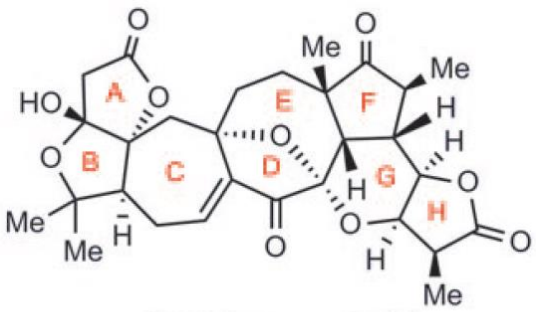
Bioactive natural products synthesis

Dong group at UT Austin

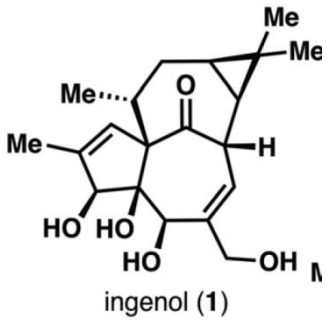
Xuan Zhou

03/13/2014



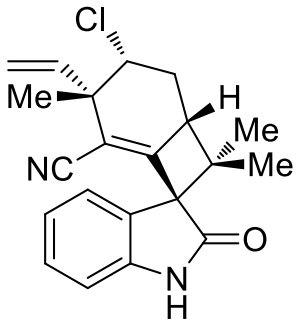
schindilactone A (**1**)

Angew. Chem. Int. Ed. **2011**, *50*, 7373-7377



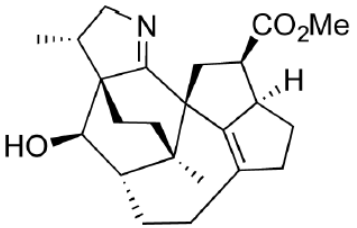
ingenol (**1**)

Science, **2013**, *341*, 878-883



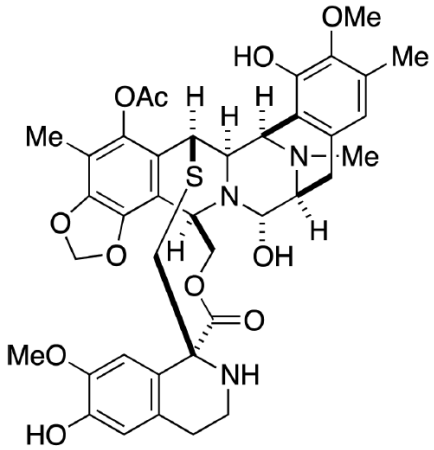
welwitindolinone A

Nature, **2007**, *446*, 404-406



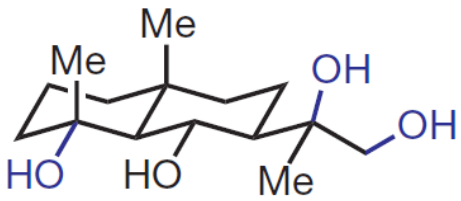
(–)-Calyciphylline N (**1**)

J. Am. Chem. Soc, **2014**, *136*, 870-873



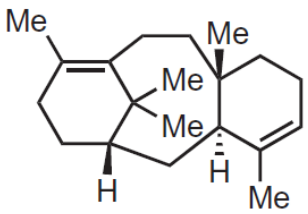
ecteinascidin 743 (**1**)

J. Am. Chem. Soc, **2013**, *135*, 13684-13687



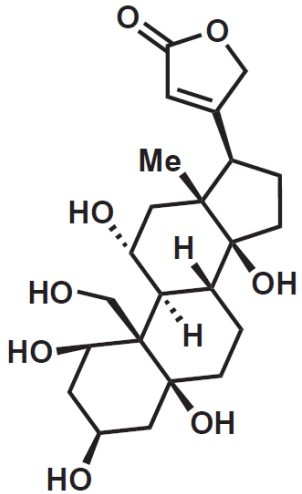
8: eudesmantetraol

Nature, **2009**, *459*, 824-828



Taxadiene

Nature chem. **2012**, *4*, 21-25



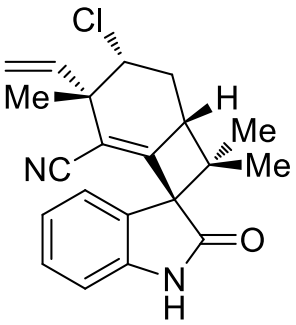
ouabagenin (**1**)

Science, **2013**, *339*, 59-63

Phil S. Baran

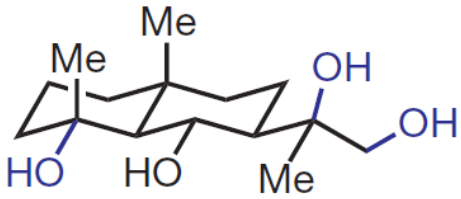
- Born on 10 August 1977, in Denville, New Jersey, USA
- B.S. with Honors in Chemistry - Advisor: Prof. D.I. Schuster, New York University (1995-1997)
- Ph.D. in Chemistry - Advisor: Prof. K.C. Nicolaou, The Scripps Research Institute (1997-2001)
- Postdoctoral Associate - Advisor: Prof. E.J. Corey, Harvard University (2001-2003)
- Assistant Professor of Chemistry, The Scripps Research Institute - June 2003
- Associate Professor of Chemistry (with tenure), The Scripps Research Institute - July 2006

Publications of *Phil S. Baran*



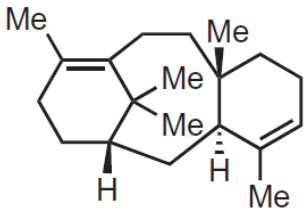
welwitindolinone A

Nature, **2007**, *446*, 404-406



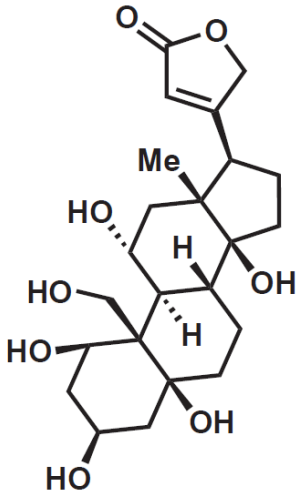
8: eudesmantetraol

Nature, **2009**, *459*, 824-828



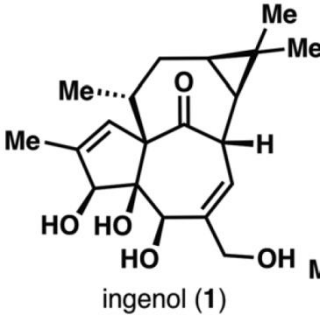
Taxadiene

Nature chem. **2012**, *4*, 21-25



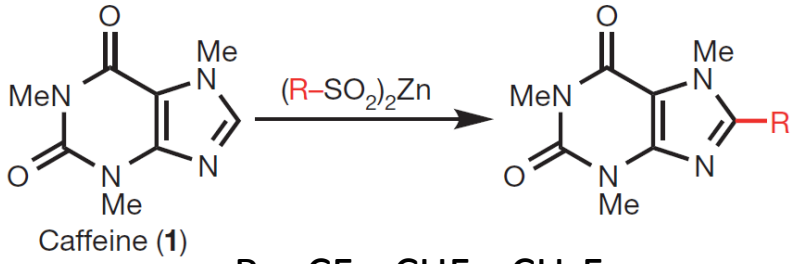
ouabagenin (**1**)

Science, **2013**, *339*, 59-63



ingenol (**1**)

Science, **2013**, *341*, 878-883



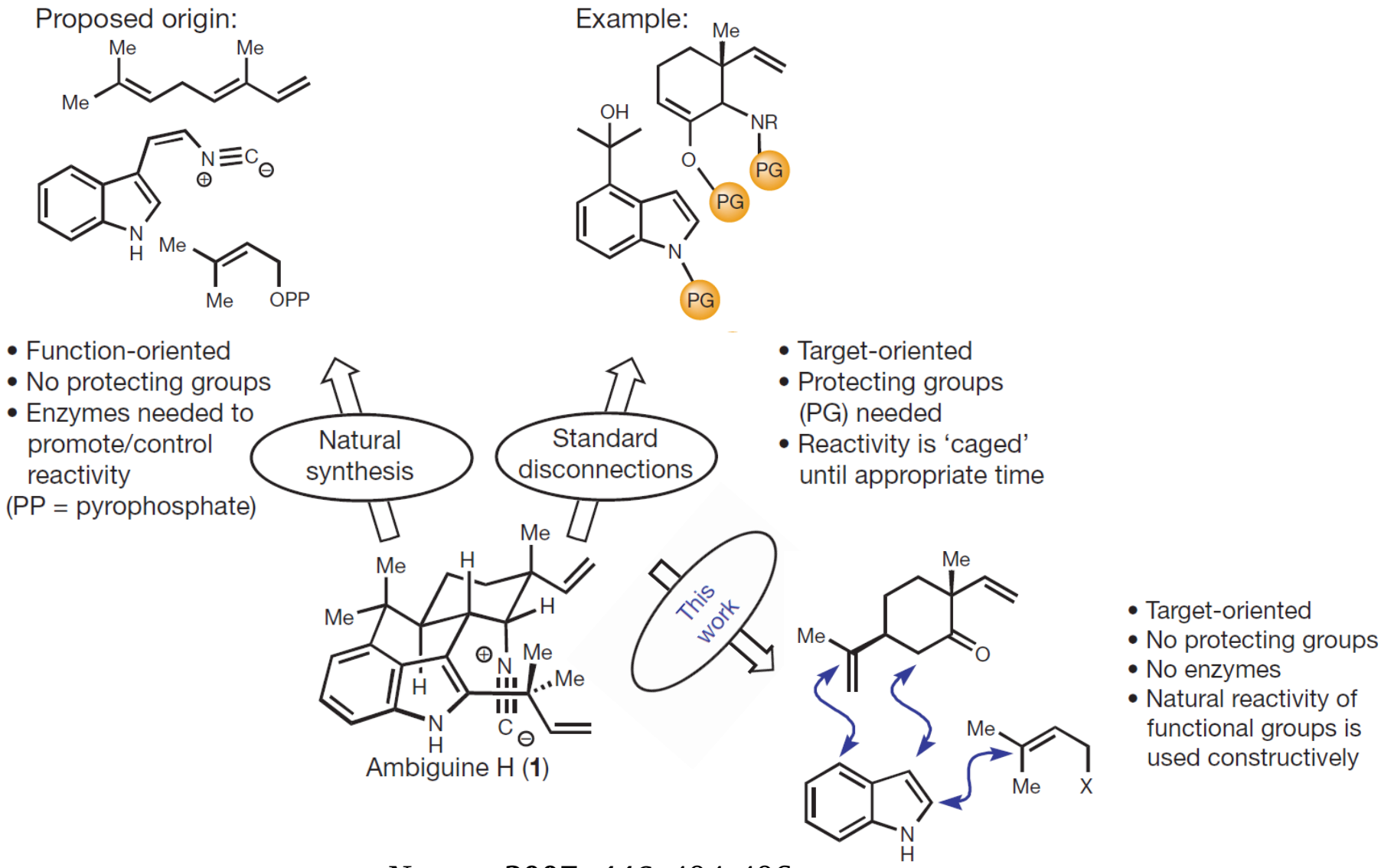
Caffeine (**1**)

R = CF_3, CHF_2, CH_2F

Nature, **2012**, *492*, 95-100

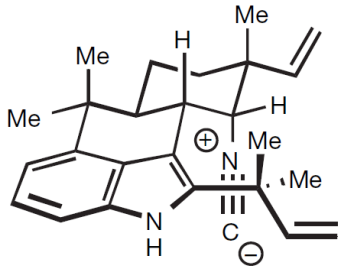
More than 90 papers were published from 2004 to now, include 30 JACS, 25 Angew. Chem and 10 Nature, Science, Nature Chem, PNAS papers.

1. Protecting groups free synthesis of natural products

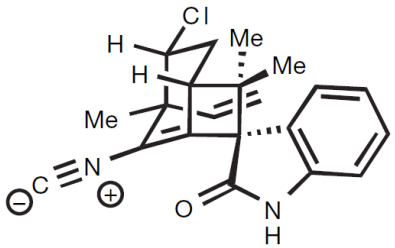


Nature, **2007**, *446*, 404-406

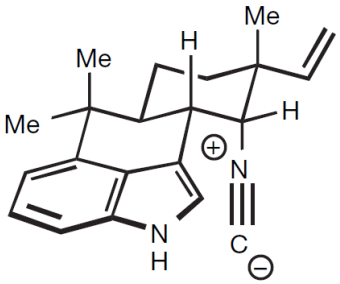
Proposed biosynthetic relationships of welwitindolinone alkaloid families



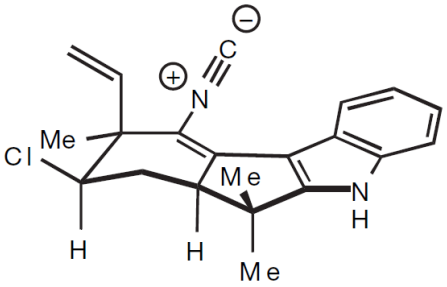
Ambiguine H (**1**)



Welwitindolinone A (**4**)

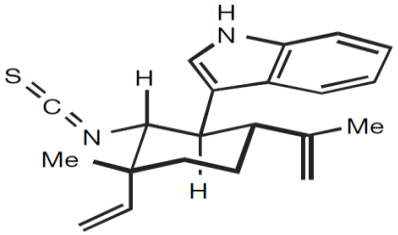


Hapalindole U (**2**)

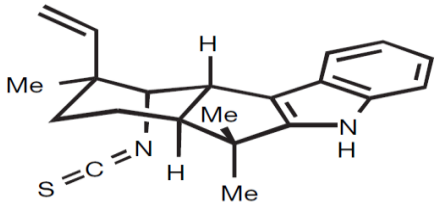


Fischerindole I (**5**)

