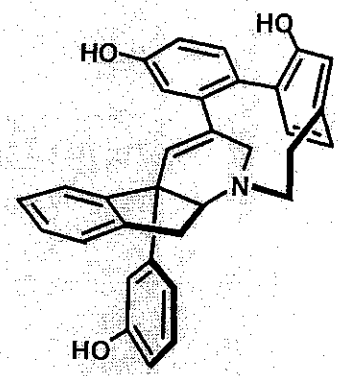
Literature Seminar (D2 part) / 2007.05.02./ Kuramochi Akiyoshi

A Key Person: Phil. S. Baran
Let's consider total synthesis over his acievements

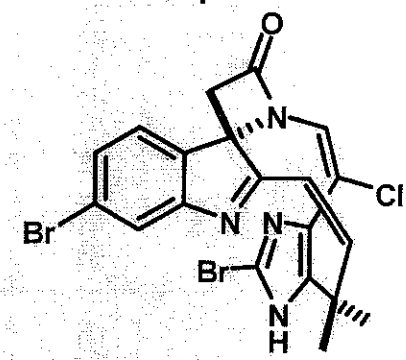
Chapter 1: Baran's 8 rules

Chapter 2



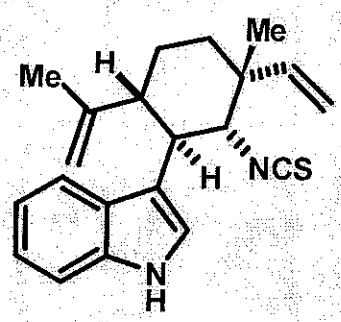
Haouamine A
(JACS 2006, *128*, 3908.*)*

Chapter 3



Chartelline
(JACS 2006, *128*, 14028.*)*

Chapter 4



Hapalindole
(JACS 2004, *126*, 7450.*)*

Chapter 5

How about Phil S. Baran?

Chapter 6

My view of organic synthsis

His other works

- Okaramine N (*JACS* 2003, *125*, 5628.) [Postdoc at Corey]
- Sceptrin (*JACS* 2004, *126*, 3726, *JACS* 2007, *129*, 4762.)
- Stephacidin A (*ACIE* 2005, *44*, 606.)
- Welwitindolinone A (*JACS* 2005, *127*, 15394.)

Chap. 1

Total synthesis of marine natural products without using protecting groups

Phil S. Baran[1], Thomas J. Maimone[1] & Jeremy M. Richter[1]

The field of organic synthesis has made phenomenal advances in the past fifty years, yet chemists still struggle to design synthetic routes that will enable them to obtain sufficient quantities of complex molecules for biological and medical studies. Total synthesis is therefore increasingly focused on preparing natural products in the most efficient manner possible. Here we describe the preparative-scale, enantioselective, total syntheses of members of the hapalindole, fischerindole, welwitindolinone and ambiguine families, each constructed without the need for protecting groups—the use of such groups adds considerably to the cost and complexity of syntheses. As a consequence, molecules that have previously required twenty or more steps to synthesize racemically in milligram amounts can now be obtained as single enantiomers in significant quantities in ten steps or less. Through the extension of the general principles demonstrated here, it should be possible to access other complex molecular architectures without using protecting groups.

(Baran, P. S. et al. *Nature* 2007, *446*, 404.)

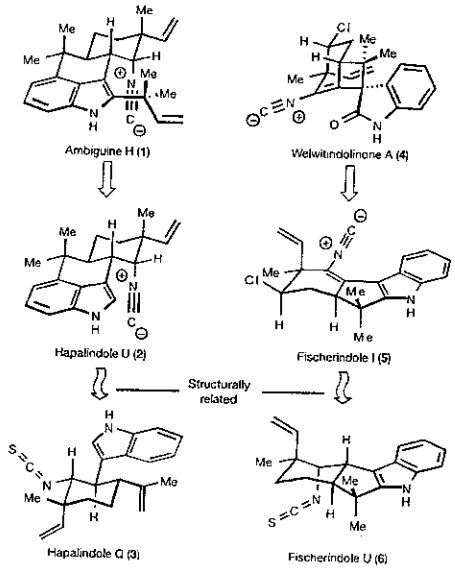


Figure 2 | Representative members of the ambiguine, fischerindole, hapalindole and welwitindolinone alkaloid families and proposed biosynthetic relationships.

 # Synthetic schemes leading to two compounds is shown in the appendix.
(no comments in this seminar.)

In some cases, the use of protecting groups may offer a more efficient or even the sole solution ... such as poly-ketides, -peptides, -saccharides, and -nucliotides.

Baran's 8 rules

(1) redox reactions that do not form C-C bonds should be minimized

(2) the percentage of C-C bond forming events within the total number of steps in a synthesis should be maximized

(3) disconnections should be made to maximize convergency

(4) the overall oxidation level of intermediates should linearly escalate during assembly of the molecular framework
(except in cases where there is strategic benefit such as an asymmetric reduction)

(5) where possible, cascade (tandem) reactions should be designed and incorporated to elicit maximum structural change per step

(6) the innate reactivity of functional groups should be exploited so as to reduce the number of (or perhaps even eliminate) protecting groups

(7) effort should be spent on the invention of new methodology of facilitate the aforementioned criteria and to uncover new aspects of chemical reactivity

(8) if the target molecule is of natural origin, biomimetic pathways (either known or proposed) should be incorporated to the extent that they aid the above considerations

⇩

short synthesis

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Chap. 2

Total Synthesis of (±)-Haouamine A

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Received January 15, 2006; E-mail: pbaran@scripps.edu

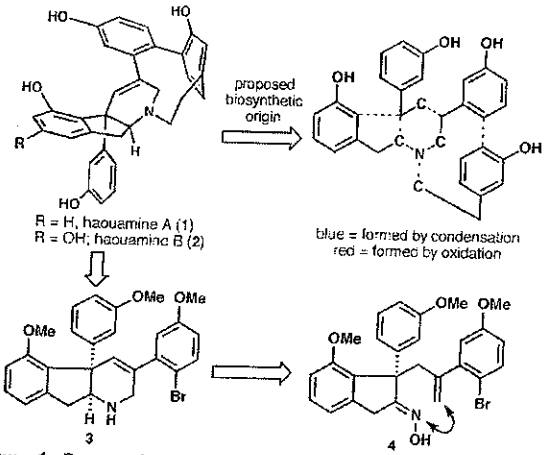


Figure 1. Retrosynthetic analysis of haouamine A (1).

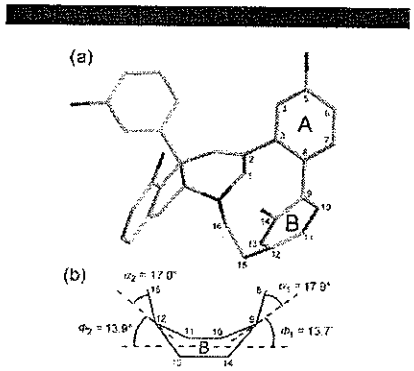


Figure 1. (a) X-ray structure of haouamine A (with the original atom and ring numbering); (b) noteworthy derivations from planarity in ring B.

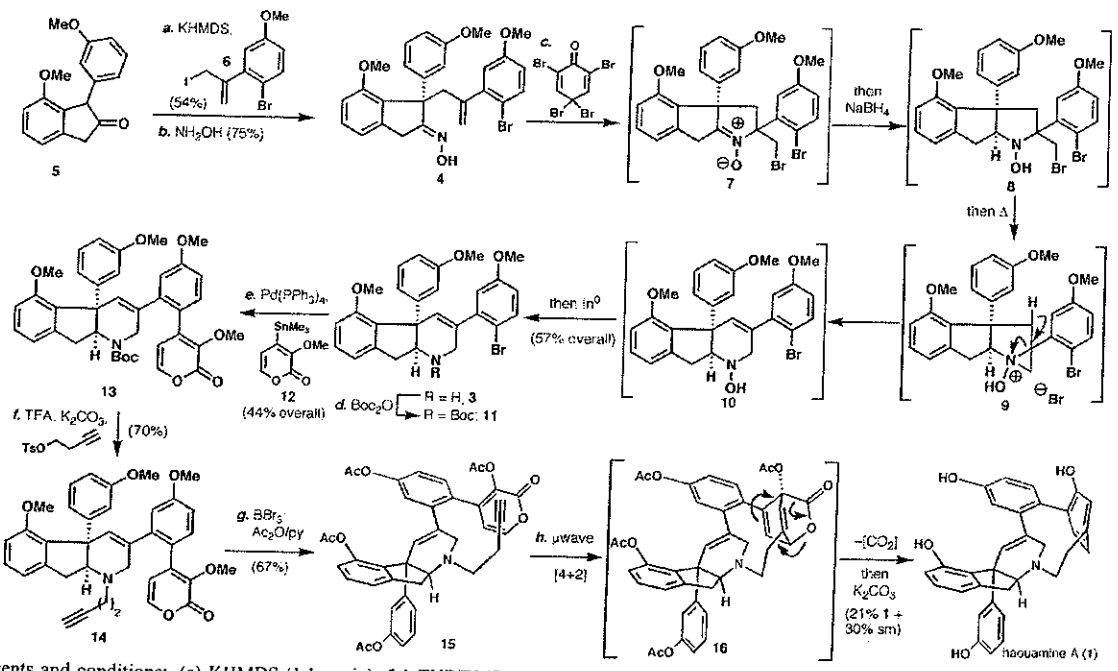
(Wipf, P. et al. *OL* 2006, *8*, 1901.)

