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Stereoselective Control in 1,3-Dipolar Cycloaddition of Nitrones to Substituted Styrenes

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Abstract: *The stereochemistry of 1,3-dipolar cycloaddition of C-methyl-N-phenylnitrone 1 with substituted styrenes has been investigated. The presence of an hydroxyl function at the ortho position in the dipolarophile completely controls the stereochemical course of the reaction with the exclusive formation of cis cycloadduct 7. MNDO calculations help to rationalise the obtained results on the basis of an intermolecular hydrogen bonding, which leads to changes in the FMO properties so improving a stabilizing secondary orbital interaction in the E-endo transition state leading to cis isomer.*

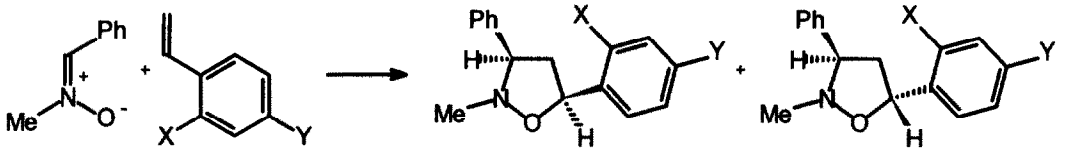
Formation of C-C and C-O bonds through 1,3-dipolar cycloaddition leading to isoxazolidine derivatives has been successfully exploited in organic synthesis.[1-6] The synthetic strategy is strictly dependent from the rationalization of the factors which control and define the regio- and stereochemistry of the initial cycloaddition process. The possibility of transferring, via the ring opening, the stereochemical features, achieved in cycloadducts, into open-chain derivatives, makes the isoxazolidine compounds as valuable synthons in methodologies functionalized to the synthesis of natural and biologically active compounds.[7-14]

The observed stereochemical results are mainly explained in terms of secondary orbital interactions[15-18] and/or steric requirements.[9,11,19-22] Other factors, as hydrogen bonding or dipole-dipole electrostatic[23-26] interactions, have been reported to control the stereochemical course of the cycloaddition process.

Our interest in using nitrone cycloaddition, as a synthetic tool towards differently functionalized open-chain molecules,[27-32] has focused our attention on the degree of stereoselectivity observed for the reaction of some representative nitrones with various dipolarophiles. In this paper we report on the stereochemical features associated with the reaction of *C*-phenyl-*N*-methylnitrone with substituted styrenes, in order to shed new light on the parameters which concur to define the stereoselectivity of the nitrone cycloaddition process.

RESULTS AND DISCUSSION

The reaction of *C*-phenyl-*N*-methylnitrone **1** with styrene **2** gives, as reported [33], a 2:1 mixture of *cis* and *trans* 5-phenyl-substituted isoxazolidines **6** and **10**. In contrast with these results, the introduction of a hydroxylic function at the ortho position in the dipolarophile modifies dramatically the reaction course. Heating a 1:1 mixture of nitrone **1** with 2-hydroxystyrene **3** in toluene at 120 °C for 5 days gives rise to the (3 RS,5 SR)-2-methyl-3-phenyl-5-(2-hydroxy)phenyl-isoxazolidine **7** as the only obtained adduct (Scheme 1).



1 2-5 6-9 10-12

Compounds	X	Y	Yield (%)	Epimeric ratio *cis/trans*
2	H	H	95[33]	**6:10** (66:34)[33]
3	OH	H	92	**7** (100)
4	H	OH	94	**8:11** (66:34)
5	MeO	H	94	**9:12** (66:34)

Scheme 1

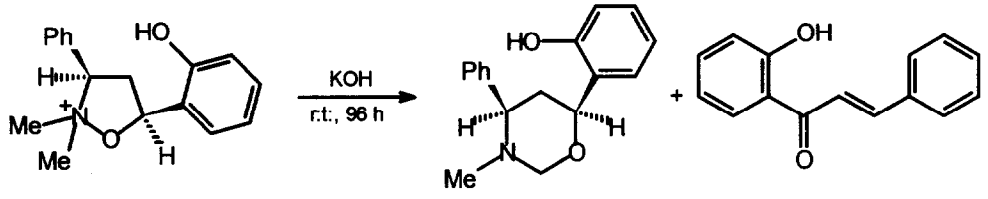
^{1}H NMR analysis of the crude reaction mixture confirms the regio- and stereospecificity of the cycloaddition process. In fact, the doublet of doublets at 5.15 δ (J_{cis} = 10.0 Hz and J_{trans} = 6.0 Hz) is diagnostic of 5-substituted derivatives;[4,17] the regiochemistry of the process is in general accord with a maximum orbital overlap of nitrone LUMO-dipolarophile HOMO, which affords 5-substituted isoxazolidines.[17]

