

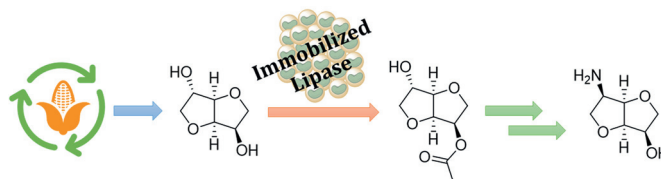
An Efficient and Practical Chemoenzymatic Route to (3*R*,3*aR*,6*R*,6*aR*)-Hexahydrofuro[3,2-*b*]furan-6-amino-3-ol (6-Aminoisomannide) from Renewable Sources

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Abstract The synthesis of 6-aminoisomannide is easily achieved starting from the renewable, inexpensive, and commercially available isosorbide in 66% overall yield. A biocatalyzed highly regioselective acetylation of the 3-*endo* hydroxyl group of isosorbide was followed by the stereospecific interconversion of the 6-*exo* hydroxyl group into an azido group, through reaction with trifluoromethanesulfonic anhydride, followed by nucleophilic displacement of the triflate group by sodium azide. Finally, reduction of the azido group and deacetylation of the 3-hydroxy group were performed in one pot using LiAlH₄.

Key words isomannide, isosorbide, chiral amino alcohols, supported enzyme, lipase

Optically active amino alcohols are among the most versatile chemical structures that can be employed as chiral inducers for asymmetric catalysis.¹ They are useful not only as chiral ligands, as in the enantioselective addition of dialkylzinc reagents to carbonyl compounds,^{2,3} but also as precursors of other chiral derivatives used as ligands in metal-catalyzed enantioselective reactions^{4,5} or as chiral organocatalysts.⁶ Most chiral amino alcohols are derived from natural compounds, such as carbohydrates or amino acids, which are readily available enantiopure sources and possess suitable stereochemical features for good asymmetric induction. In particular, the manipulation of the chiral pool available from biomass, which appears very attractive for the synthesis of asymmetric auxiliaries⁷ and organocatalysts,⁸ could represent a simple and economical way to ob-

tain chiral amino alcohols endowed with interesting stereochemical features.⁹ Among the biomass-based precursors suitable for the synthesis of amines and amino alcohols, a great deal of attention has been addressed to (3*R*,3*aR*,6*R*,6*aR*)-hexahydrofuro[3,2-*b*]furan-3,6-diol and its (3*R*,3*aR*,6*S*,6*aR*) diastereoisomer, also known as isomannide and isosorbide, respectively. They are renewable, inexpensive, and commercially available chiral compounds derived from the dehydration of sorbitol and mannitol, respectively, which are waste products formed during the processing of corn oil and byproducts from the starch industry.¹⁰ Isomannide (**1**) and isosorbide (**2**) possess a vaulted structure due to the *cis* junction of the two tetrahydrofuran rings with two hydroxyl groups that in isomannide are directed toward the inner of the chiral cavity (Figure 1). Thanks to these stereochemical features, isomannide derivatives constitute real chiral pockets, inside which enantioselective processes can take place with high effectiveness.¹¹ For these reasons most of the amino derivatives of isohexides show the isomannide stereochemistry.^{12–14}

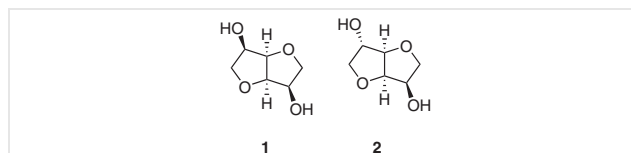
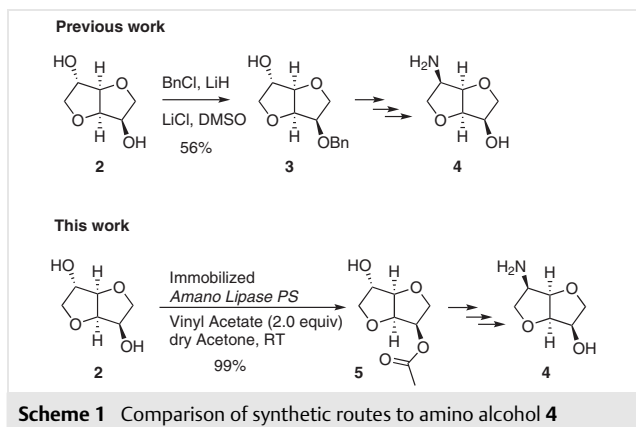


