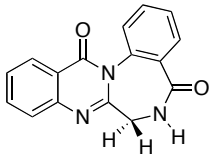
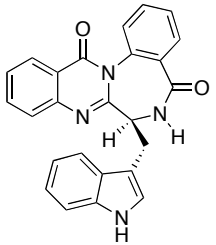
Microwave-Assisted Concise Total Syntheses of Quinazolinobenzodiazepine Alkaloids

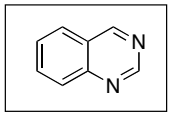
Ji-Feng Liu, Mira Kaselj, Yuko Isome, Jennifer Chapnick, Bailin Zhang, Grace Bi, Daniel Yohannes, Libing Yu, and Carmen M. Baldino, Arqule, Inc.,
J. Org. Chem. **2005**, 10488-1-493

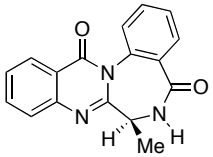


Sclerotigenin

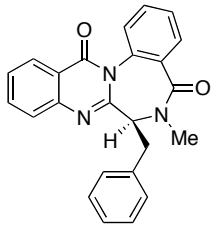


Asperlicin C





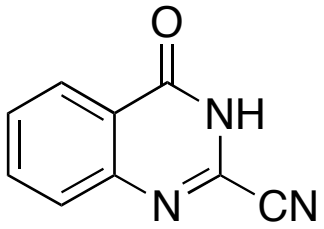
Circumdatin F



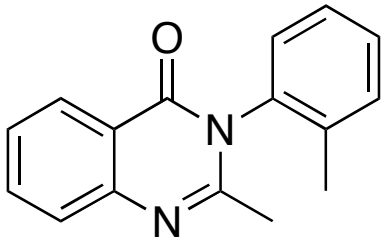
Benzomalvin A

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.

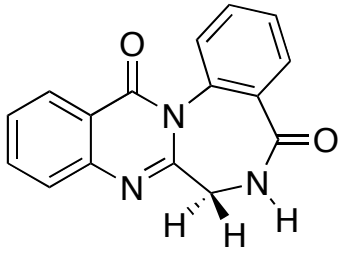
Kackler, I. K.; Zaheer, S. H. *J. Indian Chem. Soc.* **1951**, *28*, 344.

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

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

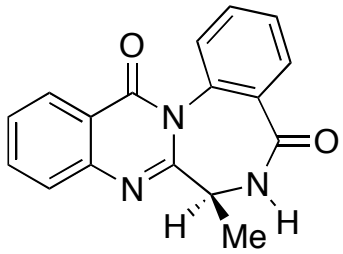
Nat. Prod. Rep., **2004**, 21, 650-668.

