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Cycloaddition of nitrones to 1,3-diarylpropenones and subsequent transformations of the resulting isoxazolidines

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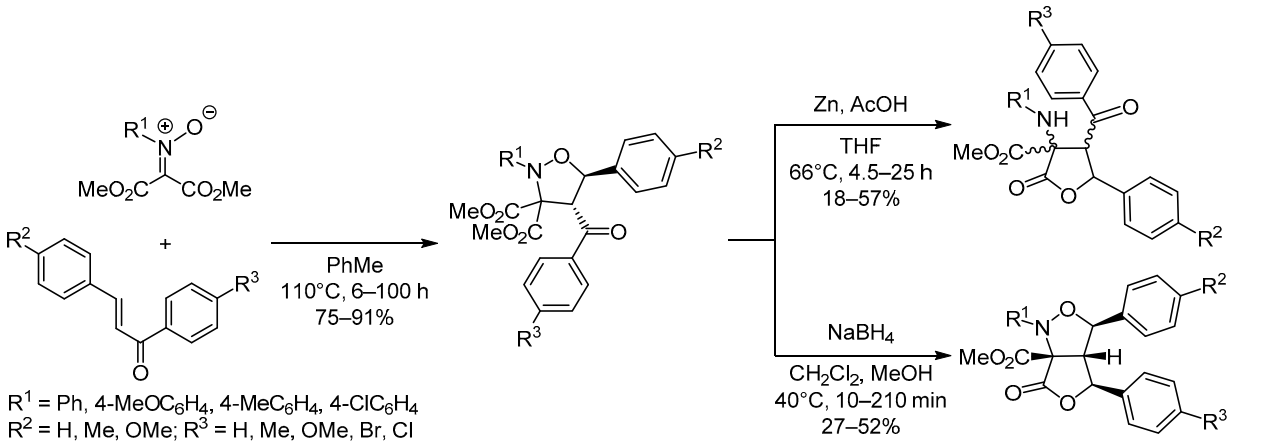


Ketonitrones containing two ester groups react regio- and stereoselectively with 1,3-diarylpropenones to form isoxazolidines with ester groups at position 3 of the ring. The action of zinc in acetic acid on these isoxazolidines causes opening of the ring with the formation of 3-amino alcohols, the subsequent cyclization of which leads to polysubstituted lactones. Reduction of the benzoyl group of isoxazolidine with sodium borohydride leads, as a result of subsequent transformations, to the formation of substituted 1,3,4-triaryl-6-oxodihydro-1*H*,3*H*-furo[3,4-*c*]isoxazole-6a(6*H*)-carboxylates as single diastereomers.

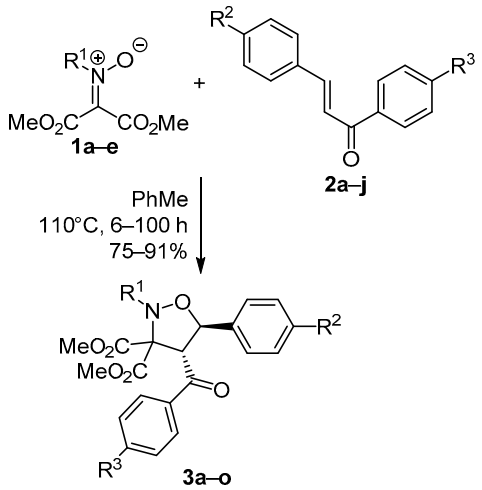
Keywords: chalcones, isoxazolidines, nitrones, 1,3-dipolar cycloaddition, reduction.

The isoxazolidine ring is an important structural fragment of many heterocyclic compounds with valuable pharmacological properties, such as antiviral,[1] antibacterial,[2] and antitumor activity.[3] In addition, isoxazolidines are widely used in the synthesis of various organic compounds, including natural compounds.[4] One of the most common and convenient method for the synthesis of isoxazolidines is the 1,3-dipolar cycloaddition of nitrones to alkenes. The high regio- and stereoselectivity of this reaction makes it possible to create with high selectivity several new stereocenters in one step, which makes this method indispensable in asymmetric synthesis.[5] Isoxazolidines are easily opened at the N–O bond by the action of reducing agents with the formation of 3-amino alcohols, which are valuable starting materials for the synthesis of various classes of organic compounds, in particular alkaloids and antibiotics.[6]

The aim of this work was to obtain highly functionalized isoxazolidines by the 1,3-dipolar cycloaddition of ketonitrones containing two ester groups to chalcones and to study the transformations of the reaction products under the action of reducing agents. Previously, reactions of ketonitrones containing two ester groups at the carbon atom were carried out only with dimethyl acetylenedicarboxylate,[7a] *N*-vinylpyrrole and *N*-vinylindole,[1d,7b] allenes,[7d,e] methylenecyclopropanes,[7f] and itaconimides.[7g] It was shown that the regioselectivity of the addition of ketonitrones can differ from that of aldonitrones.[7e,f]

The reaction of nitrones **1a**–**e** with 1,3-diarylpropenones **2a**–**j** was carried out in PhMe at 110°C (Scheme 1, Table 1). In all cases, the reaction proceeds regio- and stereoselectively with the formation of isoxazolidines **3a**–**o** as single diastereomers in good yields.

Scheme 1. Cycloaddition of ketonitrones **1a**–**e** to 1,3-diarylpropenones **2a**–**j**



The composition and structure of compounds **3a**–**o** were established on the basis of spectral data. The ^{1}H NMR spectra of compounds **3a**–**o** contain the characteristic doublets of the methine protons at the C-4,5 atoms of the isoxazolidine ring. The ^{13}C NMR spectra contain signals of two methine carbon atoms and a quaternary carbon atom of the isoxazolidine ring. Thus, the ^{1}H NMR spectrum of compound **3l** contains signals of the methine protons at C-4 and C-5 atoms at 5.42 and 5.54 ppm (doublets, J = 9.0 Hz). In the ^{13}C NMR spectrum of the same compound, the signals of the C-4 and C-5 carbon atoms are at 62.6 and 83.4 ppm, and the signal of the quaternary carbon atom C-3 appears at 82.8 ppm. The regio- and stereochemistry of the resulting cycloadducts was determined based on the data of two-dimensional NMR experiments (Fig. 1). In the ^{1}H–^{13}C HMBC spectrum of compound **3l**, correlations between the 5-CH methine proton and the C-1 *ipso*-carbon atom and the C-2 and C-6 *ortho*-carbon atoms of the aromatic ring can be observed, while for the 4-CH methine proton, only a correlation with the C-1 *ipso*-quaternary carbon atom of the aromatic ring is present.

Interactions corresponding to the assigned structure are also observed in the NOESY spectrum. No cross peak

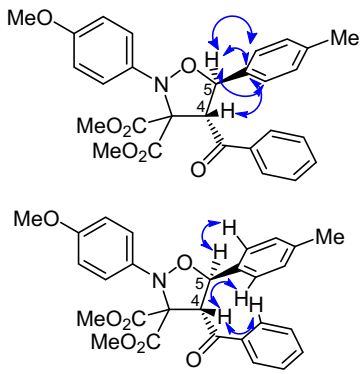


Figure 1. The characteristic correlations in the ^{1}H–^{13}C HMBC and NOESY spectra of compound **3l**.

Table 1. The conditions of the reaction and yields of isoxazolidines **3a**–**o**

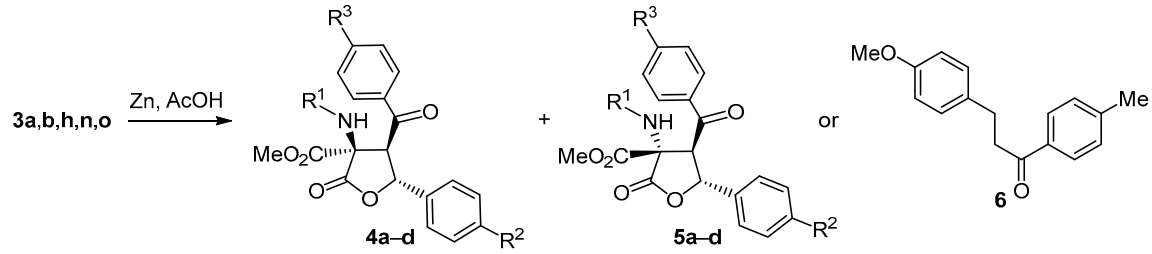
Nitrone	R^1	Propenone	R^2	R^3	Time, h	Product	Yield, %
1a	Ph	**2a**	H	OMe	37	**3a**	87
1a	Ph	**2b**	Me	Br	37	**3b**	85
1b	4-MeC_6H_4	**2c**	H	H	20	**3c**	84
1b	4-MeC_6H_4	**2d**	H	OMe	20	**3d**	91
1b	4-MeC_6H_4	**2e**	H	Br	25	**3e**	87
1b	4-MeC_6H_4	**2f**	Me	H	25	**3f**	77
1b	4-MeC_6H_4	**2g**	Me	Cl	20	**3g**	89
1b	4-MeC_6H_4	**2h**	OMe	Me	25	**3h**	62
1b	4-MeC_6H_4	**2i**	OMe	Br	20	**3i**	91
1c	4-$MeOC_6H_4$	**2c**	H	H	6	**3j**	65
1c	4-$MeOC_6H_4$	**2e**	H	Br	7	**3k**	75
1c	4-$MeOC_6H_4$	**2f**	Me	H	7	**3l**	83
1c	4-$MeOC_6H_4$	**2g**	Me	Cl	6	**3m**	75
1d	4-ClC_6H_4	**2d**	H	OMe	30	**3n**	87
1e	Me	**2j**	Cl	Me	100	**3o**	65

