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1,3-DIPOLAR CYCLOADDITION BETWEEN HETARYL NITRONES AND METHYL ACRYLATE: THEORETICAL STUDY AND APPLICATION TO THE SYNTHESIS OF FUNCTIONALIZED PYRROLIDINES

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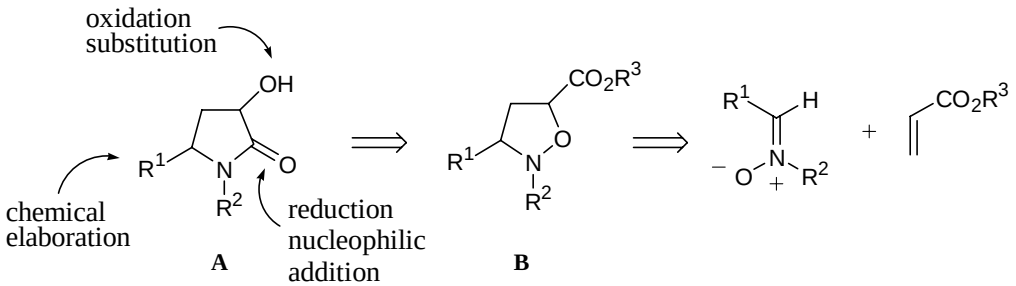
Abstract - The 1,3-dipolar cycloaddition reaction of *N*-benzyl-*C*-(hetaryl)nitrones gave preferentially *trans*-substituted 3,5-disubstituted isoxazolidines (*endo* approach) which can be further converted into the corresponding 5-hetaryl-3-hydroxy-2-pyrrolidinones. A theoretical study of the cycloaddition reaction by using both semiempirical (AM1, PM3) and *ab initio* (HF/3-21G, HF/6-31G*//3-21G) methods has also been carried out. In all cases the obtained results are in good qualitative agreement with the experimental observations.

INTRODUCTION

Saturated nitrogen heterocycles are present in a vast number of biologically active compounds[1] and several of these compounds are characterized by the presence of pyrrolidine ring systems.[2] In particular, 5-substituted 3-hydroxy-2-pyrrolidinones (**A**) are potentially important building blocks because they can be transformed into a variety of highly functionalized pyrrolidines.[3] The lactam moiety (**A**) can be reduced by choosing the proper conditions to either hemiaminals[4] or pyrrolidines;[5] the C-2 position of the heterocycle is also susceptible to nucleophilic addition.[6] The hydroxyl group can be oxidized,[7] substitution of that group can be carried out *via* the Mitsunobu reaction[8] and the side chain (R^1) can be chemically transformed to more elaborated compounds.[9]



Scheme 1

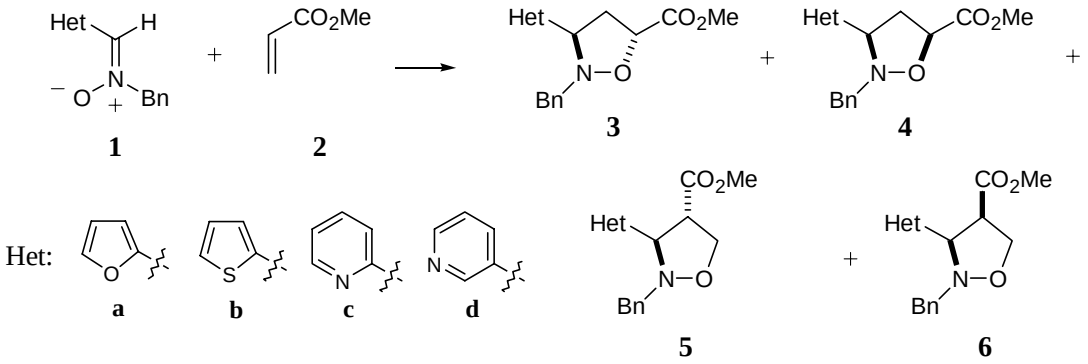
In addition to these synthetically useful properties, 5-substituted 3-hydroxy-2-pyrrolidinones can be readily prepared from the corresponding 3-substituted 5-(alkoxycarbonyl)isoxazolidines (**B**), which should be available by 1,3-dipolar cycloadditions of a nitrone with simple acrylates. So far, there have

been several reports concerning nitrone cycloadditions with acrylates,[10] whereas few examples have been reported on the conversion of the resulting isoxazolidines to 3-hydroxy-2-pyrrolidinones (**B**).[11]

In our continuing efforts to develop nitrone-based synthetic methodologies[12] we found that *N*-benzyl-*C*-(2-thiazolyl)nitrone is a very useful synthetic intermediate which combines the nitrone functional group reactivity and the synthetic utility of the thiazole ring.[13] Having decided to extend this concept to other hetaryl nitrones, we report here the 1,3-dipolar cycloaddition of several hetaryl nitrones with methyl acrylate to furnish 3,5-disubstituted isoxazolidines.[14] We also show here that the reductive ring cleavage of the adducts provides a useful method to prepare 5-hetaryl-3-hydroxy-2-pyrrolidinones. In addition, a comparative theoretical study of the cycloaddition reaction has been carried out.

RESULTS AND DISCUSSION

Nitrones (**1**) were easily prepared from reaction of the corresponding aldehydes with *N*-benzyl-hydroxylamine as described.[15] The configuration of nitrones (**1**) was firmly established by spectroscopic methods. Both the ^{1}H NMR spectra in non-aromatic ($CDCl_3$) and aromatic (C_6D_6) solvents (ASIS-effect),[16] and NOE experiments[17] clearly indicated the (Z)-configuration of nitrones (**1**). In addition, these nitrones showed to be stable under the reaction conditions: they can be stored for several months, even in solution, under an inert atmosphere, at ambient temperature without apparent decomposition. Likewise, a solution of nitrones (**1**) in toluene-d_8 was heated at 90 °C for 6 h and ^{1}H NMR spectra were recorded each 30 minutes. All spectra exhibited signals only due to the starting (Z)-nitrone, thus suggesting that nitrones (**1**) exist in Z form, not only at ambient temperature but also at temperatures close to those raised in the cycloaddition reaction.



Scheme 2

The results of the cycloaddition of nitrones (**1**) with methyl acrylate are illustrated in Scheme 2 and summarized in Table 1. Cycloaddition reactions were performed by mixing the reagents under Ar atmosphere and the indicated reaction conditions (solvent, time and temperature). In all cases isoxazolidine-5-carboxylate regioisomers were obtained as major adducts, the best results being obtained at lower temperature although with partial conversions.

Table 1. 1,3-Dipolar cycloaddition of nitrones (**1**) with methyl acrylate (**2**).

