Université de Montréal

Man, Machine, and Heuristics in Synthesis Planning

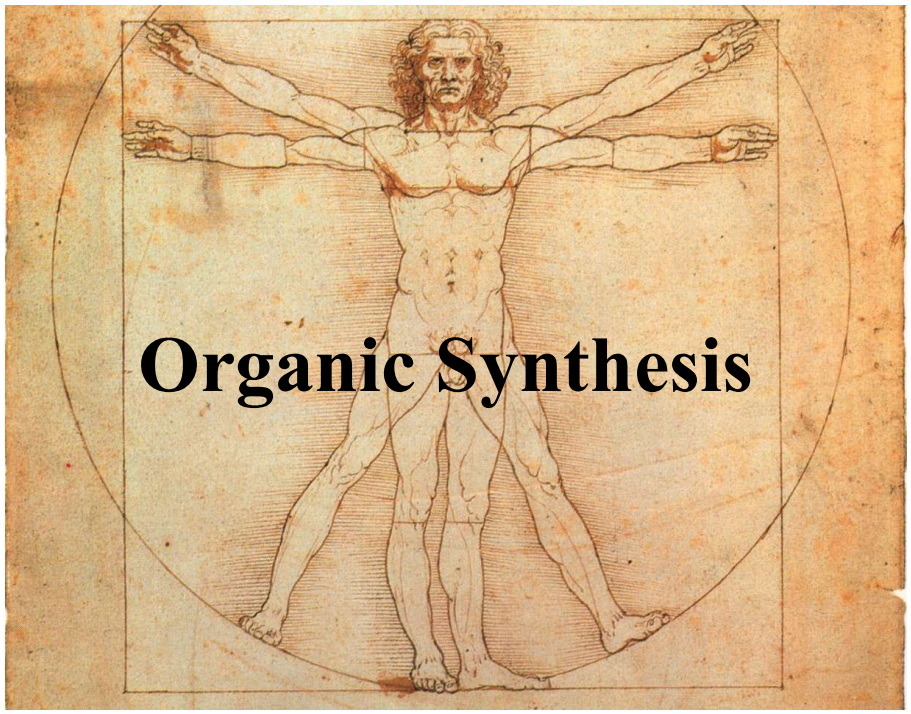
Stephen Hanessian
University of Montreal

ORGANIC CHEMISTRY - A *CENTRAL* SCIENCE

Food and Commodities

Drug Design

Unnatural Products



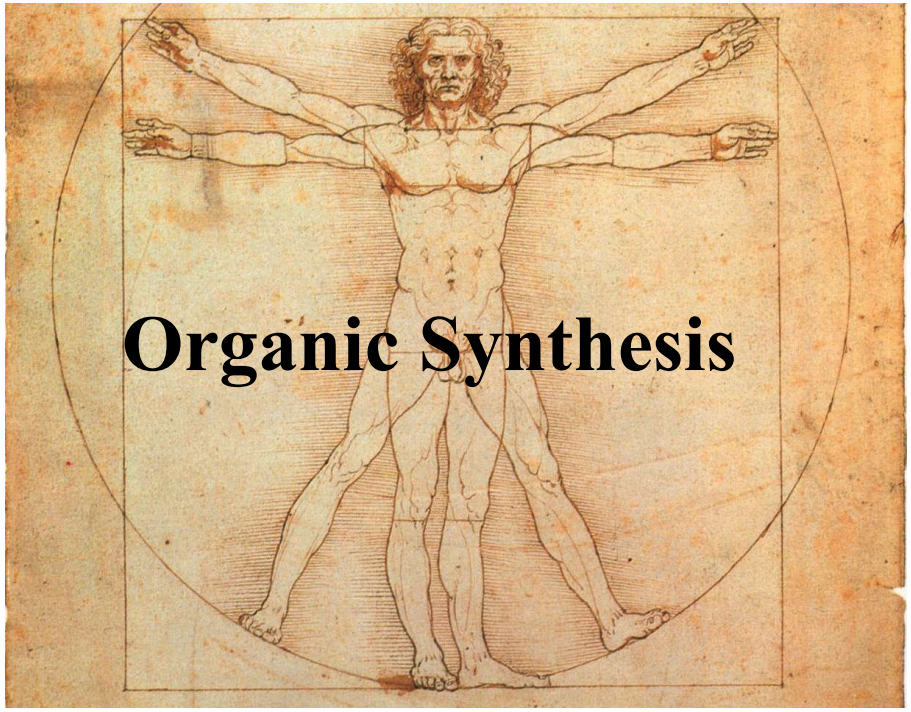
Natural Products

Materials

Life Processes

ORGANIC CHEMISTRY - FROM *CONCEPT* TO *PRACTICE*

Concept **Design**



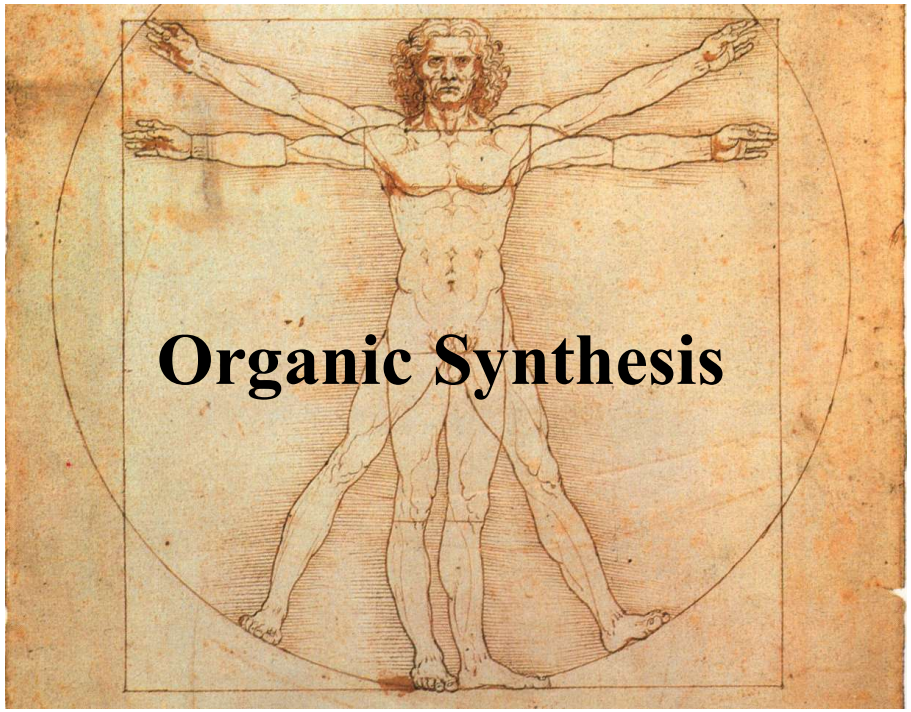
Practice **Knowledge**

« 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 »

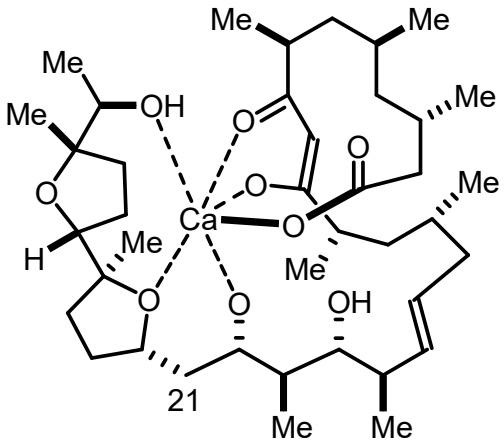
Louis Pasteur

Logic and Imagery

« The first taste is with the eye »

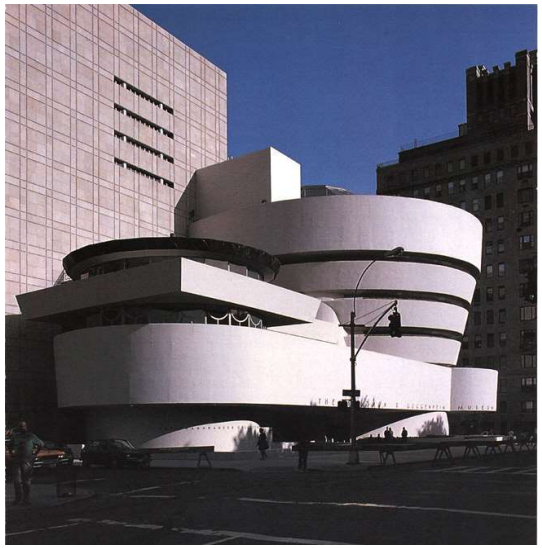
Sophocles

Synthesis

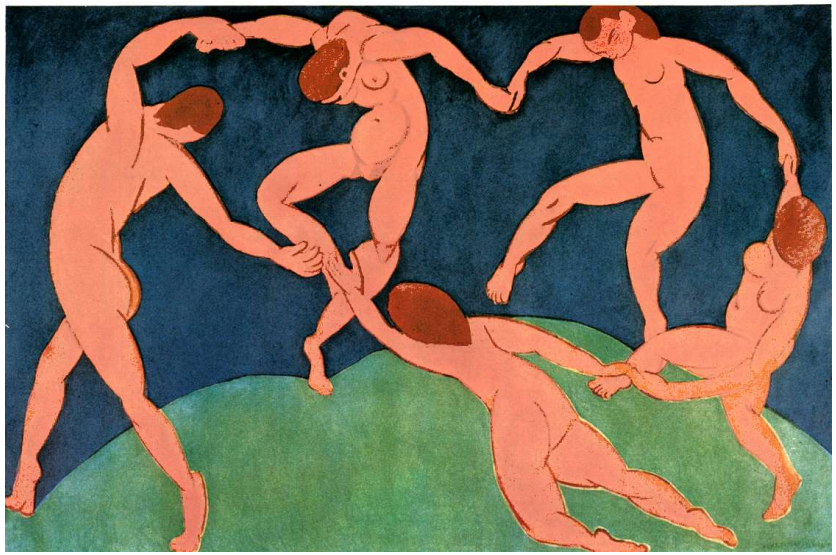


IONOMYCIN Ca salt

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

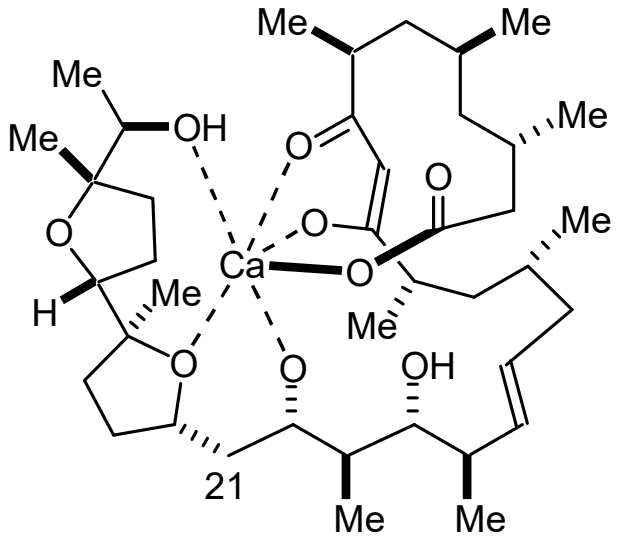
visual, emotional, mental

⇓

Artist's sketch

Psyche

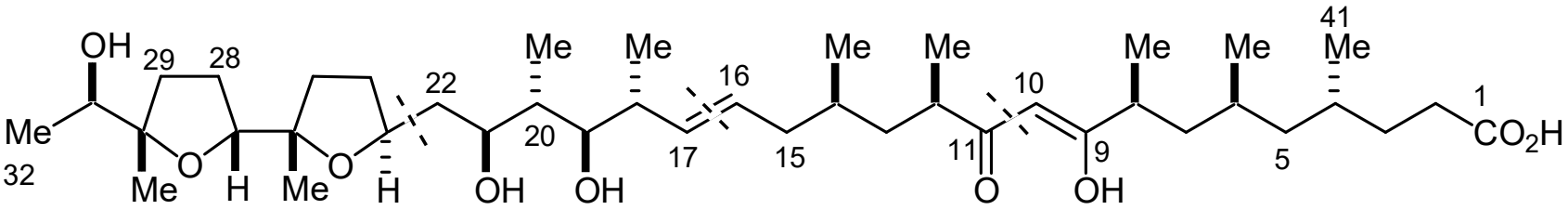
Imagery



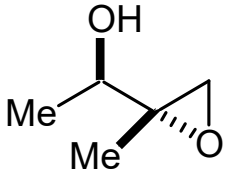
Logic

Knowledge

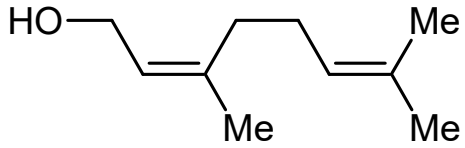
IONOMYCIN Ca salt



Ionomycin

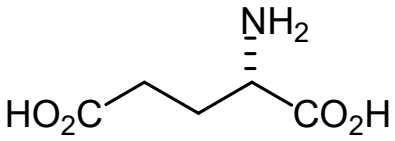


C_{29}-C_{32}

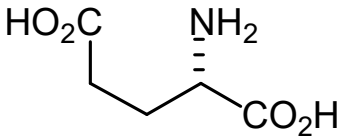


Geraniol

C_{23}-C_{28}



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



L-Glutamic acid

C_1-C_{41}

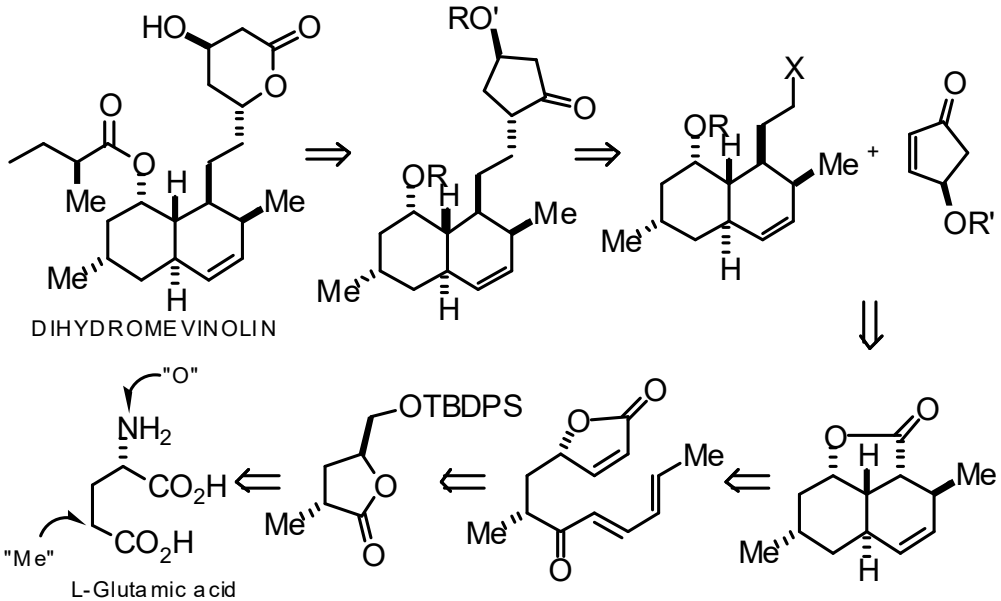
Hanessian, Cooke, Dehoff, Sakito *J. Am. Chem. Soc.* **1990**, *112*, 5276

Psyche, Logic and Imagery

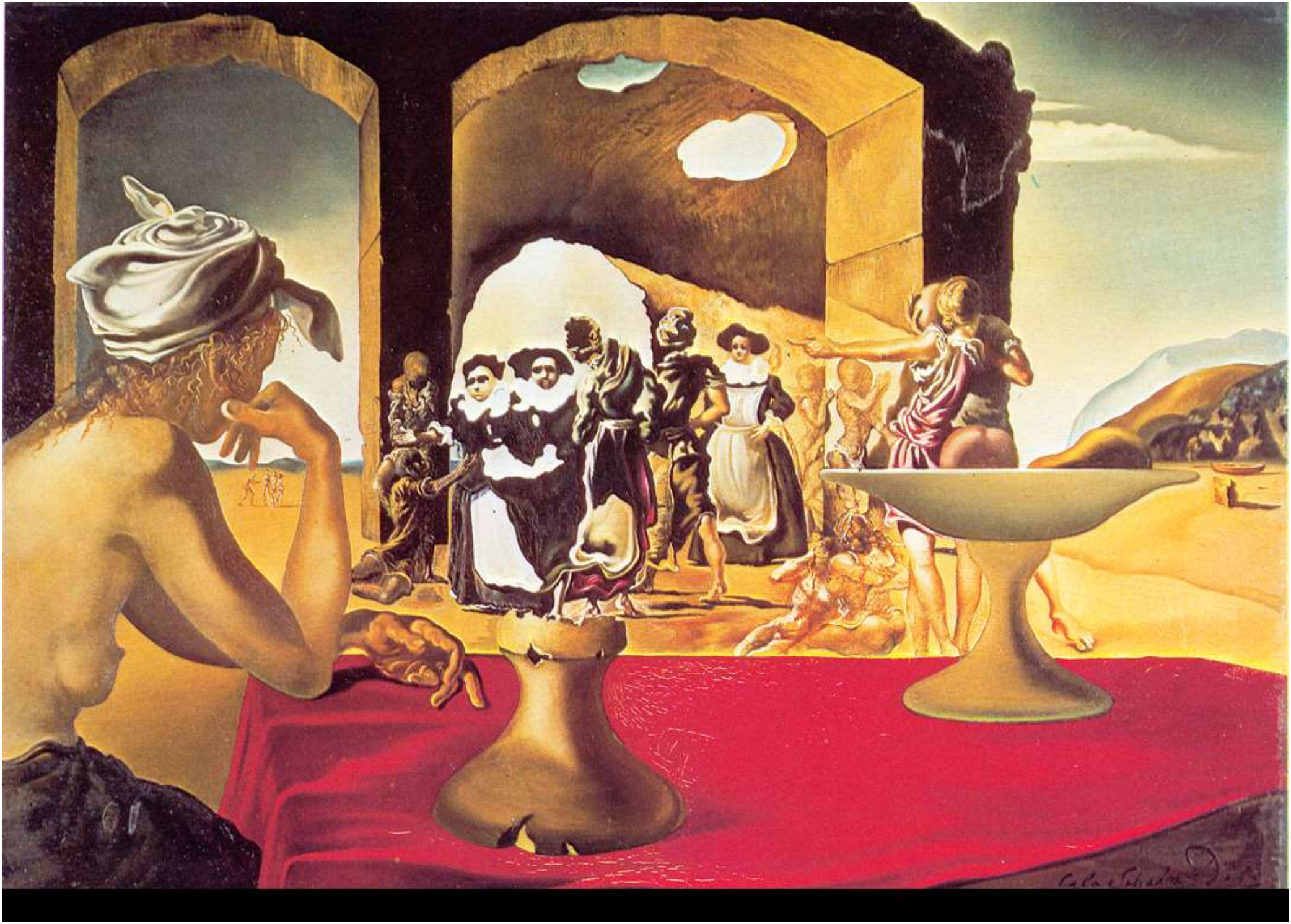
SEEING THROUGH THE MIND'S EYE

(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



THE CHIRON PROGRAM, V.5.0 2005

Hanessian Laboratory

Department of Chemistry

University of Montreal

AN INTERACTIVE COMPUTER PROGRAM FOR STEREOCHEMICAL ANALYSIS AND HEURISTIC SYNTHESIS PLANNING

APPLICATIONS IN ORGANIC SYNTHESIS, MEDICINAL CHEMISTRY, TEACHING, AND DATA BASE MANAGEMENT

Visit the website: http://osiris.corg.umontreal.ca

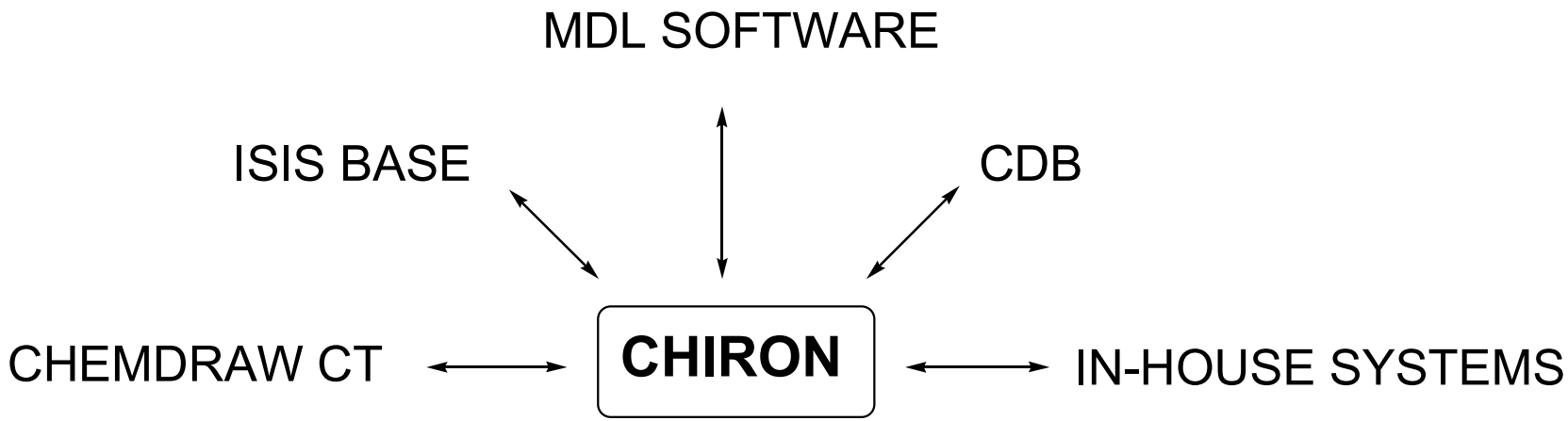
CHIRON PROGRAM OPTIONS

CARS-2D	Computer Assisted Reaction Scheme - Drawing in 2D
CASA	Computer Assisted Stereochemical Analysis
CAPS	Computer Assisted Precursor Selection
Interface	MDL, ChemDraw, ISIS, In-House Programs.

