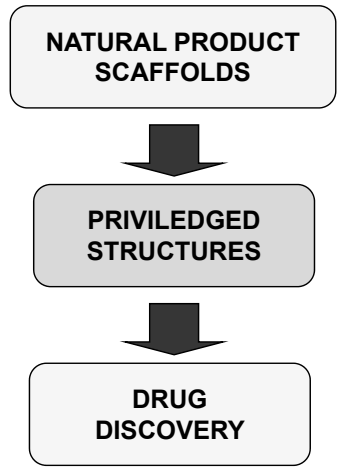
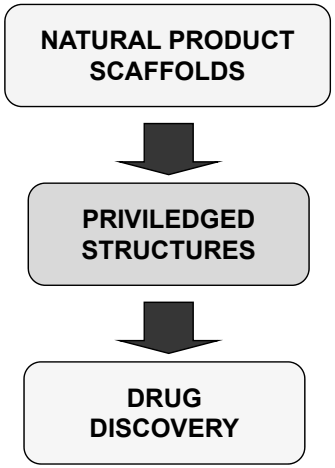
Structure of the presentation

- Inspirations from Nature: Scoping the interface between Organic Synthesis and Natural Products.
- Recent total syntheses from my group
- A parting message



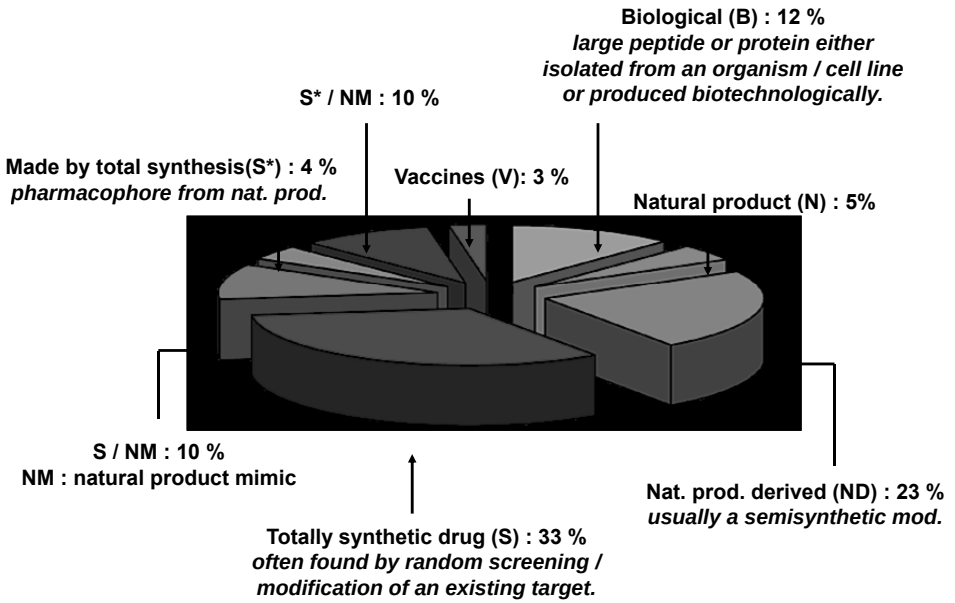
Natural products are "***forged in the crucible of evolution***", are unmatched for their diversity and structural density and are already validated for binding to protein domains.



Amplification of 'locked-in' co-evolutionary memories further enhance the appeal of natural products in the '..omics' era as new molecular targets surface

SOURCES OF FDA APPROVED DRUGS (1981 – 2002)

(Source: *J. Nat. Prod.* 2003, *66*, 1022)



All available anticancer drugs, 1940 -2006

Source: Newman & Cragg, *J. Nat. Prod.* 2007, *70*, 461;
Lee, *J. Nat. Prod.* 2010, *73*, 500-516.

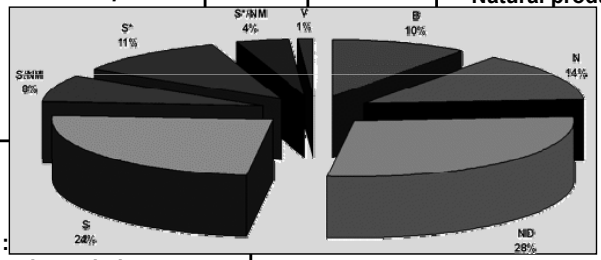
Biological (B) : 12 %
large peptide or protein either isolated from an organism / cell line or produced biotechnologically.

S* / NM : 10 %

Made by total synthesis(S*) : 4 %
pharmacophore from nat. prod.

Vaccines (V): 3 %

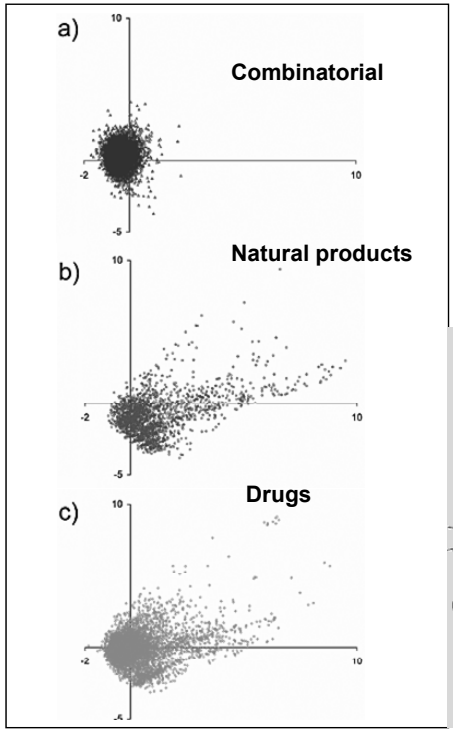
Natural product (N) : 5%



S / NM :
NM : natural product mimic

Totally synthetic drug (S) : 33 %
often found by random screening / modification of an existing target.

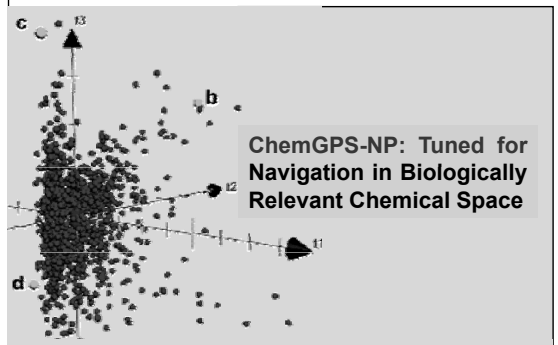
Nat. prod. derived (ND) : 23 %
usually a semisynthetic mod.



PROPERTY DISTRIBUTION: PREEMINENCE OF NAT. PRODS.

In chemical diversity space, combinatorial compounds densely populate a small area, whereas natural products are more spread out.

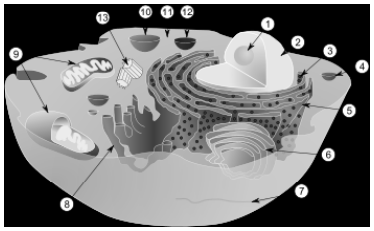
J. Chem. Inf. Comput. Sci. 2003, *43*, 218



Larsson, Gottfries, Muresan, Backlund, *JNP.* **2007,** *70*, 789

NP'S and Drug Discovery – an Extraordinary Niche

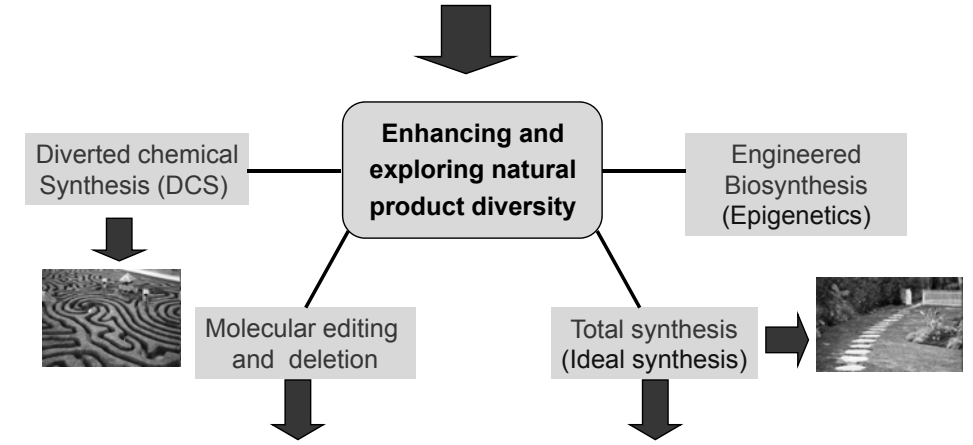
- Ability to interact with many specific targets within the cell;
- For majority of significant targets within the cell there exist at least one cognate natural product ligand;
- No target is resistant to modulation through interactions with NP's, polyketides and terpenoids seem to be particularly versatile;
- Key interrogators of biological systems – to probe the individual function of all gene products in the cell.(Chemical genomics)



A typical animal cell. Within the cytoplasm, the major organelles and cellular structures include: (1) nucleolus (2) nucleus (3) ribosome (4) vesicle (5) rough endoplasmic reticulum (6) Golgi apparatus (7) cytoskeleton (8) smooth endoplasmic reticulum (9) mitochondria (10) vacuole (11) cytosol (12) lysosome (13) centriole.

http://en.wikipedia.org/wiki/Organelles

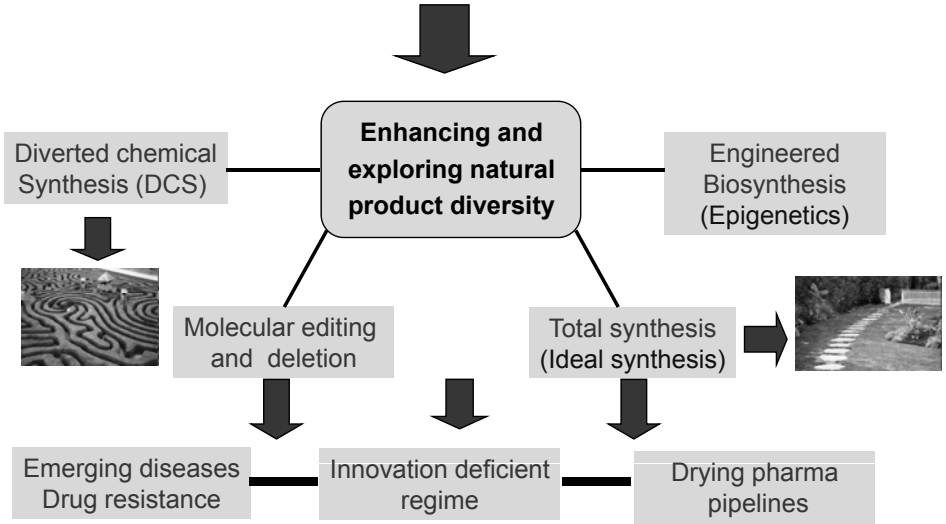
Intrinsic synergy between NP's and synthesis



Tool box for exploring the therapeutic potential
Simplifying complexity, retaining activity, better access

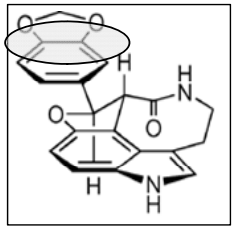
J. J. La Clair. *Nat. Prod. Rep.* **2010**, *27*, 969-995

Intrinsic synergy between NP's and synthesis



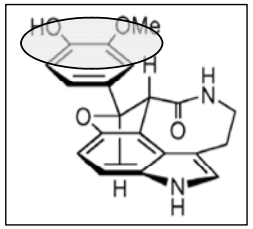
J. J. La Clair. *Nat. Prod. Rep.* **2010**, *27*, 969-995

Why natural products based diversity is important? – minimal structural change makes the difference



Decursivine[+]

Active against *Plasmodium falciparum*



Serotobenine

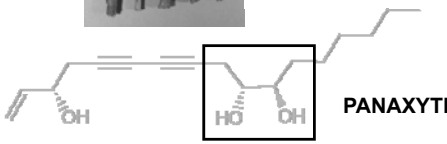
Not active

How natural products undergo evolutionary fine-tuning of their bioactivity ?