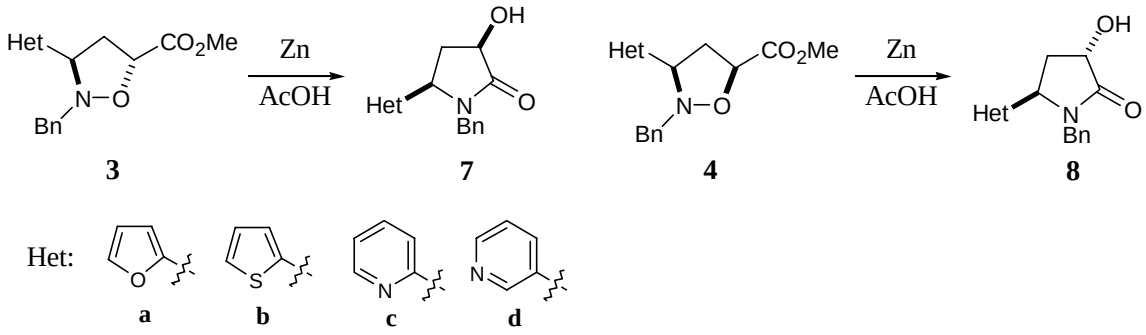
Entry	nitrone	solvent	temp [°C]	time	conversion [%]	**3** : **4** : **5** : **6**	yield [%]
1	**1a**	CH_2Cl_2	25	60 d	90	74 : 14 : 12 : 0	96
2	**1a**	CH_2Cl-CH_2Cl	25	75 d	100	68 : 10 : 22 : 0	94
3	**1a**	neat	25	15 d	90	76 : 12 : 12 : 0	93
4	**1a**	CH_2Cl_2	reflux	48 h	100	54 : 40 : 6 : 0	60
5	**1a**	CH_2Cl-CH_2Cl	reflux	16 h	100	58 : 28 : 14 : 0	96
6	**1a**	$CHCl_3$	reflux	24 h	100	50 : 36 : 14 : 0	93
7	**1a**	toluene	reflux	12 h	100	58 : 22 : 20 : 0	68
8	**1a**	neat	reflux	5 h	100	70 : 17 : 13 : 0	80
9	**1a**	neat	5	14 d	100	74 : 11 : 15 : 0	94
10	**1a**	neat	-18	60 d	50	100 : 0 : 0 : 0	95
11	**1b**	CH_2Cl-CH_2Cl	25	14 d	10	100 : 0 : 0 : 0	97
12	**1b**	toluene	25	14 d	18	90 : 10 : 0 : 0	89
13	**1b**	CH_2Cl_2	25	75 d	74	83 : 17 : 0 : 0	86
14	**1b**	neat	25	14 d	56	85 : 15 : 0 : 0	89
15	**1b**	neat	5	75 d	55	100 : 0 : 0 : 0	94
16	**1b**	neat	reflux	2 h	100	80 : 14 : 6: 0	85
17	**1c**	CH_2Cl-CH_2Cl	25	60 d	100	70 : 21 : 9 : 0	90
18	**1c**	toluene	25	60 d	100	75 : 16 : 9 : 0	96
19	**1c**	CH_2Cl_2	25	75 d	100	71 : 20 : 9 : 0	92
20	**1c**	neat	25	60 d	100	71: 21 : 8 : 0	93
21	**1c**	neat	5	75 d	100	74 : 19 : 7 : 0	86
22	**1c**	neat	-18	75 d	95	74 : 18 : 6 : 0	96
23	**1c**	neat	reflux	2 h	100	69 : 20 : 11 : 0	79
24	**1d**	CH_2Cl-CH_2Cl	25	14 d	100	67 : 20 : 13 : 0	86
25	**1d**	toluene	25	14 d	100	66 : 20 : 14 : 0	90
26	**1d**	CH_2Cl_2	25	14 d	100	70 : 19 : 11 : 0	92
27	**1d**	neat	25	10 d	100	82 : 14 : 4 : 0	88
28	**1d**	neat	5	14 d	100	75 : 16 : 9 : 0	96
29	**1d**	neat	-18	20 d	60	76 : 16 : 8 : 0	94
30	**1d**	neat	reflux	2 h	100	65 : 21 : 14 : 0	80

As can be seen from Table 1, *endo* selectivities were observed in all of the examples. Such a selectivity increased as the temperature decreased and in some instances (Table 1, entries 10, 11 and 15) the *trans*-3,5-regioisomer (*endo* attack) was obtained as the only product of the reaction. No change in the ratio of the regioisomers was observed over a longer period of time in solution.

The regiochemistry of the cycloaddition process was readily deduced from the ^{1}H NMR spectra. In each case there was a doublet-of-doublets at δ 4.00-4.70 which corresponded to the H_5 proton in compounds (**3-4**); the alternative observed isoxazolidine-4-regioisomer (**5**) displayed two vicinal hydrogen atoms

(coupling constant J > 12 Hz) which were assigned to the C-5 protons. In addition, isoxazolidine-5-carboxylate regioisomers also showed a doublet-of-doublets for H_3 whereas compounds (**5**) showed a doublet for the same proton. The *cis/trans* stereochemistry was assigned on the basis of NOE experiments and in the case of all the isoxazolidine-5-carboxylate regioisomers was further confirmed by their transformation into 3-hydroxy-2-pyrrolidinones (see below).

The major isoxazolidine-5-carboxylate regioisomers (**3**) and (**4**) were converted into 5-hetaryl-3-hydroxy-2-pyrrolidinones (**7**) and (**8**), respectively (with the exception of **8b**), by reduction with Zn in acetic acid in good yields (Scheme 2). Configurational assignment of the obtained pyrrolidinones (**7**) and (**8**) further confirmed the previously assigned stereochemistry of isoxazolidines (**3**) and (**4**).



Scheme 3

From the NOE enhancements observed (Figure 1) the *cis* arrangement of hetaryl and hydroxyl substituents is obvious for compounds (**7**) thus confirming the *trans* stereochemistry of the precursor isoxazolidines (**3**). Similarly, the NOE experiments demonstrated the *trans* disposition of substituents in **8**, thus confirming the *cis* configuration of compounds (**4**).

