S0957-4166(96)00110-3

Lewis-Acid Promoted Addition of 2-Trimethylsilyloxyfuran to Nitrones: Synthesis and Absolute Configuration of Tetrahydro-2-benzyl-3-(1-benzyloxyethyl)-furo[2,3-d]isoxazol-5(2H)ones
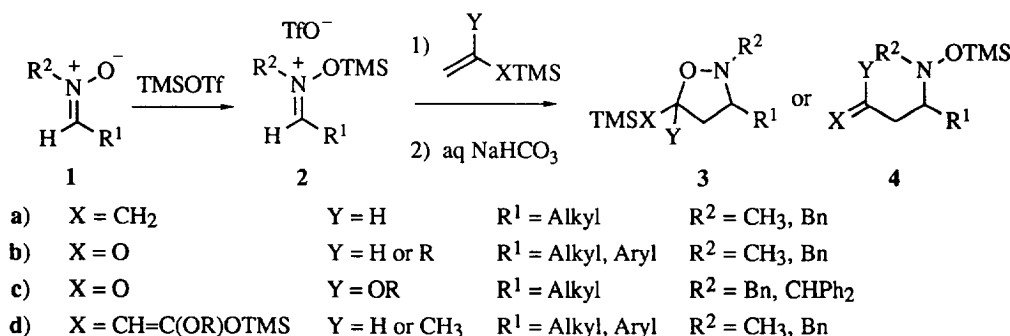
Carlo Castellari, Marco Lombardo, Graziano Pietropaolo and Claudio Trombini*

Dipartimento di Chimica "G.Ciamician", Università di Bologna, via Selmi 2, I-40126 Bologna, Italy

Abstract: A straightforward synthesis of tetrahydro-2-benzyl-3-(1-benzyloxyethyl)-furo[2,3-d]isoxazol-5(2H)ones is reported, based on the Lewis acid-catalysed addition of 2-trimethylsilyloxyfuran to the N-benzyl nitrone of (S)-lactaldehyde.
Copyright © 1996 Elsevier Science Ltd

Nitrones 1 offer interesting advantages with respect to imines, hydrazones and other nitrogen derivatives of aldehydes in reactions with nucleophiles. They possess the highest polarised C=N bond and a reactive oxygen atom which can bring about the intramolecular formation of a C-O bond leading to isoxazolidines. This behaviour was observed in the reaction of nitrones with silylated nucleophiles in the presence of trimethylsilyl trifluoromethanesulphonate (TMSOTf) under Mukaiyama/Sakurai conditions[1-4] (Scheme 1). Nitrones are easily complexed by TMSOTf to give N-silyloxyiminium ions 2 which are trapped by nucleophiles to give either cyclic adducts 3 deriving from a formal 1,3-dipolar cycloaddition, or 1,3-addition products 4. Allyltrimethylsilane[1], silylenolethers[2], silyl ketene acetals[3] and vinyl silyl ketene acetals[4] gave products 3a, 3b, 4c and 4d, respectively, in quite good yields.

a)	X = CH$_2$	Y = H	R^1 = Alkyl	R^2 = CH$_3$, Bn
b)	X = O	Y = H or R	R^1 = Alkyl, Aryl	R^2 = CH$_3$, Bn
c)	X = O	Y = OR	R^1 = Alkyl	R^2 = Bn, CHPh$_2$
d)	X = CH=C(OR)OTMS	Y = H or CH$_3$	R^1 = Alkyl, Aryl	R^2 = CH$_3$, Bn

Scheme 1

1059

Recently we observed that 2-trimethylsilyloxyfuran 5[5] regioselectively adds to prochiral nitrones in the presence of TMSOTf affording γ-substituted unsaturated γ-lactones which are easily converted into tetrahydrofuro[2,3-d]isoxazol-5(2H)-ones upon treatment with silica gel or Bu$_4$NF[6]. Here we wish to report a detailed study of the reaction of 5 with N-benzyl nitrone of (S)-lactaldehyde 6 in the presence of several Lewis acids and under different experimental conditions.

