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

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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

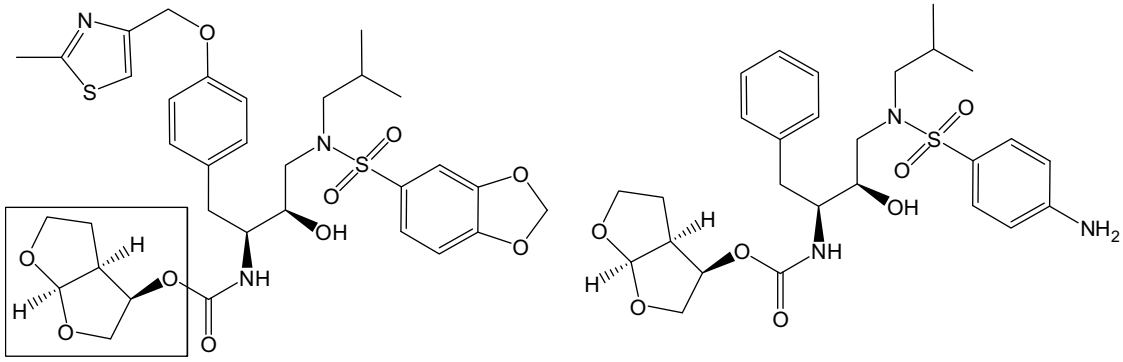

Figure 1. Structures of protease inhibitors Brecanavir and Darunavir with the bis-THF moiety.

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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-

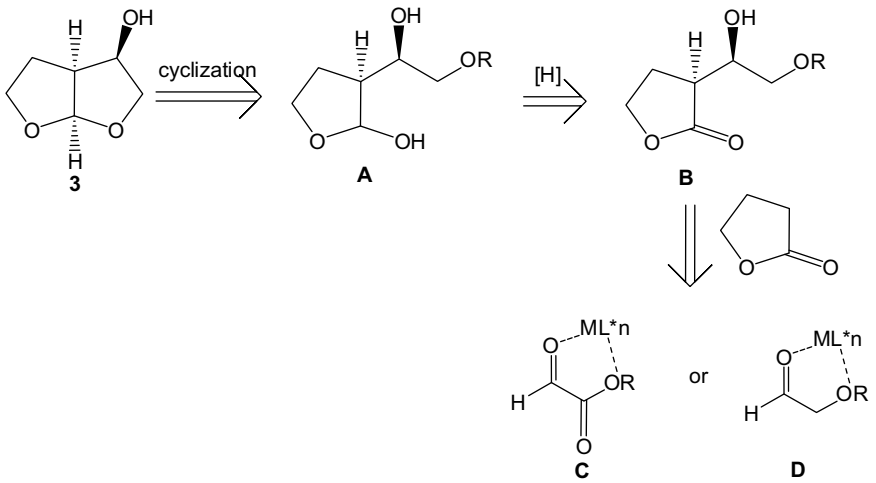
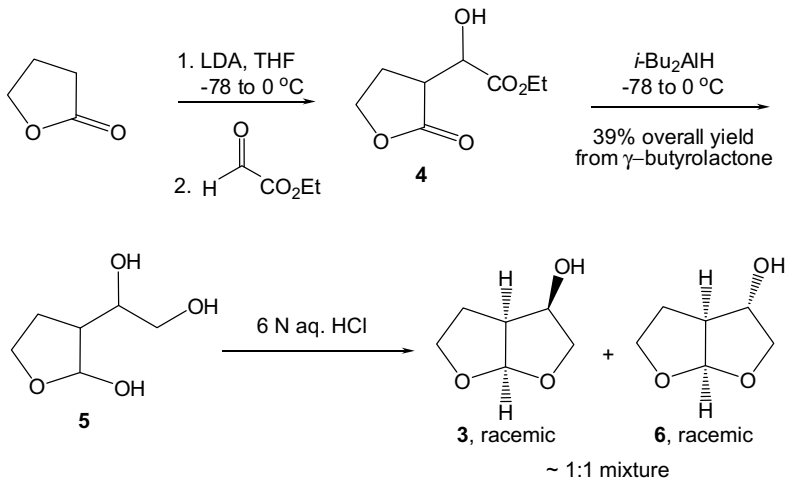


Figure 2. Strategy for asymmetric synthesis of bis-tetrahydrofuran alcohol **3**.