Figure 1 Chemical structures of isomannide (**1**) and isosorbide (**2**)

In order to obtain the amino alcohol derivative **4** with the desired stereochemistry, a straightforward approach is represented by the regioselective and stereospecific interconversion of the *exo* hydroxyl group of isosorbide to an amino group.¹⁵ This transformation has been described and involves regioselective protection of the *endo* hydroxyl, conversion of the *exo* hydroxyl into a benzenesulfonate

group followed by its displacement by benzylamine; the hydrogenolysis of the two benzyl groups gives the target amino alcohol (Scheme 1).¹⁶



The weak points of this protocol are the selective protection step, giving the *endo* benzyl ether **3** in 56% yield and the displacement of the benzenesulfonate group at high temperature, causing the formation of an elimination by-product.¹⁷ Strategies to overcome these issues and develop a high-yielding synthetic protocol require a highly selective protection for the *endo* hydroxyl group as well as a nucleophilic displacement of a good leaving group under mild reaction conditions.

Lipase-catalyzed transesterification of isosorbide has been previously reported for the regioselective synthesis of monoesters.^{18–24} In general, the selectivity has been toward the *endo* hydroxyl group. Therefore, a biocatalyzed selective acetylation of the isosorbide *endo* hydroxyl represents a high-yield protection step.^{23,24} The transesterification has also been performed using immobilized enzymes, allowing an easy recovery of the product. However, long reaction times were generally observed to obtain complete conversion of isosorbide.^{22,23}

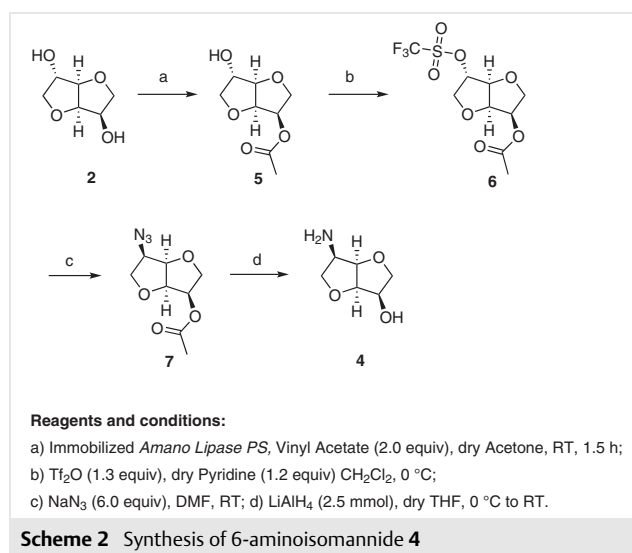
Nucleophilic displacement can be performed using a stronger nucleophile than benzylamine, which can react under mild conditions and can be easily converted into an amino group. Sodium azide fulfills these requirements thanks to its high nucleophilicity and because the obtained organic azides are easily reduced to the corresponding amines in high yield.²⁵

Herein we present a new straightforward synthetic protocol to access (3*R*,3*aR*,6*R*,6*aR*)-hexahydrofuro[3,2-*b*]furan-6-amino-3-ol (6-aminoisomannide), whose key points are the enzyme-catalyzed regioselective acetylation of isosorbide (Scheme 1) and the introduction of the azido group under mild reaction conditions. The synthesis of the acetate **5** has been achieved under optimized conditions by using Amano Lipase PS which was immobilized by adsorption onto a methacrylate resin. Moreover, the reusability of the

biocatalyst was investigated and the efficient biocatalytic step was evaluated on a preparative scale.

Amano PS Lipase was immobilized onto octadecyl methacrylate resin ECR8806 according to the supplier protocol.²⁶ Adsorption of lipases onto hydrophobic supports is a very easy immobilization method that allows derivatives to be obtained that are more active and stable than other immobilized lipases.²⁷ Indeed, by using this method the active site is usually unaffected by interaction with the matrix, causing little or no conformational changes of the enzyme. The highly hydrophobic surface of octadecyl methacrylate is particularly suitable for reversible but strong adsorption of lipases and the immobilized derivatives show excellent performance in applications in fully organic anhydrous solvents.²⁷

As reported in Scheme 2, the first step of the synthesis was the regioselective enzymatic protection of isosorbide **2** to give the monoacetate **5**. Starting from a known protocol²⁴ an initial screening of the reaction conditions was made employing the supported enzyme (see Table S1, Supporting Information).