between the signals of protons at carbon atoms C-4 and C-5 is detected (Fig. 1). Therefore, the results obtained indicate that the cycloaddition of *N*-aryl-*C*,*C*-bis(methoxycarbonyl)-nitrones **1a**–**e** to 1,3-diarylpropenones **2a**–**j** proceeds regio- and stereoselectively as a concerted process with retention of the configuration of the starting dipolarophile. The observed regioselectivity of the addition is similar to that established earlier for the reaction of chalcones with aldonitrones.[8]

As noted above, the isoxazolidine ring can be cleaved under the action of reducing agents with the formation of 3-amino alcohols, the subsequent intramolecular cyclization of which can lead to various compounds, in particular to lactones and lactams.[7f,9] In this work, isoxazolidines **3a**,**b**,**h**,**n**,**o** were heated with an excess of zinc dust and AcOH in MeOH (Scheme 2, Table 2), leading to the formation of a mixture of diastereomeric α-amino-γ-butyrolactones **4** and **5**, which were separated by column chromatography. The low yields of the reduction products can be explained by the fact that even with prolonged heating the starting isoxazolidine remained in the reaction mixture. It should be noted that isoxazolidine **3o** containing a methyl group at the nitrogen atom did not undergo the reaction under these conditions. The change of MeOH to THF in the reduction of isoxazolidine **3h** led to an increase in the reaction time and the formation of 3-(4-methoxyphenyl)-1-(4-tolyl)propan-1-one (**6**), along with lactones **4c** and **5c**.

In the ^{1}H NMR spectrum of compound **4a**, the signals of the methine protons of the five-membered ring are doublets at 4.73 and 6.19 ppm with a spin-spin coupling constant (SSCC) of 8.9 Hz, whereas for compound **5a**, the corresponding spin-spin coupling constant is 9.9 Hz. In both cases, the SSCCs are almost identical to the SSCCs of

Scheme 2. Reduction of isoxazolidines **3a**,**b**,**h**,**n**,**o** under the action of Zn in AcOH



4, **5 a** R^1 = Ph, R^2 = H, R^3 = OMe; **b** R^1 = Ph, R^2 = Me, R^3 = Br; **c** R^1 = 4-MeC_6H_4, R^2 = OMe, R^3 = Me; **d** R^1 = 4-ClC_6H_4, R^2 = H, R^3 = OMe

the starting isoxazolidine. Consequently, it can be assumed that the *trans* orientation of substituents at positions 4 and 5 of the ring is retained during the reduction, and the products differ in the configuration of the C-3 atom. This conclusion is additionally confirmed by the data of two-dimensional NOESY spectra, and the final relative configuration of the products was determined by X-ray structural analysis of compound **4c** (Fig. 2), which also demonstrates the *trans* orientation of the ester and benzoyl groups at positions 3 and 4 of the ring.

Thus, the reductive cleavage of the N–O bond in isoxazolidines **3** by zinc dust in AcOH leads to spontaneous cyclization of the resulting 3-amino alcohols into the corresponding lactones. In addition, we also tried to create a new reaction center by reduction of the carbonyl group present in isoxazolidines **3**. The reaction of isoxazolidines **3e**,**f**,**i**–**m** with $NaBH_4$ in a CH_2Cl_2–MeOH mixture at 40°C leads to the formation of lactones **7a**–**g** in 27–52% yields (Scheme 3). It should be noted that the presence of an electron-donating *p*-anisyl substituent at the nitrogen atom decreases the reaction time (to 10–40 min for lactones **7a**–**d**, 210 min for lactones **7e**–**g**), while substituents in other positions of the ring do not significantly affect the reaction rate.

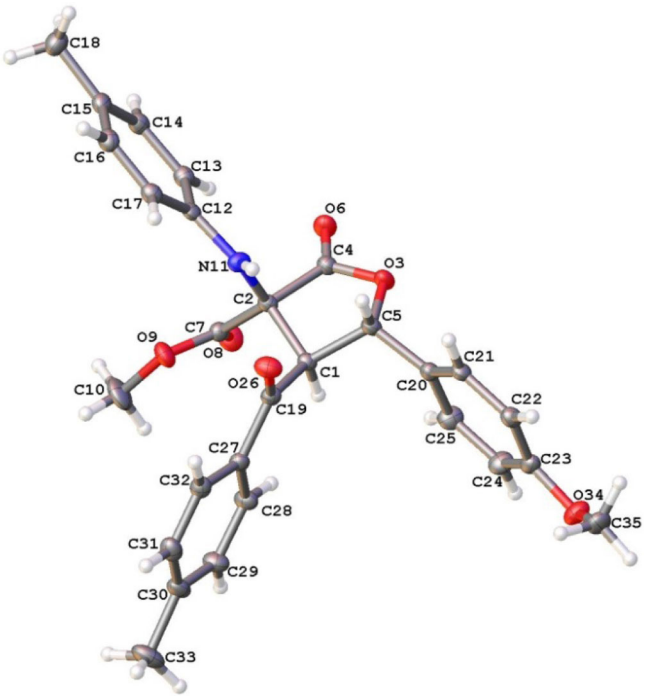
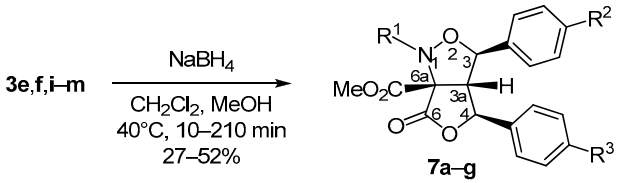


Figure 2. Molecular structure of compound **4c** with atoms represented as thermal vibration ellipsoids of 50% probability.

Table 2. The conditions and yields of the reaction products of reduction of isoxazolidines **3a**,**b**,**h**,**n**,**o** under the action of Zn in AcOH

Compound	Conditions	Product (yield, %)		Product ratio
3a	MeOH, 66°C, 4.5 h	**4a** (29)	**5a** (57)	0.6:1
3b	MeOH, 66°C, 4.5 h	**4b** (39)	**5b** (18)	1:0.4
3h	MeOH, 66°C, 4.5 h	**4c** (27)	**5c** (38)	0.7:1
3h	THF, 66°C, 25 h	**4c** (26)	**6** (22)	1:0.8
3n	MeOH, 66°C, 4.5 h	**4d** (34)	**5d** (36)	0.9:1
3o	MeOH, 66°C, 4.5 h	–	–	–

Scheme 3. Reduction of isoxazolidines **3e**,**f**,**i**–**m** under the action of $NaBH_4$



7 a R^1 = 4-$MeOC_6H_4$, R^2 = H, R^3 = H; **b** R^1 = 4-$MeOC_6H_4$, R^2 = H, R^3 = Br; **c** R^1 = 4-$MeOC_6H_4$, R^2 = Me, R^3 = H; **d** R^1 = 4-$MeOC_6H_4$, R^2 = Me, R^3 = Cl; **e** R^1 = 4-MeC_6H_4, R^2 = H, R^3 = Br; **f** R^1 = 4-MeC_6H_4, R^2 = Me, R^3 = H; **g** R^1 = 4-MeC_6H_4, R^2 = OMe, R^3 = Br

The structure of products **7a**–**g** was established on the basis of spectral data. Thus, the ^{1}H NMR spectrum of compound **7c** contains signals of the proton at the C-3 carbon atom as a doublet (5.31 ppm, J = 6.5 Hz), the proton at the C-4 carbon atom as a doublet (5.61 ppm, J = 3.4 Hz), and the proton at the C-3a carbon atom as a doublet of doublets (3.82 ppm, J = 6.5, J = 3.4 Hz). The relative configuration was established based on the data of X-ray structural analysis of compound **7e** (Fig. 3).

