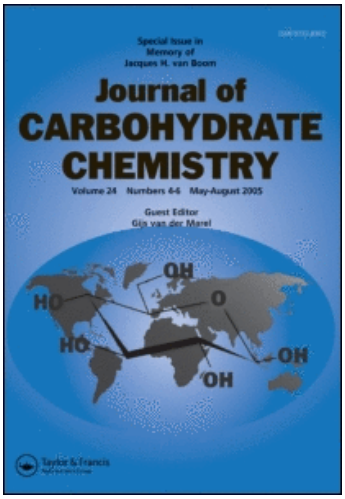

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Báñez, J. M. Sanz , López, J. A. Sastre , Patiño, M. R. Molina , Santacana, T. Gómez and García, C. Romero-Ávila(1999) 'Synthesis of 3-Aryl-5-*C*-Glycosylisoxazoles from Several Aldehydo-Sugar Derivatives', Journal of Carbohydrate Chemistry, 18: 4, 403 — 417

To link to this Article: DOI: 10.1080/07328309908544005

URL: http://dx.doi.org/10.1080/07328309908544005

J. CARBOHYDRATE CHEMISTRY, 18(4), 403–417 (1999)

SYNTHESIS OF 3-ARYL-5-*C*-GLYCOSYLISOXAZOLES FROM SEVERAL ALDEHYDO-SUGAR DERIVATIVES

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Received July 19, 1998 - Final Form March 12, 1999

ABSTRACT

The synthesis of several 3-aryl-5-glycosylisoxazole derivatives has been achieved. By condensation of the protected aldehydo-sugars 2,3-*O*-isopropylidene-D-glyceraldehyde (**1**), 2,3:4,5-di-*O*-isopropylidene-aldehydo-D-arabinose (**2**) and D-xylose (**3**), and 2,5-anhydro-3,4,5-tri-*O*-benzoyl-D-mannose (**4**) with benzoylmethylenetriphenylphosphorane, enulose derivatives were formed, which were later converted into a,ß-unsaturated ketoximes. These ketoximes were oxidatively cyclized with iodine and, after removal of the hydroxyl protecting groups, 3-phenyl-5-glycosylisoxazoles were formed.

INTRODUCTION

Isoxazoles have served as important building blocks in the construction of new molecule systems for several reasons. First, they can be very efficiently prepared from readily available precursors; second, they can be conveniently modified, thus allowing the transformation of molecules with simple structure into functionally complex derivatives; third, the isoxazole ring survives under a variety of chemical reactions, permitting an easy manipulation of other parts of the molecule; and finally, the lability of the nitrogen-oxygen

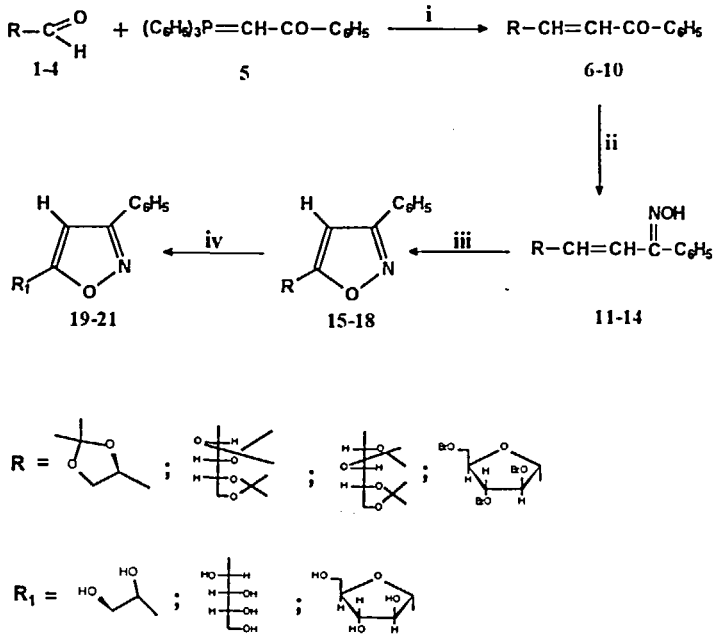
bond to catalytic or chemical reductions under mild conditions unravels a vast array of different functionalities.[1] The most general approach for this kind of compound is probably the cycloaddition of acetylenic derivatives with nitrile oxides generated by a variety of methods.[2] Of these, several have been employed: the dehydrohalogenation of hydroxamyl chlorides[3] and the dehydration of primary nitro paraffins.[4] This method, which utilizes available precursors such as aldehydes and nitro compounds, is more frequently used because of the difficult accessibility to acetylenic compounds. However, the use of the easily available alkenes,[5] instead of alkynes, is possible followed by a transformation into Δ^2-isoxazolines derivatives,[6] later converted into the corresponding isoxazoles by dehydrogenation.

Isoxazole derivatives are also obtained from *O*-stannylated aldoximes used as key intermediates[7] from aliphatic and aromatic nitrile oxides,[8] by reaction of terminal alkynes with nitric acid in the presence of a catalytic amount of ammonium tetrabutyl tetrachloroaurate,[9] from furanone glycoside,[10] or by cyclization of an intermediate which contains all of the five atoms of the isoxazole ring, whose substituents in the resulting isoxazole system are unequivocally located.[11] Another general method for isoxazole preparation utilizes β-aminoenones and hydroxylamine.[12] The reaction has been carried out with α-bromoenones, and the synthesis of isomeric isoxazoles could be regiospecifically controlled by changing the base.[13]

At the same time, the natural occurrence of a number of *C*-glycosyl nucleosides, many of which show antiviral or antitumoral activity, has provided a lot of research on this type of compound.[14] The isolation of a number of nucleoside antibiotics[15,16] such as formycin, pyrazofurin and showdomycin, has stimulated much interest in the synthesis of *C*-glycosyl nucleosides.