ACD PRECURSOR DATABASE

CLASSIFICATION	NUMBER OF PRECURSORS
Acyclic-3	4,907
Acyclic-4	3,949
Acyclic-5	3,112
Acyclic-6	1,963
Acyclic-7	8,619
Aromatic	55,781
Aromatic-condensed	3,984
Carbocyclic	1,369
Carbocyclic-branched	3,175
Carbocyclic-bridged	2,009
Combination	50,090
Heteroaromatic	13,615
Heteroaromatic-condensed	10,150
Heterocyclic	9,150
Macrocyclic	1,233
Nucleoside	1,102
Polyaromatic	6,298
Polycarbocyclic	951
Polyheteroaromatic	3,354
Polyheterocyclic	1,071
Steroid	6,202
	Total : 192,084

CHIRON INTERFACES



OTHER OPTIONS :

- SIMILARITY SEARCHING AND MATCHING
- AUTOMATIC RESHAPING
- DIVERSITY SEARCHING

CHIRON PROGRAM DATABASE

- **Commercial :** 11908, 817 Chiral
- **Synthetic :** 4330, 1800 Chiral
- **ACD :** 192,084
- **Med. Chem. Intermediates :** 601
- **Sources :** Aldrich, Fluka, Others
  Primary literature
  Organic Syntheses
  Organic Reactions
  Review Articles
- **Precursors :** Chiral Non-Racemic
  Racemic
  Achiral
  Other

CHIRON PROGRAM PRECURSOR CLASSES

CLASSES

Acyclic-3
Acyclic-4
Acyclic-5
Acyclic-6
Acyclic-7-Plus
Carbocyclic
Carbocyclic-Branched
Carbocyclic-Bridged
Polycarbocyclic
Heterocyclic
Polyheterocyclic
Aromatic
Polyaromatic
Aromatric-Condensed
Heteroaromatic
Polyheteroaromatic
Heteroaromatic-Condensed
Combination
Macrocyclic
Nucleoside
Steroid

FUNCTIONAL GROUPS

Acid-COOX/Lactone
Aldehyde
Ketone
Methyl-Ketone
Alcohol-OX
Diol-Polyol
Acetal-OO/SS
Methyl
Amine-NHX
Nitrile
Amide-CONHX/Lactam
Nitro/Nitroso
Ether
Epoxide
Halogen

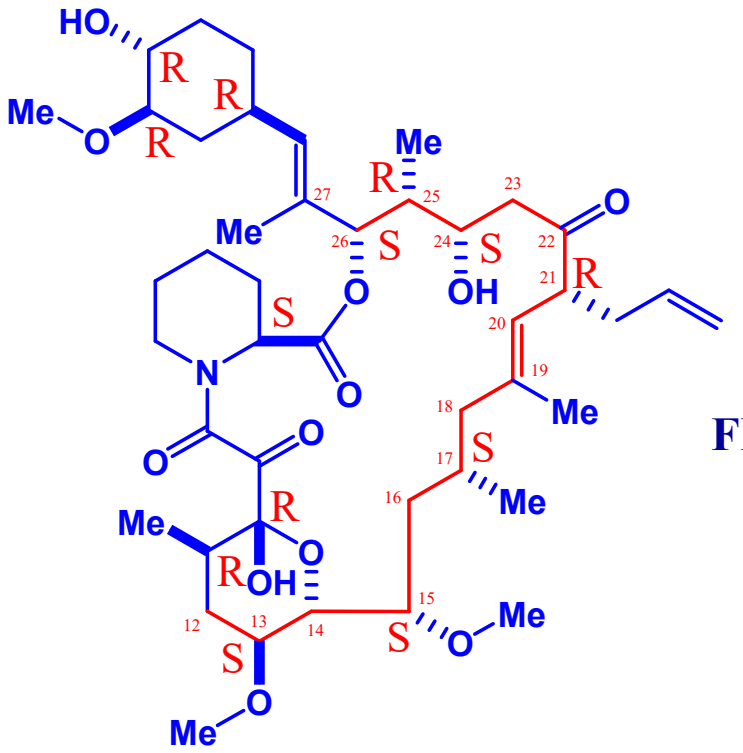
Alkene
Alkyne
Organometallic
Phosphonate
Phosphine
Thiol
Sulfide
Sulfoxide
Sulfone
CH_2
Phenyl
Phenol
Aniline
Toluene
Methylene

CHIRON PROGRAM PLATFORMS

- **Silicon Graphics (XCHIRON)**
- **MacIntosh Standalone (MacCHIRON)**
- **PC – Windows (ChemDraw or Isis_Draw needed)**

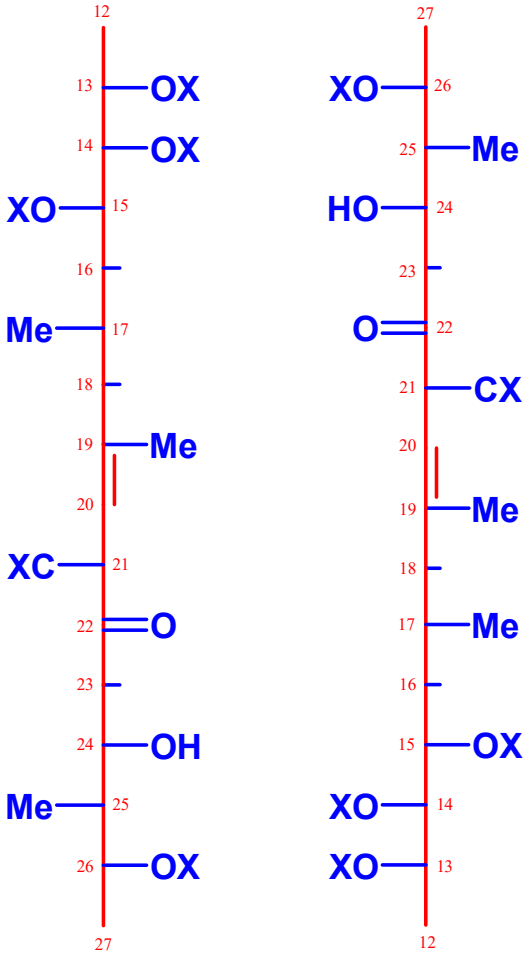
COMPUTER ASSISTED STEREOCHEMICAL ANALYSIS (CASA)

R/S notation



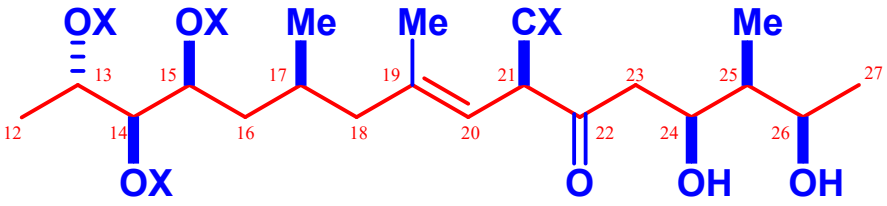
FK506

Fischer projections



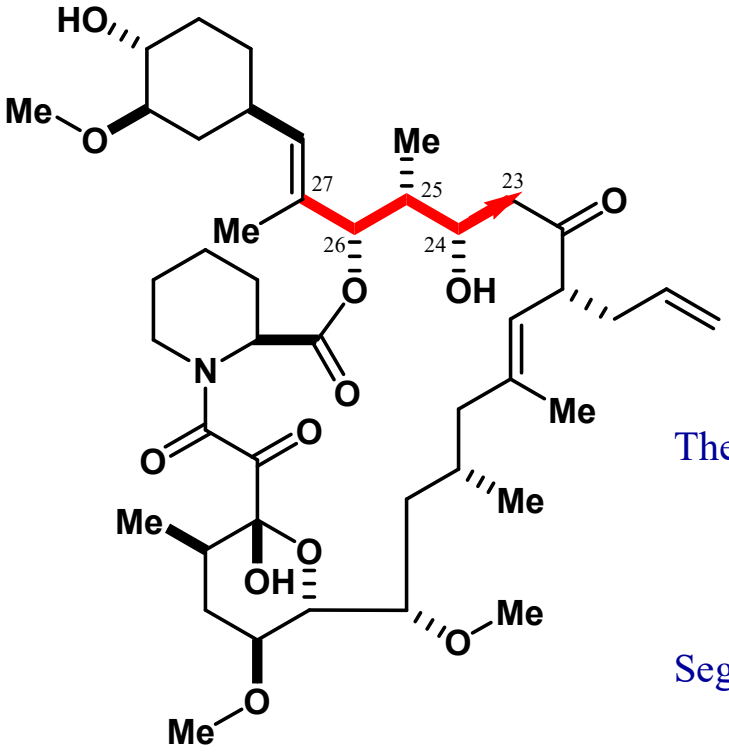
erythro / threo

Extended projection



anti / syn

CHIRAL SUBSTRUCTURES SEARCHING- DISCOVERY OF "IDENTICAL" SEGMENTS



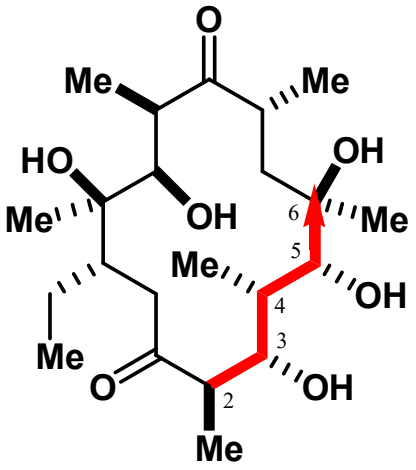
FK506

The C_{27}-C_{23} (FK506),

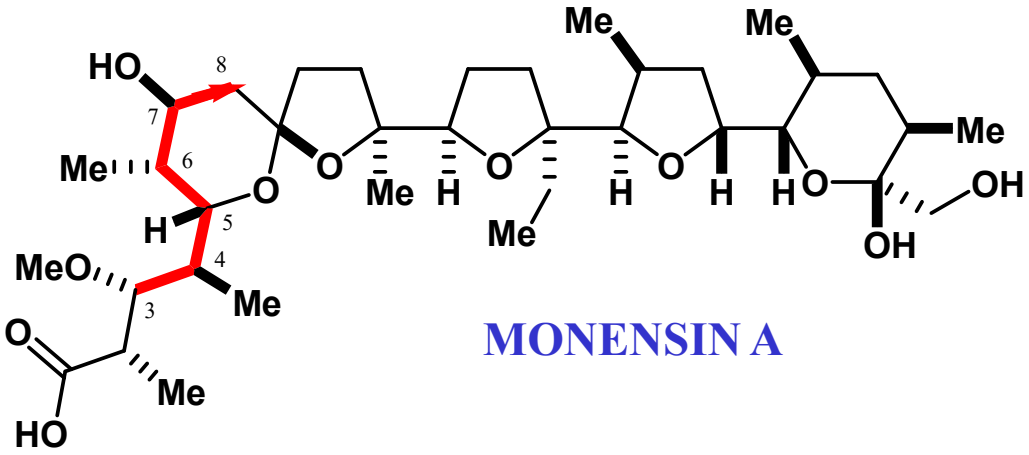
C_4-C_8 (Monensin A) and

C_2-C_6 (Erythronolide A)

Segments are identical (superimposable).

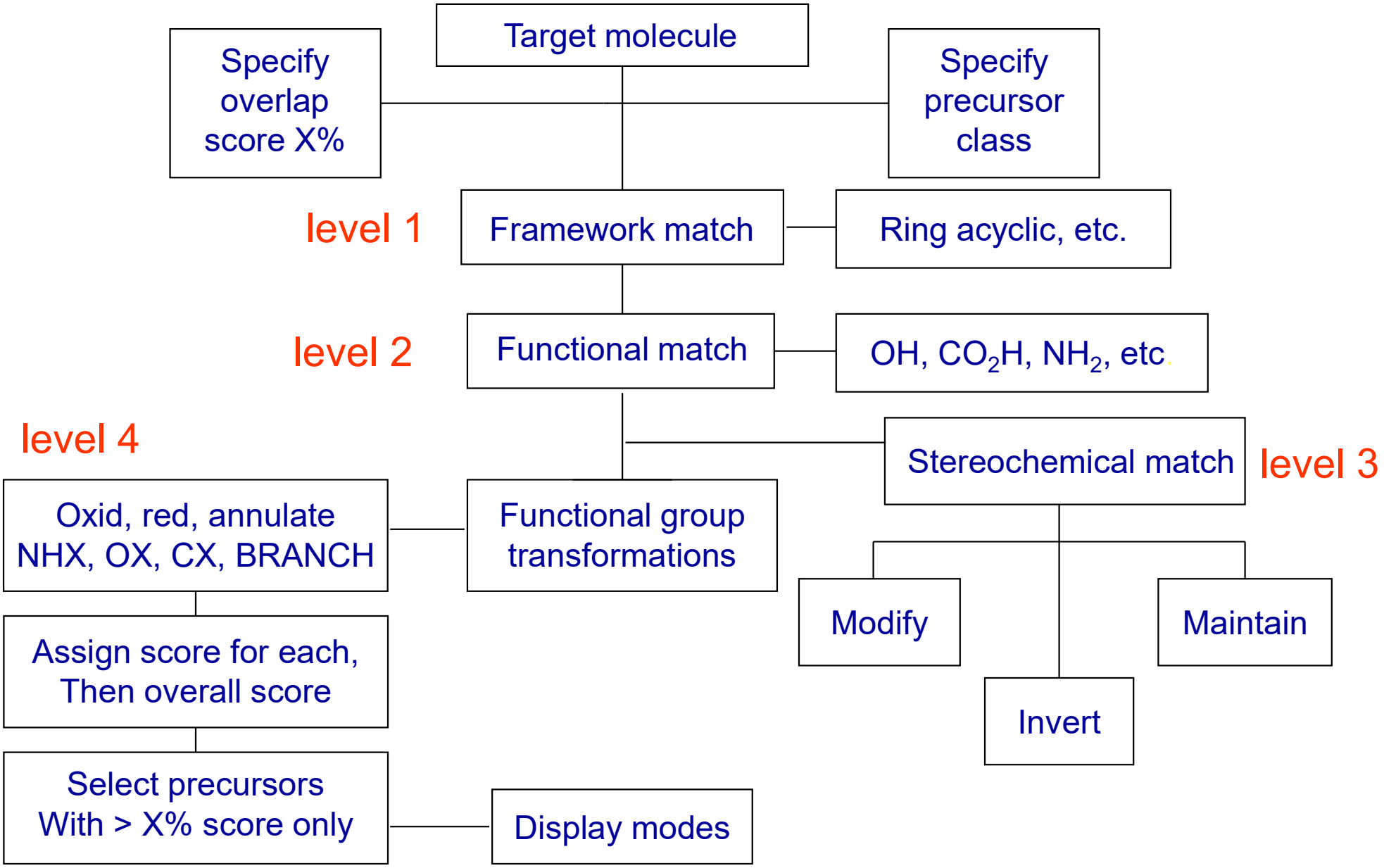


ERYTHRONOLIDE A

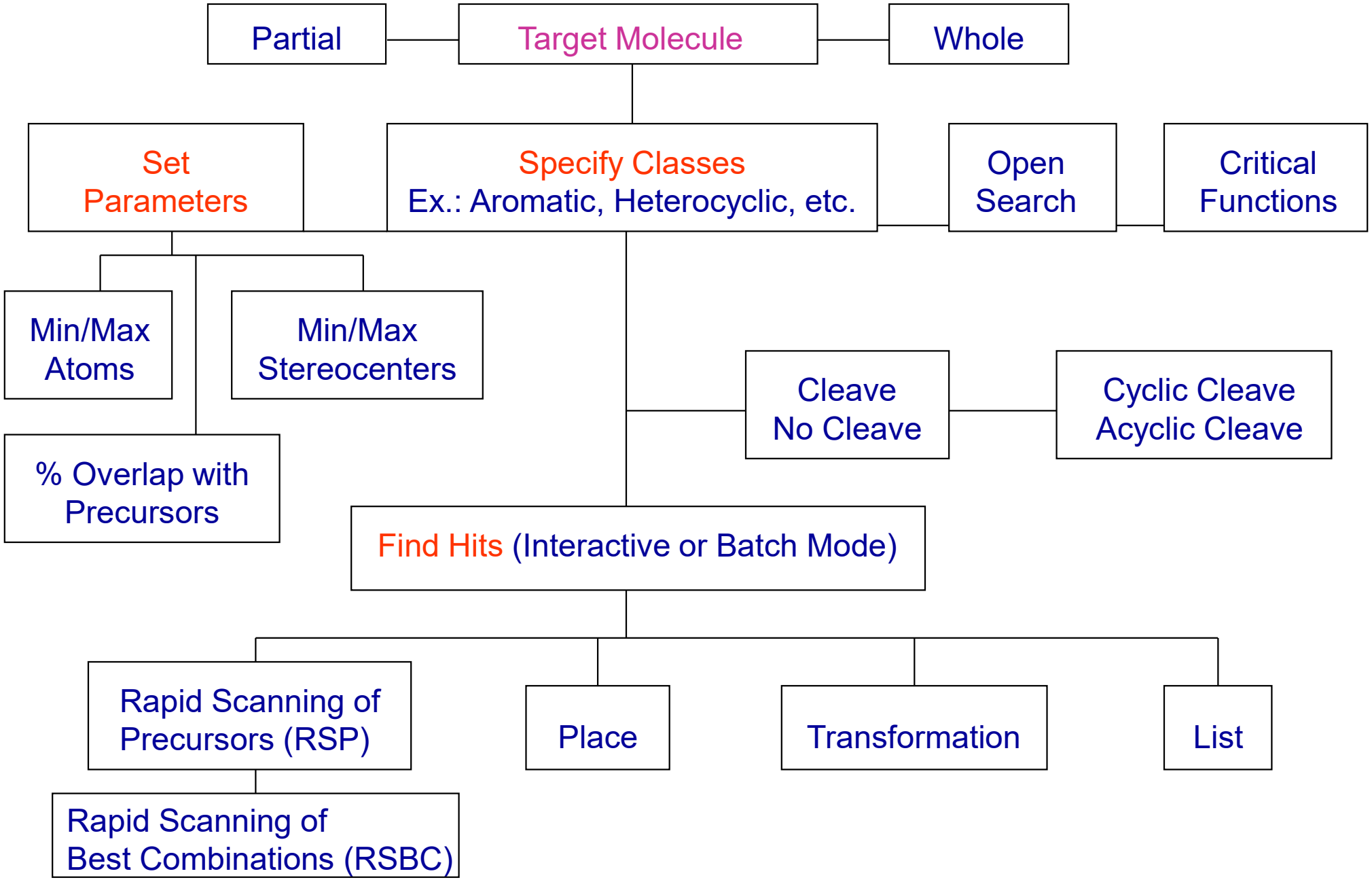


MONENSIN A

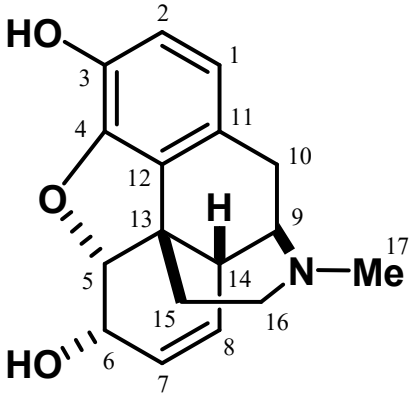
CAPS PRECURSOR SEARCHING PROTOCOL



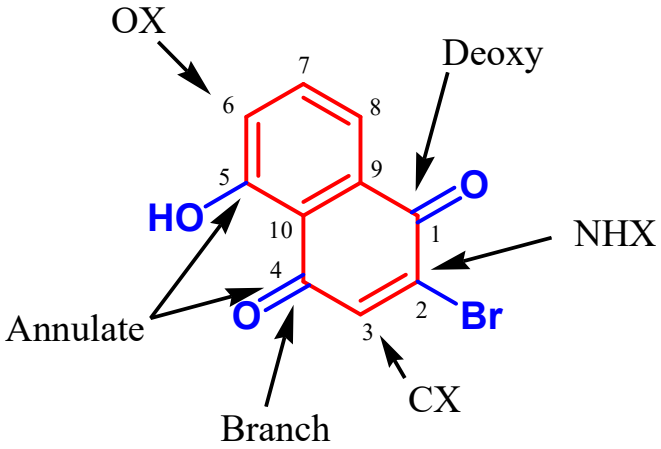
CAPS SEARCH CHOICES



COMPUTER ASSISTED PRECURSOR SELECTION (CAPS)



