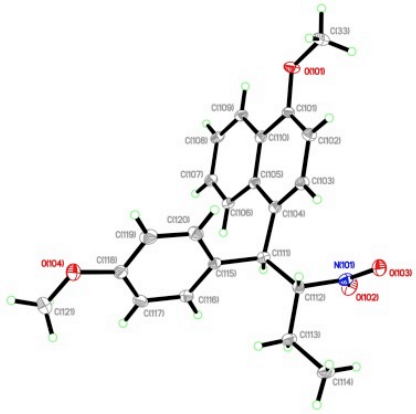
See also: Olah, Bach, Lautens, Beller, Rueping for related systems;
Diarylmethanes review: Ameen, D.; Snape, T.J. *MedChemRev*. **2013,**
Friedel- Crafts review: Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org Chem.* **2010**, 1-24

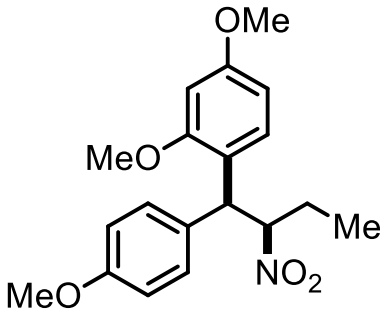
Gold catalyzed 1,1’-diaryl 2−nitro alkanes



3:1 syn/anti

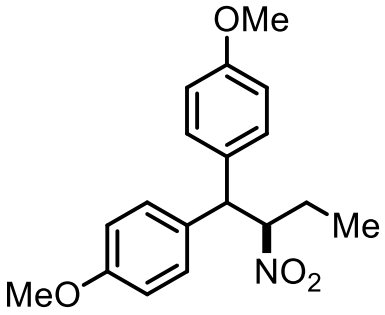
20:1 anti (X-ray)



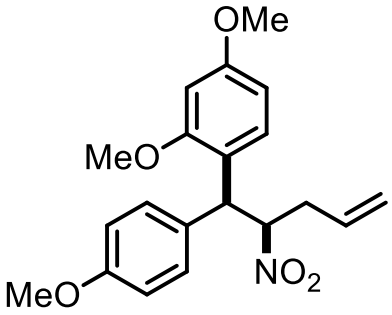


95%,dr 20:1

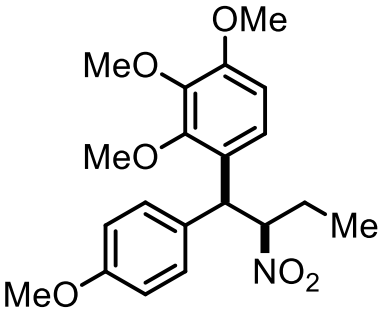
with HBF_4 : 81%, dr 13:1



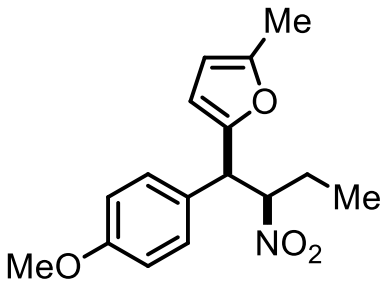
>95%



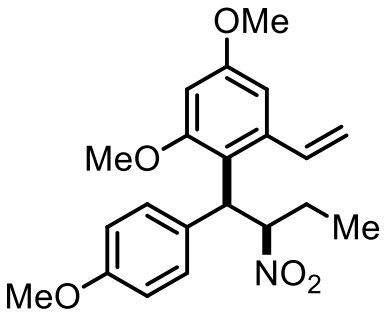
66%, dr 20:1



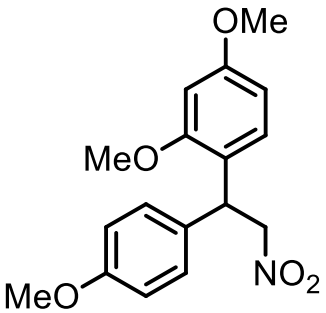
89%, dr 20:1



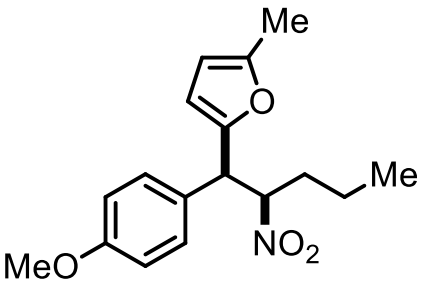
>78%, dr 20:1



87%, dr 20:1

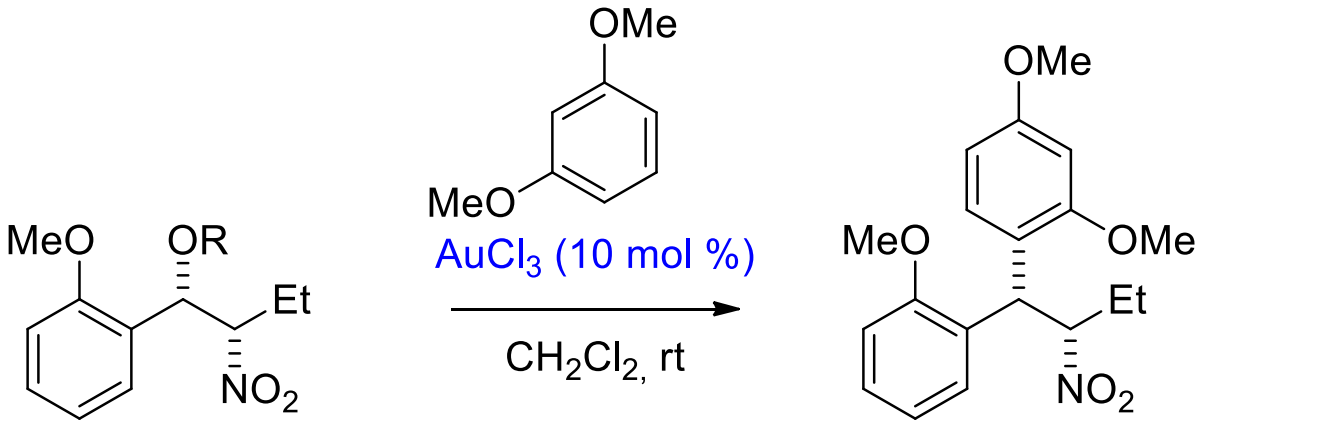


>95%



60%, dr 20:1

Kinetic diastereomer differentiation



syn-**15a** R = H
syn-**15b** R = Ac
20:1

16
from *syn*-**15a** 53%,[b] dr 12:1, 24 h
from *syn*-**15b** 81%,[c] dr 12:1, 16 h

anti-**15a** R = H
anti-**15b** R = Ac
20:1

as above

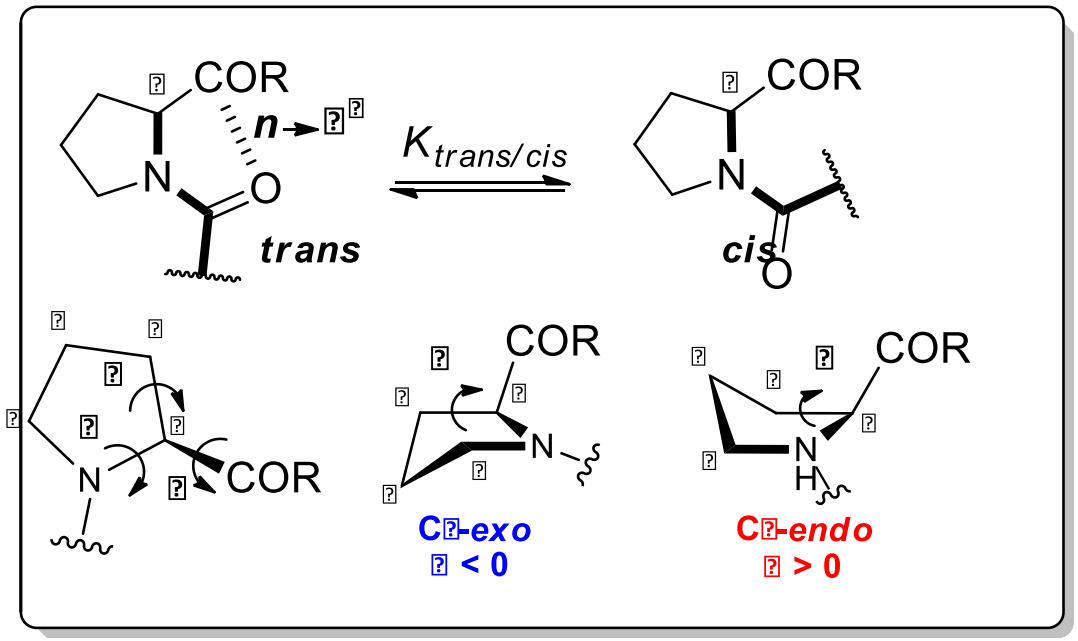
no reaction[d]

[a]Ratios were determined by ^{1}H NMR analysis of the crude materials and yields were obtained after purification. [b] From TLC analysis, the reaction did not achieve full conversion over a period of 24 h. [c]Full conversion within 16 h by TLC analysis. [d]No conversion was observed by TLC analysis, after 24 h.

with Chénard, E. *Org Lett*. **2014**, *16*, 2668

Concept:

Stereoelectronic effects in proline amides



***cis*-bonded AA**

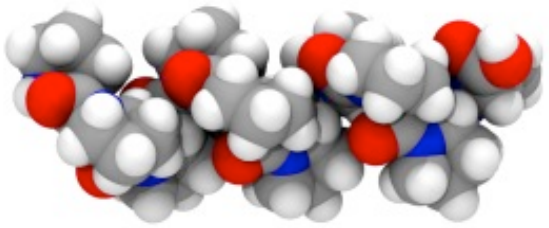
less than 1 %

***cis*-bonded Pro**

around 6 %

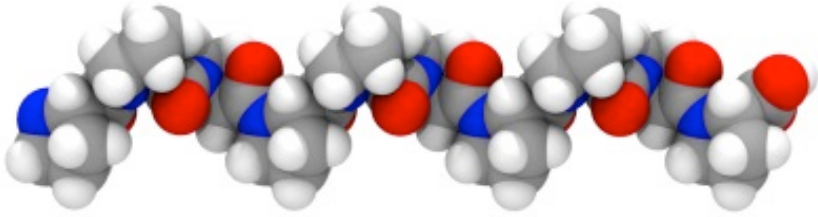
Polyproline I and II helical conformations

PPI



Looser left handed-helix with all-trans amide bonded residues and a helical pitch of ca. 9.4 Å

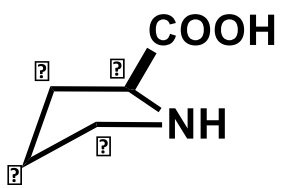
PPII



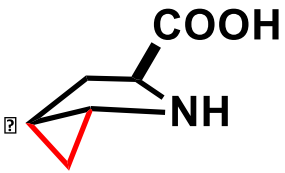
Compact right-handed helix with all-cis amide bonded residues and a helical pitch of 5.6 Å

Shoulders, M. D.; Raines, R. T. *Ann.Rev. Biochem*. **2009**, *78*, 929

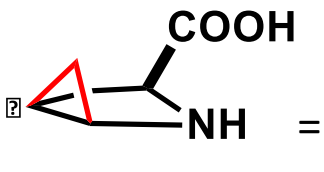
Proline 4,5-methanologues: structural and stereoelectronic properties



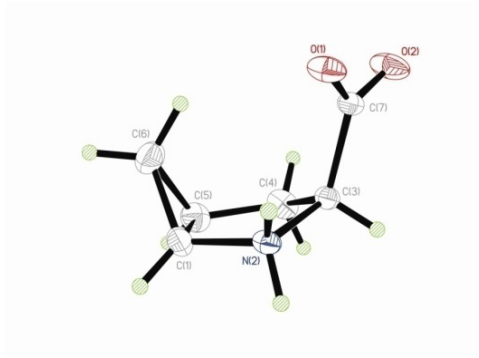
L-proline
RMDS 0.165 Å
C□-*exo*

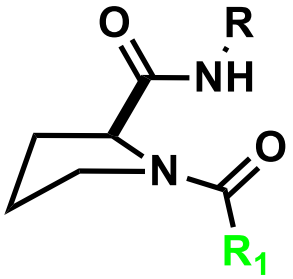


trans-RMDS 0.110 Å
C□-*exo*

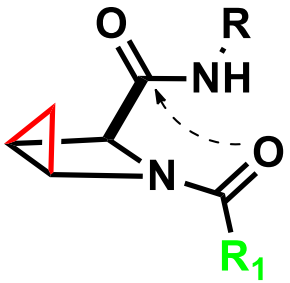


cis-RMDS 0.001 Å
C□-*endo*



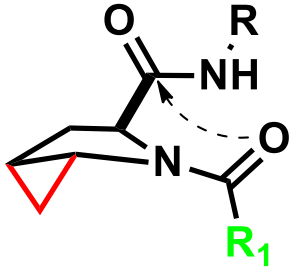


trans-(amide)



n→□* interaction

cis/*trans*-(amide)



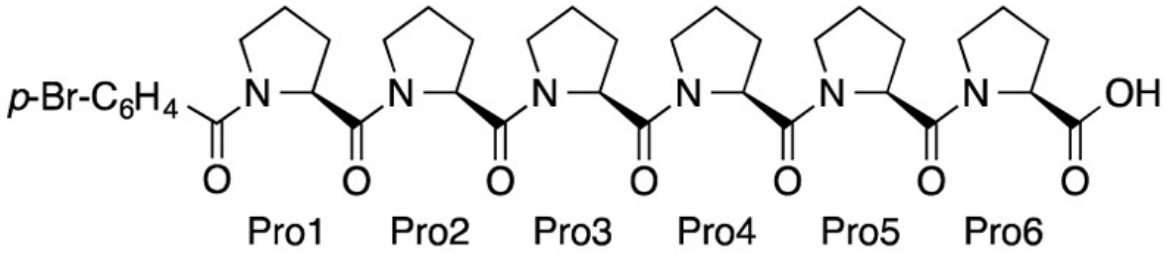
n→□* interaction

trans/*trans*-(amide)

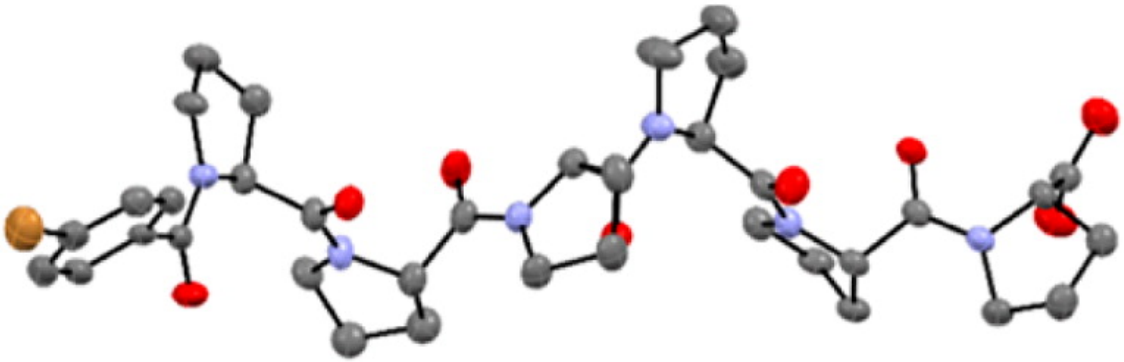
‘Proline Methanologues: Design, Synthesis, Structural Properties and Applications in Medicinal Chemistry,’ Vilchis-Reyes, M. A.; Hanessian ,S.
in *‘Topics in Heterocyclic Chemistry*, Lubell . W. Ed, 2015, pp1-45

Polyproline II helix: a crystal structure, at last

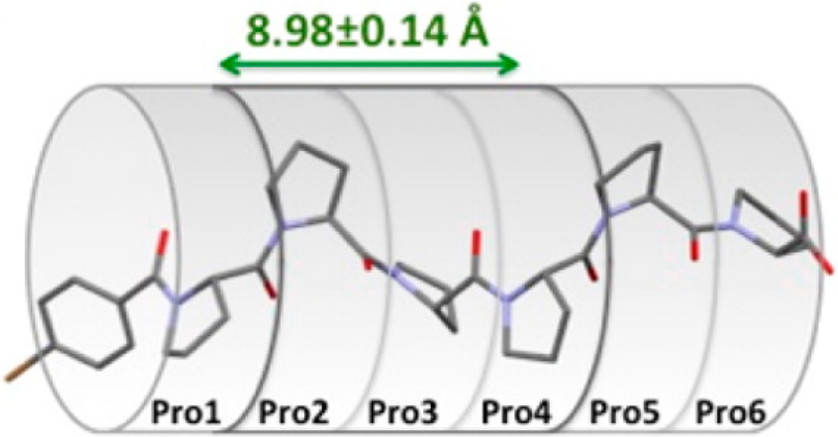
a)



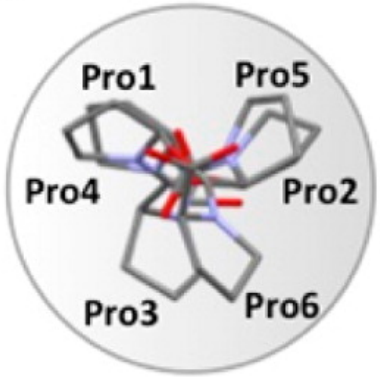
b)



c)



d)



(a) Hexaproline p-Br-C_6H_4-Pro_6-OH.

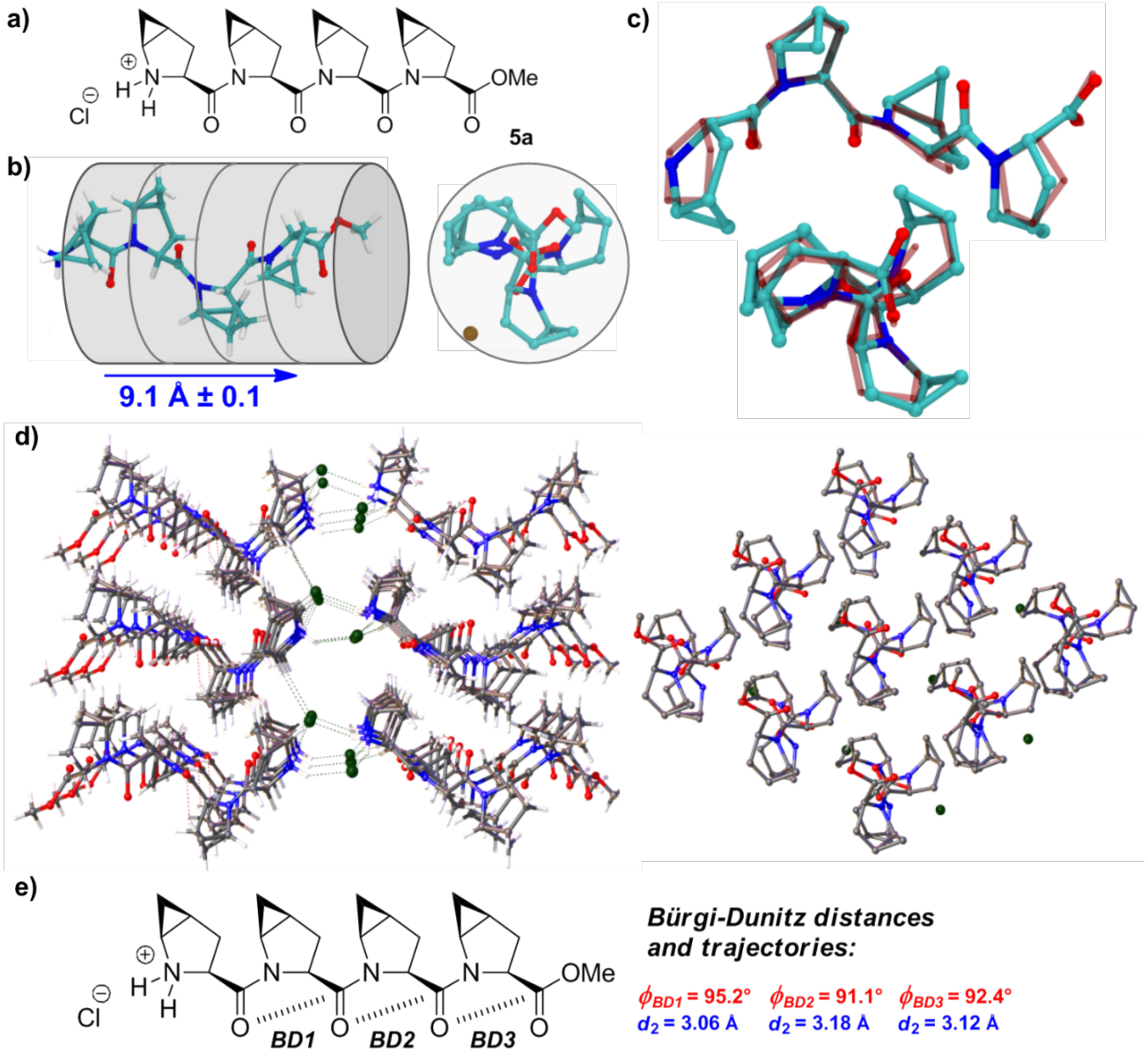
(b) Crystal structure (ORTEP).

