# SYNTHESIS OF 2,3-UNSATURATED *O*-GLYCOSIDES FROM OPTICALLY ACTIVE ALCOHOLS VIA FERRIER REARRANGEMENT: CONFIGURATIONAL STUDIES

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## ABSTRACT

4-[3-(aryl)-1,2,4-oxadiazol-5-yl] butanones **4a-e** have been reduced to optically active 4-[3-(aryl)-1,2,4-oxadiazol-5-yl] butanols **5a-e** with baker's yeast. We subjected the alcohols possessing (*S*)-configuration to Ferrier' rearrangement with tri-*O*-acetyl-D-glucal **6** which furnished new unsaturated *O*-glycosides **7a-e**. The crystallographic data of the glycosides **7b** confirmed the (*S*)-configuration for the aglycone portion of the carbon atom.

**Keywords:** Configuration; Crystallographic data**;** baker's yeast

## INTRODUCTION

1,2,4-oxadiazoles can be considered as bioisosters of amides and esters.[1a-c] Their biological importance is well documented.[2] Their properties make this class of compounds quite attractive to the pharmaceutical industry. Many articles indicate that a number of researchers, including those in our own group, have been trying to synthesize 1,2,4-oxadiazole with asymmetric center on the side-chain to improve the performance of these molecules as drugs.[3,4,1a,5a,b,6] In recent years, new methods have been used for the synthesis of 1,2,4-oxadiazole with one or more stereocenters.[7,8] Thus, Porcheddu *et al.*[7] proposed a methodology for the synthesis of various disubstituted 1,2,4-oxadiazoles for the preparation of heterocycles with a stereocenter with 100% enantiomeric purity. Asymmetric reduction of prochiral ketones into chiral non-racemic secondary alcohols is a fundamental process in the synthesis of organic compounds of biological interest.[6,7] Though numerous chemical methodologies are known in the synthesis of these secondary chiral alcohols, difficulties still remain in attaining high yields with enantiomeric excess.[7] For example, the sodium borohydride ($NaBH_4$) reduction of ketones may apparently be promoted either by the electrophilic activation of the substrate or the nucleophilic activation of the reagent—or, of course, both. This, in fact, leads to a possible asymmetric variant of the borohydride reaction, catalysis by an optically active alcohol in an inert solvent.[8] Several oxidoreductases are capable of efficiently reducing ketones with a combination of co-factors such as NADPH or NADH.[9] The use of whole cells, such as in baker's yeast (*Saccharomyces cerevisiae*), for chiral reduction is economically attractive due to its availability, low cost and ease of handling and disposal.[9] Because of the great significance of 1,2,4-oxadiazoles, and in particular oxadiazoles containing stereocenter in their side-chain which are being synthesized, we focused our attention first on reducing the side-chain keto group to alcohol. In this paper, we report on a asymmetric reduction of 4-[3-(aryl)-1,2,4-oxadiazol-5-yl] butanones **4a-e** using bakers' yeast. These alcohols were characterized and later on allowed to react with tri-*O*-acetyl-D-glucal to obtain 2,3-unsaturated *O*-glycosides.

## EXPERIMENTAL

**Instruments and reagents**

Melting points were determined on using an Electrothermal digital melting point apparatus (model IA9100) and are uncorrected. IR spectra were recorded as KBr films on a Brucker IFFS66 series Fourier transform spectrophotometer. Specific rotations were measured with a Perkin–Elmer polarimeter model 241. NMR spectra were recorded with a Varian Unity Plus instrument (300/75 MHz for $^1H/^{13}C$) spectrometer, using $CDCl_3$ as the solvent. Chemical shifts are reported in parts per million (ppm) downfield from an internal TMS (trimethylsilane) reference. Elemental analysis was performed with a Carlo Erba instrument model E-1110. Silica gel coated plates with a fluorescent indicator ($PF_{254}$) were used for thin-layer chromatography (TLC), and the spots were detected under ultraviolet light. The solvent system for running the TLC plates was a mixture of 1:9 ethyl acetate–dichlromethane. Silica gel 60 (230 – 400 mesh) was employed for liquid chromatography. All commercially available reagents were used directly without purification unless otherwise stated. All the solvents used in reactions were distilled for purity.

