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Note

Synthesis of 3-*C*-(methyl β-D-xylofuranosid-3-yl)-5-phenyl-1,2,4-oxadiazole

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Abstract

Nucleophilic addition of KCN to 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose gave the *xylo* cyanohydrin stereoselectively. Several xylos-3-yl-1,2,4-oxadiazole derivatives were synthesized from this cyanohydrin and were converted into 3-*C*-(methyl β-D-xylofuranosid-3-yl)-5-phenyl-1,2,4-oxadiazole. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Xylosyl 1,2,4-oxadiazole derivatives; Neighboring-group participation effect; Asymmetric synthesis; Isocarbonucleoside

1. Introduction

The synthesis of isonucleosides and isocarbonucleosides has been carried out in a search for compounds having anticancer and antiviral activities [1–3]. Isocarbonucleosides constitute a class of nucleoside analogues in which the nucleobase is linked by a carbon–carbon bond to a ribose carbon other than C-1. It is anticipated that isocarbonucleosides may have increased chemical and enzymatic stability under physiological conditions. The synthesis of carbonucleosides has been reported by several laboratories [4–6]. We have described the synthesis of D-xylopyranosyl-1,2,4-oxadiazoles and have found that D-xylopyranosyl carbonucleosides have potent biological activities [7,8]. Recently, a number of 5-aryl-1,2,4-oxadiazolines have been shown to possess anti-HIV activity [9]. In this paper, we describe the stereoselective synthesis of isocarbonucleoside, 3-*C*-(methyl β-D-xylosid-3-yl)-5-phenyl-1,2,4-oxadiazole (**10**) (see Scheme 1) for a study of its biological activities.

2. Results and discussion

5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentos-3-ulose (**1**) was prepared from D-xylose [10,11]. Addition of cyanide ion to the carbonyl group in ketose **1** took place stereoselectively to give only one isomer, **2**. The stereoselectivity was probably because of the steric hindrance by the 5-substituent on the upper face of the furanose ring to the approaching cyanide ion. Benzoylation of **2** gave the dibenzoate **3**, which was converted into the key intermediate, the amidoxime **4**, with hydroxylamine in methanol. Compound **4** was then condensed with acetic anhydride,

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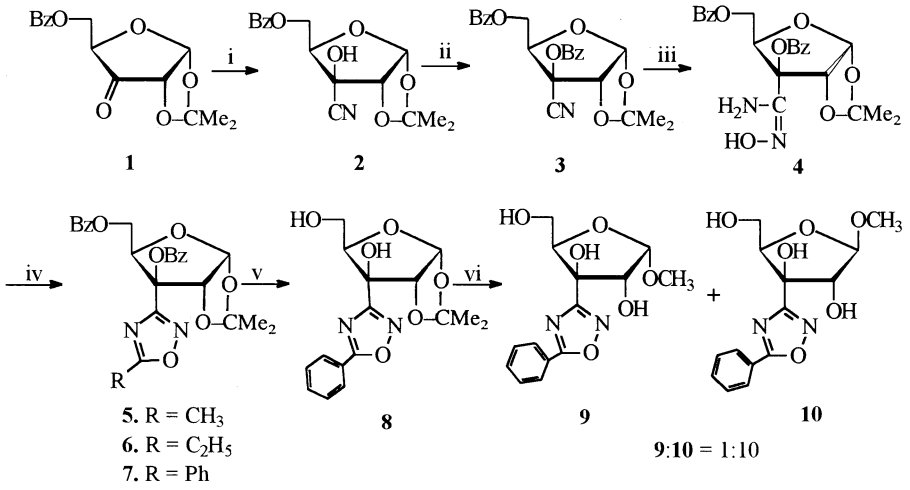
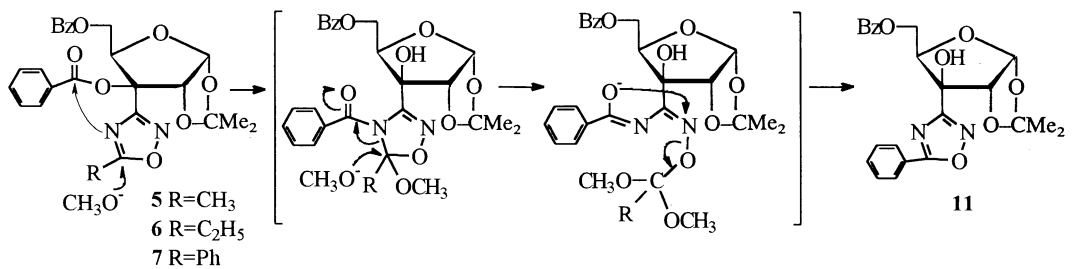


