Lectures 7 + 8: Indoles

Tuesday, April 12th and Wednesday April 13th, 2011

Background music: Johann Sebastian Bach

Syntheses discussed:

- pyrano[3,4-b]indoles
  Wyeth, J. Med. Chem. 2004, 47, 6603
- melatonin
  Reddy, OPRD 1999, 3, 155
- carbocyclic[g]indoles
- Maxalt (rizatryptan)
  Merck
- LY311727
- MK-677
  Merck, Tetrahedron 1997, 53, 10983

Selected named indole syntheses:

- Lescol (fluvastatin)
  Novartis, OPRD 2001, 5, 519
- MDL-103371
  Aventis, OPRD 2000, 4, 477
- indolomorphinan
- Amerge (naratriptan)
  GSK, AstraZeneca
- LY311727
- intermediate en route to glycogen synthase inhibitor
  Lilly, J. Med. Chem. 2004, 47, 3934

Problems of the day:

1. Br + 1. THF/H2O
   2. ZnCl2, heat
   Product and mechanism

2. Br
   1. HCl
   2. NaOH
   identify all 3 products formed

3. O
   5N NaOH
   NaNO2
   HCl

4. Br
   1. PhNH2/Pr
   2. ZnCl2

Reading assignment: Li chapter 3; HC chapter 17; Richter indole/pyrrole handout

Partial list of concepts/transforms discussed:

- Fischer
- Japp-Klingemann
- Bischler
- Batcho–Leimgruber
- Hemetsberger
- Reissert
- Nenitzescu
- Madelung
- Heck
- Sundberg
5. Provide at least three distinct routes to the following indole:

6. How would you prepare $^{14}$C labeled Amerge?

7. Provide routes to the following fluorinated indole isomers using the indicated sm:

8. Propose a synthesis of MK-677

9. Provide (multiple) routes to the following indoles: