Rising Stars Of Synthesis: The Post-doctoral work of Scott A. Snyder

J. Am. Chem. Soc. 2006, 128, 740

Tetrahedron Lett. 2006, 47, 2083

dolabellatrienone

β-araneosene

palominol
Scott A. Snyder

-B. S. Williams College, Summa Cum Laude

-Ph. D. The Scripps Research Institute, under K. C. Nicolaou

-Postdoc- Harvard University, under E. J. Corey

-Author on more than 30 papers, patents and books, including Classics II.

-As a Ph. D. describes more than six new bond constructions developed, along with two syntheses of Diazonamide A.

-Junior faculty at Columbia in Fall, 2006.
**The Dolabellane diterpenoids**

-Dolabellanes are produced principally by mollusks, coelenterates and brown algae.

- The biological activity of the dolabellanes includes cytotoxicity, antibacterial, antifungal, antiviral, antimalarial, molluscidal, ichthyotoxic, and phytotoxicity.

-The first dolabellane isolated was β-aranesone (1975).

-Now, more than 140 compounds have been isolated with this structure.

-They are characterized by the [9.3.0] nucleus, which is on the biosynthetic pathway to the fusicoccanes, dolastanes, and neodolabellanes.

![Chemical structures and reactions involving dolabellanes](image-url)
# Biological Activity of the Dolabellanes

Table 1. Biological Properties of Naturally Occurring Dolabellane Diterpenes.

<table>
<thead>
<tr>
<th>Struct. No.</th>
<th>Source</th>
<th>Collection Site</th>
<th>Biological Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>15,16</td>
<td><em>Aplysia dactylomela</em></td>
<td>Canary Islands</td>
<td>antimicrobial activity (Gram-positive and Gram-negative bacteria)*</td>
<td>6,7</td>
</tr>
<tr>
<td>22,23</td>
<td><em>Clavularia viridis</em></td>
<td>Japan</td>
<td>cytotoxic (P388 leukemia cells) and ichthyotoxic activity</td>
<td>16-18</td>
</tr>
<tr>
<td>24</td>
<td><em>Clavularia viridis</em></td>
<td>Japan</td>
<td>inhibits cell division in fertilized sea urchin eggs</td>
<td>18</td>
</tr>
<tr>
<td>25</td>
<td><em>Clavularia viridis</em></td>
<td>Xisha Islands, China</td>
<td>inhibits K+ induced contractions of blood aortic strips</td>
<td>20</td>
</tr>
<tr>
<td>27-29</td>
<td><em>Clavularia viridis</em></td>
<td>Xisha Islands, China</td>
<td>Ca^{2+} channel blocker in isolated smooth rabbit muscles</td>
<td>21</td>
</tr>
<tr>
<td>28</td>
<td><em>Clavularia viridis</em></td>
<td>Xisha Islands, China</td>
<td>50% negative inotropic activity and 43.7% bradycardia activity, decreases blood pressure of rats</td>
<td>21</td>
</tr>
<tr>
<td>27-29,33</td>
<td><em>Clavularia viridis</em></td>
<td>Xisha Islands, China</td>
<td>cytotoxic (Ehrlich ascites carcinoma cells)</td>
<td>21</td>
</tr>
<tr>
<td>36,37,42</td>
<td><em>Eunicea laciniata</em></td>
<td>Puerto Rico</td>
<td>weakly cytotoxic (HCT 116 cells)</td>
<td>28-30</td>
</tr>
<tr>
<td>37</td>
<td><em>Eunicea laciniata</em></td>
<td>Puerto Rico</td>
<td>antimicrobial activity (Gram-negative bacteria)</td>
<td>28-30</td>
</tr>
<tr>
<td>43-46</td>
<td><em>Eunicea laciniata</em></td>
<td>Puerto Rico</td>
<td>weakly cytotoxic (HeLa cells)</td>
<td>28-30</td>
</tr>
<tr>
<td>52</td>
<td><em>Dictyota dichotoma</em></td>
<td>Sicily, Italy</td>
<td>cytotoxic and in vivo antiviral activity (influenza and adenoviruses)</td>
<td>35</td>
</tr>
<tr>
<td>52-55</td>
<td><em>Dictyota dichotoma</em></td>
<td>Sicily, Italy</td>
<td>antimicrobial activity (Gram-positive and Gram-negative bacteria)</td>
<td>35</td>
</tr>
<tr>
<td>57</td>
<td><em>Dictyota dichotoma</em></td>
<td>Sicily, Italy</td>
<td>cytotoxic (KB cells)</td>
<td>36</td>
</tr>
<tr>
<td>58,62,63</td>
<td><em>Dictyota sp.</em></td>
<td>Sicily, Italy</td>
<td>antimicrobial activity</td>
<td>38</td>
</tr>
<tr>
<td>83-86</td>
<td><em>Dictyota dichotoma</em></td>
<td>Cádiz, Spain</td>
<td>cytotoxic (P-388 mouse lymphoma, A-549 human lung carcinoma, HT-29 human colon carcinoma, MEL-28 human melanoma cells)</td>
<td>45</td>
</tr>
<tr>
<td>88</td>
<td><em>Dictyota pardalis</em></td>
<td>Australia</td>
<td>weak but specific antimalarial activity</td>
<td>49</td>
</tr>
<tr>
<td>106-108</td>
<td><em>Diophus fasciola</em></td>
<td>Yugoslavia</td>
<td>ichthyotoxic, phytotoxic</td>
<td>55</td>
</tr>
<tr>
<td>112-114</td>
<td><em>Odontoschisma demudatum</em></td>
<td>Japan</td>
<td>growth-inhibitory activity on a series of plant pathogenic fungi</td>
<td>60</td>
</tr>
<tr>
<td>123-140</td>
<td><em>Chrozephora obliqua</em></td>
<td>Egypt</td>
<td>hypoglycemic activity*</td>
<td>64,65</td>
</tr>
</tbody>
</table>

