Total Synthesis and Stereochemical Reassignment of Mandelalide A

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Contents

- Introduction
- Total synthesis by Xu’s group
- Total synthesis by Fürstner’s group
- Summary
Introduction
Total synthesis by Xu’s group

Mandelalide A (1)

Glycosylation

Suzuki coupling

HWE olefination

3

2
Total synthesis by Xu's group

Prins cyclization

Rychnovsky-Bartlett cyclization
Total synthesis by Xu’s group

9

a) NaH, 2,6-dichlorobenzyl bromide, Bu₄NI, THF, 94%
b) 9-BBN; then NaOH, H₂O₂, reflux, 96%

10

c) DMP, NaHCO₃, CH₂Cl₂, 98%
d) LiCl, trimethyl phosphonoacetate DIPEA, CH₃CN, 95%
e) DIBAL-H, THF, 98%

Horner-Wadsworth-Emmons olefination

11

f) I₂, CH₃CN, 94%

12

g) K₂CO₃, MeOH, 84%
h) Cul, vinylmagnesium bromide, THF, 95%

13

i) TBSOTf, 2,6-lutidine, CH₂Cl₂, 98%
j) DDQ, CH₂Cl₂, 89%

14

j) DDQ, CH₂Cl₂, 89%
Horner-Wadsworth-Emmons olefination

**Erythro, kinetic adduct**

**Threo, thermodynamic adduct**

*erythro (kinetic) or threo (thermodynamic)*

95%
Total synthesis by Xu’s group

HO

k) DMP, NaHCO₃, CH₂Cl₂, 96%

l) [ICH₂PPh₃]I, NaHMDS, HMPA, THF, 82 %

Witting-Stok-Zhao olefination

m) AD-mix-α, tBuOH/H₂O, 82%

16:17 = 2:1

n) TBSCI, imidazole, DMAP, CH₂Cl₂, 96%

o) dimethylphosphonoacetic acid, 2,4,6-trichlorobenzoyl chloride, Et₃N; then DMAP, toluene, 92%

5

14

15

16

17
Sharpless dihydroxylation

(DHQD)$_2$-PHAL = 1,4-bis(9-O-dihydroquinidine)phthalazine

(DHQ)$_2$-PHAL = 1,4-bis(9-O-dihydroquinine)phthalazine
Prins cyclization of aldehyde 6 and homoallylic alcohol 7
Total synthesis by Xu’s group

\[ \text{HO} \quad \text{O} \quad \text{OBn} \quad 18 \quad \text{a) Pd/C, H}_2, \text{MeOH, 97%} \quad 19 \quad \text{b) NaH, PMBBr, Bu}_4\text{N}, \text{THF, 98%} \]

\[ \text{HO} \quad \text{O} \quad \text{BPin} \quad 21 \quad \text{c) TBAF, THF, 97%} \quad \text{d) DMP, NaHCO}_3, \text{CH}_2\text{Cl}_2, 98\% \quad \text{e) 20, K}_2\text{CO}_3, \text{MeOH}/\text{THF, 94%} \]

\[ \text{HO} \quad \text{O} \quad \text{OPMB} \quad 20 \quad \text{f) pinacolborane, dicyclohexylborane, THF} \quad \text{g) DDQ, CH}_2\text{Cl}_2/\text{buffer (pH 7), 68%} \]
Total synthesis by Xu’s group

\[ \text{22} \overset{\text{a) trimethyl orthoformate, CSA, MeOH}}{\longrightarrow} \text{23} \]
\[ \text{22} \overset{\text{b) NaH, MeI, DMF}}{\longrightarrow} \text{23} \]
\[ \text{23} \overset{\text{c) TFA, CH}_2\text{Cl}_2/\text{H}_2\text{O}}{\longrightarrow} \text{24} \]
\[ \text{23} \overset{\text{d) TBSOTf, 2,6-lutidine, CH}_2\text{Cl}_2}}{\longrightarrow} \text{24} \]
\[ \text{3} \overset{\text{e) m-CPBA, CH}_2\text{Cl}_2}}{\longrightarrow} \text{24} \]
Total synthesis by Xu’s group

\[ \text{BPin} \quad 4 \quad + \quad \text{ OTBS} \quad 5 \quad \rightarrow \quad \text{OTBS} \quad 25 \]

\[ \text{OTBS} \quad 26 \quad \rightarrow \quad \text{OTBS} \quad 2 \]