The results show that, to obtain complete conversion, the use of anhydrous acetone was crucial, due to the high activity of lipases in the hydrolytic reverse reaction. Therefore, after immobilization the supported enzyme was carefully dried under vacuum to avoid the presence of traces amount of water. The immobilization process led to better results in terms of substrate conversion, maybe due to a purification of the commercial enzyme during this process.

Analysis of the crude mixtures during the screening by means of ¹H NMR spectroscopy never revealed the presence of the *exo* acetate, nor could it be detected by GC-FID analysis of reaction mixtures. In some cases, the diacetate was obtained. Lowering the amount of vinyl acetate from 3.0

equivalents to 2.0 equivalents allowed us to obtain the desired pure product, as confirmed by GC-FID analysis (see Figure S3, Supporting information). The optimal amount of the catalyst to convert isosorbide into **5** in a short time was found to be 0.7% w/w enzyme/substrate.

Therefore, as reported in Scheme 2, by using immobilized lipase with 2 equivalents of vinyl acetate in dry acetone at room temperature the acetate **5** was obtained in quantitative yield and excellent selectivity (>99%, GC-FID) in very short reaction time (1.5 h), which makes this protocol far superior to those reported in the literature.^{22,23} Under these optimized reaction conditions, the biotransformation was conducted on a preparative scale (9.6 mmol of isosorbide).

The biocatalyst was also tested for its reuse. At the end of the reaction, the enzyme was filtered, washed, and reused in consecutive reactions under the same experimental conditions.

In each cycle, complete conversion of the substrate and high selectivity were obtained. These results show that the immobilized lipase can be reused in subsequent runs without loss in selectivity. However, a gradual drop in enzyme activity was observed but this is not an issue as complete conversion of the substrate can still be achieved in reasonable reaction times. Complete conversion of the substrate and high selectivity were observed for the first two cycles after 3 h and 8 h, respectively. Notably, for large-scale applications the enzyme may be desorbed after its inactivation and the support may be reused.²⁶

Once the 3-hydroxyl had been protected, the stereospecific interconversion of the 6-*exo* hydroxyl into 6-*endo* amine was achieved according to standard procedures (Scheme 2).

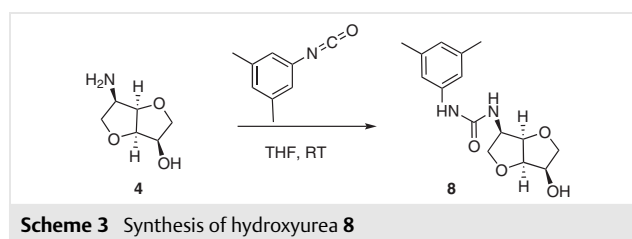
By reacting acetate **5** with trifluoromethanesulfonic anhydride in the presence of pyridine at 0 °C the corresponding triflate **6** was obtained in 90% yield. It is noteworthy that the reaction is clean, and the pure product is obtained after simple workup (hydrolysis followed by liquid–liquid extraction), without any further purification.

Nucleophilic displacement of the triflate group by sodium azide presented some initial problems. Under standard reaction conditions, i.e., heating a 1:1.5 triflate–NaN₃ mixture in DMF at 100 °C, the conversion of **6** was complete in short reaction times (2 h), but 45% of an elimination side product was obtained. In order to improve the chemoselectivity of the process, the reaction temperature was lowered to 50 °C and complete conversion of the substrate was achieved in 5 h, but formation of a 40% yield of the elimination product was still observed. At room temperature, triflate **6** reacted smoothly with NaN₃ in DMF over a longer reaction time (30 h), but, unfortunately, a 40% yield of the elimination side product was still observed. To drive the reaction wholly toward the azide **7** an excess of sodium azide

was used. These conditions markedly reduced the reaction time (16 h) and product **7** was obtained in 73% yield after chromatographic purification.

The two final steps, reduction of the azido group and deprotection of the 3-hydroxy group, were performed in one pot, employing lithium aluminum hydride as reducing agent for both groups. The reaction was conducted at room temperature with a slight excess of LiAlH₄ in dry THF, and the conversion of substrate **7** was complete after 24 h. The workup procedure was crucial and it was performed with a stoichiometric amount of water, in order to obtain oxides that could be readily filtered off. Avoiding solvent extraction is mandatory to prevent loss of the amino alcohol in the aqueous phase, due the water solubility of the compound. The pure amino alcohol **4** was then obtained in quantitative yield after removal of the solvent.

Amino alcohol **4** can be used as precursor of other chiral derivatives, such as the hydroxyurea **8**, obtained according to Scheme 3.



Scheme 3 Synthesis of hydroxyurea **8**

As a proof of concept this derivative was used, as a chiral solvating agent, in the enantiodiscrimination of the 3,5-dinitrobenzoylphenylglycine methylester. The hydroxyurea **8** produced splitting of various signals in the NMR spectrum of the racemic amino acid derivative (Figure 2): the baseline separation of the proton signals of the 3,5-dinitrobenzoyl group therefore allows a ready determination of the enantiomeric composition of nonracemic mixtures.

In conclusion, we have developed a straightforward and efficient synthesis of 6-aminoisomannide, an amino alcohol with interesting structural features that make it a good candidate as chiral auxiliary or as precursor of other chiral auxiliaries, such as hydroxyureas or hydroxythioureas. The use of a supported enzyme for the acetylation step allowed us to obtain a quantitative yield of the protected precursor with a completely regioselective reaction, which was successfully used also on preparative scale. In this way, the synthetic route, which starts from the biomass-based precursor isosorbide, allowed us to obtain the amino alcohol **4** in 66% overall yield in four steps with only one chromatographic purification of an intermediate. Starting from amino alcohol **4** chiral derivatives to be used in enantiodiscriminating processes can be readily obtained. Further studies are in progress on this topic.

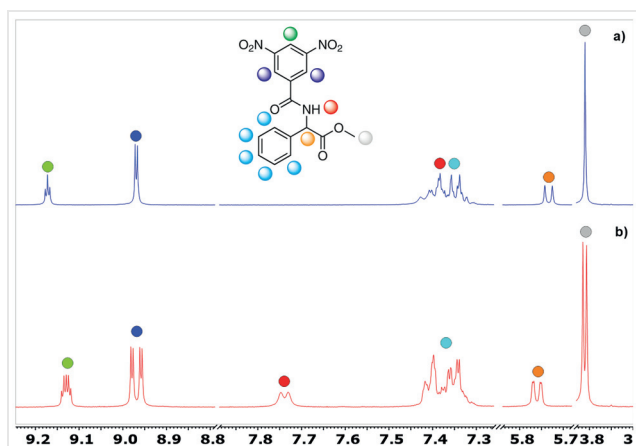


Figure 2 Selected regions of the ^1H NMR spectrum (401 MHz, chloroform-*d*, 25 °C) of: a) 3,5-dinitrobenzoylphenylglycine methyl ester (c 30 mM); b) 1:1 mixture **8**-3,5-dinitrobenzoylphenylglycine methyl ester (c 30 mM).

General Remarks

All the reactions involving sensitive compounds were carried out under dry argon, in flame-dried glassware. Amano Lipase PS, from *Burkholderia cepacia* ($\geq 30,000$ U/g, pH = 7.0, 50 °C) was obtained from Sigma-Aldrich. If not noted otherwise, reactants and reagents were commercially available and used as received from Alfa Aesar, Purolyte, Carlo Erba, TCI-Chemicals, and Sigma-Aldrich. Dichloromethane and tetrahydrofuran were dried and degassed by an MB-SPS solvent purification system. Analytical TLC was performed on precoated silica gel ALUGRAM Xtra G/UV254 plates. Purifications were performed by flash chromatography on silica gel (40–63 μm). Melting points were measured on a Reichert Thermovar Type 300429 Microscope. ^1H NMR spectra were recorded in chloroform-*d* or in deuterium oxide on a Bruker 400 MHz NMR spectrometer. The following abbreviations are used: br s = broad singlet, s = singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, q = quartet, m = multiplet. ^{13}C NMR spectra were recorded at 101 MHz and ^{19}F NMR spectra were recorded at 378 MHz. ^1H NMR and ^{13}C NMR chemical shifts (ppm) are referred to TMS as external standard. GC-FID analyses were performed on a GC instrument with a split/splitless injector and FID detector (Column: J&W HP-5ms GC Column, 30 m, 0.25 mm, 0.25 μm ; method: 70 °C (hold 1 min); 20 °C min^{-1} to 250 °C (hold 5 min); 20 °C min^{-1} to 280 °C (hold 10 min); t_{R} = 6.7 min (isosorbide); 8.0 min (**5**); 8.4 min (isosorbide diacetate)). UV-vis measurements were performed on a JASCO-V750 UV-vis spectrophotometer. Elemental analyses were obtained using an Elementar Vario MICRO cube equipment. Optical rotations were measured in 1 dm cells at the sodium D line, using an Anton Paar MCP 300 Polarimeter.

