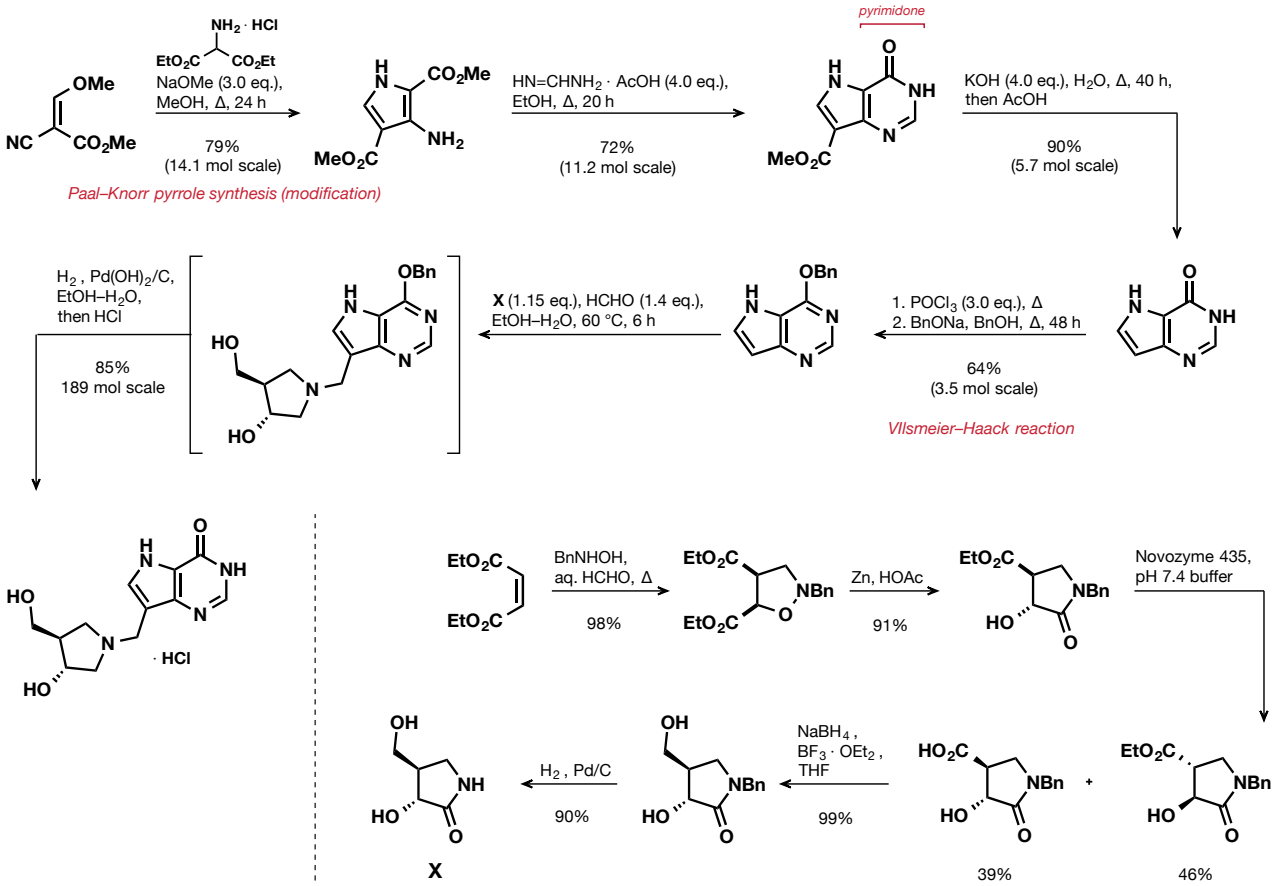
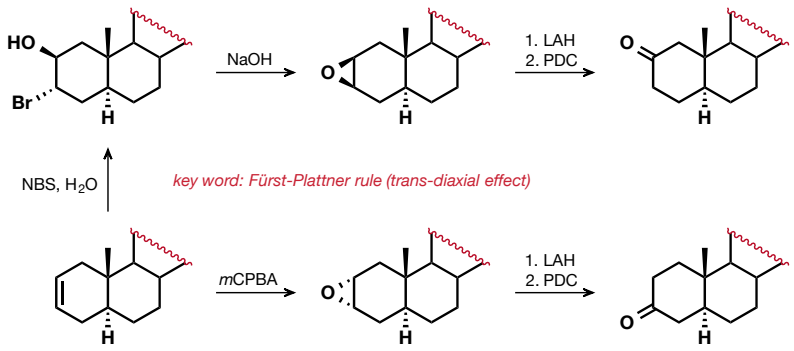
Problem Set Seminar — April 2014

