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An efficient synthesis of aziridines from ephedrines

Alejandro Cruz *, Itzia Irene Padilla-Martínez, Efrén V. García-Báez

Departamento de Ciencias Básicas de la Unidad Profesional Interdisciplinaria de Biotecnología del IPN, Av. Acueducto s/n Barrio la Laguna Ticomán, México, D.F. 07340, Mexico

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ABSTRACT

The reaction of chlorodeoxyephedrine hydrochlorides with one, two, and three molar equivalents of base was studied. Isochlorodeoxy*pseudo*epherines were identified and assigned by ^{1}H and ^{13}C NMR data as intermediate compounds in the formation of *cis*-aziridines. *Erythro* and *threo* ephedrinethylethers were isolated as new compounds and analyzed by spectroscopic data. In addition, the *erythro* isomer was studied by X-ray diffraction.

1. Introduction

Ephedrines are very important substances in asymmetric synthesis; they are widely used as building blocks in the synthesis of heterocycles, as ligands for metallic or organometallic complexes and as reagents or catalytic agents in organic chemistry.[1] Due to their relevance in several areas, we are currently developing synthetic methods to obtain heterocycles,[2] which could be used as chiral inductors or catalysts in asymmetric synthesis.

The intermediates that we had been using for the synthesis of heterocycles derived from ephedrines or *nor*ephedrines **1** are the hydrochlorides of chlorodeoxy*pseudo*ephedrines and chlorodeoxy*norpseudo*ephedrine **3**.[2a,b,d–f] These hydrochlorides were obtained from the chlorination reaction of ephedrine or *nor*ephedrine **1** with thionyl chloride. The stereochemistry and functional group effects on the chlorination reaction mechanisms were revisited.[3] Recently, we reported the synthesis of 2-imine-heterocycles from chlorodeoxy*pseudo*ephedrines hydrochlorides **3** and heterocyanates[2f] to proceed through the *cis*-aziridinium **6**, Scheme 1. This intermediate explains the retention of configuration in the heterocycle formed. In fact, this aziridinium intermediate has been proposed in other reactions carried out with retention of the C-1 configuration.[4]

There are some procedures reported in the literature for the formation of aziridines from ephedrines. (1) From the sulfate esters of ephedrine and *nor*ephedrine, which are cyclized to a mixture of aziridines (45:55 *cis*/*trans*) by treatment with hot aqueous potassium hydroxide in 84% yield.[5] (2) *Pseudo*ephedrine was readily converted to the corresponding *cis*-aziridine in a 74% yield by using triphenylphosphine dibromide under mild conditions. In contrast, ephedrine gave only a polymeric material.[6] (3) Pfister treated ephedrine with triphenylphosphine in the presence of diethylazodicarboxylate in ether or THF for 2 h with good yields of the *trans*-aziridine (84%).[7] This procedure was extended to *pseudo*ephedrine to form the *cis*-aziridine whereas *nor*ephedrine required three days to give the corresponding *trans*-aziridine.[8] (4) The corresponding *cis*-aziridines were obtained in 65% yield from ephedrine[9] and *nor*ephedrine[10] by stereospecific cyclization of the corresponding chlorodeoxy*pseudo*ephedrine hydrochlorides **3** with NaOH 20% aqueous solution. In this context, and in order to improve the yields of aziridines, we performed a detailed study of this last reaction by using bases such as NaOH, K_2CO_3, NH_3, and Et_3N in water, ethanol, and chloroform as solvents.