Structurally related



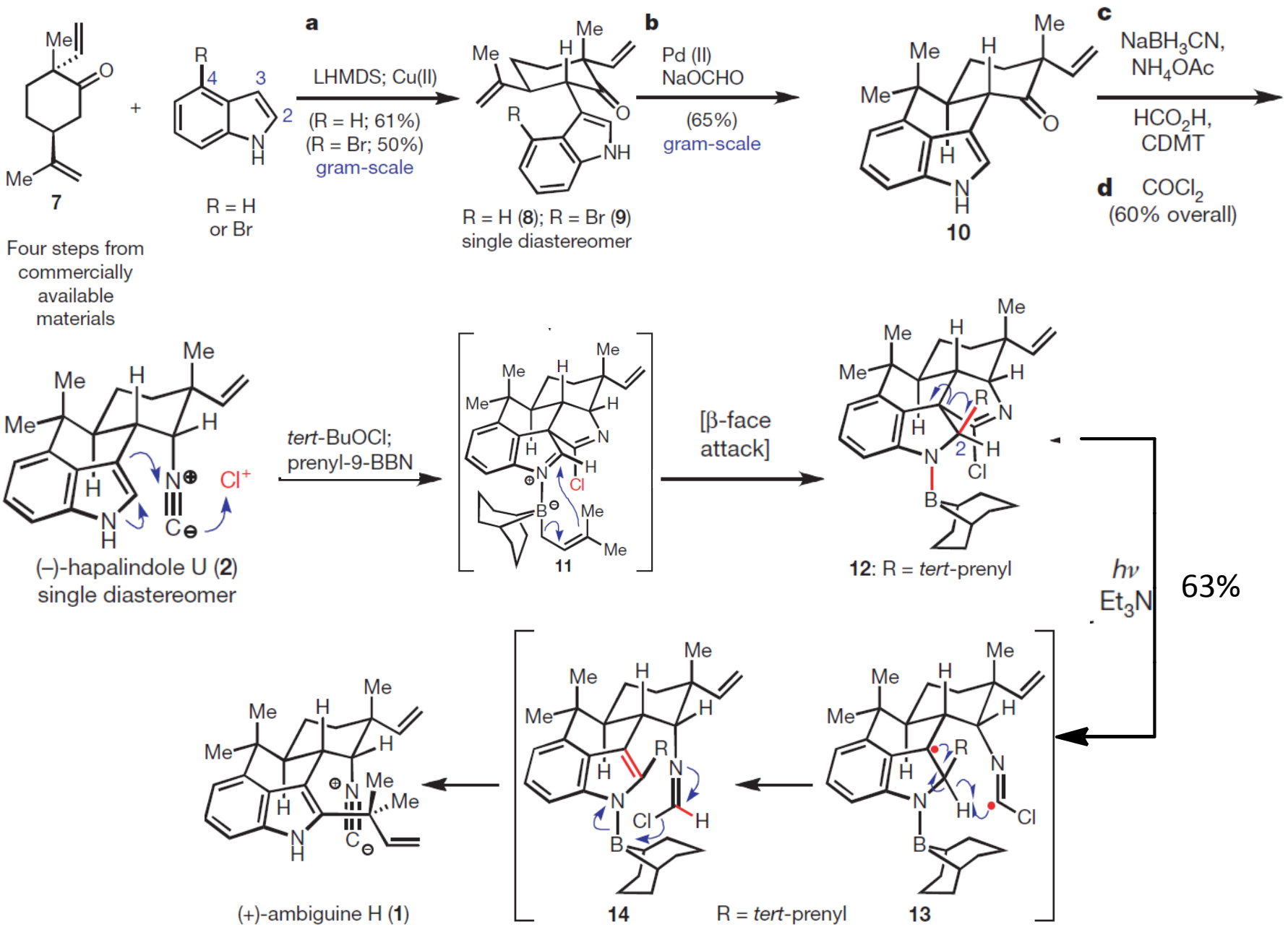
Hapalindole Q (**3**)



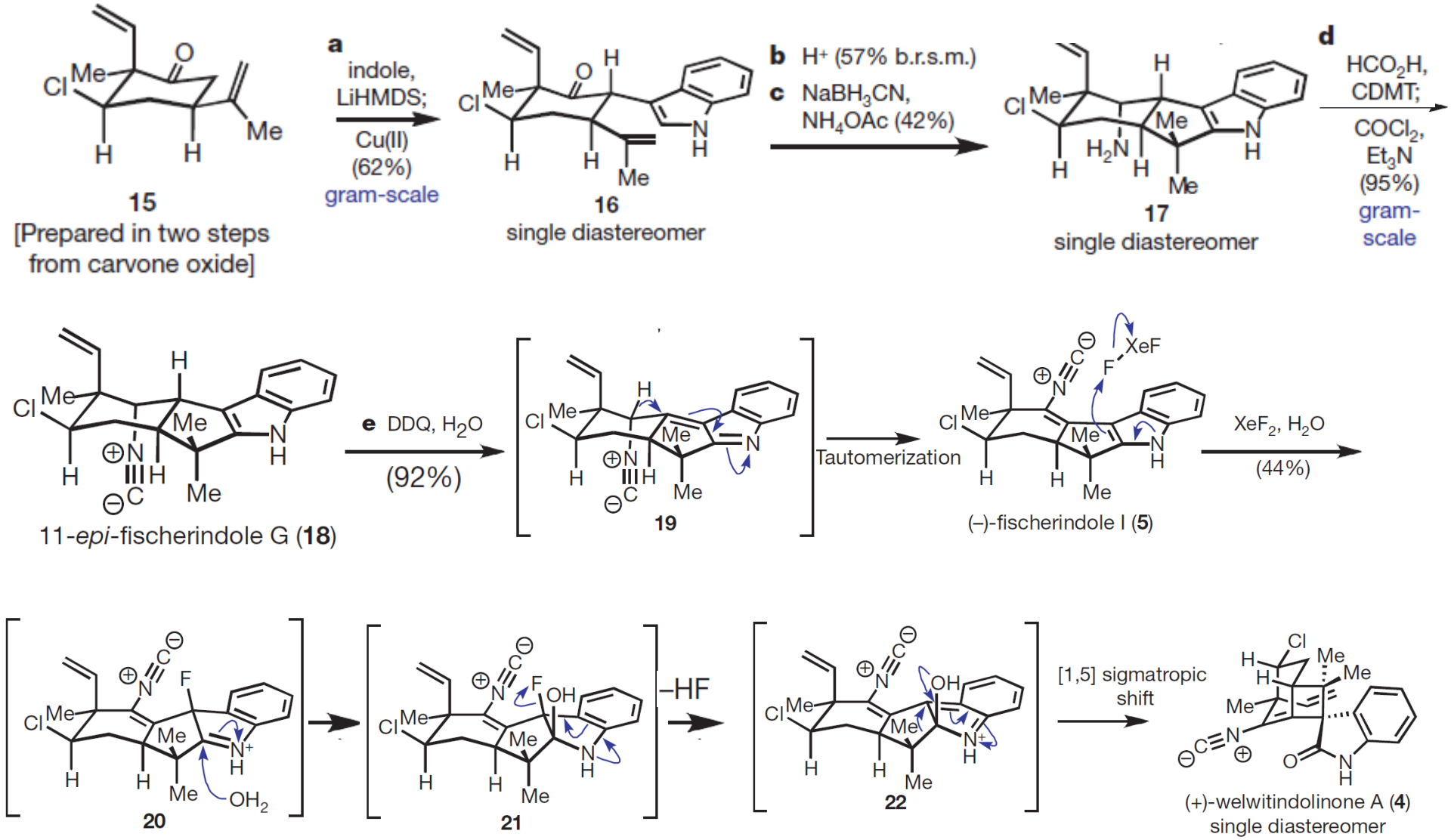
Fischerindole U (**6**)

Only 5 mg isolated, in yields
Ranging from 0.00671% (for 2)
To 0.0213% (for 5)

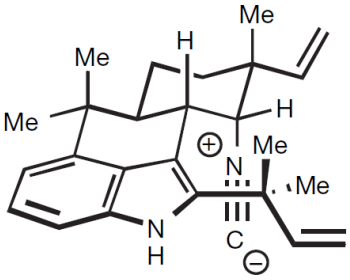
Total synthesis of hapalindole U and ambiguine H



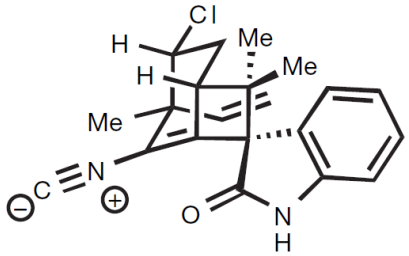
Total synthesis of welwitindolinone A and fischerindole I



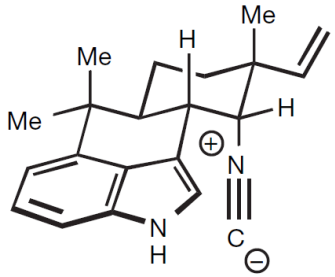
Why this work worth Nature?



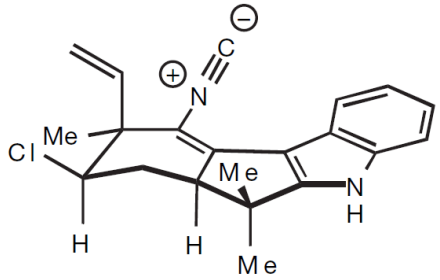
Ambiguine H (**1**)



Welwitindolinone A (**4**)



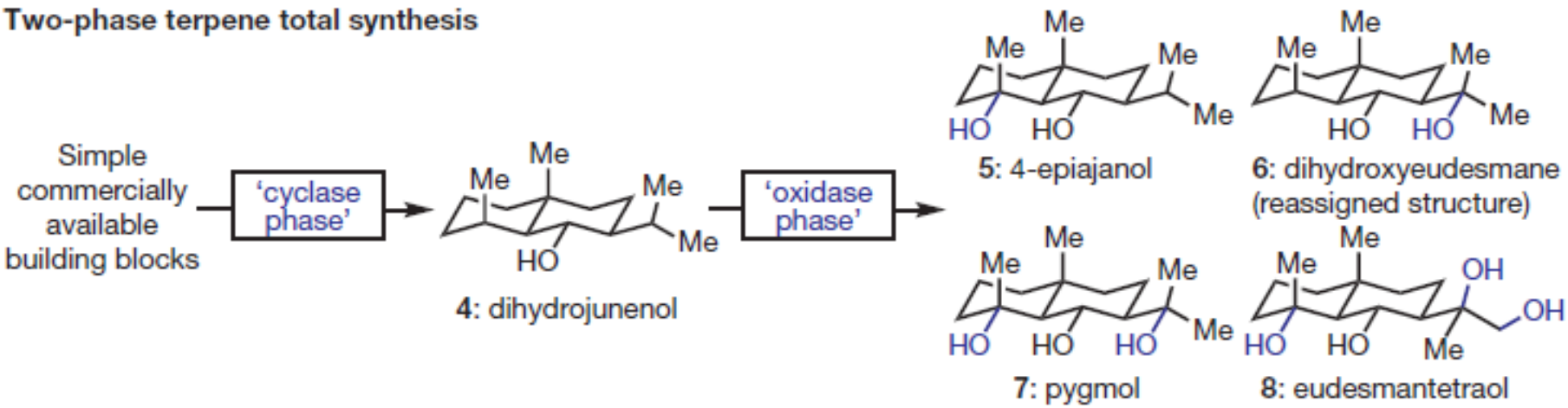
Hapalindole U (**2**)



Fischerindole I (**5**)

- Biomimetic synthesis
- Short synthesis route (7-10 total steps)
- Gram scale synthesis compare to 0.0067% (2) and 0.0213% (5) isolated yield
- Protecting groups free total synthesis of complex natural product

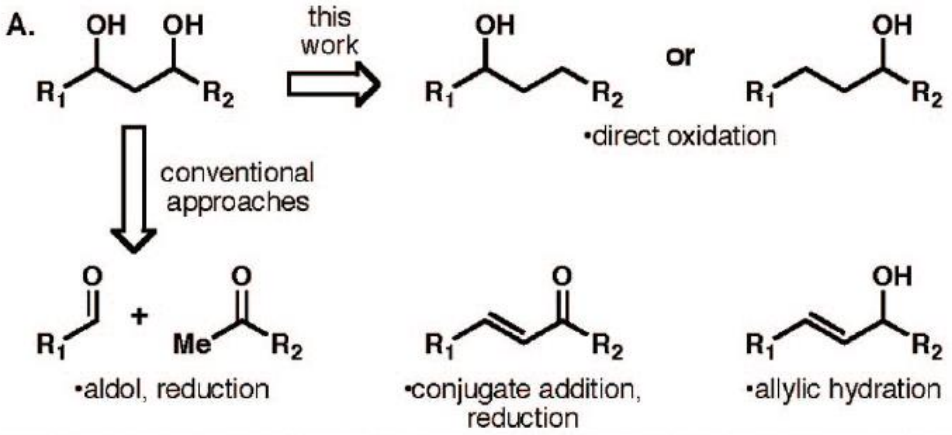
2. Total synthesis of eudesmane terpenes by site –selective C-H oxidations

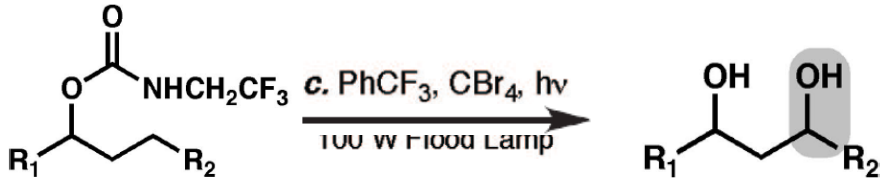


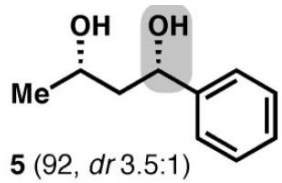
• Over 55,000 members of terpenes isolated so far, have long history provided human with flavours, fragrances, hormones, medicines.
• Eduesmane family of terpenes containing over 1000 members, most are in high oxidation state
• difficult targets for synthesis, only 4 has been prepared

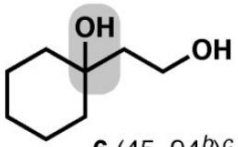
Nature, **2009**, *459*,824-828

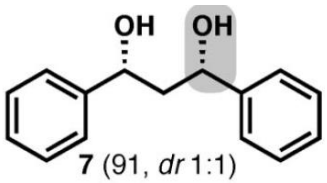
1,3-Diol synthesis via controlled Radical-mediate C-H functionalization

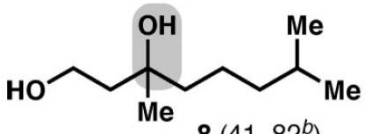


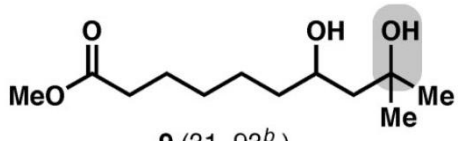


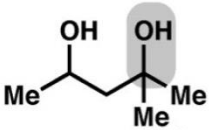

5 (92, *dr* 3.5:1)

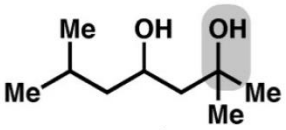

6 (45, 94[b])[c]

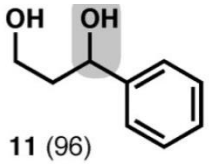

7 (91, *dr* 1:1)

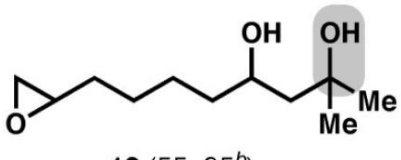

8 (41, 82[b])

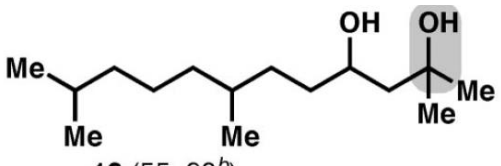

9 (31, 93[b])


10 (70, 98[b])[d]


4 (69, 95[b])

