Total Synthesis of (S)-Cularine via Nucleophilic Substitution on a Catechol

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• Found in plants of the *Dicentra* and *Corydalis* families (poppies).
• Parent compound for the cularine group of isoquinoline alkaloids.
  • Biosynthesized from crassifoline by oxidative cyclization.
• Challenging due to 1,7,8-trisubstituted tetrahydroisoquinoline core and catechol moiety:
• This work: concise enantioselective total synthesis of (S)-cularine through a mild, formal S_N Ar on an electron-rich catechol.
Retrosynthetic Analysis:

1. (S)-cularine
2. crassifoline
3. 

- Cu-catalyzed cyclization
- Pomeranz-Fritsch cyclization
- Diastereoselective Grignard addition

Commercially available compounds:

4. 
5. 
6. 
7.

- HO
- MeO
- OMe
- OMe
- OBn
- OMe
- OBn
TBS Protection:

\[ \text{R-O-H} + \text{TBS-Cl} \rightarrow \text{TBS-O-R} \]

Titanium-Mediated Condensation:

\[ \text{EtO-Ti(OEt)_3} + \text{O}_2\text{S}^{-}\text{Bu} \rightarrow \text{O}_2\text{S}^{-}\text{Bu} \]

Diastereoselective Grignard Addition:

\[ \text{O}_2\text{S}^{-}\text{Bu} \text{ClMg} \rightarrow \text{HN-S}^{-}\text{Bu} \]
Pomeranz-Fritsch Cyclization:
**IBX Oxidation:**

1. Phenol (14) undergoes oxidation with IBX (1.2 equiv.) to form 15.
2. 15 is then treated with Na$_2$S$_2$O$_4$ (aq) in DMF at RT for 3 hr, yielding 82% yield.
3. 15 is further oxidized with NaIO$_4$ (1.2 equiv.) in a 2:1 CH$_2$Cl$_2$:H$_2$O mixture at RT for 1 hr to form 16.

**Sodium Periodate Oxidation:**

1. Phenol (14) undergoes oxidation with NaIO$_4$ (1.2 equiv.) to form a peri-ketone intermediate.
2. The peri-ketone is then treated with Na$_2$S$_2$O$_4$ (aq) to form a peri-hydroxy intermediate.
3. The peri-hydroxy intermediate undergoes tautomerization to form the target product.
Cu-Catalyzed Aerobic Coupling:

TBAF Deprotection/Cyclization:
Lithium Naphthalenide Deprotection:

Amine Methylation:

(S)-cularine 1
14 steps LLS
15% overall yield