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X-Ray Crystallographic and Proton Nuclear Magnetic Resonance Studies of β-Hydroxy-*N*-nitrosamines derived from α-Amino Acids and Ephedrine

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Abstract—β-Hydroxy-*N*-nitrosamines derived from L-leucine, L-valine, L-phenylalanine, D-phenylglycine and (1*R*,2*S*)-ephedrine have been synthesized and analyzed. These compounds all exhibit rotameric populations of (*E*)- and (*Z*)-stereoisomers that are a result of the barrier to rotation about the *N*-nitroso (N–N=O) group. A correlation is made between the X-ray crystallographic data of the *N*-nitroso-ephedrine derivative **6** and the ^{1}H NMR of the *N*-nitrosamines **4a**–**4d**. From this comparison, the identities and ratios of (*E*)- and (*Z*)-rotamers were unambiguously assigned. Finally, the ^{1}H NMR also provides some insight into the conformational changes that occur when the nitrosamine rotamers interconvert.

Introduction

In connection with an ongoing research project that focuses on the chemistry of chiral, non-racemic tetrahydro-1,3,4-oxadiazin-2-ones, several β-hydroxy-*N*-nitrosamines were prepared. The *N*-nitrosamines represent a large class of compounds that are of interest because they are known to have carcinogenic properties.[1] Nonsymmetrical *N*-nitrosamines such as β-hydroxy-nitrosamines exists as (*E*)- and (*Z*)-rotamers due to the stereochemical nature of the N–N=O moiety. As with amides[2a] and carbamates,[2b] contributing resonance structures are invoked as giving rise to the barrier of rotation (Fig. 1).

In the course of our synthesis efforts we were faced with the interesting problem of assigning the identity and ratios of the rotamers. Karabatsos and Taller had conducted earlier studies on the assignment of (*E*)- and (*Z*)-stereochemistry of *N*-nitrosamines based on comparative ^{1}H NMR studies.[3] Herein we report on the ^{1}H NMR and X-ray crystallographic data of a representative *N*-nitrosamine derived from (1*R*,2*S*)-ephedrine. These data are compared to the ^{1}H NMR data of β-hydroxy-*N*-nitrosamines derived from α-amino acids.

Results and Discussion

The α-amino acids **2a**–**2d** [**2a**: R=$(CH_3)_2$CH– (L-Val); **2b**: R=$PhCH_2$– (L-Phe); **2c**: R=$(CH_3)_2CHCH_2$– (L-Leu); **2d**=Ph– (D-Phg)] were acylated with benzoyl chloride in basic media to afford the corresponding *N*-benzoylated α-amino acids (Scheme 1). These compounds were then cleanly reduced to the *N*-benzyl-*vic*-aminoalcohols **3a**–**3d** by using the protocol originated by Kanth[4a] and Periasamy and developed by Meyers[4b] (B_2H_6/tetrahydrofuran generated in situ from $NaBH_4$ and I_2, Scheme 1). The *N*-benzyl-*vic*-aminoalcohols were treated with *tert*-butyl nitrite[5] in

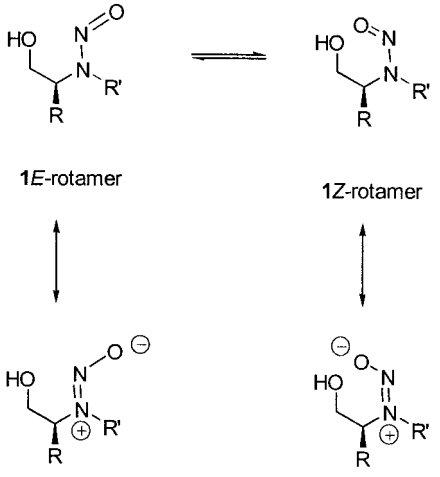

Figure 1. The (*E*)- and (*Z*)-rotamers of the β-hydroxy-*N*-nitrosamines.

Keywords: nitrosamines; X-ray crystallography; conformation.
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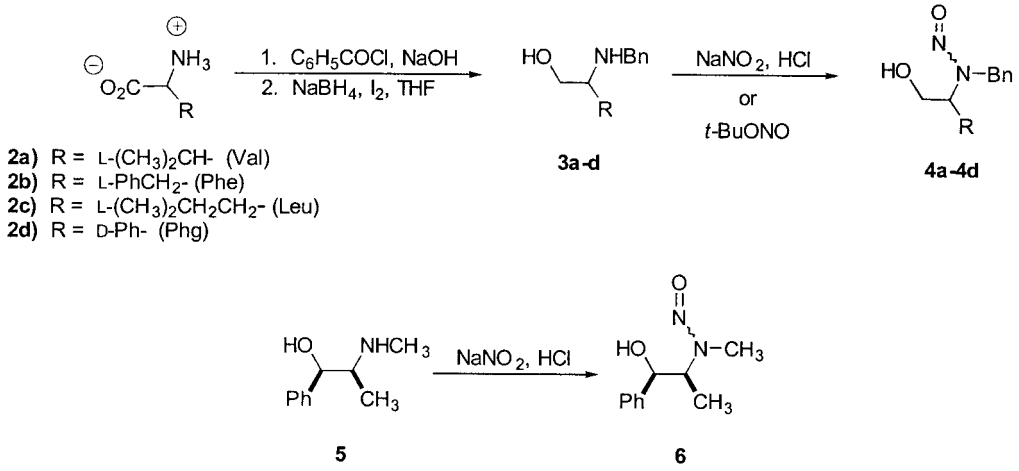

Scheme 1. Synthesis of the *N*-nitrosamines **4a**–**4d** and **6**.

anhydrous diethyl ether to afford β-hydroxy-*N*-nitrosamines **4**. These conditions were satisfactory in the case of **3a** and **3c**. However, the remaining aminoalcohols were not soluble in the reaction medium. Consequently, the aminoalcohols **3b** and **3d** were treated with sodium nitrite ($NaNO_2$) in the presence of an aqueous HCl/THF mixture to afford the corresponding β-hydroxy-*N*-nitrosamines **4b** and **4d** in good yield.[6] In like fashion, (1*R*,2*S*)-ephedrine (**5**) was cleanly nitrosated ($HCl/NaNO_2$) to afford the *N*-nitrosoephedrine derivative **6**.

