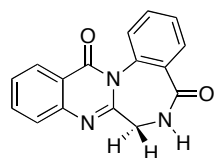
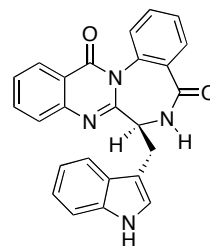


# Microwave-Assisted Concise Total Syntheses of Quinazolinobenzodiazepine Alkaloids

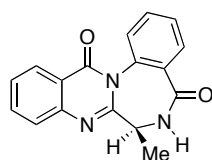
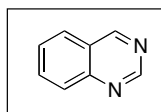
Ji-Feng Liu, Mira Kaselj, Yuko Isome, Jennifer Chapnick, Bailin Zhang, Grace Bi, Daniel Yohannes,  
Libing Yu, and Carmen M. Baldino, Arqule, Inc.,  
*J. Org. Chem.* **2005**, 10488-1-493



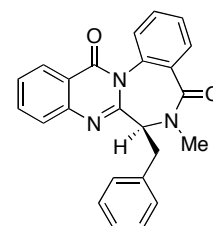
**Sclerotigenin**



**Asperlicin C**



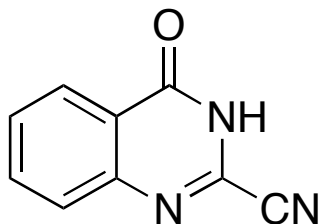
**Circumdatin F**



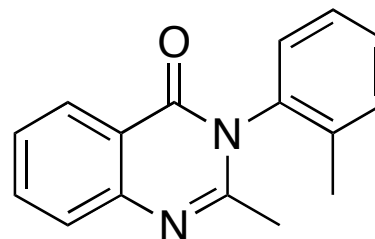
**Benzomalvin A**

Claire Coleman, Current Literature Jan 21 2006

## First Quinazoline Synthesised in late 1860's



First synthetic quinazoline



**Methaqualone**  
sedative-hypnotic effects

Griess, P. *Berichte* **1869**, 2, 415.  
Griess, P. *Berichte* **1878**, 11, 1985.

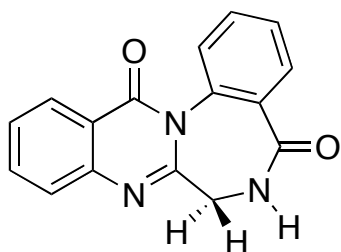
Kackler, I. K.; Zaheer, S. H. *J. Indian Chem. Soc.* **1951**, 28, 344.

Quinazoline alkaloids (*ca.* 150)\* have been isolated from several families in the plant kingdom, bacteria, animal species and biogenetically derived from anthranilic acid.

\**Current Organic Chemistry*, **2003**, 7, 659-677.

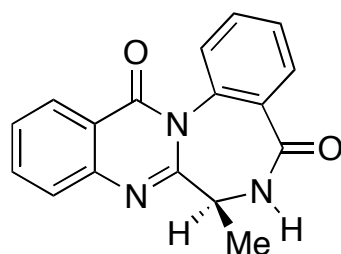
*Nat. Prod. Rep.*, **2004**, 21, 650-668.