Quinazolinobenzodiazepine Alkaloids



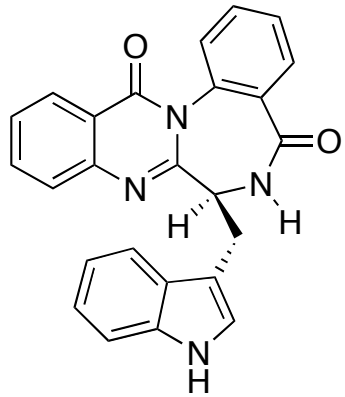
Sclerotigenin

anti-insectant
Snider 1998
Thomas 2003



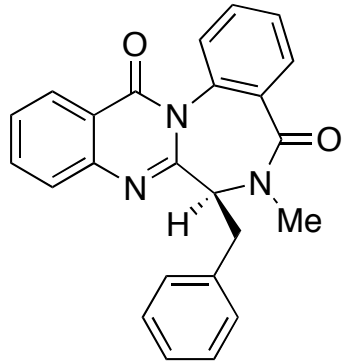
Circumdatin F

Snider
Bergman



Asperlicin C

CCK antagonist
Snider
Bock

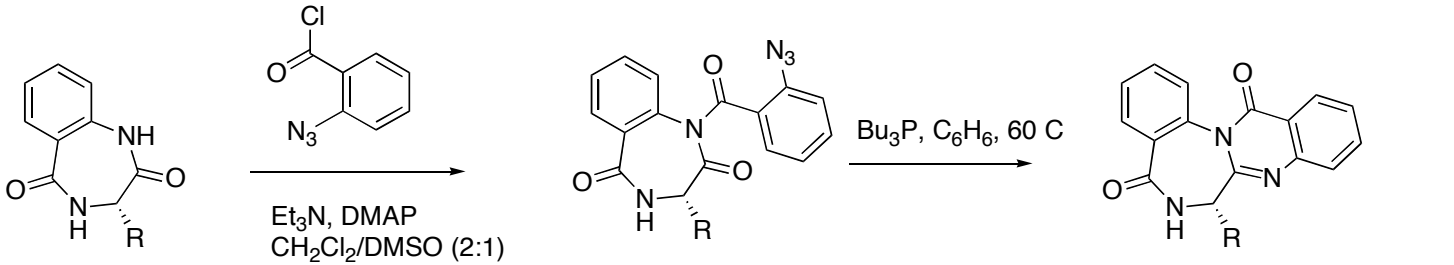


Benzomalvin A

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



Sclerotigenin R = H

46 % 2 steps

Circumdatin F R = Me

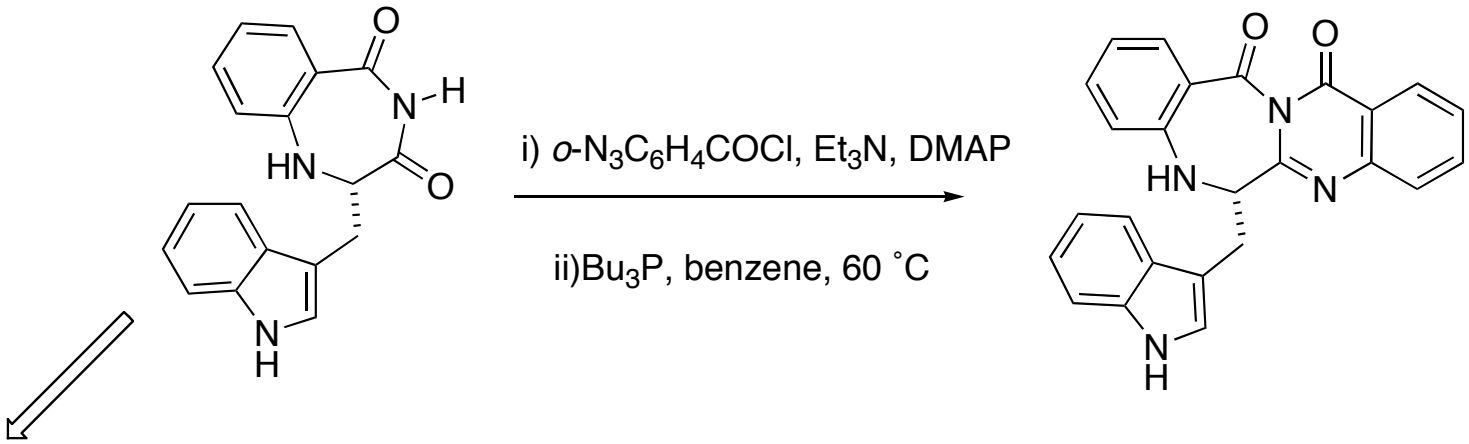
69 %

(Eguchi-aza Wittig protocol)

(antiinsectant from organic extracts of sclerotia of Penicillium sclerotigenum)