[+] Isolated from *Raphidophora decursiva, CucPhuong National Park, Vietnam*

DERIVATIZATION : A RESOURCE IN DRUG DISCOVERY

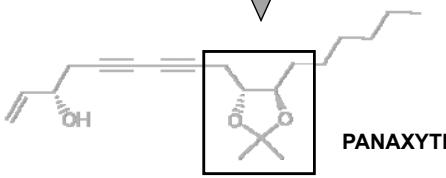
Active ingredient responsible for the anti-tumor activity of red ginseng; possible neutraceutical for long term cancer prevention and therapy; not compromised in MDR.



PANAXYTRIOL [IC_{50} 12.09 µM CCRF - CEM]

single functional group transformation

A six fold increase in cytotoxicity

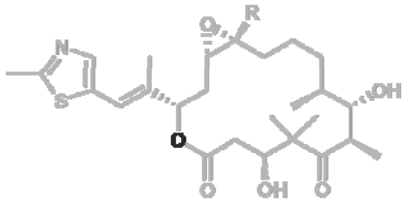


PANAXYTRIOL ACETONIDE [IC_{50} 1.98 µM CCRF - CEM]

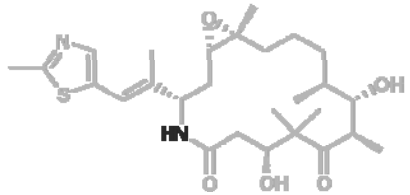
S. J. Danishefsky *et al. J. Org. Chem.* **2005;** F. Ng *et. al. Tetrahedron Lett*. 2008

Minimal molecular reformation addresses toxicity issues

…tone ⟶ …tam



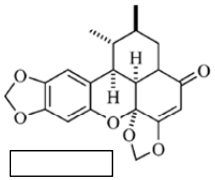
Epothilones A, B…; R= H, CH_3….
Isolation: *Sorangium cellulosum*
Potent microtubule inhibitor but serious toxicity issues



IXEMPRA (Ixabepilone)
Semisynthetic
New therapy for metastatic and advanced breast Cancer

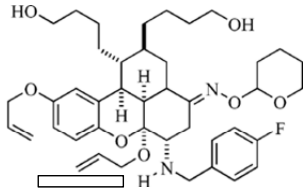
FDA approval Oct. 2007; alone or in combination with capecitabine for patients no longer responding to anthracyclines and taxanes

Enhancing Nature: Promise of natural product based libraries



Carpanone

No biological activity



CLL -19

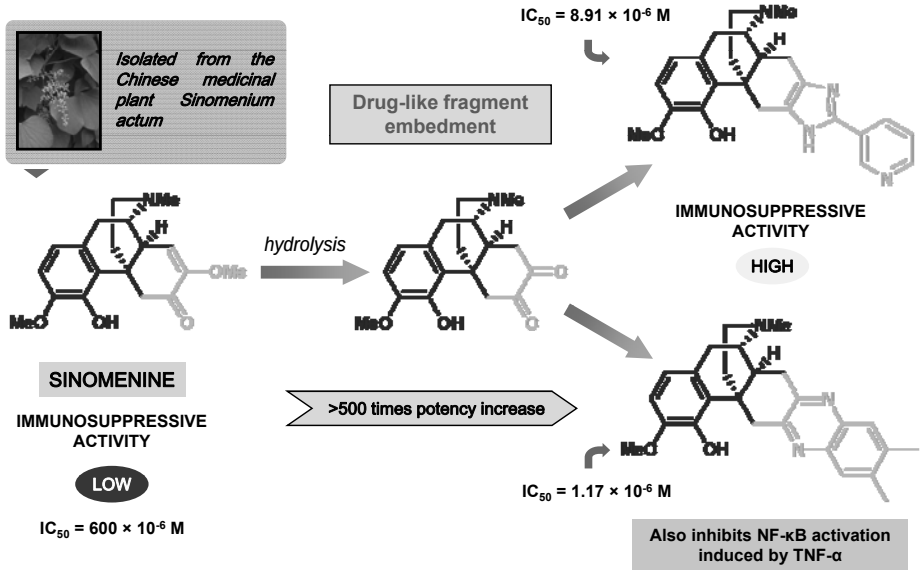
Inhibits exocytosis from Golgi

Library based on carpanone through combinatorial synthesis campaign led to an inhibitor of vesicular trafficking

B.C Goess *et. al JACS*, **2006**, *128*, 5391

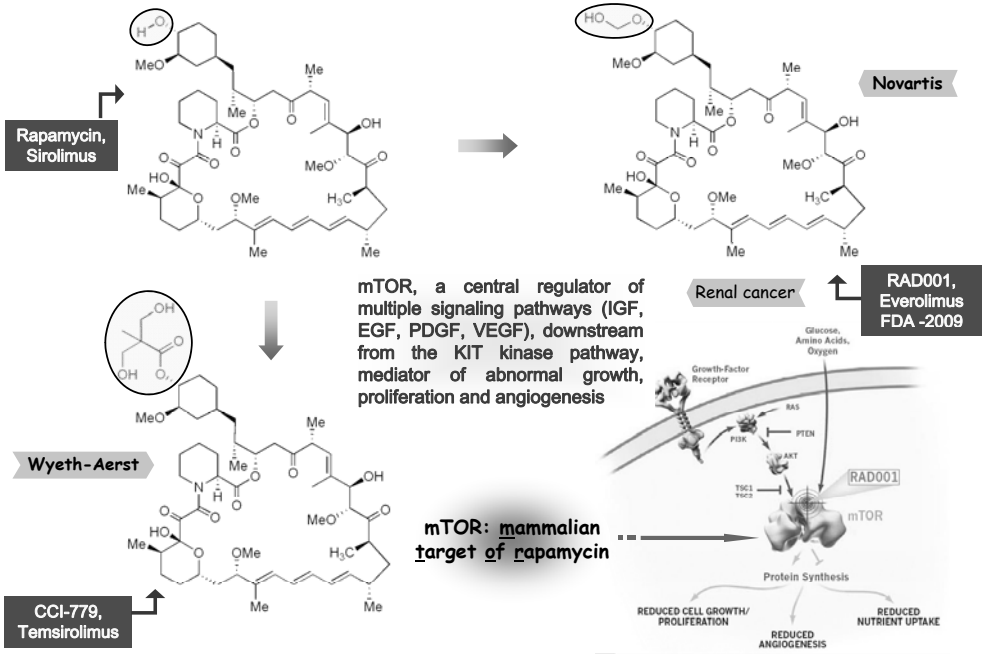
R. N. Daniels *et al. Org. Lett.*, **2008**, *10*,4097

FORGED BY NATURE, TEMPERED BY SCIENCE

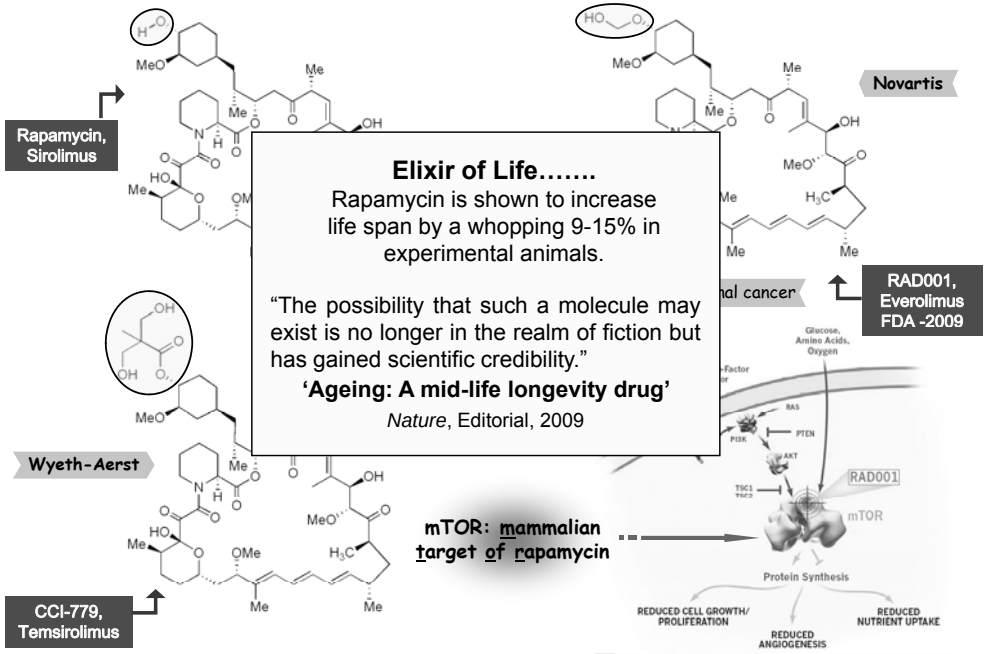


Z-J Yao et al. Tetrahedron Letters, 2010, *51*, 485

Molecular tweaking: From immunosuppressant to anticancer agents



Molecular tweaking: From immunosuppressant to anticancer agents



Elixir of Life…….

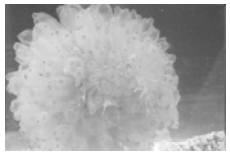
Rapamycin is shown to increase life span by a whopping 9-15% in experimental animals.

"The possibility that such a molecule may exist is no longer in the realm of fiction but has gained scientific credibility."

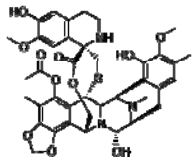
'Ageing: A mid-life longevity drug'

Nature, Editorial, 2009

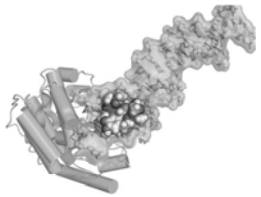
YONDELIS® - First marine natural product based anticancer drug



Ecteinascidia turbinata, a translucent marine tunicate, source of Yondelis.

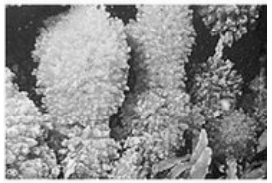


Trabectedin, ET -743

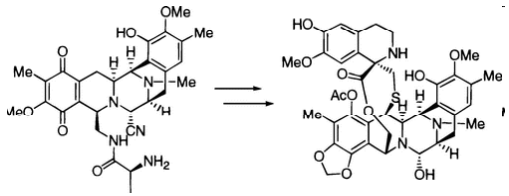


Binding of trabectedin to the complex DNA–XPG

Approved for the treatment of advanced soft tissue sarcoma; undergoing clinical trials for the treatment of breast, prostate, and pediatric sarcomas.



1 ton of sea squirts lead to 1 g of ET 743 and ~5 g were needed for a clinical trial

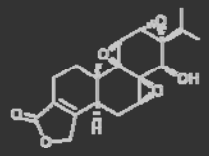


Cyanosafracin B

A semisynthetic process developed by PharmaMar starting from Safracin B, an antibiotic obtained by fermentation of the bacterium Pseudomonas fluorescens.

C. Cuevas and A. Francesch. *Nat. Prod. Rep*. 2009, *26*, 322

Triptolide: "Untamed prehistoric memories"



Potential wonder drug ! TRIPTOLIDE

Chinese herb *lei gong teng* (雷公藤, *Tripterygium wilfordii* Hook. f., Radix *Tripterygium wilfordii*, three-wing-nut)

- Extracted from the famous toxic Chinese herb *lei gong teng*
- SIDE EFFECTS: Highly toxic (*lei gong teng* is nicknamed the "Heartbreaking Grass" or "Seven Steps to Death")
- Since 2004, 50-100 publications per year on its bioactivity
- Immunosuppressive, anti-inflammatory - spinal cord & kidney inflammation, anti-asthmatic. Active against tuberculosis, arthiritis, psoriasis, dermatitis, Reiter syndrome, renal diseases…
- Potential anticancer agent, targets TNF-α and HSP-70 and inhibits NF-κ B activation; promise as a cure for lung, kidney and brain cancer.

A CONNOISSEUR'S CHOICE FOR

Molecular engineering and analogue design targetted towards

◆ Reducing toxicity ◆ Increasing efficacy ◆ Improving selectivity

Is it possible to fractionate biological activity?

Triptolide Induces Cell Death in Pancreatic Cancer Cells by Apoptotic and Autophagic Pathways
Mujumdar, n.; Mackenzie, T.; Dudeja, V.; Chugh, R.; Antonoff, M.; Borja–Cacho, D.; Sangwan, V.; Dawra, R.; Vickers, S.; Saluja, A. K. *Gastroenterology,* doi:10.1053/j.gastro.2010.04.046

Triptolide circumvents drug-resistant effect and enhances 5-fluorouracil antitumor effect on KB cells
Chen, Y-W.; Lin,G-J; Chuang, Y-P; Chia, W-T; Hueng, D-Y; Lin, C-K; Nieh, S; Sytwu, H-K. *Anticancer Drugs*, **2010**.