1. Synthesis of Inhibitor BCX-4208 *(BioCryst Pharmaceuticals)*

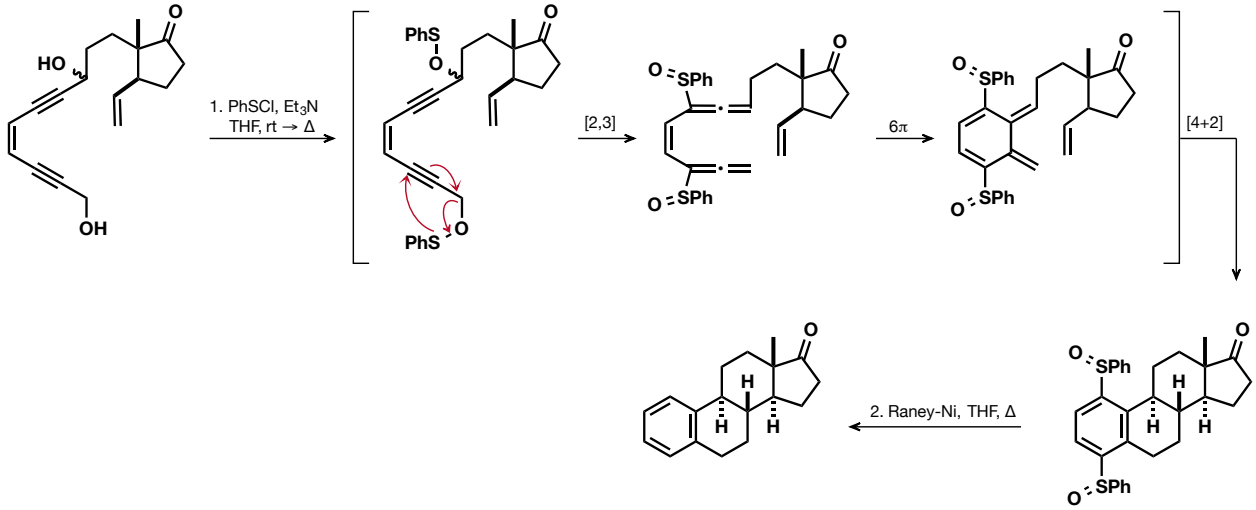
Org. Process Res. Dev. **2009**, *13*, 928–932.



