Shenvi Lab Group Meeting
September 11, 2017

Robert Burns Woodward

Hannah Burdge

"How does one tell the chemical community anything about Woodward which… they do not already know?"

1917: Born in Boston, MA

"To give you a brief glimpse of his childhood I quote from an article in the Boston Daily Globe of June 8, 1937: "As a boy in short pants in Quincy Grammar School, he consistently brought home report cards dimmed with a pair of D's for conduct and effort. The Woodward youngster, who was always playing in the cellar with a chemistry set, received three double promotions hurdling the fourth, seventh and tenth grades, all the while whispering in classes, chewing bubble gum, being the last one in after recess and pulling little girls' long curls.' I can assure you, after ten years of close association with Bob Woodward, that things have certainly changed since his earlier days— I don't think I have seen him blowing bubble gum in a long while." —David Dolphin

"[At age 12, Woodward] invited [Robert Putnam] over to see what was apparently his first experiment. He proposed to make hydrogen gas. On a card table he had some solid reagents and a large Erlenmeyer flask fitted with a thistle tube and an exit tube. He poured in some hydrochloric acid on the zinc in the flask. Before I could stop him, he ignited the issuing gas. A big explosion occurred, smashing the equipment and the bottle of reagents. We were not hurt… I noticed that his mother, who was present, did not complain or seem disturbed." — Robert Putnam

1933: Begins attending MIT at age 16; obtains both BS and PhD in 4 years

"[Woodward] was admitted to MIT on scholarship, but… was forced to withdraw after the fall semester of his sophomore year. Astonishingly, he lost his scholarship due to poor grades!… During the spring and summer of 1935, he earned enough money to re-register at MIT without a scholarship and… signed up in the first term of his junior year for 186 credit hours of classes. Since there are only 168 hours in a week, even counthing nights and weekends, he skipped a few classes." —Frank H. Westheimer

"We saw we has a person who posessed a very unusual mind and we wanted it to function at its best. If the red tape necessary for less brilliant minds had to be cut, we let it go… We think he will make a name for himself in the scientific world." — James Flack Norris (Woodward's PhD advisor)

Undergraduate thesis: "Preliminary studies on the synthesis of polynuclear hydroaromatic ring systems", 1936

PhD thesis: "A synthetic attack on the oestrone problem", 1937

1937: Spends a fruitless summer at the University of Illinois before moving to Harvard in the fall, first as a postdoc under Elmer P. Kohler, then as an instructor, finally working his way up through the ranks to full professor.

"[Woodward] managed to alienate— well, to outrage— two of the most powerful of America's chemists. A number of explanations have been advanced for his social failure; my explanation rests on the assumption that Bob failed to conceal adequately that he was much brighter than the Illinois professors." —Frank H. Westheimer

Selected awards and honors:
John Scott Medal (1945)
RSC's Davy Medal (1959)
Donner Professor of Science (1960)
ACS's Roger Adams Medal (1961)
Pius XI Gold Medal (1969)
National Medal of Science (1964)
Nobel Prize in Chemistry (1965)
Willard Gibbs Medal (1967)
Lavoisier Medal (1968)
Hanbury Memorial Medal (1970)

Selected famous students:
(indicates a Wooward graduate student,*
^ indicates a Woodward postdoc)
Harry H. Wasserman* (1944-1949)
Ronald C. D. Breslow* (1955-1959)
Ian Fleming^ (1963-1964)
Pierre Deslongchamps^ (1965)
Kendall N. Houk* (1964-1968)
Yoshito Kishi^ (1966-1969)
Stuart L. Schreiber* (1979)

Note: It is widely believed that, should he have lived to see it, Woodward would have shared the 1981 Nobel Prize in chemistry awarded to Ken Fukui and Roald Hoffmann "for their theories, developed independently, concerning the course of chemical reactions"

1979: Woodward dies in Cambridge, MA of a heart attack at the age of 62

"In his last years he became much more social, not in a global sense, but in his relationships. When he was in Cambridge we had dinner at least once a week… The night before he died we had a wonderful dinner together at the Stockyard and left him in a very good mood when we separated at about 11:00 p.m." —Elkan Blout

"Woodward himself only slept three or four hours a night; he was in his office early and stayed late, at least 6 days a week. If one calculates that he used a sixth of the day lesser mortals waste sleeping, he really lived to the age of 73, not 62." —Frank H. Wesheimer

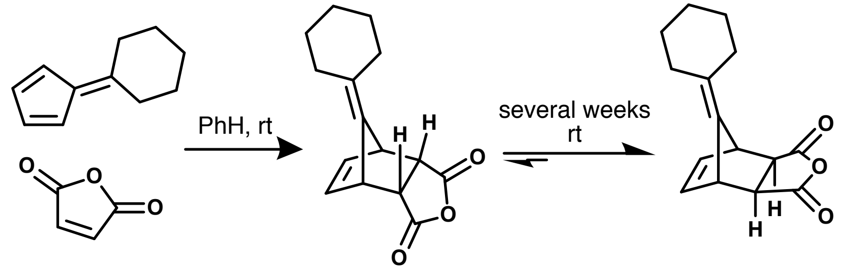
"A sedan chair crafted… for Woodward's birthday in 1978. Woodward was delighted. 'This hearkens back to days of yore— days of the monarchy— in my opinion, better days'. Bearers: (left) Stuart Schreiber, now at Harvard; (center, almost hidden by an unidentified bystander) Howard E Simmons III, now at DuPont, and (right) Gibbons, now finance minister of Bermuda."

In the Beginning: A Love of the Diels—Alder

"In 1983 Woodward gave a lecture at an American Chemical Society meeting in which he described his pleasure at seeing the original publication by Diels and Alder describing the discovery of the reaction that bears their name and his lifetime preoccupation with that reaction. He made use of the Diels-Alder reaction in a marginally commendable (in his own words) approach to the synthesis of oestrone during the middle 1930s in the course of his work for his Ph.D. degree. Much later he used the Diels-Alder reaction with greater effect in the syntheses of cholesterol, cortisone, and reserpine." —Elkan Blout

"I was only dimly aware, through allusions in those books, of the existence of the original journal literature. I now decided that this matter deserved exploration and I took the forthright step of writing to the German consul-general at Boston—one Baron von Tippelskirch (really!)—intimating that I heard that chemical research was actively pursued in Germany, and that its fruits were described in publications which appeared at regular intervals. Could I enlist his kindness in helping me to procure samples of such publications?" —RBW, on his own procurement of the seminal publication of the Diels—Alder reaction at age 11

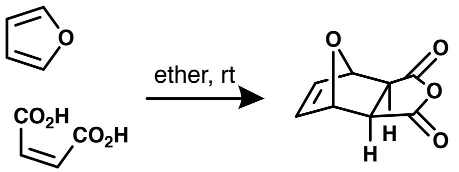
Woodward and Baer, JACS, 1944, 66, 645 - 649



initial *endo* adduct
kinetic product

equilibrated *exo* adduct
thermodynamic product

Woodward and Baer, JACS, 1948, 70, 1161 - 1166



exo adduct only

"The furan-maleic acid reaction is extraordinarily readily reversible, with the result that attempts at removal of solvent, or extraction, result preferentially in removal of furan, by volatilization or extraction, with continuous displacement of the equilibrium until no adduct remains."

Woodward and Baer, JACS, 1944, 66, 645 - 649

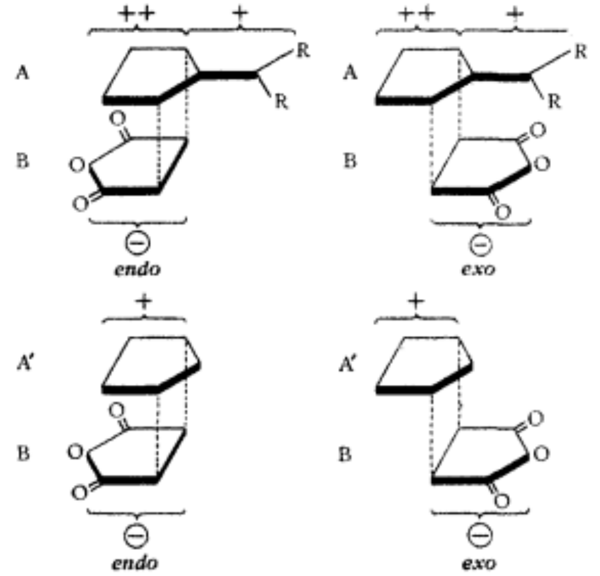
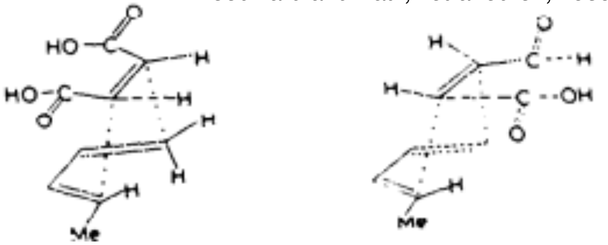


Fig. 2.—Models of intermediate complexes in the addition of maleic anhydride [B] to a fulvene [A] and to a simple diene [A′]. Dotted lines indicate points of union in the final products.

Woodward and Katz, Tetrahedron, 1959, 5, 70 - 89



"…while the principle of maximum accumulation of unsaturated centers is in the first instance empirical, it has been given physical meaning through the proposal that electrostatic and electrodynamic attractive forces associated with the mobile electronic systems not directly involved in the bond-forming processes lower the energy of intermediates such as [an endo transition state… as compared with the alternative [exo transition state]."

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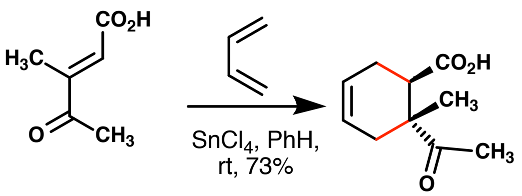
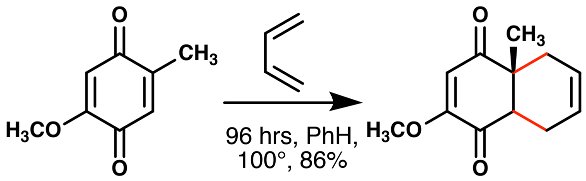
From Diels—Alder to the Future

Hannah Burdge

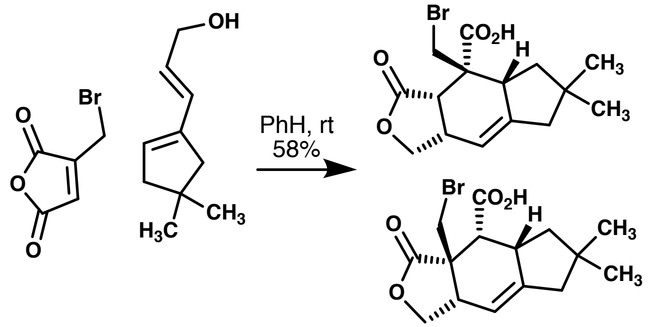
Woodward's uses of the Diels—Alder in total synthesis: selected examples



From the synthesis of vitamin B_{12}
Pure Appl. Chem. 1973, 33, 45



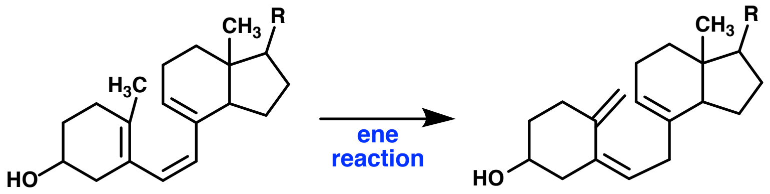
From the synthesis of cholesterol
JACS, 1952, 74, 4332



From the synthesis of marasmic acid
JACS, **1976**, *98*, 6075

"The Wooward Challenge" — "glaring examples of no-mechanism problems"

1



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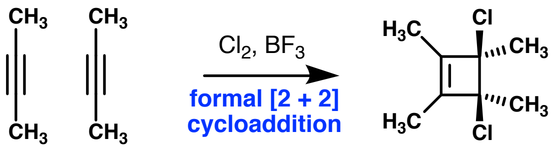

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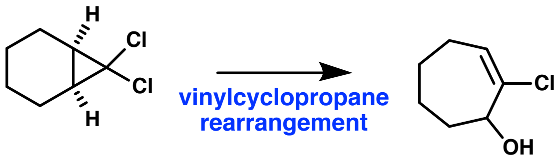

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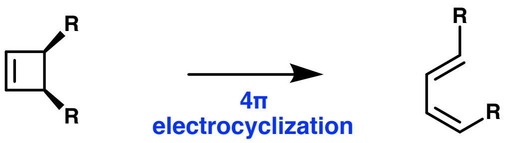
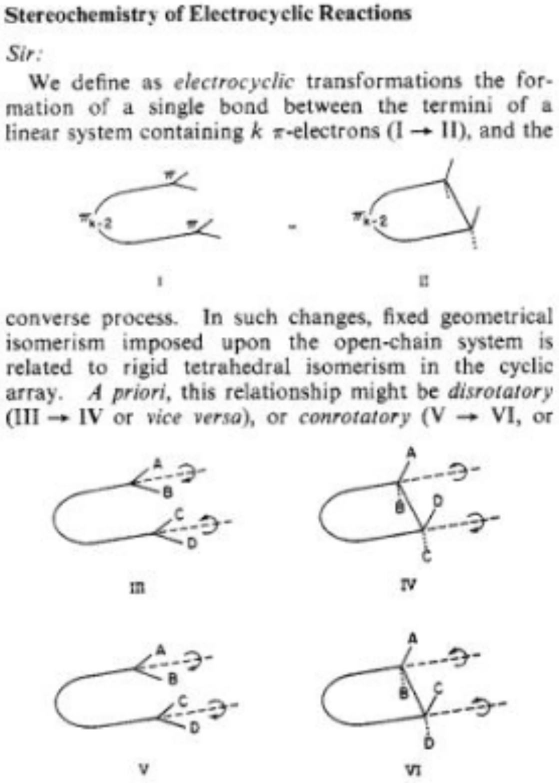


