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DIASTEREOSELECTIVE SYNTHESIS AND ANTIFUNGAL ACTIVITY OF GLYCOSYL ISOXAZOLINES[+]

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ABSTRACT

Glycosyl nitrile oxides, generated *in situ* by reaction of glycosyl oximes (**3a, 3b, 4**) with *N*-chlorosuccinimide and DBU, on 1,3-dipolar cycloaddition with substituted alkenes resulted in glycosyl isoxazolines (**5, 7-28**) in diastereoselective manner. The extent of diastereoselection varies with the nature of substituent both in sugar and alkenes. The compounds synthesized were screened *in vitro* against many fungi wherein two of the compounds (**12**, **23**) showed significant inhibition against *Sporothrix schenckii, Trychophyton mentegrophytes* and *Cryptococcus neoformans* with MIC of 12.5 and 6.25 μg/mL respectively.

Key Words: Cycloaddition; Isoxazoline; DBU; Antifungal activity.

INTRODUCTION

1,3-Dipolar cycloaddition reactions of nitrones and nitrile oxides with alkenes for the synthesis of five membered heterocycles of synthetic and biological importance is known for quite sometime.[1-3] Isoxazolines are isosters of oxazolidinones which is well-established class of antibacterial agents. Isooxazolines themselves have recently been reported to be of great significance as antibacterial and antifungal agents.[4-5]

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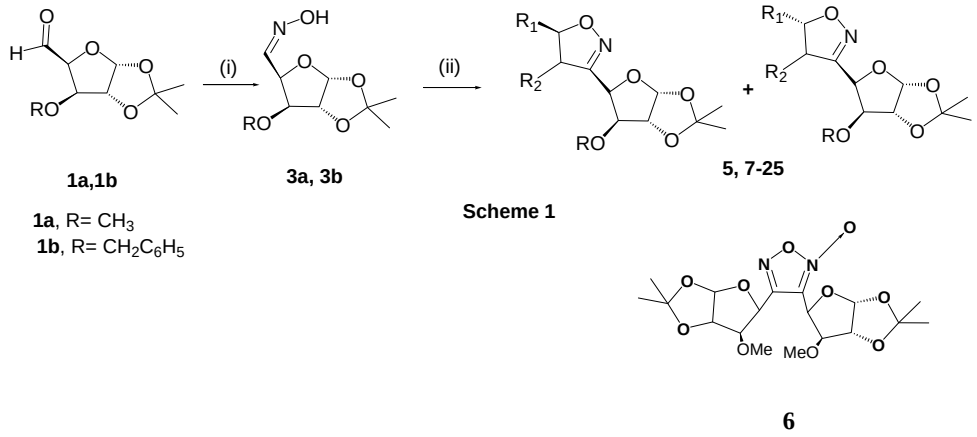
The stereochemistry in 1,3-dipolar cycloadditions is controlled either by choosing an appropriate substrate or controlling the geometry of the transition state during progress of the reaction by agents acting as catalyst or co-catalyst. Existing reports for 1,3 dipolar additions using optically active nitrile oxides in are scanty but of great synthetic value.[6-8] Application of chiral nitrile oxides generated *in situ* by reaction of oximes with *N*-bromosuccinimide in presence of bases such as pyridine or triethylamine to get isoxazolines diastereoselectively have recently been reported.[9] Because of role of carbohydrates as chiral pool for asymmetric synthesis, sugar derived chiral nitrones have been used to synthesize fused or bridged isoxazoline, oxepans and pyrans.[10] Synthetic application of carbohydrate derived chiral building blocks as precursors for the synthesis of nitrogenated compounds such as amino sugars, alkaloids and amino acids has also been well documented.[11] Asymmetric 1,3 dipolar cycloaddition because of its versatility in the construction of chiral compounds like amino alcohol, β-hydroxy ketones, amino acids and many antibiotics are of much importance.[12] Keeping the above facts in mind and in continuation of our work on the development of sugar derivatives as chemotherapeutic agents,[13] we were prompted to synthesise glycosylated isoxazolines, which may serve as intermediates for the synthesis of a variety of compounds. The compounds synthesized were screened against *Candida albicans, Candida parapsilosis* (ATCC 22019), *Cryptococcus neoformans, Aspergillus fumigatus, Sporothrix schenckii* and *Trychophyton mentagrophytes* as per guidelines of NCCLS using RPMI 1640 medium buffered with MOPS.

RESULTS AND DISCUSSION

The glycosyl oximes[14] (**3a, 3b, 4**) were prepared from the respective uloses (**1a, 1b, 2**) by reaction with hydroxylamine hydrochloride separately in good yields. Glycosyl nitrile oxides (dipoles) were generated *in situ* by reaction of the oximes with *N*-cholorosuccinimide catalyzed with diazabicyclo undecene (DBU) separately. The intermediate nitrile oxides on reaction with different dipolarophiles (alkenes) gave 3-glycosyl-2-isoxazolines in good yields with varying diastereoselection.

Thus reaction of glycosyl oxime **3a** with *N*-chlorosuccinimide followed by treatment with DBU resulted in the formation of intermediate nitrile oxide (un-isolated), which on treatment with ethyl acrylate at 0°C gave a mixture of products from which only two products could be isolated by column chromatography. The faster moving compound was found to be a diastereomeric mixture (3:1, as determined by PMR spectrum) of 5(*R,S*)-carbethoxy-3-(3'-*O*-methyl-1',2'-*O*-isopropylidene-tetrahydro-1',4'-furanos-4'-yl)-isoxazole (**5**) in 70 % yield. The diastereomers could not be separated by column chromatography. The structure was established on the basis of spectroscopic data and analysis. The second product was found to be a furoxan derivative (**6**, 20 %) formed by dimerisation of the nitrile oxide. Its structure was also established on the basis of spectroscopic data and analysis. Compound **5** in IR spectrum exhibited absorption band at 1744 and 1625 cm^{-1} indicating the presence of COOEt and C=N of the isoxazoline ring respectively. In ^{1}H NMR spectrum a *dd* signal for two protons at δ 3.4 while a one-proton *m* at around δ 5.0 accounted the methylene protons and H-5 of the isoxazoline ring respectively. In ^{13}C NMR spectrum a signal corresponding to C=N appeared at δ 157,

and signals corresponding to C-4 and C-5 of the isoxazoline ring at δ 40 and 87 respectively besides other usual signals. Compound **6** showed a peak at 434 in FABMS corresponding to $(M+H)^+$, while ^{1}HNMR spectrum showed duplicate signals for all the protons in sugar moiety and no proton signal corresponding to isoxazoline ring were observed. Similarly, reaction of **3a** with dipolarophiles including ethyl vinyl ether, vinyl acetate, methyl vinyl ketone, acrylo nitrile, allyl bromide, allyl phenol, allyl anisole, allyl alcohol and crotonic acid separately resulted in the formation of respective glycosyl isoxazolines (**7-15**) as diastereomeric mixture in fair to good yields. The structures of all the compounds were in accordance with their spectroscopic data and analysis.



