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1,3-Dipolar Cycloadditions VI [1]. Structure and Conformation of Cycloadducts from Reactions of C-Aryl-N-phenylnitrones with Substituted Cinnamic Acid Amides

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Summary. Studies on cycloadditions of C,N-diarylnitrones to cinnamic acid amides were carried out. The diastereoisomeric (**I**, **II**) and (in some cases) regioisomeric (**III**) cycloadducts obtained were characterized by spectroscopic and X-ray data. Conformational studies were carried out by molecular modelling.

Keywords. 1,3-Dipolar cycloaddition; Nitrones; Cinnamic acid amides; X-Ray crystallography; Conformational analysis.

Introduction

1,3-Dipolar cycloadditions of nitrones to olefins have been studied extensively [2, 3]. Certain areas, however, remain relatively unexplored, such as the detailed investigation of the regio-chemical and stereochemical course of the cycloaddition of nitrones to 1,2-disubstituted electron-deficient olefins. We report here our studies involving the cycloaddition of C,N-diarylnitrones to cinnamic acid amides.

Results and Discussion

1,3-Dipolar cycloaddition of C-aryl-N-phenylnitrones **1–4** to N-cinnamoyl-piperidines **5–7** afforded mixtures of diastereoisomeric products (types **I**, **II**); small amounts of regioisomeric products (type **III**) were obtained when the aryl rings had electron-withdrawing substituents. Structure elucidations were accomplished by spectroscopic (particularly NMR) and X-ray techniques.

The reactions were carried out using equimolar amounts of the reactants in refluxing toluence under nitrogen [4, 5] for about 30–40 h. At the end of this

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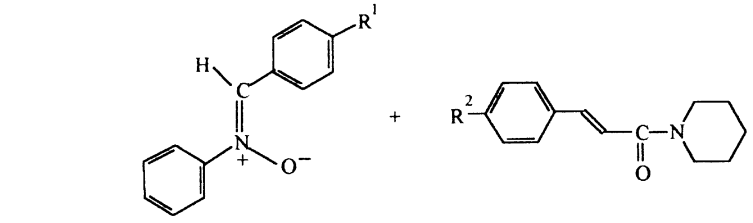
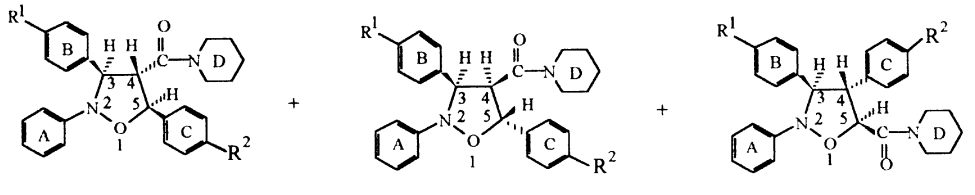


1: R^1 = Cl **3**: R^1 = OMe
2: R^1 = NO_2 **4**: R^1 = H

5: R^2 = Cl
6: R^2 = NO_2
7: R^2 = H



I **II** **III**

Major (all-*trans* product)	Minor (3,4 -*cis*-4,5-*trans* product)	All-*trans* regioisomer
8 : R^1 = NO_2, R^2 = Cl	**9** : R^1 = NO_2, R^2 = Cl	**10** : R^1 = NO_2, R^2 = Cl
11 : R^1 = R^2 = Cl	**12** : R^1 = R^2 = Cl	**13** : R^1 = R^2 = Cl
14 : R^1 = OMe, R^2 = Cl	**15** : R^1 = OMe, R^2 = Cl	——
16 : R^1 = H, R^2 = Cl	**17** : R^1 = H, R^2 = Cl	——
18 : R^1 = Cl, R^2 = NO_2	**19** : R^1 = Cl, R^2 = NO_2	**20** : R^1 = Cl, R^2 = NO_2
21 : R^1 = R^2 = H	**22** : R^1 = R^2 = H	——

Scheme 1

period, only small amounts of the dipolarophile survived. Removal of the solvent under reduced pressure and chromatography over neutral alumina furnished the products. The all-*trans* (type **I**) and the diastereoisomeric 3,4-*cis*-4,5-trans (type **II**) 5-aryl-4-piperidinyloxo-isoxazolidine cycloadducts were isolated for all substrates in this series of reactions. The regioisomeric (type **III**) 4-aryl-5-piperidinyloxo-isoxazolidines were also obtained in certain cases (Scheme 1). Product ratios of the cycloadducts were determined by ^{1}H NMR analysis of crude reaction mixtures. For three typical series of cycloadducts, *i.e.* $R^1 = NO_2$, $R^2 = Cl$; $R^1 = R^2 = Cl$; and $R^1 = H$, $R^2 = Cl$, product ratios were found to be 100:12:9 (**8**:**9**:**10**), 100:12:11 (**11**:**12**:**13**), and 100:10 (**16**:**17**), respectively. The all-*trans* isomer (type **I**) was the major product in this series. The structures and substitution patterns of the three types of cycloadducts followed from spectroscopic investigations.

All compounds showed amide bands at 1630–1660 cm^{-1} in their IR spectra. The three types could be differentiated from their ^{1}H and ^{13}C NMR characteristics. Decoupling and two-dimensional ^{1}H, ^{1}H-COSY experiments established 2-phenyl-

3,4,5-trisubstituted isoxazolidine derived structures for all cycloadducts; the sequence -O-C(5)H-C(4)H-C(3)H-N(2)Ar- was found to be present in all cases. Two-dimensional long-range COSY experiments revealed correlations between the benzylic proton and C(3)-H for all three types of cycloadducts. Such long range correlations may result from C(5)-H and the benzylic protons in types **I** and **II** as well as from the benzylic protons and C(4)-H in type **III** cycloadducts. Thus, types **I** and **II** are 2-phenyl-3,5-diaryl-4-piperidinyloxo-isoxazolidine derivatives stereoisomeric at C(3); the relative *trans*-C(4)H-C(5)H stereochemistry follows from the substrate amide. Type **III** cycloadducts, on the other hand, are regioisomers with 2-phenyl-3,4-diaryl-5-piperidinyloxo-isoxazolidine structures. X-Ray crystallographic analysis of representatives of type **I** (**16**) and type **III** (**20**) finally confirmed the structural and stereochemical features of the cycloadducts. In the ^{1}H NMR spectra, chemical shifts of C(3)H, C(4)H, and C(5)H were sharply differentiated in the three types of cycloadducts. The C(3)H doublet (in the series **11**, **12**, **13**) appeared at *ca*. 5.2 ppm in **I** and *ca*. 4.7 ppm in **II** compounds, C(5)H was found as a doublet in the region of *ca*. 5.3 ppm (**I**) and *ca*. 6.0 ppm (**II**). C(4)H resonated comparatively upfield for both types (3.7 ppm). In the regioisomeric type **III** series, H-3 and H-5 were shielded by ~0.7 and ~1.0 ppm, respectively, compared to type **I**; the benzylic H-4 (double doublet) was deshielded by ~0.7 ppm. These relationships were typical of all series.

