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

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Dedicated to Professor Benito Alcaide in his 60th birthday

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(3H)-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(3H)-ones is not cleaved by LiAlH₄.

Keywords: Azepines, isoxazolines, isoxazolidines, 1,3-dipolar cycloaddition, furan-2(5H)-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(5H)-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(5H) [and 7(6H)]-ones from the adducts obtained from reactions of 5-alkoxyfuran-2(5H)-ones with 11H-dibenzo[b,e]azepine
5-oxide (1)\textsuperscript{10b} and nitrile oxides,\textsuperscript{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-\textit{d}]isoxazole\textsuperscript{12} structures bearing diverse functionalities. In this paper we report the results obtained in the reactions of commercially available furan-2(5\textit{H})-one 2 and methoxyfuranone (3)\textsuperscript{13} with nitrone 1\textsuperscript{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.\textsuperscript{10b}

With the adducts 6 and 7 in hand, their reactions with LiAlH\textsubscript{4} (LAH) were studied. In the presence of an excess of the reagent (1.5 equiv mol), 6 and 7 afforded diol 8\textsuperscript{10b} in 89\% and 93\% yield, respectively (Scheme 2). Diol 8 can be used as the starting material in the synthesis of racemic pyrroloazepines.\textsuperscript{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-methyloxy- (or 3-ethoxy)-1,3,3a,6,7,8,8a,8b-octahydropyrolo[3,4-\textit{d}]pyrrolo[1,2-\textit{b}]isoxazol-1-ones are transformed into the corresponding aminotriols.\textsuperscript{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-H₃ = 5.72 ppm, coupled with exchangeable proton, and δ-C₃ = 100.2 ppm). Hemiacetalic proton is not coupled with its vicinal H₃a, which indicates a trans relationship between them (Scheme 3). The regioisomeric structure 1 (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(5H)-ones with NaBH₄, 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 aminoalcohols 10-11 was satisfactorily carried out by hydrogenolysis with H₂/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-α]dibenzo[c,f]azepine 12 by double mesylation followed by reaction with benzylamine (Scheme 4). Pyrrolo[3’,4’:4,5]isoxazolo[2,3-α]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 stereoisomers 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.

\[
\begin{align*}
\text{Toluene, } 80 \degree C, 2.5 \text{ h} & \quad 46 : 54 \\
\text{Toluene, rt, 2.5 h, 45\%} & \quad 72 : 28 \\
\text{Acetonitrile, rt, 3 h, 58\%} & \quad 84 : 16
\end{align*}
\]

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(5H)-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 cycloaddition\(^{18}\) (II or III instead I, according to the Sutsmann classification)\(^ {19}\). 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).

\[
\begin{align*}
\text{NH}_2\text{R} & \quad \text{rt} \\
\text{15} & \quad \text{18} (75\%) \\
\text{15} & \quad \text{19} (87\%) \\
\text{15} & \quad \text{20} (65-62\%) \\
\text{15} & \quad \text{21} (6-22\%)
\end{align*}
\]

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(3aH)-one, but contrast with those reported by Fišera for the 6-ethoxy-3-phenylderivative, 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(3H)-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 ¹³C chemical shift (>165 ppm) of the C=O group, as well as the value of the coupling constant J₆,₆a (ca. 0 Hz) confirm the pyrrolinone structure assigned to these compounds.

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### 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 ¹³C 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.

(±)-(R₃aS₁₄aS₁₄b)-3a,10,14b,14c-Tetrahydrofuro[3′,4′:4,5]isoxazolo[2,3-a][dibenzo[c,f]azepin-1(3H)-one [(±)-6]. To a solution of 1.4 mmol of furan-2(5H)-one (2) in 10 mL of CHCl₃ was added, under argon atmosphere and at room temperature, 1.4 mmol of 11H-dibenzo[b,e]azepine 5-oxide (1). After 18 hours the solvent was removed under reduced pressure. By precipitation with CHCl₃ and washing with acetone pure 6 was obtained as a white solid. Yield 92%. Mp 192-193 °C. Anal. calcd. for C₁₈H₁₅NO₃: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.54; H, 5.16, N, 4.63. IR (KBr) \( \nu_{\text{max}} \) 1756, 1602, 1587, 1484, 1299, 1286 cm⁻¹.

\[ ^1H \text{NMR (300 MHz, CDCl}_3 \] \( \delta \) 7.65-7.58 (1H, m), 7.41-7.18 (6H, m), 7.08-6.99 (1H, m), 5.11 (1H, H₃a, ddd, \( J = 6.9, 4.7, \) and 1.0 Hz), 4.67 (1H, H₃b, dd, \( J = 11.3 \) and 1.0 Hz), 4.57 (1H, H₁₄a, d, \( J = 5.9 \) Hz), 4.56 (1H, H₃b, dd, \( J = 11.3 \) and 4.7 Hz), 4.46 (1H, H₁₀b, d, \( J = 14.8 \) Hz), 3.85 (1H, H₁₀a, d, \( J = 14.8 \) Hz). \[ ^13C \text{NMR (75.6 MHz, CDCl}_3 \] \( \delta \) 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 (CH₂).