## Quinazolinobenzodiazepine Alkaloids



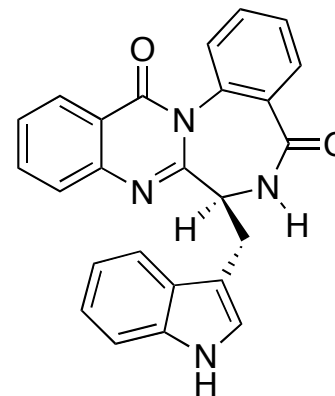
**Sclerotigenin**

anti-insectant  
Snider 1998  
Thomas 2003



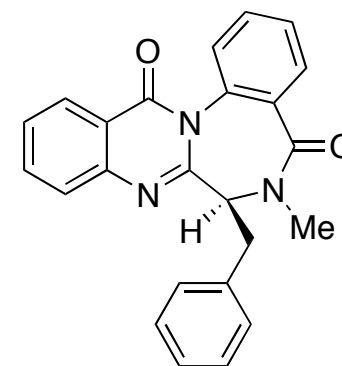
**Circumdatin F**

Snider  
Bergman



**Asperlicin C**

CCK antagonist  
Snider  
Bock



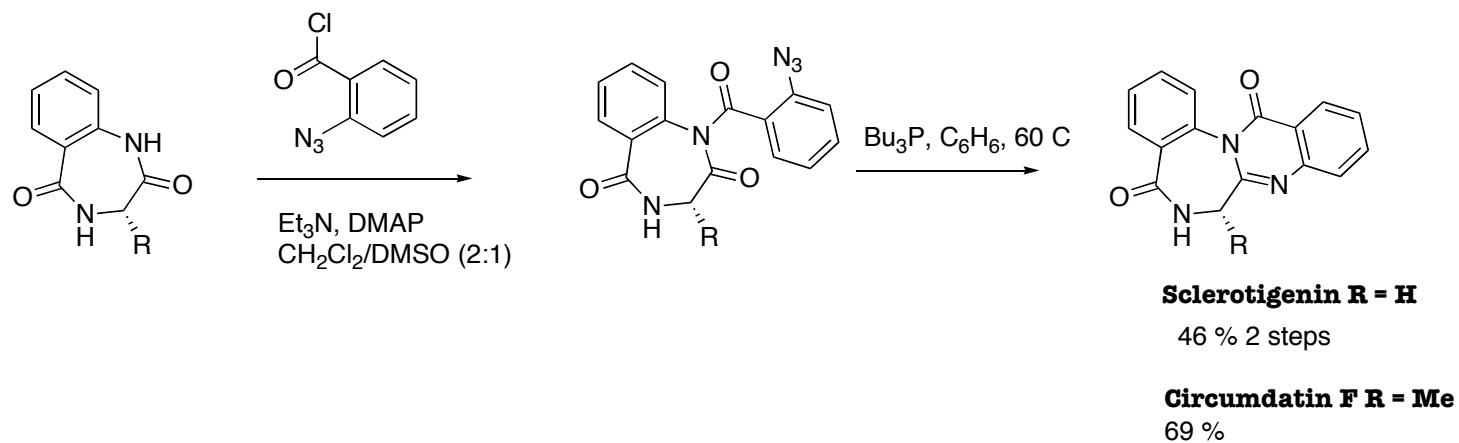
**Benzomalvin A**

Okamoto

Review: *Natural Product Reports*, **2004**, 21, 650-668.

All of these methodologies required multiple steps and gave low to moderate yields

## Sniders' Synthesis of Sclerotigenin

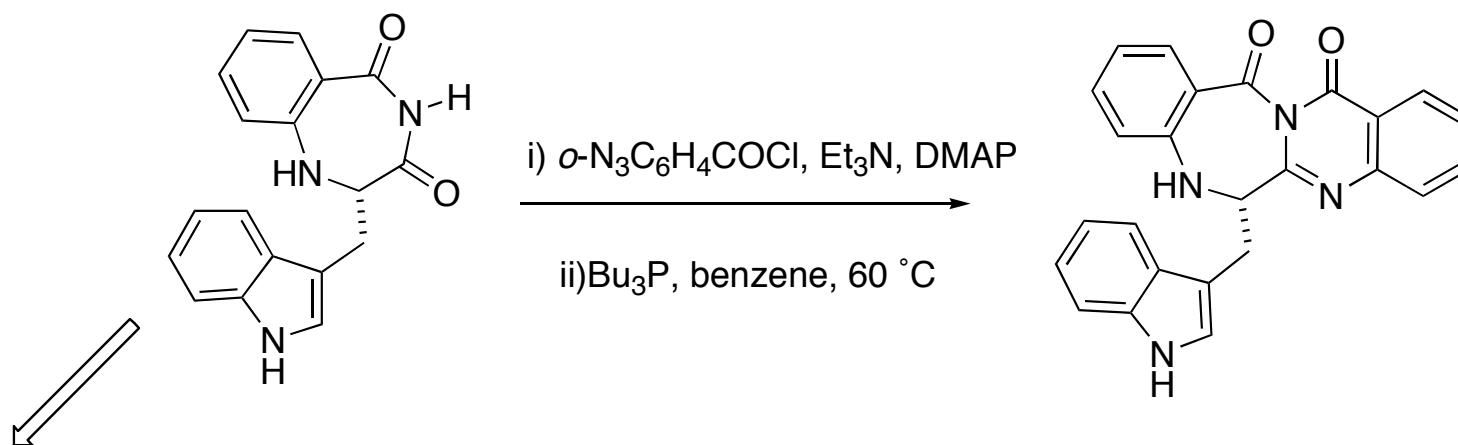


(Eguchi-aza Wittig protocol)

(antiinsectant from organic extracts of sclerotia of *Penicillium sclerotigenum*)

*Tetrahedron*, 57, **2001**, 3301-3307.

