HHS Public Access

Author manuscript

Tetrahedron Lett. Author manuscript; available in PMC 2016 June 03.

Published in final edited form as:

Tetrahedron Lett. 2015 June 3; 56(23): 3314–3317. doi:10.1016/j.tetlet.2015.01.019.

Enantioselective Synthesis of Dioxatriquinane Structural Motifs for HIV-1 Protease Inhibitors Using a Cascade Radical Cyclization†

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Abstract

Synthesis of novel HIV-1 protease inhibitors incorporating dioxatriquinane-derived P2-ligands is described. The tricyclic ligand alcohol contains five contiguous chiral centers. The ligand alcohols were prepared in optically active form by an enzymatic asymmetrization of mesodiacetate, cascade radical cyclization, and Lewis acid catalyzed reduction as the key steps. Inhibitors with dioxatriquinane-derived P2-ligands exhibited low nanomolar HIV-1 protease activity.

Keywords

HIV-1 protease; Inhibitor; Cascade; Radical; Dioxatriquinane

The introduction of HIV-1 protease inhibitors into antiretroviral therapy (ART) has greatly improved the outlook for patients with HIV infection and AIDS.[1,2] However, the emergence of multidrug resistant HIV-1 variants has raised major concerns about the prospects of long-term treatment options.[3,4] Consequently, there is a critical need for more effective protease inhibitors for the treatment of the growing number of treatment-experienced HIV/AIDS patients carrying multidrug-resistant HIV-1 strains.[4,5] In an effort to combat drug resistance, our structure-based design strategy targeting the protein backbone has led to the design and discovery of a variety of novel HIV-1 protease inhibitors. This includes FDA approved inhibitor darunavir (**1**, Figure 1), which is an exceptionally potent inhibitor that exhibits broad-spectrum activity against multidrug-resistant HIV-1 variants.[5-8]

Our inhibitor design strategy involves maximizing inhibitor-HIV-1 protease interactions in the active-site, particularly promoting extensive hydrogen bond interactions with the protein backbone atoms.[9,10] The detailed X-ray structural analyses of darunavir-bound protease

†This paper is dedicated to the memory of Professor Harry Wasserman of Yale University, a beloved teacher, scholar, artist, and editor who made a great difference in so many of our lives.

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Supplementary Data: Supplementary data associated with this article can be found in the online version.

complexes revealed a series of conserved interactions between the inhibitor and key backbone atoms of HIV-1 protease. This backbone-binding molecular design strategy corroborated observed superior drug-resistance properties of darunavir and its P2' 4-methoxysulfonamide derivative (**2**, TMC-126) compared to other FDA approved inhibitors.[8, 11]

Subsequently, based upon examination of the protein-ligand X-ray structure of darunavir-bound HIV-1 protease, we have designed fused *tris*-tetrahydrofuan (*tris*-THF) as the P2-ligand and incorporated it in inhibitor **3** in order to promote additional interactions in the HIV-1 protease active site.[12] Indeed, inhibitor **3** with a *syn-anti-syn*-fused *tris*-THF ligand exhibited nearly 10-fold improvement of potency against highly resistant clinical HIV-1 strains compared to darunavir. The corresponding inhibitor with a *syn-syn-syn*-fused *tris*-THF ligand also provided very potent inhibitor, however, it was somewhat less effective than inhibitor **3**.[12,13] Interestingly, our recent work indicated that the top oxygen of tris-THF may not be critical to the overall potency of the inhibitor.[14] In an effort to ascertain the contribution of the middle oxygen of the *tris*-THF ligand toward the ligand binding site interactions, we sought to synthesize the corresponding *syn-anti-syn*- and *syn-syn-syn*-fused 1,6- dioxatriquinane derivatives and compare enzyme inhibitory activity of the analogs with inhibitor **3**. Herein, we report our enantioselective syntheses of (3*R*,3*aS*,3*bR*,6*aS*,7*aS*)-octahydro-2*H*-cyclopenta[1,2-*b*:4,3-*b*′]-bis-furan-3-ol and (3*R*,3*aS*,3*bS*,6*aR*,7*aS*)-octahydro-2*H*-cyclopenta[1,2-*b*:4,3-*b*′]-bis-furan-3-ol using cascade radical cyclization and enzyme-catalyzed desymmetrization as the key steps. We have then incorporated these ligands into HIV-1 protease inhibitors and evaluated their inhibitory potency.

