Total Synthesis of (+)-Muironolide A

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Current literature
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Phorbas amaranthus
Muironolide A was isolated by Molinski and co-workers from the Western Australian sponge *Phorbas* in 1993.

Structure of muironolide A from minor HPLC fraction (90 μg) was determined by NMR in the same group in 2008.

Antifungal activity against *Cryptococcus neoformans*.

Cytotoxic activity against some colon tumor cell.

**Introduction**
Retrosynthetic Analysis of (+)-Muironolide A

Blocks 11, 23, ent-23, 24

Blocks 13 and 18

exo-IMDA

lactone formation
any order

Block 3

[Ln]
Synthesis of Building Block 11, 23, 24

1. TFA
2. TESCl, Imidazol

65%

Cl

Cl

O

OSiEt₃

23

95%

Cl

Cl

i-Pr₂NEt

Cl

Cl

O

CO₂H

11

[Ru(cymene)Cl]₂, t-BuOMe,
(R,R)-TsDPEN, HCO₂H, Et₃N

Cl

Cl

OH

CO₂¹Bu

96%

H

H

H

H

75%

Cl

Cl

OH

CO₂¹Bu

90%

1. TFA
2. TESCl, Imidazol

Cl

OSiEt₃

24
Synthesis of Building Block 3a and 3b

1. O₃, CH₂Cl₂, Me₂S
2. Me₃SiCl/MeCl, HCO₂Na
3. HCl (1N), MeOH → 79%

1. DMSO, (CF₃CO)₂O, i-Pr₂NET, 2. [Ru(cymene)Cl]₂, t-BuOMe, (R,R)-TsDPEN, HCO₂H, Et₃N → 78%
dr 10:1

1. BOMCl, i-Pr₂NET, n-Bu₄NI
2. CH₂=C(Me)CHO, HG II → 62%
E:Z 10:1

O

BOM

CCl₃

1. CH₂=CHCO₂Me, HG II → 89%
E:Z >20:1

64%
E:Z >20:1

3a

3b

V

Cl

O

O

3a

3b

PMBHN

Cl

H

O

O

O

H

HG II

HG II

O

O
Attempt of Synthesis (+)-Muironolide A via Blocks 3b, 13 and 16
Synthesis of Building Block 22 via Blocks 3a and 18
Completion of the Total Synthesis

1. LiCl, DMF microwave, 170 °C
2. Py, DMAP
3. DDQ, H₂O/Dioxane

C21-epi-muironolide A (original assignment)

C22,C23-epi-muironolide A

(+) -muironolide A (revised structure)
Differences in the $^{13}$C NMR Chemical Shift between I, II, III and Natural Muironolide A

![Graphs showing chemical shifts for carbon atoms labeled as 1 to 27.]

**I**
- C21-epi-muironolide A (original assignment)
- $\delta$($^{13}$C) values

**II**
- C22-C23-epi-muironolide A
- $\delta$($^{13}$C) values

**III**
- (1)-muironolide A (revised structure)
- $\delta$($^{13}$C) values

Carbon atom numbering for each structure is shown.
Conclusions

- First total synthesis of (+)-Muironolide A
- Delivered 25 mg of the compound paves the way for systematic evaluation of biological activity
- Reassignment of the absolute configuration of the natural product
- Key-steps of the synthesis:
  - macrolactone formation by Yamaguchi reagent
  - *exo*-selective lanthanide-catalyzed IMDA
  - thermolysis of dioxinone phosphonate with protected amine
  - ruthenium-catalyzed reduction
Thank you for your attention!
Asymmetric Transfer Hydrogenation by Chiral Ruthenium(II) Complex and HCOOH/Et$_3$N

Scheme 7  Catalytic cycle of catalyst 1 via a concerted six-membered transition state.

J. Vaclavik, P. Sot, P. Vilhanova, J. Pechacek, M. Kuzma and P. Kacer Molecules 2013, 18, 6804-6828
Thermolysis of dioxinone phosphonate with nucleophiles

Intramolecular Diels-Alder reaction