Citation: Kong, Y.; Boggu, P.R.; Park, G.M.; Kim, Y.S.; An, S.H.; Kim, I.S.; Jung, Y.H. Total Synthesis of Eliglustat via Diastereoselective Amination of Chiral para-Methoxycinnamyl Benzyl Ether. Molecules 2022, 27, 2603. https://doi.org/10.3390/molecules27082603

Received: 22 March 2022
Accepted: 14 April 2022
Published: 18 April 2022

Publisher’s Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

Abstract: Eliglustat (Cerdelga®, Genzyme Corp. Cambridge, MA, USA) is an approved drug for a non-neurological type of Gaucher disease. Herein, we describe the total synthesis of eliglustat starting from readily available 1,4-benzodioxan-6-carbaldehyde via Sharpless asymmetric dihydroxylation and diastereoselective amination of chiral para-methoxycinnamyl benzyl ethers using chlorosulfonyl isocyanate as the key steps. Notably, the reaction between syn-1,2-dibenzyl ether and chlorosulfonyl isocyanate in the mixture of toluene and hexane (10:1) afforded syn-1,2-amino alcohol at a 62% yield with a diastereoselectivity > 20:1. This observation can be explained by competition between the $S_N1$ and the $S_N2$ mechanisms, leading to the retention of stereochemistry.

Keywords: amination; eliglustat; chlorosulfonyl isocyanate; Sharpless asymmetric dihydroxylation; total synthesis

1. Introduction

The 1,2-amino alcohol motif has received considerable attention because of its essential role as a fundamental building block [1–3] and its presence in several pharmaceutical agents [4–15], including more than 80 FDA-approved drugs [7]. For example, eliglustat (1, Cerdelga®, Genzyme Corp. United States) has been used for treating Gaucher disease by inhibiting glucosylceramide synthase [4–6]. Florfenicol (2) is mainly used in veterinary medicine for treating bovine respiratory disease [8–10]. Droxidopa (3) has been used as a prodrug of neurotransmitter norepinephrine [11–13]. Zetomipzomib (4, KZR-616), a first-in-class inhibitor of the immunoproteasome, selectively targets the LMP7 and LMP2 subunits of the immunoproteasome [14,15] (Figure 1).

In particular, eliglustat is a medication used to treat a non-neurological type of Gaucher disease and was approved by the United States FDA in 2014 [4–7]. Due to its potent biological activity and unique structural features, several synthetic approaches for the preparation of eliglustat have been developed [16–21]. For example, the Genzyme company reported the synthesis of eliglustat from 1,4-benzodioxan-6-carbaldehyde through a chiral aldol reaction with the chiral-pooled intermediate of phenylglycinol [19]. Xu and coworkers described the total synthesis of eliglustat through a Crimmins aldol reaction of 1,4-benzodioxan-6-carbaldehyde used with Evans auxiliary [20]. Moreover, the synthesis of eliglustat using an organocatalytic asymmetric Henry reaction as a key step was also reported [21]. As part of an ongoing research program aimed at the total synthesis of pharmacologically active compounds via stereoselective amination of chiral benzyl ethers using chlorosulfonyl isocyanate (CSI) [22–26], we herein report the total synthesis of eliglustat from commercially available 1,4-benzodioxan-6-carboxaldehyde via diastereoselective amination of chiral para-methoxycinnamyl benzyl ethers using CSI.
2. Results and Discussion

The retrosynthetic analysis of eliglustat (1) is shown in Scheme 1. It shows that 1 was synthesized through ozonolysis, reductive amination, the removal of protected groups, and acylation from the intermediate 5. The required syn-1,2-amino alcohol motif of 5 was prepared via the diastereoselective installation of an NHCbz moiety into syn-1,2-dibenzyl ether 6 using CSI, which in turn was easily derived from 2,3-dihydrobenzo[6][1,4]dioxine-6-carbaldehyde (7) as a starting material.

Our initial study focused on the efficient construction of syn-1,2-dibenzyl ether 6, which was subjected to a stereoselective amination methodology to give the protected syn-1,2-amino benzyl ether 5 (Scheme 2). The Horner–Wadsworth–Emmons olefination of 7 with trimethyl phosphonoacetate in the presence of sodium hydride afforded olefin 8 at a 98% yield. The Sharpless asymmetric dihydroxylation [27] of olefin 8 with AD-mix-β furnished the chiral syn-1,2-diol 9 at an 82% yield. Next, the syn-1,2-diol 9 was protected with acetone to produce 10 at an 83% yield. The reduction of an ester group on 10 to a primary alcohol followed by Swern oxidation and Wittig olefination provided the para-methoxycinnamyl
derivative 11 (E:Z ratio of 1:3) at a 67% yield over three steps. The removal of acetal and the subsequent benzylation of syn-diol 12 furnished the syn-1,2-dibenzyl ether 6 at a 71% yield.

Next, we screened the optimal reaction conditions for the stereoselective amination of syn-1,2-dibenzyl ether 6 using CSI (Table 1). The coupling of 6 and CSI in dichloromethane at 0 °C furnished the corresponding carbamate 5 at a 29% yield with a diastereoselectivity of 1.2:1 (Table 1, entry 1). An examination of the effect of solvents under various temperatures indicated that the improved yield and diastereoselectivity were achieved by using toluene, affording 5 (Table 1, entry 9). After further screening, we found that the highest diastereoselectivity (dr > 20:1) was obtained in a mixture of toluene and n-hexane (10:1) at −78 °C with an improved yield of 62% (Table 1, entry 11).