RNA polymerase – An important molecular target of triptolide in cancer cells
J. Jingxuan, *Cancer Lett.* **2010***, 292*, 142

570 Minnelide as an Emerging Single Therapeutic Agent Against Pancreatic Cancer
Chugh, R.; Patil, S.; Sangwan, S.; Vickers, S. M.; Georg, G. I.; Saluja, A. K. *Gastroenterology* **2010,** 138, S-80

….. clinical candidate derived from **natural** products—minnelide, a water-soluble pro-drug of triptolide, for pancreatic cancer ... Was announced by the center's director, Gunda I. Georg, said at the launch. *Chemical & Engineering News,* 87(41), October 12, 2009

What natural product targets interests us?

- Architecturally enticing
- Unusual, efficacious bioactivity profile

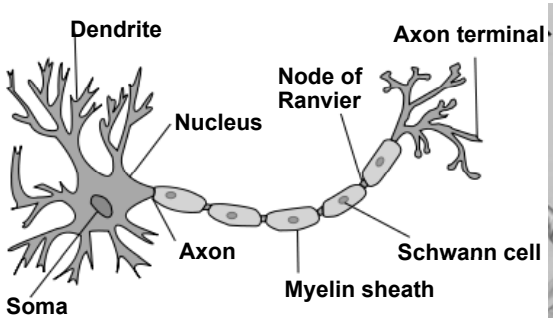
(*Interceptors of key cellular pathways; specific inhibitors/promoters of key enzymes)*

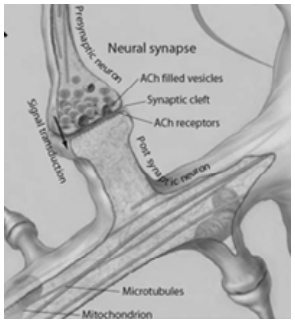
…….Snap shots of recent total synthesis

Total synthesis through generally applicable ('global') approaches that create diversion and diversity

Neurodegeneration – An Emerging Challenge

- Neurotrophic agents: Implicated in neuronal health (survival and repair) and stimulation of axonal growth;
- ChAT enhancers: Trigger higher levels of cerebral acetylcholine



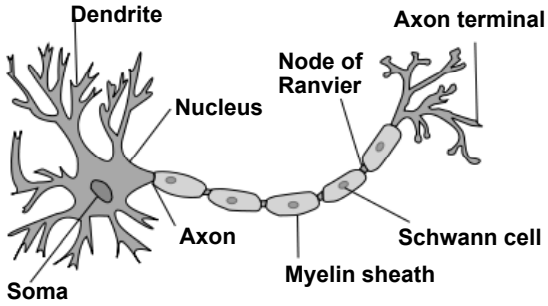


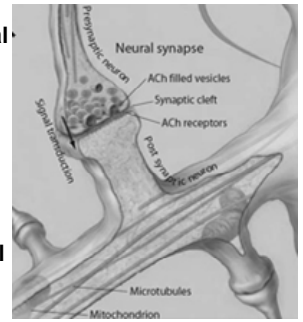
200 billion neurons; 10k types; each with 5k-200k connections; Dendritic tree (inflow), axon (outflow)

Passage of neurotransmitters, such as acetylcholine (ACh), across the synaptic cleft ...

Neurodegeneration – An Emerging Challenge

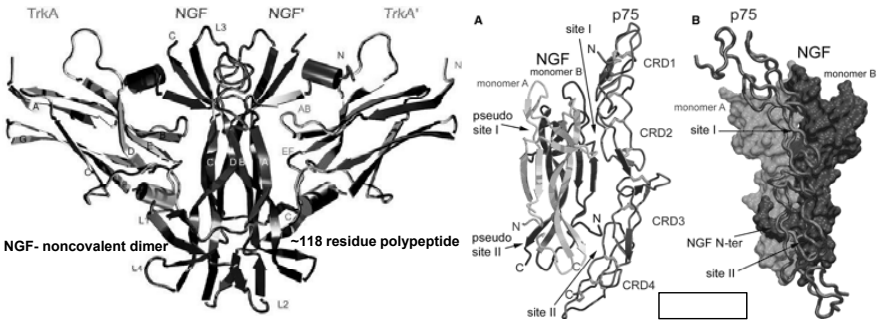
- Neurotrophic agents: Implicated in neuronal health (survival and repair) and stimulation of axonal growth;
- ChAT enhancers: Trigger higher levels of cerebral acetylcholine





Antineurodegenerative agents are still an elusive goal; mechanistic understanding is sketchy but CNS active natural products and analogues are a promising prospect

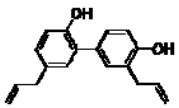
Neurotrophins: natural polypeptides - NGF, BDNF,NT-3, NT-4, CNTF…



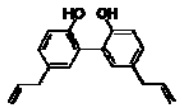
Neurotrophins activate two types of cell surface receptors, the Trk A -C and the shared p75NTR (LNGFR) . X-ray structures. *Science* 2004, *304*,,870

What about SMNP as neurotrophic agents?

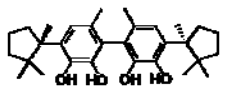
Neurotrophically active natural products – Diverse structures



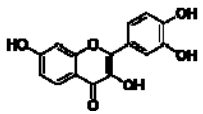
Honokiol



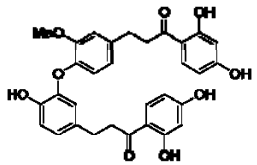
Magnolol



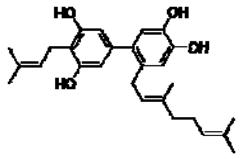
Mastigophorenes A and B



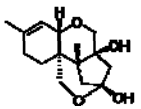
Fisetin



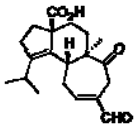
Verbenachalcone



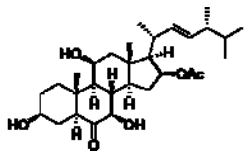
Clusiparalicoline A



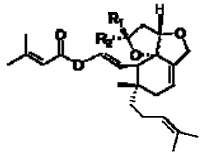
Paecilomycine A



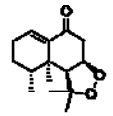
Scabronin G



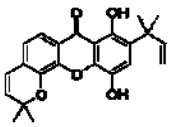
NGA0187



Neovibsanin A: R_1 = OMe, R_2 = Me
Neovibsanin B: R_1 = Me, R_2 = OMe

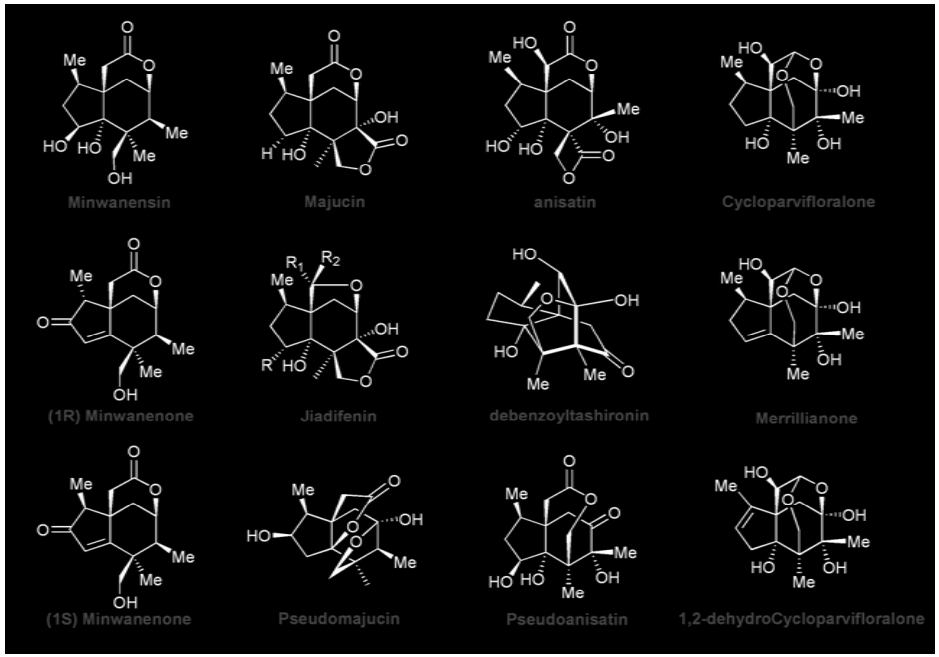


Nardosinone

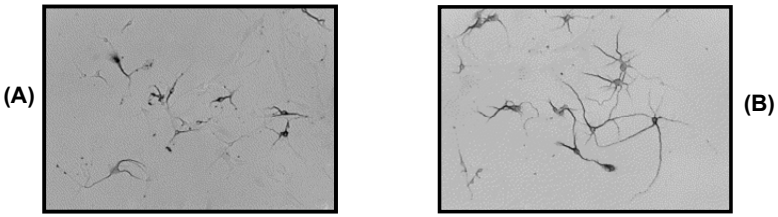


Garciniaxanthone B

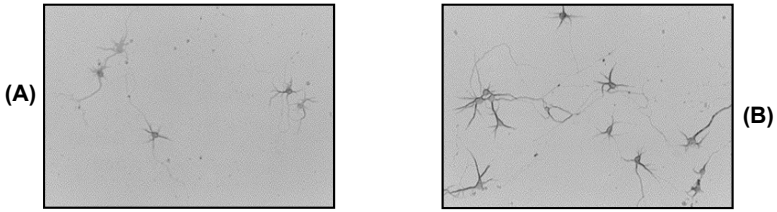
Seco-prezizaanes with neurotrophic activity – Gold mine



Seco-prezizaanes in action….



Rat cortical neurons, 0.5% EtOH (A) and 0.1 μM merrilactone (B), showing the promotion of neurite outgrowth.



Rat cortical neuronal culture in 0.5% EtOH (A) and 0.1 μM 11-*O*-debenzoyltashironin (B)

TOWARDS THE SYNTHESIS OF NEUROTROPHIC AGENTS…

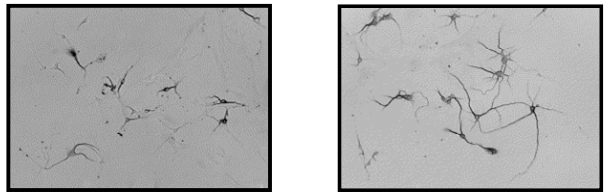
Total synthesis of Merrilactone A

A NOVEL NEUROTROPHIC SEQUITERPENE DILACTONE

Merrilactone A

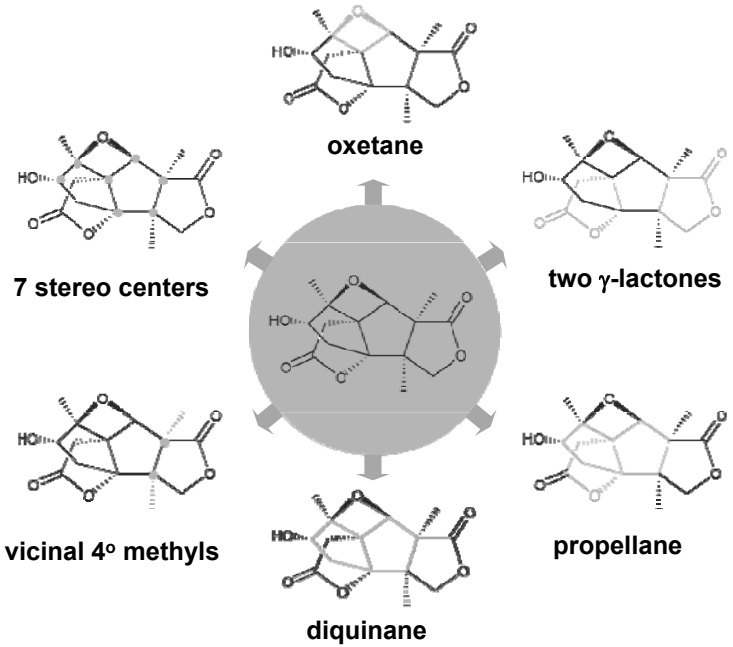
- Isolated from the pericarps of *Illicium merrillianum* by Fukuyama *et. al.**
- Promotes neurite outgrowth in rat cortical neurons.* **Tetrahedron Lett.* **2000**, *41*, 6111

