JOC*Note*

Totally Selective Synthesis of Enantiopure (3*S*,5*S*)- and (3*R*,5*R*)-4-Amino-3, 5-dihydroxypiperidines from Aminodiepoxides Derived from Serine

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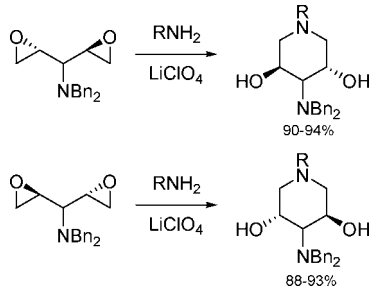

The transformation of enantiopure (2*R*,4*R*)- and (2*S*,4*S*)-*N*,*N*-dibenzyl-1,2:4,5-diepoxypentan-3-amine, **1** and **2**, into the corresponding enantiopure (3*S*,5*S*)- and (3*R*,5*R*)-3,5-dihydroxy-3-aminopiperidines, **3** and **4** respectively, is described. The opening of the two epoxide rings with a range of amines takes place with total regioselectivity and high yields, in the presence of $LiClO_4$. A mechanism to explain this transformation is proposed.

Glycosidases inhibitors are a pharmacologically important class of compounds, and consequently, an important number of glycosidase inhibitors have been developed.[1] Among these, polyhydroxylated piperidines,[5] which can be regarded as 1-azasugars having a nitrogen atom at the anomeric position, have been the subject of intense research. The inhibitory activity of 1-azasugars, also called iminosugars, is due to their ability to mimic the transition state for the enzymatic glycosidase hydrolysis. Thus, polyhydroxylated piperidines[2] have demonstrated their utility in the treatment of carbohydrate-mediated diseases.

In recent years, much attention has been focused toward the development of the efficient synthesis of different polyhydroxylated piperidines due to their potential therapeutic applications and the need to discover efficient routes for the synthesis of biologically active analogues. The main synthetic strategy described in the literature to obtain polyhydroxylated piperidines utilizes carbohydrates as starting materials and, in general, requires a large number of steps. Thus, the development of new methods for the synthesis of enantiopure 1-azasugars from alternative starting compounds is of considerable interest.[6] In addition, no synthesis of both enantiomers of polyhydroxylated piperidines has been reported.

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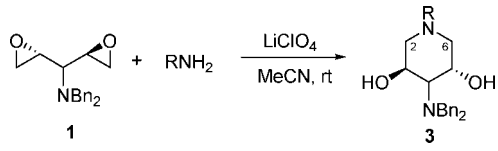
SCHEME 1. Synthesis of (3*S*,5*S*)-3,5-Dihydroxy-3-aminopiperidine 3



Moreover, the synthesis of enantiopure organic compounds with C_2 symmetry or pseudo-C_2 symmetry has also received much attention due to their important synthetic applications. These compounds are used as chiral ligands[7] and to prepare chiral catalysts,[8] and the core unit of pseudopeptide HIV protease inhibitors and other bioactive compounds[9] present this symmetry. Consequently, the polyhydroxylated piperidines with pseudo-C_2 symmetry present a double interest: as 1-azasugar compounds and as building blocks.

Previously, we have described an efficient synthesis of the pseudo-C_2 symmetric (2*R*,4*R*)- and (2*S*,4*S*)-*N*,*N*-dibenzyl-1,2:4,5-diepoxypentan-3-amine, **1** and **2**, in enantiomerically pure form.[10] Both aminodiepoxides were prepared from the same the natural α-aminoacid, L-serine.

Herein, we describe a synthetic application of these aminodiepoxides **1** and **2** to obtain the pseudo-C_2 symmetric (3*S*,5*S*)- and (3*R*,5*R*)-3,5-dihydroxy-3-aminopiperidines in enantiopure form, **3** and **4**, respectively.

