A versatile C-5 synthon - Ethyl-3-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-difluoro-3-hydroxypropanoate in High Chemical and Optical purity: Observations on the Development of a Practical Bulk Process

ABSTRACT
A practical and efficient protocol is described for the synthesis of ethyl-3-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-difluoro-3-hydroxypropanoate (2), which is an important intermediate for the preparation of gemcitabine hydrochloride. Literature survey reveals that this diastereomer exists with its other stereomer ethyl 3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-difluoro-3-hydroxypropanoate in 3:1 ratio. Our observations on differences in physical properties of diastereomers lead us to purify and characterize this important diastereomer in high optical purity that could be readily adaptable on industrial scale.

KEYWORDS
Reformatski, Gemcitabine, Diastereomers, Process Chemistry, Green Chemistry

Introduction
The drive towards higher levels of achievement in organic synthesis both in terms of methodology and complexity of target remains unabated. The science is driven by the continuous discovery of novel and complex structures from nature that fascinates and challenges synthetic organic chemists, while the need to improve our ability to synthesize organic molecules in more efficient and economic ways (1).

Contemporary asymmetric synthesis is a widely used method for stereocontrolled creation of C-C bonds in organic molecules (2). During recent years, this approach to organic synthesis greatly contributed to progress in the directed introduction of various functionalities, and in the highly controlled formation of new centres of chirality. Preparation of the desired optical isomers by application of chiral starting materials is very advantageous, enabling precise planning and efficient realization of synthesis pathways (Chiron approach) (3).

Many monosaccharides and their readily available derivatives are versatile substrates for the synthesis of optically active target molecules (4). Besides the great diversity and important structural array offered by these monosaccharides also poses a problem of separation of these structurally related isomers. These challenges trigger the creativity of a synthetic chemist to devise a process to separate the desired molecule with the correct stereochemistry.

A typical mixture of ethyl-3-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-difluoro-3-hydroxypropanoate (2) and ethyl 3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-difluoro-3-hydroxypropanoate (3) is one of such problems; The separation of these diastereomers with high purity might be of advantage as it is characterized by (a) ready availability from natural sources, (b) by pronounced versatility due to the presence of the ester functionality, protected diol functionality, biologically more important difluoro functionality and a free hydroxyl group with defined stereochemistry for further functional group manipulations (Figure 1).

This C-5-synthon could be a potential chemical entity for stereocontrolled organic syntheses. Could be an interesting block for diversity oriented synthesis (DOS), such as the reactions using the ester group of 2 and 3 to form new C-C bonds, reduction to carbonyl, nucleophilic additions, aldol condensations and cycloadditions, chiral C-5-synthons, Wittig reactions and stereocontrolled functionalization of the resulting double bonds. The hydroxy group with the defined stereochemistry could be an important functionality, for instance it could initiate a click chemistry affording quite a compact structural frame.

It could find numerous applications in preparations of drugs like gemcitabine hydrochloride (5,6), could be used for combinatorial chemistry to form libraries of New Chemical Entities (NCEs), could be an important fragment for the natural product synthesis. Ethyl-3-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-difluoro-3-hydroxypropanoate (2) is a key raw material for the synthesis of gemcitabine hydrochloride (Scheme 1).
Scheme 1. Synthesis of Gemcitabine

For the development of this potent anticancer agent we required an expedient, practical route for ethyl-3-(4(R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxypropanoate (\(2\)) that would be readily adaptable at industrial scale. The reported procedures (7-10) for obtaining this material bear witness to the generally unsatisfactory nature of existing technologies for its synthesis.

Our involvement with this compound as a key raw material required development of a robust, environmentally friendly process that should be adaptable on industrial scale. We report here our findings, which represent improvements on existing literature procedures and provide access to (\(2\)) of high quality, in an efficient, greener and reliable manner.

