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Stereoselective Synthesis of Glycomimetic Amines From Biomass-Derived Cyrene

Debora Pratesi | Marta Rigacci | Francesca Cardona | Camilla Matassini | Andrea Goti

Department of Chemistry "Ugo Schiff" – DICUS, University of Florence, Sesto Fiorentino (FI), Italy

Correspondence: Camilla Matassini (camilla.matassini@unifi.it) | Andrea Goti (andrea.goti@unifi.it)

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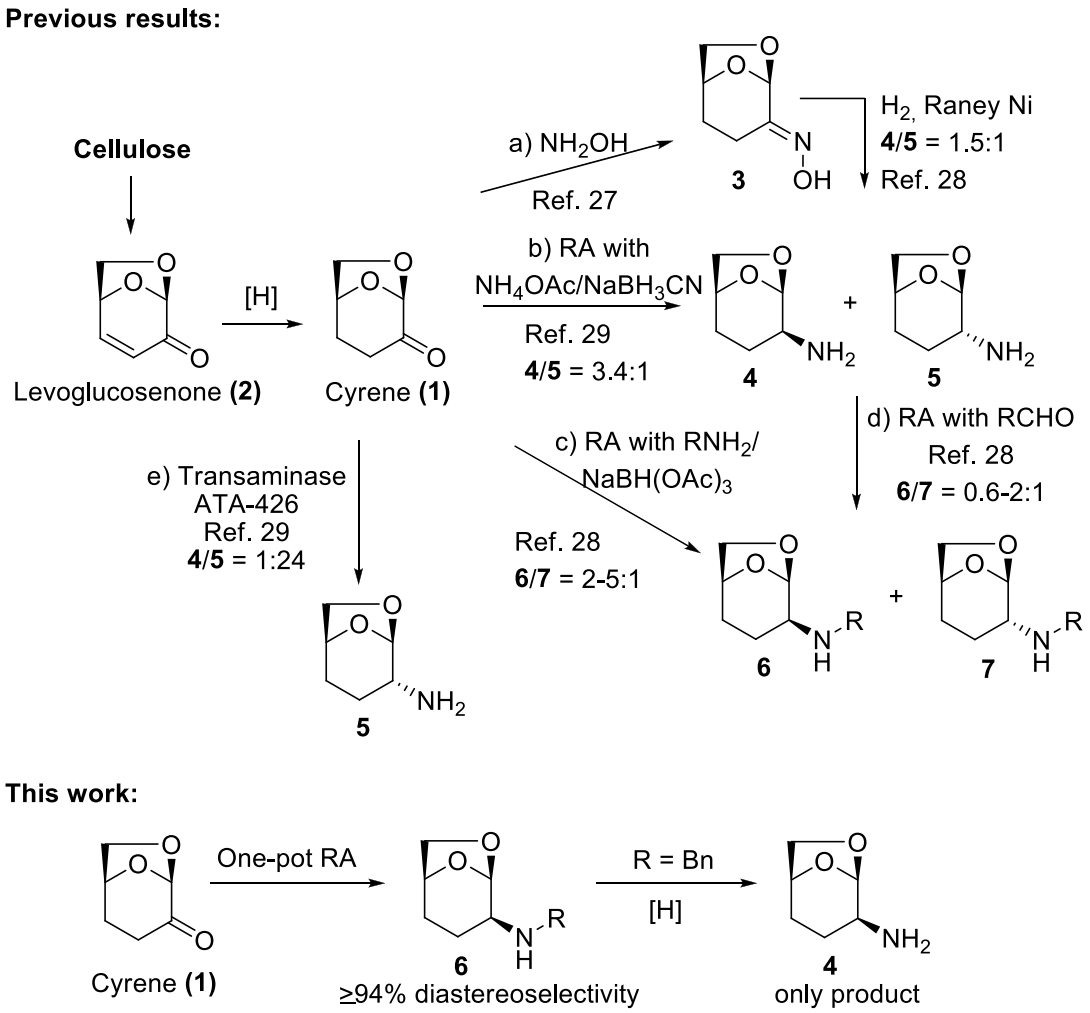
ABSTRACT