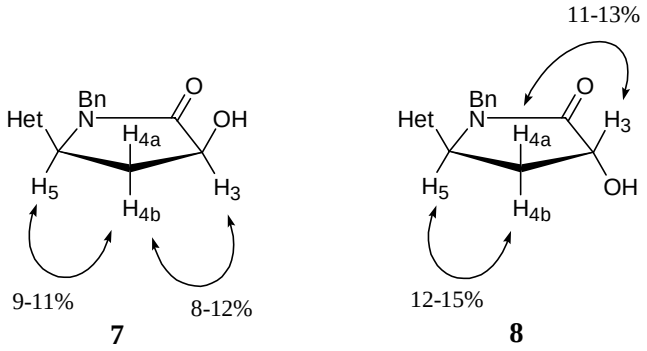


Figure 1. Selected NOE data for compounds (**7**) and (**8**). η_{obs} values, recorded as percent of η_{max}.

Theoretical calculations. The regiochemistry of the reaction can be adequately explained by the FMO approach.[18] Molecular orbital calculations by the PM3 method[19] showed (Figure 2) that the energy differences between the HOMO of nitrones (**1**) and the LUMO of methyl acrylate (**2**) were smaller than that of the opposite combination (LUMO of nitrone and HOMO of (**2**)) thus suggesting that the reactions were controlled by interactions $HOMO_{nitrone}$-$LUMO_{alkene}$ (Figure 2 shows the HOMO-LUMO values for compounds (**1**) and (**2**), and the corresponding coefficients for the relevant atoms). As a result, isoxazolidine-5-carboxylate regioisomers are obtained preferentially. The observed portion of the

isoxazolidine-4-carboxylate regioisomers can be due to the close values of the corresponding coefficients calculated for C and N atoms in the nitrones.

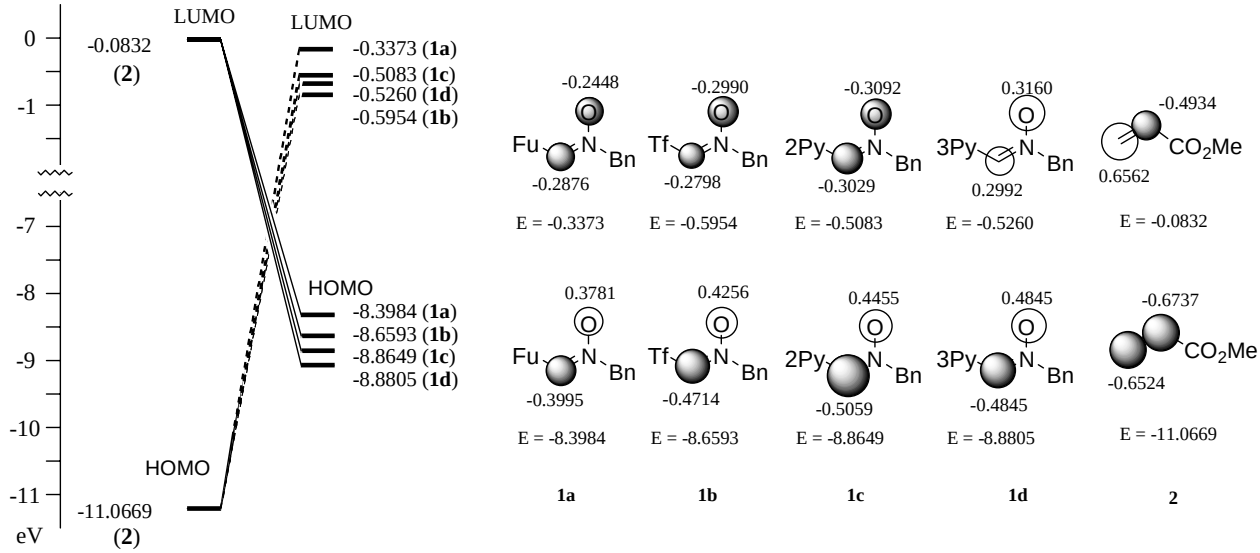


Figure 2. HOMO and LUMO energies and relevant coefficients for nitrones (**1**) and methyl acrylate (**2**).

The *endo* preference in the formation of the major 3,5-regioisomers can be rationalized in terms of the possible transition states. To this aim quantum chemical calculations at semiempirical (AM1 and PM3) and *ab initio* (HF/3-21G and HF/6-31G*//3-21G) levels were used to locate transition state structures.[20] The structures of nitrones (**1**) and methyl acrylate (**2**) as well as the corresponding products (**3-4**) has been fully optimized at the AM1, PM3 and HF/3-21G levels for the purpose of comparison. Single point energy calculations were carried out at the HF/6-31G* level using the 3-21G geometries.[21] The location of the *endo* and *exo* transition states for the reaction of nitrones (**1**) with (**2**) was made by the calculation of a reaction path profile leading to either *endo*-(**3**) or *exo*-(**4**) adducts, followed by a further optimization and characterization (frequency analysis) of the transition state. In addition, starting from each transition state, both sides of the reaction path were investigated using the internal reaction coordinate procedure. In all cases, it could be verified that the transition states proceed from the reactants (nitrone + alkene) and give rise to the products (isoxazolidines). The corresponding energies of reactants, transition states and products are summarized in Table 2 and the optimized transition structures are shown in Figure 3.

In all cases the most stable transition state is predicted to be the same (i.e. *endo*), irrespective of the theory level used. However, the overall ΔE‘s and barrier heights for the studied systems appear to be sensitive to the level of theory employed. Thus, whereas rather different values were obtained for AM1 and HF/3-21G levels, quite similar barrier heights were found for PM3 and single point HF/6-31G*//3-21G calculations. These findings are in agreement with previous studies which showed PM3 calculations to be qualitatively reliable for 1,3-dipolar cycloadditions.[22] In each case, the observed geometries are similar for all hetaryl nitrones. The C-C and C-O distances represent the reaction coordinates. The HF/3-21G calculations give rise to C-C bond lengths longer than those obtained by semiempirical methods, and similar values for C-O bond lengths, thus confirming the preference of HF/3-21G calculations for

asynchronicity. In any case, all the methods predict asynchronous transition states with the C-O bond distance shorter than the C-C bond distance, in good agreement with previous reports.[23]