## Synthesis of (-)-Asperlicin C



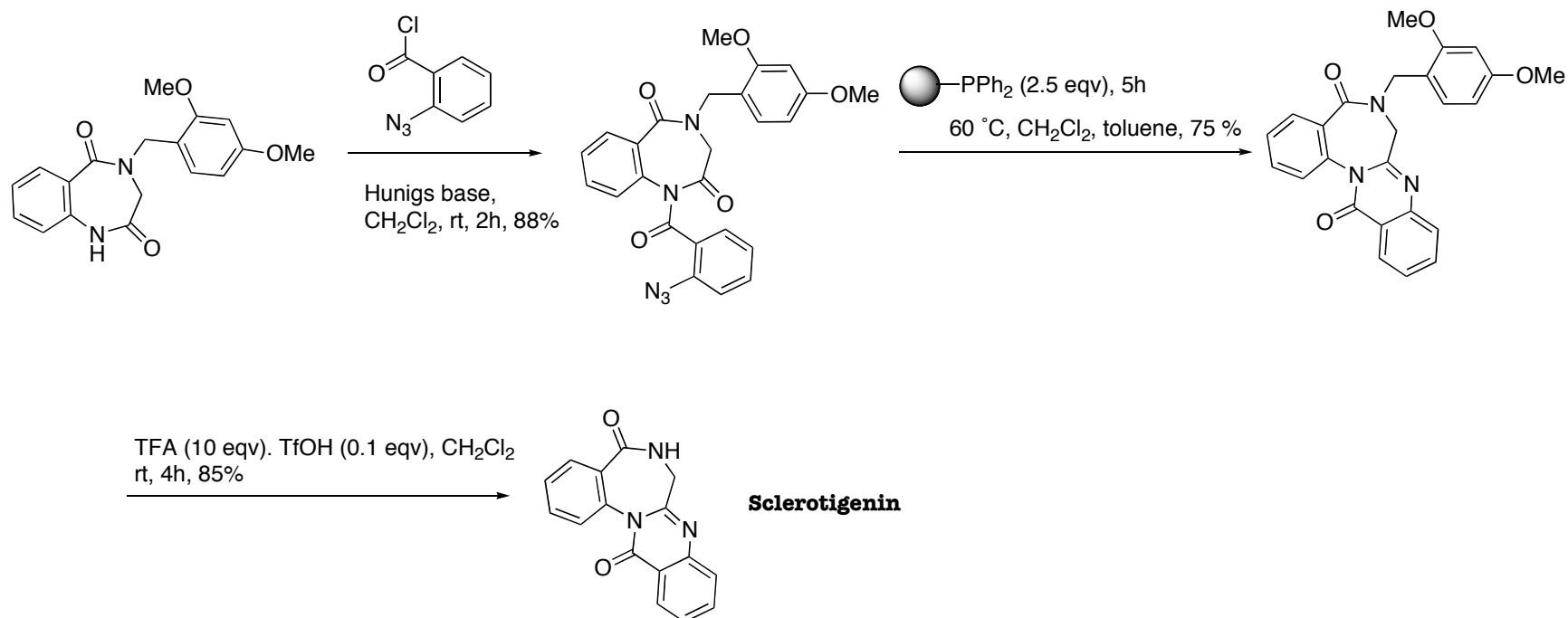
2 step procedure by Posner, *J. Org. Chem.*, **1987**, *52*, 1644-1646

64% 2 steps

Snider *et al* *J. Am. Chem. Soc.* **1998**, *120*, 6417-6418.

Also Bock *et al*, *J. Org. Chem.* **1987**, *52*, 1646-4647. (first total synthesis using regioselective annulation of benzodiazepinedione with anthranilic acid)

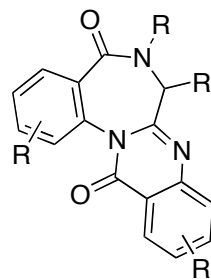
## Diverse Multi-Arrayed Library of the Circumdatin family of Natural products



Sclerotigenin prepared as model before library  
Polymer supported phosphine in key step intramolecular aza-wittig

*Synthesis*, **2003**,1707-1711. Hoffmann-LaRoche

## Diverse Natural Product like Library of Circumdatins

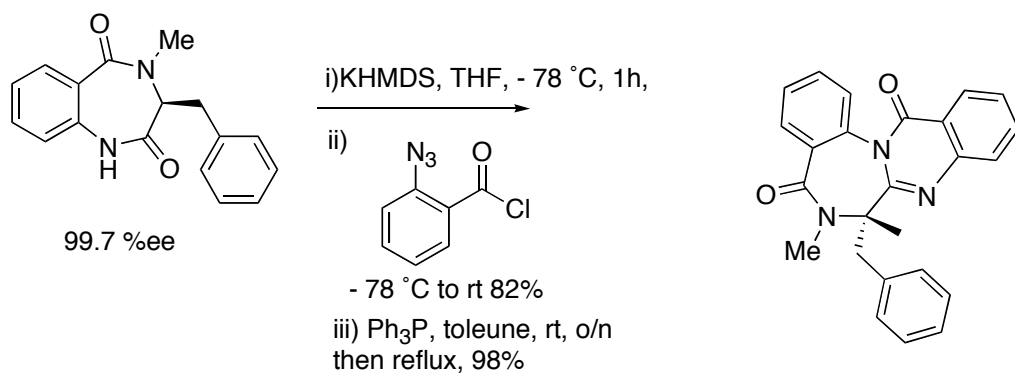
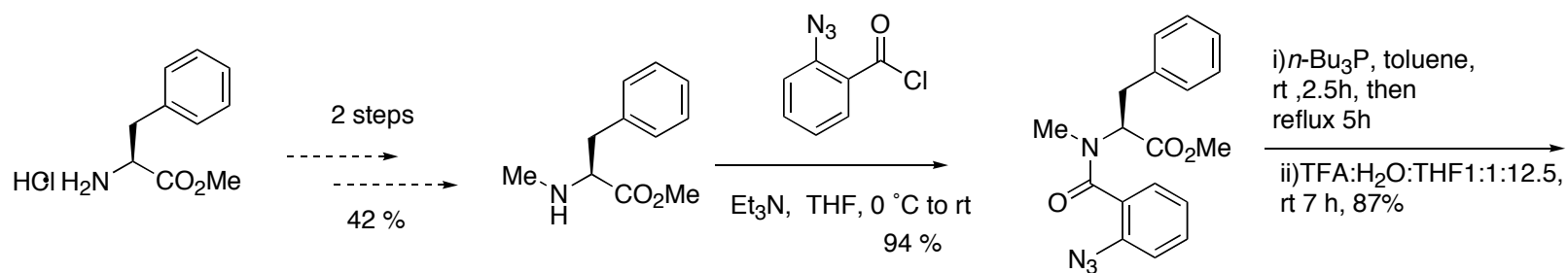