MORPHINE

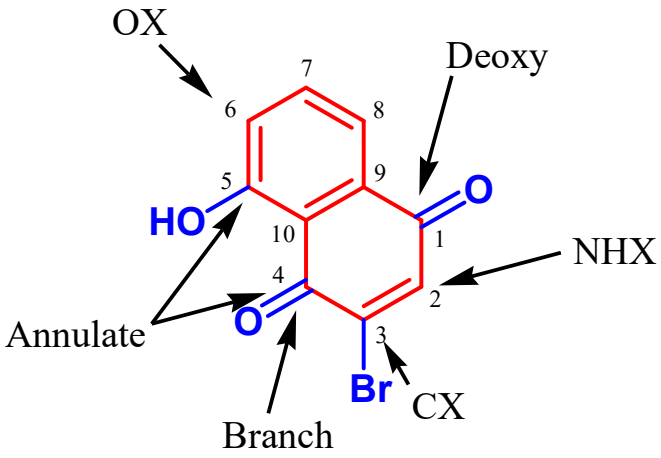


2-Bromo-5-hydroxy-1,4-naphthoquinone

J.R.Grundwell et al; T.L., 21, 4305 (1980)

DB=CHIRON, F=COMBINATION

61% # 83, P-M : 1-10/10-12

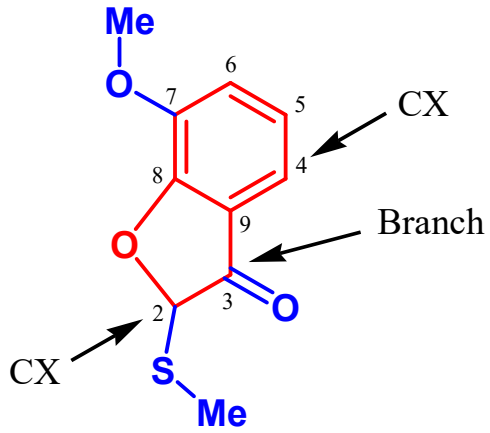


3-Bromo-5-hydroxy-1,4-naphthoquinone

J.R.Grundwell et al; T.L., 21, 4305 (1980)

DB=CHIRON, F=COMBINATION

61% # 84, P-M : 1-10/10-12



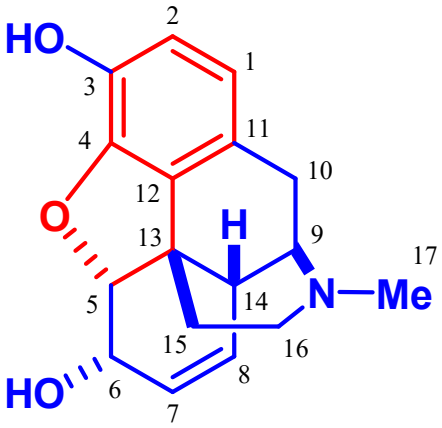
dl-7-Methoxy-2-(methylthio)-3(2H)-benzofuranone

D.T. Connor et al; J. Het. Chem., 18, 587 (1981)

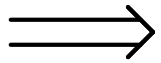
DB=CHIRON, F=COMBINATION

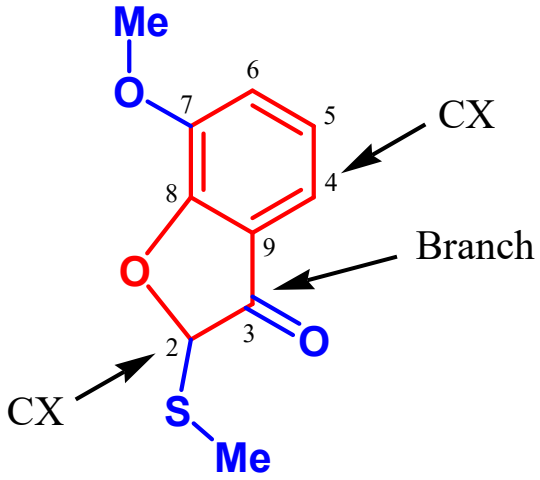
59% # 112, P-M : 1-19/9-12

COMPUTER ASSISTED PRECURSOR SELECTION (CAPS)



MORPHINE





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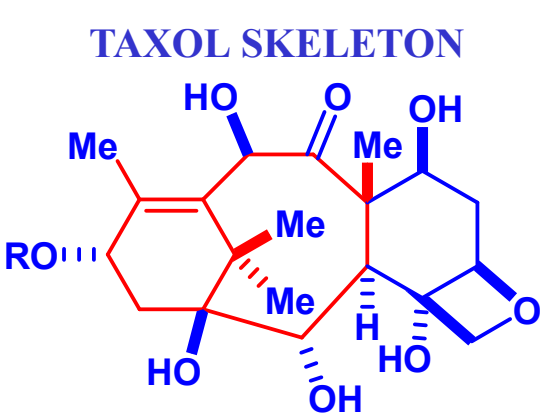
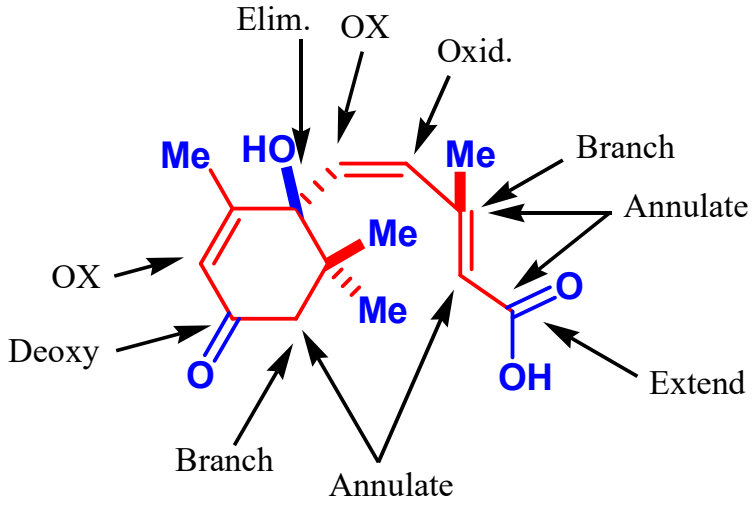
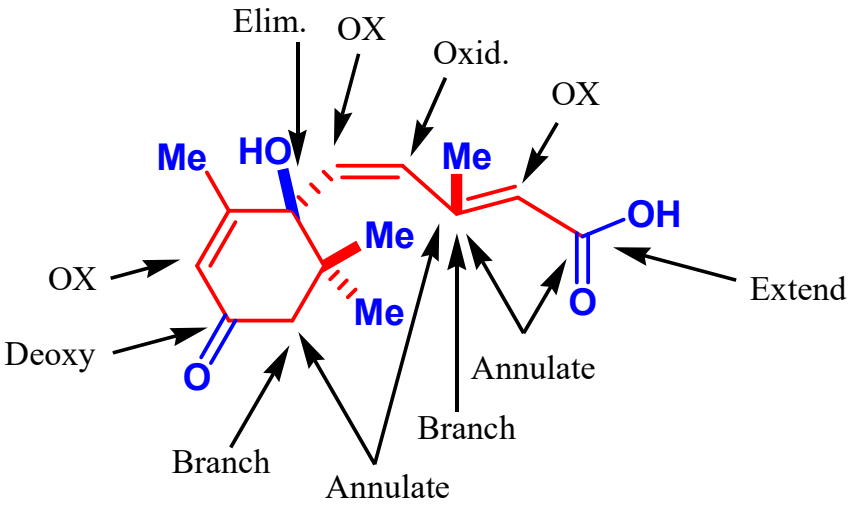




(+)-Abscisic acid
Flu. 0010, F=CARBOCYCLIC-BRANCHED
25% # 283, P-M : 1-6/17-19



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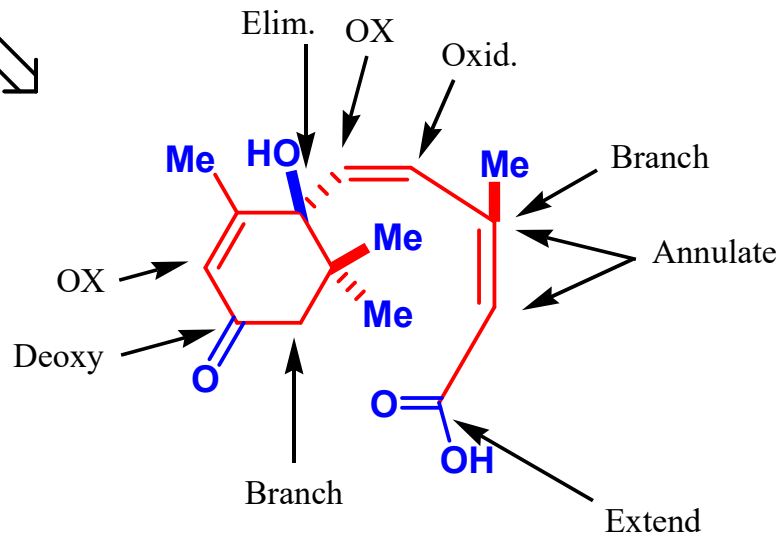
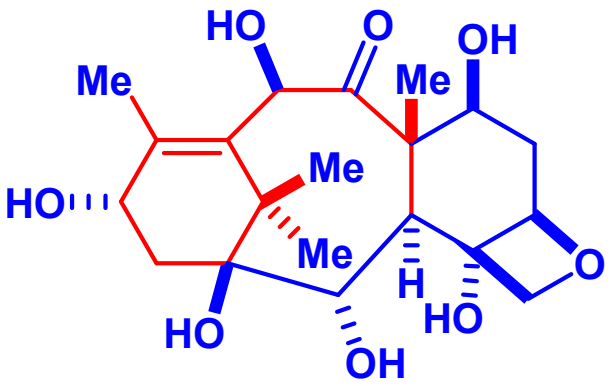
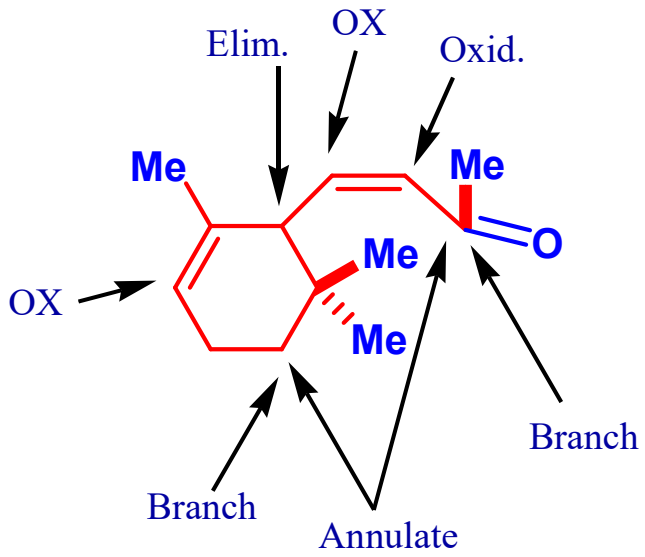


(+)-Abscisic acid
Flu. 0010, F=CARBOCYCLIC-BRANCHED
25% # 283, P-M : 1-6/17-19

COMPUTER ASSISTED PRECURSOR SELECTION (CAPS)



TAXOL SKELETON

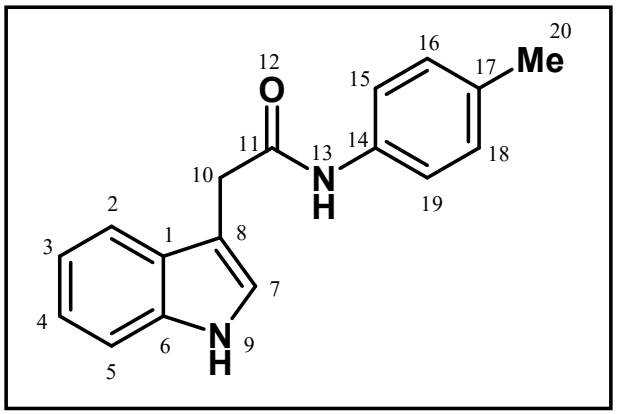


alpha-Ionone
Ald I-1,240-9, F=CARBOCYCLIC-BRANCHED
37% # 85, P-M : 7-16/13-18

CHEMICAL DIVERSITY OPTION

Search Parameters:

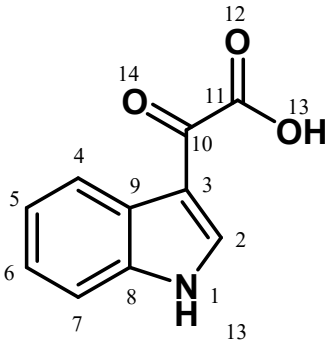
- Exact Match Option
- Amide Cleavage
- Critical Atoms

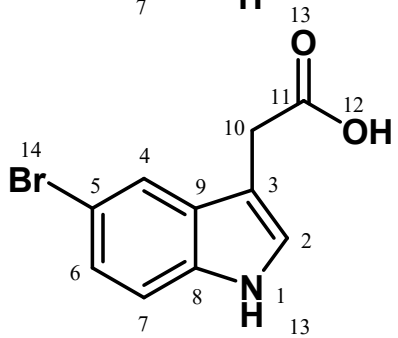


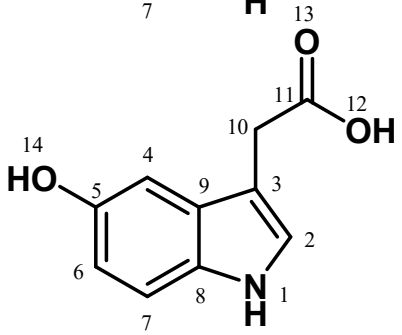
Databases:

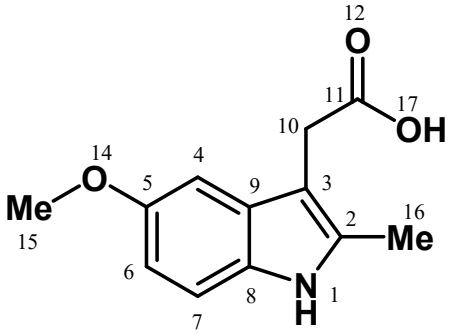
- Aldrich
- Chiron Program

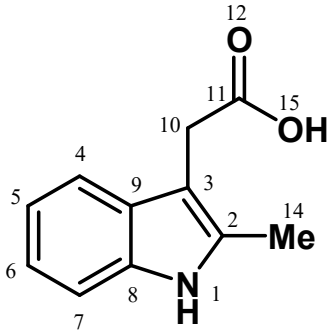
Heteroaromatic-Condensed (15 Hits)



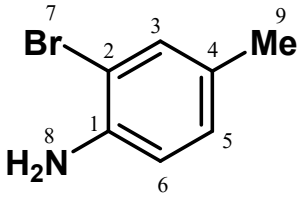


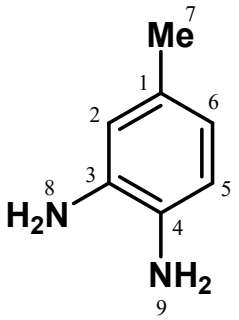


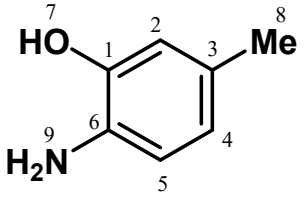


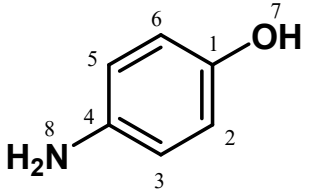


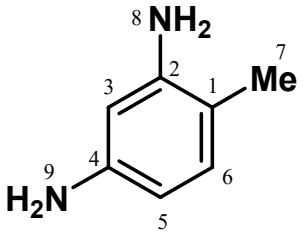
Aromatic (92 Hits)

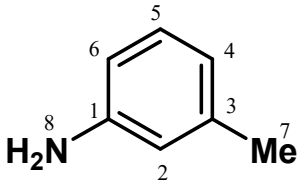






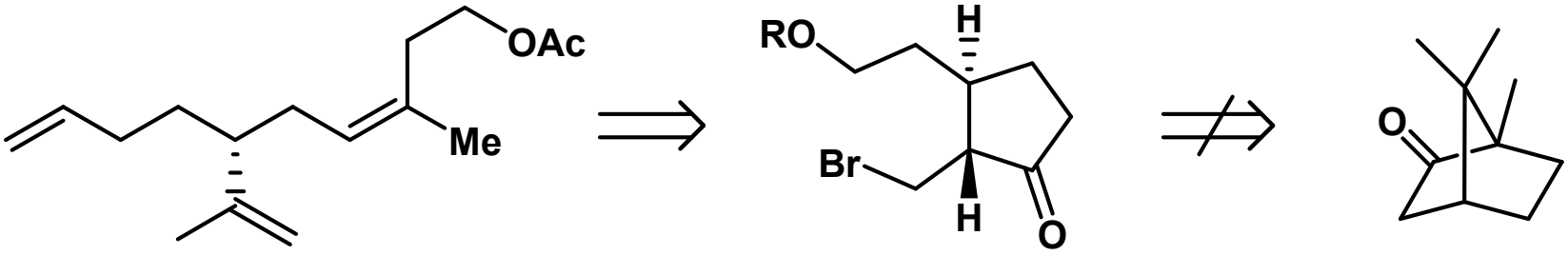






SOME LIMITATIONS

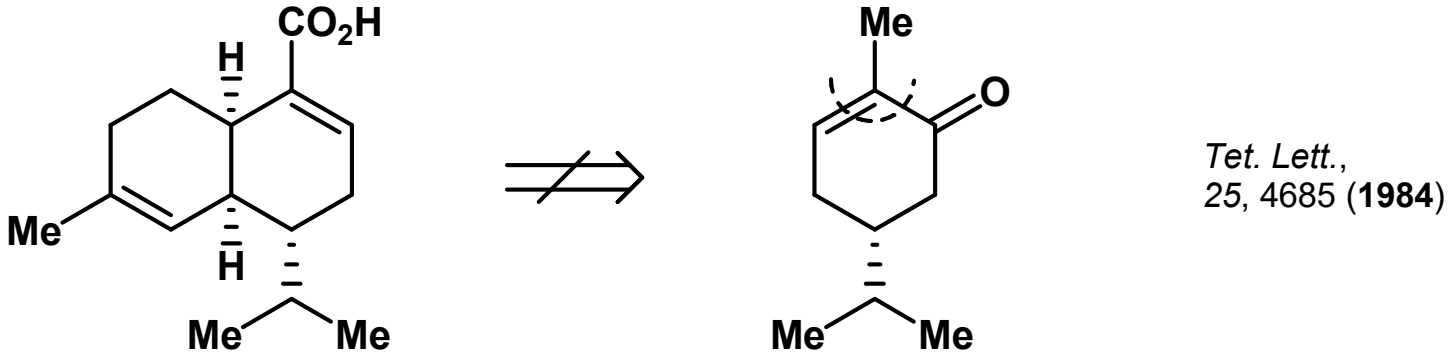
- **THE PROGRAM DOES NOT RECOGNIZE SKELETAL REARRANGEMENTS**



PHEROMONE **(+)-CAMPHOR**

Can. J. Chem., *63*, 3182 (**1985**)

- **THE PROGRAM WILL NOT CLEAVE TWICE (EXCISION)**



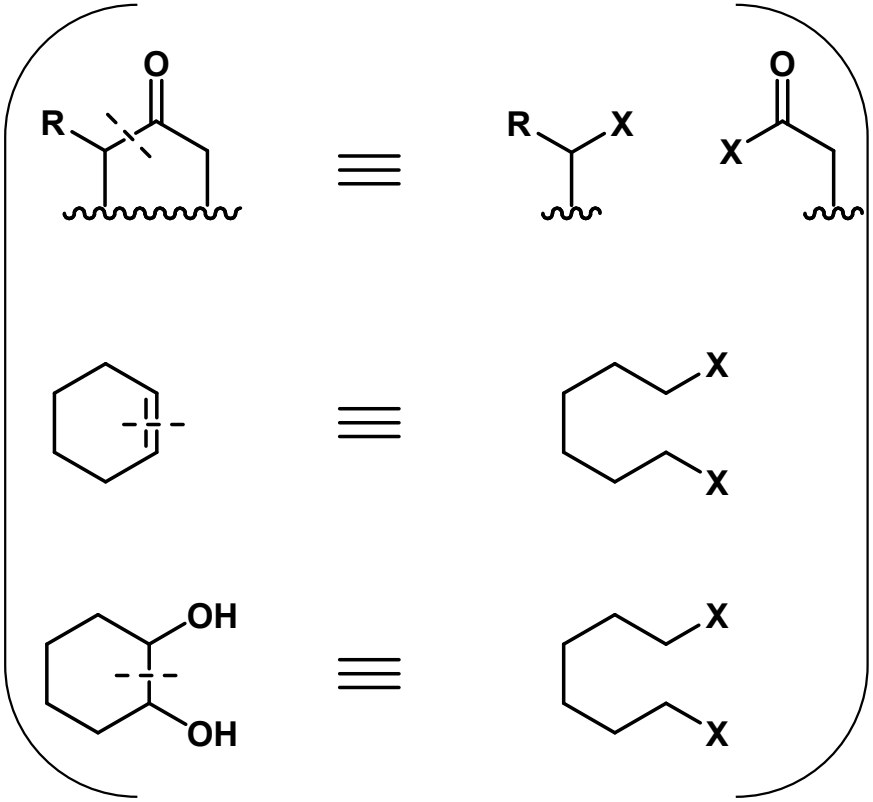
SCLEROSPORIN **(*R*)-CARVONE**

Tet. Lett., *25*, 4685 (**1984**)