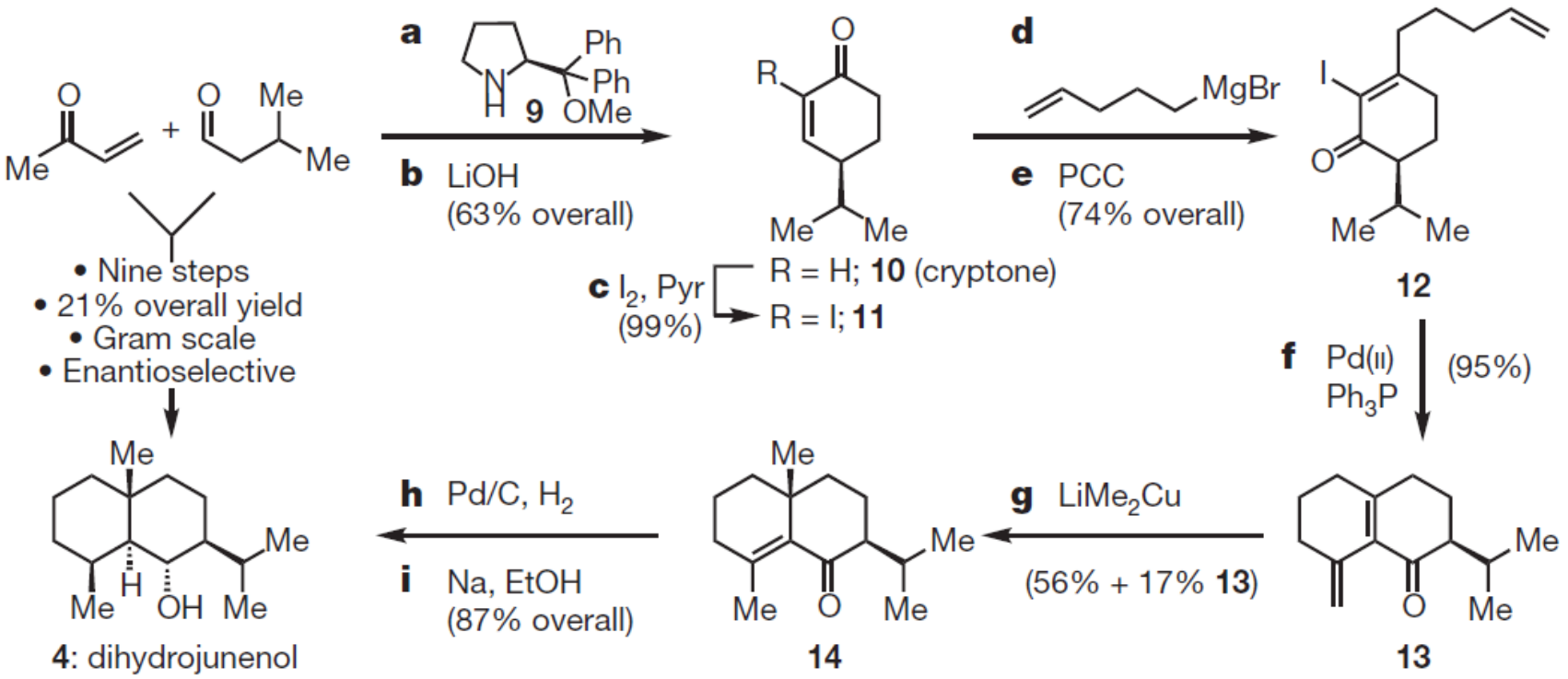

11 (96)


12 (55, 95[b])


13 (55, 93[b])

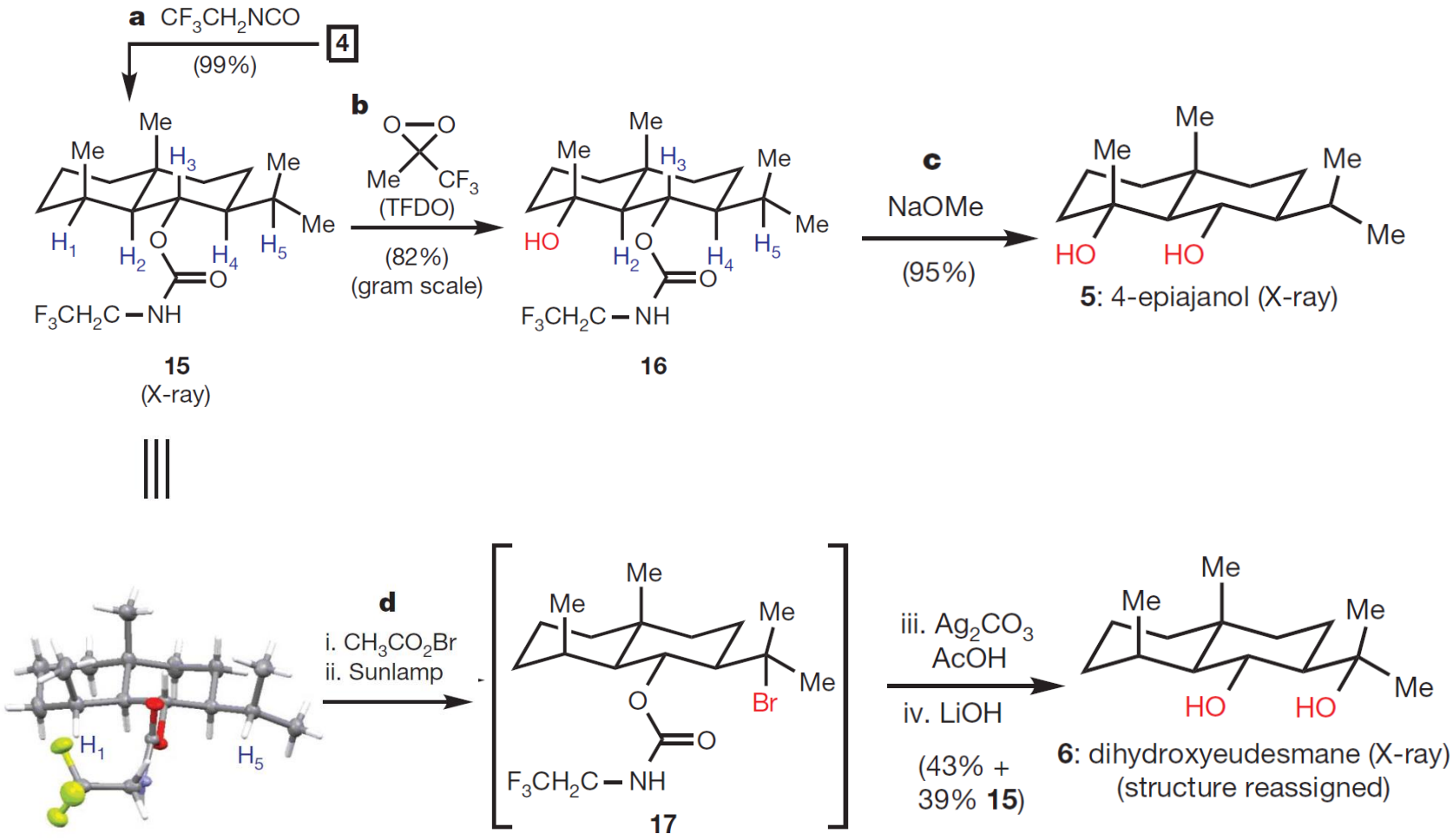
J. Am. Chem. Soc, **2008**, *130*, 7247-7249

Gram scale total synthesis of dihydrojunenol



Nature, **2009**, *459*,824-828

total synthesis of dihydroxyeudesmane

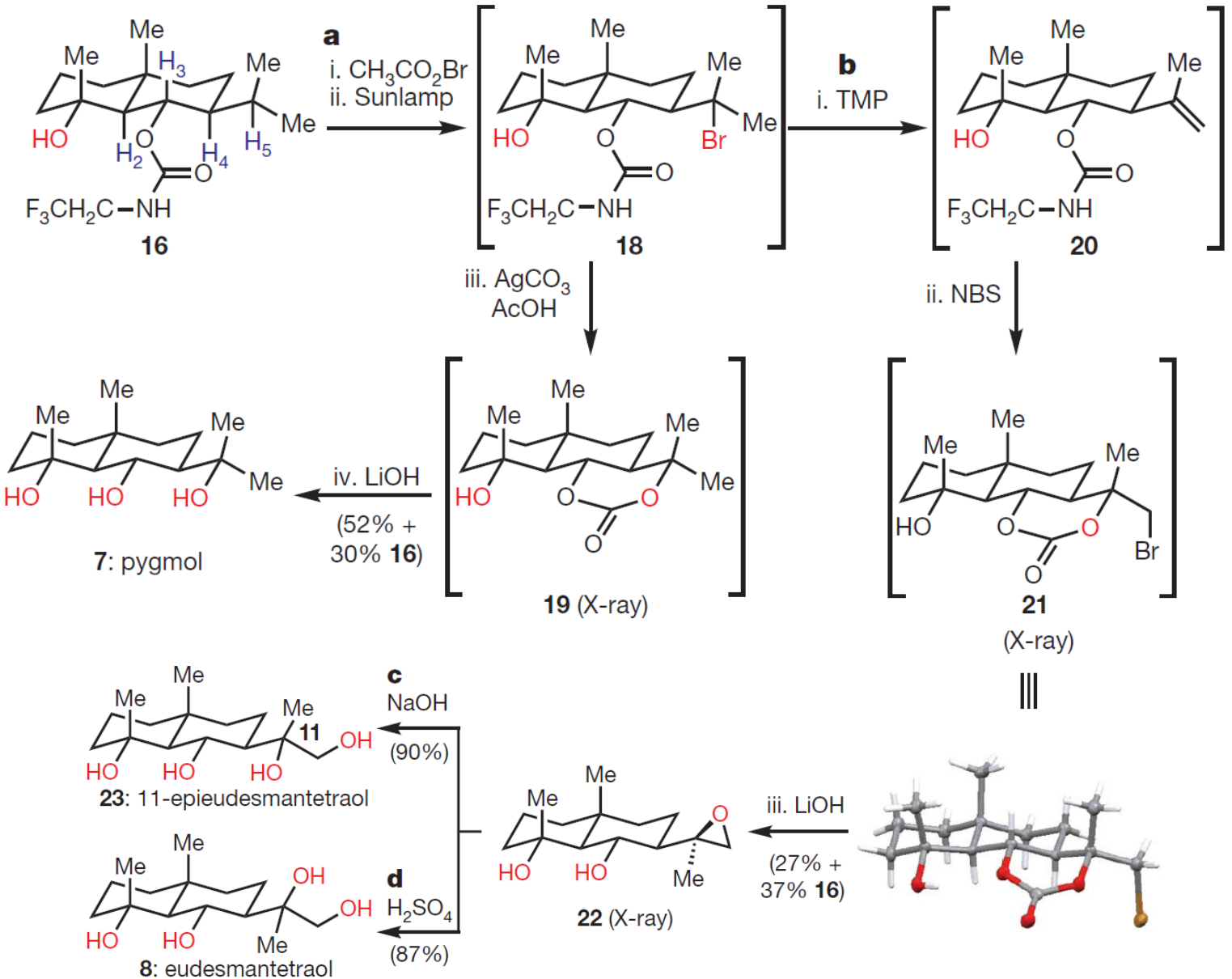


$$\delta_{C3} = 73.6 \text{ p.p.m.} > \delta_{C2} = 55.2 \text{ p.p.m.} \approx \delta_{C4} =$$

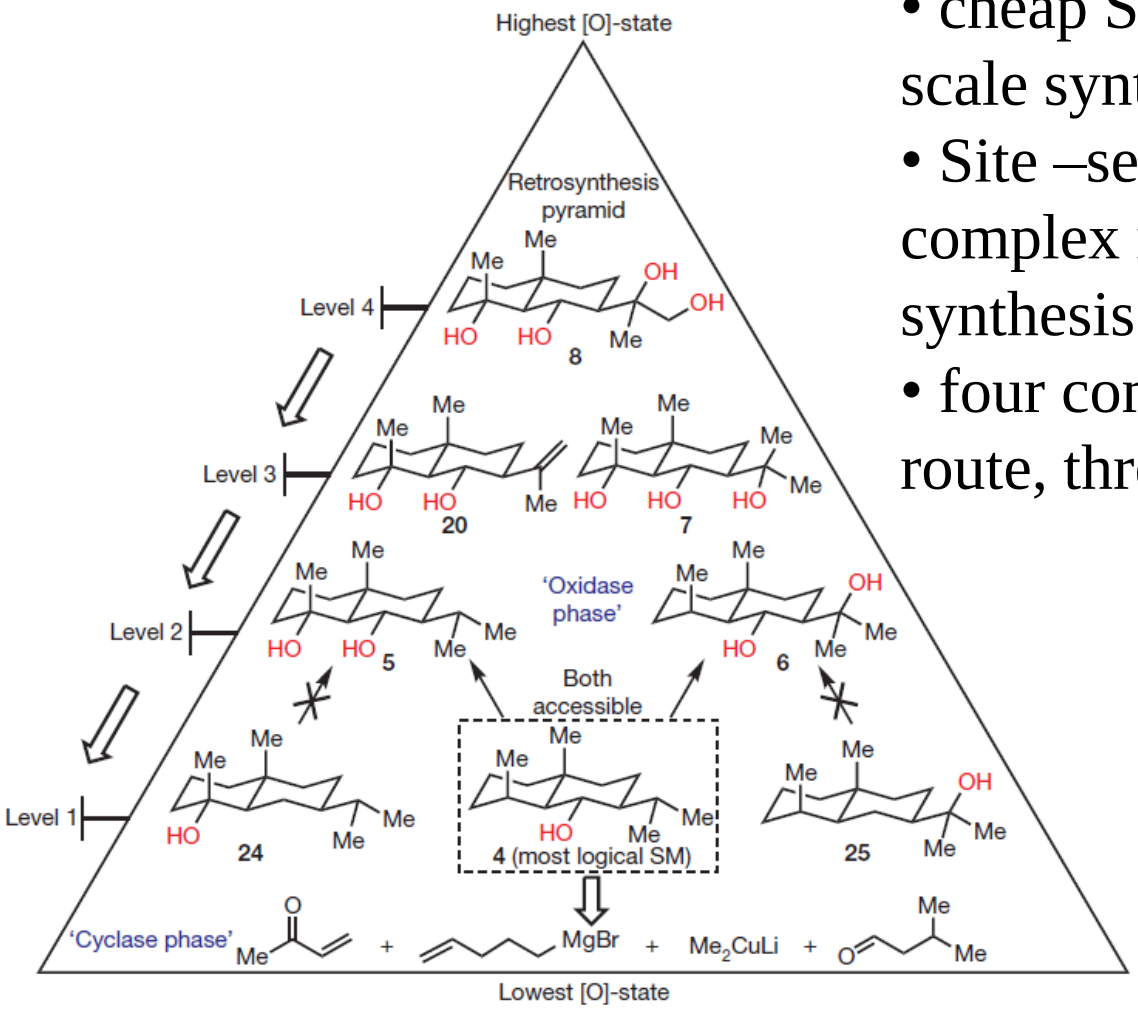
$$50.2 \text{ p.p.m.} > \delta_{C1} = 27.5 \text{ p.p.m.} \approx \delta_{C5} = 26.6 \text{ p.p.m.}$$