In conclusion, isoxazolidines containing two ester groups at position 3 and a benzoyl group at position 4 upon reduction with zinc in AcOH undergo the opening of the N–O bond with the formation of 3-amino alcohols **A**. The

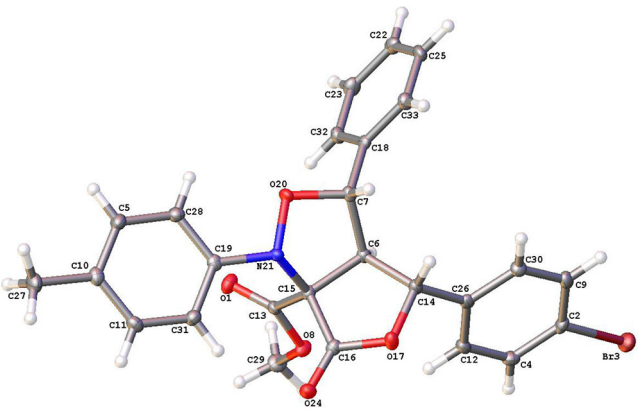
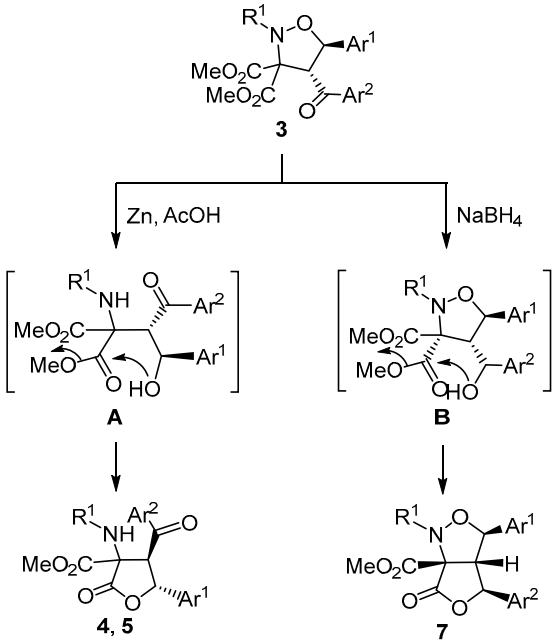


Figure 3. Molecular structure of compound **7e** with atoms represented as thermal vibration ellipsoids of 50% probability.

subsequent attack by the lone electron pair of the oxygen atom of the carbonyl atom of the ester group in alcohols **A** leads to the formation of lactones **4** and **5**. In turn, reduction of the benzoyl group of isoxazolidines with $NaBH_4$ gives alcohols **B**, the subsequent similar tandem transformation of which leads to bicyclic lactones **7**. In the latter case, only one stereoisomer is formed, most likely due to the difficulty in the approach of the reagent to the prochiral carbonyl group on the side of the C-3 atom containing two ester substituents (Scheme 4).

Scheme 4. Transformations of isoxazolidines **3** under the action of reducing agents



Experimental

IR spectra were registered on BrukerTensor 27 and Shimadzu FT-IR IRAffinity-1 spectrophotometers in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance 400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ (C_6D_6 for ^{1}H NMR of compound **3d**), using residual solvent signals (7.26 ppm for ^{1}H nuclei and 77.2 ppm for ^{13}C nuclei) as internal standard. High-resolution mass spectra were recorded on a Bruker Maxis HRMS-ESI-qTOF mass spectrometer at electrospray ionization in positive mode. Monitoring of the reaction progress and assessment of the purity of synthesized compounds were done by TLC on Silufol UV-254 plates.

Nitrones[10] and 1,3-diarylpropenones[11] were obtained according to published methods.

Synthesis of isoxazolidines 3a–o (General method). A solution of nitrone **1a–e** (1.0 mmol) and 1,3-diarylpropenone **2a–j** (1.0 mmol) in PhMe (10 ml) was heated at 110°C under argon atmosphere until the disappearance of the starting nitrone for 6–100 h (TLC control). The solvent was evaporated under reduced pressure, and the residue was recrystallized from EtOH.

Dimethyl (4*RS*,5*RS*)-4-(4-methoxybenzoyl)-2,5-diphenylisoxazolidine-3,3-dicarboxylate (3a). Yield 415 mg (87%), white powder, mp 148–149°C. IR spectrum, ν, cm^{-1}: 1762, 1733 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.24 (3H, s, OCH_3); 3.55 (3H, s, OCH_3); 3.81 (3H, s, OCH_3); 5.50 (1H, d, *J* = 9.1, CH); 5.54 (1H, d, *J* = 9.1, CH); 6.82–6.87 (2H, m, H Ar); 7.14–7.20 (1H, m, H Ar); 7.30–7.40 (5H, m, H Ar); 7.53–7.59 (4H, m, H Ar); 7.75–7.79 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 52.4 (OCH_3); 52.7 (OCH_3); 55.5 (OCH_3); 62.8 (CH); 82.8 (C); 83.4 (CH); 113.9 (2CH); 121.0 (2CH); 125.7 (CH); 127.4 (2CH); 128.2 (2CH); 128.7 (2CH); 129.1 (CH); 130.2 (C); 130.9 (2CH); 135.7 (C); 146.2 (C); 164.0 (CO); 167.1 (CO); 194.5 (CO). Found, *m*/*z*: 498.1531 [M+Na]$^+$. $C_{27}H_{25}NNaO_7$. Calculated, *m*/*z*: 498.1523.

Dimethyl (4*RS*,5*RS*)-4-(4-bromobenzoyl)-2-phenyl-5-(*p*-tolyl)isoxazolidine-3,3-dicarboxylate (3b). Yield 460 mg (85%), white powder, mp 148–150°C. IR spectrum, ν, cm^{-1}: 1774, 1733 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, CH_3); 3.24 (3H, s, OCH_3); 3.55 (3H, s, OCH_3); 5.48 (1H, d, *J* = 9.1, CH); 5.49 (1H, d, *J* = 9.1, CH); 7.12–7.18 (3H, m, H Ar); 7.27–7.33 (2H, m, H Ar); 7.41–7.45 (2H, m, H Ar); 7.51–7.55 (4H, m, H Ar); 7.60–7.66 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.2 (CH_3); 52.5 (OCH_3); 52.8 (OCH_3); 62.9 (CH); 82.8 (C); 83.3 (CH); 121.0 (2CH); 125.8 (CH); 127.3 (2CH); 128.2 (2CH); 129.1 (C); 129.5 (2CH); 129.9 (2CH); 132.0 (2CH); 132.1 (C); 135.9 (C); 139.2 (C); 146.1 (C); 166.9 (CO); 167.0 (CO); 195.6 (CO). Found, *m*/*z*: 576.0429 [M+K]$^+$. $C_{27}H_{24}BrKNO_6$. Calculated, *m*/*z*: 576.0419.

Dimethyl (4*RS*,5*RS*)-4-benzoyl-5-phenyl-2-(*p*-tolyl)-isoxazolidine-3,3-dicarboxylate (3c). Yield 400 mg (84%), white powder, mp 168–169°C. IR spectrum, ν, cm^{-1}: 1772, 1734 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, s, CH_3); 3.27 (3H, s, OCH_3); 3.54 (3H, s, OCH_3); 5.49 (1H, d, *J* = 9.1, CH); 5.52 (1H, d, *J* = 9.1, CH); 7.11 (2H, d, *J* = 8.3, H Ar); 7.30–7.38 (5H, m, H Ar); 7.45 (2H, d, *J* = 8.4, H Ar); 7.48–7.56 (3H, m, H Ar); 7.72–7.78 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.4 (CH_3); 52.8 (OCH_3); 53.1 (OCH_3); 63.4 (CH); 83.2 (C); 83.8 (CH); 121.7 (2CH); 127.9 (2CH); 128.9 (2CH); 129.1 (2CH); 129.2 (2CH); 129.3 (2CH); 129.5 (CH); 134.1 (CH); 136.0 (C); 136.1 (C); 137.5 (C); 143.9 (C); 167.4 (CO); 167.5 (CO); 197.0 (CO). Found, *m*/*z*: 460.1775 [M+H]$^+$. $C_{27}H_{26}NO_6$. Calculated, *m*/*z*: 460.1755.

