Synthesis of condensed isoxazolines and isoxazolidines *via* cycloaddition to furan-2(5*H*)-ones

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Dedicated to Professor Benito Alcaide in his 60th birthday

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Abstract

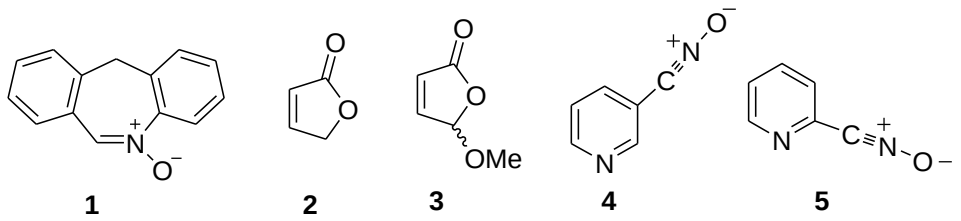
Cycloadditions of nitrone **1** and pyridylnitrile oxide **4** to furanones **2** and **3** afford tetrahydrofuro[3',4':4,5]isoxazolo[2,3-*a*]dibenzo[*c*,*f*]azepin-1(3*H*)-ones and furo[3,4-*d*]isoxazolin-4(*H*)-ones, respectively, in a totally regioselective manner. The resulting adducts evolve into the corresponding pyrroloisoxazole systems by treatment with ammonium hydroxide and hydrazine hydrate in good yield. The N-O bond of isoxazolo[2,3-*a*]dibenzo[*c*,*f*]azepin-1(3*H*)-ones is not cleaved by $LiAlH_4$.

Keywords: Azepines, isoxazolines, isoxazolidines, 1,3-dipolar cycloaddition, furan-2(5*H*)-ones, nitrones

Introduction

The valuable and diverse biological activity of molecules containing isoxazoline/isoxazolidine rings,[1] pyrroloazepines,[2] pyrrolinones,[3] or 2,3,3a,8-tetrahydrodibenzo[*c*,*f*]isoxazolo[2,3-*a*]azepines,[4] confers on them a high pharmacological value. 1,3-Dipolar cycloadditions, by using nitrile oxides and nitrones as dipoles, are one of the best reported methods for building isoxazoline and isoxazolidine skeletons, respectively.[5,6] In an earlier work we reported the efficiency of 5-alkoxyfuran-2(5*H*)-ones as dipolarophiles in reactions with diazoalkanes,[7] alkyl-, bromo- or benzonitrile oxides,[8] azomethine ylides,[9] nitrones,[10] and carbonyl ylides.[11] One of the most significant features of adducts formed in these reactions is the versatility of their functionalities, which allows the subsequent synthesis of other heterocyclic systems, that are not easily obtained from other precursors. In this sense, we have reported the regioselective synthesis of functionalized pyrroloazepines and isoxazolo[4,5-*d*]pyridazin-4(5*H*) [and 7(6*H*)]-ones from

the adducts obtained from reactions of 5-alkoxyfuran-2(5*H*)-ones with 11*H*-dibenzo[*b*,*e*]azepine 5-oxide (**1**)[10b] and nitrile oxides,[8b] respectively. With these precedents, we reasoned that it would be interesting to develop some strategies involving the use of furanones with the aim of obtaining new pyrrolo[3,4-*d*]isoxazole[12] structures bearing diverse functionalities. In this paper we report the results obtained in the reactions of commercially available furan-2(5*H*)-one **2** and methoxyfuranone (**3**)[13] with nitrone **1**[4] and pyridylnitrile oxides **4** and **5** (Scheme 1), and the transformation of the resulting adducts into the corresponding pyrrolinones.

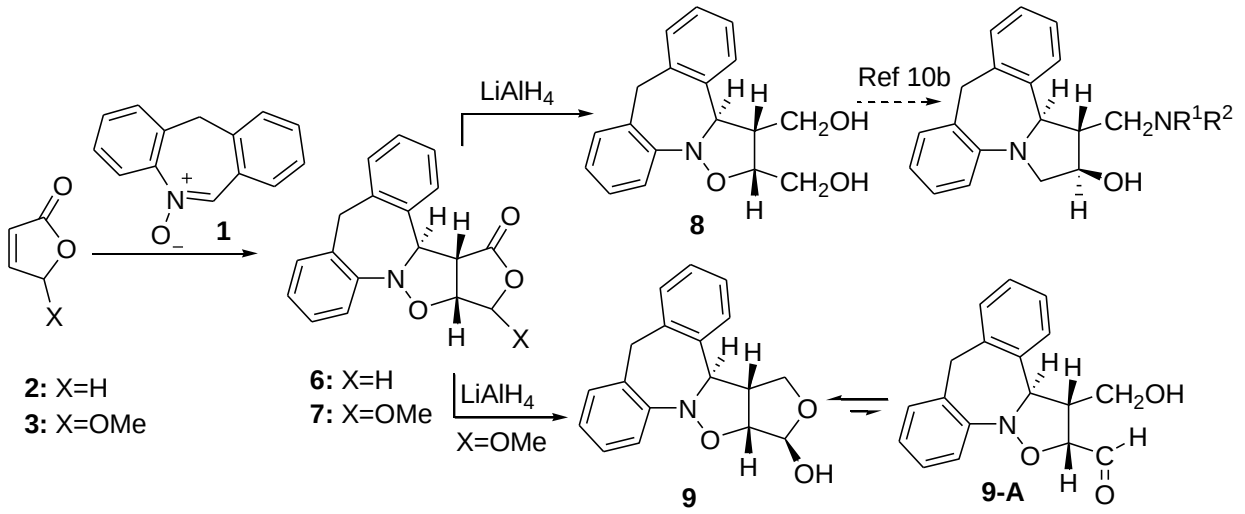


Scheme 1

Results and Discussion

The 1,3-dipolar cycloaddition at room temperature of nitrone **1** to commercially available furanone **2** afforded **6** in 92% yield after 18 hours (Scheme 2). The reaction was totally regioselective. Similar results were obtained from reaction of **1** with methoxyfuranone **3**, affording **7** in 84% yield**.**[10b]

