



## **THE DEVELOPMENT OF A PRACTICAL AND LARGE SCALE BENIGN SYNTHESIS OF OCTAHYDROBENZO[G]QUINOLINES UNDER THE ASPECT OF GREEN CHEMISTRY**

**R. Nordmann<sup>1</sup>, M. Baenziger<sup>2</sup>, U. Sunay<sup>2</sup>, W. Stampfer<sup>2</sup>, J. Cercus<sup>2</sup>**

*1 - Sandoz, Preclinical Research, 4002 Basel*

*2 - Novartis Pharma, Chemical and Analytical Development, 4002 Basel, Switzerland*

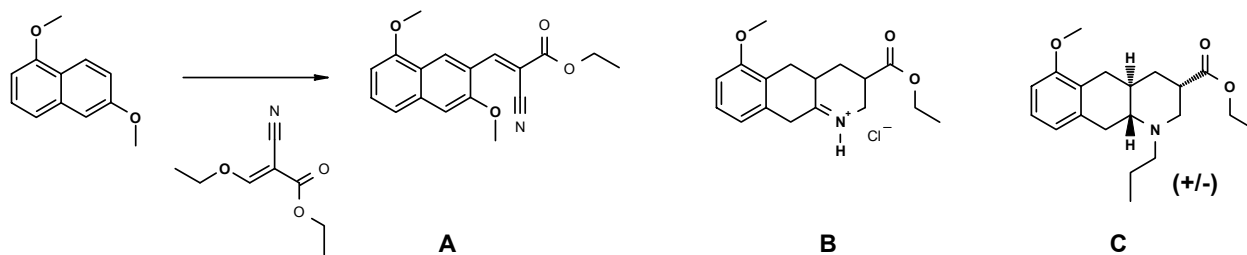
*markus.baenziger@novartis.com*

3-substituted octahydrobenzo[g]quinolines are important intermediates for pharmaceutically active compounds.

The research synthesis of this compound class started from 1,6-dimethoxynaphthalene. In a quite laborious and low yielding synthesis the desired compound could be obtained. Several for development and production prohibitive reagents like S-phenyl benzene thiosulfonate; Al/Hg or NaCNBH<sub>3</sub> were used in the research synthesis. Furthermore a low yielding and tedious chromatographic separation of diastereomers was necessary.

During the development a short and efficient synthesis, which is feasible for large scale manufacturing of rac (3S,4aR,10aR)-6-methoxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline-3-carboxylic acid methylester (Compound C) was investigated.

All the atoms of the skeleton are introduced in the first step (intermediate A), the reaction of 7-lithiated 1,6-dimethoxynaphthalene with ethoxymethylenecyanoacetic acid ethylester in an atom economic fashion. Both starting materials are commercially available and cheap. Subsequent hydrogenation, followed by Birch reduction and acidic cyclization gave the 6-methoxy-2,3,4,4a,5,10-hexahydrobenzo[g]quinoline-3-carboxylic acid hydrochloride (B) in high yield. The trans fusion of the two six membered rings was established after NaBH<sub>4</sub> reduction. After esterification, N-propylation and kinetic protonation of an intermittently formed trimethylsilylketene acetal, the desired product (C) was isolated in high yield. The overall yield of the final development process could be increased dramatically from 2 % (research synthesis) to 28 %!



Lit.    Organic Process Research & Development (2000), 4(6), 460-466  
      J.Med.Chem., 28, 367 (1985).