Experimental Section
Preparation of (erythro)-ethyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propionate (\(2\)):

To the SL round bottom flask fitted with overhead stirrer, condenser, pressure equalizing dropping funnel, 1.8 L of tetrahydrofuran was added. Zn dust (180 g, 3 mol) and trimethylsilyl chloride (28.76 ml, 0.21 mol) were added to it under stirring. The mixture was stirred at room temperature for 15 min and then heated to reflux and mixture of 2,3-O-isopropylidene-D-glyceraldehyde (180 g, 1.4 mol) and bromodifluoroethyl acetate (248 ml, 2 mol) was added through dropping funnel to the reaction mixture slowly over a period of 30-40 min. The reaction was stirred with reflux for another 2 h. After 2 h the reaction mass was cooled to room temperature and poured into the mixture of 143 ml of conc. HCl and 1100 gm ice under stirring. The mixture was stirred for 15 min and the organic layer was separated. The aqueous layer was further extracted with ethyl acetate (200 ml). The collective organic layer was washed with brine followed by 5% aq sodium bicarbonate solution. The organic layer was dried over sodium sulfate and concentrated under vacuum to yield the erythro/threo mixture. The yellow colored oil so obtained was subjected to distillation at 2 mm Hg mercury at 75-80°C, the desired isomer 2 comes out as colorless liquid (220g).

Results and Discussion

The reported process involves, (R)-2,3-O-isopropylidene carbosaldehyde (Scheme 2). It was treated with ethyl bromo difluoroacetate under Reformatsky condition to yield compound 1, which contains R- and S-isomers in the ratio 3:1 and this mixture was purified by column chromatography to get the pure R-isomer (\(2\)).

Scheme 2. Synthesis of diastereomer 2.

In nearly all the processes described for the synthesis of gemcitabine hydrochloride involving 2 extends without separation of these diastereomers and proceeds with the mixture and separation was made at latter stage (Fractional crystallization) that is depicted as under (Scheme 3).

Scheme 3. Diastereomeric fractional crystallization

This described process involves telescoping of three steps i.e. starting from (1) to culminating at diastereomeric fractional crystallization in one pot. Purity is the parameter that defines whether the telescoping of the reactions could be possible or not. Starting with impure reactants or intermediates, results in not more than a mess.

Though this is one pot process but raises some serious concerns: (a) The process starts with the impure material; (b) Carrying unwanted 25% material does not only raise the cost by excess reagents but also wastage of high valued item; (c) The diastereomeric separation involved requires high solvent load, reagents, exceeds number of unit operations and low and high temperature conditions; (d) The serious difficulty of the process lies in the inconsistency and difficulty in diastereomeric separation; (e) The impurities load jeopardizes the efficient separation of diastereomers. Recrystallization step has to be repeated to get quality product. This certainly is a grey area of the whole process. In all of the processes so far for the synthesis of gemcitabine proceeds with either the impure ester and purify the bezoylated lactone product or separating the ester through column chromatography.

The expensive, laborious, waste generating and pollution creating column chromatographic separation is not advisable at large scale production.

The ideal synthesis as articulated by Wender,\(^{11}\) that where the target is made from readily available starting materials in one simple, safe, environmentally acceptable, and resource effective operation that proceed quickly and in quantitative yield, is a standard that all chemist should strive to achieve. Ideally reactions should give inexpensive, environmentally benign starting material, reagent and solvents and produce the target compound not only in high yield but also in high quality as well, with minimum impurities that are easily removed preferable by crystallization. So this problem triggered us for the design of a new, improved process (Scheme 4).

Scheme 4. Improved process for preparation of 2.

In the improved process (R)-2,3-O-isopropylidene gyceraldehyde was treated with ethyl bromo difluoroacetate under Reformatsky condition to yield the (1), as the diastereomeric
mixture of R,R- and R,S-isomers in the ratio 3:1. The Diastereomeric mixture was subjected to distillation under high vacuum, the desired isomer comes out in desired optical purity leaving behind the undesired isomer.

Conclusions
This improved process gives birth to potential chemical entities with desired and predictable stereochemistry that could be used for the exploration of chemical universe. Moreover the separation was affected by simple vacuum distillation and thereby making them available on industrial scale. It involves the telescoping process to start with a highly pure material and logically more favorable to end up with the pure product. It's an early separation and therefore more economical. No unnecessary reagent and solvent load makes the process more greener, environment friendly, economical and cost effective. The separation is very easy to affect which could be readily adaptable on large scale for multi-gram production in industries. The process gives the margin for optical enrichment through repeated distillation making it consistent in quality and optical purity.

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