The X-ray analysis of the cycloadduct **16** (type **I**; $R^1 = H$, $R^2 = Cl$) showed that the compound had all-*trans* stereochemistry, including the lone pair of ring nitrogen (N2, *trans* to C(3)H) (Fig. 1). It has been found experimentally that the

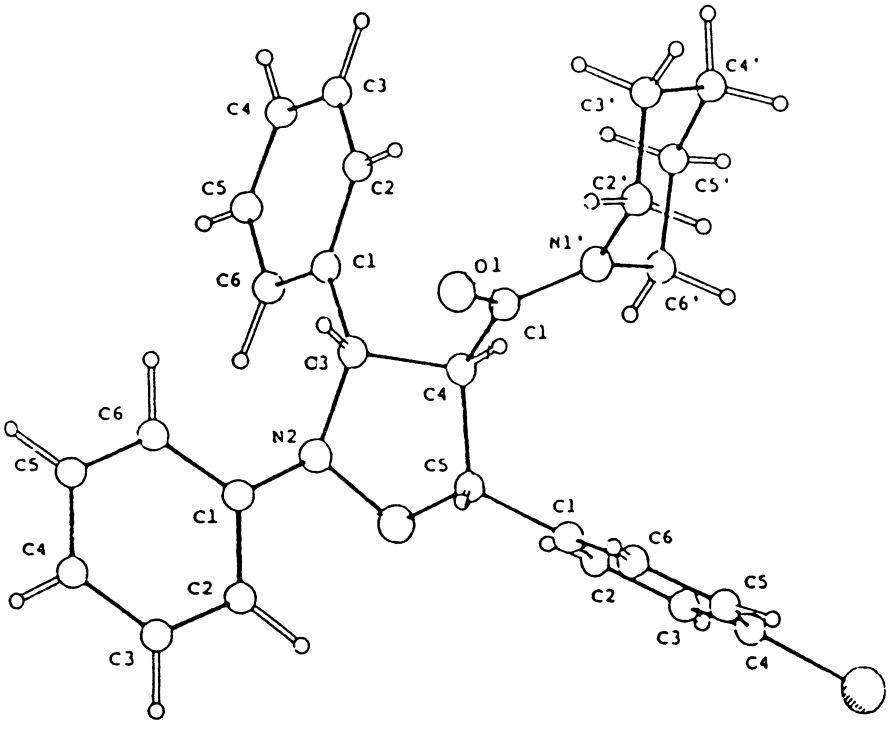


Fig. 1. Structure of **16** (all-*trans* isomer)

Table 1. Relative values of potential energy of **16** and **20**

Isomer	Relative potential energy
	kJ/mol
All-*trans* (**16**; type **I**)	0.0
3,4-*cis* (**17**; type **II**)	16.3
All-*trans* (**20**; type **III**)	0.0
3,4-*cis* (**23**)	12.6

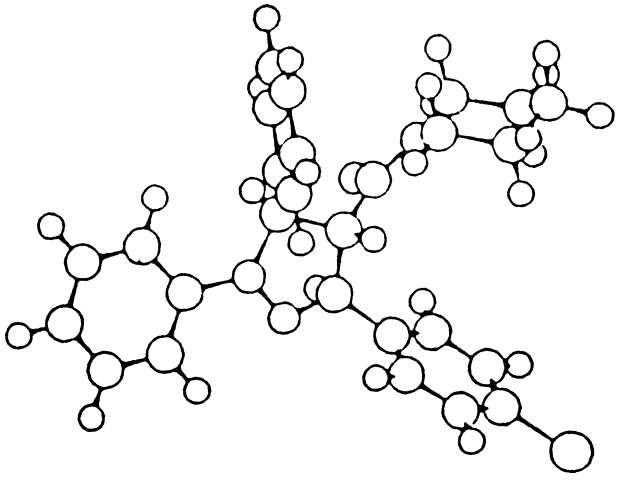


Fig. 2. Molecular modelling of **16** (all-*trans* isomer)

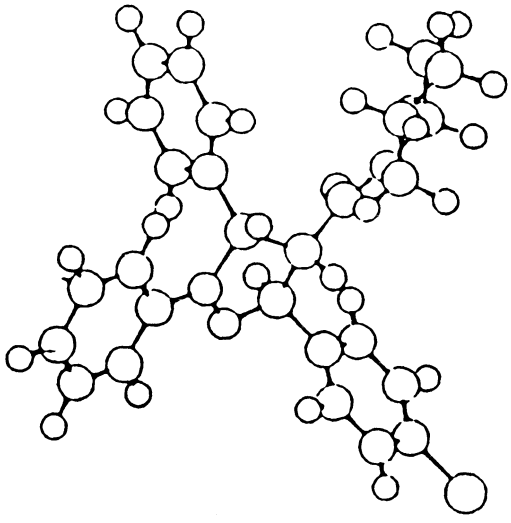


Fig. 3. Molecular modelling of **17** (3,4-*cis* isomer)

all-*trans* isomer of type **I** was the major product in this cycloaddition series. The minor cycloadducts with 3,4-*cis* (type **II**) orientation of the isoxazolidine ring protons were characterized on the basis of one- and two-dimensional NMR experiments by comparison to the major all-*trans* isomer. X-Ray studies of compound **20** (type **III**, $R^1 = NO_2$, $R^2 = Cl$) showed that the compound is regioisomeric to type **I** adducts and has all-*trans* stereochemistry (Fig. 4).

Our endeavour was also focussed on the conformational analysis and energy minimization of the regio- and stereoisomers by taking advantage of the X-ray crystallographic data of **16** and **20**. Energy minimization has been achieved by the conjugate gradient method using the DISCOVER module of the Insight-II molecular modelling package (MSI Inc) running on a Silicon Graphics Indigo 2 workstation [6, 7]. For all different isomers the energy minimizations were carried out for 2000 steps, and in most of the cases the RMS derivative of energy reached a value of 0.001 kcal/mol when the minimizations were stopped. The derived structures are given in Figs. 2, 3, 5, and 6. The structures of **16** (Fig. 1) and **20** (Fig. 4) are similar to those in Figs. 2 and 5 which were obtained by molecular modelling.

