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Highly Regio- and Stereoselective Formation of 2-Hydroxy-5,6-dihydro-2H-1,4-oxazines. An X-Ray and ^{13}C NMR Study.

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Abstract: (-)-Norephedrine and (-)-norpseudoephedrine undergo condensation with a wide variety of 1,2-diketones to yield the corresponding 2-hydroxy-5,6-dihydro-2H-1,4-oxazines with high regio- and stereoselectivity. The X-ray structure analysis of five of the compounds studied shows that the stereochemistry at the newly formed stereogenic center is S in all cases.

Previous investigations of the condensation of 1,2-diketones with β–aminoalcohols have shown that these reactions proceed with high regio- and stereoselectivity to afford a wide variety of products.[1,2] The products described so far include acyclic, mono, di- and tricycles, the more versatile reaction being that of ethanolamine with butanedione which affords: α–diimine complexes with transition metals[3], bisoxazolidines[4], *cis*-4a,8a-dimethyl-[1,4]oxazino-[3,2-b][1,4]oxazine and 2-hydroxy-5,6-dihydro-2,3-dimethyl-1,4-oxazine[1,5], 5,6,8,9-tetramethyl-1-aza-4,7,10-trioxatricyclo [4,3,0,$1^{5,9}$] decan-8-ol[6], as well as N-alkyl-2,3-epoxymorpholines and N-alkyl-2-morpholones.[2,7] Concerning this type of reactions, we have reported the preparation and characterization of isomeric five- and six- membered-fused bisheterocycles derived from ephedrine and pseudoephedine based on measurement of the ^{13}C satellite coupling constants in the 300 MHz NMR spectra.[8] The same method was also applied to the characterization of isomeric dibenzothiazolyl and benzothiazino-benzothiazine type structures.[9] A reinvestigation of the reaction of ethanolamine with butanedione lead us to the preparation of two additional tricyclic products[10] : 12,13-dimethyl-2,7-dioxa-5,10-diaza-tricyclo-[4.4.4.0]-*trans*-tetradecan-12,13-diol and N,N´-(4",5"-dimethyl)-1",2"-phenylene-2,2-dimethyl-bis-oxazolidine.

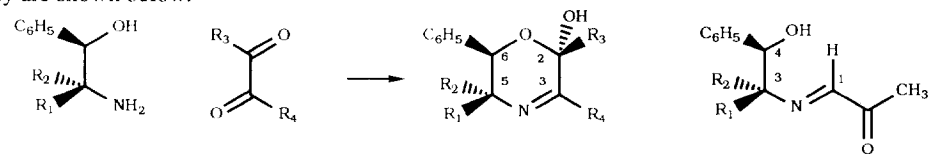
We report herein a systematic study of the condensation of eight 1,2-diketones with (1R,2S)-norephedrine and (1R,2R)-norspeudoephedrine, a pair of diastereomeric aminoalcohols which have found extensive applications in asymmetric synthesis.[11] The diketones studied include butanedione, 3,4-hexanedione, 1,2-cyclohexanedione, benzil, 2,3-pentanedione, 2,3-hexanedione, 1-phenyl-1,2-propanedione and pyruvic aldehyde.

The aim of the study was to investigate the reactivity of a wide range of diketones as well as the influence

of a change in configuration at the carbon supporting the amine group. The reactions proceed with high regio- and stereoselectivity to yield the corresponding 2-hydroxy-5,6-dihydro-1,4-oxazines, except for benzil and pyruvic aldehyde. The configuration at the newly formed stereogenic center was established by X-ray diffraction analysis of five of the oxazines described in this study.

RESULTS AND DISCUSSION

The reactions were carried out using equimolar ratios of β-aminoalcohol to 1,2-diketone in ethylether for 10 to 30 min to give the corresponding 2-hydroxy-1,4-oxazine. In contrast to a previous report,[1] attempts to obtain bicyclic products by carrying out the reaction in a 2:1 molar ratio of β–aminoalcohol to 1,2-diketone under different reaction conditions failed to afford bisoxazolidine or oxazino-oxazine derivatives. In the case of symmetric diketones, the reactions were performed at room temperature while high regioselectivity was attained at 0°C with nonsymmetrical ketones. The structures of the 2-hydroxy-5,6-dihydro-2H-1,4-oxazines described in this study are shown below.