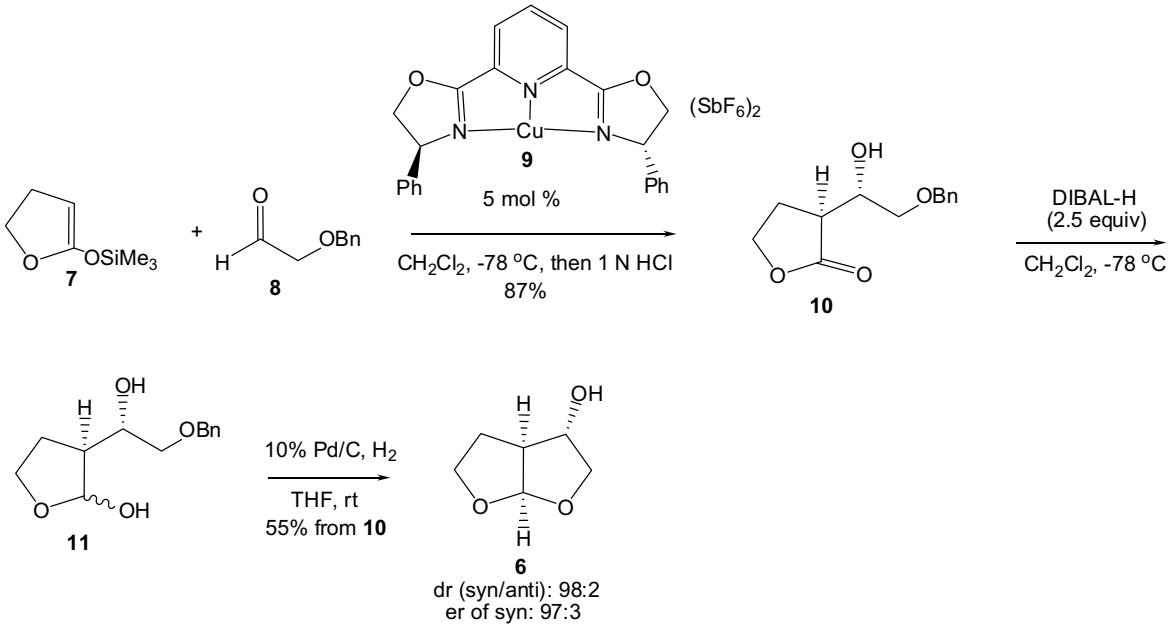
Scheme 1.

ing (benzyloxy)acetaldehyde.[7] Furthermore, the silylketene acetal derived from γ-butyrolactone was among many of the more successful reported examples.[7a,b] Following the Evans protocol on the aldol reactions, we carried out the synthetic sequence as shown in Scheme 2.

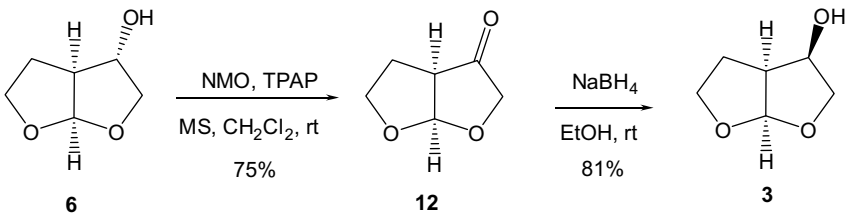
Trimethylsilyl (TMS) ketene acetal **7** was prepared from γ-butyrolactone, LDA, and trimethylsilyl chloride.[5a] The Mukaiyama aldol reaction of **7** and (benzyloxy)acetaldehyde **8** was carried out as reported by Evans et al.[7a] Catalysis by 5 mol % of the chiral catalyst [Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$ **9** gave a TMS intermediate which, upon hydrolysis with 1 M HCl, provided 87% yield of the alcohol **10** as shown in Scheme 2.

Interestingly, high diastereoselectivity (*syn*/*anti*) and enantioselectivity of **6** (vide infra) were observed although only one half of the catalyst loading[7b] was employed. The *anti*-orientation of the OTMS to the alkyl group on the silylketene acetal double bond of **7** was considered to be the key for the excellent control at both stereogenic centers. As expected, the *syn*-selective Mukaiyama aldol reaction of the butyrolactone silylketene acetal **7** placed the hydroxy group of **10** on the α-side, which had to be inverted.