**General Procedure for the *Synthesis of 4-[3-(aryl)-1,2,4-oxadiazol-5-yl]-butan-2-ones***

The reaction of **1a**–**e** was with levulinic acid **2** and conducted according to the method of Srivastava et al.[10,11]

***Synthesis of 4-[3-(aryl)-1,2,4-oxadiazol-5-yl]-butanols***

In a shaker with suspension of baker´s yeast ( 50g ), and sucrose (12g) in deionized water (400 mL ) a solution of 4-[3-(aryl)-1,2,4-oxadiazol-5-yl]-2-butanones (1.30g, 6.01 mmol) was added. The suspension was shaken at room temperature and the reduction followed by TLC. After 72h, the product was extracted into ethyl acetate (3 x 100mL) followed by separation of the layers. The combined organic extracts were dried ($Na_2SO_4$), filtered, and the solvent removed under vacuum. The crude product was purified immediately by chromatography over silica gel using hexane/ethyl acetate (8:2) producing chromatographically pure **5a-e** (Figure 1). The details are given below.

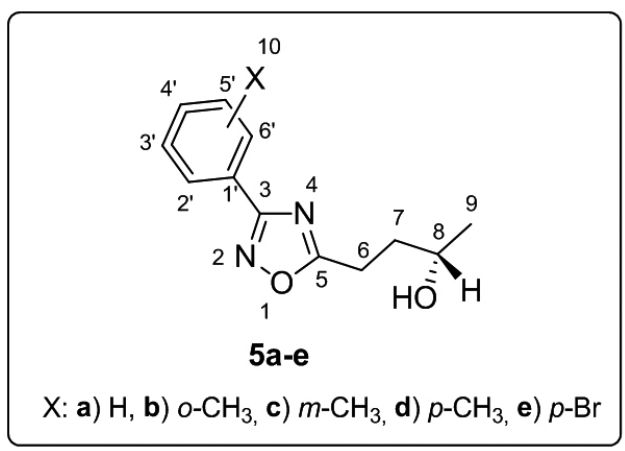


**Figure 1.** 4-[3-(aryl)-1,2,4-oxadiazol-5-yl]-butanols (**5a-e**)-

*4-[3-phenyl-1,2,4-oxadiazol-5-yl]-2-butanol (5a):* Yield 60%, $R_f$=0.23 (dichromethane–ethyl acetate, 9:1); $[\alpha]_D^{25}$=+7°± 2° (*c*=0.59, $CHCl_3$); IR $\nu_{max}$ (KBr): 3414, 1590, 1365, 1026, 757 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 8.07–8.04 (m, 2H, H-2' and H-6'), 7.49–7.45 (m, 3H, H-3', H-4' and H-5'), 3.95 (m, 1H, H-8), 3.10 (t, 2H, *J* 7.7 Hz, H-6 and H-6"), 2.11 (s, 1H, OH), 2.07-2.04 (m, 2H, H, H-7 and H-7"), 1.28 (d, 3H, *J* 6.2 Hz, $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta$ 179.9 ( C=N), 168.2 (C=N), 131.1 (C-1'), 128.8 (C-4'), 127.4 (C-3'), 126.7(C-2'), 67.2( C-8),


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35.7 (C-7), 24.0 (C-6), 23.2 ($CH_3$). Anal. Calcd for ($C_{12}H_{14}O_7N_2.1/8H_2O$): C, 65.36; H, 6.48; N, 12.70 Found: C, 65.12; H, 6.81; N, 12.38.

*4-[3-(**o**-tolyl)-1,2,4-oxadiazol-5-yl]-2-butanol (5b):* Yield 64%, $R_f$=0.32 (dichromethane–ethyl acetate, 9:1); $[\alpha]_D^{25}$=+11.25 (*c*=1.2, $CHCl_3$); IR $\nu_{max}$ (KBr): 3410, 1570, 1365, 760 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.97 (d, 1H, J 7.5, H-2'), 7.39–7.28 (m, 3H, H-2', H-3' and H-4'), 3.97 (m, 1H, H-8), 3.11 (t, 2H, *J* 7.5 Hz, H-6 and H-6"), 2.62 ( s, 3H, Ph-$CH_3$ ), 2.20 (s, 1H, OH), 2.03 (m, 2H, H, H-7 and H-7"), 1.28 (d, 3H, *J* 6.0 Hz, $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta$ 179.2 ( C=N), 169.1 (C=N), 138.5 (C-1'), 131.7 (C-2'), 130.9 (C-3'), 130.3 (C-6'), 126.4(C-5'), 126.3(C-4'), 67.7( C-8), 60.8 (C-7), 35.6 (C-6), 23.8 ($CH_3$), 23.2 (Ph-$CH_3$). Anal. Calcd for ($C_{13}H_{16}O_7N_2$): C, 67.22 H, 6.94; N, 12.06 Found: C, 67.12; H, 6.46; N, 12.30.

*4-[3-(**m**-tolyl)-1,2,4-oxadiazol-5-yl]-2-butanol (5c):* Yield 59%, $R_f$=0.32 (dichromethane–ethyl acetate, 9:1); $[\alpha]_D^{25}$=+6.6 (*c*=0.65, $CHCl_3$); IR $\nu_{max}$ (KBr): 3400, 1570, 1350, 750 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.87-7.84 (m, 2H, Ph-H), 7.38–7.27 (m, 2H, Ph-H), 4.15 (m, 1H, H-8), 3.11 (dt, 2H, *J* 1.3Hz, *J* 8.8Hz, H-6 and H-6"), 2.41 (s, 1H, OH), 2.01 (s, 3H, Ph-$CH_3$), 1.98 (m, 2H, H, H-7 and H-7"), 1.28 (d, 3H, *J* 6.0 Hz, $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta$ 180.2 ( C=N), 171.5 (C=N), 139.0 (C-1'), 132.2 (C-3'), 129.1 (C-4'), 128.2 (C-6'), 126.9 (C-5'), 124.8 (C-2'), 67.1( C-8), 60.7 (C-7), 35.7 (C-6), 23.8 ($CH_3$), 21.4 (Ph-$CH_3$). Anal. Calcd for ($C_{13}H_{16}O_7N_2$): C, 67.22 H, 6.94; N, 12.06 Found: C, 67.10; H, 6.48; N, 12.26.

*4-[3-(**p**-tolyl)-1,2,4-oxadiazol-5-yl]-2-butanol (5d):* Yield 58%, $R_f$=0.37 (dichromethane–ethyl acetate, 9:1); $[\alpha]_D^{25}$=+ 11.4 (*c*=1.2, $CHCl_3$); IR $\nu_{max}$ (KBr): 3400, 1590, 1355, 767 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.96 (d, 2H, *J* 8.1 Hz, H-2'), 7.28 (d, 2H, *J* 7.7 Hz, H-3'), 3.95 (m, 1H, H-8), 3.08 (t, 2H, *J* 7.5 Hz, H-6 and H-6"), 2.40(s, 3H, Ph-CH3), 2.15 (s, 1H, OH), 2.01 (m, 2H, H, H-7 and H-7"), 1.28 (d, 3H, *J* 6.2 Hz, $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta$ 180.1( C=N), 168.5 (C=N), 141.8 (C-1'), 129.9 (C-3'), 127.7 (C-2'), 124.3 (C-4'), 67.3 ( C-8), 35.6 (C-7), 24.0 (C-6), 23.5 ($CH_3$), 21.9 (Ph-$CH_3$). Anal. Calcd for ($C_{13}H_{16}O_7N_2$): C, 67.22 H, 6.94; N, 12.06 Found: C, 67.35; H, 6.68; N, 12.15.

*4-[3-(**p**-bromo)-1,2,4-oxadiazol-5-yl]-2-butanol (5e):* Yield 55%, $R_f$=0.33 (dichromethane–ethyl acetate, 9:1); $[\alpha]_D^{25}$=+ 4.47 (*c*=1.7, $CHCl_3$); IR $\nu_{max}$ (KBr): 3410, 1590, 1350, 767 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.94 ((dd, 2H, *J* 1.8 Hz *J* 6.7 Hz, H-2'), 7.27 (dd, 2H, *J* 1.8 Hz *J* 6.9 Hz, H-3'), 3.92 (m, 1H, H-8), 3.09(dt, 2H, *J* 1.5 Hz, *J* 9.0 Hz, H-6 and H-6"), 2.15 (s, 1H, OH), 2.02 (m, 2H, H, H-7 and H-7"), 1.28 (d, 3H, *J* 6.2 Hz, $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta$ 180.5( C=N), 167.8 (C=N), 140.7 (C-1'), 132.5 (C-3'), 129.2 (C-2'), 126.1(C-4'), 67.2( C-8), 38.2 (C-7), 24.0 (C-6), 23.5 ($CH_3$). Anal. Calcd for ($C_{12}H_{13}O_7N_2Br$): C, 48.50 H, 4.41; N, 9.43 Found: C, 48.46; H, 4.61; N, 9.23.

**General Procedure for the Synthesis of (*S*)-1-methyl-[3-(aryl)-1,2,4-oxadiazol-5-yl]-propyl-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides (7a–e)**

The reaction of **5a**–**e** with compound **6** were conducted according to the method of Toshima et al.[12] Figure 2.The details are given below.