The stereochemical assignment to **7** as the *cis* isomer has been performed on the basis of spectrometric parameters. The ^{1}H NMR showed for two methylene protons at C_4 two multiplets centered at 2.59 and 3.10 δ; the downfield resonance corresponds to the C_4 proton in a *cis* position with respect to phenyl substituents at C_3 and C_5, because of the additive deshielding effects of two aromatic substituents on the same side of the pentatomic ring. Furthermore, H_3 proton resonates as a doublet of doublets at 3.70 δ (J_{cis} = 12.0 Hz and J_{trans} = 7.2 Hz).

The configurational assignment has been confirmed by NOEDS spectroscopy. The positive NOE observed for H_5 on irradiating the H_3 proton is clearly indicative of their *cis* relationship.

The structure was further supported through the reactivity with bases of the corresponding isoxazolidinium salt **13**,[27,31] obtained by treatment of **7** with MeI. In fact, as we have already reported,[31] the ring-opening reaction of isoxazolidinium salts by treatment with bases is controlled by the stereochemistry of H_5. The *trans* isomers give rise to α,β-enones as the exclusive products, while *cis* isomers show a competitive formation of tetrahydro-1,3-oxazines (as the major compounds) and α,β-enones.

The treatment of **13** with aqueous KOH at r.t. for 96 h gives a mixture of 3-methyl-4-(RS)-phenyl-6-(SR)-(2-hydroxy)phenyl-1,3-tetrahydrooxazine **14** (78% yield) and 2'-hydroxychalcone **15** (15% yield) (Scheme 2).



13 14 15

Scheme 2

The stereochemistry of the isoxazolidine precursor is maintained in the obtained tetrahydro-1,3-oxazine. Configurational assignment to **14** has been achieved by NOEDS spectroscopy: the NOE enhancement observed for H_6, when H_4 is irradiated, indicates that they are topologically close together.

On these basis, structure of **7** remains unequivocally assigned.

In order to evaluate if the observed diastereospecificity is related to the presence of the free hydroxylic functionality and/or to its position in the benzene ring, we have examined the 1,3-dipolar cycloaddition reaction of **1** with 4-hydroxystyrene **4** and 2-methoxystyrene **5**.

The reactions of **1** with **4** and **5**, performed in the same experimental conditions, gave rise to a mixture of *cis* (**8**, **9**) and *trans* (**11**, **12**) isomers respectively (Scheme 1), in the same relative ratio (66:34).

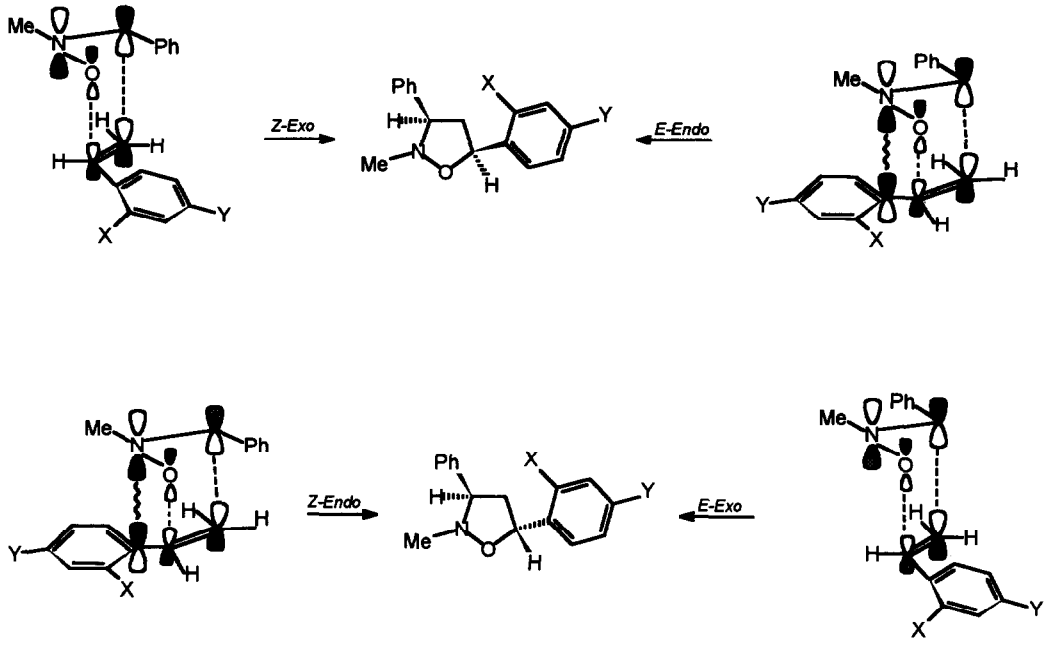
The comparison between the reactions of nitrone **1** with dipolarophiles **2-5** clearly points out that the diastereospecificity observed with compound **3** is associated to the presence of the free hydroxylic group at the ortho position in the benzene ring.