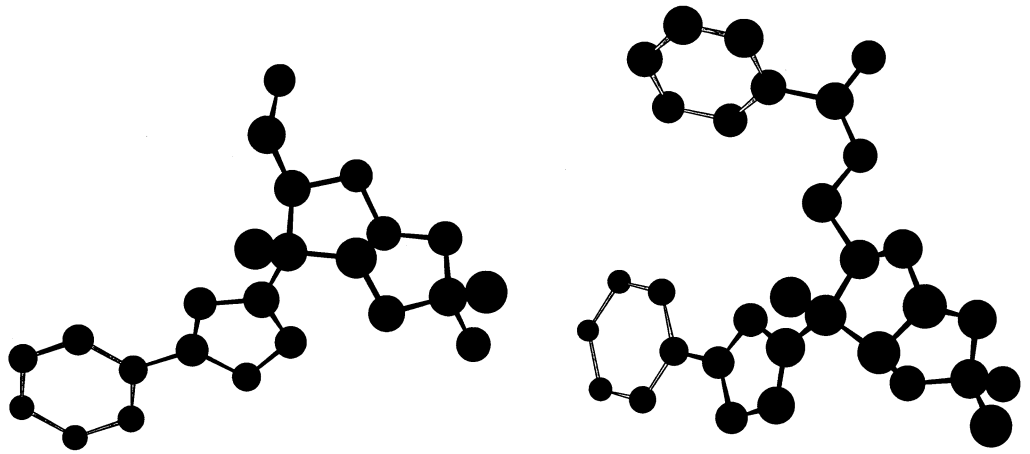
Scheme 1. (i) KCN–Et_2O–H_2O; (ii) BzCl–Py; (iii) NH_2OH–CH_3OH; (iv) Ac_2O, $(CH_3CH_2CO)_2O$ or benzoyl chloride, respectively; (v) MeOH–NaOMe, pH 7–8, 1 h; and (vi) 1% anhydrous HCl–MeOH.

propanoic anhydride, and benzoyl chloride to give the 1,2,4-oxadiazole derivatives **5**, **6**, and **7**, respectively. Interestingly, when compounds **5**, **6**, and **7** were treated with sodium methoxide in methanol at pH 7–8 and at room temperature (rt) for 1 h, only one product, the 5-phenyloxadiazole **8**, was obtained in yields of 72–95%. In contrast, after 10 min, the intermediate **11** was isolated. In general, a 5-*O*-benzoyl group on a furanose ring can be debenzoylated more readily than a 3-*O*-benzoyl group. However, no 5-*O*-debenzoyl-3-*O*-benzoyl intermediates were found in the foregoing reactions. The 3-benzoyl group probably undergoes intramolecular replacement through neighboring participation (Scheme 2). Witanowski et al. reported that an increase of solvent polarity favors delocalization of electrons from oxygen to nitrogen with concomitant accumulation of charge on N-4 more than on N-2 in oxadiazole systems [12]. Conjugations between the benzene and oxadiazole rings make the system more stable. The intramolecular replacements of **5**, **6**, and **7** result in the same product, **8**, by way of **11**. The structures of **8** and **11** have been established by X-ray crystallographic analysis (Fig. 1).

When **8** was treated under reflux in 1% hydrochloric acid in methanol, a 1:1 mixture of α and β methyl xylosides **9** and **10** was obtained. To modify this ratio, **8** was treated with 1% anhydrous HCl–anhydrous methanol at rt, giving **9** and **10** in 1:10 ratio. Moreover, when the reaction temperature was kept at −10 °C, only a trace of the isomer **9** was formed. The isomer can be easily isolated by column chromatography or recrystallization. It is suggested that in aqueous methanol and at high temperature, the glycosylation proceeds by an S_N1 process to afford the 1:1 anomeric mixture. However, with anhydrous methanol and low temperature, the reaction proceeds more by S_N2 nucleophilic attack, which results in a high ratio of the β isomer **10**. The ^1H NMR spectra of **9** and **10** confi-



Scheme 2. A possible mechanism for intramolecular replacement in **5**, **6**, and **7**.