Dimethyl (4*RS*,5*RS*)-4-(4-methoxybenzoyl)-5-phenyl-2-(*p*-tolyl)isoxazolidine-3,3-dicarboxylate (3d). Yield 430 mg (91%), white powder, mp 185–187°C. IR spectrum, ν, cm^{-1}: 1772, 1734 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.16 (3H, s, CH_3); 3.08 (3CH, s, OCH_3); 3.12 (3H, s, OCH_3); 3.42 (3H, s, OCH_3); 6.05 (1H, d, *J* = 9.1, CH); 6.12 (1H, d, *J* = 9.1, CH); 6.50 (2H, d, *J* = 7.2, H Ar); 7.00–7.15 (5H, m, H Ar); 7.75 (2H, *J* = 8.7, H Ar); 7.95–8.08 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.4 (CH_3); 52.8 (OCH_3); 53.1 (OCH_3); 55.9 (OCH_3); 63.1 (CH); 83.1 (C); 83.8 (CH); 114.3 (2CH); 121.7 (2CH); 127.9 (2CH); 129.1 (2CH); 129.2 (2CH); 129.4 (CH); 130.6 (C); 131.4 (2CH); 136.0 (C); 136.2 (C); 144.0 (C); 164.4 (C); 167.5 (CO); 167.6 (CO); 195.1 (CO). Found, *m*/*z*: 490.1417 $[M+H]^+$. $C_{28}H_{28}NO_7$. Calculated, *m*/*z*: 490.1860.

Dimethyl (4*RS*,5*RS*)-4-(4-bromobenzoyl)-5-phenyl-2-(*p*-tolyl)isoxazolidine-3,3-dicarboxylate (3e). Yield 460 mg (87%), white powder, mp 186–187°C. IR spectrum, ν, cm^{-1}: 1762, 1729 (CO). ^{1}H NMR spectrum, δ, ppm(*J*, Hz): 2.31 (3H, s, CH_3); 3.27 (3H, s, OCH_3); 3.55 (3H, s, OCH_3); 5.44 (1H, d, *J* = 9.1, CH); 5.47 (1H, d, *J* = 9.1, CH); 7.11 (2H, d, *J* = 8.3, H Ar); 7.30–7.37 (3H, m, H Ar); 7.43 (2H, d, *J* = 8.5, H Ar); 7.48–7.53 (4H, m, H Ar); 7.58–7.63 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.0 (CH_3); 52.5 (OCH_3); 52.8 (OCH_3); 63.0 (CH); 82.7 (C); 83.3 (CH); 121.3 (2CH); 127.4 (2CH); 128.8 (4CH); 129.1 (C); 129.2 (CH); 129.9 (2CH); 132.0 (2CH); 135.5 (C); 135.8 (2C); 143.4 (C); 166.9 (CO); 167.1 (CO); 195.7 (CO). Found, *m*/*z*: 538.0877 $[M+H]^+$. $C_{27}H_{25}BrNO_6$. Calculated, *m*/*z*: 538.0860.

Dimethyl (4*RS*,5*RS*)-4-benzoyl-2,5-di(*p*-tolyl)isoxazolidine-3,3-dicarboxylate (3f). Yield 369 mg (77%), white powder, mp 141–143°C. IR spectrum, ν, cm^{-1}: 1766, 1730 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (6H, s, $2CH_3$); 3.27 (3H, s, OCH_3); 3.53 (3H, s, OCH_3); 5.46 (1H, d, *J* = 9.1, CH); 5.52 (1H, d, *J* = 9.1, CH); 7.08–7.16 (4H, m, H Ar); 7.36 (2H, d, *J* = 7.8, H Ar); 7.40–7.46 (4H, m, H Ar); 7.50 (1H, t, *J* = 7.4, H Ar); 7.73–7.80 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.0 (CH_3); 21.2 (CH_3); 52.4 (OCH_3); 52.7 (OCH_3); 62.8 (CH); 82.8 (C); 83.3 (CH); 121.2 (2CH); 127.5 (2CH); 128.5 (2CH); 128.6 (2CH); 128.8 (2CH); 129.4 (2CH); 132.5 (C); 133.6 (CH); 135.5 (C); 137.2 (C); 139.0 (C); 143.6 (C); 167.1 (CO); 167.1 (CO); 196.7 (CO). Found, *m*/*z*: 474.1919 $[M+H]^+$. $C_{28}H_{28}NO_6$. Calculated *m*/*z*: 474.1911.

Dimethyl (4*RS*,5*RS*)-4-(4-chlorobenzoyl)-2,5-di(*p*-tolyl)-isoxazolidine-3,3-dicarboxylate (3g). Yield 495 mg (89%), white powder, mp 163–164°C. IR spectrum, ν, cm^{-1}: 1772, 1734 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, s, CH_3); 2.32 (3H, s, CH_3); 3.26 (3H, s, OCH_3); 3.55 (3H, s, OCH_3); 5.46 (1H, d, *J* = 9.3, CH); 5.47 (1H, d, *J* = 9.3, CH); 7.07–7.18 (4H, m, H Ar); 7.33 (2H, d, *J* = 8.6, H Ar); 7.37–7.46 (4H, m, H Ar); 7.70 (2H, d, *J* = 8.6, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.4 (CH_3); 21.7 (CH_3); 52.9 (OCH_3); 53.2 (OCH_3); 63.2 (CH); 83.2 (C); 83.7 (CH); 121.7 (2CH); 127.8 (2CH); 129.2 (2CH); 129.4 (2CH); 129.9 (2CH); 130.3 (2CH); 132.7 (C); 135.9 (C); 136.1 (C); 139.6 (C); 140.7 (C); 143.9 (C); 167.4 (CO); 167.5 (CO); 196.0 (CO). Found, *m*/*z*: 508.1531 $[M+H]^+$. $C_{28}H_{27}ClNO_6$. Calculated, *m*/*z*: 508.1521.

Dimethyl (4*RS*,5*RS*)-5-(4-methoxyphenyl)-4-(4-methylbenzoyl)-2-(*p*-tolyl)isoxazolidine-3,3-dicarboxylate (3h). Yield 328 mg (62%), white powder, mp 110–112°C. IR spectrum, ν, cm^{-1}: 1768, 1728 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, s, CH_3); 2.35 (3H, s, CH_3); 3.26 (3H, s, OCH_3); 3.54 (3H, s, OCH_3); 3.77 (3H, s, OCH_3); 5.42 (1H, d, *J* = 9.0, CH); 5.49 (1H, d, *J* = 9.0, CH); 6.86 (2H, d, *J* = 8.7, H Ar); 7.09 (2H, d, *J* = 8.3, H Ar); 7.15 (2H, d, *J* = 8.1, H Ar); 7.40–7.51 (4H, m, H Ar); 7.66 (2H, d, *J* = 8.3, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.9 (CH_3); 21.6 (CH_3); 52.3 (OCH_3); 52.6 (OCH_3); 55.2 (OCH_3); 62.7 (CH); 82.8 (C); 83.2 (CH); 114.2 (2CH); 121.3 (2CH); 127.5 (C); 128.6 (2CH); 128.7 (2CH); 129.0 (2CH); 129.4 (2CH); 134.8 (C); 135.5 (C); 143.6 (C); 144.6 (C); 160.2 (C); 167.1 (CO); 167.2 (CO); 196.2 (CO). Found, *m*/*z*: 504.2006 $[M+H]^+$. $C_{29}H_{30}NO_7$. Calculated, *m*/*z*: 504.2017.

Dimethyl (4*RS*,5*RS*)-4-(4-bromobenzoyl)-5-(4-methoxyphenyl)-2-(*p*-tolyl)isoxazolidine-3,3-dicarboxylate (3i). Yield 460 mg (81%), white powder, mp 148–150°C. IR spectrum, ν, cm^{-1}: 1772, 1734 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, s, CH_3); 3.26 (3H, s, OCH_3); 3.55 (3H, s, OCH_3); 3.78 (3H, s, OCH_3); 5.40 (1H, d, *J* = 9.1, CH); 5.45 (1H, d, *J* = 9.1, CH); 6.87 (2H, d, *J* = 8.7, H Ar); 7.10 (2H, d, *J* = 8.7, H Ar); 7.40–7.53 (6H, m, H Ar); 7.62 (2H, d, *J* = 8.6, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.4 (CH_3); 52.9 (OCH_3); 53.2 (OCH_3); 55.7 (OCH_3); 63.2 (CH); 83.1 (C); 83.5(CH); 114.6 (2CH); 121.7 (2CH); 127.5 (C); 129.2 (2CH); 129.3 (2CH); 129.5 (C); 130.4 (2CH); 132.5 (2CH); 136.1 (C); 136.2 (C); 143.8 (C); 160.7 (C); 167.4 (CO); 167.5 (CO); 196.2 (CO). Found, *m*/*z*: 590.0787 $[M+Na]^+$. $C_{28}H_{26}BrNNaO_7$. Calculated, *m*/*z*: 590.0785.

