# METHODS FOR THE PREPARATION OF (3R,3AS,6AR) HEXAHYDRO-FURO[2,3-B]FURAN-3-OL

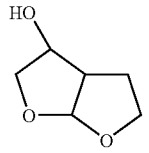
## CROSS REFERENCE TO RELATED APPLICATIONS

This application is the national stage of Application No. PCT/EP2005/051452, filed Mar. 31, 2005, which claims priority from EPO Patent Application No. 04101336.8 filed 31 Mar. 2004, the entire disclosures of which are hereby incorporated in their entirely.

The present invention relates to methods for the preparation of (3R,3aS,6aR) hexahydro-furo[2,3-b]furan-3-ol as well as a novel intermediate, (3aR,4S,6aS) 4-methoxy-tetrahydro-furo[3,4-b]furan-2-one for use in said methods. More in particular the invention relates to a stereoselective method for the preparation of (3R,3aS,6aR) hexahydro-furo[2,3-b]furan-3-ol, and to a method amenable to industrial scaling up.

Hexahydro-furo[2,3-b]furan-3-ol is an important pharmacological moiety present in the structure of retroviral protease inhibitors such as those described by Ghosh et al. in *J. Med. Chem.* 1996, 39(17), 3278-3290, EP 0 715 618, WO 99/67417, and WO 99/65870. Said publications are hereby incorporated by reference.

Several methods for the preparation of hexahydro-furo[2,3-b]furan-3-ol are known.




Ghosh et al. in *J. Med. Chem.* 1996, 39(17), 3278-3290, describe an enantioselective synthesis to obtain both (3R,3aS,6aR) and (3S,3aR,6aS) hexahydro-furo[2,3-b]furan-3-ol in optically pure form starting from 3(R)-diethyl malate and 3(S)-diethyl malate, respectively. Ghosh et al. also disclose the synthesis of a racemic mixture of the (3R,3aS,6aR) and (3S,3aR,6aS) enantiomers of hexahydro-furo[2,3-]furan-3-ol, starting from 2,3-dihydrofuran, followed by an enzymatic resolution of the final product. Pezeck et al. in *Tetrahedron Lett.* 1986, 27, 3715-3718, also describe a route for the synthesis of hexahydro-furo[2,3-b]-furan-3-ol using ozonolysis. Hexahydro-furo[2,3-b]furan-3-ol is also described as an intermediate in the synthesis of optically active perhydrofuro[2,3-b]furan derivatives in the publication by Uchiyama et al., in *Tetrahedron Lett.* 2001, 42, 4653-4656.

WO 03/022853 relates an alternative method which involves the synthesis of (3R,3aS,6aR) hexahydro-furo[2,3-b]furan-3-ol which method starts from a 2,3-diprotected-2,3-dihydroxy-propionaldehyde, which is transformed into a derivative encompassing a nitromethyl and one or two carboxylate moieties. Said derivative is subsequently transformed by a Nef reaction into a tetrahydrofuran compound, which is reduced and submitted to a intramolecular cyclization reaction to obtain the (3R,3aS,6aR) hexahydro-furo[2,3-b]furan-3-ol.

In order to transform the starting material, i.e. 2,3-diprotected-2,3-dihydroxy-propionaldehyde, into a derivative encompassing one or two carboxylate moieties, WO03/022853 describes different routes, which include a Wittig reaction using phosphorous ylides; a Horner-Emmons reaction using phosphonates in the presence of a base; a Knoevenagel type of condensation reaction using malonate derivatives; or alternatively applying Reformatsky reagents, i.e. precursors of —C(═O)—O— moieties such as cyanide. In particular, the examples disclosed therein, focus on two routes: the Knoevenagel and the Wittig routes.



The Knoevenagel route as illustrated in WO03/022853, consists of the addition of dimethyl malonate to a dry solution of the starting material 2,3-O-isopropylidene-glyceraldehyde to produce 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester with 2 carboxylates incorporated. Since the starting material is produced in aqueous solution, a laborious isolation procedure encompassing an extraction with tetrahydrofuran and water removal needs to be applied. This extraction and water removal require large amounts of tetrahydrofuran and production time. Further, the yield of the Knoevenagel reaction of 2,3-O-isopropylidene-glyceraldehyde to 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester exhibits a ceiling value of approximately 77% since intrinsically inevitable side reactions occur, even after optimization of conditions.

Due to the fact that the obtained di-carboxylated intermediate is a viscous oil, i.e. 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester, it needs to be introduced into the subsequent Michael addition as a solution in methanol. Methanol distillation after quench into aqueous $NaHCO_3$ solution, after the acidic Nef and cyclization reactions, but before extraction with an organic solvent such as ethyl acetate has disadvantages. Since the intermediate resulting from the acidic Nef and cyclization reactions, i.e. 4-methoxy-2-oxo-hexahydro-furo[3,4-b]furan-3-carboxylic acid methyl ester, is a labile compound in water, and the methanol distillation requires relatively high temperatures (up to 30° C. to 40° C.), decomposition of the intermediate occurs to polar compounds. These polar compounds remain in the aqueous phase and are further lost because they are not extracted to the organic phase. Since the methanol can not be removed prior to the extractions, a considerable volume is required in the work-up of 4-methoxy-2-oxo-hexahydro-furo[3,4-b]furan-3-carboxylic acid methyl ester.

During decarboxylation of 4-methoxy-2-oxo-hexahydro-furo[3,4-b]furan-3-carboxylic acid methyl ester there is significant by-product formation, i.e. (4-hydroxy-2-methoxy-tetrahydro-furan-3-yl)-acetic acid. Furthermore, crystallization of 4-methoxy-tetrahydro-furo[3,4-b]furan-2-one results in a brown solid due to concomitant polymerizations.

In addition, for the purification of 4-methoxy-tetrahydro-furo[3,4-b]furan-2-one, at least two acid-base extractive cascades are needed to remove the acid for the cyclization, thus resulting in an overall yield of 4-methoxy-tetrahydro-furo[3,4-b]furan-2-one of 52% based on 4-methoxy-2-oxo-hexahydro-furo[3,4-b]furan-3-carboxylic acid methyl ester, which is considered sub-optimal.

All the factors mentioned above disencourage the use of the Knoevenagel route. In fact, the decarboxylation step in this route presents an intrinsic disadvantage when compared to the Wittig route in that such decarboxylation step is not required with the latter.

WO03/022853 in Example I provides a Wittig route which employs triethyl phosphono acetate (TEPA) to obtain 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-acrylic acid ethyl ester. The subsequent Michael addition to 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-acrylic acid ethyl ester, presents limitations in that it produces a nitromethane adduct, i.e. 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-4-nitro-butyric acid ethyl ester, with a syn:anti ratio of approximately 8:2. Subsequent reduction fol-