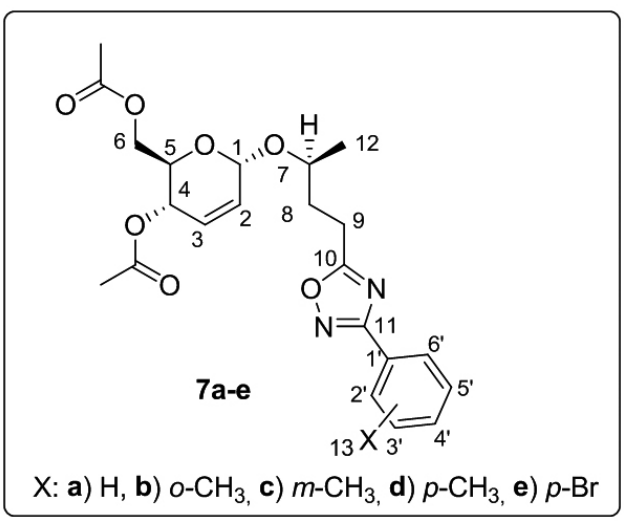



**Figure 2.** *(S)*-1-methyl-[3-(aryl)-1,2,4-oxadiazol-5-yl]-propyl-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranosides (**7a–e**).

*(**S**)-1-Methyl-[3-(phenyl)-1,2,4-oxadiazol-5-yl] propyl-4,6-di-**O**-acetyl-2,3-dideoxy-α-D-**erythro**-hex-2-enopyranoside (7a):* Yield 72%; $R_f$=0.65 (dichromethane–ethyl acetate, 9:1); mp 65.4–66.3°C; $[\alpha]_D^{20}$=+61° (*c*=0.53, $CHCl_3$); IR $\nu_{max}$ (KBr): 1745, 1571, 1368, 1229, 1033, 757 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 8.08–8.03 (m, 2H, H-2' and H-5'), 7.49–7.47 (m, 3H, H-3', H-4' and H-5'), 5.95 (d, 2H, *J* 10.5 Hz, H-3), 5.85 (dd, 1H, *J* 10.5 Hz, *J* 2.7 Hz, H-2), 5.33 (dd, 1H, *J* 9.9 Hz, *J* 1.5 Hz, H-4), 5.04 (s, 1H, H-1), 4.28–4.16 (m, 2H, H-6 and H-6′), 4.15 (dd, 1H, *J* 9.9 Hz, H-5), 4.09 (m, 1H, H-7), 3.80 (m, 2H, H-9 and H-9′), 3.59 (m, 2H, H-8 and H-8′), 2.09 (s, 3H, OAc), 2.08 (s, 3H, OAc), 1.26 (d, *J* 6.0 Hz, $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta$ 180 (OAc), 171.1 (C=N), 168.6 (C=N), 131.4 (C-1'), 129.4 (C-3), 129.3 (C-3'), 128.3 (C-2), 128.2 (C-2'); 127.2 (C-4'), 94.6 (C-1), 73.1 (C-7), 67.5 ( C-5), 64.7 (C-6), 64.6 (C-4), 61.5 (C-8), 34.1 (C-9), 21.3 (C-12), 15.6 (CO-$CH_3$). Anal. Calcd for ($C_{22}H_{26}O_7N_2$): C, 61.38; H, 6.08; N, 6.50 Found: C, 61.59; H, 6.14; N, 6.36.

*(**S**)-Methyl-[3-(**o**-tolyl)-1,2,4-oxadiazol-5-yl] propyl 4,6-di-**O**-acetyl-2,3-dideoxy-α-D-**erythro**-hex-2-enopyranoside (7b):* Yield 73%; $R_f$=0.84 (dichromethane–ethyl acetate, 9:1); mp 72–73°C; $[\alpha]_D^{20}$=+80.4° (*c*=0.7, $CHCl_3$); IR $\nu_{max}$ (KBr): 1743, 1370, 1223, 1033, 741 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.97-795 (d, 1H, J 7.3 Hz, H-2'), 7.37–7.27 (m, 3H, H-3', H-4' and H-5'), 5.87 (d, 1H, J 19.3 Hz, H-3), 5.78 (tt, 1H, *J*=10.3 and 2.0 Hz, H-2), 5.29 (d, 1H, J 8.4 Hz, H-4), 5.17 ( s, 1H, H-1), 4.28-4.15 (m, 4H, H-5, H-6, H-6'and H-7), 4.11–3.98 (m, 2H, H-12 and H-8), 3.19-3.04 (m, 2H, H-9 and H-9′), 2.62 (s, 3H, Ar-$CH_3$), 2.15-2.10 (m, 2H, H-8 and H-8'), 2.10 (s, 3H, OAc), 2.09 (s, 3H, OAc), 1.25 (d, 3H, *J* 6.2 Hz, $CH_3$). $^{13}C$ NMR ($CDCl_3$): $\delta$ 181 (OAc), 171.3(C=N), 170.1 (C=N), 139.6 (C-1'), 138.5 (C-2), 131.7 (C-3), 130.8 (C-2'), 130.3 (C-3'); 129.5 (C-6'), 128.3(C-5'), 126.0 (C-4'), 91.3 (C-1), 72.2 (C-7), 67.2( C-5), 65.8 (C-6), 63.5 (C-4), 34.6(C-8), 23.6 (C-9), 21.3 (C-12), 21.1(CO-$CH_3$), 20.6 ($CH_3$). Anal. Calcd for ($C_{22}H_{26}O_7N_2$): C, 62.15; H, 6.35; N, 6.30. Found: C, 62.26; H, 6.44; N, 6.22.