283 isolated products from 382 individual reactions

**Buchi Syncore 24**



## Benzomalvin A

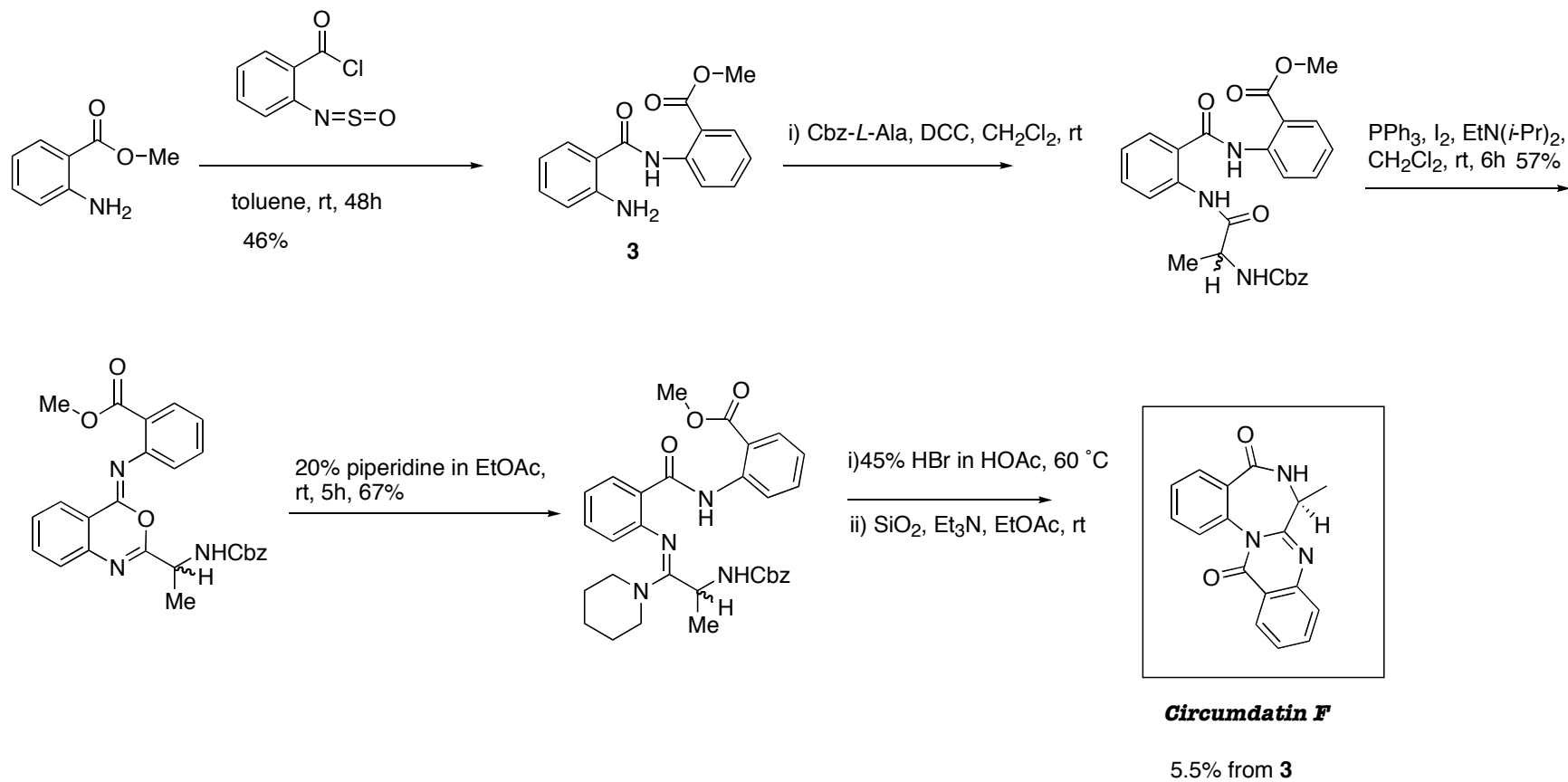


**(-)-Benzomalvin A**

Okamoto *et al*, *Tetrahedron*, **1998**, 7997-8008.

