Fraud in chemistry.

"HOLMES WAS WORKING HARD OVER A CHEMICAL INVESTIGATION."

Summary

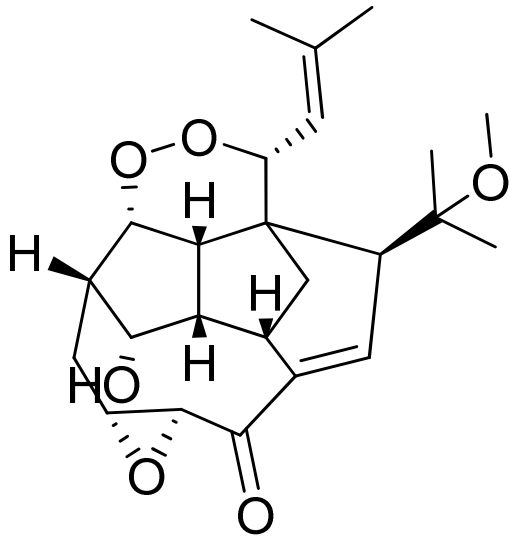
- Definitions
- Case 1: James La Clair's hexacyclinol
- Case 2: Sames - Sezen
- Other chemist misconducts
- Causes and consequences
- Fraud in Science

Scientific misconduct

- Fabrication
- Falsification
- Plagiarism

The hexacyclinol case

L'escamoteur - Jérôme BOSCH 1475



Hexacyclinol’s structure by U. Gräfe’s team

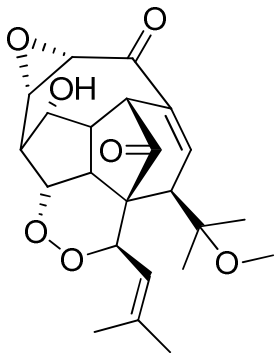
Panus Rudis

Isolated in 2002 by Udo Gräfe’s.
Showed anti-proliferative activity agains Malaria.

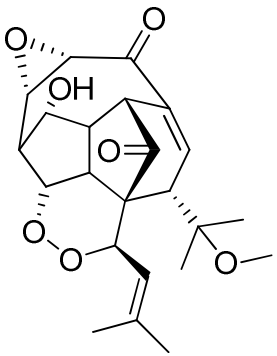
!

B. Schlegel, A. Härtl, H.-M. Dahse, F. A. Gollmick, U. Gräfe, H. Dörfelt, B. Kappes **2002**, *Journal of Antibiotics,* **55,** (9), 814–817.

J. J. La Clair's approach



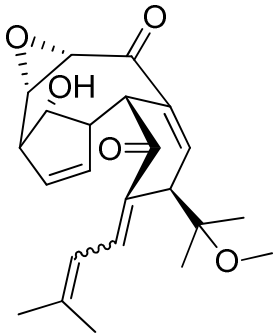
hexacyclinol



epi-5-hexacyclinol

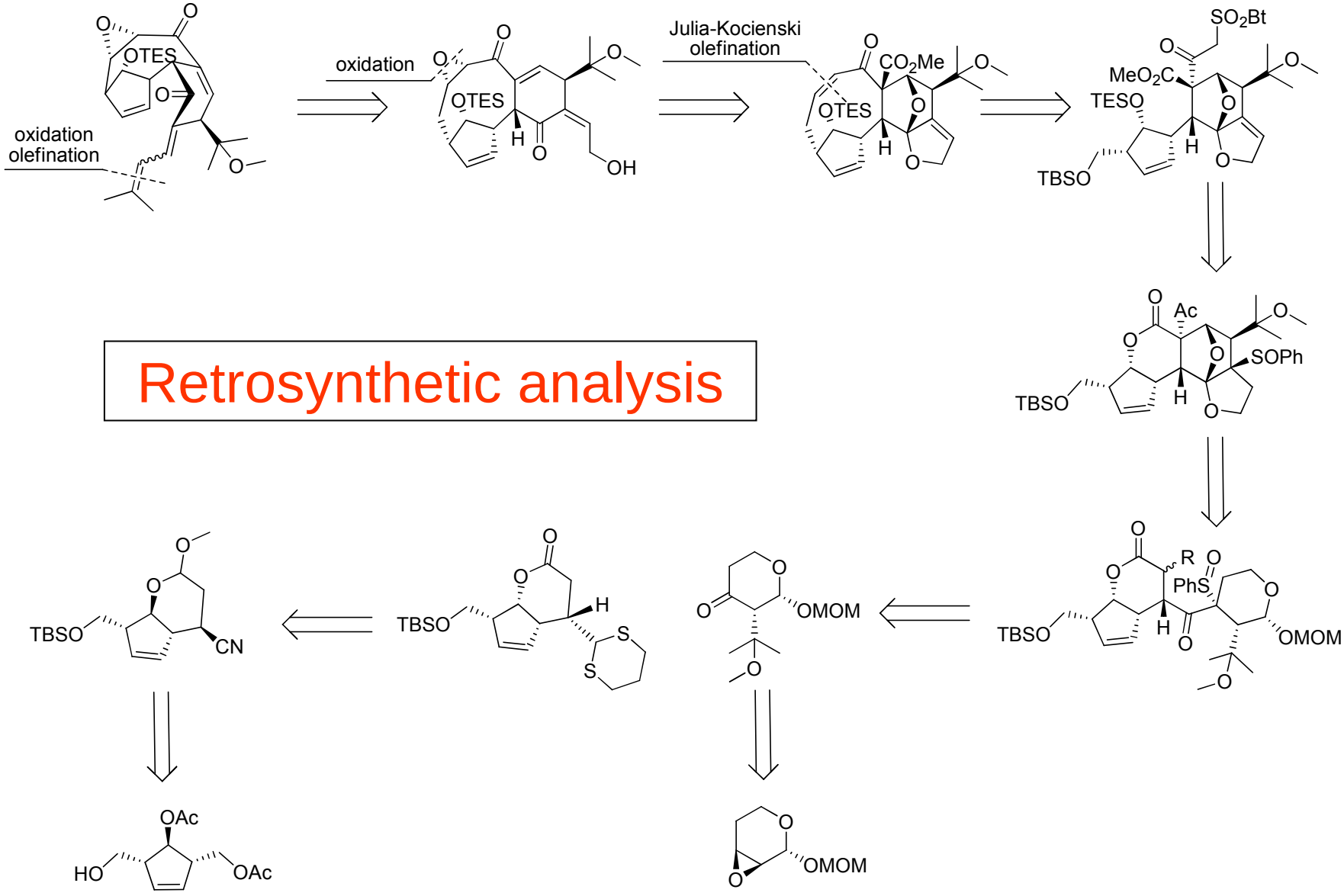
in vacuo, neat, 95%

O_2, rose bengal, MeOH, hν, 0 °C, 89%

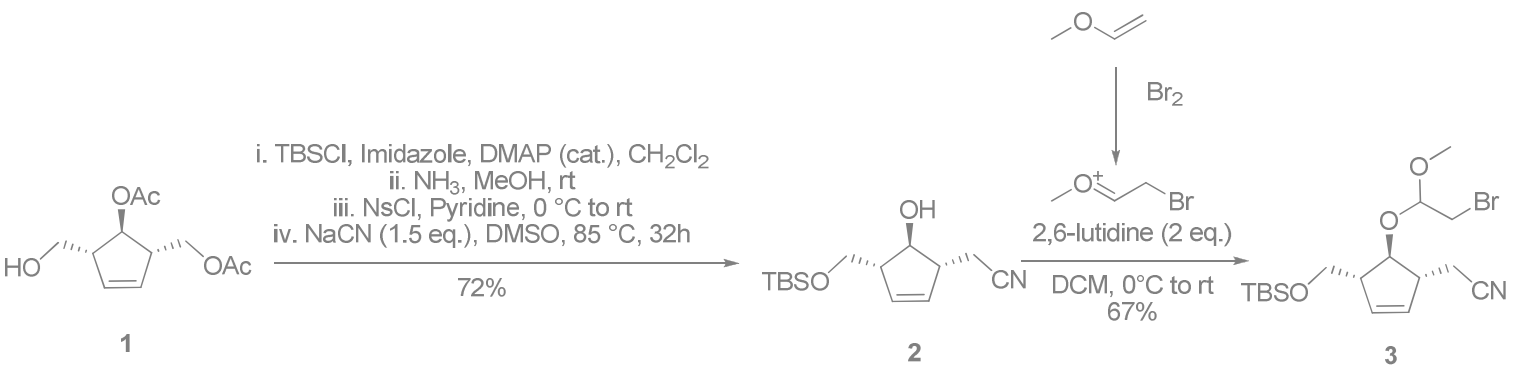


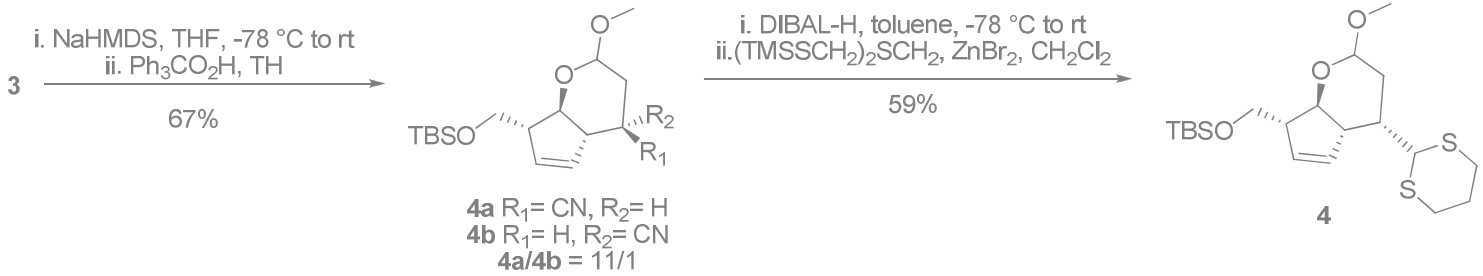
desoxohexacyclinol

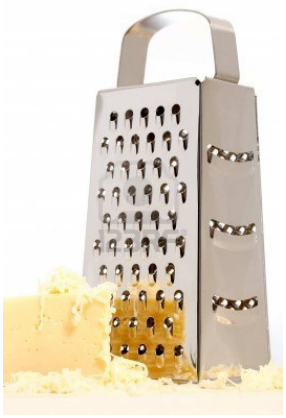
J. J. La Clair, unpublished results

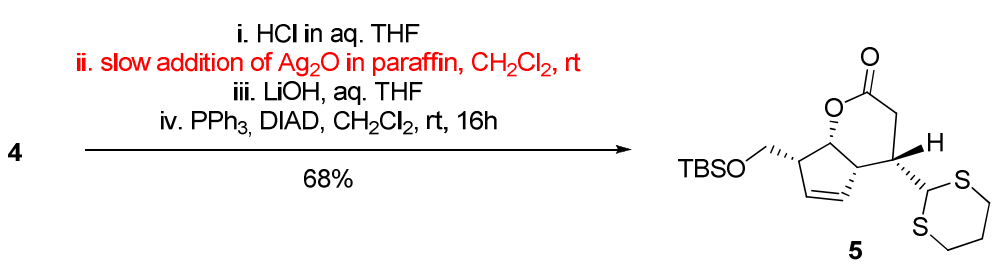

oxidation
olefination
oxidation
Julia-Kocienski
olefination
Retrosynthetic analysis