The reaction of 5 with nitrone 6 in the presence of TMSOTf follows the catalytic cycle depicted in Scheme 2: the regioselective attack of 5 to the intermediate N-silyloxyiminium ion 7 affords the carbonium ion 8, then a fast silyl group transfer from 8 to a molecule of starting nitrone generates 9 restoring the catalytic species 7.
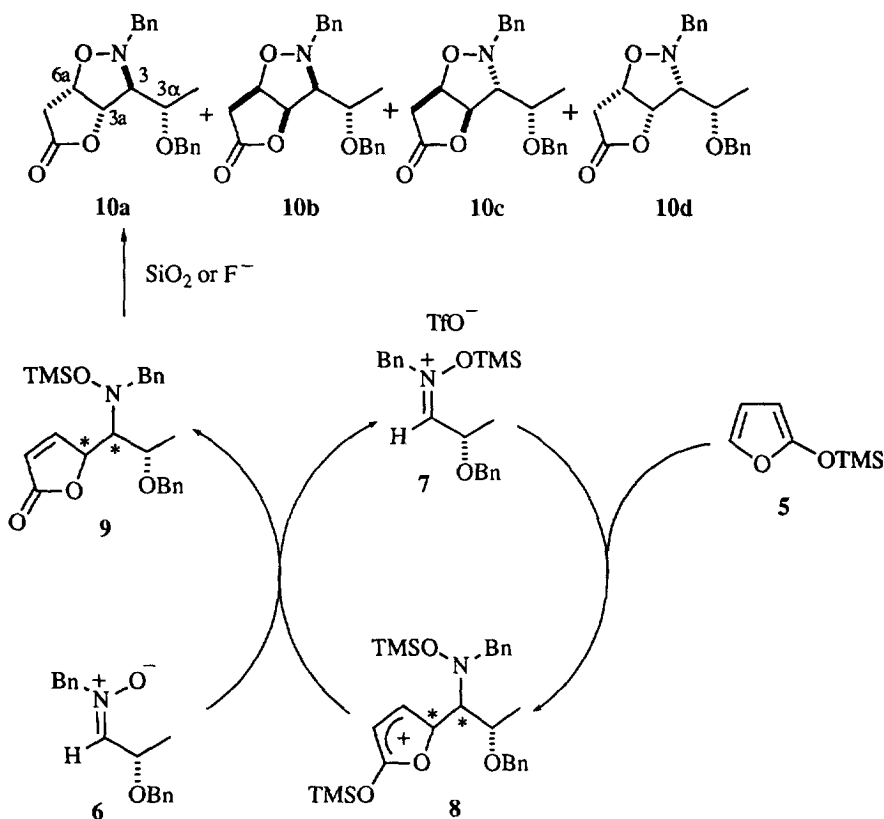
Scheme 2

The GC-MS chromatogram of the crude reaction mixture, after quenching with aq NaHCO$_3$, revealed the presence of four diastereoisomeric butenolides 9 in the 26:51:10:12 ratio[7]. Subsequent cyclisation (Bu$_4$NF/THF,25°C,10 min) to four diastereomeric tetrahydro-2-benzyl-(1-benzyloxyethyl)-furo[2,3-d]isoxazol-5(2H)-ones 10a-d was confirmed by GC-MS analysis of the reaction mixture. Descriptors a-d reflect the order of elution in GC-MS. Silica gel flash-chromatography allowed us to separate the two major products 10a and 10c and to collect only a mixture of the two minor isomers 10b and 10d. NMR data and NOE[8] measurements unambiguously assigned 10a and 10c the expected *anti* stereorelationship at the C3 - C3a

stereocentres, and **10b** and **10d** the syn C3-C3a stereochemistry. On the other hand NMR data did not give any useful information about the C3-C3α relative stereochemistry in all products **10a-d**. The observation that very good crystals of **10a** separated out of a saturated solution in diethyl ether offered the solution to the attribution of absolute configuration to the dominant isomer **10a**. In fact, X-ray analysis (Figure 1) revealed that *anti* product **10a** corresponded to [3S[3α(R*),3aβ,6aβ]]-tetrahydro-2-benzyl-3-(1-benzyloxyethyl)-furo[2,3-d] isoxazol-5(2H)-one, and, hence, **10c** had to coincide with the [3R[3α(S*),3aβ,6aβ]] isomer.

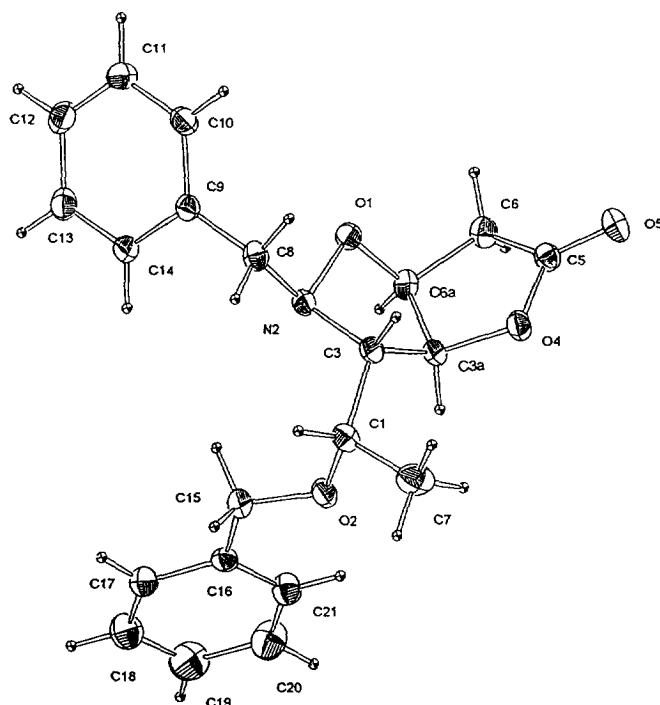**Figure 1.** ORTEP drawing of [3S[3α(R*),3aβ,6aβ]]-**10a**. Selected bond lenghts (Å) and angles (deg) are as follows: O1-C6a 1.426(2), O1-N2 1.468(2), O4-C5 1.352(2), O4-C3a 1.449(2), N2-C3 1.475(2), C3-C3a 1.525(3), C3a-C6a 1.519(3), C5-C6 1.483(3), C6-C6a 1.503(3), C6a-O1-N2 102.29(13), C5-O4-C3a 110.7(2), O1-N2-C3 101.22(12), N2-C3-C3a 102.11(14), O4-C3a-C6a 106.4(2), O4-C3a-C6a 106.4(2), O4-C3a-C3 111.0(2), C6-C3a-C3 104.5(2), O4-C5-C6 111.0(2), C5-C6-C6a 105.1(2), O1-C6a-C6 110.1(2), O1-C6a-C3a 103.8(2), C6-C3a-C6a 104.8(2).