RESULTS AND DISCUSSION

In a previous work,[17a] the synthesis of 3-alkyl-, 3-aryl, 3,4-dialkyl-, 3-aryl-4-alkyl- and 3-alkyl-4-bromo-5-glycosylisoxazoles has been reported. This paper deals with the synthesis of different *C*-glycosylisoxazoles prepared from several aldehydo-sugar derivatives (see scheme 1).

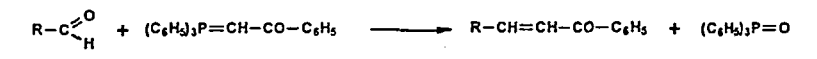


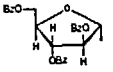
Scheme 1. Reagents and conditions: **i**, CH_2Cl_2, rt; **ii**, $HONH_2$·HCl, Pyridine, MeOH, rt; **iii**, I_2/KI, $NaHCO_3$, THF, reflux; **iv**, AcOH:H_2O (9:1), 90 °C.

The aldehydo-sugars **1-4** were condensed with benzoylmethylenetriphenylphosphorane (**5**) to give the polyhydroxylate chain lengthened by two or three carbon atoms.[17b,c] The aldehydo-sugars 2,3-*O*-isopropylidene-D-glyceraldehyde (**1**), synthesized via the Schmid method,[18] 2,3:4,5-di-*O*-isopropylidene-aldehydo-D-arabinose (**2**), 2,3:4,5-di-*O*-isopropylidene-aldehydo-D-xylose (**3**), and 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-mannose (**4**), obtained from D-arabinose, D-xylose and D-glucosamine hydrochloride, according to methods reported in the literature,[19-23] were used as starting substrates. The a,ß-unsaturated ketones **6-10** were formed according to the conditions of the Wittig[24] reaction between the aldehydo-sugars **1-4** and benzoylmethylenetriphenylphosphorane (**5**).[25]

The condensation reaction of **1** with the ylide **5** yielded two geometric isomers **6** (*Z*) and 7 (*E*) in a ratio of 1:2.5, thus yielding a higher quantity of the *E*-configured isomer. One signal for an olefinic proton appears in the ^{1}H NMR spectrum of **6** at δ 6.48 ($J_{2,3}$ = 11.6, J_{vic} = 1.4, H-2), while the corresponding signal for the *E*-isomer appears at δ 6.93

Table 1. Synthesis of α,β-unsaturated ketones (6-10)



Compound	Configuration	R	$[\alpha]_D$ ($CHCl_3$)	Yield (%)
6	(*Z*)		+268.9° (*c*, 1.33)	24
7	(*E*)		+69.7° (*c*, 1.21)	60
8	(*E*)		+30.3° (*c*, 0.75)	71
9	(*E*)		+26.6° (*c*, 1.13)	62
10	(*E*)		-43.1° (*c*, 2.09)	61

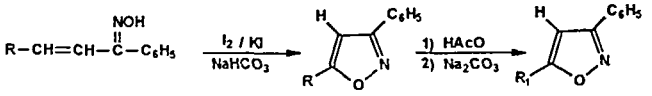
($J_{2,3}$=15.3, J_{vic}=4.5, H-2). Other spectral data are given in the experimental section and are consistent with the structure of **6** and **7**.

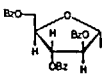
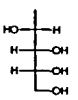
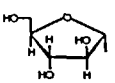
It was observed that with an increasing number of carbons in the open chain aldehydo-sugar the olefinic hydrogen chemical shifts appear at lower fields, with the highest value for compound **10**, in which the signal of the aforementioned hydrogens were found in the field of the aromatic hydrogens (7.23-7.63 ppm).

By treatment of a,ß-unsaturated ketones **6-10** with hydroxylamine hydrochloride in dry methanol at room temperature and using pyridine as base,[26,17a] a,ß-unsaturated ketoximes **11-14** were formed, which were used for the next reaction without further purification.

Oxidative cyclization[27] of the aforementioned oximes **11-14** with iodine, potassium iodide and sodium bicarbonate in tetrahydrofuran yielded 3-aryl-5-glycosylisoxazoles, **15-18**. This reaction occurred in the absence of oxygen, and the reaction times depended on the oxime used. Although the yields increased when an excess of iodine-potassium iodide was used,[28] it was considered that a rather mild basic medium should be used instead of a strong one, in order to avoid elemental iodine forming equilibrium iodide-iodate.

Table 2. *C*-glycosylisoxazole derivatives (15-21)



Compound	R	R_1	$[\alpha]_D$ ($CHCl_3$)	mp (°C)	Yield[a] (%)
15		--	+6.0° (*c*, 1.13)	Syrup	55
16		--	+19.3° (*c*, 1.29)	77-78	49
17		--	-26.2° (*c*, 1.72)	Syrup	45
18		--	+30.5° (*c*, 1.08)	55-56	51
19	--		+30.4° (*c*, 0.62) (acetone)	89-90	95
20	--		+36.0° (*c*, 0.47) (MeOH)	183-184	90
21	--		+63.3° (*c*, 0.55)	Syrup	81

a. isolated product

After removal of the hydroxyl protecting groups,[29,30] *C*-glycosylisoxazoles **19-21** were obtained in nearly quantitative yields. Biological activities of these compounds are currently being investigated.