The diastereomeric ratio was determined by 1H NMR analysis. As shown in Figure 2 (case selected), a single proton at the chiral position was significantly distinguishable in the 1H NMR spectra. As a result, higher diastereoselectivity was obtained in the mixed solvent system of toluene and n-hexane (entry 11) than in other single nonpolar solvent systems with CH2Cl2 (entry 1 and 2), n-hexane (entry 5) and toluene (entry 9).
Table 1. Optimization of diastereoselective amination of 6.

| Entry | Solvent       | T (°C) | Yield (%) | dr |
|-------|---------------|--------|-----------|----|
| 1     | CH₂Cl₂        | 0      | 29        | 1.2:1 |
| 2     | CH₂Cl₂        | −40    | 27        | 2.3:1 |
| 3     | CH₂Cl₂        | −78    | 34        | 5.4:1 |
| 4     | n-Hexane      | 0      | 28        | 1.3:1 |
| 5     | n-Hexane      | −40    | 56        | 3.7:1 |
| 6     | n-Hexane      | −78    | 59        | 5:1  |
| 7     | Toluene       | 0      | 24        | 2.1:1 |
| 8     | Toluene       | −40    | 51        | 5.1:1 |
| 9     | Toluene       | −78    | 54        | 5.6:1 |
| 10    | Toluene/n-Hexane | −40    | 58        | 12:1 |
| 11    | Toluene/n-Hexane | −78    | 62        | >20:1 |

*a Reaction conditions: (i) compound 6 (0.2 mmol), chlorosulfonyl isocyanate (3.93 mmol), Na₂CO₃ (2.56 mmol), and solvent (0.05 M) at indicated temperature for 24 h; (ii) 25% Na₂SO₃ at room temperature for 13 h; b isolated yield; c diastereomeric ratios were determined through ¹H NMR analysis.

Figure 2. ¹H NMR analysis of diastereoselectivity of CSI amination. The conditions and diastereomeric ratios are as follows. Entry 1: in CH₂Cl₂ at 0 °C, dr = 1.2:1, Entry 2: in CH₂Cl₂ at −40 °C, dr = 2.3:1, Entry 5: in n-Hexane at −40 °C, dr = 3.7:1, Entry 9: in Toluene at −78 °C, dr = 5.6:1, Entry 11: in Toluene/n-Hexane (1:10) at −78 °C, dr = >20:1.
The origin of the diastereoselectivity can be explained by competition between the $S_{N}i$ pathway leading to a retention of stereochemistry through a four-membered transition state and the $S_{N}1$ pathway through a carbocation intermediate [28] (Scheme 3). The improved diastereoselectivity in mixed nonpolar solvents (toluene and $n$-hexane) at low temperatures ($−78 °C$) might be realized by the increased formation of a tight ion pair intermediate (IIA) rather than a carbocation intermediate (IIB).

Scheme 3. Proposed reaction mechanism of CSI-mediated amination.

To complete the total synthesis of 1, an ozonolysis reaction of compound 5 was performed to afford the corresponding aldehyde, which was converted to the tertiary amine 13 by reductive amination with pyrrolidine (Scheme 4). The Pd-catalyzed hydrogenolysis of 13 afforded syn-1,2-amino alcohol 14 at an 81% yield. Finally, the acylation of amino alcohol 14 with $n$-octanoyl chloride furnished eliglustat (1) at a 53% yield. The analytical data ($^1$H NMR) and melting point of the synthesized eliglustat (1) were in full agreement with those reported in the literature [19].
Scheme 3. Proposed reaction mechanism of CSI-mediated amination.

To complete the total synthesis of 1, an ozonolysis reaction of compound 5 was performed to afford the corresponding aldehyde, which was converted to the tertiary amine 13 by reductive amination with pyrrolidine (Scheme 4). The Pd-catalyzed hydrogenolysis of 13 afforded syn-1,2-amino alcohol 14 at an 81% yield. Finally, the acylation of amino alcohol 14 with n-octanoyl chloride furnished eliglustat (1) at a 53% yield.

The analytical data (1H NMR) and melting point of the synthesized eliglustat (1) were in full agreement with those reported in the literature [19].

Scheme 4. Synthesis of eliglustat 1.

3. Materials and Methods

3.1. General Information

Commercially available reagents were used without additional purification unless otherwise stated. All reactions were performed under an inert atmosphere of nitrogen. The nuclear magnetic resonance spectra (1H and 13C NMR) were recorded on an Agilent 400 MR 400 MHz Spectrometer with Oxford NMR AS400 Magnet spectrometers in CDCl₃ solution, and the chemical shifts were reported as parts per million (ppm). Resonance patterns were reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation of br was used to indicate a broad signal. The coupling constants (J) were reported in hertz (Hz). The IR spectra were recorded on a JASCO FT/IR-4600 spectrophotometer and were reported as cm⁻¹. Optical rotations were measured with a JASCO P-2000 polarimeter in the solvent specified. Thin layer chromatography (TLC) was carried out using plates coated with Kieselgel 60 F254 (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230–400 mesh) was used. The liquid chromatography-mass spectra (LC/MS) were recorded on an AGILENT 1260 infinity II/InfinityLab LC/MSD system. The high-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 mass spectrometer. Copies of 1H and 13C NMR Spectra are in the Supplementary Materials.