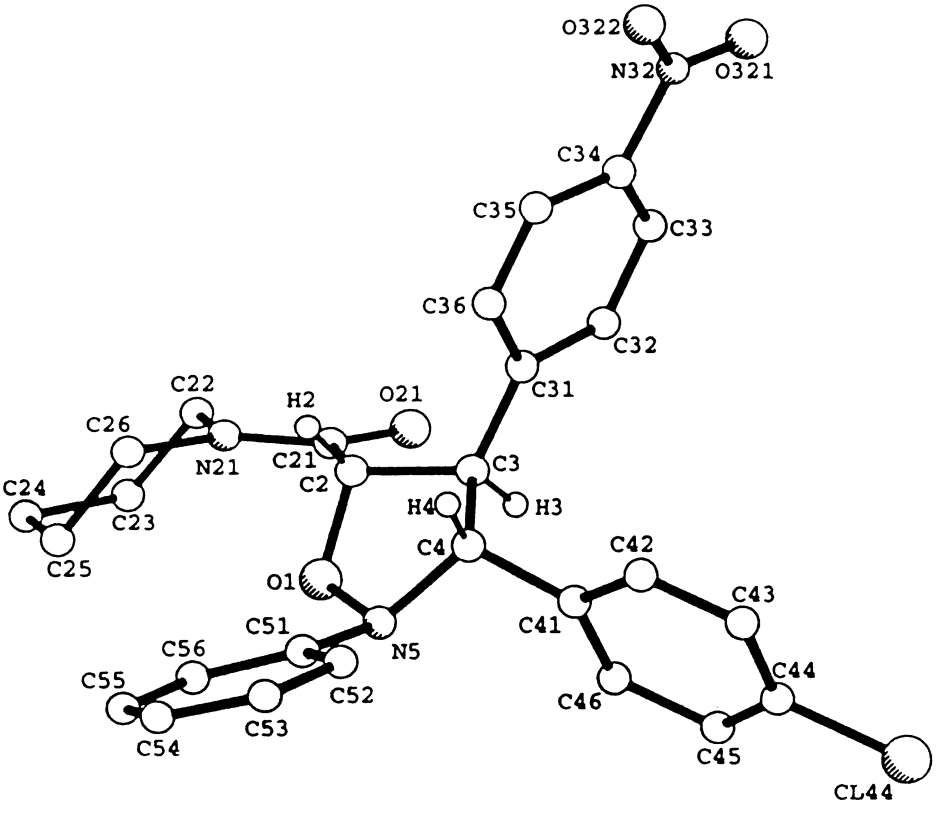


Fig. 4. Structure of **20** (all-*trans* regioisomer)

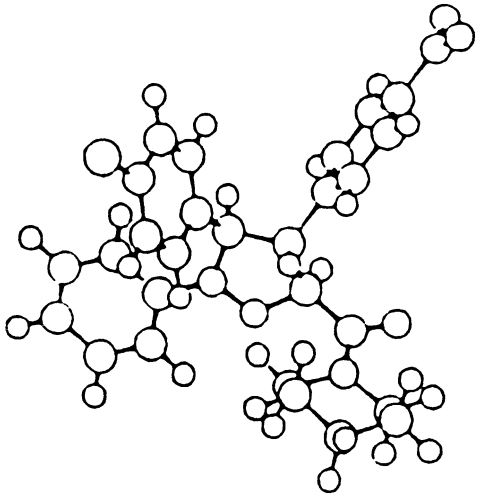


Fig. 5. Molecular modelling of **20** (all-*trans* regioisomer)

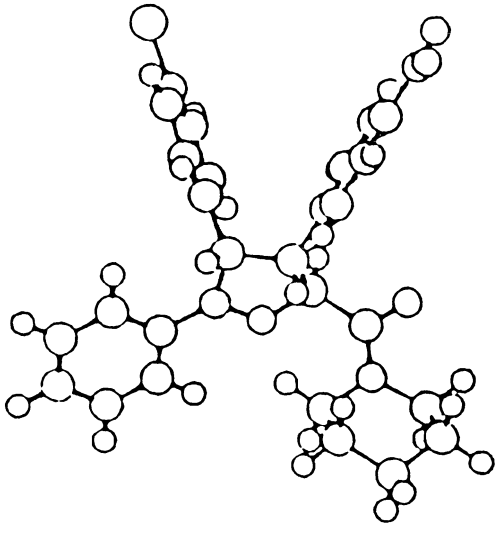


Fig. 6. Molecular modelling of **23** (3, 4-*cis* regioisomer)

Experimental

Melting points were recorded on an electrically heated Kofler Block apparatus and are uncorrected. Silica gel (60–120 mesh) was used for column chromatography. Anhydrous Na_2SO_4 was used for drying extracts. Analytical samples were routinely dried over $CaCl_2$ *in vacuo* at room temperature. IR spectra were recorded in KBr pellets or as thin films on a Perkin-Elmer 682 spectrometer. UV spectra were measured on a Hitachi U-3501 spectrometer in 95% aldehyde-free methanol. Mass spectra were recorded with a JEOL JEM-D 300 mass spectrometer. NMR spectra ^{1}H: 300 MHz, ^{13}C: 75.5 MHz) were recorded on a Bruker AM-300L spectrometer using *TMS* as standard ^{1}H NMR assignments were confirmed by decoupling, COSY, and COSY-LR experiments; ^{13}C NMR assignments by DEPT and two-dimensional correlation experiments. Chemical shifts are given in ppm, coupling constants in Hz. A–C refers to the respective rings (Scheme 1). Elemental analyses

were in good agreement with calculated values. X-Ray structural analyses were performed on a four-circle automatic diffractometer PHILIPS PW 1100 using the SHELXS programme. The refinement of the structure was done by the SHELX76 and SHELX93 programmes. X-Ray data are deposited at the Cambridge Structural Data Centre under numbers AB0001/INDCUCH and AB0002/INDCUCH.

General Method

A solution of piperidide **5–7** (0.0066 mol) in anhydrous toluene (50 cm^3) was added to a hot solution of nitrone **1–4** (0.0066 mol) in anhydrous toluene (20 cm^3). The reaction mixture was refluxed under a nitrogen atmosphere for 30–40 h. The solvent was removed from the crude reaction mixture, and the mixture was chromatographed over neutral alumina to separate the products.