- **THE PROGRAM DOES NOT TAKE PROTECTIVE GROUPS INTO ACCOUNT**

CLEAVED AND RESHAPED PRECURSORS : A NEW DIMENSION IN HEURISTIC ANALYSIS

Cyclic match

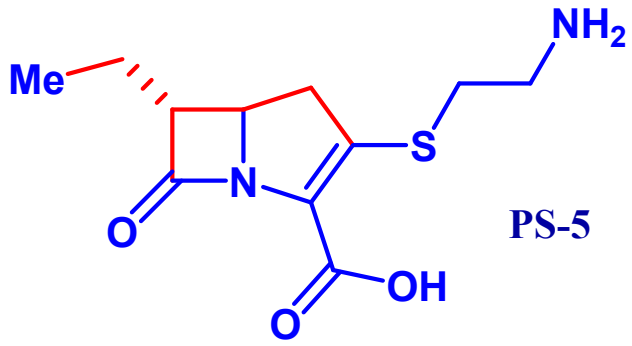


CHIRON Program

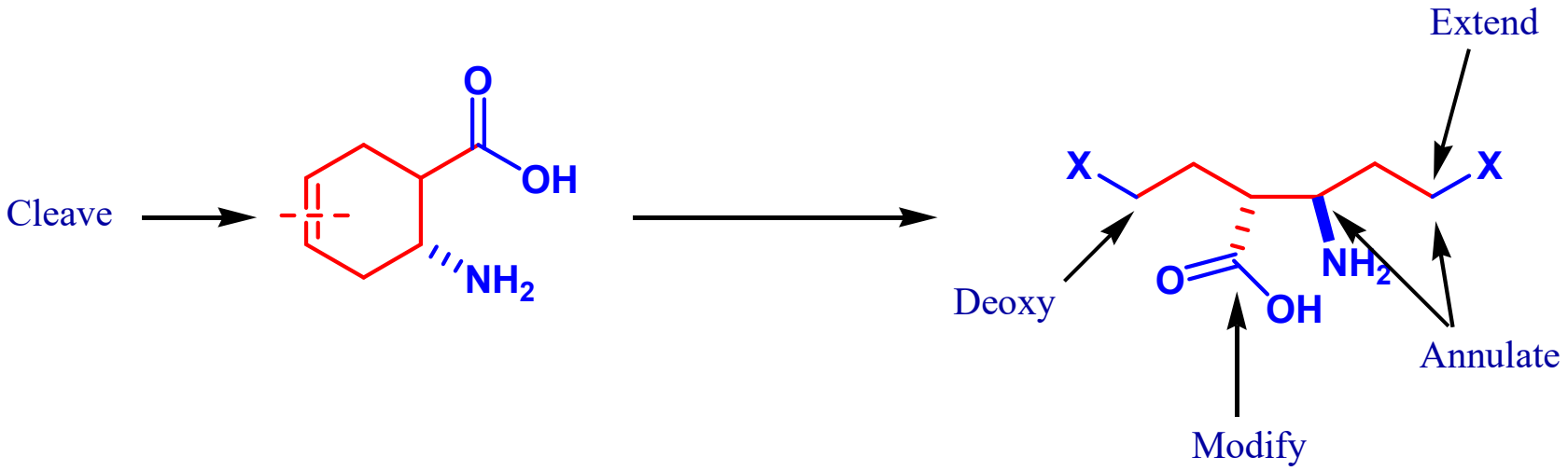
1. Recognizes the relationship of a cyclic ketone, diol, alkene to acyclic equivalents

2. Does cleavage and reshaping on target substructure

CLEAVED AND RESHAPED PRECURSORS : A NEW DIMENSION IN HEURISTIC ANALYSIS

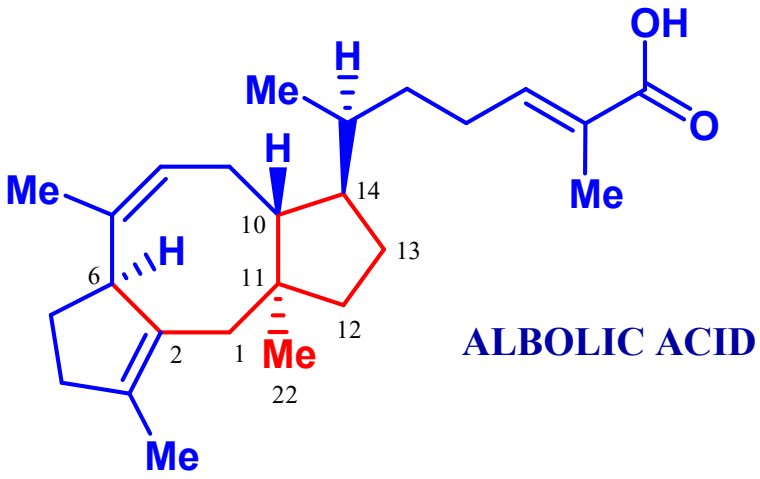


PS-5

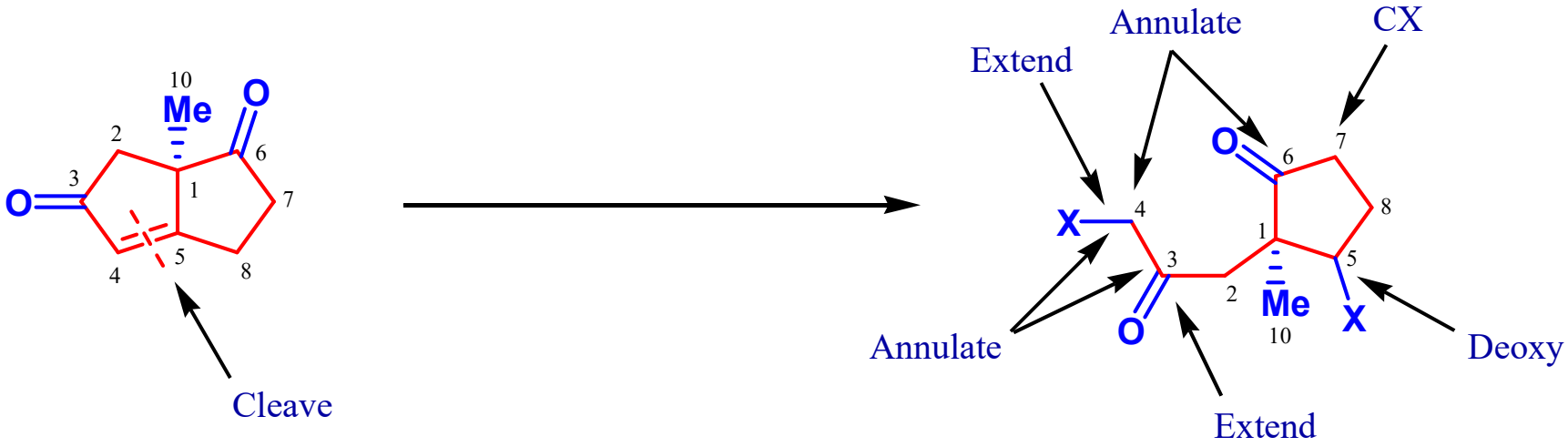


(1R,2R)-2-Amino-4-cyclohexene-1-carboxylic acid [M]
S. Kobayashi et al., T.L., 25, 2557 (1984)
81% # 11, P-M : 7-7/6-8 (Cleaved)

CLEAVED AND RESHAPED PRECURSORS : A NEW DIMENSION IN HEURISTIC ANALYSIS

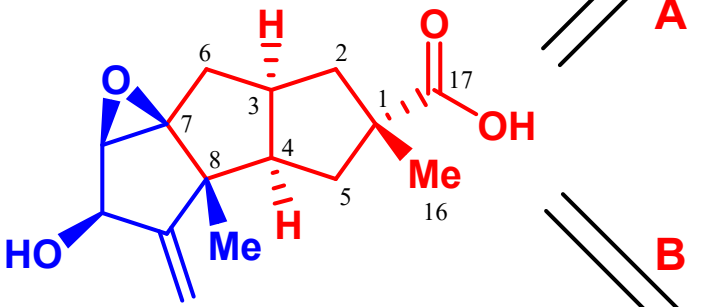


ALBOLIC ACID



(R)-5-Methylbicyclo[3.3.0]oct-1-ene-3,6-dione
D.W. Brooks et al., JOC, 52, 2036, 1987
F=POLYCARBOCYCLIC
54% # 106, P-M : 10-22/8-13 (Cleaved)

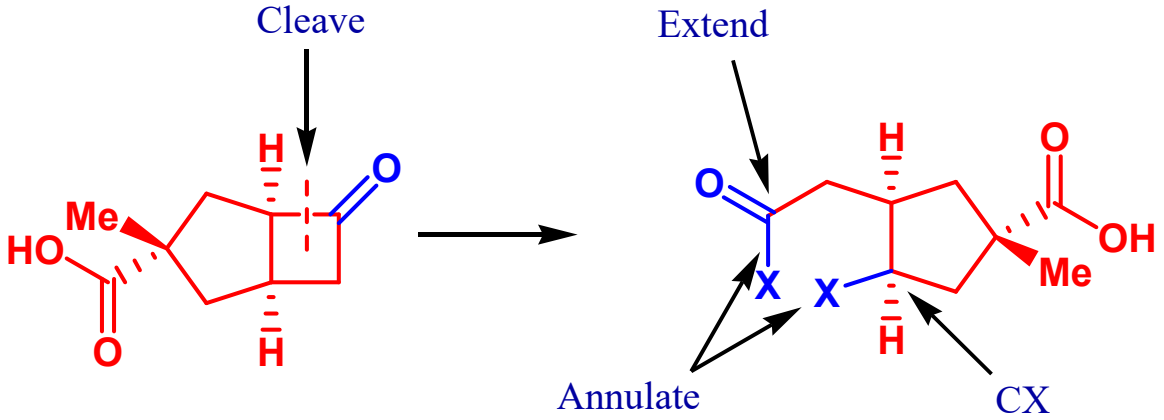
CLEAVED AND RESHAPED PRECURSORS : A NEW DIMENSION IN HEURISTIC ANALYSIS



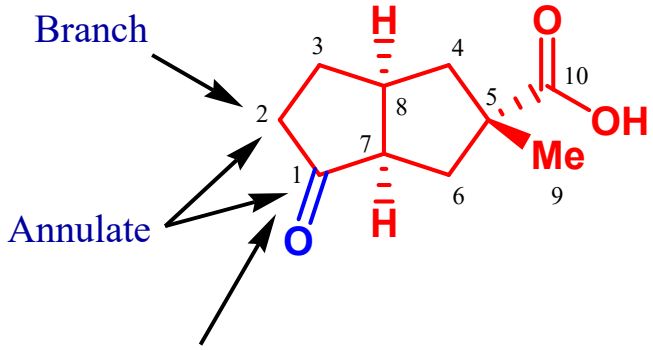
HIRSUTIC ACID

A

B

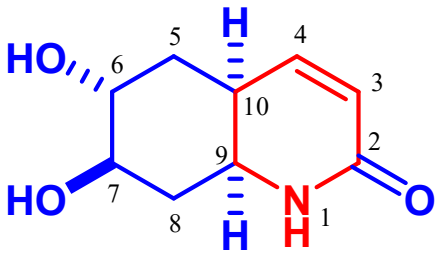


(4S,6R,7R)-Bicyclo[3.2.0]-4-carboxy-4-methyl-1-heptanone
A.E. Greene, JOC, 50, 3957 (1985)
F=POLYCARBOCYCLIC
69% # 16, P-M : 1-7/9-17 (Cleaved and reshaped)

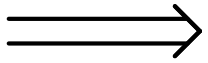


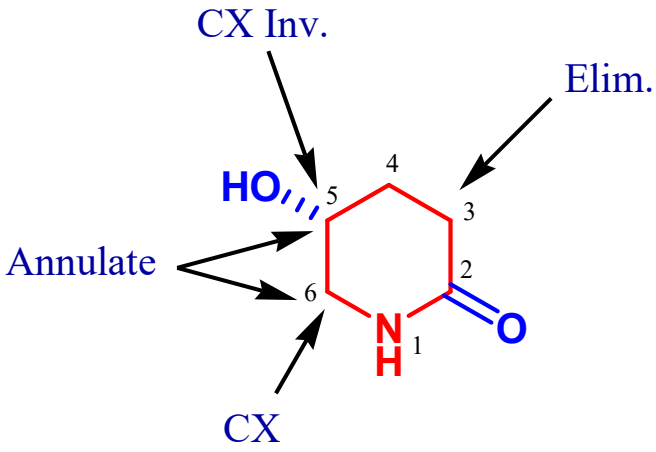
(5S,7S,8R)-Bicyclo[3.3.0]-5-carboxy-5-methyl-1-octanone
A.E. Greene, JOC, 50, 3957 (1985)
F=POLYCARBOCYCLIC
84% # 25, P-M : 9-16/10-17 (Greene's choice)

MAN, MACHINE AND HEURISTICS IN SYNTHESIS PLANNING



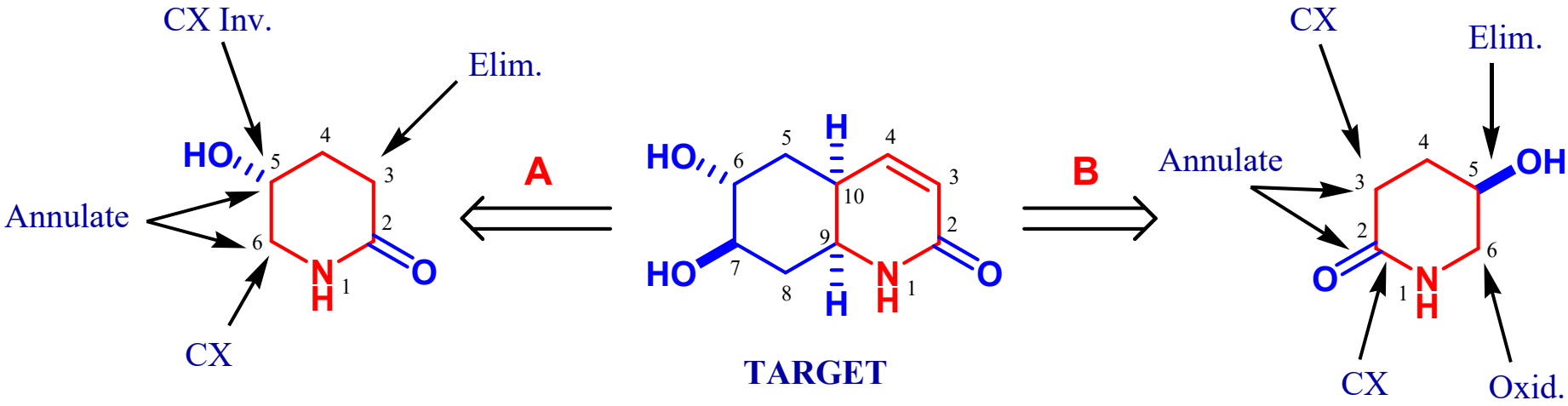
TARGET





(R)-5-Hydroxy-2-piperidone
C.C. Deanne et al., JCS Chem. Commun., 813 (1969)
DB=CHIRON, F=HETEROCYCLIC
28% # 44, P-M : 1-1/6-9

MAN, MACHINE AND HEURISTICS IN SYNTHESIS PLANNING

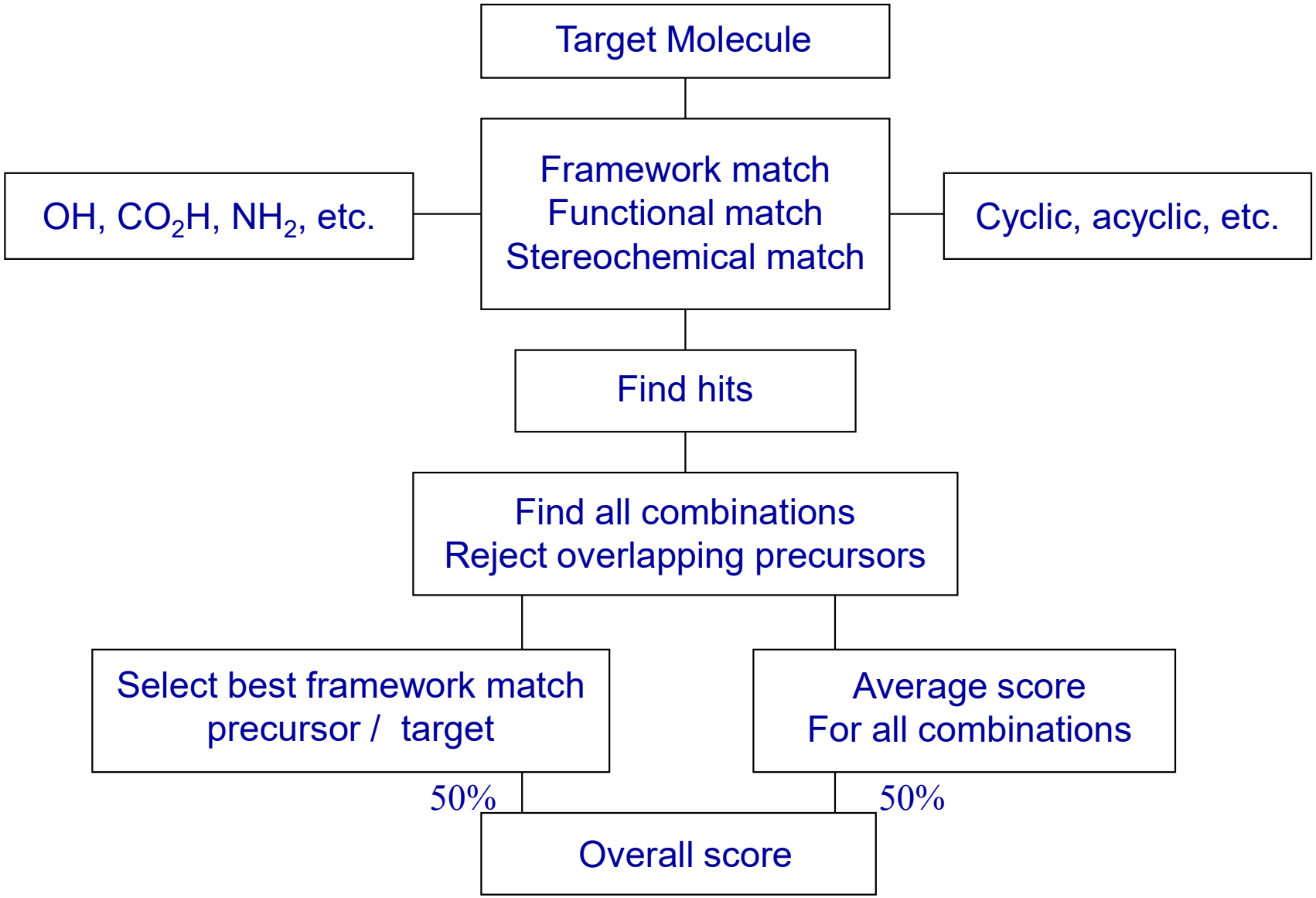


(R)-5-Hydroxy-2-piperidone
C.C. Deanne et al., JCS Chem. Commun., 813 (1969)
DB=CHIRON, F=HETEROCYCLIC
28% # 44, P-M : 1-1/6-9

(R)-5-Hydroxy-2-piperidone
C.C. Deanne et al., JCS Chem. Commun., 813 (1969)
DB=CHIRON, F=HETEROCYCLIC
26% # 44, P-M : 1-1/6-2

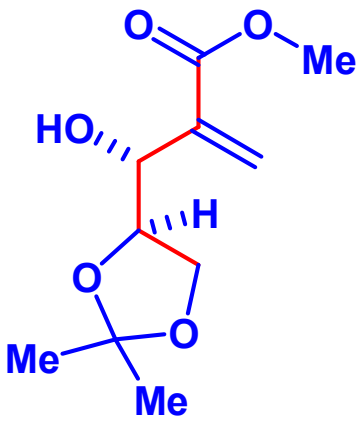
WHAT A DIFFERENCE A "FLIP" MAKES

BEST COMBINATIONS

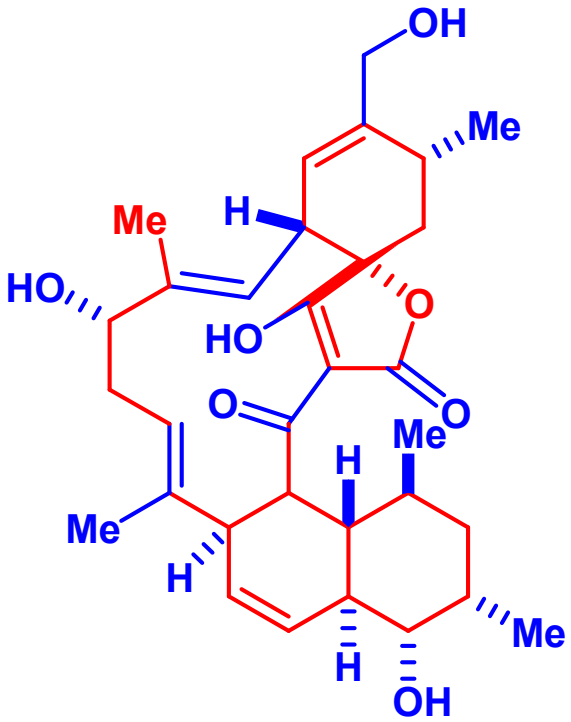


BEST COMBINATIONS

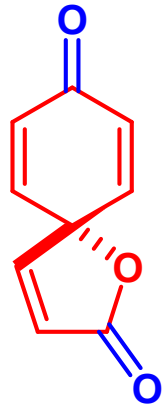
Hit # 1
Overall Score=66%
Overlap Index=83%
Average Precursor Score=68%



