Tetrahedron: *Asymmetry* 19 (2008) 2015–2019

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Highly diastereo- and enantioselective catalytic synthesis of the bis-tetrahydrofuran alcohol of Brecanavir and Darunavir

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ARTICLE INFO

Article history:
Received 15 May 2008
Accepted 27 July 2008
Available online 5 September 2008

ABSTRACT

An efficient highly diastereo- and enantioselective synthesis of the bis-tetrahydrofuran (bis-THF) alcohol of several HIV protease inhibitors, including Brecanavir and Darunavir, has been achieved utilizing an Evans Mukaiyama aldol reaction of (benzyloxy)acetaldehyde and a silyl ketene acetal. The lactone alcohol intermediate from the catalytic aldol reaction was reduced to a lactol. Palladium catalyzed hydrogenolysis removed the benzyl protection and promoted an in situ cyclization to form the epimer of the bis-THF alcohol in a 98:2 diastereomeric ratio and 97:3 enantiomeric ratio. The alcohol epimer was readily converted to the target in two steps by oxidation to a ketone followed by highly selective reduction to the bis-THF alcohol.

1. Introduction

Acquired immunodeficiency syndrome (AIDS) is a chronic, life-threatening condition caused by the human immunodeficiency virus (HIV). By damaging or destroying the cells of the immune system, HIV interferes with the body's ability to effectively fight off viruses, bacteria and fungi that cause the disease. In the 27 years since the first reports of the disease, AIDS has become a global epidemic. HIV protease inhibitors are important components of the current drug regimens to treat HIV infection. Protease inhibitors interrupt HIV replication at a later stage in its life cycle by interfering with an enzyme known as HIV protease.[1] Among these drugs are saquinavir (Invirase), ritonavir (Norvir), indinavir (Crixivan), lopinavir, nelfinavir (Viracept), amprenavir (Agenerase), atazanavir (Reyataz), tipranavir (Aptivus), and Darunavir (Prezista). Due to the emergence of drug resistance, there are significant efforts to develop exceedingly potent inhibitors with excellent resistance profiles. The design of novel protease inhibitors targeting the protease backbone atoms is an effective strategy.[1] Brecanavir or GW640385 **1** (Fig. 1)[2] was a potent new protease

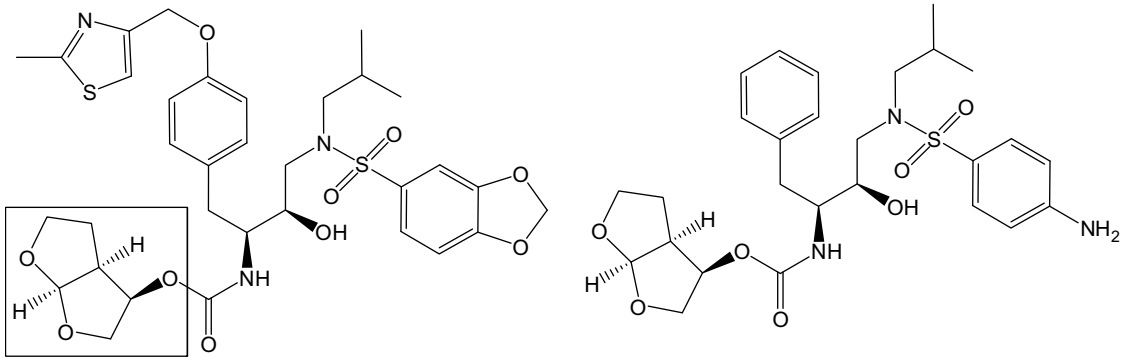

Figure 1. Structures of protease inhibitors Brecanavir and Darunavir with the bis-THF moiety.

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doi:10.1016/j.tetasy.2008.07.037

inhibitor in phase 2 clinical trial for treatment of drug-resistant HIV and received Fast Track Designation from the US Federal Drug Administration (FDA). An important structural feature of **1** is the fused bicyclic tetrahydrofuran or bis-tetrahydrofuran (bis-THF) moiety. Initially incorporated in the structure-based drug design for Protease inhibitors by Ghosh et al., the bis-THF and its significance as a nonpeptide P_2 ligand for withstanding potency against drug-resistant HIV is well documented.[1,3]

The bis-THF unit is also present in the recently FDA approved Darunavir or TMC-114 **2**,[1,4a–c] and other protease inhibitors reported in development as HIV drug candidates.[1] Darunavir was approved as new HIV treatment for patients who have not responded to treatment with existing drugs.