(c) Segmental side view.

(d) View along the axis.

Wennemers, H. et al. J. Am. Chem. Soc. **2014**, *136*, 15829;
see also Madalengoitia, J. et al. *J.Org.Chem.* **2001**, *66*, 455

The shortest proline oligomer to adopt a PPII helical shape

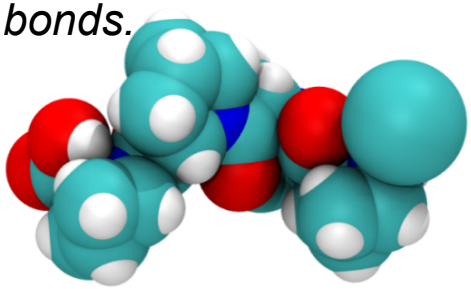


(a) Tetrameric cis-4,5-methano-L-proline methyl ester hydrochloride

(b) Side-view and view along the helical axis of the crystal structure showing a typical polyproline II helix conformation.

(c) Hexameric oligoproline from Wennemers et al.

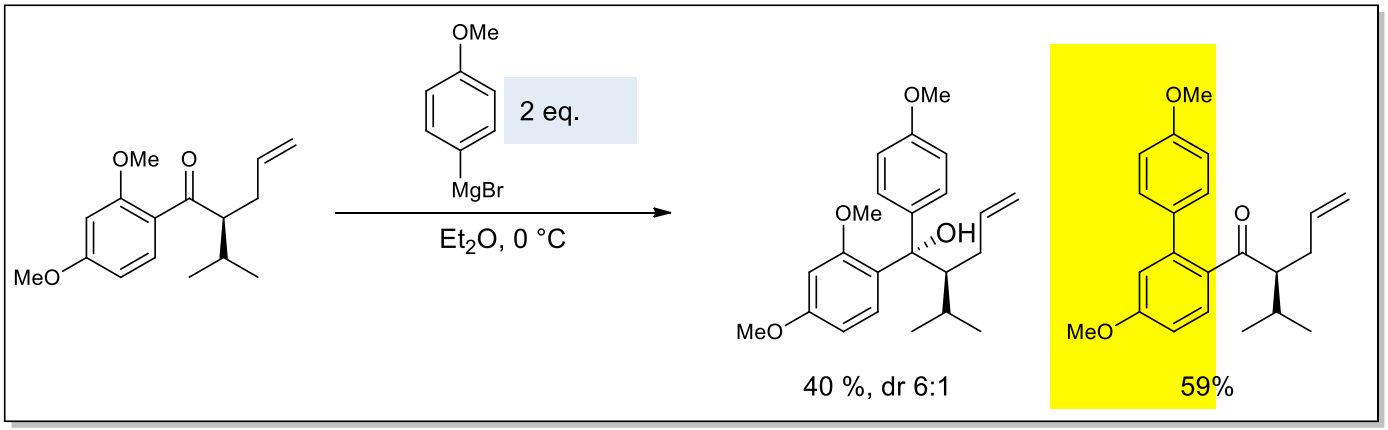
(d) Packing shows central chloride ions interacting with surrounding N-H and C_α-H bonds.

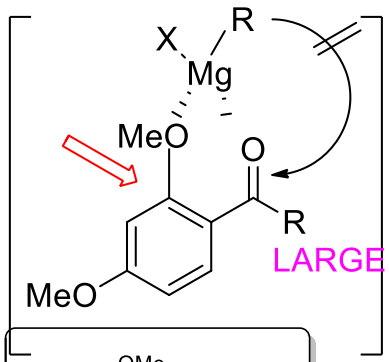


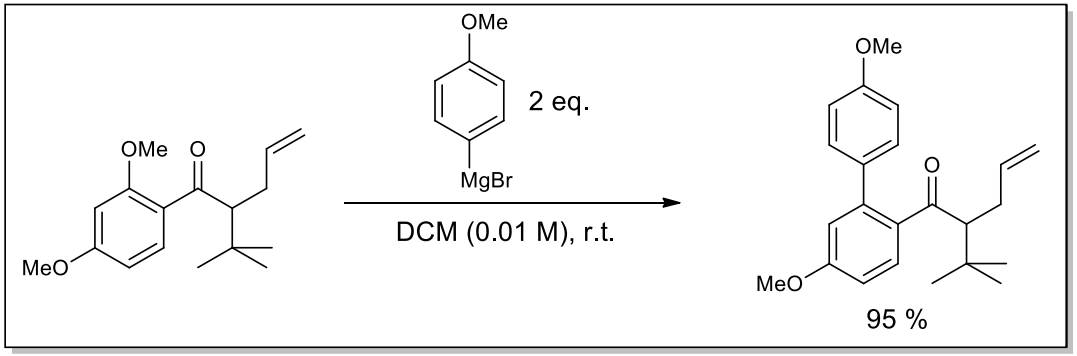
with Berger, G.; Vilchis, M. *Angewandte Chem. Int. Ed*. **2015**, *54*, 13268

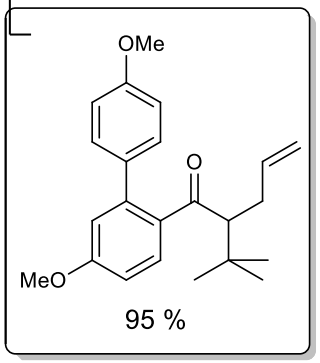
Logic and knowledge-based ideas

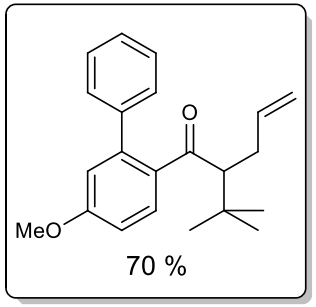
1,4- Aromatic alkylation via methoxy activation: An AHA moment!

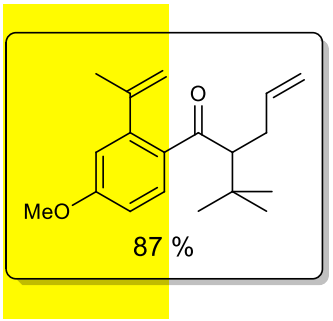


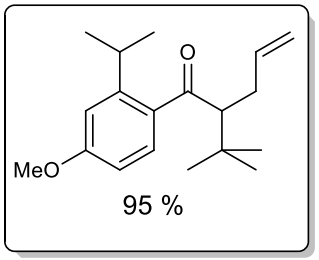


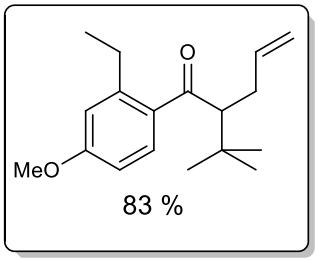










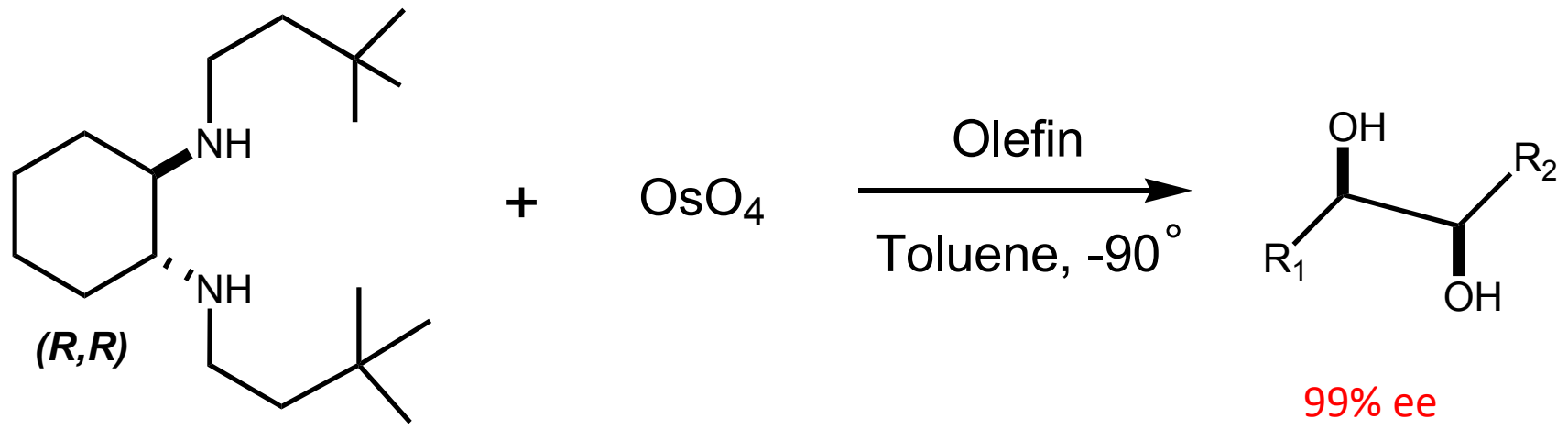


with Grélier, G.; Chénard, E.; Buschleb, M. *Synthesis*, **2015**, *47*, 1317

See also:Jimenez-Oses, G.; Brockway, A. J.; Shaw, J. T.; Houk, K. N. *J. Am. Chem. Soc.*, **2013**, *135*, 6633; Fuson, R. C.; Speck, S. B. *J. Am. Chem. Soc.*, **1942,** *64*, 2446

Chance-based outcomes

1,2 -*trans* (*R,R*)-Diaminocyclohexane (DACH)as a ligand in asymmetric synthesis

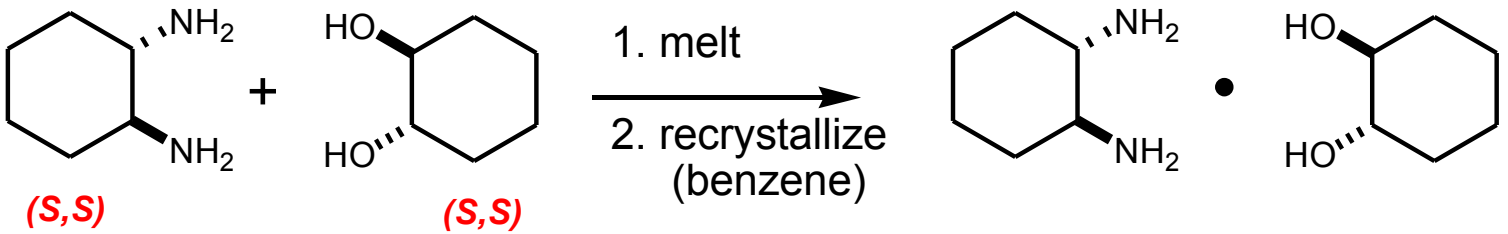


99% ee

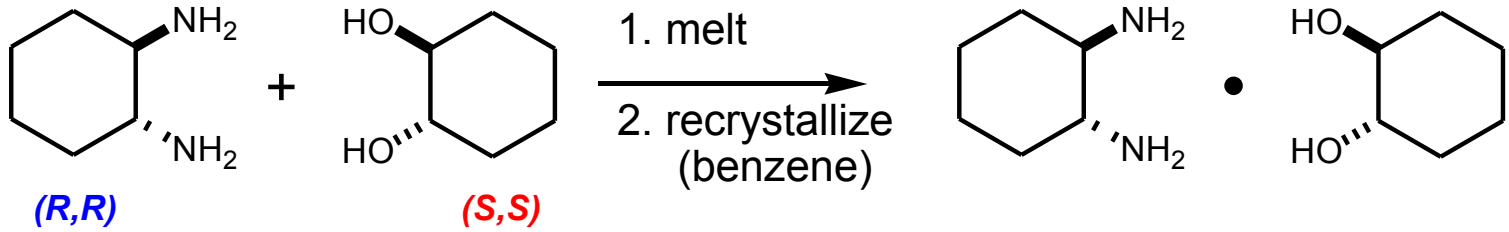
NMR of crude product showed new entity comprizing the diamine and the diol

with Meffre P., Girard M., Beaudoin S., Sanceau J. Y., Bennani Y., *J. Org. Chem.* **1993**, *58*, 1991.

What is the nature of the "complex"?



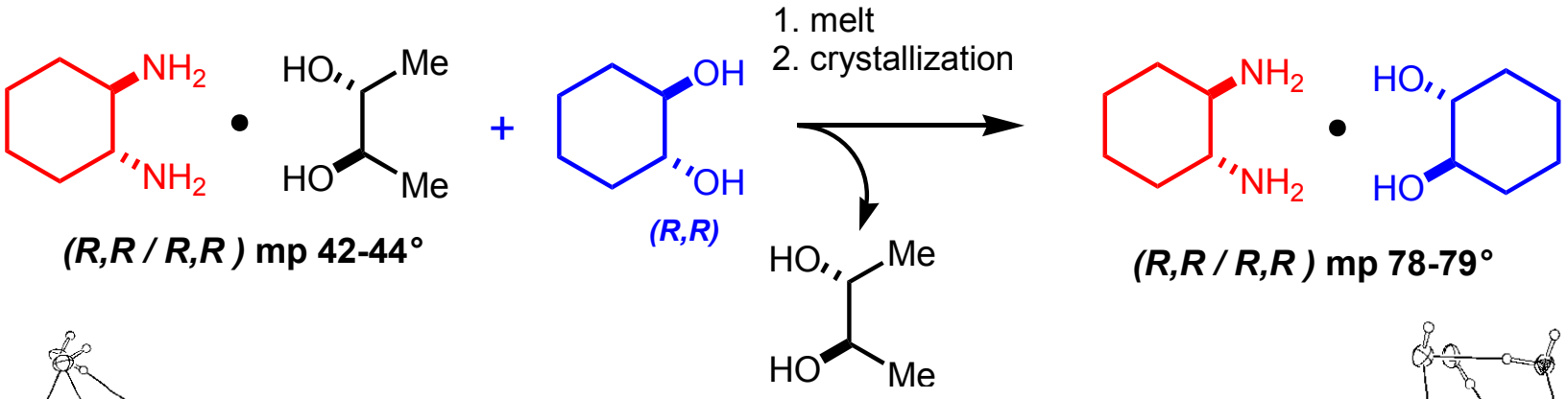
HOMOCHIRAL
mp 78-79°
$[\alpha]_D$ +38.2° ($CHCl_3$)



HETEROCHIRAL
mp 63-65°
$[\alpha]_D$ -1° ($CHCl_3$)

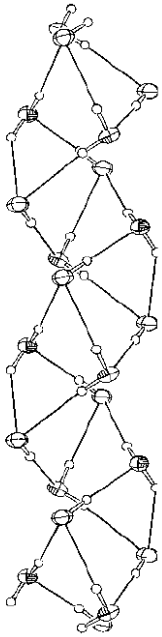
with Gomtsyan A., Simard M., Roelens S., *JACS* **1994**, *116*, 4495.
*with*Simard M., Roelens S., *JACS* **1995**, *117*, 7630.
with Saladino, R., Margarita, R., Simard, M. *Chem. Eur. J.* **1999**, *5*, 2169.
Saladino, R., Hanessian S. In *Crystal Design: Structure and Function,* "Molecular Recognition and Self-Assembly Between Amines and Alcohols (Supraminols)", Chapter 2, Ed. G.R. Desiraju, John Wiley, 77-151 (2003).

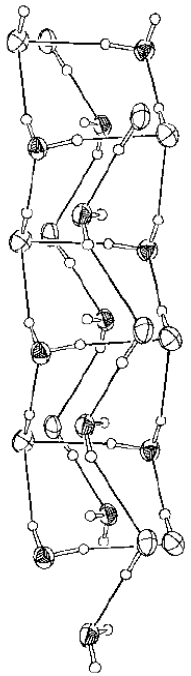
Dominant supraminols



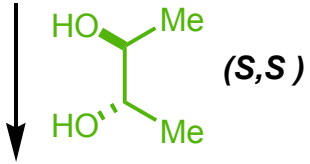
***(R,R / R,R)* mp 42-44°**

***(R,R / R,R)* mp 78-79°**



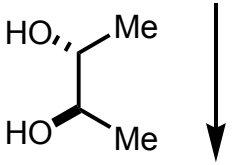


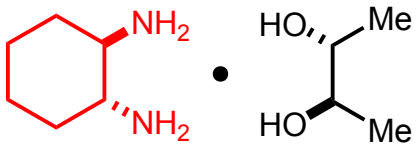
Fully H-bonded NH2 and OH core structures



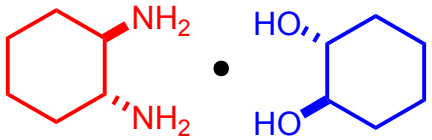
(S,S)

(R,R)