How should bent benzene ring B be constructed?

Not surprisingly, several standard appraoches such as transitional metal based biaryl coupling, Witkop photocyclization, and intramolecular alkylation all failed.

... a nonaromatic conformational mimic of the bent aromatic ring might serve as a viable precursor if it wer able to undergo subsequent aromatization.
<u>The pyrone-alkyne Diels-Alder reaction</u> fits these criteria.

Scheme 1. Short Total Synthesis of 1[a]



[a] Reagents and conditions: (a) KHMDS (1.1 equiv), 5:1 THF/DMPU, 0 °C, 30 min; **6** (1.5 equiv), −78 to 23 °C, 54%; (b) $NH_2OH{\cdot}HCl$ (20 equiv), NaOAc (15 equiv), EtOH, reflux, 24 h, 75%; (c) 2,4,4,6-tetrabromo-2,5-cyclohexadienone (2.2 equiv), DCE, 0 °C, 30 min, then $NaBH_4$ (5.0 equiv), EtOH, 50 °C, 1 h; In powder (2.0 equiv), 2:1 EtOH/saturated aqueous NH_4Cl, reflux, 3.5 h, 57% overall; (d) Boc_2O (1.2 equiv), DCM, 30 min; (e) **12** (1.6 equiv), $Pd(PPh_3)_4$ (0.1 equiv), CuI (0.2 equiv), toluene, reflux, 12 h, 44% overall; (f) 10:1 DCM/TFA, 3 h; 4-tosyloxybutyne (5.0 equiv), K_2CO_3 (2.5 equiv), CH_3CN, reflux, 6 h, 70%; (g) BBr_3 (10.0 equiv), DCM, −78 to 23 °C, 1:1 Ac_2O/pyr, 3 h, 67%; (h) DCB (0.001 M), 250 °C, BHT (7.7 equiv), 10 h; PTLC; K_2CO_3 (4.0 equiv), MeOH, 30 min, 21% **1** + 30% **15**. BHT = 2,6-di-*tert*-butylmethyl phenol; DCE = 1,2-dichloroethane; KHMDS = potassium hexamethyldisilazide; DCB = *o*-dichlorobenzene.

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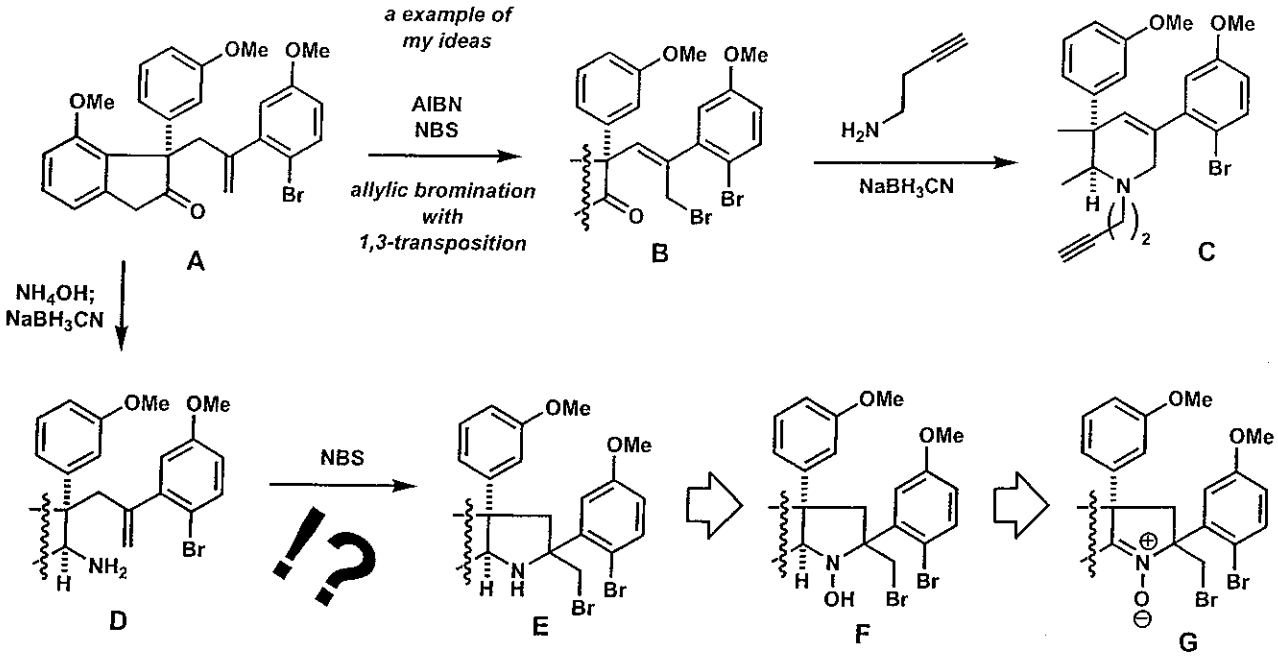
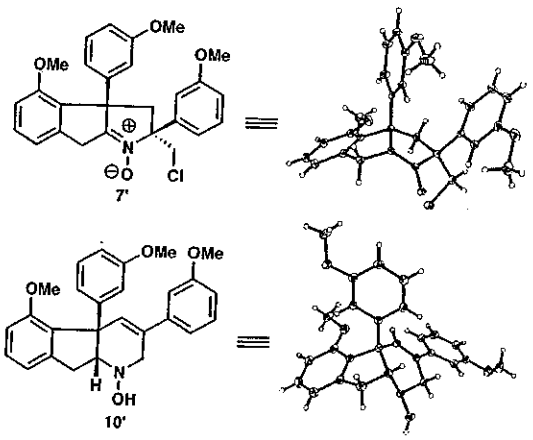
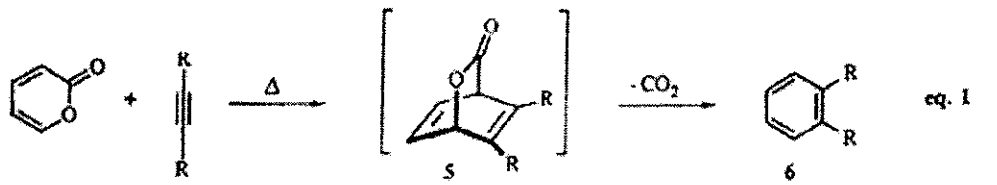
Cascade cyclization for indenotetrahydropyridine ring?



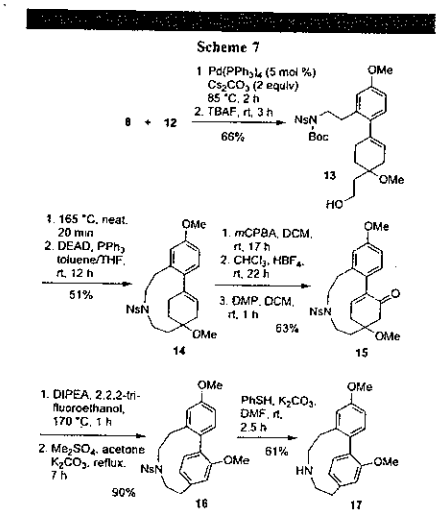


How should bent benzene ring B be constructed?



Tetrahedron 1992, *48*, 9111.

Wipf's methodology



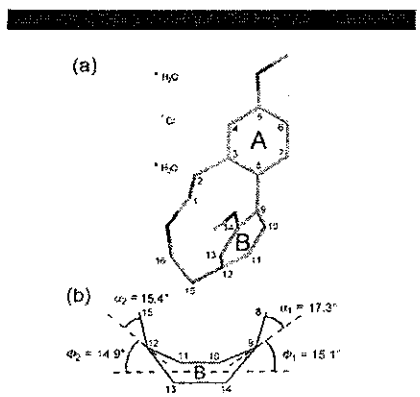


Figure 2. (a) X-ray structure of **17**·HCl (with atom and ring numbering based on haouamine A; the structure also contains two water molecules and a chloride, which are labeled separately); (b) characteristic angles in ring B.

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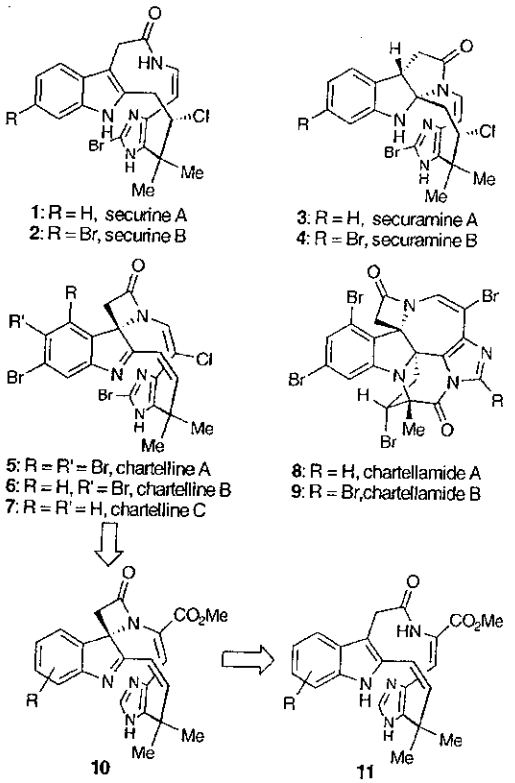
Chap. 3

Natural Product Synthesis

A Remarkable Ring Contraction En Route to the Chartelline Alkaloids**

Phil S. Baran, Ryan A. Shenvi, and Christos A. Mitsos*

ACIE 2005, *44*, 3714.