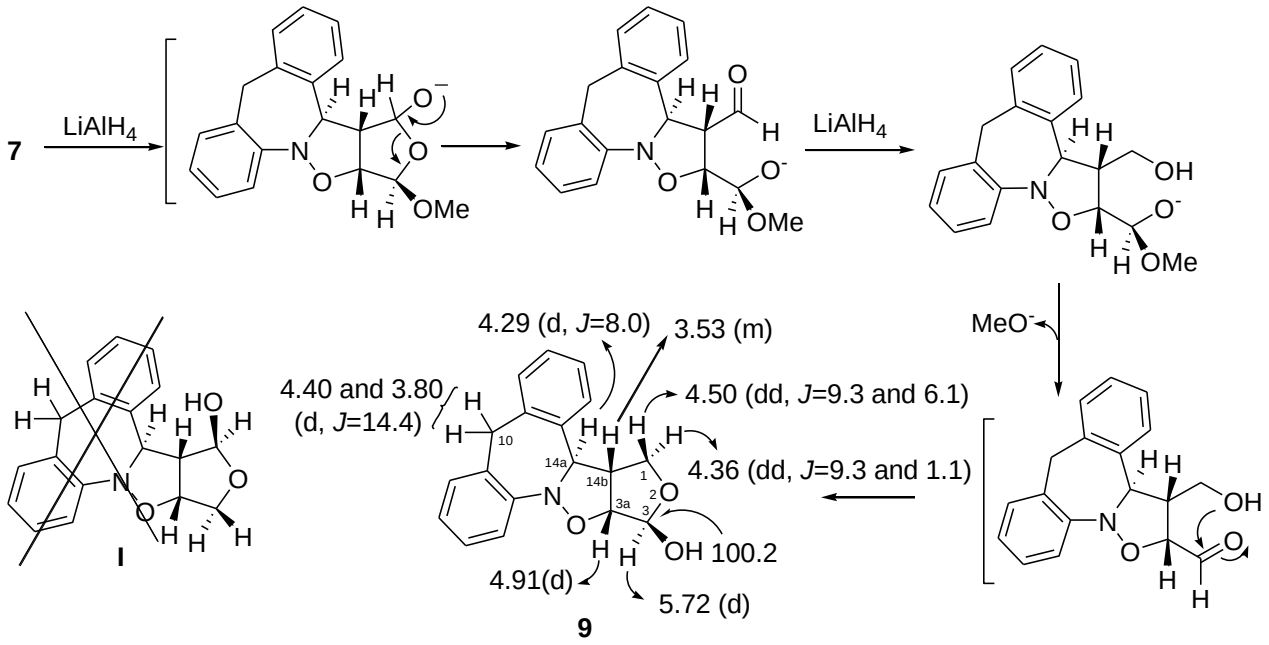
With the adducts **6** and **7** in hand, their reactions with $LiAlH_4$ (LAH) were studied. In the presence of an excess of the reagent (1.5 equiv mol), **6** and **7** afforded diol **8**[10b] in 89% and 93% yield, respectively (Scheme 2). Diol **8** can be used as the starting material in the synthesis of racemic pyrroloazepines.[10b] However, when the reduction of **7** was carried out by using 0.7 equiv mol of LAH and the reaction was quenched after 5 min, a 35:65 mixture of diol **8** and hemiacetal **9** was obtained in almost quantitative yield. Upon chromatographic separation, compounds **9** and **8** were isolated in 63% and 24% yield, respectively. It is noteworthy that the reductive ring cleavage of the isoxazolidine ring of **6** and **7** does not take place with LAH (even using 2.5 equiv mol of the reagent), whereas under similar conditions, 3-menthyloxy- (or 3-ethoxy)-1,3,3a,6,7,8,8a,8b-octahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1-ones are transformed into the corresponding aminotriols.[14,10a]



Scheme 2

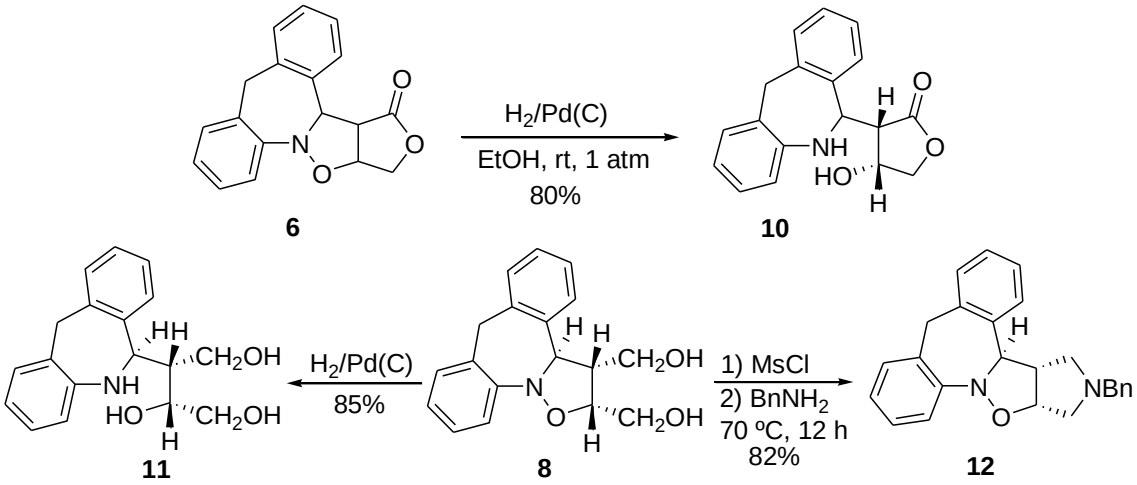
The structure **9** was unequivocally established from its analytical and spectroscopic data (Scheme 3) as well as by chemical transformations (monoacetylation). The presence of the hemiacetal group was determined by NMR (δ-H_3 = 5.72 ppm, coupled with exchangeable proton, and δ-C_3 = 100.2 ppm). Hemiacetalic proton is not coupled with its vicinal H_{3a}, which indicates a *trans* relationship between them (Scheme 3). The regioisomeric structure **I** (Scheme 3) can be ruled out from the chemical shifts and coupling constants of the methyne groups marked as 3a [(δ-H = 4.91 (*d*) and δ-C = 86.8 ppm)] and 14b [(δ-H = 4.29 (*m*) and δ-C = 74.0 ppm)] in Scheme 3.

According to the structure assigned to **9**, it is the carbonyl group of compound **7** which suffers the reduction under the latter conditions. It contrasts with the well-documented reduction of 5-alkoxyfuran-2(5*H*)-ones with $NaBH_4$, which affords products resulting from the reduction of the acetal moiety C-5 (C-3 in compound **9**). The formation of the stable hemiacetal **9** can be explained by assuming the nucleophilic hydride addition to the carbonyl group at **7**, followed by ring opening of lactone, reduction of the aldehyde with simultaneous elimination of methanol, and final cyclization into the hemiacetal **9** (Scheme 3).