Dimethyl (4*RS*,5*RS*)-4-benzoyl-2-(4-methoxyphenyl)-5-phenylisoxazolidine-3,3-dicarboxylate (3j). Yield 312 mg (66%), white powder, mp 157–158°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.29 (3H, s, OCH_3); 3.53 (3H, s, OCH_3); 3.79 (3H, s, OCH_3); 5.45 (1H, d, *J* = 9.0, CH); 5.54 (1H, d, *J* = 9.0, CH); 6.81–6.89 (2H, m, H Ar); 7.28–7.39 (5H, m, H Ar); 7.47–7.58 (5H, m, H Ar); 7.70–7.79 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 52.3 (OCH_3); 52.8 (OCH_3); 55.4 (OCH_3); 62.8 (CH); 82.7 (C); 83.5 (CH); 113.4 (2CH); 123.4 (2CH); 127.5 (2CH); 128.5 (2CH); 128.7 (2CH); 128.8 (2CH); 129.1 (CH); 133.6 (CH); 135.7 (C); 137.1 (C); 139.0 (C); 158.0 (C); 167.0 (CO); 167.2 (CO); 196.8 (CO). Found, *m*/*z*: 476.1726 $[M+H]^+$. $C_{27}H_{26}NO_7$. Calculated, *m*/*z*: 476.1704.

Dimethyl (4*RS*,5*RS*)-4-(4-bromobenzoyl)-2-(4-methoxyphenyl)-5-phenylisoxazolidine-3,3-dicarboxylate (3k). Yield 415 mg (75%), white powder, mp 160–161°C. IR spectrum, ν, cm^{-1}: 1776, 1735 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.29 (3H, s, OCH_3); 3.54 (3H, s, OCH_3); 3.79 (3H, s, OCH_3); 5.43 (1H, d, *J* = 9.0, CH); 5.46 (1H, d, *J* = 9.0, CH); 6.82–6.89 (2H, m, H Ar); 7.29–7.37 (3H, m, H Ar); 7.47–7.55 (6H, m, H Ar); 7.58–7.63 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 52.4 (OCH_3); 52.9 (OCH_3); 55.4 (OCH_3); 62.8 (CH); 82.7 (C); 83.4 (CH); 113.4 (2CH); 123.4 (2CH); 127.4 (2CH); 128.8 (2CH); 129.2 (C, CH); 129.9 (2CH); 132.0 (2CH); 135.5 (C); 135.8 (C); 138.9 (C); 158.1 (C); 166.94 (CO); 167.2 (CO); 195.8 (CO). Found, *m*/*z*: 576.0634 $[M+Na]^+$. $C_{27}H_{24}BrNNaO_7$. Calculated, *m*/*z*: 576.0628.

Dimethyl (4*RS*,5*RS*)-4-benzoyl-2-(4-methoxyphenyl)-5-(*p*-tolyl)isoxazolidine-3,3-dicarboxylate (3l). Yield 410 mg (83%), white powder, mp 124–125°C. IR spectrum, ν, cm^{-1}: 1772, 1729 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, s, CH_3); 3.28 (3H, s, OCH_3); 3.52 (3H, s, OCH_3); 3.79 (3H, s, OCH_3); 5.42 (1H, d, *J* = 9.0, CH); 5.54 (1H, d, *J* = 9.0, CH); 6.81–6.88 (2H, m, H Ar); 7.13 (2H, d, *J* = 7.9, H Ar); 7.36 (2H, t, *J* = 7.9, H Ar); 7.42 (2H, d, *J* = 8.0, H Ar); 7.47–7.56 (3H, m, H Ar); 7.72–7.79 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.2 (CH_3); 52.3 (OCH_3); 52.8 (OCH_3); 55.4 (OCH_3); 62.6 (CH); 82.8 (C); 83.4 (CH); 113.4 (2CH); 123.3 (2CH); 127.5 (2CH); 128.5 (2CH); 128.6 (2CH); 129.4 (2CH); 132.5 (C); 133.6 (CH); 137.2 (C); 139.0 (C); 139.1 (C); 158.0 (C); 167.1 (CO); 167.2 (CO); 196.9 (CO). Found, *m*/*z*: 490.1860 $[M+H]^+$. $C_{28}H_{28}NO_7$. Calculated, *m*/*z*: 490.1860.

Dimethyl (4*RS*,5*RS*)-4-(4-chlorobenzoyl)-2-(4-methoxyphenyl)-5-(*p*-tolyl)isoxazolidine-3,3-dicarboxylate (3m). Yield 392 mg (75%), white powder, mp 121–123°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, CH_3); 3.28 (3H, s, OCH_3); 3.54 (3H, s, OCH_3); 3.79 (3H, s, OCH_3); 5.40 (1H, d, *J* = 9.0, CH); 5.47 (1H, d, *J* = 9.0, CH); 6.79–6.89 (2H, m, H Ar); 7.14 (2H, d, *J* = 7.8, H Ar); 7.30–7.35 (2H, m, H Ar); 7.37–7.45 (2H, m, H Ar); 7.47–7.55 (2H, m, H Ar); 7.65–7.74 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.2 (CH_3); 52.4 (OCH_3); 52.9 (OCH_3); 55.4 (OCH_3); 62.7 (CH); 82.8 (C); 83.4 (CH); 113.4 (2CH); 123.4 (2CH); 127.4 (2CH); 129.0 (2CH); 129.5 (2CH); 129.9 (2CH); 132.3 (C); 135.5 (C); 139.0 (C); 139.1 (C); 140.3 (C); 158.0 (C); 167.0 (CO); 167.2 (CO); 195.7 (CO). Found, *m*/*z*: 524.1487 $[M+H]^+$. $C_{28}H_{27}ClNO_7$. Calculated, *m*/*z*: 524.1471.

Dimethyl (4*RS*,5*RS*)-2-(4-chlorophenyl)-4-(4-methoxybenzoyl)-5-phenylisoxazolidine-3,3-dicarboxylate (3n). Yield 445 mg (87%), white powder, mp 192–193°C. IR spectrum, ν, cm^{-1}: 1770, 1736 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.33 (3H, s, OCH_3); 3.54 (3H, s, OCH_3); 3.81 (3H, s, OCH_3); 5.49 (1H, d, *J* = 9.0, CH); 5.50 (1H, d, *J* = 9.0, CH); 6.79–6.85 (2H, m, H Ar); 7.24–7.29 (2H, m, H Ar); 7.31–7.37 (3H, m, H Ar); 7.46–7.54 (4H, m, H Ar); 7.70–7.77 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 52.5 (OCH_3); 52.8 (OCH_3); 55.5 (OCH_3); 62.7 (CH); 82.5 (C); 83.5 (CH); 113.9 (2CH); 122.2 (2CH); 127.4 (2CH); 128.3 (2CH); 128.8 (2CH); 129.2 (CH); 130.1 (C); 130.9 (C); 131.0 (2CH); 135.4 (C); 144.7 (C); 164.1 (CO); 166.9 (CO); 194.3 (CO). Found, *m*/*z*: 532.1128 $[M+Na]^+$. $C_{27}H_{24}ClNNaO_7$. Calculated, *m*/*z*: 532.1134.

Dimethyl (4*RS*,5*RS*)-5-(4-chlorophenyl)-2-methyl-4-(4-methylbenzoyl)isoxazolidine-3,3-dicarboxylate (3o). Yield 280 mg (65%), white powder, mp 109–111°C. IR spectrum, ν, cm^{-1}: 1770, 1738 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.35 (3H, s, CH_3); 2.97 (3H, s, CH_3); 3.58 (3H, s, OCH_3); 3.87 (3H, s, OCH_3); 5.12 (1H, d, *J* = 8.0, CH); 5.25 (1H, d, *J* = 8.0, CH); 7.14 (2H, d, *J* = 8.1, H Ar); 7.27 (2H, d, *J* = 8.5, H Ar); 7.36 (2H, d, *J* = 8.5, H Ar); 7.56 (2H, d, *J* = 8.1, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.6 (CH_3); 40.5 (CH_3); 52.5 (OCH_3); 52.9 (OCH_3); 63.1 (CH); 80.4 (C); 83.5 (CH); 128.8 (2CH); 128.9 (2CH); 129.0 (2CH); 129.4 (2CH); 134.2 (C); 134.8 (C); 135.0 (C); 144.9 (C); 166.7 (CO); 167.8 (CO); 196.7 (CO). Found, *m*/*z*: 454.1030 $[M+Na]^+$. $C_{22}H_{22}ClNNaO_6$. Calculated, *m*/*z*: 454.1028.

