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The efficient synthesis of (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol and its isomers

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ABSTRACT

The stereoselective synthesis of all the possible stereoisomers of bis-tetrahydrofyran alcohol, a ligand used for obtaining HIV protease inhibitors including Darunavir **1** and Brecanavir **2** has been achieved. A key intermediate 4-pentenal **5** was obtained by employing a Wittig olefination-Claisen rearrangement protocol from D-glyceraldehyde derivative **3** as a source of chirality. The 4-pentenal was readily converted in the bis-THF alcohol moiety in three steps.

1. Introduction

Human Immunodeficiency Virus (HIV) causes acquired immunodeficiency syndrome (AIDS),[1] a condition in humans in which the immune system begins to fail, leading to life-threatening opportunistic infections. Since its recognition in 1981, AIDS has become one of the most destructive pandemics in recorded history. The current treatment for HIV infection consists of highly active antiretroviral therapy (HAART), which substantially reduces both the mortality and the morbidity of HIV infection.[2] The discovery of HIV-protease inhibitors (PIs) and their utilization in HAART have been a major turning point in the management of AIDS. Due to the rapid emergence of drug resistance, the development of novel PIs targeting the protease backbone atom with an excellent resistance profile has proven to be an effective strategy.[3] Darunavir[3] (TMC-114) **1** is most recent FDA-approved second generation PI to treat HIV infection.[4] Darunavir represents an important treatment option for patients with drug-resistance HIV. The important structural feature of **1** is that it possesses a bis-tetrahydrofuran (bis-THF) moiety as the P_2 ligand that maximizes hydrogen bonding and hydrophobic interactions in the protease S2 subsite (Fig. 1). The significance of bis-THF as a nonpeptide P2 ligand for withstanding potency against drug-resistance HIV is well documented.[3,5]

The bis-THF unit is also present in Brecanavir[6] (GW640385) **2** and other protease inhibitors represented in the development of HIV drug candidates.[5] The bis-THF template is also a subunit of Ginkgolides A–C, an important class of natural products with significant biological activities.[7] Due to its significant role in anti-HIV drugs,[5] bis-THF alcohol has received considerable synthetic interest and numerous reports describing its synthesis have been reported.[8] Some synthetic approaches involve the synthesis of the racemic form of a bis-THF alcohol followed by enzymatic resolution.[8a–h] These methods require multiple steps to establish the relative stereochemistry of the bicyclic skeleton before the enzymatic resolution. Other synthetic approaches describe asymmetric syntheses,[8i–n] but in most of these cases, moderate diastereo- and enantioselectivity are reported, while some others require resolution to give the enantiopure bis-THF alcohols. Other approaches, such as utilizing chiral pool starting materials such as enantiomerically pure diethyl malate,[8o,p] and glyceraldehyde derivatives,[8q,r] generally report good stereochemical control in the synthesis, but are rather lengthy. Therefore there is enough scope to develop a more efficient synthetic approach for the synthesis of bis-THF alcohol. Herein, we report our efforts toward the synthesis of all four stereoisomers of a bis-THF alcohol.

2. Results and discussions

4-Pentenals, accessible through a Wittig olefination-Claisen rearrangement[9] protocol have proven to be quite versatile and useful intermediates.[10] Present efforts were directed toward the synthesis of all the stereoisomers of a bis-THF alcohol in high enantiomeric purity using a 4-pentenal, obtainable from a D-glyceraldehyde derivative.