Original steps: Ag_2O, 5% in paraffin



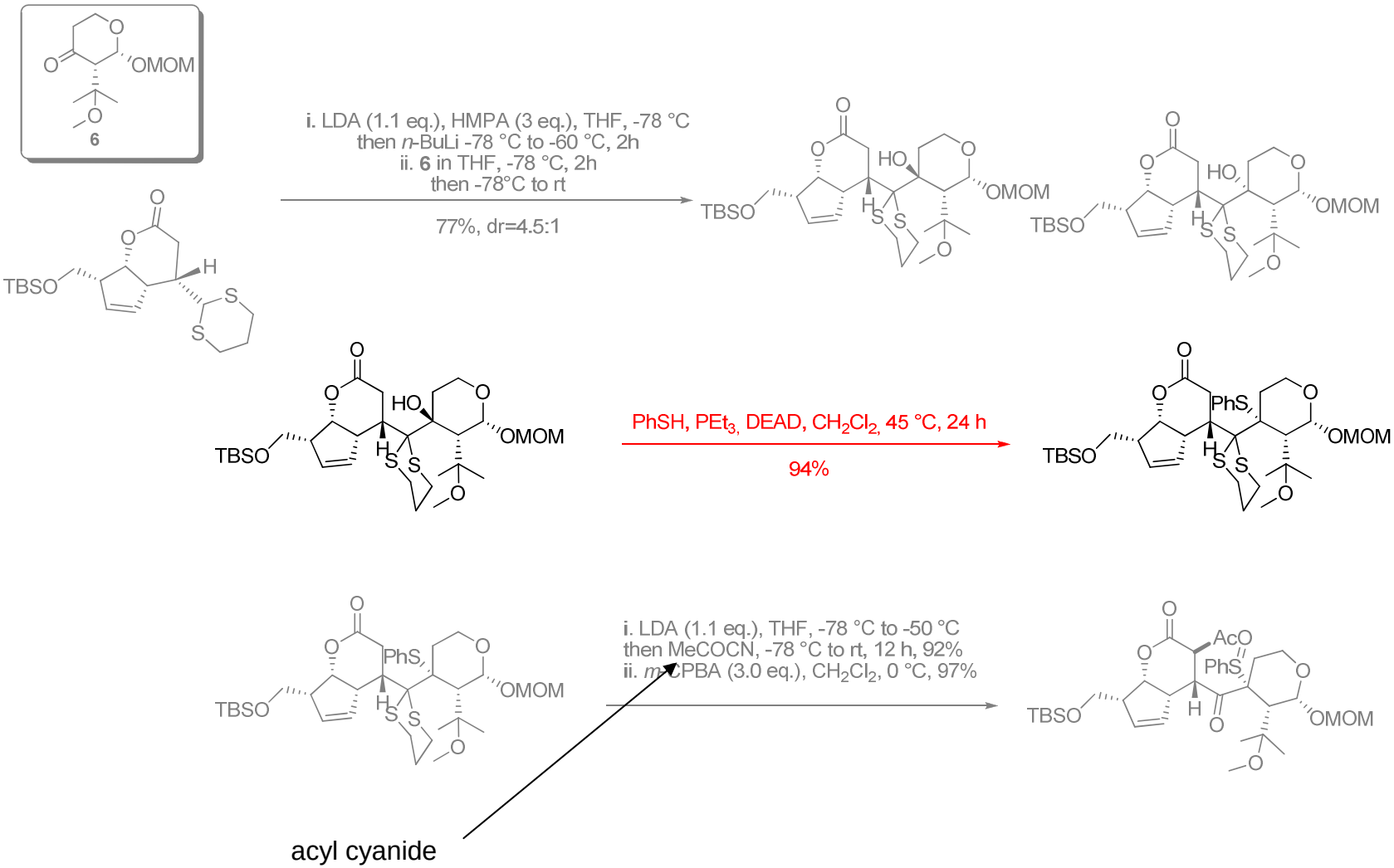






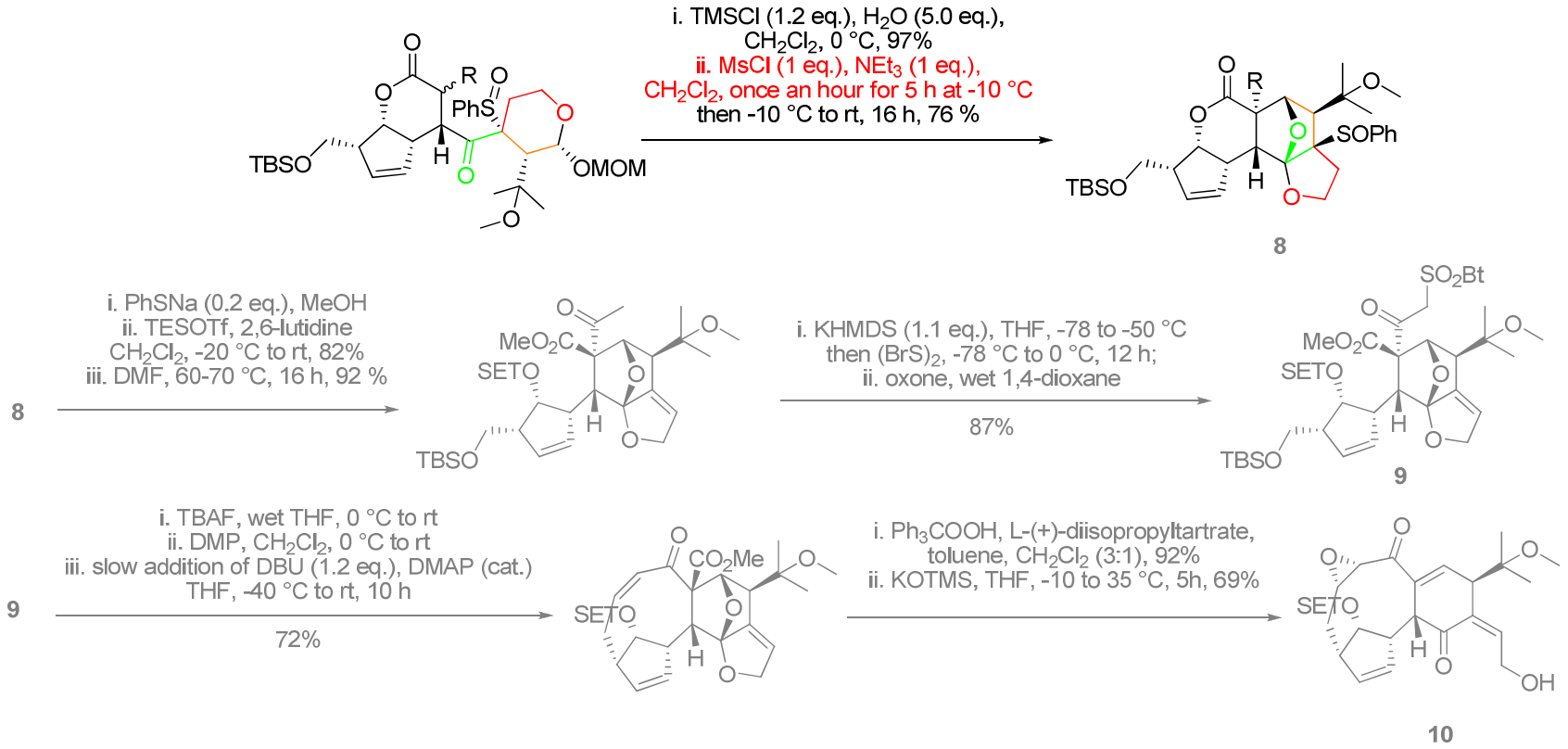
J. J. La Clair, *Angew. Chem. Int. Ed.* **2006,** 45, 2769-2773

Original steps: Mitsunobu reaction on tertiary alcohol

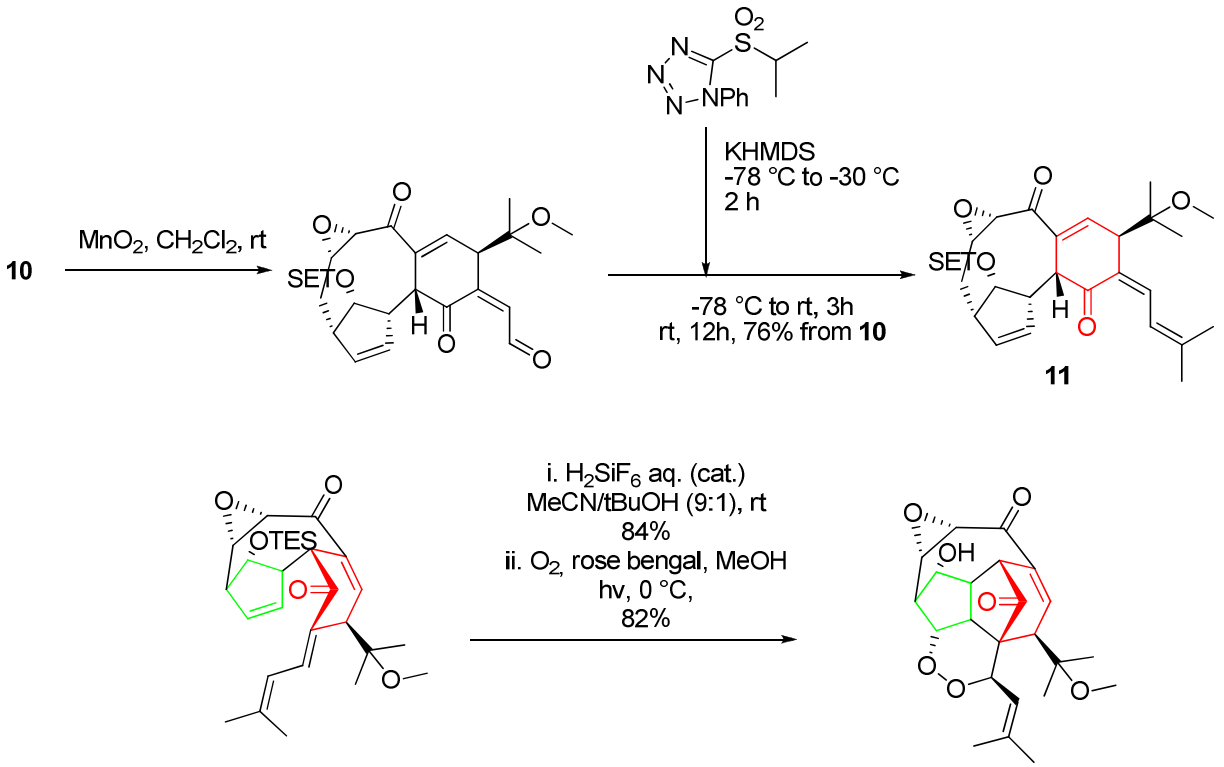


J. J. La Clair, *Angew. Chem. Int. Ed.* **2006,** 45, 2769-2773

Original steps: A cascade ring formation

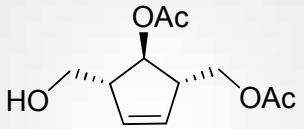


J. J. La Clair, *Angew. Chem. Int. Ed.* **2006,** 45, 2769-2773



J. J. La Clair, *Angew. Chem. Int. Ed.* **2006,** 45, 2769-2773

34 steps !
1% overall yield
87%$_{av}$ per step
Gramscale



164 g required

J. J. La Clair, *Angew. Chem. Int. Ed.* **2006,** 45, 2769-2773

(Not a picture of J. J. La Clair.)