2. Results and discussion

2.1. Chlorination reaction of ephedrine hydrochlorides

To obtain the *threo* and *erythro* isomers of chlorodeoxyephedrines **3**, **4** as starting materials for the synthesis of *cis*- and *trans*-aziridines, the stereoselective chlorination with $SOCl_2$ was used. It is well known that the reaction of ephedrine or *nor*ephedrine hydrochlorides **1** with thionyl chloride at room temperature proceeds stereoselectively with inversion of the C-1 configuration (S_N2 mechanism) to give the corresponding hydrochlorides of chlorodeoxy*pseudo*ephedrines **3**, respectively, Scheme 1. However, the same reaction with the hydrochlorides of *pseudo*ephedrines **2** gives a 60:40 mixture of *threo*/*erythro* chlorodeoxystereoisomers **3**/**4**, respectively,[3] Scheme 2. In order to improve the stereoselectivity, we carried out the same chlorination reaction of *pseudo*ephedrine stereoisomers **2** at 0 °C. Under these conditions, only the corresponding *threo* chlorodeoxystereoisomers **3** were stereoselectively obtained (S_Ni mechanism).

On the other hand, we found that the pure *threo* isomer **3** can be transformed to a 60:40 mixture of the *threo*/*erythro* stereoisomers when it is heated (80–90 °C) in DMSO-d_6 solution for five hours in the NMR tube. This transformation has also been observed when a 60:40 mixture of these hydrochlorides are acidified with HCl to obtain a 35:65 ratio.[3]

* Corresponding author. Tel.: +15557296000/56323; fax: +15557296000/56325.
E-mail addresses: alecruz@ipn.mx, alcralmx@hotmail.com (A. Cruz).

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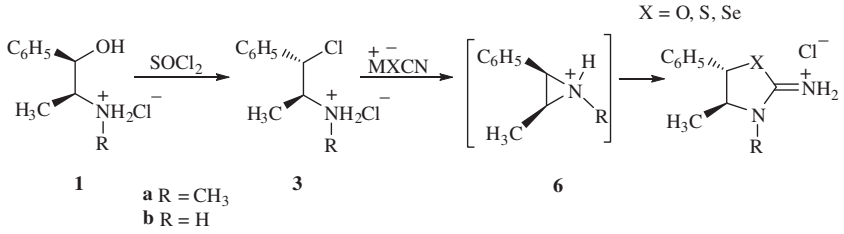
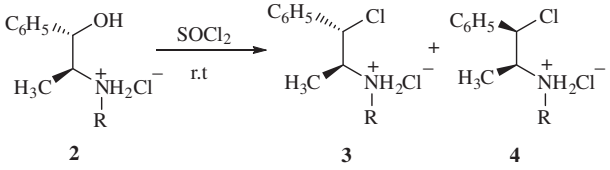


Scheme 1. Aziridinium **6** as intermediate to obtain 2-iminium heterazolidines.

Chlorodeoxyephedrine hydrochloride **4a** was separated by fractional crystallization from a 60:40 mixture of *threo*/*erythro* chlorodeoxy-hydrochlorides **3a**/**4a**, in the last crop of crystals of an ethanolic solution. However, chlorodeoxy*nor*ephedrine **4b** could not be separated from **3b** by this procedure.



Scheme 2. Chlorodeoxyephedrine hydrochlorides from the chlorination reaction of *pseudo*ephedrines **2**.

2.2. Study of chlorodeoxyephedrines reaction with bases

It is known that the reaction of chlorodeoxy*pseudo*ephedrine hydrochlorides **3** with 20% aqueous NaOH affords the corresponding *cis*-aziridine **9** in 65% yield.[10] In order to improve this result, we decided to carry out the same reaction but using ammonia, sodium hydroxide, potassium carbonate, or triethylamine in ethanol or chloroform with one, two, or three molar equivalents of the corresponding base to detect the intermediates: some results are summarized in Table 1.

Table 1
Proportion of products from the reaction of chlorodeoxy*pseudo*ephedrine **2at** with bases

Moles of base	Solvent	Reaction time (h)	**1a/2a**	**3a**	**8a**	**9a**	**10a**
6 NH_3/H_2O	EtOH (96%)	8 (reflux)	30/10	10	0	50	0
1 NaOH	EtOH (96%)	24 (stirring)	10/0	57	0	33	0
2 K_2CO_3	EtOH	72 (reflux)	0	20	10	50	20
2 or 3 K_2CO_3	$CHCl_3$	72 (reflux)	0	20	20	40	0
3 K_2CO_3	EtOH	72 (reflux)	0	0	0	80	20

Compound **3a** was reacted with an excess of aqueous ammonia (27%) in refluxing ethanol for 8 h. NH_4Cl was filtered off, ethanol evaporated, and *cis*-aziridine **9a** (50%) was separated with chloroform from the ethanolic residue, and hydrochloride **3a** (10%) in a mixture with ephedrine **1a**/*pseudo*ephedrine **2a** hydrochlorides (30%/10%) was identified in the solid residue as a result of partial hydrolysis of compound **3a** because of the presence of water.