a R_1=CH_3 R_2=H
b R_1=H R_2=CH_3

1a R_3= R_4=CH_3
1b R_3= R_4=CH_3
2a R_3=R_4=CH_2CH_3
2b R_3=R_4=CH_2CH_3
3a R_4=CH_3, R_3=CH_2CH_3
3b R_4=CH_3, R_3=CH_2CH_3
4a R_4=CH_3, R_3=$CH_2CH_2CH_3$
4b R_4=CH_3, R_3=$CH_2CH_2CH_3$
5a R_4=CH_3, R_3=C_6H_5
5b R_4=CH_3, R_3=C_6H_5
6a R_3= R_4= $(CH_2)_4$
6b R_3= R_4= $(CH_2)_4$

7a

Conclusive evidence for the formation of 1,4-dihydrooxazines **1** to **6** was obtained from the ^{13}C nmr spectra which show signals at 166 and 96 ppm due to the C=N and ketal groups, respectively. Complete assignment of the ^{13}C nmr spectra of all oxazines was achieved by two dimensional $^1H[^{13}C]$ correlated spectra with the aid of homonuclear decoupling techniques. The ^1H and ^{13}C nmr data are summarized in the experimental section. In the case of the proton nmr spectra, a homonuclear five bond coupling constant (^5J = 2 Hz) between the pseudoaxial H-5 and the protons at the R_4 substituent is observed in norpseudoephedrine derived oxazines allowing unequivocal assignment of the methyl or methylene groups in **1b**, **2b**, **3b**, **5b** and **6b**. The corresponding five bond coupling of the pseudoequatorial hydrogen in norephedrine derivatives was sometimes observed. In accordance with the general trends, the CH_3-5 methyl group in norephedrine and norpseudoephedrine derivatives appears around 13 and 18 ppm, respectively. The H-5 and H-6 signals appear at lower field in norephedrine derivatives H-5, 3.70-3.89; H-6, 4.98-5.30) compared to norpseudoephedrine derivatives (H-5, 3.30-3.65; H-6, 4.27-4.52).

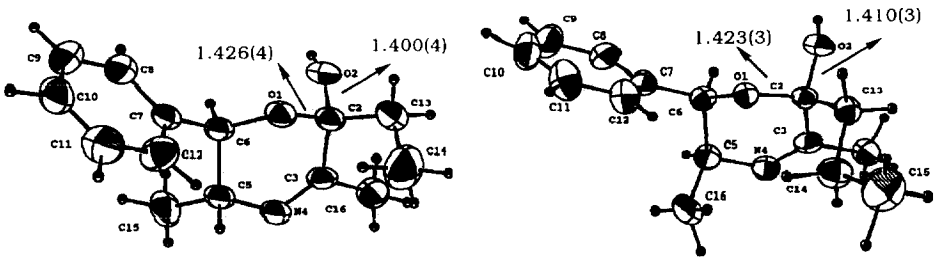
In the case of less reactive ketones such as benzil, the reaction was carried out in benzene at reflux, under this conditions the reaction was not stereoselective yielding a mixture of oxazines and oxazolidines, as evidenced

by ^{13}C NMR analysis of the crude reaction mixture which shows a signal at 196 ppm due to the carbonyl group present in the oxazolidine derivative.

Reaction of nonsymmetric 1,2-diketones at 0 ^{o}C favors exclusive formation of one of the isomers by attack of the amine to the more reactive and /or less hindered carbonyl group. Under these conditions the reactions proceed with high regio- and diastereselectivity. In contrast, the reaction of norephedrine and pyruvic aldehyde afforded a complex mixture of products among which the β-hydroxy-imino-ketone **7a** was isolated in low yields. The ^{1}H nmr spectrum of **7a** shows the existence of an equilibrium with the corresponding 1,3-oxazolidine.

The configuration at the newly formed stereogenic center (C-2) is S in all cases, as established by X-ray analysis of compounds **1a**, **4a**, and **6a**, derived from norephedrine, as well as **3b** and **5b** from norpseudoephedrine. The results can be rationalized by initial formation of an hydroxyimino-ketone intermediate having a Z stereochemistry which undergoes the 6-*exo-trig* ring closure (favored according to Baldwin's rules[12]), followed by attack of the hydroxyl group to the *Si* face of the carbonyl group, leading in all cases to a pseudoaxial hydroxyl group. This diastereoselectivity is not affected by a change in configuration at C-5.