Since the defining of the significant role of the bis-THF alcohol in the discovery of HIV drugs,[3] many syntheses have been reported.[4] One approach utilizes substrate control starting from chiral pool materials such as D-glyceraldehyde derivatives.[4b–d] The most notable synthesis along this approach was reported by Quaedflieg et al. starting from (*S*)-2,3-*O*-isopropylideneglyceraldehyde.[4b] Generally, a good stereochemical control was reported with this approach. A second approach involves the synthesis of the racemic form of the bis-THF alcohol followed by enzymatic resolution.[4a,e–g] Despite the need for multiple steps to establish the relative stereochemistry of the bicyclic structure prior to the enzymatic resolution, this synthetic approach has been demonstrated to be highly practical. One such synthesis has been scaled up to a tonnage quantity in production of **1**.[4g] A third approach by Uchiyama et al. utilizes the asymmetric oxyselenenylation of 2,3-dihydrofuran.[4h] While this is interesting, this approach obtained only 78:22 diastereoselectivity and the need of eight steps to the bis-THF target made the synthesis inefficient. Recently, Ghosh and co-workers reported an asymmetric synthesis based on an anti-aldol reaction of an ester-derived titanium enolate.[4i] However, this is still a substrate controlled synthesis as stoichiometric amount of a chiral indanol is required. Most recently, research groups at Gilead Sciences (GS) and GlaxoSmithKline (GSK) independently developed short syntheses based on chiral Lewis acid catalyzed cycloaddition of glycolaldehyde and 2,3-dihydrofuran.[4j,k] While both the GS and the GSK syntheses were relatively efficient due to the overall short synthetic sequences, they failed to achieve high diastereo and enantioselectivities at the same time. An enzymatic enhancement was still required to make the bis-THF alcohol of sufficient enantiomeric purity. A highly diastereo and enantioselective synthesis through chiral catalysis proved to be elusive.

Our goal was to achieve an efficient synthesis of the bis-THF alcohol **3** in high enantiomeric purity through stereoselective synthesis employing catalytic reagent control as shown in Figure 2. The bicyclic [2.2.0] ring structure of **3** means that only one of the two bridge-head stereocenters needs to be controlled, and the other stereocenter is formed in the cyclization via the acetal formation. This line of thinking led to intermediates such as lactol **A** or, at one oxidation state higher, lactone **B**.

The skeleton of **B** in turn could be secured from the addition of γ-butyrolactone to ethyl glyoxylate **C** or a glycolaldehyde equivalent **D**. Such an addition would set the two stereocenters in either a *syn*- or *anti*-fashion. The structure of target bis-THF alcohol **3** requires anti addition. We envisioned that the addition would be catalyzed by a chiral catalyst (M^*L_n), which would chelate with the adjacent carbonyl and alkoxy groups of ethyl glyoxylate **C** or the glycolaldehyde derivative **D** as the basis for the introduction of the asymmetry. Herein, we report our efforts on this synthetic strategy and ultimately a relatively short synthesis of the bis-THF alcohol **3** in high enantio- and diastereoselectivities.

2. Results and discussion

There have been many reports on the addition of the lithium enolate of γ-butyrolactone to aldehydes or ketone.[5] To assess the feasibility of the intramolecular cyclization of a lactol such as **A** (Fig. 2) to a bis-THF alcohol, we initially examined the addition of the enolate of γ-butyrolactone to the more reactive ethyl glyoxylate (Scheme 1). The enolate of γ-butyrolactone requires an *E*-configuration. Addition to ethyl glyoxylate provided α-hydroxyester **4** as a mixture of diastereomers.

Reduction with diisobutylaluminum hydride (DIBAL-H) afforded triol **5**. The high water solubility and apparent instability of **5** led to a poor yield (39%) and low purity of **5**. Nevertheless, treatment of **5** with 6 M HCl indeed gave rise to the bis-THF alcohols as a nearly 1:1 mixture of the α- and β-epimers **3** and **6** (racemic). The low diastereoselectivity was not surprising based on the literature reports involving the addition of the lithium enolate of γ-butyrolactone to aldehydes.[5b] Given the low diastereoselectivity of the aldol reaction with the glyoxylate ester,[6] the water solubility, and the questionable stability of triol **5**, we shifted our efforts toward the addition of a better defined silyl enolate to a protected glycolaldehyde **D** (Fig. 2).

We noted that Evans et al. have extensively studied the catalytic enantioselective aldol additions of enolsilanes to aldehydes includ-

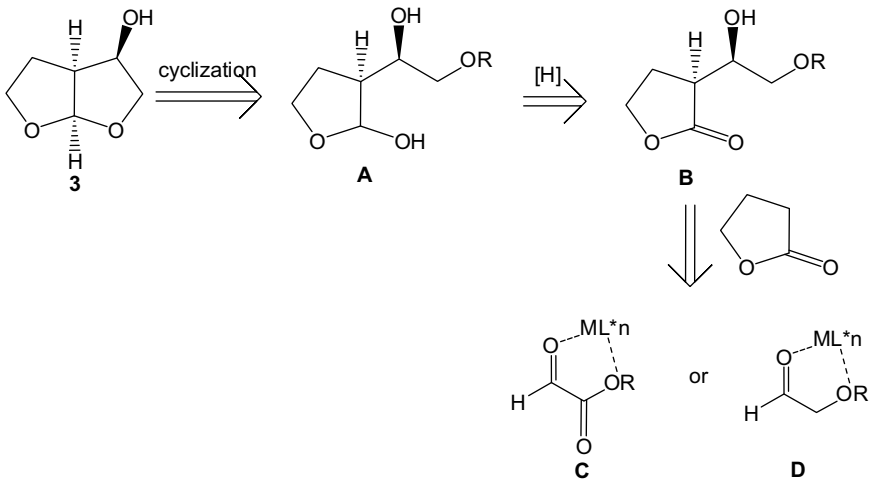

Figure 2. Strategy for asymmetric synthesis of bis-tetrahydrofuran alcohol **3**.