



**Trip Report:
229th ACS Meeting
San Diego Convention Center
San Diego, California
March 13 – 17, 2005**

Jerod Robertson, Ph.D.

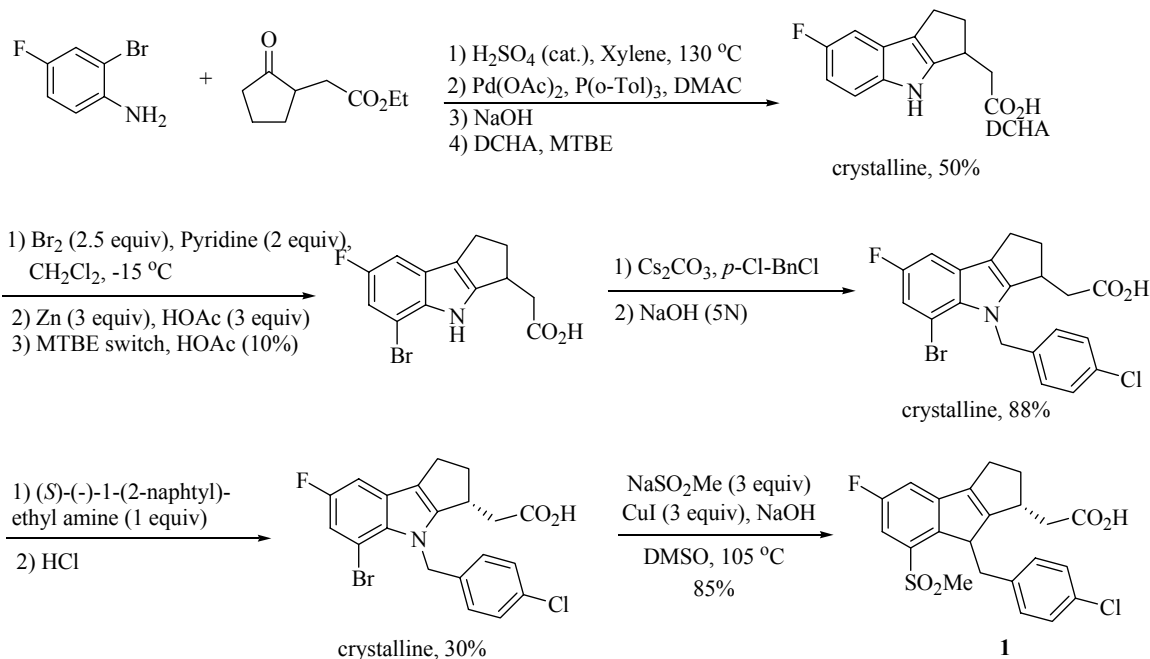
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“Development of a Practical Asymmetric Synthesis of a DP Receptor Antagonist”

Zhihui Peng, Process Research, Merck & Co., Inc., NJ, USA.

Dr. Peng presented work on the process work carried out at Merck on the development of a DP receptor antagonist **1**. The first generation process involved an inefficient classical resolution (see Scheme 1). The linear synthesis involved six steps and the overall yield was 10%. Although the process avoided chromatographic purification, the late stage, low yielding resolution, as well as undesired zinc and copper waste, made the process inefficient.