Nature, **2009**, *459*,824-828

total synthesis of prgmol and eudesmantetraol



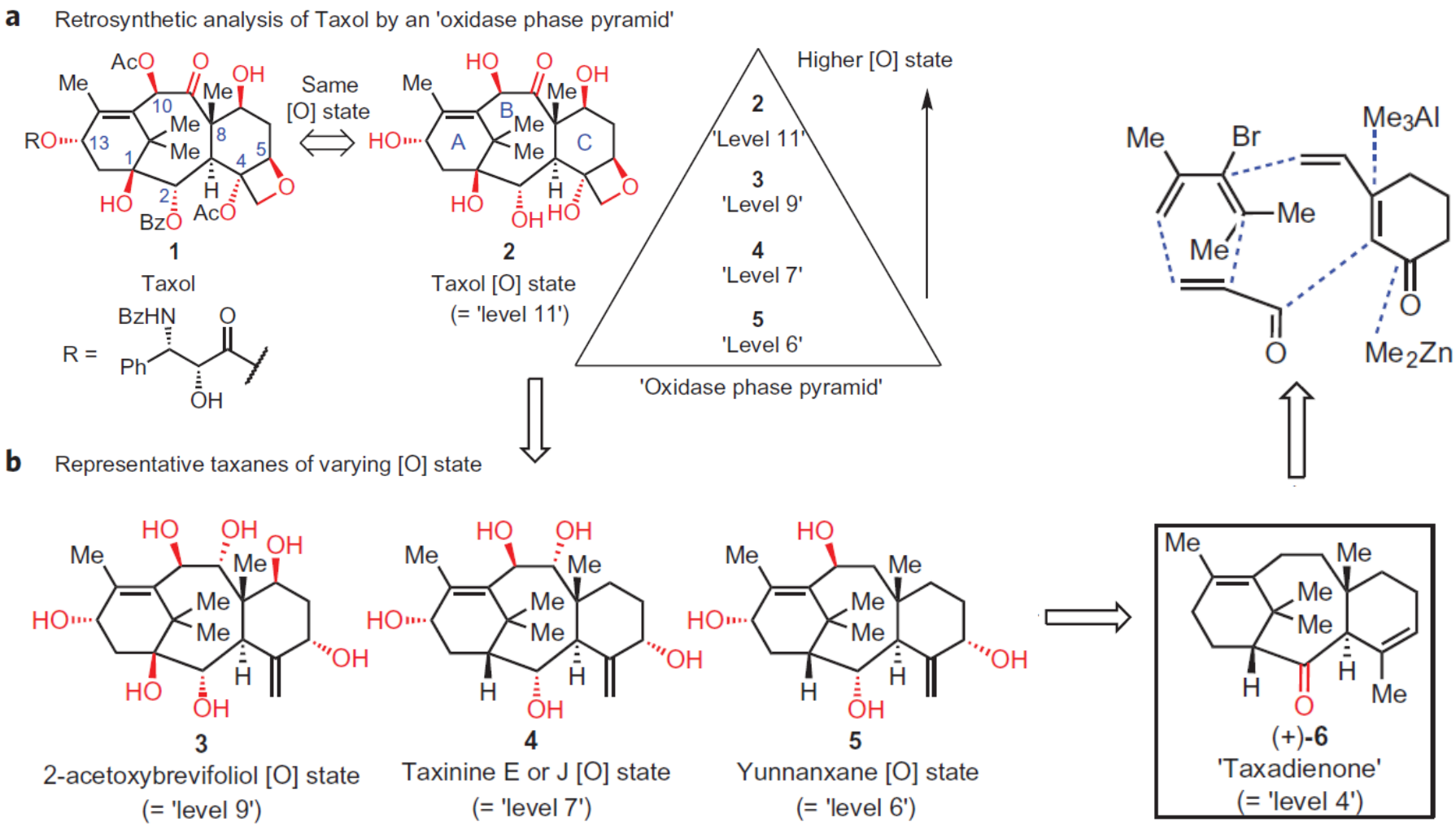
Why nature?



- biomimetic "two-phase" concept
- cheap SM and high yield gram scale synthesis
- Site –selective oxidations in complex natural product total synthesis
- four compound in one synthesis route, three are first reported

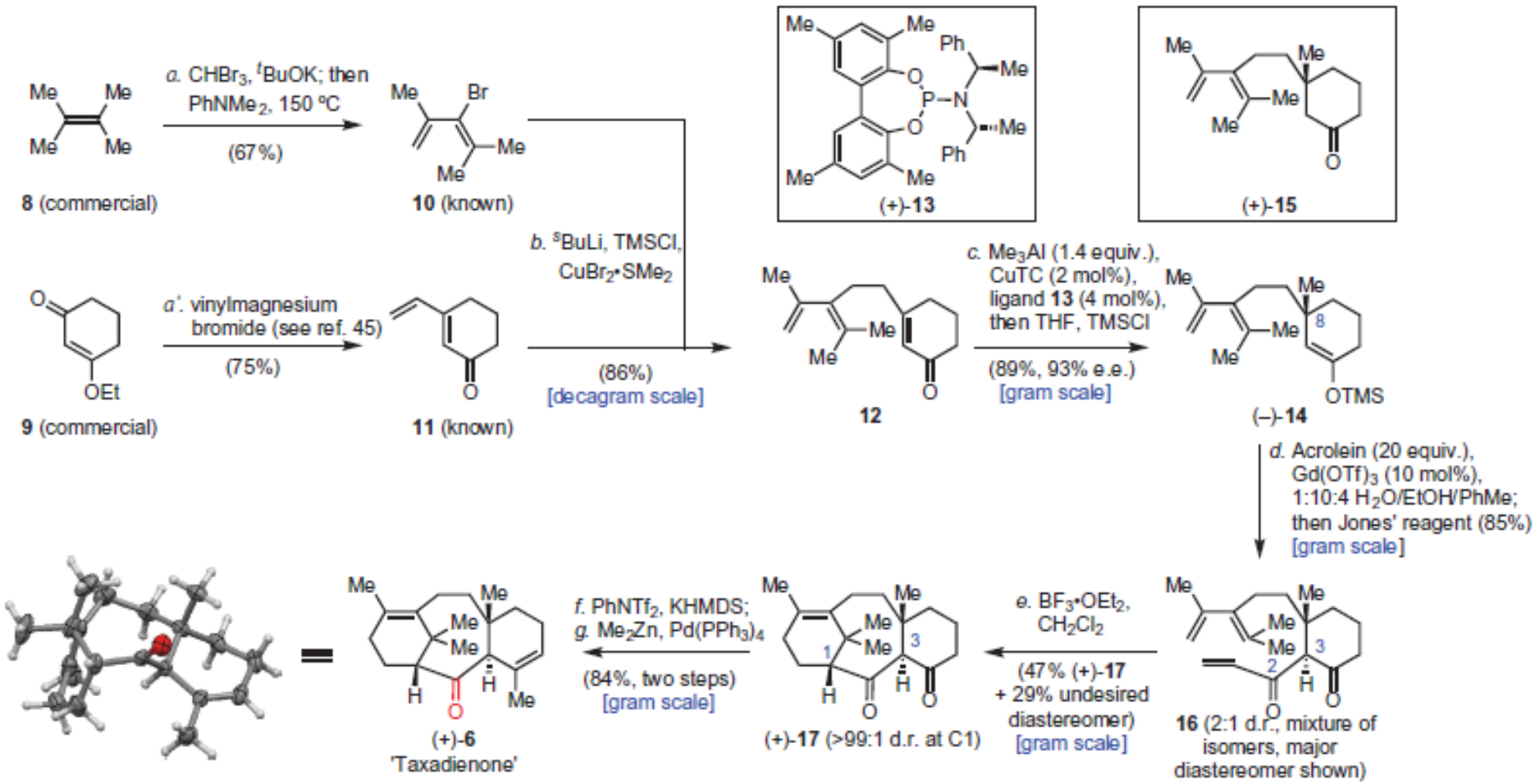
Compound 4, 6, 7, 8 were respectively Constructed in 9, 12, 13 and 15 steps in 21, 9, 9 and 4% overall yield.

Scalable enantioselective total synthesis of taxanes



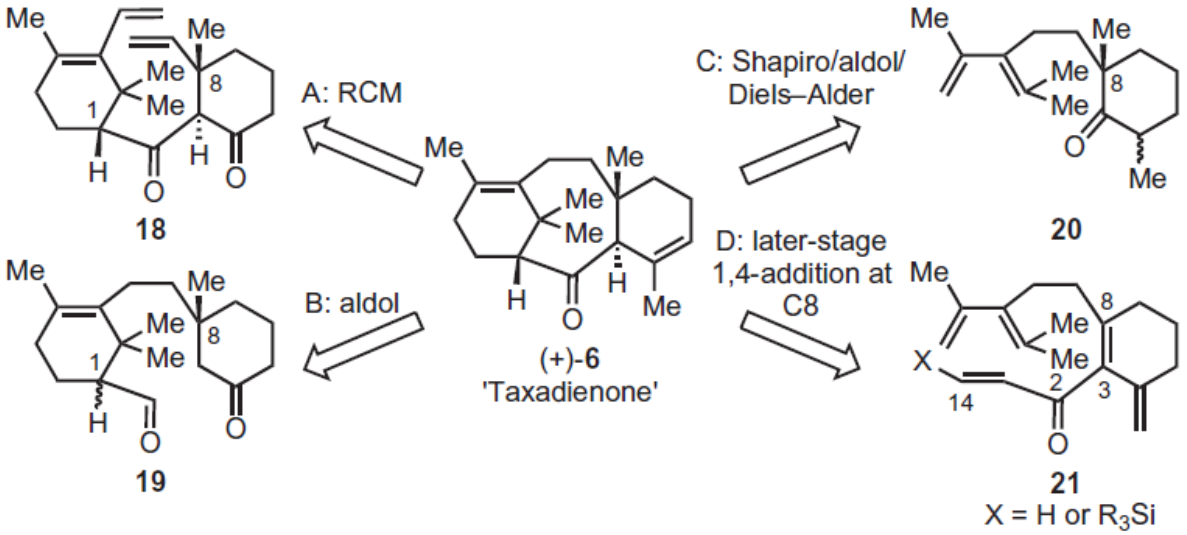
Nature chem. **2012**, *4*, 21-25

Scalable enantioselective total synthesis of taxanes

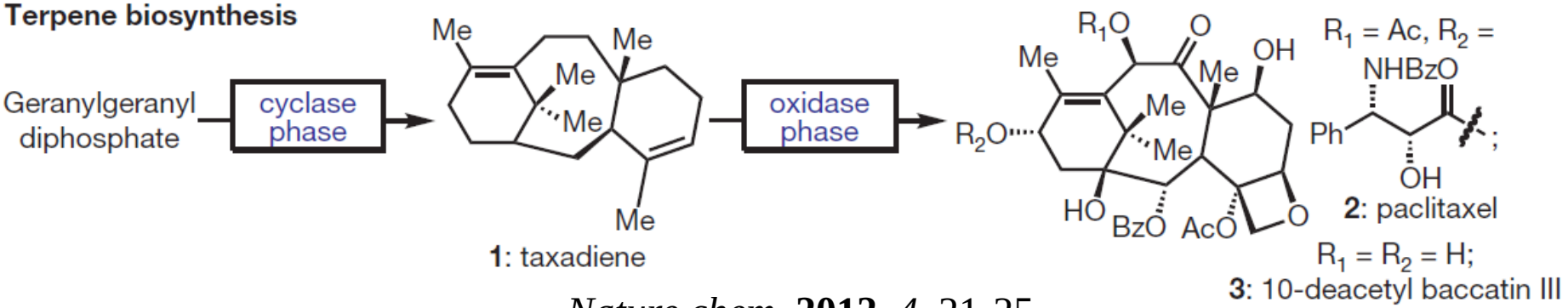


7 steps 20% overall yield

From nature chem to nature?

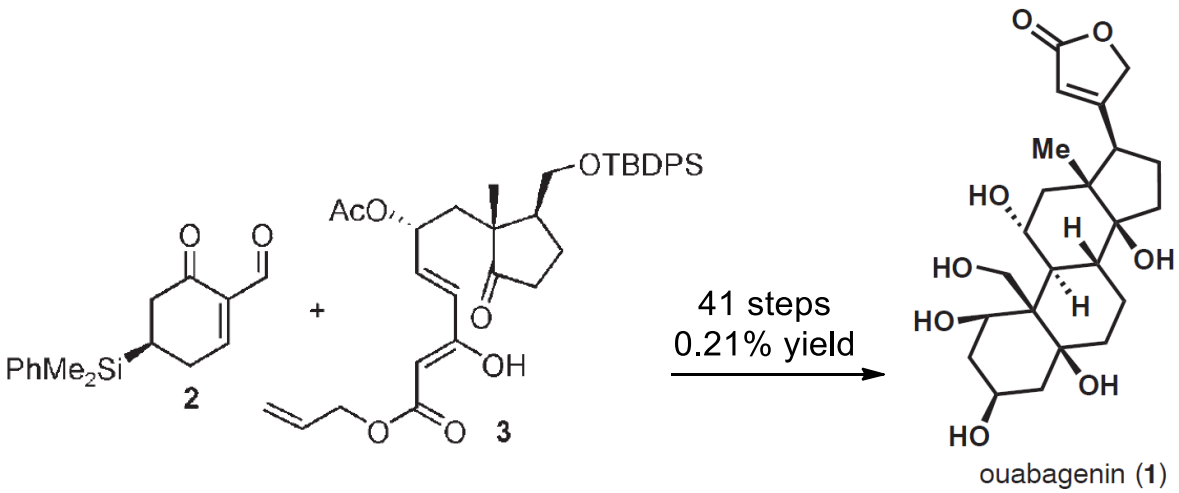


- Gram scale synthesis, short synthesis route and high yield
- Rapid synthesis
- Intermediate of Taxol