EXPERIMENTAL

General methods. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium using benzophenone radical as an indicator, and stored under argon before use. Other solvents and reagents were purified and dried according to standard procedures.

Extracts were dried over anhydrous $MgSO_4$ or Na_2SO_4 and solvents evaporated under reduced pressure at 40-50 °C. Reaction courses and product mixtures were monitored as a routine by thin-layer chromatography (TLC) on glass plates coated with silica gel G (Merck), spots being visualised with iodine vapours or by charring with sulfuric acid in ethanol (10 %). Column chromatography was performed using Silica Gel Merck 60 (70-230 mesh, ASTM). Melting points were obtained in open capillary tubes with a Gallenkamp MFB-595 and are uncorrected. Optical rotations were measured with a 141 Perkin-Elmer polarimeter. ^{1}H NMR spectra were recorded with Bruker AC-80 and AC-300 spectrometers. Chemical shift values are expressed in ppm (δ), relative to Me_4Si as the internal reference. J-values are given in Hz. The ^{13}C NMR spectra were recorded with Bruker AC-80 and AC-300 spectrometers. IR spectra were measured using a Nicolet FTIR-20-SX spectrometer. Mass spectra were recorded by the direct-insertion technique, using an HP-588-A spectrometer at 70 eV with a temperature source of 200 °C. Elemental analyses were determined with a Carlo Erba Elemental Analyzer 1106.

Synthesis of starting materials:

2,3-*O*-Isopropylidene-D-glyceraldehyde (1). This was synthetized from 1,2:5,6-di-*O*-isopropylidene-D-mannitol, following Schmid's method.[18]

2,3:4,5-Di-*O*-isopropylidene-aldehydo-D-arabinose (2) and D-xylose (3). From commercial D-arabinose and D-xylose (Fluka), D-arabinose and D-xylose diethyl dithioacetal were respectively synthetized following Zinner's method.[20] From those products, 2,3:4,5-di-*O*-isopropylidene-D-arabinose and D-xylose diethyl dithioacetal were obtained following the method reported in the literature,[21] and were demercaptalized as described[23] to give 2,3:4,5-di-*O*-isopropylidene-aldehydo-D-arabinose and D-xylose, **2** and **3**, respectively.

3,4,6-Tri-*O*-benzoyl-2,5-anhydro-D-mannose (4). By procedures found in the literature,[19] 2,5-anhydro-D-mannose was prepared from D-glucosamine hydrochloride, and was transformed into 2,5-anhydro-D-mannose diethyl dithioacetal[20] and, after benzoylation, into 3,4,6-tri-*O*-benzoyl-2,5-anhydro-D-mannose diethyl dithioacetal.[22] By demercaptalization,[23] 3,4,6-tri-*O*-benzoyl-2,5-anhydro-aldehydo-D-mannose, **4**, was obtained.

Benzoylmethylenetriphenylphosphorane (5). This compound was prepared as described in the literature.[25]

Reactions of aldehydo-sugar derivatives, 1-4, with benzoylmethylenetriphenylphosphorane, 5. The condensation reactions of the aldehydo-sugar derivatives, **1-4,** with benzoylmethylenetriphenylphosphorane, **5**, were carried out as previously indicated.[17a,31]

(*Z* and *E*)-1-*C*-Phenyl-2,3-dideoxy-4,5-*O*-isopropylidene-D-*glycero*-pent-2-enose (6 and 7). A solution of **1** (1.47 g, 0.011 mol) in methylene chloride (30 mL) was slowly added to a stirred solution of **5** (5.51 g, 0.015 mol) in the same solvent (10 mL). The mixture was maintained for 6 h at room temperature and the solvent was evaporated. The residue was chromatographed on a silica gel column (hexane-diethyl ether 9:1), to yield **6** (0.62 g, 24 %) and **7** (1.57 g, 60 %) as yellow syrups.

Data of **6**: R_f 0.7 (hexane-diethyl ether 1:1); IR (KBr) 3000 (C=C), 2900-2850 (C-H), 1670 (C=O), 1620 (C=C), 1380-1370 ($C(CH_3)_2$), 1230-1010 (C-O-C-O-C), 750 (C=C, *Z*), 760-690 (Ar); ^{1}H NMR ($CDCl_3$) δ 1.40 and 1.48 (6H, 2s, $C(CH_3)_2$), 3.69 (1H, dd, $J_{5,5'}$ = 8.3, $J_{5,4}$ = 6.8, 5-H), 4.53 (1H, dd, $J_{5',5}$ = 8.3, $J_{5',4}$ = 7.1, 5'-H), 5.37 (1H, ddd, $J_{4,5}$ = 6.8, $J_{4,5'}$ = 7.1, $J_{4,3}$ = 6.4, 4-H), 6.48 (1H, dd, $J_{2,3}$= 11.6, J_{vic} = 1.4, 2-H), 6.97 (1H, dd, $J_{3,2}$ = 11.6, $J_{3,4}$ = 6.4, 3-H), 7.38-7.57 (3H, m, Ar), 7.85-8.00 (2H, m, ArH); *m/z* 232 (1 %, M^+), 174 (2), 145 (1), 127 (34, $C_7H_{11}O_2^+$), 105 (77, $C_7H_5O^+$), 77 (98, $C_6H_5^+$), 69 (100) and 43 (94, $C_2H_3O^+$).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.45; H, 6.92.