3RS-(3R,4S*,5R*)-2-Phenyl-3-(4-nitrophenyl)-5-(4-chlorophenyl)-4-piperidinyloxo-isoxazolidine* (**8**; $C_{27}H_{26}N_3O_4Cl$)

Pale yellow crystals; m.p.: 132°C; yield: 1.56 g (40.6%); IR: $\nu = 2920$-2840 (m, -CH_2-), 1630 (s, amide >C=O), 840 (m, 1, 4-disubstituted benzene ring), 760, 700 (m, monosubstituted benzene ring); cm^{-1}; UV: $\lambda_{max}(\log\varepsilon) = 267(3.07)$ nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 5.48 (1H, d, $J = 8.0$, H-3), 3.73(1H, dd, $J = 8.0$, 9.4, H-4), 5.30 (1H, d, $J = 9.4$; H-5), 3.60 and 2.72 (2H, m each, H-2′, H-6′), 1.41 (4H, m, H-3′,4′), 0.94 (2H, m, H-5′), 6.97 (2H, d, $J = 8.4$, A,H-2,6), 6.98 (1H, m, A,H-4), 7.27 (2H, t, $J = 8.0$, A,H-3,5), 7.73 (2H, d, $J = 8.4$, B,H-2,6), 8.27 (2H, d, $J = 8.4$, B,H-3,5), 7.40–7.44 (C, 4H, m) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz) 74.87 (C-3), 62.74 (C-4), 84.22 (C-5), 43.90 (C-2′), 25.70 (C-3′), 24.07(C-4′), 26.30 (C-5′), 46.90 (C-6′), 165.66 (>C=O), 151.39 (A,C-1), 114.09 (A,C-2,6), 129.11 (A,C-3,5), 122.27 (A,C-4), 147.58 (B,C-1), 127.93 (B,C-2,6), 124.37 (B,C-3,5), 147.60 (B,C-4), 134.96 (C,C-1), 127.00 (C,C-2,6), 127.93 (C,C-3,5), 134.15 (C,C-4) ppm; MS (EI): $m/z = 491$ (M^+), 379 (M^+-$C_6H_{10}NO$), 267 (M^+-$C_{13}H_9N_2O_2$), 225 (379-C_8H_7OCl), 165 (249-$C_5H_{10}N$) 179 (225-NO_2), 139 (M^+-$C_{20}H_{20}N_3O_3$-2H).

3RS-(3R,4S*,5R*)-2-Phenyl-3-(4-nitrophenyl)-5-(4-chlorophenyl)-4-piperidinyloxo-isoxazolidine* (**9**; $C_{27}H_{26}N_3O_4Cl$)

White flakes; m.p.: 155°C; yield: 203 mg (7.5%); IR: $\nu = 2940$-2860 (m, -CH_2-), 1640 (s, amide >C=O), 850, 830 (m, 1,4-disubstituted benzene ring), 750, 690 (m, mono-substituted benzene ring) cm^{-1}; UV: $\lambda_{max}(\log\varepsilon) = 253$ (3.61) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 5.98 (1H, d, $J = 9.2$, H-3), 3.79 (1H, dd, $J = 9.2$, 10.4, H-4), 4.91 (1H, d, $J = 10.4$, H-5), 3.49 and 3.10 (2H, m each, H-2′, H-6′), 1.3–1.6 (6H, m, H-3′,4′,5′), 6.94 (2H, d, $J = 7.9$, A,H-2,6), 6.99 (1H, t, $J = 7.4$, A,H-4), 7.23 (2H, m, A,H-3,5), 7.71 (2H, d, $J = 8.6$, B,H-2,6), 8.25 (2H, d, $J = 8.6$, B,H-3,5), 7.45 (2H, d, $J = 8.5$, C,H-2,6), 7.37 (2H, d, $J = 8.5$, C,H-3,5) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 71.99 (C-3), 58.13 (C-4), 80.90 (C-5), 42.66 (C-2′), 25.20 (C-3′), 24.11 (C-4′), 26.30 (C-5′), 46.60 (C-6′), 164.93 (>C=O), 149.11 (A,C-1), 116.03 (A,C-2,6), 129.37 (A,C-3,5), 123.09 (A,C-4), 144.89 (B,C-1), 128.83 (B,C-2,6), 123.47 (B,C-3,5), 147.60 (B,C-4), 135.85 (C,C-1), 128.06 (C,C-2,6), 128.83 (C,C-3,5), 134.22 (C,C-4) ppm; MS (EI): $m/z = 491$ (M^+), 379 (M^+-$C_6H_{10}NO$), 267 (M^+-$C_{13}H_9N_2O_2$), 249 (M^+-$C_{13}H_{10}N_2O_3$), 225 (379-C_8H_7OCl), 179 (225-NO_2), 165 (249-$C_5H_{10}N$), 139 (M^+-$C_{20}H_{20}N_3O_3$-2H).

3RS-(3R,4S*,5R*)-2-Phenyl-3-(4-nitrophenyl)-4-(4-chlorophenyl)-5-piperidinyloxoisoxazolidine* (**10**; $C_{27}H_{26}N_3O_4Cl$)

Pale yellow amorphous solid; yield: 163 mg (6%); IR: $\nu = 2940$-2860 (m, -CH_2-), 1640 (s, amide >C=O), 850 (m, 1,4-disubstituted benzene ring), 770, 700 (m, monosubstituted benzene ring); cm^{-1}; UV: $\lambda_{max}(\log\varepsilon) = 260(3.73)$ nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 5.18 (1H, d, $J = 9.1$, H-3), 4.51

(1H, t, $J = 9.0$, H-4), 4.77 (1H, d, $J = 8.6$, H-5), 3.55 and 2.78 (2H, m each, H-2′, H-6′), 1.62 (4H, m, H-3′,4′), 0.98 (2H, m, H-5′), 6.88 (2H, d, $J = 8.5$ A,H-2,6), 6.95 (1H, m, A,H-4), 7.22 (2H, m, A,H-3,5), 8.10 (2H, d, $J = 8.4$, B, H-2,6), 8.42 (2H-d, $J = 8.4$, B, H-3,5), 7.49–7.53 (C, 4H, m) ppm.