THE NEUROTROPHIC ACIVITY OF MERRILACTONE

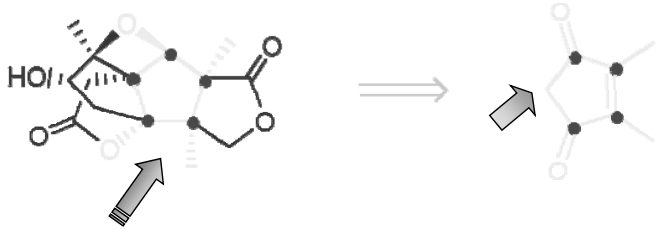


6-day-old culture of rat cortical neurons treated with 0.5% EtOH (A) and 0.1 μM merrilactone (B), showing clearly the promotion of neurite outgrowth.*

SURVEYING THE COMPLEXITY OF MERRILACTONE

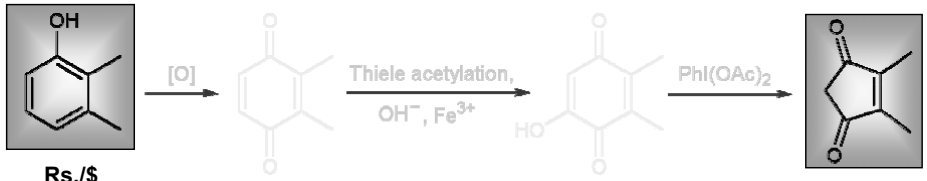


TARGET MERRILACTONE : CHOICE OF SYNTHON



structural core – penta-substituted cyclopentane ring

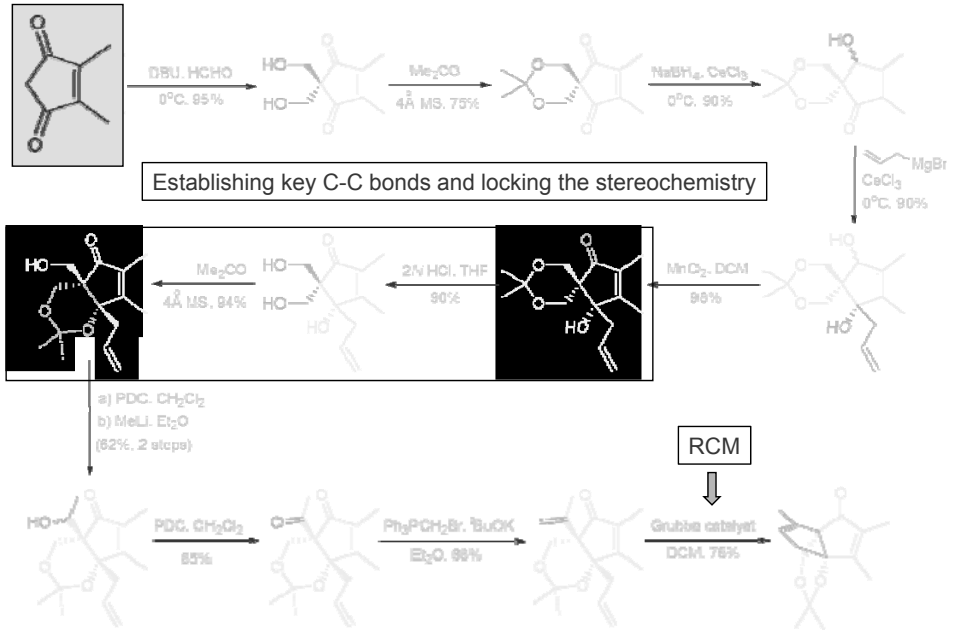
- **amenability to desymmetrization**
- **readily available staring material**



Rs./$

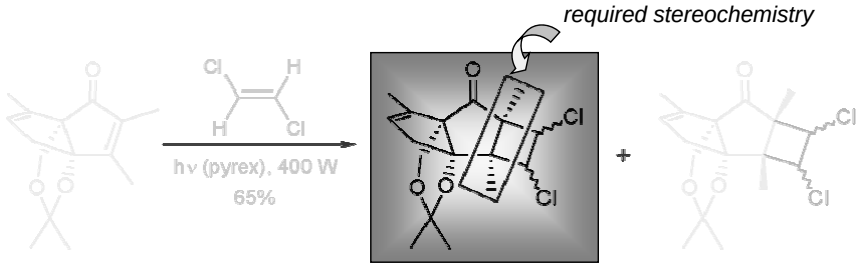
5 – 10 g
< 1 week

TOWARDS THE TOTAL SYNTHESIS OF MERRILACTONE



FACE SELECTIVE (2+2)- PHOTOCYCLOADDITION

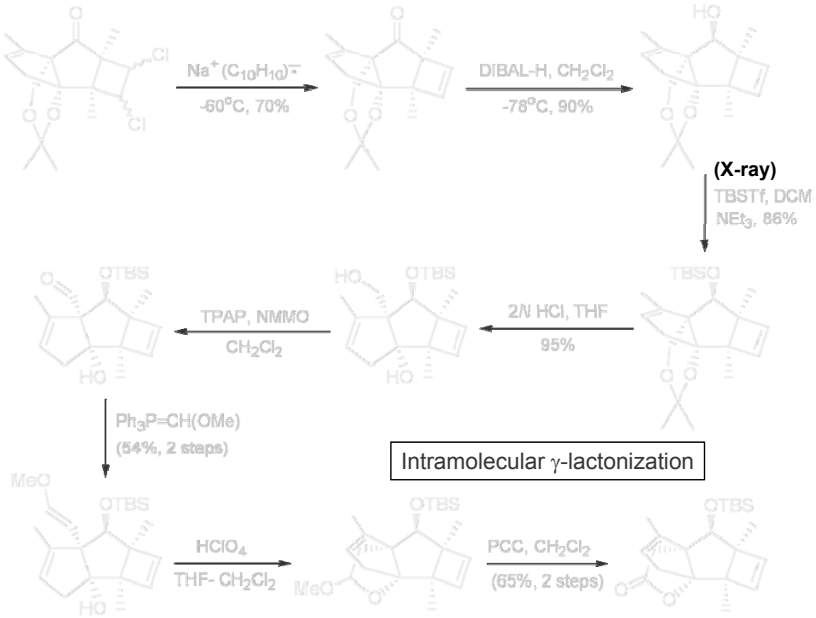
DCE ≡ acetylene ≡ cyclobutene ≡ γ-lactone



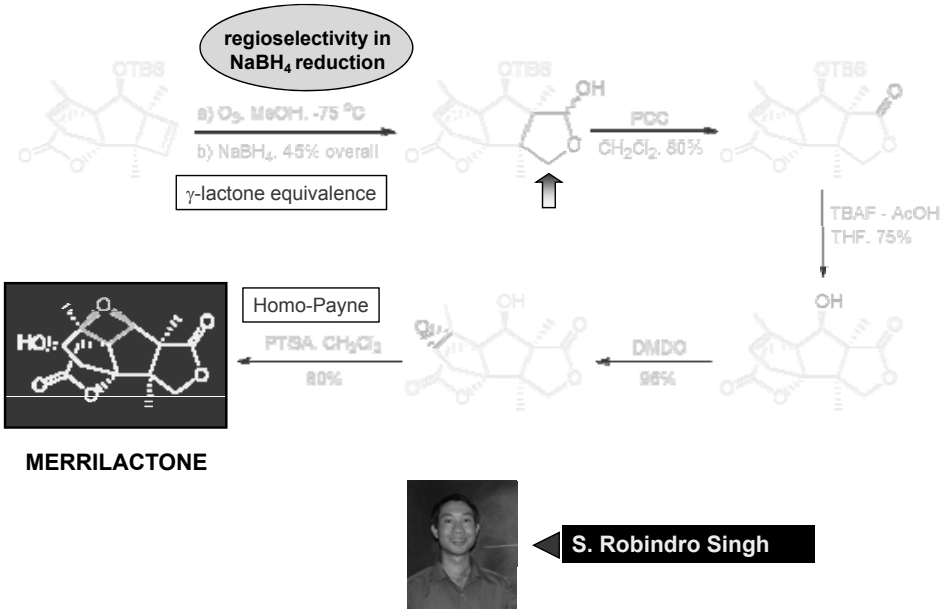
(2 : 1)

The greater steric bulk of the acetonide moiety controls π-face selection

SEQUENTIAL CONSTRUCTION OF THE LACTONE MOIETIES



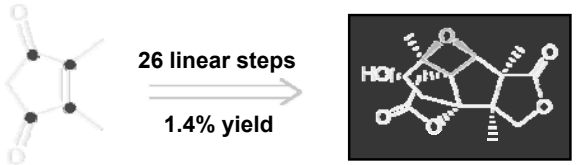
TOTAL SYNTHESIS OF MERRILACTONE



MERRILACTONE

S. Robindro Singh

TOTAL SYNTHESIS OF MERRILACTONE

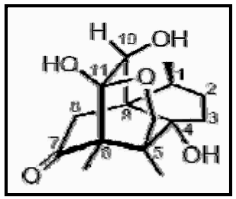


Key steps: Directed dihydroxylation; RCM reactions; intramolecular lactonization; [2+2]-photocycloaddition; reductive ozonolysis; homo-Payne rearrangement

Elements of diverted synthesis embedded (*end-to-end*)

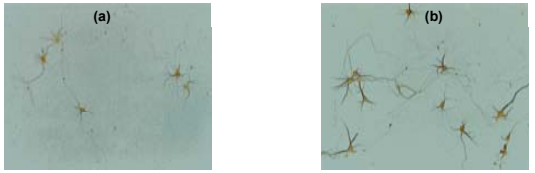
TASHIRONIN: HIGHLY OXYGENATED TETRACYCLIC HEMIKETAL SESQUITERPENE NATURAL PRODUCT

Illicium Floridanum



11-O-Debenzoyltashironin*

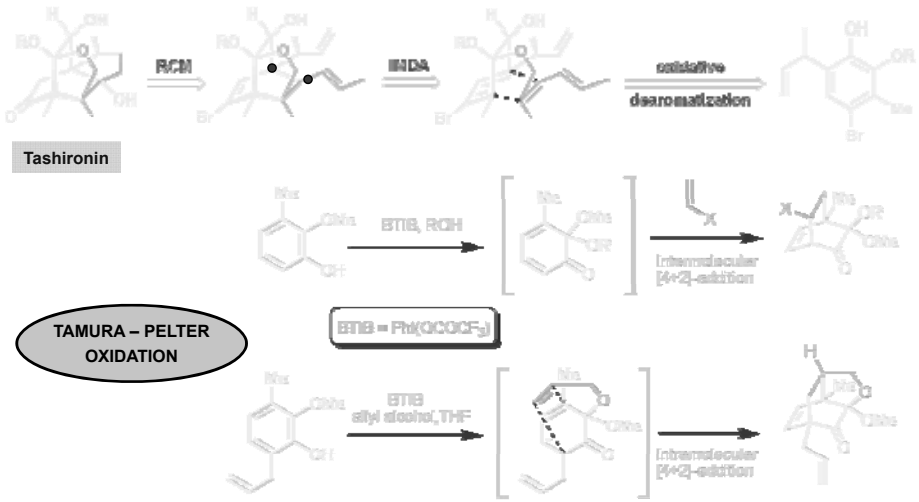
- North American *Illicium* species
- Tashironin was isolated from *Illicium tashiroi* pericarps or fruits
- Tetracyclic hemiketal system with *allo*-cedrane framework
- Induces neurite outgrowth in fetal rat cortical neurons at concentration as low as 0.1 mM*



Neurotrophic effect of 11-*O*-debenzoyltashironin in rat cortical neuronal culture: (a) control culture treated with 0.5% EtOH; (b) culture treated with (0.1 *m* M)*.