Attempts to grow crystals of β-hydroxy-*N*-nitrosamines **4a**–**d** suitable for X-ray crystallography studies were not successful. Fortunately, a suitable crystal of *N*-nitrosoephedrine (**6**) was grown by slow diffusion of hexanes into a CH_2Cl_2 solution of **6** at room temperature. The molecular structure of **6** is represented in Fig. 2.

The *N*-nitroso group, N2–O1, has a bond distance of 1.23(1) Å, which is consistent with its formal double bond, but the N1–N2 distance of 1.302(8) is closer to a double bond than a single bond. An average distance of the N–N bond in *N*-nitrosamines is 1.31 Å.[7] The bond angles about N1 (i.e. C2–N1–C1, 121.7(6)°; C2–N1–N2, 114.2(6)° and C1–N1–N2, 124.1(6)° are closer to that expected for a sp^2 hybridized nitrogen rather than an sp^3 hybridized nitrogen suggesting that the pair of electrons formally located on N1 are delocalized as would be expected for *N*-nitrosamines.[7] In terms of the overall conformation of the *N*-nitrosoephedrine, the C2–N1–C1–N2–O1 group has a mean plane deviation of 0.0013 Å with C2 the farthest from the plane, 0.0125(0.0062) Å. The angle between the mean planes of the aromatic residue C5–C6–C7–C8–C9–C10 and the nitroso moiety C2–N1–C1–N2–O1 is 53.8(3.4)°. Intermolecular hydrogen bonding (O2–H2…O1′) is evidenced by the following bond distances and bond angle: O2–H2, 1.088(5) Å; H2…O1, 1.942(6) Å; O2…O1, 3.023(8) Å and a bond angle of O2–H2…O1, 172.1(3)°. There is also a weaker interaction between H2 and N2: H2…N2, 2.122(6) Å; O2–H2…N2, 3.082(8) Å and an O2–H2…N2 angle of 145.6(4)°. This latter interaction also helps to draw electron density away from N1 as discussed above.

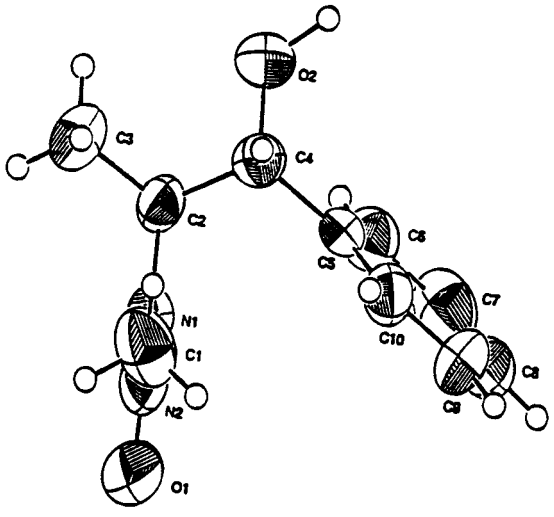

Figure 2. ORTEP diagram of **6** (50% probability ellipsoids).

Correlation of the X-ray crystal structure with the ^1H NMR unambiguously establishes the identities of the rotamers. The X-ray crystallographic data describe a molecular geometry that corresponds to the *E*-rotamer (Fig. 1) for the *N*-nitrosoephedrine (**6**). Based on X-ray crystallographic analysis, the identities of the individual rotamers can then be easily assigned in the 400 MHz ^1H NMR spectrum. The major isomer that was analyzed by X-ray crystallographic analysis is the major isomer in the ^1H NMR spectrum. Specifically, there are two diagnostic peaks in the ^1H NMR that are employed in determining the identity and ratio of rotamers (Fig. 3). The diagnostic signals for ***Z*-6** and ***E*-6** are based on the methyl group bonded to the N–N═O moiety. The resonance signal that represents the major rotamer for ***E*-6** occurs at 3.02 ppm and the signal that represents the minor rotamer occurs at 3.78 ppm (***Z*-6**-isomer). In the case of the *E*-rotamer, the methyl group is in the shielding region of the *N*-nitroso group, whereas the methyl group is not in the shielding region of the nitroso group in the *Z*-rotamer. This system where the *E*-rotamer alkyl group is shielded and *Z*-rotamer alkyl group is not shielded provides the basis for the determination of the identities and ratios of isomers for the nitrosamines (Table

