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Arkivoc **2019**, part v, 50-59

Regio - and stereoselective synthesis of the iminosugars – 4-substituted 1-benzylpiperidine-3,5-diols

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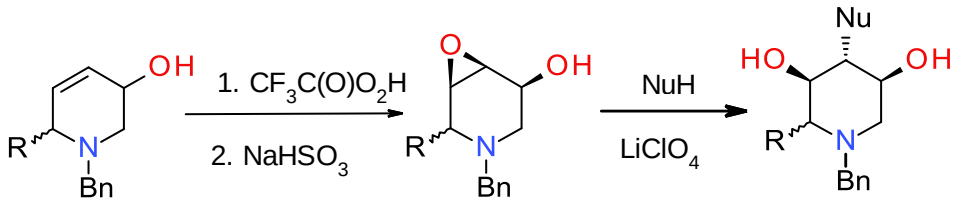
Received 08-03-2018 **Accepted** 11-28-2018 **Published on line** 02-13-2019

Abstract

We report a new approach to preparing iminosugars – 4-substituted 1-benzylpiperidin-3,5-diols by reaction of 1-benzyl-4,5-epoxypiperidine-3-ols in the presence of lithium perchlorate. This regio- and stereoselective synthesis proceeds via successive nucleophilic cleavage of 1-benzyl-4,5-epoxypiperidin-3-ols by benzylamine, thiophenol and diallylamine. Initial 1-benzyl-4,5-epoxypiperidin-3-ols were obtained by oxidation of trifluoroacetates of 1-benzyl-1,2,3,6-tetrahydropyridin-3-ols.



Keywords: Epoxypiperidines, iminosugars, stereoselective synthesis, polyhydroxylated piperidines

Introduction

Functionalized piperidines are versatile synthons for the directed design of synthetic analogues of diverse piperidine alkaloids and are common structural targets in pharmacological research.[1-3] A new interesting research area has recently emerged regarding polyhydroxylated piperidines as enzymatic inhibitors particularly for glycosidases, sialidases or neuraminidases.[1,2] Iminosugars are potentially useful for the therapy of the metabolic disorders such as diabetes, viral and bacterial infections, tumors, lysosomal storage diseases.[3,4] For instance, the alkaloid nojirimycin **1** is a strong inhibitor of α- and β-glucosidases involved in the metabolism of carbohydrates. Some derivatives of polyhydroxylated piperidines **1-6,** for example 1-deoxynojirimycin **2** are used for the treatment of Alzheimer's disease[5] and Farby disease.[6]

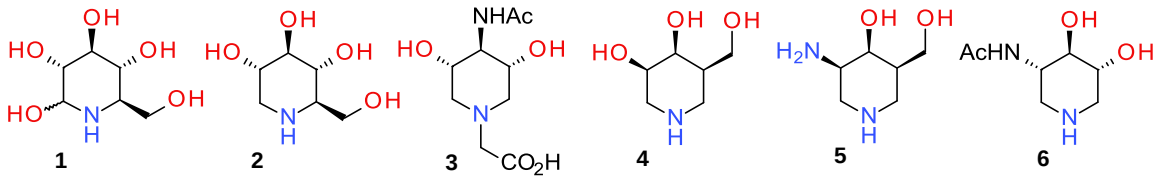


Figure 1. The hydroxylated piperidine alkaloids **1-6**.

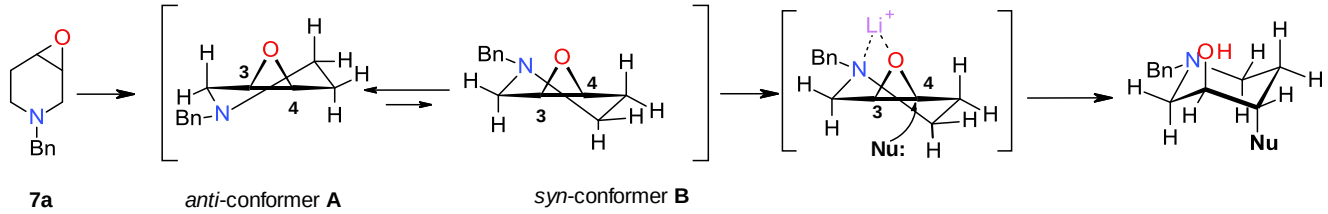
It has been found[7-10] that introduction of an amino group into the structure of iminosugars (compounds **3,5,6**) leads to a change of their activity towards enzyme targets. For example, 4-acetamido-3,5-dihydroxypiperidine **3** inhibits sialidase – a virus neuroaminidases incorporated in the membranes of certain viruses. Galactoisofagomine **4** is an inhibitor of *β*-galactosidase, while its counterpart 3-azaanalog **5** with the same configuration of stereocentres selectively inhibits *β*-glucosidase.[7,8] Stereochemical analogue of galactoisofagomine 3-acetaminopiperidine **6** selectively inhibits *β*-*N*-acetylglucosaminidase and is not active towards other types of glycosidases.[9,10] High therapeutic potential of iminosugars, in particular analogues **1-6,** stimulated intensive structural and stereochemical studies of new iminosugars. The same is true for the development of new practical and selective methods for the synthesis of iminosugars[11-13] and their analogues using enzymatic and asymmetric methods.[14-16] There is a limited number of approaches suitable for the preparation of 3,4,5-trisubstituted and 2,3,4,5-tetrasubstituted piperidines.[15,16] For this reason, the development of convenient and effective ways of synthesis of polysubstituted piperidines would significantly increase chance of finding new selective inhibitors.

Result and Discussion

We report here a novel approach to regio- and stereoselective synthesis of 4-substituted 1-benzylpiperidin-3,5-diols **10a-e** via nucleophilic cleavage of convenient key 1-benzyl-4,5-epoxypiperidin-3-ols **9a-c** by benzylamine, diallylamine and thiophenol in CH_3CN at room temperature with yields 55-78% in the presence of hard Lewis acid (2 equivalents of lithium perchlorate).