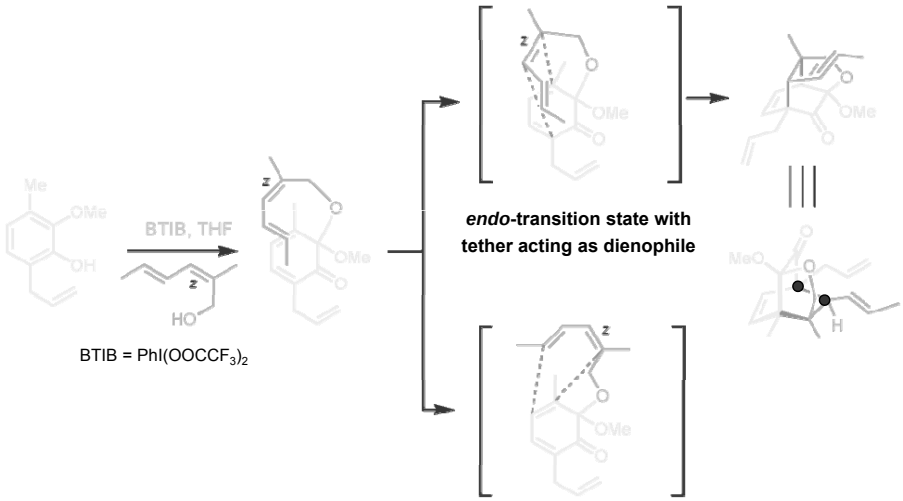
* Fukuyama et al. *J. Nat. Prod.* **2001,** *64,* 428

RETROSYNTHETIC THEME: OXIDATIVE DEAROMATIZATION- IMDA- RCM PROTOCOL

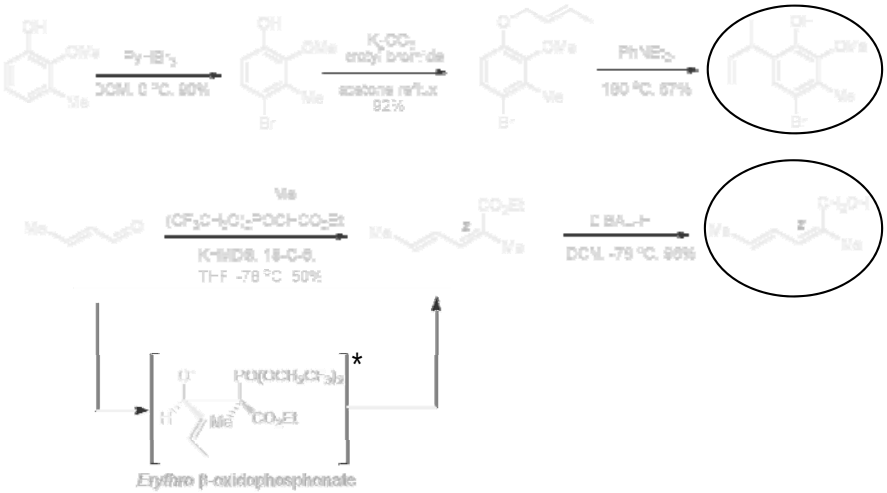


Liao, C. C.; Peddinti, R. K. *Acc. Chem. Res*. **2002**, *35*, 856
Magdziac, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev*. **2004**, *104*, 1383

A CONCEPTUAL POSTULATE FOR IMDA WHEN TETHER CONTAINS *Z*, *E* DOUBLE BONDS

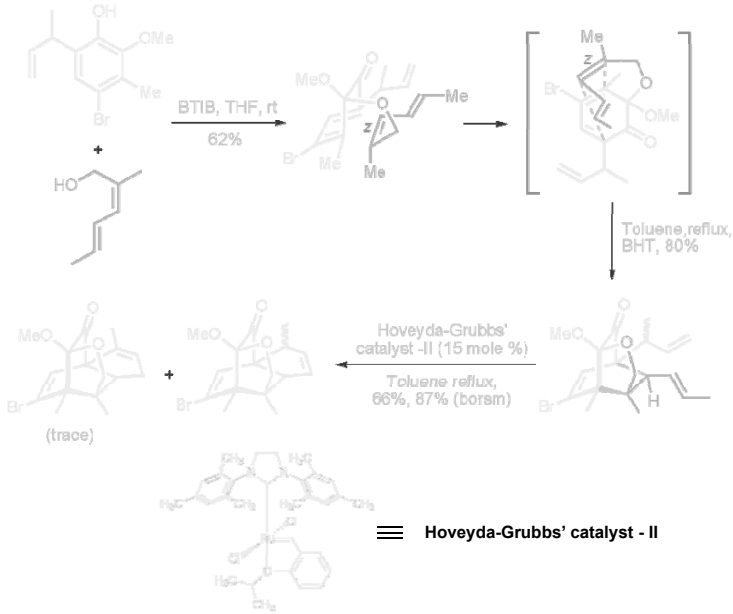


TARGET TASHIRONIN: ACCESSING THE BUILDING BLOCKS

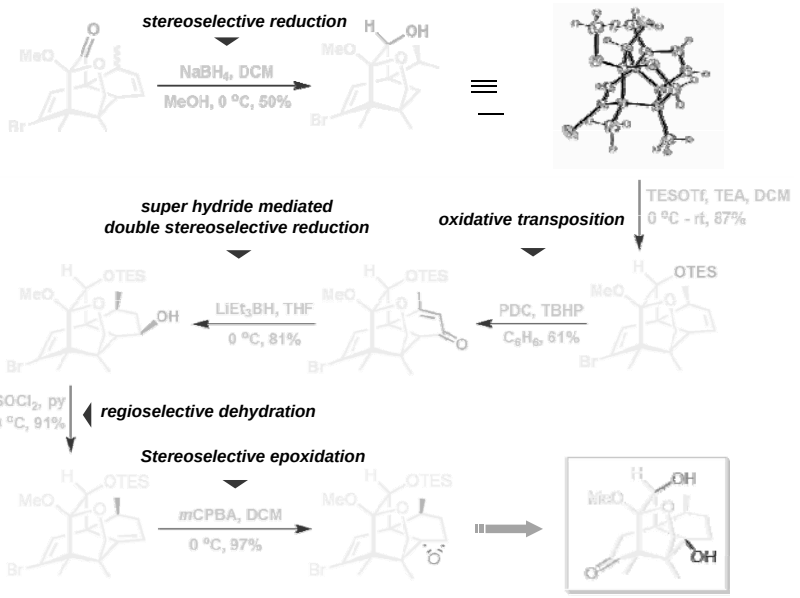


*Still, W. C.; Gennari, C. *Tetrahedron Lett*. 1983, *24*, 4405

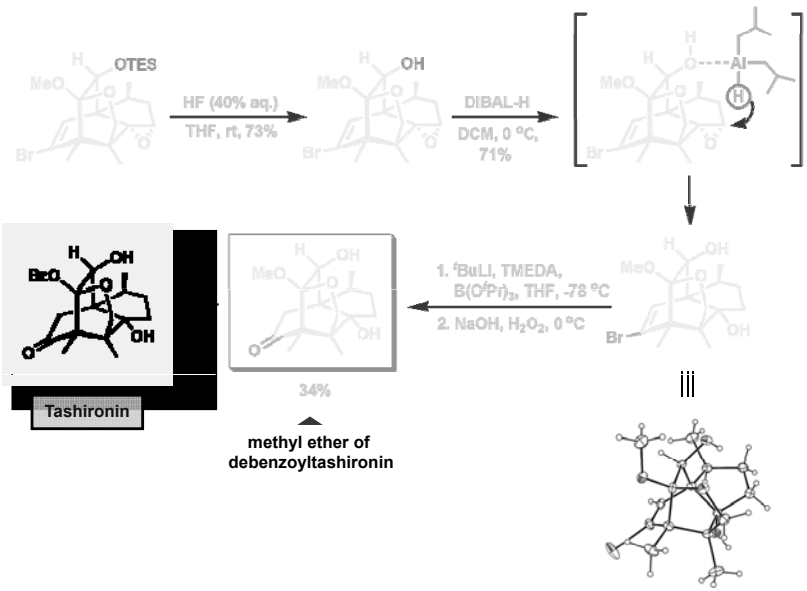
TARGET TASHIRONIN: ACQUISITION OF THE TETRACYCLIC CORE