3.2. Experimental Procedure

3.2.1. Synthesis of (E)-Methyl 3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)acrylate (8)

To a solution of sodium hydride (0.67 g, 16.75 mmol) in dry tetrahydrofuran (25 mL), trimethylphosphonoacetate (4.93 mL, 30.46 mmol) was added at 0 °C. The resultant mixture was stirred for 10 min, and a solution of 1,4-benzodioxan-6-carboxaldehyde 7 (2.50 g, 15.23 mmol) in tetrahydrofuran (25 mL) was added. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was slowly quenched with ice water and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (5~40% EtOAc/n-hexanes) to afford 8 (3.27 g) at a 97.5% yield as a white solid (Rf = 0.46 (20% EtOAc/n-hexanes); mp 66–68 °C (lit, mp 66–68 °C) [29,30]; IR(neat) ν 3905, 3855, 3809, 3730, 3680, 3626, 3556, 3408, 2947, 2829, 1714, 1635, 1610, 1579, 1508, 1435, 1309, 1286, 1252, 1174, 1124, 1063, 1032, 916, 887, 856, 814, 650, 492, 463, 432, 422, and 405 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 7.57 (d, J = 15.9 Hz, 1H), 7.07–6.98 (m, 2H), 6.85 (d, J = 8.2 Hz, 1H), 6.27 (d, J = 15.9 Hz, 1H), 4.26 (s, 4H), and 3.78 (s, 3H); 13C NMR (101 MHz, CDCl₃) δ 167.6, 145.7, 144.4, 143.7, 128.0, 117.4, 116.7, 115.8, 64.5, 64.2, and 51.6; ESI-MS m/z: [M + H]⁺ Calcd for C₁₂H₁₂O₄ 221.08 found 221.0; HRMS (EI) m/z: [M⁺] Calcd for C₁₂H₁₂O₄ 220.0736 found 220.0735.
3.2.2. Synthesis of Methyl (2S,3R)-3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2,3-Dihydroxypropanoate (9)

To a stirred clear solution of 8 (0.62 g, 2.82 mmol) in tert-BuOH (28 mL), water (28 mL), AD-mix-β (3.95 g, 5.07 mmol), and methansulfonamidine (0.29 g, 3.10 mmol) were added. The resulting reaction mixture was stirred for 32 h at room temperature. Sodium sulfite (0.53 g, 4.22 mmol) was added to the reaction mixture and stirred for an additional 2 h at room temperature. The heterogeneous mixture was filtered and rinsed with dichloromethane (DCM). The aqueous layer was extracted with DCM (2 × 50 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (0–60% EtOAc/n-hexanes) to afford 9 (0.59 g) at an 82.4% yield as a white solid (Rf = 0.1 (30% EtOAc/n-hexanes); mp 96 °C; [α]D 25 = −33.7 (c 0.1, MeOH); IR(neat) ν 3855, 3809, 3705, 3680, 3411, 2970, 2866, 2843, 2360, 2077, 1734, 1655, 1562, 1456, 1385, 1236, 1055, 1032, 1014, 885, 627, 492, 465, 449, 444, 426, 413, and 403 cm⁻¹; 1H NMR (400 MHz, DMSO-d6) δ 173.2, 143.2, 142.8, 135.6, 119.8, 116.6, 116.0, 76.0, 74.0, 64.5, and 51.9; ESI-MS m/z: [M + H]+ Calcd for C12H14O6 255.09 found 257; [M + Na]+; HRMS (EI) m/z: [M]+ Calcd for C12H14O6 254.0790 found 254.0786.

3.2.3. Synthesis of Methyl (4S,5R)-5-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2,2-Dimethyl-1,3-Dioxolane-4-Carboxylate (10)

To a solution of 9 (1.46 g, 5.74 mmol) in dry acetone (30 mL), p-TsOH (0.1 g, 0.57 mmol) was added. The resulting reaction mixture was stirred for 18 h at room temperature. The mixture was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (0–20% EtOAc/n-hexanes) to afford 10 (1.40 g) at an 82.8% yield as a colorless oil (Rf = 0.3 (20% EtOAc/n-hexanes); mp 96 °C; [α]D 20 = +82.6 (c 0.01, MeOH); IR(neat) ν 3855, 3809, 3732, 3410, 2989, 2945, 2831, 2360, 1757, 1593, 1510, 1439, 1381, 1290, 1259, 1209, 1101, 1068, 1026, 889, 818, 492, 464, 457, 444, 432, 424, and 410 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 6.95 (d, J = 1.9 Hz, 1H), 6.92–6.82 (m, 2H), 5.04 (d, J = 7.7 Hz, 1H), 4.32 (d, J = 7.7 Hz, 1H), 4.26 (d, J = 7.7 Hz, 1H), 4.20 (s, 4H), 4.10 (dd, J = 7.5, 3.9 Hz, 1H), and 3.58 (s, 3H); 13C NMR (101 MHz, DMSO-d6) δ 173.2, 143.2, 142.8, 135.6, 119.8, 116.6, 116.0, 76.0, 74.0, 64.5, and 51.9; ESI-MS m/z: [M + H]+ Calcd for C13H16O6 295.12 found 297; [M + Na]+; HRMS (EI) m/z: [M]+ Calcd for C13H14O6 294.0790 found 294.0786.

3.2.4. Synthesis of 6-((4R,5R)-5-(4-Methoxystyryl)-2,2-Dimethyl-1,3-Dioxolan-4-yl)-2,3-Dihydrobenzo[b][1,4]di-Oxine (11)

To a solution of lithium aluminum hydride (0.89 g, 25.48 mmol) in dry tetrahydrofuran (40 mL), a solution of 10 (2.50 g, 8.49 mmol) in tetrahydrofuran (40 mL) was added at 0 °C. The reaction mixture was stirred for 18 h at 80 °C and quenched very carefully with water at 0 °C. The aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford crude alcohol. The crude compound was used for the next step without further purification.