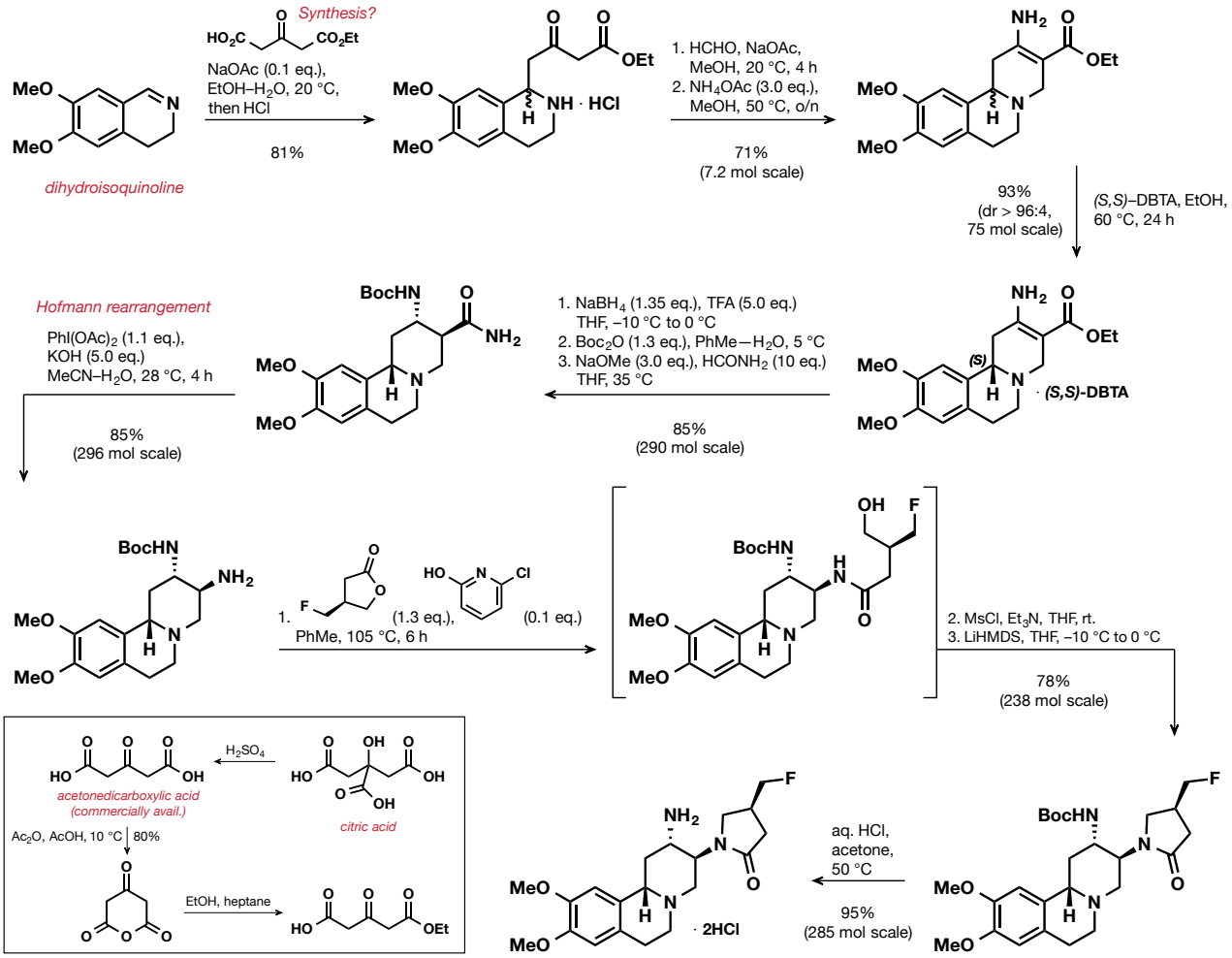
2. Propose conditions for the following transformations.



3. Propose a mechanism for the following transformation.



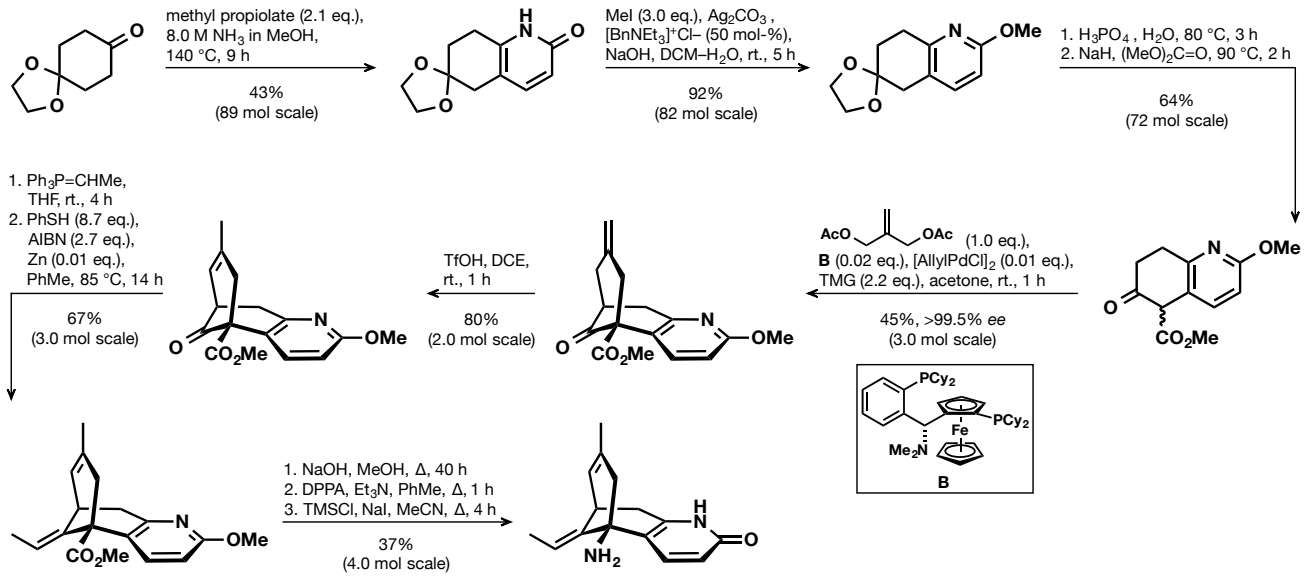
4. Synthesis of Carmegliptin *(F. Hoffmann–La Roche LTD.)*