Cyrene, a low-cost commercial chiral compound widely available from the pyrolysis of cellulose containing materials including waste biomass, was employed in the preparation of secondary amines. The process exhibited nearly complete stereoselectivity for the D-manno configured amines (*endo* amines) within the 2,3,4-trideoxy hexose structure. Debenzylation of the *N*-benzylamine via catalytic hydrogenation provided the first synthesis of the diastereomerically pure primary amine, employable in turn for accessing the same (2*S*)-configured *endo* amines exclusively through reductive amination with aldehydes. This unprecedented access to pure *endo* amine furnishes a versatile chiral synthetic intermediate to nitrogenated glycomimetics.

1 | Introduction

Cyrene (dihydrolevoglucosenone or 6,8-dioxabicyclo[3.2.1]octan-2-one, **1**) is a bicyclic ketone featuring an intramolecular acetal functionality. It is produced via a two-step process from cellulose-based biomass [1], involving the hydrogenation of levoglucosenone (LGO, **2**), the precursor directly derived from biomass pyrolysis (Scheme 1). Levoglucosenone is a highly promising platform molecule due to its exceptional potential for functionalization. It serves as an attractive chiral building block for synthesizing a wide range of natural products and non-natural analogs [2]. Its structural features make levoglucosenone a versatile and privileged synthetic intermediate for high-value chemicals in pharmaceuticals [3–5], materials chemistry [6–8], and asymmetric synthesis as a precursor of chiral auxiliaries or catalysts [9]. Over the years, several efforts have been made to optimize the pyrolysis conditions of cellulose for the production of LGO. Recently, Huber and coworkers reported a high-yielding procedure (up to 51%) to obtain LGO from cellulose using a sulfuric acid solution in tetrahydrofuran (THF) [10]. The subsequent hydrogenation of LGO to Cyrene typically employs palladium-based catalysts (e.g., Pd/Al_2O_3 and Pd/C) [11], though rhodium and zirconia-supported catalysts have also been investigated [12, 13]. Furthermore, in 2018, Allais and coworkers proposed a biocatalytic reduction of levoglucosenone to Cyrene using an alkene reductase [14]. These advancements have significantly lowered the cost of LGO and Cyrene, making them commercially available chemicals attractive as synthetic intermediates and, in the case of Cyrene, as a green reaction medium.

The physicochemical properties of Cyrene, combined with its high biocompatibility and sustainability, support its use as an alternative green solvent for organic synthesis. Its relatively high boiling point (227°C) is ideal for microwave-assisted reactions, while its easy removal from reaction mixtures, due to its high miscibility with water, allows for simple aqueous workups and solvent recovery by distillation. The polarity parameters of Cyrene are similar to those of NMP (*N*-methyl-2-pyrrolidone) and DMF (*N*,*N*-dimethylformamide), and its solvent power is comparable to that of DMSO. However, unlike these conventional dipolar aprotic solvents, Cyrene exhibits significantly lower toxicity and environmental impact, making it a safer and more sustainable substitute [15, 16]. Numerous examples of reactions employing Cyrene as a solvent have been reported in the literature, including the synthesis of amides, ureas, and



SCHEME 1 | Previous syntheses of nitrogenated derivatives from Cyrene and accomplishment of this work.

isocyanates, C–C coupling reactions, fluorinations, *N*-alkylation reactions, and amine formylation [17].

Beyond its use as a solvent in organic synthesis, Cyrene is a valuable scaffold for further functionalization [18]. For instance, it may be envisaged as a suitable framework for the introduction of nitrogen functionalities to synthesize biologically relevant compounds. Due to our longstanding interest in the synthesis and application of nitrogenated glycomimetics, either with an iminosugar [19–21] or an aminosugar [22–24] structure, we investigated methods to access aminosugar-type compounds directly from LGO [25, 26] or Cyrene [25]. In the case of Cyrene, we planned to convert the carbonyl group into an amino one, targeting a simple entry to 2,3,4-deoxy-2-amino glyco derivatives via reductive amination (RA) routes.