*(**S**)-Methyl-[3-(**m**-tolyl)-1,2,4-oxadiazol-5-yl] propyl 4,6-di-**O**-acetyl-2,3-dideoxy-α-D-**erythro**-hex-2-enopyranoside (7c):* Yield 73%; $R_f$=0.84 (dichromethane–ethyl acetate, 9:1); mp 68–69°C; $[\alpha]_D^{20}$=+67.1° (*c*=1.35, $CHCl_3$); IR $\nu_{max}$ (KBr): 1740, 1595, 1353, 1030, 735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.88–7.85 (d, 2H, *J* 9.7 Hz H-6' and H-2'), 7.38–7.27 (m, 2H, H-3' and H-4'), 5.87 (d, 2H, *J* 9.9 Hz, H-3), 5.79 (d, 2H, *J* 9.9 Hz, H-2), 5.27 (d, 1H, *J* 9.4 Hz, H-4), 5.16 (s, 1H, H-1), 4.29–4.19 (m, 2H, H-6 and H-6′), 4.15–3.99 (m, 1H, H-5 and H-7), 3.19–3.03 (m, 2H, H-9 and H-9'), 2.42 (s, 3H, Ph-$CH_3$) 2.15-2.07 (m, 2H, H-8 and H-8'), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc), 1.24 (d, 3H, *J* 6.0 Hz, $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta$ 179.9 (OAc), 171.1(C=N), 170.4 (C=N), 139.0 (C-1'), 132.2 (C-2), 129.4 (C-3), 129.1 (C-2'), 128.3 (C-3'); 128.1 (C-5'), 127.0(C-4'), 124 (C-6'), 91.5 (C-1), 72.2 (C-7), 67.6 ( C-5), 65.5 (C-6), 63.5 (C-4), 34.1 (C-8), 23.6 (C-9), 21.6 (C-12), 21.3(CO-$CH_3$), 19.6 (Ph-$CH_3$). Anal. Calcd for ($C_{22}H_{26}O_7N_2$): C, 62.15; H, 6.35; N, 6.30. Found: C, 62.23; H, 6.53; N, 6.05.

*1-(**S**)-Methyl-[3-(**p**-tolyl)-1,2,4-oxadiazol-5-yl] propyl 4,6-di-**O**-acetyl-2,3-dideoxy-α-D-**erythro**-hex-2-enopyranoside (7d):* Yield 70%; $R_f$=0.85 (dichromethane–ethyl acetate, 9:1); mp 71–72°C; $[\alpha]_D^{20}$=+43.5° (*c*=1.06, $CHCl_3$); IR $\nu_{max}$ (KBr): 1744, 1370, 1034, 756 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.94 (d, 2H, *J* 8.1 Hz, H-2'), 7.27 (d, 2H, *J* 7.7 Hz, H-3'), 5.90 (d, 1H, *J* 10.2 Hz, H-3), 5.82 (d, 1H, *J* 10.2 Hz, H-2), 5.26 (d, 1H, *J* 9.4 Hz, H-4), 5.12 (s, 1H, H-1), 4.27–4.12 (m, 2H, H-6 and H-6′), 4.01–3.86 (m, 2H, H-5 and H-7), 3.05 (m, 2H, H-9 and H-9′), 2.41 (s, 3H, Ar-$CH_3$), 2.15 (m, 2H, H-8 and H-8′), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc), 1.24 (d, 3H, *J* 6.0 Hz, $CH_3$). $^{13}C$ NMR ($CDCl_3$): $\delta$ 179.8 (OAc), 171.1(C=N), 170.6 (C=N), 141.8 (C-1'), 129.9 (C-2), 129.4 (C-3), 128.3 (C-2'), 127.6 (C-3'); 124.4 (C-4'), 91.9 (C-1), 67.6 (C-7), 65.5( C-6), 63.5 (C-6), 34.1(C-8), 23.6 (C-9), 21.9 (C-12), 21.4(CO-$CH_3$), 19.8 (Ph-$CH_3$). Anal. Calcd for ($C_{22}H_{26}O_7N_2$): C, 62.15; H, 6.35; N, 6.30. Found: C, 62.58; H, 6.69; N, 6.15.