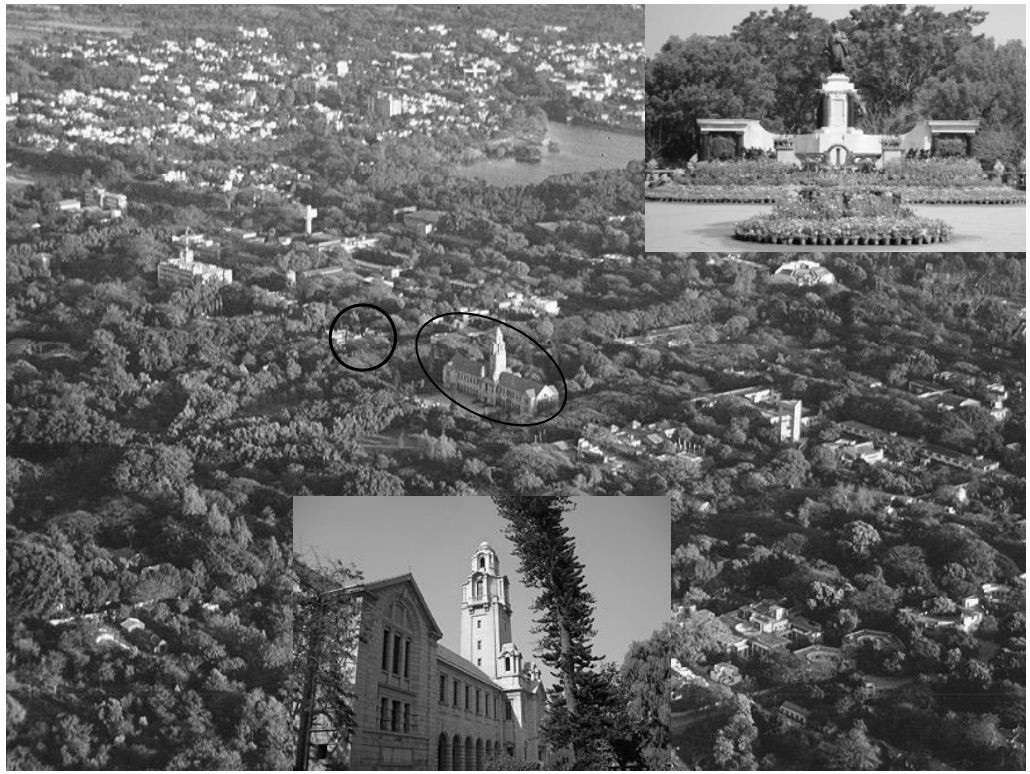


TARGET TASHIRONIN: FINAL CHEMICAL MANOEUVER



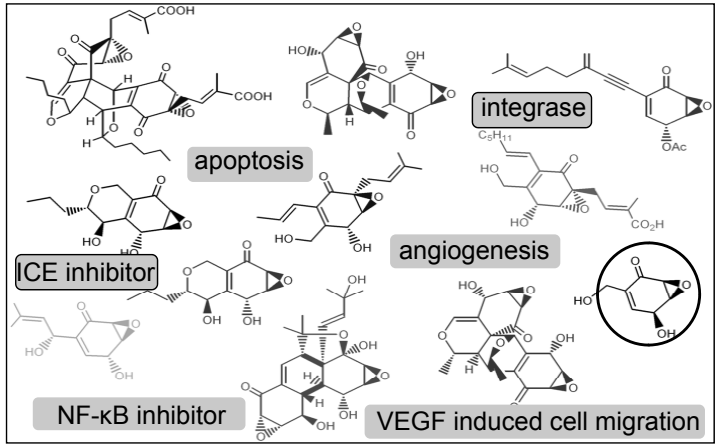
TOTAL SYNTHESIS ACCOMPLISHED





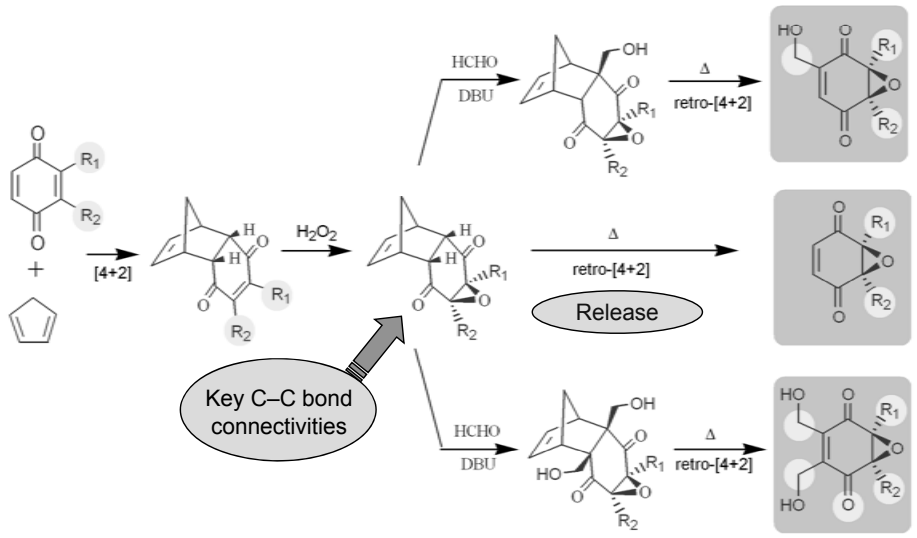
Complex targets ➡ General solutions

Case of bioactive epoxyquinones

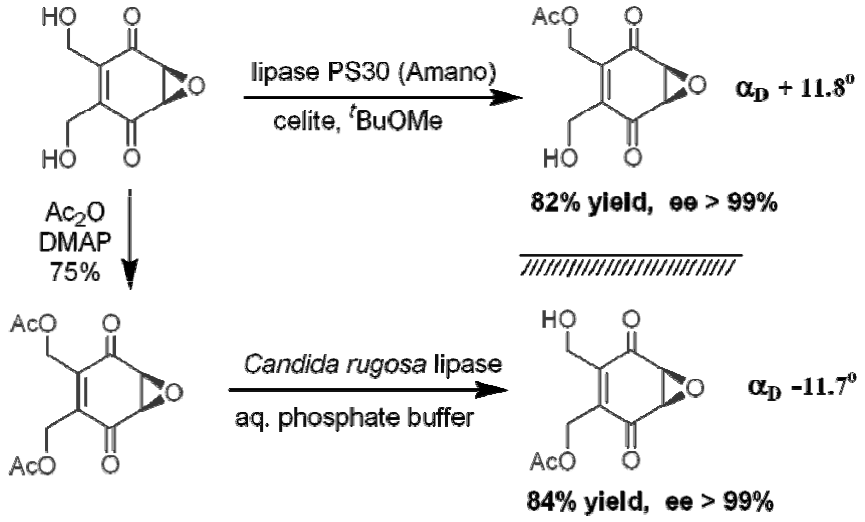


Reviews: Miyashita & Imanishi, *Chem Rev*. **2005**, *105*, 4515
Marco-Contelles et al. *Chem Rev*. **2004**, *104*, 2857

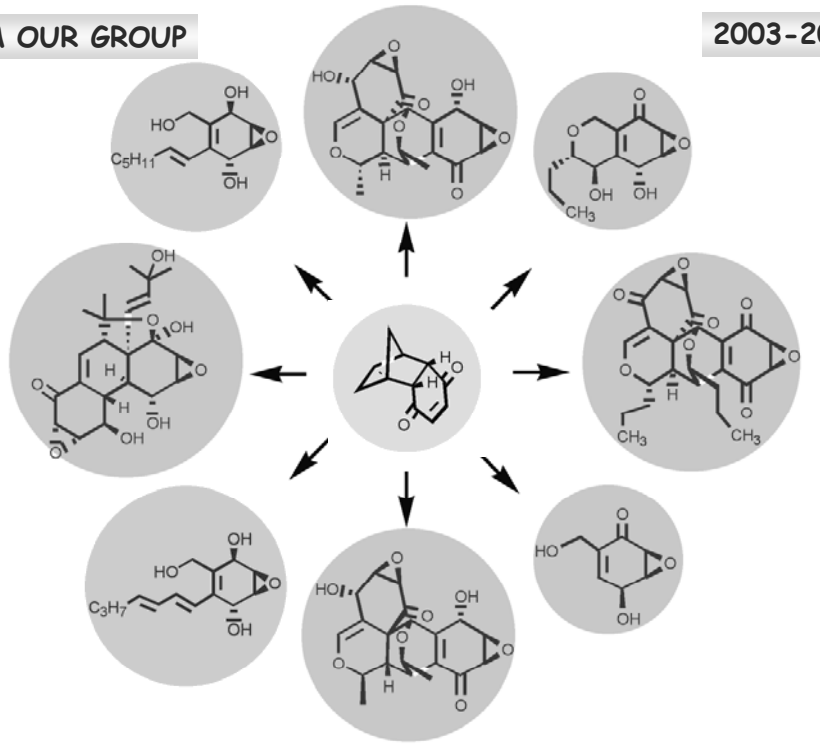
A 'Global' Route to Epoxyquinone Natural Products



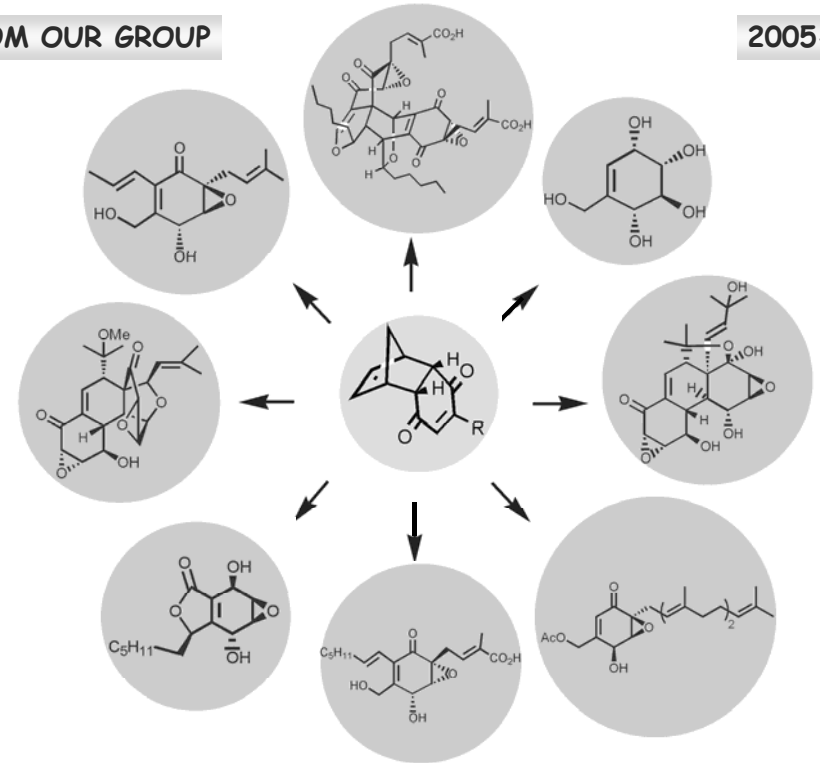
'*Meso trick*' for enantiodivergence



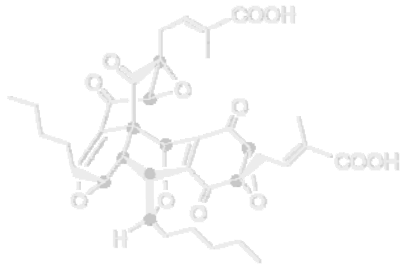
FROM OUR GROUP **2003-2004**



FROM OUR GROUP **2005-2007**



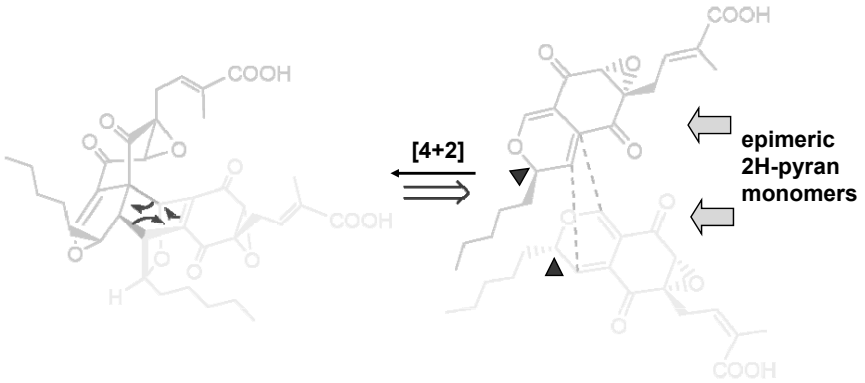
TORREYANIC ACID: A NOVEL BIOLOGICALLY ACTIVE EPOXYQUINONE NATURAL PRODUCT



- Isolated from an endophytic fungus *Pestalotiopsis microspora, JOC* **1996***, 61,* 3232.
- Potent activator of human cancer cell lines sensitive to the PKC agonist, TPA.
- Inducer of apoptosis in cancer cells
- Complex heptacyclic architecture with 10-stereogenic centres and 12 oxygen atoms
- Total Syntheses: 1. Li, Johnson, Porco, *J. Am. Chem. Soc*. **2003**, *125*, 5095.
  2. Mehta, Pan, *Org. Lett*. **2004**, *6*, 3985

THE PROPOSED BIOSYNTHESIS REDUCES THE COMPLEXITY BY HALF!

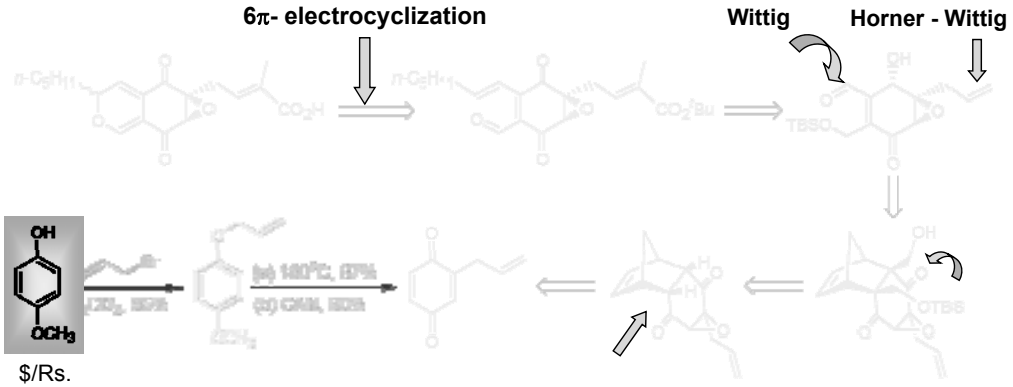
Torreyanic acid can be considered to be a Diels – Alder heterodimer of two epimeric 2*H* – pyran monomers.



Review: Williams *et al. Angew. Chem. Intl. Ed*. **2003**, *42*, 3078

RETROSYNTHETIC ANALYSIS OF TORREYANIC ACID

A common access to the two epimeric 2H- pyran monomers



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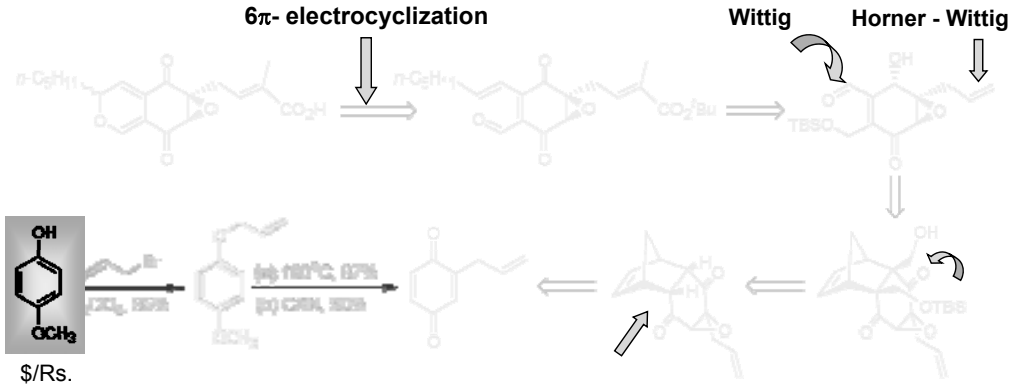
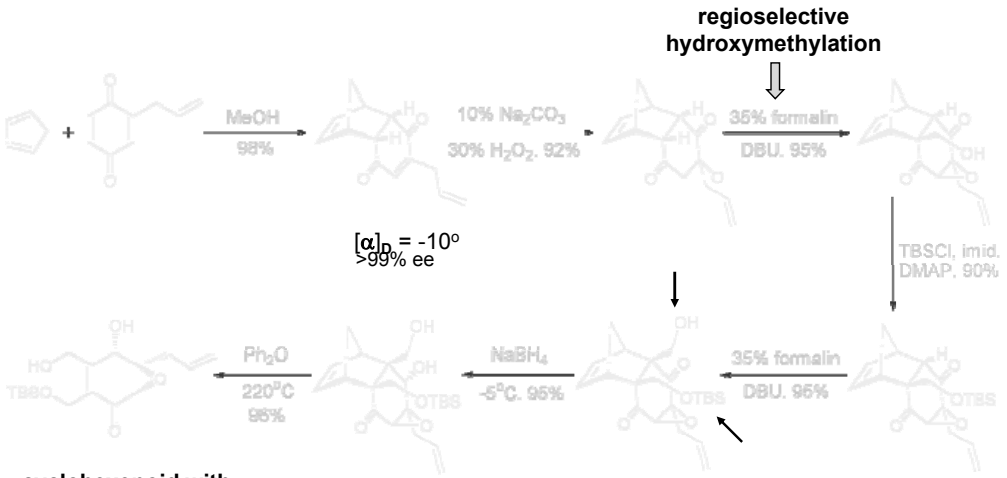