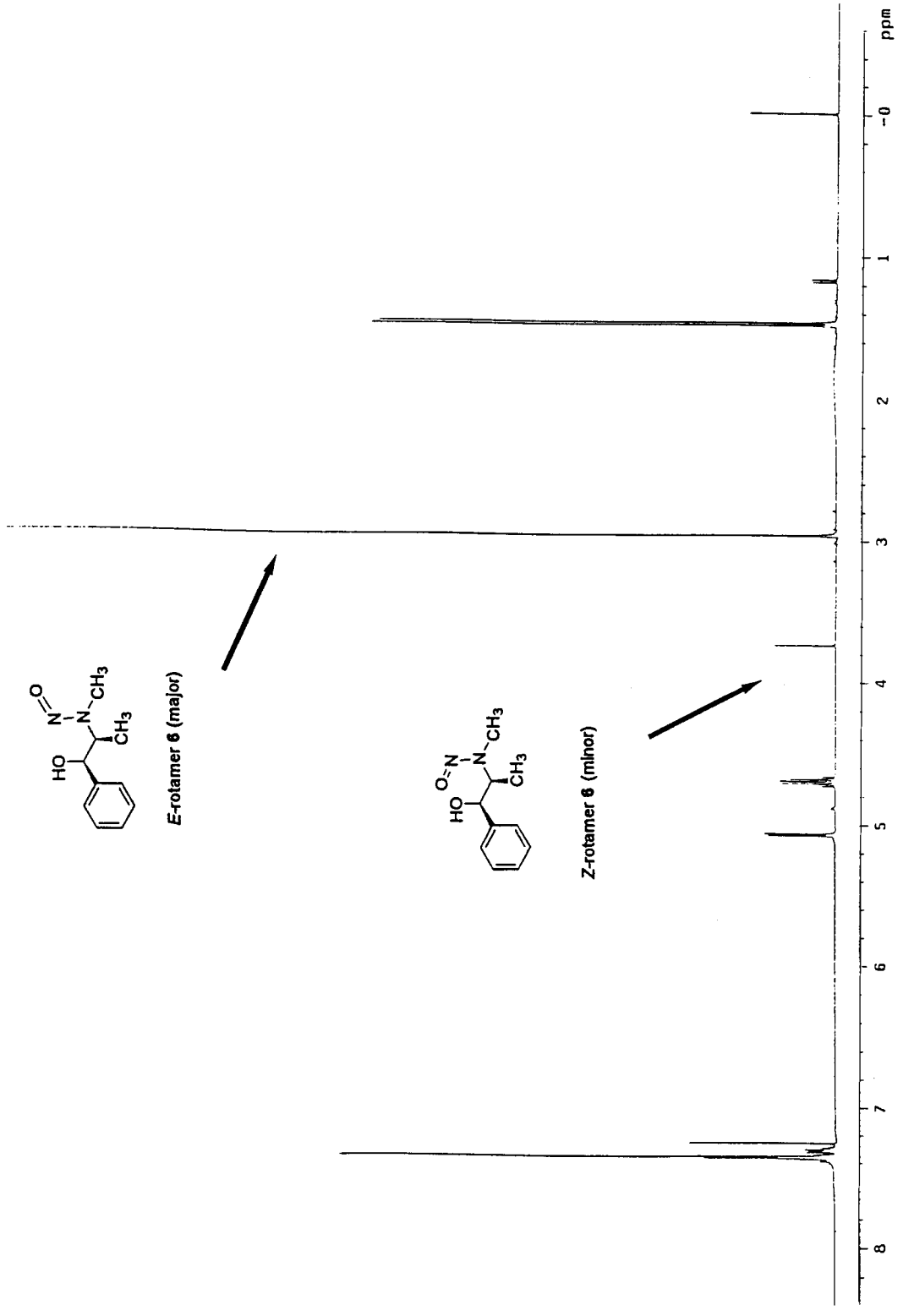

Figure 3. 400 MHz ^{1}H NMR spectrum of *N*-nitrosoephedrines, *E*-**6** and *Z*-**6**.

Table 1. 400 MHz ^{1}H NMR data for **4a**–**d** and **6**

Compound	δ (center)	Description	$\Delta\nu$ (Hz)	J (Hz)
E-**4a** (major isomer)	4.82	*AB* quartet	48	14
Z-**4a** (minor isomer)	5.23	singlet	–	–
E-**4b** (major isomer)	4.72	*AX*	170	14.8
Z-**4b** (minor isomer)	5.14	*AB*	112	15.2
E-**4c** (major isomer)	4.74	*AB*	96.7	14.6
Z-**4c** (minor isomer)	5.3	*AB*	62	16
E-**4d** (major isomer)	4.7	*AX*	647	14.7
Z-**4d** (minor isomer)	5.2	*AX*	208	16
E-**6** (major isomer)	3.02	singlet	–	–
Z-**6** (minor isomer)	3.78	singlet	–	–

1). It was determined that in all cases the major isomer is the *E*-rotamer. This observation agrees with the general trend that steric forces control the orientation of the *N*-nitroso group.[3]

The ^{1}H NMR resonance signal of interest in the case of the *N*-nitrosamines derived from the α-aminoacids is that of the methylene unit of the benzyl group ($-CH_2Ph$) attached to the N–N=O moiety. This resonance signal offers considerably more intrinsic information on structural features as compared to that of the resonance signal of the methyl group that is present in the ephedrine-nitrosamine **6**. Under both (*E*)- and (*Z*)-conformational circumstances, the diagnostic methyl group of **6** appears as a singlet. In contrast, the benzyl group is a better reporter of its immediate surroundings because of the diastereotopic relationship of the hydrogens.

In the case of the L-valine derived nitrosamine the major rotamer, ***E*-4a**, shows a diagnostic *AB*quartet centered at 4.82 ppm with a coupling constant of J=14.0 Hz and $\Delta\nu$=48 Hz in the 400 MHz ^{1}H NMR spectrum (Fig. 4). The corresponding minor rotamer ***Z*-4a** has a diagnostic resonance signal that is a singlet centered at 5.23 ppm. This apparent change in the nature of the signal may represent a major conformational change to alleviate torsional strain induced by the presence of the sterically demanding isopropyl group. In contrast to the valine based **4a** system, the 400 MHz ^{1}H NMR spectrum of the major rotamer of the phenylalanine derived β-hydroxy-*N*-nitrosamine ***E*-4b** (Fig. 5) shows an *AX* spin system centered at 4.72 ppm with a coupling constant of 14.8 Hz and a $\Delta\nu$=170 Hz. The ^{1}H NMR spectrum of the minor isomer ***Z*-4b** shows an *AB* spin system centered at 5.14 ppm with a coupling constant of 15.2 Hz and a $\Delta\nu$=112 Hz. This similarity of the signals would seem to indicate that there is no major conformational change (Fig. 5). This is not surprising considering that the phenylalanine derivative does not have the bulky isopropyl group present.

The ^{1}H NMR of the major rotamer of the L-leucine derived *N*-nitrosamine ***E*-4c** shows an *AB* spin system centered at 4.74 ppm with a coupling constant of 14.6 Hz and $\Delta\nu$=96.7 Hz. The ^{1}H NMR of the minor isomer ***Z*-4c** is centered at 5.30 ppm with a coupling constant of 16.0 Hz and a $\Delta\nu$=62 Hz. This system is a reflection of the phenylalanine system. The steric environments of the leucine derivative [R=$-CH_2CH(CH_3)_2$] and phenylalanine derivative [R=$-CH_2Ph$] are similar and it is expected that the proton NMR would represent this. Furthermore, the conformational changes that these molecules would undergo would be similar (Fig. 6).