Reduction of the furanone ring

**Method A.** To a solution of isoxazolidines 6 or 7₁₀ᵇ (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 Na₂SO₄ 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 (Na₂SO₄) and the solvent was removed under reduced pressure to give a 35:65 mixture of (±)-8 and (±)-9.

(±)-(R₂R₃,R₃a)-2,3,3a,8-Tetrahydrodibenzo[c,f]isoxazolo[2,3-a]azepine-2,3-diyldimethanol [(±)-8]. 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 °C (white solid), (Literature mp 126-128 °C).ₐ Anal. calcd. for C₁₈H₁₉NO₅: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.59; H, 6.46; N, 4.64. IR (KBr) \( \nu_{\text{max}} \) 3539, 3376, 1600, 1486, 1051. \[ ^1H \text{NMR (300 MHz, CDCl}_3 \] \( \delta \) 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\(_3\)) \(\delta\) 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\(_2\)).

(\(\pm\))-(\(R_3^3,R_3^4,S_1^3a,R_1^4b\))-Hexahydro-1H-furo[3',4':4,5]isoxazolo[2,3-a]dibenzo[c,f]azepinyl-3-ol \([\(\pm\)-9].\) Compound \([\(\pm\)-9] was obtained from isoxazolidine 7 following method B and isolated as a white solid by column chromatography in (hexane/ethyl acetate, 3:1). Yield 63%. Mp 187-189 °C (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) \(\nu_{max}\) 3378, 1491, 1250, 1080 cm\(^{-1}\).

\(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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) \(\nu_{max}\) 1747, 1487, 1221, 1083 cm\(^{-1}\).

\(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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 (\(\pm\))-6 or (\(\pm\))-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.

(\(\pm\))-3-(6,11-Dihydro-5H-dibenzo[b,e]azepin-6-yl)-4-hydroxydihydrofuran-2(3H)-one \([\(\pm\)-10].\) Obtained by hydrogenolysis of isoxazolidine 6 and was precipitated with ethyl ether. Yield 80%. Mp 143-144 °C (yellow solid). IR (KBr) \(\nu_{max}\) 3383, 1764, 1603, 1581, 1492, 1315 and 1155 cm\(^{-1}\). \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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\(_6\)), dd, \(J = 4.4\) and 3.2 Hz). \(^{13}\)C NMR (75.6 MHz, CDCl\(_3\)) \(\delta\) 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<sub>2</sub>)-3-[(R<sub>6</sub>)-6',11'-Dihydro-5H-dibenzo[b,e]azepin-6'-yl]butan-1,2,4-triol  [(±)-11]. Compound 11 was obtained from diol 8 after 12 hours with H<sub>2</sub>/Pd(C) and was purified by column chromatography (hexane/aceton, 1:1). Yield 85%. IR (KBr) v<sub>max</sub> 3899-3375, 1701, 1604, 1493, 1315 cm<sup>-1</sup>.<br>

1<sup>H</sup> NMR (300 MHz, CDCl<sub>3</sub>) 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).<br>

13<sup>C</sup> NMR (75.6 MHz, CDCl<sub>3</sub>) δ 144.7 (C), 138.7 (C), 137.0 (C), 129.2 (CH), 129.1 (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<sub>2</sub>), 61.0 (CH<sub>2</sub>), 60.3 (CH), 48.6 (CH), 40.0 (CH).<br>

(±)-(R<sub>3a</sub>)-2-Benzyl-2,3,3a,8,10a,10b-hexahydro-1H-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<sub>4</sub>Cl 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<sub>2</sub>SO<sub>4</sub> 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%.<br>

1<sup>H</sup> NMR (300 MHz, CDCl<sub>3</sub>) 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).<br>

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

Method A. A mixture of furioisoxazolidine 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.<br>

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<sub>2</sub>SO<sub>4</sub>) and the solvent removed under reduced pressure. The crude solid was analyzed by <sup>1</sup>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.<br>