Immobilization of Lipase PS

The immobilization was carried out following the protocol provided by Purolyte: 5.48 g of Purolyte octadecyl methacrylate resin ECR8806 was added to a solution of Amano Lipase PS (6.16 mg in 41 mL of phosphate buffer 20 mM, pH = 7.0). The suspension was gently stirred for 24 h at room temperature. After this time the support was filtered, washed with phosphate buffer (20 mL, 2.9 mM, pH = 7.0), and dried under vacuum.

Enzymatic Assay

The activities of native and immobilized enzyme were determined by using a discontinuous variant of the known assay.²⁸ To a solution of the native enzyme (0.5 mL, 50.0 $\mu\text{g mL}^{-1}$ in phosphate buffer 100 mM, pH = 7.0) or to a dispersion of the immobilized enzyme (0.54 mg in 0.5 mL of phosphate buffer 100 mM, pH = 7.0), 0.5 mL of *p*-nitrophenylpalmitate (14.3 mM solution in ethanol) were added, and the mixture was incubated at 32 °C and 400 rpm for 5 min. The reaction was quenched by addition of 0.5 M Na_2CO_3 (0.5 mL) and centrifuged for 10 min at 6000 rpm. The supernatant was diluted with distilled water and the amount of *p*-nitrophenol released was determined spectrophotometrically. One enzyme unit (U) was defined as the amount of enzyme necessary to release 1 μmol of *p*-nitrophenol per minute under assay conditions.

(3*R*,3*aR*,6*S*,6*aR*)-Hexahydrofuro[3,2-*b*]furan-3-methylcarboxylate-6-ol (**5**)²⁴

In a two-necked round-bottom flask, under an argon atmosphere, vinyl acetate (1.8 mL, 19.5 mmol) and immobilized Amano Lipase PS (1.15 g, 23771 U) were added to a gently stirred solution of isosorbide (1.41 g, 9.6 mmol) in dry acetone (19 mL). The mixture was gently stirred at room temperature and progress of the reaction was monitored by GC-FID. After 1.5 h complete conversion of the starting material was observed. The reaction was terminated by filtering the immobilized enzyme, which was washed with acetone (2 \times 19 mL). The organic phases were combined, and the solvent was removed under reduced pressure to afford the chemically pure product as a pale-yellow oil (1.81 g, quantitative yield; > 99% purity as determined by GC-FID).

^1H NMR (401 MHz, chloroform-*d*): δ = 5.13 (q, J = 5.4 Hz, 1 H), 4.83 (t, J = 4.8 Hz, 1 H), 4.39 (dt, J = 4.5, 0.9 Hz, 1 H), 4.35–4.28 (m, 1 H), 3.96–3.84 (m, 3 H), 3.75 (dd, J = 9.8, 5.3 Hz, 1 H), 2.45 (s, 1 H), 2.11 (s, 3 H).

^{13}C NMR (101 MHz, chloroform-*d*): δ = 170.7, 88.3, 80.5, 76.3, 75.7, 74.3, 70.3, 20.8.

$[\alpha]_{\text{D}}^{20} + 105.7$ (c 1.0, CHCl_3); lit²⁹ $[\alpha]_{\text{D}}^{20} + 107.7$ (c 1.0, CHCl_3).

