The Application of Microwave Acceleration to the Synthesis of Pyrrole Containing Marine Natural Products

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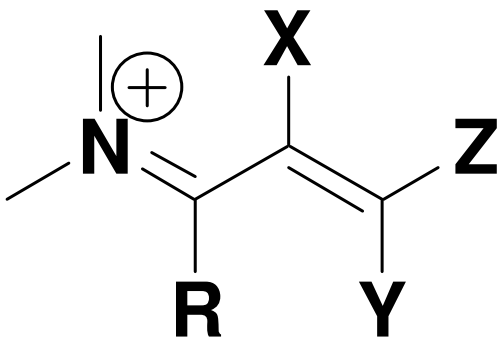
Topics to be Discussed

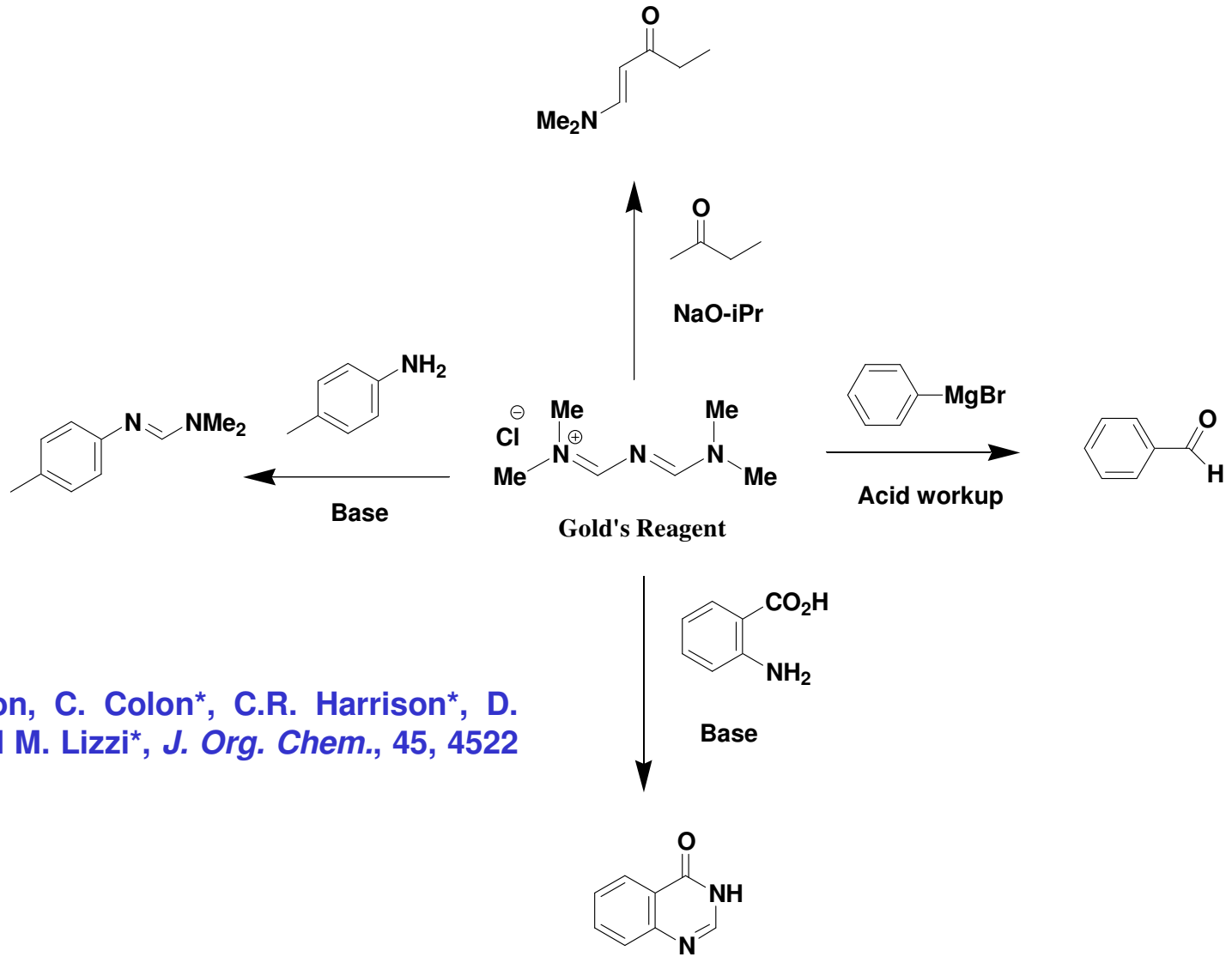
- Background and General Overview of the Vinylogous Iminium Salt Research Program
- Microwave Applications to Pyrrole Chemistry And Pyrrole Containing Marine Natural Products

Research Goals



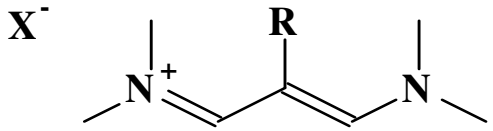
- Develop new reactions and methodology and understand the chemistry.
- Attach unique substituents and understand the chemical reactivity and the biological properties.
- Apply this knowledge to the synthesis of biologically interesting molecules.

Azavinamidinium Salt
Aldrichimica Acta, Vol. 19, #2, pp.43-46 (1986)

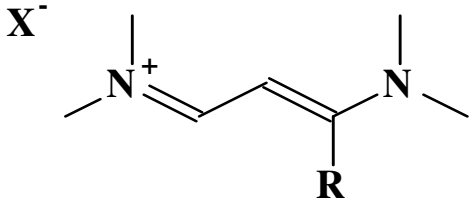


J. Gupton, C. Colon*, C.R. Harrison*, D. Polk and M. Lizzi*, *J. Org. Chem.*, 45, 4522 (1980)

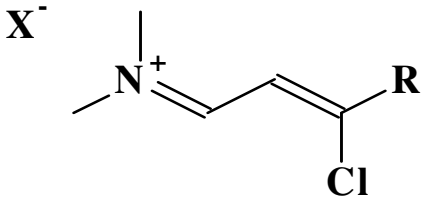
Types of Vinylogous Iminium Salt Derivatives



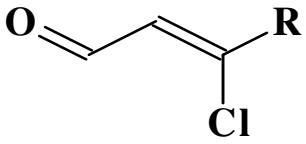
Vinamidinium Salt



Vinamidinium Salt



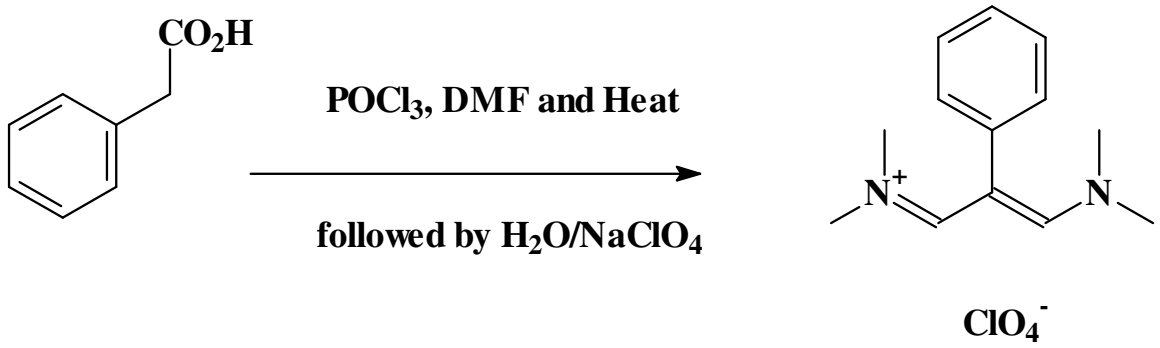
Chloropropeniminium Salt

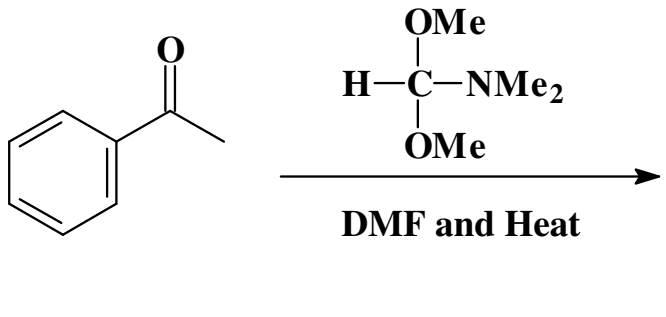


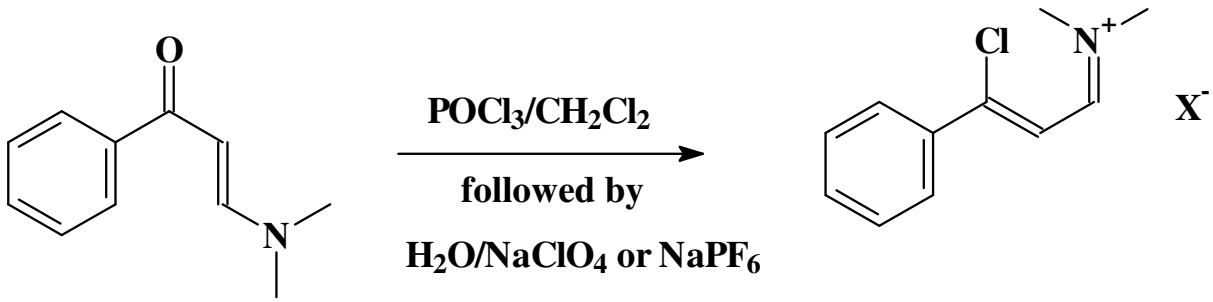
Beta Chloroenal

H. McNab and D. Loyd, *Angew. Chem. Int. Ed. Engl.*, 15, 459 (1976)

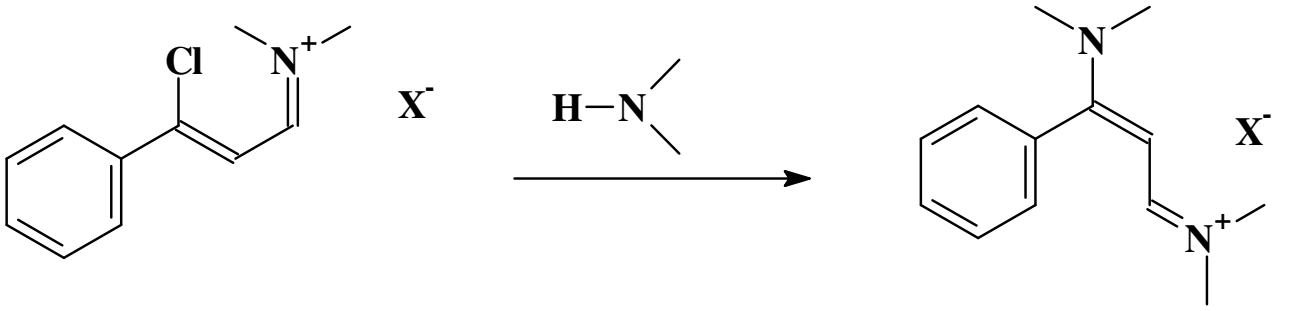
Methods of Synthesis of Vinylogous Iminium Salts