Scheme 3

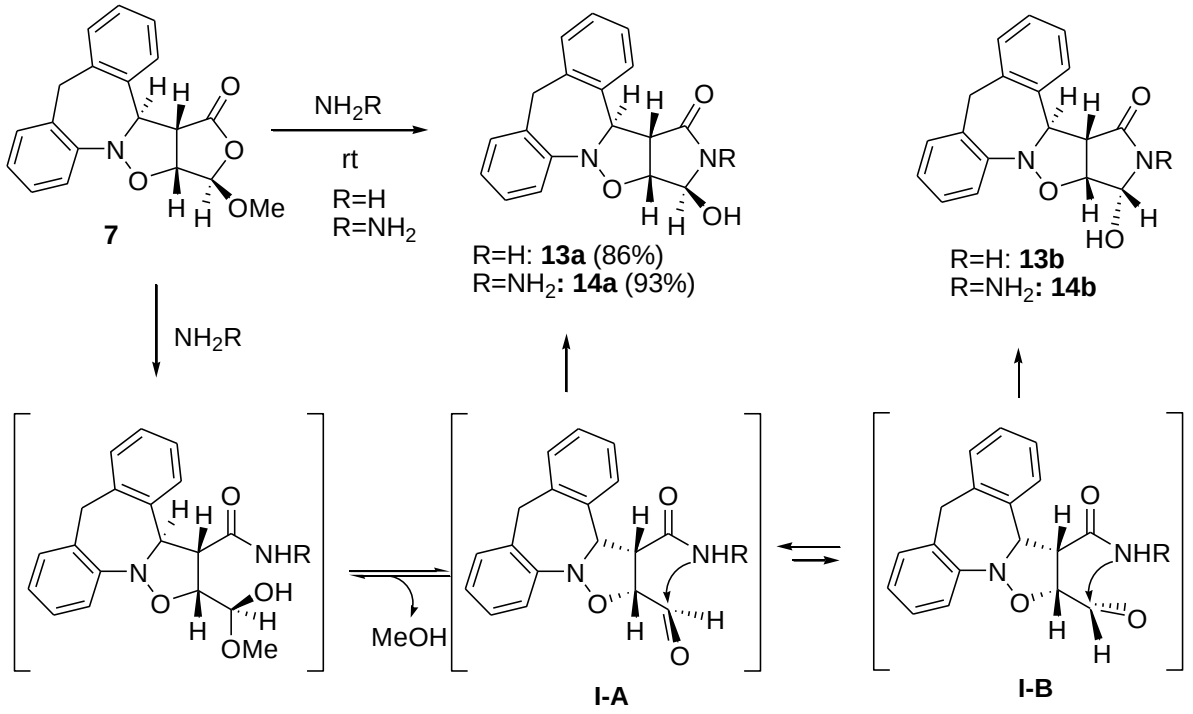
The cleavage of the N-O bond in isoxazolidines **6** and **8** into aminoalcoholes **10**-**11** was satisfactorily carried out by hydrogenolysis with H_2/Pd(C) 10% in ethanol (Scheme 4), under conditions similar to those that we had previously reported for related compounds.[10b]



Scheme 4

Isoxazolidine **8** was transformed into pyrrolo[3',4':4,5]isoxazolo[2,3-*a*]dibenzo[*c*,*f*]azepine **12** by double mesylation followed by reaction with benzylamine (Scheme 4). Pyrrolo[3',4':4,5]isoxazolo[2,3-*a*]dibenzo[*c*,*f*]azepin-1-one derivatives were obtained by reaction

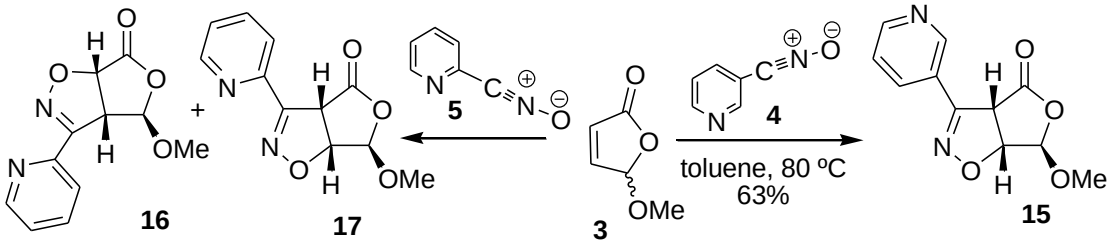
of **7** with nitrogenated nucleophiles (Scheme 5). When the reactions were carried out under heterogeneous phase with ammonium hydroxide or hydrazine hydrate, **13a** or **14a** were isolated in good yields as the sole products. However, inseparable mixtures of steroisomers **a** and **b** (epimer at hemiaminal carbon) of compounds **13** and **14** were obtained when the reactions were performed in THF or ethanol as the solvents. Under these conditions, reaction times are shorter than those required under heterogeneous phase. The formation of isomers **a** and **b** can be rationalized by assuming that the opening of the lactone ring by the amine and subsequent elimination of methanol generates aldehyde **I**, which can adopt two plausible conformations around the C-CHO bond (**I-A** and **I-B**). The subsequent attack of nitrogen to each one of these conformations (**I-A** and **I-B**) would afford isomers **a** and **b**, respectively. The higher stability of conformation **A** (**B** must be less stable due to electrostatic repulsion between both oxygen atoms, Scheme 5) can account for the major or sole formation of the **a** isomers.



Scheme 5

Next we studied some reactions of the furanones with nitrile oxides. The reaction of **3** with nicotinonitrile oxide **4**,[15] generated "in situ" by slow addition of triethylamine (with a syringe pump) on to 3-[chloro(hydroxymino)methyl]pyridinium chloride, afforded **15** as the sole adduct in good yield after 4 hours (Scheme 6). The complete regioselectivity and stereoselectivity observed in this reaction are not unexpected, since a similar behavior had been observed in reactions of **3** with other nitrile oxides.[8c] By contrast, reactions of nitrile oxide **5** with furanone **3** afforded mixtures of regioisomers **16** and **17** under all experimental conditions assayed (Scheme

6), although the stereoselectivity remains complete (*anti* with respect to the methoxy group at **3**). Both **16** and **17** could be isolated as pure compounds by column chromatography.

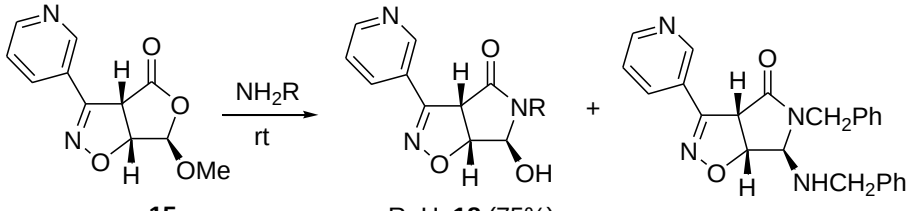


Toluene, 80 ºC, 2.5 h	46	:	54
Toluene, rt, 2.5 h, 45%	72	:	28
Acetonitrile, rt, 3 h, 58%	84	:	16

Scheme 6

It is noteworthy that the favoured regioisomer obtained from **5**[15] and **3** is different to that resulting from **4** and the other nitrile oxides so far studied with 5-alkoxyfuran-2(5*H*)-ones unsubstituted at the C-C double bond.[16,8c,17] It can be rationalized by assuming that the electron-withdrawing effect of the 2-pyridinyl group lowers the energy at the HOMO of the nitrile oxide, thus modifying the type of cycloadition[18] (II or III instead I, according to the Sutsman clasification)[19]. A similar effect can be invoked in order to justify the higher regioselectivity observed in acetonitrile (it must provoke a higher stabilization of the HOMO than toluene).

Reactions of furo[3,4-*d*]isoxazole **15** with nitrogenated nucleophiles provided compounds exhibiting isoxazoline-pyrrolidine condensed rings (Scheme 7). Hence, **15** reacted at room temperature with ammonium hydroxide and hydrazine hydrate, without solvent, giving compounds **18** and **19**, respectively, as the sole products in good yields. Under similar conditions, benzylamine afforded a mixture of pyrrolinones **20** and **21** (Scheme 7).