Table 2. Heats of formation of reactants, transition states and products

compound[a]	AM1[b]	PM3[b]	HF/3-21G[c]	HF/6-31G*//3-21G[c]
1a	27.460	9.049	-432.8989481	-435.3251625
1b	76.442	44.815	-754.0199583	-757.9833409
1c	83.927	43.475	-450.8610996	-453.3947607
1d	54.282	43.522	-450.8565002	-453.3920750
2	70.112	67.456	302.9820245	304.6783803
endo-**Ts$_a$**	-20.566 (22.09)	-25.337 (33.03)	-735.8527543 (17.71)	-739.951446 (32.69)
exo-**Ts$_a$**	-18.146 (24.51)	-23.202 (35.20)	-735.8461707 (21.84)	-739.9486357 (34.45)
endo-**Ts$_b$**	2.286 (-4.04)	10.778 (33.42)	-1056.9730545 (18.15)	-1062.6092547 (32.92)
exo-**Ts$_b$**	4.911 (-1.42)	12.888 (35.53)	-1056.9669277 (22.00)	-1062.6064921 (34.66)
endo-**Ts$_c$**	8.947 (-4.87)	8.986 (32.97)	-753.8162191 (16.88)	-758.0234055 (31.21)
exo-**Ts$_c$**	11.408 (-2.41)	10.836 (34.82)	-753.8103783 (20.55)	-758.0214302 (32.45)
endo-**Ts$_d$**	6.534 (22.36)	9.011 (32.95)	-753.8100990 (17.84)	-758.0187997 (32.41)
exo-**Ts$_d$**	8.933 (24.76)	10.930 (34.86)	-753.8044410 (21.39)	-758.0170094 (33.54)
3a	-87.956	-72.237	-735.9457227	-740.0489486
4a	-87.603	-70.461	-735.9422965	-740.0469555
3b	-48.650	-51.760	-1057.0655946	-1062.7067705
4b	-48.870	-51.460	-1057.0618399	-1062.7047668
3c	-43.359	-54.226	-753.9105677	-758.1222079
4c	-42.160	-54.465	-753.9108882	-758.1232296
3d	-44.862	-54.305	-753.9056097	-758.1181522
4d	-43.503	-54.283	-753.9073141	-758.1203852

[a] **a**, **b**, **c** and **d** series refer to 2-furyl, 2-thienyl, 2-pyridyl and 3-pyridyl series, respectively. [b] Kcal mol^{-1}. [c] Hartrees (barriers in TS's are given in Kcal mol^{-1})

CONCLUSION

In conclusion, functionalized pyrrolidines having an heterocyclic substituent are accessible starting from the 1,3-dipolar cycloaddition reactions of the corresponding hetaryl nitrones to methyl acrylate. The reduction of the intermediate isoxazolidines takes place with good yields. The observed 3,5-regioselectivity in the formation of the isoxazolidines is well-explained by the FMO theory and the *endo* preference for the nitrone attack can be qualitatively rationalized by using both semiempirical and *ab initio* theoretical calculations. Cartesian coordinates and PDB files of the calculated structures are available from the authors upon request.

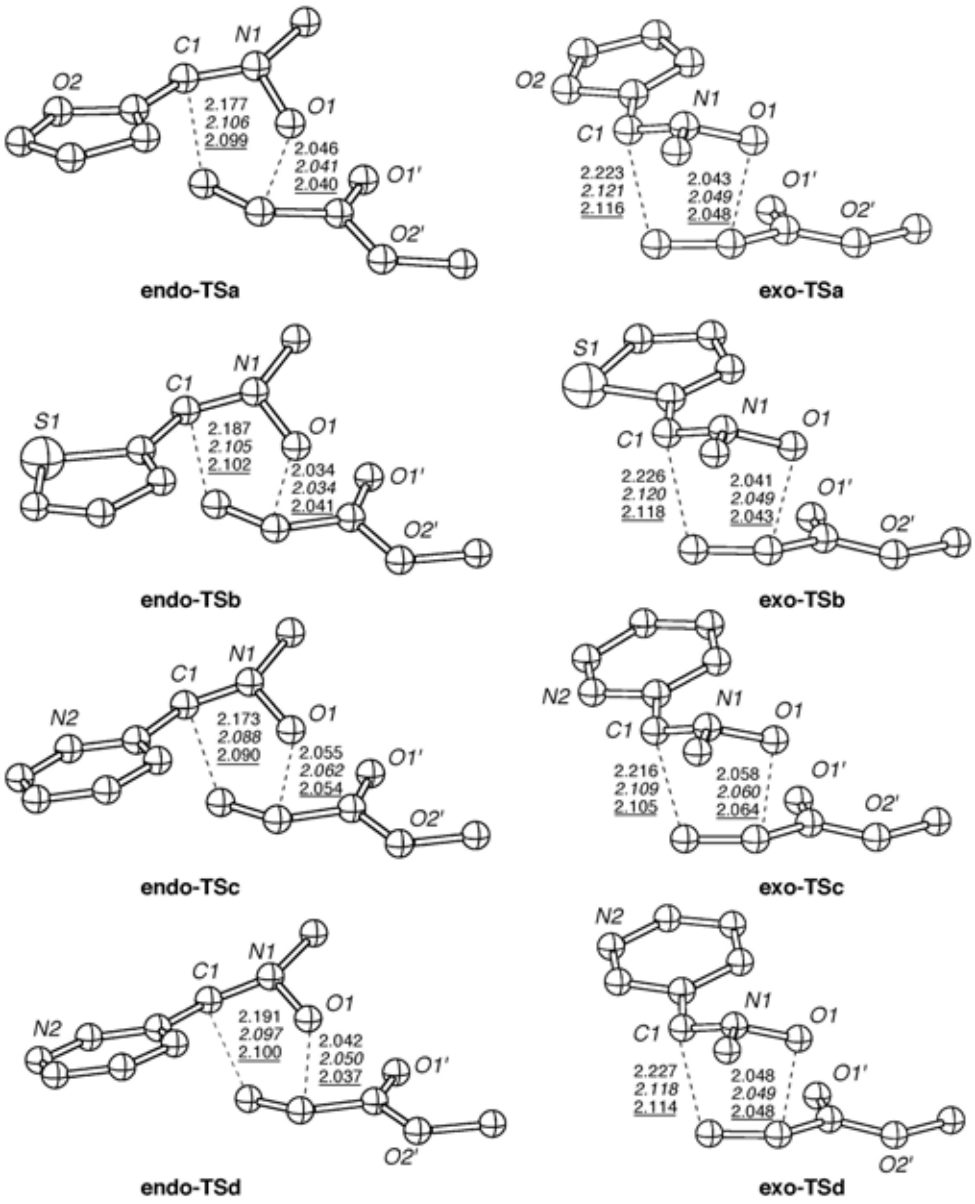


Figure 3. Optimized transition states for the cycloaddition of nitrones (**1**) with (**2**). Forming bond lengths are given for HF/3-21G (normal typeface), PM3 (italic typeface) and AM1 (underlined typeface) calculations.

