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Asymmetric One-Pot Synthesis of (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol: A Key Component of Current HIV Protease Inhibitors

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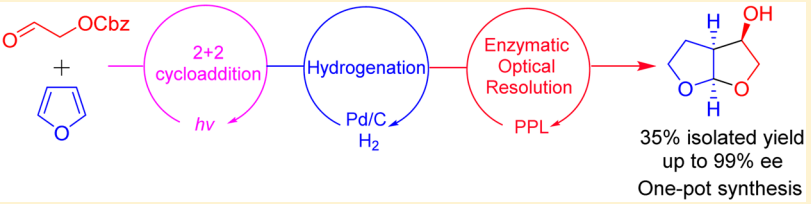
Supporting Information



ABSTRACT: A concise and efficient synthesis of (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol, a key building block for several clinical and experimental HIV protease inhibitors including the highly important drug darunavir, was achieved via a one-pot procedure using furan and Cbz-protected glycol aldehyde as starting materials. A [2+2]-photocycloaddition between both reactants which can be prepared from wood-based starting materials according to the principles of xylochemistry, followed by hydrogenation and lipase-catalyzed kinetic resolution afforded the target compound in high yield and up to 99% *ee*.

Acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV), is a degenerative disease of the immune system and has become a pressing medical concern globally.[1] Currently, highly active antiretroviral therapy (HAART), a therapy combining protease inhibitors (PIs) and reverse transcriptase inhibitors, is proven to be an effective treatment against AIDS.[2] To this end, continuous efforts have been devoted to develop both new and existing classes of HIV PIs due to resistance.[3] Darunavir (**1**, Figure 1),[4] brecanavir (**2**),[5] GS-8374 (**3**),[6] and SPI-256 (**4**)[7] are novel HIV PIs and have shown high efficacy in treatment of multidrug-resistant HIV. A common structural feature of these compounds is the (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol (bis-THF alcohol) moiety. The significance of bis-THF alcohol derivatives for combating drug-resistance is well documented.[8] It was shown that both oxygens of the bis-THF ligand effectively form hydrogen bonds to the NH of Asp 30 and Asp 29 located in the S_2 binding domain of HIV-1 protease.[9] It turned out that ring size, position of the oxygens and stereochemistry of the bis-THF ligand are crucial.[10]

Various methods are available for the construction of the bis-THF alcohol structure owing to its importance in drug discovery.[11] One representative strategy, first reported by Ghosh and co-workers,[9] used the ex-chiral pool approach which was also employed in later syntheses based on D-diethyl malate,[10] D-glucal,[12] and D-glyceraldehyde derivatives.[13] Another approach involves the synthesis of racemic bis-THF alcohol followed by enzymatic optical resolution.[14] Futher approaches included the use of (1*S*,2*R*)-1-tosylamido-2-indanol as a chiral auxiliary,[8] asymmetric direct cross-aldol reaction of 4-(benzyloxy)butanal with benzyloxyacetaldehyde or ethyl

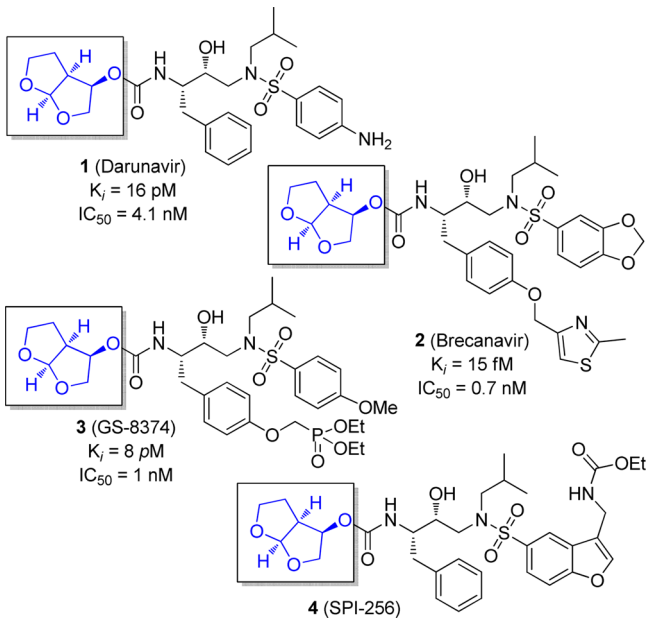


Figure 1. Structures of HIV-protease inhibitors **1**−**4**.