The timing of the inversion of the carbinol stereocenter was important and we chose to invert the stereocenter after the ring closure to have better stereocontrol with the bicyclic structure. Thus lactone **10** was reduced to lactol **11** with DIBAL-H.[8] The configuration of the hemiacetal stereocenter was not assigned. The lactol intermediate **11** was found to be quite water soluble. As a result, the crude lactol from the non-aqueous workup with MeOH–NH_4Cl was used directly for the next step. Atmospheric hydrogenolysis with catalytic 10% Pd on charcoal in THF revealed the primary alcohol, which cyclized instantaneously to provide bis-THF alcohol **6**, the α-epimer of the target **3**, as a crystalline solid in 55% overall yield. Analysis of crude **6** by chiral GC, with racemic **6** and **3** as references, showed a diastereomeric ratio of 98:2 (**6**/**3**) and an enantiomeric ratio of 97:3 for **6**.[9] Interestingly, the enantiomeric ratio for **3** was only 54:46. This indicated very low enantioselectivity for the minor anti-aldol product from the Mukaiyama



Scheme 2.



Scheme 3.

reaction. Evans did not report the enantiomeric ratio of the anti aldol product.[7a,b]

Oxidation of alcohol **6** to ketone **12** was readily accomplished in 75% yield with 4-methylmorpholine N-oxide (NMO) in the presence of catalytic amount of tetrapropylammonium perruthenate (TPAP).[10] Reduction with $NaBH_4$ provided bis-tetrahydrofuran alcohol **3** in 81% yield. The exclusive reduction of the bicyclic ketone to the β-hydroxy isomer was utilized by Ghosh in his synthesis of **3** via a chiral pool approach.[4c] The high selectivity was a result of the delivery of the hydride from the more exposed convex side of the bicyclic structure of **12**, giving rise to the desired β-alcohol **3** (Scheme 3).

The analytical data including NMR spectra and specific rotation matched those reported by other groups[4b,c] as well as us from a previous synthesis via glycolaldehyde and 2,3-dihydrofuran.[4k]

Overall, the synthesis including the inversion of the stereocenter is five steps from the catalyzed Mukaiyama reaction. While the synthesis is shorter than many reported syntheses starting from the chiral pool materials or racemic syntheses followed by resolution,[4] it is longer than our recently reported two-step formal synthesis of **3** based on a highly diastereoselective addition of glycolaldehyde to 2,3-dihydrofuran[4k] followed by a reported one-step enzymatic enhancement.[4d,j] However, in light of the high selectivities achieved via the Evans chemistry, the overall efficiency of the synthesis is noteworthy.

3. Conclusion

A highly diastereo- (98:2) and enantioselective (97:3) synthesis of the bis-THF alcohol (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol, which is an important structural moiety in several protease inhibitors, has been achieved through application of the Evans Mukaiyama aldol reaction. The OH epimer of the bis-THF alcohol was prepared in three steps including the aldol reaction. Highly selective inversion of the alcohol stereocenter, taking advantage of the bicyclic structure, provided the target bis-THF alcohol efficiently. To our knowledge, this represents the first reported example of substoichiometric catalysis to obtain both excellent diastereo- and enantioselectivities in the synthesis of this important compound.

4. Experimental

4.1. General

The melting points were determined by a SRS OptiMelt automated melting point system, and are uncorrected. All reactions were run with magnetic stirring and under nitrogen. Concentration by rotary evaporation or distillation was carried out under house vacuum of 12–20 torr. ^{1}H NMR spectra were recorded in a Varian 400 MHz spectrometer, and ^{13}C was recorded at 75 MHz. TLC monitoring was performed on silica gel plates 60 F_{254}, 2.5 × 7.5 cm. Chiral GC analysis was conducted on a Hewlett Packard HP 5890 GC under conditions as described in Ref. 9. Optical rotation was measured with a Perkin Elmer 241 Polarimeter with a 10 cm cell at the wavelength of sodium line D (λ = 589 nm).

