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DETERMINATION OF THE NITROGEN CONFIGURATION IN EPHEDRINE N-BORANES AND A STUDY OF THEIR ASSISTED STEREOSPECIFIC DEUTERATION OF NH

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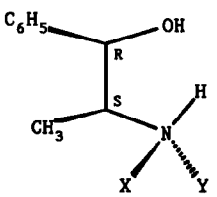
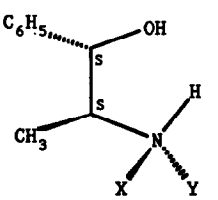
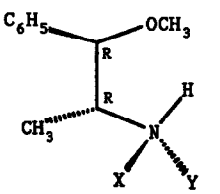
Abstracts. Ephedrine, *pseudo*ephedrine and *pseudo*ephedrine-methyl-ether react stereoselectively with BH_3.DMS to give N→BH_3 adducts, which are N-epimers of stable configuration. The nitrogen configuration was established from NMR data. Assisted stereospecific deuteration of OH was demonstrated by comparison with the behaviour of *pseudo*ephedrine-methyl-ether N-BH_3 adducts. The analysis of the preferred conformers gave us an explanation of the observed stereochemistry.

We have reported previously the N-BH_3 adducts of the ephedrine family[1-2]. These adducts were synthesized by adding BH_3·DMS to the free aminoalcohols at low temperature. The analogous N-BH_3 derivatives of *pseudo*ephedrine-methyl-ether were also prepared and reported herein. *Nor*ephedrine, *norpseudo*ephedrine, N-methyl-ephedrine and N-methyl-*pseudo*-ephedrine afforded only one product with diastereotopic N-substituents[1-2]. (-)-(1R,2S) Ephedrine or (+)-(1S,2S)-*pseudo*ephedrine or (-)-*pseudo*ephedrine-methyl-ether each afforded two N-epimers. Encouraged by these results we proceeded to establish the nitrogen configuration, Figure 1.







1 (S_N) X = BH_3, Y = CH_3
2 (R_N) X = CH_3, Y = BH_3
3 (R_N) X = CH_3, Y = BH_3
4 (S_N) X = BH_3, Y = CH_3
5 (S_N) X = BH_3, Y = CH_3
6 (R_N) X = CH_3, Y = BH_3

Figure 1

Determination of the nitrogen configuration.

All these compounds (1-6) gave evidence of a stable nitrogen configuration. The diastereomeric mixtures were separated on a chromatographic column without hydrolysis or N-epimerization. We were not able to crystallize the isolated N-epimers in order to establish their configuration by an X-ray diffraction study. Therefore, we were interested in analyzing the NMR data in order to deduce the N-configuration. First of all, we evaluated by molecular mechanics calculations[3] the energy of the three staggered conformers of each epimer. We found one preferred conformer for each isomer (only two gauche interactions, instead of three for the other two conformers). The preferred conformations of *pseudo*ephedrine and ephedrine adducts are shown in Figures 2 and 3: They have the common feature that the phenyl group is antiperiplanar to the nitrogen atom. This conformation coincides with that found in the solid state by an X-ray diffraction study of (-) *O*,N,N-trimethylephedrinium iodide 7 (Figure 4) which is a good model to compare with the borane adducts because the nitrogen of 7 does not have an acidic proton as in 1-6.

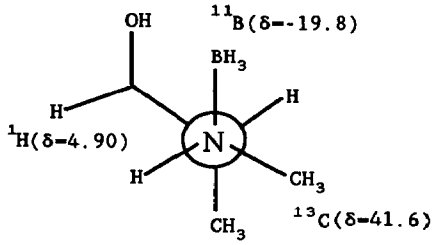


Figure 2. Preferred conformations of epimers of *pseudo*ephedrine N-BH3.