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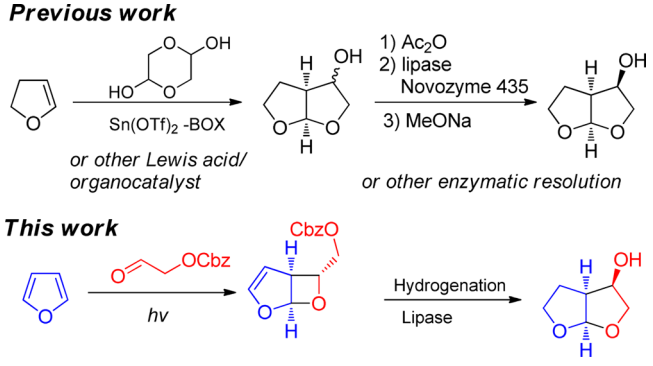
glyoxylate,[15] and Evans–Mukaiyama aldol reaction of benzyloxyacetaldehyde with a silyl ketene acetal[16] as well as asymmetric oxyselenenylation of 2,3-dihydrofuran.[17]

In addition, one-pot procedures were also reported as efficient methods for the production of bis-THF alcohol.[18] Xie and co-workers have reported a synthesis using the asymmetric Lewis acid-catalyzed reaction of 2,3-dihydrofuran with glycolaldehyde dimer (Scheme 1).[18b] The formal cycloaddition was

Scheme 1. Strategies for the Synthesis of Bis-THF Alcohol



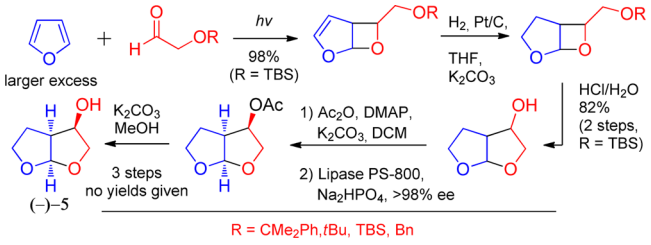
catalyzed by $Sn(OTf)_2$ and Evans's BOX ligands in hexafluoroisopropanol at 0 °C and provided bis-THF alcohol in a 98:2 diastereomeric ratio. A similar route was also described by Yu and co-workers using $Yb(fod)_3$ as the Lewis acid.[18a] This process, however, required an oxidation (TEMPO, NaOCl) followed by $NaBH_4$ reduction, acetylation, and lipase resolution (PS-C "Amano I") to afford the bis-THF alcohol in 97–98% *ee* and yields of 28–35%. Both routes make use of chiral BOX ligands to control the absolute stereochemistry of the aldol reaction but suffered from low enantioselectivity so that an additional enzymatic resolution step was required to obtain the target alcohol in sufficient optical purity. Recently, Itoh and co-workers reported a condensation of 2,3-dihydrofuran with glycol aldehyde using Schreiner's thiourea catalyst.[18c] Again, an enzymatic resolution was included to improve the enantioselectivity.

These syntheses, however, suffer to various extents from limitations, such as multiple steps, utilization of expensive metal catalysts and/or starting materials, or low diastereo- or enantioselectivity, requiring additional operations to achieve acceptable values. Therefore, there is still a need for a high-yielding and scalable process to the optically pure form of the bis-THF alcohol. Herein, we report an efficient one-pot access to this compound involving photocycloaddition combined with hydrogenation as well as enzymatic optical resolution (Scheme 1).

Doan and co-workers reported a novel strategy in a patented synthesis of (−)-**5** (Scheme 2).[19] They used the photocycloaddition of several protected glycol aldehydes to furan to obtain the protected oxetane acetal. Hydrogenation followed by acid-catalyzed deprotection resulted in a racemic mixture of bis-THF alcohol. Acetylation, followed by resolution through lipase PS-800 resulted in the formation of the bis-THF acetate, which was subsequently treated with potassium carbonate to afford the desired product (−)-**5** in 98% *ee* (no yield reported).

In comparison to Doan's route we focused on maximizing cost-efficiency and environmental sustainability by using inexpensive, readily available and sustainable starting materials, avoiding chlorinated solvents and minimizing waste and

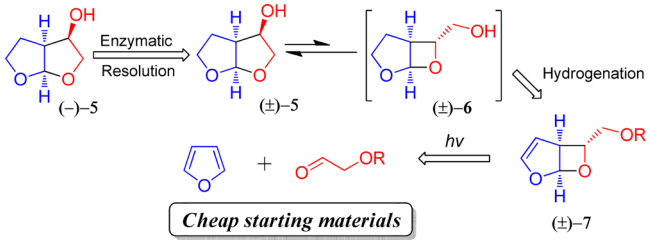
Scheme 2. Doan's Route to Bis-THF Alcohol (−)-5



purification steps. To fulfill these criteria, we optimized each step and assembled them into a one-pot procedure.

The photochemical [2+2] cycloaddition of aldehydes and ketones to furan is well-known and has been used by Schreiber et al. as a key step to furnish the core of Asteltoxin.[20] Inspired by this seminal work, we envisioned that the target molecule (−)-**5** could be accessible via enzymatic resolution of (±)-**5** which could be constructed from oxetane **7** through hydrogenation and rearrangement (Scheme 3). Ideally, reduction of

Scheme 3. Strategy for Synthesis of Bis-THF Alcohol



the C=C double bond and removal of the protecting group of compound **7** could be achieved in a single operation giving intermediate **6** which would undergo subsequent rearrangement under thermodynamic control to give (±)-**5**. Oxetane (±)-**7** could be easily prepared from furan and a protected glycol aldehyde by the [2+2] photocycloaddition, the latter being accessible from inexpensive ethylene glycol. Ideally, the enzymatic resolution could be combined with the hydrogenation as well as the photocycloaddition into an even simpler three-step one-pot procedure.

To test the feasibility of this strategy, Cbz-protected glycol aldehyde **9** was used to optimize reaction conditions. The carbobenzoxy group was chosen for *O*-protection due to its ease of introduction, the removal under the conditions of double bond hydrogenation as well as its economics. While the *O*-benzyl group should have the same characteristics, its use is prohibited by an efficient Norrish-type II reaction upon irradiation leading to scission of the C–O bond. The intermolecular [2+2] cycloaddition of aldehyde **9** proceeds readily, giving the *exo* product in almost quantitative yield in furan without formation of the *endo* isomer (Table 1, entry 1). While Doan et al. used furan as a solvent in their protocol, we aimed at reducing the required amount of this component. First, the effect of changing the solvent in the reaction was investigated. As shown in Table 1, the cycloaddition proceeds efficiently in polar solvents (entries 2–3 vs 4). MTBE was finally chosen as the solvent for further studies due to its good performance as well as its availability and low toxicity. Additionally, widespread experience with MTBE in industrial processes and in lipase catalyzed biotransformations exists.[21] To further improve the reaction, the furan/aldehyde ratio was

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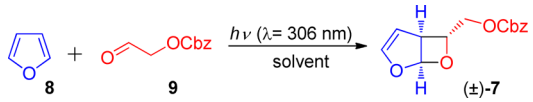
Table 1. Optimization of the Reaction Conditions[a]



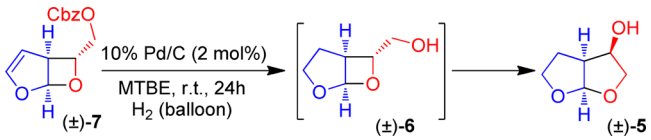
entry	solvent	ratio **8**:**9**	time (h)	conv (%)[b]
1	Furan		20	> 99 (93)
2	MTBE	1:1	24	90
3	CH_2Cl_2	1:1	24	90
4	Hexane	1:1	24	21
5	MTBE	2:1	24	92
6	MTBE	5:1	20	> 99 (93)

[a]All reactions were performed in 1 mmol scale and 5 mL of degassed solvent under UV irradiation (λ_{max}= 306 nm). [b]Conversion of **9** as determined by ^{1}H NMR spectroscopy, isolated yield of (±)-7 in brackets.

optimized. When the reactions were carried out with 2 equiv of furan, the product was obtained in slightly higher yield compared to an equimolar ratio (cf. entry 5 vs 2−4). A further increase in the amount of furan to a 5:1 ratio led to complete conversion of **9**, and desired product **7** could be obtained in 93% isolated yield (entry 6). It is noteworthy that the purity of aldehyde **9** is crucial for the current [2+2] photocycloaddition. When crude aldehyde **9** was used, only trace amounts of the cycloaddition product (±)-**7** were detected under various conditions. The low molar extinction coefficient of aliphatic aldehydes in the $n \rightarrow \pi^*$-absorption band around 300 nm probably accounts for this behavior as even small quantities of UV-absorbing contaminants can prevent excitation.[22] After purification of aldehyde **9** by vacuum distillation, no problems were encountered.