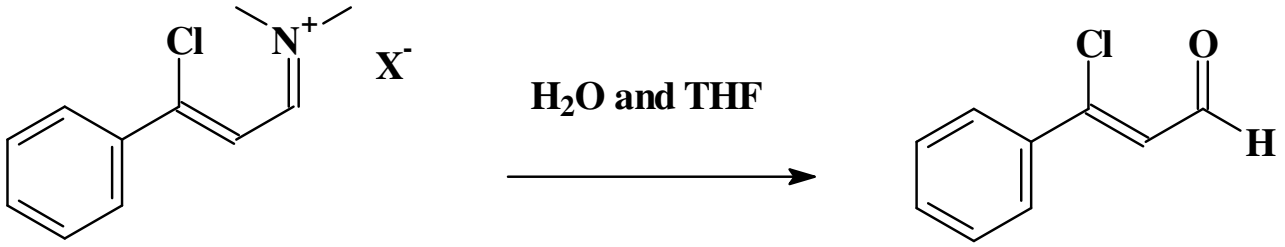




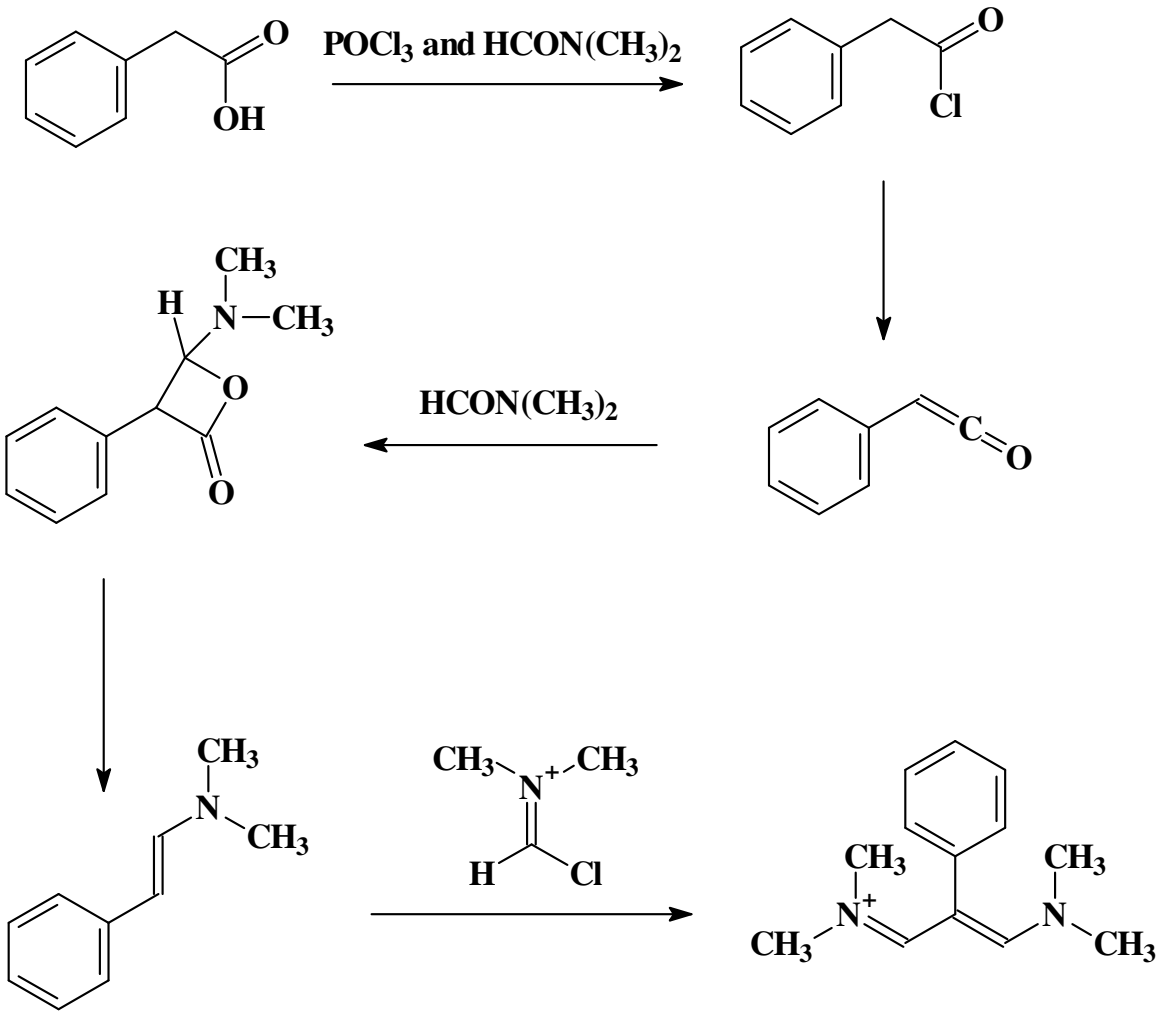


Methods of Synthesis of Vinylogous Iminium Salts

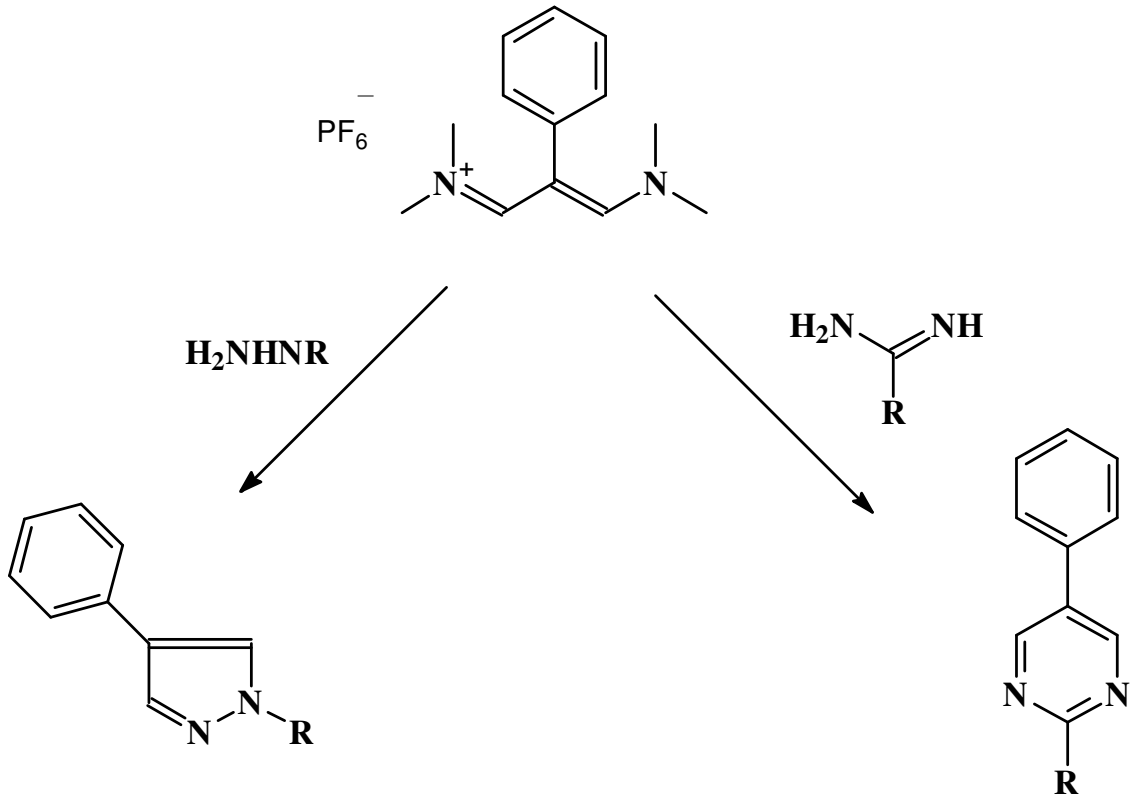




Mechanism for the Formation of an Aryl Vinamidinium Salt

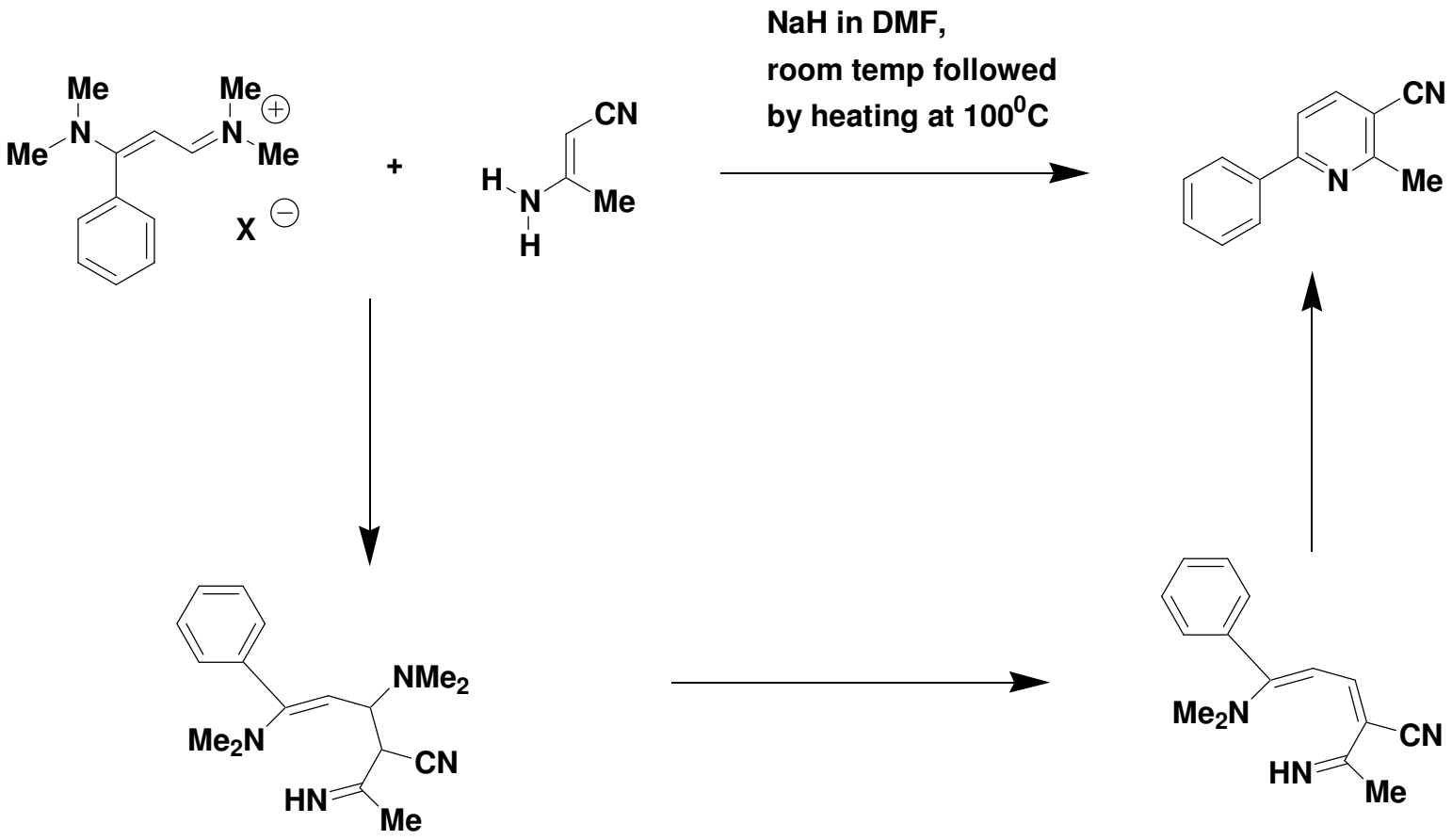


Vinylogous Iminium Salts as Masked 1,3-Dicarbonyl Compounds



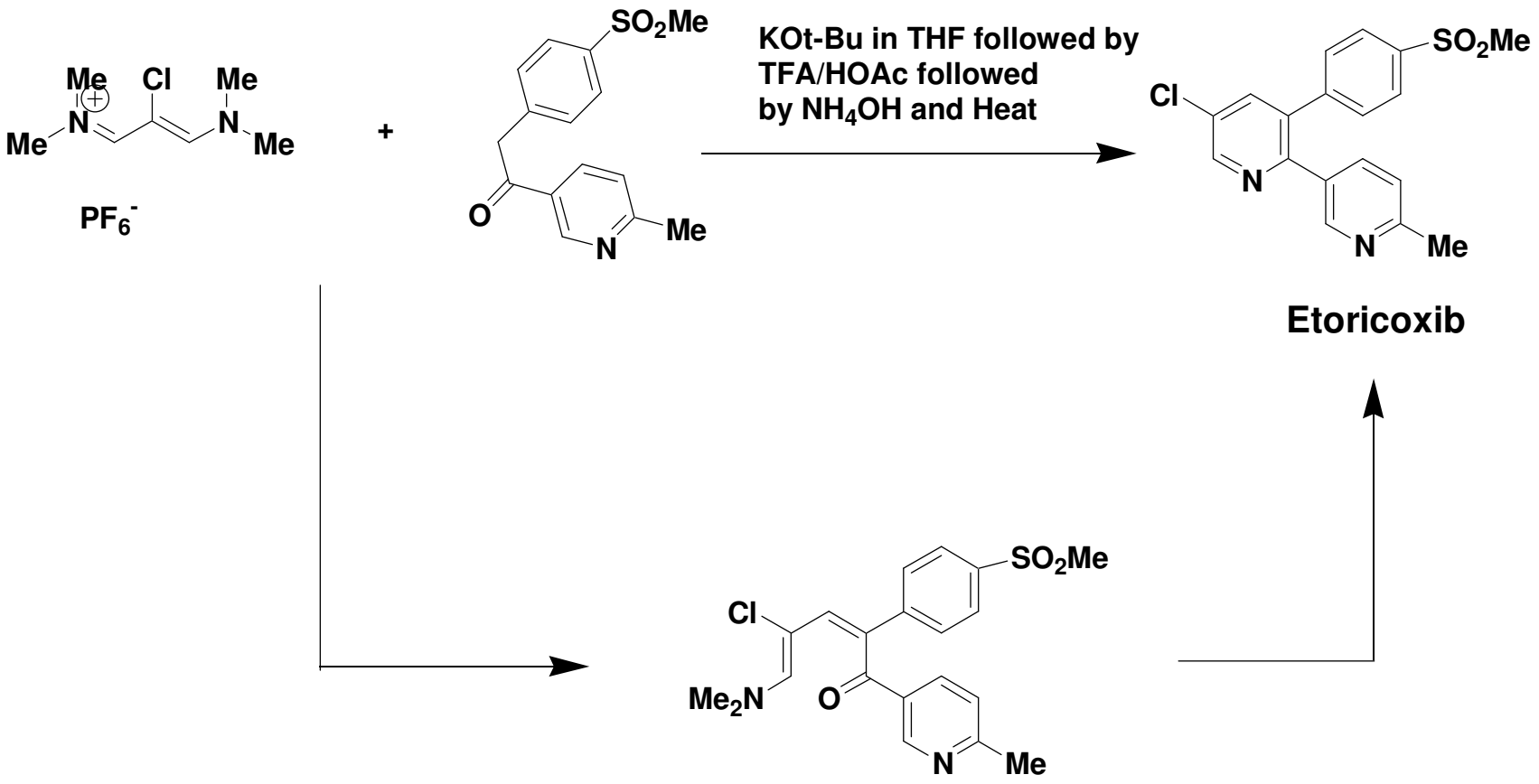
H. McNab and D. Loyd, *Angew. Chem. Int. Ed. Engl.*, 15, 459 (1976)

Some Reactions Developed by the Gupton Group
Pyridine Formation



J. Gupton, S. Petrich, F. Hicks*, D. Wilkinson*, J. Tarrant, S. Bruno*, M. Vargas*, K. Hosein* and J. Sikorski,, *Tetrahedron*, 51, 1575 (1995).

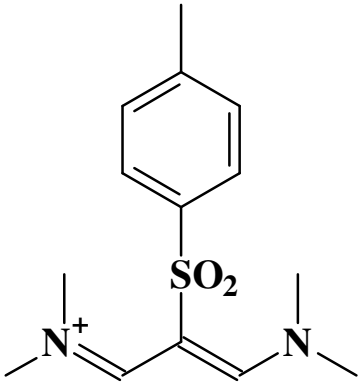
Merck Route to Etoricoxib

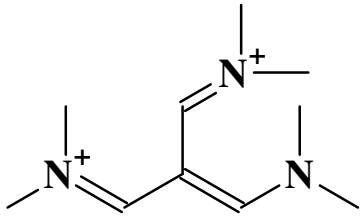


I. Davies, et al, *J. Org. Chem.*, 2000, 65, 8415

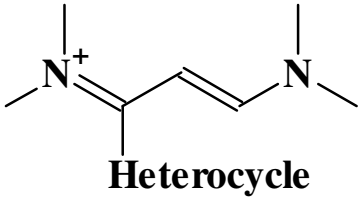
Some Interesting Substituent Groups Developed by the Gupton Group and Collaborators

J. Gupton, J. Gall*, S. Riesinger*, S. Smith*, K. Bevirt*, J. Sikorski and Z. Arnold, *J. Heterocyclic Chem.*, 28, 1281 (1991).

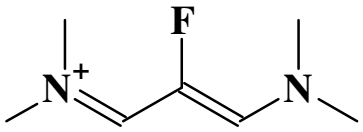


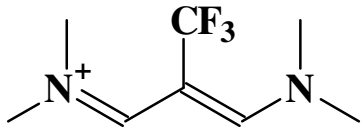


J. Gupton, S. Riesinger*, J. Gall*, A. Shah and K. Bevirt*, *J. Org. Chem.*, 56, 976 (1991).



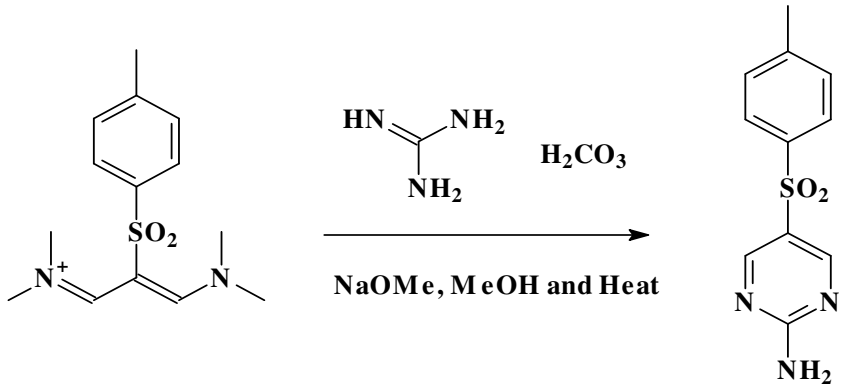
J. Gupton, F. Hicks*, D. Wilkinson*, S. Petrich and J. Sikorski, *Heterocycles,* 37, 487 (1994)



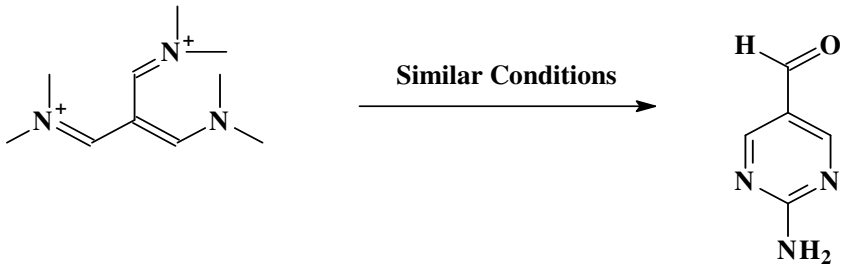


H. Yamanaka, X. Shi, and T. Ishihara and J. Gupton, *Tetrahedron Lett.*, 36, 1527 (1995).

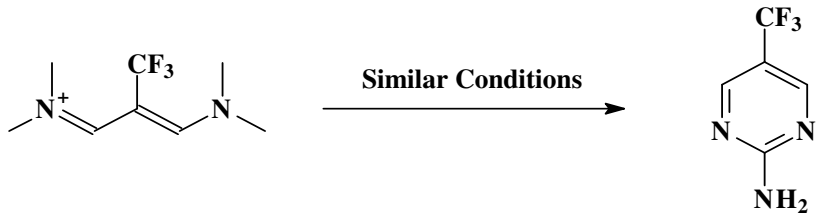
Substituent Group Incorporation into Heterocycles



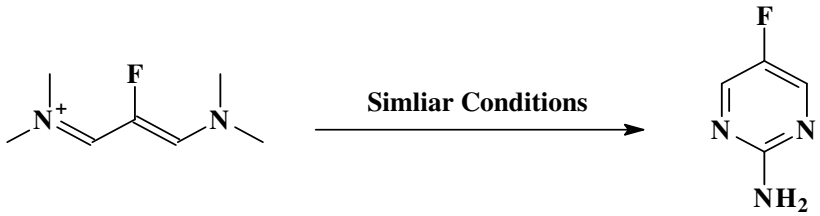
J. Gupton, S. Riesinger*, J. Gall*, A. Shah and K. Bevirt*, *J. Org. Chem.*, 56, 976 (1991)



J. Gupton, J. Gall*, S. Riesinger*, S. Smith* K. Bevirt*, J. Sikorski and Z. Arnold, *J. Heterocyclic Chem.*, 28, 1281 (1991)

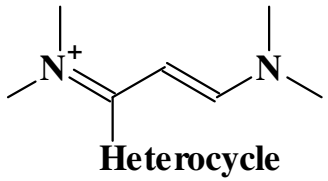


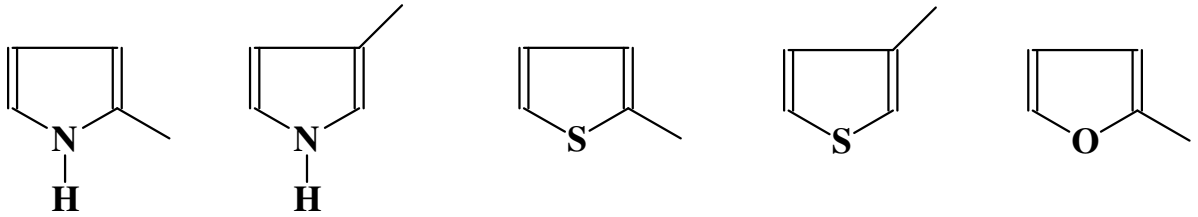
H. Yamanaka, T. Takekawa, K. Morita, T. Ishihara and J. Gupton, *Tetrahedron Lett.*, 37, 1829 (1996)

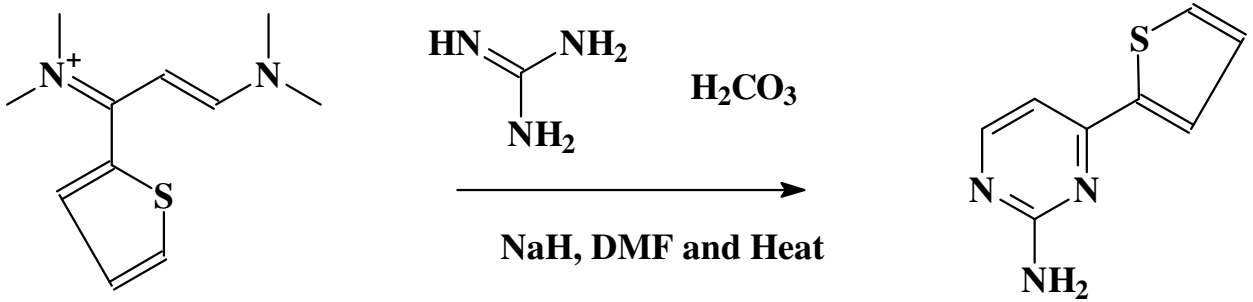


H. Yamanaka, X. Shi, T. Ishihara and J. Gupton, *Tetrahedron Lett.*, 36, 1527 (199

Heterocyclic Substitutents Developed by the Gupton Group

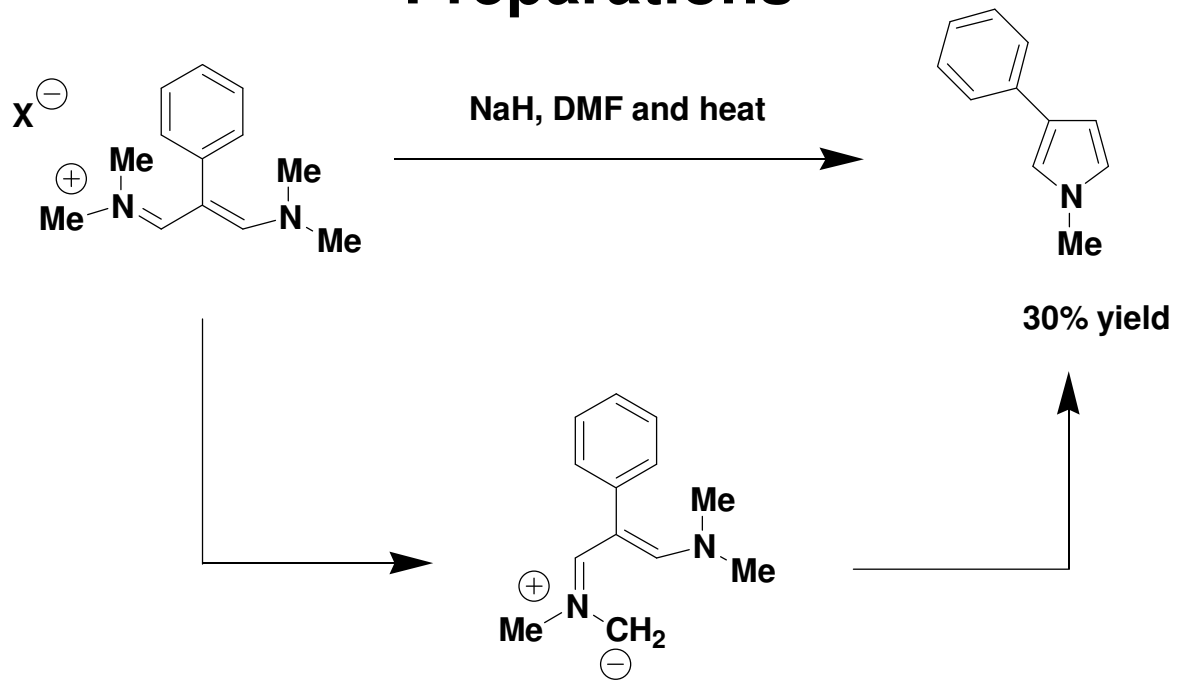




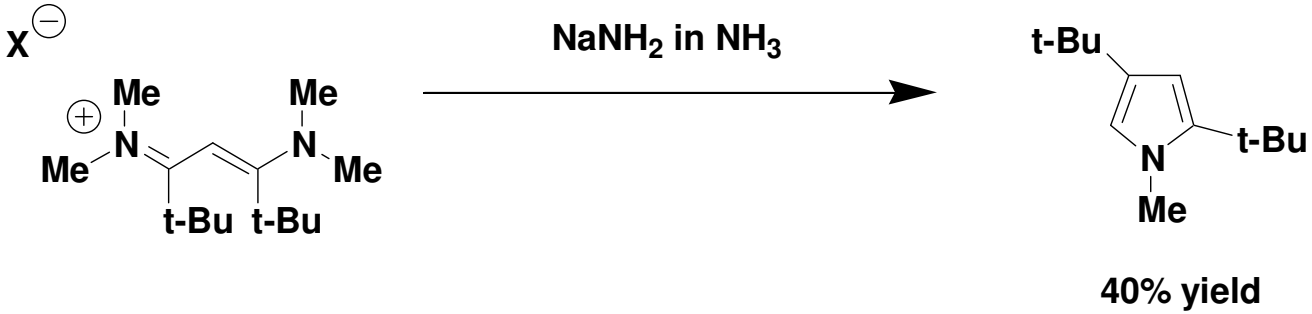


J. Gupton, F. Hicks*, D. Wilkinson*, S. Petrich and J. Sikorski, *Heterocycles,* 37, 487 (1994)

Initial Reports for Using Vinamidinium Salts in Pyrrole Preparations

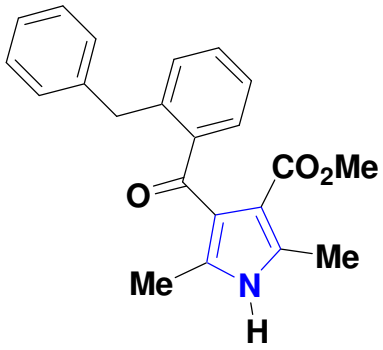


Z. Arnold, et al, *Czech. Chem. Commun., 30, 46 (1965)*

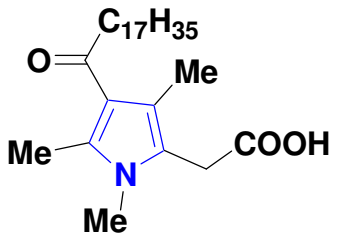


R. Gompper, et al, *Synthesis*, 213 (1979)

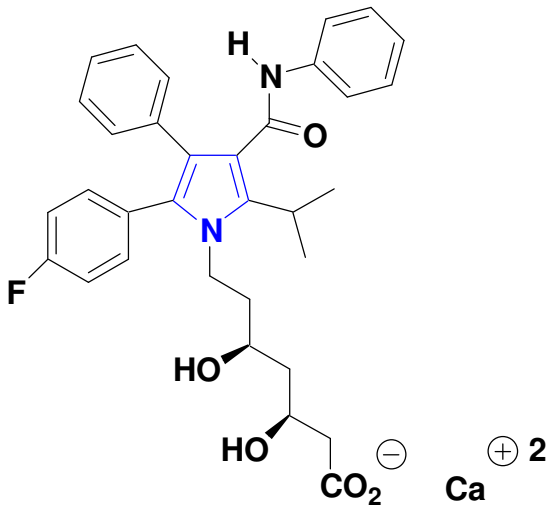
Some Biologically Interesting Highly Functionalized Pyrroles