Woodward, Hoffman, JACS, 1965, 87 (2), 395 - 397



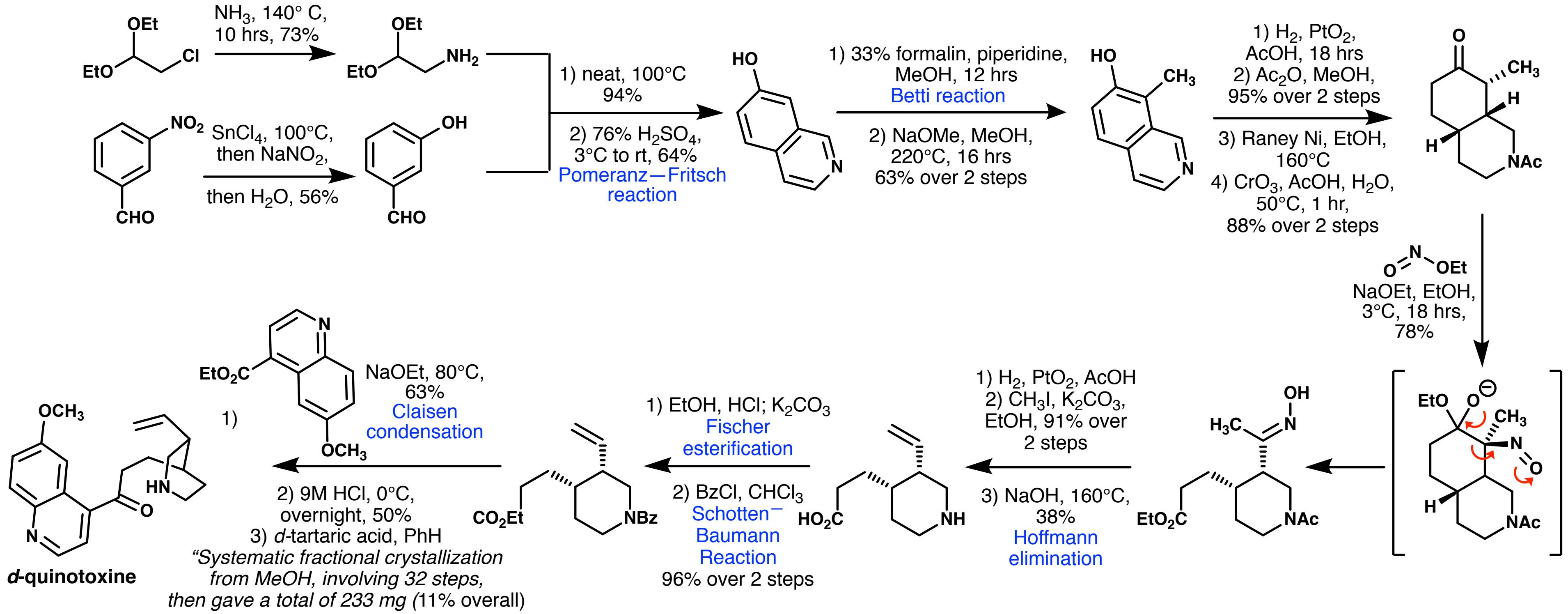
Stereochemistry of Electrocyclic Reactions

Sir:

We define as *electrocyclic* transformations the formation of a single bond between the termini of a linear system containing *k* π-electrons (I → II), and the converse process. In such changes, fixed geometrical isomerism imposed upon the open-chain system is related to rigid tetrahedral isomerism in the cyclic array. *A priori*, this relationship might be *disrotatory* (III → IV or *vice versa*), or *conrotatory* (V → VI, or

"Woodward's contribution (to the Woodward—Hoffmann rules colaboration) was recognizing the chemical problem; abstracting it from a complex literature, new and old, bringing this to the attention of Hoffmann and inviting his participation, more than that, proposing a frontier orbital explanation based on phases and nodes of the relevant orbitals, writing the first half of the manuscript, assembling and melding the two halves together; and writing an especially self-assured cover letter to JACS." —Jeff Seeman, *JOC,* 2015, 80, 1163

Classics in Woodwardian Synthesis: Quinine



NH_3, 140° C, 10 hrs, 73%

$SnCl_4$, 100°C, then $NaNO_2$, then H_2O, 56%

1) neat, 100°C 94%
2) 76% H_2SO_4, 3°C to rt, 64%
Pomeranz—Fritsch reaction

1) 33% formalin, piperidine, MeOH, 12 hrs
Betti reaction
2) NaOMe, MeOH, 220°C, 16 hrs
63% over 2 steps

1) H_2, PtO_2, AcOH, 18 hrs
2) Ac_2O, MeOH, 95% over 2 steps
3) Raney Ni, EtOH, 160°C
4) CrO_3, AcOH, H_2O, 50°C, 1 hr, 88% over 2 steps

NaOEt, EtOH, 3°C, 18 hrs, 78%

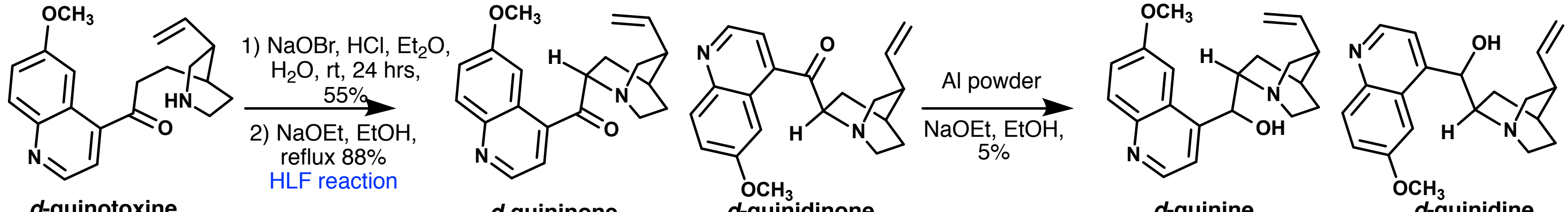
1) H_2, PtO_2, AcOH
2) CH_3I, K_2CO_3, EtOH, 91% over 2 steps
3) NaOH, 160°C, 38%
Hoffmann elimination

1) EtOH, HCl; K_2CO_3
Fischer esterification
2) BzCl, $CHCl_3$
Schotten−Baumann Reaction
96% over 2 steps

1) NaOEt, 80°C, 63%
Claisen condensation
2) 9M HCl, 0°C, overnight, 50%
3) *d*-tartaric acid, PhH
"Systematic fractional crystallization from MeOH, involving 32 steps, then gave a total of 233 mg (11% overall)

***d*-quinotoxine**

This constitutes a formal synthesis of quinine based on literature precedent from Kindler and Rabe, 1918:



***d*-quinotoxine**
obtained from degradation of quinine in AcOH/H_2O

1) NaOBr, HCl, Et_2O, H_2O, rt, 24 hrs, 55%
2) NaOEt, EtOH, reflux 88%
HLF reaction

***d*-quininone** ***d*-quinidinone**
(equilibrating mixture)

Al powder
NaOEt, EtOH, 5%

***d*-quinine**
mixture of diastereomers

***d*-quinidine**
mixture of diastereomers

The Aftermath of Quinine: Questions and Answers

From *Time* magazine's article on the quinine total synthesis

Cartoon published in the *Oregon Journal*

Public perception of the Woodward and Doering quinine synthesis was fawning and hopeful:

"one of the greatest scientific achievements of our time"—the Kentucky Messenger, Owensboro

"a notable peace victory … of great benefit to mankind … a victory for science … " —the Virginia Gazette, Alexandria

"…a promise of life and health for millions now suffering and dying from malaria"—the Philadelphia Inquirer

"The final step—commercial production—still remained to be taken. Chemists Woodward & Doering had made only 1/100 of an ounce from five pounds of expensive, involved chemicals."—Time magazine

…However, professional doubts were raised based on reproducibility of the Rabe and Kindler paper due to lack of experimental detail:

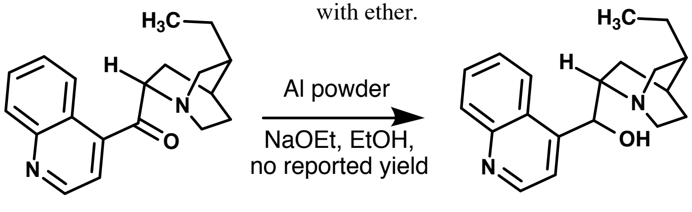
"The synthesis proceeds in three stages: quinotoxine when treated with sodium hypobromite is converted into N-bromquinotoxine; by use of alkali, hydrogen bromide is removed and quininone is formed; finally the quininone when treated with aluminum powder in alcohol in the presence of sodium ethoxide yields quinine. The use of this unusual reducing mixture represents the real advance in the synthesis of the series of cinchona alkaloids. Regarding the more detailed formulation of the reactions we have used… we refer to paper XV: The partial synthesis of cinchonine. Ber. 44, 2088 [1911]*… 16.3 g synthetic quininone when treated with the aforementioned reducing mixture yielded, besides 0.9 g quinidine, 2 g of analytically pure quinine." —Rabe and Kindler, in their original synthesis of quinine from quinotoxine

*This paper contains a detailed experimental section with regards to the HLF reaction; however, for reduction procedures, it points to a 1908 paper (also by Rabe) detailing a "partial synthesis of chinchonine from chinchonatoxine", which itself makes quick mention of reduction with both sodium and iron, but not with aluminum

"In these two papers, Woodward and Doering describe primarily the synthesis of cis-3-vinyl-4-piperidinopropionic acid. ⍰This was an impressive achievement. But it wasn⍰'t quinine.⍰" —Gilbert Stork

Experimental details for the conversion of hydrocinchoninone to cinchonine were, however, reported in a 1932 paper by Rabe:

100 g of ketone [hydrocinchoninone, see Scheme 6C] were dissolved in 1 liter of 99.5% alcohol and treated with a solution of 84 g of sodium in 1280 cc absolute alcohol. Aluminum powder, 84 g, was added with vigorous stirring. The reaction, at first vigorous, is completed by warming to light boiling for two hours with addition of about 400 cc of absolute alcohol. After being filtered when hot, the solution was made acid to Congo Red with dilute hydrochloric acid, and the alcohol was distilled off. The reduction products so obtained were liberated with 30% aqueous sodium hydroxide and extracted with ether.

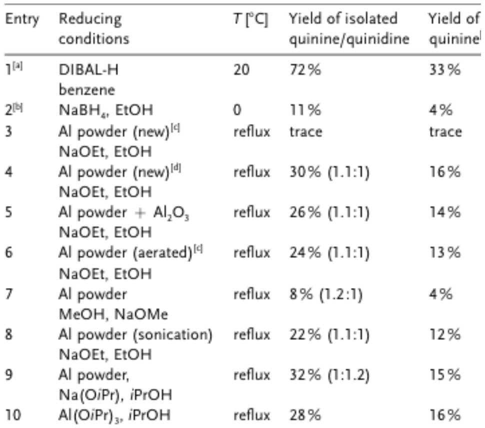


***d*-hydrocinchoninone**

***d*-hydrocinchonine**
mixture of diastereomers

Eur. J. Inorg. Chem, 1939, 72(28), 263

In addition to reports in 1973 by Uskokovic and coworkers that this reduction is possible using DIBAL, Smith and Williams in 2008 were able to produce quinine from quininone by introducing Al^{III} impurities *via* aeration or doping with Al$_2$O$_3$



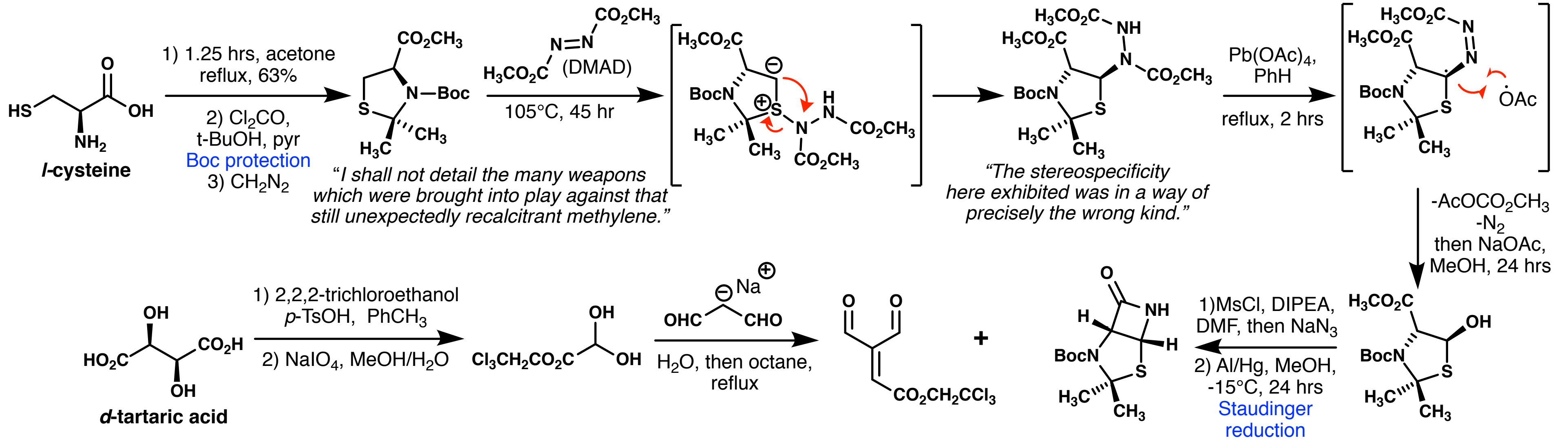
Entry	Reducing conditions	T [°C]	Yield of isolated quinine/quinidine	Yield of quinine
1[a]	DIBAL-H benzene	20	72%	33%
2[b]	NaBH$_4$, EtOH	0	11%	4%
3	Al powder (new)[c] NaOEt, EtOH	reflux	trace	trace
4	Al powder (new)[d] NaOEt, EtOH	reflux	30% (1.1:1)	16%
5	Al powder + Al$_2$O$_3$ NaOEt, EtOH	reflux	26% (1.1:1)	14%
6	Al powder (aerated)[c] NaOEt, EtOH	reflux	24% (1.1:1)	13%
7	Al powder MeOH, NaOMe	reflux	8% (1.2:1)	4%
8	Al powder (sonication) NaOEt, EtOH	reflux	22% (1.1:1)	12%
9	Al powder, Na(O*i*Pr), *i*PrOH	reflux	32% (1:1.2)	15%
10	Al(O*i*Pr)$_3$, *i*PrOH	reflux	28%	16%

ACIE, 2008, 47, 1736

"I therefore also conclude that the Woodward–Doering/ Rabe–Kindler total synthesis of quinine is a valid achievement."
—Jeff Seeman,
ACIE, 2007, 46, 1378

Classics in Woodwardian Synthesis: Cephalosporin C

Hannah Burdge


l-cysteine

1) 1.25 hrs, acetone reflux, 63%
2) Cl_2CO, t-BuOH, pyr
Boc protection
3) CH_2N_2

$H_3CO_2C-N{=}N-CO_2CH_3$ (DMAD)
105°C, 45 hr

"I shall not detail the many weapons which were brought into play against that still unexpectedly recalcitrant methylene."