Having established optimal conditions for the photocycloaddition, the hydrogenation step was examined next. After extensive screening, the optimized reaction condition was obtained as follows (Table 2): 10% Pd/C (2 mol%) and (±)-7

Table 2. Hydrogenation of the Photocycloaddition Product[a]



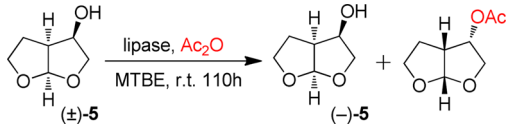
entry	reaction condition	yield of **5** (%)[b]
1	see equation	90
2	solvent MeOH	84
3	solvent THF	27
4	1 equiv. K_2CO_3	67
5	solvent MeOH, 1 equiv. K_2CO_3	82

[a]All reactions were run at 1 mmol scale. [b]Yields of isolated product.

in MTBE under hydrogen (ambient pressure) at room temperature. Reduction of the C=C double bond and O-deprotection could be realized via hydrogenation, providing the desired product racemic bis-THF aclohol (±)-**5** in 90% isolated yield (Table 2, entry 1). Screening of solvents revealed that MTBE was optimal for the hydrogenation. MeOH and THF were also suitable for the reaction, but the yields were generally lower (entries 2−3). Oxetane (±)-**6** was observed as a discrete intermediate by ^{1}H NMR spectroscopy when the reaction was performed in the presence of a base like K_2CO_3 (entries 4−5). This intermediate was however unstable and rearranged readily during purification by column chromatography or upon storage to form the thermodynamically more stable bis-THF alcohol (±)-**5**.[23]

With racemic bis-THF alcohol in hand, the enzymatic optical resolution was optimized. To avoid the acylation of (±)-**5** as an additional step, the enzyme should be used for an enantioselective acylation of one enantiomer rather than a hydrolysis of the racemic ester.[19] First, the catalytic activity of different enzymes was examined (Table 3). As shown in Table

Table 3. Screening of Different Lipases[a]



#	lipase	conv.[b]	*ee* (−)-**5** (%)[c]	*ee* acetate (%)[c]	s factor[d]
1	*CAL-A*	> 99			
2	*CAL-B*	70	97	47	10
3	*RML*	58	17	< 1	1
4	*TLL*	46	57	60	7
5	*PFL*	76	61	25	3
6	*PPL*	53	97	95	165
7	*PCL*	51	97	96	> 200

[a]All the reactions were run at 1 mmol scale, 50% w/w lipase. [b]Conversion of (±)-**5** as determined by ^{1}H NMR. [c]ee determined by chiral GC. [d]Stereoselectivity factor.

3, *Candida antarctica* lipase A (CAL-A) failed to give optically pure bis-THF alcohol due to complete acetylation of (±)-**5** (Table 3, entry 1). *Candida antarctica* lipase B (CAL-B) provided the target compound with excellent enantiomeric excess, but the reaction needs to be monitored carefully to prevent overacetylation of the desired enantiomer of the alcohol (entry 2). *Rhizomucor miehei* lipase (RML), *Thermomyces lanuginosa* lipase (TLL), and *Pseudomonas fluorescens* lipase (PFL) were able to produce enantioenriched alcohol **5**, but low stereoselectivites were observed (entries 3−5). The optical resolution using porcine pancreatic lipase (PPL) and *Pseudomonas cepacia* lipase (PCL) was very efficient, giving (−)-**5** with 97% *ee* (entries 6−7). For both enzymes, the difference in the reaction rates of both enantiomers is so large that the reaction ceases automatically at 50% conversion of the substrate.