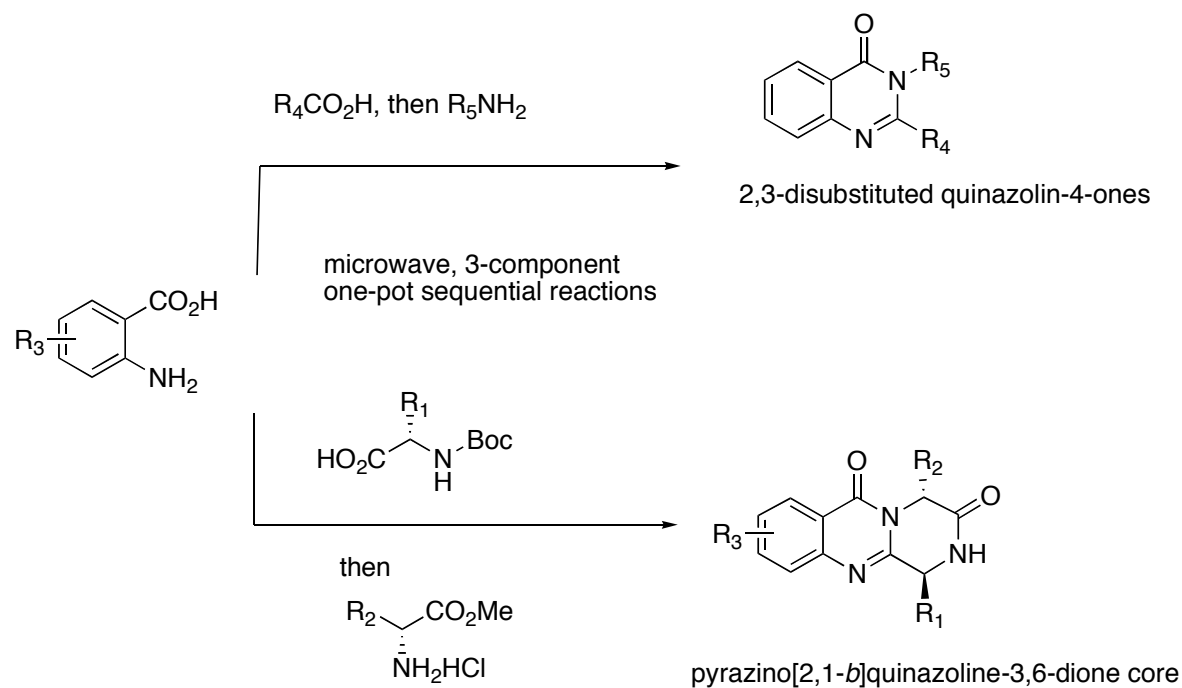


## Circumdatin F (Bergman-2001)



Bergman *et al.*, *J. Org. Chem.* **2001**, *66*, 2784-2788.

# One Pot Syntheses of 2,3-Disubstituted Quinazolin-4-ones and Pyrazino [2,1-*b*]quinazoline-3,6-diones



Liu *et al*, *Tetrahedron Lett.* **2005**, *46*, 1241-1244.

Liu *et al*, *J. Org. Chem.* **2005**, *70*, 6339-6345.

# **Total Syntheses of Quinazolinobenzodiazepine Alkaloids**

*Liu et al*

Developed a novel domino process for the synthesis of Quinazolinobenzodiazepine Alkaloids including