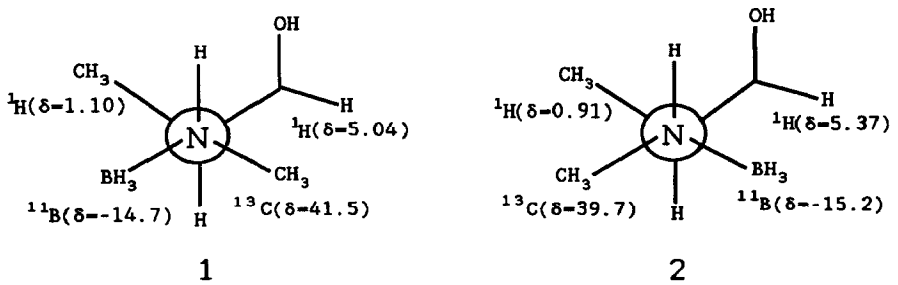


Figure 3. Preferred conformations of epimers of ephedrine N-BH3.

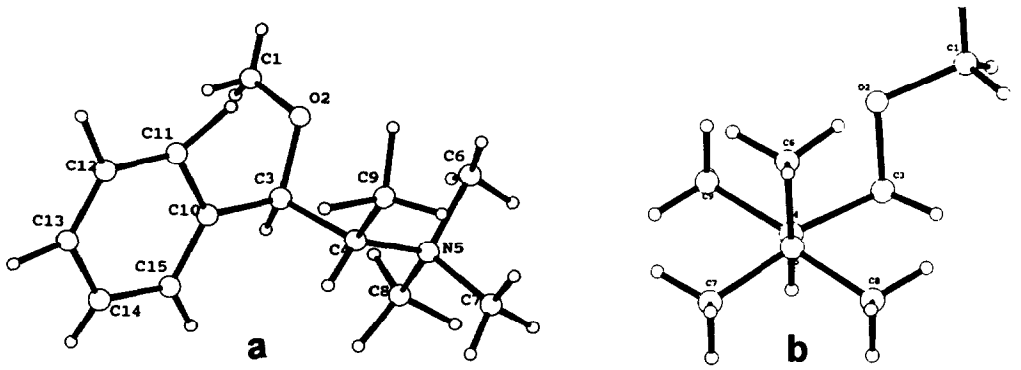


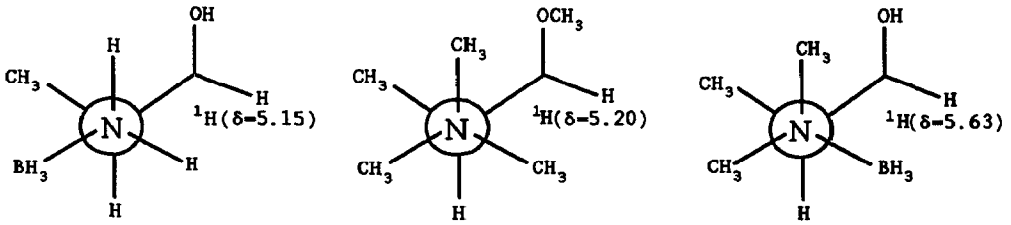
Figure 4. Crystal X-ray diffraction of compound 7: a) ORTEP diagram and b) view along N-C4 in order to show the preferred conformation around this bond, the phenyl group was omitted for clarity. Selected interatomic distances and angles are as follows: O2-C1 1.443(8), O2-C3 1.408(6), N5-C4 1.538(6), N5-C6 1.508(8), N5-C7 1.508(7), N5-C8 1.496(7), C3-C4 1.544(7), C3-C10 1.487(7). C1-O2-C3 112.6(4), C4-N5-C6 112.9(5), C4-N5-C7 109.0(4), C4-N5-C8 110.5(4), C6-N5-C7 107.3(5), C6-N5-C8 110.6(5), C7-N5-C8 106.2(4), O2-C3-C4 107.1, O2-C3-C10 114.5(4), C4-C3-C10 109.2(4), N5-C4-C3 114.4(4), N5-C4-C9 111.2(4), C3-C4-C9 111.5(4). C10-C3-C4-N5 160.4.