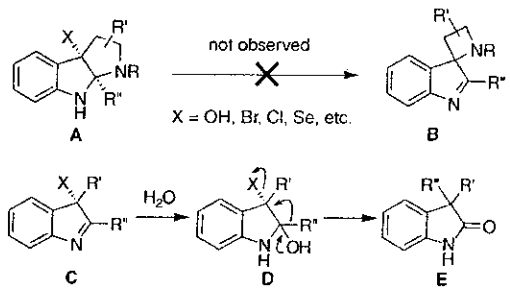


Scheme 1. Structures of the chartellines, chartellamides, securines, and securamines, and the retrosynthetic analysis of the carbocyclic skeleton.

With such a dense array of sensitive and exotic functionalities, such as *spiro-β-lactam, indolenine, chloroenamide, and 2-Br-imidazole units ...*

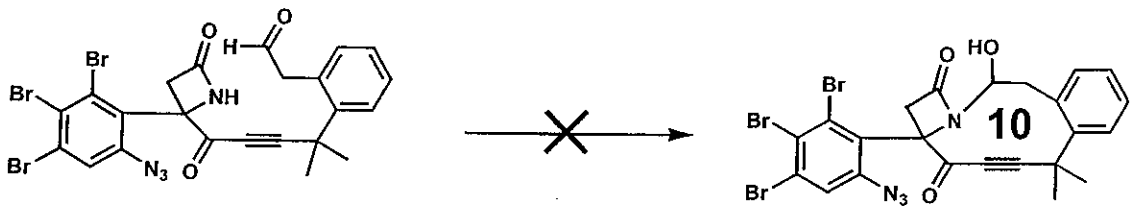
It is understandable why no member of this family has yet succumbed to total synthesis since *their isolation over two decades ago.*

How should spiro-β-lactam be constructed?



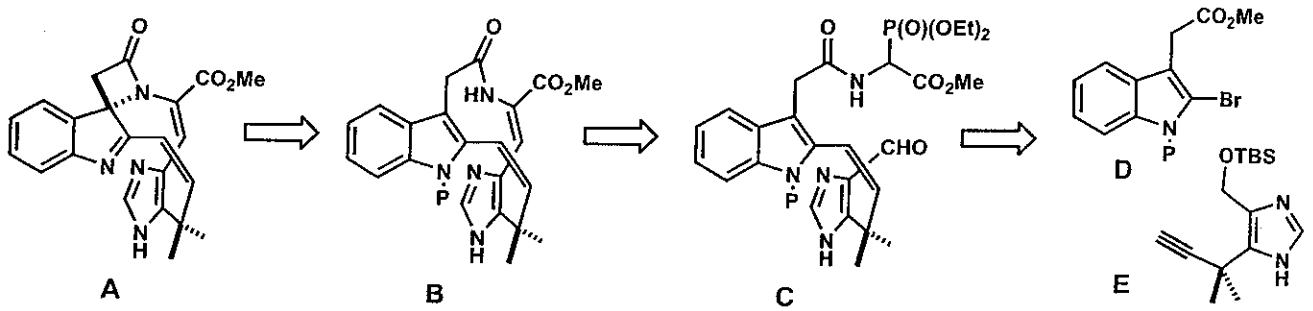
Scheme 2. The known reactivity profile of oxidized indoles suggests that the proposed rearrangement (**11**→**10**) is unlikely to occur.

Morimoto, T.; Fukuyama, T. et al. PhD Thesis (2006)



Notwithstanding this bleak outlook (= no precedents), we hypothesized that π-stacking and confromational effects in the macrocycle 11 would provide sufficient driving force for a bromine induced ring contraction to yield 10 (via an intermediate of type A).

[Retrosynthetic Analysis]



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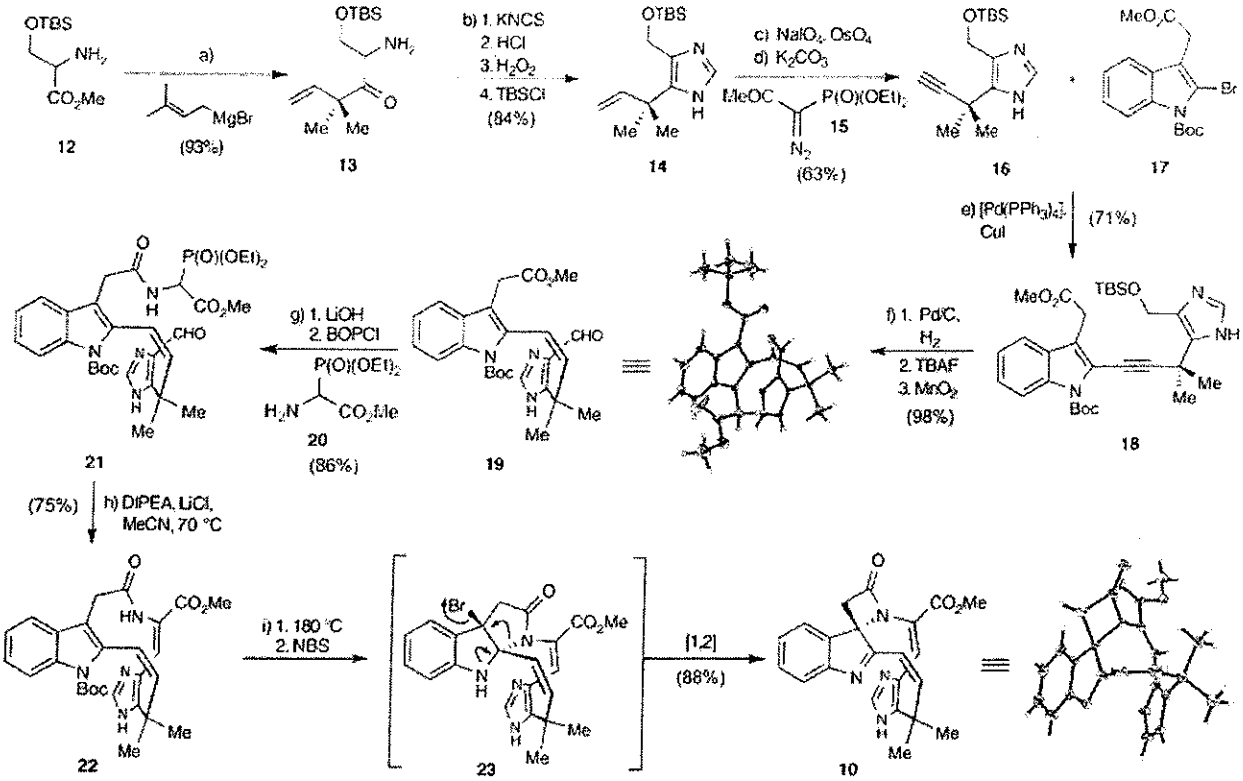
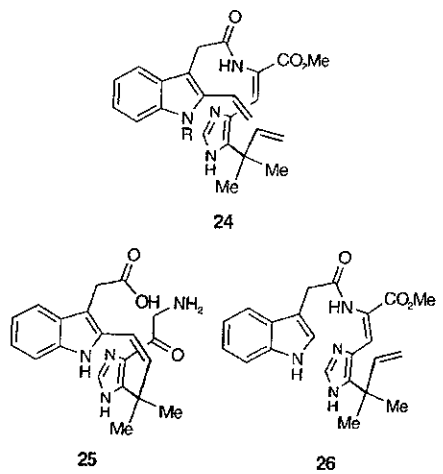


Scheme 3. Construction of the complete chartelline, securine, and securamine carbocyclic skeletons. Reagents and conditions: a) prenylmagnesium bromide, THF, −78 °C, 93%; b) 1. KNCS (20 equiv), NH_4Cl (20 equiv), toluene 105–110 °C, 4 h; 2. 6 N HCl, 25 °C, 20 min; 3. i. H_2O_2 (11 equiv), THF, 25 °C, 6 h; ii. 2 M NaOH/saturated aq $NaHCO_3$ (4:1), 25 °C, 1 h; 4. TBSCl (1.0 equiv), Et_3N (1.0 equiv), CH_2Cl_2, 25 °C, 84% from **13**; c) $NaIO_4$ (3.0 equiv), OsO_4 (0.03 equiv), THF/H_2O (2:1), 25 °C, 18 h; d) **15** (1 equiv), K_2CO_3 (1.5 equiv), MeOH, 25 °C, 6 h, 63% from **14**; e) $[Pd(PPh_3)_4]$ (0.3 equiv), CuI (0.7 equiv), $iPrNH_2$ (10 equiv), DME, 70 °C, 30 min, 71%; f) 1. H_2, 10% Pd/C (0.1 equiv), $MgSO_4$ (2 equiv), EtOH, 25 °C, 4 h; 2. TBAF (1.1 equiv), THF, 0—25 °C, 3 h; 3. MnO_2 (20 equiv), CH_2Cl_2, 25 °C, 8 h, 98% from **18**; g) 1. LiOH (3 equiv), THF/H_2O (4:1), 25 °C, 5 h; 2. **20** (2.6 equiv), BOPCl (1.5 equiv), DIPEA (2.0 equiv), 0 °C, 2 h, 86% from **19**; h) LiCl (9.0 equiv), DIPEA (20 equiv), CH_3CN, 70 °C, 4 h, 75%; i) 1. 180 °C, 8 min; 2. NBS (1.0 equiv), $KHCO_3$ (20 equiv), THF/H_2O, 35 min, 88% from **22**. TBS = *tert*-butyldimethylsilyl , KNCS = potassium thiocyanate, Boc = *tert*-butoxycarbonyl, DME = 1,2-dimethoxyethane, TBAF = tetra butylammonium fluoride, BOPCl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride, DIPEA = diisopropylethylamine, NBS = *N*-bromosuccinimide.