Data of **7**: R_f 0.5 (hexane-diethyl ether 1:1); IR (KBr) 3070 (C=C), 2900-2800 (C-H), 1675 (C=O), 1625 (C=C), 1380-1370 ($C(CH_3)_2$), 1250-1060 (C-O-C-O-C), 920 (C=C, *E*), 760 (Ar); ^{1}H NMR ($CDCl_3$) δ 1.45 and 1.49 (6H, 2s, $C(CH_3)_2$), 3.73 (1H, dd, $J_{5,5'}$ = 8.2, $J_{5,4}$ = 7.3, 5-H), 4.24 (1H, dd, $J_{5',5}$ = 8.2, $J_{5,4}$ = 6.6, 5'-H), 4.80 (1H, ddd, $J_{4,5'}$ = 6.6, $J_{4,5}$ = 7.3, $J_{4,3}$ = 4.5, 4-H), 6.93 (1H, dd, $J_{2,3}$ = 15.3, J_{vic} = 4.5, 2-H), 7.23 (1H, dd, $J_{3,2}$ = 15.3, $J_{3,4}$ = 4.5, 3-H), 7.39-7.56 (3H, m, ArH), 7.88-8.02 (2H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 25.20 and 26.45 ($C(CH_3)_2$), 69.51 (C-5), 74.41 (C-4), 109.60 ($C(CH_3)_2$), 124.40 (C-2), 128.31, 128.54 and 133.01 (CHAr), 137.34 (CAr), 148.95 (C-3), 190.41 (CO); *m/z* 217 (17 %, M^+-15), 202 (6, M^+-30), 175 (10, $(M+1)^+$-C_3H_6O), 144 (32), 131 (19, $C_9H_7O^+$), 105 (54, $C_7H_5O^+$), 77 (60, $C_6H_5^+$) and 43 (100, $C_2H_3O^+$).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.43; H, 6.97.

(*E*)-1-*C*-Phenyl-2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-D-*arabino*-hept-2-enose (8). 2,3:4,5-di-*O*-isopropylidene-aldehydo-D-arabinose, (**2**, 3.1 g, 13.48 mmol) in

anhydrous methylene chloride (60 mL) was treated with a stirred solution of **5** (7.68 g, 20.21 mmol) in the same solvent (20 mL). The mixture was maintained for 26 h at room temperature and concentrated as described in the general procedure. The residue was chromatographed (hexane-diethyl ether 9:1). The isolated compound **8** (2.77 g, 62 %) was a yellow solid: mp 45-46 °C; R_f 0.5 (hexane-diethyl ether 1:1); IR(KBr) 3000 (C=C), 2900-2850 (C-H), 1670 (C=O), 1630 (C=C), 1380-1370 $C(CH_3)_2$, 1270-1060 (C-O-C-O-C), 980 (C=C, *E*), 760-700 (Ar); ^{1}H NMR ($CDCl_3$) δ 1.35, 1.40 and 1.46 (12H, 3s, $2C(CH_3)_2$), 3.65-4.20 (4H, m, 5,6,7,7'-H), 4.67 (1H, dd, $J_{4,5}$ = 7.6, $J_{4,3}$ = 3.2, 4-H), 7.16 (2H, m, 2,3-H), 7.39-7.60 (3H, m, ArH), 7.91-8.03 (2H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 24.97 and 26.56 ($2(CH_3)_2$), 67.37 (C-7), 75.30 (C-6), 79.35 (C-5), 81.06 (C-4), 109.68 and 110.02, ($2C(CH_3)_2$), 124.95 (C-2), 128.38 and 132.70 (CHAr), 137.43 (CAr), 144.68 (C-3), 190.05 (CO); *m/z* 332 (4 %, M^+), 317 (6, M^+-15), 274 (6, M^+-C_3H_6O), 232 (14, M^+-$C_5H_8O_2$), 216 (14), 169 (66), 126 (3), 105 (100, $C_7H_5O^+$), 77 (59, $C_6H_5^+$) and 43 (76, $C_2H_3O^+$).

Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.70; H, 7.25.

