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The Chiron Approach to (3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-ol, a Key Subunit of HIV-1 Protease Inhibitor Drug, Darunavir

Arun K. Ghosh,
Department of Chemistry and Department of Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907, United States

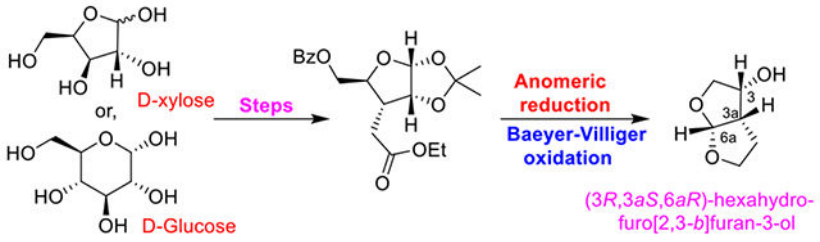
Shivaji B. Markad,
Department of Chemistry and Department of Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907, United States

William L. Robinson
Department of Chemistry and Department of Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907, United States

Abstract

We describe an enantioselective synthesis of (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-ol which is a key subunit of darunavir, a widely used HIV-1 protease inhibitor drug for the treatment of HIV/AIDS patients. The synthesis was achieved in optically pure form utilizing commercially available sugar derivatives as the starting material. The key steps involve a highly stereoselective substrate-controlled hydrogenation, a Lewis acid catalyzed anomeric reduction of a 1,2-*O*-isopropylidene-protected glycofuranoside, and a Baeyer–Villiger oxidation of a tetrahydrofuranyl-2-aldehyde derivative. This optically active ligand alcohol was converted to darunavir efficiently.

Graphical Abstract



Corresponding Author: Department of Chemistry and Department of Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907, United States; akghosh@purdue.edu.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02396.
^{1}H and ^{13}C NMR spectra for all new compounds; HPLC data for compound **11** (PDF)

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02396

The authors declare no competing financial interest.

The development of combination antiretroviral therapies (cART) has transformed Acquired Immunodeficiency Syndrome (AIDS) from a fatal disease into a manageable chronic condition.[1,2] The Human Immunodeficiency Virus Type-1 (HIV-1) protease inhibitor drugs are an important component of cART regimens.[3,4] Darunavir (**1**, Figure 1) is the most recent FDA approved HIV-1 protease inhibitor drug for the treatment of patients with HIV-1 infection and AIDS.[5,6] It is exceedingly potent and has exhibited broad-spectrum activity against highly multidrug-resistant HIV-1 variants.[7,8] It received FDA approval in 2006 for the treatment of HIV/AIDS patients who are harboring multidrug-resistant HIV-1 variants and do not respond to other approved therapies. Darunavir received full approval in 2008 for all HIV/AIDS patients including pediatrics.[5,9] Darunavir is a widely used protease inhibitor drug, and it has become the front-line therapy for treatment of HIV/AIDS. Darunavir was specifically designed to promote "backbone binding" through extensive hydrogen bonding interactions with the HIV-1 protease active site backbone atoms.[8,10] One of the key features of darunavir is the stereochemically defined bicyclic (3*R*,3*aS*,6*aR*)-*bis*-tetrahydrofuran (*bis*-THF) heterocycle as the P2-ligand.[7,10] Our extensive structure–activity studies and X-ray crystallographic studies established the *bis*-THF ligand as the privileged ligand for the S2 subsite of HIV-1 protease for a variety of very potent HIV-1 protease inhibitors with clinical potential.[11–13]

Darunavir is readily synthesized by formation of the urethane between the *bis*-THF ligand alcohol **2** and amino-alcohol derivative **3**.[14] The *bis*-THF ligand structure contains three contiguous stereocenters. We and others reported a number of syntheses of *bis*-THF ligand alcohol **2** in optically active form.[14] Our initial synthesis of *bis*-THF alcohol was achieved utilizing (3*R*)-diethyl malate as the key starting material.[15] We reported an efficient racemic synthesis of *bis*-THF alcohol which was resolved by using a lipase-catalyzed enzymatic resolution to provide the optically active ligand.[16] We also investigated the stereoselective photochemical route to *bis*-THF alcohol where 1,3-dioxolane was added to a chiral furanone derivative.[17] These procedures provided access to optically active *bis*-THF ligand alcohol. However, the optical purity of ligand alcohol was in the range 92–96% *ee*. Quaedflieg and co-workers reported a large-scale synthesis of *bis*-THF ligand alcohol utilizing a diastereoselective Michael addition as the key step.[18] Black and co-workers reported an asymmetric synthesis of *bis*-THF ligand alcohol using a Mukaiyama aldol reaction with a silyl ketene acetal.[19] Yu and co-workers reported a large-scale synthesis of a racemic *bis*-THF ligand from glycolaldehyde dimer and 2,3-dihydrofuran using $Yb(fod)_3$ catalyst.[20] Xie and co-workers also reported a similar Lewis acid catalyzed synthesis of racemic *bis*-THF alcohol.[21] For our continued interest in optically pure *bis*-THF ligand, we have investigated the feasibility of a carbohydrate-based synthesis of *bis*-THF alcohol. Herein, we report an optically active synthesis of *bis*-THF utilizing inexpensive D-xylofuranose or D-glucose as the starting materials. The overall route may furnish convenient access to quantities of optically pure *bis*-THF ligand alcohol.

Our chiron approach[22,23] to the synthesis of optically active *bis*-THF alcohol **2** begins with commercially available 1,2-*O*-isopropylidine-*α*-D-xylofuranose **4** as shown in Scheme 1. Selective protection of the primary alcohol as a benzoate derivative with 1.1 equiv of benzoyl chloride in the presence of pyridine and a catalytic amount of DMAP in CH_2Cl_2 at

0 °C for 30 min furnished **5** in 95% yield. Swern oxidation of **5** provided the corresponding ketone which was subjected to Wittig olefination with commercially available (carbethoxymethylene)triphenylphosphorane in CH_2Cl_2 at 23 °C for 24 h to afford *α,β*-unsaturated ester **6** along with a small amount of its isomer in a 8:1 mixture. The *Z*-isomer **6** was separated by silica gel chromatography in 85% yield over two steps. Catalytic hydrogenation of olefin **6** over 10% Pd/C in ethanol at 23 °C under a hydrogen-filled balloon afforded saturated derivative **7** as the only isolated product in 96% yield. Saturated ester **7** was converted to *γ*-lactone derivative **8** by exposure to $BF_3{\cdot}OEt_2$ (8 equiv) followed by Et_3SiH (3 equiv) in CH_2Cl_2 at −78 to 23 °C for 6 h.[24,25] Bicyclic lactone **8** was isolated in 87% yield. Presumably, the reaction of the isopropylidene derivative with a Lewis acid resulted in the formation of an oxocarbenium ion intermediate. Silane reduction then provided the corresponding alcohol which formed the *γ*-lactone under the acidic conditions. The overall transformation is quite efficient. The reaction was carried out on gram scale to provide an excellent yield of *γ*-lactone **8**. Hydrolysis of the benzoate ester using K_2CO_3 in MeOH at 23 °C for 15 min furnished bicyclic alcohol **9** in 85% yield. Alcohol **9** was converted to methyl acetal **10** in a three-step sequence involving (1) Dess-Martin oxidation of the primary alcohol to the corresponding aldehyde, (2) *m*-CPBA-promoted Baeyer–Villiger oxidation at 0 °C for 2 h, and (3) exposure of the resulting formate to 6% HCl in MeOH at 0 °C. Acetal **10** was obtained in 41% yield over three steps. Reduction of lactone **10** by $LiAlH_4$ in THF at −78 to 23 °C for 1 h followed by exposure of the resulting diol to aqueous HCl at 0 to 23 °C furnished *bis*-THF alcohol **2** $[\alpha]_D^{23} = -12.3°$ (*c* 0.73, MeOH; lit[17] $[\alpha]_D^{23} = -12.4°$ (*c* 1.16, MeOH)) in 63% yield over two steps.[18] The optical purity of alcohol (−)-**2** was determined after its conversion to *p*-nitrocarbonate **11**.[26] The reaction of (−)-**2** with *p*-nitrophenylchloroformate in the presence of pyridine in CH_2Cl_2 at 0 to 23 °C for 12 h provided nitrocarbonate **11** in 92% yield. Chiral HPLC analysis of **11** on a CHIRALPAK OD-H column revealed an enantiomeric purity of 99% *ee* (please see Supporting Information).