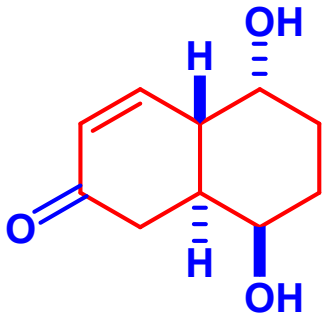
DB=CHIRON, F=ACYCLIC-5 # 216
Precursor List # 2, Score=79%
C. Benezra et al; JOC, 50, 157 (1985)



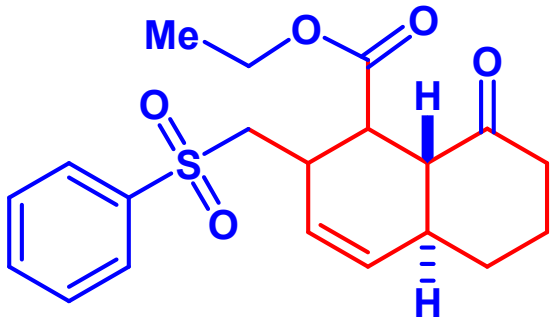
KIJANOLIDE



DB=CHIRON, F=COMBINATION # 499
Precursor List # 25, Score=62%
A. McKillop et al; Synlett, 201 (1992)



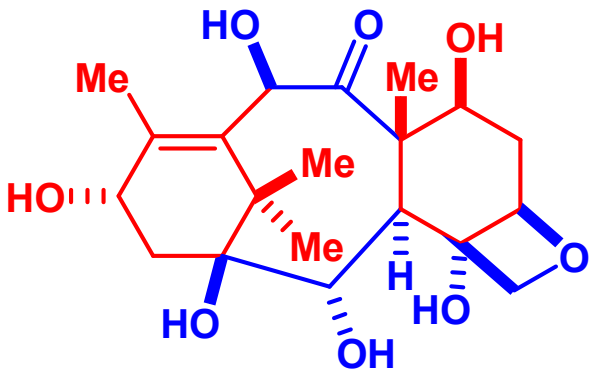
DB=CHIRON, F=POLYCARBOCYCLIC # 367
Precursor List # 21, Score=63%
C.T. Hsu et al; JACS, 105, 593 (1983)



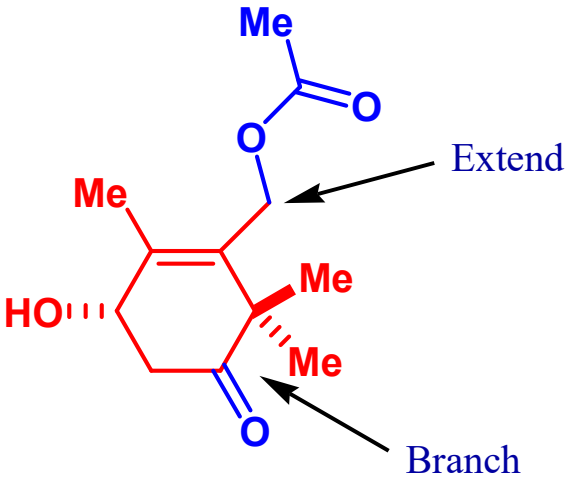
DB=CHIRON, F=POLYCARBOCYCLIC # 531
Precursor List # 8, Score=70%
J.P. Marino et al; JACS, 110, 7916 (1988)

BEST COMBINATIONS

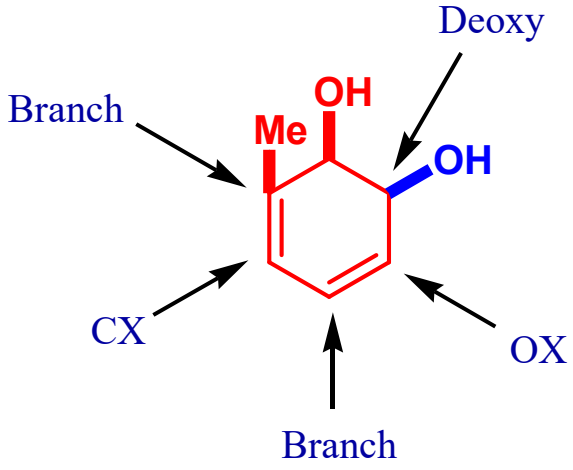
Hit # 1
Overall Score=69%
Overlap Index=81%
Average Precursor Score=70%



TAXOL

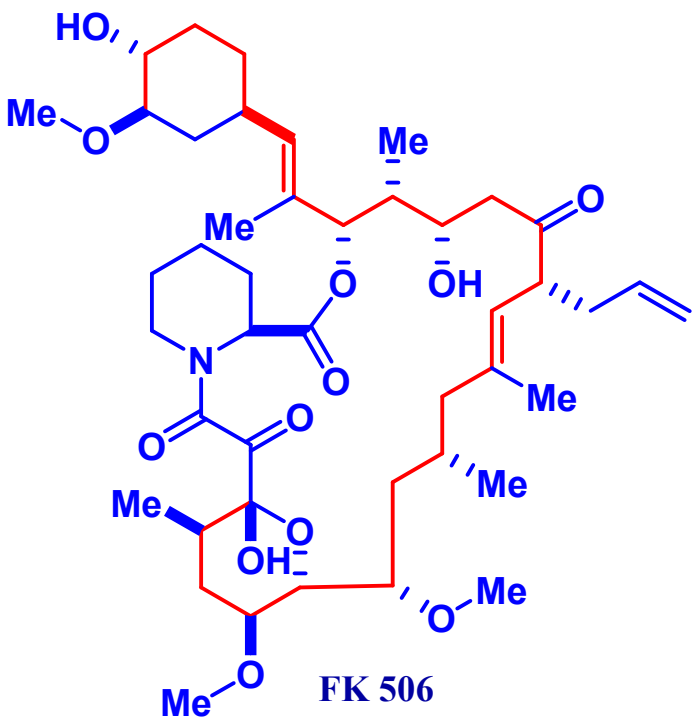


dl-2,2,4-Trimethyl-3-acetoxymethyl-5-hydroxy-3-cyclohexenone
K.C. Nicolaou et al; JCS Chem. COmmun., 1117 (1992)
DB=CHIRON, F=CARBOCYCLIC-BRANCHED
86% # 570, P-M : 7-17/10-10

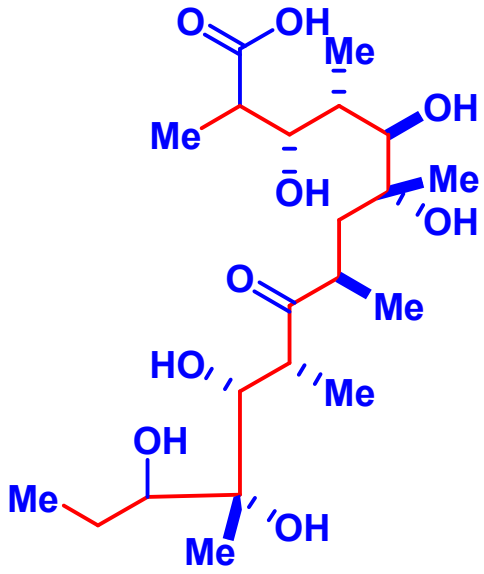


dl-cis-3-Methyl-3,5-cyclohexadiene-1,2-diol
Aldrich 31,982-1
DB=COMMERCIAL, F=CARBOCYCLIC-BRANCHED
54% # 47, P-M : 9-19/6-5 (Rac. Inv.)

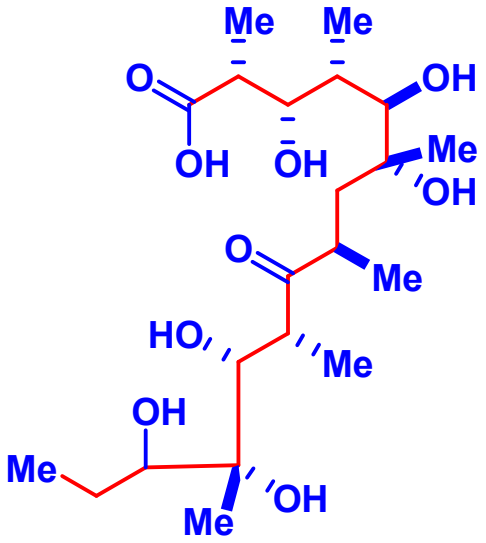
MATCH OPTION



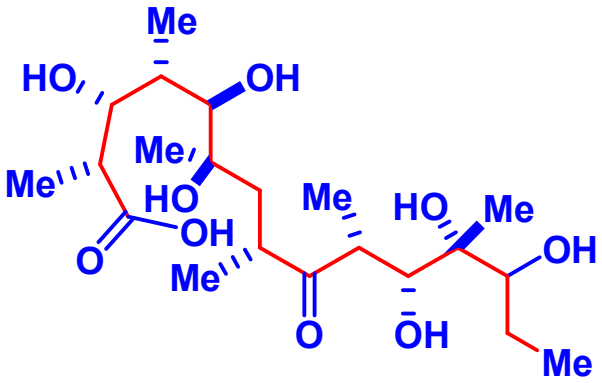
FK 506



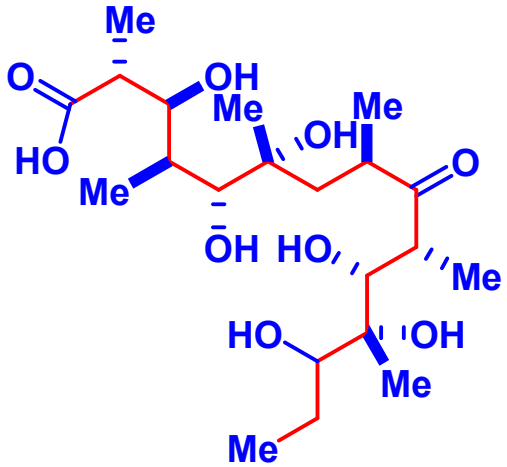
ERYTHRONOLIDE A SECO ACID MATCH
DB=USER, F=WORKING_FILE
Match # 5, P-M : 1-35/15-12



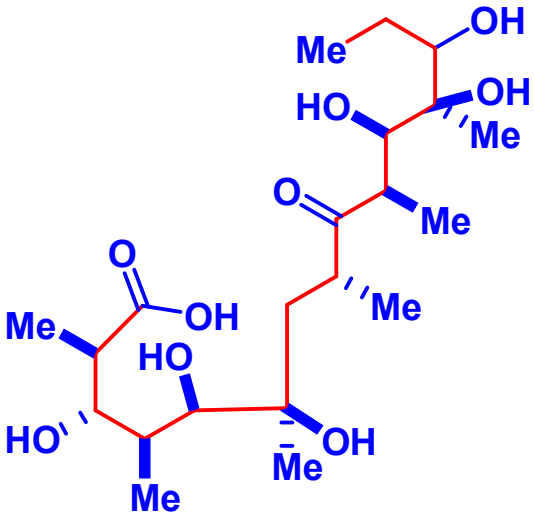
ERYTHRONOLIDE A SECO ACID MATCH
DB=USER, F=WORKING_FILE
Match # 5, P-M : 1-26/15-12



ERYTHRONOLIDE A SECO ACID MATCH
DB=USER, F=WORKING_FILE
Match # 5, P-M : 1-30/15-48

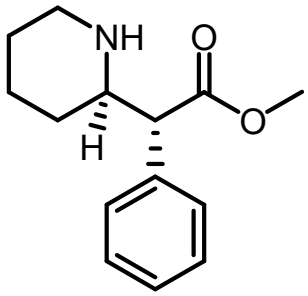


ERYTHRONOLIDE A SECO ACID MATCH
DB=USER, F=WORKING_FILE
Match # 5, P-M : 1-30/15-16



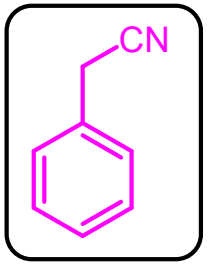
ERYTHRONOLIDE A SECO ACID MATCH
DB=USER, F=WORKING_FILE
Match # 5, P-M :1-10/15-24

CHIRON ANALYSIS OF EXISTING DRUGS

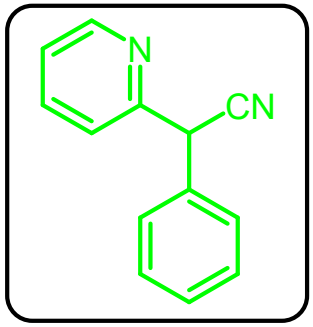


Dexmethylphenidate

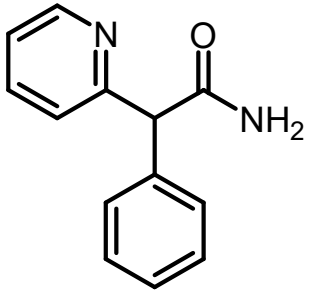
Psychostimulant



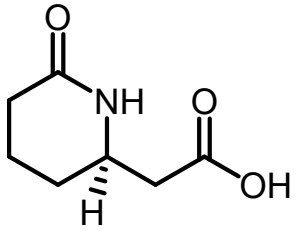
Aldrich
Score=85%



ACD Combination
Score=90%



ACD combination
Score=90%

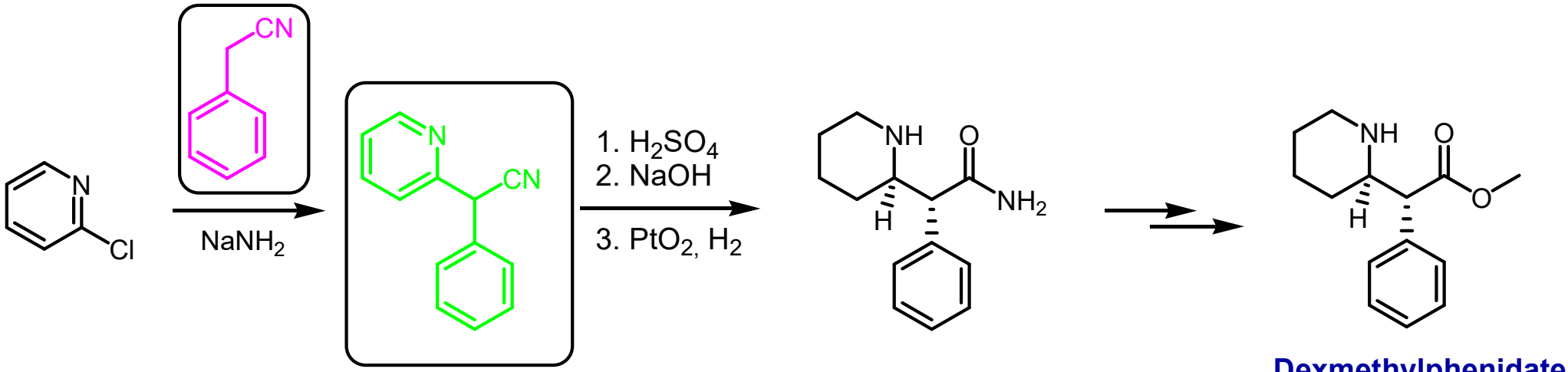


Chiron Heterocyclic
Nagao, Y *JOC* **1990**, 1148
Score=86%

Chiron Program search (all databases, min. score = 75%) : best precursors

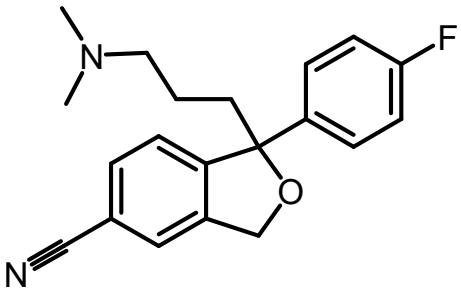
Reported synthesis :

Patent: Khetani, V.; Konnecke, W.; Ge, C. U.S., 6359139, 19 March 2002



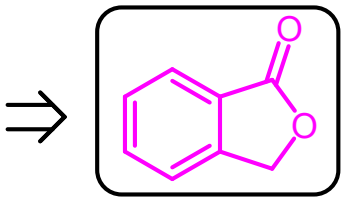
Dexmethylphenidate

CHIRON ANALYSIS OF EXISTING DRUGS

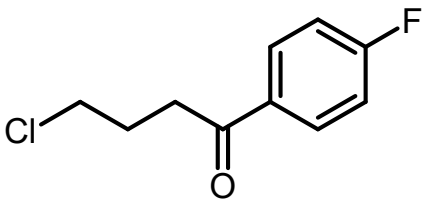


Escitalopram

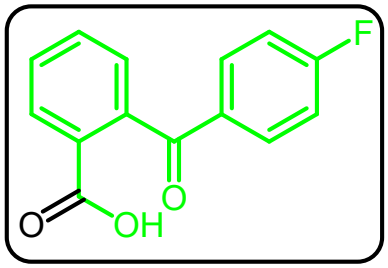
Antidepressant



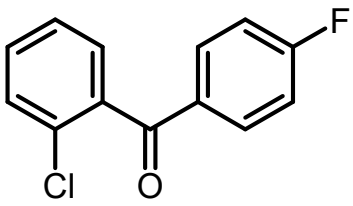
Fluka
Score=87%



Aldrich
Score=90%



Aldrich
Score=84%

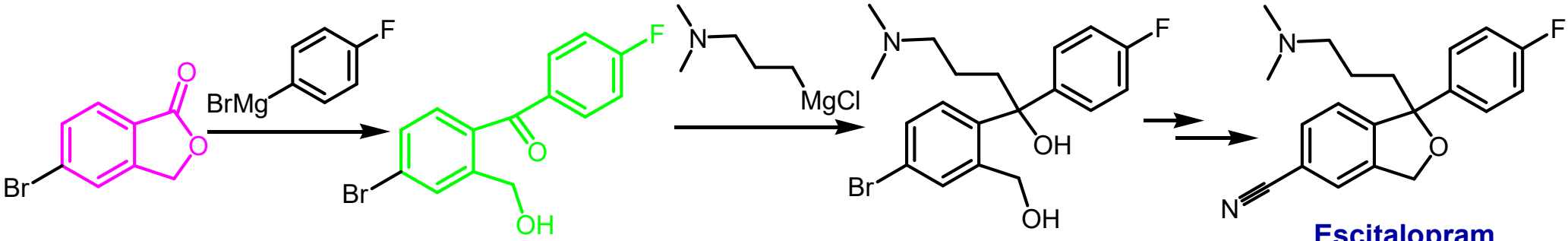


Aldrich
Score=76%

Chiron Program search (all databases, min. score = 75%) : best precursors

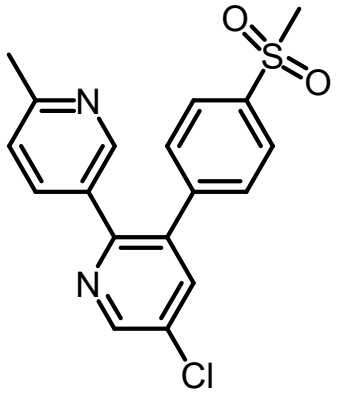
Reported synthesis :

Patent: Petersen, H.; Bregnedal, P.; Bogeso, K.P. PCT Int. Appl., 9819513, 14 May 1998



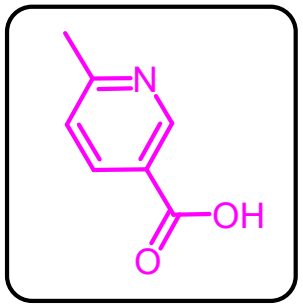
Escitalopram

CHIRON ANALYSIS OF EXISTING DRUGS

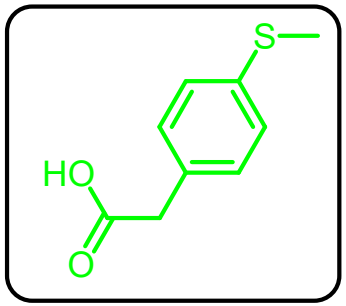


Etoricoxib

Antiarthritic, analgesic



Aldrich
Score=72%

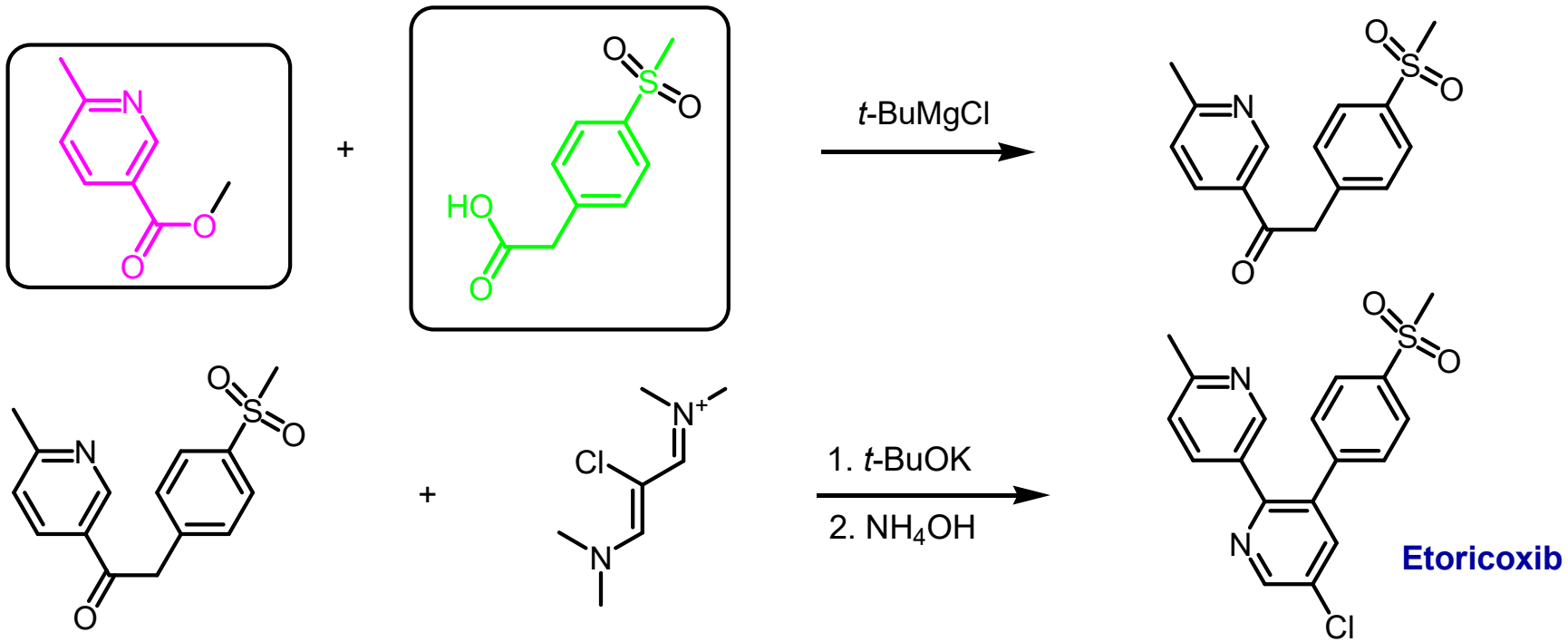


Aldrich
Score=68%

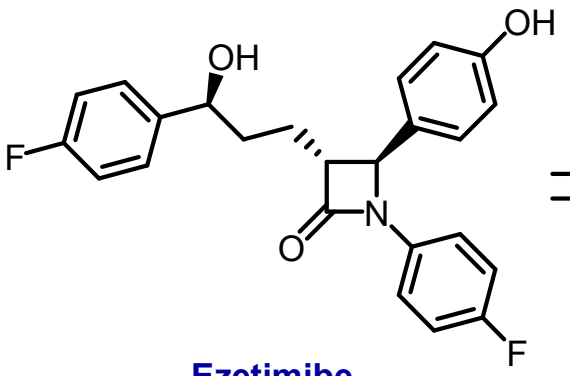
Chiron Program search (all databases, min. score = 75%) : best precursors

Reported synthesis :

Davies, I.W.; Marcoux, J.-F.; Corley, E.G.; Journet, M.; Cai, D.-W.; Palucki, M.; Wu, J.; Larsen, R.D.; Rossen, K.; Pye, P.J.; DiMichele, L.; Dormer, P.; Reider, P.J. *J. Org.Chem.* **2000**, *65*, 8415-8420.