4.2. Preparation of (3*S*)-3-[(1S)-2-(benzyloxy)-1-hydroxyethyl]-dihydrofuran-2(3*H*)-one

4.2.1. (4,5-Dihydro-2-furanyloxy)(trimethyl)silane 7[5a]

To a solution of 12.2 g (120 mmol) of *N*,*N*-diisopropylamine in 110 mL of THF were added 44.0 mL (110 mmol) of 2.5 M *n*-BuLi in hexanes with ice cooling. The mixture was stirred for 15 min, cooled to −78 °C and treated over 3.5 min with a solution of 8.60 g (100 mmol) of γ-butyrolactone and 13.0 g (120 mmol) of trimethylsilyl chloride (TMSCl) in 70 mL of THF. The mixture was warmed to ambient temperature and stirred for 2.5 h. The mixture was evaporated to remove most of the THF, diluted with 35 mL of hexanes and filtered through a short pad of Celite 545 to remove the off-white solids. The filtrate was concentrated to an oil. A short path distillation at 100–110 °C (17–45 torr) afforded 12.9 g (82%) of the TMS ketene acetal **7** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.26 (s, 9H), 2.65 (dt, J = 2.1, 9.0 Hz, 2H), 3.70 (t, J = 2.1 Hz, 1 H), 4.31 (t, J = 9.0 Hz, 2H).

4.2.2. [Cu((*S*,*S*)-Phenyl-bis(oxazolinyl)pyridine)](SbF$_6$)$_2$ 9[7a]

To a suspension of 91 mg (0.68 mmol) of anhydrous $CuCl_2$ in 55 mL of CH_2Cl_2 was added 250 mg (0.68 mmol) of (*S*,*S*)-bis(phenyloxazolinyl)pyridine in one portion at ambient temperature. The mixture was stirred in the absence of light for 2 h, followed by addition of 465 mg (1.35 mmol) of $AgSbF_6$ in one portion. After being stirred for 2 h, the mixture was filtered through a plug of densely packed cotton in a frit funnel to give a dark green solution. This solution was stored in the refrigerator and used as 0.0125 M solution of catalyst **9** in CH_2Cl_2 without further purification and analysis.

4.2.2.1. (3*S*)-3-[(1*S*)-2-(Benzyloxy)-1-hydroxyethyl]dihydro-furan-2(3*H*)-one 10.[7b] To 2.0 mL (0.025 mmol in CH_2Cl_2) of catalyst **9** were added 70 μL (0.49 mmol) of (benzyloxy)acetaldehyde **8** and 94 mg (0.59 mmol) of the silylketene acetal 7 at −78 °C. The mixture was stirred for 1 h and TLC showed no aldehyde left (R_f 0.36, 30% EtOAc in hexanes). The reaction mixture was gradually warmed to ambient temperature and filtered through a 1.5 × 2.0 cm plug of silica gel. The silica gel plug was eluted with 20 mL of *t*-butyl methyl ether (MTBE). The combined filtrate and eluent were then concentrated. The resultant oil (300 mg) was dissolved in THF, treated with 1.5 mL 1 N aqueous HCl and stirred for 15 min at ambient temperature. The mixture was diluted with 5 mL of water and extracted with 15 mL of MTBE. The organic layer was washed successively with saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to give 205 mg of thick oil. Chromatography on silica gel (50% EtOAc in hexanes) provided 101 mg (87%) of lactone alcohol **10** as a thick oil: $[\alpha]_D^{25} = -8.0$ (*c* 2.61, CH_2Cl_2), lit.[7b] $[\alpha]_D^{rt} = -8.3$ (*c* 4.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 2.25(dddd, J = 3.2, 7.2, 9.4, 12.6 Hz, 1H), 2.40 (dq, J = 12.6, 9.3 Hz, 1H), 2.55 (d, J = 3.2 Hz, 1H), 2.77 (dt, J = 3.7, 9.6 Hz, 1H), 3.59

(m, 2H), 4.22 (dt, J = 7.2, 9.1 Hz, 1H), 4.40 (m, J = 3.2, 2H), 4.59 (s, 2H), 7.36 (m, 5H).