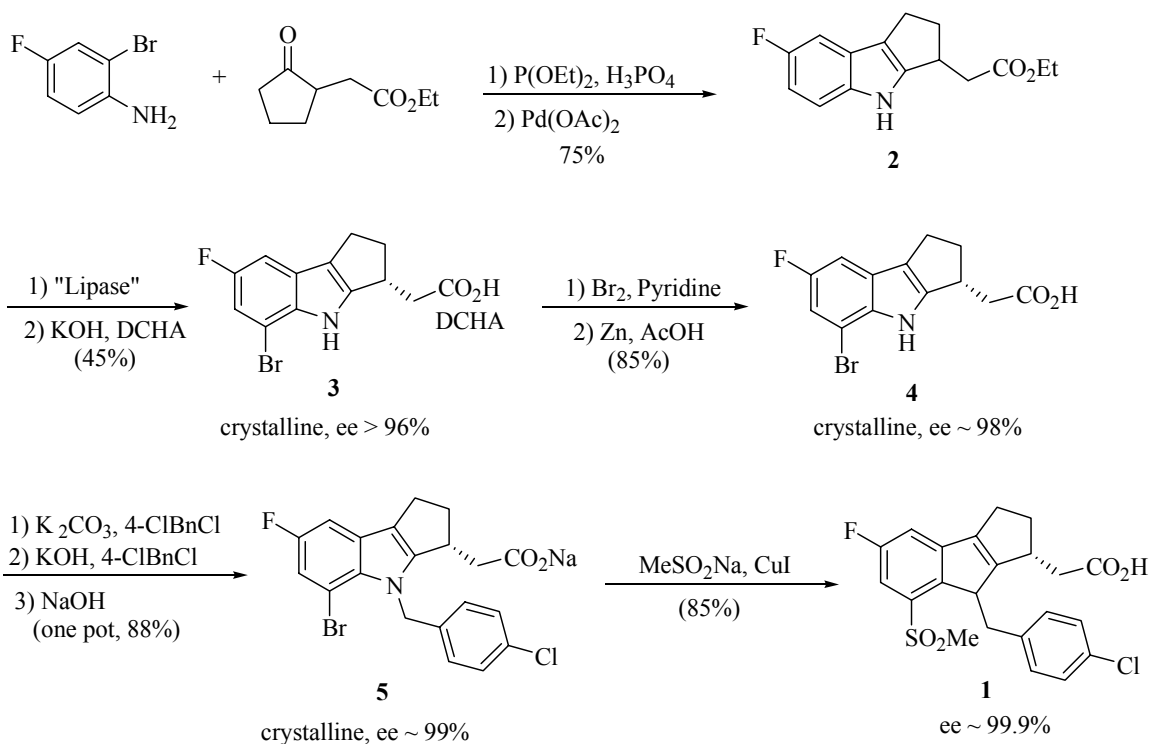
Scheme 1



The second generation process involved a much more efficient enzymatic resolution (see Scheme 2). The overall yield of the six synthetic steps was 20% and it was envisioned that the undesired, unreacted ester could be recycled. Furthermore, this synthetic sequence was successfully scaled up in the pilot plant to produce 26 kg of final material.

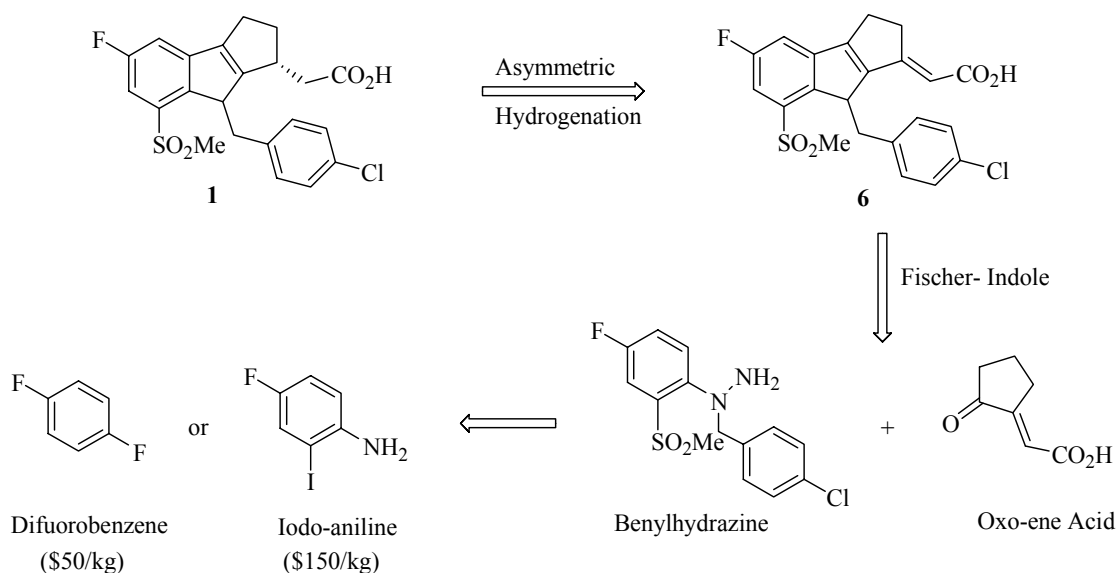
The problems identified with the synthesis in Scheme 2 were namely the racemic synthesis of intermediate **2**, the zinc waste generated in the bromination of intermediate **3**, as well as the copper waste generated in the final sulfonylation reaction to prepare **1**.