The stereochemical outcome does not appear to be affected by the polarity of the reaction solvent. In fact, no relevant differences have been observed when the cycloaddition of **1** to **3** was performed in *n*-butanol, *N,N*-dimethyl formamide, 1,2-diethoxyethane. These results, therefore, rule out the possibility that hydrogen bonding between the solvent and the 2-hydroxystyrene could exert some influence in determining the stereochemistry of the process.

The rationalization of the obtained results requires a detailed evaluation of the different stabilization effects, which operate in the transition states leading to two diastereoisomeric *cis* and *trans* cycloadducts, as well as the possibility of interconversion of the *E* and *Z* forms of the reacting nitrone, under the conditions of the reaction before cycloaddition takes place.

On this basis, the preferential formation of *cis* cycloadducts **6**, **8** and **9**, in the reaction of **1** with **2**, **4** and **5** respectively, is explained by assuming that the *trans* form of the nitrone **1** is in equilibrium with a small amount of the *cis* isomer and that the major adduct is that derived from the minor, but more reactive rotamer of the nitrone. There are good literature precedence for this suggestion.[17,34] Although there is a significant barrier to rotation in nitrone **1** (29.6 kcal/mol at 8 °C), this barrier is not sufficient to prohibit *cis-trans* interconversion under the conditions of the dipolar cycloaddition.[17]

MNDO calculations (Table 1) show, in fact, that in the determinant LUMO-dipolo HOMO-dipolarophile interaction involved for the cycloaddition of **4** and **5** with **1**, the *E-endo* transition state reveals a secondary orbital interaction which favours this approach over its *exo* counterpart, thereby accounting for the preferential formation of the *cis* isomers (Scheme 3).



Scheme 3

The alternative possibility of the *Z-exo* attack, also leading to *cis* isomers, does not appear to be stabilized by any secondary orbital interaction.

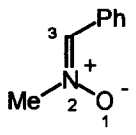
The stereochemical outcome of the cycloaddition reaction involving the 2-hydroxystyrene **3** is markedly different. Only a single adduct was detected, and this was shown to possess the *cis* structure **7**. An additional stabilizing effect, linked to the presence of the free OH group at C_2, should operate in the transition state leading to **7**.

The formation, in the transition state of the cycloaddition process, of an intermolecular hydrogen bonding involving the oxygen atom of the 1,3-dipole and the hydroxylic functionality at C_2 of the benzene ring will result in a modification of the reacting frontier orbital properties. As a consequence, in fact, while the MO's of **1** are basically 'protonated nitrone' orbitals, those of dipolarophile resemble those of the corresponding phenate ion.

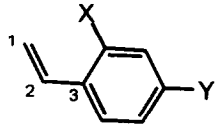
Scheme 4 shows the MO's of the protonated nitrone **12** and the phenate **13**.

The important changes upon the formation of the hydrogen bond were a substantially lowering of the HOMO and LUMO energies in the 1,3-dipole, an increase of the dipolarophile HOMO and an increase in the magnitude of the HOMO coefficient at C_1 of the phenyl substituent.

