Endiandric Acids A-D (and E-G)

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Natural Source

• Comes from *Endiandra introrsa*, a rare rainforest tree in Australia.
• First isolated in the early 1980’s by D. St. C. Black’s group.
• Found in nature as racemates, despite having 8 stereocenters.
• Endiandric acid C has been reported to have better antibiotic activity than the other acids A-G

Bandaranayake, *JSCC*, 1980, 902
Endiandric Acids A-D

endiandric acid A
endiandric acid B
endiandric acid C
endiandric acid D
endiandric acid D
endiandric acid E
endiandric acid F
endiandric acid G

a: conrotatory $\pi$ electron electrocyclization
b: disrotatory $6 \pi$ electron electrocyclization

Bandaranayake, JCS CC, 1980, 902
Conrotatory vs Disrotatory

Conrotatory has C2 symmetry about the pi bonds
Disrotatory has a plane of symmetry about the pi bonds
Retrosynthesis
Retrosynthesis
Synthesis of Common Intermediates

1. 

2. CuCl, NH₄Cl, O₂ (90%) Glaser acetylene coupling

3. H₂, Lindlar catalyst, quinoline, DCM/MeOH 25 ºC (55%)

4. Iodoetherification -20 to 0 ºC (100%)

5. 2. NaCN, HMPA 25 ºC (93% overall)

6. 2. Zn, AcOH 25 ºC (80% overall)

7. t-BuPh₂SiCl, imid. DMF, 25 ºC

8. 1. PPh₃, CBr₄ DCM, 0 ºC

9. Dibal-H DCM, -78 ºC (95%)

10. OSit-BuPh₂
Appel Reaction

1. $\text{PPh}_3, \text{CBr}_4$
   DCM, $0^\circ\text{C}$
2. $\text{NaCN}, \text{HMPA}$
   $25^\circ\text{C}$
(93% overall)
Endiandric acid A,B

1. LDA, THF, -78 °C, 25 °C (75%)
2. PhCH₂, 110 °C (100%)
3. NaCN, HMPA, 25 °C (95% overall)

KOH, H₂O₂, 95% (95%)
Endiandric acid C

1. Dibal-H, DCM, -78 °C
2. (EtO)2P(O)CH2CHCHPh
   LDA, THF, -78 -> 25 °C
(71%)

11 steps, 14% yield
Endiandric acid D
What About Black’s Hypothesis?

• Nature doesn’t have access to all the fancy tools synthetic chemists do.
• Black’s hypothesis was a polyene cyclization cascade could form all of these, if the appropriate polyene could be found
Biomimetic Retrosynthesis
Making the Coupling Partners
Coupling
“One Step” Biomemetic Synthesis

1. H₂, Lindlar’s, quinoline
   DCM, 25 °C
2. PhCH₃, 100 °C

endiandric ester A (30% after heating)
endiandric ester B (28% yield after heating, B:C/4.5:1)
endiandric ester C
endiandric ester D (12% before heating)
endiandric ester E (10% before heating)
endiandric ester F (15% before heating)
endiandric ester G (12% before heating)
Lessons Learned

• Experimental support for Black’s hypothesis regarding natural origin of products
• Demonstrates the power of polyene cyclization in organic synthesis. Especially considering the amount of stereocenters created in one reaction, coded into the geometry of the double bonds.
• Trivia: Why should we all know the name K.C. Nicolaou?