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

Synthesis of (-) Asperlicin C

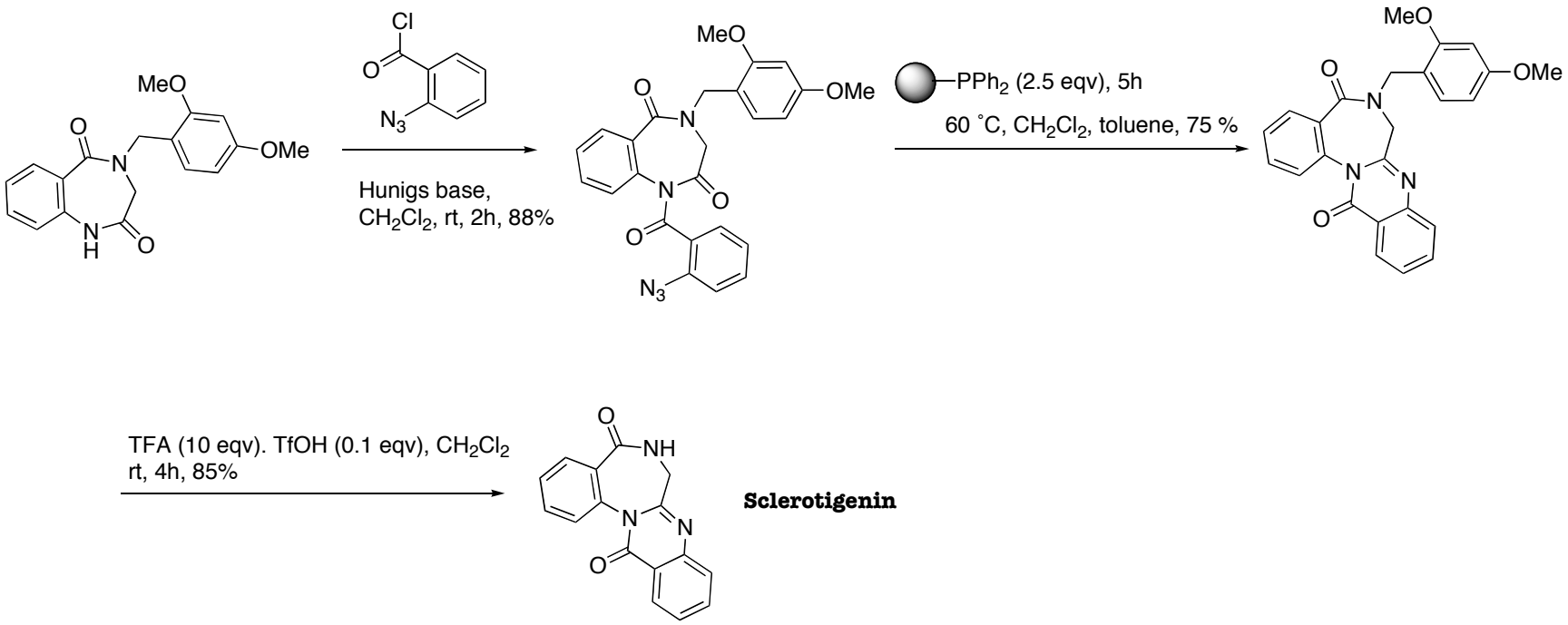


2 step procedure by Posner, *J. Org. Chem*, **1987**, *52*, 1644-1646

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 benzodazepinedione with anthranilic acid)

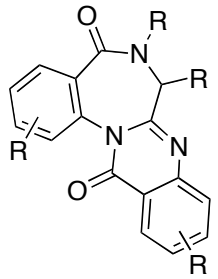
Diverse Multi-Arrayed Library of the Circumdatin family of Natural products



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

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

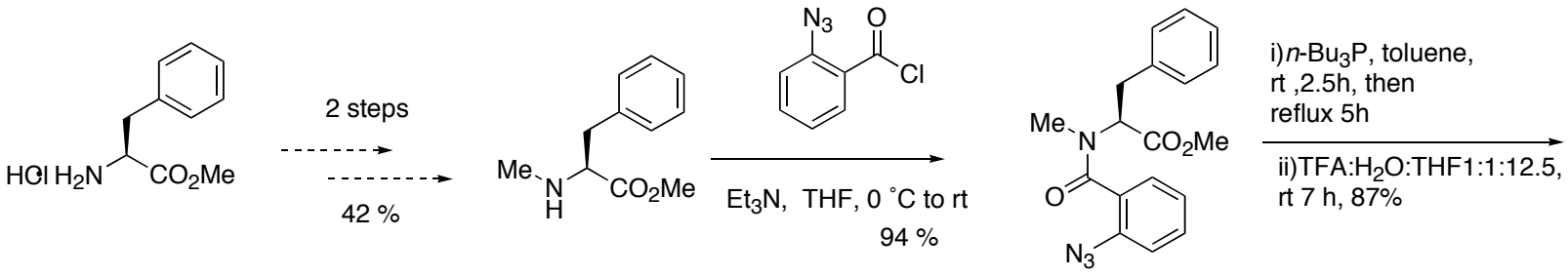
Diverse Natural Product like Library of Circumdatins