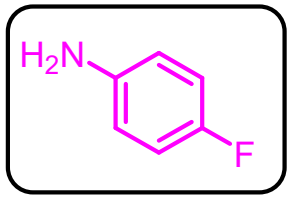


CHIRON ANALYSIS OF EXISTING DRUGS

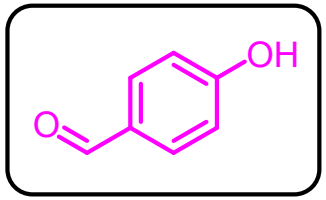


Ezetimibe

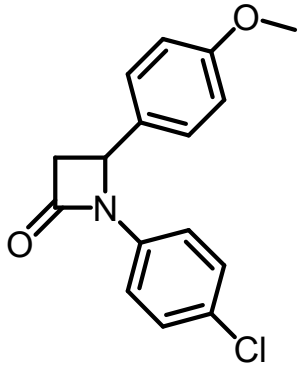
Hypolipidemic



ACD Aromatic
Score=97%



Aldrich
Score=89%

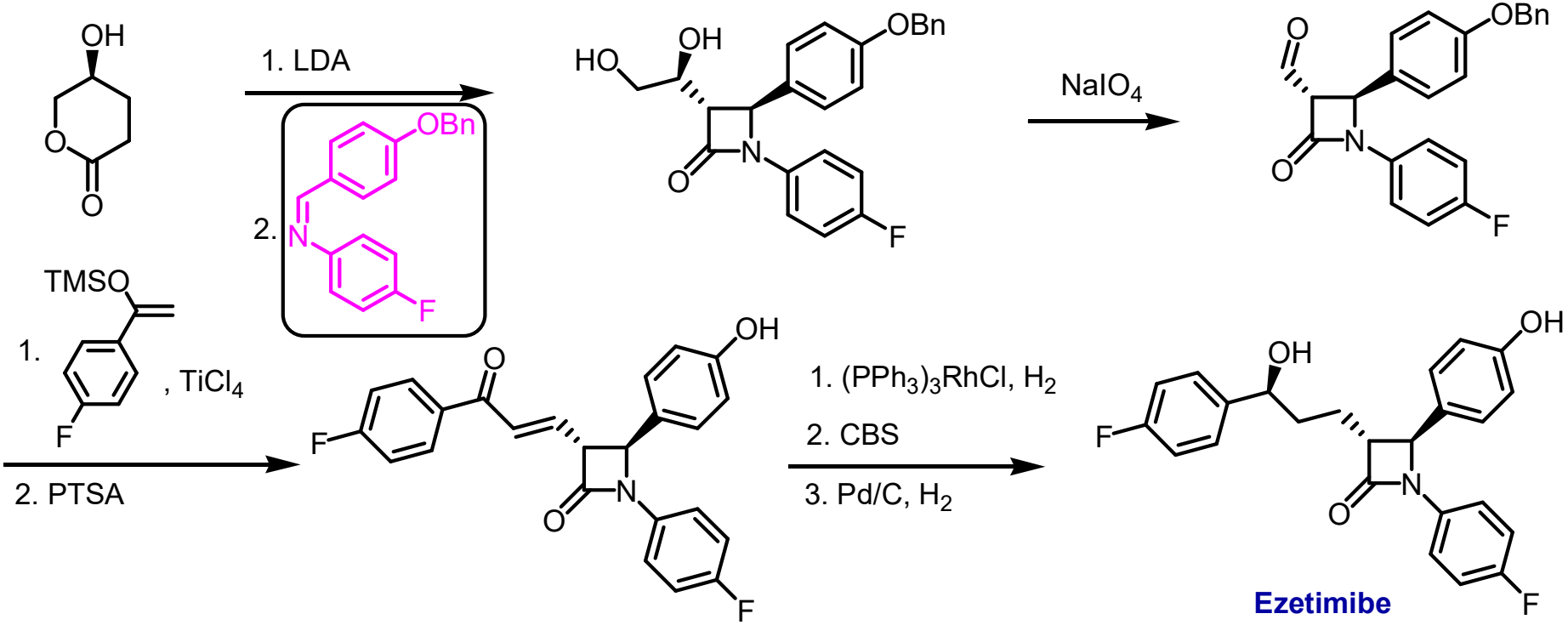


ACD combination
Score91%

Chiron Program search (all databases, min. score = 75%) : best precursors

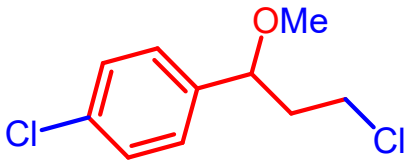
Reported synthesis :

Wu, G.; Wong, Y.; Chen, X.; Ding, Z. *J. Org.Chem.* **1999**, *64*, 3714-3718.

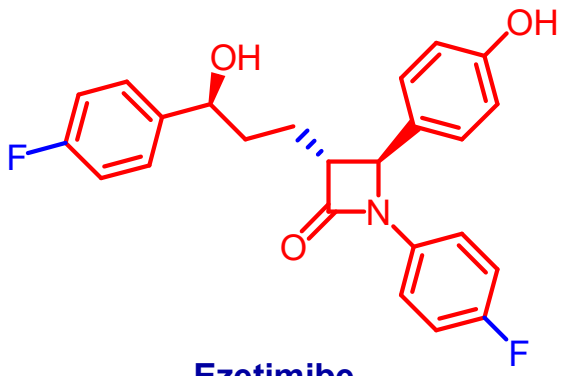


BEST COMBINATION

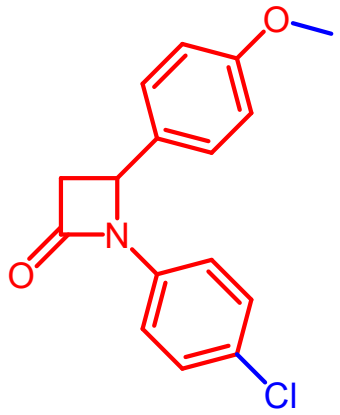
Overall Score = 90%
Overlap Index = 100%
Average Precursor Score = 91%



ACD Aromatic
Score=92%

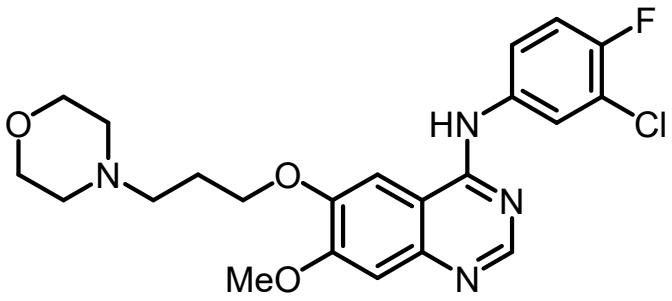


Ezetimibe



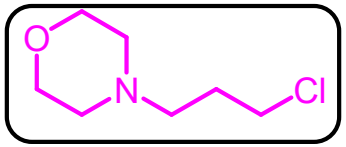
ACD combination
Score=91%

CHIRON ANALYSIS OF EXISTING DRUGS

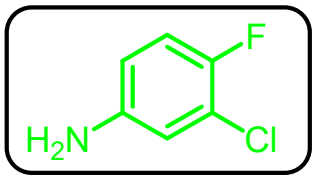


Gefitinib

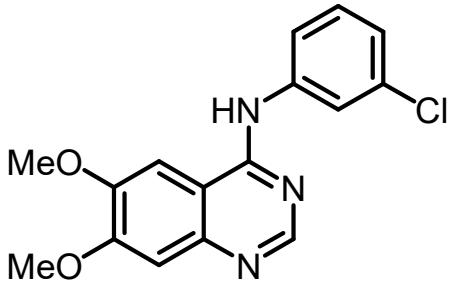
Antineoplastic



ACD Heterocyclic
Score=98%



Aldrich
Score=97%

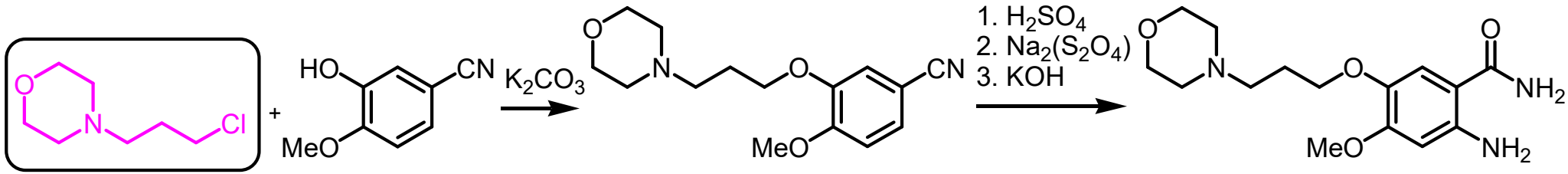


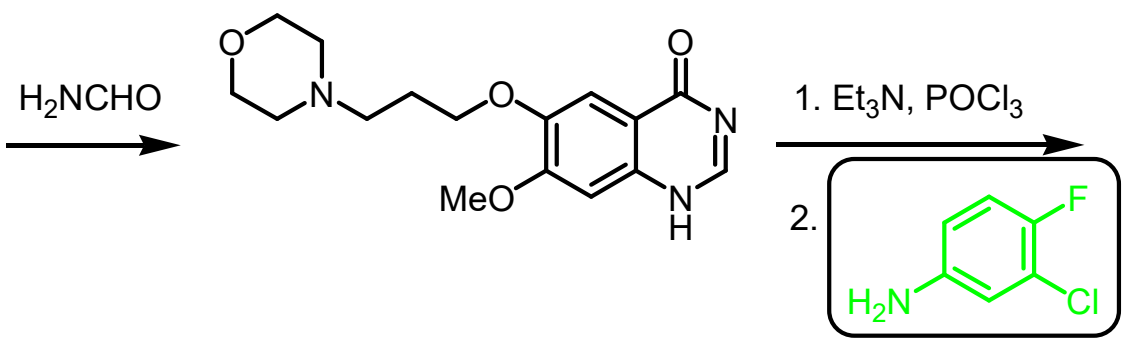
ACD Heteroaromatic-condensed
Score=100%

Chiron Program search (all databases, min. score = 75%) : best precursors

Reported synthesis :

Patent: Gilday, J.P.; Moody, D. PCT Int. Appl., 2004024703, 25 March 2004.

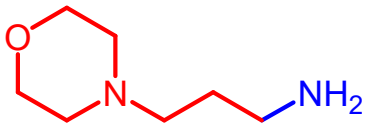




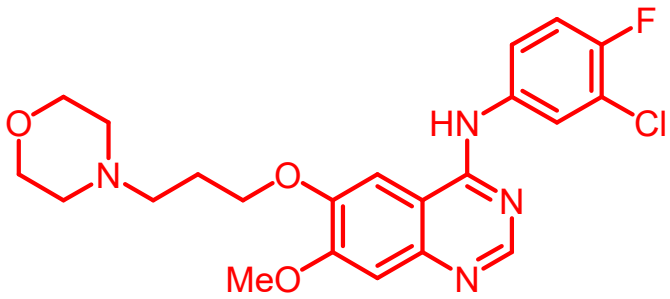
Gefitinib

BEST COMBINATION

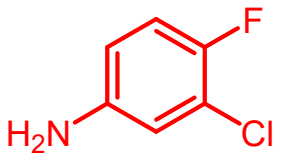
Overall Score = 84%
Overlap Index = 89%
Average Precursor Score = 98%



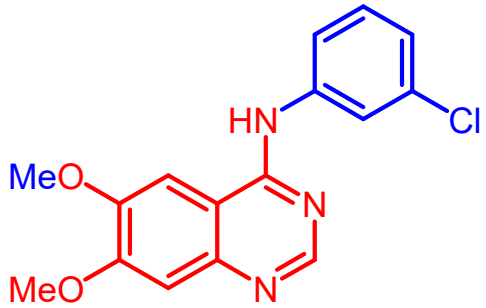
Aldrich
Score=98%



Gefitinib

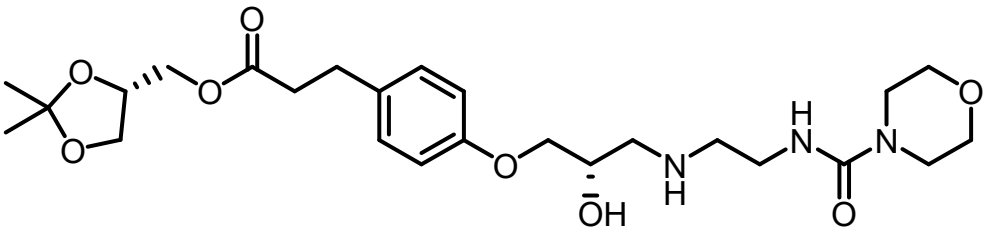


Aldrich
Score=97%



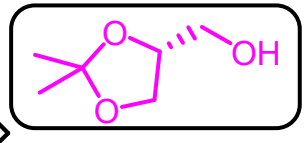
ACD Heteroaromatic-condensed
Score=100%

CHIRON ANALYSIS OF EXISTING DRUGS

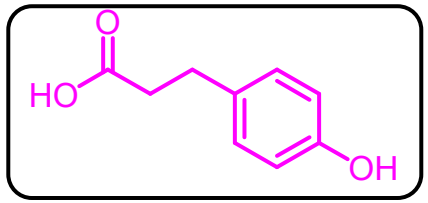


Landiolol

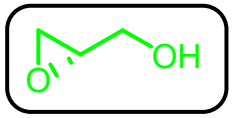
Antiarrythmic



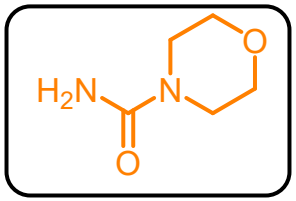
ACD Heterocyclic
Score=97%



Chiron Aromatic
McKillop, *Synlett* **1992**, 201
Score=97%



Aldrich
Score=92%

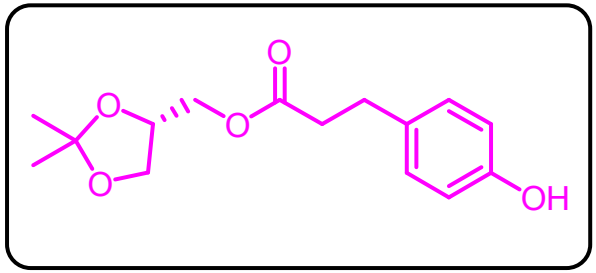


ACD Heterocyclic
Score=97%

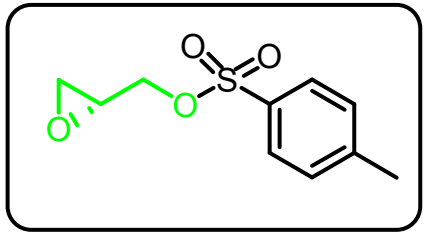
Chiron Program search (all databases, min. score = 75%) : best precursors

Reported synthesis :

Iguchi, S.; Iwamura, H.; Nishizaki, M.; Hayashi, A.; Senokuchi, K.; Kobayashi, K.; Sakaki, K.; Hachiya, K.; Ichioka, Y.; Kawamura, M. *Chem. Pharm. Bull.* **1992**, *40*, 1462-1469.

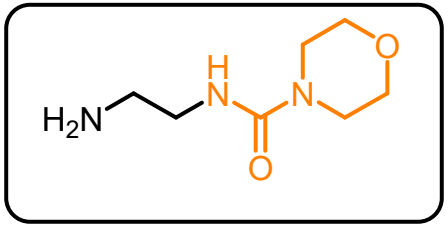


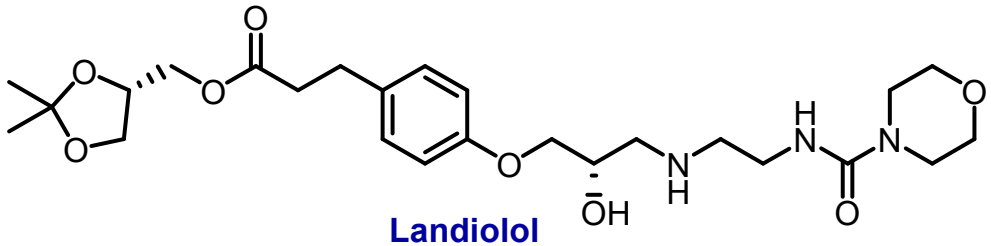
+



1. K_2CO_3

2.