*(**S**)-Methyl-[3-(**p**-bromophenyl)-1,2,4-oxadiazol-5-yl] propyl 4,6-di-**O**-acetyl-2,3-dideoxy-α-D-**erythro**-hex-2-enopyranoside (7e):* Yield 69%; $R_f$=0.89 (dichromethane–ethyl acetate, 9:1); $[\alpha]_D^{20}$=+83.9° (*c*=0.28, $CHCl_3$); IR $\nu_{max}$ (KBr): 1735, 1590, 1370, 760 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.86 (d, 2H, *J*=8.4 Hz, H-2'), 7.54 (d, 2H, *J*=8.4 Hz, H-3'), 5.83 (d, 1H, *J* 9.9 Hz, H-3), 5.71 (d, 1H, *J* 9.9 Hz, H-2), 5.22 (d, 1H, *J* 9.4 Hz, H-4), 5.08 (s, 1H, H-1), 4.21–4.06 (m, 2H, H-6 and H-6′), 4.02 (m, 2H, H-5 and H-7), 3.02 (m, 2H, H-9 and H-9′), 3.27 (m, 2H, H-8 and H-8'), 2.02 (s, 3H, OAc), 2.00 (s, 3H, OAc), 1.18 (d, 3H, *J* 6.0 Hz, $CH_3$). $^{13}C$ NMR ($CDCl_3$): $\delta$ 180.5 (OAc), 173.4 (C=N), 167.6 (C=N), 140.0 (C-1'), 132.5 (C-2), 129.4 (C-3), 129.1 (C-2'), 126.1 (C-3'), 126.0 (C-4'), 92.0 (C-1), 72.2 (C-7), 67.6 (C-5), 65.1( C-6), 63.4 (C-4), 34.1(C-8), 30.0 (C-9), 21.3 (C-12), 21.1(CO-$CH_3$). Anal. Calcd for ($C_{22}H_{25}O_7N_2Br$): C, 51.88;

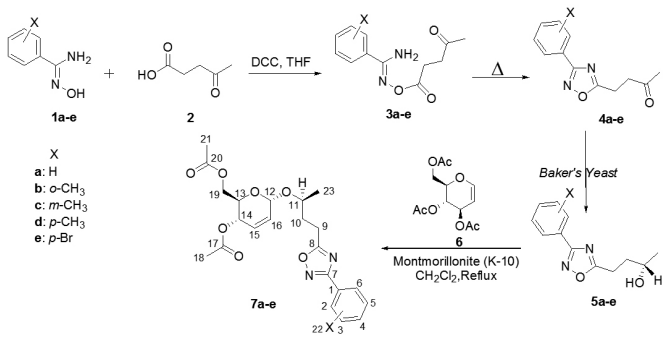
H, 4.95; N, 5.50. Found: C, 51.58; H, 4.68; N, 5.19.

**X-ray single crystal structure determination**

Single crystal X-ray diffraction data of the title compound were collected at room temperature on a Nonius BV diffractometer using Mo-Kα radiation (λ = 0.71073 Å) through the program COLLECT [19]. Details of the crystal structure of $C_{22}H_{25}N_2O_7$ are listed in Table 1. The crystal structure has been solved and refined in the triclinic symmetry, space group P-1, using the WINGX environment [21] and based on SHELXS-97 [22] and SHELXL-97 [23]. The cell dimensions were determined by least-squares fit of angular settings of 2897 reflections in the θ range from $1.70^0$ to $28.91^0$. The intensities were measured by φ scan mode for θ range from $1.70^0$ to $28.91^0$ with hkl values ($0 \le h \le 6$, $-12 \le k \le 13$, $-16 \le l \le 16$). 2897 reflections were treated as observed ($I > 2\sigma(I)$). The models were refined by full-matrix least squares on F2 using SHELXL-97 [34]. The program ORTEP-3 [35] was used for graphic representation and the program WINGX [36] to prepare material for publication.