3RS-(3R,4S*,5R*)-2-Phenyl-3-(4-chlorophenyl)-5-(4-chlorophenyl)-4-piperidinyloxoisoxazolidine* (**11**; $C_{27}H_{26}N_2O_2Cl_2$)

White crystals; m.p.: 125°C; yield: 1.34 g (42%); IR: $\nu = 2930$-2850 (m, -CH_2-), 1640 (s, amide >C=O), 1015 (s, aryl-Cl), 845, 825 (m, 1,4-disubstituted benzene ring), 770, 700 (m, monosubstituted benzene ring) cm^{-1}; UV: $\lambda_{max}(\log\varepsilon) = 316$ (3.79), 224 (4.92) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 5.22 (1H, d, $J = 8.2$, H-3), 3.79 (1H, dist t, H-4), 5.35 (1H, d, $J = 9.4$, H-5), 3.54 and 2.76 (2H, m each, H-2′, H-6′), 1.35 (4H, m, H-3′,4′), 0.77 and 0.94 (1H, m each, H-5′), 6.96 (2H, m, A,H-2, 4,6), 7.25 (2H, dist. t, A,H-3,5), 7.34–7.52 (8H, m, B,C, H-2,6,3,5) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 75.20 (C-3), 63.73 (C-4), 83.86 (C-5), 43.64 (C-2′), 25.70 (C-3′), 24.14 (C-4′), 26.22 (C-5′) 46.64 (C-6′), 166.07 (>C=O), 151.78 (A,C-1), 114.25 (A,C-2,6), 129.98 (A,C-3,5), 121.99 (A,C-4), 139.61 (B,C-1), 127.59 (B,C-2,6), 128.98 (B,C-3,5), 134.80 (B,C-4), 134.62 (C,C-1), 127.65 (C,C-2,6), 129.24 (C,C-3,5), 133.63 (C,C-4) ppm; MS (EI): $m/z = 480$ (M^+), 368 (M^+-C_5H_{10}N-CO), 341, 303, 268, 249 ($C_{14}H_{16}$NOCl, cycloreversion), 214 (C_5H_{10}NCl), 205, 165 (249-C_5H_{10}N), 139, 137, 101, 91, 84 (base peak).

3RS-(3R,4R*,5S*)-2-Phenyl-3-(4-chlorophenyl)-5-(4-chlorophenyl)-4-piperidinyloxo-isoxazolidine* (**12**; $C_{27}H_{26}N_2O_2Cl_2$)

White needle-shaped crystals; m.p.: 131°C; yield: 210 mg (6.6%); IR: $\nu = 2920$-2850 (m, -CH_2-), 1640 (s, amide >C=O), 1010 (m, aryl-Cl), 820 (m, 1,4-disubstituted benzene ring), 750, 690 (m, monosubstituted benzene ring) cm^{-1}; UV: $\lambda_{max}(\log\varepsilon) = 248$ (4.12), 223 (4.20) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 4.75 (1H, d, $J = 10.4$, H-3), 3.73 (1H, dd, $J = 9.1$, 10.4, H-4), 5.99 (1H, d, $J = 9.1$, H-5), 3.40–3.48 (2H, m, H-2′), 2.82 and 3.03 (1H, m each, H-6′), 1.44 (6H, m, H-3′,4′,5′), 6.94–7.00 (3H, m, A,H-2, 4,6), 7.21 (2H, t, $J = 8.3$, A,H-3,5), 7.47 (2H, d, $J = 8.5$,B,H-2,6), 7.34 (2H, d, $J = 8.5$, B,H-3,5), 7.43 (2H, d, $J = 8.5$, C,H-3,5) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 72.32 (C-3), 58.38 (C-4), 80.72 (C-5), 42.53 (C-2′), 25.16 (C-3′) 24.17 (C-4′), 26.10 (C-5′) 46.44 (C-6′), 165.48 (>C=O), 149.48 (A,C-1), 116.27 (A,C-2,6), 130.03 (A,C-3,5), 122.81 (A,C-4), 136.36 (B,C-1), 128.19 (B,C-2,6), 128.71 (B,C-3,5), 135.99 (B,C-4), 134.24 (C,C-1), 128.19 (C,C-2,6), 128.71 (C,C-3,5), 134.02 (C,C-4) ppm; MS (EI): $m/z = 480$ (M^+), 368 (M^+-C_5H_{10}N-CO), 249 ($C_{14}H_{16}$NOCl, cycloreversion), 214 (C_5H_{10}NCl), 165 (249-C_5H_{10}N), 139.

3RS-(3R,4S*,5R*)-2-Phenyl-3-(4-chlorophenyl)-5-(4-chlorophenyl)-4-piperidinyloxo-isoxazolidine* (**13**; $C_{27}H_{26}N_2O_2Cl_2$)

White amorphous solid; yield: 180 mg (5.7%); IR: $\nu = 2920$-2860 (m, -CH_2-), 1630 (s, amide >C=O), 1010 (m, aryl-Cl), 840 (s, 1,4-disubstituted benzene ring), 760, 700 (m, monosubstituted benzene ring); cm^{-1}; UV: $\lambda_{max}(\log\varepsilon) = 242(1.17), 223(4.47)$ nm; ^{1}H NMR ($CDCl_3, \delta, 300$ MHz): 4.49 (1H, d, $J = 8.2$, H-3), 4.38 (1H, dist t, H-4), 4.93 (1H, d, $J = 9.5$, H-5), 3.7–3.85 (2H, m, H-2′), 3.52 and 3.43 (1H, m each, H-6′), 1.60–1.70 (6H, m, H-3′,4′,5′), 7.10–7.14 (3H, m, A,H-2,4,6), 7.26 (2H, t, A,H-3,5), 7.42 (2H, d, $J = 8.6$, B,H-2,6), 7.33 (2H-d, $J = 8.6$, B,H-3,5), 7.29 (2H, d, $J = 8.4$, C,H-2,6), 7.37 (2H, d, $J = 8.5$, C,H-3,5) ppm.