TORREYANIC ACID: ACCESSING THE POLYFUNCTIONALIZED CYCLOHEXENOID CORE



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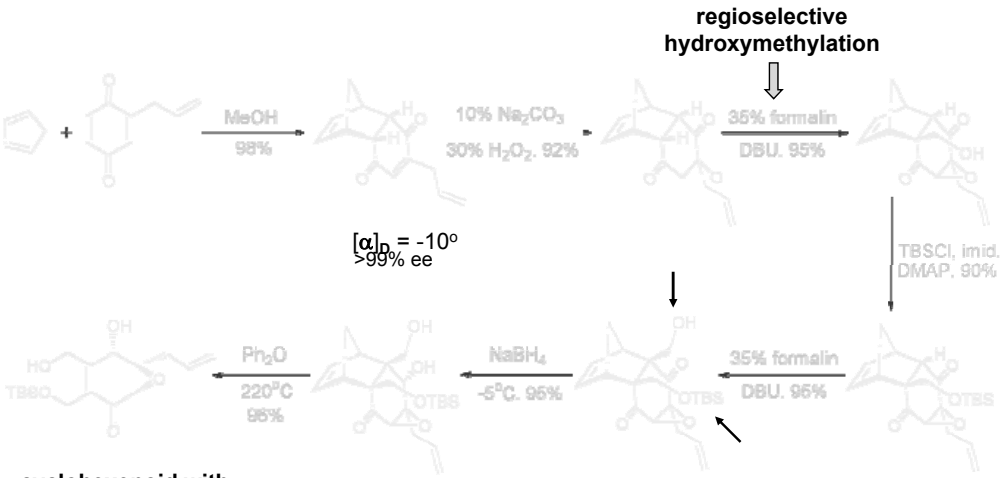
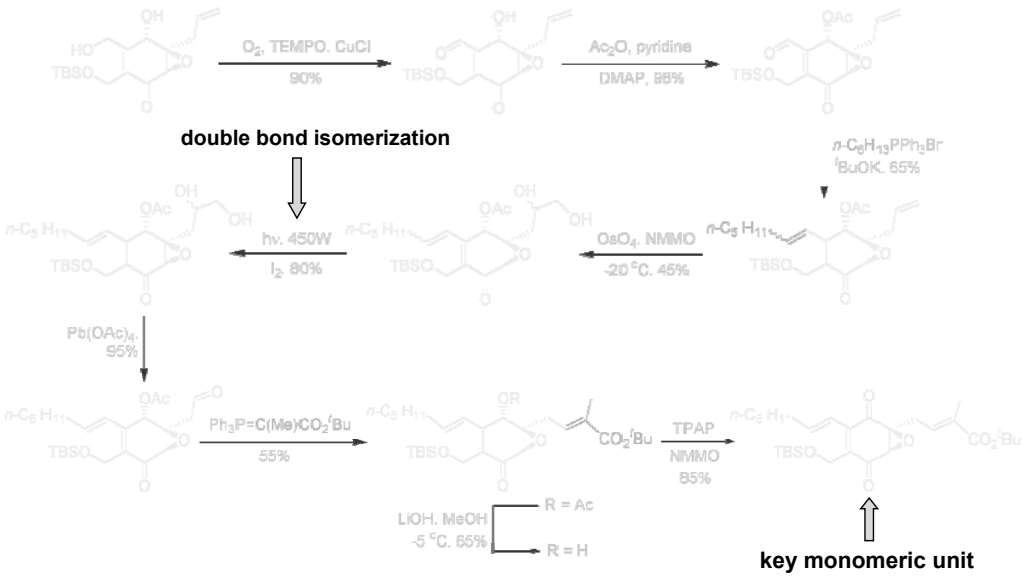
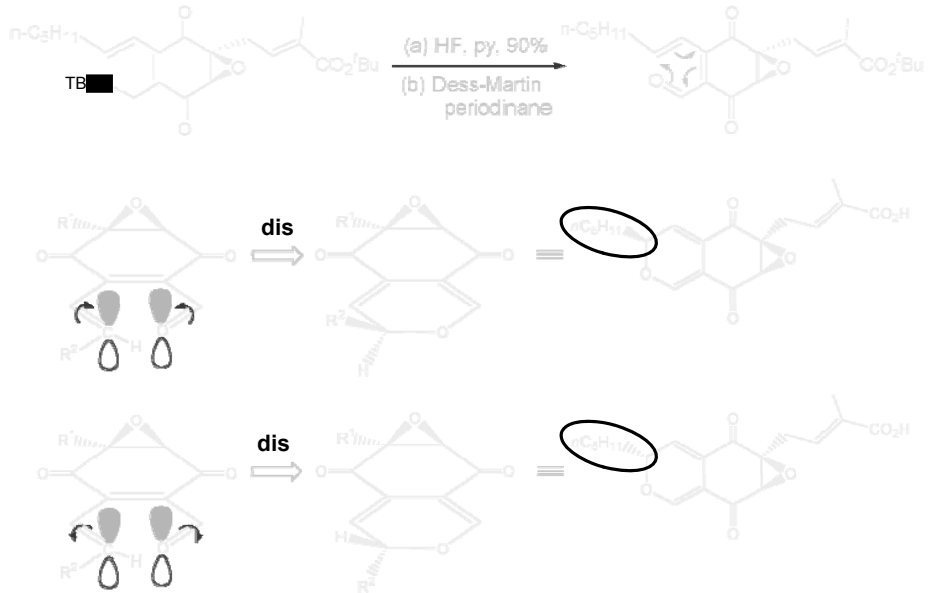


SYNTHESIS OF THE KEY MONOMERIC UNIT



GENERATION OF THE KEY EPIMERIC 2*H* - PYRAN UNITS



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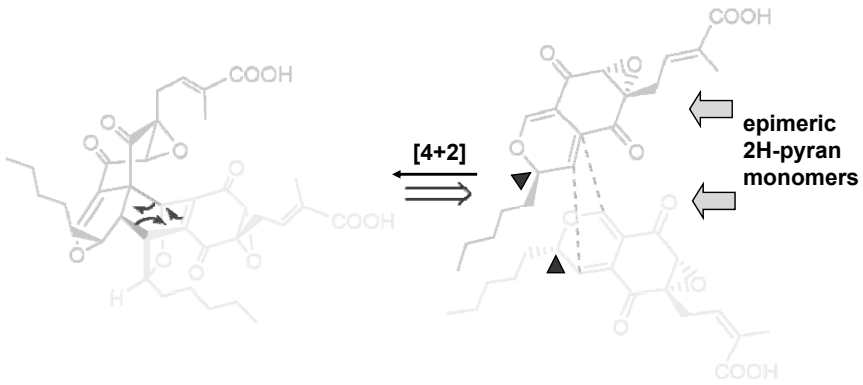
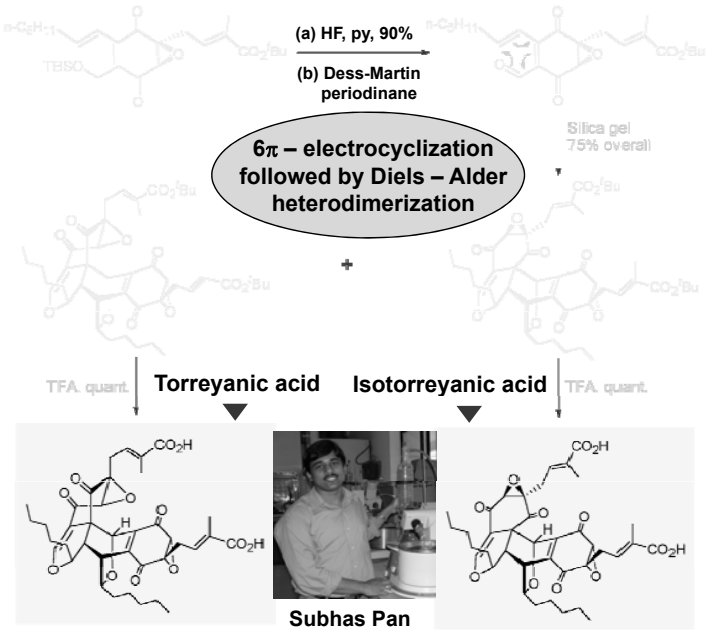
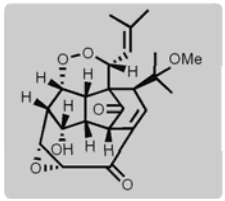


TOTAL SYNTHESIS OF TORREYANIC ACID



HEXACYCLINOL



Proposed Structure by Gräfe

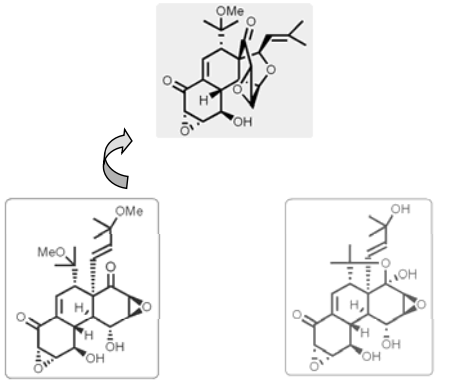
Based on 1D and 2D NMR analysis

Schlegel, B.; Härtl, A.; Dahse, H. -M.; Gollmick, F. A.; Gräfe, U.; Dörfelt, H.; Kappes, B. *J. Antibiot.* 2002, *55*, 814.

Debatable Total Synthesis Reported by J. J. La Clair

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

Revised Structure by Rychnovsky

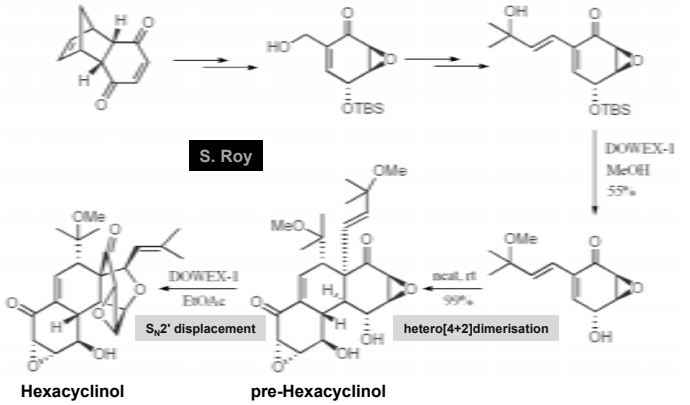


- Biosynthetic Sibling Relationship Between Hexacyclinol and Panepophenanthrin
- Calculated ^{13}C NMR Chemical Shift Correlations

Rychnovsky, S. D. *Org. Lett.* 2006, *8*, 2895.

Porco, J. A., Jr.; Su, S.; Lei, X.; Bardhan, S.; Rychnovsky, S. D. *Angew. Chem. Int. Ed.* 2006, *45*, 5790.

Enantioselective Total Synthesis of Hexacyclinol



Antiproliferative metabolite: IC_{50} values ~1μg/ml.

Original structure assignment : U. Grafe *et al.* *J. Antibiot.* 2002, *55*, 814

'Fantasy' synthesis: J. J. La Clair, *Angew. Chem. Int. Ed.* 2006, *45*, 2769

Revised structure : S. D. Rychnovsky, *Org. Lett.* 2006, *8*, 2895.

Synthesis: J. A. Porco, S. D. Rychnovsky *et al. Angew. Chem. Int. Ed.* 2006, *45*, 5790

G. Mehta, S. Roy. *Tet. Letters*. 2008, *49*, 1417.

What is the message ?

