IASOC 2002
NEW FRONTIERS AND FUTURE CHALLENGES
IN ORGANIC SYNTHESIS

The Power of Visual Imagery in Organic Synthesis

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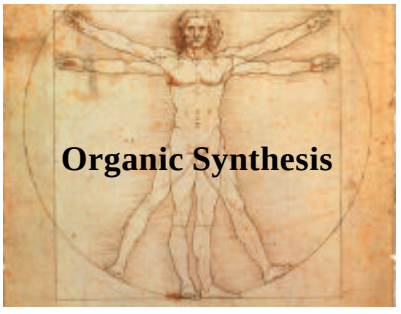
Université de Montréal
Montréal, Canada

ORGANIC CHEMISTRY - A *CENTRAL* SCIENCE

Food and Commodities **Drug Design**

Unnatural Products



Natural Products

Materials **Life Processes**

ORGANIC CHEMISTRY - FROM CONCEPT TO KNOWLEDGE

Concept **Design**

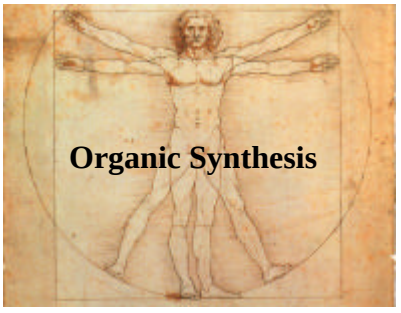
Execution **Knowledge**

« Knowledge is the daughter of experience »

Leonardo

ORGANIC CHEMISTRY - A *MENTAL* SCIENCE

Psyche **Imagery**



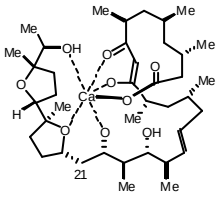
Logic **Knowledge**

« Dans les champs d'observation le hasard ne favorise que les esprits préparés »

Louis Pasteur

Logic and Imagery
« The first taste is with the eye »

Synthesis



IONOMYCIN Ca salt

Architecture

Art

⇓ Simplification of complexity

visual, relational, mental

⇓

Chemist's synthesis plan

⇓ Reduction of dimensions

visual, orderly, mental

⇓

Architect's blueprint

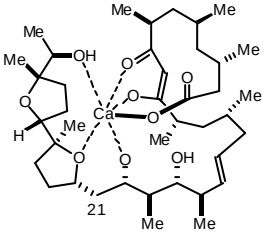
⇓ Creation of shapes, forms and values

visual, emotional, mental

⇓

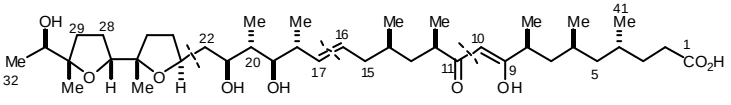
Artist's sketch

Psyche ⇕ Imagery

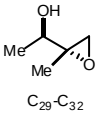


IONOMYCIN Ca salt

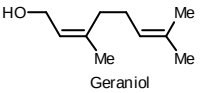
Logic ⇕ Knowledge



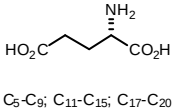
Ionomycin



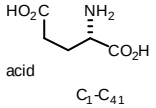
C_{29}-C_{32}



Geraniol
C_{23}-C_{28}



C_5-C_9; C_{11}-C_{15}; C_{17}-C_{20}



L-Glutamic acid

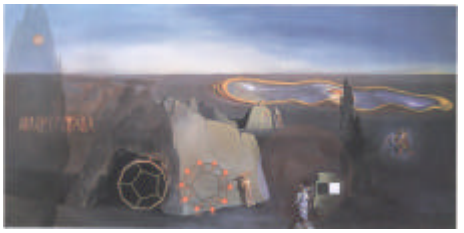
C_1-C_{41}

Hanessian, Cooke, Dehoff, Sakito *J. Am. Chem. Soc.* **1990**, *112*, 5276

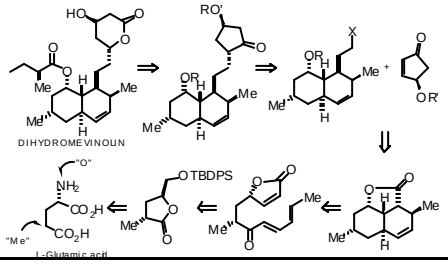
Psyche, Logic and Imagery

SEEING THROUGH THE MIND'S EYE

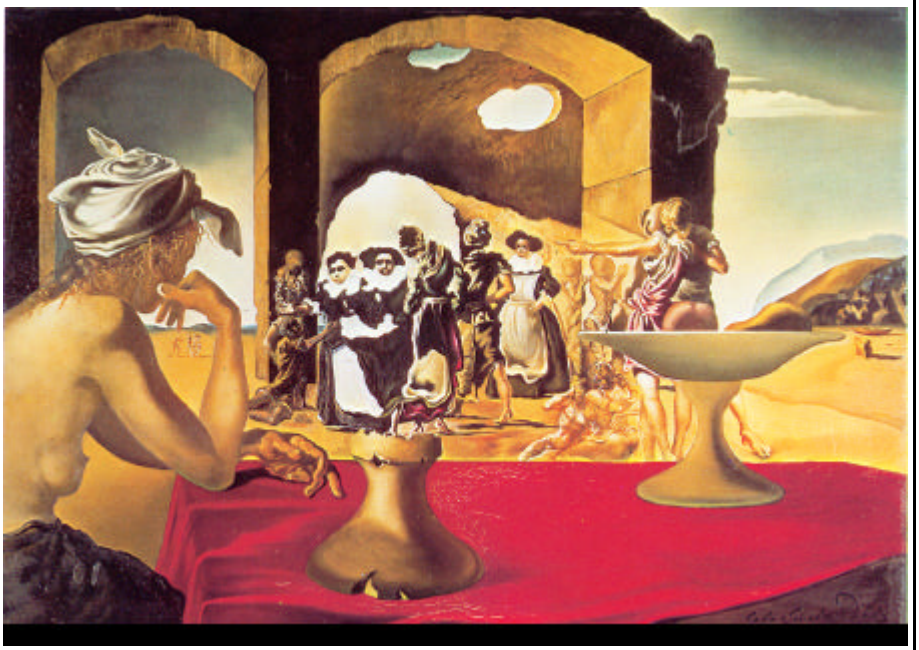
(The False Mirror)
R. Magritte, 1928



(Searching for the Fourth Dimension)
S. Dali, 1979



(Dihydromevinolin)
Hanessian, Roy, Petrini, Hodges, DiFabio
Carganico, *J. Org. Chem.*, **1990**, *55*, 5766