## RESULTS AND DISCUSSION

Initially 4- [3-(aryl)-1,2,4-oxadiazol-5-yl]-butan-2-one was prepared by using an appropriate benzamidoxime or arylamidoxime and levulinic acid in the presence of DCC in methylene chloride to get *O*-acyl intermediates, which were cyclized to 1,2,4-oxadiazoles following the common procedure.[10,11] The mechanism of formation of 1,2,4-oxadiazoles from amidoximes and an acid, employing DCC as a carbonyl group activator is straight forward. The first step is the intermediate **3a-e** production followed by thermal cyclodehydration to generate **4a-e**.[10,11] The compounds 4-[3-(aryl)-1,2,4-oxadiazol-5-yl]-butan-2-one **4a-e** were reduced by use of bakers' yeast under conventional conditions.[7] Optically active 4-[3-(aryl)-1,2,4-oxadiazol-5-yl]-2-butanols **5a-e** is a useful intermediate for the synthesis of *O*-glycoside. Compounds **5a**–**e** were used to carry out Ferrier's rearrangement.[12,13] Reaction of these alcohols individually with tri-*O*-acetyl-D-glucal **6** after short reaction times produced the corresponding alkyl 2,3-unsaturated glycosides **7a-e** in good yields, with the α-anomer being the greater or the exclusive product (Scheme 1).




**Scheme 1.** Synthesis of 1-(*S*)-methy-[3-(*o*-tolyl)-1,2,4-oxadiazol-5-yl] propyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**7a-e**)

Excellent enantiopurity of each of the generated alcohols **5a-e** was attained (>90% ee). $^1$H NMR spectroscopy in the presence of the chiral shift reagent europium tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorate, conducted on both racemic and enantiopure samples, determined that each of the products isolated **5a-e** was enantiopure, demonstrating that baker's yeast was capable of effecting selective reduction. Thus, the compounds **5a-e** can fit into the active site of the yeast reductase to facilitate hydride delivery to the carbonyl group.

The results of the baker's yeast reduction of these compounds are shown in the Table 1. Since the spectra of both (+)- and (- )- 4-[3-(aryl)-1,2,4-oxadiazol-5-yl]-butanols are identical, the usual chemical shift reagent would not help our analysis. However, if one uses a chemical shift reagent that is itself chiral, one can begin to distinguish the two enantiomers by their NMR spectra. The two enantiomers, which are chiral, will interact differently with the chiral shift reagent. The complexes formed from the (*R*) and (*S*) isomers and with (+)-camphor containing the shift reagent will be diastereomers. Diastereomers usually have different physical properties, and the NMR spectra are no exception. The two complexes will be formed with slightly differing geometries. Although the effect is small, it is large enough to begin to see differences in the NMR spectra of the two enantiomers. In particular, the originally superimposed methylene and methine multiplets will begin to be resolved.

**Table 1.** Baker's yeast reduction of compounds **4a-e**

| Entry | Product | Reaction Time (h) | Yield[a] (%) | ee (%)[b] | $[\alpha]_D^{20}(CHCl_3)$ |
|---|---|---|---|---|---|
| **1** | **5a** | 72 | 60 | 92(*S*) | +7°± 2° (*c*=0.59) |
| **2** | **5b** | 72 | 64 | 90(*S*) | +11.25 (c=1.2) |
| **3** | **5c** | 72 | 59 | 94(*S*) | +6.6 (c=0.65) |
| **4** | **5d** | 72 | 58 | 93(*S*) | +11.4 (c=1.2) |
| **5** | **5e** | 72 | 55 | 84(*S*) | +4.47 (c=1.7) |

[a] Isolated yield
[b] Absolute configuration in parenthesis.

The $^1$H NMR spectra of **7a-e** show chemical shifts at $1.24 \le \delta \le 1.26$ ppm, respectively; as a doublet with a coupling constant $6.0 \le J \le 6.2$ Hz, which is due to the methyl group of the aglycone. The methyl group of the aglycone of 2,3-unsaturated glycosides with configuration (*R)* absorbs at a slightly lower field (δ 1.32 ppm).[13] The products **7a-e** produced an anomeric proton at δ 5.04-5.17 ppm as a singlet indicating the axial configuration of the 1-methyl-[3-(aryl)-1,2,4-oxadiazol-5-yl]-propyl group. Hence, it is concluded that compounds **7a-e** are exclusively the α-anomer.

The $^{13}$C NMR spectrum of the compounds **7a-e** exhibits between 18 and 21 carbon atoms, all approximately equal in height; several of them have characteristic chemical shifts. The presence of a peak between 91.5-94.6 ppm is typical of anomeric carbons of glucosides (C-1); additional peaks at 129.4, 128.3, 67.5, 64.7 and, 64.6 ppm support the idea that the compound contains α-glucopyranose moiety. A DEPT spectrum reveals that the peaks lathes 179.8-180.5 (OAc), 173.4-171.1 (C=N), 167.6-170.6(C=N), and 131.4-141.8 (C-1') ppm lack protons, those at 23.9 (C-9), 34.6 and 65.8 (C-6) ppm are methylene groups, and all other carbons bear one hydrogen.