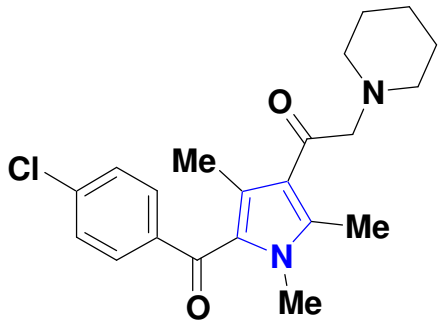
Calcium channel activator



Cytosolic phospholipase A inhibitor

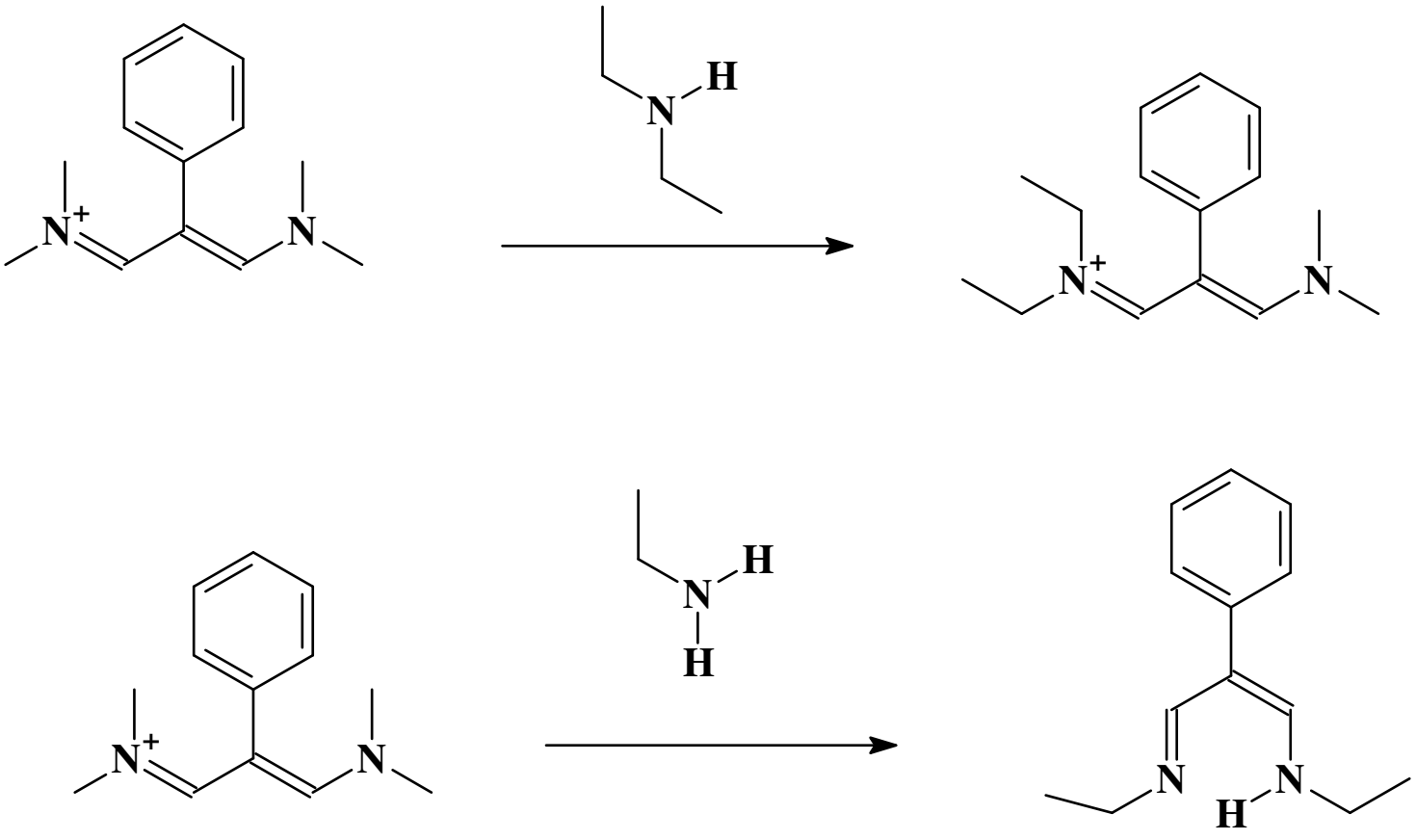


Lipitor, cholesterol lowering drug

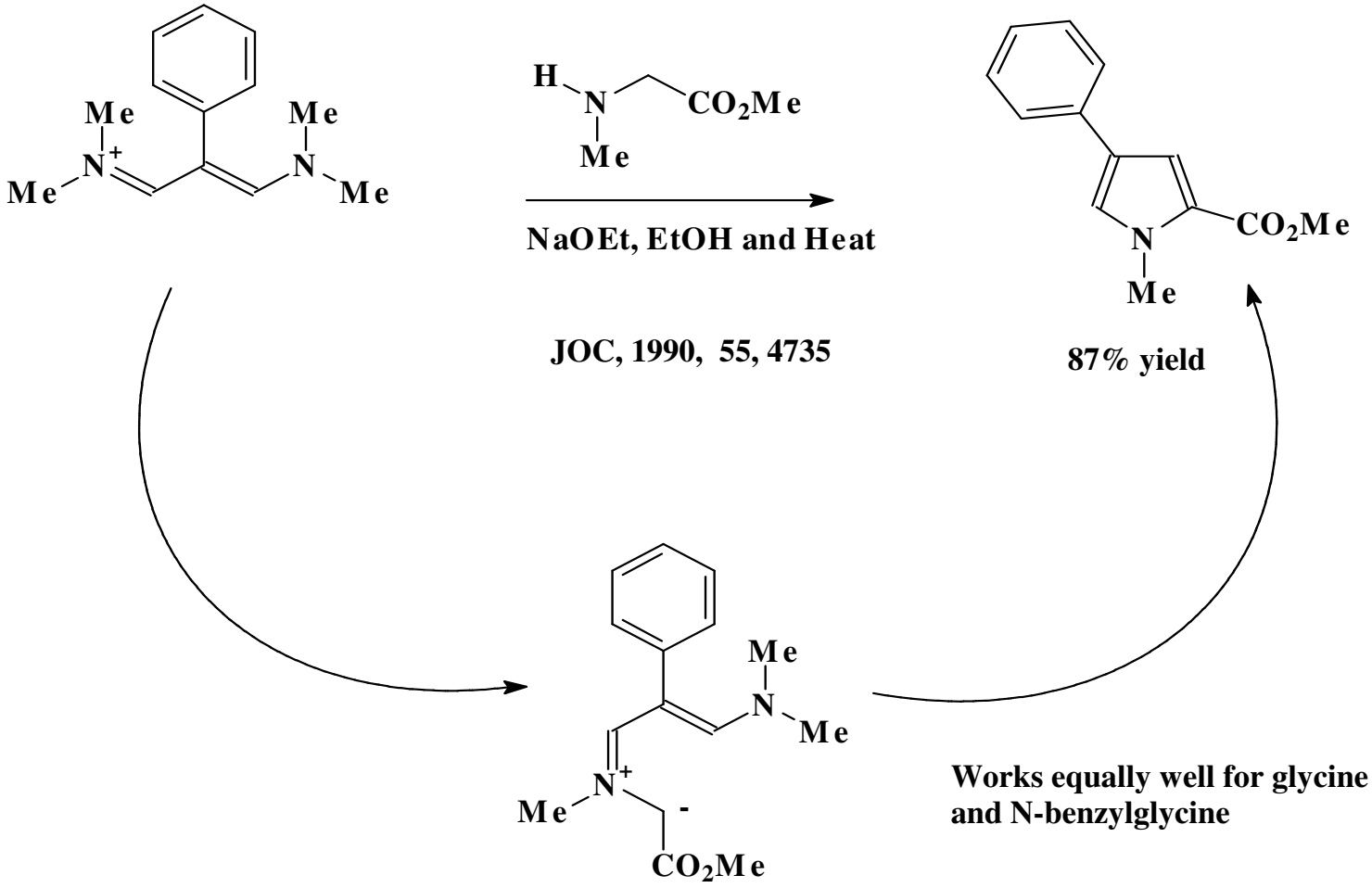


Anticonvulsant

The Amine Exchange Process

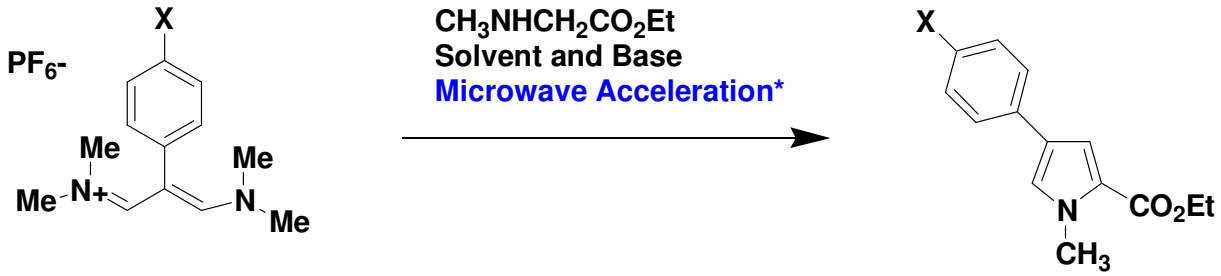


Initial Efforts by the Gupton Group
Preparation of 2,4-Disubstitutedpyrroles



J. Gupton, R. Yu*, D. Krolikowski*, S. Riesinger*
and J. Sikorski, *J. Org. Chem.*, 55, 4735 (1990)

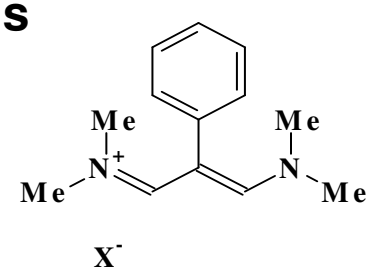
Microwave Accelerated Formation of Pyrroles from Vinamidinium Salts

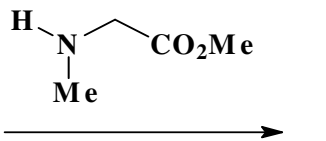


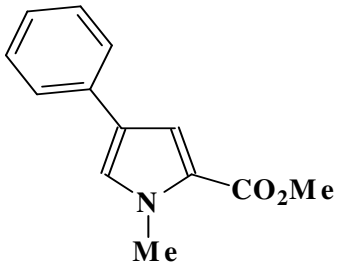
X	Solvent	Base	% Yield	Remarks
MeO	DMF	None	60	**Pyrrole formed as only prod.**
MeO	DMF	DABCO	91	"
MeO	DMF	Et_3N	71	"
MeO	DMF	Cs_2CO_3	82	"
MeO	DMF	Pyridine	69	"
MeO	DMF	DBU	33	"
MeO	i-PrOAc	DABCO	----	**Gross mix.**
MeO	Acetonitrile	DABCO	91	**Pyrrole formed as only prod.**
MeO	THF	DABCO	----	**Gross mix.**
MeO	Toluene	DABCO	----	**Gross mix.**
MeO	i-PrOH	DABCO	----	**Gross mix.**
MeO	DMF	DABCO	33	**Traditional heating**

***Microwave reactions were run at 50 watts of power for 14 mins at the boiling point of the respective solvent.**

Pyrrole Forming Reactions Using Vinylogous Iminium Salts



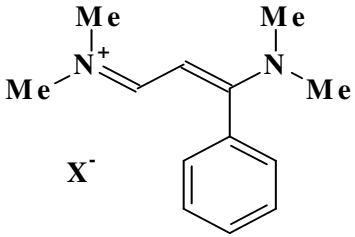


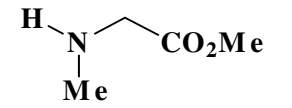


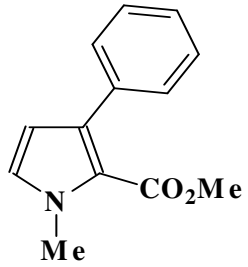
J. Gupton, R. Yu*, D. Krolikowski*, S. Riesinger* and J. Sikorski, *J. Org. Chem.*, 55, 4735 (1990)

JOC, 1990, 55, 4735

87% yield



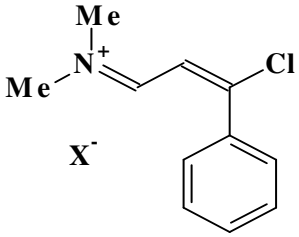


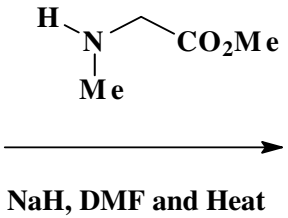


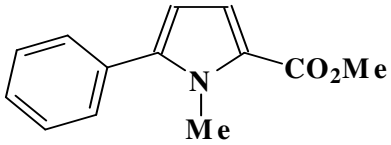
J. Gupton, S. Petrich, L. Smith, M. Bruce, P.Vu*, K. Du, E. Dueno, C. Jones and J. Sikorski, *Tetrahedron*, 52, 6879 (1996)

Tetrahedron, 1996, 52, 6879

50% yield





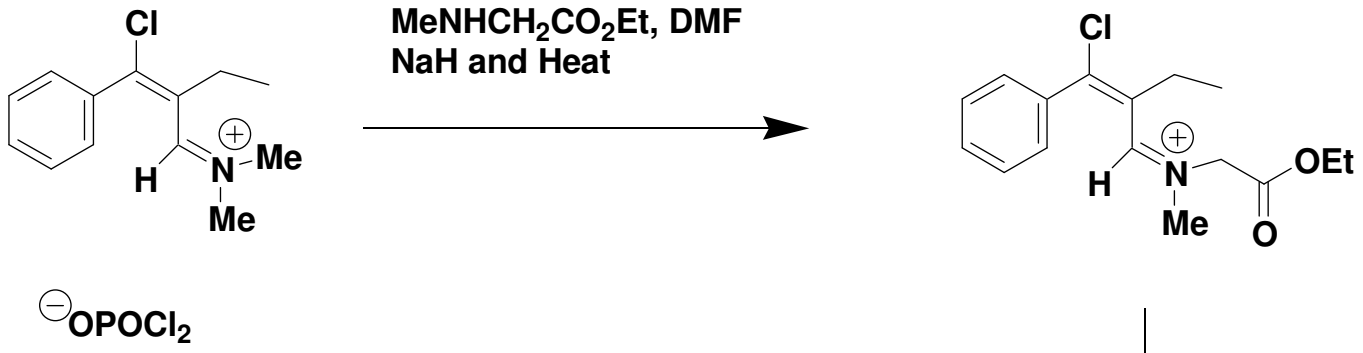


J. Gupton, D. Krolikowski*, R. Yu*, P. Vu*, J. Sikorski, M. Dahl and C. Jones, *J. Org. Chem.*, 57, 5480 (1992)

JOC, 1992, 57, 5480

80% yield

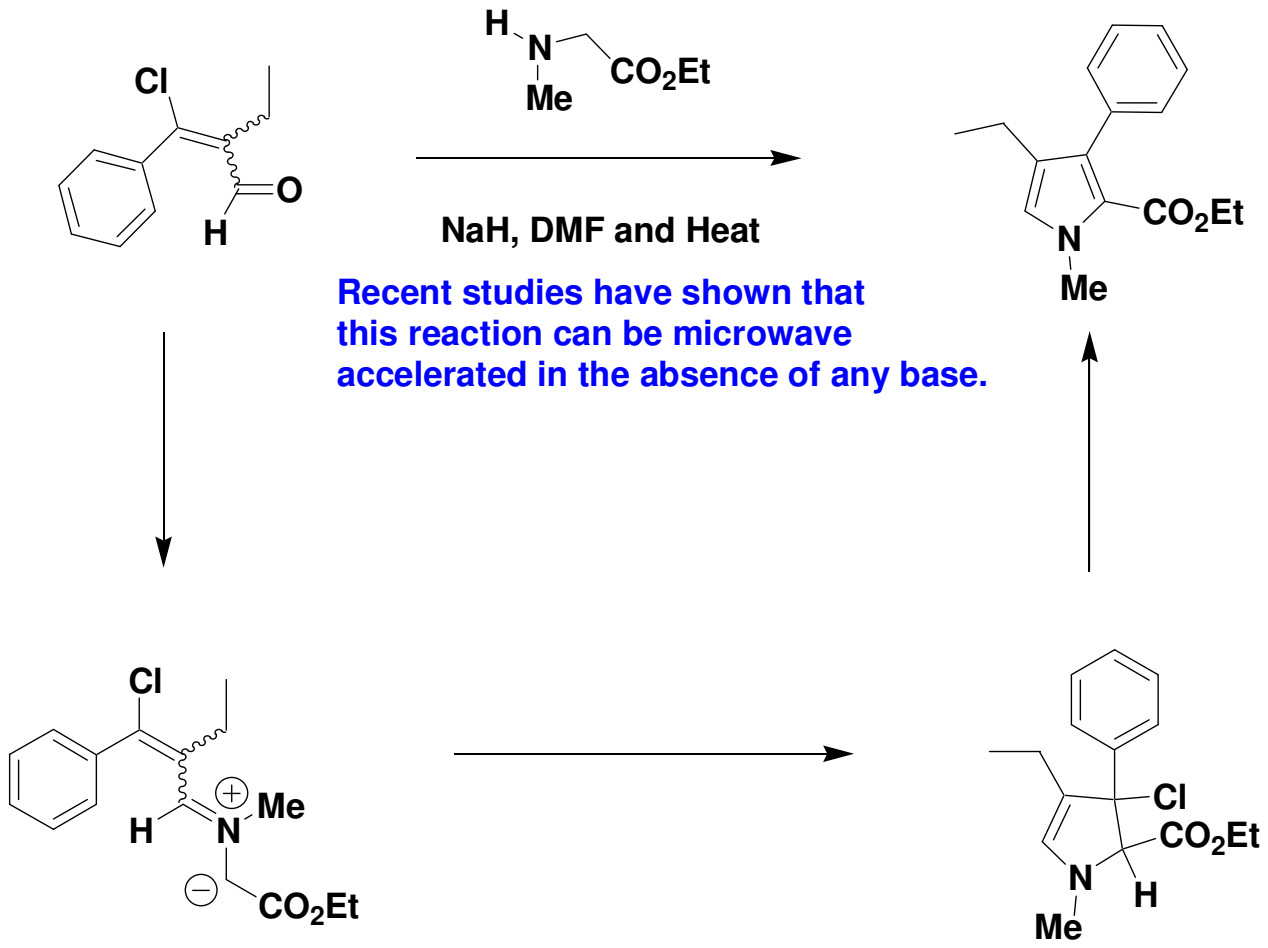
Gupton Group Preparation of 2,3,4-Trisubstitutedpyrroles