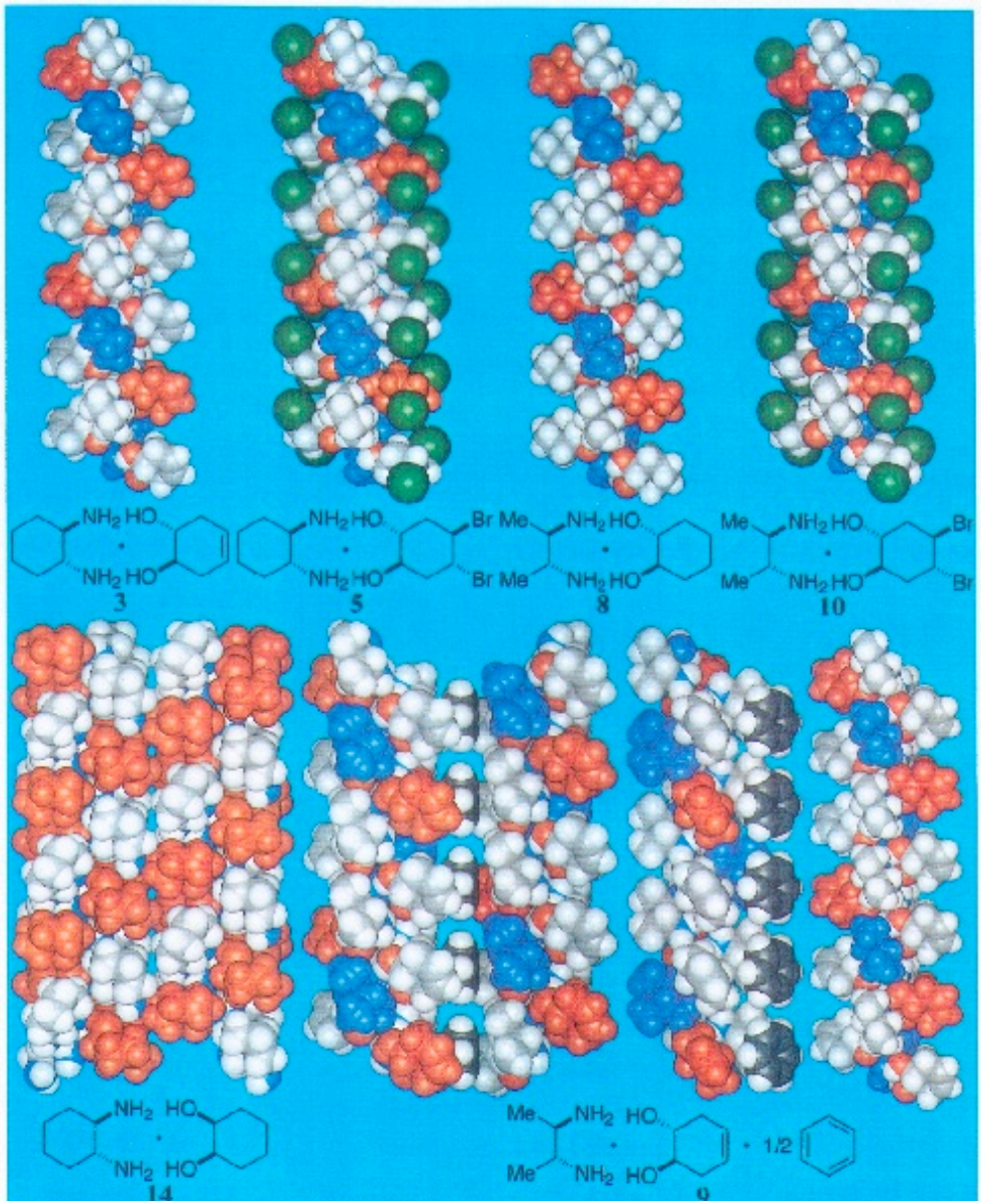


unchanged

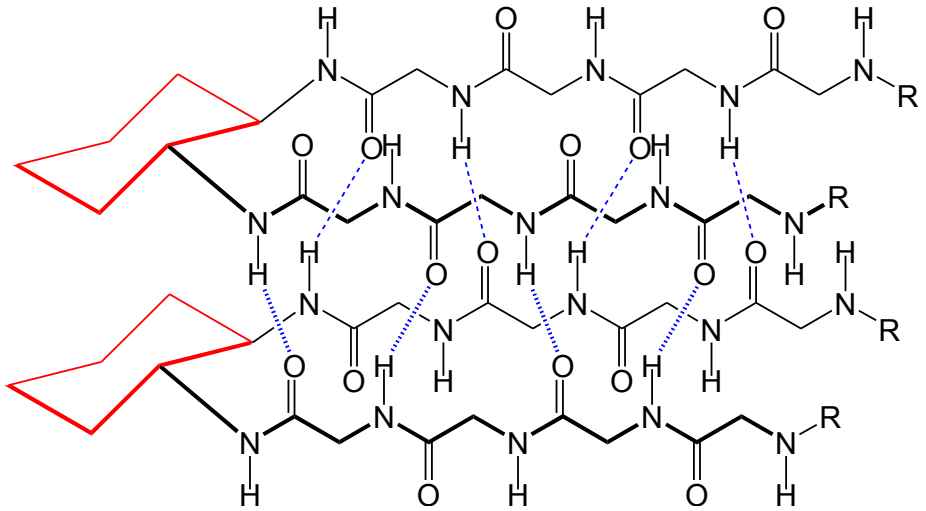


unchanged

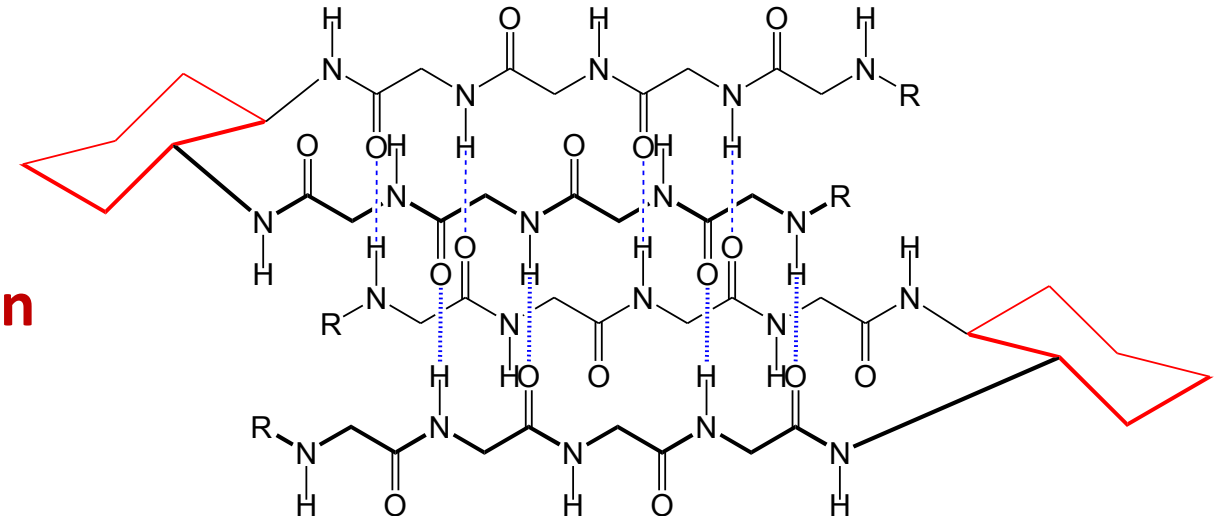
The power of observation and open-eyed serendipity: *Supraminols*



Objective: beta sheets with *bis*- L,D- tripeptides anchored on 1,2-*trans*-DACH Superstructures

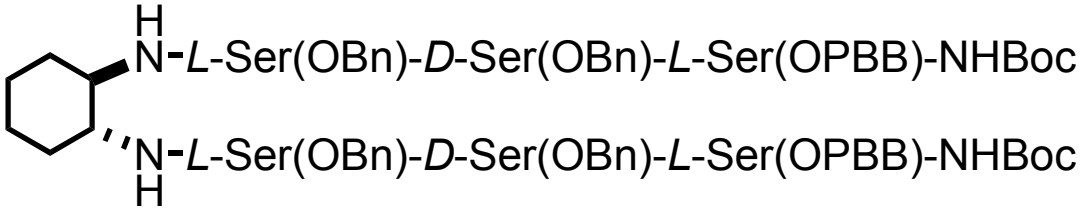


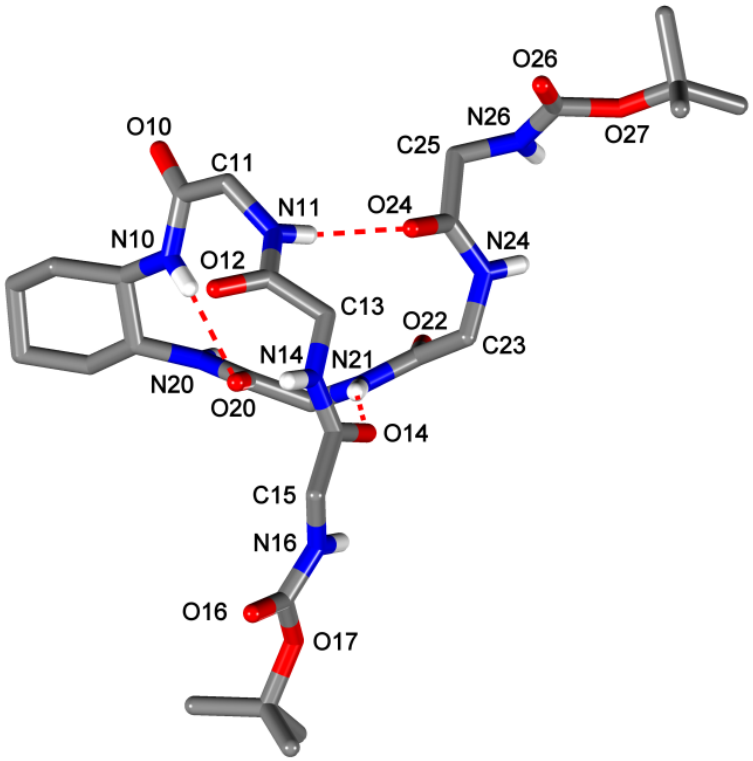
Head-to-head orientation

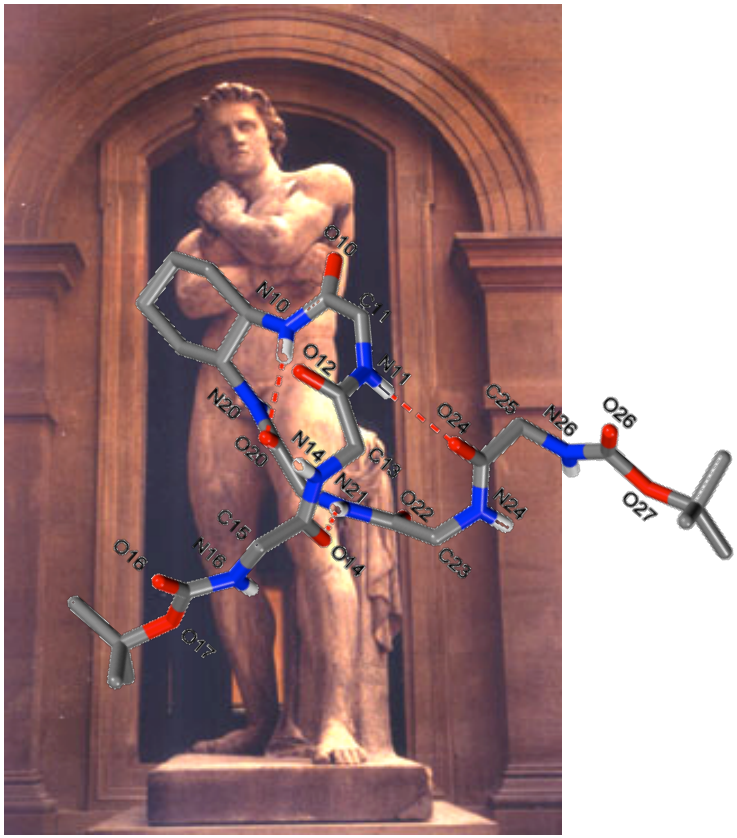


Head-to-tail orientation

Self-embracing peptide arms



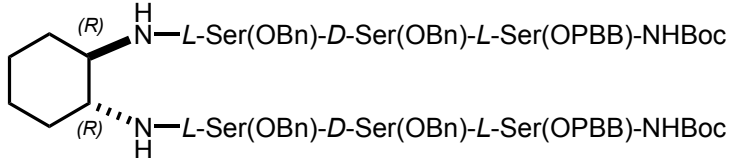


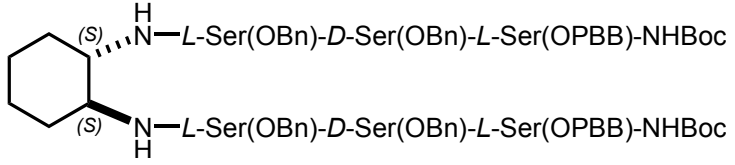


Foyatier's Spartacus

X-ray structure of an individual 1*R*,2*R*- DACH-bis-tripeptide showing intramolecularly H-bonded strands that cross over each other like the self-embracing arms of Fogatier's statue of Spartacus. Side-chains and hydrogen atoms (except those attached to nitrogen) have been omitted for clarity. Two distinct but similar conformations A and B are observed in the crystal; only one is shown.

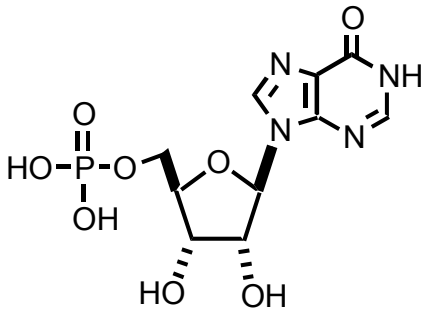
1,2-R,R DACH vs 1,2- *S,S* DACH



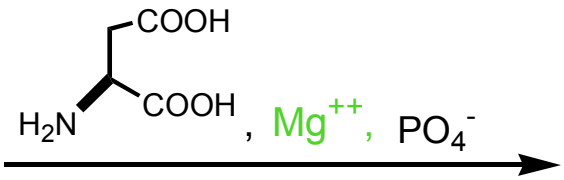


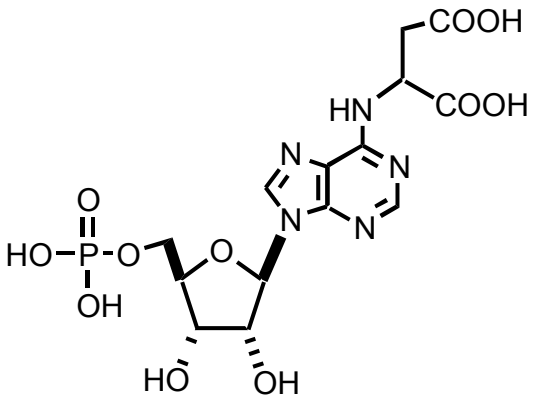
Selected vignettes exploring the third dimension

ONE ENZYME: TWO INHIBITORS



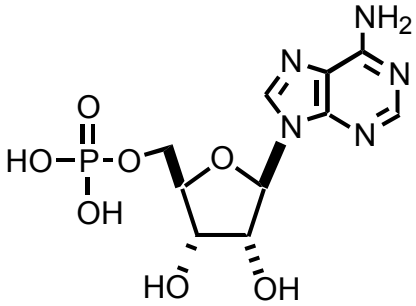
IMP



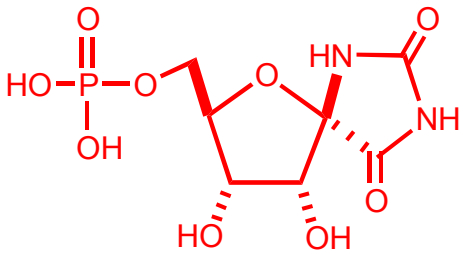


ASMP

Adenylosuccinate lyase → Fumarate

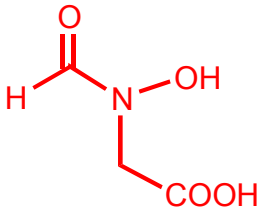


AMP



HMP

IMP mimic



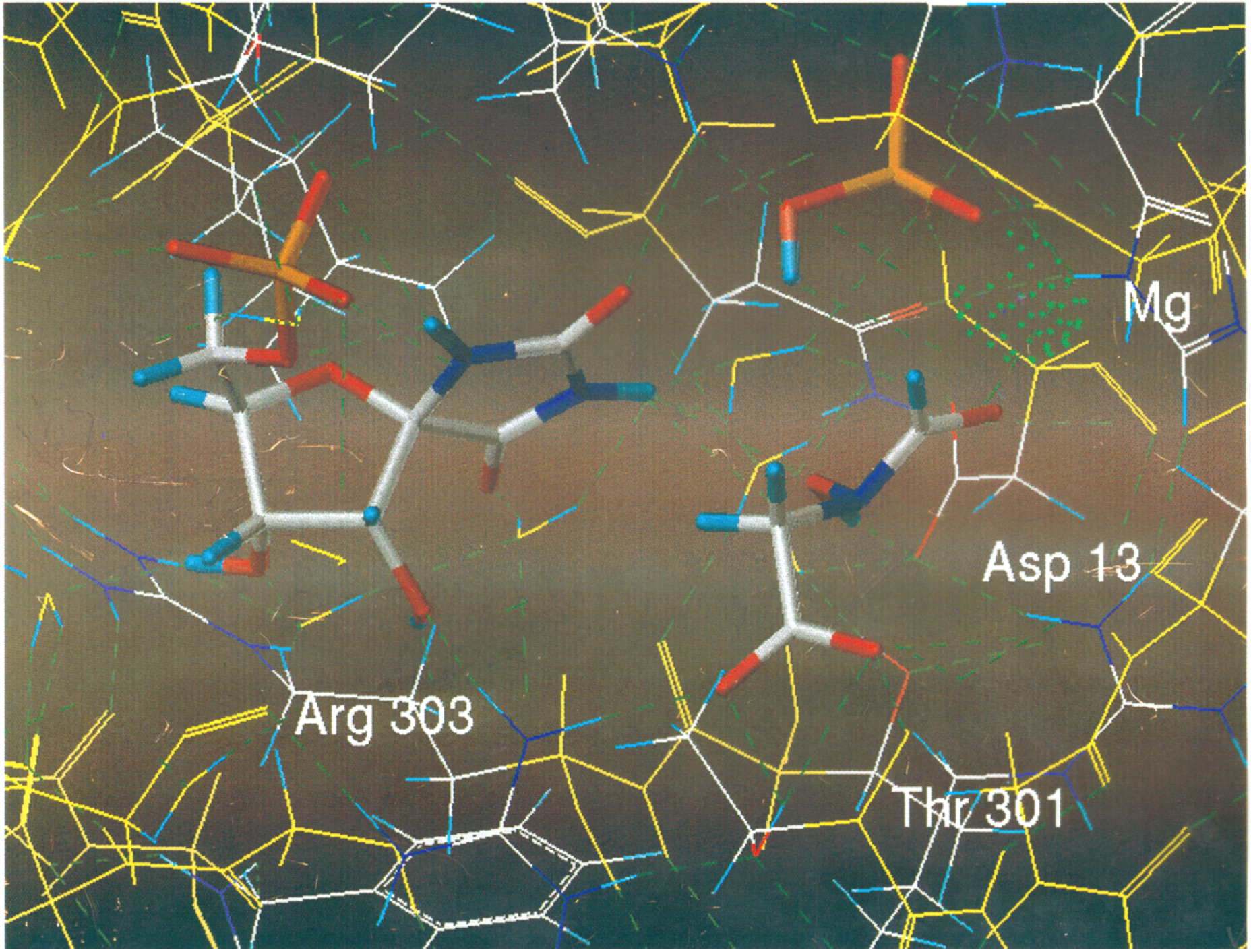
Hadacidin

Aspartate mimic

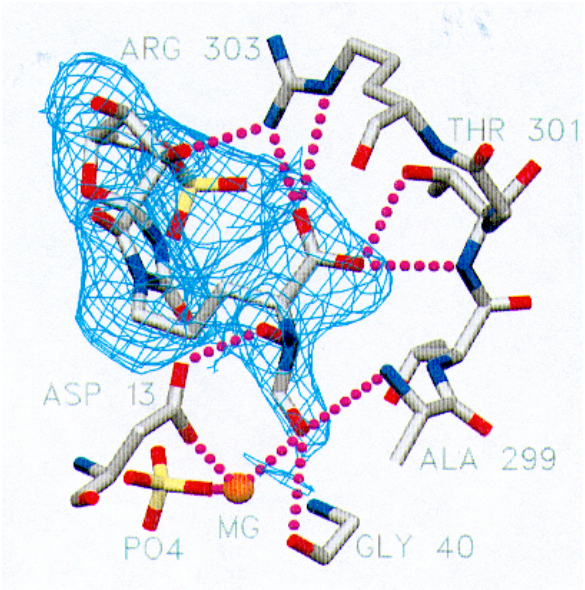
(competitive inhibitor)

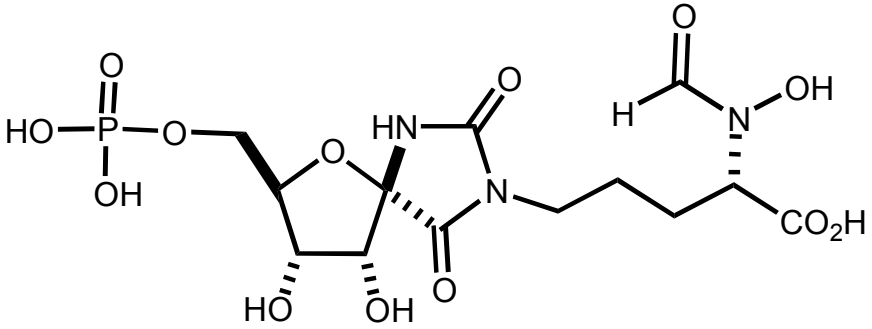
R. B. Honzatko *et al*, *Biochemistry*, **1996**, *35*, 15753
Iowa State University