We have also converted commercially available 1,2:5,6-di-*O*-isopropylidene-*α*-D-glucofuranose **12** to *bis*-THF ligand alcohol **2**. As shown in Scheme 2, Swern oxidation of **12** followed by Horner–Wadsworth–Emmons reaction of the resulting ketone provided *α,β*-unsaturated ester derivative **13** as a 4:1 *Z/E* mixture in 48% yield over two steps.[27] The isomers were separated, and the *Z*-ester **13** was treated with 80% aqueous AcOH at 23 °C for 60 h to provide the corresponding diol.[28] The resulting diol was hydrogenated over 10% Pd/C under a hydrogen-filled balloon at 23 °C for 24 h to afford the saturated diol **14** in 66% yield over two steps. Diol **14** was converted to alcohol **15** by exposure to $NaIO_4$ in MeOH at 0 to 23 °C for 2 h.[28] The resulting aldehyde was reacted with $NaBH_4$ in MeOH at 0 °C for 1 h to furnish **15** in 88% yield over two steps.[25] Protection of the primary alcohol as benzoate ester **7** was carried out with benzoyl chloride in the presence of Et_3N. Benzoate derivative **7** has been converted to *bis*-THF alcohol **2** as described in Scheme 1. Alcohol **2** was converted to mixed activated carbonate **16** by treatment with *N,N'*-disuccinimidyl carbonate in the presence of Et_3N in CH_2Cl_2 at 23 °C.[17,29] The synthesis of darunavir is shown in Scheme 3. Commercially available epoxide **17** was reacted with isobutylamine in 2-propanol at 60 °C for 22 h. Reaction of the resulting amino alcohol with 4-nitrobenzenesulfonyl chloride in CH_2Cl_2 in the presence of Et_3N at 23 °C for 5 h afforded Cbz-containing sulfonamide

derivative **18** in 71% yield over two steps.[30] For the synthesis of darunavir, the Cbz-derivative **18** was subjected to catalytic hydrogenation with mixed activated carbonate **16** in the presence of Et_3N in THF under a hydrogen-filled balloon at 23 °C for 17 h to provide carbamate **1** (darunavir) in 53% yield. The hydrogenation condition accomplished deprotection of Cbz-group, reaction of the resulting amine with mixed succinimidyl carbonate to form the carbamate, and reduction of the aromatic nitro group to the amine.[31]

In conclusion, we describe here a convenient synthesis of (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-ol (**2**) in optically pure form using commercially available glucose or xylose derivatives. The key synthetic steps involved a highly diastereoselective substrate controlled hydrogenation of an α,β-unsaturated ester, an efficient $BF_3{\cdot}OEt_2$-catalyzed deprotection of an isopropylidene group and subsequent silane reduction, a Baeyer–Villiger oxidation, and an acid-catalyzed cyclization. Overall, the synthesis of the *bis*-THF ligand alcohol involves more steps than other published syntheses. However, the main advantage of the current route is the enantioselective synthesis using inexpensive sugars as the starting materials, efficient reaction steps, and high optical purity of the *bis*-THF alcohol. The route has the potential for scale-up. The *bis*-THF alcohol was converted to mixed activated succinimidyl carbonate. Catalytic hydrogenation of this carbonate with a Cbz-derivative of a dipeptide isostere furnished darunavir.

EXPERIMENTAL PROCEDURES

General Methods.

All chemical and reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Solvents were purified as follows: CH_2Cl_2 was distilled from calcium hydride or purified using a solvent purification system; methanol was used without further purification; tetrahydrofuran was distilled from sodium/benzophenone. The flasks were fitted with rubber septa and kept under a positive pressure of argon. Heated reactions were ran using an oil bath on a hot plate equipped with a temperature probe. TLC analysis was conducted using glass-backed thin-layer silica gel chromatography plates (60 Å, 250 μm thickness, F-254 indicator). Flash chromatography was done using a 230–400 mesh, a 60 Å pore diameter silica gel. ^{1}H NMR spectra were recorded on 400 and 500 MHz spectrometers. ^{13}C NMR spectra were recorded at 100 MHz NMR. Chemical shifts are reported in parts per million and referenced to the deuterated residual solvent peak ($CDCl_3$, 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). NMR data are reported as δ value (chemical shift), *J*-value (Hz), and integration, where s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, dd = doublet doublets, and so on. Optical rotations were recorded on a digital polarimeter. Low resolution mass spectra (LRMS) spectra were recorded using a quadrupole LCMS under positive electrospray ionization (ESI+). High-resolution mass spectrometry (HRMS) spectra were recorded at the Purdue University Department of Chemistry Mass Spectrometry Center. These experiments were performed under ESI+ and positive atmospheric pressure chemical ionization (APCI+) conditions using an Orbitrap XL Instrument.

((3a*R*,5*R*,6a*R*)-6-Hydroxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methyl Benzoate (5).

A solution of commercially available 1,2-*O*-isopropylidene-*α*-D-xylofuranose **4** (3 g, 15.8 mmol) in dry CH_2Cl_2 (40 mL) was cooled to 0 °C. To the mixture were added 1.90 mL (23.6 mmol) pyridine and a catalytic amount (192 mg) of *N,N*-dimethylaminopyridine. The resulting mixture was stirred at 0 °C for 10 min, at which time 2 mL (17.3 mmol) benzoyl chloride were added to it dropwise over a period of 30 min. The reaction mixture was stirred at 0 °C for an additional 30 min and then quenched by the addition of 20 mL of a saturated solution of NH_4Cl. The reaction was allowed to warm to 23 °C, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with an aqueous solution of $CuSO_4$, water, and brine. The organic solution was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (50% EtOAc in hexane) to afford **5** as an oil (4.43 g, 95%). R_f = 0.2 (50% EtOAc/hexanes, SiO_2 plate). $[\alpha]_D^{23} = +15.5$ (*c* 0.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.08–8.01 (m, 2H), 7.62–7.54 (m, 1H), 7.49–7.40 (m, 2H), 5.95 (d, *J* = 3.6 Hz, 1H), 4.83–4.73 (m, 1H), 4.59 (d, *J* = 3.6 Hz, 1H), 4.43–4.34 (m, 2H), 4.18 (dd, *J* = 4.2, 2.3 Hz, 1H), 3.36–3.31 (m, 1H), 1.50 (s, H), 1.32 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ* 167.3, 133.5, 129.8 (2C), 129.1, 128.4 (2C), 111.8, 104.6, 84.9, 78.4, 74.3, 61.2, 26.7, 26.0. LRMS (ESI) *m/z*: $[M + H]^+$ 295.1. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd $C_{15}H_{18}O_6Na$ 317.0996; found 317.0998.

(3a*R*,5*R*,6a*S*)-2,2-Dimethyl-6-oxotetrahydrofuro[2,3-*d*][1,3]-dioxol-5-yl)methyl Benzoate (6).