We have previously developed a regio- and stereospecific synthesis of racemic and enantiopure *trans*-4-amino-1-benzylpiperidin-3-ols[17,18] via nucleophilic ring opening of epoxide **7a** under mild conditions with high yields in the presence of Lewis acid (lithium perchlorate, 1 equivalent). There is a general consensus that this outcome of the nucleophilic ring opening is promoted by the bidentate coordination of epoxide **7a** organized

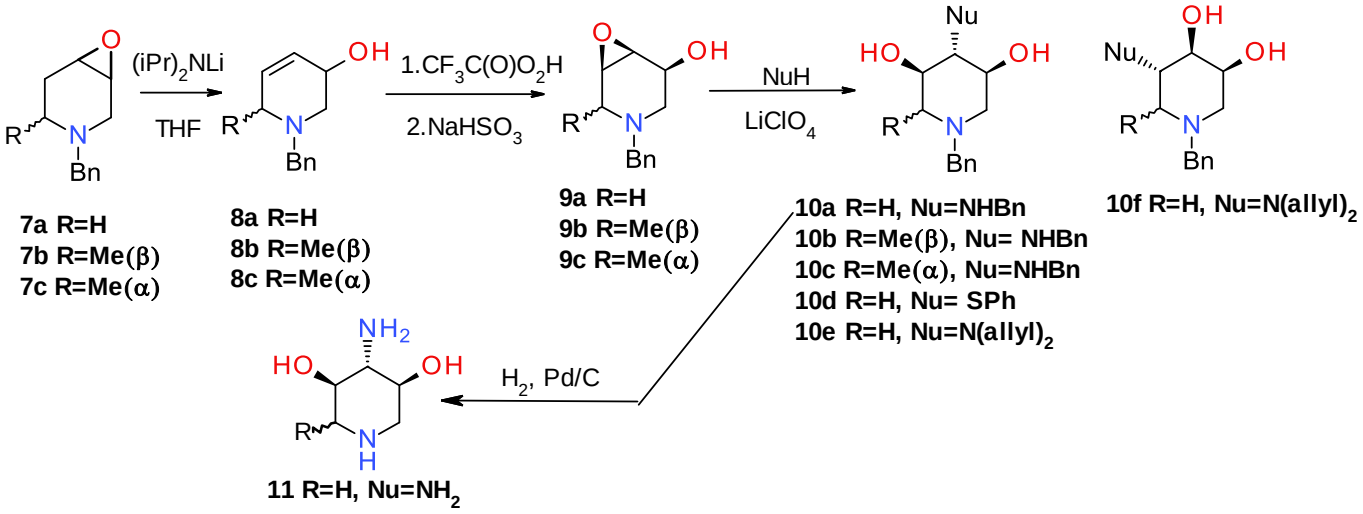
to produce only 4-substituted regioisomer.[19-23] Such coordination activates the epoxide ring for the nucleophilic attack and shifts the conformational equilibrium (originally in favor the *anti*-conformer **A** by ~1.6 kcal/mol[17]) entirely towards the lithium complex of *syn*-conformer **B**, producing only 4-substituted regioisomer upon the epoxide cleavage.



Scheme 1. Regio- and stereospecific ring opening of 1-benzyl-3,4-epoxypiperidine **7a**.

The regio- and stereospecific synthesis of the *trans*-3-amino-1-benzylpiperidine-4-ols was also performed using the complex of a hard Lewis acid diisobutylaluminum hydride (DIBAL-H) with Lewis bases - primary and secondary amines.[24-25]

The present work proceeds the stereochemical investigations of nucleophilic ring opening of epoxypiperidines **7a-c**. Targeted 4-substituted 1-benzylpiperidine-3,5-diols **10a-e** which are stereochemical analogues of iminosugars **1-6,** were prepared according to Scheme **2**. The initial 1-benzyl-4,5-epoxypiperidine-3-ols **9a-c** were produced by oxidation of trifluoroacetates of 1-benzyl-1,2,3,6-tetrahydropyridine-3-ols **8a-c** with trifluoroperacetic acid (5 equivalents) at 0° C in anhydrous CH_2Cl_2.[17,26]



Scheme 2. The sequence of synthesis steps of 4-substituted 1-benzylpiperidine-3,5-diols **10a-e, 11**.

The key allyl alcohols **8a-c** were produced by rearrangement of 1-benzyl-3,4-epoxy piperidines **7a-c** under the influence of lithium diisopropylamide in THF at -70° C under argon atmosphere.[18] Epoxidation of the allyl alcohol **8a** generates a single compound with a mass molecular ion (*m/z* 205) corresponding to the epoxy alcohol **9a,** which was isolated by column chromatography on silica gel with 63% yield. The epoxy alcohols **9b,c** were produced with the 58-65% yields under similar conditions. Formation of the epoxy alcohols **9a-c** was confirmed by the presence of a signal at 50-60 ppm and at 65 ppm in ^{13}C NMR spectra, which are typical for

C-4/C-5 atoms of 1-benzyl-4,5-epoxy piperidines[26] and the C-3 hydroxyl group, respectively. The pseudo equatorial direction of the 3-hydroxy group was determined based on the large vicinal coupling constant $^{3}J_{2a,3a}$ (7-8 *Hz*) of the axial protons connected to the C-2 and C-3 stereocenters of the piperidine core. Basing on NMR ^{1}H and ^{13}C spectral data, it was found that the epoxidation proceeds as a *syn* process and leads to the formation of epoxides **9a-c** with *cis* orientation of epoxy and the 3-hydroxy groups.

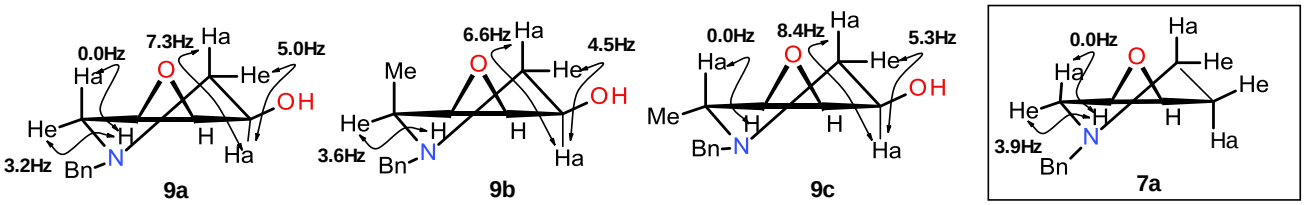


Figure 2. Preferred *anti*-conformation half chair of the epoxy alcohols **9a-c** with *cis*-orientation of 4,5-epoxy and pseudo equatorial 3-hydroxyl groups.