J. Gupton, K. Keertikar, K. Krumpe, B. Burnham, K. Dwornik*, S. Petrich, K. Du, M. Bruce, P. Vu*, M. Vargas*, K. Hosein* and J. Sikorski, *Tetrahedron*, 54, 5075 (1998)

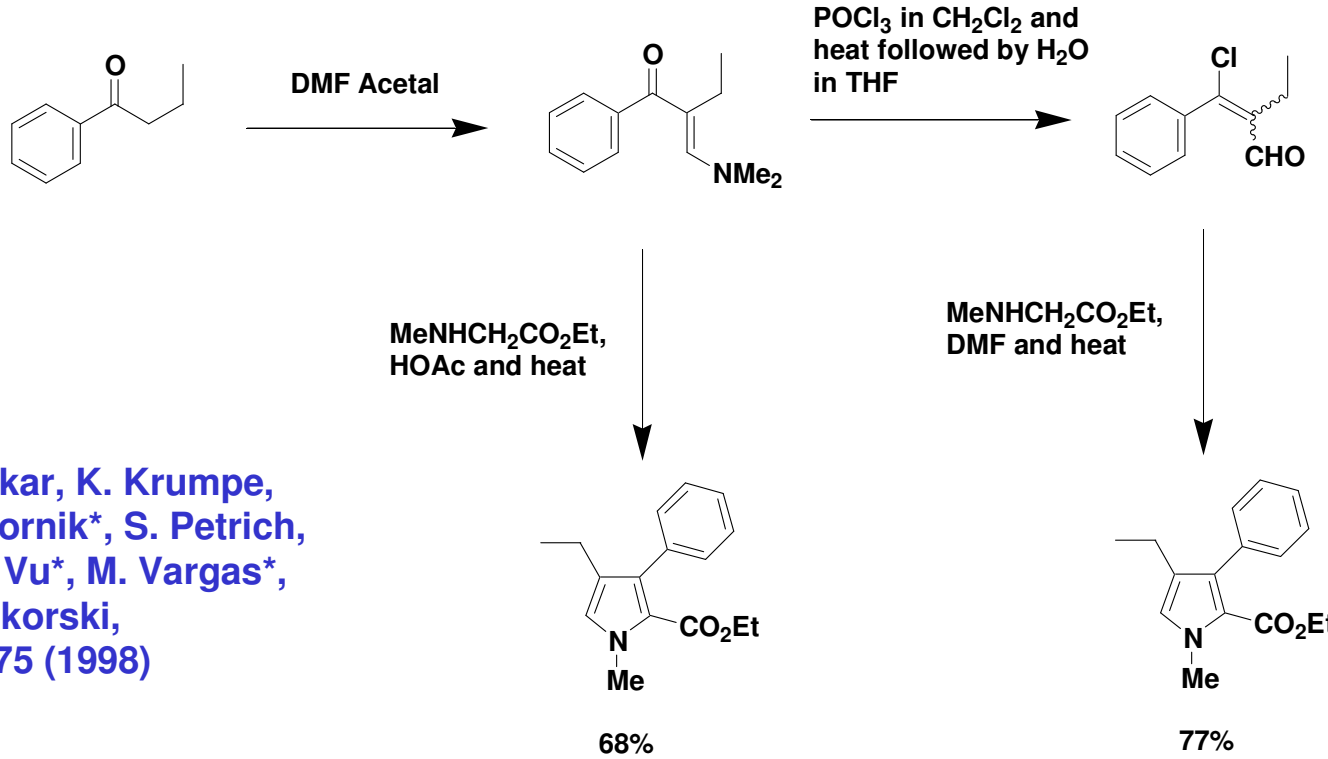
60% Yield
Reaction works well for glycine and N-benzylglycine

The Use and Application of 3-Chloroenals

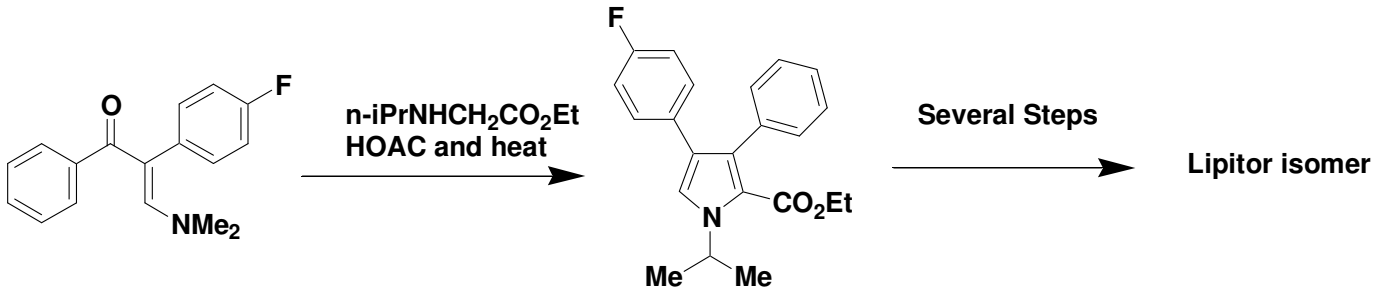


J. Gupton, K. Keertikar, K. Krumpe, B. Burnham, K. Dwornik*, S. Petrich, K. Du, M. Bruce, P. Vu*, M. Vargas*, K. Hosein* and J. Sikorski, *Tetrahedron*, 54, 5075 (1998)

Pfizer Synthesis of Lipitor Regioisomer



J. Gupton, K. Keertikar, K. Krumpe, B. Burnham, K. Dwornik*, S. Petrich, K. Du, M. Bruce, P. Vu*, M. Vargas*, K. Hosein* and J. Sikorski, *Tetrahedron*, 54, 5075 (1998)



85%

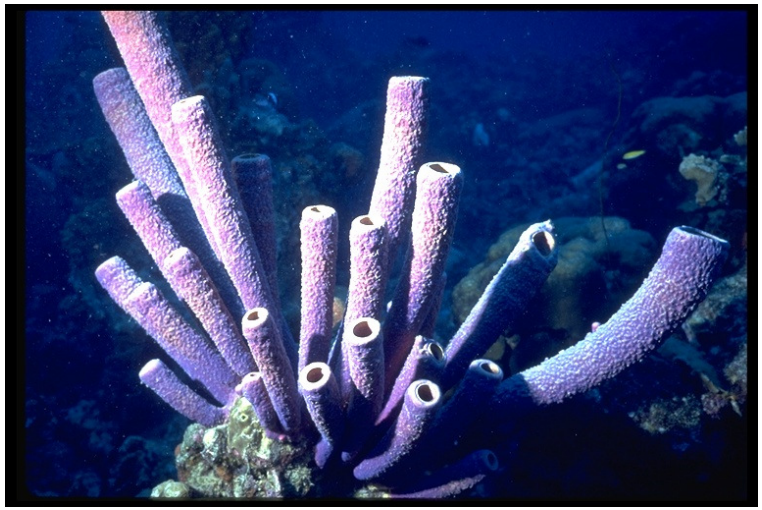
J. Pfefferkorn, et al, *Tetrahedron, 63, 8124 (2007)*

Marine Natural Products

Marine natural products continue to be an area of intense investigation.

- **novel structures**
- **interesting biological properties.**

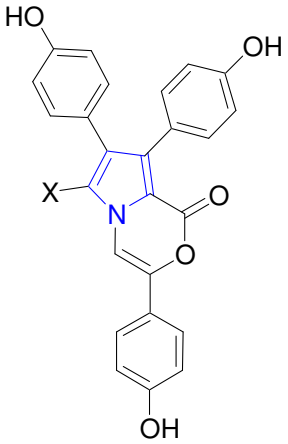
Ascidian
Eugene Weber
©California Academy of Sciences



Tube sponge
Eugene Weber
©California Academy of Sciences

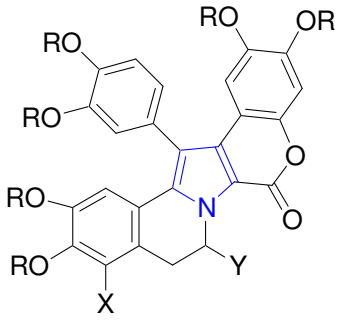
***Lamellaria* sp.**
E. Eugenia Patten
©Callifornia Academy of Sciences

Some Pyrrole Containing Marine Natural Products



Lukianol A X = H
Lukianol B X = I

Lamellarins

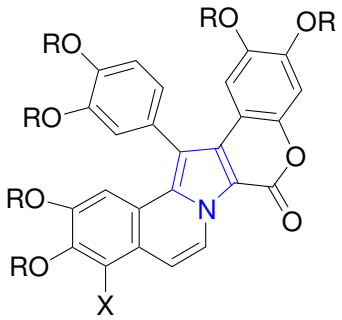


30

X = MeO or HO or H

Y = HO or H

R = Me or H



31

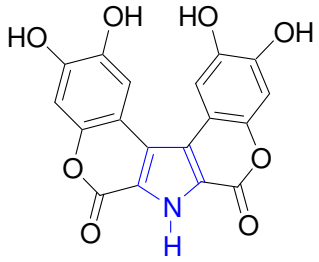
X = MeO or HO or H

R = Me or H or SO_3Na

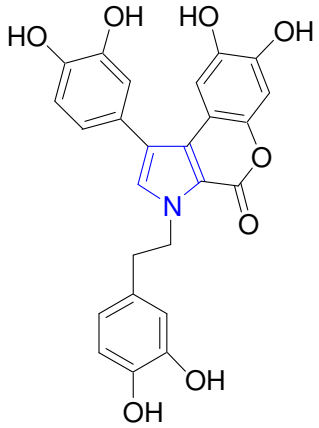
Z = oxygenated phenyl group connected by a one or two carbon tether to nitrogen; a carbonyl group may be present in the tether.

J. Gupton, "Pyrrole Natural Products with Antitumor Properties", Chapter. 2, pp 53-92 in *"Heterocyclic Antitumor Antibiotics: Topics in Heterocyclic Chemistry, Vol.2"*, Ed. by M. Lee, Springer-Verlag, Berlin/Heidelberg, 2006

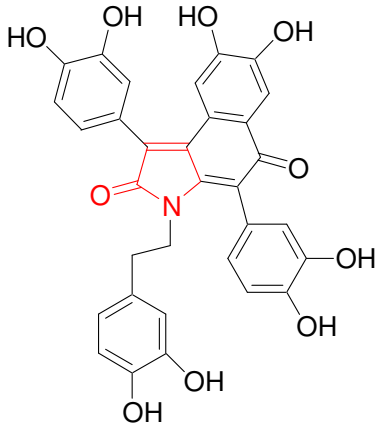
Some Pyrrole Containing Marine Natural Products



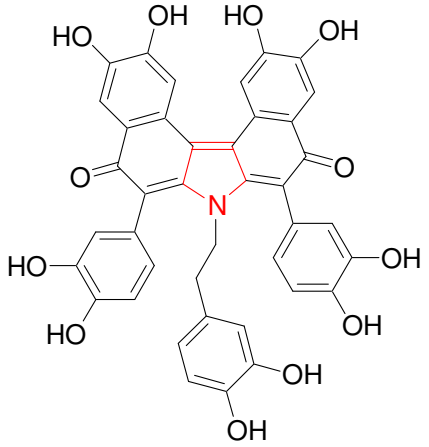
Ningalin A



Ningalin B



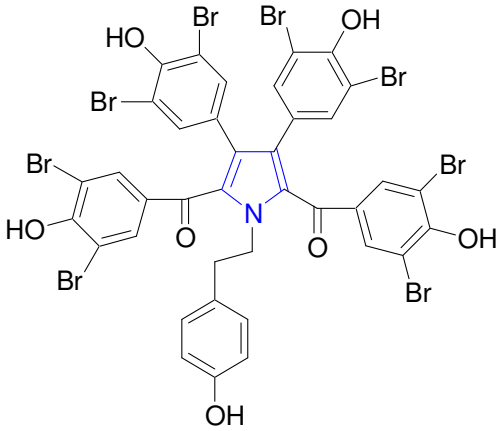
Ningalin C



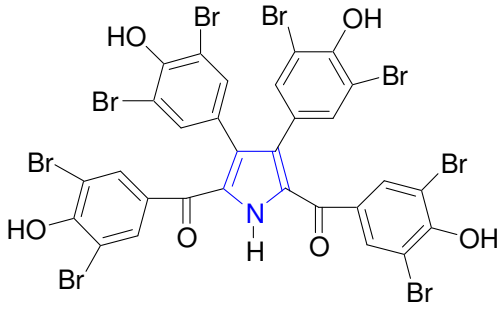
Ningalin D

J. Gupton, "Pyrrole Natural Products with Antitumor Properties", Chapter. 2, pp 53-92 in *"Heterocyclic Antitumor Antibiotics*: *Topics in Heterocyclic Chemistry, Vol.2"*, Ed. by M. Lee, Springer-Verlag, Berlin/Heidelberg, 2006

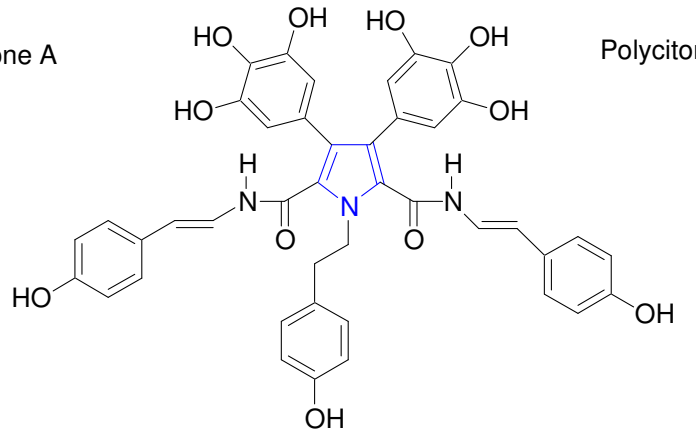
Some Pyrrole Containing Marine Natural Products



Polycitone A



Polycitone B



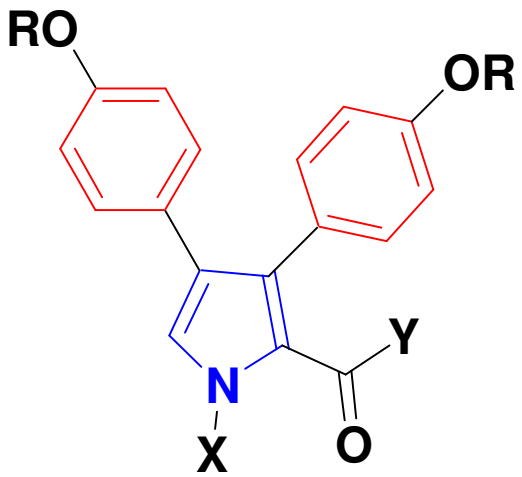
Storniamide A

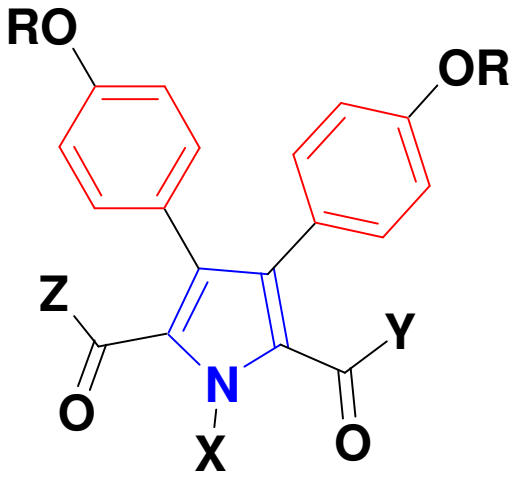
J. Gupton, "Pyrrole Natural Products with Antitumor Properties", Chapter. 2, pp 53-92 in *"Heterocyclic Antitumor Antibiotics*: *Topics in Heterocyclic Chemistry, Vol.2"*, Ed. by M. Lee, Springer-Verlag, Berlin/Heidelberg, 2006

Workers in the Field

- Boger
- Steglich
- Banwell & Goodwin
- Furstner
- Bullington
- Bailly
- Guitian
- Cava
- Faulkner
- Handy
- Iwao, Ishibashi
- Nagle
- Ruchirawat
- Albericio, Alvarez
- Wong
- Beccalli
- Correia
- Piers

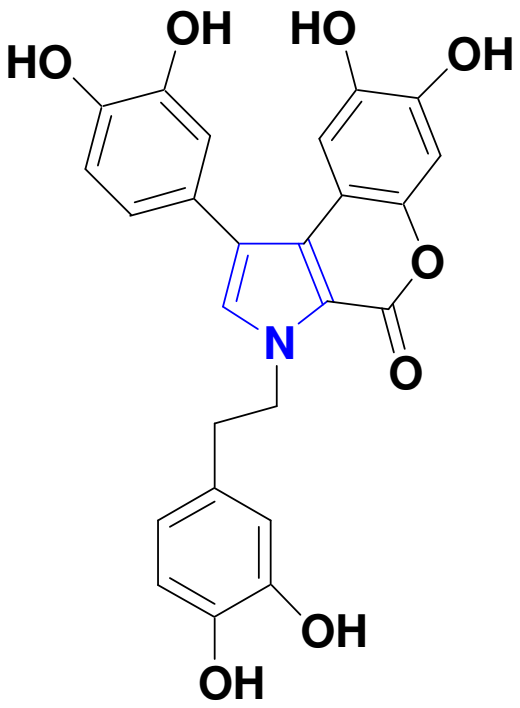
Some Common Structural Features of Pyrrole Containing Marine Natural Products





