Zoanthamine Alkaloids

\[ C_{30}H_{41}N_{0.5} \]

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08/03/04
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Isolation of Zoanthamine

- Isolated from *Zoanthus* sp. from the Visakhapatnam coast of India.

- Obtained 90mg from 10kg (wet weight), purified and crystallized from MeOH.

- Structure determined by X-ray.

Norzoanthamine and Zoanthenol

- Isolated from *Zoanthus* sp. from the Amami islands in Japan.

- Obtained 21 mg from 5 Kg of wet specimens, purified and crystallized from MeOH

- Absolute configuration determined by derivatization

- Isolated from *Zoanthus* sp. from Punta Hidalgo (Canary Islands).

- Obtained 2.4 mg from 0.5 Kg of wet specimens, purified and obtained as amorphous solid

- Structure determined by NMR analysis

Biological Activities of Zoanthamine Alkaloids

Chart 1.

- 2, 3, and 4 show anti tumor activity
- 5 - 8 inhibit the growth of murine leukemia cells
- 5 is a promising candidate for antiosteoporotic drug

Proposed Biosynthesis of Zoanthamine Alkaloids

-Zoanthamine alkaloids are considered as terpinoids based on molecular formula but, the biogenesis of these compounds are not clear

- Uemura suggests polyketide pathway which involves Diels-Alder and hemianinal formation

Ring Closing Hemiaminal Formation

1: (R = Me) Zoanthamine
2: (R = H) Norzoanthamine
3: 28-deoxyzoanthamine
4: CEF-ring portion

5: 47%
6: LDA, HMPA, 6; H$_2$SO$_4$, MeOH; then NaOH
7: 89%
8: ZnCl$_2$, Et$_2$O
9: 84% (dr 22/1)

- Ketalization/amination/dehydration can produce tetracyclic hemiaminal 4

Formation of Bishemiaminal for DEFG Ring Closure

Zoanthamine

\[ \text{Pd/C, H}_2 \rightarrow \text{No deprotection} \]
\[ \text{MeOH} \]

\[ \text{Pd/C, H}_2 \rightarrow \text{decomposition of deprotected intermediate} \]
\[ \text{AcOH} \]

\[ \text{2N HCL} \]
\[ \text{THF} \]

Formation of Bishemiaminal

- In presence of dehydrating reagent, second hemiaminal can be formed

Biomimetic Approach: Intramolecular Diels-Alder Reaction

- Tanner: construction of BC-ring by IMDA reaction

- Williams: construction of AB-ring by IMDA reaction

Model Study: ABC-ring System by IMDA

(S)-(-)-periillyl alcohol

11 steps

1: 11 steps → 1

THF, -78°C

2: 81%

MnO₂

CH₂Cl₂

3: 76%

toluene

4: quant. single diastereomer

Preparation of IMDA Precursor

- Also prepared:

IMDA Using Nitroalkene

Table 1. Diels–Alder Cyclizations of 4a–d

<table>
<thead>
<tr>
<th>entry</th>
<th>triene</th>
<th>conditions*</th>
<th>% yieldb</th>
<th>5 endo:6 exo</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>A, 89 h</td>
<td>63</td>
<td>73:27</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>A, 28 h</td>
<td>70</td>
<td>70:30</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>A, 36 h</td>
<td>72</td>
<td>61:39</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>A, 42 h</td>
<td>80</td>
<td>73:27</td>
</tr>
<tr>
<td>5</td>
<td>4b</td>
<td>B, 1.5 h</td>
<td>39</td>
<td>89:11</td>
</tr>
<tr>
<td>6</td>
<td>4d</td>
<td>B, 6 h</td>
<td>38</td>
<td>92:8</td>
</tr>
</tbody>
</table>

* Conditions: A, benzene, 85 °C; B, Et$_3$AlCl (2.0 equiv), CH$_2$Cl$_2$, −78 °C. b Purified yields. *Ratios determined from $^1$H NMR (400 MHz) data of crude mixtures.

Scheme 4. Diels–Alder Cyclization of (E,E)-Nitrotriene 17 and Completion of the Synthesis of Enone 2

![Chemical structures showing the reaction process](image)

Figure 1. $^1$H NMR studies of NOE interactions for Diels–Alder products 18 and 19.

Strategies Not Based on IMDA

- Diels-Alder/Cyclopropane Opening

Norzoanthamine  Zoanthenol

- Enolate alkylation

- Heck reaction (for Zoantheol ABC-ring)

Diastereoselective Synthesis of ABC-ring System

Norzoanthamine

Diastereoselective Synthesis of ABC-ring System

Cyclopropanation/Opening

Heck Coupling for Zoanthenol Core

Heck Coupling for Zoaanthanol Core

Total Synthesis of Norzoanthamine

Fig. 1. Molecular structures of norzoanthamine (1) and zoanthamine (2) and retrosynthesis of norzoanthamine (1).

Total Synthesis of Norzoanthamine

Total Synthesis of Norzoanthamine

1. DIBAL
2. Ph₃PCD₃Br, KHMDS
3. 9-BBN; H₂O₂

Total Synthesis of Norzoanthamine

Conclusion

-Zonanthamine Alkaloids possess interesting biological activities and complex structure

-Proposed biosynthesis of these alkaloids include cyclization of bishemiaminal moiety from a primary amine, two ketones and a carboxylic acid

-The IMDA reaction seems to provide the most efficient route to the ABC ring

-Various successful model studies have been documented, but the most challenging task is to establish the three quaternary stereogenic centers

-Miyashita group employed highly efficient and selective transformations for the total synthesis of norzoanthamine