"The stereospecificity here exhibited was in a way of precisely the wrong kind."

$Pb(OAc)_4$, PhH
reflux, 2 hrs

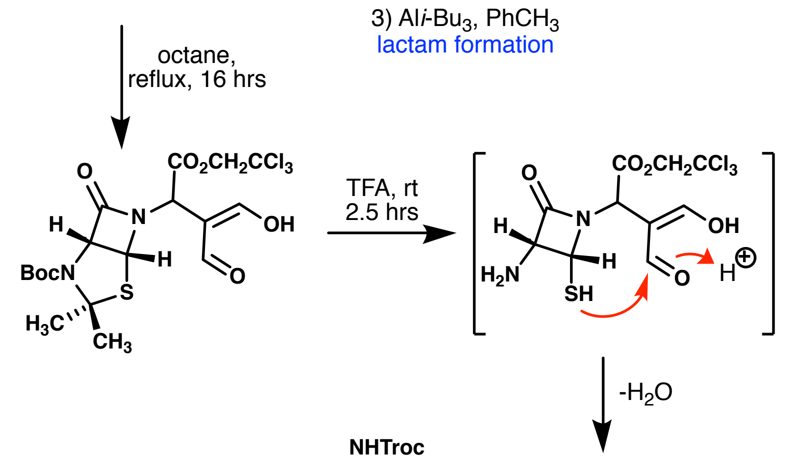
$-AcOCO_2CH_3$
$-N_2$
then NaOAc, MeOH, 24 hrs

1)MsCl, DIPEA, DMF, then NaN_3
2) Al/Hg, MeOH, -15°C, 24 hrs
Staudinger reduction
3) Al*i*-Bu_3, $PhCH_3$
lactam formation

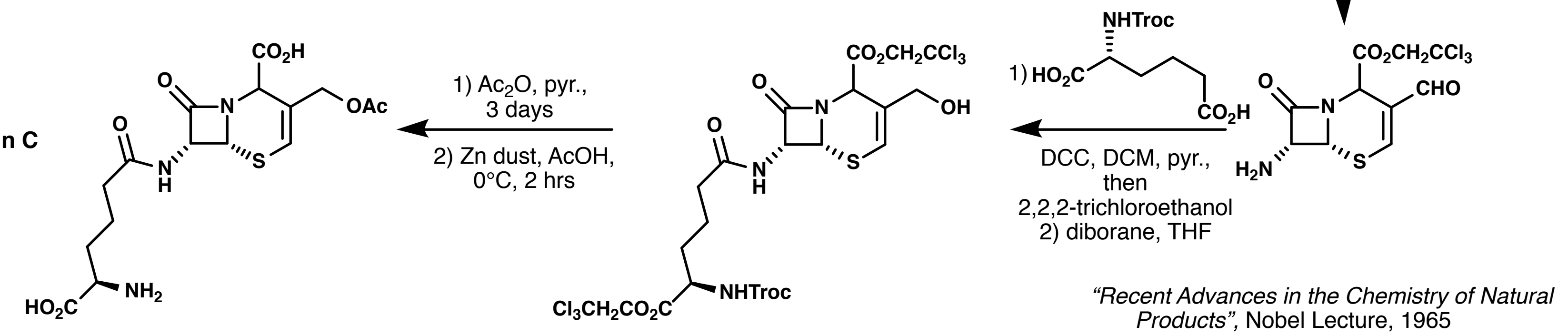
d-tartaric acid

1) 2,2,2-trichloroethanol
p-TsOH, $PhCH_3$
2) $NaIO_4$, MeOH/H_2O

OHC–CH(⁻ Na⁺)–CHO
H_2O, then octane, reflux


octane, reflux, 16 hrs

TFA, rt
2.5 hrs


$-H_2O$

1) HO_2C–CH(NHTroc)–$CH_2CH_2CH_2$–CO_2H
DCC, DCM, pyr., then 2,2,2-trichloroethanol
2) diborane, THF

1) Ac_2O, pyr., 3 days
2) Zn dust, AcOH, 0°C, 2 hrs

cephalosporin C

"Recent Advances in the Chemistry of Natural Products", Nobel Lecture, 1965
JACS, 1966, 88 (4), pp 852 – 853

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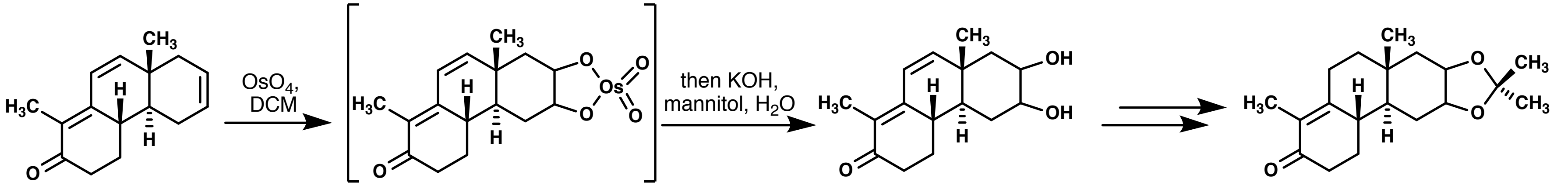
Woodward's Greatest Hits: Tetracyclines and Steroids

Hannah Burgde

Cholesterol:



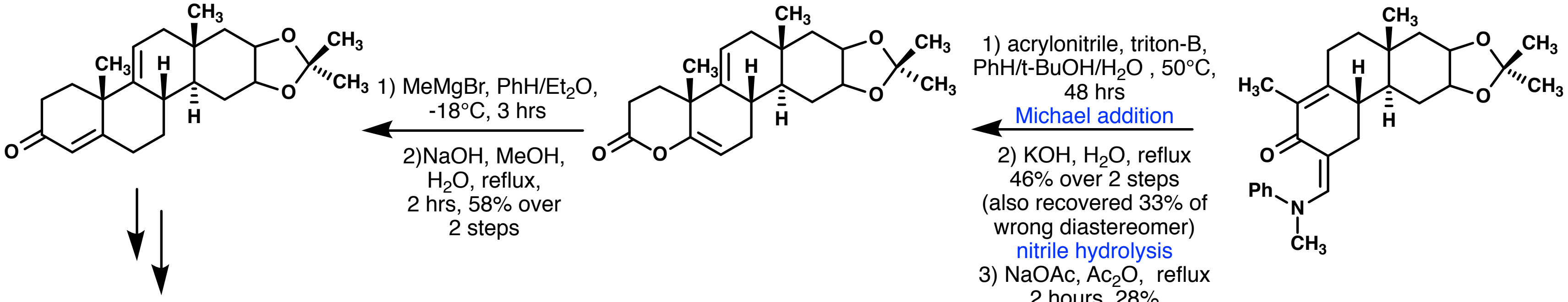
OsO_4, DCM

isolable osmate ester

then KOH, mannitol, H_2O

HCO_2Et, $NaOCH_3$, PhH, overnight, then $HNPhCH_3$, MeOH, rt
88% over 2 steps

"By pure chance, the two great men met early on a Monday morning on an Oxford train platform in 1951. Robinson politely asked Woodward what kind of research he was doing these days; Woodward replied that he thought Robinson would be interested in his recent synthesis of cholesterol. Robinson, incensed and shouting, "Why do you always steal my research topic?", hit Woodward over the head with his umbrella."—Sir Derek Barton



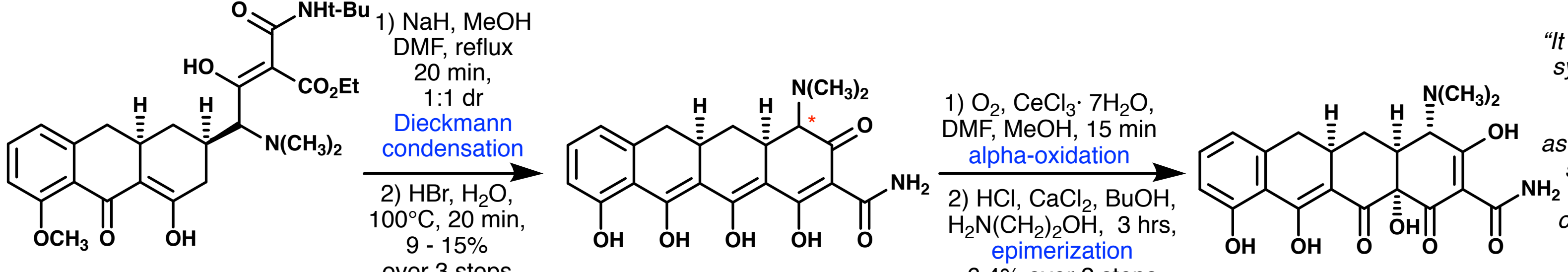
1) acrylonitrile, triton-B, PhH/t-BuOH/H_2O , 50°C, 48 hrs
Michael addition
2) KOH, H_2O, reflux
46% over 2 steps
(also recovered 33% of wrong diastereomer)
nitrile hydrolysis
3) NaOAc, Ac_2O, reflux
2 hours, 28%

1) MeMgBr, PhH/Et_2O, -18°C, 3 hrs
2)NaOH, MeOH, H_2O, reflux, 2 hrs, 58% over 2 steps

formal synthesis of cholesterol, cortesone, testosterone, adrosterone, and progesterone

JACS, 1951, **73**, 3547
JACS, 1952, **74**, 4223

tetracyclines



1) NaH, MeOH
DMF, reflux
20 min,
1:1 dr
Dieckmann condensation
2) HBr, H_2O,
100°C, 20 min,
9 - 15%
over 3 steps

"…it is less remarkable that the discovery of proper conditions for the cyclization reaction was difficult, than that they could be found at all."

1) O_2, $CeCl_3 \cdot 7H_2O$,
DMF, MeOH, 15 min
alpha-oxidation
2) HCl, $CaCl_2$, BuOH,
$H_2N(CH_2)_2OH$, 3 hrs,
epimerization
6.4% over 2 steps

***rac*-6-demethyl-6-deoxytetracycline**

"It is of particular interest that the synthetic racemic compound is just half as active against pathogenic organisms as its natural counterpart; the not surprising, but none-the-less interesting, conclusion may be drawn that the unnatural isomer is completely devoid of biological activity."

Pure Appl. Chem. ,1963, 6, 561
JACS, 1968, 90, 439

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Woodward's Greatest Hits: Colchicine

Hannah Burgde

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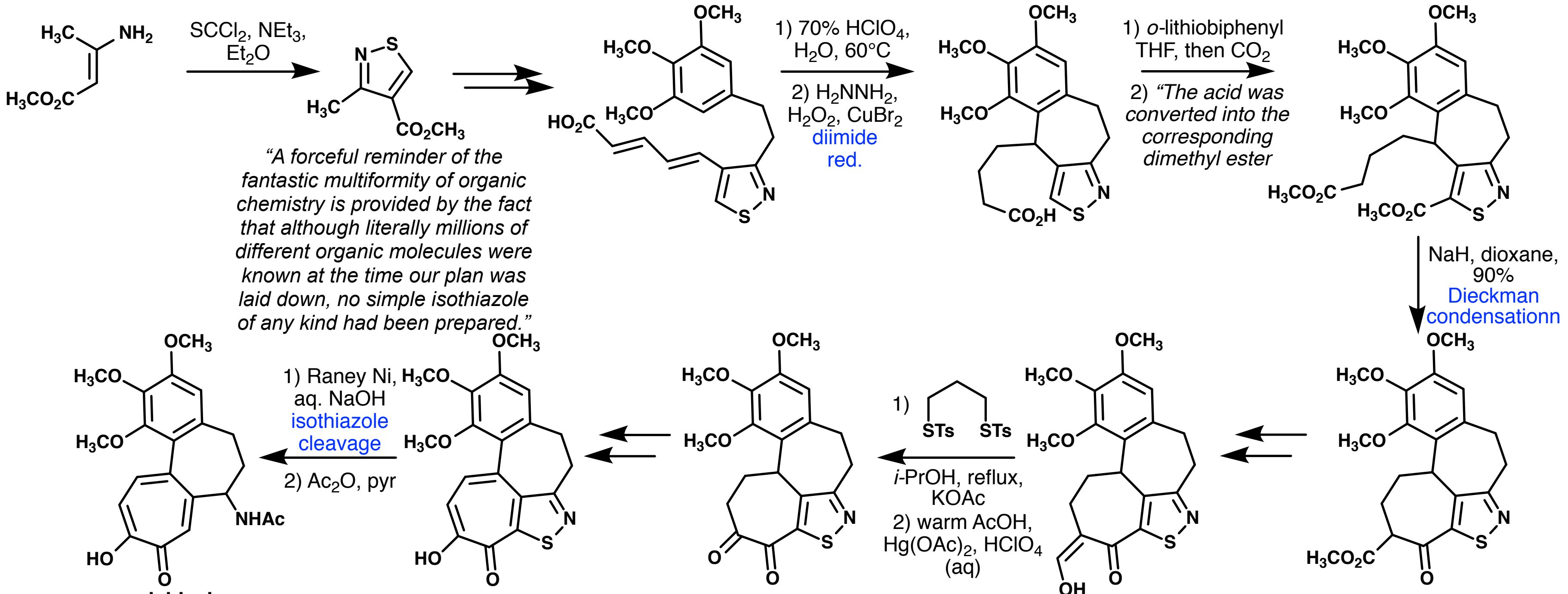
colchicine: the finished route