EXPERIMENTAL SECTION

General Remarks. The reaction flasks and other glass equipment were heated in an oven at 130°C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the position of the spots were detected with 254 nm UV light or by spraying with one of the following staining systems: 50% methanolic sulfuric acid, 5% ethanolic fosfomolibdic acid and iodine. Preparative column chromatography was performed on columns of silica gel (60-240 mesh) and with solvents that were distilled prior to use. Preparative centrifugally accelerated radial thin layer chromatography (PCAR-TLC)[24] was performed with a Chromatotron® Model 7924 T (Harrison Research, Palo Alto, CA, USA); the rotors (1 or 2 mm layer thickness) were coated with silica gel Merck grade type 7749, TLC grade, with binder and fluorescence indicator (Aldrich 34,644-6) and the eluting solvents were delivered by the

pump at a flow-rate of 0.5-1.5 mL min^{-1}. Melting points were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity or on a Bruker 300 instrument in $CDCl_3$ at 55 °C. Chemical shifts are reported in ppm (δ) relative to $CHCl_3$ (δ = 7.26) in $CDCl_3$. Optical rotations were taken at 25 °C on a Perkin-Elmer 241 polarimeter. Elemental analysis were performed on a Perkin Elmer 240B microanalyzer. Nitrones (**1**) were prepared according the reported procedure.[13] Methyl acrylate (**2**) was purchased (Aldrich) and distilled prior the use.

General Protocol for the Cycloaddition of Nitrones (1) with Methyl Acrylate (2). A solution of the appropriate nitrone (**1**) (1 mmol) was dissolved in methyl acrylate (**2**) (4.3 g, 50 mmol) and the resulting mixture was stirred at reflux under an Ar atmosphere until no more nitrone was observed by TLC. The mixture was evaporated under reduced pressure and the products ratio was established by ^1H NMR analysis of the crude product. The residue was purified by preparative, centrifugally accelerated, radial, thin layer chromatography (Chromatotron®). Eluent is indicated in brackets for each compound.

(3*S,5*R**)-2-Benzyl-3-(2-furyl)-5-(methoxycarbonyl)isoxazolidine (3a):** (161 mg, 56%); R_f = 0.26 (Hexane / Et_2O, 70:30); oil; ^1H NMR δ 2.81-2.90 (m, 2H, H_{4a}, H_{4b}), 3.76 (s, 3H, OCH_3), 4.10 (br s, 2H, H_{AB}), 4.42 (t, 1H, *J* = 8.1 Hz, H_3), 4.64 (t, 1H, *J* = 7.3 Hz, H_5), 6.29 (m, 2H, H'_3,H'_4), 7.20-7.43 (m, 6H, ArH,H'_5); ^{13}C NMR δ 37.9, 51.4, 62.4, 66.1, 74.7, 108.4, 110.5, 127.1, 128.1, 128.6, 137.2, 142.3, 150.3, 170.3. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.74; H, 6.04; N, 4.98.

(3*R,5*R**)-2-Benzyl-3-(2-furyl)-5-(methoxycarbonyl)isoxazolidine (4a):** (40 mg, 14%); R_f = 0.30 (Hexane / Et_2O, 70:30); oil; ^1H NMR δ 2.74 (ddd, 1H, *J* = 5.8, 7.3, 12.6 Hz, H_{4a}), 2.90 (ddd, 1H, *J* = 7.3, 9.0, 12.6 Hz, H_{4b}), 3.76 (s, 3H, OCH_3), 4.03 and 4.20 (2d, 2H, *J* = 13.6 Hz, H_{AB}), 4.21 (t, 1H, *J* = 7.3 Hz, H_3), 4.71 (dd, 1H, *J* = 5.8, 9.0 Hz, H_5), 6.29 (dd, 1H, *J* = 0.8, 3.2 Hz, H'_3), 6.32 (dd, 1H, *J* = 1.6, 3.2 Hz, H'_4), 7.21-7.40 (m, 6H, ArH,H'_5); ^{13}C NMR δ 38.2, 52.2, 62.2, 67.5, 75.5, 108.1, 110.4, 127.2, 128.2, 128.8, 137.3, 142.5, 151.5, 172.0. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.71; H, 6.12; N, 5.01.

(3*R,4*S**)-2-Benzyl-3-(2-furyl)-4-(methoxycarbonyl)isoxazolidine (5a):** (29 mg, 10%); R_f = 0.33 (Hexane / Et_2O, 70:30); oil; ^1H NMR δ 3.68 (dt, 1H, *J* = 6.9, 7.6, H_4), 3.70 (s, 3H, OCH_3), 3.89 and 4.01 (2d, 2H, *J* = 13.8 Hz, H_{AB}), 4.21 (m, 2H, H_{5a},H_{5b}), 4.29 (d, 1H, *J* = 6.9 Hz, H_3), 6.30 (m, 2H, H'_3,H'_4), 7.20-7.36 (m, 5H, ArH), 7.40 (t, 1H, *J* = 1.2 Hz, H'_5); ^{13}C NMR δ 52.3, 52.5, 59.7, 66.1, 68.5, 108.7, 110.3, 127.2, 128.1, 128.7, 136.9, 142.7, 150.5, 172.4. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.71; H, 5.80; N, 4.62.

(3*S,5*R**)-2-Benzyl-3-(2-thienyl)-5-(methoxycarbonyl)isoxazolidine (3b):** (206 mg, 68%); R_f = 0.32 (Hexane / Et_2O, 75:25); oil; ^1H NMR δ 2.67-2-83 (m, 1H, H_{4a}), 2.97 (ddd, 1H, *J* = 7.8, 9.3, 12.9 Hz, H_{4b}), 3.73 (s, 3H, OCH_3), 4.01 and 4.06 (2d, 2H, *J* = 14.1 Hz, H_{AB}), 4.42 (t, 1H, *J* = 8.2 Hz, H_3), 4.62 (dd, 1H, *J* = 4.9, 9.3 Hz, H_5), 6.92-6.98 (m, 1H, $H_{4'}$), 7.07 (br d, 1H, *J* = 3.2 Hz, $H_{3'}$), 7.19-7.44 (m, 6H, ArH and

$H_{5'}$); ^{13}C NMR δ 42.5, 53.5, 59.8, 64.4, 74.3, 126.6, 127.3, 127.9, 128.0, 128.4, 128.8, 136.5, 142.0, 171.7. Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.42; H, 5.58; N, 4.55.