We assume that high *syn* stereoselectivity of the epoxidation of allyl alcohols **8a-c** is connected with the assistance of 3-hydroxyl group due to formation of the intermediates **I** or **II**, stabilized by hydrogen bonds, including the nitrogen atom of the piperidine cycle. Apparently, the peculiarities of a Lewis acid coordinating with epoxide must play a significant role in the relative stability and structure of the reaction intermediates.

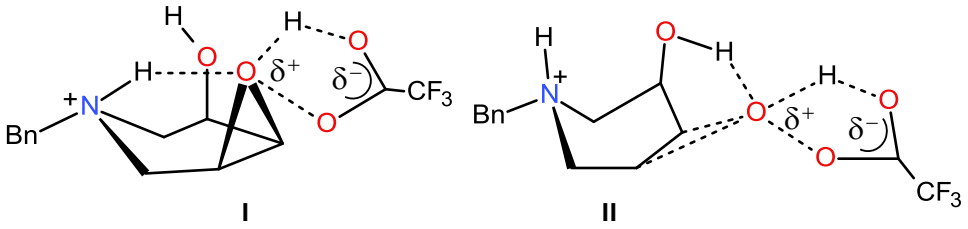


Figure 3. Plausible structures of intermediates **I** and **II**.

Consequently, *syn*-epoxidation of allyl alcohols **8a-c** leads to the formation of the epoxy alcohols **9a-c** of preferably in *anti*-conformation half chair with pseudo equatorial 3-hydroxyl group. (**Figure 2**). Previously *syn*-stereoselectivity has been observed upon epoxidation of *N*-ethoxycarbonyl-3-hydroxy-1,2,3,6-tetrahydropyridine with a free 3-hydroxy group. However, a decrease in *syn*-stereoselectivity with dominated *anti*-isomer has been reported for oxidation of *N*-carbamoyl-1,2,3,6-tetrahydropyridine with protected 3-hydroxy group (3-benzyloxy-, 3-acetoxy-, 3-tert-butyldiphenylsilyloxy-groups).[27-29]

Next, we carried out stereoselective synthesis of targeted 4-substituted 1-benzylpiperidine-3,5-diols **10a-e** via nucleophilic cleavage of the epoxy alcohols **9a-c** with benzylamine, thiophenol and diallylamine. Reactions were performed in anhydrous CH_3CN at room temperature in the presence of lithium perchlorate (two equivalents) with good yields. According to ^{1}H NMR and chromatographic monitoring, the ring opening of epoxy alcohols **9a-c** with benzylamine and thiophenol afforded single regio- and stereoisomer 4-substituted (3*R,*4*r,*5*S*)-1-benzylpiperidines **10a,b,e** and racemic 1-benzyl-2-methyl-4-benzylaminopiperidine-3,5-diols **10c,d** which were isolated with 55-71% yields. Under the same experimental conditions, the opening of epoxy alcohol **9a** with diallylamine afforded a mixture of **10e** and **10f** in a ratio of 4:1, according to ^{1}H NMR spectra of the reaction mixture. These compounds were easily separated by column chromatography and were isolated

in 64 and 12% yield, respectively. Also the (3*R*,4*r*,5*S*)-4-aminopiperidine-3,5-diol **11** was obtained by removing of both benzyl groups from the compound **10a** through hydrogenolysis above Pd/C10% in CH_3OH with 82% yield.

According to ^{1}H NMR spectra the major isomer **10e** is 1-benzyl-4-diallylaminopiperidine-3,5-diol and the minor one **10f** is 1-benzyl-5-diallylaminopiperidine-3,4-diol. Furthermore, masses of protonated molecules ($[M+H]^+$) **10a**, **10e** were measured within 2 ppm mass accuracy: $C_{19}H_{25}N_2O_2$ *m/z* 313.19159 (calculated 313.1911), $C_{18}H_{27}O_2N_2$ m/z 303.20719 (calculated 303.2067) respectively. The most intensive fragment ions in the MS/MS spectra of the studied compounds corresponded to loss of H_2O, NH_3 molecules (NH_2Bn or $NH(allyl)_2$ correspondingly), both consequently or 2 molecules of H_2O. All together these facts reveal the proposed structures of 4-substitued 1-benzylpiperidin-3,5-diols. This is another case where the regio- and stereoselectivity of the nucleophilic attack on the epoxide ring at C-4 yields predominantly the 4-substituted 1-benzylpiperidine-3,5-diol **10e**, though with some decrease in the regioselectivity. Spatial structures of amino alcohols **10a,d,e** were established according to the general view of their ^{13}C NMR spectra. For aminodiol **10a** there are 3 carbon signals of the piperidine ring at 59.3 ppm (C2, C6), 67.7 ppm. (C4) and 69.8 ppm. (C3, C5), which are similar for all of the 3,4,5-trisubstituted piperidine derivatives **10a,d,e**. Equatorial arrangement of the 3,5-dihydroxy groups and a substituent at C-4 in **10a-e** is established in accordance with the values of vicinal coupling constants $^3J_{3a,4a}$ and $^3J_{4a,5a}$ (8-10 *Hz)*. In the minor 1-benzyl-5-diallylaminopiperidine-3,4-diol **10f** the *trans*-diequatorial orientation of the 4-hydroxy and 5-diallylamino groups was determined according the values of vicinal coupling constants $^3J_{5a,6a}$ and $^3J_{5a,4a}$ (10.9 and 10.6 *Hz)* of axial protons, respectively. The value of vicinal coupling constant $^3J_{3,4}$ (3.3 *Hz*) of the proton at C3 corresponds to the axial orientation of hydroxyl group at C-3.