1a,1b

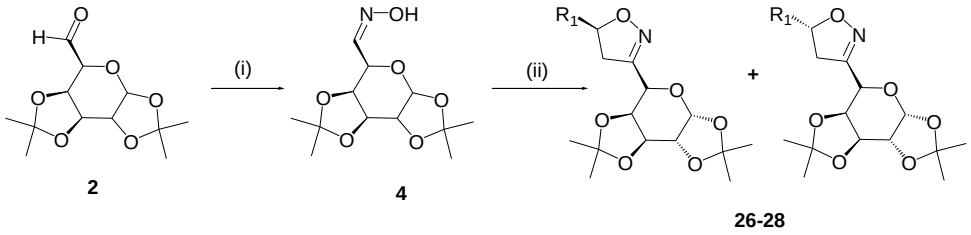
1a, R= CH_3
1b, R= $CH_2C_6H_5$

3a, 3b

5, 7-25

Scheme 1

6



2

4

26-28

Scheme 2

Reagents & condition: (i) NH_2OH, DMAP, Alcohol, Pyridine
(ii) NCS, $R_1CH=CH_2$, DBU, CH_3CN, 0 -RT

In the next attempt a glycosyl oximes with bulky 3-*O*-benzyl substituent was chosen as starting material to see the steric effect on diastereoselection. Thus the reaction

of oxime **3b** with *N*-chlorosuccinimide in presence of DBU followed by treatment of the intermediate nitrile oxide with ethyl acrylate gave compound **16** in 75 % yield. Similar reaction of **3b** with ethyl vinyl ether, vinyl acetate, methyl vinyl ketone, acrylo nitrile, allyl bromide, allyl phenol, allyl anisole, allyl alcohol and crotonic acid resulted in the formation of respective glycosyl isoxazolines (**17-25**) in good yield with improved diastereoselection (Table 1). The structure of all the products was determined on the basis of spectroscopic data and analysis. Among all the compounds (**5**, **7-25**) the

Table 1: Glycosyl isoxazolines synthesized

Entry	Compound No.	R	R_1	R_2	%Yield	Ratio of Isomers[#]
1	**5**	CH_3	$COOC_2H_5$	H	70	75:25
2	**7**	CH_3	OC_2H_5	H	60	60:40
3	**8**	CH_3	$OCOCH_3$	H	60	62:38
4	**9**	CH_3	$COCH_3$	H	54	55:45
5	**10**	CH_3	CH_2CN	H	55	55:45
6	**11**	CH_3	CH_2Br	H	58	60:40
7	**12**	CH_3	CH_2PhOH	H	75	75:25
8	**13**	CH_3	CH_2PhOCH_3	H	79	65:35
9	**14**	CH_3	CH_2OH	H	60	55:45
10	**15**	CH_3	COOH	CH_3	58	60:40
11	**16**	CH_2Ph	$COOC_2H_5$	H	75	80:20
12	**17**	CH_2Ph	OC_2H_5	H	65	65:35
13	**18**	CH_2Ph	$OCOCH_3$	H	75	65:35
14	**19**	CH_2Ph	$COCH_3$	H	59	60:40
15	**20**	CH_2Ph	CH_2CN	H	50	62:38
16	**21**	CH_2Ph	CH_2Br	H	80	70:30
17	**22**	CH_2Ph	CH_2PhOH	H	75	90:10
18	**23**	CH_2Ph	CH_2PhOCH_3	H	80	75:25
19	**24**	CH_2Ph	CH_2OH	H	65	65:35
20	**25**	CH_2Ph	COOH	CH_3	55	65:35
21	**26**	--	$COOC_2H_5$	H	65	--
22	**27**	--	CH_2PhOH	H	55	70:30
23	**28**	--	CH_2OH	H	75	--

[#]determined on the basis of integration of ^1H NMR signal

maximum diastereoselection (9:1) was noticed in reaction of **3b** with allyl phenol to give compound **22**.

In yet another sequence of reactions, galactopyranosyl oxime (**4**), obtained from compound (**2**) and hydroxylamine hydrochloride, on treatment with *N*-chlorosuccinimide catalyzed by DBU resulted in intermediate glycosyl nitrile oxide, which on *in situ* reaction with ethyl acrylate gave galactopyranosyl isoxazolines (**26**) in 65 % yield. The structure of the compound **26** was confirmed on the basis of IR, NMR and MS spectral data. The MS showed the peak corresponding to $(M+H)^+$ while IR spectrum exhibited absorption band at 1745 cm^{-1} and 1631 cm^{-1} for the ester and C=N of the isoxazole ring repectively. In ^1H NMR spectrum two *m* at δ 4.82 and δ 3.45 each accounting for diastereomeric H-5 and two protons of H-4 respectively of isoxazoline ring besides other usual signals.

The maximum diastereoselection, noticed in the dipolar addition of allyl phenol to furanosyl nitrile oxide prompted us to see the extent of diastereoselection in the intermediate galactopyranosyl nitrile oxide and allyl phenol where the two diastereomers (**27**) were obtained in 7:3 ratio. Similar reaction of **4** with allyl alcohol gave isoxazolines **28** in 75 % yield.

Formation of two diastereomers and preference of one over the other could be rationalised considering the Houk and Felkin Anh models of the transition states formed during the reaction. According to Houk model the major product arises from transition state I in which the largest group occupies the anti position, the medium group the inside position, and the smallest group occupy the outside position.[2, 15] Out of many other possible conformations the minor product arises from the transition state-II. It is assumed

that the inside position is less sterically demanding than the outside position due to oxygen atom of the incoming nitrile oxide.

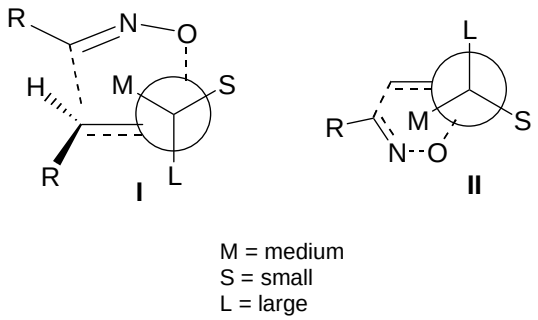


Figure 1: Houk TS Model

Antifungal evaluation of the compounds

The Minimum inhibitory concentration (MIC) for each compound against the test fungi was determined by using broth micro-dilution techniques as per guidelines of NCCLS M-27A[16]. MIC of standard antifungals and synthetic compounds were measured in 96 well tissue culture plate (Cellstar Greiner Bio One, Germany) using RPMI 1640 media buffered with MOPS (3-[N-Morpholino] propanesulfonic acid) (Sigma Chemical Co.). Starting inocula of test cultures were maintained at 1.0-5.0 $\times 10^3$ cfu/mL. All the compound are tested between the range of 50-0.78 μg/ml. Microtiter plates were incubated at 35°C in a moist, dark chamber, and MICs were recorded spectrophotometrically (Softmax pro® 4.3, Versamax microplate reader, Molecular Devices) after 48 h for *Candida* spp. and 72 h for C*ryptococcus* spp. and mycelial fungi. While for *T. mentegrophytes* reading is documented after 96 hours.