Encouraged by these preliminary results, reactions with different acylating agents were then carried out to find suitable conditions using the inexpensive PPL (Table 4). Isopropenyl acetate as the acyl donor failed to give satisfactory conversion even at long reaction times. This may be attributed to the steric hindrance of the acetylating agent (Table 4, entry 1). The use of vinyl acetate or acetic anhydride offered good enantioselectivities instead, but long reaction times were still needed to obtain satisfactory conversions (entries 2−3). Longer-chain (propionyl, butyryl) acyl residues were transferred more efficiently and with higher enantioselectivity by PPL (entries 4−5). (*S*)-Bis-THF alcohol (−)-**5** could be propionylated completely, resulting in >99% ee of the (*R*)-bis-THF alcohol when reduced amounts of PPL and propionic anhydride were used (entry 6). In addition, implementing the enzymatic resolution and hydrogenation starting from compound (±)-7 into the one-pot procedure had little impact on the course of

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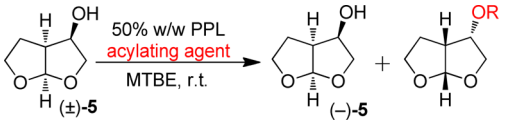
Table 4. Screening of Acylating Agents[a]



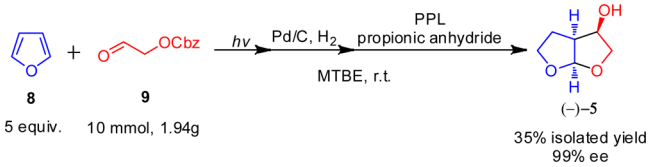
#	reagent (equiv)	time (h)	covn. (%)[b]	*ee* of (−)-**5** (%)[c]
1	IPA (3.0)	160	5	
2	VA (3.0)	95	50	96
3	Ac_2O (3.0)	64	50	93
4	$(n\mathrm{PrCO})_2O$ (3.0)	24	52	95
5	$(\mathrm{EtCO})_2O$ (3.0)	24	52	97
6[d]	$(\mathrm{EtCO})_2O$ (1.0)	48	51(43)[e]	99
7[d,f]	$(\mathrm{EtCO})_2O$ (1.0)	48	51	> 99

[a]All reactions were run at 1 mmol scale. [b]Based on ^{1}H NMR analysis of the crude reaction mixtures. [c]ee was determined by chiral GC. [d]10% w/w PPL was used. [e]Isolated yield of (−)-**5**. [f]One-pot process with hydrogenation step starting from (±)-**7**. IPA: Isopropenyl acetate, VA: vinyl acetate.

the reaction (entry 7). The use of butyric anhydride was not further pursued due to the unpleasant odor (entry 5).

The success of above reactions prompted us to develop a larger scale one-pot procedure to prove the scalability of the current protocol, in which involved photocycloaddition of furan and Cbz-protected glycol aldehyde, hydrogenation as well as enzyme-catalyzed kinetic resolution (Scheme 4). Cbz-protected

Scheme 4. Gram-Scale One-Pot Synthesis of Enantiopure Bis-THF Alcohol (−)-5



glycol aldehyde **7** (10.0 mmol, 1.94 g) and furan in MTBE were allowed to react in the Rayonet photochemical reactor for 36 h. Excess furan was removed in vacuo and the residue remaining in the vessel was redissolved in MTBE and treated with Pd/C and H_2 (balloon), followed by the addition of PPL and propionic anhydride. The enzymatic optical resolution process was carried out at room temperature for 72 h. The resulting mixture was filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography to give (−)-**5** in 35% overall yield and 99% *ee*. For better recycling of the hydrogenation catalyst, an additional filtration step can be inserted prior to addition of the enzyme. Therefore, the current one-pot procedure is potentially interesting for industrial application. In addition, as furan, ethylene glycol and toluene (required to produce Cbz-Cl) can be prepared from woody biomass,[24] the present route fulfills key criteria of xylochemistry.[25]

In summary, a one-pot procedure for the preparation of (−)-bis-THF alcohol **5** was developed. The process involved a [2+2] photocycloaddition of furan and a protected glycol aldehyde as a key step in which all three stereogenic centers were created in the correct relative configuration and complete diastereoselectivity. In the subsequent hydrogenation, the C=C double bond and the carbobenzoxy group could be removed simultaneously, giving a labile oxetane acetal which directly rearranged to the desired product. Addition of PPL and propionic anhydride to the resulting reaction mixture produced the desired enantiopure bis-THF alcohol. This current protocol is highly practical due to (1) mild conditions and easy-to-operate one-pot features, (2) inexpensive and readily available reagents, and is (3) environmentally friendly and should be amenable to production on a larger scale. It represents the shortest and simplest route to this important intermediate reported so far.