The D-phenylglycine nitrosamine derivative has the most striking ^{1}H NMR of this set of compounds. The ^{1}H NMR of the major rotamer ***E*-4d** shows a resonance signal at 4.74 ppm with a coupling constant of 14.7 Hz and $\Delta\nu$=647 Hz. The ^{1}H NMR spectrum of the corresponding minor rotamer ***Z*-4d** is centered at 5.20 ppm with a coupling constant of 16.0 Hz and a $\Delta\nu$=207.3 Hz. The *AX* spin system for the minor isomer ***Z*-4d** is positioned in between the doublets of the ***E*-4d** rotamer. The broad $\Delta\nu$ may be an indication that the aromatic ring is rotated away from plane of the nitroso group to alleviate any steric strain. This rotation away from the plane most likely extends the diagnostic benzyl group ($-CH_AH_BPh$) resonance signals further into the shielding (H_A: δ=3.83 ppm) and deshielding (H_B: δ=5.49 ppm) region of the proton NMR. The phenylglycine derivative is more closely related to the valine derivative in that there is a significant change in conformation based on the reporter group.

Fig. 6 represents potential conformations that the *N*-nitrosamines may adopt in the *E*-rotamer and *Z*-rotamer. These conformations have been constructed based on the earlier independent works of Karabatsos[3] and Nauman.[8] Karabatsos demonstrated that the methylene protons that are *syn* to the oxygen of the N–N=O group resonate at higher fields and the methylene protons that are *anti* resonate at lower fields. Consequently, the preferred conformation of the methylene group of *N*-nitrosamines **4a**–**4d** must be in or near the plane of the nitroso group. Nauman showed that the conformation of *N*-nitrosamines is also dependent on the steric interactions of the two alkyl substituents, R_1 and R_2, that span the *N*-nitroso group (R_1R_2N–N=O). The *N*-nitrosamines in Fig. 6 have been arranged so that there are no major steric interactions across the span of the nitroso group. This arrangement leaves the appended alcohol in an *anti*-conformation relative to the nitroso group. The conformations of Fig. 6 also reflect information gathered from the X-ray crystallographic data of *N*-nitrosamine **6**.

In regard to the factors that contribute to the conformational analysis of the *N*-nitrosamines of this work, the argument is made that the optimal conformation of the *N*-nitrosamines depends on the orientation of the N–N=O group, steric interactions across the span of the *N*-nitroso group and to a lesser degree hydrogen bonding. There is clearly intermolecular hydrogen bonding (O–H…O=N) in the solid state but there is no apparent indication of such extensive hydrogen bonding in the solution state of the NMR samples. The hydrogen bonding observed in the solid state may be a consequence of the conformation that is adopted by *N*-nitrosamine rather than a result of hydrogen bonding forces dictating the overall conformation. Another consideration that must be taken into account is that of intramolecular hydrogen bonding in the solution state. Intramolecular hydrogen bonding (O–H…N=O) significantly increases the non-bonding steric interactions across the N–N=O span and so is considered to play a very minor role if any. These statements do not entirely rule out different modes of hydrogen bonding. There is still a possibility

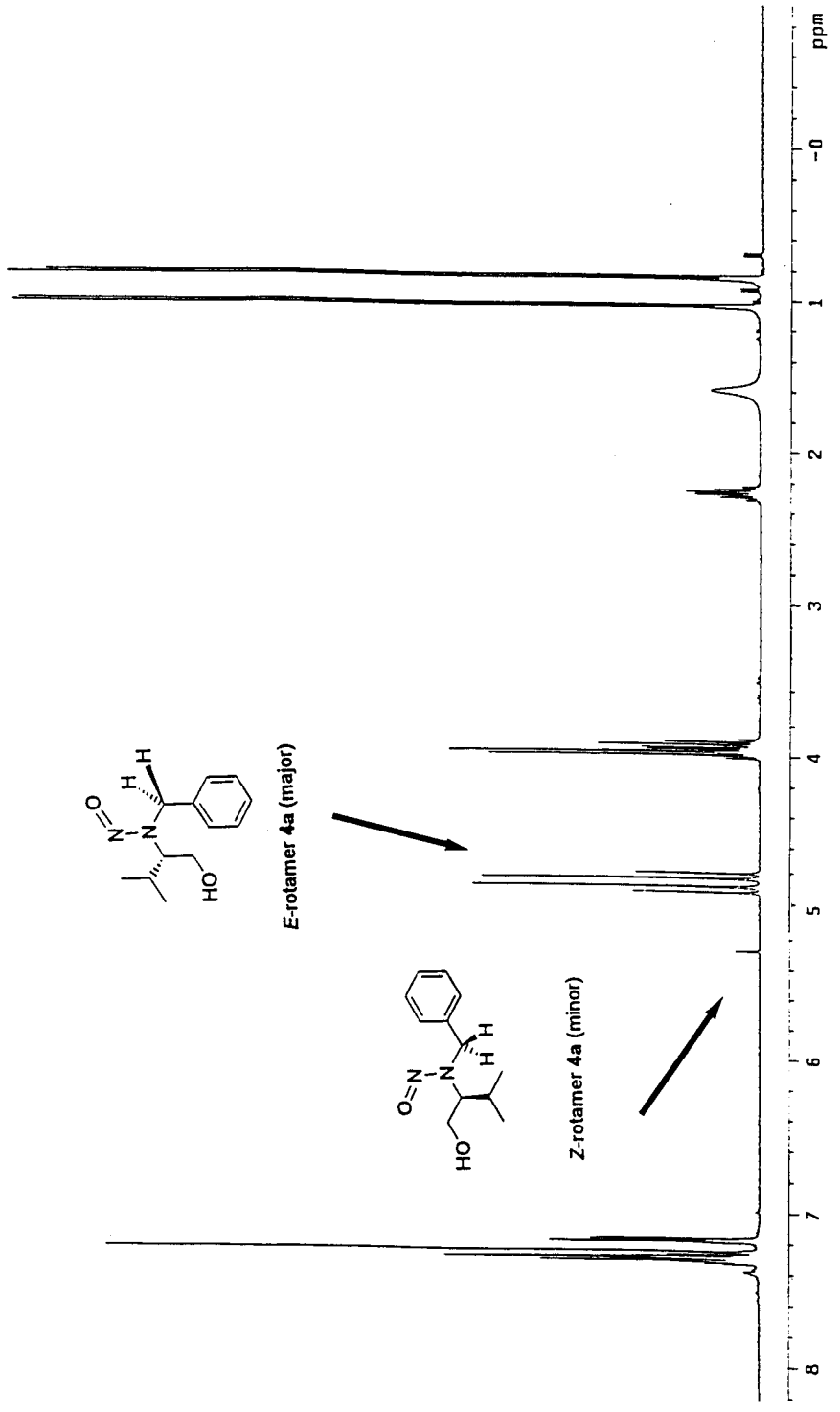

Figure 4. 400 MHz ^{1}H NMR spectrum of β-hydroxy-*N*-nitrosamine **4a**.