Previous approaches to nitrogenated derivatives from Cyrene are limited (Scheme 1). In the first one, condensation of Cyrene with hydroxylamine to the corresponding oxime **3** was reported (Scheme 1a) [27]. The oxime was subsequently converted into the amines **4** and **5** in a 3:2 diastereomeric ratio by Ni Raney-catalyzed hydrogenation [28]. While the present work was in progress, a few examples of RA reaction with Cyrene have been reported. Kuhl and coworkers described the synthesis of the two amines **4** and **5** in a 3.4:1 ratio by using ammonium acetate (NH_4OAc) and sodium cyanoborohydride ($NaBH_3CN$) as the reducing agent (Scheme 1b) [29]. As expected on the basis of steric hindrance, the reducing agent attacked preferentially the *Re*-face, but with a low selectivity. Shortly after, a broader study of the RA of Cyrene was reported by Wijtmans et al. [28], who carried out a series of RA reactions under different sets of conditions, affording an ample fragment library. Most of the RAs on Cyrene were limited to the use of benzyl-type amines and were carried out by a one-pot procedure, in which the generated imine intermediates were reduced using sodium triacetoxyborohydride ($NaBH(OAc)_3$) (Scheme 1c), affording mixtures of the corresponding amines **6** and **7**, mostly in scarce yields, with low diastereomeric ratios (2–5:1 in favor of amines **6**). Only two amines were obtained in two steps using sodium borohydride ($NaBH_4$) as the reducing agent. This procedure afforded the corresponding secondary amines **6** and **7** in good stereoselectivity but poor yields (47% for R = CH_2Cp, 11% for R = CH_2[3-(1-MeIm)]). Another set of secondary amines **6** and **7** has been described in the same work, obtained by RA but starting from the preformed diastereomeric mixture of amines **4**/**5** obtained by the reduction of the oxime **3**. Consequently, their synthesis suffered from low diastereomeric ratios (1–2:1), besides being affected by scanty 10%–33% yields (Scheme 1d). To date, the only highly stereoselective approach for the amination of Cyrene has been achieved by a biosynthetic-catalyzed procedure, which afforded amine **5**. A catalyst-controlled transamination approach

with the use of transaminase ATA-426 [30–32] allowed the authors to obtain amine **5** with a good diastereoselectivity (24:1 dr, Scheme 1e) [29, 33].

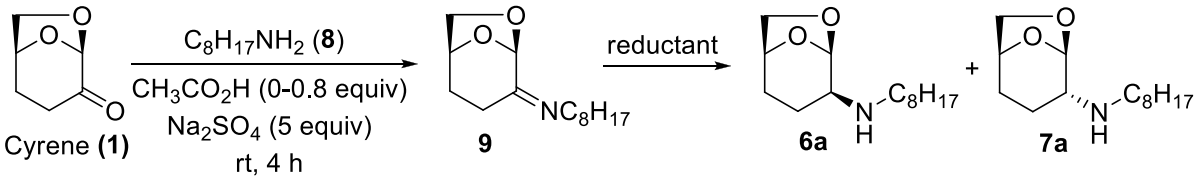
To the best of our knowledge, no synthetic route able to yield amine **4** free from its diastereomer **5** has been reported so far, nor a general method for accessing the corresponding secondary amines **6** with high stereoselectivity has been developed. In this work, we report an RA procedure which furnishes products **6** with nearly complete diastereoselectivity and good yields and the preparation of the primary amine **4** as a sole isomer from one of the primary products (Scheme 1).

2 | Results and Discussion

A representative RA reaction of Cyrene (**1**) with octylamine (**8**) followed by treatment with a reducing agent was initially investigated in order to define the optimal operative conditions for obtaining the corresponding secondary amine **6a**/**7a** with a high diastereoselective ratio (Scheme 2 and Table 1). The expected major diastereomer was the (2*S*)-configured amine **6a** on the basis of the steric hindrance of the CH_2O bridge which should hamper the attack of the reducing agent to imine **9** from the top (*Si* face), as illustrated in Figure 1. Accordingly, the *endo* amine **4** was obtained as the major compound by RA with ammonium acetate by Kuhl and coworkers, albeit with a moderate selectivity [29].