The hydrolyzing role of water was confirmed when chlorodeoxy*pseudo*-hydrochlorides **3a** or **3b** were refluxed in water for 8 hours to obtain a stereoisomeric mixture of the corresponding ephedrines **1a**/**2a** or *nor*ephedrines **1b**/**2b** in a 60:40 proportion, respectively.

When hydrochloride **3a** was reacted with one molar equivalent of NaOH in stirring ethanol for 24 h at room temperature, *cis*-aziridine **9a** (33%) and hydrochloride **3a** (57%), in a mixture with ephedrine **1a** (10%) as the hydrolysis product, were observed.

On the basis of these results, compound **3a** was refluxed in anhydrous ethanol for 24 h in the presence of two molar equivalents of K_2CO_3 as base. Bicarbonate and KCl were filtered off, ethanol removed under vacuum, *cis*-ziridine **9a** was extracted with chloroform and the ^{1}H NMR spectrum of the remaining solid showed a mixture of two compounds in a 2:1 proportion. The major compound was identified as the corresponding hydrochloride **3a**. For the minor compound, the ^{1}H chemical shift of the methyne protons H-1 (doublet) and H-2 (doublet of quartet) appears at 4.09 and 4.83 ppm, respectively. The multiplicity of these signals is inter-changed in position compared with that of the major compound **3a**. In addition, the same coupling constant values for H-1 (doublet) were measured for both compounds (approx. 10 Hz). On the other hand, the C–Me absorption at 1.28 ppm in the minor compound is characteristic of a methyl group on a carbon bearing a chlorine atom.[4a] These results allowed us to identify the formation of the isochlorodeoxy*pseudo*ephedrine hydrochloride **8a** as the minor compound, whose formation is explained by chloride opening on the C3 of the aziridinium intermediate **6a**, Scheme 3. Under these conditions *cis*-aziridine **9a**, hydrochloride **3a**, and isohydrochloride **8a** are formed through acid-base equilibria of aziridinium **6a** with chlorodeoxy*pseudo*ephedrine **5a** or isochlorodeoxy*pseudo*-ephedrine **7a**. In addition, a new solid precipitated from the chloroform solution, its NMR spectrum is in agreement with *pseudo*ephedrinylthylether hydrochloride **10a**, formed by the ethanolysis of the aziridinium intermediate **6a**.

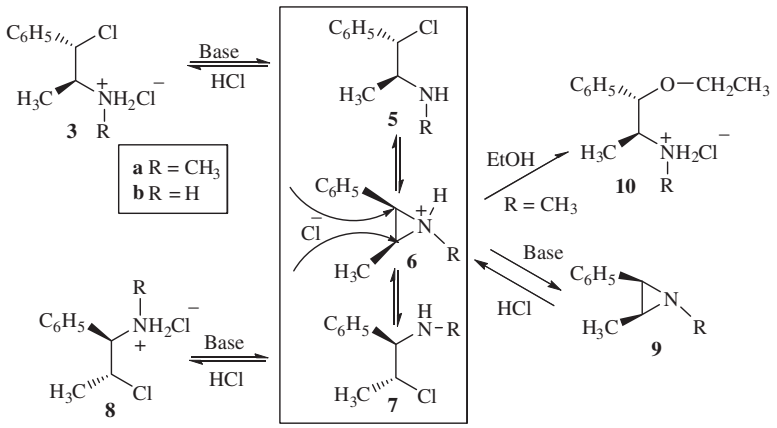
When the same reaction was carried out with chlorodeoxy*nor*-*pseudo*ephedrine hydrochloride **3b**, only *cis*-aziridine **9b** was extracted with chloroform and the corresponding mixture of hydrochlorides **3b** and isohydrochloride **8b** in a 2:1 proportion was identified in the remaining solid. The corresponding *nor*-*pseudo*ephedrinethyl ether **10b** was not observed.