Reduction of isoxazolidines 3a,b,h,n,o by Zn in AcOH (General method). Glacial AcOH (3 ml) and activated Zn dust (1.3 g, 20.0 equiv) were added to a cooled (ice bath) solution of isoxazolidine **3a**,**b**,**h**,**n**,**o** (1.0 mmol) in MeOH (30 ml) (or THF (20 ml)). The mixture was vigorously stirred at 66°C for 4.5 h or 25 h (in the case of compound **3h** to obtain compounds **4c** and **6**), and the precipitate was filtered off. The filtrate was neutralized with saturated aqueous $NaHCO_3$. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2. The combined organic solution was dried over Na_2SO_4. The solvent was evaporated under reduced pressure, the residue was purified by column chromatography (eluent hexane–EtOAc). The resulting product was recrystallized from a hexane–Et_2O, 5:1 mixture.

Compound **4a** (46 mg, 29%) and compound **5a** (90 mg, 57%) were obtained as a result of the reduction of isoxazolidine **3a** (166 mg, 0.35 mmol).

Methyl (3*RS*,4*RS*,5*RS*)-4-(4-methoxybenzoyl)-2-oxo-5-phenyl-3-(phenylamino)tetrahydrofuran-3-carboxylate (4a). White powder, mp 117–118°C. IR spectrum, ν, cm^{-1}: 1796, 1783 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.66 (3H, s, OCH_3); 3.84 (3H, s, OCH_3); 4.73 (1H, d, *J* = 8.9, 4-CH); 5.26 (1H, s, NH); 6.19 (1H, d, *J* = 8.9, 5-CH); 6.75–6.83 (3H, m, H Ar); 6.87 (2H, d, *J* = 8.6, H Ar); 7.15 (2H, t, *J* = 7.8, H Ar); 7.30–7.46 (5H, m, H Ar); 7.71 (2H, d, *J* = 8.6, H Ar). ^{13}C NMR spectrum, δ, ppm: 53.5 (OCH_3); 55.6 (OCH_3); 58.2 (CH); 68.4 (C); 80.0 (CH); 114.2 (2CH); 115.5 (2CH); 119.8 (CH); 125.6 (2CH); 128.9 (2CH); 129.0 (2CH); 129.1 (CH); 129.3 (C); 130.8 (2CH); 136.6 (C); 143.1 (C); 164.9 (C); 167.8 (CO); 169.1 (CO); 192.8 (CO). Found, *m*/*z*: 468.1426 $[M+Na]^+$. $C_{26}H_{23}NNaO_6$. Calculated, *m*/*z*: 468.1418.

Methyl (3*RS*,4*SR*,5*SR*)-4-(4-methoxybenzoyl)-2-oxo-5-phenyl-3-(phenylamino)tetrahydrofuran-3-carboxylate (5a). White powder, mp 160–162°C. IR spectrum, ν, cm^{-1}: 1786 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.81 (3H, s, OCH_3); 3.94 (3H, s, OCH_3); 4.91 (1H, d, *J* = 9.9, 4-CH); 4.99 (1H, s, NH); 6.32 (1H, d, *J* = 9.9, 5-CH); 6.64–6.76 (4H, m, H Ar); 6.87–6.96 (1H, m, H Ar); 7.27–7.41 (5H, m, H Ar); 7.42–7.51 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 53.7 (OCH_3); 54.2 (OCH_3); 55.6 (CH); 71.0 (C); 79.4 (CH); 113.9 (2CH); 115.3 (2CH); 120.0 (CH); 125.6 (2CH); 129.0 (C, CH); 129.1 (2CH); 129.9 (2CH); 131.3 (2CH); 137.1 (C); 141.3 (C); 164.6 (C); 166.8 (CO); 169.7 (CO); 193.2 (CO). Found, *m*/*z*: 468.1430 $[M+Na]^+$. $C_{26}H_{23}NNaO_6$. Calculated, *m*/*z*: 468.1418.

Compound **4b** (40 mg, 39%) and compound **5b** (18 mg, 18%) were obtained as a result of the reduction of isoxazolidine **3b** (100 mg, 0.20 mmol).

Methyl (3*RS*,4*RS*,5*RS*)-4-(4-bromobenzoyl)-2-oxo-3-(phenylamino)-5-(*p*-tolyl)tetrahydrofuran-3-carboxylate (4b). White powder, mp 145–147°C. IR spectrum, ν, cm^{-1}: 1795, 1728 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.33 (3H, c CH_3); 3.66 (3H, s, OCH_3); 4.81 (1H, d, *J* = 8.6, 4-CH); 5.07 (1H, s, NH); 6.21 (1H, d, *J* = 8.6, 5-CH); 6.72–6.79 (3H, m, H Ar); 7.14–7.23 (4H, m, H Ar);

7.31–7.35 (2H, m, H Ar); 7.41–7.47 (2H, m, H Ar); 7.70–7.74 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.2 (CH_3); 53.6 (OCH_3); 58.6 (CH); 68.5 (C); 80.0 (CH); 115.7 (2CH); 120.1 (CH); 125.6 (2CH); 128.2 (2CH); 128.9 (2CH); 129.0 (2CH); 129.7 (2CH); 133.7 (C); 134.5 (C); 136.4 (C); 139.2 (C); 143.0 (C); 168.0 (CO); 169.0 (CO); 194.8 (CO).

Methyl (3*RS*,4*SR*,5*SR*)-4-(4-bromobenzoyl)-2-oxo-3-(phenylamino)-5-(*p*-tolyl)tetrahydrofuran-3-carboxylate (5b). Light-yellow amorphous solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.38 (3H, s, CH_3); 3.97 (3H, s, OCH_3); 4.90–5.03 (2H, m, NH, 4-CH); 6.31 (1H, d, *J* = 10.0, 5-CH); 6.66–6.73 (3H, m, H Ar); 6.78–6.82 (1H, m, H Ar); 7.18–7.27 (5H, m, H Ar); 7.29–7.40 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.2 (CH_3); 53.3 (OCH_3); 60.5 (CH); 71.0 (C); 79.3 (CH); 115.4 (2CH); 120.1 (CH); 125.7 (2CH); 128.6 (2CH); 128.8 (2CH); 129.7 (2CH); 129.8 (2CH); 133.9 (2C); 134.3 (C); 136.0 (C); 141.2 (C); 166.8 (CO); 169.6 (CO); 195.4 (CO). Found, *m*/*z*: 530.0566 $[M+Na]^+$. $C_{26}H_{22}BrNNaO_5$. Calculated, *m*/*z*: 530.0574.

Compound **4c** (30 mg, 27%) and compound **5c** (42 mg, 38%) were obtained as a result of the reduction of isoxazolidine **3h** (116 mg, 0.23 mmol).

Methyl (3*RS*,4*RS*,5*RS*)-5-(4-methoxyphenyl)-4-(4-methylbenzoyl)-2-oxo-3-(*p*-tolylamino)tetrahydrofuran-3-carboxylate (4c). White powder, mp 162–164°C. IR spectrum, ν, cm^{-1}: 1768, 1727 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.21 (3H, s, CH_3); 2.38 (3H, s, CH_3); 3.69 (3H, s, OCH_3); 3.78 (3H, s, OCH_3); 4.76 (1H, d, *J* = 9.0, 4-CH); 4.98 (1H, s, NH); 6.17 (1H, d, *J* = 9.0, 5-CH); 6.70 (2H, d, *J* = 8.4, H Ar); 6.88 (2H, d, *J* = 8.8, H Ar); 6.96 (2H, d, *J* = 8.1, H Ar); 7.21 (2H, d, *J* = 8.1, H Ar); 7.34 (2H, d, *J* = 8.8, H Ar); 7.61 (2H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.5 (CH_3); 21.7 (CH_3); 53.6 (OCH_3); 55.3 (OCH_3); 58.7 (CH); 69.0 (C); 80.1 (CH); 114.4 (2CH); 116.2 (2CH); 127.3 (2CH); 128.4 (2CH); 128.5 (C); 129.5 (4CH); 129.7 (C); 134.0 (C); 140.6 (C); 145.8 (C); 160.2 (C); 168.1 (CO); 169.3 (CO); 194.1 (CO). Found, *m*/*z*: 496.1735 $[M+Na]^+$. $C_{28}H_{27}NNaO_6$. Calculated, *m*/*z*: 496.1731.