As we wanted to screen several reagents in the reduction of intermediate imine **9**, including those which would reduce the starting ketone as well, we decided to ascertain the complete formation of the imine before adding the reducing agent. Thus, progression of the condensation of equimolar amounts of Cyrene and octylamine with acetic acid (0.8 equiv) and sodium sulfate (5 equiv) at room temperature in different anhydrous solvents was checked by ^{1}H NMR. The disappearance of the signal of the hydrogen at C-1 in **1** ($\delta = 5.04$ ppm), replaced by a signal at $\delta = 5.39$ ppm for the same hydrogen in **9** (in $CDCl_3$ solution), attested the end of reaction and complete formation of the imine after 4 h at room temperature. It was successively ascertained that the acid catalysis is unnecessary at all; thus, the last trials were carried out without added acetic acid. The results of our attempts in terms of recovered yields and **6a**/**7a** diastereomeric ratios with the use of different reducing agents and reaction conditions are reported in Table 1.

Classical reductants for RA, which may also be used in a single operation together with the amine and ketone, were investigated at first. Both catalytic hydrogenation over Pd/C at rt and reduction with sodium cyanoborohydride at 0°C resulted in good yields of amines **6a**/**7a** but with moderate selectivity (84% with 6.2:1 dr and 75% with 4.3:1 dr, respectively; Table 1, entries 1–2). Using more powerful but more sterically demanding hydride reductants (Table 1, entries 3–6) failed to give the desired amines, with the only product identified at the end of the reaction being the starting ketone **1**, likely deriving from the hydrolysis of the unreacted imine **9** during the quenching of the reaction. Finally, the use of 3 mol equivalent of sodium borohydride at rt was found effective in producing the major amine **6a** with a satisfactory 20:1 diastereoselectivity albeit at the expenses of a more moderate ca. 50% yield (Table 1, entry 7). However, the formation of a single amine in a highly selective manner is essential, taking into account the general inseparability of the amines by simple chromatographic methods [28, 29], confirmed also in the case



SCHEME 2 | Reductive amination of Cyrene (**1**) with *n*-octylamine (**8**) as the sample reaction for optimization of the diastereoselectivity.

TABLE 1 | Screening of the reaction conditions in the reductive step of imine **9**.

Entry[a]	Solvent[b]	Reductant	Temperature, time	Yield (dr)[c,d]
1	MeOH	H_2, Pd/C	rt, 18 h	84% (6.2:1)
2	CH_2Cl_2	$NaBH(OAc)_3$	0°C to rt, 3 days	75% (4.3:1)
3	CH_2Cl_2	L-Selectride	0°C to rt, 2 days	n. r.
4	THF	K-Selectride	0°C to rt, 18 h	n. r.
5	Toluene	Red-Al	0°C to 60°C, 2 days	n. r.
6	THF	L-Selectride	−20°C to rt, 18 h	n. r.
7	MeOH	$NaBH_4$	0°C to rt, 30 min	52% (20:1)
8	MeOH	$NaBH_4$	−20°C, 30 min	51% (25:1)
9	MeOH	$NaBH_4$	−78°C, 30 min	69% (>25:1)

[a]For the formation of imine **9** in the first step of the process, CH_3CO_2H (0.8 equiv) was used in entries 1–5.
[b]All solvents were dried before their use.
[c]The diastereomeric ratios dr were evaluated from the ^{13}C NMR spectra of the crude reaction mixtures (see text).
[d]In entries 3–6, n. r. means that no trace of amines **6a**/**7a** was evidenced at the end of the reaction (see text).