Antimalarial Drugs

DOI: 10.1002/anie.200504033

Total Syntheses of Hexacyclinol, 5-*epi*-Hexacyclinol, and Desoxohexacyclinol Unveil an Antimalarial Prodrug Motif**

*James J. La Clair**

In memory of Udo Gräfe

J. J. La Clair is the single author.

J. J. La Clair, *Angew. Chem. Int. Ed.* **2006,** 45, 2769-2773

J. J. La Clair is not an ungrateful person.

[*] Dr. J. J. La Clair
Xenobe Research Institute
P.O. Box 4073, San Diego, CA 92164-4073 (USA)
Fax: (+1) 858-401-3083
E-mail: i@xenobe.org

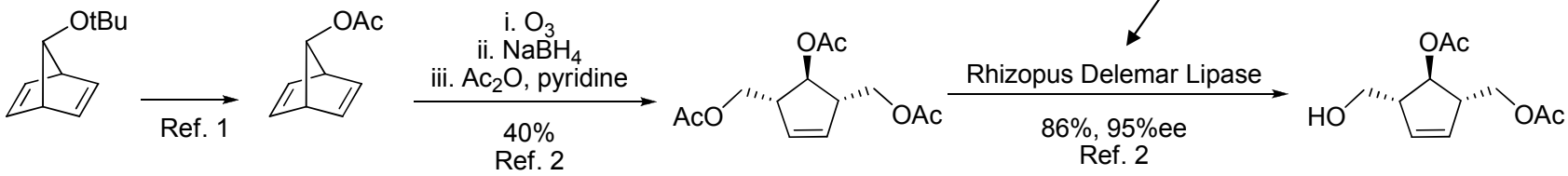
[**] A considerable portion of this work was conducted during 1999–2002 at Bionic Bros GmbH, Germany. J.J.L.C. acknowledges the assistance of five technicians.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

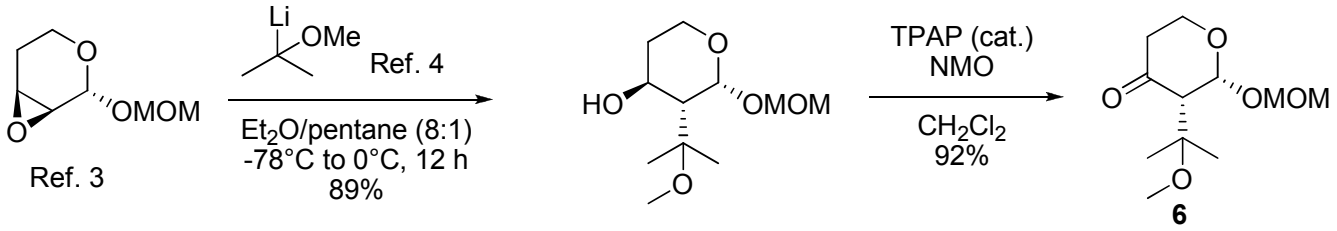
Angew. Chem. Int. Ed. **2006**, *45*, 2769–2773

Not only 34 steps.

desymmetrization



(1) (a) Baumgarten, H. E. Org. Synth. 1973, 5, 151.
(b) Cheikh, A. B.; Craine, L. E.; Recher, S. G.; Zemlicka, J. J. Org. Chem. 1988, 53, 929.
(2) M. Tanaka, Y. Norimine, T. Fujita, H. Suemune, K. Sakai, J. Org. Chem. 1996, 61, 6952.



(3) G. Anker, J. Attaghrai, D. Picq, D. Anker, Carbohydr. Res. 1987, 159, 159
(4) T. Cohen, J. R. Matz, J. Am. Chem. Soc. 1980, 102, 6900

SUPPORTING INFORMATION

FOR

Total Syntheses of the Hexacyclinol, 5-Epi-hexacyclinol and Desoxohexacyclinol Unveils an Anti-Malarial Prodrug Motif

James J. La Clair*

Xenobe Research Institute, PO BOX 4073, San Diego, California 92164-4073

*Email: i@xenobe.org

INDEX:

[22] **Note added in proof**: The ^{1}H NMR spectra for this Communication were determined by contract services. The spectra provided in the Supporting Information were collected by N. Voss (Berlin, Germany). The operator added the peak for $CDCl_3$ to the spectrum of synthetic hexacyclinol (**1**), however, this was done incorrectly at $\delta \approx 7.5$ ppm and against the request of the author. Additionally, one spectrum was duplicated and a copy of the spectra for natural 5-*epi*-hexacyclinol was not provided.

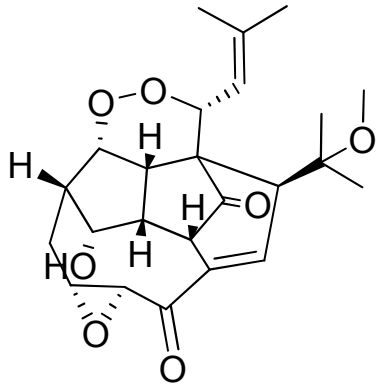
Predicting NMR Spectra by Computational Methods: Structure Revision of Hexacyclinol

Scott D. Rychnovsky*

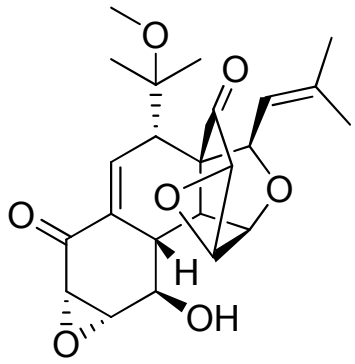
Department of Chemistry, 1102 Natural Sciences II, University of California—Irvine, Irvine, California 92697-2025

srychnov@uci.edu

Received May 9, 2006



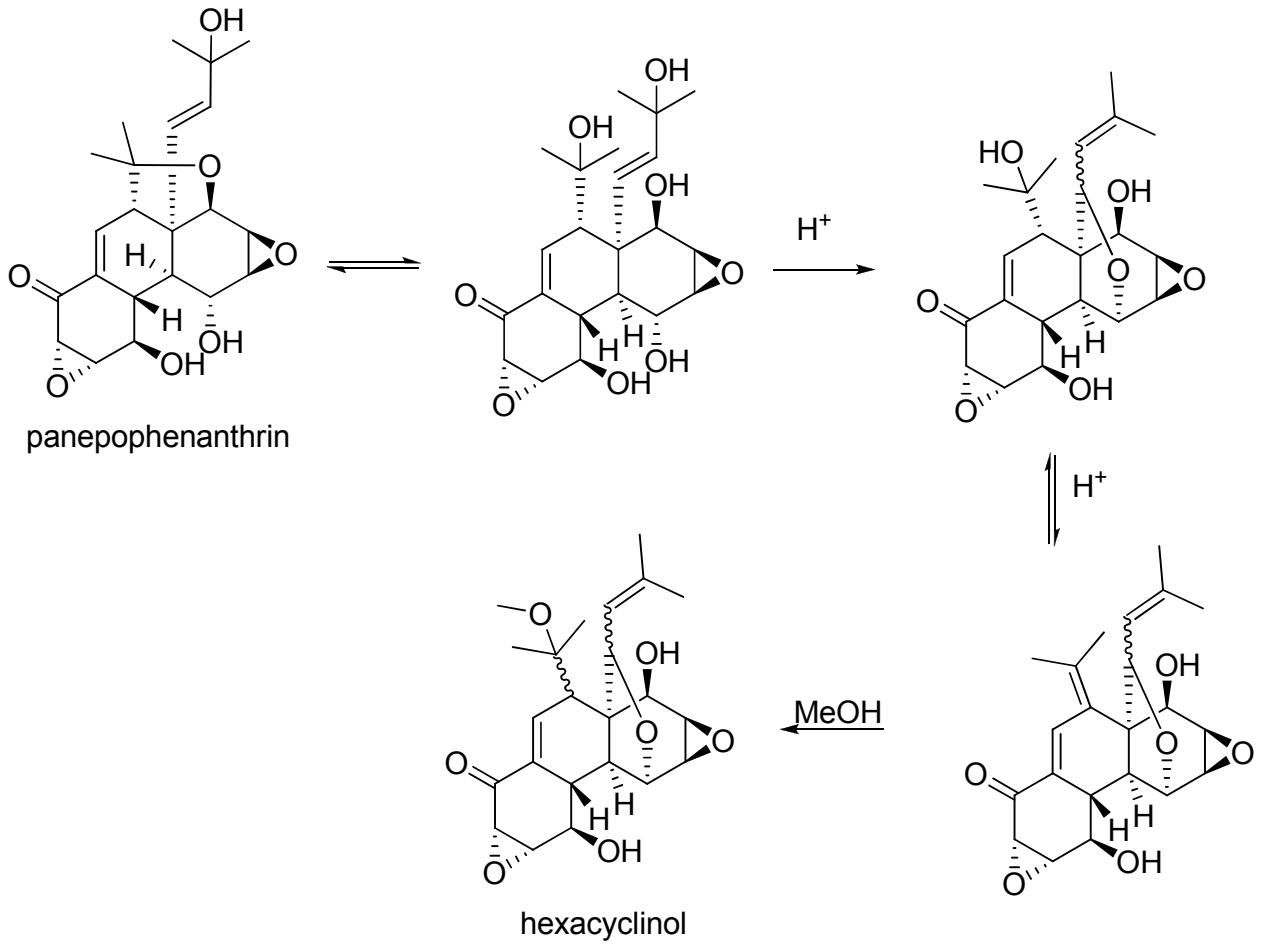
U. Gräfe, 2002



S. Rychnovsky, 2006

S. D. Rychnovsky, *Org. Lett.* **2006,** 8, 13, 2895-2898

Hexacyclinol could derivate from panepophenanthrin whose synthesis was already known



S. D. Rychnovsky, *Org. Lett.* **2006,** 8, 13, 2895-2898

For syntheses of panepophenanthrin prior to the hexacylinol's case:

X. G. Lei, R. P. Johnson, J. A. Porco, *Angew. Chem. Int. Ed.* **2003**, 42, 33, 3913-3917

J. E. Moses, L. Commeiras, J. E. Baldwin, R. M. Adlington, *Org. Lett.* **2003**, 5, 17, 2987-2988

G. Mehta, S. S. Ramesh, *Tetrahedron Lett.* **2004** 45, 9, 1985-1987

G. Mehta, K. Islam, *Tetrahedron Lett.* **2004,** 45, 41, 7683-7687

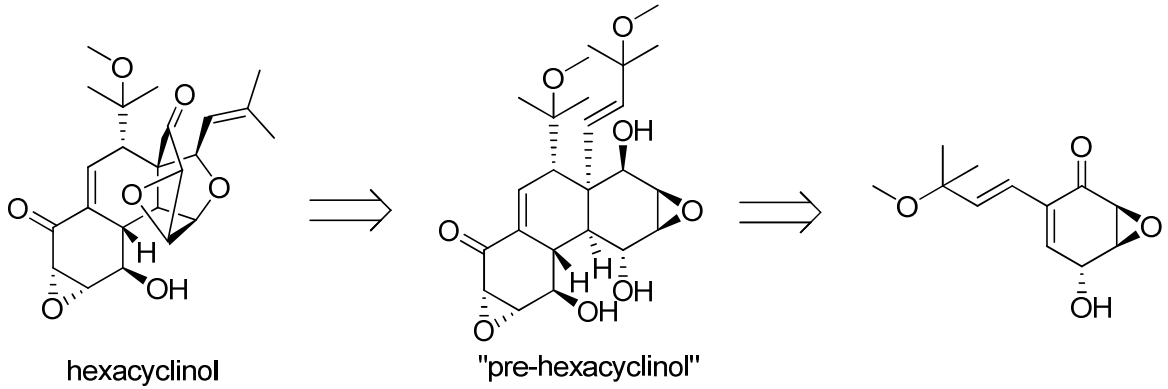
Hellooo STeRéO !