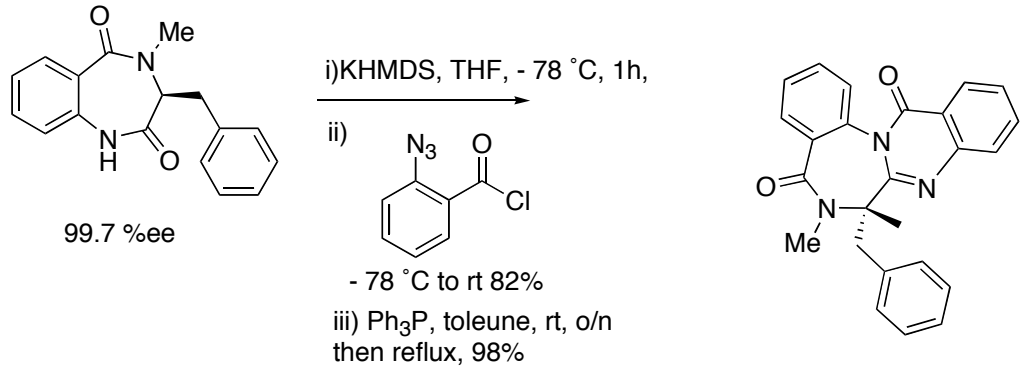


283 isolated products from 382 individual reactions

Buchi Syncore 24

Benzomalvin A