At first, 2,3-*O*-cyclohexylidene-D-glyceraldhyde[11] **3** was subjected to a Wittig olefination reaction with allyloxymethylenetriphenylphorane in dry THF at 55 °C to give the corresponding allyl vinyl ether **4** in 78% yield (Scheme 1). The ^{1}H NMR spectrum of compound **4** indicated that the resulting allyl vinyl ether was an inseparable mixture of *E*- and *Z*-isomers in 1:1.5 ratio. The mixture of allyl vinyl ethers **4** underwent a Claisen rearrangement in refluxing xylene to afford aldehyde **5** as an inseparable mixture of diastereomers. The ratio of theses aldehydes was estimated to be 1:2.7

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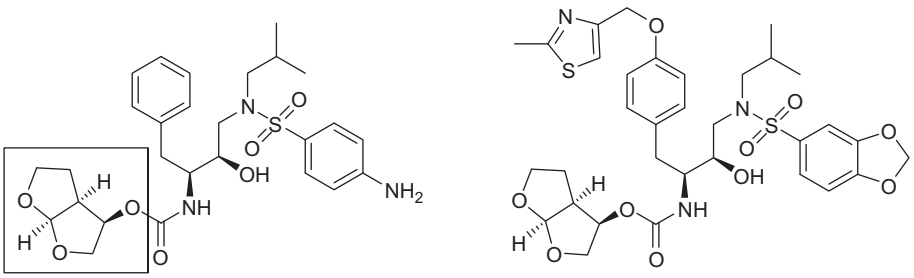


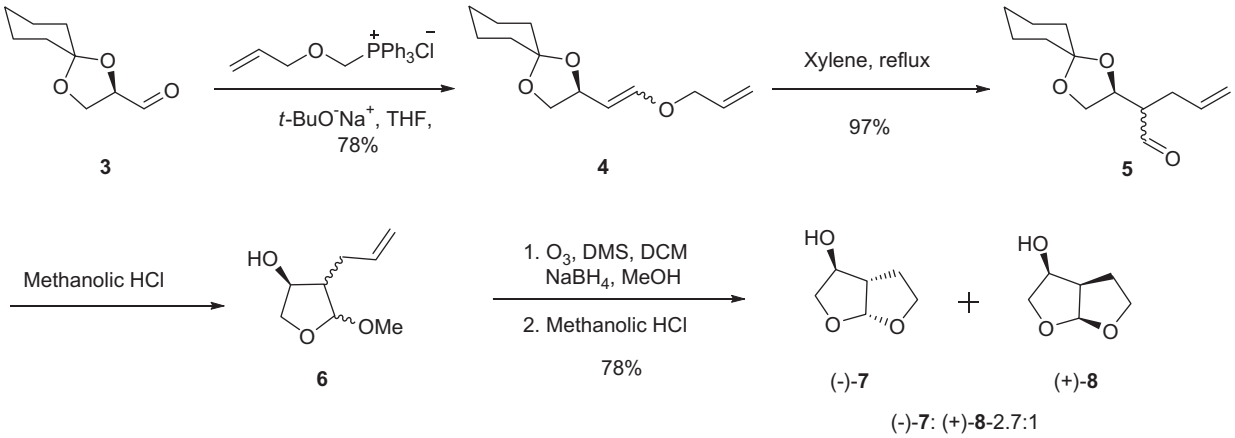
Figure 1. Structure of Darunavir and Brecanavir containing a bis-THF moiety.

from the ^{1}H NMR spectrum. The diastereomeric mixture of aldehyde **5** on treatment with catalytic methanolic HCl gave methyl acetal **6** containing a chromatographically inseparable mixture of four diastereomers. The mixture of methyl acetal **6** was subjected to ozonolytic cleavage of the terminal olefin followed by sodium borohydride reduction of the resulting aldehyde to an alcohol. The crude mixture of alcohols upon treatment with methanolic HCl gave a mixture of bisfuran alcohols which were readily separated to give bis-THF alcohols (−)-**7** $[\alpha]_D^{28} = -24.1$ (*c* 1.1, $CHCl_3$), {Lit.[8q] $[\alpha]_D^{23} = -25.1$ (*c* 1.05, $CHCl_3$)} and (+)-**8** $[\alpha]_D^{28} = +10.8$ (*c* 1.2, MeOH), {Lit.[8o] $[\alpha]_D^{23} = +12.2$ (MeOH)} in the ratio of 2.7:1.