3RS-(3R,4S*,5R*)-2-Phenyl-3-(4-methoxyphenyl)-5-(4-chlorophenyl)-4-piperidinyloxo-isoxazolidine* (**14**; $C_{28}H_{29}N_2O_3Cl$)

White needle-shaped crystals; m.p.: 156°C; yield: 1.61 g (51%); IR: $\nu = 2980$-2860 (m, -CH_2-), 1640 (s, amide >C=O), 1015 (s, aryl-Cl), 845, 825 (s, 1,4-disubstituted benzene ring), 770, 700 (m,

monosubstituted benzene ring) cm^{-1}; UV: $\lambda_{max}(\log\varepsilon) = 282$ (4.36) nm; ^1H NMR ($CDCl_3$, δ, 300 MHz): 5.11 (1H, d, $J = 8.4$, H-3), 3.75 (1H, br t, $J \sim 8.9$, H-4), 5.41 (1H, d, $J = 9.9$, H-5), 3.50 and 2.79 (2H, m each, H-2′, H-6′), 1.42 (4H, m, H-3′4′), 0.85 (2H, m, H-5′), 3.82 (3H, s, -OCH_3), 6.94 (3H, m, A,H-2,4,6), 7.23 (2H, dd, $J = 7.3$, 8.4, A,H-3,5), 7.44–7.47 (2H, m, overlapped signal, B,H-2,6), 6.99 (2H, d, $J = 7.8$, B,H-3,5), 7.44–7.47 (2H, m, overlapped signal, C,H-2,6), 7.36 (2H, d, $J = 8.4$, C,H-3,5) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 75.66 (C-3), 63.74 (C-4), 83.59 (C-5), 43.55 (C-2′), 25.71 (C-3′), 24.20 (C-4′), 26.17 (C-5′), 46.60 (C-6′), 54.28 (OCH_3), 166.46 (>C=O), 152.10 (A,C-1), 114.41 (A,C-2,6), 128.89 (A,C-3,5), 121.64 (A,C-4), 132.73 (B,C-1), 127.53 (B,C-2,6), 114.46 (B,C-3,5), 159.29 (B,C-4), 135.39 (C,C-1), 127.64 (C,C-2,6), 128.89 (C,C-3,5), 134.39 (C,C-4) ppm.

3RS-(3R,4R*,5S*)-2-Phenyl-3-(4-methoxyphenyl)-5-(4-chlorophenyl)-4-piperidinyloxo-isoxazolidine* (**15**; $C_{28}H_{29}N_2O_3Cl$)

White flakes; m.p.: 144°C; yield: 226 mg (7%); IR: $\nu = 2940$-2860 (m, -CH_2-), 1640 (s, amide >C=O), 1040 (s, aryl-Cl), 850, 830 (s, 1,4-disubstituted benzene ring), 750, 700 (m, monosubstituted benzene ring) cm^{-1}; UV: $\lambda_{max}(\log\varepsilon) = 250$ (4.44) nm; ^1H NMR ($CDCl_3$, δ, 300 MHz): 4.73 (1H, d, $J = 10.4$, H-3), 3.67 (1H, dist t, $J \sim 9.8$, H-4), 6.00 (1H, d, $J = 9.1$, H-5), 3.3–3.5 (2H, m, H-2′) 2.82 and 3.00 (1H, m each, H-6′), 1.22–1.52 (6H, m, H-3′,4′,5′), 3.82 (3H, s, -OCH_3), 6.87–6.94 (2H, m, A,H-2,4,6), 7.20 (2H, dd, $J = 8.6$, 7.2, A,H-3,5), 7.40 (2H, d, $J = 8.6$, B,H-2,6), 6.98 (2H, d, $J = 8.6$, B,H-3,5), 7.49 (2H, d, $J = 8.5$, C,H-2,6), 7.34 (2H, d, $J = 8.5$, C,H-3,5) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 72.76 (C-3), 58.58 (C-4), 80.63 (C-5), 42.39 (C-2′), 25.14 (C-3′), 24.20(C-4′), 25.99 (C-5′), 46.35 (C-6′), 55.21 (OCH_3), 165.89 (>C=O), 151.29 (A,C-1), 113.66 (A,C-2,6), 128.66 (A,C-3,5), 128.27 (A,C-4), 133.85 (B,C-1), 126.26 (B,C-2,6), 113.66 (B,C-3,5), 159.54 (B,C-4), 135.63 (C,C-1), 128.54 (C,C-2,6), 128.66 (C,C-3,5), 134.95 (C,C-4) ppm.

3RS-(3R,4S*,5R*)-2,3-Diphenyl-5-(4-chlorophenyl)-4-piperidinyloxoisoxazolidine* (**16**; $C_{27}H_{27}N_2O_2Cl$)

White crystalline solid; m.p.: 144°C; yield: 884 mg (30%); IR: $\nu = 2940$-2860 (m, -CH_2-), 1645 (s, amide >C=O), 1100 (m, aryl-Cl), 840 (m, 1,4-disubstituted benzene ring), 770, 700 (m, monosubstituted benzene ring) cm^{-1}; UV: $\lambda_{max}(\log\varepsilon) = 243$ (3.80), 222 (3.53) nm; ^1H NMR ($CDCl_3$, δ, 300 MHz): 5.18 (1H, d, $J = 8.3$, H-3), 3.77 (1H, t, $J \sim 8.8$, H-4), 5.40 (1H, d, $J = 9.4$, H-5), 3.50 and 2.73 (2H, m each, H-2′,H-6′), 1.38–1.40 (4H, m, H-3′,4′), 0.84 (2H, m, H-5′), 7.00 (2H, d, $J = 7.8$, A,H-2,6), 6.92 (1H, t, $J = 7.2$, A,H-4), 7.21 (2H, dist t, $J = 7.5$, A,H-3,5), 7.54 (2H, d, $J = 7.1$, B,H-2,6), 7.33–7.37 (3H, m, B,H-3,4,5), 7.42 (2H, m, C,H-2,6), 7.31 (2H, m, C,H-3,5) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 76.00 (C-3), 63.84 (C-4), 83.55 (C-5), 43.55 (C-2′), 25.78 (C-3′), 24.10 (C-4′), 26.11 (C-5′), 46.69 (C-6′), 166.66 (>C=O), 151.93 (A,C-1), 114.78 (A,C-2,6), 128.90 (A,C-3,5), 121.66 (A,C-4), 140.93 (B,C-1), 126.40 (B,C-2,6), 126.40 (B,C-2,6), 128.90 (B,C-3,5), 127.72 (B,C-4), 135.87 (C,C-1), 128.72 (C,C-2,6), 128.90 (C,C-3,5), 134.40 (C,C-4) ppm.