To avoid ethanolysis, chloroform was used in the reaction of chlorodeoxy*pseudo*-hydrochlorides **3a** or **3b** with two or three molar equivalents of K_2CO_3. In both cases, the ^{1}H NMR spectra showed compounds **3**/**8** in a mixture with the corresponding *cis*-aziridine **9** in a 1:1:2 proportion, respectively.

Finally, the best results were obtained when the reactions were carried out with three molar equivalents of the base in refluxing anhydrous ethanol by 72 h. From hydrochloride **3a**, *cis*-aziridine **9a** (80%) in mixture with the free ether **10a** (20%) was obtained. From hydrochloride **3b**, only *cis*-aziridine **9b** was obtained in 96% yield. From a 60:40 mixture of *threo*/*erythro* chlorodeoxy-hydrochlorides **3b**/**4b**, a mixture of *cis*/*trans*-aziridines in the initial proportion was detected. When this mixture was kept for a month in a chloroform solution, only the *cis* isomer was observed by NMR.

The same results were observed when Et_3N was used instead of Na_2CO_3 using ethanol as solvent.

The ^{1}H and ^{13}C NMR spectral data of the corresponding *cis*-aziridines **9a** and **9b** showed the characteristic chemical shift reported in the literature.[8,10] However, a Hetcor experiment was recorded to unequivocally assign the close signals, 47.7 to *N*–CH_3 and 47.5 ppm



Scheme 3. Intermediates involved to get *cis*-aziridines **9** from chlorodeoxy*pseudo*ephedrine hydrochlorides **3**.

to C-2. It is interesting to note that C-2 and C-3 resonances are shifted to high frequencies by approximately 10 ppm when N–H is changed by *N*-methyl group.

The attempts to isolate the corresponding aziridinium intermediates **6a** or **6b** from the corresponding reaction of *cis*-aziridines with HCl always led to the corresponding chlorodeoxy*pseudo*derivatives **3a** or **3b**, suggesting a fast hydrolysis in acid media. With the aim of synthesizing the *trans*-aziridine **9at**, the chlorodeoxyephedrine **4a** was reacted with three molar equivalents of K_2CO_3 in refluxing ethanol for 72 h. Under these conditions the *erythro* isomer of the ether **10a** was isolated as the only product. Compound **10ae** crystallized from ethanol and its X-ray diffraction structure was obtained, Figure 1. The molecular structure of **10ae** showed *C*-methyl and phenyl groups *syn* positioned and *C*-methyl and *N*-methyl groups in a gauche conformation. Intermolecular NH···Cl^- (2.21, 2.33 Å) and intramolecular Cl^-···HN (2.34 Å) and NH···O (2.48 Å) distances are in the range for hydrogen bonding interactions.[3]