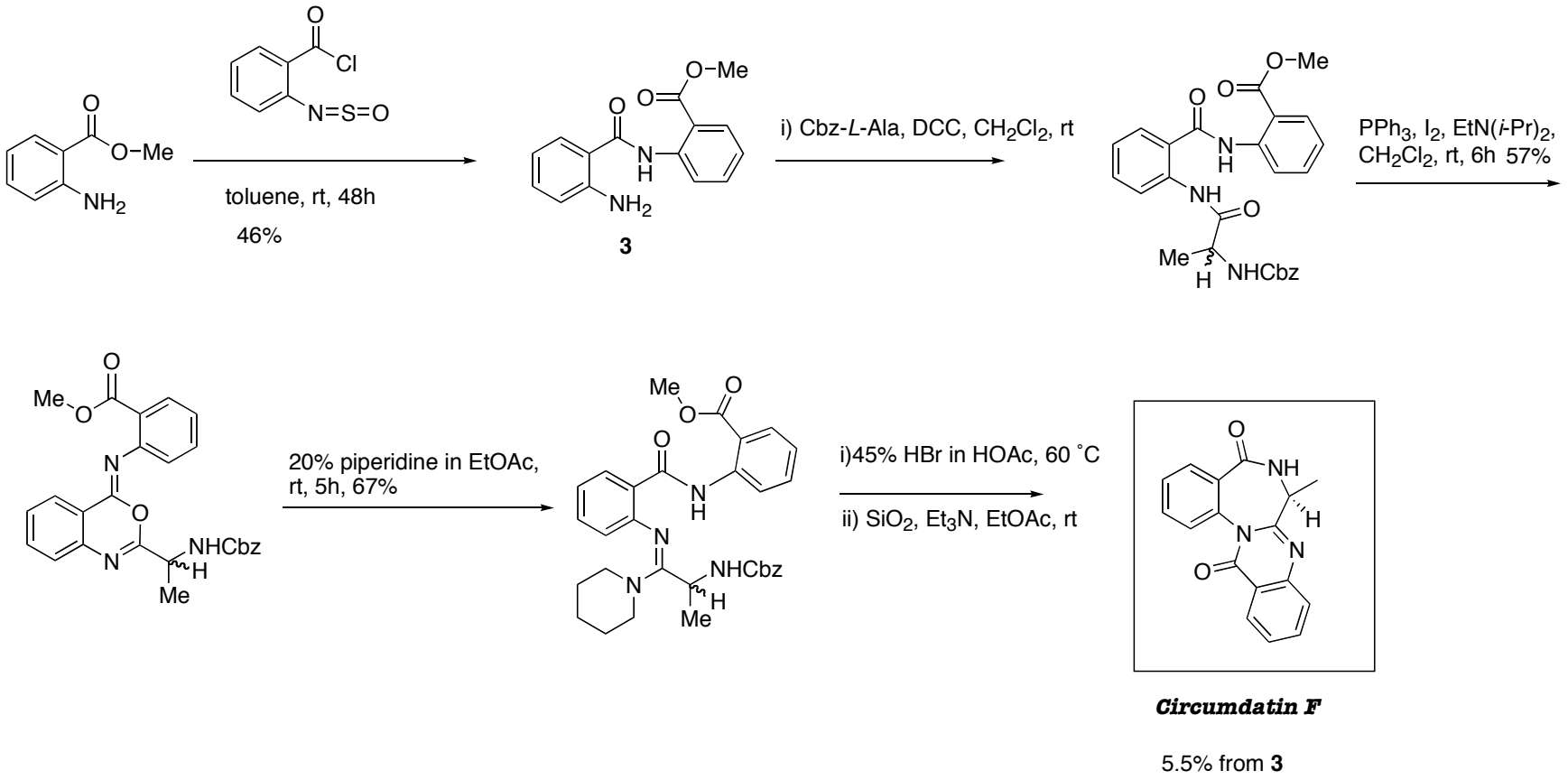




(-)-Benzomalvin A

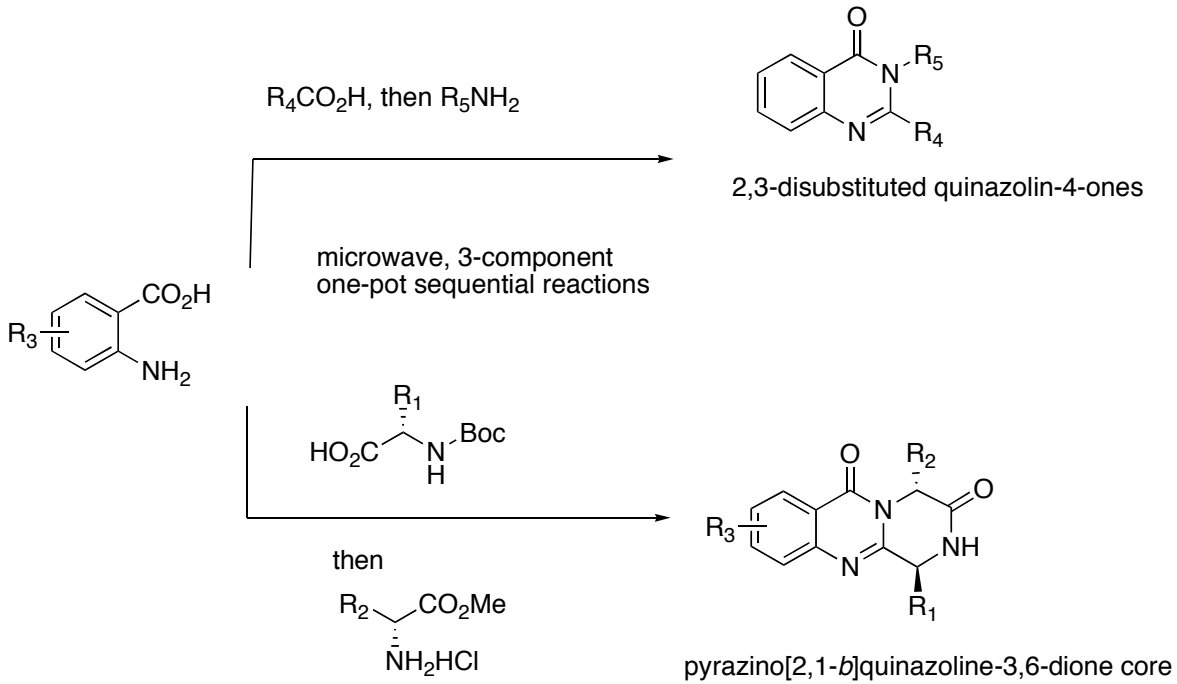
Okamoto *et al*, *Tetrahedron*, **1998**, 7997-8008.