To a solution of oxalyl chloride (1.09 mL, 12.74 mmol) in dry dichloromethane (25 mL), dimethyl sulfoxide (1.81 mL, 25.48 mmol) in dichloromethane (25 mL) was added at −78 °C. The reaction mixture was stirred for 1 h at −78 °C. To the reaction mixture, a solution of the alcohol in dichloromethane (25 mL) was added slowly and stirred for another 1 h at the same temperature. Then, trimethylamine (5.92 mL, 42.47 mmol) was added, and the resulting mixture was stirred for an additional 30 min. The reaction mixture was carefully quenched with water. The aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford crude carboxaldehyde.
Freshly prepared 4-methoxybenzyltriphenylphosphonium chloride (3.56 g, 8.49 mmol) was placed in a dry round-bottomed flask under a nitrogen atmosphere and diluted with dry tetrahydrofuran (50 mL). To the reaction mixture, n-Buthyllithium (4.08 mL, 10.19 mmol, 2.5 M in tetrahydrofuran) was added dropwise at 0 °C. The resulting reaction mixture was stirred for 30 min until the mixture turned to a deep red solution. A solution of aldehyde in dry tetrahydrofuran (25 mL) was added slowly, and the resultant mixture was stirred for 4 h at room temperature. The reaction mixture was carefully quenched with water and extracted with EtOAc (2 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (0–30% EtOAc/n-hexanes) to afford 11 (2.1 g, E/Z = 1:3) at a 67.1% yield (three steps overall) as a colorless oil (RI = 0.33 (20% EtOAc/n-hexanes); [α]^{20} = +92.3 (c 0.01, MeOH); IR(neat) ν 3396, 2981, 2935, 2877, 2835, 1641, 1506, 1508, 1460, 1435, 1373, 1286, 1246, 1165, 1122, 1047, 968, 922, 885, 845, 814, 733, 577, 553, 503, 453, 436, 420, and 407 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.34–7.29 (m, 0.5 H, E-form), 6.94 (d, \(J = 1.7\) Hz, 1H), 6.89–6.80 (m, 4H), 6.74–6.67 (m, 2H), 6.52 (d, \(J = 15.8\) Hz, 0.25 H, E-form), 6.06 (dd, \(J = 15.8, 7.4\) Hz, 0.25 H, E-form), 5.64 (dd, \(J = 11.5, 9.0\) Hz, 0.75 H, Z-form), 4.66 (dd, \(J = 21.6, 8.4\) Hz, 1H), 4.58 (ddd, \(J = 9.0, 8.4, 0.9\) Hz, 0.75 H, Z-form), 4.32 (ddd, \(J = 8.5, 7.4, 1.0\) Hz, 0.25 H, E-form), 4.26–4.19 (m, 4H), 3.79 (s, 0.75 H, E-form), 3.76 (s, 2.25 H, Z-form), 1.58 (d, \(J = 17.0\) Hz, 1.50 H, E-form), and 1.56 (d, \(J = 3.1\) Hz, 4.50 H, Z-form); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) δ 159.0, 143.6, 143.6, 135.8, 134.0, 128.4, 127.9, 124.9, 119.8, 117.4, 115.6, 113.4, 109.0, 82.8, 79.1, 64.4, 64.3, 55.2, 27.4, and 27.1 (Z-form); 159.5, 143.5, 143.5, 134.0, 130.5, 130.3, 129.0, 122.3, 119.8, 117.2, 115.4, 113.9, 109.0, 84.6, 82.7, 64.4, 64.3, 55.3, 27.3, and 27.2 (E-form); ESI-MS m/z: [M + H]+ Calcd for \(\text{C}_{22}\text{H}_{24}\text{O}_{5}\) 369.44 found 391.0; [M + Na]+; HRMS (El) m/z: [M]+ Calcd for \(\text{C}_{22}\text{H}_{24}\text{O}_{5}\) 368.1624 found 368.1620.

3.2.5. Synthesis of (1R,2R)-1-(2,3-Dihydrobenzo[\(b\)]1,4dioxin-6-yl)-4-(4-Methoxyphenyl)but-3-ene-1,2-diol (12)

To a solution of 11 (0.7 g, 1.90 mmol) in MeOH (15 mL), 1N HCl (5 mL) was added and stirred for 4 h at room temperature. The reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10–60% EtOAc/n-hexanes) to afford 12 (0.50 g) at an 80.1 yield (RI = 0.17 (30% EtOAc/n-hexanes); [α]^{20} = +121.6 (c 0.01, MeOH); IR(neat) ν 3413, 2933, 2877, 2835, 2249, 1606, 1506, 1460, 1433, 1284, 1246, 1174, 1122, 1065, 972, 912, 885, 843, 814, 727, 646, 571, 496, 495, 436, 418, and 403 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.07–7.03 (m, 2H), 6.83 (d, \(J = 1.3\) Hz, 1H), 6.60–6.77 (m, 4H), 6.51 (d, \(J = 11.7\) Hz, 1H), 5.57 (dd, \(J = 11.7, 9.0\) Hz, 1H), 4.56–4.51 (m, 1H), 4.49 (d, \(J = 7.0\) Hz, 1H), 4.21 (s, 4H), 3.79 (s, 3H), and 3.74–3.72 (m, 2H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) δ 158.8, 143.3, 143.3, 133.6, 130.0, 130.8, 127.7, 119.9, 117.1, 115.9, 113.6, 71.9, 68.0, 64.3, 64.3, and 55.2; ESI-MS m/z: [M + H]+ Calcd for \(\text{C}_{19}\text{H}_{20}\text{O}_{5}\) 329.14 found 351.10; [M + Na]+; HRMS (El) m/z: [M]+ Calcd for \(\text{C}_{19}\text{H}_{20}\text{O}_{5}\) 328.1318 found 328.1309.