(3*R,5*R**)-2-Benzyl-3-(2-thienyl)-5-(methoxycarbonyl)isoxazolidine (4b):** (36 mg, 12%); R_f = 0.38 (Hexane / Et_2O, 75:25); oil; ^{1}H NMR δ 2.75 (ddd, 1H, *J* = 7.6, 9.0, 12.7 Hz, H_{4a}), 2.86 (ddd, 1H, *J* = 7.6, 9.0, 12.7 Hz, H_{4b}), 3.79 (s, 3H, OCH_3), 4.03 and 4.10 (2d, 2H, *J* = 13.9 Hz, H_{AB}), 4.42 (t, 1H, *J* = 7.3 Hz, H_3), 4.71 (dd, 1H, *J* = 5.4, 9.0 Hz, H_5), 6.98 (dd, 1H, *J* = 3.4, 4.9 Hz, $H_{4'}$), 7.04 (d, 1H, *J* = 3.4 Hz, $H_{3'}$), 7.25-7.39 (m, 5H, ArH), 7.40-7.44 (m, 1H, $H_{5'}$); ^{13}C NMR δ 42.5, 52.0, 60.1, 64.4, 75.2, 125.4, 125.6, 126.6, 127.1, 128.0, 128.8, 137.3, 142.0, 171.7. Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.44; H, 5.79; N, 4.71.

(3*R,4*S**)-2-Benzyl-3-(2-thienyl)-4-(methoxycarbonyl)isoxazolidine (5b):** (15 mg, 5%); R_f = 0.44 (Hexane / Et_2O, 75:25); oil; ^{1}H NMR δ 3.52 (q, 1H, *J* = 6.8 Hz, H_4), 3.77 (s, 3H, OCH_3), 3.88 and 4.14 (2d, 2H, *J* = 14 Hz, H_{AB}), 4.29 (d, 2H, *J* = 6.6 Hz, H_{5a},H_{5b}), 4.54 (d, 1H, *J* = 7.1 Hz, H_3), 7.02 (dd, 1H, *J* = 3.4, 5.1 Hz, $H_{4'}$), 7.14 (dd, 1H, *J* = 1.2, 3.4 Hz, $H_{3'}$), 7.25-7.45 (m, 6H, ArH and $H_{5'}$); ^{13}C NMR δ 52.3, 57.4, 59.8, 68.5, 68.8, 125.8, 126.0, 127.0, 127.4, 128.3, 129.0, 137.5, 142.2, 172.4. Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.21; H, 5.72; N, 4.50.

(3*S,5*R**)-2-Benzyl-3-(2-pyridyl)-5-(methoxycarbonyl)isoxazolidine (3c):** (161 mg, 54%); R_f = 0.28 (Hexane / Et_2O, 60:40); oil; ^{1}H NMR δ 2.88 (td, 1H, *J* = 7.3, 12.5 Hz, H_{4a}), 2.98 (ddd, 1H, *J* = 5.6, 8.5, 12.5 Hz, H_{4b}), 3.70 (s, 3H, OCH_3), 3.94 and 4.24 (2d, 2H, *J* = 13.4 Hz, H_{AB}), 4.33 (dd, 1H, *J* = 5.6, 7.3 Hz, H_3), 4.55 (dd, 1H, *J* = 7.3, 8.5 Hz, H_5), 7.04-7.35 (m, 5H, ArH), 7.47-7.57(m, 2H, $H_{3'}$ and $H_{5'}$), 8.44-8.45(m, 2H, $H_{4'}$ and $H_{6'}$); ^{13}C NMR δ 39.2, 51.9, 61.7, 69.5, 76.1, 121.5, 122.2, 127.0, 128.0, 128.8, 137.2(2C), 148.8, 159.1, 172.1. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.73; H, 6.38; N, 9.07.

(3*R,5*R**)-2-Benzyl-3-(2-pyridyl)-5-(methoxycarbonyl)isoxazolidine (4c):** (48 mg, 16%); R_f = 0.25 (Hexane / Et_2O, 60:40); oil; ^{1}H NMR δ 2.81 (ddd, 1H, *J* = 5.1, 6.8, 12.9 Hz, H_{4a}), 3.02 (ddd, 1H, *J* = 8.3, 9.3, 12.9 Hz, H_{4b}), 3.64 (s, 3H, OCH_3), 3.99 (s, 2H, H_{AB}), 4.15 (dd, 1H, *J* = 6.8, 8.3 Hz, H_3), 4.67 (dd, 1H, *J* = 5.1, 9.3 Hz, H_5), 7.04-7.25 (m, 5H, ArH), 7.54-7.56 (m, 2H, $H_{3'}$ and $H_{5'}$), 8.42-8.44 (m, 2H, $H_{4'}$ and $H_{6'}$); ^{13}C NMR δ 40.1, 51.9, 60.4, 70.3, 75.1, 121.7, 122.5, 127.1, 128.1, 128.3, 136.7, 137.0, 148.9, 159.5, 172.0. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.69; H, 5.88; N, 9.15.

(3*R,4*S**)-2-Benzyl-3-(2-pyridyl)-4-(methoxycarbonyl)isoxazolidine (5c):** (27 mg, 9%); R_f = 0.31 (Hexane / Et_2O, 60:40); oil; ^{1}H NMR δ 3.75 (s, 3H, OCH_3), 3.98 (td, 1H, *J* = 5.3, 8.3 Hz, H_4), 4.01 and 4.09 (2d, 2H, *J* = 13.4 Hz, H_{AB}), 4.26 (t, 1H, *J* = 8.3 Hz, H_{5a}), 4.35 (dd, 1H, *J* = 5.3, 8.3 Hz, H_{5b}), 4.51 (d, 1H, *J* = 5.3 Hz, H_3), 7.08-7.30 (m, 7H, ArH, $H_{3'}$ and $H_{5'}$), 7.60 (dt, 1H, *J* = 1.6, 7.7 Hz, $H_{4'}$), 8.53 (dd, 1H, *J* = 1.6, 4.8 Hz, $H_{6'}$); ^{13}C NMR δ 52.2, 54.4, 60.2, 68.7, 73.0, 122.3, 122.4, 127.2, 128.2, 129.0, 136.4, 137.0, 149.2, 159.0, 173.0. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.32; H,

6.14; N, 9.4.

(3*S,5*R**)-2-Benzyl-3-(3-pyridyl)-5-(methoxycarbonyl)isoxazolidine (3d):** (155 mg, 52%); R_f = 0.25 (Et_2O); oil; ^{1}H NMR δ 2.62 (ddd, 1H, *J* = 8.1, 8.6, 12.6 Hz, H_{4a}), 2.84 (ddd, 1H, *J* = 5.2, 7.1, 12.6 Hz, H_{4b}), 3.76 (s, 3H, OCH_3), 3.91 and 4.07 (2d, 2H, *J* = 13.8 Hz, H_{AB}), 4.08 (t, 1H, *J* = 7.4 Hz, H_3), 4.63 (dd, 1H, *J* = 5.2, 8.6 Hz, H_5), 7.09-7.76 (m, 7H, ArH, $H_{4'}$ and $H_{5'}$), 8.49 (dd, 1H, *J* = 1.6, 4.7 Hz, $H_{6'}$), 8.57 (d, 1H, *J* = 2.0 Hz, $H_{2'}$); ^{13}C NMR δ 42.6, 52.2, 60.9, 66.5, 75.5, 123.5, 127.3, 128.2, 128.9, 134.7, 134.8, 136.9, 149.3 (2C), 171.7. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.29; H, 5.875; N, 9.51.