The N-configuration of **1-4** can be established if the NMR data is analyzed in relation to the more stable conformer of each isomer and compared with the NMR data of oxazolidines N-BH_3 derived from *pseudo*ephedrine. In the latter, we have found that the BH_3 chemical shift is very sensitive to steric effects due to the neighbouring methyl groups, the crowded borane being shifted to lower frequencies. A similar effect was observed for the ^{13}C δ of the C-methyl group[4-6]. As well as a ^{1}H deshielding effect through space produced by the borane group over the neighbouring protons[4-6].

We have observed similar chemical behaviour for the N-BH_3 ephedrine derivatives (**1-6**)[7] from which a good fit of the NMR data trends has been obtained compared with the corresponding oxazolidines N-BH_3 adducts. For the mixture of **3** and **4** two different ^{11}B δ for BH_3 groups are obtained, indicating one has a more crowded borane (-19.8 ppm, **3**) than the other (-14.9 ppm, **4**), Figure 2. At the same time the crowded borane is accompanied by a less hindered N-CH_3 (^{13}C δ = 41.6 ppm). The molecule with the less hindered N-BH_3 group (**4**) has a crowded methyl group (^{13}C δ = 32.9 ppm). In addition, the proton CH-O is sensitive to the BH_3 approach, therefore, when BH_3 is antiperiplanar to the C-1 it appears at 4.41 ppm (**4**) whereas when it is in a gauche position (**3**) appears at 4.90 ppm. Compounds **5** and **6** present the same spectral behaviour indicating the same conformer populations.

The NMR analyses for the ephedrine adducts **1** and **2** must be different than in the *pseudo* series, because the BH_3 and the N-CH_3 are in places of similar steric hindrance. The configuration was assigned by analyzing the chemical shift of C1-H which distinguishes if a borane is antiperiplanar to C-1 (**1**) or gauche (**2**), also the C-CH_3 indicates by a similar effect the position of the borane, (Figure 3). A similar effect of the borane on the C1-H can be observed for three examples, Figure 5. In (-)-*nor*ephedrine, the preferred conformer

8 has the BH_3 antiperiplanar to the fragment [CH(C_6H_5)OR] and does not affect the C1-H. It has an analogous value to that of compound 7. The N-BH_3 adduct derived from (-)-N-methyl-ephedrine 9 shows that C1-H is affected because the conformer shown must have a significant population. A deshielding effect of the nitrogen substituents over the C1-H can be discarded if comparison is made with compound 7.



8 7 9

Figure 5. Effect of the nitrogen substitutions on the C1-H of ephedrine derivatives.

As a consequence of the NMR analyses the nitrogen configuration of compounds 1-6 can be assigned as depicted in Figure 1.

Stereoselective formation of N-epimers.

Once the N-epimer configurations were assigned, we examined the ratio of kinetic products in the adduct formation. The addition of $BH_3 \cdot SMe_2$ was done at -70°C, stirred for 10 minutes and the solvent evaporated in vacuum (10 minutes at room temperature). The reaction products were dissolved in $CDCl_3$ and a drop of D_2O was added in order to hydrolyze the borates. A ^1H NMR spectrum was immediately recorded and the N-epimers ratio evaluated from the ratio of N-CH_3 signals (1/2 = 80/20, 3/4 and 5/6 70/30). It was found that a stereoselective addition of BH_3 had occurred. The explanation for the stereoselectivity is based on the assumption that BH_3 approaches the aminoalcohol molecule in an antiperiplanar position to the bulky fragment -CH(C_6H_5)OR, Figure 6. Two configurations are possible for the nitrogen atom in order to make the lone pair available for the BH_3 group which explain both reaction products. One of these approaches is not favoured owing to a repulsion of the N-CH_3 with the oxygen atom (2 and 6). For simplicity only the (-)-O-methyl-*pseudo*ephedrine derivatives (5 and 6) are depicted in Figure 6.

Assisted stereospecific deuteration.

We observed in ^1H NMR spectra that addition of D_2O to the (-)-ephedrine (1 or 2) or to the (+)-*pseudo*ephedrine adducts 3 or 4 makes the OH exchange immediately, whereas the weak acid N-H exchanges very slowly (5 h at 55°C, in $CDCl_3$ and D_2O).