Methyl (3*RS*,4*SR*,5*SR*)-5-(4-methoxyphenyl)-4-(4-methylbenzoyl)-2-oxo-3-(*p*-tolylamino)tetrahydrofuran-3-carboxylate (5c). White powder, mp 156–157°C. IR spectrum, ν, cm^{-1}: 1792, 1733 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, s, CH_3); 2.35 (3H, s, CH_3); 3.80 (3H, s, OCH_3); 3.94 (3H, s, OCH_3); 4.88 (1H, s, NH); 4.95 (1H, d, *J* = 9.9, 4-CH); 6.27 (1H, d, *J* = 9.9, 5-CH); 6.60 (2H, d, *J* = 8.4, H Ar); 6.89 (2H, d, *J* = 8.7, H Ar); 7.08 (2H, d, *J* = 8.2, H Ar); 7.12 (2H, d, *J* = 8.2, H Ar); 7.32–7.42 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.5 (CH_3); 21.7 (CH_3); 53.9 (OCH_3); 54.1 (OCH_3); 55.3 (CH); 71.2 (C); 79.3 (CH); 114.4 (2CH); 115.6 (2CH); 127.4 (2CH); 128.9 (C); 129.0 (2CH); 129.3 (C); 129.4 (2CH); 130.3 (2CH); 133.6 (C); 138.9 (C); 145.5 (C); 160.2 (C); 166.8 (CO); 169.9 (CO); 194.9 (CO). Found, *m*/*z*: 474.1931 $[M+H]^+$. $C_{28}H_{28}NO_6$. Calculated, *m*/*z*: 474.1911.

Compound **4d** (49 mg, 34%) and compound **5d** (52 mg, 36%) were obtained as a result of the reduction of isoxazolidine **3n** (153 mg, 0.30 mmol).

Methyl (3*RS*,4*RS*,5*RS*)-3-[(4-chlorophenyl)amino]-4-(4-methoxybenzoyl)-2-oxo-5-phenyltetrahydrofuran-3-carboxylate (4d). White powder, mp 76–78°C. IR spectrum, ν, cm^{-1}: 1784, 1756 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.66 (3H, s, OCH_3); 3.84 (3H, s, OCH_3); 4.73 (1H, d, *J* = 9.0, 4-CH); 5.36 (1H, s, NH); 6.14 (1H, d, *J* = 9.0, 5-CH); 6.75 (2H, d, *J* = 8.9, H Ar); 6.87 (2H, d, *J* = 9.0, H Ar); 7.10 (2H, d, *J* = 8.9, H Ar); 7.30–7.40 (5H, m, H Ar); 7.70 (2H, d, *J* = 9.0, H Ar). ^{13}C NMR spectrum, δ, ppm: 53.8 (OCH_3); 54.4 (OCH_3); 55.6 (CH); 70.8 (C); 79.4 (CH); 114.3 (2CH); 116.7 (2CH); 124.7 (C); 125.5 (2CH); 128.8 (2CH); 129.0 (2CH); 129.2 (C); 129.3 (CH); 130.9 (2CH); 136.3 (C); 141.9 (C); 164.7 (C); 166.6 (CO); 169.3 (CO); 192.9 (CO). Found, *m*/*z*: 586.0121 $[M+Ag]^+$. $C_{26}H_{22}AgClNO_6$. Calculated, *m*/*z*: 586.0181.

Methyl (3*RS*,4*SR*,5*SR*)-3-[(4-chlorophenyl)amino]-4-(4-methoxybenzoyl)-2-oxo-5-phenyltetrahydrofuran-3-carboxylate (5d). White powder, mp 161–162°C. IR spectrum, ν, cm^{-1}:1792, 1752 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.82 (3H, s, OCH_3); 3.95 (3H, s, OCH_3); 4.82 (1H, d, *J* = 9.9, 4-CH); 5.02 (1H, s, NH); 6.31 (1H, d, *J* = 9.9, 5-CH); 6.60 (2H, d, *J* = 8.8, H Ar); 6.75 (2H, d, *J* = 8.9, H Ar); 7.26 (2H, d, *J* = 8.8, H Ar); 7.35–7.45 (5H, m, H Ar); 7.48 (2H, d, *J* = 8.9, H Ar). ^{13}C NMR spectrum, δ, ppm: 53.8 (CH_3); 54.4 (CH_3); 55.6 (CH); 70.9 (C); 79.4 (CH); 113.9 (CH); 114.0 (CH); 116.2 (CH); 124.9 (C); 125.4 (2CH); 127.6 (CH); 128.1 (CH); 129.1 (2CH); 129.8 (2CH); 130.7 (CH); 131.3 (CH); 136.9 (2C); 140.0 (2C); 164.7 (C); 166.6 (CO); 169.4 (CO); 192.9 (CO). Found, *m*/*z*: 480.1207 $[M+H]^+$. $C_{26}H_{23}ClNO_6$. Calculated, *m*/*z*: 480.1208.

3-(4-Methoxyphenyl)-1-(*p*-tolyl)propan-1-one (6). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.41 (3H, s, CH_3); 2.98–3.04 (2H, m, CH_2); 3.21–3.27 (2H, m, CH_2); 3.79 (3H, s, OCH_3); 6.85 (2H, d, *J* = 8.7, H Ar); 7.17 (2H, d, *J* = 8.7, H Ar); 7.25 (2H, d, *J* = 7.9, H Ar); 7.86 (2H, d, *J* = 7.9, H Ar). The obtained data coincide with those published.[12]

Reduction of isoxazolidines 3e,f,i–m with $NaBH_4$ (General method). $NaBH_4$ (1.0 mmol) was added with vigorous stirring at 40°C to a solution of the starting isoxazolidine **3e**,**f**,**i**–**m** (0.5 mmol) in CH_2Cl_2–MeOH, 1:2 mixture (15 ml). The reaction mixture was heated until the disappearance of the starting isoxazolidine (TLC control). After the completion of the reaction, H_2O was added to the reaction mixture, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure, the residue was purified by column chromatography (eluent hexane–EtOAc). The resulting product was recrystallized from EtOH.

Methyl (3*RS*,3a*SR*,4*SR*,6a*SR*)-1-(4-methoxyphenyl)-6-oxo-3,4-diphenyldihydro1*H*,3*H*-furo[3,4-*c*]isoxazole-6a(6*H*)-carboxylate (7a) was obtained from isoxazolidine **3j** (119 mg, 0.25 mmol). Yield 58 mg (52%), light-yellow powder, mp 119–120°C. IR spectrum, ν, cm^{-1}: 1797, 1733 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.54 (3H, s, OCH_3); 3.81 (3H, s, OCH_3); 3.86 (1H, dd, *J* = 6.2, *J* = 3.5, 3a-CH); 5.38 (1H, d, *J* = 6.2, CH); 5.66 (1H, d, *J* = 3.5,

CH); 6.85–6.95 (2H, m, H Ar); 7.19–7.26 (2H, m, H Ar); 7.32–7.50 (8H, m, H Ar); 7.50–7.60 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 53.0 (OCH_3); 55.4 (OCH_3); 67.3 (CH); 78.4 (C); 81.5 (CH); 84.3 (CH); 113.8 (2CH); 119.5 (2CH); 125.0 (2CH); 126.8 (2CH); 128.9 (CH); 129.0 (2CH); 129.1 (2CH); 129.2 (CH); 135.8 (C); 138.3 (C); 139.2 (C); 156.6 (C); 166.9 (CO); 169.4 (CO). Found, *m*/*z*: 468.1427 $[M+Na]^+$. $C_{26}H_{23}NNaO_6$. Calculated, *m*/*z*: 468.1418.

Methyl (3*RS*,3a*SR*,4*SR*,6a*SR*)-4-(4-bromophenyl)-1-(4-methoxyphenyl)-6-oxo-3-phenyldihydro-1*H*,3*H*-furo[3,4-*c*]isoxazole-6a(6*H*)-carboxylate (7b) was obtained from isoxazolidine **3k** (277 mg, 0.50 mmol). Yield 104 mg (40%), light-yellow powder, mp 162–164°C. IR spectrum, ν, cm^{-1}: 1777, 1764 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.52 (3H, s, OCH_3); 3.76 (1H, dd, *J* = 6.3, *J* = 3.5, 3a-CH); 3.79 (3H, s, OCH_3); 5.33 (1H, d, *J* = 6.3, CH); 5.58 (1H, d, *J* = 3.5, CH); 6.83–6.92 (2H, m, H Ar); 7.03–7.11 (2H, m, H Ar); 7.37–7.46 (5H, m, H Ar); 7.46–7.54 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 53.1 (OCH_3); 55.4 (OCH_3); 67.3 (CH); 78.2 (C); 80.7 (CH); 84.3 (CH); 113.9 (2CH); 119.5 (2CH); 123.0 (C); 126.6 (2CH); 126.7 (2CH); 129.1 (2CH); 129.3 (CH); 132.3 (2CH); 135.6 (C); 137.4 (C); 139.11 (C); 156.7 (C); 166.8 (CO); 169.2 (CO).