(3*R,5*R**)-2-Benzyl-3-(3-pyridyl)-5-(methoxycarbonyl)isoxazolidine (4d):** (51 mg, 17%); R_f = 0.29 (Et_2O); oil; ^{1}H NMR δ 2.60 (ddd, 1H, *J* = 4.5, 8.2, 12.8 Hz, H_{4a}), 2.95 (td, 1H, *J* = 8.5, 12.8 Hz, H_{4b}), 3.74 (s, 3H, OCH_3), 3.83- 3.91 (m, 1H, H_5), 3.85 and 4.00 (2d, 2H, *J* = 14.9 Hz, H_{AB}), 4.21 (t, 1H, *J* = 8.4 Hz, H_3), 7.15-7.33 (m, 6H, ArH and $H_{5'}$), 7.69-7.76 (m, 1H, $H_{4'}$), 8.46-8.48 (m, 1H, $H_{6'}$), 8.52 (d, 1H *J* = 2.0 Hz, $H_{2'}$); ^{13}C NMR δ 42.0, 52.0, 59.3, 66.9, 74.7, 123.5, 127.1, 128.1, 128.5, 134.6, 134.8, 136.6, 149.3 (2C), 172.1. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.52; H, 5.73; N, 9.11.

(3*R,4*S**)-2-Benzyl-3-(3-pyridyl)-4-(methoxycarbonyl)isoxazolidine (5d):** (33 mg, 11%); R_f = 0.32 (Et_2O); oil; ^{1}H NMR δ 3.38 (dt, 1H, *J* = 5.6, 8.1 Hz, H_4), 3.71 (s, 3H, OCH_3), 3.87 and 3.93 (2d, 2H, *J* = 13.9 Hz, H_{AB}), 4.15 (d, 1H, *J* = 7.2 Hz, H_3), 4.23 (t, 1H, *J* = 8.5 Hz, H_{5a}), 4.27 (dd, 1H, *J* = 5.6, 8.5 Hz, H_{5b}), 7.16-7.29 (m, 6H, ArH and $H_{5'}$), 7.76 (td, 1H, *J* = 1.9, 7.9 Hz, $H_{4'}$), 8.51 (dd, 1H, *J* = 1.5, 4.8 Hz, $H_{6'}$), 8.64 (d, 1H, *J* = 2.1 Hz, $H_{2'}$); ^{13}C NMR δ 52.3, 56.8, 59.8, 68.3, 70.6, 123.7, 127.4, 128.1, 128.8, 134.8, 135.1, 136.8, 149.5(2C), 172.1. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.66; H, 5.95; N, 9.49.

General Protocol for the Reduction of Isoxazolidines. To a solution of the corresponding isoxazolidine (0.5 mmol) in THF (5 mL) were added AcOH (10 mL) and H_2O (5 mL). The resulting solution was treated with Zn dust (0.2 g, 3 mmol) and heated at 60 °C for 5 h. The reaction mixture was allowed to cool to rt and filtered; the filtrate was treated with saturated aq. Na_2SO_4 and the resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative, centrifugally accelerated, radial, thin-layer cromatography (Chromatotron®). Eluent is indicated in brackets for each compound.

(3*R,5*R**)-1-Benzyl-5-(2-furyl)-3-hydroxy-2-pyrrolidinone (7a):** (118 mg, 92%); R_f = 0.30 (Et_2O); white solid; mp 134-136 °C (Et_2O); ^{1}H NMR δ 2.23 (dt, 1H, *J* = 8.6, 12.9 Hz, H_{4a}), 2.67 (ddd, 1H, *J* = 6.8, 8.6, 12.9 Hz, H_{4b}), 3.32 (br s, 1H, ex. D_2O, OH), 3.61 and 4.89 (2d, 2H, *J* =14.7 Hz, H_{AB}), 4.41 (t, 1H, *J* = 8.6 Hz, H_3), 4.43 (dd, 1H, *J* = 6.8, 8.6 Hz, H_5), 6.25 (dd, 1H, *J* =0.7, 3.2 Hz, $H_{3'}$), 6.34 (dd, 1H, *J* = 1.8, 3.2 Hz, $H_{4'}$), 7.11-7.30 (m, 5H, ArH), 7.39 (dd, 1H, *J* =0.7, 1.8 Hz, $H_{5'}$); ^{13}C NMR δ 33.8, 44.8, 51.3, 69.4, 110.1, 110.4, 127.6, 128.3, 128.6, 136.0, 143.3, 150.6, 174.1. Anal. Calcd for $C_{15}H_{15}NO_3$: C,

70.02; H, 5.88; N, 5.44. Found: C, 70.16; H, 5.70; N, 5.61.

(3*S,5*R**)-1-Benzyl-5-(2-furyl)-3-hydroxy-2-pyrrolidinone (8a):** (123 g, 96%); R_f = 0.41 (Et_2O); white solid; mp 91-93 °C (Et_2O); ^{1}H NMR δ 2.22 (dt, 1H, *J* = 8.8, 13.0 Hz, H_{4a}), 2.54 (ddd, 1H, *J* = 2.1, 8.8, 13.0 Hz, H_{4b}), 3.66 and 4.97 (2d, 2H, *J* =14.7 Hz, H_{AB}), 4.30 (br s, 1H, ex. D_2O, OH), 4.48 (dd, 1H, *J* = 2.1, 8.8 Hz, H_5), 4.80 (t, 1H, *J* = 8.8 Hz, H_3), 6.16 (dd, 1H, *J* =0.8, 3.3 Hz, $H_{3'}$), 6.30 (dd, 1H, *J* = 1.8, 3.3 Hz, $H_{4'}$), 7.30-7.18 (m, 5H, ArH), 7.39 (dd, 1H, *J* =0.8, 1.8 Hz, $H_{5'}$); ^{13}C NMR δ 33.8, 44.8, 51,5, 69.1, 108.5, 110.3, 127.7, 128.3, 128.7, 135.5, 143.0, 151.8, 175.1. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.28; H, 5.59; N, 5.27.