Antifungal activity

It is evident from the antifungal activity data (Table 2) that except compound **14** all the compounds belonging to glycosyl isooxazolines exhibited inhibition of fungal growth at a concentration ranging from 50 μg/mL to 6.25 μg/mL. A glycosyl isoxazoline (**23)** with a hydrophobic 3'-*O*-benzyl substituent in sugar ring was found to be the most active against a dermatophyte *T. mentagrophytes* (MIC 6.25 μg/mL), while compound **12** with 3'-*O*-methyl substituent was less potent with MIC value of 12.5 μg/mL indicating the importance of hydrophobicity in fungal growth inhibition.

Table 2 Antifungal activity of glycosyl-isoxazolines showing MIC against different fungal strains.

Compd. No.	Cn	Ss	Tm	Compd. No.	Cn	Ss	Tm
5	25	25	25	**17**	25	50	50
7	25	12.5	25	**18**	50	50	50
8	25	50	25	**19**	12.5	50	25
9	25	25	50	**20**	25	50	50
10	50	50	50	**21**	25	25	25
11	25	12.5	50	**22**	12.5	50	12.5
12	12.5	50	12.5	**23**	25	--	6.25
13	25	50	12.5	**24**	25	25	12.5
14	>50	>50	>50	**25**	Nd	nd	nd
15	12.5	50	50	**26**	12.5	50	50
16	12.5	50	25	**27**	25	50	50
Ketoconazole	0.12	0.50	0.25	**28**	12.5	50	50

Cn = *Cryptococcus neoformans* Tm = *Trychophyton mentagrophytes* Ss = *Sporothrix schenckii*,
The compounds did not show any activity against *Candida albicans*, *Candida parapsilosis* (ATCC 22019) *and Aspergillus fumigatus* at the concentrations tested.

EXPERIMENTAL

General methods. Thin-layer chromatography was carried out on silica gel (Kiesel 60-F254, Merck) and spots were developed in iodine vapours and also by spraying with 5% sulfuric acid in alcohol followed by heating at 100 ºC. Column chromatography was carried out on flash silica gel (230-400 mesh, Merck) using the indicated eluent. IR spectra were recorded as thin films on KBr plates with a Perkin Elmer 881 spectrophotometer. NMR spectra were recorded on Bruker spectrometers 200 and 300 MHz and reference used was $CDCl_3$. Chemical shifts were given as δ ppm values and '*J*' values were given in Hertz (Hz). Elemental analyses were performed on a Perkin-Elmer 2400 II elemental analyzer. The optical rotations were measured in a 1.0 dm tube with Jasco dip-140 polarimeter in chloroform. The excess of the reagents or solvents were evaporated under reduced pressure at a bath temperature between the ranges 55-60 ºC.

General Procedure for the preparation of compounds 3a, 3b & 4:

5-Deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-5-oximinyl-α-D-xylofuranose (3a). A mixture of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranos-5-ulose (**1**, 10.0 g, 49.5 mmol), hydroxylamine hydrochloride (3.48 g, 50.0 mmol) and dimethyl aminopyridine (6.1 g, 50.0 mmol) in ethanol and pyridine (25 mL each) was magnetically stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure and the crude mass, thus obtained, was dissolved in ethylacetate (2 x 100 mL), washed with water (2 x 20 mL) and dried (Na_2SO_4). Solvents evaporated under reduced pressure to get syrup which on column chromatography (SiO_2) using hexane: ethyl acetate (17:3) as eluant afforded the required compound **3** as colourless viscous oil, Rf 0.55 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{20}$ –32.6º (*c* 0.175, $CHCl_3$), MS (FAB) = m/z 218 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 3396, 2989, 2836, 2143, 1710, 1630, 1457, 1379; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.47 (d, *J*= 7.3 Hz, 1H, CH=N, anti isomer), 6.90 (d, *J*= 3.4 Hz, 1H, CH=N, syn isomer), 5.96 (d, *J* = 2.5 Hz, 2H, diastereomeric H-1), 5.20 (dd, *J*=3.4 and 3.3 Hz, 1H, H-4, syn isomer), 4.73 (dd, *J* = 7.3 and 3.3 Hz, 1H, H-4, anti isomer), 4.61 (d, *J* = 2.5

Hz, 2H, H-2 of each isomer), 4.15 and 3.81 (d, *J* = 3.3 Hz, 1H, H-3 of each isomer), 3.40 and 3.39 (s, 3H, OCH_3 of each isomer), 2.10 (s, exchangable with D_2O, 1H, N-OH), 1.51 and 1.33 [each s, 12H, $C(CH_3)_2$ of each isomer].

Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.93; H, 7.11; N, 6.32.

3-*O*-Benzyl-5-deoxy-1,2-*O*-isopropylidene-5-oximinyl-α-D-xylofuranose (3b).

Colourless Solid, Mp 159 °C, Rf 0.65 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{20}$ –42.7° (*c* 0.275, $CHCl_3$), MS (FAB) = m/z 294 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 3412, 3251, 2995, 2371, 2162, 1628, 1450, 1384; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.67 (s, 1H, CH=N), 7.30 (m, 5H, ArH), 6.98 (d, *J*= 3.9 Hz, 1H, CH=N), 5.99 (d, *J* = 3.7 Hz, 1H, H-1), 5.23 (m, 1H, H-4), 4.61 (m, 3H, H-2 and $-OCH_2Ph$), 4.37 (d, *J*=3.2 Hz, 1H, H-3), 1.50 and 1.32 [s, 6H, $C(CH_3)_2$].

Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found C, 61.65; H, 6.73; N, 4.55.

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-oximinyl-α-D-galactopyranose (4).

Colourless Solid, Mp 82 °C, Rf 0.60 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{25}$ –53.4° (*c* 0.28, $CHCl_3$); MS (FAB) = m/z 274 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 3396, 2989, 2836, 2143, 1710, 1630, 1457, 1379; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.48 (d, *J* = 7.3 Hz, 1H, CH=N, anti isomer), 6.80 (d, *J* = 3.4 Hz, 1H, CH=N, syn isomer) 5.57 (d, *J* = 4.9 Hz, 2H, diastereomeric H-1), 4.66 (m, 2H, H-3 and H-2), 4.33 (m, 2H, H-4 and H-5) 1.55, 1.51 and 1.33 [s, 12H, $C(CH_3)_2$ of each isomer],

Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.74; H, 7.01; N, 5.13

General Procedure for the preparation of compounds 5, 7-28:

5(*R,S*)-Carbethoxy-3-[(*1'R, 2'R, 3'S, 4'R*)-1',2'-*O*-isopropylidene-3'-*O*-methyl-tetrahydrofuranos-4'-yl]-2-isoxazoline (5). To a stirring solution of compound **3a** (0.6 g, 2.76 mmol) in acetonitrile (7.0 mL) at 0°C *N*-chlorosuccinimide (0.37g, 2.80 mmol) was added and stirring continued for 1.5 h. Conversion of the oxime to chloroxime was monitored by thin layer chromatography. DBU (0.42g, 2.76mmol) was slowly added to the reaction mixture followed by addition of ethyl acrylate (1.4 g, 14.0 mmol) and the reaction continued for 4h. Solvent was evaporated and the residue obtained was dissolved in ethyl acetate (50 mL), washed with water (2 x 25 mL) and saturated solution of NaCl