Table 1. HOMO-LUMO Energies of Nitrone **1** and Styrenes **2-5**



1



2-5

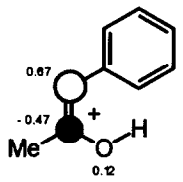
Compound		E (eV)	C1	C2	C3
1	HOMO	-8.50	0.61	-0.25	-0.41
	LUMO	-0.64	0.33	0.47	0.45
2	HOMO	-8.84	0.46	0.33	-0.46
	LUMO	-0.10	0.42	-0.27	-0.48
3	HOMO	-8.58	0.42	0.29	-0.45
	LUMO	-0.13	0.38	-0.23	-0.48
4	HOMO	-8.53	0.41	0.26	-0.48
	LUMO	-0.13	0.40	-0.26	-0.46
5	HOMO	-8.54	0.42	0.28	-0.45
	LUMO	-0.097	0.39	-0.24	-0.48

From these changes, the dominant LUMO nitrone-HOMO dipolarophile orbital interaction is greatly facilitated by the suggested hydrogen bonding, which lowers the dipole LUMO and raises the dipolarophile HOMO energies to a large extent. Furthermore, the secondary orbital interaction between the C_3 atom of the benzene ring and the nitrogen atom of the nitrone, in the *E-endo* approach leading to *cis* isomer **7**, is greatly improved, because the coefficient at C_3 in the phenate ion becomes very large.

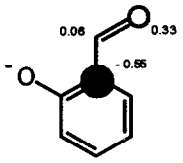
Therefore, a 'tighter' transition state in cicloaddition reaction of *C*-phenyl-*N*-methylnitrone **1** and 2-hydroxystyrene **3**, resulting from the greatly increased secondary orbital interaction, can reasonably to be expected to explain the observed stereospecificity.

The stereochemical arguments put forth to explain the stereospecifity observed in the 1,3-dipolar cycloaddition of **1** to 2-hydroxystyrene **3** have been checked with 2,3,4,5-tetrahydropyridine-1- oxide **16**.

For cyclic nitrones it has been reported that the influence of steric factors dominates the stereochemical results of the cycloaddition process[4]: the *E-endo* transition state, leading to *cis* isomers, can benefit from a favourable secondary orbital interaction, but suffers from steric compressions associated with the interaction of the phenyl group in the incoming dipolarophile and the appropriate ring hydrogens of the nitrone.



LUMO



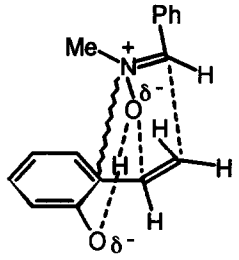
HOMO

E (HOMO) = - 13.44 eV

E (LUMO) = - 5.74 eV

E (HOMO) = - 2.75 eV

E (LUMO) = + 4.68 eV

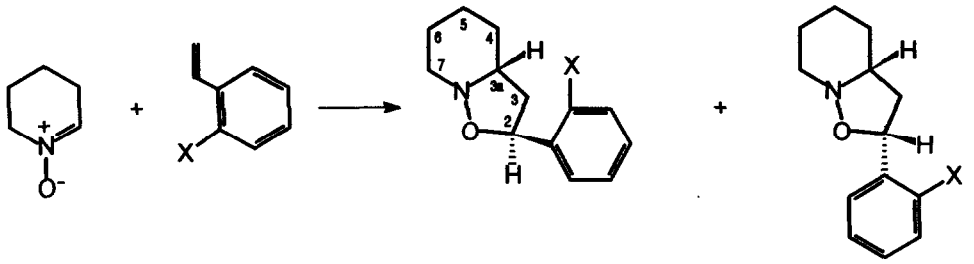


Scheme 4

As a result, 1,3-dipolar cycloaddition of **16** to styrene **2** is highly stereoselective and furnishes a 98:2 mixture of *trans* and *cis* isomers **17a** and **18a** (Scheme 5)[38]. The process is amenable to the an *E-exo* transition state with the secondary orbital interactions, associated with the alternative *E-endo* approach, playing a very minor role.

The same reaction performed with 2-hydroxystyrene leads to a 85:15 mixture of **17b** and **18b**, as detected by GC/MS analysis and confirmed by gas liquid chromatography[38]. The stereochemical assignment for the major isomer **17a**, isolated by flash chromatography of the crude reaction mixture, has been achieved by selective decoupling and NOE experiments, performed on the corresponding isoxazolidinium salt **19**, obtained in quantitative yield from MeI treatment[39].

In particular, irradiation of the resonance of 2-H results in a positive enhancement of the signals for the CH_2 protons adjacent to the nitrogen atom and of the upfield resonance of H_3. Likewise, when H_{3a} was irradiated, the signal for the methyl group was enhanced, together with the downfield resonance of H_3. These results, are indicative of an anti relationship between H_2 and H_{3a} with respect to the 5-membered ring.