Reported Biological Properties of Pyrrole Containing Marine Natural Products

- Inhibition of HIV-1 Integrase for the HIV-1 virus in cell culture
- Sequestration of metals such as Fe
- Inhibitor of the growth of SV40 transformed fibroblast cells
- Inhibitor of cell division (sea urchin eggs)
- Inhibitor of Topoisomerase I (lamellarins)
- Immunomodulatory activity
- Cytotoxic activity against various cancer cell lines
- Multidrug resistant reversal activity (P-glycoprotein efflux pumps/cancer cell lines)
- Inhibitor of calmodulin activated brain phosphodiesterase
- Antibiotic activity against gram positive bacteria

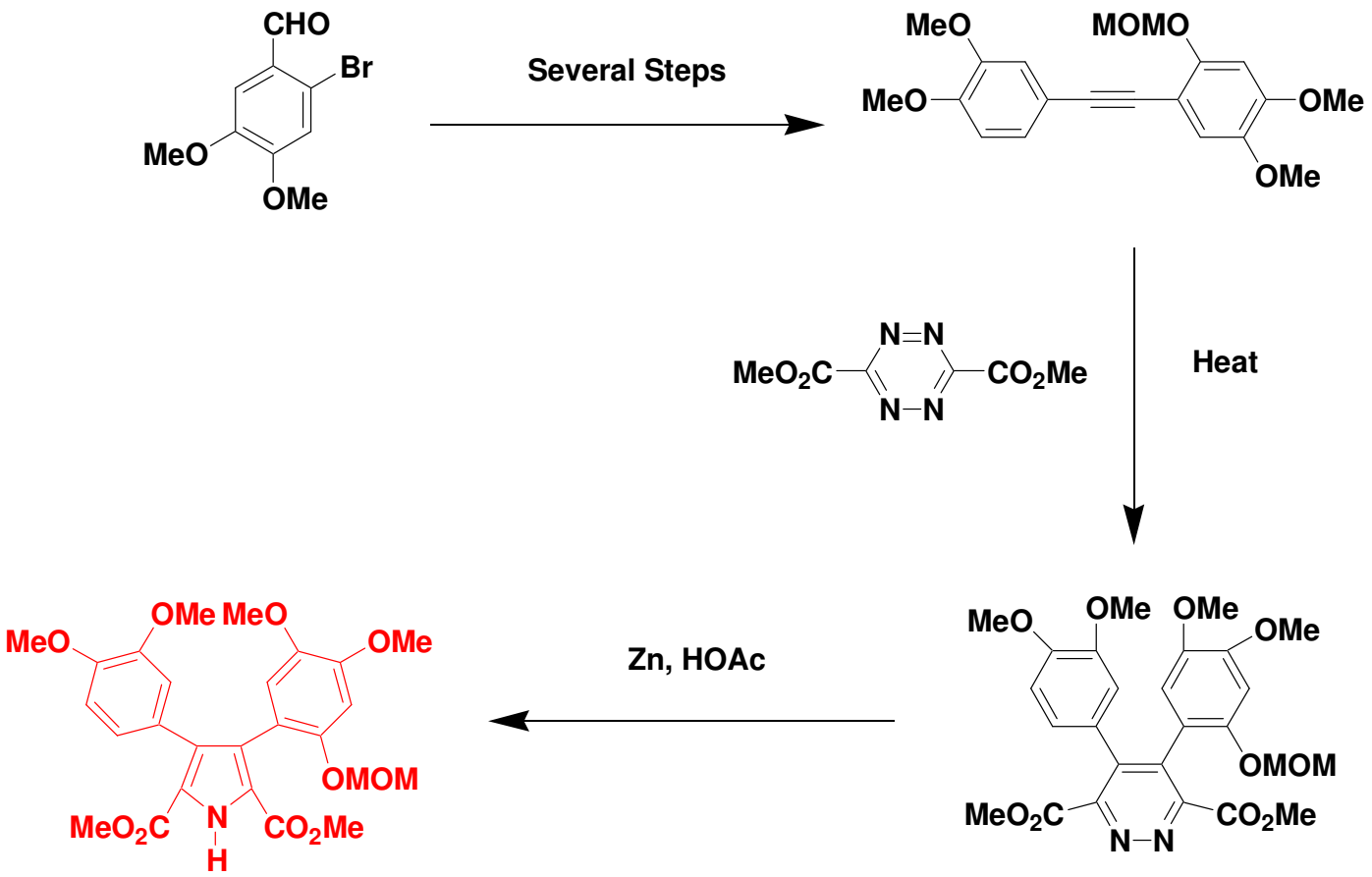


Ningalin B

Isolated in 1997 from the genus Didemnum

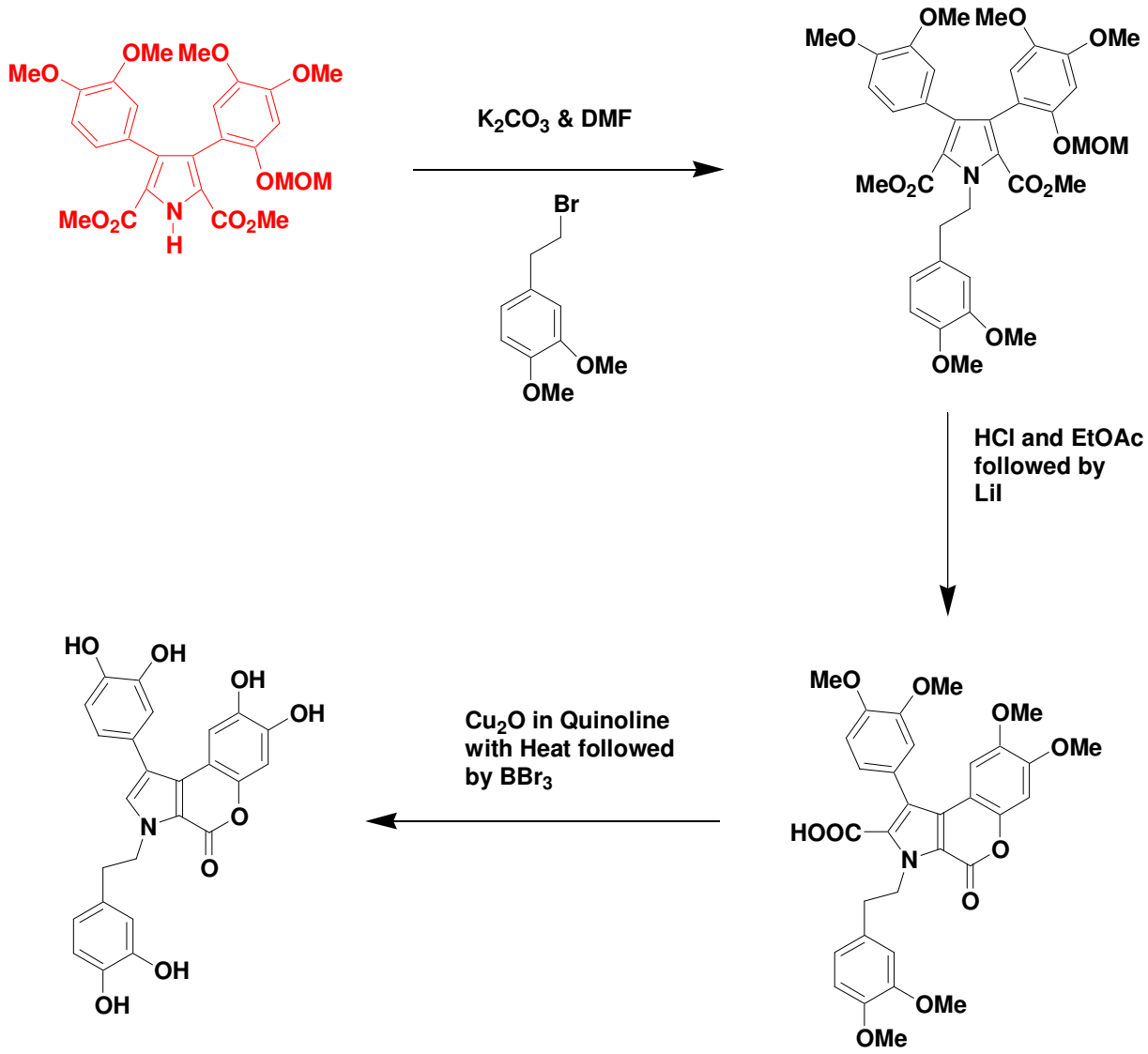
Kang, H., Fenical, W., *J. Org. Chem.*, *62*, 3254 (1997)

Boger Synthesis of Ningalin B



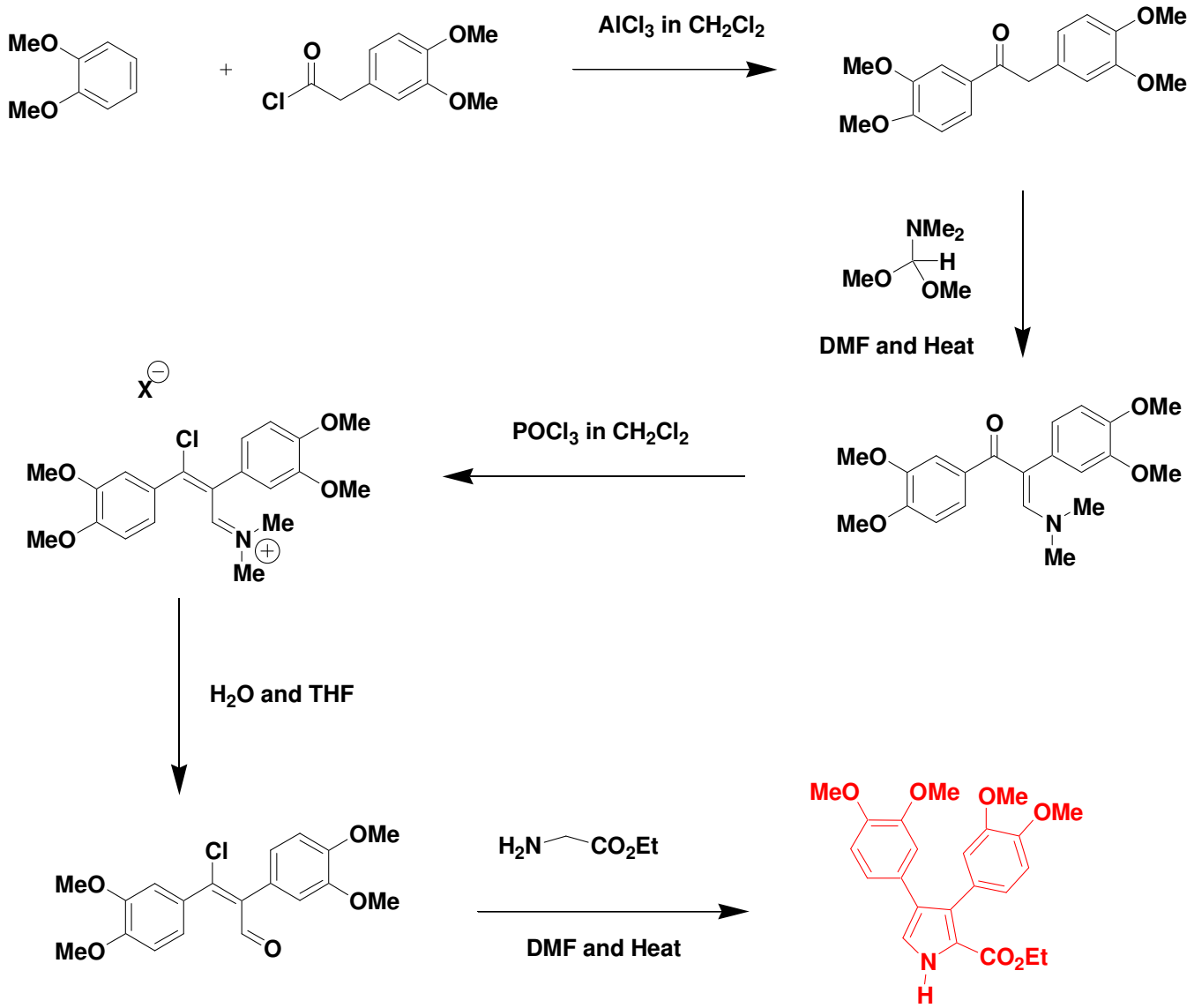
D. Boger, D. Soenen, C. Boyce, M. Hedrick and Q. Jin, *J. Org. Chem.*, 65, 2479 (2000)

Boger Synthesis of Ningalin B



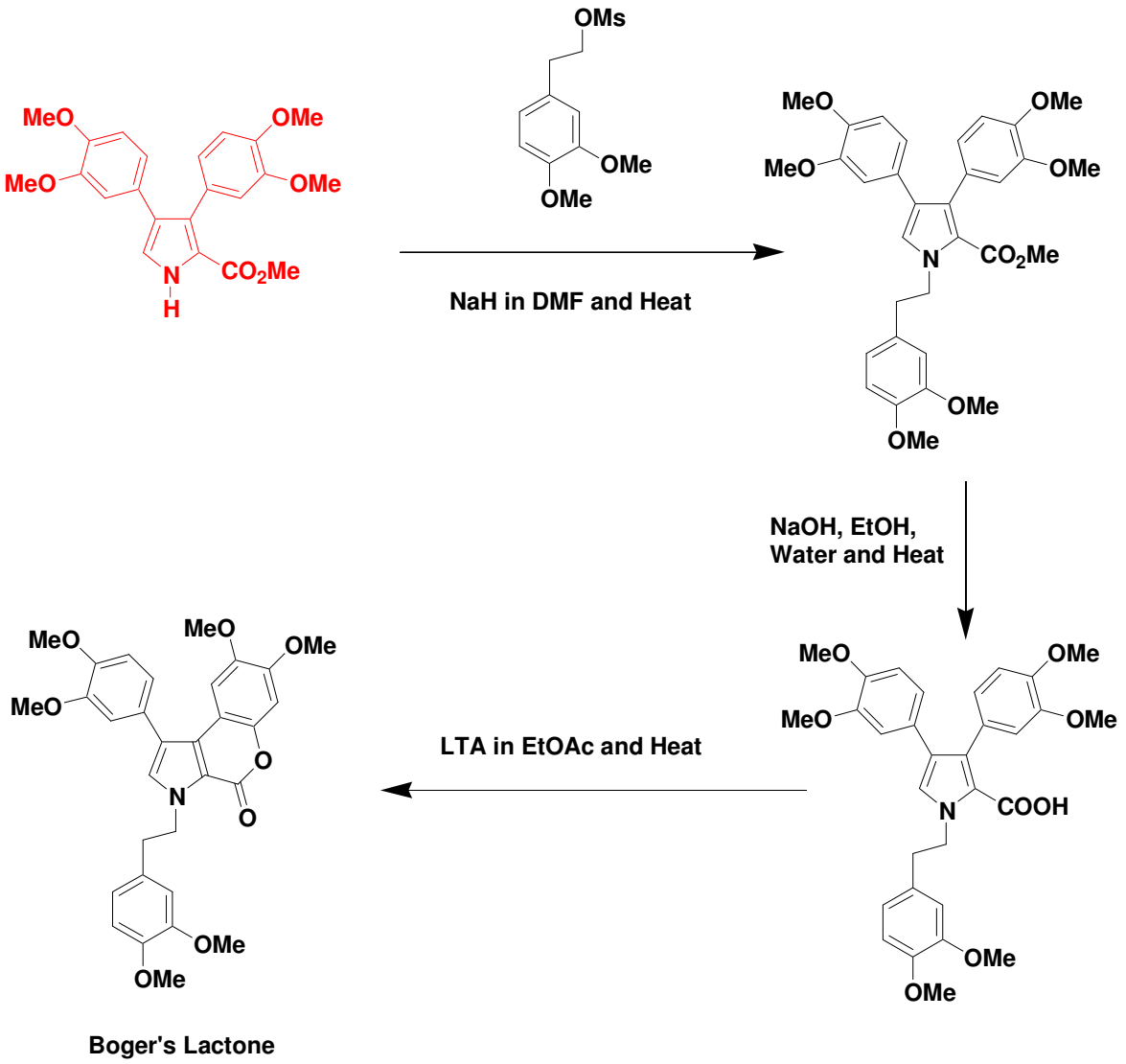
D. Boger, D. Soenen, C. Boyce, M. Hedrick and Q. Jin, *J. Org. Chem.*, 65, 2479 (2000)

Gupton Group Synthesis of Ningalin B



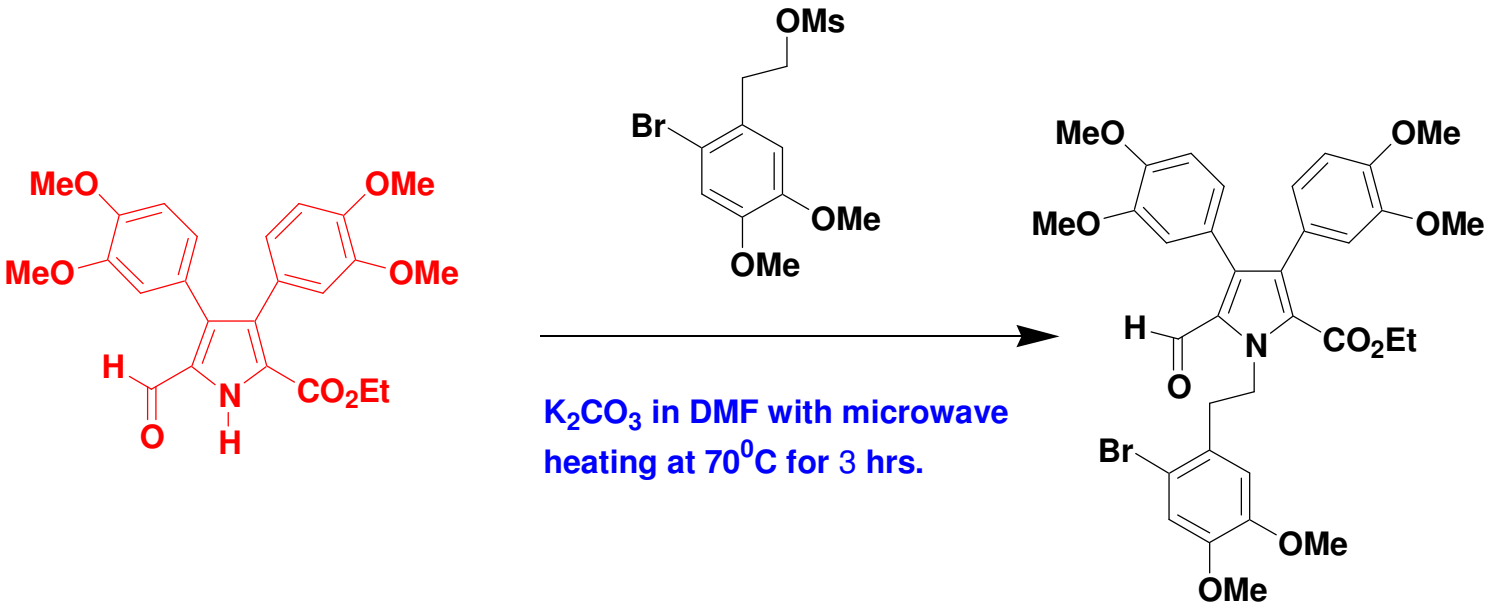
J. Gupton, S. Clough, R. Miller, J. Lukens*, C. Henry*, R. Kanters and J. Sikorski, *Tetrahedron,* 59, 207-215 (2003)