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

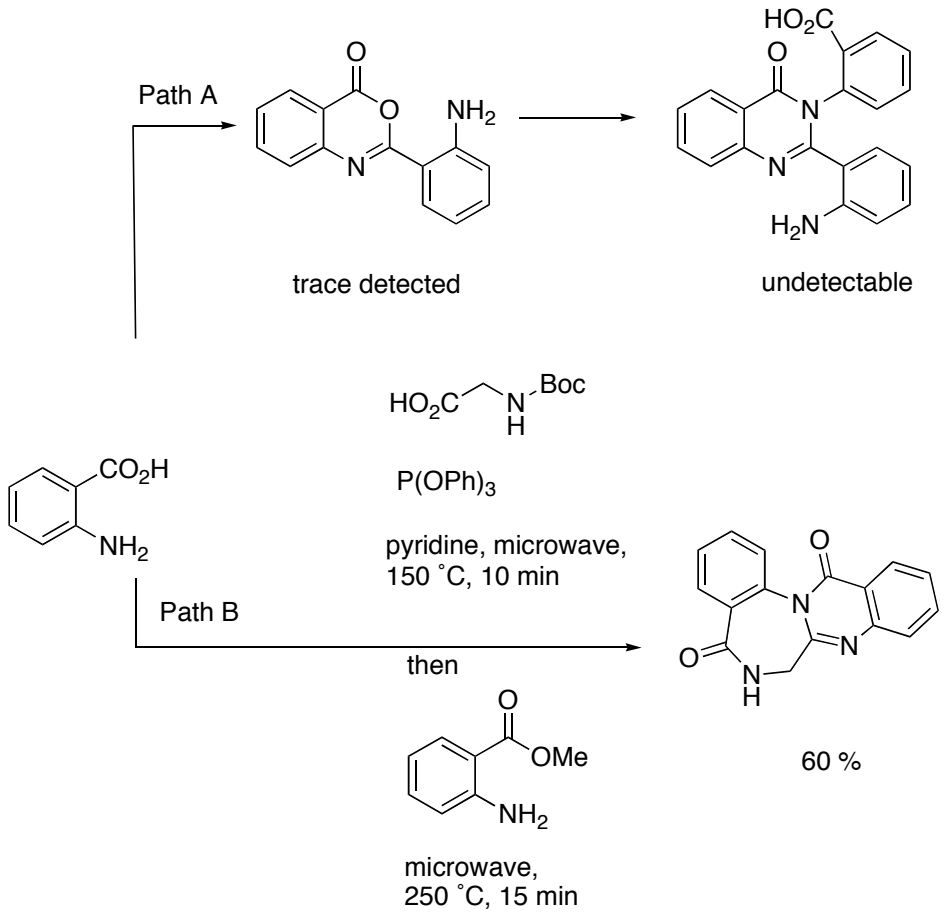
Liu *et al*

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

Sclerotigenin
(±) - Circumdatin F
(±)-Aspercilin C
(±)-Benzomalvin A
Circumdatin E analogues

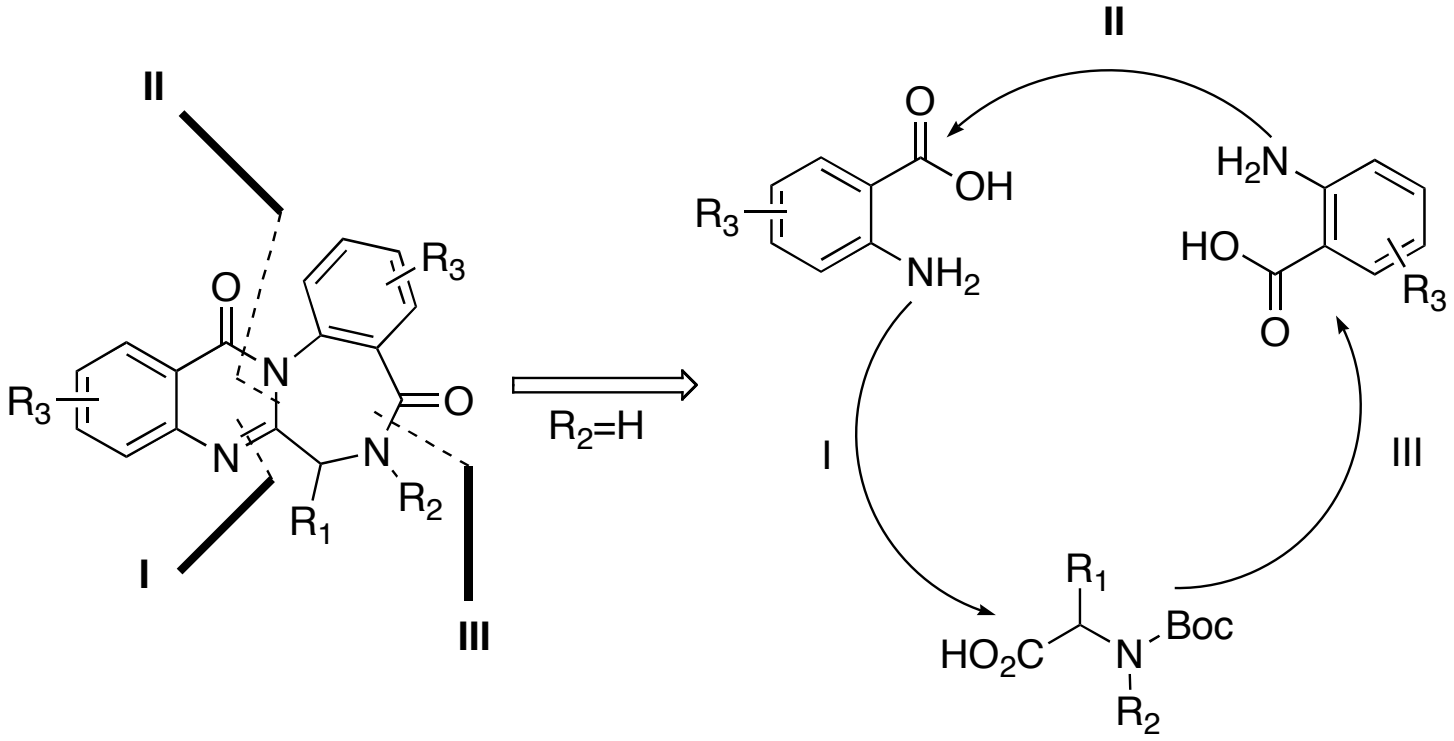
Using one reagent, one protecting group and readily available anthranilic acids and Boc-amino acids