"Colchicine was isolated for the first time in a more or less pure state by Pelletier and Caventou — those same great pioneers who deprived quinine, strychnine, veratrine, and many other substances of their hiding places"



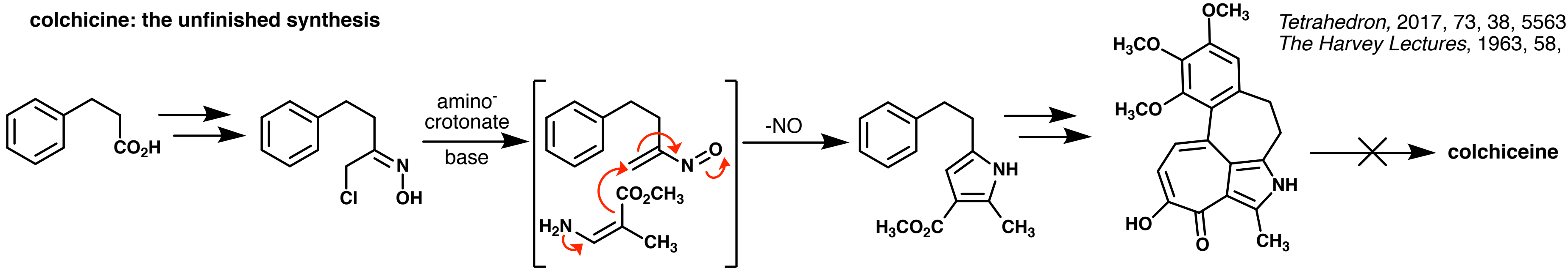
"A forceful reminder of the fantastic multiformity of organic chemistry is provided by the fact that although literally millions of different organic molecules were known at the time our plan was laid down, no simple isothiazole of any kind had been prepared."

***rac*-colchiceine**

"Our investigation now entered a phase which was tinged with melancholy. Our isothiazole ring had served admirably in every anticipated capacity and some others as well...it had mobilised its special directive and reactive capacities dutifully, and had not once obtruded a willful and diverting reactivity of its own. Now it must discharge but one more responsibility to permit itself gracefully to be dismantled, not to be used again until someone might see another opportunity to adopt so useful a companion on another synthetic adventure. And perform this final act with grace it did."

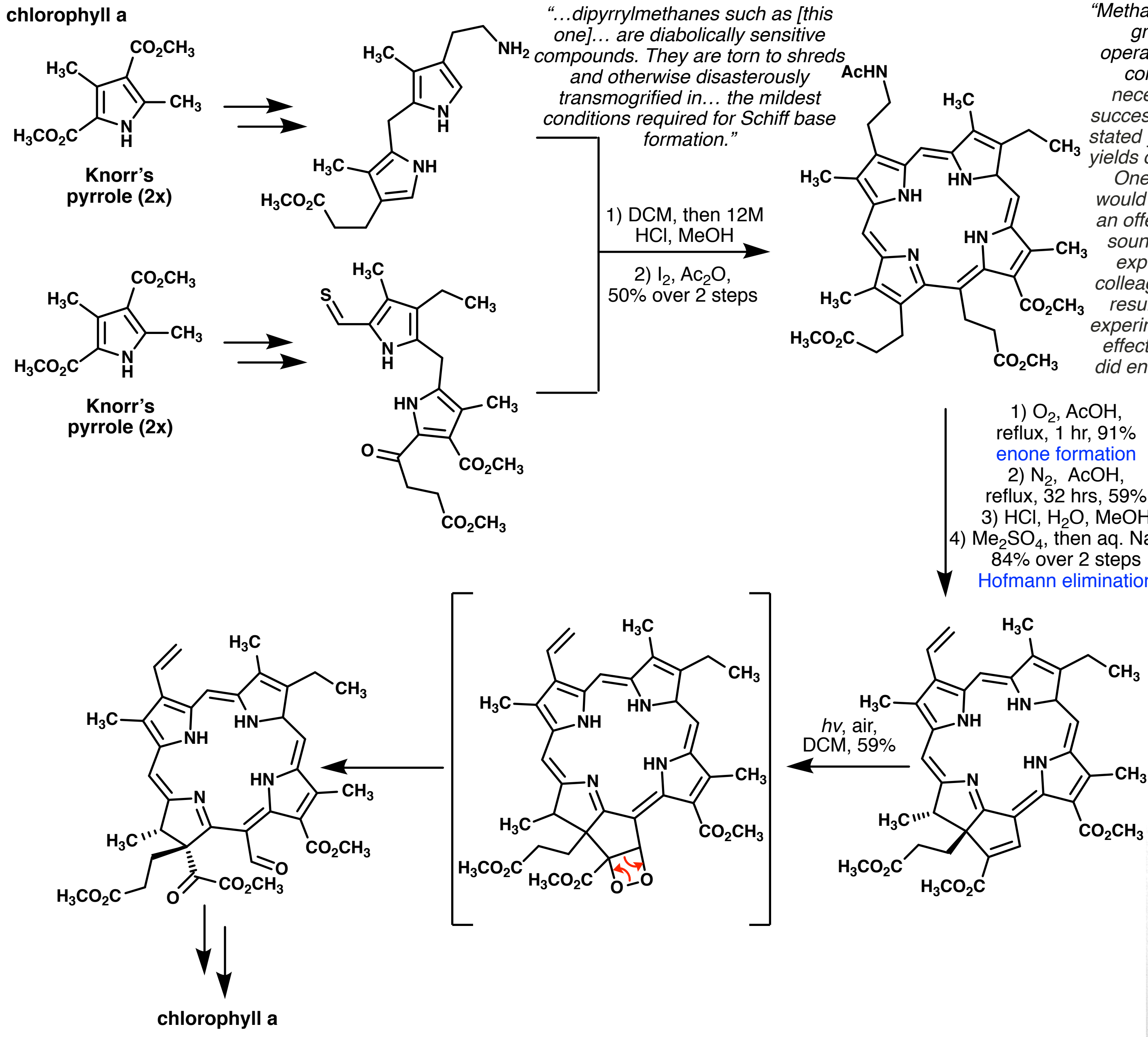
colchicine: the unfinished synthesis

Tetrahedron, 2017, 73, 38, 5563
The Harvey Lectures, 1963, 58, 21



"In spring 1959, it looked like RBW and I would both lecture on the synthesis of colchicine at the forthcoming Gordon Conference. RBW did not know the details of our progress at that time, of how we had advanced to the stage of the desacetylamino colchiceine relay compound of which we knew that at Harvard, they were able to make it by Hofmann degradation from the natural product. Woodward did not show up at the Gordon Conference and I remember having visited him after the conference at Harvard where he listened to my colchicine story with great interest."—Albert Eschenmoser

Woodward’s Greatest Hits



chlorophyll a

Knorr’s pyrrole (2x)

Knorr’s pyrrole (2x)

“…dipyrrylmethanes such as [this one]… are diabolically sensitive compounds. They are torn to shreds and otherwise disasterously transmogrified in… the mildest conditions required for Schiff base formation.”

1) DCM, then 12M HCl, MeOH
2) I_2, Ac_2O, 50% over 2 steps

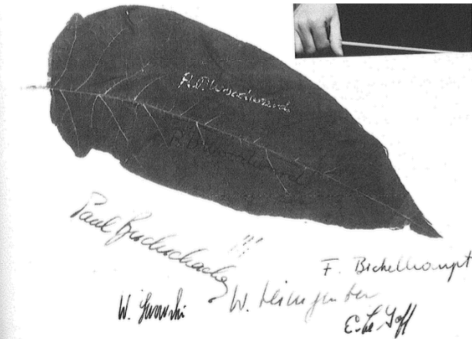
“Methanolic HCl was… measured by pouring into a graduated cylinder… While these pouring operations may seem to negate other operations conducted under anhydrous nitrogen…The necessity of this whimsical prerequisite for the successful execution of the reaction series with the stated yield was repeatedly verified. Without it, final yields of porphyrin lower by 10-15% were obtained. One of us, who swore a colourful oath that he would never, by pouring the acid, be party to such an offence against what he regarded (wrongly) as sound scientific procedure, was forced by cruel experience to suffer the ignominy of having a colleague pour his acid for him in order to achieve results comparable with his fellows. Numerous experiments designed to elucidate the cause of the effect led us to no conclusive rationalisation, nor did enable us to substitute a more respectable – if not easier – alternative procedure”

1) O_2, AcOH, reflux, 1 hr, 91%
enone formation
2) N_2, AcOH, reflux, 32 hrs, 59%
3) HCl, H_2O, MeOH
4) Me_2SO_4, then aq. NaOH
84% over 2 steps
Hofmann elimination

“Purpurins are members of a sub-class of chlorins; the introduction of unsaturated substituents into the gamma position of the chlorin system frequently results in a change from the normal green to a purplish hue.”

hv, air, DCM, 59%

chlorophyll a

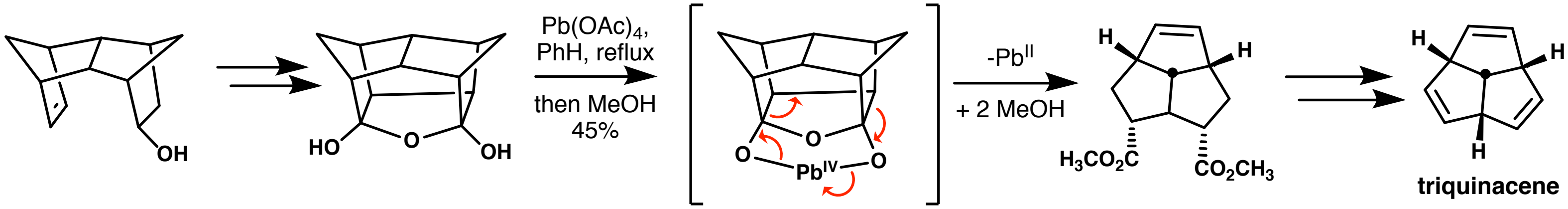


Shenvi Lab Group Meeting
September 11, 2017

One-Hit Wonders: Triquinacene and Marasmic Acid

Hannah Burdge

triquinacene

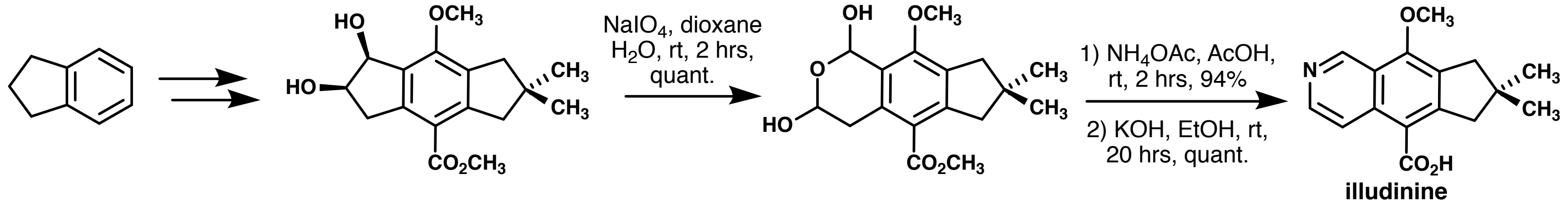


"While our measurements must be interpreted with the reserve which respect for the long arm of coincidence should always engender, they provide at present no evidence of delocalization among the π-electron systems of the double bonds of triquinacene in the ground state."

JACS, 1964, 86, 3162.

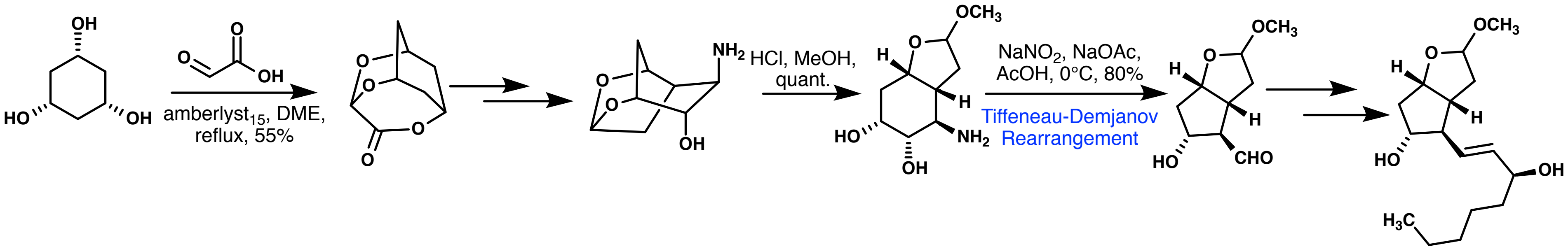
The hitherto unknown hydrocarbon… triquinacene, posesses three double bonds so situated in fixed positions as to provide valuable information about the postulated phenomenon of homoaromaticity.

illudinine



JACS, 1977, 99, 8007.

