Literature Presentation

Total Synthesis of (+)-Perophoramidine & Determination of the Absolute Configuration


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Perophoramide was first isolated from colonial ascidian *Perophora namei* by Chris M. Ireland et al. in 2002.

Perophoramide is the first reported metabolite from the genus *Perophora*.

It exhibits cytotoxicity toward the HCT116 colon carcinoma cell line and induces apoptosis via PARP (poly ADP ribose polymerase) cleavage within 24h.
Previous work on the synthesis of Perophoramidine:

-- First completed synthesis (racemic)

-- Dehaloperophoramidine (racemic)

-- Substructure was synthesized (racemic)
How did they develop this synthesis route?

During the synthesis of communesin:

14, $R_1 = \text{Br}$, $R_2 = \text{CO}_2\text{Me}$
$R_3 = \text{N}_3$, $R^* = \text{H}$

Hetero-Diels-Alder
Synthesis starts:

18

\[
\text{allylMgBr, Et}_2\text{O, 25 °C, 2h} \quad 85 - 88\%
\]

19

\[
\text{TBSOTf, 2,6-lutidine, DCM, 25 °C, 20h} \quad 95-97\%
\]

20

\[
\text{O}_3/\text{Me}_2\text{S, -78°C - 25 °C, DCM, 30h} \quad 76-84\%
\]

20'

\[
\text{(Boc)}_2\text{O, NaOH, DCM, 25 °C, 2h} \quad 87 - 93\%
\]

20

\[
\text{TBSO}^+\text{NHR}^* \quad \text{a. R}^*\text{NH}_2, \text{KHSO}_4, \text{toluene, 50°C, 2h}
\]

19'

\[
\text{b. NaBH}_4, \text{MeOH, 0 °C} \quad 81 - 85\% \text{ over 2 steps}
\]

21

\[
\text{TBAF, THF, 25°C, 1h} \quad 89 - 90\%
\]

\[
\text{SOCl}_2, \text{pyridine} \quad \text{DCM, 0°C, 15min}
\]

22

\[
\text{R}^*\text{NHBOc, DCM, 0°C, 15min}
\]

23

\[
\text{?}
\]
4.5 equiv of AgClO₄
toluene, -78 °C, 17-43h

27a R = Br, R* = (S)-^BuSO  11 : 1
28a R = Br, R* = (S)-PhCHMe  1 : 2
29a R = H, R* = (S)-^BuSO  6.2 : 1
30a R = H, R* = (S)-PhCHMe  1 : 1.7

27b R = Br, R* = (S)-^BuSO  88% yield
28b R = Br, R* = (S)-PhCHMe  81% yield
29b R = H, R* = (S)-^BuSO  69% yield
30b R = H, R* = (S)-PhCHMe  69% yield
The image shows a chemical reaction scheme. The first reaction involves reaction with MeNH₂/MeOH at 25°C for 2 hours, followed by CHCl₃ reflux for 10 hours, with a yield of 77%. The second reaction involves treatment with MnO₂ in DCM at 25°C for 3 hours, yielding 76%. The third reaction involves treatment with PPTs in CHCl₃, refluxing for 2 hours, with a quantitative yield.
Determination of the absolute stereochemistry:

29a $R^* = (S)$-t-BuSO
30a $R^* = (S)$-PhCHMe
31 $R^* = (S)$-t-BuSO
32 $R^* = (S)$-PhCHMe

a. TMSOTf, 2,6-lutidine, DCM, 0 °C, 2h, 82 - 85%
b. MeNH$_2$/MeOH, 25 °C, 12h
c. (Boc)$_2$O, Na$_2$CO$_3$, DCM, 25 °C, 2h, 78% - 80%(b+c)
d. Li/NH$_3$, THF, -78 °C, 30min, 83%
e. NaOH, DCM, 25 °C, 12h, 81%
Summary:

The first asymmetric total synthesis of (+)-perophoramidine has been achieved in 17 steps with ~11% overall yield.

Key step: chiral-auxiliary-induced hetero-Diels-Alder reaction to generate the core structure.

Absolute stereochemistry was determined by X-ray analysis and comparison of the rotation of synthetic (+)-perophoramidine with that of the natural product.
Thanks!
\[
\text{NH}_2
\]
\[
\text{Py.}
\]
reflux, 20h
82%

1. NaH, DMF, 0°C,
2. CH\textsubscript{3}I dropwise
2h, 0°C
89%