3.2.6. Synthesis of 6-((1R,2R)-1,2-Bis(benzyloxy)-4-(4-methoxyphenyl)but-3-en-1-yl)-2,3-dihydrobenzo[\(b\)]1,4dioxine (6)

A solution of 12 (0.40 g, 1.22 mmol) in THF (5 mL) was added to a mixture of sodium hydride (60% dispersed in mineral oil, 0.15 g, 3.78 mmol) and tetra n-butylammonium iodide (0.045 g, 0.12 mmol) in THF (10 mL) at room temperature and stirred for 10 min at room temperature. Benzyl bromide (0.43 mL, 3.65 mmol) was added, and the resulting mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with a 50% aqueous NaHCO\(_3\) solution and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (0–20% EtOAc/n-hexanes) to afford 6 (0.44 g) at a 71.0% yield as a yellow oil (RI = 0.28 (20% EtOAc/n-hexanes); [α]^{20} = +57.0 (c 0.01, MeOH); IR(neat) ν 3413, 3060, 3028, 2931, 2870, 2835, 1952, 1873, 1811, 1641, 1606, 1591, 1504, 1454, 1433, 1387, 1348, 1284, 1248, 1203, 1176, 1155, 1092, 1063, 1030, 910, 885, 843, 816, 791, 735, 696, 511, 496, 463, 451, 434, 418, and 407 cm\(^{-1}\); \(^1\)H
NMR (400 MHz, CDCl₃) δ 7.37–7.30 (m, 4H), 7.29–7.25 (m, 1H), 7.21 (dd, J = 5.0, 1.9 Hz, 3H), 7.12 (dd, J = 6.8, 2.9 Hz, 2H), 7.10–7.04 (m, 2H), 6.90 (dd, J = 1.8 Hz, 1H), 6.87–6.81 (m, 2H), 6.79–6.74 (m, 2H), 6.62 (d, J = 11.7 Hz, 1H), 5.48 (dd, J = 11.8, 9.9 Hz, 1H), 4.61 (d, J = 12.1 Hz, 1H), 4.58 (dd, J = 10.0, 5.6 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 5.7 Hz, 1H), 4.37 (d, J = 12.1 Hz, 1H), 4.29 (d, J = 12.0 Hz, 1H), 4.27 (s, 4H), and 3.80 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 158.6, 143.2, 143.1, 138.6, 138.5, 133.3, 131.9, 130.0, 129.3, 128.3, 128.0, 127.8, 127.7, 127.7, 127.4, 127.2, 121.1, 116.9, 116.8, 113.4, 83.1, 76.9, 70.8, 70.1, 64.4, 64.3, and 55.3; ESI-MS m/z: [M + H]⁺ Calcd for C₃₃H₃₂O₅ 509.23 found 531.2; [M + Na]⁺; HRMS (EI) m/z: [M]⁺ Calcd for C₃₃H₃₂O₅ 508.2250 found 508.2245.

3.2.7. Synthesis of Benzyl ((1R,2R)-1-(Benzylxylo)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-(4-Methoxyphenyl)-but-3-en-2-yl)carbamate (5)

To a stirred solution of 6 (0.10 g, 0.20 mmol) and sodium carbonate (0.27 g, 2.56 mmol) in a mixture of anhydrous toluene/n-hexane (10:1, 4.0 mL), chlorosulfonyl isocyanate (0.34 mL, 3.93 mmol) was added at −78 °C under a N₂ atmosphere. The reaction mixture was stirred for 24 h at −78 °C and quenched with water very carefully (caution: highly exothermic). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were placed into a 100 mL round-bottomed flask and 25% aqueous solution of sodium sulfate (10 mL) was added. The mixture was further stirred for 12 h at room temperature. The EtOAc layer was separated, and the remaining compound was further extracted with EtOAc (30 mL) from the aqueous layer. The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (0–20% EtOAc/n-hexanes) to afford 5 (0.067 g) at a 62.0% yield as a colorless oil (Rf = 0.15 (20% EtOAc/n-hexanes)); [α]D²⁰ = +80.8 (c 0.01, MeOH); IR (neat) ν 3413, 3060, 3028, 2931, 2870, 2835, 1952, 1873, 1811, 1641, 1606, 1591, 1504, 1454, 1433, 1387, 1348, 1284, 1248, 1203, 1176, 1155, 1092, 1063, 1030, 910, 885, 843, 816, 791, 735, 669, 511, 496, 463, 451, 434, 418, and 407 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.33 (m, 3H), 7.31 (dt, J = 6.0, 3.4 Hz, 2H), 7.27–7.22 (m, 5H), 7.20 (dd, J = 7.7, 1.9 Hz, 3H), 6.77 (d, J = 8.2 Hz, 1H), 6.74–6.65 (m, 4H), 6.42 (d, J = 11.4 Hz, 1H), 5.74 (dd, J = 11.4, 9.8 Hz, 1H), 5.65 (t, J = 9.7 Hz, 1H), 5.24 (d, J = 12.1 Hz, 1H), 5.14 (d, J = 12.1 Hz, 1H), 4.66 (d, J = 9.7 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.25–4.21 (m, 4H), 4.12 (d, J = 11.6 Hz, 1H), and 3.77 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 162.0, 155.7, 143.4, 143.3, 137.9, 136.5, 135.1, 131.3, 128.6, 128.4, 128.2, 127.9, 127.9, 127.8, 127.7, 127.1, 126.5, 120.2, 112.0, 111.6, 82.1, 70.9, 66.6, 64.3, 64.3, 62.1, and 58.7; ESI-MS m/z: [M + H]⁺ Calcd for C₃₄H₃₄NO₆ 552.24 found 552.0; HRMS (EI) m/z: [M⁺] Calcd for C₃₄H₃₄NO₆ 551.2308 found 551.2302.