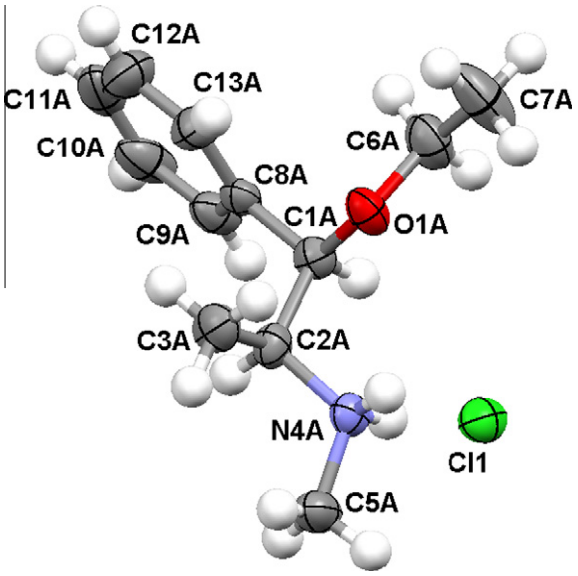


Figure 1. Molecular structure of compound **10ae**. Some selected bond lengths (Å) and bond/torsion angles (°): O1A–C1A, 1.422(5); O1A–C6A, 1.439(6); N4A–C2A, 1.501(5); N4A–C5A, 1.499(7); C1A–C2A, 1.531(6); C1A–C8A, 1.506(6); O1A–C1A–C2A, 106.7(3); O1A–C1A–C8A, 113.7(3); C2A–C1A–C8A, 111.8(4); N4A–C2A–C1A, 109.1(3); N4A–C2A–C3A, 109.6(4).

3. Conclusions

The chlorination reaction of *pseudo*ephedrines **2a** or **2b** with $SOCl_2$ at 0 °C stereoselectively afforded chlorodeoxy*pseudo*ephedrines **3a** or **3b**, respectively. However, when the same chlorination reactions were carried out at 25 °C, a 40:60 mixture of the *erythro*/*threo* isomers were obtained by thermal isomerization.

The reaction of the hydrochlorides **3a** and **3b** with three molar equivalents of a mild base in anhydrous ethanol affords the corresponding *cis*-aziridine in 80% and 96% yields, respectively. Solvolysis is the main side reaction which lowers the aziridine yield. However, the ethanolysis byproduct **10at** is easily separated from chloroform solutions. In the same conditions our attempts to obtain *trans*-aziridines from **4a** lead to the novel compound **10ae**, suggesting the fast ethanolysis of the incipiently formed *trans*-aziridine **9at**. The molecular structure of **10ae** was confirmed by X-ray.

4. Experimental

4.1. General

Melting points were measured on an Electrothermal IA apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz (^1H, 300.08; ^{13}C, 75.46 MHz). The spectra were measured with tetramethylsilane as internal reference following standard techniques. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC: **10ae**, (748350). X-ray diffraction cell refinement and data collection: CAD-4 EXPRESS;[11] data reduction: JANA98;[12] programs used to solve structure: SHELXS-97;[13] software used to prepare material for publication: *WinGX*.[14]

4.2. (1*S*,2*S*)-Chlorodeoxypseudoephedrine hydrochloride 3a

To (1*S*,2*S*)-(+)-pseudoephedrine hydrochloride **2a** (1.0 g, 4.96 mmol) on ice-water bath, $SOCl_2$ (1.43 mL, 19.8 mmol) was slowly added. After stirring for 5 h, excess of $SOCl_2$ was removed under vacuum. The resulting white solid was washed with acetone and filtered (1.02 g, 94%); mp 198–200 °C; $[\alpha]_D^{30} = +10.5$ (CH_3OH, *c* 0.1), ^1H NMR [δ, ppm, DMSO-d_6]: 9.45 (br, 2H, $^+NH_2CH_3$), 7.4 (m, 5H, Ph), 5.45 (d, 1H, ^3J = 9.4 Hz, C1-H), 3.96 (dq, 1H, J = 9.4, 6.7 Hz, C2-H), 2.60 (s, 3H, N–CH_3), 1.03 (d, 3H, ^3J = 6.7 Hz, C2–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 137.92 (Ci), 129.98 (Cp),

129.71 (Co), 129.71 (Cm), 62.98 (C1), 58.93 (C2), 29.84 (N–CH_3); 13.59 (C2–CH_3).

