Introduction
Multi-step synthesis of complex molecules

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UNIVERSITÉ DE LYON
Université Claude Bernard Lyon 1

Course program

I – Introduction

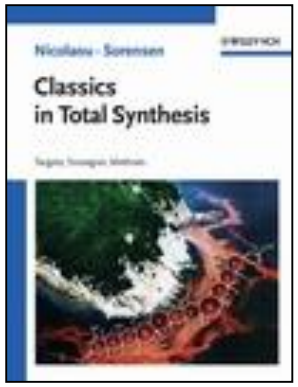
II – Concepts

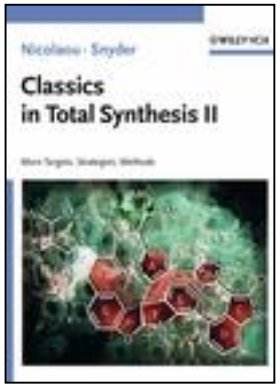
III - Synthesis of acyclic systems

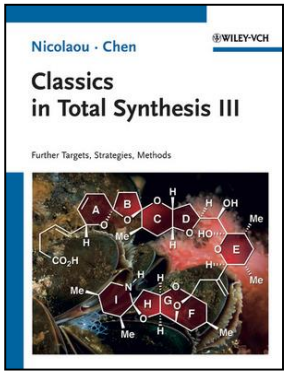
IV – Synthesis of cyclic and polycyclic systems

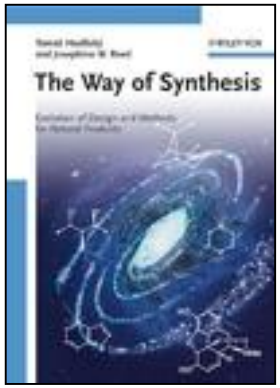
V - Illustrations

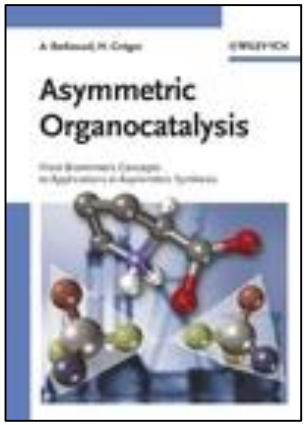
Bibliography

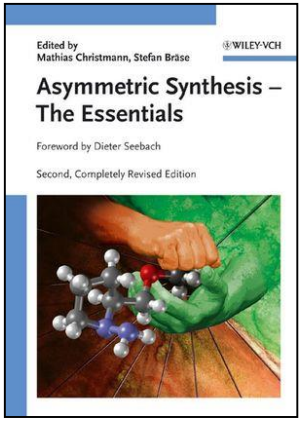


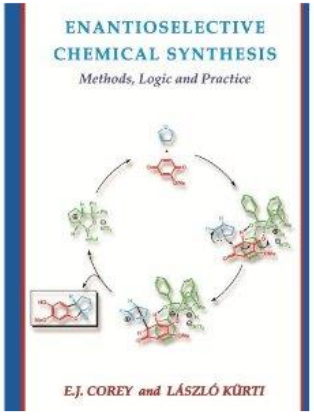


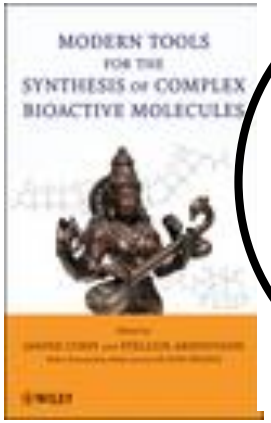


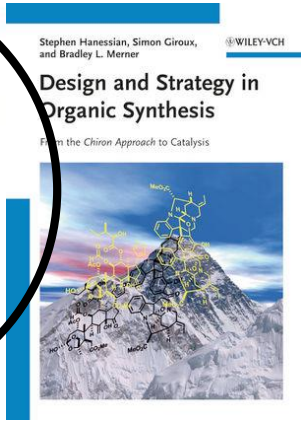


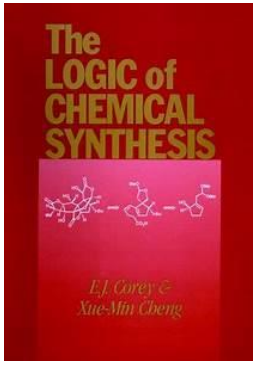


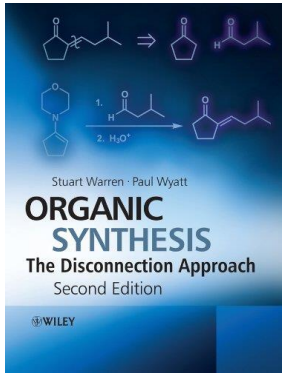


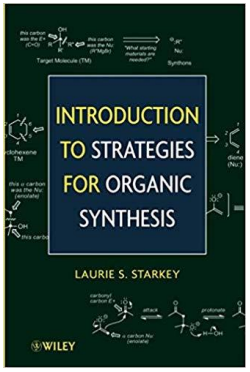


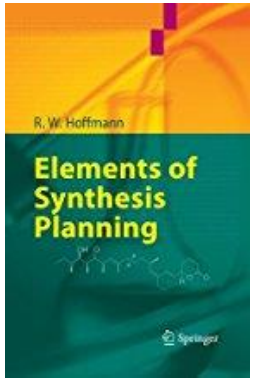


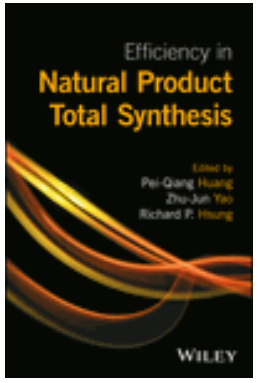


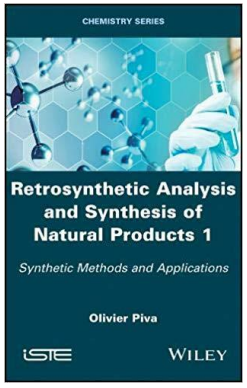












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Organic Chemistry Portal

Organic Chemistry Highlights

https://www.organic-chemistry.org/Highlights/2020

ChemistryViews

https://www.chemistryviews.org/view/0/index.html

(Non-standard) journal abbreviations used in this course:

ACIE = Angewandte Chemie International Edition; CEJ = Chemistry a European Journal; ChemComm = Chemical Communications; ChemRev = Chemical Reviews; EurJOC = European Journal of Organic Chemistry; JACS = Journal of the American Chemical Society; JOC = Journal of Organic Chemistry; OL = Organic Letters; TL = Tetrahedron Letters; Tet = Tetrahedron; TetAsym = Tetrahedron: Asymmetry.

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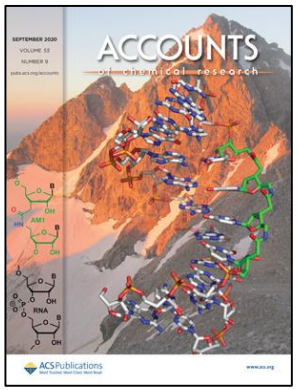

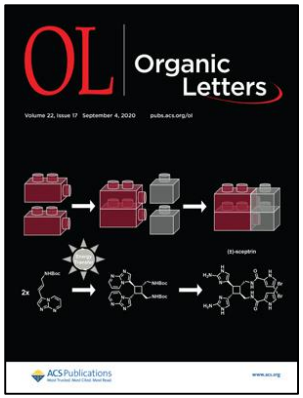

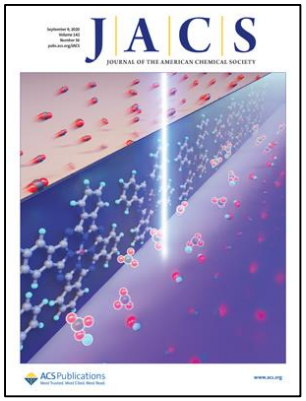

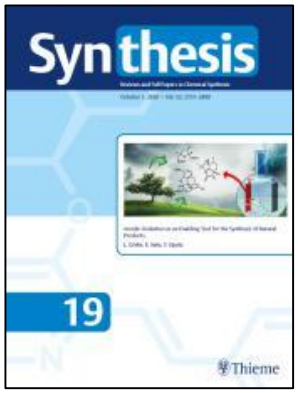

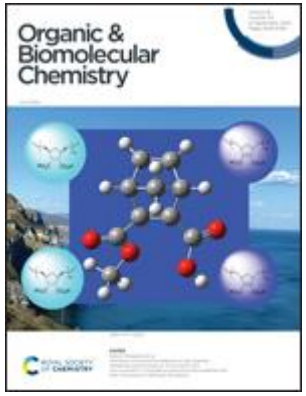

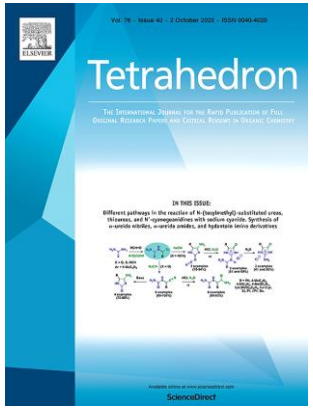

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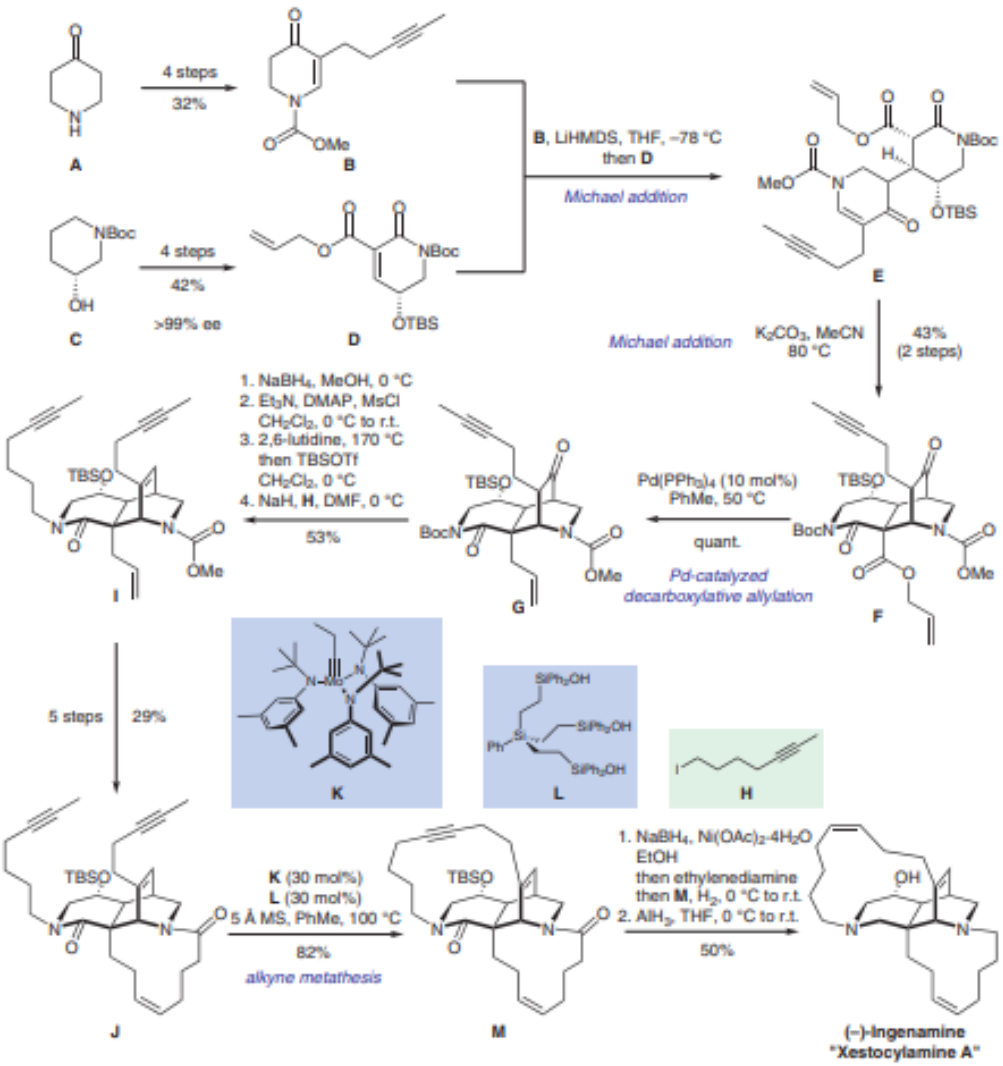
Z. MENG, A. FÜRSTNER* (MAX-PLANCK-INSTITUT FÜR KOHLENFORSCHUNG, MÜLHEIM AN DER RUHR, GERMANY)

Total Synthesis Provides Strong Evidence: Xestocyclamine A is the Enantiomer of Ingenamine
J. Am. Chem. Soc. **2020**, *142*, 11703–11708.

Total Synthesis of (–)-Ingenamine



Category

Synthesis of Natural Products and Potential Drugs

Key words

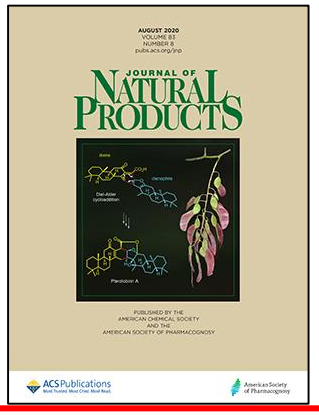
ingenamine

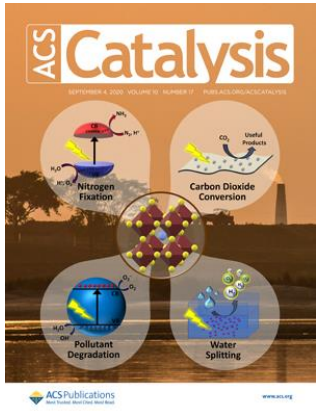
xestocyclamine A

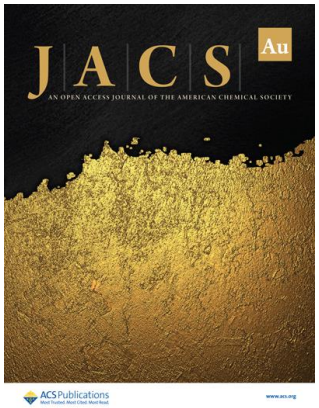
Michael addition

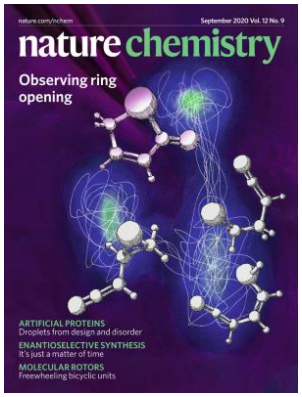
decarboxylative allylation

alkyne metathesis









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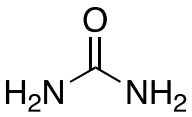
I - Introduction

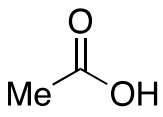
1. History of organic synthesis
2. Therapeutic relevance of natural products
3. Interest of natural product synthesis

1. History of organic synthesis

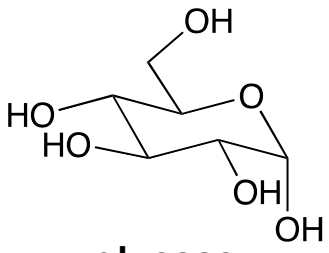
Some milestones from 1828 to 1944…



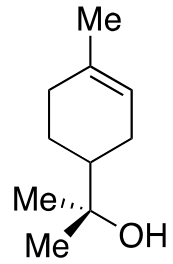
urea
Wöhler, 1828



acetic acid
Kolbe, 1845

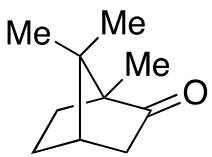


glucose
Fischer, 1890

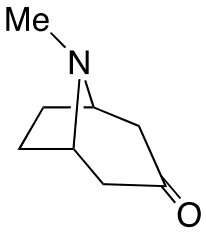


α-terpineol
Perkin, 1904

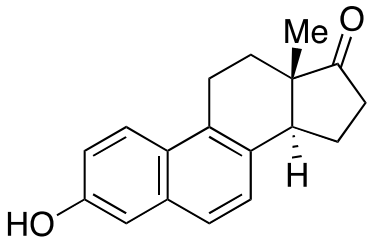
E. Fischer
(Nobel prize 1902)



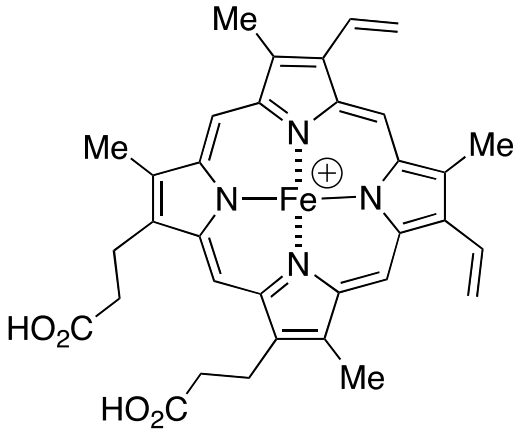
camphor
Komppa, 1903
Perkin, 1904



tropinone
Robinson, 1917

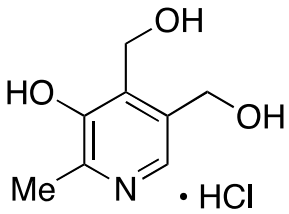


equilenin
Bachmann, 1939

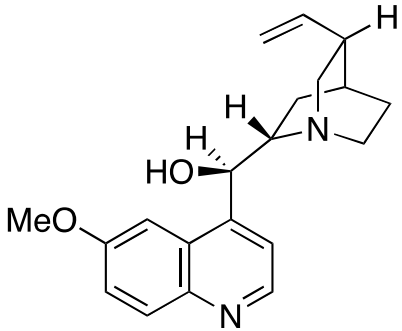


heme
Fischer, 1929

Sir R. Robinson
(Nobel prize 1947)



pyridoxine hydrochloride
Folkers, 1939

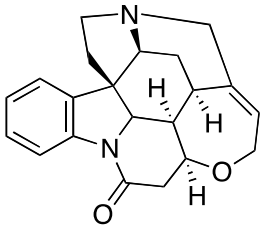


quinine
Woodward & Doering, 1944

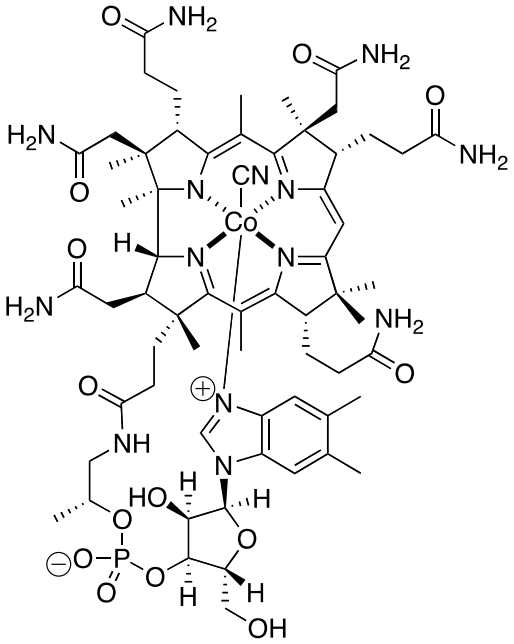
R. B. Woodward
(Nobel prize 1965)

1. History of organic synthesis

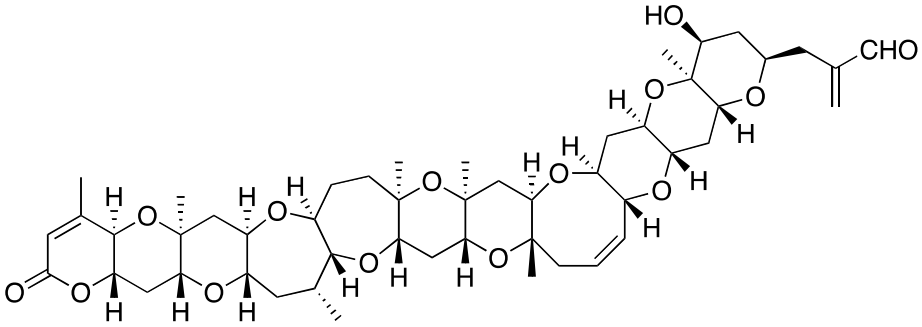
increasing complexity from the 2nd half of 20th century…



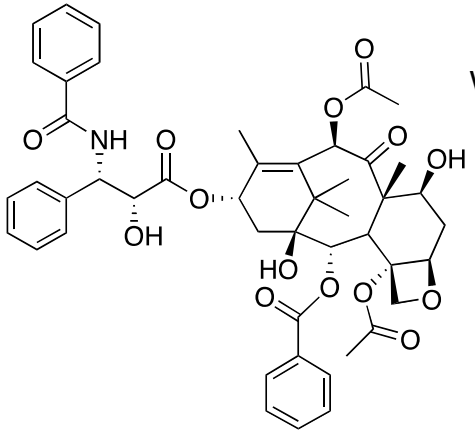
strychnine (1954)
Woodward



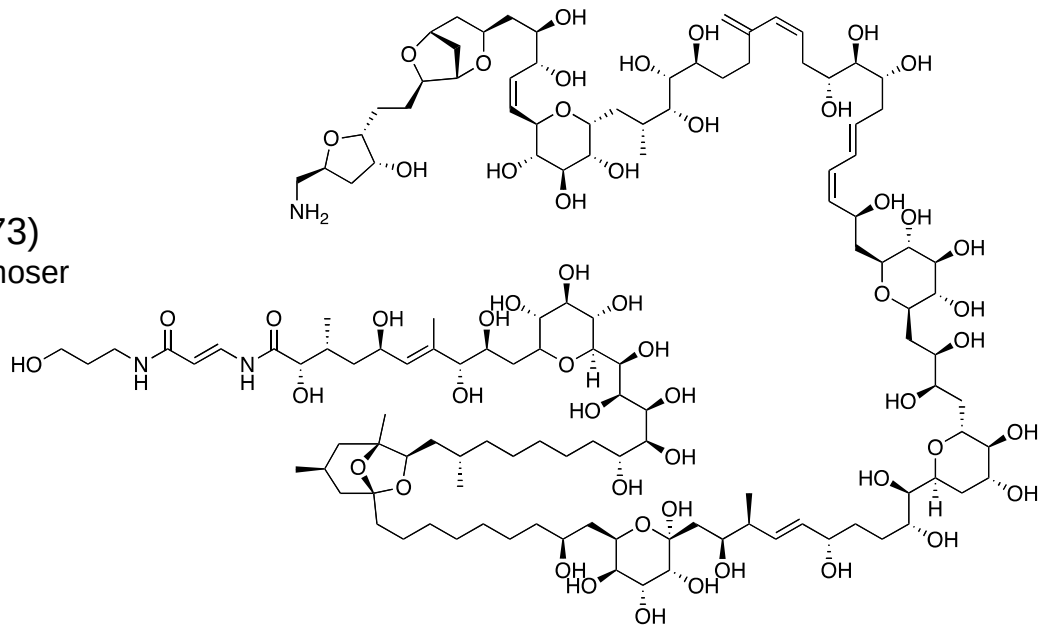
vitamin B12 (1973)
Woodward & Eschenmoser



brevetoxin B (1995)
Nicolaou



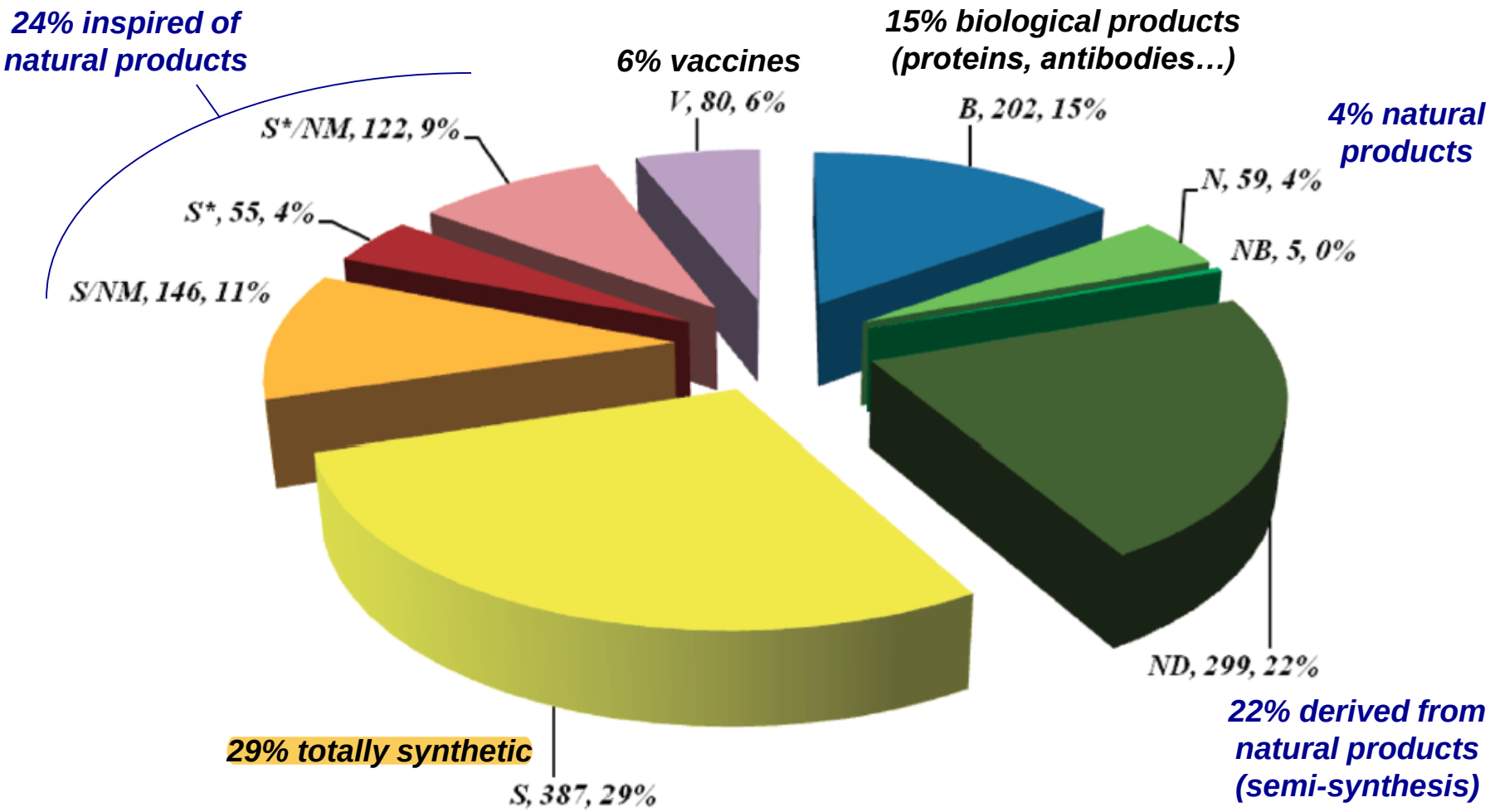
Taxol™ (1994)
Holton - Nicolaou - Danishefsky



palytoxin (1994)
Kishi

2. Therapeutic relevance of natural products

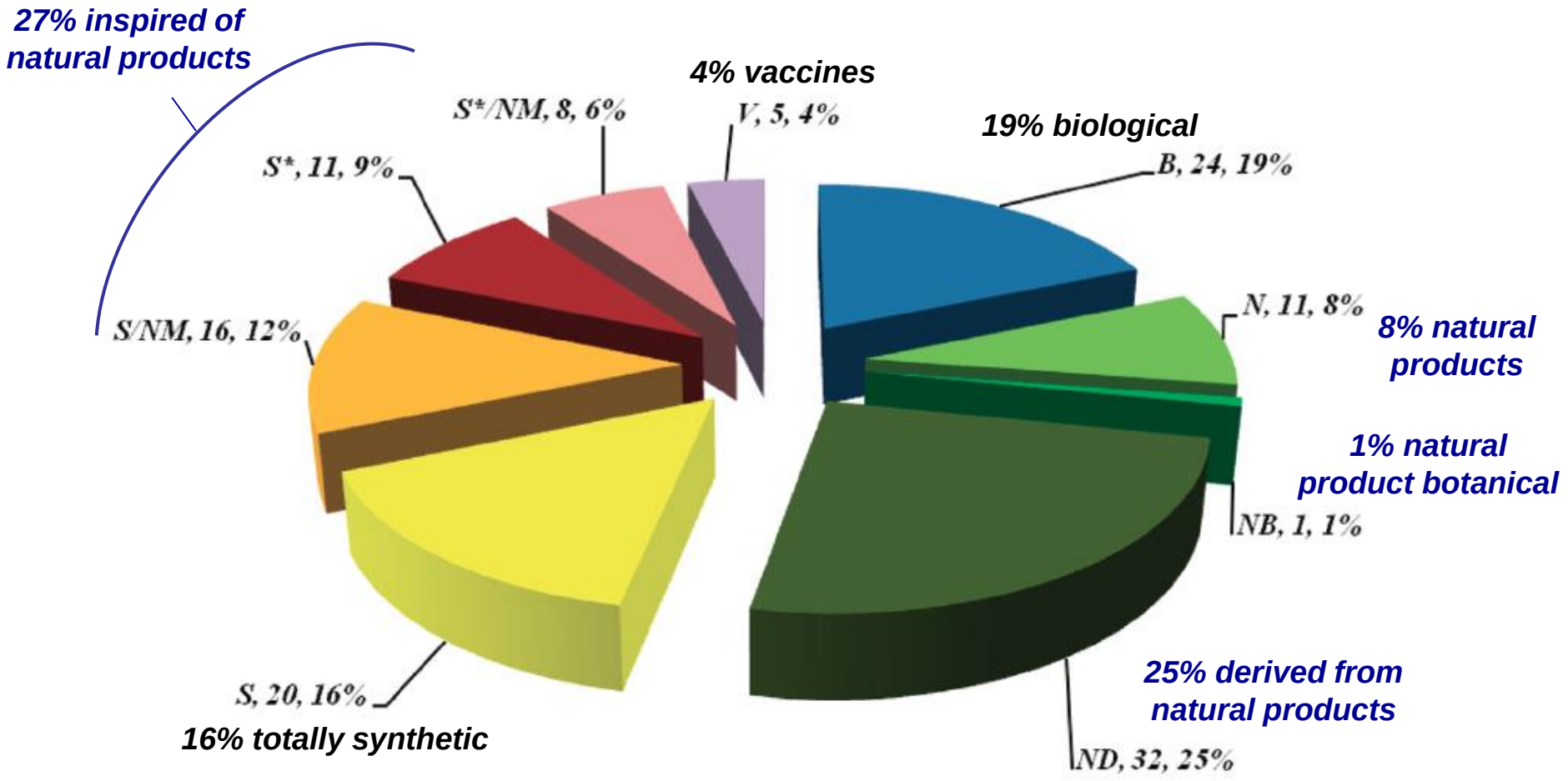
origin of 1355 new approved drugs 1981-2010:
50% derived or inspired from natural products