(2 x 25mL) and dried (Na_2SO_4). The solvent evaporated under reduced pressure to get a crude product which was chromatographed over SiO_2 using hexane: ethyl acetate (17: 3) as eluent to give compound **5** as colourless oil, Rf 0.70 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{25}$ +49.1° (*c* 0.175, $CHCl_3$), MS (FAB) = m/z 316 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 2985, 2362, 1744, 1625, 1540, 1377; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.96 (d, *J* = 3.6 Hz, 1H, H-1'), 5.13 (d, *J* = 3.6 Hz, 1H, H-4') 4.99 (t, *J*= 9.6 Hz, 1 H, H-5), 4.60 (d, *J*=3.7 Hz, 1H, H-2'), 4.24 (q, *J* = 2H, OCH_2), 3.89 (d, *J*= 3.6 Hz, 1H, H-3'), 3.42-3.46 (m, 2H, 2H, H-4 isoxzoline ring), 3.38 (s, 3H, OCH_3), 1.50 and 1.33 [s, 3H, C (CH_3)$_2$], 1.28 (t, *J* = 7.1 Hz, -OCH_2CH_3).^{13}C NMR ($CDCl_3$): δ 170.6 (C=O), 157.1 (C=N); 112.7 [$C(CH_3)_2$]; 105.0 (C-1'); 87.3 (C-5), 81.8 (C-2'); 77.7 (C-4'); 76.2 (C-3); 62.2 (OCH_2); 58.4 (OCH_3), 40.5 (C-4); 27.2, 26.7 [>$C(CH_3)_2$] and 14.5 (CH_2CH_3).

Anal. Calcd for $C_{14}H_{21}NO_7$: C, 53.33; H, 6.71; N, 4.44. Found: C, 53.46; H, 6.92; N, 4.31.

3,4-*Bis*-[*(1'R,2'R,3'S,4'R)*-1',2'-*O*-isopropylidene-3'-*O*-methyl-tetrahydrofuranos-4'-yl]-1,2,5-oxadizole-2-oxide (6). Colourless oil, Rf 0.40 (hexane:ethyl acetate, 7:3); MS (FAB) = m/z 431 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 2988, 2839, 1609, 1475, 1379; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.07 and 6.01 (each d, *J* = 3.6 Hz, each 1H, H-1'), 5.55 and 5.28 (each d, *J* = 3.0 and 3.3 Hz, each 1H, H-4'), 4.67 (d, *J* =3.6 Hz, 2H, H-2'), 4.17 and 3.89 (each d, *J* =3.0 and 3.3 Hz, each 1H, H-3'), 3.33 and 3.29 (each s, each 3H, OCH_3), 1.53 and 1.36 [each s, each 6H, C (CH_3)$_2$].

Anal. Calcd for $C_{18}H_{26}N_2O_{10}$: C, 50.23; H, 6.09; N, 6.51; O, 37.17 Found: C, 50.43; H, 6.37; N, 6.32.

5(*R,S*)-Ethoxy-3-[*(1'R,2'R,3'S,4'R)*-1',2'-*O*-isopropylidene-3'-*O*-methyl-tetrahydrofuranos-4'-yl]-2-isoxazoline (7). Colourless oil, Rf 0.65 (hexane:ethyl acetate, 3:1); $[\alpha]_D^{25}$ –86.5º (*c* 0.275, $CHCl_3$), MS (FAB) = m/z 288 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 2983, 2362, 1616, 1453, 1378, 1300 ^1H NMR ($CDCl_3$, 200 MHz): δ 5.96 (d, *J* = 3.6 Hz, 1H, H-1), 5.55 (dd, *J*= 6.5 and 2.3 Hz, 1H, H-5), 5.11 (d, *J* = 3.2 Hz, 1H, diastereomeric H-4'), 4.59 (d, *J*=3.6 Hz, 1H, diastereomeric H-2'), 3.90 (d, *J*=3.2 Hz, 1H, diastereomeric H-3'), 3.84 and 3.55 (each m, 2H, -OCH_2CH_3), 3.36 (s, 3H, OCH_3), 3.06 (dd, *J* = 12.5 and 6.5 Hz, 1H, $H\text{-}4_A$), 2.98 (dd, *J* = 12.5 and 2.3 Hz, 1H, $H\text{-}4_B$),1.50

and 1.33 [s, 6H, C (CH_3)$_2$], 1.28 (t, *J* = 7.0 Hz, -CH_2CH_3).

Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.71; H, 7.41; N, 4.67.

5(*R,S*)-Acetoxy-3-[(1'*R*,2'*R*,3'*S*,4'*R*)-1',2'-*O*-isopropylidene-3'-*O*-methyl-tetrahydrofuranos-4'-yl]-2-isoxazoline (8). Colourless oil, Rf 0.60 (hexane:ethyl acetate, 4:1); $[\alpha]_D^{25}$ – 38.6° (*c* 0.21, $CHCl_3$), MS (FAB) = m/z 302 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 2992, 2258, 1775, 1635, 1564, 1458, 1379; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.68 (dd, *J* = 6.4 and 1.4 Hz, 1H, H-5), 5.98 (d, *J* = 3.6 Hz, 1H, H-1'), 5.16 (d, *J* = 3.3 Hz, 1H, H-4'),4.63 (d, *J*=3.6 Hz, 1H, diastereomeric H-2), 3.93 (d, *J* =3.3 Hz, 1H, diastereomeric H-3'), 3.41 and 3.35 (s, 3H, diastereomeric -OCH_3), 3.26 (dd, *J* = 6.4 and 1.4 Hz, 1H, H-4_A) 3.16 (dd, *J* = 16.6 Hz, 1H, H-4_B) 2.05 (s, 3H, -$COCH_3$), 1.51 and 1.34 [s, 6H, C (CH_3)$_2$].

Anal. Calcd for $C_{13}H_{19}NO_7$: C, 51.82; H, 6.36; N, 4.65. Found: C, 52.12; H, 6.47; N, 4.44.

5(*R,S*)-Acetyl-3-[*(1'R,2'R,3'S,4'R)*-1',2'-*O*-isopropylidene-3'-*O*-methyl-tetrahydrofuranos-4'-yl]-2-isoxazoline (9). Colourless oil, Rf 0.70 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{25}$ –34.7° (*c* 0.375, $CHCl_3$), MS (FAB) = m/z 286 $(M+H)^+$; IR (Neat) : ν_{max} cm^{-1} 2988, 2362, 1722, 1627, 1438, 1376; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.96 (d, *J* = 3.7 Hz, 1H, H-1'), 5.10 (d, *J* = 3.5Hz, 1H, diastereomeric H-4'), 4.85 (m, 1H, H-5), 4.61 (d, *J* = 3.7 Hz, 1H, diastereomeric H-2'), 3.89 (d, *J* = 3.5 Hz, 1H, diastereomeric H-3'), 3.41 (s, 3H, OCH_3), 3.34 (m, 2H, H-4), 2.26 (s, 3H, $COCH_3$), 1.50 and 1.34 [s, 6H, $C(CH_3)_2$].