Gupton Group Synthesis of Ningalin B

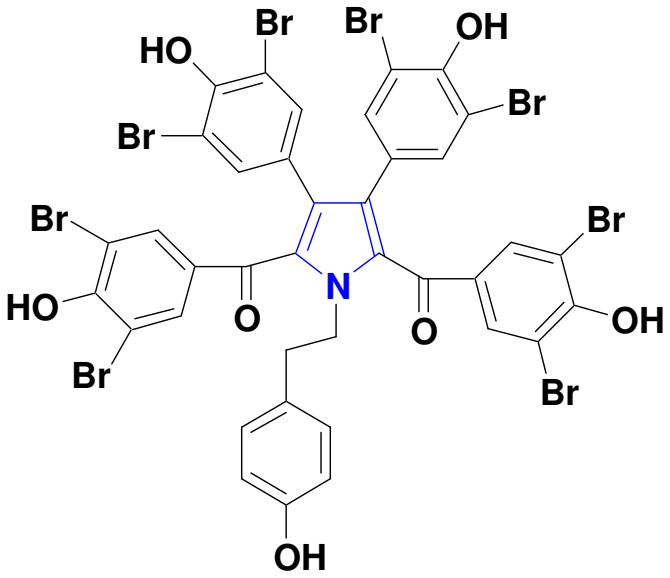


J. Gupton, S. Clough, R. Miller, J. Lukens*, C. Henry*, R. Kanters and J. Sikorski, *Tetrahedron,* 59, 207-215 (2003)

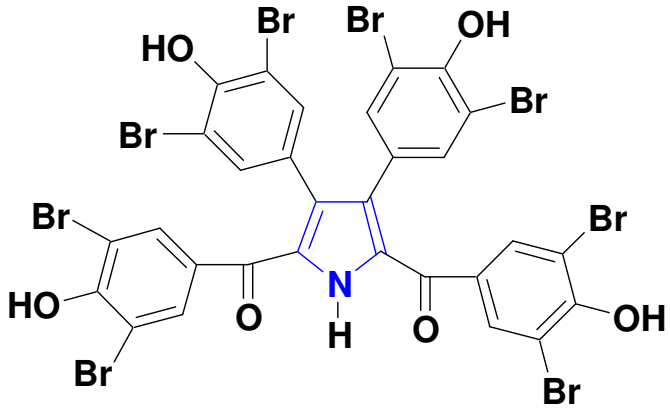
Gupton Group Modifications to the Synthesis of Ningalin B Related Compounds



Key intermediate for the synthesis of Lamellarin G trimethyl ether



Polycitone A

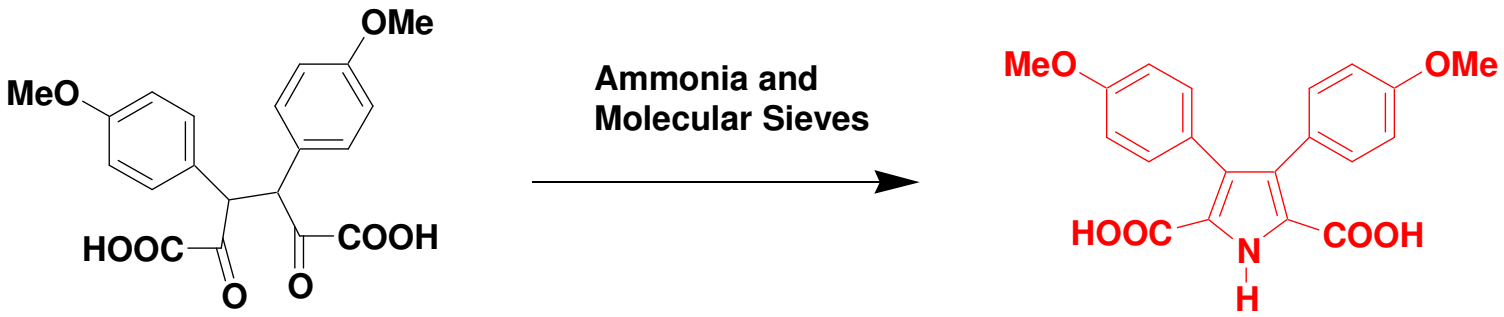


Polycitone B

Isolated from an Indo Pacific Ascidian

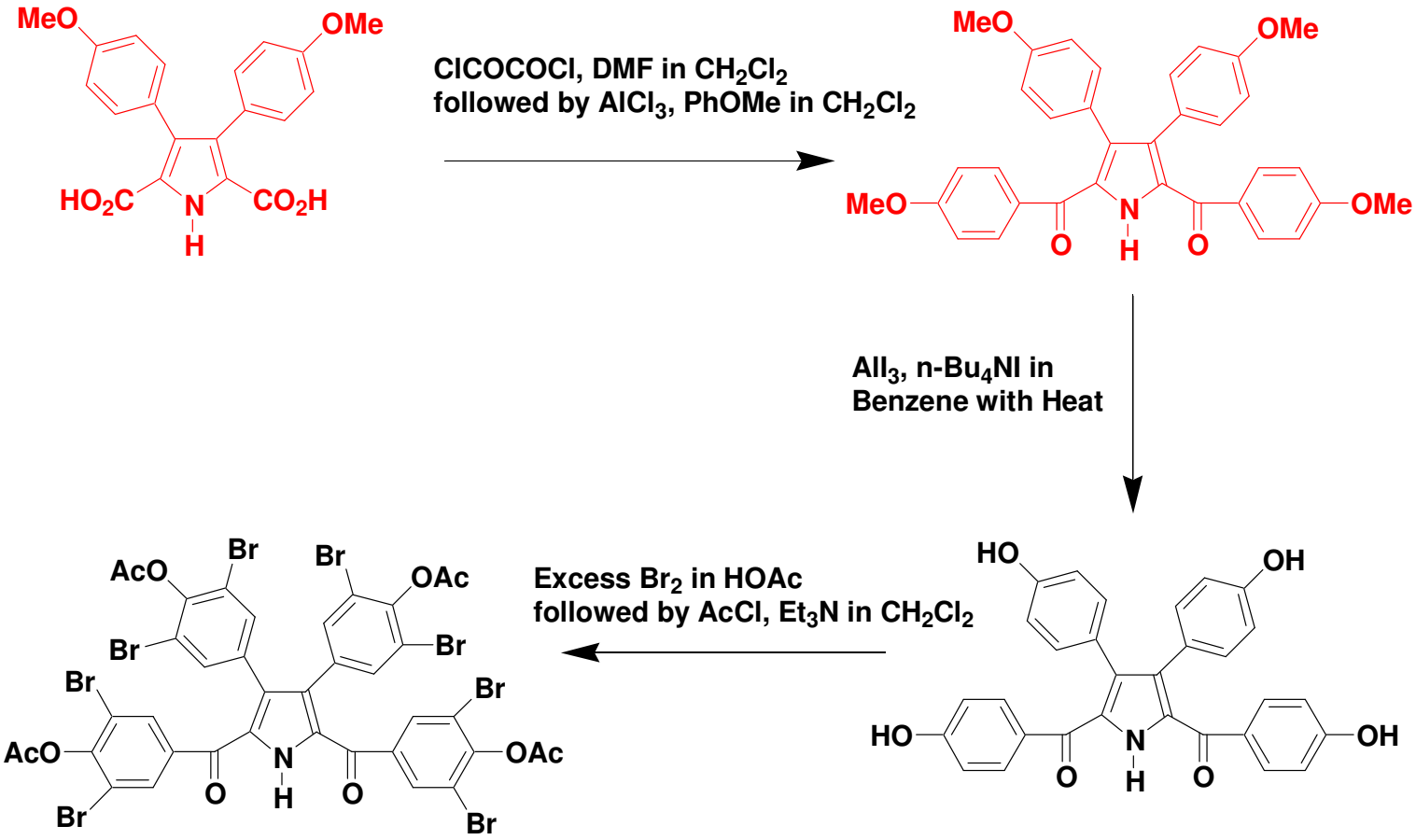
Rudi, A., Goldberg, I., Stein, Z., Frolow, F., Benayahu, Y., Schleyer, M. and Kashman, Y., *J. Org. Chem., 59*, 999-1003 (1994); Rudi, A., Evan, T., Aknin, M. and Kashman, Y., *J. Nat. Prod., 63*, 832-833 (2000).

Steglich Synthesis of Polycitone A

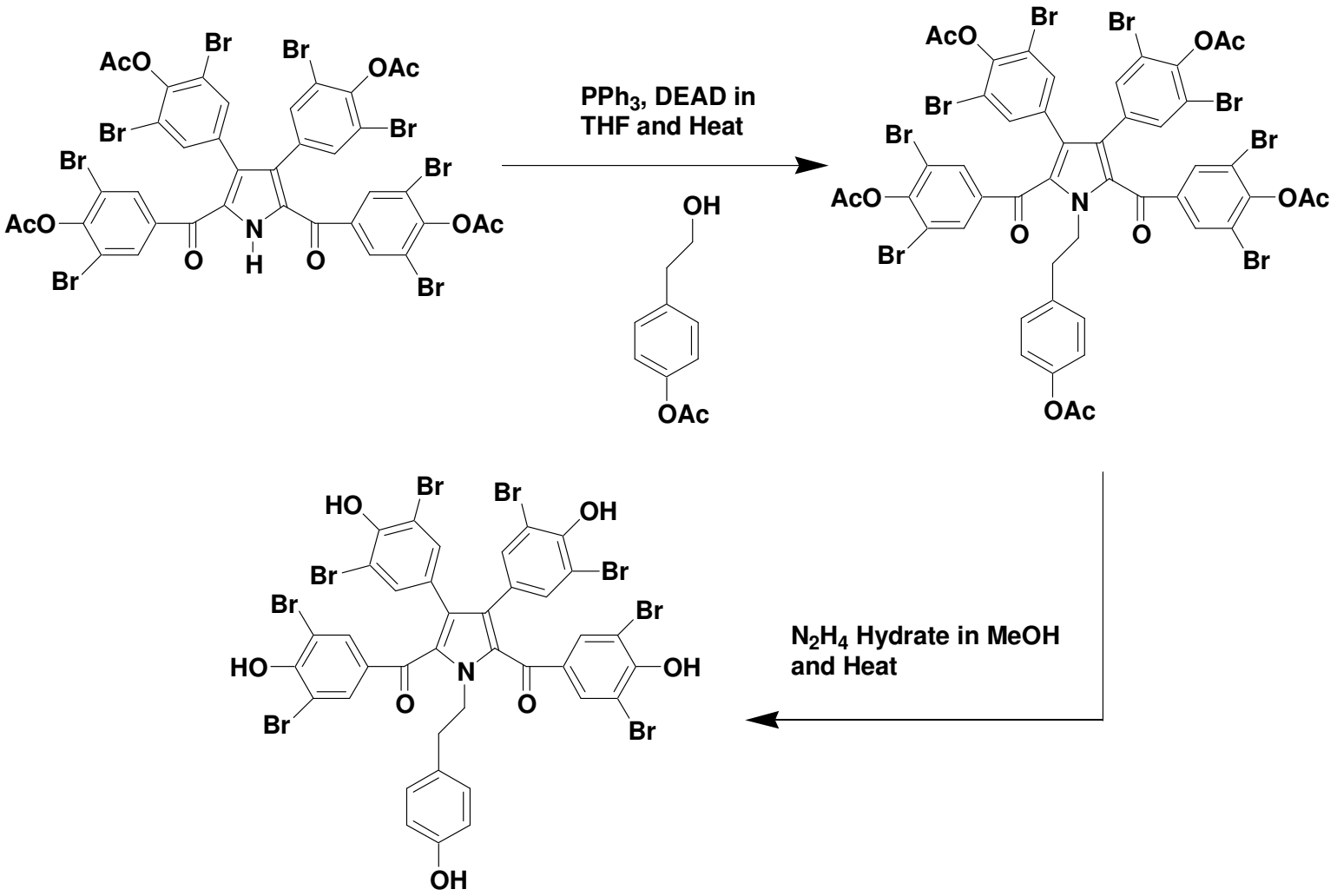


W. Steglich, et al, *Org. Lett.*, 2002, 4, 3287-3288

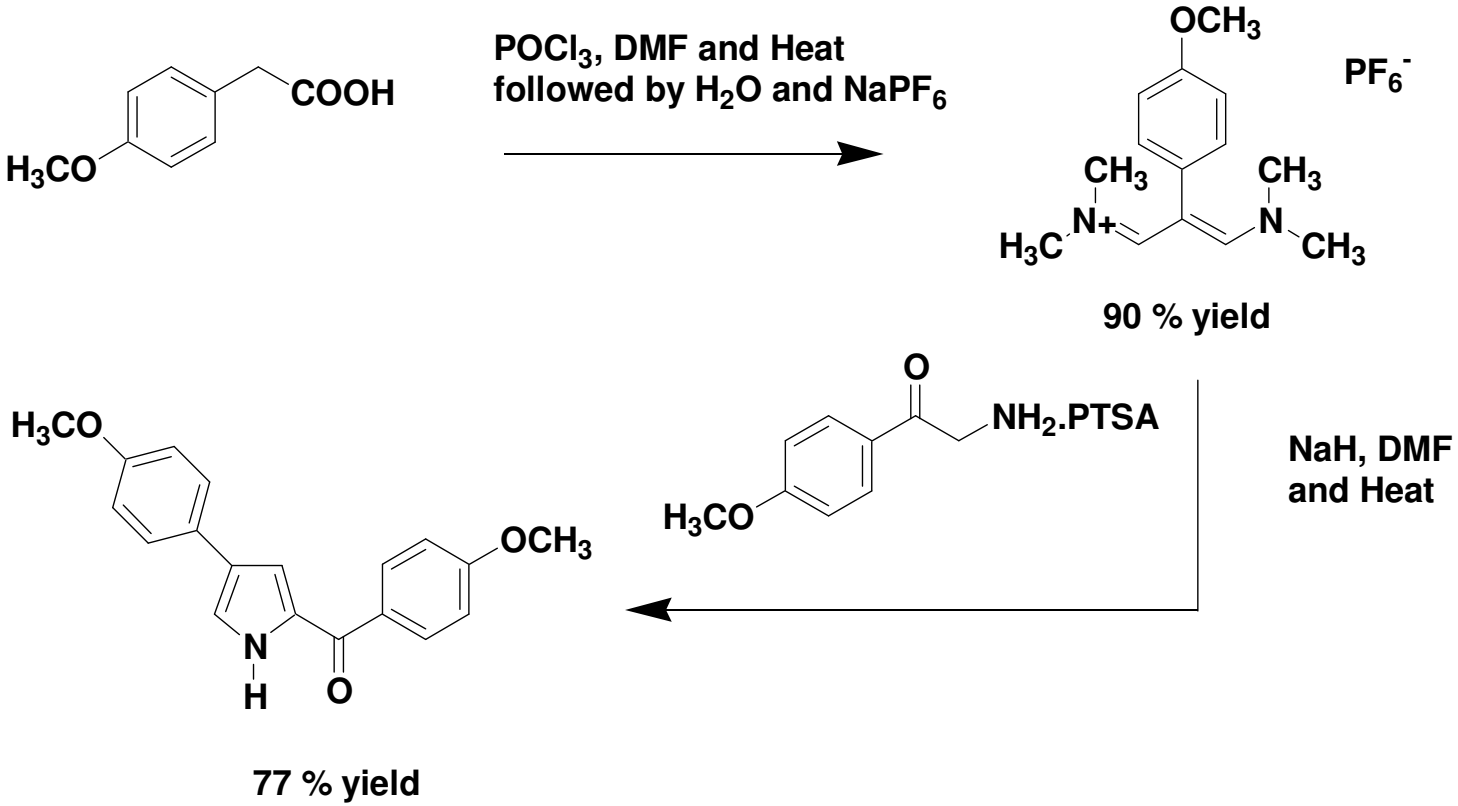
Steglich Synthesis of Polycitone A



Steglich Synthesis of Polycitone A

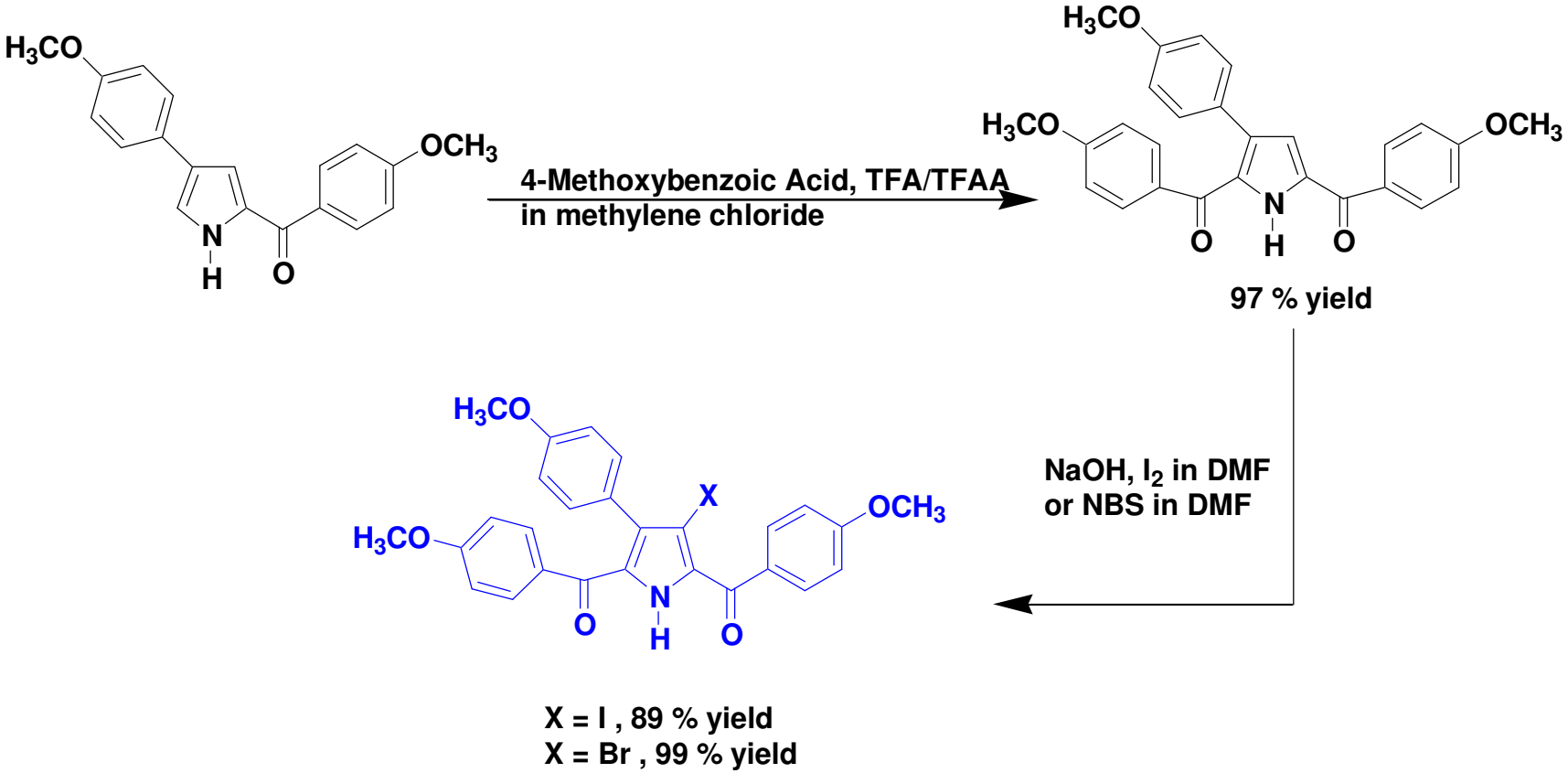


Gupton Group Relay Synthesis of the Polycitones



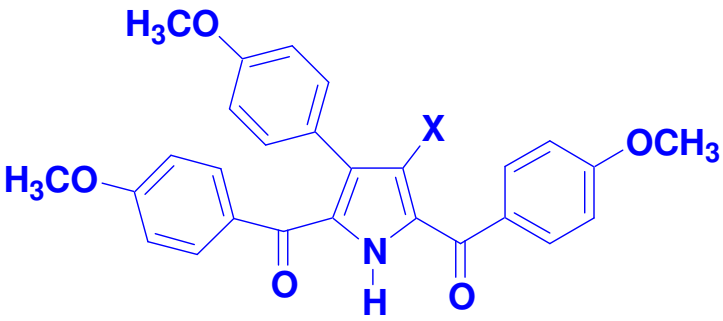
J. Gupton, R. Miller, S. Clough, K. Krumpe, E. Banner, R. Kanters, K. Du, K. Keertikar, N. Lauerman*, J. Solano*, B. Adams*, D. Callahan*, B. Little*, A. Scharf* and J. Sikorski, *Tetrahedron,* 61, 1845-1854 (2005).

