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

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Optically active amino alcohols are among the most versatile chemical structures that can be employed as chiral inducers for asymmetric catalysis. They are useful not only as chiral ligands, as in the enantioselective addition of dialkylic reagents to carbonyl compounds, but also as precursors of other chiral derivatives used as ligands in metal-catalyzed enantioselective reactions or as chiral organocatalysts. 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 auxiliaries and organocatalysts, could represent a simple and economical way to obtain chiral amino alcohols endowed with interesting stereochemical features. Among the biomass-based precursors suitable for the synthesis of amines and amino alcohols, a great deal of attention has been addressed to (3R,3aR,6R,6aR)-hexahydrofuro[3,2-b]furan-3,6-diol and its (3R,3aR,6S,6aS)-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. 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 to 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. For these reasons most of the amino derivatives of isohexides show the isomannide stereochemistry.

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. 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 enol 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 enol 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 enzyme-catalyzed regioselective acetylation of isosorbide.22,23 The transesterification has been previously reported for the regioselective synthesis of monoesters.18–24 In general, the selectivity has been toward the enzyme-catalyzed regioselective acetylation of isosorbide.22,23

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.

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.
Enzymatic Assay

The activities of native and immobilized enzyme were determined by using a discontinuous variant of the known assay. To a solution of the native enzyme (0.5 mL, 50.0 μg 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 Na₂CO₃ (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.

(3R,3aR,6S,6aR)-Hexahydrofuro[3,2-b]furan-3-methylcarboxylate-6-ol (5)³⁴

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 × 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).

Immobilization of Lipase PS

The immobilization was carried out following the protocol provided by Purolite: 5.48 g of Purolite octadecyl methacrylate resin ERC8806 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.
washed with H2O (10 mL) and dried over anhydrous Na2SO4. After filtration, the solvent was removed under reduced pressure to give the pure product as a pale-yellow oil (1.79 g, 90%).

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

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 = 10.0, 6.0 Hz, 1 H), 3.80 (dd, J = 10.0, 5.2 Hz, 1 H), 2.12 (s, 3 H).

[α]D 25 +126.9 (c 0.22, MeOH); lit.16 [α]D 25 +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-azido-3-methylcarboxylic acid (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 to give the pure product as a yellow oil that was purified by flash chromatography (silica gel, hexane–ethyl acetate = 8:2) to give the pure product as a pale-yellow oil (1.79 g, 90%).

Rf 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 (dd, 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.


Found: C, 61.91; H, 6.85; N, 9.65.

[α]D 25 +167.4 (c 0.51, CHCl3).

Mp 158–160 °C.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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References and Notes

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(26) For the ECR Enzyme Immobilization Procedures, see Purolite Lifetech™ web page (accessed date: July 5th, 2021): https://www.purolite.com/ls-product/ecr8806m