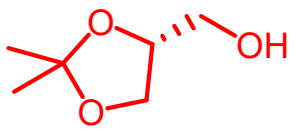




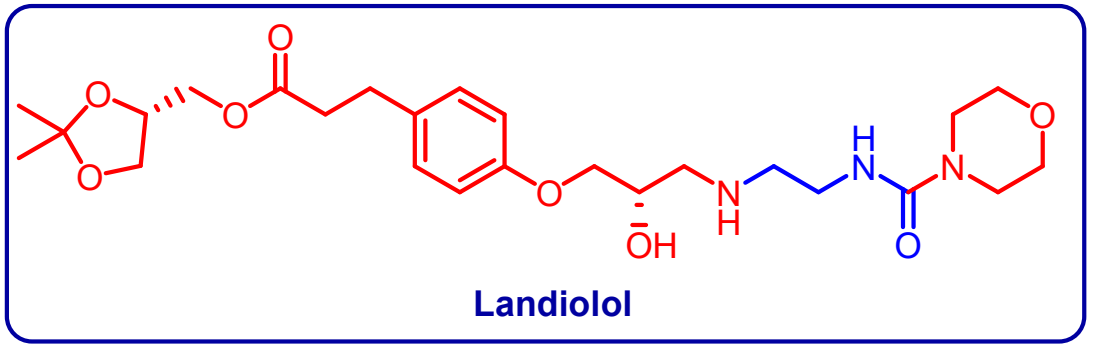
Landiolol

BEST COMBINATION

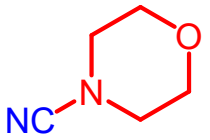
Overall Score = 76%
Overlap Index = 82%
Average Precursor Score = 97%



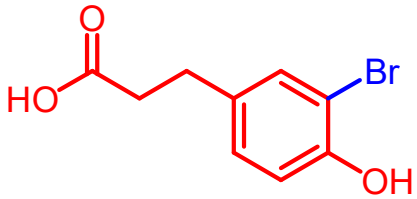
ACD Heterocyclic
Score=97%



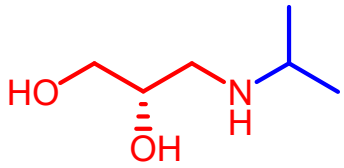
Landiolol



Aldrich
Score=98%

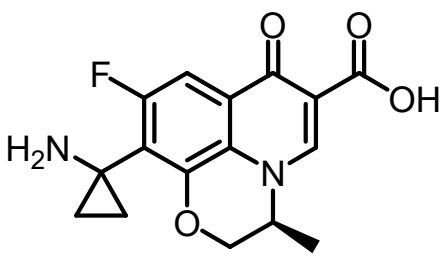


ACD Aromatic
Score=97%



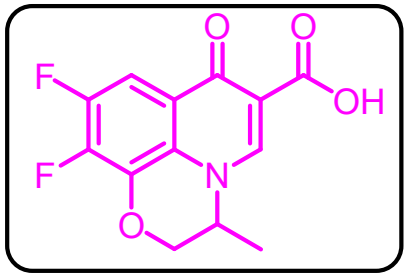
ACD Acyclic-3
Score=97%

CHIRON ANALYSIS OF EXISTING DRUGS

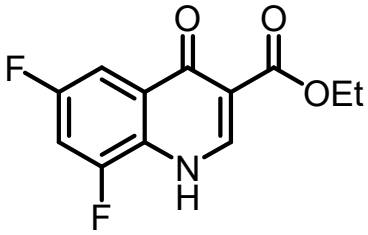


Pazufloxacin

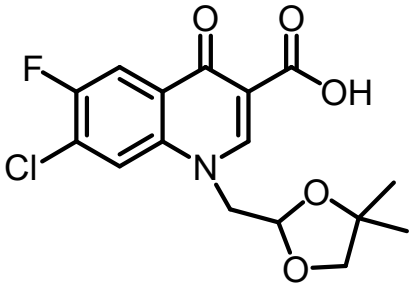
Antibacterial



ACD Combination
Score=93%



ACD Combination
Score=88%

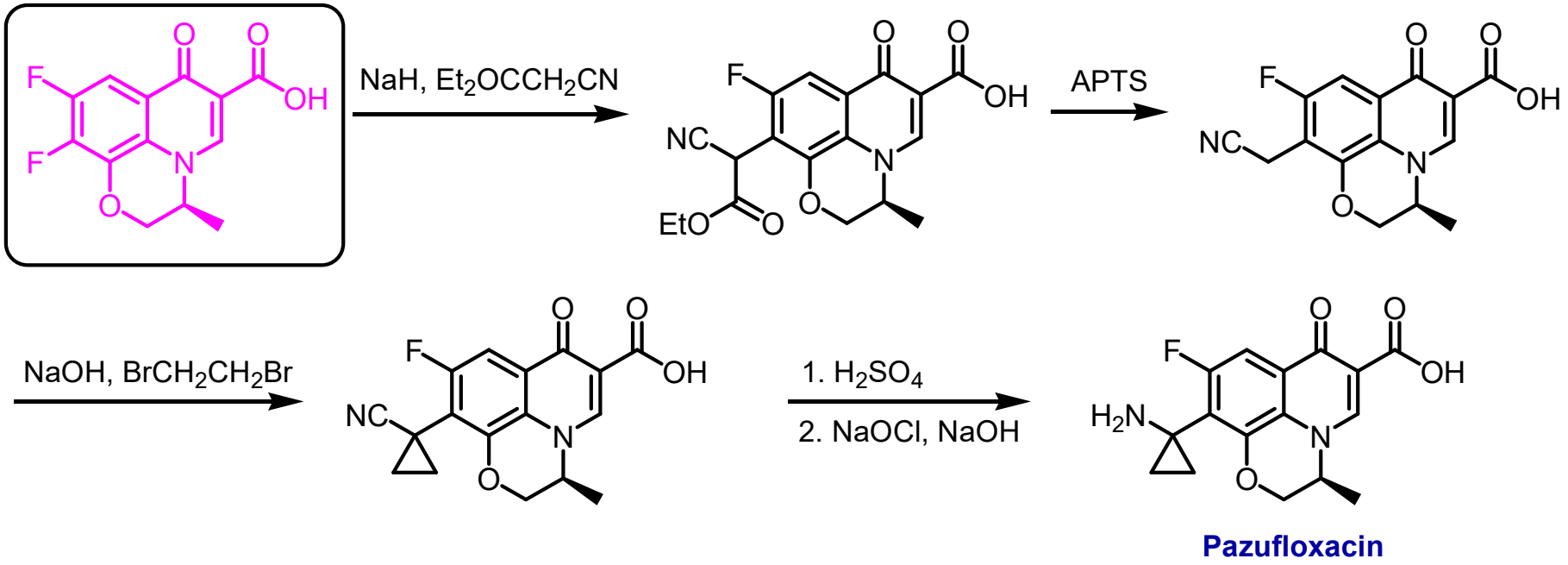


ACD Combination
Score=80%

Chiron Program search (all databases, min. score = 75%) : best precursors

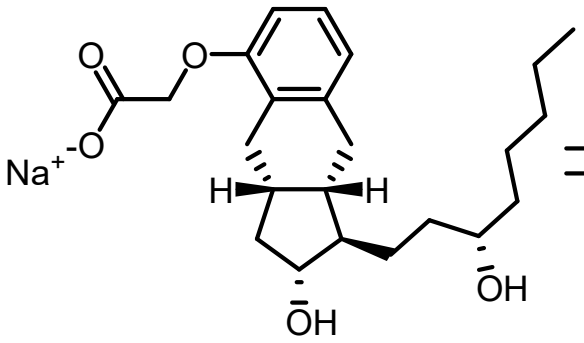
Reported synthesis :

Zhang, W.Z.; Shu, J.Y. *Wuhan Daxue Xuebao, Lixueban* **2003**, *49*, 227-230.
Liang, Y. *Zhongguo Yiyao Gongye Zazhi* **2001**, *32*, 529-531.



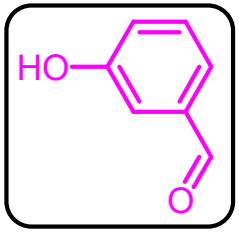
Pazufloxacin

CHIRON ANALYSIS OF EXISTING DRUGS

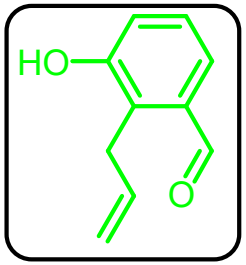


Treprostinil sodium

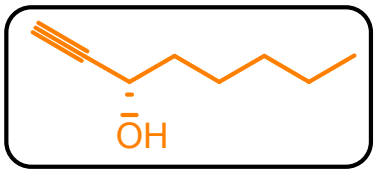
Antihypertensive



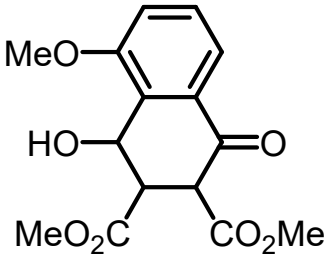
Aldrich
Score=75%



ACD Aromatic
Score=82%



Chiron Acyclic-7plus
Sih, CJ *JACS* **1972**, 3643
Score=88%

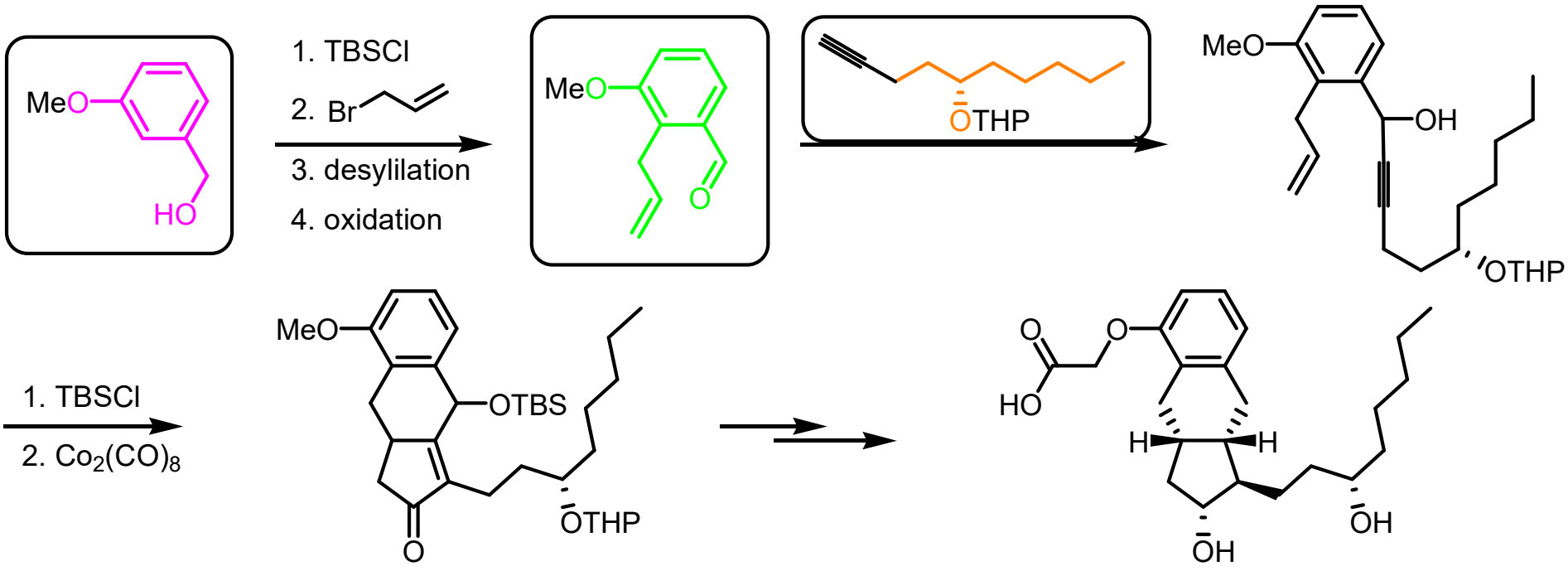


Chiron Combination
Dodsworth, DJ *JCS*
Perkin Trans I **1981**, 2120
Score=75%

Chiron Program search (all databases, min. score = 75%) : best precursors

Reported synthesis :

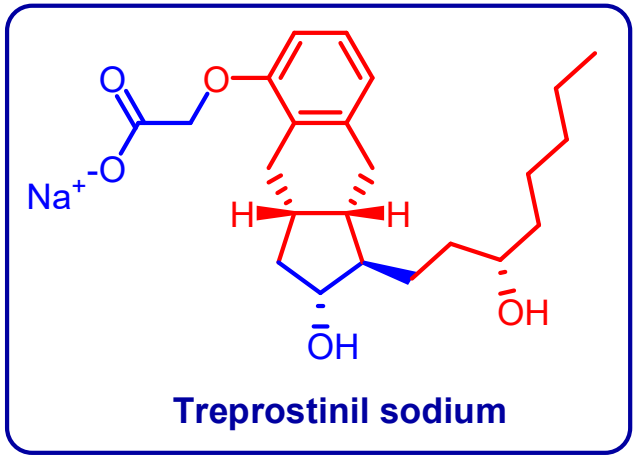
Patent: Moriarty, R.M.; Penmasta, R.; Guo, L.; Rao, M.S.; Staszewski, J.P. U.S., 6441245, 27 Aug. 2002



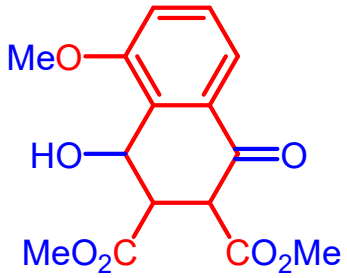
Treprostinil

BEST COMBINATION

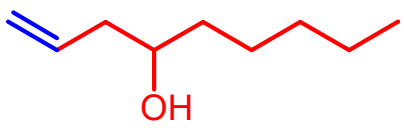
Overall Score = 78%
Overlap Index = 83%
Average Precursor Score = 83%



Treprostinil sodium

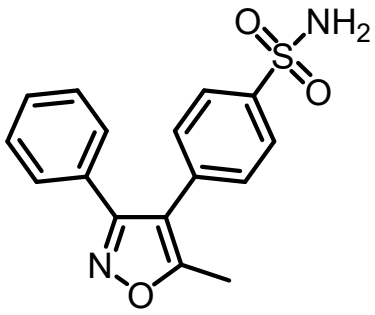


Chiron Combination
Dodsworth, DJ *JCS Perkin Trans I* **1981**, 2120
Score=75%



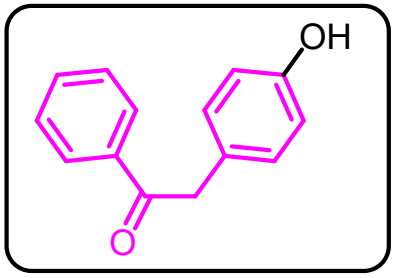
ACD Acyclic-7plus
Score=91%

CHIRON ANALYSIS OF EXISTING DRUGS

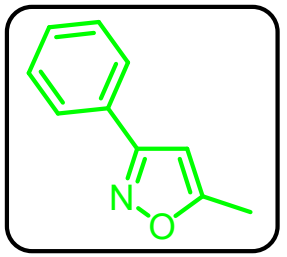


Valdecoxib

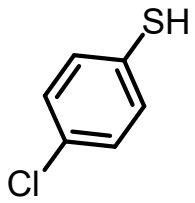
Antiarthritic



Chiron Polyaromatic
Mukaiyama, T. *Chem. Lett.* **1987**, 479
Score=73%



ACD Combination
Score=86%

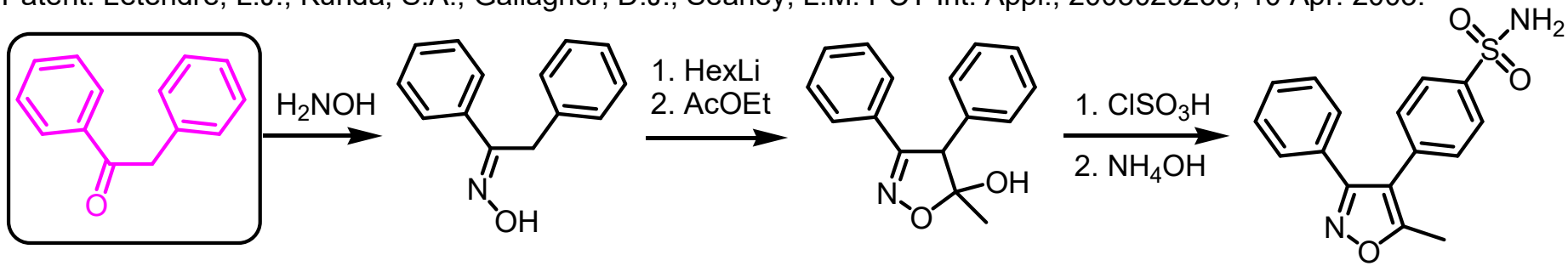


Aldrich
Score=83%

Chiron Program search (all databases, min. score = 65%) : best precursors

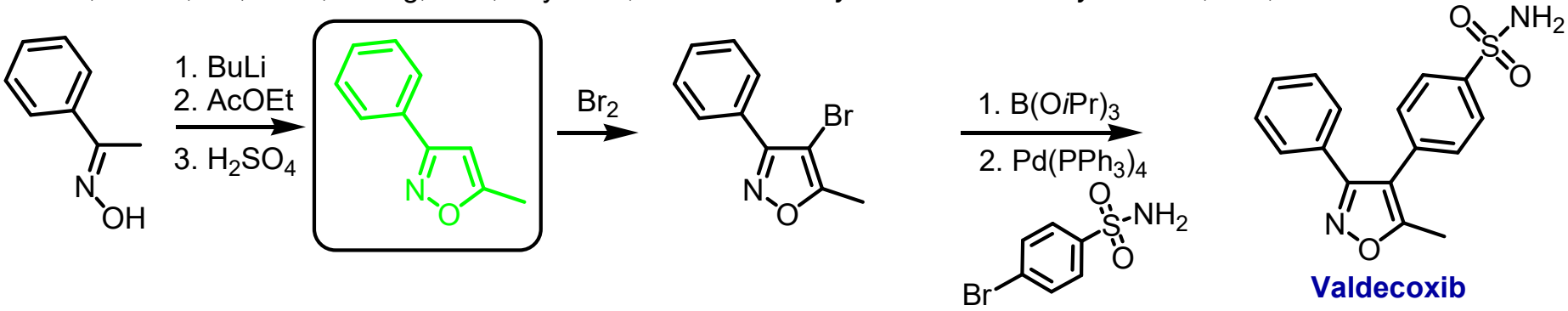
Reported synthesis :

Patent: Letendre, L.J.; Kunda, S.A.; Gallagher, D.J.; Seaney, L.M. PCT Int. Appl., 2003029230, 10 Apr. 2003.



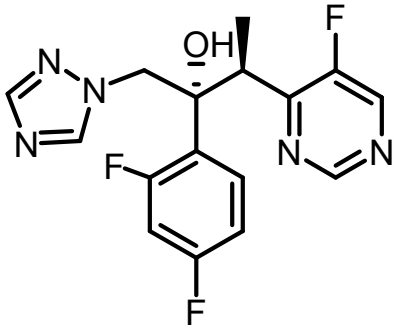
Valdecoxib

Kumar, J.S.D.; Ho, M.M.; Leung, J.M.; Toyokuni, T. *Advanced Synthesis and Catalysis* **2002**, *344*, 1146-1151.



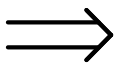
Valdecoxib

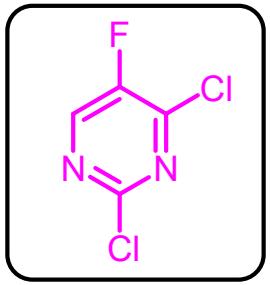
CHIRON ANALYSIS OF EXISTING DRUGS



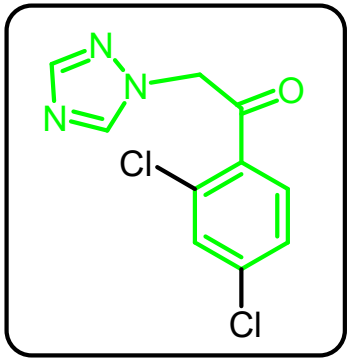
Voriconazole

Antifungal





ACD Heteroaromatic
Score=77%

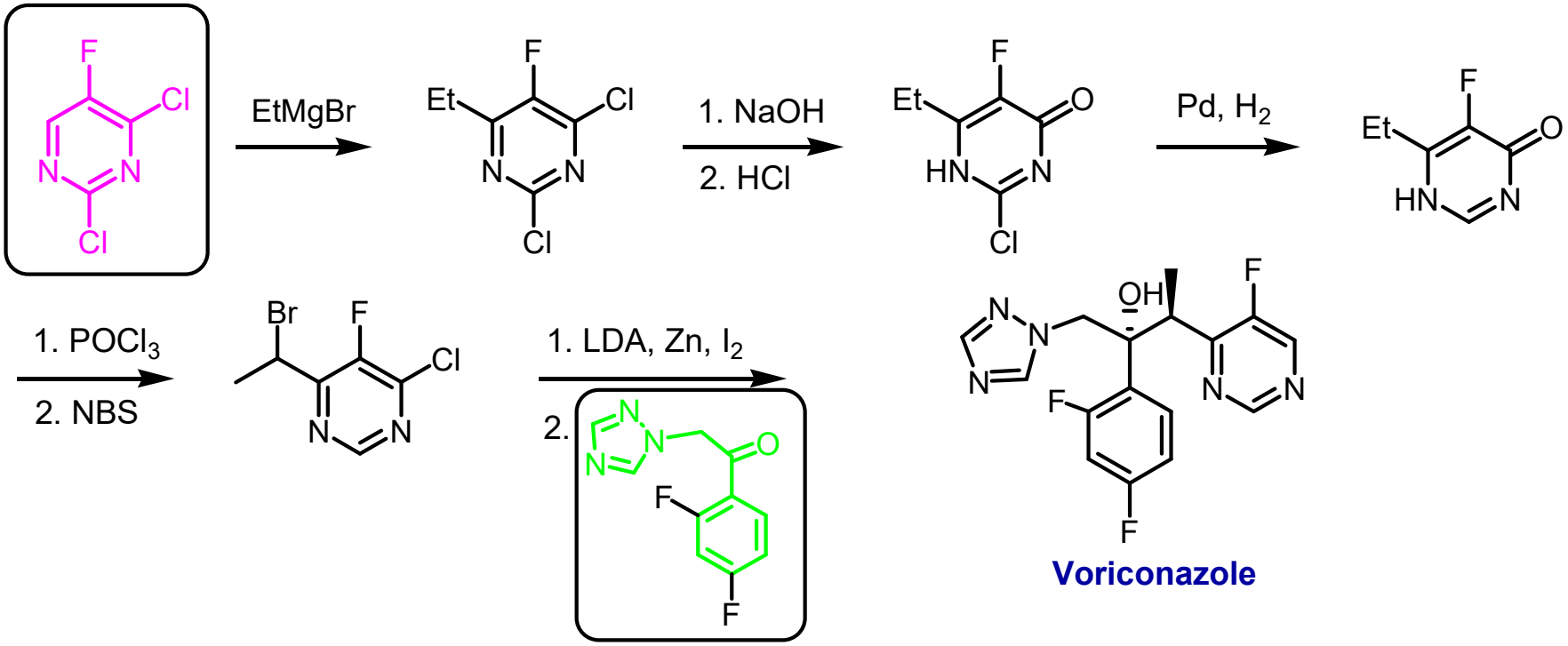


ACD Combination
Score=91%

Chiron Program search (all databases, min. score = 75%) : best precursors

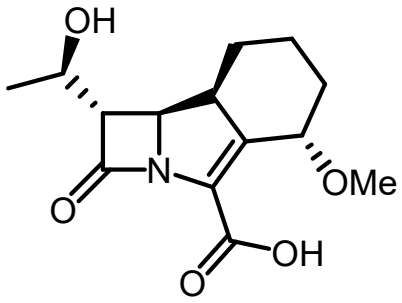
Reported synthesis :

Butters, M.; Ebbs, J.; Green, S.P.; MacRae, J.; Morland, M.C.; Murtiashaw, C.W.; Pettman, A.J. *Organic Process Research and Development* **2001**, *5*, 28-36.