How many unpublished data???



Scheme 4. Selected dead-end routes to the chartelline, securamine, and securine carbocyclic skeletons.

others:

- **CO_2Me appendage (why? for cyclization?)**
- **indole coupling via *oxidation-reduction*. (not like Baran)**

... Completion of the total synthesis of the chartellines and related alkaloids will be reported shortly.

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Total Synthesis of (±)-Chartelline C

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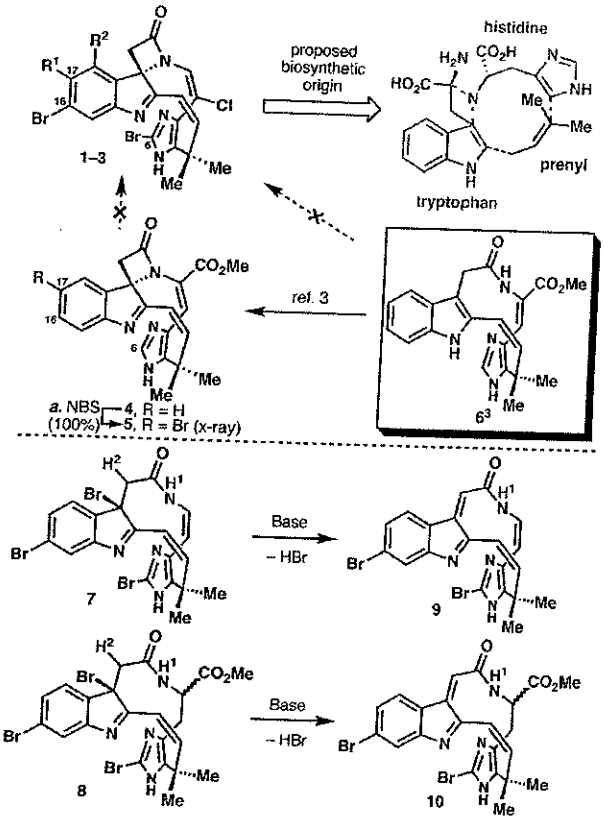
Received August 17, 2006; E-mail: pbaran@scripps.edu

***JACS* 2006, *128*, 14028.**

Scheme 1. Postuated Biosynthetic Origins of the Chartelline Alkaloids [Chartelline C (1): R^1 = H, R^2 = H; Chartelline A (2): R^1 = Br, R^2 = Br; Chartelline B (3): R^1 = H, R^2 = Br] and Some Informative Dead-Ends

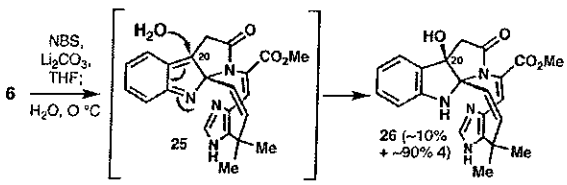


Baran's belief was defeated.

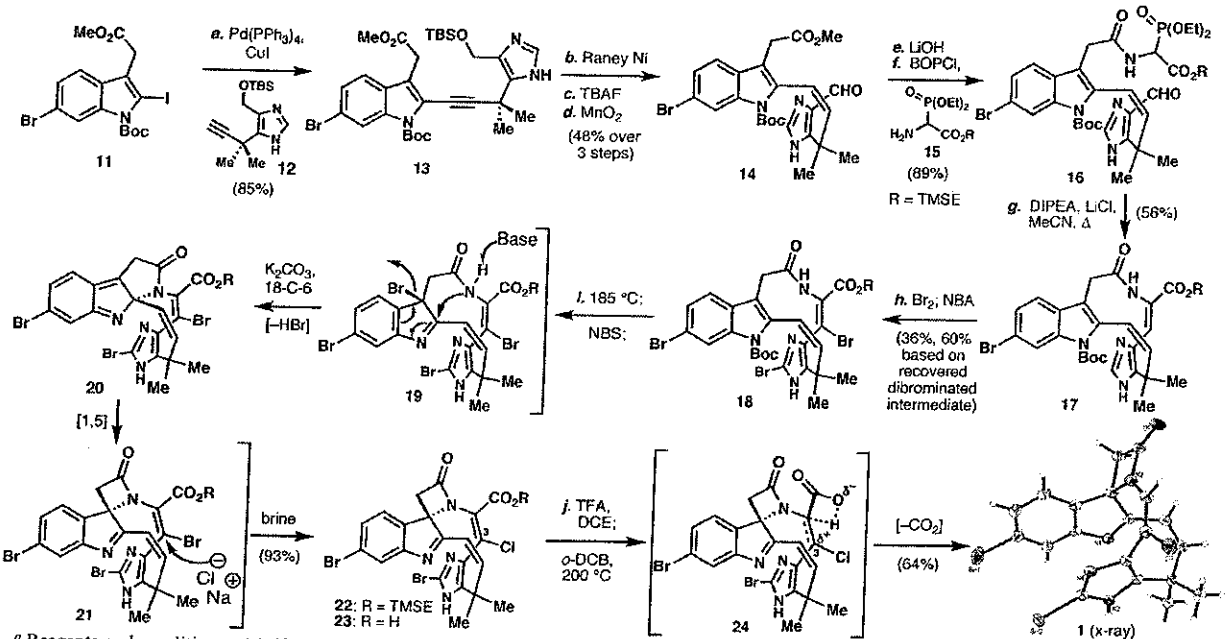
late-stage Br introduction failed.

Decrease of acidity at N-H proton should cause the failure of cyclization.

Scheme 3. C-20 Hydroxy-Pyrroloindoline Formed During the Rearrangement of **6** — **4**



Scheme 2. Total Synthesis of (±)-Chartelline C[a]



[a] Reagents and conditions: (a) **12** (0.9 equiv), CuI (0.2 equiv), $Pd(PPh_3)_4$ (0.1 equiv), DME/Et_3N (1:1), 50 °C, 7 h, 85%; (b) Raney Ni, MeOH, 20 °C, 5 h, 80%; (c) TBAF (1.1 equiv), THF, 20 °C, 4 h; (d) MnO_2 (20 equiv), CH_2Cl_2, 20 °C, 8 h, 60% overall; (e) LiOH·H_2O (3 equiv), THF/H_2O 4:1, 20 °C, 3.5 h; (f) **15** (2.6 equiv), BOPCl (1.5 equiv), DIPEA (2 equiv), CH_2Cl_2, 0 °C, 9 h, 89% overall; (g) LiCl (10 equiv), DIPEA (20 equiv), MeCN, 70 °C, 6 h, 56%; (h) Br_2, (1.0 equiv), $CaCO_3$ (20 equiv), PhH, 20 °C, 6 h; then NBA (1 equiv), PhH, 20 °C, 12 h, 36%, 60% (see above); (i) 185 °C, 1.5 min (× 4); MeCN, 3 Å m.s., NBS (1 equiv), 20 °C; then 18-C-6, K_2CO_3, 20 °C, 1 h; then $NaHCO_3$ (sat. aq), then brine, 15 min, 93% (j) TFA/DCE 1:1, 20 °C, 4 h; o-DCB, 200 °C, 5 min, 64%.

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Chap. 4

Direct Coupling of Indoles with Carbonyl Compounds: Short, Enantioselective, Gram-Scale Synthetic Entry into the Hapalindole and Fischerindole Alkaloid Families

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Received April 13, 2004; E-mail: pbaran@scripps.edu

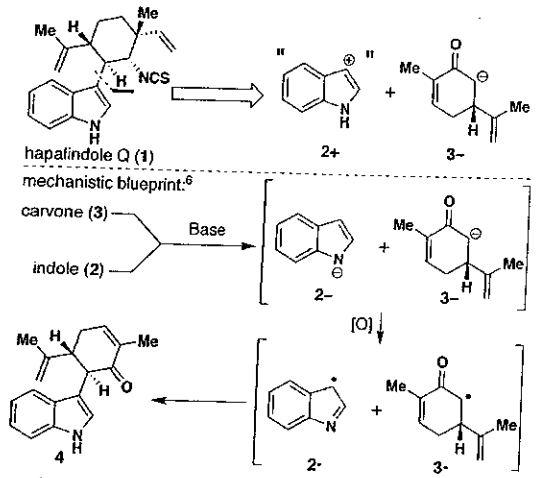
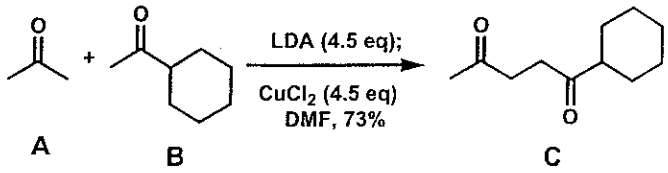
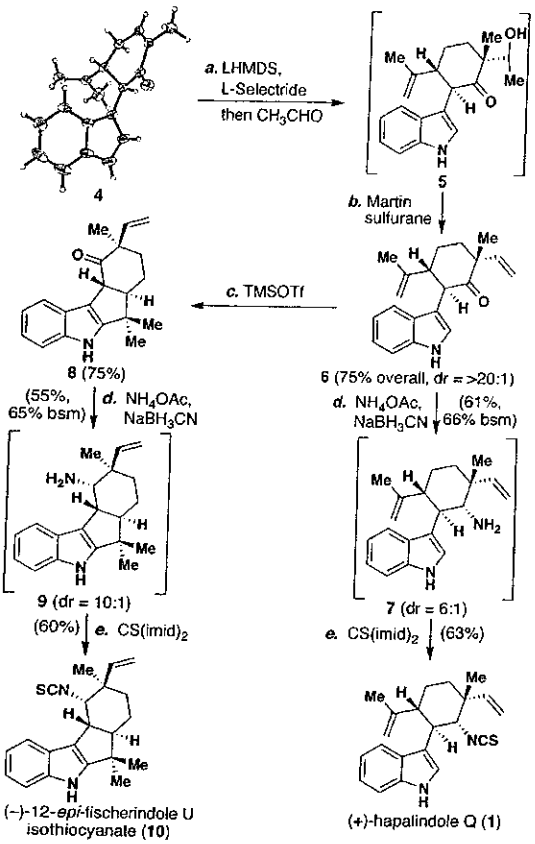


Figure 1. Retrosynthetic analysis of (+)-**1** leads to the invention of a direct coupling of indoles with carbonyl compounds.