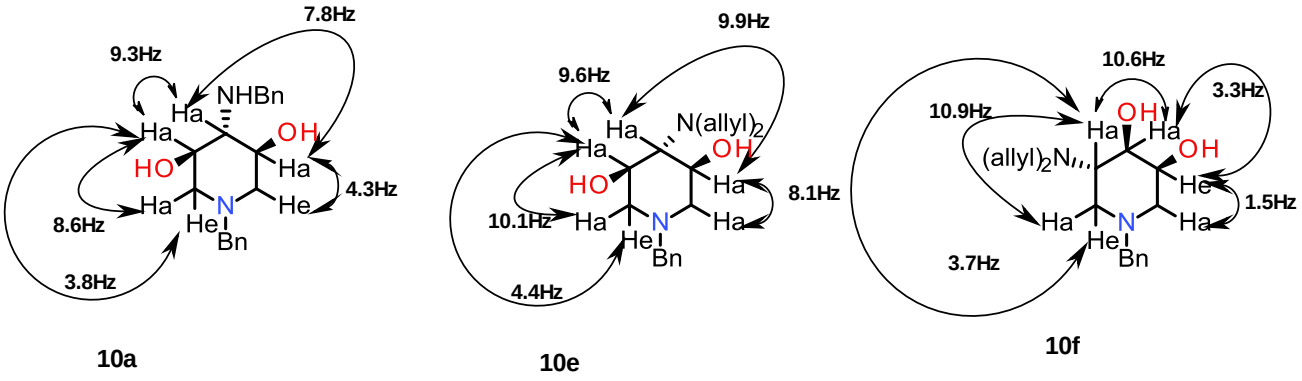
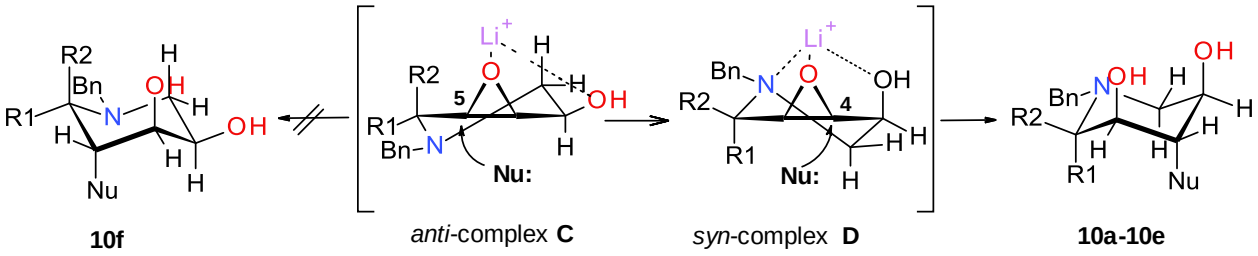


Figure 4. The values of vicinal coupling constants (Hz) of the protons in 1-benzylpiperidinediols **10 a,e,f**.

The structure and stereochemistry of the 4-substituted 1-benzylpiperidine-3,5-diols **10a-e, 11** were confirmed by the spectral and elemental analysis of their free bases or dihydrochlorides.

It should be emphasized that according to the rule of Fuerst-Plattner[30], the nucleophilic opening of the epoxy alcohols **9a-c** must pass "*trans*-diaxially", preferably by the C-5 position of the *anti*-conformer **C**, with the formation of 5-substituted 1-benzylpiperidine-3,4-diols of the "**10f**" type.



Scheme 3. Plausible mechanism of the nucleophilic opening of the epoxy alcohols **9 a-c**.

However, our stereochemical study indicated the preservation of the dominant regio- and stereoselective ring opening of epoxyalcohols **9a-c** at the C-4 position of the piperidine core with the formation of

4-substituted 1-benzylpiperidine-3,5-diols **10a-e**. The observed highly regioselective opening at the C4 position of the piperidine core can be explained by the participation of a more preferred *syn*-complex **D**, which is activated by a bidentate coordination of the lithium cation to the nitrogen atom of the piperidine core and the oxygen atoms of the 4,5-epoxy and 3-hydroxy groups.

Conclusions

We developed a new approach to a Lewis acid-catalyzed nucleophilic ring opening of 1-benzyl-4,5-epoxypiperidine-3-ols **9a-c** which leads to iminosugars – 4-substituted 1-benzylpiperidine-3,5-diols **10a-e**, **11**. The regio- and high stereoselective synthesis of 4-substituted 1-benzylpiperidine-3,5-diols **10a-e,11** opens a possibility for receiving the key intermediates for new iminosugar analogs and other bioactive compounds. We also developed the synthesis and performed conformational analysis of 1-benzyl-4,5-epoxypiperidine-3-ols **9a-c**, which are convenient polyfunctional blocks for the preparation of new biologically active polyhydroxylated and aminohydroxylated piperidine derivatives.

Experimental Section

General. The NMR spectra were recorded on Varian VXR-400 and Brucker DRX-500 spectrometers using $CDCl_3$, CD_3OD and DMSO-d_6 as solvents. Chemical shifts are given in δ (ppm) relative to TMS as internal standard. Elemental analysis was performed with a Perkin-Elmer 2400 CHNS elemental analyzer. GC-MS analysis was performed on spectrometer HP5989x-G and Finnigan SSQ7000, ionizing electrons energy 70 eV, capillary column DB5 30 m. The structures of **10a**, **10e** and **11** were confirmed with Orbitrap Elite mass-spectrometer (Thermo Fisher Scientific, USA) with an electrospray ionization (ESI) source. Formic acid (Sigma Aldrich, St. Louis, Missouri, USA) was added to the methanol solutions of all samples for the analysis in positive mode. The system was controlled by the Xcalibur software, which was also used for data collection and data processing. The methanol solution of each compound was introduced through syringe pump directly into the ion source at 5 μl/min. Sheath gas flow rate was from 10 to 25 arbitrary units, auxiliary and sweep gas flow rate was set to zero. Capillary temperature was set to 275°C and spray voltage to 3.5 kV. Accurate mass measurements were carried out in Orbitrap analyzer with 480000 resolving power. Elemental composition of each fragment ion was calculated within 5 ppm mass accuracy. MS/MS experiments were carried out using both collision induced dissociation (CID) fragmentation triggering techniques at 20 arbitrary units. Nitrogen was used as collision gas.

The scanned masses in CID were settled from 85 to 500 Da, mass window was 1 Da. The spectra were recorded during 30 s. Silica gel 60 (230-400 mesh) was used for flash column chromatography. Silufol was used for TLC.