Example for an experimental:
A suspension of amide **28** (120 kg, 296 mol) in a mixture of H_2O (1000 kg) and MeCN (522 kg) was treated within 30 min at 15–28 °C with 50% aq KOH (166.0 kg, 1479 mol, 5 equiv) and the resulting suspension stirred at 24–28 °C for 30 min. To the suspension was added within 34 h at 24–28 °C a solution of iodosobenzene diacetate (106 kg, 329 mol, 1.10 equiv) in a mixture of H_2O (270 kg) and MeCN (448 kg). After the addition, the suspension was stirred at 24–28 °C for 1 h. Upon complete conversion (<0.1% by area (HPLC) of starting material), the suspension was concentrated under reduced pressure and at a maximum internal temperature of 45 °C (70 °C jacket temperature) to a residual volume of approximately 1200 L. The pH of the mixture was adjusted to pH 9.5 by treatment with 37% aq HCl (33.8 kg) at 20–40 °C. THF (210 kg) and PhMe (1040 kg) were added at 20–40 °C, and the resulting mixture was heated to 70–75 °C and stirred at this temperature for 30–60 min. The agitator was stopped, and the biphasic mixture was allowed to separate for 30 min. The lower aqueous layer was discharged and the organic layer washed with H_2O (180 kg) at 70–75 °C. From the organic layer, THF and H_2O were removed by azeotropic distillation with PhMe at a maximum internal temperature of 70 °C. At the end of the distillation the THF content should be <0.5%, and the volume of the mixture was adjusted to 1700–1800 L. The mixture was heated to 70–80 °C to obtain a dimmish solution. To remove the urea byproduct, the solution was filtered at 70–80 °C. The first reactor, the filter, and the transfer lines were rinsed with hot PhMe (400 kg). The filtrate was concentrated at a maximum internal temperature of 80 °C under reduced pressure to a residual volume of 1000–1100 L, whereby the product partly precipitated. The suspension was heated to 90 °C to obtain a clear solution. The solution was cooled to 8 °C within 7 h and subsequently stirred at this temperature for 2 h. The crystals were filtered off using a centrifuge, washed in two portions with cooled PhMe (<0 °C; 300 L), and dried at 60 C/<30 mbar for 7 h to afford 94.6 kg (85%) of amine **10** as slightly yellow crystals with an assay (HPLC) of 99.8% (w/w) with <0.10% of the corresponding enantiomer (by chiral HPLC).

5. Synthesis of (–)-Huperzine A *(Shasun Pharma Solutions, UK)*

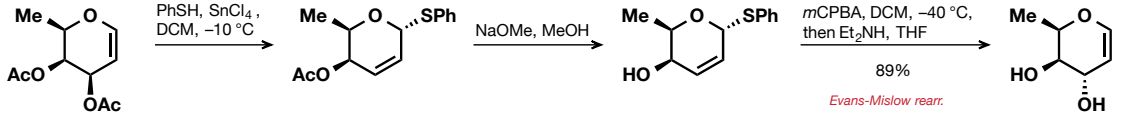
Org. Process Res. Dev. **2012**, *16*, 635–642.



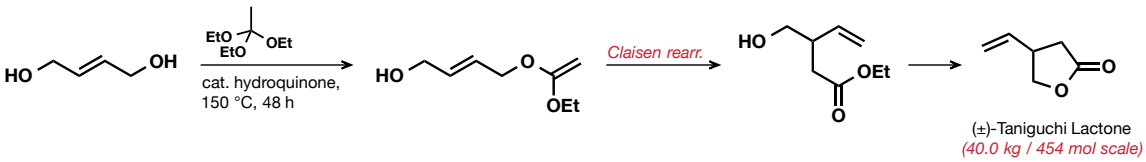
(–)-Huperzine A

275 g per batch,
99.9 % purity, >99.5% *ee*

6. Propose plausible conditions for the following transformation (3 steps in the synthesis of D. Gin). D. Gin, *Angew. Chem. Int. Ed.* **2001**, *40*, 1128.



7. Synthesis of (±)-Taniguchi Lactone *Org. Process Res. Dev.* **2014**, asap.



8. Synthesis of MK-7655 *(Merck)*