One of precedents:
Saegusa, T. et al. *J. Am. Chem. Soc.* 1975, 97, 2912.



Scheme 1. Enantioselective Total Syntheses of (+)-**1** and (−)-**10**[a]



[a] Reagents and conditions: (a) LHMDS (1.5 equiv), THF, −78 °C, 20 min then L-Selectride (1.05 equiv), 1 h, then CH_3CHO (6.0 equiv), −78→23 °C, 2 h; (b) Martin sulfurane (1.1 equiv), $CHCl_3$, 10 min, 75% overall; (c) TMSOTf (3.0 equiv), MeOH (1.1 equiv), CH_2Cl_2, 0 °C, 1 h, 75% bsm; (d) $NaBH_3CN$ (10 equiv), NH_4OAc (40 equiv), MeOH, THF, 150 °C, 2 min, 61% (**7**); for **9**: same reagents, 23 °C, 48 h, 55%; (e) $CS(imid)_2$ (1.1 equiv), CH_2Cl_2, 0→23 °C, 3 h, 63% (**1**), 60% (**10**).

Total Synthesis of Hapaindole Q without Using Protecting Groups

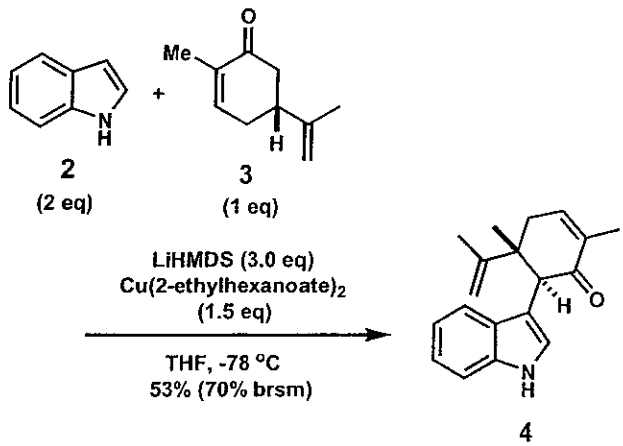
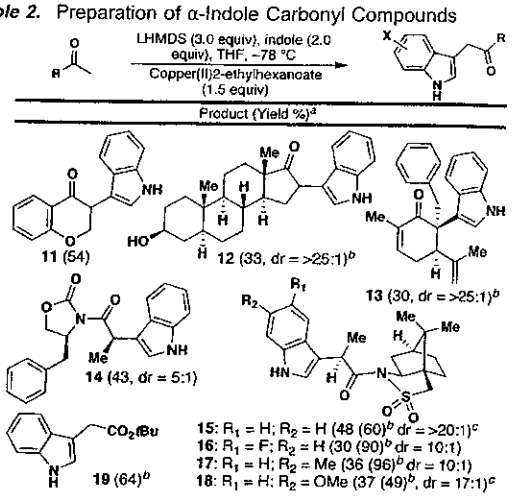


Table 2. Preparation of α-Indole Carbonyl Compounds



[a] Isolated yield after chromatography. [b] Yield based on recovered sm. [c] LDA used.

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Chap. 5

for his outstanding achievements in the art of organic synthesis

Woodward, R. B. (1965)

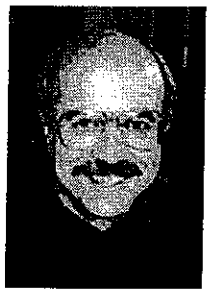
for his development of the theory and methodology of organic synthesis

Presentation Speech by Professor Salo Gronowitz in Nobel Prize.

Corey, E. J. (1990)

Corey has thus been rewarded with the Prize for three intimately connected contributions, which form a whole.
Through retrosynthetic analysis and introduction of new synthetic reactions, he has succeeded in preparing biologically important natural products.
Corey's contributions have turned the art of synthesis into a science.

1945 ***1990*** ***2000***



art with his intuition

systematize with retrosynthesis

application of retrosynthesis

???

We must synthesis Taxol in 3 stpes with a bathtub.

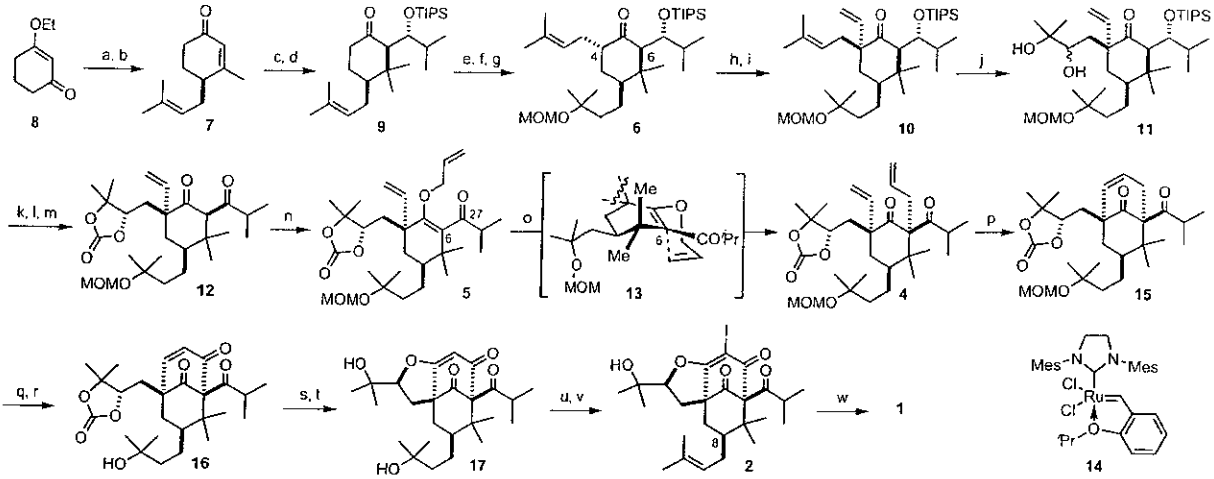
Baran's 8 rules

1) less redox reaction
2) more C-C formation
3) convergency
4) linear escalation of [O]
5) cascade reaction
6) no protecting groups
7) new methodology
8) biomimetic reaction

Haouamine A
Hapalindole Q
Chartelline

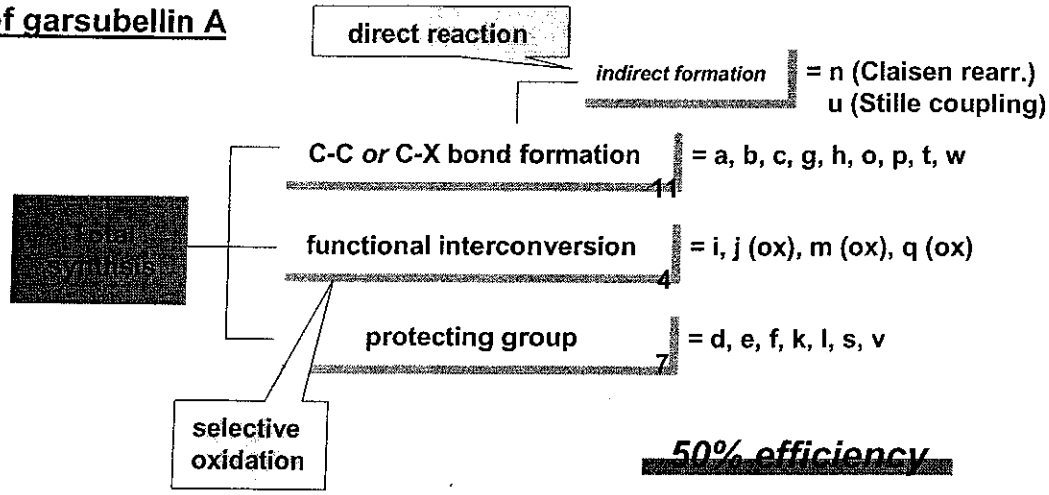
short synthesis
efficient synthesis

Scheme 3. Total Synthesis of (±)-Garsubellin A[a]