For the target inhibitor **4**, the synthesis of the corresponding *syn-anti-syn*-fused 1,6-dioxatriquinane structural template, (3*R*,3*aS*,3*bR*,6*aS*,7*aS*)-octahydro-2H-cyclopenta-[1,2-*b*:4,3-*b*′]-bis-furan-3-ol, is shown in Scheme 1. This tricyclic ligand alcohol contains five contiguous chiral centers. We planned to utilize a cascade radical cylization for the synthesis of this tricyclic framework with defined configuration. The efficiency of such related cascade radical cylization was previously demonstrated by Curran and Rakiewicz during the synthesis of hirsutine, a triquinane system.[15,16] The synthesis of a related 1,6-dioxatriquinane derivative was also reported by Hanessian and Leger using a radical cyclization.[17] For our present work, we planned to employ a haloacetal radical cyclization strategy pioneered by Stork and co-workers.[18,19] Our synthesis began with the preparation of monoacetate **5** in multigram quantity using enzymatic asymmetrization of *meso*-diacetate with acetyl cholinesterase as described previously.[20] Formation of the Mosher ester of **5** revealed that the enantiomeric purity of **5** was 95% ee.[21,22] The hydroxyl group was protected as the TBS-ether with TBSCl in the presence of imidazole in THF in near quantitative yield. Hydrolysis of the resulting acetate afforded the alcohol **6** in quantitative yield. To set the bottom tetrahydrofuran stereochemistry, alcohol **6** was subjected to Mitsunobu inversion[23] with diisopropyl azodicarboxylate (DIAD), triphenylphosphine, and *p*-nitrobenzoic acid to provide the corresponding nitrobenzoate derivative. Ester hydrolysis with K_2CO_3 in methanol afforded alcohol **7** in 91% yield in two steps.

Treatment of alcohol **7** with NBS and ethyl vinyl ether in CH_2Cl_2 afforded bromo acetal **8** as a mixture (1:1) of diastereomers in 72% yield. Removal of the TBS group with $n Bu_4N^+F^-$

(TBAF) in THF provided the corresponding alcohol. Treatment of the resulting mixture of alcohol with NaH and propargyl bromide in the presence of nBu$_4$N$^+$I$^-$ (TBAI) furnished the radical cyclization precursor **9** in 78% yield in two steps. The cascade cyclization using tri-*n*-butyltin hydride in refluxing toluene in the presence of AIBN resulted in a mixture (1:1) of tricyclic alkene derivative **10** in 54% yield. Reduction of acetal **10** with Et_3SiH in the presence of $BF_3.OEt_2$ afforded tricyclic alkene **11** as a single isomer in 98% yield.[24] Ozonolytic cleavage of **11** at -78 °C followed by reduction of the resulting ketone with $NaBH_4$ at -15 °C furnished endo alcohol **12** as single isomer in 71% yield.

The synthesis of 1,6-dioxatriquinane alcohol with *syn- syn-syn*-fused structural motif is shown in Scheme 2. The overall strategy is similar to the synthesis of alcohol **12**. As shown, optically active TBS-alcohol **6** was converted to bromo acetal **13** utilizing ethyl vinyl ether and NBS in CH_2Cl_2. Removal of the TBS-group followed by treatment of the resulting alcohol with NaH and propargyl bromide in the presence of TBAI gave the cyclization precursor **14** in 85% yield in two steps. The cascade cyclization using tri-*n*-butyltin hydride as described above generated the tricyclic alkene **15** in 79% yield. Acetal reduction with Et_3SiH in the presence of $BF_3.OEt_2$ provided the alkene **16** in 76% yield.[24] Ozonolytic cleavage followed by $NaBH_4$ reduction afforded optically active *syn-syn-syn*-fused (3*R*,3*aS*, 3*bS*, 6*aR*,7*aS*)-octahydro-2H-cyclopenta[1,2-*b*:4,3-*b*′]-bis-furan-3-ol (**17**) in 85% yield.