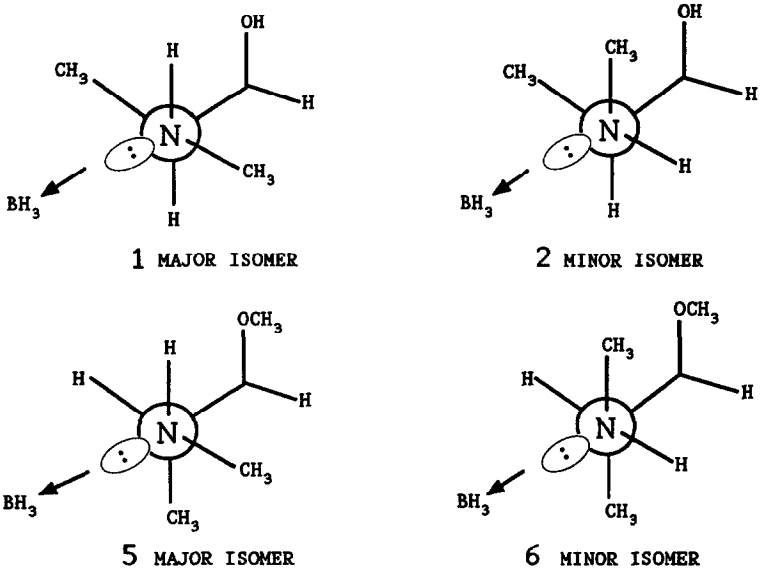


Figure 6. Proposed explanation for the stereoselective formation of ephedrine N-BH3 epimers.

The deuteration was followed in the NMR spectra by monitoring the N-CH3 resonances which loose the ^{3}J(H-N-CH3) coupling. If a pure isomer is employed in the experiment the exchange occurs without epimerization. When deuteration is made in the presence of NaOD, the N-H deuteration is very fast and occurs with N-epimerization to give 50 % of each isomer). Deuteration and epimerization occur faster in (-)-ephedrine isomers than in the (+)-*pseudo*ephedrines.

The latter observations mean that: a) the energy of inversion of the nitrogen anion is very high (slow inversion[8]) and that deprotonation-protonation is very fast, and or b) that the stereospecific exchange NH/ND occurs by assistance of the lone pair of the oxygen atom, with subsequent migration of deuterium as shown in Figure 7. c) In the presence of NaOD deuteration is fast because the O-anion formed from the aminoalcohol helps to remove the N-H. Epimerization is also faster because the N-anion has under these basic conditions a lifetime long enough to allow the nitrogen inversion, which is a slow process, necessary for epimerization, Figure 8.

In order to check the role of the proton at the oxygen atom, we have repeated the deuteration experiments with the N-BH3 epimers 5 and 6 derived from (-) pseudoephedrine-methyl-ether 10. The pure isomer 5 was heated in the presence of D2O for 3 hours without deuteration. In similar conditions the same isomer derived from *pseudo*ephedrine 3 is completely deuterated, indicating clearly the role of the O-H in the deuteration, as is shown in Figure 7.