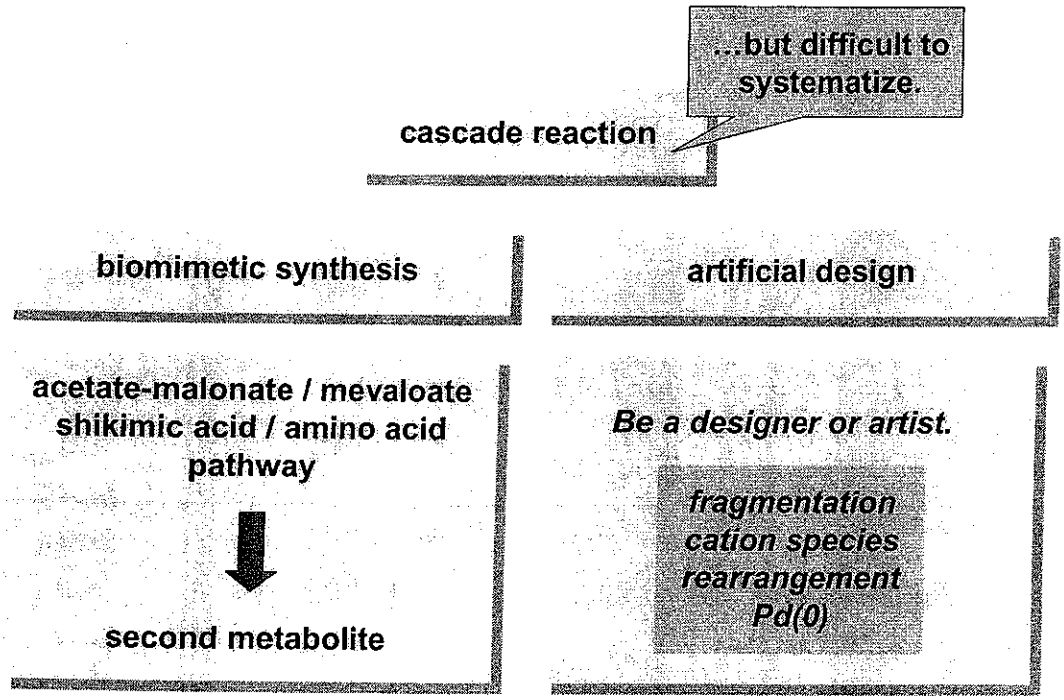


[a] Conditions: (a) LDA; prenyl bromide, Bu_4NI. (b) MeLi·LiBr; HCl, 100% (two steps). (c) MeMgBr, CuI (22 mol %); ^iPrCHO, 61%. (d) TIPSOTf, 2,6-lutidine, 92%. (e) $PhSiH_3$, $Co(acac)_2$ (20 mol %), O_2, 73%. (f) MOMCl, $^iPr_2NEt$, Bu_4NI, 96%. (g) KHMDS, prenyl bromide, Bu_4NI, 98%. (h) LDA, TMEDA; CH_3CHO, 94%. (i) Martin sulfurane, 98%. (j) AD-mix-α (0.4 mol % of Os), $CH_3SO_2NH_2$. (k) Triphosgene, pyridine; separation, 30% (two steps). (l) HF·pyridine. (m) PDC, Celite, 70% (two steps). (n) NaHMDS, MS4A, ethylene carbonate; allyl iodide, 82%. (o) NaOAc, 200 °C, 96%. (p) **14** (20 mol %), 92%. (q) $(PhSe)_2$, $PhIO_2$, pyridine. (r) CSA, 70% (two steps). (s) LiOH. (t) Na_2PdCl_4, TBHP, 71% (two steps). (u) I_2, CAN. (v) *p*-TsOH·H_2O, 80% (two steps). (w) $PdCl_2$·dppf, tributyl prenyl tin, 20%.

In the case of garsubellin A



Baran emphasizes cascade/biomimetic synthesis



10/14

Synthesis of (+)-CP-263,114

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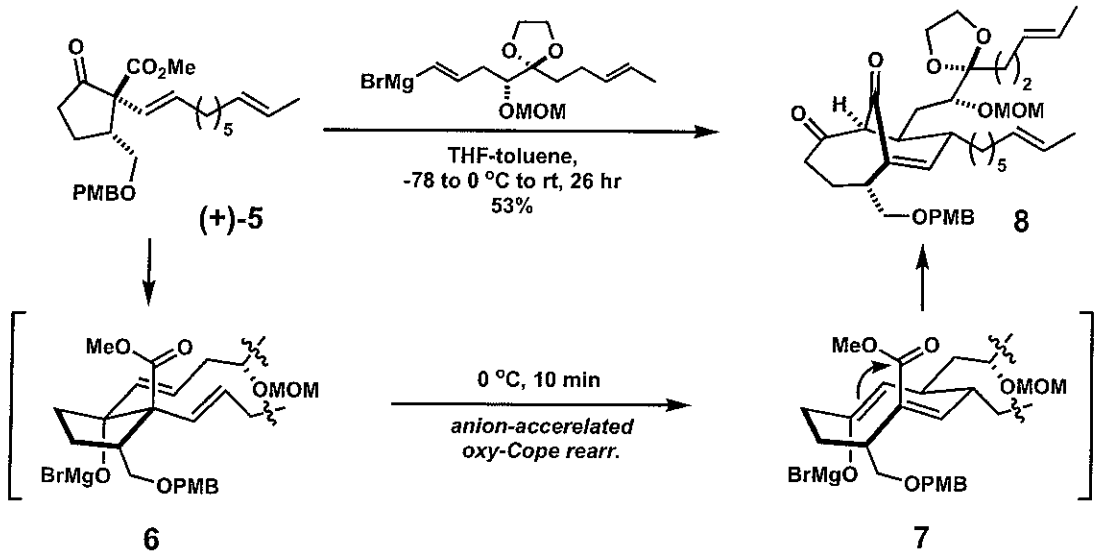
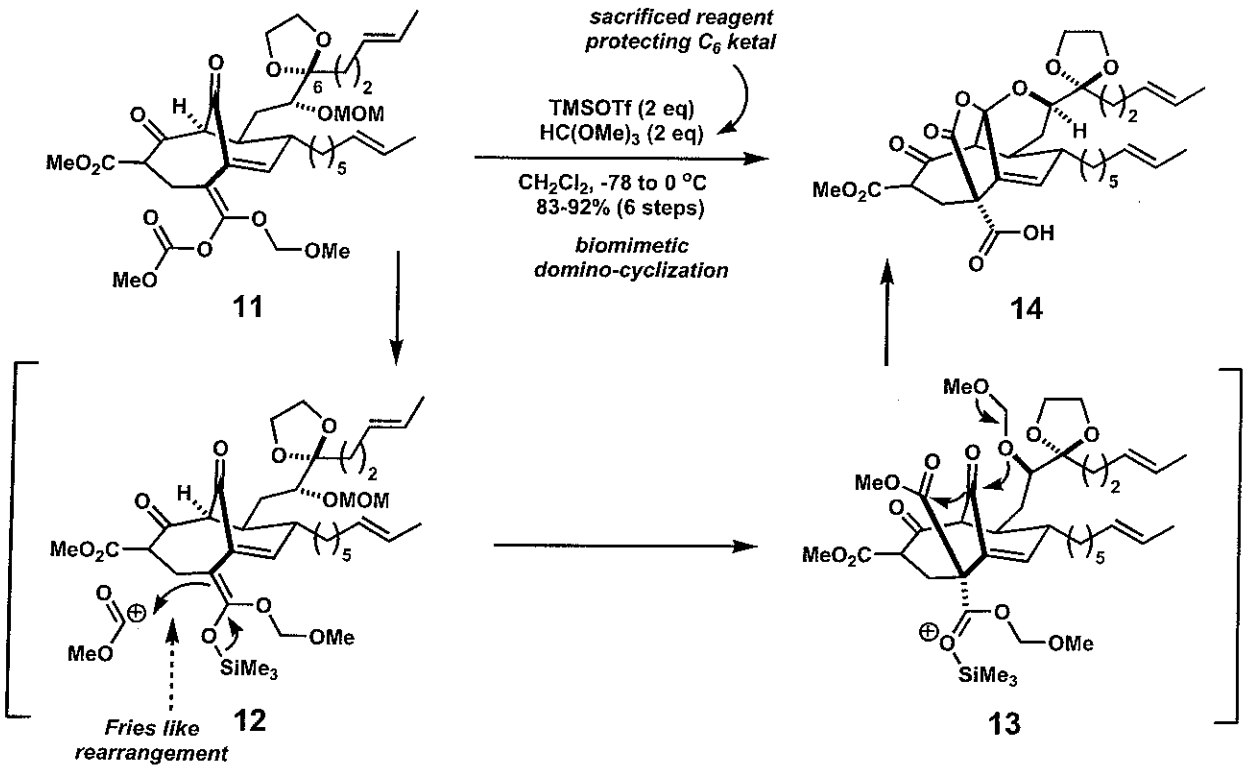
I. artificial design

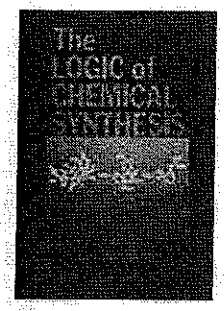


II. biomimetic synthesis



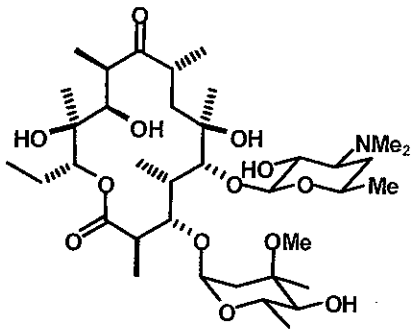
Chap 6

My view of organic synthesis



Pro and con of retrosynthesis

- **Total synthesis of enormous molecules *by force* with the strange combination of various methods, which is a sophisticated one in itself.**