* The biological activity described is actually that of the crude extract and not of the purified isolates.
Preparation of dolabellanes

\[
\text{SnBu}_3 \text{OTBDPS} \xrightarrow{\text{Pd}_2\text{dba}, \text{LiCl}} \text{Pd}_2\text{dba}, \text{LiCl} \xrightarrow{\text{DIPEA}, \text{NMP}} 96\%
\]

92% over two steps

1) HIO\textsubscript{4}, NaIO\textsubscript{4}
2) KO'Bu, (EtO)\textsubscript{2}PO

\[
\text{CH}_3 \text{OAc} \xrightarrow{\text{TBAF, AcOH}} \text{CH}_3 \text{K}_\text{O} \text{tBu}, \text{P}_\text{O}(\text{EtO})_2
\]

78% three steps

73%, 90% ee

toluene

-93 °C to -78 °C

\[
\text{H}_3\text{C} \text{OTBDPS} \xrightarrow{1) \text{TBAF, AcOH}} \text{H}_3\text{C} \text{K}_\text{O} \text{tBu}, \text{P}_\text{O}(\text{EtO})_2
\]

73%, 90% ee

toluene

-93 °C to -78 °C

\[
\text{Me}_2\text{Al}-\text{SS}-\text{SAlMe}_2
\]

65% over two steps

1) Me\textsubscript{2}Al
2) Raney Ni, THF
Preparation of dolabellanes (cont.)

1) NHM DS, TMSCl; IBX-MPO
2) Trisyl-azide, 18-C-6
BnEt₃NCl, KOH

62% over two steps

hv, MeOH then DBU, 115 °C

68%

MeLi

1) L-selectride
2) LDA, O₂
3) LAH; NaIO₄

91%

51% over three steps

13 - 15 steps
Overall yield: ~10%

PDC

dolabellatrienone

palominol

β-araneosene
Generality of Dithiolane Formation

- Reagent introduced in 1973 by Corey for protection of lactones and lactams.
- Relatively general reaction for ketones and aldehydes.
- Non-tethered sulfides undergo transesterification to generate thioesters from esters.

\[
\text{HS} \underset{\text{AlMe}_3}{\rightleftharpoons} \text{Me}_2\text{AlS} \text{SH} \rightleftharpoons \text{S} \text{S} \text{AlMe}_2
\]

Table 1. \(\text{Me}_2\text{AlSCH}_2\text{CH}_2\text{SAlMe}_2\)-Induced Dithiane Formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="#" alt="Structural formula 1" /></td>
<td><img src="#" alt="Structural formula 2" /></td>
<td>83</td>
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<tr>
<td>2</td>
<td><img src="#" alt="Structural formula 3" /></td>
<td><img src="#" alt="Structural formula 4" /></td>
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<tr>
<td>3</td>
<td><img src="#" alt="Structural formula 5" /></td>
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<td><img src="#" alt="Structural formula 7" /></td>
<td><img src="#" alt="Structural formula 8" /></td>
<td>72</td>
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<tr>
<td>5</td>
<td><img src="#" alt="Structural formula 9" /></td>
<td><img src="#" alt="Structural formula 10" /></td>
<td>68</td>
</tr>
</tbody>
</table>

\(^a\) With 3 equiv of sulfide reagent at 60 °C in 1,2-dichloroethane for 2–12 h.
Diels-Alder Cycloaddition Under Oxazaborolidinium Catalysis

CH₃
CH₃
O
OTIPS
H
H₃C
CH₃
H OTIPS
N
B O
Ph
H
H
Ph
H₃C
-93 °C to -78 °C
73%, 90% ee
toluene
O
NTf₂
(20 mol%)
Ring Contraction via Wolff Rearrangement
IBX-Mediated Dehydrogenation of Silyl Enol Ethers

- The preparation of some interesting diterpenoids.
- Development of some new methodology including a Wolff-based ring contraction.
- A little of an interesting career sure to be with us during ours.

![Chemical structures]

- dolabellatrienone
- β-araneosene
- palominol