Our initial studies were performed starting from (2*R*,4*R*)-*N*,*N*-dibenzyl-1,2:4,5-diepoxypentan-3-amine, **1**. Thus, the treatment of a solution of the aminodiepoxide **1** in acetonitrile, with a range of amines in the presence of $LiClO_4$ at room temperature, afforded the corresponding (3*S*,5*S*)-3,5-dihydroxy-3-aminopiperidines **3** in moderate or high yield (Scheme 1 and Table 1).[11]

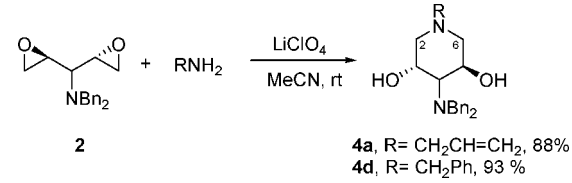
This transformation seems to be general, and the reaction could be carried out with different aliphatic (linear and cyclic) and unsaturated amines. Here, no differences were observed during the course, or the outcome of the reaction, when allyl, *n*-propyl, benzyl or cyclohexylamine were used, under the same reaction conditions. As shown in Table 1, the different (3*S*,5*S*)-4-amine-3,5-dihydroxypiperidines **3** were obtained in similar yields.

TABLE 1. Synthesis of (3*S*,5*S*)-3,5-Dihydroxy-3-aminopiperidine 3

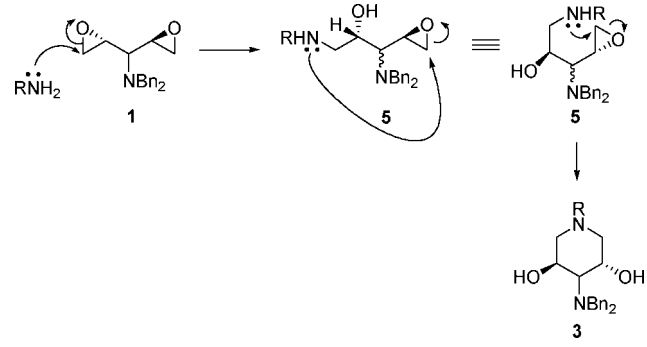
entry	3	R	Yield(%)[a]
1	**3a**	allyl	90
2	**3b**	Pr	94
3	**3c**	Cyclohexyl	93
4	**3d**	Bn	92

[a] Yield after column chromatography based on the starting amino epoxide **1**.

SCHEME 2. Synthesis of (3 *R*,5 *R*)-3,5-Dihydroxy-3-aminopiperidine 4



SCHEME 3. Proposed Mechanism



The selectivity of the reaction was determined by ^{1}H NMR spectroscopy (300 MHz) of the crude mixture of products, showing the presence of a single isomer **3**. Thus, has been shown that the ring opening of epoxide **1** with amines took place with total regioselectivity.

Synthetic methods that allow the synthesis of two pure enantiomers are very useful since in many cases, the biological or pharmaceutical properties of both enantiomers can be very different. Indeed, it has been described that one enantiomer shows therapeutic properties while the other can be toxic or inactive.[12] For this reason, and in order to extend the scope of this synthesis, we performed the reaction on (2*S*,4*S*)-*N*,*N*-dibenzyl-1,2:4,5-diepoxypentan-3-amine **2**, instead of aminodiepoxide **1** with allylamine and benzylamine, under the same reaction conditions (Scheme 2).

As was expected, no important differences were observed in comparison to the transformation from **1** and the corresponding (3*S*,5*S*)-3,5-dihydroxy-3-aminopiperidine **4a**,**d** were obtained in high yields (similar to the obtained in the synthesis of **3**) and with total selectivity (300 MHz ^{1}H NMR spectroscopy of the crude reaction mixture).