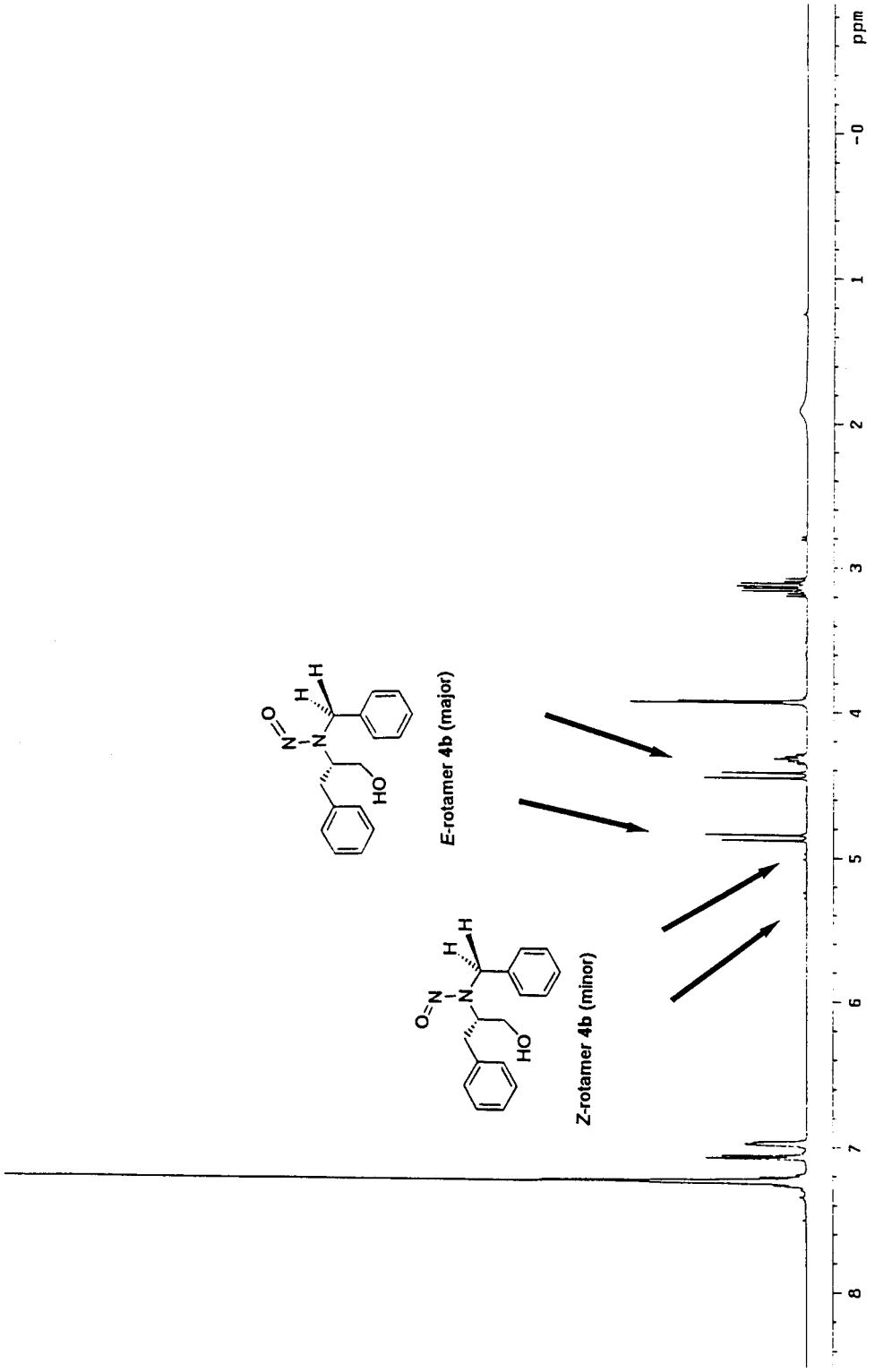

Figure. 5. 400 MHz ^{1}H NMR spectrum of β-hydroxy-*N*-nitrosamine **4b**.

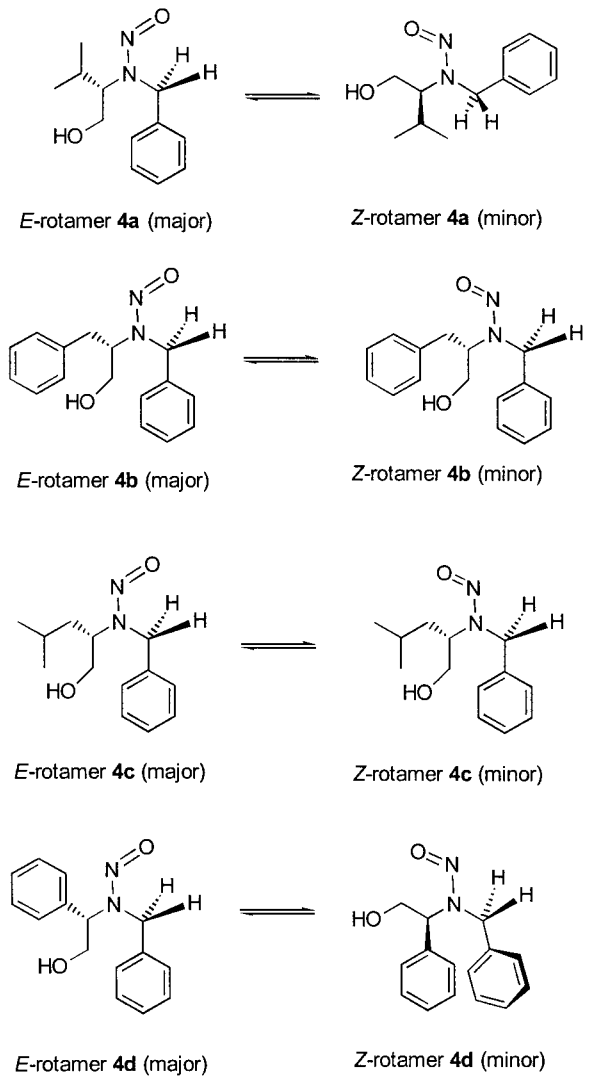

Figure. 6. Potential conformational changes in the β-hydroxy-*N*-nitrosamines.

that some hydrogen bonding does occur but it is not the major factor that controls the overall conformation.