A solution of oxalyl chloride (2.42 mL, 28.5 mmol) in 40 mL of anhydrous CH_2Cl_2 was cooled to −78 °C under an argon atmosphere. To the mixture was added DMSO (4 mL, 57.1 mmol) dropwise over a period of 15 min. After the resulting solution had been stirred at the same temperature for 10 min, a solution of alcohol **5** (4.2 g, 14.2 mmol) in anhydrous CH_2Cl_2 (10 mL) was added to it dropwise over a period of 15 min. Stirring was continued at −78 °C for an additional 30 min. Then, Et_3N (9.9 mL, 71.3 mmol) was added. The temperature of the reaction mixture was maintained at −78 °C for 10 min, and then the mixture was allowed to stir for 30 min while warming to 23 °C. The reaction was then quenched by 30 mL of water and extracted with (3×) CH_2Cl_2. The CH_2Cl_2 layer was washed with saturated aqueous $NaHCO_3$ and then brine and was dried over anhydrous Na_2SO_4. Filtration and solvent removal under reduced pressure afforded crude product which was used in the next step without further purification.

To a stirred solution of the above ketone (14.3 mmol) in dry CH_2Cl_2 (30 mL) was added (carbethoxymethylene)triphenyl-phophorane (5.96 g, 17.1 mmol). The reaction mixture was stirred under argon at 23 °C for 24 h. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography on silica (5% EtOAc/hexanes to 10% EtOAc/hexane) to yield the ester as an 8:1(*Z*/*E*) mixture of separable isomers. *Z*-isomer of ester **6** (4.4 g, 85% over 2 steps), yellow oil. R_f = 0.4 (20% EtOAc/hexanes, SiO_2 plate). $[\alpha]_D^{23} = +240$ (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.05–7.92 (m, 2H), 7.62–7.53 (m, 1H), 7.44 (dd, *J* = 8.4, 7.2 Hz, 2H), 6.03–5.95 (m, 2H), 5.78 (dt, *J* = 4.2, 1.5 Hz, 1H), 5.16 (ddt, *J* = 5.3, 3.7, 1.8 Hz, 1H), 4.57 (dd, *J* = 11.9, 3.5 Hz, 1H),

4.43 (dd, J = 11.9, 5.0 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 1.51 (s, 3H), 1.44 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 164.5, 154.5, 133.2, 129.6 (2C), 129.4, 128.4 (2C), 117.1, 112.9, 105.0, 78.1, 77.8, 65.1, 60.8, 27.3, 27.0, 14.0. LRMS (ESI) *m/z*: $[M + Na]^+$ 385.0. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd $C_{19}H_{22}O_7Na$ 385.1258; found 385.1247.

((3*aR*,5*S*,6*R*,6*aR*)-6-(2-Ethoxy-2-oxoethyl)-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methyl Benzoate (7).

To a solution of *Z*-ester **6** (4.2 g, 11.6 mmol) in anhydrous ethanol (70 mL) 10% Pd/C (147 mg, 5% w/w) was added. The resulting mixture was stirred under a hydrogen filled balloon for 6 h. Upon completion of the reaction, the mixture was filtered through Celite, and the filter cake was washed with EtOAc. Evaporation of solvent yielded a colorless oil that was purified by flash chromatography on silica (15% EtOAc/hexane) to provide ester **7** (4.02 g, 96%) as a colorless oil and as a single diastereomer. R_f = 0.4 (20% EtOAc/hexanes, SiO_2 plate). $[\alpha]_D^{23} = +52.7$ (*c* 0.584, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.15–8.00 (m, 2H), 7.60–7.52 (m, 1H), 7.43 (t, J = 7.6 Hz, 2H), 5.87 (d, J = 3.7 Hz, 1H), 4.82 (t, J = 4.2 Hz, 1H), 4.56 (dd, J = 12.3, 2.9 Hz, 1H), 4.34 (dd, J = 12.3, 5.0 Hz, 1H), 4.19–4.08 (m, 3H), 2.75 (dd, J = 17.0, 9.8 Hz, 1H), 2.54–2.33 (m, 2H), 1.53 (s, 3H), 1.32 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.7, 166.3, 133.1, 129.7 (2C), 129.6, 128.3 (2C), 111.7, 104.8, 80.8, 78.6, 63.9, 60.7, 41.4, 29.6, 26.6, 26.2, 14.0. LRMS (ESI) *m/z*: $[M + Na]^+$ 387.0. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd $C_{19}H_{24}O_7Na$ 387.1414; found 387.1421.

((3*aR*,4*S*,6*aR*)-2-Oxohexahydrofuro[3,4-*b*]furan-4-yl)methyl benzoate (8).

To a flask containing ester **7** (2.3 g, 6.3 mmol) in dry CH_2Cl_2 (20 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (6.18 mL, 50.5 mmol) dropwise over 5 min, and then Et_3SiH (3.01 mL, 18.9 mmol) was added. The reaction mixture was stirred at −78 to 23 °C for 6 h. The reaction mixture was cooled to 0 °C, quenched with a saturated solution of $NaHCO_3$ (20 mL), and extracted with (3×) CH_2Cl_2. The combined organic layer was washed with water and brine. The organic solution was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by silica gel column chromatography (50% EtOAc/hexane) to afford **8** as an oil (1.44 g, 87%). R_f = 0.3 (30% EtOAc/hexanes, SiO_2 plate). $[\alpha]_D^{23} = +9.6$ (*c* 0.015, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.06–7.97 (m, 2H), 7.65–7.54 (m, 1H), 7.52–7.35 (m, 2H), 5.15 (ddd, J = 6.7, 4.8, 1.9 Hz, 1H), 4.53–4.35 (m, 2H), 4.24 (ddd, J = 11.2, 4.8, 0.5 Hz, 1H), 4.17–4.04 (m, 2H), 2.99–2.84 (m, 2H), 2.57 (dd, J = 17.8, 1.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.3, 166.1, 133.3, 129.6(2C), 129.3, 128.4(2C), 83.9, 82.9, 72.9, 64.6, 41.4, 33.0. LRMS (ESI) *m/z*: $[M + H]^+$ 263.0. HRMS (ESI) *m/z*: $[M + H]^+$ calcd $C_{14}H_{15}O_5$ 263.0914; found 263.0920.

(3*aR*,4*S*,6*aR*)-4-(Hydroxymethyl)tetrahydrofuro[3,4-*b*]-furan-2(3*H*)-one (9).

To a stirred solution of the lactone **8** (1.2 g, 4.6 mmol) in MeOH (15 mL) at 0 °C was added K_2CO_3 (695 mg, 5 mmol), and the mixture was stirred for 15 min. The reaction mixture was concentrated under reduced pressure to remove MeOH. The obtained residue was dissolved in water (10 mL) and CH_2Cl_2 (10 mL), and the aqueous layer was extracted with (3×) 10% $MeOH/CH_2Cl_2$. The combined organic layer was washed with brine and dried over

anhydrous Na_2SO_4. The solvent was evaporated, and the residue was purified by by silica gel column chromatography (10% MeOH/CH_2Cl_2) to afford **9** (690 mg, 85%) as a colorless oil. R_f = 0.2 (80% EtOAc/hexanes, SiO_2 plate). $[\alpha]_D^{23} = -11.1$ (c 0.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (ddd, J = 6.9, 4.8, 2.0 Hz, 1H), 4.17 (dd, J = 11.0, 4.7 Hz, 1H), 4.02 (dt, J = 11.4, 2.4 Hz, 1H), 3.86–3.70 (m, 2H), 3.64–3.56 (m, 1H), 2.98–2.88 (m, 1H), 2.82 (ddd, J = 18.1, 9.3, 1.4 Hz, 1H), 2.46 (dd, J = 18.1, 1.8 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.6, 85.2, 84.3, 72.7, 62.4, 40.0, 32.8. LRMS (ESI) *m/z*: $[M + H]^+$ 159. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd $C_7H_{10}O_4Na$ 181.0471; found 181.0470.