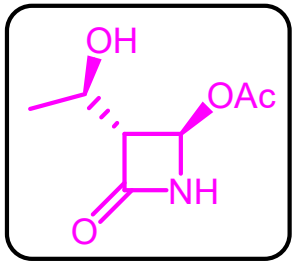
Voriconazole

CHIRON ANALYSIS OF EXISTING DRUGS

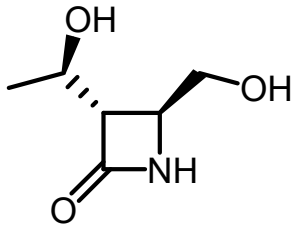


Sanfetrinem

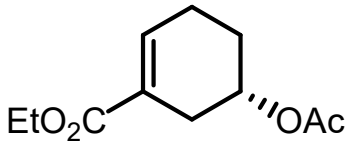
antibacterial



Chiron Heterocyclic
Uyeo, S., TL, 2143 (1991)
Score=76%



Chiron Heterocyclic
Hirai, H., TL, 4025 (1982)
Score=77%

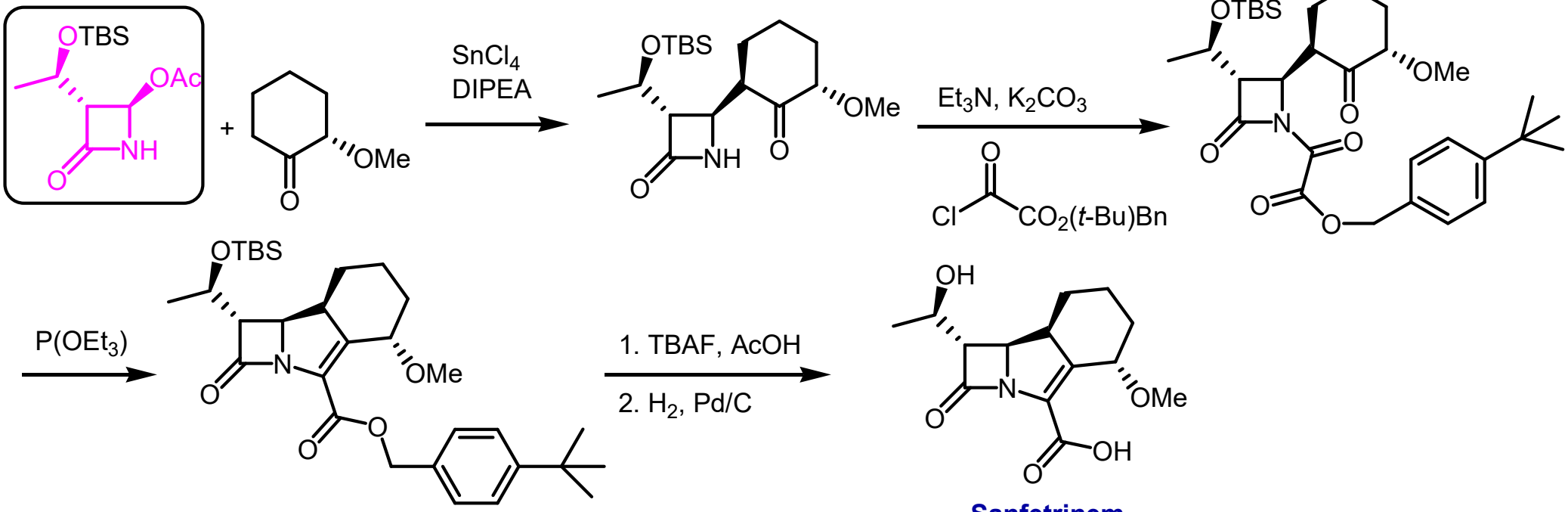


Chiron Carbocyclic-Branched
Takano, S., Tet. Asym., 837 (1992)
Score=78%

Chiron Program search (all databases, min. score = 75%) : best precursors

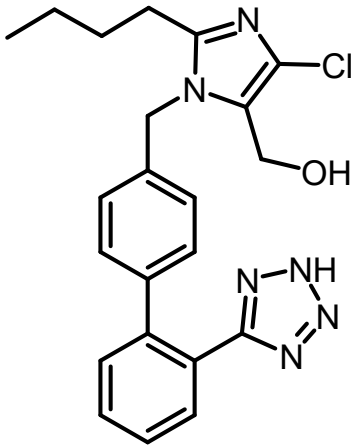
Reported synthesis :

Rossi, T.; Marchioro, C.; Paio, A.; Thomas, R.J.; Zarantonello, P. *J. Org. Chem.* **1997**, *62*, 1653-1661.
Hanessian, S.; Rozema, M.J. *J. Am. Chem. Soc*. **1996**, *118*, 9884-9891.



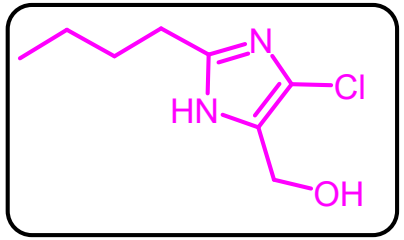
Sanfetrinem

CHIRON ANALYSIS OF EXISTING DRUGS

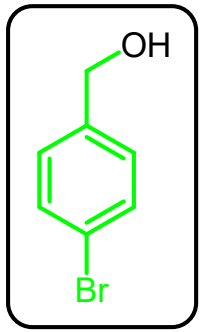


Losartan

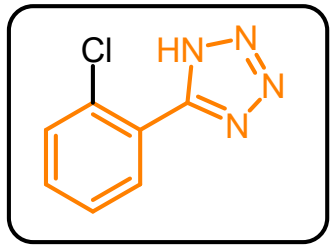
Antihypertensive



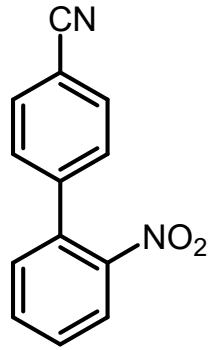
ACD Heteroaromatic
Score=100%



Aldrich
Score=83%



ACD Combination
Score=92%

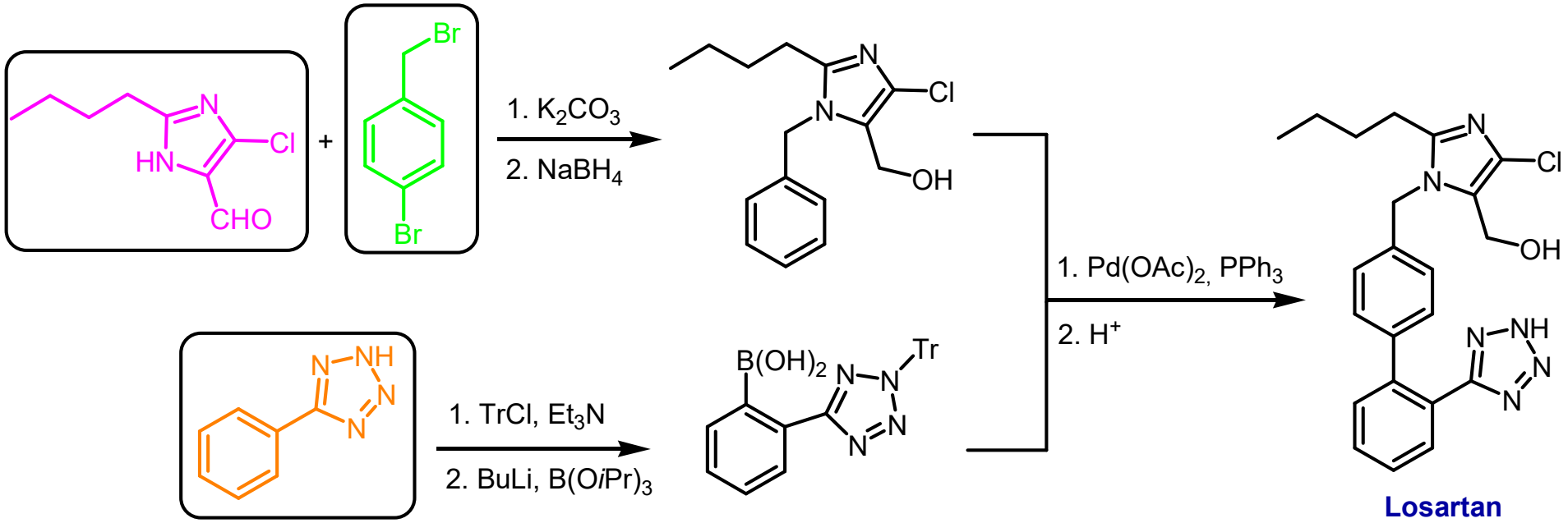


ACD Polyaromatic
Score=92%

Chiron Program search (all databases, min. score = 75%) : best precursors

Reported synthesis :

Larsen, R.D.; King, A.O.; Chen, C.Y.; Corley, E.G.; Foster, B.S.; Roberts, F.E.; Yang, C.; Liberman, D.R.; Reamer, R.A.; Tschaen, D.M.; Verhoeven, T.R.; Reider, P.J.; Lo, Y.S.; Rossano, L.T.; Brookes, A.S.; Meloni, D.; Moore, J.R.; Arnett, J.F. *J. Org. Chem.* **1994**, *59*, 6391-6394.



Losartan

CHEMPROTECT 1.0
SELECTION OF PROTECTIVE GROUPS FOR SYNTHESIS
NEW SOFTWARE FOR SYNTHETIC ORGANIC CHEMISTS

FEATURES :

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- 161 REACTION CONDITIONS
- 55706 POSSIBLE REACTIVITES
- 1413 LITERATURE REFERENCES

OPTIONS :

- **COMPATIBILITY** : allows you to find all protective groups for selected chemical functions that will be stable to 1 up to 10 reaction steps simultaneously

- **INCOMPATIBILITY** : allows you to look for conditions that modify selected protective groups (up to 10 also).

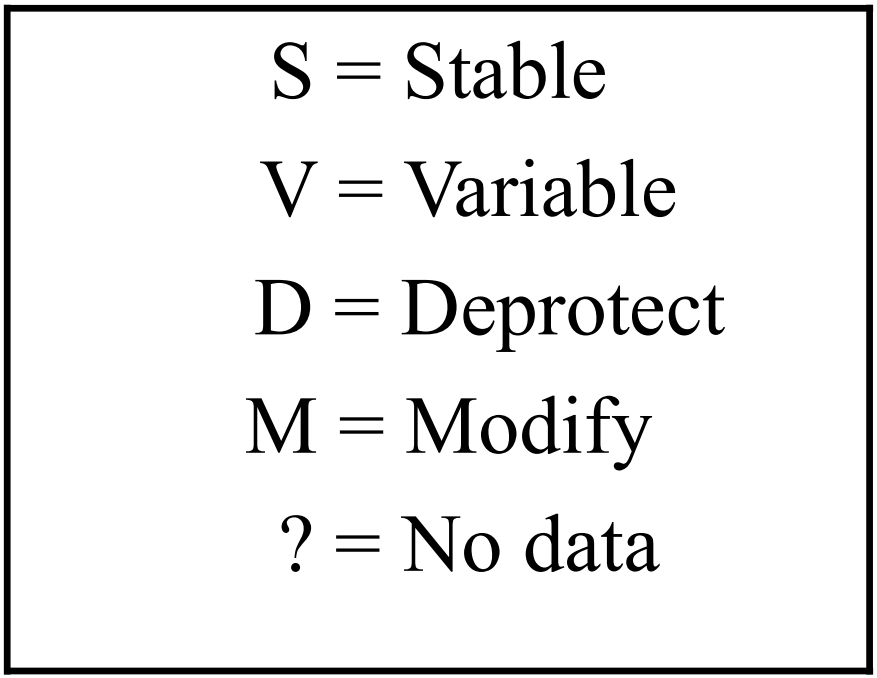
- **DEPROTECTION** : allows you to look for conditions that selectively deprotect a set of protective groups up to 10 at the same time.

AVAILABLE ON THE MACINTOSH and PC

CHEMPROTECT MATRIX

161 Conditions

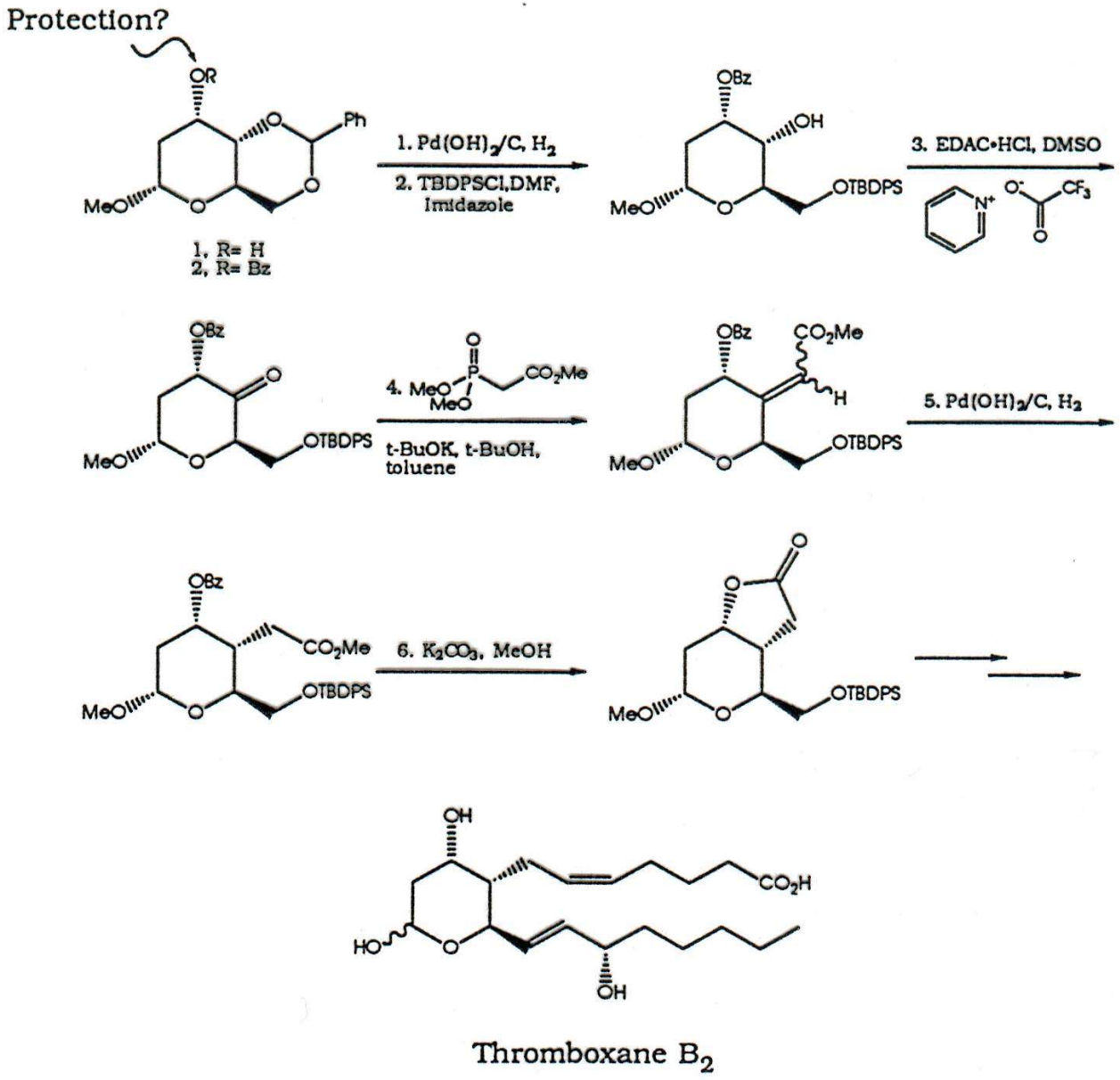
346 Groups



55706 Entries

COMPATIBILITY SEARCH

Partial synthetic steps of Thromboxane B_2



Thromboxane B_2

COMPATIBILTY SEARCH

The listing output format from ChemProtect is as follows :

COMPATIBILITY SEARCH. Wednesday January 1st 1992 12:00:00

Function to protect:

- ALCOHOL

Reaction conditions planned:

#1 Catalytic reduction
    H2, Pd-C -[136]
#2 Non-Nucleophilic base
    Pyridine; R3N, etc. -[77]
#3 Oxidation
    DMSO; Moffatt; Swern, etc. -[92]
#4 Organometal/Carbanion
    S-ylides; P-ylides; Wittig; etc. -[87]

⧫ Step #5 same as #1 -> not repeated.

COMPATIBILTY SEARCH

Suggested compatible protection for:	General References:
• ALCOHOL:	6,39,59p10.
Carbonate ester	59p104.
V SSSV [6] Methyl	73.
S SSSS [8] 2-(Methylthiomethoxy)ethyl (MTMEC0)	147.
S SSSS [13] 2,2,2-Trichloroethyl (Troc)	58,187.
S SSSS [14] 2-(Trimethylsilyl)ethyl (TMSEC)	149,188.
Carboxylate ester	61.
V SSSV [15] Acetate (Ac)	59p88,453.
S SSSS [16] Adamantoate	67,75.
V SSSV [17] Benzoate (Bz)	59p100. ➧ Author's choice
S SSSS [23] Phenoxyacetate	77,230,467.
S SSSS [25] Pivaloate (Pv)	237,321,383,404,472,473,474.
S SSSS [28] 2,4,6-Trimethylbenzoate	78,488.
Sulfonate ester	59p117.
S SSSS [29] Methanesulfonate (Ms)	151.
V SSSV [31] p-Toluenesulfonate (Ts)	51.
V SSVV [32] Trifluoromethanesulfonate	
Other ester	59p114.
V SSVS [36] N,N-Diphenylphospholidinate	
S SSSS [38] N-Phenylcarbamate	193,194.
S SSSS [39] N,N,N',N'-Tetramethylphosphorodiamidate	491.
Alkyl ether	61,209,210.
S SSSS [42] t-Butyl	22,280,281,282,283,284.
S SSSS [45] p-Methoxybenzyl (PMB)	3,57,336,337,338,339,340,341.
S SSSS [48] Methyl (Me)	59p15.
S SSSS [50] 2,2,2-Trichloroethyl	88.
Alkoxyalkyl ether	61,209,210.
S SSSS [53] 1-Ethoxyethyl (EE)	270,271,272,273,274.
S SSSS [55] 2-Methoxyethoxymethyl (MEM)	19,244.
S SSSS [57] Methoxymethyl (MOM)	28,59p17.
S SSSS [58] 4-Methoxytetrahydropyranyl (MTHP)	5,70,269.
S SSSS [60] 1-Methyl-1-methoxyethyl	28.
S SSSS [61] Tetrahydropyranyl (THP)	59p31,64,97,259.
Alkylthioalkyl ether	
V SSVS [65] Methylthiomethyl (MTM)	16,59p21.
Silyl ether	62,211.
S SSSS [67] t-Butyldimethylsilyl (TBDMS)	13,59p77.
S SSSS [70] t-Butyldiphenylsilyl (TBDPS)	53. ➧ Author's choice
S SSSS [71] t-Butylmethoxyphenylsilyl	84,153.
S SSSS [74] Triethysilyl (TES)	384,385,386.
S SSSS [75] Triisopropylsilyl (TIPS)	86,388,389,390,391,392.
S SSSS [76] Trimethysilyl (TMS)	59p68.
S SSSS [77] 2-(Trimethylsilyl)ethoxymethyl (SEM)	2,250.
S SSSS [79] Triphenylsilyl (TPS)	87,392,432,433.

COMPATIBILTY SEARCH

Selected references:

Ref#

2 - B.H. Lipshutz, J.J. Pegram; Tet. Lett., 1980,21,3343.
3 - B. Samuelsson; Acta Pharm. Suec., 1986,23,412.
5 - C.B. Reese, R. Saffhill, J.E. Sulston; Tetrahedron, 1970,26,1023.
6 - C.B. Reese; 'Protective Groups in Organic Chemistry', J.F.W. McOmie, Ed., Plenum Press, New York, 1973, pp. 95-143: "Protection of the Alcoholic Hydroxyl Groups and Glycol Systems".
13 - E.J. Corey, A. Venkateswarlu; J. Am. Chem. Soc., 1972,94,6190.
16 - E.J. Corey, M.G. Bock; Tet. Lett., 1975,3269.
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28 - A.F. Kluge, K.G. Untch, J.H. Fried; J. Am. Chem. Soc., 1972,94,7827.