ACADEMIC TARGETED SYNTHESIS

ORIGIN OF PROBLEM

- Hypothesis
- Proposal
- Theory
- Dogma
  - *Biological*
  - *Chemical*
  - *Theoretical*
  - *Computer*

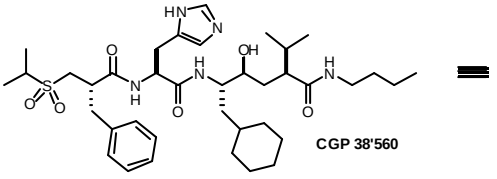
INCENTIVE FOR SYNTHESIS

- Validation
- New insights
- Intuition / Curiosity
- Design / Strategy

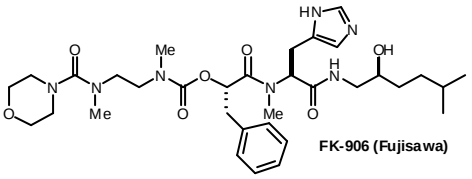
TARGET MOLECULE

- New
- Known
- Hybrid
- Analog

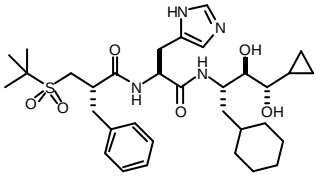
RENIN AND HYPERTENSION: THE SEARCH FOR "SMALL" INHIBITORS



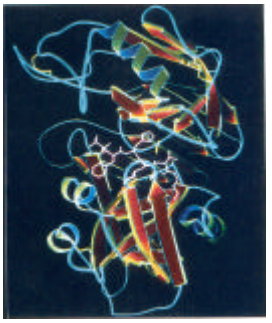
CGP 38'560

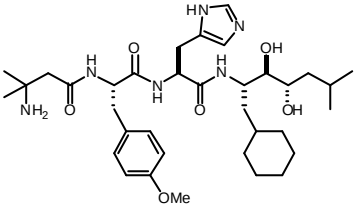


FK-906 (Fujisawa)



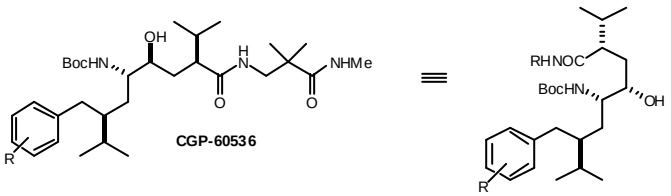
Remikiren (Roche)





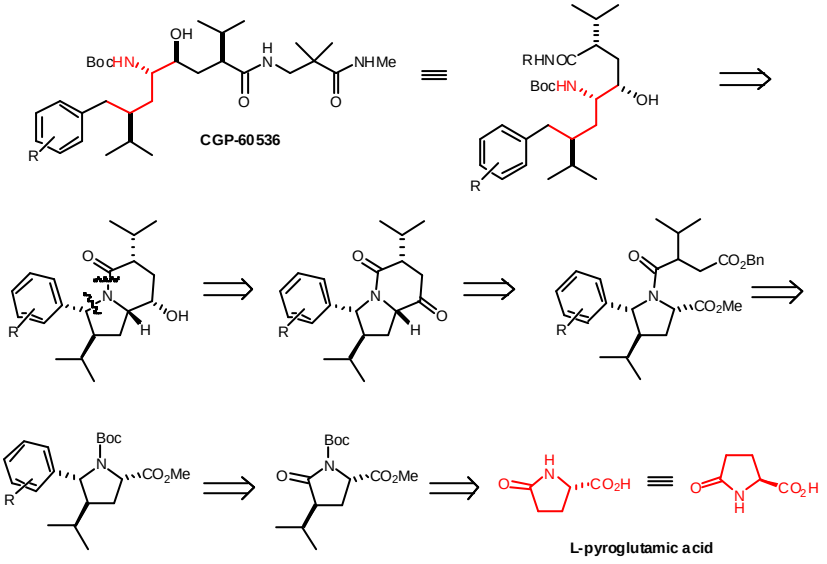
Enalkiren (Abbott)

THE VISUAL DIALOGUE - SEEING THROUGH THE MIND'S EYE



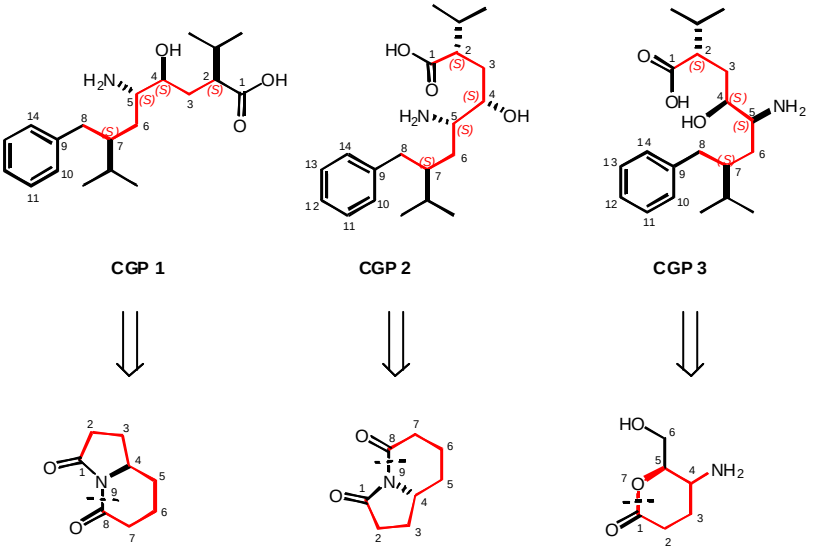
CGP-60536 : J. Rahuel, V. Rasetti, J, Maibaum, H, Rueger, R. Goschke, N.C. Cohen, S. Stutz, F. Cumin, W. Fuhrer, J.M. Wood. M.G. Grutter *Chem. Biol.* **2001**, *7*, 493

THE VISUAL DIALOGUE - SEEING THROUGH THE MIND'S EYE



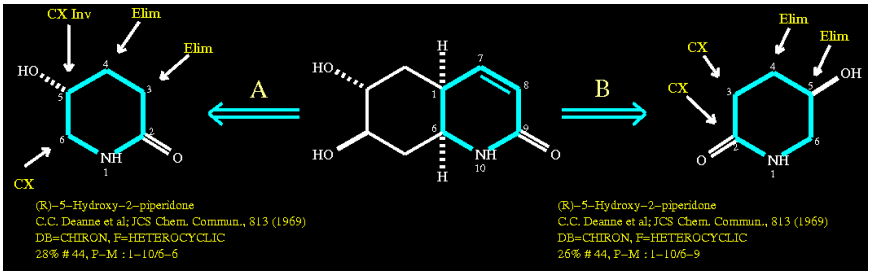
S. Hanessian *et al J. Org. Chem.* **2002**, *67*, 4261