3RS-(3R,4R*,5S*)-2,3-Diphenyl-5-(4-chlorophenyl)-4-piperidinyloxoisoxazolidine* (**17**; $C_{27}H_{27}N_2O_2Cl$)

White crystals; m.p.: 134°C; yield: 206 mg (7%); IR: $\nu = 2940$-2860 (m, -CH_2-), 1650 (s, amide >C=O), 1100 (m, aryl-Cl), 840 (m, 1,4-disubstituted benzene ring), 760, 690 (m, monosubstituted benzene ring) cm^{-1}; UV: $\lambda_{max}(\log\varepsilon) = 283$ (4.42), 220 (4.21) nm; ^1H NMR ($CDCl_3$, δ, 300 MHz): 4.76 (1H, d, $J = 10.4$; H-3), 3.70 (1H, dist. t, $J \sim 9.5$, H-4), 6.04 (1H, d, $J = 9.1$, H-5), 3.06 (2H, m, H-2′), 2.73 (2H, m, H-6′), 1.34–1.40 (4H, br m, H-3′,4′), 0.84 (2H, m, 5′), 6.98 (2H, d, $J = 7.7$, A,H-2,6), 6.92 (1H, m, A,H-4), 7.28 (2H, dist t, $J = 7.5$, A,H-3,5), 7.54 (2H, d, $J = 7.1$, B,H-2,6), 7.31–

7.45 (3H, m, B,H-3,4,5), 7.31–7.45 (4H, m, C,H-2,3,5,6) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 73.46 (C-3), 59.09 (C-4), 80.91 (C-5), 44.72 (C-2′), 24.61 (C-3′), 24.22 (C-4′), 26.14 (C-5′), 45.72 (C-6′), 165.18 (>C=O), 151.05 (A,C-1), 116.77 (A,C-2,6), 128.97 (A,C-3,5), 122.70 (A,C-4), 140.39 (B,C-1), 128.13 (B,C-2,6), 128.97 (B,C-3,5), 126.34 (B,C-4), 135.23 (C,C-1),128.20 (C,C-2,6), 128.73 (C,C-3,5), 134.43 (C,C-4) ppm.

3RS-(3R,4S*,5R*)-2-Phenyl-3-(4-chlorophenyl)-5-(4-nitrophenyl)-4-piperidinyloxo-isoxazolidine* (**18**; $C_{27}H_{26}N_3O_4Cl$)

Light yellow crystals; m.p.: 165°C; yield: 758 mg (35%); IR: $\nu = 2940$-2860 (m, -CH_2-), 1645 (s, amide >C=O), 1535,1355 (s, aromatic-NO_2), 850 (m, 1,4-disubstituted benzene ring), 755, 705 (m, monosubstituted benzene ring) cm^{-1}; UV: $\lambda_{max}(\log\varepsilon) = 276$ (3.97) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 5.15 (1H, d, $J = 9.0$, H-3), 3.75(1H, t, $J = 9.0$, H-4), 5.60 (1H, d, $J = 9.0$, H-5), 3.55 and 2.74 (2H, m each, H-2′, H-6′), 1.42 (4H, m, H-3′,4′), 0.91 and 0.83 (1H, each, m, H-5′), 6.99 (2H, d, $J = 7.9$, A,H-2,6), 7.25 (2H, t, $J \sim 8.5$, A,H-3,5), 6.99 (1H, m, A,H-4), 7.48 (2H, d, $J = 8.6$, B,H-2,6), 7.38 (2H, d, $J = 8.6$, B,H-3,5), 7.67 (2H, d, $J = 8.7$, C,H-2,6), 8.26 (2H, d, $J = 8.7$, C,H-3,5) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 75.52 (C-3), 63.60 (C-4), 82.95 (C-5), 43.74 (C-2′), 25.72 (C-3′), 24.10 (C-4′), 26.36 (C-5′), 46.66 (C-6′), 165.97 (>C=O), 151.26 (A,C-1), 115.05 (A,C-2,6), 129.35 (A,C-3,5), 122.65 (A,C-4), 138.71 (B,C-1), 127.86 (B,C-2,6), 128.97 (B,C-3,5), 134.06 (B,C-4), 144.68 (C,C-1), 127.00 (C,C-2,6), 123.92 (C,C-3,5), 148.11 (C,C-4) ppm. MS (EI): $m/z = 491$ (M^+), 379 (M^+-$C_6H_{10}NO$), 340 (M^+-$C_7H_5NO_3$), 276 (M^+-$C_{13}H_9NCl$), 256 (379-$C_6H_5N_2$), 193 (276-$C_5H_{10}N$+H), 165 (276-$C_6H_{10}NO$+H), 126, 120 (165-NO_2+H), 112, 104, 84.

3RS-(3R,4R*,5S*)-2-Phenyl-3-(4-chlorophenyl)-5-(4-nitrophenyl)-4-piperidinyloxo-isoxazolidine* (**19**; $C_{27}H_{26}N_3O_4Cl$)

White flakes; m.p.: 172°C; yield: 325 mg (15%); IR: $\nu = 2940$-2840 (m, -CH_2-), 1630 (s, amide >C=O), 1510, 1340 (s, aromatic-NO_2), 850 (m, 1,4-disubstituted benzene ring), 750, 690 (m, monosubstituted benzene ring) cm^{-1}; UV: $\lambda_{max}(\log\varepsilon) = 262$ (3.89) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 4.82 (1H, d, $J = 11.0$, H-3), 3.74 (1H, dd, $J = 11.0$, 9.0, H-4), 6.18 (1H, d, $J = 9.0$, H-5), 3.48, 3.34, 3.08, and 2.91 (1H, m each, H-2′, H-6′), 1.25–1.60 (6H, m, H-3′,4′,5′), 7.01 (2H, d, $J = 8.0$, A,H-2,6), 7.20 (2H, t, $J = 8.0$, A,H-3,5), 7.00 (1H, m, A,H-4), 7.48 (2H, d, $J = 8.5$, B,H-2,6), 7.41 (2H, d, $J = 8.5$, B,H-3,5), 7.71 (2H, d, $J = 8.8$, C,H-2,6), 8.22 (2H, d, $J = 8.8$, C,H-3,5) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 72.22 (C-3), 58.76 (C-4), 80.19 (C-5), 42.62 (C-2′), 25.16 (C-3′), 24.09, (C-4′), 26.09 (C-5′), 46.48 (C-6′), 165.20 (>C=O), 149.32 (A,C-1), 116.38 (A,C-2,6), 130.03 (A,C-3,5), 123.14 (A,C-4), 138.27 (B,C-1), 128.61 (B,C-2,6), 128.75 (B,C-3,5), 136.37 (B,C-4), 144.84 (C,C-1), 127.38 (C,C-2,6), 123.80 (C,C-3,5), 148.14 (C,C-4) ppm. MS (EI): $m/z = 491$ (M^+), 379 (M^+-$C_6H_{10}NO$), 340, (M^+-$C_7H_5NO_3$), 276 (M^+-$C_{13}H_9NCl$), 256 (379-$C_6H_5N_2$), 217, 193 (276-$C_5H_{10}N$+H), 165 (276-$C_6H_{10}NO$+H), 120 (165-NO_2+H).

