Studies on the Continuous-Flow Synthesis of Nonpeptidal bis-Tetrahydrofuran Moiety of Darunavir

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Received: 28 July 2015; accepted: 02 October 2015

The use of continuous-flow chemistry has shown to be an important tool in improving API manufacture. In the present paper, we report the use of continuous-flow reactors in the synthesis of the bicyclic side chain of antiretroviral Darunavir.

Keywords: *bis*-tetrahydrofuran, HIV protease, continuous flow

1. Introduction

In the last decade, the continuous-flow technology has attracted the attention of the organic chemistry community, both as an enabling tool to enhance organic synthesis and as a manufacturing method [1, 2] being ranked by the ACS Green Chemistry Institute as a high priority research area for pharmaceutical and fine chemical manufacturing [3].

Significant progress has been made in the synthesis of important target compounds or valuable synthetic building blocks through the use of continuous-flow technology. Several reviews describe the benefits of applying continuous-flow methods in organic synthesis, including better mixing, efficient mass and heat transfer, and the ability to readily scale-up a given flow process by applying numbering-up or scaling-out principles [1, 2]. A particularly challenging area in flow chemistry is the synthesis of active pharmaceutical ingredients (APIs), which typically involves a significant number of synthetic steps, and is therefore clearly a rather complex operation [6]. Recently, our group demonstrated the advantages of continuous-flow chemistry in the synthesis of important HIV protease inhibitor building blocks, such as Atazanavir. It was demonstrated that the use of continuous-flow chemistry increases overall yield in a telescoped process where no workup of the intermediates is necessary, reducing the unit cost of the product [4].

The acquired human immunodeficiency syndrome (AIDS) is a life threatening viral disease caused by the human immunodeficiency virus (HIV) that compromises the immune system. According to the World Health Organization, there are approximately 35 million people infected worldwide. In the decades that followed the discovery of the disease, many direct acting antivirals were developed, increasing survival and quality of life of the infected patients. However, despite these advances in the treatment of AIDS, the accessibility of lower income country population to these drugs is still a great concern representing a humanistic challenge to be overcome [5].

In the present work, we report the use of continuous-flow chemistry in the synthesis of the bicyclic side chain of another important antiretroviral, Darunavir (Figure 1), a highly active HIV protease inhibitor. Its high potency allows its use as a rescue drug in patients where standard treatment fails. Structurally, Darunavir (1) bears a (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*] furan-3-ol core which fills the hydrophobic pocket of the HIV protease and maximizes hydrogen bonding interactions with the backbone atoms of the active site [6].

Due to the importance of Darunavir in treating HIV patients and the complexity of its bicyclic side chain (2) (Scheme 1), many studies on its synthesis are reported over literature. These approaches are summarized in Scheme 1. Among them, the Lewis acid-catalyzed reaction between 2,3-dihydrofuran (**9**) and glycolaldehyde dimer (**8**) was proposed by Yu and coworkers, leading to the desired racemic bis-THF which represents the shortest route. Other approaches are those described by Ghosh and coworkers to the stereoselective synthesis of the bis-THF moiety, including Mitsunobu inversions, enzymatic resolutions, and stereoselective aldol reactions [7].

In general, achieving the desired diastereoselectivity and enantioselectivity in a few steps, associated with high chiral purity, is still a challenge [7, 8]. Recently, our group and others demonstrated that kinetic resolution under continuous-flow conditions can be an efficient alternative process with high space-time yields, when compared to batch reactions [9]. In this way, in our continuous work on developing continuous-flow process for the synthesis of HIV drugs [7], herein we report our approach for translating batch conditions to a three step continuous-flow synthesis of the nonpeptidal (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol of Darunavir based on a biocatalyzed kinetic resolution.

2. Results and Discussion

We began our studies on translating the synthesis of **2** into flow conditions from intermediate (+/−)-**10**, synthesized in three steps in 63% overall yield as reported by Ghosh and coworkers. Initially, we decided to optimize all reactions under batch conditions in order to have a better understanding of the overall process.