THE THREE FACES OF A MOLECULE



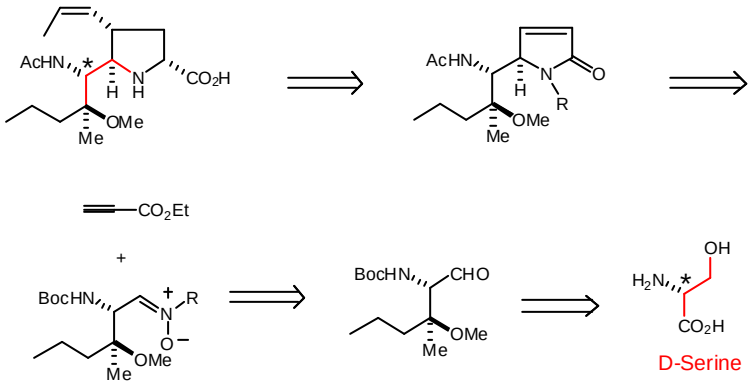
Chiron computer program output

Computer Assisted Precursor Selection – CAPS:

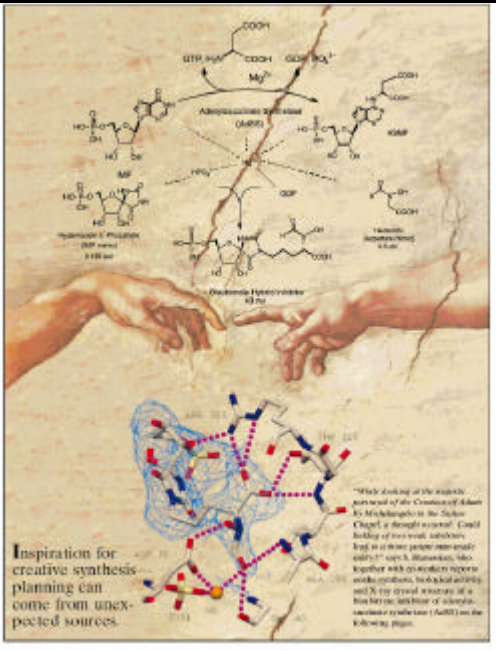


What a difference a flip makes!

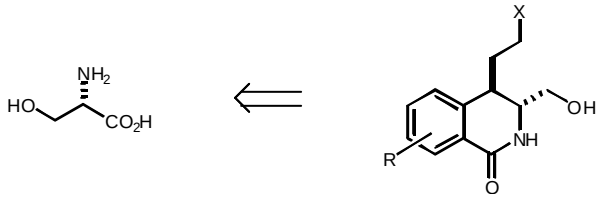
A-315675 Disconnection



S. Hanessian *et al*. *J. Am. Chem. Soc*. **2002**, *124*, 4716-4721

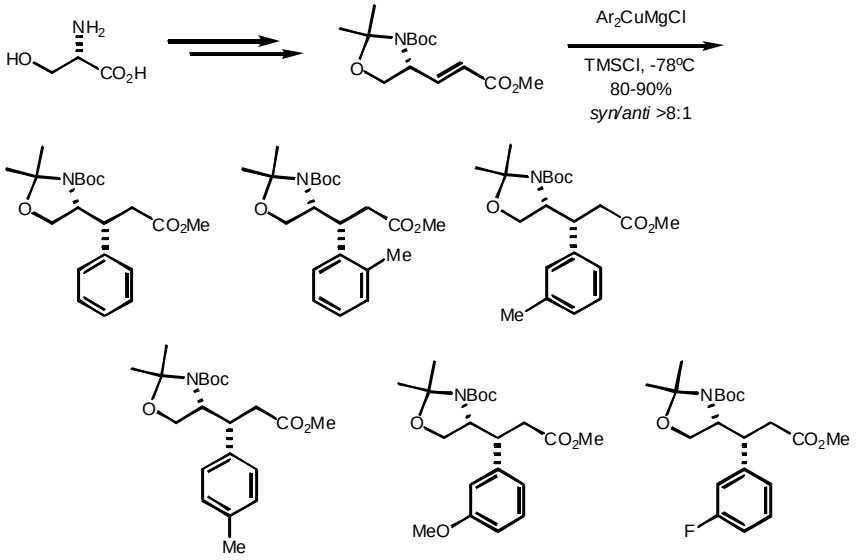


FROM SERINE TO FUNCTIONALIZED ENANTIOPURE TETRAHYDROISOQUINOLINES



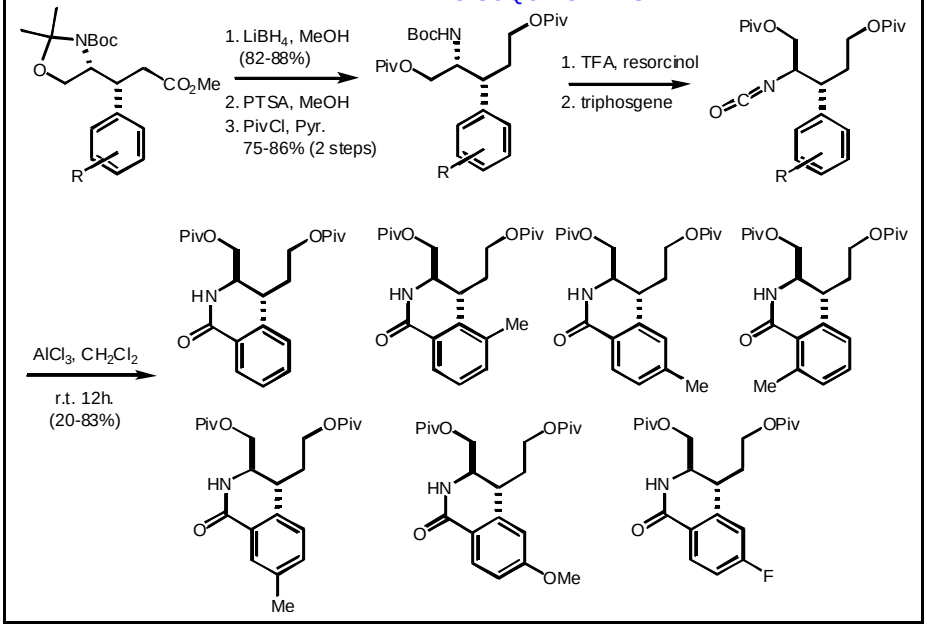
S. Hanessian *et al. Tetrahedron lett.* **2000**, *41*, 4999