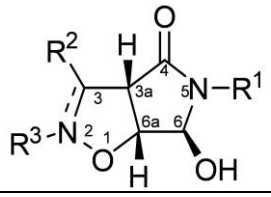
Scheme 7

The results obtained in reactions of **15** and **7** with nitrogenated nucleophiles described in this paper, are in agreement with those reported by us for 6-methoxy-3-methylfuro[3,4-*d*]isoxazol-4(3a*H*)-one,[20] but contrast with those reported by Fišera for the 6-ethoxy-3-phenylderivative,[16a] which evolves into a 50:50 mixture of epimers at C-6 of pyrrolo[3,4-*d*]isoxazolones by treatment with ammonia (in MeOH), or tetrahydroisoxazolo[3,4-*d*]pyridazin-4(3*H*)-ones by reaction with hydrazine hydrate (refluxing water/AcOH, 9:7).

The formation of isoxazolopyrrolinones **18**-**20** can be explained according to sequence depicted in Scheme 5. The formation of compound **21** can be rationalized also from intermediate **I** at Scheme 5 through of corresponding intermediate imine and subsequent cyclization by nucleophilic attack of amide nitrogen to iminic carbon.

The structures of the compounds **13**, **14**, **18**, **19**, and **20**, were established on the basis of their spectroscopic parameters. In Table 1 are collected the most significant ones. The IR absorption frequency (> 1680 cm^{-1}) and the ^{13}C chemical shift (>165 ppm) of the C=O group, as well as the value of the coupling constant $J_{6,6a}$ (ca. 0 Hz) confirm the pyrrolinone structure assigned to these compounds.[19]

Table 1. Significant NMR data for compounds **13**, **14**, **18**, **19**, and **20**.



No	R^1	R^2	R^3	^1H NMR (δ ppm)					^{13}C NMR (δ ppm)			
							J (Hz)					
				H_{3a}	H_{6a}	H_6	$J_{3a,6a}$	$J_{6,OH}$	C_{3a}	C_{6a}	C_6	C_4
13a	H	dibenzoazepine		3.73	4.57	5.14	6.8	7.4	56.2	84.0	80.6	175.6
18a	H	3-Py	--	4.87	5.05	5.11	8.9	7.1	54.3	82.3	90.0	170.9
14a	NH_2	dibenzoazepine		3.82	4.51	5.06	7.2	-	55.3	79.7	85.7	170.3
19a	NH_2	3-Py	--	4.98	4.98	5.02		6.3	53.2	85.4	86.9	165.8
20	Benz	3-Py	--	4.55	5.33	5.19	9.4	10.5	56.1	78.7	81.1	165.6

Experimental Section

General Procedures. All moisture sensitive reactions were performed in flame–dried glassware equipped with rubber septa under a positive pressure of argon. THF was distilled from sodium-benzophenone under argon. Silica gel 60 (230-400 mesh ASTM) and DC-Alufolien 60 F254 were used for flash column chromatography and analytical TLC, respectively. Melting points were determined in open capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were

recorded on Brucker AC-300 and Bruker WP-200-SY spectrometers. Chemical shifts (δ) are reported in ppm, coupling constant in Hz. Microanalyses were carried out on a LECO CHNS-932 in Laboratory of elemental analyses of SIDI of Universidad Autónoma de Madrid, and were in good agreement with the calculated values. IR spectra were recorded on a Bruker Vector 22 spectrometer.

(±)-(*R*$_{3a}$,*S*$_{14a}$,*S*$_{14b}$)-3a,10,14b,14c-Tetrahydrofuro[3',4':4,5]isoxazolo[2,3-*a*]dibenzo[*c*,*f*] azepin-1(3*H*)-one [(±)-6]. To a solution of 1.4 mmol of furan-2(5*H*)-one (**2**) in 10 mL of $CHCl_3$ was added, under argon atmosphere and at room temperature, 1.4 mmol of 11*H*-dibenzo[*b*,*e*]azepine 5-oxide (**1**). After 18 hours the solvent was removed under reduced pressure. By precipitation with $CHCl_3$ and washing with acetone pure **6** was obtained as a white solid. Yield 92%. Mp 192-193 ºC. Anal. calcd. for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.54; H, 5.16, N, 4.63. IR (KBr) ν_{max} 1756, 1602, 1587, 1484, 1299, 1286 cm^{-1}. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.65-7.58 (1H, m), 7.41-7.18 (6H, m), 7.08-6.99 (1H, m), 5.11 (1H, H_{3a}, ddd, *J* = 6.9, 4.7, and 1.0 Hz), 4.67 (1H, H_3, dd, *J* =11.3 and 1.0 Hz), 4.57 (1H, H_{14b}, d, *J* = 5.9 Hz), 4.56 (1H, H_3, dd, *J* = 11.3 and 4.7 Hz), 4.46 (1H, H_{10}, d, *J* = 14.8 Hz), 3.85 (1H, H_{14c}, dd, *J* = 6.9 and 5.9 Hz), 3.78 (d, 1H, H_{10}, *J* = 14.8 Hz). ^{13}C NMR (75.6 MHz, CD_2Cl_2) δ 177.4 (C), 147.0 (C), 137.0 (C), 135.5 (C), 130.8 (C), 129.9 (CH), 129.4 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 125.1 (CH), 116.9 (CH), 78.0 (CH), 72.0 (CH), 71.1 (CH), 57.2 (CH), 40.1 (CH_2).

Reduction of the furanone ring

Method A. To a solution of isoxazolidines **6** or **7**[10b] (0.33 mmol) in THF (5.5 mL), vigorously stirred at room temperature, was added LAH (0.82 mmol) in small portions. The reaction mixture was stirred for 30 minutes and then ethyl acetate (10 mL) and water (10 mL) were added. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The organic phase was dried over Na_2SO_4 and evaporated at reduced pressure.

Method B. To a stirred solution of isoxazolidine **7** (0.33 mmol) in THF (5.5 mL) at room temperature was added in small portions 0.24 mmol of LAH. After 30 minutes a mixture of ethyl acetate (10 mL) and water (10 mL) were added. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic layers was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a 35:65 mixture of **(±)-8** and **(±)-9**.