J. Nat. Prod. **2012**, 311.

2. Therapeutic relevance of natural products

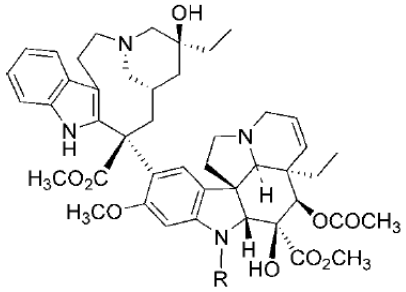
origin of new anticancer drugs 1981-2010:
61% derived or inspired from natural products



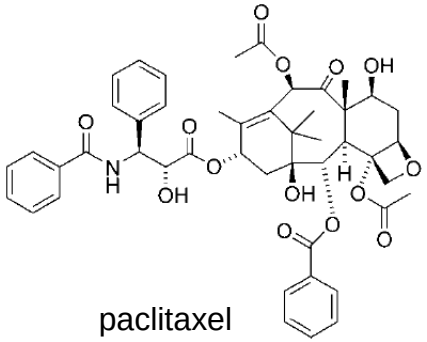
J. Nat. Prod. **2012**, 311; *Chem. Rev.* **2009**, 3012.

2. Therapeutic relevance of natural products

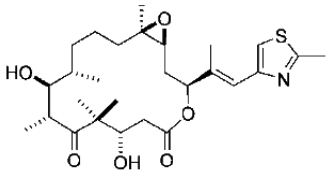
examples of anticancer natural products



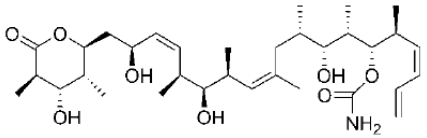
vinblastine (R=CH_3)
vincristine (R=CHO)
indole (vinca) alkaloids
tubulin



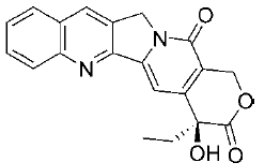
paclitaxel
diterpene
tubulin



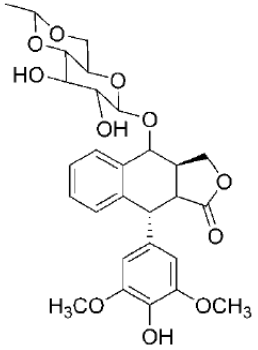
epothilone B
macrolide
tubulin



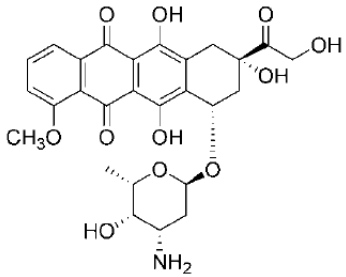
discodermolide
polyketide
tubulin



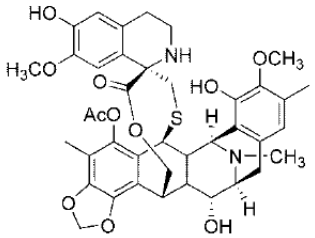
camptothecin
(quinoline) alkaloid
topoisomerase I



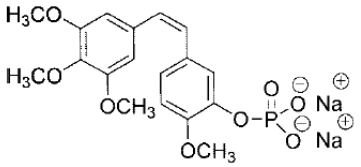
etoposide
lignan
topoisomerase II



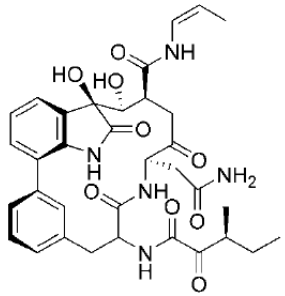
doxorubicin
anthracycline
topoisomerase II



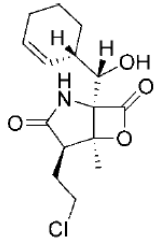
ecteinascidin 743
(tetrahydroisoquinoline) alkaloid
DNA



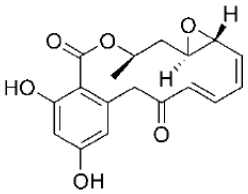
combretastatin A-4P
stillbenoid
tubulin



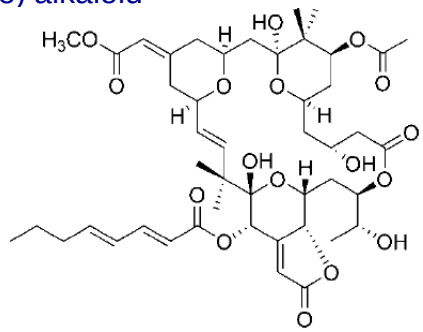
TMC-95A
cyclic peptide
proteasome



salinosporamide A
γ-lactam
proteasome



radicicol
(resorcylic acid) lactone
Hsp90



bryostatin 1
macrolide
protein kinase C

2. Therapeutic relevance of natural products

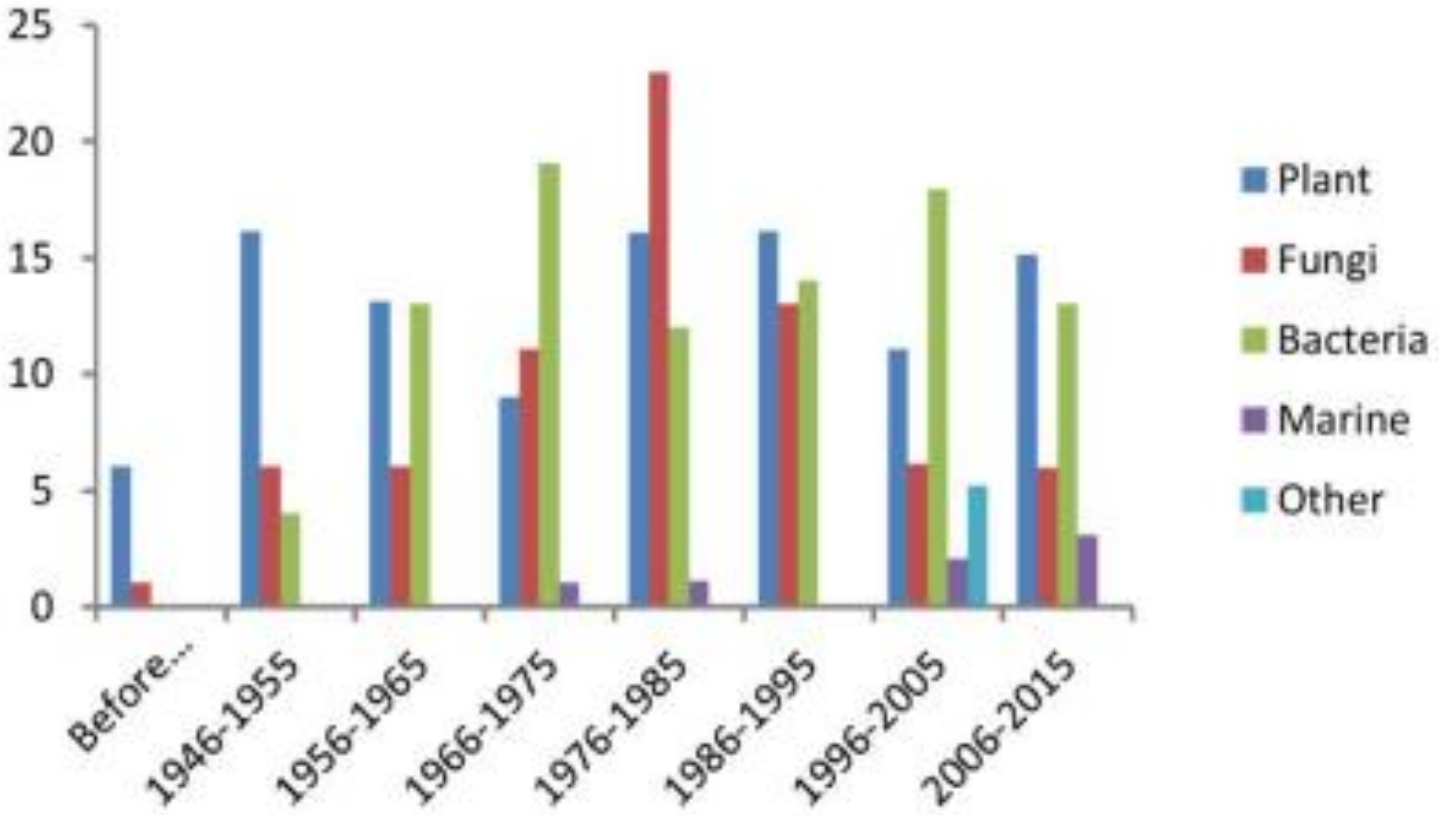


Figure 28. Number of approved NP drugs of various origin.

- The Symbiotic Relationship Between Drug Discovery and Organic Chemistry
  O. O.Grygorenko,*, D. M.Volochnyuk, S. V. Ryabukhin, D. B. Judd
  Chem. Eur. J. **2020**, *26*, 1196 – 1237

3. Interest of natural product synthesis

- Verification/correction of proposed structure
(in particular the relative and absolute stereochemistry)

- Limited availability of some NP (e. g. marine organisms)

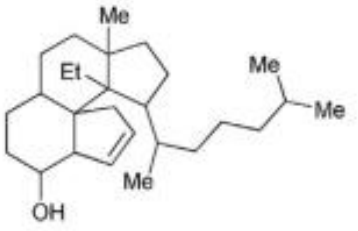
- Biological activity: synthesis of more efficient analogues (SAR)

- Structure originality (fascination?)

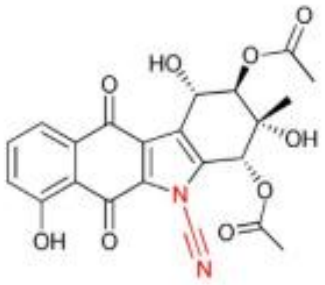
- Development/application of new synthetic methods

- Development of new synthetic strategies

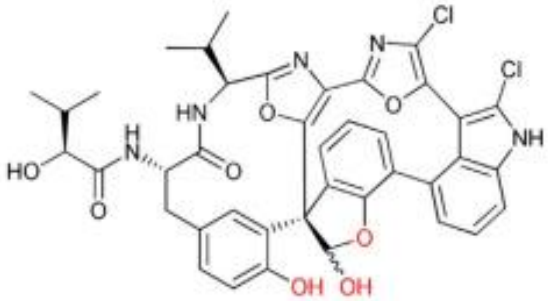
3. Interest of natural product synthesis



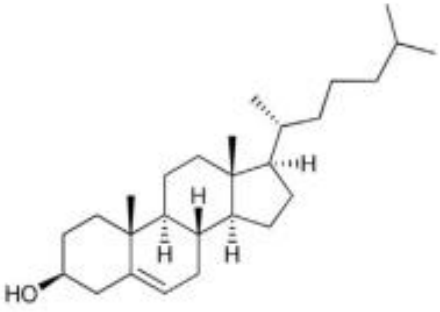
Tentative structure of cholesterol proposed in 1928



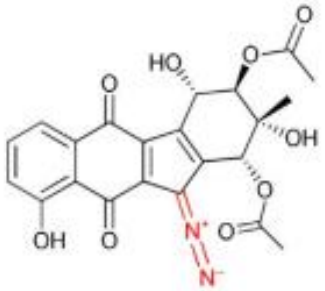
Tentative structure of kinamycin C proposed in 1973 according to X-ray data



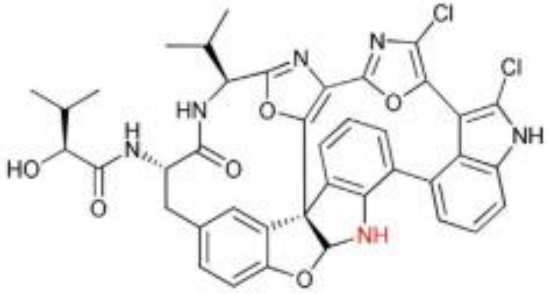
Tentative structure of diazonamide A proposed in 1991 according to X-ray data



Cholesterol



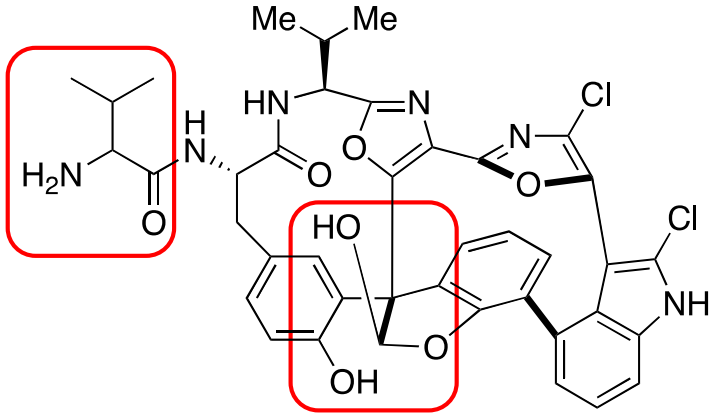
Kinamycin C



Diazonamide A

3. Interest of natural product synthesis

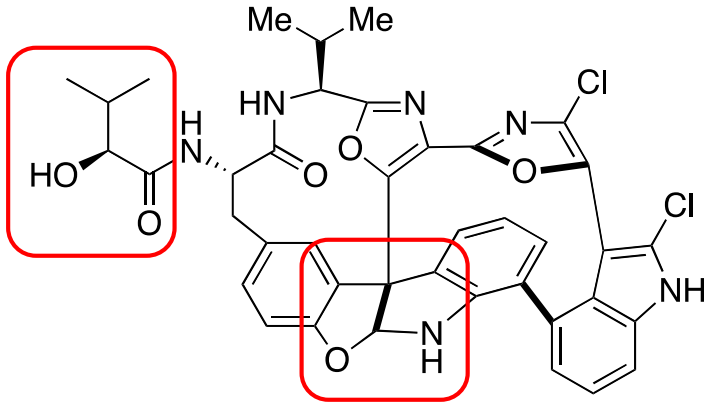
Diazonamide A



initially proposed structure (NMR, X-ray)
(Fenical, *JACS* **1991**, 2303)

- Isoled from an ascidian (marine organism): 54 mg from 256 g (yield = 0.021%)
- High cytotoxicity toward cancer cell lines (IC_{50} < 15 ng/mL)
- Original rigid structure

– H_2O



Structure revised by total synthesis
(Harran, *ACIE* **2001**, 4765&4770,
Nicolaou, *ACIE* **2002**, 3495)

3. Interest of natural product synthesis

- Verification/correction of proposed structure
(in particular the relative and absolute stereochemistry)

- Limited availability of some NP (e. g. marine organisms)

- Biological activity: synthesis of more efficient analogues (SAR)

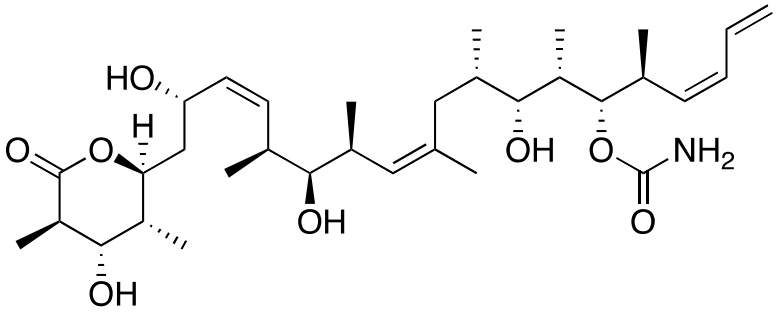
- Structure originality (fascination?)

- Development/application of new synthetic methods

- Development of new synthetic strategies

3. Interest of natural product synthesis

Discodermolide



- Isolated from a sponge: 7 mg from 434 g (yld = 0.002%)
- Potent antitumor properties (Taxol-type)
- Phase I clinical trials (Novartis)
- Development of a total synthesis by Novartis based on two academic syntheses (Smith, Paterson)

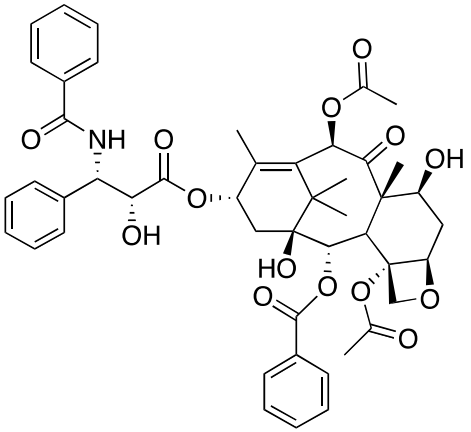
→ 60 g of discodermolide, 26 steps, 0.6% overall yield

Revue: *EurJOC* **2003**, 2193; *Org. Proc. Res. Dev.* **2004**, 92.

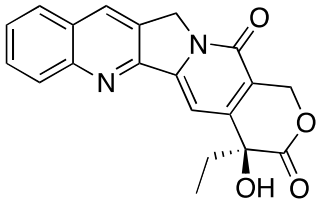
3. Interest of natural product synthesis

Famous drug analogues of natural products

Natural product

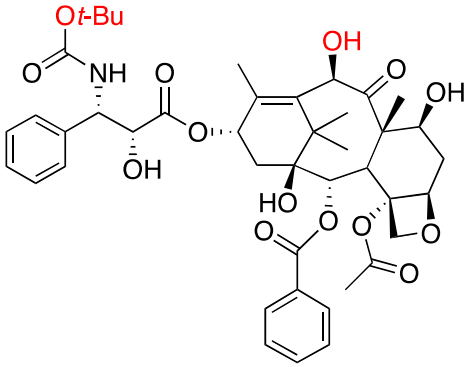


paclitaxel (Taxol®)

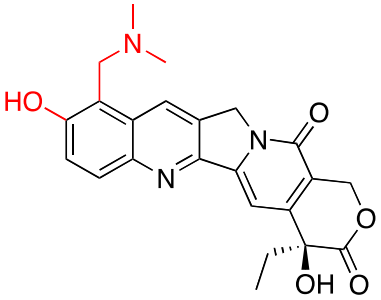


camptothecin

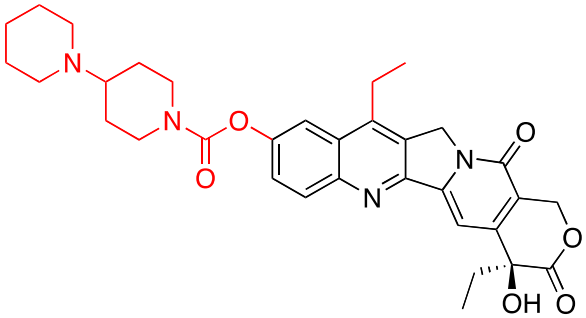
Analogue(s)



docetaxel (Taxotere®)

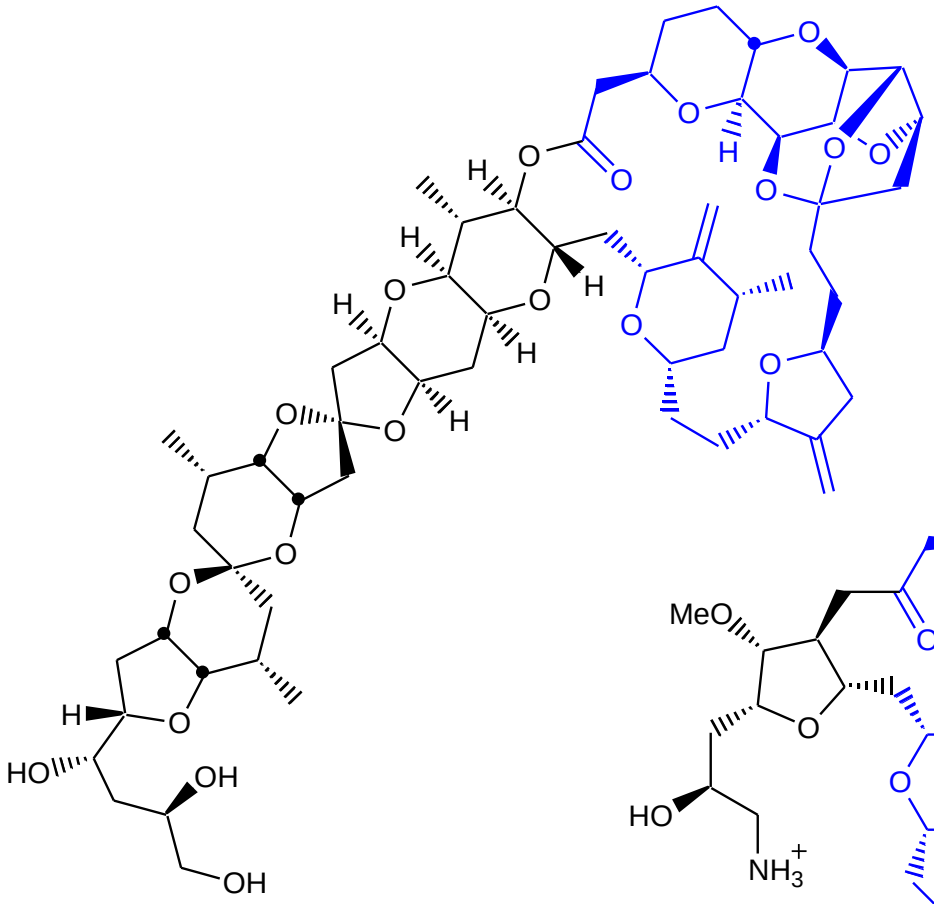


Topotecan®

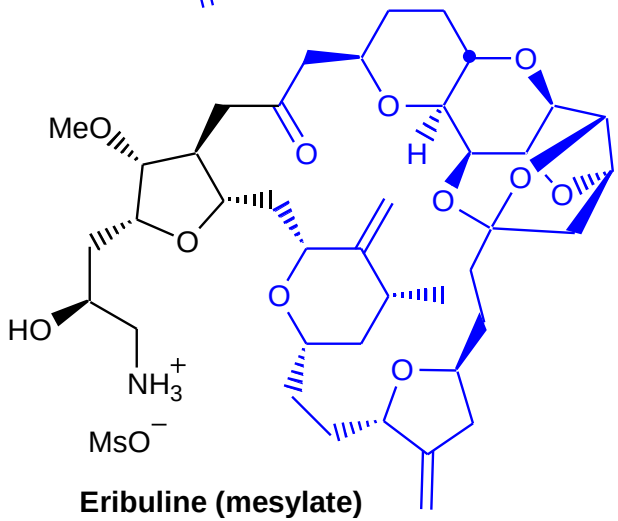


Irinotecan®

3. Interest of natural product synthesis

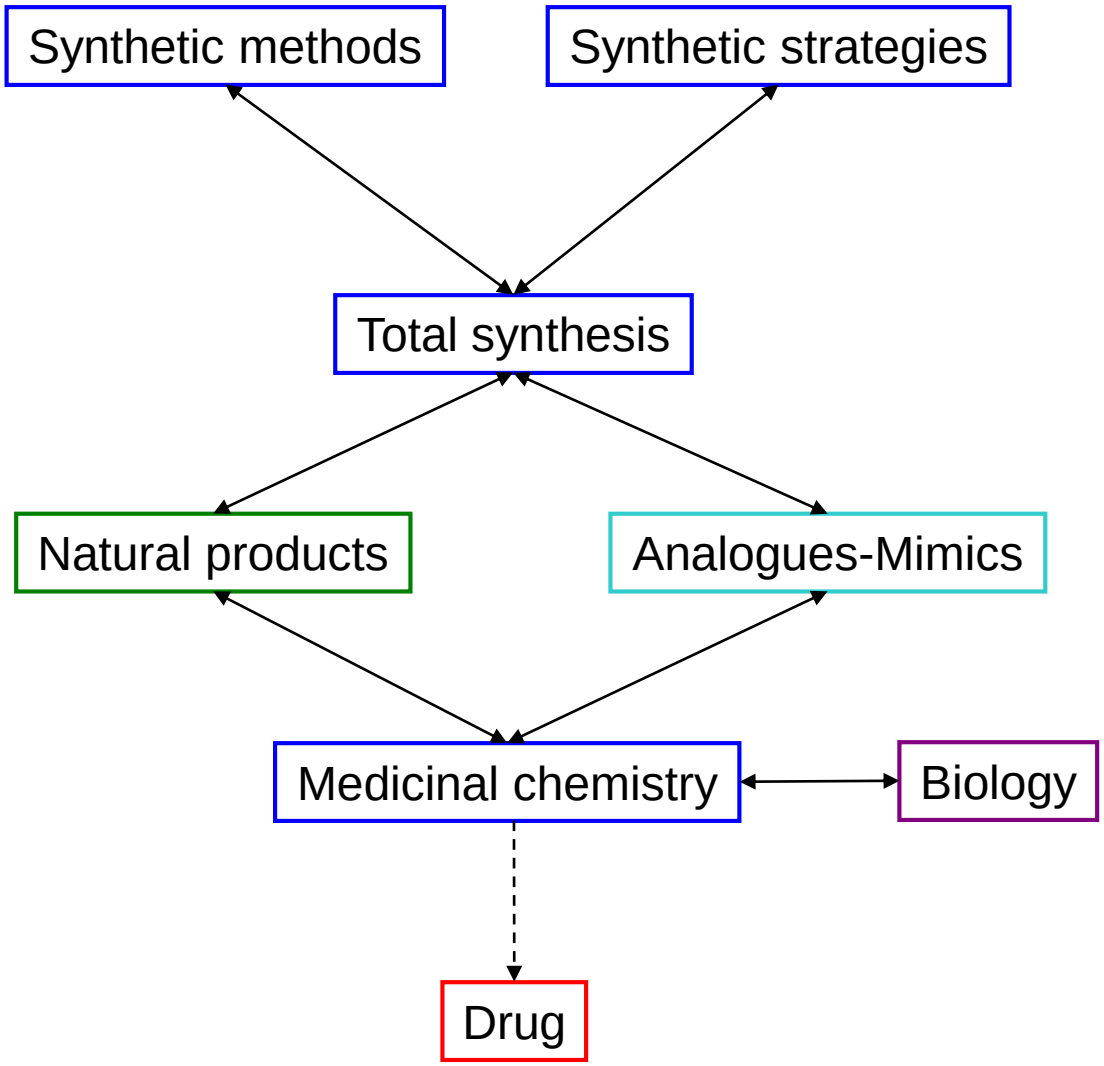


Halochondrine B



Eribuline (mesylate)