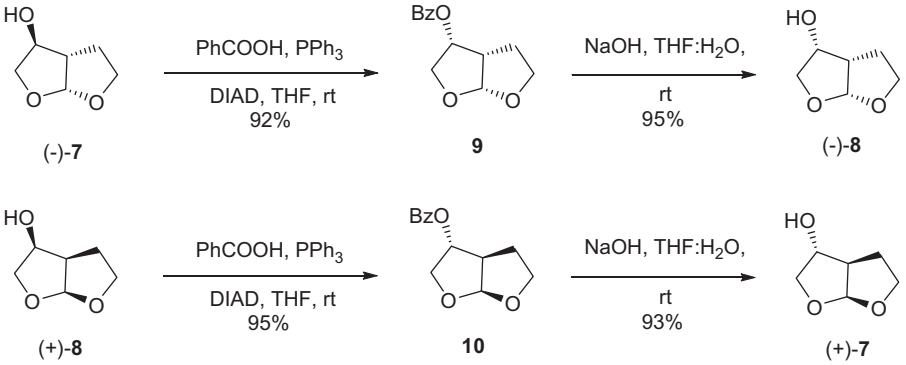
Alcohol (−)-**7** has been converted to the epimeric alcohol (−)-**8** $[\alpha]_D^{28} = -11.2$ (*c* 1.2, MeOH) {Lit.[8o] $[\alpha]_D^{23} = -11.9$, (*c* 1.24, MeOH)} using an oxidation–reduction sequence.[8r] However, with the yield of this two-step sequence being moderate, we adopted an alternative route employing a Mitsunobu reaction involving an inversion[12] with benzoic acid to give benzoate ester **9**. Aqueous sodium hydroxide-promoted hydrolysis of benzoate **9** to give alcohol (−)-**8** in 87% yield over a two-step sequence. Similarly, using the same Mitsunobu protocol, alcohol (+)-**8** was epimerized to (+)-**7** $[\alpha]_D^{28} = +24.7$ (*c* 1.05, $CHCl_3$), {Lit.[8a] $[\alpha]_D^{23} = +26.8$ ($CHCl_3$)} through benzoate derivative **10** in 88% overall yield (Scheme 2).

3. Conclusion

In conclusion, we have achieved the synthesis of all four isomers of bis-tetrahydrofuran alcohol in a high overall yield (38%) of the active isomer (−)-**8** in an effective manner.



Scheme 1. Synthesis of bis-THF alcohols (−)-**7** and (+)-**8**.



Scheme 2. Inversion of the alcohols.

4. Experimental

All solvents were distilled before use. All liquid reagents were distilled and stored under anhydrous conditions. Dry xylene was prepared by distilling it over sodium and stored over sodium wire. Methonolic HCl was prepared by passing dry HCl gas through dry MeOH. Dry THF was obtained by distillation from a dark-blue solution of sodium benzophenone radical anion under a nitrogen atmosphere. Dry DCM was prepared by distilling over calcium hydride and stored over molecular sieves (4 Å). Petroleum ether is of the 60–80 °C boiling point range. All anhydrous reactions were carried out under a nitrogen atmosphere. Silica gel (100–200-mesh) was used for column chromatography. IR spectra were recorded on a Shimadzu FTIR-8400 series instrument. ^{1}H NMR spectra [ppm, TMS—internal standard in $CDCl_3$] were recorded on VARIAN Mercury 300 MHz instrument. ^{13}C NMR spectra were recorded on Varian Mercury 75 MHz instrument. Low-resolution mass spectra were recorded on Shimadzu GCMS—QP 5050A series instrument in Chemical Ionization mode and the fragmentation pattern is given after the corresponding M^+ value. Optical rotations were measured on a JASCO-181 digital polarimeter. The elemental analyzes were obtained on a HOSLI semiautomatic C, H analyzer.