(±)-(*R*$_2$,*R*$_3$,*R*$_{3a}$)-2,3,3a,8-Tetrahydrodibenzo[*c*,*f*]isoxazolo[2,3-*a*]azepine-2,3-diyldimethanol [(±)-8].[10b] Obtained from **6** and **7** following method A and purified by column chromatography (hexane/ethyl acetate, 2:1). Yield 89% (from **6**) or 93% (from **7**). Mp 126-128 ºC (white solid), (Literature mp 126-128 ºC).[10b] Anal. calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.59; H, 6.46; N, 4.64. IR (KBr) ν_{max} 3539, 3376, 1600, 1486, 1051. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (1H, dd, *J* = 7.9 and 1.2 Hz), 7.31-7.13 (6H, m), 6.97 (1H, dt, *J* = 7.4 and 1.3 Hz), 4.47 (1H, m), 4.39 (1H, d, *J* = 8.3 Hz), 4.35 (1H, d, *J* = 14.8 Hz), 4.15-3.95 (4H, m), 3.93 (1H,

d, *J* = 14.8 Hz), 3.79 (1H, dd, *J* = 6.5 and 4.2 Hz), 3.46 (1H, dd, *J* = 8.2 and 4.6 Hz), 3.16 (1H, m). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 147.2 (C), 137.7 (C), 135.0 (C), 129.8 (C), 129.5 (CH), 128.4 (CH), 127.6 (CH), 127.5 (CH), 126.8 (CH), 126.7 (CH), 123.9 (CH), 117.4 (CH), 78.6 (CH), 67.8 (CH), 60.3 (CH_2), 60.1 (CH_2), 52.6 (CH), 40.0 (CH_2).

(±)-(*R*$_3$,*R*$_{3a}$,*S*$_{14a}$,*R*$_{14b}$)-Hexahydro-1*H*-furo[3',4':4,5]isoxazolo[2,3-*a*]dibenzo[*c*,*f*]azepinyl-3-ol [(±)-9]. Compound **(±)-9** was obtained from isoxazolidine **7** following method B and isolated as a withe solid by column chromatography in (hexane/ethyl acetate, 3:1). Yield 63%. Mp 187-189 ºC (with decomposition). Anal. calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.05; H, 5.84; N, 4.74. IR (KBr) ν_{max} 3378, 1491, 1250, 1080 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (1H, m), 7.20 (5H, m), 7.01 (2H, m), 5.72 (1H, d, *J* = 2.6 Hz), 4.91 (1H, d, *J* = 7.4 Hz), 4.50 (1H, dd, *J* = 9.3 and 6.1 Hz), 4.40 (1H, d, *J* = 14.4 Hz), 4.36 (1H, dd, *J* = 9.3 and 1.1 Hz), 4.29 (1H, d, *J* = 8.0 Hz), 3.80 (1H, d, *J* = 14.4 Hz), 3.53 (1H, m), 2.56 (1H, d, OH, *J* = 2.6 Hz). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 147.0 (C), 136.6 (C), 135.6 (C), 130.8 (C), 129.7 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 126.6 (CH), 124.0 (CH), 115.8 (CH), 100.2 (CH), 86.8 (CH), 74.0 (CH), 71.4 (CH_2), 55.8 (CH), 39.7 (CH_2).

Acetyl derivate of compound 9. A solution of **9** (10 mg, 0.034 mmol), acetic anhydride (10.5 μL, 0.11 mmol), pyridine (9 μL, 0.11 mmol), DMAP (2 mg) in dichloromethane (2 mL) was stirred until complete conversion (monitored by TLC) at room temperature. The solvent was removed under reduced pressure, and the residue purified by column chromatography (hexane/ethyl acetate, 6:1) Yield 95%. IR (KBr) ν_{max} 1747, 1487, 1221, 1083 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (1H, d, *J* = 7.3 Hz), 7.20 (5H, m), 7.01 (2H, m), 6.48 (1H, s), 4.94 (d, 1H, *J* = 7.4 Hz), 4.49-4.27 (m, 4H), 3.78 (d, 1H, *J* = 14.4 Hz), 3.56 (m, 1H), 2.12 (s, 3H).

Cleavage of the N-O bond

To a solution of 0.52 mmol of isoxazolidine **(±)-6** or **(±)-8** in ethyl acetate (or ethanol) (9 mL) was added 55 mg (0.052 mmol, 10% mol) of Pd/(C) (10%). The mixture was stirred at room temperature under hydrogen pressure for 20 or 12 hours. The reaction mixture was filtered through a Celite pad, and the cake washed with the solvent. The filtrate was concentrated at reduced pressure.

(±)-3-(6,11-Dihydro-*5H*-dibenzo[*b*,*e*]azepin-6-yl)-4-hydroxydihydrofuran-2(3*H*)-one [(±)-10]. Obtained by hydrogenolysis of isoxazolidine **6** and was precipitated with ethyl ether. Yield 80%. Mp 143-144 ºC (yellow solid). IR (KBr) ν_{max} 3383, 1764, 1603, 1581, 1492, 1315 and 1155 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.09 (5H, m), 7.02-6.93 (3H, m), 5.33 (1H, $H_{6'}$, d, *J* = 3.2 Hz), 4.79 (1H, $H_{11'}$, d, *J* = 14.3 Hz), 4.47 (1H, H_4, dd, *J* = 4.4 and 2.8 Hz), 4.34 (1H, H_5, d, *J* = 9.9 Hz), 4.19 (dd, 1H, H_5, *J* = 9.9 and 2.8 Hz), 3.49 (1H, $H_{11'}$, d, *J* = 14.3 Hz), 3.00 (1H, H_3, dd, *J* = 4.4 and 3.2 Hz). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 175.7 (C), 143.1 (C), 138.3 (C), 136.4 (C), 134.9 (C), 130.1 (CH), 128.7 (CH), 128.1 (CH), 127.7 (CH), 127.1 (CH), 124.1 (CH), 121.7 (CH), 75.9 (CH_2), 70.1 (CH), 59.1 (CH), 53.0 (CH), 39.4 (CH_2).

(±)-(*R*$_2$,*R*$_3$)-3-{(*R*$_{6'}$)-6',11'-Dihydro-5*H*-dibenzo[*b*,*e*]azepin-6'-yl}butan-1,2,4-triol [(±)-11]. Compound **11** was obtained from diol **8** after 12 hours with H_2/Pd(C) and was purified by column chromatography (hexane/acetone, 1:1). Yield 85%. IR (KBr) ν_{max} 3899-3375, 1701, 1604, 1493, 1315 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-6.96 (6H, m), 6.73 (1H, t, *J* = 7.4 Hz), 6.66 (1H, d, *J* = 7.9 Hz), 4.79 (1H, d, *J* = 7.1 Hz), 4.70 (broad, 1H, OH), 4.55 (d, 1H, *J* = 14.8 Hz), 4.31 (m, 1H), 3.89-3.64 (m, 7H), 3.57 (d, 1H, *J* = 14.8 Hz), 2.15 (broad, 1H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 144.7 (C), 138.7 (C), 137.0 (C), 129.2 (CH), 129.1 (CH), 129.0 (CH), 127.7 (C), 127.6 (CH), 127.5 (CH), 126.8 (CH), 119.8 (CH), 118.9 (CH), 71.3 (CH), 65.6 (CH_2), 61.0 (CH_2), 60.3 (CH), 48.6 (CH), 40.0 (CH).