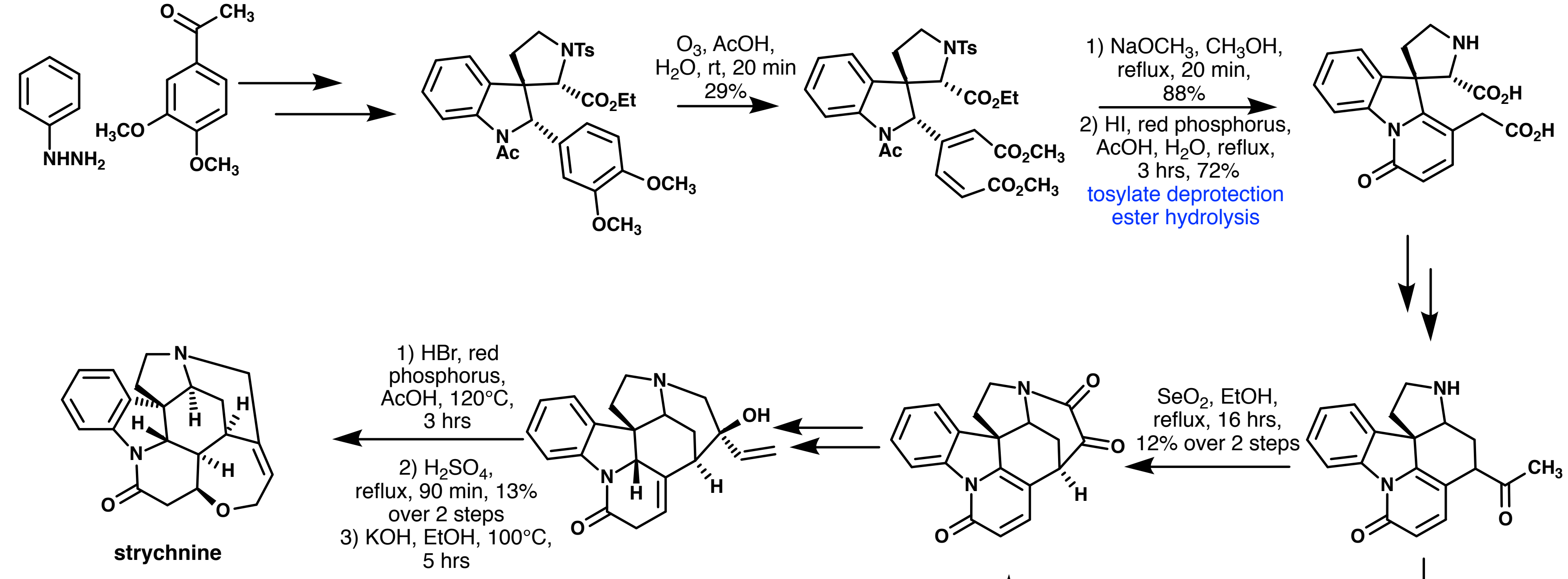
prostaglandin $F_{2}\alpha$



Formal synthesis of $PG_{F2}\alpha$

JACS, 1973, 95, 6853.

STRYCHNINE!



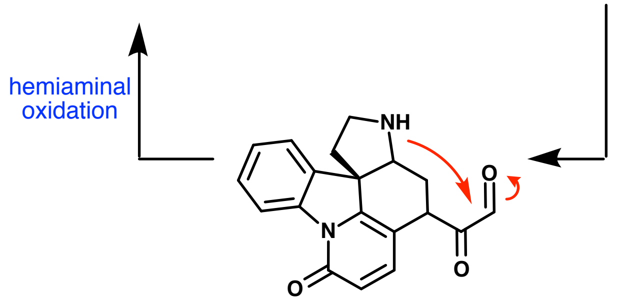
O$_3$, AcOH, H$_2$O, rt, 20 min
29%

1) NaOCH$_3$, CH$_3$OH, reflux, 20 min, 88%
2) HI, red phosphorus, AcOH, H$_2$O, reflux, 3 hrs, 72%
tosylate deprotection
ester hydrolysis

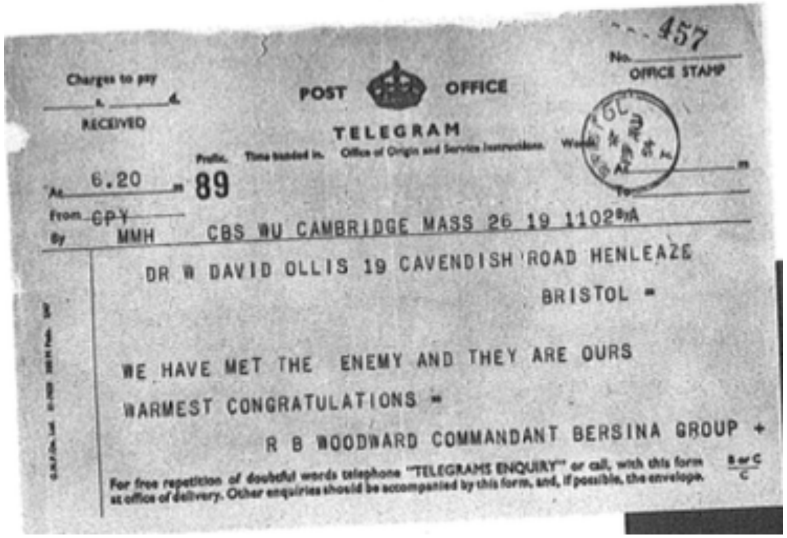
SeO$_2$, EtOH, reflux, 16 hrs, 12% over 2 steps

1) HBr, red phosphorus, AcOH, 120°C, 3 hrs
2) H$_2$SO$_4$, reflux, 90 min, 13% over 2 steps
3) KOH, EtOH, 100°C, 5 hrs

strychnine



hemiaminal oxidation



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At 6.20 m 89
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DR W DAVID OLLIS 19 CAVENDISH ROAD HENLEAZE
BRISTOL =

WE HAVE MET THE ENEMY AND THEY ARE OURS
WARMEST CONGRATULATIONS =
R B WOODWARD COMMANDANT BERSINA GROUP +

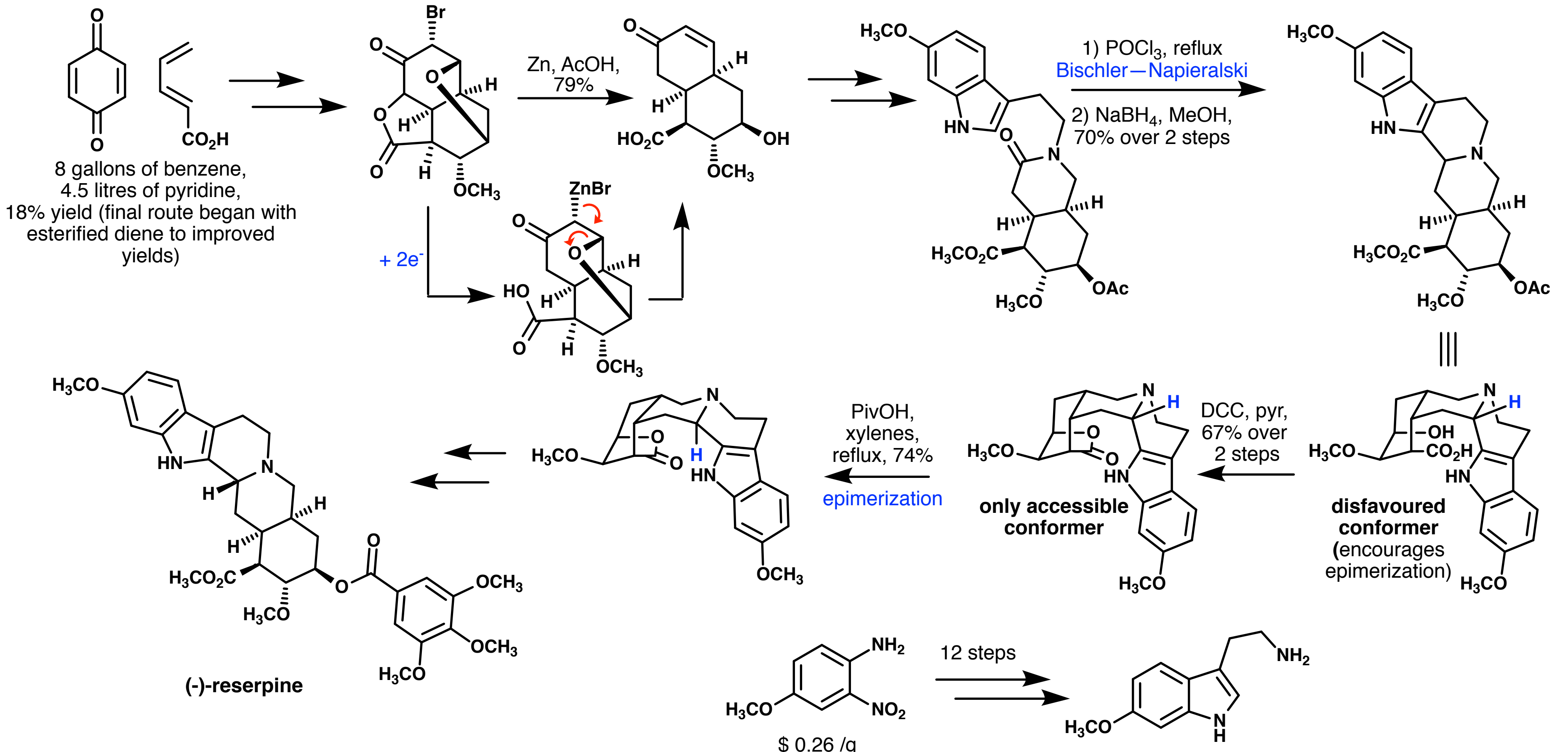
For free repetition of doubtful words telephone "TELEGRAMS ENQUIRY" or call, with this form at office of delivery. Other enquiries should be accompanied by this form, and, if possible, the envelope.

"It is a measure of Woodward's greatness that nearly four decades elapsed before Philip Magnus in 1992 carried out the second synthesis of strychnine… Today, synthetic chemists attempt to find the shortest possible routes to strychnine, which can be compared with contemporary attempts to climb Mount Everest in the fastest possible time. However, these speed trials in both fields, dependant as they are on modern technology, cannot detract from the towering achievements of the pioneers."—Peter T.J. Morris

Reserpine

Hannah Burdge

"From the first, we looked upon the synthesis of reserpine as an exercise in stereochemistry."



8 gallons of benzene,
4.5 litres of pyridine,
18% yield (final route began with
esterified diene to improved
yields)

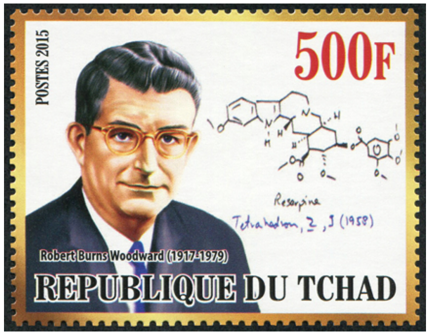
only accessible conformer

disfavoured conformer (encourages epimerization)

(-)-reserpine

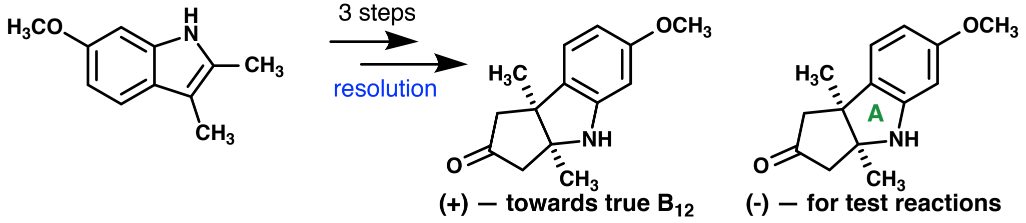
\$ 0.26 /g

"In this chapter, we have witnessed one of Woodward's most brilliant achievements, and perhaps one of the most remarkable total syntheses of all time. The strategy is brilliant and the tactics even more spectacular….The Woodward total synthesis of reserpine is an inspirational accomplishment rhat will, no doubt, remain a classic in the history of toyal synthesis." --Nicolaou and Sorenson, Classics in Total Synthesis



The B_{12} Saga

Synthesis of the A ring:

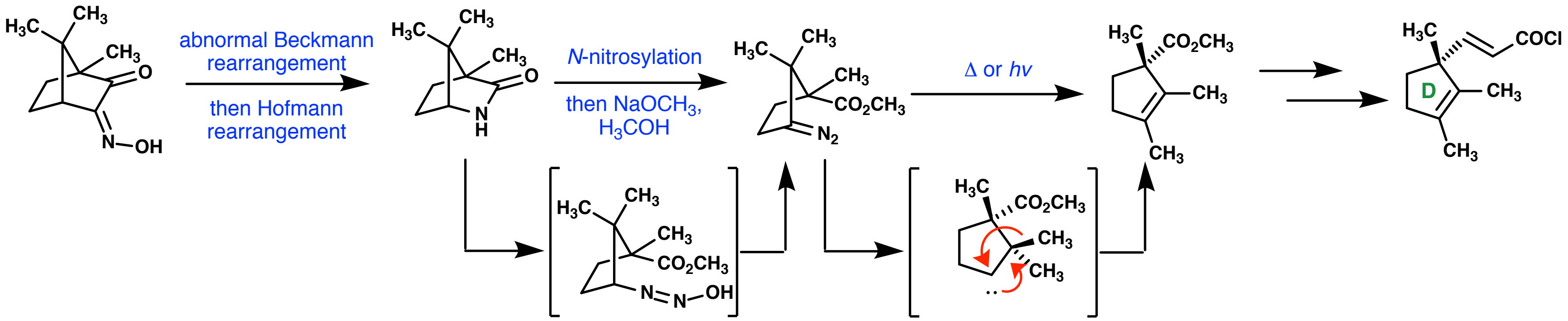


(+) — towards true B_{12} **(-) — for test reactions**

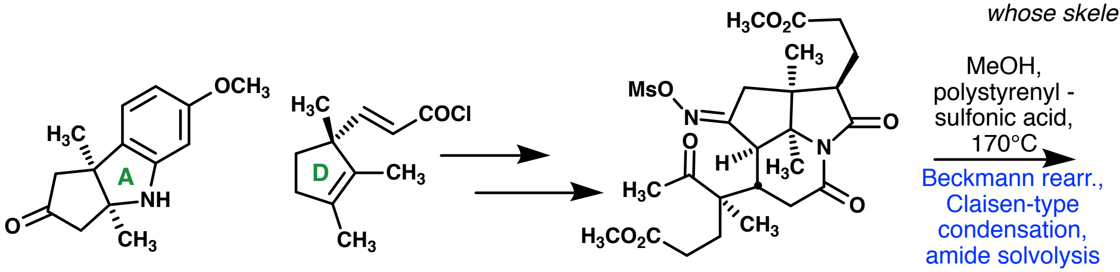
*“Perhaps also this is the point at which I should emphasize explicitly the importance of the availability of the "unnatural" enantiomer. Much as had been our progress at this point, we were not unaware that we still had far to go, and that it might be either necessary or desirable—as indeed it turned out to be—to investigate a considerable number of alternatives for further advance. In these explorations we were able to utilize **XXXVII**, confident that whatever new route we might establish through its study would be applicable to its counterpart (XXXIV) of the natural series; our experience has been such that this is just about the only kind of model study which we regard as wholly reliable! And in fact, although the reactions I shall describe in the sequel will be presented for compounds in the natural series, almost all of them were first discovered using the enantiomeric substances.” Pure Appl. Chem. 1968, **17**, 519*

Read: “The only model system worth using is the enantiomer.”