Figure 1 shows the molecular perspectives for **3b** and **4a** Unit cell parameters and basic information about data collection and structure refinement are summarized in the experimental section. The X-ray structures of **1a**, **4a**, **6a**, **3b** and **5b** show that the hydroxyl group occupies a pseudoaxial position and is opposite to the phenyl group, while the phenyl group is pseudoequatorial. In all cases C-6 is in average 0.7 Å out of the plane formed by O1-C2-C3-N4-C5. Comparison of bond distances in all compounds shows that the O2-C2 length is shorter than the O1-C2 and both are significantly shorter when compared with the O1-C6 (in all cases the latter corresponds with the average C-O distance of 1.432 Å). The X-ray data is consistent with an exo-anomeric effect[13] which favors exclusive formation of a pseudoaxial hydroxyl group in this type of molecules.



3b **4a**

Figure 1 Perspective view of the molecular structures of compounds **3b** and **4a.**

In conclusion cyclization of β-aminoalcohols with a variety of 1,2-diketones proceeds with high regio- and diastereoselectivity to yield the corresponding 2-hydroxy-5,6-dihydro-2H-1,4-oxazine. The fact that both norephedrine and norpseudoephedrine provide a single diastereomer establishes that reaction is not influenced by a change in configuration at the carbon supporting the amino group. The phenyl group attached to the hydroxyl group directs the pathway of reaction, the exclusive product being that derived from the permitted 6-exo-ring closure.The stereochemistry at the newly form stereogenic center is S in all cases as establishes by X-Ray analysis.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded using JEOL FX90Q and JEOL GSX 270 spectrometers. Chemical Shifts (ppm) are relative to $(CH_3)_4Si$. Coupling constants are quoted in Hz. The HETCOR standard pulse sequence, which incorporates quadrature detection in both domains, was used. Infrared spectra were determined on a Perkin Elmer 16F spectrophotometer. Optical rotations were measured on a Perkin Elmer 241 polarimeter, $[\alpha]_D^{25}$ values are given in 10^{-1} deg cm^2 g^{-1}. Melting points were obtained on a Gallenkamp MFB-595 apparatus and are uncorrected.

A selected crystal was set upon an automatic diffractometer, unit cell dimensions with estimated standard deviations were obtained from least-squares refinements of the setting angles of 25 well centered reflections. Two standard reflections were monitored periodically; they showed no change during data collection,.. Corrections were made for Lorentz and polarization effects. Empirical absorption corrections (Difabs)[14] were applied. Computations were performed by using CRYSTALS[15] (**1a**, **5b** and **6a**) or MOLEN (**3b** and **4b**) adapted on Micro Vax II. Atomic form factors for neutral C, N, O and H were taken from ref 16.

The structures were solved by direct method using the SHELXS86[17] and MOLEN[18] programs. Hydrogen atoms were found on difference electron density maps. Their atomic coordinates were refined with an overall isotropic temperature factor in **1a** and **6a.** Anisotropic temperature factors were introduced for all non-hydrogen atoms, except for structure **5b** where all atoms were refined isotropically. Least-squares refinements with approximation in three blocks to the normal matrix (**1a**, **5b** and **6a**) or with full matrix (**3b** and **4b**) were carried out by minimizing the $\Sigma w(|F_0|-|F_C|)^2$, where F_0 and F_C are the observed and calculated structure factors. Unit weight was used. Models reached convergence with $R=\Sigma(||F_0|-|F_C||)/\Sigma|F_0|$ and $Rw=[\Sigma w(|F_0|-|F_C||)^2/\Sigma w (F_0)^2]^{1/2}$. Criteria for a satisfactory complete analysis were the ratios of rms shift to standard deviation being less than 0.1 and no significant features in final difference map.