8 11

Fig. 1. The X-ray crystal structures of **8** and **11**.

rmed the cis and trans configurations of H-1 and H-2 of **9** and **10**, respectively.

3. Experimental

General methods.—Melting points were determined on an X_4 melting-point apparatus and the thermometers were uncorrected. Optical rotations were determined with a Perkin–Elmer 243B polarimeter. Mass spectra were obtained on either ZAB-HS or KYKY-ZHP-5 mass spectrometers. NMR spectra were recorded on Varian VXR-300 or INOVA-500 spectrometers with Me_4Si as the internal standard. Exchangeable protons were detected by addition of D_2O. Microanalyses were obtained using a Perkin–Elmer 240C elemental analyzer. Column chromatography was performed on silica gel (200–300 mesh) and Silica Gel GF_{254} was used for TLC and was purchased from the Qingdao Chemical Company, China.

1,2-O-Isopropylidene-5-O-benzoyl-3-C-cyano-α-D-xylofuranose (**2**).—A mixture of **1** (10 g, 29 mmol), ether (60 mL), water (30 mL) and KCN (5.66 g, 87 mmol) was stirred vigorously at rt overnight. The organic phase was separated and dried (Na_2SO_4). After distillation, white crystals (9.8 g, 90%) were obtained. mp 155–157 °C, $[\alpha]_D^{18}$ + 75° (*c* 2.1, EtOAc); ^{1}H NMR (Me_2SO-d_6): 1.32 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 4.10 (m, 1 H, H-5a), 4.49 (dd, 1 H, H-4), 4.52 (m, 1 H, H-5a), 4.68 (d, 1 H, $J_{2,1}$ = 3.5 Hz, H-2), 6.02 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1), 7.54 (q, 2 H, Bz–H-m), 7.70 (t, 1 H, Bz–H-p), 8.04 (q, 2 H, Bz–H-o); FABMS: *m/z* 320 $[M + 1]^+$. Anal. Calcd for $C_{16}H_{18}O_6N_2$: C, 60.18; H, 5.36; N, 4.39. Found: C, 60.12; H, 5.37; N, 4.28.

1,2-O-Isopropylidene-3,5-di-O-benzoyl-3-C-cyano-α-D-xylofuranose (**3**).—Compound **2** (1.0 g, 3.1 mmol) was dissolved in a solution of CH_2Cl_2 (10 mL) and pyridine (3 mL), and BzCl (1.1 mL) was added at 0 °C and the mixture was stirred for 4 days. Water (10 mL) and CH_2Cl_2 (20 mL) were then added and the organic layer was separated, washed with 1 M H_2SO_4 and water, and dried (Na_2SO_4) to yield white crystals (1.3 g, 98%), mp 154–156 °C, $[\alpha]_D^{18}$ − 9.34° (*c* 2.0, EtOAc); ^{1}H NMR (Me_2SO-d_6): 1.35 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 4.79 (d, $J_{5,4}$ = 6.0 Hz, 2 H, H-5), 4.90 (t, $J_{4,5}$ = 6.0 Hz, 1 H, H-4), 5.19 (d, $J_{2,1}$ = 3.6 Hz, 1 H, H-2), 6.09 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1), 7.54 (q, 2 H, Bz–H-m), 7.73 (t, 1 H, Bz–H-p), 8.01 (q, 2 H, Bz–H-o); FABMS: *m/z* 424 $[M + 1]^+$. Anal. Calcd for $C_{23}H_{21}NO_7$: C, 65.24; H, 5.00; N, 3.31. Found: C, 65.24; H, 5.00; N, 3.31.