(±)-(S<sub>3</sub>)-(R<sub>2</sub>)-(R<sub>6</sub>)-(S<sub>10</sub>)-(R<sub>14</sub>)-(S<sub>14</sub>)-(3)-Hydroxy-2,3,3a,10,14b,14c-hexahydro-1H-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<sub>4</sub>OH following method A. Yield 86%, mp 202-207 ºC (with
decomposition). IR (KBr) $\nu_{\text{max}}$ 3280, 1719, 1683, 1487 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-D$_6$) $\delta$ 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$_6$) $\delta$ 175.6 (C), 146.6 (C), 136.9 (C), 135.3 (C), 129.8 (C), 129.2 (CH), 129.1 (CH), 128.5 (2CH), 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$_{13}$H$_7$N$_3$O$_3$ + H]: 309.1233, found: 309.1236.

(±)-(R$_3$,R$_{3a}$S$_{14b}$S$_{14c}$)-3-Hydroxy-2,3,3a,10,14b,14c-hexahydro-1H-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$_2$OH and 6 following method B. It could not be separated from its epimer. $^1$H NMR (300 MHz, DMSO-D$_6$) $\delta$ 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-1H-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$_{15}$H$_{17}$N$_3$O$_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.42; H, 5.41, N, 13.10. IR (KBr) $\nu_{\text{max}}$ 3700-3100 (3314), 1680, 1617, 1483 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-D$_6$) $\delta$ 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$_6$) $\delta$ 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$_{13}$H$_7$N$_3$O$_3$ + H]: 324.1342, found: 324.1347.

(±)-(R$_3$,R$_{3a}$R$_{6a}$)-6-Methoxy-3-pyridin-3-yl-6,6a-dihydrofuro[3,4-d]isoxazol-4(3aH)-one [(±)-(15)]. To a mixture of 5-methoxyfuran-2(5H)-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 (Na₂SO₄) 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 °C (from ethyl acetate). Anal. calcd. for C₁₁H₁₀N₂O₄: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.38; H, 4.21; N, 11.96. IR (KBr) νmax 1771, 1589, 1173 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75.6 MHz, CDCl₃) 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 (CH₃), 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 CH₂CN (1.1 mL) at room temperature. NEt₃ (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 (Na₂SO₄) 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%.  

(±)-(R₃a,R₄,S₆a)-4-Methoxy-3-pyridin-2-yl-3a,6a-dihydrofuro[3,4-d]isoxazol-6(4H)-one [(±)-(16)]. Yield 46%. White solid of mp 83-85 °C. Anal. calcd for C₁₁H₁₀N₂O₄: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.09; H, 4.46; N, 11.90. IR (KBr) νmax 1781, 1583, 1347, 1131, 939 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 8.66 (1H, H₆py, broad d, J = 4.8 Hz), 8.05 (1H, H₃py, d, J = 8.1 Hz), 7.78 (1H, H₄py, m), 7.37 (1H, H₅py, ddd, J = 7.5, 4.8, and 1.1 Hz), 5.84 (1H, H₆a, d, J = 9.7 Hz), 4.58 (1H, H₃a, s, J = 9.7 Hz), 3.60 (3H, OCH₃, s). ¹³C NMR (75.6 MHz, CDCl₃) δ 172.0 (C), 155.5 (C), 149.6 (CH), 147.3 (C), 136.9 (CH), 125.1 (CH), 122.6 (CH), 78.7 (CH), 57.3 (CH₃), 56.8 (CH).  

(±)-(5₃a,R₆a,S₆a)-6-Methoxy-3-pyridin-2-yl-6,6a-dihydrofuro[3,4-d]isoxazol-4(3H)-one [(±)-(17)]. Yield 12%. White solid of mp 96-98 °C (from Et₂O-hexane). IR (KBr) νmax 1789, 1582, 1467, 1278, 1117 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 8.74 (1H, H₆py, dd, J = 4.8 and 1.1 Hz), 7.96 (1H, H₃py, m), 7.76 (1H, H₄py, m), 7.36 (1H, H₅py, ddd, J = 7.5, 4.8 and 1.1 Hz), 5.57 (1H, H₆a, s), 5.30 (1H, H₆a, d, J = 9.0 Hz), 5.11 (1H, H₃a, d, J = 9.0 Hz), 3.61 (3H, OCH₃, s). ¹³C NMR (75.6 MHz, CDCl₃) 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 (CH₃), 52.9 (CH).  