S. W. Cowan-Jacob
Novartis Crop Protection


Mg
Asp 13
Arg 303
Thr 301

AdSS - *S*-hybrid Complex

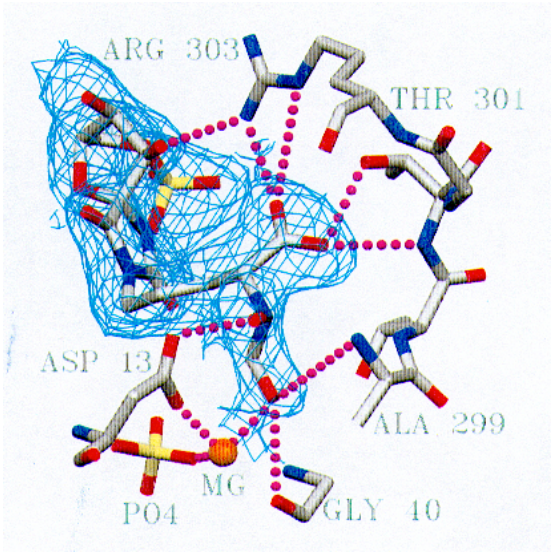


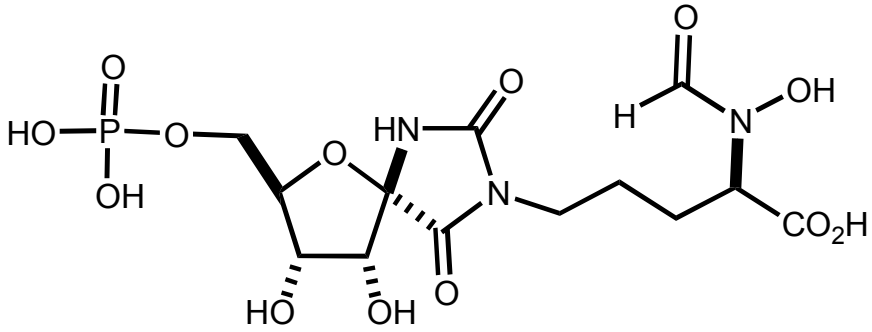


S-hybrid

Ki = 43 nM (E. coli AdSS)

AdSS - *R*-hybrid Complex



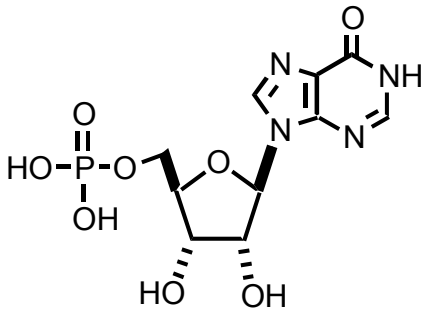


R-hybrid

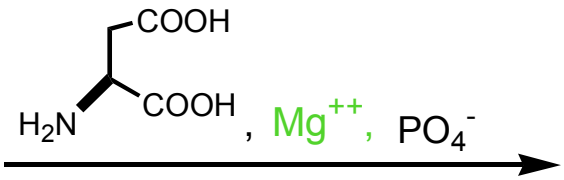
Ki = 665 nM (E. coli AdSS)

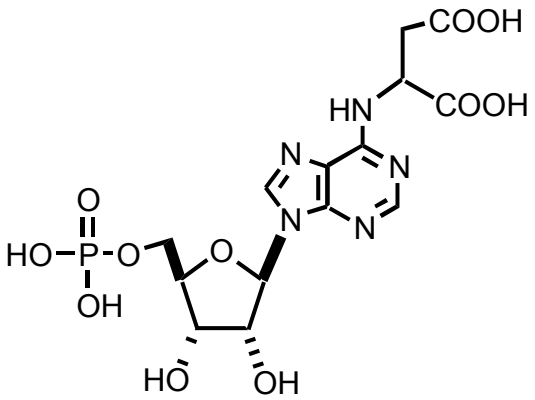
with Lu, P.-P.; Sancéau, J.-Y.; Chemla, P., Keigo, G.; Fonne-Pfister, R.; Prade, L.; Cowan-Jacob, S. W. *Angew. Chem. Int. Ed.* **1999**, *38*, 3159

ONE ENZYME: TWO INHIBITORS



IMP





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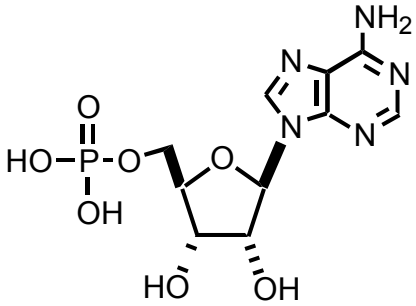
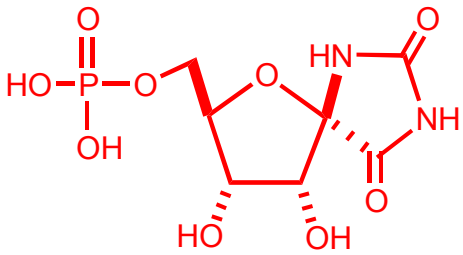
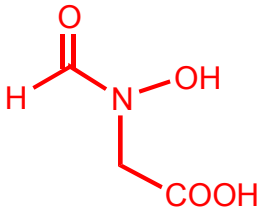


AMP



HMP

IMP mimic



Hadacidin

Aspartate mimic

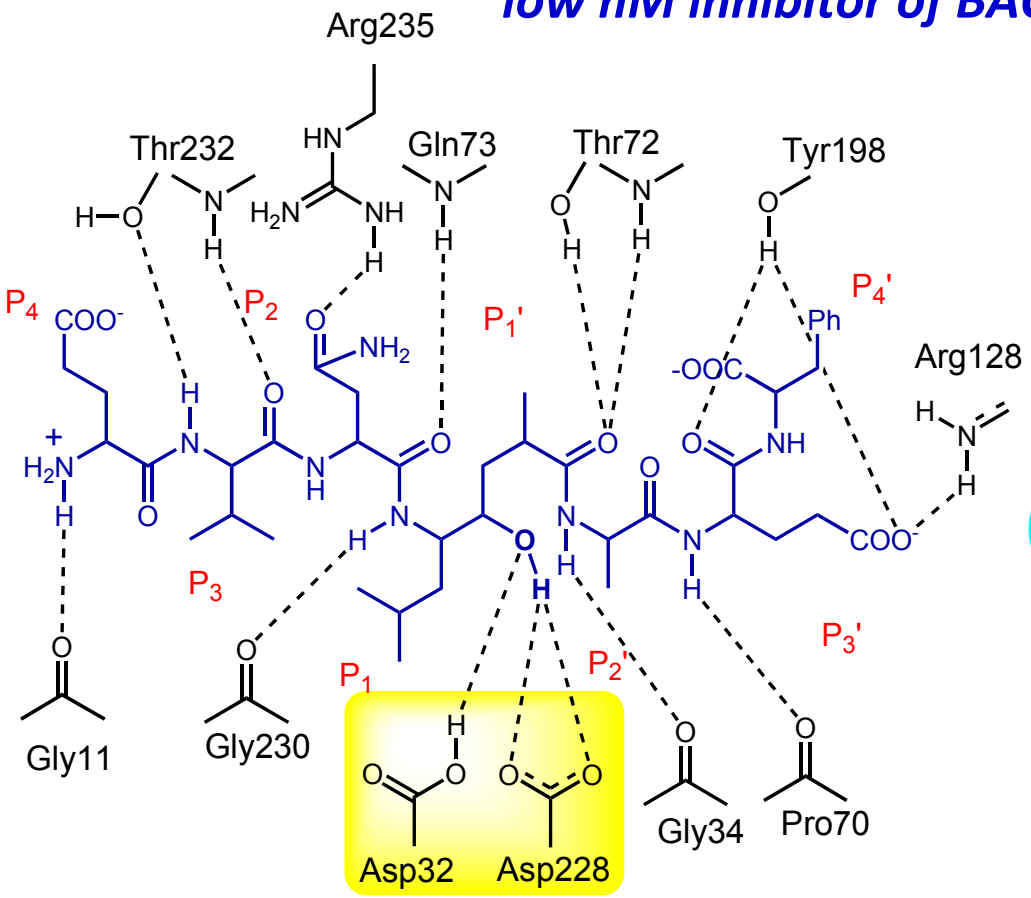
(competitive inhibitor)

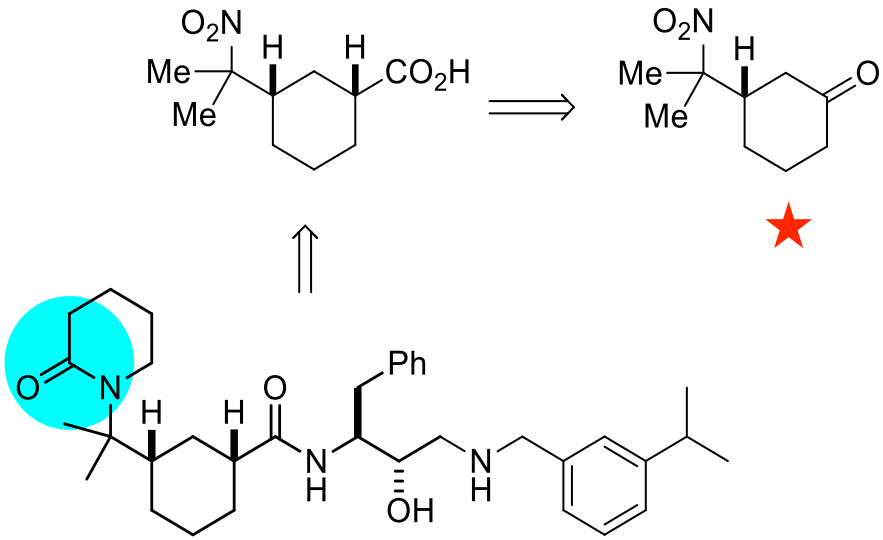
R. B. Honzatko *et al*, *Biochemistry*, **1996**, *35*, 15753
Iowa State University

S. W. Cowan-Jacob
Novartis Crop Protection

Novartis (Basel) collaboration (2003-2010)

From Tang's heptapeptide to a 'designed' minimally peptidic low nM inhibitor of BACE-1 (Alzheimer's disease)



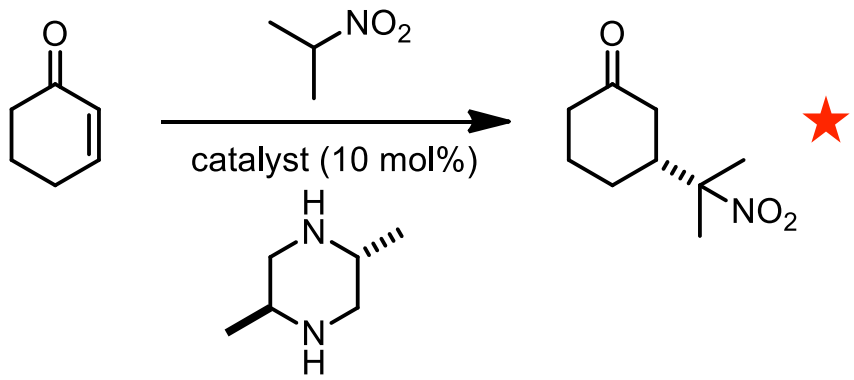


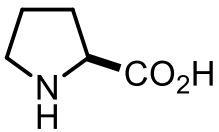
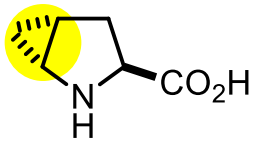
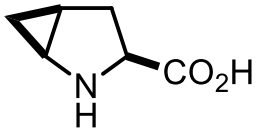
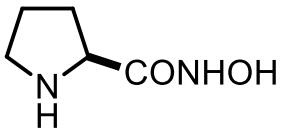
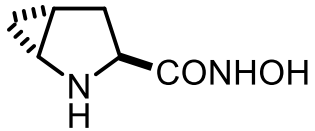
OM99-2 Tang, J.; et al. Science 2000, 290, 150
IC_{50} 1-2 nM

The N-acetyl analog shows uM activity!

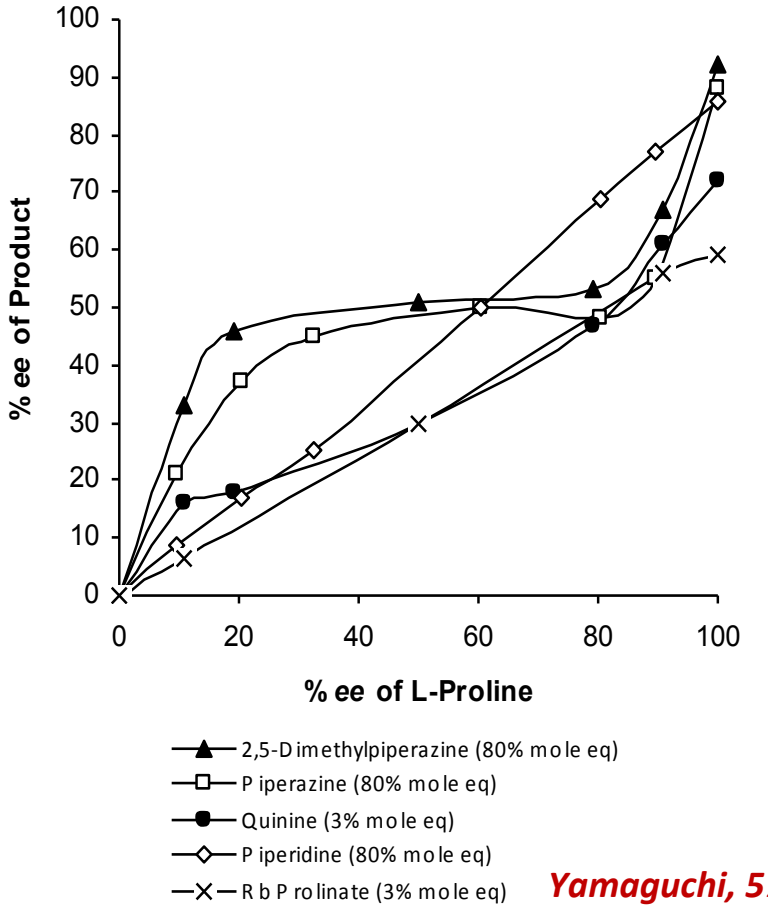
with Maji, D.K.; Govindan, S.; Matera, R.; Tintlenot-Bromley, M. *J. Org. Chem.* **2010**, *75*, 2861; Shao, Z.; Betschart, C.; Rondeau, J-M.; Neumann, U.; Tintelnot-Bromley, M. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 1924.

Metal-free, organocatalytic nitroalkane conjugate addition



catalyst	ee (%)	yield (%)
	89	83
	99	92
	75	52
	75	78
	81	65

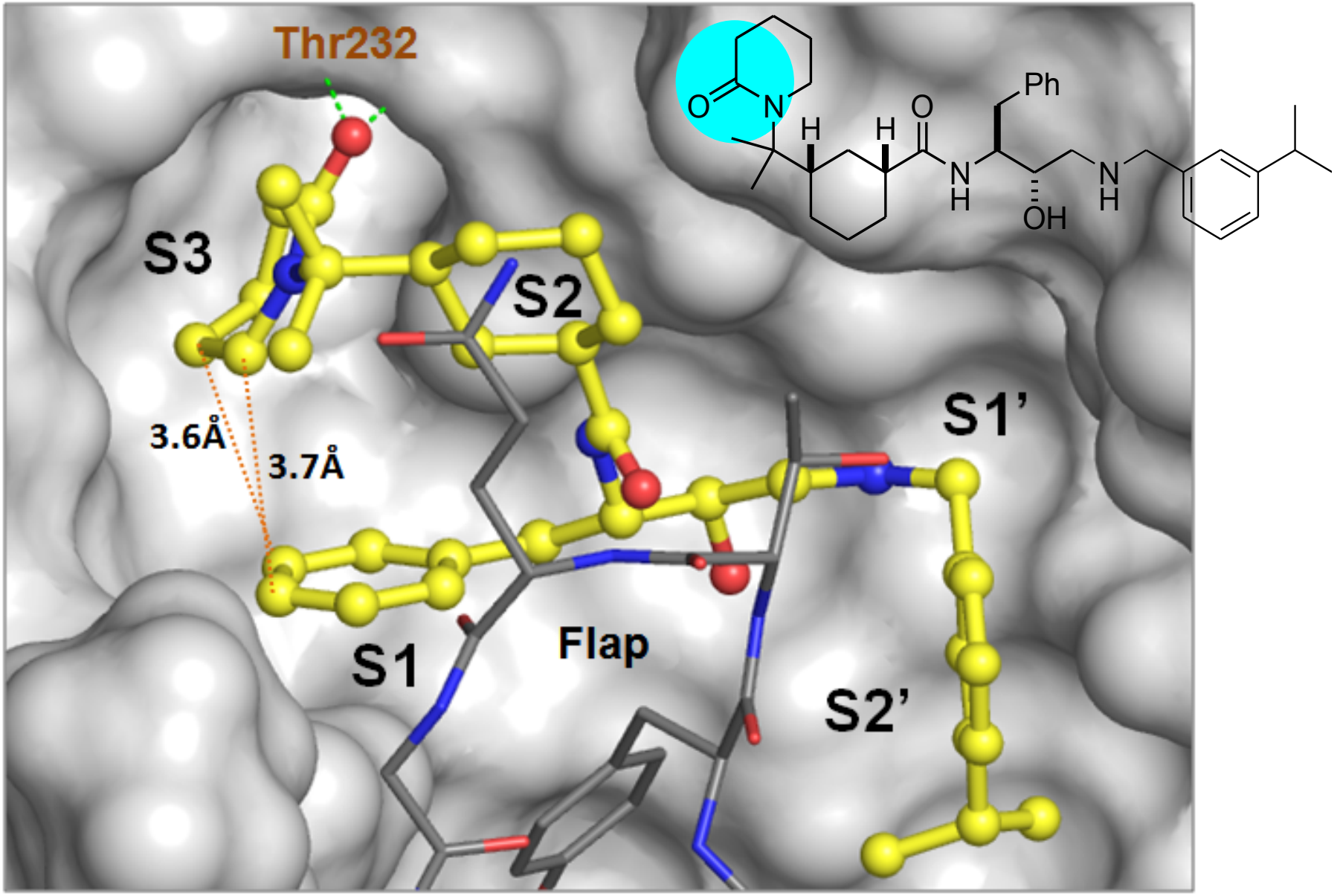
Non-linear effects in the addition of 2-nitropropane to 2-cyclohexenone



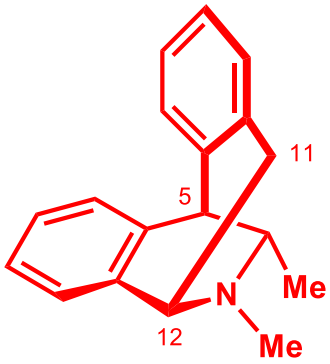
Yamaguchi, 57 % ee

with Pham, V. *Org. Lett.* **2000,** *2,* 2975;
with Shao, Z.;Warrier, J. S. *Org. Lett*. **2006**,*8*, 4787

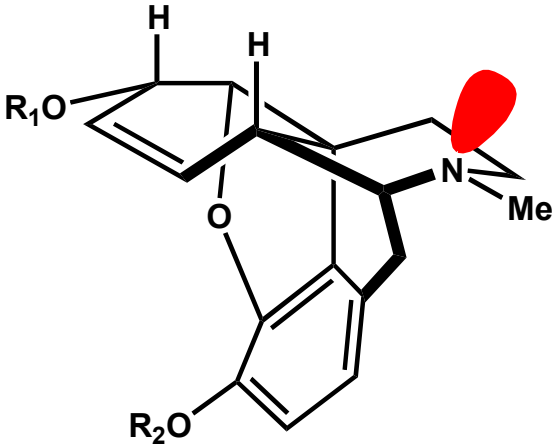
X-Ray co-crystal structure with human BACE 1