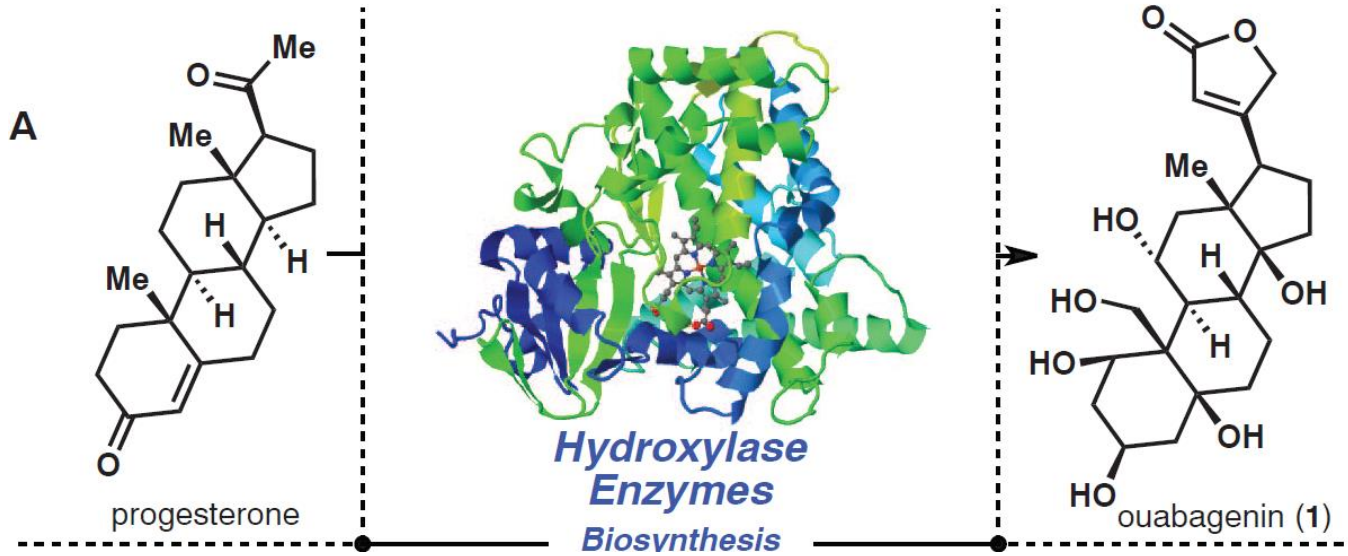


Nature chem. **2012**, *4*, 21-25

Scalable synthesis of Quabagenin



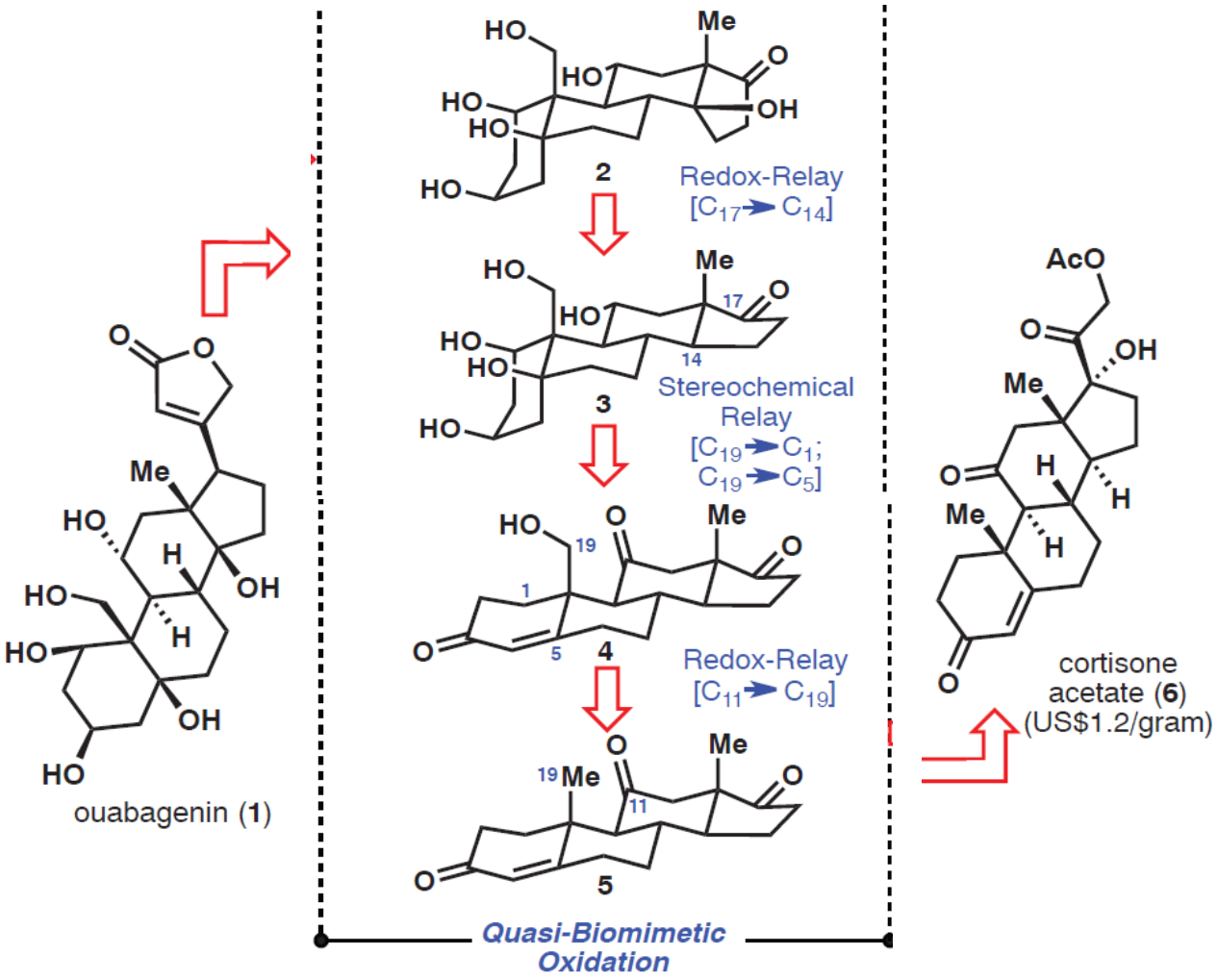
- Treatment for congrestive heart failure
- Scalable synthesis complex steroid is unknow
- Drug activity relationship studies is rare