Scheme 2



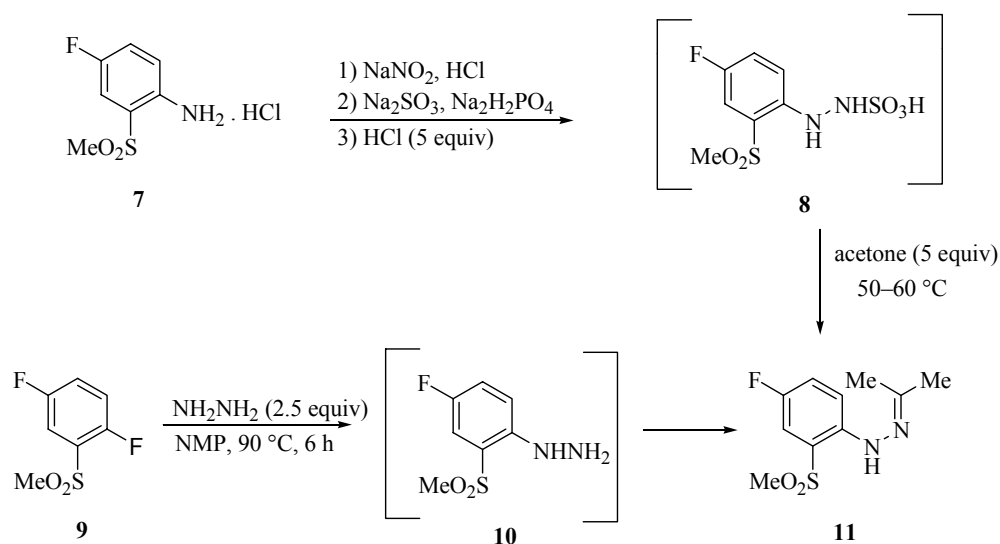
The final strategy that was ultimately used involved an asymmetric hydrogenation reaction to prepare **1** (see Scheme 3). Another key reaction in this synthesis was a Fisher-Indole reaction to prepare ene-acid **6**. The other major advantage to this approach was that it was highly convergent rather than the previous approaches which were linear. Two of the raw materials used in this synthesis were commercially available and very affordable. The cost of difluorobenzene was \$50 per kg and the cost of 2-iodo-4-fluoro-aniline was \$150 per kg.