(±)-(*R*$_{3a}$,*S*$_{10a}$,*S*$_{10b}$)-2-Benzyl-2,3,3a,8,10a,10b-hexahydro-1*H*-pyrrolo[3',4':4,5]isoxazolo[2,3-*a*]dibenzo[*c*,*f*]azepine [(±)-12]. To a solution of diol **8** (0.07 mmol) and triethylamine (0.148 mmol) in dichloromethane (1 mL), stirred at 0 ºC under argon atmosphere, was added methanesulfonyl chloride (0.148 mmol). After 10 minutes at the same temperature, a saturated NH_4Cl solution was added until neutralization. The layers were separated and the aqueous phase was extracted with dichloromethane (2 x 25 mL). The extracts were dried over Na_2SO_4 and the solvent was evaporated at reduced pressure. To the residue was added benzylamine (500 μL) and the resulting mixture was heated to 70 ºC for 20 hours. The compound **12** was isolated by column chromatography (hexane/ethyl acetate, 8:1). Yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (1H, dd, *J* = 8.1 and 1.2 Hz), 7.23 (11H, m), 6.98 (1H, dt, *J* = 7.3 and 1.2 Hz), 4.91 (1H, dd, *J* = 8.1 and 4.0 Hz), 4.44 (1H, d, *J* = 8.1 Hz), 4.35 (1H, d, *J* = 14.2 Hz), 3.86 (1H, d, *J* = 14.2 Hz), 3.84 (1H, d, *J* = 13.3 Hz), 3.65 (1H, d, *J* = 13.3 Hz), 3.25 (m, 3H), 2.61 (1H, dd, *J* = 9.7 and 6.9 Hz), 2.46 (1H, dd, *J* = 10.7 and 4.4 Hz).

Hexahydro-1*H*-pyrrolo[3',4':4,5]isoxazolo[2,3-*a*]dibenzo[*c*,*f*]azepin-2-ones

Method A. A mixture of furoisoxazolidine **7** (0.46 mmol) and 15 mL of aqueous ammonium hydroxide (25%) or 3.75 mL of hydrazine hydrate (80%) was stirred at room temperature for 20 hours or 3 hours, respectively. The precipitate was filtered off and washed with water and analysed by NMR.

Method B. A mixture of isoxazolidine **7** (0.06 mmol), 0.25 mL of aqueous ammonium hydroxide (25%) or 0.8 mL of hydrazine hydrate (80%) in 1 mL of THF (4 h. with ammonium hydroxide or 1.5 h. with hydrazine) or EtOH (1 h with both reagent) was stirred at room temperature. Then a mixture of dichloromethane (5 mL) and water (5 mL) was added. The layers were separated and the aqueous phase was extracted with dichloromethane. The combined of organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude solid was analyzed by ^{1}H NMR [(~ 86:14 of **13a**/**13b**) and (98:2 or 80:20 of **14a**/**14b** in THF or EtOH), respectively] and the compounds cannot be separated by column chromatography.

(±)-(*S*$_3$,*R*$_{3a}$,*S*$_{14b}$,*S*$_{14c}$)-3-Hydroxy-2,3,3a,10,14b,14c-hexahydro-1*H*-pyrrolo[3',4':4,5] isoxazolo[2,3-*a*]dibenzo[*c*,*f*]azepin-1-one [(±)-13a]. Compound **13a** was obtained as a sole product from **6** and NH_4OH following method A. Yield 86%, mp 202-207 ºC (with

decomposition). IR (KBr) ν_{max} 3280, 1719, 1683, 1487 cm^{-1}. ^1H NMR (300 MHz, DMSO-D_6) δ 8.84 (1H, NH, broad s), 7.75 (1H, m), 7.23 (6H, m), 6.98 (1H, m), 6.34 (1H, OH, d, *J* = 7.4 Hz), 5.14 (1H, H_3, d, *J* = 7.4 Hz), 4.57 (1H, H_{3a}, d, *J* = 6.8 Hz), 4.31 (1H, H_{14b}, d, *J* = 5.8 Hz), 4.18 (1H, H_{10}, d, *J* = 14.6 Hz), 3.93 (1H, H_{10}, d, *J* = 14.6 Hz), 3.73 (1H, H_{14c}, dd, *J* = 6.8 and 5.8 Hz). ^{13}C NMR (75.6 MHz, DMSO-D_6) δ 175.6 (C), 146.6 (C), 136.9 (C), 135.3 (C), 129.8 (C), 129.2 (CH), 129.1 (CH), 128.5 (CH), 127.7 (2CH), 127.0 (CH), 124.0 (CH), 116.8 (CH), 84.0 (CH), 80.6 (CH), 69.6 (CH), 56.5 (CH), 38.7 (CH_2). HMRS calcd for [$C_{18}H_{17}N_2O_3$ + H]: 309.1233, found: 309.1236.

(±)-(*R*$_3$,*R*$_{3a}$,*S*$_{14b}$,*S*$_{14c}$)-3-Hydroxy-2,3,3a,10,14b,14c-hexahydro-1*H*-pyrrolo[3',4':4,5] isoxazolo[2,3-*a*]dibenzo[*c*,*f*]azepin-1-one [(±)-13b]. Compound **13b** was obtained as a minor product from NH_4OH and **6** following method B. It could not be separated from its epimer. ^1H NMR (300 MHz, DMSO-D_6) δ 8.66 (1H, NH, broad s), 7.55 (1H, m), 5.98 (1H, OH, d, *J* = 10.0 Hz), 5.31 (1H, H_3, dd, *J* = 10.0 and 5.3 Hz), 4.81 (1H, H_{3a}, dd, *J* = 7.1 and 5.3 Hz), 4.47 (1H, H_{14b}, d, *J* = 6.2 Hz), 4.18 (1H, H_{10}, d, *J* = 14.7 Hz), 3.90 (1H, H_{10}, d, *J* = 14.7 Hz).

(±)-(*S*$_3$,*R*$_{3a}$,*S*$_{14b}$,*S*$_{14c}$)-2-Amino-3-hydroxy-2,3,3a,10,14b,14c-hexahydro-1*H*-pyrrolo[3',4':4,5] isoxazolo[2,3-*a*]dibenzo[*c*,*f*]azepin-1-one [(±)-14a]. This compound was obtained as a sole product, in 93% yield, from hydrazine hydrate and **6** following the method A. Mp 176-181 ºC (with decomposition). Anal. calcd. for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.42; H, 5.41, N, 13.10. IR (KBr) ν_{max} 3700-3100 (3314), 1680, 1617, 1483 cm^{-1}. ^1H NMR (300 MHz, DMSO-D_6) δ 7.81 (1H, m), 7.24 (6H, m), 6.99 (1H, m), 6.73 (1H, OH, broad s), 5.06 (1H, H_3, broad s), 4.72 (2H, NH_2, s), 4.51 (1H, H_{3a}, dd, *J* = 7.2 and 2.1 Hz), 4.28 (1H, H_{14b}, d, *J* = 5.2 Hz), 4.18 (1H, H_{10}, d, *J* = 14.7 Hz), 3.92 (1H, H_{10}, d, *J* = 14.7 Hz), 3.82 (1H, H_{14c}, dd, *J* = 7.2 and 5.2 Hz). ^{13}C NMR (75.6 MHz, DMSO-D_6) δ 170.3 (C), 146.5 (C), 136.8 (C), 135.0 (C), 129.9 (C), 129.2 (CH), 129.1 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 127.0 (CH), 124.1 (CH), 116.8 (CH), 85.7 (CH), 79.7 (CH), 69.5 (CH), 55.3 (CH), 38.6 (CH_2). HMRS calcd for [$C_{18}H_{17}N_3O_3$ + H]: 324.1342, found: 324.1347.