3.2.8. Synthesis of Benzyl ((1R,2R)-1-(Benzylxylo)-1-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-3-(Pyrrolidin-1-yl)-Propan-2-yl)carbamate (13)

To a flame-dried round-bottomed flask containing 5 (0.16 g, 0.30 mmol), dry dichloromethane (15 mL) was added. The solution was cooled to −78 °C, and a stream of O₂/O₃ was passed through the reaction for 30 min, after which the reaction was purged with a stream of O₂ for 1 min. After that, triphenyl phosphine (0.08 g, 0.30 mmol) was added and stirred for 1 h at room temperature. To the reaction mixture, pyrrolidine (0.026 mL, 0.32 mmol) and triethylamine (0.061 mL, 0.44 mmol) were added, and then sodium cyanoborohydride (0.024 g, 0.38 mmol) was added. The reaction mixture was stirred for 16 h at room temperature. The reaction mixture was quenched with water. The aqueous layer was extracted with DCM (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (0–10% MeOH/EtOAc) to afford 13 (0.12 g) at 82.3% yield as a colorless oil (Rf = 0.43 (10% MeOH/EtOAc)); [α]D²⁰ = +111 (c 0.01, MeOH); IR (neat) ν 3728, 2942, 2831, 2355, 1658, 1641, 1589, 1512, 1439, 1188, 1119, 1088, 1039, 1026, 721, 692, 525, 476, 457, 449, 438, 422, and 404 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.24 (m, 10H), 6.86 (q, J = 4.0, 3.2 Hz, 1H), 6.85–6.79 (m, 2H), 6.81–6.76 (m, 1H), 5.34 (dd, J = 85.0, 9.4 Hz, 1H), 5.14–4.98 (m,
Molecules 2022, 27, 2603

3.2.9. Synthesis of (1R,2R)-2-Amino-1-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-3-(Pyrrolidin-1-yl)propan-1-ol (14)

To a solution of 13 (47.0 mg, 0.09 mmol) in ethanol (2.0 mL), 10% palladium on carbon (10 mg) was added, and the reaction mixture was stirred for 16 h under a hydrogen atmosphere. The reaction mixture was filtered through a celite and washed with EtOH (2 × 10 mL). The filtrate was evaporated in vacuo. The residue was purified by reverse phase flash column chromatography with a C18 column (10 ~ 90% MeCN/H2O with 0.1% trifluoroacetic acid, gradient condition) to afford 14 (21 mg) at an 80.7% yield as a white solid (Rt = 0.08 (20% MeOH/EtOAc with 0.05% triethylamine); mp 92.2 °C; [α]D20 = +102.3 (c 0.01, MeOH); IR(neat) ν = 3855, 3809, 3626, 3369, 2945, 2829, 2360, 1736, 1655, 1587, 1512, 1456, 1211, 1032, 104, 462, 465, 455, 442, 430, 413, and 403 cm−1; 1H NMR (400 MHz, CDCl3) δ 6.88–6.75 (m, 3H), 4.55 (s, 1H), 4.25 (s, 4H), 3.15–3.08 (m, 1H), 2.67–2.46 (m, 6H), and 1.76 (s, 4H); 13C NMR (101 MHz, CDCl3) δ 143.3, 142.6, 135.8, 119.2, 116.9, 115.2, 75.8, 64.4, 63.4, 60.1, 54.7, 54.3, and 23.6; ESI-MS m/z: [M + H]+ Calcd for C15H22N2O3 279.17 found 279.1; HRMS (El) m/z: [M]+ Calcd for C15H22N2O3 278.1630 found 278.1628.

3.2.10. Synthesis of N-((1R,2R)-1-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-1-Hydroxy-3-(Pyrrolidin-1-yl)propan-2-yl)octanamide, Eliglustat (1)