Scheme 3



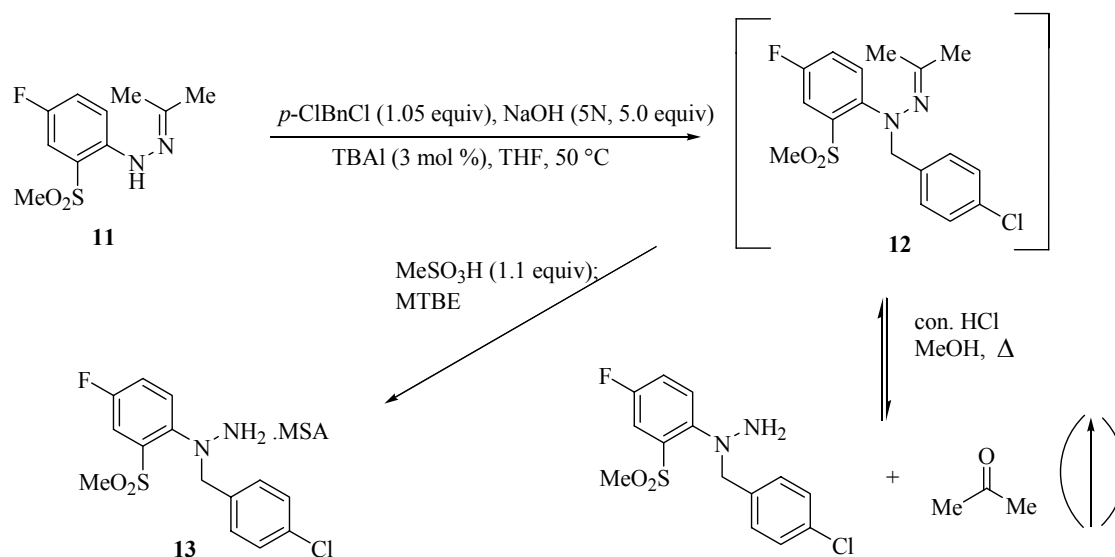
One of the key intermediates in the synthesis of **1** was hydrazine intermediate **8**. Initial efforts focused on preparing the hydrazine moiety through diazotization of the respective aniline derivative followed by reduction with either tin chloride or sodium sulfite (see Scheme 4). Although the sodium sulfite procedure avoided tin waste issues, the hydrazine was found to be unstable under basic conditions as well as product being lost during workup. During these early studies it was found that the acetone hydrazone derivative **11** could be directly crystallized from the reaction mixture with minimal loss in the mother liquor (<1%). The synthesis of hydrazine derivative **11** was further developed through a nucleophilic displacement of a fluorine group (see Scheme 4). The hydrazine intermediate **10** could be isolated as a crystalline solid in 96% yield and upon treatment with acetone, afforded the acetone hydrazone derivative **11** in 96% yield, again as a crystalline solid. The only real drawback with this synthesis was the requirement of the fluorine displacement reaction to be carried out in a Teflon-coated or hastelloy vessel.

Scheme 4



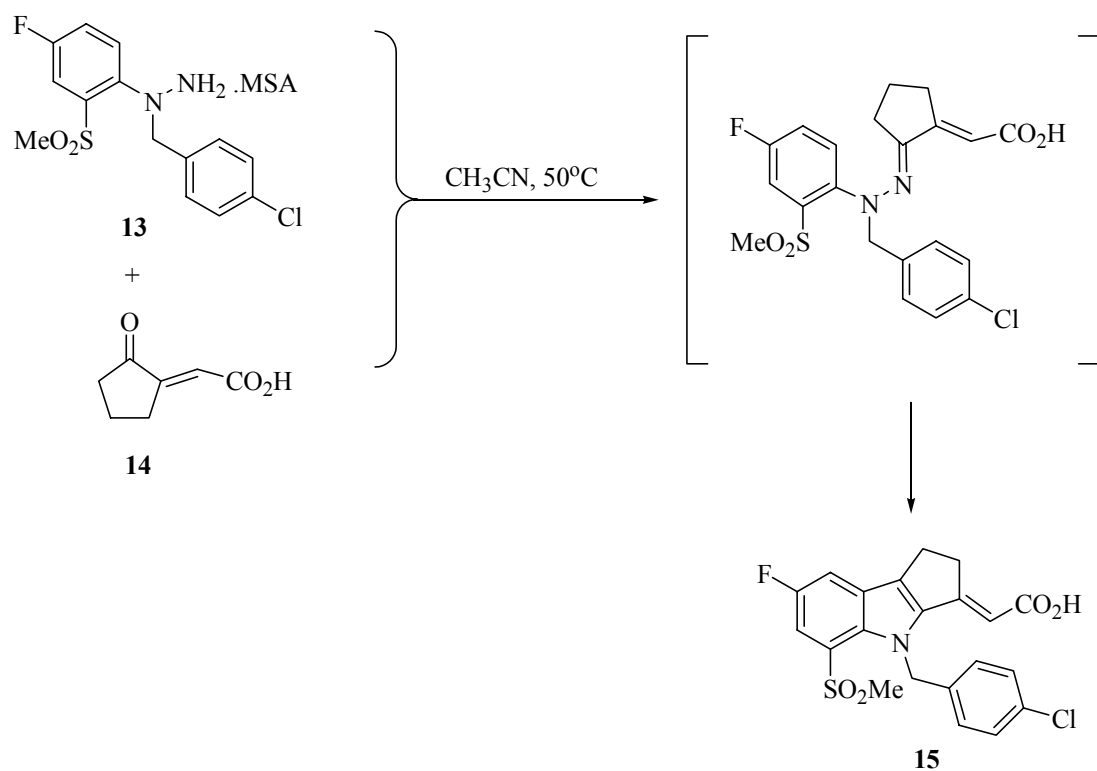
Alkylation of the acetone hydrazone derivative was achieved using *para*-chlorobenzyl chloride and catalytic tetrabutylammonium iodide to afford **12** in 98% yield (see Scheme 5). The hydrolysis of hydrazone **12** was achieved using methane sulfonic acid and the resulting salt directly crystallized from the reaction without azeotropic removal of acetone to afford **13** in 95% yield as a crystalline solid. This was a great improvement to earlier work which involved removal of acetone from the reaction mixture in order for the reaction to go to completion (see Scheme 5).