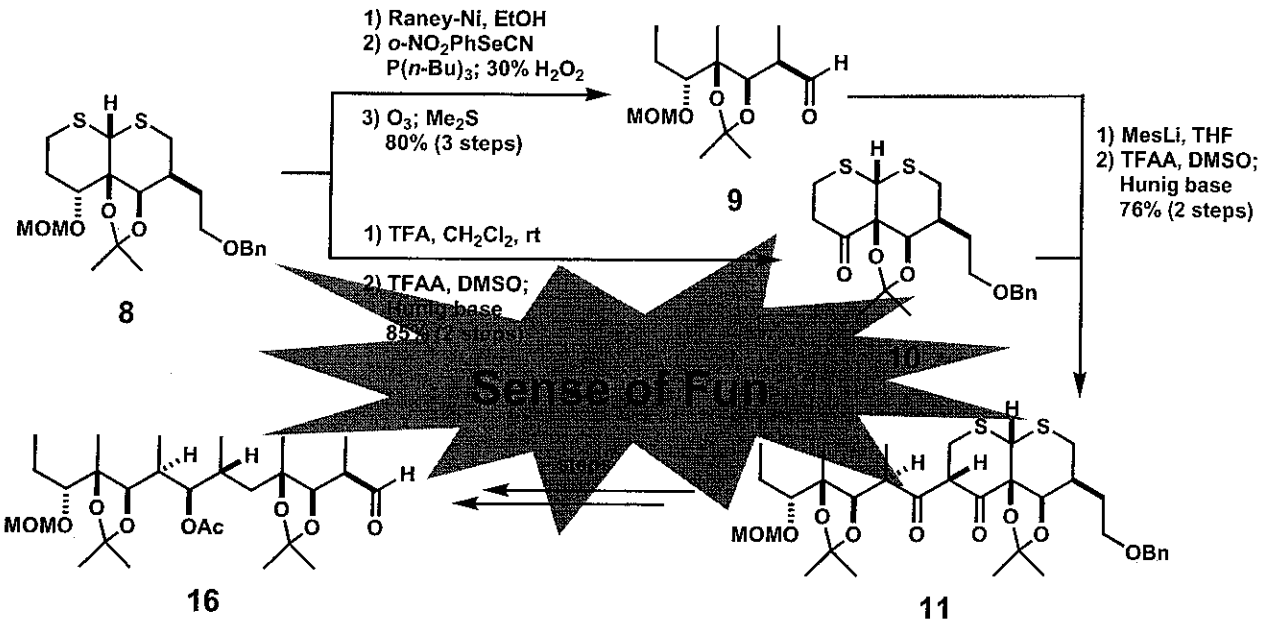


erythromycin A

- **Histrory has a lot to teach us about the future.**

Erythromycin, with all our advantages, looks at present hopelessly complex, particularly in view of its plethora of asymmetric centers.

(*Perspectives in Organic Chemistry*, Interscience, New York, 1956, P.160)



organic synthesis as an art !!

12/14

Why are Baran's syntheses all beautiful?

cascade and/or biomimetic synthesis ⟷ **functional beauty (機能美)**

The belief that Nature be beautiful.

時代は全合成に逆風が吹きつつある。全合成のもつ意義が問われているのだ。
「どうしてそこまでお金と労力を費やして、天然物を作る必要があるのか」と。「そこに化合物があるから」では、もはや通じない。

Woodwardがキニーネ(quinine)を化学的に作り上げ、「全合成」は社会に認知される学問となった。1944年のことだ。時代の争点は、「はたして化学的な手法で、複雑な天然物は作れるのか」だった。Woodwardはこれに終止符を打つ。
30年以上が過ぎ、今度はメルク(Merck)社が抗生物質チエナマイシン(thienamycin)を全合成した。この偉業の背景には「化学的な手法 で、天然物を供給しうるのか」がある。全合成が「目的」から「手段」に格上げされたわけだ。全合成の意義が強く取りざたされてきたのは、このあたりからか もしれない。

*

全合成の論文には、必ずといっていいほど「興味深い薬理作用」で「天然からは微量しか取れない」ので、「化学合成による供給が必須」という枕詞がつく。こうして研究の意義をダメ押ししようとするが、それらは往々にして建前に終わる。SchreiberのFK-506の研究のような偉業は、後にも先にも数 少ない。

むしろ、自分としては、「アートとしての全合成」と声高に開き直りたい。そもそも、全合成といった基礎科学的なものに、即物的な成果を期待されても困る……と、そこまでは言わなくても、それでもアート70・社会貢献30くらいでの分かち合いはしたい。
Woodwardの最後の仕事となった「エリスロマイシン(erythromycin)の全合成」を読んでいると、これは芸術品だと痛感する。その合成 ルートには、実験者の「楽しんでいる気持ち」がにじみ出ている。まぎれもなく芸術家が作っているのだ。1981年の仕事だから、いまから20年以上も前の もの——「そこに化合物があるから」の時代だった。

*

いま、科学は社会に対する還元が要求される。それでいてアートも楽しみたい。これからは、その両者を共存させうる全合成標的を、しっかりと選ぶ必要があるのだろう。

extraneous chlorine atom, an unwanted C–C bond, and restore the indole and isocyanide moieties. Indeed, irradiation of **12** for five hours led to ambiguine H (**1**), accomplishing all five necessary tasks in a single step (63% yield based on recovered **12**). We suggest a mechanism for this transformation in Fig. 3. If the reactive functionalities of **2** were shielded with protecting groups, such chemical reactivity would not have been apparent (that is, the Norrish-like cleavage of a chloroimidate or the use of a sensitive isonitrile to assist in the activation of a free indole). Synthetic **1** exhibited identical spectroscopic data to that reported in ref. 20 and was confirmed by X-ray crystallography (melting point 228–231 °C (dec.), hexanes/Et_2O (1:1)), representing the first total synthesis of a member of the ambiguine natural product family. Because **1** is unstable on prolonged storage, we made gram quantities of **2** and converted it to **1** as needed; see Supplementary Information for details.

Total synthesis of welwitindolinone A (4) and fischerindole I (5)

The elimination of protecting groups and reduction of the number of steps in a total synthesis can also simplify the optimization of the overall yield of a sequence. Statistics dictate that because each step in a shorter sequence carries a greater impact on the overall efficiency of a synthesis, optimization is realized more rapidly than with the corresponding longer routes[31]. The recent total syntheses of fischerindole I (**4**) and welwitindolinone A (**5**)[32] are an illustration of this point. Although they represent some of the most complex natural products to be synthesized without protecting groups[6] and required only seven to eight chemical operations, their syntheses had overall yields of only 6.9% and 1.7%, respectively, from ketone **15** (Fig. 4). The synthesis also suffered from limited scalability owing to the technically demanding nature of the final two steps of the sequence. Figure 4 depicts revised syntheses of **4** and **5** that can be conducted on a much larger scale than that reported previously and in overall yields of 13.0% and 5.7%, respectively, from **15**—via optimization of individual steps, not an alteration in general strategy.

In five simple steps from carvone oxide[32], amine **17** is accessible in large quantities via the direct coupling of chloroketone **15** with indole (62% yield) followed by Friedel–Crafts cyclization and stereocontrolled reductive amination of **16** (see Supplementary Information for details). Amine **17** is then formylated, followed by immediate dehydration with phosgene to install the isonitrile functionality and furnish 11-*epi*-fischerindole G (**18**). In our previous route, **18** provided a scaffold on which to perform the requisite unsaturation to form **5** and an ensuing ring contraction to form **4**. We reasoned that the yield and selectivity problems in that route stemmed from the choice of a chlorine-based oxidant (*tert*-BuOCl) that was both inefficient and unselective. As shown in the synthesis of ambiguine H (see below), such oxidants react readily with isonitriles. To accomplish the conversion of **18** to **5**, an oxidant was chosen that was more suited to benzylic oxidations. By simply exposing **18** to DDQ[33] in the presence of water, fischerindole I (**5**) was produced in excellent overall yield (>2 g prepared), presumably through the intermediate α,β-unsaturated imine **19**. For the ensuing oxidative ring contraction, we reasoned that a hitherto-unknown fluorohydroxylation of indole rather than chlorohydroxylation should suppress isonitrile-derived side-product formation, owing to the increased hardness of fluorine over chlorine. A method for fluorohydroxylation of the indole moiety in **5** was developed using xenon difluoride[34] and water in acetonitrile, providing welwitindolinone A scaleably (>390 mg prepared), in 44% isolated yield, and as a single diastereomer. This cascade sequence can be envisioned to proceed through fluorination of the indole nucleus to give **20**, which is trapped with water to give **21**. Elimination of fluoride would give the azaorthoquinodimethane (**22**)[35], which undergoes a [1,5] sigmatropic rearrangement to furnish the spirocyclobutane of welwitindolinone A, as a single diastereomer. The observed chemoselectivity (in the presence of two other olefins and a reactive isonitrile) of this new reaction is worthy of further study. Because **4** and **5** are unstable on prolonged storage, gram quantities of **18** are made and converted to **4** and **5** as needed (see Supplementary Information for details). The revised routes to **4** and **5** demonstrate how such mechanistically inspired reagent changes can greatly improve the overall efficiency of an extremely short synthesis. The only other reported total synthesis of **4** requires 25 steps and six protecting groups to deliver milligram quantities of racemic material[36].