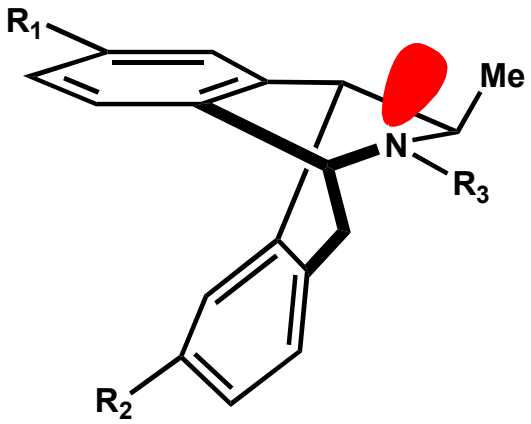


The power of visual imagery and '*seeing*' the third dimension



Isopavine A





R_1, R_2 = H; Morphine

R_1 = Me; R_2 = H; Codeine

R_1, R_2 = Me; Thebaine

Isopavine

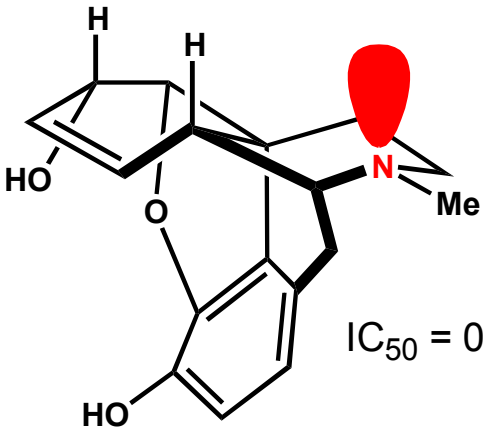
R_1, R_2 = H, OH, OMe combinations

R_3 = Alkyl, cycloalkyl

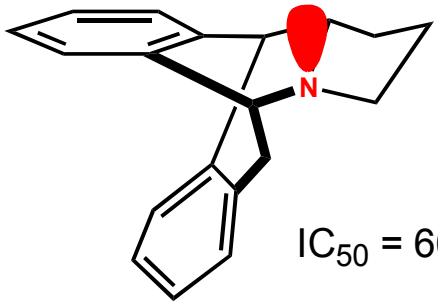
with Mauduit M . *Angew. Chem. Int. Ed.* **40** , 3810 (2001)

with Parthasarathy, S.; Mauduit, M.; Payza, K. *J. Med. Chem.* 2003 ,*46*, 34

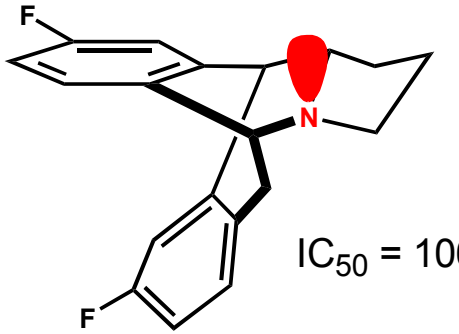
It’s the Lone Pair ! God’s gift to nitrogen



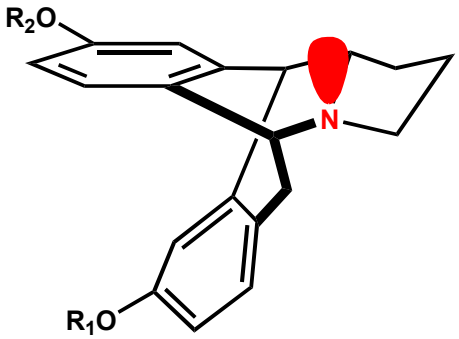
IC_{50} = 0.6 nM



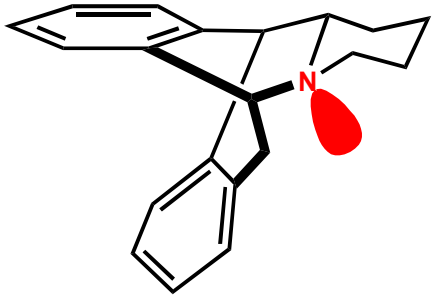
IC_{50} = 66 nM



IC_{50} = 106 nM



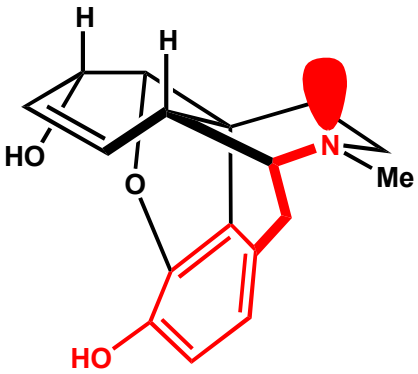
R_1, R_2 = H (morphine like)
R_1 = H; R_2 = Me (codeine like)
R_1, R_2 = Me (thebaine like)



IC_{50} = 264 nM

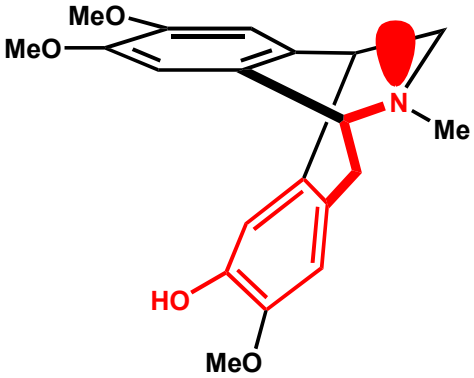
with Talbot, C.; Mauduit, M.; Saravanan, P.; Gone, J. R. *Heterocycles, **2006**, 67, 205;* Talbot, C.; Saravanan, P. *Synlett*, **2006**, 723 *). (Feature article)*

Unnatural Enantiomer of Thalisopavine as Potential Morphinomimetics ?

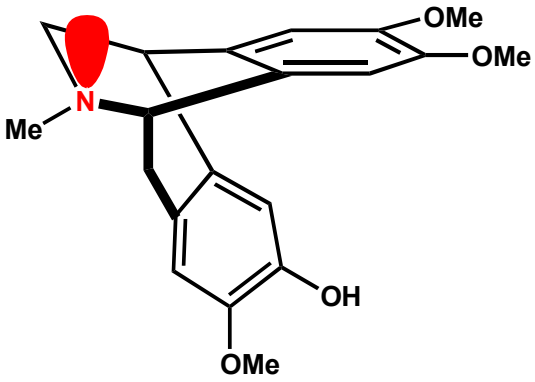


Morphine
natural enantiomer

IC_{50} = 0.6 nM



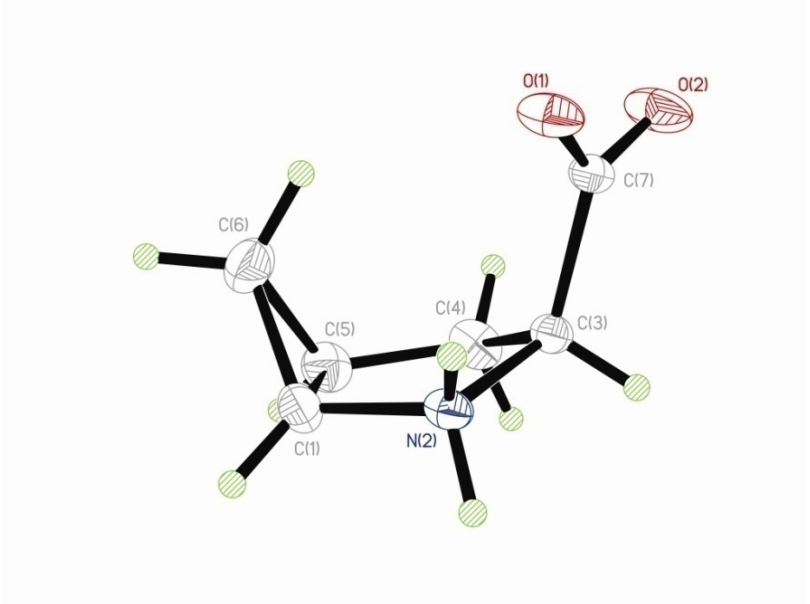
(+)-Thalisopavine
unnatural isopavine alkaloid

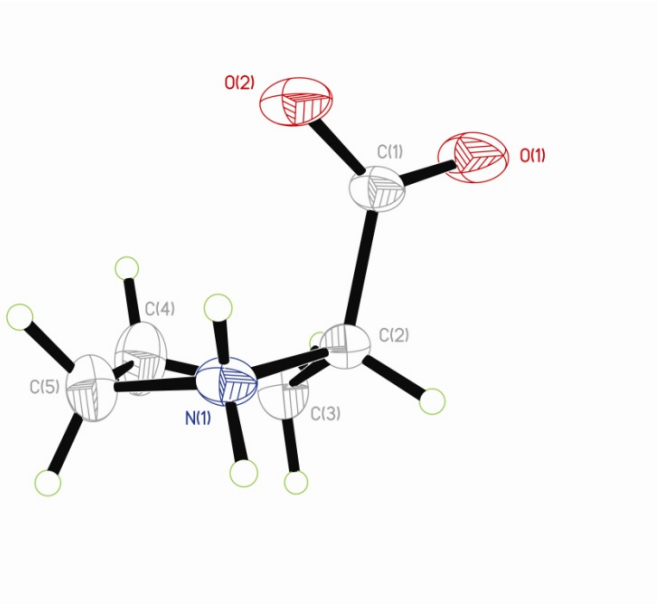


(-)-Thalisopavine
natural isopavine alkaloid

with Talbot, C.; Mauduit, M.; Saravanan, P.; Gone, J. R. *Heterocycles, **2006**, 67, 205;* Talbot, c.; Saravanan, P. *Synlett*, **2006**, 723 *). (Feature article)*

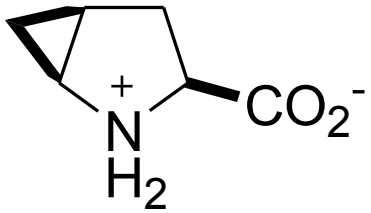
From concept to market:
The *flattening* of proline

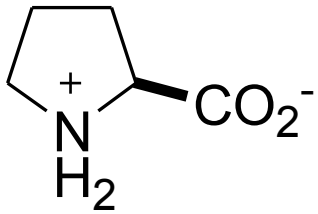




Rms = 0.001Å
C3 = 0.325 Å

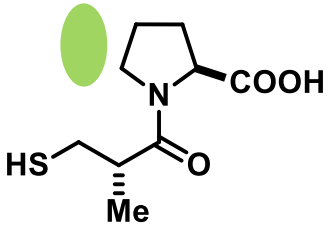
Rms = 0.161Å
C2 = -0.389Å



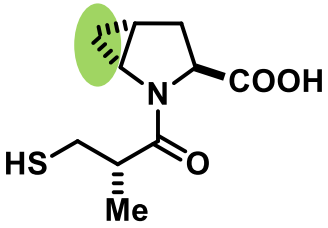


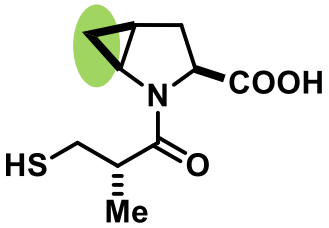
with Reinhold, U.; Gentile, G. *Angew.Chem.Int.Ed*. **1997**, *36*, 1881

Consequences of constraining the pyrrolidine ring in drug design: *Proline 4,5-methanologues*

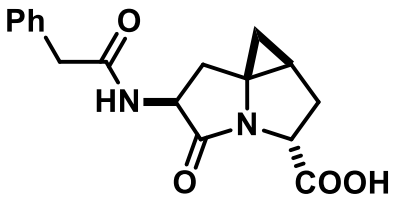


Captopril





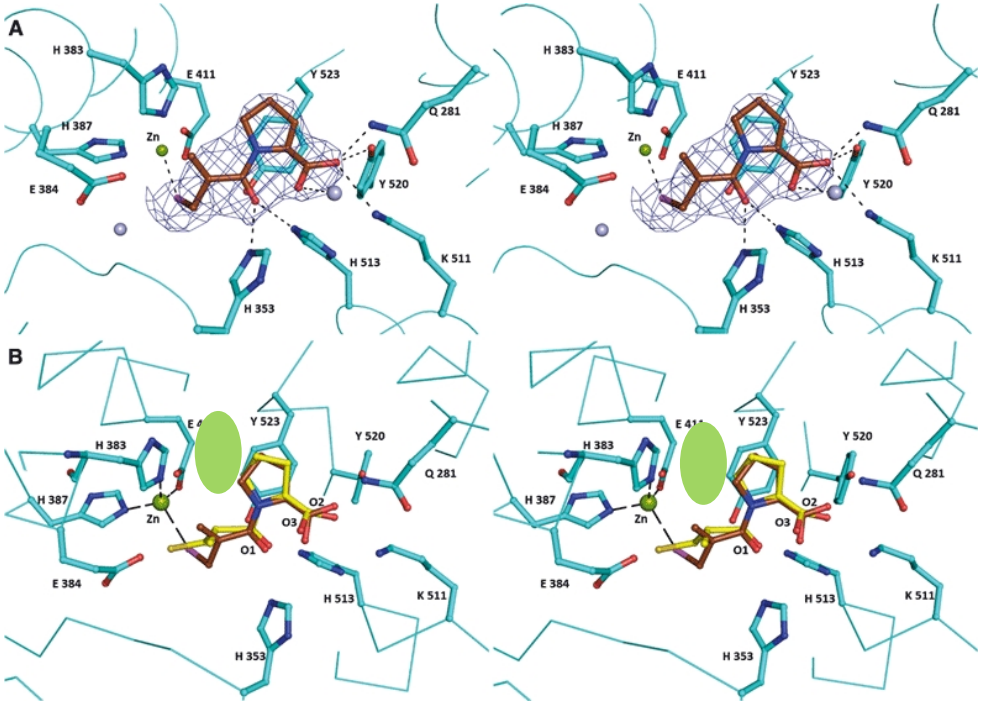
Ace inhibitors

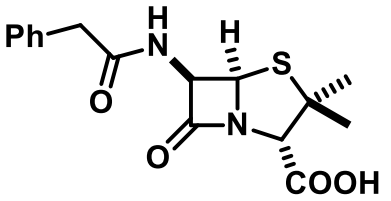


Activity of ceftazidime is enhanced

with Reinhold, U.; Saulnier, S.; Claridge, S.
Bioorg. Med. Chem. Lett. **1998**, *8*, 213

with Buckle, R.; Bayrakdarian, M.
J. Org. Chem. **2002**, *67*, 3306





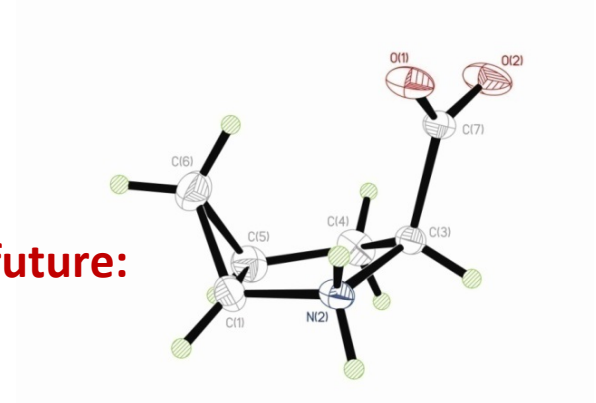
Penicillin G

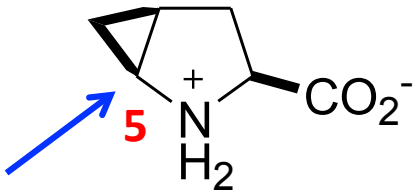
ACE co-crystal structure with captopril

Akif, M. et al. *FEBS J*. **2011**, *278*, 3644

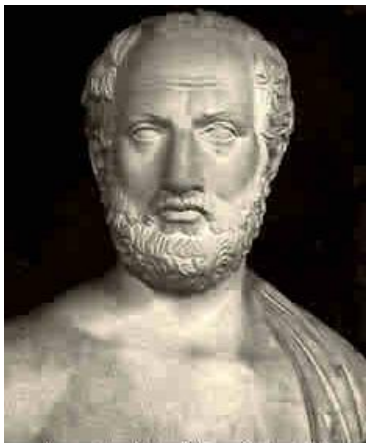
Marketed antidiabetic drug

The unseen future:





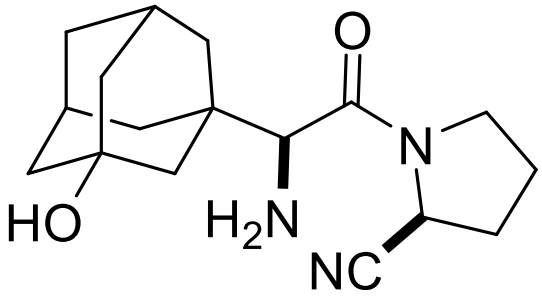
increased sp^2 character



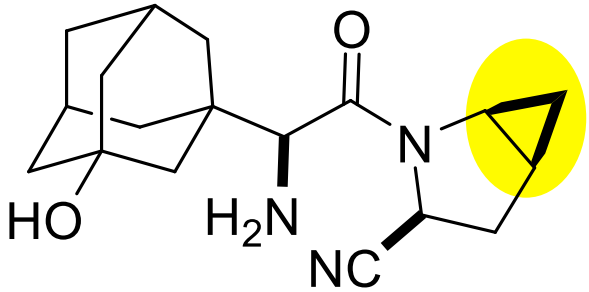
Thucydides

with Reinhold, U.; Gentile, G. *Angew.Chem.Int.Ed*. **1997**, *36*, 1881

The present:



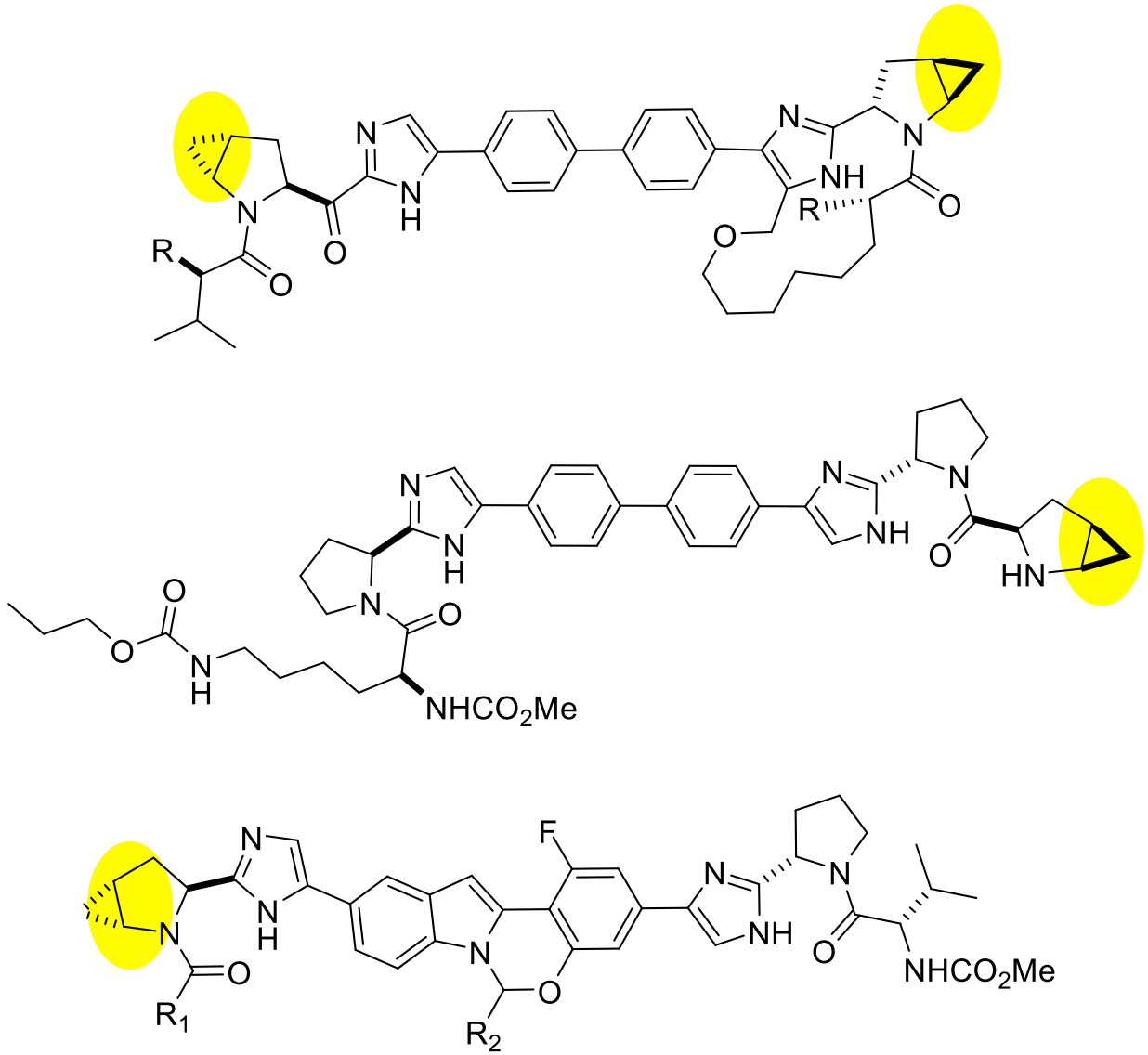
Shorter half-life



Onglyza (saxaglyptin)
BMS; AstraZeneca

Onglyza reviews: Robl, J. A.; Hamann, L. G. *Acc. Drug Discov*. The Royal Society, 2011, 1-Duez, H.; Cariou, B.; Staels, B. *Biochem.Pharmacol*. **2012**, *83*, 823; Gwaltney, S. L. II ; Stafford,J.A *Ann.Rep. Med.Chem*. **2005**, *40* 156