(±)-(*R*$_3$,*R*$_{3a}$,*S*$_{14b}$,*S*$_{14c}$)-2-Amino-3-hydroxy-2,3,3a,10,14b,14c-hexahydro-1*H*-pyrrolo[3',4':4,5] isoxazolo[2,3-*a*]dibenzo[*c*,*f*]azepin-1-one [(±)-14b]. This compound was obtained following method B along with **14a**, from **7** and hydrazine hydrate and could not be separated from its epimer. ^1H NMR (200 MHz, DMSO-D_6) δ 7.45 (1H, m), 6.27 (1H, OH, d, *J* = 8.6 Hz), 5,12 (1H, H_3, dd, *J* = 8.6 and 5.5 Hz), 4.80 (1H, H_{3a}, dd, *J* = 7.0 and 5.5 Hz), 4.60 (2H, NH_2, s), 4.36 (1H, H_{14b}, d, *J* = 6.5 Hz), 3.65 (dd, 1H, H_{14c}, *J* = 7.0 and 6.5 Hz).

Addition of pyridylnitrile oxides 4 and 5 to furanone 3

(±)-(*S*$_{3a}$,*R*$_6$,*R*$_{6a}$)-6-Methoxy-3-pyridin-3-yl-6,6*a*-dihydrofuro[3,4-*d*]isoxazol-4(3a*H*)-one [(±)-(15)]. To a mixture of 5-methoxyfuran-2(5*H*)-one **3** (253 mg, 2.22 mmol) and 3-[chloro(hydroximino)methyl]pyridinium chloride (1.5 g, 7.77 mmol) in 8 mL of toluene, heated at 80 ºC was added triethylamine (2.2 mL, 15.5 mmol) slowly (with a syringe pump to a 0.2 μl/seg rate). After stirring at 80 ºC for additional 2 hours the reaction mixture was cooled at room temperature. Then dichloromethane and water were added to reaction mixture. The organic

layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with water, dried (Na_2SO_4) and the solvent was removed in vacuo. The brown oil obtained was purified by column chromatography (hexane/ethyl acetate, 1:1) to give 328 mg of furoisoxazolone **15**. Yield 63%. Mp 110-111 ºC (from ethyl acetate). Anal. calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.38; H, 4.21; N, 11.96. IR (KBr) ν_{max} 1771, 1589, 1173 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.16 (1H, dd, *J* = 2.3 and 0.8 Hz), 8.68 (1H, dd, *J* = 4.8 and 1.7 Hz), 8.24 (1H, ddd, *J* = 8.1, 2.3, and 1.7 Hz), 7.39 (1H, ddd, *J* = 8.1, 4.8, and 0.8 Hz), 5.59 (1H, s), 5.32 (1H, d, *J* = 9.3 Hz), 4.73 (1H, d, *J* = 9.3 Hz), 3.62 (s, 3H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 169.4 (C), 151.6 (CH), 150.5 (C), 148.9 (CH), 135.0 (CH), 123.6 (CH), 123.1 (C), 108.0 (CH), 87.1 (CH), 57.6 (CH_3), 53.7 (CH).

6-Methoxy-3-pyridin-2-yl-dihydrofuro[3,4-*d*]isoxazolones (16 and **17)**

Compounds **16** and **17** were obtained from **3** (30 mg, 0.26 mmol) and 154 mg (0.78 mmol) of 2-[chloro(hydroximino)methyl]pyridinium chloride in CH_3CN (1.1 mL) at room temperature. NEt_3 (228 μl, 1.638 mmol) was added slowly (with a syringe pump to a 0.1 μl/seg rate). Dichloromethane and water were added to the reaction mixture. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with water, dried (Na_2SO_4) and the solvent was removed in vacuo. The oil obtained was analyzed by ^1H NMR (16:77:7 ratio of **17**:**16**:**3**) and purified by column chromatography (hexane/ethyl acetate, 4:1). Combined yield 58%.

(±)-(*R*$_{3a}$,*R*$_4$,*S*$_{6a}$)-4-Methoxy-3-pyridin-2-yl-*3a*,6*a*-dihydrofuro[3,4-*d*]isoxazol-6(4*H*)-one [(±)-(16)]. Yield 46%. White solid of mp 83-85 ºC. Anal. calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.09; H, 4.46; N, 11.90. IR (KBr) ν_{max} 1781, 1583, 1347, 1131, 939 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (1H, H_{6py}, broad d, *J* = 4.8 Hz), 8.05 (1H, H_{3py}, d, *J* = 8.1 Hz), 7.78 (1H, H_{4py}, m), 7.37 (1H, H_{5py}, ddd, *J* = 7.5, 4.8, and 1.1 Hz), 5.84 (1H, H_4, s), 5.45 (1H, H_{6a}, d, *J* = 9.7 Hz), 4.58 (1H, H_{3a}, d, *J* = 9.7 Hz), 3.60 (3H, OCH_3, s). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 172.0 (C), 155.5 (C), 149.6 (CH), 147.3 (C), 136.9 (CH), 125.1 (CH), 122.6 (CH), 105.2 (CH), 78.7 (CH), 57.3 (CH_3), 56.8 (CH).

(±)-(*S*$_{3a}$,*R*$_6$,*R*$_{6a}$)-6-Methoxy-3-pyridin-2-yl-6,6*a*-dihydrofuro[3,4-*d*]isoxazol-4(3*aH*)-one [(±)-(17)]. Yield 12%. White solid of mp 96-98 ºC (from Et_2O-hexane). IR (KBr) ν_{max} 1789, 1582, 1467, 1278, 1117 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.74 (1H, H_{6py}, dd, *J* = 4.8 and 1.1 Hz), 7.96 (1H, H_{3py}, m), 7.76 (1H, H_{4py}, m), 7.36 (1H, H_{5py}, ddd, *J* = 7.5, 4.8 and 1.1 Hz), 5.57 (1H, H_6, s), 5.30 (1H, H_{6a}, d, *J* = 9.0 Hz), 5.11 (1H, H_{3a}, d, *J* = 9.0 Hz), 3.61 (3H, OCH_3, s). ^{13}C NMR (75.6 MHz, $CDCl_3$,) δ 169.4 (C), 154.3 (C), 149.8 (CH), 146.5 (C), 136.7 (CH), 125.0 (CH), 122.9 (CH), 107.0 (CH), 87.4 (CH), 57.3 (CH_3), 52.9 (CH).