Conclusion

In summary, we have synthesized several examples of β-hydroxy-*N*-nitrosamines derived from commercially available α-amino acids and ephedrine. X-Ray crystallographic analysis of the ephedrine derived *N*-nitrosamine confirmed that the major rotamer was the *E*-rotamer and that there is intermolecular hydrogen bonding in the solid state. Correlation of the X-ray crystallographic data to ^{1}H NMR data provides a reliable means of determining the rotameric identity and ratio of β-hydroxy-*N*-nitrosamines derived from the α-amino acids. The (*E*)- and (*Z*)-conformations illustrated in Fig. 6 attempt to take into account the collected ^{1}H NMR evidence, the X-crystallographic data and literature precedents. Specifically, the *N*-benzyl group provides some insight into the conformational changes that occur in the β-hydroxy-*N*-nitrosamines especially in the cases of the L-valine and D-phenylglycine.

Experimental

General remarks

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from a potassium/sodium amalgam containing benzophenone ketyl. Methylene chloride (CH_2Cl_2) was distilled from calcium hydride. Lithium aluminum hydride was purchased from Aldrich Chemicals. Flash chromatography was conducted with silica gel purchased from Selecto Scientific (32–63 mesh). All ^{1}H and ^{13}C NMR spectra were recorded at 25°C on a Varian spectrometer in $CDCl_3$ operating at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (δ scale), and coupling constants (J values) are listed in hertz (Hz). Infrared spectra are reported in reciprocal centimeters (cm^{-1}) and are measured either in chloroform or as a KBr window. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Low resolution gas chromatography was performed on a Hewlett–Packard Instrument (G1800A/GCD) with an ionization voltage of 70 eV; peaks are reported as m/z (% intensity relative to the base peak). Elemental analyses were conducted by Galbraith Laboratories Inc., Knoxville, TN.

Crystal structure determination[9]

A prismatic crystal of *N*-nitrosoephedrine (**6**) was grown by slow diffusion of hexanes into a CH_2Cl_2 solution of **6** at room temperature. This crystal was mounted on a glass fiber and used for data collection at 293 K on a Nonius MACH3 automatic diffractometer (MoKα, λ= 0.71073 Å). Cell constants and an orientation matrix for data collection were obtained by least squares refinement of the diffraction data from 25 reflections. The structure was solved with direct methods and missing atoms were found by difference-Fourier synthesis. All non-hydrogen atoms were refined with anisotropic temperature factors and the hydrogen attached to oxygen was found on the difference Fourier map. The H atoms attached to carbons were fixed at d=0.96 Å, allowed to ride on the C atoms and assigned fixed isotropic temperature factor, U=0.05 Å^2. The coordinates of the H atom attached to O were refined isotropically. Refinement of the structures was made by full-matrix least-squares on F. Scattering factors are from Wassmaire and Kirfel,[10] calculations were done by maXus, version 2.0,[11] and graphics are Platon for Windows.[12]

General procedure for the reduction of the *N*-benzoylated α-amino acids 3a–3d

In a dry 1L 3-neck flask fitted with a reflux condenser and addition funnel was added $NaBH_4$ (4.05 g, 107 mmol) and freshly distilled THF (200 mL) under a nitrogen atmosphere. The α-amino acid (44.6 mmol) was then added in one portion. The addition funnel was charged with a solution of iodine (11.3 g, 44.6 mmol) in THF (100 mL). The iodine was then added dropwise and upon complete addition the mixture was heated to reflux for 12 h. The reaction was cooled to room temperature and then quenched by the addition of methanol (50 mL) to destroy any remaining diborane. The solvent was then removed by rotary evaporation to yield a white paste. The paste was dissolved

in an aqueous solution of KOH (2 M, 100 mL) and stirred for 45 min. The mixture was then diluted with EtOAc (100 mL) and the layers were separated. The organic layer was then washed with an aqueous saturated solution of brine (50 mL), dried ($MgSO_4$) and the solvent was removed by rotary evaporation to produce the desired β-amino alcohol.

(2*S*)-*N*-Benzyl-2-amino-3-methyl-1-butanol (3a). Compound **3a** was obtained as a colorless oil in 89% yield (7.60 g, 39.6 mmol): ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3H, J=6.6 Hz), 0.99 (d, 3H, J=6.6 Hz), 1.89 (m, 1H), 2.23 (s, 1H), 2.50 ('t', 1H, J=6.6 Hz), 3.39 (dd, 1H, J=7.0, 3.7 Hz), 3.66 (dd, 1H, J=10.6, 4.0 Hz) 3.81 (*AB* spin system, 2H, J=12.8, 7.3 Hz), 7.25–7.30 (m, 3H), 7.35 (d, 2H, J=4.4 Hz); ^{13}C NMR ($CDCl_3$) δ 18.2, 19.3, 28.6, 51.1, 60.1, 63.5, 126.6, 127.7, 128.0, 139.8; IR (neat): 3415, 2965 cm^{-1}; GC-MS (EI): *m/z* (% rel. abundance) 192 (1), 162 (33), 91 (100).