The solid state structure of **10a** is characterized by five stereogenic centres (C1, C3, C3a C6a and N2) all exhibiting S configuration. The X-ray structure deserves some comments. The two fused five membered rings are mutually cis[9] (dihedral angle 65.65(9)°) and, while the γ-lactone ring is flat (maximum deviation from the average plane is 0.08 Å), the isoxazolidine ring shows a half chair conformation. The coordination geometry of N2 is pyramidal (0.678(2)Å out of the plane defined by the other ring atoms). Two interesting CH···O hydrogen bonds[10] involving the O2 atom were observed: C3aH3a···O2(2.44(2)Å)[11] and H21C21···O2 (2.37(2)Å). The latter interaction determines the coplanarity of C1-O2-C15 with the phenyl ring (maximum

deviation from the average phenyl plane 0.073(4) Å).

Absolute yields and relative ratios of **10a-d**, obtained in 12 replicate reactions of **5** with nitrone **9** are reported, as mean values, in entry 1 of Table 1. Ratio **10a+10c/10b+10d** gives a measure of the diastereopreference for the C3-C3a *anti* stereochemistry, while **10a/10c** ratio reflects the Felkin selectivity of the addition reaction.

With the aim of modifying the observed stereoselectivity, we also tested achiral and chiral boron trifluoromethanesulphonates reported in Table 1, in catalytic amounts. At the first glance results collected in Table 1 appeared very disappointing since not only double stereodifferentiation was almost absent when enantiomeric boron triflates were used (entries 4,5), but also ratios of products **10a-d** ranged in a small interval. Noteworthy, ZnI_2, although less reactive than the other catalysts tested, displayed the most interesting Felkin selectivity in favour of isomer **10a**.

Table 1. One pot-two step synthesis of tetrahydro-2-benzyl-3-(1-benzyloxyethyl)-furo[2,3-d]-isoxazol-5(2H)-ones

Entry	Catalyst (%)	T (°C)	t (min)	Yield[a] (%)	10a[b] (%)	10b[b] (%)	10c[b] (%)	10d[b] (%)	10a+10c/ 10b+10d	10a/10c
1	TMSOTf(10)	-20	10	97	32	8	54	6	84/16	37/73
2	TMSOTf(10)	-78	360	76	49	3	42	6	91/9	54/46
3	$Chx_2BOTf(20)^c$	-20	15	78	47	5	32	16	79/21	60/40
4	$(-)Ipc_2BOTf(20)^d$	-20	180	56	48	4	34	14	82/18	58/42
5	$(+)Ipc_2BOTf(20)^d$	-20	150	74	59	3	25	13	84/16	70/30
6	$(+)Car_2BOTf(20)^e$	-20	240	80	52	3	38	7	90/10	58/42
7	$ZnI_2(100)$	25	240	60	63	3	7	27	69/31	90/10

[a] Cumulative isolated yield of furo[2,3-d]isoxazol-5(2H)-ones **10a-d** after the two step condensation/desilylation sequence. [b] Normalised ratios deriving from GC analysis of the crude desilylation mixtures. *Anti* and *syn* descriptors refer to the relative stereochemistry of stereocentres C3 and C3a in final products **10a-d**. [c] Dicyclohexylborontriflate. [d] Diisopinocampheylborontriflate. [e] Di-2-isocaranylborontriflate.

A possible rationale for the observed trend can be found in the recent discussion (Carreira[12], Denmark[13], and Bosnich[14]) about the stereochemical outcome of several Mukaiyama reactions. For example, when dialkyl boron triflate is used, once the addition of **5** to the boroxylated iminium ion gives rise to the expected allylic carbonium ion, a fast silyl group transfer to a molecule of starting nitrone occurs affording **7**, which activates its own catalytic cycle, namely the same catalytic cycle promoted by TMSOTf. As a consequence, the final stereochemical outcome will be similar to that observed when TMSOTf is used.