Reusability of the Biocatalyst

Under an argon atmosphere, immobilized Amano Lipase PS (172.0 mg, 3559 U) and vinyl acetate (390 μL , 4.2 mmol) were added to a solution of isosorbide in dry acetone (0.5 M, 2.8 mL). The reaction mixture was gently stirred at room temperature, and progress of the reaction was monitored by GC-FID. The reaction was quenched when complete conversion was achieved. The immobilized enzyme was filtered under argon, washed twice with dry acetone (2.8 mL, 10 min of stirring at room temperature each time) and dried under vacuum. Fresh batches of reaction medium containing isosorbide solution (0.5 M, 2.8 mL) and vinyl acetate (390 μL) were then added to the enzyme, and the mixture was stirred at room temperature to start a new cycle.

(3*R*,3*aR*,6*S*,6*aR*)-Hexahydrofuro[3,2-*b*]furan-3-methylcarboxylate-6-trifluoromethanesulfonate (**6**)¹²

Under an argon atmosphere, to a solution of **5** (1.18 g, 6.2 mmol) in dry CH_2Cl_2 (30 mL) and dry pyridine (600 μL , 7.5 mmol) at 0 °C, trifluoromethanesulfonic anhydride (1.4 mL, 8.3 mmol) was slowly added over 5 min and the mixture was stirred at 0 °C. The reaction was monitored by TLC analysis (hexane–ethyl acetate = 7:3 or CH_2Cl_2 –acetone = 9 : 1). After 3 h the reaction was quenched with cold water (10 mL), the phases were separated, and the organic phase was

washed with H₂O (10 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was removed under reduced pressure to yield the pure product as a pale-yellow oil (1.79 g, 90%).

R_f = 0.44 (hexane–ethyl acetate = 7:3); 0.88 (CH₂Cl₂–acetone = 9:1).

¹H NMR (401 MHz, chloroform-*d*): δ = 5.31 (d, *J* = 3.1 Hz, 1 H), 5.18 (q, *J* = 5.4 Hz, 1 H), 4.93 (t, *J* = 5.1 Hz, 1 H), 4.67 (d, *J* = 4.8 Hz, 1 H), 4.22 (d, *J* = 11.9 Hz, 1 H), 4.04 (dd, *J* = 11.9, 3.2 Hz, 1 H), 3.98 (dd, *J* = 10.0, 6.0 Hz, 1 H), 3.80 (dd, *J* = 10.0, 5.2 Hz, 1 H), 2.12 (s, 3 H).

¹³C NMR (101 MHz, chloroform-*d*): δ = 170.2, 118.6 (q, *J* = 318 Hz, –CF₃), 89.4, 85.6, 81.0, 73.6, 73.0, 70.8, 20.7.

¹⁹F NMR (378 MHz, chloroform-*d*): δ = –74.85.

[α]_D²⁰ +81.6 (c 0.50, CHCl₃); lit.^{12,13} [α]_D²⁰ +86.2 (c 0.52, CHCl₃).

(3R,3aR,6R,6aR)-Hexahydrofuro[3,2-*b*]furan-6-azido-3-methylcarboxylate (7)

To a solution of **6** (486.9 mg, 1.5 mmol) in *N,N*-dimethylformamide (15 mL), sodium azide (598.7 mg, 9.2 mmol) was added, and the mixture was stirred at room temperature. The reaction was monitored by TLC analysis (hexane–acetone = 8:2). After 16 h the reaction was stopped. Diethyl ether (30 mL) was added to the mixture, and the precipitated solid was filtered off. The filtrate was concentrated under reduced pressure, and the crude product was dissolved in diethyl ether (30 mL) and washed with brine–water (1:1, 15 mL). The aqueous phase was extracted with diethyl ether (3 × 30 mL), the organic phases were combined, and dried over anhydrous Na₂SO₄. After filtration, the solvent was removed under reduced pressure to give the crude product as a yellow oil that was purified by flash chromatography (silica gel, hexane–acetone = 8:2) to give the pure product as a yellow oil (233.1 mg, 73%).

R_f = 0.23 (hexane–acetone = 8:2)

¹H NMR (401 MHz, chloroform-*d*): δ = 5.13 (q, *J* = 6.0 Hz, 1 H), 4.73 (t, *J* = 5.6 Hz, 1 H), 4.62 (t, *J* = 4.9 Hz, 1 H), 4.09–4.00 (m, 2 H), 3.90 (dd, *J* = 9.7, 6.1 Hz, 1 H), 3.84 (ddd, *J* = 8.9, 6.9, 5.1 Hz, 1 H), 3.71 (t, *J* = 8.7 Hz, 1 H), 2.12 (s, 3 H).