Crystal data: $C_{13}H_{17}NO_2$ (**1a**), M=219.2, Monoclinic, a=20.570(3), b=5.987(3) c=12.643.3(3) Å, β=127.76(2)^0, V=1231(1) Å^3, space group C2, Z=4, dcalc 1.18 g cm^3, $C_{14}H_{19}NO_2$ (**3b**), M=233.31, orthorhombic, a=5.935(1), b=8.349(1) c=26.802(3) Å, V=1328(1) Å^3, space group P $2_12_12_1$, Z=4, dcalc 1.17 g cm^3; $C_{15}H_{21}NO_2$ (**4a**), M=247.3, orthorhombic, a=6.371(1), b=11.439(1) c=19.268(1) Å, V=1404(1) Å^3, space group P $2_12_12_1$, Z=4, dcalc 1.17 g cm^3; $C_{18}H_{19}NO_2$ (**5b**), M=281.4, orthorhombic, a=5.919(1), b=12.078(3) c=21.769(3) Å, V=1556(1) Å^3, space group P $2_12_12_1$, Z=4, dcalc 1.19 g cm^3; $C_{15}H_{19}NO_2$ (**6a**), M=245.3, monoclinic, a=9.510(1), b=6.831(1) c=20.687(2) Å, β=99.17(1)^0, V=1336(1) Å^3, space group P 2_1, Z=4, dcalc 1.21 g cm^3. *Data Collection* CAD4 Diffractometer, $\omega/2\theta$, μ=(MoKα) 0.71 cm^{-1}; (**1a**) 1243 reflections measured, 1199 unique, with 837 I>3σI; (**3b**) 1441 reflections measured, 1401 unique, with 1401 I>3σI; (**4a**) 1834 reflections measured, 1804 unique, with 1590 I>3σI; (**5b**) 1629 reflections measured, 1606 unique, with 592 I>3σI; (**6a**) 2649 reflections measured, 2526 unique, with 2526 I>3σI. *Refinement* (**1a**), No. of variables 148, final R=0.040, Rw=0.038; (**3b**), No. of variables 212, final R=0.051, Rw=0.051; (**4a**), No. of variables 227, final R=0.053, Rw=0.051; (**5b**), No. of variables 88, final R=0.066, Rw=0.066; (**6a**), No. of variables 325, final R=0.039, Rw=0.036.

Supplementary Material available: Tables of atomic coordinates, thermal parameters, bond lengths and angles and observed and calculated structure factors have been deposited at the Cambridge Crystallographic Data Center.

General procedure for the preparation of 1,4-oxazines. Compounds **1a, 2a** and **6a** were prepared by condensation of (1R,2S)-(-)norephedrine (**a**) with symmetric α,β-diketones while **1b**, **2b** and **6b** were prepared from (1R,2R)-(-)-norpseudoephedrine (**b**) .

(1R,2S)-(-)Norephedrine or (1R,2R)-(-)-norpseudoephedrine(1g, 6.61 mmol) was dissolved in 30 ml of ethyl ether and 2,3-butanedione (0.56g, 6.61 mmol) was added. The solution was stirred at room temperature for 15 minutes and the resulting white precipitate was filtered off and dried to give compounds **1a** or **1b.**

(2S*,5S*,6R*)-2-Hydroxy-5,6-dihydro-2,3,5-trimethyl-6-phenyl-2H-1,4-oxazine (1a) 1.35g, 96% yield; m.p. 142-143 ^{0}C; $[\alpha]_D^{25}$ -193.3 (*c* .02 in EtOH); δ_H (270 MHz, DMSO-d_6) 7.24-7.38(5H, m, arom), 6.55(1H, s, OH), 4.98(1H, d, J 2.0, H-6), 3.70(1H, dq, J 6.6, 2.0, H-5), 1.99(3H, s, CH_3-3), 1.51(3H, s, CH_3-2), 0.65(3H, d, J 6.6, CH_3-5); δ^{13}C (67.8 MHz, DMSO-d_6) 166.5(s, C=N), 139.7(s, C*i*),125.3(d, C*o*),127.4(d, C*m*), 126.7(d, C*p*), 93.3(s, C-2), 69.8(d, C-6), 55.3(d, C-5), 26.2(q, CH_3-2), 21.5(q, CH_3-3), 13.2(q, CH_3-5); υ_{max}(KBr)/cm^{-1} 3062, 1658, 1246, 1152 and 1110.

(2S*,5R*,6R*)-2-Hydroxy-5,6-dihydro-2,3,5-trimethyl-6-phenyl-2H-1,4-oxazine (1b) 1.29g, 92 % yield; m.p. 110-112 ^{0}C, $[\alpha]_D^{25}$ -51.7 (*c* .02 in EtOH); δ_H (270 MHz, DMSO-d_6) 7.28-7.38(5H, m, arom), 6.46(1H, s, OH), 4.32(1H, d, J 9.9, H-6), 3.30(1H, dqd, J 9.9 , 6.6, 2.0, H-5), 1.99(3H, d, J 2.0, CH_3-3), 1.44(3H, s, CH_3-2), 0.92(3H, d, J 6.6, CH_3-5); δ^{13}C (67.8 MHz, DMSO-d_6) 166.5(s, C=N), 139.8(s, C*i*),127.4(d, C*o*),128.1(d, C*m*), 127.7(d, C*p*), 92.3(s, C-2), 74.7(d, C-6), 56.9(d, C-5), 25.9(q, CH_3-2), 21.4(q, CH_3-3), 18.3(q, CH_3-5); υ_{max}(KBr)/cm^{-1} 3036, 1664, 1262, 1140, and 1040.

