Molecular Complexity From Aromatics

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Molecular Hybrid

Platencin

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Genesis of the Story

*Capnella imbricate*

relieves neuropathic pain defence agent against microorganism

*Coriolus consors*

*Leontopodium alpinum*

modhephene

*Coriolin*

antibiotic properties
Towards Linearly Fused Polyquinananes

The Idea

Phase 1: Synthesis of I

Phase 2: Photochemistry

Phase 3: Cleavage of cyclopropane ring

Unknown
Phase I: Synthesis of Chromophoric System

Development of indirect route was necessary:

Aromatics \[\rightarrow\] Bicyclo[2.2.2]octane ring system

Periselectivity
Regio- and Stereoselectivity
Atom Economy
Efficient generation of Molecular Complexity

not formed

Singh & Thomas
Manipulation of the Oxirane Ring

Oxidation

- CO₂

NH₄Cl, MeOH, Δ

green pathway

MeOH

black arrows

6e, electrocyclic

reduction

MeOH, Zn

6e, electrocyclic

MeOH, Zn

6e, electrocyclic

MeOH, Zn

6e, electrocyclic

MeOH, Zn

6e, electrocyclic
Modulation of Reactivity

\[
\text{MeOH-H}_2\text{O}\quad \text{Zn, NH}_4\text{Cl} \quad \text{rt}
\]

\[
\text{dioxane, } \Delta
\]

\[
85\%
\]

\[
\text{Jones'}
\]

\[
\Delta
\]

Phase 1 completed
Phase 2. Exploratory Photochemical Reactions

1,3- and 1,2-Shift:
Singh & Porinchu

Decarbonylation:
Singh, Thomas & Sharma,
Phase 3: Cleavage of Cyclopropane Ring


An Alternate Route to Polyquinanes: Photoreaction and cleavage in tandem

\[ \text{Singh, Prathap & Porinchu} \\
\text{\textit{J. Org. Chem.} \textbf{1998}, \textit{83}, 4011-17.} \]

\[ \text{Singh & Samanta} \\
\text{\textit{Tetrahedron Lett.} \textbf{1999}, 383-6.} \]

\[ \text{Singh & Vedantham & Sahu} \\
\text{\textit{Tetrahedron Lett.} \textbf{2002}, 519-22.} \]

\[ \text{Singh & Sharma} \\
\text{\textit{J.C.S. Perkin 1} \textbf{1998}, 305-312.} \]

\[ \text{For a brief summary} \\
Molecular Diversity from Aromatics
Professor Goverdhan Mehta, FRS
National Research Professor

Mehta & Singh, *Hybrid Systems through Natural product Leads: An Approach Towards New Molecular Entities*

Towards Molecular Hybrids: A Philosophical Excursion

**Digoxin**

*Useful in the treatment of irregular heart rhythms, and heart failure that cannot be controlled by other medication.*

**Digitalis lanata**

**Steroid-polyquinane Hybrid**
TBTH, AIBN, $\Delta$

1. Zn, NH$_4$Cl, aq. MeOH
2. Jones', $\Delta$

Isolation: Wang & co-workers

Broad-spectrum antibacterial activity. Inhibitor of *Staphylococcus aureus* fatty acid biosynthesis (FabF) and (FabH)

Active against gram positive bacteria (including a variety of drug resistant bacteria)

**Platencin**

*(Streptomyces Platencis MA 7339)*


Banwell, *Org.Lett.* **2008**, *10*, 4465. (Australia)


Platencin

construction of bridged bicyclo[2.2.2]octane framework

annulation of the six membered ring through one of the bridgeheads

Stereochemical disposition of enone ring, ethano bridges and exocyclic alkene

Key Intermediate

Major challenges

NR₂

TBSO

MeSSCO

bicyclo[3.2.1]octane

bicyclo[2.2.2]octane

undesired

Platencin

All the 13 carbons of platencin core, its unique network and functionalities are latent in the aromatic precursor.

*Tricyclic ring having correct relative stereochemistry and functional group disposition* is created in the very beginning of the synthesis.
Oxidative dearomatization and cycloaddition

Synthesis:
only one step need fail to jeopardize the whole program!
An alternative to induce cycloaddition

140 °C
6 h

88 %

Retro $\pi^4s+\pi^2s-\pi^4s+\pi^2s$ cycloaddition cascade
Synthesis of the Platencin core

1. Zn, NH₄Cl, aq. MeOH
2. H₂, Pd-C
3. TsCl, Et₃N

80%

1. Pd(dba)₂, (Bu)₃P, Et₃N, HCOOH
2. H₃O⁺

TMSOTf

IBX

Synthesis of the Platencin core
A formal total synthesis of (±)-platencin

The concept and methodology thus presented manifests its novelty, adaptability & diversity in creating molecular complexity from simple aromatic precursors.

Singh, Sahu, Bansal & Mobin
Conclusion
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