4.1. (*S*)-2-(2-(Allyloxy)-vinyl)-1,4-dioxospiro[4.5]-decane 4

To a suspension of 2,3-*O*-cyclohexylidene-D-glyceraldehyde **3** (10 g, 58.82 mmol) and allyloxymethylenetriphenylphosphonium-chloride (28.22 g, 76.47 mmol) in dry THF (150 ml), sodium *tert*-butoxide (7.34 g, 76.47 mmol) was added portionwise over a period of 10 min at 50–55 °C. The reaction was stirred for 1 h at the same temperature. After the completion of the reaction (TLC check), THF was removed under reduced pressure and the crude product was extracted with ethyl acetate (3 × 50 ml). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using pet ether as a mobile phase to give pure allyl vinyl ether **4** as a colorless thick liquid. The product in hand was an inseparable mixture of the *E*- and *Z*-isomers in a 1:1.5 ratio (10.3 g, 78% yield). IR (film): 2935, 1693, 1097, 927 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39–1.62 (m, 10H), 3.49 and 3.52 (2t, 1H, J = 8.5 Hz), 4.03 and 4.08 (2dd, 1H, J = 8.6 and 6.1 Hz), 4.24–4.28 (m, 2H), 4.42 and 4.48 (2dd, 1H, J = 8.5 and 6.1 Hz), 4.77 (dd, 0.4H, J = 12.2 and 8.5 Hz), 5.05 (dd, 0.6H, J = 8.6 and 7.3 Hz), 5.21–5.34 (m, 2H), 5.83–5.97 (m, 1H), 6.12 (d, 0.6H, J = 7.3 Hz), 6.55 (d, 0.4H, J = 12.2 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$): δ 23.6, 25.0, 33.3, 36.3, 69.0, 69.4, 69.5, 70.0, 72.9, 74.5, 101.6, 104.6, 109.0, 109.2, 117.6, 117.7, 132.3, 132.7, 147.7, 150.1; MS (*m*/*z*): 225(M^++1), 183, 167, 141, 83, 57, 41, 27.

4.2. (*S*)-2-(1,4-Dioxaspiro[4.5]-decan-2-yl)-pent-4-enal 5

The isomeric mixture of allyl vinyl ether **4** (10 g, 44.6 mmol) as such was dissolved in xylene (50 ml) and the solution was refluxed for 6–7 h. After completion of the reaction (TLC check), the xylene was removed under reduced pressure. The crude product was purified through silica gel column chromatography using pet ether as an eluent to afford pure 4-pentenal **5** as a colorless viscous liquid. The product in hand was the mixture of two inseparable diastereoisomers in a ratio of 1:2.7. (9.7 g, 97% yield). IR (film): 2937, 1724, 1640, 1101, 910 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40–1.67 (m, 10H), 2.22–2.27 (m, 3H), 3.64 (dd, 0.27H, J = 8.2 and 7.0 Hz), 3.73 (dd, 0.73H, J = 8.2 and 7.0 Hz), 4.07–4.17 (m, 1H), 4.25–4.35 (m, 1H), 5.04–5.17 (m, 2H), 5.66–5.89 (m, 1H), 9.74 (s, 0.73H), 9.77 (d, 0.27H, J = 3 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$): δ 23.6, 23.8, 23.9, 25.0, 30.0, 30.5, 34.5, 34.7, 36.0, 36.1, 54.4, 67.1, 67.2, 73.6, 74.7, 109.4, 109.9, 117.6, 134.2, 134.4, 202.9, 203.0.; MS (*m*/*z*): 225(M^++1), 209, 197, 183, 141, 99.

4.3. The preparation of compounds (3*S*,3a*S*,6a*R*)-hexahydro furo[2,3-*b*]furan-3-ol (−)-7 and (3*S*,3a*R*,6a*S*)-hexahydrofuro [2,3-*b*]furan-3-ol (+)-8

To a stirred solution of aldehyde **5** (9.20 g, 41.1 mmol) in dry methanol (90 mL) was added methanolic HCl (1 M, 1 ml) and the reaction mixture was stirred at rt for 30–45 min. After completion of the reaction (TLC check), the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL) and the methanol was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate (100 ml × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude methyl acetal **6** as a viscous liquid (8.23 g).