The central role of total synthesis



II - Concepts

1. General features
2. Linear *vs.* convergent syntheses
3. Divergent syntheses
4. Atom economy
5. Domino reactions
6. Retrosynthetic analysis

1. General features

Academic syntheses

- Higher overall yield (convergent synthesis) – Highly efficient
- Minimal number of steps (few PG, atom-economical reactions)
- Flexibility (adaptation to dead-ends, synthesis of analogues)
- Selectivity (chemo, regio, stereo)
- Originality - elegance

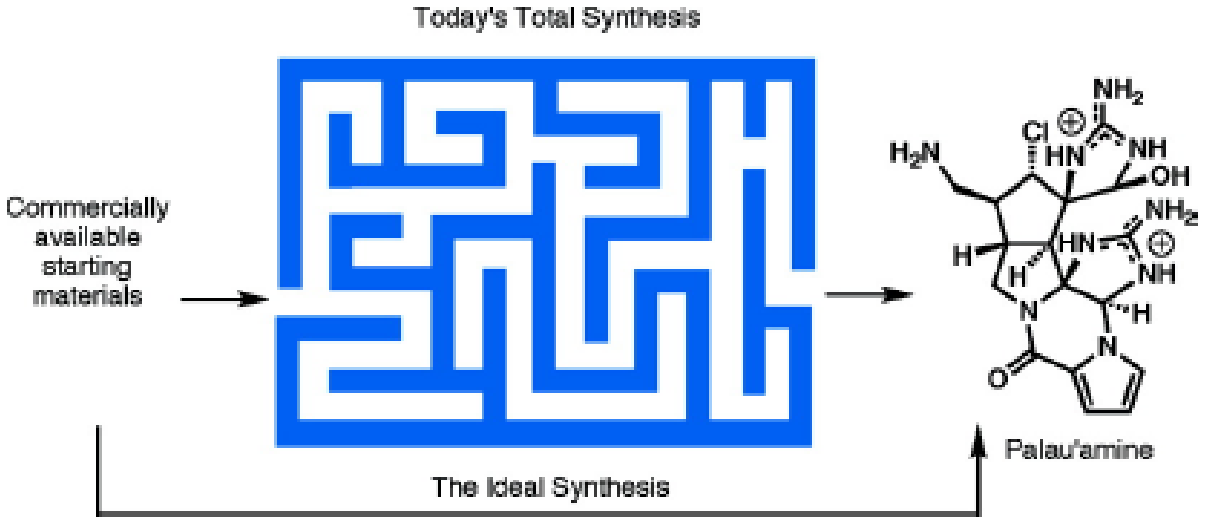
Industrial syntheses

- Minimal global cost – economically acceptable
- Minimal number of operations (work-up, purification…)
- Minimal waste and risks – environmentally acceptable
- Reproducibility

1. General features

« *The ideal synthesis* » …a sequence of only construction reactions involving no intermediary refunctionalizations, and leading directly to the target, not only its skeleton but also its correctly placed functionnality.

J. B. Hendrickson
J. Am. Chem. Soc. **1975**, *97*, 5784,



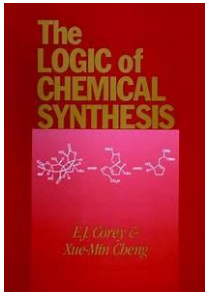
T. Gaich, P.S. Baran *J. Org. Chem.* **2010**, *75*, 4657.

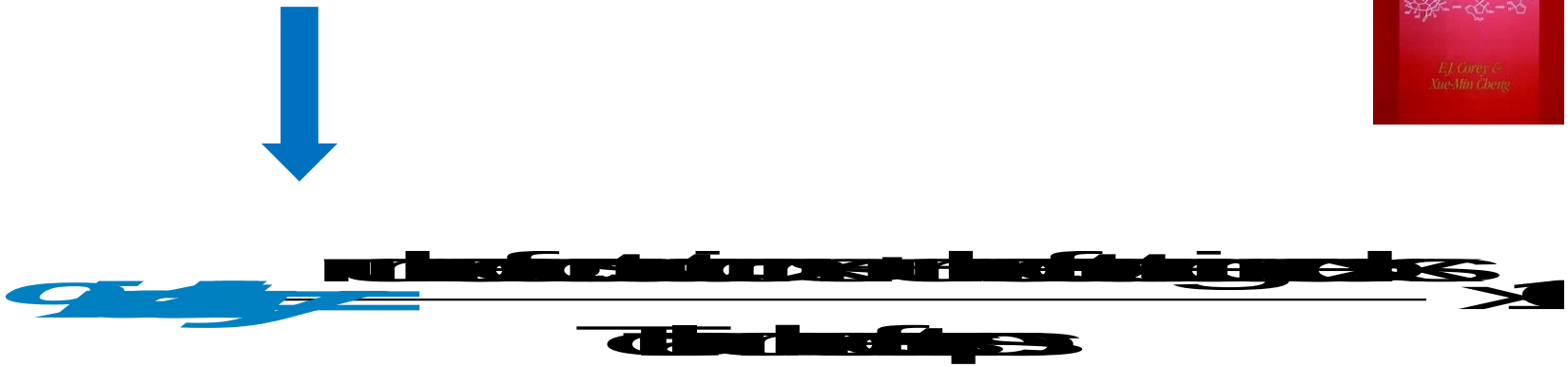
1. General features

« ***The ideal retrosynthesis*** » …a wise choice of appropriate symplifying transformations.

27

E. J . Corey
The Logic of Chemical Synthesis , **1989**





T. Gaich, P.S. Baran *J. Org. Chem.* **2010**, *75*, 4657.

Discovery of new reactions / new procedures

1. General features

Academic syntheses

- Higher overall yield (convergent synthesis)
- Minimal number of steps (few PG, atom-economical reactions)
- Flexibility (adaptation to dead-ends, synthesis of analogues)
- Selectivity (chemo, regio, stereo)
- **Originality – elegance***

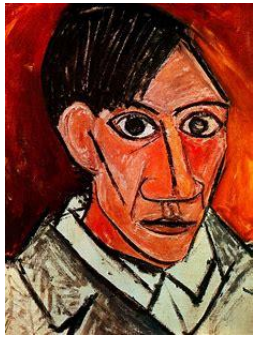
Industrial syntheses

- Minimal global cost
- Minimal number of operations (work-up, purification…)
- Minimal waste and risks
- Reproducibility

*Pursuing practical elegance in chemical synthesis
R. Noyori *Chem. Commun.* **2005**, 1807-1811.

1. General features

ART



« Asking a chemist how he came upon precisely the starting materials and reactions that so elegantly led to the desired results would probably be as meaningless as asking *Picasso* why he painted as he did. »

E. J. Corey

- Chemical synthesis = Creative activity in which art, design, imagination and inspiration play a dominant role.
- Organic synthesis = heuristic activity
- Importance of serendipity

GDCh Essays Angewandte International Edition Chemie

Chemistry and Architecture

International Edition: DOI: 10.1002/anie.201708325
German Edition: DOI: 10.1002/ange.201708325

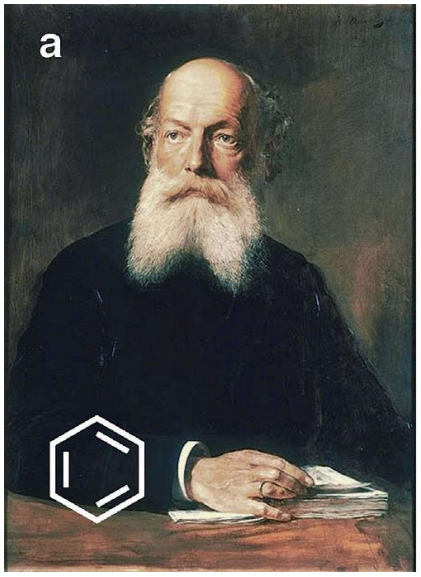
The Chemist and the Architect**

*Dirk Trauner**

architecture · self-assembly · supramolecular chemistry · symmetry · synthetic organic chemistry

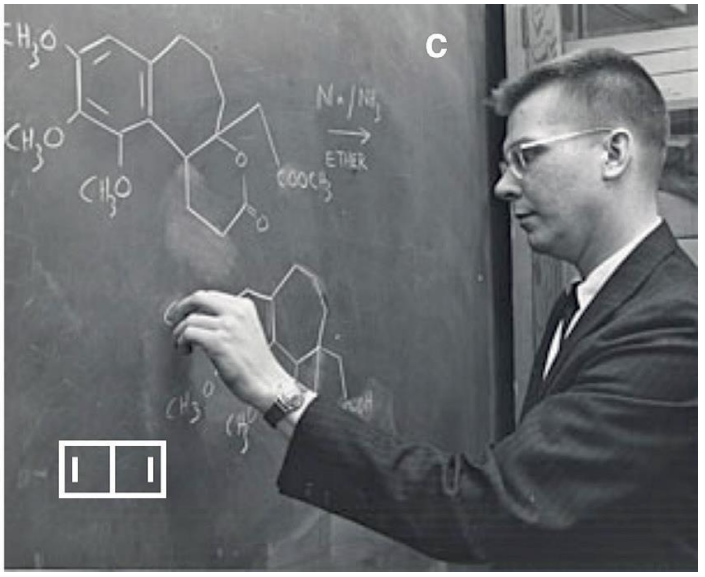
Angew. Chem. Int. Ed. 2018, 57, 4177 – 4191

To imagine a structure and then express it in material form is one of the most satisfying of human activities. It is pervasive throughout the arts and crafts and it is one of the defining features of **architecture**.
It is also at the **heart of synthetic chemistry**.



A. von Kekulé

R. Willstätter



E. Van Tamelen

Chemistry and Architecture

International Edition: DOI: 10.1002/anie.201708325
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architecture · self-assembly · supramolecular chemistry · symmetry · synthetic organic chemistry

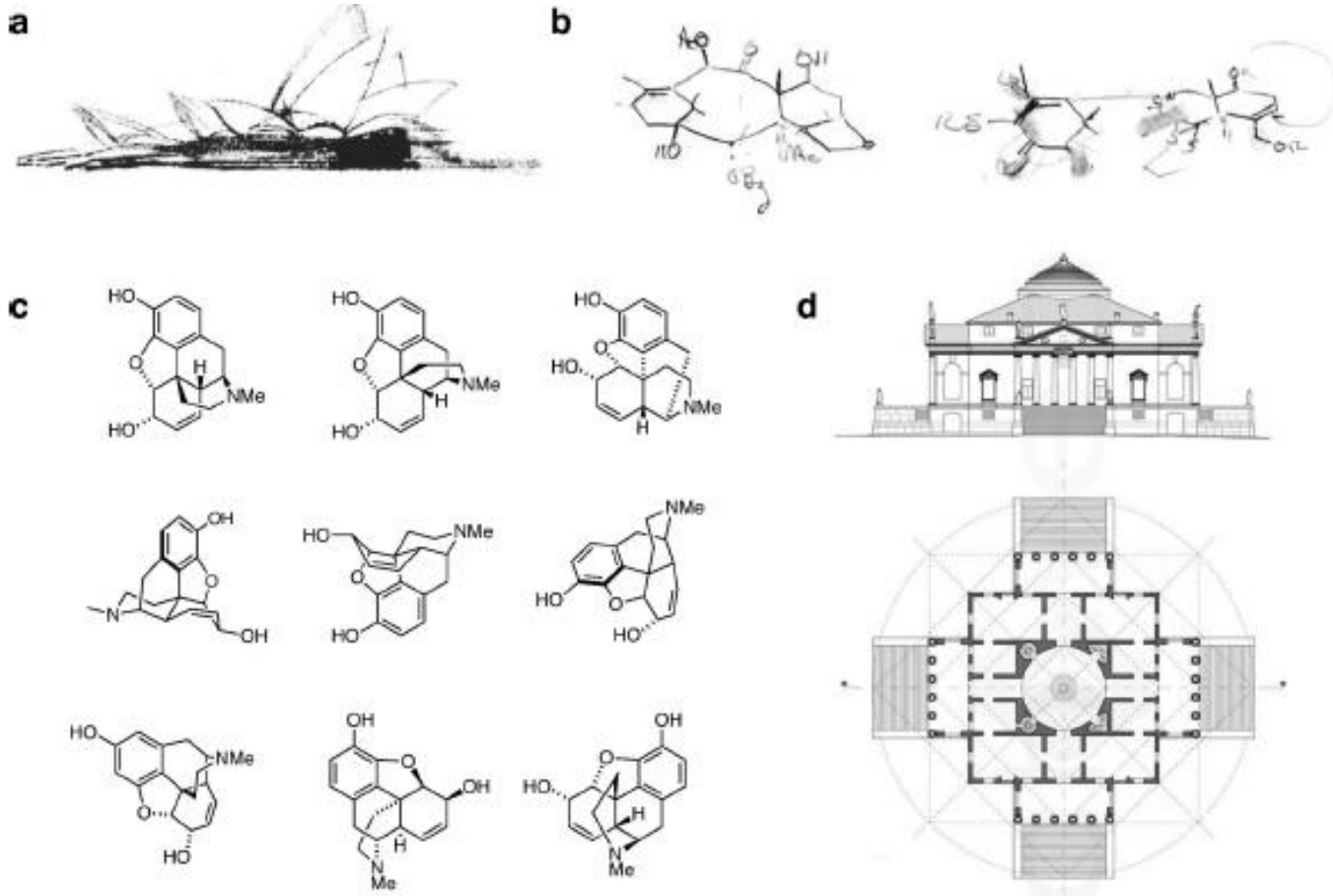
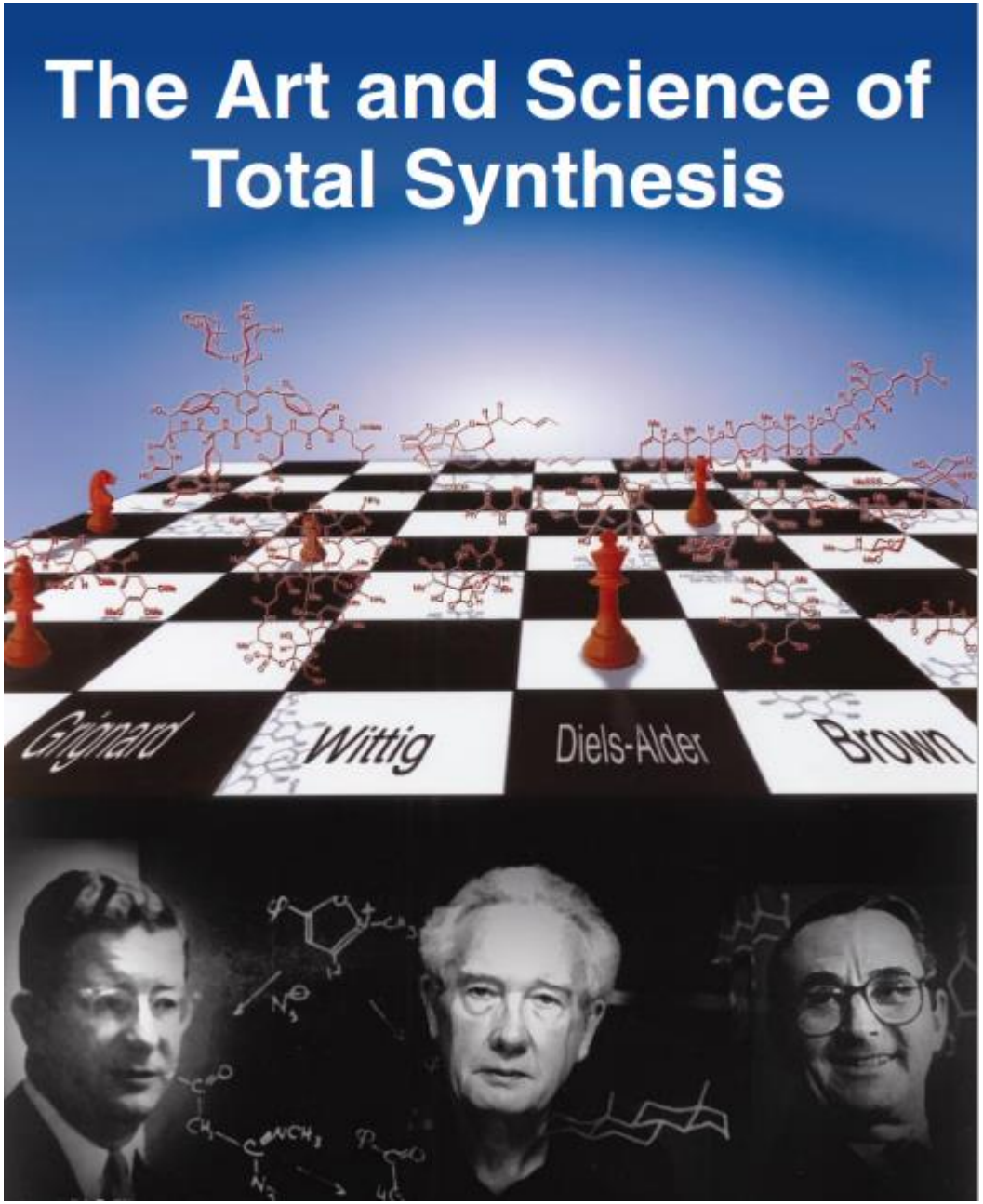


Figure 8. Drawing in chemistry and architecture. a) Utzon's sketch for the Sydney Opera house. b) Danishefsky's sketch of a taxol synthesis. c) Different drawings of morphine emphasize different aspects of the molecule. d) Different projections of Andrea Palladio's La Rotonda provide an understanding of the building.



The Art and Science of Total Synthesis at the Dawn of the Twenty-First Century**

K. C. Nicolaou,* Dionisios Vourloumis, Nicolas Winssinger, and Phil S. Baran

Angew. Chem. Int. Ed. **2000**, *39*, 44–122

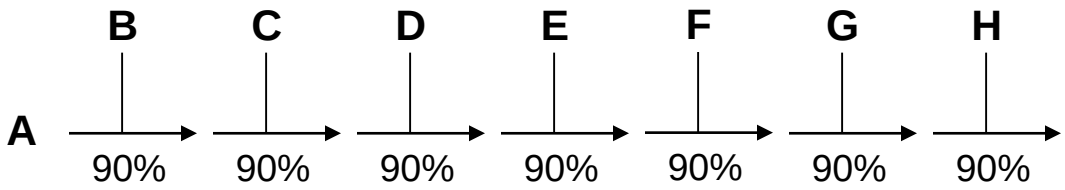
1. General features

1. E Factor

Industrie	Tonnage annuel en produit	Facteur E	Tonnage annuel En déchets	Nombre d'étapes
Pétrochimie	10^6-10^8 t	0,1	10^7 t	séparation
Chimie lourde	10^5- 10^6 t	<1 - 5	5. 10^6 t	1 - 2
Chimie fine	100 – 10^4 t	5 - 50	5. 10^5 t	3 - 4
Industrie Pharma.	10 – 1000 t	25 - > 100	10^5 t	> 6

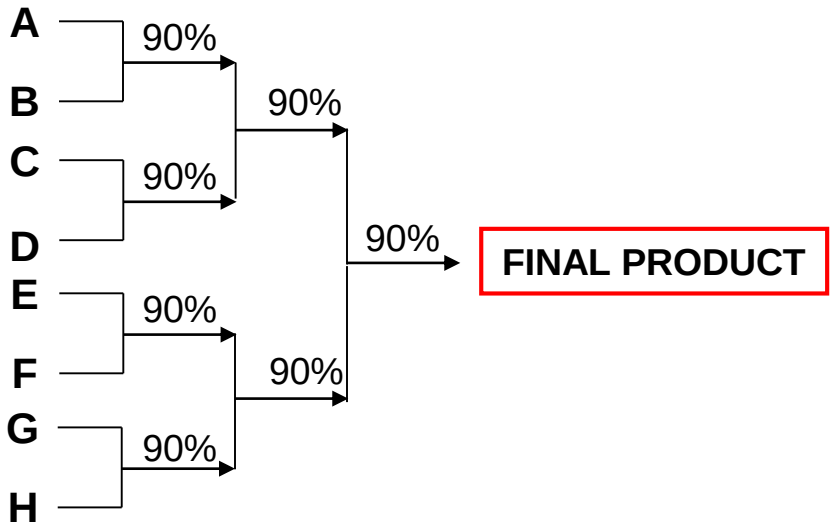
2. Linear *vs.* convergent syntheses

Linear synthesis



7 steps
overall yield = $0{,}9^7$ = 48%

Convergent synthesis



7 steps in total
longest linear sequence = 3 steps
overall yield = $0{,}9^3$ = 73%

(for 64 blocs: 53% *vs.* 0.13% !)

- higher overall yield
- better flexibility: adaptability to dead-ends, synthesis of analogues

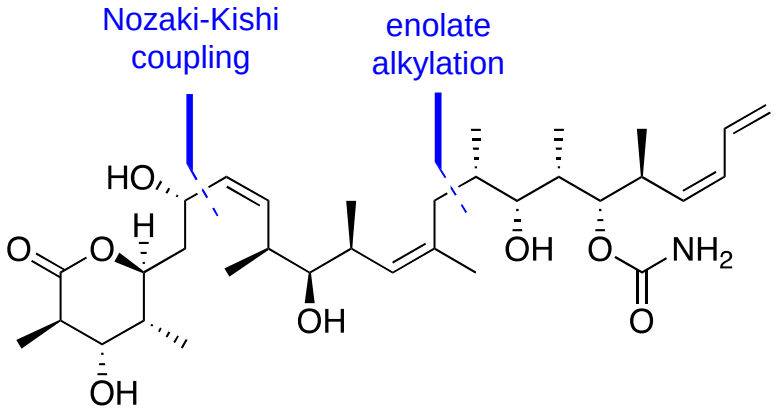

M
HK
Kita-Senri
Yamada
Minami-Senri
Senriyama
Kandai-mae
Toyotsu
Suita
Shimo
Shinjo
Awaji
Kami-Shinjō
Aikawa
Shōjaku
Settsu-shi
Ibaraki-shi
Tonda
Minami-Ibaraki
Sōjiji
I
Itakano
Zuikō-yonchōme
T
Dainichi
Moriguchi
Daidō-Toyosato
Taishibashi-Imaichi
Sembayashi-Omiya
Shimizu
Shimmori-Furuichi
Sekime-Seiiku
Sekime-Takadono
N
Kadoma-minami
Tsurumi-ryokuchi
Gamo yonchōme
Yokozutsumi
Kyōbashi
Imafuku-Tsurumi
Shigino
C
Gakken Nara-Tomigaoka
Gakken Kita-Ikoma
Shiraniwadai
Ikoma
Senri-Chūō
Momoyama-dai
Ryokuchi-kōen
Esaka
Higashi-Mikuni
Shin-Ōsaka
Nishinakajima Minamigata
Sōzenji
Minamikata
Kunijima
Tenjimbashisuji Rokuchōme
Nakazakichō
Miyakojima
Noe-Uchindai
Jūsō
Nakatsu
Umeda
HK
K
Ōgimachi
Minami-morimachi
S
Y
Nishi Umeda
Higashi-Umeda
Ōsaka Tenman-gū
Kitahama
Temmabashi
Osaka Business Park
Osaka Castle Park
Morinomiya
Midoribashi
Takaida
Aramoto
Shin-Ishikiri
Fukaebashi
Nagata
Yoshita
Nodahanshin
Yodoyabashi
Higobashi
Tamagawa
Awaza
Hommachi
Sakaisuji Hommachi
Tanimachi yonchōme
Nishi Nagahori
Nishi-ōhashi
Shinsaibashi
Matsuyamachi
Tamatsukuri
Kujō
Bentenchō
Dome-mae Chiyozaki
Taishō
Yotsubashi
Sakuragawa
Nagahoribashi
Tanimachi rokuchōme
Namba
Namba Yasaka-jinja
Nippombashi
Tanimachi kyuchōme
Shin-Fukae
Tsuruhashi
Imazato
Shōji
Kita-Tatsumi
Minami-Tatsumi
Asashiobashi
Tempozan Ferris Wheel
Ōsakakō
Daikokuchō
Ebisuchō
Tsūtenkaku
Tennōji Park
Shitennōji-mae Yūhigaoka
Tennōji
Dōbutsuen mae
Tengachaya
Abeno
Fuminosato
Shōwachō
Nishitanabe
Nagai
Abiko
Kitahanada
Shinkanaoka
Nakamozu
Tanabe
Komagawa-nakano
Hirano
Kire-Uriwari
Deto
Nagahara
Yaominami
Hanazonochō
Kishinosato
Tamade
Kitakagaya
Suminoekōen
Cosmosquare
Nakafuto
Port Town higashi
Trade Center mae
Port Town nishi
Osaka Nankō Ferry Terminal
Ferry Terminal
Nankōguchi
Nankō-higashi
Hirabayashi
P
C