¹³C NMR (101 MHz, chloroform-*d*): δ = 170.5, 82.7, 81.3, 74.1, 71.2, 70.2, 62.1, 20.7.

Elem. Anal.: calcd for C₈H₁₁N₃O₄: C, 45.07; H, 5.20; N, 19.71; O, 30.02. Found: C, 44.85; H, 5.32; N, 19.88.

[α]_D²⁰ +219.7 (c 0.61, CHCl₃).

(3R,3aR,6R,6aR)-Hexahydrofuro[3,2-*b*]furan-6-amino-3-ol (4)¹⁶

Under an argon atmosphere, to a solution of **7** (177.4 mg, 0.83 mmol) in dry THF (14 mL), LiAlH₄ (84.8 mg, 2.2 mmol) was slowly added at 0 °C. The heterogeneous mixture was stirred for 5 min at 0 °C and then it was allowed to warm slowly to room temperature. After 24 h, the mixture was cooled to 0 °C and water (190 μL) was slowly added. The solids were filtered off and washed with diethyl ether (3 × 5 mL), and the solvent was removed under reduced pressure to give the pure product as a white solid (120.0 mg, quantitative yield).

¹H NMR (401 MHz, deuterium oxide): δ = 4.62 (t, *J* = 4.8 Hz, 1 H), 4.49 (t, *J* = 4.6 Hz, 1 H), 4.48–4.40 (m, 1 H), 4.16–4.02 (m, 2 H), 3.64–3.53 (m, 2 H), 3.47–3.35 (m, 1 H).

¹³C NMR (101 MHz, deuterium oxide): δ = 82.9, 82.3, 72.9, 72.3, 71.9, 54.7.

[α]_D²⁵ +126.9 (c 0.22, MeOH); lit.¹⁶ [α]_D²⁵ +110.9 (c 0.5, MeOH).

Mp 115–117 °C; lit.¹⁶ mp 115 °C.

(3R,3aR,6R,6aR)-Hexahydrofuro[3,2-*b*]furan-6-[(3,5-dimethylphenyl)carbamoyl]amino-3-ol (8)

Under an argon atmosphere, to a solution of (3R,3aR,6R,6aR)-hexahydrofuro[3,2-*b*]furan-6-amino-3-ol **4** (89.8 mg, 0.62 mmol) in dry THF (20 mL), 3,5-dimethylphenyl isocyanate (70 μL, 0.50 mmol) was slowly added. The solution was stirred at room temperature, and the reaction was monitored by TLC analysis (CH₂Cl₂–acetone = 9:1). After 24 h, the solvent was removed under reduced pressure, and the residue was dissolved in CH₂Cl₂ (35 mL). The organic solution was washed with H₂O (3 × 10 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was removed under reduced pressure to give the crude product (195.7 mg) as a white solid. This was purified using a Biotage Isolera Chromatograph (CH₂Cl₂–acetone) to give the pure product as a white solid (105.2 mg, 72%).

¹H NMR (401 MHz, chloroform-*d*): δ = 6.90 (s, 2 H), 6.73 (s, 2 H), 5.64 (br s, 1 H), 4.58 (t, *J* = 5.0 Hz, 1 H), 4.55–4.46 (m, 2 H), 4.31 (q, *J* = 5.4 Hz, 1 H), 4.28–4.23 (m, 1 H), 3.88 (dd, *J* = 9.6, 5.5 Hz, 1 H), 3.64 (dd, *J* = 9.6, 5.2 Hz, 1 H), 3.46 (t, *J* = 8.5 Hz, 1 H), 2.27 (s, 6 H).

¹³C NMR (101 MHz, chloroform-*d*): δ = 155.5, 139.1, 138.0, 125.9, 118.7, 82.1, 81.7, 74.7, 72.6, 72.4, 53.5, 21.3.

Elem. Anal.: calcd for C₁₅H₂₀N₂O₄: C, 61.63; H, 6.90; N, 9.58; O, 21.89. Found: C, 61.81; H, 6.85; N, 9.65.

[α]_D²⁵ +67.4 (c 0.51, CHCl₃).

Mp 158–160 °C.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/a-1532-5825>.