Cis-and *trans*-4,5-methano-L-prolines and Hepatitis C activity



BMS, Enanta, Merck patents: US 2011 8623814 B2; WO 2013 052362 A1; WO 2012041014 A1

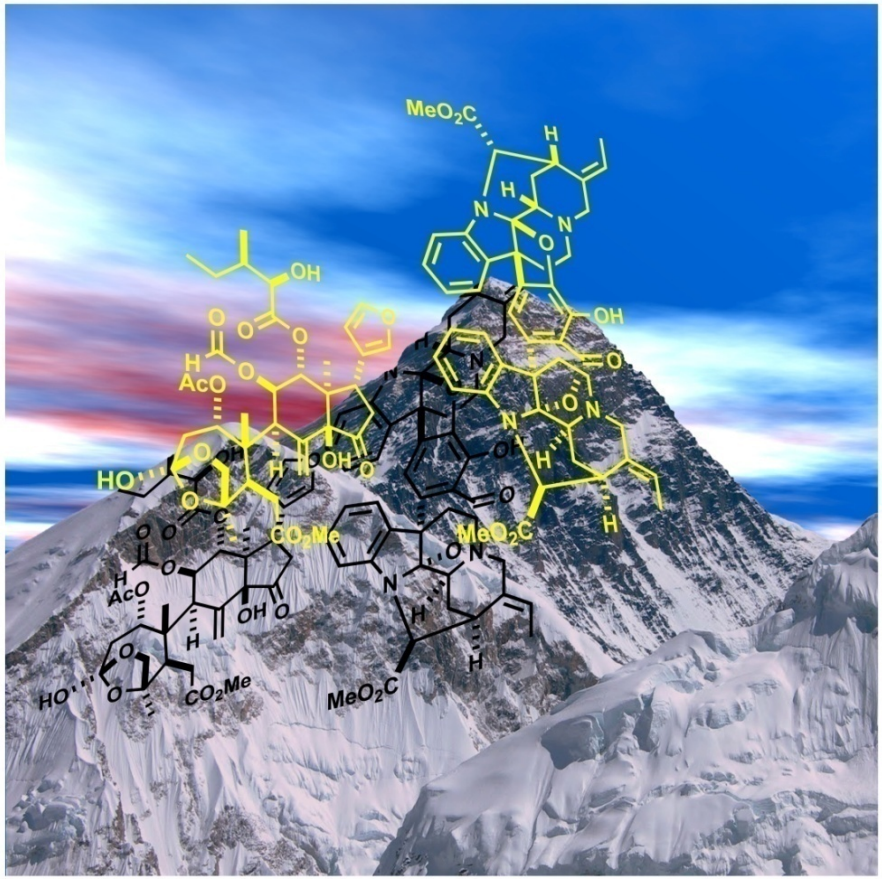
Lessons from nature and natural products

Stephen Hanessian, Simon Giroux,
and Bradley L. Merner

WILEY-VCH

Design and Strategy in Organic Synthesis

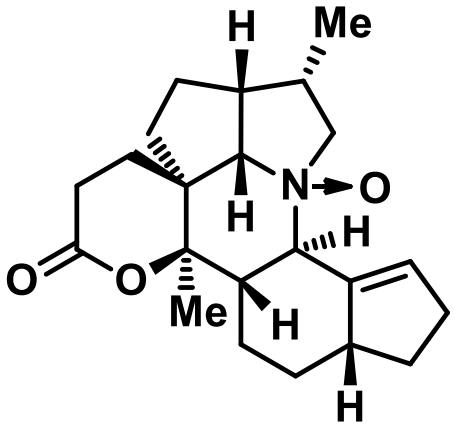
From the *Chiron Approach* to Catalysis



18 Chapters
Over 900 pages

2013

Calyciphylline B – a complex *Daphniphyllum* alkaloid

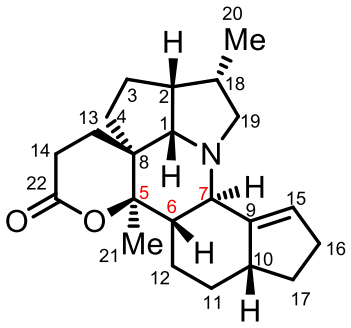


Calyciphylline B

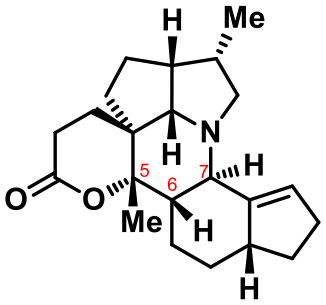
- Isolated in 2003 by Kobayashi et al. from leaves of *D. calycinum.*
- First example of a new *Daphniphyllum* alkaloid class (A – P).
- Complex hexacyclic framework; eight stereocenters; seven contiguous and one quaternary; tertiary amine oxide
- Cytotoxicity against murine lymphoma cells (for L1210, LC_{50} 12 μM).

Isolation: H. Morita , J. Kobayashi, *Org. Lett*. **2003**, *5*, 2895-2898.

Representative calyciphyllines

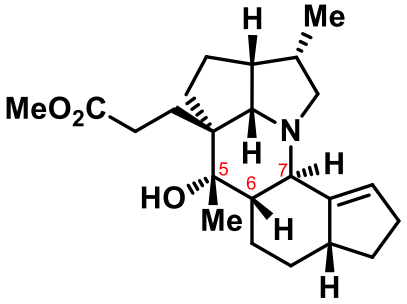


Deoxycalyciphylline B

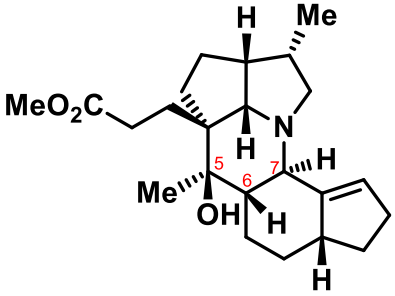


Deoxyisocalyciphylline B

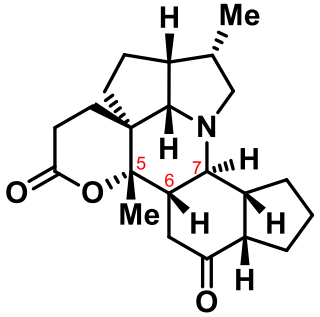
From *Daphniphyllum subverticillatum*



Caldaphnidine R
From *Daphniphyllium calycinum*

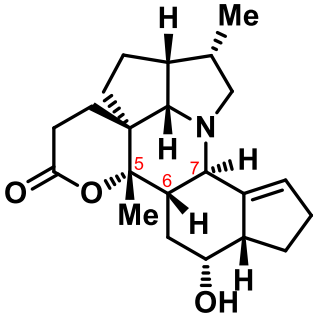


Longistylumphylline C
From *Daphniphyllium longistylum*



Daphnioldhanine J
From *Daphniphyllum oldhami*

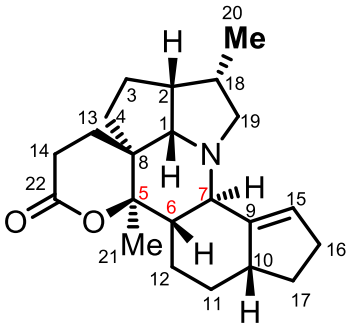
Strong activity against platelet aggregation induced by PAF



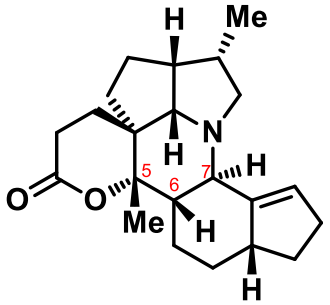
Oldhamiphylline A
From *Daphniphyllum oldhami*

S.-P. Yang, J.-M. Yue, J. Org. Chem. **2003**, *68*, 7961- 7966.; X. Chen, Z.-J. Zhan, J.-M. Yue, *Chem. Biol.* **2004**, *1*, 1513- 1518.; X. Chen, Z.-J. Zhan, J.-M. Yue, *Helvetica Chimica Acta* **2005**, *88*, 854-860; S.-Z. Mu, J.-S. Wang, X.-S. Yang, H.-P. he, C.-S. Li, Y.-T. Di, Y. Wang, Y. Zhang, X. Fang, L.-J. Huang, X.-J. Hao, *J. Nat. Prod*. **2008**, *71*, 564-569; C.-R. Zhang, S.-P. Yang, J.-M. Yue *J. Nat. Prod.* **2008**, *71*, 1663-1668.

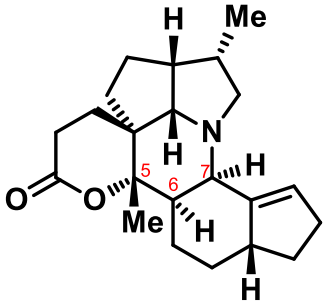
Daphlongamine H: The only C6/C7-*cis* fused calyciphylline B-type alkaloids



Deoxycalyciphylline B

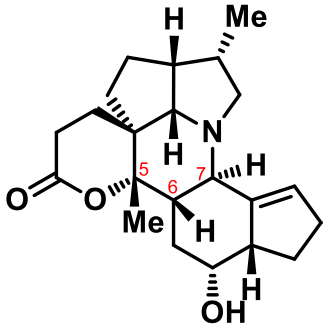


Deoxyisocalyciphylline B

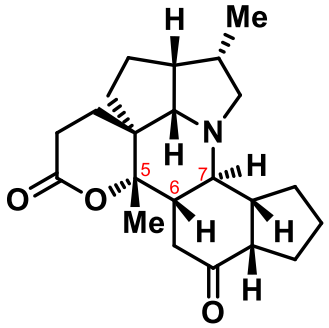


Daphlongamine H

C6/C7-*cis*



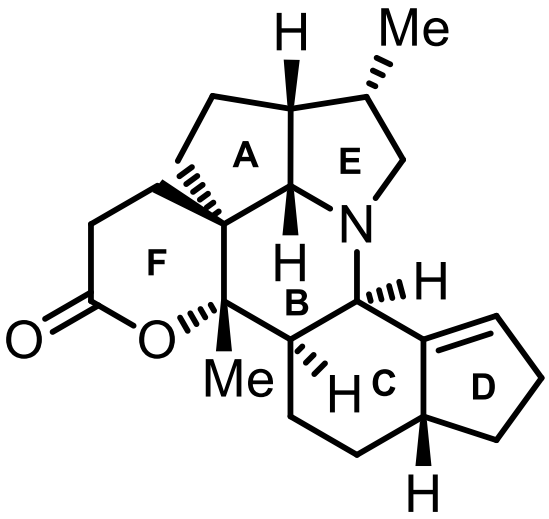
Oldhamiphylline A



Daphnioldhanine J

C.-S. Li, Y.-T. Di, Q. Zhang, Y. Zhang, C.-J. Tan, X.-J. Hao, *Helv. Chim. Acta*, **2009**, *92*, 653-659.

Daphlongamine H: The C-6/C-7 *cis*-fused exception !

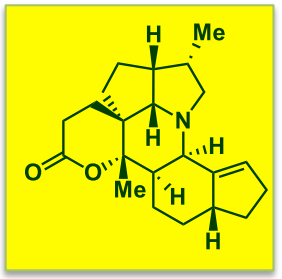


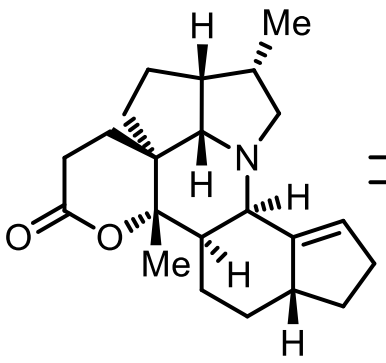
Daphlongamine H

- Isolated in 2009 by Hao and co-workers from the leaves of *D. longeracemosum* Rosenth.
- Unique *cis*-fused member of calyciphylline B family.
- Structure and absolute stereochemistry were determined by spectroscopic data analysis and correlation with previous members of the calyciphylline B family.

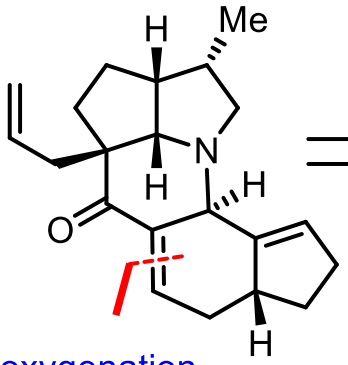
C.-S. Li, Y.-T. Di, Q. Zhang, Y. Zhang, C.-J. Tan, X.-J. Hao, *Helv. Chim. Acta*, **2009**, *92*, 653-659.

Daphlongamine H: Retrosynthesis

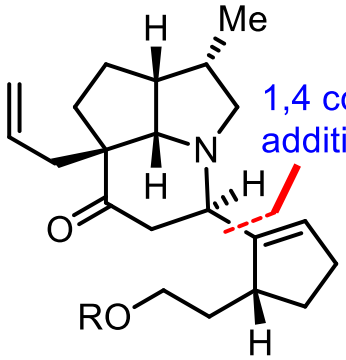




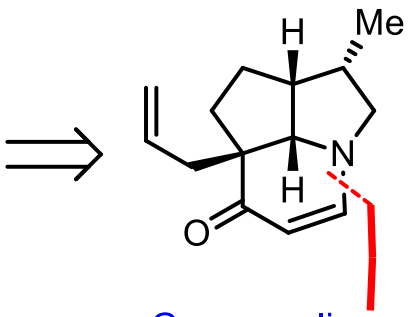
Daphlongamine H



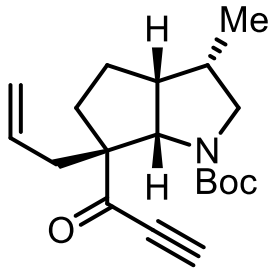
deoxygenation
& aldol reaction

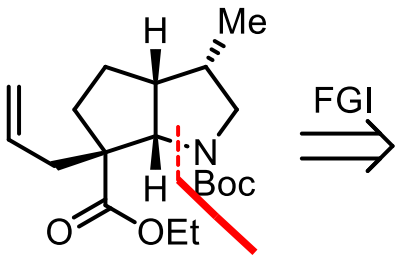


1,4 conjugate
addition



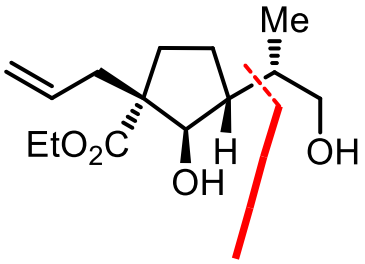
Georg cyclic
enaminone strategy





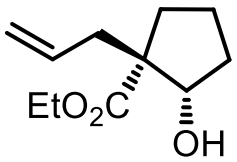
S_N2 intramolecular
cyclization

FGI

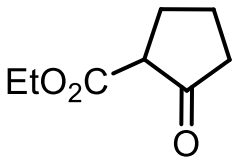


enolate S_N2 alkylaiton

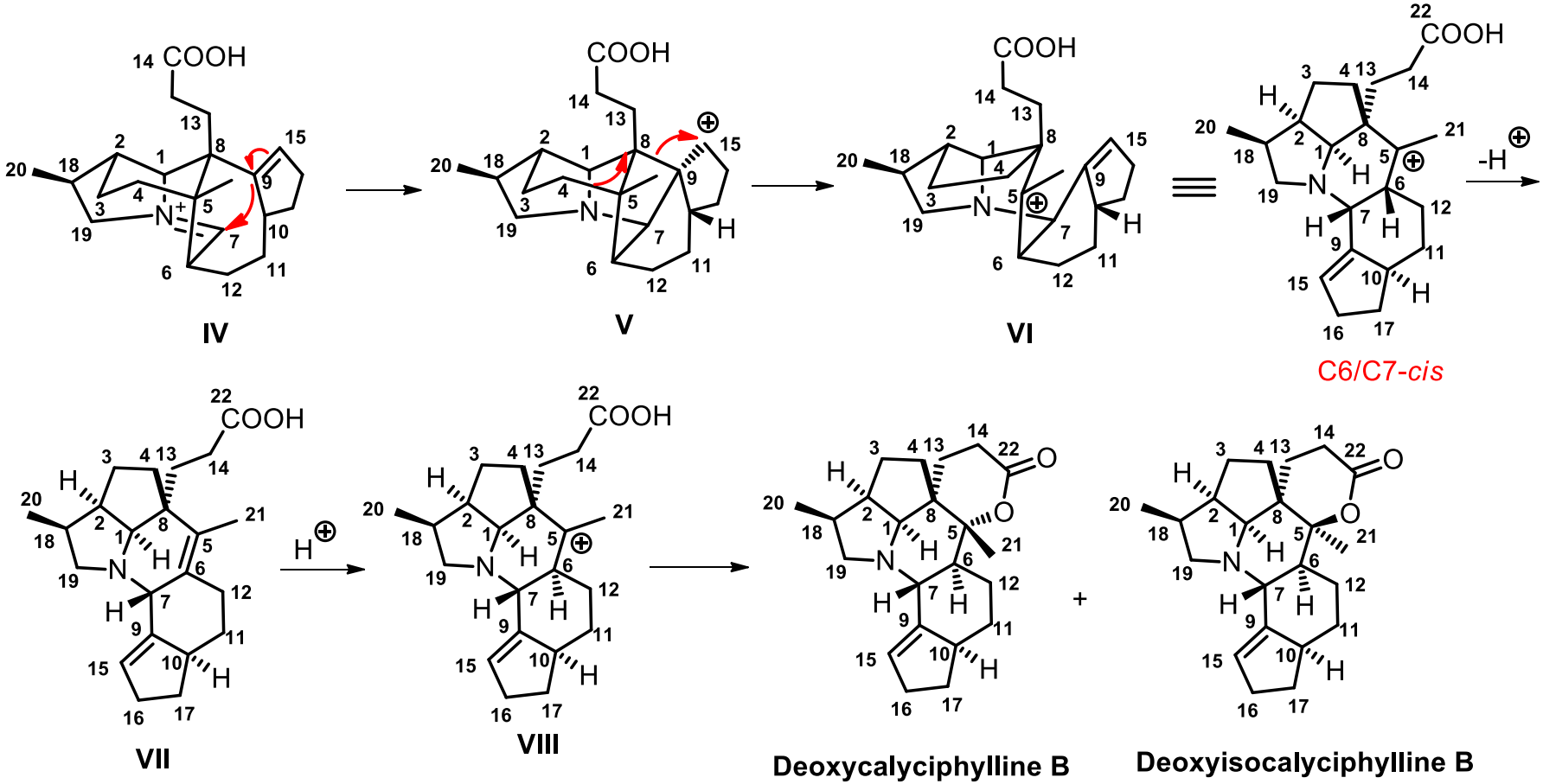
[O]