(3*aS*,6*aR*)-4-Methoxytetrahydrofuro[3,4-*b*]furan-2(3*H*)-one (10).

To a solution of alcohol **9** (200 mg, 1.3 mmol) in anhydrous CH_2Cl_2 (3 mL) were added Na_2HPO_4 (369 mg, 2.6 mmol) and DMP (1.10 g, 2.6 mmol) at 0 °C. The reaction mixture was stirred at 0 to 23 °C for 3 h and then cooled to 0 °C and quenched with a saturated solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×), and the organic layer was washed with water (10 mL) and brine. The organic solution was dried over anhydrous $NaSO_4$, filtered, and concentrated under reduced pressure to afford the aldehyde. The crude aldehyde was used in the next step without further purification.

To a stirred solution of the above crude aldehyde in anhydrous CH_2Cl_2 (10 mL) at 0 °C were added $NaHCO_3$ (211 mg, 2.52 mmol) and *m*-CPBA (577 mg, 2.5 mmol). The reaction mixture was stirred for 2 h at 0 °C and quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with (3×) CH_2Cl_2. The combined organic solvent was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the formate. The crude formate was used in the next step without further purification.

To a stirred solution of the above crude formate (1.2 mmol) in MeOH (5 mL) at 0 °C was added slowly 6% HCl/MeOH (5 mL), and the mixture was stirred for 12 h at 0 to 23 °C. The reaction mixture was then neutralized with a saturated solution of $NaHCO_3$, concentrated under reduced pressure to remove MeOH, extracted with CH_2Cl_2, and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield a crude residue that was purified by flash chromatography on silica (50% ether/hexane) to yield lactone **10** (82 mg, 41% over 3 steps) as an amorphous solid with a 3:1 mixture of separable anomers. Major Anomer: R_f = 0.4 (40% EtOAc/hexanes, SiO_2 plate). $[\alpha]_D^{23} = +70.3$ (c 0.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (dd, J = 7.1, 3.9 Hz, 1H), 4.87 (s, 1H), 4.09 (d, J = 10.9 Hz, 1H), 3.94 (dd, J = 10.9, 3.9 Hz, 1H), 3.31 (s, 3H), 3.02 (ddd, J = 11.2, 7.1, 4.0 Hz, 1H), 2.83 (dd, J = 18.6, 11.3 Hz, 1H), 2.50 (dd, J = 18.6, 4.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.9, 109.9, 82.9, 70.6, 54.5, 45.0, 31.7. LRMS (ESI) *m/z*: $[M + H]^+$ 159.1. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd $C_7H_{10}O_4Na$ 181.0471; found 181.0472.

(3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-ol (2).[17]

To a flame-dried flask was added $LiAlH_4$ (734 mg, 19.33 mmol). The flask was evacuated by vacuum and then flushed with argon. To the flask was added dry THF (38 mL). The mixture was stirred and cooled to −78 °C prior to the addition of a solution of lactone **10**

(1.02 g, 6.44 mmol) in THF (38 mL). The reaction mixture was then allowed to warm to 23 °C over 1 h. The reaction mixture was cooled to 0 °C, and then H_2O (0.7 mL), 2.0 M NaOH (0.7 mL), and H_2O (2.1 mL) were added sequentially and slowly. The mixture was stirred vigorously at 0 °C for 1.5 h, and then it was filtered through Celite with MeOH. The filtrate was concentrated under reduced pressure to afford a residue containing the crude diol.

To the flask containing the above crude diol (6.44 mmol) was added 1.0 M HCl (15 mL). The mixture was cooled to 0 °C and stirred prior to slow addition of concentrated HCl (1.5 mL). The mixture was allowed to warm to 23 °C over 1 h, and then the mixture was cooled back down to 0 °C and neutralized by portionwise addition of solid Na_2CO_3. The aqueous layer was extracted with a 10% MeOH/CH_2Cl_2 solution (5 × 150 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude ligand alcohol **2** that was purified by flash chromatography on SiO_2 (70% ether/hexanes) to yield ligand alcohol **2** (533 mg, 63% over 2 steps) as a colorless oil. R_f = 0.56 (100% EtOAc, SiO_2 plate). $[\alpha]_D^{23} = -12.3$ (*c* 0.732, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (d, *J* = 5.8 Hz, 1H), 4.45 (dtd, *J* = 8.0, 6.6, 5.2 Hz, 1H), 4.03–3.96 (m, 2H), 3.90 (ddd, *J* = 10.0, 8.6, 6.3 Hz, 1H), 3.64 (dd, *J* = 9.2, 7.0 Hz, 1H), 2.86 (dddd, *J* = 10.1, 7.9, 5.2, 2.5 Hz, 1H), 2.36–2.27 (m, 1H), 1.88 (dtd, *J* = 12.9, 9.9, 8.4 Hz, 1H), 1.79 (d, *J* = 5.3 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 109.7, 73.3, 71.1, 70.0, 46.7, 25.0.

(3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-yl (4-nitrophenyl) Carbonate (11).[26]

To a flame-dried flask were added optically active *bis*-THF alcohol (−)−2 (6 mg, 0.046 mmol) and CH_2Cl_2 (1.0 mL) followed by pyridine (7.5 μL, 0.092 mmol). The mixture was stirred under argon and cooled to 0 °C. To the mixture was quickly added 4-nitrophenyl chloroformate (19 mg, 0.092 mmol), and the resulting reaction was stirred at 23 °C for 12 h. After this period, the mixture was concentrated under reduced pressure and purified by flash chromatography (20% EtOAc/hexanes) to yield carbonate **11** (12 mg, 92% yield) as an amorphous white solid. R_f = 0.15 (30% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34–8.25 (m, 2H), 7.43–7.35 (m, 2H), 5.77 (d, *J* = 5.1 Hz, 1H), 5.32–5.20 (m, 1H), 4.15 (dd, *J* = 10.0, 6.1 Hz, 1H), 4.05 (td, *J* = 8.4, 2.6 Hz, 1H), 3.97 (tt, *J* = 10.0, 6.1 Hz, 2H), 3.15 (dddd, *J* = 10.2, 7.9, 5.1, 2.4 Hz, 1H), 2.17 (ddt, *J* = 13.2, 5.4, 2.5 Hz, 1H), 2.00 (dtd, *J* = 13.2, 10.0, 8.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1, 151.9, 145.5, 125.3, 121.6, 109.1, 77.5, 70.3, 69.5, 44.9, 25.9.

Ethyl 2-((3a*R*,5*S*,6a*R*)-5-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyldihydrofuro[2,3-*d*][1,3]dioxol-6(5*H*)-ylidene)-acetate (13).[28]

To a flame-dried flask was added CH_2Cl_2 (210 mL). The CH_2Cl_2 was stirred under argon and cooled to −78 °C prior to addition of oxalyl chloride (5.47 mL, 64.6 mmol). After 5 min, DMSO (9.18 mL, 129.2 mmol) was added dropwise to the reaction mixture. After 10 min, a solution of commercially available 1,2:5,6-di-*O*-isopropylidene-*α*-D-glucofuranose **12** (8.41 g, 32.3 mmol) in CH_2Cl_2 (20 mL) was added dropwise to the reaction mixture, and then the mixture was stirred at −78 °C for 1 h. At this time, Et_3N (22.5 mL, 161.6 mmol) was added. The temperature of the reaction mixture was maintained at −78 °C for 10 min, and then the cooling bath was removed. The mixture was allowed to stir for 30 min while warming to 23 °C. The reaction mixture was then quenched with H_2O and transferred to a separatory

funnel. The organic layer was washed with saturated aqueous $NaHCO_3$ and then with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude ketone as a brown oil. The crude ketone was used without further purification.