**Sclerotigenin**

**(±) - Circumdatin F**

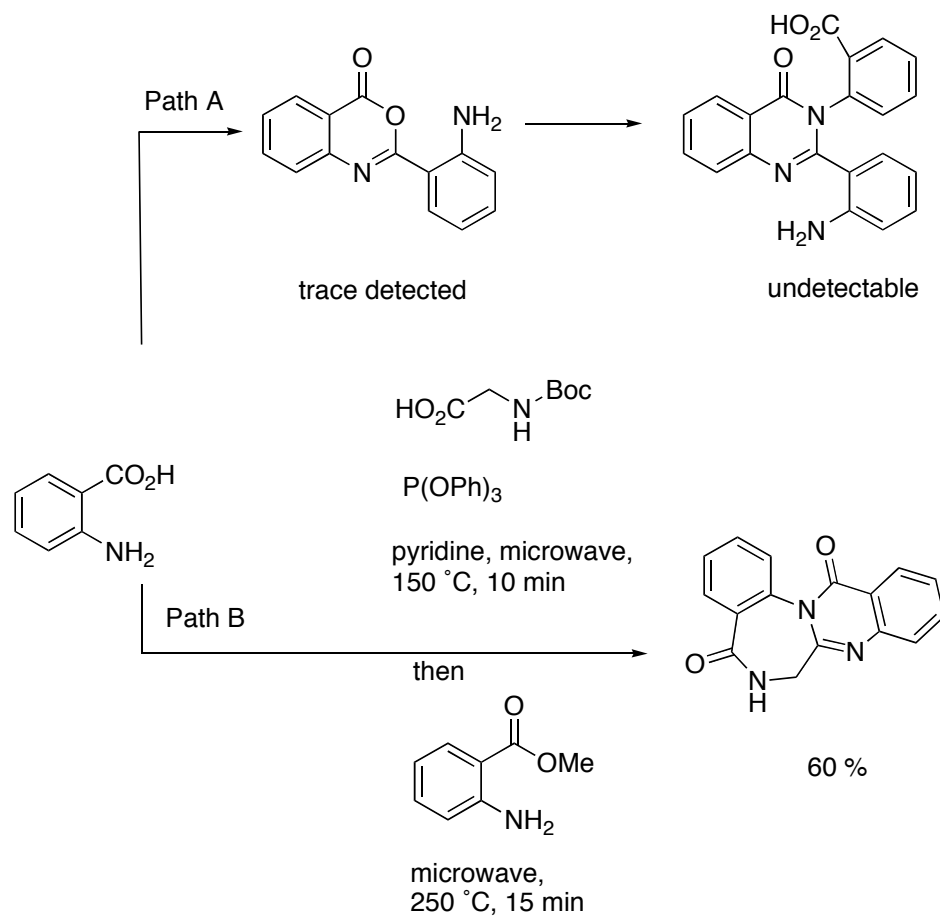
**(±)-Aspercilin C**

**(±)-Benzomalvin A**

**Circumdatin E analogues**

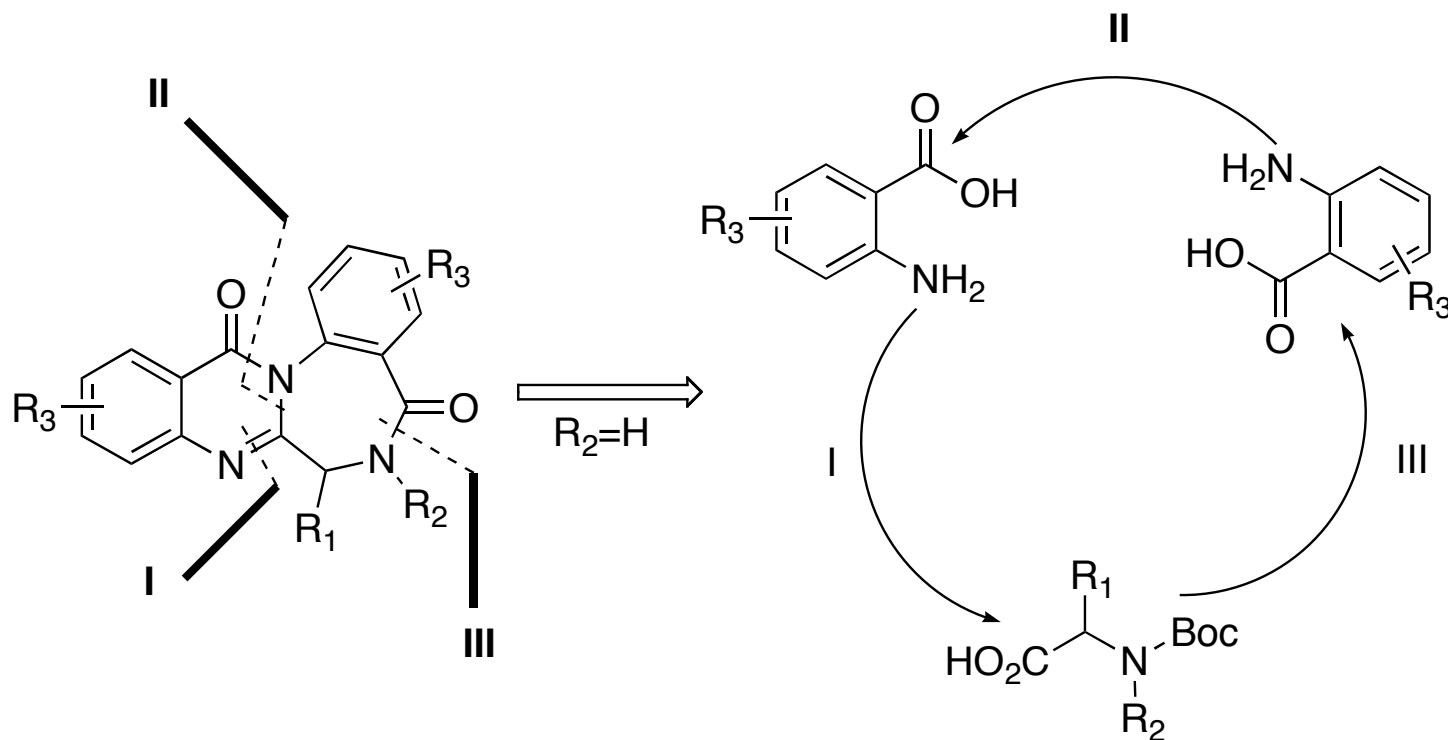
Using one reagent, one protecting group and readily available anthranilic acids and Boc-amino acids