Angew. Chem. Int. Ed. **2008**, *47*, 1272

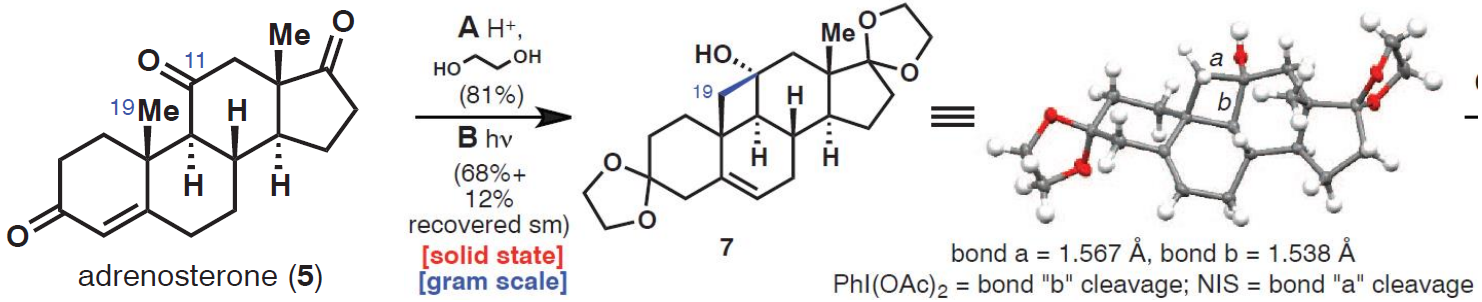
Science, **2013**, *339*, 59-63

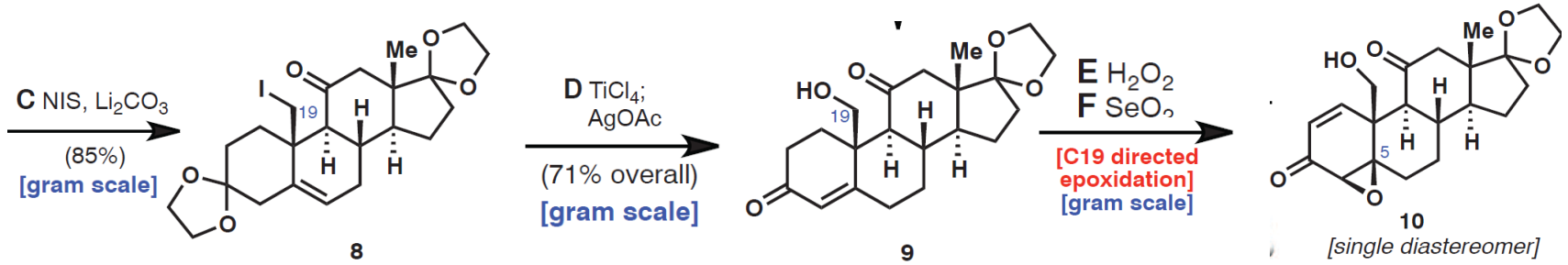
Biomimetic synthesis of ouabagenin

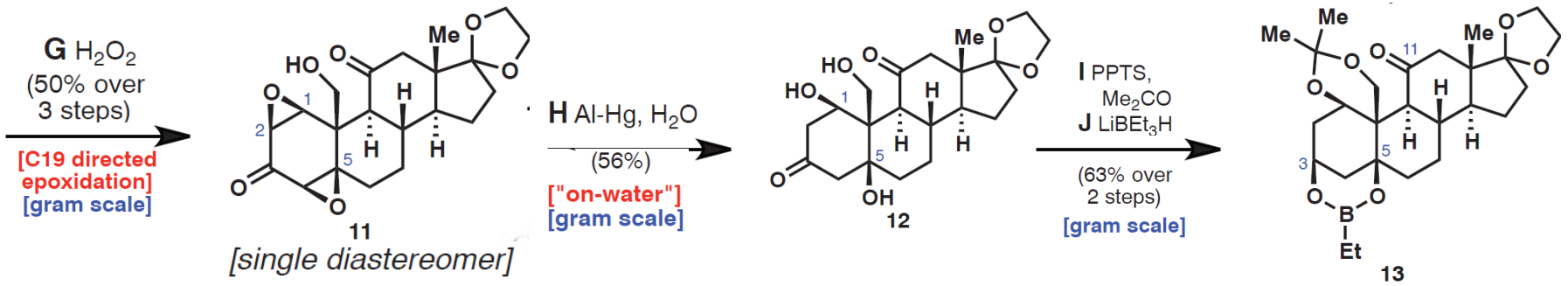


Science, **2013**, *339*, 59-63

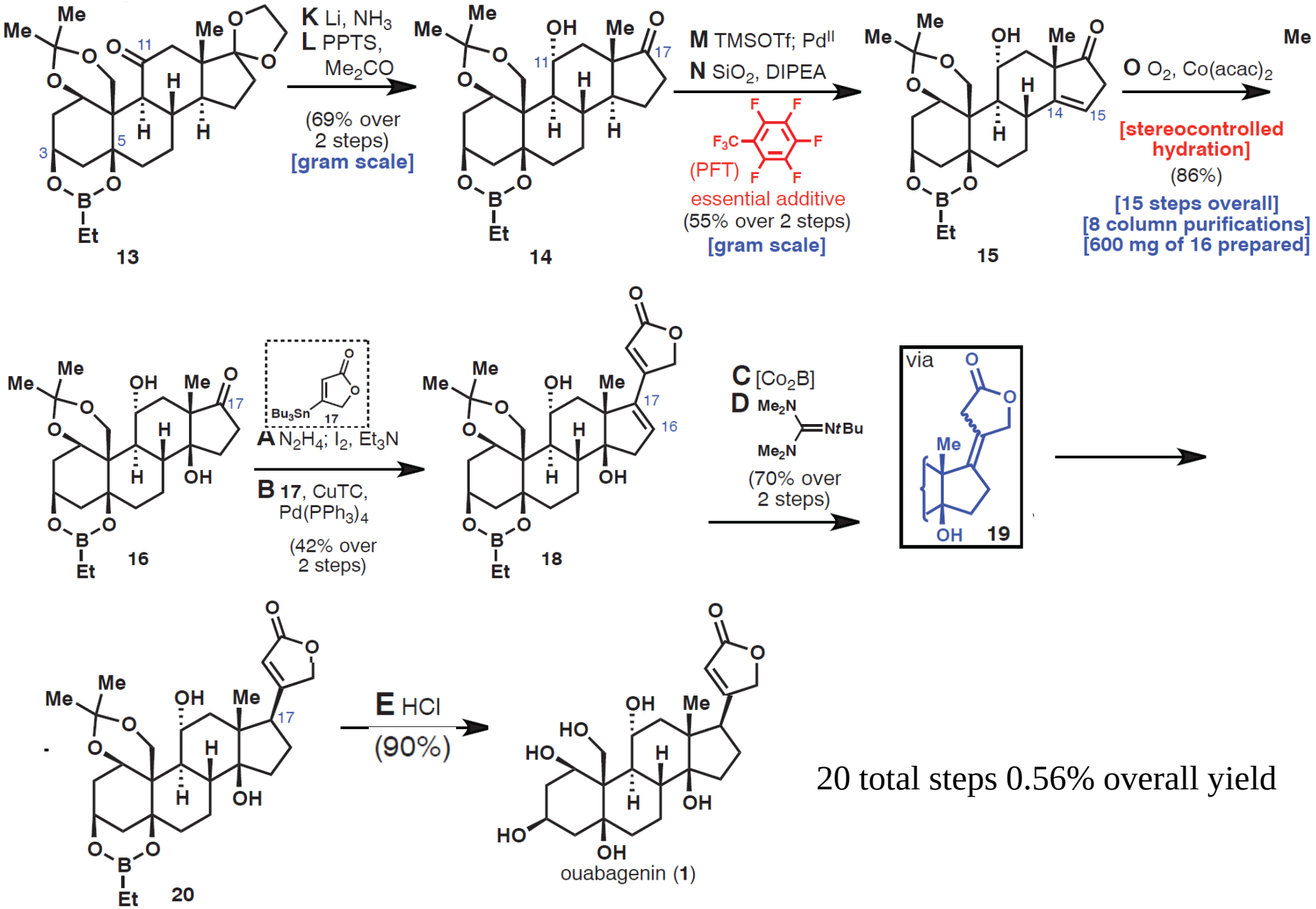
Scalable synthesis of Quabagenin



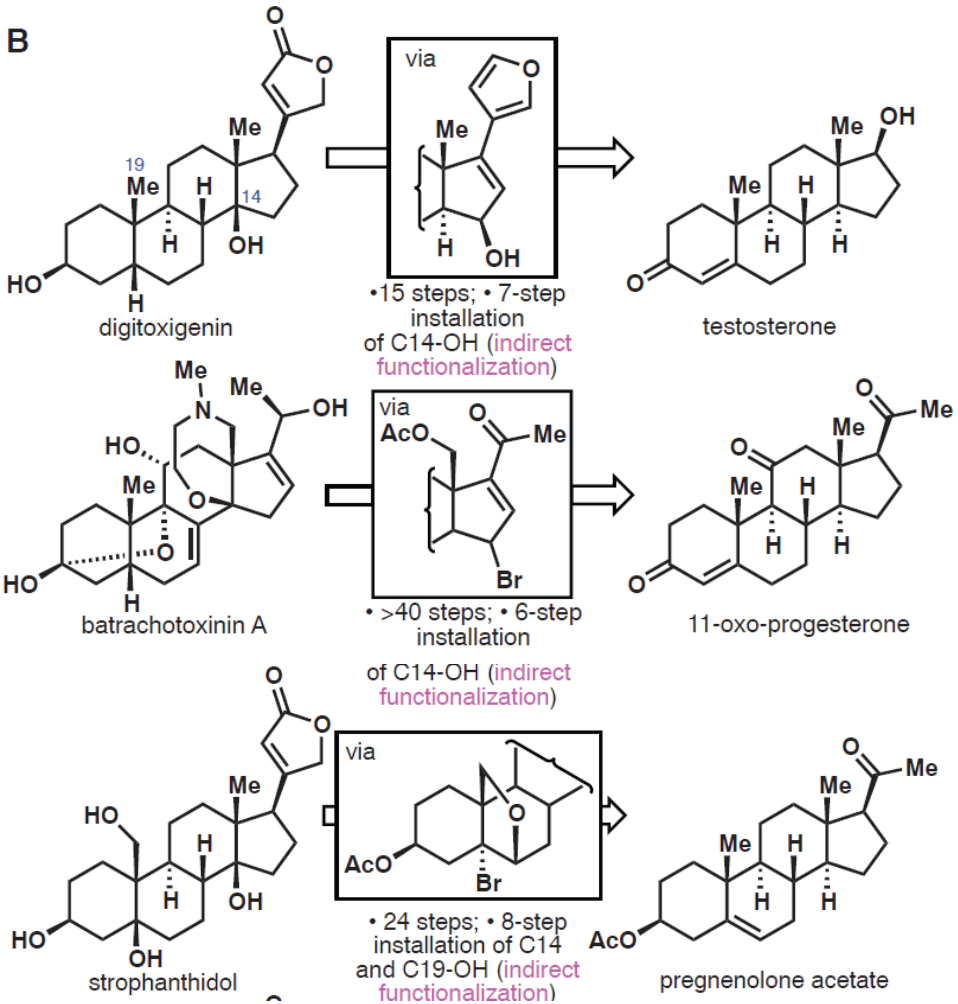


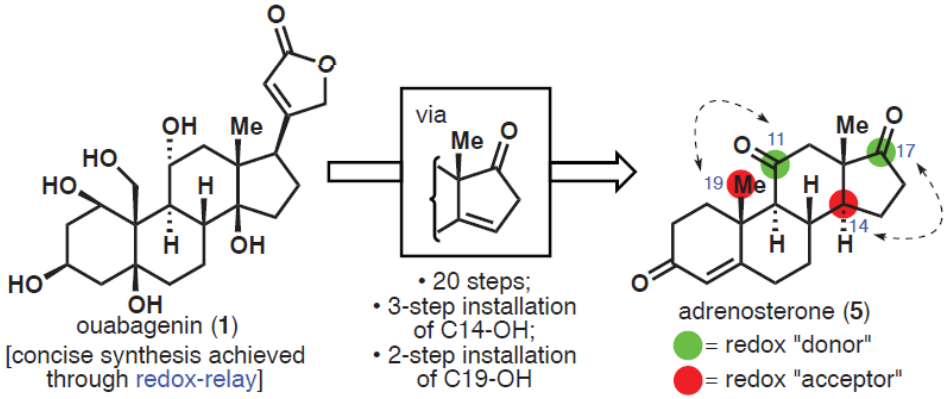


Scalable synthesis of Quabagenin



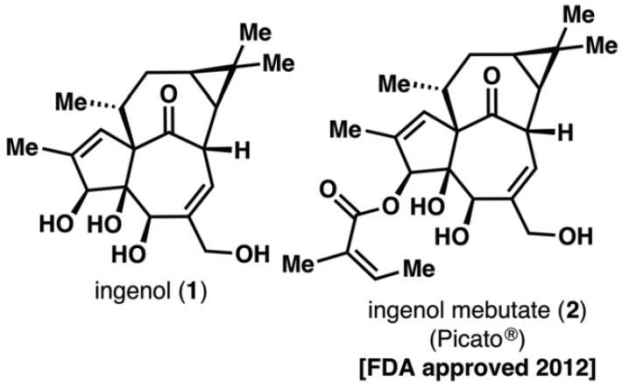
Scalable synthesis of Quabagenin





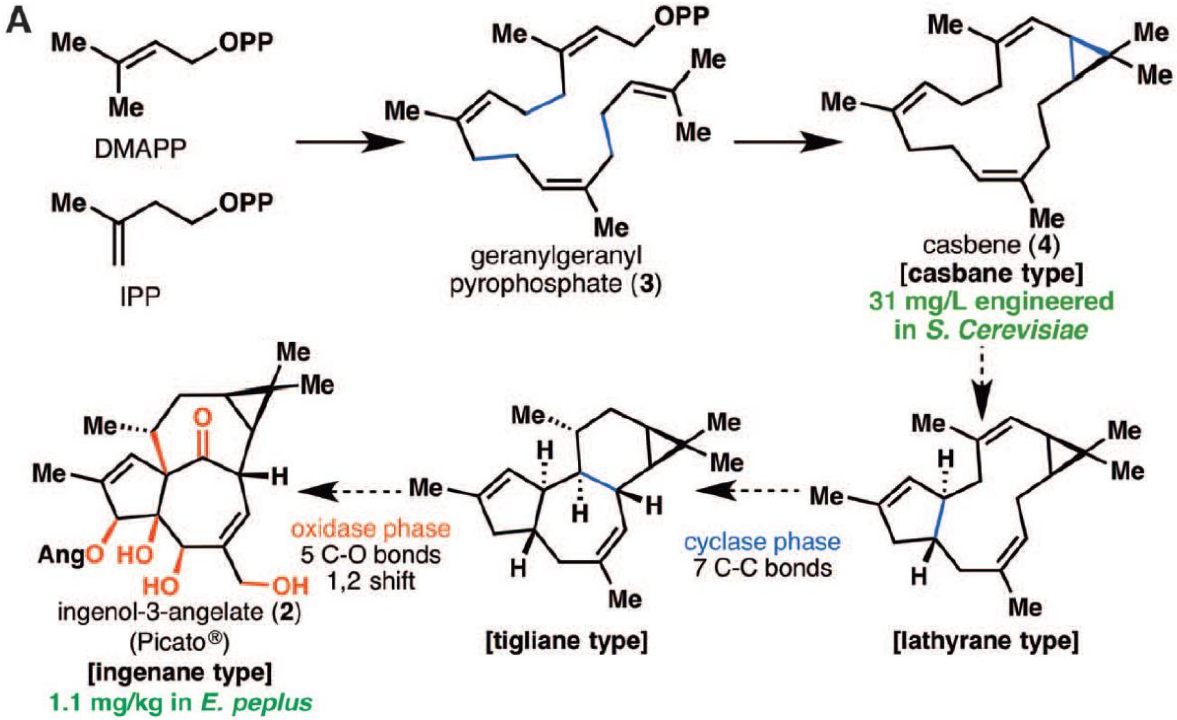
- Bioactive cardenolide as target molecular
- Almost gram scale
- Redox and stereo-relay synthesis
- More efficient synthesis route

14-step synthesis of (+)-Ingenol from (+)-3-Carene



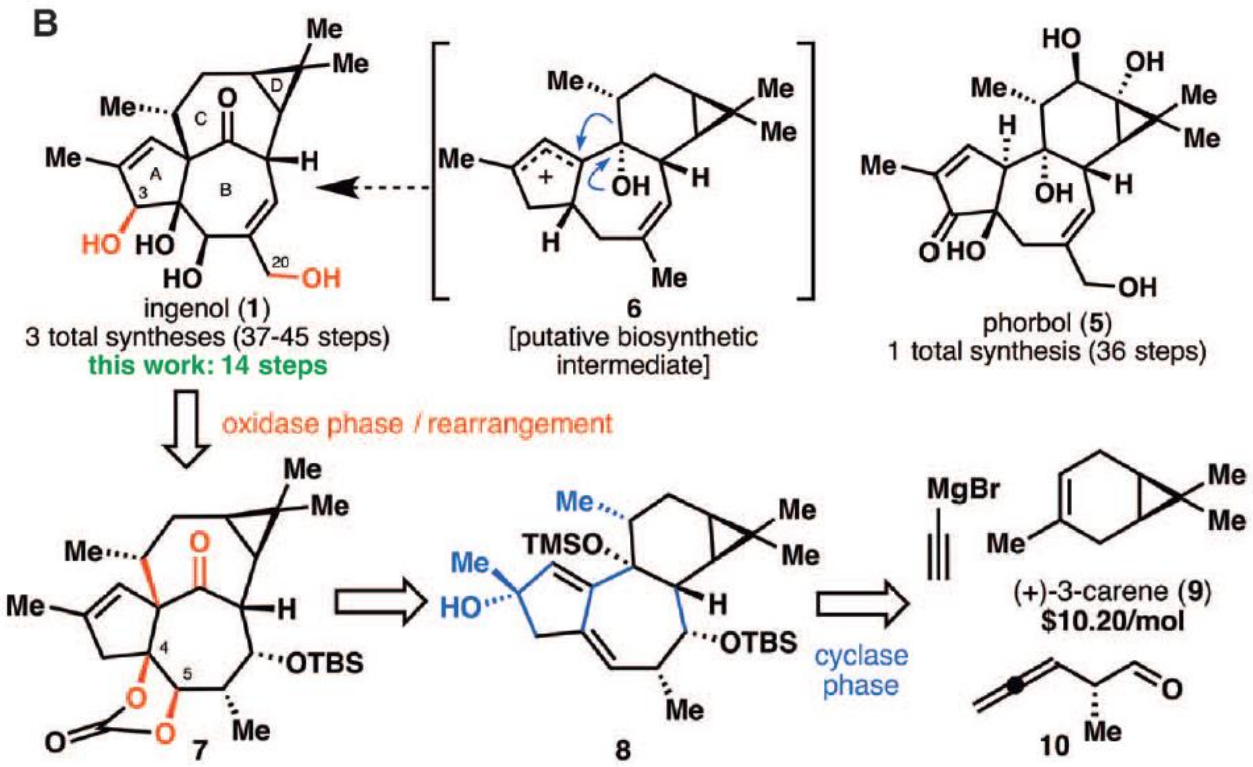
- First –in-class drug for actinic keratosis
- 0.0011% and 0.028% (w/w) isolation yield of 2 and 1
- 3 total synthesis need 37-45 steps

Proposal biosynthesis pathway



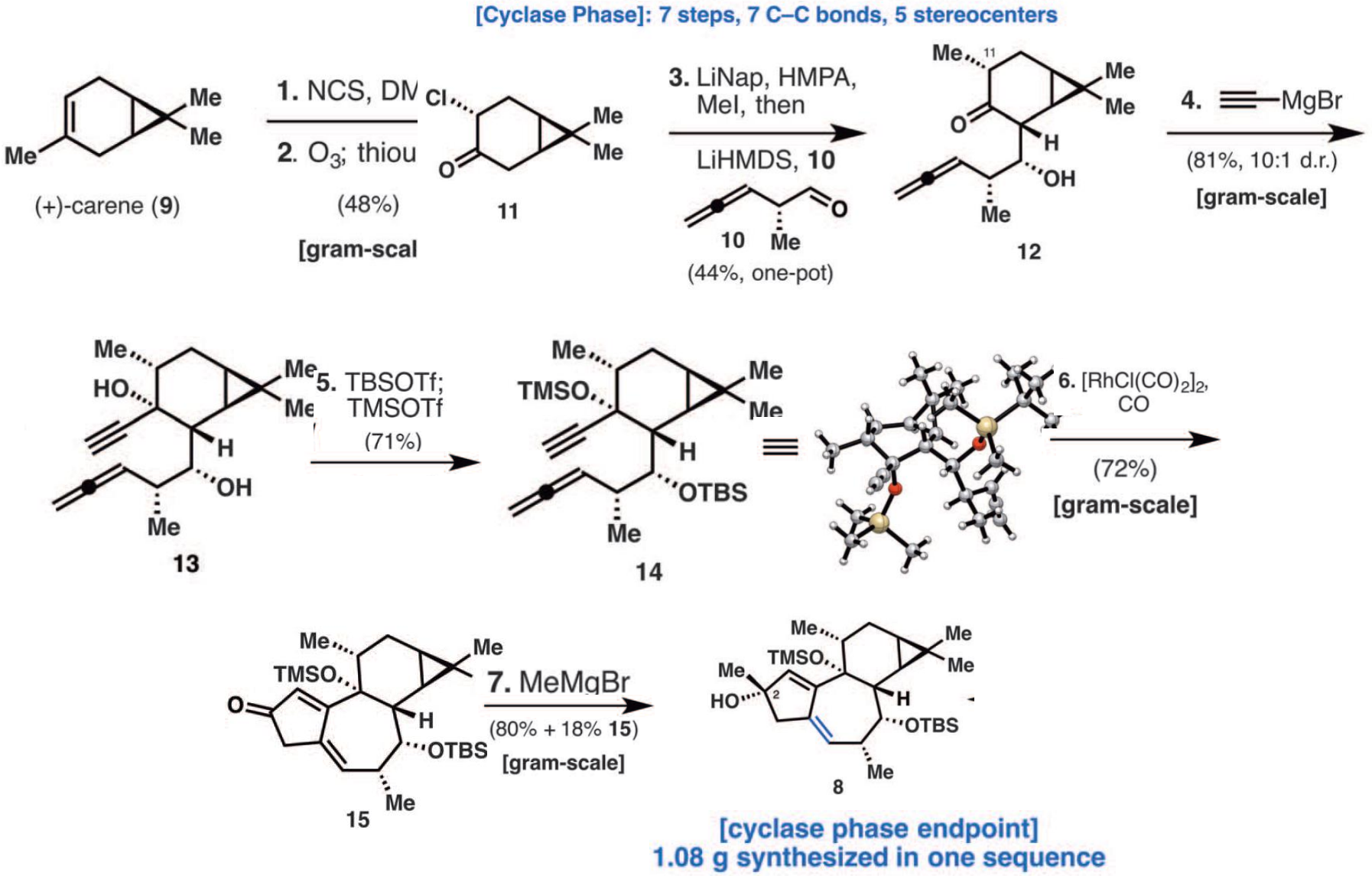
Science, **2013**, *341*,878-883

Biosynthetic inspiration and retrosynthetic analysis

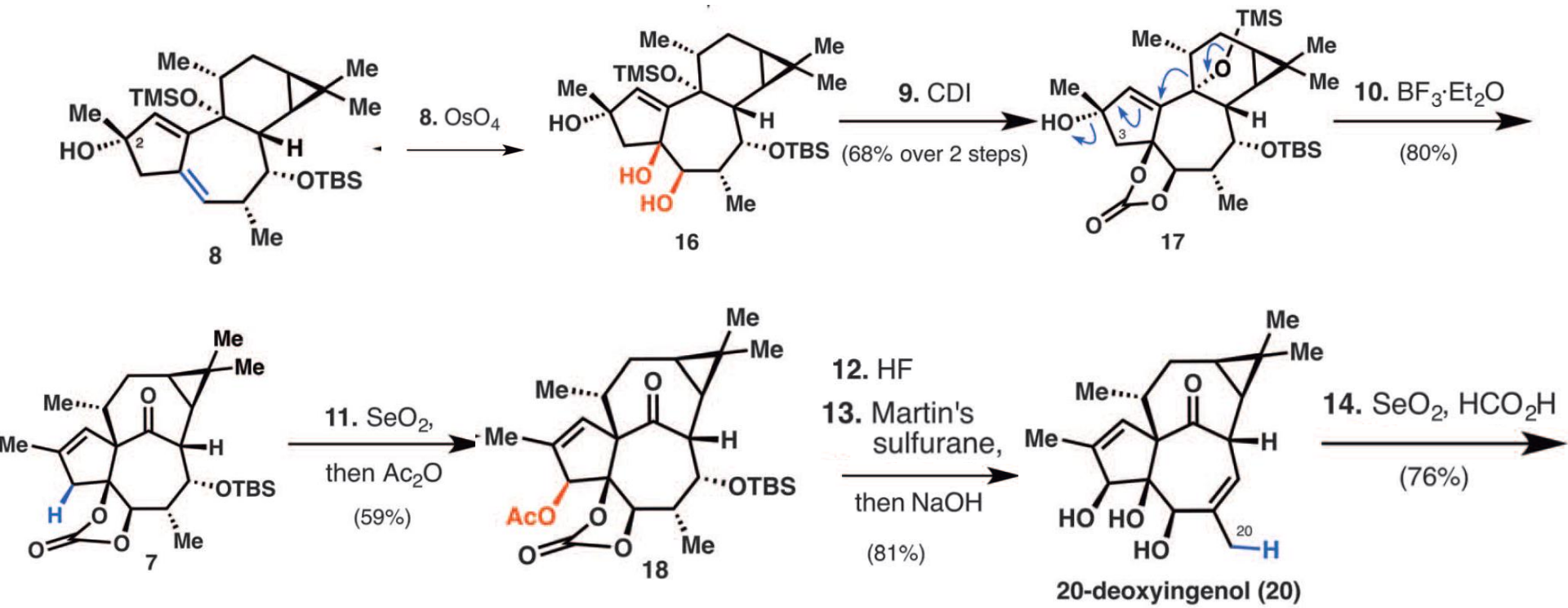


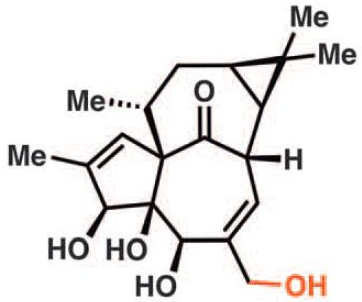
Science, **2013**, *341*,878-883

14-step synthesis of (+)-Ingenol from (+)-3-Carene



14-step synthesis of (+)-Ingenol from (+)-3-Carene

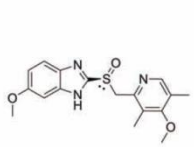
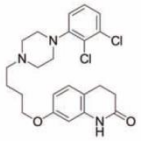
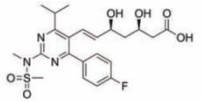
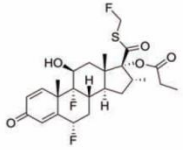
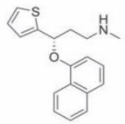
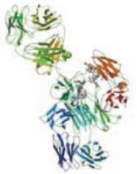
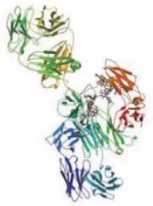
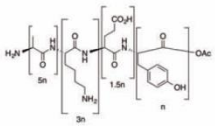
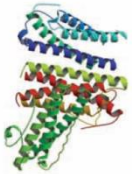
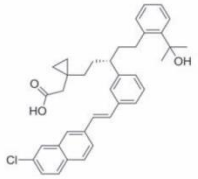
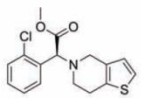
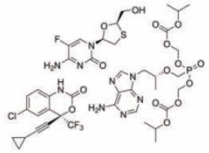
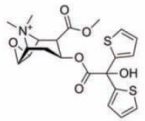
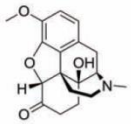
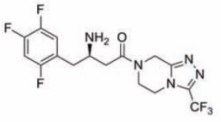
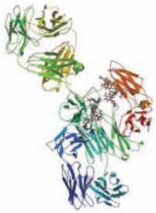