Scheme 5



The synthesis of the core structure of **1** was efficiently carried out using a Fisher-Indole reaction (see Scheme 6). Oxo-ene acid derivative **14** was inexpensively prepared in two steps from the condensation of cyclopentanone (\$10 per kg) and diethyl oxalate followed by rearrangement. Reaction of hydrazone **13** and **14** was carried out in acetonitrile at 50 °C to afford ene-acid **15** in 85% isolated yield. The product directly crystallized from the reaction mixture.

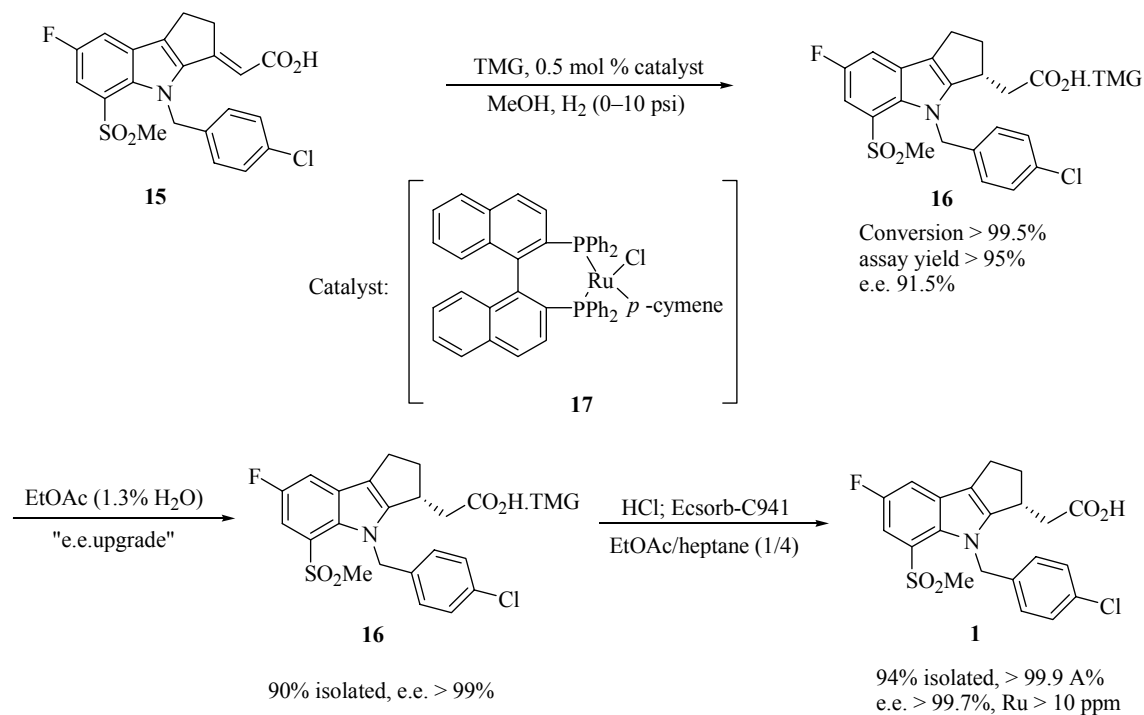
Scheme 6



The final steps involved an asymmetric hydrogenation using a ruthenium phosphine catalyst **17** (see Scheme 7). Tetramethylguanidine (TMG) was used in the reaction and salt **16** was isolated in greater than 95% yield with an enantiomeric excess (e.e.) of 91.5%. The salt was recrystallized in

ethyl acetate to afford **16** in >99% e.e. The final step in the synthesis involved isolation of the free acid to afford **1** in 94% yield and >99.7% e.e. The overall yield from cheap available starting materials was 52% and involved five chemical steps. The asymmetric synthesis involved a catalytic asymmetric hydrogenation and utilized crystalline intermediates for purity upgrades.

Scheme 7

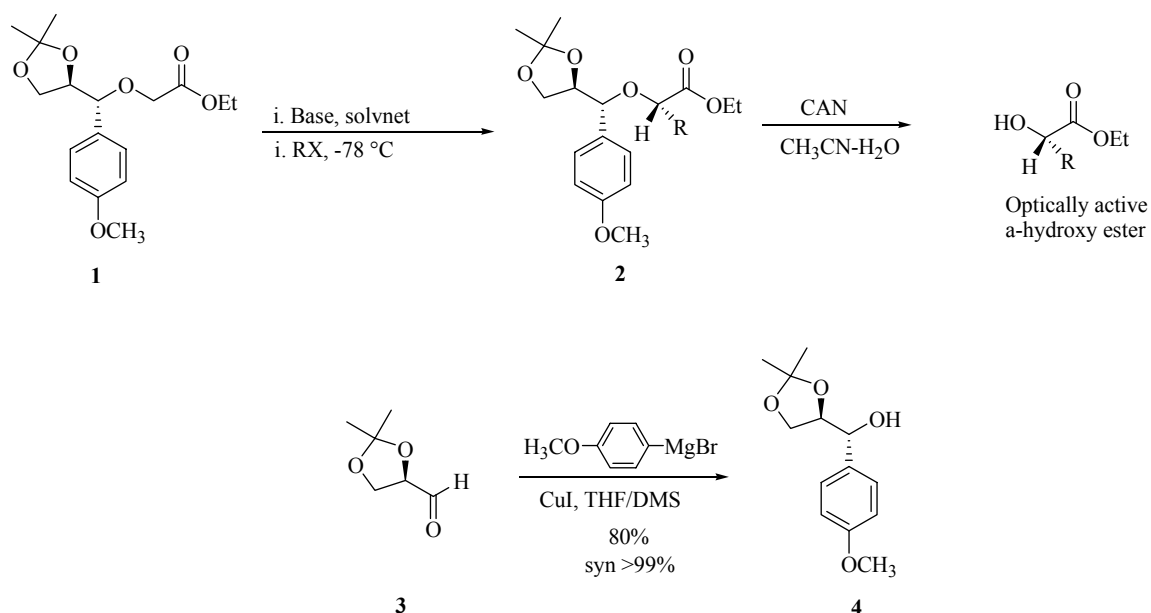


“Asymmetric Synthesis of 1,2-Diol and its Application to the Synthesis of Flutriafol”

Tae Hyun Kim, College of Pharmacy, Sookmyung Women's University, Seoul, Korea.