3-C-Amidoximino-3,5-di-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose (**4**).—Compound **3** (10 g, 42 mmol) was treated with hydroxylamine (90 mmol) to afford the white crystals [7,8] (6.36 g, 59%), mp 100–104 °C, $[\alpha]_D^{18}$ + 52.5° (*c* 1.2, EtOAc); ^{1}H NMR (Me_2SO-d_6): 1.25 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 4.56 (d, $J_{5,4}$ = 6.0 Hz, 2 H, H-5), 4.78 (d, $J_{2,1}$ = 3.6 Hz, 1 H, H-2), 5.00 (t, $J_{4,5}$ = 6.0 Hz, 1 H, H-4), 6.10 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1), 6.90 (s, 1 H, –OH, exchangeable), 6.88 (s, 1 H, –OH, exchangeable), 8.11–7.41 (m, 10 H, Bz–H), 12.99

(s, 2 H, $-NH_2$, exchangeable); FABMS: m/z 457 $[M+1]^+$.

3-C-*(3,5-Di*-O-*benzoyl-1,2*-O-*isopropylidene-α*-D-*xylofuranos-3-yl)-5-methyl-1,2,4-oxadiazole* (**5**).—A solution of **4** (1.24 g, 2.7 mmol) in Ac_2O (10 mL) was heated at 80 °C under nitrogen for 20 h. The solvent was distilled off and the resultant brown syrup was purified on a column of silica gel chromatography using petroleum–EtOAc as eluent to give white crystals (1.06 g, 81%), mp 114–116 °C, $[\alpha]_D^{18}$ + 72.95° (*c* 1.5, EtOAc); ^{1}H NMR (Me_2SO-d_6): 1.29 (s, 3 H, $-CH_3$), 1.41 (s, 3 H, $-CH_3$), 2.14 (s, 3 H, $-CH_3$), 4.45 (m, 1 H, H-5′b), 4.76 (dd, 1 H, H-4′), 5.10 (m, 1 H, H-5′a), 5.12 (d, $J_{2',1'} = 3.5$ Hz, 1 H, H-2′), 6.20 (d, $J_{1',2'} = 3.5$ Hz, 1 H, H-1′), 8.11–7.50 (m, 10 H, Bz–H); FABMS: m/z 481 $[M+1]^+$. Anal. Calcd for $C_{25}H_{24}N_2O_8$: C, 62.50; H, 5.03; N, 5.83. Found: C, 62.68; H, 5.07; N, 5.69.

3-C-*(3,5-Di*-O-*benzoyl-1,2*-O-*isopropylidene-α*-D-*xylofuranos-3-yl)-5-ethyl-1,2,4-oxadiazole* (**6**).—Compound **4** (740 mg, 1.6 mmol) was treated with propanoic anhydride (5 mL), as in the procedure just described for the preparation of **5**, to give **6** (720 mg, 90%), mp 109–110, $[\alpha]_D^{18}$ + 61.25° (*c* 0.8, EtOAc); ^{1}H NMR (Me_2SO-d_6): 0.97 (t, 3 H, $J = 7.5$ Hz, $-CH_3$), 1.28 (s, 3 H, $-CH_3$), 1.42 (s, 3 H, $-CH_3$), 2.45 (q, 2 H, $J = 7.5$ Hz, $-CH_2$), 4.44 (m, 1 H, H-5′), 4.74 (dd, 1 H, H-4′), 5.09 (m, 1 H, H-5″), 5.12 (d, $J_{2',1'} = 3.5$ Hz, 1 H, H-2′), 6.18 (d, $J_{1',2} = 3.5$ Hz, 1 H, H-1′), 8.10–7.47 (m, 10 H, Bz–H); FABMS: m/z 495 $[M+1]^+$. Anal. Calcd for $C_{26}H_{26}N_2O_8$: C, 63.15; H,5.30; N, 5.66. Found: C, 63.25; H, 5.29; N, 5.61.

