Synthetic (±)-Axinellamines Deficient in Halogen


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Current Literature
March 31, 2012
Isolation and biological activity

- Axinellamines A-D were isolated from the Australian marine sponge, *Axinella sp* (pictured right).

\[\text{(-)-axinellamine A (OH, H = } \beta)\]
\[\text{(-)-axinellamine B (OH, H = } \alpha)\]

*J. Org. Chem. 1999, 64, 731-735*

- Axinellamine A was not bactericidal at 1000 µM.

- Axinellamine B-D exhibited MIC for bactericidal action against *H. pylori* (a gram negative bacterium associated with pepticular and gastric cancer) at 1000 µM.
Biosynthesis

1: clathrodin (X, Y = H)
2: hymenidin (X = H, Y = Br)
3: oroidin (X, Y = Br)

(-)-Sceptrin

pre-axinellamine

Biosynthesis

\(-\)-axinellamine A (OH, H = \(\beta\))
\(-\)-axinellamine B (OH, H = \(\alpha\))

64, 731-735

\(-\)-massadine (X = OH)
\(-\)-massadine chloride (X = Cl)

\textit{Org. Lett.} \textbf{2003}, 5,
2255-2257

\(-\)-palau'amine

115, 3376-3377 (12,17-epi-13)
Synthetic efforts towards pyrrole-imidazole alkaloids

• Synthesis of 1,9-Dideoxy-pre-axinellamine
  

• Total syntheses of (±)-massadine and massadine chloride
  

• Total synthesis of (-)-palau’amine
  

• The Baran Group’s full paper detailing their efforts towards (-)-palau’amine, (-)-axinellamines, and massadines.
  

• A review on the biosynthesis, assymetric synthesis, and pharmacology of pyrrole-2-aminoimidazole alkaloids.
  
The Baran Group’s synthesis of (±)-axinellamines

Title paper: Two new ring systems


\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{Br} \\
& \quad 1) \text{MeOH, LiOH, 89 \%} \\
& \quad \text{HN} \quad \text{CON} \\
& \quad \text{NH}_2 \\
& \quad 2) (\text{COCl}_2) \\
& \quad \text{N} \quad \text{O} \\
& \quad \text{SMe} \\
& \quad 3) \text{ClCH}_2\text{OCH}_2\text{CH}_2\text{Si(CH}_3)_3 \\
& \quad 60\% \\
\end{align*}
\]
Title paper: Oxidative enolate coupling

Note: [(CF₃CH₂O)V(O)Cl₂] "Livinghouse reagent" only other oxidant tried that provided comparable yield and regioselectivity to Cu(OTf)₂


Exploring Symmetry-Based Logic for a synthesis of Palau’amine

Monomer forms targeted alkylidene

Title paper: unexpected spiroaminal formation


Note: Major isomer (shown) was treated with TFA and the corresponding salt was recrystallized. Relative stereochemistry was based on corresponding X-ray.
Title paper: Isomerization to monoalkylidene-containing spirocycles


$\text{TBD} = \begin{array}{c} \text{HN} \\ \text{O} \\ \text{N} \\ \text{H} \\ \text{Br} \\ \text{Br} \\ \text{N} \\ \text{NH} \\ \text{O} \\ \text{N} \\ \text{O} \\ \text{H} \\ \text{Br} \\ \text{Br} \\ \text{HN} \\ \text{NH} \\ \text{O} \end{array}$

1) TBD, THF

2) $\text{NH}_4\text{OH}$, 120 $^\circ\text{C}$, 90 min

1,2-dimethoxyethane/H$_2$O (4:1); TFA; Et$_3$N, MeOH

43% over 2 steps
Title paper: Deoxygenation and isomerization


26% of other isomer
Title paper: Oxidation and reduction

SmI$_2$ preparation

- Water, oxygen, and peroxide content in THF have little influence on the synthesis of SmI$_2$.
- Most problems associated with SmI$_2$ preparation are due to “inactive” samarium metal.
- “Inactive” samarium metal can be activated by dry stirring under argon (similar to activating magnesium).
- Solutions of SmI$_2$ can be stored, however the solution should be stirred for 1 hr prior to use.

Szostak, M.; Spain, M.; Procter, D. J. J. Org. Chem. 2012, ASAP
Final thoughts

• The synthesis of 2.0 mg of nonchlorinated (±)-Axinellamines was achieved in 13 steps in 0.016 % yield.

• Interesting formation of spiroaminals and their base-mediated isomerization into monoalkylidene spriocycles.

• The Haran Group mentions that there interest lie in synthesizing several halogenated analogs through this method and determine there impact on biological activity.

• Essential to achieving their above goal is the refinement of spiroaminal formation and isomerization.