The stereochemical assignment of alcohols **12** and **17** was supported by ^{1}H-NMR NOESY experiments (Figure 2). The observed NOE between H_a-H_b, H_b-H_c, and H_d-H_e for compound **12** is in line with the assigned *syn-anti-syn*-fused tricyclic ring system. Similarly, the observed NOE between H_a-H_b, H_b-H_c, H_d-H_e, and H_c-H_e supported the *syn-syn-syn*-fused tricyclic ring system for compound **17**.

The syntheses of inhibitors **4** and **21** are outlined in Scheme 3. Optically active ligand alcohols **12** and **17** were reacted with *p*-nitrophenyl chloroformate in the presence of *N*-methyl morpholine in CH_2Cl_2 at 23°C for 12 h to provide carbonates **18** and **19** in 60% and 62% yield respectively.[14] Reaction of these activated carbonates with amine **20** in the presence of diisopropylethylamine (DIPEA) in CH_2Cl_2 at 23°C for 12 h furnished inhibitors **4** and **21** in 65% yield.[25] These compounds showed satisfactory analytical data. Inhibitor purity was determined by reverse HPLC analysis and purity was >98% as determined by HPLC assay.[26]

Inhibitors incorporating dioxatriquinane-derived P2-ligands exhibited very potent HIV-1 protease inhibitory activity. Inhibitor structures and activity are shown in Table 1. We utilized the enzyme inhibitory assay protocol developed by Toth and Marshall[27] and the K_i values denote the mean values of at least six determinations. As can be seen, inhibitor **4**, with a stereochemically defined *syn-anti-syn*- fused (3*R*,3*aS*,3*bR*,6*aS*,7*aS*)-octahydro-2*H*-cyclopenta-[1,2- *b*:4,3-*b*′]-bis-furan-3-ol-derived urethane as the P2-ligand and *p*-methoxysulfonamide as the P2′-ligand, showed enzymatic K_i value of 1.39 nM. Inhibitor **21** with *syn-syn-syn*-fused (3*R*,3*aS*,3*bS*,6*aR*,7*aS*)-octahydro-2*H*-cyclopenta[1,2-*b*:4,3-*b*′]-bis-furan-3-ol-derived urethane also displayed a comparable enzymatic K_i value of 1.43 nM. Both compounds are very potent, however the inhibitory activity is significantly lower than *bis*-THF-derived inhibitor **2** (TMC-126) or *syn-anti-syn*-fused *tris*-THF-derived inhibitor **3**.

The difference in activity is likely due to the absence of oxygen in the dioxatriquinane-derived P2-ligands.[28] While the P2-ligands in inhibitors **3** and **4** have similar steric features, the hydrogen bonding abilty of the second oxygen in the *tris*-THF is critical to potency.[12,13]

In conclusion, we have reported novel HIV-1 protease inhibitors incorporating dioxatriquinane-derived P2-ligands. Synthesis of the tricyclic ligand alcohols is carried out stereoselectively in an optically active form. The synthesis features an enzymatic asymmetrization of mesodiacetate, a highly effienct cascade radical cyclization, and Lewis acid catalyzed reduction as the key steps. Inhibitors containing dioxatriquinane-derived ligands showed very good HIV-1 protease inhibitory activity, however the observed activity is significantly lower than *syn-anti-syn*-fused *tris*-THF- derived inhibitor **3**. The data demonstrates the importance of the ligand oxygen in ligand-binding site interactions. Further chemical modifications are currently underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support by the National Institutes of Health (GM53386) is gratefully acknowledged.

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25. For more details, please see supporting information section.
26. HPLC conditions:column, YMC pack ODS-A;flow rate, 1 mL/min; 25°C, 256 nM detection, solvent, MeCN:H_2O 90:10; retention time for compound **4**, 13.40 min; retention time for compound **21**, 14.85 min.
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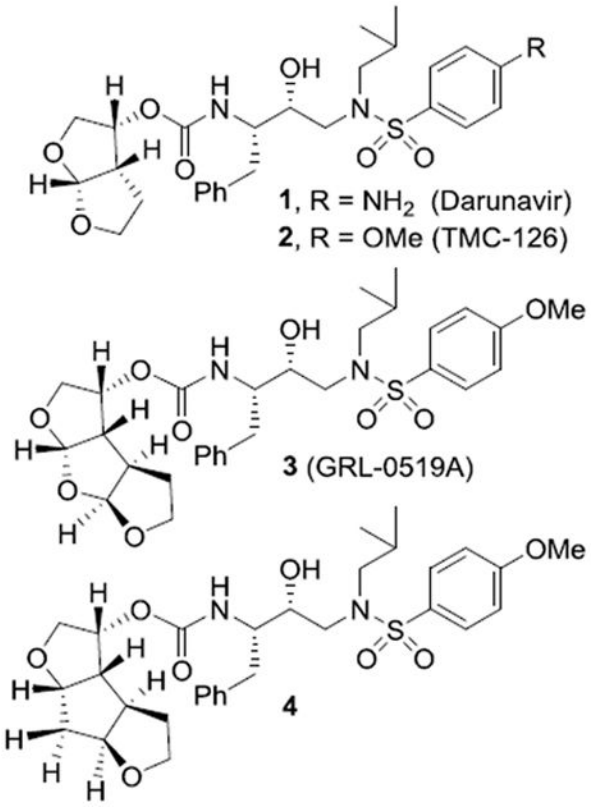