Thus, in order to minimise the contribution of catalytic cycles due to **7**, the catalyst should be used in stoichiometric amount. A new set of experiments was performed and results collected in Table 2 show an interesting result. In these conditions intermediate products **9** were not observed in the crude reaction mixture since a spontaneous cyclisation to **10a-d** occurred. The stoichiometric amount of catalyst converts all the nitrone into the oxyiminium ion, and once the cationic allylic intermediate, has been formed, in the absence of an effective silyl group acceptor like a molecule of free nitrone, it undergoes ring-closure to **10a**. Moreover, the

stereoselectivity of the process resulted greatly enhanced, and **10a** became the largely dominant product. It is interesting to note that chiral boron triflates give different products depending on their relative amount (catalytic vs stoichiometric) with respect to nitrone **6**. As concerns the irrelevant effect on product distribution effect obtained using two enantiomeric boron triflates (entries 1 and 2), we believe it is a consequence of the large distance between the chiral boron ligands and the reacting centres in the transition state.

Table 2. One step synthesis of tetrahydro-2-benzyl-3-(1-benzyloxyethyl)-furo[2,3-d]-isoxazol-5(2H)-ones

Entry	Promoter	T	t	Yield[a]	10a[b]	10b[b]	10c[b]	10d[b]	10a+10c/	10a/10c
	(1 equiv)	(°C)	(min)	(%)	(%)	(%)	(%)	(%)	10b+10d	
1	(+)Ipc$_2$BOTf	-78->25	4	88	91	-[c]	4	5	95/5	96/4
2	(-)Ipc$_2$BOTf	-78->25	4	85	93	-[c]	2	5	95/5	98/2
3	BF$_3$	-20	5	60	65	-[c]	11	24	76/24	86/14
4	TiCl$_4$	25	6	36	88	2	5	5	93/7	95/5
5	ZrCl$_4$	25	34	15	100	-[c]	-[c]	-[c]	100/0	100/0

[a] Isolated yield of furo[2,3-d]isoxazol-5(2H)-ones **10a-d**. [b] Normalised ratios deriving from GC analysis of the crude reaction mixture. [c] Isomer not detectable in GC-MS.

An attempt to account for the all S configuration of the major product **10a** is given in Figure 2. First of all let's examine (Table 3) the stereochemical outcomes deriving from the four possible relative approaches of *si* and *re* faces both of nitrone and of 2-trimethylsilyloxyfuran in terms of absolute configurations of final tetrahydrofuro[2,3-d]isoxazol-5(2H)-ones **8**.

First of all, we suppose that oxyiminium ion preserves the Z configuration at the C=N bond of starting **6**, as we demonstrated in the case of complexation with TMSOTf[2b], and that it adopts the conformation[15] required by the Felkin-Anh model, the benzyloxy group playing the role of the most demanding α-substituent (Figure 2). Approach **I** represents the incoming nucleophile **5**, along the Burgi-Dunitz trajectory, offering its *si* face to the *re* face of the nitrone, so determining the S configuration both of C3 and C3a in the *anti* relationship proper of **10a**. In approach **II** 2-trimethylsilyloxyfuran **5** offers its *re* face to the *re* face of nitrone leading to a *syn* product. As apparent from results of Tables 1 and 2, approach **II** is largely unfavoured since it does not profit from a good aromatic stacking[16] as conversely approach **I** does; this observation is in keeping with our former report[6] on the prominent role played by stabilising π-stacking interactions in directing the stereochemistry of the addition of **5** to prochiral nitrones.
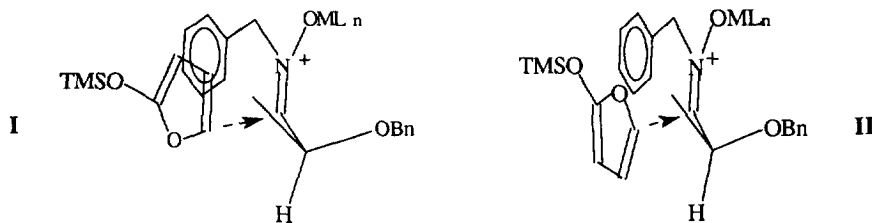

Figure 2

Inspection of molecular models easily proves that both Cram chelated model (OBn group eclipsed to C=N bond) and Felkin less favoured conformation (OBn shielding the *re* face[11]) account for the formation of *anti* product **10c**.

We wish now to point out the synthetic usefulness of tetrahydrofuro[2,3-d]isoxazol-5(2H)-ones **8**. Reductive cleavage of N-O bond on pure **10a** afforded [4S[4α,5α[R*(1R*,2R*)]]]-4-hydroxy-5-[(1-N-benzylamino-2-O-benzyl)-propil]di-hydro-2(3H)-furanone **11** (Scheme 3). The reaction was easily performed in acetic acid by the action of Zn/Cu couple prepared *in situ* in the presence of substrate **8**. Lactone **11** is a synthetic equivalent of β,γ,ε-trihydroxy-δ-amino-carboxylic acid whose versatility as densely functionalised chiral synthons is apparent.