EXPERIMENTAL SECTION

General Information. All reagents were obtained from commercial suppliers and used without further purification unless stated otherwise. Except for PPL, all enzymes were immobilized on polymeric beads to increase their stability. Anhydrous dichloromethane was distilled from calcium hydride. Anhydrous ethyl acetate was dried over molecular sieves. Anhydrous furan, MTBE, and THF were distilled from sodium and benzophenone under nitrogen. Solvents used for photocycloaddition reactions were degassed by argon sparging (30 min). Reactions requiring anhydrous conditions were performed in dried glassware under an atmosphere of argon or nitrogen. Photochemical reactions were performed in quartz glassware using a photochemical reactor equipped with a Rayonet-type circular array of 16 UV lamps (λ_{max} = 306 nm, 7.2 W each), a magnetic stirrer and a cooling fan. Flash chromatography was performed on silica gel (35−70 μm) using the specified eluent mixtures given as a volumetric ratio of components. NMR spectra were recorded with a 300 MHz spectrometer (300 MHz ^{1}H and 75 MHz ^{13}C) or with a 400 MHz spectrometer (400 MHz ^{1}H and 100 MHz ^{13}C). All ^{13}C NMR spectra were broadband ^{1}H-decoupled. The chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) and were referenced to the residual solvent signal (e.g., for $CDCl_3$: δ = 7.26 ppm for ^{1}H and δ = 77.16 ppm for ^{13}C NMR spectra). Coupling constants (J) are given in Hertz (Hz) using the conventional abbreviations (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and combinations thereof). ESI-HRMS was performed on a Q-TOF instrument with a dual source and a suitable external calibrant. Thin-layer chromatography (TLC) was carried out on 0.25 mm silica gel plates with a fluorescence indicator. Chiral GC-MS analysis was carried out on using an Astec Chiraldex β-cyclodextrin trifluoroacetyl (BTA) capillary column (20 m × 0.25 mm × 0.12 μm) and EI ionization (70 eV). The following parameters were used: flow rate of the carrier gas (helium) 1.0 mL/min, inlet temperature 50 °C, transfer line temperature 180 °C, ion source temperature 200 °C and an initial oven temperature of 90 °C for 3 min with a temperature ramp of 3 °C/min to 140 °C followed by 5 min hold and a cool-down of 15 °C/min back to 90 °C followed by 2 min hold. (3*R*,3a*S*,6a*R*)-bis-THF alcohol: t_R = 21.5 min, (3*S*,3a*R*,6a*S*)-bis-THF alcohol: t_R = 21.2 min. The optical rotations were measured at 546 and 578 nm. The data were extrapolated to a wavelength of λ = 589 nm using the Drude equation.[26]

*Benzyl (2-Oxoethyl) Carbonate (**9**).* To a solution of ethylene glycol (12.4 g, 200 mmol) and pyridine (1.74 g, 22 mmol) in dry ethyl acetate, benzyl chloroformate (3.42 g, 20 mmol) was added at 0 °C. The mixture was warmed to room temperature and stirred overnight, the mixture was washed with 1 N HCl, dried, and concentrated to give Cbz-protected glycol, which was used in the subsequent step without further purification.

Method 1. Trichloroisocyanuric acid (4.87 g, 21 mmol) was added to a solution of the Cbz-protected glycol (3.92 g, 20 mmol) in CH_2Cl_2, and the solution was stirred and maintained at 0 °C, followed by addition of TEMPO (31 mg, 0.2 mmol). After the addition, the mixture was warmed to room temperature and stirred for 15 min and then filtered over Celite, and the solvent was evaporated to yield crude aldehyde **9**, which was purified by column chromatography or distillation (105 °C/0.2 mbar) to give pure Cbz-protected glycol aldehyde **9** (2.37g, 61%, 2 steps) as a colorless oil.[27]

Method 2. To a solution of oxalyl chloride (3.05 g, 24 mmol) in CH_2Cl_2 cooled to −78 °C was added dropwise a solution of DMSO (1.72 g, 22 mmol) in CH_2Cl_2. After 5 min, a solution of Cbz-protected