- FDA approved drug as target
- Cyclase\Oxidase Phase biomimetic synthesis
- Large scale synthesis
- 14 steps compare to previous 37-40 steps
- 1.1% overall yield compare to 0.028% isolated yield

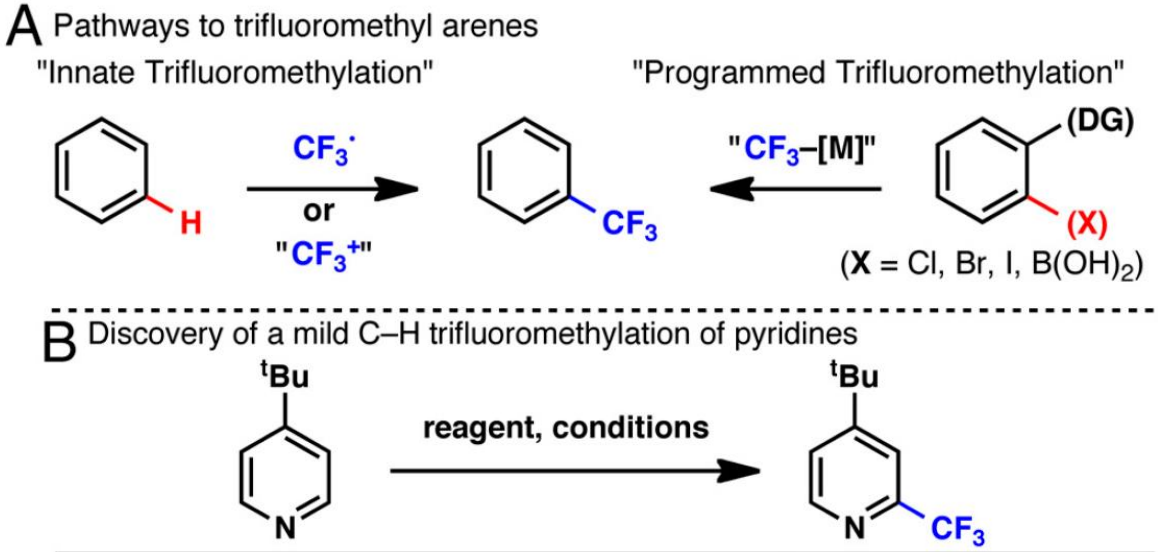
Science, **2013**, *341*,878-883

Top 18 best sell drugs in 2012

1 **NexIUM** (Esomeprazole)  AstraZeneca $5,989 Million ANTIULCERANTS	2 **Abilify** (Aripiprazole)  Otsuka $5,870 Million ANTIPSYCHOTICS	3 **Crestor** (Rosuvastatin)  AstraZeneca $5,092 Million CHOLEST&TRIGLY.REGULATOR	4 **Advair Diskus** (Fluticasone Propionate)  GlaxoSmithKline $4,889 Million CORTICOIDS	5 **Cymbalta** (Duloxetine)  Lilly $4,720 Million ANTIDEPRESS.& MOOD STAB.	6 **Humira** (Adalimumab)  abbvie $4,609 Million SPEC ANTIRHEUMATIC AGENT
7 **Enbrel** (Etanercept)  AMGEN $4,337 Million SPEC ANTIRHEUMATIC AGENT	8 **Remicade** (Infliximab)  Centocor $3,876 Million IMMUNOSUPPRESSIVE AGENTS	9 **Copaxone** (Glatiramer Acetate)  TEVA $3,581 Million IMMUNOSTIM AG EX INTFRON	10 **Neulasta** (Pegfilgrastim)  AMGEN $3,460 Million IMMUNOSTIM AG. EX. INTFRON.	11 **Singulair** (Montelukast)  MERCK $3,300 Million ANTILEUK ANTIASTHMATICS	12 **Rituxan** (Rituximab)  Genentech IN BUSINESS FOR LIFE $3,197 Million ALL OTH. ANTINEOPLASTICS
13 **Plavix** (Clopidogrel)  Bristol-Myers Squibb sanofi aventis $2,971 Million PLATELET AGGR.INHIBITORS	14 **Atripla** (Emtricitabine, Tenofovir Disoproxil & Efavirenz)  Bristol-Myers Squibb $2,899 Million HIV ANTIVIRALS	15 **Spiriva HandiHaler** (Tiotropium)  Boehringer Ingelheim $2,833 Million CHR. OBS. PULMONARY DIS.	16 **OxyContin** (Oxycodone)  PURDUE $2,808 Million NARCOTIC ANALGESICS	17 **Januvia** (Sitagliptin)  MERCK $2,670 Million DPP-IV INHIBITOR A-DIABS	18 **Avastin** (Bevacizumab)  Genentech IN BUSINESS FOR LIFE $2,661 Million ALL OTH. ANTINEOPLASTICS

9/12 Heterocyclic compound, 4/12 contain F, 6/18 monoclonal antibody

Practical and innate carbon-hydrogen functionalization of heterocycles



Entry	Reagent	Conditions[d]	Yield
1	Togni's reagent[a]	$K_2S_2O_8$, $AgNO_3$, TFA, DCM/H_2O	n.r.
2	Umemoto's reagent[b]	$K_2S_2O_8$, $AgNO_3$, TFA, DCM/H_2O	n.r.
3	TMS-CF_3[c]	NaF, DCM	n.r.
4	TMS-CF_3	$K_2S_2O_8$, $AgNO_3$, TFA, DCM/H_2O	n.r.
5	TMS-CF_3	tBuOOH, $FeSO_4$, $AgNO_3$, TFA, DCM/H_2O	n.r.
6	$K(MeO)_3B$-CF_3	$K_2S_2O_8$, $AgNO_3$, TFA, DCM/H_2O	n.r.
7	$K(MeO)_3B$-CF_3	tBuOOH, $AgNO_3$, TFA, DCM/H_2O	n.r.
8	KF_3B-CF_3	$K_2S_2O_8$, $AgNO_3$, TFA, DCM/H_2O	n.r.
9	KF_3B-CF_3	$K_2S_2O_8$, $Cu(OTf)_2$, TFA, DCM/H_2O	n.r.
10	**$NaSO_2CF_3$**	**$K_2S_2O_8$, $AgNO_3$, TFA, DCM/H_2O, 50 °C**	**20 %**

Proc. Natl Acad. Sci. USA. **2011**, *108*, 14411-14425

A new reagent for direct difluoromethylation

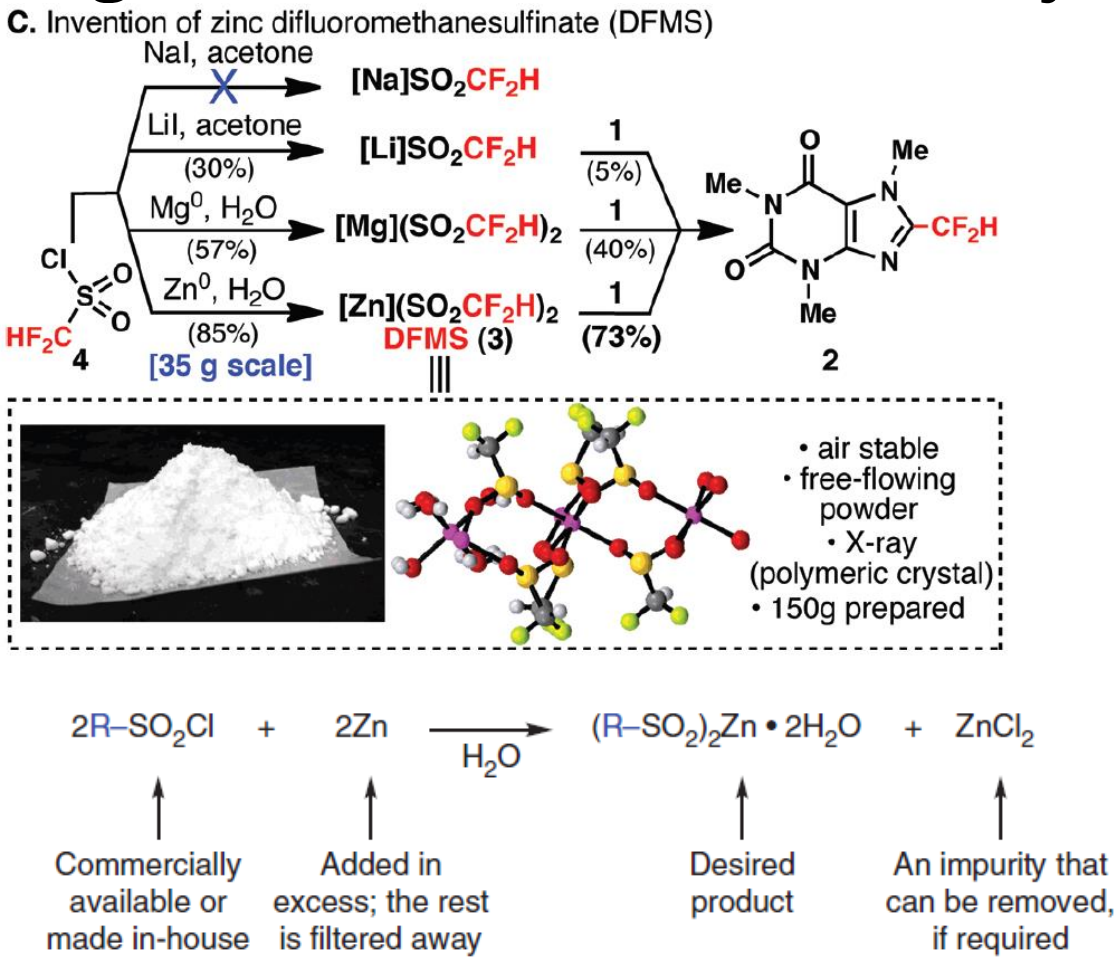
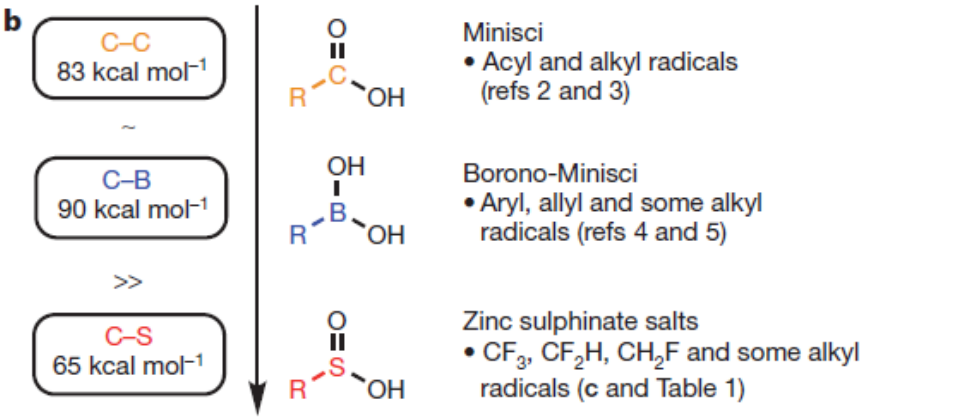


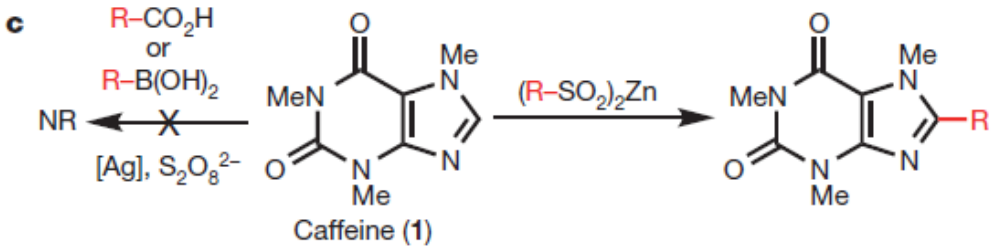
Figure 2 | The synthesis of zinc bis(alkanesulfinate) reagents.

J. Am. Chem. Soc, **2012**, *134*, 1494-1497

Nature protocols, **2013**, *8*, 1042-1043

Practical and innate carbon-hydrogen functionalization of heterocycles





The $(RSO_2)_2Zn$ toolkit was prepared by: $R\text{–}SO_2Cl \xrightarrow[H_2O]{Zn} (R\text{–}SO_2)_2Zn$

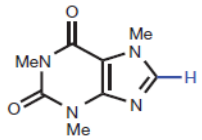
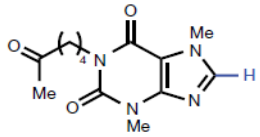
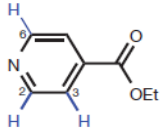
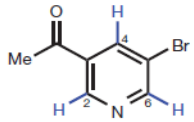
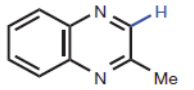
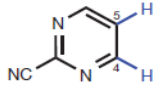
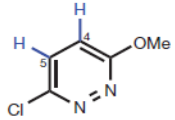
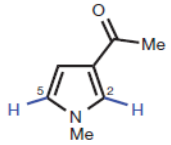
R group	Acronym	Amount prepared	Sigma–Aldrich catalogue number
$-CF_3$ (X-ray)	TFMS (**A**)	>500 g	L510106
$-CF_2H$ (X-ray)	DFMS (**B**)	>500 g	L510084
$-CH_2CF_3$	TFES (**C**)	>100 g	L511234
$-CH_2F$	MFMS (**D**)	37 g	—
$-CH(CH_3)_2$	IPS (**E**)	>200 g	L511161
$-(CH_2CH_2O)_3CH_3$	TEGS (**F**)	20 g	—

Nature, **2012**, *492*, 95-100

Substrate scope of the zinc sulphinate salt toolkit

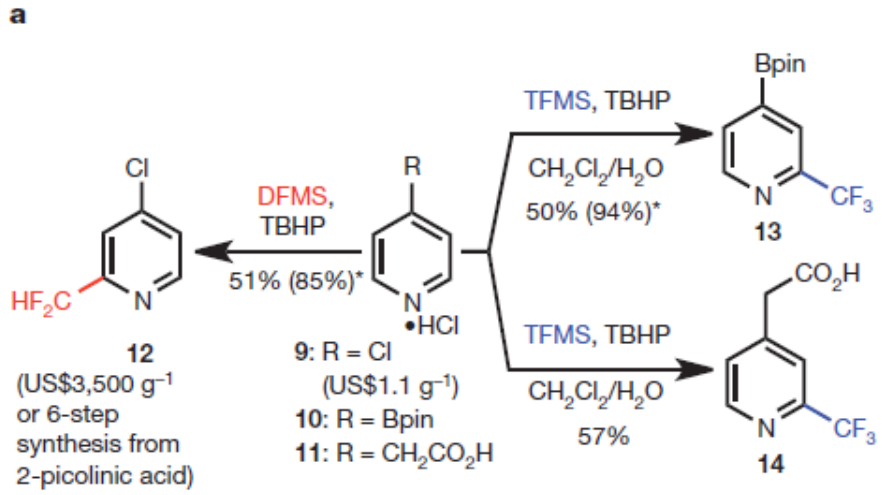
Zinc sulphinate salt

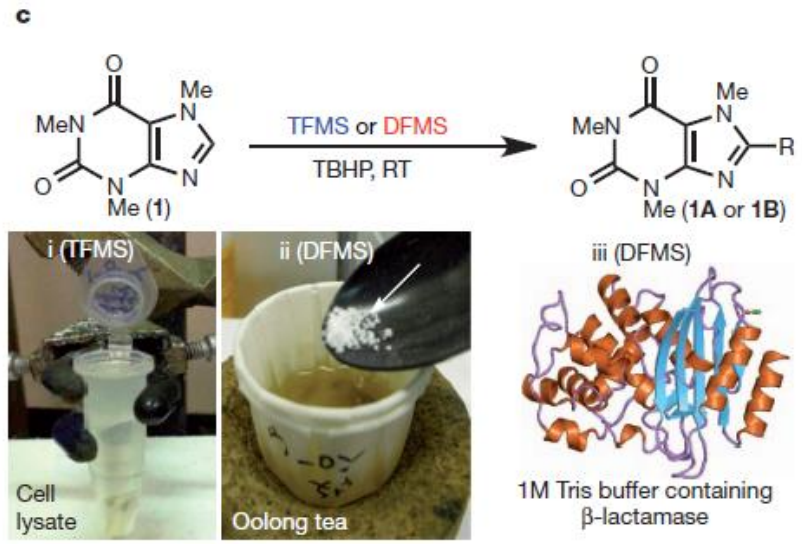
Open flask, operational simplicity, >50 examples