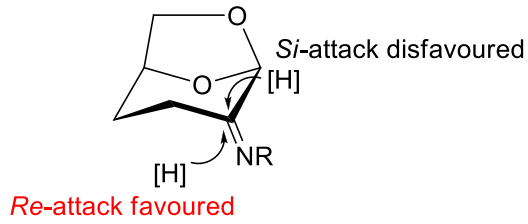
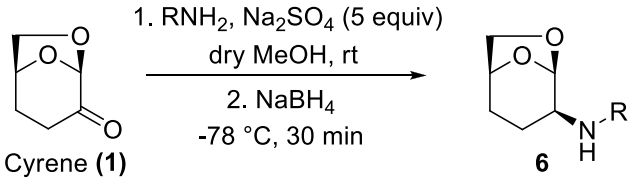


FIGURE 1 | Possible diastereofacial nucleophilic attacks to Cyrene-derived imines.

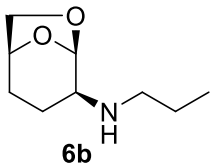
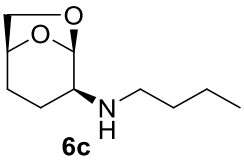
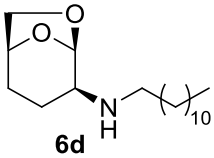
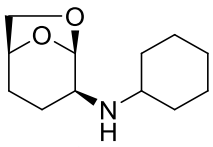
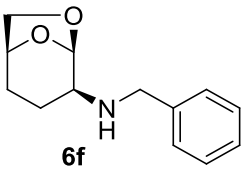


SCHEME 3 | Diastereoselective reductive amination of Cyrene (**1**) with primary amines to give (*S*)-configured amine **6** using $NaBH_4$.

of **6a**/**7a** mixtures. On lowering the reaction temperature of the reduction step to −20°C or −78°C, the diastereoselectivity could be further improved up to a remarkable > 25% dr (Table 1, entries 8–9). Reduction of the reaction temperature allowed by the more reactive hydride reagent is believed to play the most important role in increasing the diastereoselectivity of the reaction. It might be speculated that a contribution is also given by a stereoelectronic factor, with the more nucleophilic $NaBH_4$ attacking preferentially the *Re* face according to a Felkin–Anh model. It is worthy to note that no signal of the two diastereomers was discriminated in the ^{1}H NMR spectrum. Consequently, assuming that the relaxation times for the same carbon atom in the two diastereoisomers will not differ substantially and the measured integrals may give a good estimation, the reported diastereomeric ratios were evaluated by integration of the signals of C-2 which were distinct in the ^{13}C NMR of the crude reaction mixture ($\delta = 57.2$ ppm for **6a** and $\delta = 55.5$ ppm for **7a**). Assignment of the major product as amine **6a** was tentative, made on the basis of the above considerations (Figure 1). This assignment was later proved for an analogous secondary amine and further confirmed for the primary amine **4** (see below).

Having established suitable operative conditions for the diastereoselective RA of Cyrene (**1**), the sodium borohydride-induced RA has been extended to a set of primary amines, including linear and cyclic aliphatic amines and benzylamine (Scheme 3 and Table 2). In each case, complete formation of the intermediate imine has been ascertained as before by ^{1}H NMR prior the addition

TABLE 2 | Reductive aminations of Cyrene (**1**) with primary amines using $NaBH_4$.

Entry	Amine (equiv)	Reaction time[a]	Product	Yield (dr)[c,d]
1	*n*-Propylamine (1.5)	18 h	 **6b**	96% (>25:1)
2	*n*-Butylamine (1.0)	4 h	 **6c**	60% (20:1)
3	*n*-Dodecylamine (1.2)	18 h	 **6d**	83% (>25:1)
4	Cyclohexylamine (1.2)	18 h	 **6e**	46% (15:1)
5	Benzylamine (1.2)	18 h	 **6f**	76% (>25:1)

[a]Reaction time for formation of the imine in the first step of the process.
[b]Isolated yield of the amine.
[c]The diastereomeric ratios dr were evaluated from the ^{13}C NMR spectra of the crude reaction mixtures.