3-C-*(3,5-Di*-O-*benzoyl-1,2*-O-*isopropylidene-α*-D-*xylofuranos-3-yl)-5-phenyl-1,2,4-oxadiazole* (**7**).—Compound **4** (640 mg, 1.4 mmol) was treated with BzCl (480 mg), as described for the preparation of **5**, to give **7** (660 mg, 85%), mp 154–155 °C, $[\alpha]_D^{18}$ + 95.22° (*c* 0.77, EtOAc); ^{1}H NMR (Me_2SO-d_6): 1.33 (s, 3 H, $-CH_3$), 1.47 (s, 3 H, $-CH_3$), 4.55 (m, 1 H, H-5b′), 4.91 (dd, 1 H, H-4′), 5.22 (m, 1 H, H-5a′), 5.38 (d, 1 H, $J_{2,1} = 3.6$ Hz, H-2′), 6.32 (d, $J_{1,2} = 3.6$ Hz, 1 H, H-1′) 8.08–7.30 (m, 15 H, Bz–H, Ph–H); FABMS: m/z 557 $[M+1]^+$. Anal. Calcd for $C_{31}H_{28}N_2O_8$: C, 66.90; H, 5.07; N, 5.03. Found: C, 66.97; H, 5.32; N, 4.96.

3-C-*(1,2*-O-*Isopropylidene-α*-D-*xylofuranos-3-yl)-5-phenyl-1,2,4-oxadiazole* (**8**).—Compounds **5**, **6** or **7** were treated with NaOMe in MeOH at pH 7–8 for 1 h at rt, to give the same product **8** in yields of 72–95%, mp 156–157 °C, $[\alpha]_D^{18}$ + 126.2° (*c* 0.96, EtOAc); ^{1}H NMR (Me_2SO-d_6): 1.20 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 3.64 (m, 1 H, H-5b′), 3.77 (m, 1 H, H-5a′), 4.58 (dd, 1 H, H-4′), 4.67 (d, $J_{2',1'} = 3.5$ Hz, 1 H, H-2′), 4.88 (t, 1 H, exchangeable, OH-3′), 6.00 (d, $J_{1',2'} = 3.5$ Hz, 1 H, H-1′), 6.43 (s, 1 H, exchangeable, OH-5′), 7.63 (q, 2 H, Bz–H-m), 7.72 (t, 1 H, Bz–H-p), 8.12 (q, 2 H, Bz–H-o). ^{13}C NMR (Me_2SO-d_6): 26.5 ($-CH_3$), 26.6 ($-CH_3$), 60.0 (C-5′), 78.0 (C-4′), 81.8 (C-2′), 86.0 (C-3′), 104.3 ($-C[CH_3]_2$), 111.6 (1′-C), 123.2 (Ph), 127.8 (Ph-m), 129.7 (Ph-o), 133.4 (Ph-p), 169.4 (C-3) 174.8 (C-5); FABMS: m/z 335 $[M+1]^+$. The crystal system is orthorhombic, space group $P22_12_1$, crystal data: formula $(C_{16}H_{18}O_6N_2)_2$, unit-cell volume $V = 3356.7(3)$ [3]. The details of unit-cell parameters are: $a = 6.732(2)$, $b = 15.729$ (1), $c = 31.701(1)$ Å. Four molecules are contained in one unit cell $Z = 4$.

3-C-*(Methyl α*-D-*xylofuranosid-3-yl)-5-phenyl-1,2,4-oxadiazole* (**9**) *and 3*-C-*(methyl β*-D-*xylofuranosid-3-yl)-5-phenyl-1,2,4-oxadiazole* (**10**).—Compound **8** (470 mg, 1.4 mmol) was treated with 1% anhydrous HCl–MeOH at rt to give **9** (33 mg, 7.6%) and **10** (335 mg, 77%), isolated by column chromatography using petroleum–EtOAc as eluent. Compound **9** was colorless crystals: mp 146–147 °C, $[\alpha]_D^{18}$ + 25.7° (*c* 0.93, EtOAc); ^{1}H NMR (Me_2SO-d_6): 3.42 (s, 3 H, OCH_3-1′), 3.86 (dd, 1 H, H-4′), 3.96 (m, 2 H, H-5), 4.03 (d, 1 H, H-2′), 4.70 (d, $J_{1',2'} = 0.0$ Hz, 1 H, H-1′), 5.08 (1 H, OH-5′, exchangeable), 5.09 (1 H, OH-2′, exchangeable), 6.38 (1 H, OH-3′, exchangeable), 7.64 (m, 2 H, Ph–H), 7.70 (m, 1 H, Ph–H), 8.11 (d, 2 H, Ph–H); ^{13}C NMR (Me_2SO-d_6): 56.0 (OCH_3), 66.3 (C-4′), 69.0 (C-5′), 70.7 (C-2′), 99.7 (1′-C), 123.5 (Ph), 127.7 (Ph-m), 129.6 (Ph-o), 133.1 (Ph-p), 171.6 (C-3), 174.2 (C-5); FABMS: m/z 309 $[M+1]^+$. Anal. Calcd for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.08. Found: C, 54.59; H, 5.26; N, 9.10. Compound **10** was colorless crystals: mp 181–82 °C, $[\alpha]_D^{18}$ − 46.9° (*c* 1.6, EtOAc); ^{1}H NMR (Me_2SO-d_6): 3.40 (1 H, H-2′), 3.41 (s, 3 H,