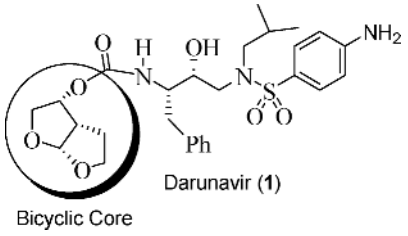

Figure 1. Darunavir structure (**1**)

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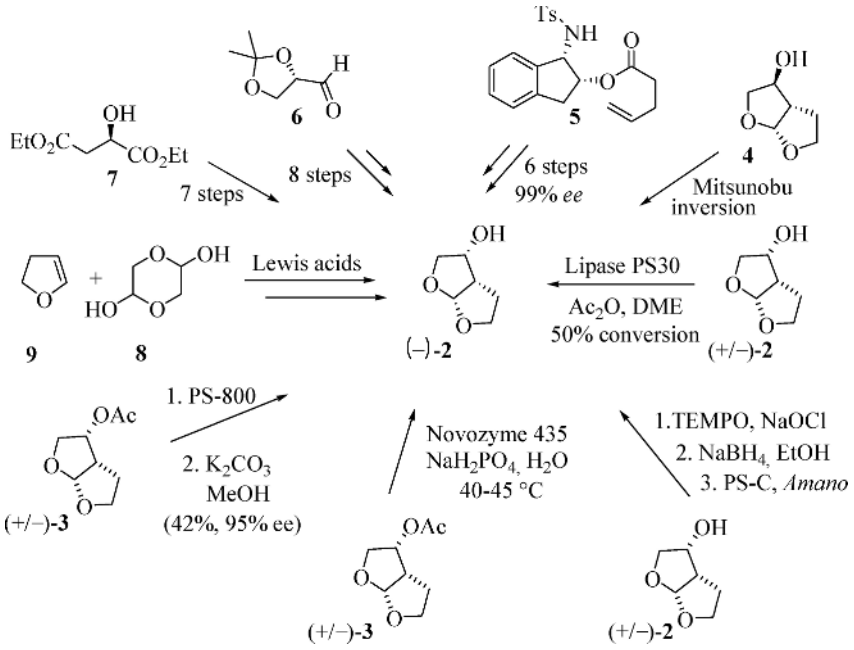
DOI: 10.1556/1846.2015.00031

First published online: 28 November 2015

Scheme 1. Approaches to the synthesis of bis-THF (−)-**2**



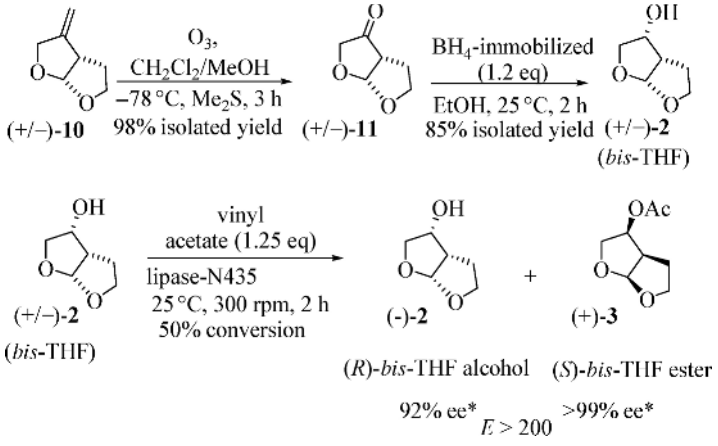
First, we have performed the ozonolysis reaction of (+/−)-**10**. When submitted to the ozonolysis conditions, intermediate (+/−)-**10** led the desired racemic ketone (+/−)-**11** in 98% yield after 3 h of reaction (Scheme 2). With the ketone in hands, the next step was a hydride mediated reduction of ketone (+/−)-**11**. Data from the literature [6, 7] and experience from our laboratory shows that the use of sodium borohydride presents some drawbacks in this transformation such as the use of low temperatures (<0 °C) as well as the need of tedious workup due to the moderate solubility of the product in the aqueous phase. In order to overcome these difficulties and anticipating the future study of this transformation under continuous-flow, we decided to introduce a novel method for the reduction of the ketone **11** by employing borohydride immobilized on amberlyst. The use of this heterogeneous reductant in ethanol led to the racemic alcohol (+/−)-**2** in 85% isolated yield [7, 10]. Compared to the classical reduction of **11** with $NaBH_4$ described in the literature [2], this protocol has some advantages: the reaction is conducted at room temperature; the workup is easier (filtration over celite under vacuum) which avoids the above mentioned tedious extraction in aqueous media that can carry much of the alcohol to the aqueous phase.