1-Benzyl-3,4-epoxypiperidines 7a-c and **1-benzyl-1,3,5,6-tetrahydropyridine-3-ols 8a-c** were prepared according to the procedures described previously.[17, 18]

General method for preparation of 1-benzyl-4,5-epoxypiperidine-3-ols 9a-c. To a mixture of 46.7% water solution of hydrogen peroxide (0.34 g, 4.7 mmol) and anhydrous CH_2Cl_2 (5ml) was added at 0 ^oC and vigorous stirring a solution of $(CF_3CO)_2O$ (3.08 g,14.5 mmol) in anhydrous CH_2Cl_2 (2ml). The stirring at the same temperature was continued 1.5 h. To thus obtained solution of $CF_3C(O)O_2H$ (0.19 g, 1.0 mmol) prepared from 1-benzyl-1,2,3,6-tetrahydropyridine-3-ol (**8a**) (0.19 g, 1.0 mmol) and CF_3CO_2H in anhydrous CH_2CL_2 (3 ml) at 0 ^oC. The epoxidation was monitored by TLC till complete consumption of initial 1-benzyl-1,2,3,6-tetrahydropyridine-3-ol (**8a**). In 5 h the excess oxidant was decomposed by addition of aqueous $NaHSO_3$ while vigorous stirring at 0-5 ^oC. The organic layer was extracted with CH_2Cl_2 (4×15 мл). The combined organic extracts were dried with Na_2SO_4, the solvent was removed on a rotary evaporator. The crude product (0.31 g) was applied to a column packed with silica gel with hexane, gradient elution with system hexane-EtOAc, the content of EtOAc from 20 to 100%. The organic extracts were combined, the solvent was removed in a vacuum.

(3*SR*,4*SR*,5*RS*)-1-Benzyl-4,5-epoxypiperidine-3-ol (9a). (0.23 g, 63%), colorless oily substance, R_f 0.5 (hexane / $CH_3)_2CO$ 4:1). MS, *m/z* ($I_{rel.}$,%): 205 (3) [M 188 (1), 176 (1), 160 (3), 158 (3), 144 (1), 133 (28), 128 (1), 121 (1), 120 (14), 118 (2), 114 (2), 104 (3), 91 (100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (bs, 1H, OH), 2.22 (dd, *J* 11.4, 7.0 Hz, 1H, H2$_a$), 2.51 (ddd, *J* 11.4, 5.0, 1.2 Hz, 1H, H2$_e$), 2.75 (bd, *J* 13.5 Hz, 1H, H6$_a$), 2.81 (bdd, *J* 13.5, 1.2 Hz, 1H, H6$_e$), 3.40 (m, 2H, H*4*, H*5*), 3.49 (s, 2H, Ph-CH_2), 4.05 (m, *J* 7.0, 5.0 Hz, 1H, H3$_a$,), 7.21-7.32 (m, 5H, *Ph*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.8, 53.6 (2C), 61.5, 65.4, 70.8, 127.6, 128.4 (2C), 129.2 (2C), 136.4.

(3*SR*,4*SR*,5*RS*,6*SR*)-1-Benzyl-6-methyl-4,5-epoxypiperidine-3-ol (9b) (0.16 g 63%) was performed from *cis*-1-benzyl-6-methyl-1,2,3,6-tetrahydropyridine-3-ol (**8b**) (0.22 g, 1.1 mmol). Reaction time 5 h, colorless oil, R_f 0.6 (hexane/$(Me)_2CO$ 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, *J* 6.6 Hz, 3H, CH_3), 2.31 (dd, *J* 12.3, 4.6 Hz, 1H, H2$_e$), 2.49 (dd, *J* 12.3, 6.6 Hz, 1H, H2$_a$), 2.61 (bs, 1H, O*H*), 2.97 (dq, *J* 3.5, 6.6 Hz, 1H, H6$_e$), 3.31 (dd, *J* 3.8, 3.5 Hz, 1H, H*5*), 3.44 (dd, *J* 3.8, 3.5 Hz, 1H, H*4*), 3.44 (AB-system, *J* 13.6 Hz, 1H, Ph-CH_2), 3.72 (AB-system, *J* 13.6 Hz, 1H, Ph-CH_2), 3.95 (ddd, *J* 6.6, 4.6, 3.5 Hz, 1H, H3$_a$), 7.19-7.30 (m, 5H, *Ph*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 51.1, 51.8, 53.5, 57.0, 58.9, 64.9, 127.1, 128.3 (2C), 128.7 (2C), 138.5.

(3*SR*,4*SR*,5*RS*,6*RS*)-1-Benzyl-6-methyl-4,5-epoxypiperidine-3-ol (9c) (0.23 g, 58%), was performed from *trans*-1-benzyl-2-methyl-1,2,3,6-tetrahydropyridine-3-ol (**8c**) (0.40 g, 2.0 mmol). Reaction time 5 h, colorless oil, R_f 0.6 (hexane/$(CH_3)_2CO$ 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, *J* 6.8 Hz, 3H, CH_3), 2.06 (bs, 1H, O*H*), 2.09 (dd, *J* 11.4, 8.4 Hz, 1H, H2$_a$), 2.61 (dd, *J* 11.4, 5.3 Hz, 1H, H2$_e$), 2.88 (q, *J* 6.8 Hz, 1H, H6$_a$), 3.16 (d, *J* 4.3 Hz, 1H, H*5*), 3.24 (AB-system, *J* 13.7 Hz, 1H, Ph-CH_2), 3.38 (dd, *J* 4.3, 2.8 Hz, 1H, H*4*), 3.84 (AB-system, *J* 13.7 Hz, 1H, Ph-CH_2), 3.95 (ddd, *J* 8.4, 5.3, 2.3 Hz, 1H, H3$_a$), 7.19-7.30 (m, 5H, *Ph*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 50.0, 52.9, 53.4, 58.2, 59.3, 66.5, 127.1, 128.3 (2C), 128.7 (2C), 138.3.