Scheme 3
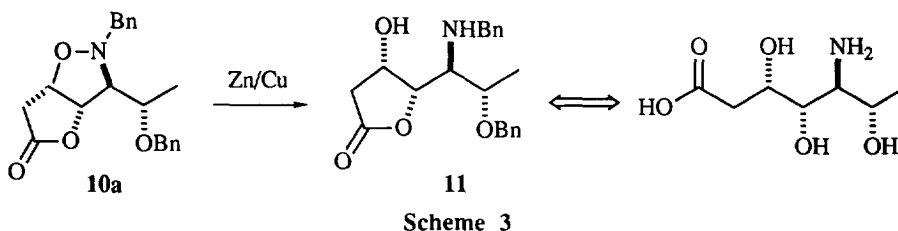
In conclusion, we have broadened the scope of the reaction of 2-trimethylsilyloxyfuran with nitrones i) by examining the action of several Lewis acids as promoters in various conditions, and ii) by using a chiral nitrone deriving from lactaldehyde. In agreement with our previous results, the choice of the benzyl substituent on nitrogen drives the reaction toward the formation of C3-C3a *anti* tetrahydrofuro[2,3-d]isoxazol-5(2H)-ones. These intermediates offer interesting synthetic opportunities and, in particular, work aimed at synthesizing enantiomerically pure 2-substituted 3,4-piperidinediols starting from **11** or its epimers is in progress.

Experimental Section

^{1}H-NMR and ^{13}C-NMR spectra of CDCl$_3$ solutions were recorded at 300 and 75 MHz respectively with a Varian Gemini 300 spectrometer. Chemical shifts are reported in ppm relative to internal standard Me$_4$Si (δ). IR spectra were recorded on NICOLET 205 spectrometer. Optical rotations was performed on Perkin-Elmer 241. Gas chromatographic-mass spectrometric analyses (GC-MS) were performed with HP 5890 instrument connected to a quadrupole mass detector HP 5970 (cross-linked methyl silicone glass capillary column, 0.33-μm film thickness). The column temperature was programmed from 50 to 250°C at 10°C/min and was then held at 250°C for 10 min. Retention time (t$_R$) are reported in minutes. Water contents of CH$_2$Cl$_2$ (< 3 ppm) was measured with Karl-Fisher titrator Mettler DL18. Reactions were performed in oven-dried glassware under atmosphere of dry argon. Dialkylboron triflates (Table 1, entries 3-6) were prepared according to a standard literature procedure[17]

X-Ray Crystallography

Crystals of **10a** were grown from a solution of n-hexane. *Crystal Data*. C$_{21}$H$_{23}$NO$_4$ M = 1866.7, Orthorhombic, a = 10.158(3), b = 10.886(2), c = 16.881(6) Å, V= 1866 Å^3, space group P2$_1$2$_1$2$_1$ (No.19), Z

= 4, Dx = 1.26 g cm^{-3}. Colourless flat prisms. Crystal dimensions: 0.38 x 0.20 x 0.10 mm. μ = 0.087 mm^{-1}.
Data Collection and Processing.- Diffraction intensities were collected on an Enraf-Nonius CAD-4 diffractometer at room temperature with ω scan mode (scan angle = 1.0 + 0.35 tan θ), λ(MoKα) = 0.71069 Å. Reflections measured (θ range 2-27° ,h,k,±l) 4472, unique reflections used 4044 [merging R = 0.013, no absorption correction, no crystal decay]

Structure Analysis and Refinement. - The structure was solved by direct methods which allowed the positions of all non-hydrogen atoms and refined by least-squares methods (based on F^2) using the SHELXS 86 and SHELXL 93 systems of programs[18]. All the non-hydrogen atoms were allowed to vibrate anisotropically. The hydrogen atoms were experimentally located and isotropically refined. No. of refined parameters 327, GOF on F^2 = 1.037, R$_1$ on F, I > 2 σ (I), = 0.033 , wR$_2$ (on F^2) = 0.090. Selected bond lengths [Å] and angles [deg] in Figure 1 (e.s.d.'s are in parentheses)[19].

Sythesis of N-benzyl nitrone of (S)-lactaldehyde 6

N-Benzylhydroxylamine hydrochloride (1.596 g, 10 mmol) was added to a stirred solution of sodium acetate (984 mg, 12 mmol) in water/methanol 2:3 (20 mL). After five minutes (S)-lactaldehyde (1.64 g, 10 mmol) was added and stirring was continued for 30 minutes at room temperature. The solution was extracted with chloroform, the combined organic layers were dried over Na$_2$SO$_4$ and solvent was removed under vacuum.The crude nitrone 6 (2.287 g, 85%) was purified by flash-chromatography eluting with cyclohexane/acetate 7:3.
[α]$_D^{20}$= +33.8 (c=1.9, chloroform); mp = 57°C; GC: t$_R$ = 21.33; IR (neat): ν = 3034, 2854, 1593, 1455, 1292, 1164, 1106, 705, 697 cm^{-1}; MS: m/z (% relative intensity) = 251(M$^+$-15, 1), 223(3), 208(2), 160(15), 145(30), 144(26), 132(26), 118(8), 91(100), 65(14), 51(2); ^{1}H-NMR: δ = 7.39-7.32 (m, 10H), 6.69-6.66 (d, J=6.49 Hz, 1H, azomethinic), 4.86-4.82 (m, 3H, CH + NCH$_2$Ph), 4.59-4.42(dd, J=11.68 Hz, 2H, OCH$_2$Ph), 1.39-1.36(d, J=6.49 Hz, 3H, CH$_3$); ^{13}C-NMR: δ = 141.6(azomethinic), 137.9(Cquat), 132.4(Cquat), 129.4-127.8, 72.0(NCH$_2$Ph), 70.5(CH), 69.5(OCH$_2$Ph), 17.2(CH$_3$); Anal. Calcd. for C$_{17}$H$_{19}$NO$_2$: C,75.81; H,7.11. Found: C,75.53; H,7.22.