Senri-Chūō
Momoyama-dai
Ryokuchi-kōen
Esaka
Higashi-Mikuni
Shin-Ōsaka
Nishinakajima Minamigata
Jūsō
Nakatsu
Umeda
Nodahanshin
Nishi Umeda
Yodoyabashi
Tamagawa
Higobashi
Awaza
Hommachi
Nishi Nagahori
Kujō
Bentenchō
Dome-mae Chiyozaki
Taishō
Asashiobashi
Tempozan Ferris Wheel
Ōsakakō
Cosmosquare
Nakafuto
Port Town higashi
Trade Center mae
Port Town nishi
Ferry Terminal
Nankōguchi
Nankō-higashi
Hirabayashi
Suminoekōen
Hanazonochō
Kishinosato
Tamade
Kitakagaya
Kita-Senri
Yamada
Minami-Senri
Senriyama
Kandai-mae
Toyotsu
Suita
Shimo Shinjo
Awaji
Sōzenji
Minamikata
Kunijima
Nakazakichō
Tenjimbashisuji Rokuchōme
Higashi-Umeda
Ōgimachi
Minami-morimachi
Kitahama
Ōsaka Tenman-gū
Osaka City Central Hall
Nishi-ōhashi
Shinsaibashi
Nagahoribashi
Yotsubashi
Sakuragawa
Namba
Namba Yasaka-jinja
Daikokuchō
Ebisuchō
Nippombashi
Dōbutsuen mae
Tengachaya
Aikawa
Kami-Shinjō
Miyakojima
Noe-Uchindai
Matsuyamachi
Tamatsukuri
Tanimachi kyuchōme
Tanimachi rokuchōme
Shitennōji-mae Yūhigaoka
Tsūtenkaku
Tennōji Park
Tennōji
Abeno
Fuminosato
Shōwachō
Nishitanabe
Nagai
Abiko
Kitahanada
Shinkanaoka
Nakamozu
Settsu-shi
Ibaraki-shi
Tonda
Minami-Ibaraki
Sōjiji
Shōjaku
Itakano
Zuikō-yonchōme
Dainichi
Daidō-Toyosato
Moriguchi
Taishibashi-Imaichi
Sembayashi-Omiya
Sekime-Takadono
Shimizu
Shimmori-Furuichi
Sekime-Seiiku
Kadoma-minami
Tsurumi-ryokuchi
Gamo yonchōme
Yokozutsumi
Kyōbashi
Imafuku-Tsurumi
Shigino
Osaka Business Park
Temmabashi
Osaka Castle Park
Morinomiya
Midoribashi
Takaida
Aramoto
Shin-Ishikiri
Ikoma
Gakken Nara-Tomigaoka
Gakken Kita-Ikoma
Shiraniwadai
Fukaebashi
Nagata
Yoshita
Shin-Fukae
Imazato
Tsuruhashi
Shōji
Kita-Tatsumi
Minami-Tatsumi
Tanabe
Komagawa-nakano
Hirano
Kire-Uriwari
Deto
Nagahara
Yaominami
T

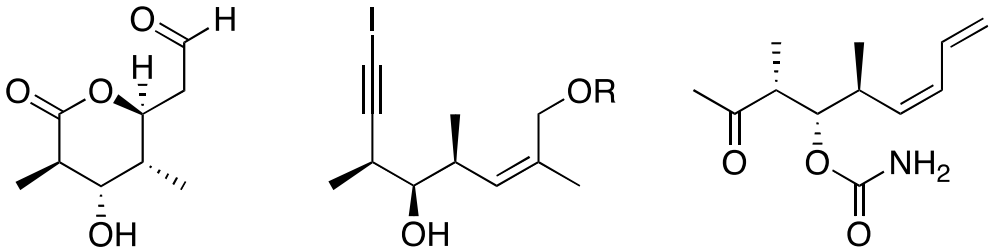
OSAKA

2. Linear *vs.* convergent syntheses

Convergent synthesis: example of discodermolide (Schreiber)



Fragments:



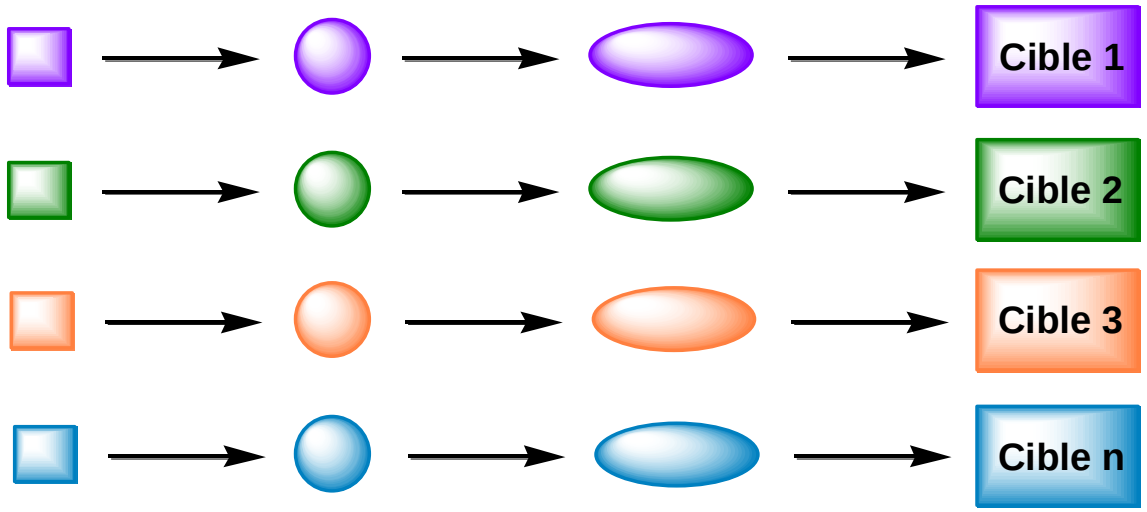
A **B** **C**

Possible strategies: (**A**+**B**)+**C** or **A**+(**B**+**C**)

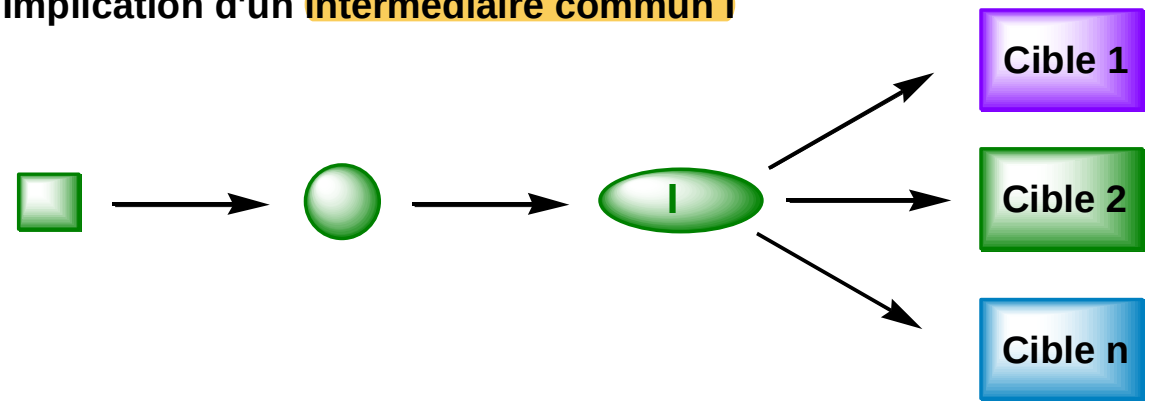
Schreiber, *JACS* **1996**, 11054.

5. Directed OS / Target-OS

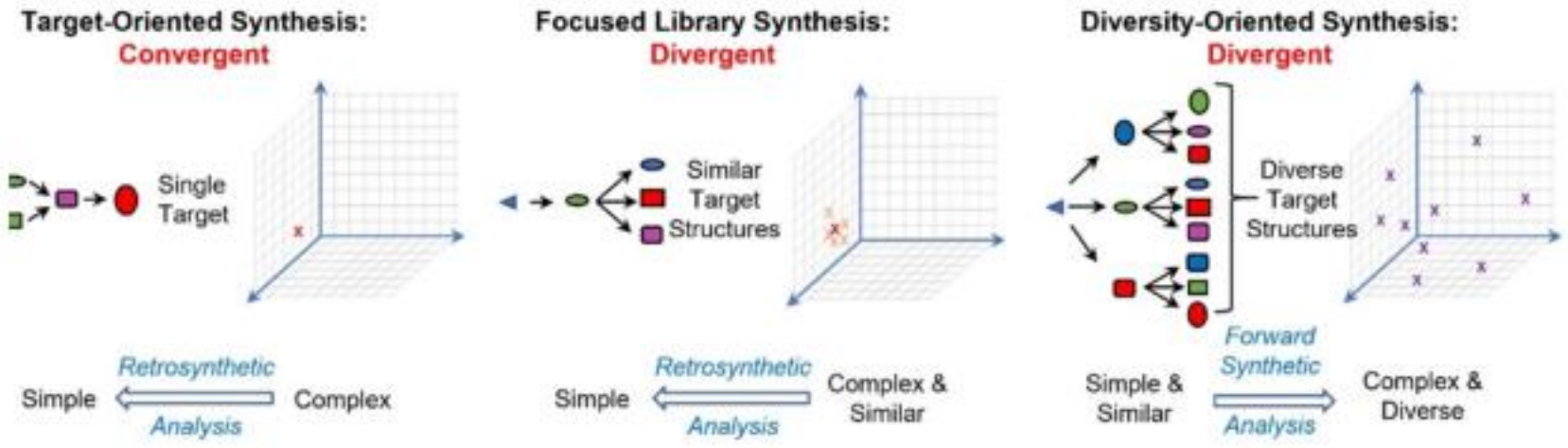
Synthèse orientée vers la cible:
Diversification par synthèse parallèle



Synthèse divergente
Implication d'un intermédiaire commun I

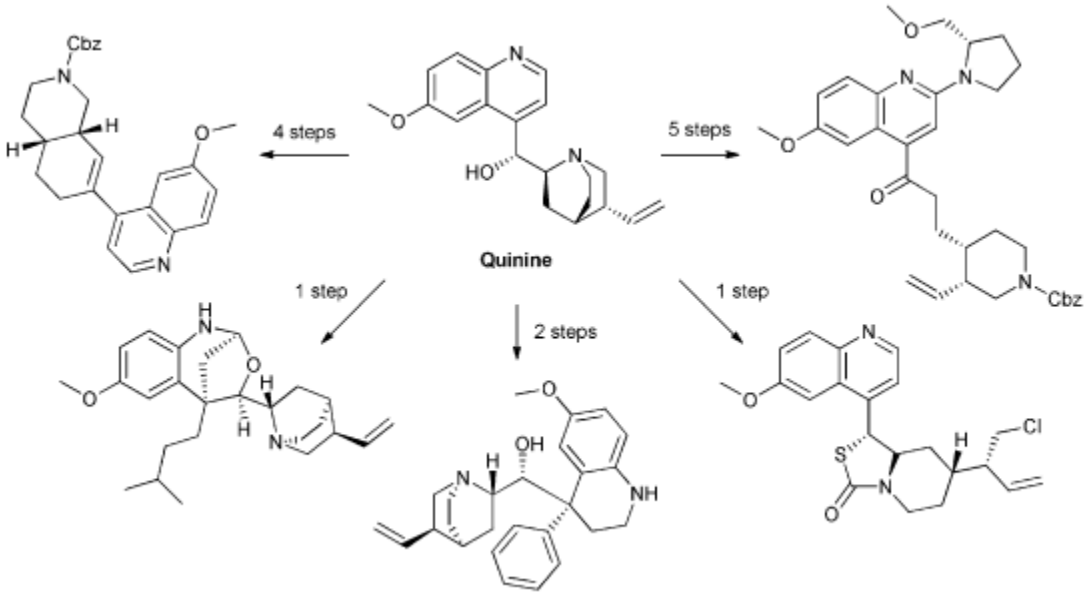


5. Directed OS / Target-OS



- The Symbiotic Relationship Between Drug Discovery and Organic Chemistry
  O. O.Grygorenko,*, D. M.Volochnyuk, S. V. Ryabukhin, D. B. Judd
  Chem. Eur. J. **2020**, *26*, 1196 – 1237

5. Directed OS / Target-OS



- The Symbiotic Relationship Between Drug Discovery and Organic Chemistry
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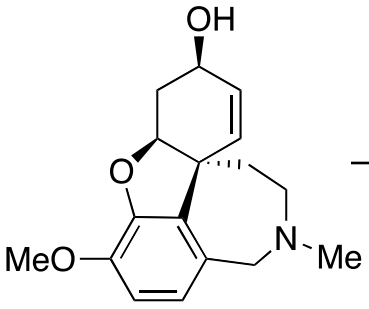
  Chem. Eur. J. **2020**, *26*, 1196 – 1237

3. Divergent syntheses

Diversity-oriented synthesis (as opposed to 'target-oriented synthesis')

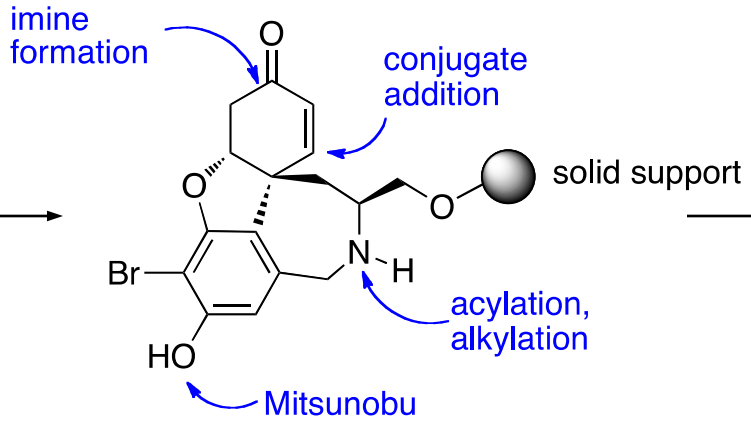
Interest: generation of a great number of analogues for biological screenings

Natural product (or mimic), synthetic intermediate → **A**, **B**, **C**, **D**, **…**, **Y**, **Z**

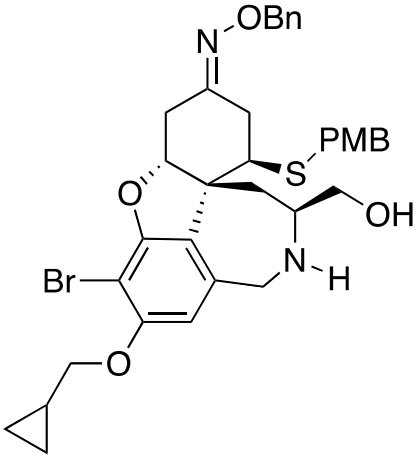


galanthamine

inhibitor of acetylcholinesterase



molecular scaffold for chemical library synthesis



secramine

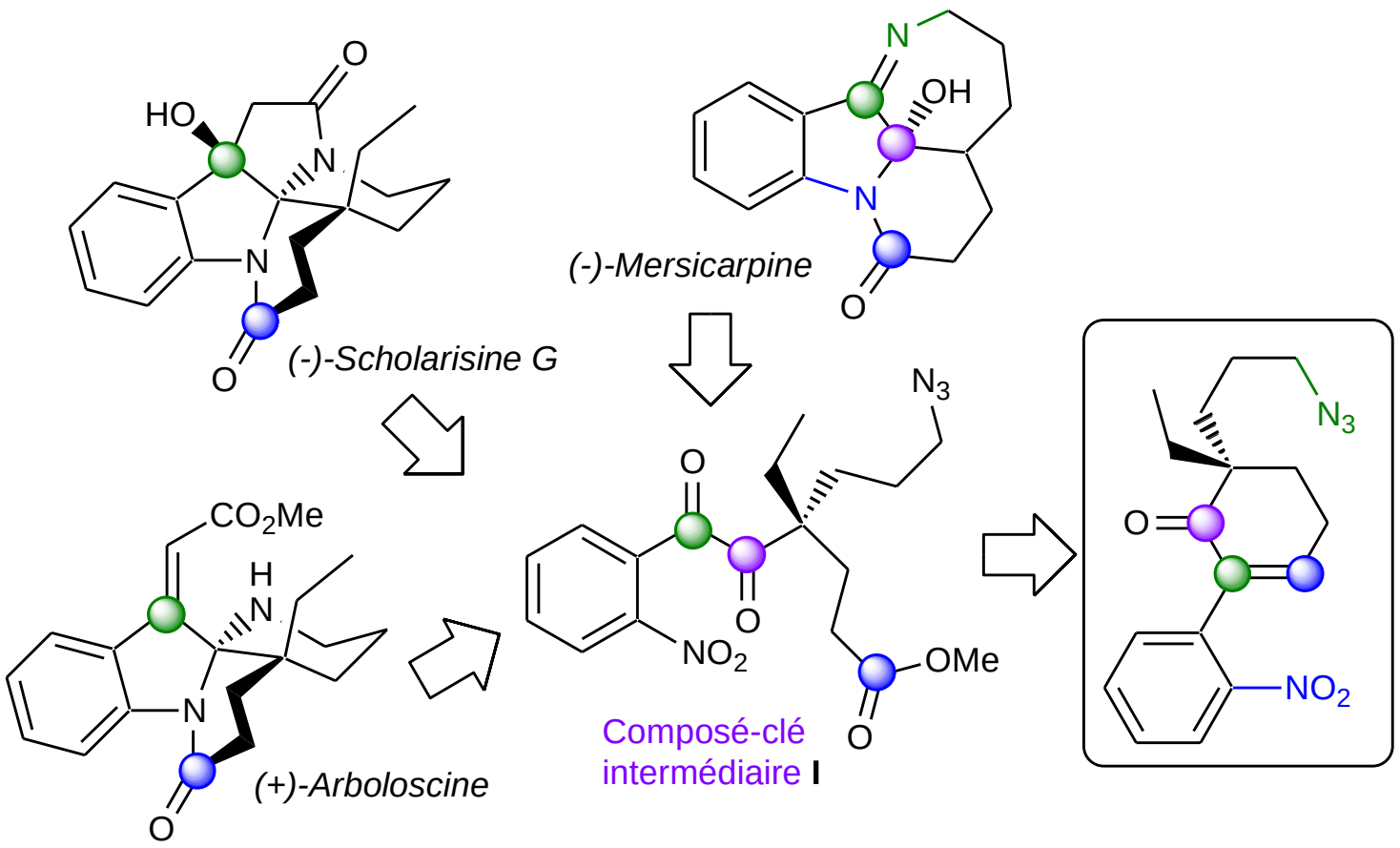
inhibitor of protein migration

synthesis of 2527 molecules!

Revue DOS: *Nat. Prod. Rep.* **2008**, 719.

Shair, *JACS* **2001**, 6740.

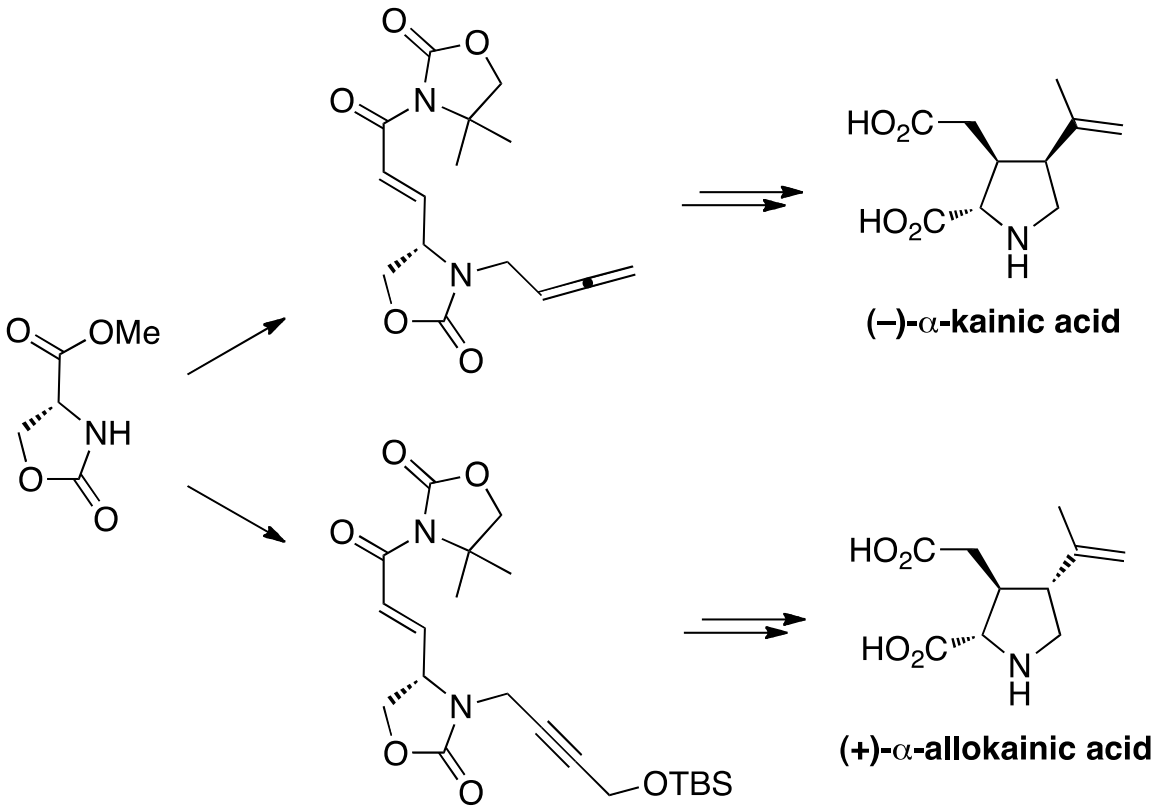
5. DOS / TOS



Z. Xu, Q. Wang, J. Zhu *J. Am. Chem. Soc.* **2015**, *137*, 6712-6724,

3. Divergent syntheses

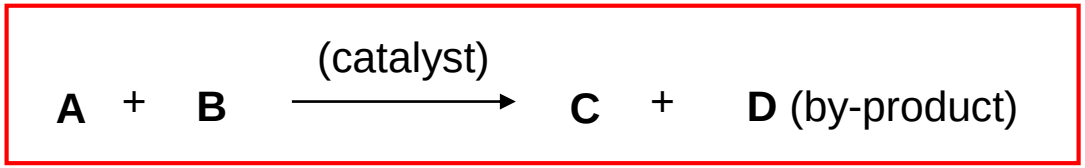
Stereodivergent syntheses: access to several stereoisomers of a natural product from a common enantiomerically pure precursor (enantio/diastereodivergence)



Montgomery, *JACS* **1999**, 11139.

4. Atom economy

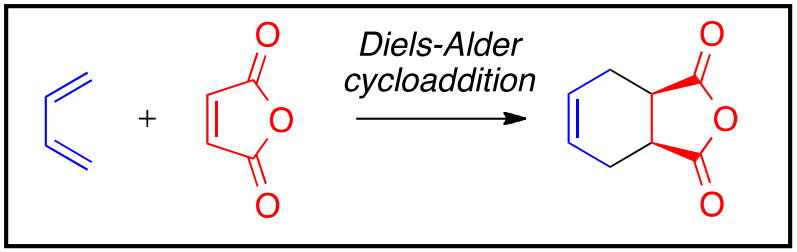
Describes reactions for which most (or all) atoms of the reactants are found in the structure of the desired product:

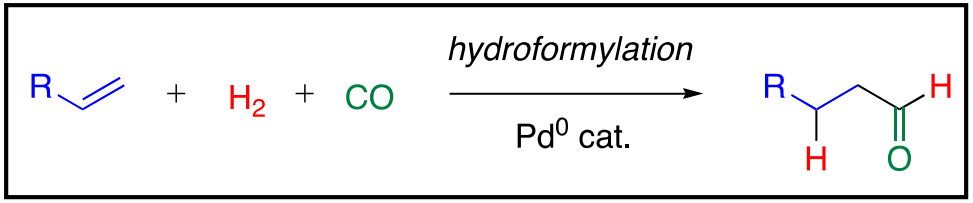


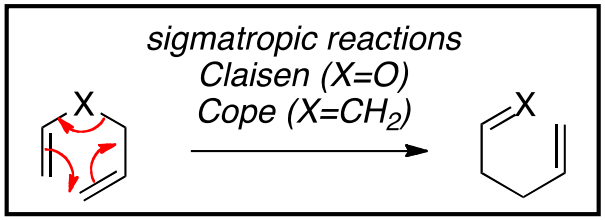
D = small and non-toxic (H_2O, CO_2…), if any

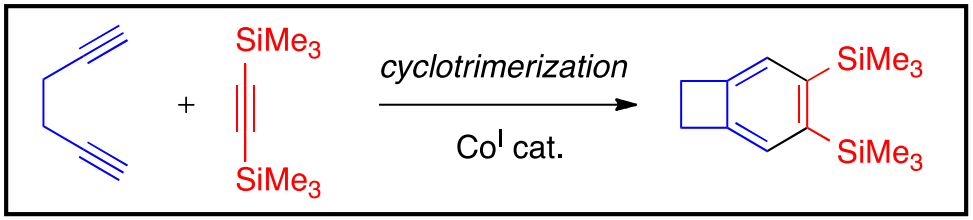
Examples:

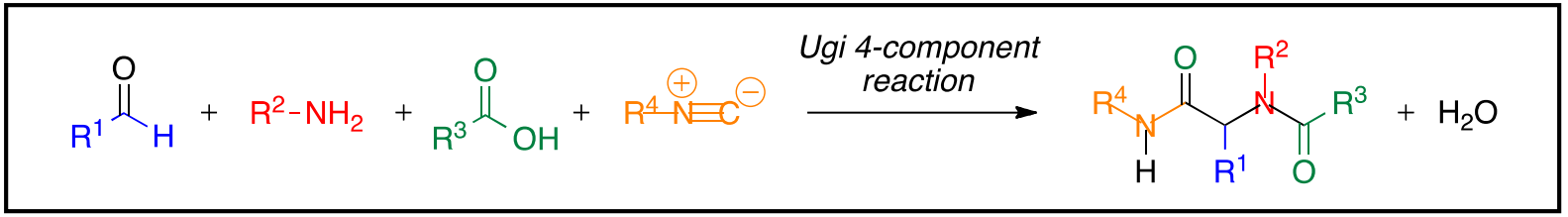
Trost, *ACIE* **1995**, 259.