Methyl acetal **6** was dissolved in DCM (50 mL) and a stream of ozonized oxygen bubbled through it at −78 °C, until the blue color persisted (25–40 min). After the solution was flushed with nitrogen for 5 min, dimethyl sulfide (25 mL) was added and the reaction mixture was allowed to warm to room temperature. After evaporation of the solvent, the crude aldehyde was obtained as a colorless viscous liquid. The crude aldehyde was dissolved in 5% aqueous methanol (50 mL) and cooled to 0 °C. Next, $NaBH_4$ (1.56 g, 41.1 mmol) was added portionwise over a 10 min. period and the mixture was stirred for an additional 15 min. After completion of the reaction (TLC check), the reaction was quenched with saturated ammonium chloride solution. The mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and a brine solution. The layers were separated and the aqueous layer was extracted with ethyl acetate (100 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 6.14 g of the crude diol as a colorless viscous liquid.

The crude diol was dissolved in dry THF (60 mL) after which methanolic HCl (1 M, 0.6 mL) was added at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. After completion of the reaction (TLC check), the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (15 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using methanol/chloroform (2:98) as the mobile phase to provide 2.88 g of bis-THF alcohol (−)-**7** as a white amorphous solid and 1.06 g of bis-THF alcohol (+)-**8** as a colorless viscous liquid in the ratio of 2.7:1 (3.94 g, 81% yield).

4.3.1. (3*S*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol (−)-7

$[\alpha]_D^{28} = -24.1$ (*c* 1.1, $CHCl_3$); IR (KBr): 2955, 1656, 1217, 1024 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67–1.76 (m, 1H), 2.11–2.24 (m, 1H), 2.79–2.84 (m, 1H), 3.00 (br s, 1H, exchangeable with D_2O), 3.80–3.92 (m, 3H), 3.97 (dd, 1H, J = 10.3 and 3.1 Hz), 4.23 (s, 1H), 5.88 (d, 1H, J = 4.9 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$): δ 28.6, 51.8, 67.7, 75.1, 77.4, 108.7; Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.49; H, 7.61.

4.3.2. (3*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-3-ol (+)-8

$[\alpha]_D^{28} = +10.8$, (*c* 1.2, MeOH); IR (film): 2928, 1641, 1217, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80–1.93 (m, 1H), 2.28–2.36 (m, 1H), 2.82–2.90 (m, 1H), 3.04 (br s, 1H, exchangeable with D_2O), 3.61 (dd, 1H, J = 8.8 and 7.6 Hz), 3.85–4.01 (m, 3H), 4.43 (dd, 1H, J = 14.7 and 7.1 Hz), 5.68 (d, 1H, J = 5.2 Hz); ^{13}C NMR:

(75 MHz, $CDCl_3$): δ 24.7, 46.4, 69.8, 70.5, 72.9, 109.4; Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.54; H, 7.65.

4.4. (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-yl benzoate 9

To a stirred solution of alcohol (−)-**7** (1.02 g, 7.84 mmol), triphenylphosphine (4.11 g, 15.7 mmol) and benzoic acid (1.91 g, 15.7 mmol) in dry THF (50 mL) at 23 °C was added diisoproylazodicarboxylate (DIAD, 3.1 mL, 15.7 mmol). The resulting mixture was stirred at that temperature for 1 h. After completion of the reaction, the reaction was quenched by adding water. The layers were separated and the aqueous layer was extracted with ethyl acetate (25 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using ethyl acetate/pet ether (5:95) mobile phase to give benzoate ester **9** as a colorless viscous liquid (1.68 g, 92% yield). IR (film): 1721, 1458, 1274, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.89–2.02 (m, 1H), 2.08–2.16 (m, 1H), 3.15–3.23 (m, 1H), 3.92–4.07 (m, 3H), 4.20 (dd, 1H, *J* = 9.9, 6.4 Hz), 5.44–5.51 (m, 1H), 5.81 (d, 1H, *J* = 4.3 Hz), 7.46 (t, 2H, *J* = 7 Hz), 7.70 (t, 1H, *J* = 7 Hz), 7.03 (d, 2H, *J* = 7 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$): δ 26.3, 45.2, 69.6, 70.9, 73.4, 109.3, 128.5, 129.6, 130.1, 133.4, 165.9; Anal. Calcd for $C_{13}H_{14}O_4$: C, 56.65; H, 6.02. Found: C, 56.84; H, 5.89.

