Microwave-Assisted Concise Total Syntheses of Quinazolinobenzodiazepine Alkaloids

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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.

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


Quinazolinobenzodiazepine Alkaloids

Sclerotigenin
anti-insectant
Snider 1998
Snider
Thomas 2003
Bergman

Circumdatin F

Asperlicin C
CCK antagonist
Snider
Bock

Benzomalvin A
Okamoto

All of these methodologies required multiple steps and gave low to moderate yields
Sniders’ Synthesis of Sclerotigenin

\[ \text{Eguchi-aza Wittig protocol} \]

(antiinsectant from organic extracts of sclerotia of Penicillium sclerotigenum)

Synthesis of (-) Asperlicin C


64% 2 steps


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

Circumdatin F (Bergman-2001)

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

Total Syntheses of Quinazolinobenzodiazepine Alkaloids

Liu et al

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

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

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

Path A

Path B

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

![Chemical structure diagram]

R₁ = H, Sclerotigenin, 55%
R₁ = Me, Circumdatin F, 32%
R₁ = CH₂Indole, Asperlicin C, 20%
R₁ = Bn, Benzomalvin A precursor, 23%
Formal Total Synthesis of (±)-Aspercilin E

\[
\begin{align*}
&\text{(rac)-Asperlicin C} \\
\rightarrow& \quad \text{\textsuperscript{1}O}_2, \text{rose bengal, CH}_3\text{OH} \\
&\quad \text{pyridine (5%), } 0\, ^\circ\text{C, 5h} \\
&\text{(rac)-Asperlicin E} \quad 32\%
\end{align*}
\]

Synthesis of (±)-Benzomalvin A

i) LiHMDS (2.5 eqv), THF, -78 °C

ii) MeI, rt, 30 min

(rac)-Benzomalvin A
Three-Component One -Pot Syntheses of analogues of Circumdatin E

R₃ = 4-F
R₃ = 5- Me

P(OPh)₃
pyridine, microwave, 150 °C, 10 min
then

R₃ = 4-F, 34%
R₃ = 5- Me, 29%

• 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