General method for preparation of 4-substituted 1-benzylpiperidine-3,5-diols 10a-e. Anhydrous $LiClO_4$ (0.11 g, 1 mmol), was added to 1-benzyl-4,5-epoxypiperidine-3-ol (**9a**) (0.10 g, 0.5 mmol) in anhydrous CH_3CN (5 ml). The mixture was stirred until it became homogeneous, $BnNH_2$ (0.05 g, 0,5 mmol) was added, and the mixture was stirred for 72 h at room temperature. The progress of the reaction was monitored by TLC following displacement of the initial epoxy derivative. The mixture was treated with brine (1,5 ml), the solvent was distilled off under reduced pressure, and the resulting dispersion was extracted with CH_2Cl_2 (5×1мл). The combined organic extracts were dried with Na_2SO_4, the solvent was removed on a rotary evaporator.

(3*R*,4*r*,5*S*)-1-Benzyl-4-benzylaminopiperidine-3,5-diol (10a) (0.08 g, 58%). The crude product was white crystals, mp 186-187 °C (from EtOAc). HRMS for ($C_{19}H_{25}N_2O_2$ [M+H]$^+$) Calcd: 313.1911. Found: 313.19159. Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 72.80; H, 7.59; N, 8.73. R_f 0.3 (hexane/ $(CH_3)_2CO$ 2:1). ^{1}H NMR (400 MHz, CD_3OD, DMSO d_6) δ 1.78 (t, *J* 10.2 Hz, 2H, H*2*$_a$, H*6*$_a$), 2.15 (t, *J* 9.1 Hz, 1H, H*4*$_a$), 2.78 (dd, *J* 10.2, 3,5 Hz, 2H, H*2*$_e$, H*6*$_e$), 3.35 (m, 5H, H*3*$_a$, H*5*$_a$, O*H*, N*H*), 3.45 (s, 2H, Ph-CH_2), 3.94 (s, 2H, Ph-CH_2), 7.17-7.35 (m, 10H, 2×Ph). ^{13}C NMR (100 MHz, CD_3OD, DMSO d_6) δ 52.7, 59.3 (2C), 61.4, 67.7, 69.8 (2C), 126.4, 126.9, 127.9 (2C), 128.1 (2C), 128.1 (2C), 128.8 (2C), 138.2, 141.7.

(2*SR*,3*SR*,4*RS*,5*SR*)-1-Benzyl-2-methyl-4-benzylaminopiperidine-3,5-diol (10b) (0.09 g,65%) was performed from 1-benzyl-6-methyl-4,5-epoxypiperidin-3-ol (**9b**) (0.09 g, 0.41 mmol) and $BnNH_2$ (0.05 g, 0.41 mmol). The crude product was applied to a column packed with silica gel with hexane, gradient elution with system hexane/EtOAc, the content of EtOAc from 30 to 100%. Reaction time 72 h, pale yellow crystals, mp 133-134 ºC (from EtOAc). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.40; H, 7.79; N, 8.32. R_f 0.5 (hexane /$(CH_3)_2CO$ 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, *J* 6.8 Hz, 3H, C*H*$_3$), 2.49 (dd, *J* 11.4, 8.6 Hz, 1H, H*6*$_a$), 2.56 (bs, 3H, O*H*, N*H*), 2.72-2.67 (m, 2H, H*4*$_a$, H*6*$_e$), 3.14 (bd, *J* 4.3, 1H, H*2*$_e$), 3.64 (AB-system, *J* 13.4 Hz, 2H, Ph-CH_2), 3.63-3.72 (m, 2H, H*3*$_a$, H*5*$_a$), 3.97 (AB-system, *J* 12.9 Hz, 2H, Ph-CH_2), 7.21-7.37 (m, 10H, 2×*Ph*). ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.1, 51.0, 51.7, 56.3, 58.1, 62.0, 69.8, 71.6, 127.1, 127.3, 128.3 (2C), 128.3 (2C), 128.6 (2C), 128.6 (2C), 138.9, 139.8.

(2*RS*,3*SR*,4*RS*,5*SR*)-1-Benzyl-2-methyl-4-benzylaminopiperidine-3,5-diol (10c) (0.06 g (55%) was performed from 1-benzyl-6-methyl-4,5-epoxypiperidin-3-ol (**9c**) (0.07 g, 0.32 mmol) and of $BnNH_2$ (0.04 g, 0.32 mmol). The crude product was applied to a column packed with silica gel with hexane, gradient elution with system hexane/EtOAC, the content of EtOAc from 30 to 100%. Reaction time 96 h,, pale yellow crystals, mp 146-147 ºC (from EtOAc). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.44; H, 7.85; N, 8.37. R_f 0.4 (hexane /$(CH_3)_2CO$ 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, *J* 6.1 *Hz*, 3H, C*H*$_3$), 1.92 (dd, *J* 10.9, 10.1 *Hz*, 1H, H*6*$_a$), 2.21 (dq, *J* 8.1, 6.1 *Hz*, 1H, H*2*$_a$), 2.40 (dd, *J* 9.9, 9.6 *Hz*, 1H, H*4*$_a$), 2.87 (br s, 3H, O*H*, N*H*), 2.95 (dd, *J* 10.9, 4.4 *Hz*, 1H, H*6*$_e$), 3.16-3.24 (m, 2H, H*3*$_a$, Ph-C*H*), 3.63 (ddd, *J* 10.1, 9.6, 4.4 *Hz*, 1H, H*5*$_a$), 3.99 (AB-system, *J* 13.2 *Hz*, 2H, Ph-CH_2), 4.07 (d, *J* 13.6 *Hz*, 1H, Ph-C*H*), 7.22-7.38 (m, 10H, 2×*Ph*). ^{1}H NMR (100 MHz, $CDCl_3$) δ 16.5, 50.7, 56.8, 57.8, 62.0, 67.9, 68.2, 73.4, 127.1, 127.6, 128.3 (2C), 128.6 (4C), 128.9 (2C), 138.5, 138.6.