16 2: X=H 3: X=OH 17 a: X=H b: X=OH 18 a: X=H b: X=OH

Scheme 5

The obtained distribution of stereoisomers **17b** and **18b** agrees with the considerations above reported. In fact, with respect to the 1,3-dipolar cycloaddition of **16** with styrene, the improved secondary orbital interaction, consequent to the suggested intermolecular hydrogen bonding between the oxygen atom of the dipole and the OH function at the phenyl group of the dipolarophile, slightly shifts the process through the *E-endo* approach, even if steric effects continue to maintain a predominant control on the reaction course.

In conclusion, a secondary orbital interaction, between the LUMO coefficient at the nitrogen atom of the 1,3-dipole and the HOMO coefficient at C_3 of the dipolarophile, has a significant effect in determining the stereoselectivity of the cycloaddition reaction of *C*-phenyl-*N*-methylnitrone to substituted styrenes. The presence of a hydroxyl group at the ortho position in the benzene ring shifts the stereochemical course towards the exclusive formation of the *cis* isomer. This is a consequence of an intermolecular hydrogen bond between reactants which affords, owing to the changes in the frontier orbital properties, an enhancement of the secondary orbital interaction and therefore a stabilization of the *E-endo* transition state.

EXPERIMENTAL

M.p.s. were measured on a Kofler apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer elemental analyzer. Infrared spectra were recorded on a Perkin-Elmer 377 instrument. ^{1}H NMR spectra were measured on a Bruker WM 300 spectrometer in $CDCl_3$ as solvent. Chemical shifts are in ppm (δ) from TMS as internal standard. NOE difference spectra were obtained by subtracting alternatively right-off-resonance free induction decays (FIDS) from right-on-resonance-induced FIDS. Mass spectra were taken at 70 eV on a Varian Mat CH-5 DF spectrometer and GC-MS HP 5859 A instruments. FAB mass spectra were recorded in glycerol solutions on a VG ZAB 2F mass spectrometer equipped with a MSSCAN stearable gun operated with xenon gas at 9.5 keV at resolution 1000.

Merck silica gel 60 H was used for preparative short-column chromatography.

Isoxazolidines **6** and **10** have been already reported in literature[33]. Compounds **7-9, 11, 12** were obtained by 1,3-dipolar cycloaddition of *C*- phenyl-*N*-methylnitrone and the appropriate olefins.

Reaction of nitrone 1 with alkenes 2-4.

General procedure. A solution of nitrone (1.5 mmol) and alkene (4.5 mmol) in anhydrous toluene (10 ml) was heated at 120 °C, under stirring, until tlc showed the disappearance of the starting nitrone (5 days). The solvent was removed and the residue subjected to flash chromatography on silica gel column with ether-hexane 85:15 as eluent.

Reaction of **1** *with 2-hydroxystyrene. (3RS, 5SR)-2-methyl-3-phenyl-5-(2-hydroxy)-phenyl-isoxazolidine* **7** has been obtained in 92% yield. Yellow oil; ν_{max} 3070-3020, 1737, 1581, 1485, 1256, 1111, 1046, 951, 832, 756, 698 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.80 (s, 3H, N-CH_3), 2.59 (m, 1H, H_4), 3.10 (m, 1H, H_4), 3.70 (dd, 1H, H_3, J=12.0 and 7.2 Hz), 5.15 (dd, 1H, H_3, J = 10.0 and 6.0 Hz), 6.60-7.60 (m, 9H, Ar-H). MS: m/z 255 (M^+, 19), 209 (100), 207 (55), 136 (57), 134 (55), 121 (43), 120 (47), 106 (25), 105 (41), 91 (71). (Found: C, 75.31; H, 6.69; N, 5,52%. Calc. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.48%).