4.3. (1*R*,2*R*)-Chlorodeoxynorpseudoephedrine hydrochloride 3b

Synthesized as **3a**, (1*R*,2*R*)-(+)-norpseudoephedrine hydrochloride **2b** (1.0 g, 5.33 mmol) to get **3b** as a white solid (0.82 g, 74%), mp 205–207 °C; $[\alpha]_D^{33} = -10.4$ (*c* 0.1, H_2O); ^{1}H NMR [δ, ppm, DMSO-d_6]: 8.68 (br, 3H, $^+NH_3$), 7.45 (m, 5H, Ph), 5.26 (d, 1H, ^3J = 9.7 Hz, C1-H), 3.83 (dq, 1H, *J* = 9.7, 6.7 Hz, C2-H), 1.03 (d, 3H, ^3J = 6.7 Hz, C2–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 138.08 (Ci), 129.9 (Cp), 129.65 (Co), 128.51 (Cm), 65.0 (C1), 52.92 (C2), 16.91 C2–CH_3; IR (KBr, ν_{max}/cm^{-1}): 3420 (NH_3), 3058, 3014 (Ar), 2996, 2974, 2958 (CH, CH_3), 716, 692 (Cl); Elemental Anal. Calcd: C, 52.4461; H, 6.3570; N, 6.7956. Found: C, 53.1263; H, 6.4989; N, 7.5554.

4.4. (1*R*,2*S*)-Chlorodeoxyephedrine hydrochloride 4a

Synthesized as **3a**, (1*R*,2*S*)-(+)-ephedrine hydrochloride **1a** (1.0 g, 4.96 mmol) at room temperature to get 0.96 g (88%) of a mixture of chlorodeoxy stereoisomers **4a/3a** (40:60 *erythro*/*threo*). The *erythro* chlorodeoxy hydrochloride **4a** was separated from the *threo* isomer **3a** by a fractional crystallization from ethanol as a white solid (0.2 g). ^{1}H NMR [δ, ppm, DMSO-d_6]: 9.45 (br, 2H, $^+NH_2Me$), 7.35 (m, 5H, Ph), 5.93 (d, 1H, ^3J = 3.2 Hz, C1-H), 3.70 (dq, 1H, *J* = 3.2, 6.4 Hz, C2-H), 2.60 (s, 3H, N–CH_3), 1.13 (d, 3H, ^3J = 6.4 Hz, C2–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 137.15 (Ci), 128.80 (Cp), 129.32 (Co), 128.04 (Cm), 63.45 (C1), 59.58 (C2), 31.19 (N–CH_3); 10.63 (C2–CH_3).

4.5. (1*S*,2*R*)-Chlorodeoxynorephedrine hydrochloride 4b

This compound was identified when the *threo* chlorodeoxy hydrochloride **3b** in DMSO-d_6 solution is heated (80–90 °C) for five hours in the NMR tube to get a 60:40 mixture of the **3b/4b** stereoisomers.

^{1}H NMR [δ, ppm, DMSO-d_6]: 8.8 (br, 3H, $^+NH_3$), 7.45 (m, 5H, Ph), 5.65 (d, 1H, ^3J = 4.4 Hz, C1-H), 3.70 (dq, 1H, *J* = 4.4, 6.4 Hz, C2-H), 1.17 (d, 3H, ^3J = 6.4 Hz, C2–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 135.63 (Ci), 129.93 (Cp), 129.65 (Co), 128.51 (Cm), 64.76 (C1), 52.51 (C2), 13.72, (C2–CH_3).

4.6.

The isochlorodeoxy-derivatives **8a** and **8b** were identified as intermediates in a solid mixture with the corresponding chlorodeoxy-derivatives **3a** and **3b** when the reactions of the corresponding chlorodeoxy-hydrochlorides **3a** or **3b** were reacted with two molar equivalents of K_2CO_3 in refluxing chloroform for 72 h.

4.6.1. (1*R*,2*R*)-Isochlorodeoxypseudoephedrine hydrochloride 8a

^{1}H NMR [δ, ppm, DMSO-d_6]: 9.35 (br, 2H, $^+NH_2CH_3$), 7.5 (m, 5H, Ph), 4.76 (dq, 1H, 8.5, 6.4 Hz, C2-H), 4.49 (d, 1H, ^3J = 8.5 Hz, C1-H), 2.59 (s, 3H, N–CH_3), 1.26 (d, 3H, ^3J = 6.4 Hz, C2–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 132.61 (Ci), 130.34 (Cp), 130.00 (Co), 129.83 (Cm), 68.45 (C1), 58.07 (C2), 32.08 (N–CH_3); 22.44 (C2–CH_3).