(3*R,5*R**)-1-Benzyl-5-(2-thienyl)-3-hydroxy-2-pyrrolidinone (7b):** (129 mg, 94%); R_f = 0.23 (Et_2O); white solid; mp 131-133 °C (EtOAc); ^{1}H NMR δ 2.06 (td, 1H, *J* = 9.0, 12.9 Hz, H_{4a}), 2.86 (ddd, 1H, *J* = 6.4, 8.1, 12.9 Hz, H_{4b}); 3.63 and 4.98 (2d, 2H, *J* = 14.6 Hz, H_{AB}), 4.42 (t, 1H, *J* = 8.8 Hz, H_5), 4.60 (dd, 1H, *J* = 6.4, 9.0 Hz, H_3), 6.90 (dd, 1H, *J* = 1.2, 3.4 Hz, $H_{3'}$), 6.96 (dd, 1H, *J* = 3.4, 5.1 Hz, $H_{4'}$), 7.03-7.06 (m, 1H), 7.24–7.27 (m, 5H, ArH), 7.33–7.34 (m, 1H, $H_{5'}$); ^{13}C NMR δ 38.8, 44.6, 53.6, 69.6, 126.4, 126.9, 127.4, 127.7, 128.5, 128.6, 136.1, 142.9, 174.9. Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12. Found: C, 66.17; H, 5.39; N, 5.03.

(3*R,5*R**)-1-Benzyl-5-(2-pyridyl)-3-hydroxy-2-pyrrolidinone (7c):** (123 mg, 92%); R_f = 0.46 (Et_2O / MeOH, 90:10); foam; ^{1}H NMR δ 2.05(td, 1H, *J* = 3.0, 13.9 Hz, H_{4a}), 2.59 (td, 1H, *J* = 7.8, 13.9 Hz, H_{4b}), 3.58 and 4.89 (2d, 2H, *J* = 14.9 Hz, H_{AB}), 4.33 (dd, 1H, *J* = 3.0, 7.8 Hz, H_5), 4.45 (dd, 1H, *J* = 3.0, 7.8 Hz, H_3), 5.50 (br s, 1H, OH), 7.04-7.24 (m, 7H, ArH, $H_{3'}$ and $H_{5'}$), 7.63 (dd, 1H, *J* = 1.8, 7.7 Hz, $H_{4'}$), 8.54 (ddd, 1H, *J* = 0.9, 1.8, 4.8 Hz, $H_{6'}$); ^{13}C NMR δ 35.0, 44.9, 60.8, 69.8, 123.1, 123.3, 127.6, 128.3, 128.6, 136.0, 137.2, 150.0, 158.2, 174.6. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.48; H, 5.89; N, 10.59.

(3*S,5*R**)-1-Benzyl-5-(2-pyridyl)-3-hydroxy-2-pyrrolidinone (8c):** (125 mg, 93%); R_f = 0.53 (Et_2O / MeOH, 90:10); white solid; mp 153-155°C (EtOAc); ^{1}H NMR δ 2.29 (td, 1H, *J* = 8.9, 12.9 Hz, H_{4a}), 2.46 (ddd, 1H, *J* = 2.1, 8.2, 12.9 Hz, H_{4b}), 3.63 and 5.00 (2d, 2H, *J* = 14.9 Hz, H_{AB}), 3.80 (br s, 1H, OH), 4.53 (dd, 1H, *J* = 2.1, 8.9 Hz, H_5), 4.86 (t, 1H, *J* = 8.2 Hz, H_3), 6.96-6.99(m, 1H, ArH), 7.10-7.25 (m, 6H, ArH, $H_{3'}$ and $H_{5'}$), 7.59 (dt, 1H, *J* = 1.8, 7.7 Hz, $H_{4'}$), 8.56 (ddd, 1H, *J* = 1.0, 1.8, 4.8 Hz, $H_{6'}$); ^{13}C NMR δ 35.7, 45.4, 59.8, 69.0, 121.4, 122.8, 127.6, 128.4, 128.6, 135.7, 136.7, 150.4, 159.3, 175.7. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.79; H, 6.17; N, 10.62.

(3*R,5*R**)-1-Benzyl-5-(3-pyridyl)-3-hydroxy-2-pyrrolidinone (7d):** (129 mg, 96%); R_f = 0.26 (EtOAc); oil; ^{1}H NMR δ 1.91 (td, 1H, *J* = 7.6, 13.7 Hz, H_{4a}), 2.77 (td, 1H, *J* = 7.7, 13.7 Hz, H_{4b}), 3.55 and 4.93 (2d, 2H, *J* = 14.2 Hz, H_{AB}), 4.31 (t, 1H, *J* = 7.6 Hz, H_5), 4.49 (t, 1H, *J* = 7.7 Hz, H_3), 6.40 (br s, 1H, OH), 6.94 (br s, 1H, ArH), 7.19-7.23 (m, 4H, ArH), 7.25 (dd, 1H, *J* = 4.4, 7.7 Hz, $H_{5'}$), 7.60 (d, 1H, *J* = 7.7 Hz, $H_{4'}$), 8.37 (s, 1H, $H_{2'}$), 8.56 (d, 1H, *J* = 4.4 Hz, $H_{6'}$); ^{13}C NMR δ 37.2, 44.8, 56.3, 69.4, 124.2,

124.3, 127.9, 128.4, 128.8, 135.1, 135.6, 149.0, 149.7, 175.9. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.84; H, 5.86; N, 10.32.

(3*S,5*R**)-1-Benzyl-5-(3-pyridyl)-3-hydroxy-2-pyrrolidinone (8d):** (123 mg, 92%); R_f = 0.31 (EtOAc); oil; ^{1}H NMR δ 2.26 (ddd, 1H, *J* = 3.5, 8.0, 13.4 Hz, H_{4a}), 2.39 (td, 1H, *J* = 7.8, 13.4 Hz, H_{4b}), 3.60 and 5.00 (2d, 2H, *J* = 14.8 Hz, H_{AB}), 4.51 (dd, 1H, *J* = 3.5, 7.8 Hz, H_5), 4.67 (t, 1H, *J* = 7.9 Hz, H_3), 6.37 (br s, 1H, OH), 7.04-7.08 (m, 1H, ArH), 7.15-7.40 (m, 5H, ArH and $H_{5'}$), 7.71 (d, 1H, *J* = 7.9 Hz, $H_{4'}$), 8.37 (br s, 1H, $H_{2'}$), 8.51-8.53 (m, 1H, $H_{6'}$); ^{13}C NMR δ 37.0, 44.9, 56.6, 68.6, 123.9, 124.2, 127.4, 128.3, 128.6, 134.4, 135.7, 149.1, 149.4, 175.0. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.82; H, 5.90; N, 10.5.

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