Synthesis of Tetrahydro-2-benzyl-3-(1-bezyloxyethyl)-furo[2,3-d]isoxazol-5(2H)ones 10a-d catalysed by TMSOTf (Table 1, entry 1)

2-(Trimethylsilyloxy)-furan (673 μL, 4 mmol) was added to a solution of 6 (1.076 g, 4 mmol) in CH$_2$Cl$_2$ (15 mL). The solution was cooled under argon at -20°C, TMSOTf (73 μL, 0.4 mmol) was added and the reaction mixture was stirred for 20 min. The solution was quenched with saturated aqueous NaHCO$_3$ and extracted with ether. The organic layer was dried over Na$_2$SO$_4$ and concentrated under vacuum. To the residue dissolved in THF (10 mL) 1.1M Bu$_4$N$^+$F$^-$ in THF (3.65 mL, 4 mmol) was added and the solution was stirred for 10 minutes. The solvent was removed under vacuum and title compounds 10a-d were isolated by flash-chromatography in overall 97% yield.

[3S[3α(R),3aβ,6aβ]]-Tetrahydro-2-benzyl-3-(1-benzyloxyethyl)-furo[2,3-d]isoxazol-5(2H)-one 10a*
R$_f$ = 0.28 (cyclohexane/ethyl acetate 1:1); [α]$_D^{20}$= +53.4 (c=2.01, chloroform); mp = 108-112°C; GC: t$_R$ = 26.8; IR (neat): ν = 2900, 2840, 1770, 1440, 1360, 1250, 1140, 1060, 900, 740 cm^{-1}; MS: m/z (% relative intensity) = 353(M$^+$, 3), 252(2), 218(11), 160(4), 92 (8), 91(100), 65(5); ^{1}H-NMR: δ = 7.40-7.28 (m, 10H), 5.32 (dd, J=4.5/2.7 Hz, 1H, H-3a), 4.64 (s, 2H, OCH$_2$Ph), 4.63 (dt, J=4.5/1.9 Hz, 1H, H-6a), 4.15 (d,

J=13.8 Hz, 1H, NCH$_2$Ph), 3.97 (d, J=13.8 Hz, 1H, NCH$_2$Ph), 3.60 (dq, J=6.5/2.7 Hz, 1H, CH-OBn), 3.09 (t, J=2.7 Hz, 1H, H-3), 2.70 (m, 2H, H-6), 1.30 (d, J=6.5 Hz, 3H, CH$_3$); ^{13}C-NMR (HETCOR): δ = 174.8(C=O), 138.2(Cquat), 136.7(Cquat), 128.7, 128.3, 127.6, 127.5, 87.9(C-3a), 77(C-3), 76.4(OCH$_2$Ph), 72.1(CH-OBn), 71.8(C-6a), 61.7(NCH$_2$Ph), 34.3(C-6), 17.9(CH$_3$); Anal. Calcd. for C$_{21}$H$_{23}$NO$_4$: C,71.37; H,6.56. Found: C,71.49; H,6.45.

[3R[3α(S),3aβ,6aβ]]-Tetrahydro-2-benzyl-3-(1-benzyloxyethyl)-furo[2,3-d]isoxazol-5(2H)-one 10c*
R$_f$ = 0.18 (cyclohexane/ethyl acetate 1:1); [α]$_D^{20}$= -25.35 (c=1.05, chloroform); GC: t$_R$ = 27.4; IR (neat): ν = 2900, 1770, 1600, 1480, 1440, 1360, 1140, 1060, 900, 740 cm^{-1}; ^{1}H-NMR: δ = 7.40-7.22 (m, 10H), 5.03 (dd, J=4.7/2.5 Hz, 1H, H-3a), 4.67-4.60 (m, 1H, H-6a), 4.62 (d, J=11.6 Hz, 1H, OCH$_2$Ph), 4.51 (d, J=11.6 Hz, 1H, OCH$_2$Ph), 4.27 (d, J=13.8 Hz, 1H, NCH$_2$Ph), 4.00 (d, J=13.8 Hz, 1H, NCH$_2$Ph), 3.64 (quint., J=6.4 Hz, 1H, CH-OBn), 3.27 (dd, J=6.4/2.5 Hz, 1H, H-3), 2.72 (m, 2H, H-6), 1.30 (d, J=6.4 Hz, 3H, CH$_3$); ^{13}C-NMR: δ = 174.6(C=O), 137.8(Cquat), 136.9(Cquat), 128.8, 128.4, 128.3, 128.1, 127.8, 127.4, 89.2(C-3a), 76.2(C-3), 74.8(OCH$_2$Ph), 73.7(C-6a), 70.9(CH-OBn), 62.6(NCH$_2$Ph), 34.3(C-6), 16.2(CH$_3$); Anal. Calcd. for C$_{21}$H$_{23}$NO$_4$: C,71.37; H,6.56. Found: C,71.28; H,6.51.