To a flame-dried flask was added NaH (60% in oil) (2.37 g, 59 mmol). The flask was evacuated and placed under argon prior to addition of dry THF (91 mL). The mixture was stirred and cooled to 0 °C prior to the dropwise addition of triethyl phosphonoacetate (12.3 mL, 62.2 mmol). After 15 min, a solution of the above crude ketone (31.1 mmol) in dry THF (31 mL) was added slowly at 0 °C. The reaction mixture was kept at a temperature of 0 °C for 30 min, and then the reaction mixture was allowed to warm to 23 °C over 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl, extracted with Et_2O, and washed with brine. The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield a brown oil that was purified by flash chromatography on SiO_2 (15% ether/hexanes to 25% ether/hexanes) to yield *α,β*-unsaturated ester **13** as a 4:1 (*Z*/*E*) mixture of separable isomers (combined yield for mixture of isomers, 48% over 2 steps). *Z*-isomer of ester **13**: (3.95 g, 39% over 2 steps), amorphous solid. R_f = 0.60 (50% ether/hexanes, SiO_2 plate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (dd, J = 2.2, 1.4 Hz, 1H), 5.82 (d, J = 4.2 Hz, 1H), 5.73 (dt, J = 4.2, 1.4 Hz, 1H), 4.66 (ddt, J = 6.0, 2.2, 1.4 Hz, 1H), 4.28–4.19 (m, 2H), 4.12–4.06 (m, 1H), 4.03–3.97 (m, 2H), 1.49 (s, 3H), 1.43 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 155.8, 118.0, 112.9, 110.3, 105.0, 80.0, 78.5, 76.9, 67.4, 60.8, 27.4, 27.2, 26.8, 25.5, 14.3. *E*-isomer of ester **13E**: (963 mg, 9% over 2 steps). R_f = 0.65 (50% ether/hexanes, SiO_2 plate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (t, J = 1.9 Hz, 1H), 5.92 (d, J = 4.8 Hz, 1H), 5.75 (q, J = 1.9 Hz, 1H), 5.9 (dt, J = 4.8, 1.9 Hz, 1H), 4.34 (ddd, J = 7.9, 6.3, 2.6 Hz, 1H), 4.17 (qt, J = 7.4, 3.8 Hz, 2H), 3.96 (dd, J = 8.8, 6.3 Hz, 1H), 3.56 (dd, J = 8.8, 7.9 Hz, 1H), 1.42 (s, 3H), 1.37 (s, 3H), 1.32–1.27 (m, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.7, 158.1, 118.2, 113.8, 109.2, 103.9, 82.3, 80.1, 79.1, 65.5, 60.9, 27.99, 27.96, 26.2, 25.8, 14.3.

Ethyl-2-((3a*R*,5*S*,6*R*,6a*R*)-5-((*R*)1-,2-dihydroxyethyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)acetate (14).[28]

To a flask were added *Z*-ester **13** (1.77 g, 5.4 mmol) and 80% AcOH/H_2O (20 mL). The mixture was stirred at 23 °C for 60 h. The reaction mixture was then concentrated under reduced pressure, and the resultant crude orange oil was purified by flash chromatography on SiO_2 (50% EtOAc/hexanes) to yield the deprotected *α,β*-unsaturated ester (1.14 g, 74%) as a colorless oil. R_f = 0.45 (75% EtOAc/hexanes, SiO_2 plate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (dd, J = 2.2, 1.5 Hz, 1H), 5.86 (d, J = 4.2 Hz, 1H), 5.74 (dt, J = 4.2, 1.5 Hz, 1H), 4.79 (ddd, J = 6.6, 2.2, 1.4 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.80–3.67 (m, 3H), 2.95 (d, J = 6.6 Hz, 1H), 2.45 (s, 1H), 1.48 (s, 3H), 1.41 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.3, 155.7, 117.7, 113.0, 104.9, 80.0, 78.4, 73.5, 63.5, 60.9, 27.4, 27.2, 14.3.

To a flame-dried flask was added a solution of the above *α,β*-unsaturated ester (1.06 g, 3.68 mmol) in anhydrous ethanol (16 mL) followed by 10% Pd/C (53 mg, 5% w/w). The flask

containing the mixture was evacuated by vacuum and flushed with argon three times, and then it was evacuated by vacuum and flushed with hydrogen three times. The reaction mixture was then left to stir under an atmosphere of hydrogen (1 atm) for 24 h. The reaction mixture was then filtered through Celite with EtOAc and concentrated under reduced pressure to yield a crude colorless oil that was purified by flash chromatography on SiO_2 (3% MeOH/CH_2Cl_2) to yield the saturated diol **14** (950 mg, 89%) as a colorless syrup. R_f = 0.45 (75% EtOAc/hexanes, SiO_2 plate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (d, J = 3.7 Hz, 1H), 4.76 (dd, J = 4.8, 3.7 Hz, 1H), 4.13 (qd, J = 7.1, 3.2 Hz, 2H), 3.82–3.60 (m, 4H), 3.24 (d, J = 5.4 Hz, 1H), 2.91 (t, J = 5.6 Hz, 1H), 2.77–2.63 (m, 2H), 2.42–2.31 (m, 1H), 1.46 (s, 3H), 1.28 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.9, 111.9, 104.8, 81.6, 81.1, 73.7, 63.9, 60.8, 43.2, 30.5, 26.7, 26.4, 14.3.

(3a*R*,4*S*,6a*R*)-6-Hydroxy-4-(hydroxymethyl)tetrahydrofuro-[3,4-*b*]furan-2(3*H*)-one (15).[28]

To a flask were added saturated diol **14** (866 mg, 3.0 mmol) and MeOH (15 mL). The mixture was stirred and cooled to 0 °C prior to portionwise addition of $NaIO_4$ (1.28 g, 6.0 mmol). The reaction mixture was then allowed to warm to 23 °C over 2 h while stirring vigorously. The reaction mixture was filtered through Celite with MeOH and concentrated under reduced pressure to yield a residue that was dissolved in H_2O and CH_2Cl_2 and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude aldehyde that was used without further purification.

The above crude aldehyde was dissolved in MeOH (15 mL) and cooled to 0 °C prior to portionwise addition of $NaBH_4$ (226 mg, 6.0 mmol). The reaction mixture was stirred at 0 °C for 1 h. The mixture was then concentrated under reduced pressure to remove MeOH. Saturated aqueous NH_4Cl was added, and the organics were extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield a colorless oil that was purified by flash chromatography on SiO_2 (40% EtOAc/hexanes) to yield ester **15** (683 mg, 88% over 2 steps) as a colorless oil and as a single diastereomer. R_f = 0.25 (40% EtOAc/hexanes, SiO_2 plate). $[\alpha]_D^{23} = +65.8$ (c 1.31, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (d, J = 3.8 Hz, 1H), 4.77 (t, J = 3.9 Hz, 1H), 4.15 (dttd, J = 10.8, 7.4, 3.7, 1.2 Hz, 2H), 3.91–3.83 (m, 2H), 3.60–3.52 (m, 1H), 2.69 (ddd, J = 16.8, 8.3, 1.1 Hz, 1H), 2.48–2.33 (m, 2H), 2.05 (s, 1H), 1.48 (s, 3H), 1.31 (s, 3H), 1.26 (td, J = 7.1, 1.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.4, 111.9, 104.8, 81.7, 81.5, 61.5, 60.9, 39.8, 29.9, 26.8, 26.4, 14.3.

