Enantiospecific Total Synthesis of $N$-Methylwelwitindolinone D Isonitrile

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Contents

1. Introduction of the Corresponding Author
2. Introduction of Welwitindolinones
3. Total Synthesis of Welwitindolinone D by Garg Group
4. Total Synthesis of Welwitindolinone D by Rawl Group
5. Summary
1. Introduction of the Corresponding Author

B.S., New York University (2000, Marc Walters)

Ph.D., California Institute of Technology (2005, Brian Stoltz)

NIH postdoctoral scholar (2005-2007, Larry Overman)

Joined the faculty at UCLA (2007)

Research: total synthesis of natural products, transition-metal catalyzed cross-coupling

Neil K. Garg
2. Introduction of Representative Welwitindolinones

1. D was isolated from *Fischerella muscicola* and *Fischerella major*;
2. Biological activities: antifungal effects, microtubule depolymerization.
Figure 2. Structural Analysis of Welwitindolinone D Isonitrile

1. Oxindole-fused bicyclo[4.3.1] framework;
2. Five stereocenters, two quaternary carbons;
3. A heavily substituted cyclohexyl ring;
4. An ether linkage between C3 and C14.
3. Total Synthesis of Welwitindolinone D by Garg Group

Scheme 1. Retrosynthetic Analysis of 1

1. N-methylwelwitindolinone D isonitrile (1)

2. Late Stage Introduction of Tetrahydrofuran Ring

3. 2

4. 4

5. 5

6. 6
Scheme 2. Total Synthesis of 1

6 \[\overset{\text{K}_2\text{CO}_3, \text{MeOH}}{\longrightarrow} \overset{\text{I}_2, \text{MeOH}}{\text{54\% yield, 2 steps}}\]

7 \[\overset{\text{TBSCI, imidazole, DMAP, Bu}_4\text{NI, DMF}}{\longrightarrow} \overset{\text{90\% yield}}{\text{8}}\]

9 \[\overset{\text{NaNH}_2 (10.5 \text{ equiv.}) \text{, } t-\text{BuOH (3.5 equiv.)}}{\longrightarrow} \overset{\text{46\% yield}}{\frac{6}{12} = 2.5:1}\]

5 \[\overset{\text{OTBS}}{\text{8}}\]

10 \[\overset{\text{Me}}{\text{Br}}\]

11 \[\overset{\text{Me}}{\text{OTBS}}\]
Scheme 3. Elaboration of 5 to Keto Oxindole 3

1. NBS, CH$_2$Cl$_2$; NaHCO$_3$
2. HCl, EtOH, 80 $^\circ$C

83% yield, 2 steps

TBSCl, imidazole, DMAP, Bu$_4$NI, DMF

92% yield

1. LiAlD$_4$, THF, -78 to 0 $^\circ$C
2. Cl$_3$CC(O)NCO, K$_2$CO$_3$, MeOH

quantitative yield, 2 steps

AgOTf, Phl(OAc)$_2$, bathophenanthroline

70% yield
Scheme 4. Unexpected Formation of Cyclobutane 17

3 → CuBr₂, THF → 71% yield → 15

15 → NaH, air, THF → 97% yield → 17

(X-ray)
Table 1: Conversion of 15 to Acetate 18 and Cyclized Product 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Conversion to products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>18 (%)</td>
</tr>
<tr>
<td>1</td>
<td>Mn(OAc)$_3$ (4.0 eq.), AcOH, 80 °C</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>Mn(OAc)$_3$ (4.0 eq.), AcOH, 150 °C</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Mn(OAc)$_3$ (4.0 eq.), AcOH, 150 °C; K$_2$CO$_3$, MeOH, H$_2$O, 70 °C</td>
<td>0</td>
</tr>
</tbody>
</table>
Scheme 5. Double C–H Functionalization of Substrate 3 to Install the Tetrahydrofuran Ring

\[ \text{Bu}_3\text{NF, air, CH}_3\text{CN} \quad 71\% \text{ yield} \]
Scheme 6. Completion of (+)-1

1. LiAlH₄, THF  
   92% yield

2. Ba(OH)₂, H₂O, IBX, TFA, DMSO  
   66% yield, 2 steps

3. HCO₂H, Ac₂O  
   THF, 0 °C to rt  
   77% yield, 2 steps

4. Burgess reagent, THF, Benzene  
   77% yield, 2 steps

(+)-1
4. Total Synthesis of Welwitindolinone D by Rawal Group

Scheme 1. Retrosynthetic Analysis of 1

Scheme 2. Synthesis of Cyclization Precursor 4

1. CuBr•Me2S, $\text{MgBr}$; Then HCO2CH2CF3
2. Me2SO4, K2CO3, DMF
50% yield, 2 steps 5:8 = 15:1

MeMgBr, 0 °C, THF
quantitative yield

KHMD, TMSCI

6. TMSOTf, THF; Then HClO4 (aq.)
78% yield, 2 steps
Scheme 3. Synthesis of Pentacycle 13

Scheme Description:

1. **Reaction 1**: 
   - Starting material: 4
   - Reagents: Pd(OAc)$_2$ (30 mmol%), $P$Bu$_3$ (30 mmol%), KHMDS
   - Conditions: 80 °C, toluene
   - Product: 3
   - Yield: 73%

2. **Reaction 2**:
   - Product: 3
   - Reagents: HF, DCM, DMP, DCM
   - Step 1: 1HF, DCM
   - Step 2: DMP, DCM
   - Yield: 91% over 2 steps

3. **Reaction 3**:
   - Product: 3
   - Reagents: KHMDS, NBS, THF
   - Yield: 91%

4. **Reaction 4**:
   - Product: 12
   - Reagents: DMDO, acetone, NaHCO$_3$
   - Yield: 41%

5. **Conversion**:
   - Product: 12
   - Reagents: DMDO
   - Product: 13

Note: The scheme illustrates the synthesis of Pentacycle 13 through a series of reactions involving ring closures and functional group transformations.
Scheme 4. Synthesis of N-Methylwelwitindolinone D Isonitrile (1)

13 \rightarrow \text{NH}_2\text{OH.HCl} \quad \text{Py, MeOH} \quad 94\% \text{ yield} \quad \rightarrow \text{14}

\text{NCS, DMF; then 15, NEt}_3, \text{THF} \quad 65\% \text{ yield} \quad \rightarrow \text{16} \rightarrow \text{17, toluene, 110}^\circ \text{C} \quad 54\% \text{ yield} \quad \rightarrow \text{17:} \quad \begin{array}{c}
\text{HN} \\
\text{NH}
\end{array}

\begin{array}{c}
\text{MeN} \\
\text{Ph}
\end{array}

15: \begin{array}{c}
\text{HN} \\
\text{NH}
\end{array}

\begin{array}{c}
\text{MeN} \\
\text{Ph}
\end{array}

\text{16} \rightarrow \text{17:} \quad \begin{array}{c}
\text{HN} \\
\text{NH}
\end{array}

\begin{array}{c}
\text{MeN} \\
\text{Ph}
\end{array}
5. Summary

Rawal group in 2011:
1. first total synthesis;
2. 14 steps, 4.8% overall yield.

Garg group in 2013:
1. enantiospecific total synthesis;
2. 17 steps, 2.8% overall yield.
The welwitindolinone family of natural products has attracted tremendous attention from the synthetic community over the past two decades. Interest in these compounds stems from their promising biological profiles, in addition to their compact, yet daunting structures. Synthetic efforts toward the welwitindolinones have led to at least ten methods for building the bicyclo[4.3.1] core that is common to most of these natural products. However, the sheer difficulty associated with late-stage manipulations has plagued most synthetic routes and only a few completed syntheses have been reported in recent years.
In summary, we have completed the enantiospecific total synthesis of N-methylwelwitindolinone D isonitrile. Several unexpected hurdles, including the formation of the unusual cyclobutane-containing compound 17 were overcome en route to the natural product. Our total synthesis features a double C-H functionalization of keto oxindole 3 to introduce the tetrahydrofuran ring of 1 and is achieved in 17 steps from readily available carvone derivative 6.
谢谢大家，请多批评指正！
**Burgess Reagent** 由氯磺酰异氰酸酯与甲醇和三乙胺在苯中反应制取：

![Burgess Reagent Reaction Diagram]

**Burgess Reagent 脱水机理**：

![Burgess Reagent Dehydration Diagram]
Mechanism of Ioximes to Isothiocyanates

\[
\begin{align*}
R &= C\equiv NOH & \xrightarrow{NCS} & [R\xrightarrow{\text{Cl}} C\equiv NOH] & \xrightarrow{\text{Et}_3N} & [R\xrightarrow{\ominus} C\equiv NO]\nn & \xrightarrow{H_2N} \xrightarrow{\text{NH}_2} \xrightarrow{\text{O}} & R\xrightarrow{\ominus} N\equiv C\equiv S & + & H_2N \xrightarrow{\text{NH}_2} \\
\end{align*}
\]

Mechanism for Desulfurization of the Isothiocyanate