The mechanism proposed to explain the transformation of **1** into **3** is depicted in Scheme 3. The ring opening of the oxirane by the amine would be favored by the presence of $LiClO_4$, as has been previously reported.[13] Thus, one of the oxirane rings would be opened by the amine at the less hindered position,[14] affording the amino alcohol **5**. The amine function in intermedi-

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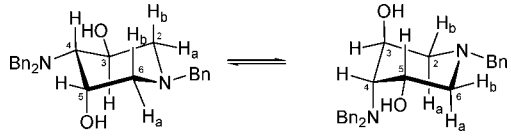

I II

FIGURE 1. Conformational equilibrium of piperidine **3d**.

ate **5** participates in a nucleophilic attack to the second oxirane ring at the less hindered position, affording the piperidine ring. A similar mechanism could explain the transformation of aminodiepoxides **2** into the enantiomers **4**.

The variation of symmetry at the C-3 carbon of **1** along the transformation of **1** into **3**, shown is Scheme 3, presents a theoretical interest: the C-3 carbon of the aminodiepoxide **1** is not a stereogenic center since both oxirane rings in **1** are chemically equivalents. Conversely, the C-3 carbon in intermediate **5**, generated after the reaction of the aminodiepoxide with the amine (NH_2 R), is a stereogenic center. As a consequence of the chemical equivalence of both oxirane rings, the amine could equally attack both oxirane rings to give intermediate **5** as mixture of epimers in a 1/1 ratio. An intramolecular attack by the amine group (NHR) to the other oxirane ring afforded the piperidine **3**, in which the C-4 carbon (formerly the C-3 carbon in compound **1**) is not a stereogenic center due the symmetry of the obtained piperidine (the two substituents at the C-4 carbon of compound **3** are the same).

The structure of compounds **3** and **4**, as depicted in Schemes 1, 2, and 3, was established based on IR, ^{1}H, ^{13}C NMR spectra including DEPT, HMBC, HSQC, and NOESY experiments on the 4-amino-3,5-dihydroxypiperidine **3d**.

An HMBC NMR experiment on **3d** showed correlation between methylene hydrogens of C-2, and C-6 (see Schemes 1 and 2 for the numbering protocol) and the benzylic protons from the cyclic nitrogen. Similarly, a correlation was observed between the methylene hydrogens at C-6 and the methylene and methine hydrogens at C-2 and C-5, respectively. Correlation between methine protons at C-3 and C-5 was also observed. Moreover, NOESY experiments showed correlation between geminal hydrogens of the C-2 and C-6 methylenes. This correlation is observed in six-member cyclic molecules due to a conformational equilibrium that produces an exchange of the environment of methylene protons (Figure 1, **I** and **II**). Hence, all these data were consistent with the assigned structures for compounds **3** and **4** (Schemes 1 and 2).

The configurational assignments of piperidines **3** were established by ^{1}H NMR coupling constant analysis and NOESY experiments on **3d** (Figure 1). The H-4 signal shows J = 10.3, 2.0 Hz which is in accordance with a *trans* relative configuration between H-4 and H-3, and *cis* for H-4 and H-5. Moreover, the NOE interaction of H-4 with H-5, H-2, and H-6, and the absence of NOE interactions between H-4 and H-3, would also support the configuration of compounds **3** and **4**. This stereochemical assignment is also in agreement with the proposed ring-opening mechanism.

This proposed structure and the absolute configurational assignment of compounds **3** or **4** was unambiguously confirmed by the single-crystal X-ray analysis of **3c**.[15] The structure and absolute configuration of the other compounds **3a**,**b**,**d** and **4a,d**, as depicted in Schemes 1 and 2, was assigned by analogy.

In conclusion we have described a new and short synthesis of both enantiomers (3*S*,5*S*)- and (3*R*,5*R*)-3,5-dihydroxy-3-aminopiperidines **3** or **4** in enantiopure form, by double ring opening reaction of epoxides of (2*R*,4*R*)- and (2*S*,4*S*)-*N*,*N*-dibenzyl-1,2:4,5-diepoxypentan-3-amine, **1** or **2** with a range of amines at room temperature in the presence of $LiClO_4$. This reported method is simple, and the starting aminodiepoxides **1** or **2** are readily available from serine. The opening of the epoxide ring takes place with total regioselectivity.