FROM SERINE TO FUNCTIONALIZED ENANTIOPURE TETRAHYDROISOQUINOLINES

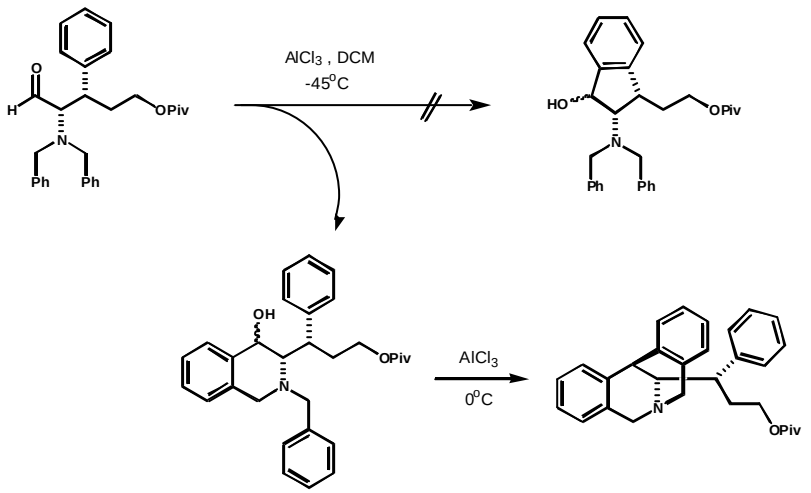


S. Hanessian, K. Sumi *Synthesis* **1991**, 1083
S. Hanessian, W. Wang, Y. Gai *Tetrahedron Letters* **1996**, *37*, 7477

FROM SERINE TO FUNCTIONALIZED ENANTIOPURE TETRAHYDROISOQUINOLINES

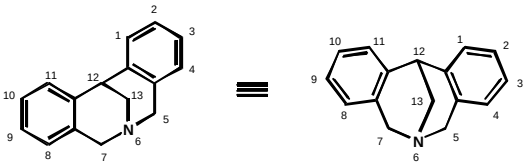


A Welcome Distraction



Dihydro-methano-dibenzo azocine nucleus

Azocine

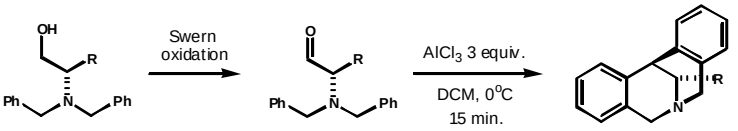


7,12-Dihydro-5*H*-6,12-methano-dibenzo[*c*,*f*]azocine

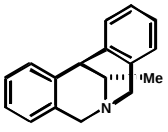
Tetrahydro-6,12-methanodibenzo[*c*,*f*]azocine

Dibenzo[*c*,*f*]-1-azabicyclo[3.3.1]nonane

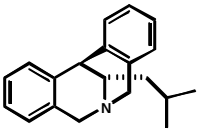
Reference : H. Takayama, *Tetrahedron Letters*, **1978**, 1307



78%



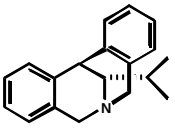
$[\alpha]_D$ + 37 (c 1 $CHCl_3$)



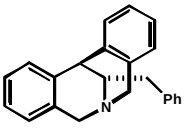
87%

$[\alpha]_D$ + 32 (c 2.2 $CHCl_3$)

90%



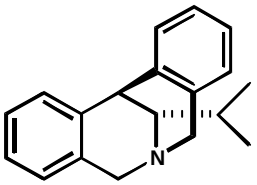
$[\alpha]_D$ + 47 (c 1.2 $CHCl_3$)



82%

$[\alpha]_D$ + 44 (c 2 $CHCl_3$)

S. Hanessian *et al. Tetrahedron* **2002**, *58*, 1485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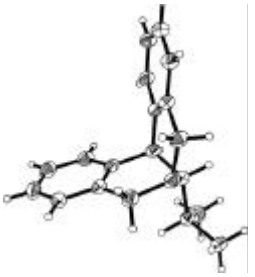
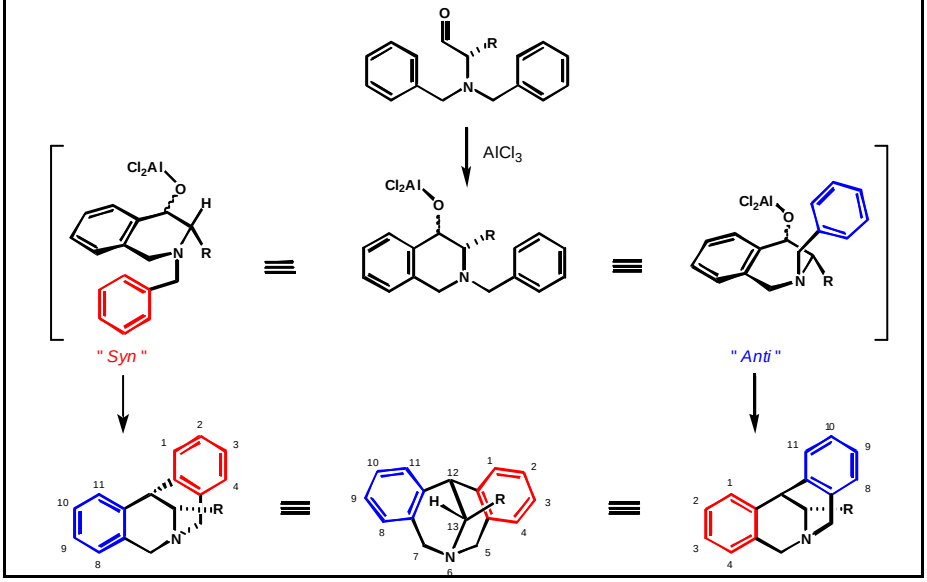
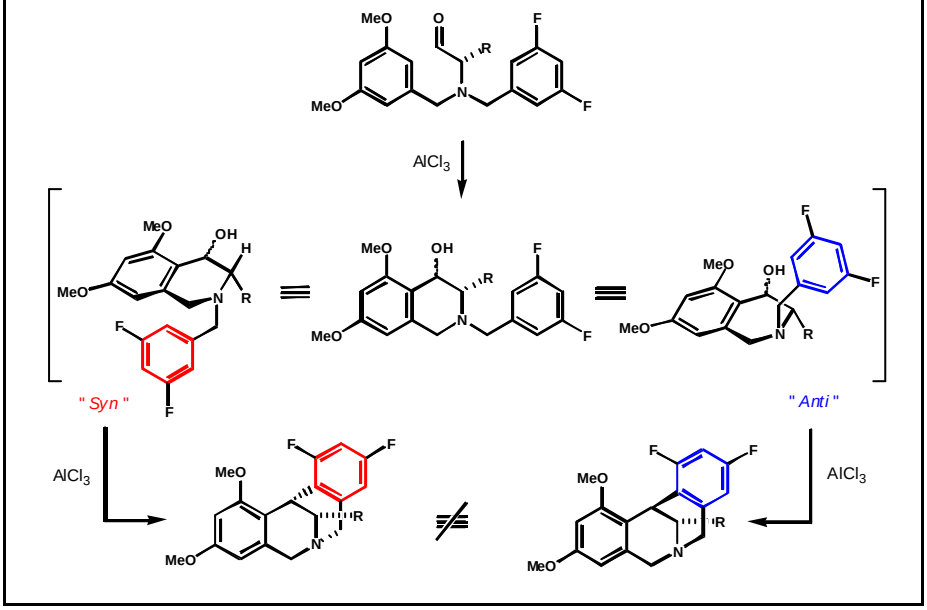
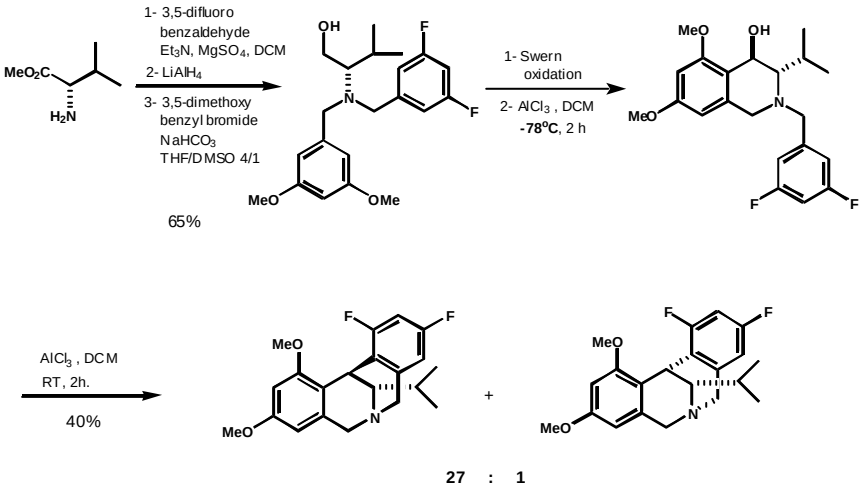