2,5-Dioxopyrrolidin-1-yl ((3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl) Carbonate (16).[17]

To a flame-dried flask were added *bis*-THF ligand alcohol **2** (84 mg, 0.65 mmol) and acetonitrile (2.5 mL). To the mixture was added triethylamine (180 μL, 1.29 mmol) followed by commercially available *N,N'*-disuccinimidyl carbonate (248 mg, 0.97 mmol). The mixture was stirred under argon at 23 °C for 16 h, and then saturated aqueous $NaHCO_3$ was added. The organics were extracted with a solution of 10% MeOH/CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography on SiO_2 using EtOAc to yield **16** (51 mg, 29% yield (quantitative yield brsm)) as a white solid. R_f = 0.85 (EtOAc, SiO_2 plate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71

(d, J = 5.1 Hz, 1H), 5.22 (dt, J = 8.2, 6.0 Hz, 1H), 4.13–4.05 (m, 1H), 4.00 (td, J = 8.4, 2.5 Hz, 1H), 3.91 (ddd, J = 10.6, 8.8, 5.9 Hz, 2H), 3.16–3.04 (m, 1H), 2.82 (s, 4H), 2.11 (ddt, J = 13.5, 5.4, 2.4 Hz, 1H), 1.95 (dddd, J = 13.4, 10.3, 9.5, 8.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 151.3, 109.3, 79.7, 70.1, 69.7, 45.2, 26.0, 25.5.

((3*aR*,5*S*,6*R*,6*aR*)-6-(2-Ethoxy-2-oxoethyl)-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methyl Benzoate (7, from 12).

To a flame-dried flask was added a solution of **15** (16 mg, 0.1 mmol) in CH_2Cl_2. To the mixture was added triethylamine (42 μL, 0.3 mmol), and the mixture was then cooled to 0 °C prior to addition of benzoyl chloride (35 μL, 0.3 mmol). The mixture was then allowed to warm to 23 °C, and it was stirred under argon for 18 h. The mixture was then diluted with water, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on SiO_2 with 20% EtOAc/hexanes provided the desired benzoate ester **7** (15 mg, 65% yield) as a colorless oil. R_f = 0.30 (20% EtOAc/hexanes, SiO_2 plate). $[\alpha]_D^{23} = +52.7$ (c 0.55, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15–8.00 (m, 2H), 7.60–7.52 (m, 1H), 7.43 (t, J = 7.6 Hz, 2H), 5.87 (d, J = 3.7 Hz, 1H), 4.82 (t, J = 4.2 Hz, 1H), 4.56 (dd, J = 12.3, 2.9 Hz, 1H), 4.34 (dd, J = 12.3, 5.0 Hz, 1H), 4.19–4.08 (m, 3H), 2.75 (dd, J = 17.0, 9.8 Hz, 1H), 2.54–2.33 (m, 2H), 1.53 (s, 3H), 1.32 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.7, 166.3, 133.1, 129.7 (2C), 129.6, 128.3 (2C), 111.7, 104.8, 80.8, 78.6, 63.9, 60.7, 41.4, 29.6, 26.6, 26.2, 14.0. LRMS (ESI) *m/z*: $[M + Na]^+$ 387.0. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd $C_{19}H_{24}O_7Na$ 387.1414; found 387.1421.

Benzyl-((2*S*,3*R*)-3-hydroxy-4-((*N*-isobutyl-4-nitrophenyl)-sulfonamido)-1-phenylbutan-2-yl)carbamate (18).[17]

To a flask were added commercially available benzyl (1*S*)-1-[(2*S*)-2-oxiranyl]-2-phenylethylcarbamate (**17**) (200 mg, 0.7 mmol) and isopropanol (2.8 mL). To the mixture was added isobutylamine (0.43 mL, 4.26 mmol). A reflux condenser was attached, and the mixture was stirred and heated at 60 °C for 22 h. The mixture was concentrated under reduced pressure to afford the corresponding aminoalcohol as an amorphous solid that was used in the next step without further purification.

The crude aminoalcohol (0.71 mmol) was dissolved in CH_2Cl_2 (7 mL) and transferred to a flame-dried flask. The mixture was cooled to 0 °C prior to the addition of triethylamine (0.3 mL, 2.1 mmol) and then 4-nitrobenzenesulfonyl chloride (236 mg, 1.1 mmol). The mixture was placed under argon and stirred at 0 °C for 5 min. The cooling bath was removed, and the reaction was warmed to 23 °C and stirred for 5 h. The mixture was transferred to a separatory funnel, and 1.0 M HCl was added. The organics were extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography on SiO_2 using 20% EtOAc/hexane and then 30% EtOAc/hexane as the eluent to yield the desired CBz-protected amine **18** (231 mg, 71% over 2 steps) as an amorphous solid. R_f = 0.30 (30% EtOAc/hexanes, SiO_2 plate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35–8.24 (m, 2H), 7.92 (d, J = 8.5 Hz, 2H), 7.38–7.12 (m, 10H), 4.99 (td, J = 18.2, 17.1, 10.6 Hz, 3H), 3.92–3.80 (m, 2H), 3.62 (s, 1H), 3.26–3.11 (m, 2H), 3.05–2.84 (m, 4H), 1.85 (dt, J = 13.8, 6.8 Hz, 1H), 0.86 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.7, 150.1,

144.8, 137.3, 136.3, 129.5, 128.8, 128.7, 128.6, 128.3, 128.0, 126.9, 124.4, 72.3, 67.0, 57.9, 55.6, 52.8, 35.6, 27.1, 20.1, 19.9.

(3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-yl-((2*S*,3*R*)-4-((4-amino-*N*-isobutylphenyl)-sulfonamido)-3-hydroxy-1-phenyl-butan-2-yl)carbamate (1).