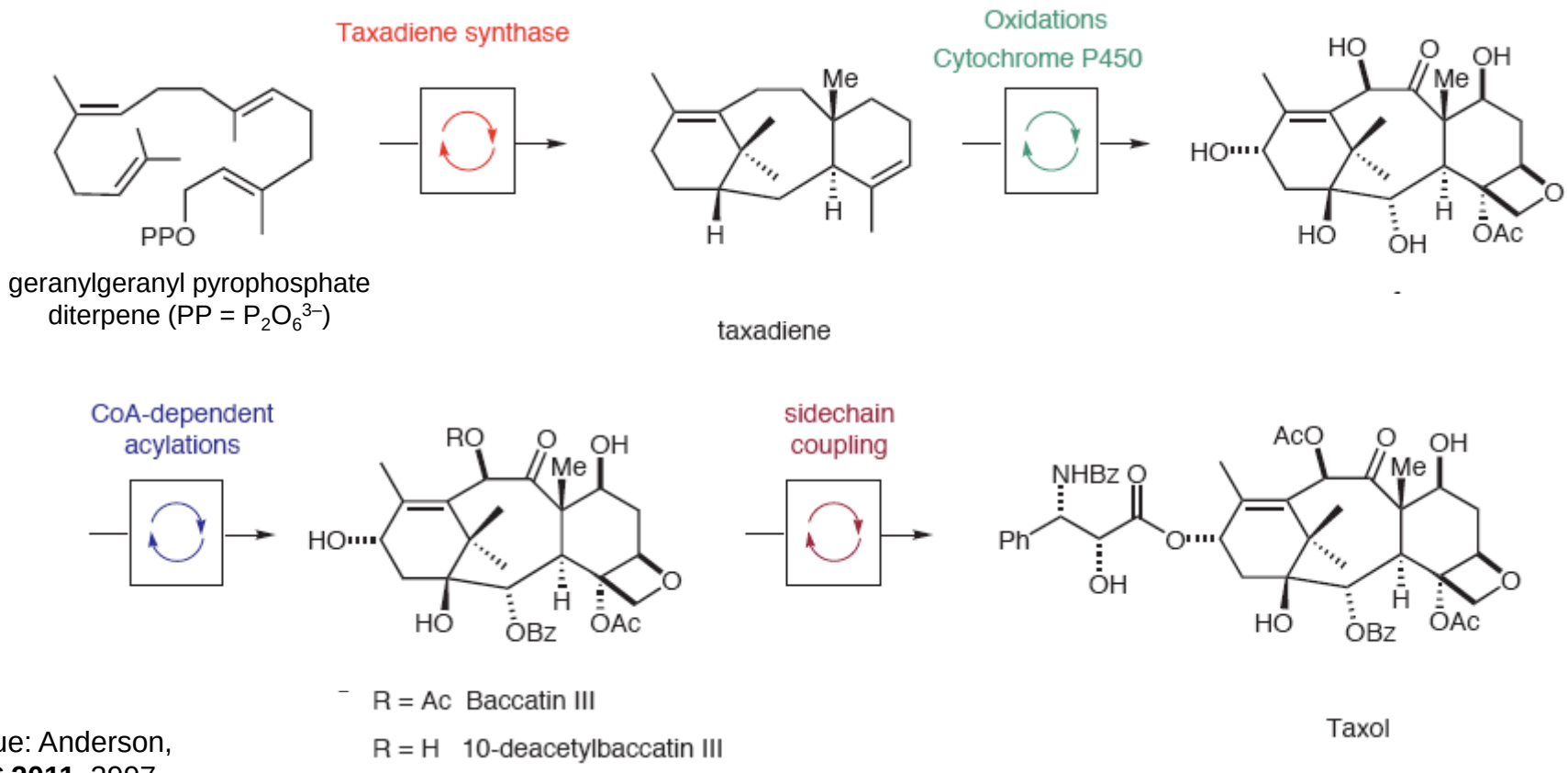




5. Domino reactions (cascade, tandem)

Definition: reactions which involve the formation of at least two bonds under the same conditions without further addition of reagent or catalyst.
If conditions are modified (including the addition of a reagent): *one-pot* reaction.

Domino reactions are often *biomimetic* = inspired of biosynthesis.
Example of Taxol biosynthesis:



geranylgeranyl pyrophosphate
diterpene (PP = $P_2O_6^{3-}$)

taxadiene

R = Ac Baccatin III

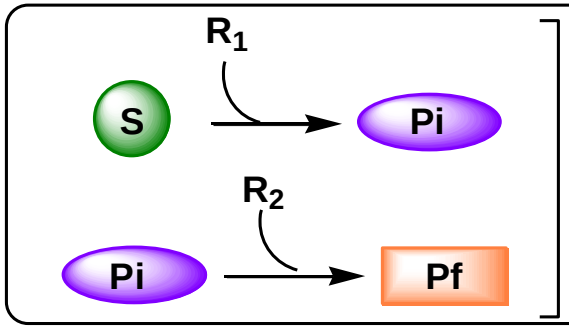
R = H 10-deacetylbaccatin III

Taxol

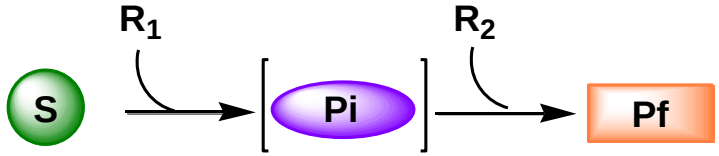
Revue: Anderson,
OBC **2011**, 3997.

5. Domino reactions (cascade, tandem)

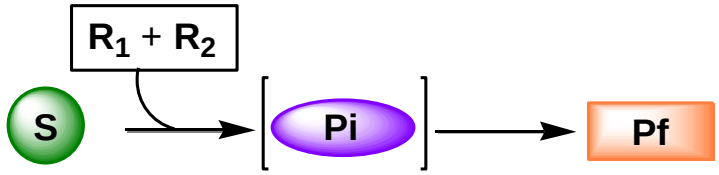
Definition: reactions which involve the formation of at least two bonds under the same conditions without further addition of reagent or catalyst.
If conditions are modified (including the addition of a reagent): *one-pot* reaction.



Synthèse classique
en deux étapes distinctes:
- **Action de R_1**
- **Isolement de Pi**
- **Action de R_2**



Approche "en un pot" séquentielle :
R_1 introduit en premier réagit pour donner P_i puis R_2 est ajouté et conduit au produit P_f



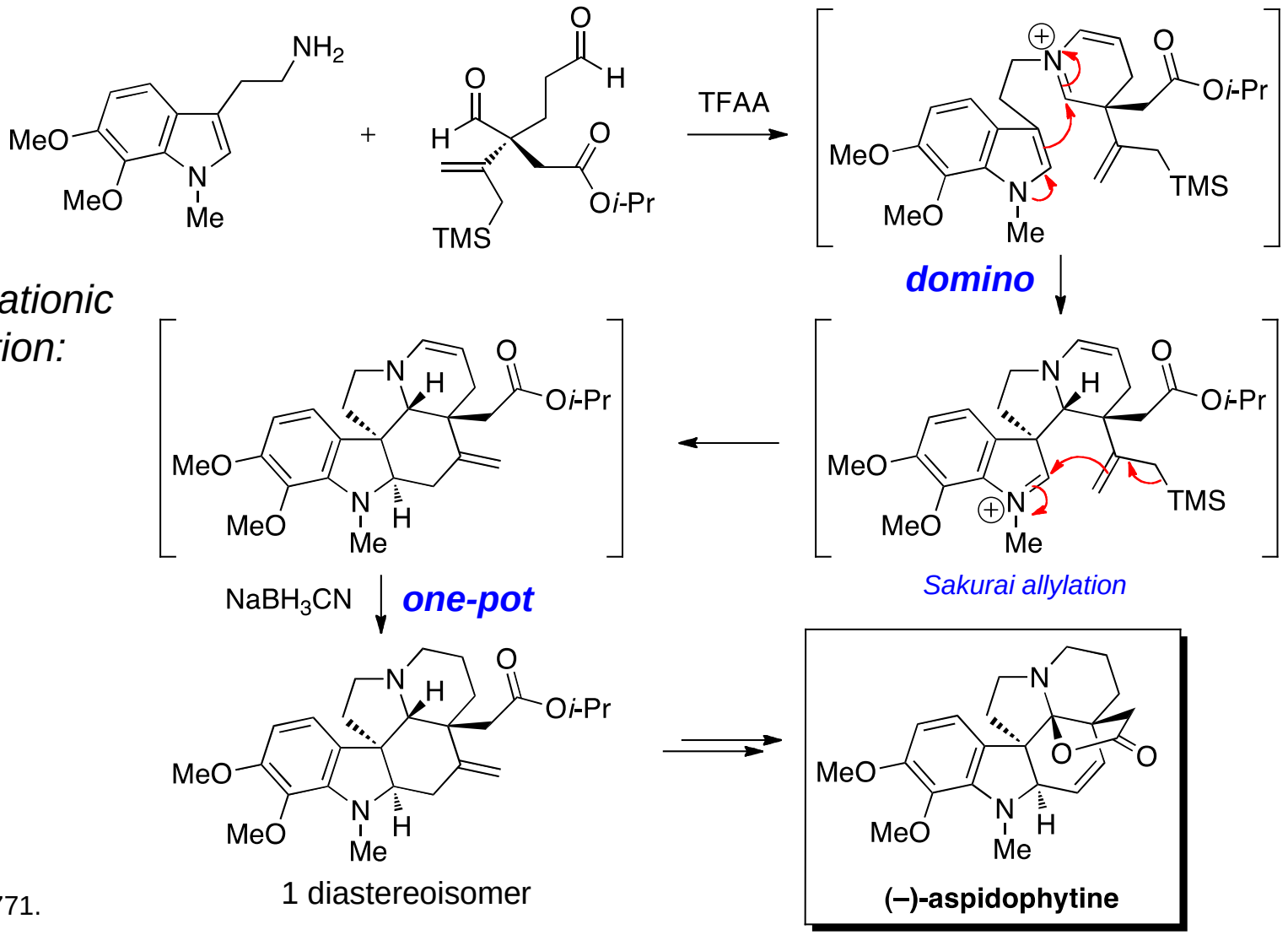
Approche "en un pot" en cascade :
R_1 et R_2 introduits simultanément; R_2 n'interfère pas et R_1 agit en premier. Une fois formé in situ, P_i réagit avec R_2 pour conduire à P_f

Recent developments in enantioslective multicalyzed tandem reactions - H. Pelissier, *Tetrahedron* **2013**, *69*, 7171-7210.
Asymmetric synthesis of natural products and medicinal drugs through one-pot recation strategies – B-C Hong, A. Raja, V M Sheth *Synthesis* **2015**, 3257-3285,

5. Domino reactions (cascade, tandem)

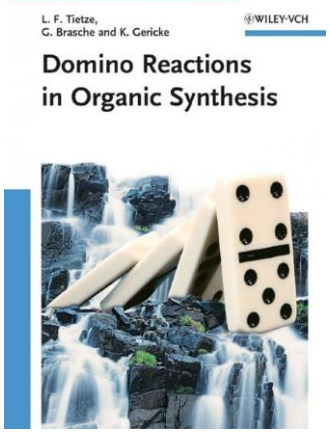
Different types of domino reactions: cationic, anionic, radical, pericyclic, transition metal-catalyzed… that can be combined.

example of cationic domino reaction:



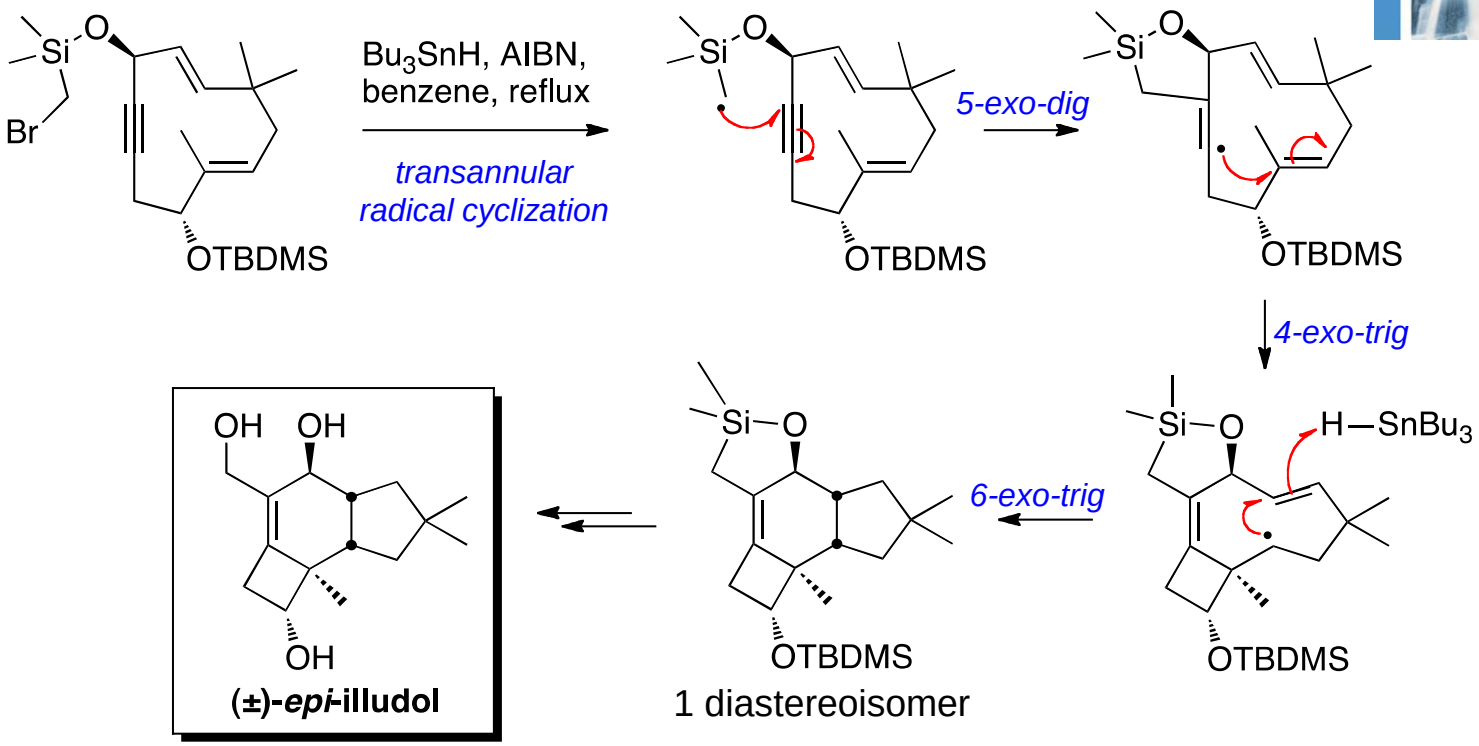
Corey, *JACS* **1999**, 6771.

5. Domino reactions (cascade, tandem)



Intramolecular domino reactions are often highly diastereoselective !

example of radical domino reaction:



paris 6

M. Malacria, *J. Am. Chem. Soc.* **1997**, 3427.

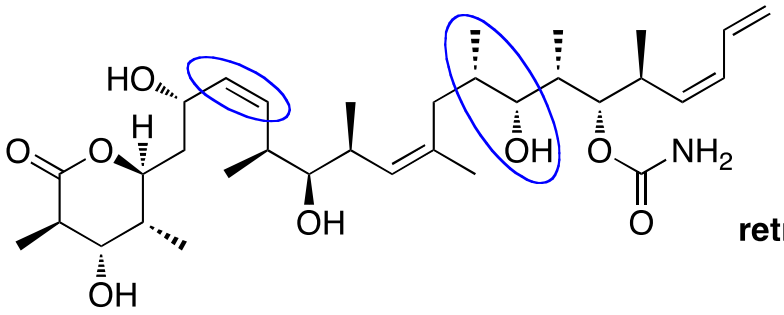
Rev.: Cascade reactions in total synthesis. K. C. Nicolaou, D.J. Edmonds, P. G. Bulger *Angew. Chem Int Ed.* **2006**, *45*, 7134-7186.

6. Retrosynthetic analysis

Definition (Corey): method of analysis which allows the transformation of a target molecule into progressively more simple structures, along a pathway leading to simple or commercially available molecules.

Retron: Structure (or substructure) observed in the target molecule, which can be disconnected into various fragments by application of a reaction or synthetic method (called 'transform').

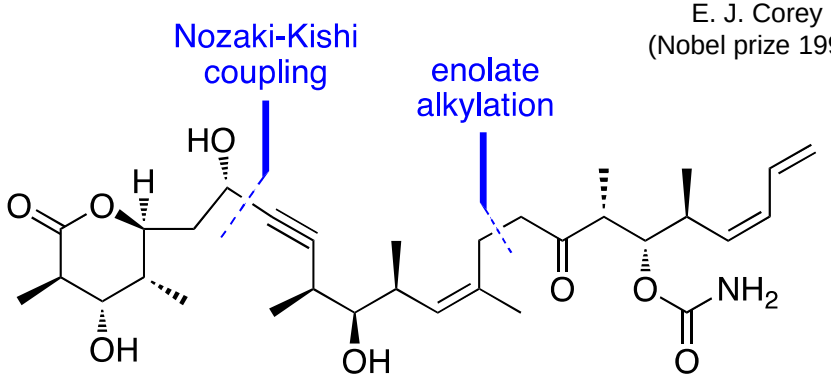
E. J. Corey
(Nobel prize 1990)



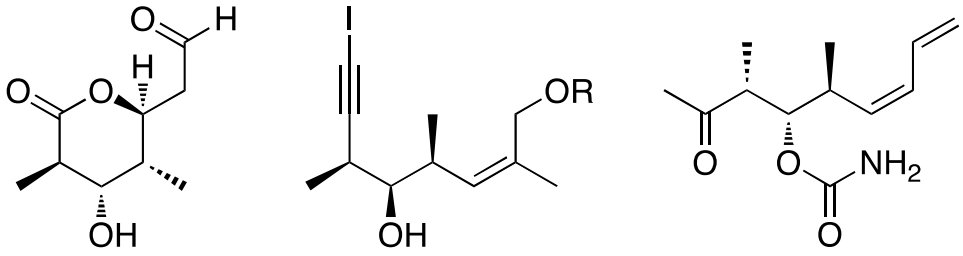
(+)-discodermolide

transforms

retrosynthetic arrow



retron

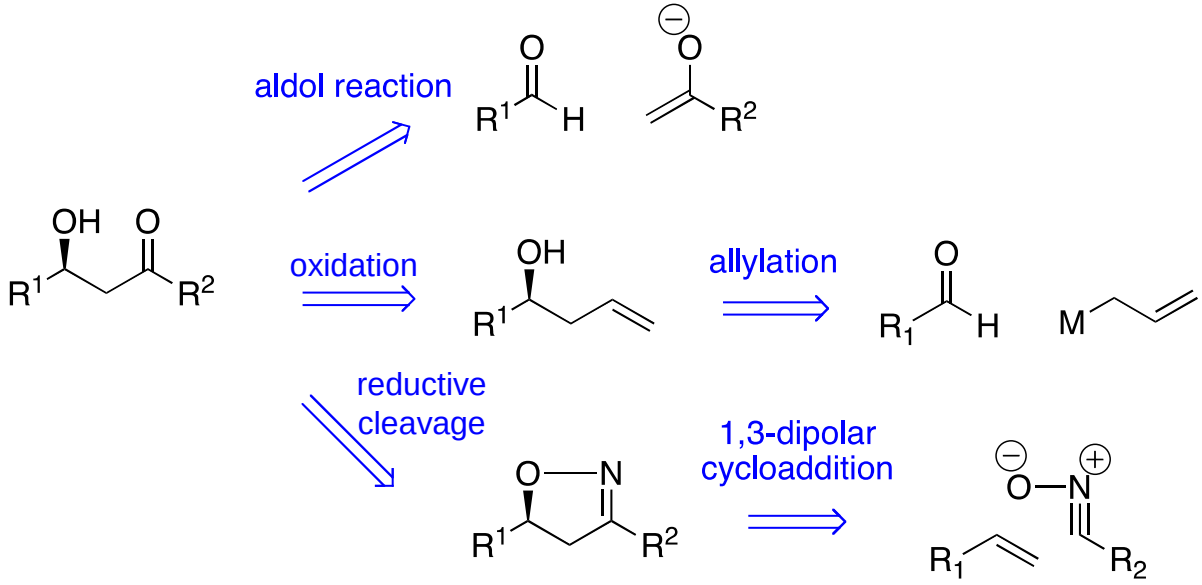


fragments

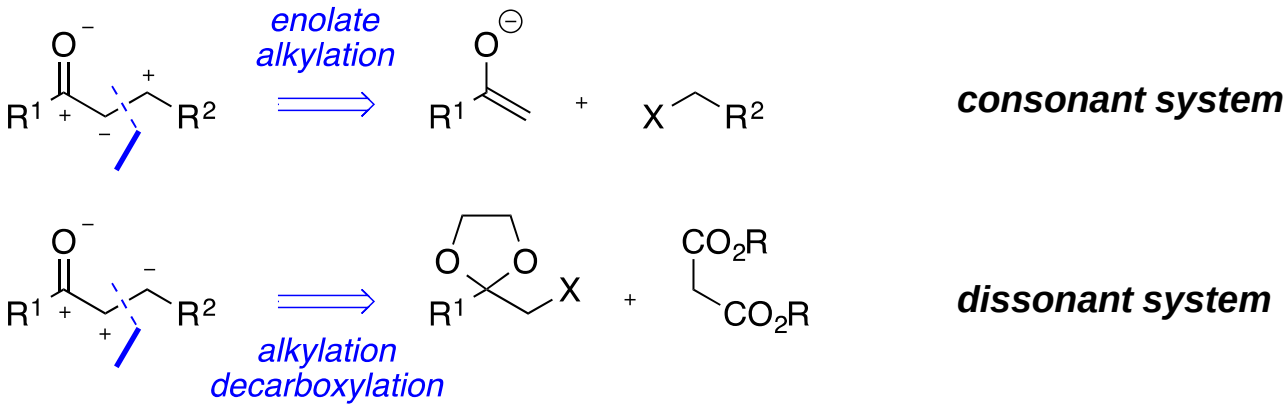
Schreiber, *JACS* **1996**, 11054.

6. Retrosynthetic analysis

The same retron may be obtained by different methods:



Consonant *vs.* dissonant systems:

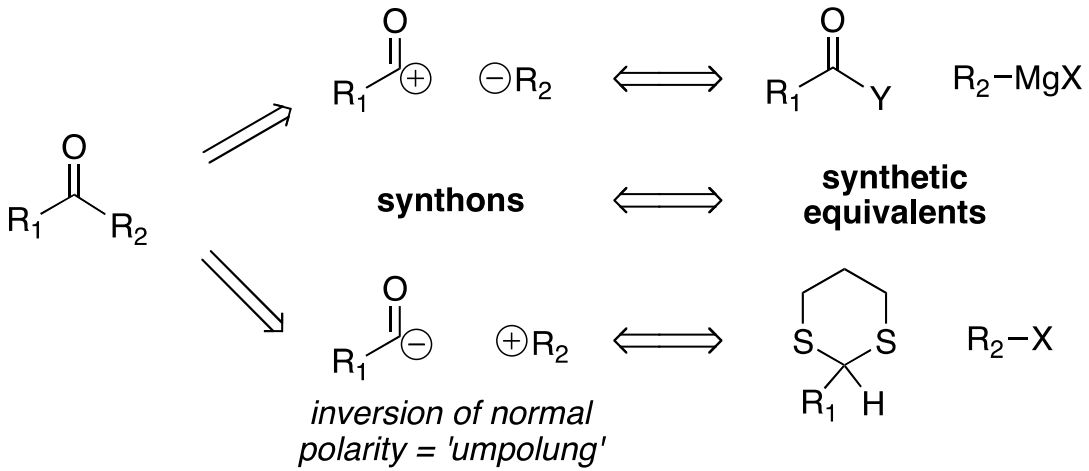


consonant system

dissonant system

6. Retrosynthetic analysis

Synthon: formal entity resulting from a bond disconnection



consonant system: respects 'natural' polarities

dissonant system

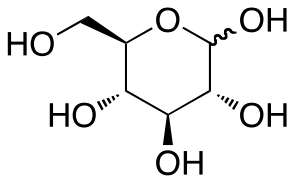
NB: the term 'synthon' is often confused with 'synthetic intermediate' or 'fragment'.

6. Retrosynthetic analysis

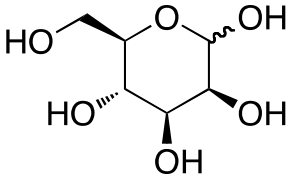
Chiron: substructure of the target molecule which may be obtained from the 'chiral pool', *i. e.* a homochiral commercially available compound (usually, a smaller natural product).

A few important chiral pool molecules:

Sugars

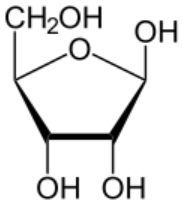


***D*-glucose**



***D*-mannose**

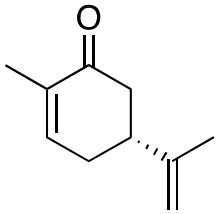
hexoses



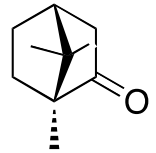
***D*-ribose**

pentose

Terpenes



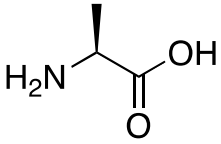
(–)-carvone



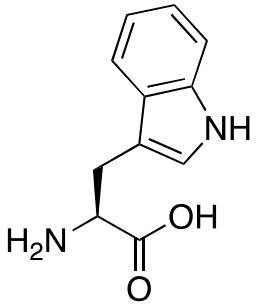
(+)-camphor

miscellaneous

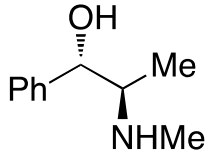
Amino-acids
(22 proteinogenic)



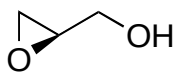
***L*-alanine**



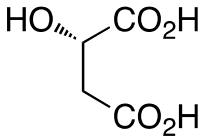
***L*-tryptophan**



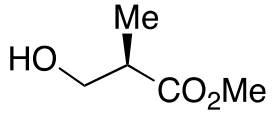
(–)-ephedrine



(+)-glycidol



***L*-malic acid**

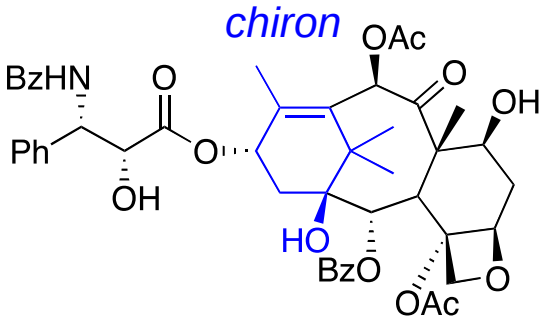


Roche ester (*R*)

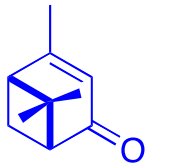
6. Retrosynthetic analysis

<u>Note:</u> the term 'enantiospecific' is sometimes employed to characterize syntheses that start from a chiral pool molecule (in cases where the enantiomer of the starting material would lead to the enantiomer of the target molecule).

<u>Examples:</u>

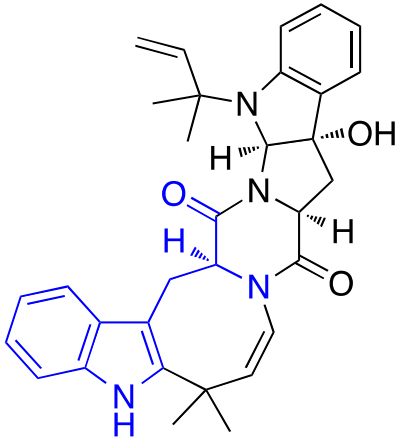


Taxol

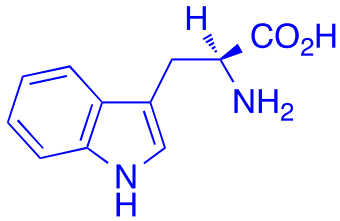


(+)-verbenone

Corey, *JACS* **2003**, 5628.