(3*R*,4*r*,5*S*)-1-Benzyl-4-phenylthiopiperidine-3,5-diol (10d) (0.18 g, 71%) was performed from of 1-benzyl-4,5-epoxypiperidin-3-ol (**9a**) (0.15 g, 0.8 mmol) and PhSH (0.10 g, 0.8 mmol). Reaction time 72 h, pale yellow crystals, mp 229-230 ºC (from EtOAc). Anal. Calcd for $C_{18}H_{21}NO_2S$: C, 68.54; H, 6.71; N, 4.44. Found: C, 68.30; H, 6.52; N, 4.36. R_f 0.6 (hexane /$(CH_3)CO$ 2:1). ^{1}H NMR (400 MHz, DMSO d_6) δ 2.15 (br t, 2H, H*2*$_a$, H*6*$_a$), 2.69 (t, *J* 9.6 *Hz*, 1H, H*4*$_a$), 3.04 (br dd, 2H, H*2*$_e$, H*6*$_e$), 3.49 (m, 2H, H*3*$_a$, H*5*$_a$), 3.67 (br s, 2H, Ph-CH_2), 5.09 (br s, 2H, O*H*), 7.21-7.68 (m, 10H, 2×*Ph*). ^{13}C NMR (100 MHz, DMSO d_6) δ 55.1, 59.2 (2C), 59.8, 65.1 (2C), 127.1, 129.1 (2C), 130.0 (2C), 132.0 (2C), 132.4 (2C), 133.4, 135.5.

(3*R*,4*r*,5*S*)-1-Benzyl-4-diallylaminopiperidine-3,5-diol (10e) and (3*RS*,4*SR*,5*RS*)-1-benzyl-5-diallylamino-piperidine-3,4-diol (**10f**) were performed similarly to compound **10a** from 0.15 g (0.8 mmol) of 1-benzyl-4,5-epoxypiperidin-3-ol (**9a**) and 0.10 g (1.0 mmol) of $(allyl)_2NH$. Reaction time 120 h. The crude mixture of isomers **10e** and **10f** was separated chromatographically using a column packed with silica gel in hexane. Elution was performed with a mixture hexane-ethyl acetate, the content of ethyl acetate from 30 to 100%. The major isomer **10e** (0.16 g, 64%), pale yellow oily substance, R_f 0.4 (hexane/ $(CH_3)_2CO$ 2:1). HRMS for ($C_{18}H_{27}O_2N_2$ [M+H]$^+$) Calcd: 303.2067. Found: 303.20719. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 1.89 (t, *J* 10.2 *Hz*, 2H, H*2*$_a$, H*6*$_a$), 2.44 (brt, *J* 9.4 *Hz*, 1H, H*4*$_a$), 2.99 (dd, *J* 10.4, 3,5 *Hz*, 2H, H*2*$_e$, H*6*$_e$), 3.48 (m, 4H, CH_2=CH-CH_2), 3.54 (s, 2H, Ph-CH_2), 3.7 (m, 2H, H*3*$_a$, H*5*$_a$), 5.14 (m, 4H, CH_2=CH-CH_2), 5.90 (m, 2H, CH_2=C*H*-CH_2), 7.21-7.33 (m,

5H, *Ph*). ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 55.5 (2C), 60.8 (2C), 62.9, 67.5 (2C), 71.4, 117.9 (2C), 128.4, 129.5 (2C), 130.2 (2C), 137.5 (2C), 138.79.

The minor isomer **10f** (0.03 g,12%), pale yellow oily substance, R_f 0.5 (hexane / $(CH_3)_2CO$ 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (t, *J* 10.9 *Hz*, 1H, H6$_a$), 2.15 (dd, *J* 12.4, 1.5 *Hz*, 1H, H2$_a$), 2.58 (bs, 2H, O*H*), 2.93 (ddd, *J* 11.0, 3.7, 2.2 *Hz*, 1H, H6$_e$), 2.98 (dd, *J* 14.2, 5.1 *Hz*, 2H, CH_2=CH-CH_2), 3.02 (m, 1H, H2$_e$), 3.12 (ddd, *J* 10.9, 10.6, 3.8 *Hz*, 1H, H5$_a$), 3.32 (dd, *J* 14.2, 5.1 *Hz*, 2H, CH_2=CH-CH_2), 3.58 (AB-system, *J* 13.4 *Hz*, 2H, Ph-CH_2), 4.04 (m, 1H, H3$_e$), 5.08-5.18 (m, 4H, CH_2=CH-CH_2), 5.75 (m, 2H, CH_2=C*H*-CH_2), 7.23-7.35 (m, 5H, *Ph*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.4, 52,9 (2C), 56.7, 57.6, 62.2, 67.5, 70.2, 117.5 (2C), 127.2, 128.3 (2C), 128.9 (2C), 136.3 (2C), 137.4. Anal. Calcd for $C_{18}H_{28}N_2O_2Cl_2$ (mixture of dihydrochlorides **10e** and **10f**): C, 57.60; H, 7.51; N, 7.47. Found: C, 57.43; H, 7.39; N, 7.3.

(3*R*,4*r*,5*S*)-4-Aminopiperidine-3,5-diol (11) (0.035 g, 82%). To **10a** (0.10g, 0,32 mmol) in CH_3OH (5 ml) under in present of Pd/C10% (0,02g) was hydrogenated at room temperature under atmospheric pressure with monitoring by TLC. The stirring was continued 24 h. Catalyst was filtered off and the solvent was removed on a rotary evaporator. White crystals, mp 121-122 ^{o}C (from CH_3OH/diethyl ether), HRMS for ($C_5H_{13}N_2O_2$ $[M+H]^+$) Calcd: 133.0972. Found: 33.09741. ^{1}H NMR (400 MHz, CD_3OD) δ 2.33 (dd, *J* 12.6, 10,6 *Hz,* 2H, H2$_a$, H6$_a$), 2.48 (t, *J* 9.4 *Hz*, 1H, H4$_a$), 2.99 (dd, *J* 12.6, 4,6 *Hz*, 2H, H2$_e$, H6$_e$), 3.28 (m, 2H, H3$_a$, H5$_a$, C$\underline{D}_3$OD), 4.83 (m, 5H, O*H*, *NH, NH$_2$,* $CD_3O\underline{D}$). ^{13}C NMR (100 MHz, CD_3OD) δ 52.1 (2C), 63.0, 72.6 (2C).

Acknowledgements

This study was performed with financial support by the Russian Foundation for Basic Research (Grants 14-03-00183-a, 11-03-01034-a).