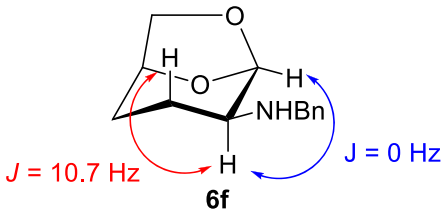


FIGURE 2 | Relevant coupling constants of the hydrogen atom at C-2 for configurational assignment to amine **6f**.

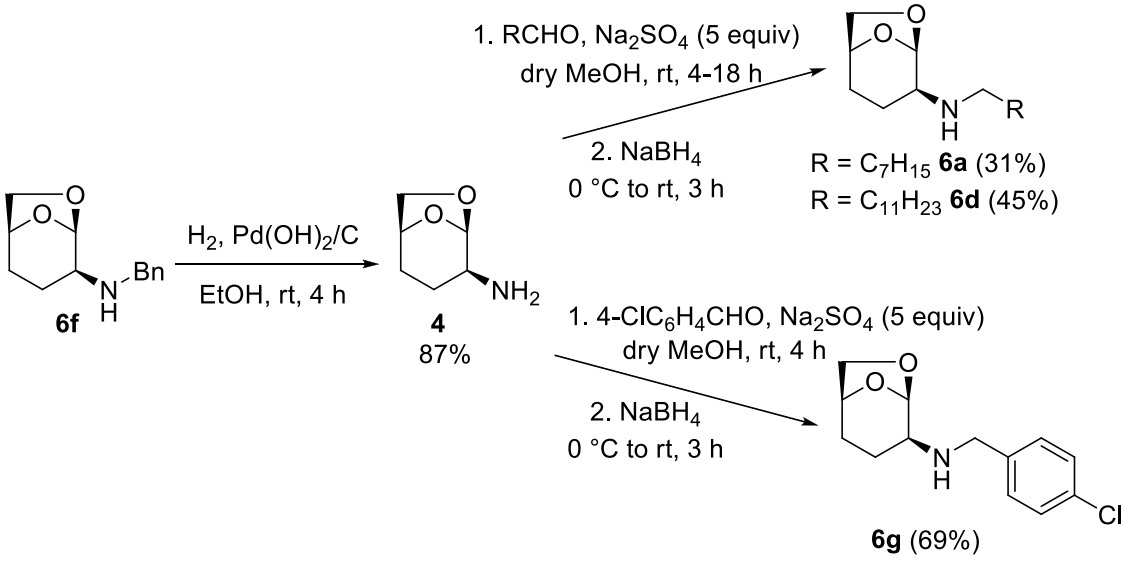
of $NaBH_4$. All reactions gave amine **6** in satisfactory to good yields and excellent diastereoselectivity, ranging from 15:1 for cyclohexylamine (Table 2, entry 4) to > 25:1 for *n*-propylamine, *n*-dodecylamine, and benzylamine (Table 2, entries 1, 3, and 5, respectively).

Albeit in some cases a signal for the minor isomers was discernible (typically at ca. 3.8–4.0 ppm, likely ascribable to the C-6 hydrogens), it is unclear if it should be assigned to one or two hydrogens. Therefore, it was preferred to rely on the integration of the C-2 signals for all the diastereomeric couples, besides being consistent for all compounds. A representative example of the diastereomeric ratio determination by integration of the C-2 signals in the crude reaction mixtures is reported in Figure S11 for the **6f**/**7f** diastereomeric couple.