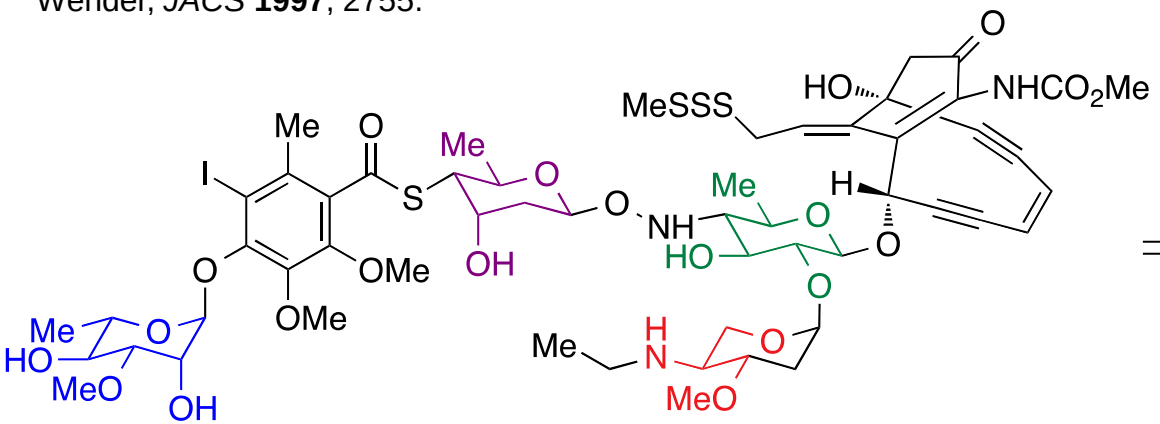


okaramine N



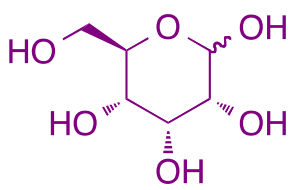
L-tryptophan

Wender, *JACS* **1997**, 2755.

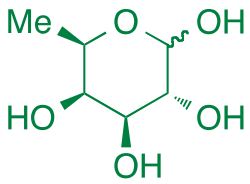


calicheamicin γ^{I}_{1}

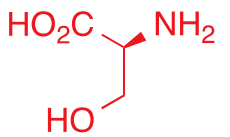
L-rhamnose



D-allose



D-fucose



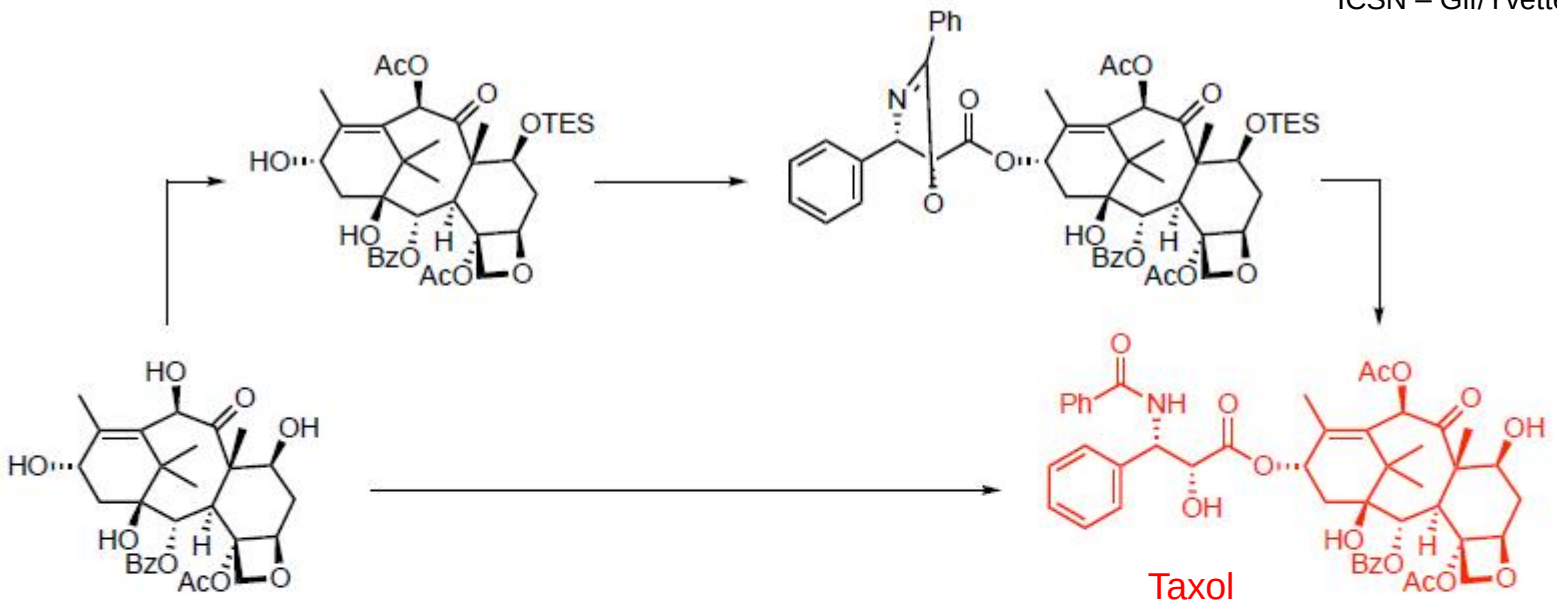
L-serine

Nicolaou, *JACS* **1993**, 7593.

6. Retrosynthetic analysis

ICSN – Gif/Yvette

Hemisynthesis



10-Deacetylbaccatin

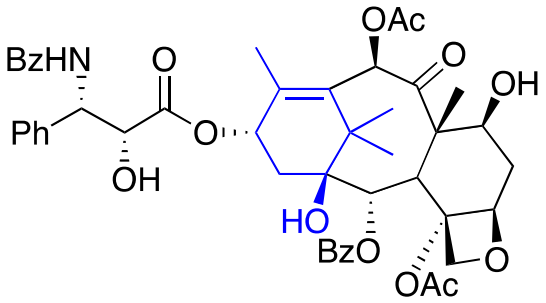
Taxol

Gennari, C. *ACIEE* **1996**, 35, 1723

Owing to the chemical complexity of paclitaxel, its commercial production by total synthesis is not likely to be economical. However, the naturally derived 10-deacetylbaccatin is readily available in relatively high yield from the needles of the European yew

6. Retrosynthetic analysis

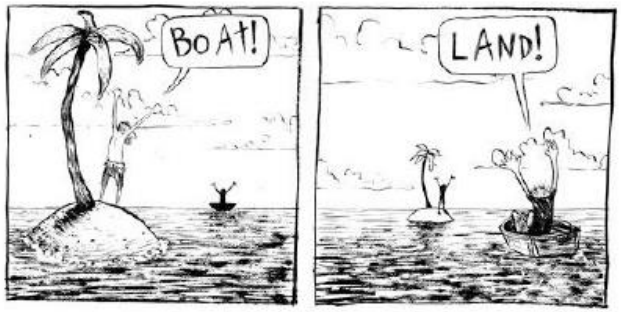
Target molecule



Taxol

Total synthesis

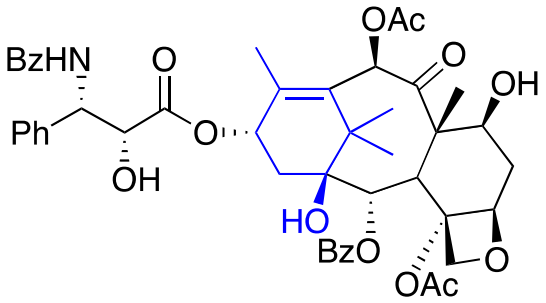
different **points of view**
different **feelings**



draw a target molecule from different **points of view** to catch a **pattern**

6. Retrosynthetic analysis

Target molecule

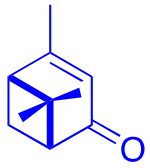


Taxol

Chiron approach
preservation of stereochemistry

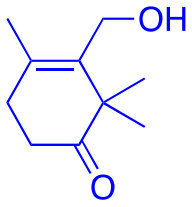
Retron approach
creation of stereochemistry
(enzymatic methods,
asymmetric synthesis)

Chiral pool molecule



(+)-verbenone

Achiral molecule



Strategy:

- Strategy refers to the general plan to reach the target molecule.
- Retrosynthetic arrows will provide a clear idea of the strategy

Tactics

- Tactical issues deal with the actual execution of the plan.
- Tactic depends to the structure and reactivity

6. Retrosynthetic analysis

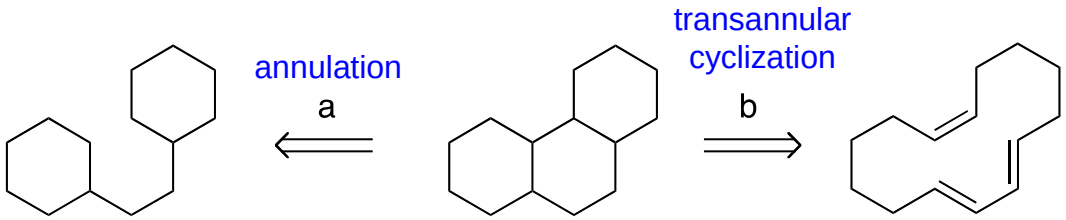
Different types of **synthetic strategies**:

- Based on one (or several) key transformations building key bonds and rings

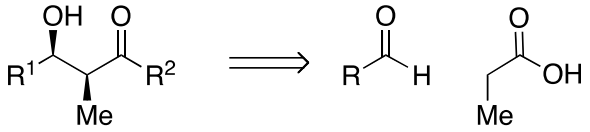
  = "transform goal" (e. g.: Diels-Alder reaction, metathesis, domino reaction…)

- Based on starting materials (retron/chiron approaches)

- Based on 'topology': structural simplification by disconnection of strategic bonds (applies in particular to polycyclic systems)



- Based on stereochemistry: structural simplification by elimination of stereocenters by using, in the synthetic sense, reactions that are known to efficiently control stereochemistry (e. g.: Diels-Alder, aldol reactions…)



- Based on the creation/suppression/manipulation of functional groups (C=C, C=O…)

- A combination of different strategies (complex targets)

Characteristics of an efficient total synthesis

1. Prefer a convergent rather than linear approach

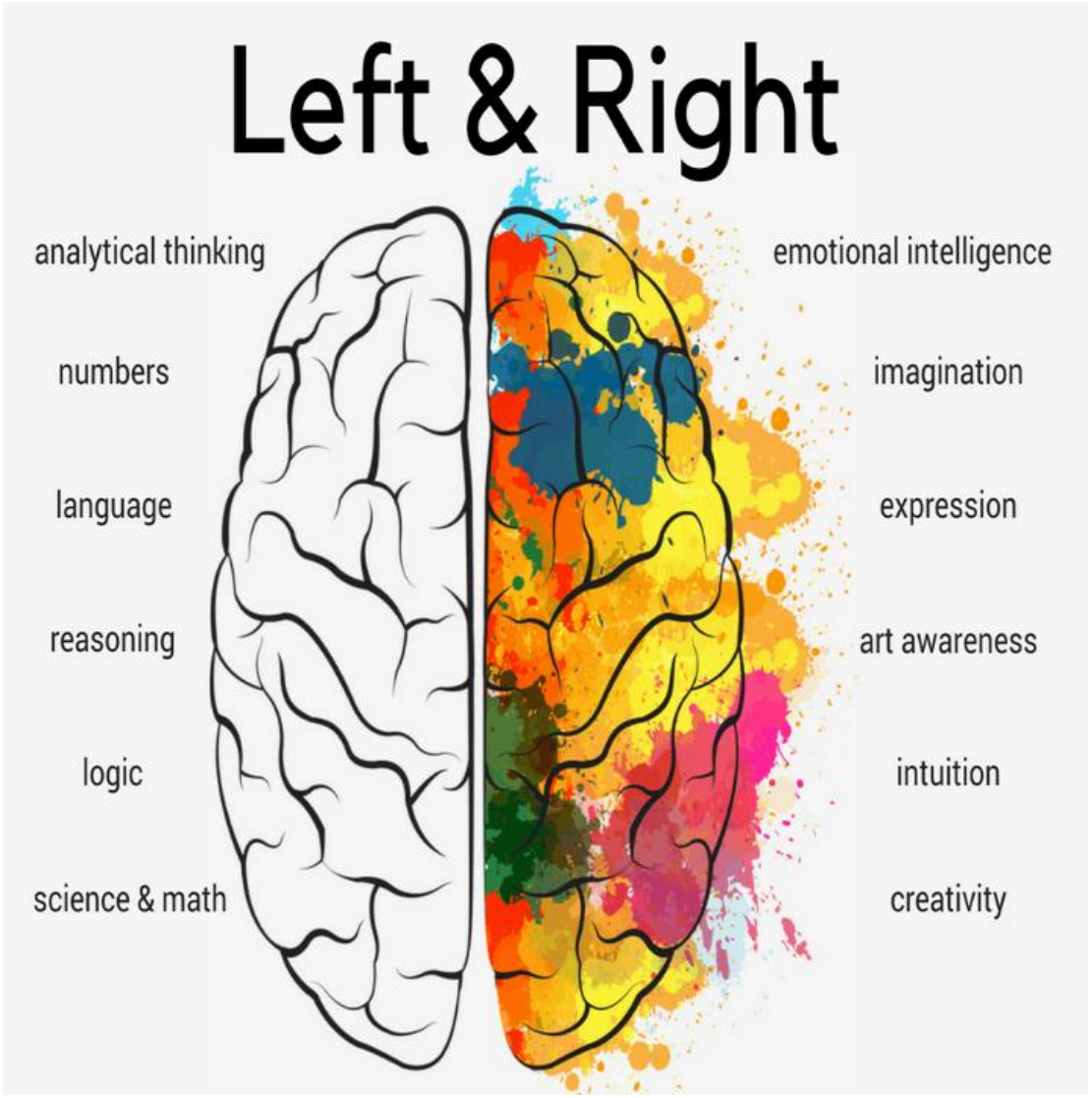
2. Exploit the reactivity of functional groups (consonance) and minimize the number of protecting groups

3. Avoid non-strategic changes in degrees of oxidation (strategic: bond formation, stereoselectivity)

4. Use as many domino reactions as possible

5. Favor biomimetic and chiron approaches

6. Retrosynthetic analysis



Tactics

Strategy

https://mc2.bid4papers.com/blog/8-ways-left-brain-thinkers-boost-creativity/

6. Retrosynthetic analysis

How to start?

1. Detailed analysis of the target structure: elements of symmetry, presence of chirons, strategic bonds and rings…

2. Application of key reactions to disconnect the target and obtain more simple fragments (principle of maximum convergence)

3. Analysis of chemical reactivity issues (selectivity, functional group tolerance, topology, use of protecting groups)

Topological strategies

1. Do not disconnect building-block type groups
2. Disconnect to obtain symmetrical precursors
3. Disconnect bonds between carbon and heteroatoms (O, N, S, P,…)
4. Disconnect bonds that attach rings to chains (can be 1,2 or 3 bonds away from the ring
5. Do not disconnect skeletal bonds that are attached directly to remote stereocenters
6. Do not disconnect stereocenters that are far (more than 3C away) from functionnal groups
7. Disconnect bonds between functional groups

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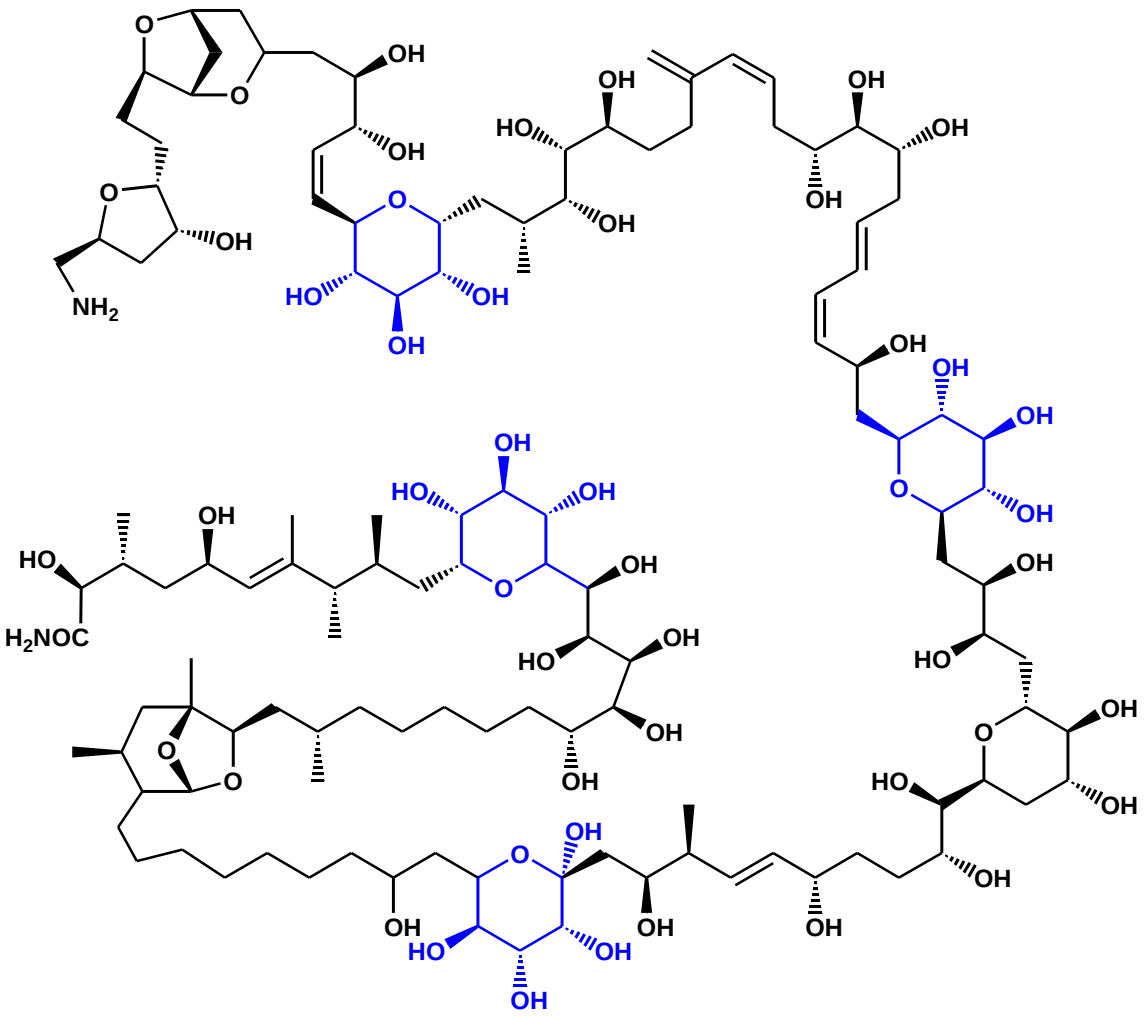
6. Retrosynthetic analysis

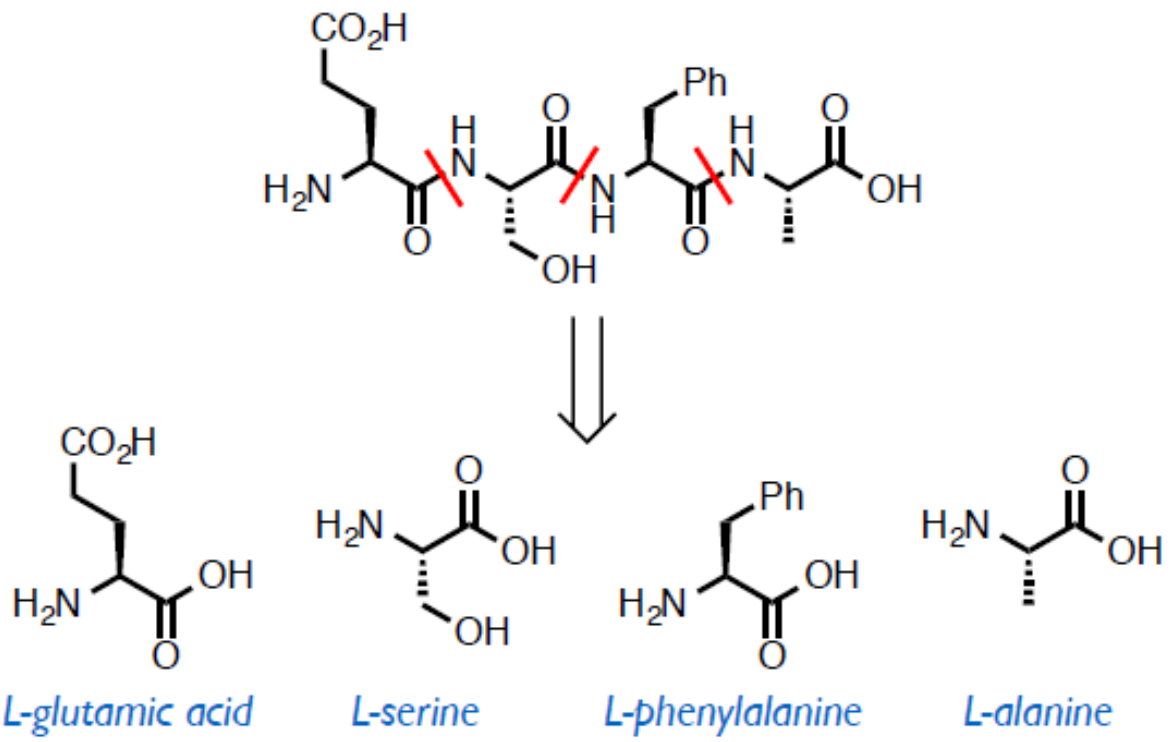


64 Centres
2^{64} stereoisomers
18 446 744 073 709 552 000

Palytoxine

Y. Kishi *et al.*
J. Am. Chem. Soc. **1989**, *111*, 7525. 64 Centres

6. Retrosynthetic analysis



Important features:

Use of suitable Protective groups, coupling reagents

and the order of events: Synthetic sequence <=> **TACTICS**

Topological strategies

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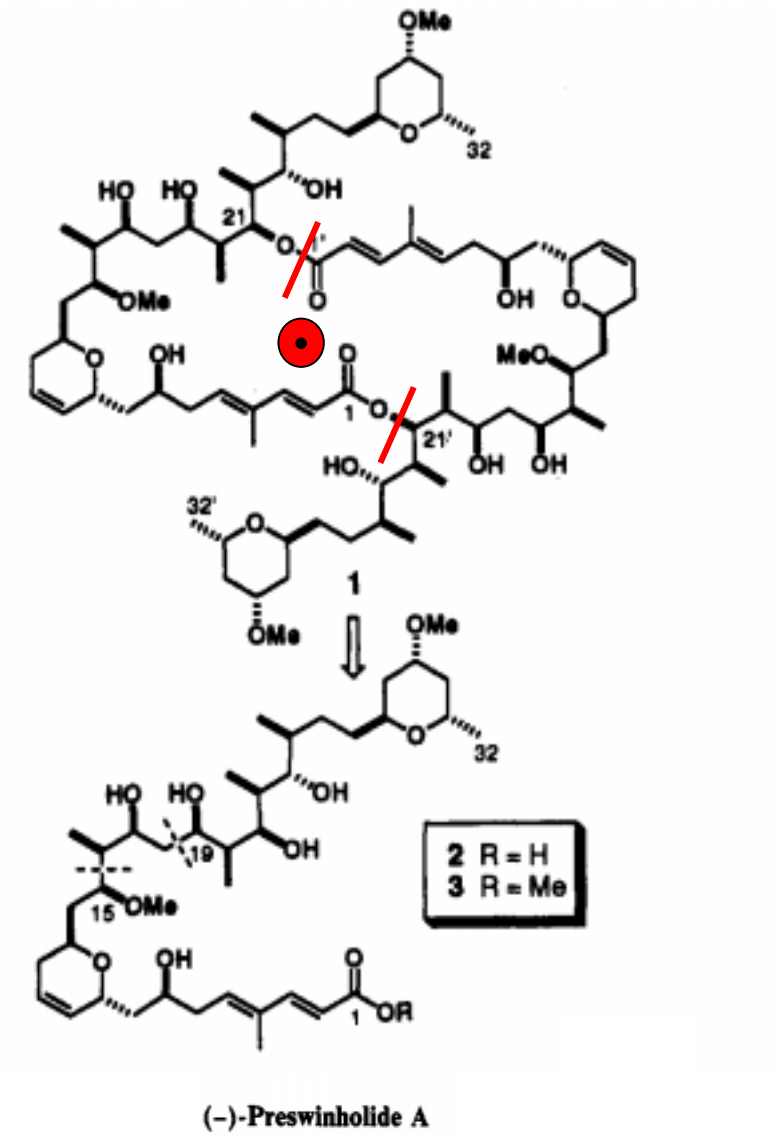
6. Retrosynthetic analysis

Swinholide and preswinholide



(–)-Preswinholide A

Axe C_2

theonella swinhoei

http://souslesmers.free.fr/i/dahe/dahe000092.jpg

Total Synthesis of Swinholide A and Hemiswinholide A

Ian Paterson,* Kap-Sun Yeung, Richard A. Ward, John G. Cumming, and Julian D. Smith

University Chemical Laboratory
Lensfield Road, Cambridge, CB2 1EW, U.K.