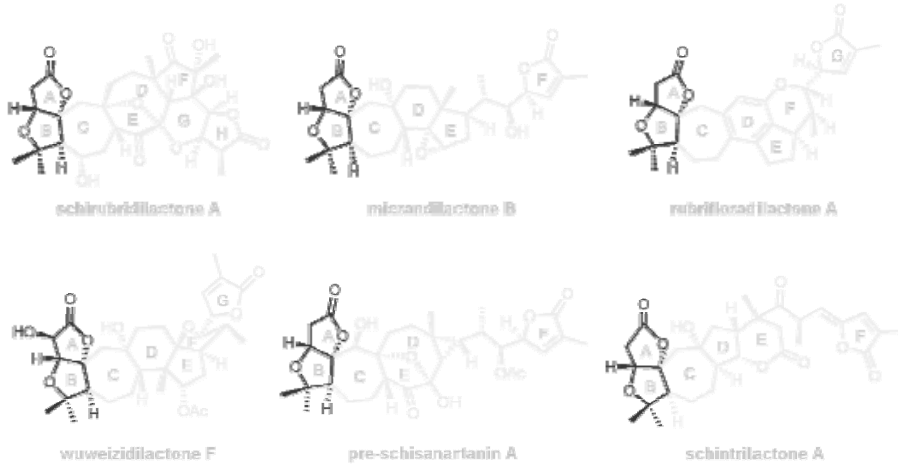
Natural products synthesis strategies should be **simple**, scalable, diversity oriented and conceptualized to address a whole class of natural products to fully harness their therapeutic potential

The art of simplicity is a puzzle of complexity

- Doug Horton

'Practice what you preach'

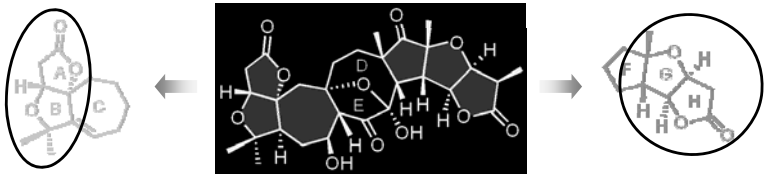
Structurally novel nor-triterpenoids of Schisandraceae



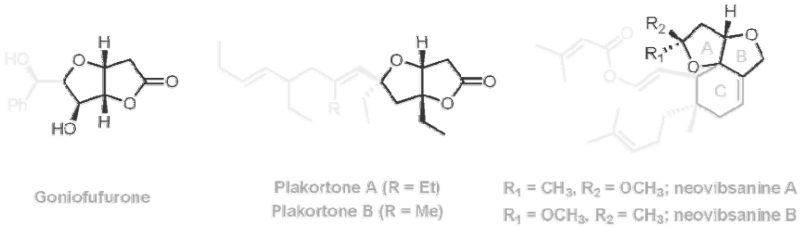
Complex variegated architecture:7+ rings, 12+stereocenters, 10+ oxygens
Broad ranging bioactivity profile: antitumor, antihepatitis, anti-HIV……

Reviews: Xiao, W-L *et al. Nat. Prod. Rep.* ***2008***, 25, 871-891

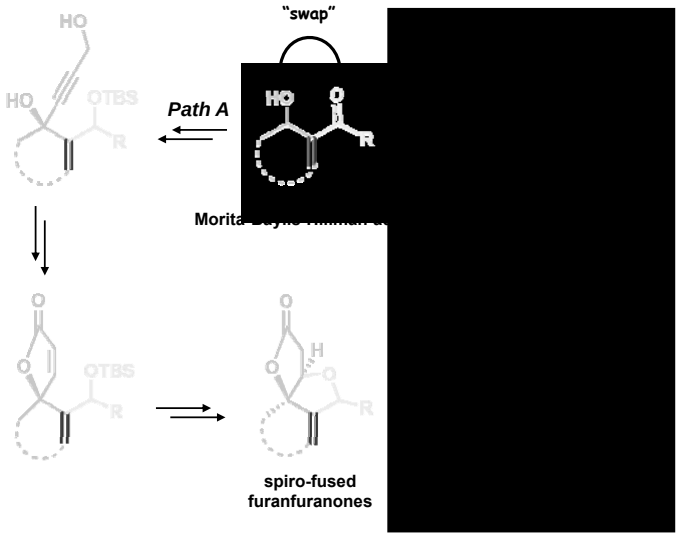
Structurally variegated furo-furanone natural products



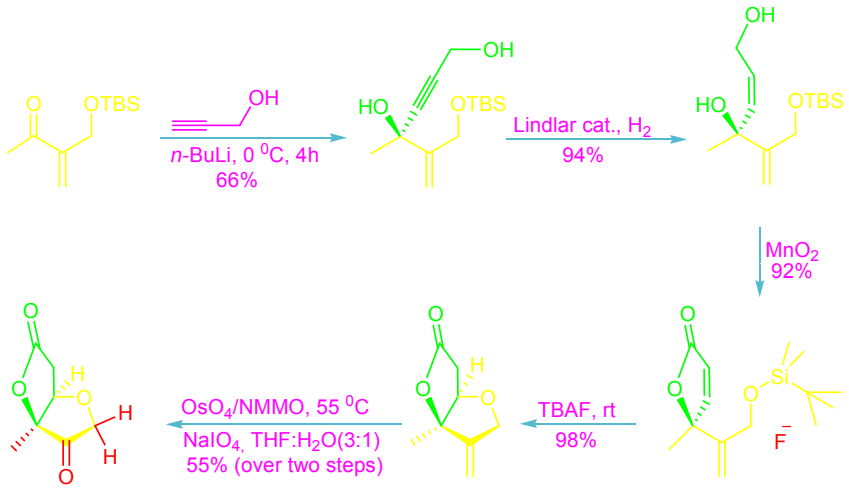
Other bioactive natural product types…



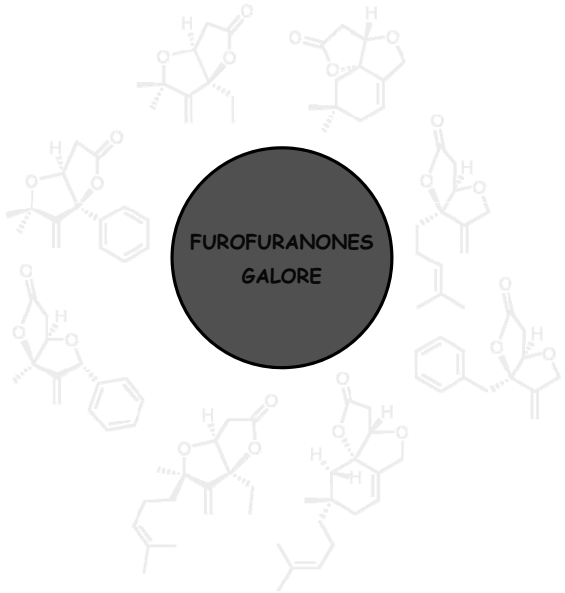
Bidirectional approach to furo[3.2b]furanones: A postulation!!!



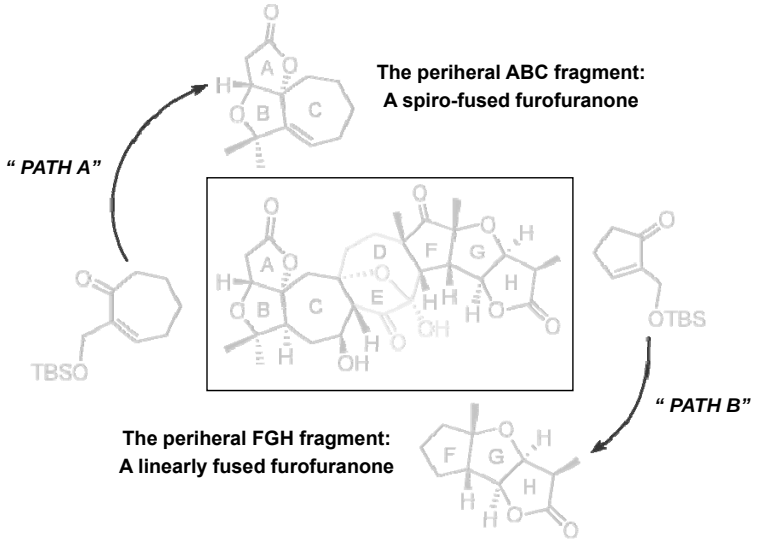
A short, flexible approach to furo[3.2-*b*]-furanones



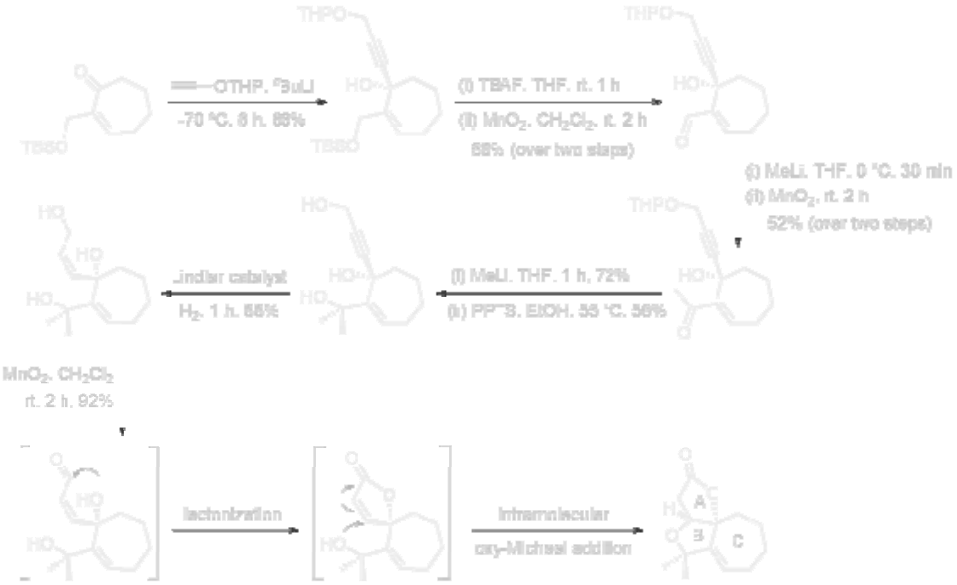
Furo[3.2b]-furanones unlimited from MBH adducts



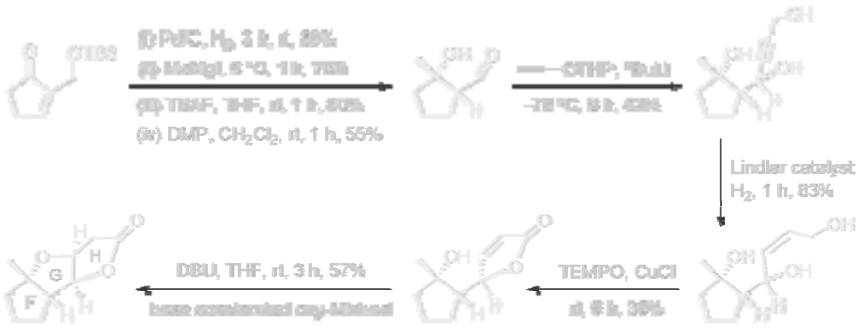
Bidirectional approach towards rubridifloradilactone C



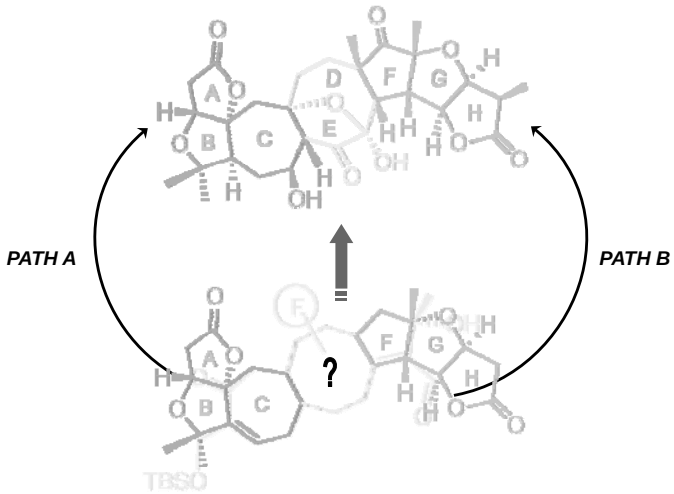
Construction of the ABC fragment



Construction of the FGH fragment



A unification of the bidirectional approach to rubridifloradilactone C



Work in progress…..

The parting message ?

Reinventing the triumvirate of natural products, organic synthesis and drug discovery in the '…omics' era is the way forward rowards drug discovery and improved human health and wellbeing.

It may be worth recalling that decline in natural products chemistry has been coincidental with the declining pharma pipelines