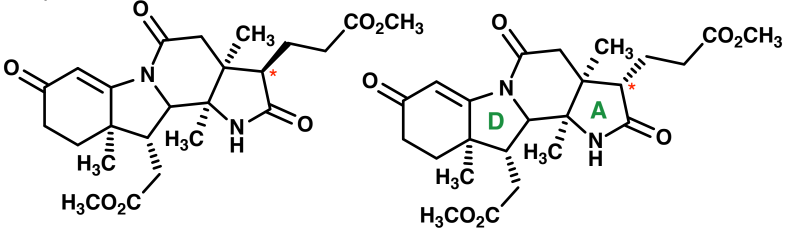
Synthesis of the D ring:



A-D fragment union:



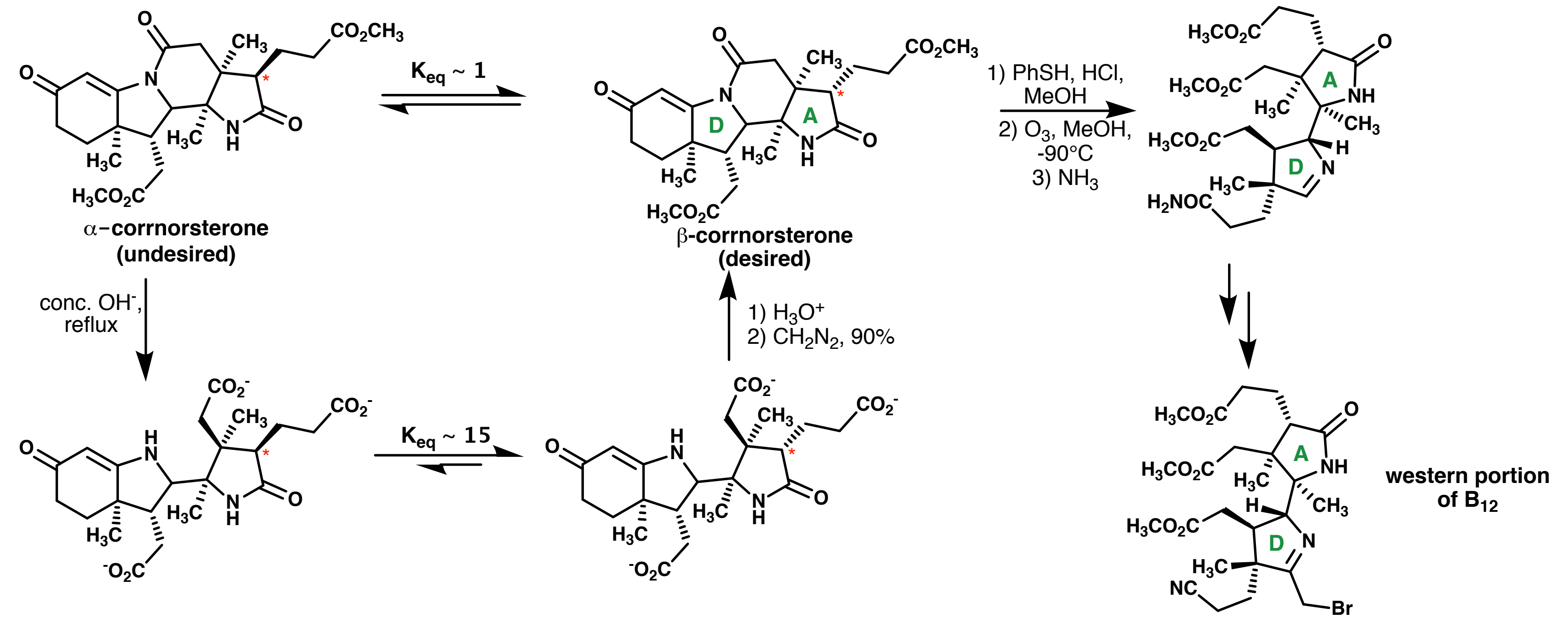
“The product… we have more or less jocularly dubbed ‘corrnorsterone’. The ‘cor’ in this appelation representd our hope that the substance is destined one day to be transformed into a corrin; the 'norsterone' devolves from the fact ithat [it] is a ketone whose skeleton is that of a norsteroid if nitrogens be ignored; finally, if the name be pronounced in Slurvian, it becomes 'cornerstone!"



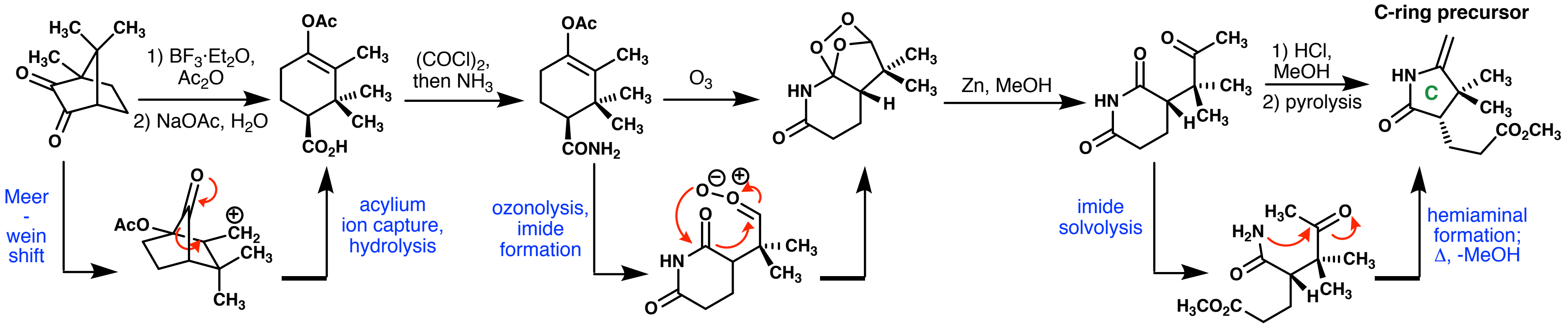
α−corrnorsterone (major, undesired)

β-corrnorsterone (minor, desired)

The B_{12} Saga



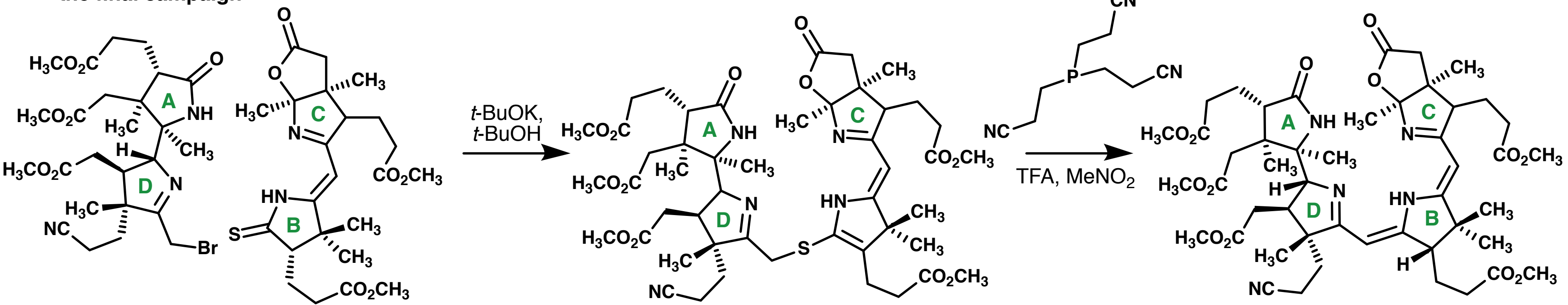
Synthesis of the C ring:



"When [the amide] is treated with ozone, a rather amusing sequence of changes occurs which results in a 'false' ozonide— false in that it appears to be the product of ozonization of quire another substance than its actual precursor."

Pure Appl. Chem. 1973, 33, 45.
Pure Appl. Chem. 1971, 25, 283.
Pure Appl. Chem. 1968, 17, 519.
Science 1977, 196, 1410.

the final campaign

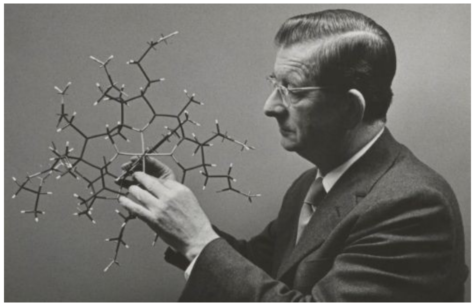


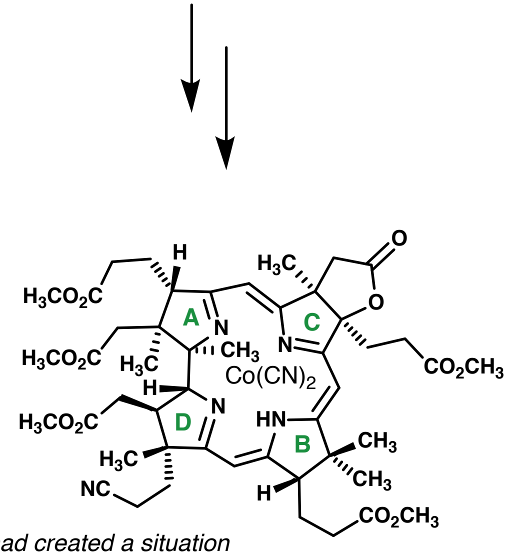
western portion

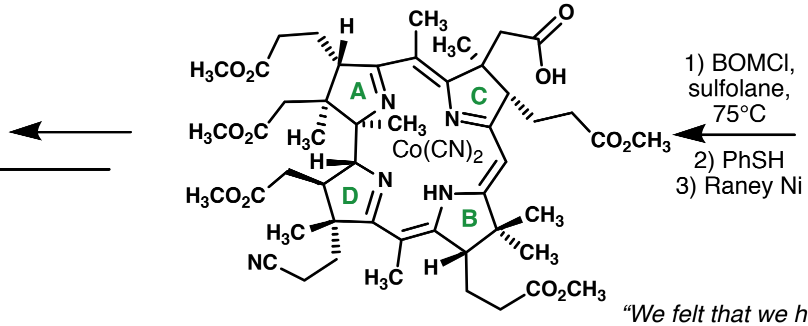
eastern portion (thiodextrolin)
synthesized from C
ring precursor by the
Eschenmoser group

cyanocorrigenolide

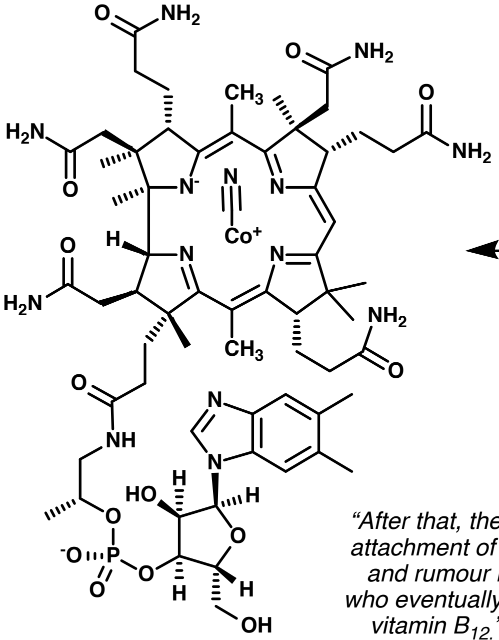
"…a kind of hopeful name, given since we had aspirations that the compound might someday be turned into a corrin"







"We felt that we had created a situation in which C.10 was virtually inaccessible — just simply so crowded by groups whose sheer bulk was protecting it that it would be very difficult indeed to get any reagent to attack the C.10 position."