References

1. Compain, P.; Martin, O.R.; *Iminosugars. From synthesis to therapeutic applications*. Wiley: Chichester, England, 2007; pp 7-30, 131-149.
2. Stütz, A. E.; *Iminosugars as Glycosidase Inhibitors: Nojirimicin and Beyond.* Wiley: Weinheim, Germany, 1999, p 10-85.
3. Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000,** 11–36.
4. Asano, N. *Curr.Top.Med.Chem*. **2003**, 3, 471–484. https://doi.org/10.2174/1568026033452438
5. John V.; Moon J.B.; Pulley S.R.; Rich D.H.; Brown D.L.; Jagodzinska B.; Jacobs J.S.; WO Patent 2003043987, 2002-US37037.
6. Hoffmann T.; Koblet A.; Peters J.-U.; Schider P.; Sleight A.; Stadler, H.; U.S.Patent 2005/0090533, 2005.
7. Lohse, A.; Jensen, H.; Bach, P.; Bols, M. *J. Chem. Soc., Perkin Trans*. *1* **2000**, 659-665. https://doi.org/10.1039/a908340e
8. Bernotas, R.C.; Ganem, B. *Carbohydr*. *Res*. **1987**, 167, 312-316. https://doi.org/10.1016/0008-6215(87)80290-2
9. Parr, B.; Horestein, B.A. *J. Org. Chem*. **1997,** 62, 7489–7494. https://doi.org/10.1021/jo9708497
10. Huryn, S.K.; Okabe, M. *Chem. Rev*. **1992,** 92, 1745–1768.

https://doi.org/10.1021/cr00016a004
11. Rejman, D.; Pohl, R.; Dracinsky, M. *Eur. J. Org. Chem*. **2011**, 11, 2172-2187. https://doi.org/10.1002/ejoc.201001610
12. José Luis Díaz, J.L.; Fernández-Forner, D.; Bach, J.; Lavilla, R. *Chem. Commun*. **2008**, 2799-2813.
13. Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M.P. *J. Org. Chem*. **2007**, 72 (21),7980-7991. https://doi.org/10.1021/jo701452a
14. Olofsson, B.; Bogar, K.; Fransson, A-B.L.; Backvall, J-E. *J.Org.Chem*. **2006**, 71, 8256–8260. https://doi.org/10.1021/jo0615091
15. Amat, M.; Escolano, C.; Lozano, O.; Llor, N.; Bosch. *J. Org. Lett*. **2003** , 5, 3139-3142. https://doi.org/10.1021/ol035199+
16. Terán, A.O.; Concellón, J.M.; Rivero, I.A. *Arkivoc,* **2009**, (*ii*) 288-297. http://dx.doi.org/10.3998/ark.5550190.0010.227
17. Veselov, I.S.; Trushkov, I.V.; Zefirov, N.S.; Grishina G.V. *Russ. J. Org*. *Chem*. **2009**, 45, 1062-1072 . *(Zh.Org. Khim*., **2009**, *45*, 1062-1072).
18. Grishina, G. V.; Veselov, I. S.; Nelyubina, Y. V.; Surovaya, A. N.; Zefirov, N. S. *Arkivoc,* **2011**, (x*),* 107-117. http://dx.doi.org/10.3998/ark.5550190.0012.a09
19. Tokuda, O.; Aikawa, T.; Ikemoto, T.; Kurimoto, I. *Tetrahedron Lett*. **2010**, 51, 2832-2834. https://doi.org/10.1016/j.tetlet.2010.03.061
20. Scheunemann, M.; Hennig, L.; Funke, U.; Steinbach, J. *Tetrahedron* **2011,** 67, 3448-3456. https://doi.org/10.1016/j.tet.2011.03.045
21. Villar-Barro, A.; Gotor,V.; Brieva, R. *Tetrahedron* **2015**, 71, 6907-6912. https://doi.org/10.1016/j.tet.2015.07.014
22. Ortiz, A.; Young, I. S.; Sawyer, J. R.; Hsiao, Y.; Singh, A.; Sugiyama, M.; Corbett, R. M.; Chau, M.; Shi, Z.; Conlon, D. A. *Org. Biomol. Chem.* **2012**, 10, 5253-5257. https://doi.org/10.1039/c2ob25411e
23. Young, I. S.; Ortiz, A.; Sawyer, J. R.; Conlon, D. A.; Buono, F. G.; Leung, S. W.; Burt, J. L.; Sortore, E. W. *Process. Dev Res Org.* **2012**, 16, 1558-1565. https://doi.org/10.1021/op300174w
24. Grishina, G.V.; Veselov, I.S.; Safronova, E. N.; Mazur, D.M.; Samoshin, V.V. *Tetrahedron Lett.* **2017**, 58, (21), 2019-2022. https://doi.org/10.1016/j.tetlet.2017.04.017
25. Mazur, D.M.; Grishina, G.V. Lebedev, A.T. *J. Pharm. Biomed. Anal*. **2017**, 140, 322-326. https://doi.org/10.1016/j.jpba.2017.03.066
26. Grishina, G.V.; Borisenko, A.A.; Veselov, I.S.; Petrenko, A.M. *Russ. J. Org. Chem*. **2005**, 41, 272-278. (*Zh. Org. Khim*., **2005**, 41, 281-287). https://doi.org/10.1007/s11178-005-0156-4
27. Miyashita, K.; Park, M.; Adachi, S.l.; Seki S.; Obika, S.; Imanishi, T. *Bioorg. Med. Chem. Lett*. **2002**, 12, (7), 993-1144. https://doi.org/10.1016/S0960-894X(02)00085-9
28. Kawada, Y.; Kodama, T.; Miyashita, K.; Imanishi, T.; Obika, S. *Heterocycles* **2010**, 80, 1249-1265. https://doi.org/10.3987/COM-09-S(S)112
29. Ouchi, H.; Mihara, Y.; Watanabe, H.; Takahata, H. *Tetrahedron Lett*. **2004**, 45, 7053- 7056. https://doi.org/10.1016/j.tetlet.2004.07.127
30. Eliel, E.L.; Wilen, S.R.; Doyle, M.P. *Basic Organic Stereochemistry*, Wiley: New York, parts 9-11.