Topological Eye-Teaser

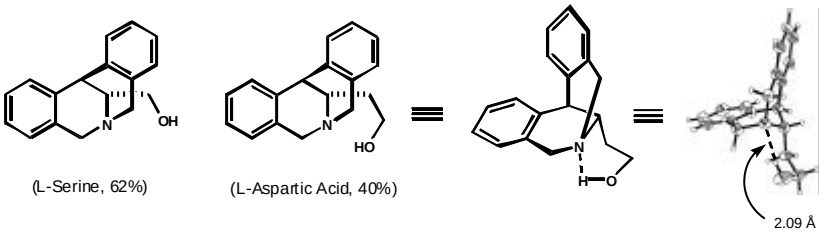


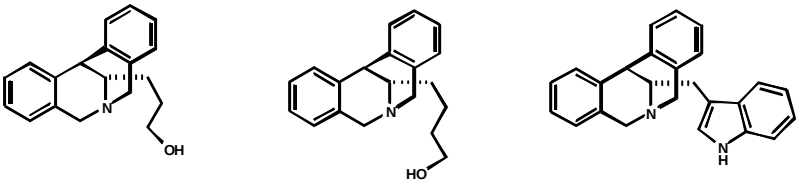
Topological Eye-Teaser



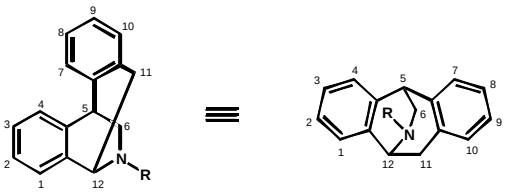


Functionalized Azocines



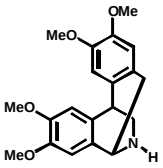


The isopavinan Nucleus

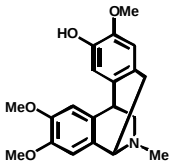


Review : B. Gozler, *The Alkaloids*, **1987**, *31*, 317

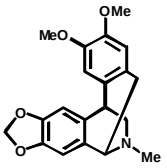
Natural Isopavinan Alkaloids



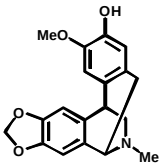
(-)-isopavine



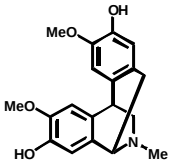
(-)-Thalisopavine



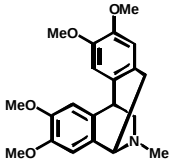
(-)-Amurensinine



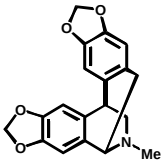
(-)-Amurensine



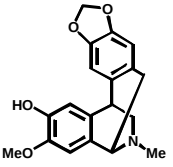
(-)-Thalidine



(-)-*O*-Methylthalisopavine

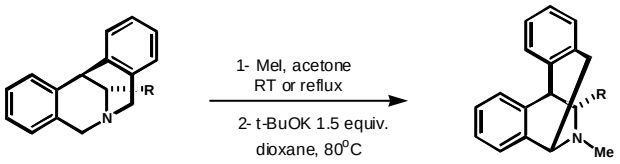


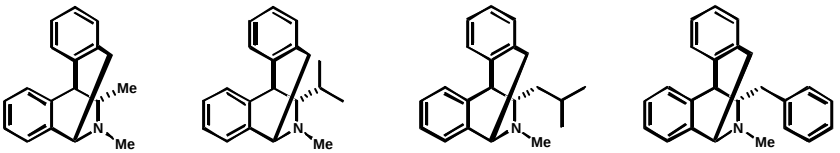
(-)-Reframidine



(-)-Reframoline

Asymmetric Synthesis of Isopavinan Alkaloids





85%

$[\alpha]_D$ - 150 (c 1 $CHCl_3$)

88%

$[\alpha]_D$ -133 (c 1 $CHCl_3$)

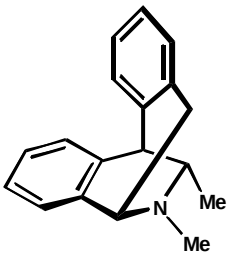
78%

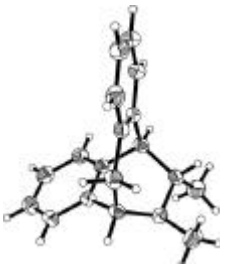
$[\alpha]_D$ - 105.8 (c 1 $CHCl_3$)