(*E*)-1-*C*-Phenyl-2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-D-*xylo*-hept-2-enose (9). Compound **3**, (3.08 g, 13.39 mmol) was dissolved in anhydrous methylene chloride (62 mL), and subsequently treated with a stirred solution of **5** (5.09 g, 13.39 mmol) in the same solvent (20 mL). The mixture was maintained at room temperature for 24 h following the procedure previously described. The residue was chromatographed (hexane-diethyl ether 4:1) to give compound **9** (2.71 g, 61 %) as a yellow syrup: R_f 0.3 (hexane-ethyl acetate 2:0.5); IR(KBr) 3000 (C=C), 2950-2850 (C-H), 1670 (C=O), 1625 (C=C), 1380-1370 ($C(CH_3)_2$), 1280-1070 (C-O-C-O-C), 980 (C=C, *E*), 780-690 (Ar); ^{1}H NMR ($CDCl_3$) δ 1.39, 1.42 and 1.48 (12H, 3s, $2C(CH_3)_2$), 3.85-4.29 (4H, m, 5,6,7,7'-H), 4.63 (1H, ddd, $J_{4,5}$ = 7.7, $J_{4,3}$ = 4.7, J_{vic} = 0.9, 4-H), 6.94 (1H, dd, $J_{2,3}$ = 15.3, J_{vic} = 0.9, 2-H), 7.17 (1H, dd, $J_{3,2}$ = 15.3, $J_{3,4}$ = 4.7, 3-H), 7.45-7.59 (3H, m, ArH), 7.90-8.02 (2H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 25.45, 26.17 and 26.86 ($2(CH_3)_2$), 65.62 (C-7), 74.48 (C-6), 77.03 (C-5), 80.46 (C-4), 109.95 and 110.49 ($2C(CH_3)_2$), 126.43 (C-2), 128.66-133.11 (CHAr), 137.43 (CAr), 143.62 (C-3), 189.87 (CO); *m/z* 332 (0.2 %, M^+), 317 (16, M^+-15), 274 (4, M^+-C_3H_6O), 232 (2), 202 (24, $C_{10}H_{18}O_4^+$), 157 (8), 144 (100), 105 (71, $C_7H_5O^+$), 101 (45, $C_5H_9O_2^+$), 77 (26, $C_6H_5^+$) and 43 (48, $C_2H_3O^+$).

Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.73; H, 7.22.

(*E*)-1-*C*-Phenyl-4,7-anhydro-5,6,8-tri-*O*-benzoyl-2,3-dideoxy-D-*manno*-oct-2-enose (10). This experiment was carried out following the aforementioned procedure by reaction of **4** (3.23 g, 6.8 mmol) and **5** (5.52 g, 11.9 mmol) in methylene chloride (60 mL). The residue was chromatographed (methylene chloride-hexane 10:1), to give **10** (2.8 g, 71 %) as a colorless syrup: R_f 0.3 (hexane-diethyl ether 2:1); $[\alpha]_D$ + 28° (*c* 1.42, acetone), $[\alpha]_D$ + 30.3° (*c* 0.75, $CHCl_3$); IR(KBr) 3010 (C=C), 2800 (C-H), 1720 (COO), 1670 (C=O), 1625 (C=C), 1270-1110 (C-O), 970 (C=C, *E*), 750-710 (Ar); ^{1}H NMR ($CDCl_3$) δ 4.73-4.79 (3H, m, 4',5', 5''-H), 5.15 (1H, s, 1'-H), 5.61-5.63 (1H, m, 3'-H), 5.75 (1H, s, 2'-H), 7.23-7.63 (14H, m, 2,3-H and 12H (ArH)), 7.95-8.13 (8H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 64.04 (C-5'), 78.75 (C-1'), 81.31 (C-2'), 82.48 (C-3'), 83.47 (C-4'), 125.99 (C-2), 128.41-133.75 (CHAr and CAr), 137.30 (CAr), 143.11 (C-3), 165.34, 165.53 and 166.27 (COO), 190.00 (CO).

Anal. Calcd for $C_{35}H_{28}O_8$: C, 72.91; H, 4.89. Found: C, 72.96; H, 4.85.

Synthesis of α,β-unsaturated ketoximes. A solution of hydroxylamine hydrochloride (0.92 g, 13.2 mmol) in methanol (20 mL) was added to a stirred solution of α,ß-unsaturated ketones, **6-10** (1.77g 5.33 mmol) in pyridine (33 mL) and methanol (90 mL).[26,17a] The solution was stirred at room temperature for a period of two or three hours, the crude of the reaction was coevaporated repeatedly with toluene and the residue, oximes **11-14**, with characteristic absorptions between 3450-3300 (N-OH), 1680-1600 (C=N) and 1620-1590 (C=C), were used directly, without any purification, for the formation of *C*-glycosylisoxazole derivatives.

Synthesis of isoxazole derivatives by cyclization of α,β-unsaturated ketoximes. To a solution of a α,ß-unsaturated ketoxime in methanol and THF, a solution of sodium bicarbonate with iodine and potassium iodide was added.[27,17a] The reaction was carried out in darkness and maintained at reflux for a period of time. A saturated solution of sodium bisulfite was added to eliminate the excess of iodine. Once the organic layer was separated, the aqueous phase was extracted three times with diethyl ether (30 mL). The organic extracts were dried with anhydrous sodium sulfate, and the solvent was evaporated at reduced pressure, obtaining a syrup later purified by column chromatography.

3-Phenyl-5-(1,2-*O*-isopropylidene-D-*glycero*-dihydroxyethyl)isoxazole (15). A solution of potassium iodide (4.38 g, 26.4 mmol) and iodine (2.1 g, 8.27 mmol) in water