3RS-(3R,4S*,5R*)-2-Phenyl-3-(4-chlorophenyl)-5-(4-nitrophenyl)-4-piperidinyloxoisoxazolidine* (**20**; $C_{27}H_{26}N_3O_4Cl$)

Pale yellow crystals; m.p.: 135°C; yield: 650 mg (30%); IR: $\nu = 2960$-2880 (m, -CH_2-), 1660 (s, amide >C=O), 1540, 1360 (s, aromatic-NO_2), 860, 840 (m, 1,4-disubstituted benzene ring), 770, 710 (m, monosubstituted benzene ring) cm^{-1}; UV: $\lambda_{max}(\log\varepsilon) = 269$ (4.01) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 4.60 (1H, d, $J = 8.0$, H-3), 3.71 (1H, br t, $J = 7.5$, H-4), 4.94 (1H, d, $J = 7.1$, H-5), 3.82, 3.77, 3.52, and 3.43 (1H, m each, H-2′,6′), 1.60–1.70 (6H, m, H-3′,4′,5′), 6.95 (2H, d, $J = 7.7$, A,H-2,6), 7.02 (1H, t, $J = 7.7$, A,H-4), 7.23 (2H, t, $J = 7.7$, A,H-3,5), 7.27–7.32 (4H, m, B,H-2,6,3,5), 7.45 (2H, d, $J = 8.3$, C,H-2,6), 8.15 (2H, d, $J = 8.3$, C,H-3,5) ppm; ^{13}C-NMR ($CDCl_3$, δ, 75.5 MHz):

77.99 (C-3), 61.06 (C-4), 81.98 (C-5), 43.89 (C-2′), 25.53 (C-3′), 24.45(C-4′), 26.70 (C-5′), 47.02 (C-6′), 164.74 (>C=O), 149.76 (A,C-1), 115.83 (A,C-2,6), 129.02 (A,C-3,5), 123.10 (A,C-4), 137.71 (B,C-1), 128.35 (B,C-2,6), 129.15 (B,C-3,5), 134.03 (B,C-4), 145.96 (C,C-1), 129.32 (C,C-2,6), 124.14 (C,C-3,5), 147.43 (C,C-4) ppm. MS (EI): $m/z = 491$ (M^+), 350 (M^+-$C_7H_{11}NO_2$), 276 (M^+-$C_{13}H_9NCl$), 215 (M^+-$C_{14}H_{12}N_2O_4$).

3RS-(3R,4S*,5R*)-2,3,5-Triphenyl-4-piperidinyloxoisoxazolidine* (**21**; $C_{27}H_{28}N_2O_2$)

White crystals; m.p.: 135°C; yield: 1.05 g (42%); IR: $\nu = 2940$-2860 (m, -CH_2-), 1640 (s, amide >C=O), 760, 710 (m, monosubstituted benzene ring cm^{-1}; UV: $\lambda_{max}(\log\varepsilon) = 255$ (4.10) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 5.27 (1H, d, $J = 8.2$, H-3), 3.83 (1H, dist t, $J \sim 8.8$, H-4), 5.37 (1H, d, $J = 9.5$, H-5), 3.44–3.57 and 2.74 (2H, m each, H-2′,6′), 1.36 (4H, m, H-3′,4′), 0.86 (2H, m, H-5′), 7.03 (2H, d, $J = 8.6$, A,H-2,6), 6.92 (1H, t, $J = 7.3$, A,H-4), 7.23 (2H, dist t, A,H-3,5), 7.56 (2H, d, $J = 7.2$, B,H-2,6), 7.35–7.40 (3H, m, B,H-3,4,5), 7.48 (2H, d, $J = 8.3$, C,H-2,6), 7.35–7.40 (3H, m, C,H-3,4,5) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 75.92 (C-3), 63.99 (C-4), 84.68 (C-5), 43.58 (C-2′), 25.70 (C-3′), 24.20 (C-4′), 26.01 (C-5′), 46.78 (C-6′), 166.63 (>C=O), 152.30 (A,C-1), 114.17 (A,C-2,6), 129.02 (A,C-3,5), 121.58 (A,C-4), 141.46 (B,C-1), 126.23 (B,C-2,6), 128.87 (B,C-3,5), 128.80 (B,C-4), 136.36 (C,C-1), 126.62 (C,C-2,6), 128.74 (C,C-3,5), 127.77 (C,C-4) ppm; MS (EI): $m/z = 412$ (M^+), 306 (M^+-C_7H_6O), 300 (M^+-$C_6H_{10}NO$), 222 (306-$C_5H_{10}N$), 214, 195 (300-C_7H_5O), 144, 180 ($C_{13}H_{10}N^+$), 131.

3RS-(3R,4R*,5S*)-2,3,5-Triphenyl-4-piperidinyloxoisoxazolidine* (**22**; $C_{27}H_{28}N_2O_2$)

White amorphous solid; yield: 138 mg (6.5%); IR, $\nu = 2920$-2860 (m, -CH_2-), 1630 (s, amide >C=O), 770, 690 (m, monosubstituted benzene ring) cm^{-1}; UV: $\lambda_{max}(\log\varepsilon) = 268$ (3.91) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 4.64 (1H, d, $J = 10.5$, H-3), 3.59 (1H, dist t, H-4), 5.98 (1H, d, $J = 8.9$ H-5), 3.57 and 2.82 (2H, m each, H-2′,H-6′), 1.41 (4H, m, H-3′,4′), 0.93 (2H, m, H-5′), 7.32 (2H, d, $J = 8.2$, A,H-2,6), 6.99 (1H, m, A,H-4), 7.41–7.51 (2H, overlapped signal, A,H-3,5), 7.60 (2H, d, $J = 8.3$, B,H-2,6), 7.44–7.51 (3H, overlapped signal, B,H-3,4,5), 7.56 (2H, d, $J = 7.8$, C,H,-2,6), 7.44–7.51 (3H, overlapped signal, C,H-3,4,5) ppm.

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