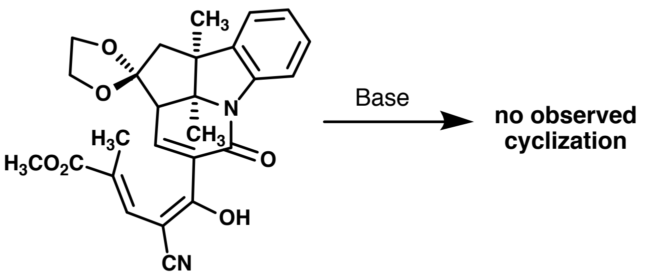
cyanocobalamin
(a.k.a. vitamin B_{12})

"After that, the procedure of Bernhauer et al.for the attachment of the nucleotide moiety was executed, and rumour has it that it was Woodward himself who eventually isolated the 'beautiful red' crystals of vitamin B_{12}." —Riether and Mulzer, Eur. J. Org. Chem. 2003, 30-45

"The contrast [of Eschenmoser's alternative B_{12} synthesis] with Woodward's… reveals the central weakness of Woodward's approach to synthesis, namely, his tendency to employ well-tried reactions in novel sequences rather than innovate wholly new reactions. Nevertheless, the old warrior had made a major contribution to one of the most outstanding syntheses of the 20th century."—Peter T.J. Morris

A Fortuitous Discovery: The Woodward Challenge Continues

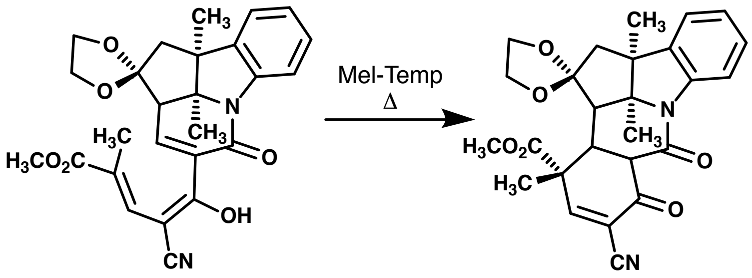
Woodward et. al. anticipated the following Michael reaction *en route* to the B_{12} A ring:



Base

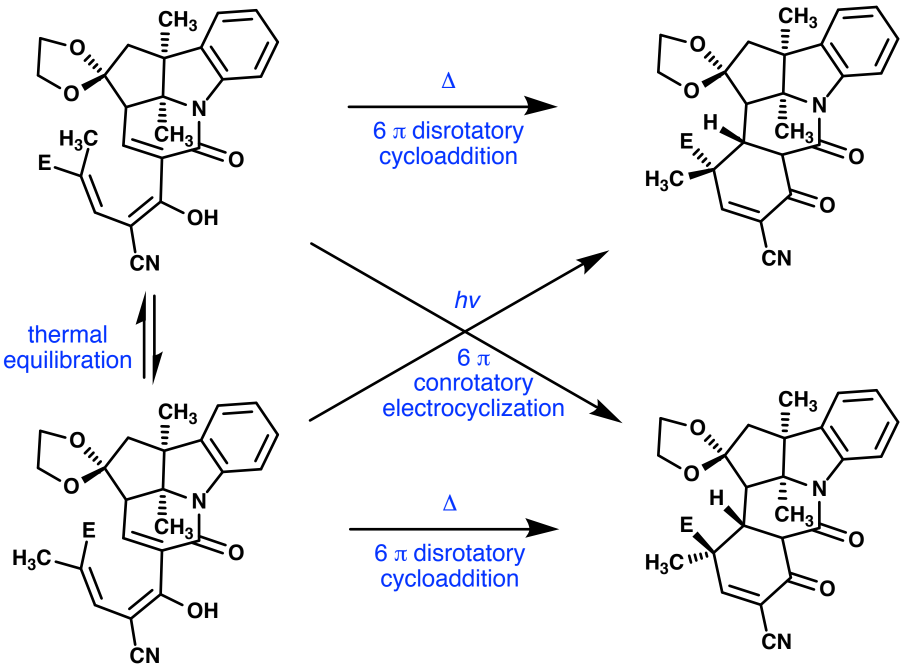
no observed cyclization

However, instead, while observing a melting point…



Mel-Temp
Δ

"BUT as our investigation proceeded, it became more and more clear that our stereochemical anticipations had been dead wrong… Here was a real dilemma. I had analysed the situation very carefully in the light of what I regarded tas the best contemporary theoretical principles, and I had reached an absolutely wrong conclusion. I was appalled. Now I stood before— so to speak— the 5th mysterious reaction AND this one was my own!"



Δ

6 π disrotatory cycloaddition

thermal equilibration

hv

6 π conrotatory electrocyclization

Δ

6 π disrotatory cycloaddition

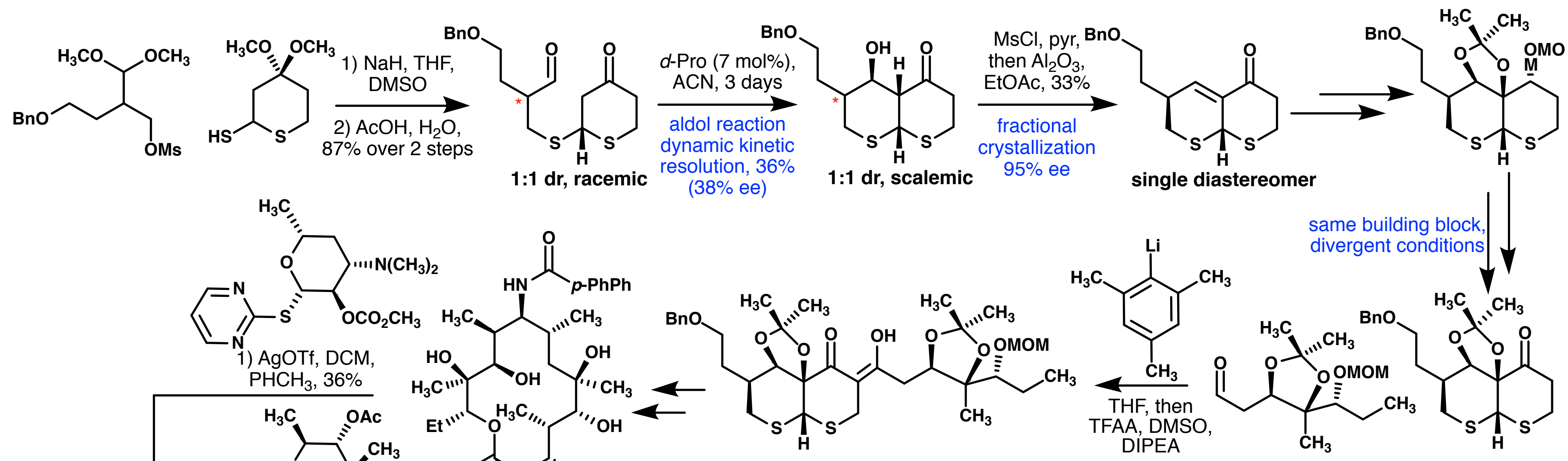
"I REMEMBER very clearly— and it still surprises me somewhat— the crucial flash of enlightenment came to me in <u>algebraic</u>, rather than in <u>pictorial</u> or <u>geometric form</u>. Out of the blue, it occurred to me that the coefficients of the terminal terms in the mathematical expression representing the [HOMO] of butadiene were of opposite sign, while those of the corresponding expression for hexatriene possessed the same sign."

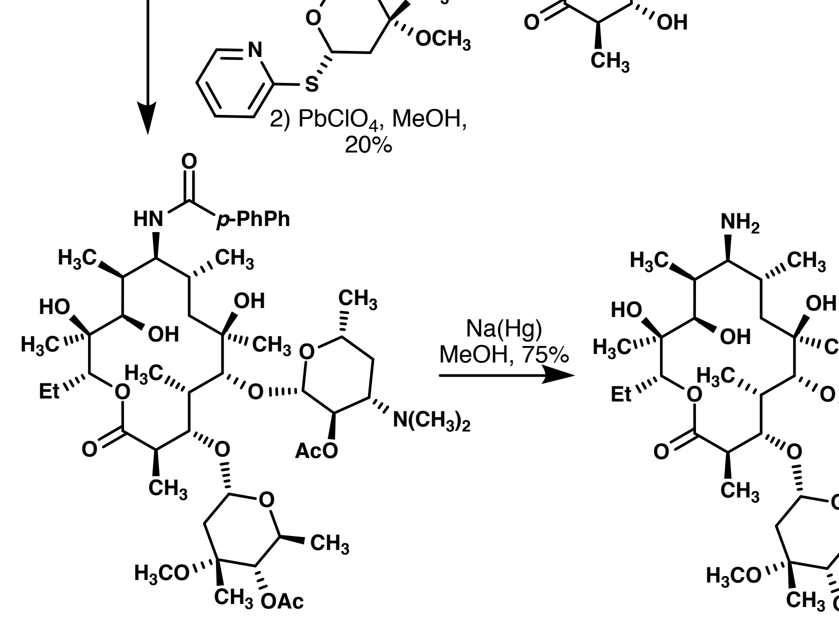
R.B. Woodward, Cope Award Lecture

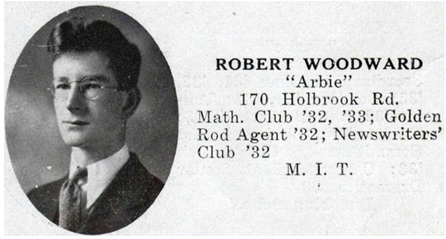
Shenvi Lab Group Meeting
September 11, 2017

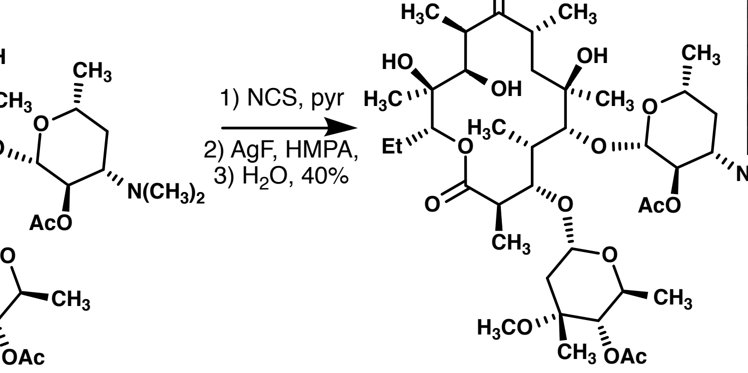
Erythromycin: An Old Soldier's Last Stand

Hannah Burdge






ROBERT WOODWARD
"Arbie"
170 Holbrook Rd.
Math. Club '32, '33; Golden Rod Agent '32; Newswriters' Club '32
M. I. T.

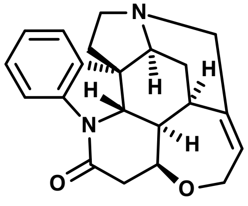


(-) erythromycin A

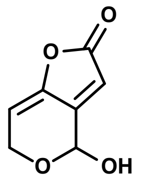
"We are indebted to Professor Yoshito Kishi for his help and encouragement and, in particular, for his acceptance of the role of principal investigator upon Professor Woodward's death."

A Jack of All Trades

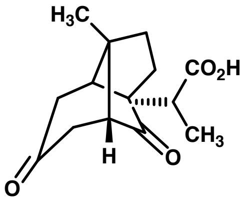
Woodward's structural elucidation studies were numerous:



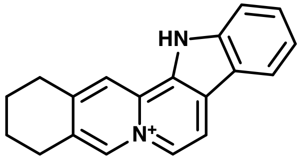
strychnine
JACS, 1948, 70, 2508



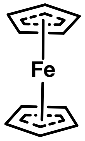
patulin
JACS, 1949, 71, 758



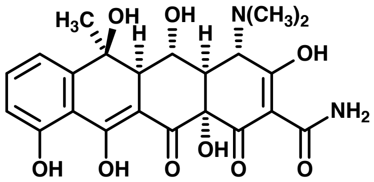
santonic acid
JACS, 1948 70, 4216



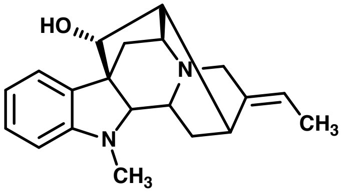
sempervirine
JACS, 1949, 71, 379



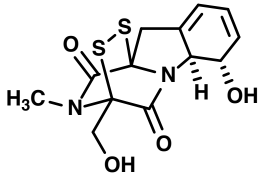
ferrocene
JACS, 1952, 74, 2125



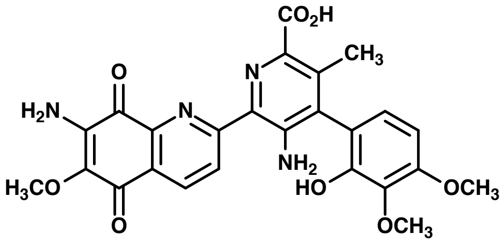
terramycin
JACS, 1952, 74, 3708



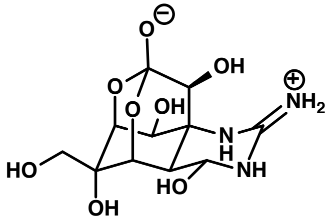
tetraphyllicine
JACS, 1956, 78, 1259



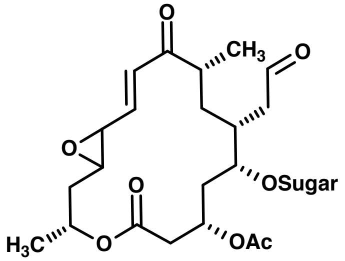
gliotoxin
JACS, 1958, 80, 1001



streptonigrin
JACS, 1963, 85, 2532



tetrodotoxin
JACS, 1964, 86, 5030



magnamycin
JACS, 1965, 87, 4662

He also created some novel compounds and reagents of his own:

penem antibiotics: combining the key pieces of cephalosporins and penicillins
Philosophical Transactions of the RSC, 1980, 289(1036), 239