(45 mL) was added in the darkness to a stirred solution of compound **11**, (1.86 g, 7.54 mmol) and sodium bicarbonate (2.53 g, 30.12 mmol), in a mixture of tetrahydrofuran (30 mL) and water (23 mL). Following the previously described procedure, a residue was obtained which was chromatographed (chloroform-ethyl acetate 50:1), to give compound **15** (1.11, 55 %) as a yellow syrup: R_f 0.7 (hexane-diethyl ether 1:1); IR(KBr) 3020 (C=N, isoxazole), 2900-2800 (C-H), 1607 (C=N, isoxazole), 1475 (C=C, isoxazole), 1380-1370 $C(CH_3)_2$), 1200-1070 (C-O-C-O-C), 690 (Ar); ^{1}H NMR ($CDCl_3$) δ 1.48 and 1.55 (6H, 2s, $C(CH_3)_2$), 4.16 (1H, dd, $J_{2',2''}$ = 8.7, $J_{2',1'}$ = 6.0, 2'-H), 4.39 (1H, dd, $J_{2'',2'}$ = 8.7, $J_{2'',1'}$ = 6.6, 2''-H); 5.26 (1H, t, $J_{1',2'}$ = 6.0, 1'-H), 6.59 (1H, s, 4-H), 7.45-7.47 (3H, m, ArH), 7.79-7.82 (2H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 20.21 and 20.96 ($C(\underline{C}H_3)_2$), 63.14 (C-2'), 65.02 (C-1'); 94.67 (C-4), 105.53 ($\underline{C}(CH_3)_2$) 121.46, 123.56 and 124.72 (CHAr and CAr), 156.94 (C-3), 166.22 (C-5); *m/z* 245 (4 %, M^+), 230 (43, M^+-15), 188 (65), 144 (26, $C_9H_6ON^+$),), 118 (12), 101 (19, $C_5H_9O_2^+$), 77 (62, $C_6H_5^+$) and 43 (72, $C_2H_3O^+$).

Anal. Calcd for $C_{14}H_{15}O_3N$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.49; H, 6.16; N, 5.73

3-Phenyl-5-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetrahydroxybutyl)isoxazole (16). A solution of compound **12** (3.5 g, 10.09 mmol) dissolved in tetrahydrofuran (40 mL) and water (30 mL) containing sodium bicarbonate (3.39 g, 40 mmol) was treated with a solution of potassium iodide (5.86 g, 35 mmol) and iodine (2.82 g, 11.1 mmol) in water (61 mL) following the previously described procedure. Purification by column chromatography (dichloromethane-diethyl ether 50:1), gave compound **16** (1.71 g, 49 %) as a yellow solid: mp 77-78 °C; R_f 0.7 (dichloromethane-diethyl ether 50:1, twice); IR(KBr) 3050 (C=N, isoxazole), 2950-2900 (C-H), 1600 (C=N, isoxazole), 1470 (C=C, isoxazole), 1385 ($C(CH_3)_2$), 1250-1075 (C-O-C-O-C), 775-700 (Ar); ^{1}H NMR (DMSO) δ 1.19, 1.24 and 1.44 (12H, 3s, $2C(CH_3)_2$), 3.86 (1H, dd, $J_{4',4''}$ = 8.6, $J_{4',3'}$ = 4.2, 4'-H), 4.09 (1H, dd, $J_{4'',4'}$ = 8.6, $J_{4'',3'}$ = 6.0, 4''-H), 4.21-4.34 (2H, m, 3',2'-H), 5.14 (1H, d, $J_{1',2'}$ = 7.1, 1'-H), 7.18 (1H, s, 4-H), 7.49-7.53 (3H, m, ArH), 7.86-7.89 (2H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 25.06, 26.41 and 27.03 ($2C(\underline{C}H_3)_2$), 66.95 (C-4'), 73.48 (C-3'), 76.47 (C-2'), 80.39 (C-1'), 100.94 (C-4), 109.83 and 111.28 ($2\underline{C}(CH_3)_2$), 126.72, 128.84 and 129.96 (CHAr and CAr), 162.18 (C-3), 170.41 (C-5); *m/z* 345 (7 %, M^+), 330 (19, M^+-15), 273 (17), 230 (38, $C_{11}H_{18}O_5^+$), 186 (43, $C_9H_{14}O_4^+$), 144 (15, $C_9H_6ON^+$), 101 (100, $C_5H_9O_2^+$), 77 (27, $C_6H_5^+$) and 43 (57, $C_2H_3O^+$).

Anal. Calcd for $C_{19}H_{23}O_5N$: C, 66.08; H, 6.71; N, 4.06. Found: C, 65.97; H, 6.68; N, 3.99.