Hexacyclinol

DOI: 10.1002/anie.200602854

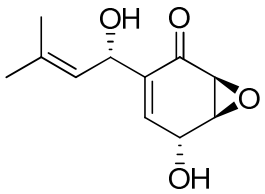
Total Synthesis and Structure Assignment of (+)-Hexacyclinol**

John A. Porco, Jr., Shun Su, Xiaoguang Lei, Sujata Bardhan, and Scott D. Rychnovsky*

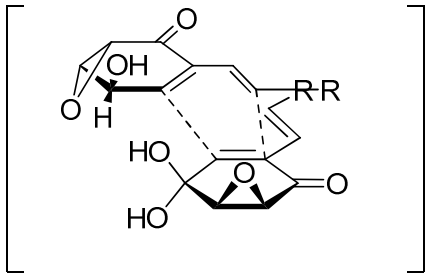


hexacyclinol

"pre-hexacyclinol"

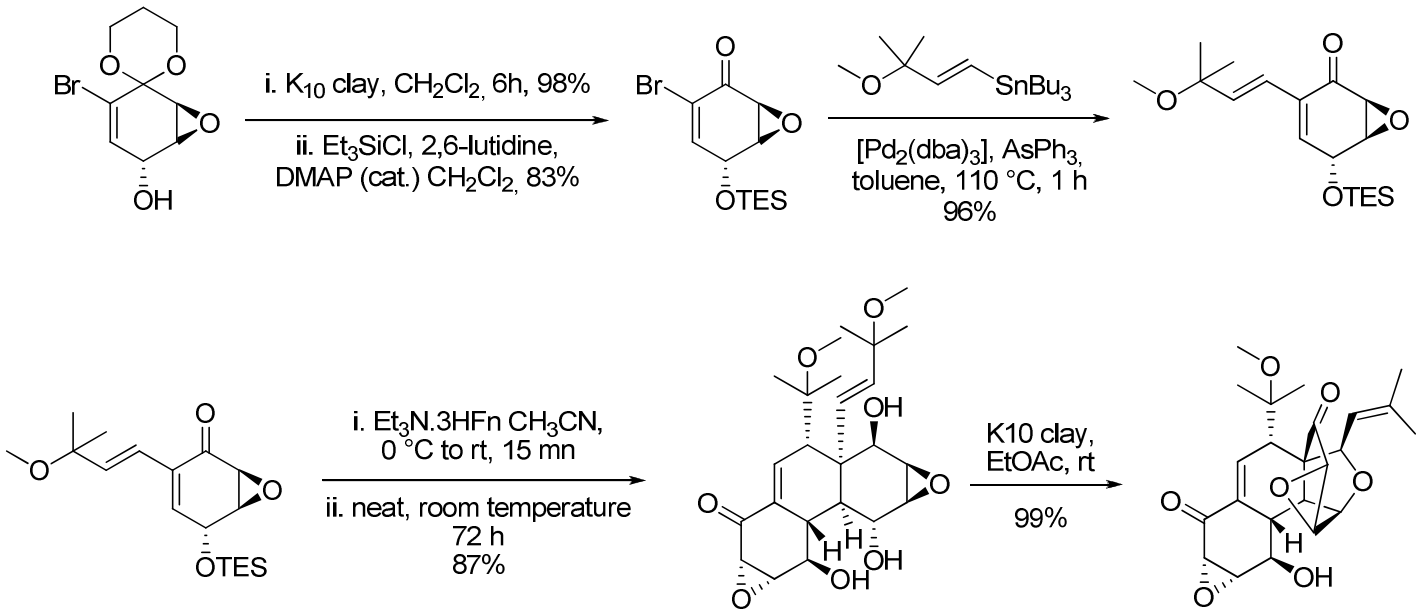


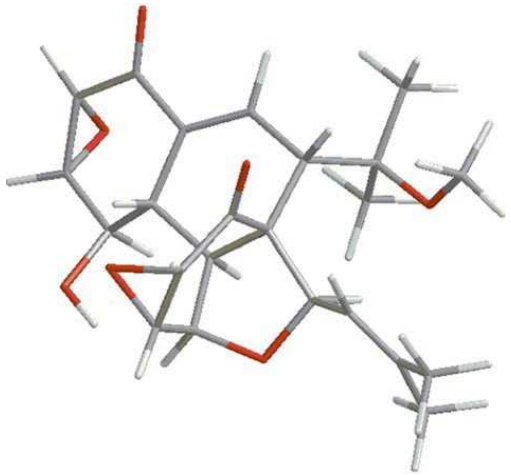
Panepoxydon



J. A. Porco, Jr., S. Su., X. Lei, S. Bardhan, S. D. Rychnovsky, *Angew. Chem. Int. Ed.* **2006**, 45, 5790-5792
J. B. Shotwell, S. Hu, E. Medina, M. Abe, R. Cole, C. M. Crews, J. L. Wood, *Tetrahedron Lett.* **2000**, 41, 9639.

Hexacyclinol's synthesis by the Porco group.





Hexacyclinol XRay structure

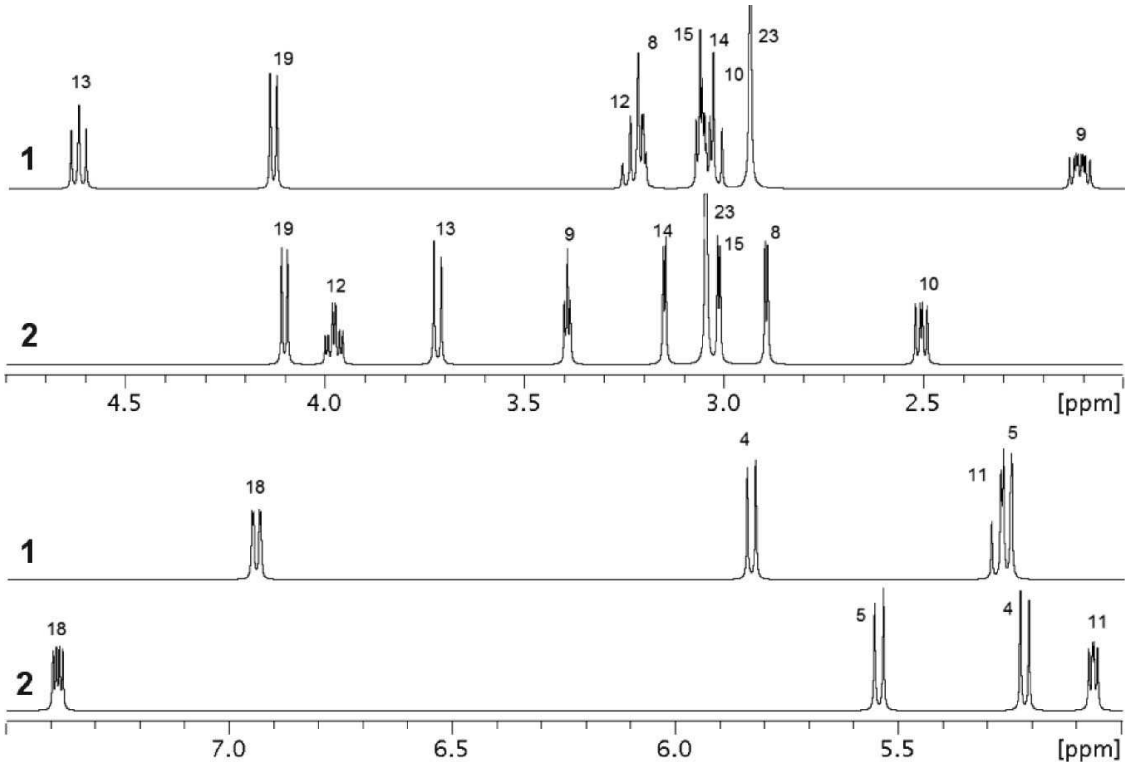
ORGANIC LETTERS

2009
Vol. 11, No. 6
1409−1412

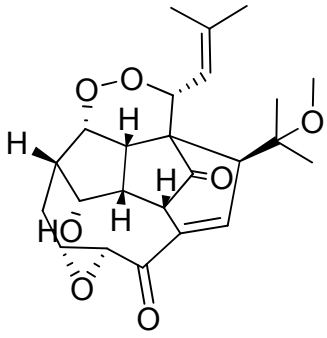
Can Two Molecules Have the Same NMR Spectrum? Hexacyclinol Revisited

Giacomo Saielli[†] and Alessandro Bagno*[,‡]

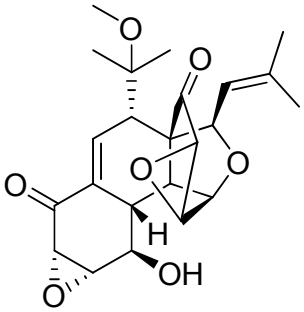
Istituto CNR per la Tecnologia delle Membrane, Sezione di Padova, and Dipartimento di Scienze Chimiche, Università di Padova, via Marzolo 1, 35131 Padova (Italy)



Calculated 1H spectra of hexacyclinol



1
U. Gräfe, 2002



2
S. Rychnovsky, 2006

Finally…

Angewandte
Retraction

The following article from *Angewandte Chemie International Edition*, "Total Syntheses of Hexacyclinol, 5-*epi*-Hexacyclinol, and Desoxohexacyclinol Unveil an Antimalarial Prodrug Motif" by James J. La Clair, published online on February 9, 2006 in Wiley Online Library (http://onlinelibrary.wiley.com), has been retracted by agreement between the author, the journal Editor in Chief, Peter Gölitz, and Wiley-VCH Verlag GmbH & Co. KGaA. The retraction has been agreed due to lack of sufficient Supporting Information. In particular, the lack of experimental procedures and characterization data for the synthetic intermediates as well as copies of salient NMR spectra prevents validation of the synthetic claims. The author acknowledges this shortcoming and its potential impact on the community.

Total Syntheses of Hexacyclinol, 5-*epi*-Hexacyclinol, and Desoxohexacyclinol Unveil an Antimalarial Prodrug Motif

J. J. La Clair* _____ **2769–2773**

Angew. Chem. Int. Ed. **2006**, *45*

DOI: 10.1002/anie.200504033

J. J. La Clair, *Angew. Chem. Int. Ed.* **2012**, 51, 11647-11662

- Suspicious data.
- Disproof by modelisation and synthesis.

- Editor and referees should have been more critic.
- This case illustrates the importance of supporting information.

- J. J. La Clair still denies frauding.