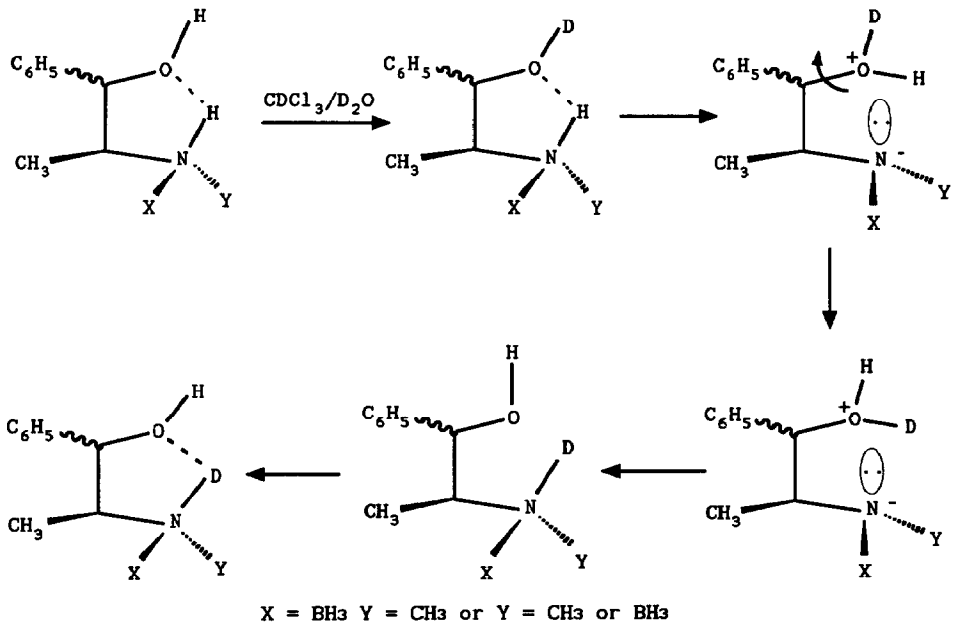


Figure 7. OH Assistance of deuteration of ephedrine N-BH3 adducts.

The OH assistance also explains why ephedrine deuteration and inversion occurs faster than in *pseudo*ephedrine under the same conditions. Examination of both conformers in which the OH can assist the deuteration, shows that compound **1** is more stable (only two gauche interactions) and therefore more populated than the equivalent conformer in compound **3** (three gauche interactions), Figure 9.

In the presence of NaOD deuteration of **5** occurs without epimerization, under the same conditions, compound **3** is completely N-epimerized (50-50 %). Only after 12 hours at room temperature 33% of epimerization of **5** is found. By heating the solution 10 hours at 70° a 50/50 ratio of isomers is obtained. Therefore, in a basic medium the role of the O-anion in the assistance of deuteration is demonstrated, in **3** the deuteration is faster because the O-anion helps to remove the N-H, while in **5** this anion can not be formed. In addition the bulky methyl group hinders the $^{-}$OD approach and removal of the N-H. The decrease in the epimerization rate for **5** is connected with the difficulty in forming the N-anion whose concentration must be low and in consequence the epimerization slower.

A mixture of N-epimers **5/6** (50/50) was reacted with D_2O (3 hours at 70°) under which strong conditions slow deuteration was found for both: Interestingly a different deuteration speed was found for each of the O-methylated isomers. Isomer **6** was deuterated faster than **5**. We have no explanation for this fact which is also structurally dependent.