(2S*,5S*,6R*)-2-Hydroxy-5,6-dihydro-2,3-diethyl-5-methyl-6-phenyl-2H-1,4-oxazine (2a) From norephedrine (1g, 6.61 mmol) and 3,4-hexanedione (0.75g, 6.61 mmol), 1.57g , 96% yield of **2a**; m.p. 102-104 ^{o}C; $[\alpha]_D^{25}$ -138.5 (*c* .02 in EtOH) ; δ_H (270 MHz, $CDCl_3$) 7.19-7.35(5H, m, arom), 5.01(1H, d, J 3.1, H-6), 3.76(1H, dq, J 3.0, 6.7, H-5), 2.48 and 2.27 (2H, dq, J 16.5, 7.3, CH_2-9), 1.91(2H, m, CH_2-7), 1.13(3H, t, J 7.3, CH_3-10), 0.96(3H, t, J 7.3, CH_3-8), 0.78(3H, d, J 6.7, CH_3-5); δ^{13}C (67.8 MHz, $CDCl_3$) 169.9(s, C=N), 139.5(s,C*i*), 125.5(d, C*o*), 128.1(d, C*m*), 127.0(d,C*p*), 96.7(s, C-2), 70.4(d, C-6), 56.1(d, C-5), 32.5(t, CH_2-7), 26.7(t, CH_2-9),13.6(q, CH_3-5), 10.7(q, CH_3-10), 8.5(q, CH_3-8) υmax(KBr)/cm^{-1} 3170, 1662, 1456, 1122 and 1024.

(2S*,5R*,6R*)-2-Hydroxy-5,6-dihydro-2,3-diethyl-5-methyl-6-phenyl-2H-1,4-oxazine (2b) From norpseudoephedrine (1g, 6.61 mmol) and 3,4-hexanedione (0.75g, 6.61 mmol), 1.57g, 96% yield of **2b**; m.p. 90-92 ^{o}C; $[\alpha]_D^{25}$ -11.3 (*c*, .02 in EtOH); δ_H (270 MHz, $CDCl_3$) 7.26-7.39(5H, m, arom), 4.29(1H, d, J 9.2, H-6), 3.40(1H, dqd, J 9.2, 6.6, 2.0, H-5), 2.32 and 2.50 (2H, ddq, J=14.5, 7.3, 2.0, CH_2-9), 1.80, and 1.99(2H, dq, J 14.5, 7.3, CH_2-7), 1.17(3H, t, J 7.3, CH_3-10), 0.93(3H, t, J 7.3, CH_3-8), 1.07(3H, d, J 6.9, CH_3-5); δ^{13}C (67.8 MHz, $CDCl_3$) 169.2(s, C=N), 139.6(s,C*i*), 127.4(d, C*o*), 128.4(d, C*m*), 128.2(d,C*p*), 96.1(s, C-2) 75.9(d, C-6), 57.8(d, C-5), 33.1(t, CH_2-7), 26.8(t, CH_2-9), 18.6(q, CH_3-5), 10.8(q, CH_3-10), 8.1(q, CH_3-8); υ_{max}(KBr)/cm^{-1} 3144, 1670, 1456, 1472 and 1110.

(2R*,3S*,8aS*)-8a-Hydroxy-2,3,5,6,7,8-hexahydro-3-methyl-2-phenyl-8aH-1,4-benzoxazine (6a). From norephedrine (1g, 6.61 mmol) and 1,2-cyclohexanedione (0.74g, 6.61 mmol), 1.4g, 87 % yield of **6a;** m.p. 162-164^{o}C , $[\alpha]_D^{25}$ -259.6 (*c* .02 in EtOH); δ_H (270 MHz $CDCl_3$) 7.38-7.26 (5H, m, arom), 5.15(1H, d, J 3.1, H-2), 3.77 (1H, dqd, J 6.7, 3.1, 1.8, H-3), 2.60 (1H, dddd, J 13.5, 13.4, 6.9, 1.8, H-5ax), 2.40(1H ,dquintet, J 13.5, 2.0 , H-5eq), 2.10 (1H, dt, J 10.4, 2.8, H-8eq), 1.90-1.96 (3 H, m, H-7ax,eq, H-8ax), 1.90(1H, ddt, J 13.6, 13.7, 4.0, H-6eq), 1.52 (1H, tt, J 13.7, 3.6 , H-6ax), 0.84 (3H, d, J 6.7 , CH_3-3); δ^{13}C