Tetrahydro-2-benzyl-3-(1-benzyloxyethyl)-furo[2,3-d]isoxazol-5(2H)-one 10b
R$_f$ = 0.23 (cyclohexane/ethyl acetate 1:1); GC: t$_R$ = 27.1; ^{1}H-NMR: δ = 7.41-7.21 (m, 10H), 5.22 (dd, J=5.4/4.4 Hz, 1H, H-3a), 4.87-4.81 (m, 1H, H-6a), 4.73 (d, J=15.0 Hz, 1H, NCH$_2$Ph), 4.65 (d, J=11.3 Hz, 1H, OCH$_2$Ph), 4.47 (d, J=11.3 Hz, 1H, OCH$_2$Ph), 3.99-3.91 (m., 1H, CH-OBn), 3.75 (d, J=15.0 Hz, 1H, NCH$_2$Ph), 2.86 (dd, J=8.7/4.4 Hz, 1H, H-3), 2.76-2.68 (m, 2H, H-6), 1.46 (d, J=6.1 Hz, 3H, CH$_3$).

Tetrahydro-2-benzyl-3-(1-benzyloxyethyl)-furo[2,3-d]isoxazol-5(2H)-one 10d
R$_f$ = 0.25 (cyclohexane/ethyl acetate 1:1); GC: t$_R$ = 28.4; ^{1}H-NMR: δ = 7.41-7.21 (m, 10H), 5.32 (t, J=5.5 Hz, 1H, H-3a), 4.90 (sextet, J=5.9/3.1, 1H, H-6a), 4.64 (d, J=11.2 Hz, 1H, OCH$_2$Ph), 4.57 (d, J=11.2 Hz, 1H, OCH$_2$Ph), 4.34 (d, J=14.5 Hz, 1H, NCH$_2$Ph), 4.04 (dq.,J=6.3/5.1 1H, CH-OBn), 3.83 (d, J=14.5 Hz, 1H, NCH$_2$Ph), 3.13 (t, J=5.1 Hz, 1H, H-3), 2.76-2.68 (m, 2H, H-6), 1.34 (d, J=6.3 Hz, 3H, CH$_3$).

One-pot synthesis of tetrahydro-2-benzyl-3-(1-benzyloxyethyl)-furo[2,3-d]isoxazol-5(2H)one catalysed by Ipc$_2$BOTf (Table 2, entries 1-2)
Nitrone **9** (135 mg, 0.5 mmol) was added at 0°C to a solution of Ipc$_2$BOTf (0.5 mmol) in CH$_2$Cl$_2$ (15 mL). To the solution cooled at -78°C. 2-Trimethylsilyloxyfuran (84 μL, 0.5 mmol) was added and the temperature was allowed to raise to 20°C within 4 hours. After quenching with saturated aqueous NaHCO$_3$, extraction with ether and solvent removal, flash chromatography (cyclohexane/ethyl acetate 7:3) of the crude reaction mixture afforded **10a-d** in overall 85% yield.

Reduction of [3S[3α(R*),3aβ,6aβ]]-Tetrahydro-2-benzyl-3-(1-benzyloxyethyl)-furo[2,3-d]isoxazol-5(2H)one
To a mixture of zinc (1 g, 15.3 mmol) in acetic acid (7 mL), **10a** (400 mg, 1.13 mmol) and copper acetate (250 mg, 0.6 mmol) were subsequently added under vigorous stirring at 60°C. After 90 min the reaction mixture was cooled to room temperature and pH was adjusted to 9 with NaOH 6N. After filtration, washing of the solid residue with hot chloroform and extraction of the aqueous phase, the collected organic layers were dried

(Na_2SO_4) and concentrated under vaccum. Pure **11** (261 mg, 0.74 mmol) was obtained by flash-chromatography (cyclohexane/ethyl acetate 6:4) in overall 65% yield.