To a solution of 14 (17.0 mg, 0.06 mmol) and triethylamine (0.017 mL, 0.12 mmol) in dry DCM (1.2 mL), octanoyl chloride (0.013 mL, 0.08 mmol) was added at 0 °C and stirred for 2 h at the same temperature. The reaction mixture was quenched with water (5 mL), and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by reverse phase flash column chromatography with a C18 column (10–90% MeCN/H2O with 0.1% trifluoroacetic acid, gradient condition) to afford 1 (13 mg) at a 52.6% yield as a white solid (Rt = 0.33 (20% MeOH/EtOAc with 0.05% triethylamine); mp 86.7 °C (lit, mp 87–88 °C) [19]; [α]D20 = +124.6 (c 0.01, MeOH); IR(neat) ν = 3855, 3809, 3730, 3636, 3369, 2945, 2829, 2360, 1736, 1655, 1512, 1381, 1234, 1053, 1032, 887, 490, 465, 444, 424, 413, and 405 cm−1; 1H NMR (400 MHz, CDCl3) δ 6.84 (d, J = 2.0 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 6.76 (dd, J = 8.3, 2.0 Hz, 1H), 5.81 (d, J = 7.5 Hz, 1H), 5.49 (d, J = 3.3 Hz, 1H), 4.23 (s, 4H), 4.17 (dddd, J = 7.7, 5.6, 4.6, 3.3 Hz, 1H), 2.77 (qd, J = 12.9, 5.1 Hz, 2H), 2.69–2.57 (m, 4H), 2.11–2.05 (m, 2H), 1.81–1.72 (m, 4H), 1.50 (p, J = 7.5 Hz, 2H), 1.28–1.16 (m, 8H), and 0.85 (t, J = 7.1 Hz, 3H) [19]; 13C NMR (101 MHz, CDCl3) δ 173.4, 143.4 142.8, 134.4, 133, 129.0, 115.0, 115.0, 75.6, 64.3, 57.9, 55.2, 52.2, 36.8, 31.6, 29.1, 29.0, 25.6, 23.6, 22.6, and 14.1; ESI-MS m/z: [M + H]+ Calcd for C23H36N2O4 405.28 found 405.2; HRMS (El) m/z: [M]+ Calcd for C23H36N2O4 404.2675 found 404.2672.

4. Conclusions

In conclusion, we described an asymmetric total synthesis of eliglustat 1 starting from readily available 2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde (7) via Sharpless asymmetric dihydroxylation and a stereoselective amination reaction using chlorosulfonyl isocyanate (CSI) as key steps. The optimal reaction conditions for the diastereoselective CSI reaction of syn-1,2-dibenzyl ether were identified. The retention of the configuration at the para-methoxyxynamicly position can be explained by the Sn2i mechanism.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27082603/s1, Copies of 1H and 13C NMR spectra.
Author Contributions: Conceptualization, Y.K., P.R.B. and Y.H.J.; writing—original draft preparation, Y.K. and P.R.B.; resources, G.M.P., Y.S.K. and S.H.A.; writing—review and editing, P.R.B. and I.S.K.; supervision, Y.H.J.; funding acquisition, Y.H.J. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the National Research Foundation of Korea (NRF) funded by the Korean government (MSIP) (No. 2020R1I1A1070288).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data are contained within the article or Supplementary Materials.

Acknowledgments: We thank the National Research Foundation of Korea (NRF) and Brine Korea 21.

Conflicts of Interest: The authors declare that they have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