The Sames-Sezen case

Le Tricheur à l'as de carreau - Georges de la Tour 1635

Pr. Dalibor Sames

Bengü Sezen

1996 – Awarded PhD degree (University of Arizona)
1998 – Assistant Professor (Columbia University)
2003 – Associate Professor (Columbia University)

9 awards

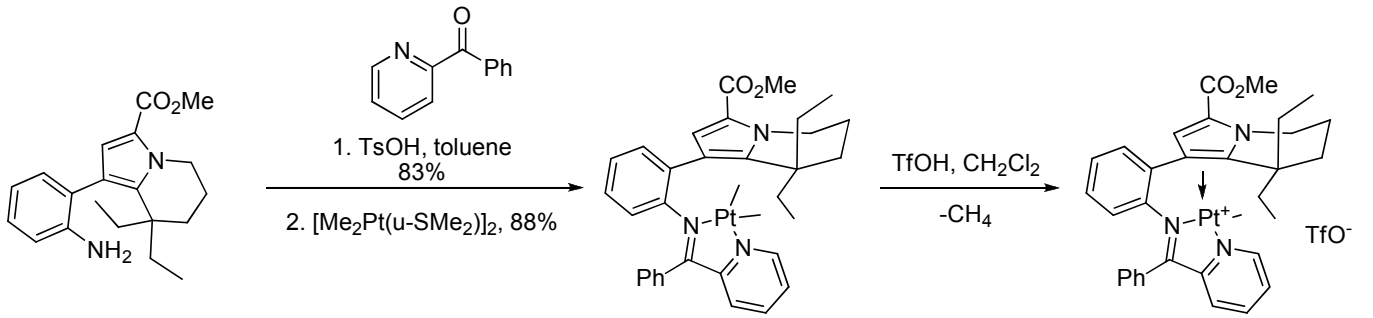
2000 – joins Pr. D. Sames group
2002 – 1st fraudulent paper
2002 – first reproducibility concerns
2005 – Awarded PhD degree
2011 – PhD retractation

<u>Research topics:</u>

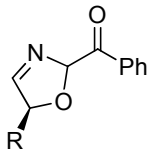
C-H bond functionalization

synthesis of imagin agents

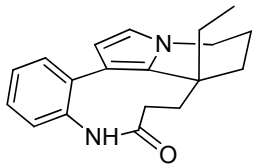
Previously in Pr. D. Sames group



Enantioselectivity ?



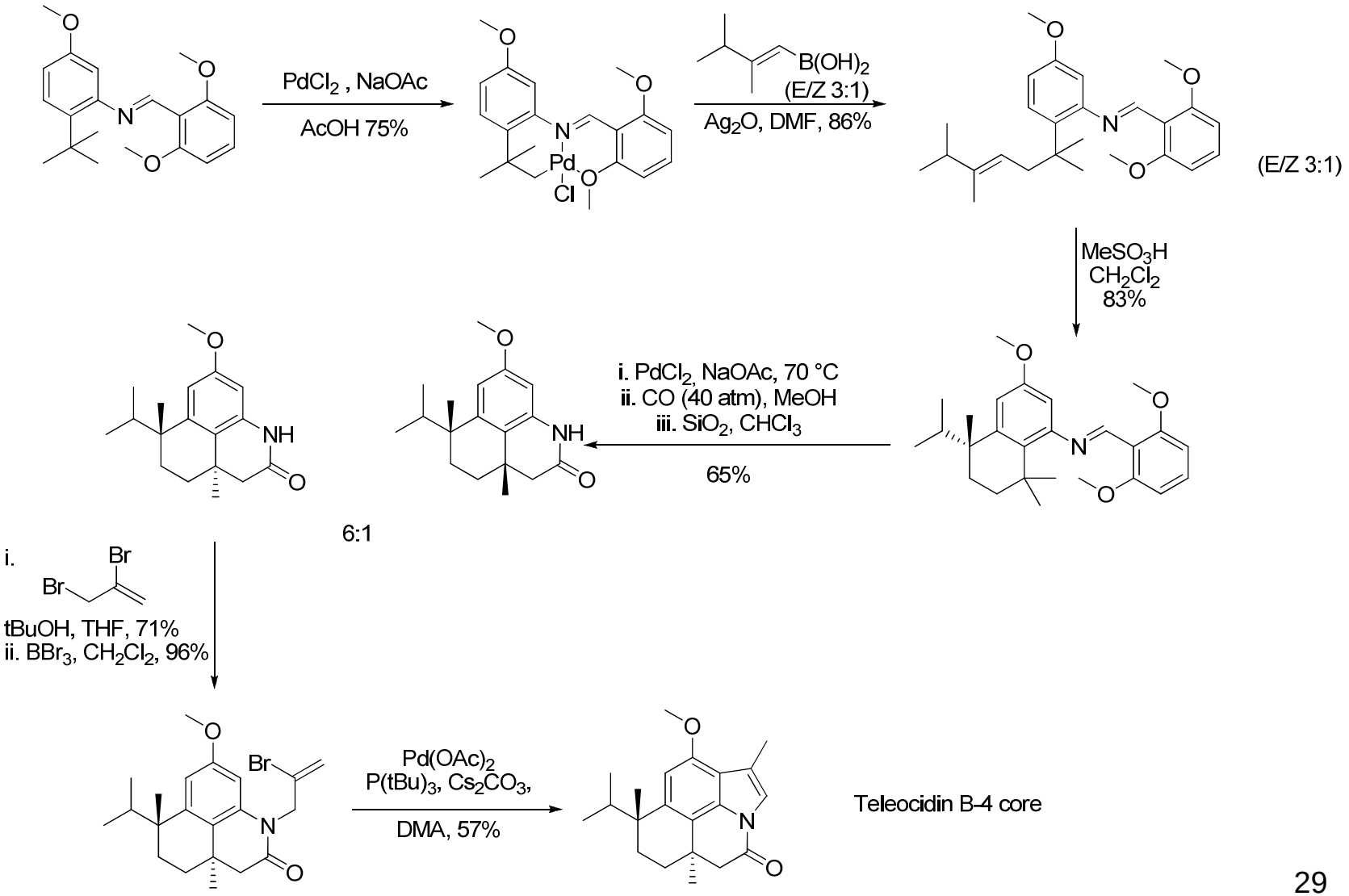
up to 76% ee if R = Cy



(-)-Rhazinilam

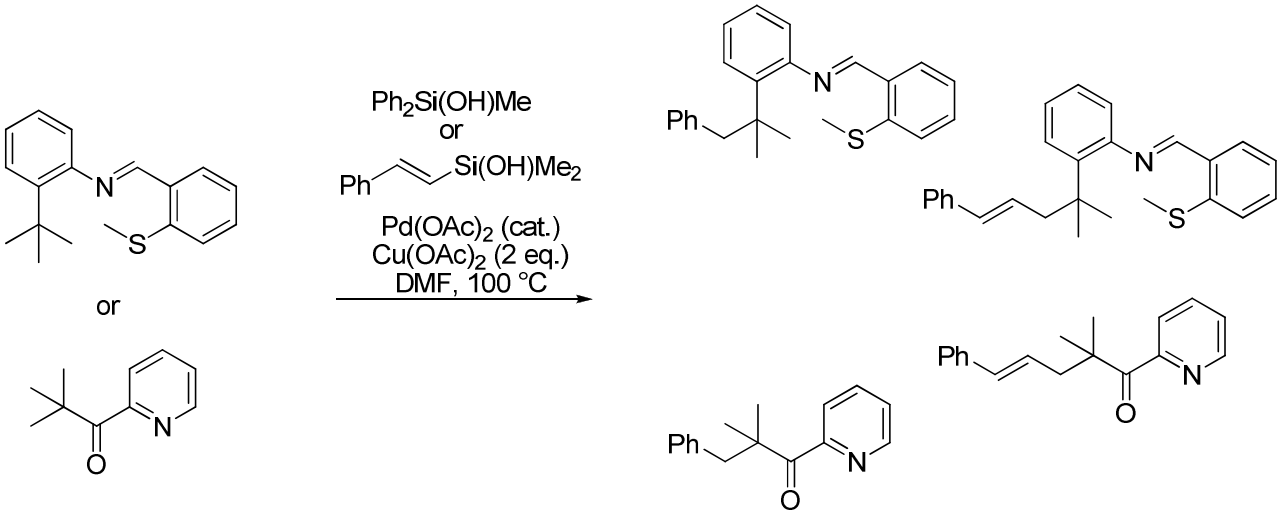
J. A. Johnson, N. Li, D. Sames, *J. Am. Chem. Soc.* **2002**, 124, 24, 6900-6903

1st paper by Sezen and Sames



B. D. Dangel, K. Godula, S. W. Youn, B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2002**, 124, 11856-11857

First retracted paper

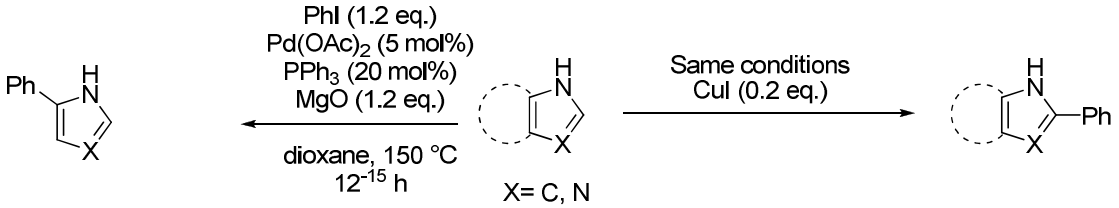


Retracted due to inability to reproduce the published results.
Cited 44 times (12 after paper retractation).

B. Sezen, R. Franz, D. Sames, *J. Am. Chem. Soc.* **2002**, 124, 13372-13373
This paper was retracted on June 21, 2006 (J. Am. Chem. Soc. 2006, 128, 8364)

Retracted papers.

(1)



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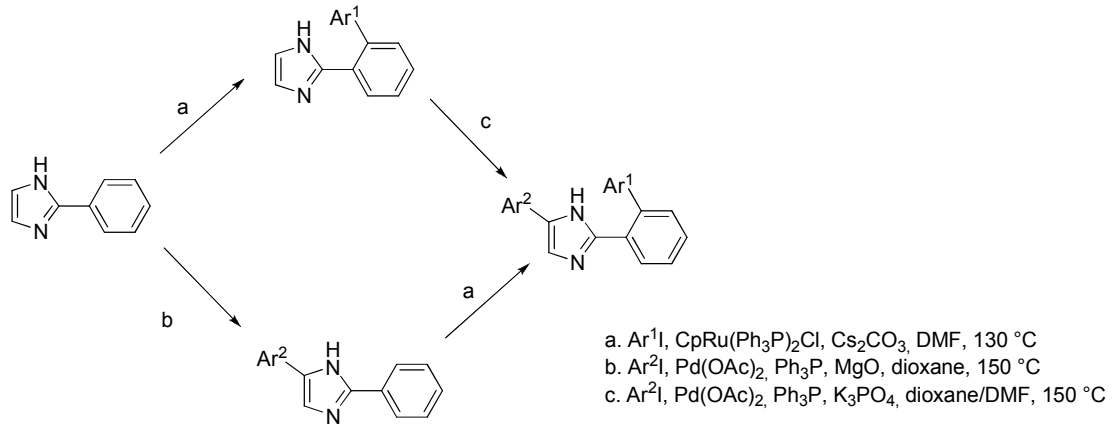
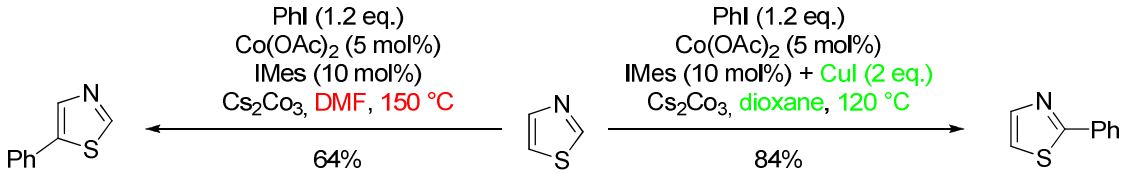