Figure 1.
Structure of darunavir (**1**) and PIs **2**-**4**.

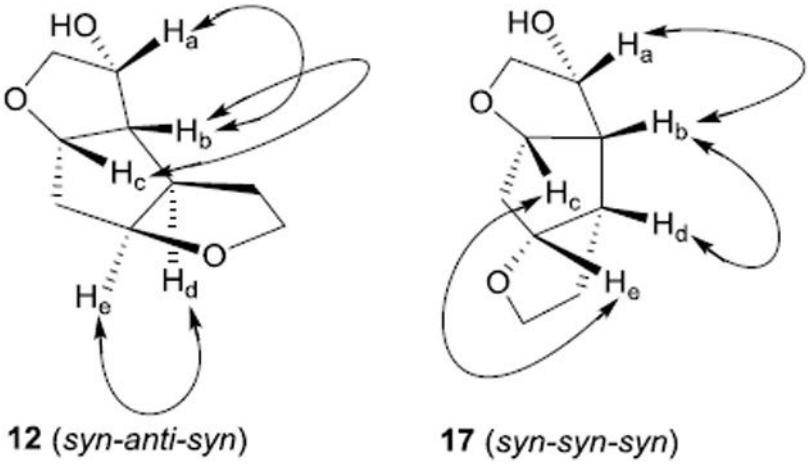
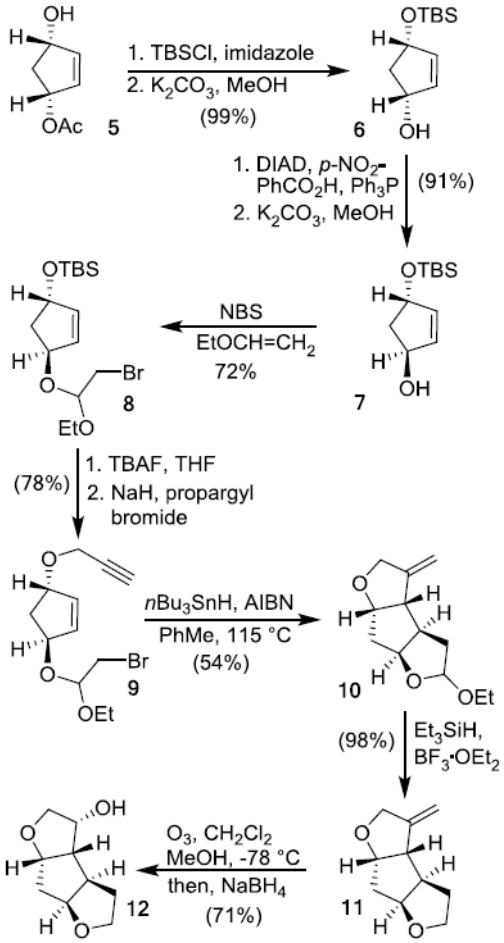
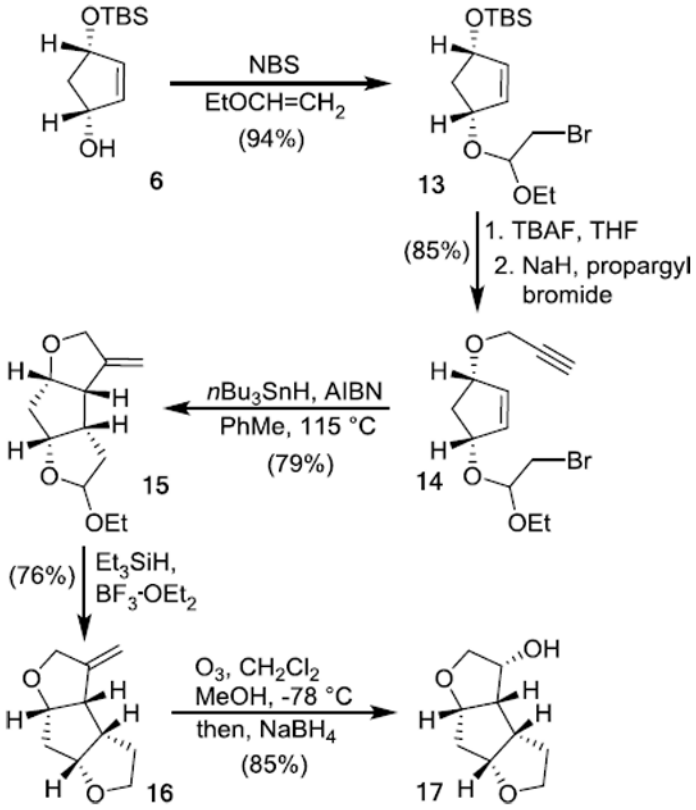