(67.8 MHz, $CDCl_3$) 168.6 (s, C=N), 139.3 (s, C*i*), 125.5 (d, C*o*), 128.3 (d, C*m*), 127.1 (d, C*p*), 93.7 (s, C-8a), 71.1 (d, C-2), 56.6 (d, C-3), 40.7 (t, C-8), 35.7 (t, C-5), 27.2 (t, C-6), 22.4 (t, C-7), 13.6 (q, CH_3-3); υ_{max}(KBr)/cm^{-1} 3028, 1666, 1448, 1368, 1238 and 1052.

(2R*,3R*,8aS*)-8a-Hydroxy-2,3,5,6,7,8-hexahydro-3-methyl-2-phenyl-8aH-1,4-benzoxazine (6b). From norpseudoephedrine (1g, 6.61 mmol) and 1,2-cyclohexanedione (0.74g, 6.61 mmol), 1.45 g, 90 % yield of **6b** ; m.p. 142-144^{0}C ; $[\alpha]_D^{25}$ -99.6 (*c* .01 in EtOH); δ_H (270 MHz, $CDCl_3$) 7.34-7.32 (5H, m, arom), 4.46 (1H, d, J 9.5, H-2), 3.40 (1H, dqd J 9.5, 7.0, 2.8 , H-3), 2.60 (1H, dddd, J 13.2, 13.0, 5.3, 2.8, H-5ax), 2.31 (1H dquint, J 13.2, 2.0, H-5eq), 2.12 (1 H, dquint, J 13.3, 2 , H-8eq), 1.96 (1H, dm, J 13.3, H-6eq), 1.82 (1 H, tt , J 13.2 , 3.5, H-8ax), 1.74-1.62 (2H, m, H-7ax, eq), 1.53 (1H, tt, J 13.5, 3.3, H-6ax), 1.0 (3H, d, J 7.0, CH_3-3); δ^{13}C (67.8 MHz, $CDCl_3$) 169.1 (s, C=N), 139.3 (s, C*i*), 127.6 (d, C*o*), 128.4 (d, C*m*), 128.2 (d, C*p*), 92.7 (s, C-8a), 75.8 (d, C-2), 57.8 (d, C-3), 40.4 (t, C-8), 35.5 (t, C-5), 27.1 (t, C-6), 22.4 (t, C-7), and 18.2 (q, CH_3-3); υ_{max}(KBr)/cm^{-1} 3022, 1670, 1456, 1126 and 1070.

The following procedure is representative for the condensation with unsymmetrical diketones. (1R-2S)-(-)Norephedrine or (1R-2R)-(-)-norpseudoephedrine (1g, 6.61 mmol) was dissolved in 30 ml ethyl ether and 2,3-pentanedione (0.66g, 6.61 mmol) was added. The solution was stirred at 0^{0}C for 30 minutes and the white precipitate filtered off to give **3a** or **3b**.

(2S*,5S*,6R*)-2-Hydroxy-5,6-dihydro-2-ethyl-3,5-dimethyl-6-phenyl-2H-1,4-oxazine (3a) 1.40g, 90% yield; m.p. 122-124^{0}C; $[\alpha]_D^{25}$-175.7 (c .02 in EtOH); δ_H (270 MHz, $CDCl_3$) 7.20-7.35(5H, m, arom), 5.03(1H, d, J 2.9, H-6), 3.71(1H, dq, J 6.9, 2.8, H-5), 2.06(3H, d, J 0.9, CH_3-3), 1.91(2H, m, CH2-7), 0.96(3H, t, 7.5, CH_3-8), 0.78(3H, d, J 6.9, CH3-5); δ^{13}C(67.8 MHz, $CDCl_3$) 166.5(s,C=N), 139.3(s, C*i*), 125.5(d, C*o*), 128.2(d, C*m*), 127.1(d, C*p*), 96.4(s, C-2), 70.5(d, C-6), 56.2(d, C-5), 32.5(t, CH_2-7), 21.7(q, CH_3-3), 13.6(q, CH_3-5), 8.4(t, CH_3-8); υ_{max}(KBr)/cm^{-1} 3024, 1666, 1452, 1130 and 1034.