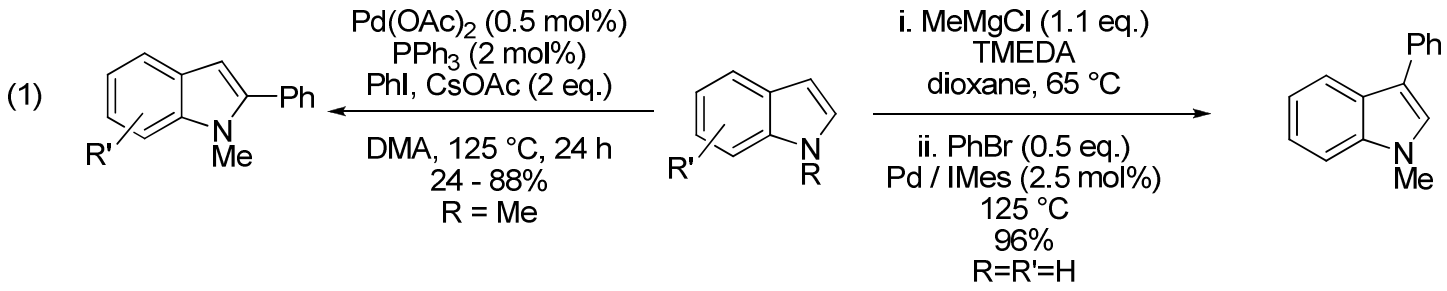
(3)

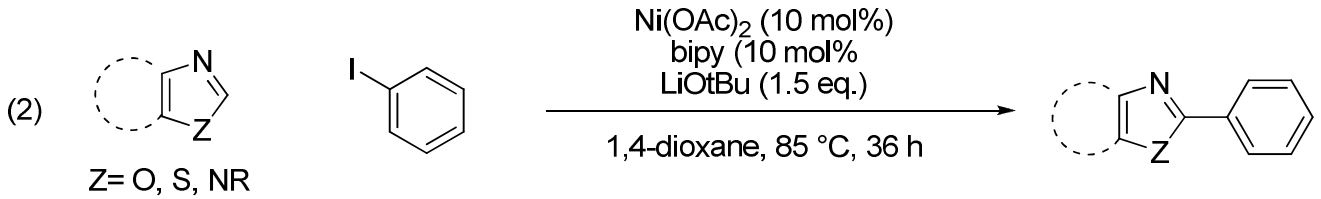


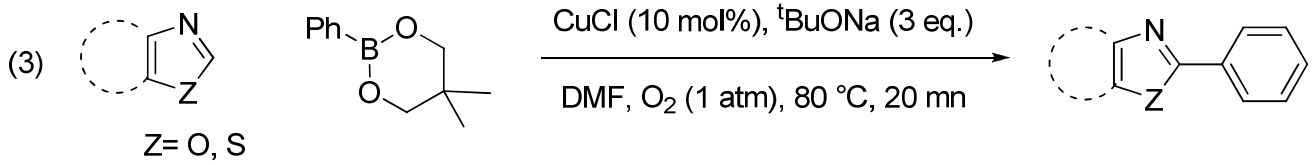
(1) B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2003**, 124, 5274-5275
(2) B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2003**, 124, 10580-10585
(3) B. Sezen, D. Sames, *Org. Lett.* **2003**, 5, 20, 3607-3610
PCT Int. Appl., 2004069394, 19 Aug 2004

(1) and (2) were retracted on June 21st, 2006 (*J. Am. Chem. Soc.* **2006**, 128, 8364).
(3) was retracted on June 15th, 2006 (*Org. Lett.* **2006**, 8, 2899)

Developped since then.



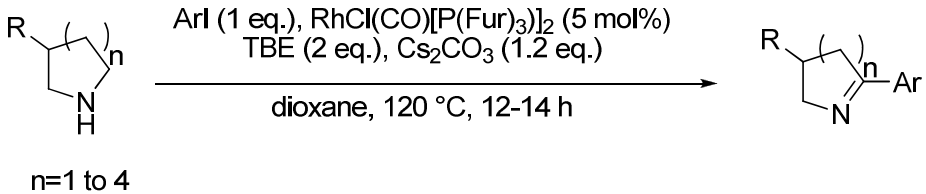




(1) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc*. **2005**, 127, 8050-8057.
(2) J. Canivet., J; Yamaguchi, I. Ban, K. Itami, *Org. Lett.* **2009**, 11, 1733-1736,
T. Yamamoto, K. Muto, J. Canivet, J. Yamaguchi, K. Itami, M. Komiyama, *Chem. Eur. J.* **2011**, 10113 – 10122
(3) F. Yang, Z. Xu, Z. Wang, Z. Yu, R. Wang, *Chem. Eur. J.* **2011** , p. 6321 - 6325

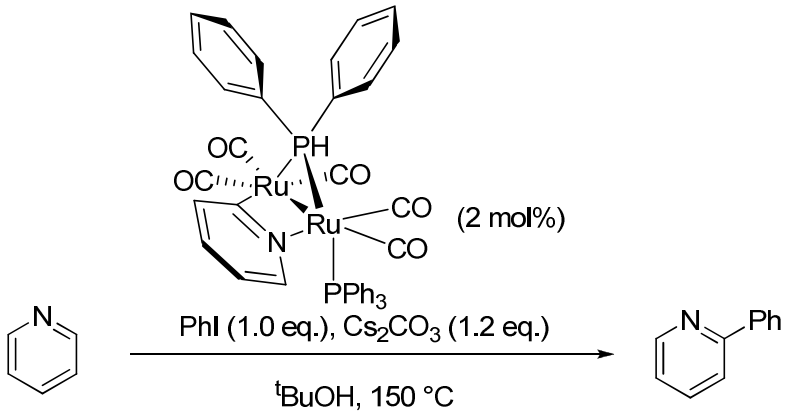
Retracted papers.

(1)

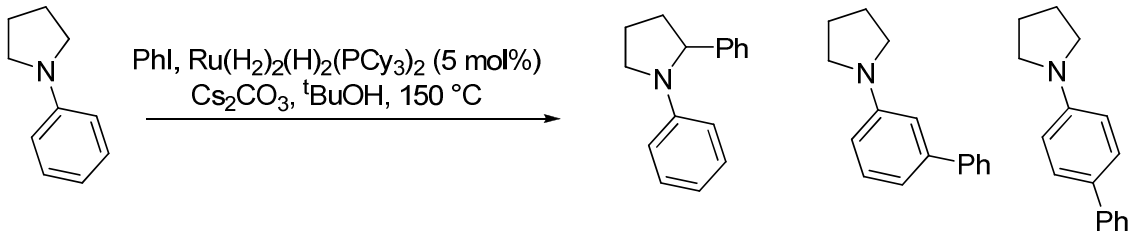


n=1 to 4

(2)



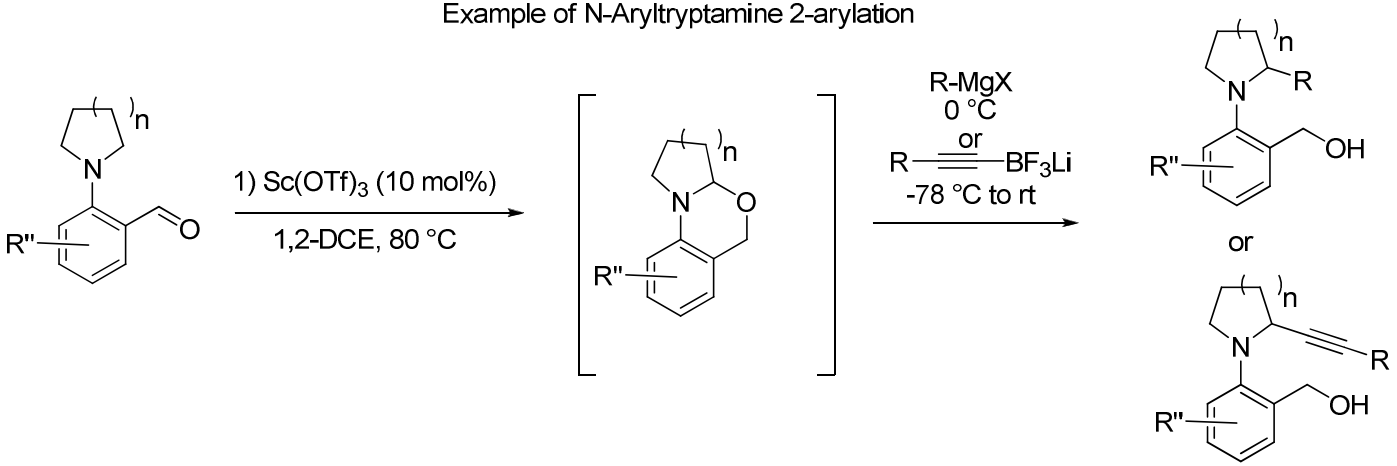
(3)



(1) B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2004**, 126, 13244-13246
(2) K. Godula, B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2005**, 127, 3648-3649
(3) B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2005**, 127, 5284-5285
These papers were retracted on March 8th, 2006

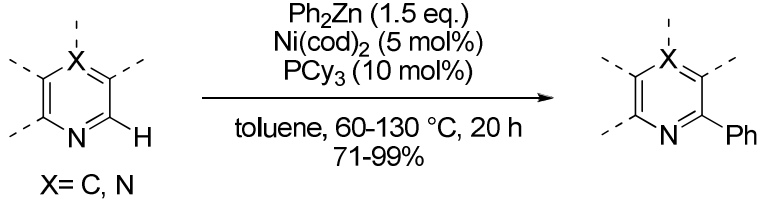
Developped since then.

Example of N-Aryltryptamine 2-arylation



I. D. Jurberg, B. Peng, E. Wöstefeld, M. Wasserloos, N. Maulide, *Angew. Chem. Int. Ed.* **2012**, 51, 1950-1953

Example of pyridine 2-arylation

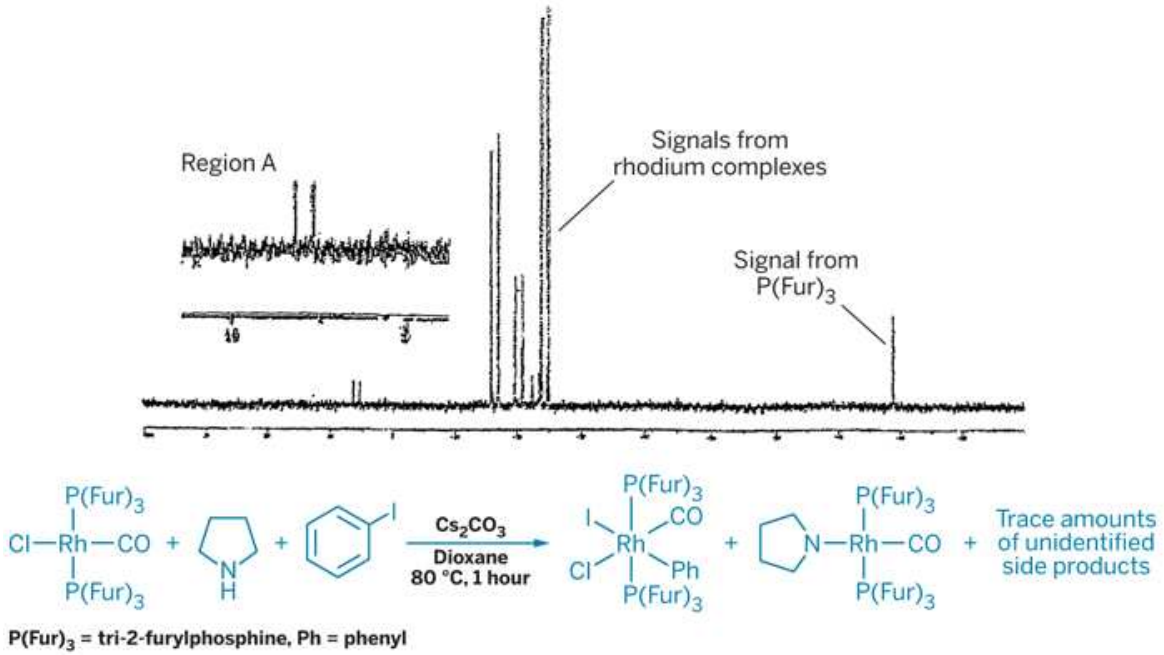


M. Tobisu, I. Hyodo, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 12070-12071

The Fraud

- Fabricated NMR:
  - Duplication of methylene chloride signal
  - Duplication of triphenylphosphine signal
  - Presence of correcting fluid on published specta

- Bengü Sezen's misconduct proven after being trapped by a co-worker
- Neglected lab notebook handling



Example of fabricated NMR

Source: W. G. Schulz, *Chemical & Engineering* News, 08.08.2011, 89, 32, 40 - 43

How about Pr. D. Sames role ?