Methyl (3*RS*,3a*SR*,4*SR*,6a*SR*)-1-(4-methoxyphenyl)-6-oxo-4-phenyl-3-(*p*-tolyl)dihydro-1*H*,3*H*-furo[3,4-*c*]isoxazole-6a(6*H*)-carboxylate (7c) was obtained from isoxazolidine **3l** (244 mg, 0.50 mmol). Yield 73 mg (32%), light-yellow powder, mp 130–131°C. IR spectrum, ν, cm^{-1}: 1792, 1747 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.38 (3H, s, CH_3); 3.51 (3H, s, OCH_3); 3.79 (3H, s, OCH_3); 3.82 (1H, dd, *J* = 6.5, *J* = 3.4, 3a-CH); 5.31 (1H, d, *J* = 6.5, CH); 5.61 (1H, d, *J* = 3.4, CH); 6.81–6.94 (2H, m, H Ar); 7.17–7.25 (4H, m, H Ar); 7.31–7.38 (3H, m, H Ar); 7.38–7.47 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.3 (CH_3); 53.0 (OCH_3); 55.4 (OCH_3); 67.2 (CH); 78.4 (C); 81.3 (CH); 84.1 (CH); 113.8 (2CH); 119.4 (2CH); 125.0 (2CH); 126.9 (2CH); 128.8 (CH); 129.1 (2CH); 129.7 (2CH); 132.5 (C); 138.3 (C); 139.2 (C); 139.3 (C); 156.5 (C); 166.9 (CO); 169.5 (CO). Found, *m*/*z*: 482.1583 $[M+Na]^+$. $C_{27}H_{25}NNaO_6$. Calculated, *m*/*z*: 482.1574.

Methyl (3*RS*,3a*SR*,4*SR*,6a*SR*)-4-(4-chlorophenyl)-1-(4-methoxyphenyl)-6-oxo-3-(*p*-tolyl)dihydro-1*H*,3*H*-furo[3,4-*c*]isoxazole-6a(6*H*)-carboxylate (7d) was obtained from isoxazolidine **3m** (131 mg, 0.25 mmol). Yield 64 mg (52%), light-yellow powder, mp 166–167°C. IR spectrum, ν, cm^{-1}: 1782, 1764 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.38 (3H, s, CH_3); 3.52 (3H, s, OCH_3); 3.74 (1H, dd, *J* = 6.6, *J* = 3.4, 3a-CH); 3.79 (3H, s, OCH_3); 5.29 (1H, d, *J* = 6.5, CH); 5.58 (1H, d, *J* = 3.3, CH); 6.80–6.90 (2H, m, H Ar); 7.08–7.15 (2H, m, H Ar); 7.23 (2H, d, *J* = 7.9, H Ar); 7.29–7.36 (2H, m, H Ar); 7.35–7.44 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.3 (CH_3); 53.1 (OCH_3); 55.4 (OCH_3); 67.2 (CH); 78.3 (C); 80.5 (CH); 84.4 (CH); 113.8 (2CH); 119.3 (2CH); 126.3 (2CH); 126.8 (2CH); 129.3 (2CH); 129.8 (2CH); 132.3 (C); 134.8 (C); 136.9 (C); 139.2 (C); 139.4 (C); 156.6 (C); 166.9 (CO); 169.3 (CO). Found, *m*/*z*: 516.1164 $[M+Na]^+$. $C_{27}H_{24}ClNNaO_6$. Calculated, *m*/*z*: 516.1184.

Methyl (3*RS*,3a*SR*,4*SR*,6a*SR*)-4-(4-bromophenyl)-6-oxo-3-phenyl-1-(*p*-tolyl)dihydro-1*H*,3*H*-furo[3,4-*c*]isoxazole-6a(6*H*)-carboxylate (7e) was obtained from isoxazolidine **3e** (268 mg, 0.50 mmol). Yield 85 mg (33%), yellow powder, mp 184–185°C. IR spectrum, ν, cm^{-1}: 1767 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, s, CH_3); 3.52 (3H, s, OCH_3); 3.72 (1H, dd, *J* = 6.6, *J* = 3.4, 3a-CH); 5.33 (1H, d, *J* = 6.6, CH); 5.58 (1H, d, *J* = 3.3, CH); 7.00–7.19 (4H, m, H Ar); 7.34 (2H, d, *J* = 8.2, H Ar); 7.38–7.58 (7H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.8 (CH_3); 53.1 (OCH_3); 67.6 (CH); 78.1 (C); 80.5 (CH); 84.2 (CH); 117.0 (2CH); 123.0 (C); 126.6 (2CH); 126.8 (2CH); 129.1 (2CH); 129.2 (2CH); 129.4 (CH); 132.3 (2CH); 133.4 (C); 135.4 (C); 137.3 (C); 143.5 (C); 166.9 (CO); 169.1 (CO). Found, *m*/*z*: 530.0577 $[M+Na]^+$. $C_{26}H_{22}BrNNaO_5$. Calculated, *m*/*z*: 530.0574.

Methyl (3*RS*,3a*SR*,4*SR*,6a*SR*)-6-oxo-4-phenyl-1,3-bis-(*p*-tolyl)dihydro-1*H*,3*H*-furo[3,4-*c*]isoxazole-6a(6*H*)-carboxylate (7f) was obtained from isoxazolidine **3f** (236 mg, 0.50 mmol). Yield 69 mg (31%), yellow powder, mp 141–143°C. IR spectrum, ν, cm^{-1}: 1736 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.33 (3H, s, CH_3); 2.41 (3H, s, CH_3); 3.54 (3H, s, OCH_3); 3.80 (1H, dd, *J* = 6.8, *J* = 3.2, 3a-CH); 5.34 (1H, *J* = 6.8, CH); 5.64 (1H, d, *J* = 3.3, CH); 7.14 (2H, d, *J* = 8.2, H Ar); 7.18–7.29 (4H, m, H Ar); 7.31–7.40 (5H, m, H Ar); 7.42 (2H, d, *J* = 7.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.8 (CH_3); 21.3 (CH_3); 52.9 (OCH_3); 67.5 (CH); 78.3 (C); 81.1 (CH); 84.3 (CH); 116.9 (2CH); 125.0 (2CH); 126.9 (2CH); 128.8 (CH); 129.1 (2CH); 129.2 (2CH); 129.7 (2CH); 132.3 (C); 133.2 (C); 138.3 (C); 139.3 (C); 143.7 (C); 167.1 (CO); 169.5 (CO). Found, *m*/*z*: 444.1807 $[M+H]^+$. $C_{27}H_{26}NO_5$. Calculated, *m*/*z*: 444.1805.

Methyl (3*RS*,3a*SR*,4*SR*,6a*SR*)-4-(4-bromophenyl)-3-(4-methoxyphenyl)-6-oxo-1-(*p*-tolyl)dihydro-1*H*,3*H*-furo[3,4-*c*]isoxazole-6a(6*H*)-carboxylate (7g) was obtained from isoxazolidine **3g** (142 mg, 0.28 mmol). Yield 40 mg (27%), light-yellow powder, mp 132–134°C. IR spectrum, ν, cm^{-1}: 1792, 1747 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, s, CH_3); 3.51 (3H, s, OCH_3); 3.68 (1H, dd, *J* = 7.0, *J* = 3.1, 3a-CH); 3.84 (3H, s, OCH_3); 5.27 (1H, d, *J* = 7.0, CH); 5.54 (1H, d, *J* = 3.1, CH); 6.93–6.98 (2H, m, H Ar); 7.01–7.06 (2H, m, H Ar); 7.11 (2H, d, *J* = 8.3, H Ar); 7.29–7.36 (2H, m, H Ar); 7.40–7.50 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.8 (CH_3); 53.0 (OCH_3); 55.4 (OCH_3); 67.4 (CH); 78.2 (C); 80.2 (CH); 84.2 (CH); 114.5 (2CH); 116.8 (2CH); 122.9 (C); 126.5 (2CH); 126.8 (C); 128.5 (2CH); 129.2 (2CH); 132.2 (C); 133.3 (2CH); 137.4 (C); 143.6 (C); 160.5 (C); 167.0 (CO); 169.3 (CO). Found, *m*/*z*: 560.0691 $[M+Na]^+$. $C_{27}H_{24}BrNNaO_6$. Calculated, *m*/*z*: 560.0679.

X-ray structural analysis of compounds 4c and 7e was performed on an Xcalibur diffractometer. Single crystals were obtained by crystallization from CH_2Cl_2–EtOH mixture. The full set of X-ray structural data for compounds **4c** and **7e** was deposited at the Cambridge Crystallographic Data Center (deposits CCDC 1547675 and 1534240, respectively).

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of all synthesized compounds is available at the journal website at http://link.springer.com/journal/10593.

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