\( a) \text{Pd(PPh}_3\text{)}_4, \text{Ag}_2\text{O, THF/H}_2\text{O, 88\%} \)

\( b) \text{TEMPO, Ph(OAc)}_2, \text{CH}_2\text{Cl}_2 \quad 44\% \)

\( c) \text{LiCl, DIPEA, CH}_3\text{CN} \)

\( d) \text{3, M.S. (4 \text{ Å), DTBMP, TFO, 86\%}} \)
Total synthesis by Xu’s group

\[ \text{TBSO} \]

\[ \text{TBSO} \]

\[ \text{OMe} \]

\[ \text{OTBS} \]

\[ \text{26} \]

e) TBAF, DMF/THF, (1: 43% yield; 27: 9% yield)

\[ \text{Mandelalide A (1)} \]

(Proposed Structure)

\[ \text{27} \]
Total synthesis by Fürstner’s group

Total synthesis by Fürstner's group

\[ \text{HO} \quad \text{OH} \]

a) \([\text{Ir(cod)Cl}_2] (5 \text{ mol\%}), 11 (10 \text{ mol\%}), 3\text{-nitro-4-chlorobenzoic acid (20 mol\%)} \]
\[ \text{Cs}_2\text{CO}_3, 1,4\text{-dioxane, 71\%} \]

b) \(\text{I}_2, \text{NaHCO}_3, \text{MeCN, 81\%}\)

c) \(\text{TBSOTf, 2,6-lutidine, CH}_2\text{Cl}_2, 96\%\)

(d.r. > 29:1, 99\% ee)

\[ \text{OH} \quad \text{OH} \]

(d.r. = 5:1)

\[ \text{OAc} \]

\[ \text{OTBS} \]

\[ \text{OTBS} \]

2

3

4

11

12

5

6

7

d) \(\text{LDA, LiCl, THF, 76\%}\)

e) \(\text{LDA, BH}_3\text{•NH}_3, \text{THF, 96\%}\)

f) methyl acrylate, 12 (3 mol\%), \(\text{CH}_2\text{Cl}_2, 83\%\)

g) Dess-Martin periodinate, \(\text{CH}_2\text{Cl}_2, 77\%\)

(d.r. = 97:3)
Total synthesis by Fürstner’s group

- **7**
  - h) CH₃, CrCl₂, THF, 72% (Takai olefination)

- **8**
  - i) propynyl sodium, B(O Me)₃, THF, [Pd(dppe)Cl₂]CH₂Cl₂ (10 mol%), 81%

- **13**
  - k) 13, LiHMDS, THF, 41-54% (E/Z = 7:1)

- **9** R = Me
  - j) Me₃SiOK, Et₂O, 80%

- **10** R = H

**O**

**CO₂Me**

**O**

**CO₂Me**

**OTBS**

**OTBS**
Total synthesis by Fürstner’s group

a) TBDPSCI, imidazole, CH₂Cl₂, 94%
b) [Co₂(CO)₈] (8 mol%), CO (1 atm), N-(trimethylsilyl)morpholine, EtOAc, 74%
c) 16, THF, then pour into aq. HCl, 83%
d) [Cu(MeCN)₄]BF₄ (5 mol%), N-Methylimidazole (10 mol%), 2,2'-bipyridine (5 mol%), TEMPO (5 mol%), CH₂CN, air, 94%
e) (R,R)-27, Sc(OTf)₃ (5 mol%), CH₂Cl₂, 82%
f) TESCl, Et₃N, DMAP, CH₂Cl₂, 90%
g) 17, 28 (8 mol%), CH₂Cl₂, 79%