3-Phenyl-5-(1,2:3,4-di-*O*-isopropylidene-D-*xylo*-tetrahydroxybutyl)isoxazole (17). This experiment was carried out following the aforementioned procedure by reaction of compound **13** (2.19 g, 6.31 mmol) and sodium bicarbonate (2.13 g, 25.4 mmol), in tetrahydrofuran (25 mL) and water (19 mL) with a solution of potassium iodide (3.67 g, 22.1 mmol) and iodine (1.77 g, 6.97 mmol) in water (38 mL) during 8 h. The residue was chromatographed (chloroform-ethyl acetate 19:1), to give compound **17**, (1.20 g, 45 %) as a yellow syrup: R_f 0.8 (hexane-diethyl ether 1:1); IR(KBr) 3000 (C=N, isoxazole), 2990-2980 (C-H), 1615 (C=N, isoxazole), 1450 (C=C, isoxazole), 1380-1370 ($C(CH_3)_2$), 1260-1070 (C-O-C-O-C), 770-690 (Ar); ^{1}H NMR ($CDCl_3$) δ 1.29, 1.33 and 1.58 (12H, 3s, $2C(CH_3)_2$), 4.00 (1H, dd, $J_{4',4''}$ = 8.8, $J_{4',3'}$ = 4.0, 4'-H), 4.14 (1H, dd, $J_{4'',4''}$ = 8.8, $J_{4'',3'}$ = 6.1, 4''-H), 4.24 (1H, ddd, $J_{3',4'}$ = 4.0, $J_{3',4''}$ = 6.1, $J_{3',2'}$ = 7.4, 3'-H), 4.32 (1H, dd, $J_{2',1'}$ = 7.3, $J_{2',3'}$ = 7.4, 2'-H), 5.13 (1H, d, $J_{1',2'}$ = 7.3, 1'-H), 6.63 (1H, s, 4-H); ^{13}C NMR ($CDCl_3$) δ 25.45, 26.12, 26.44 and 26.78 ($2C(\underline{C}H_3)_2$), 65.54 (C-4'), 71.83 (C-3'), 75.44 (C-2'), 80.26 (C-1'), 100.67 (C-4), 110.00 and 111.28 ($2\underline{C}(CH_3)_2$), 126.81 and 129.96 (CHAr and CAr), 162.19 (C-3), 169.88 (C-5); *m/z* 345 (11 %, M^-), 330 (33, M^+-15), 243 (15), 230 (93, $C_{11}H_{18}O_5^+$), 186 (50, $C_9H_{14}O_4^+$), 144 (22, $C_9H_6ON^+$), 101 (100, $C_5H_9O_2^+$), 77 (38, $C_6H_5^+$) and 43 (67, $C_2H_3O^+$).

Anal. Calcd for $C_{19}H_{23}O_5N$: C, 66.08; H, 6.71; N, 4.06. Found: C, 66.25; H, 6.68; N, 4.15.

3-Phenyl-5-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)isoxazole 18). Compound **14**, (1.2 g, 2 mmol), sodium bicarbonate (0.8 g, 9.5 mmol), tetrahydrofuran (9 mL) and water (7 mL) was treated with a solution of potassium iodide (1.39 g, 8.4 mmol), iodine (0.66 g, 2.6 mmol) and water (14 mL). The mixture was stirred for 6 h following the previously described procedure. Purification by column chromatography (chloroform-ethyl acetate 50:1), gave compound **18** (0.53 g, 51 %) as a yellow solid: mp 55-56 °C; R_f 0.5 (hexane-diethyl ether 1:1); IR(KBr) 3061 (C=N, isoxazole), 2950-2920 (C-H), 1718 (COO), 1600 (C=N, isoxazole), 1450 (C=C, isoxazole), 1260-1110 (C-O-C-O-C), 760-700 (Ar); ^{1}H NMR (DMSO) δ 4.68-4.79 (2H, m, 5',5''-H), 4.83-4.87 (1H, m, 4'-H), 5.81 (1H, dd, $J_{3',4'}$ = 3.3, $J_{3',2'}$ =1.9, 3'-H), 5.85 (1H, d, $J_{1',2'}$ = 1.9, 1'-H), 5.94 (1H, dd, $J_{2',1'}$ =$J_{2',3'}$ = 1.9, 2'-H), 7.39-8.07 (21H, m, 4-H and 20 ArH); ^{13}C NMR ($CDCl_3$) δ

62.82 (C-5'), 78.58 (C-1'), 78.72 (C-2'), 80.98 (C-3'), 83.01 (C-4'), 101.06 (C-4), 126.84-129.92 (CHAr), 133.12-133.75 (CAr), 162.47, 165.35 and 166.21 (COO), 165.28 (C-3), 169.30 (C-5); *m/z* 589 (0.02 %, M^+), 362 (3), 317 (32, $C_{21}H_{17}O_3^+$), 240 (11), 224 (3), 144 (2, $C_9H_6NO^+$), 116 (1, $C_8H_6N^+$), 105 (100, $C_7H_5O^+$), 77 (22, $C_6H_5^+$) and 51 (4).

Anal. Calcd for $C_{35}H_{27}O_8N$: C, 71.31; H, 4.58; N, 2.38. Found: C, 70.89; H, 4.64; N, 2.31.

3-Phenyl-5-(D-*glycero*-dihydroxyethyl)isoxazole (19). A solution of **15** (0.88 g, 3.5 mmol) in 90 % aqueous acetic acid[29,30] (50 mL) was stirred at 90 °C for 1 h. Then the mixture was coevaporated several times with benzene, and the residue was crystallized from hexane-ethyl acetate 10:1 to give **19** (0.7 g, 95 %) as a white solid: mp 89.4-90 °C; R_f 0.4 (diethyl ether); IR(KBr) 3355 and 3194 (C-OH), 2930-2876 (C-H), 1597 (C=N, isoxazole), 1465 (C=C, isoxazole), 1400 (O-H), 1286-1045 (C-O), 765-689 (Ar); ^{1}H NMR (DMSO) δ 3.65-3.70 (2H, m, 2',2''-H), 4.72 (1H, dt, $J_{1',OH1'}$ = 5.9, $J_{1',2'}$ = 5.7, 1'-H), 5.01 (1H, t, $J_{OH1',1'}$ = 5.9, OH-1', disappears with D_2O), 5.89 (1H, d, $J_{OH2',2'}$ = 5.7, OH-2', disappears with D_2O), 6.93 (1H, s, 4-H); ^{13}C NMR (DMSO) δ 65.01 (C-2'), 68.01 (C-1'), 99.71 (C-4), 126.68-129.91 (CHAr and CAr), 162.06 (C-3), 173.73 (C-5); *m/z* 205 (1 %, M^+), 175 (4), 146 (27, $C_9H_8ON^+$), 116 (8, $C_8H_6N^+$), 104 (18, $C_5H_{12}O_2^+$), 77 (100, $C_6H_5^+$), 63 (18, $C_2H_7O_2^+$), 51 (63), 42 (43, $C_2H_3O^+$).