## Synthesis of Sclerotigenin



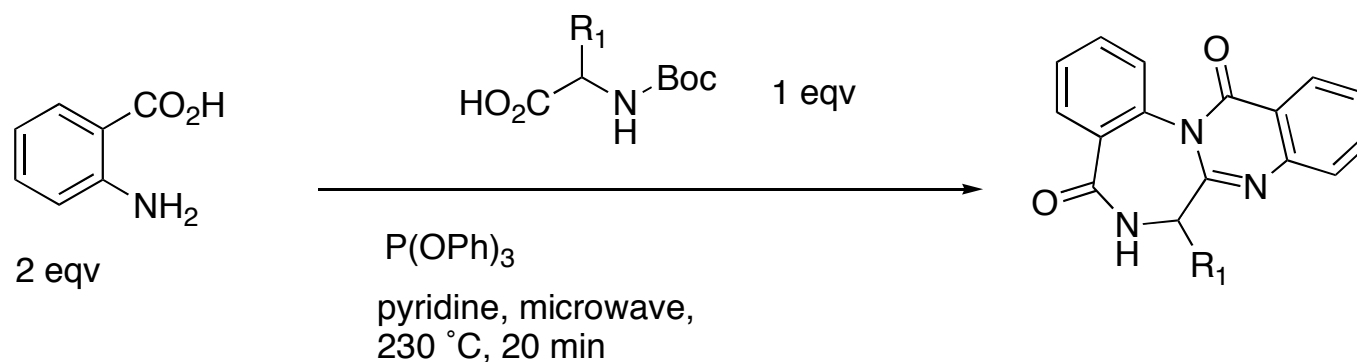
three-component one pot reaction

## Retrosynthetic Strategy for the “Symmetric” Quinazolinobenzodiazepine Alkaloids via Domino Reactions



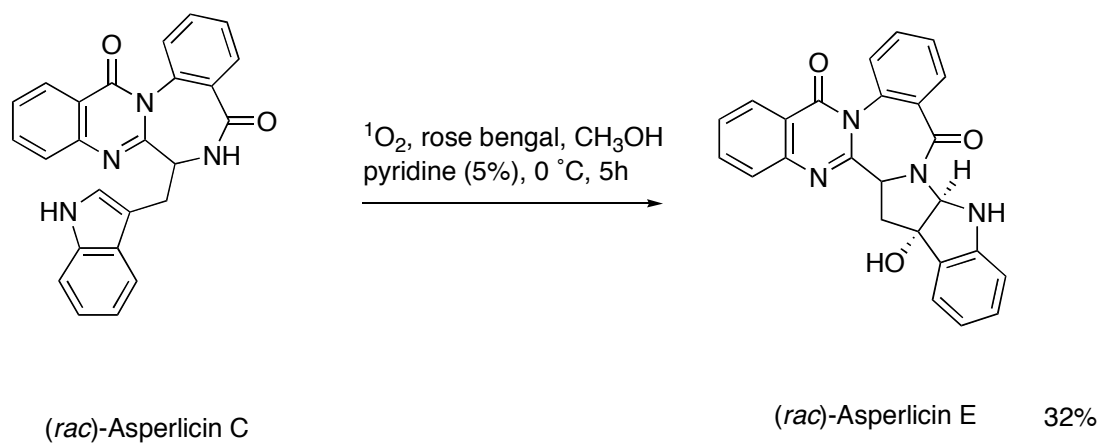
reaction sequence would be I, II then III to give products  
not II, I then III to give by-products

# One Step total Syntheses of Sclerotigenin ( $\pm$ ) - Circumdatin F ( $\pm$ )-Aspercilin C and the precursor of ( $\pm$ )-Benzomalvin A