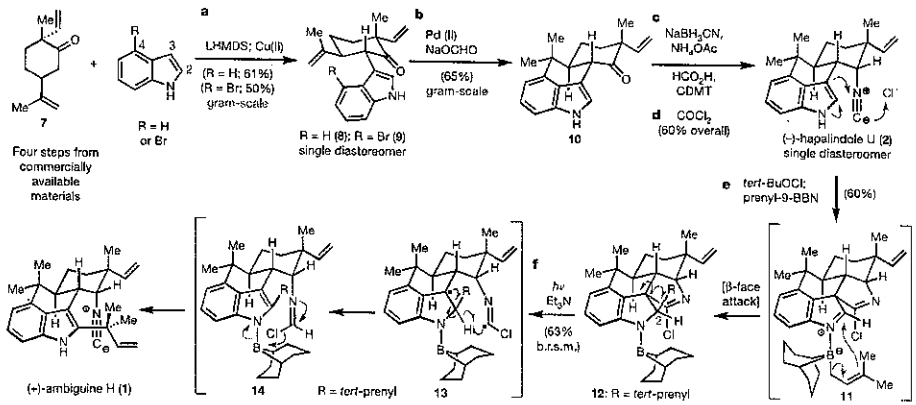


Figure 3 | Protecting-group-free synthesis of ambiguine H (1) and hapalindole U (2). Reagents and conditions as follows. **a**, Indole (1.9 equiv.), ketone **7** (1.0 equiv.), LHMDS (3.4 equiv.), Cu(II)-2-ethylhexanoate (1.5 equiv.), THF, starting temperature −78 °C, 5 min to 25 °C, yield is 61%; or 4-bromoindole (2.8 equiv.), ketone **7** (1.0 equiv.), LHMDS (4.4 equiv.), Cu(II)-2-ethylhexanoate (2.0 equiv.), THF, −78 °C, 5 min to 25 °C, 50%. **b**, $[Pd(P(o\text{-}tol)_3OAc]_2$ (0.05 equiv.), NaOCHO (1.25 equiv.), TBAB (2.0 equiv.), Et_3N (2.2 equiv.), DMF, 80 °C, slow addition of Pd over 5 h, 65%. **c**, NH_4OAc (40 equiv.), $NaCNBH_3$ (9.3 equiv.), MeOH/THF, microwave irradiation at 150 °C, 2.5 min; then HCO_2H (2.0 equiv.), CDMT (2.2 equiv.), DMAP (0.05 equiv.), NMM (2.2 equiv.), DCM, 2 h, 25 °C. **d**, $COCl_2$ (2.0 equiv.), Et_3N (17.5 equiv.), DCM, 0 °C, 60% over two steps. **e**, *tert*-BuOCl (1.15 equiv), DCM, −78 °C, 12 min; then prenyl-9-BBN (2.0 equiv), −78 °C, 30 min, 60%. **f**, Et_3N (5.0 equiv.), benzene, *hv*, 5 h, 63% b.r.s.m. (based on recovered starting material). LHMDS, lithium hexamethyldisilazide; THF, tetrahydrofuran; TBAB, *tetra-n*-butyl ammonium bromide; Et_3N, triethylamine; DMF, *N,N*-dimethylformamide; CDMT, 2-chloro-4,6-dimethoxy-1,3,5-triazine; DMAP, 4-*N*-dimethylaminopyridine; NMM, *N*-methylmorpholine; DCM, dichloromethane; 9-BBN, 9-borabicyclo-nonane. For selected physical data for compounds **1**, **2**, **7**–**10** and **12**, see the Supplementary Information. Compounds **2**, **12** and **1** were verified by X-ray crystallography.

Discussion

Taken together with the concepts of "atom economy"[37] and "step economy,"[38] we followed several general guidelines during the planning stage (retrosynthetic analysis)[39] of these syntheses: (1) redox reactions that do not form C–C bonds should be minimized[40], (2) the percentage of C–C bond-forming events within the total number of steps in a synthesis should be maximized[39,40], (3) disconnections should be made to maximize convergency[41], (4) the overall oxidation level of intermediates should linearly escalate during assembly of the molecular framework (except in cases where there is strategic benefit such as an asymmetric reduction)[42], (5) where possible, cascade (tandem) reactions should be designed and incorporated to elicit maximum structural change per step[43], (6) the innate reactivity of functional groups should be exploited so as to reduce the number of (or perhaps even eliminate) protecting groups[6,44], (7) effort should be spent on the invention of new methodology to facilitate the aforementioned criteria and to uncover new aspects of chemical reactivity[45], (8) if the target molecule is of natural origin, biomimetic pathways (either known or proposed) should be incorporated to the extent that they aid the above considerations[1,2,44–46]. Although these principles have existed conceptually and separately for several years[1,2,6,47], this series of total syntheses cohesively applies them as a whole.

Despite the demonstrated advantages, there are some limitations to deliberately excluding protecting groups from the synthesis of complex molecules. For instance, their inclusion within a synthetic plan may allow for a certain level of security, because perceived functional-group incompatibilities can be dealt with at the outset. Indeed, omitting protecting groups during the retrosynthetic planning stages of a complex molecule might involve a certain amount of risk and speculation, owing to the unpredictable reactivity that is inevitably encountered at the late stages of a total synthesis[38]. In some cases, the use of protecting groups may offer a more efficient or even the sole solution. For example, the total synthesis of certain classes of molecules, such as poly-ketides, -peptides, -saccharides, and -nucleotides, will perhaps always require some level of protection (not only owing to a lack of chemoselectivity but also the practical issues of purification and characterization).

In summary, representative members of a large class of natural products consisting of four different families have been constructed by adhering to the general principles outlined above. The enantioselective total syntheses of ambiguine H (**1**), hapalindole U (**2**), welwitindolinone A (**4**), and fischerindole I (**5**) require only seven to ten steps from commercially available materials and can easily be performed on a preparative scale using inexpensive reagents. Of those steps, approximately half involved C–C bond formation and aside from a stereoselective reductive amination, the oxidation states of intermediates gradually escalated from beginning to end. Certain aspects of these convergent syntheses also benefited from insights into their biosynthetic origins and the incorporation of designed cascade reactions. Finally, the deliberate exclusion of protecting groups from the overall synthetic design facilitated the development and discovery of new chemical reactions by harvesting the intrinsic reactivity within organic molecules.

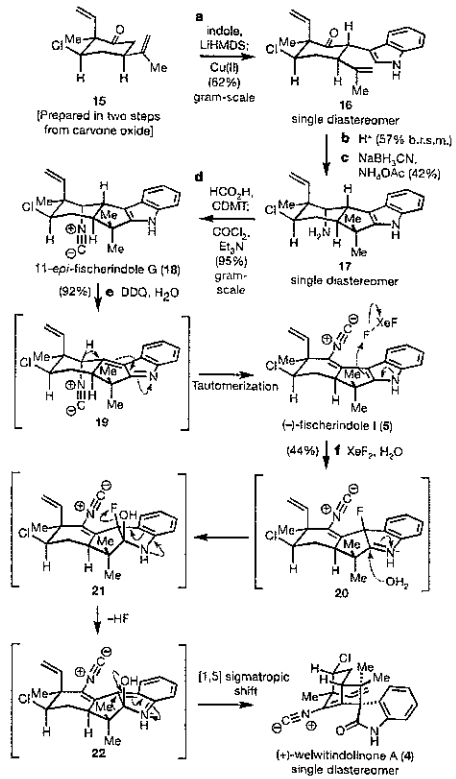


Figure 4 | Protecting-group-free total synthesis of fischerindole I (5) and welwitindolinone A (4). Reagents and conditions as follows. **a**, Indole (2.0 equiv.), LiHMDS (3.3 equiv.), THF, −78 °C, 30 min, copper(II)-2-ethylhexanoate (1.5 equiv.), −78 to 23 °C, 20 min, 62%. **b**, Montmorillonite K-10 clay, microwave irradiation at 120 °C, 6 min, 57% b.r.s.m. **c**, NH_4OAc (40 equiv.), $NaCNBH_3$ (7.5 equiv.), 3 Å molecular sieves, MeOH/THF, sonication, 18 h, 42%. **d**, HCO_2H (2.0 equiv.), CDMT (2.2 equiv.), DMAP (0.1 equiv.), NMM (2.2 equiv.), DCM, 23 °C, 30 min; Et_3N (17.5 equiv.), $COCl_2$ (2.0 equiv.), DCM, 0 °C, 10 min, 95%. **e**, DDQ (2.5 equiv.), H_2O, THF, 0 °C, 30 min, 92%. **f**, XeF_2, H_2O, MeCN, 23 °C, 5 min; 44%. DDQ, 2,3-dichloro-5,6-dicyanobenzoquinone; MeCN, acetonitrile. For selected physical data for compounds **18**, **5** and **4** see the Supplementary Information.

METHODS

All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Yields refer to chromatographically and spectroscopically homogenous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography. For full experimental details and procedures for all reactions performed and full characterization (^1H and ^{13}C nuclear magnetic resonance, high-resolution mass spectrometry, infrared, optical rotation, melting point, and R_f value) of all new compounds, see the Supplementary Information.

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1. Nicolaou, K. C. & Sorensen, E. J. *Classics in Total Synthesis* (VCH, New York, 1996).
2. Nicolaou, K. C. & Snyder, S. A. *Classics in Total Synthesis II* (Wiley-VCH, Weinheim, 2003).
3. Wöhler, F. Ueber die Künstliche Bildung des Harnstoffe Poggendorfs. *Ann. Phys. Chem.* 12, 253–256 (1828).
4. Service, R. F. Race for molecular summits. *Science* 285, 184–187 (1999).