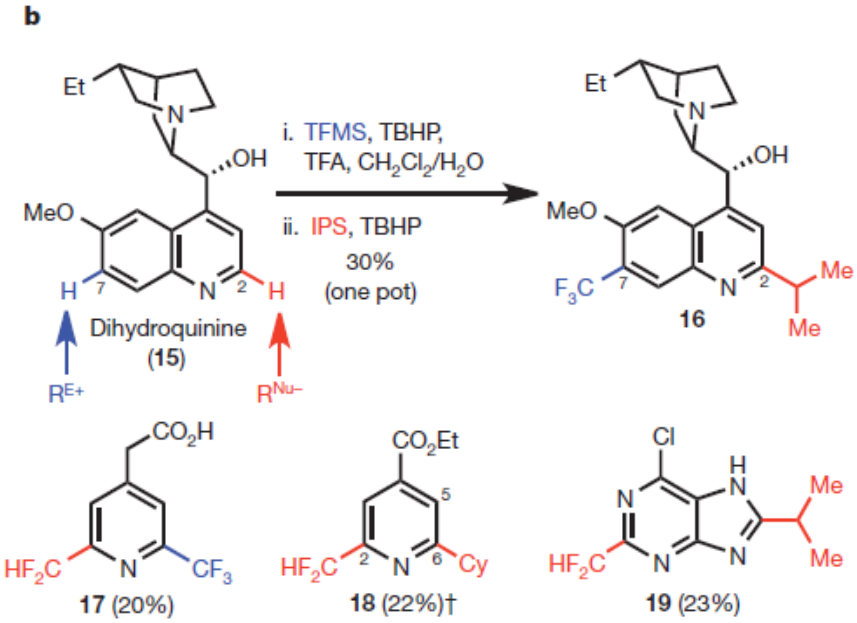
	Heterocycle	Zn salt, R					
		CF_3 (**A**)	CF_2H (**B**)	CH_2CF_3 (**C**)	CH_2F (**D**)	$CH(CH_3)_2$ (**E**)	$(CH_2CH_2O)_3CH_3$ (**F**)
1		89 (100)† **1A**	73 (57)†§§ **1B**	51# **1C**	80# **1D**	41** **1E**	40†† **1F**
2		79 (100)† **2A**	72 (41)†§§ **2B**	44# **2C**	75# **2D**	37** **2E**	49†† **2F**
3		35 (77)† [4:1 C2:C3] **3A**	66 (100)† [only C2] **3B**	18 (85)# [4:1 C2:C3] **3C**	73¶‡‡ [17:1 C2:C2&C6] **3D**	47§ [C2:C2&C6 1.4:1] **3E**	41†† [only C2] **3F**
4		66 (65)†§§ [2.3:1 C6:C2] **4A**	60 (96)† [C2:C6:C4 3:2:1] **4B**	33# [1.4:1 C6:C4] **4C**	NR **4D**	41†† [only C6] **4E**	NR **4F**
5		75 (100)† [5 products] **5A**	50 (67)† **5B**	31 (77)‡ **5C**	56# **5D**	43** **5E**	32** **5F**
6		42 (44)‖ [2.7:1 C4:C5] **6A**	21 (44)‖ [1.6:1 C4:C5] **6B**	21** [only C5] **6C**	NR **6D**	46** [2.1:1 C4:C5] **6E**	16†† [3.4:1 C4:C5] **6F**
7		45 (90)‖ [only C4] **7A**	57 (71)‖ [6:1 C4:C5] **7B**	NR **7C**	NR **7D**	49** [10:1 C4:C5] **7E**	32 (38)†† [only C4] **7F**
8		76 (91)† [7.4:1 C2:C5] **8A**	65 (100)† [only C2] **8B**	58** [1.4:1 C2:C5] **8C**	40§ [only C2] **8D**	17** [only C2] **8E**	10 (43)†† [only C2] **8F**

50/52 have not been reported before!

Substrate scope of the zinc sulphinate salt toolkit

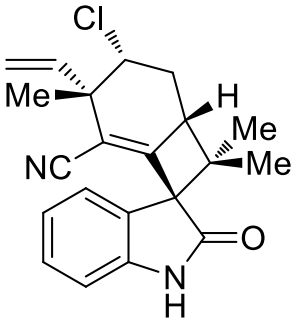






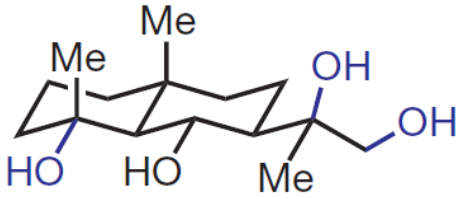
- C-H fuctionalization of medicinally important hetercycles
- Ten different Zinc sulphinate compound developed four of them are available from Sigma-Aldrich
- Mide reaction conditions
- Now widely used in medicinal chemistry (Pfizer)

Summary



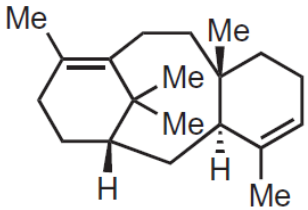
welwitindolinone A

Nature, **2007**, *446*, 404-406



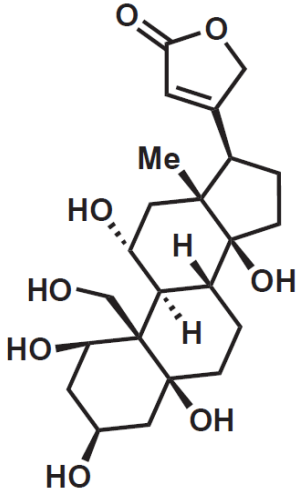
8: eudesmantetraol

Nature, **2009**, *459*, 824-828



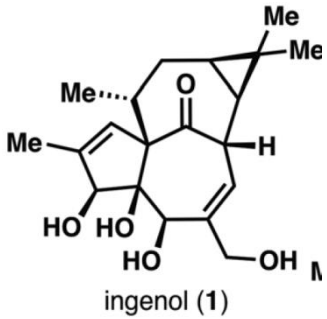
Taxadiene

Nature chem. **2012**, *4*, 21-25



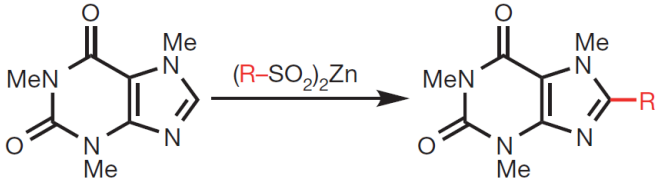
ouabagenin (**1**)

Science, **2013**, *339*, 59-63



ingenol (**1**)

Science, **2013**, *341*, 878-883



Caffeine (**1**)

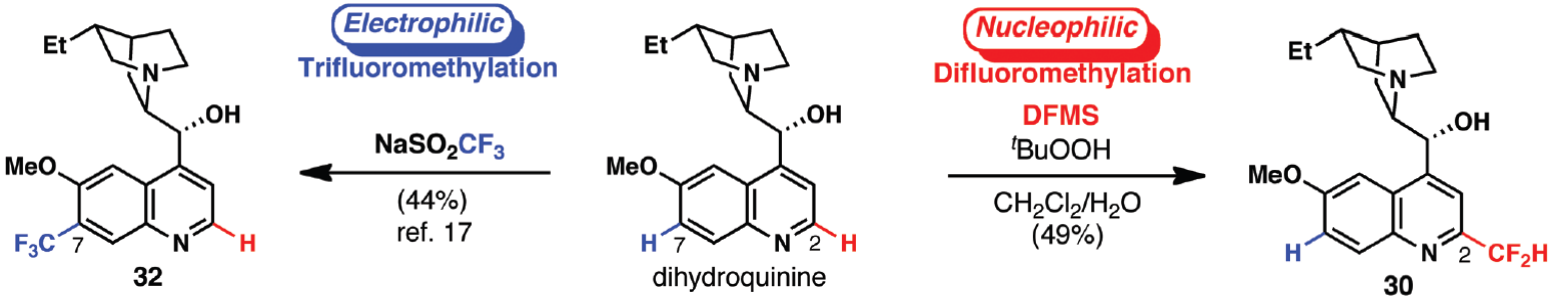
R = CF_3, CHF_2, CH_2F

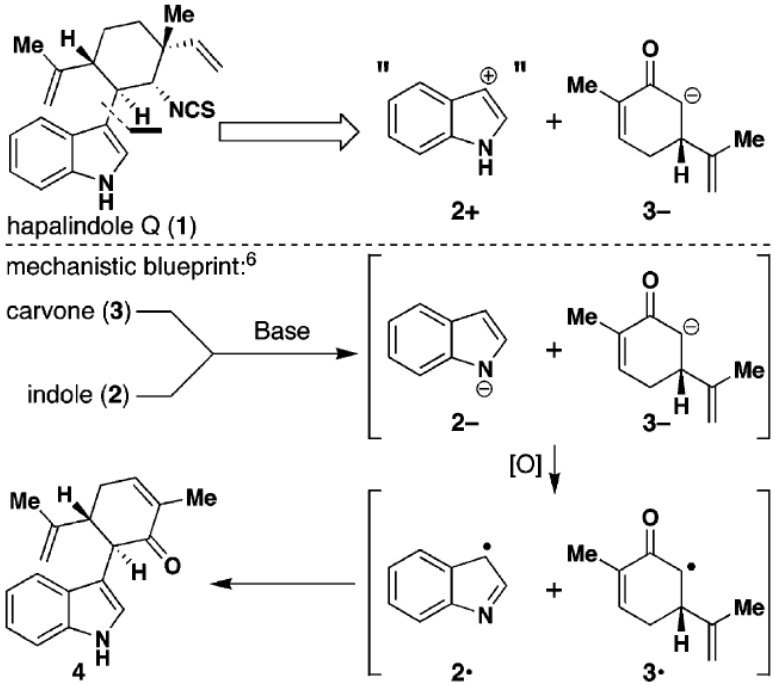
Nature, **2012**, *492*, 95-100

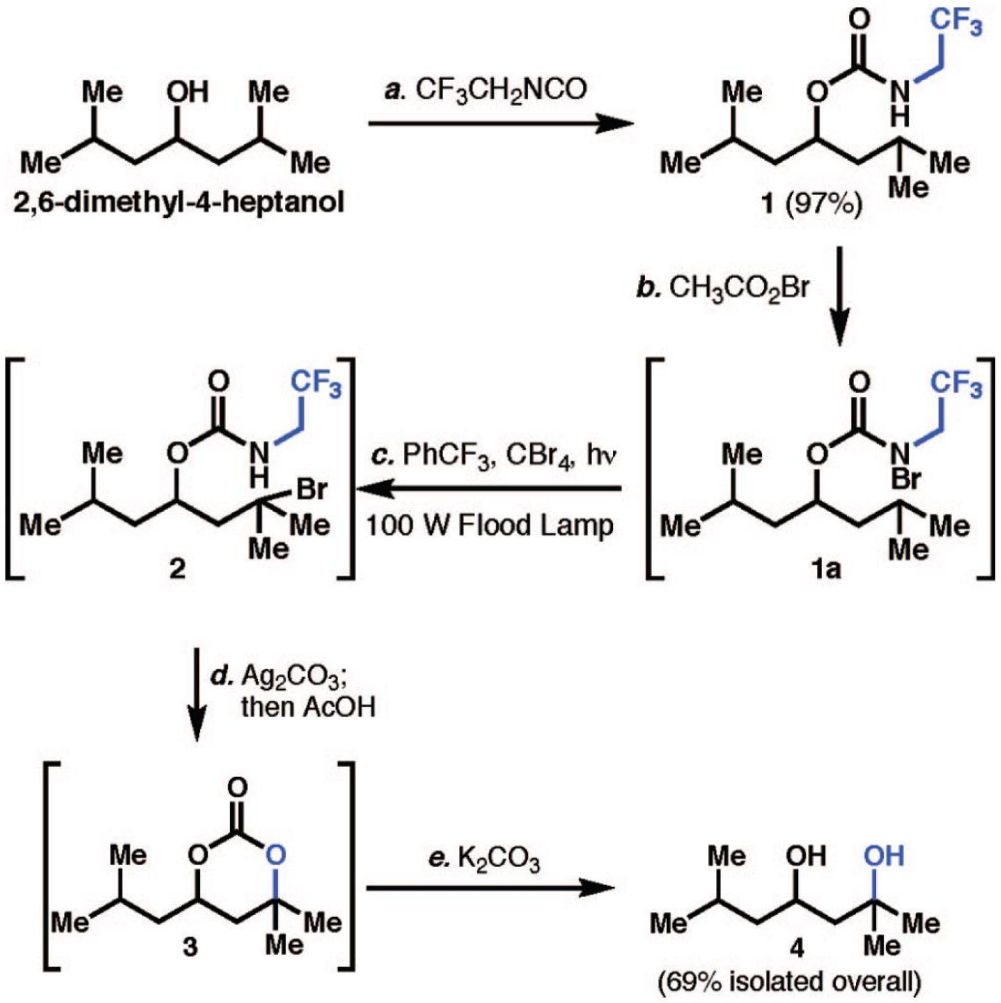
- New metods is more important than complex molecular
- Drug or bioactivity compound as target (from chemistry to industrial)
- Biomimetic synthesis (protecting group free/cyclo-oxid phase)
- Large scale synthesis
- More efficient synthesis route (multiple compound in one synthesis route/ high yield/shorter steps)
- Useful chemistry (Publish papers and earn money)

Thanks!

Reactivity of fluoroalkyl radicals: $\bullet CF_3$ and $\bullet CF_2H$






Me
OH
Me
Me
Me
2,6-dimethyl-4-heptanol
a. CF3CH2NCO
O
CF3
Me
O
N
H
Me
Me
Me
1 (97%)
b. CH3CO2Br
O
CF3
Me
O
N
Br
Me
Me
Me
1a
c. PhCF3, CBr4, hν
100 W Flood Lamp
O
CF3
Me
O
N
H
Br
Me
Me
Me
2
d. Ag2CO3;
then AcOH
O
Me
O
O
Me
Me
Me
3
e. K2CO3
Me
OH
OH
Me
Me
Me
4
(69% isolated overall)