Experimental Section

General Procedure. To a stirred solution of the corresponding aminodiepoxide **1** or **2** (2 mmol) in dry acetonitrile (8 mL) was added $LiClO_4$ (2 mmol) at room temperature. After stirring for 5 min, the corresponding amine (3 mmol) was added dropwise at the same temperature, and the mixture was stirred at room temperature for 48 h. After this time, the reaction was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuum. Flash column chromatography on silica gel (hexane/EtOAc 10/1) provided pure compounds **3** or **4**.

(3*S*,5*S*)- and (3*R*,5*R*)-enantiomers showed identical spectroscopical data except $[\alpha]^{20}_D$ which were indicative.

1-Allyl-4-dibenzylamino-3,5-dihydroxypiperidine. (3*S*,5*S*)-**3a** $[\alpha]^{20}_D$= +90.9 (*c* 1.00, $CHCl_3$); (3*R*,5*R*)-**4a** $[\alpha]^{20}_D$= −91.0 (c 1.00, $CHCl_3$); Colorless solid; Mp 101 °C; ^{1}H NMR (300 MHz, CDCl3) δ 7.45−7.15 (m, 10 H), 5.91−5.71 (m, 1 H), 5.25−5.10 (m, 2 H), 4.35−4.28 (m, 1H), 4.25−4.10 (m, 1H), 3.95 (AB syst., J = 13.9 Hz, 2 × 2H), 3.38 (br s, 2H), 3.31−3.20 (m, 1H), 3.10 (d, J = 6.3 Hz, 2H), 3.01 (dt, J = 12.0, 3.2 Hz, 1H), 2.32 (dd, J = 10.7, 2.0 Hz, 1H), 2.13 (apparent d, J = 11.4 Hz, 1 H), 1.85 (apparent t, J = 10.1 Hz, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 139.6 (2 × C), 133.7 (CH), 128.7 (2 × CH), 128.4 (2 × CH), 127.0 (2 × CH), 118.8 (CH_2), 64.7 (CH), 64.3 (CH), 62.4 (CH), 60.4 (CH_2), 59.6 (CH_2), 58.5 (CH_2), 54.4 (2 × CH_2); MS (70 eV, EI) *m*/*z* (%) 352 [M^+, <1], 261 (23), 91 (100); HRMS (70 eV) calcd for [$C_{22}H_{28}N_2O_2$ − CH_2Ph] 261.1597, found 261.1598; IR (KBr): 3445, 2922, 2815, 1639 cm^{-1}; R_f = 0.25 (hexane/EtOAc 10:1)

4-Dibenzylamino-3,5-dihydroxy-1-propylpiperidine. (3*S*,5*S*)-**3b** $[\alpha]^{20}_D$= +52.8 (*c* 0.68, $CHCl_3$); Pale-yellow solid; Mp 70 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.23−7.13 (m, 10H), 4.19−4.14 (m, 1H), 4.02−3.97 (m, 1H), 3.81 (AB syst., J = 13.8 Hz, 2 × 2H), 3.17−3.06 (m, 1H), 2.98 (br s, 2H), 2.79 (d, J = 11.4 Hz, 1H), 2.22 (t, J = 7.2 Hz, 2H), 2.18 (d, J = 10.5 Hz, 1H), 1.96 (d, J = 12.5 Hz, 1H), 1.66 (t, J = 9.9 Hz, 1H), 1.38−1.22 (m, 2H), 0.77 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.7 (2 × C), 128.7 (4 × CH), 128.4 (4 × CH), 127.0 (2 × CH), 64.8 (CH), 64.3 (CH), 62.5 (CH), 60.0 (CH_2), 59.1 (CH_2), 58.6 (CH_2), 54.4 (2 × CH_2), 19.7 (CH_2), 11.5 (CH_3); MS (70 eV, EI) *m*/*z* (%) 354 [M^+, <1], 263 (22), 91 (100); HRMS (70 eV) calcd for [$C_{22}H_{30}N_2O_2$ − CH_2Ph] 263.1754, found 263.1756; IR (KBr) 3426, 2933, 1642, 1455, 1375 cm^{-1}; R_f = 0.35 (hexane/EtOAc 3:1)