(±)-(S₃a,S₆a,R₆a)-6-Hydroxy-3-pyridin-3-yl-3a,5,6,6a-tetrahydro-4H-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 CH₂Cl₂ and AcOEt to give 94 mg of compound 18 as a white solid. Yield 75%. Mp 191 °C (with decomposition). IR (KBr) νmax 3213, 1710, 1596, 1083 cm⁻¹. ¹H NMR
(300 MHz, DMSO-d6) δ 9.04 (1H, H2py, d, J = 2.0 Hz), 8.95 (1H, NH, s), 8.63 (1H, H6py, dd, J = 4.9 and 1.6 Hz), 8.24 (1H, H4py, dt, J = 8.1 and 2.0 Hz), 7.49 (1H, H5py, ddd, J = 8.1, 4.9, and 0.8 Hz), 6.50 (1H, OH, d, J = 7.1 Hz), 5.11 (1H, H6, d, J = 7.1 Hz), 5.05 (1H, H6a, d, J = 8.9 Hz), 4.87 (1H, H3a, d, J = 8.9 Hz). 13C NMR (75.6 MHz, DMSO-d6) δ 179.0 (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).

Reaction with benzylamine
A) A mixture of furoisoxazoline 15 (88 mg, 0.16 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 (Na2SO4). The solvent was removed under reduced pressure and the crude product was analyzed by 1H 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 CH2Cl2 (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 (Na2SO4) and the solvent was removed under reduced pressure. The crude solid was analyzed by 1H NMR (74:26 of pyrroloisoxazolones 20 and 21) and purified by column chromatography (hexane/ethyl acetate, 1:2). Combined yield 84%.

(±)-(S3a,S6,R6a)-5-Amino-6-hydroxy-3-pyridin-3-yl-3a,5,6,6a-tetrahydro-4H-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 CH2Cl2. Pyrroloisoxazolone 19 (33 mg) was obtained as a white solid. Yield 87%. Mp 201-202 °C (with decomposition). Anal. calcd for C10H10N4O2: C, 51.28; H, 4.30; N, 23.92. Found: C, 50.92; H, 4.36; N, 23.72. IR (KBr) νmax 3286, 3187, 3124, 1694, 1623, 1594, 1093 cm-1. 1H NMR (300 MHz, DMSO-d6) δ 9.06 (1H, H2py, dd, J = 2.4 and 1.6 Hz), 8.64 (1H, H6py, dd, J = 4.8 and 1.6 Hz), 8.25 (1H, H4py, m), 7.50 (1H, H5py, ddd, J = 8.1, 4.8, and 0.8 Hz), 6.90 (1H, OH, d, J = 6.3 Hz), 5.02 (1H, H6, d, J = 6.3 Hz), 4.98 (2H, H6a and H3a, s), 4.62 (2H, NH2, s). 13C NMR (75.6 MHz, DMSO-d6) δ 165.8 (C), 153.0 (C), 151.1 (CH), 148.8 (CH), 135.1 (CH). 124.2 (C), 123.9 (CH), 86.9 (CH), 85.4 (CH), 53.2 (CH).

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(±)-(S₃a,S₆,R₆a)-5-Benzyl-6-(benzylamino)-3-pyridin-3-yl-3a,5,6,6a-tetrahydro-4H-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. ¹H NMR (300 MHz, CDCl₃) δ 9.24 (1H, H₂py, d, J = 2.4 Hz), 8.65 (1H, H₆py, dd, J = 4.8 and 1.8 Hz), 8.38 (1H, H₄py, m), 7.29 (11H, H₅py and Ph, m), 5.25 (1H, H₆a, dd, J = 9.4 and 5.5 Hz), 4.84 (1H, d, J = 14.2 Hz), 4.47 (1H, H₆, m), 4.46 (1H, H₃a, 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). ¹³C NMR (75.6 MHz, CDCl₃) 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 (CH₂), 43.8 (CH₂).

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References and Notes


13 The reaction of 5-alkoxyfuran-2(5H)-ones with nitrone 1 and the reduction of the resulting adducts to give diol 8 (both racemic and enantiomerically pure) have been reported previously by us in the sequence followed to prepare pyrroloazepines (reference 10b).


17 However, has been reported that 1,3-dipolar cycloaddition of nitrile oxides to furan-2(5H)-ones substituted at the 5-position by sulphur bearing group, afford mixtures of regioisomeric adducts (regioselectivity ranging between 64/16 and 84/16). The predominant orientation in
these additions was the same as that observed with 5-alkoxyfuranones. See, Alguacil, R.; Fariña, F.; Martin, M. V. *Tetrahedron* **1996**, *52*, 3457.

18 Feringa has established by AM1 calculus that the cycloaddition of benzonitrile oxide to 5-menthloxyfuran-2(5H)-one is of type I, see reference 14.