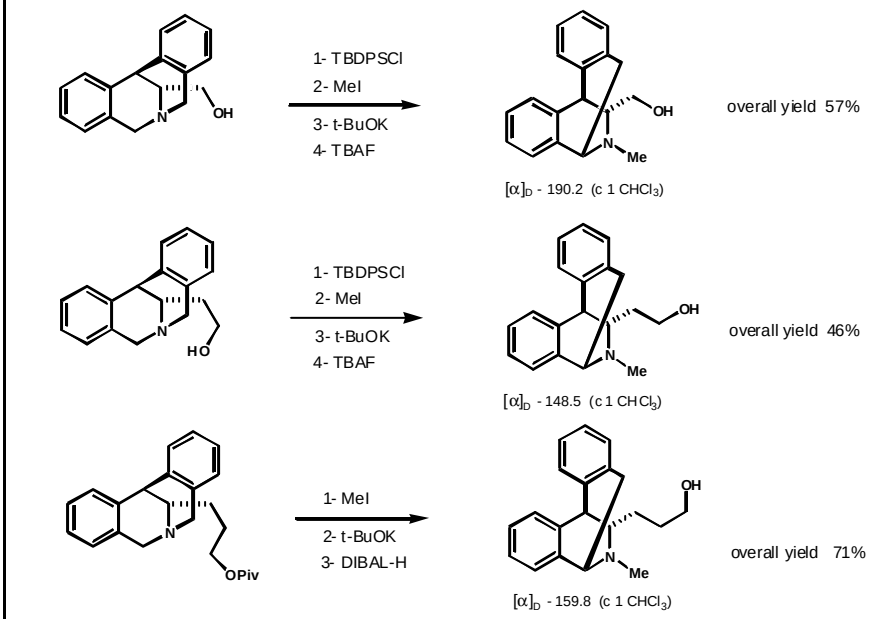
75%

$[\alpha]_D$ - 79.2 (c 1 $CHCl_3$)

S. Hanessian *et al. Angew. Chem. Int. Ed.* **2001**, *40*, 3810

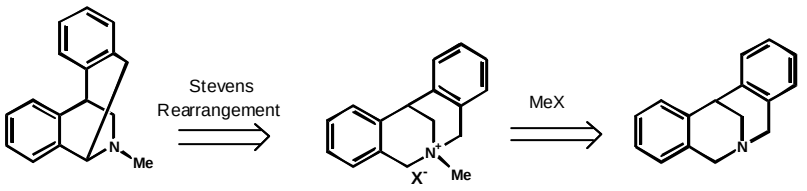




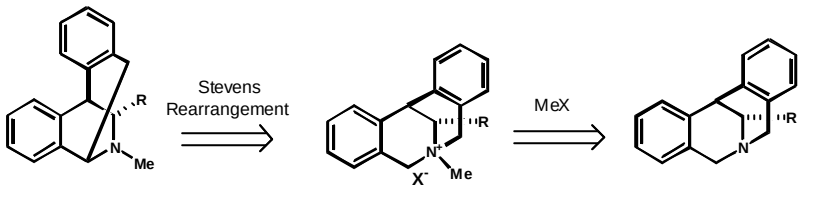


[1,2]-Stevens rearrangement

Background : H. Takayama, *Heterocycles*, **1978**, *9*, 1545-1548

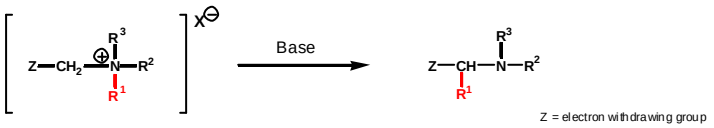


Proposal :

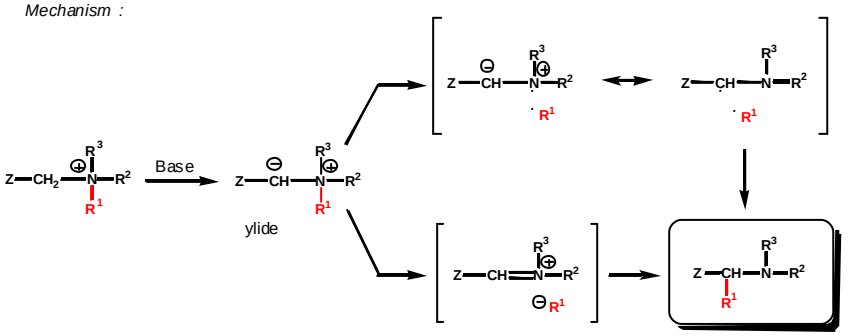


[1,2]-Stevens rearrangement

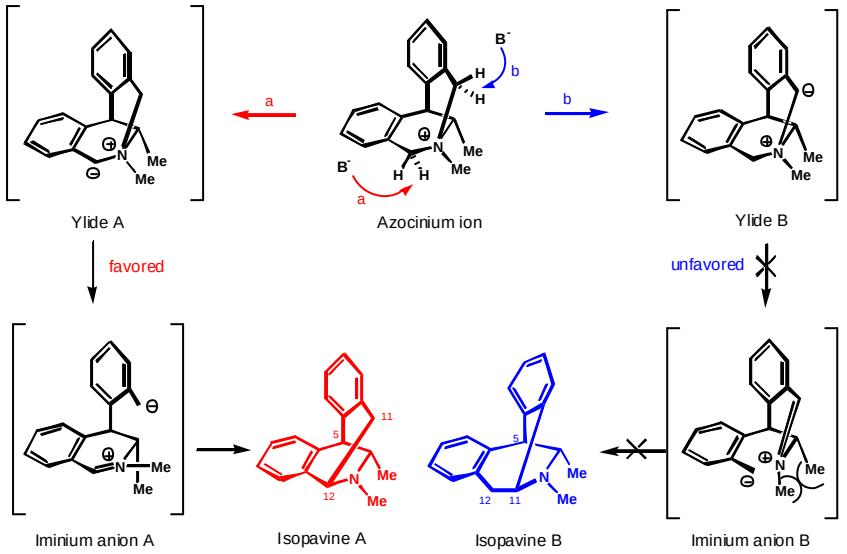
Principle of the reaction :

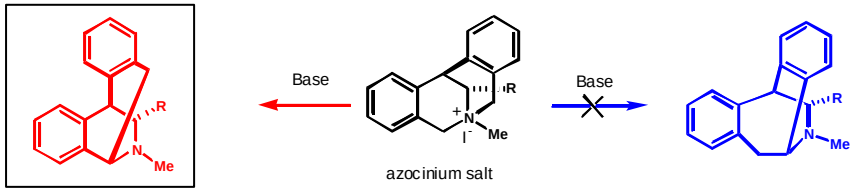


Mechanism :