Subsequently, the enzymatic resolution of racemic intermediate **2** was studied. We performed the reaction with Novozym435 in order to evaluate the efficiency of this widely used and commercially available lipase for this substrate [7]. The reaction was carried out in methyl *tert*-butyl ether and dichloromethane (8.5:1.5), and used vinyl acetate as the acyl donor at 25 °C. The reaction was followed for 2 h, furnishing the desired alcohol (−)-**2** in 41% of conversion and 92% ee (Scheme 2).

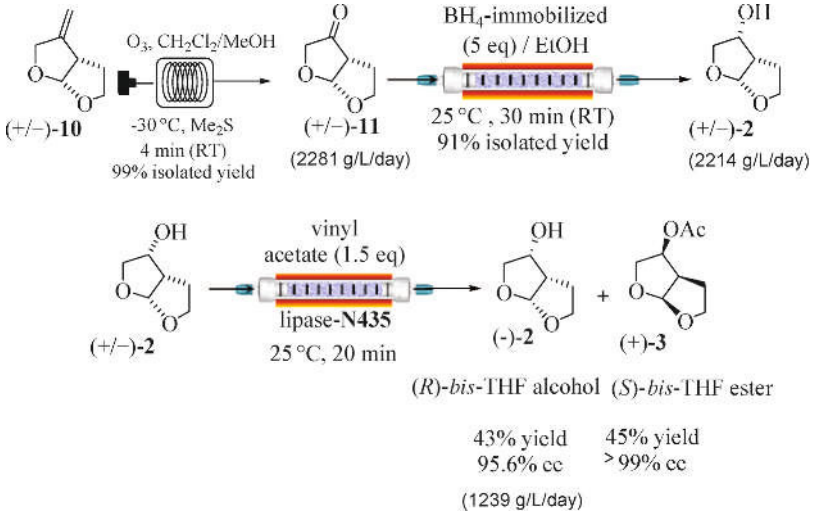
Taking the batch conditions as a starting point, we moved forward towards the development of a continuous-flow methodology to the synthesis of intermediate (−)-**2** from (+/−)-**10**.

The first reaction was ozonolysis of alkene (+/−)-**10** under continuous-flow conditions (Scheme 3). Hence, a solution of alkene (+/−)-**10** in dichloromethane and methanol was prepared, and this solution was pumped through the IceCube™ flow reactor with Ozone module with a residence time of 4 min at −30 °C. The reaction was quenched with dimethyl sulfide, achieving the product (+/−)-**11** in 99% yield. Under continuous-flow conditions, the

Scheme 2. Racemic synthesis and enzymatic resolution route synthesis of bis-THF. Enantiomeric excess (ee) and enantiomeric ratio (*E*) were calculated as described in Supporting Information



Scheme 3. Racemic synthesis and enzymatic resolution route proposed in the continuous-flow synthesis of Darunavir (**1**)



reaction time could be drastically decreased from 3 h to 4 min, which leads to a more efficient process for the ozonolysis (152 g/L/day for batch) of alkene (+/−)-**10** (Scheme 3). Other experiments were carried out at different residence times, but lower conversions were obtained.