(2*S*)-*N*-Benzyl-2-amino-3-phenyl-1-propanol (3b). Compound **3b** was obtained as a waxy solid that was recrystallized by the addition of hexanes and by slow cooling down to 4°C. In this way, *N*-benzoylphenylalanine (14.2 g, 52.8 mmol) afforded the title product as a crystalline wax (10.1 g, 84%). Mp: 67–68°C; ^{1}H NMR ($CDCl_3$) δ 2.08 (br s, 1H), 2.80 (dd, 1H, J=10.0, 7.0 Hz), 2.76 (dd, 1H, J=39, 7.0 Hz), 2.94–3.00 (m, 1H), 3.34 (dd, 1H, J=9.0, 5.0 Hz), 3.65 (dd, 1H, J=10, 4 Hz), 3.78 (s, 2H), 7.15–7.32 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 38.5, 51.2, 59.5, 62.6, 126.4, 127.1, 128.0, 128.5, 128.6, 129.2, 138.4, 140.0; IR (KBr): 3279, 3022, 2995 cm^{-1}; GC-MS (EI): *m/z* (% rel. abundance) 240 (1), 91 (100).

(2*S*)-*N*-Benzyl-2-amino-4-methyl-1-pentanol (3c). L-*N*-Benzoylleucine (8.00 g, 34.0 mmol) afforded compound **3c** as a white crystalline solid after recrystallization from CH_2Cl_2/hexanes in 72% yield (5.23 g, 25.2 mmol. Mp: 58–59°C; ^{1}H NMR ($CDCl_3$) δ 0.90 ('t', 6H, J=6.8 Hz, diastereomeric methyl groups), 1.22–1.29 (m, 1H), 1.39–1.46 (m, 1H), 1.60–1.67 (m, 1H), 2.07 (s, 1H), 2.76 (dq, 1H, J=7.0, 2.9 Hz), 3.28 (dd, 1H, J=10.6, 6.2 Hz), 3.67 (dd, 1H, J=10.4, 3.6 Hz), 3.80 (*AB*q, 1H, J=12.8, 7.6 Hz), 4.70 (s, 1H), 7.33–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.7, 23.1, 25.0, 40.9, 50.8, 56.2, 63.0, 127.0, 128.0, 128.3, 139.5; IR (KBr) 3287, 3060, 2958 cm^{-1}; GC-MS (EI): *m/z* (% rel. abundance)190 (1), 176 (47), 91 (100).

(2*R*)-*N*-Benzyl-2-amino-2-phenyl-1-ethanol (3d). D-*N*-Benzoylphenylglycine (**2d**) (10.0 g, 39.2 mmol) yielded the corresponding β-aminoalcohol as an oil that was recrystallized using EtOAc/hexanes (6.85 g, 77% yield). Mp: 70–71°C; ^{1}H NMR ($CDCl_3$) δ 2.33 (broad s, 1H), 3.56 (*X* of *ABX*, 1H, $\Delta\nu_{AB}$=6.0 Hz, J=10.6 Hz), 3.70 (*AB* spin system, $\Delta\nu_{AB}$=63.0 Hz, J=13.0 Hz), 3.72 (dd, 2H, J=10.6, 4.4 Hz), 3.78 (dd, J=8.8, 4.4 Hz), 7.29–7.41 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 51.0, 63.6, 66.6, 126.8, 127.0, 127.4, 127.9, 128.1, 128.4, 139.6, 140.1; IR (neat) 3247, 1097, 978 cm^{-1}; GC-MS (EI): *m/z* (rel. abundance) 196 (52), 91 (100).

(2*S*)-*N*-Benzyl-*N*-nitroso-2-amino-3-methyl-1-butanol (4a). In a flame-dried, nitrogen purged round bottom flask was placed *N*-benzylvalinol **3a** (10.5 g, 54.4 mmol) and freshly distilled diethyl ether (5 mL). *tert*-Butyl nitrite (16.8 mL, 136 mmol) was then added by syringe. The mixture was then heated to reflux for 12 h followed by cooling to room temperature and removal of the solvent by rotary evaporation to yield a viscous oil. The oil was determined to be a mixture of *E* and *Z* isomers (~8.5:1 ratio, ca. 89% *E-rotamer*). The material was crystallized by cooling to 4°C in a solution of hexanes and CH_2Cl_2 to yield white crystals in 67% yield (8.04 g). Mp: 56–58°C; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3H, J=7.0 Hz), 1.04 (d, 3H, J=7.0 Hz), 1.60 (br s, 1H), 2.30 (m, 1H, J=6.8 Hz), 3.99 (m, 1H), 4.04 (d, 2H, J=7.2 Hz), 4.82 (*AB*q, 2H, $\Delta\nu$=48.0 Hz, J=14.0 Hz), 7.17–7.20 (m, 2H), 7.27–7.34 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.2, 29.8, 49.9, 63.5, 72.2, 129.0, 129.5, 129.9, 135.8; IR (KBr) 3209, 2980, 1438, 1018 cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.53; H, 8.29; N, 12.49.

(2*S*)-*N*-Benzyl-*N*-nitroso-2-amino-3-phenyl-1-propanol (4b). (*S*)-*N*-Benzylphenylalanol (**2b**) (2.07 g, 8.59 mmol) was dissolved in THF (15 mL) and an aqueous solution of HCl (7.20 mL, 19.7 mmol). To this reaction mixture was added sodium nitrite (0.651 g, 9.45 mmol) in small portions. The reaction stirred for 12 h before dilution with EtOAc (50 mL) and an aqueous solution of HCl (3 M, 50 mL). The layers were separated and the organic layer was extracted with an aqueous saturated solution of brine (50 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed via rotary evaporation. The crude residue was dissolved in the minimum amount of CH_2Cl_2 followed by the addition of hexane. This solution was allowed to stand at room temperature and crystal formation occurred after several hours. This process afforded the title compound as a mixture of *E* and *Z* isomers (~5.7:1 ratio, ca. 85% *E-rotamer*) in 73% yield (1.70 g). Mp: 81–82°C; ^{1}H NMR ($CDCl_3$) δ 1.79 (br s, 1H), 2.83 (d, 1H, J=7.3 Hz), 3.20 (*AB* of *ABX*, 2H, $\Delta\nu_{AX}$=22.4 Hz, $\Delta\nu_{BX}$=14.0 Hz, J_{AB}=14.1 Hz), 3.96 (d, 2H, J=6.0 Hz), 4.72 (*AX* spin system, 4H, $\Delta\nu_{AX}$=170 Hz, J=14.8 Hz,), 7.00 (s, 2H), 7.01 (d, 2H, J=7.3 Hz), 7.25–7.38 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 38.7, 49.7, 65.3, 67.4, 128.0, 129.0, 129.3, 129.8, 129.9, 130.0, 130.2, 135.0, 138.0; IR (KBr) 3343, 3087, 2924 cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 70.93; H, 6.70; N, 10.34. Found: C, 70.71; H, 6.70; N, 10.26.