Reaction of **1** *with 4-hydroxystyrene*. First eluted product was *(3RS, 5SR)-2-methyl-3-phenyl-5-(4-hydroxy)phenyl-isoxazolidine* **8**, 62% yield. Yellow oil; ν_{max} 3600, 1612, 1599, 1520, 1453, 1373, 1270, 1175, 1034, 829, 760, 700 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.43 (m, 1H, H_4), 2.69 (s, 3H, N-CH_3), 3.07 (m, 1H, H_4), 4.03 (dd, 1H, H_3, J=12.0 and 8.0 Hz), 5.25 (t, 1H, H_5, J=10.0 and 10.0 Hz), 6,80-7.34 (m, 9H, Ar-H). MS: 255 (M^+, 29), 210 (15), 209 (100), 194 (9), 165 (8), 136 (80), 134 (54), 120 (26), 115 (28), 107 (16), 91(27). (Found: C, 75.33; H, 6.73; N, 5,46%. Calc. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.48%). Further elution gave *(3RS, 5RS)-2-methyl-3-phenyl-5-(4-hydroxy)phenyl-isoxazolidine* **11**, 32% yield. Yellow oil; ν_{max} 3580, 1610, 1599, 1514, 1506, 1447, 1323, 1272, 1170, 1031, 835, 757, 700 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.43-2.85 (m, 2H, 4-CH_2), 2.67 (s, 3H, N-CH_3), 3.88 (dd, 1H, H_3, J=12.5 and 8.2 Hz), 5.20 (t, 1H, H_5, J=8.0 and 8.0 Hz), 6.75-7.20 (m, 9H, Ar-H). MS: 255 (M^+, 31), 209 (100), 136 (75), 134 (60), 120 (30), 115 (29), 107 (8), 91 (35). (Found: C, 75.23; H, 6.74; N, 5,50%. Calc. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.48%).

Reaction of **1** *with 2-methoxystyrene*. First eluted product was *(3RS, 5SR)-2-methyl-3-phenyl-5-(2-methoxy)phenyl-isoxazolidine* **9**, 62% yield. Yellow oil; ν_{max} 3031, 1601, 1588, 1489, 1462, 1437, 1286, 1240, 1106, 1047, 1032, 754, 700 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.26 (m, 1H, H_4), 2.70 (s, 1H, N-CH_3), 3.17 (m, 1H, H_4), 2.69 (s, 3H, N-CH_3), 3.71 (dd, 1H, H_3, J=11.0 and 9.0 Hz), 3.79 (s, 3H, OCH_3), 5.50 (t, 1H, H_5, J=8.0 and 8.0 Hz), 6,70-7.68 (m, 9H, Ar-H). MS: 269 (M^+, 27), 224 (12), 223 (87), 208 (5), 165 (7), 145 (9), 135 (41), 134 (100), 119 (32), 107 (11), 103 (7), 91 (34). (Found: C, 75.78; H, 7.14; N, 5,24%. Calc. for $C_{17}H_{19}NO_2$: C,75.81; H,7.11; N,5.20%). Further elution gave *(3RS, 5RS)-2-methyl-3-phenyl-5-(2-methoxy)phenyl-isoxazolidine* **12**, 32% yield. Yellow oil; ν_{max} 2990, 1601, 1589, 1492, 1462, 1434, 1305, 1286, 1243, 1045, 1028, 755, 698 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.03- 2.93 (m, 2H, 4-CH_2), 2.69 (s, 3H, N-CH_3), 3.70 (dd, 1H, H_3, J=12.5 and 8.2 Hz), 3.76 (s, 3H, O-CH_3), 5.53 (dd, 1H, H_5, J=9.6 and 6.8 Hz), 6.73-7.59 (m, 9H, Ar-H). MS: 269 (M^+, 28), 237 (19), 223 (82), 207 (7), 191 (6), 178 (9), 165 (15), 147 (8), 135 (54), 134 (100), 119 (35), 103 (28), 91 (59). (Found: C, 75.76; H, 7.08; N, 5,22%. Calc. for $C_{17}H_{19}NO_2$: C, 75.81; H,7.11; N, 5.20%).

Reaction of isoxazolidine **7** *with iodomethane*. A solution of isoxazolidine (1mmol) and iodomethane (2 ml) in anhydrous THF (20 ml) was heated at 40 °C under stirring for 8 h. The solvent was removed at reduced pressure and the residue was subjected to flash-chromatography on silica gel column, with cyclohexane-ethyl

acetate 97:3 as eluent, to give in a nearly quantitative yield *(3RS, 5SR)-2,2-dimethyl-3-phenyl-5-(2-hydroxy)-phenylisoxazolidinium iodide* **13**. White solid; m.p. 95-8 °C; ν_{max} 3600, 3015, 1606, 1501, 1459, 1341, 1296, 1263, 1231, 1197, 1005, 958, 909, 833, 760, 703 cm^{-1}. ^1H NMR: δ (DMSO-d_6) 2.98-3.78 (m, 2H, 4-CH_2), 3.15(s, 3H, N-CH_3), 3.69 (s, 3H, N-CH_3), 5.80-6.34 (m, 2H, H_3 and H_5), 6.82-8.00 (m, 9H, Ar-H). FAB: m/z : 270 [$(M-1)^+$]. (Found: C, 51.44; H, 5.10; N, 3.50%. Calc. for $C_{17}H_{20}INO_2$ (397.23): C, 51.40; H, 5.08; N, 3.52%).