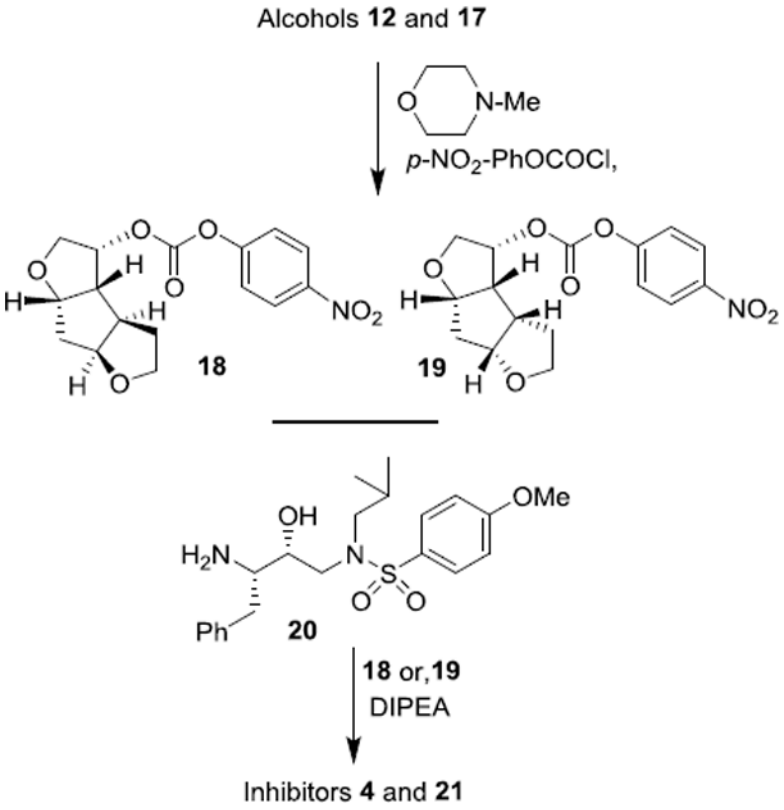
Figure 2. ^{1}H NOESY analysis of alcohols 12 and 17



Scheme 1. Synthesis of *syn-anti-syn*-fused dioxatriquinane ring system



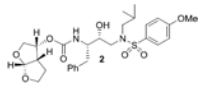
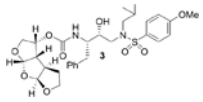
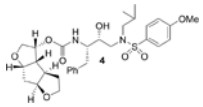
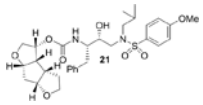
Scheme 2. Synthesis of *syn-syn-syn*-fused ring system



Scheme 3. Synthesis of inhibitors 4 and 21

Table 1

HIV-1 Protease Inhibitory Activity of compounds

Entry	Inhibitor	K_i (nM)
1		0.014
2		0.006
3		1.39
4		1.43

(Darunavir displayed K_i = 0.016 nM in this assay)