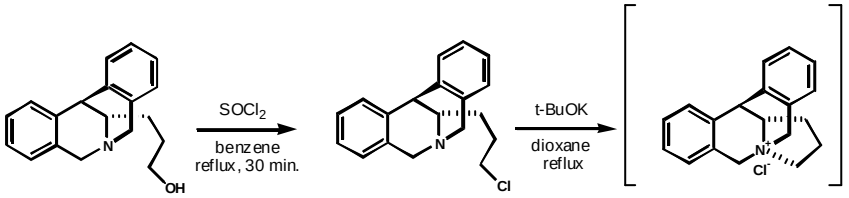


Diastereoselective [1,2]-Stevens Rearrangement





However…

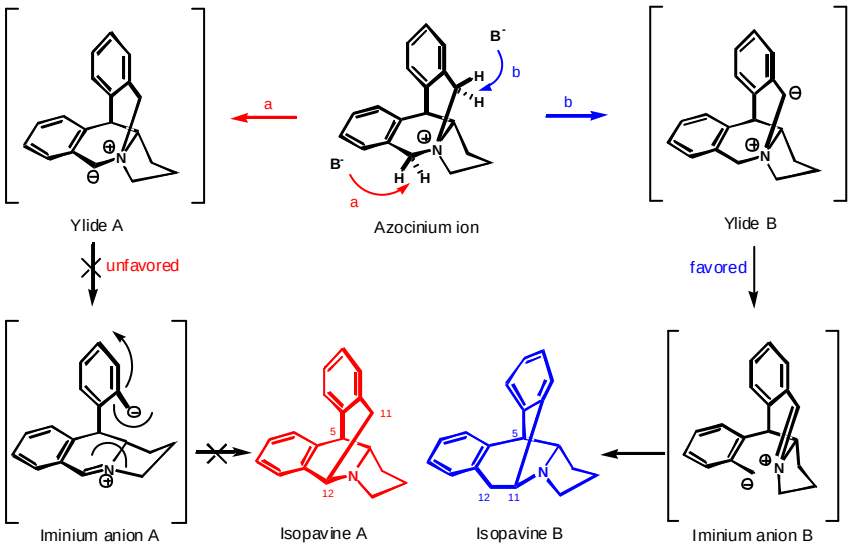


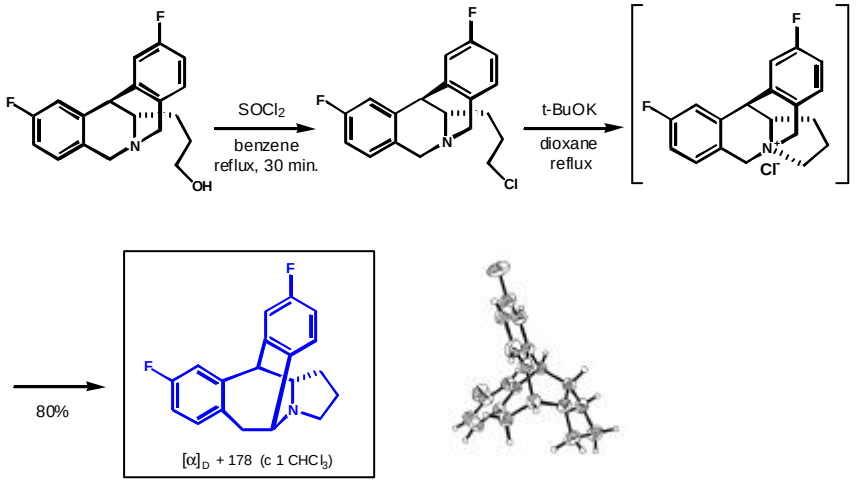
80%

$[\alpha]_D$ + 180.1 (c 1 $CHCl_3$)

and not

Diastereoselective [1,2]-Stevens Rearrangement





Of Pain and Men

" As the psychologist and physician know very well, pain or the prospect of pain often are feared more than death"

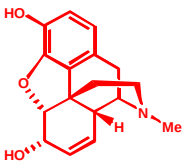
Helen of Troy offering wine to Telemacchus, to which she had added " a drug to quit all pain and strife, and to bring forgetfulness of every ill"

Homer, in the Odyssey

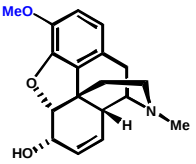
From "The Curse of Opium: Requital through Medicinal Organic Chemistry"
Bernard Belleau

CIC Medal Adress, 1979

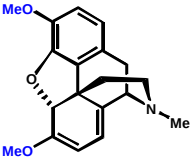
The Opium Alkaloids



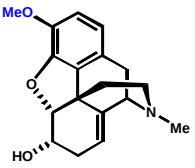
(-)-Morphine



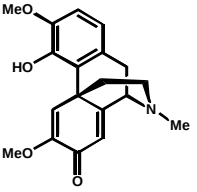
(-)-Codeine



(-)-Thebaine



(-)-Neopine

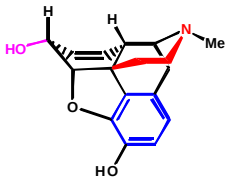


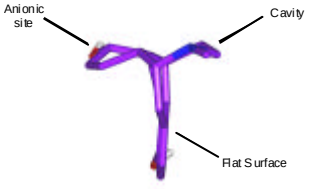
(-)-Salutaridine

OPIUM (*Papaver somniferum*) :		
	Morphine	12 %
	Codeine	1 %
	Thebaine	0,5 %
	Neopine	trace
	Salutaridine	trace

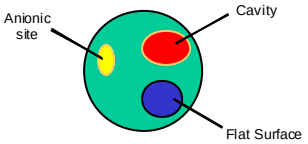
Structure Activity Relationships

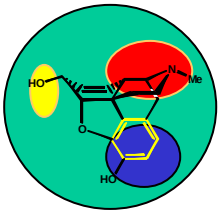
Morphine is the prototype m-receptor agonist





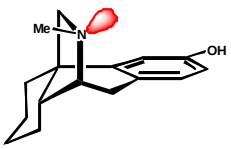
Opioid Receptor Surface



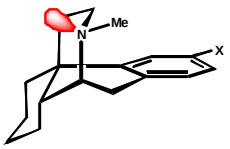


Hommage to the late Bernard Belleau

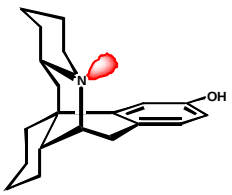
"Importance of the Nitrogen Lone Electron Pair Orientation in Stereospecific Opiates"
J. Med. Chem., **1974**, *17*, 907.



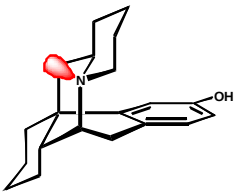
D-normorphinane
"inactive"



morphinane
"active"

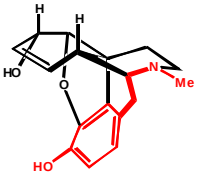


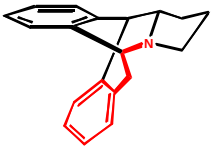
16α,17-butano-morphinane
"inactive"

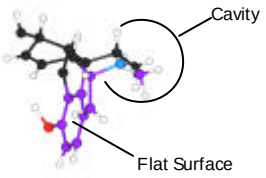


16β,17-butano-morphinane
"active"

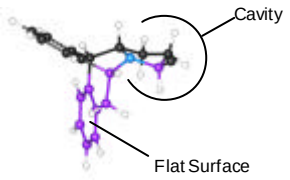
Isopavines as Potential Morphinomimetics ?