4.6.2. (1*S*,2*S*)-Isochlorodeoxynorpseudoephedrine hydrochloride 8b

^{1}H NMR [δ, ppm, DMSO-d_6]: 7.65–7.40 (m, 5H, Ph), 4.63 (dq, 1H, *J* = 9.7, 6.6 Hz, C2-H), 4.47 (d, 1H, ^3J = 9.7 Hz, C1-H), 1.26 (d, 3H, ^3J = 6.6 Hz, C4–CH_3). ^{13}C NMR [δ, ppm, DMSO-d_6]: 137.29 (Ci), 129.82 (Cp), 129.48 (Co), 127.96 (Cm), 60.91 (C1), 59.41 (C2), 22.35 (C2–CH_3).

4.7. *cis*-(2*S*,3*R*)-1,2-Dimethyl-3-phenylaziridine 9a

(1*S*,2*S*)-Chlorodeoxypseudoephedrine hydrochloride **3a** (1.0 g, 4.54 mmol) and K_2CO_3 (1.88 g, 13.64 mmol) were dissolved in 5 mL of anhydrous ethanol and refluxed during 72 h, the resulted $KHCO_3$ and KCl in suspension were filtered off and ethanol was evaporated. The resulting mixture was dissolved in $CHCl_3$. From this solution compound **10a** precipitated and was filtered off as a white solid (0.1 g). Chloroform was eliminated to give the corresponding aziridine **9a** as viscous liquid (0.53 g, 80% yield): $[\alpha]_D^{20} = -131$ (*c* 0.8, EtOH) ^{1}H NMR [δ, ppm, $CDCl_3$]: 7.25 (m, 5H, Ph), 2.50 (s, 3H, N–CH_3), 2.44 (d, 1H, ^3J = 6.7 Hz, C2-H), 1.68 (dq, 1H, *J* = 6.7, 5.9 Hz, C2-H), 0.92 (d, 3H, ^3J = 5.9 Hz, C2–CH_3). ^{13}C NMR [δ, ppm, $CDCl_3$]: 137.76 (Ci), 128.11 (Co), 127.96 (Cm), 126.7 (Cp), 47.82 (C2), 47.71 (C3), 43.14 (N–CH_3); 12.85 C3–CH_3. *z*/*e* (%): 146 (100), 147 (16), 148 (2).

4.8. *Threo*-(1*S*,2*S*)-ephedrinylethylether hydrochloride 10a

^{1}H NMR [δ, ppm, $CDCl_3$]: 7.3 (m, 5H, Ph), 4.40 (d, 1H, ^3J = 9.7 Hz, C1-H), 3.31 (dq, *J* = 19.1, 7.0 Hz, 2H, O–CH_2), 3.17 (dq, 1H, *J* = 9.7, 6.7 Hz, C2-H), 1.16 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 1.08 (d, 3H, ^3J = 6.7 Hz, C2–CH_3). ^{13}C NMR [δ, ppm, $CDCl_3$]: 137.80 (Ci), 129.0 (Co), 128.99 (Cm), 127.82 (Cp), 82.65 (C1), 64.71 (C2), 60.59 (O–CH_2), 31.52 (N–CH_3), 15.36 (CH_2CH_3), 13.72 (C2–CH_3). *z*/*e* (%): 58 (100), 77 (9.6), 194 (18.4).