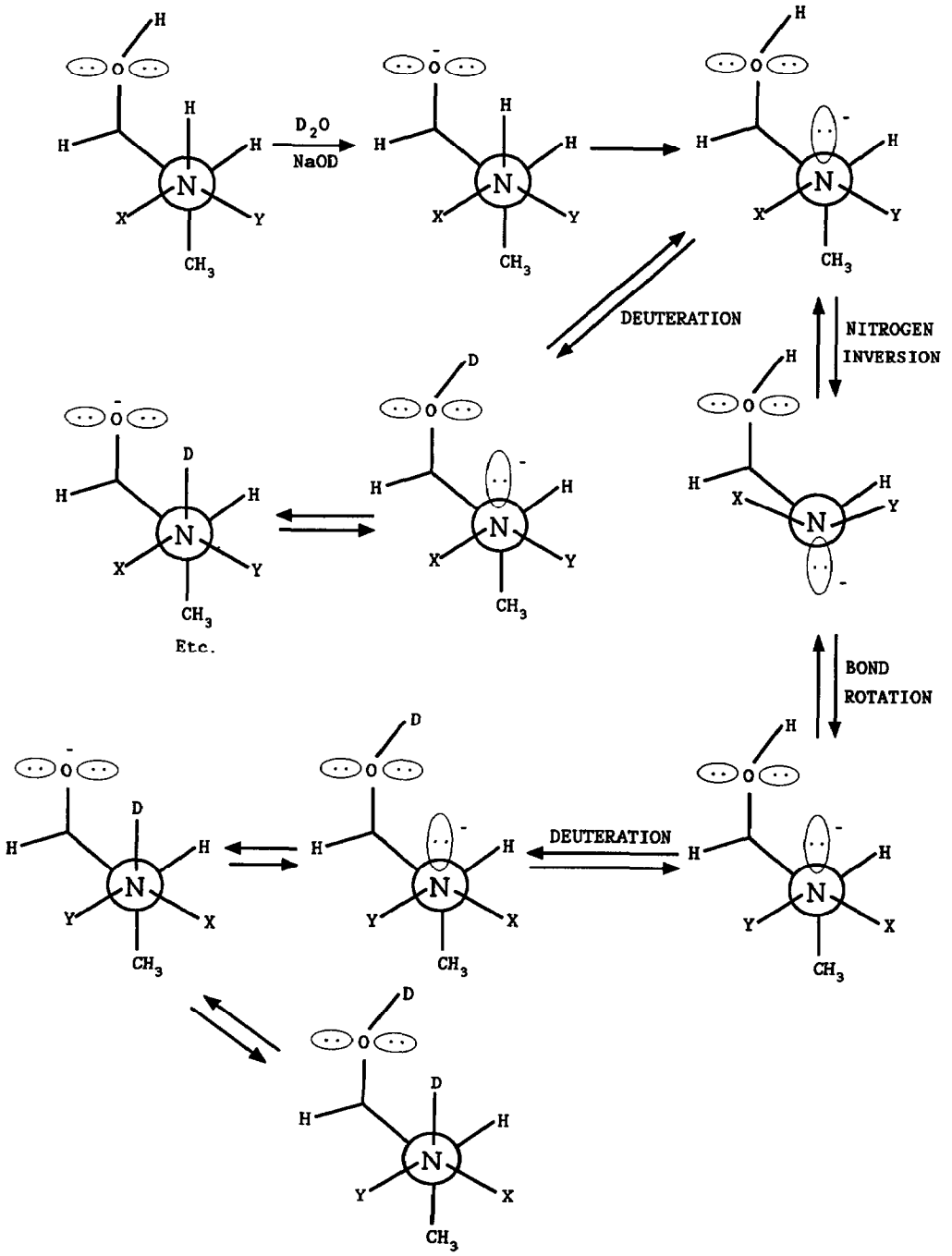
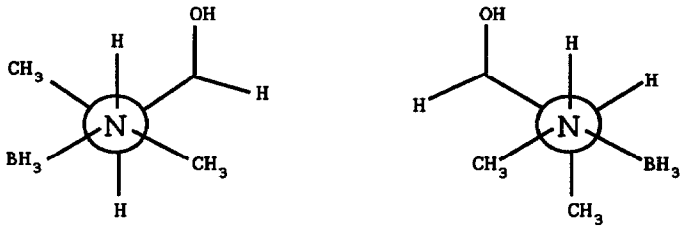


Figure 8. Proposed path for deuteration and N-epimerization in ephedrines N-BH3 adducts.



1 3

Figure 9. Conformers of compounds **1** and **3** which allows the OH assistance of deuteration.

Conclusions.

Borane is a useful tool for transforming nitrogen into a configurationally stable stereogenic center. The electronic and steric effects of BH_3 allow with the aid of the NMR chemical shifts determination of the configuration of the nitrogen[1,2,4-6]. The stereospecific deuteration of N-H in N-BH_3 ephedrines is evidence of the existence of a N-anion with a enough high energy barrier inversion to allow the deprotonation deuteration to occur without inversion. At the same time the role of the OH in the reactivity of the N-H was demonstrated. The ephedrine *(erythro)* and *pseudo*ephedrine *(threo)* alkaloids are interesting structures for stereochemical studies, for example the different reaction products found in methylation reactions; the O-methylation and the N-monomethylation for *norpseudo*ephedrine whereas for *nor*ephedrine under the same reaction conditions O-methylation was accompanied with trimethylation of the nitrogen.

Experimental.