(2S*,5R*,6R*)-2-Hydroxy-5,6-dihydro-2-ethyl-3,5-dimethyl-6-phenyl-2H-1,4-oxazine (3b) 1.4g, 91% yield; m.p. 110-112 ^{0}C $[\alpha]_D^{25}$ -5.3 (*c* .01 in EtOH); δ_H (270 MHz, CDCl3) 7.26-7.38(5H, m, arom), 4.33(1H, d, J 9.2, H-6), 3.37(1H,dqd, J 9.2, 6.6, 2.0, H-5), 2.10(3H, d, J 2.0, CH_3-3), 1.80 and 1.95(2H, dq, J 13.9, 7.3, CH_2-7), 1.05(3H, d, J 6.6, CH_3-5), 0.94(3H, t, J 7.3, CH_3-8); δ^{13}C (67.8MHz,$CDCl_3$) 166.3(s, C=N), 139.5(s, C*i*), 127.4(d, C*o*), 128.4(d, C*m*), 128.2(d, C*p*), 95.7(s, C-2), 75.9(d, C-6), 57.9(d, C-5), 33.0(t, CH_2-7), 21.8(q,CH_3-3), 18.4(q, CH_3-5), 8.0(t, CH_3-8); υ_{max} (KBr)/cm^{-1} 3166, 1662, 1430, 1272, 1120 and 1050.

(2S*,5S*,6R*)-2-Hydroxy-5,6-dihydro-3,5-dimethyl-6-phenyl-2-propyl-2H-1,4-oxazine (4a). From norephedrine (1g, 6.61 mmol) and 1,2-hexanedione (0.75g, 6.61 mmol), 1.50g, 92 % yield of **4a**; m.p. 164-166 ^{0}C; $[\alpha]_D^{25}$ -102.2 (*c* .01 in EtOH); δ_H (270 MHZ, $CDCl_3$) 7.24-7.38(5H, m, arom), 5.10(1H, d, J 3.0, H-6), 3.78(1H, dqq, J 6.9, 2.9, 0.7, H-5), 2.10(3H, d, J 0.7 Hz, CH_3-3), 1.89-1.87(2H, dt, J 22.0, 10.9, CH_2-7), 1.68, 1.37(2H, m, CH_2-8), 1.00(3H, t, J 7.3, CH_3-9), 0.81(3H, d, J 6.9, CH_3-5); δ^{13}C (67.8 MHz, $CDCl_3$) 165.8(s, C=N), 139.8(s,C*i*), 125.2(d, C*o*), 127.9(d, C*m*), 126.7(d, C*p*) 95.1(s, C-2), 69.4(d, C-6), 55.0(d, C-5), 40.6(t, CH_2-7), 21.5(q, CH_3-3),17.1(t, CH_2-8), 14.1(q, CH_3-9), 13.6(q, CH_3-5); υ_{max}(KBr)/cm^{-1} 3060, 1664, 1498, 1166 and 1062.

(2S*,5R*,6R*)-2-Hydroxy-5,6-dihydro-3,5-dimethyl-6-phenyl-2-propyl-2H-1,4-oxazine (4b). From norpseudoephedrine (1g, 6.61 mmol) and 2,3-hexanedione (0.75g, 6.61 mmol), 1.4g, 88 % yield of **4b;** m.p. 94-97 ^{0}C; $[\alpha]_D^{25}$ -11.2 (*c* .02 in EtOH); δ_H (270 MHz, $CDCl_3$) 7.27-7.38(5H, m, arom), 6.34(1H,

-OH), 4.27(1H, d, J 9.2, H-6), 3.32(1H, dq, J 9.2, 6.6, H-5), 1.96(3H, s, CH_3-3), 1.71-1.73(2H, dt, J 22.0, 13.2, CH_2-7), 1.45-1.19(2H, m, CH_2-8), 0.91(3H, d, J 6.6, CH_3-5), 0.90(3H, t, J 7.3, CH_3-9); $\delta^{13}C$ (67.8 MHz, $CDCl_3$) 166.3(s, C=N), 140.0(s,C*i*), 127.3(d, C*o*), 128.1(d, C*m*), 127.7(d, C*p*) 94.3(s, C-2), 74.7(d, C-6), 57.1(d, C-5), 40.8(t, CH_2-7), 21.4(q, CH_3-3), 18.3(q, CH_3-5), 16.7(t, CH_2-8), 14.0(q, CH_3-9); υ_{max}(KBr)/cm^{-1} 3033, 1678,1462, 1363, 1304, 1177, and 1024.