To a flask were added carbamate derivative **18** (48 mg, 0.1 mmol) and THF (1 mL). To the mixture were added triethylamine (24 μL, 0.17 mmol), succinimidyl carbonate **16** (26 mg, 0.1 mmol), and then 10% Pd/C (10 mg). The mixture was placed under a hydrogen balloon. The flask containing the mixture was evacuated under vacuum briefly and then flushed with hydrogen. This was repeated two more times, and then the mixture was left to stir under a balloon of hydrogen at 23 °C for 17 h. The mixture was then filtered through Celite with ethyl acetate, concentrated under reduced pressure, and purified by flash chromatography on SiO_2 using 50% EtOAc/CH_2Cl_2 as the eluent to yield compound **1** (Darunavir) (25 mg, 53%) as an amorphous solid. R_f = 0.5 (75% EtOAc/hexanes, SiO_2 plate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.8 Hz, 2H), 7.23 (m, 5H), 6.77 (d, J = 8.3 Hz, 2H), 5.64 (d, J = 5.1 Hz, 1H), 5.04 (dd, J = 20.8, 8.5 Hz, 2H), 3.87 (td, J = 20.4, 16.5, 8.6 Hz, 5H), 3.78–3.60 (m, 3H), 3.22–2.75 (m, 8H), 1.85–1.74 (m, 1H), 1.62 (t, J = 10.7 Hz, 1H), 1.45 (d, J = 13.4 Hz, 1H), 0.92 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.6, 149.8, 137.8, 129.6, 129.5, 128.6, 127.1, 126.7, 115.0, 109.5, 73.5, 72.9, 71.1, 69.8, 58.9, 55.3, 53.8, 45.6, 35.8, 27.4, 25.9, 20.3, 20.1. HRMS (APCI) *m/z*; $[M + H]^+$ calcd $C_{27}H_{38}N_3O_7S$, 548.2425; found 548.2430.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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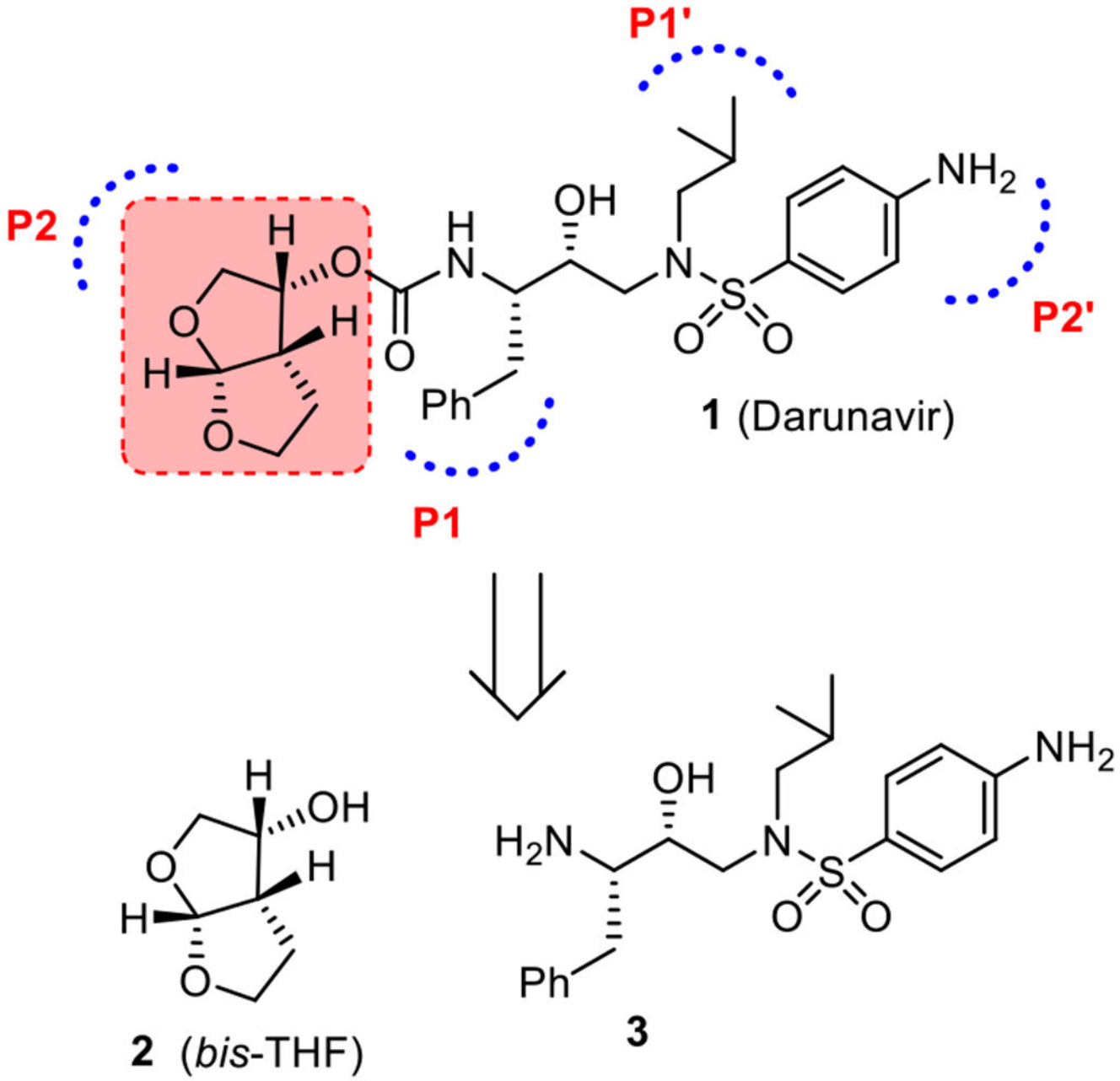
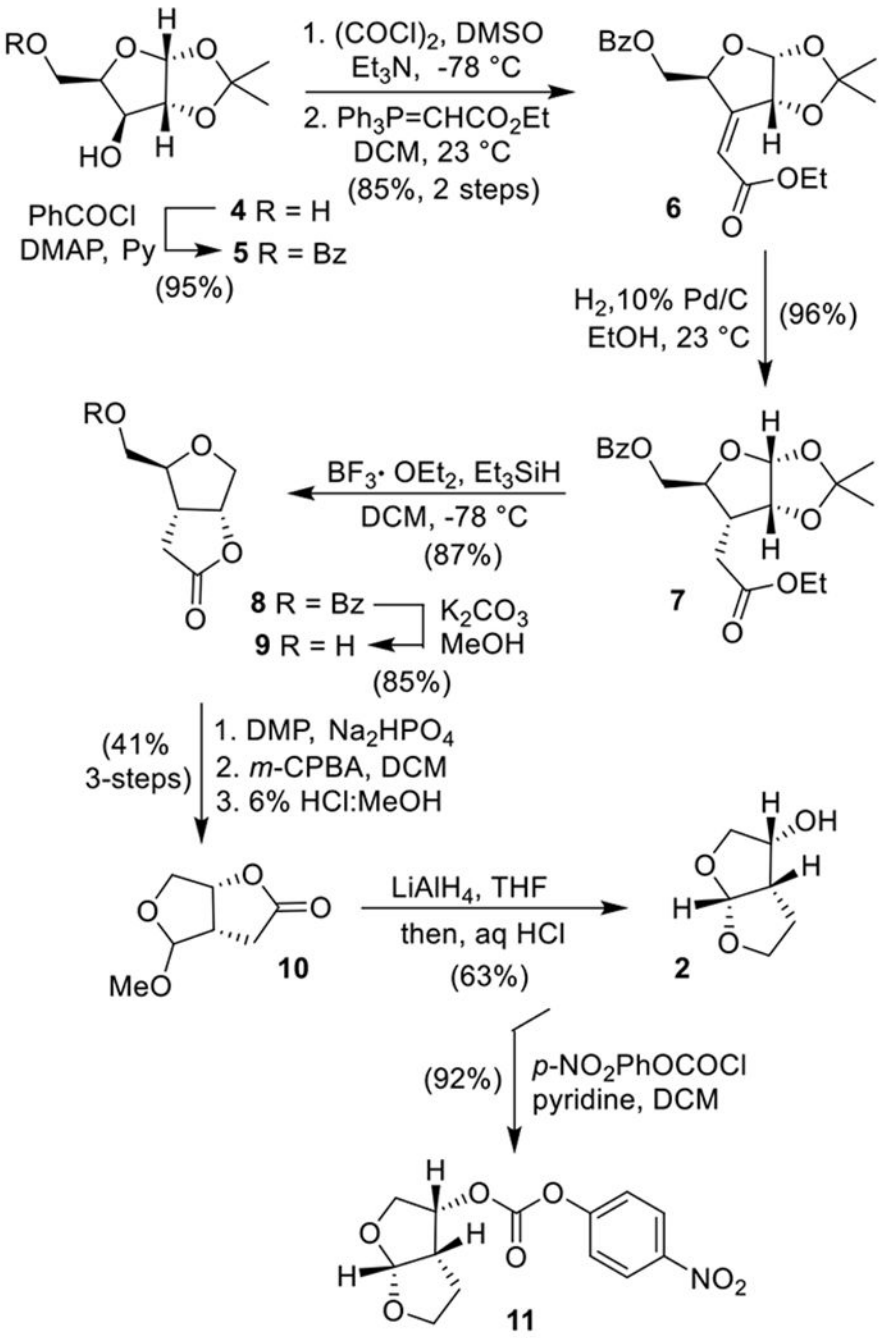
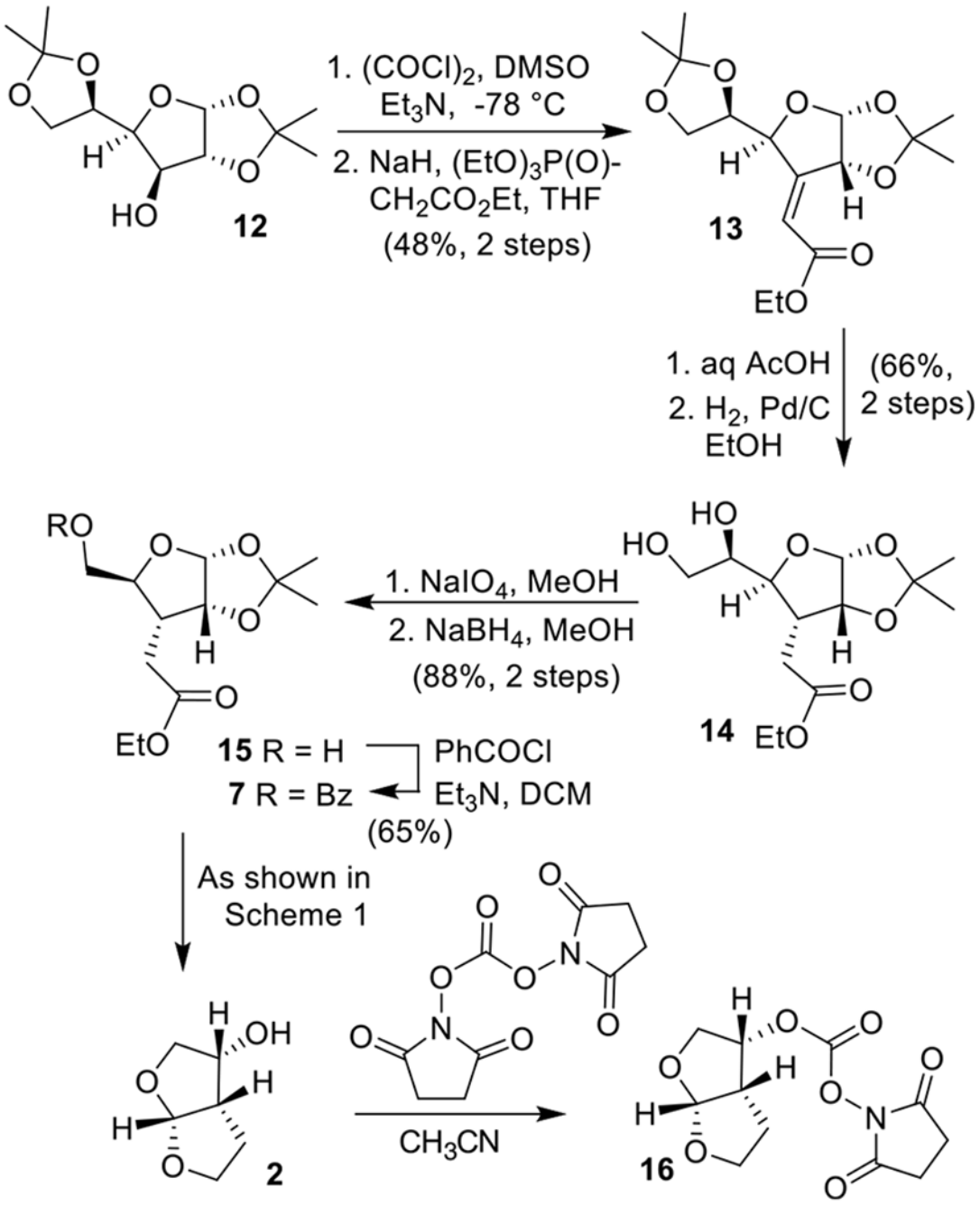