[4S[4α,5α[R(1R*,2R*)]]]-4-hydroxy-5-[(1-N-benzylamino-2-O-benzyl)-propy]-dihydro-2(3H)-furanone* **11**
R_f = 0.3 (cyclohexane/ethyl acetate 1:4); $[α]_D^{20}$= +27.2 (c=0.50, CH_2Cl_2); IR (neat): ν = 3300(broad), 3290(NH), 3010, 2910, 2770, 1775, 1440, 1140, 1020, 725, 690 cm^{-1}; ^{1}H-NMR: δ = 7.41-7.19 (m, 10H), 4.69 (d, J=11.7 Hz, 1H, OCH$_2$Ph), 4.61-4.56 (m, 1H, H-6a), 4.48 (dd, J=6.1/3.5 Hz, 1H, H-3a), 4.43 (d, J=11.7 Hz, 1H, OCH$_2$Ph), 3.96 (dq., J=6.5/3.3 Hz, 1H, CH-OBn),3.75 (d, J=12.9 Hz, 1H, NCH$_2$Ph), 3.69 (d, J=12.9 Hz, 1H, NCH$_2$Ph), 3.18 (dd, J=6.1/3.3 Hz, 1H, H-3), 2.65 (dd,J=17.6/5.1 Hz, 1H, H-6), 2.54 (dd,J=17.6/1.0 Hz, 1H, H-6), 1.33 (d, J=6.5 Hz, 3H, CH$_3$); ^{13}C-NMR (HETCOR): δ = 175.8(C=O), 138.7(Cquat), 137.8(Cquat), 128.5, 128.4, 128.2, 127.8, 127.4, 127.3, 80.9(C-3a), 71.9(CH-OBn), 70.5(OCH$_2$Ph), 69.5(C-6a), 60.9(C-3), 51.7(NCH$_2$Ph), 38.2(C-6), 15.7(CH$_3$); Anal. Calcd. for $C_{21}H_{25}NO_4$: C,70.96; H,7.09. Found: C,70.71; H,7.16.

References and Notes

1. Dhavale,D.D.; Trombini,C. *Heterocycles*, **1992**, *34*, 2253.
2. (a) Dhavale,D.D.; Trombini,C. *J.Chem.Soc.Chem.Commun.* **1992**, 1268; (b) Camiletti,C.; Dhavale,D.D.; Gentilucci,L.; Trombini,C. *J.Chem.Soc. Perkin Trans.1*, **1993**, 3157.
3. (a) Kita,Y.; Ithoc,F.; Tamura,O.; Ke,Y.Y.; Tamura,Y. *Tetrahedron Lett.* **1987**, *28*, 1431; (b) Kita,Y.;, Tamura,O.; Ithoc,F.; Kishino,H.; Miki,T.; Kohno,M.; Tamura,Y. *J. Chem. Soc. Chem. Comm.* **1988**, 761.
4. Camiletti,C.; Dhavale,D.D.; Donati,F.; Trombini,C. *Tetrahedron Lett*, **1995**,*36*, 7293.
5. For an excellent review on the use of 2-trimethylsilyloxyfuran in the synthesis of homochiral compounds see: Casiraghi,G.; Rassu,G. *Synthesis*, **1995**, 607.
6. Camiletti,C.; Poletti,L.; Trombini, C. *J.Org.Chem.*, **1994**, *59*, 6843.
7. GC-MS analysis of the reaction mixture shows four peaks at t_R = 26.1 / 27.9 / 28.1 / 28.3 min respectively; they display the same mass spectrum: MS: *m/z* (% relative intensity) = 342 (M$^+$ - $C_4H_3O_2$, 30), 290 (M$^+$ - CH$_3$CHOBn, 6), 236 (2), 195 (2), 91 (100).
8. Upon irradiation at H3a isomers **10a** and **10c** only showed a 10-15% enhancement of H6a, while isomers **10b** and **10d**, besides to H6a showed a 4-7% NOE effect at H3, thus confirming the C3a-C3 syn stereorelationship.
9. Bond distances of the bicyclic system are in accord with the interatomic distances found in the structure of (3R,6R,7R,11S)-7-acetoxymethyl-5,8,10-trioxa-1-azatricyclo[4.3.2.0]undecan-4-one:
    see Suwiniska,K.; Panfil,I.; Belzecki,C.; Chimilewski,M. *Acta Crystallogr.,Sect.C*, **1989**, *C45*, 1836.
10. Among weak directional interactions, intermolecular CH···O hydrogen bonds are considered important factors in determining crystal packing: see Desiraju,G.R. *Angew.Chem.Int.Ed.Engl.*,**1995**, *34*, 2311.
11. The inspection of molecular model of C shows that a possible C3aH3a···O2 H-bond should be

destabilized by an eclipsed interaction between C1-C7 and C3-N2 bonds.

12. Carreira,E.M.; Singer,R.A. *Tetrahedron Lett.*, **1994**, *35*, 4323.

13. Denmark,S.E.; Chen, C.-T. *Tetrahedron Lett.*, **1994**, *35*, 4327.

14. Hollis,T.K.; Bosnich,B. *J.Am.Chem.Soc.*, **1995**, *117*, 4570.

15. On the basis of 1,3-allylic strain the conformation presenting the C-H bond almost coplanar to the C=NOMLn framework should be the stablest arrangement ; see Hoffmann,R.W. *Chem.Rev.*,**1989**,*89*, 1841.

16. Jones,G.B.; Chapman,B.J. *Synthesis*, **1995**, 475.

17. Paterson,I.; Goodman,J.M.; Lister,M.A.; Schumann,R.C.; McClure,C.K.; Norcross,R.D. *Tetrahedron*, **1990**, *46*, 4663.

18. (a) Sheldrick,G.M. *Acta Crystallogr.Sect.A*, **1990**,*46*,467; (b) Sheldrick,G.M. *J.Appl.Cryst.* in the press.

19. Atomic coordinates, bond lenghts and angles, and thermal parameters have been deposited at the Cambridge Data Center.