Anal. Calcd for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.97; H, 6.91; N, 4.83.

5(*R,S*)-Cyanomethyl-3-[(1'R,2'R,3'S,4'R)-1',2'-*O*-isopropylidene-3'-*O*-methyl-tetrahydrofuranos-4'-yl]-2-isoxazoline (10). Colourless oil, Rf 0.55 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{25}$ –21.0° (*c* 0.25, $CHCl_3$), MS (FAB) = m/z 269 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 2933, 2950, 2845, 2362, 1638, 1453, 1383; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.97

(d, *J* = 3.6 Hz, 1H, H-1'), 5.21 (m, 1H, H-5), 5.17 (d, *J* = 3.6 Hz, 1H, H-4'), 4.64 (d, *J* = 3.6 Hz, 1H, H-2'), 3.95 (d, *J* = 3.6 Hz, 1H, H-3'), 3.49 (m, 2H, H-4), 3.45 (s, 3H, OCH_3), 1.51 and 1.35 [s, 6H, C $(CH_3)_2$].

Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.58; H, 6.70; N, 9.78.

5(*R,S*)-Bromomethyl-3-[*(1'R, 2'R, 3'S, 4'R)*-1',2'-*O*-isopropylidene-3'-*O*-methyl-tetrahydrofuranos-4'-yl]-2-isoxazoline (11). Colourless oil, Rf 0.60 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{25}$ +3.4° (*c*0.4125, $CHCl_3$), MS (FAB) = m/z 336 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 2984, 2937, 2367, 1623, 1442, 1378; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.98 (d, *J* = 3.7 Hz, 1H, diastereomeric H-1'), 5.09 (d, *J* = 3.6 Hz, 1H, H-4'), 4.82 (m, 1H, H-5), 4.62 (d, *J* =3.7 Hz, 1H, diastereomeric H-2'), 3.90 and 3.95 (d, *J* = 3.6 Hz, 1H, diastereomeric H-3'), 3.56, 3.40 (s, 3H, diastereomeric -OCH_3), 3.30 (m, 2H, H-4), 1.50, 1.48, 1.34 and 1.32 [s, 6H, C $(CH_3)_2$]; ^{13}C NMR ($CDCl_3$): δ 157.4 (C=N); 112.2 [$C(CH_3)_2$]; 105.9, 105.7 (C-1'); 87.5 (C-5), 84.8 (C-2'); 81.9, 81.8 (C-4'); 79.5, 76.3 (C-3'); 59.2 and 58.3 (-OCH_3), 40.7 (C-4); 33.2 (CH_2Br), 27.3, 27.2 and 26.5 [>$C(CH_3)_2$].

Anal. Calcd for $C_{12}H_{18}BrNO_5$: C, 42.87; H, 5.40; N, 4.17. Found: C, 43.12; H, 5.71; N, 4.02.

5(*R,S*)-(2-Hydroxy phenylmethyl)-3-[(1'R, 2'R, 3'S, 4'R)-1',2'-*O*-isopropylidene-3'-*O*-methyl-tetrahydrofuranos-4'-yl]-2-isoxazoline (12). Colourless oil, Rf 0.65 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{25}$ –34.2° (*c* 0.275, $CHCl_3$); MS (FAB) = m/z 350 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 3404, 2936, 2364, 1599, 1454, 1376, 1220; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.12 (m, 4H, ArH), 5.97 (d, *J* = 3.8 Hz, 1H, H-1'), 5.08 (m, 1H, H-5), 4.84 (d, *J* = 3.6 Hz, 1H, H-4'), 4.60 (d, *J*=3.8 Hz, 1H, H-2'), 3.87 (d, *J* = 3.6 Hz, 1H, H-3'), 3.46 (dd, *J* = 5.1 and 1.4 Hz, 2H, CH_2Ar), 3.40 (s, 3H, OCH_3), 3.33 (m, 2H, H-4), 1.49, 1.45, 1.35 and 1.30 [s, 6H, diastereomeric $C(CH_3)_2$].

Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 62.09; H, 6.92; N, 3.97.

5(*R,S*)-(4-Methoxy phenylmethyl)-3-[(1'R, 2'R, 3'S, 4'R)-1',2'-*O*-isopropylidene-3'-*O*-methyl-tetrahydrofuranos-4'-yl]-2-isoxazoline (13). Colourless oil, Rf 0.65 (hexane:ethyl acetate, 3:1); $[\alpha]_D^{25}$ – 17.6° (*c* 0.375, $CHCl_3$), MS (FAB) = m/z 364 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 2987, 2936, 1612, 1514, 1458, 1377; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.14 and 6.84 (d, *J* = 6.6 Hz, 2H, ArH), 5.94 (d, *J* = 3.7 Hz, 1H, H-1'), 5.07 (d, *J* = 3.4Hz, 1H, H-4'), 4.70 (m, 1H, H-5), 4.59 (d, *J*=3.7 Hz, 1H, H-2'), 3.87 (d, *J* = 3.4 Hz, 1H, H-3'), 3.78 (s, 3H, -ArOCH$_3$), 3.35 (s, 3H, -OCH$_3$), 2.98 (m, 2H, ArCH$_2$), 2.84 (m, 2H, H-4), 1.50 and 1.33 [s, 6H, C (CH$_3$)$_2$].

Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.98; H, 7.19; N, 3.61.

5(*R,S*)-Hydroxymethyl-3-[('1*R*,2'*R*,3'*S*,4'*R*)-1',2'-*O*-isopropylidene-3-*O*-methyl-tetrahydrofuranos-4'-yl]-2-isoxazoline (14). Colourless oil, Rf 0.35 (hexane:ethyl acetate, 3:2); $[\alpha]_D^{25}$ –76.1° (*c* 0.3625, $CHCl_3$), MS (FAB) = *m/z* 274 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} ^1H NMR ($CDCl_3$, 200 MHz): δ 5.98 (d, *J* = 3.7 Hz, 1H, H-1'), 5.09 (d, *J* = 3.3 Hz, 1H, diastereomeric H-4'), 4.80 (m. 1H, H-5), 4.62 (d, *J* = 3.7 Hz, 1H, H-2'), 3.90 (d, *J* = 3.5 Hz, 1H, H-3'), 3.72 (dd, *J* = 13.6 and 2.9 Hz, -CH$_A$OH), 3.58 (dd, *J* = 13.6 and 5.4 Hz, -C*H*$_B$OH), 3.39 (s, 3 H, -OCH$_3$), 3.18 (dd, *J* = 18.0 and 10.8 Hz, -H-4$_A$), 2.95 (dd, *J* = 18.0 and 8.0 Hz, H-4$_B$), 1.51 and 1.34 [s, 6H, C(CH$_3$)$_2$].

Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.96; H, 7.32; N, 5.01.

5(*R,S*)-Carboxy-3-[(1'*R*,2'*R*,3'*S*,4'*R*)-1',2'-*O*-isopropylidene-3'-*O*-methyl-tetrahydrofuranos-4'-yl]-2-isoxazoline (15). Colourless oil, Rf 0.40 (hexane:ethyl acetate, 1:1); $[\alpha]_D^{25}$ -41º (*c* 0.4, $CHCl_3$), MS (FAB) = m/z 302 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 3352, 2937, 2362, 1769, 1709, 1658, 1622, 1447, 1378; ^1H NMR ($CDCl_3$, 200 MHz): δ 9.76 (bs, exchangeable with D_2O, 1H, -COOH), 7.22 (m, 1H, H-5), 5.99, 5.91 (d, *J* = 3.6 Hz, 1H, diastereomeric H-1'), 4.84 (d, *J* = 3.3 Hz, 1H, H-4'), 4.59 (d, *J* = 3.6 Hz, 1H, H-2'), 4.13 (d, *J*= 3.3 Hz, 1H, H-3'), 3.43 (s, 3H, -OCH$_3$), 1.95 (d, *J* = 6.9 Hz, 3H, CH$_3$), 1.81 (m, 1H, H-4) 1.49 and 1.33 [s, H, C(CH$_3$)$_2$].

Anal. Calcd for $C_{13}H_{19}NO_7$: C, 51.82; H, 6.36; N, 4.65. Found: C, 52.07; H, 6.54; N, 4.48.

5(*R,S*)-carbethoxy-3-[(1'*R*,2'*R*,3'*S*,4'*R*)-3'-*O*-Benzyl-1',2'-*O*-isopropylidene-tetrahydrfuranos-4'-yl]-2-isoxazoline (16). Colourless oil, Rf 0.70 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{25}$ +30.5° (*c* 0.4, $CHCl_3$), MS (FAB)= m/z 392 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 2986, 2361, 1745, 1620, 1448, 1377, 1215. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.32 (m, 5H, ArH) 5.99 (d, *J* = 3.7 Hz, 1H, H-1'), 5.15 (d, *J*= 3.2 Hz, 1H, H-4'); 4.93 (t, *J* = 9.3 Hz, 1H, H-5) 4.57 (m, 2H, OCH_APh and H-2'), 4.17 (m, 4H, $-OCH_2$, OCH_BPh and H-3'); 3.40 (m, 2H, H-4); 1.49 and 1.32 [each s, each 3H, C $(CH_3)_2$], 1.25 (t, *J* = 7.1 Hz, $-OCH_2CH_3$).^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.6 (C=O), 157.3 and 156.7 (C=N); 137.3, (ArC), 129.0, 128.9, 128.5, 128.4, 128.0 (ArCH), 112.7 [$C(CH_3)_2$]; 105.7 (C-1'); 85.3 (C-2'); 84.8 (C-4'); 82.6, 82.57 (C-3); 72.8 ($-OCH_2Ph$), 62.2, 62.0 ($-OCH_2$), 40.6, 40.5 (C-4); 27.2, 26.7 [$>C(CH_3)_2$], 14.5 (CH_3).

Anal. Calcd for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.58. Found: C, 61.64; H, 6.57; N, 3.32.

5(*R,S*)-Ethoxy-3-[*(1'R,2'R,3'S,4'R)*-3'-*O*-Benzyl-1',2'-*O*-isopropylidene-tetrahydrofuranos-4'-yl]2-isoxazoline (17). Colourless oil, Rf 0.65 (hexane:ethyl acetate, 3:1); $[\alpha]_D^{20}$ –23.8º (*c* 0.275, $CHCl_3$), MS (FAB) = m/z 364 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 2981, 2362, 1626, 1456, 1377; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.35 (m, 5H, ArH), 6.00 (d, *J* = 3.1 Hz, 1H, diastereomeric H-1'), 5.54 (m, 1H, diastereomeric H-5), 5.15 (d, *J* = 3.3 Hz, 1H, H-4'), 4.64 (m, 3H, H-2' and $-OCH_2Ph$), 4.13 (d, *J*=3.3 Hz, 1H, H-3'), 3.86 and 3.53 (each m, 2H, $-OCH_2CH_3$), 1.49 and 1.33 [s, 6H, C $(CH_3)_2$].

Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.96; H, 7.11; N, 3.68.

5(*R,S*)-Acetoxy-3-[(1'*R*,2'*R*,3'*S*,4'*R*)-3'-*O*-benzyl-1',2'-*O*-isopropylidene-tetrahydrofuranos-4'-yl]-2-isoxazoline (18). Colourless oil, Rf 0.65 (hexane:ethyl acetate, 3:1); $[\alpha]_D^{25}$ – 38.2° (*c* 0.738, $CHCl_3$), MS (FAB) = m/z 318 $(M-OCOCH_3)^+$; IR (Neat): ν_{max} cm^{-1} 3022, 2937, 1751, 1610, 1456, 1377; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.34 and 7.21 (m, 5H, ArH), 6.66 (m, 1H, H-5), 6.00 (d, *J* = 3.5 Hz, 1H, H-1'), 5.20 (d, *J*

= 3.4 Hz,1H, H-4'), 4.64 (m, 2H, -OCH_APh and H-2'), 4.47 (d, *J* =11.6 Hz, 1H, -OCH_BPh), 4.17 (d, *J* = 3.4 Hz, 1H, H-3'), 3.23 (m, 2H, H-4), 2.03 and 1.90 (s, 3H, diastereomeric $COCH_3$), 1.50 and 1.33 [s, 6H, C (CH_3)$_2$]; ^{13}C NMR ($CDCl_3$): δ 170.4, 169.9 (C=O), 158.0 (C=N); 137.4, 137.1 (ArC), 129.1, 128.9, 128.6, 128.4, 128.2, 128.0, 127.8 (ArCH), 112.8 ad 109.9 [$C(CH_3)_2$]; 105.8, 105.7 (C-1'); 95.8, 95.7 (C-5); 85.2, 84.9 (C-2'), 82.8, 82.6 (C-4'); 76.3, 76.1 (C-3'); 72.9, 72.7 (-OCH_2Ph), 42.8, 42.6 (C-4); 27.3, 26.7 [>$C(CH_3)_2$], 21.4, 21.2 ($COCH_3$).

Anal. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.68; H, 6.32; N, 3.58.

5(*R,S*)-Acetyl-3'-*O*-benzyl-3-[(1'*R*,2'*R*,3'*S*,4'*R*)-1',2'-*O*-isopropylidene-tetrahydrofuranos-4'-yl]-2-isoxazoline (19). Colourless oil, Rf 0.65 (hexane:ethyl acetate, 3:1); $[\alpha]_D^{25}$ – 24.5° (*c* 0.2, $CHCl_3$), MS (FAB) = m/z 362 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 2987, 2935, 2363, 1722, 1624, 1496, 1449, 1377; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.33 and 7.23 (m, 5H, ArH), 6.00 (d, *J* = 3.7 Hz, 1H, H-1'), 5.12 (m, 1H, diastereomeric H-4'), 4.81 (m, 1H, diastereomeric H-5), 4.61 (m, 3H, -OCH_2Ph and H-2'), 4.15, 4.13 (d, *J* = 3.6 Hz, 1H, diastereomeric H-3'), 3.29 (m, 2H, H-4), 2.25, 2.13 (s, 3H, diastereomeric $COCH_3$), 1.50 and 1.33 [s, 6H, C (CH_3)$_2$].

Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88. Found: C, 63.44; H, 6.71; N, 3.64.

5(*R,S*)-cyanomethyl-3-[*(1'R, 2'R, 3'S, 4'R)*-3'-*O*-Benzyl-1',2'-*O*-isopropylidene-tetrahydrofuranos-4'-yl]-2-isoxazoline (20). Colourless oil, Rf 0.60 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{25}$ –21.9° (*c* 0.4875, $CHCl_3$), MS (FAB) = m/z 345 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 2988, 2936, 2364, 1620, 1453, 1379, 1314, 1218; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.35 and 7.22 (m, 5H, ArH), 6.00 (d, *J* = 3.7 Hz, 1H, H-1'), 5.18 (d, *J* = 3.5 Hz, 1H, diastereomeric H-4'), 5.08 (t, *J* = 8.5 Hz, 1H, H-5), 4.65 (m, 2H, H-2 and –OCH_BPh), 4.46 (d, *J*=11.6 Hz, 1H, -OCH_APh), 4.17 (d, *J* = 3.5 Hz, 1H, H-3'), 3.51 and 3.44(d, 2H, H-4), 1.51 and 1.34 [each s, each 3H, $C(CH_3)_2$]; ^{13}C NMR ($CDCl_3$): δ, 157.9 (C=N); 136.7 (Ar-C), 129.2, 128.8, 128.6, 128.0 (Ar-CH), 117.0 (C≡N), 112.9 [$C(CH_3)_2$]; 105.9 (C-1'); 85.4, 84.8 (C-4'); 83.4 (C-2'); 76.1, 75.7 (C-3');73.1, 72.9 (-OCH_2Ph), 66.3, 66.2

(C-5), 42.3 (C-4); 27.3, and 26.7 [>C(CH_3)$_2$].

Anal. Calcd for $C_{19}H_{22}N_2O_5$: C, 63.67; H, 6.19; N, 7.82. Found: C, 63.89; H, 6.34; N, 7.66.

5(*R,S*)-Bromomethyl-3-[*(1'R,2'R,3'S,4'R)*-3'-*O*-Benzyl-1',2'-*O*-isopropylidene-tetrahydrofuranos-4'-yl]-2-isoxazoline (21). Colourless oil. Rf 0.65 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{25}$ +3.2 (*c* 0.98, $CHCl_3$); MS (FAB) = m/z 412 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 2985, 2365, 2144, 1631, 1452, 1377, 1312; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.33 (m, 5H, ArH), 6.01 (d, *J* = 3.6 Hz, 1H, H-1'), 5.13 (d, *J* = 3.5 Hz, 1H, H-4'), 4.80 (m, 1H, H-5), 4.66 (m, *2*H, H-2' and –OCH_APh), 4.50 (d, *J* = 11.6 Hz, 1H, –OCH_BPh), 4.16 (d, *J* = 3.5 Hz, 1H, diastereomeric H-3'), 3.46 (dd, *J* = 10.3 and 4.6 Hz, 1H, H-4_A), 3.23 (m, 3H, H-4_A and CH_2Br), 1.55, 1.50 and 1.30 [s, 6H, $C(CH_3)_2$].

Anal. Calcd for $C_{18}H_{22}BrNO_5$: C, 52.44; H, 5.38; N, 3.40. Found: C, 52.70; H, 5.57; N, 3.32.

5(*R,S*)-(2-Hydroxy phenylmethyl)-3-[(1'*R*, 2'*R*, 3'*S*, 4'*R*)-3'-*O*-Benzyl-1',2'-*O*-isopropylidene-tetrahydrofuranos-4'-yl]-2-isoxazoline (22). Colourless oil, Rf 0.70 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{25}$ –42.5° (*c* 0.15, $CHCl_3$), MS (FAB) = m/z 426 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 3395, 2985, 2366, 1592, 1493, 1456, 1377; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.32 (m, 9H, ArH), 6.60 (s, exchangeable with D_2O, 1H, ArOH), 6.01, 5.97 (d, *J* = 3.8 Hz, 1H, diastereomeric H-1'), 5.07 (d, *J* = 3.5 Hz, 1H, H-4'), 4.87 (m, 1H, H-5), 4.61 (m, 3H, -OCH_2Ph and diastereomeric H-2'), 4.13, 4.08 (d, *J* = 3.5 Hz, 1H, distereomeric H-3), 3.40 (d, *J* = 6.4 Hz, 1H, -CH_APhOH), 3.16 (dd, *J* = 18.8 and 10.2 Hz, 1H, H-4_A) 2.95 (m, 2H, CH_BPhOH and H-4_B), 1.48, 1.47, 1.31 [s, 6H, diastereomeric $C(CH_3)_2$];

Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.96; H, 6.69; N, 3.12.

5(*R,S*)-(4-Methoxyphenylmethyl)-3-[*(1'R,2'R,3'S,4'R)*-3'-*O*-Benzyl-1',2'-*O*-isopropylidene-tetrahydrofuranos-4'-yl]-2-isoxazoline (23). Colourless oil, Rf 0.70 (hexane:ethyl acetate, 3:1); $[\alpha]_D^{25}$ +8.64° (*c* 0.3125, $CHCl_3$), MS (FAB) = m/z 440 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 2994, 2936, 2365, 1612, 1513, 1457, 1378; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.30 and 6.58 (m, 2H, diatereomeric ArH), 5.98 (d, *J* = 3.4 Hz, 1H,

H-1'), 5.12 (d, *J* = 3.6 Hz, 1H, H-4'), 4.65 (m, 3H, H-5, H-2' and -OCH_APh), 4.48 (d, *J* = 11.7 Hz, 1H, -OCH_BPh), 4.16, 4.13 (d, *J* = 3.6 Hz, 1H, diastereomeric H-3), 3.78 and 3.74 (s, 3H, diastereomeric Ar-OCH_3), 3.12-2.57 (m, 4H, CH_2Ar and H-4), 1.58, 1.41 and 1.25 [s, 6H, $C(CH_3)_2$]; ^{13}C NMR ($CDCl_3$): δ, 158.8 and 157.5 (C=N); 137.4 (ArC), 130.69, 129.40, 129.0, 128.6, 128.5, 128.2, 127.9 and 114.4 (ArCH), 112.6 (CMe_2), 105.6 (C-1'), 85.4 , 85.2 (C-2'), 82.7, 82.5 (C-4'), 82.0 (C-3'), 76.8 (C-5), 72.8 (OCH_2Ph), 55.6 (Ar-OCH_3), 40.70 (CH_2-Ar), 40.3 (C-4), 27.28 and 26.73 [$C(CH_3)_2$].