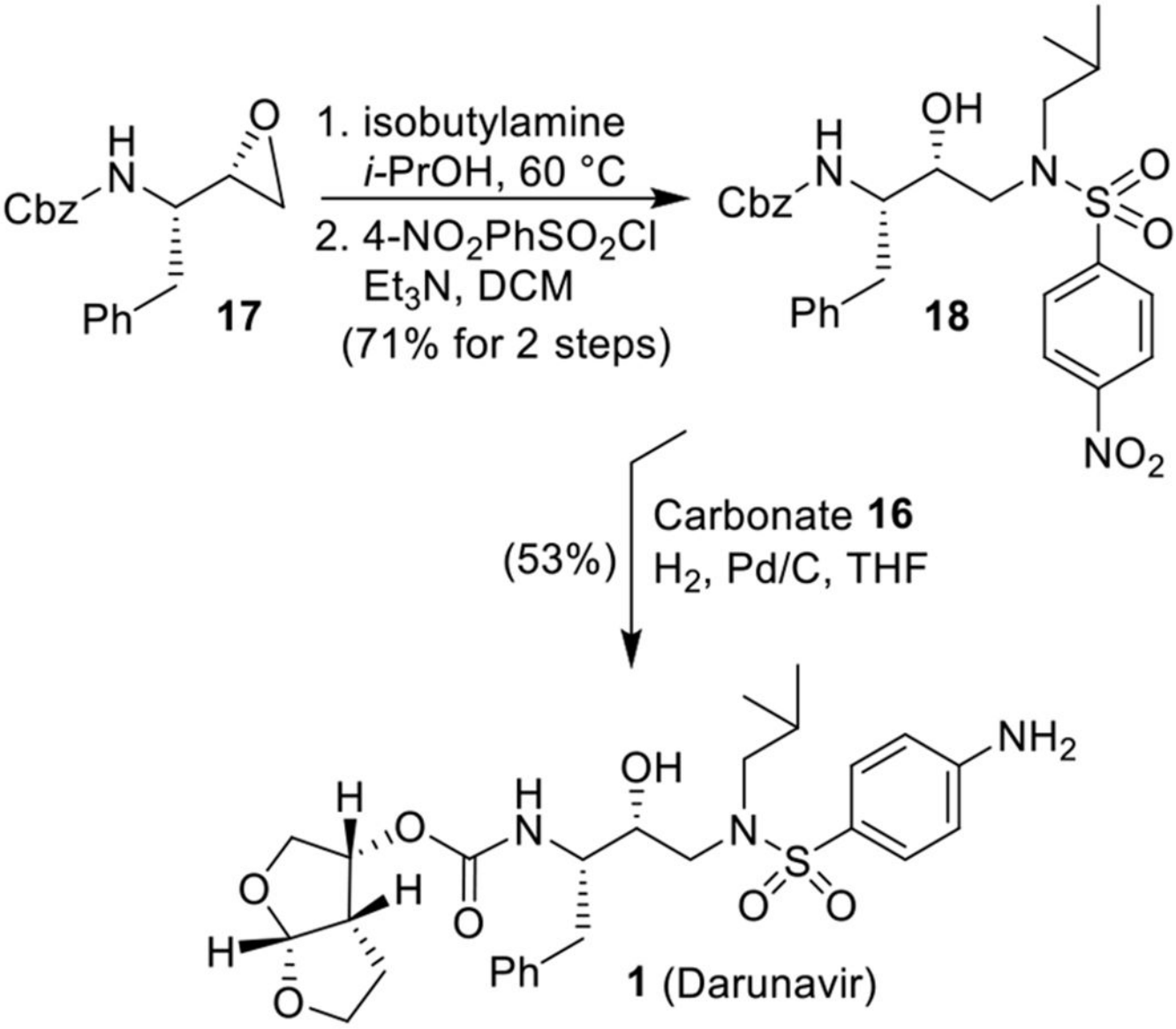
Figure 1.
Structure of darunavir (**1**), *bis*-THF (**2**), and aminoalcohol **3**.



Scheme 1.
Synthesis of Optically Active *bis*-THF Ligand from D-Xylose



Scheme 2.
Synthesis of Optically Active *bis*-THF Ligand from D-Glucose



Scheme 3.
Synthesis of Darunavir (1)