An Enantioselective Total Synthesis of (+)-Duocarmycin SA

Bristol-Myers Squibb Company

• Duocarmycins are a subset of potent antitumor antibiotics isolated from Streptomyces bacteria in the 1980s.
• Contains a 1,1a,2,3-tetrahydro-5H-cyclopropanindol-5-one that is responsible for cytotoxicity.
• (+)-Duocarmycin SA is both the most potent and most stable of these compounds.
• Synthesis conducted over 17 steps with a 24.4% total yield, and is “flexible to allow analogous study but also concise and efficient to facilitate material throughput”
Retrosynthetic Analysis

Enantioselective Indole Reduction

Late-Stage Amidation

Enantioselective Indole 2,3-bond Reduction

VNS-Cyclization
**Reaction Scheme**

1. **Step 1:**
   - Reaction: TsCl, Et₃N
   - Products: S2

2. **Step 2:**
   - Reaction: LiBH₄; TBSCl, imidazole
   - Products: 3

3. **Step 3:**
   - Reaction: Cl⁻ → N⁺H⁻
   - Products: S2

4. **Step 4:**
   - Reaction: H₂O
   - Products: S3

5. **Step 5:**
   - Reaction: OH⁻ → TBS⁻
   - Products: 3

**Overall Yield:** 86% (four steps)
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84% (2 steps)
$\text{MeO}_2\text{C} \quad \text{N} \quad \text{SO}_2\text{Ph} \quad \text{OTBS}$

$\text{Cs}_2\text{CO}_3, \text{DMSO}$

$\text{MeO}_2\text{C} \quad \text{HN} \quad \text{OTBS}$

$73\%$ (three steps)