Ring-opening reaction of isoxazolidinium salt **13**. 1.8 mmol of **13** were added to 20 ml of 1M aq. KOH, under stirring. The mixture was stirred at room temperature for 96 h, until all the isoxazolidinium salt had been consumed as monitored by TLC (MeOH/$CHCl_3$, 20/80). The reaction mixture was then treated with 10% $NaHCO_3$ (20 ml), saturated with sodium chloride and extracted with chloroform (3 x 30 ml). The combined organic extracts were evaporated under reduced pressure and the resulting oil was subjected to short column chromatography (silica gel; ethyl acetate/hexane 35:65) to give *2'-hydroxychalcone* **15** as the first eluted product, 15%yield. Yellow solid, m.p. 82-5°C: ν_{max} 3620-3150, 3080-2980, 1650, 1590, 1575, 1492, 1453, 1440, 1370, 1354, 1310, 1220, 1152, 1040, 975, 860, 760, 700 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 6.89-8.10 (m, 11H, Ar-H and -CH=CH-), 12.86 (s, 1H, -OH). MS: m/z: 224 (M^+, 89), 223 (98), 180 (48), 165 (28), 147 (100), 134 (28), 131 (26), 121 (59), 120 (68), 103 (52), 93 (17), 91 (35). (Found: C, 80.38; H, 5,35%. Calc. for $C_{15}H_{12}O_2$:C,80.34;H, 5.39%). Further eluted fractions gave *3-methyl-4(RS)-phenyl-6(SR)-(2-hydroxy)phenyl-1,3-tetrahydro-oxazine* **14**, 78% yield. White solid; m.p. 172-4 °C; ν_{max} 3500-3250, 2996-2780, 1595, 1461, 1397, 1362, 1269, 1240, 1208, 1160, 1139, 1112, 1076, 1040, 968, 790, 756, 704 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.96 (m, 2H, 5- CH_2), 2.01 (s, 3H, N-CH_3), 3.55 (dd, 1H, H_4, J=10.0 and 3.8 Hz), 4.20 (d, 1H, H_2), 4.78 (d, 1H, H_2), 5.72 (m, 1H, H_6), 6.70-7.58 (m, 9H, Ar-H). MS: 269 (M^+, 23), 224 (20), 223 (16), 208 (20), 207 (25), 147 (20), 134 (16), 131 (36), 121 (42), 120 (39), 118 (40), 104 (100), 91 (33). (Found: C, 75.78; H, 7.06; N, 5.15%. Calc. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20%).

Reaction of 16 with 2-hydroxystyrene. First eluted product was (2SR,3aRS)-2-(2-hydroxy)phenyl-3,3a,4,5,6,7-hexahydro-2H-isoxazolo[2,3- a]pyridine **17b**, 73% yield. Yellow solid; m.p. 150-2 °C; ν_{max} 3590, 1620, 1485, 1230, 1046, 756, 690 cm^{-1}. ^1H NMR: δ($CDCl_3$) 1.4-1.7 (m, 6H), 2.36 (dd, 1H, H_3, J = 12.6 and 9.3 Hz), 2.55 (ddd, 1H, H_3, J = 12.6, 6.3 and 4.3 Hz), 3.10 (m, H_7), 3.55 (m, H_{3a}), 3.60 (dd, 1H, H_7, J = 14.8 and 3.5 Hz), 5.09 (dd, 1H, H_2, J = 9.3 and 6.3 Hz), 6,7-7.2 (m, 5H, aromatic protons and OH). MS: m/z 219 (M^+,55), 202 (100), 131 (28),120 (35). (Found: C, 71.10; H, 7.90; N, 6.41 %. Calc. for $C_{13}H_{17}NO_2$ C, 71.19; H, 7.82; N, 6.39%).

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