Gupton Group Relay Synthesis of the Polycitones

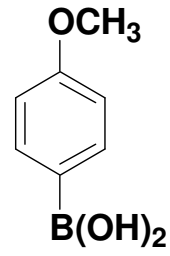


X = I , 89 % yield
X = Br , 99 % yield

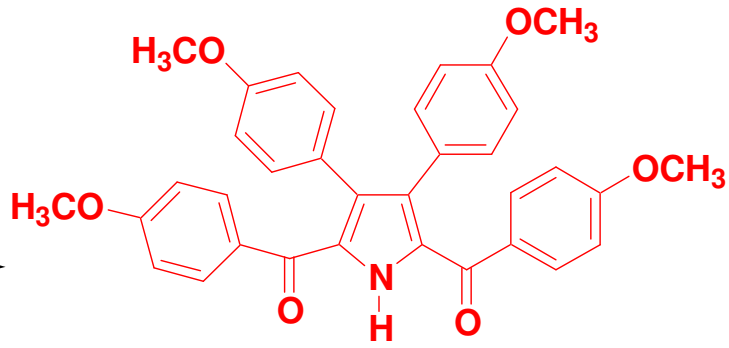
Gupton Group Relay Synthesis of the Polycitones



X = I
X = Br



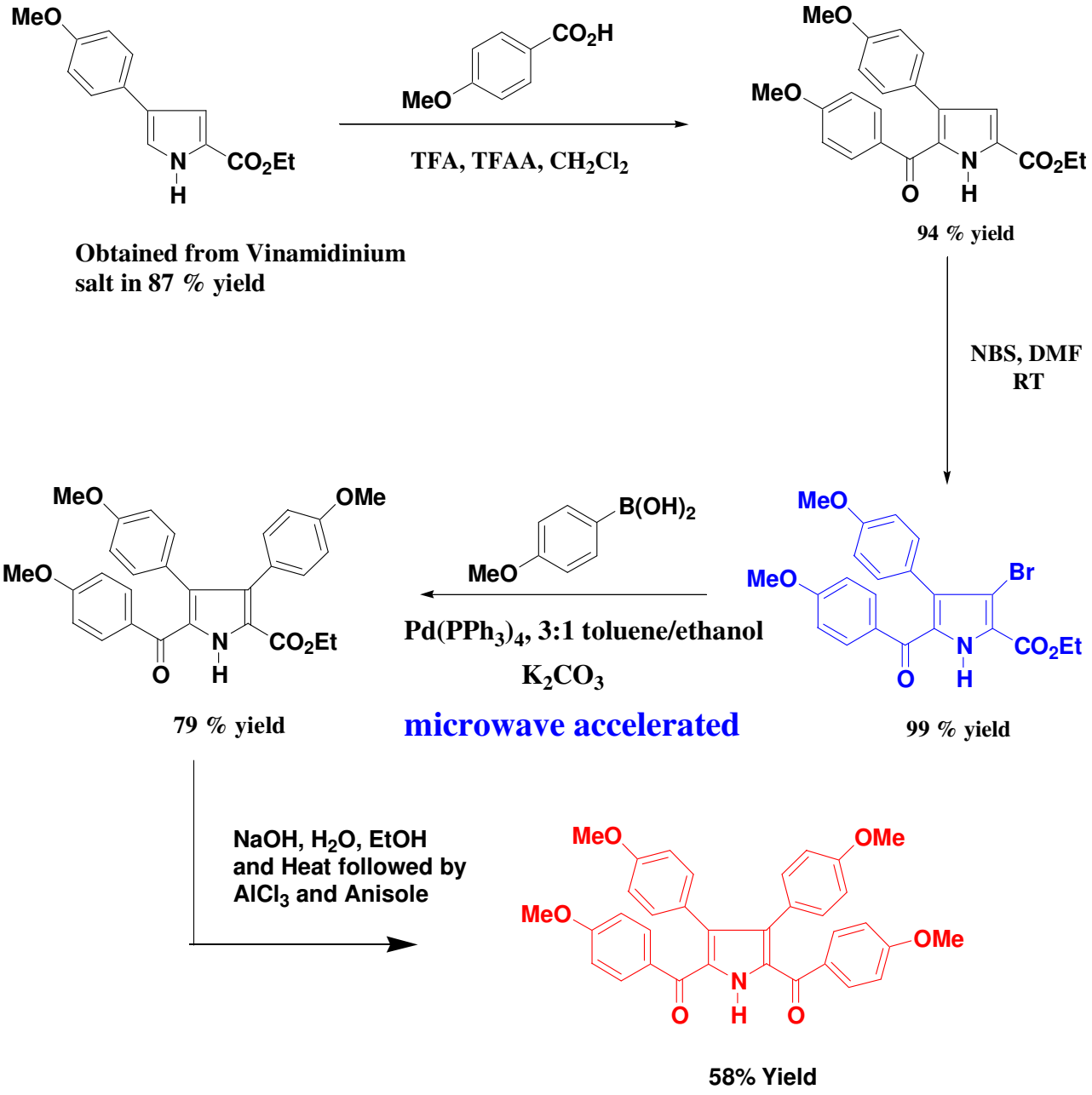
$Pd(PPh_3)_4$, Toluene
K_2CO_3, EtOH and Heat



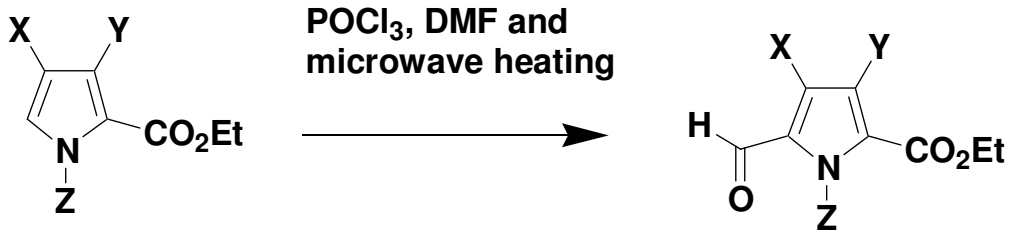
21 % yield conventional heating

64 % yield microwave acceleration

Modified Reaction Sequence For the Polycitones

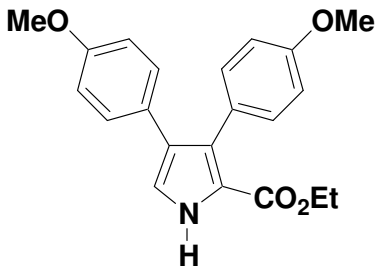


Microwave Accelerated Vilsmeier-Haack Formylation of Selected Pyrroles



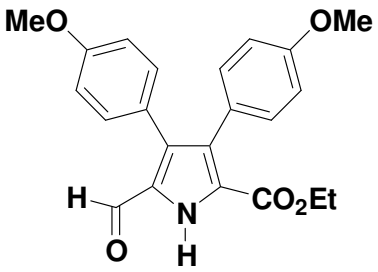
Compound	X	Y	Z	% Yield for **22**
a	3,4,5-trimethoxyphenyl	H	H	76
b	4-bromophenyl	H	H	70
c	3,4-dimethoxyphenyl	H	H	63
d	phenyl	H	H	91
e	4-chlorophenyl	H	H	84
f	4-methylphenyl	H	H	67
g	4-methoxyphenyl	H	H	81
h	4-methylphenyl	H	Me	81
i	4-methoxyphenyl	H	Me	81
j	3,4-dimethoxyphenyl	H	Me	62
k	4-methoxyphenyl	4-methoxyphenyl	H	90

Alternate Gupton Group Synthesis of the Polycitones



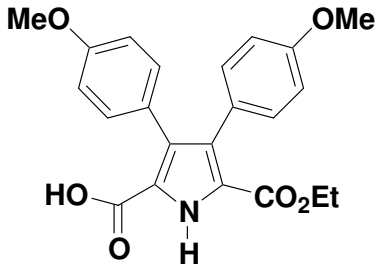
Lukianol Synthon

$POCl_3$, DMF and
Microwave acceleration



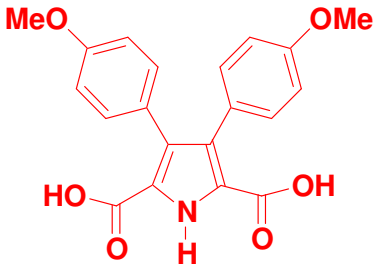
>90% Yield

$NaClO_2$, H_2O/DMSO
and buffer



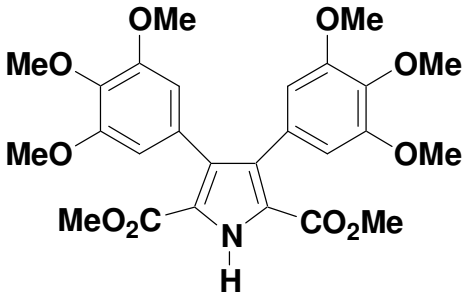
88% Yield

NaOH and EtOH/H_2O



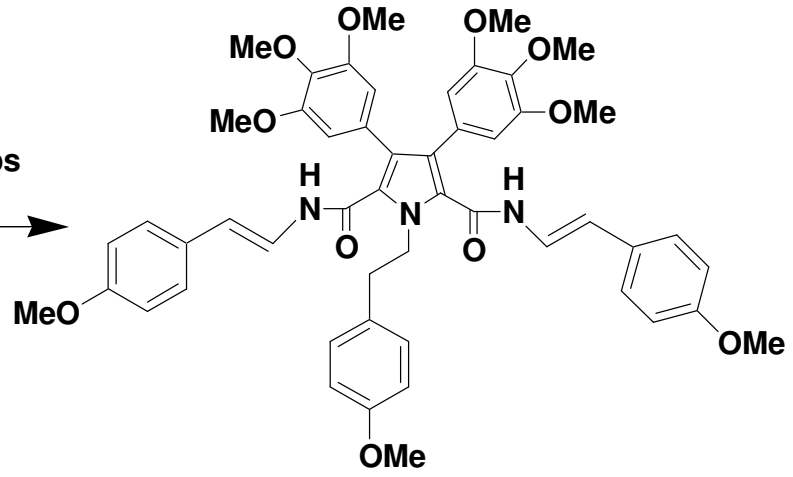
53% Yield
Steglich Synthon

Boger Storniamide Synthesis



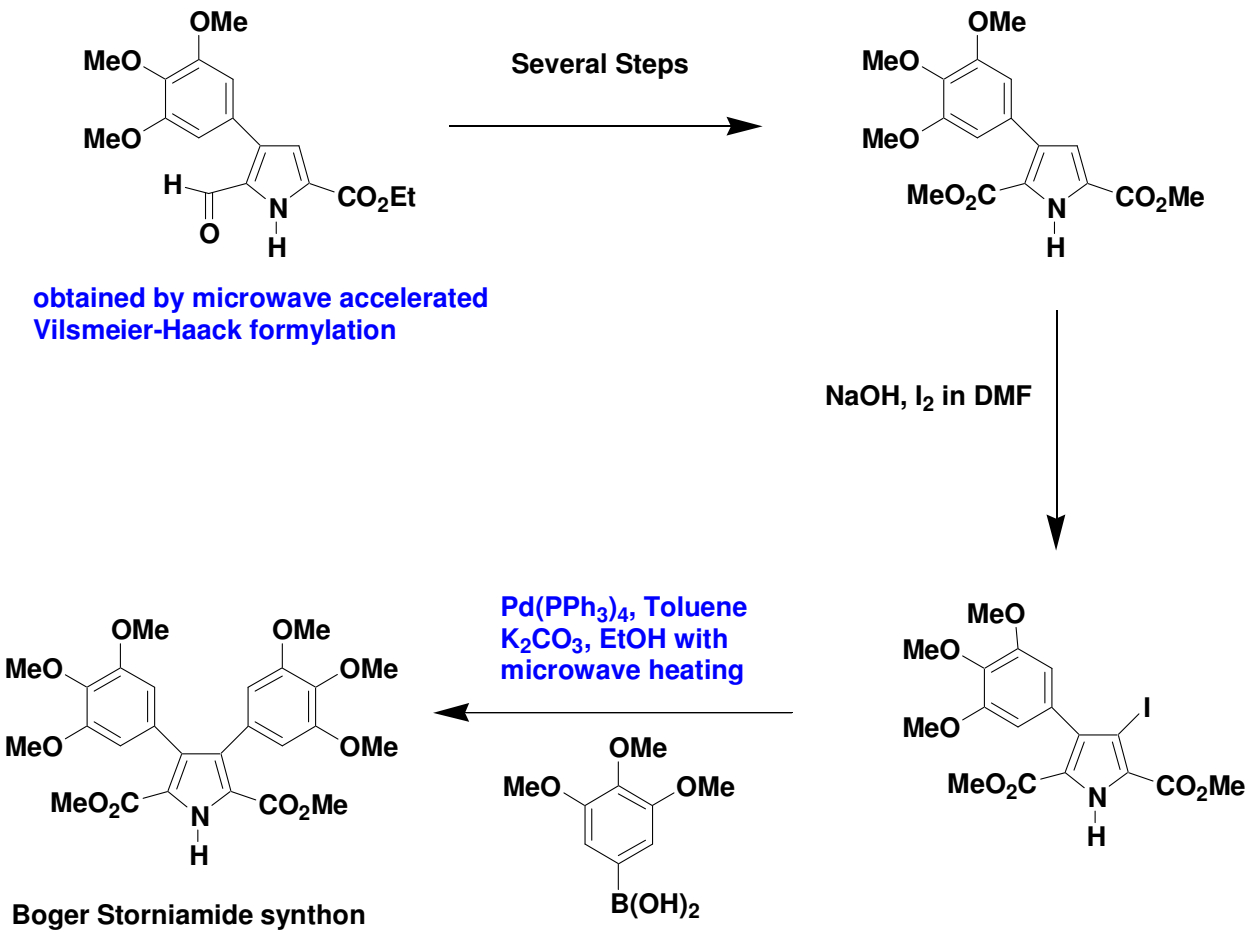
Boger Storniamide synthon

Several Steps



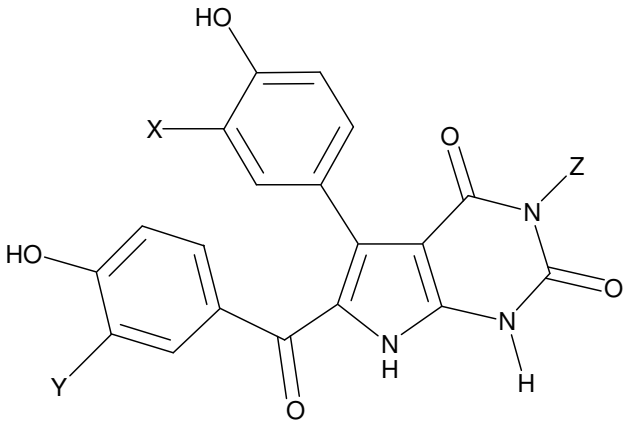
Permethyl Storniamide A

Gupton Group Relay Synthesis of Storniamide



J. Gupton, E. Banner, M. Sartin*, M. Coppock*, J. Hempel*, A. Kharlamova*, D. Fisher*, B. Giglio*, K. Smith*, M. Keough*, T. Smith, R. Kanters, R. Dominey and J. Sikorski, "Application of Vinylogous Iminium Salt Derivatives and Microwave Accelerated Vilsmeier-Haack Reactions to Efficient Relay Syntheses of the Polycitone and Storniamide Natural Products", *Tetrahedron,* 64, 5246-5243 (2008).

Rigidin Type Marine Alkaloids



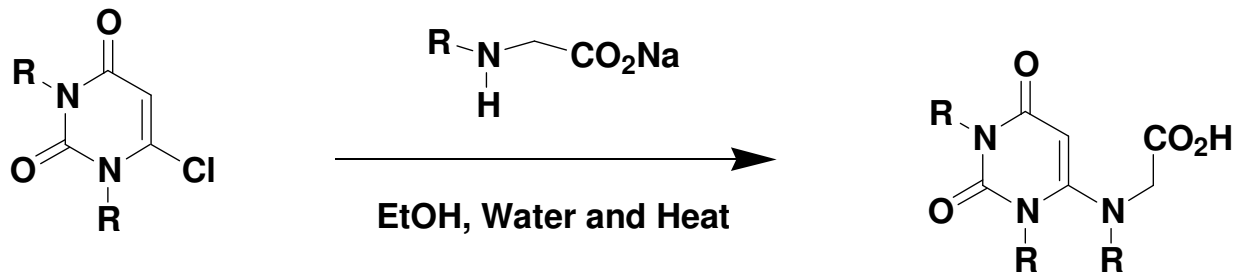
Rigidin X = Y = Z = H
Rigidin B X = H, Y = OCH_3
Rigidin C X = OCH_3, Y = Z = H
Rigidin D X = Y = OCH_3, Z = H
Rigidin E X = Y = H, Z = CH_3

Eudistoma regium
Photo by: Life at the Edge of Reef
www.edge-of-reef.com

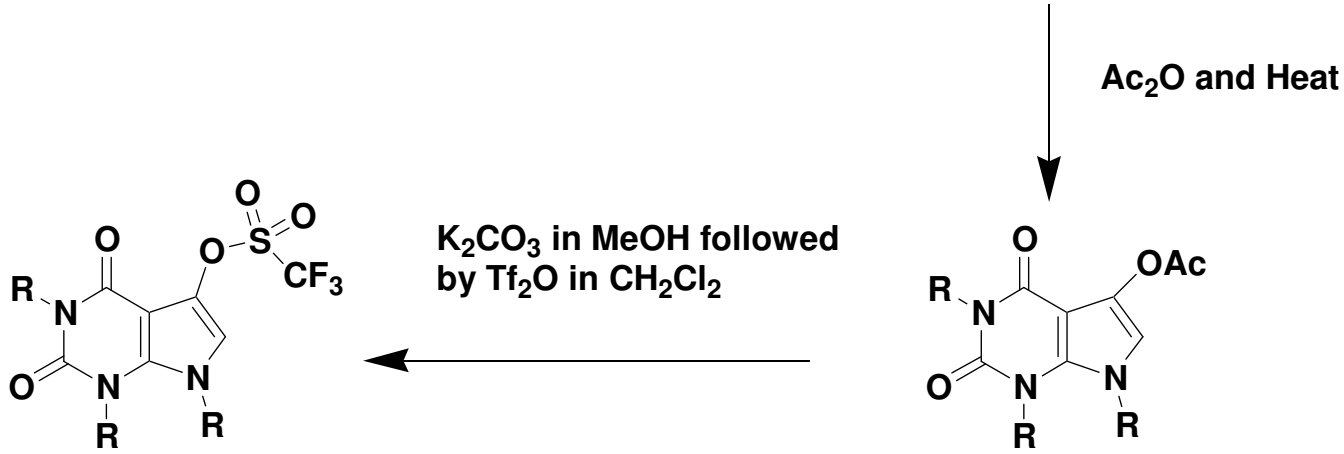
Isolated from an Okinawan marine tunicate and an inhibitor of calmodulin

Kobayshi, J., Cheng, J., Kikuchi, Y., Ishibashi, Y., Yamamura, S., Ohizumi, Y., Ohta, T. and Nozoe, S., *Tetrahedron Lett.*, *31*, 4617-4620 (1990). Tsuda, M., Nozawa, K., Shimbo, K. and Kobayashi, J., *J. Nat. Prod.,66*, 292-294 (2003). Davis, R., Christensen, L.; Richardson, A., da Rocha, and Ireland, C., *Marine Drugs, 1*, 27-33 (2003).