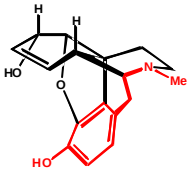


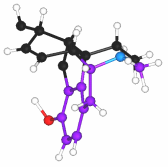
(X-ray)

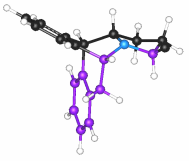


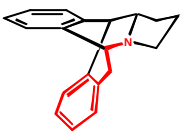
(minimized)

Isopavines as Potential Morphinomimetics ?



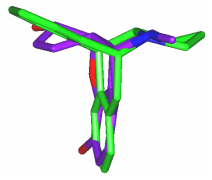






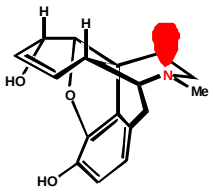
IC_{50} = 0.6 nM

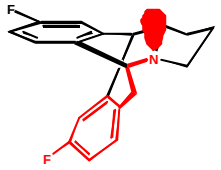
IC_{50} = 66 nM

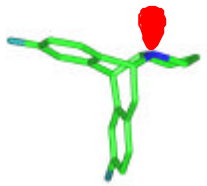


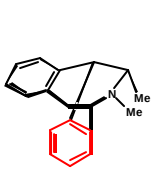
S. Hanessian *et al. J. Med. Chem.* In Press

The Lone Pair !









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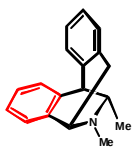

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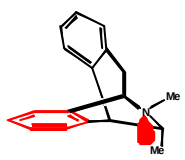
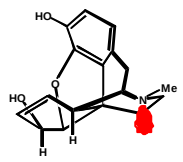
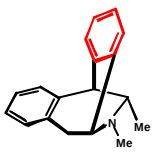




From L-Alanine

IC_{50} = 635 nM

Enantiomer of Morphine is 100 times less active



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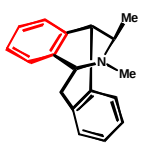

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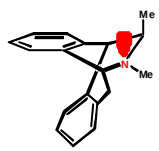
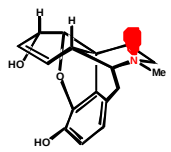


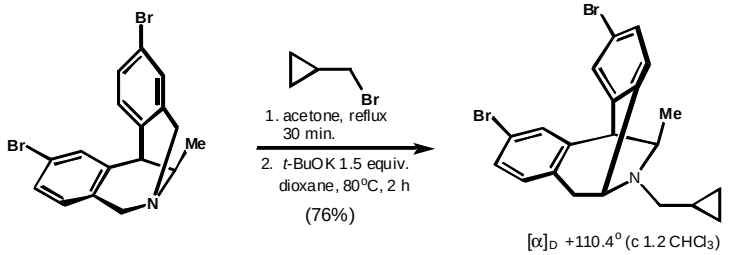


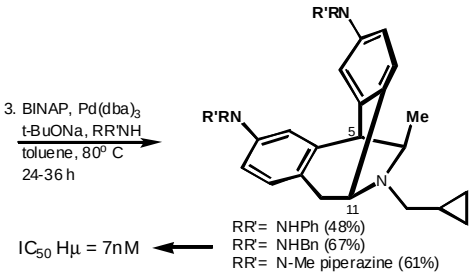
From D-Alanine

IC_{50} ?

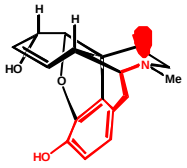
IC_{50} = 0.6 nM

Synthesis of Bis-Anilino Isopavine Analogs



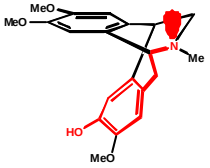


Unnatural Enantiomer of Thalisopavine as Potential Morphinomimetics ?

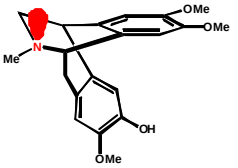


Morphine
natural enantiomer

IC_{50} = 0.6 nM



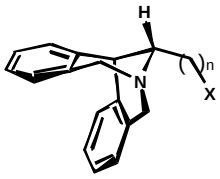
(+)-Thalisopavine
unnatural isopavine alkaloid



(-)-Thalisopavine
natural isopavine alkaloid

Azocine Ligands For Catalysis

Principle:



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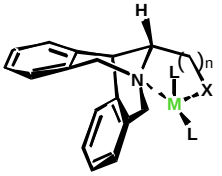
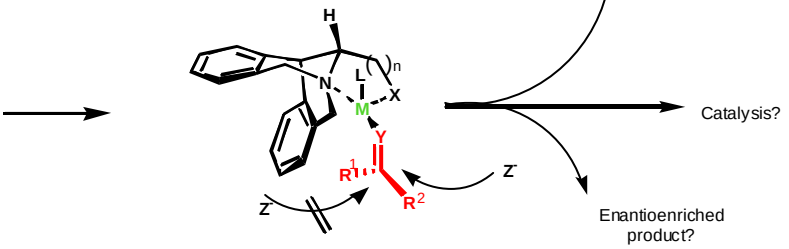


X= OH, OR, SR, NHR, NR_2, $OPPh_2$, PPh_2

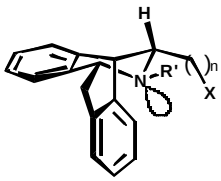
n= 1, 2

M= Cu, Zn, Li, Mg, Pd, etc.



Isopavine Ligands For Catalysis

Principle:



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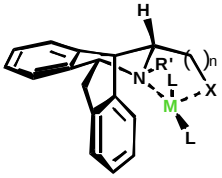
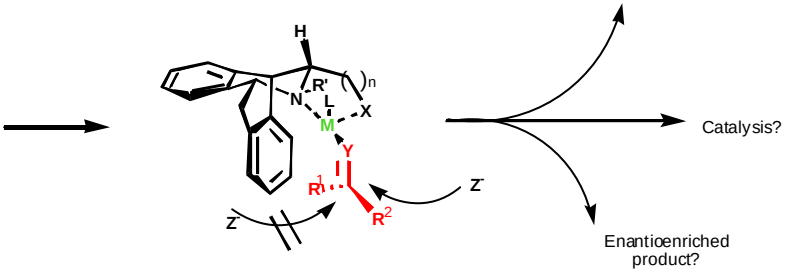


X= OH, OR, SR, NHR, NR_2, $OPPh_2$, PPh_2

n= 1, 2

M= Cu, Zn, Li, Mg, Pd, etc.



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