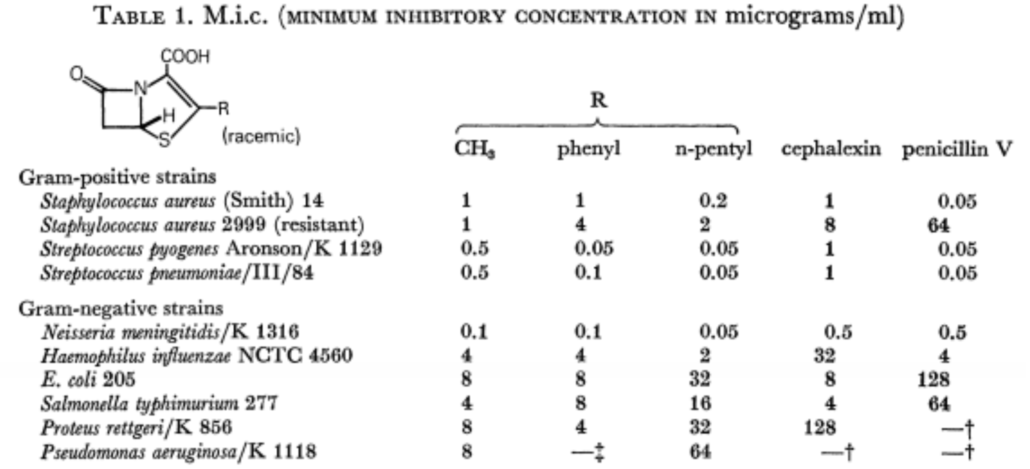
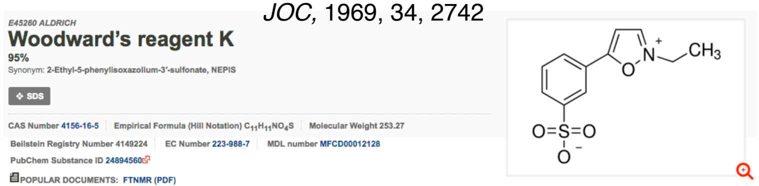


TABLE 1. M.i.c. (MINIMUM INHIBITORY CONCENTRATION IN micrograms/ml)

	R				
	CH_3	phenyl	n-pentyl	cephalexin	penicillin V
Gram-positive strains					
Staphylococcus aureus (Smith) 14	1	1	0.2	1	0.05
Staphylococcus aureus 2999 (resistant)	1	4	2	8	64
Streptococcus pyogenes Aronson/K 1129	0.5	0.05	0.05	1	0.05
Streptococcus pneumoniae/III/84	0.5	0.1	0.05	1	0.05
Gram-negative strains					
Neisseria meningitidis/K 1316	0.1	0.1	0.05	0.5	0.5
Haemophilus influenzae NCTC 4560	4	4	2	32	4
E. coli 205	8	8	32	8	128
Salmonella typhimurium 277	4	8	16	4	64
Proteus rettgeri/K 856	8	4	32	128	—†
Pseudomonas aeruginosa/K 1118	8	—‡	64	—†	—†

Woodward's reagent: for use in low-racemization peptide coupling
JOC, 1969, 34, 2742

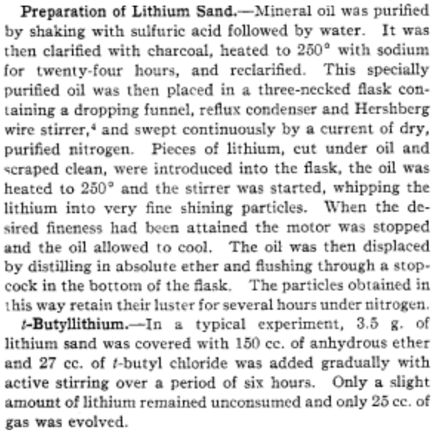


E45260 ALDRICH
Woodward's reagent K
95%
Synonym: 2-Ethyl-5-phenylisoxazolium-3'-sulfonate, NEPIS

SDS

CAS Number 4156-16-5 | Empirical Formula (Hill Notation) $C_{11}H_{11}NO_4S$ | Molecular Weight 253.27
Beilstein Registry Number 4149224 | EC Number 223-988-7 | MDL number MFCD00012128
PubChem Substance ID 24894560
POPULAR DOCUMENTS: FTNMR (PDF)

***t*-BuLi (really!):** arose from an (unsuccessful) attempt to synthesize tri-*t*-butylcarbinol
JACS, 1941, 63, 3229

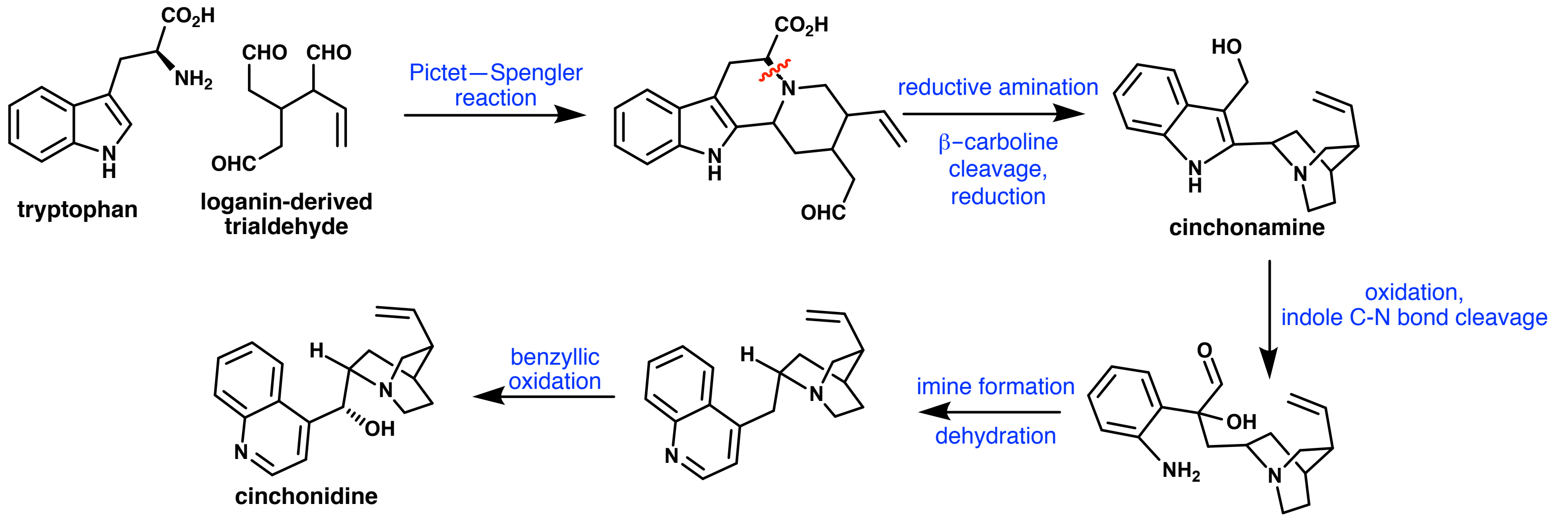


Preparation of Lithium Sand.—Mineral oil was purified by shaking with sulfuric acid followed by water. It was then clarified with charcoal, heated to 250° with sodium for twenty-four hours, and reclarified. This specially purified oil was then placed in a three-necked flask containing a dropping funnel, reflux condenser and Hershberg wire stirrer,[4] and swept continuously by a current of dry, purified nitrogen. Pieces of lithium, cut under oil and scraped clean, were introduced into the flask, the oil was heated to 250° and the stirrer was started, whipping the lithium into very fine shining particles. When the desired fineness had been attained the motor was stopped and the oil allowed to cool. The oil was then displaced by distilling in absolute ether and flushing through a stopcock in the bottom of the flask. The particles obtained in this way retain their luster for several hours under nitrogen.

***t*-Butyllithium.**—In a typical experiment, 3.5 g. of lithium sand was covered with 150 cc. of anhydrous ether and 27 cc. of *t*-butyl chloride was added gradually with active stirring over a period of six hours. Only a slight amount of lithium remained unconsumed and only 25 cc. of gas was evolved.

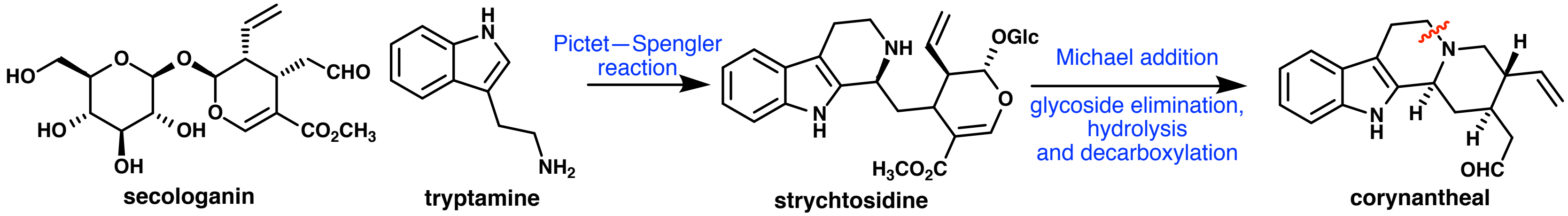
Biosynthetic Hits and Misses

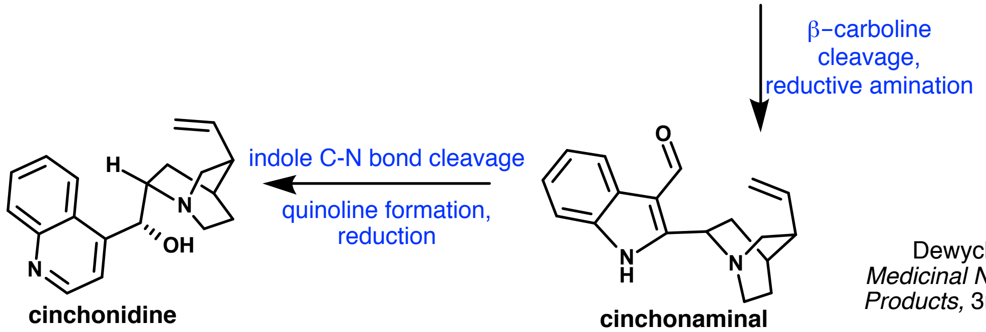
Woodward's hypothesis for the biosynthesis of the cinchona alkaloids:



Alkaloids, 3, 54 (1953)

However, subsequent work disproved Woodward's initial hypothesis:





Dewyck, *Medicinal Natural Products,* 3rd edn

Despite this misstep, Woodward correctly postulated the sterol biosynthetic pathway elucidated by Konrad Bloch (Nobel Prize in Physiology and Medicine, 1964)

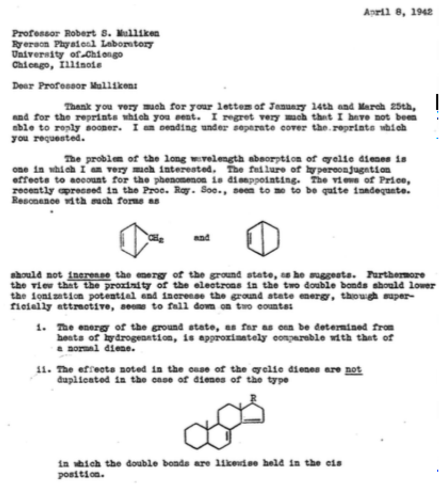
Shenvi Lab Group Meeting
September 11, 2017

RBW: The Man, the Myth, the Legend

Hannah Burdge

subject matter not covered in this survey:

The Woodward Rules for enone and diene structural elucidation using UV/Vis



April 8, 1942

Professor Robert S. Mulliken
Ryerson Physical Laboratory
University of Chicago
Chicago, Illinois

Dear Professor Mulliken:

Thank you very much for your letters of January 14th and March 25th, and for the reprints which you sent. I regret very much that I have not been able to reply sooner. I am sending under separate cover the reprints which you requested.

The problem of the long wavelength absorption of cyclic dienes is one in which I am very much interested. The failure of hyperconjugation effects to account for the phenomenon is disappointing. The views of Price, recently expressed in the Proc. Roy. Soc., seem to me to be quite inadequate. Resonance with such forms as

CH_2 and

should not increase the energy of the ground state, as he suggests. Furthermore the view that the proximity of the electrons in the two double bonds should lower the ionization potential and increase the ground state energy, though superficially attractive, seems to fall down on two counts:

i. The energy of the ground state, as far as can be determined from heats of hydrogenation, is approximately comparable with that of a normal diene.

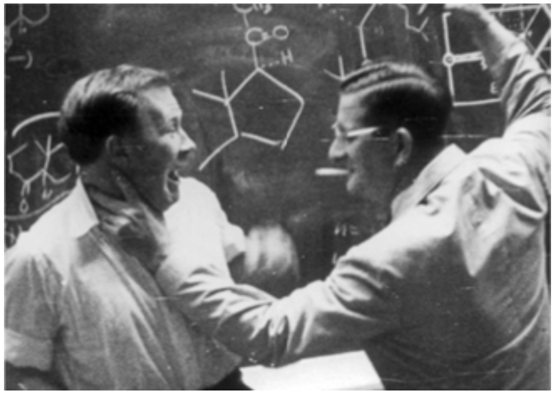
ii. The effects noted in the case of the cyclic dienes are not duplicated in the case of dienes of the type

R

in which the double bonds are likewise held in the cis position.

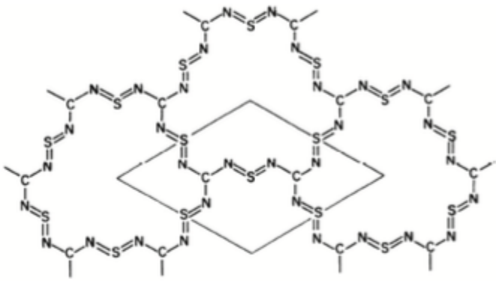
JACS, 1942, 64, 72
JACS, 1942, 64, 76

The Octant Rule for determining absolute configuration of cyclohexanones empirically from Cotton Effect signs



JACS, 1961, 83, 4013

Late-life interest in organic superconductors



Proc. R. Soc. (London). Series A. 1979, 366, 23
JACS, 1981, 103, 1540

Some parting words from The Man Himself:

To the question “Why does the chemist synthesize things?”,
Woodward once replied:
“The structure known, but not yet accessible by synthesis, is to the chemist what the unclimbed mountain, the uncharted sea, the untilled field, the unreached planet, are to other men. The achievement of the objective itself cannot but thrill all chemists, who even before they know the details of the journey can apprehend from their own experiences the joys and elations, the disappointments and false hopes, the obstacles overcome, the frustrations subdued, which they experienced who traversed a road to the goal. The unique challenge which chemical synthesis provides for the creative imagination and the skilled hand ensures that it will endure as long as men write books, paint pictures, and fashion things which are beautiful, or practical, or both."