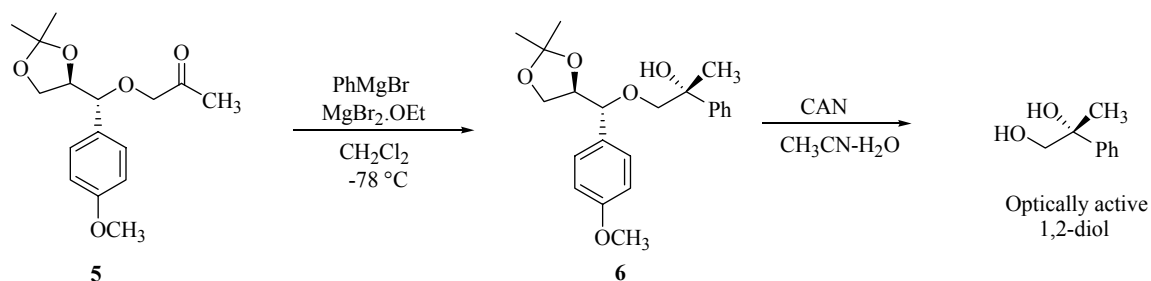
Tae Hyun Kim presented work on the development of an asymmetric synthesis of a 1,2-diol and its application to the synthesis of the fungicide flutriafol. Earlier work in the same group had shown that optically active α -hydroxy esters **2** could be prepared in a highly diastereoselective fashion through a tridentate, chelation-controlled, alkylation of an α -alkoxyketone **1** (see Scheme 8). Preparation of chiral auxiliary **4** was prepared through an organocuprate addition on the readily available chiral material **3**.

Scheme 8



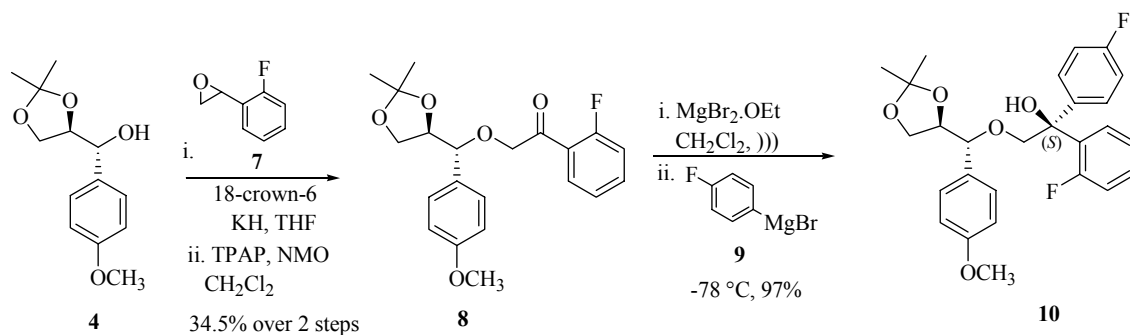
The methodology of these chiral auxiliaries was further extended through a highly diastereoselective 1,2-addition of a Grignard reagent (see Scheme 9). The diastereoselectivity was 99% when a phenyl group was introduced and the chiral auxiliary was cleaved using the reagent ammonium cerium nitrate (CAN).

Scheme 9



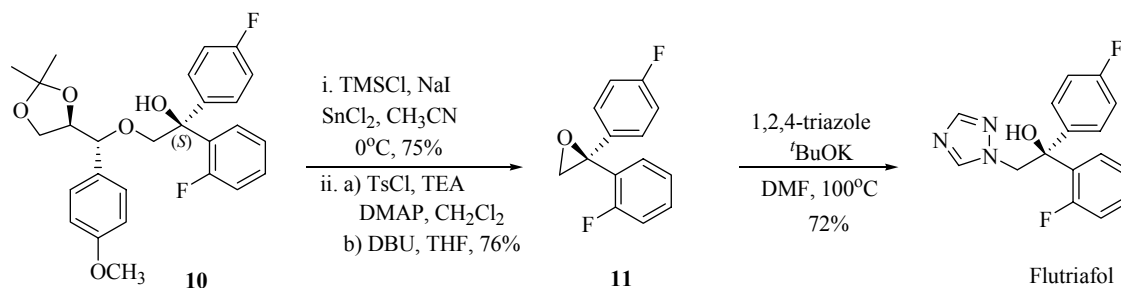
This methodology was utilized in the synthesis of (+)-flutriafol. Treatment of the chiral auxiliary **4** with epoxide **7** followed by a TPAP oxidation afforded ketone **8** (see Scheme 10). The diastereoselective 1,2-addition was achieved by treating **8** with Grignard reagent **9** and afforded the desired product **10** in 97% yield with a diastereoselectivity ratio of 170:1.