A lack of quality control

- Hardly reproducible experiments (reported since 2002)
- Failure in spin-off projects
- Good results required Sezen to be alone in the lab
- Neglected lab notebook redaction

A deaf ear

- Many reproducibility concerns were raised while Sames published 5 more papers
- 3 students left the group

Deed polls

- Sames ran his own investigation paralelly to the official one
- He requested paper retraction

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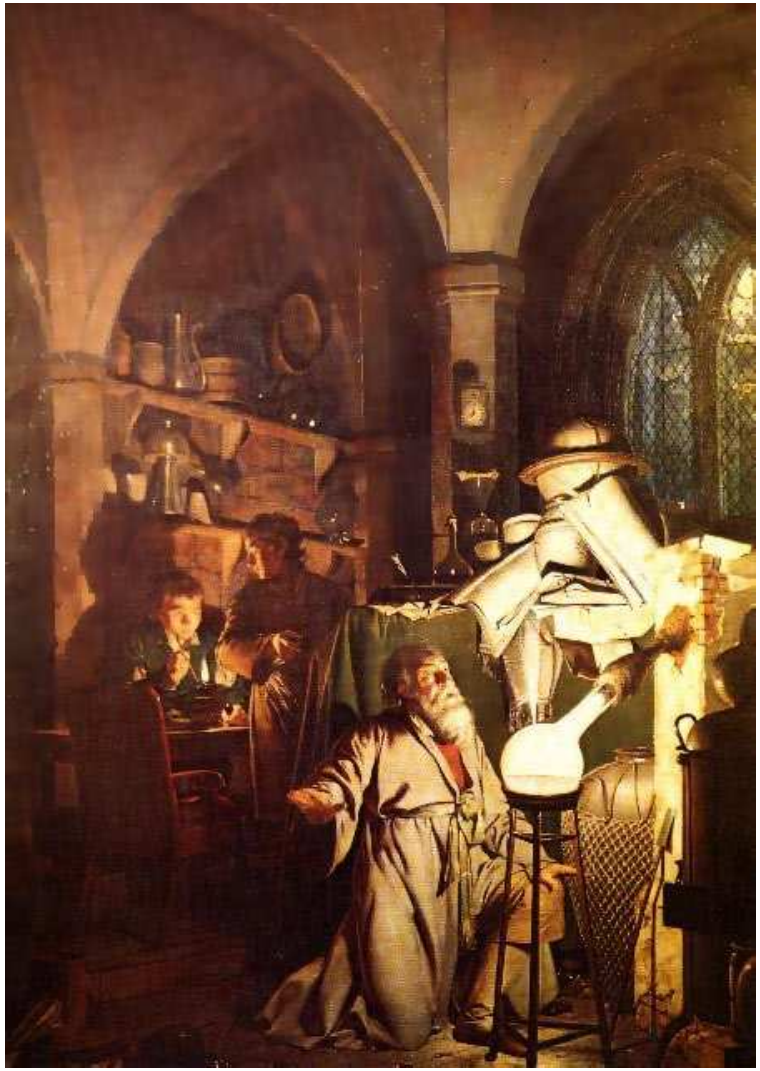
- Fabricated results.
- Falsified NMR.
- Lousy record keeping.
- Lack of experiment reproducibility.
- Scientific misbehavious in the lab.

- Such groundbreaking experiments should have been reproduced by someone else.
- Pr. D. Sames was way too confident in B. Sezen’s results.

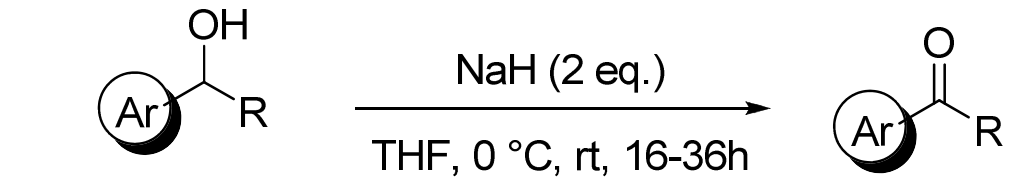
- B. Sezen still denies fraud.

Other chemistry frauds



The Alchymist, In Search of the Philosophers' Stone – Joseph Wright of Derby, 1771.

Sodium hydride oxydation



Ar= aryl, heteroaryl
R= alkyl, aryl, alkenyl

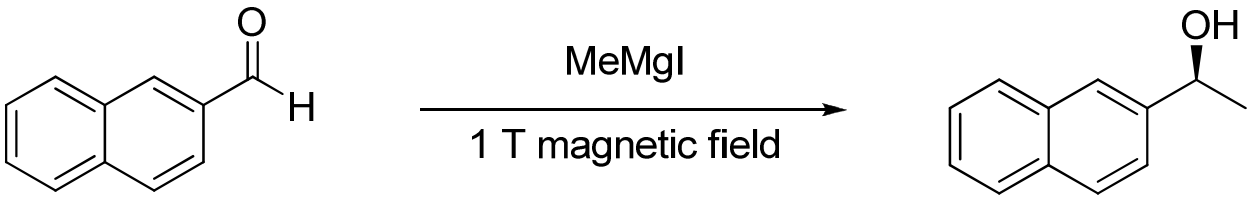
Unfortunately, the reaction conditions were not completely anaerobic…
Probably not a fraud, rather a lack of scientific method.

Referee and editor's mistake.

X. Wang, B. Zhang, D. Z. Wang, *J. Am. Chem. Soc*. **2009** DOI: 10.1021/ja904224y
withdrawn before it was published

NMR-induced enantioselectivity

« Enantioselective Reactions in a Static Magnetic Field »[1]



ee = 98%

Enantioenriched compound had fraudulously been introduced.

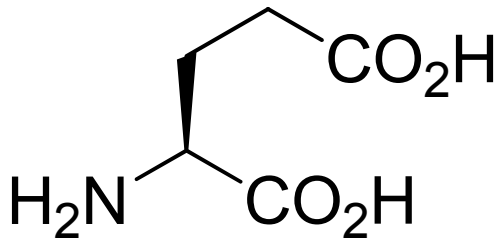
« No Enantioselective Reactions in a Static Magnetic Field »[2] was rapidly published.

Research advisor should have tried to reproduce the experiment.

(1) G. Zadel, C. Eisenbraun, G.-J. Wolff, E. Breitmaier, *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 454
(2) E. Breitmaier, *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1207

When fraud isn't fraud

A student was asked to prepare racemic glutamic acid.



His product was optically active.
He was expelled from Votocek's laboratory.

Enantioenrichment upon recrystallisation.

» Research advisor's fault. Work was actually reproducible.

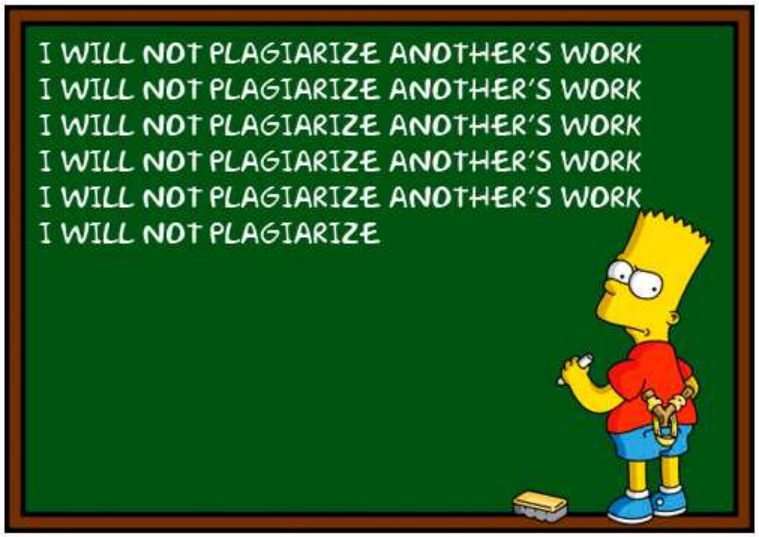
V. Prelog, *My 132 Semesters of Chemistry Studies*, ACS: Washington, DC, 1991, p. 93

Why do people fraud ?

- Fame:
  - H index boost.
  - Awards.
  - Scientific acknowledgement.
  - Buzz.
  - Be the « first » to publish.

- Money:
  - Funding.
  - Competing interest (ghost authorship).
  - « Publish or Perish ».

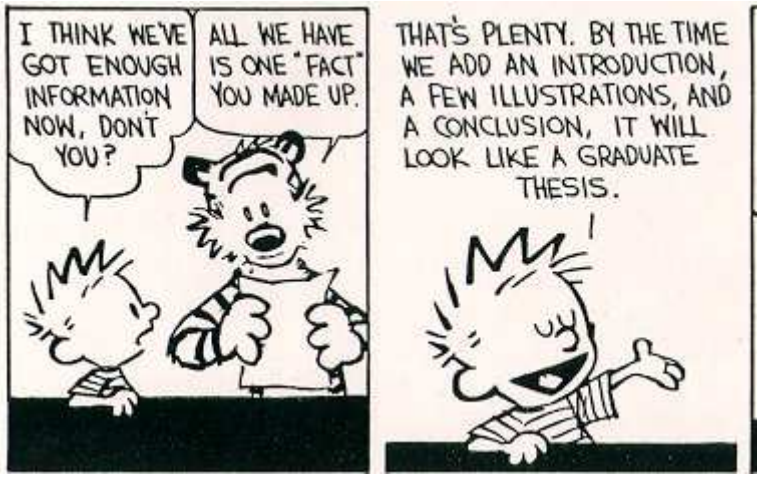
How do people fraud ?



- Fabrication.
- Falsification.
- Plagiarism:
  - Paquette / Martin case[1].
  - Pattium Chiranjeevi case.
  - Self-plagiarism.
  - Student stealing ideas from Pr. P. S. Baran[2,3].
  - Cordova – Blackmond case[4].