Anal. Calcd for $C_{11}H_{11}O_3N$: C, 64.39; H, 5.40; N, 6.83. Found: C, 64.49; H, 5.18; N, 6.76.

3-Phenyl-5-(D-*arabino*-tetrahydroxybutyl)isoxazole (20). Compound **16** (0.73 g, 2.1 mmol) in 90 % aqueous acetic acid (12 mL) was stirred at 90 °C for 2 h to give compound **20** (0.60 g, 92 %) as a white solid: mp 183-184 °C (from AcOEt-hexane); R_f 0.06 (AcOEt), R_f 0.6 (2-propanol); IR(KBr) 3460 and 3277 (C-OH), 2938-2886 (C-H), 1615 (C=N, isoxazole), 1435 (C=N, isoxazole), 1402 (O-H), 1085-1049 (C-O), 770-694 (Ar); ^{1}H NMR (DMSO) δ 3.41-3.48 (1H, m, 4''-H), 3.55-3.67 (3H, m, 2',3',4'-H), 4.42 (1H, t, $J_{OH4',4'}$ = 5.6, OH-4', disappears with D_2O), 4.76 (2H, dd, $J_{OH3',3'}$ = 7.7, $J_{OH2',2'}$ = 5.6, OH-2',3', disappears with D_2O), 5.03 (1H, d, $J_{1',OH1'}$ = 7.3, 1'-H), 5.59 (1H, d, $J_{OH1',1'}$ = 7.3, OH-1', disappears with D_2O), 6.85 (1H, s, 4-H), 7.49-7.53 (3H, m, ArH),

7.84-7.88 (2H, m, ArH); ^{13}C NMR (DMSO) δ 63.55 (C-4'), 66.44 (C-3'), 70.82 (C-2'), 72.68 (C-1'), 99.99 (C-5), 126.45-129.75 (CHAr), 129.01 (CAr), 161.55 (C-3), 175.47 (C-5); *m/z* 306 (6 %, M^++41), 294 (13, M^++29), 266 (100, M^++1), 230 (2), 216 (4), 188 (60, $C_7H_{11}O_5N^+$), 176 (15), 146 (24, $C_9H_8ON^+$), 131 (2), 103 (18, $C_5H_{11}O_2^+$).

Anal. Calcd for $C_{13}H_{15}O_3N$: C, 58.86; H, 5.70; N, 5.28. Found: C, 53.45; H, 7.05; N, 8.91.

3-Phenyl-5-(α-D-arabinofuranosyl)isoxazole (21). Compound **18** (1.1 g, 1.87 mmol) in methanol (100 mL) was treated[30] with a 0.3 N sodium carbonate solution (2.5 mL). The mixture (pH 9) was stirred for 1 h at rt, after adding acetic acid to neutrality (2 mL) it was concentrated to dryness. The residue was chromatographed (chloroform-methanol, 9:1) to give compound, **21** (0.41 g, 85 %) as a white foam: R_f 0.38 (chloroform-methanol 10:1); IR(KBr) 3433 (C-OH), 2924 (CH), 1613 (C=N, isoxazole), 1442 (C=C, isoxazole), 1404 (O-H), 770-690 (Ar); ^{1}H NMR (DMSO) δ 3.62-3.69 (1H, m, 5'-H), 3.72-3.79 (1H, m, 5''-H), 4.02-4.13 (2H, m, 3',4'-H), 4.32 (1H, d, $J_{1'\text{-}OH1'}$ = 5.5, 1'-H), 4.82 (1H, t, $J_{OH2',2'}$ = 5.6, 2'-OH, disappears with D_2O), 4.95 (1H, d, $J_{2',OH2'}$ = 5.6, 2'-H), 5.20 (1H, d, $J_{OH3',3'}$ = 4.3, 3'-OH, disappears with D_2O), 5.62 (1H, d, $J_{OH5',5'}$ = 6.1, 5'-OH, disappears with D_2O), 6.74 (1H, s, 4-H), 7.49-7.53 (3H, m, ArH), 7.84-7.88 (2H, m, ArH); ^{13}C NMR(DMSO) δ 61.82 (C-5'), 77.25 (C-4'), 78.03 (C-3'), 80.92 (C-2'), 85.10 (C-1'), 99.90 (C-4), 126.49-129.89 (CHAr and CAr), 161.73 (C-3), 172.50 (C-5); *m/z* 277 (13 %, M^+), 241 (4), 230 (4), 188 (44, $C_7H_{10}O_5N^+$), 174 (100), 144 (80, $C_9H_6ON^+$), 117 (21, $C_8H_7N^+$), 104 (35), 77 (97, $C_6H_5^+$), 51 (37).

Anal. Calcd for $C_7H_{11}O_3N$: C, 60.60; H, 5.48; N, 5.27. Found: C, 60.65; H, 5.45; N, 5.05.

ACKNOWLEDGMENT

Thanks to Junta de Castilla y León (Consejería de Cultura) for financial support.

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