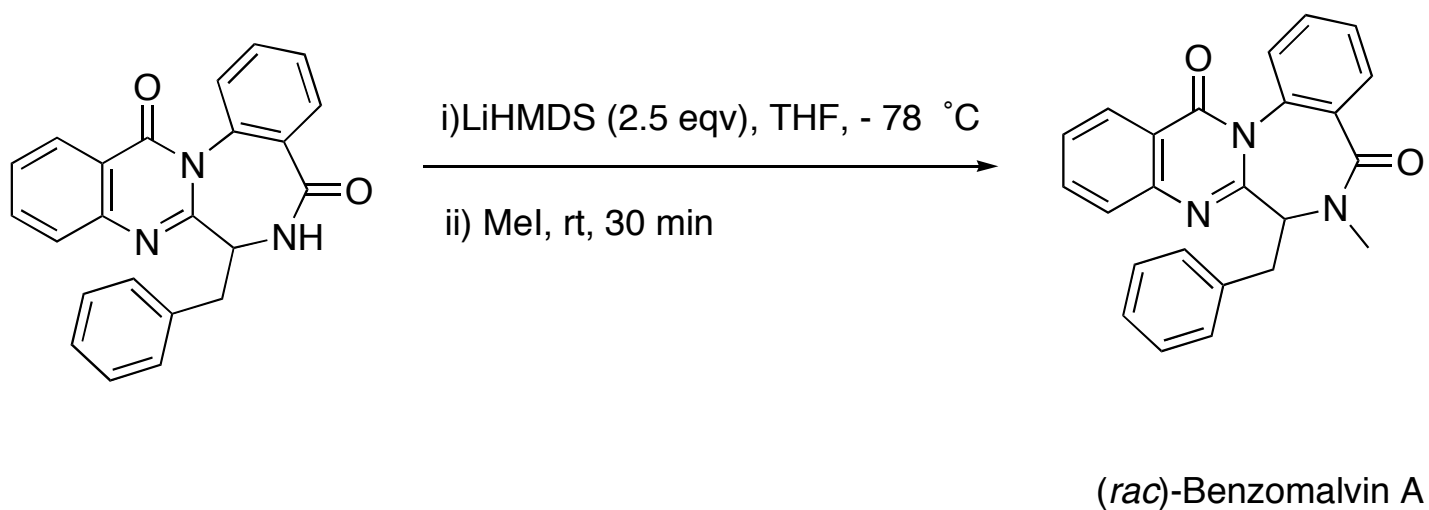
- R<sub>1</sub> = H, **Sclerotigenin**, 55%
- R<sub>1</sub> = Me, **Circumdatin F**, 32%
- R<sub>1</sub> = CH<sub>2</sub>Indole, **Aspercilin C**, 20%
- R<sub>1</sub> = Bn, **Benzomalvin A precursor**, 23%

## Formal Total Synthesis of (±)-Aspercilin E



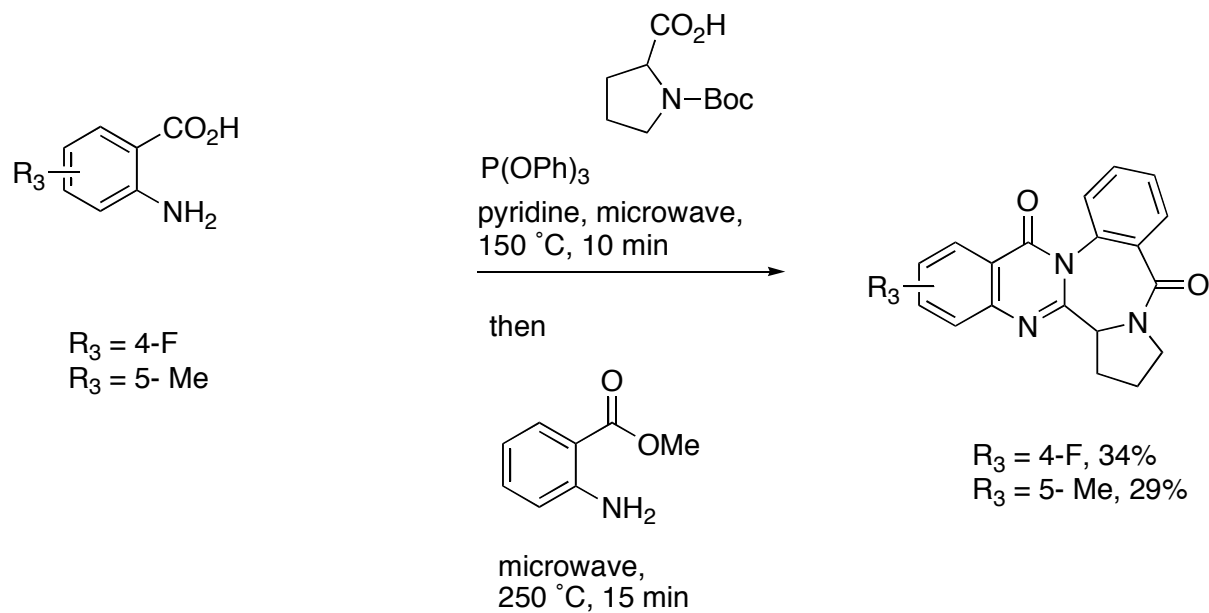
conditions- Bock *et al*, *J. Org. Chem.* **1987**, 52, 1646-4647.

## Synthesis of ( $\pm$ )-Benzomalvin A





## Three-Component One -Pot Syntheses of analogues of Circumdatin E



•non-symmetric Quinazolinobenzodiazepine Alkaloids

## Summary

- Microwave assisted one pot total synthesis of the Quinazolinobenzodiazepine Alkaloids of Sclerotigenin ( $\pm$ ) - Circumdatin F ( $\pm$ )-Aspercilin C via novel domino reactions
- Two step total synthesis of ( $\pm$ )-Benzomalvin A and formal total synthesis of ( $\pm$ )-Asperlicin E
- Access to symmetric and non-symmetric Quinazolinobenzodiazepine Alkaloids using 1 reagent, 1 protecting group and 1 solvent

### Future directions

- Microwave assisted high-throughput natural product combinatorial libraries
- Other scaffolds