chemoenzymatic
resolution
and alkylation

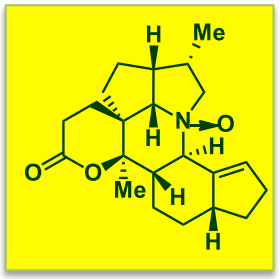


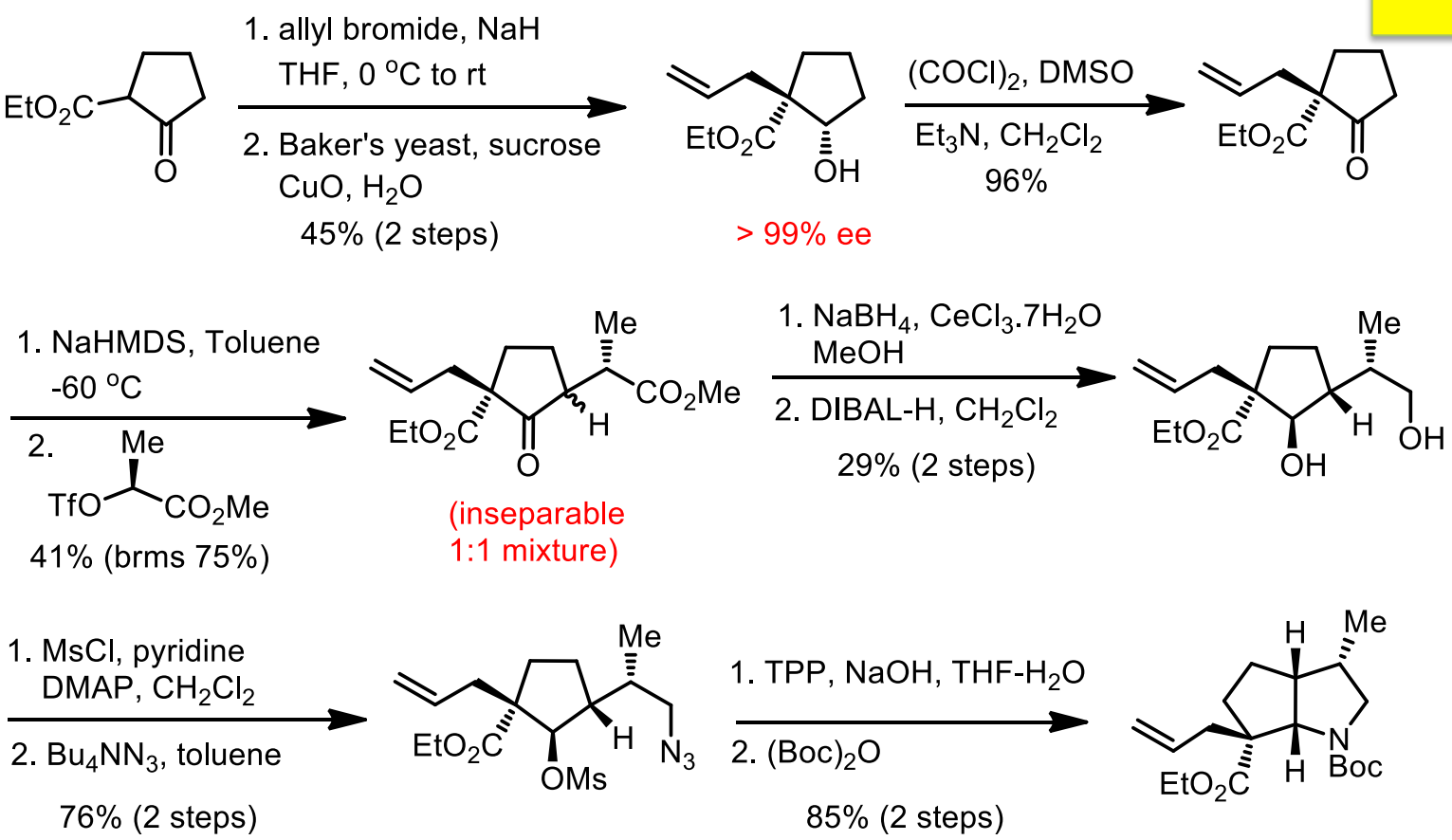
Yue's proposed biosynthetic pathway toward deoxycalyciphylline B



S.-P. Yang, J.-M. Yue, J. Org. Chem. **2003**, *68*, 7961- 7966.

Chemoenzymatic synthesis of the functionalized aza-octahydropentalene core

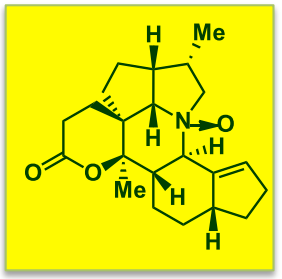


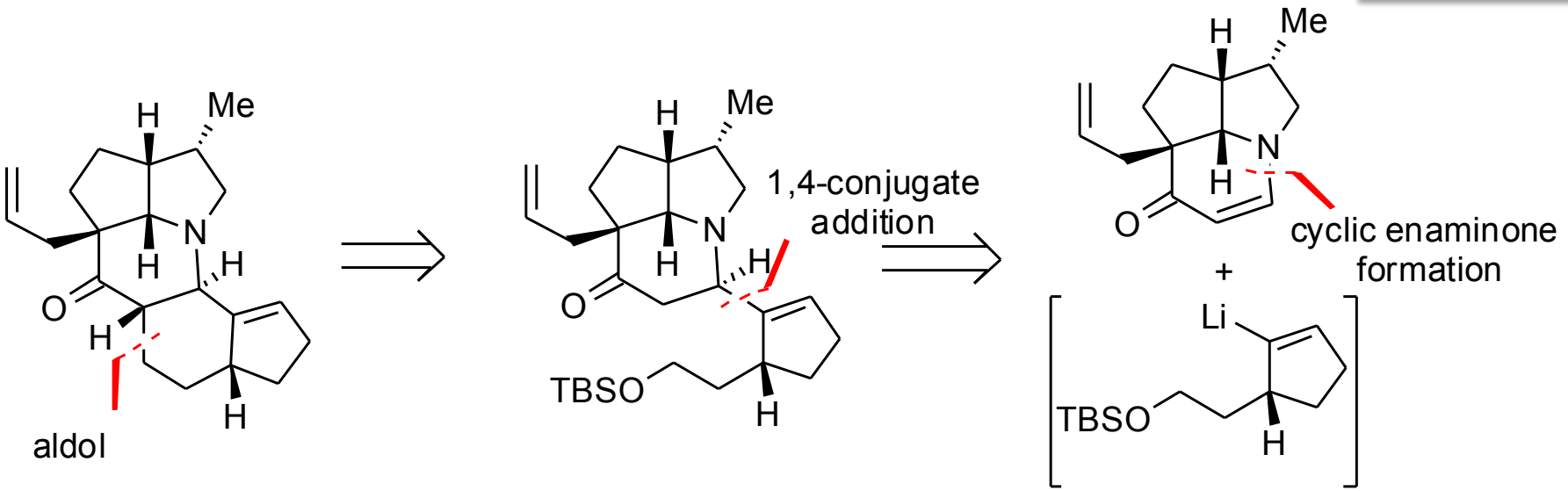


with A. K. Chattoapdhyay, V. L. Ly, S.Jakkepally, G. Berger. *Angew. Chem. Int. Ed.* **2016**, *55*, 2577-2581.

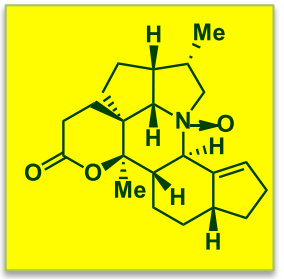
Baker's yeast: Z. Hng, Z. Wang, K. Ding, Adv. Synth. *Catal.* **2011**, *9*, 1584- 1590.; C. A. M. Fraga, E. J. Barreiro, *Chirality.* **1996**, *8*, 305- 310.

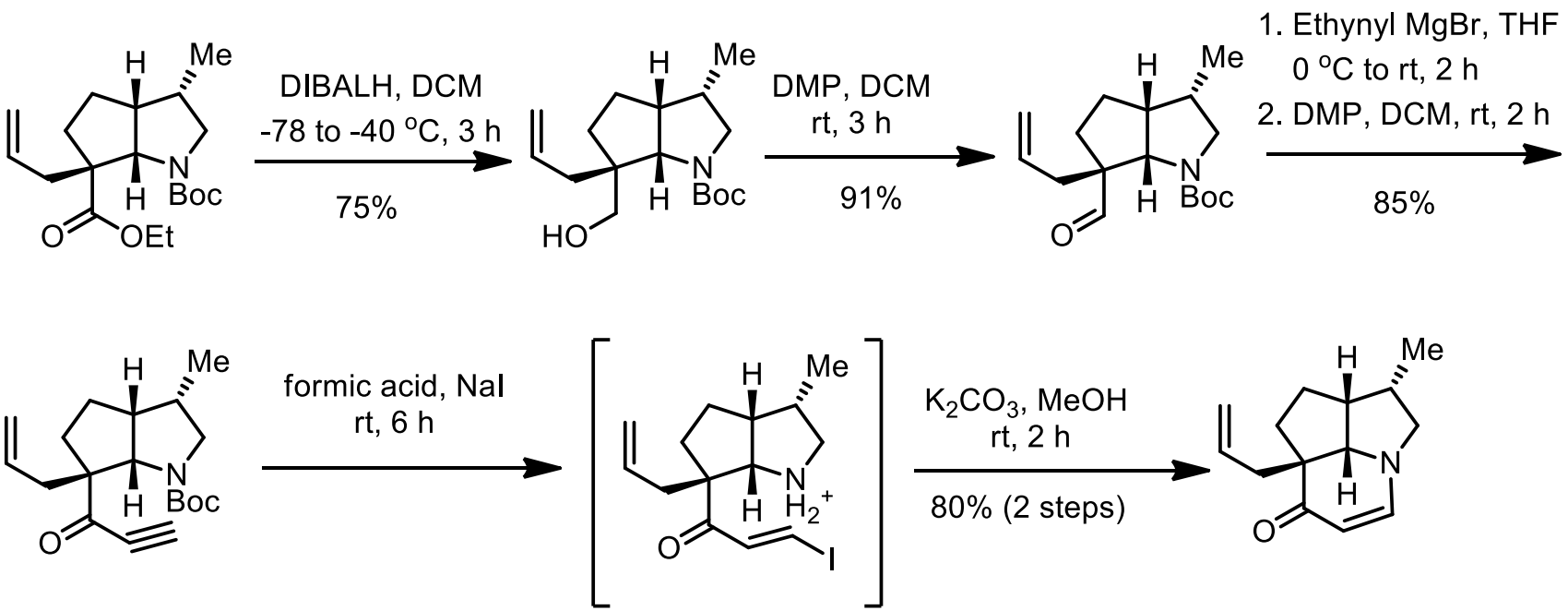
Enaminone/Michael/aldol strategy





Synthesis of the tricyclic enaminone

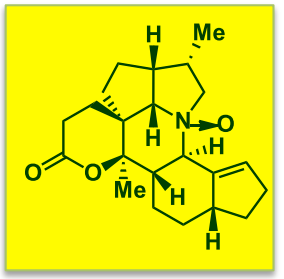


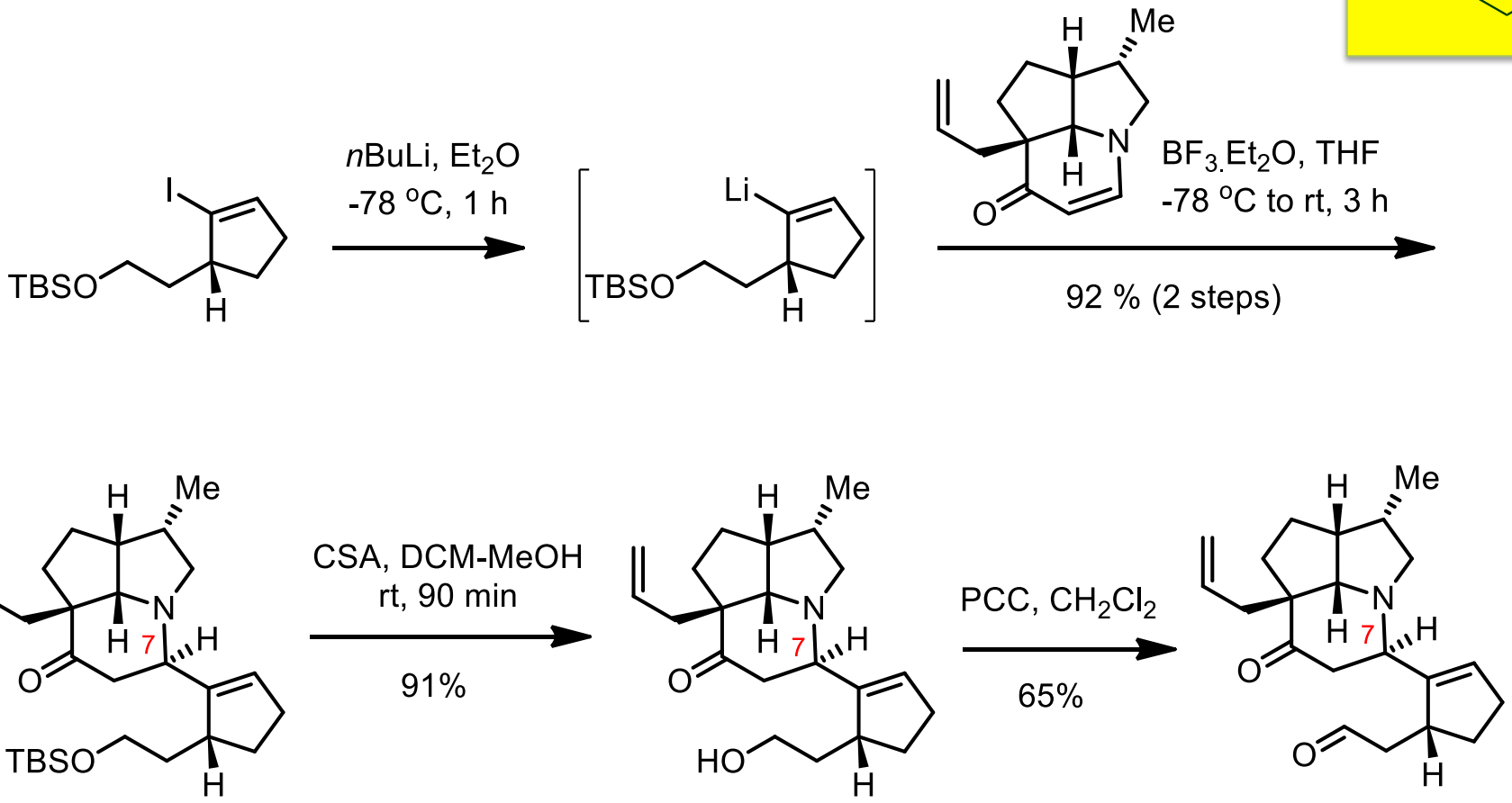


For enaminone reviews, see: A. K. Chattopadhyay, S. Hanessian, *Chem. Commun*, **2015**, 16437-16449;
A. K. Chattopadhyay, S. Hanessian, *Chem. Commun*, 2015, 16450-16467.

See also: M. J. Niphakis, B. J. Turunen, G. I. Georg, *J. Org. Chem.* **2010**, *75*, 6793-6805; B. J. Turunen, G. I. Georg, *J. Am. Chem. Soc.* **2006**, *128*, 8702-8703

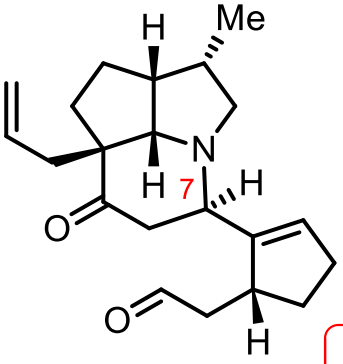
Michael addition on enaminone





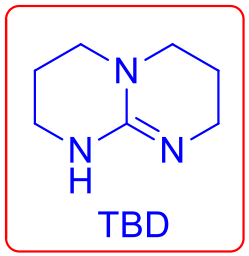
Organo lithium addition to enaminone, see: J. D. Brown, M. A. Foley, D. L. Comins, *J. Am. Chem. Soc.* **1988**, *110*, 7445-7447.

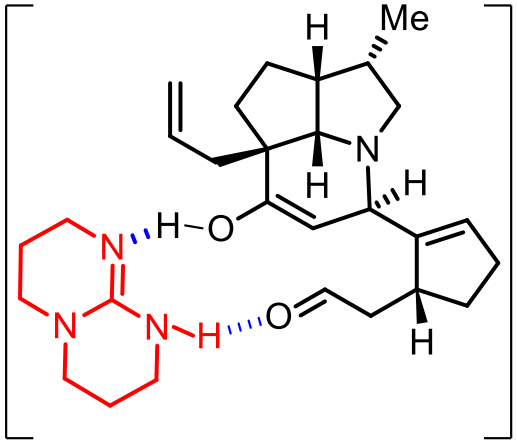
Synthesis of the pentacycle

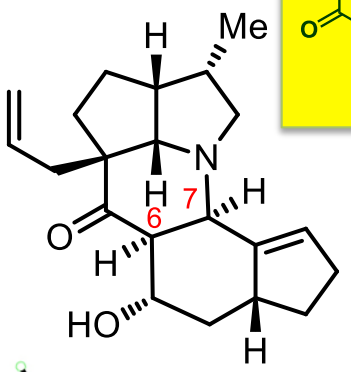


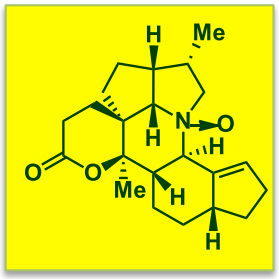
TBD, THF
rt, 48 h

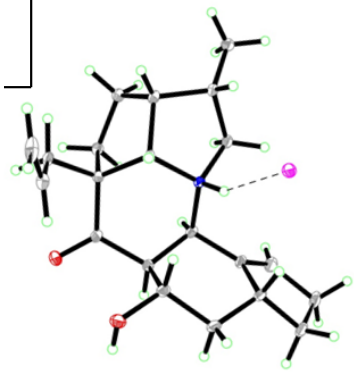
90%





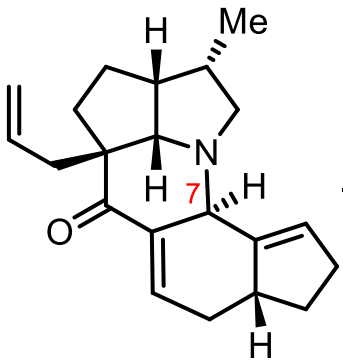






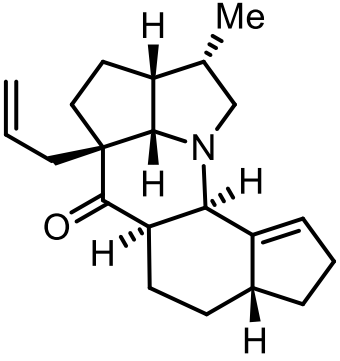
*p*TSA, 1,1,2-trichloroethane
55 °C, 4 h