References and Notes

- Lait, S. M.; Ranric, D. A.; Keay, B. A. *Chem. Rev.* **2007**, *107*, 767.
- Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.
- Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
- Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.
- Darcel, S. J. C.; Uziel, J. In *Phosphorus Ligands Asymmetric Catal. Synth. Appl.*; Boerner, A., Ed.; Wiley-VCH: Weinheim, **2008**, 1211–1233.
- Parvin, T.; Yadav, R.; Choudhury, L. H. *Org. Biomol. Chem.* **2020**, *18*, 5513.

- (7) Caruso, L.; Puglisi, A.; Gillon, E.; Benaglia, M. *Molecules* **2019**, *24*, 1.
- (8) Meninno, S.; Lattanzi, A. *Catal. Today* **2017**, *285*, 39.
- (9) Botta, M. C.; Biava, H. D.; Spanevello, R. A.; Mata, E. G.; Suárez, A. G. *Tetrahedron Lett.* **2016**, *57*, 2186.
- (10) Koert, U. *e-EROS Encycl. Reagents Org. Synth.* **2012**, 1.
- (11) Zullo, V.; Górecki, M.; Guazzelli, L.; Mezzetta, A.; Pescitelli, G.; Iuliano, A. *J. Mol. Liq.* **2020**, 114528.
- (12) Van Buu, O. N.; Aupoix, A.; Hong, N. D. T.; Vo-Thanh, G. *New J. Chem.* **2009**, *33*, 2060.
- (13) Nguyen Van Buu, O.; Aupoix, A.; Vo-Thanh, G. *Tetrahedron* **2009**, *65*, 2260.
- (14) Carcedo, C.; Knight, J. C.; Pope, S. J. A.; Fallis, I. A.; Dervisi, A. *Organometallics* **2011**, *30*, 2553.
- (15) Metal-catalyzed direct amination of isosorbide gave mixtures of diastereosomeric amino alcohols, see: Niemeier, J.; Engel, R. V.; Rose, M. *Green Chem.* **2017**, *19*, 2839.
- (16) Huynh, K. D.; Ibrahim, H.; Kolodziej, E.; Toffano, M.; Vo-Thanh, G. *New J. Chem.* **2011**, *35*, 2622.
- (17) Huynh, K. D.; Ibrahim, H.; Toffano, M.; Vo-Thanh, G. *Tetrahedron: Asymmetry* **2010**, *21*, 1542.
- (18) Seemayer, R.; Bar, N.; Schneider, M. P. *Tetrahedron: Asymmetry* **1992**, *3*, 1123.
- (19) Mukesh, D.; Sheth, D.; Mokashi, A.; Wagh, J.; Tilak, J. M.; Banerji, A. A.; Thakkar, K. R. *Biotechnol. Lett.* **1993**, *15*, 1243.
- (20) Chalecki, Z.; Guibé-Jampel, E. *Synth. Commun.* **1997**, *27*, 3847.
- (21) Brown, C.; Marston, R. W.; Quigley, P. F.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1809.
- (22) Roy, A.; Chawla, H. P. S. *Enzyme Microb. Technol.* **2001**, *29*, 490.
- (23) Matt, L.; Parve, J.; Parve, O.; Pehk, T.; Pham, T. H.; Liblikas, I.; Vares, L.; Jannasch, P. *ACS Sustain. Chem. Eng.* **2018**, *6*, 17382.
- (24) Saxon, D. J.; Nasiri, M.; Mandal, M.; Maduskar, S.; Dauenhauer, P. J.; Cramer, C. J.; Lapointe, A. M.; Reineke, T. M. *J. Am. Chem. Soc.* **2019**, *141*, 5107.
- (25) Richardson, A. C. *Methods in Carbohydrate Chemistry, Vol. VI*; Academic Press: London, **1972**, 218.
- (26) For the ECR Enzyme Immobilization Procedures, see Purolite Lifetech™ web page (accessed date: July 5th, 2021): <https://www.purolite.com/ls-product/ecr8806m>
- (27) Guisan, J.; Bolivar, J.; López-Gallego, F.; Rocha, J. *Immobilization of Enzymes and Cells*; Humana Press: New York, **2020**.
- (28) Winkler, U. K.; Stuckmann, M. *J. Bacteriol.* **1979**, *138*, 663.
- (29) Berini, C.; Lavergne, A.; Molinier, V.; Capet, F.; Deniau, E.; Aubry, J. M. *Eur. J. Org. Chem.* **2013**, 1937.