The next step was to evaluate the continuous-flow reduction with the immobilized borohydride. For such, the hydride was packed on a glass column and the substrate dissolved in ethanol, pumped through the packed bed reactor with a residence time of 30 min at 25 °C.

The racemic alcohol was then achieved in 91% isolated yield. Comparing the reductions, we can see that the yield was higher under continuous flow than in batch and the reaction time was lower. Besides that, the easier workup and purification steps in continuous flow were advantageous since the solid reagent was into the column. On the other hand, the need to pack and unpack the reactor with the solid reactant may not be a simple operation and, additionally, the limited number of equivalents clearly limited the space-time yield of this step. With these concerns in mind, we decided to change from a hydride mediated reduction under continuous flow to the use of hydrogen gas. For such, a H-Cube Pro™ system was used. After intense optimization, the use of Ruthenium (5%) on charcoal catalyst at 75 °C in 1.39 min residence time furnished the desired product (+/−)-**2** quantitatively, as depicted in Scheme 4. With this continuous-flow hydrogenation protocol, a very high increase in the space-time yield was observed (6.700 g/L/day of (+/−)-**2**).

With the purpose to transfer all reactions to continuous-flow, we decided to run the kinetic resolution of (+/−)-**2** using the starting parameters from optimization under batch conditions (Scheme 3). The kinetic resolution of intermediate (+/−)-**2** under continuous-flow conditions achieved higher conversions and enantiomeric ratios than in batch (Scheme 3). Under continuous-flow conditions, after increasing residence time to 20 min, high conversions could be obtained (Table 1, Entry 4), achieving the desired alcohol (−)-**2** in 46% yield (96% ee) and the ester (+)-**3** in 45% yield (>99% ee), while under batch conditions, 2 h was needed achieving 41% conversion and

Scheme 4. Continuous-flow hydrogenation of (+/−)-**11**

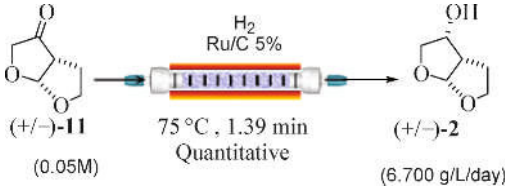


Table 1. Optimization of kinetic resolution of bis-THF alcohol catalyzed by lipase N-435 under continuous-flow conditions at 25 °C

Entry	Residence time (min)	Conversion[a]	E^b	Space-time yield (g of (−)-2/L/day)
1	5	24%	>200	2409
2	10	40%	>200	2037
3	15	42%	>200	1419
4	20	49%	>200	1239

[a] See Supporting Information for details.
[b] *E*(ee)=enantiomeric ratio.

92% ee, as described above. Besides that, under continuous flow, the productivity increased from 0.69 kg to 1.2 kg of chiral alcohol (−)-**2** per liter per day, leading to a more efficient process for kinetic resolution of the racemic alcohol (+/−)-**2** (Table 1, Entry 4).

3. Conclusion

The abovementioned results show that the use of continuous-flow chemistry protocols represents an important improvement in the synthesis of the bicyclic core of Darunavir. The results demonstrate that this technology leads to a faster synthesis due to reduced reaction times and reduced workup manipulations, which has strong impact on the overall cost and environmental issues. Additionally, the performed ozonolysis, BH_4 mediated reduction, and kinetic resolution under continuous-flow showed increasing productivity when compared to batch reactions.

Supporting Information

Electronic Supplementary Material (ESM) can be found in the online version at doi: 10.1556/1846.2015.00031.

Acknowledgments. We thank CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior), CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico), FAPERJ (Fundação Carlos Chagas Filho de Amparo a Pesquisa do Estado do Rio de Janeiro), and FINEP (Agência Financiadora de Estudos e Projetos) for financial support.

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