J. Am. Chem. Soc. **1994,** *116,* 9391–9392

J. Am. Chem. Soc. **1994,** *116,* 2615–2616

Crucial point: Selective acylation

Tactic issue

Topological strategies

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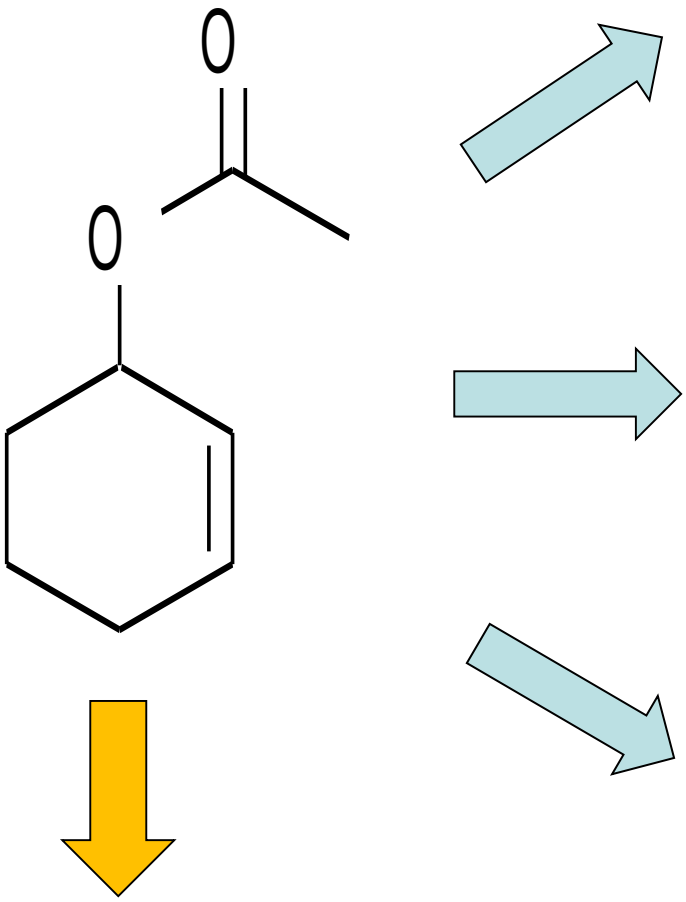
6. Retrosynthetic analysis



6. Retrosynthetic analysis

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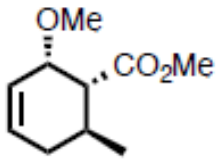
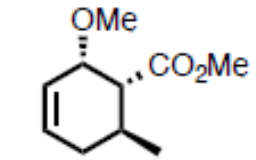
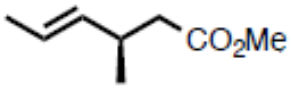
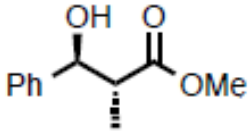
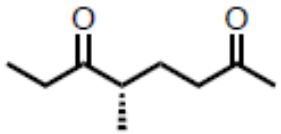
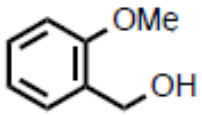
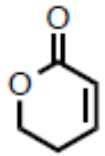
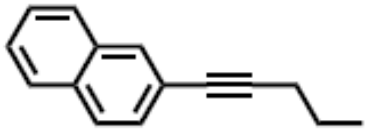
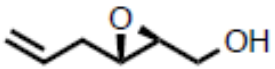
7. **Disconnect bonds between functional groups**

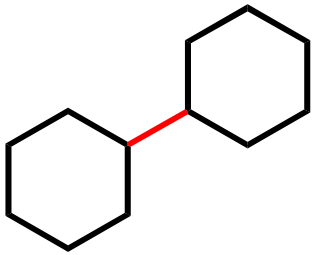
Target	Retron	Transform	Precursors



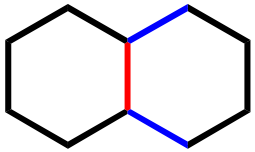
Target	Retron	Transform	Precursors
			
			
			
			

Target	Retron	Transform	Precursors
			
			
			
			

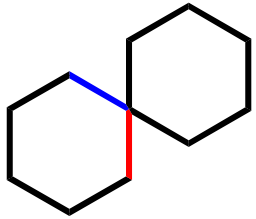
Polycyclic systems



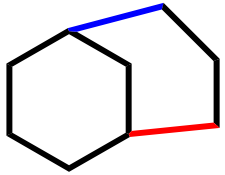
Connection directe



fusionné

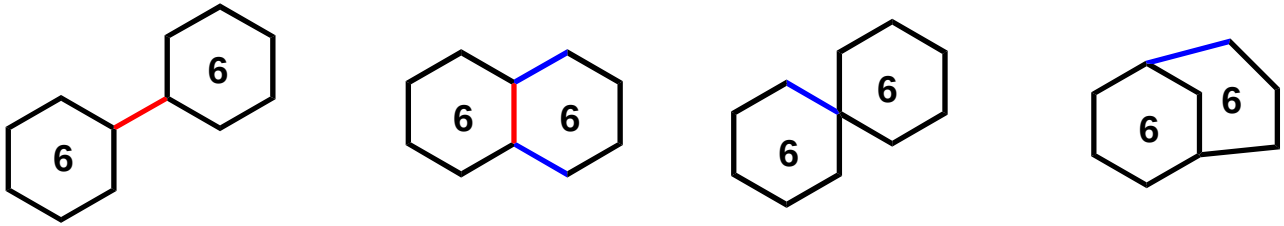


spiranique



ponté

Polycyclic systems



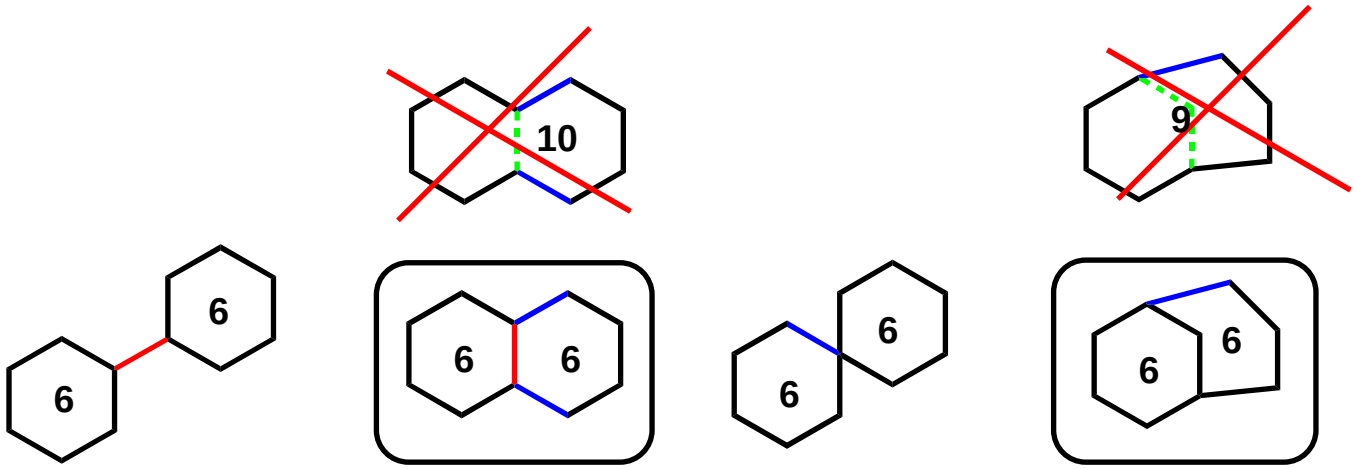
Directly

Fused rings

Spiranic

Bridged

Polycyclic systems – disconnection (Corey)



Rule #1
A strategic bond must be in a four-, five-, six- or seven-membered "primary" ring (relatively easy to form)

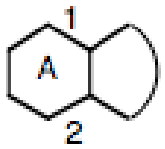
6. Retrosynthetic analysis

Some rules for the disconnection of polycyclic systems (Corey)

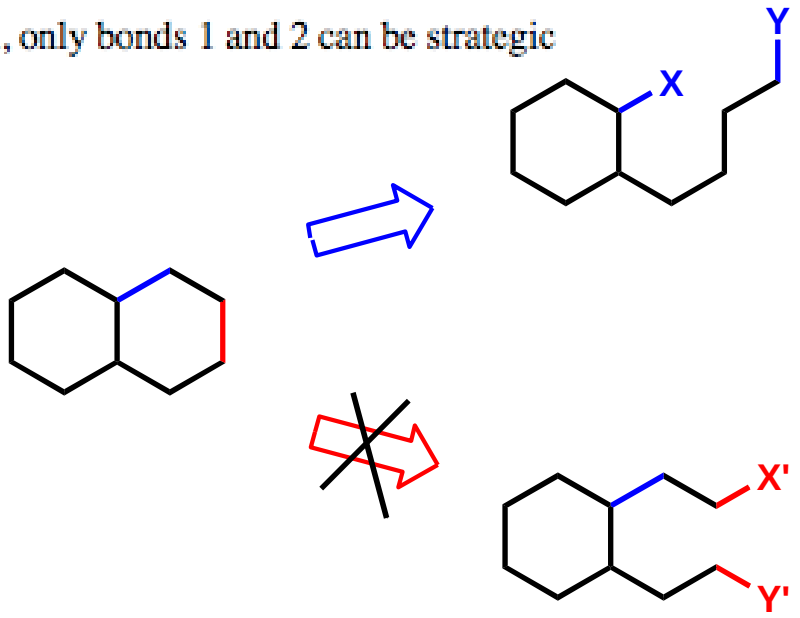
Rule #2

A strategic bond must be directly attached to another ring (exo to another ring, except three-membered rings) because a ring disconnection which produces two functionalized appendages leads to a more complex system than a ring disconnection that lead to one or no functionalized appendages.

⇒ **mimimize appendages on rings!**



Out of six bonds in ring A, only bonds 1 and 2 can be strategic



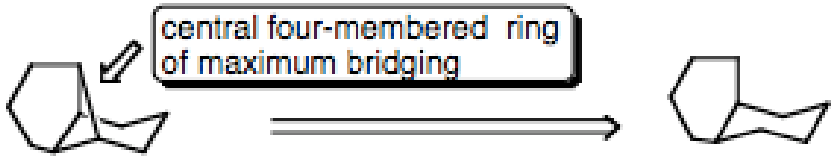
Too Flexible

Corey, *JACS* **1975**, 6116.

6. Retrosynthetic analysis

Rule #3: break bridging rings

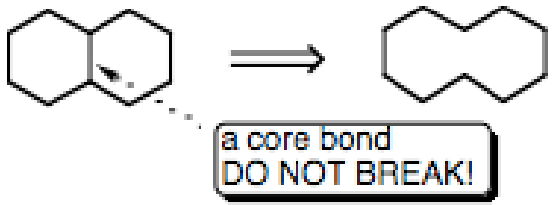
To achieve maximal simplification of the cyclic system, strategic bonds should be in the ring(s) which exhibits the greatest degree of bridging.



Disconnection of any bond in that central four-membered ring produces a major network simplification to a decalin system.

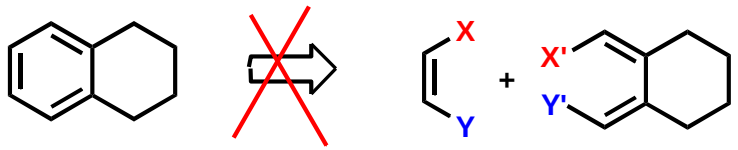
Rule #4: do not break core bonds

To avoid the formation of rings having greater than 7 members, any bond common to a pair of bridged or fused rings whose envelop is > 8-membered cannot be considered strategic.
The bonds that are eliminated from this rule are termed **core bonds**.



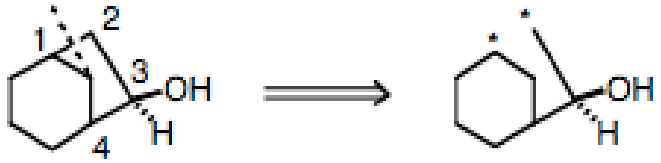
Rule #5: aromatic rings

Bonds within aromatic rings are not considered to have potential strategic character.



Rule #6: minimize appendages with chiral centers

If a cyclic arc linking a pair of common atoms contains a chiral carbon atom, then none of the bonds in the cyclic arc may be considered strategic.



Don't!

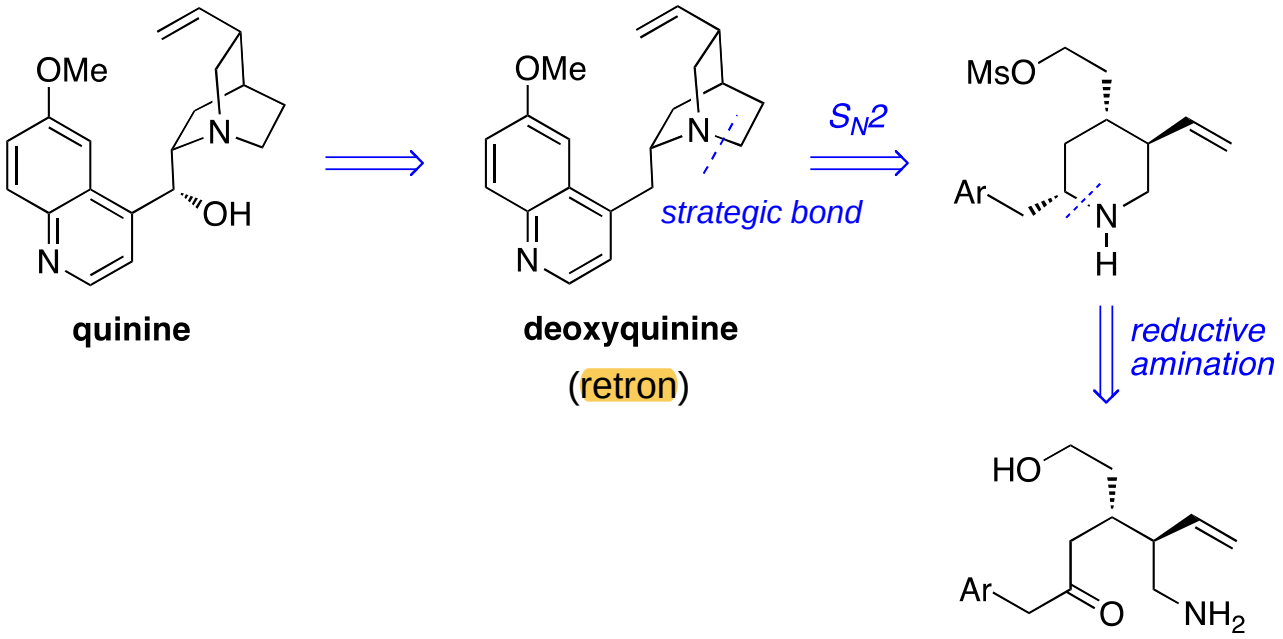
Rule #7 : The C-Heterobond Procedure

To the set of strategic bonds determined by rules 1-6, C-X bonds (X = O, N, S) are added!

6. Retrosynthetic analysis

Example of retrosynthetic analyses: 1. Stork's synthesis of (–)-quinine

G. Stork

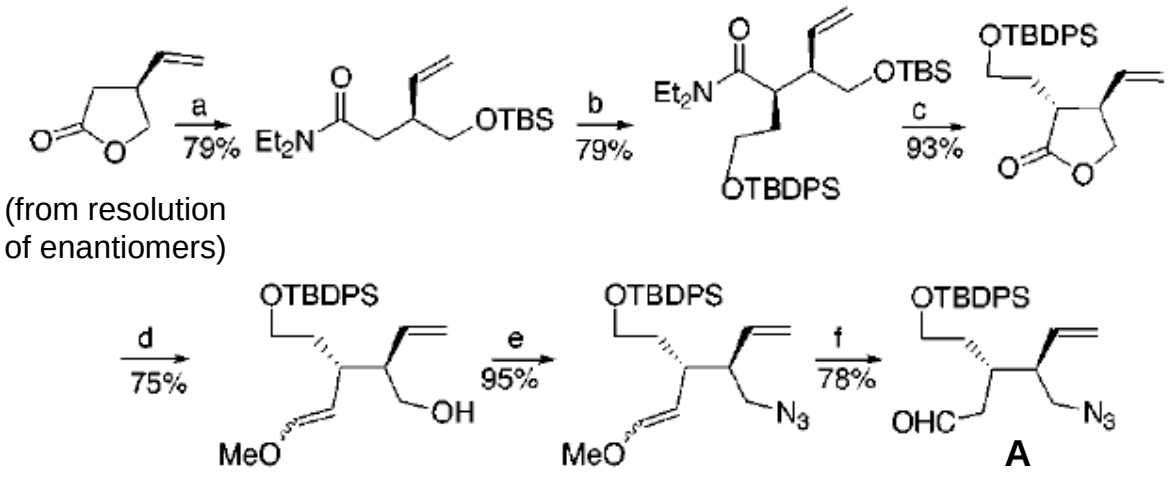


G. Stork, *J. Am. Chem Soc.* **2001**, 3239.

T.S. Kaufman, E.A. Ruveda *Angew. Chem. Int. Ed*. **2005**, 44, 854 - 885

6. Retrosynthetic analysis

Synthesis of quinine (1): acyclic fragment



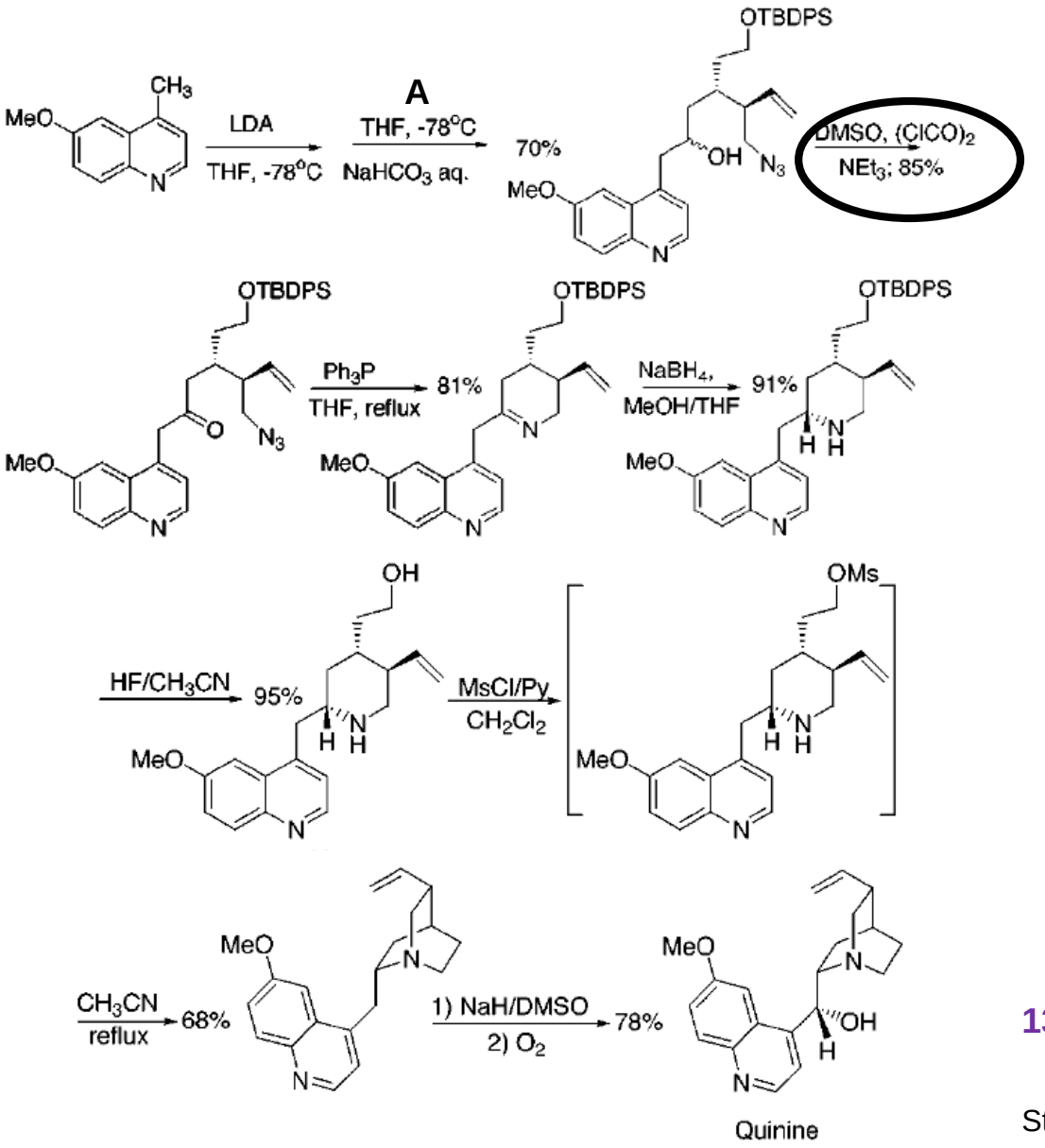
[a] Conditions: (a) (1) $Et_2NH/AlMe_3$, (2) TBS−Cl/Imidazole/DMF. (b) LDA, −78 °C, $ICH_2CH_2OTBDPS$. (c) PPTS (0.3 equiv), EtOH, 12 h, then xylenes, reflux 8−10 h. (d) (1) DIBAL-H, −78 °C, (2) $Ph_3P{=}CHOMe$. (e) $Ph_3P/DEAD$, $(PhO)_2P(O)N_3$. (f) 5 N HCl, THF/CH_2Cl_2.

6 steps: 32%

Stork, *JACS* **2001**, 3239.

6. Retrosynthetic analysis

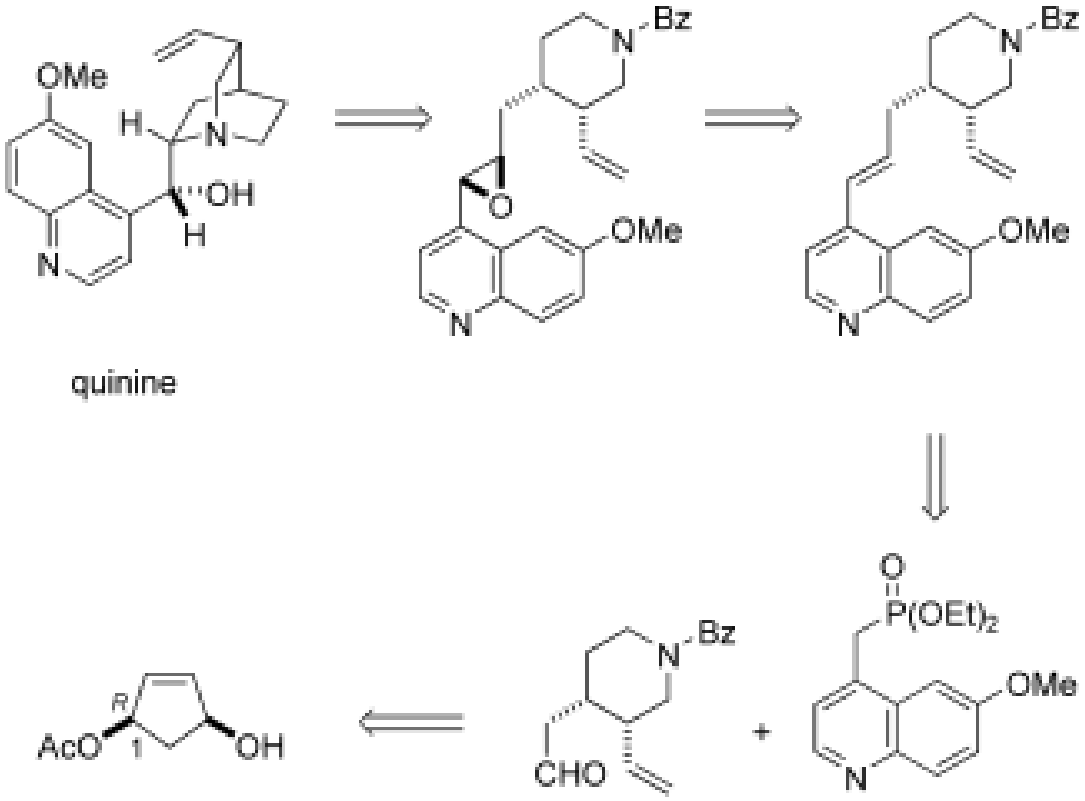
Synthesis of quinine (2)



13 steps: 7.1%

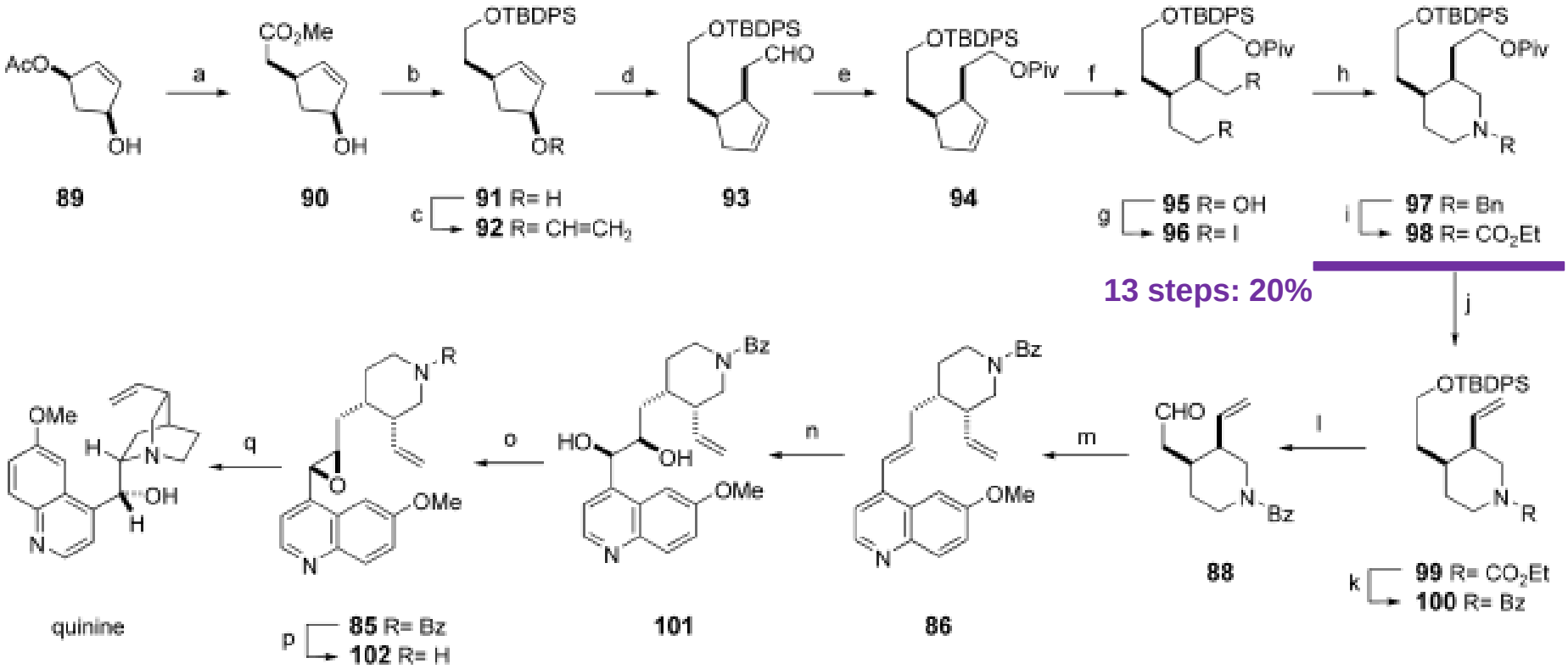
Stork, *JACS* **2001**, 3239.