After purification by flash column chromatography, all the amines **6a–f** have been obtained in a > 97% purity, presenting in some cases only traces (<3%) of their hardly separable diastereoisomers. No signal in the NMR spectra of *N*-alkyl amines **6a–e** was deemed suitable for assigning the configuration of the experimentally observed major products. The hydrogen atom placed at C-2 by the reducing agent might serve the scope, assuming an axial position in the hypothesized preferred attack to the *Re* face (Figure 1) or in an equatorial one if the *Si* face would be attacked. However, in the ^{1}H NMR spectra of amines **6a–e,** these protons resonate at $\delta = 2.67–2.50$ ppm but overlap to the signals of the hydrogen atoms adjacent to nitrogen in the alkyl chain, and no information on their coupling constants can be drawn. Conversely, in *N*-benzylamine, **6f** the C-2 proton signal falls at $\delta = 2.68$ ppm as a dd with coupling constants $J = 10.7$ and 5.4 Hz, which are consistent with vicinal ax–ax and ax–eq coupling constants, respectively, in a fixed chair-like conformation as depicted in Figure 2 according to previous computational and structural findings [29]. No coupling constant is observable with proton at C-1, consistent with a dihedral angle close to 90°. The corresponding hydrogen in its (2*R*) diastereoisomer was found to resonate as a narrow multiplet at $\delta = 2.63–2.52$ ppm [29]. The observed set of couplings and comparison with the literature clearly testify for the (*S*) configuration at the newly generated chiral center, deriving from the occurred preferential attack at the *Re* face of intermediate imine. Thus, all the amines **6** are assigned the same (*S*) configuration at C-2.

The benzylamine **6f** was then debenzylated by hydrogenation over $Pd(OH)_2/C$ to afford the amine **4** (Scheme 4) with a D-manno configuration at C-2 (*endo* amine), thus accomplishing the first synthesis of this amine free from its diastereoisomer **5**. Analogous to the *N*-benzyl derivative **6f**, the hydrogen at C-2 in the ^{1}H NMR spectrum of amine **4** resonates at $\delta = 2.74$ ppm as a dd with coupling constants $J = 10.1$ and 4.4 Hz, which compares well with the corresponding proton of the major compound assigned as the (2*S*) diastereoisomer in a 3:2 mixture of **4** and **5** ($\delta = 2.76$ ppm, dd, $J = 11.1$, 5.0 Hz), while the same proton in the minor one gave a multiplet at $\delta = 2.83–2.79$ ppm [28].

Diastereomerically pure amine **4** can be used in turn as a starting material for obtaining amines **6** by RA with diverse aldehydes (Scheme 4). Direct RA with aliphatic amines under H_2 (balloon) over Pd/C gave the desired secondary amines in unsatisfactory amounts (ca. 20% yields). The one-pot procedure via formation of the intermediate imine from octanal or dodecanal followed by reduction with $NaBH_4$ furnished the expected amines **6a** and **6d**, respectively, in moderate yields, yet superior to those previously obtained from the diastereomeric mixture of amines **4** and **5** with benzyl type aldehydes [28]. Conversely, 4-chlorobenzaldehyde afforded the *endo* amine **6g** exclusively in a good 69% yield. The latter compound showed NMR data compatible with those reported for the 1.6:1 *exo*/*endo* diastereomeric mixture previously



SCHEME 4 | Synthesis of amine **4** by debenzylation of **6f** and its use as synthetic intermediate.

obtained in poor yield (24%) by RA of the **4**/**5** mixture, with some uncertainties regarding the previous tentative diastereomeric assignment [28].

3 | Conclusion

Cyrene, a low-cost commercial chiral compound largely available from pyrolysis of cellulose containing materials including waste biomass, was employed for introducing amine functionalities in the carbohydrate skeleton. Optimization of the RA procedure was achieved by using sodium borohydride at −78°C after complete formation of the intermediate imine, allowing the preparation of secondary amines with nearly complete stereoselectivity for the D-manno configured amines (*endo* amines) in the 2,3,4-trideoxy hexose structure. Debenzylation of the amine **6f** by catalytic hydrogenation ensured the first synthesis of diastereomerically pure amine **4**, which was used in turn for accessing (2*S*)-configured amines **6** solely by means of RA reactions with aldehydes. The unprecedented access to *endo* amine **4** free from its *exo* diastereoisomer furnishes a chiral synthetic intermediate useful for a large range of transformations to nitrogenated glycomimetics, taking also into account the possible opening of the oxymethylene bridge of the products [9, 18, 33, 34].

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.