^1H (270 MHz) and ^{13}C (67.8 MHz) NMR spectra were recorded with TMS as internal reference and ^{11}B NMR (86.55 MHz) spectra with $BF_3 \cdot OEt_2$ as external reference, ^{15}N NMR (27.25 MHz) spectra with nitromethane as reference. Crystal data is in ref. 9. Computations for compound 7 were performed by using MOLEN[10] adapted for a Micro Vax II. Atomic form factors for neutral C, N, O and H were taken from ref. 11. Hydrogen atoms were found on difference electron density maps.

(-)-O-Methyl-*pseudo*ephedrine 10 and (-)-O,N,N-trimethylephedrinium iodide 7. The same reaction conditions performed on *norpseudo*ephedrine afford the O-methyl ether (**10**) and *nor*ephedrine gave **7**. In a flask provided with a Dean-Stark trap and magnetic stirring, 4.2 g (27.77 mmol) of (-) *norpseudo*ephedrine, 6.17 g (83.31 mmol) of ethyl formate, traces of

p-toluensulfonic acid and 30 ml of xylene were refluxed for 18 h, the solvent was removed by vacuum. The reaction mixture was dissolved in 30 ml of dry THF and cooled down at 0° C; 1.33 g (55.4 mmol) of NaH were added, the suspension was stirred for 30 min to 0°C then 30 min at 23°C. The flask was provided with a dry ice-acetone trap and 7.0 ml (111.08 mmol) of CH_3I was added. The mixture was refluxed 3 h, the volatiles were eliminated in vacuum. Then water was added to the residue and it was extracted with CH_2Cl_2 (at pH 7). The solvent was evaporated, 10 ml of ethanol, 20 ml of water and 20 ml of HCl (37%) were added to the reaction product and the mixture was refluxed for 3 h. 9.66 g of NaOH dissolved in 25 ml of H_2O were slowly added at rt., pH was adjusted to 7. The reaction product was extracted with CH_2Cl_2 (5x), dried with Na_2SO_4 and the solvent was evaporated, to give a transparent liquid which distilled at 55°C (0.050 mm Hg), Yield 3.2 g (70 %), $[\alpha]_D^{23}$= -104.5 (THF, conc 1.7 g/100 ml). ^1H NMR ($CDCl_3$) δ OCH_3 3.17 (s), C1H 3.86 (d, J = 8.6), C2H 2.74 (d,q, J = 8.6 and 6.5), C-CH_3 0.76 (d, J = 6.5), N-CH_3 2.43 (s) NH 2.22 (b), C_6H_5 7.2-7.4 (m). ^{13}C NMR ($CDCl_3$) OCH_3 56.68, C1 88.33, C2 60.17, C-CH_3 15.37, N-CH_3 33.70, C*i* 139.58, C*o* 127.79, C*m* 128.26, C*p* 127.89.

Compound 7. Similar reaction conditions as above performed in (-)-*nor*ephedrine afforded compound 7. Anal. for $C_{13}H_{22}ONI$, Calcd. C 46.57, H 6.61, N 4.18; Found C 46.54, H 6.30, N 4.25. mp 225-230°C, $[\alpha]_D^{23}$ = -60.9 ($CHCl_3$, conc 1.3 g/100 ml). ^1H NMR ($CDCl_3$) δ OCH_3 3.59 (s), C1H 5.17 (d, J = 2), C2H 4.04 (q,d, J = 6.6 and 2), C-CH_3 1.24 (d, J = 6.6), N-CH_3 3.37 (s) C_6H_5 7.31-7.54 (m). ^{13}C NMR ($CDCl_3$) OCH_3 56.91, C1 79.69, C2 73.46, C-CH_3 8.25, N-CH_3 53.19, C*i* 135.71, C*o* 127.08, C*m* 128.86, C*p* 128.51.

(-)-O-Methyl-*pseudo*ephedrine N-BH_3 adducts, 5 and 6. 2.7 g (15.1 mmol) of (-)-O-methyl-*pseudo*ephedrine were dissolved in 10 ml of dried THF in a round flask with nitrogen inlet and cooled down at -70°, 8.4 ml of a solution 1.97 M of BH_3•DMS (16.6 mmol). The reaction was stirred for 10 min at -70°C and 30 min at rt. The solvent is evaporated in vacuo. The N-epimers were separated in a silica gel chromatographic column (230-400 mesh, 0.040-0.63 mm) using as eluent hexane/ethyl acetate 70/30. Compound 5 is isolated in 60 % whereas 6 in 5 %. The rest is the isomer mixture.