(1) O*ffice of Research Integrity newsletter* June **1993**, 1, 3,
(2) J. Gong, G. Lin, C.-C. Li, Z. Yang, *Org. Lett.* **2009**, 4770-4773
(3) P. J. Krawczuk; N. Schöne, P. S. Baran, *Org. Lett.* **2009**, 4774-4776
(4) W. G. Schulz, *Chemical & Engineering News* March 12 **2007**, 85, 12, 35-38

Of the importance of good refereeing

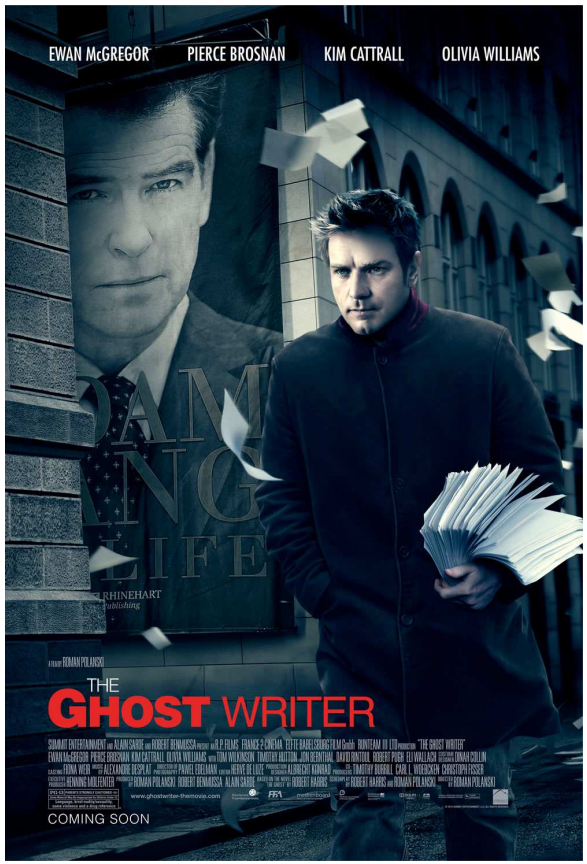


- Supporting information is essential.
- Narrow-mindedness: Beluzov case[1].
- Conflict of interest.
- Lack of references.
- References to withdrawn papers.
- Fake references.

(1) Winfree, A. T., *J. Chem. Educ.* **1984**, 61, 661

How about co-authors ?

Liability: co-signing a paper is being responsible of its content.

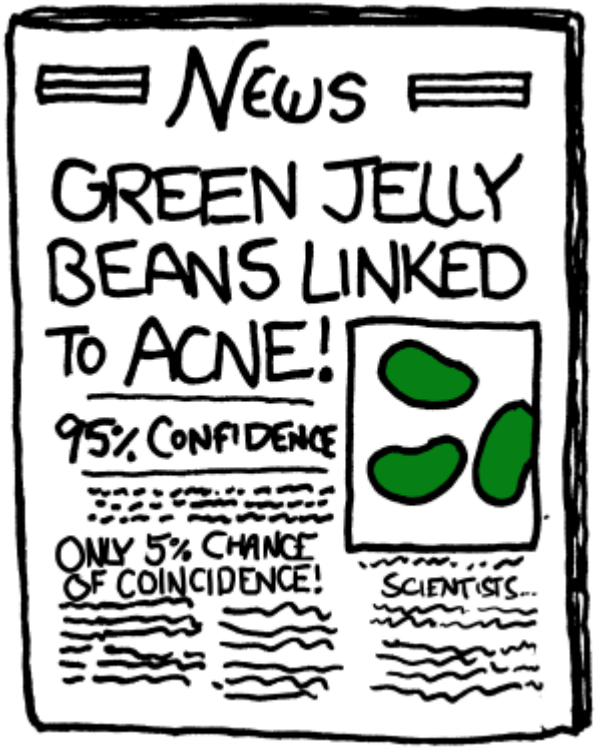


Editing groups

- A delicate issue:
  - Legal liabilities.
  - Economic consequences.
- Editing groups must ensure the referee's work was correctly done.
- Editing groups misbehaviours:
  - Lack of retracted paper labelling
  - Paper unavailability (Breslow case).
  - Referee quality control ?

Examples of fraud in science

- Wakefield's article linking MMR vaccine and autism.
- Hwang Woo-suk's human embryon cloning.
- Stapel[1] scandal in economics.
- Viswa Jit Gupta in archaeology.

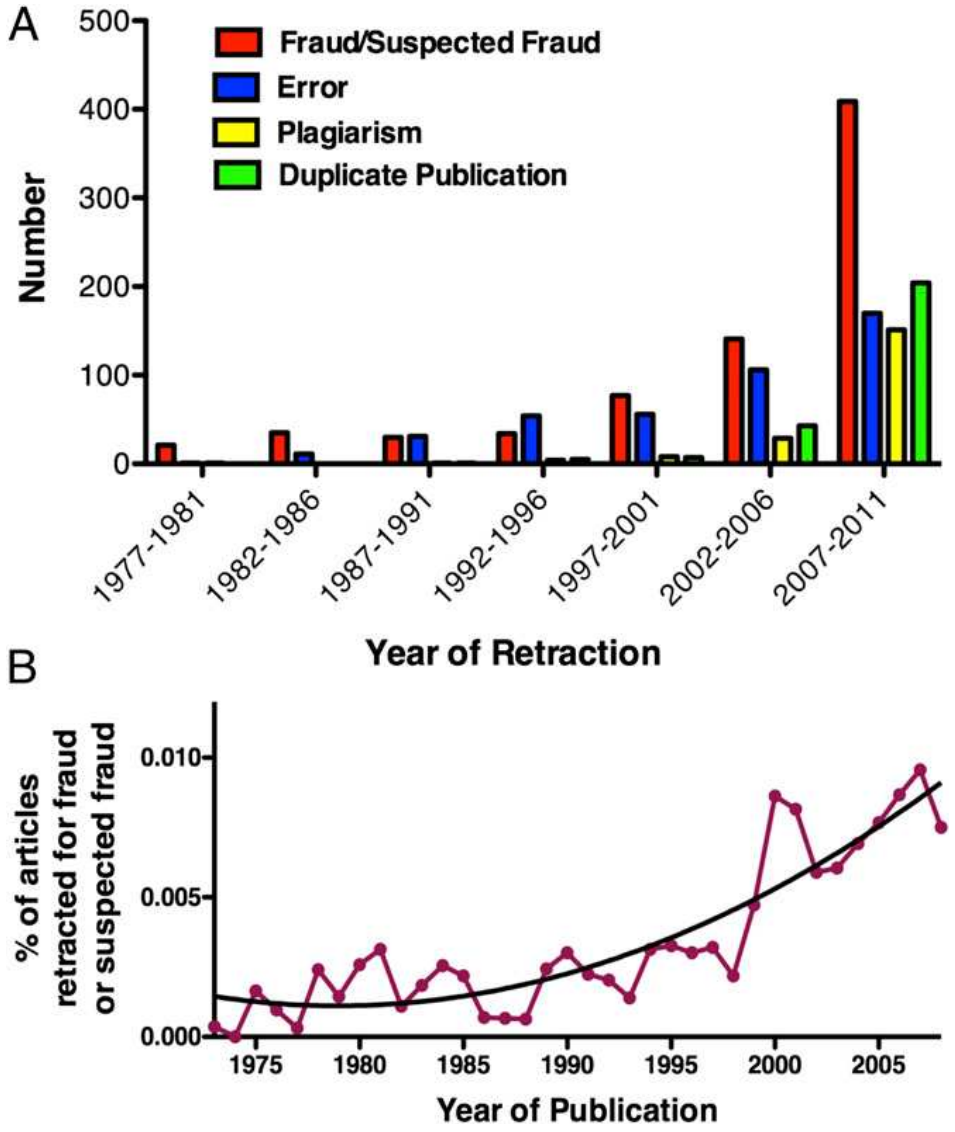


(1) *Nature* **479**, 15 (2011), doi:10.1038/479015a

Retractions (PubChem index)

(A) Number of retracted articles for specific causes by year of retraction

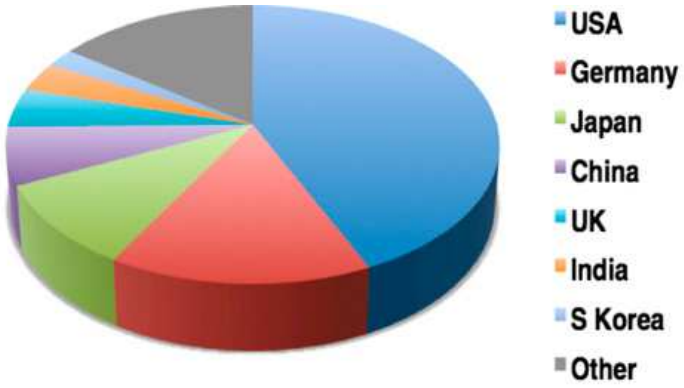
(B) Percentage of published articles retracted for fraud or suspected fraud by year of publication

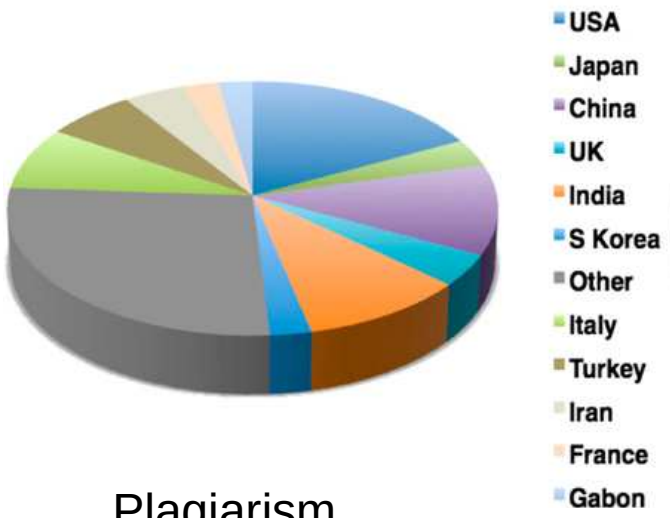


Source: F. C. Fang, R. G. Steen, A. Casadevall, *PNAS* **2012** doi: 10.1073/pnas.1212247109

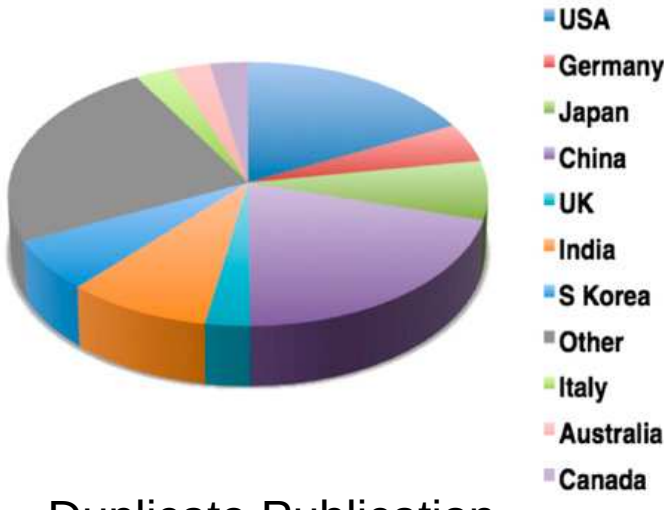
Misconduct (PubChem index)

Fraud or suspected Fraud





Plagiarism



Duplicate Publication

Source: F. C. Fang, R. G. Steen, A. Casadevall, *PNAS* **2012** doi: 10.1073/pnas.1212247109

« Know your enemy and know yourself
and you can write a hundred papers without disaster. »

See also

“On Hype, Malpractice, and Scientific Misconduct in Organic Synthesis”, R. Carlson, T. Hudlicky, *Helvetica Chimica Acta* **2012**, 95, 2052-2062

“Fraud in Organic Chemistry”, M. B. Rubin, *Chemistry in New Zealand* **2011**, 128-132

A blog tracking retractions: http://retractionwatch.wordpress.com/

The Office for Research Integrity: http://ori.hhs.gov/

Many blogs on which scientific misconducts were discussed:

http://blog.chembark.com/

http://www.corante.com/

http://storify.com/carmendrahl/a-history-of-the-hexacyclinol-hoo-hah

http://chemjobber.blogspot.fr/