OCH_3-1′), 3.71 (dd, 1 H, H-4′), 3.79 (m, 1 H, H-5b′), 3.96 (m, 1 H, H-5a′), 4.92 (d, $J_{1',2'} =$ 8.0 Hz, 1 H, H-1′), 5.30 (1 H, OH-5′, exchangeable), 5.44 (1 H, OH-2′, exchangeable), 5.74 (1 H, OH-3′, exchangeable), 7.65 (m, 2 H, Ph–H), 7.71 (m, 1H, Ph–H), 8.13 (d, 2 H, Ph–H); ^{13}C NMR (Me_2SO-d_6): 55.9 (OCH_3), 63.9 (C-5′), 72.2 (C-4′), 75.4 (C-3′), 78.2 (C-2′), 102.2 (C-1′), 123.6 (Bz), 127.7 (Bz-m), 129.6 (Bz-o), 133.1 (Bz-p), 171.0 (C-3), 173.4 (C-5); FABMS: m/z 309 $[M+1]^+$. Anal. Calcd for $C_{14}H_{16}N_2O_6$ (308.29): C, 54.54; H, 5.23; N, 9.08. Found: C, 54.43; H, 5.32; N, 9.07.

3-C-(5-O-Benzoyl-1,2-O-isopropylidene-α-D-xylofuranos-3-yl)-5-phenyl-1,2,4-oxadiazole (**11**).—Compounds **5**, **6**, or **7** were treated with NaOMe in MeOH at pH 7–8 for 10 min at rt. The mixture was extracted with EtOAc, the organic phase was separated and dried (Na_2SO_4). Evaporation afforded colorless crystals of **11**, isolated by column chromatography eluting with petroleum–EtOAc, mp 130–131 °C, $[\alpha]_D^{18}$ +49.4° (*c* 1.13, EtOAc); ^{1}H NMR (Me_2SO-d_6): 1.25 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 4.56 (m, 2 H, H-5′), 4.77 (d, $J_{2',1'} = 3.5$ Hz, 1 H, H-2′), 4.98 (m, 1 H, exchangeable, OH-4′), 6.09 (d, $J_{1',2} = 3.5$ Hz, 1 H, H-1′), 6.87 (s, 1 H, exchangeable, OH-3′), 8.11–7.42 (m, 10 H, Bz–H, Ph–H); ^{13}C NMR (Me_2SO-d_6): 26.5 (–CH_3), 26.6 (–CH_3), 62.5 (C-5′), 78.0 (C-4′), 78.4 (C-2′), 86.0 (C-3′), 104.6 (C=O), 112.1 (1′-C), 123.0 (Bz-p), 127.8 (Bz-m), 128.6 (Bz-m), 129.1 (Bz-o), 129.3 (Bz-p), 129.6 (Bz-o), 133.4 (Bz-3, 3′), 165.4 (–C[CH_3]$_2$), 169.3 (C-3), 174.9 (C-5); FABMS: m/z 439 $[M+1]^+$. Anal. Calcd for $C_{23}H_{22}N_2O_7$: C, 63.01; H, 5.06; N, 6.39. Found: C, 62.97; H, 5.10; N, 6.40. The crystals belong to the orthorhombic system, space group $P2_12_12_1$, unit-cell parameters: $a =$ 10.839(4), $b = 12.016(3)$, $c = 16.230(7)$ Å, unit-cell volume $V = 2113.8(13)$ [3]. The number of molecules in one unit cell $Z = 4$.

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