4.3. (3*S*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol 6

To a solution of 50 mg (0.21 mmol) of lactone **10** in 1.5 mL of CH_2Cl_2 was added 0.53 mL (0.53 mmol) of DIBAL-H (1 M in hexanes) at −78 °C over 3 min. The mixture was stirred for 30 min after which TLC showed no lactone left (R_f 0.37, 50% EtOAc in hexanes). The reaction was treated with 0.5 mL of methanol and gradually warmed to ambient temperature. After the addition of 100 mg of NH_4Cl, the mixture was stirred for 30 min. The resultant slurry was filtered through a short plug of Celite 545 and the filter cake was washed thoroughly with about 20 mL of CH_2Cl_2. The combined filtrates were concentrated to 60 mg of crude lactol **11** as a white solid. The solid was dissolved in 10 mL of THF, treated with 45 mg of 10 wt % Pd on charcoal in a round bottomed flask. Following the application of a vacuum of about 50 torr to the flask, a hydrogen balloon was inserted via the septum. The reaction was stirred at ambient temperature for 30 min and TLC (R_f 0.26, 100% EtOAc) showed no lactol **11** left. The reaction mixture was filtered through a short plug of Celite 545 and the filter cake was washed with 10 mL of THF. Evaporation provided 15.1 mg (55% from lactone **10**) of bis-THF alcohol **6** as a crystalline solid. A sample of the solid was dissolved in MeCN/MTBE for analysis by chiral GC, along with the reference samples of racemic **6** and **3**. The analysis showed the ratio of 69.42 :2.32:0.94:0.81 for the four compounds **6**, *ent*-**6**, **3,** and *ent*-**3**, at 9.2, 8.9, 7.8, and 7.5 min. This corresponds to a diastereomeric ratio of 98:2 (**6** and *ent*-**6** to **3** and *ent*-**3,** or *syn*/*anti*) and enantiomeric ratios of 97:3 and 54:46 for the *syn*- and *anti*-diastereomers, respectively. Compound **6**: mp 67 °C. $[\alpha]_D^{25}$ = −29.6 (*c* 1.40, $CHCl_3$), lit.[4c] $[\alpha]_D^{23} = -25.1$ (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.73 (m, 1H), 1.86 (br s, 1H), 2.20 (m, 1H), 2.83 (m, 1H), 3.87 (m, 3H), 4.01 (m, 1H), 4.24 (bs, 1H), 5.90 (d, J = 4.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 29.0, 52.3, 68.1, 75.4, 78.1, 109.1. HRMS calcd for $C_6H_{11}O_3$ (MH^+): 131.0703, found: 131.0698.

4.4. (3a*R*,6a*R*)-Tetrahydrofuro[2,3-*b*]furan-3(2H)-one 12

To a solution of 12 mg (0.09 mmol) of alcohol **6** in 2 mL of CH_2Cl_2 were added 3 mg (0.01 mmol) of tetrapropylammonium perruthenate (TPAP), 16 mg (0.14 mmol) of 4-methylmorpholine N-oxide (NMO), and 200 mg of 4 Å molecular sieves with ice cooling. The mixture was warmed to ambient temperature and stirred for 2 h. TLC showed no alcohol **6** left (R_f 0.55%, 50% EtOAc in hexanes). The reaction mixture was filtered through a short plug of silica gel. Elution with 50% EtOAc in hexanes afforded 8.9 mg (75%) of ketone **12** as a white solid: $[\alpha]_D^{25} = -151.9$ (*c* 0.89, $CHCl_3$), lit.[4c] $[\alpha]_D^{23} = -126.6$ (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.25 (m, 2H), 3.00 (dd, J = 6.8, 6.8 Hz, 1H), 3.82 (m, 1H), 4.06 (m, 1H), 4.17 (s, 2H), 6.08 (d, J = 6.0 Hz, 1H).

4.5. (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol 3

To a solution of 8.9 mg (0.07 mmol) of ketone **12** in 1.5 mL of absolute ethanol was added 4 mg (0.10 mmol) of sodium borohydride at −15 °C. The reaction was gradually warmed to ambient temperature over 3 h. The reaction was treated with saturated brine and diluted with 20 mL of EtOAc. The EtOAc layer was concentrated partially and filtered through a short plug of silica gel. Elution with 80–100% EtOAc in hexanes afforded 7.31 mg (81%) of target bis-THF alcohol **3** as an oil: $[\alpha]_D^{22} = -11.6$ (*c* 0.73, MeOH), lit.[4c] $[\alpha]_D^{23} = -12.4$ (*c* 1.3, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.89 (m, 1H), 2.04 (d, J = 6 Hz, 1H), 2.31 (m, 1H), 2.87 (m, 1H), 3.65 (dd, J = 7.1, 9.2 Hz, 1H), 3.89 (m, 1H), 3.99 (m, 2H), 4.46 (m, 1H), 5.70 (d, J = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 24.9, 46.5, 69.9, 70.6, 73.0, 109.5. HRMS calcd for $C_6H_{11}O_3$ (MH^+): 131.0703, found: 131.0697.

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