Compound 5. Anal. for $C_{11}H_{17}ON$, Calcd. C 68.48, H 10.37, N 7.25; Found C 68.37, H 10.27, N 7.21. mp 98-102°C, Mass Spectra M^+ 192.30. $[\alpha]_D^{23}$ = -100 ($CHCl_3$, conc 0.9 g/100 ml. ^{11}B ($CDCl_3$) -20.7 (q J = 95), ^{15}N ($CDCl_3$) -350.5 (d, 71 Hz). ^1H NMR ($CDCl_3$) δ OCH_3 3.23 (s), C1H 4.42 (d, J = 9.2), C2H 2.86 (d,q,d, J = 8.4, 6.7 and 1.4), C-CH_3 0.90 (d, J = 6.5), N-CH_3 2.61 (d, J = 6) NH 5.09 (b), C_6H_5 7.27-7.41 (m). ^{13}C NMR ($CDCl_3$) OCH_3 56.56, C1 83.62, C2 64.43, C-CH_3 8.98, N-CH_3 41.94, C*i* 137.81, C*o* 127.81, C*m* 128.67, C*p* 128.67.
Compound 6. $[\alpha]_D^{23}$ = -100 ($CHCl_3$, conc 0.9 g/100 ml). ^{11}B ($CDCl_3$) -15.2 (q J = 95), ^{15}N ($CDCl_3$) -352.3 (d, 71 Hz). ^1H NMR ($CDCl_3$) δ OCH_3 3.19 (s), C1H 3.94 (d, J = 10.3), C2H 3.22 (m), C-CH_3 0.93 (d, J = 7), N-CH_3 2.42 (d, J = 6) NH 4.78 (b), C_6H_5 7.2-7.41 (m). ^{13}C

NMR (CDCl3) OCH_3 56.45, C1 83.49, C2 63.04, C-CH_3 8.57, N-CH_3 33.07, C*i* 137.31, C*o* 127.68, C*m* 128.80, C*p* 128.40.

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7. The ^{13}C NMR data of compounds **1-4** are not reported in the literature:
1 C1 73.4, C2 65.1, C-CH_3 9.5, N-CH_3 41.5, C*i* 140.7, C*o* 126.3, C*m* 128.6, C*p* 128.6.
2 C1 72.1, C2 64.8, C-CH_3 9.2, N-CH_3 39.7, C*i* 140.7, C*o* 125.8, C*m* 128.6, C*p* 127.8.
3 C1 74.3, C2 64.4, C-CH_3 8.8, N-CH_3 41.6, C*i* 140.5, C*o* 126.9, C*m* 128.7, C*p* 128.4.
4 C1 73.9, C2 63.1, C-CH_3 8.3, N-CH_3 32.9, C*i* 140.4, C*o* 126.7, C*m* 128.5, C*p* 128.2.
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9. Crystal data: **7** {$C_{13}H_{22}INO$}, FW 335.23, system orthorhombic P, space group $P2_12_12_1$, a 7.959(0) Å, b 17.119(1) Å, c 11.063(0) Å, $\alpha^\circ = \beta^\circ = \gamma^\circ =$ 90.00, V 1507.4 Å, Z 4, radiation MoKα, μ 20.8 cm^{-1}, d calc 1.48 gcm^{-3}, 2θ range 2.8-50.0, scan type w/2θ, scan width 0.6 + 1.500 tan θ, scan speed 2.0<sp<20.0 $^\circ m^{-1}$, reflections collected 2964, unique reflections 2964, abs. coef. corr. 0.821<coeff<0.923, no. of reflections with I>3σ(I) 2964, R 0.041, RW 0.038, weighting scheme unity, no. of variables 211, diffractometer CaD4F.
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