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glycol (3.92 g, 20 mmol) in CH_2Cl_2 was added. The reaction mixture was then stirred for 15 min at −78 °C and triethylamine (12.1 g, 120 mmol) was added in one portion. After 10 min at −78 °C, the mixture was allowed to warm to room temperature and diluted with CH_2Cl_2. The organic layer was successively washed with a saturated aqueous solution of NH_4Cl. The combined organic extracts were dried and concentrated to give crude aldehyde, which was purified by column chromatography or distillation (105 °C/0.2 mbar) to give pure Cbz-protected glycol aldehyde **9** (2.79g, 72%, 2 steps) as a colorless oil.[28]

Method 3. To a solution of glycerol (18.4 g, 200 mmol) and pyridine (1.74 g, 22 mmol) in dry ethyl acetate, benzyl chloroformate (3.42 g, 20 mmol) was added at 0 °C. The mixture was warmed to room temperature and stirred overnight, the mixture was washed with 1 N HCl, dried, and concentrated to give Cbz-protected glycerol, which was used in the subsequent step without further purification.

To a solution of Cbz-protected glycerol (3.92 g, 20 mmol) in methanol, $NaIO_4$ (6.42 g, 30 mmol) was added at 0 °C, and the resulting mixture was stirred at room temperature overnight. The formed precipitate was removed by filtration. Most of the solvent was removed by a rotary evaporator to give an oily residue, which was purified by column chromatography or distilled under reduced pressure (105 °C/0.2 mbar) to give aldehyde **9** (2.60 g, 67%, 2 steps) as a colorless oil.[29]

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm =9.65 (s, 1H), 7.48−7.35 (m, 5H), 5.24 (s, 2H), 4.71 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm =195.4, 154.7, 134.6, 128.8, 128.7, 128.4, 71.2, 70.7. Spectral data are in agreement with literature values.[30]

exo-2,7-Dioxabicyclo[3.2.0]hept-3-en-6-ylmethyl Benzyl Carbonate ((±)-7). Cbz-protected glycol aldehyde **9** (194 mg, 1.00 mmol) and furan **8** (340 mg, 5.00 mmol) in MTBE (5 mL) were mixed in a 10 mL photolysis flask equipped with a magnetic stir bar and placed in the Rayonet-type photochemical reactor. Nitrogen was sparged throughout the duration of the reaction, and the solution was stirred vigorously. TLC analysis indicated completion of the reaction after 20 h. The reaction mixture was concentrated to give a crude residue, which was purified by flash column chromatography (cyclohexane/EtOAc = 5/1) to give (±)-7 as colorless oil (244 mg, 93%). ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.45−7.35 (m, 5H, Ar−H), 6.67−6.63 (m, 1H, H-3), 6.33 (d, J = 4.3 Hz, 1H, H-1), 5.35 (t, J = 2.9 Hz, 1H, H4), 5.22 (s, 2H, −CH_2-Ph), 4.73 (dt, J = 3.5, 1.8 Hz, 1H, H-6), 4.44 (dd, J = 12.0, 3.5 Hz, 1H, CH_aH$_b$), 4.32 (dd, J = 12.0, 3.5 Hz, 1H, CH$_a$H$_b$), 3.72−3.65 (m, 1H, H-5).^{13}C NMR, HSQC, HMBC (100 MHz, $CDCl_3$): δ/ppm =155.1 (C═O), 148.5 (C-3), 135.0 (Ar−C1′), 128.7 (Ar−C3′, Ar−C5′), 128.7 (Ar−C4′), 128.4 (Ar−C2′, Ar−C6′), 107.9 (C-1), 103.6 (C-4), 87.9 (C-6), 70.0 (−CH_2Ph), 68.8 (−CH_2-), 46.6 (C-5). HRMS−ESI (m/z): [M+Na]$^+$ calcd for $C_{14}H_{14}O_5$, 285.0739; found: 285.0742.