(d.r. = 98:2 94% ee)
Total synthesis by Fürstner’s group

BnO<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH=CH<sub>2</sub>, 87%,
BnO<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH=CH<sub>2</sub>, 87%,
BnO<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH=CH<sub>2</sub>, 87%,
BnO<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH=CH<sub>2</sub>, 87%,
Evans-Tishchenko reaction

\[
\begin{align*}
\text{BnO} & \quad \text{TESO} \\
\text{OH} & \quad \text{OTBDPS} \\
\text{H} & \quad \text{iPr}
\end{align*}
\]

\[
\begin{align*}
\text{SmI}_2 \\
\text{iPrCHO} & \quad \text{TBDPSO} \\
\text{TESO} & \quad \text{OBn}
\end{align*}
\]

\[
\begin{align*}
\text{OBn} & \quad \text{TESO} \\
\text{OH} & \quad \text{OTBDPS} \\
\text{H} & \quad \text{iPr}
\end{align*}
\]
Total synthesis by Fürstner’s group

a) Allyl alcohol, H₂SO₄ (cat.), 78%
b) butane-2,3-dione, MeC(OMe)₃, pTsOH·H₂O, MeOH, 72%
c) NaH, Mel, DMF, 64%
d) i) trifluoroacetic acid/H₂O (20:1)
   ii) Ac₂O, DMAP, Et₃N, CH₂Cl₂, 68%
e) SeO₂, HOAc, 1,4-dioxane, 86%
f) Cl₃CCN, Cs₂CO₃, CH₂Cl₂, 98%
Total synthesis by Fürstner’s group

10 + 26 → 34

a) DCC, DMAP, CH₂Cl₂, 64% (α,β,γ) isomers = 1:5:1
b) DBU (25 mol%), MeCN, 91%

c) 35 (10 mol%), M.S., toluene, 72%

d) Zn(Cu/Ag), THF/MeOH:H₂O (1:1:1), 88%
e) pTsOH·H₂O (cat.), CH₂Cl₂:MeOH (2:1) 90%

36 → 37
Total synthesis by Fürstner’s group

Chemical structures and reactions:

- Reaction (f): 33, TESOTf (30 mol%), CH₂Cl₂, M.S. (4 Å), 88%
- Reaction (g): K₂CO₃, MeOH, 80%
- Reaction (h): HF·pyridine, pyridine, THF, 80%
Summary

Xu’s group
1. Convergent approach
2. 20 steps.

Fürstner’ group
1. Catalysis-based total synthesis.
2. 21 steps, 4.5% overall yield.
Mandelalide A (1) is an extraordinary glycosylated macrolide that was recently isolated from a new species of Lissoclinum ascidian, collected from Algoa Bay, South Africa. Intriguing structural features of mandelalide A include a 24-membered α,β-unsaturated macrolactone, which entails a conjugated diene, a trisubstituted tetrahydrofuran (THF) moiety, and a trisubstituted tetrahydropyran (THP) fragment appended with an unusual carbohydrate unit. Furthermore, a total of nine stereogenic centers are present in the carbon backbone of mandelalide A. Mandelalide A exhibited potent cytotoxicity to human NCI-H460 lung cancer cells (IC\textsubscript{50}: 12 nM) and mouse Neuro-2A neuroblastoma cells (IC\textsubscript{50}: 29 nM). We have been engaged in a program devoted to the total synthesis of biologically active marine natural products. Herein, we disclose the total synthesis of mandelalide A and the resulting reassignment of the stereochemical configuration of the natural product.
In summary, we have achieved the total synthesis of the proposed structure of mandelalide A. The convergent approach features a highly diastereoselective Prins cyclization for the construction of the tetrahydropyran subunit and Rychnovsky–Bartlett cyclization for the preparation of the tetrahydrofuran moiety. Suzuki coupling, Horner–Wadsworth–Emmons macrocyclization, and glycosylation also served as key reactions for the total synthesis. The application of this strategy to the synthesis of mandelalide B is in progress, and the results will be reported in due course.