(2S*,5S*,6R*)-2-Hydroxy-5,6-dihydro-3,5-dimethyl-2,6-diphenyl-2H-1,4-oxazine (5a) From norephedrine (1g, 6.61 mmol) and 1-phenyl-1,2-propanedione (0.98g, 6.61 mmol) , 1.7g, 91 % of **5a**; m.p. 129-130 °C; $[\alpha]_D^*$ +194.9 (*c* .02 in EtOH); δ_H (270 MHz, $CDCl_3$) 7.23-7.68(10H, m, arom), 5.30(1H, d, J 3.3, H-6), 3.89(1H, dq, J 6.6, 3.3, H-5), 1.69(3H, s, CH_3-3), 0.88(3H, d, J 6.6, CH_3-5); $\delta^{13}C$ (67.8 MHz, $CDCl_3$) 164.8(s, C=N),139.4 and 141.6(s, C*i*), 125.3 and 126.8(d, C*o*), 128.0(d, C*m*), 126.8 and 128.2(d,C*p*), 95.4(s, C-2), 70.0(d, C-6), 55.0(d, C-5), 21.7(q, CH_3-3),14.1(q, CH_3-5); υ_{max}(KBr)/cm^{-1} 3028, 1666, 1448, 1368, 1238 and 1052.

(2S*,5R*,6R*)-2-Hydroxy-5,6-dihydro-3,5-dimethyl-2,6-diphenyl-2H-1,4-oxazine (5b). From norpseudoephedrine (1g, 6.61 mmol) and 1-phenyl-1,2-propanedione (0.98g, 6.61 mmol), 1.6 g, 86.5 % yield of **5b**; m.p. 123-125 °C; $[\alpha]_D^*$ +405.6 (*c*. 02 in EtOH); δ_H (270 MHz, $CDCl_3$) 7.19-7.63(10H, m, arom), 4.52(1H, d, J 9.2, H-6), 3.65(1H, dq, J 9.2, 7.2, H-5), 1.67(3H, s, CH_3-3), 1.01(3H, d, J 7.2, CH_3-5); $\delta^{13}C$ (67.8 MHz, $CDCl_3$) 165.2(s, C=N),139.5 and 142.1(s,C*i*), 126.3(d, C*o*), 128.1(d, C*m*), 127.8(d, C*p*), 94.4(s, C-2), 77.2(d, C-6), 56.9(d, C-5), 21.4(q, CH_3-3),18.4(q, CH_3-5); υ_{max}/cm^{-1}(KBr) 3033, 1673, 1467, 1235 and 1072.

1-acetyl-N-(3-methyl-4-phenyl-ethanol)-imine (7a).To a solution of (1R,2S)-(-)norephedrine (1g, 6.61mmol) in 30 ml tetrahydrofuran were added 0.56g (7.85 mmol) of 40% aqueous pyruvic aldehyde and the reaction mixture was stirred at room temperature for 10 hours. The solvent was evapored to dryness and 30 ml of a (1:1) hexane-CH_2Cl_2 mixture was added to yield a yellow precipitate of **7a** (0.5g , 36%) ; m.p. 153-154 °C; δ_H (270 MHz, DMSO-d_6) 8.47(1H, s, H-1), 7.35-7.25 (5H, m, arom), 4.84 (1H, d, J 3.5, H-4), 3.28 (1H, dq, J 3.5,J 6.6, H-3), 1.78(3H, s, CH_3CO) and 0.87(3H, d, J 6.6 ,CH_3-3); $\delta^{13}C$ (67.8 MHz, DMSO-d_6) 175.4 (s, C=O), 167.2 (d, C=N), 71.8 (d, C-4), 51.5 (d, C-3), 23.8(q, CH_3-CO), 12.1(q, CH_3-3); υ_{max}(KBr)/cm^{-1} 3042, 1534, 1410, 1102 and 1062.

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