(*S*)-*N*-Benzyl-*N*-nitroso-2-amino-4-methyl-1-pentanol (4c). In a flame-dried, nitrogen purged round bottom flask containing a stir bar was placed (*S*)-*N*-benzylleucinol (**3c**) (4.10 g, 19.8 mmol) and CH_2Cl_2 (15 mL). To this reaction mixture was added *tert*-butylnitrite (5.3 mL, 44 mmol) via syringe. This reaction mixture was allowed to stir for 12 h at reflux and the solvent removed under reduced pressure to afford the title compound as an oil. The crude reaction material is a mixture of *E* and *Z* rotamers (~8.5:1 ratio, ca. 90% *E-rotamer*). The residue was chromatographed (SiO_2, 3:2 hexanes/EtOAc; column dimensions 11×5 cm; 28 fractions at 3 mL each) to afford the product in 76% yield (3.54 g): ^{1}H NMR ($CDCl_3$) δ 0.84 (dd, 6H, J=8.0, 5.9 Hz), 1.78 (br s, 1H), 3.85 (d, 2H, J=6.2 Hz), 4.47–4.50 (m, 1H), 4.84 (*AX* spin system, 2H, $\Delta\nu_{AB}$=96.7 Hz, J=14.6 Hz), 7.16–7.18 (m, 1H), 7.28–7.38 (m, 4H); ^{13}C NMR ($CDCl_3$) δ IR (KBr): 3404, 3031, 2957, 1452 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85. Found: C, 65.53; H, 8.74; N, 11.72.

(*S*)-*N*-Benzyl-*N*-nitroso-2-amino-2-phenyl-1-ethanol (4d). (*S*)-*N*-benzylphenylglycinol (**3d**) (2.0 g, 8.8 mmol) was dissolved in THF (10 mL) and an aqueous solution of HCl (6.40 mL, 17.6 mmol). To this reaction mixture was added sodium nitrite (0.638 g, 9.25 mmol) in portions. The reaction stirred for 12 h before dilution with EtOAc (50 mL) and an aqueous solution of HCl (3 M, 50 mL). The layers were separated and the organic layer was extracted with an aqueous saturated solution of brine (50 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed via rotary evaporation. The crude residue was dissolved in the minimum amount of CH_2Cl_2 followed by the addition of hexanes. This solution was allowed to stand at room temperature and crystal formation occurred after several hours. This process afforded the title compound as a mixture of *E* and *Z* isomers (~12.5:1 ratio, ca. 92% *E-rotamer*) in 53 % yield (1.20 g). Mp: 55–56°C; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 1H), 4.12 (dd, 1H, J=11.7, 4.8 Hz), 4.49 (dd, 1H, J=12.4, 8.4 Hz), 5.1 (dd, 1H, J=8.4, 4.4 Hz), 4.70 (*AX* spin system, 4H, $\Delta\nu_{AB}$=647 Hz, J=14.7 Hz), 7.03–7.05 (m, 2H), 7.21–7.23 (m, 2H), 7.28–7.3 (m, 3H), 7.38–7.40 (m, 3H); ^{1}H NMR (CD_3OD) δ 4.05 (dd, 3H, J=10.0, 5.7 Hz), 4.41 ('t,' 3H, J=8.8 Hz), 4.71 (*AX* spin system, 4H, $\Delta\nu_{AB}$= 303 Hz, J=14.8 Hz), 5.24 (dd, 3H, J=6.5, 5.5 Hz), 6.99–7.02 (m, 3H), 7.18–7.20 (m, 2H), 7.24–7.27 (m, 2H), 7.30–7.33 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 48.2, 65.7, 69.7, 128.5, 129.0, 129.3, 129.9, 130.0, 130.2, 134.8, 136.8. Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.99; H, 6.34; N, 10.92.

(1*R*,2*S*)-*N*-Methyl-*N*-nitroso-2-amino-1-phenyl-1-propanol (6). In a 100 mL round bottom flask equipped with a stir bar was placed (1*R*,2*S*)-(+)-ephedrine (**5**) (20.00 g, 121.0 mmol) and THF (40 mL). After the mixture became homogeneous an aqueous solution of HCl (100 mL, 1 M, 100 mmol) was added, followed by the addition of sodium nitrite (9.186 g, 133.1 mmol) in small portions over 10 min. and stirred for 24 h. The mixture was then diluted with a saturated aqueous solution of $NaHCO_3$ (60 mL). The reaction mixture was then extracted with EtOAc (3×60 mL) and the extract was washed with saturated aqueous NaCl (50 mL). The resulting solution was dried (Na_2SO_4) and the solvent was removed by rotary evaporation. This yielded a yellow solid which was recrystallized with using a mixture of CH_2Cl_2 and hexanes to yield a yellow crystalline solid (20.99 g, 89%): Mp=92–94°C. ^{1}H NMR ($CDCl_3$): 1.47 (d, 3H, J=6.96 Hz), 2.40 (bs, 1H), 2.96 (s, 3H), 4.69 (m, 1H), 5.07 (d, 1H, J=5.1 Hz), 7.35–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): 13.4, 31.4, 65.3, 74.6, 126.4, 128.4, 128.8, 141.0; IR (KBr): 3374, 2983, 1452; GCMS (EI): *m/z* (% rel. abundance) 159 (1), 105 (95), 77 (100).

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9. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. The atomic coordinates and equivalent isotropic displacement coefficients are included in the deposited material (CCDC 141801) as are a complete list of bond distances and angles. Copies of available material can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033 or e-mail: deposit@ccdc.am.ac.uk).

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