(±)-(*S*$_{3a}$,*S*$_6$,*R*$_{6a}$)-6-Hydroxy-3-pyridin-3-yl-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-one [(±)-(18)]. A mixture of furoisoxazolone **15** (134 mg, 0.57 mmol) and ammonium hydroxide 25% (1.31 mL, 8.5 mmol) was stirred at room temperature for 30 minutes. The solid was filtered off and washed with CH_2Cl_2 and AcOEt to give 94 mg of compound **18** as a white solid. Yield 75%. Mp 191 ºC (with decomposition). IR (KBr) ν_{max} 3213, 1710, 1596, 1083 cm^{-1}. ^1H NMR

(300 MHz, DMSO-d_6) δ 9.04 (1H, H_{2py}, d, *J* = 2.0 Hz), 8.95 (1H, NH, s), 8,63 (1H, H_{6py}, dd, *J* = 4.9 and 1.6 Hz), 8.24 (1H, H_{4py}, dt, *J* = 8.1 and 2.0 Hz), 7.49 (1H, H_{5py}, ddd, *J* = 8.1, 4.9, and 0.8 Hz), 6.50 (1H, OH, d, *J* = 7.1 Hz), 5.11 (1H, H_6, d, *J* = 7.1 Hz), 5.05 (1H, H_{6a}, d, *J* = 8.9 Hz), 4.87 (1H, H_{3a}, d, *J* = 8.9 Hz). ^{13}C NMR (75.6 MHz, DMSO-d_6) δ 170.9 (C), 153.1 (C), 151.1 (CH), 148.9 (CH), 135.3 (CH), 124.4 (C), 124.0 (CH), 90.0 (CH), 82.3 (CH), 54.3 (CH).

(±)-(*S*$_3$,*S*$_6$,*R*$_{6a}$)-5-Amino-6-hydroxy-3-pyridin-3-yl-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-*d*] isoxazol-4-one [**(±)-(19)].** A mixture of furoisoxazoline **15** (38 mg, 0.16 mmol) and hydrazine hydrate to 80% (14.8 μL, 0.24 mmol) was stirred at room temperature for 2 hours. The solid was filtered off and washed with CH_2Cl_2. Pyrroloisoxazolone **19** (33 mg) was obtained as a white solid. Yield 87%. Mp 201-202 ºC (with decomposition). Anal. calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 50.92; H, 4.36; N, 23.72. IR (KBr) ν_{max} 3286, 3187, 3124, 1694, 1623, 1594, 1093 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.06 (1H, H_{2py}, dd, *J* = 2.4 and 1.6 Hz), 8.64 (1H, H_{6py}, dd, *J* = 4.8 and 1.6 Hz), 8.25 (1H, H_{4py}, m), 7.50 (1H, H_{5py}, ddd, *J* = 8.1, 4.8, and 0.8 Hz), 6.90 (1H, OH, d, *J* = 6.3 Hz), 5.02 (1H, H_6, d, *J* = 6.3 Hz), 4.98 (2H, H_{6a} and H_{3a}, s), 4.62 (2H, NH_2, s). ^{13}C NMR (75.6 MHz, DMSO-d_6) δ 165.8 (C), 153.0 (C), 151.2 (CH), 148.8 (CH), 135.1 (CH). 124.2 (C), 123.9 (CH), 86.9 (CH), 85.4 (CH), 53.2 (CH).

Reaction with benzylamine

A) A mixture of furoisoxazoline **15** (88 mg, 0.38 mmol) and benzylamine (415 μL, 3.8 mmol) was stirred at room temperature for 3 hours. The reaction mixture was dissolved in dichloromethane and washed with water. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was analyzed by ^{1}H NMR (91:9 of pyrroloisoxazolones **20** and **21**) and purified by column chromatography (hexane/ethyl acetate, 1:2). Combined yield 71%.

B) To a solution of **15** (91 mg, 0.39 mmol) in CH_2Cl_2 (1 mL) was added benzylamine (85 μL, 0.78 mmol) at room temperature. After 3 hours under stirring the reaction mixture was washed with water. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude solid was analyzed by ^{1}H NMR (74:26 of pyrroloisoxazolones **20** and **21**) and purified by column chromatography (hexane/ethyl acetate, 1:2). Combined yield 84%.

(±)-(*S*$_{3a}$,*R*$_6$,*R*$_{6a}$)-5-Benzyl-6-hydroxy-3-pyridin-3-yl-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-*d*] isoxazol-4-one [**(±)-(20)].** Method A: Yield 65%. Method B: Yield 62%. White solid of mp 171-173 ºC (from Et_2O). IR (KBr) ν_{max} 3085, 1699, 1688, 1597, 1130 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (1H, H_{2py}, d, *J* = 1.8 Hz), 8.67 (1H, H_{6py}, dd, *J* = 4.9 and 1.6 Hz), 8.37 (1H, H_{4py}, m), 7.38 (1H, H_{5py}, ddd, *J* = 8.1, 4.9, and 0.7 Hz), 7.35 (5H, Ph, m), 5.33 (1H, H_{6a}, dd, *J* = 9.4 and 5.6 Hz), 5.19 (1H, H_6, dd, *J* = 10.5 and 5.6 Hz), 4.88 (1H, d, *J* = 14.5 Hz), 4.55 (1H, H_{3a}, d, *J* = 9.4 Hz,), 4.18 (1H, d, *J* = 14.5 Hz), 3.57 (1H, OH, d, *J* = 10.5 Hz). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 165.6 (C), 153.5 (C), 151.4 (CH), 149.1 (CH), 135.5 (CH), 135.2 (C), 129.0 (CH), 128.9 (CH), 123.8 (C), 123.5 (CH), 81.1 (CH), 78.7 (CH), 56.1 (CH), 43.9 (CH_2).

(±)-(*S*$_{3a}$,*S*$_6$,*R*$_{6a}$)-5-Benzyl-6-(benzylamino)-3-pyridin-3-yl-3a,5,6,6a-tetrahydro-4*H*-pyrrolo [3,4-*d*]isoxazol-4-one [(±)-(21)]. Method A. Yield 6%. Method B: Yield 22%. Yellow solid. Mp 148-149 ºC. IR (neat) ν_{max} 3333, 1694, 1593, 910, 733, 701 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (1H, H_{2py}, d, *J* = 2.4 Hz), 8.65 (1H, H_{6py}, dd, *J* = 4.8 and 1.8 Hz), 8.38 (1H, H_{4py}, m), 7.29 (11H, H_{5py} and Ph, m), 5.25 (1H, H_{6a}, dd, *J* = 9.4 and 5.5 Hz), 4.84 (1H, d, *J* = 14.2 Hz), 4.47 (1H, H_6, m), 4.46 (1H, H_{3a}, d, *J* = 9.4 Hz), 4.25 (1H, d, *J* = 14.2 Hz), 3.97 (1H, d, *J* = 13.2 Hz), 3.84 (1H, d, *J* = 13.2 Hz), 2.36 (1H, NH, broad s). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 165.9 (C), 153.2 (C), 151.1(CH), 149.0 (CH), 139.4 (C), 135.9 (C), 135.4 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 127.8 (CH) 127.4 (CH), 124.2 (C), 123.4 (CH), 79.4 (CH), 73.6 (CH), 55.9 (CH), 50.8 (CH_2), 43.8 (CH_2).

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