Anal. Calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.54; H, 6.81; N, 3.07.

5(*R,S*)-Hydroxymethyl-3-[(1'*R*,2'*R*,3'*S*,4'*R*)-3'-*O*-Benzyl-1',2'-*O*-isopropylidene-tetrahydrofuranos-4'-yl]-2-isoxazoline (24). Colourless oil, Rf 0.40 (hexane:ethyl acetate, 3:2); $[\alpha]_D^{25}$ -11º (*c* 0.28, $CHCl_3$), MS (FAB) = m/z 350 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 3426, 2934, 2365, 1628, 1454, 1379; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.33, (m, 5H, ArH), 6.01 (d, *J* = 3.3 Hz, 1H, H-1'), 5.10 (d, *J* = 3.3 Hz, 1H, H-4'), 4.67 (m. 3H, H-5, -OCH_APh and H-2'), 4.51 (d, *J* = 11.4 Hz, 1H, -OCH_BPh), 4.15 (d, *J* = 3.3 Hz, 1H, H-3'), 3.58 (dd, *J* = 12.0 and 3.0 Hz, -CH_AOH), 3.46 (dd, *J* = 12.0 and 5.7 Hz, -CH_BOH), 3.09 (dd, *J* = 17.4 and 10.8 Hz, -H-4_A), 2.95 (dd, *J* = 17.4 and 7.8 Hz, H-4_B), 1.50 and 1.34 [s, 6H, $C(CH_3)_2$].

Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 62.06; H, 6.82; N, 3.91.

5(*R,S*)-Carboxy-3-[(1'*R*,2'*R*,3'*S*,4'*R*)-3'-*O*-Benzyl-1',2'-*O*-isopropylidene-tetrahydrofuranos-4'-yl]-2-isoxazoline (25). Colourless oil, Rf 0.45 (hexane:ethyl acetate, 1:1); $[\alpha]_D^{25}$ –27.6° (*c* 0.1375, $CHCl_3$), MS (FAB) = m/z 378 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 3280, 2984, 2933, 2362, 1770, 1708, 1658, 1587, 1481, 1379; ^1H NMR ($CDCl_3$, 200 MHz): δ 9.65 (bs, 1H, exchangeable with D_2O, COOH), 7.31 and 7.23 (m, 5H, ArH), 6.00 (m, 2H, diastereomeric H-5 and H-1'), 4.88 (d, *J* = 3.2 Hz, 1H, H-4'), 4.60 (m, 3H, -OCH_2 and H-2'), 4.37, 4.10 (d, *J* = 3.2 Hz, 1H, diastereomeric H-3'), 1.94 (m, 1H, H-4), 1.47, 1.30 (s, 3H, C $(CH_3)_2$], 1.27 (d, *J* = 6.9 Hz, 3H, CH_3).

Anal. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.47; H, 6.14; N, 3.71.

5(*R,S*)-Ethoxy-3-[*(1'R,2'R,3'S,4'R)*-1',2':3',4'-di-*O*-isopropylidene-tetrahydropyranos-5'-yl]-2-isoxazoline (26). Colourless oil; Rf 0.65 (hexane:ethyl acetate, 4:1); $[\alpha]_D^{20}$ –60.4º (*c* 0.275, $CHCl_3$); MS (FAB) = m/z 372 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 2980, 2939, 2365, 1745, 1631, 1445, 1377, 1223; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.54 (d, *J* = 4.9 Hz, 1H, H-1'), 5.10 (m, 1H, H-5'), 4.82 (m, 1H, H-5), 4.34 (dd, *J* = 7.7 and 2.3 Hz, 1H, H-3'), 4.33 (m, 4H, $-OCH_2$, H-2' and H-4'), 3.45 (m, 2H, H-4), 1.55, 1.46, 1.34 and 1.33 [s, 12H, $C(CH_3)_2$], 1.30 (t, *J* = 7.1 Hz, 3H, CH_3).

Anal. Calcd for $C_{17}H_{25}NO_8$: C, 54.98; H, 6.79; N, 3.77. Found: C, 55.22; H, 6.95; N, 3.58.

5(*R,S*)-(2-Hydroxy phenylmethyl)-3-[(1'*R*, 2'*R*, 3'*R*, 4'*S*) 1',2':3',4'-di-*O*-isopropylidene-tetrahydropyranos-5'-yl]-2-isoxazoline (27). Colourless oil; Rf 0.65 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{20}$ –23.6º (*c* 0.2875, $CHCl_3$); MS (FAB) = m/z 405 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 3467, 2985, 2362, 1747, 1597, 1455, 1374; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.03 (m, 2H, ArH), 6.86 (m, 2H, ArH), 6.70 (bs, 1H, ArOH), 5.65 (m, 1H, H-5), 5.55 (d, *J* = 4.7 Hz, 1H, diastereomeric H-1'), 4.62 (m, 2H, H-5' and H-3'), 4.31 (m, 4H, H-2', H-4' and CH_2Ar)), 3.09 (m, 2H, H-4), 1.51, 1.43 and 1.31 [s, 12H, $C(CH_3)_2$].

Anal. Calcd for $C_{21}H_{27}NO_7$: C, 62.21; H, 6.71; N, 3.45. Found: C, 62.31; H, 6.88; N, 3.39.

5(*R,S*)-(Hydroxymethyl)-3-[(1'*R*,2'*R*,3'*R*,4'*S*)-1',2':3',4'-tetrahydropyranos-5'-yl]-2-isoxazoline (28). Colourless solid Mp 124 °C; Rf 0.35 (hexane:ethyl acetate, 7:3); $[\alpha]_D^{25}$ –76.1º (*c* 0.3625, $CHCl_3$); MS (FAB) = m/z 330 $(M+H)^+$; IR (Neat): ν_{max} cm^{-1} 3469, 2985, 2929, 2362, 1744 1599, 1446, 1379; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.55 (d, *J* = 4.9 Hz, 1H, H-1'), 4.67 (m, 3H, H-5, H-5' and H-3'), 4.34 (m, 2H, H-2', and H-4'), 3.66 (m, 2H, diastereomeric C*H*$_2$OH), 3.23 (dd, *J* = 17.5 and 10.4 Hz, 1H, H-4_A), 2.94 (dd, *J* = 17.5 and 7.4 Hz, 1H, H-4_B), 1.55, 1.46 and 1.34 [s, 12H, $C(CH_3)_2$]. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.3 (C=N); 109.6, 108.9 [$C(CH_3)_2$]; 96.1 (C-1'); 80.4 (C-2'); 73.6, 73.5 (C-4'); 70.6 (C-3'); 70.2 (C-5'), 72.8 (C-5'), 64.8 (C-5), 63.7 (CH_2OH), 37.0 (C-4); 25.9,

25.8, 24.7 and 24.2 [>C(CH_3)$_2$].

Anal. Calcd for $C_{15}H_{23}NO_7$: C, 54.70; H, 7.04; N, 4.25. Found: C, 54.99; H, 7.23; N, 4.17.

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