Edstrom Route to Rigidin

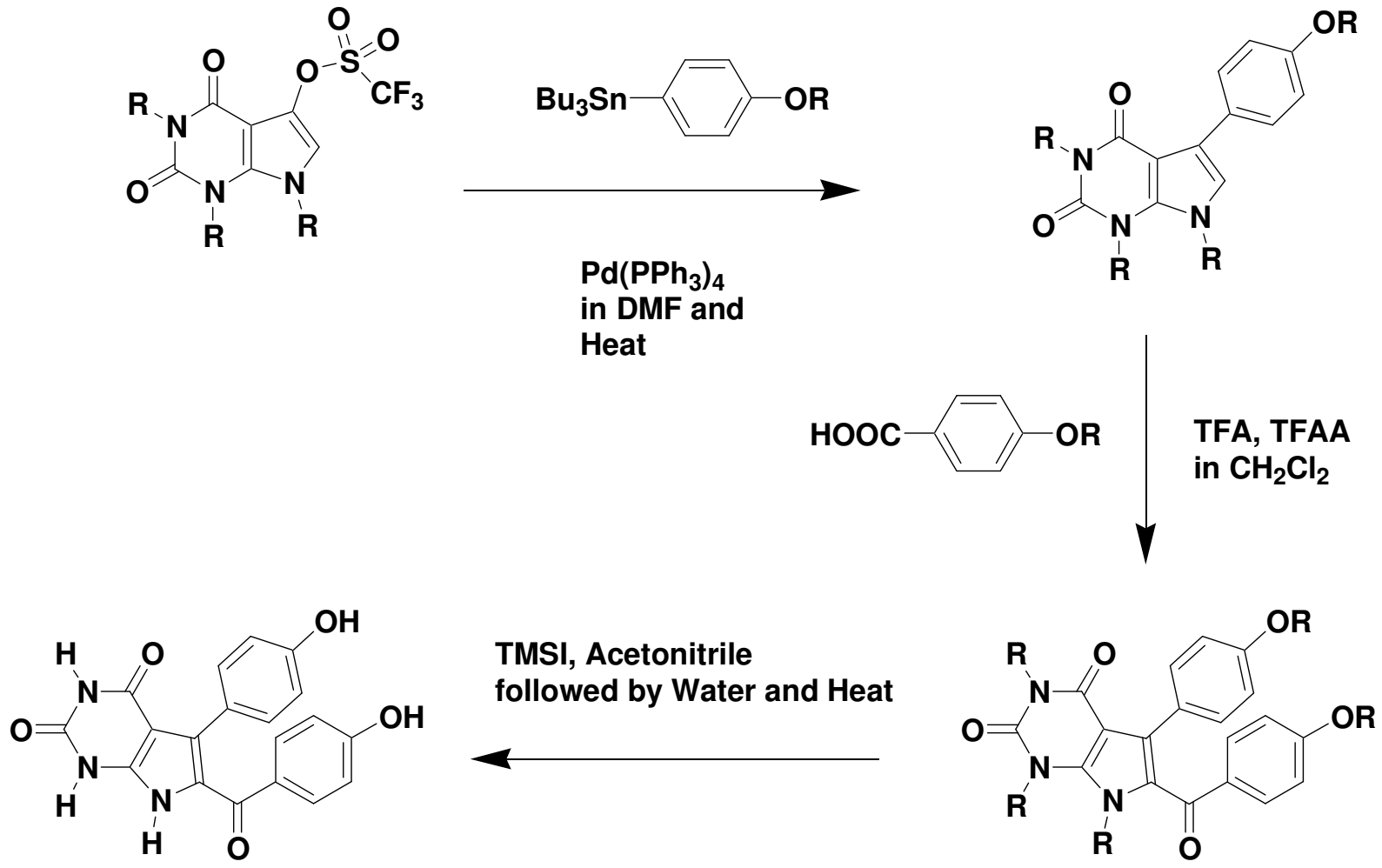


R = benzyl protecting group

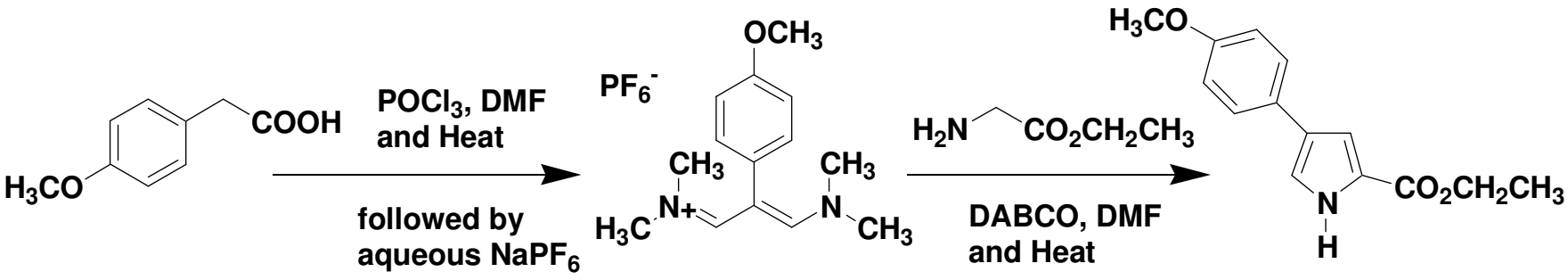


Edstrom, E. and Wei, Y., *J.Org. Chem.*, *58*, 403-407 (1993)

Edstrom Route to Rigidin



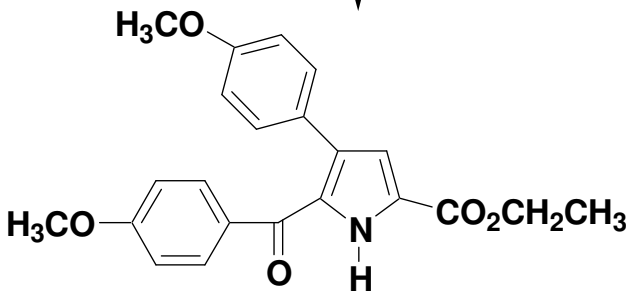
Gupton Group Route to Rigidin Precursor



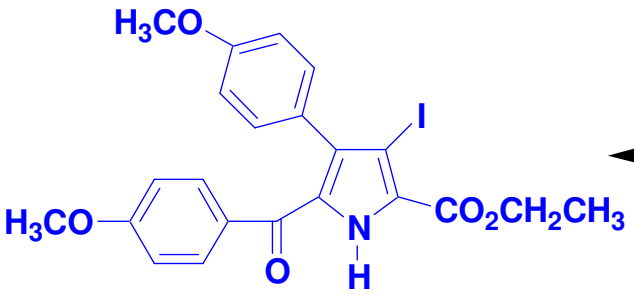
90% Yield

85% Yield

J. Gupton, E. Banner, A. Scharf*, B. Norwood,
R. Kanters, R. Dominey, J. Hempel*, A. Kharlamova*,
I. Bluhn-Chertudi*, C. Hickenboth*, B. Little*, M. Coppock*,
K. Krumpe, B. Burnham, H. Holt., K. Du, K. Keertikar, A. Diebes,
S. Ghassemi and J. Sikorski, *Tetrahedron,* 62, 8243-8255 (2006).

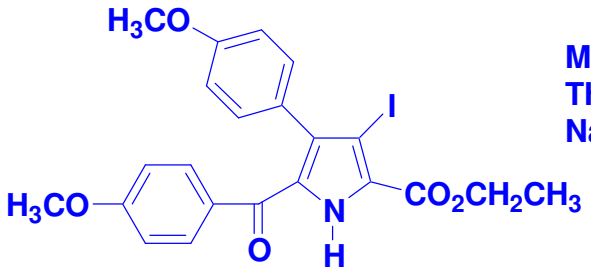


94% Yield

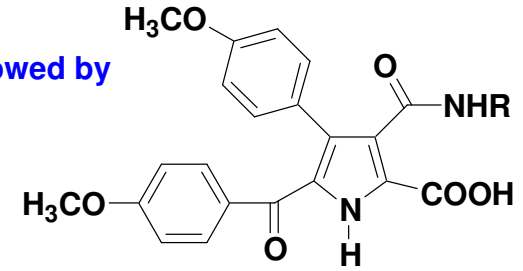


89% Yield

Conversion of Precursor to Rigidin

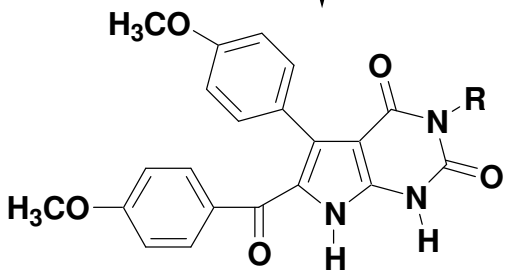


$Mo(CO)_6$, $Pd(OAc)_2$, DBU, NH_2R
THF and Microwave Heating followed by
NaOH, H_2O/EtOH and Heat



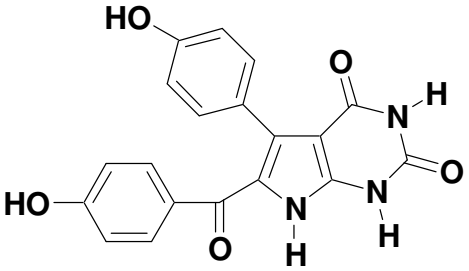
72% Yield

$(PhO)_2PON_3$, Et_3N
Toluene and Heat



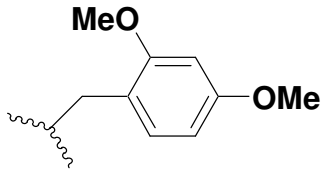
69% Yield

Excess BBr_3 in CH_2Cl_2



74% Yield

R =



Summary Comments on Vinylogous Iminium Salts and Their Derivatives

- Efficient three carbon synthons
- Contain important substituent groups
- Efficient precursors to highly functionalized pyrroles and pyrrole containing marine alkaloids.
- Microwave acclerated reactions prove to be key to many important transfromations.

Funding

- **NIH Area**
- NSF MRI
- Camille & Henry Dreyfus
- Research Corp.
- ACS-PRF
- **Biotage**
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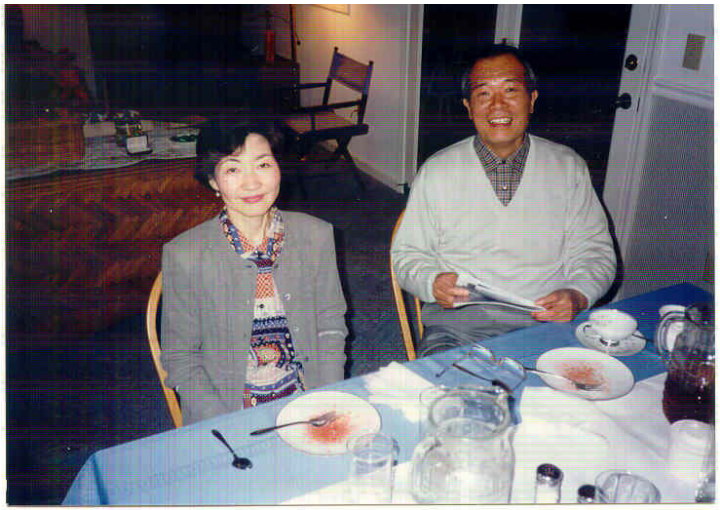
- Gottwald Endowment
- Dow Chemical
- Monsanto-Searle
- American Cyanamid
- Ciba-Geigy
- Jeffress Memorial Trust
- Kresge Foundation
- Puryear-Topham Endowment
- Merck

Research Collaborators

Jim Sikorski

Sue Mooberry

Milton Brown



Hiroki Yamanaka and wife Fukiko

Research Collaborators

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David Gewirtz

Tim Smith

Keith Krumpe

Research Collaborators

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- Glenn Cunningham
- Jim Sikorski
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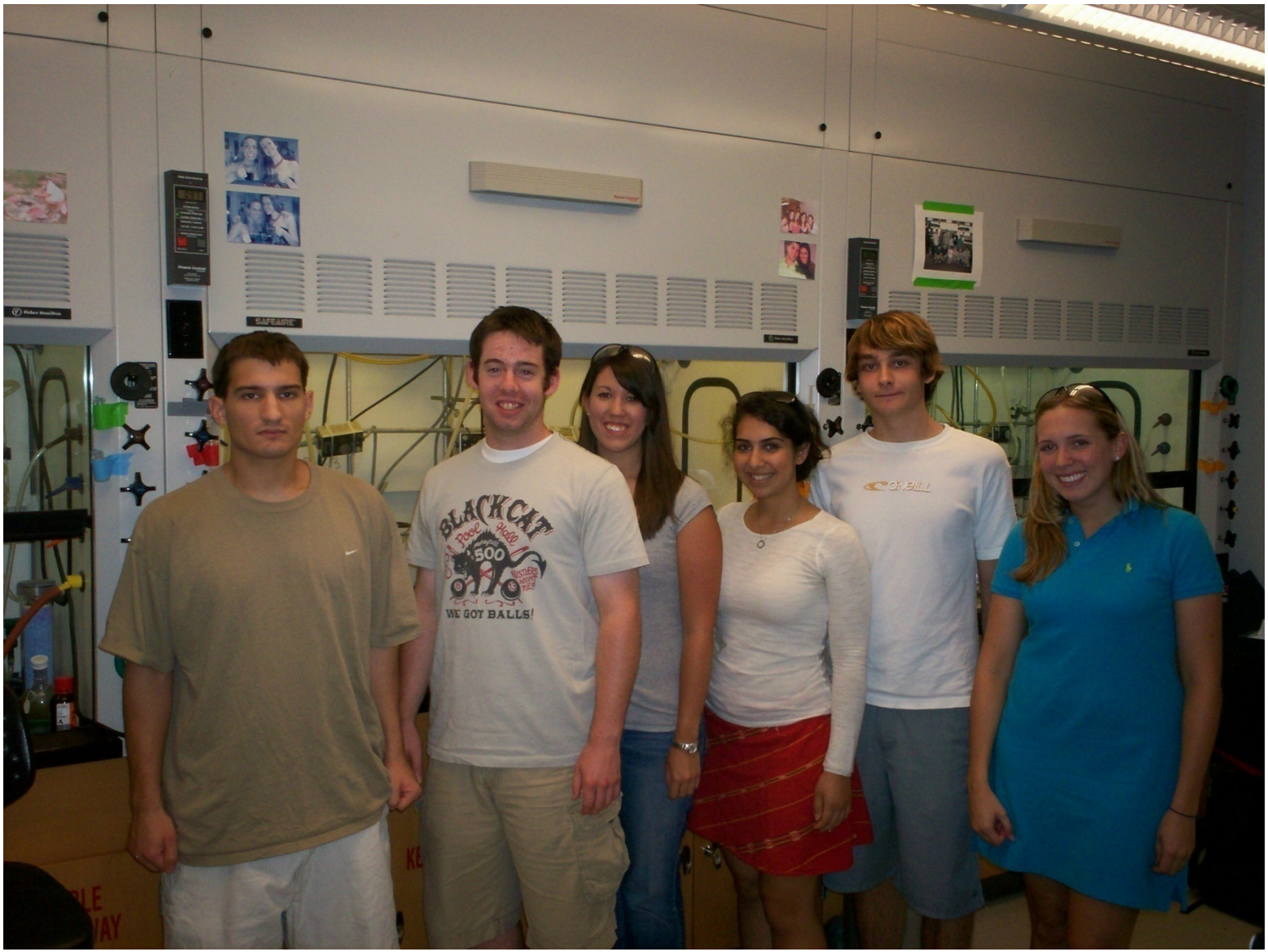
- Alan Katritzky
- Zednek Arnold
- Iris Hall
- Keith Krumpe
- Bruce Burnham
- Stuart Clough
- Milt Brown
- Sue Mooberry
- Ernest Hamel
- David Gewirtz
- Glen Kellogg
- Andrew Yeudall
- Tim Smith
- Rene Kanters
- Brad Norwood

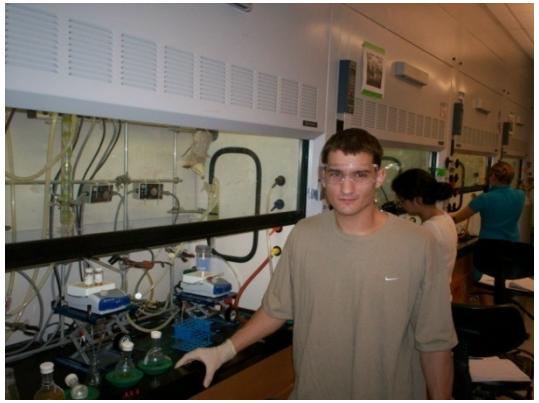
Gupton Research Group 2006-2007

Gupton Research Group 2007-2008

Gupton Research Group Summer 2008

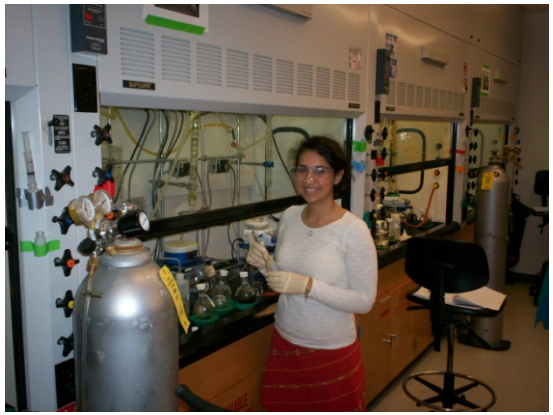


Gupton Research Group Summer 2008



Ben Giglio

James Eaton



Mona Hovaizi

Kristin Smith

Lizzie Rieck

Peter Barelli

UR Night at the Diamond June 2008

Gottwald Center for the Sciences