Scheme 10



The final steps in the synthesis of (+)-flutriafol involved cleavage of the chiral auxiliary followed by epoxide formation through the formation of a tosylate (see Scheme 11). The final step involved treatment of epoxide **11** with 1,2,4-triazole to afford (+)-flutriafol.

Scheme 11

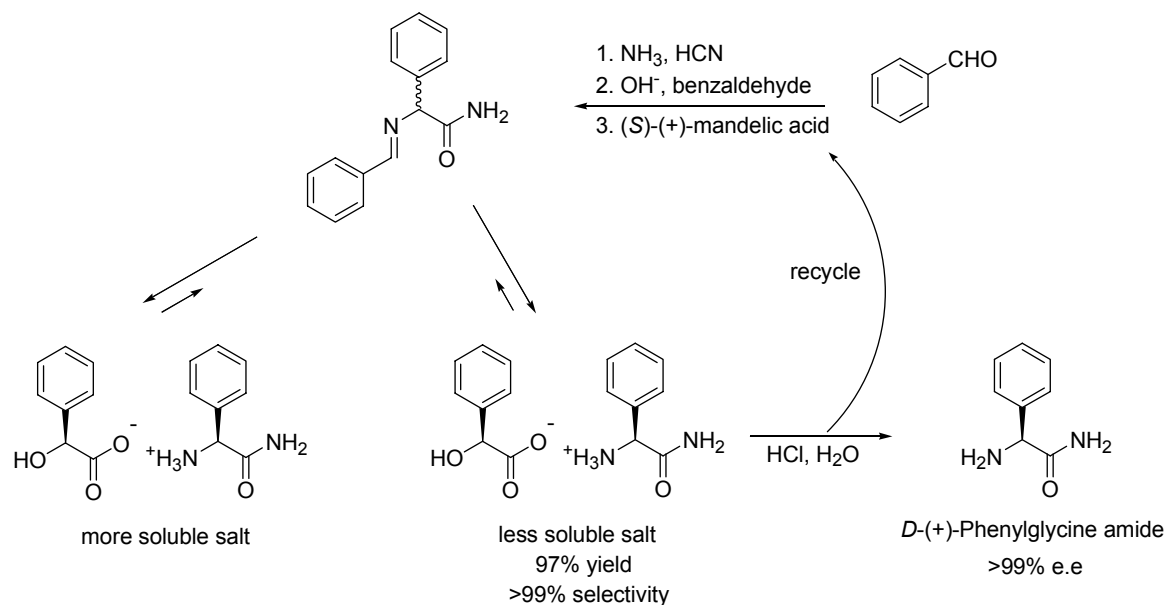


“Crystallization-induced Resolutions with *in-situ* Racemization – Synthesis of *D*-(+)-Phenylglycine Amide”

Natascha Sereinig, DSM Pharma Chemicals, The Netherlands.

Natascha Sereinig introduced a poster highlighting some of DSM Pharma Chemicals proprietary technology. These technologies have been developed in collaboration with industrial and academic institutions. One of the most interesting technologies developed was the isolation of enantiomerically pure of *D*-(+)-phenylglycine amide through a crystallization-induced resolution with *in-situ* racemization. This process offers the advantage over a normal resolution or even a dynamic resolution in that a 100% yield can be realized. Scheme 12 highlights the process of this resolution and *in-situ* racemization.

Scheme 12



Racemization of the product occurs in the Schiff base state and there is an equilibrium between the Schiff base and the more soluble salt of phenylglycine amide and (*S*)-(+)-mandelic acid. The desired salt precipitates out of solution which upon treating with acid affords enantiomerically pure product. The chiral (*S*)-(+)-mandelic acid can be recovered and recycled back to produce additional product.