References
1. Bergmeier, S.C. The Synthesis of Vicinal Amino Alcohols. Tetrahedron 2000, 56, 2561–2576. [CrossRef]
2. Ager, D.J.; Prakash, I.; Schaad, D.R. 1,2-Amino Alcohols and Their Heterocyclic Derivatives as Chiral Auxiliaries in Asymmetric Synthesis. Chem. Rev. 1996, 96, 835–876. [CrossRef]
3. Paleo, M.R.; Cabeza, I.; Sardina, F.J. Enantioselective addition of doethylzinc to aldehydes catalyzed by N-(9-phenylfluoren-9-yl)beta-amino alcohols. J. Org. Chem. 2000, 65, 2108–2113. [CrossRef] [PubMed]
4. Shayman, J.A. Eliglustat tartrate. Drugs Future 2010, 35, 613–620. [CrossRef]
5. Bennett, L.L.; Turcotte, K. Eliglustat tartrate for the treatment of adults with type 1 Gaucher disease. Drug Des. Dev. Ther. 2015, 9, 4639–4647. [CrossRef] [PubMed]
6. Poole, R.M. Eliglustat: First global approval. Drugs 2014, 74, 1829–1836. [CrossRef]
7. Sehl, T.; Maugeri, Z.; Rother, D. Multi-step synthesis strategies towards 1,2-amino alcohols with special emphasis on phenylpropanolamines. J. Mol. Catal. B Enzym. 2015, 114, 65–71. [CrossRef]
8. Syriopoulou, V.P.; Harding, A.L.; Goldmann, D.A.; Smith, A.L. In vitro antibacterial activity of fluorinated analogs of chloramphenicol and thiamphenicol. Antimicrob Agents Chemother. 1981, 19, 294–297. [CrossRef]
9. Shen, J.; Wu, X.; Hu, D.; Jiang, H. Pharmacokinetics of florfenicol in healthy and Escherichia coil-infected broiler chickens. Res Vet. Sci. 2002, 73, 137–140. [CrossRef]
10. Gaunt, P.S.; Langston, C.; Wrzesinski, C.; Gao, D.; Adams, P.; Crouch, L.; Sweeney, D.; Endris, P. Multidose pharmacokinetics of orally administered florfenicol in the channel catfish (Ictalurus punctatus). J. Vet. Pharmacol. Ther. 2013, 36, 502–506. [CrossRef]
11. Goldstein, D.S. L-Dihydroxyphenylserine (L-DOPS): A norepinephrine prodrug. Cardiovasc. Drug Rev. 2006, 24, 189–203. [CrossRef] [PubMed]
12. Mathias, C.J. L-dihydroxyphenylserine (Doxidopa) in the treatment of orthostatic hypotension. Clin. Auton. Res. 2008, 18, 25–29. [CrossRef]
13. Kaufmann, H.; Freeman, R.; Biaggioni, I.; Low, P.; Pedder, S.; Hewitt, L.A.; Mauney, J.; Feirtag, M.; Mathias, C.J. Droxidopa for neurogenic orthostatic hypotension; a randomized, placebo-controlled, phase 3 trial. Neurology 2014, 83, 328–335. [CrossRef] [PubMed]
14. Johnson, H.W.B.; Lowe, E.; Anderl, J.L.; Fan, A.; Muchamuel, T.; Bowers, S.; Moebius, D.C.; Kirk, C.; McMinn, D.L. Required Immunoproteasome Subunit Inhibition Profile for AntiInflammatory Efficacy and Clinical Candidate KZR-616 (2S,3R)-N-((S)-3-(Cyclopent-1-en-1-yl)-1-((R)-2-methyloxiran-2-yl)-1-oxopropan-2-yl)-3-hydroxy-3-(4-methoxyphenyl)-2-((S)-2-(2-morpholinoacetyl)amino)propanamide). J. Med. Chem. 2018, 61, 11127–11143. [PubMed]
15. Fang, Y.; Johnson, H.; Anderl, J.L.; Muchamuel, T.; McMinn, D.; Morisseau, C.; Hammock, B.D.; Kirk, C.; Wang, J. Role of Epoxide Hydrolases and Cytochrome P450s on Metabolism of KZR-616, a First-in-Class Selective Inhibitor of the Immunoproteasome. Drug Metab. Dispos. 2021, 49, 810–821. [CrossRef] [PubMed]
16. Wang, B. N-(1-Hydroxy-3-(pyrrolidinyl)propan-2-yl)pyrrolidine-3-carboxamide Derivatives as Glucosylceramide Synthase Inhibitors.WO Patent WO2015069937 A1, 7 May 2015.
17. Inokuchi, J.I.; Yoshimura, Y.; Go, S. Glucosylceramide synthase inhibitor. WO Patent WO2017040301 A1, 30 November 2017.
18. Van den Berg, R.J.B.H.N.; Van Rijssel, E.R.; Ferraz, M.J.; Houben, J.; Strijland, A.; Donker-Koopman, W.E.; Wennekes, T.; Bonger, K.M.; Ghisaidoobe, A.B.T.; Hoogendoorn, S.; et al. Synthesis and Evaluation of Hybrid Structures Composed of Two Glucosylceramide Synthase Inhibitors. ChemMedChem. 2015, 10, 2042–2062. [CrossRef]
19. Hirth, B.H.; Siegel, C. Synthesis of Udip-Glucose: N-Acylsphingosine Glucosyltransferase Inhibitors. WO Patent WO2003008399 A1, 30 January 2003.
20. Liu, X.; Li, X.; Yang, H.; Shi, X.; Yang, F.; Jiao, X.; Xie, P. Concise and efficient synthesis of eliglustat. Synth. Commun. 2018, 48, 594–599. [CrossRef]
21. Xu, X.N. Preparation Method of Eliglustat. CN Patent CN104557851 A, 29 April 2015.
22. Kim, I.S.; Jung, Y.H. Recent advances in the total synthesis of indolizidine iminosugars. *Heterocycles* **2011**, *83*, 2489–2507. [CrossRef]
23. Dong, G.R.; Hong, S.M.; Kim, S.I.; Kim, I.S.; Jung, Y.H. Stereoselective Synthesis of (−)-α-Conhydrine and Its Pyrrolidine Analogue. *Eur. J. Org. Chem.* **2012**, *2012*, 4200–4205. [CrossRef]
24. Kim, S.J.; Jeon, T.H.; Min, I.S.; Kim, I.S.; Jung, Y.H. Asymmetric total synthesis of (S)-dapoxetine. *Tetrahedron Lett.* **2012**, *53*, 3680–3682. [CrossRef]
25. Lee, S.H.; Park, S.J.; Kim, I.S.; Jung, Y.H. Asymmetric total synthesis of (β)-indatraline via diastereoselective amination of chiral ethers using chlorosulfonyl isocyanate. *Tetrahedron* **2013**, *69*, 1877–1880. [CrossRef]
26. Ma, S.-H.; Kim, Y.S.; Jung, J.M.; Boggu, P.R.; Kim, I.S.; Jung, Y.H. Total synthesis of chromanol 293B and cromakalim via stereoselective amination of chiral benzylic ethers. *Tetrahedron Lett.* **2020**, *61*, 151431. [CrossRef]
27. Junttila, M.H.; Hormi, O.O.E. Methanesulfonamide: A Cosolvent and a General Acid Catalyst in Sharpless Asymmetric Dihydroxylations. *J. Org. Chem.* **2009**, *74*, 3038–3047. [CrossRef]
28. Lee, S.H.; Kim, I.S.; Li, Q.R.; Dong, G.R.; Jeong, L.S.; Jung, Y.H. Stereoselective Amination of Chiral Benzylic Ethers Using Chlorosulfonyl Isocyanate: Total Synthesis of (+)-Sertraline. *J. Org. Chem.* **2011**, *76*, 10011–10019. [CrossRef] [PubMed]
29. Weaver, D.F.; Campbell, A.J. Heterocyclic Anti-Epileptogenic Agents and Methods of Use Thereof. U.S. Patent US20030114441 A1, 19 June 2003.
30. Yang, R.; Lv, M.; Xu, H. Synthesis of Piperine Analogs Containing Isoxazoline/Pyrazoline Scaffold and Their Pesticidal Bioactivities. *J. Agric. Food Chem.* **2018**, *66*, 11254–11264. [CrossRef] [PubMed]