Synthesis of Sclerotigenin



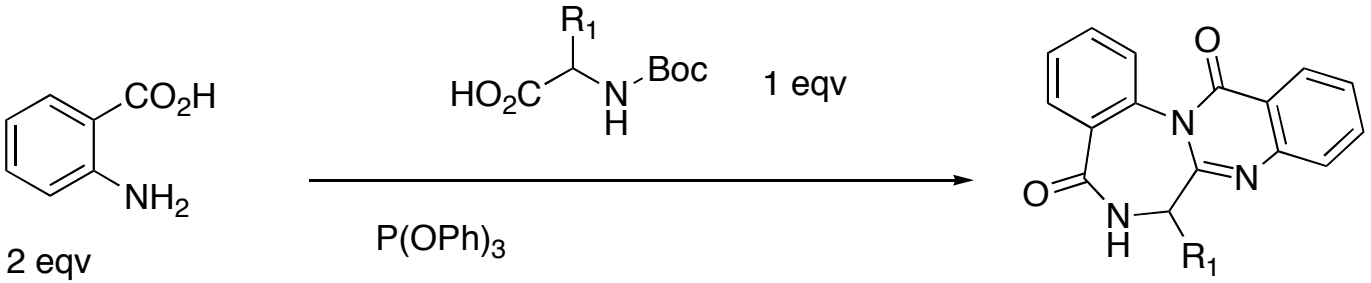
three-component one pot reaction

Retrosynthetic Strategy for the "Symmetric" Quinazolinobenzodiazepine Alkaloids via Domino Reactions



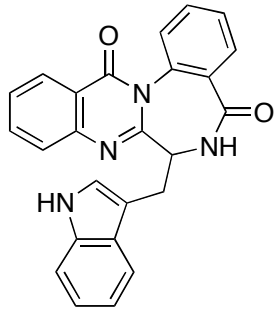
reaction sequence would be I, II then III to give products
not II, I then III to give by-products

One Step total Syntheses of Sclerotigenin (±) - Circumdatin F (±)-Aspercilin C and the precursor of (±)-Benzomalvin A



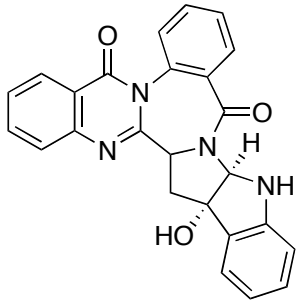
R_1= H, **Sclerotigenin**, 55%
R_1 = Me, **Circumdatin F**, 32%
R_1 = CH_2Indole, **Asperlicin C**, 20%
R_1 = Bn, **Benzomalvin A precursor**, 23%