4.9. *cis*-(2*R*,3*S*)-2-Methyl-3-phenylaziridine 9b

Synthesized as **10a**, (1*R*,2*R*)-chlorodeoxynorpseudo-ephedrine hydrochloride **3b** (1.0 g, 4.85 mmol) and K_2CO_3 (2.0 g, 14.55 mmol), aziridine **9b** precipitate as white solid (0.62 g, 96% yield): mp 61 °C, (lit.[10] 68 °C); $[\alpha]_D^{20} = +69.1$ (*c* 4.43 × 10^{-3}, $CHCl_3$), {lit.[10] $[\alpha]_D^{25} = -74$ (*c* 3, EtOH)}; IR (KBr) 3218, 1600 cm^{-1}; ^{1}H NMR [δ, ppm, $CDCl_3$]: 7.26 (m, 5H, Ph), 3.18 (d, 1H, ^3J = 6.4 Hz, C2-H), 2.34 (dq, 1H, C2-H, ^3J = 6.4, 5.6 Hz), 0.88 (d, 3H, ^3J = 5.6 Hz, C2–CH_3). ^{13}C NMR [δ, ppm, $CDCl_3$]: 137.86 (Ci), 128.11 (Co), 128.02 (Cm), 126.83 (Cp), 37.33 (C2), 32.39 (C3), 13.83 C3–CH_3. *z*/*e* (%): 132 (100), 133 (12), 77 (19.25), 28 (53.2). IR (KBr, ν_{max}/cm^{-1}): 3308 (NH), 3060, 3026 (Ar), 2992, 2958, 2926 (CH, CH_3); Elemental Anal. Calcd: C, 81.1600; H, 8.3239; N, 10.5161. Found: C, 81.0615; H, 8.3238; N, 11.1770.

4.10. *Erythro*-(1*R*,2*S*)-ephedrinylethylether 10ae

Sythesized as **10a**, (1*R*,2*S*)-chlorodeoxyephedrine hydrochloride **4a** (0.2 g, 0.11 mmol) and K_2CO_3 (0.046 g, 0.33 mmol) to get ether **10ae** as white solid (0.2 g, 96% yield): mp = 185–186 °C; $[\alpha]_D^{20} = -68.5$ (*c* 3.08 × 10^{-3}, EtOH) ^{1}H NMR [δ, ppm, $CDCl_3$]: 7.30 (m, 5H, Ph), 4.98 (d, 1H, ^3J = 2.9 Hz, C1-H), 3.51 (dq, *J* = 7.0, 4.7 Hz, 2H, O–CH_2), 3.27 (dq, 1H, *J* = 2.9, 6.7 Hz, C2-H), 1.26 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 1.21 (d, 3H, ^3J = 6.7 Hz, C2–CH_3). ^{13}C NMR [δ, ppm, $CDCl_3$]: 137.82 (Ci), 128.86 (Co), 126.83 (Cm), 128.37 (Cp), 79.78 (C1), 65.41 (C2), 59.77 (O–CH_2), 30.75 (N–CH_3), 15.52 (CH_2–CH_3), 9.81 (C2–CH_3). *z*/*e* (%): 58 (100), 77 (11.2), 194 (6.2).

4.10.1. Crystal data

Formula, $C_{12}H_{20}NOCl$; formula weight, 229.74; crystal system, monoclinic; space group, P21 (No. 4); *a*, *b*, *c* [Å], 14.1041(19), 7.1403(10), 14.642(2); α, β, γ [°], 90, 113.044(2), 90; *V* [°^{3}], 1356.9(3); *Z*, 4; *D*(calcd) [g/cm^3], 1.125; Mu(MoKa) [mm], 0.260; *F*(0 0 0), 496; crystal size [mm], 0.35 × 0.30 × 0.20.

4.10.2. Data collection

Temperature (*K*), 293; radiation [Å], MoKa 0.71073; Theta Min–Max [Deg], 1.5–25.0; dataset: −16:16; −8:8; −17:17; Tot., Uniq.

Data, *R*(int), 13286, 4798, 0.070; Observed data [I >2.0 sigma(I)], 3086; refinement: Nref, Npar, 4798, 271; *R*, *wR*2, *S*: 0.0654, 0.1320, 1.02; $w = 1/[s^2(F_o^2) + (0.0422P)^2]$ where $P = (F_o^2+2F_c^2)/3$; Max. and Av. Shift/Error, 0.00, 0.00; Flack x, 0.10(10): Min. and Max. Resd. Dens. [e/Ang^3], −0.18, 0.20.

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