4-Dibenzylamino-1-cyclohexyl-3,5-dihydroxypiperidine. (3*S*,5*S*)-**3c** $[\alpha]^{20}_D$= +61.3 (*c* 0.70, $CHCl_3$); Yellow solid; Mp 65 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.31−7.06 (m, 10H), 4.20−4.11 (m, 1H), 3.99−3.90 (m, 1H), 3.84 (AB syst., J = 14.0 Hz, 2 × 2H), 3.04 (dd, J = 10.3, 4.4 Hz, 1H), 2.95 (br s, 2H), 2.77 (d, J = 11.3 Hz, 1H), 2.30−2.19 (m, 1H), 2.17 (apparent t, J = 12.2 Hz, 1H), 1.91 (apparent t, J = 8.8 Hz, 1H), 1.66−1.60 (m, 4H), 1.51 (d, J = 12.3 Hz, 1H), 1.20−0.91 (m, 6H);^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.8 (2 × C), 128.7 (4 × CH), 128.4 (4 × CH), 127.0 (2 × CH), 65.3 (CH), 64.0 (CH), 63.4 (CH), 63.2 (CH), 56.2 (CH_2),

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(15) CCDC 687287 contains the supplementary crystallographic data for compound **3c**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or the Cambridge Data Center 12 Union Road Cambridge CB2 1EZ UK fax (+44)1223−336−033 or deposit@ccdc.cam.ac.uk).

55.0 (CH_2), 54.4 (2 × CH_2), 29.0 (CH_2), 28.8 (CH_2), 26.0 (CH_2), 25.7 (2 × CH_2); MS (70 eV, EI) *m*/*z* (%) 394 [M^+, <1], 303 (15), 91 (100); HRMS (70 eV) calcd for [$C_{25}H_{34}N_2O_2$ − CH_2Ph] 303.2067, found 303.2071; IR (KBr) 3430, 2924, 1455 cm^{-1}; R_f = 0.26 (hexane/EtOAc 10:1)

1-Benzyl-4-dibenzylamino-3,5-dihydroxypiperidine. (3*S*,5*S*)-**3d** $[\alpha]^{20}_D$= +45.5 (*c* 0.22, $CHCl_3$); (3*R*,5*R*)-**4d** $[\alpha]^{20}_D$= −44.3 (c 0.20, $CHCl_3$); Yelow solid; Mp 105 °C; ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.35−7.00 (m, 15H), 4.20−4.11 (m, 1 H), 4.05−3.92 (m, 1H), 3.69 (AB syst., *J* = 13.8 Hz, 2 × 2H), 3.45 (AB syst., *J* = 12.1 Hz, 2H), 3.08 (ddd, *J* = 10.4, 5.1, 2.4 Hz, 1H), 2.96 (br s, 2H), 2.81 (dt, *J* = 11.6, 2.9 Hz, 1H), 2.19 (dd, *J* = 10.4, 2.0, Hz, 1H), 2.00 (dd, *J* = 11.6, 1.1, Hz, 1H), 1.69 (apparent t, *J* = 10.1 Hz, 1H); ^{13}C RMN (75 MHz, $CDCl_3$) δ 139.7 (2 × C), 137.4 (C), 128.9 (2 × CH), 128.7 (4 × CH), 128.4 (4 × CH), 128.3 (2 × CH), 127.4 (2 × CH), 127.0 (2 × CH), 65.0 (CH), 64.5 (CH), 62.7 (CH), 61.8 (CH_2), 59.9 (CH_2), 58.6 (CH_2), 54.4 (2 × CH_2); MS (70 eV, EI) *m*/*z* (%) 402 [M^+, <1], 311 (10), 91 (100); HRMS (70 eV) calcd for [$C_{26}H_{30}N_2O_2$ − CH_2Ph] 311.1754, found 311.1749; IR (KBr): 3418, 3022, 2916, 2810, 1489, 1451 cm^{-1}; R_f = 0.40 (hexane/EtOAc 3:1)

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **3**, and crystallographic data (CIF) of **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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