4.5. (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol (−)-8

To a stirred solution of benzoate ester **9** (1.49 g, 6.36 mmol) in 10% aqueous methanol (20 mL), sodium hydroxide (382 mg, 9.55 mmol) was added and reaction mixture was stirred at ambient temperature for 30 min. After completion of the reaction, the mixture was concentrated under reduced pressure. The crude residue was partitioned between ethyl acetate and brine. The layers were separated and the aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using methanol/chloroform (2:98) as the mobile phase to give bis-THF alcohol (−)-**8** as a colorless viscous liquid (785 mg, 95% yield). $[\alpha]_D^{28} = -11.2$ (*c* 1.2, MeOH); IR (film): 2924, 1633, 1263, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.81–1.94 (m, 1H), 2.28–2.36 (m, 1H), 2.51 (br s, 1H, exchangeable with D_2O), 2.82–2.91 (m, 1H), 3.63 (dd, 1H, *J* = 9.3 and 7.1 Hz), 3.86–4.02 (m, 3H), 4.45 (dd, 1H, *J* = 14.3 and 7.1 Hz), 5.69 (d, 1H, *J* = 5.5 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$): δ 24.8, 46.5, 69.8, 70.7, 73.0, 109.5; Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.42; H, 7.68.

4.6. (3*R*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-3-yl benzoate 10

Following a similar experimental procedure for the preparation of benzoate ester **9**, the bis-THF alcohol (+)-**8** (938 mg, 7.21 mmol) gave benzoate ester **10** as a colorless thick liquid (1.60 g, 95% yield). IR (film): 1718, 1452, 1274, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.91–2.00 (m, 1H), 2.21–2.34 (m, 1H), 2.99–3.06 (m, 1H), 3.87–4.00 (m, 2H), 4.13 (d, 1H, *J* = 11.2 Hz), 4.18 (dd, 1H, *J* = 11.2, 2.9 Hz), 5.33 (d, 1H, *J* = 2.9 Hz), 5.95 (d, 1H, *J* = 5.3 Hz), 7.45 (t, 2H, *J* = 7.6 Hz), 7.58 (t, 1H, *J* = 7.6 Hz), 8.04 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$): δ 29.1, 49.4, 67.9, 72.7, 80.3, 108.9, 128.4, 166.1; Anal. Calcd for $C_{13}H_{14}O_4$: C, 56.65; H, 6.02. Found: C, 56.79; H, 5.91.

4.7. (3*R*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-3-ol (+)-7

Following a similar experimental procedure for the hydrolysis of benzoate ester **9**, benzoate ester **10** (1.37 g, 5.85 mmol) gave bis-THF alcohol (+)-**7** as a white amorphous solid (705 mg, 93% yield). $[\alpha]_D^{28} = +24.7$ (*c* 1.05, $CHCl_3$); IR (KBr): 2926, 1639, 1219, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.65–1.74 (m, 1H), 2.09–2.22 (m, 1H), 2.78–2.84 (m, 1H), 3.38 (br s, 1H, exchangeable with D_2O), 3.78–3.90 (m, 3H), 3.97 (dd, 1H, *J* = 10.2 and 3 Hz), 4.21 (d, 1H, *J* = 3 Hz), 5.87 (d, 1H, *J* = 4.7 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$): δ 28.8, 51.9, 67.8, 75.2, 77.7, 108.8; Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.58; H, 7.60.

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