Formal Total Synthesis of (±)-Aspercilin E



(*rac*)-Asperlicin C

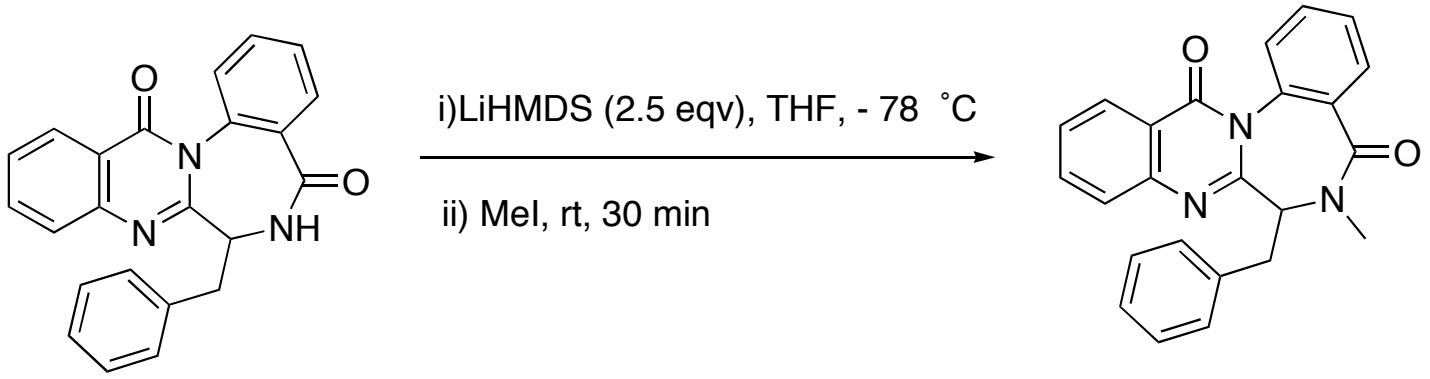
$^1O_2$, rose bengal, CH_3OH
pyridine (5%), 0 ˚C, 5h



(*rac*)-Asperlicin E 32%

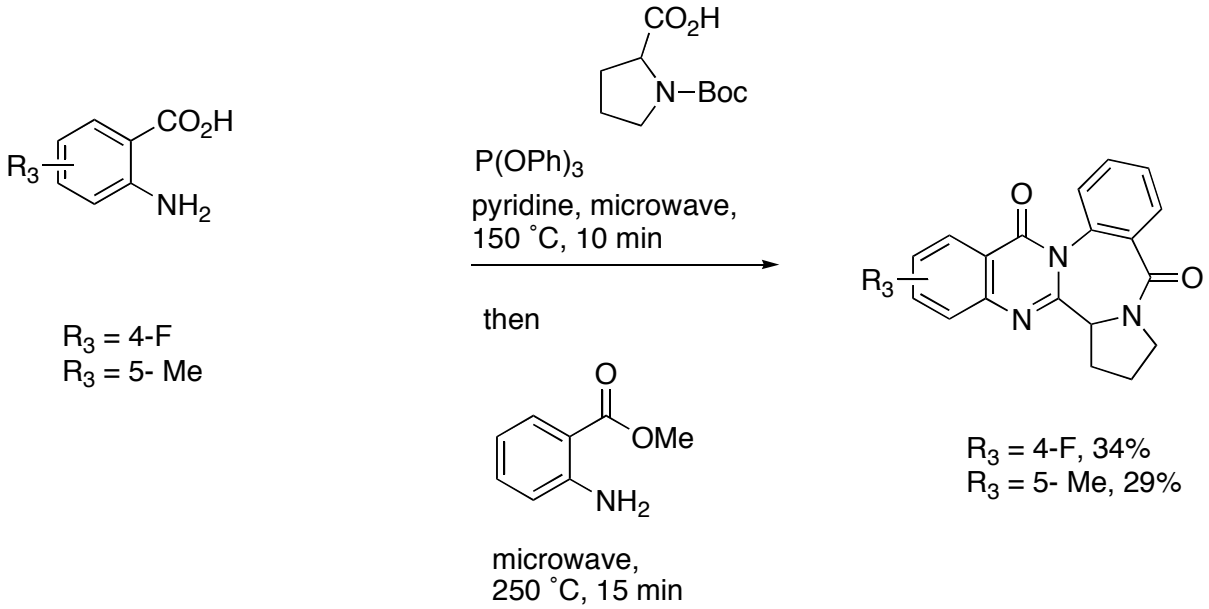
conditions- Bock *et al*, *J. Org. Chem.* **1987**, *52*, 1646-4647.

Synthesis of (±)-Benzomalvin A



(*rac*)-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 (±) - Circumdatin F (±)-Aspercilin C via novel domino reactions

- Two step total synthesis of (±)-Benzomalvin A and formal total synthesis of (±)-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