anti-Hexahydrofuro[2,3-b]furan-3-ol ((±)-5). The compound (±)-7 (262 mg, 1.00 mmol), 10% Pd/C (21 mg, 0.02 mmol), and MTBE (10 mL) were combined, and the reaction vessel was evacuated and backfilled with hydrogen (balloon). The reaction mixture was stirred under hydrogen for 24 h. The catalyst was filtered off using Celite, and the filtrate was evaporated to give a crude residue which was purified by flash column chromatography (cyclohexane/EtOAc = 1/1) to give (±)-**5** as colorless oil (117 mg, 90%). ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ/ppm =5.66 (d, J = 5.2 Hz, 1H, H-6a), 4.41 (*pseudo*-q, $^3J \approx$ 7.2 Hz, 1H, H-3), 4.02−3.79 (m, 3H, H-2a,5), 3.60 (dd, J = 9.1, 7.2 Hz, 1H, H-2b), 2.84 (dddd, J = 10.1, 7.2, 5.2, 2.6 Hz, 1H, H-3a), 2.49 (s, 1H, O*H*), 2.30 (dd-*pseudo*-t, ^2J = 12.9 Hz, ^3J = 5.8 Hz, $^3J \approx$ 2.6 Hz, 1H, H-4a), 1.85 (d-*pseudo*-td, ^2J = 12.9 Hz, $^3J \approx$ 10.1 Hz, ^3J = 8.4 Hz, 1H, H-4b). ^{13}C NMR, HSQC, HMBC (75 MHz, $CDCl_3$): δ/ppm =109.6 (C-6a), 73.1 (C-2), 70.9 (C-3), 70.0 (C-5), 46.6 (C-3a), 25.0 (C-4). Spectral data are in agreement with literature values.[18c]

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-ol ((−)-5). To a stirred solution of (±)-**5** (130 mg, 1.00 mmol) in MTBE (10 mL) was added PPL (13 mg, 10% w/w) and the propionic anhydride (130 mg, 1.00 mmol). The reaction mixture was stirred for 22 h at room temperature and was filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the resulting residue was purified by flash column chromatography (cyclohexane/EtOAc = 1/1) to give (−)-**5** as colorless oil (49.5 mg, 43%). $[\alpha]_D^{26}$= −11.5 (c = 1.25, MeOH), (lit:[10] $[\alpha]_D^{26}$ = −11.9, c = 1.24, MeOH). *ee* = 99%. The NMR data corresponded to those of the racemic compound (±)-**5**. The enantiomeric excess of **5** was determined by chiral GC analysis using an Astec Chiraldex β-cyclodextrin trifluoroacetyl (BTA) capillary column: major isomer (3*R*,3a*S*,6a*R*): t_R = 21.5 min; minor isomer (3*S*,3a*R*,6a*S*): t_R = 21.2 min.

General One-Pot Procedure for the Synthesis of (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol ((−)-5). Cbz-protected aldehyde **9** (1.94 g, 10 mmol), furan (3.40 g, 50 mmol), and MTBE (20 mL) were placed in a quartz round-bottomed flask (50 mL) equipped with a magnetic stir bar and placed in the Rayonet photochemical reactor. The reaction mixture was kept under nitrogen atmosphere and irradiated until TLC indicated complete consumption of the starting aldehyde (usually 36 h). Excess furan was removed in vacuo on a rotary evaporator. Palladium on activated charcoal (212 mg, 0.20 mmol) was added and the reaction vessel was evacuated and backfilled with hydrogen (balloon) at room temperature and ambient pressure for 36 h. After this time, the hydrogen balloon was removed,, PPL (194 mg, 10% w/w) and the acetylating agent, in this case propionic anhydride (1.30 g, 10 mmol), were added. The reaction vessel was flushed with argon and the reaction mixture was stirred at room temperature. After 72 h, the suspension was filtered (paper, washed with CH_2Cl_2) and evaporated to dryness in vacuo. The resulting residue was purified by flash column chromatography (cyclohexane/EtOAc = 1/1) to give (−)-**5** as colorless oil (455 mg, 35%). $[\alpha]_D^{30}$= −11.5 (c = 1.25, MeOH), (lit:[10] $[\alpha]_D^{26}$ = −11.9, c = 1.24, MeOH). *ee* = 99%. The NMR data corresponded to those of the racemic compound (±)-**5**. The enantiomeric excess of **5** was determined by chiral GC analysis using an Astec Chiraldex β-cyclodextrin trifluoroacetyl (BTA) capillary column: major isomer (3*R*, 3a*S*, 6a*R*): t_R = 21.5 min; minor isomer (3*S*, 3a*R*, 6a*S*): t_R = 21.2 min.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02588.

Copies of NMR spectra for all synthesized compounds and GC-MS data of compound (−)-**5**, detailed comparison of the reported procedures with those reported in the literature (PDF)

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Notes

The authors declare no competing financial interest.

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