Second retrosynthesis - Kobayashi's synthesis of (–)-quinine



J. Igarashi, M. Katsukawa, Y.-G. Wang, H. P. Acharya, Y. Kobayashi, *Tetrahedron Lett.* **2004**,*45*, 3783.

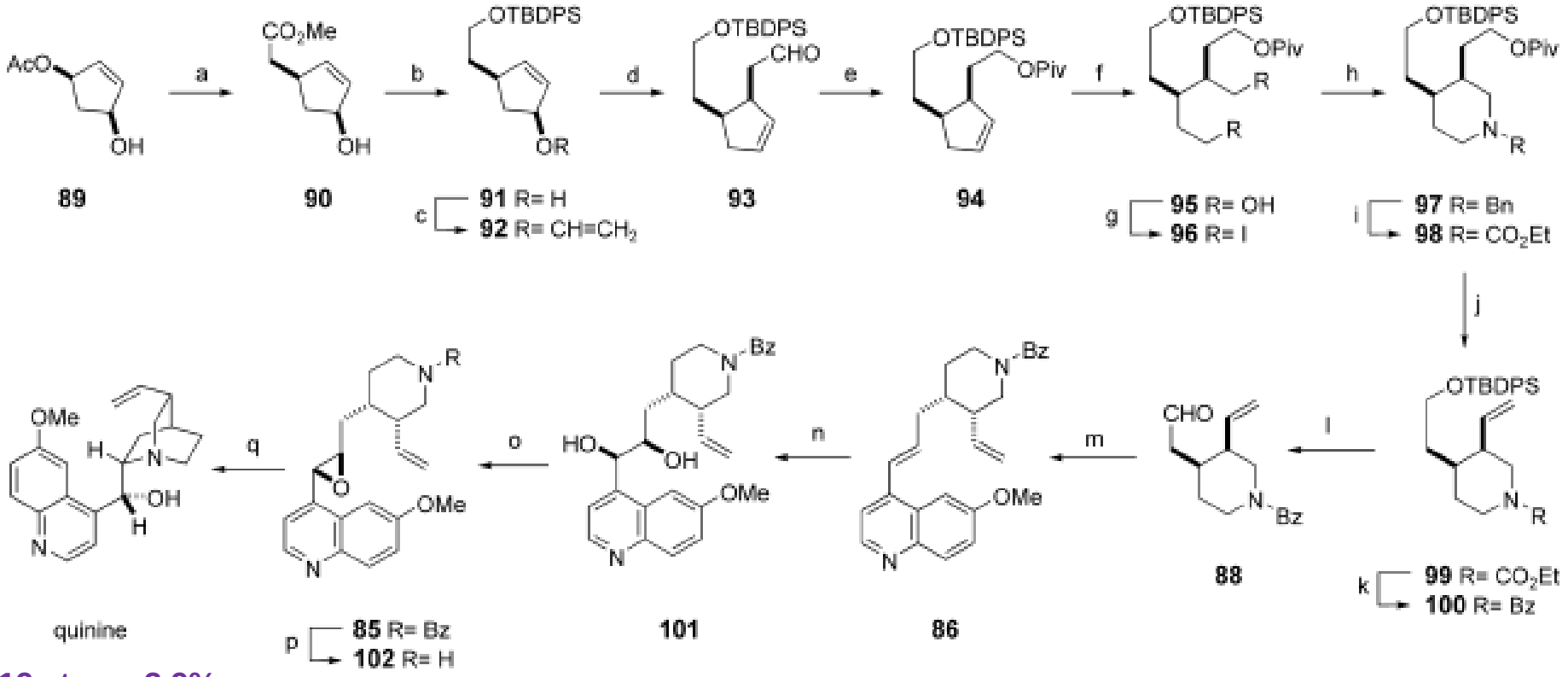
Kobayashi's synthesis of (–)-quinine



a) 1. $CH_2(CO_2Me)_2$, *t*BuOK, $[Pd(PPh_3)_4]$ (cat.); 2. KI, DMF, 125 °C (70 %)
b) 1. $LiAlH_4$; 2. TBDPSCl, imidazole (63 %);
c) $H_2CCHOEt$, $Hg(OAc)_2$ (cat.);
d) 190 °C;
e) 1. $NaBH_4$; 2. *t*BuCOCl, Et_3N, CH_2Cl_2 (66 %);
f) 1. O_3, *n*PrOH, [78 °C; 2. $NaBH_4$ (81 %);
g) I_2, PPh_3, imidazole (88 %);
h) $BnNH_2$, dioxane (98 %);
i) $ClCO_2Et$, PhMe (99 %);

J. Igarashi, M. Katsukawa, Y.-G. Wang, H. P. Acharya, Y. Kobayashi, *Tetrahedron Lett.* **2004**,*45*, 3783.

Kobayashi's synthesis of (–)-quinine

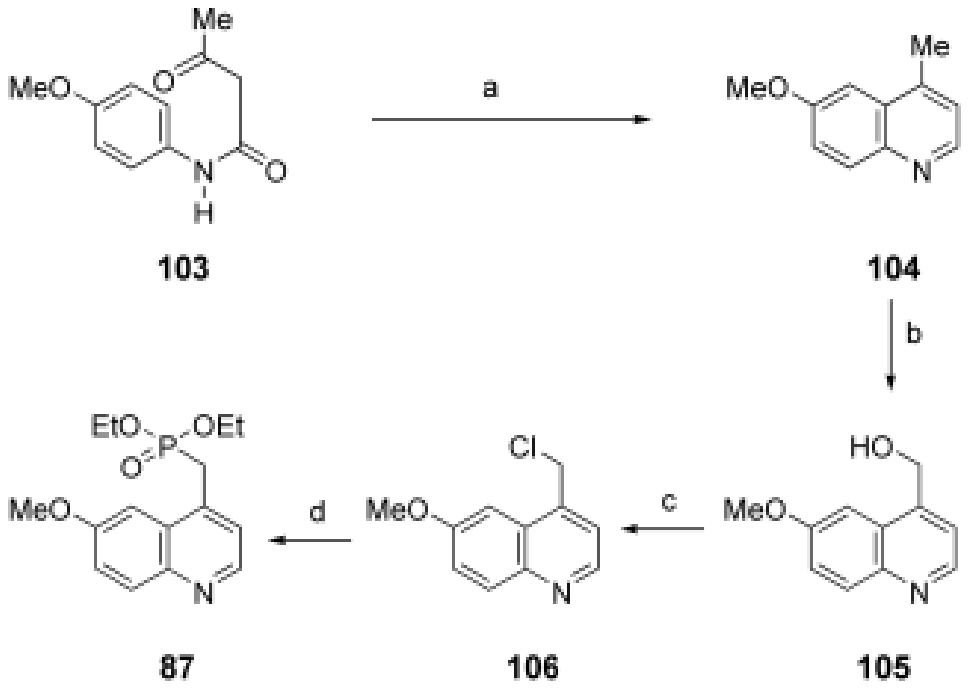


19 steps: 3.9%

j) 1. NaOEt, EtOH; 2. *o*-NO_2-C_6H_4SeCN; PBu_3, THF; 3. 35 % H_2O_2, THF (77 %);
k) 1. MeLi, 0 °C; 2. BzCl (61 %);
l) 1. TBAF; 2. PCC (80 %);
m) **87**, NaH, THF, RT (82 %);
n) AD-mix-β, 0 °C;
o) $MeC(OMe)_3$, PPTS (cat.), CH_2Cl_2, TMSCl, K_2CO_3, MeOH (95 %);
p) DIBAL-H, PhMe; q) DMF, 160 °C (66 % from **85**).

J. Igarashi, M. Katsukawa, Y.-G. Wang, H. P. Acharya, Y. Kobayashi, *Tetrahedron Lett.* **2004**,*45*, 3783.

Kobayashi's synthesis of (–)-quinine



a) 1. H_2SO_4; 2. $POCl_3$; 3. Zn, AcOH (72 %);
b) *m*-CPBA, CH_2Cl_2, RT; 2. Ac_2O, RT; 3. K_2CO_3, MeOH (43 %);
c) $SOCl_2$, CH_2Cl_2, reflux (71 %); d) H-P(O)$(OEt)_2$, *n*BuLi, THF (70 %).

J. Igarashi, M. Katsukawa, Y.-G. Wang, H. P. Acharya, Y. Kobayashi, *Tetrahedron Lett.* **2004**,*45*, 3783.

7. Retrosynthetic analysis and I.A.

GDCh Highlights Angewandte International Edition Chemie

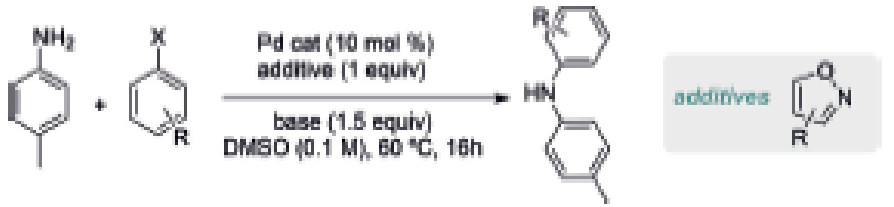
Reaction Prediction

International Edition: DOI: 10.1002/anie.201803562
German Edition: DOI: 10.1002/ange.201803562

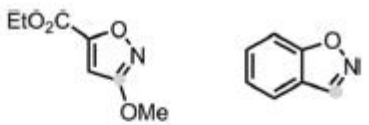
Machine Learning for Organic Synthesis: Are Robots Replacing Chemists?

*Boris Maryasin, Philipp Marquetand, and Nuno Maulide**

Buchwald–Hartwig reaction · high-throughput synthesis robot · machine learning · nanomole-scale reactions



Angew. Chem. Int. Ed. 2018, 57, 6978 – 6980



C3 δ (ppm)	26.54	50.58
undergoes oxidative addition on treatment with $Pd(PPh_3)_4$	✖	✔

Figure 1. Simplified diagram depicting isoxazole additives to Buchwald–Hartwig coupling reactions, compared in terms of the C3 ^{13}C NMR chemical shift descriptor and the experimentally confirmed propensity to undergo N–O oxidative addition upon exposure to a Pd^0 precatalyst.[11]

8. Computer-aided synthesis

ACCOUNTS of chemical research

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Chemist Ex Machina: Advanced Synthesis Planning by Computers

Published as part of the Accounts of Chemical Research special issue "Data Science Meets Chemistry".

Karol Molga, Sara Szymkuć, and Bartosz A. Grzybowski*

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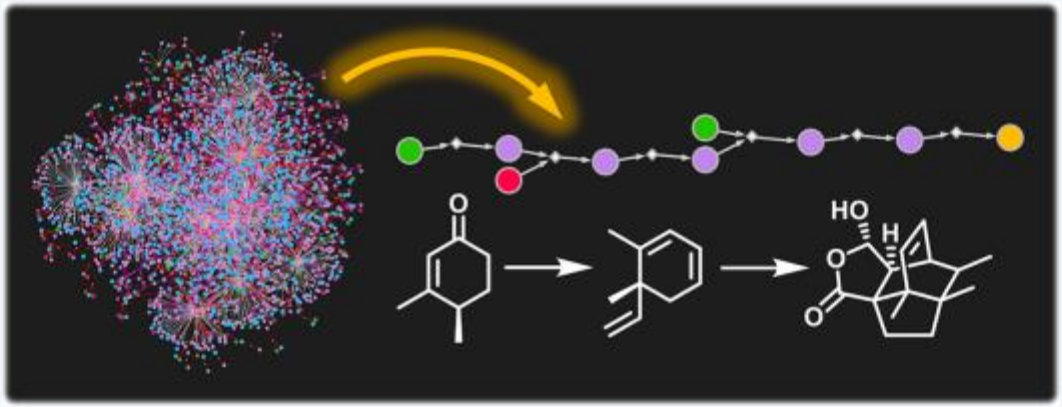
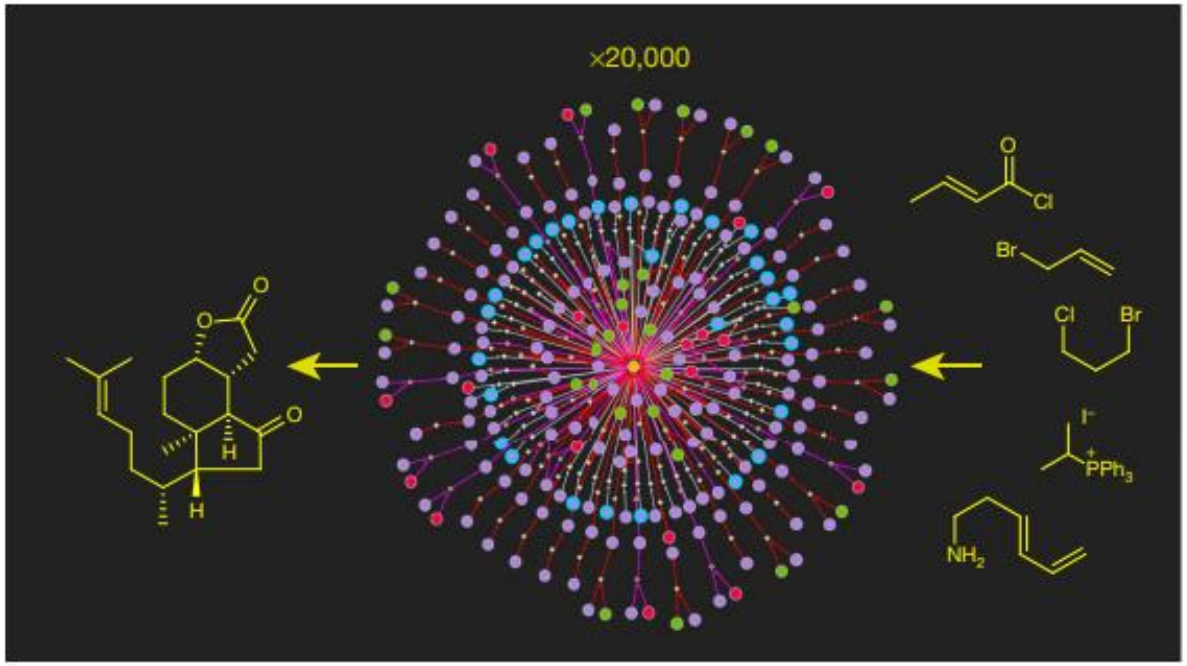


8. Computer-aided synthesis



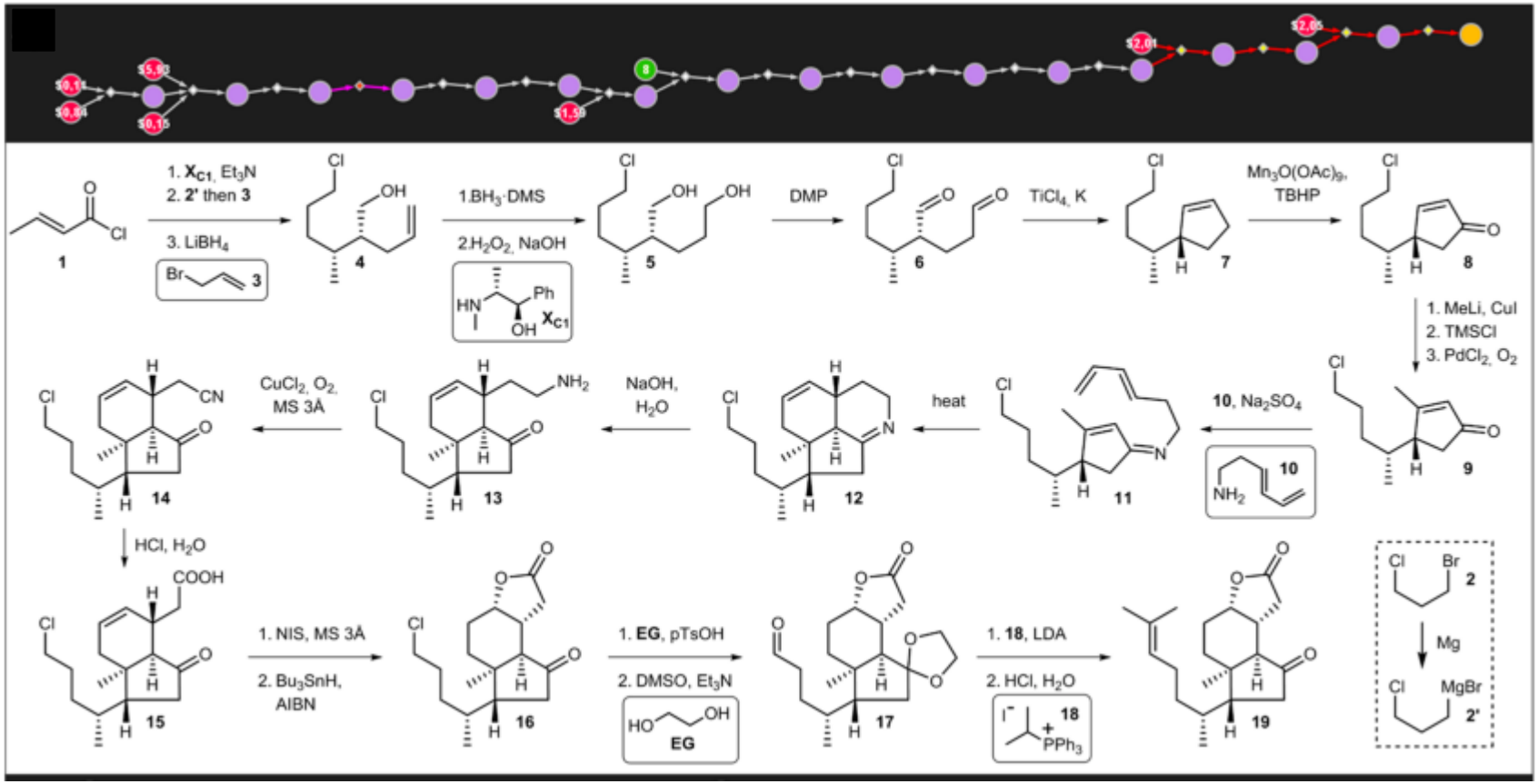
| Automatic synthesis planning over large networks of possible reactions. This screenshot from Chematica illustrates the synthetic possibilities the machine considers for just one intermediate en route to the natural product aplykurodinone-1 (shown on the left). When designing the full pathway (Extended Data Fig. 6) that traces to the simple starting materials (shown on the right), the program explored and evaluated around 20,000 such graphs connected into a very large network of synthetic options. Each graph comprises one-reaction-step options (white reaction arrows) and multistep sequences (FGIs; red arrows). Nodes correspond to specific molecules: orange, current retron; violet, unknown substances; green, literature-reported substances; red, commercially available chemicals; blue halos, protection needed.

Chematica

B. Mikulak-Klucznik et al. *Nature* **2020**, *588*, 83-88.

SYNTHIA™ Retrosynthesis Software (sigmaaldrich.com)

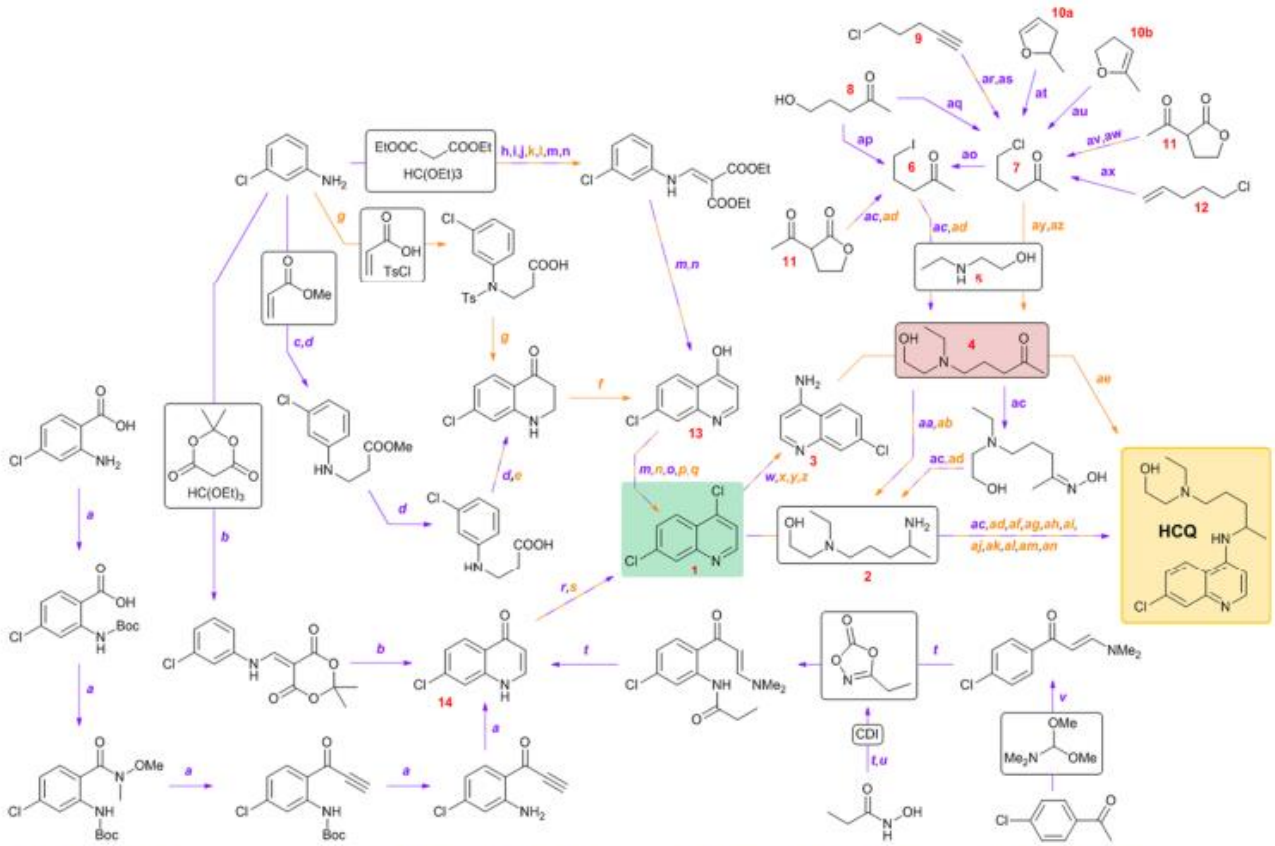
8. Computer-aided synthesis



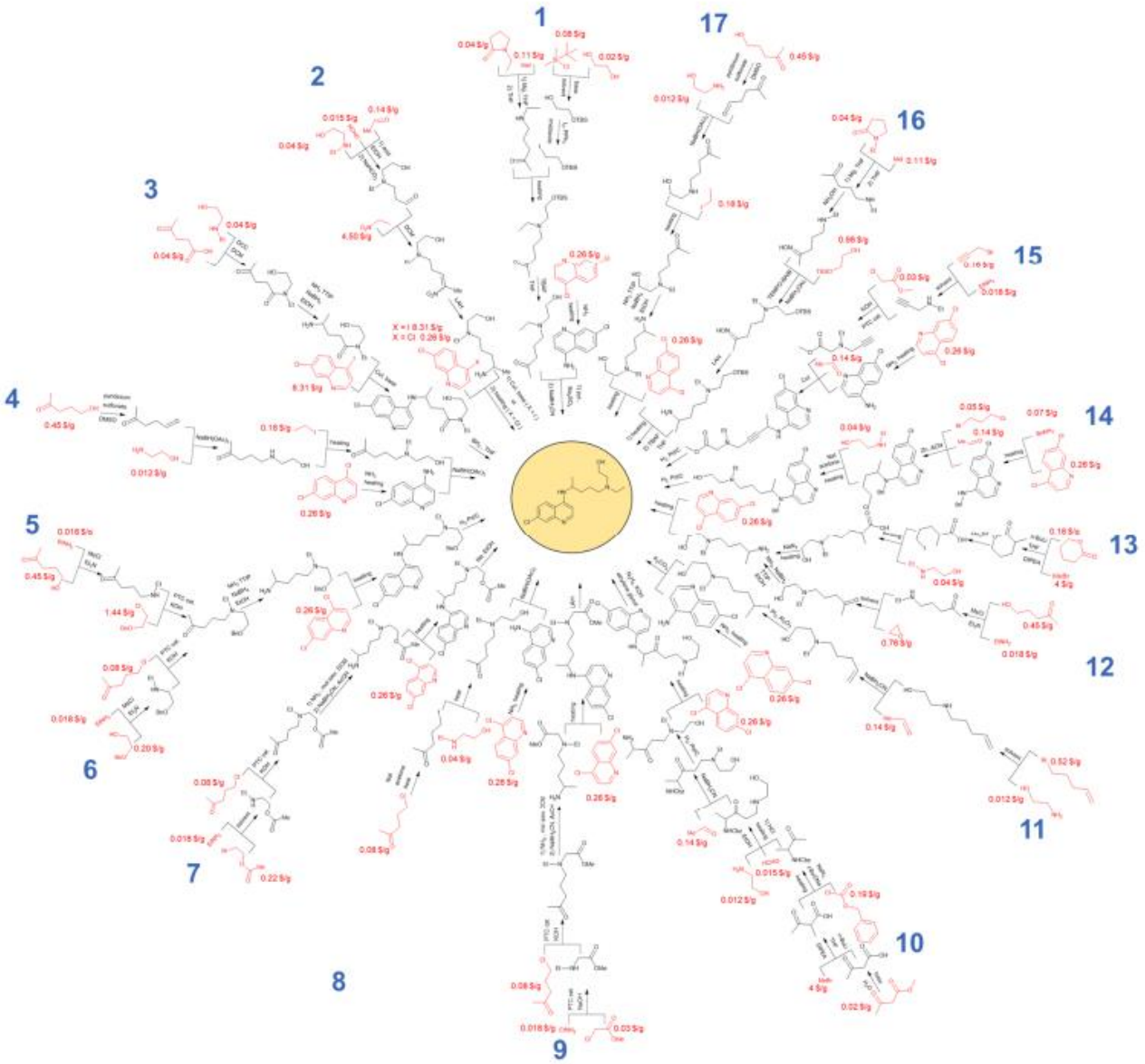
Aplykurodinone-1

B. Mikulak-Klucznik et al. *Nature* **2020**, *588*, 83-88

8. Computer-aided synthesis



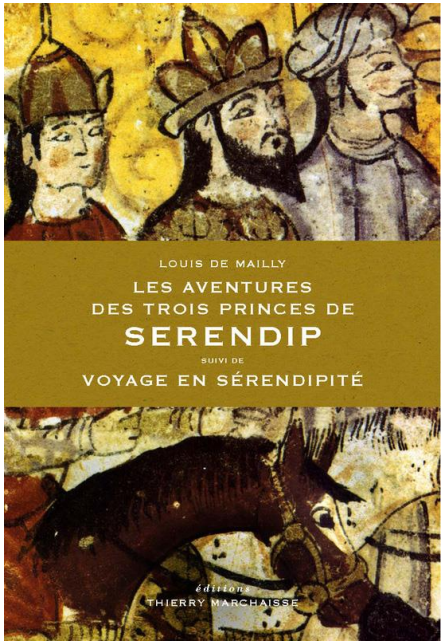
Computer-assisted planning of hydroxychloroquine's syntheses commencing from inexpensive substrates and bypassing patented routes. Bartosz A. Grzybowski et al. *ChemRxiv* (2020), 1-14



Novel syntheses of hydroxychloroquine (HCQ) designed automatically by *Chematica*.

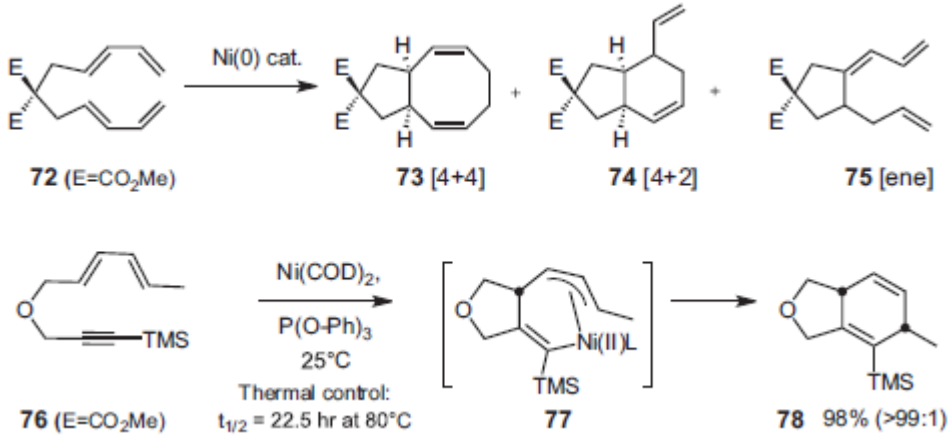
Computer-assisted planning of hydroxychloroquine's syntheses commencing
from inexpensive substrates and bypassing patented routes. Bartosz A. Grzybowski et al. *ChemRxiv* (2020), 1-14

9. Serendipity



« La **sérendipité**, art de rencontrer quelque chose que l'on ne cherchait pas, est une source pour la créativité et l'innovation et les exemples sont nombreux, notamment en chimie thérapeutique. »

C. Monneret *Actualité chimique* – mai 2014 – 385.

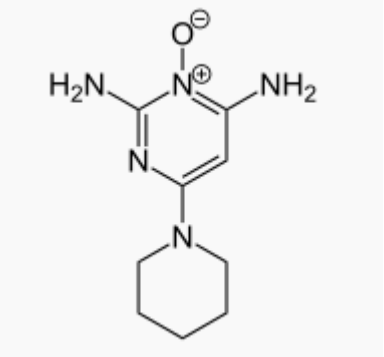


Toward the ideal synthesis and transformative therapies: the roles of step economy and function oriented synthesis.
P. A. Wender *Tetrahedron* **2013**, *69*, 7529-7550.

"Dans les champs de l'observation, le hasard ne favorise que les esprits préparés." ("In the field of observation, chance favours only the prepared mind.") **L. Pasteur**

9. Serendipity

« C'est aussi l'histoire du minoxidil, initialement destiné à
traiter l'hypertension artérielle. Quelle ne fut pas la surprise des médecins de voir la chevelure des hypertendus ainsi traités devenir plus drue, et la chute de leurs cheveux ralentie.
Le minoxidil deviendra un traitement de référence contre la calvitie. Il est certain que les profits du laboratoire Upjohn s'en sont trouvés améliorés. »



C. Monneret *Actualité chimique* – mai 2014 – 385.