85%



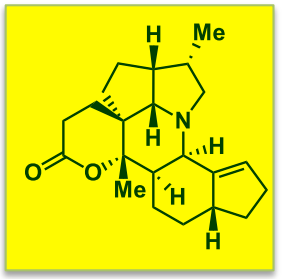
L-Selectride, Et_2O
-78 to 0 °C, 2 h

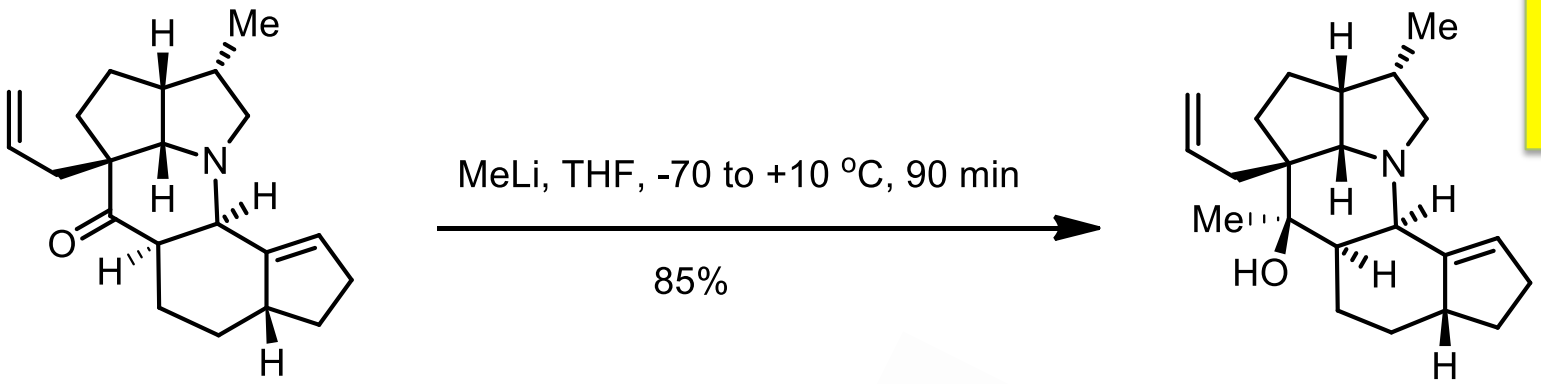
60%

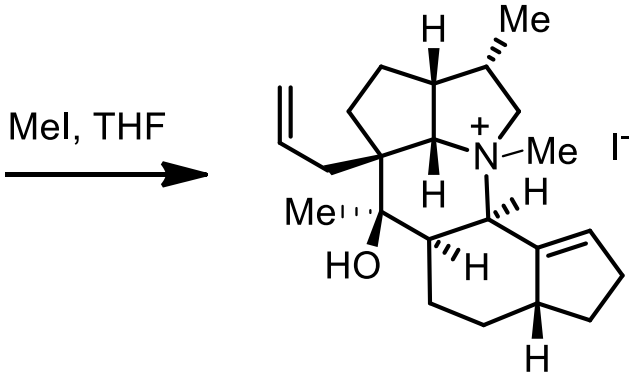


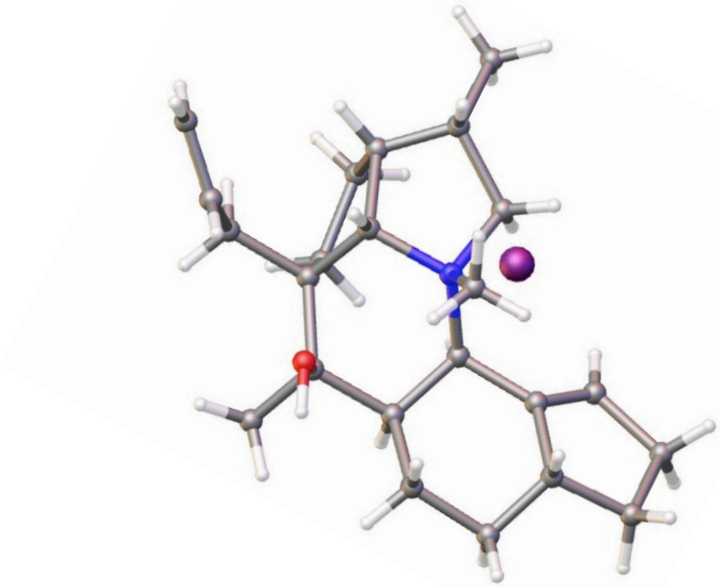
***J* = 3.5 HZ**

MeLi addition to Ketone









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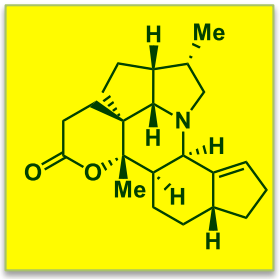
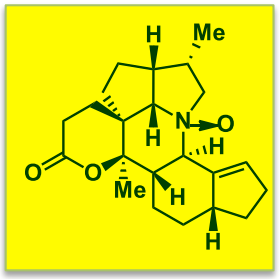
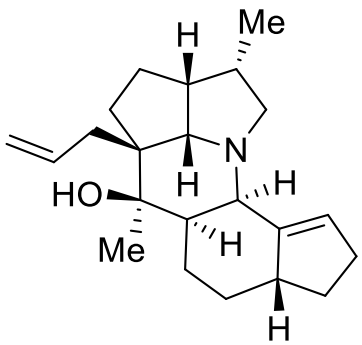
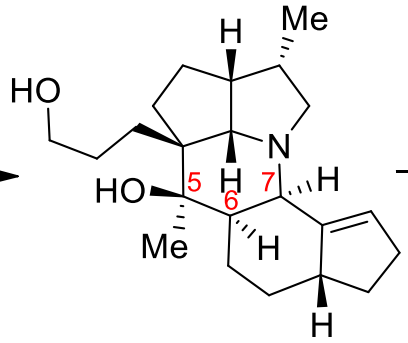


Toward isodaphlongamine H and 6-*epi*-calyciphylline B



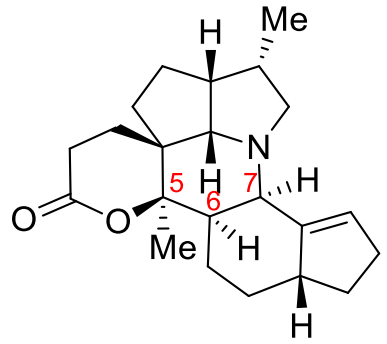


1. 9-BBN, THF, rt
2. NaOOH, rt



PCC, DCM, rt, 3 h

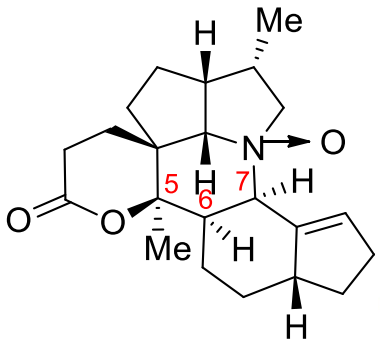
65 % (2 steps)



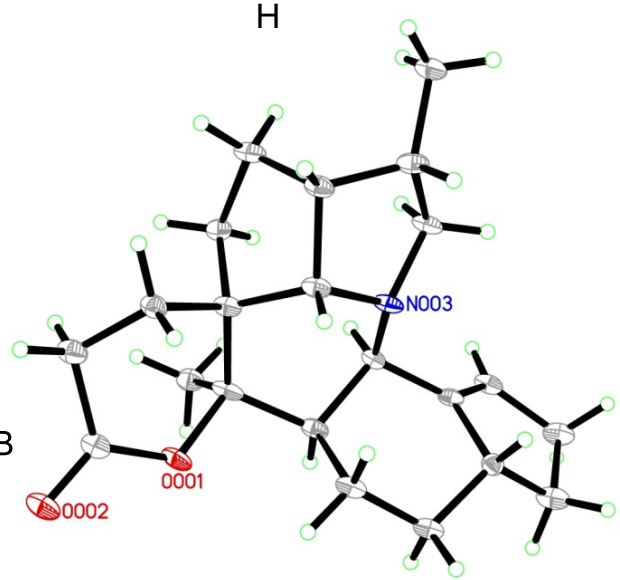
5-Isodaphlongamine H
or
6-*epi*-Deoxycalyciphylline B

*m*CPBA, CH_2Cl_2
15 min, rt

80%

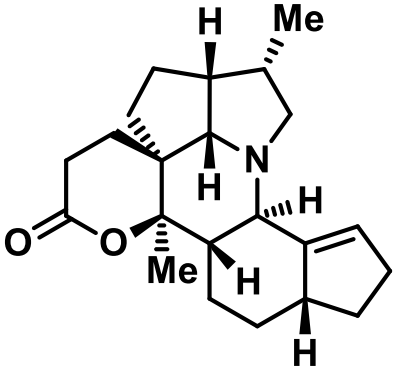


6-*epi*-Calyciphylline B

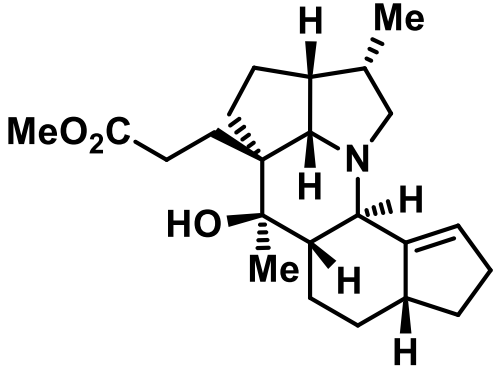


Syntheses of 5-iso-daphlongamine H and 6-epi-calyciphylline B were accomplished in 24 and 25 linear steps starting with commercially available 2-carbethoxycyclopentenone.

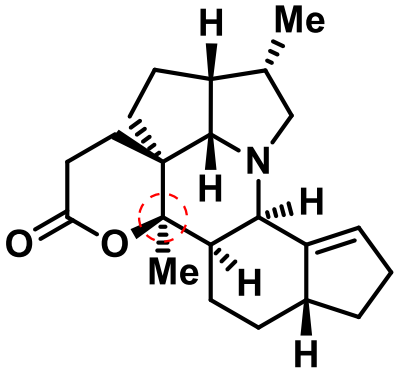
Isodaphlongamine H: The missing link of the calyciphylline B-type alkaloid series?



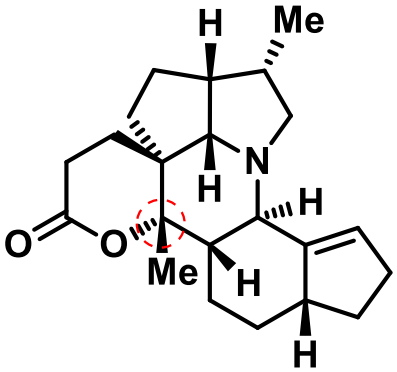
Deoxycalyciphylline B
From leaves of
D. subverticillatum



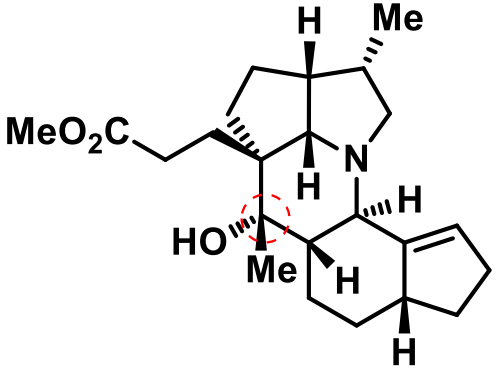
Longistylumphylline C
From leaves of
D. longistylum



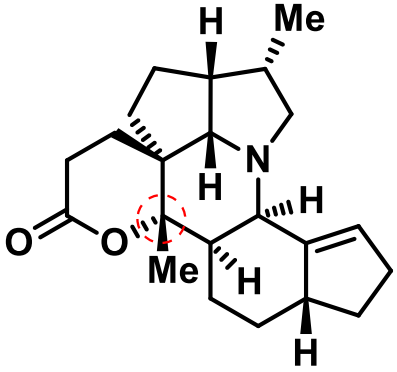
missing link
Synthetic product



Deoxyisocalyciphylline B
From leaves of
D. subverticillatum

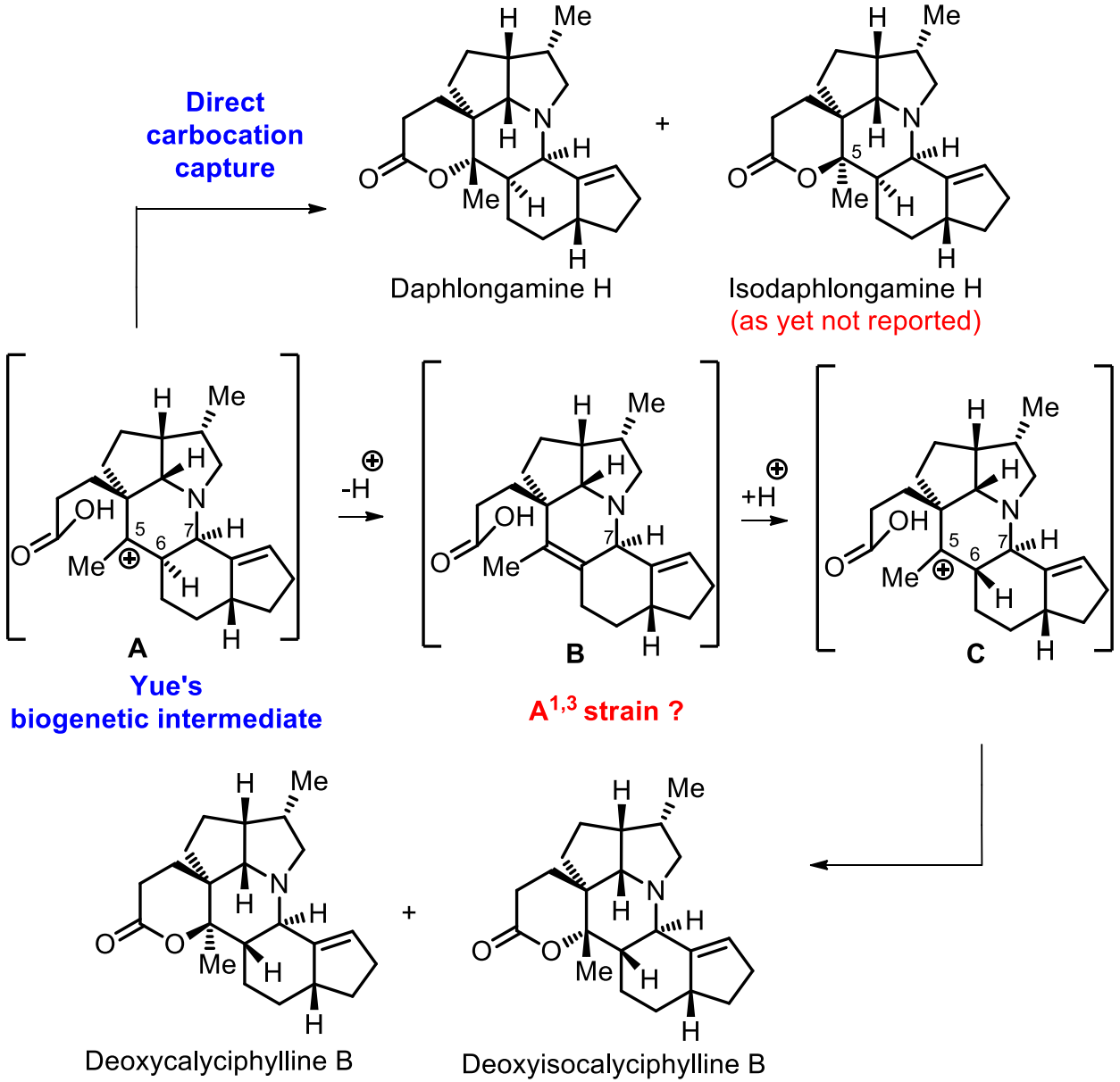


Caldaphnidine R
From leaves of
D. calycinum



Daphlongamine H
From leaves of
D. longeracemosum

A possible biogenetic conundrum



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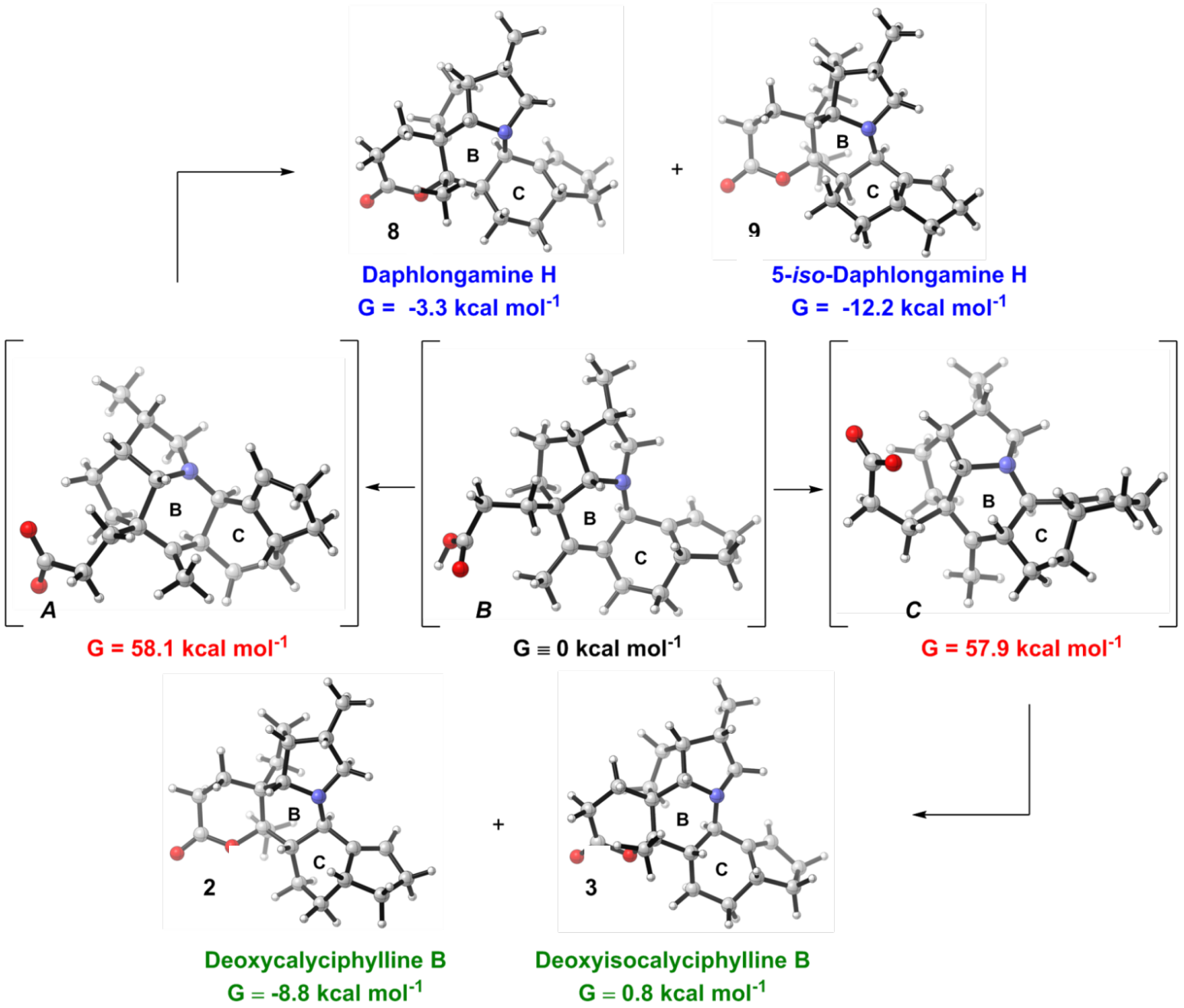
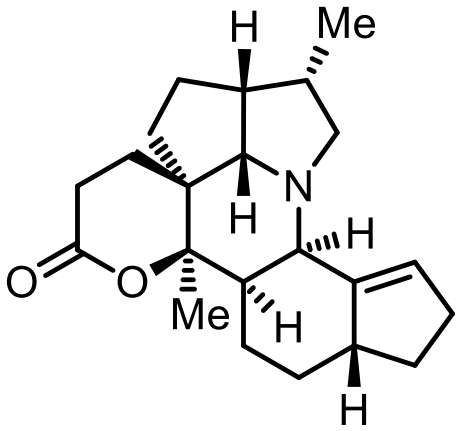
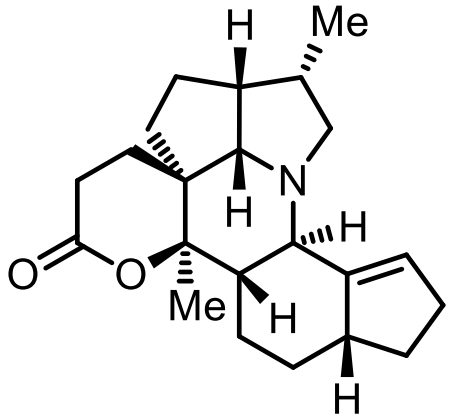
Relative energy difference of natural and synthetic products:



Anticancer activity



5-iso-Daphlongamine H (synthetic)



Deoxycalyciphylline B (natural)

GI_{50} = >30 μM, all cell lines

GI_{50} = 38 μM against HOP-92 (non-small cell lung cancer)
GI_{50} = 35 μM against SNB-75 (CNS cancer)
GI_{50} = 48 μM against MDA-MB-435 (melanoma)
GI_{50} = 43 μM against UO-31 (renal cancer)

- In-vitro studies were performed on sixty human cancer cell lines including leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate, and breast.
- 5-isodaphlongamine H is two fold less active than deoxycalyciphylline B on other cell lines.