The compound **7b,** which had better crystals, was subjected to X-ray crystallography. These crystals had the configuration (*S*) at the carbon atom containing the methyl group in the aglycone moiety. The crystallographic data provided precise information regarding the configuration (at C-11). As expected, the configurations at C(12), C(13) and C(14) are (*R*), (*S*) and (*S*), respectively. The ortep diagram is shown in Figure 3.

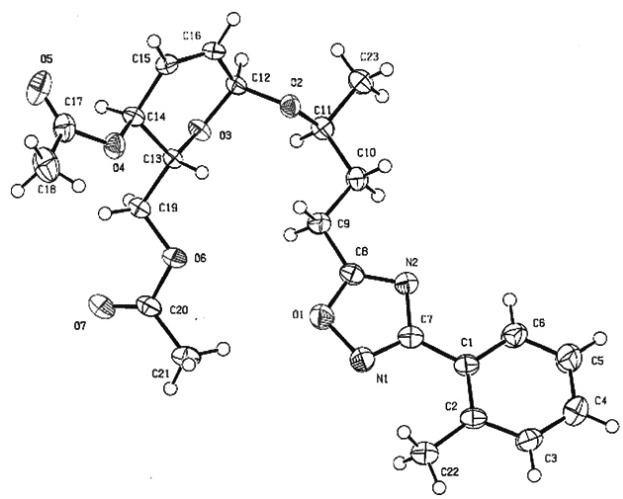



**Figura 3.** Ortep diagram of compound 1-(*S*)-methy-[3-(*o*-tolyl)-1,2,4-oxadiazol-5-yl] propryl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **7b**.

The crystallographic data supported the attributions made from the proton magnetic resonance spectroscopy. All distances and angles for (**7b**) are consistent with the expected values. The crystal data and structure refinement for (*S*)-Methyl-[3-(*o*-tolyl)-1,2,4-oxadiazol-5-yl] propyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**7b**) is shown in Table 2.

**Table 2.** Crystal data and structure refinement for (*S*)-Methyl-[3-(*o*-tolyl)-1,2,4-oxadiazol-5-yl] propyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**7b**):

| | |
|---|---|
| Empirical formula | $C_{22}H_{25}N_2O_7$ |
| Formula weight | 429.44 |
| Temperature (K) | 293 (2) |
| Radiation wavelength (A˚) | 0.71073 |
| Crystal system | Triclinic |
| Space group | P1 |
| Unit cell dimensions | |
| *a* (A˚) | 4.6485(9), α=75.76°(3) |
| *b* (A˚) | 10.170(2), β=89.62° (3) |
| *c* (A˚) | 12.373(3), δ=81.02°(3) |
| Volume (A˚ 3) | 559.66(19) |
| Z | 1 |
| Calculated density | 1.274 |
| Absorption coefficient | 0.096 |
| F(000) | 227 |
| Crystal size (mm) | 1.0·0.2·0.2 |
| Theta Range for data collection | 1.70–28.91 |
| Limiting índices | $0 \le h \le 6$, $-12 \le k \le 13$, $-16 \le l \le 16$ |
| Reflections collected/unique | 2897/2897 [$R_{int}$=0.0000] |
| Completeness to theta = 28.91 | 98.0 |
| Absorption correction | None |
| Refinement method | Full-matrix least-squares on F2 |
| Data/restraints/parameters | 2897/3/293 |
| Goodness-of-fit on F 2 | 0.776 |
| Final *R* indices [*I*>2**s**(*I*)] | *R* 1=0.0486, *wR*2=0.1565 |
| *R* indices (all data) | *R* 1=0.0628, $wR_2$=0.1792 |
| Absolute structure parameter | -0.5(12) |
| Largest diff.peak and hole. | 0.239 and -0.260 e.A |

## CONCLUSIONS

In summary, we have been able to synthesize the unsaturated *O*-glycosides **7a–e** by Ferrier' rearrangement of tri-*O*-acetyl-D-glucal **2** with 4-[3-(aryl)-1,2,4-oxadiazol-5-yl] butanols **4a-e**. The reaction of 4-[3-(aryl)-1,2,4-oxadiazol-5-yl] butanones **3a-e** with baker's yeast provided optically active alcohols **4a-e** possessing the *(S)*-configuration. The crystallographic data of the glycosides **7b** confirmed the *(S)*-configuration at the carbon atom in the aglycone portion.

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### CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

### SUPPLEMENTARY INFORMATION

The crystallographic data (CCDC) for compound **7b** were deposited at Cambridge structural database. These data can be obtained free of charge from the director, CCDC, 12 Union road, Cambridge CB21EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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